Updates in Endometrial Cancer: Adjuvant Chemotherapy

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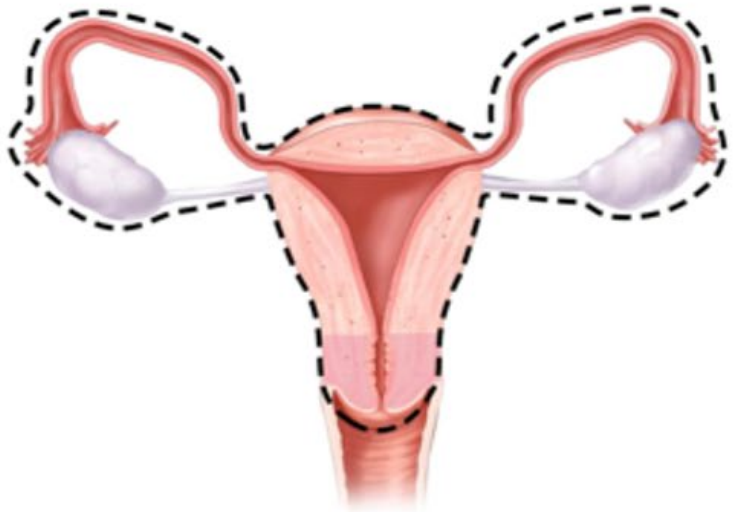
Ochsner Health

Objectives

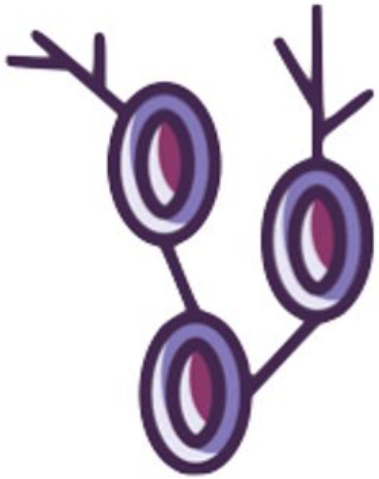
- Review adjuvant chemotherapy for advanced stage endometrial cancer (EC)
- *Briefly* review adjuvant chemotherapy for early stage, “high-risk” EC
- Review first and second line adjuvant chemotherapy strategies for recurrent EC

Treatment of apparent early-stage EC



Hysterectomy

+/-



Lymph Node Evaluation

Which patients benefit from adjuvant therapy?

- Many different classification systems based on prognostic pathological features
  - Histologic subtype, grade, myometrial invasion, and LVSI (no/focal/substantial)
- European Society of Gynecologic Oncology (**ESGO**)/European Society of Radiation Oncology (**ESTRO**)/European Society of Pathology (**ESPO**) guidelines:
  - High risk
    - Stage I-IVA non-endometrioid histology (serous, clear cell undifferentiated carcinoma, carcinosarcoma) with myometrial invasion and no residual disease
    - Stage III-IVA with no residual disease

Concin N, et al. Int J Gynecol Cancer. 2021

Case 1: 62yo with a new diagnosis of stage IA serous EC

- Prognostic pathological features: **35% MI**, -LVSI
- **Low-level evidence demonstrated benefit to adjuvant CT in early stage, serous EC with MI**
- Descriptive analysis of 142 patients with stage I serous EC
- Median F/U was 47 months
- Overall risk of recurrence:
  - Stage IA without MI: 11.8%
  - Stage IB with <50% MI: 17%
  - Stage IC with >50% MI: 31%
- Total of 25 recurrences (18%) which varied by adjuvant treatment strategy
  - Observation: 33%
  - RT: 20%
  - CT +/- RT: 11%
- *Conclusion: Adjuvant CT +/- RT demonstrated a significant reduction in overall recurrence and improved PFS (p=0.01) in patients with early stage serous EC with MI*

Ruscito, et al. Ann Surg Oncol. 2016

Case 2: 70yo with a new diagnosis of stage IA serous EC

- Prognostic pathological factors: **0% MI,** -LVSI
- **Low-level evidence did not demonstrate a benefit to adjuvant CT in early stage, serous EC without MI**
- Retrospective study of 85 patients with stage IA, **non-invasive**, high-grade EC
- **Most patients were serous (66%)**
- Adjuvant treatment included 1) CT +/- EBRT or VBT , 2) EBRT or VBT, or 3) observation
- 3Y PFS = 95%, 3Y OS = 99%
- Adjuvant treatment type was not associated with a difference in outcomes
- *Conclusion: Adjuvant CT did not demonstrate an improvement in PFS, OS in patients with type II endometrial cancers that are non-invasive*
- But it is still important to discuss it with patients!

Ruscito, et al. Ann Surg Oncol. 2016

Is there a benefit to adjuvant CT in early stage, "high-risk" endometrioid EC?

- No high-level evidence demonstrating that adjuvant CT improves oncological outcomes
- 14% risk of distant recurrence in stage IA grade 3 endometrioid EC
- 30% risk of distant recurrence in stage IB grade 3 endometrioid EC
- GOG 249: multi-center, non-inferiority P3RCT
- 601 patients with "high-risk" early-stage EC with lymphadenectomy
  - Endometrioid histology with uterine risk factors: grade 2-3, ≥50% MI, LVSI
  - Serous or clear cell histology
  - Stage II
- It is unclear how many patients were stage IA,B grade 3 endometrioid EC
- Randomized to VBT + CT vs EBRT
- **No significant difference in 5Y RFS, OS**
- Significantly *more toxicity in patients treated with adjuvant CT* + VBT

Randall, et al. J Clinic Oncol. 2019

Case 3: 75yo with stage IIIC1 grade 2 endometrioid EC

- GOG 258: multi-center, non-inferiority P3RCT
- 707 patients with advanced stage endometrioid endometrial cancer who underwent surgery with lymphadenectomy (97%)
- Randomized to CT *vs* CT + EBRT
  - CT
    - Carboplatin AUC 5-6 and Paclitaxel 175 mg/m^2 for 6 cycles
    - No VBT
  - CT + EBRT
    - EBRT 4500 cGy with radiosensitizing cisplatin 50 mg/m^2
    - Carboplatin AUC 5-6 and Paclitaxel 175 mg/m^2 for 4 cycles
    - +/- VBT
- Primary endpoint: PFS
- **No significant difference in 5Y PFS (59% vs 58%, p = NS)**

Ruscito, et al. Ann Surg Oncol. 2016

Advanced stage, non-endometrioid histology

- Treatment is the same
- Consider adding Trastuzumab in patients with HER2+ serous EC

Fader et al. J Cilinc Oncol. 2018

What's the benefit of adding adjuvant EBRT to CT?

- GOG 258 : No difference in PFS in patients with advanced stage endometrial cancer treated with EBRT + VBT vs CT
- **Adding EBRT significantly reduces recurrences**
  - 5Y vaginal recurrence (2% vs 7%)
  - Pelvic and para-aortic recurrence (11% vs 20%)
- But is associated with significantly more grade 3+ AE (60% vs 12%)
  - Most commonly hematologic
  - Remained higher 1 month after completion of therapy but normalized after 6 months except for grade 2 sensory neuropathy (9% vs 0%)

Maetei et al. N Engl J Med. 2019

Is there a benefit to maintenance avastin?

- NRG/GOG 86P: 3-arm P2RCT
- 349 patients with newly diagnosed stage III-IVA and IVB or recurrent EC
  - Carboplatin AUC6/Paclitaxel 175 mg/m^2/Avastin 15 mg/kg
  - Carboplatin AUC5/Paclitaxel 135 mg/m^2/Temsirolimus 25 mg
  - Carboplatin AUC5/Ixabepilone/Avastin 15 mg/kg
- Primary endpoint: PFS
- All endpoints were compared to the Carboplatin/paclitaxel arm in GOG 209
- **No significant difference in PFS any group compared to the historical cohort**

Aghajanian, et al. Gynecol Oncol. 2018

Palliative CT therapy for recurrences

- 1L: Platinum-based combination chemotherapy
- 2L:
  - **Mutational burden**
    - **MMRd: Pembrolizumab**
    - **MMRp: Pembrolizumab & Lenvatinib**
  - *Single agent chemotherapy*

The standard: platinum-based therapy

- GOG 209: Multi-center, non-inferiority P3RCT
- 1,381 patients with stage IV and recurrent endometrial cancer
- Randomized to liposomal doxorubicin/cisplatin vs carboplatin/paclitaxel
- Primary endpoint: OS
- **No significant difference in median OS, PFS (HR 1.02, HR 1.032)**
- Significantly less toxicity in carboplatin/paclitaxel arm

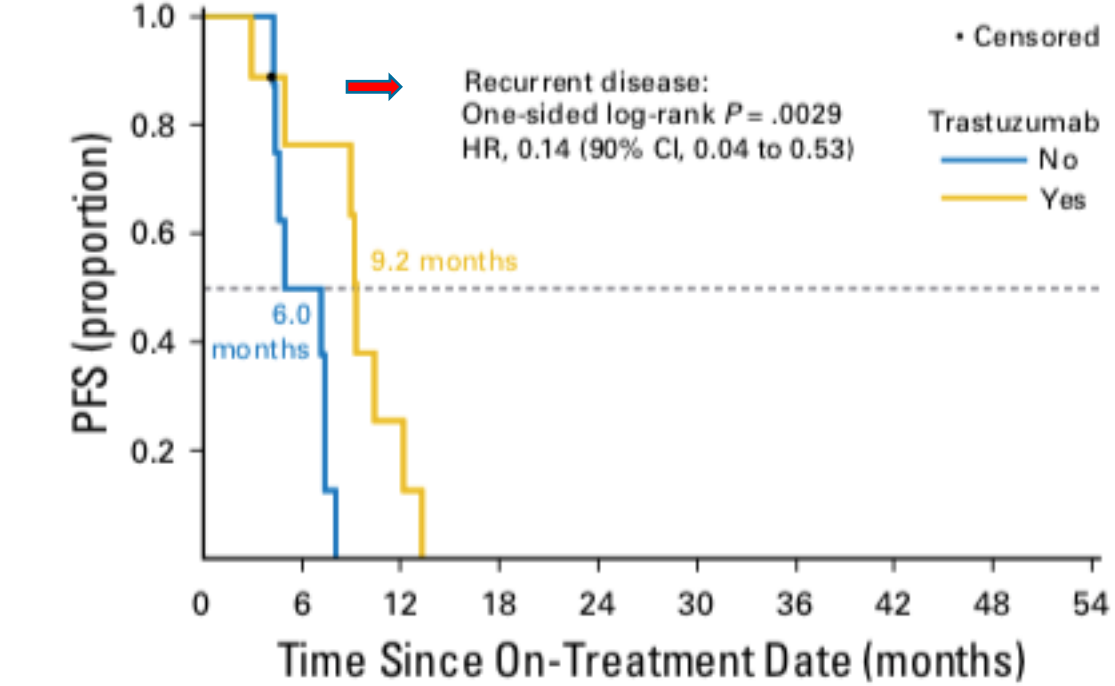
- Low-level evidence to support retreating patients with recurrent EC with platinum-based CT (50% PR, 15% SD)

Miller, et al. J Clinic Oncol. 2021
Rubinstein, et al. Gynecol Oncol. 2019.

Trastuzumab improves outcomes in serous histology

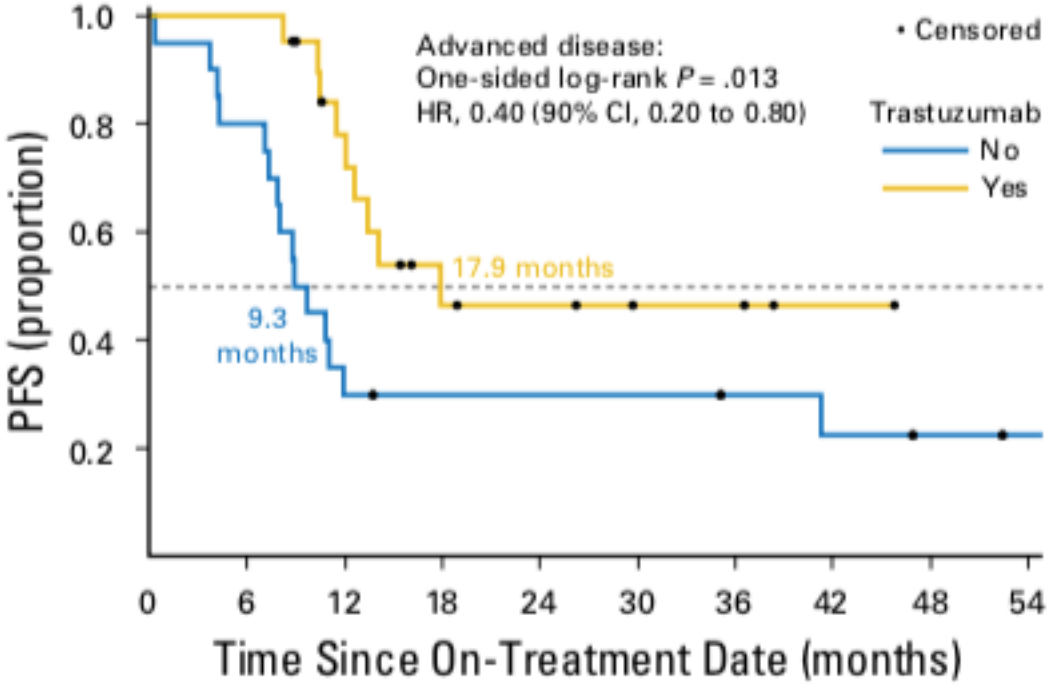
- Multi-center, phase II RCT
- 61 patients with stage III or IV or recurrent HER2/neu-positive serous EC
  - IHC score of 3+ or 2+ with FISH
- Randomized to *Carboplatin AUC/Paclitaxel 175 mg/m^2* **+/- Trastuzumab** at 8 mg/kg for the first cycle and 6 mg/m^2 in subsequent cycles
- Treated until disease progression or toxicity
- Primary endpoint: PFS

Fader et al. J Cilinc Oncol. 2018



No. at risk

No	8	4	0	
Yes	9	6	2	0



No. at risk

No	20	16	6	5	5	5	4	3	2	1
Yes	21	21	13	6	5	3	3	1	0	

Minimal toxicity: CBC, CMP, 2D Echo every 3 months

Fader et al. J Cilinc Oncol. 2018

Patients that progress on platinum-based therapy are in trouble…

Phase II trial of liposomal doxorubicin at 40 mg/m^2 every 4 weeks in endometrial carcinoma: A Gynecologic Oncology Group Study

Howard D. Homesley[a,*], John A. Blessing[b], Joel Sorosky[c,1], Gary Reid[d,e], Katherine Y. Look[f]

12%

A phase II study of gemcitabine (gemzar, LY188011) in the treatment of recurrent or persistent endometrial carcinoma: A gynecologic oncology group study ☆

David L. Tait[a,*], John A. Blessing[b], James S. Hoffman[c], Kathleen N. Moore[d], Nick M. Spirtos[e], Jason A. Lachance[f], Jacob Rotmensch[g], David S. Miller[h]

4%

A Phase II Trial of Topotecan in Patients with Advanced, Persistent, or Recurrent Endometrial Carcinoma: A Gynecologic Oncology Group Study[1]

David Scott Miller, M.D.,*[2] John A. Blessing, Ph.D.,† Samuel S. Lentz, M.D.,‡ and Steven E. Waggoner, M.D.§

9%

Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a gynecologic oncology group study

Sarah Lincoln M.D. [a], John A Blessing Ph.D. [b], Roger B Lee M.D. [c], Thomas F Rocereto M.D. [d]

27%

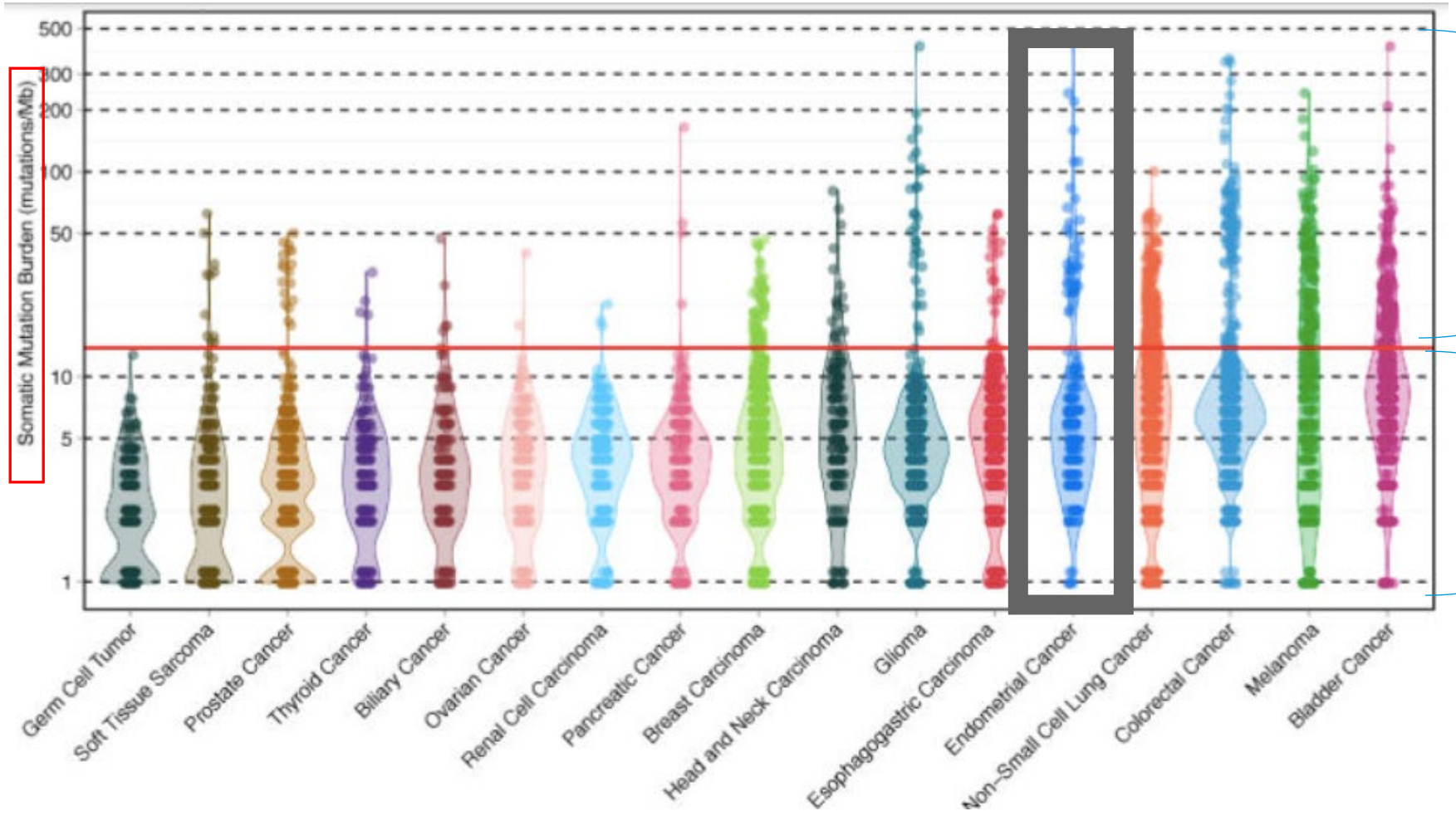
Phase II Trial of Bevacizumab in Recurrent or Persistent Endometrial Cancer: A Gynecologic Oncology Group Study

Carol Aghajanian, Michael W. Sill, Kathleen M. Darcy, Benjamin Greer, D. Scott McMeekin, Peter G. Rose, Jacob Rotmensch, Mack N. Barnes, Parviz Hanjani, and Kimberly K. Leslie

14%

2L therapy: taking advantage of the mutation load

Threshold for high mutational burden: 13.7 mutations/Mb



Zehir A, et al. Nat Med. 2017

Pembrolizumab: Accelerated FDA approval

- FDA approved in May 2017 for MSI-H or MMR deficient cancers
- Based on 5 uncontrolled, multi-cohort, multi-center, single-arm clinical trials
  - N=149 (90 Colorectal cancers, 59 other tumors)
  - **Objective response rate: 39.6% (95% CI 31.7-47.9)**
    - 11 CR and 48 PR
  - 78% DOR >6 months

[10]*https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm577093.htm*

The first of many trials in gynecologic cancers

- Multi-cohort, open-label, phase Ib basket trial
- PD-L1 positive advanced solid tumors
- Pembrolizumab 10 mg/kg every 2 weeks
- Primary endpoint: ORR
- Secondary endpoints: DOR, PFS, OS, safety and tolerability

Ott, et al. J Clinical Oncol. 2017

KEYNOTE-28: The endometrial cancer cohort

- 75 patients screened, 36 (48%) were **PD-L1 positive but non-selected**, 24 enrolled
- Most were endometrioid histology and received ≥ 2 prior lines of CT

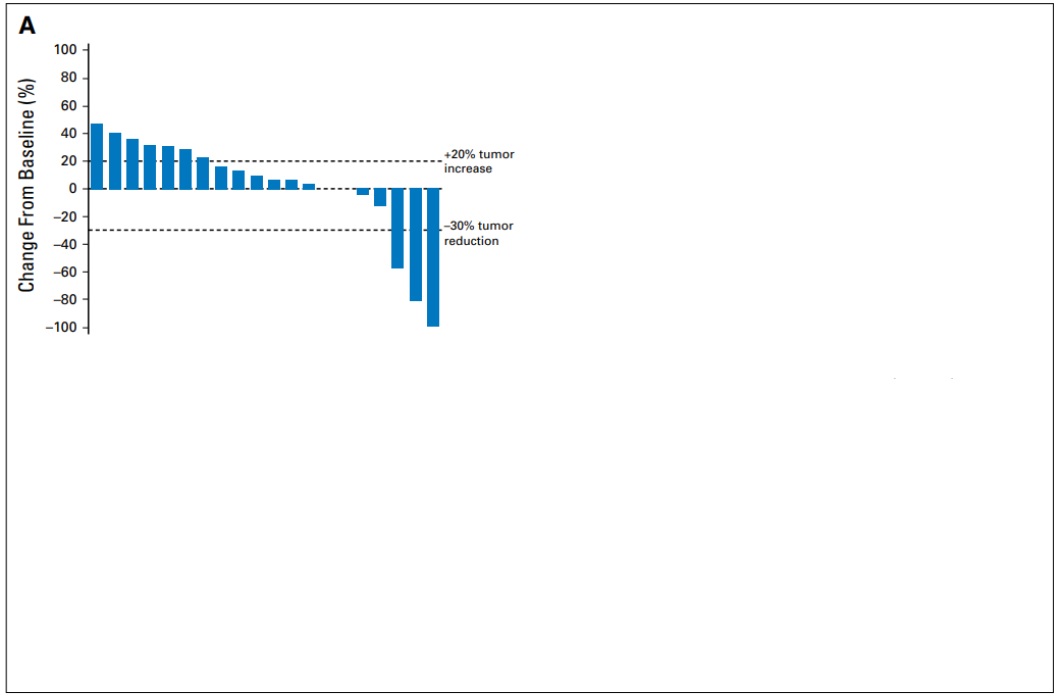


Fig 2. (A) Maximum change from baseline in tumor size (n = 20). (B) Longitudinal change from baseline in tumor size (n = 20). (C) Treatment exposure and response duration (n = 20). PR, partial response.

Poor efficacy in non-biomarker selected endometrial cancers (MMRp)

Study & Drug	Patient Population	ORR
KEYNOTE-28 Pembrolizumab (N=24)	Advanced stage or metastatic PD-L1 positive endometrial cancer	13%
PHAEDRA Durvalamub (N=36)	Advanced stage or metastatic endometrial cancer	3%
GARNET Dostarlimab (N=94)	Previously treated, recurrent endometrial cancer	20%
Phase II Avelumab (N= 16)	Advanced stage endometrial cancer	6%

Much better responses in biomarker-selected endometrial cancers (MSI-H/MMRd)

Study & Drug	Patient Population	ORR
KEYNOTE-158 Pembrolizumab (N=49)	Advanced stage or metastatic MMRd endometrial cancer	57%
PHAEDRA Durvalamub (N=35)	Advanced stage or metastatic endometrial cancer	43%
GARNET Dostarlimab (N=70)	Previously treated, recurrent endometrial cancer	43%
Phase II Avelumab (N= 15)	Advanced stage endometrial cancer	27%

KEYNOTE-158: The endometrial cancer cohort

- Non-randomized, open-label, phase II
- **Biomarker selective**: MSI-H/MMRd advanced solid tumors
- Pembrolizumab 200 mg IV every 3 weeks for a maximum of 35 cycles

TABLE 3. Antitumor Activity for Tumor Types With Greatest Enrollment

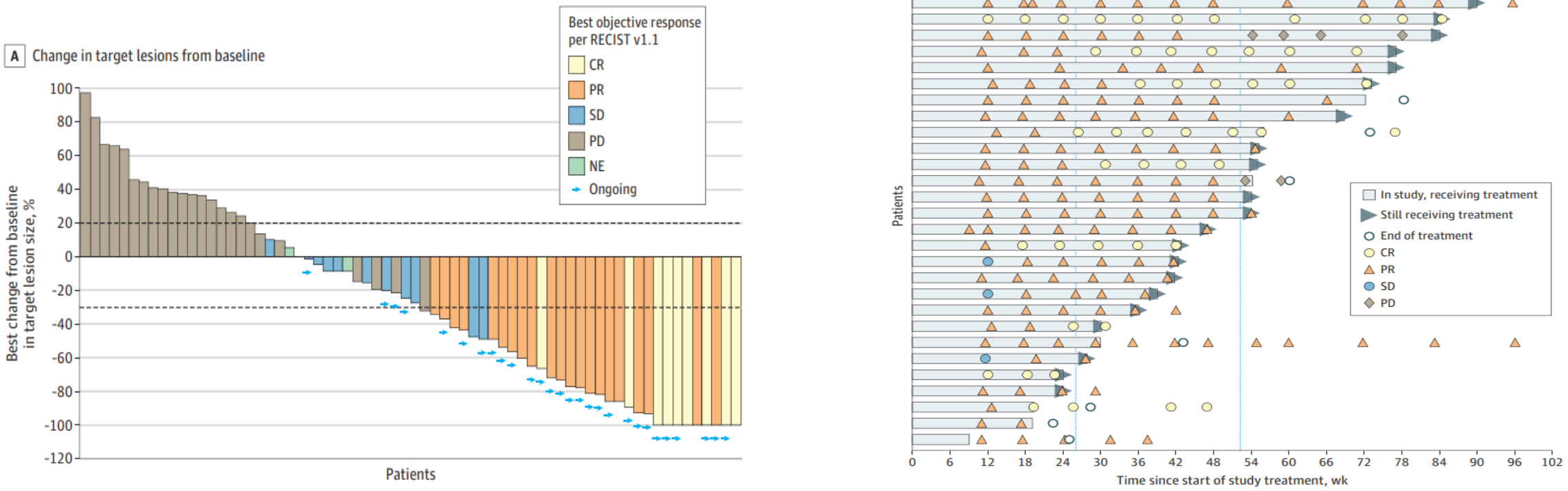
Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)	NR (6.3 to 28.4+)
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.

Biomarker-selected patients: deep & sustained response

Figure 2. Tumor Best Percentage Change in Lesion Size From Baseline in the Efficacy-Evaluable Population (n = 71) and Duration of Treatment in Responders (n = 30)



FDA approved immunotherapy

- MSI-H, MMRd: Pembrolizumab
- TMB-H: Pembrolizumab
- MMRd: Dostarlimab-dxly

What about MMRp EC? (low mutational burden)

- Combination therapy!

- Combining immunotherapy with anti-angiogenic therapy
  - Reverses immunosuppressive effects
  - Reduces T-Cell regulatory activity
  - Improves T-Cell trafficking and infiltration into tumor bed
  - Increases immune cell recruitment

Giving patients with low mutation burden a little push: KEYNOTE-146/Study III

- Multi-center, phase Ib/II of selected solid tumors
- 108 patients with previously treated endometrial cancer
- Most patients had endometrioid histology and MSS/MMRp (85%)
- Lenvatinib 20 mg PO & Pembrolizumab 200 mg IV every 3 weeks
- Primary endpoint: ORR (partial or complete) at 24 weeks
- Results: ORR_{24} = 38% (CR 7%, PR 32%), Median DOR = 21 months

Makker, et al. J Clinical Oncol. 2021

2L therapy for recurrent EC: A new standard of care?

- KEYNOTE-775: International, multi-center P3RCT
- 827 patients with **advanced, recurrent, or persistent EC** with measurable disease who received at **least 1-2 platinum-based CT** randomized to
  - Lenvatinib 20mg PO qD/Pembrolizumab 200 mg IV
  - Physicians' choice CT (doxil or weekly paclitaxel)
- Most patients were MMRp (84%), endometrioid histology (59%), and received 1 prior line of CT (79%)
- Primary endpoints: PFS, OS in all patients and in patients with MMRp
- Lenvatinib/pembrolizumab demonstrated improved PFS and OS (HR 0.60, 0.68)
  - Persisted in all subgroup analyses (MM status, histology, and number of previous lines of CT)
- **Conclusion: Lenvatinib/Pembrolizumab demonstrated improved PFS and OS in MMRp recurrent EC when compared to traditional single agent CT**

Makker, et al. NEJM. 2022

But what about toxicity?

- 22% discontinue treatment due to AE
- 70% had a dose interruption
- 70% of patients had a grade 3+ AE
- Low-level studies to suggest equal efficacy and less toxicity with a starting dose of Lenvatinib 14 mg

Makker, et al. J Clinical Oncol. 2021
How, et al. Gynecol Oncol. 2021

The future: combination immunotherapy and CT

- NRG GY-018: platinum-based chemotherapy +/-pembrolizumab with maintenance pembrolizumab
- AtTEnd/MaNGO: platinum-based chemotherapy +/- atezolizumab with maintenance atezolizumab
- RUBY: platinum-based chemotherapy +/- dostarliumab
- DUO-E: platinum-based chemotherapy +/- durvalumab +/- olaparib

Conclusions

- Carboplatin/paclitaxel is the standard of care for most recurrent EC
- A new molecular classification of EC based on mutational burden (MMR status) is useful to guide treatment of recurrent EC

Questions?