Disclosures

Interests

- Advisory Board: Clovis, Episla Bio

Off Label Usage

- I WILL include discussion of investigational or off-label use of a product in my presentation.

Endometrial Cancer
Outline

- Epithelial endometrial cancer
  - Epidemiology
  - Histologic subtypes
  - Risk Factors
  - Treatment
- Uterine sarcoma

Endometrial Cancer
Epidemiology

- Third most common cancer among women in US
- Most common gynecologic cancer in Europe and North America
- Fourth most common cause of cancer in women
- 80% present in early stage
  - 5 year OS
    - 74-91% Stage I or II
    - 57-66% Stage III
    - 20-26% Stage IV
- Incidence is lower in blacks but mortality rate is higher

Lancet Oncol 2014; 15:e268-78

Epithelial Endometrial Carcinoma

Endometrial cancer

Type I
- 85% endometrial cancer
- Endometrioid histology
- Unopposed estrogen
- Obesity
- Hormone receptor positivity
- Endometrial hyperplasia
- Usually lower grade

Type 2
- Clear cell
- Papillary serous
- Carcinosarcoma (MMMT)
- All considered high grade
- Worse prognosis

Lancet Oncol 2014; 15:e268-78

Endometrial Cancer

Risk factors

Risk Factor	Relative Risk
Obesity > 30 lbs > 50lbs	 3x 10x
Late menopause	2.4x
Diabetes Mellitus	2.8x
Unopposed Estrogen	9.5x
Complex Atypical Hyperplasia	29x
Tamoxifen therapy	2x
Nulliparity	2x
PCOS (chronic anovulation)	3x
Lynch syndrome (HNPCC)	22-50% lifetime risk
Cowden syndrome	13-19% lifetime risk

Smith, CA *Cancer J Clin* 2001; 51:38
Setiawan, *J Clin Oncol* 2013; 31:2607

Tamoxifen

- Increased risk 0.9 to 2 per 100
- Greatest cumulative risk after 5 years of use
- Cancers tend to be well differentiated, estrogen-receptor positive, and early stage
- Screening: immediate evaluation of vaginal bleeding

Endometrial hyperplasia

Classification	Progression to malignancy
Simple	1%
Complex	3%
Simple atypical	8%
Complex atypical	29%

- Treatment options:
  - **Hysterectomy**
  - Progestin therapy
  - Surveillance

Endometrial Cancer
2009 FIGO staging

Stage	Description
IA	Tumor confined to uterus, <50% myometrial invasion
IB	Tumor confined to uterus, ≥50% myometrial invasion
II	Cervical stromal invasion
IIIA	Tumor invasion into serosa or adnexa
IIIB	Vaginal or parametrial involvement
IIIC1	Pelvic node involvement
IIIC2	Paraaortic node involvement
IVA	Tumor invasion into bladder or bowel mucosa
IVB	Distant metastases (including abdominal metastases) or inguinal lymph node involvement

Staging, Classification and Prognosis

Stage	Proportion at diagnosis	5 yr survival
Stage I	80%	83%
Stage II	11%	73%
Stage III	6%	52%
Stage IV	2%	27%

- Locoregional disease
  - Low-risk disease: stage IA, grades 1-2
  - Intermediate-risk disease: other stage I, stage II
  - High-risk disease: all stage III and IVA
- Disseminated disease: stage IVB or recurrent

Endometrial cancer
Treatment

Low risk disease

- Stage IA, histologic grade 1,2 (endometrioid)
- Management:
  - Hysterectomy plus surgical staging
    - Bilateral salpingo-oophorectomy
    - Pelvic washings
    - Examination of abdominal cavity
    - Pelvic/para-aortic lymph nodes vs. sentinel nodes
- Surgical resection yields 5 year survival >95%

- Surgical management only

Intermediate risk

- All stage I grade 3
- Stage IB
  - Deeper invasion of grade 1,2 and other risk factors*
  - Stage II
    - Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus, does not include endocervical glandular involvement
- Approximate survival with surgery alone 85%

- **How do we improve outcomes?**

*Risk factors: grade 2 or 3; outer third myometrial invasion, LVSI

Intermediate risk endometrial carcinoma

GOG 99

- Stage I gr 3, stage II
- TAH-BSO, sentinel node sampling, pelvic washings
- Randomization: no further RT vs. pelvic RT

	No RT	Pelvic RT
Vaginal recurrences	13	2
Local recurrences	7.4%	1.6%
PFI at 2 yrs	88%	97% (p=0.007)
Survival at 4 yrs	86%	92% (p=0.55)

- Radiation reduces recurrence risk
- Radiation does not improve OS in intermediate risk disease

Keys et al, Gyn Oncol 92: 744-751, 2004

PORTEC 2

- Pelvic EBRT versus vaginal brachytherapy
- High intermediate risk
  - Stage IC grade 1 or 2 (more than half of myometrium)
  - Stage IB grade 2
  - Stage IIA (endocervical involvement)
  - Clear cell and serous histology excluded
- No significant difference in outcomes

	Vaginal recurrence	Pelvic recurrence	Distant
EBRT	4/214 (1.6%)	1/214 (0.5%)	13/214 (5.7%)
VBT	3/213 (1.8%)	8/213 (3.8%)	16/213 (8.3%)

Lancet 2010;375(9717):816-823

High Intermediate Risk

- High intermediate risk*
  - Age greater than 70 and one risk factor
  - Age greater the 50 with two risk factors
  - Any age with three risk factors
- Risk factors: grade 2 or 3, outer third myometrial invasion, LVSI, positive peritoneal cytology
- Higher risk for recurrence
  - Consider radiation therapy; optimal strategies a bit unclear

*definitions can vary a bit

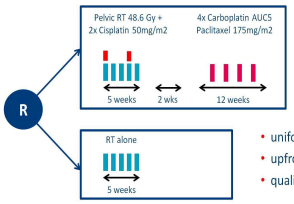
Can we improve outcomes with chemotherapy?

PORTEC 3 (intermediate and high risk)

PORTEC-3 trial design

Intermediate Risk Endometrial Carcinoma

Eligibility Criteria
- Stage I G3 with LVSI or deep invasion
- Stage II-III
- Stages I-III serous or clear cell (>25%)
- PS 0-2
- No macro residual



- uniform treatment schedule
- upfront pathology review
- quality of life analysis

PORTEC-3 results 6/2/2017

Presented By Stephanie de Boer at 2017 ASCO Annual Meeting

Portec III: Eligibility

- Eligibility Criteria
- Stage I G3 with LVSI or deep invasion
- Stage II-III
- Stages I-III serous or clear cell (>25%)
- PS 0-2
- No macro residual

Tumour characteristics	RT alone	CTRT
Histology		
Endometrioid grade 1-2	39.7%	38.5%
Endometrioid grade 3	32.1%	32.4%
Serous/ clear cell/ other	28.2%	29.1%
LVSI		
Yes	58.2%	59.7%
No	41.8%	40.3%
Stage (%)		
I	29.4%	29.7%
II	27.3%	24.2%
III	43.3%	46.1%

PORTEC III: Stage I-II OS/FFS

Stage	Patients	% FF 5yr	HR (P)	% Alive 5yr	HR (P)
I-II	365				
CTRT	178	81%	O.77 (0.26)	84%	0.79 (0.38)
RT	187	77%		82%	

Portec III

Stage I-II Conclusions

- No significant difference in 5-year FFS and 5-year OS
- Significantly more toxicity with CTRT in first 12 months
- PORTEC III does not support the use of concurrent chemotherapy/radiotherapy followed by chemotherapy in stage I-II endometrial carcinoma

Endometrial Carcinoma

Intermediate risk disease

- Surgical resection yields 85% 5-year survival
- Surgery followed by pelvic radiation improves local control but does not impact survival
- Recommended management: resection of all gross disease +/- radiation
- Serous,clear cell histology: except it stage IA, no myometrial invasion: consider chemotherapy with consideration of radiation therapy

High risk locoregional disease

Treatment

High risk locoregional disease

- Stage III (adnexal, serosal, vaginal, pelvic/PA node involvement)
- Stage IVA (bladder/rectal) involvement
- Surgery: relapse rate >50%
- Management:
  - Role of radiation vs. chemotherapy?

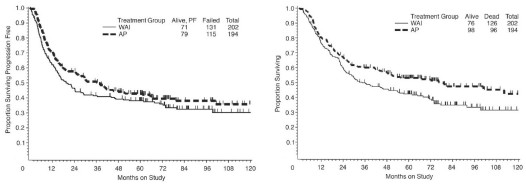
GOG 122

- Stage III-IV disease
- TAH-BSO, tumor debulking to less than 2 cm
- Tumor confined to abdomen or pelvis

Regimen 1	Regimen 2
Abdomino-pelvic RT	Doxorubicin (A) 60mg/m2 Cisplatin (P) 50 mg/m2

J Clin Oncol 2008 1(24):36-44.

GOG 122

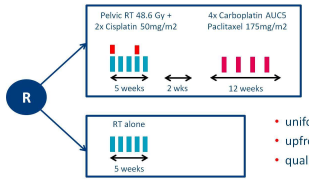


- AP chemotherapy significantly improves PFS and OS compared to whole abdominal radiation
- The risk of progression or death is reduced by 30%, the risk of death by 34%.

PORTEC III

PORTEC-3 trial design

- High risk Endometrial Cancer (HREC)



- uniform treatment schedule
- upfront pathology review
- quality of life analysis

PORTEC-3 results 6/2/2017

Portec III: Eligibility

Tumour characteristics	RT alone	CTRT
Histology		
Endometrioid grade 1-2	39.7%	38.5%
Endometrioid grade 3	32.1%	32.4%
Serous/ clear cell/ other	28.2%	29.1%
LVSI		
Yes	58.2%	59.7%
No	41.8%	40.3%
Stage (%)		
I	29.4%	29.7%
II	27.3%	24.2%
III	43.3%	46.1%

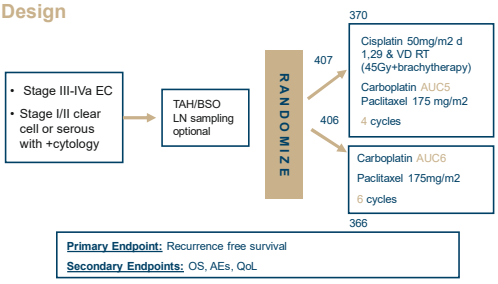
PORTEC III
Stage III OS/FFS

Stage	Patients	% FF 5yr	HR (P)	% Alive 5yr	HR (P)
I-II	365				
CTRT	178	81%	O.77 (0.26)	84%	0.79 (0.38)
RT	187	77%		82%	
III	295				
CTRT	152	69%	0.66 (0.032)	79%	0.69 (0.114)
RT	143	58%		70%	

Portec III
Conclusions

- 5-year FFS and OS for stage III vs stage I-II
  - FFS: 64% stage III vs 79% stage I-II (p<0.001)
  - OS: 74% stage III vs 83% stage I-II (p=0.003)
- 5-year FFS and OS in stage III for CTRT vs RT
  - 5-year FFS: 69% CTRT vs 58% RT (HR 0.66, CI 0.45-0.97, p=0.032)
  - 5-year OS: 79% CTRT vs 70% RT (HR 0.69, CI 0.44-1.09, p=0.114)
- What about chemotherapy without radiation?

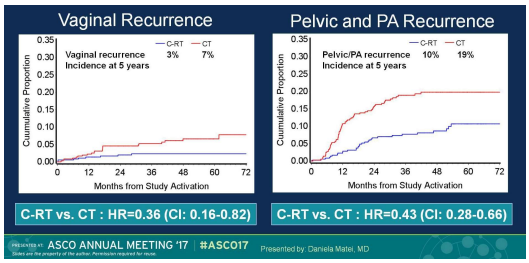
GOG 258
Trial Design



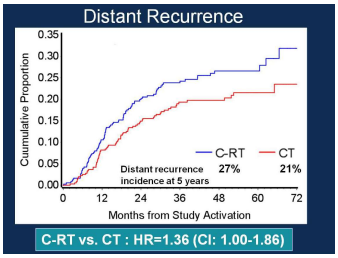
Primary Endpoint: Recurrence free survival
Secondary Endpoints: OS, AEs, QoL

NEJM 2019;380:2317-2326

GOG 258
Local Recurrence Rates

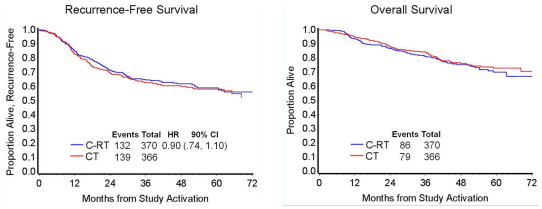


GOG 258
Distant Recurrence Rates



C-RT vs. CT : HR=1.36 (CI: 1.00-1.86)

GOG 258
Results



NEJM 2019;380:2317-2326

GOG 258
Conclusions

- Chemo-RT did not improve RFS compared to chemotherapy alone
- Chemo-RT reduced the incidence of vaginal, pelvic and para-aortic recurrences
- Distant recurrences were more common in the chemo-RT arm
- Survival data is not yet mature

- Management recommendations:
- Surgery followed by adjuvant therapy
  - Chemotherapy
  - Radiation can be considered to reduce local recurrence risk

Locregional disease summary

- Evidence support chemotherapy following bulk surgical reduction for stages III-IVa disease
  - Weight of evidence favors carboplatin/paclitaxel when metastatic studies are taken into account
- Role of radiation remains a question in local/regionally advanced disease
  - Current studies suggest this could be option
  - May help with local control
  - Further follow-up and survival data on GOG258 are needed before final conclusion

Disseminated disease

Treatment

Disseminated Disease

- Systemic treatment options
  - Hormone therapy (low grade)
  - Chemotherapy
  - Immunotherapy

Hormone therapy

- Low grade endometrioid histology
  - Grade 1, 2
  - Longer disease free intervals
  - ER/PR+
  - Asymptomatic/minimally symptomatic disease
- Progestins favored
  - Average response rate around 20%
  - Response correlate with grade and receptor status (highest in grade 1 with high ER/PR expression) RR 44%
    - Medroxyprogestersone acetate/tamoxifen (alternating)
    - Megestrol acetate/tamoxifem (alternating)
    - Progestational agents
    - Aromatase inhibitors
    - Tamoxifen
    - Fulvestrant

Chemotherapy

GOG 209

- Metastatic or recurrent endometrial cancer
- Non-inferiority study, 1381 women

Standard (TAP)	Experimental (TC)
Doxorubicin 45mg/m^2 D1	Carboplatin AUC6
Cisplatin 50mg/m^2 D1	Paclitaxel 175 (135) mg/m^2
Paclitaxel 160 mg/m^2 D2	

- TC not inferior to TAP (PFS and OS)
  - PFS @13m in each arm
  - ORR @ 51% in each arm
- Toxicity profile favors TC
- TC for now is the chemotherapy of choice for patients with advanced or recurrent endometrial carcinoma

Gynecol Oncol. 2012;1255:771.

Trastuzumab in uterine serous carcinomas

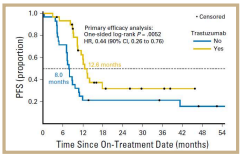
- Eligibility
  - High grade serous histology
  - Stage III; IV or recurrent HER2/neu positive disease
- Regimen
  - Carboplatin/paclitaxel +/- trastuzumab
- Enrollment:
  - 61 patients
    - Majority were adjuvant therapy
    - About 15% were recurrent disease

J Clin Oncology (2018) 36(20): 2044-2051

Metastatic endometrial cancer

Recent treatment changes

- Addition of trastuzumab to carboplatin and paclitaxel in high grade serous histology



Annals of Oncology (2019) 30 (suppl_5): v403-v434
J Clin Oncology (2018) 36(20): 2044-2051

Trastuzumab in UPSC

Population	Patients	PFS PC	PFS PCT	HR (CI)	P value
All	58	8.0 mos	12.6 mos	0.44 (0.26-0.76)	0.005
Stage III-IV	41	9.3 mos	17.9 mos	0.40 (0.20-0.80)	0.013
Recurrent	17	6.0 mos	9.2 mos	0.14 (0.04-0.53)	0.003

Updated OS: 24.2m versus 29.6 m (HR 0.58 (0.34-0.99) p= 0.0462)
- benefit restricted to the stage III/IV disease; not in recurrent disease, but underpowered

J Clin Oncology (2018) 36(20): 2044-2051
Clin Cancer Res; 26(10):2020

Endometrial Carcinoma

Targeted Therapy

- One randomized phase II trial suggests that the addition of trastuzumab to paclitaxel/carboplatin in HER2+ patients improves PFS.
- Bevacizumab can be considered

J Clin Oncol. 2011 29(16):2259-2265

Immunotherapy

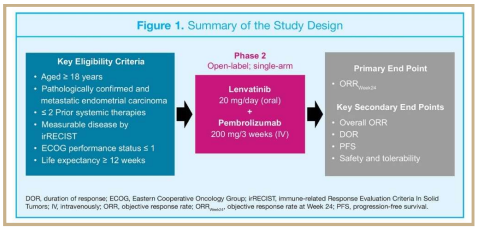
Pembrolizumab

MSI-H endometrial cancer

- FDA approval for Pembrolizumab for MSI-H tumors and MMR deficient tumors
- Pembrolizumab for MSI-high endometrial cancers
  - RR 57%
- Endometrial cancer has a pooled MSI-H/dMMR prevalence of about 26%
  - More common is endometrioid histology

Lorenzi et. al. J Oncol 2020

Study 111/KEYNOTE-146
Lenvatinib and Pembrolizumab



J of Clin Oncology 36(15) suppl 5596-5596, 2018
Lancet Oncology 20(5);711-718 2019

Study 111/KEYNOTE-146
Response

	Investigator review (n=53)	Independent review (n=53)
Objective response at week 24	21 (39·6%; 26·5–54·0)	24 (45·3%; 31·6–59·6)
Objective response at data cutoff	21 (39·6%; 26·5–54·0)	25 (47·2%; 33·3–61·4)
Best overall response		
Complete response	1 (1·9%)	3 (5·7%)
Partial response	20 (37·7%)	22 (41·5%)
Stable disease	25 (47·2%)	19 (35·8%)
Progressive disease	4 (7·5%)	5 (9·4%)
Unknown or not assessable	3 (5·7%)	4 (7·5%)
Median duration of response, months		
Median (95% CI)	NE (7·4–NE)	NE (5·8–NE)
Range*	1·2–23·4	1·2–23·4
IQR	7·4–NE	NE–NE
Proportion with responses ≥6 months	12 (83·0%; 55·9–94·2)	11 (79·3%; 48·5–92·9)
Proportion with responses ≥12 months	7 (64·5%; 32·8–84·2)	8 (79·3%; 48·5–92·9)
Median time to response, months (95% CI; IQR)	2·7 (1·3–2·8; 1·3–2·8)	2·6 (1·4–2·8; 1·4–3·7)

Data are n (%; 95% CI) or n (%), unless otherwise specified. NE=not estimable (because of an insufficient number of events at the data cutoff to estimate the median or upper limits of the 95% CI). *Some patients had ongoing responses.

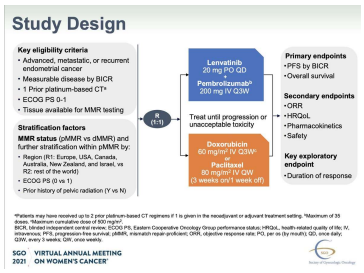
Table 2: Tumour responses as assessed by investigators or independent reviewers

J of Clin Oncology 36(15) suppl 5596-5596, 2018 ; Lancet Oncology 20(5);711-718 2019

FDA Accelerated Approval
Pembrolizumab and Lenvatinib

- September 17, 2019
- Advanced endometrial carcinoma that is not MSI-H or dMMR and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation

KEYNOTE-774/ Study 309
Schema

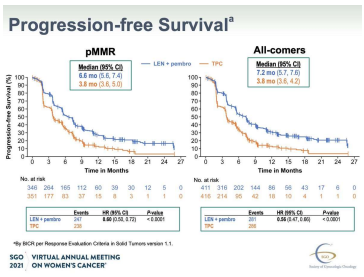


*Patients may have received up to 2 prior platinum-based CT regimens if 1 is given in the neoadjuvant or adjuvant treatment setting. †Maximum of 35 doses. ‡Maximum cumulative dose of 500 mg/m². BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; PFS, progression-free survival; pMMR, mismatch repair-proficient; ORR, objective response rate; PO, per os (by mouth); QD, once daily; Q3W, every 3 weeks; QW, once weekly.

SGO VIRTUAL ANNUAL MEETING 2021 ON WOMEN'S CANCER

Vicky Makker, MD; *SGO* 2021

KEYNOTE-774/ Study 309
Results

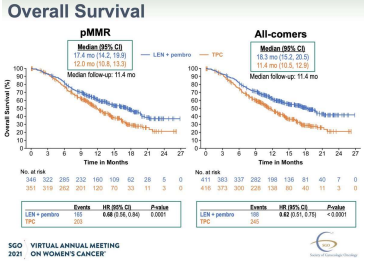


[a]By BICR per Response Evaluation Criteria in Solid Tumors version 1.1.

SGO VIRTUAL ANNUAL MEETING 2021 ON WOMEN'S CANCER

Vicky Makker, MD; SGO 2021

KEYNOTE-774/ Study 309
Results



SGO VIRTUAL ANNUAL MEETING 2021 ON WOMEN'S CANCER

Vicky Makker, MD; SGO 2021

KEYNOTE-774/ Study 309

Conclusions

- Phase III data support the rapid approval of lenvatinib and pembrolizumab in recurrent endometrial cancer
- Consider this option early for women with recurrent/metastatic endometrial cancer

Endometrial Carcinoma

Treatment by Disease Categories

- Locoregional disease
  - Low-risk disease: surgery
  - Intermediate-risk disease: surgery +/- vaginal radiation (? chemotherapy in stage II)
  - High-risk disease: surgery + chemotherapy (? radiation)
    - Consider trastuzumab in HER2 HGS histology
- Disseminated disease
  - Chemotherapy (paclitaxel/carboplatin)
  - Progestins in ER+PR+ patients (lower grade endometrioid)
  - Pembrolizumab MSI/dMMR (add lenvatinib if not)
  - Possible roles: bevacizumab, trastuzumab

Uterine sarcomas

Uterine Sarcomas

- Account for about 4% of uterine cancers
- Carcinosarcoma (Malignant Mixed Mullerian Tumor)
  - Metaplastic (dedifferentiated) carcinomas (biphasic histology)
  - Adjuvant chemotherapy even in early stage disease
    - Cisplatin/ifosfomide or ifosfomide/paclitaxel in the past
    - Carboplatin/paclitxel is not inferior to ifosfomide/paclitaxel
    - Carboplatin/paclitaxel now preferred regimen
  - Radiation often used in localized disease

J Clin Oncol. 2019;37S:ASCO #5500.

Leiomyosarcomas

- High risk cancer
  - 50-60% recurrence rate when limited to the uterus
- No adjuvant therapy in stage I or II
  - No benefit to pelvic radiation
  - No benefit to adjuvant doxorubicin
- Advanced disease after surgery
  - Adjuvant therapy debated
  - Clinical trials evaluating role of chemotherapy
- Metastatic disease
  - Gemcitabine and docetaxel
  - Doxorubicin, ifosfamide, gemcitabine

Endometrial stromal sarcoma

- Low grade tumors
- Express estrogen receptor
- Surgical management
- Hormone blockade
  - Consider post operative hormone blockade in more advanced stages
  - Hormone blockade in recurrent disease
  - Aromatase inhibitors preferred
  - Megestrol acetate/medroxyprogesterone

Uterine Sarcomas
Final Thoughts

- Carcinosarcomas are not sarcomas
  - Adjuvant therapy
    - Chemotherapy (carboplatin/paclitaxel)
    - Consider radiation therapy
- Uterine leiomyosarcomas
  - Very high recurrence risk
  - Surgical resection
  - Role of systemic therapy and radiation poorly understood
- Endometrial stromal sarcomas
  - Low grade
  - Surgery and hormonal modulation

THANK YOU