Gynecologic Oncology Tumour Board:

MSKCC and Cancer Institute (WIA), Chennai

5th August 2022
0530pm IST

Memorial Sloan Kettering Cancer Center

Cancer Institute (WIA)
Adyar, Chennai

Dr Jayashree N,
MS, Fellowship in Gyn onco, MCh
Gynaecologic Oncologist

Dr P K Jayachandran,
MD, DM, FRCP
Medical Oncologist

Dr Kanchan M, MD
Onco Pathologist

Dr Pushkala S, MS
Senior Resident,
Surgical Oncology

Clinical History

- 27 year nullipara , married for 18 months , anxious to conceive
- Under evaluation of infertility for 6 months, taken drugs for ovulation induction 4 months back
- Had regular menstrual cycles with moderate flow, no dysmenorrhea
- She had painful micturition , vague pain in lower abdomen
- Underwent Ultrasound , (complex right ovarian mass, raised Ca 125)
- She was referred to us for further evaluation –RMI 249
- No known comorbid illness / surgeries in the past
- No family history of malignancy

Clinical Examination

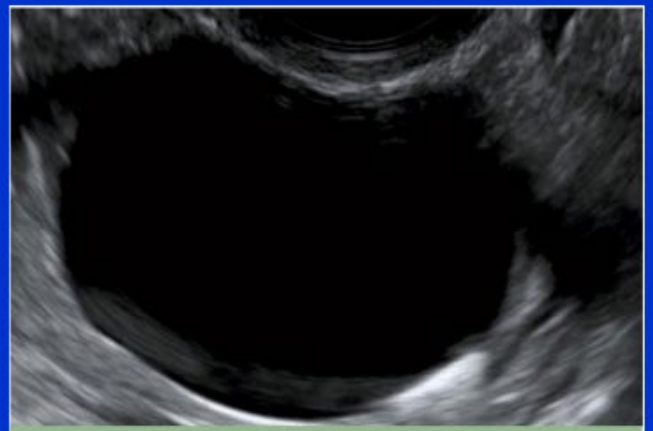
- WHO performance status -1
- No pallor or pedal edema
- No palpable cervical / axillary / inguinal nodes
- Breast examination normal
- On per abdomen examination no mass, ascites or organomegaly
- Pelvic exam – cervix normal, uterus normal in size , anteverted, 6 cm mass palpable through right and posterior fornix. Rectal mucosa free.

Investigations

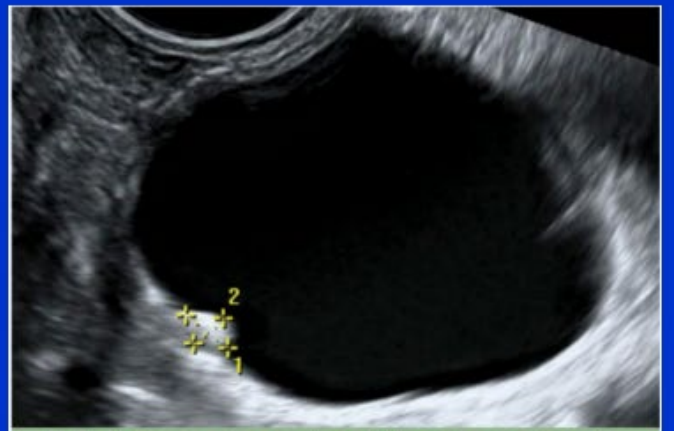
- Hematological and biochemical parameters – WNL (including Hb / albumin)

- Tumor markers:
  - Serum AFP – 5.2 ng/mL
  - Serum CEA – 1.5 ng/mL
  - Serum Ca 125 – 83.2 U/mL

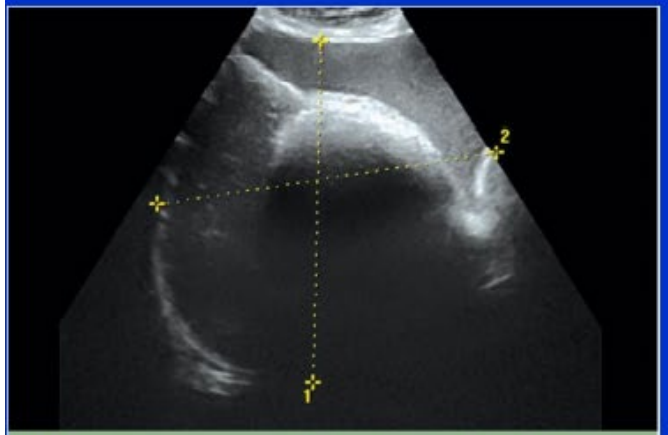
Using IOTA a mass is classified as **benign** if at **least one B-Feature is present** and no M-features are present.



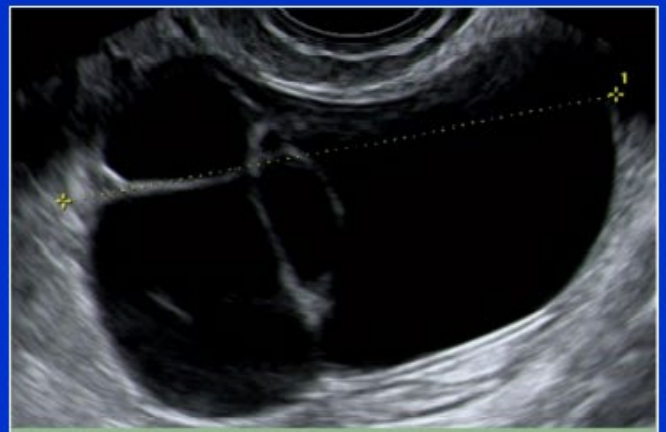
B1: Unilocular cyst



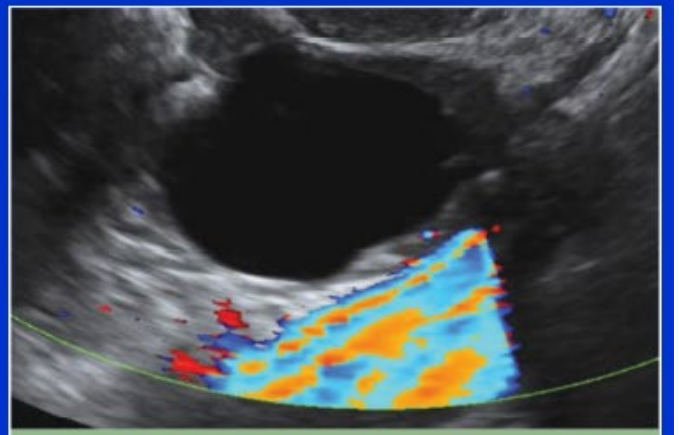
B2: Presence of solid components, with largest diameter < 7 mm



B3: Presence of acoustic shadows

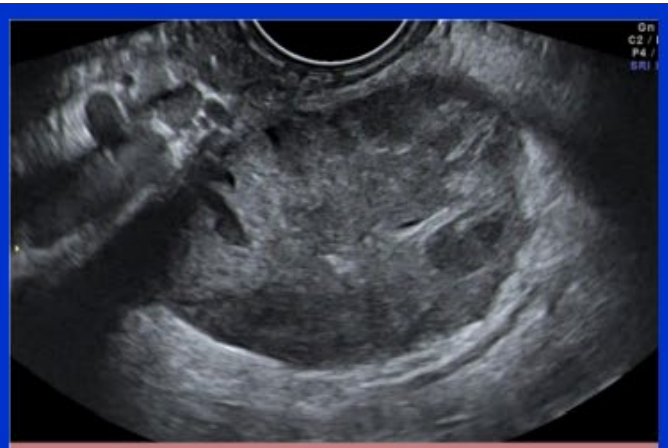


B4: Smooth multilocular tumor, with largest diameter < 100 mm

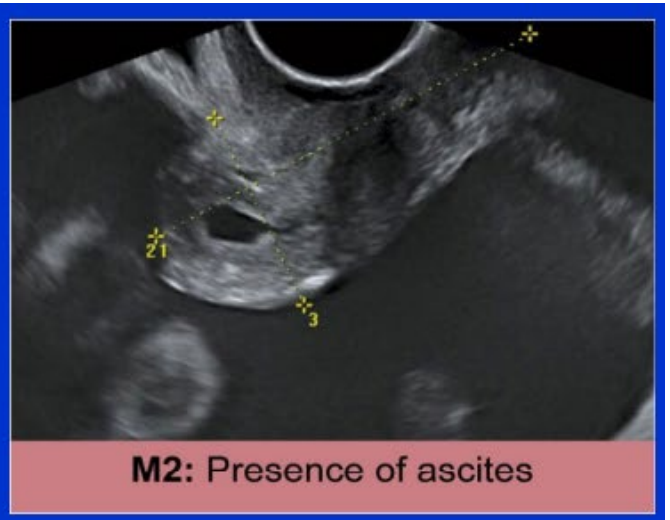


B5: No blood flow (color score 1)

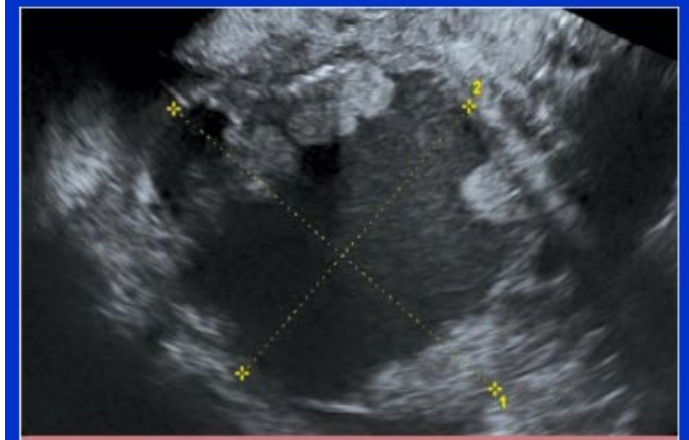
Using **IOTA** Rules a mass is classified as **malignant if at least one M-feature is present** and no B-features are present.



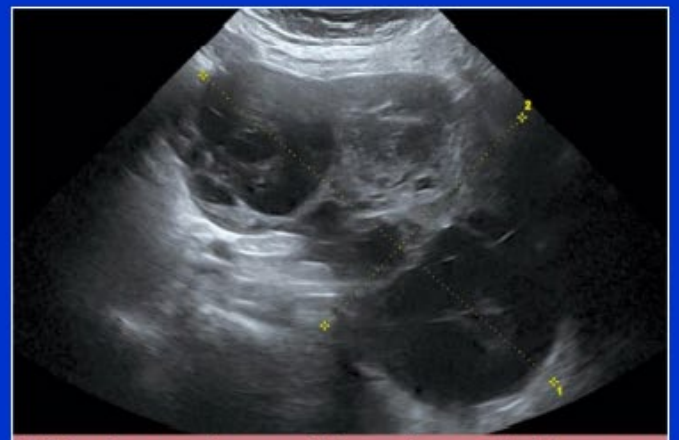
M1: Irregular solid tumor



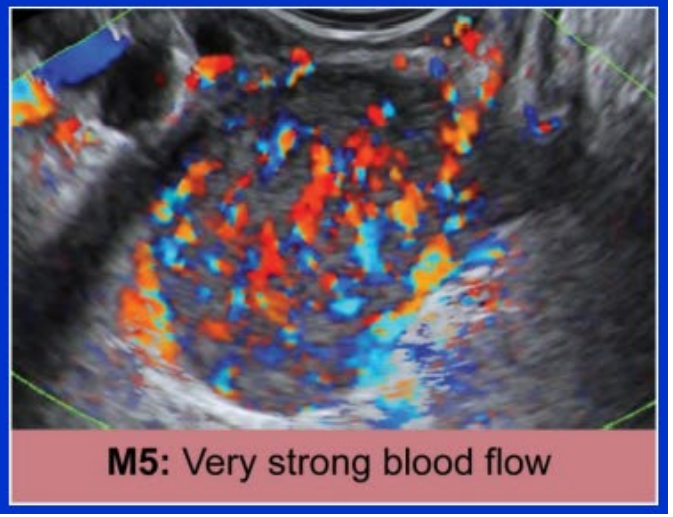
M2: Presence of ascites



M3: At least four papillary structures



M4: Irregular multilocular solid tumor with largest diameter ≥ 100 mm



M5: Very strong blood flow

Ultrasound Pelvis (TVS):

- Uterus and cervix normal.
- Right ovary enlarged 6 x 5 x 4 cm with
- multiloculated cystic mass with solid irregular intramural nodules
- showing increased internal vascularity, M5
- Left ovary measures 3 x 2cm appears normal
- Mild ascites. M2

- IOTA – M2, M5

Risk of Malignancy index

Risk of malignancy index (RMI) = ultrasound findings x menopause status x Ca125 (U/ml)

Findings	Points
Ultrasound findings include: • multilocular cyst • solid area • metastases • ascites • bilateral lesions	0 points: no features (unilocular) 1 point: 1 feature 3 points: 2–5 features
Menopausal status	1 point – premenopausal
	3 points – postmenopausal*
Ca125 (U/ml)	Actual level

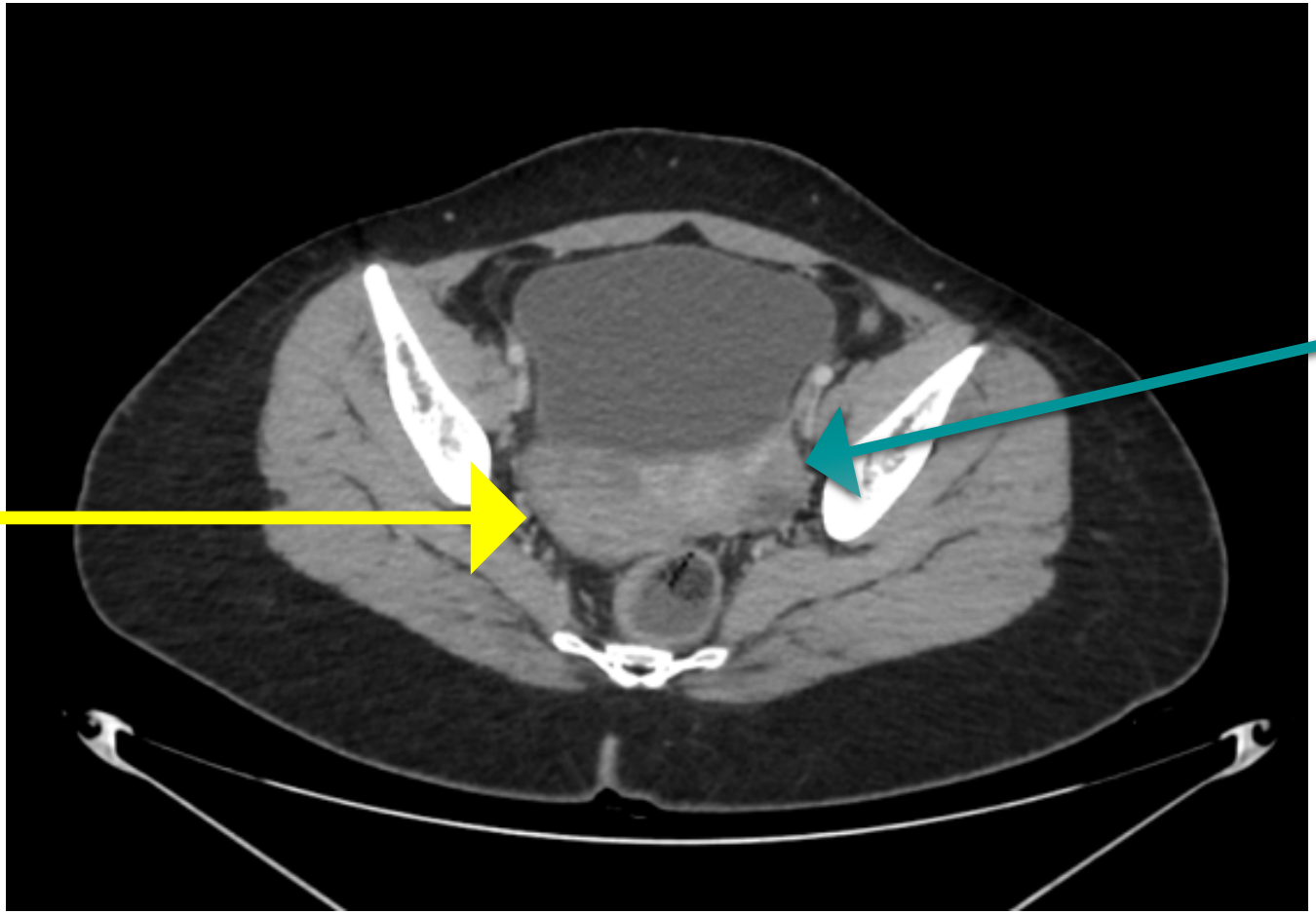
RMI = 3 x 1 x 83 = 249

- **If a cut off value of 200 is used to discriminate benign from malignant ovarian masses,**
- **There is a good correlation, with a sensitivity of 87% and a specificity of 97%.**

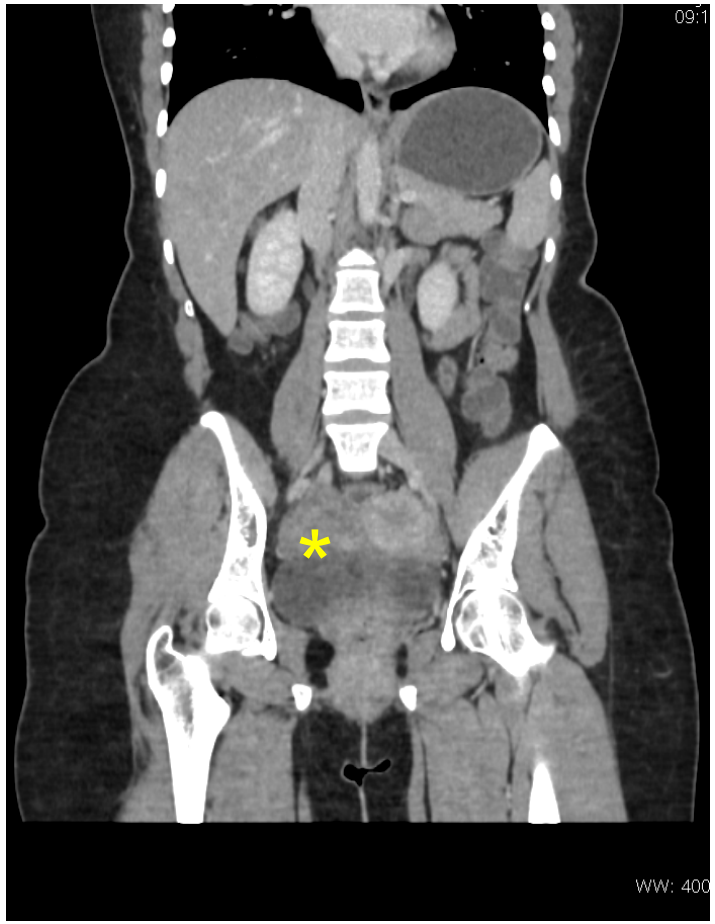
Jacobs et al Br J O bstet Gynaecol 1990 : 97 : 922-9

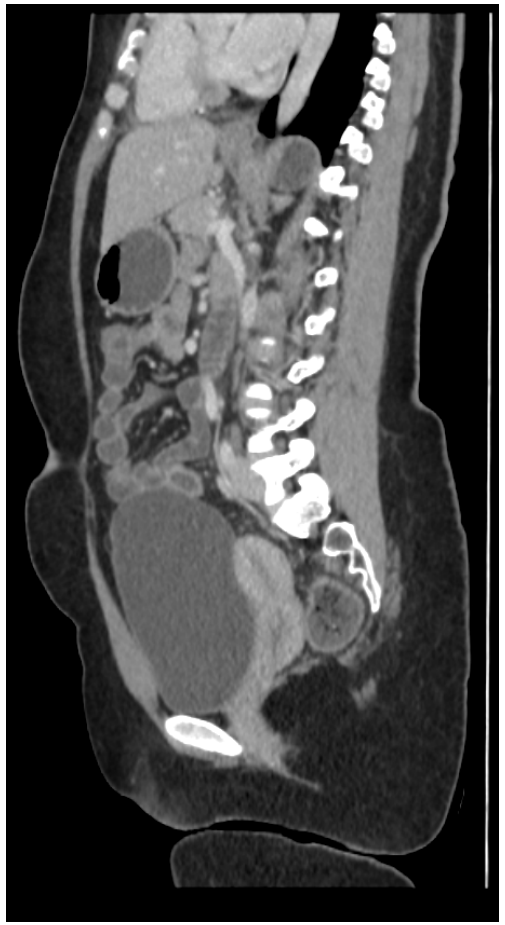
CECT Abdomen and Pelvis

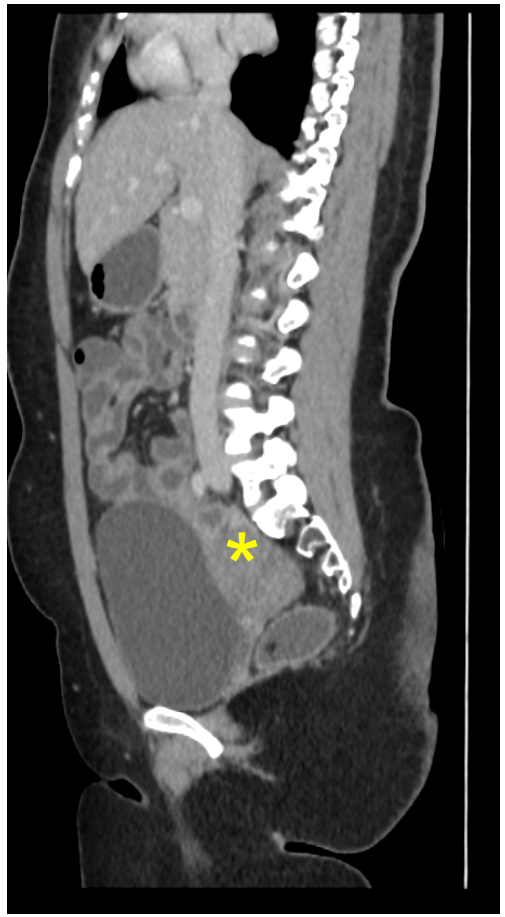
Image



CECT Abdomen and Pelvis







Poll Question

Patient is concerned about her fertility. She is requesting for minimal invasive surgery.

1. Can this patient be operated laparoscopically?
   a) Yes b) No c) Maybe

2. Can fertility preserving surgery offered to this patient?
   a) Yes b) No c) Maybe

Findings on Diagnostic Laparoscopy

- Ascites ~ 200 ml, clear
- Right ovarian mass 7 x 6 x 6 cm, with papillary clusters
- Left ovary grossly normal with 1 x 1 cm surface deposit
- POD deposit measuring 3 x 4 cm
- UV pouch deposit measuring 2 x 1 cm
- Omentum grossly normal
- Few enlarged Right pelvic nodes
- Multiple sub centimetric nodules present over Right sub-diaphragm

Poll Question

1. Can fertility preserving surgery offered to this patient?
   a) Yes b) No c) Maybe

2. Can frozen section help in deciding the extent of surgery?
   a) Yes b) No c) Maybe

Frozen Section Report

Right ovarian tumour – Serous borderline tumour

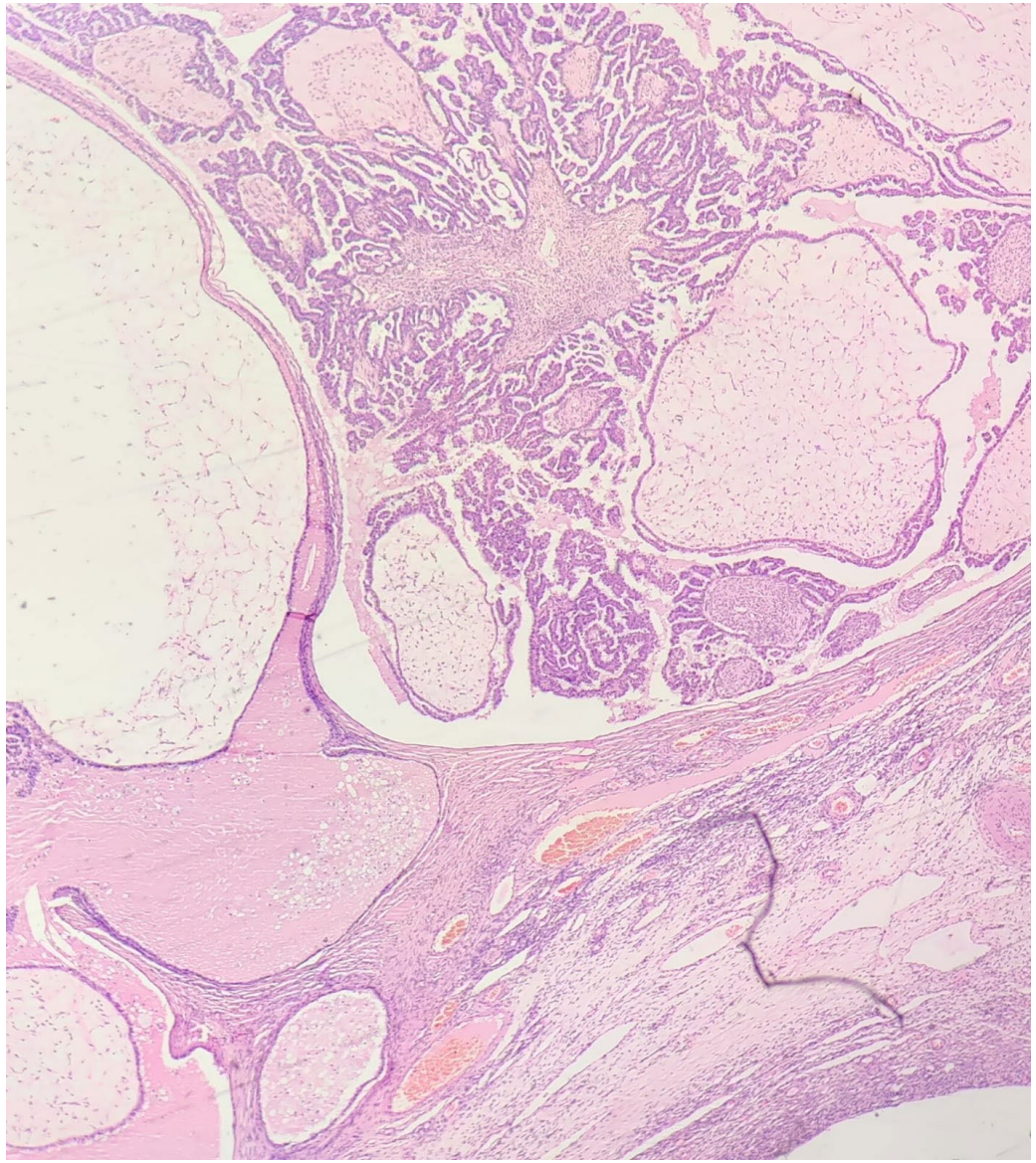
Surgery done

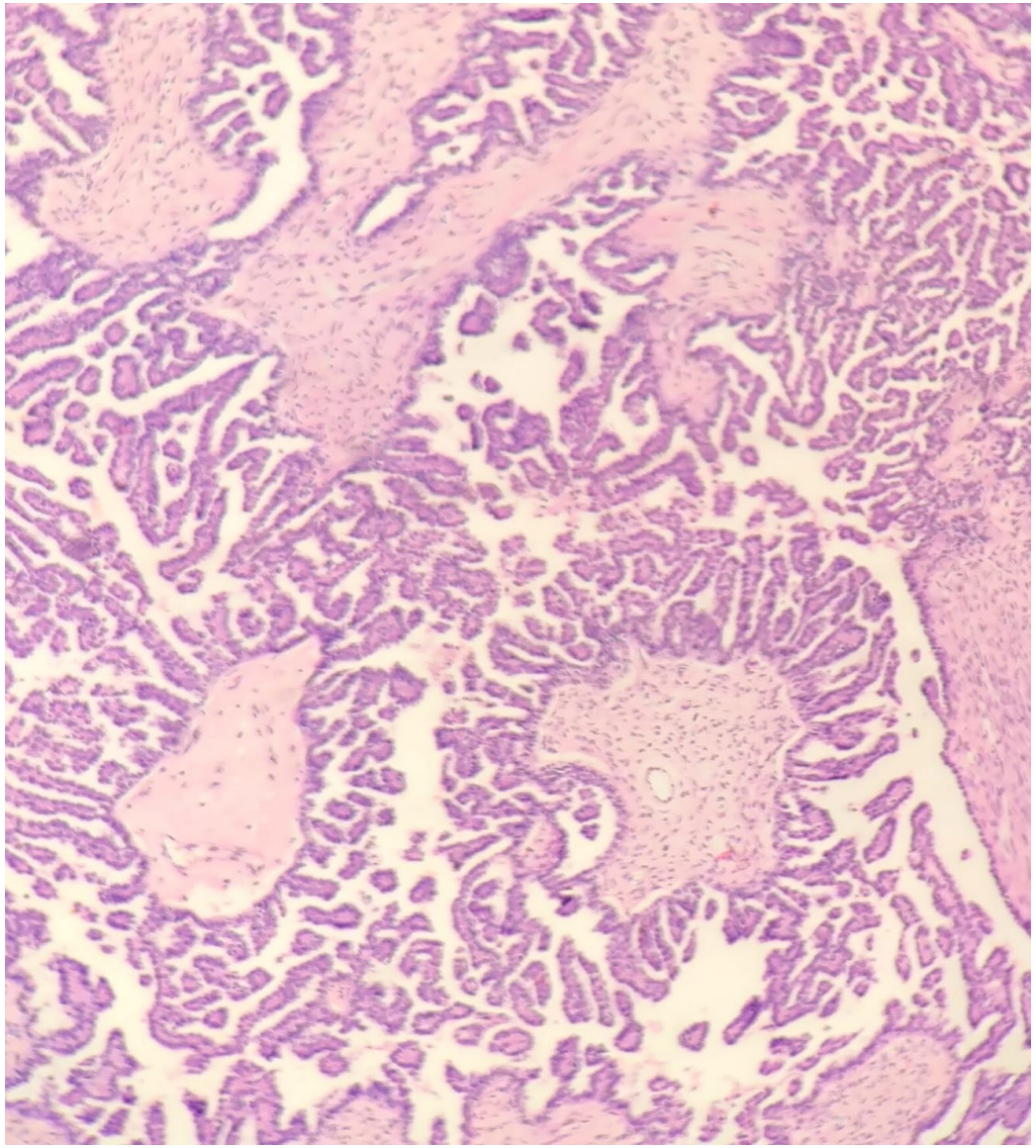
Right Salphingo oophorectomy , left ovarian surface deposit excision , infracolic omentectomy , right subdiaphragmatic peritonectomy , right pelvic lymph node dissection and paraaortic lymph node sampling

Histopathological examination report

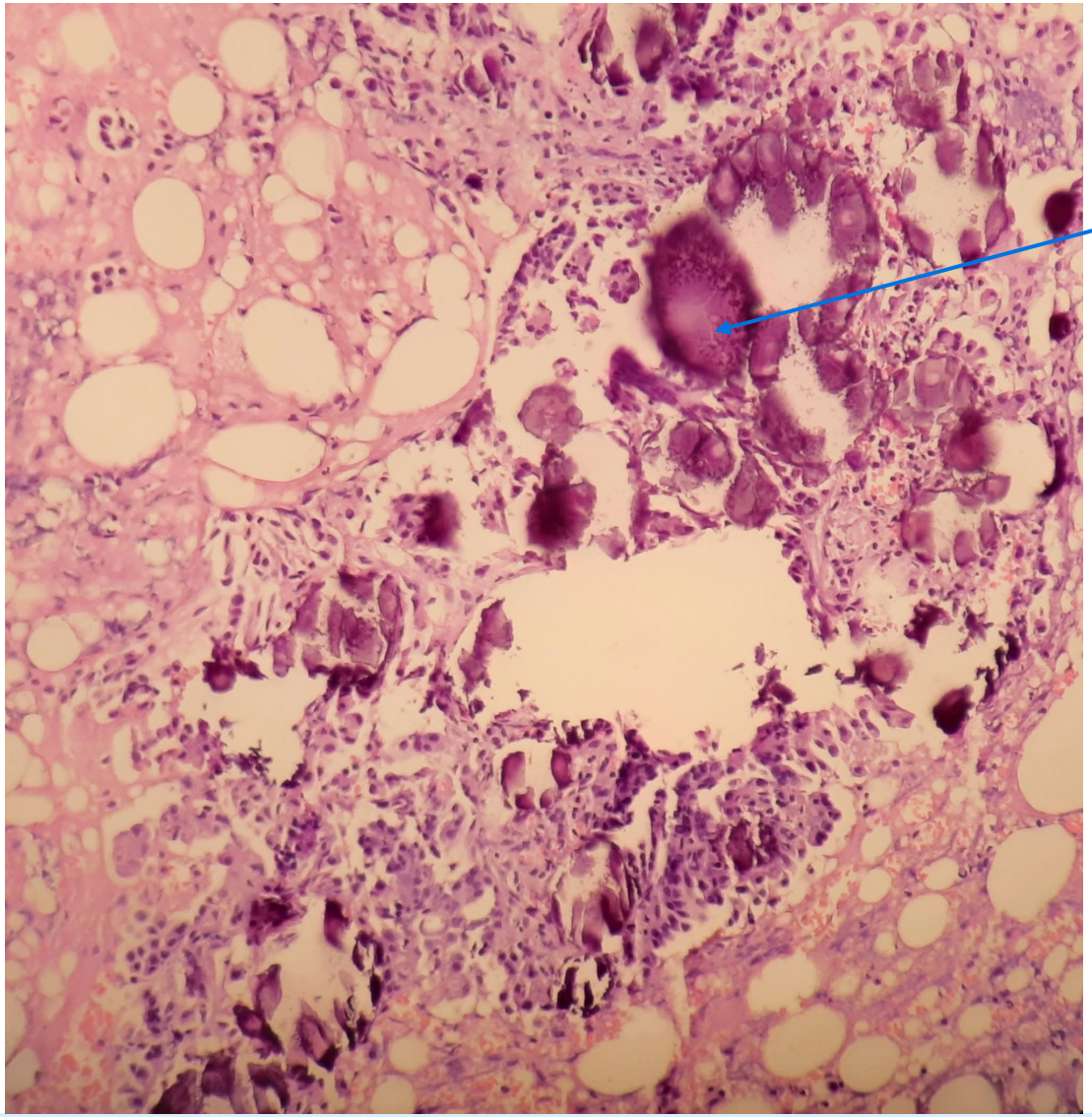
- Right ovary – serous borderline tumour (micropapillary type) 10 x 7 x 3 cm
- Left ovarian surface – shows non invasive tumour deposit 0.8 cm
- Subdiaphragmatic nodules and POD peritoneum shows non-invasive epithelial implants
- One Right pelvic node shows involvement by serous borderline tumour in subcapsular sinus
- Omentum, bladder peritoneum, falciform ligament – free of tumour
- Paraaortic nodes – Free of tumor

Serous borderline tumour (micropapillary)



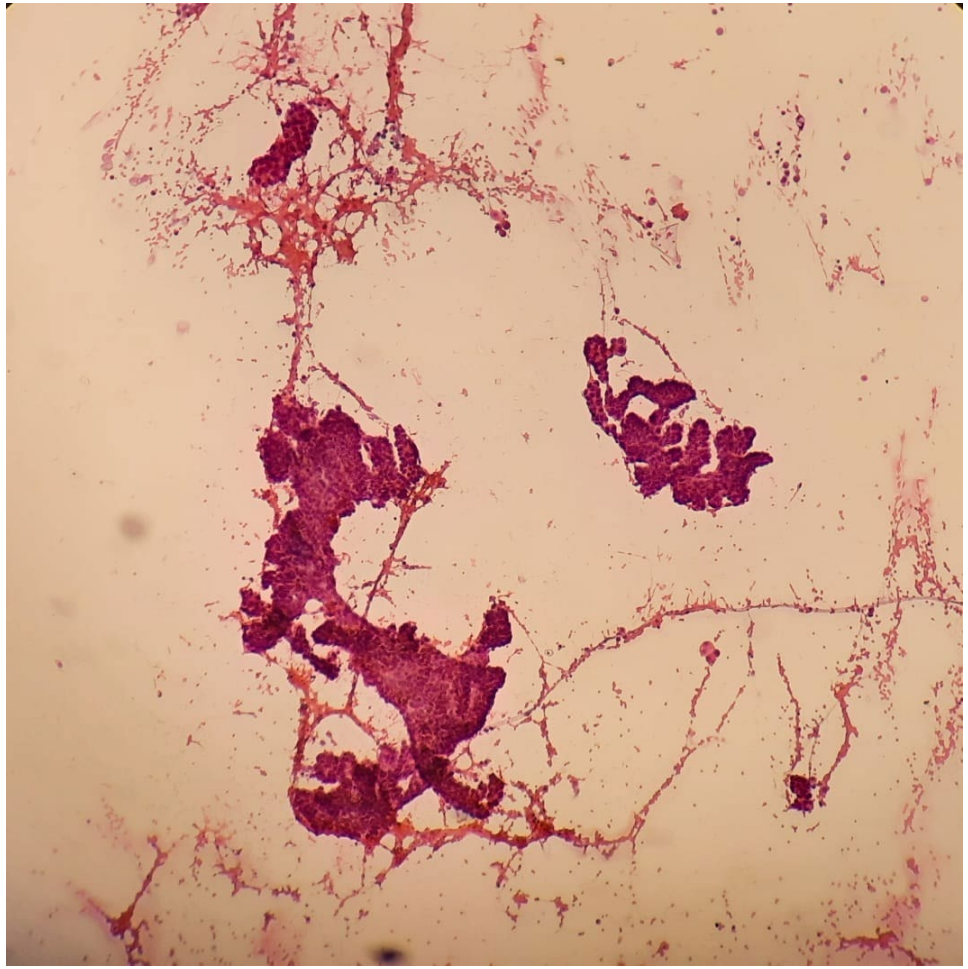


Non invasive epithelial implant

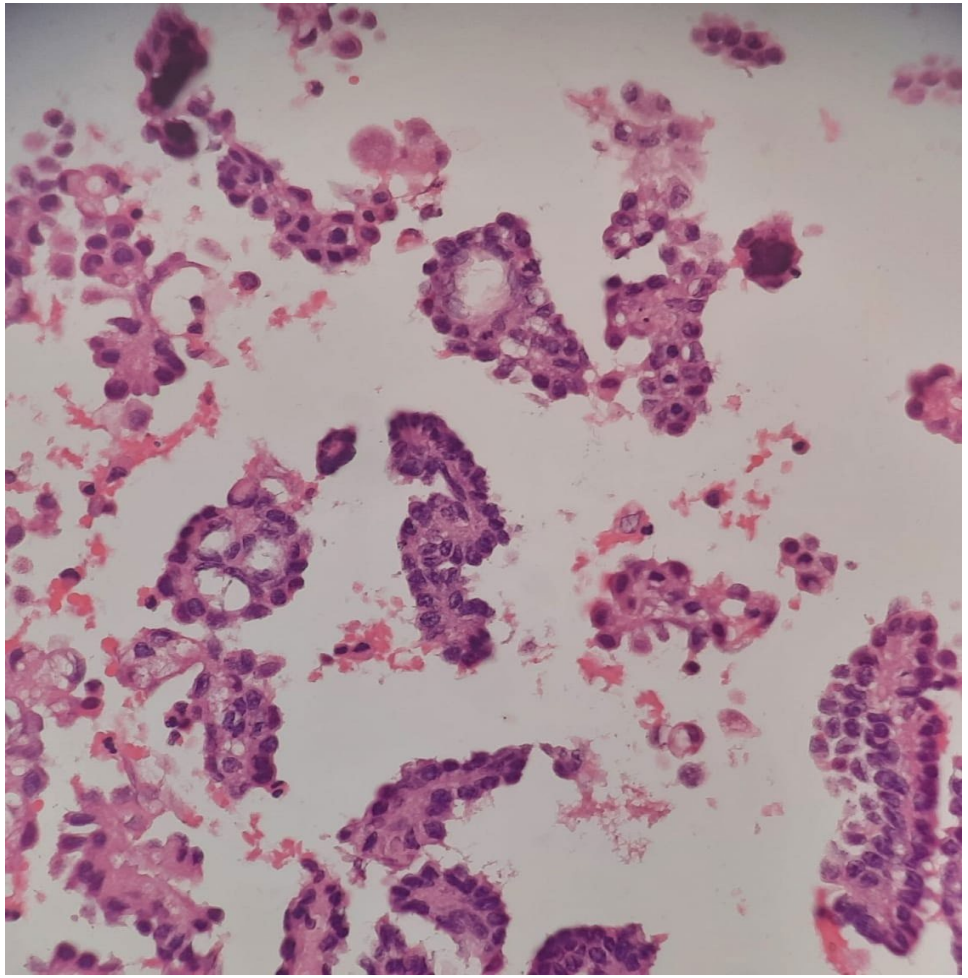


Psammomatous Calcification

Ascitic fluid cytology Positive for neoplastic cells



Fluid Smear



Cell block

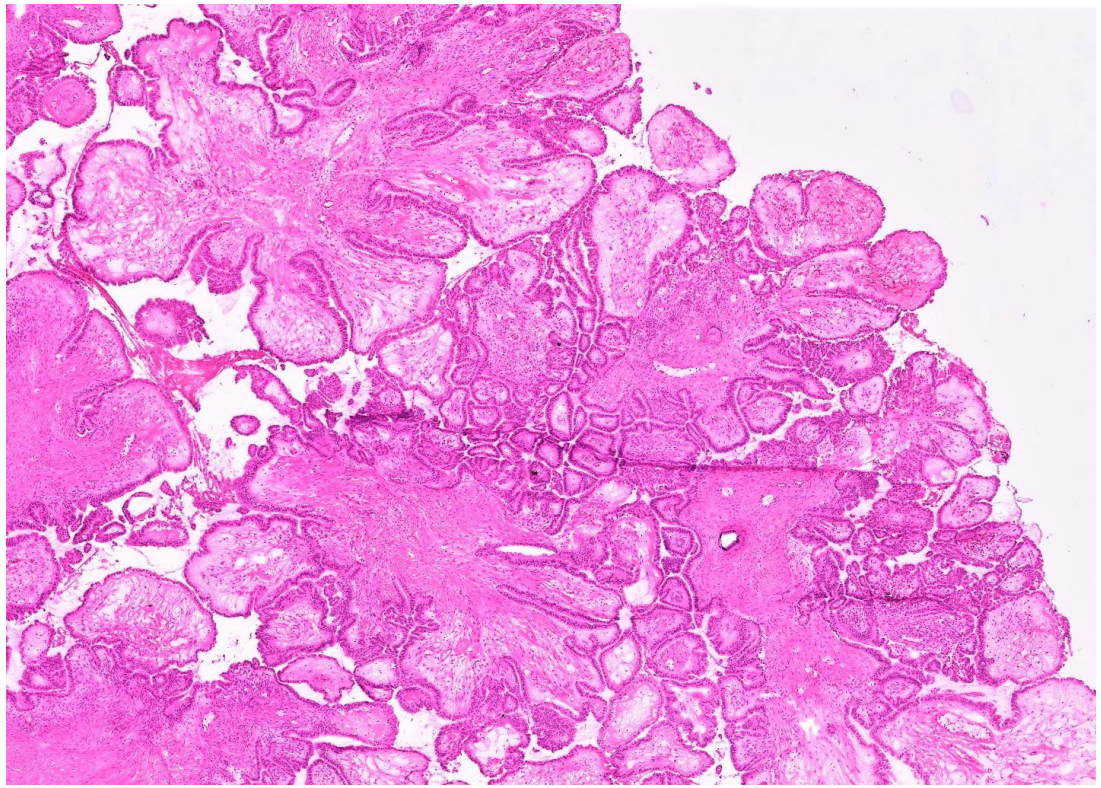
Poll question

1. With frozen section report suggestive of Serous borderline tumour does lymphadenectomy need to be done?
   a) Yes b) No c) Maybe

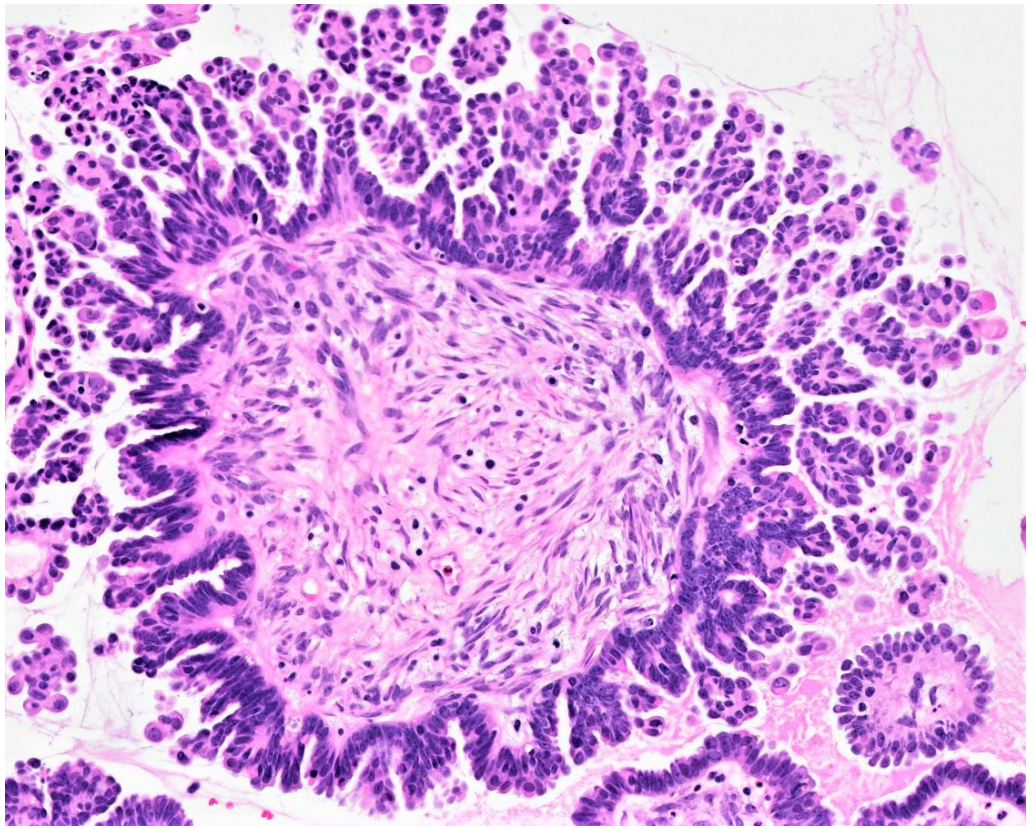
2. Does this patient need chemotherapy?
   a) Yes b) No c) Maybe

Conventional SBT Vs Micropapillary SBT

- Hierarchical branching



- Medusa Head



On follow-up

After a DFI of 30 months , while on follow-up, patient had symptoms of pain abdomen and difficulty while passing stools. Serum Ca 125 – 56.2U/ml.

CECT abdomen and pelvis suggestive of mass in the paracolic region near caecum measuring 5 x 4cm , another mass in the pelvis measuring 4 x 3 cm abutting rectum and left ureter.

Poll question

Patient was advised for surgery.

1. Patient requests for fertility preservation during surgery, can we offer her fertility preservation?

   a) Yes b) No c) Maybe

2. Is there a role for adjuvant chemotherapy / hormonal therapy in this scenario?

   a) Yes b) No c) Maybe

Fertility Preservation in Women with Ovarian Tumour

Dr Jayashree Natarajan

Gyn Oncologist

Cancer Institute (WIA), Adyar, Chennai

Outline

- Introduction
- Factors determining fertility preservation in gynaecological malignancies
- Fertility sparing surgeries in patients with
  - Borderline ovarian tumours
  - Epithelial ovarian tumours
  - Germ cell tumours
  - Sex cord stromal tumours
  - Pregnancy with ovarian tumours

BURDEN OF PROBLEM

- Of the 6.6 million cancers occurring worldwide in the female population, 1.09 million (16%) affect the female genital organs

- Up 20% will be diagnosed in women of reproductive age.

  -15-45% of cervical cancers

  - 5-29% of endometrial cancers

  -12-34% of primary ovarian malignancies

will be found in women eligible for fertility preservation.

Martinelli F et al., Fertility Sparing Options in Gynecologic Oncology. Trends Gynecol Oncol. 2016;1(1): e101.

Over arching questions to be considered

- Does the cancer patient desire interventions to preserve fertility?
- What is the quality of evidence supporting current and forthcoming options for preservation of fertility in females?
- What is the role of the oncologist in advising patients about fertility preservation options?

Loren AW et al, J Clin Oncol, 2013

Criteria for Fertility Preservation

- Age, marital status, time available
- Desire to preserve fertility with pre-treatment counselling
- Tumour factor – histopathological type/ grade/ depth of invasion/ stage/ risk of recurrence
- Pre-operative evaluation
- Willingness to follow-up
- Appropriate follow-up protocol

Needs

- Appropriate team to counsel
- Multiple sessions
- Discussion in tumour board
- Documentation

BORDERLINE OVARIAN TUMOURS

- Fertility sparing surgery (FSS) can be done at any stage
- Unilateral /bilateral cystectomy or unilateral oophorectomy with cystectomy on other ovary or USO with peritoneal staging
- Careful inspection of other side ovary
- Biopsy from other ovary – risk of infertility 14%
- Risk of recurrence
  - Cystectomy – 30%; USO- 11%; BSO -7% ; HBSO-1.7%

Interventions for treatment of borderline ovarin tumours(review). The Cochrane collaboration:the Cochrane library 2019; issue 9.

BORDERLINE TUMOURS

- Fertility and subsequent treatment depends on
  - Stage
  - Histology of tumour

	Pregnancy Rate	Risk of lethal recurrence
Early stage	54%	0.5%
Advanced stage	34%	2%

Emile D et al., Human Reproduction Update. 2013;19(2):151–166.

CONSERVATIVE VS RADICAL SURGERY IN BOT

- Zanetta et al., study with 189 patients undergoing conservative treatment and 150 undergoing radical surgery

	Surgery	Recurrence	DFS
Stage I n=283 (83%)	Conservative	15%	99%
	Radical	2.5%	100%
Stage II-III n=36 (47%)	Conservative	40%	100%
	Radical	13%	85%

Zanetta G et al,. J clin oncol. 2001; 19(10):2658-64

Review

Conservative surgery in ovarian borderline tumours: A meta-analysis with emphasis on recurrence risk

Conclusion:

- Cystectomy in unilateral serous BOT - higher recurrence rate- no impact on survival
- USO is advisable in the case of mucinous BOT.
- Bilateral BOT (almost always serous) - More conservative approach (BC)

Vasconcelos I et al., European J Cancer.2015;51(5):620-631

Epithelial Ovarian Cancers

- Primarily a disease of post menopausal women
- Incidence in reproductive age group – 3-17%
- In women less than 35 years 7-8 % stage I
- Factors influencing outcomes of FSS
- stage
- grade
- histology
- completeness of staging

Outcomes of Fertility-Sparing Surgery for Stage I Epithelial Ovarian Cancer: A Proposal for Patient Selection

- N= 211 patients (stage IA, n 126; stage IC, n 85) from 30 institutions.
- Median duration of follow-up - 78 months.
- Five-year overall survival and recurrence-free survival :-

	Stage IA			Stage IC		
	Favorable Histology	Clear cell ca	Grade 3	Favorable Histology	Clear cell ca	Grade 3
OS	100%	100%	100%	96.9%	93.3%	66.7%
RFS	97.8%	100%	33.3%	92.1%	66.0%	66.7%

- 45/84 (53.6%) - nulliparous at FSS and married at the time of investigation gave birth to 56 healthy children.

Satoh T et al., J Clin Oncol.2010; 28:1727-1732.

Oncofertility in patients with stage I epithelial ovarian cancer: fertility-sparing surgery in young women of reproductive age

- N=108 stage I Epithelial ovarian ca patients
- Median follow up – 83months
- grade 3 or clear cell carcinoma are the independent risk factors for recurrence, has endometriosis in background and undergo radical surgery
- FSS did not affect DFS or OS among patients with stage I EOC and high risk patients with stage IC2-3, grade 3 or clear cell carcinoma
- 32 out of 52 (65.4%) attempted to get pregnant,

  28 (82.4%) achieve successful pregnancy and delivery

Jiang X et al., World J Surg Oncol. 2017; 15:154

Long-term results of fertility-sparing treatment compared with standard radical surgery for early-stage epithelial ovarian cancer

- N=1031 patients from 2 institutions
- 242 underwent FSS, 789 underwent radical surgery
- Median duration of follow up 11.9 years
- No role of FSS with Recurrence free interval or cancer specific survival.
- Tumour grade poor prognostic factor for recurrence free survival and cancer free survival
- Low grade tumour and young age are good prognostic factors

Frusio R et al., British J Cancer.2016;115: 641-648

Epithelial Ovarian Cancers

Recommendation for fertility sparing surgery in young patients with unilateral stage I ovarian cancer – ASCO 2010

Stage	Favourable histology	Clear cell histology	Grade 3
IA	FSS	FSS + Adjuvant chemotherapy	NO FSS
IC	FSS + Adjuvant chemotherapy	NO FSS	NO FSS

Favourable histology-
(non-clear cell histology grade 1/2)

- Serous
- Mucinous
- Endometrioid
- Mixed

Germ Cell Tumours of Ovary

Malignant GCT overall incidence 5%

More than 80% cases occur in women less than 30years

50 -70 % occur in stage I, bilaterality rare.

Dysgerminoma better DFS /less risk of recurrence other than other MOGCTS.

Meisel JL et al,Gynecol Oncol. 2015
Cicin I et al,Am J Clin Oncol. 2009

GERM CELL TUMOUR OF OVARY

- Malignant GCT overall incidence -5% of ovarian malignant neoplasm
- More than 80 % occur in women less than 30 years
- 50-70% occur in stage I
- Bilateral disease - in 10 to 12 percent of cases. (propensity for bilateralilty- benign cystic teratoma, dysgerminoma, or a tumor with components of dysgerminoma)

Tewari K, et al., Obstet Gynecol. 2000;95:128.
Seigel RL, et al., Ca Cancer J Clin. 2016;16:66:7.

Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors: a multicenter study

Satoshi Tamauchi, MD; Hiroaki Kajiyama, MD, PhD; Masato Yoshihara, MD; Yoshiki Ikeda, MD; Nobuhisa Yoshikawa, MD, PhD; Kimihiro Nishino, MD, PhD; Fumi Utsumi, MD, PhD; Kaoru Niimi, MD, PhD; Shiro Suzuki, MD, PhD; Fumitaka Kikkawa, MD, PhD

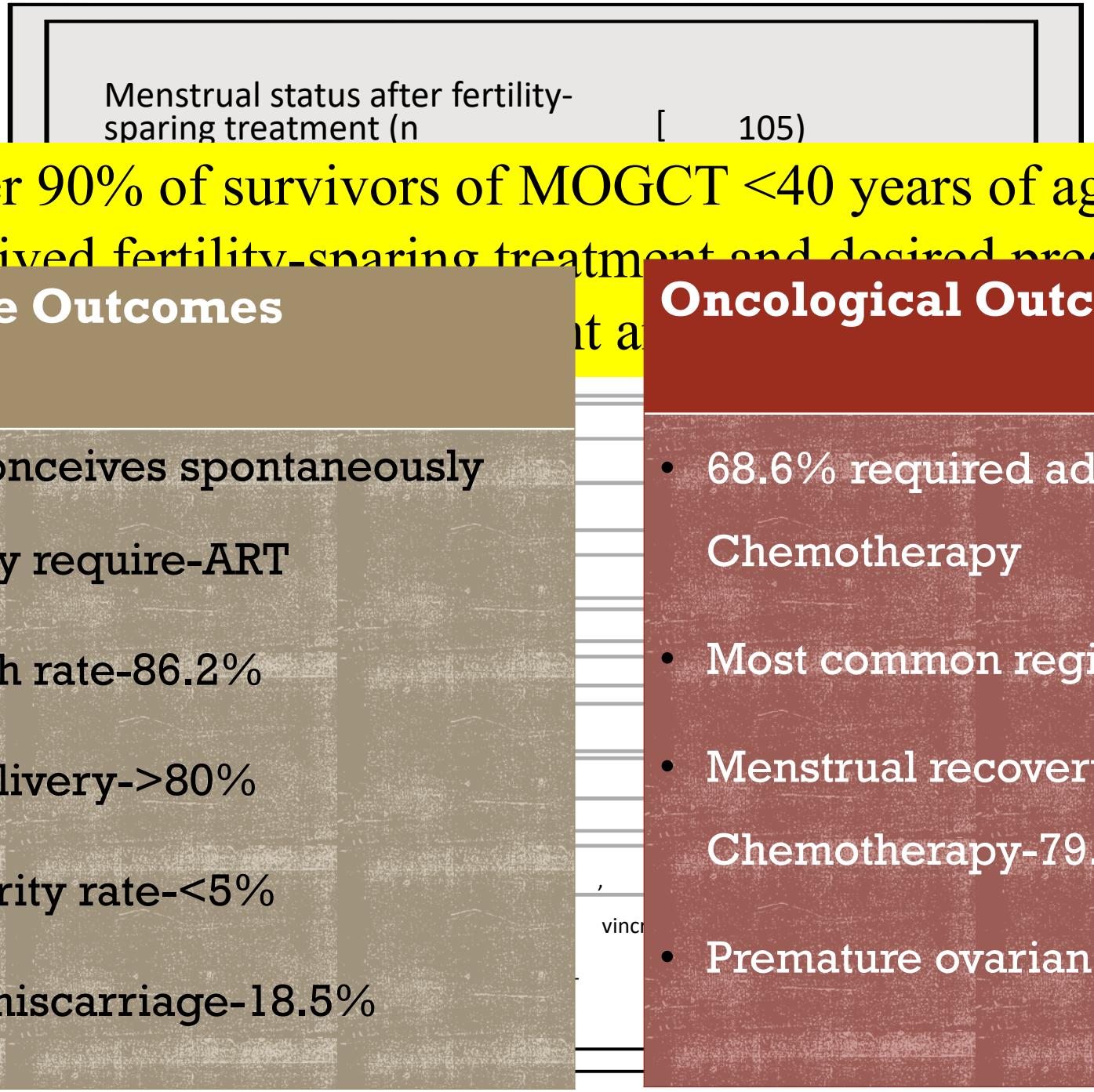
- 105 MOGCT patients who has undergone FSS
- 1966-2016
- 42 /45 patients pregnant.
- Total number of pregnancies – 65
- 56 babies were born to 40 survivors

Tamauchi S et al., Am J Obstet Gynecol. 2018;19(4):385:e1-e7.

Backgrounds of patients who gave birth (n = 40)

Median age at FST, y (range)	25.1 (11.2—32.8)
Median age at first pregnancy after FST, y (range)	30.1 (22.1—40.0)
Median duration from FST to first delivery, y (range)	4.4 (1.3—19.2)
Married at FST	2.8 (1.3—5.9)
Unmarried at FST	6.6 (2.0—19.2)
Histological type, n (%)	
IMT	20 (50.0)
YST	10 (25.0)
DYS	12 (30.0)
FIGO stage, n (%)	
I	34 (85.0)
II	3 (7.5)
III	5 (12.5)
IV	0 (0.0)
Adjuvant chemotherapy, n (%)	30 (75.0)
BEP	20 (50.0)
PVB	7 (17.5)
PVAC/VAC	3 (7.5)
Pregnancy after recurrent MOGCT	2 (5.0)

BEP, bleomycin/etoposide/cisplatin; *DYS*, dysgerminoma; *FIGO*, International Federation of Gynecology and Obstetrics; *FST*, fertility-sparing treatment; *IMT*, immature teratoma; *MOGCT*, malignant ovarian germ cell tumor; *PVAC*, cisplatin/vincristine/actinomycin D/cyclophosphamide; *PVB*, cisplatin/vinblastine/bleomycin; *VAC*, vincristine/actinomycin D/cyclophosphamide; *YST*, yolk sac tumor.



Over 90% of survivors of MOGCT <40 years of age who received fertility-sparing treatment and desired pregnancy

Reproductive Outcomes

- >90% conceives spontaneously
- <5% may require-ART
- Live birth rate-86.2%
- Term delivery->80%
- Prematurity rate-<5%
- Rate of miscarriage-18.5%

Oncological Outcomes

- 68.6% required adjuvant Chemotherapy
- Most common regimen used-BEP
- Menstrual recovery after Chemotherapy-79.2%
- Premature ovarian failure-2.9%

NACT IN GERM CELL TUMOUR

- 23 patients received NACT (Jan 88- Dec 2009)
- Median age was 19 years (14-28 years)
- FIGO stages III - 20 and IV - 3. Histology subtypes were: dysgerminoma, n = 14, mixed GCT, n=6 and 3 had endodermal sinus tumor.
- Following NACT - 21 patients responded
  - CR – 16; PR – 5; PD -1; lost to follow u after 2 cycles -2
- 18 of 21 responders underwent surgery
  - ; 13/18 had pathological CR
- 21 of 23 patients are alive and disease-free at a median follow-up of 74 months.
- 18/21 patients have resumed menstruation and 10 eligible patients have delivered 13 full term healthy babies.

Talukdar S et al., Gynecol Oncol. 2014;132(1):28-32.

MALIGNANT SEX CORD STROMAL TUMOURS

- Most sex cord stromal tumours are stage I
- Less than 5% are bilateral
- Uterine tumours may be coexisting – needs uterine evaluation before planning for FSS
- USO is optimal for fertility preservation
- If bilateral USO with cystectomy can be offered
- Routine PLND not mandatory

Brown J et al , Gynecol Oncol,2009

Analysis of oncologic and reproductive outcomes after fertility-sparing surgery in apparent stage I adult ovarian granulosa cell tumors

- **N=** 113 (FSS -61; 52 - radical surgery)
- Median follow-up of 99.2 months (range 20.2-394.3 months),
- 30 patients had recurrent disease (17 in the FSS group and 13 in the radical surgery group)
- No difference in disease-free survival between the groups who underwent FSS or radical surgery (P = 0.550).
- In FSS group, incomplete staging was significantly associated with the risk of recurrence (P = 0.024).
- Of the 22 patients desiring pregnancy, 19 achieved 20 singleton pregnancies.
- Pregnancy rate was 86.4% and the live birth rate was 95%.

Wang D et al., Gynecol Oncol. 2018 Nov;151(2):275-281.

Timelines in patients undergoing FSS

Prechemo

ovarian function asessment

During Chemotherapy

GNRH analogue with add back therapy

Postchemotherpy surveillance of ovarian function – AMH 6months post chemo

Planning /ART if required for pregnancy

Or

Oocyte cryopreservation

TO SUMMARISE

- "FERTILITY without compromising CURABILITY" should be the goal
- FSS options depends on stage / histology / grade
- Patient should be aware of the available options and understand the outcomes

Recurrent Low-Grade Serous Ovarian Cancer

Presented by Ryan M. Kahn, MD MHS

Memorial Sloan Kettering Cancer Center

Cancer Institute (WIA)
Chennai

Sarah Chiang, MD
Gynecologic Pathologist

Rachel Grisham, MD
Gynecologic Medical Oncology

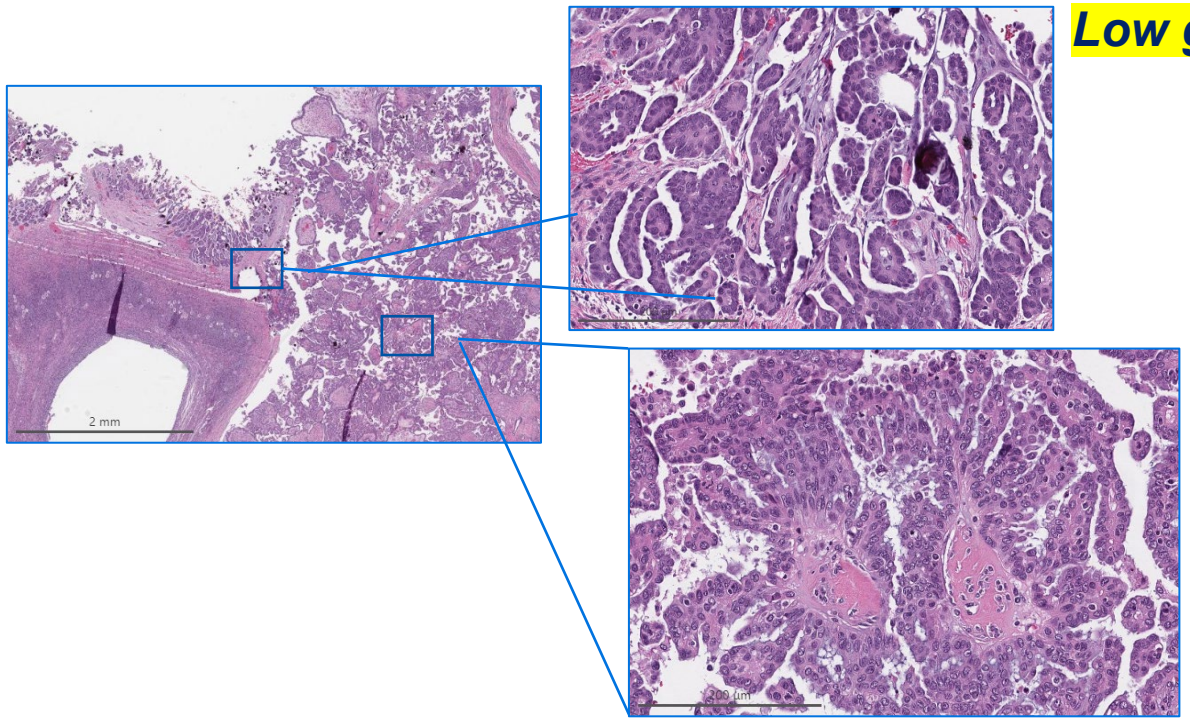
Kara Long Roche, MD, MSc, FACOG
Gynecologic Oncologist

Ryan M. Kahn, MD MHS
Gynecologic Oncology Fellow

35-year-old with recurrent low-grade serous ovarian cancer (LGSOC)

Initially diagnosed s/p cytoreductive surgery with complete gross resection and then completed adjuvant Carboplatin / Paclitaxel x 6 cycles

Pathology



Low grade serous carcinoma

Serous borderline tumor

- LGSOC involving bilateral ovaries, fallopian tubes, omentum, peritoneum, sigmoid colon, appendix, bladder
- Right ovary exhibits borderline tumor of serous type

Molecular Profile

- p53 wt
- MSS, TMB 0.8
- *TMPRSS2, CHEK2* mutations

Audience Poll Question:

For patients with newly diagnosed, advanced stage LGSOC, what approach do you most commonly take?

A. No adjuvant treatment
B. Platinum doublet
C. Platinum doublet with bevacizumab
D. Bevacizumab alone
E. Hormonal therapy
F. Other

Treatment Course

- Remained NED for 12 months following adjuvant therapy
- At 12 months, imaging demonstrated recurrence in port sites and peritoneum
- Then began on Carboplatin / Doxil
- CT s/p 8wks following treatment showed POD

Audience Poll Question:

What therapy do you commonly treat with after a first recurrence for LGSOC?

A. *Platinum doublet*
B. *Platinum doublet with bevacizumab*
C. *Paclitaxel*
D. *Paclitaxel with bevacizumab*
E. *Hormonal therapy*
F. *Other*

Treatment Course

- Remained NED for 12 months following adjuvant therapy
- At 12 months, imaging demonstrated recurrence in port sites and peritoneum
- Began on Carboplatin / Doxil
- CT s/p 8wks following treatment showed POD
- Underwent secondary cytoreductive surgery with HIPEC

Audience Poll Question:

Do you commonly administer HIPEC to patients with advanced ovarian cancer?

A. Yes
B. No

Audience Poll Question:

Do you commonly administer HIPEC to patients with LGSOC specifically?

A. Yes
B. No

Treatment Course

- Remained NED for 12 months following adjuvant therapy
- At 12 months, imaging demonstrated recurrence in port sites and peritoneum
- Began on Carboplatin / Doxil
- CT s/p 8wks following treatment showed POD
- Underwent secondary cytoreductive surgery with HIPEC
- Began on maintenance megace -> letrozole for 24 months
- POD after 24 months, began on Enzalutamide study for 4 months

Audience Poll Question:

Do you commonly test for estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR) positivity in LGSOC?

A). Yes
B). No

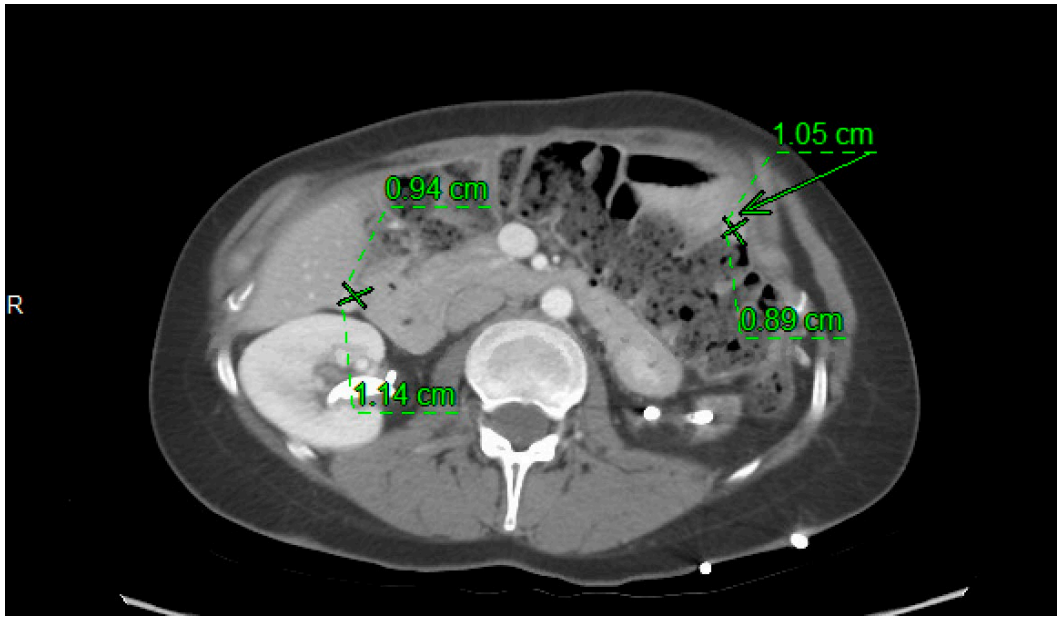
Treatment Course

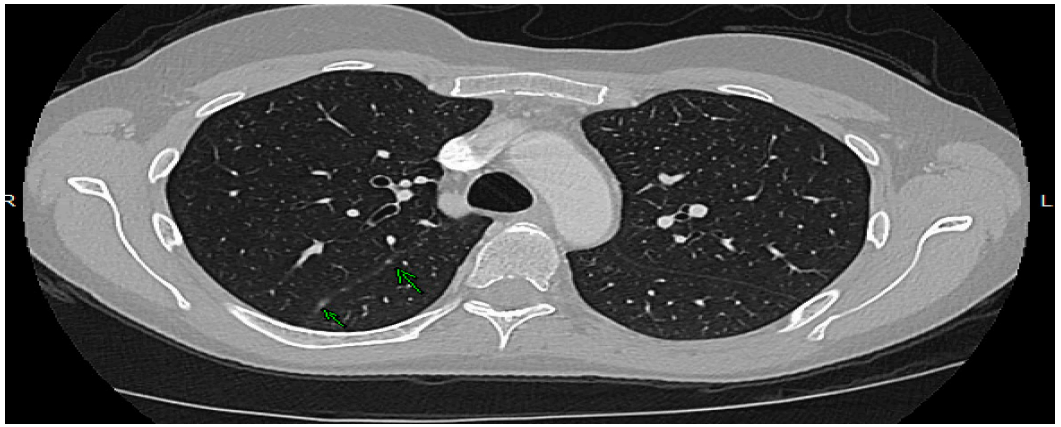
- Remained NED for 12 months following adjuvant therapy
- At 12 months, imaging demonstrated recurrence in port sites and peritoneum
- Began on Carboplatin / Doxil
- CT s/p 8wks following treatment showed POD
- Underwent secondary cytoreductive surgery with HIPEC
- Began on maintenance megace -> letrozole for 24 months
- POD after 24 months, began on Enzalutamide study for 4 months
- Began on Cytoxan/Avastin for 26 months then POD
- Began on Tamoxifen for a year then POD

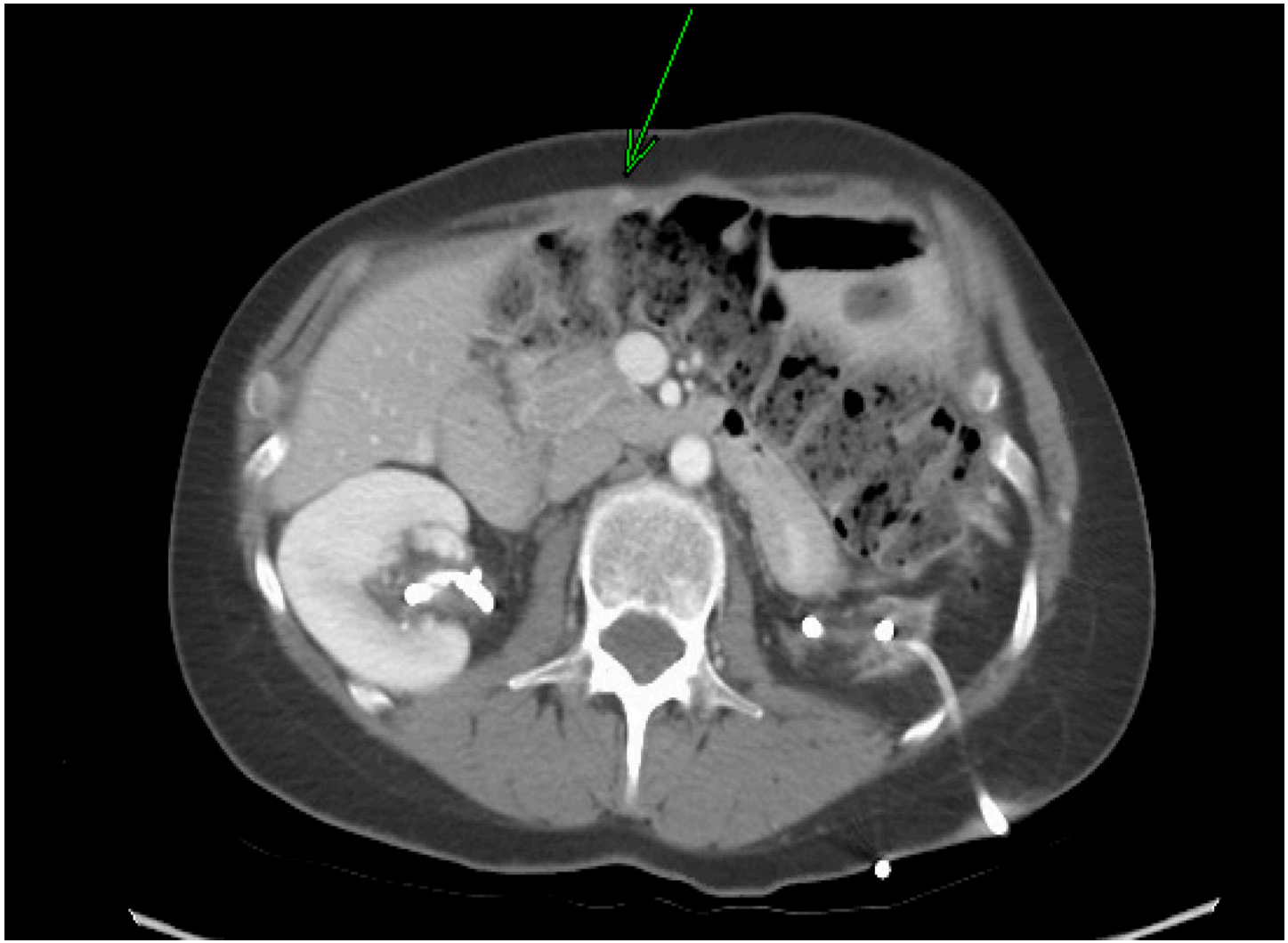
Treatment Course

- Remained NED for 12 months following adjuvant therapy
- At 12 months, imaging demonstrated recurrence in port sites and peritoneum
- Began on Carboplatin / Doxil
- CT s/p 8wks following treatment showed POD
- Underwent secondary cytoreductive surgery with HIPEC
- Began on maintenance megace -> letrozole for 24 months
- POD after 24 months, began on Enzalutamide study for 4 months
- Began on Cytoxan/Avastin for 26 months then POD
- Began on Tamoxifen for a year then POD
- Began on clinical trial (VS-6766, Defactinib)

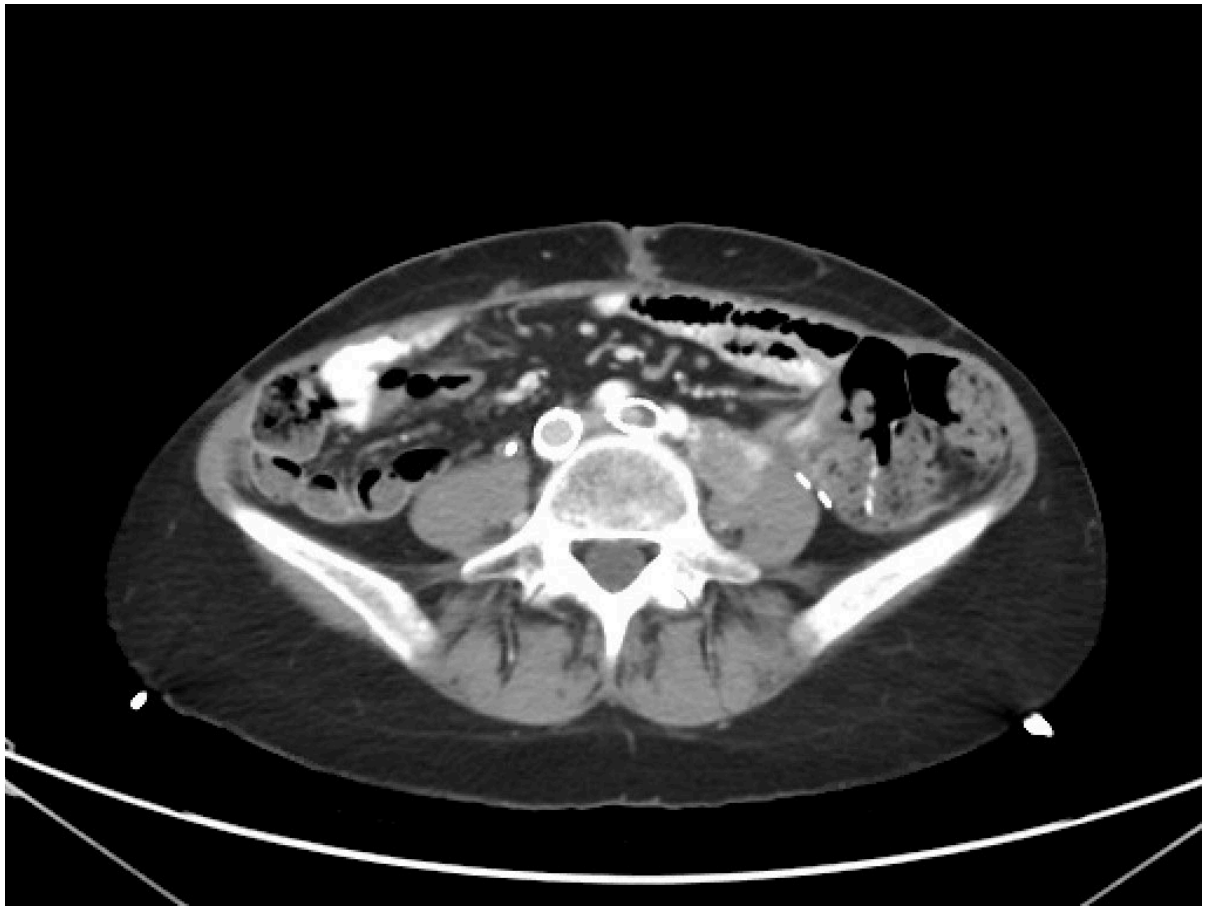
IMAGING



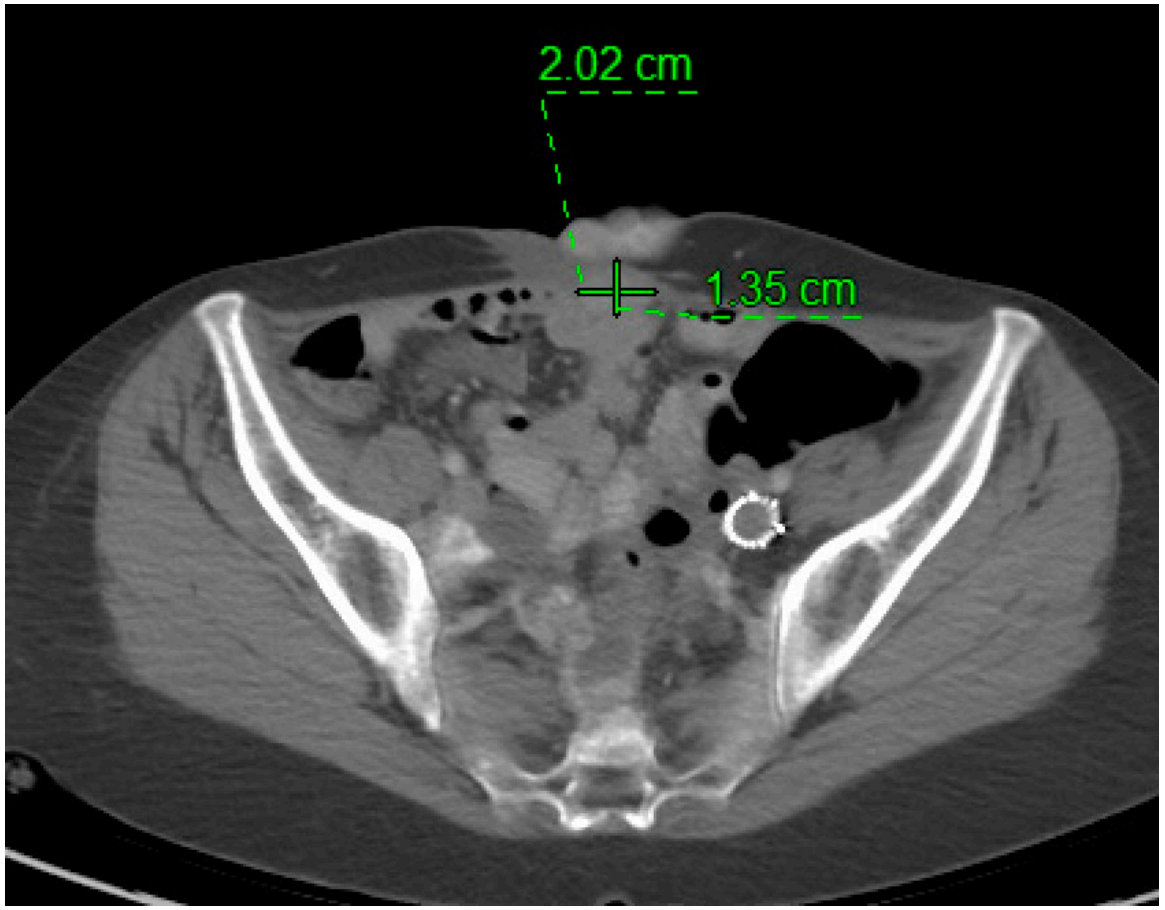




IMAGING



4 months after treatment: CT w/ decreased disease



10 months after treatment: CT with stable disease

Audience Poll Question:

Do you commonly test for RAS pathway molecular alterations in LGSOC?

A). Yes
B). No

Low-Grade Serous Ovarian Cancer

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Chennai

Q&A

Memorial Sloan Kettering Cancer Center

Cancer Institute (WIA)
Chennai

Thank you!

Memorial Sloan Kettering Cancer Center

Cancer Institute (WIA) Chennai

MSK & CI (WIA) Tumor Board

Memorial Sloan Kettering Cancer Center presents

Molecular Profile and Current Treatment Strategies for Low Grade Serous Ovarian Cancer

Presented by Rachel Grisham, MD

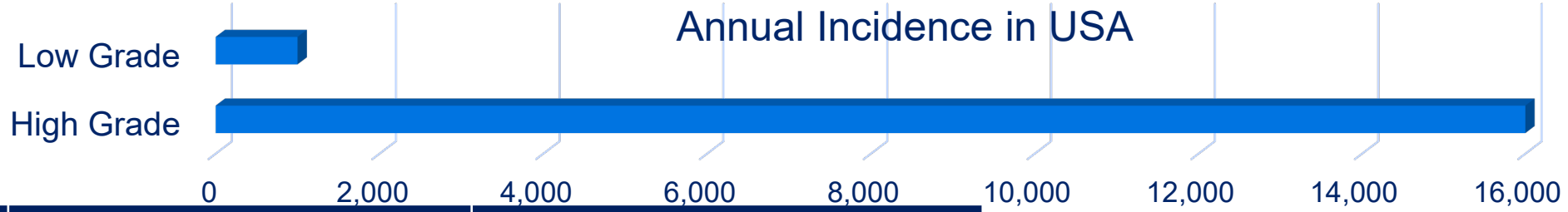
Memorial Sloan Kettering Cancer Center

Cancer Institute (WIA)
Chennai

Ovarian Cancer Type as a Biomarker

	High Grade Serous	Clear Cell	Endometrioid	Mucinous	Low Grade serous
Genetic Risk Factors	BRCA 1/2	HNPCC	HNPCC	Confirm Diagnosis	**None Known**
Precursor Lesion	Serous Tubal Intraepithelial Carcinoma (STIC)	Endometriosis	Endometriosis	?Teratoma	**Serous Borderline Disease**
Molecular Genetics	P53, BRCA, Homologous Recombination Deficiency (HRD)	PI3K, ARID1A, MSI	PTEN, ARID1A, MSI	KRAS, HER2	**BRAF, KRAS, NRAS**
Potential Drugs	• PARPi • Wee1 • ATR • DNAPK	• mTOR • ARID1A	• mTOR • ARID1A	• Trastuzumab • TDM-1	• **MEKi** • **FAKi** • **RAFi**

Molecular and Clinical Features



Clinical/Molecular Features	Low Grade Serous (LGS)	High Grade Serous (HGS)
Median Age at Diagnosis	40-50's years	50-60's years
Molecular Genetics	Mutant: BRAF, RAS Wild type: p53	Mutant: p53, BRCA, HRD Wild type: BRAF, RAS
GOG158 (Stage III, Optimal) Blinded Pathology Review Upfront Chemotherapy (Paclitaxel + Carboplatin)	N=21 PFS: 45 months OS: 126.2 months	N=220 PFS: 19.8 months OS: 53.8 months
Response Rate to Neoadjuvant Chemotherapy ***24 women at MDACC, neoadjuvant*** ***5114 women, AGO database*** ***4 phase III trials, suboptimal debulking***	4-23%	80-90%
Rate of Hormone Receptor Positivity	ER:87-96% PR: 58-84%	ER: 43-86% PR: 19-55%

Grisham, RN. Oncology 2016; 7:650-2. J Natl Cancer Inst 2014;106(4):1-8; Bodurka et al. Cancer 2012;118:3087-94; Schmeler et al. Gynecol Oncol 2008;108:510-4; Grabowski et al, 2016. Gershenson et al. Gynecol Oncol 2009; 114(1):48-52. Pujade-Lauraine et al. J Clin Oncol 2014; 32(13):1302-8. Aghajanina et al. J Clin Oncol 2012; 30(17): 2039-45. Chen et al, Scientific Reports 7(16922), 2017. Voutsadakis, Clin Med Insights Oncol, 2016. Gaduci et al, Cancers, 2020.

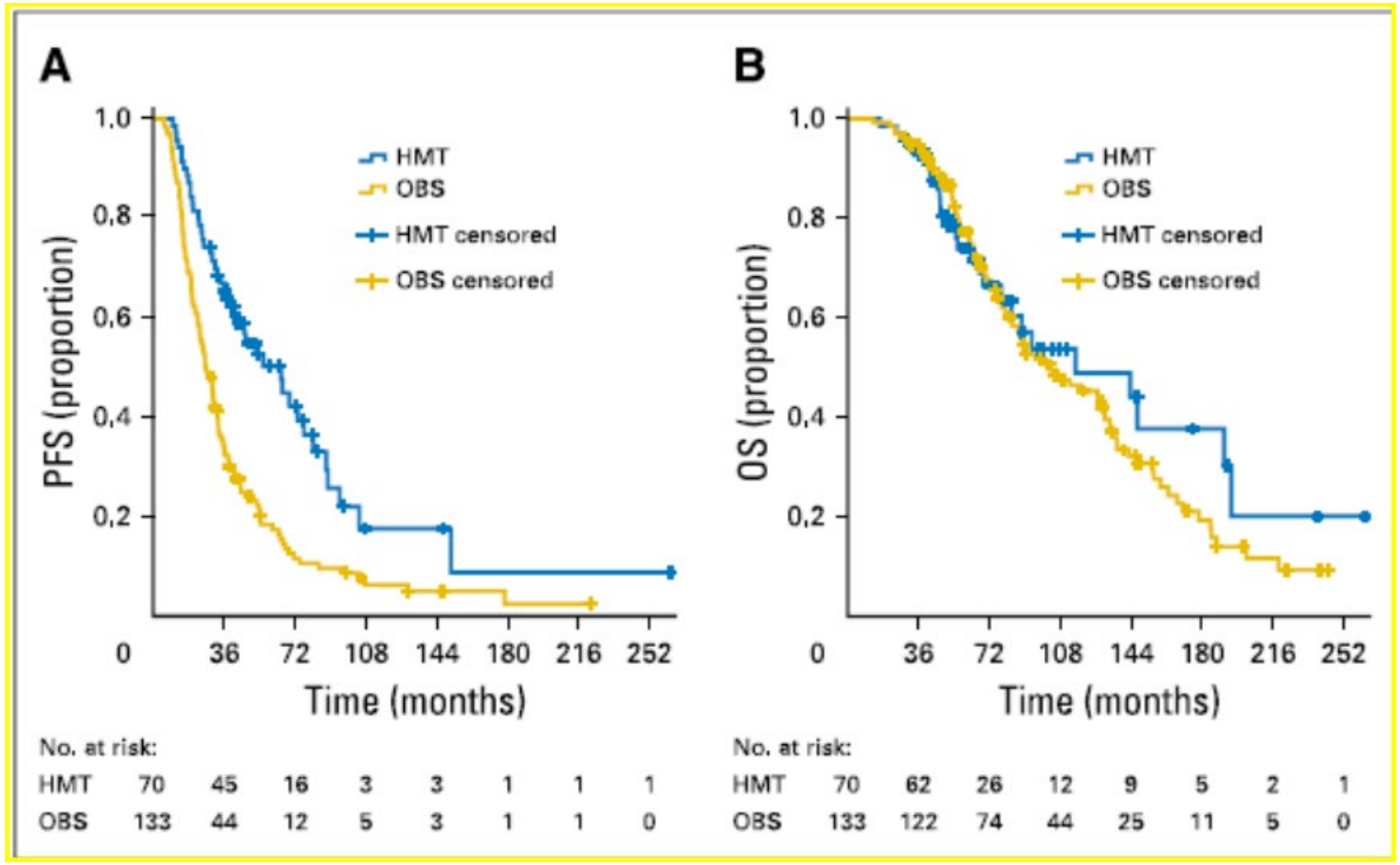
Endocrine Therapy

	CR		PR		SD		PD		Total
Regimen	PSe	PRe	PSe	PRe	PSe	PRe	PSe	PRe	
Anastrozole	1	0	0	0	9	5	2	4	21
Fulvestrant	0	0	0	0	1	0	1	0	2
Letrozole	3	1	2	0	9	8	4	6	33
Leuprolide	0	0	0	0	5	1	1	1	8
Megestrol acetate	0	0	0	0	0	0	0	1	1
Tamoxifen	1	0	0	0	8	3	1	4	17
Raloxifene	0	0	0	0	1	0	0	0	1
Anastrozole + leuprolide	0	0	0	0	1	0	0	0	1
Letrozole + leuprolide	0	0	0	0	1	1	0	1	3
Tamoxifen + leuprolide	0	0	0	0	1	1	0	0	2
Total	5	1	2	0	36	19	9	17	89

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PSe, platinum-sensitive; PRe, platinum-resistant.

- Retrospective Study
- 64 patients
- 89 Regimens
- Most commonly anastrozole, letrozole or tamoxifen used
- Recurrent Disease
- Overall Response Rate = 9% (8/89)

Endocrine Maintenance Therapy



Retrospective, MDACC
-Stage II-IV LGSOC
-HMT vs observation following surgery and platinum based chemotherapy
-1981- 2013, 203 patients (133 obs, 70 HMT)
-most common HMT letrozole or tamoxifen
-MEDIAN PFS 26.4 months (obs) vs 64.9 months (HMT); (P<0.001)

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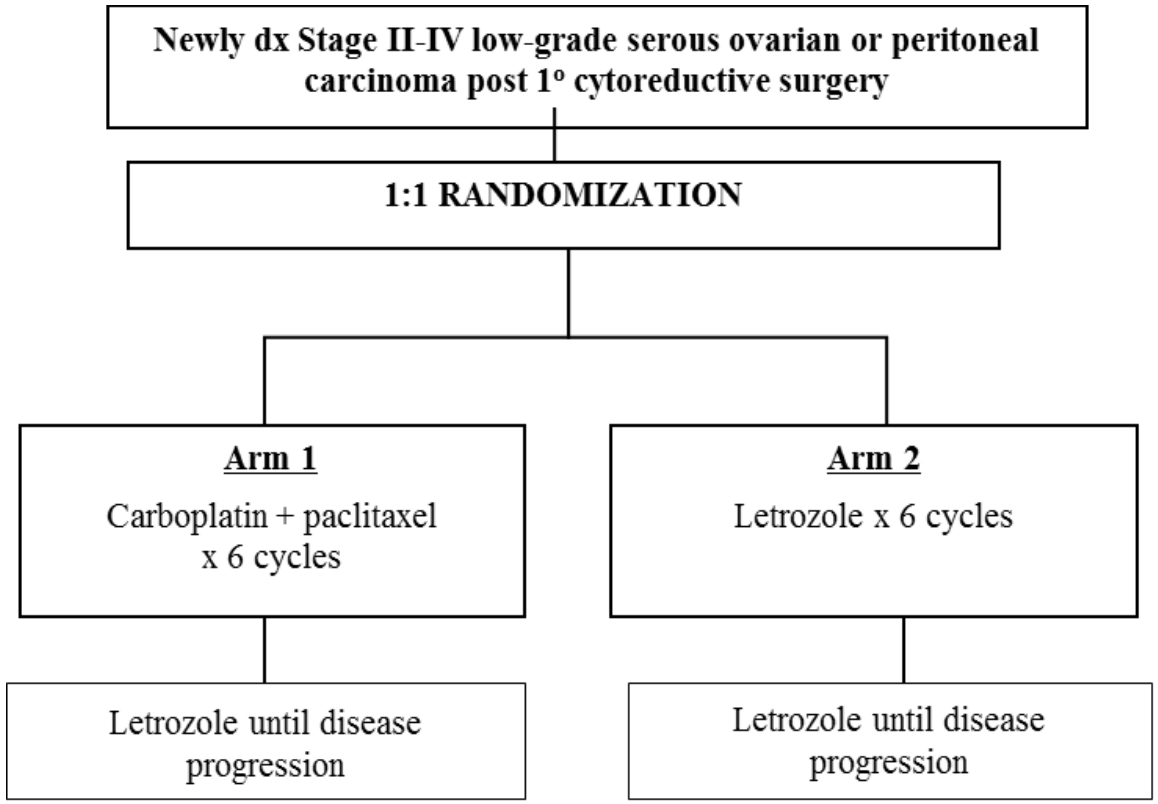
First Line Treatment

NRG-GY019

A Randomized Phase III, Two-Arm Trial of Paclitaxel/Carboplatin/Maintenance Letrozole Versus Letrozole Monotherapy in Patients with Stage II-IV, Primary Low-Grade Serous Carcinoma of the Ovary or Peritoneum

NRG-GY019 Study Schema



Patients stratified based on:

1) Residual disease following primary cytoreductive surgery
   a) No gross residual disease
   b) Any gross residual disease
2) Country/Region of enrollments
   i. US/Canada
   ii. Asia
   iii. Europe

- Randomization 1:1 ratio
- P53 tumor testing required, no central pathology review

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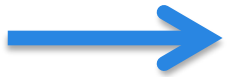
Chennai

Use of Targeted Therapies for Recurrent LGSOC and Identification of Potential Biomarkers of Enhanced Response

GOG 239- Selumetinib (AZD6244)

Eligibility:
- Prospective Central Pathology
- Recurrent
- Measurable Disease
- No Restrictions on Prior Therapy (median: 3)

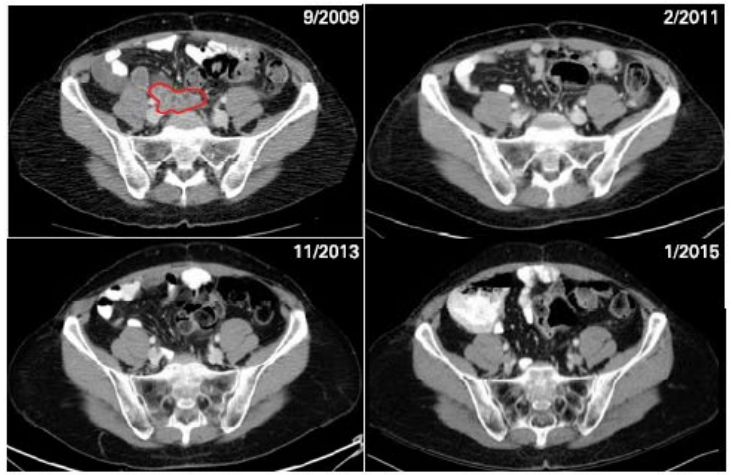


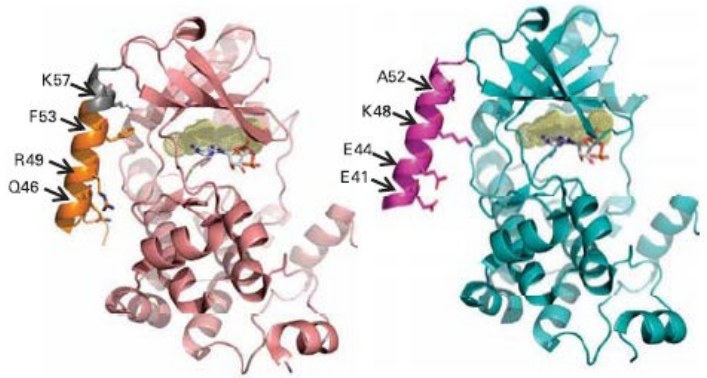
Selumetinib 50 mg oral BID

GOG 239- Selumetinib (AZD6244)

- Objective Response Rate 15% (8/52 patients)
  - 1 complete response
  - 7 partial responses
- Median PFS: 11 months
- 34/52 patients had sufficient DNA for analyses
- Sequenom analysis was used to look for hotspot alterations in codon 600 of BRAF or codon 12/13 of KRAS

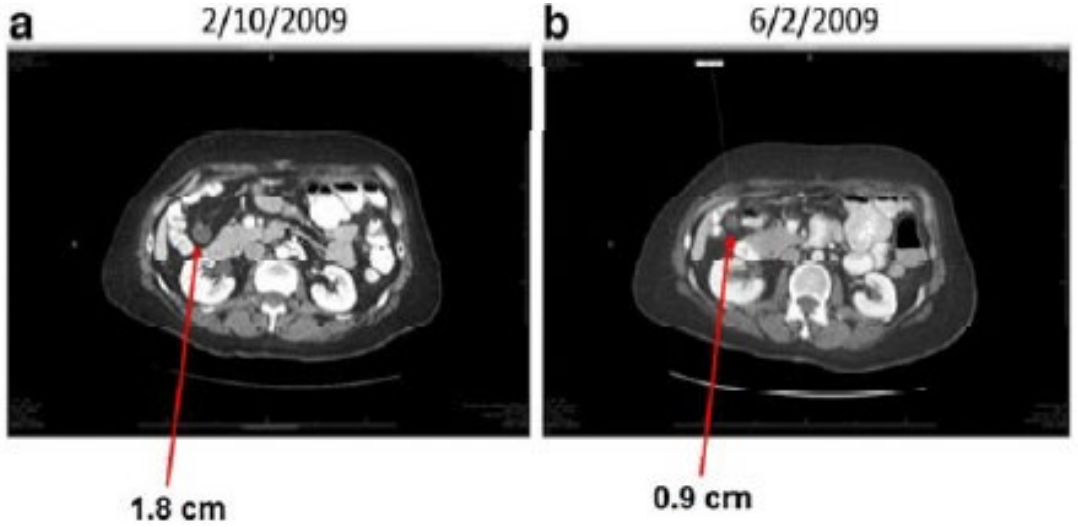
Farley et al, Lancet Oncology, 2012





- Initiated selumetinib October, 2009
- Sustained CR
- 15-bp in-frame deletion within the *MAP2K1* gene

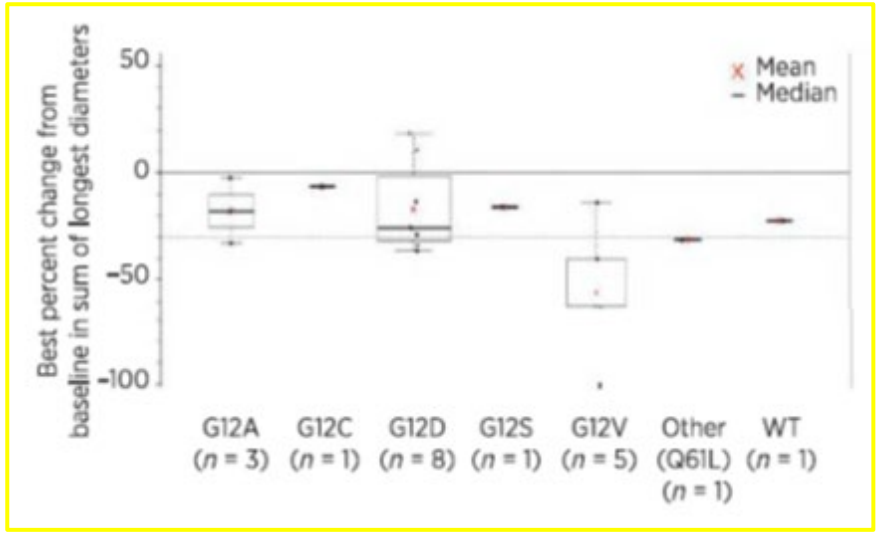
- Initiated selumetinib June, 2008
- PR with calcified disease
- Progression with dose holding and regression with resumption
- KRAS G12V mutant



Grisham et al, JCO, 2015; Takekuma et al, Gynecologic Oncology Research and Practice, 2016

Phase Ib Dose Escalation of Pan-PI3K inhibitor BKM120 With Oral MEK Inhibitor Trametinib

21 patients with ovarian cancer (4 escalation, 17 expansion) , 15/21 well differentiated serous
median of 3 priors (1-14), 91% KRAS mutant
ORR 29% (1 confirmed CR, 5 confirmed PR)
ORR 50% at RP2D (1 confirmed CR, 3 confirmed PR)
Additional 2/21 (10%) had unconfirmed PR (one progressed, other resected)
DCR was 76%
Median duration of SD
was 11 months
Trend towards improved
response in G12V



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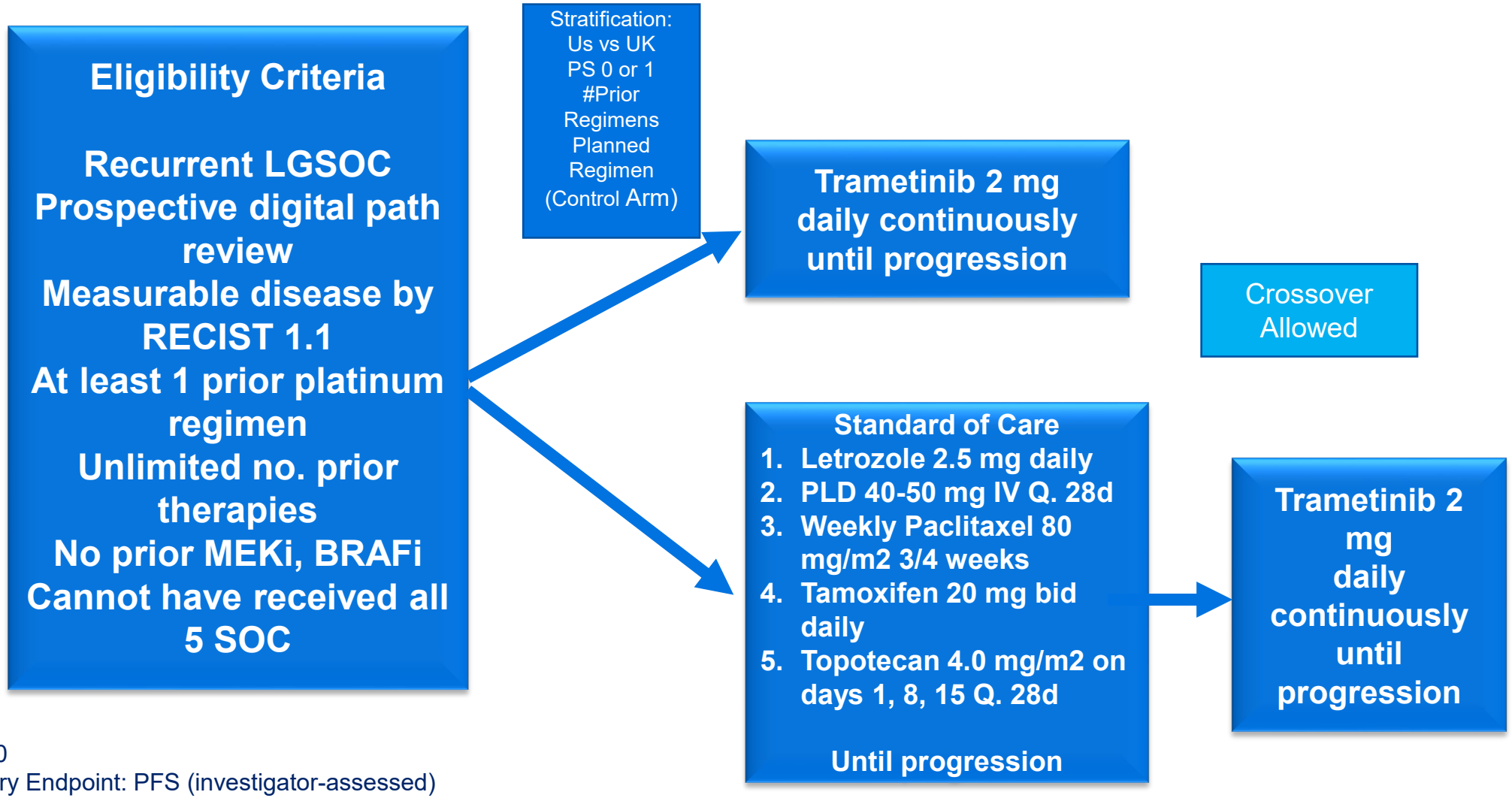
Cancer Institute (WIA) Chennai

GOG281: A Randomized Phase II/III Study to Assess the Efficacy of Trametinib in Patients with Recurrent or Progressive Low-Grade Serous Ovarian or Peritoneal Cancer

D M Gershenson, A Miller, W Brady, J Paul, K Carty, W Rodgers, D Millan, R L Coleman, K N Moore, S Banerjee, K Connolly, A A Secord, D M O'Malley, O Dorigo, S Gaillard, H Gabra, P Hanjani, H Huang, L Wenzel, C Gourley

Presented by D. Gershenson at ESMO 2019

GOG281 Study Design



N=260
Primary Endpoint: PFS (investigator-assessed)

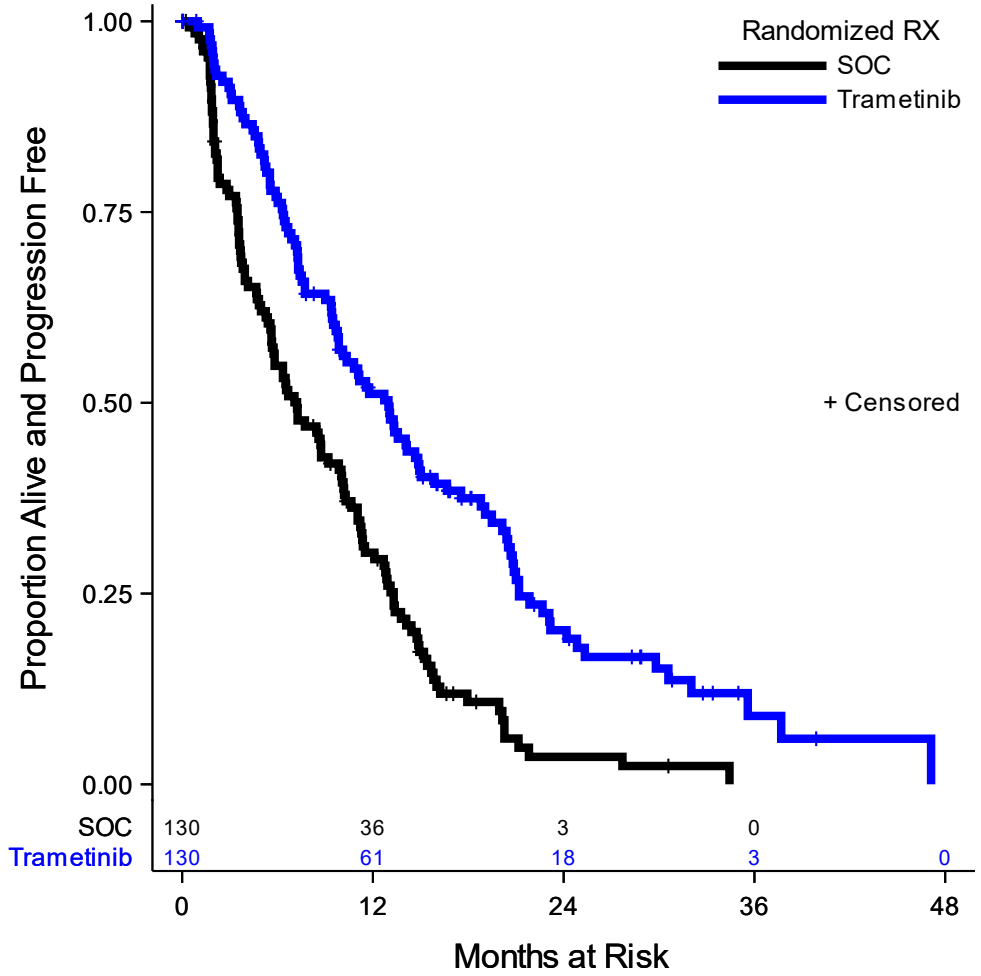
Presented by D. Gershenson ESMO 2019

Baseline Patient Characteristics

Characteristic	Control	Trametinib	Overall
Prior Lines of Therapy			
1	30 (23.1%)	29 (22.3%)	59 (22.7%)
2	37 (28.5%)	39 (30%)	76 (29.2%)
≥3	63 (48.5%)	62 (47.7%)	125 (48.1%)
Country			
UK	28 (21.5%)	27 (20.8%)	55 (21.2%)
US	102 (78.5%)	103 (79.2%)	205 (78.8%)
Reason for Tx Discontinuation			
Still on Tx	7 (5.4%)	14 (10.8%)	21 (8.1%)
Disease Progression	81 (62.3%)	55 (42.3%)	136 (52.3%)
AE/Complication	16 (12.3%)	46 (35.4%)	62 (23.8%)
WD/Refused after RX	12 (9.2%)	3 (2.3%)	15 (5.8%)
Other	14	12	26

Presented by D. Gershenson ESMO 2019

Progression-Free Survival



	Trametinib	Control (SOC)
Median (Months) 95% CI	13.0 (9.9 – 15.0)	7.2 (5.6 - 9.9)
Hazard Ratio 95% CI	0.48 (0.36 – 0.64)	
One-sided p-value	< 0.0001	

Presented by D. Gershenson ESMO 2019

RECIST 1.1 Response

Arm	No. Pts CR + PR /Treated	Objective Response Rate (95% CI)	Stable Disease Rate	Response Duration Months (95% CI)	Odds Ratio For ORR (95% CI)	P-Value
Trametinib	**34/130**	**26.2% (19.0-34.0)**	**59.2%**	**13.6 (8.1-18.8)**		
					5.4 (2.4-12.2)	**< 0.0001**
Control (SOC)	**8/130**	**6.2% (2.0-10.0)**	**70.8%**	**5.9 (2.8-12.2)**		
Letrozole	6/44	13.6%	70.5%			
Tamoxifen	0/27	0%	66.7%			
Paclitaxel	1/11	9.1%	63.6%			
PLD	1/40	2.5%	80.0%			
Topotecan	0/8	0%	50.0%			

Presented by D. Gershenson ESMO 2019

Memorial Sloan Kettering Cancer Center

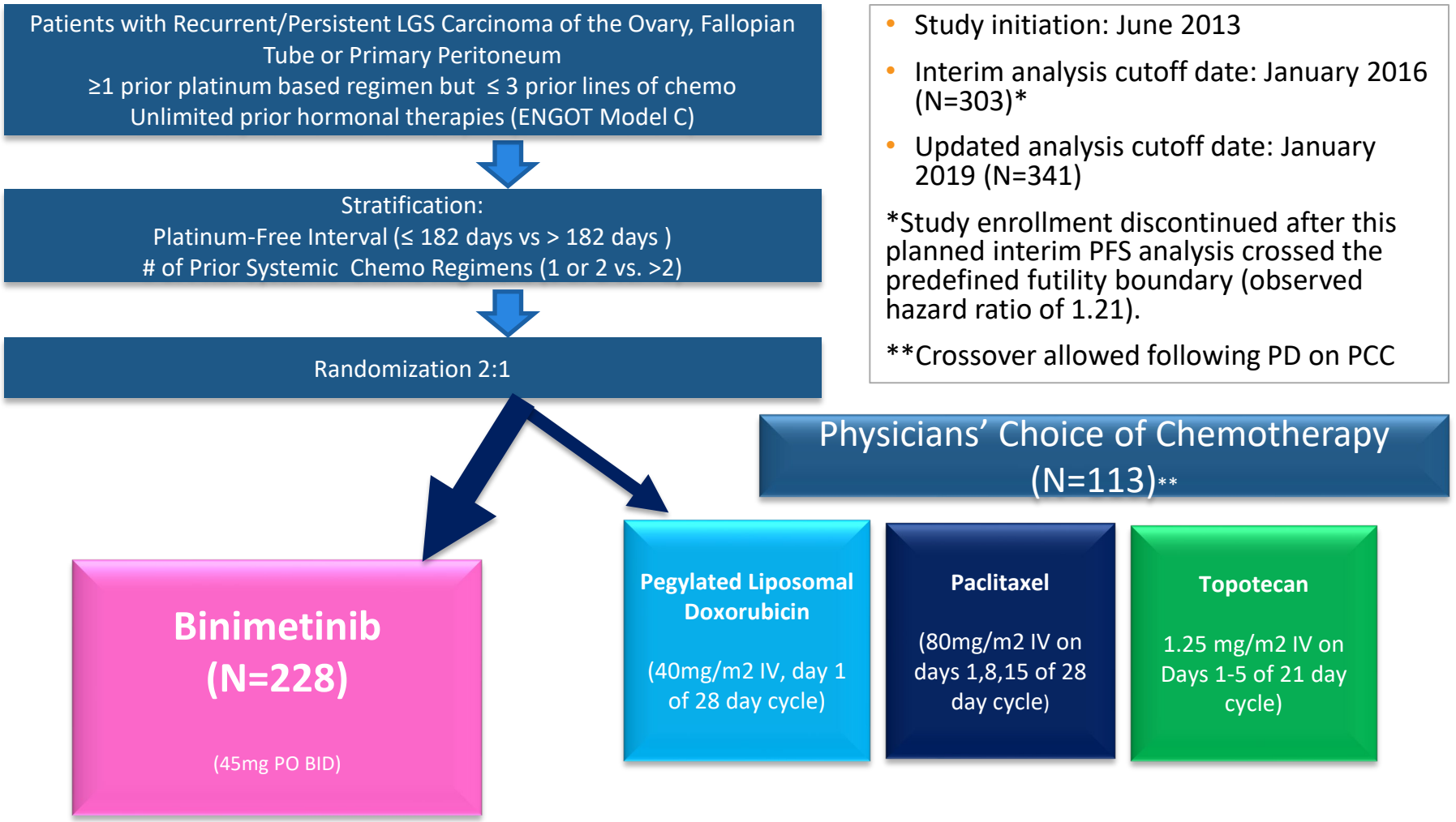
Cancer Institute (WIA) Chennai

MILO/ENGOT-ov11: Phase-3 Study of Binimetinib versus Physician's Choice Chemotherapy in Recurrent or Persistent Low-grade Serous Carcinomas of the Ovary, Fallopian Tube, or Primary Peritoneum

Rachel Grisham , Bradley J Monk ,Susana Banerjee , Robert L Coleman , Amit M Oza Martin K Oehler, Elsa Kalbacher, Mansoor Raza Mirza, Josep M del Campo Christian Marth, Anneke Westermann, Sandro Pignata, NIcoletto Colombo, David Cibula, Felix Hilpert , Carol Aghajanian, Esther Drill , Victor Sandor, Adam P Boyd , Ignace Vergote

Presented at IGCS 2019

Study Design



- Study initiation: June 2013
- Interim analysis cutoff date: January 2016 (N=303)*
- Updated analysis cutoff date: January 2019 (N=341)

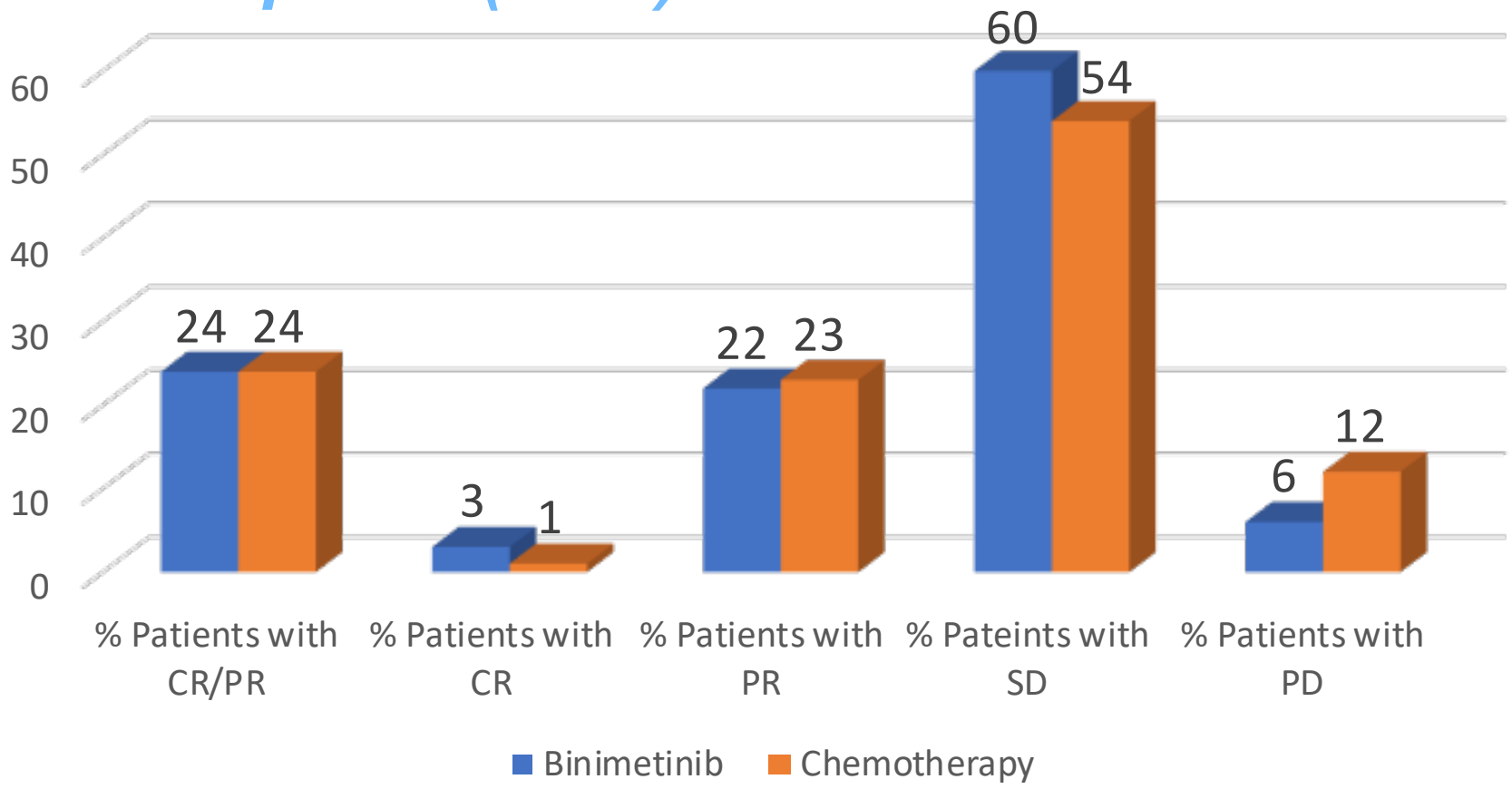
*Study enrollment discontinued after this planned interim PFS analysis crossed the predefined futility boundary (observed hazard ratio of 1.21).

**Crossover allowed following PD on PCC

Presented at IGCS 2019

Updated Results

Best RECIST Response (local)



Updated analysis cutoff date: January 2019 (N=341)

Updated Results

Molecular Analysis

- Foundation Medicine was attempted on all patients at study entry
- 215 evaluable patients with molecular results available
- 49 mutations detected at frequency of >5%, most commonly *KRAS*
- 33% of patients with *KRAS* mutation

Treatment Group	N	PFS Events	KRAS mutant (%)
Binimetinib	144	74	46 (32%)
Physicians Choice	71	38	24 (34%)

KRAS Mutation & Higher Response Rates

original reports

MILO/ENGOT-ov11: Binimetinib Versus Physician's Choice Chemotherapy in Recurrent or Persistent Low-Grade Serous Carcinomas of the Ovary, Fallopian Tube, or Primary Peritoneum

Bradley J. Monk, MD[1]; Rachel N. Grisham, MD[2]; Susana Banerjee, PhD[3]; Elsa Kalbacher, MD[4]; Mansoor Raza Mirza, MD[5]; Ignacio Romero, MD[6]; Peter Vuylsteke, MD[7,8]; Robert L. Coleman, MD[9]; Felix Hilpert, MD[10]; Amit M. Oza, MD[11]; Anneke Westermann, MD, PhD[12]; Martin K. Oehler, MD, PhD[13]; Sandro Pignata, MD, PhD[14]; Carol Aghajanian, MD[1]; Nicoletta Colombo, MD[15]; Esther Drill, DrPH[2]; David Cibula, MD, PhD[16]; Kathleen N. Moore, MD[17]; Janna Christy-Bittel, MSN[18]; Josep M. del Campo, MD[19]; Regina Berger, PhD[20]; Christian Marth, MD, PhD[21]; Jalid Sehouli, MD[22]; David M. O'Malley, MD[23]; Cristina Churruca, MD[24]; Adam P. Boyd, PhD[18]; Gunnar Kristensen, MD, PhD[25]; Andrew Clamp, MD, PhD[26]; Isabelle Ray-Coquard, MD, PhD[27]; and Ignace Vergote, MD, PhD[28]

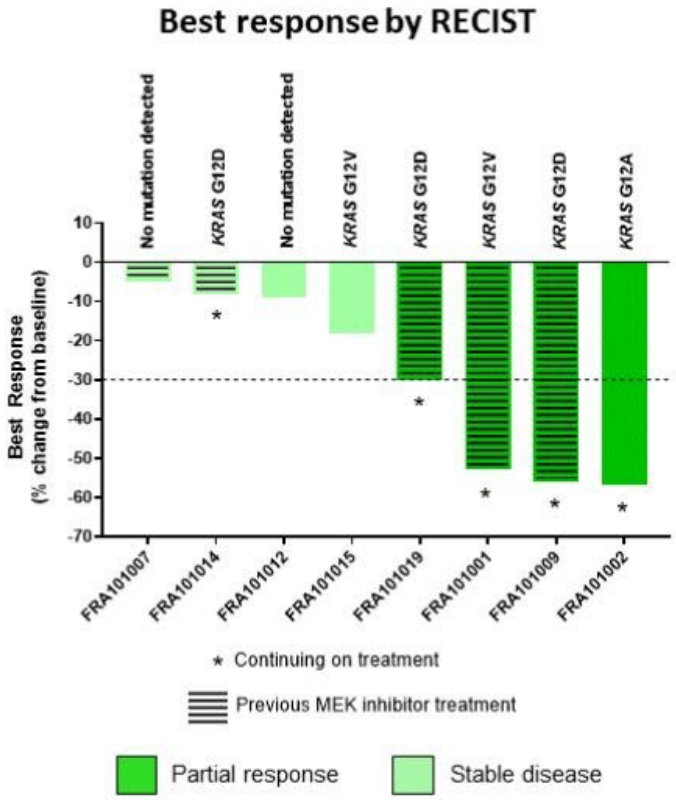
TABLE 3. Best Response by Local RECIST 1.1 Radiology Read in those patients treated with binimetinib

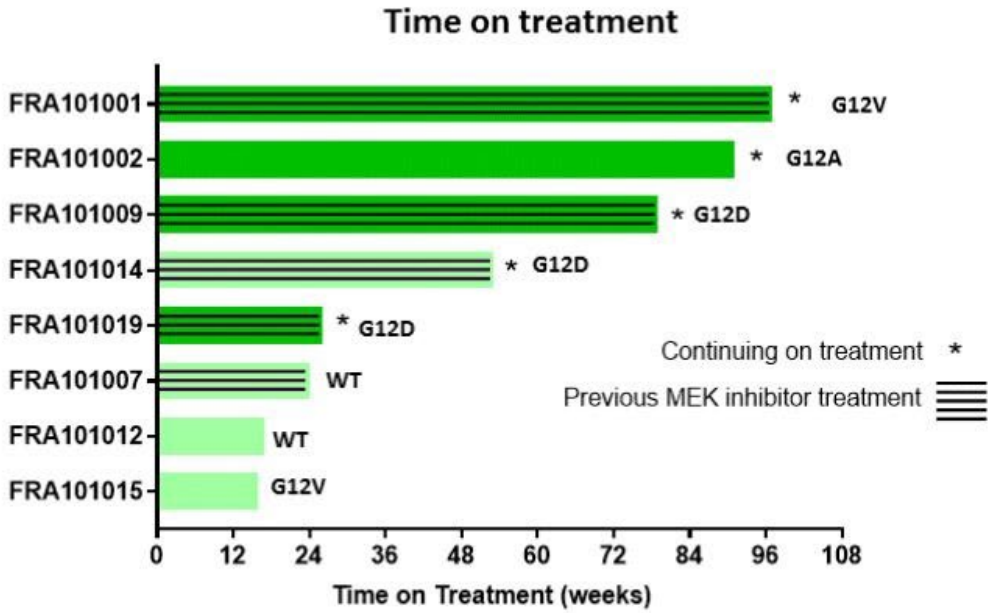
Local Best Response	*KRAS* Mutant (n = 43), No. (%)	*KRAS* Wild-Type (n = 90), No. (%)	*P*
			.004
CR/PR	19 (44)	17 (19)	
SD/PD	24 (56)	73 (81)	

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

FRAME Study Interval Results

Efficacy – Low Grade Serous Ovarian Cancer





- All PRs confirmed with subsequent scan per RECIST

Presented by U. Banerji, AACR 2020

Memorial Sloan Kettering Cancer Center

Cancer Institute (WIA) Chennai

GOG-3052; ENGOT-ov60/NCRI; RAMP201

A Phase 2 Study of VS-6766 (Dual RAF/MEK Inhibitor) Alone and In Combination with Defactinib (FAK Inhibitor) in Recurrent Low-Grade Serous Ovarian Cancer (LGSOC)

Memorial Sloan Kettering Cancer Center

Cancer Institute (WIA) Chennai

Novel Hormonal Therapies/Combination Therapy

Phase II Trial of Ribociclib and Letrozole in ER+ Ovarian/Endometrial Cancers

- ER+ recurrent, measurable disease
- Initially required pRB + by IHC (12/13+)
- 400 mg ribociclib and 2.5 mg letrozole PO daily until POD
- PFS12 of 50% in ovarian cancer cohort
- HGSOC (n=17) median PFS 2.8 months
- Best responses seen in LGSOC

LGSOC:

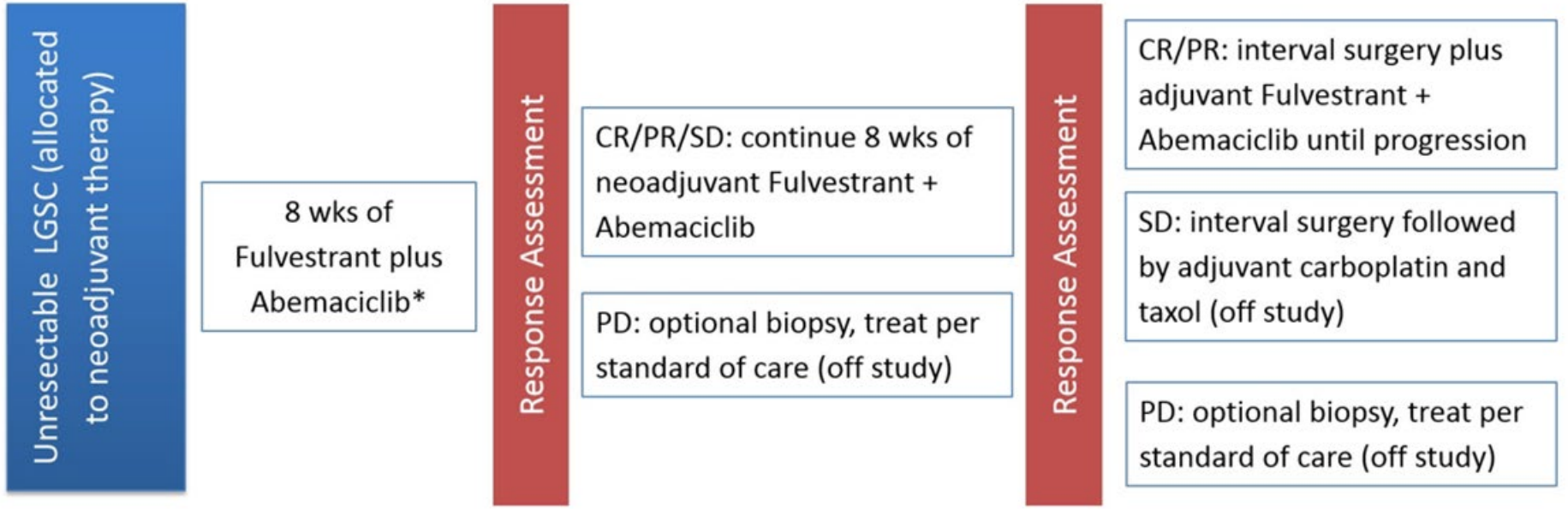
- 1 complete, 2 partial responses
- 2 remained on treatment >30 months at time of study publication

Table 2 Subset analysis of PFS	
Total Patients PFS ≥24 **weeks**	**11/40 (27.5%)**
Ovarian group	4/20 (20.0%)
Low-grade serous	3/3 (100.0%)*
High-grade serous	1/17 (5.9%)
Endometrial group	7/20 (35.0%)
Grade 1 to 2	5/11 (45.5%)
High-grade	2/9 (22.2%)

*Patients on treatment for 36+, 30+ and 27 months.
PFS, progression-free survival.

Colon-Otero et al, ESMO Open, 2020

A Pilot Phase II Study of Neoadjuvant Fulvestrant Plus Abemaciclib in Women with Advanced Low Grade Serous Carcinoma



LGSC: Low grade serous carcinoma

Endpoints: clinical benefit rate, biomarkers

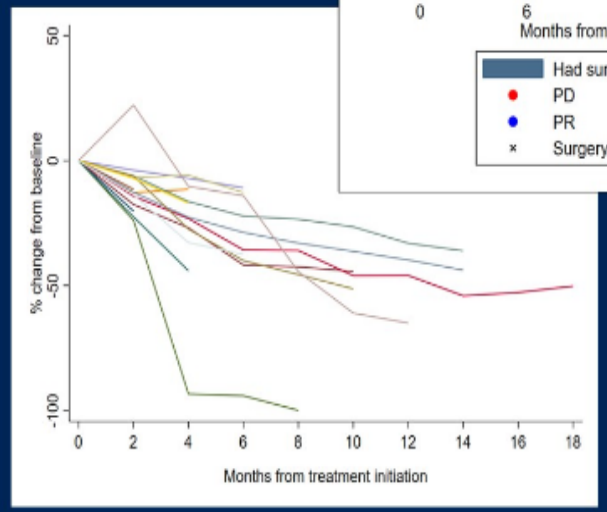
*** Pre/perimenopausal patients will also receive GnRH agonist**

CR=complete response PR=partial response SD=stable disease PD=progression of disease

Schema provided by Dr. Amir Jazaeri; presented at ASCO 2022 by Dr. Lauren Cobb

Promising Response Rate Seen For Abemaciclib in Combination with Fulvestrant

Results



Best overall response:
Complete response – 1/15 (6.7%)
Partial response – 8/15 (53.3%)
*Of 9 patients with PR or CR, average time to PR was 6.67 months
Stable disease – 6/15 (40%)
BOR Clinical Benefit Rate – 100%

Interval cytoreductive surgery:
Underwent surgical resection to date – 7/15 (47%)
Achieved complete gross resection – 5/7 (71%)
Achieved optimal cytoreduction – 7/7 (100%)

*Five patients have transitioned to letrozole maintenance
*Adverse events (grade 3 or 4) possibly related to abemaciclib occurred in 2 patients (13.3%) and included acute kidney injury (6.7%) and neutropenia (6.7%).

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Summary of Current Status of LGSOC

- Molecularly distinct disease (MAPK alterations) with low incidence but higher prevalence due to younger age at diagnosis and extended course of disease
- Standard of care is chemotherapy (RR of 4-24) or single agent endocrine therapy (RR of ≤ 13%)
- No drugs are currently FDA approved for LGSOC
- Promising results seen with single agent MEK inhibitors (RR of 26%)
  - NCCN compendium listed but not FDA approved for this disease
  - Potential to enhance activity by combination with PI3K inhibitor, RAF inhibitor, FAK inhibitors, VEGF inhibitor or endocrine therapy
- Single agent endocrine therapy is currently widely used and well tolerated but with low response rates
  - Multiple opportunities to enhance RR with combination strategies, such as in combination with CDK 4/6 inhibitor