

**Case #5—  
Stage IIIC Endometrial Cancer:  
What's the Best Approach?**

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# Clinical Case Summary

- A 63-year-old woman with postmenopausal bleeding
- **Endometrial Biopsy:** FIGO grade 2 endometrial adenoca
- **Surgery with Full Surgical Staging:** TAH, BSO, pelvic, and paraaortic node dissection, pelvic washings for cytology
- **Pathology:** Grade 2 endometrial adenocarcinoma
  - About 55% myometrial invasion
  - Lymphovascular invasion and
  - 1/13 pelvic nodes positive, all para-aortic nodes negative, washings negative
  - **ER 20%, PgR 15%**
- **Comorbidity:** Diabetes type II well controlled with metformin
- **Chest X-ray and All Laboratory Tests:** Normal
- **Preoperative ECOG Performance Status:** 1

# Molecular Features of Endometrial Cancer

- **Type 1**
  - Up to 80% of US cases
  - Endometrioid histology, associated with estrogen exposure
  - Associated with microsatellite instability syndrome
  - Almost uniform abnormality in mTOR pathway, with KRAS, PI3K, or PTEN alteration
- **Type 2**
  - Most commonly papillary serous or clear cell histology
  - No estrogen association
  - Aggressive course
  - P53 mutation

## Part I:

**Does surgical staging in endometrial cancer improve survival?**

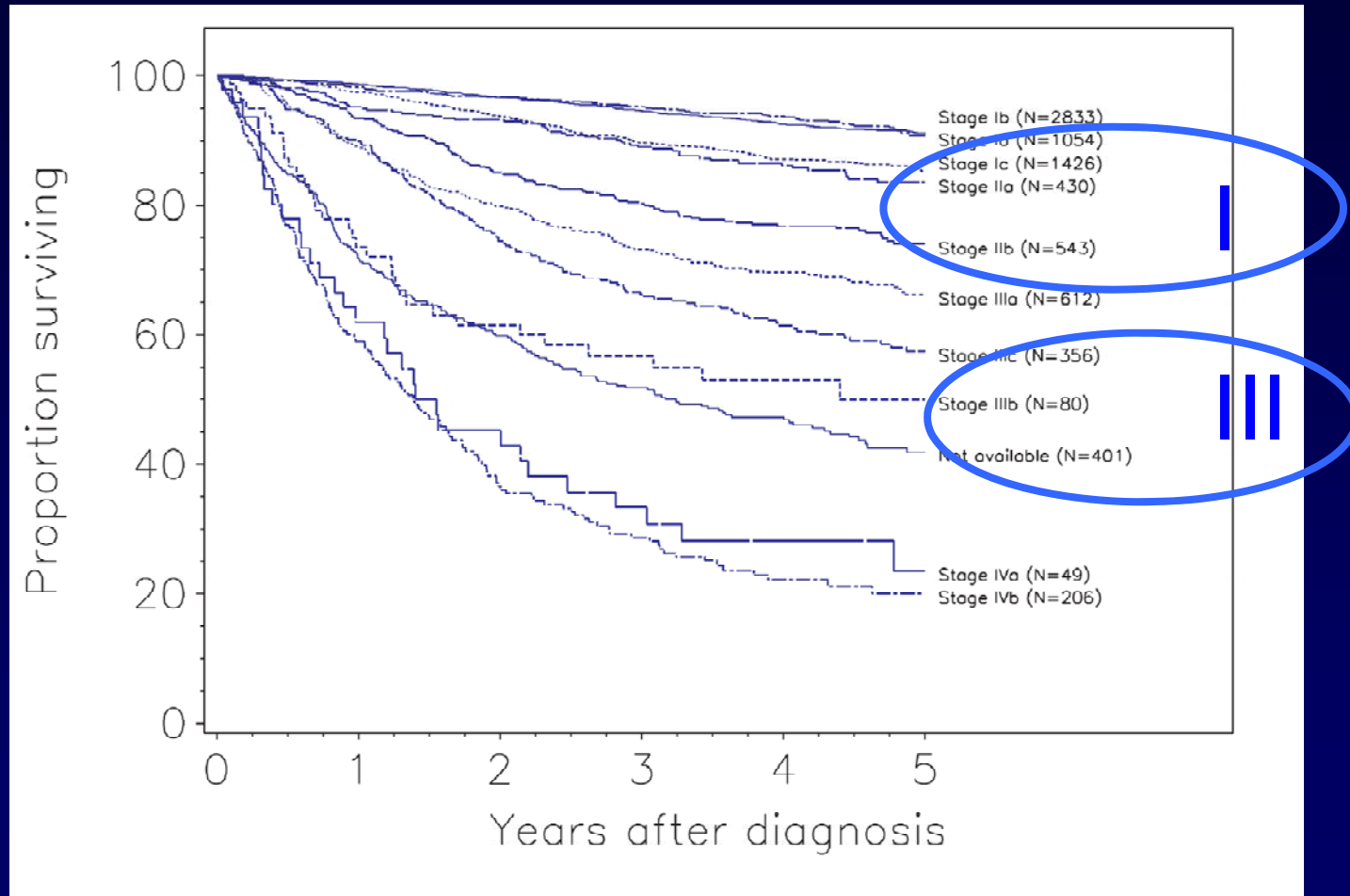
- 1. Yes**
- 2. No**
- 3. I do not know**

# Endometrial Carcinoma Staging

## FIGO Stage

Stage	Description	Frequency %	Survival %
I	Confined to corpus	75	90
II	Extension to cervix	13	60
III	Regional spread	9	40
IV	Bladder/rectal mucosa or extrapelvic metastases	3	< 10

# FIGO Surgical Stage and Overall Survival: Patients Treated 1999-2001



# Staging of Cancer of the Uterine Corpus 1988

Stage		Characteristics
Stage I (grade 1, 2, or 3)*	IA	Limited to the endometrium
	IB	Invasion of less than one half of the myometrium
	IC	Invasion of one half or more than one half of the myometrium
Stage II (grade 1, 2, or 3)	IIA	Endocervical glandular involvement only
	IIB	Cervical stromal invasion
Stage III (grade 1, 2, or 3)	IIIA	Invades serosa and/or adnexa and/or positive peritoneal cytology
	IIIB	Vaginal metastases
	IIIC	Metastases to pelvic and/or para-aortic lymph nodes
Stage IV (grade 1, 2, or 3)	IVA	Invasion of bladder and/or bowel mucosa
	IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

\*Tumor confined to the uterine corpus



Meeting Report

The new FIGO staging system for cancers of the vulva, cervix, endometrium and sarcomas

- **Stage I\*: Tumor confined to the corpus uteri**
  - IA\*: No or less than half myometrial invasion
  - IB\*: Invasion equal to more than half of the myometrium
- **Stage II\*: Tumor invades cervical stroma, but does not extend beyond the uterus\*\***
- **Stage III\* : Local and/or regional spread of the tumor**
  - IIIA\*: Tumor invades the serosa of the corpus uteri and/or adnexae †
  - IIIB\*: Vaginal and/or parametrial involvement †
  - IIIC\*: Metastases to pelvic and/or para-aortic lymph nodes (LNs) †
    - IIIC1\*: positive pelvic LNs
    - IIIC2\*: positive para-aortic LNs with or without positive pelvic LNs
- **Stage IV\*: Tumor invades bladder and/or bowel mucosa, and/or distant metastases**
  - IVA\*: Tumor invasion of bladder and/or bowel mucosa
  - IVB\*: Distant metastases, including intra-abdominal metastases and/or inguinal LNs

\*Either G1, G2, or G3 for all Stages;

\*\*Endocervical glandular involvement only - now considered as Stage I, not Stage II;

†Positive cytology has to be reported separately without changing the stage

Mutch DG. *Gynecol Oncology*. 2009;115(3):325-328.

# Impact of Lymphadenectomy on Survival: Four Studies

- **Kilgore 1995<sup>1</sup>**: Retrospective analysis of 3 groups:
  - I: 212 patients with multiple node sampling sites (4) and median 11 nodes excised
  - II: 205 patients, samples <4 sites and <4 nodes excised
  - III: 208 patients without node samples
  - Better survival in group I ( $P = .0002$ )
  - Recurrence rate lower in group I vs group III ( $P = .019$ )
- **Cragun 2005<sup>2</sup> and Trimble 1998<sup>3</sup>**
  - Survival only improved in patients with grade 3 histology
- **Chan 2006<sup>4</sup>**
  - 12,333 patients - survival analyzed by number of nodes resected (1 node; 2-5 nodes; 6-10 nodes; 11-20 nodes; >20 nodes)
  - The more nodes resected the better survival in IR HR stage IIIC and IV

# Impact of Surgical Staging on Treatment

- **STUDY:**

- 181 women with preoperatively identified endometroid G1 cancer
- 82% LDN (omitted if high surgical risk)
- 19% upgraded
- 3.9% of G1 were N+
- 26% HR (deep inv, G3, serous, clear cell, mesodermic, cervix)
- 29% changes in planned treatment (17% avoid, 12 % received)

- **CONCLUSIONS:**

- Surgical staging in patients presenting with grade 1 endometrial cancer significantly impacted postoperative treatment decisions in 29% of patients
- Omitting lymphadenectomy in patients presenting with grade 1 endometrial cancer may lead to inappropriate postoperative management

## Part I:

**Does surgical staging in endometrial cancer improve survival?**

- 1. Yes**
- 2. No**
- 3. I do not know**

## Part II:

**Which of the following postoperative treatment strategies would you choose for this patient with stage IIIc endometrial carcinoma?**

- 1. Pelvic +/- para-aortic radiotherapy**
- 2. Chemotherapy followed by radiotherapy**
- 3. Chemotherapy alone**
- 4. Hormonal therapy**
- 5. Observation with no adjuvant therapy**

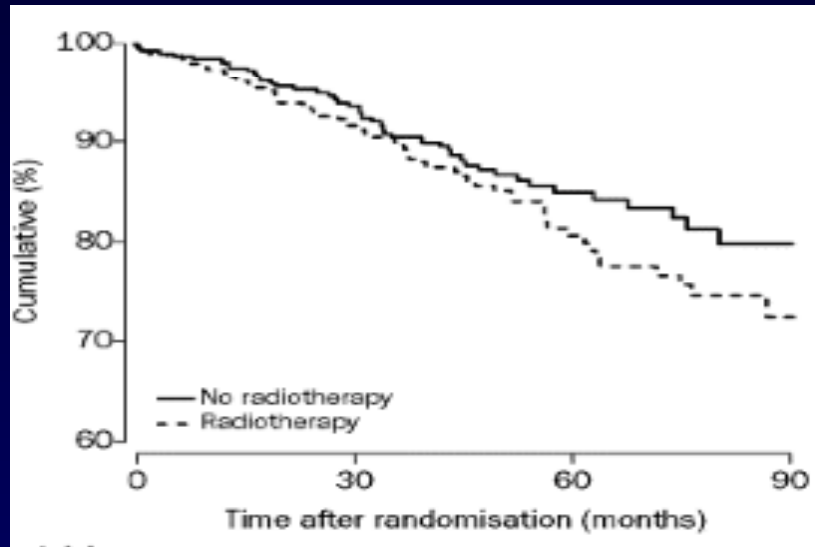
# Stage IIIC Endometrial Cancer

## Part II:

- **Stage IIIC is a systemic disease**

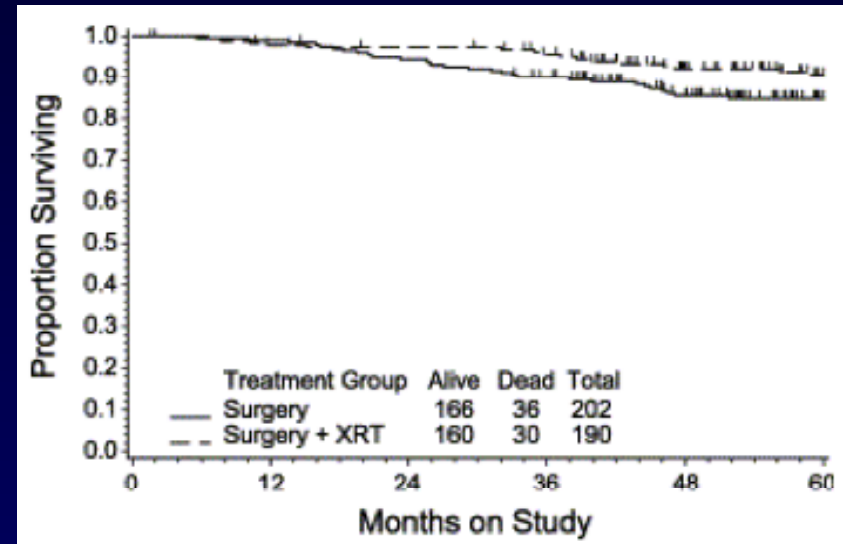
- Stage III/IV EC is a systemic disease
- 3-year PFS is ~60%
- Most recurrences are extrapelvic (~75%)
- Systemic chemotherapy is the mainstay of treatment

# RT Improves Local Control but Not OS



## PORTEC<sup>1</sup>

- 5-year OS
  - Obs: 85%
  - RT: 81%,  $P = .3$



## GOG 99<sup>2</sup>

- 2-year OS
  - Obs: 86%
  - RT: 92%, HR = 0.86,  $P = .55$

# Endometrial Carcinoma: Role of Chemotherapy

## PROSPECTIVE STUDIES

- GOG 122
- NSGO – EORTC 55991
- JGOG 233

Randomized Phase III Trial of Whole-Abdominal  
Irradiation Versus Doxorubicin and Cisplatin  
Chemotherapy in Advanced Endometrial Carcinoma:  
A Gynecologic Oncology Group Study

Marcus E. Randall, Virginia L. Filiaci, Hyman Muss, Nick M. Spirtos, Robert S. Mannel, Jeffrey Fowler,  
J. Tate Thigpen, and Jo Ann Benda

**STAGE III-IV**  
**RT < 2 cm**  
**N = 422**  
**(396 assessable)**

**R  
A  
N  
D  
O  
M  
I  
Z  
E**

**ERT 30 Gy +  
15 Gy boost to pelvis ±  
para-aortic nodes**

**N = 202**

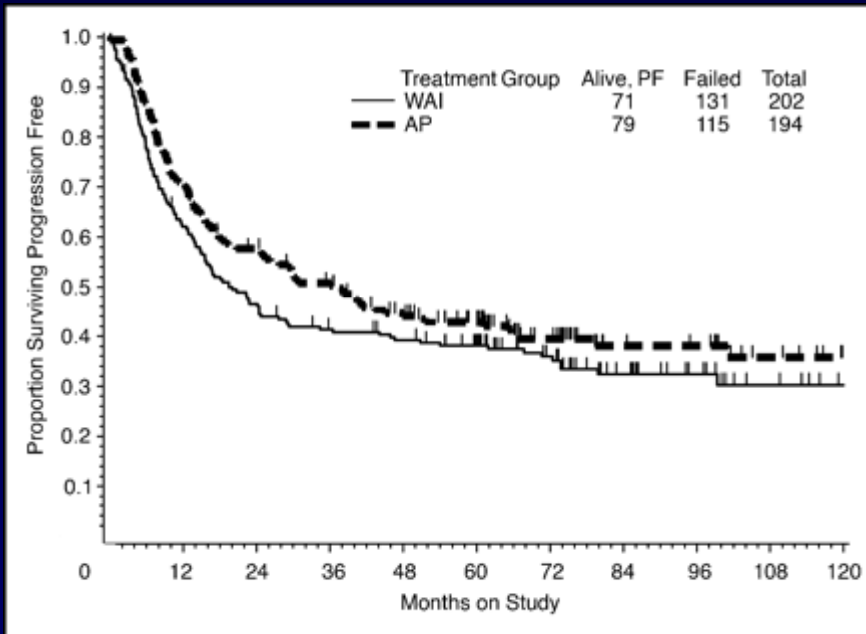
**CDDP 50 mg/m<sup>2</sup> +  
DOX 60 mg/m<sup>2</sup> every  
3 weeks for 8 cycles**

**N = 194**

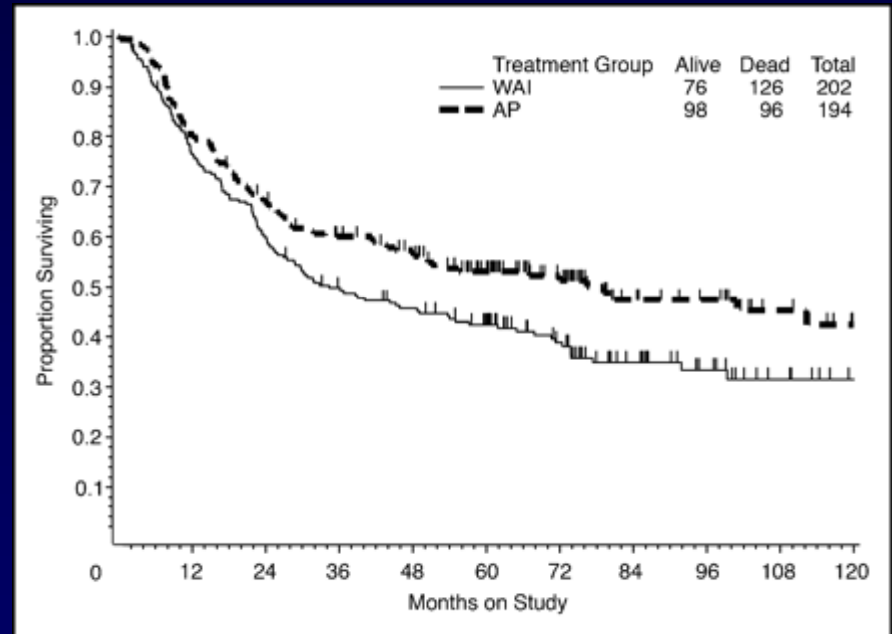
- FIGO stage III or IV
- Any histology (25% type 2)
- Residual tumor ≤ 2 cm after surgery (16%)

# GOG 122: Survival Data

## Progression-Free Survival

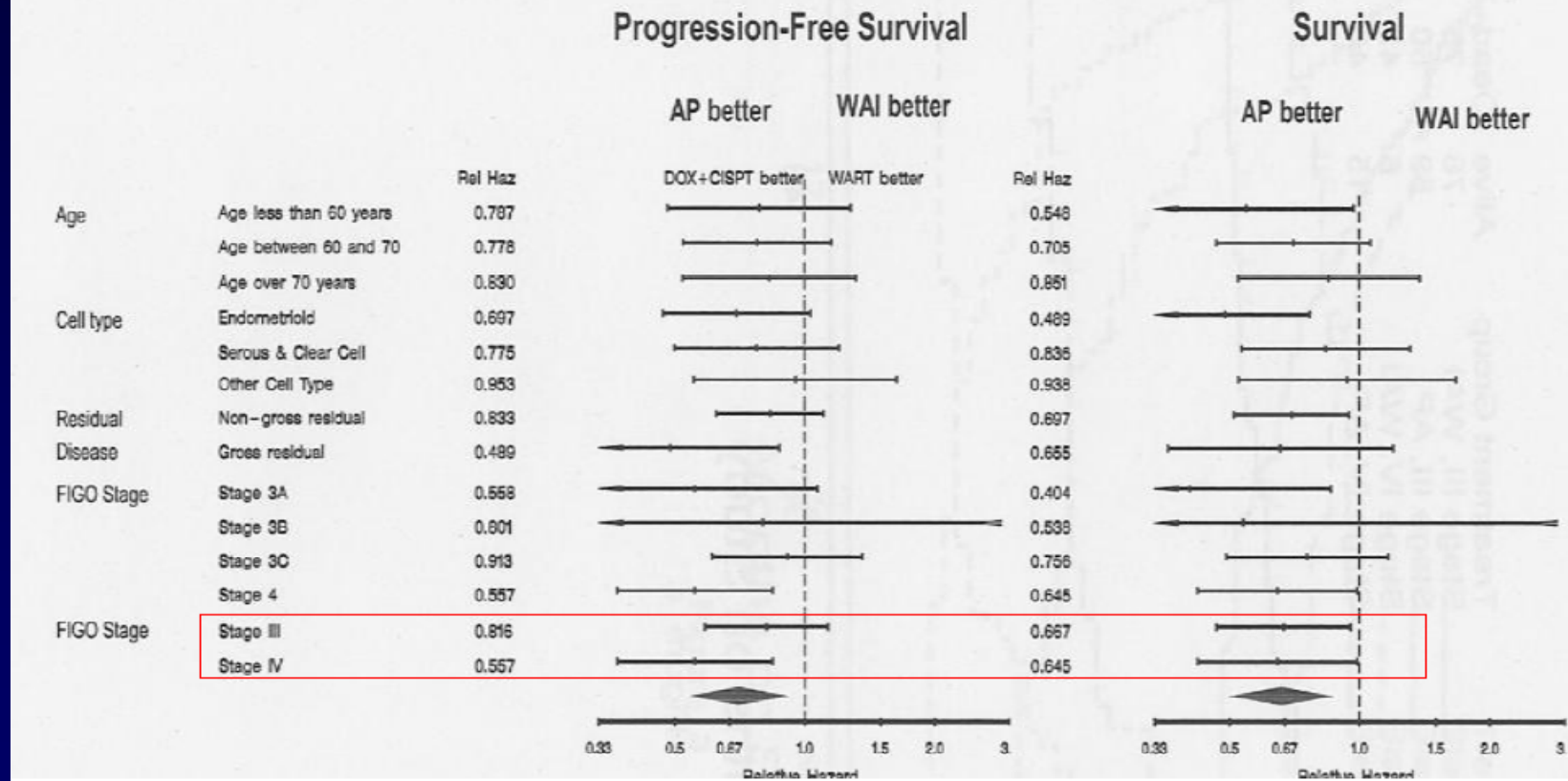


## Overall Survival



# GOG 122: Subgroup Analyses

Treatment Hazard Ratio with 95% CI by Prognostic Group and Endpoint



# NSGO EC-9501/EORTC 55991: Adjuvant Chemotherapy + Irradiation vs Irradiation—Study Schema

## ELIGIBILITY CRITERIA:

- Patients with FIGO stages I, II, IIIA (+ peritoneal cytology only), IIIC (+ pelvic lymph nodes only) if high risk
- All patients with serous, clear cell or anaplastic carcinoma

TAH-BSO +  
surgical  
debulking  
 $\leq 2$  cm  
intraperitoneal  
residual tumor  
(N = 382)

R  
A  
N  
D  
O  
M  
I  
Z  
E

RT + CT\* or CT + RT  
(n = 186)

RT  $\geq 44$  Gy ( $\pm$  BT)  
(n = 196)

Follow up 4.3 years

\*Chemotherapy: doxorubicin + cisplatin (AP), or carboplatin + paclitaxel (TP), or carboplatin + doxorubicin + cisplatin (TAP), or paclitaxel + epirubicin + carboplatin (TEP)

Hogberg T, et al. *J Clin Oncol*. 2007;25(18S): Abstract 5503.

# NSGO EC-9501/EORTC 55991: Treatment Disposition

- 382 patients randomized; 196 RT, 186 RT/CT
- Arms balanced for histologic grade, type
- **Radiation**
  - 92% in each arm completed radiation
  - Median radiation dose in each arm 46 Gy
  - Brachytherapy 39% in RT arm, 44% in RT/CT arm
- **Chemotherapy**
  - Completed 70%, not completed 27%

# NSGO EC-9501/EORTC 55991: Results

Outcome, %	RT (n = 196)	RT/CT (n = 186)	P Value
<b>5-year PFS</b>			
• All patients	72	79	.03
• Ca deaths	74	83	.01
• CT complete	73	87	.009
<b>5-year OS</b>			
• All patients	74	82	.08
• Ca specific	78	88	.02

# Endometrial Carcinoma: Summary of Adjuvant Studies

Treatment				Proposals
<b>RT vs Ø</b> <b>St I-II</b>	GOG-99 (neg)	PORTEC (neg)	ASTECC (neg)	
<b>RT vs CT</b>	GOG-122 (+ Cht)	JGOG233 (+ Cht-III)	<b>St III-IV</b>	GOG-704
<b>RT vs</b> <b>RT+CT</b>	NSGO (+Rt-Cht)	GOG-184	<b>St III-IV</b>	NSGO PORTEC-3
<b>Others</b>	Italian			

# NSGO/EORTC Proposal: Schema

- Stages I-III A intermediate risk
- Randomize between:
  - Regimen 1:  
Radical surgery +  
Chemotherapy (AP, TC, TAP) +  
EBRT  $\geq 44$  Gy, optional brachytherapy
  - Regimen 2:  
Radical surgery +  
Chemotherapy (AP, TC, TAP)

## PORTEC 3

- High-risk patients eligible: IBG3, ICG3, IIG3, IIIA, and IIIC
- Randomize between pelvic RT alone and chemo-RT + consolidation chemo
- Chemo-RT: Standard pelvic RT with cisplatin 50 mg/m<sup>2</sup>, days 1, 22
- Consolidation chemo: carboplatin (AUC 5) and paclitaxel (175 mg/m<sup>2</sup>) x 4 cycles
- Open to accrual, 800 patients planned

# GOG 704 Study Schema

Surgical debulking: Optimal  
Stage III and IVA

RANDOMIZE

XRT 45 Gy  
Cisplatin 50 mg/m<sup>2</sup> D1, D28  
Vaginal brachytherapy

Carboplatin AUC 6  
+ paclitaxel 175 mg/m<sup>2</sup> Q3W x 4

Carboplatin AUC 6  
+ paclitaxel 175 mg/m<sup>2</sup> Q3W x 6

## Part II: Stage IIIC Endometrial Cancer

- Stage IIIC is a systemic disease
- RT improves local control but not OS
- CT improves survival
  - To be defined
    - Better scheme of CT
    - RT or no RT
- To include in ongoing clinical trials

# What Would I Recommend?

## Part II:

Which of the following postoperative treatment strategies would you choose for this patient with stage IIIC endometrial carcinoma?

1. Pelvic +/- para-aortic radiotherapy
2. Chemotherapy followed by radiotherapy
3. Chemotherapy alone
4. Hormonal therapy
5. Observation with no adjuvant therapy
6. **CLINICAL TRIALS**

### Part III:

- She received adjuvant chemotherapy with cisplatin and doxorubicin followed by pelvic radiotherapy
- Fifteen months later **she was investigated due to biliary colic and gallbladder stones. Three suspected nodular lesions up to 2.5 cm were detected in the liver by a CT scan of the abdomen/pelvis. Fine needle biopsy confirmed metastases.**
- Lung CT was normal
- Renal function test are normal, liver tests were slightly elevated

## Part III:

**What would you recommend for this patient now?**

- 1. Hormonal therapy**
- 2. Surgery for liver metastases**
- 3. Re-treat with cisplatin + doxorubicin**
- 4. Carboplatin + paclitaxel**
- 5. Carboplatin + pegylated liposomal doxorubicin**
- 6. Clinical trial of chemotherapy and antiangiogenic agent**

# Treatment of Endometrial Cancer

- **Initial treatment consists of surgery and/or radiation**
- **For those with recurrent or metastatic tumors despite surgery and radiation, the first-line therapy is well established and consists of chemotherapy or hormonal therapy**
- **Second-line therapy is largely ineffective and include chemotherapy or hormonal therapy. Clinical trials are strongly recommended (NCCN)**

# Chemotherapy for Endometrial Cancer

- Taxanes, doxorubicin, platinum agents first and second line
- In untreated patients:
  - Single-agent RR up to 35%
  - Combination RR up to 70%
- PFS up to 8 months, OS up to about 15 months
- Recent review of randomized studies of chemotherapy (11 trials) including 3000 patients
  - Modest increase in PFS and OS
  - Toxic
  - No single regimen recommended
  - Carboplatin/paclitaxel probably favored in US
- Second line: No consensus

# Hormonal Therapy for Endometrial Cancer<sup>1</sup>

- Progestins, anti-estrogens, SERMs, aromatase inhibitors
- Typically better differentiated and more indolent tumors treated up front (endometrioid tumors)
- RR up to 30%
- No good data on superiority of one agent over another or of dose of choice
- Randomized comparison of 220 mg vs 1000 mg MPA<sup>2</sup>
  - No difference: ORR 25%, CR 17%, PFS 3.2 months, OS 11 months
- Second-line: No consensus

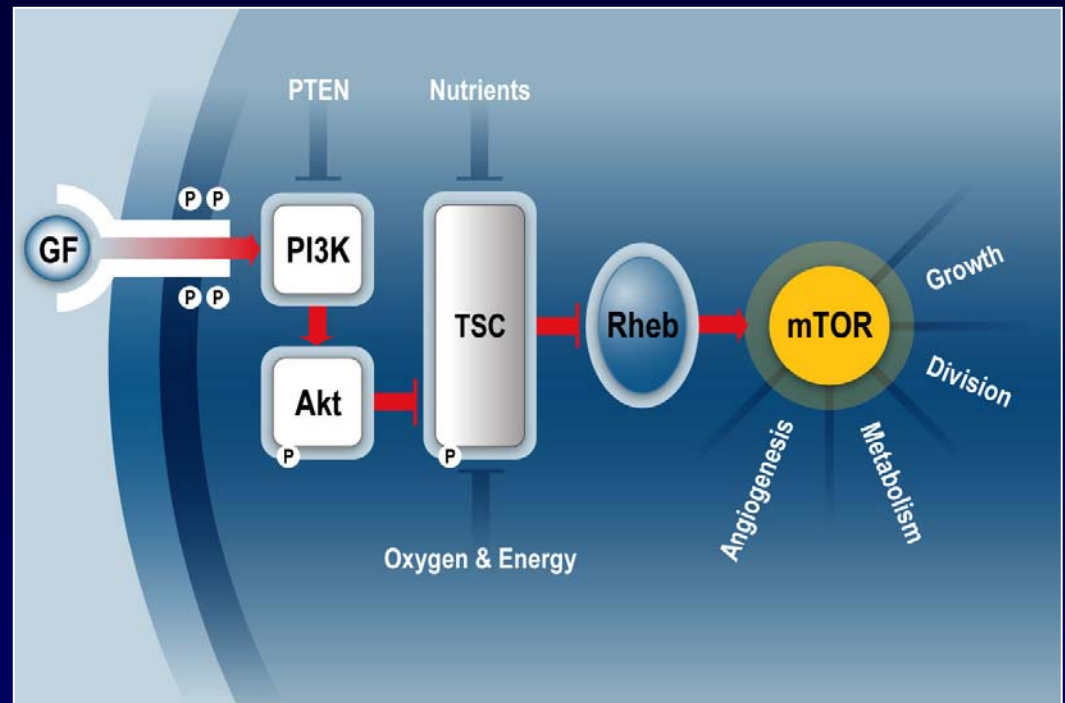
1. Lai CH, et al. *Curr Opin Obstet Gynecol*. 2006;18(1):29-34. 2. Thigpen JT, et al. *J Clin Oncol*. 1999;17(6):1736-1744.

# Molecular Features of Endometrial Cancer

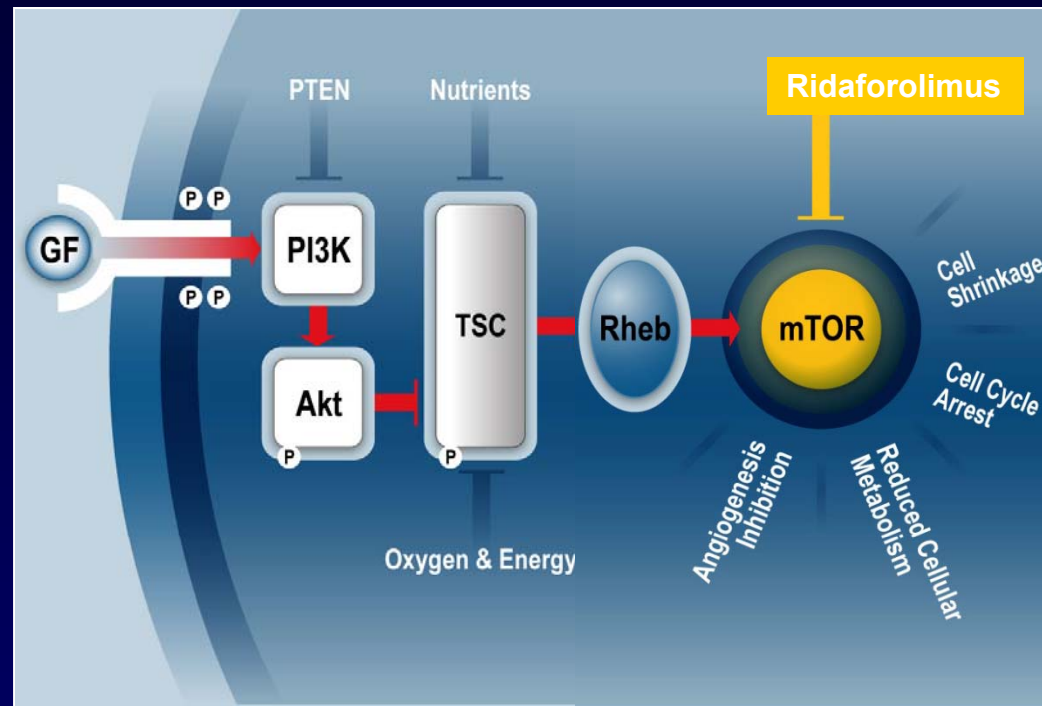
- Type 1
  - Up to 80% of cases
  - Endometrioid histology, associated with estrogen exposure
  - Associated with microsatellite instability syndrome
  - **Almost uniform abnormality in mTOR pathway, with KRAS, PI3K, or PTEN alteration**
- Type 2
  - Most commonly papillary serous or clear cell histology
  - No estrogen association
  - Aggressive course
  - P53 mutation

# mTOR Cell-Signaling Pathway

- A “master cellular switch”
  - Inputs—growth factors, nutrients, oxygen status, energy state
  - Outputs—cell growth, division, metabolism, angiogenesis
- mTOR in cancer: A clinically validated target
  - mTOR pathway activated in several tumor types
  - Changes render tumors hypersensitive to mTOR inhibition
  - mTOR inhibition attacks multiple pathways through a single target



# Ridaforolimus Inhibition of mTOR



- Interferes with cell growth, division, metabolism, and angiogenesis

# Ridaforolimus Phase II Trial in Advanced Endometrial Cancer: Results

- 45 patients with advanced endometrial cancer
- Primary endpoint
  - Clinical benefit response rate to exceed Simon 2-stage criteria of  $\geq 25\%$
  - Clinical benefit defined as CR or PR or stable disease  $\geq 16$  weeks by modified RECIST guidelines
- **Observed clinical benefit response rate: 29%**
- Concluded that ridaforolimus has single-agent activity in endometrial cancer

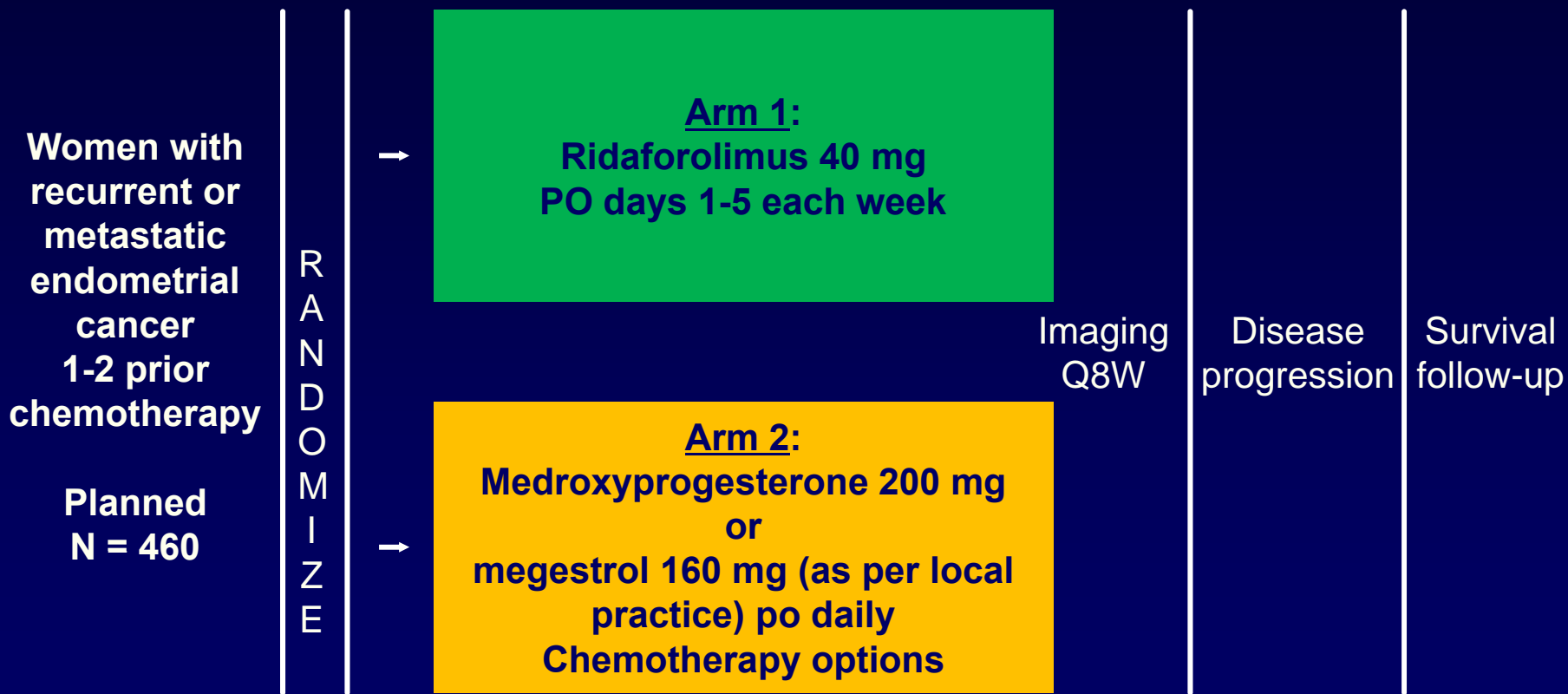
# Temsirolimus (CCI-779) in Endometrial Cancer

- **Phase II study in recurrent or metastatic patients (NCIC CTG Trial IND 160a)<sup>1</sup>**
  - 28 patients evaluable for response
  - 25% partial response; 14% with independent review
  - 57% stable disease (at 8 weeks)
  - PTEN did not predict response to therapy
  - Active in chemotherapy naive endometrial cancer
- **Phase II study of temsirolimus 25 mg IV weekly in previously treated patients<sup>2</sup>**
  - 27 patients evaluable for response
  - 7% partial responses (2 adeno)
  - 44% stable disease (7 adeno, 5 serous)
  - PTEN, p56K pAKT, and pmTOR did not correlate with response

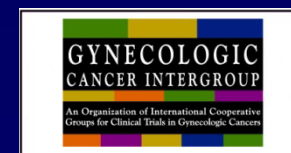
# Everolimus (RAD001) in Endometrial Cancer

- **Phase II study of RAD001 10 mg PO daily**
  - Endpoint: Efficacy
  - 35 patients (28 evaluable for efficacy)
  - 43% CBR (12/28) all with stable disease
  - Median 4 cycles (range 2-10)
  - 17 patients had tissue for immunohistochemistry
    - Expression of pAKT, mTOR, pmTOR and ER-alpha was not associated with response
    - 7 of 10 with patients with loss of PTEN had SD

# EN 8: A Phase III Study of Standard Therapy vs Ridaforolimus in Women with Recurrent or Metastatic Endometrial Cancer Who Have Previously Received Chemotherapy



Interested Groups: ACRIN, AGO-AUST, AGO-OVAR, ANZGOG?, DUTCH GOG, EORTC, GEICO, GINECO, JGOG, MANGO, MITO, NCRI, NSGO, SWOG



# What Would I Recommend?

## Part III:

1. Hormonal therapy
2. Surgery for liver metastases
3. Re-treat with cisplatin + doxorubicin
4. Carboplatin + paclitaxel
5. Carboplatin + pegylated liposomal doxorubicin
6. Clinical trial of chemotherapy and antiangiogenic agent

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Thank you!

