Línies Futures Quimioteràpiques per la Recidiva Endometrial

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Introducció

- The most common gynecologic malignancy in Western World.
  - Increasing incidence and mortality
  - 20% over the last decade
- 43.470 new cases per year in the U.S→7,959 cancer deaths (ACS, 2010).
  - Fourth most common cancer in women in in the US.
  - Life-time risk 1/40
- Specific 5 years cancer survival 85%.

Endometrial Carcinoma Subtypes

Type I EC

Endometrioid ADC

- 80 % EC
- Frequently coexist or preceded by endometrial hiperplasia
- Related to unopposed estrogen
- Typically shows ER+
- Low grade tumors
- Most confined to the uterous
- Favorable prognosis
  - 5 years specific OS: 85%

Type II EC

Serous Papillary and Clear Cell

- 10 % EC
- Developing from atrophic or polyp endometrium
- No strogen related
- Typically ER –
- High grade tumors
- Advanced stage
- Poor prognosis
  - 5 years specific OS: 58%

Bokhman JV et al. Gyn Oncol 1983

Endometrial Carcinoma Subtypes and Molecular alterations

Type I Endometrioid

- PTEN loss of function (up to 60%)
- PIK3CA mutation (30%)
- K-ras mutation (10-30%)
- FGFR mutations (12-16%)
- Microsatellite instability (20-45%)
- Nuclear accumulation of B-catenin (18-47%)

Type II Papillary serous

- P53 mutations (90%)
- E-cadherine inactivation (60-90%)
- Her-2/neu (40-80%)

Prognostic Factors EC

- **FIGO stage**
- Depth of MMI
- Grade
- **Histology: Type I vs Type II**

Other Prognostic Factors.

- Positive Peritoneal citology
- LVSI
- Tumor size (>2cm)

Prognostic Factors EC: FIGO + Histology

Endometrioid		Serous/Clear cell
Stage I-II	84%	62%
Stage III-IV	16%	38%
5-year survival rates		
Stage I-II	70-90%	50-60%
Stage III-IV	15-40%	5-20%

Deaths from Uterine Cancer

Non-endometrioid cancers disproportionately contribute to deaths

Risk Stratification (FIGO 2009): Basis for Adjuvant Chemotherapy

- Low risk : 55% of patients
  - IA (<50% IM) G1-2 endometrioid carcinoma

- Intermediate risk: 30% of patients
  - IA(<50% IM) G3 endometrioid carcinoma
  - IB (> 50% IM) G1-2 endometrioid carcinoma

- High risk: 15% of patients
  - IB-G3 : **31% distant failure/5yr OS: 58%**
  - II, III-IV: **5yr OS: 20-70%**
  - Any stage and clear cell or serous carcinoma

FIGO staging 2009. Pecorelli et al.

ADVANCED / RECURRENT ENDOMETRIAL CARCINOMA TREATMENT

- HORMONOTHERAPY
- CHEMOTHERAPY
- MOLECULAR TARGETED THERAPIES

Hormone Therapy EC

Study	Drug	*n*	G1 (%)	G2 (%)	G3 (%)
Piver *et al.*[52]	MPA/HPC	55	20[a]	—	6.7
Thigpen *et al.*[55]	MPA	47	18	52	30
Thigpen *et al.*[48]	MPA	205	37	23	9
Lentz *et al.*[56]	MA	37	37[a]	—	8
Thigpen *et al.*[69]	TAM	68	23	14	3
Fiorica *et al.*[23]	MA/TAM	61	33	24	22
Jeyarajah *et al.*[18]	Leuprorelin	32	100	15	25

MA, megestrol acetate; TAM, tamoxifen; HPC, hydroxyprogesterone caproate.

[a] G1 and G2 combined.

Predictors of response:

- Well differentiated tumors
- Long disease free interval
- Pulmonary metastasis
- Estrogen and/or Progesterone receptor positive

ADVANCED / RECURRENT ENDOMETRIAL CARCINOMA TREATMENT

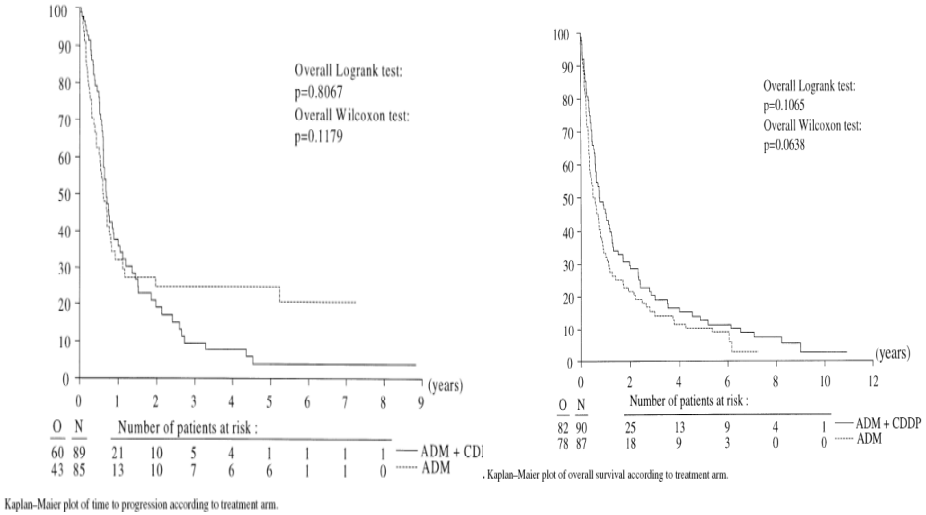
CHEMOTHERAPY

- Active drugs commonly employed first line:
  - Doxorubicin
  - Cisplatin
  - Paclitaxel

CHEMOTHERAPY BASED ON DOXORUBICIN +- CISPLATIN

EORTC 55872. *Aapro et al. Annals of Oncol 2003*

- Significant higher ORR : 43% vs 17%, p 0.001



Kaplan-Maier plot of time to progression according to treatment arm.

. Kaplan-Maier plot of overall survival according to treatment arm.

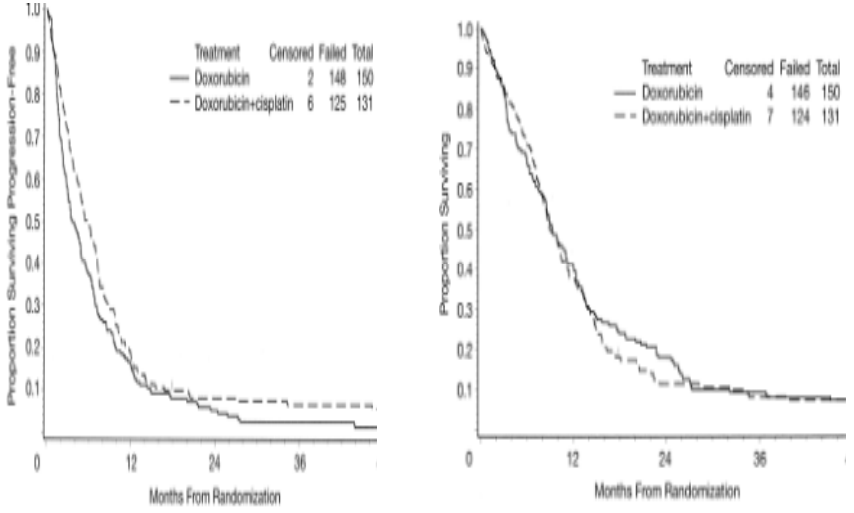
NO SIGNIFICANT DIFFERENCES

PFS (8 m vs 7m, p 0.8067)

OS (9m vs 7m, p 0.107)

GOG # 107. *Thigpen et al. JCO 2004*

- Significant higher ORR: 42% vs 25%, p 0.004



SIGNIFICANT DIFFERENCES

PFS (5.7 m vs 3.8m, HR 0.73 [0.57-0.939] p 0.014) but NOT OS (9 m vs 9.2 m, HR 0.928 [0.72-1.18])

Chemotherapy or Radiotherapy in Advanced EC

- GOG-122: *Randall et al, JCO January 2006*
  - WAI vs Cisplatin-Doxorubicin

PFS

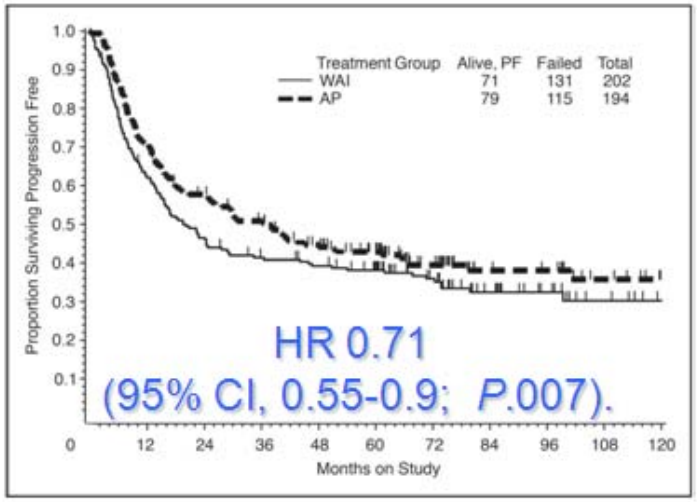


Fig 1. Progression-free survival by randomized treatment group. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation; PF, progression free.

Δ PFS@ 60 months of 12%
(50% for AP *v* 38% for WAI).

OS

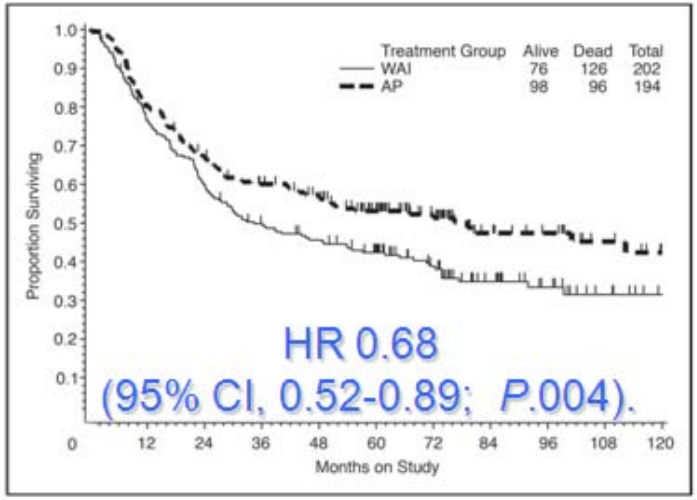


Fig 2. Survival by randomized treatment group. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation.

Δ PFS@ 60 months of 13%
(55% for AP v 42% for WAI).

Is Adding Taxanes Beneficial?

Original article

Annals of Oncology 15: 1173–1178, 2004
DOI: 10.1093/annonc/mdh316

Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study

G. F. Fleming[1]*, V. L. Filiaci[2], R. C. Bentley[3], T. Herzog[4], J. Sorosky[5], L. Vaccarello[6] & H. Gallion[7]†

ORR	Serous	Others
Doxo-CDDP	41 %	40 %
Doxo-Paclitaxel	37 %	43 %

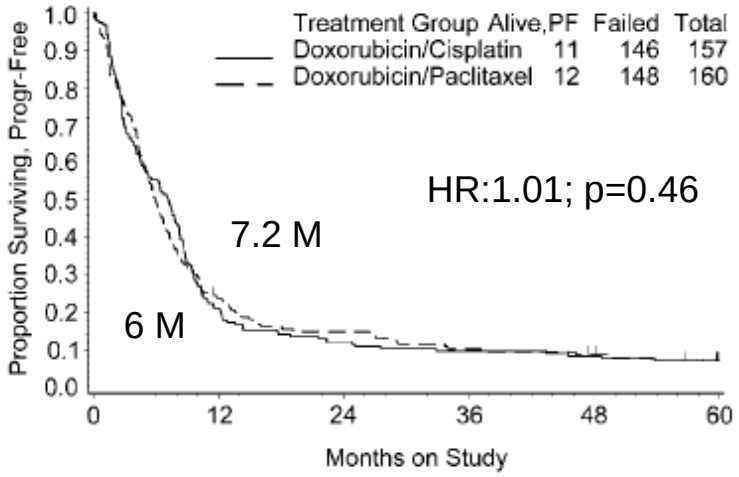


Figure 1. Progression-free survival (PFS) by randomized treatment.

NO improvement in RR, PFS or OS, with higher toxicity.

GOG # 163

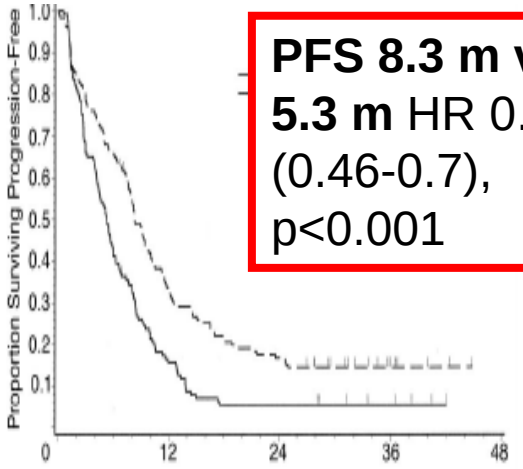
VOLUME 22 · NUMBER 11 · JUNE 1 2004

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

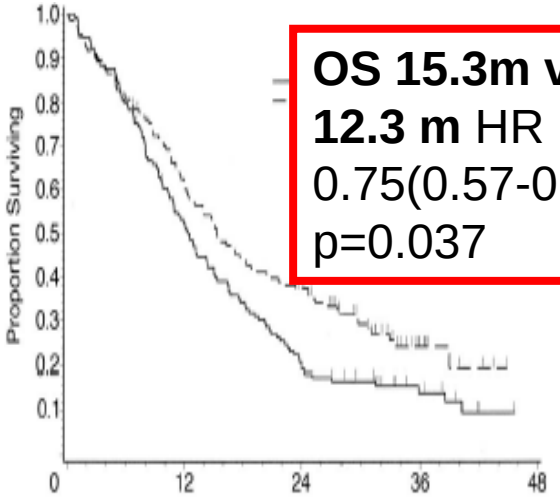
Phase III Trial of Doxorubicin Plus Cisplatin With or Without Paclitaxel Plus Filgrastim in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study

Gini F. Fleming, Virginia L. Brunetto, David Cella, Katherine Y. Look, Gary C. Reid, Adnan R. Munkarah, Richard Kline, Robert A. Burger, Annekathryn Goodman, and R. Tucker Burks

- N= 263 EC stage III, IV, or recurrent and CT naïve patients.
- Doxo 60 mg/m2+CDDP 50 mg/m2 vs Doxo 45 mg/m2 +CDDP 50 mg/m2+ Paclitaxel 160 mg/m2 3h day 2 + G-CSF(d3-12)
- 7 cycles (47% vs 52%)
- Improvement RR TAP 57% vs AP 34%



PFS 8.3 m vs 5.3 m HR 0.6 (0.46-0.7), p<0.001



OS 15.3m vs 12.3 m HR 0.75(0.57-0.98, p=0.037

PACLITAXEL/ CARBOPLATIN ENDOMETRIAL CARCINOMA

Table 6. Summary of published studies on carboplatin and paclitaxel in advanced and recurrent endometrial cancer

Authors	Type of study	Number of points	Stage	Previous therapy	Chemotherapy	RR (%)	PFS (months)	OS (months)
Price[9]	Phase II, prospective	20	A + R	NR	Paclitaxel, 135–175 mg/m^2; Carboplatin, AUC 5	63	NR	NR
Hoskins[7]	Phase II, prospective	63	A + R	No chemotherapy	Paclitaxel, 175 mg/m^2; Carboplatin, AUC 5–7	50–78	NR	15–26
Scudder[10]	Phase II, prospective	57	A + R	Prior chemotherapy	Paclitaxel, 175 mg/m^2; Carboplatin, AUC 6; Amifostine	40	7	14
Sovak	Retrospective	85	A + R	Prior chemotherapy	Paclitaxel, 60–175 mg/m^2; Carboplatin, AUC 4–6	43	5.3	13.2

A, advanced; R, recurrent; AUC, area under the curve; NR, not reported.

GOG-0209

STAGE III & IV OR RECURRENT
ENDOMETRIAL CANCER
Measurable Disease

REGIMEN I
Doxorubicin 45 mg/m^2 IV day 1
Cisplatin 50 mg/m^2 day 1
3-hr Paclitaxel 160 mg/m^2 day 2
G-CSF

REGIMEN II
Carboplatin AUC = 6 IV day 1
3-hr Paclitaxel 175 mg/m^2 day 1

Second Line EC Treatment

Chemotherapy in Recurrent EC

- Active drugs commonly employed first line:
  - Doxorubicin
  - Cisplatin
  - Paclitaxel

- Lack of agents in second or later line treatment
- NO FDA aproved agents in women previously treated with chemotherapy

129-Series: Agents tested

AGENT	N	RR (%)	Prob (PFS>6m)	OS
Etoposide	25	0	0.08	8.7
Paclitaxel	48	25	0.21	9.9
Pegylated Liposomal Doxorubicin	43	9	0.23	8.2
Topotecan	28	7	0.25	9.0
Oxaliplatin	52	13	0.27	10.9
Docetaxel	27	8	0.11	6.4
Pemetrexed	27	4	0.28	9.4
Ixabepilone	50	12	0.20	8.7

RR Thresholds: 10% - 25%

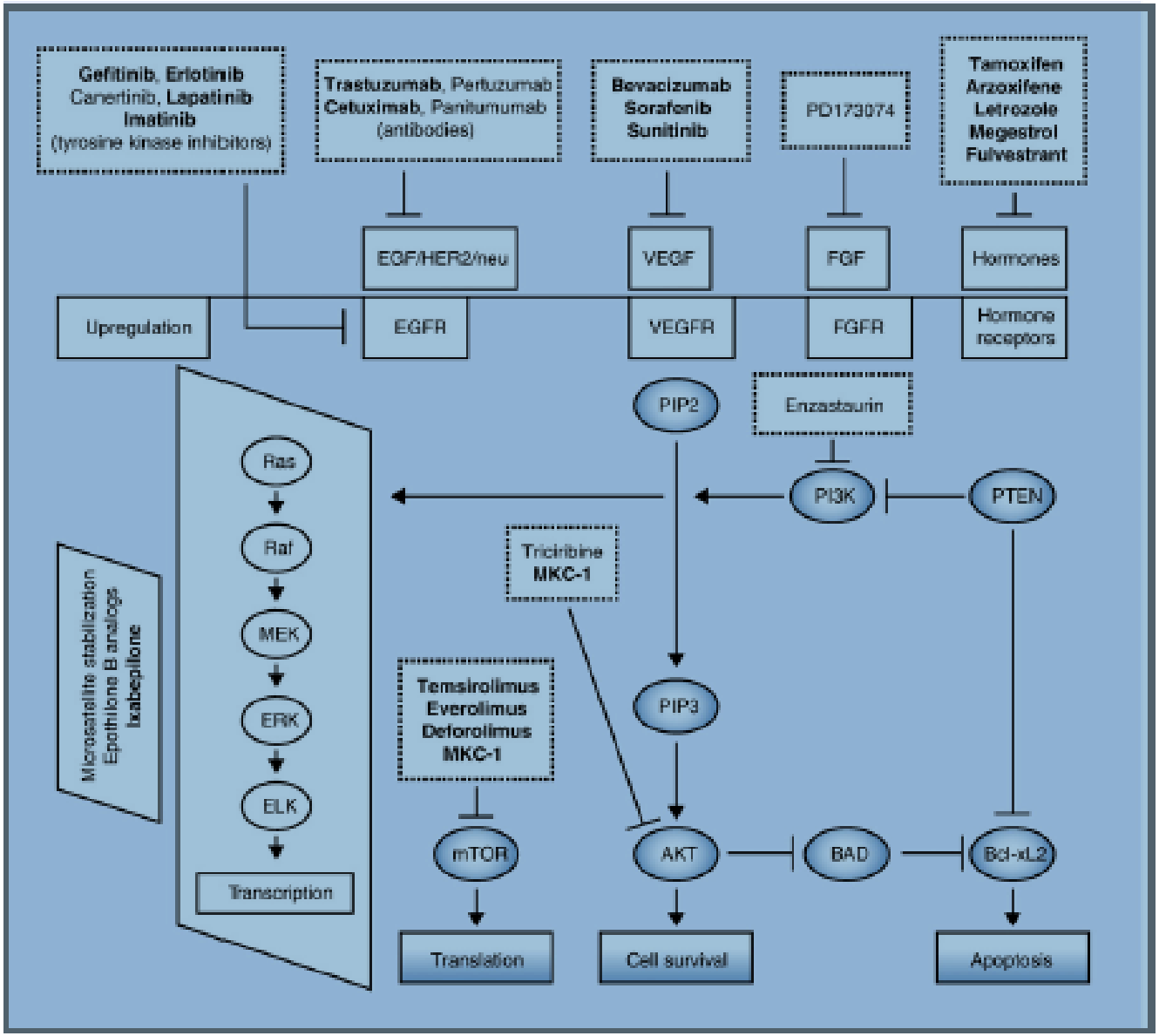

ADVANCED, RECURRENT AND METASTATIC ENDOMETRIAL CANCER
THE FUTURE

Endometrial Cancer:
Molecular Targeted Therapies

Molecular Alterations in EC

	Type 1 Carcinoma	Type 2 Carcinoma
PI3KCA mutation	35-40%	15%
PTEN inactivation	55-80%	5 %
K ras mutation	15-30%	0-5%
B-Catenin mutation	20-40%	0-3%
Microsatellite Instability	15-45%	0-5%
p53 mutation	10-20%	80-90%
E-Cadherin inactivation	10-20%	60-90%
Her2- overexpression	7-10%	20-28%
FGFR-2 mutation	12-16%	1%
p16 inactivation	10%	40%

Targets and Targeted Therapies in EC



Clinical Trials: Exploring biologic therapy

- Gynecologic Oncology Group
  - Biologics: 229-series
  - Major eligibility: Advanced, recurrent or metastatic
  - Up to two prior chemotherapeutic regimens allowed
  - No prior non-cytotoxic agents allowed (excl hormone therapy)
  - Active agent of interest: PFS at 6 months
  - OS and RR are secondary endpoints
  - Thresholds:
    - PFS6m: 15%, 35%
    - Response Rate: 20%, 40%

229-Series: Agents tested

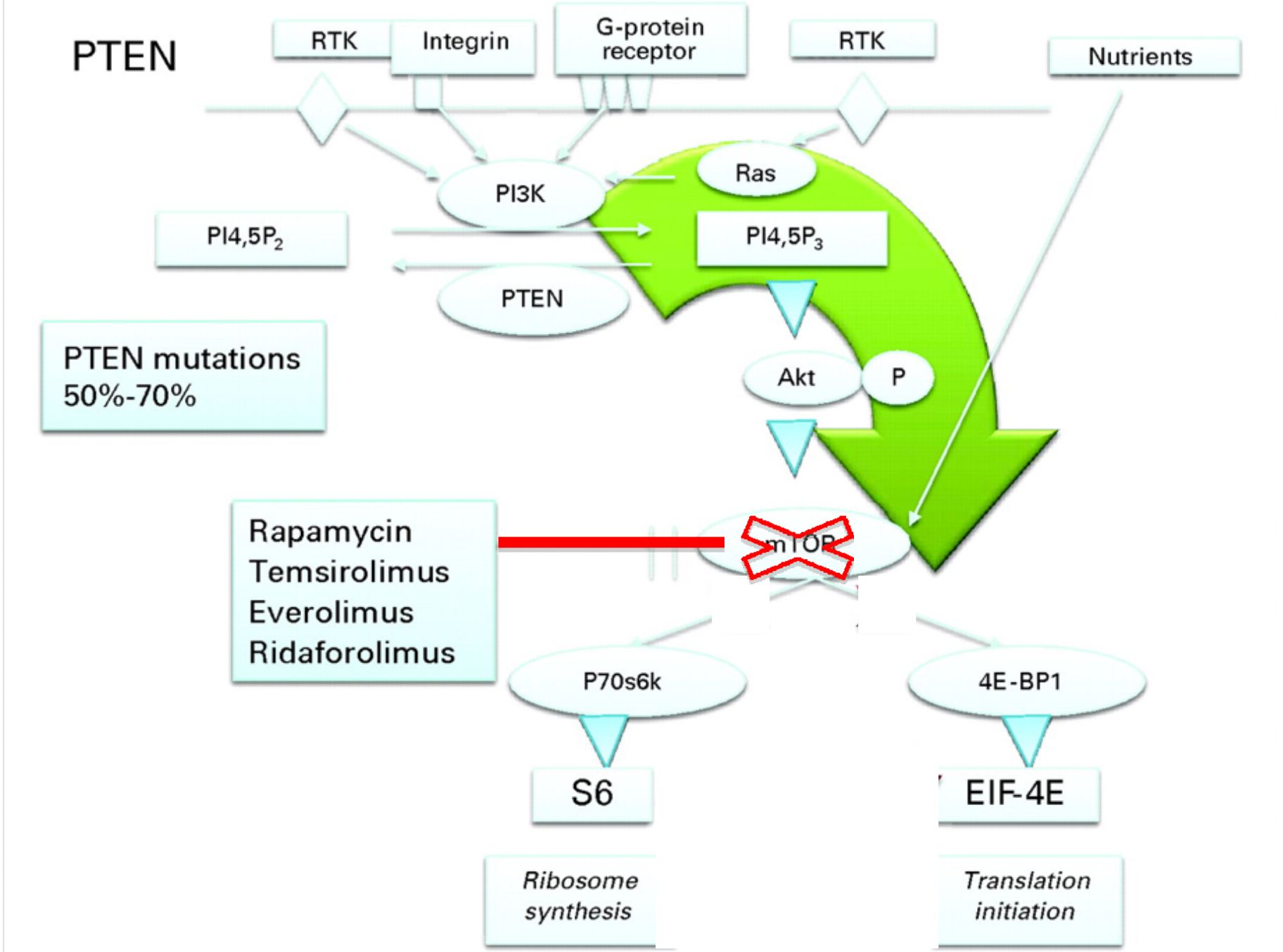
AGENT	N	RR (%)	Prob (PFS>6m)
Gefitinib	26	3.8	0.15
Lapatanib	30	3.3	0.10
Bevacizumab	52	13.5	0.40

- Ongoing studies (completed accrual):
  - VEGF-TRAP

KM Lesslie, et al. J Clin Oncol 2009;27:e165-t2; C Aghajanian, et al. J Clin Oncol 2011; 29:2259-2265

Novel agents/combinations being tested

- mTOR inhibitors
- Fibroblast growth factor receptor (FGFR) inhibitors
- Receptor Tyrosine Kinase (RTK) inhibitors


PTEN
RTK
Integrin
G-protein receptor
RTK
Nutrients
PI3K
Ras
PI4,5P2
PI4,5P3
PTEN
PTEN mutations
50%-70%
Akt
P
Rapamycin
Temsirolimus
Everolimus
Ridaforolimus
mTOR
P70s6k
4E-BP1
S6
EIF-4E
Ribosome synthesis
Translation initiation

PTEN and Endometrial Carcinoma

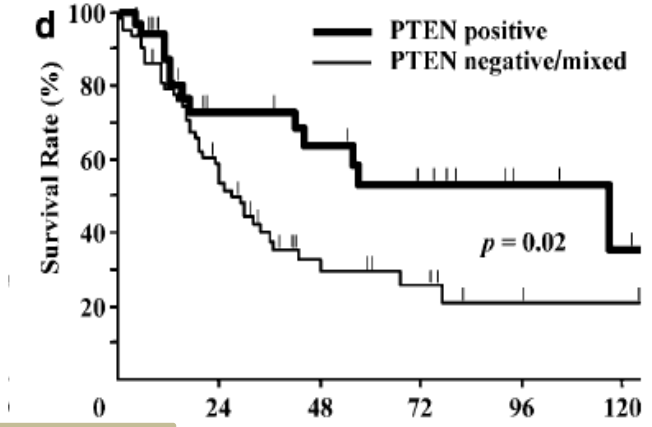
- **PTEN is inactivated in up to 83% of EC** and is the most common genetic defect in EC type I.
  - Mutations 35-40%
  - Deletions or epigenetic silencing by hypermetilation
  - Inactivation of both alleles generates PTEN protein null function
- PTEN acts as a gatekeeper for endometrial carcinogenesis.
- PTEN mutations more frequent in early stage EC
  - Stage I (55%) vs Stage III/IV (20%)
- PTEN as prognostic factor is controversial
  - 75% of EC presented with stage I
  - Predominantly observed in endometrioid carcinomas

PTEN EXPRESSION IS ASSOCIATED WITH PROGNOSIS FOR PATIENTS WITH ADVANCED ENDOMETRIAL CARCINOMA UNDERGOING POSTOPERATIVE CHEMOTHERAPY

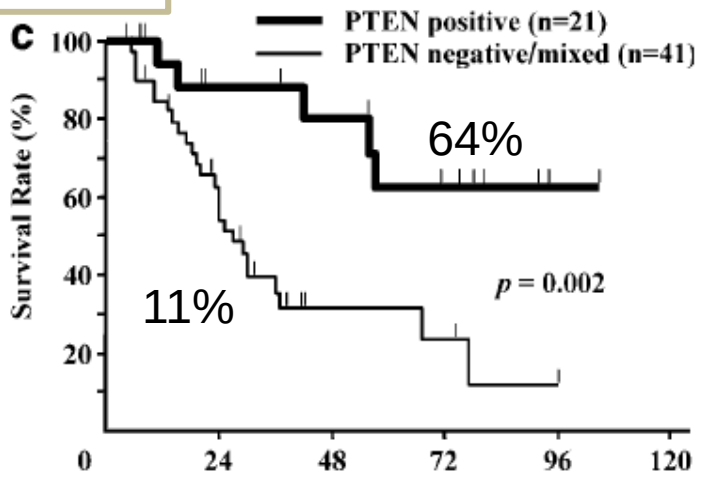
N= 98	PTEN staining		p
	Negative/mixed (n = 64)	Positive (n = 34)	
Age (years)			
Mean	58.1	59.4	0.50
Range	30–75	36–78	
FIGO stage			
IIIc	55	32	0.32
IV	9	2	
Myometrial invasion			
<1/2	14	9	0.61
≥1/2	50	25	
Histologic grade			
G1	21	16	0.38
G2	25	11	
G3	18	7	

- 2/3 pts underwent platinum based CT.

Overall Survival



Adjuvant CT



Kanamori Y. Int J Cancer 2002

PTEN mutation in endometrial cancers is associated with favorable clinical and pathologic characteristics.

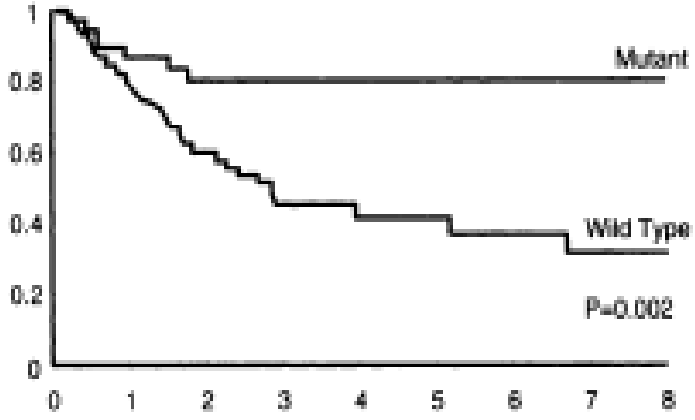
Risinger et al. CCR 1996

PTEN mut: 32%

	All cases (n = 136) No./total	(%)	P
Histologic grade			
Well differentiated	14/29	(48%)	0.1
Moderately differentiated	16/57	(28%)	
Poorly differentiated	14/50	(28%)	
Histologic type			
Endometrioid	43/115	(37%)	0.004
Serous/clear cell	1/21	(5%)	
Myometrial invasion*			
None	7/14	(50%)	0.06
Inner third	14/44	(32%)	
Middle third	13/34	(38%)	
Outer third	9/44	(20%)	
Stage			
IA	6/11	(55%)	0.01
IB	16/37	(43%)	
IC	7/17	(41%)	
II	1/5	(20%)	
IIIA†	3/18	(17%)	
IIIB			
IIIC	5/24	(21%)	
IV	6/24	(25%)	
Recurrence			
No	38/93	(41%)	0.003
Yes	6/43	(14%)	

	All cases (n = 136) No./total	(%)	P
DNA ploidy			
Diploid (DNA index <1.2)	21/54	(39%)	0.20
Aneuploid (DNA index ≥1.2)	5/22	(23%)	
p53 overexpression			
No	35/89	(39%)	0.006
Yes	5/36	(14%)	
Microsatellite instability			
No	20/81	(25%)	0.004
Yes	12/20	(60%)	

Overall Survival

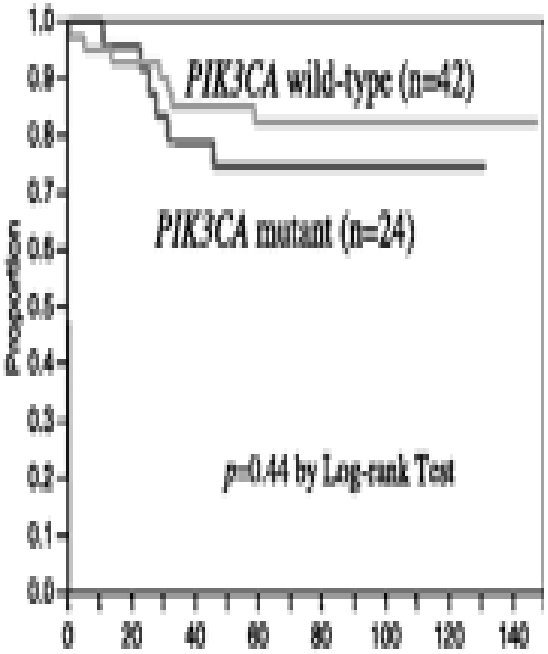


PI3KCA mutations in EC

- PI3KCA mutations in EC range from **35%-40**%, mainly in Exon 9 (helicoidal domain) or Exon 20 (kinase domain).
- Type PIK3CA mutations are different according to grade.
- Exon 9 mutations have not been reported in type II tumors, whereas Exon 20 mutations have been reported in 21% and correlates with Stage, Grade and deeper MI

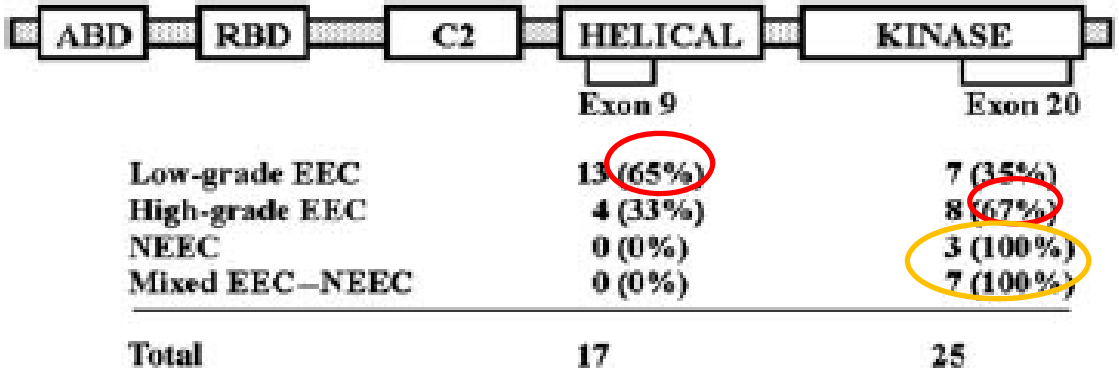
Catasus et all. Modern Pathology 2008.

PI3KCA mutations in EC



Katsutoshi Oda, et al. CCR 2005

- PI3KCA mutational status alone is not a marker of poor prognostic
- PI3KCA mut not associated with grade or stage



Low-grade EEC	13 (65%)	7 (35%)
High-grade EEC	4 (33%)	8 (67%)
NEEC	0 (0%)	3 (100%)
Mixed EEC–NEEC	0 (0%)	7 (100%)
Total	17	25

Lluis Catasus et al. Modern Pathology 2009

- PI3KCA mutational status related with grade and histology

Coexisting mutations in EC

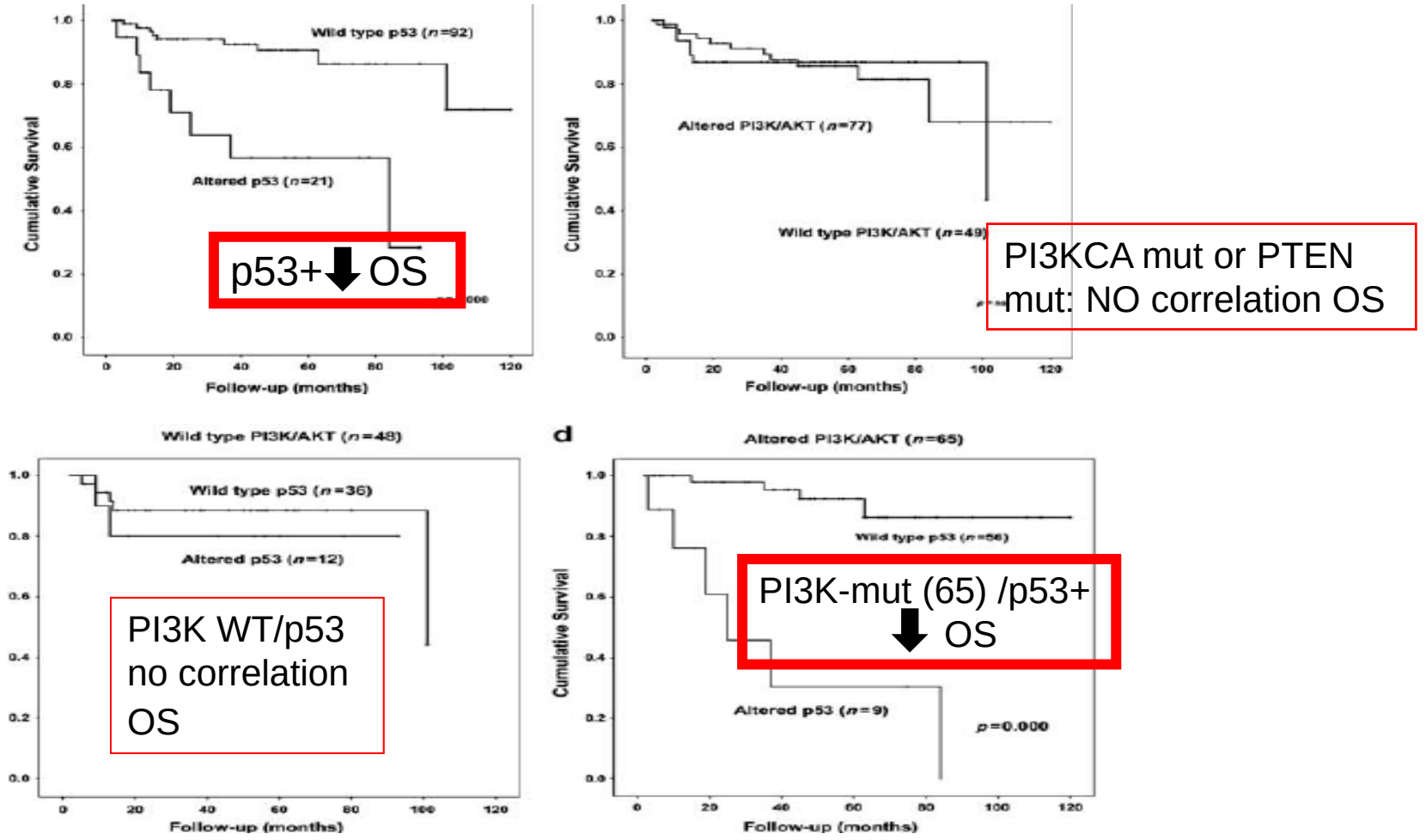
- PTEN mutations more frequent than PI3KCA
- PI3KCA mut not affect prognostic caused by PTEN

- PI3KCA mutation and p53 alterations are associated with poor prognosis (type 2)

Catasus et al. Modern Pathology 2009.

Concomitant PI3K–AKT and p53 alterations in endometrial carcinomas are associated with poor prognosis

Lluis Catasus, Alberto Gallardo, Miriam Cuatrecasas and Jaime Prat



Modern Pathology 2009

mTOR Inhibitors
Endometrial Carcinoma

mTOR Inhibitors EC

- Deforolimus
- Everolimus
- Temsirolimus
- Ridaforolimus
- Everolimus + Letrozol

mTOR Inhibitors EC

AGENT	N	Prior Regimens	RR (%)	CBR (%)	Duration of SD (Median, m)	Histologies
Temsirolimus[2]	19	0	25	82	8.7	E
Temsirolimus[2]	27	1	7	51	3.5	E
Deferolimus[1]	45	2	7	33	<4	Any
Everolimus[2]	35	2	0	43	4.5	E

CBR: CR + PR + SD $\geq$ 8 weeks

Common AE:

Fatigue (30%); Anemia (30%);

[1]N. Colombo et al, ASCO 2007;[2] BM Slomovitz et al, Cancer 2010;

mTOR Inhibitors EC

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Study of Temsirolimus in Women With Recurrent or Metastatic Endometrial Cancer: A Trial of the NCIC Clinical Trials Group

- N= 60 (29 endometrioid, 31 other)
- N= 60 (33 chemo-naive, 27 prior chemo)

Table 3. Response by Grade and Histology in Chemotherapy-Naive (Group A) and Chemotherapy-Treated (Group B) Patients

	Group A (n = 29)				Group B (n = 25)			
	PR		SD		PR		SD	
Response	No.	%	No.	%	No.	%	No.	%
RECIST response (investigator assessed)	7	24	20	69	2	4	12	48

93%

50%

AE: Fatigue (63%); Rash (40%); Mucositis (50%); Pneumonitis (40%)

PTEN, Histology and mTOR Inhibitors in EC

Response by Grade and Histology in Chemotherapy-Naive (Group A) and Chemotherapy-Treated (Group B) Patients

Response	Group A (n = 29)				Group B (n = 25)			
	PR		SD		PR		SD	
	No.	%	No.	%	No.	%	No.	%
RECIST response (investigator assessed)	7	24	20	69	2	4	12	46
Grade								
1	2/6		4/6		0/2		2/2	
2	1/12		7/12		0/3		0/3	
3	1/12		8/12		1/18		7/18	
Histology								
Endometrioid	2/19		12/19		1/10		5/10	
Serous/clear cell	2/6		3/6		0/10		6/10	

- **PTEN Loss (IHQ): NO CORRELATION WITH RESPONSES**
  - Group A: 20/33
  - Group B: 11/27
- **PTEN mutations** (17/31 group A). **NO CORRELATION WITH RESPONSES**
- **HISTOLOGY: NO CORRELATION WITH RESPONSES**
- **EFFICACY RELATED WITH NO PRIOR CHEMOTERAPY!!!**

Oza A et al, JCO 2011

A Randomized, Phase 2 Trial of Ridaforolimus Compared With Progestin or Chemotherapy in Female Adult Patients With Advanced Endometrial Carcinoma

A.M. Oza,[1] A. Poveda,[2] A. Clamp,[3] S. Pignata,[4] G. Scambia,[5] J.M. Del Campo,[6] M. McCormack,[7] L. Sevcik,[8] B. M. Schwartz,[9] S. Guan,[10] R. Lee,[10] J.D. Cheng,[10] F. Haluska[11]

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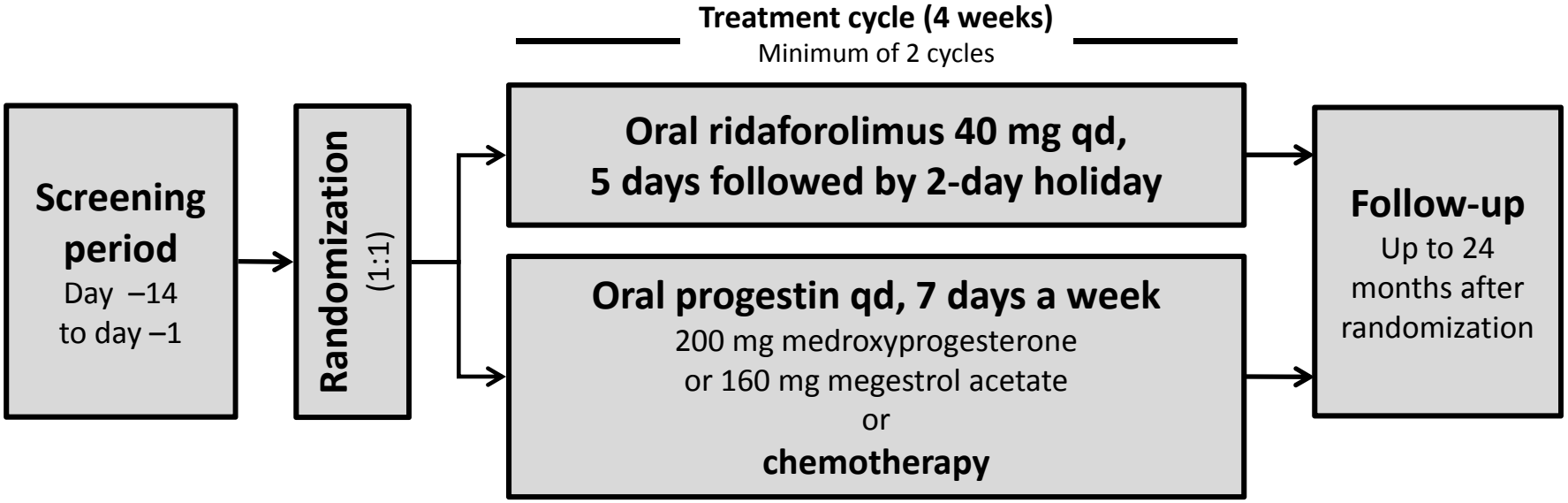
[7]University College Hospital, London, United Kingdom
[8]University Hospital Ostrava, Ostrava, Czech Republic
[9]Schwartz Gyn Onc PA, Brightwaters, NY, United States
[10]Merck Research Laboratories, North Wales, PA, United States
[11]ARIAD Pharmaceuticals Inc., Cambridge, MA, United States

This trial was sponsored by Merck and Co.

ASCO Annual '11 Meeting

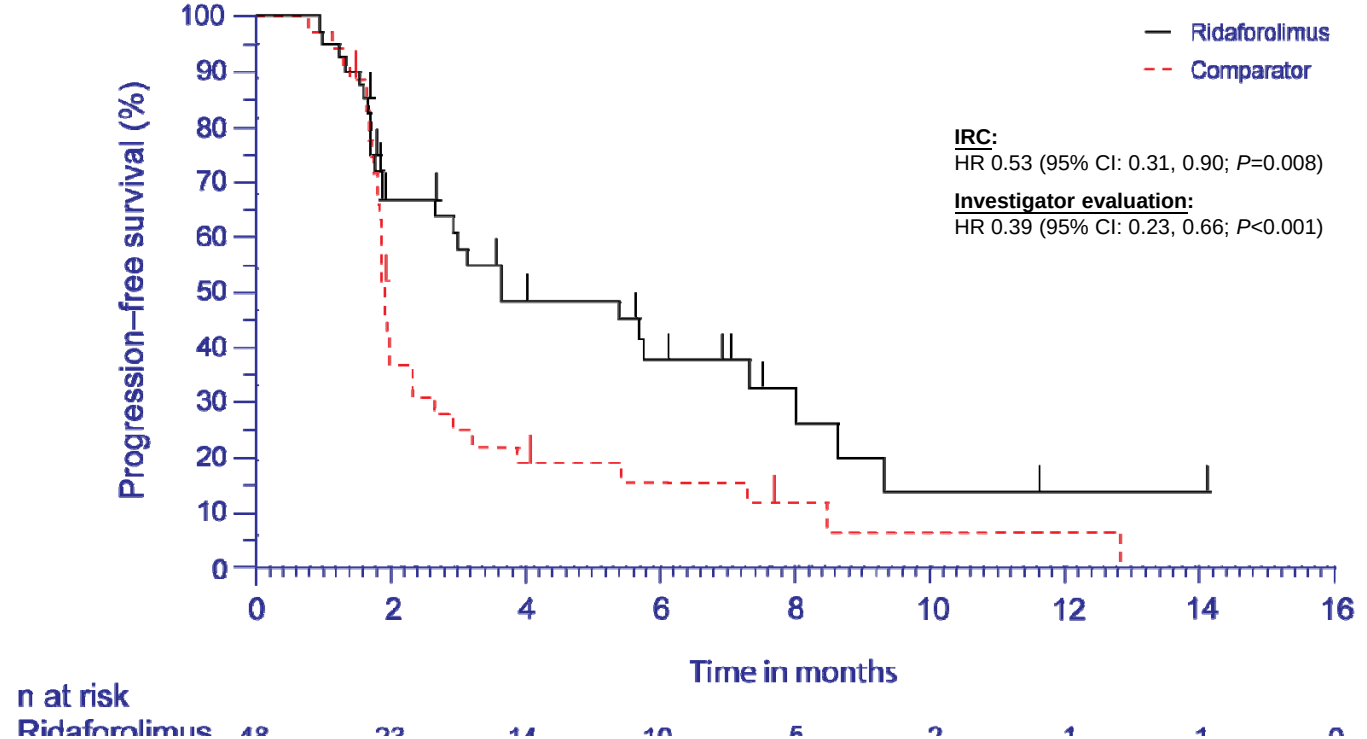
Study design overview



- Randomized, open-label, active control, multicenter trial (39 sites)
- 114 patients enrolled to receive ridaforolimus or progestin
  - 50% non-endometrioid
  - Chemotherapy added as an option for the control group after trial initiation
- Efficacy assessed by CT scan every 8 weeks (RECIST guidelines)

Progression-free survival

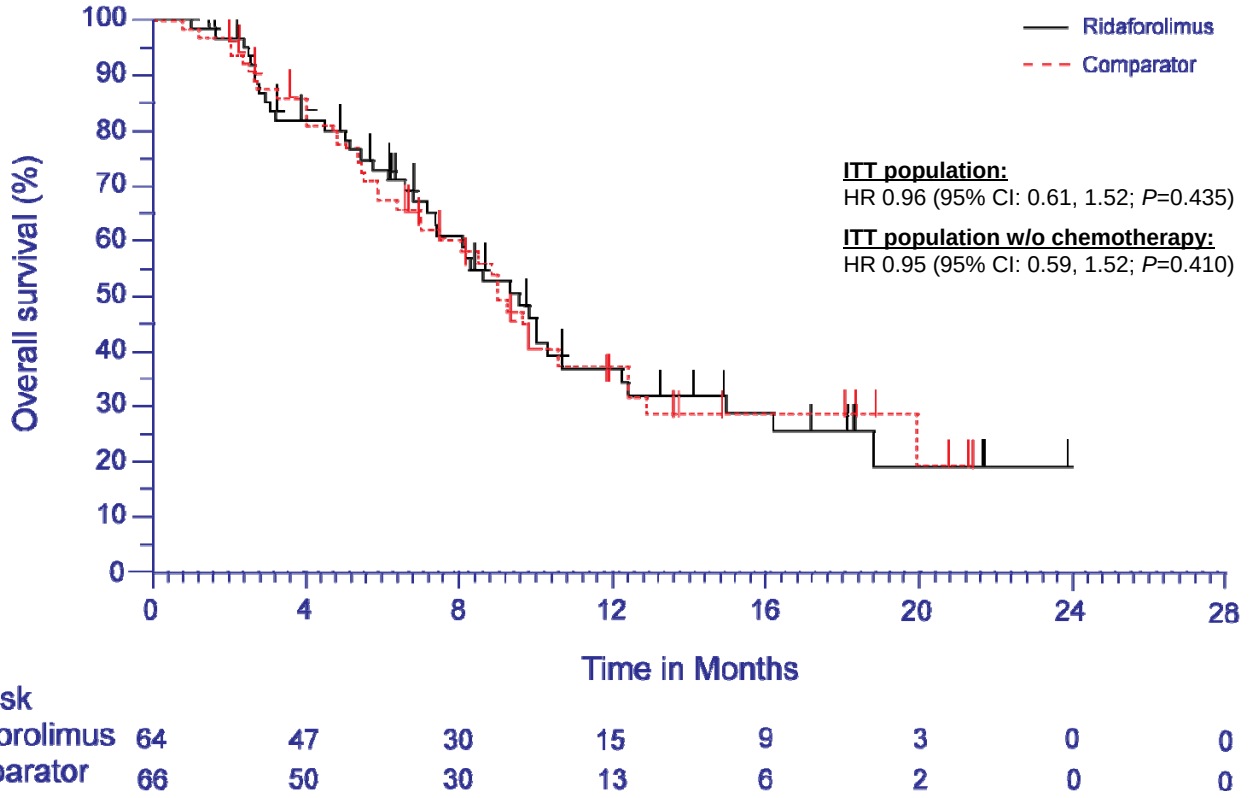
(treated patients with at least one baseline and one posttreatment radiological scan)



	Ridaforolimus (N=48)		Comparator (N=47)	
	IRC		IRC	
Median PFS, months	3.6		1.9	
Clinical Benefit Rate	17 (35.4%)		10 (21.3%)	

Overall survival

(ITT population)



	Ridaforolimus (N=64)	Comparator (N=66)	Comparator w/o chemotherapy (N=53)
Median OS, months	9.6	9.0	8.9
95% CI for median OS	(7.4, 12.3)	(7.0, 12.2)	(6.7, 10.6)
Deaths, n (%)	38 (59.4)	38 (57.6)	32 (60.4)
Deaths at 4 months, n (%)	11 (17.2)	11 (16.7)	9 (17.0)

ITT=intention to treat; HR=hazard ratio; CI=confidence interval; OS=overall survival

Most common adverse events reported in ≥ 20% of all patients in any group

(All patients as treated)

Treatment-related AE, n (%)	Ridaforolimus (N=64)		Comparator (N=65)	
	All grades, n (%)	Grade 3/4, n (%)	All grades, n (%)	Grade 3/4 , n (%)
Diarrhea	30 (46.9)	6 (9.4)	7 (10.8)	1 (1.5)
Mucosal inflammation	25 (39.1)	3 (4.7)	0	0
Anorexia	23 (35.9)	3 (4.7)	3 (4.6)	1 (1.5)
Nausea	19 (29.7)	2 (3.1)	13 (20.0)	2 (3.1)
Asthenia	19 (29.7)	5 (7.8)	7 (10.8)	0
Vomiting	18 (28.1)	3 (4.7)	11 (16.9)	0
Hyperglycemia	18 (28.1)	12 (18.8)	2 (3.1)	0
Abdominal pain	17 (26.6)	2 (3.1)	11 (16.9)	3 (4.6)
Stomatitis	17 (26.6)	4 (6.3)	2 (3.1)	0
Fatigue	16 (25.0)	3 (4.7)	12 (18.5)	1 (1.5)
Rash	16 (25.0)	0	1 (1.5)	0
Anemia	15 (23.4)	8 (12.5)	10 (15.4)	2 (3.1)
Pyrexia	13 (20.3)	0	1 (1.5)	1 (1.5)
Hypercholesterolemia	13 (20.3)	2 (3.1)	0	0

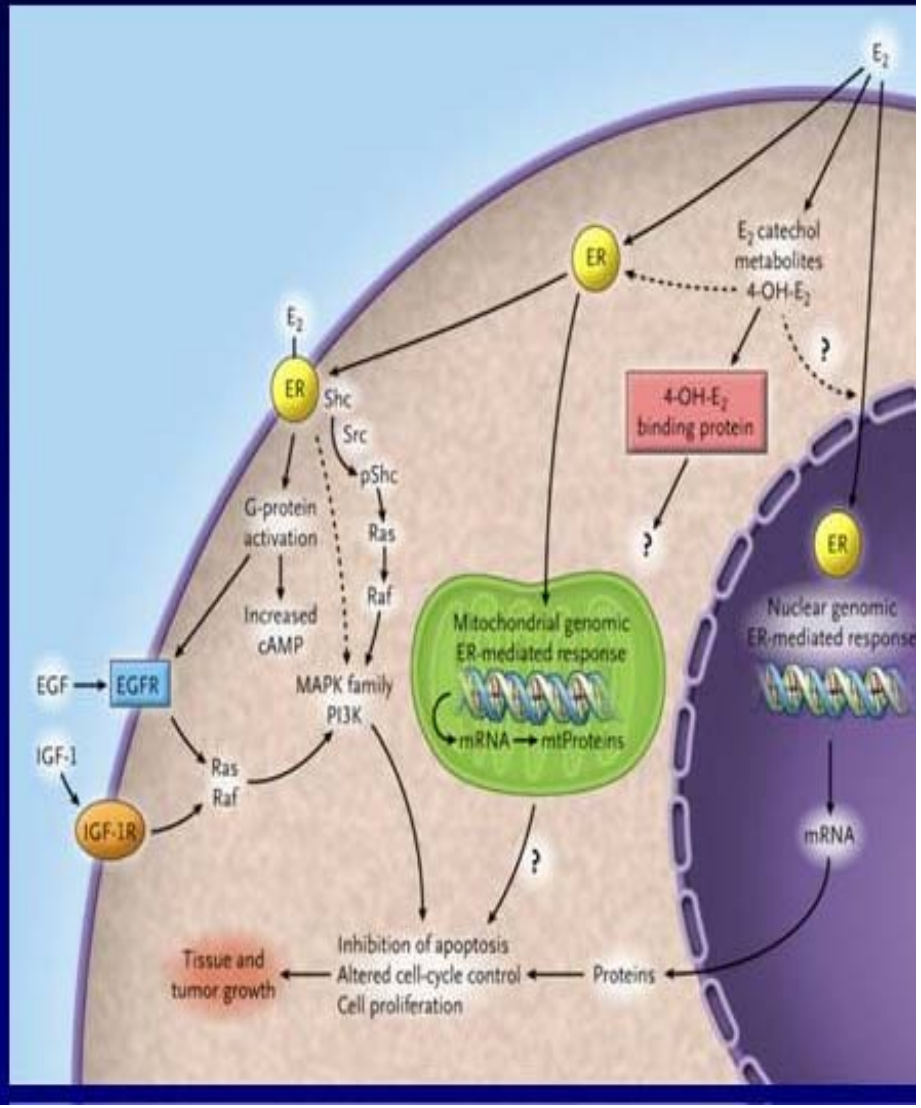
AE=adverse event

mTOR Inhibitors EC Summary

- Efficacy: depending on prior chemotherapy
  - RR: 0-25%
  - CBR: 30-83%
  - PFS: 4 – 8 months
  - OS: ?
- Common AE: Fatigue, Anemia, Mucositis, Diarrhea, Hyperglycemia.
- Efficacy not related with PTEN status
- Future: Combination with Hormones, Chemotherapy and dual inhibitors

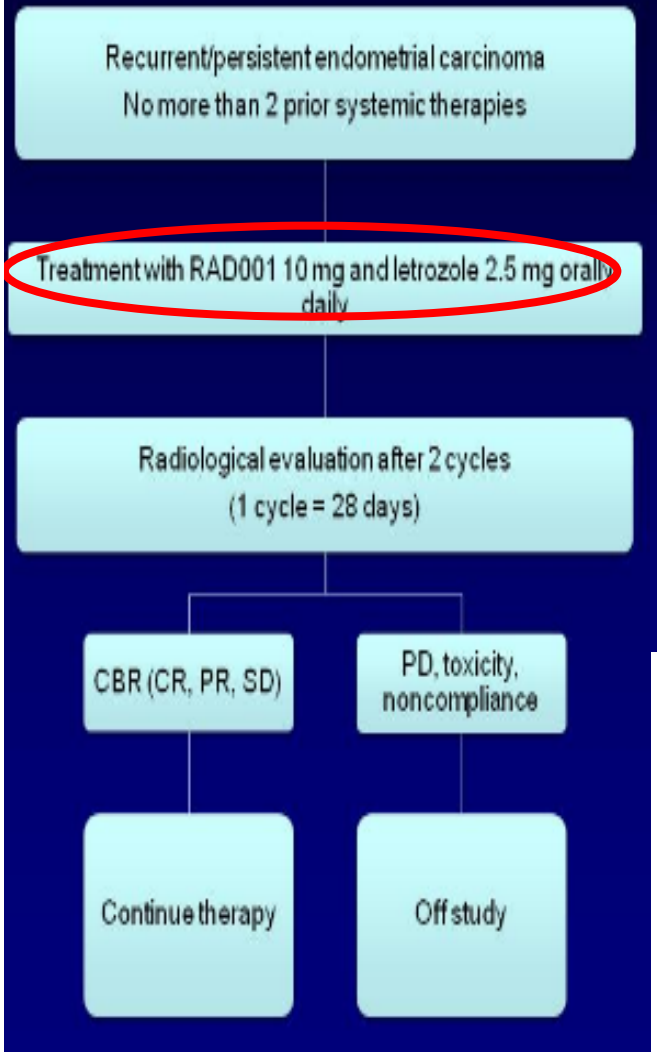
mTOR & ER: a Relevant Combination?

- ER functions through genomic, non-genomic and mitochondrial pathways
- Mediated in part through MAPK
- mTOR offers dual inhibition in E_2-sensitive tumors



A Phase II Study of Letrozole and RAD001 (Everolimus) in Patients with Advanced or Recurrent Endometrial Cancer

Study Schema



Efficacy

- 43% CBR (10/24); 4 CR, 0 PR, 6 SD
- Mean: 7.5 cycles
- Median 9 cycles (range 4-12)
- CBR:
  - 6/10 currently on treatment
  - 2 CR completed treatment/observation
  - 2/10 progression

AE: Fatigue, Stomatitis, Nausea, Hyperglicemia

Molecular Alterations in EC

	Type 1 Carcinoma	Type 2 Carcinoma
PI3KCA mutation	35-40%	15%
PTEN inactivation	55-80%	5 %
K ras mutation	15-30%	0-5%
B-Catenin mutation	20-40%	0-3%
Microsatellite Instability	15-45%	0-5%
p53 mutation	10-20%	80-90%
E-Cadherin inactivation	10-20%	60-90%
Her2- overexpression	7-10%	20-28%
FGFR-2 mutation	12-16%	1%
p16 inactivation	10%	40%

Anti-Her2 Agents EC Rationale

- HER2 neu overexpression and gene amplification 20-30% serous carcinomas.
- Conflicting results respect Her2 Expression/Amplification and incidence or prognostic implications in EC.
- No standarized method of scoring HER 2 in EC.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

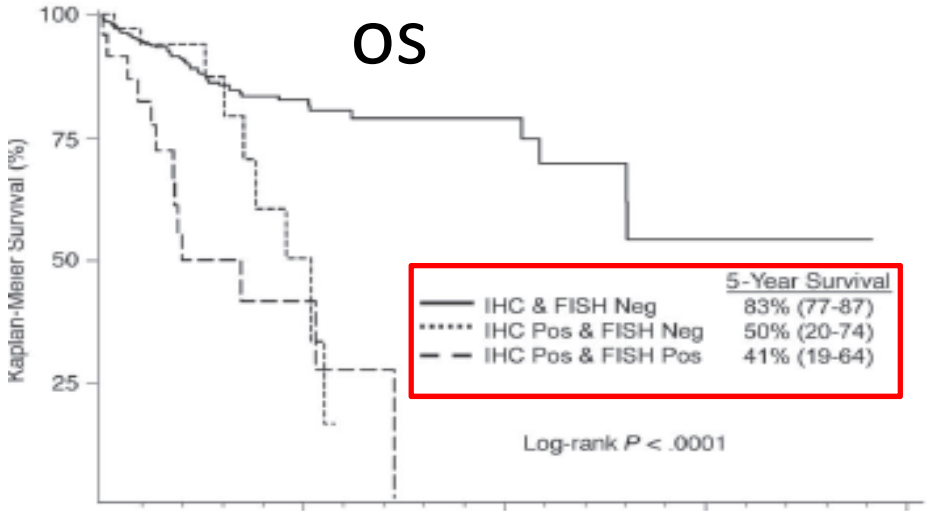
HER-2 Is an Independent Prognostic Factor in Endometrial Cancer: Association With Outcome in a Large Cohort of Surgically Staged Patients

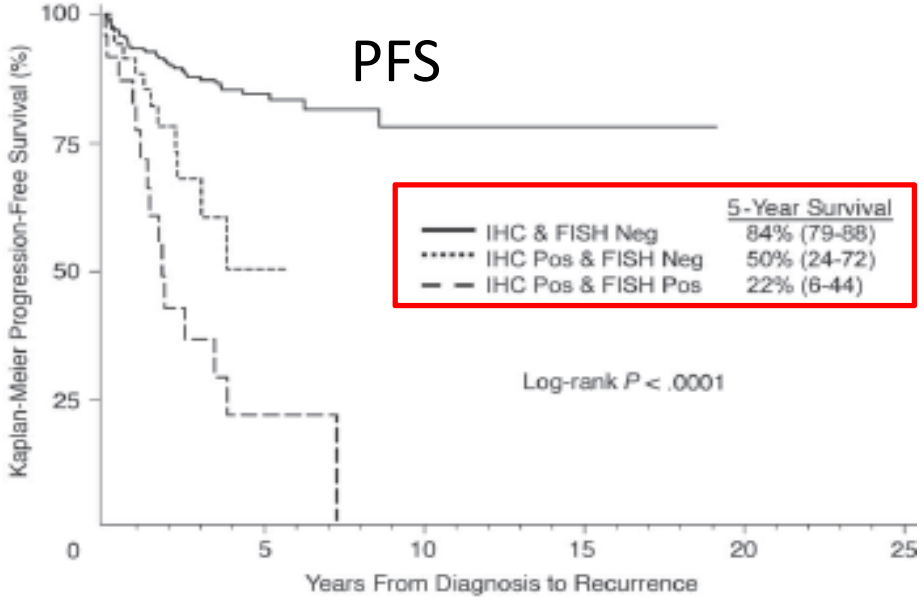
Morrison et al, JCO 2006

N 483

	Patients		HER-2 Positive IHC		HER-2 Positive FISH	
	No.	%	No.	%	No.	%
Stage						
I	289	60	26	9	7	2
II	46	10	9	20	4	9
III	109	23	22	20	11	10
IV	39	8	13	33	9	23
Histologic Subtypes						
Endometrioid grade 1	184	38	6	3	1	1
Endometrioid grade 2	116	24	8	7	3	3
Endometrioid grade 3	63	13	18	29	5	8
Mixed epithelial	27	6	7	26	2	7
MMT	26	5	3	12	1	4
Serous	58	12	25	43	17	29
Clear cell	9	2	3	33	2	22

- **Her2 IHC+ and FISH+:**
  - Higher grade
  - Non-endometrioid histology
  - N +
  - Myometrial invasion.





Contents lists available at ScienceDirect

Gynecologic Oncology

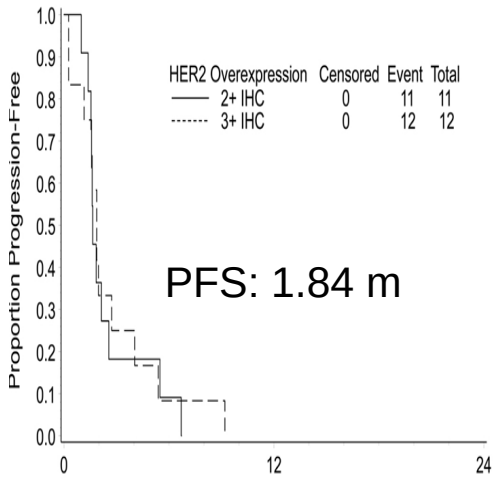
journal homepage: www.elsevier.com/locate/ygyno

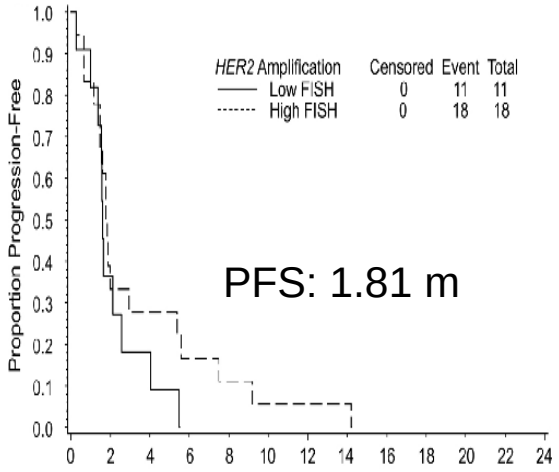
Phase II Trial of Trastuzumab in Women with Advanced or Recurrent, HER2-Positive Endometrial Carcinoma: a Gynecologic Oncology Group Study

Characteristic	Number of
Age	
50–59	8
60–69	11
70–79	12
80–89	2
Performance Status	
0	18
1	13
2	2
Cell Type	
Adenocarcinoma, unspecified	1
Clear cell carcinoma	3
Endometrioid adenocarcinoma	13
Mixed epithelial	5
Serous adenocarcinoma	11
Pathology Grade	
1	4
2	3
3	26
Prior Radiotherapy	
No	16
Yes	17
Prior Chemotherapy	
0 Regimens	8
1 Regimen	16
2 Regimens	6
3+ Regimens	3
Disease	
Advanced	7
Recurrent	26

- 286 tumors screened: 11.5% Her2 amplified.
  -33 patients: 23 (IHQ 2+ or 3+) and 18 FISH + (*HER2*/CEP 17 ratio >2.0).

- No major objetive response were observed: 12 SD.
- No correlation HER2 IHQ + or FISH + with ORR, PFS or OS

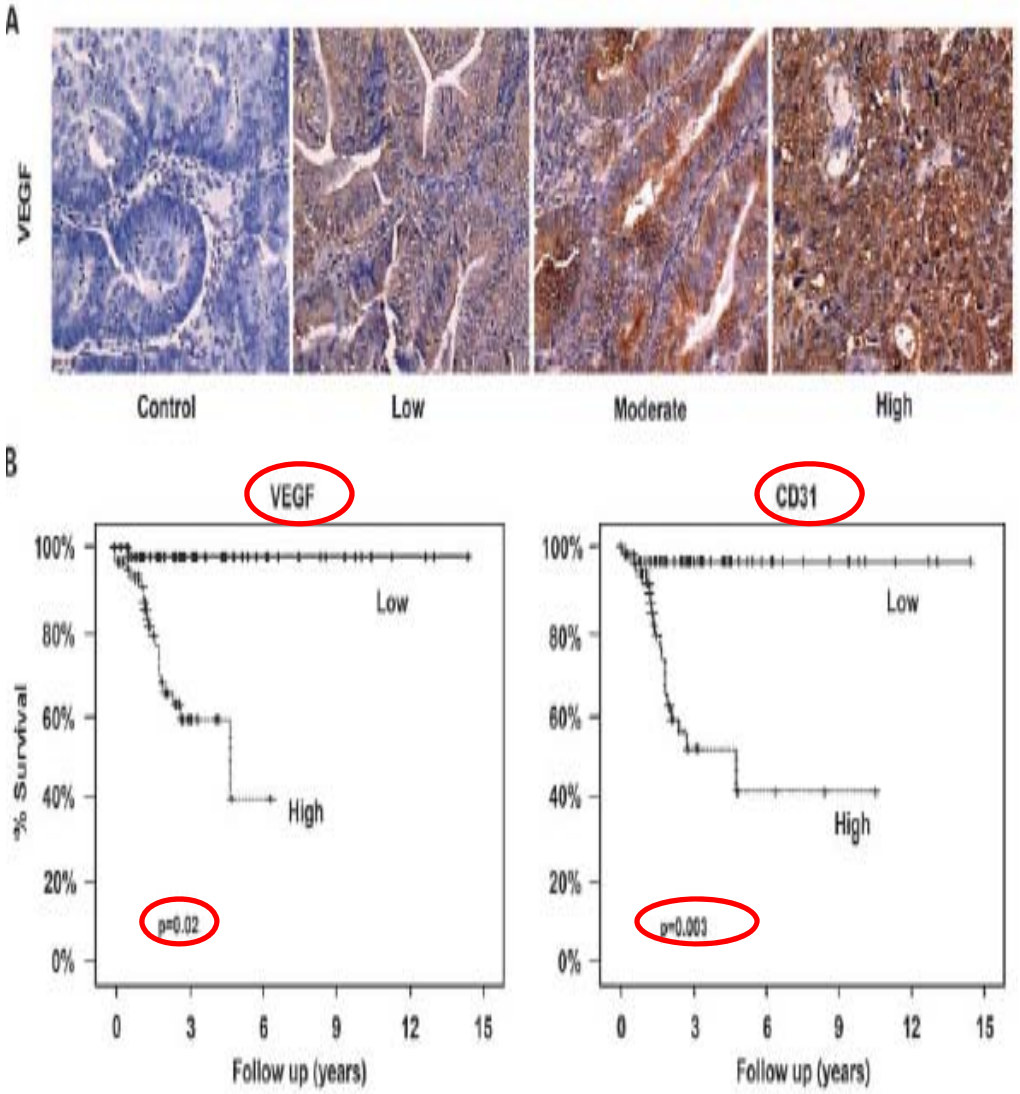




Fleming et al. Gyn Oncol 2010

Antiangiogenic Agents in Endometrial Cancer

Antiangiogenic Agents EC Rationale



- N: 111 type I. 34 % (III-IV)

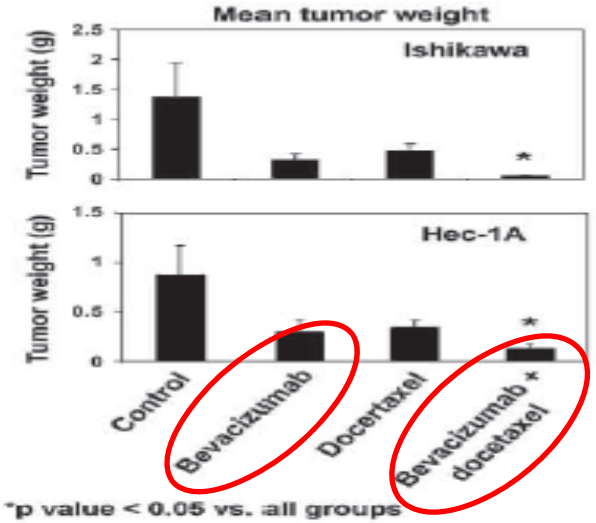
- **High grade VEGF(IHQ) 56%, associated with:**
  - Stage III/IV (p=0.004)
  - High MVD counts (p<0.001)

- High MVD was associated:
  - Stage III/IV (p= 0.003)
  - Grade 3 (p= 0.04)

- **Independent predictors of shorter survival:**
  - Advanced stage (p=0.04)
  - Grade 3 (p= 0.003)
  - **High VEGF (p= 0.03)**
  - **High MVD (p= 0.037)**

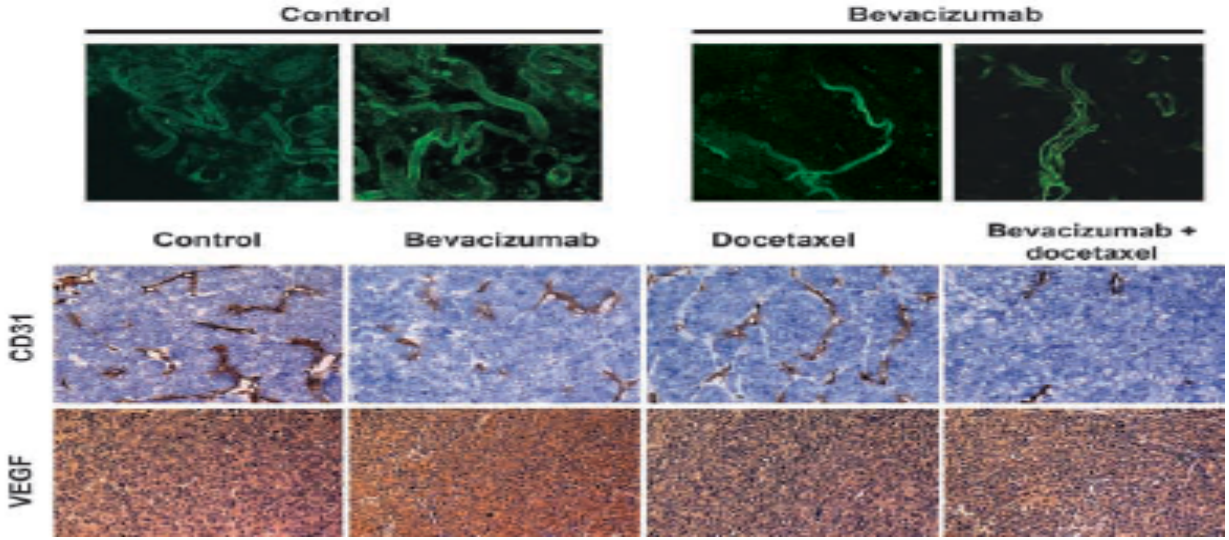
Kamat CCR 2007

Antiangiogenic Agents EC Rationale



Mean tumor weight reduction:
- Bev: 77% (p=0.15)
-Docetaxel: 66% (p=0.46)

-**Bev+Doc: 97% (p <0.01)**



Effects on tumor vasculature (MVD-CD31 staining)

-Bev: ⬇40%
-Bev-Doc:⬇ 50-70%

VOLUME 29 · NUMBER 16 · JUNE 1 2011

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

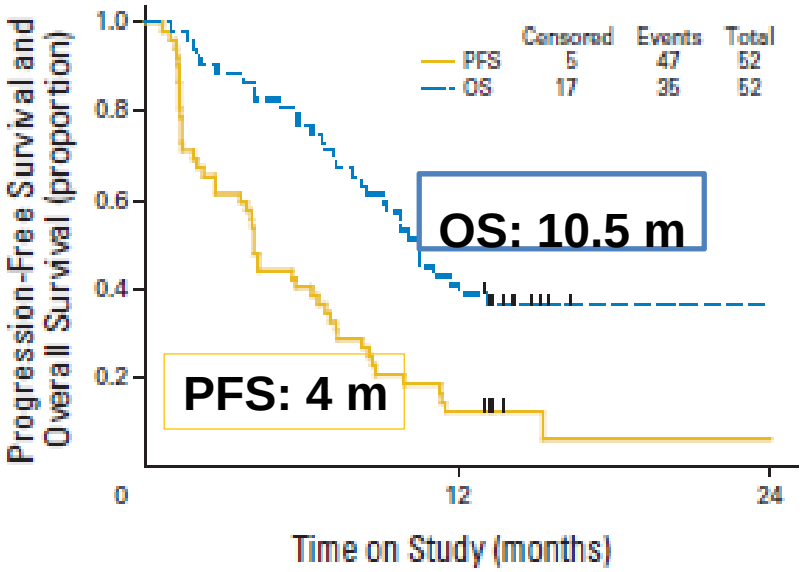
Phase II Trial of Bevacizumab in Recurrent or Persistent Endometrial Cancer: A Gynecologic Oncology Group Study

Table 2. Patient Characteristics and Activity of Bevacizumab

Characteristics	No. of Patients (N = 62)	%
Age, years		
Median	62	
Range	32-84	
Performance status		
0	34	65.4
1	17	32.7
2	1	1.9
Histology		
Endometrioid	26	50
Serous	14	26.9
Mixed epithelial	5	9.6
Clear cell	4	7.7
Adenocarcinoma, unspecified	1	1.9
Mucinous	1	1.9
Undifferentiated	1	1.9
Tumor grade		
1	3	5.8
2	12	23.1
3	37	71.2
No. of prior regimens		
1	33	63.5
2	19	36.5

Activity:

- ORR 13.5%:1CR+6RP
- Median response: 6 months
- **5 responses were Type 2 EC**
- 40% pts progression free at 6 months



Aghajanian et al. JCO 2011

Endometrial Cancer: Antiangiogenic Agents

Agent	Prior Chemo	RR	OS
Thalidomide	1-2	12.5%	6.3 mos
Bevacizumab	1-2	15%	10.5 mos
VEGF-trap (aflibercept)	1-2	Pending	
Sorafenib	0-1	5%	11.4 mos
Sunitinib (#5038)	0-2	12.5% (first stage)	
Brivanib	1-2	Ongoing	

Anti EGFR Agents EC Rationale

- EGFR is expressed in 67% of endometrial cancers (IHQ).
- EGFR correlates with higher histologic grade, age and deeper myometrial invasion.
- EGFR + patients have a significantly poorer prognosis, particularly in >50 years of age.

Niikura H et al. Hum Pathol 1995

Anti- EGFR Agents EC

- Phase II ERLOTINIB in Recurrent or metastasic EC.
- N=34 ADC. **No prior CT**
- EGFR positive IHQ: 61%.
- Efficacy:
  - **4 pts PR: 12.5%** (3/4 EGFR+ and **NO EGFR MUTATIONS**)
  - **SD 47%: (3.8 months)**
- No evidence of FISH amplification and response

Oza JCO 2008

- Phase II GEFITINIB in persistent/recurrent EC.
- N=26 **1 or 2 prior CT**
- End point: PFS 6 months
- Efficacy:
  - **4 pts PFS> 6 months**
  - **1 CR, 7 SD**

Leslie et all. ASCO 2009

FGFR-2 mutations in EC

- Recent identification of activating mutations in FGFR-2 in EC.
- The majority of the mutations are identical to germline mutations 2 or 3 that cause *Craniosynostosis and Hypochondroplasia Syndromes (S252W and P253R).*
- Predominantly occur in **EC type I (16%)** and are mutually exclusive with KRAS mutations, but occur in the presence of PTEN mutations.

FGFR-2 mutations in EC

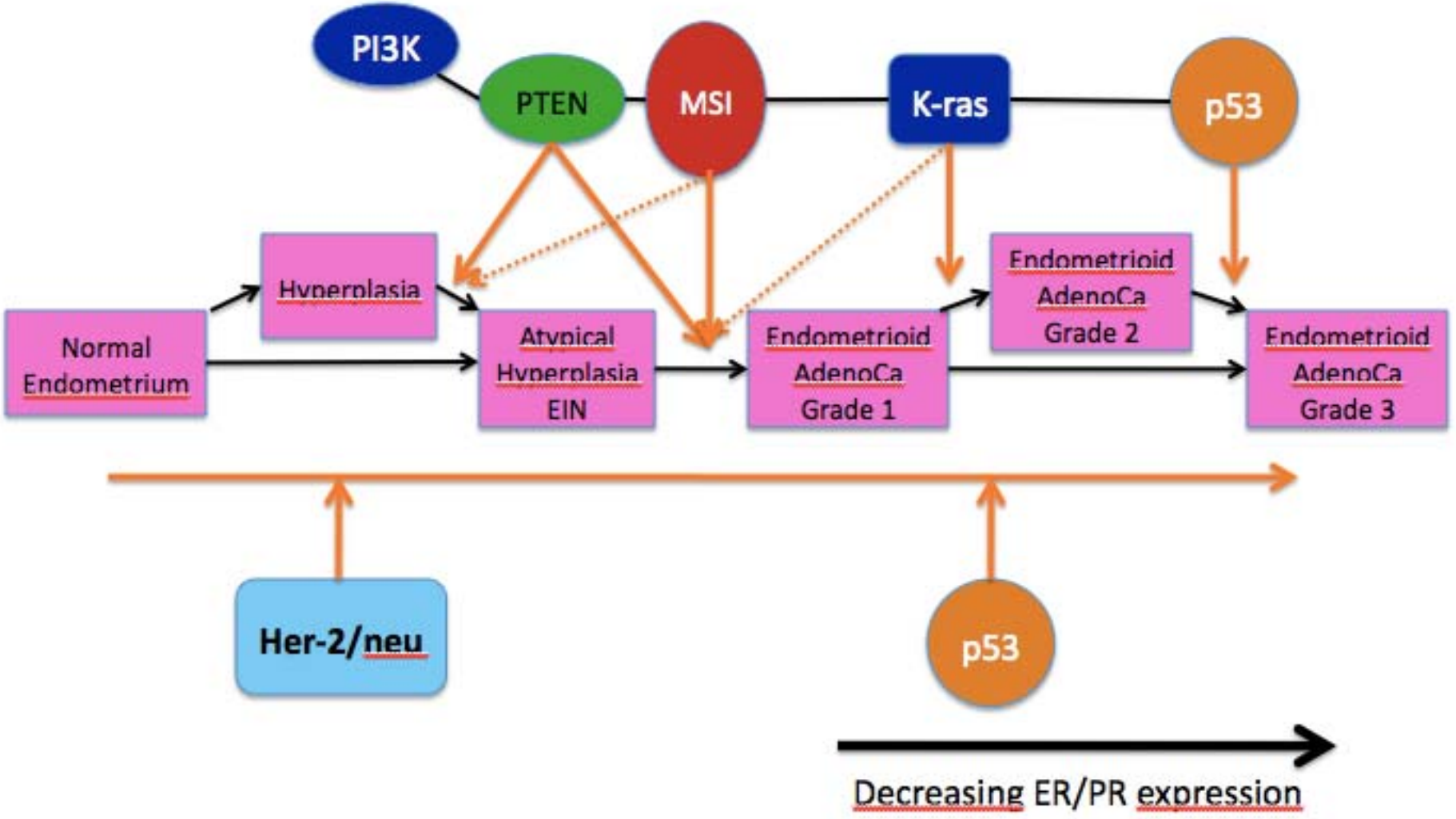
- FGFR induced signalling cascade is dependent on E-cadherine, and operates by a sustained activation of the MAPK-ERK pathway.
  - This suggests that E-cadherine plays a role beyond changes in cellular adhesion
- In vitro studies in EC cell lines with activating FGFR-2 mutations have shown selectively sensitive to a small-mollecule EGFR inhibitor, PD173074.
- In vitro: Use of pan-FGFR inhibitors induces cell cycle arrest in cell lines with activating mutations of FGFR2

FGFR Inhibitors in development:

	Brivanib	BIBF 1120
Formulation	Oral	Oral
Targets	FGFR2, VEGF	FGFR, VEGF, PDGF
Trial	GOG 229 I	GOG 229 K
Trial Status	Enrollment completed	Activation pending

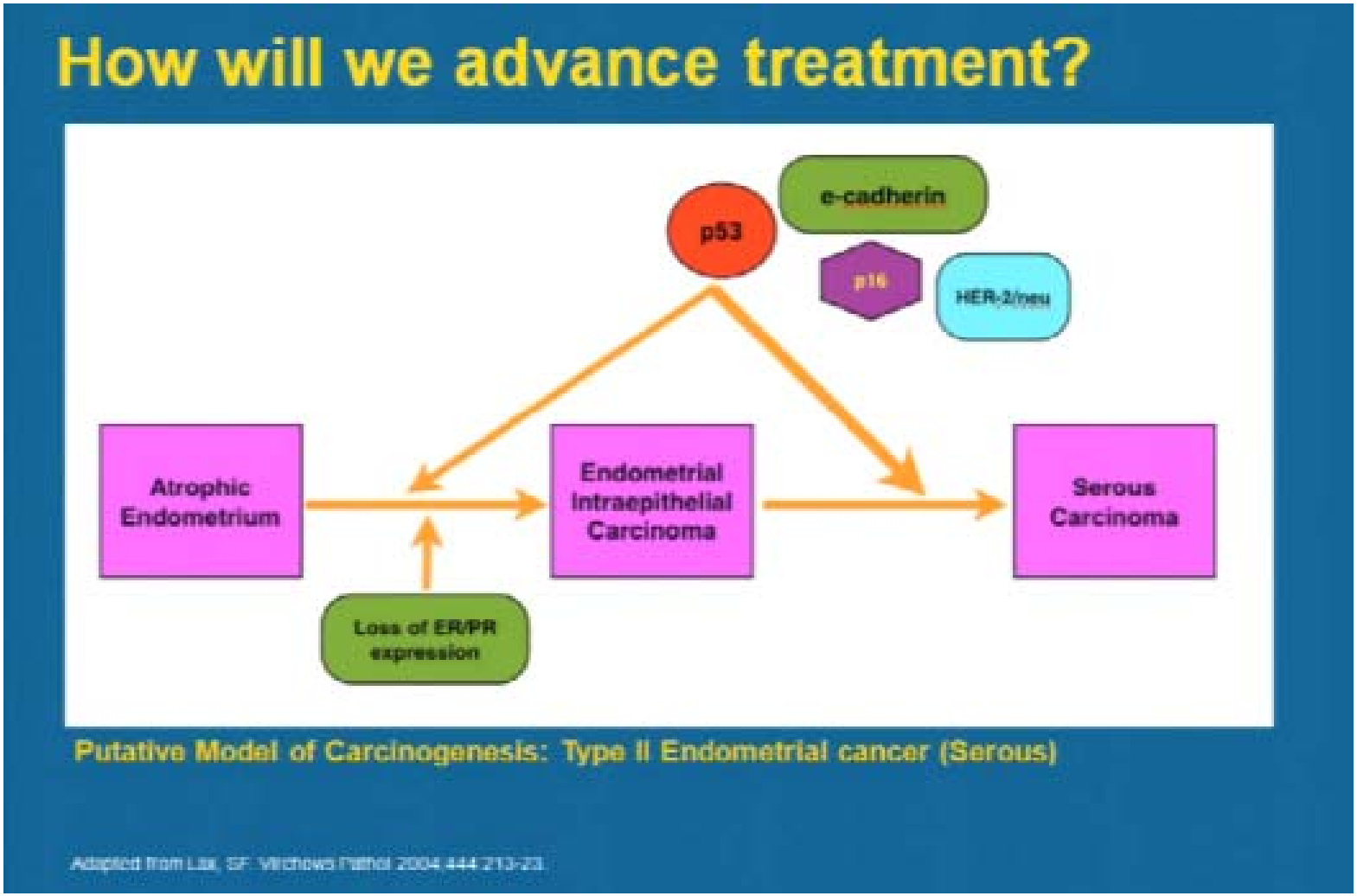
How will we advance treatment?

Putative model of Carcinogenesis: Type I EC



Adapted from Lax, SF Wirchows Pathol 2004

Type 2 Endometrial Cancer:Serous



Next Steps
Endometrial Carcinoma

- PI3K inhibitors development: BKM 120 ; XL147
- PI3KCA – mTOR inh: In vitro PI3KCA mut rather than PTEN loss predicts response.
  - Monotherapy: BEZ 235, PF-05212384
  - CT combination: BEZ 235-Paclitaxel
- AKT inhibitors: MK2206
- CT + mTOR inhibitors: GOG 86P: CBP/Paclitaxel/BEV vs Temsirolimus (First- line)
- Hormonotherapy + mTOR inhibitors: Letrozol +RAD001
- Antiangiogenic agents +mTOR: Bevacizumab + Temsirolimus
- FGFR inhibitors: AZD2171 (Cediranib), BIBF1120

Conclusions

- EC is increasing in incidence and mortality
- EC is a heterogeneous disease with distinct molecular and clinical characteristics.
- The role of citotoxic agents have been exhaustively studied resulting in improved survival but at expense of toxicity.
- Increasingly detailed data on the molecular alterations underlying EC are known and Targeted therapies are progressively emerginig.
- mTOR; HER2 and VEGF inhibitors have been tested in phase II trial as single agents with modest results but no stratification based on molecular subtype was performed.
- Histology and grade remain important.