

Treatment of Recurrent Endometrial Cancer and Evaluation of New Agents

Andres Poveda, MD
Fundación Instituto Valenciano de Oncología
Valencia, Spain
acog@fivo.org



Endometrial Cancer

Summary-1

- The most common gynecologic cancer in developed countries
- The majority of EC (72%) is diagnosed in early stages; however 15%-20% of these carcinomas will recur

Endometrial Cancer

5-Year Survival by Stages

- Stage I 90%
- Stage II 60% to 77%
- Stage III 27% to 40%
- Stage IV 0% to 5%

Pathology of Endometrial Cancer

- Pathology
 - Adenocarcinoma (75%-80%)
 - Uterine papillary serous (<10%)
 - Clear cell (4%)
 - Mucinous (1%)
 - Squamous cell (<1%)
 - Mixed (10%)

Pathology of Endometrial Cancer

GCIG Rare Tumors Working Group

<u>Pathology</u>	<u>5-Year Survival</u>
– Adenocarcinoma	83%
– Uterine papillary serous	53%
– Clear cell	62%
– Mucinous (1%)	
– Squamous cell (<1%)	
– Mixed (10%)	

Endometrial Carcinoma Recurrent Characteristics

- Uncommon in low-risk patients
- Most common in:
 - Advanced-stage disease:
 - 30% limited to the pelvis
 - >60% have components of distant metastases
 - High-risk features in primary tumor:
 - Papillary serous and clear cell
 - >50% of myometrial invasion
 - Grade 3

Endometrial Cancer Summary-2

- For advanced or recurrent disease, survival has remained unchanged over the last 20 years (median survival:7-15 months), highlighting the need for better therapies
- The improved understanding of deregulated pathways in EC have led to clinical trials testing approaches with the key drivers of these pathways.

Management THE PAST



Endometrial Carcinoma Single-Agent Phase II Studies

Drug	RR%	Reference
– Doxorubicin (50m ² -60/m ²)	20-35	Thigpen, 1994 ¹
– Epirubicin	25	Calero, 1989 ²
– Cisplatin (not active in resistsants)	20-30	Various
– Carboplatin	30	Various
– Paclitaxel	35.7	Ball, 1996 ³
– Wkly paclitaxel	2/2	Ota, 2000 ⁴
– Docetaxel (n = 46)	33	Gordon, 2002 ⁵
– PLD (heavily pretreated)	10	Muggia, 2002 ⁶

RR, response rate

1. Thigpen JT, et al. *J Clin Oncol.* 1994;12(7):1408-1414.
2. Calero F, et al. *Proc Am Soc Clin Oncol.* 1989;8: Abstract 156.
3. Ball HG, et al. *Gynecol Oncol.* 1996;62(2):278-281.
4. Ota S, et al. *Cancer Lett.* 2000;160(1):9-12.
5. Gordon AN, et al. *Ann Oncol.* 2002;109(13 supplement 5): Abstract 396O.
6. Muggia FM, et al. *J Clin Oncol.* 2002;20(9):2360-2364.

Endometrial Carcinoma Randomized Studies

Drug(s)	OR, %	Endpoints/Result
A vs AC (Thigpen 1994) ¹	No differences	PFS/NS
A vs CAF (Horton 1982) ²	No differences	OS/NS
A vs AP (Thigpen 2004) ³	27 vs 46 ($P = .004$)	PFS, OS/ $P = .14$, NS
A vs AP (Aapro 2003) ⁴	17 vs 43	RR/ $P < .001$
AP vs AT (Fleming 2004) ⁵	40 vs 43	PFS/NS
AP vs TAP (Fleming 2004) ⁶	57 vs 33 ($P < .001$)	PFS + /OS + ($P < .01$)
AP vs TC (Weber 2003) ⁷	27 vs 35	A-1819 ASCO 2003; R phase II N = 70 P)
TAP vs TC GOG-209⁸	Miller D, et al. <i>Gyn Oncol.</i> 2012;125(3): Abstract LBA1. (SGO presentation)	

1. Thigpen JT, et al. *J Clin Oncol.* 1994;12(7):1408-1414. 2. Horton J, et al. *Cancer.* 1982;49(12):2441-2445.

3. Thigpen JT, et al. *J Clin Oncol.* 2004;22(19):3902-3908. 4. Aapro MS, et al. *Eur J Cancer.* 2003;39(8):1141-1143.

3. Dimopoulos MA, et al. *Gynecol Oncol.* 2000;78(1):52-57. 5. Fleming GF, et al. *Ann Oncol.* 2004;15(8):1173-

1178. 6. Fleming GF, et al. *J Clin Oncol.* 2004;22(11):2159-2166. 7. Weber B, et al. *Proc Am Soc Clin Oncol.*

2003;22(Supplement): Abstract 1819. 8 Miller D, et al. *Gyn Oncol.* 2012;125(3): Abstract LBA1.

Chemotherapy for Endometrial Cancer Summary

- 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 most used schedule
- Second line: No consensus (activity of single agents: 4%-22% RR)

Hormonal Therapy for Endometrial Cancer Summary

- Progestins, antiestrogens, SERMs, aromatase inhibitors
- Typically better differentiated and more indolent tumors treated up front (endometrioid tumors)
- RR up to 30% (not evaluated for serous/clear cell)
- No positive data on superiority of one agent over another or of dose of choice
- Randomized comparison of 220 mg vs 1000 mg MPA: no difference. ORR 25%, CR 17%, PFS 3.2 months, OS 11 months¹
- **Second line: no consensus**

Lai CH, et al. *Curr Opin Obstet Gynecol.* 2006;18(1):29-34.

1. Thigpen JT, et al. *J Clin Oncol.* 1999;17(6):1736-1744.

Management THE PRESENT



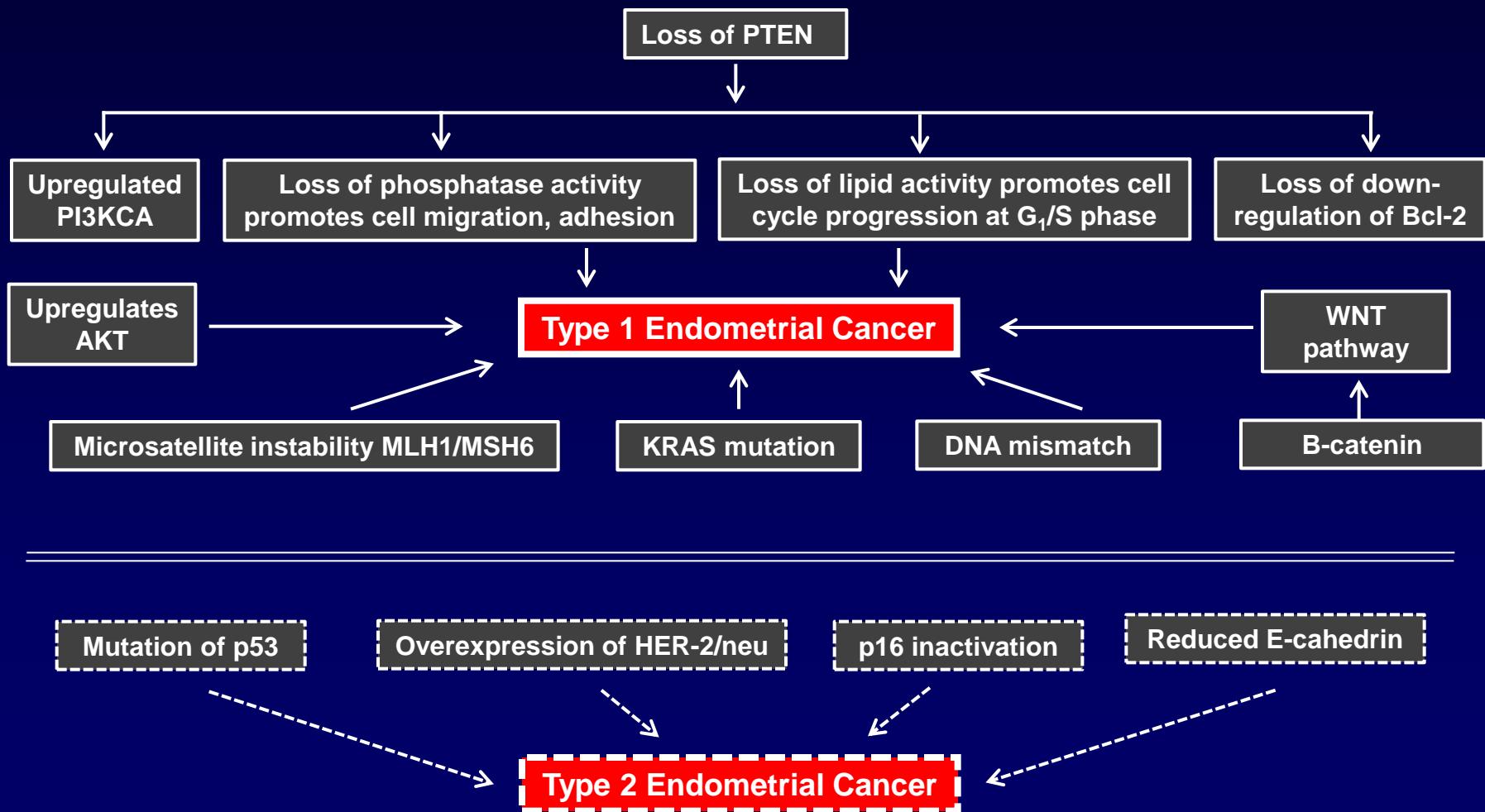
Molecular Features of Endometrial Cancer

- 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**

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
 - UPSC: 60%-90%
 - UCCC: 14%

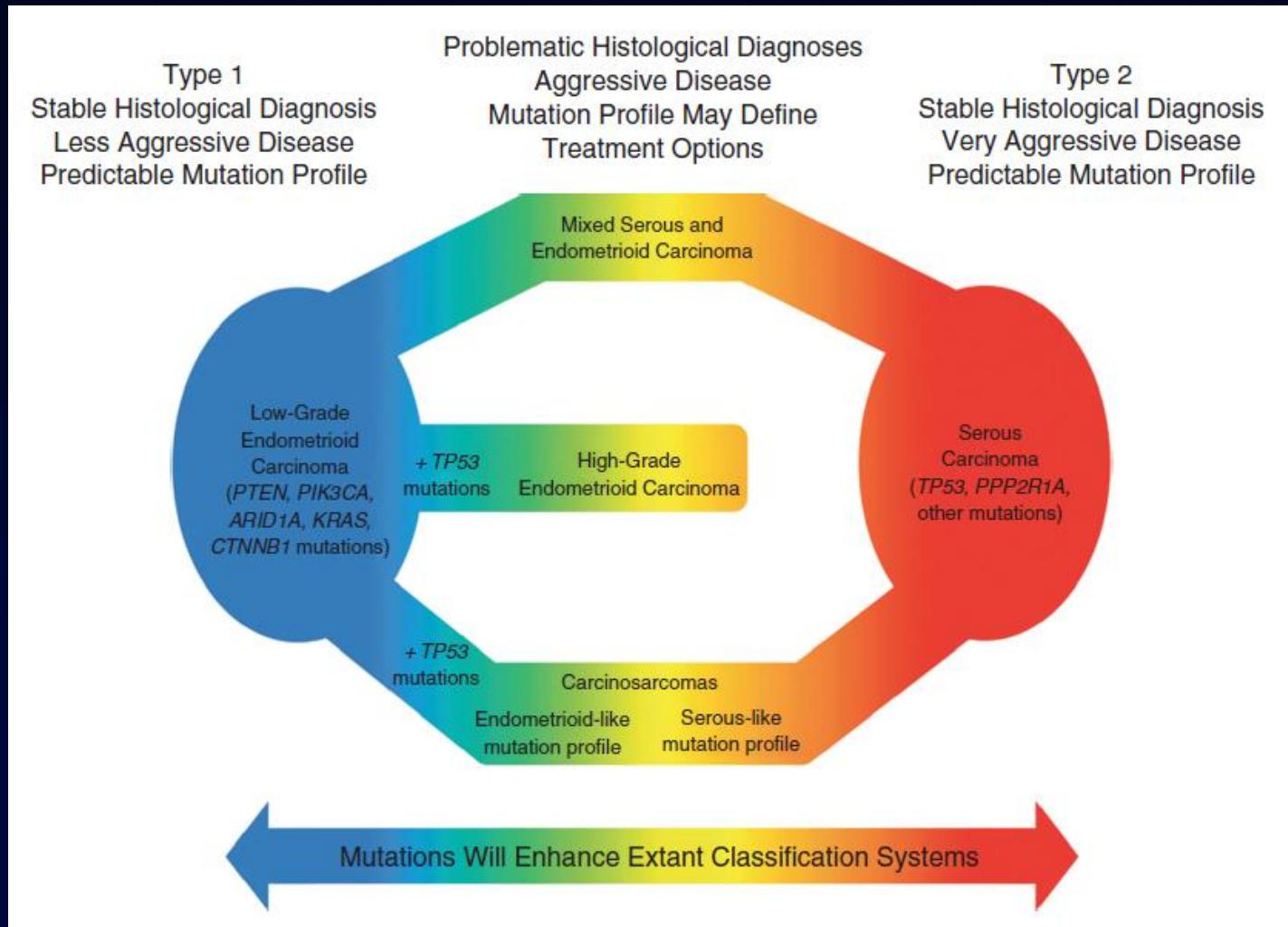
Endometrial Cancer Morphologic and Molecular Classification



Molecular Alterations in Endometrial Cancer

	Type 1 Carcinoma, %	Type 2 Carcinoma, %
<i>PTEN</i> inactivation	55-80	5
<i>PI3KCA</i> mutation	35-40	15
<i>KRAS</i> mutation	15-30	0-5
<i>B-catenin</i> mutation	20-40	0-3
<i>FGFR-2</i> mutation	12-16	1
Microsatellite instability	15-45	0-5
<i>p53</i> mutation	10-20	80-90
E-cadherin inactivation	10-20	60-90
HER2 overexpression	7-10	20-28
<i>p16</i> inactivation	10	40

Morphologic and Molecular Classification of Endometrial Cancer: Rationale for Treatment



ARTICLE

OPEN

doi:10.1038/nature12113

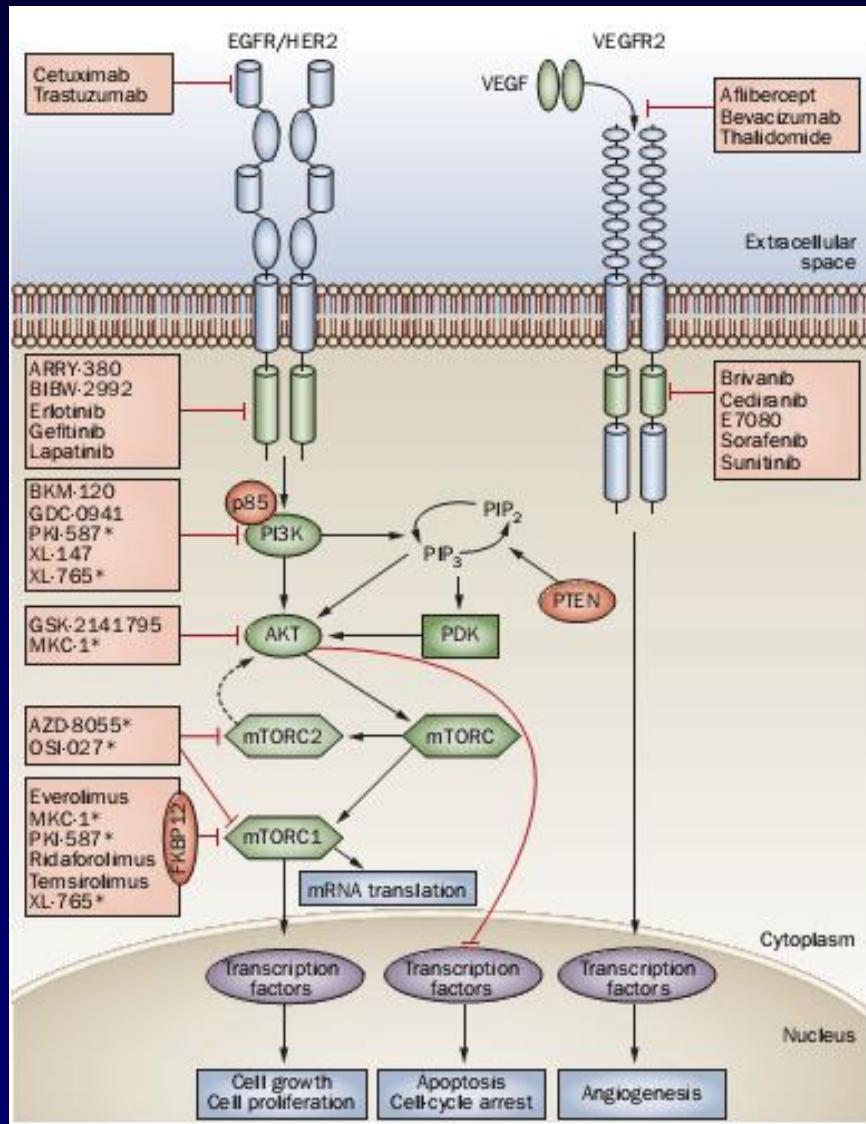
Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

We performed an integrated genomic, transcriptomic and proteomic characterization of 373 endometrial carcinomas using array- and sequencing-based technologies. Uterine serous tumours and ~25% of high-grade endometrioid tumours had extensive copy number alterations, few DNA methylation changes, low oestrogen receptor/progesterone receptor levels, and frequent TP53 mutations. Most endometrioid tumours had few copy number alterations or TP53 mutations, but frequent mutations in PTEN, CTNNB1, PIK3CA, ARID1A and KRAS and novel mutations in the SWI/SNF chromatin remodelling complex gene ARID5B. A subset of endometrioid tumours that we identified had a markedly increased transversion mutation frequency and newly identified hotspot mutations in POLE. Our results classified endometrial cancers into four categories: POLE ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high. Uterine serous carcinomas share genomic features with ovarian serous and basal-like breast carcinomas. We demonstrated that the genomic features of endometrial carcinomas permit a reclassification that may affect post-surgical adjuvant treatment for women with aggressive tumours.

Potential Molecular Targets

EGFR



Antiangiogenics

EGFR Inhibitors

Agent	Setting	RR%	Biomarker	Reference
Trastuzumab	EC 11.5% Endom 7% Serous 28% CC 38%	0%	HER2 not predictive (18% amplification FISH)	Fleming 2010¹
Erlotinib	1st-2nd line EC	13%	EGFR (not predictive) IHQ mutation	Oza 2008²
Cetuximab	EC 1st-4th line	5%		NR Slomovitz 2010³

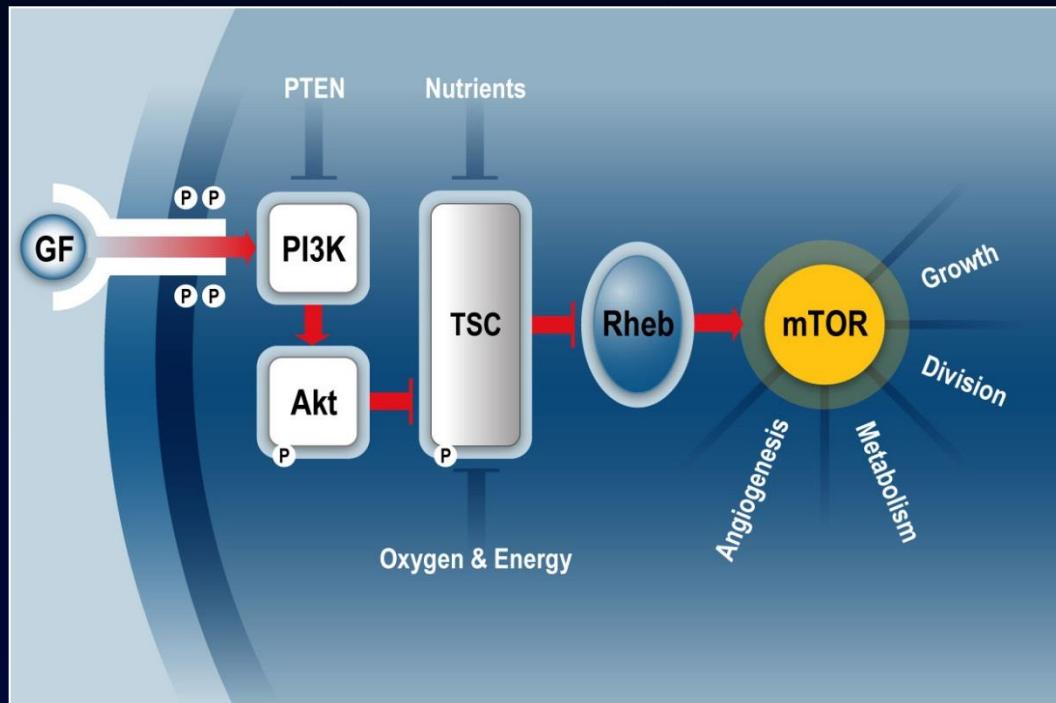
- New ways:
 - Combination chemotherapy
 - BIBW-2992 (HER2+ EGFR) selection of patients BIOMARKERS
 - Combine PI3Kinh

1. Fleming GF, et al. *Gynecol Oncol.* 2010;116(1):15-20. 2. Oza AM, et al. *J Clin Oncol.* 2008;26(26):4319-4325.

3. Slomovitz B, et al. *Gynecol Oncol.* 2010;116(supplement 1): Abstract 13.

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
 - mTOR inhibition attacks multiple pathways through a single target



Faivre S, et al. *Nat Rev*. 2006;5(8):671-688. Shaw RJ, et al. *Nature*. 2006;441(7092):424-430. Vignot S, et al. *Ann Oncol*. 2005;16(4):525-537. Wan X, et al. *Oncologist*. 2007;12(8):1007-1018.

PTEN Endometrial Carcinoma

- PTEN **inactivated in up to 83% of EEC** and is the most common genetic defect in EC type I (vs 5% in type 2) Dedes KJ, et al. *Nat Rev Clin Oncol.* 2011;8(5):302-306.
- Higher PTEN mutation frequency in MSI tumors (60% vs 25%)
- Difficult to evaluate PTEN expression or mutations as prognostic factors:
 - EC usually presented as stage I: good prognosis
 - PTEN mutations are predominantly observed in endometrioid carcinomas
 - Some mutations related to favorable prognosis

PTEN–PI3KCA–AKT–mTOR: Published Trials

Drug	Prior Tx	RR	Biomarker	Publication
Everolimus (PO)	≤2	0%	PTEN loss function predictor CBR (p NS)	Slomovitz 2010 ¹
Tensirolimus	No	14%	PTEN	Oza 2011 ²
	Yes	4%	PI3K/Akt/mTOR pathway No correlation with RR	Oza 2011 ²
Ridaforolimus (IV)	≤2	7.4%		Colombo 2007 ³
Ridaforolimus (PO)	No	7.7%	NR PTEN PI3K	Mackay 2011 ⁴
Ridaforolimus (PO) vs Hormonotherapy	≤2	PFS 3.6 PFS 1.9 HR = 0.53; one-sided P = .008)	NR	Oza 2011 ⁵ Oza A, Poveda A, Pignata S, et al. In press ⁶

1. Slomovitz BM, et al. *Cancer*. 2010;116(23):5415-5419. 2. Oza AM, et al. *J Clin Oncol*. 29(24):3278-3285. 3. Colombo N, et al. *J Clin Oncol*. 2007;25(18S supplement June 20): Abstract 5516. 4. Mackay H, et al. *J Clin Oncol*. 2011;29(supplement): Abstract 5013. 5. Oza AM, et al. *J Clin Oncol*. 2011;29(supplement): Abstract 5009. 6. Oza AM, et al. In Press.

PTEN-PI3KCA-AKT-mTOR: Published Trials

Drug

Everolimus (PO)

Temsirolimus

Ridaforolimus (I)

Ridaforolimus (I)

Ridaforolimus (I)

VS

Hormonotherapy

Publication

Slomovitz 2010¹

Oza 2011²

Oza 2011²

Colombo 2007³

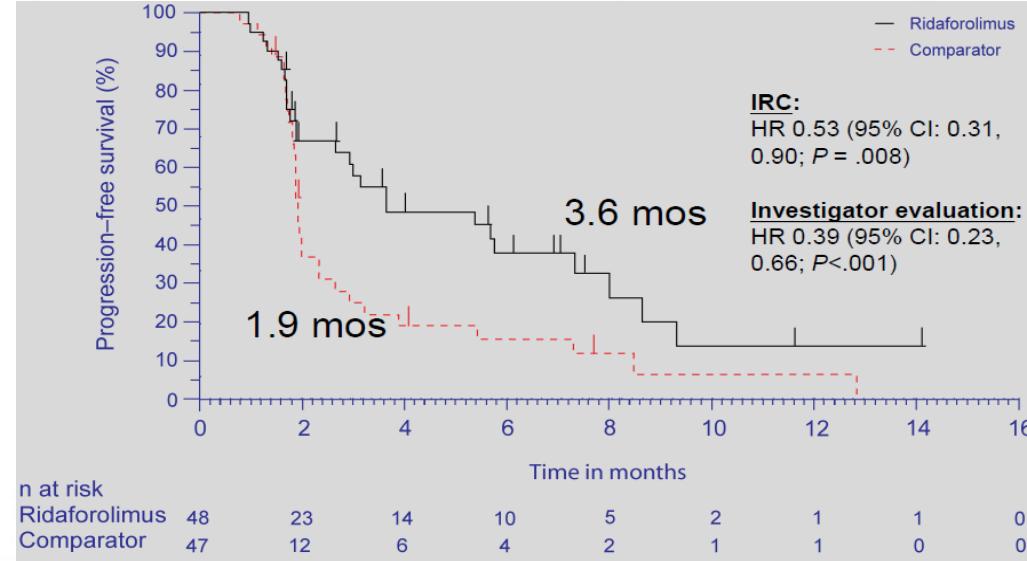
Mackay 2011⁴

Oza 2011⁵

**A A, Poveda A,
Shata S, et al. In
press⁶**

Progression-free survival

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



	Ridaforolimus (N=48)		Comparator (N=47)	
	IRC	Investigator evaluation	IRC	Investigator evaluation
Median PFS, months	3.6	5.6	1.9	1.9
95% CI for median PFS	(2.7, 7.3)	(4.4, 6.8)	(1.9, 2.3)	(1.8, 2.7)
PFS events at 4 months, n (%)	19 (39.6)	11 (22.9)	28 (59.6)	32 (68.1)

one-sided $P = .008$

1. Slomovitz BM, et al. *Cancer*. 2010;116(23):5415-5419.
2. Oza AM, et al. *J Clin Oncol*. 29(24):3278-3285.
3. Colombo N, et al. *J Clin Oncol*. 2007;25(18S supplement June 20): Abstract 5516.
4. Mackay H, et al. *J Clin Oncol*. 2011;29(supplement): Abstract 5013.
5. Oza AM, et al. *J Clin Oncol*. 2011;29(supplement): Abstract 5009.
6. Oza AM, et al. In Press.

Molecular Determinants of Outcome With Mammalian Target of Rapamycin Inhibition in Endometrial Cancer

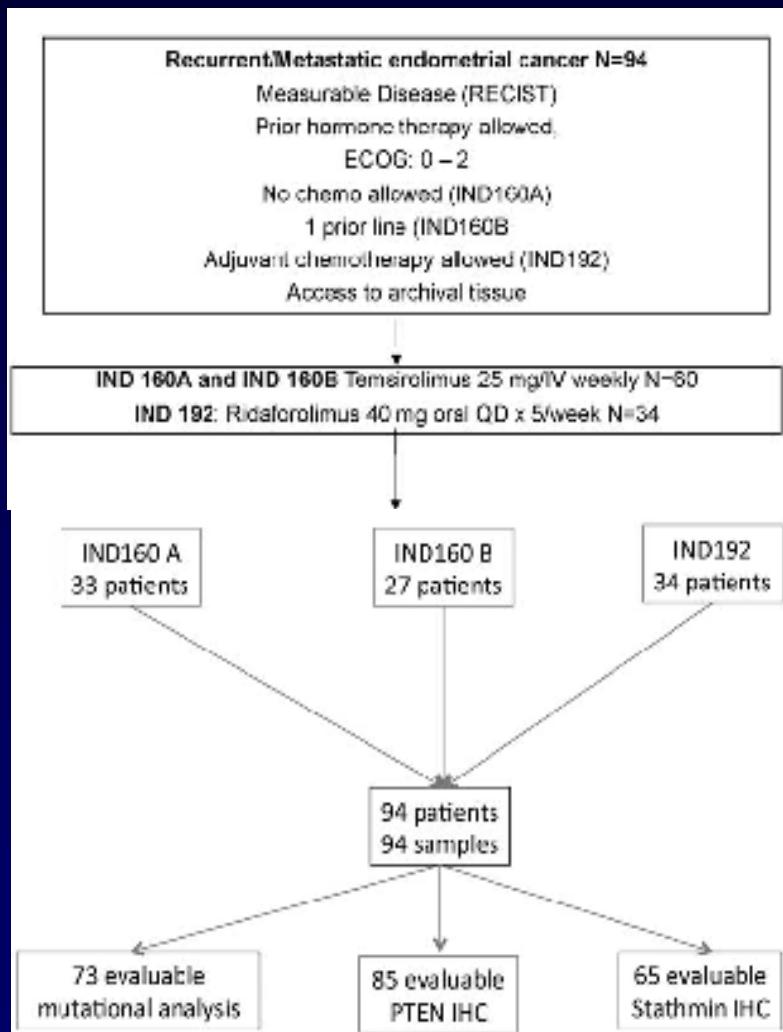


TABLE 2. Mutational Analysis and Association With Outcomes Among 73 Evaluable Patients

Mutation Group	No. (%)	Response (%) ^a	Progression (%) ^b	P	P
Any mutation				1.00	1.00
Yes	32 (43.8)	3 (9.4)	10 (31.3)		
No	41 (56.2)	4 (9.8)	13 (31.7)		
PIK3CA mutation				.40	.79
Yes	21 (28.6)	3 (14.3)	6 (28.6)		
No	52 (71.2)	4 (7.7)	17 (32.7)		
Type of PIK3CA mutation					
R88Q	7 (9.6)				
H104R	6 (8.2)				
E545K	4 (5.5)				
C420R	2 (2.7)				
H1047L	1 (1.4)				
P539R	1 (1.4)				
E542K	1 (1.4)				
KRAS mutation				.58	.49
Yes	10 (13.7)	0 (0.0)	2 (20.0)		
No	63 (86.3)	7 (11.1)	21 (33.3)		

Group	No.	Response (%) ^a	P	Progression (%) ^b	P
PTEN expression			0.46		.35
Negative	46	3 (6.5)		12 (26.1)	
Positive	39	5 (12.8)		14 (35.9)	
Stathmin expression			0.89		.34
Negative	2	0 (0.0)		1 (50.0)	
Weak	21	2 (9.5)		5 (23.8)	
Moderate	27	2 (7.4)		7 (25.9)	
Strong	15	2 (13.3)		7 (46.7)	
Histologic subtype			0.74		.69
Endometrioid	66	6 (9.1)		19 (28.8)	
Clear cell	4	0 (0.0)		0 (0.0)	
Serous	12	2 (16.7)		3 (25.0)	

Angiogenesis Inhibitors

Agent	Setting	RR %	Biomarker	Reference
Sorafenib	EC 1 st or 2 nd line	5	NR	Nimeiri 2010 ¹
Sunitinib	EC ≤1	15	NR	Correa 2010 ²
Aflibercept	Leiomyosarcoma Carcinosarcoma	0 0	NR	Mackay 2012 ³
Bevacizumab	EC ≤2	15	Low VEGF-A Good prognosis Adjusted [HR], 0.350; 95% CI, 0.153 to 0.797)	Aghajanian 2011 ⁴

1. Nimeiri HS, et al. *Gynecol Oncol*. 2010;111(1):37-40. 2. Correa R, et al. *J Clin Oncol*. 2010;28(supplement 15s): Abstract 5038. 3. Mackay HJ, et al. *Gynecol Oncol*. 2012;125(1):136-140. 4. Aghajanian C, et al. *J Clin Oncol*. 2011;16):2259-2265.

Angiogenesis Inhibitors

Agent	Setting	RR %	Biomarker	Reference
Sorafenib	EC 1 st or 2 nd line	5		
Sunitinib	EC ≤1	15		
Aflibercept	Leiomyosarcoma	0		
	Carcinosarcoma	0		
Bevacizumab	EC ≤2	15		

C

Plasma VEGF-A (pg/mL)	Alive	Dead	Total
Low < 76.9	6	11	17
High ≥ 76.9	3	14	17

Overall Survival (proportion)

Time on Study (months)

1. Nimeiri HS, et al. *Gynecol Oncol*. 2010;111(1):37-40. 2. Correa R, et al. *J Clin Oncol*. 2010;28(supplement 15s): Abstract 5038. 3. Mackay HJ, et al. *Gynecol Oncol*. 2012;125(1):136-140. 4. Aghajanian C, et al. *J Clin Oncol*. 2011;16:2259-2265.

Angiogenesis Inhibitors

Agent	Setting	RR, %	Biomarker	Reference
Nindetanib	EC 1 st or 2 nd line	9.4	NR	Dizon 2014 ¹
Brivanib	EC ≤2	18.6	Yes	Powell 2014 ²
Brivanib	ESMO 2014 Oral		Yes	Konecny 2014 ³
Lenvatinib	EC ≥1 plat-line	14.3	Low Ang-2 Better prognosis	Vergote 2013 ⁴

1. Dizon DS, et al. *Gynecol Oncol.* 2014;135(3):441-445. 2. Powell MA, et al. *Gynecol Oncol.* 2014;135(1):38-43.

3. Konecny GE, et al. *Ann Oncol.* 2014;25 (Suppl 4): Abstract LBA27. 4. Vergote I, et al. *J Clin Oncol.* 2013;(31s):Abstract 5520.

A PHASE 2 TRIAL OF LENVATINIB IN PATIENTS WITH ADVANCED OR RECURRENT ENDOMETRIAL CANCER: ANGIOPOIETIN-2 AS A PREDICTIVE MARKER FOR CLINICAL OUTCOMES

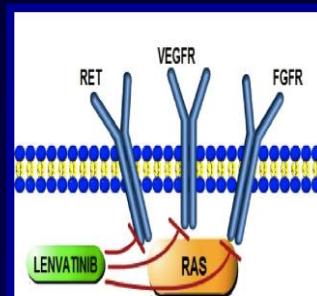
I. Vergote,¹ M. Teneriello,² M.A. Powell,³ D.S. Miller,⁴ A.A. Garcia,⁵ O.N. Mikheeva,⁶ T. Pinter,⁷ M. Bidzinski,⁸ C.L. Cebotaru,⁹ J. Fan,¹⁰ M. Ren,¹⁰ N. Meneses,¹⁰ Y. Funahashi,¹¹ T. Kadowaki,¹¹ J.P. O'Brien,¹⁰ and R.T. Penson¹²

¹University Hospitals Leuven, Leuven, Belgium; ²US Oncology, The Woodlands, Texas; ³Washington University School of Medicine, St. Louis, Missouri; ⁴University of Texas Southwestern Medical Center, Dallas, Texas; ⁵University of Southern California, Los Angeles, California;

⁶State Healthcare Institution Leningrad Regional Oncology Center, St. Petersburg, Russia; ⁷Aladar Patz Teaching County Hospital, Gyor, Hungary; ⁸Maria Skłodowska-Curie Memorial Institute, Warsaw, Poland; ⁹Institute of Oncology "Prof. Dr. Ion Chiricuta," Cluj-Napoca, Romania;

¹⁰Eisai Inc., Woodcliff Lake, New Jersey; ¹¹Eisai Inc., Andover, Massachusetts; ¹²Massachusetts General Hospital Cancer Center and DFCI, Boston, Massachusetts

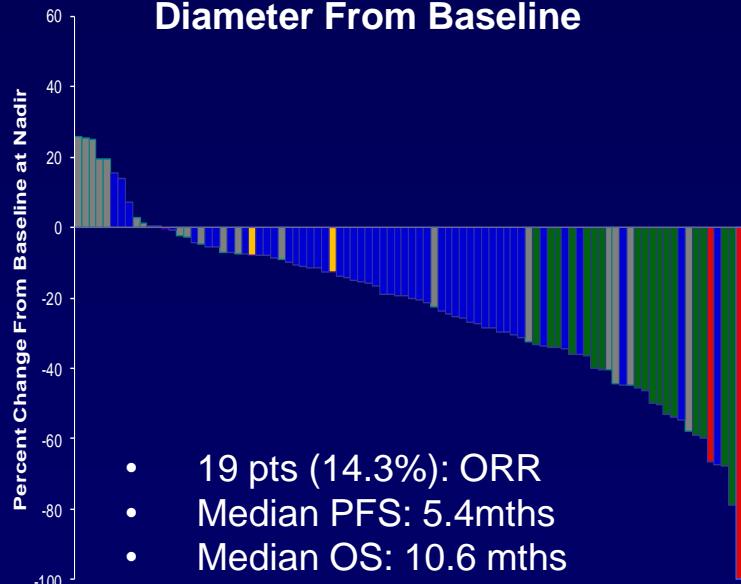
- **Lenvatinib: TKI of VEGFR1-3; FGFR1-4, PDGFR β RET, KIT**
- N = 133 pts advanced or recurrent EC
- All 1 prior Platinum QT
- Prior RDT: 82%
- **Lenvatinib:** 24mg qd in a 28-day cycle



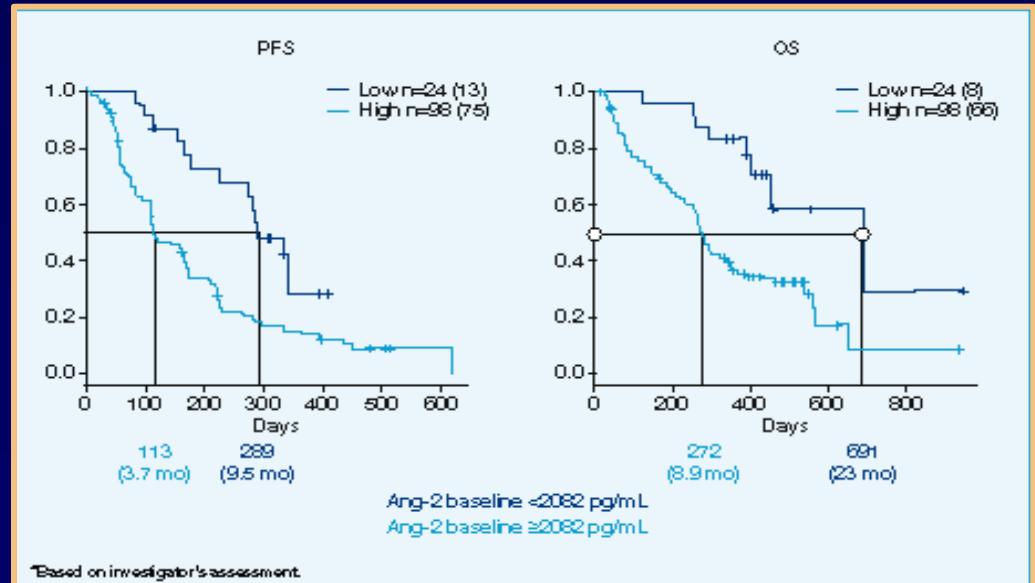
Phase II Single-Arm Objectives:

- Safety and efficacy of lenvatinib
- Identify predictive markers for lenvatinib response

Maximum % Change in Sum of Diameter From Baseline



Observed Progression-Free Survival and Overall Survival in Low and High Ang-2



ASCO 2014

- More than 5000 abstracts
- Oral Session: 0/10

ESMO 2014

- More than 2700 abstracts
- Oral Session: 1/5

Management THE FUTURE



Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

Summary

- **4 Categories of Endometrial Cancer:**
 - Pole Ultramutated
 - MSI Hypermutated
 - Copy-Number Low
 - Copy-Number High
- **Share Genomic Features:**
 - Uterine Serous
 - Ovarian Serous
 - Basal-Like Breast

Metformin

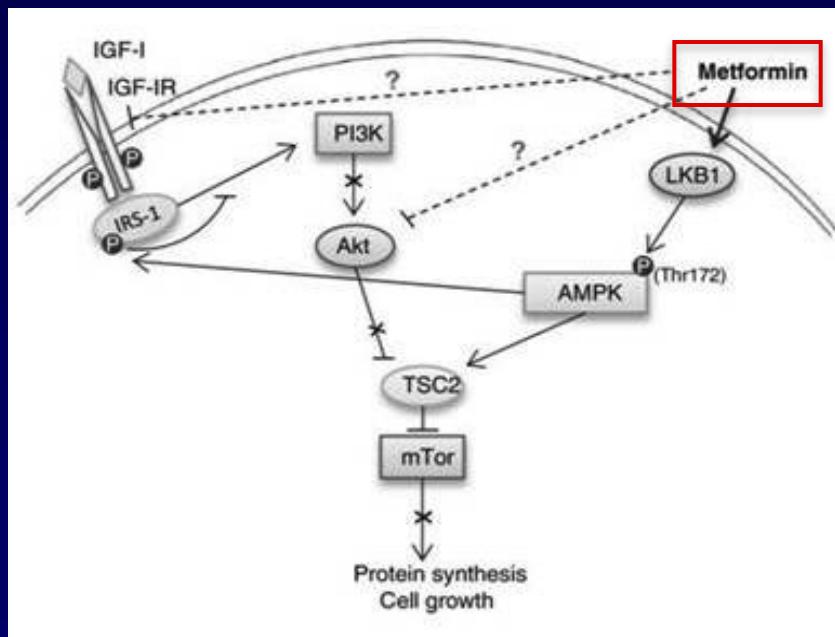
Mechanism of Action:

▪ Direct:

- Activates AMPK- Inhibition of mTOR

▪ Indirect:

- Increases insulin sensitivity
- Decrease gluconeogenesis
- Decreases circulating insulin levels

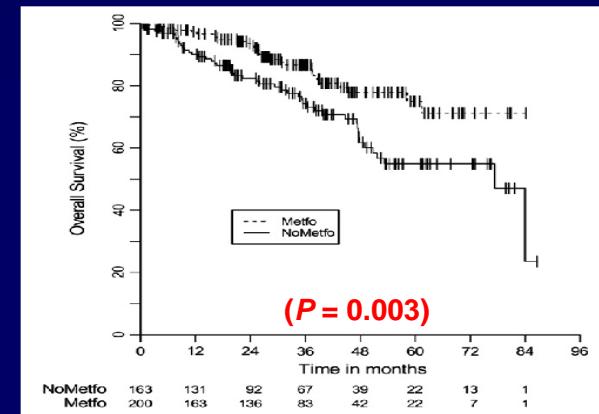


1. Adapted from *J Pancreas* 2013;14(4); 2.Cantrell LA, et al. *Gynecol Oncol.*

2010;116(1):92-98. 3. Hanna RK, et al. *Gynecol Oncol.* 2012;125(2):458-469.

4. Ko EM, et al. *Gynecol Oncol.* 2014;132(2):438-442.

- Metformin is currently used as the first line treatment for type II diabetes mellitus.
- Population based studies have suggested a protective role for metformin in the prevention of solid tumor malignancies in diabetic patients.
- Metformin is a potent inhibitor of cell proliferation in EC cell lines. This effect is partially mediated through inhibition of the mTOR pathway.²
- Metformin in combination with paclitaxel resulted in a synergistic anti-proliferative effect in these cell lines.³
- Metformin is associated with improved survival in endometrial cancer⁴



Metformin Study

- Phase II/III
- N = 240/300 pts (500pts)
- 1^o Endpoint: PFS/OS

GOG#0286B

Eligibility:

- Stage III or IVA EC measurable disease
- Stage IVB or Recurrent EC (whether there is measurable disease or not)
- No prior chemotherapy

Arm 1:

Paclitaxel 175 mg/m² IV over 3 hours day 1

Carboplatin AUC = 5 IV day 1

Metformin 850 mg oral QD, beginning on day 1. If tolerated for 4 weeks, the dose will be increased to metformin 850 mg BID.

Maintenance regimen: Metformin 850 mg oral BID until disease progression or prohibition of further therapy.

Arm 2:

Paclitaxel 175 mg/m² IV over 3 hours day 1

Carboplatin AUC = 5 IV day 1

Placebo for Metformin 850 mg oral QD, beginning on day 1. If tolerated for 4 weeks, the dose will be increased to placebo for metformin 850 mg BID.

Maintenance regimen: Matched placebo oral until disease progression or prohibition of further therapy.

PI: Victoria Bae-Jump, M.D. PhD

Open: 17/March/2014

ClinicalTrials.gov Identifier:NCT02065687

Chemo+/-AA+/-MTORi Study

- Phase II Randomized
- 1^o Endpoint: PFS
- N = 349

GOG#0086P

Eligibility:

- Stage III or IVA EC measurable disease
- Stage IVB or recurrent EC (whether there is measurable disease or not)
- No prior chemotherapy

Arm 1:

Paclitaxel 175 mg/m² IV over 3 hours day 1

Carboplatin AUC = 6 IV day 1

Bevacizumab 15mg/kg IV day 1

Maintenance regimen - Bevacizumab 15mg/kg IV every 21 days until disease progression or prohibition of further therapy.

Arm 2:

Paclitaxel 175 mg/m² IV over 3 hours day 1

Carboplatin AUC = 5 IV day 1

Temsirolimus 25 mg IV days 1 and 8

Maintenance regimen – Temsirolimus 25 mg IV weekly. Days 1,8 and 15 until disease progression or prohibition of further therapy.

Arm 3:

Ixabepilone 30 mg/m² IV over 1 hour day 1

Carboplatin AUC = 6 IV day 1

Bevacizumab 15mg/kg IV day

Maintenance regimen - Bevacizumab 15mg/kg IV every 21 days until disease progression or until prohibition further therapy.

PI: Carol Aghajanian, M.D.

From: 9/14/2009 to 9/9/2014

ClinicalTrials.gov Identifier:NCT00977574

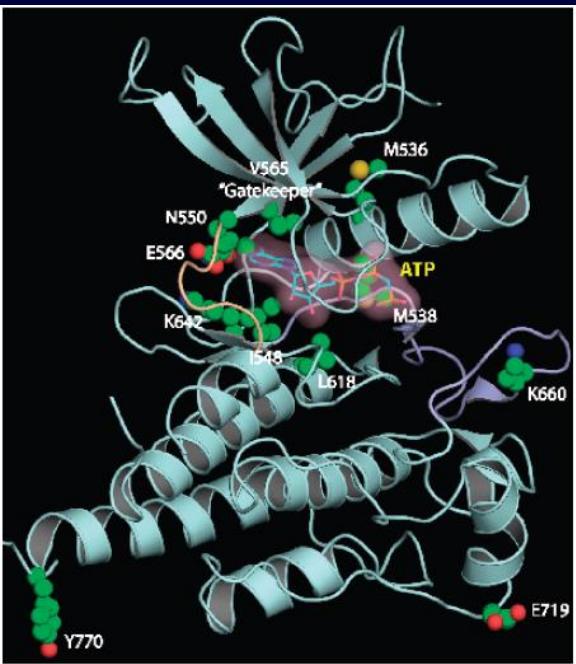
Developing Agents in Endometrial Cancer

- PI3K/AKT inhibitors
- Dual mTOR and PI3K inhibitors
- Fibroblast growth factor receptor inhibitors (FGFRi)
- PARP inhibitors
- Tyrosine kinase receptor inhibitors (RTKi)
- Other antiangiogenic agents

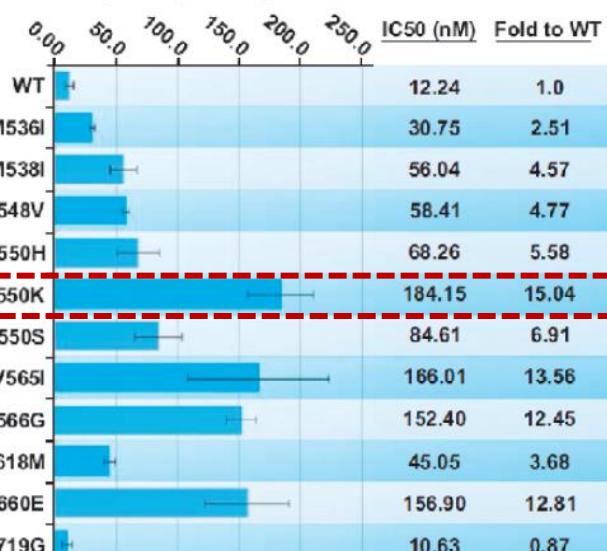
AA: FGFR-2 Mutations in EC

- Recent identification of activating mutations in FGFR-2 in EC
- The majority of the mutations are identical to germline mutations that cause *craniosynostosis and hypochondroplasia syndromes (S252W and P253R)*.
- Predominantly occur in EC type I (16%). Mutually exclusive with KRAS mutations, but associated with PTEN mutations.
- Signalling cascade depending on E-cadherin and related with MAPK-ERK pathway
- FGFRi are currently in development: Brivanib (GOG-229 I), BIBF1120 (ENGOT), TKI 258

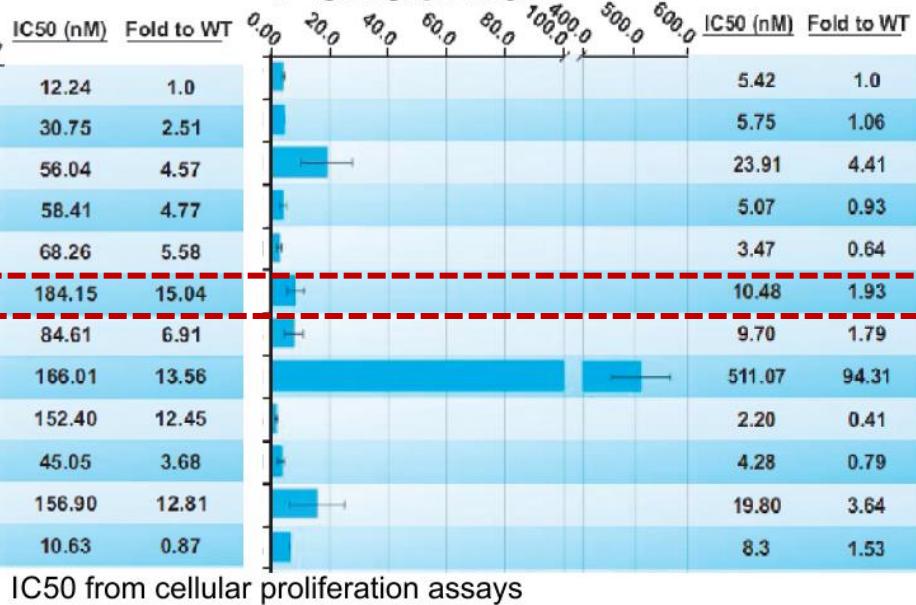
FGFR Mutations and TKI Activity



Dovitinib



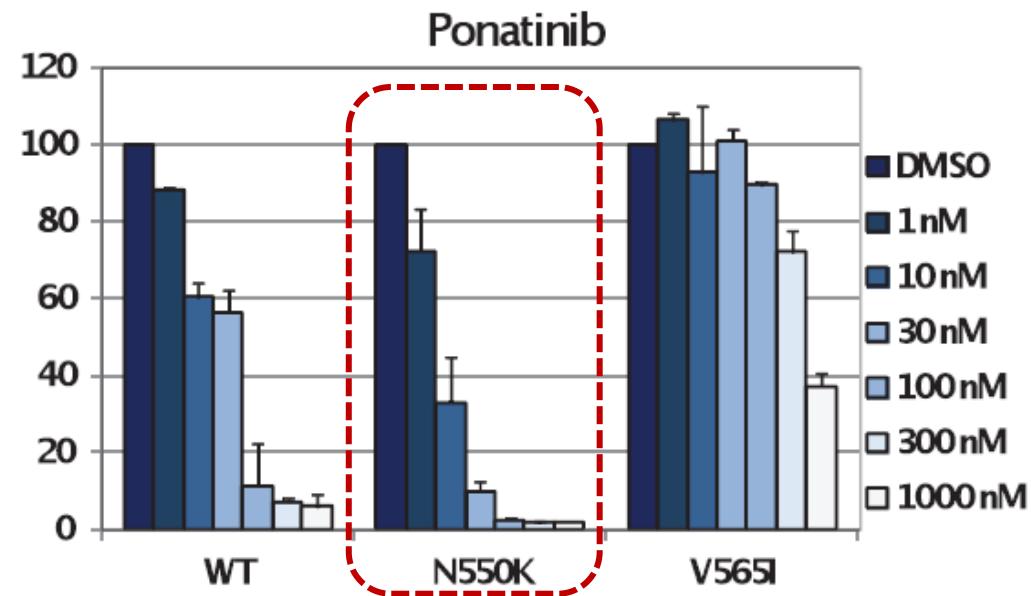
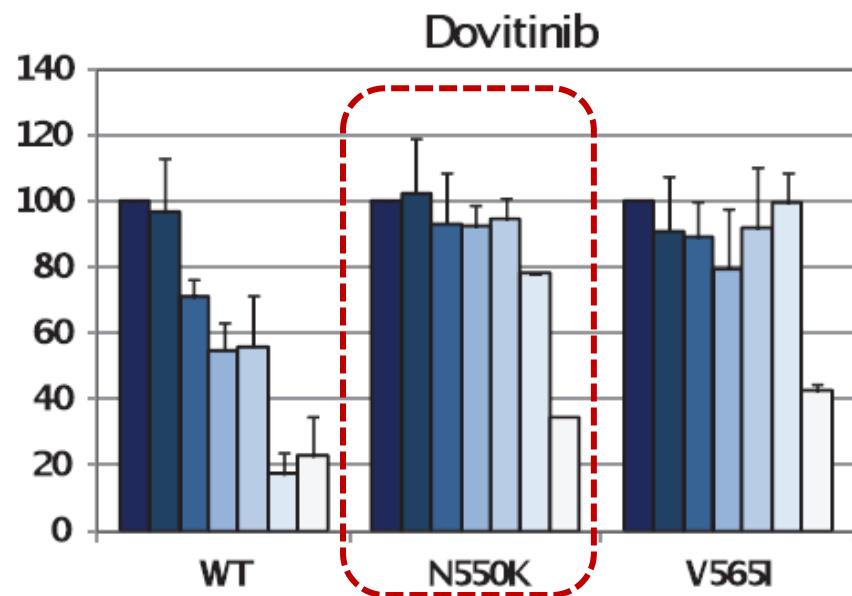
Ponatinib



IC50 from cellular proliferation assays

FGFR Mutations and TKI Resistance

Inhibition of FGFR2 Phosphorylation



Phase 2 Study of Second-Line Dovitinib (TKI258) in Patients With Fibroblast Growth Factor Receptor 2 (*FGFR2*)-Mutated or Nonmutated Advanced and/or Metastatic Endometrial Cancer

Gottfried E. Konecny, Neil Finkler, Agustin A. Garcia, Domenica Lorusso, Paula S. Lee, Rodney Rocconi, Peter C. Fong, Matt Squires, Kaushal Mishra, Allison Upalawanna, Yongyu Wang, Rebecca Kristeleit

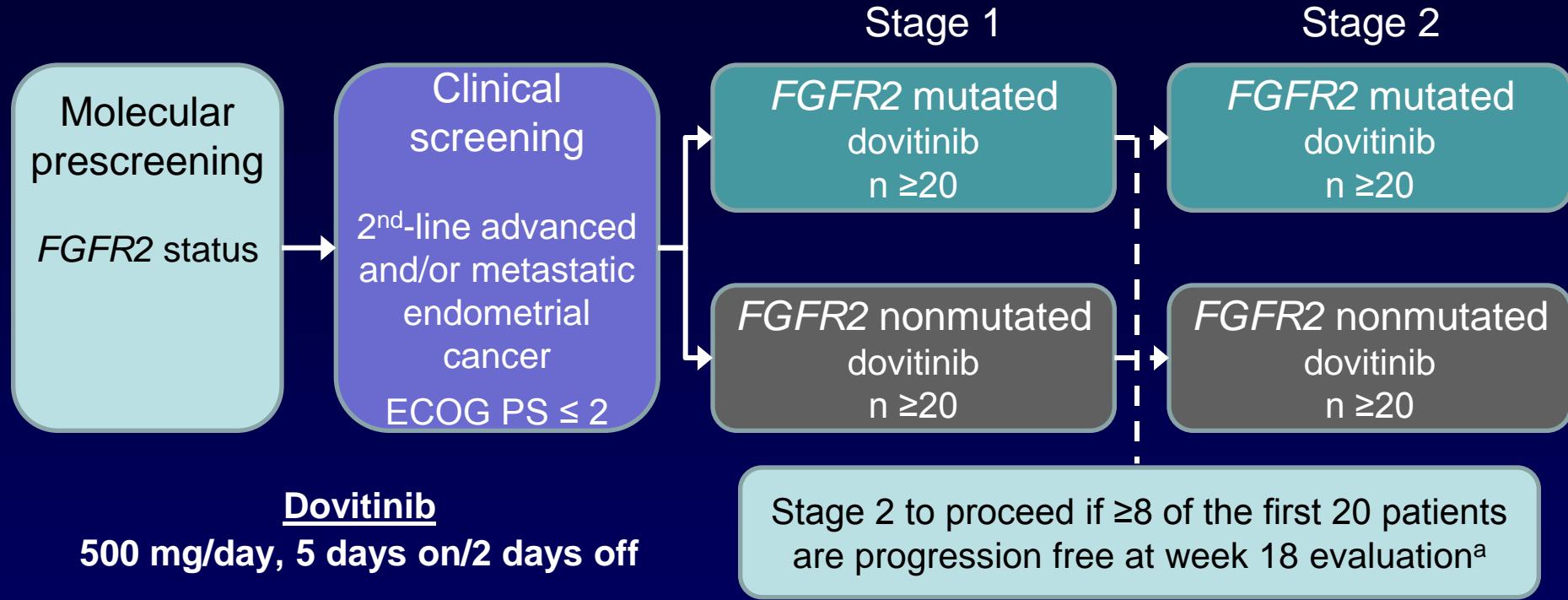
European Society for Medical Oncology 2014

Background

- Activating mutations in *FGFR2*, identified in 10%-15% of primary endometrial cancers, are associated with disease progression and poor outcome¹⁻⁴
- Dovitinib (TKI258) is an oral tyrosine kinase inhibitor that targets FGFR, VEGFR, PDGFR, and other kinases⁵
- Dovitinib demonstrated dose-dependent growth inhibition of *FGFR2*-mutated and *FGFR2*-nonmutated endometrial xenografts⁶

1. Pollock PM, et al. *Oncogene*. 2007;26(50):7158-7162. 2. Dutt A, et al. *Proc Natl Acad Sci U S A*. 2008;105(25):8713-8717. 3. Cheung LW, et al. *Cancer Discov*. 2011;1(2):170-185. 4. Byron SA, et al. *PLoS ONE*. 2012;7(2):e30801. 5. Lee SH, et al. *Clin Cancer Res*. 2005;11(10):3633-3641. 6. Konecny G, et al. *Mol Cancer Ther*. 2013;12(5):632-642.

Phase II Study Design



Primary endpoint

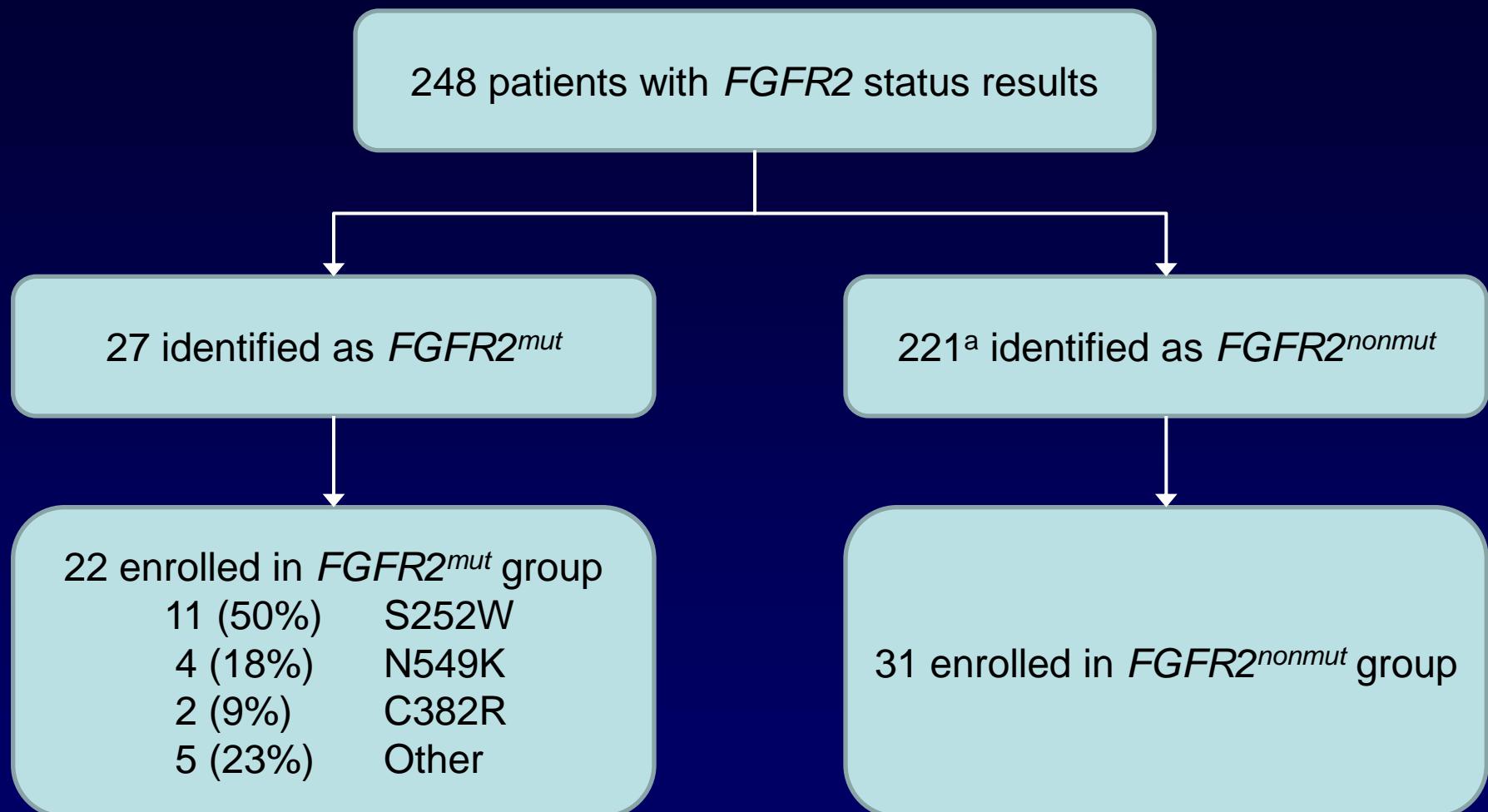
Percentage of patients progression free after 18 weeks

Secondary endpoints

Overall response rate, disease control rate, duration of response, PFS, overall survival, safety, tolerability, pharmacokinetics, pharmacodynamics

^a A positive conclusion at final analysis required 18-week PFS rate ≥50% in any group.

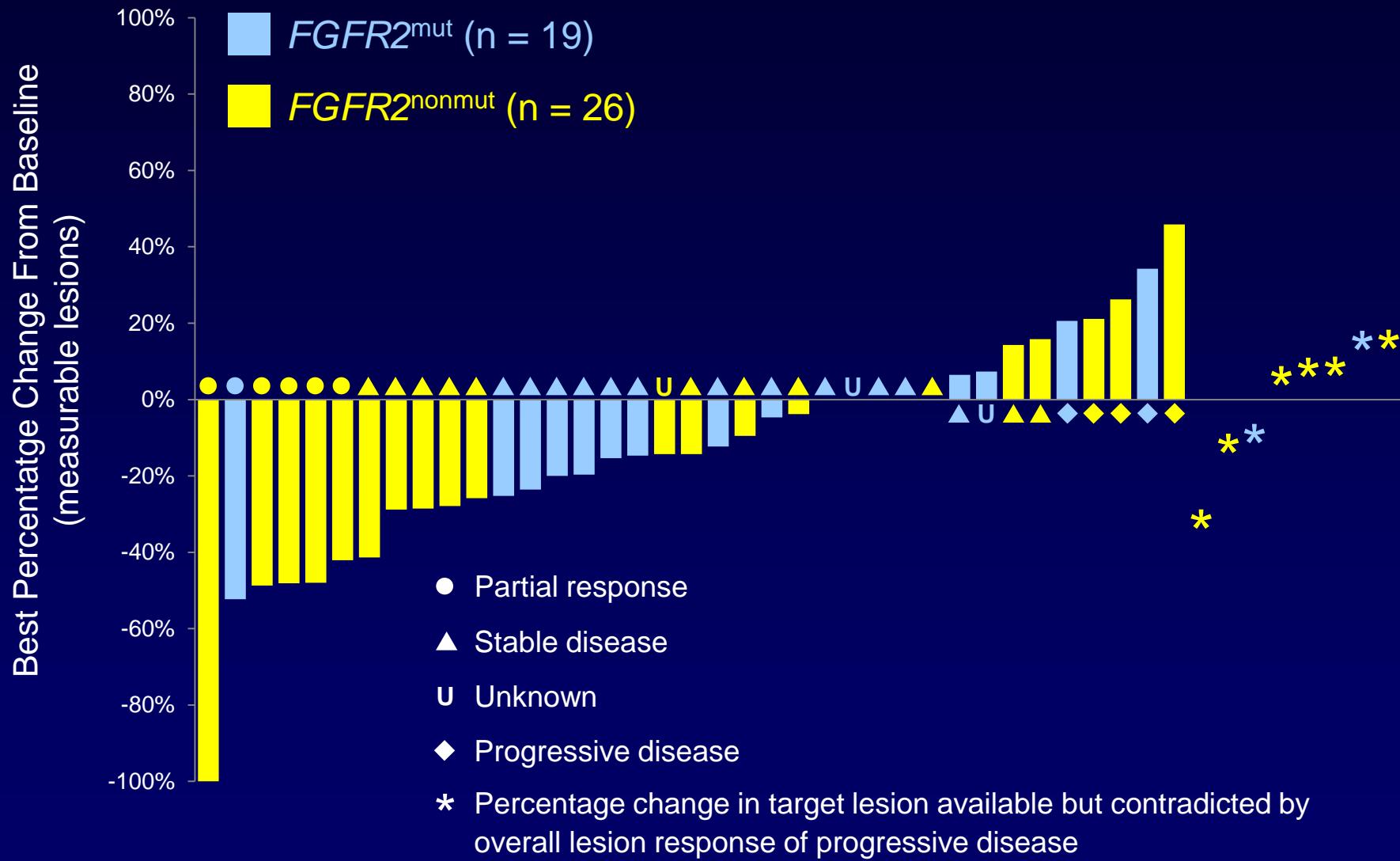
***FGFR2* Molecular Prescreening**



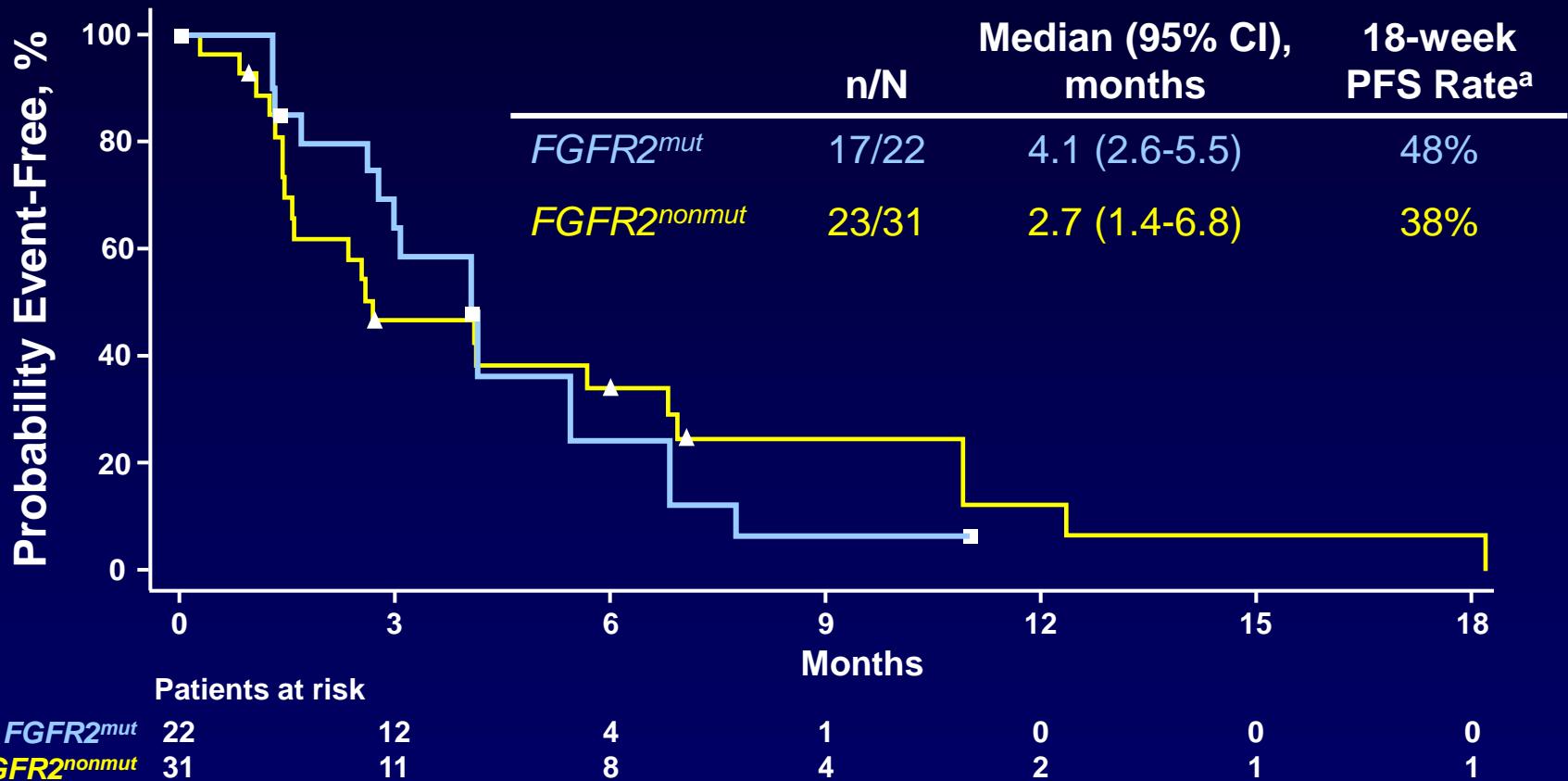
FGFR2 mutation rate ≈ 11%

^a 166 patients identified after enrollment to *FGFR2*^{nonmut} group complete.

Best Change From Baseline

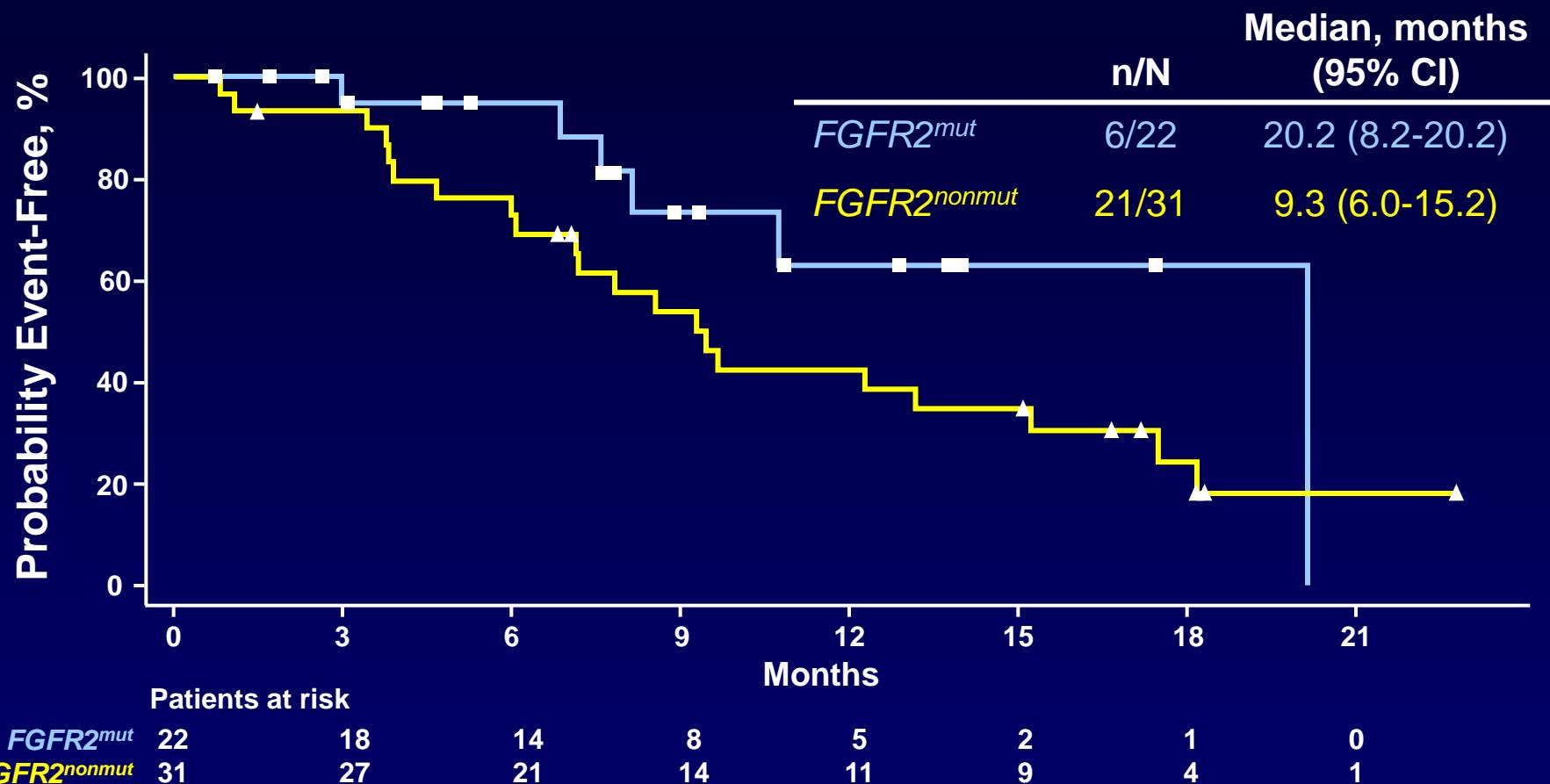


Progression-Free Survival



^a 18-week PFS rate from Kaplan-Meier analysis.

Overall Survival



Conclusions

- Single-agent dovitinib demonstrated clinically meaningful activity in both groups
 - Higher PR rate was observed in the *FGFR2^{nonmut}* vs *FGFR2^{mut}* group
 - There was a trend toward greater median PFS and survival in the *FGFR2^{mut}* group
- The overall safety profile was similar to that observed in other dovitinib trials
 - However, the incidence of thrombosis appeared more common in this patient population

What Did We Learn?

- In aggregate, type I endometrial cancer is associated with frequent (nonoverlapping) mutations in KRAS, CTNNB1, FGFR2, and PIKC3A, with associated pathway activation.
- In recurrent disease, targeting VEGF (with bevacizumab) demonstrates activity that appears equal or superior to multi-targeted TKIs, including anti-FGFR2.
- Some TKIs may not be effective in the setting of common activating mutations within the kinase domain of FGFR2, due to restricted binding
- Understanding, and optimizing, the net contribution of each pathway awaits randomized trials that incorporate stratification based on prior treatment and analysis of biospecimens.

Endometrial Cancer Summary

- Increasing incidence and mortality
- Current most important PF: stage, histology, and grade
- Lack of second-line treatment in R/M patients:
encourage clinical trial participation in this unmet need
- Molecular alterations are frequent
 - Mainly, in relation with better prognosis: histology and stage
- Current confusing data about targeted therapies results
 - mTORi similar efficacy in type 1 or 2
 - Modest results as single agents in phase II trials
- Need for validated predictive biomarkers to design future trials (ie, targeting the PI3KCA pathways needs further investigation and clarification of relevant biomarkers)

Thank You!



apoveda@fivo.org

2015

Progress and Controversies in Gynecologic Oncology Conference

