Emerging diagnostic and therapeutic targets in gynecological cancers

PI3K/AKT pathways in ovarian and endometrial cancers

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Disclosure information of Cristiana Sessa

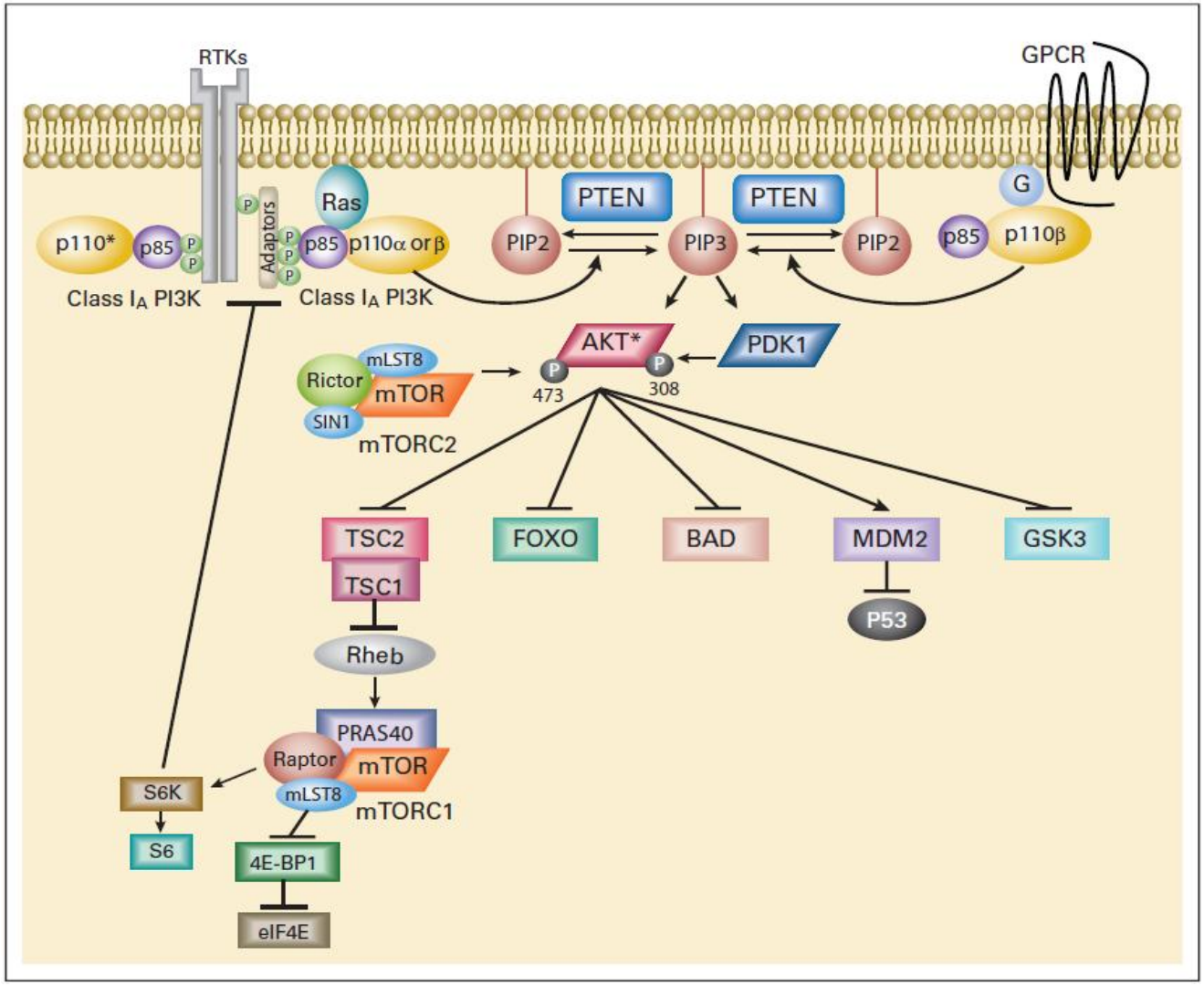
Relationships Relevant to this session

Advisory Board: OSI

Corporate-sponsored research: OSI

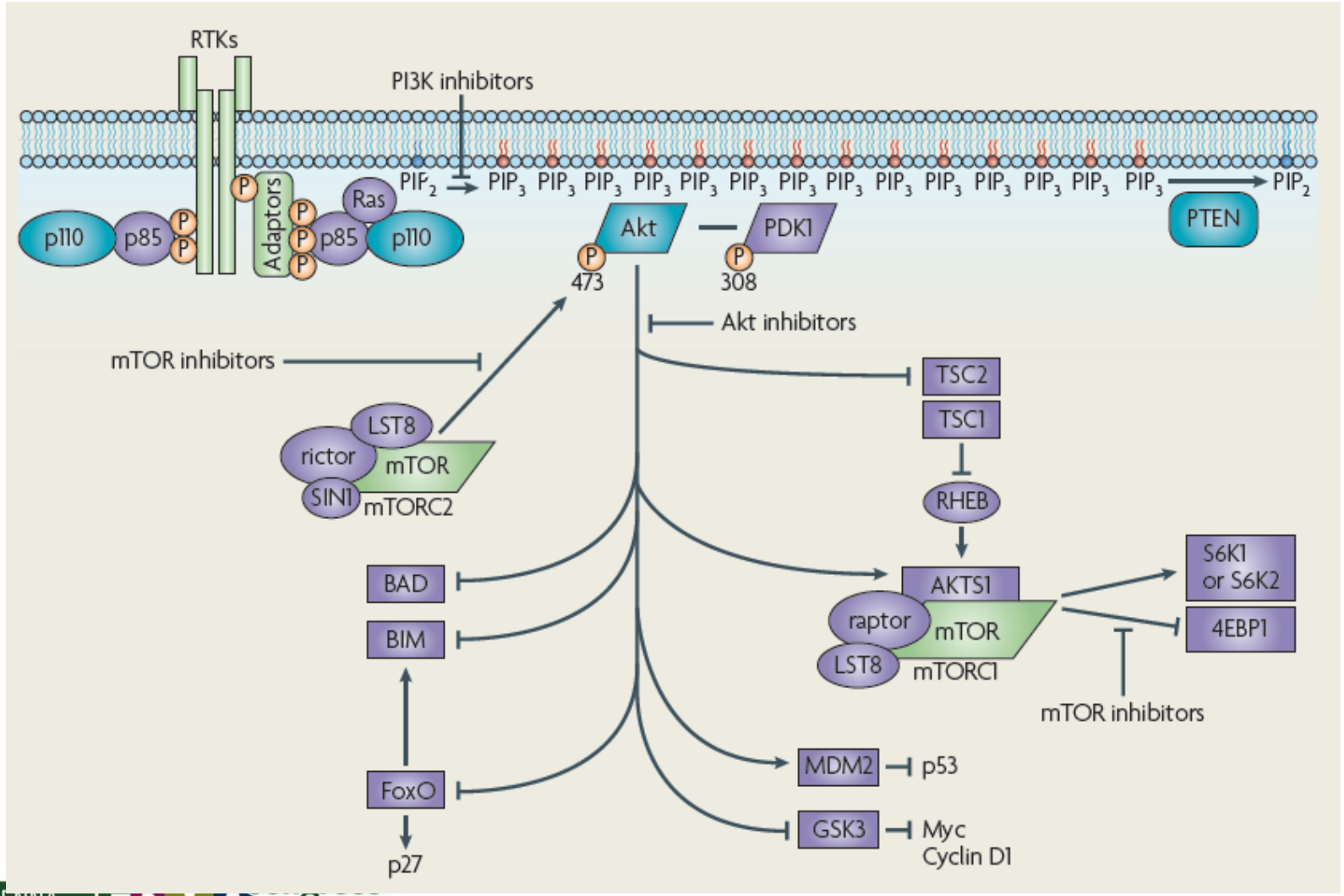
No other relevant relationship

The PI3K signaling cascade



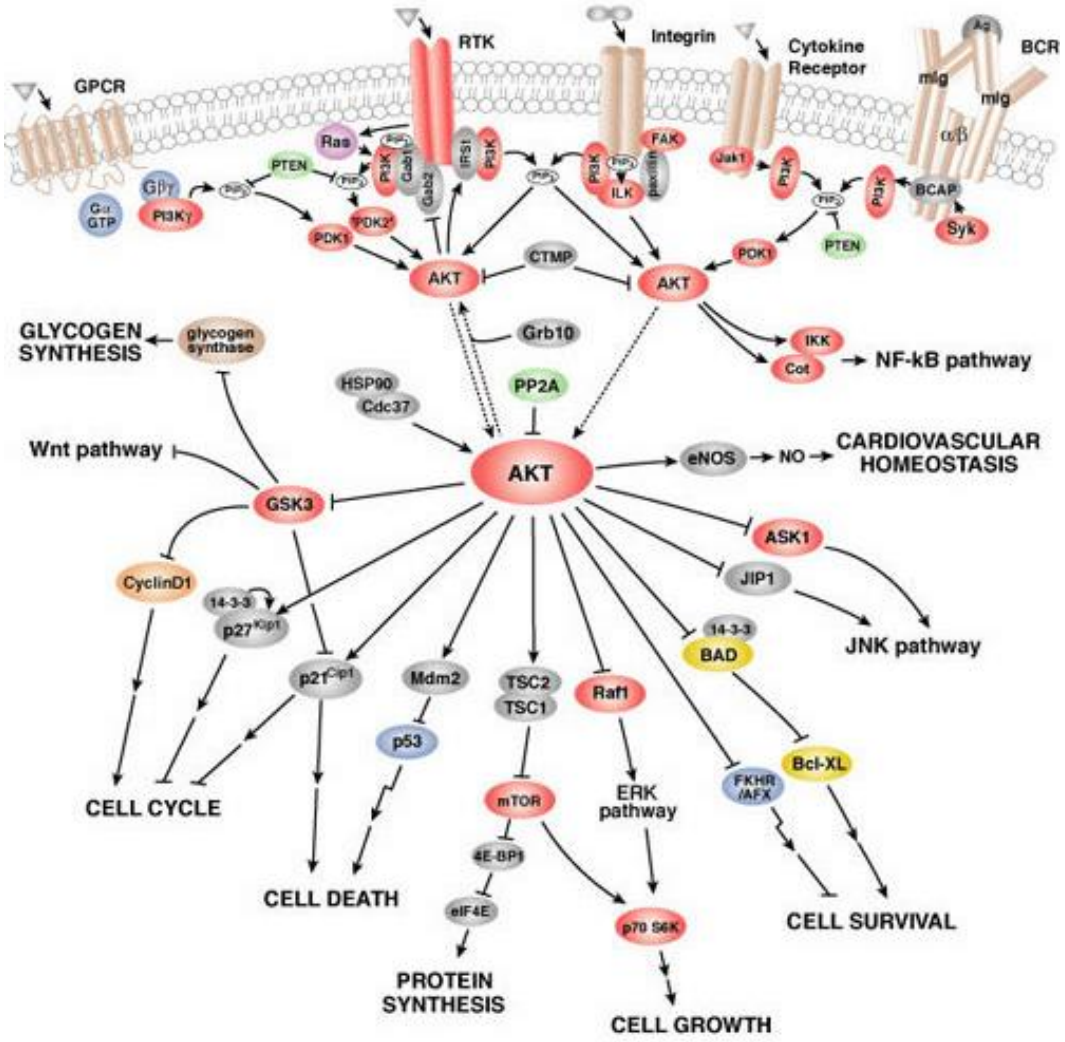
Courtney et al, J Clin Onc, 2010

Components of PI3K-AKT pathway as therapeutic targets



Engelman, Nat Rev Cancer, 2009

Relevance of PI3K / AKT signalling axis in cancer



Multiple regulators altered

RTK activations: EGFR, MET, KIT, HER_2

Activating mutations: $p110_a$, AKT

Inactivating mut / deletions: PTEN, LKB_1

Amplifications: $p110_a$, p85, AKT_1, AKT_2, PDK_1, p70S6K

PI3K / AKT pathway inhibitors in clinical development

Dual PI3K nd mTOR inhibitors		
BEZ 235	**Novartis**	**Phase II (endom)**
PF 0469, PF 0521	**Pfizer**	**Phase II (endom)**
XL 765	**Exelixis**	**Phase II**
GDC 0980	**Genentech**	**Phase II**
PI3K inhibitors		
BKM 120	**Novartis**	**Phase II (endom)**
XL 147	**Exelixis**	**Phase II (endom)**
GDC 0941	**Genentech**	**Phase II**
CAL 101	**Calistoga**	**Phase II**
AKT inhibitors		
GSK 214 1795	**GSK**	**Phase I**
GDC 0068	**Genentech**	**Phase IB**
MK 2206	**Merck**	**Phase IB**
mTOR inhibitors		
OSI 027	**Astella**	**Phase I**
AZD 2014	**Astrazeneca**	**Phase I**
CC223	**Celgene**	**Phase II**

PI3K pathway alterations and ovarian cancer

	% of cancers with		
Gene	**Amplification**	**Mutations**	**Overexpression**
PIK3CA	9-11%	8-12%	32%
PIK3R1	ND	ND	ND
AKT1	12-27%	2%	12%
KRAS	5%	2-24%	30-52%
BRAF		36%*	
PTEN	27% deletion	3-8%	

*exclusively in low grade serous

PIK3CA mutations and response to PI3K/AKT/mTOR inhibitors in patients with breast and gynecological malignancies

No of cases with mutations

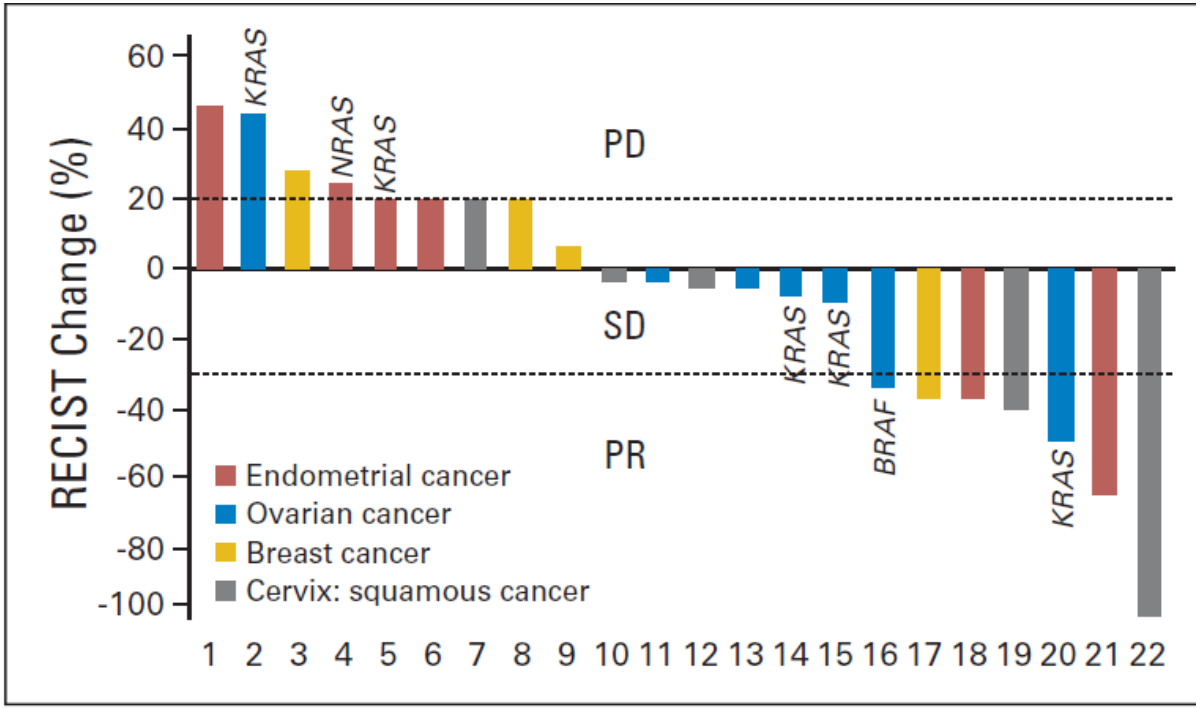
	Ovary	Breast	Endometrium	Cervix
PIK3CA mut (%)	7 (28%)	6 (24%)	7 (28%)	5 (20%)
KRAS mut (%)	5*	1	3**	1
B RAF (%)	2	0	0	0
N RAS	1		2**	

* 3 cases with both PI3K / KRAS mut

** 2 cases with both PI3K / KRAS or N RAS mut

Janku et al, JCO, 2012

PIK3CA mutations and response to PI3K/AKT/mTOR inhibitors in patients with breast and gynecological malignancies



Waterfall plot of PIK3CA mut patients treated with PI3K / AKT / mTOR inhibitors

Janku et al, JCO, 2012

Development of combinations with PI3K Inhibitors in ovarian cancer

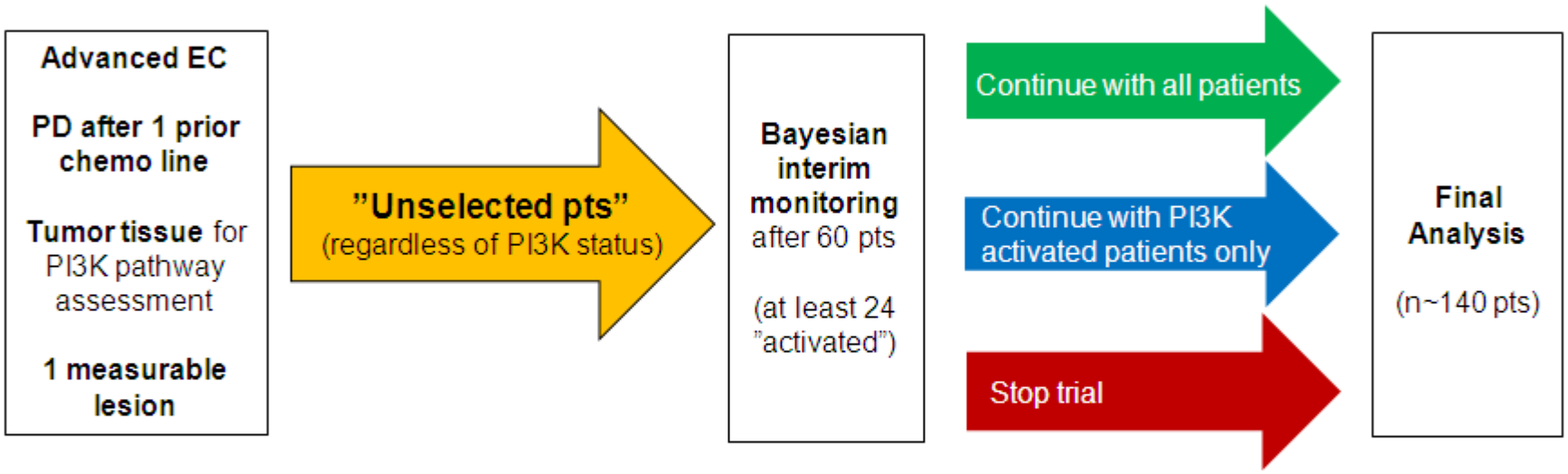
- Dysregulation of PI3K / AKT signalling contributes to resistance to anticancer therapies
- In ovarian cancer xenograft the combination of PI3K inhibitor and carboplatin seems to be more effective than either agent alone
- The high redundancy and cross interaction requires targeting the pathway at different levels
- Molecular characterization could be useful
    - in representative preclinical models for the development of effective combinations
    - in clinical trials for the retrospective identification of mutations indicative of sensitivity to the agents studied

mTOR inhibitors in endometrial cancer

	ROUTE	DOSE	1st LINE ACTIVITY	2nd LINE ACTIVITY
Temsirolimus NCIC IND 160	IV	25 mg Q wk (100mg/mo)	~25% RR (60% SD)	7% RR (2/27)
Everolimus	PO	10 mg QD (56mg/mo*)	ND	0% RR CBR 40%
Ridaforolimus Columbo et al.	IV	12.5 QDx5 Q2 wk (130mg/mo)	ND	9% RR (4/45) CBR 30%
Ridaforolimus **NCIC IND 192**	**PO**	**40 QDx5 Q wk** **(160mg/mo*)**	**RR endpoint**	**205 RP2** **PFS endpoint**

PI3Ki in Endometrial Cancer

Example: Single agent Phase 2 in 2nd-line EC



- Objectives
  - Primary: ORR by RECIST in patients with „PI3K pathway activation" AND in „all patients"
  - Secondary: additional efficacy (ORR in „non-activated" pts, DCR, PFS), safety, biomarker

Signaling pathway abnormalities in endometrial cancer

	Endometrioid	Nonendometrioid
PTEN loss	35-50%	10%
PIK3CA mut	40%	15%
AKT1 mut	2%	
$FGFR_2$	12%	
$PIK3R_1$ mut	20%	
$PIK3R_2$ mut	5%	
KRAS mut	17%	17%

Cheung et al, Cancer Discov., 2011

Signaling pathway abnormalities in endometrial cancer

Conclusions

- PI3K and KRAS pathways are drivers in the pathogenesis of EC
- Frequent mutations of PIK3R1 (p85a) and PIK3R2 (p85β) cause destabilization of PTEN and increase of AKT phosphorylation
- Cells with concomitant KRAS and PI3K pathway mutations have
  - >GI50% of rapamycin than with PI3K pathway mutation alone
  - relative sensitivity to MEK inhibition
- Rational targeted therapeutic combinations are needed to overcome feedback loops in the PI3K pathway

Cheung et al, Cancer Discov., 2011