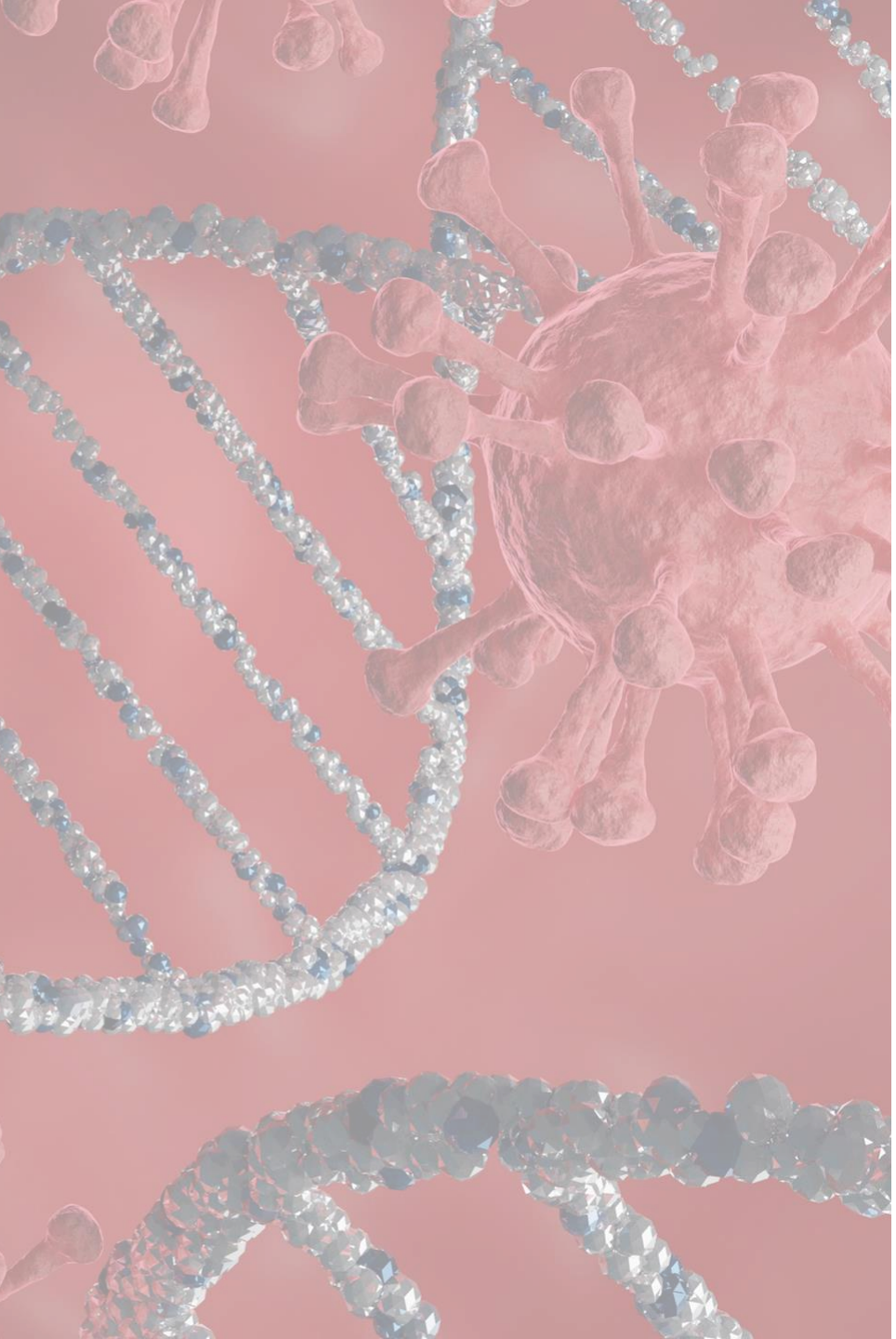


Stephanie Lheureux

- Targeting mTOR & PIC3CA

Targeting PI3K/Akt/mTor pathway

Are you ready for the challenge?

Stephanie Lheureux MD - PhD

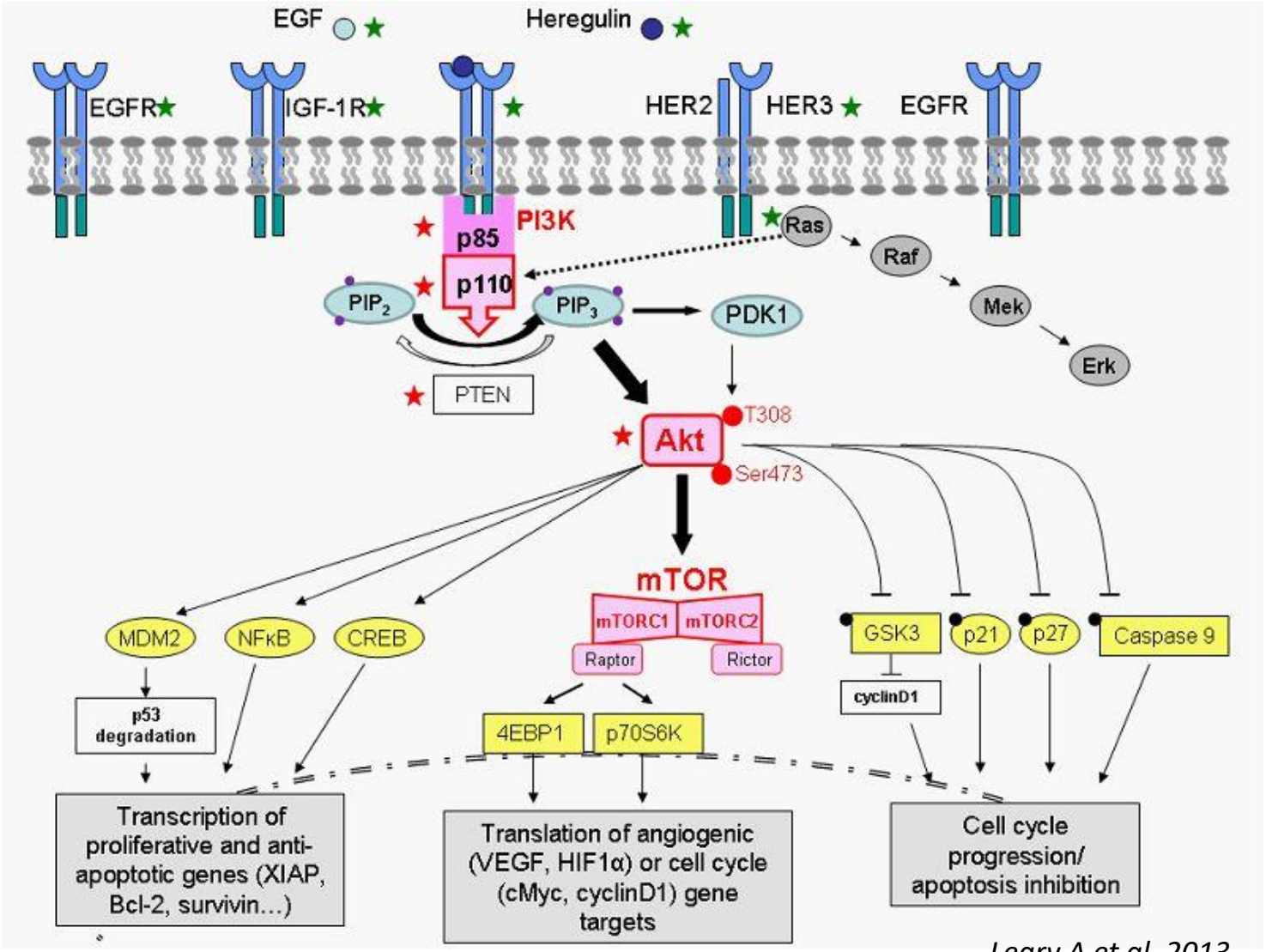
Clinician Investigator – Drug Development Program
Site Lead, Gynecology Oncology
Co-director of the Beyond Chemotherapy Program
Westaway Chair for Ovarian Cancer Research
Princess Margaret Cancer Centre
Associate Professor – University of Toronto (UFT)

PI3K Pathway & Regulation

Key Aspects of Cancer Biology
Glucose Uptake & Metabolism,
Cellular Growth & Survival

* **Upstream Activation of PI3K pathway**
  - *Directly*: via Growth Factor Receptor & Ligands
  - *Indirectly*: Cross-talk - Ras pathway

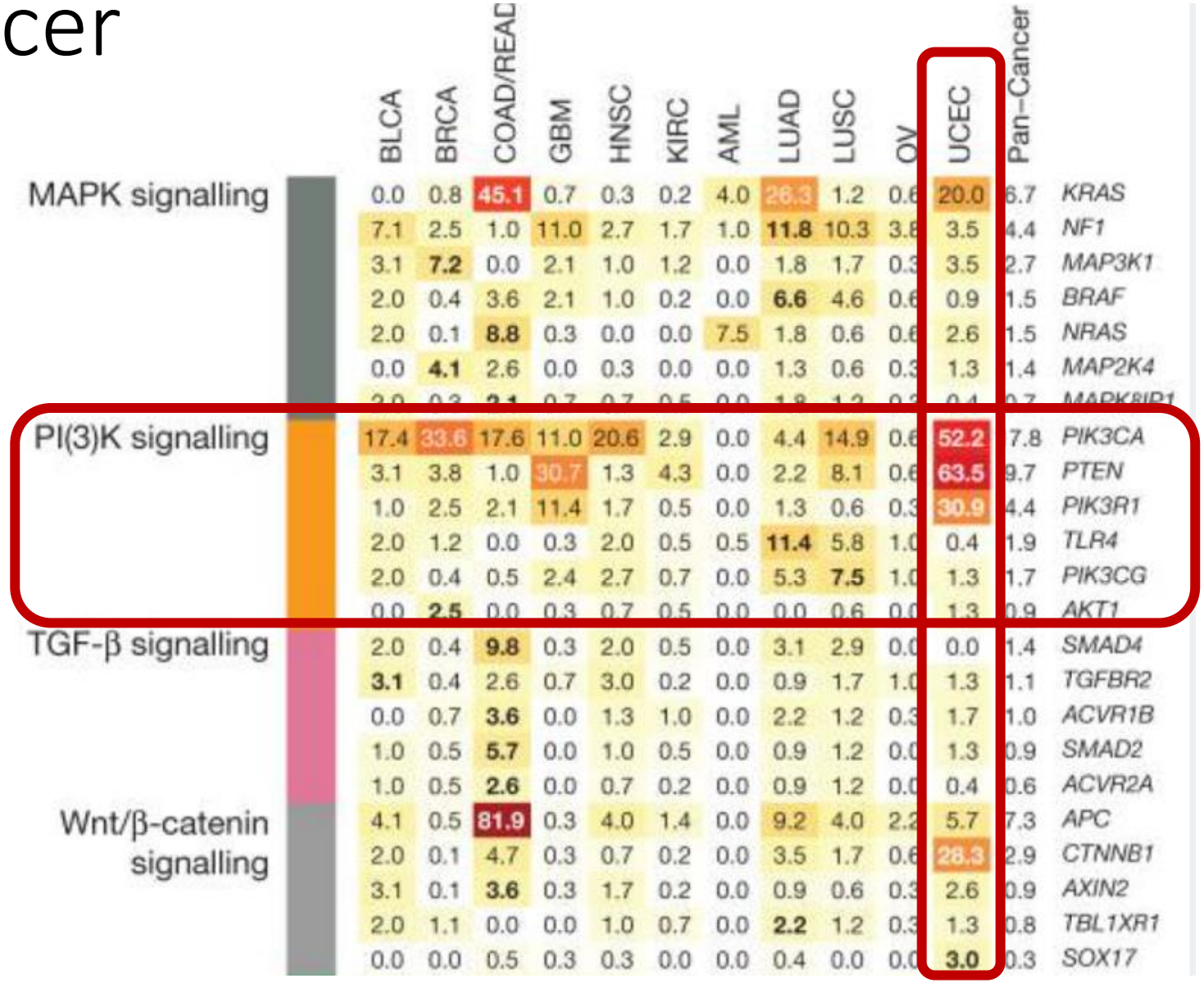
* **Intrinsic Activation of PI3K pathway**
  - Gain of Function Mutation Amplification PI3K-AKT
  - Loss of negative regulator PTEN *(Inactivating mutation – CN loss – Homozygous deletion)*



Leary A et al, 2013

PI3K pathway & Cancer

Significantly Mutated Genes
from 20 cellular processes in cancer
identified in 12 cancer types.



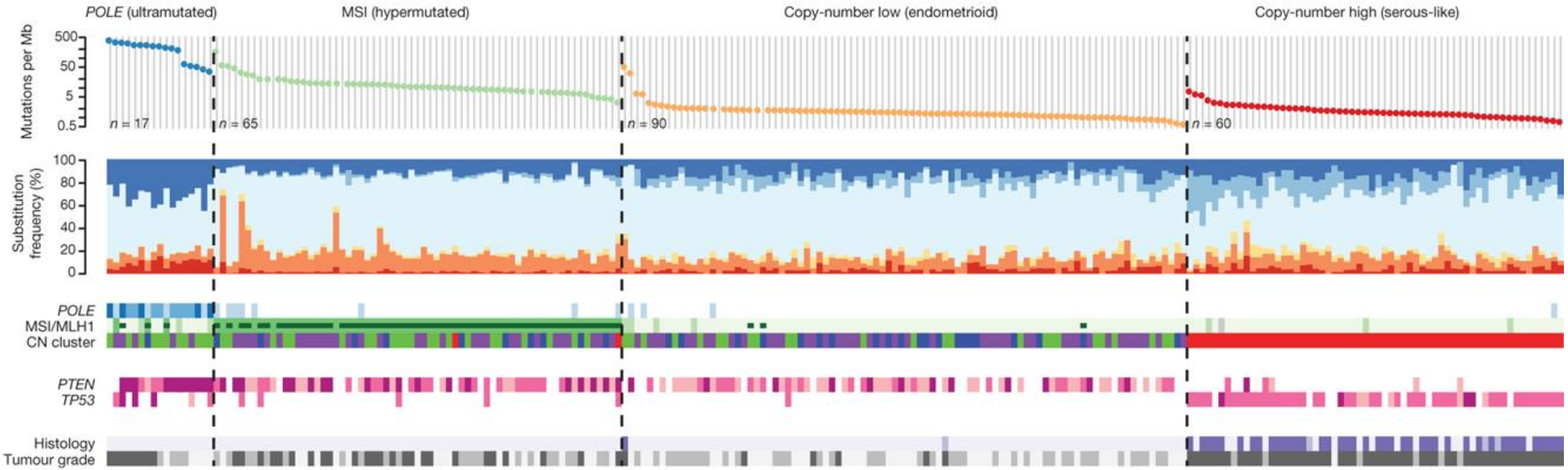
C Kandoth et al, Nature 2013

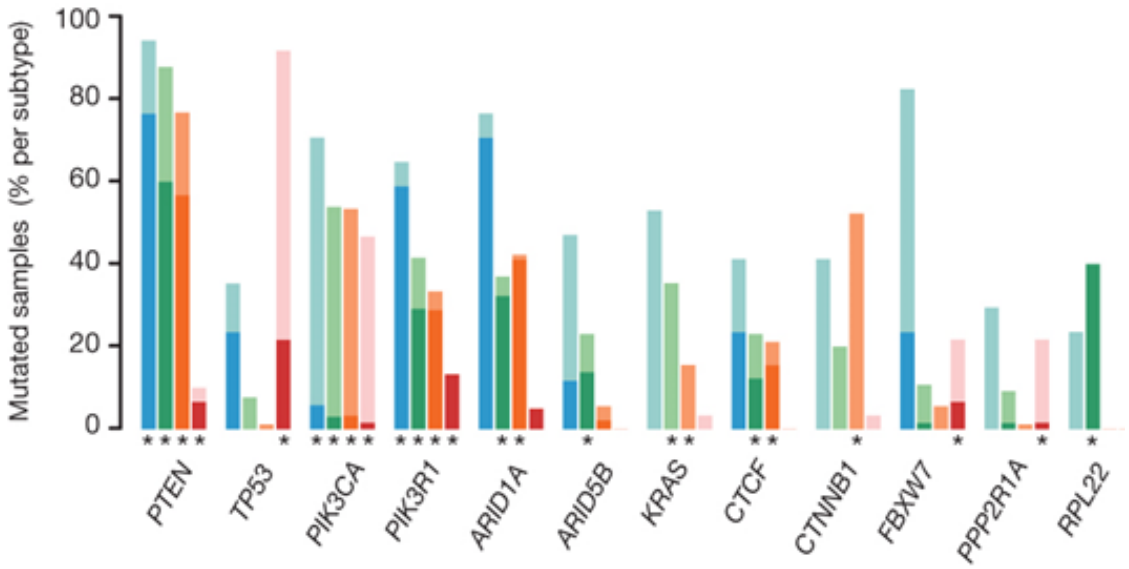
PI3K and Endometrial Cancer

Incidence of Genetic Alterations in Type I & II

Gene (reference)	Incidence of genetic aberrations in endometrial cancer, %	
	Type I	Type II
PTEN (12)		
Sequence abnormalities	70	35
Protein loss	75	43
PIK3CA (13, 14)	41–52	33–38
PIK3R1 (14, 15)	21–43	12–17
AKT1 (16)	2	Undetected
RTKs		
HER2 amplification (17)	3	18
HER2 overexpression (17, 18)	8	18–31
FGFR (19, 20)	12–16	~1
EGFR overexpression (21, 22)		~50–80
KRAS (23, 24)	13–26	2

B. Slomovitz and R. Coleman, 2012

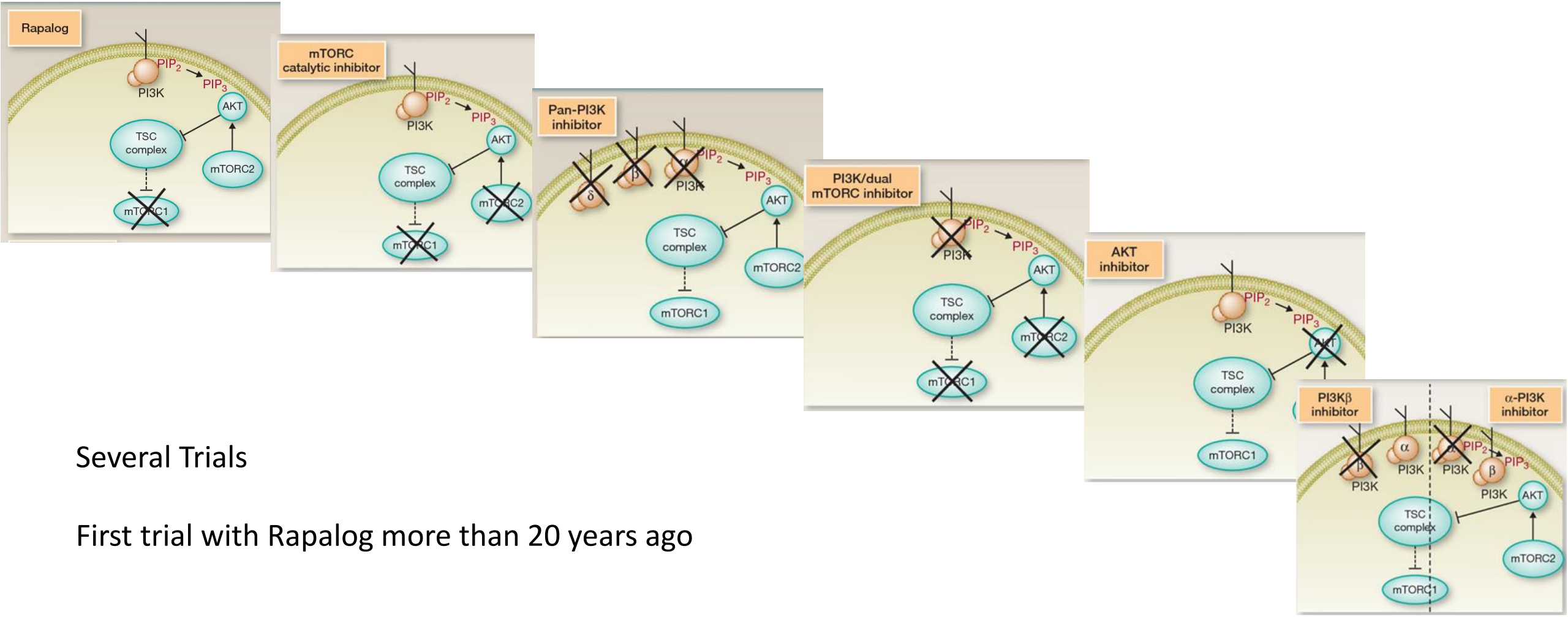




- **POLE** (Ultramutated): Highest rate of PTEN (94%), PI3KCA (71%), and PIK3R1 (65%) Alterations
- **MSI** (Hypermutated): KRAS – PTEN Mutations frequent
- **Copy Number Low** (Endometrioid): PTEN, PIK3CA and beta-catenin Mutations
- **Copy Number High** (Serous-like): p53 most altered (92%), PI3K (47%) and PTEN (11%) – HER2 amplifications (25%)

G Getz et al - TGCA, Nature 2013

Drug Development for Target



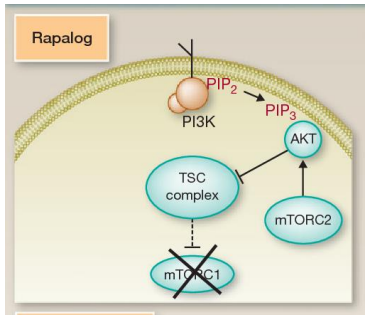
Several Trials

First trial with Rapalog more than 20 years ago

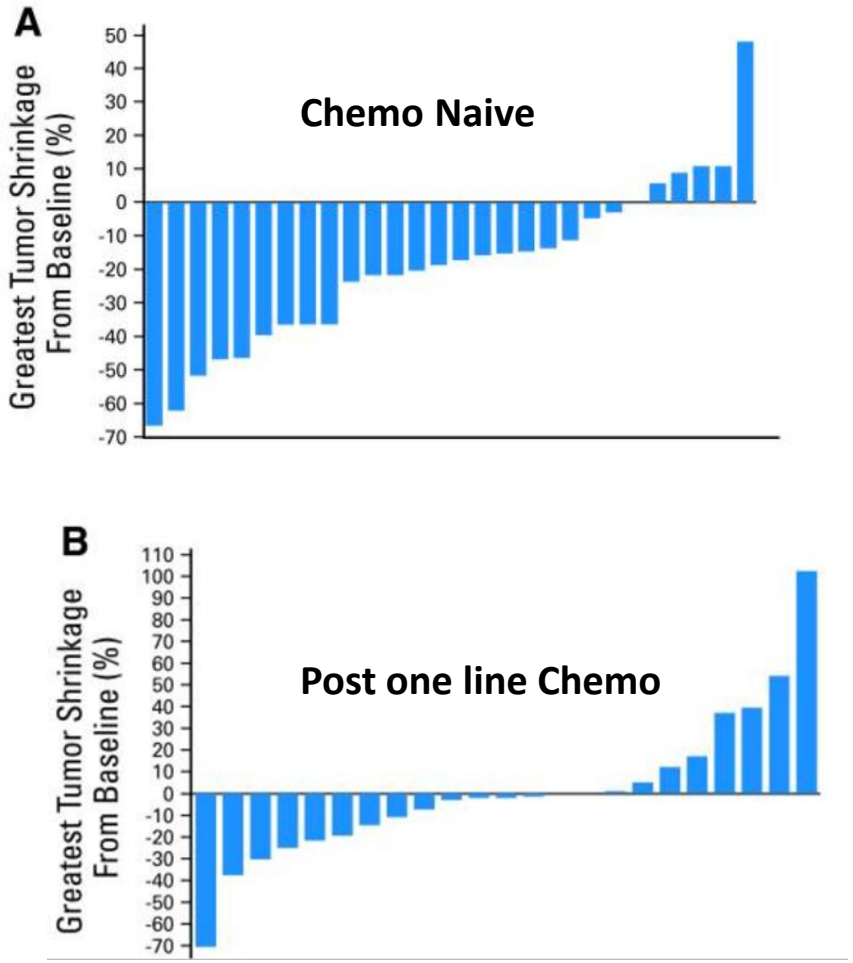
Lheureux et al 2014 Exp Opin Investig Drugs

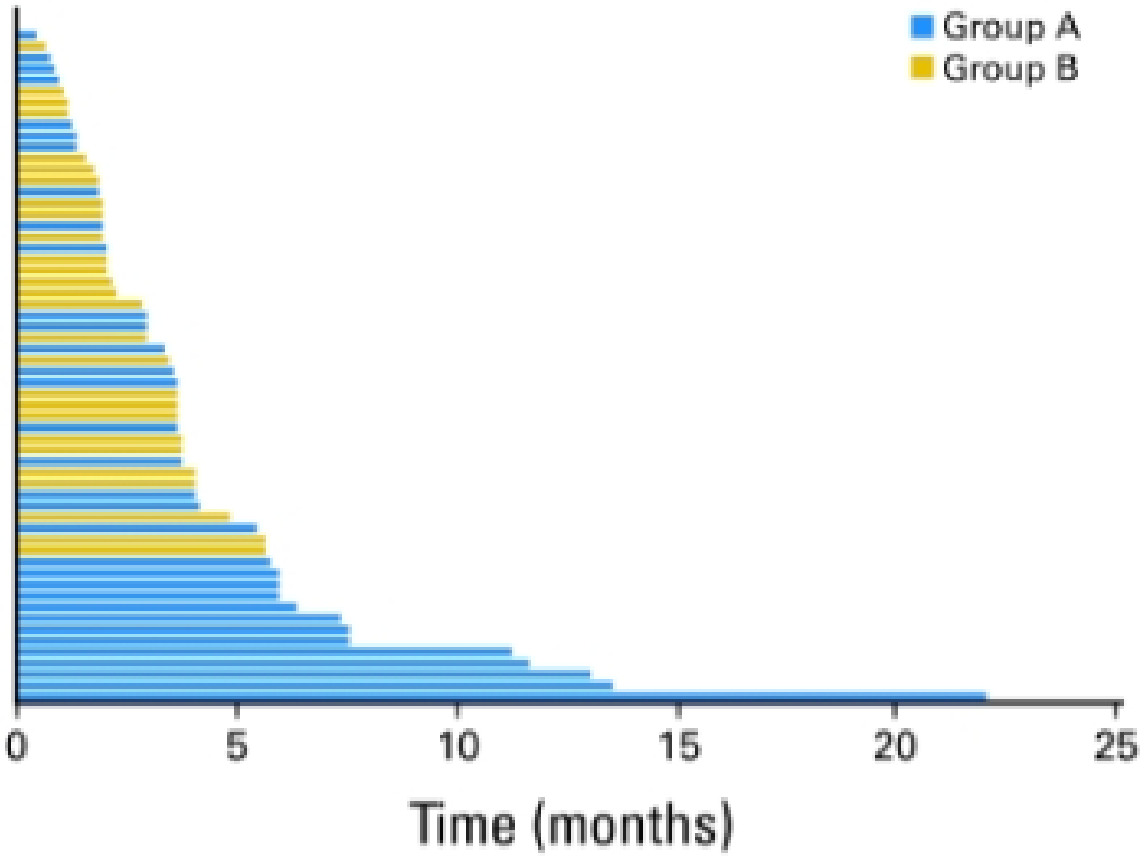
A. Myers, CCR 2013

Temsirolimus – Single Agent



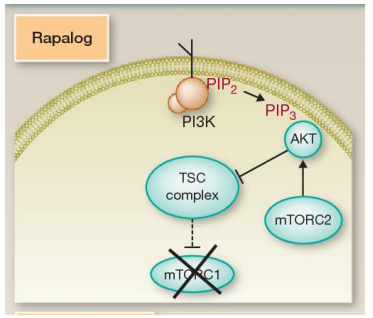
Recurrent or Metastatic Endometrial Cancer – Single Arm – 2 Cohorts





Oza AM et al, JCO 2011

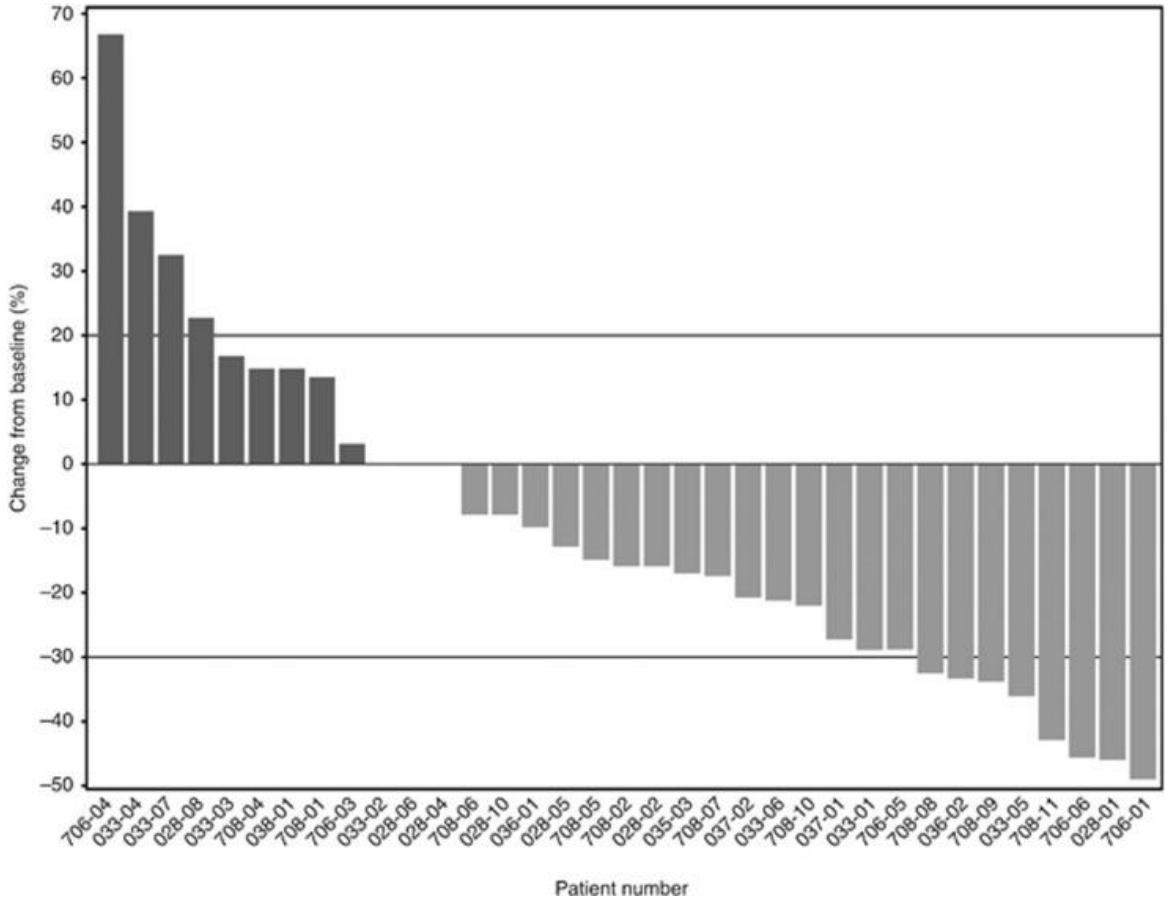
Ridaforolimus – Single Agent



- **Open-label**, Multicentre, Phase 2
- Advanced - Metastatic Endometrial Cancer

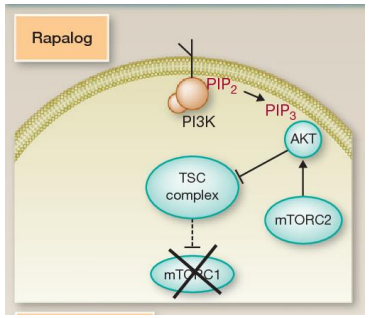
- Ridaforolimus 12.5 mg IV OD for 5 consecutive days every 2 weeks in a 4-week cycle

- **AE:** Diarrhoea (58%) and Mouth sores (56%)
- **Most common grade <u>></u> 3**: Anaemia (27%) and Hyperglycaemia (11%)



Colombo N et al, BJC 2013

Ridaforolimus – Single Agent



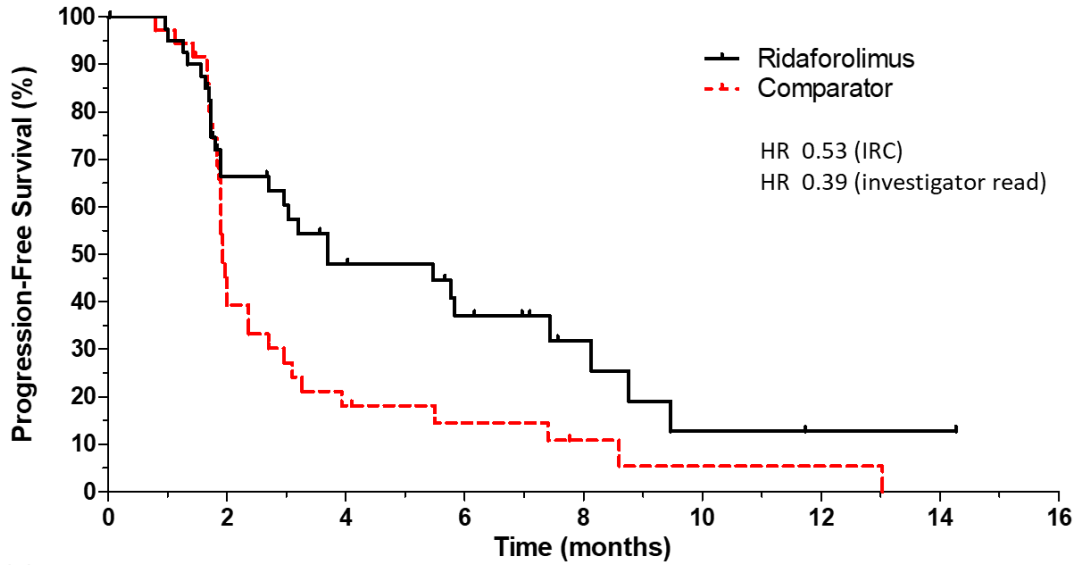
Randomized – Open label

Metastatic/Recurrent EC
Progressive disease post
1 or 2 lines of chemotherapy
No hormonal therapy

Oral ridaforolimus 40 mg qd, 5 days followed by 2-day holiday

Oral progestin qd, 7 days a week
200 mg medroxyprogesteron
or 160 mg megestrol acetate

Chemotherapy added as option



n at risk									
Ridaforolimus	48	23	14	10	5	1	1	1	0
Comparator	47	13	6	4	2	1	1	0	0

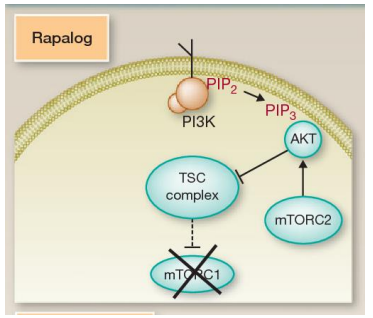
Treatment discontinuation due to AE: 33% with Ridaforolimus vs 6% with the Comparator

Common (> 10%) grade 3 toxicities: Hyperglycemia, Anemia, and Diarrhea

	Ridaforolimus (N=48)		Comparator (N=47)	
	IRC	Investigator read	IRC	Investigator read
Median survival, months	3.6	5.6	1.9	1.9

Oza AM et al, JCO 2015

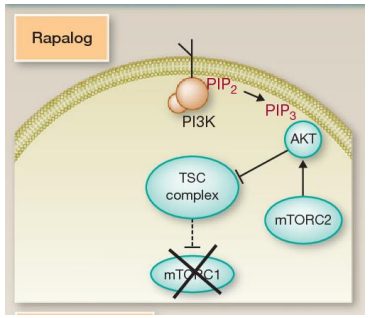
Everolimus – Single Agent



- Progressive or Recurrent endometrial cancer who had received one or two prior chemotherapeutic
- Histologically-confirmed Endometrioid Endometrial Adenocarcinoma.
  Serous, clear cell, carcinosarcoma, sarcoma, or other histologic subtypes were excluded.
- Of the 28 evaluable patients
  - No complete or partial response
  - Median duration of SD = 4.5 months (range 2 −10)
- 49% of pts required dose reduction to 5 mg daily because of stomatitis (n=10), hyperglycemia (n=3), thrombocytopenia, hypertriglyceridemia, rash and fever.

Slomovitz BM et al, Cancer 2010

Everolimus – Single Agent



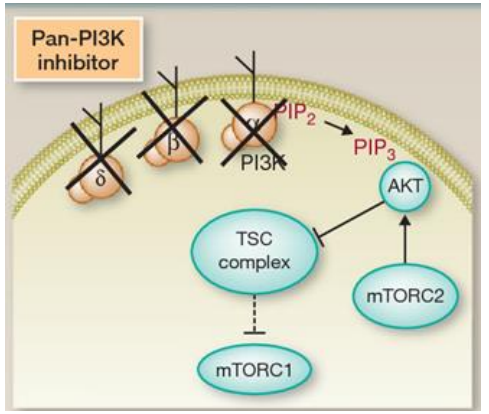
Everolimus: Second- or Third-line treatment of Advanced EC - ENDORAD phase II trial

	Total Population (*N*=44)		Endometrioid histology (*n*=28)		Serous histology (*n*=11)		Other histology (*n*=5)	
Response, *n* (%)	**3 Months**	**6 Months**	**3 Months**	**6 Months**	**3 Months**	**6 Months**	**3 Months**	**6 Months**
Partial response	2 (5)	4 (9)	1 (4)	3 (11)	1 (9)	1 (9)	0	0
Stable disease	14 (32)	12 (27)	10 (36)	8 (29)	2 (18)	2 (18)	2 (40)	2 (40)
Progressive disease	25 (57)	25 (57)	15 (54)	15 (54)	8 (73)	8 (73)	2 (40)	2 (40)
Not evaluable	3 (6)	3 (6)	2 (7)	2 (7)	0	0	1 (20)	1 (20)

Median duration of response was 3.1 months

Ray-Coquard et al, BJC 2013

Pi3K inhibitor – Single Agent

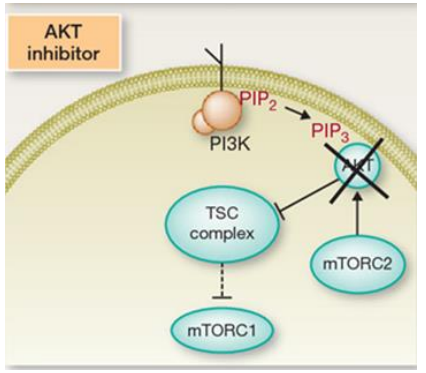


- **Pilaralisib** – Single Arm
  - Recurrent EC up to two prior lines of chemotherapy.
  - Most Common AE: were rash (40.3%), diarrhea (37.3%) and fatigue (28.4%).
  - In 67 pts: ORR = 6.0% - PFS > 6 months was 11.9%
  - Clinical activity not associated with any molecular alteration of the PI3K pathway.

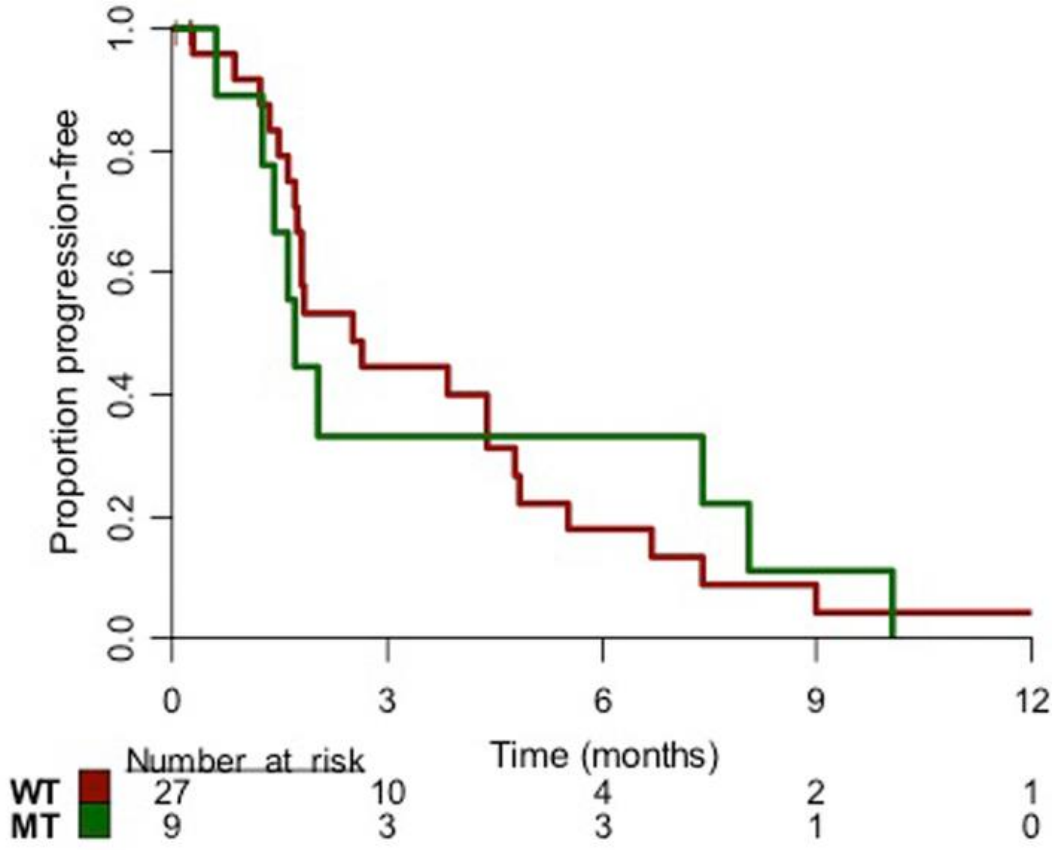
- **BKM120** – Single Arm
  - Recurrent EC - no more than one prior chemotherapy regimen
  - Stratified by Low & High-grade histology
  - Unfavourable safety profile: Grade 3/4 tox including cutaneous rash (54%), depressive events (47%), and anxiety (40%)
  - Minimal anti-tumour activity

Matulonis U et al, Gynecol Oncol 2015
Heudel PE et al, BJC 2017

AKT inhibitor – Single Agent

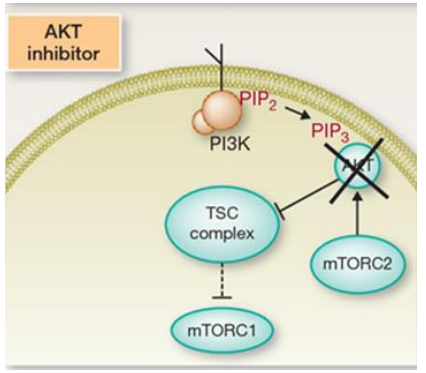


- Phase 2 - MK-2206
- Recurrent EC all histologies except carcinosarcoma
- Biomarker stratification: PI3K mutation
- 36 evaluable patients: 1 PR – Limited Activity
- 40% of patients requiring a dose reduction for a dermatologic-related adverse event
- Exploratory Analysis: Only serous histology linked to greater than 6 months PFS when compared to other histologies



Myers AP et al, Int J Cancer 2020

AKT inhibitor – Single Agent

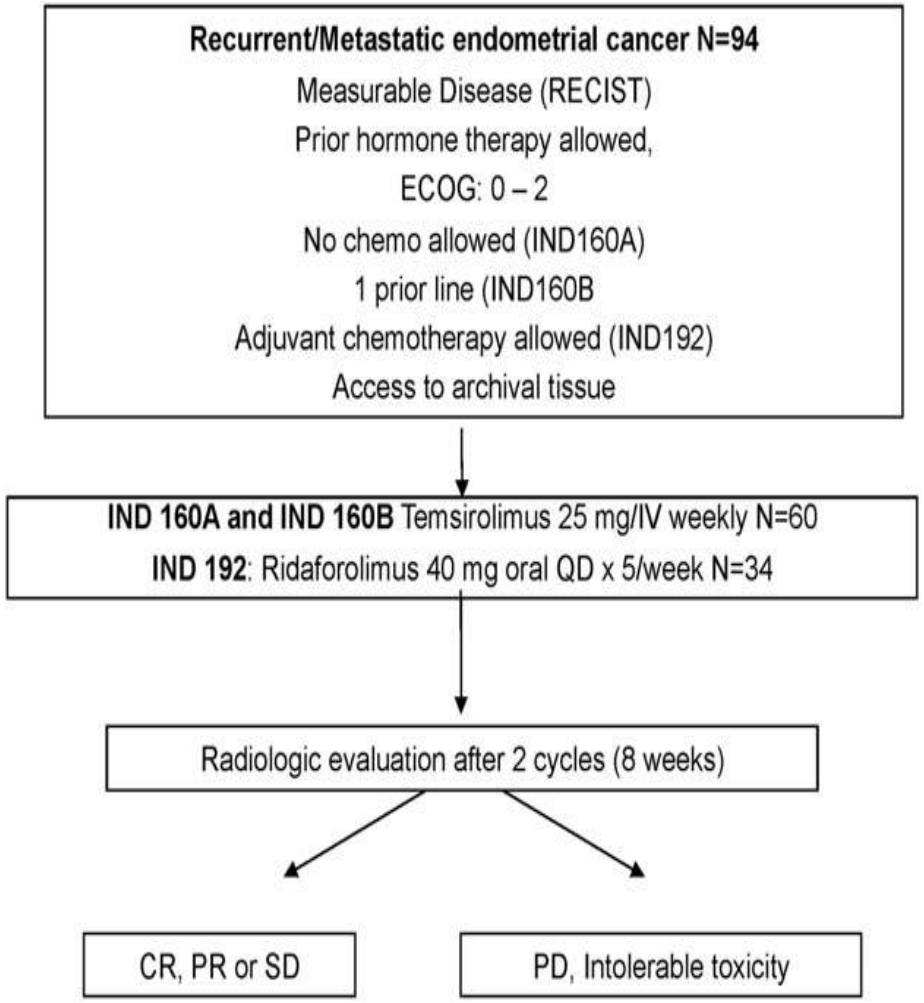


- Phase II, single-stage of MK-2206 in pts with Advanced or Recurrent High-grade Serous Endometrial Cancer, who had received up to two lines of prior therapy
- MK-2206 (135 mg) orally once per week, in continuous 28-day cycles.
- 14 patients received treatment
- Limited Activity
  - Median PFS = 2 months (95% CI: 1.6 to 4.4)
  - Median OS = 6.4 months (95% CI: 5.1 to not reached)

Stover EH et al, Gynecologic Oncology Reports 2022

Biomarkers

Retrospective Analyses



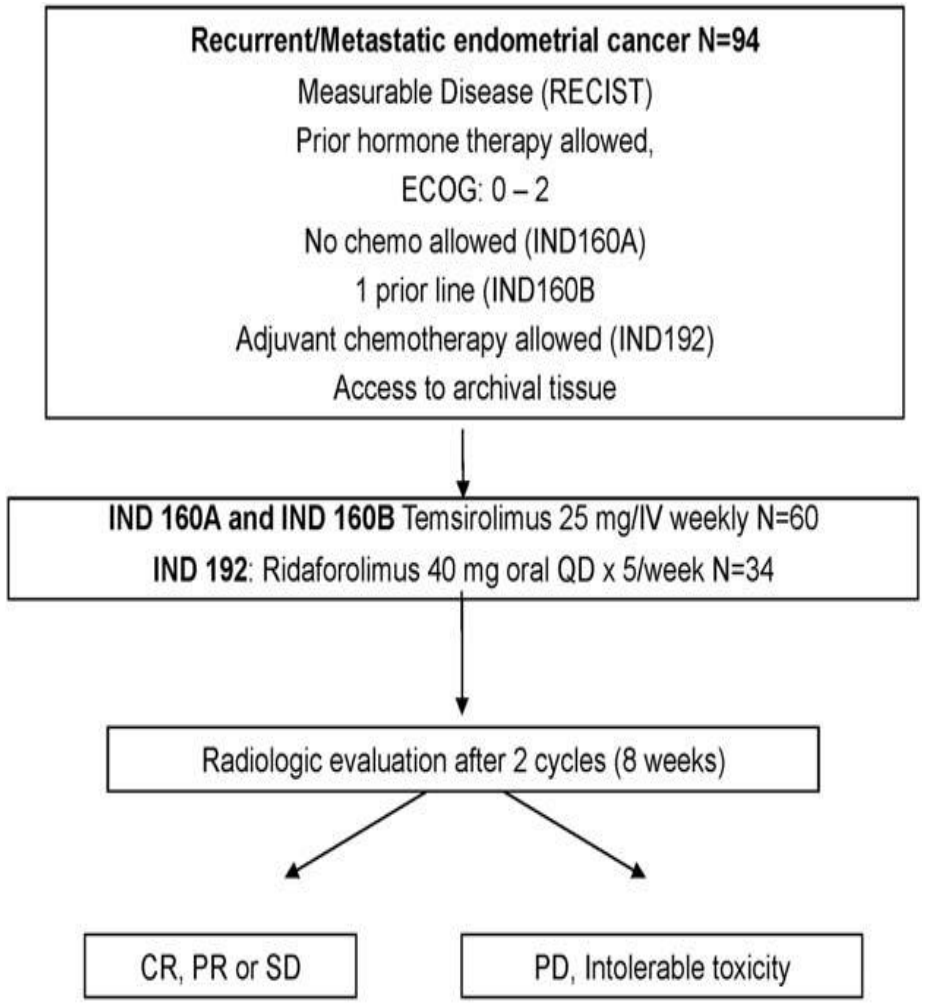
No Correlation with PTEN Expression

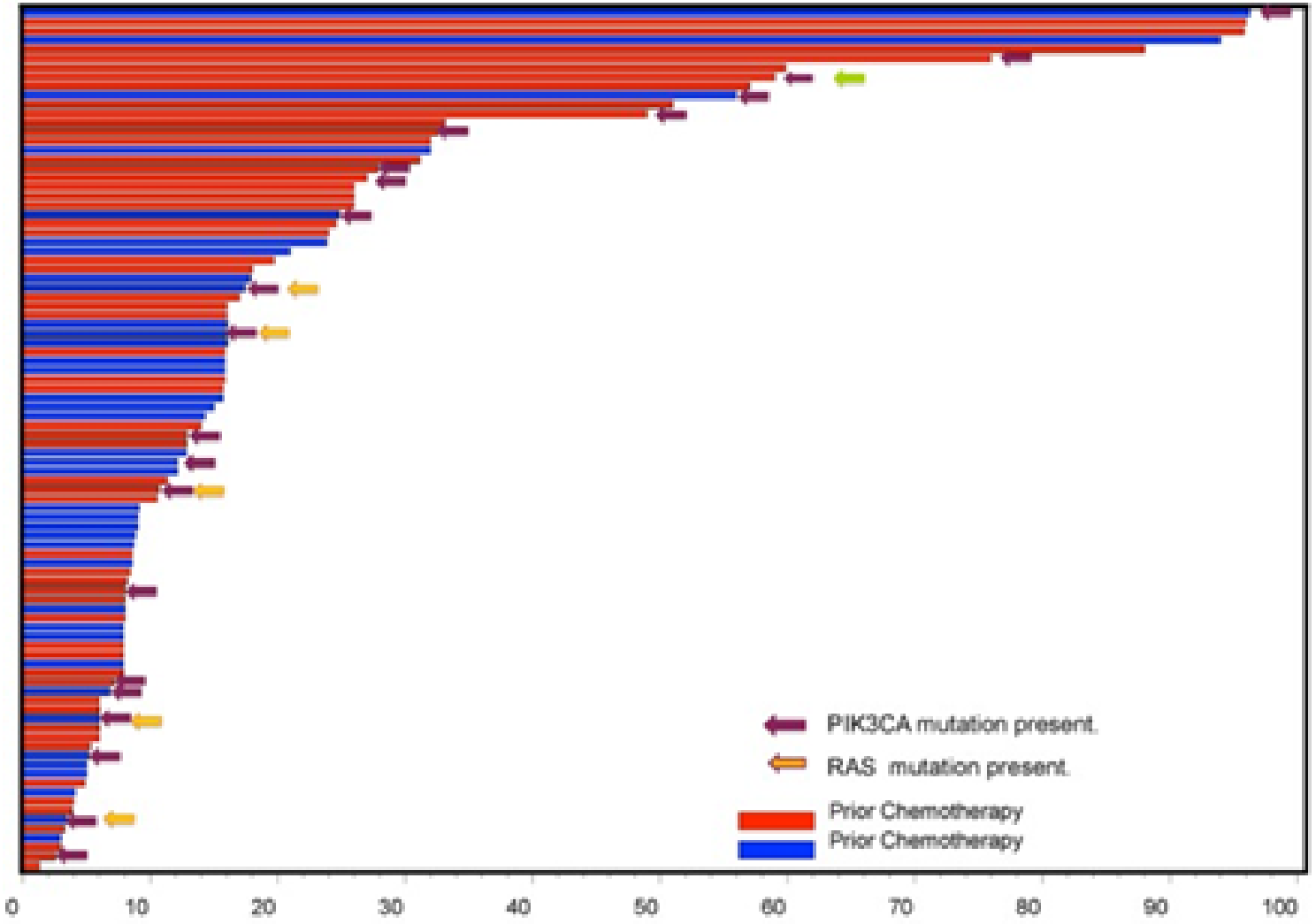
Group	No.	Response (%[a])	*P*	Progression (%[a])	*P*
PTEN expression			0.46		.35
Negative	46	3 (6.5)		12 (26.1)	
Positive	39	5 (12.8)		14 (35.9)	
Stathmin expression			0.89		.34
Negative	2	0 (0.0)		1 (50.0)	
Weak	21	2 (9.5)		5 (23.8)	
Moderate	27	2 (7.4)		7 (25.9)	
Strong	15	2 (13.3)		7 (46.7)	
Histologic 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)	

H Mackay et al 2014 Cancer

Retrospective Analyses

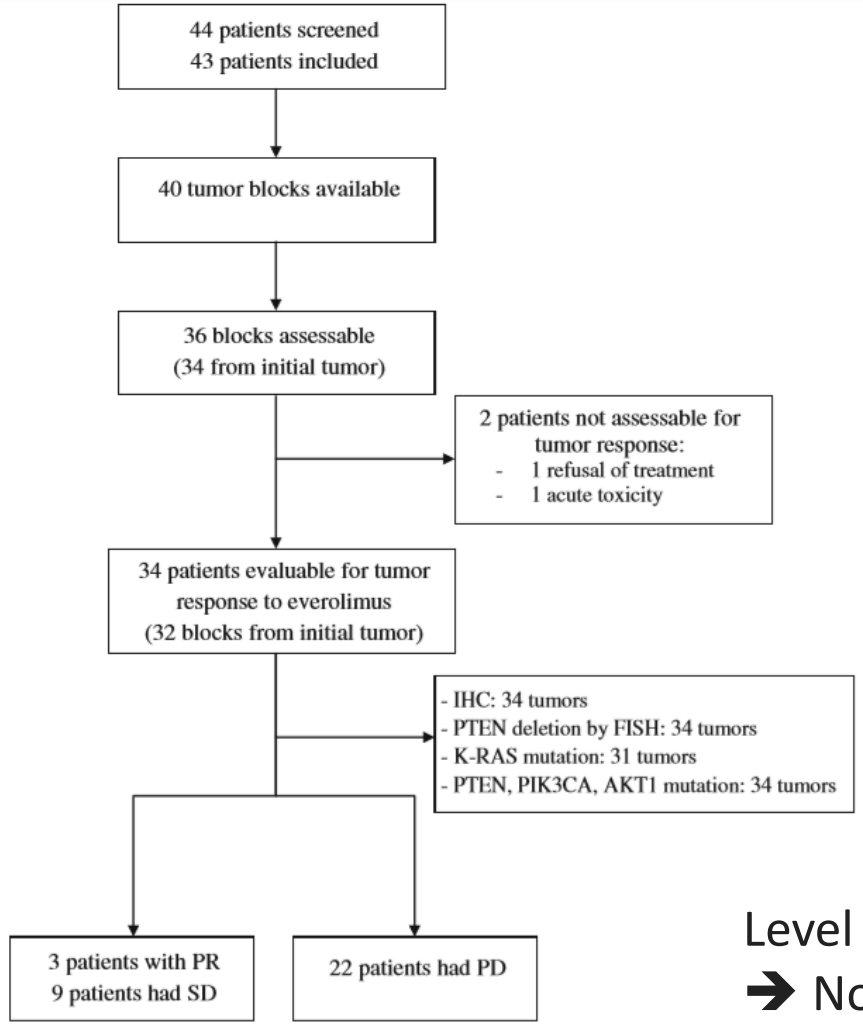
Higher responses in chemo-naïve patients





H Mackay et al 2014 Cancer

Everolimus – Biomarkers



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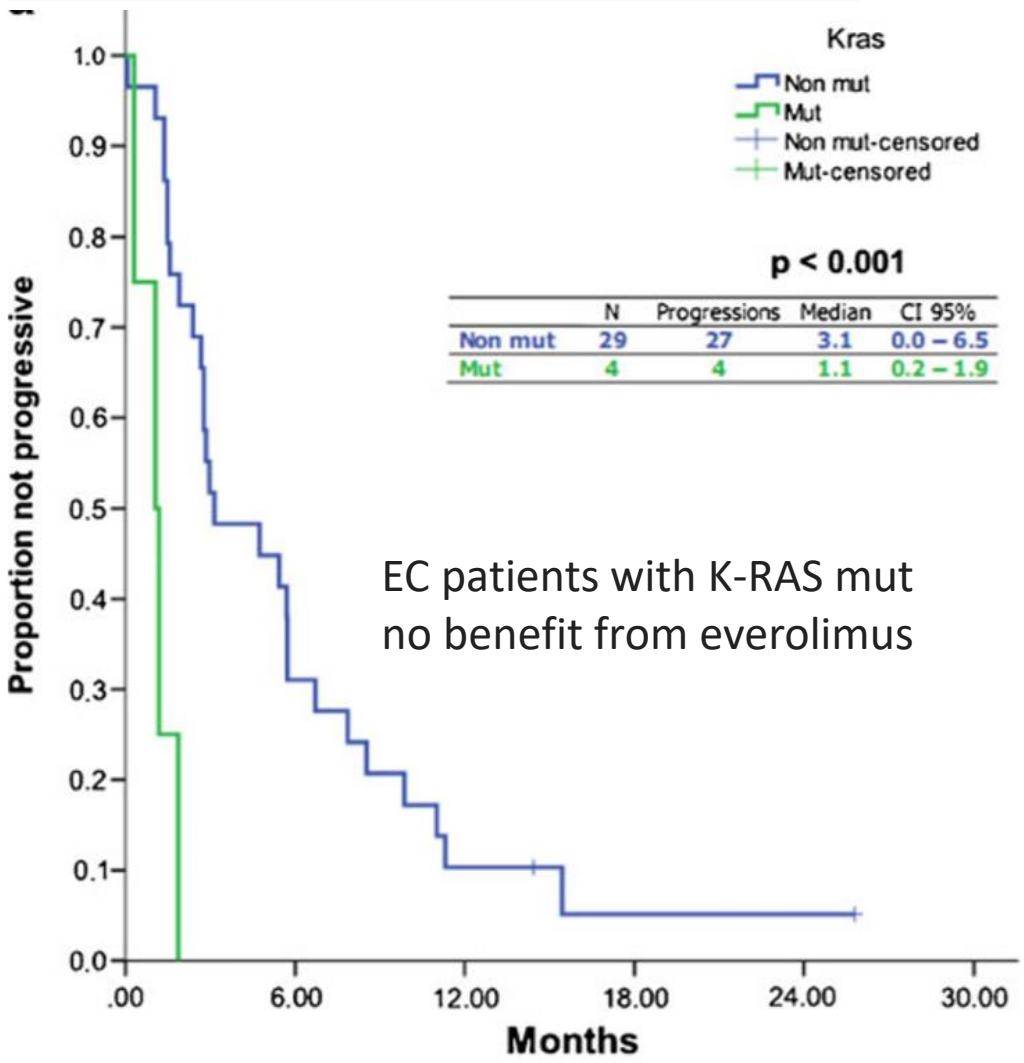
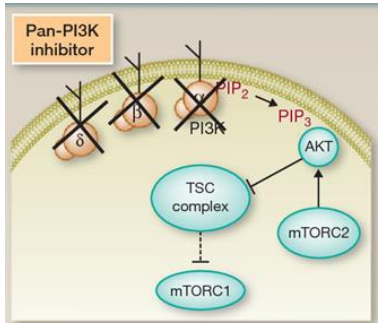


EC patients with K-RAS mut
no benefit from everolimus

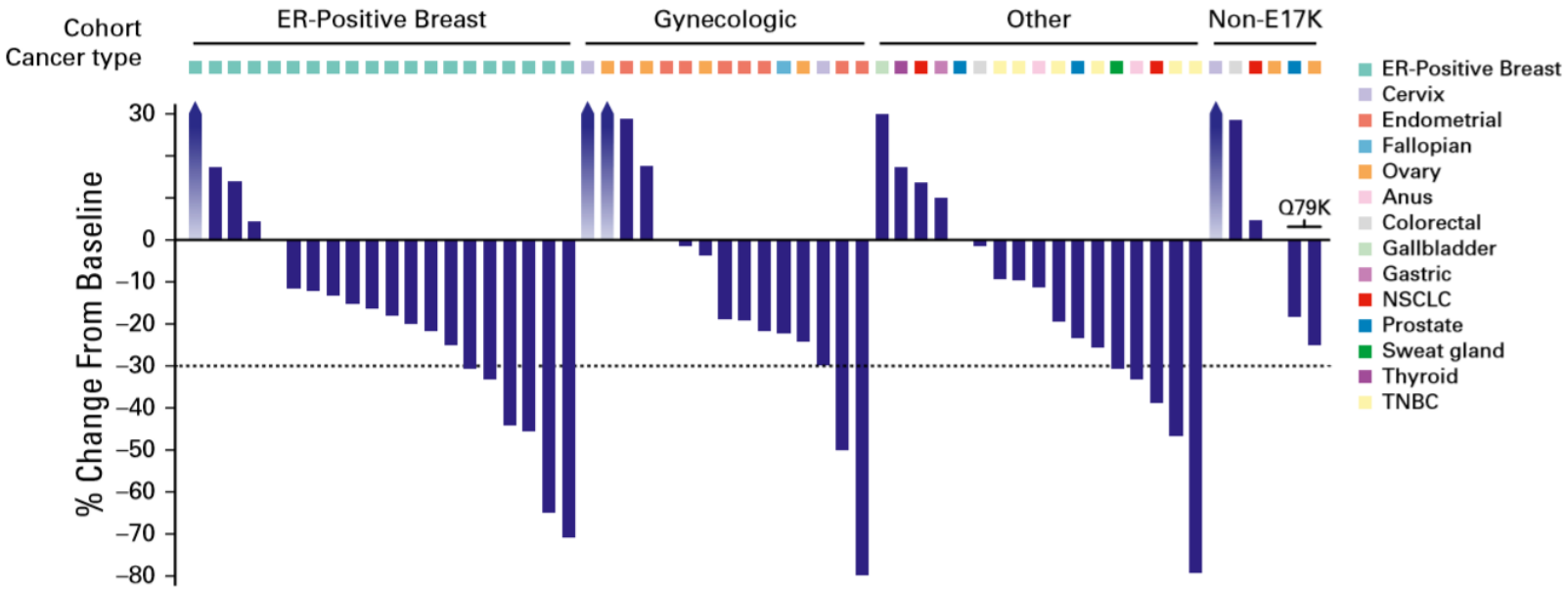
Level of expression of proteins of the PI3K/mTOR pathway
➔ No predictor of response to everolimus

O Tredan et al, Targ Oncol 2012

Target AKT – Specific Mutation



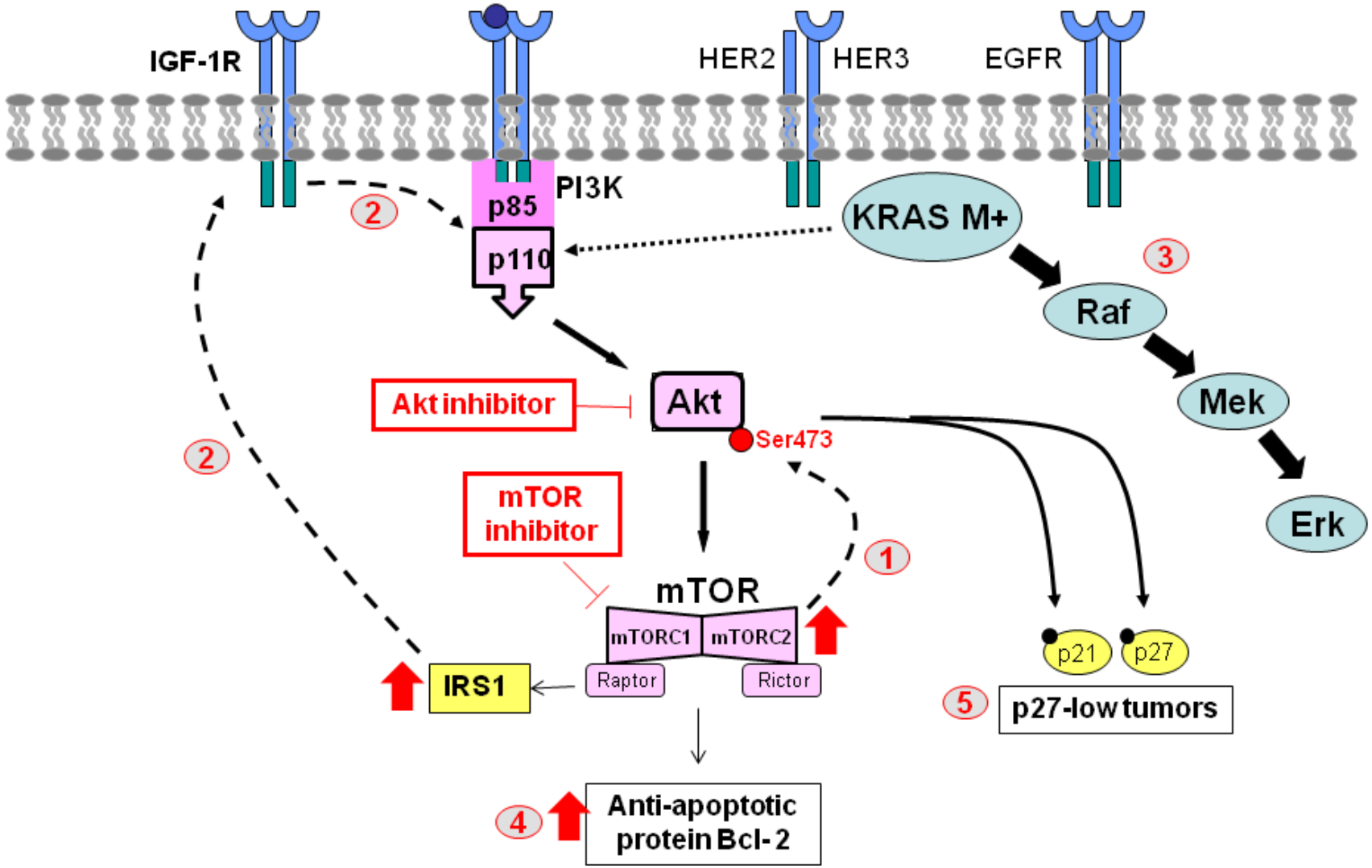
- **Basket Trial** – AZD5363 – pan-AKT kinase Inhibitor in Solid Tumors With AKT1 Mutations
- AKT1 E17K Mutant tumors
- Gyne: Median of 5 lines of prior therapy – median PFS = 6.6 months



Hyman DM et al, JCO 2017

Mechanisms of Resistance

Pathway Dependence: Cross Talks & Adaptation



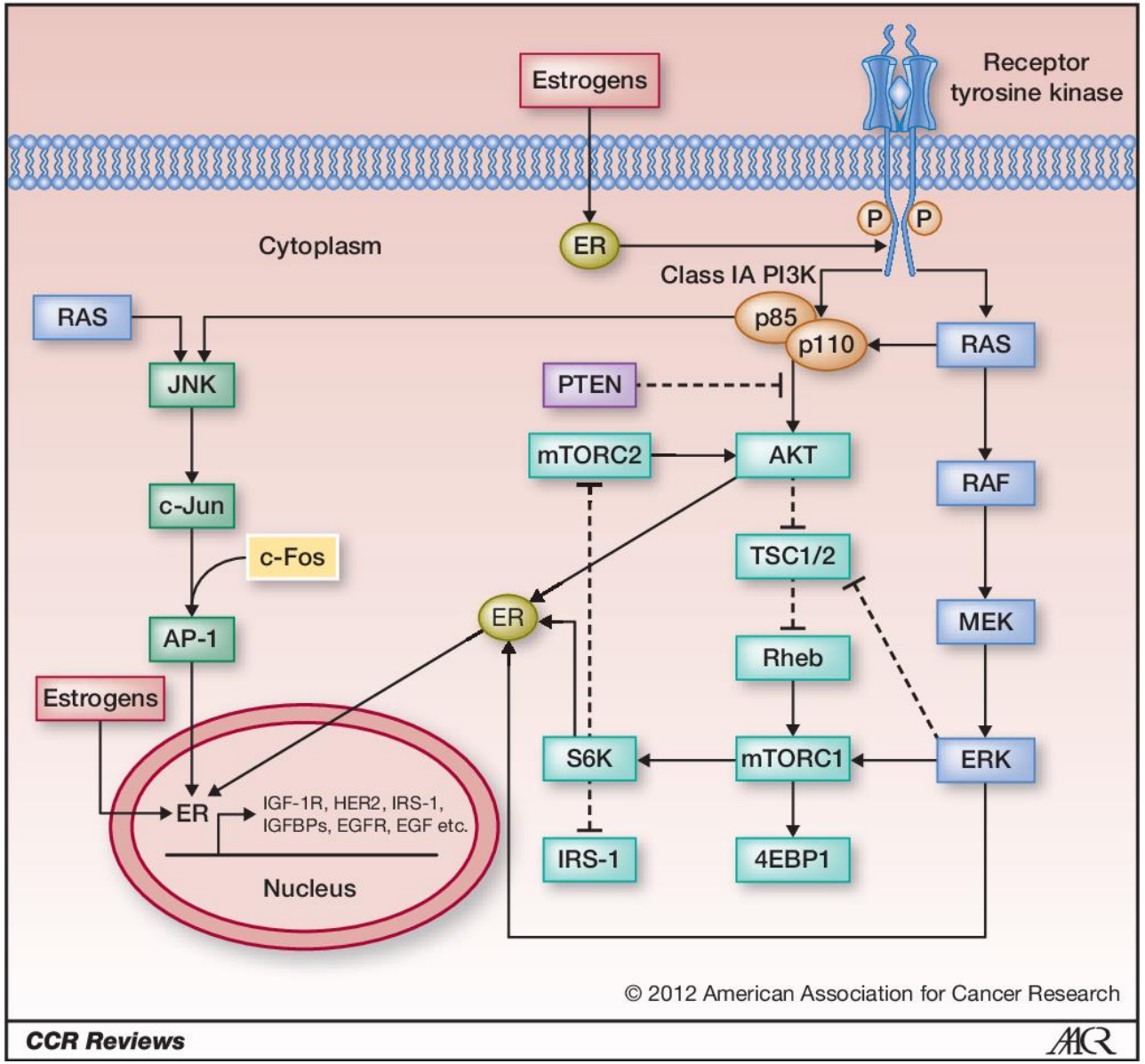
Leary A et al, 2013

Other Factors

- Drug / off-on Target Effect
  - Importance of PK/PD data
  - Dose / Schedule
  - Ensure pathway inhibition
  - Drug Engineering
- Tumor Context – Level of addiction to PI3K inhibition
  - Metabolic
  - Histologic
  - Mutational – presence / absence of other mutations
- Heterogeneity – Sub-clonal mutation
- Patient Selection

➔ Combination therapy to avoid primary & acquired Resistance

Targeting Other Signaling pathways



B. Slomovitz and R. Coleman, 2012

Combination of PI3K and MEK inhibition

- Recurrent EC Measurable disease
- All Histologies eligible except carcinosarcoma
- Plan for randomized, phase II, open label trial to compare the MEK inhibitor-trametinib, alone or combination with the AKT inhibitor - GSK2141795

AFTER Patient safety lead-in.

- High Level of Toxicity ➔ Trial stopped
- A reduced dose was better tolerated, however, Insufficient Activity

➔ Potential to target other kinase in the Ras pathway

Westin SN et al, Gynecol Oncol 2019

Combination with Hormonal Therapy

Temsirolimus + Alternating Megestrol acetate & Tamoxifen

- High rate of thromboembolic disease (5/22 pts) in the combination arm ➔ STOP Early
- Addition of megestrol & tamoxifen did not enhance the activity of temsirolimus: RR 14 vs 22%

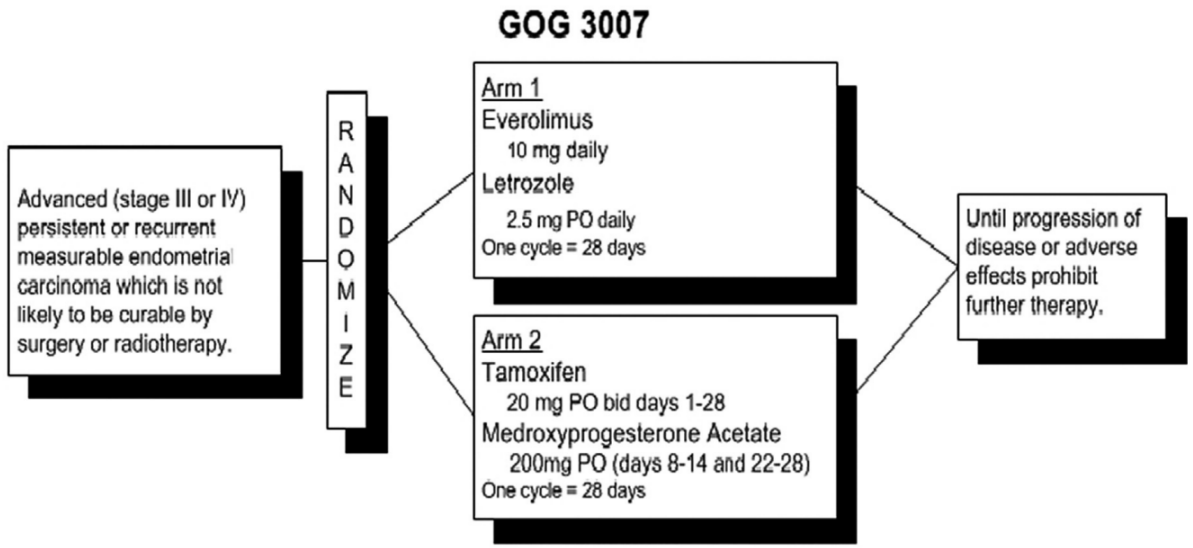
Fleming G et al, Gynecol Oncol 2014

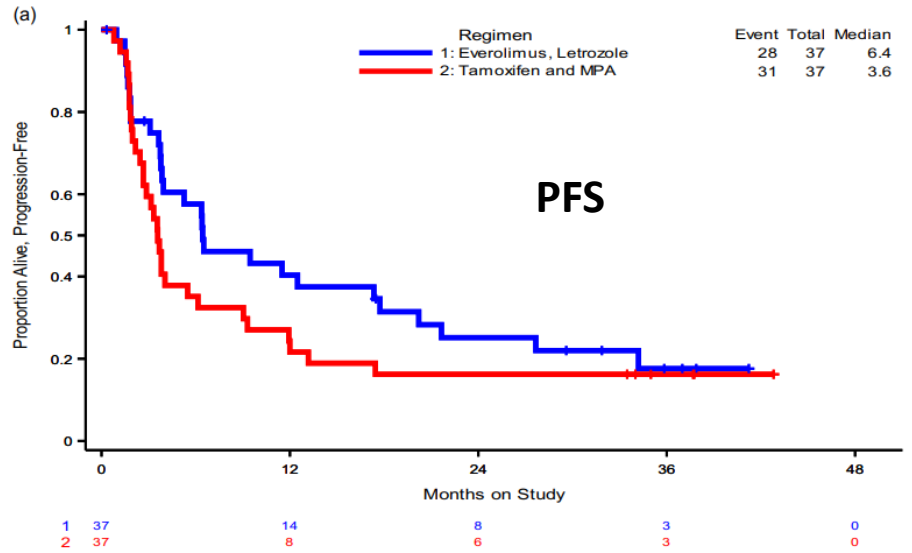
Everolimus + Letrozole

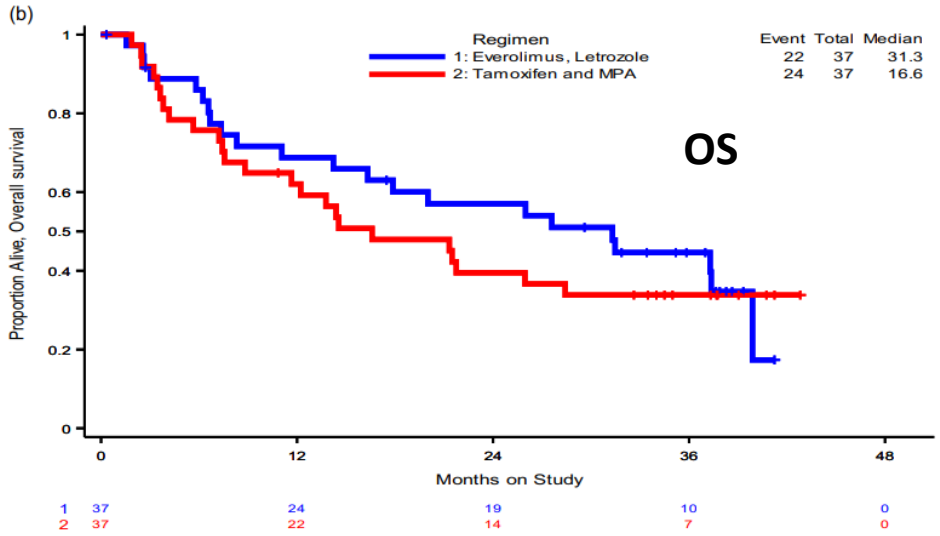
- Trial was hormone Receptor agnostic - Up to two prior cytotoxic regimen
- CBR = 40% and ORR = 32%
- None of the patients discontinued treatment as a result of toxicity
- Correlative Analyses
  - Serous histology: Predictor of Lack of Response
  - Endometrioid histology & *CTNNB1* mutations: Response to everolimus & letrozole

Slomovitz BM et al, JCO 2015

mTOR inhibitor + Hormonal Therapy



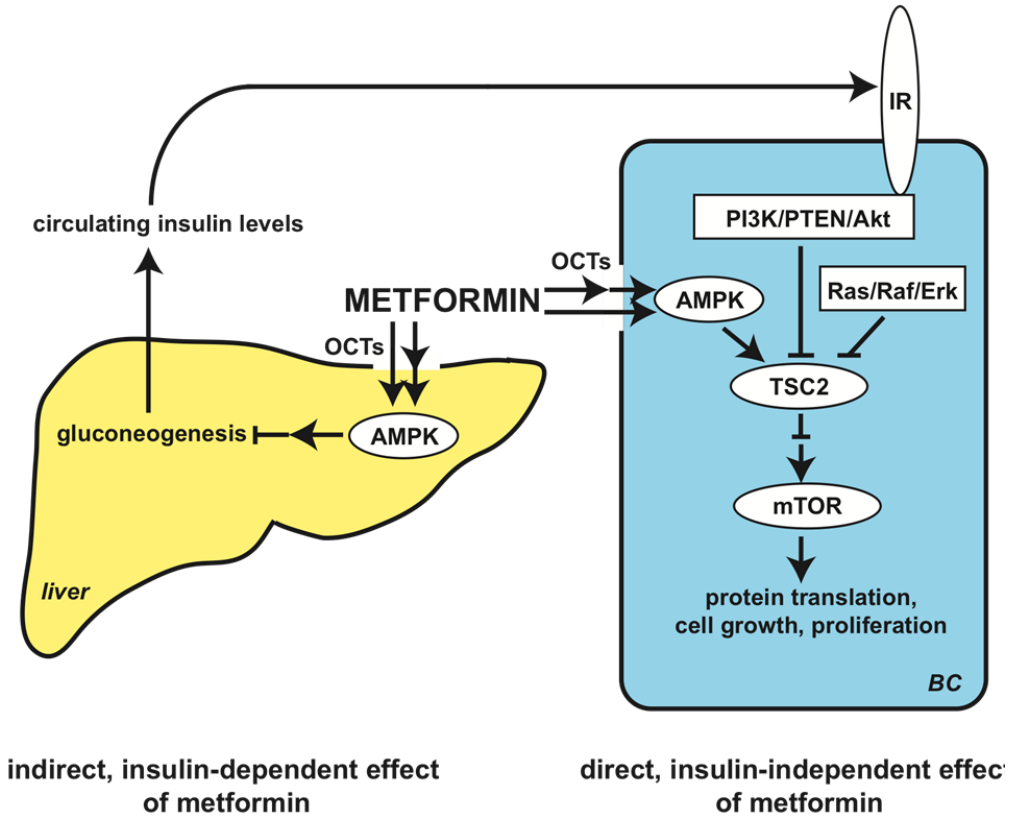




- Everolimus & letrozole: Similar RR compared to hormonal therapy (24 vs 23%)
- Median PFS: 6.3 mths for everolimus & letrozole *vs* 3.8 mths
- PFS Benefit improved when compared to the hormonal regimen in pts chemotherapy naïve at recurrence (21.6 vs 6.6 mths)

Slomovitz BM et al, Gynecol Oncol 2022

What about Triplet Combination



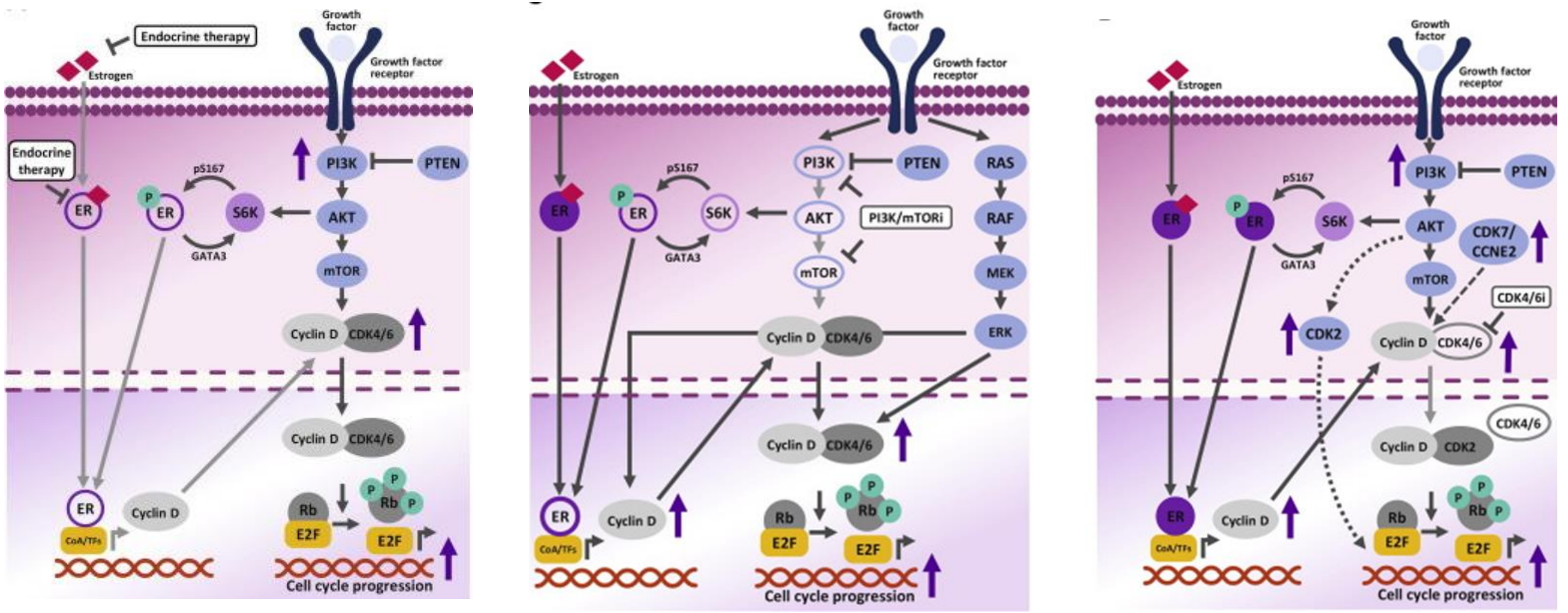
- Phase II study: **Everolimus & Letrozole & Metformin**
- Recurrent Endometrioid or mixed-endometrioid EC (n=54) - No more than two prior chemotherapy regimens
- **CBR = 50% & ORR= 28%**
- Median duration of response: 7 mths – PFS6m of 41%.
- **PgR status by IHC**: Correlation with response

  CBR =90% & ORR = 45% for tumor PgR expression
- Presence of PTEN or PIK3CA mutation not associated with response to mTOR inhibition
- No association between KRAS status & response

Goodwin PG et al, JCO, 2009

Soliman PT et al, CCR 2020

Other triplet Combination Strategies



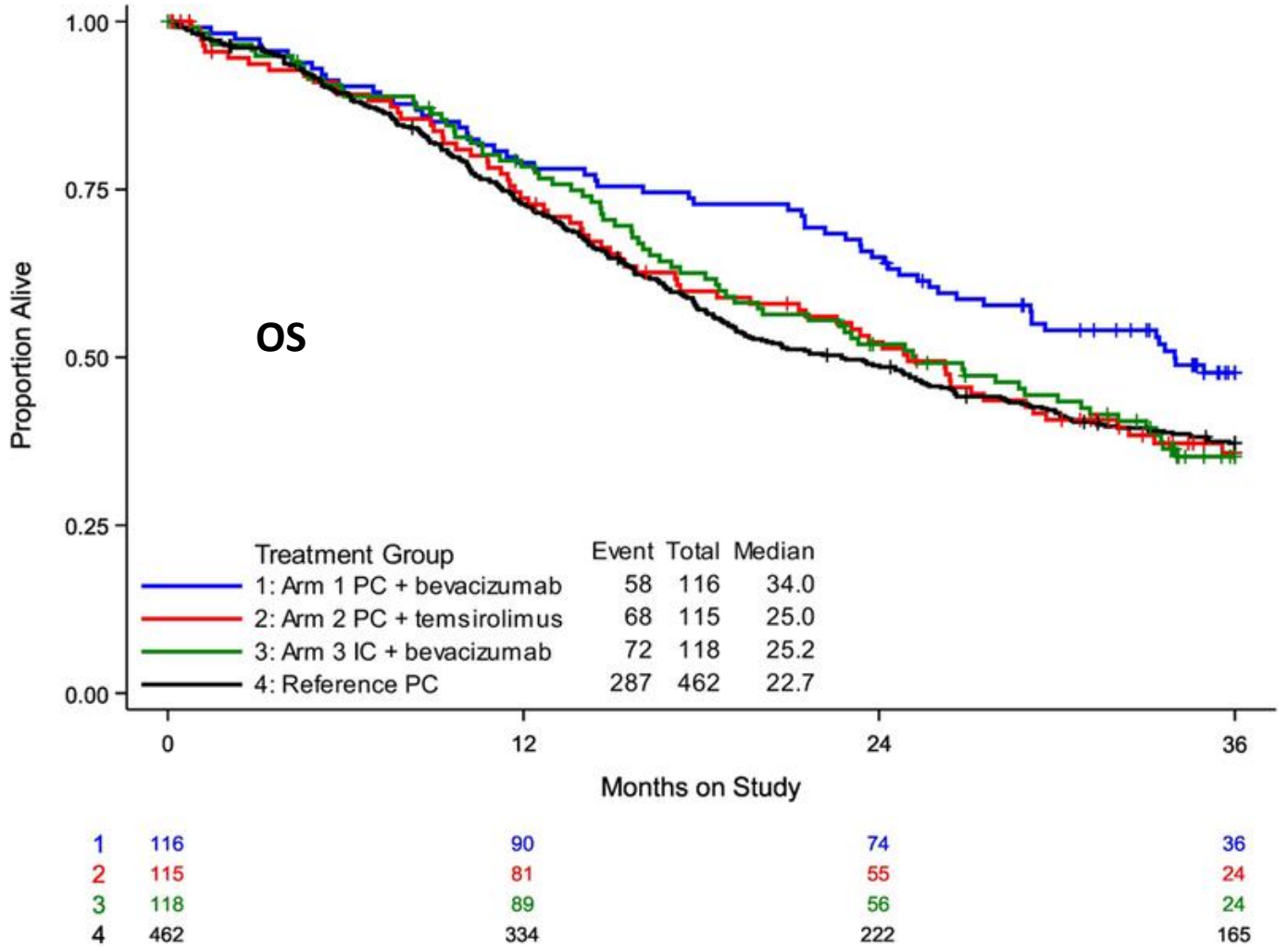
Cortés et al. Cancer Treat Rev 2017

➔ Phase II study of everolimus, letrozole, and the cyclin-dependent kinase (CDK) 4/6 inhibitor ribociclib

Combination with DNA Damage Agent

Chemotherapy

- A phase II study - three-arm design: paclitaxel/carboplatin/bevacizumab - paclitaxel/carboplatin/ temsirolimus - ixabepilone/carboplatin/bevacizumab
- Primary therapy for measurable stages III and IV or recurrent EC

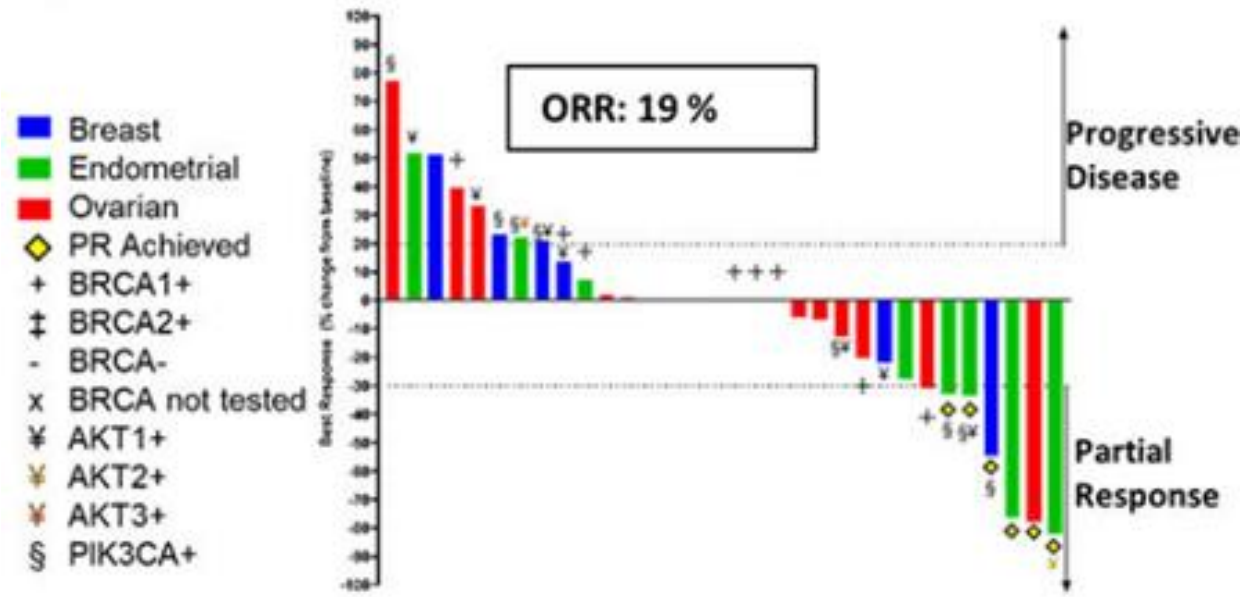


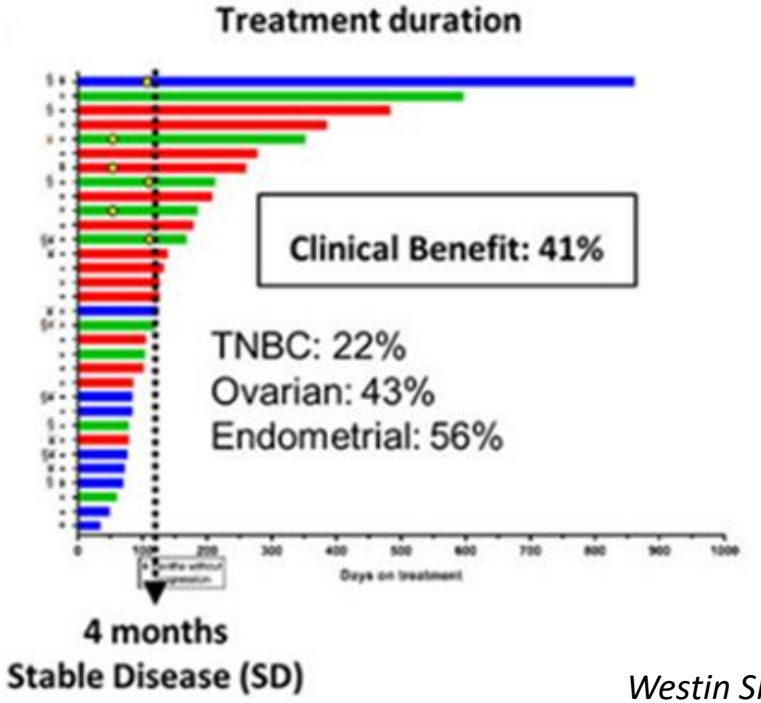
Aghajanian C, et al Gynecol Oncol 2018

Combination with DNA Damage Agent

PARP + AKT inhibitors

- Olaparib & Capivasertib
- Correlations between response & immune activity, cell cycle alterations and DNA damage response.
- Therapy resistance associated with receptor tyrosine kinase and RAS-MAPK pathway activity, metabolism and epigenetics.





Westin SN et al, CCR 2021

Pi3K & microenvironment

Angiogenesis combination

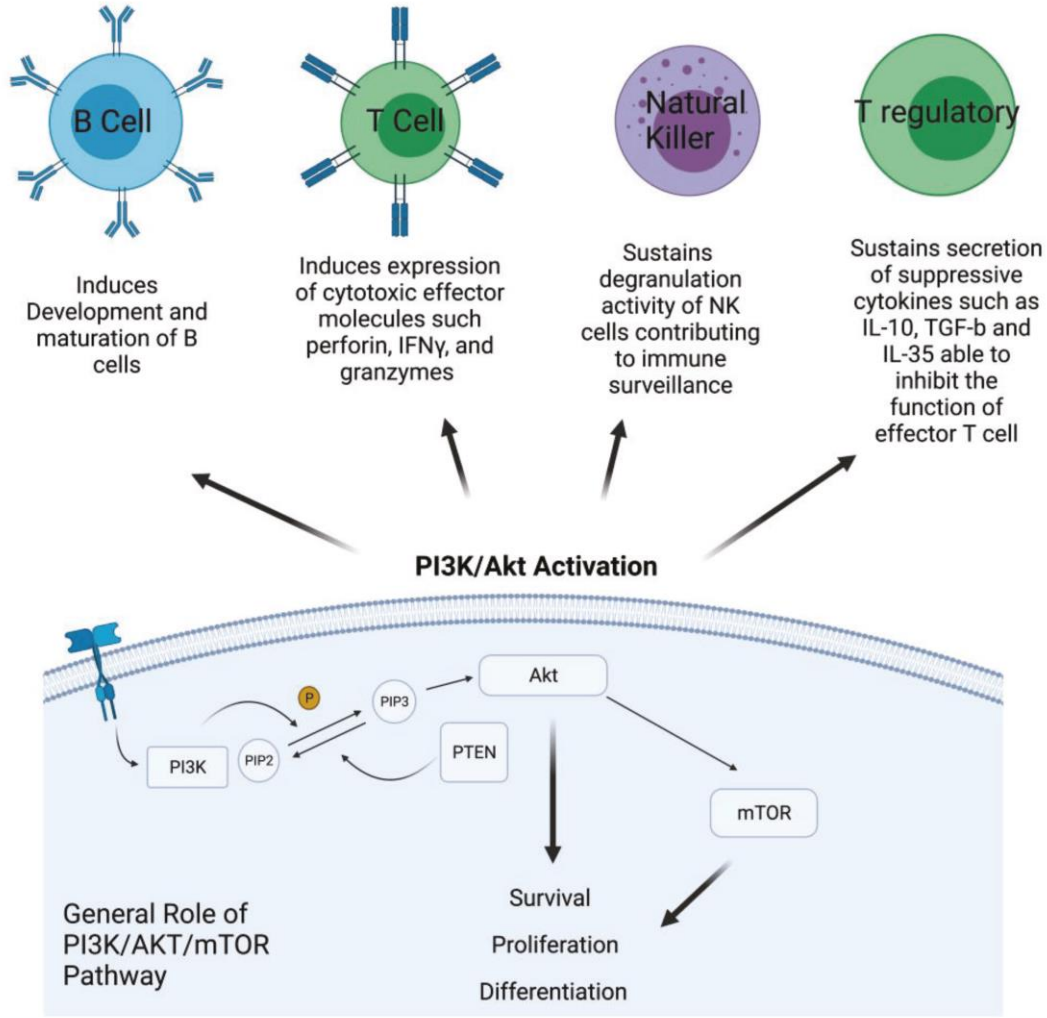
- Temsirolimus + bevacizumab
- Promising ORR 24.5% and PFS6m of 46.9%
- BUT significant toxicity – 38.8% stopped due to side effects
- 2 Gastro-intestinal Vaginal fistulas, 2 intestinal perforations and 1 grade 4 thrombosis

Alvarez EA et al Gyn onc 2013

mTOR in optimizing the immune response

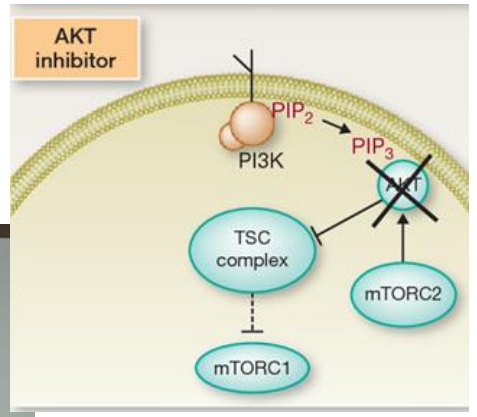
- **PI3K/Akt Pathway: The Indestructible Role of a Vintage Target as a Support to the Most Recent Immunotherapeutic Approaches**

- PI3Ks: Emerging as critical factors in regulating anti-tumor immunity
  - by either promoting an immunosuppressive tumor microenvironment
  - or by controlling the activity & the tumor infiltration of cells involved in the immune response.
- Significant pharmaceutical efforts are dedicated to inhibiting the PI3K pathway, with the main goal to target the tumor and, at the same time, to enhance the anti-tumor immunity



Caforio M et al, Cancer 2021

Basket Trial



AFT-50 EndoMap: A Phase IB/II Multi-Cohort Study of Targeted Agents With Atezolizumab for Patients With Recurrent or Persistent Endometrial Cancer (NCT04486352)

Eligibility criteria:

- Recurrent EC
- ≥1 prior chemotherapy (platinum &/or taxane)
- ≤2 prior chemotherapy regimens
- No prior CITs

Patients with recurrent or persistent endometrial cancer
Received 1–2 prior systemic therapies

↓

Core biopsy for prospective FoundationOne® CDx (F1CDx) testing

↓

Study cohort assignment [a]

↓

Enrollment

Cohort 1: Biomarker-negative	Cohort 2: PI3K/AKT1/PTEN signature	Cohort 3: LOH >=16%	Cohort 4: ERBB2/HER2 mutated or amplified	Cohort 5: MSI-H and/or tTMB >=10 mut/Mb
Bevacizumab 10 mg/kg q2w + atezolizumab 1680 mg q4w	Ipatasertib 400 mg daily + atezolizumab 1680 mg q4w	Talazoparib 1 mg daily + atezolizumab 1680 mg q4w	Trastuzumab Emtansine 3.6 mg/kg q3w + atezolizumab 1200 mg q3w	Tiragolumab 840 mg q4w + atezolizumab 1680 mg q4w

Primary endpoint:

ORR

Secondary endpoints:

- 6-month PFS
- DCR
- DoR
- 2-year PFS
- OS
- Safety

EndoMAP. NCT04486352. Updated April 21, 2021. Accessed June 6, 2021.
https://clinicaltrials.gov/ct2/show/NCT04486352
PI: B Slomovitz, Co-PI: E Cantillo, A Secord, J Moroney, E Alvarez

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Conclusion

- Importance of well designed Clinical trials

- Translational Analyses
  - Biomarkers
  - Pharmacodynamics
  - Alternative to tissue

- Creative Drug Engineering

- Data Integration - AI

➔ Combination - Schedule

What is Necessary for a "Druggable" Target

- Tumor or process has an **identifiable** target
- Tumor or process demonstrates oncogenic **addiction** or is a result of gene alteration
- The pathological target **informs** the disease process (prognostic implication)
- Target can be **engaged** (either activated or inactivated) or **leveraged** (synthetic lethality)
- Therapeutic intervention produces **benefit** (predictive implication)

Courtesy from Dr Rob Coleman presentation

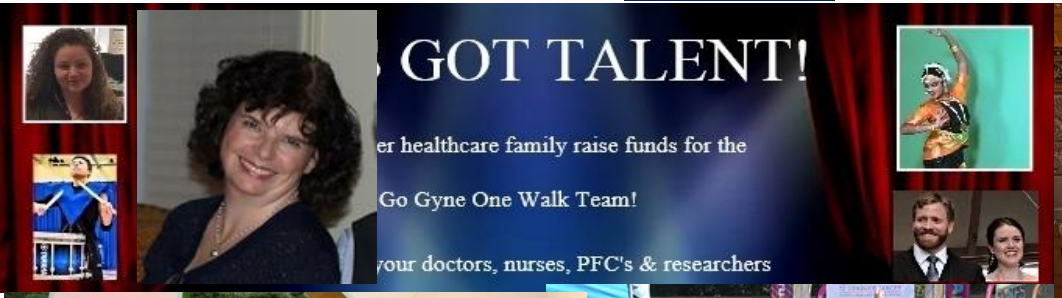
HOPE

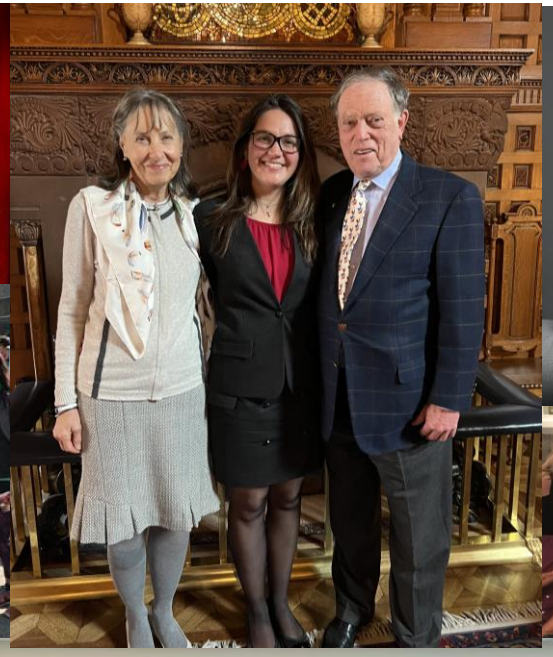
ddp BRAS DRUG DEVELOPMENT PROGRAM

The Westaway Chair

UNIVERSITY OF TORONTO

Thank you to patients, clinical & research teams & research funds





Canadian Cancer Society

NIH NATIONAL CANCER INSTITUTE

OICR Ontario Institute for Cancer Research

Ontario Cancer Care Ontario

The Princess Margaret Cancer Foundation

Thank you