A phase 1b study of miransertib (ARQ 092) in combination with anastrozole in patients with *PIK3CA* or *AKT1*-mutant ER+ endometrial and ovarian cancer

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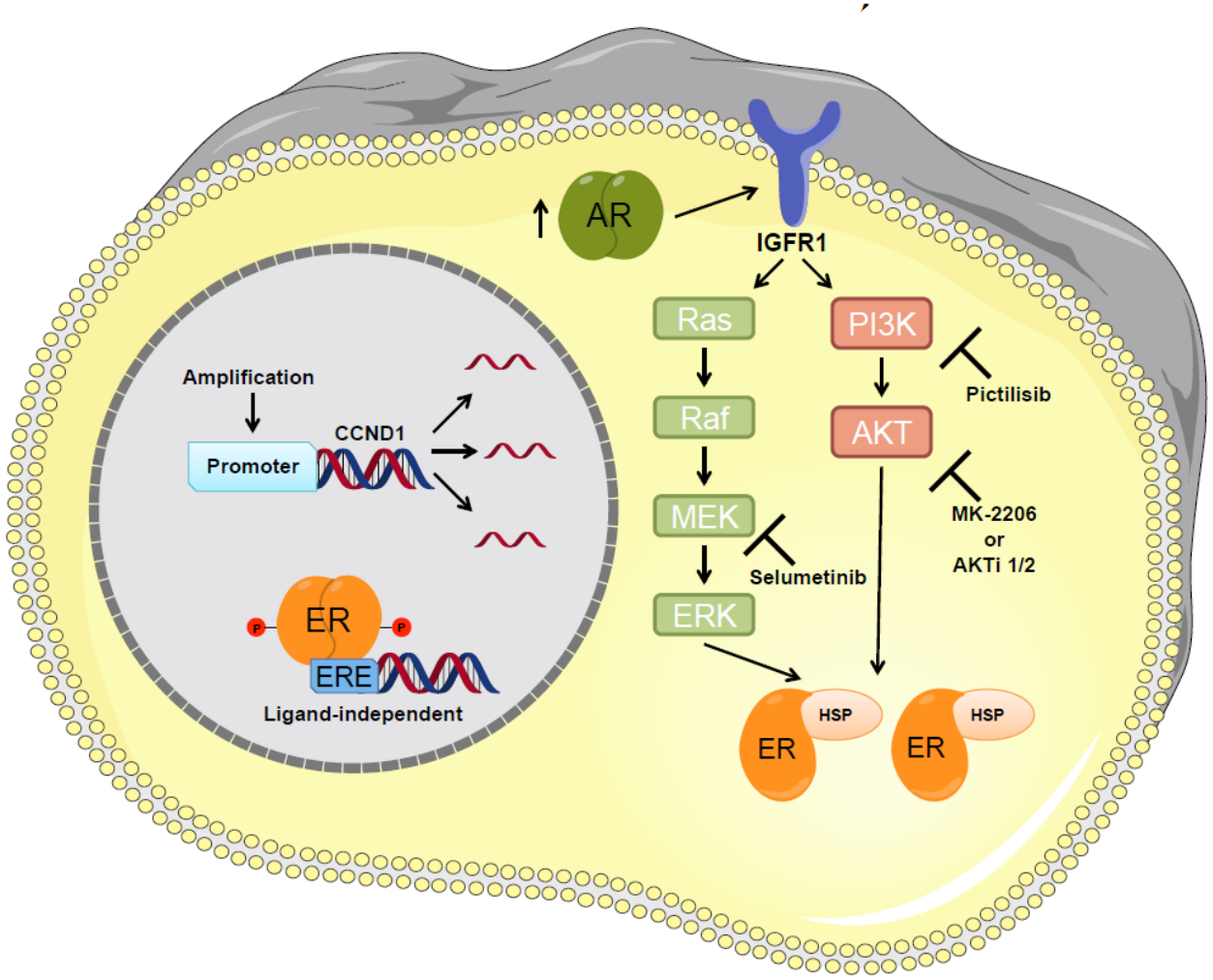
Disclosures

Vicky Makker, MD

- **Advisory Board:** Eisai Co., Ltd, Takeda, Merck Serono
- **Honoraria:** Eisai Co., Ltd

ER and PI3K Pathway in Endometrial Cancer

- PI3K-pathway most deregulated in endometrial cancer (~80%)
  - Enriched for tumors that co-express the ER
- Combined AI + mTOR inhibition ↑PFS in ER+ breast cancer[1]
- Combined AI + mTOR inhibition results in high CBR and RR in recurrent endometrial cancer[2]



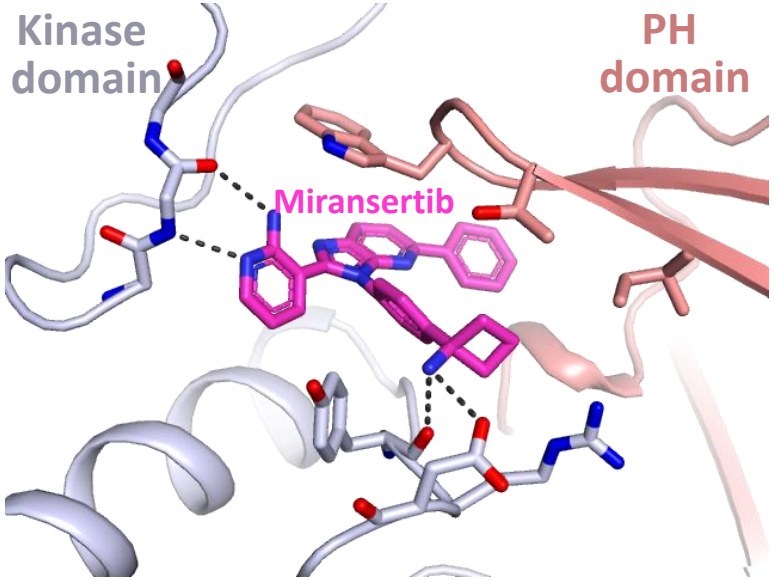
Adapted from Augusto *et al.*, Endocr Relat Cancer. 2018

1- Baselga, NEJM, 2012
2- Slomovitz, JCO 2015

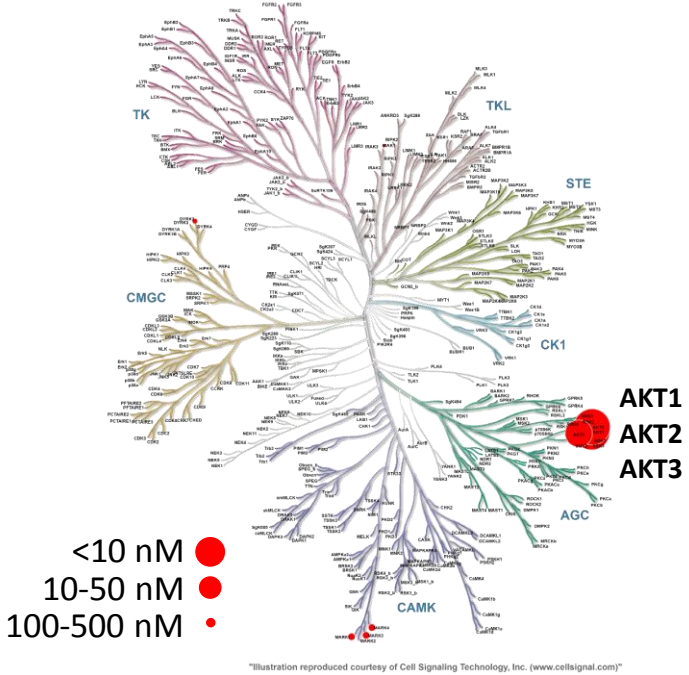
Miransertib (ARQ 092) in Endometrial Cancer

- Miransertib, a highly selective allosteric AKT inhibitor, suppresses PIK3CA/AKT1 mutant dependent kinase signaling, and is efficacious in endometrial tumor models

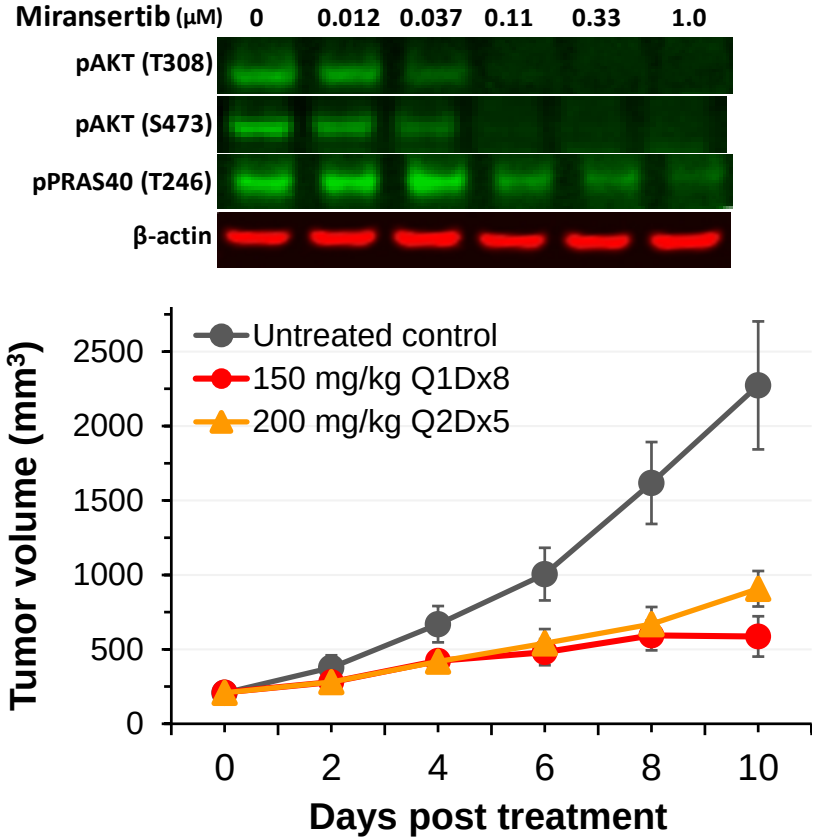
Allosteric (Type III) Inhibitor



Kinase selective



Inhibition in endometrial PIK3CA^{MUT} AN3CA cell line



Yu *et al*., PLoS one, 2015

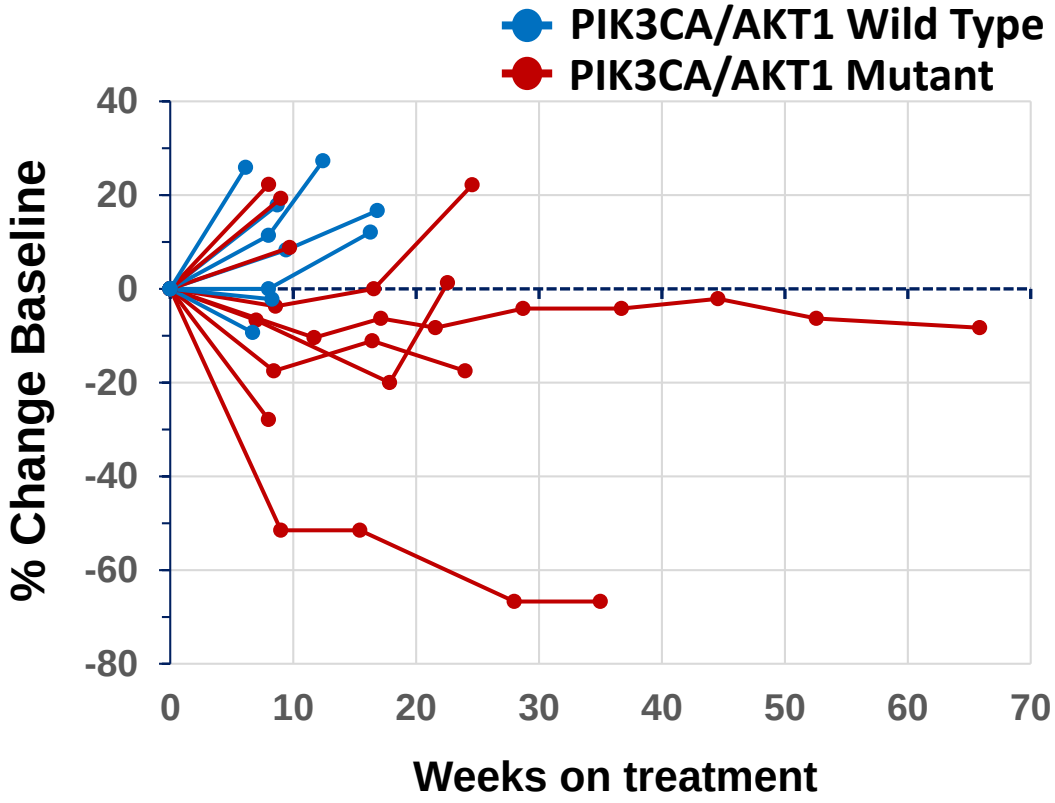
Lapierre *et al*., J. Med. Chem, 2016

Prior Single Agent Experience in Endometrial Cancer

23 Endometrial Patients
Treated at Doses:
10 mg QD to 350 mg BID QW

- **13 subjects PIK3CA/AKT1 wild type**
- **10 subjects PIK3CA/AKT1 mutant**

	PIK3CA/AKT1 Mutant N=10	PIK3CA/AKT1 Wild Type N=13
Overall Response Rate	**1 (10%)**	**0**
Clinical Benefit Rate	**7 (70%)**	**3 (23%)**
Stable Disease	6 (60%)	3 (23%)
Progressive Disease	3 (30%)	3 (23%)
Not Evaluable	0	7 (54%)

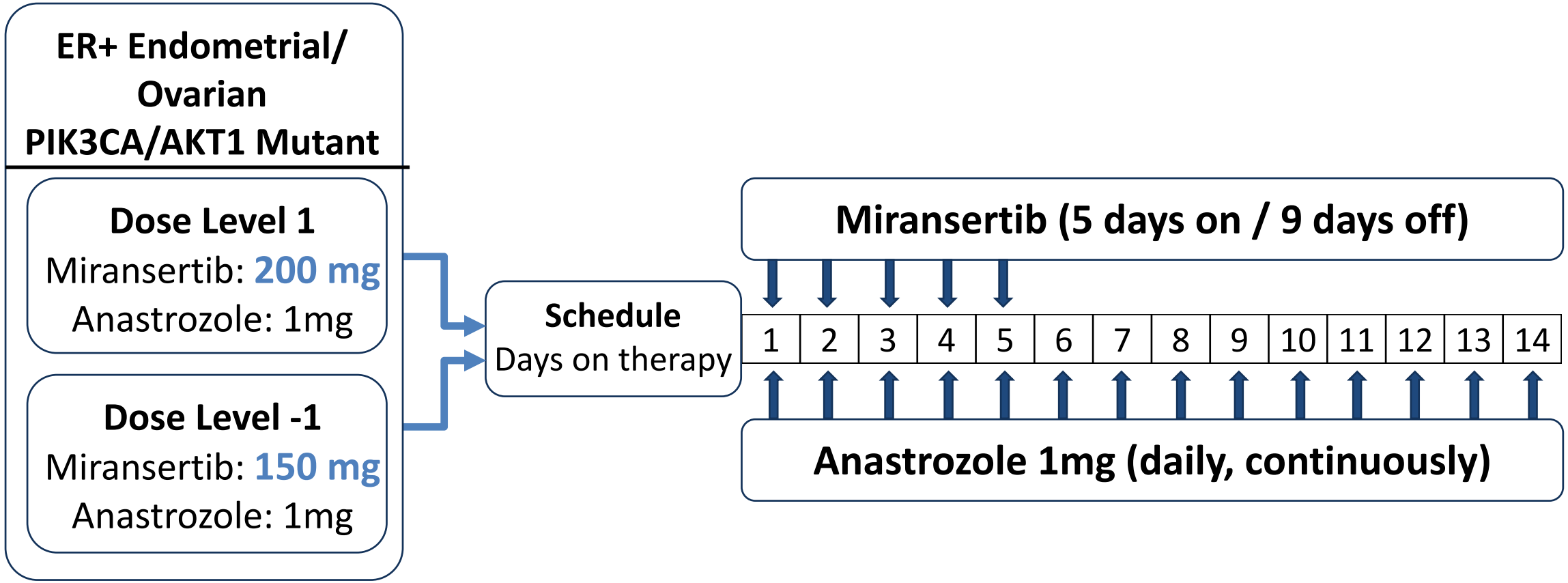


NCT01473095

ARQ 092 + Anastrozole Phase Ib Endpoints

- **Primary**
  - Characterize the safety and tolerability of miransertib and anastrozole combination therapy
- **Secondary**
  - Assess PK profile of the combination
  - Assess the preliminary anti-tumor activity of the combination
  - Determine the recommended Phase 2 dose (RP2D) of the combination

Study Schema



- Dose escalation/ de-escalation according to 3+3 design
- TEAEs / related AE assessed per CTCAE v. 4.03
- Responses were evaluated per RECIST 1.1

Key Patient Eligibility

- Endometrial or ovarian cancer
- Any histology
- ER+ by immunohistochemistry
- *PIK3CA* or *AKT1* mutation documented by local sequencing assays
- Well-controlled diabetes on oral hypoglycemics permitted
- Unlimited prior lines of therapy
- Prior endocrine therapy, including AIs, permitted

Patient Demographics

	Endometrial (N=8)	Ovarian (n=3)	All (N=11)
Age, median (Range)	**60 (37-70)**	**72 (60-76)**	**60 (37-76) Years**
Histology, N (%)			
Serous	4 (50%)	2 (66.7%)	6 (54.5%)
Endometrioid	3 (37.5%)	1 (33.3%)	4 36.4%)
Mixed	1 (12.5%)	0	1 (9.1%)
ECOG, N (%)			
0	5 (62.5%)	1 (33.3%)	6 (54.5%)
1	3 (37.5%)	2 (66.7%)	5 (45.5%)
Prior therapy			
System therapies, median (range)	2.5 (1-4)	5 (2-5)	3 (1-5)
Endocrine therapy, N (%)	3 (37.5%)	3 (100%)	6 (54.5%)
Radiation therapy, N (%)	5 (62.5%)	0	5 (45.5%)
Surgery, N (%)	3 (37.5%)	2 (66.7%)	5 (45.5%)

Safety – DLTs and Grade 3 Related AEs

- 2 DLTs observed (both at the miransertib 200mg):
  - ALT increase, grade 3
  - Maculo-papular rash, grade 3
- 5 patients had Grade 3 related AEs (across all cycles):
  - Maculo-papular rash (n=2)
  - ALT increase (n=2)
  - Hyperglycemia (n=1)
- No grade 4/5 related AEs

Miransertib 150 mg + anastrozole 1 mg QD selected as the RP2D

All Adverse Events, Miransertib-Related

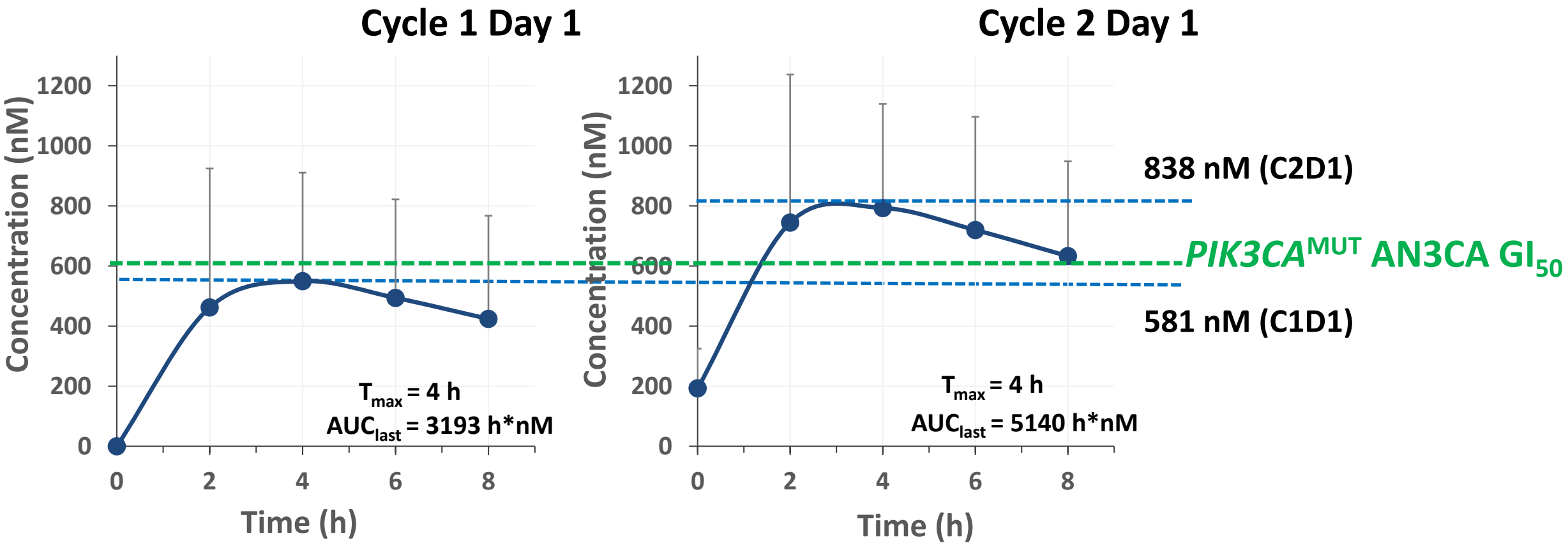
Preferred Term	Grade 1/2, N (%)	Grade 3, N (%)	All grades, N (%)
Nausea	6 (54.5)	-	6 (54.5)
Rash/Rash maculo-papular	2 (18.2)	2 (18.2%)	4 (36.4)
Decreased appetite	2 (18.2)	-	2 (18.2)
Diarrhea	2 (18.2)	-	2 (18.2)
Dry mouth	2 (18.2)	-	2 (18.2)
Pruritus	2 (18.2)	-	2 (18.2)
Acne	1 (9.1)	-	1 (9.1)
ALT/AST increase	-	2 (18.2%)	2 (18.2)
Alkaline phosphatase increased	1 (9.1)	-	1 (9.1)
Cognitive disorder	1 (9.1)	-	1 (9.1)
Constipation	1 (9.1)	-	1 (9.1)
Dry skin	1 (9.1)	-	1 (9.1)
Fatigue	1 (9.1)	-	1 (9.1)
Hyperglycaemia	-	1 (9.1%)	1 (9.1)
Mucosal inflammation	1 (9.1)	-	1 (9.1)
Vision blurred	1 (9.1)	-	1 (9.1)
Weight decreased	1 (9.1)	-	1 (9.1)

Drug Related SAE, Dose Reduction and Treatment Discontinuation

	Miransertib 200mg (N=6)	Miransertib 150mg (N=5)
Serous Adverse Events, N (%)	1 (16.7%) (Grade 3 hyperglycemia)	0
Dose Reduction, N (%)	3 (50%) (Grade 3: ALT/AST increase, hyperglycemia, rash - 1 each)	0
Treatment Discontinuation*, N (%)	0	0

* for miransertib-related AEs

Mean Plasma Concentration-Time Profiles



- Miransertib (150 mg) accumulates after repeat exposure reaching steady state by cycle 2 day 1 with peak concentration measured >800 nM

Treatment Outcome by Patient

Primary Site	Histology	Grade	Mutation	No. prior therapies	Best response	Duration on Tx (weeks)
Endometrial Cancer (N=8)						
Endometrial	Mixed endometrioid/serous	3	PIK3CA H1047R	3	CR	70 (ongoing)
Endometrial	Endometrioid	2	PIK3CA H1047R	4	uPR	24*
Endometrial	Serous	3	PIK3CA N345K	2	uPR	16
Endometrial	Serous	3	AKT1 E17K	1	uPR	16
Endometrial	Endometrioid	1	PIK3CA H1047R	4	SD	12
Endometrial	Endometrioid	1	PIK3CA E545K & H1047L	2	SD	4
Endometrial	Serous	3	PIK3CA C901F	4	PD	8
Endometrial	Serous	3	PIK3CA R115L	1	PD	8
Ovarian Cancer (N=3)						
Ovary	Endometrioid	1	PIK3CA T1025S	2	PD	8
Ovary	Serous	3	PIK3CA H1047R	5	PD	7
Ovary	Serous	3	PIK3CA E542K	5	PD	5

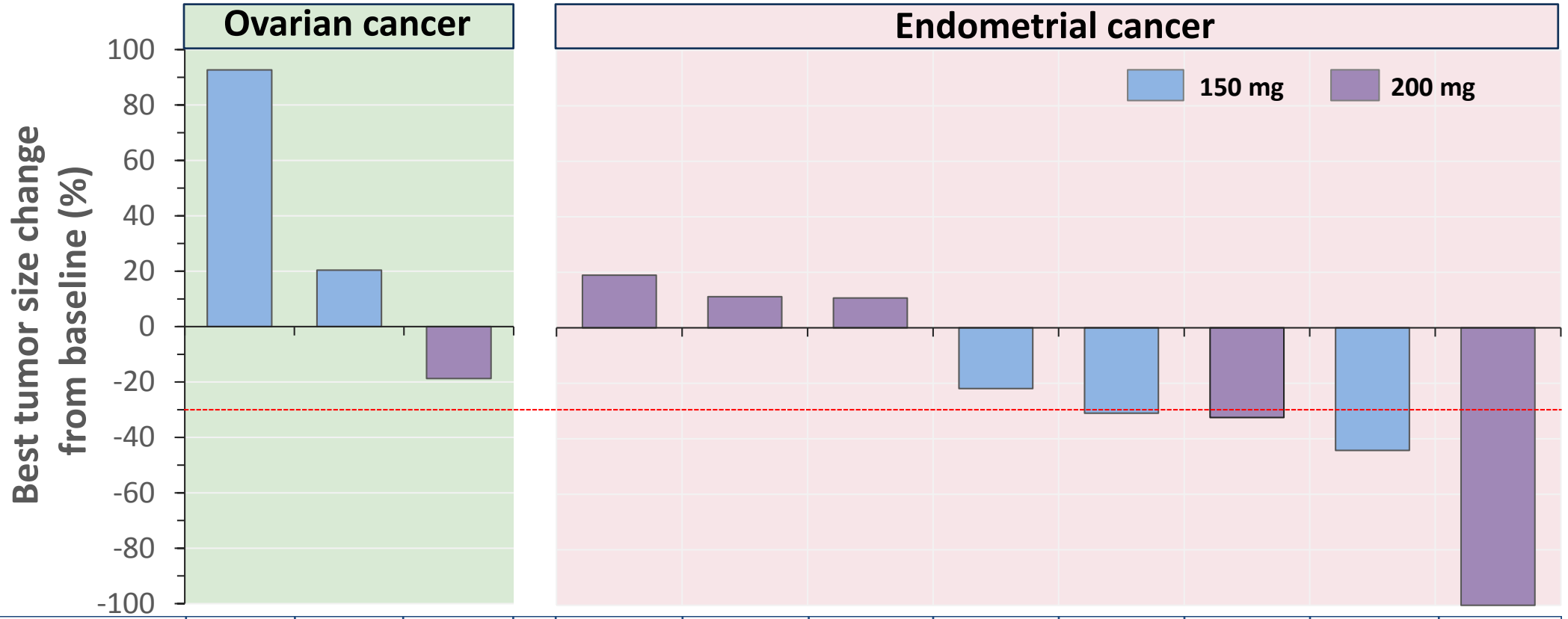
*PD at 24 weeks but continues for ongoing benefit at 66+ weeks; uPR= unconfirmed Partial Response

Preliminary Efficacy Data

	Endometrial Cancer N=8	Ovarian Cancer N=3
Overall Response Rate, % (CI)	**12.5% (0.32-52.7)**	**0% (0 - 70.8)**
Best Response		
Complete Response, N (%)	1 (12.5%)	0
Unconfirmed PR, N (%)	3 (37.5%)	0
Stable Disease, N (%)	2 (25.0%)	0
Progressive Disease, N (%)	2 (25.0%)	3 (100%)

- Mutations in responding patients: *PIK3CA* (n=3) and *AKT1* (n=1)
- 50% (2/4) responding patients had received ≥1 prior line of endocrine therapy
- All patients had receive ≥1 prior line of platinum-containing therapy

Best % Change in Tumor Size



Weeks on Therapy	8	5	7	8	4	12	8	16**	24*	16	70+
Prior Endocrine Therapy	Tam	Let	Let		Let				Anas	Tam	
Histology	Endo	Ser	Ser	Ser	Endo	Endo	Ser	Ser	Endo	Ser	Ser/ Endo

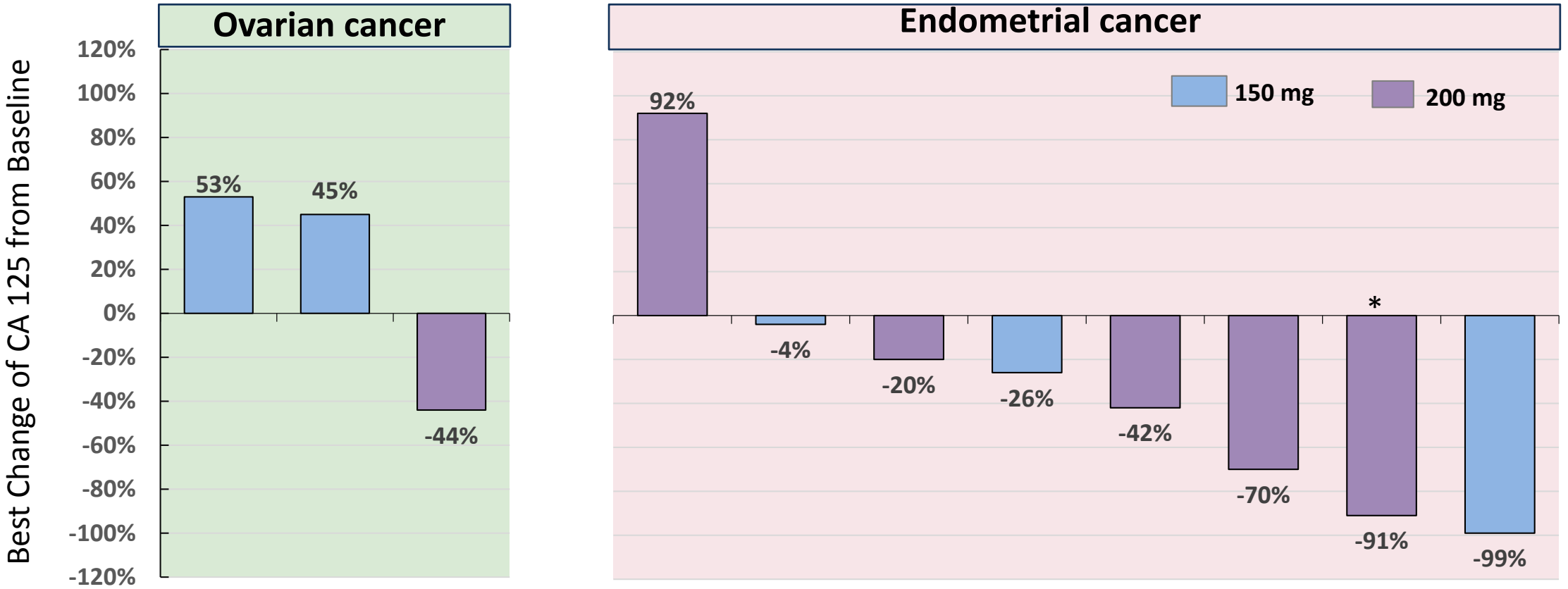
Tam = Tamoxifen
Let = Letrozole
Anas = Anastrozole

Endo = Endometrioid
Ser = Serous

* This patient had PD at 24 weeks but continues for ongoing benefit at 66+ weeks.

** AKT1-E17K mutation

Best % Change of CA125 from Baseline



*This patient had PD at 24 weeks but continues for ongoing benefit at 66+ weeks.

Conclusions

- Manageable safety profile of combo (miransertib 150mg, anastrozole 1mg)
- Miransertib 150mg PK exposure in predicted efficacious range
- Tumor regressions observed in patients with 1) prior endocrine & platinum-therapy exposure, and 2) serous histology
- Data warrant continued enrollment at recommended dose in *PIK3CA* / *AKT1*-mutant endometrial cancer

Acknowledgments

- Thanks to all patients who have participated in this study and their families