A Randomized Phase 2 Trial Comparing Efficacy of the Combination of the PARP-inhibitor Olaparib and the Anti-angiogenic Cediranib Against Olaparib Alone in Recurrent Platinum-sensitive Ovarian Cancer

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Background: cediranib and olaparib are active agents in ovarian cancer

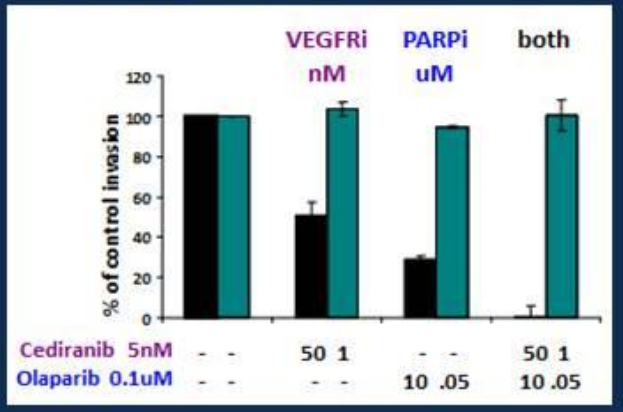
- Cediranib
  - Oral tyrosine kinase inhibitor of VEGFR-1, -2, -3
  - Major toxicities: fatigue, diarrhea, hypertension
  - Overall response rate 17%, median PFS 5.2 months in Phase 2 trial in recurrent ovarian cancer[1]
- Olaparib
  - Oral PARP-inhibitor
  - Major toxicities: fatigue, myelosuppression, nausea
  - Overall response rate between 25-40% in BRCA mutation carriers; 24% in BRCA wild-type patients[2,3]
  - Median PFS ~7-9 months in Phase 2 trials[2,3]

[1]Matulonis et al., *J Clin Oncol* 2009, 27(33): 5601-6
[2]Gelmon et al., *Lancet Oncol* 2011, 12(9): 852-61
[3]Kaye et al., *J Clin Oncol* 2012, 30(4): 372-9

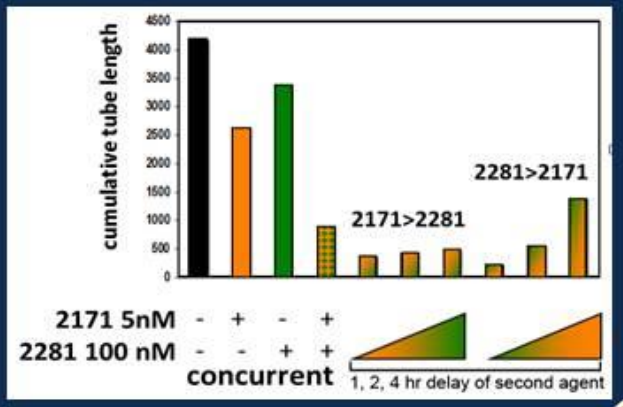
Cediranib and olaparib have synergistic activity *in vitro*

- Pre-clinical data suggesting potential synergy between PARPi and anti-angiogenics
- PARP inhibition or PARP knockout results in decreased *in vivo* angiogenesis[1]
- Sensitivity to PARP inhibitors increased in hypoxic cells[2]

Effect of ced/olap on cell invasion:



Effect of ced/olap on microvascular cell tube organization:



[1]Tentori et al., *Eur J Cancer* 2007, 43(14): 2124-33
[2]Hegan et al., *PNAS* 2010, 107(5): 2201-6

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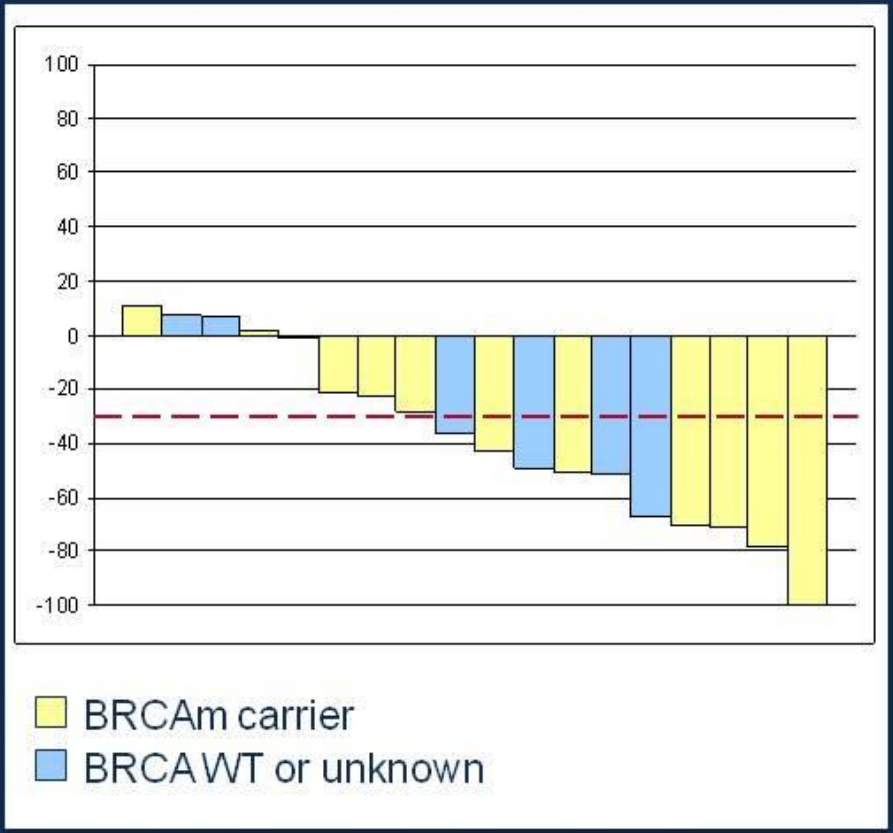
Phase 1 study of cediranib and olaparib demonstrated activity in ovarian cancer patients

- Dose escalation study of cediranib and olaparib in recurrent ovarian and triple negative breast cancer
- Overall response rate in ovarian pts: 44% (8 of 18 RECIST evaluable pts)
  - additional 3 SD ≥ 6 mos



Liu et al., *Eur J Cancer* 2013, 49(14): 2972-8

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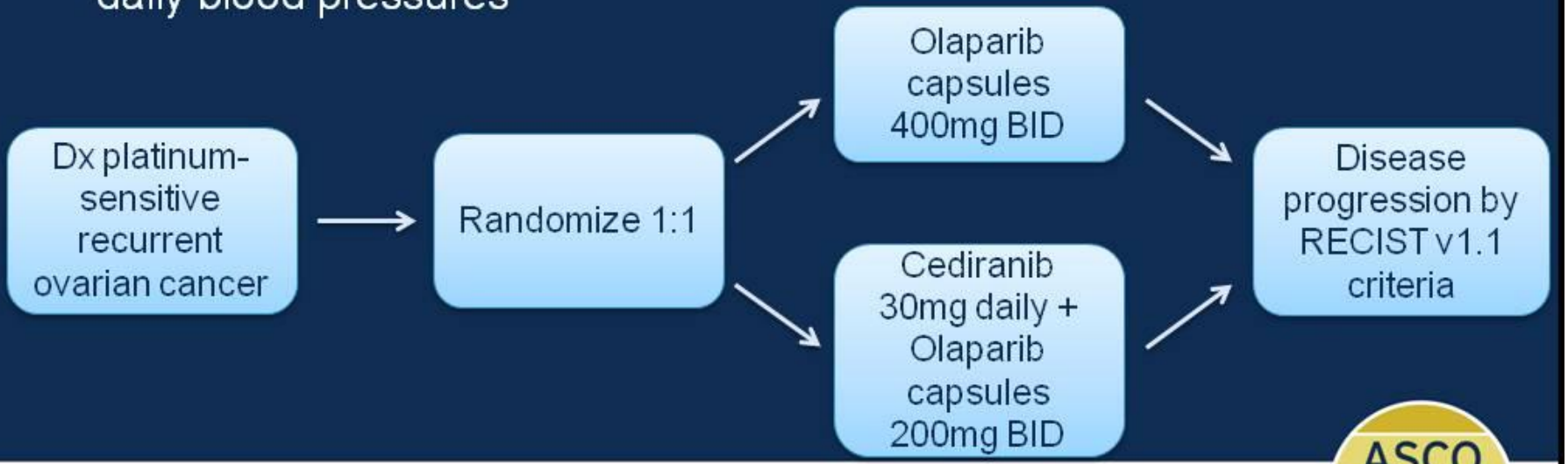
Study Objectives

- Primary:
  - Compare progression-free survival of cediranib/olaparib to olaparib alone in recurrent platinum-sensitive high-grade serous ovarian cancer
- Secondary:
  - Assess additional measures of efficacy: response rate and overall survival
  - Assess toxicities of cediranib/olaparib compared to olaparib alone
- Translational:
  - Assess change in markers of angiogenesis and correlate with treatment and response
  - Will be presented at the Gynecologic Cancer Poster Highlights Session on Monday, Abstract #5535 (Jung-Min Lee)

Study Design

- Phase 2 open-label randomized study
- 1:1 randomization to cediranib/olaparib combination or single agent olaparib
- Platinum-sensitive recurrent ovarian, fallopian tube, or primary peritoneal cancer
- Continuation on treatment with CT or MRI imaging every 8 weeks until disease progression by RECIST v1.1 criteria
- Patients randomized to cediranib/olaparib arm required to take twice daily blood pressures



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Key eligibility criteria

- Recurrent platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer
  - Platinum-sensitivity defined as no recurrence within 6 months of last receipt of platinum
- High-grade serous or endometrioid histology
  - High-grade tumors of other histology allowed if documented deleterious germline BRCA mutation
- No prior receipt of PARP-inhibitor (prior iniparib allowed)
- No prior anti-angiogenic in the recurrent setting (upfront anti-angiogenic allowed)
- Prior lines:
  - No limit on number of prior platinum-based therapies
  - Up to 1 non-platinum-based line of therapy in recurrent setting
- Presence of RECIST 1.1 measurable disease

Statistical Considerations

- Open-label, randomized Phase 2 design
- 1:1 randomization
- Stratification factors
  - germline BRCA status (known deleterious mutation carrier vs. non-carrier vs. unknown)
  - prior receipt of anti-angiogenic
- Target accrual 90 pts
  - Powered to detect a hazard ratio (HR) of 0.57, with an alpha of 0.10 and 86% power
- Analyses based upon intention to treat
- No subgroup analyses were pre-specified

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Study Status and Data Analysis

- Enrollment completed May 2013
  - 46 patients randomized to olaparib alone
  - 44 patients randomized to cediranib/olaparib
- Pre-planned interim analysis in November 2013 at 50% of planned events
  - DSMB recommended completion of study analysis and release of data
- Data cut-off for analysis March 30, 2014
- Median follow-up time of 16.6 months (range 0.4 to 28.5 months)

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Patient Characteristics

	Olaparib (N = 46)	Cediranib/olaparib (N = 44)	P-value
Age, median (range)	58.1 (32.7-81.9)	57.8 (41.9-85.6)	0.33
ECOG performance status			
0	34 (73.9%)	31 (70.5%)	0.82
1	12 (26.1%)	13 (29.5%)	
BRCA mutation status			
Carrier	24 (52.2%)	23 (52.3%)	0.92
Non-carrier	11 (23.9%)	12 (27.3%)	
Unknown	11 (23.9%)	9 (20.5%)	
Prior anti-angiogenic therapy			
No	40 (87.0%)	38 (86.4%)	1.00
Yes	6 (13.0%)	6 (13.6%)	
Prior platinum-free interval			
6-12 months	26 (56.5%)	23 (52.3%)	0.83
>12 months	20 (43.5%)	21 (47.7%)	
Number of prior lines			
1	17 (37.0%)	26 (59.1%)	0.11
2	18 (39.1%)	10 (22.7%)	
3+	11 (23.9%)	8 (18.2%)	
Baseline CA125 (range)	115.3 (10.9-11,512.0)	68.0 (4.0-1,351.0)	0.08

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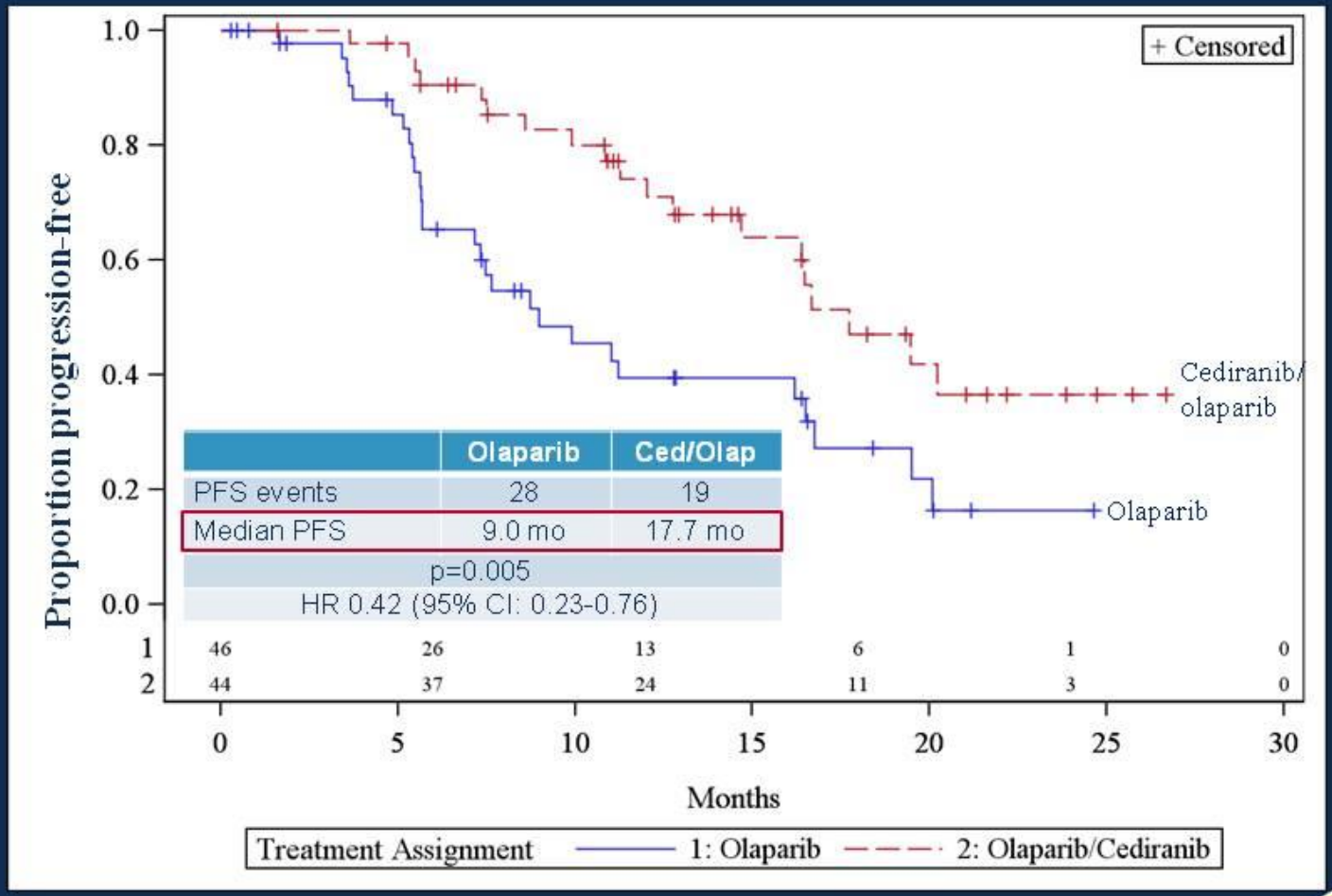
Primary Outcome: Cediranib/olaparib significantly increased PFS compared to olaparib alone



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Secondary Outcome: Cediranib/olaparib significantly increased overall response rate (ORR) compared to olaparib alone

Best overall response

Arm	Treated	CR		PR		SD		PD	
	N	N	%	N	%	N	%	N	%
Olap	46	2	4.4	20	43.5	19	41.3	1	2.2
Ced/Olap	44	5	11.4	30	68.2	8	18.2	0	0

Comparison of overall response rate (ORR)

Arm	ORR	
	N	%
Olaparib alone	22	47.8
Cediranib/Olaparib	35	79.6
	p=0.002	

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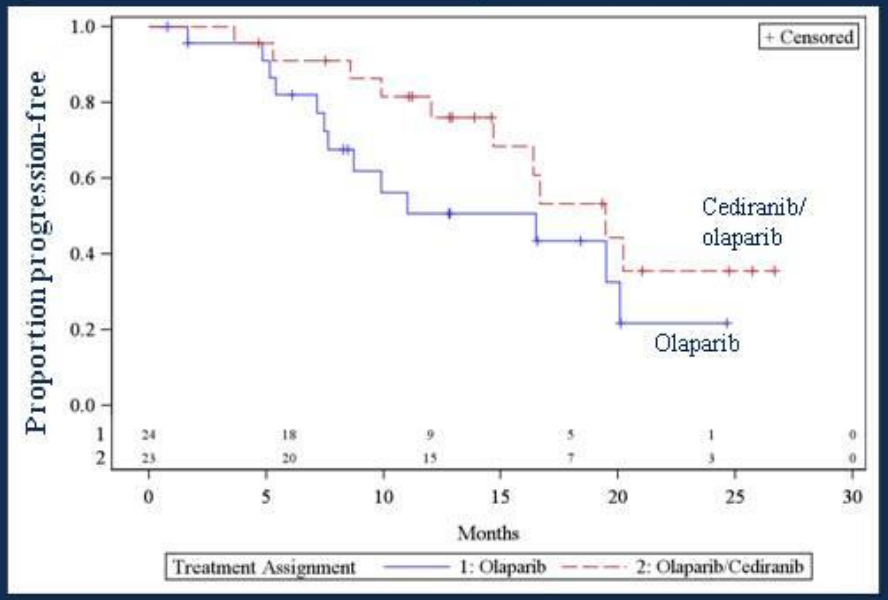
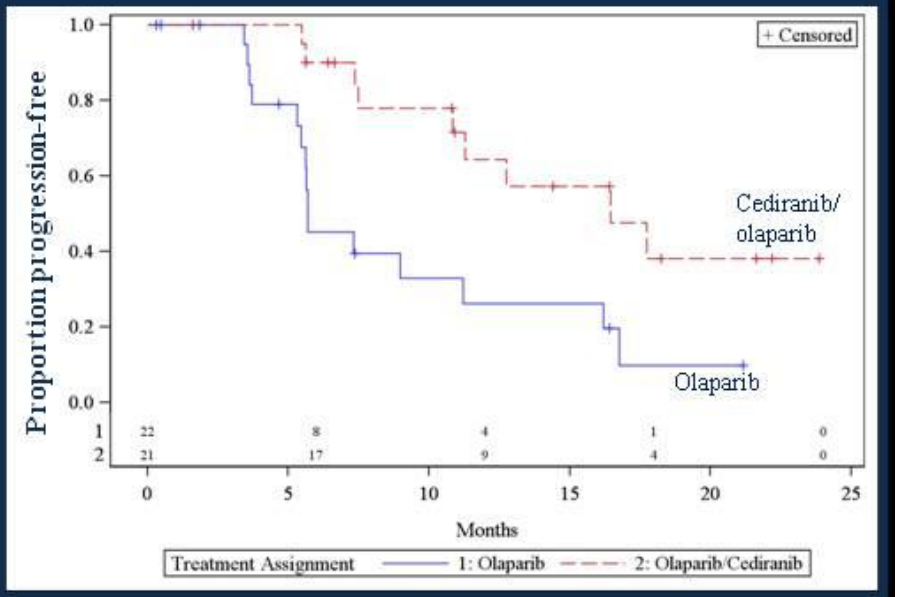
Cediranib/olaparib significantly increased PFS in patients without a BRCA mutation

BRCA mutation carrier



BRCA non-carrier/unknown



	BRCA Mutation Carrier		BRCA Non-carrier/Unknown	
	Olaparib	Ced/Olap	Olaparib	Ced/Olap
PFS events	13	10	15	9
Median PFS	16.5 mo	19.4 mo	5.7 mo	16.5 mo
	p=0.16		p=0.008	
	HR 0.55 (95% CI: 0.24-1.27)		HR 0.32 (95% CI: 0.14-0.74)	

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Treatment-related Adverse Events

Adverse Event	Olaparib alone (N = 46)			Cediranib/Olaparib (N = 44)		
	Maximum Grade			Maximum Grade		
	2	3	4	2	3	4
Non-Hematologic						
Hypertension	-	-	-	15 (34)	17 (39)	1 (2)
Diarrhea	-	-	-	20 (46)	10 (23)	-
Fatigue	7 (15)	5 (11)	-	12 (27)	12 (27)	-
Nausea	12 (26)	-	-	7 (16)	2 (5)	-
Headache	-	-	-	4 (9)	2 (5)	-
Hypothyroidism	1 (2)	-	-	6 (14)	-	-
Hematologic						
Anemia	2 (4)	-	-	1 (2)	-	-
Neutrophil count decreased	4 (9)	-	-	2 (5)	-	-
WBC decreased	3 (7)	-	-	2 (5)	-	-
Platelet decreased	-	-	-	1 (2)	-	-

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Tolerability of cediranib/olaparib combination

- Increased rate of Grade 3 and 4 AEs
- Toxicities generally manageable with symptom management and dose holds/reductions
  - Diarrhea managed with imodium, lomotil
  - Dose reductions in 34 of 44 (77%) of cediranib/olaparib arm patients compared to 11 of 46 (24%) in olaparib alone arm
- 4 patients off-treatment for toxicity, all in cediranib/olaparib arm
  - Toxicities included: 1 MDS, 1 weight loss, 1 avascular necrosis (in setting of pre-existing avascular necrosis history), 1 vaginal fistula formation
- Withdrawal from study treatment for other causes balanced between arms
  - Withdrawal of consent (1 cediranib/olaparib vs. 3 olaparib)
  - MD decision (1 cediranib/olaparib vs. 1 olaparib)
  - Clinical PD (5 cediranib/olaparib vs. 6 olaparib)

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Conclusions

- Combination of cediranib and olaparib was more active than olaparib alone
  - Improved PFS: median PFS 9.0 vs. 17.7 months (HR 0.42, p = 0.005)
  - Increased ORR: 48% vs. 80% (p = 0.002)
  - OS data not mature (16 total OS events)
- Activity observed in both BRCA mutation carriers and BRCA non-carrier/unknown patients
- Toxicity profile was acceptable
  - Most common toxicities were hypertension, diarrhea, fatigue
  - Generally manageable with symptom management and dose holds/reductions

– Degree of activity supports additional clinical evaluation of cediranib/olaparib combination in ovarian cancer

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Acknowledgments

- Patients and their families
- Study teams and investigators at participating sites
  - Dana-Farber Cancer Institute
  - Massachusetts General Hospital
  - National Cancer Institute
  - University of Michigan
  - University of Chicago
  - Cedars-Sinai Medical Center
  - Beth Israel Deaconess Medical Center
  - Fort Wayne Medical Oncology and Hematology
  - NorthShore Medical Group
- This study was sponsored by CTEP/NCI and supported by an NIH grant under the American Recovery and Reinvestment Act (ARRA).