

Systemic Therapy Options for BRCA-Deficient Ovarian Cancer

Cristiana Sessa, MD

**Oncology Institute of Southern Switzerland
Bellinzona, Switzerland**



Effect of BRCA 1/2 Mutations on Long-Term Survival of Patients With Invasive Ovarian Cancer: The National Israeli Study of Ovarian Cancer

- Case control study (1994-1999) in Israel; median follow-up 6.2 yrs
- 1036 pts entered; 779 tested for 3 BRCA1/BRCA2 mutations; 605 of Ashkenazi origin

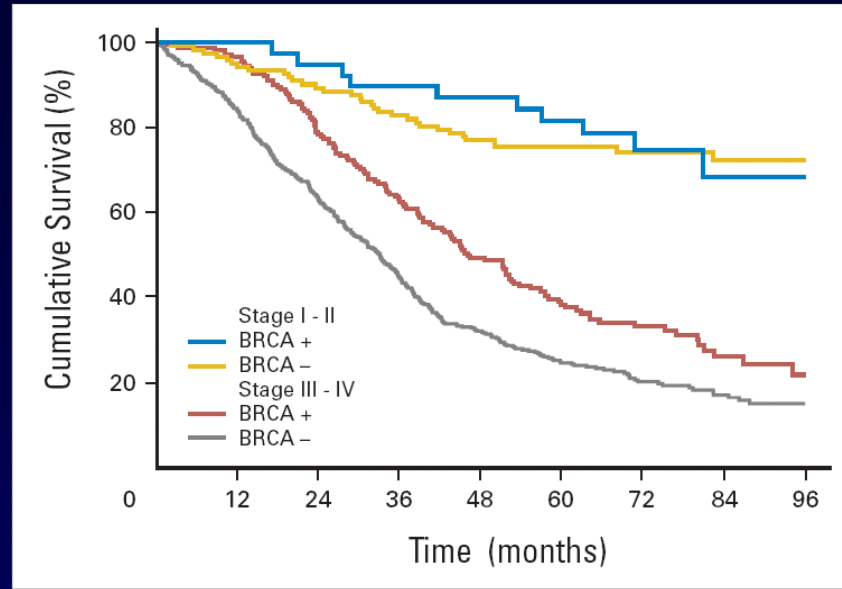
Median and 5 yrs Survival of Ashkenazi Patients With OvC

Variable	Noncarriers				Carriers				Log-Rank <i>P</i> for Noncarriers v Carriers
	No.	Median Survival	95% CI	5-Year Survival (%)	No.	Median Survival	95% CI	5-Year Survival (%)	
Total	392	37.9	35.1 to 40.8	34.4	213	53.7	45.5 to 64.1	46.0	.002
Grade									
Well/moderate	103	55.9	40.2 to *	45.1	27	70.7	38.6 to *	55.0	.8
Poorly/anaplastic	207	36.3	32.5 to 39.3	31.5	150	53.3	46.1 to 70.7	45.4	.0003
Morphology									
Serous	222	38.4	35.5 to 42.2	32.5	133	52.4	43.7 to 63.1	44.9	.03
Nonserous†	147	35.6	29.2 to 45.4	36.0	79	62.1	44.8 to 88.3	50.0	.009

*Upper limit could not be calculated.

†Mucinous tumors were excluded.

Survival in OvC Related to BRCA1/2 Mutations



Survival by stage and BRCA 1/2 mutation status

5yr survival (%)

	non carriers	carriers	P
median	34	46	.003
poorly anaplastic	31	45	.001
non serous	36	50	.009
stage III	27	38	.002
stage IV	7	36	.01

Chetrit A, et al. *J Clin Oncol.* 2008;26(1):20-25.

Phase III Trial of Bevacizumab in the Primary Treatment of Advanced Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer: A Gynecologic Oncology Group (GOG) Study

**R.A. Burger,¹ M.F. Brady,² M.A. Bookman,³
J.L. Walker,⁴ H.D. Homesley,⁵ J. Fowler,⁶
B.J. Monk,⁷ B.E. Greer,⁸ M. Boente,⁹ S.X. Liang¹⁰**

¹Fox Chase Cancer Center, Philadelphia, PA; ²Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY; ³University of Arizona Cancer Center, Tucson, AZ; ⁴University of Oklahoma Health Sciences Center, Oklahoma City, OK; ⁵Brody School of Medicine, Greenville, NC; ⁶James Cancer Hospital at the Ohio State University, Hilliard, OH; ⁷University of California, Irvine Medical Center, Orange, CA; ⁸Seattle Cancer Care Alliance, Seattle, WA; ⁹Minnesota Oncology and Hematology, Minneapolis, MN; ¹⁰State University of New York at Stony Brook, Stony Brook, NY, USA

GOG-0218: Schema

**Front-line:
Epithelial OV, PP
or FT cancer**

- Stage III optimal (macroscopic)
- Stage III suboptimal
- Stage IV

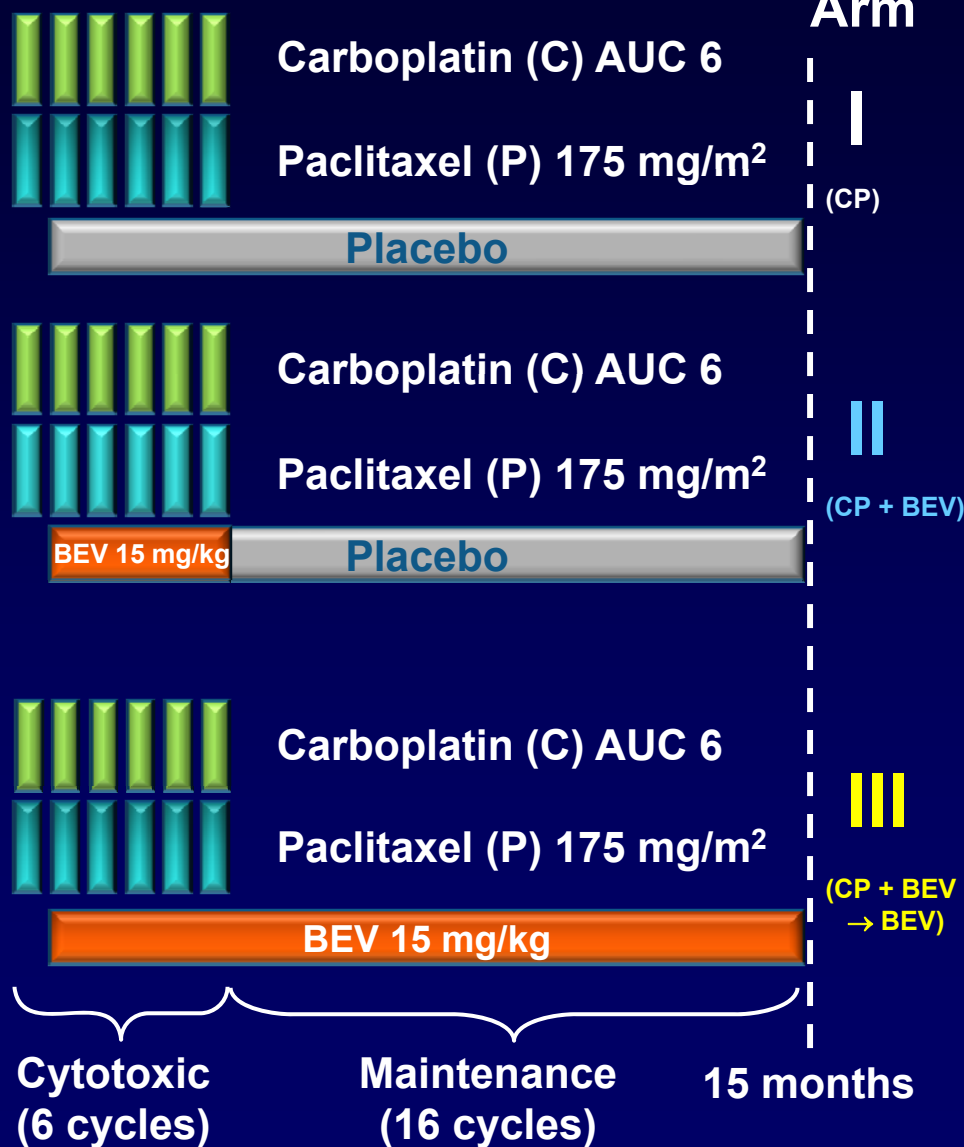
n=1800 (planned)

Stratification variables:

- GOG performance status (PS)
- Stage/debulking status

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1:1:1



GOG-0218: Analysis Plan

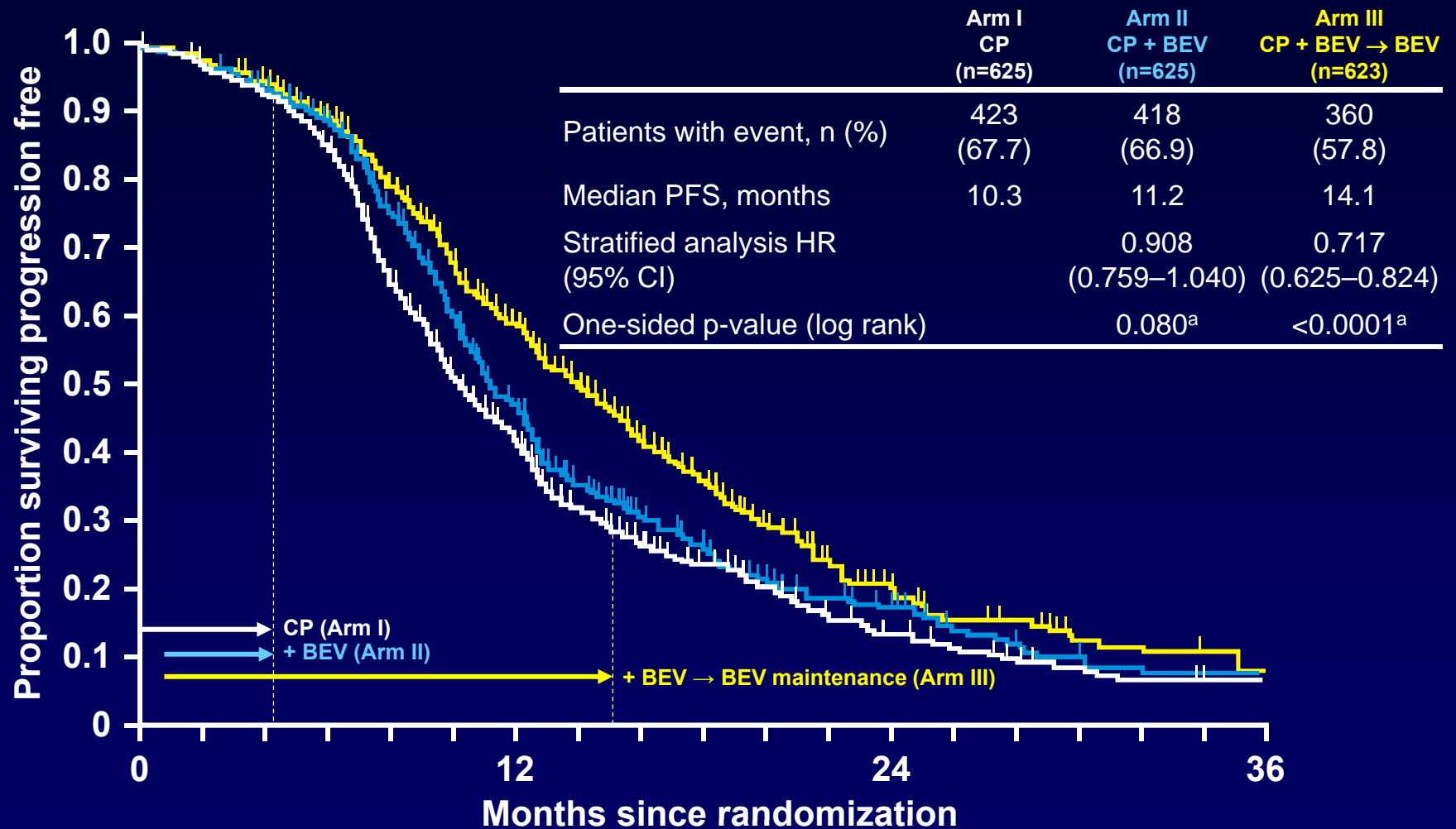
- **Primary analysis**
 - Compare investigator-determined progression-free survival (PFS) for each BEV arm vs control
 - If both results positive, compare Arm III (CP + BEV → BEV) vs Arm II (CP + BEV)
 - Disease progression based on: RECIST, global clinical deterioration, or CA125¹
 - Planned sample size of 1800 based on:
 - 90% power to detect PFS hazard ratio (HR) ≤ 0.77
 - Median PFS shift: 14.0 months → 18.2 months
- **Secondary analyses: Overall survival (OS), safety, quality of life; correlative laboratory studies**

1. Gynecologic Cancer Intergroup Criteria - Rustin GJ, et al. *J Natl Cancer Inst.* 2004;96(6):487-488.
Burger RA, et al. *J Clin Oncol.* 2010;28(18S): Abstract LBA1.

GOG-0218: Study Conduct

- 1873 patients from 336 sites (US, Canada, South Korea, Japan), October 2005–June 2009
- Key protocol amendments
 - Inclusion of optimally debulked (macroscopic residual disease) patients
 - Primary endpoint changed to PFS
- Final data analysis triggered by number of events in control arm
- Analyses
 - Efficacy population: n = 1873 (intent to treat)
 - Safety population: n = 1816 (intent to treat, as of cycle 2)
- Median follow-up: 17.4 months (range 0.0–50.7 months)

GOG-0218: Investigator-Assessed PFS



GOG-0218: Conclusions

- **GOG-0218 met the primary objective in the front-line treatment of advanced ovarian (epithelial OV, PP, and FT) cancer; PFS with CP + BEV → BEV maintenance (Arm III) statistically superior to CP alone (Arm I)**
 - PFS with CP + BEV (Arm II) not statistically superior to CP (Arm I)
- **Interpretation of survival analysis limited**
- **Treatment regimen generally well tolerated; adverse events (including GI perforation) similar to previous BEV studies**
- **BEV – first molecular targeted and first anti-angiogenic agent to demonstrate benefit in this population**
- **CP + BEV → BEV maintenance should be considered one standard option**

GOG-0218: Discussion

Strengths

- Well conducted, adequately powered for PFS/OS
- Evaluated both concurrent +/- maintenance BEV
- Standard GCIIG definition of PD used (objective+CA125)
- Bias in PFS reduced by
 - blinding treatment
 - identical timing of CA125, imaging on all arms

Weaknesses - few

- Change in primary endpoint to PFS

Conclusions and more questions

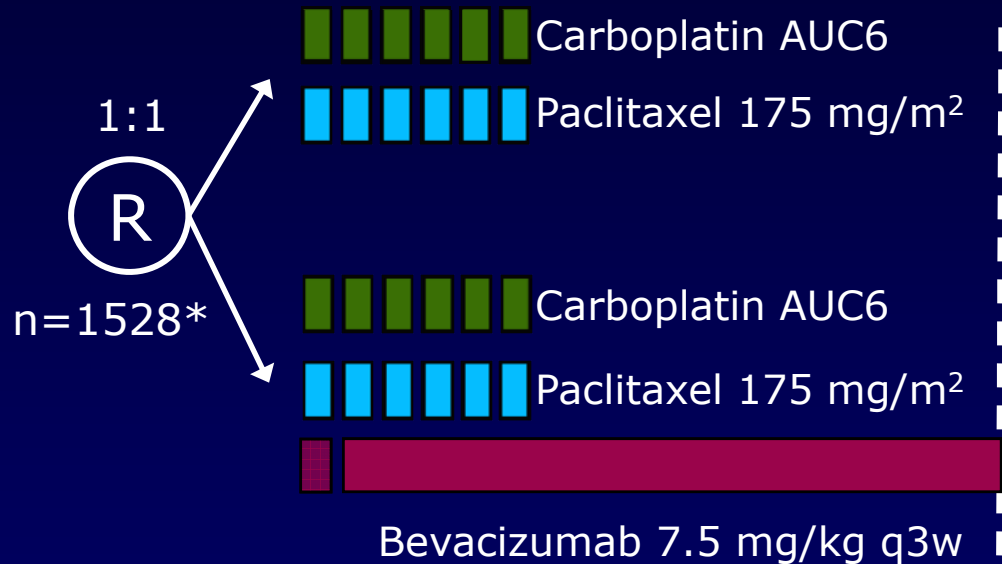
- Use of BEV in standard practice is premature
- PFS gain alone, of this magnitude, of unclear benefit to patients
- Need mature overall survival
- Need QoL data covering period of progression
- ICON 7 results awaited

**ICON7: A Phase III Gynaecologic Cancer
InterGroup (GCIG) Trial of Adding
Bevacizumab to Standard Chemotherapy in
Women With Newly Diagnosed Epithelial
Ovarian, Primary Peritoneal, Or Fallopian
Tube Cancer**

**Tim Perren, Ann Marie Swart, Jacobus Pfisterer,
Jonathan Ledermann, Alain Lortholary, Gunnar Kristensen, Mark
Carey, Philip Beale, Andreas Cervantes, Amit Oza
on behalf of GCIG ICON7 collaborators
(MRC/NCRI, AGO-OVAR, GINECO, NSGO, ANZGOG, GEICO, NCIC-CTG)**

Schema

Academic-led, industry-supported trial to investigate use of bevacizumab and to support licensing



Stratification variables:

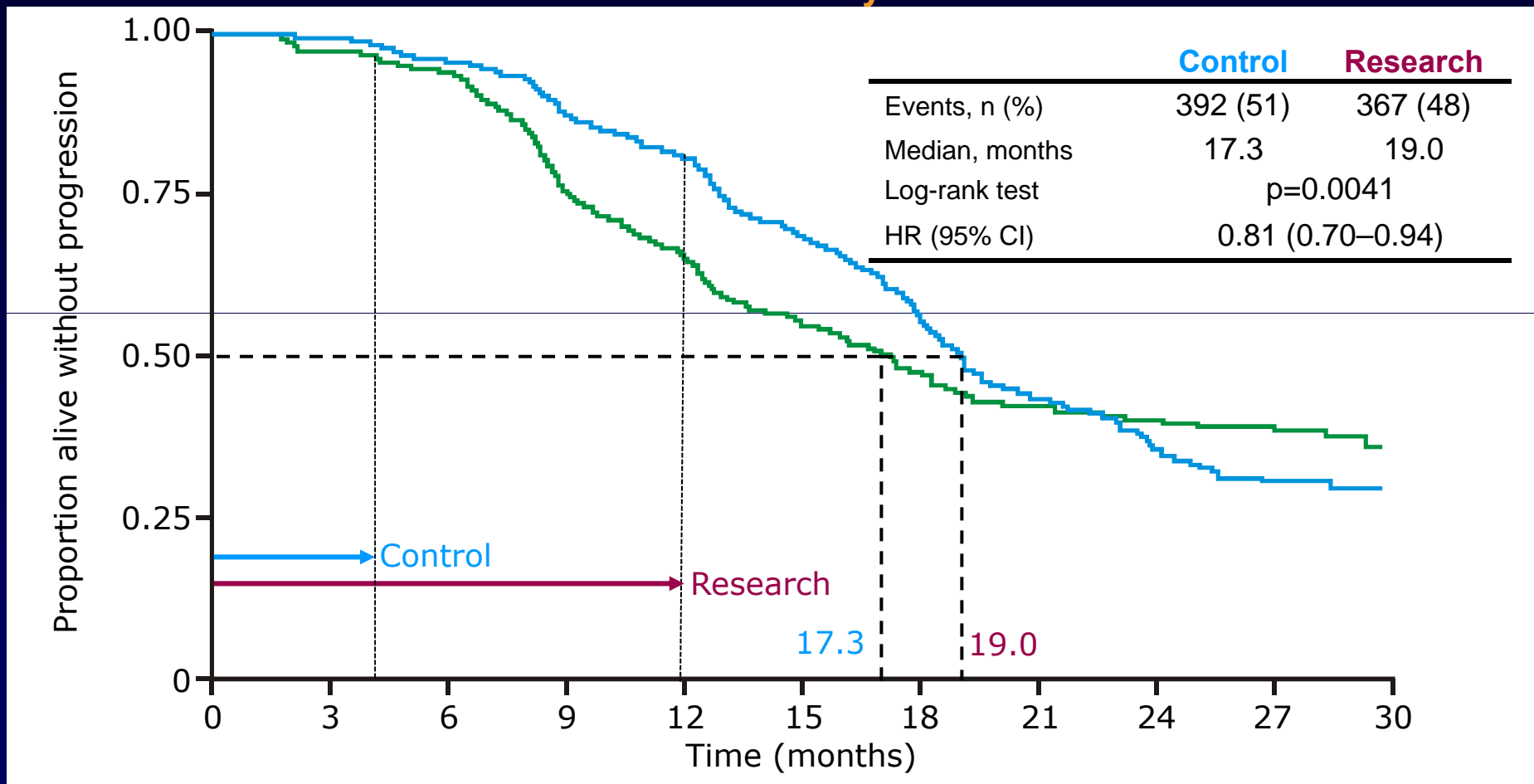
- **Stage & extent of debulking:**
 I–III debulked ≤1cm vs
 I–III debulked >1 cm vs
 IV and inoperable stage III
- **Timing of intended treatment start**
 ≤4 vs >4 weeks after surgery
- **GCIG group**

*Dec 2006 to Feb 2009

	Year 1	Years 2–3	Years 4–5
CT	Baseline; after cycles 3 & 6; at 9 & 12 months	Every 6 months	As indicated
CA-125/clinical assessment	Every chemotherapy cycle; every 6 weeks during maintenance phase	Every 3 months	Every 6 months

Progression-Free Survival

Academic Analysis



Number at risk

	0	3	6	9	12	15	18	21	24	27	30
Control	764	723	693	556	464	307	216	143	91	50	25
Research	764	748	715	647	585	399	263	144	73	36	19

Perren T, et al, Ann Oncol. 2010;21(Suppl 8): LBA 4.

Conclusions

- **The addition of concurrent and maintenance bevacizumab (7.5 mg/kg for 12 months) to standard chemotherapy statistically significantly improved PFS**
- **Due to nonproportional hazards, benefit is complicated to describe:**
 - **15% improvement in PFS at 12 months**
 - **1.7 month improvement in median PFS**
 - **1.5 month overall improvement in PFS (restricted mean)**
 - **Treatment effect is numerically greater in advanced-stage patients**
- **Second positive phase III trial of bevacizumab in ovarian cancer**
- **Treatment was well-tolerated with no new safety concerns**
- **Longer term PFS, mature OS, and translational research results are anticipated in 2012**
- **Results of ICON7 will influence treatment decisions and design of future clinical trials**

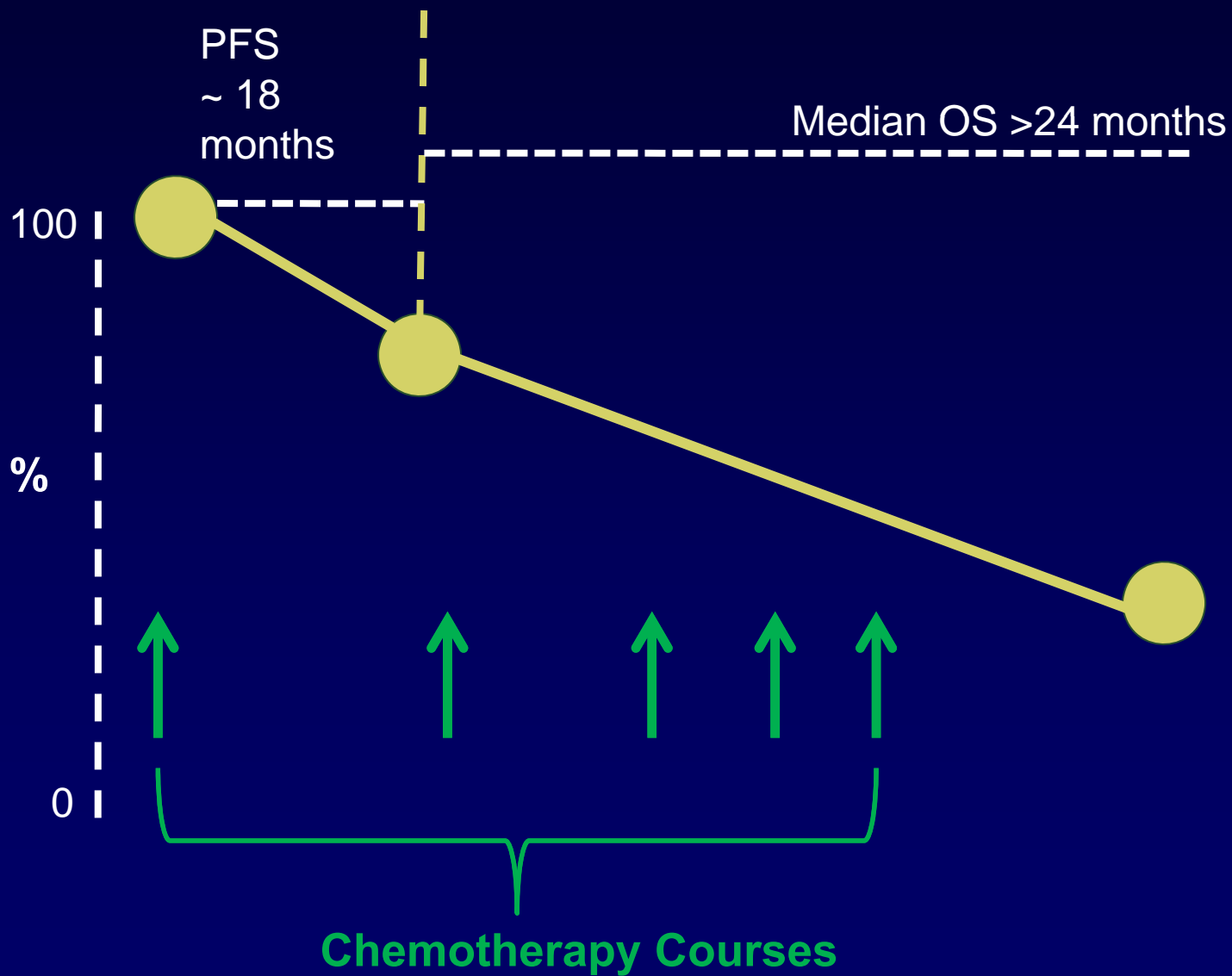
Information on applications to obtain samples to icon7@ctu.mrc.ac.uk

4th Ovarian Cancer Consensus Conference
June 25-27, 2010
Vancouver, BC

Front-Line Phase III Trials

- **Both PFS and OS are important primary endpoints.**
PFS is most often preferred because of the confounding effect of the post-recurrence/progression therapy on OS
- **Standard arm must contain a taxane and a platinum agent for 6 cycles. Recommended regimen: Paclitaxel (175mg/m²) and Carboplatin (AUC 5-6) every 3 weeks**
- **BEV could be incorporated in the control arm of a randomized trial as a consequence of the results of a trial with BEV that met its primary endpoint**

Ovarian Cancer Treatment Pathway



Aims of Treatment

~75% patients with advanced ovarian cancer develop recurrent or progressive disease

- **Select the best timing to initiate chemotherapy**
 - Balance of efficacy and toxicity
 - In asymptomatic patients, quality of life needs to be maintained; in those with symptoms it needs to be improved
- **Control symptoms and extend survival**
 - Chemotherapy is the principal modality
 - Uncertain role for surgery
- **Best selection from a wide choice of chemotherapy**
 - Drugs should be selected on basis of probability of response
 - Sequencing – combination or sequential
 - Emerging role of novel targeted therapies – clinical trials

Recurrent Ovarian Cancer: Population Characteristics

	Response to platinum	
	Time to recurrence	Response to further platinum
Platinum-sensitive	>12 mo	30% - 60%
Platinum-partially sensitive	6 - 12 mo	25% - 30%
<hr/>		
Platinum-resistant	<6 mo	<10%
Platinum-refractory	No initial response	N/A

Combination Chemotherapy for 'Platinum-Sensitive' Disease

	ICON4/ OVAR 2.2 ¹	GEICO ²	OVAR 2.5 ³	CALYPSO C/Pax ⁴	CALYPSO C/PLD ⁴
>12 mo TFI	75%	58%	60%	64%	65%
Prior Taxane	43%	87%	67%	99%	99%
>1 line	8%	15.6%	0	17%	12%
PFS (months)	12*	11.2	8.6	9.4	11.3

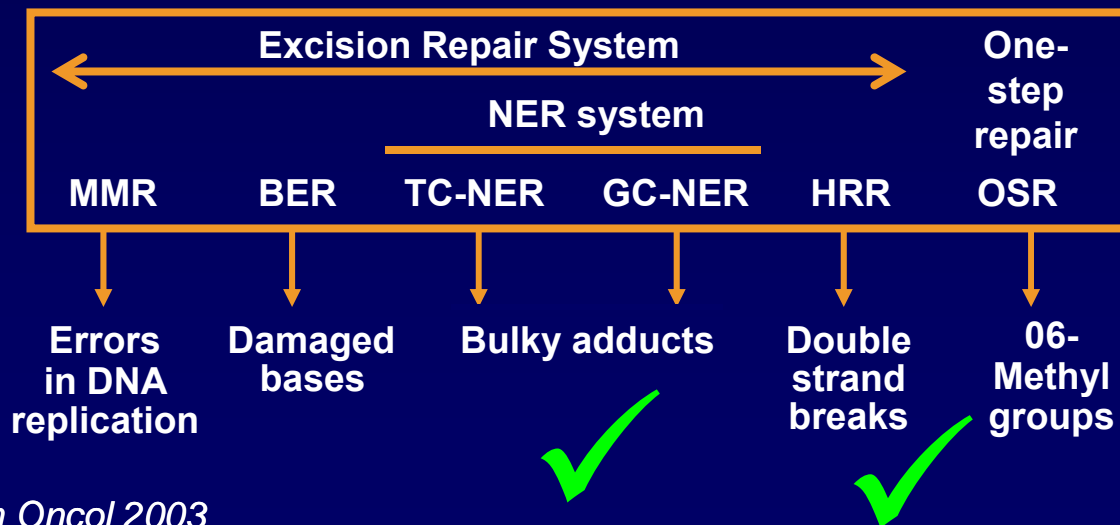
* Significant OS

1.Parmer MK, et al. *Lancet*. 2003;361:2099-2106. 2. Gonzalez-Martin AJ, et al. *Ann Oncol*. 2005;16(5):749-755.
3.Pfisterer J, et al. *J Clin Oncol*. 2006;24(29):4699-4707. 4.Pujade-Lauraine E, et al. *J Clin Oncol*. 2009;27(18S):
Abstract LBA5509.

Trabectedin MoA

Interaction With DNA Repair Systems

- **Trabectedin antitumoral activity is mediated by DNA damage.**
 - Producing bulky DNA adducts
 - Producing double strand breaks in the DNA
- **Sensitivity/resistance to trabectedin is mediated by the efficacy of two DNA repair mechanisms**
 - Nucleotide excision repair
 - Homologous recombination repair



OVA 301 Study Eligibility Criteria

Only one prior platinum-based chemotherapy

Platinum-resistant (PFI < 6 months) or platinum-sensitive (PFI > 6 months)

Measurable disease (RECIST)

Study Design

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**PLD 50 mg/m² 90
minute infusion q 4
weeks**

**PLD 30 mg/m² 90 minute
infusion followed by
trabectedin* 1.1 mg/m² 3
hour infusion, q 3 weeks**

*Premedication with dexamethasone is
required

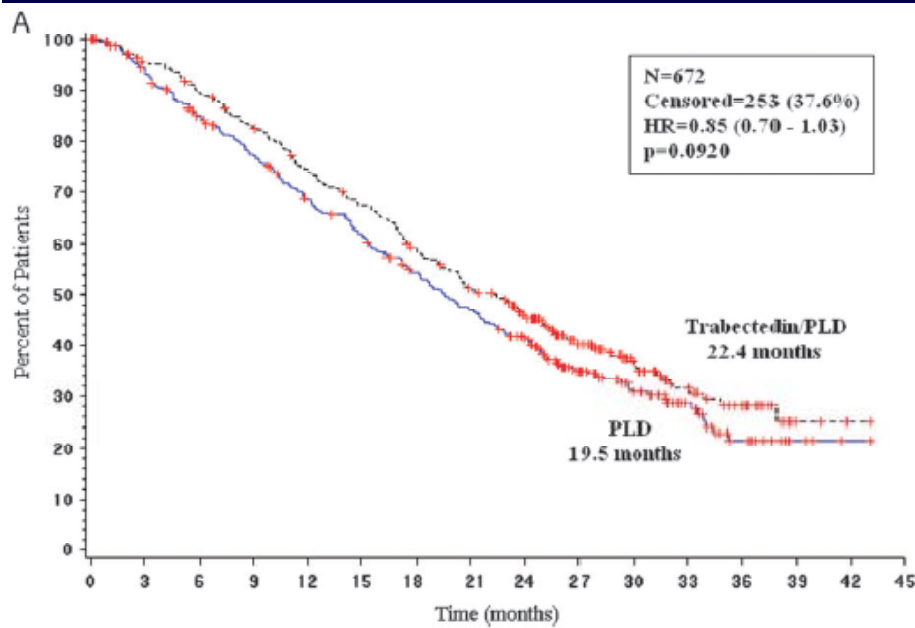
- Assessment q8wks (RECIST, QoL)
- Endpoint Primary PFS (RECIST)
- Endpoint Secondary PFS (IA)

*TFI = treatment-free interval

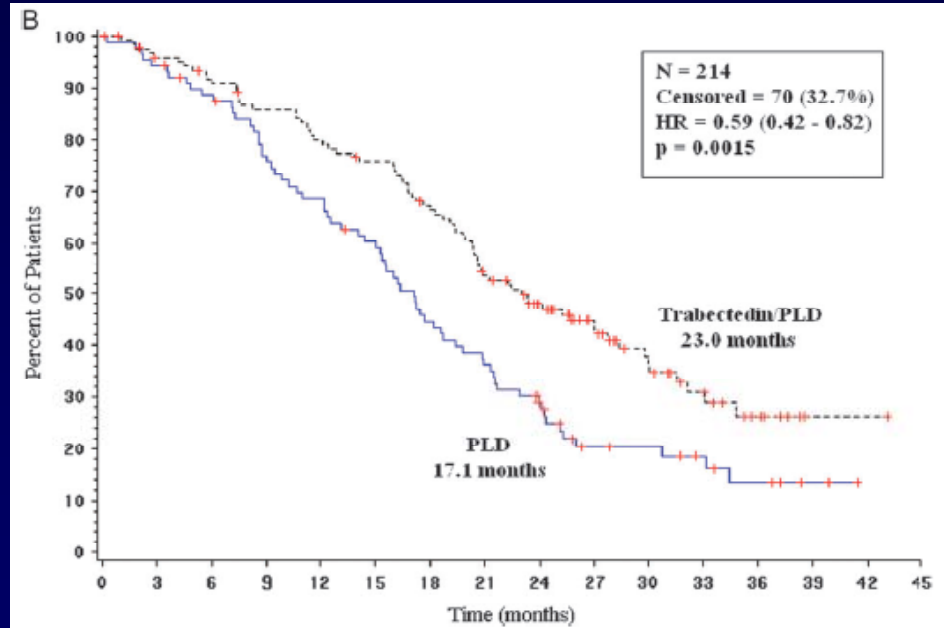
OVA 301 Study Update Results

Median overall survival

All patients



Platinum-sensitive patients



Platinum-Resistant/Refractory Group

Persistent disease:

little or no response to first-line therapy

Good partial or complete response and early relapse

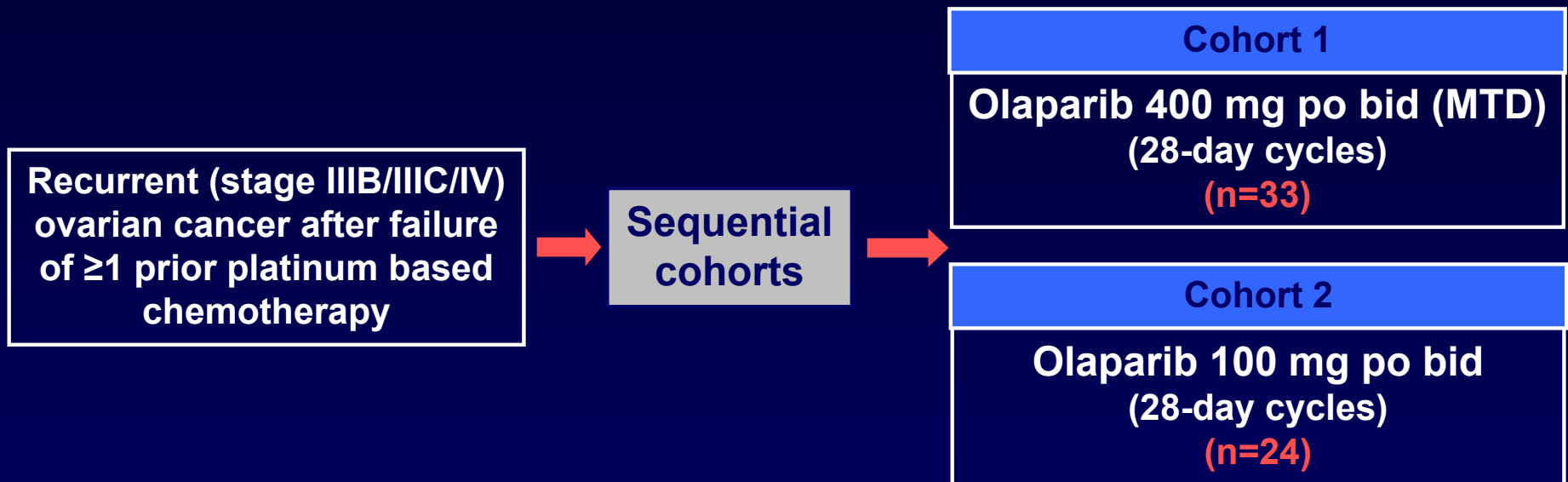
- Asymptomatic disease
- Disease likely to cause organ dysfunction
- Symptomatic progression or relapse

PLDH Versus Topotecan Survival by Platinum Sensitivity

Population	N	HR	<i>P-value</i>	Non-stratified <i>P-value</i>
All randomized	481	1.23	0.038	0.025
All treated	474	1.216	0.05	0.032
Resistant/Refractory	255	1.069	0.618	
Sensitive	219	1.43	0.017	
Partially sensitive (6 mo - 12 mo)	122	1.58	0.021	
Sensitive (> 12 mo)	97	1.15	0.057	

Study design

An open-label, single-arm, multicenter Phase II study



Patients

- Confirmed germline *BRCA1* or *BRCA2* mutation
- Measurable disease
- ECOG performance status 0–2

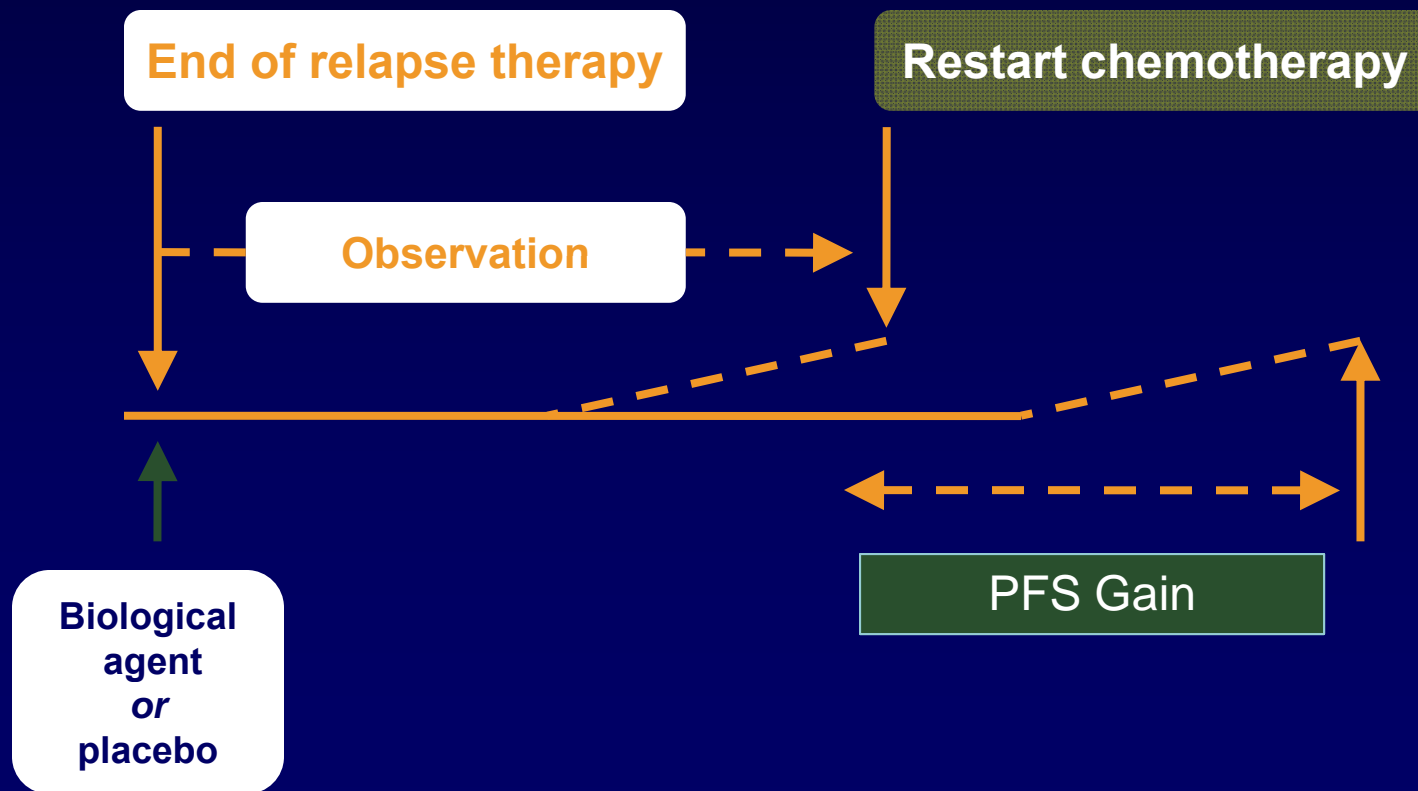
MTD, maximum tolerated dose (determined during Phase I evaluation)

Efficacy of OLAPARIB in Recurrent OvC

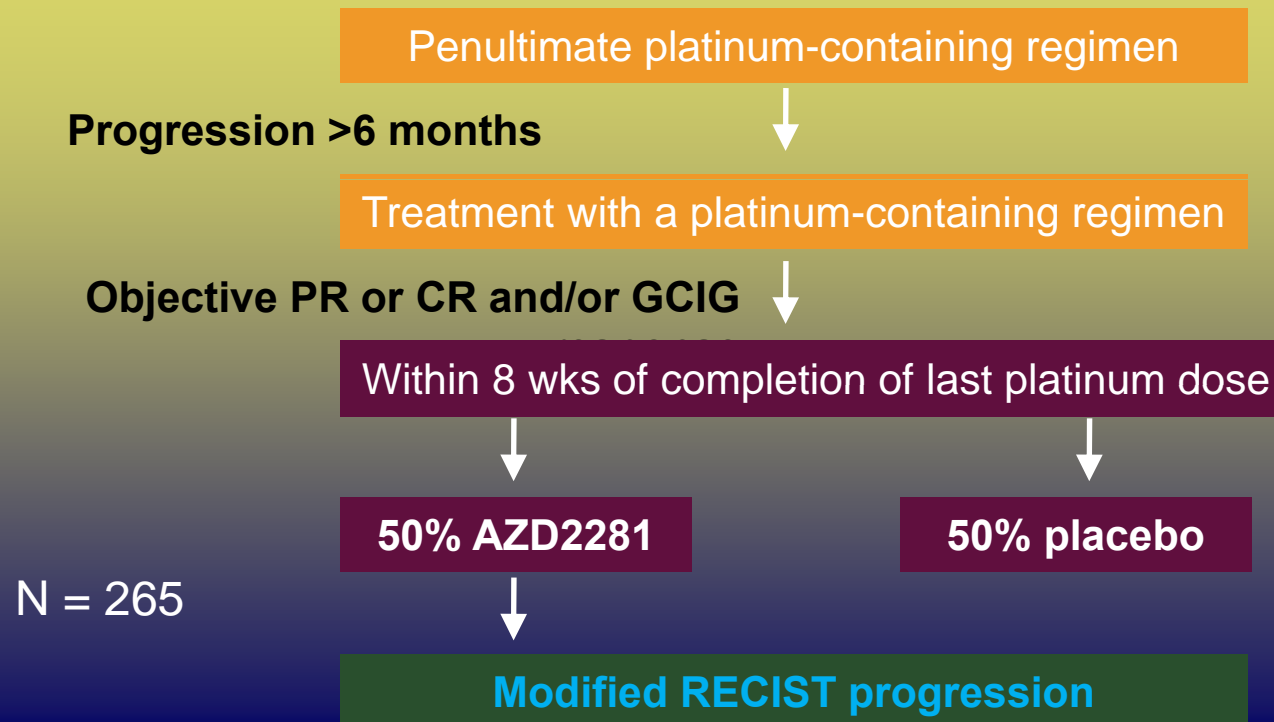
	400 mg bid (n = 33)	100 mg bid (n = 24)
Objective Response rate, n (%)	11 (33)	3 (13)
Platinum sensitive , n (%)	5/13	3/6
Platinum resistant , n (%)	6/20	0/18
Clinical benefit rate (%)	52	21
Median PFS (95% CI)	5.8 (2.8-10.6)	1.9 (1.8-3.6)
ITT analysis		

Trial Design to Evaluate Novel Agents

Maintenance treatment post-chemotherapy for relapsed ovarian cancer



Study 19: Olaparib in Platinum-Responding Recurrent Serous Ovarian Cancer



Olaparib (AZD2281; KU0059436)

Recurrent Ovarian Cancer

- **Significant improvement in control of disease by intermittent courses of chemotherapy – many patients now have 3 - 4 lines of treatment**
- **Combinations with platinum provide greater benefit than monotherapy**
- **Novel targeted therapy may extend survival further**
- **Challenge is timing of treatment, balancing control of symptoms, side effects of treatment, quality of life**