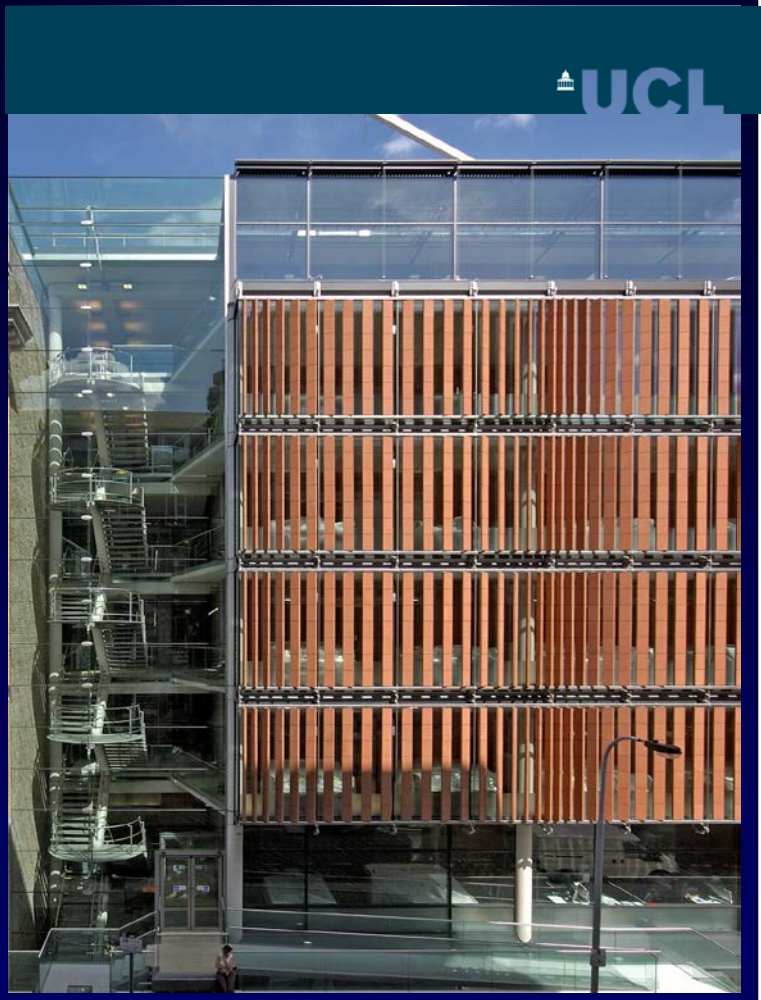
Keeping the Lid on Ovarian Cancer: Targeted Therapeutic Approaches



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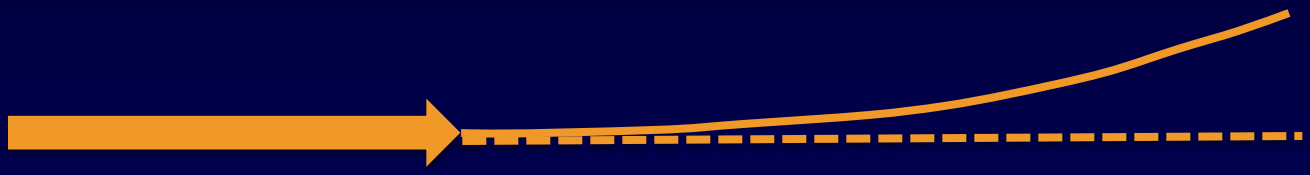
Maintenance Therapy



First line
PFS 18m median

Platinum-sensitive
Recurrence
PFS 8-11m median

Chemotherapy

Chemotherapy

Aims of Maintenance Therapy

- Prolongation of disease control
  - Extending PFS & OS
- Affecting ‘cure’: eradication of minimal residual disease
- Acceptable long-term treatment
  - Low toxicity
  - Preservation of quality of life

Antiangiogenesis The Story So Far…….

- First Line:
  - Increase in PFS but no overall survival benefit
    - Bevacizumab improves PFS by 3.8 months (GOG 218) and 2.4 months (ICON7)
    - High-risk ICON 7 (Stage IV or residual disease) 5.5 months
    - Pazopanib PFS benefit 5.6 months
    - Convenience of pazopanib has to be balanced against toxicity - 58 % required dose reduction, 33% discontinuation
    - Nintedanib increases median PFS 0.7 months (OVAR-12); no benefit for sorafenib
  - Survival benefit in subgroup
    - ICON 7 'high risk' and GOG 218 Stage IV

Perren TJ, et al. *N Engl J Med.* 2011;365(26):2484-2496.
Burger RA, et al. *N Engl J Med.* 2011;365(26):2473-2483.
du Bois A, et al. *J Clin Oncol.* 2014;32(30):3374-3382.
du Bois A, et al. *Int J Gynecol Cancer.* 2013;23(8suppl1): Abstract LBA1.

Antiangiogenesis: Platinum-Sensitive Relapse

- **Second-line:**
  - **Increase in PFS**
    - **Bevacizumab increases median PFS by 4 months**
    - **Cediranib increases median PFS by 2.4 months (3.1 months using restricted mean)**
  - **Survival**
    - **Bevacizumab – no benefit but long post-progression survival and high rate of crossover**
    - **Cediranib – increase in median OS of 6 months - but underpowered**

Aghajanian C, et al. *J Clin Oncol.* 2012;20(17):2039-2045.
Ledermann JA, et al. *Eur J Cancer.* 2013;49:s3.

Toxicity and QoL- Antiangiogenic Maintenance

- **Bevacizumab**
  - Hypertension, proteinuria, bleeding, fistula, and allergy
  - No detriment to QoL (ICON 7)
- **VEGFR TKIs**
  - Hypertension, diarrhea, fatigue, nausea
  - Dose reductions 58% pazopanib
  - No detriment to QoL with cediranib - but are we studying the maintenance phase of treatment adequately?
  - Cessation of treatment
    - 36% discontinued for nonprogression (ICON 7)
    - 40% discontinued for nonprogression (OCEANS)
    - 23% discontinued during the maintenance phase (ICON 6)

Perren TJ, et al. *N Engl J Med.* 2011;365(26):2484-2496.
Ledermann JA,et al. *Eur J Cancer.* 2013;49:s3.
Aghajanian C, et al. *J Clin Oncol.* 2012;20(17):2039-2045.

Summary: Antiangiogenic Maintenance Therapy

	First Line	Platinum-Sensitive Recurrence
With chemotherapy and as maintenance	Bevacizumab: GOG 218 Bevacizumab: ICON7 Nintedanib: OVAR-12	Bevacizumab: OCEANS Cediranib: ICON 6
Maintenance only	Pazopanib: OV-16 Sorafenib: (phase II)	

Bevacizumab licensed for first-line and second-line use by EMA, but not submitted to FDA

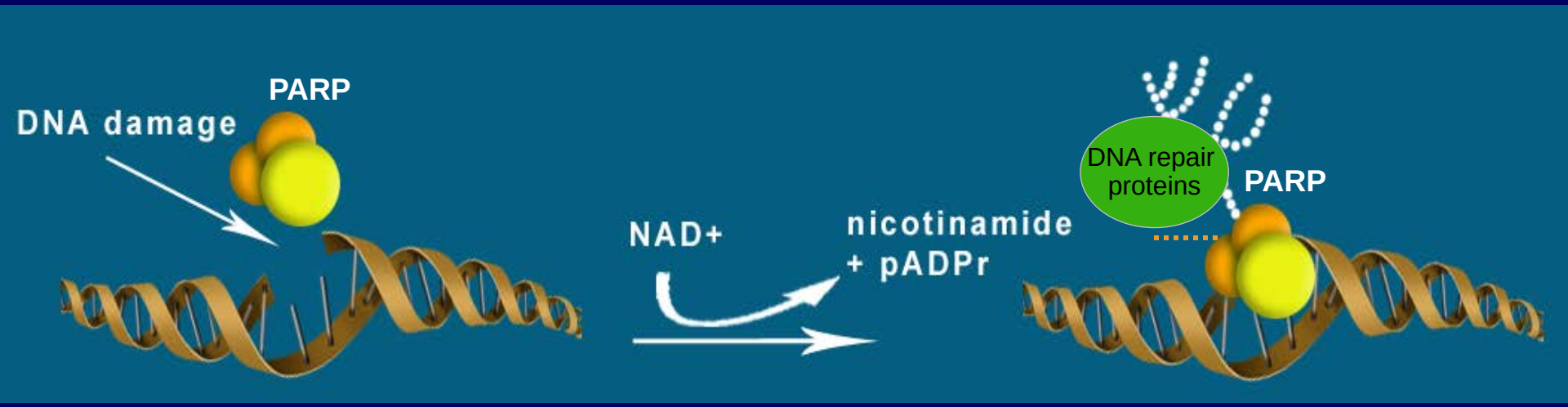
Cediranib?

Selection

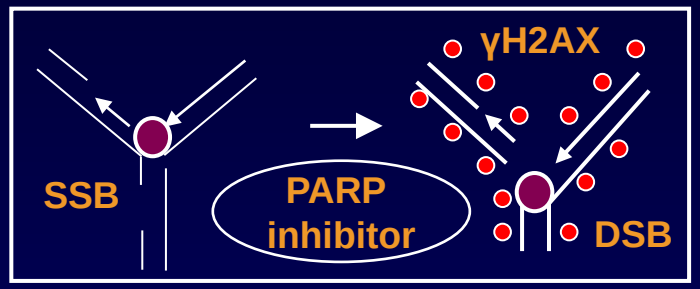
- **High-risk subgroup of ICON 7 & stage IV GOG 218**
- **Patterns of circulating biomarkers - no firm conclusions**
- **Possible detrimental effect in high-grade patients with ‘immune signature’**

Poly(ADP-Ribose) Polymerase

- A key regulator of DNA damage repair processes
- Involved in DNA base-excision repair (BER)
- Binds directly to DNA damage
- Produces large branched chains of poly(ADP-ribose)
- Attracts and assists BER repair effectors

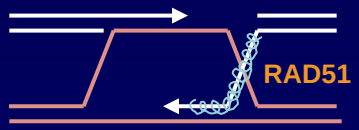


PARP Inhibition and Tumor-Selective Synthetic Lethality



DNA replication fork arrest and collapse

Normal HR repair



HR-based repair

Chromosome stability

Cell survival

Impaired HR repair

Alternative error-prone repair mechanism

Chromosomal instability

Cell death

DSB, double-strand break; HR, homologous recombination; SSB, single-strand break

Slide provided with permission by Andrew Tutt

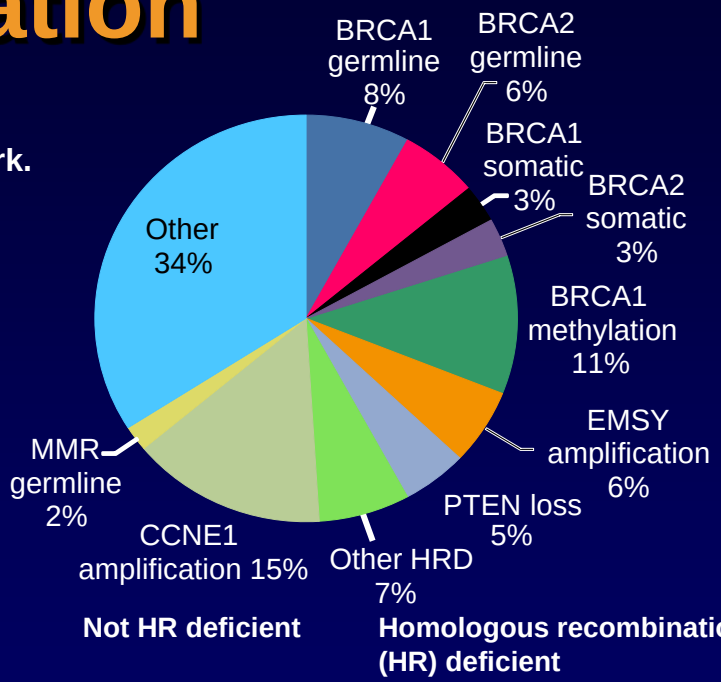
Farmer H, et al. *Nature.* 2005;434(7035):917-921.
Bryant HE, et al. *Nature.* 2005;434(7035):913-917.

Strategy for PARPi Development

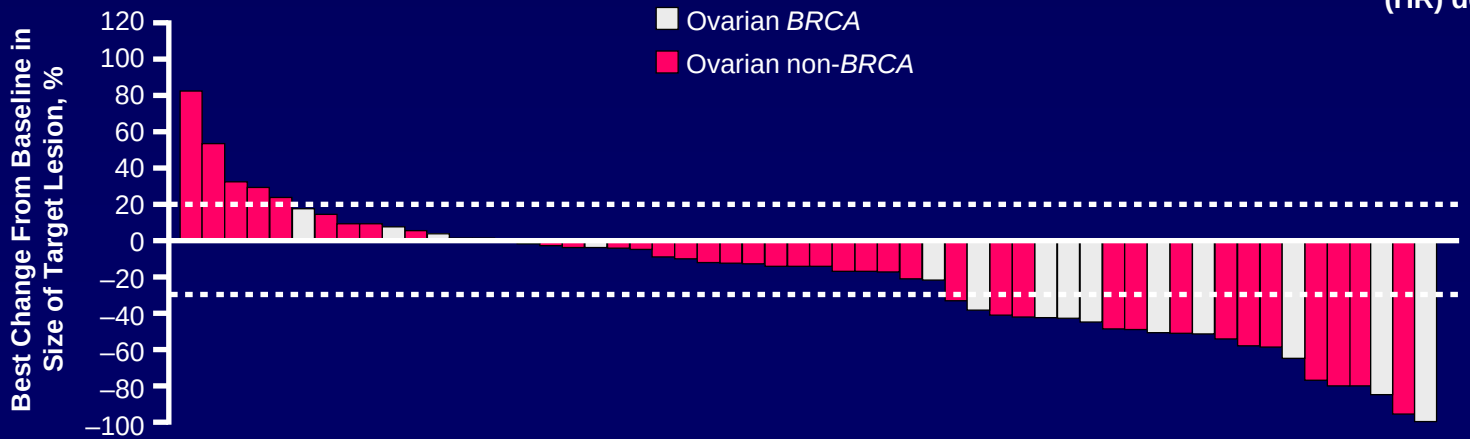
- **Phase I and II trials demonstrate significant activity in patients with *BRCA* mutation**
- **Randomized trial with olaparib shows tumor shrinkage and similar outcome compared to PLD chemotherapy**
  - Should PARP inhibitors be given with chemotherapy?
  - Should PARP inhibitors be given to maintain response?
  - Who benefits? – patients with *BRCA* mutations or wider group?

PARP Inhibitors Without Germline *BRCA* Mutation

Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-615.



Phase II trial of olaparib in ovarian cancer patients with *BRCA* and *BRCA* wildtype



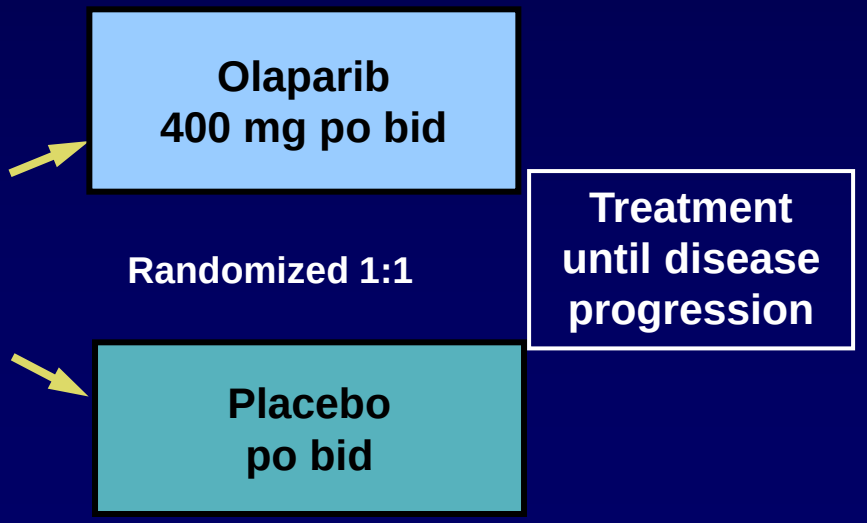
Gelmon KA, et al. *Lancet Oncol.* 2011;12(9):852-861.

Olaparib Maintenance in Relapsed Ovarian Cancer – 'Study 19'

- Assess the efficacy of olaparib as a maintenance treatment in patients with platinum-sensitive, high-grade serous ovarian cancer
- Randomized, double-blind, placebo-controlled phase II trial

Patient eligibility:

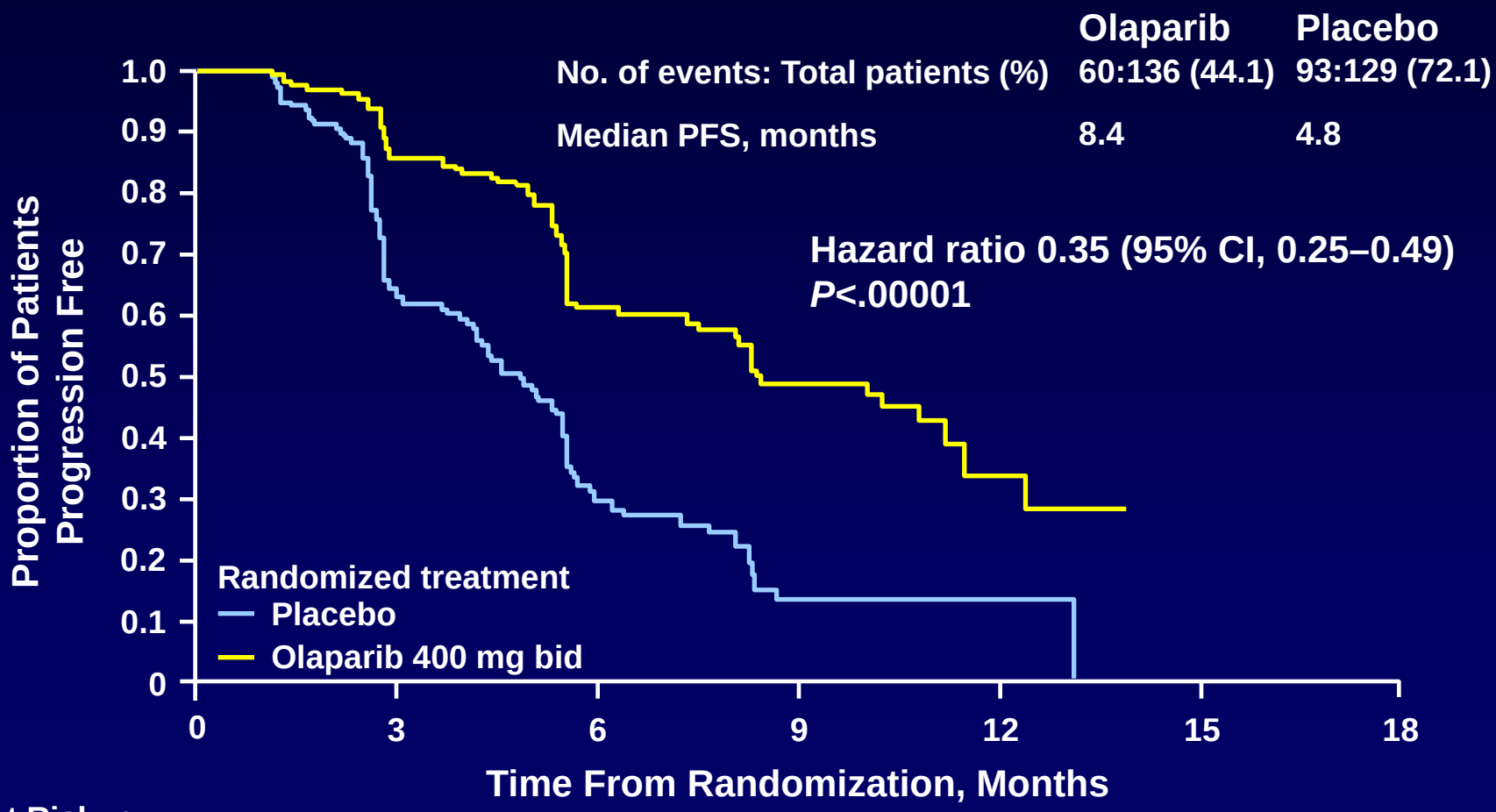
- Platinum-sensitive, high-grade serous ovarian cancer
- ≥2 previous platinum regimens
- Last chemotherapy: platinum based with a maintained response
- Stable CA-125 at trial entry
- Randomization stratification factors:
  - Time to disease progression on penultimate platinum therapy
  - Objective response to last platinum therapy
  - Ethnic descent



Ledermann J, et al. *N Engl J Med.* 2012;366:1382-1392.

ClinicalTrials.gov identifier: NCT00753545

Primary Outcome: Progression-Free Survival



Ledermann J, et al. *N Engl J Med.* 2012;366(15):1382-1392.

Toxicity and Tolerability

- Low-grade nausea/vomiting
- Fatigue
- Anemia

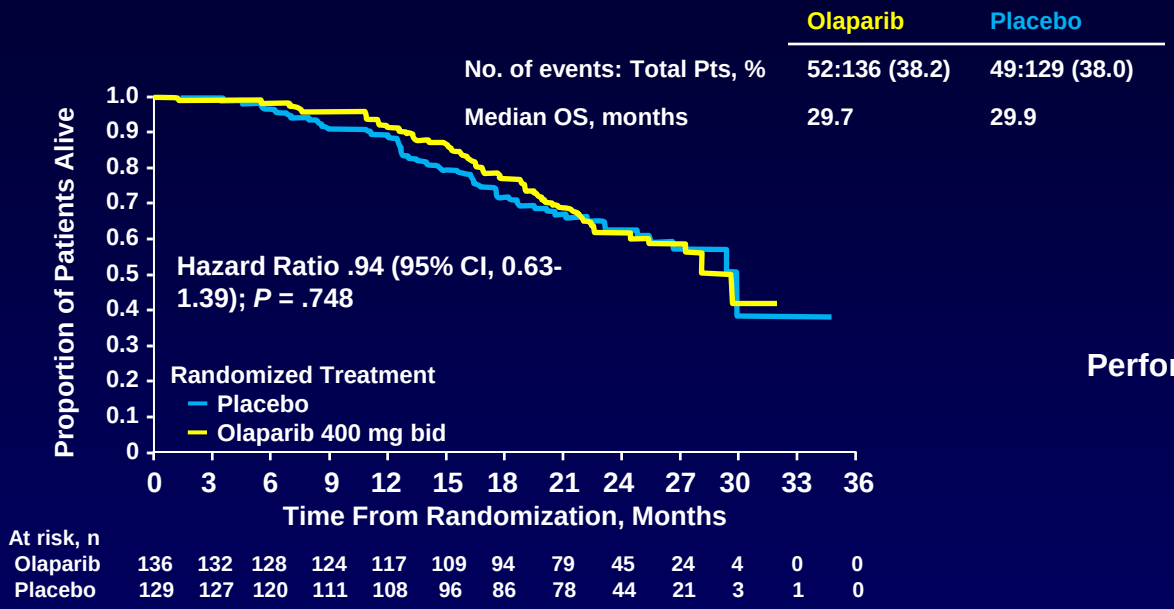
	Olaparib 400 mg bid n = 136	Placebo n = 128
Discontinuations due to AEs, n (%)	3 (2)	1 (1)
Dose interruptions due to AEs, n (%)	41 (30)	12 (9)
Dose reductions due to AEs, n (%)	26 (19)	3 (2)
Median treatment duration, days	207	141

No detrimental impact on HRQoL (Treatment Outcome Index of FACT-0) compared with placebo

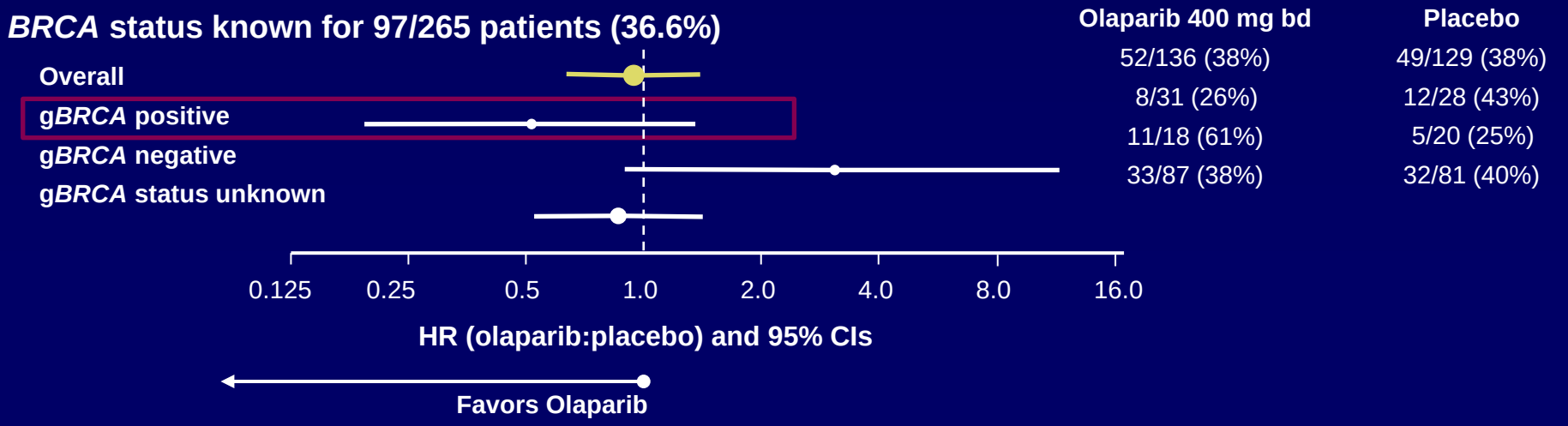
- overall study population and patients with a *BRCA*m

Ledermann J, et al. *J Clin Oncol.* 2011;29(28):3798-3804.
Ledermann J, et al. *Ann Oncol*. 2014;25(s4): Abstract 885PD.

Interim Survival Analysis



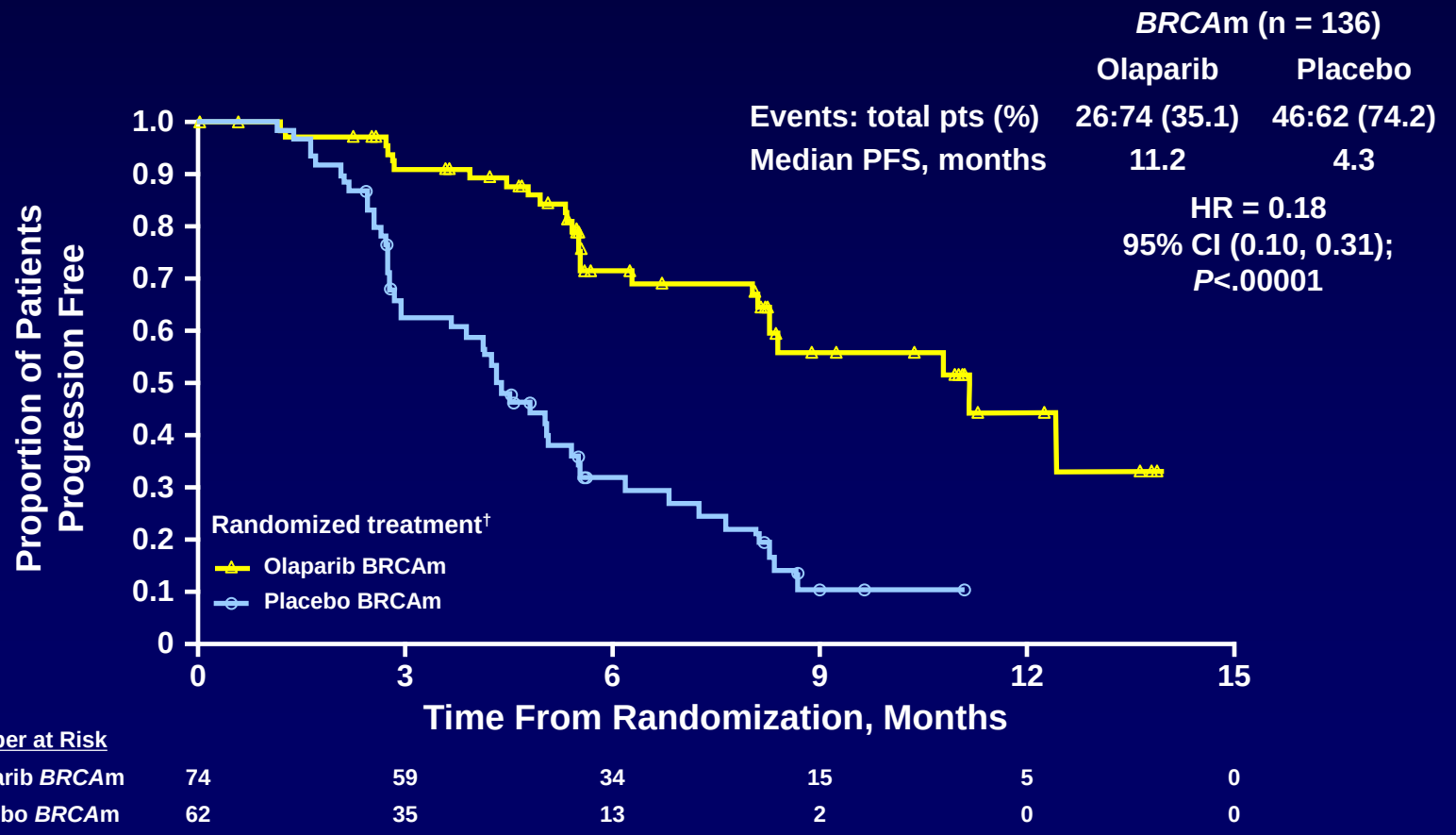
Performed at 38% maturity



Ledermann J, et al. *J Clin Oncol.* 2013;31:(15s). Abstract 5505.

PFS in Patients With a *BRCA* Mutation*

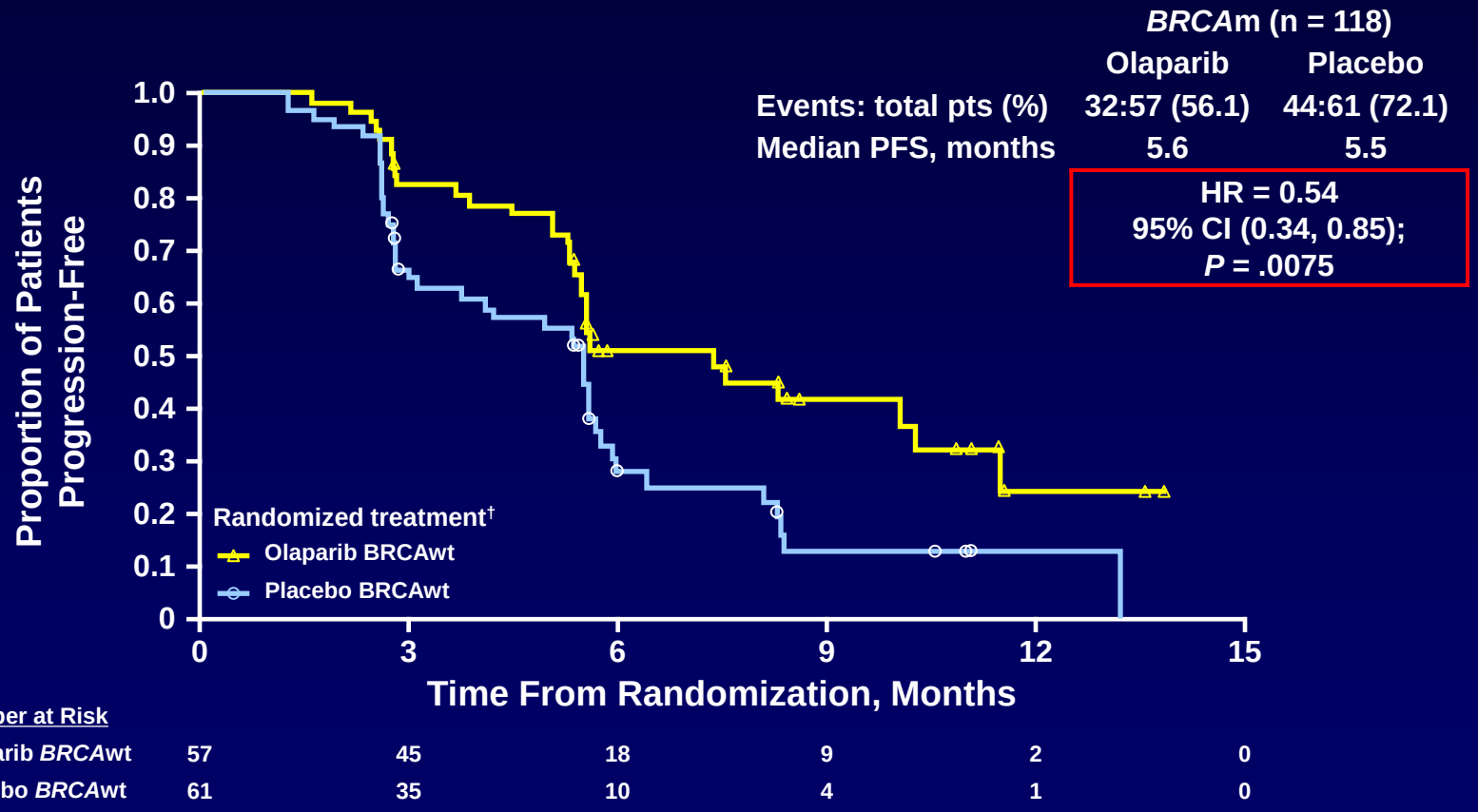
- 136 (51.3%) patients had a known deleterious *BRCA*m (*BRCA*m dataset)
- 118 (44.5%) patients were defined as *BRCA1/2* wildtype for this analysis
- 11 (4.2%) patients had neither a tumor nor a germline result available



*Includes patients with germline and/or somatic mutations; †patients were treated until disease progression

Ledermann J, et al. *Lancet Oncol.* 2014;15(8):852-861.

PFS in *BRCA*wt Patients



Number at Risk

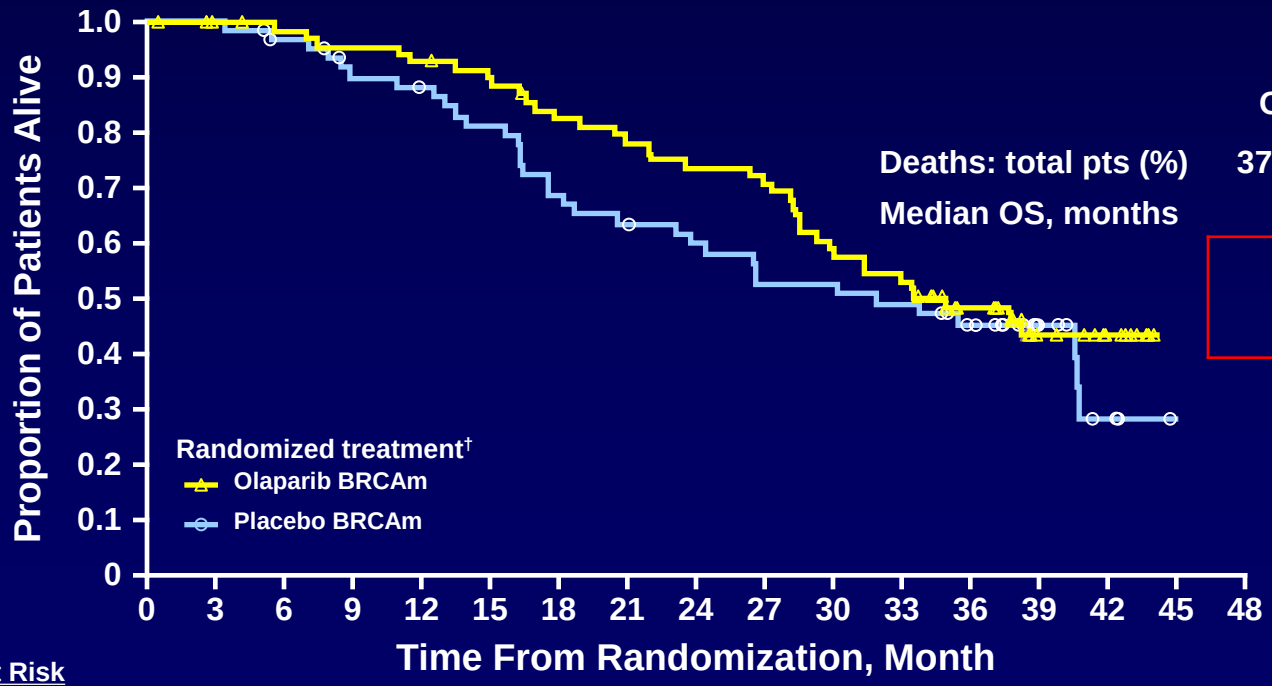
Olaparib *BRCA*wt	57	45	18	9	2	0
Placebo *BRCA*wt	61	35	10	4	1	0

*BRCA*wt, wildtype (includes patients with no known *BRCA*m or a mutation of unknown significance);
†Patients were treated until disease progression

Ledermann J, et al. *Lancet Oncol.* 2014;15(8):852-861.

OS in Patients With a *BRCA1/2* Mutation*

- An interim OS analysis was performed after 154 deaths (58% maturity)
- No statistically significant benefit was observed in the overall population (HR = 0.88, 95% CI, 0.64–1.21, *P* = .442) or in patients with a *BRCA*m



	*BRCA*m (n = 136)	
	Olaparib	Placebo
Deaths: total pts (%)	37:74 (50.0)	34:62 (54.8)
Median OS, months	34.9	31.9

HR 0.73
95% CI (0.45, 1.17)
P = .192

Number at Risk

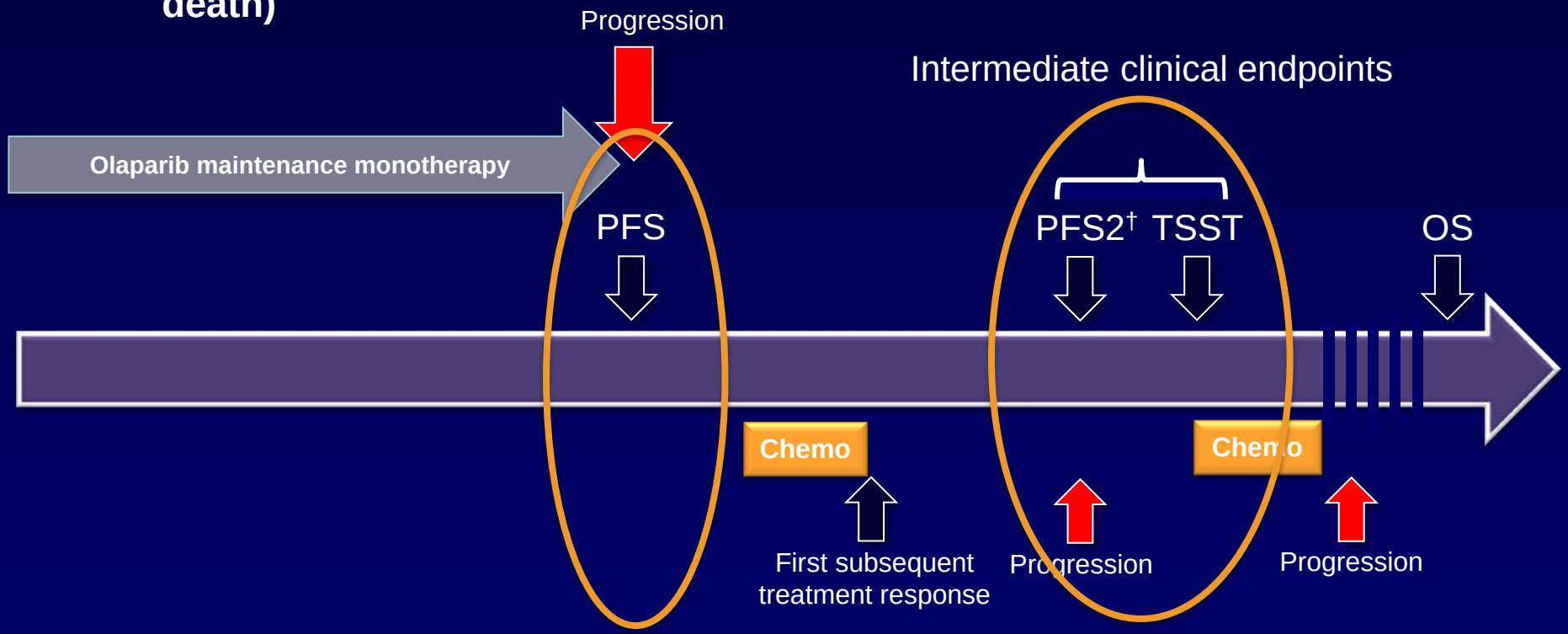
Olaparib *BRCA*m	74	71	69	67	65	62	56	53	50	48	39	36	26	12	7
Placebo *BRCA*m	62	62	58	52	50	46	39	36	33	29	29	27	21	10	4

*Includes patients with germline and/or somatic mutations; †patients were treated until disease progression

Ledermann J, et al. *Lancet Oncol.* 2014;15(8):852-861.

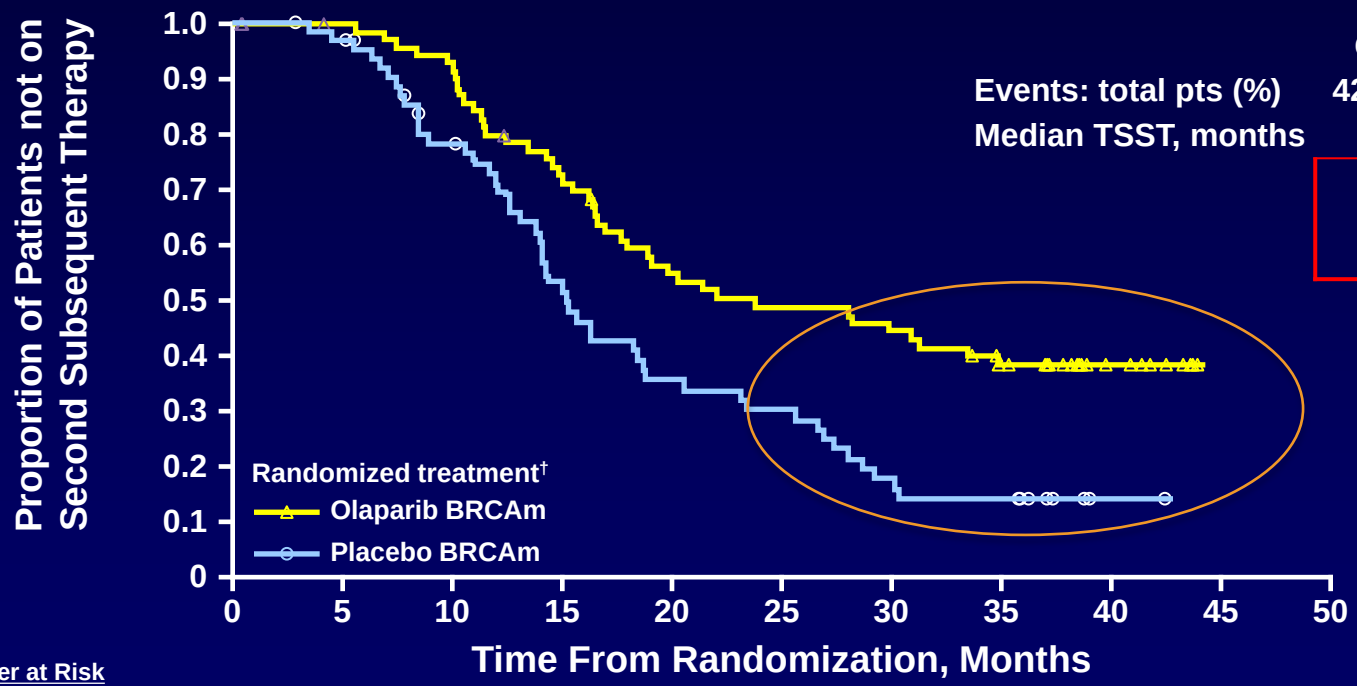
Time to Second Subsequent Therapy – A New Exploratory Endpoint

- **TSST (time from randomization to second subsequent therapy or death)**
- **PFS2 (time from randomization to second objective disease progression or death)**



All patients who received treatment were included in exploratory endpoint analyses

TSST in Patients With a *BRCA1/2* Mutation*



	BRCAm (n = 136)	
	Olaparib	Placebo
Events: total pts (%)	42:74 (56.8)	49:62 (79.0)
Median TSST, months	23.8	15.2

HR 0.44
95% CI (0.29, 0.67)
P = .00013

Number at Risk

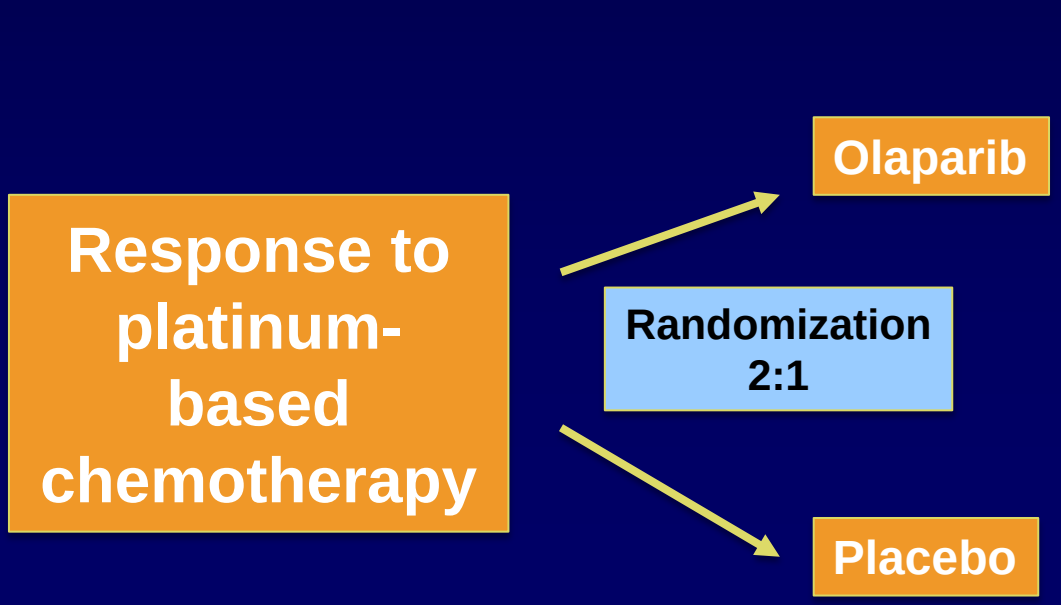
Olaparib *BRCA*m	74	70	65	50	37	33	30	23	9	0	0
Placebo *BRCA*m	62	60	45	30	20	17	10	8	1	0	0

*Includes patients with germline and/or somatic mutations; †patients were treated until disease progression

Ledermann J, et al. *Lancet Oncol.* 2014;15(8):852-861.

SOLO-1 & SOLO 2 Program *BRCA*m Population Only

First-line maintenance or maintenance in 'platinum-sensitive' setting



SOLO-1 344 patients
2 years

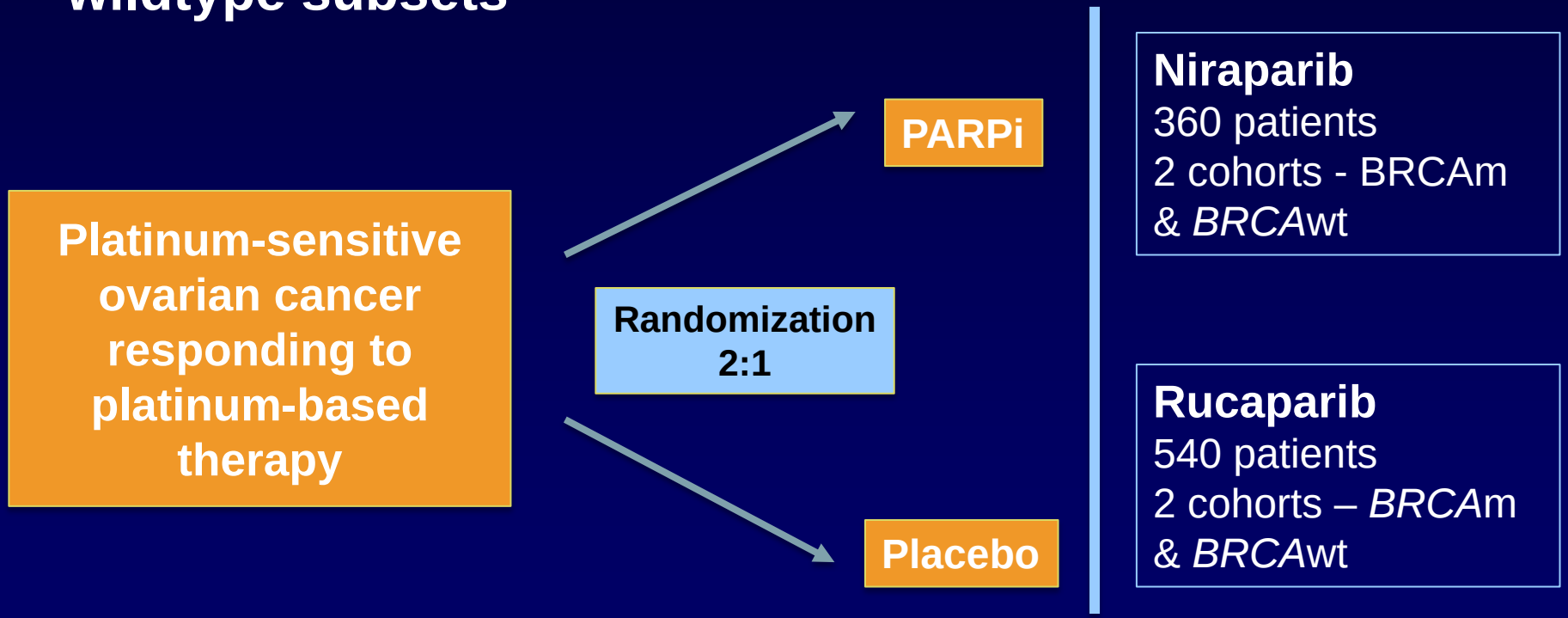
PFS/PFS2/OS + QoL

SOLO-2 264 patients
to progression

PFS/PFS2/OS + QoL

NOVA and ARIEL3 Program

Both studies include a *BRCA*m and high-grade serous wildtype subsets



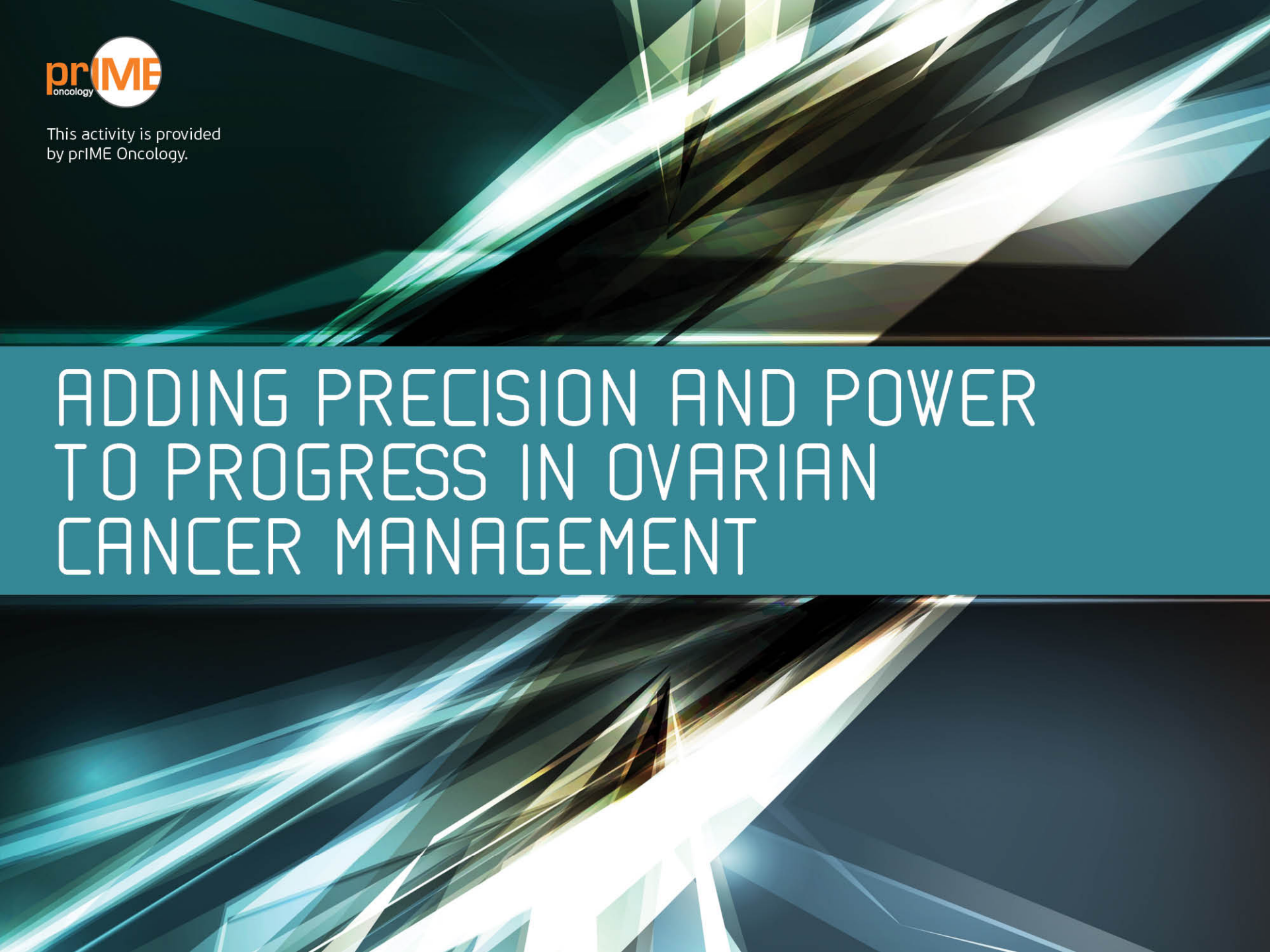
Identification of companion diagnostic marker to select patients with HRD, most likely to benefit

Maintenance Antiangiogenic Therapy

- Moderate clinical benefit from antiangiogenic therapies in first- and second-line maintenance
  - Some clinical subgroups may have greater benefit
  - No clear biomarkers to predict benefit
- Toxicity of oral agents needs to be balanced against inconvenience of intravenous therapy
- QoL studies with bevacizumab and cediranib have not shown a detriment

Maintenance PARP Inhibitor Therapy

- **PARP inhibitor maintenance therapy**
  - **Marked effect on delaying progression of patients with ‘platinum-sensitive’ disease, especially in *BRCA*m population**
  - **Significant but lesser effect in *BRCA* wild-type patients with high-grade serous cancer**
- **Prolonged exposure does not impair QoL; well tolerated by most patients**



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ADDING PRECISION AND POWER TO PROGRESS IN OVARIAN CANCER MANAGEMENT