Personalized Treatment for Relapsed Ovarian Cancer- What Is the Evidence?

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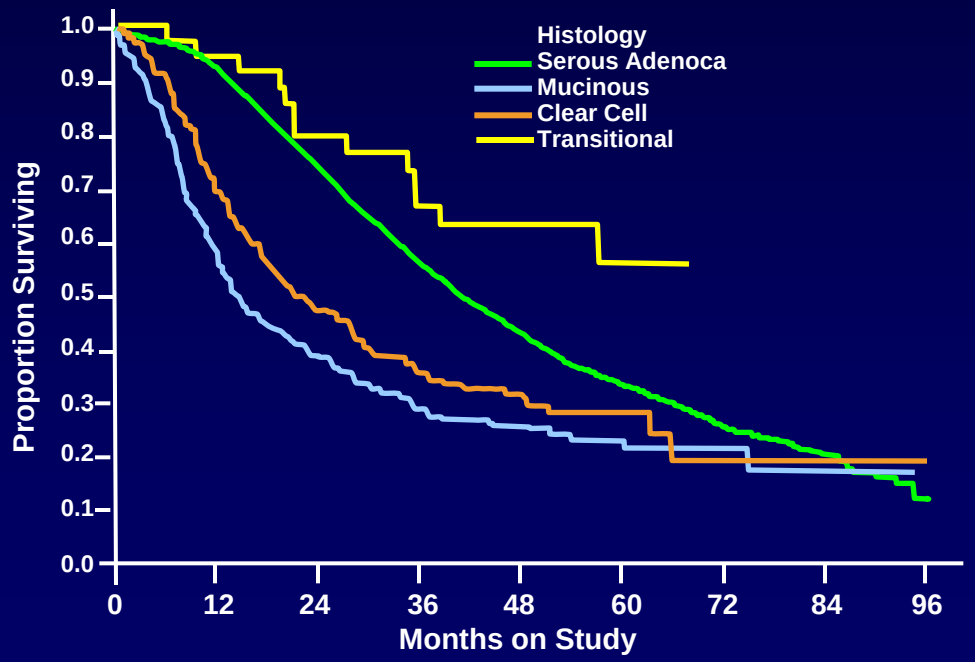
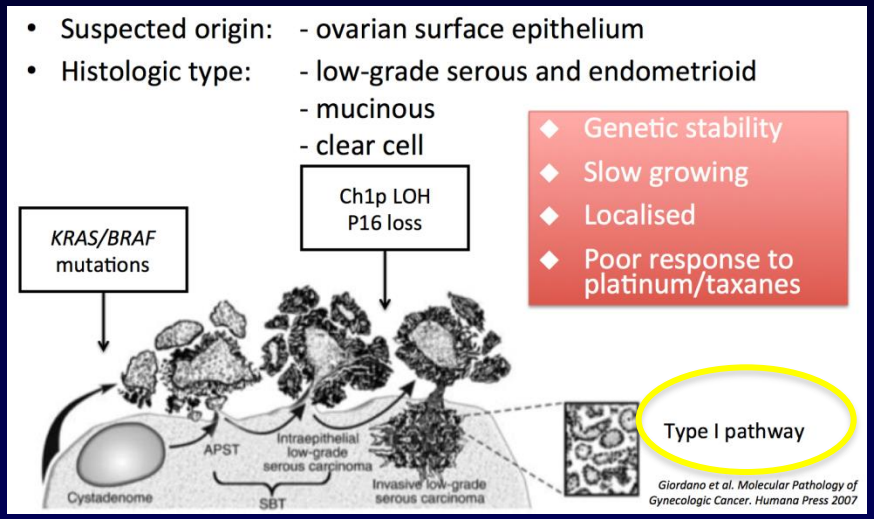
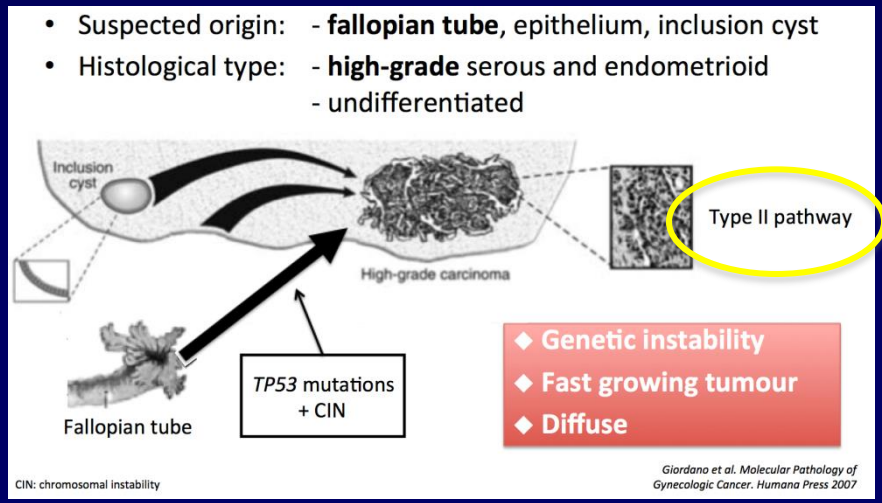
Ovarian Cancer Not One Disease

8704 patients from 7 randomized trials



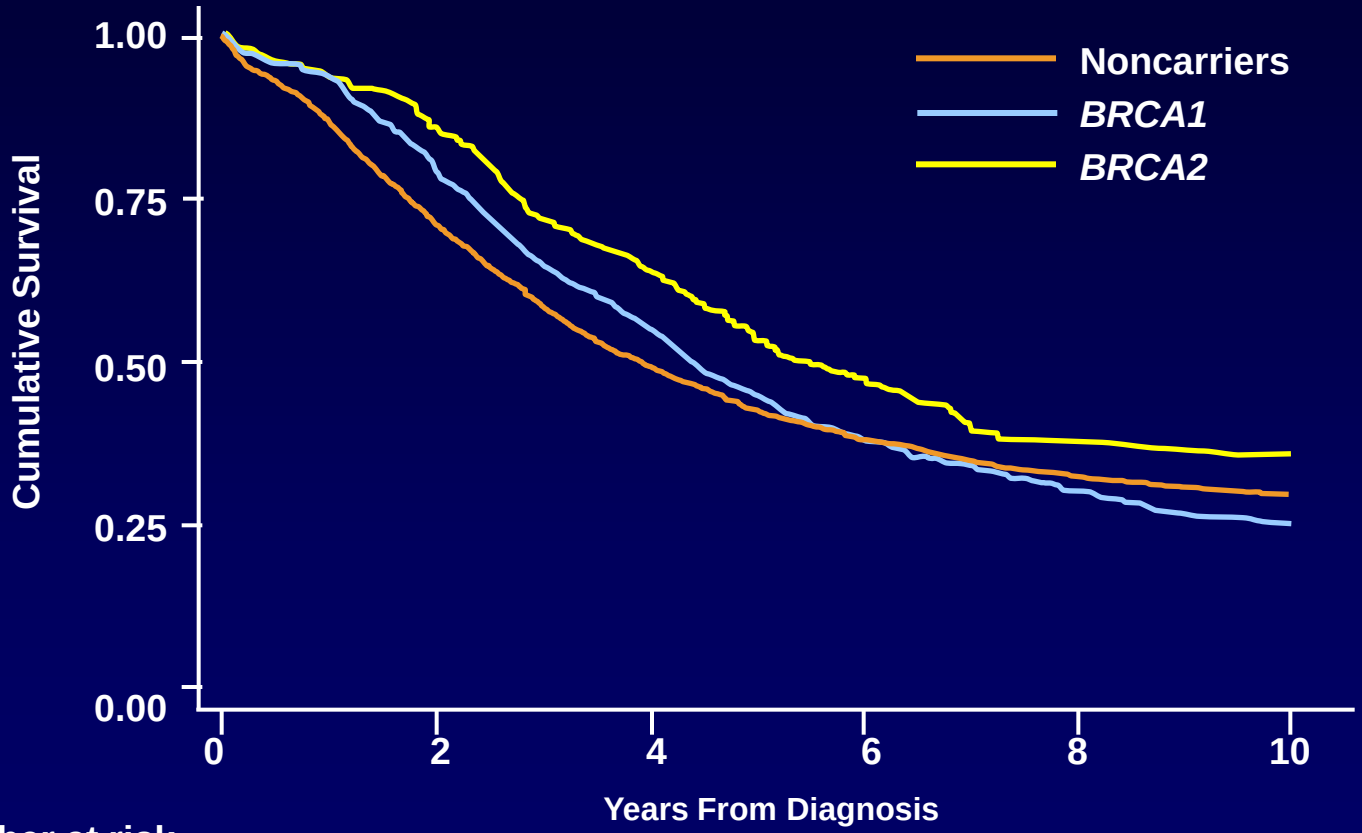
Mackay HJ, et al. *Int J Gynecol Cancer.* 2010;20(6):945-952.





But we still give all patients the same treatment!

Survival of Patients With Ovarian Cancer and *BRCA* Mutations



Number at risk						
Noncarriers	1924	2914	2295	1657	1120	812
Carriers						
BRCA1	404	676	499	323	198	118
BRCA2	162	278	239	152	86	

Candido Dos Reis FJ, et al. *Clin Cancer Res.* 2014 Nov 14. [Epub ahead of print].

Examples of Predictive Cancer Biomarkers in Solid Tumors

Tumor Type	Biomarker
Breast	ER; HER2/*neu*
Colorectal	EGFR; KRAS; UGT1A1
Gastric	HER2/*neu*
GIST	c-KIT
GBM	EGFR; PDGFRα
Lung	ALK; EGFR; KRAS; ROS1; PDL1
Medullary thyroid	RET
Melanoma	BRAF; PDL1

EGFR, epidermal growth factor receptor; ER, estrogen receptor; GBM, glioblastoma; GIST, gastrointestinal stromal tumor; PDGFRα, platelet-derived growth factor receptor alpha; PDL1, programmed death ligand 1

The Cancer Genome Atlas (TCGA) Project High-Grade Serous Ovarian Carcinoma

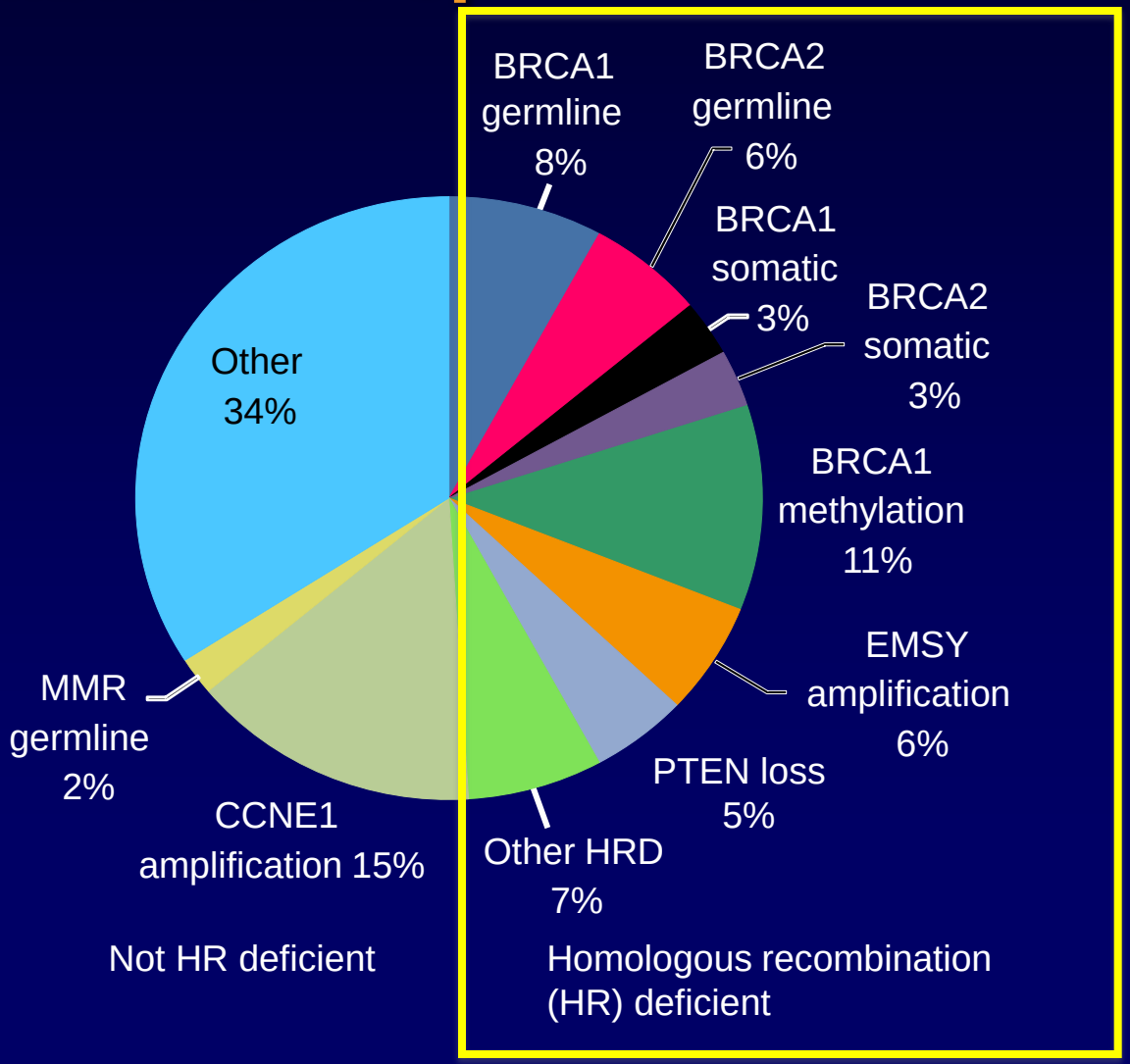
- ***TP53*** **mutations present in 96%**
- **Significant occurrence of mutation in 9 other genes but prevalence low**
  - **Including:** ***NF1; BRCA1; BRCA2; RB1; CDK12***

- **Huge genomic disarray: Very high number of structural chromosomal abnormalities. Significant focal DNA copy number aberrations and promoter methylations events**

- **Genes involved in homologous recombination are frequently affected → suggests high sensitivity to PARP inhibitors**

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

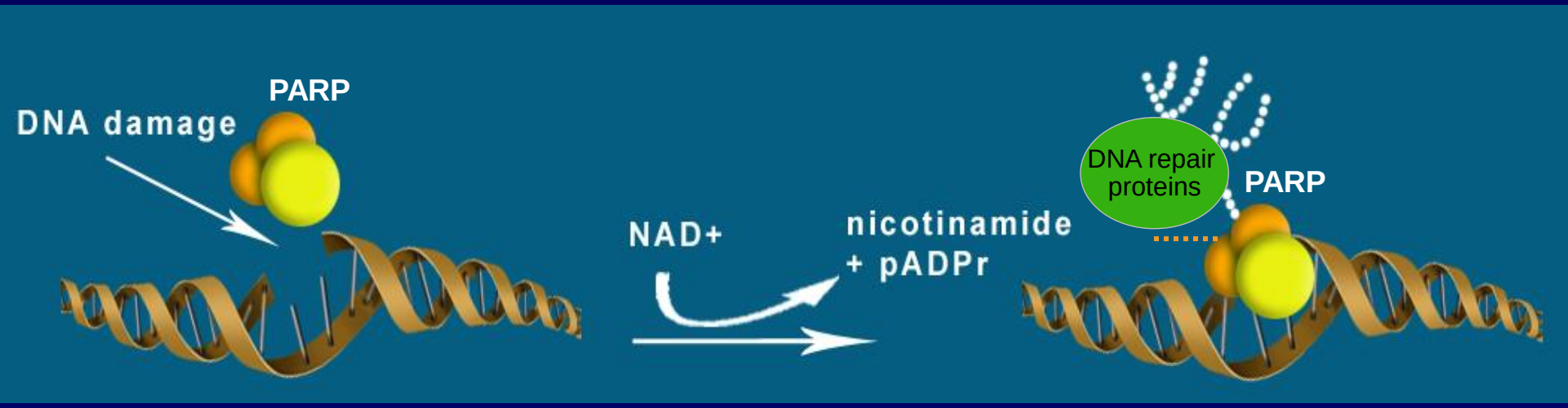
The HR Phenotype and the Potential of PARP Inhibitors in Sporadic Ovarian Cancer



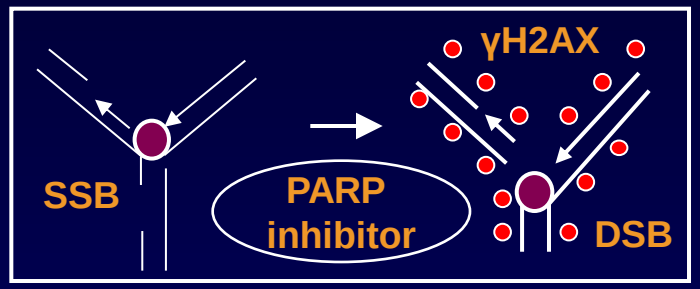
Levine D. 2011. The Cancer Genome Atlas, Molecular Profiling of Serous Ovarian Cancer. Data retrieved from cBio Cancer Genomics Portal http://www.cbioportal.org/public-portal/. Accessed 12 August 2012.

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

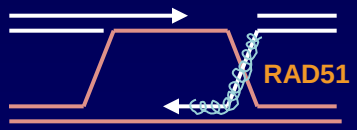


PARP Inhibition and Tumor-Selective Synthetic Lethality



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

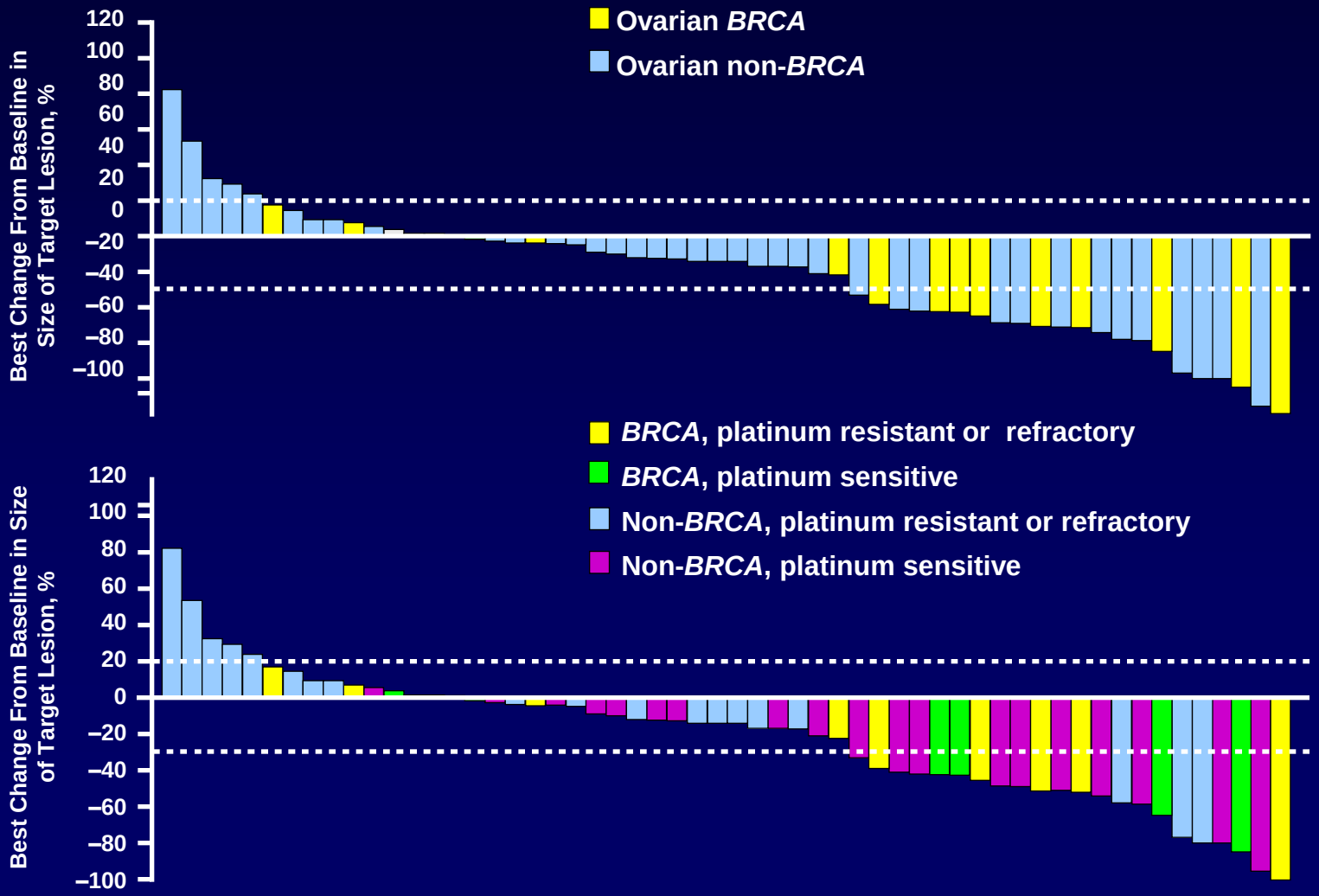
Farmer H, et al. *Nature.* 2005;434(7035):917-921.
Bryant HE, et al. *Nature.* 2005;434(7035):913-917.

Phase I and II Studies With Olaparib, an Orally Active PARP Inhibitor

	Olaparib Phase I and *BRCA* Mutation Expansion Studies[1,2]	Olaparib Phase II *BRCA*	Olaparib Phase II *BRCA*
Olaparib dose	200 mg bid	400 mg bid	100 mg bid
RECIST CR/PR	14/50 (28%)	11/33 (33%)	3/24 (13%)
SD	3/50 (6%) (≥4 months)	12/33 (36%) (8 weeks)	14/24 (58%) (8 weeks)
Median duration of response	~214 d	290 d	269 d

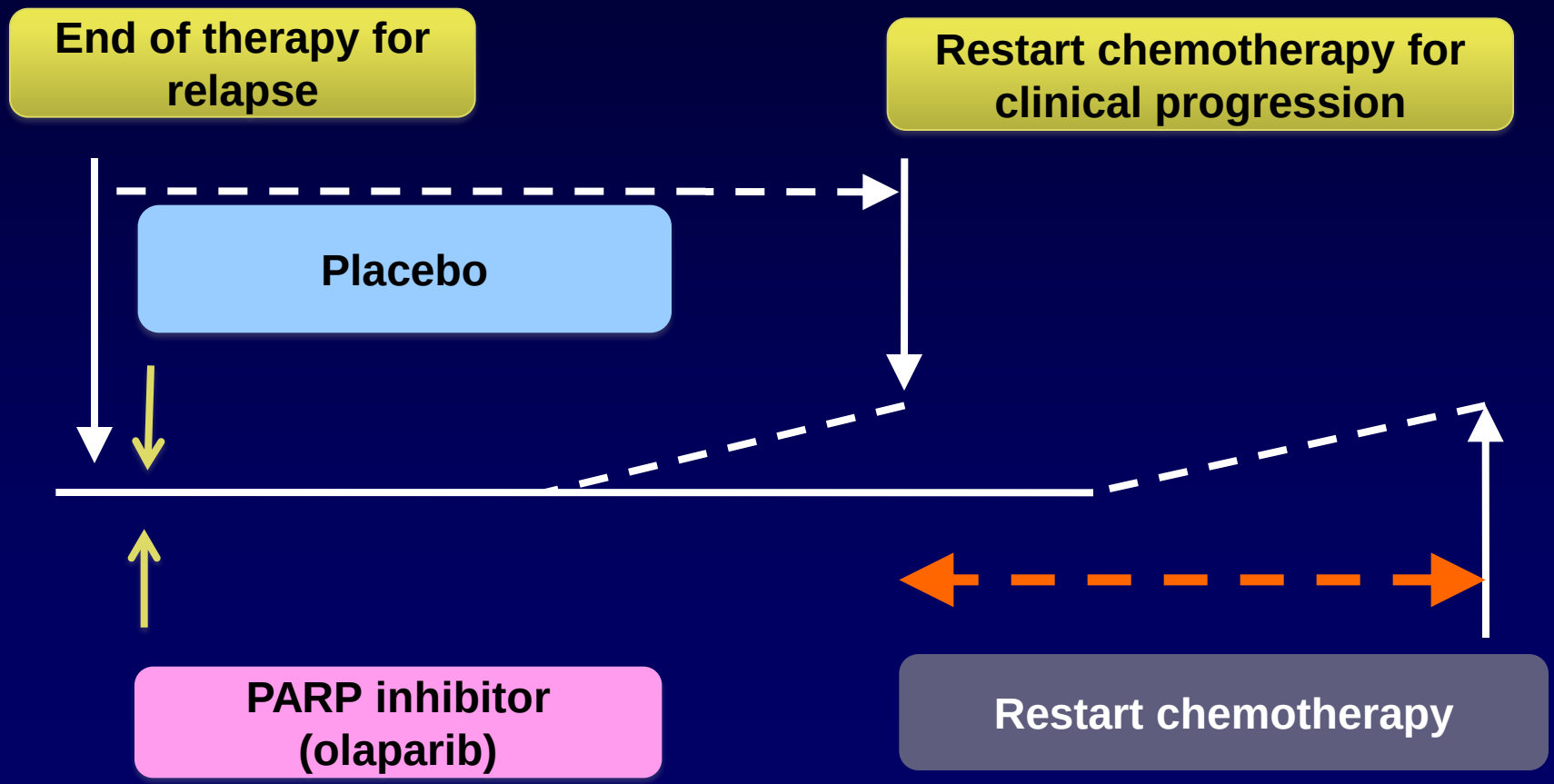
1. Fong PC, et al. *N Engl J Med* 2009;361(2):123-134. 2. Fong PC, et al. *J Clin Oncol.* 2010;28(15):2512-2519
3. Audeh MW, et al. *Lancet* 2010;376(9737):245-251.

Olaparib in *BRCA* and Non-*BRCA* Ovarian Cancer



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

Treatment Pathway for Recurrent Ovarian Cancer



Randomized Maintenance Trials

Randomized Trial of Maintenance Olaparib in Platinum-Sensitive High Grade Serous Relapsed Ovarian Cancer - 'Study 19'

Study aim and design

Patients:

- **Platinum-sensitive high-grade serous ovarian cancer**
- ≥2 previous platinum regimens
- Last chemotherapy was platinum-based to which they had a maintained PR or CR prior to enrolment
- Stable CA-125

265 patients

Olaparib 400 mg PO bid

Randomized 1:1

Placebo PO bid

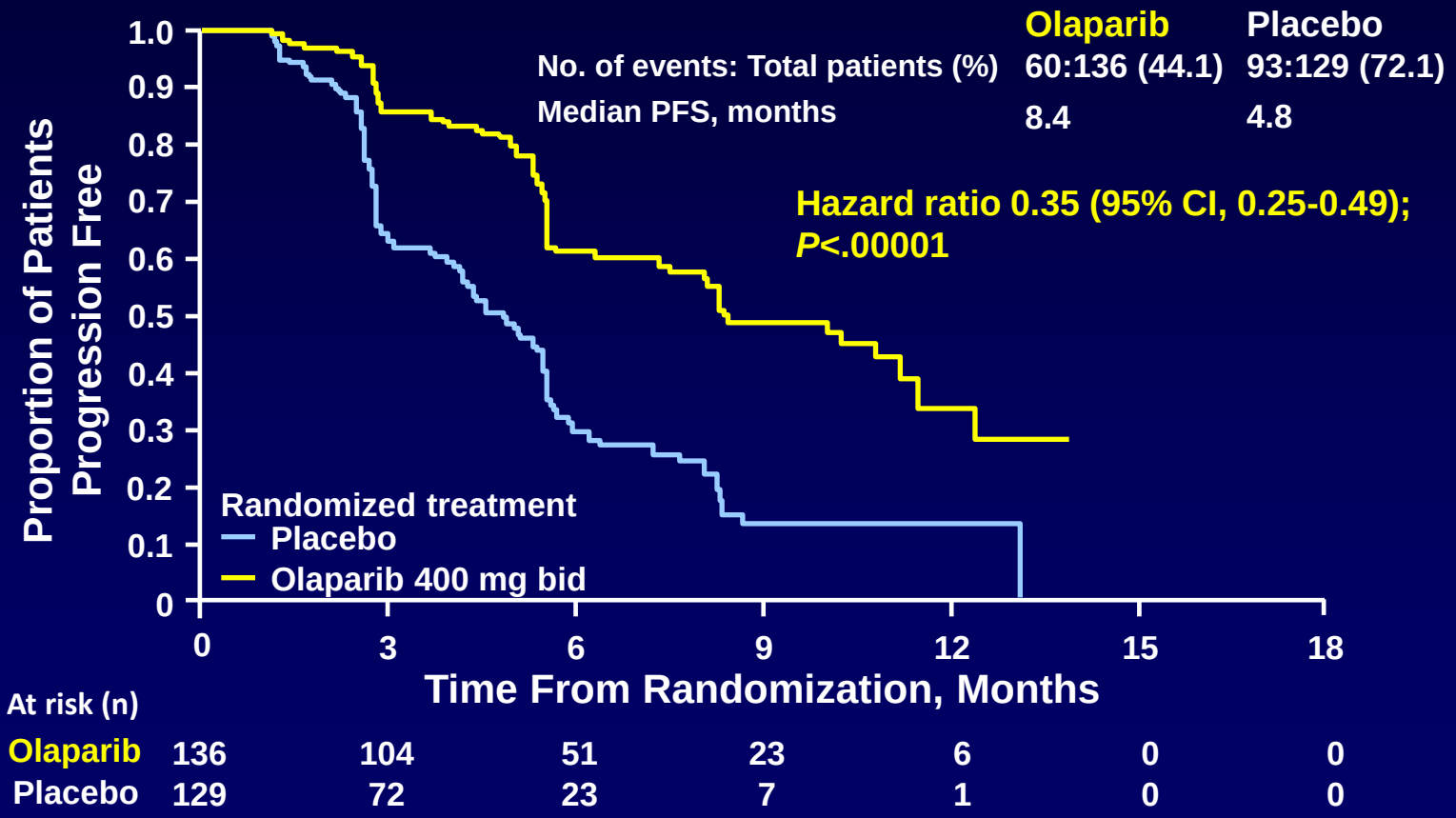
Treatment until disease progression

Sept 2008- Feb 2010
16 countries; 82 sites

Primary endpoint :
Progression-free survival (PFS)

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

Progression-Free Survival



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

Common Adverse Events*

	Olaparib 400 mg bid (n = 136)		Placebo (n = 128)	
	Percentage of Patients			
Adverse Event			Grade 1/2	Grade 3/4
Any event	61	35	70	20
Nausea	66	2	35	0
Fatigue	42	7	34	3
Vomiting	29	2	13	1
Diarrhea	21	2	20	2
Headache	18	0	11	1
Decreased appetite	18	0	13	0
Abdominal pain	16	2	23	3
Anemia	12	5	4	1
Dyspepsia	16	0	9	0

*Adverse events graded according to maximum CTCAE version 3.0 grade, experienced by >15% of patients in either treatment group

Ledermann J, et al. *N Engl J Med.* 2012;366(15):1382-1392. Ledermann JA, et al. *J Clin Oncol.* 2011;29(suppl); Abstract 5003.

Toxicity and Tolerability

	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

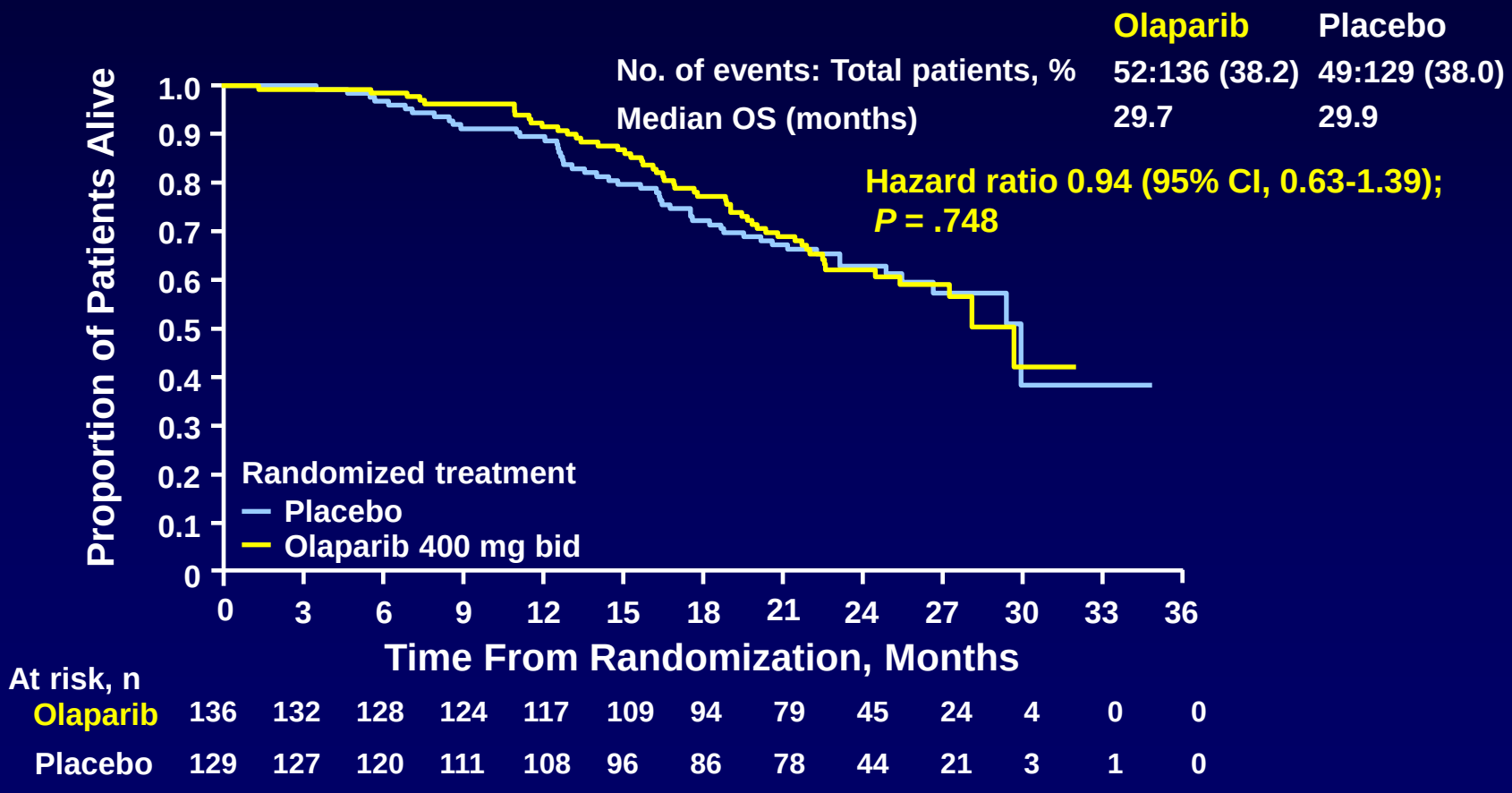
No detrimental impact on HRQoL (Treatment Outcome Index of FACT-0) compared with placebo

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

AE, adverse event; *BRCAm,* BRCA mutation; HRQoL, health-related quality of life

Ledermann JA, et al. *J Clin Oncol.* 2011;29(28):3798-3804. Ledermann J, et al. *Ann Oncol*. 2014;25(suppl 4): Abstract 885PD.

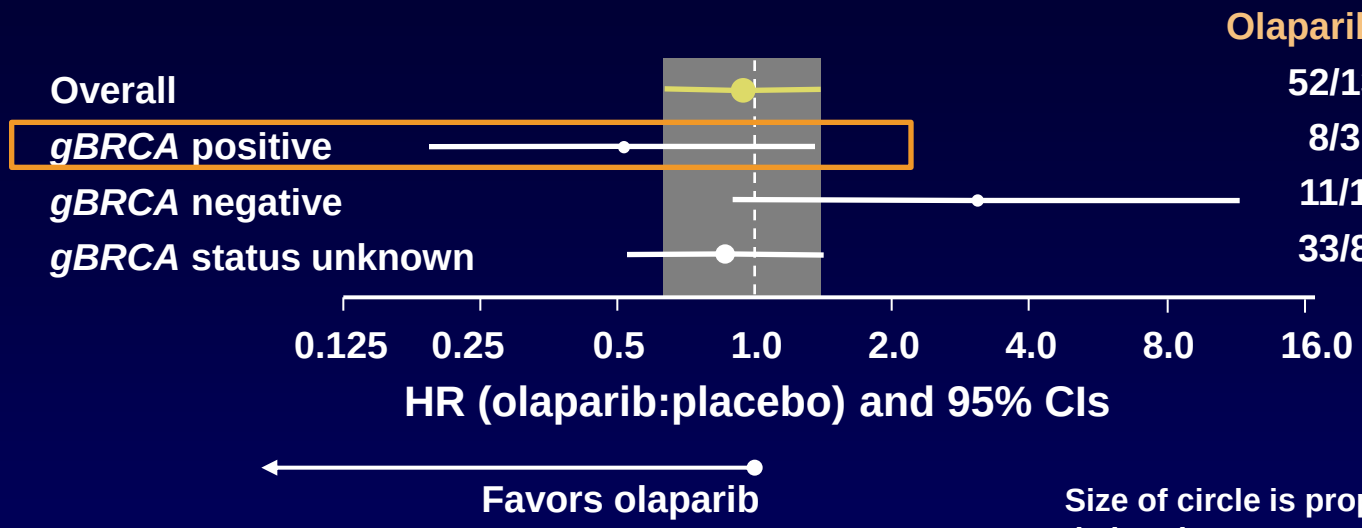
Overall Survival (OS): Interim Analysis*



*Performed at 38% maturity

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

BRCA Status



Size of circle is proportional to number of events
Purple band represents 95% CI for overall population

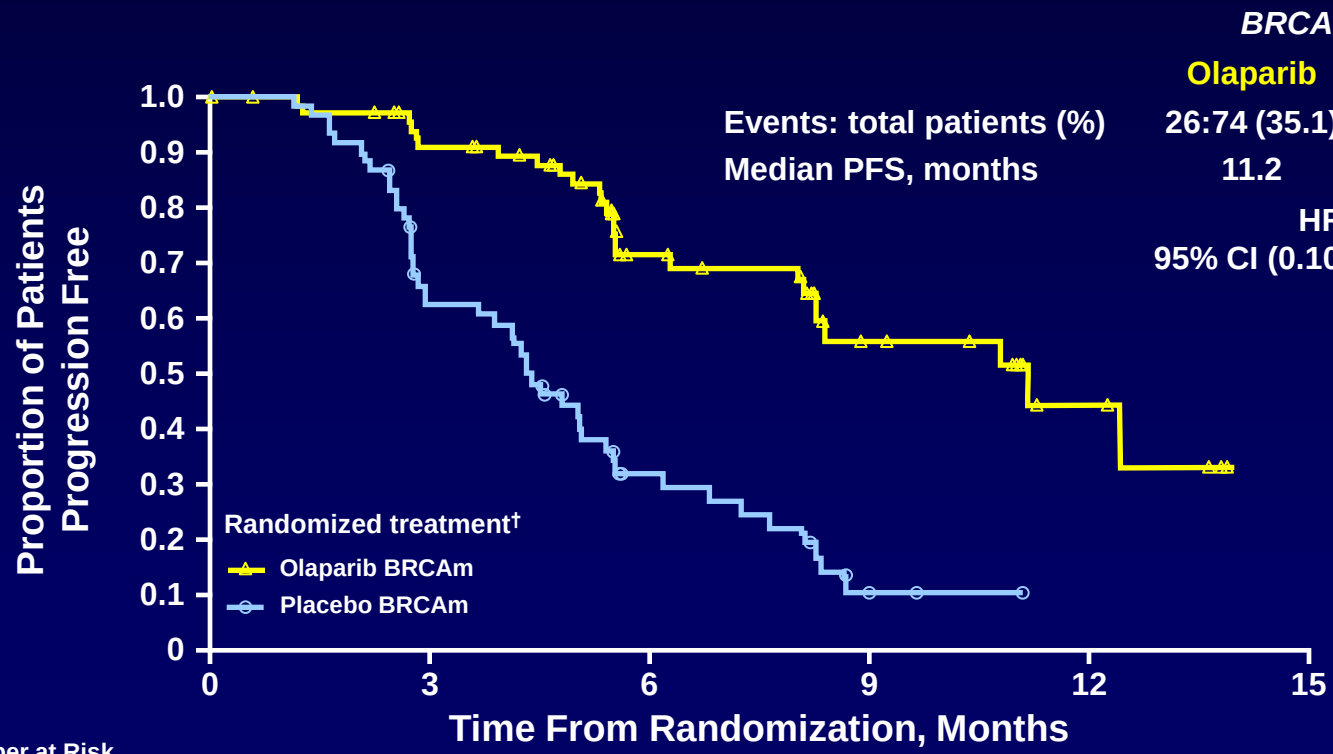
***BRCAm* status was not required for study entry, but was known for 97/265 patients (36.6%)**

	Olaparib (n = 136)	Placebo (n = 129)
BRCA mutation status, n (%)*		
BRCA1	25 (18)	20 (16)
BRCA2	6 (4)	7 (5)
BRCA1 & BRCA2	0	1 (1)
Known negative	18 (13)	20 (16)
Unknown	87 (64)	81 (63)

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

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 *BRCA1/2wt* for this analysis**
- **11 (4.2%) patients had neither a tumor nor a germline result available**



Number at Risk

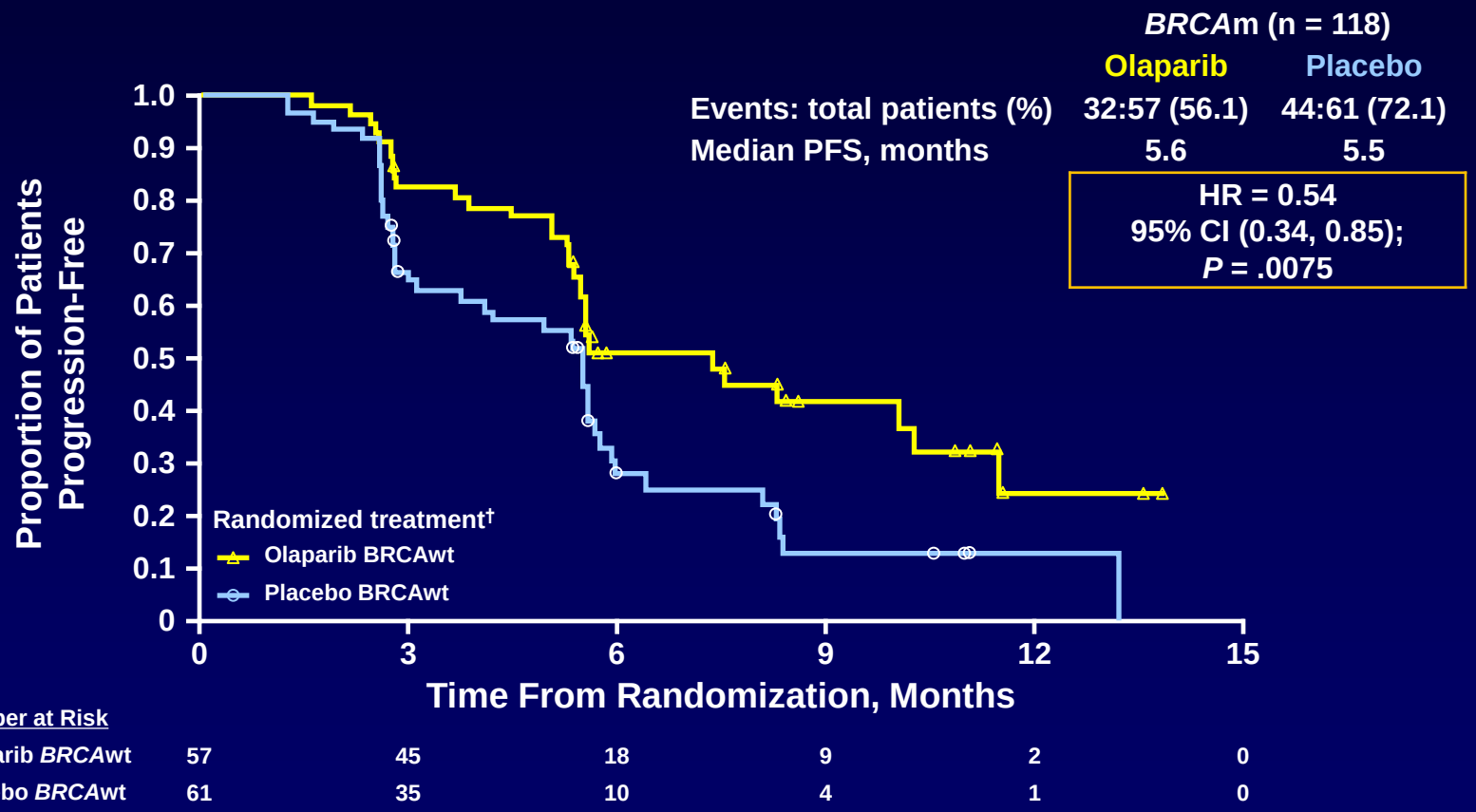
Olaparib *BRCA*m	74	59	34	15	5	0
Placebo *BRCA*m	62	35	13	2	0	0

BRCAwt, BRCA wildtype

*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 *BRCAwt* Patients



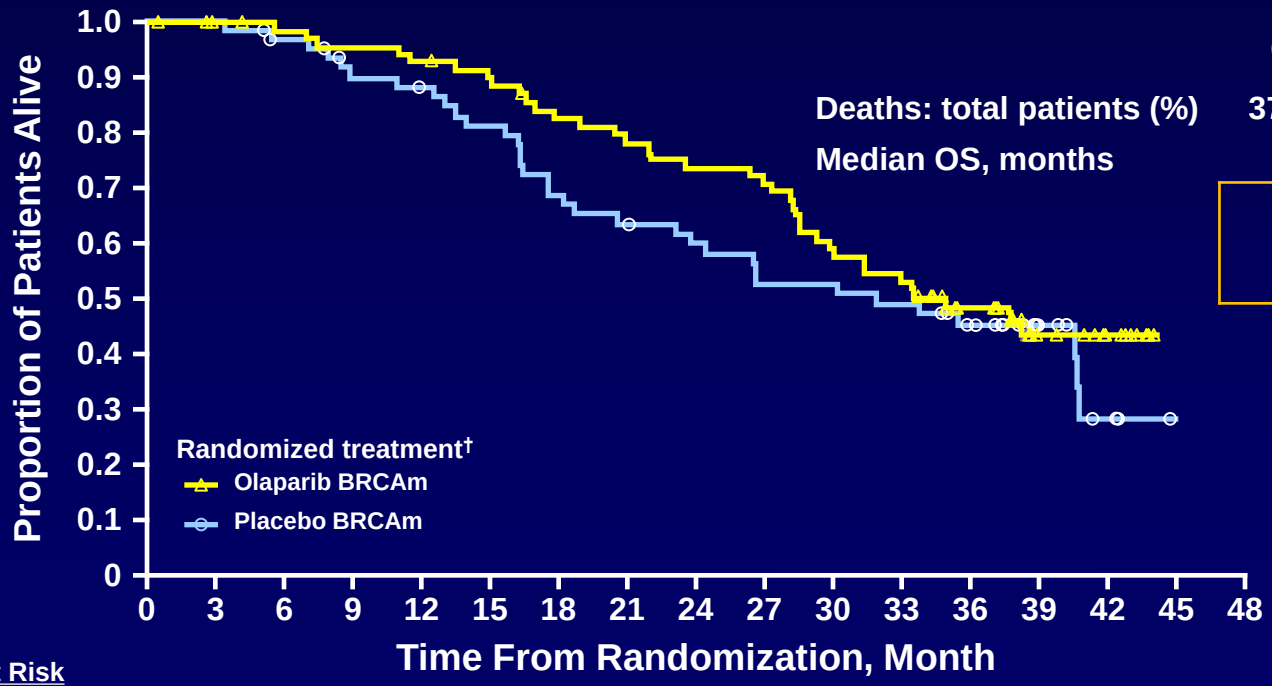
BRCAwt includes patients with no known *BRCA*m or a mutation of unknown significance

†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 patients (%)	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

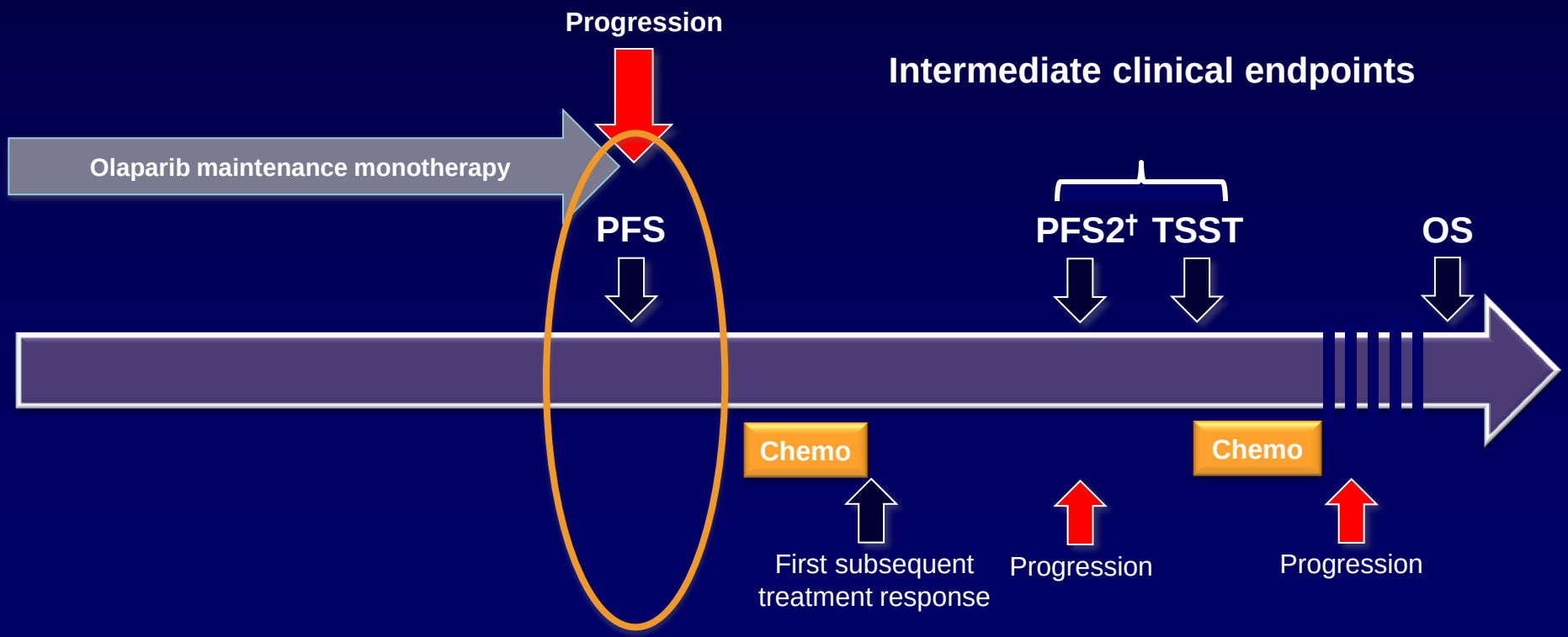
Olaparib *BRCA*m	74	71	69	67	65	62	56	53	50	48	39	36	26	12	7
Placebo *BRCA*m	62	62	58	52	50	46	39	36	33	29	29	27	21	10	4

*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

Time to Second Subsequent Therapy – A New Exploratory Endpoint

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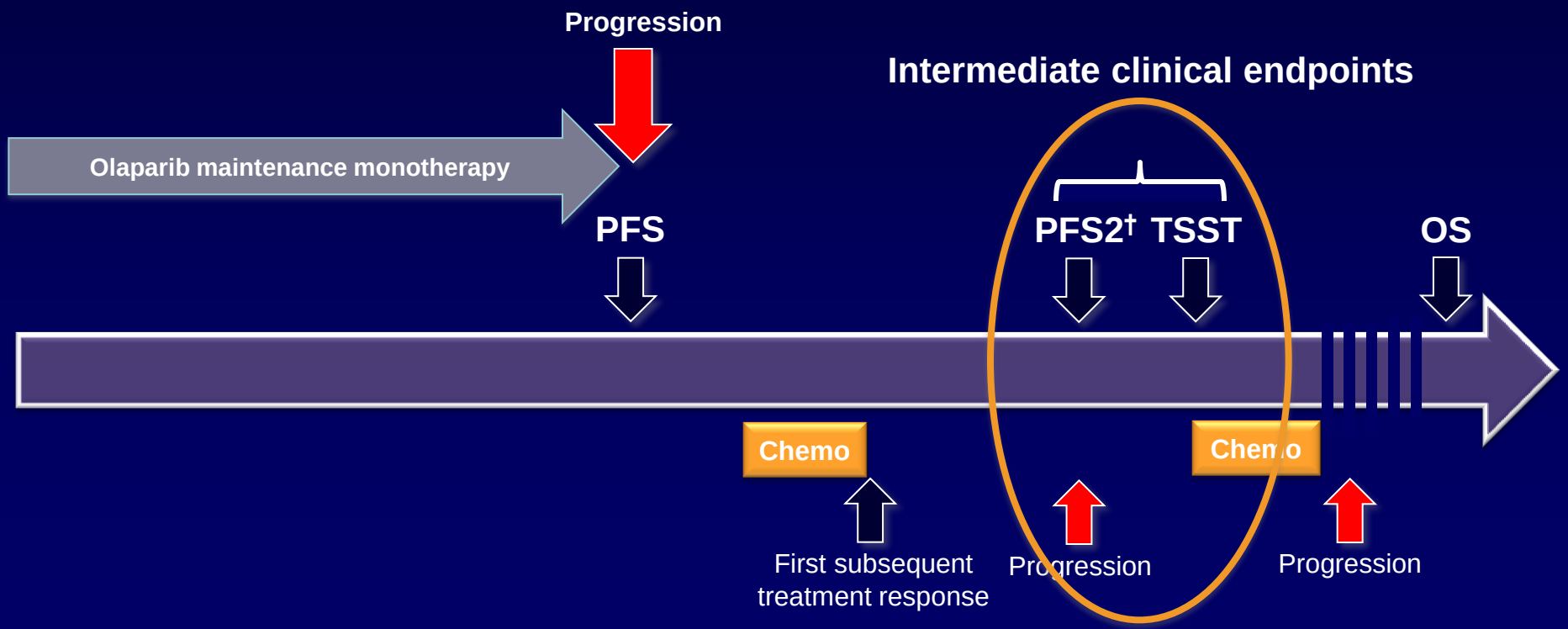
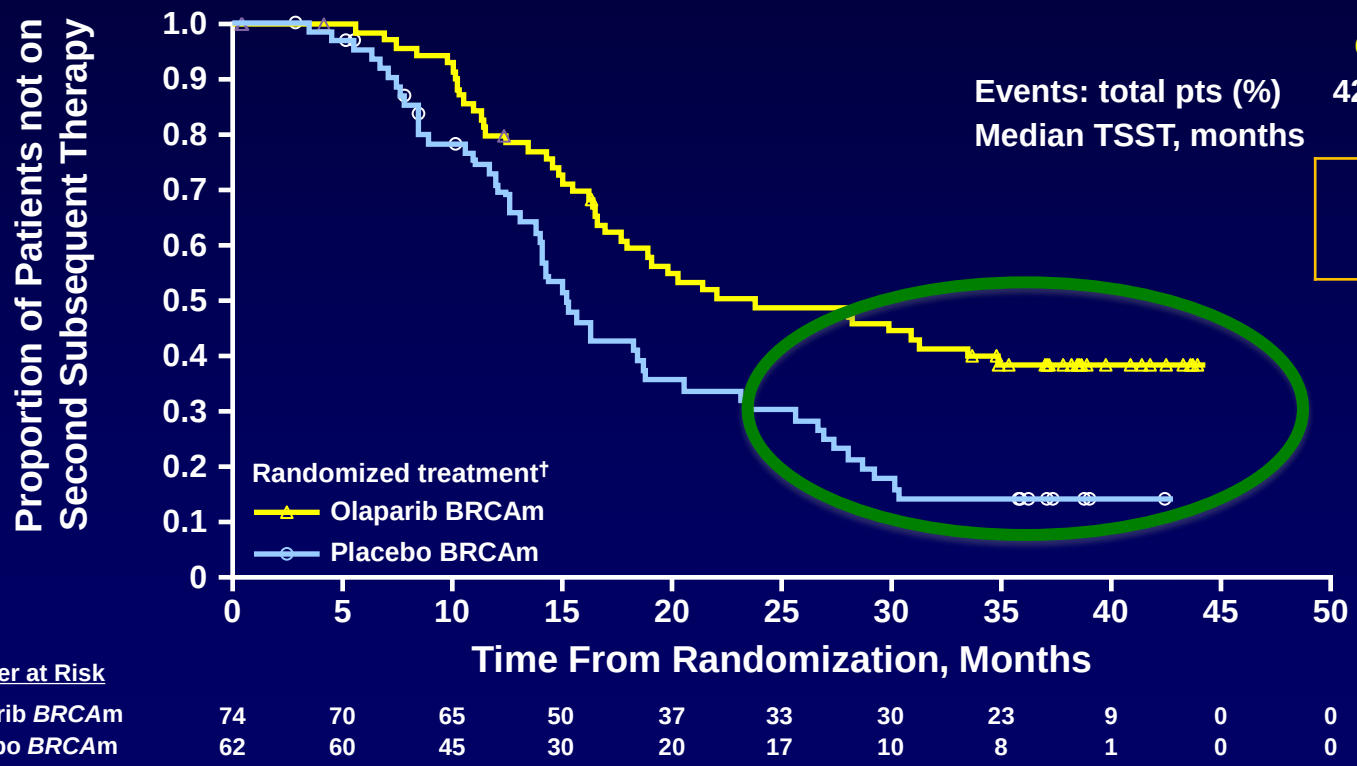


All patients who received treatment were included in exploratory endpoint analyses

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

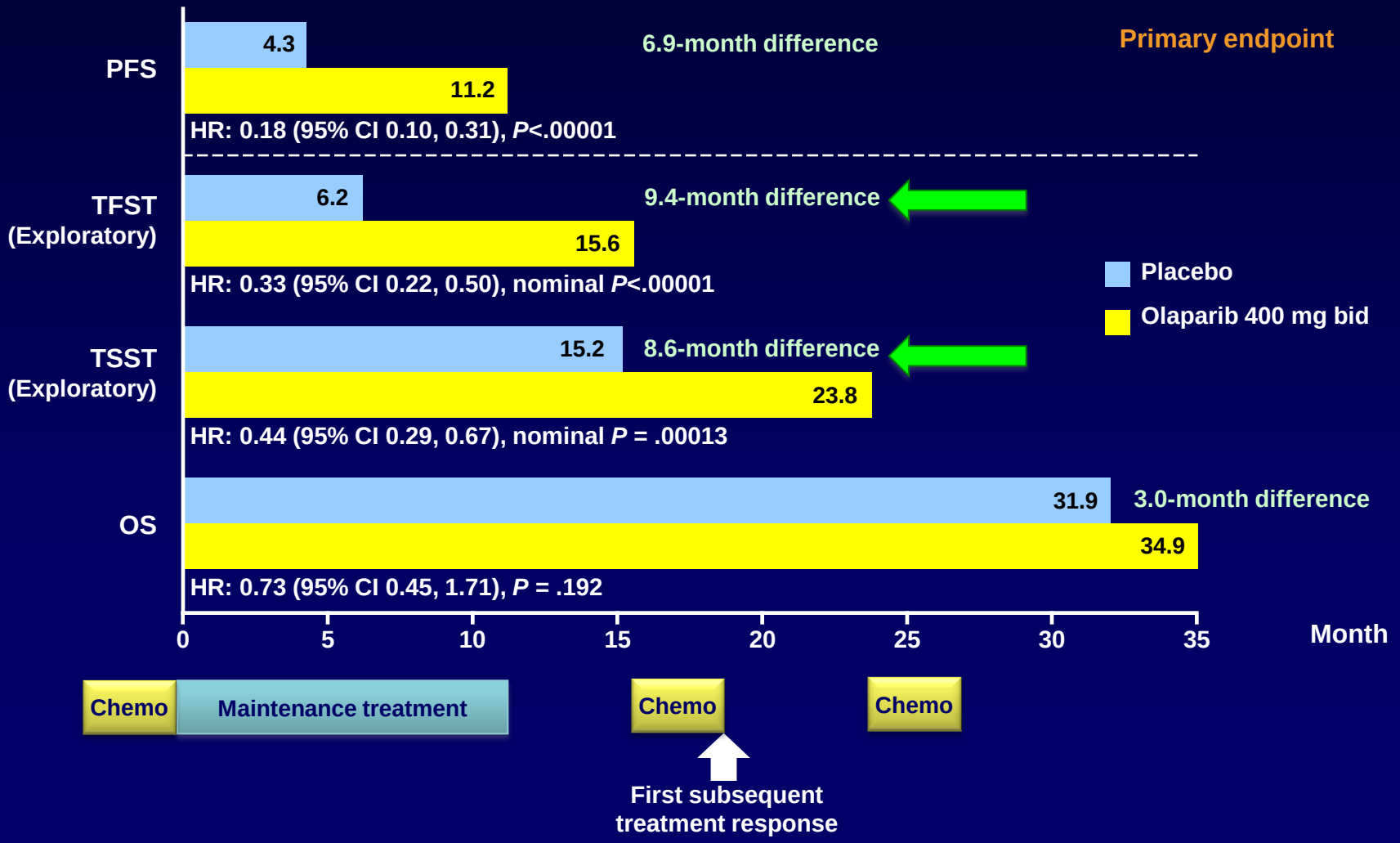
Number at Risk

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.

Overview of Efficacy Analyses in Patients With a *BRCA1/2* Mutation

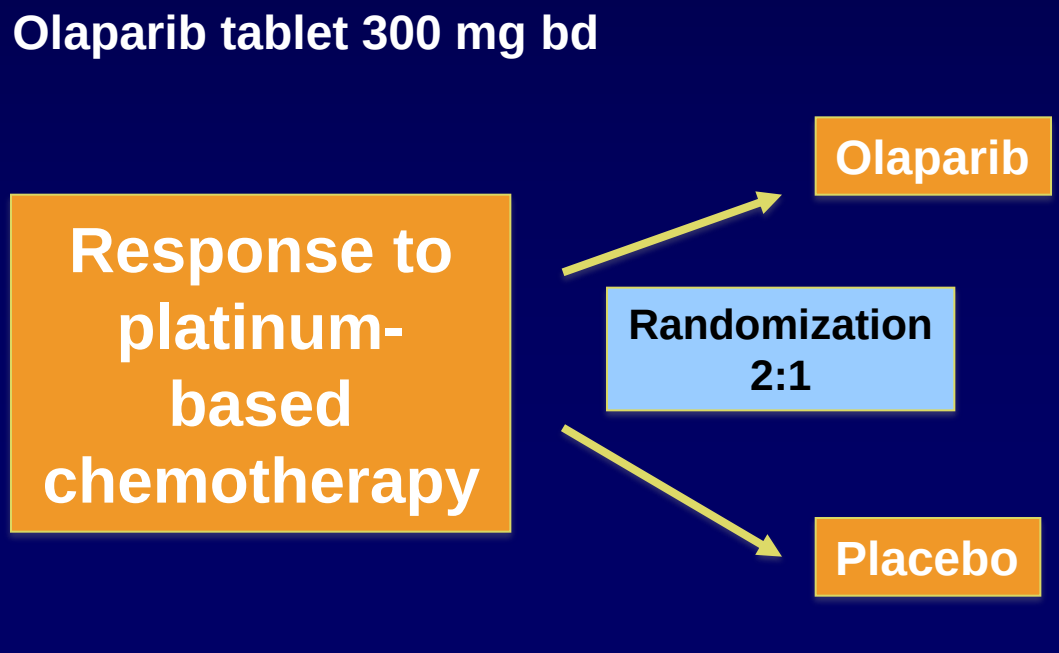


Ledermann J, et al. *Lancet Oncol.* 2014;15(8):852-861.

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

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

Olaparib tablet 300 mg bd



SOLO-1 344 patients
2 years

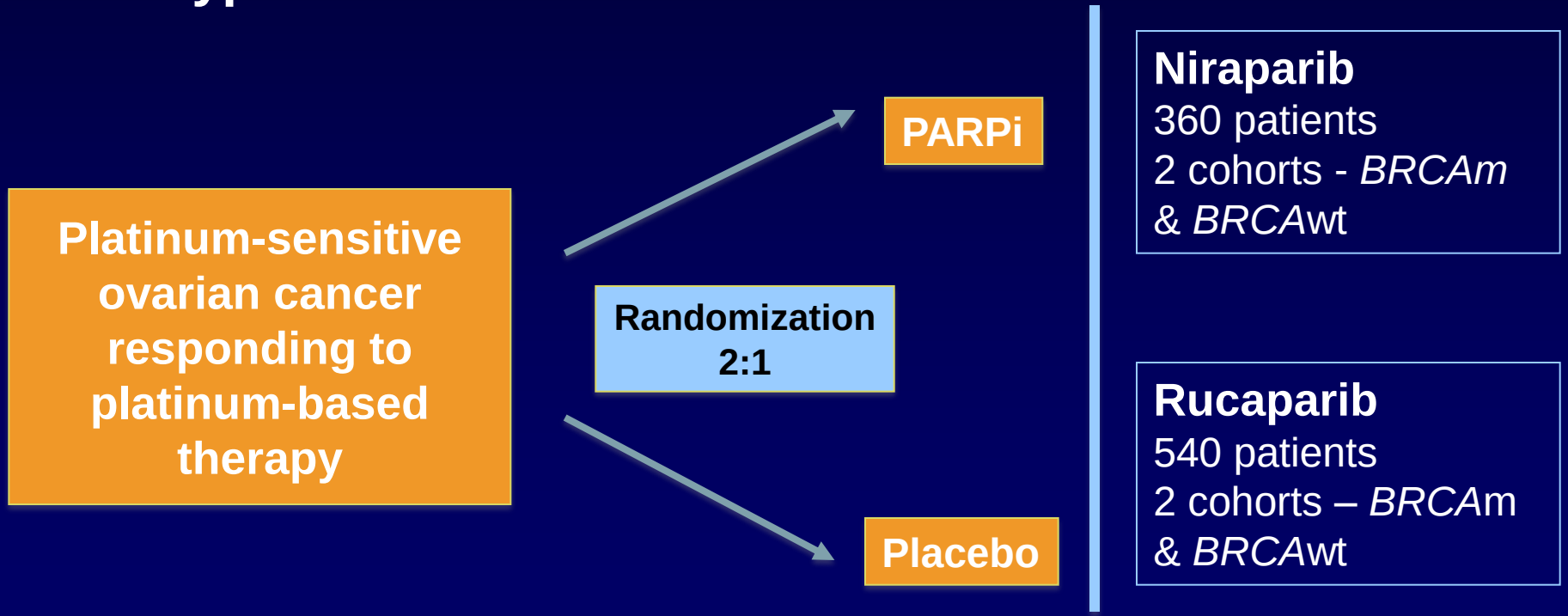
PFS/PFS2/OS + QoL

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

HRD, homologous recombination deficiency

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 *BRCAwt* patients with high-grade serous cancer**
- **Prolonged exposure does not impair QoL; well tolerated by most patients**
- **Ongoing trials of 3 different PARP inhibitors as maintenance therapy for ovarian cancer**

Olaparib

- **Now licensed by the European Medicines Agency (EMA) for maintenance therapy of relapsed high grade serous ovarian/ tubal/peritoneal cancer after a response to platinum-based chemotherapy in *BRCA*-mutated ovarian cancer**
- **First target specific therapy in ovarian cancer**
- **Testing for a *BRCA* mutation in all patients is now essential. Mutations are seen in ~20% of high-grade serous disease and a significant number of *BRCAm*-positive patients do not have a family history of breast/ovarian cancer**

Integrating New Therapies Into Ovarian Cancer Management: Does *BRCA* Status Matter?