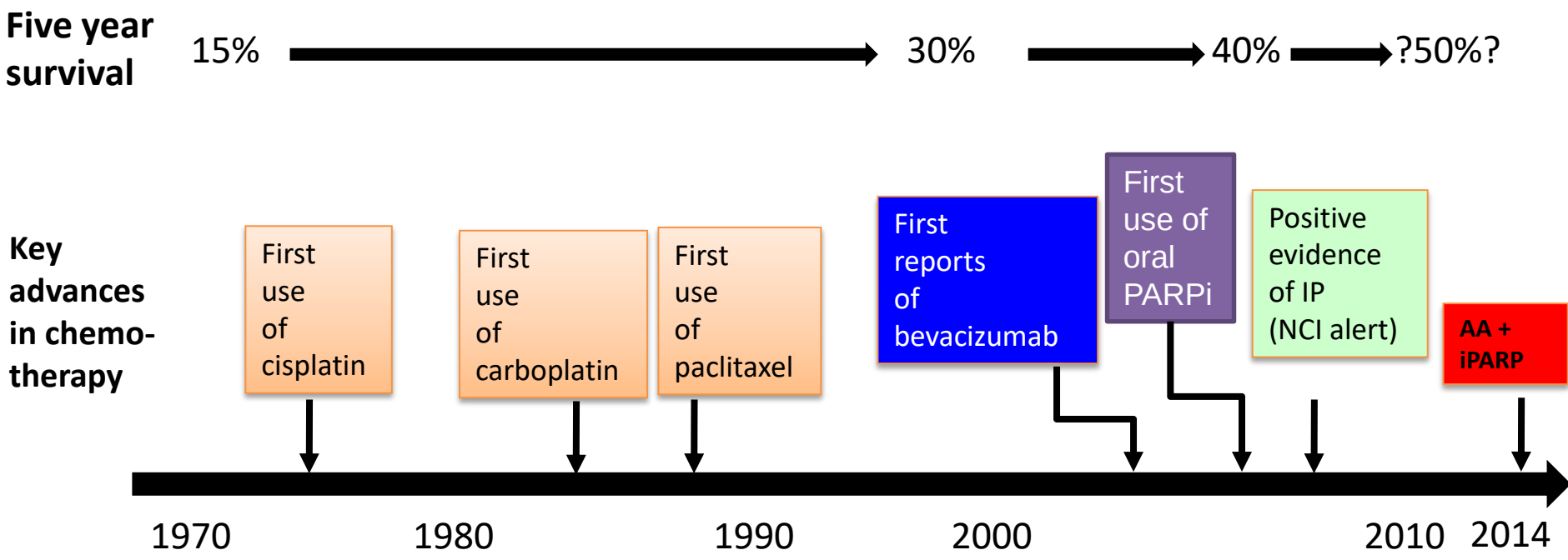
TARGETED THERAPY IN OVARIAN CANCER

Andres Poveda, MD
GCIG Chair
Valencia, Spain

Progress In The Design of Cars: MB Evolution over 40 years

Progress In The Management of Ovarian Cancer: Evolution Over 40 Years



MODIFIED FROM PROF KAYE

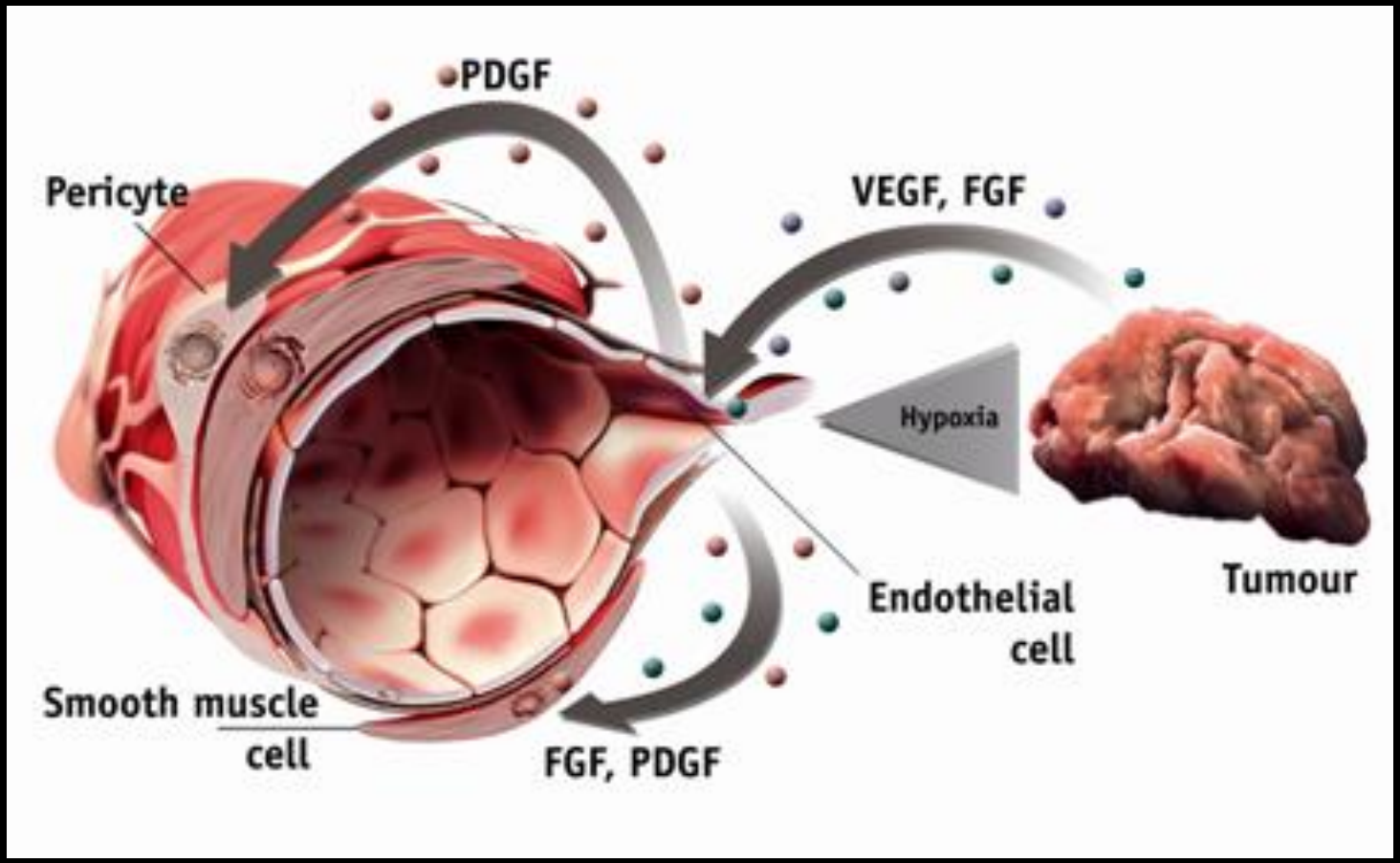
GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

MOLECULAR AGENTS AND TARGETED THERAPY

- The most promising targets in clinical trials are **angiogenesis and homologous recombination deficiency**.
- Other promising targets currently being studied based on ovarian cancer biology include:
  - PI3-Kinase and Ras/Raf pathways
  - Folate receptor

4th Ovarian Cancer Consensus Conference *Int J Gynecol Cancer 2011*.

Angiogenesis: A Complex Process



Bevacizumab Provides Proof of Concept for Anti-VEGF Therapy

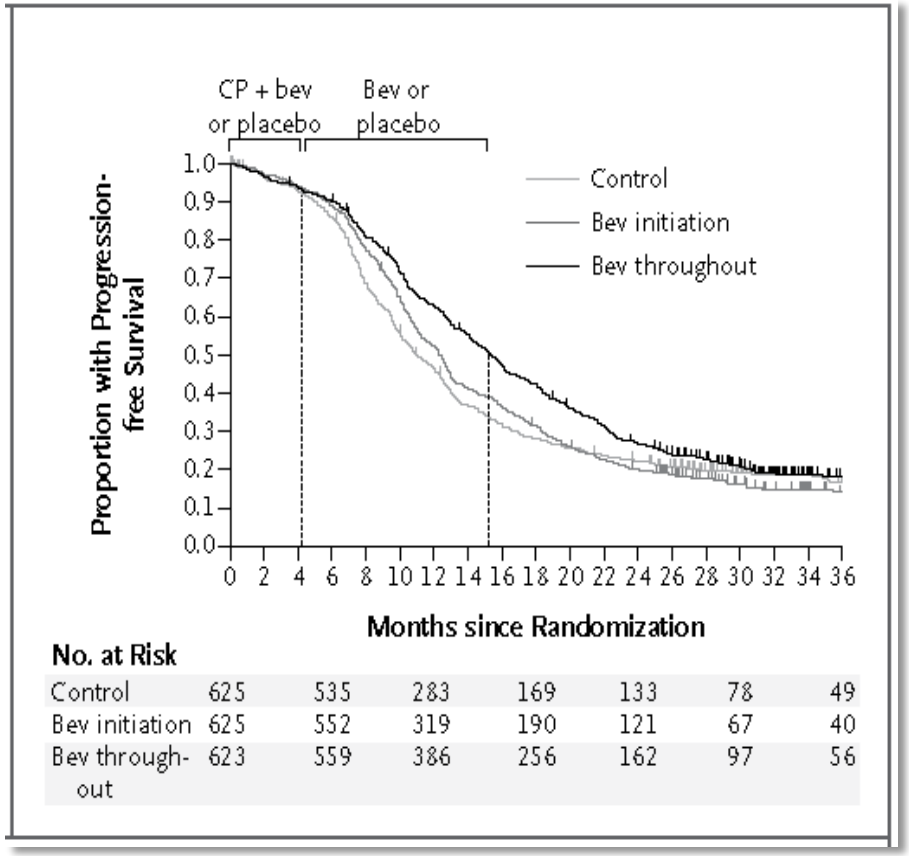
Four positive phase III trials of bevacizumab in ovarian cancer patients

Front-line		*Recurrent*	
GOG Gynecologic Oncology Group	ICON7 Bevacizumab in Ovarian Cancer	OCEANS	AURELIA Avastin Use in Platinum-resistant Epithelial Ovarian Cancer
Advanced, stage III/IV patients	Early and advanced stage patients	Recurrent, platinum sensitive	Recurrent, platinum resistant
PFS HR = 0.72[1]	PFS HR = 0.81[2]	PFS HR = 0.48[3]	PFS HR = 0.48[4]

Bevacizumab is approved for front-line use in patients with stage IIIB–IV ovarian cancer and in platinum-sensitive relapse

1. Burger RA, et al. *N Engl J Med.* 2011;365(26):2473-2483. 2. Perren TJ, et al. *N Engl J Med*. 2011;365(26):2484-2496. 3. Aghajanian C, et al. *J Clin Oncol*. 2012;30(17):2039-2045. 4. Pujade-Lauraine E, et al. *J Clin Oncol*. 2012;30(15S): Abstract LBA5002.

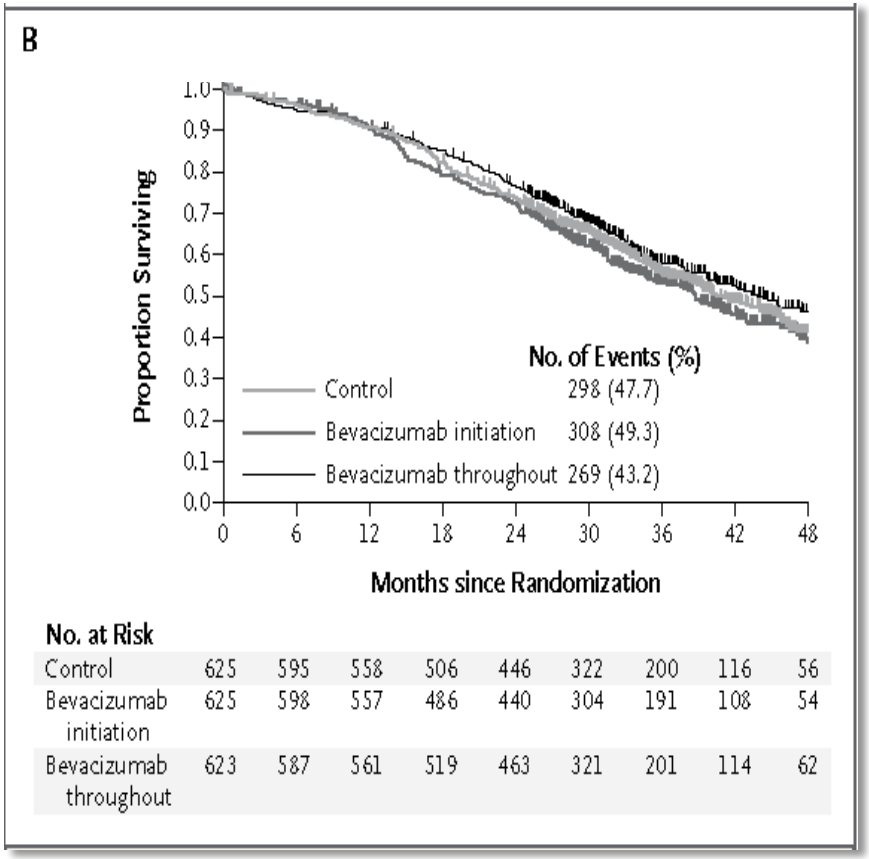
GOG#218:
Results



No. at Risk

Control	625	535	283	169	133	78	49
Bev initiation	625	552	319	190	121	67	40
Bev through-out	623	559	386	256	162	97	56

HR: 0.717(95% CI, 0.625 to 0.824)(P<0.001).



No. at Risk

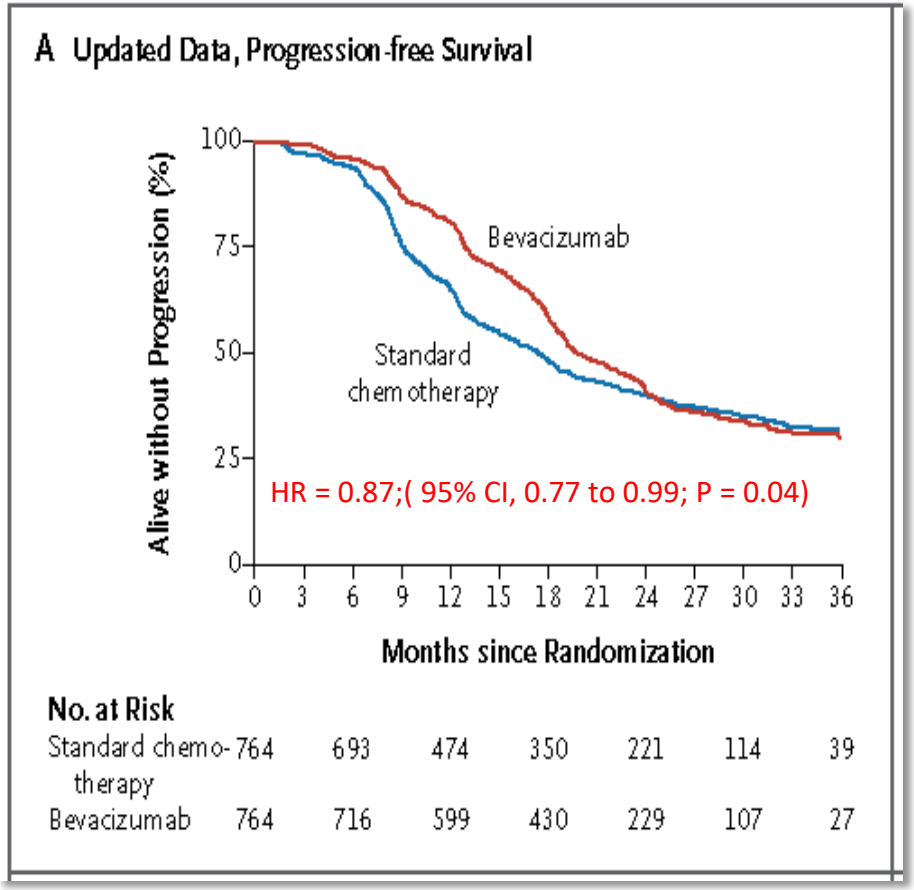
Control	625	595	558	506	446	322	200	116	56
Bevacizumab initiation	625	598	557	486	440	304	191	108	54
Bevacizumab throughout	623	587	561	519	463	321	201	114	62

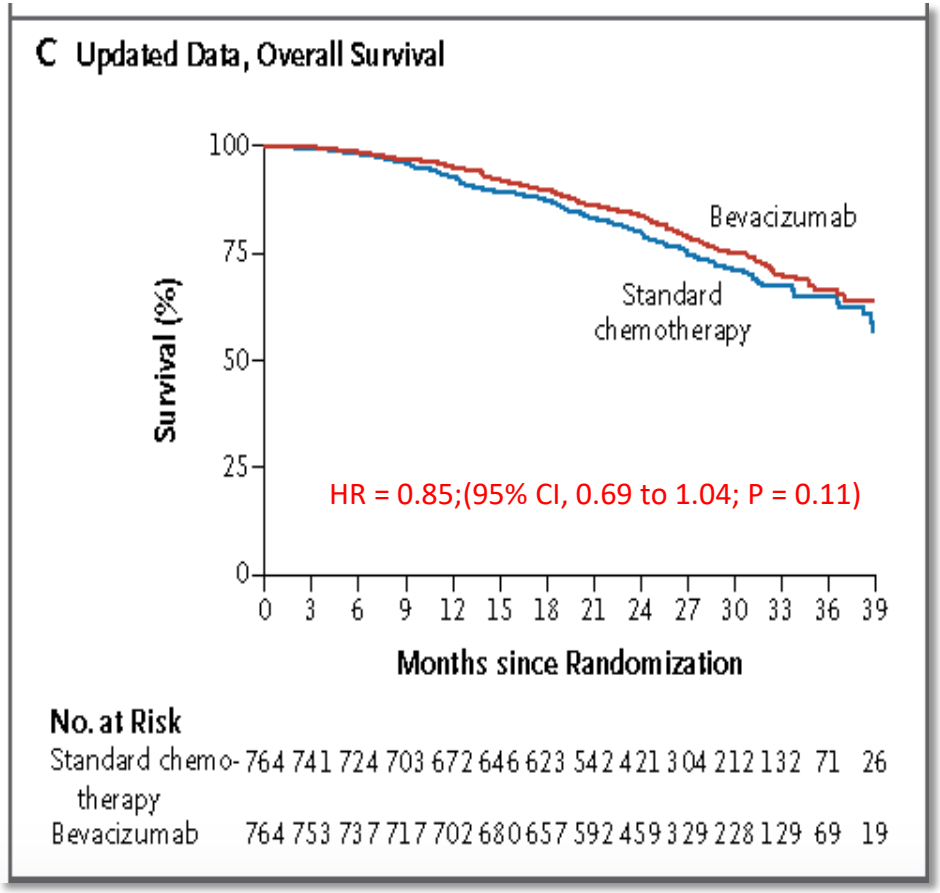
HR:0.915 (95% CI,0.727 to 1.152; P = 0.45)

Burger R. Et al; Engl J Med 2011;365:2473-83.,

ICON-7: Results

(Global Population)

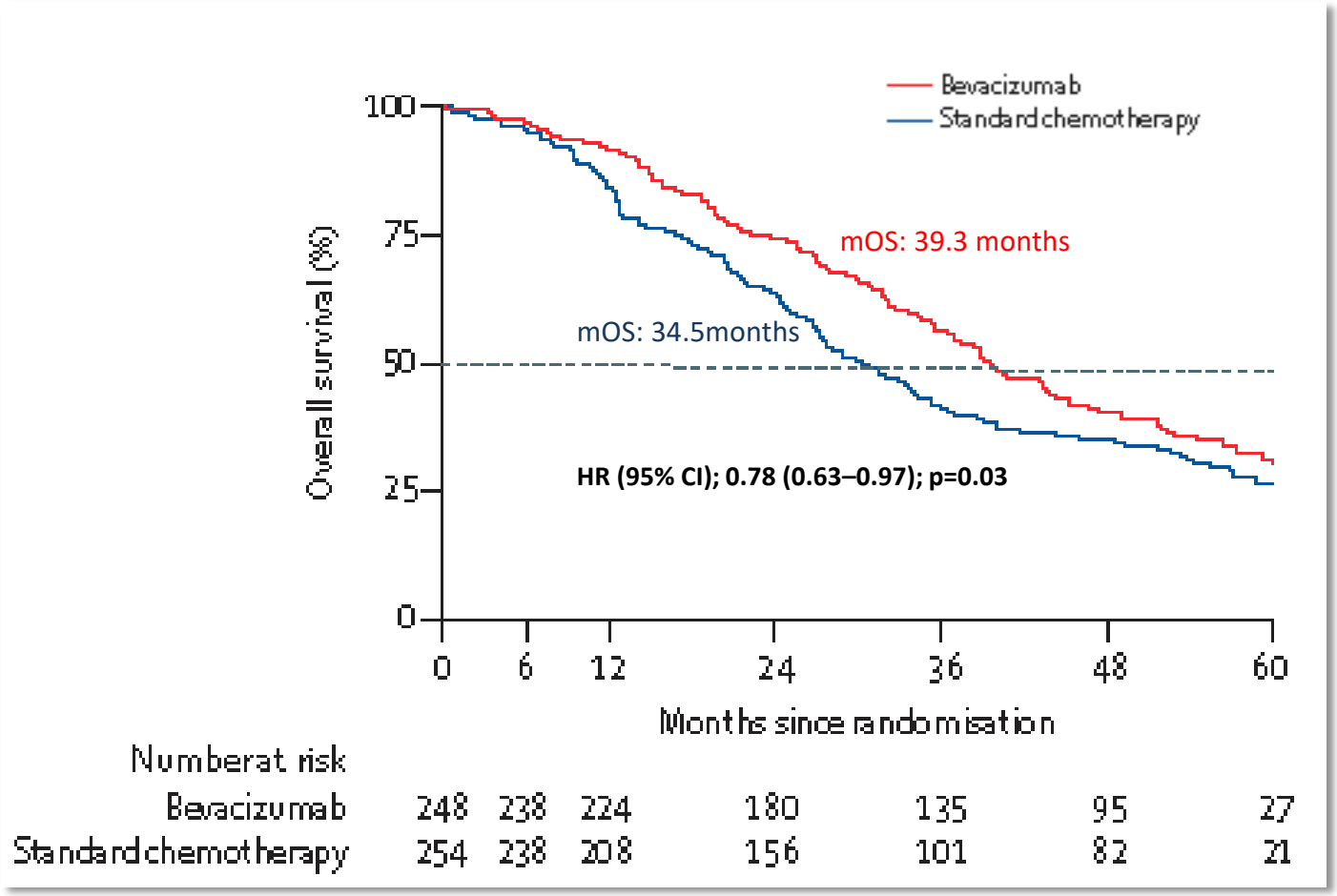




Perren T et al .N Engl J Med. 2011 Dec 29;365(26):2484-96

ICON-7 Final Overall Survival Results:

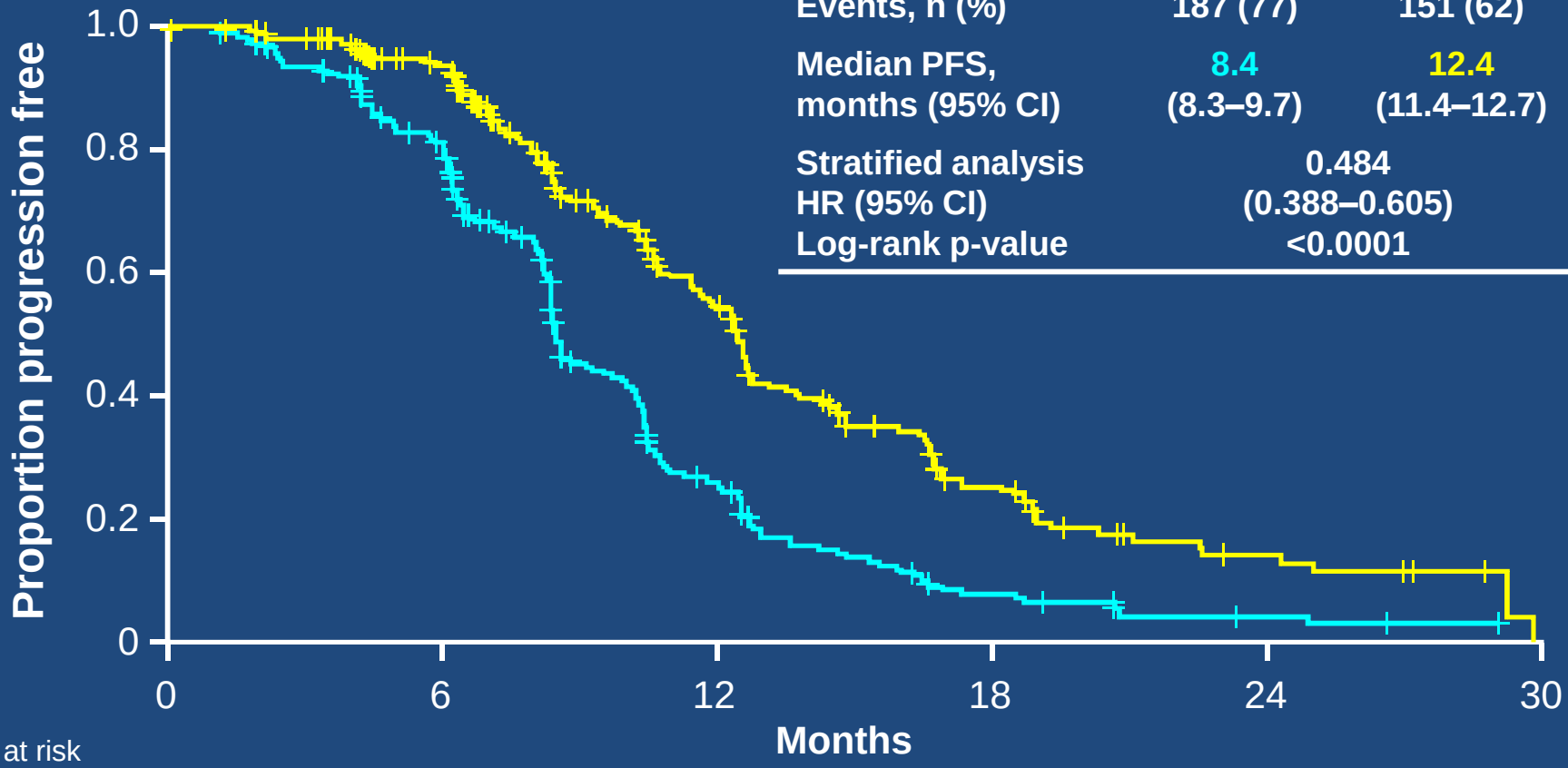
PFS: High Risk of progression (FIGO stage IV or III and suboptimal RD>1cm)



Oza A, et al; Lancet Oncol 2015; June 24, 2015

OCEANS: Platinum-sensitive recurrent OC
Primary analysis of PFS

	CG + PL (n=242)	CG + BV (n=242)
Events, n (%)	187 (77)	151 (62)
Median PFS, months (95% CI)	8.4 (8.3–9.7)	12.4 (11.4–12.7)
Stratified analysis HR (95% CI)	0.484 (0.388–0.605)	
Log-rank p-value	<0.0001	



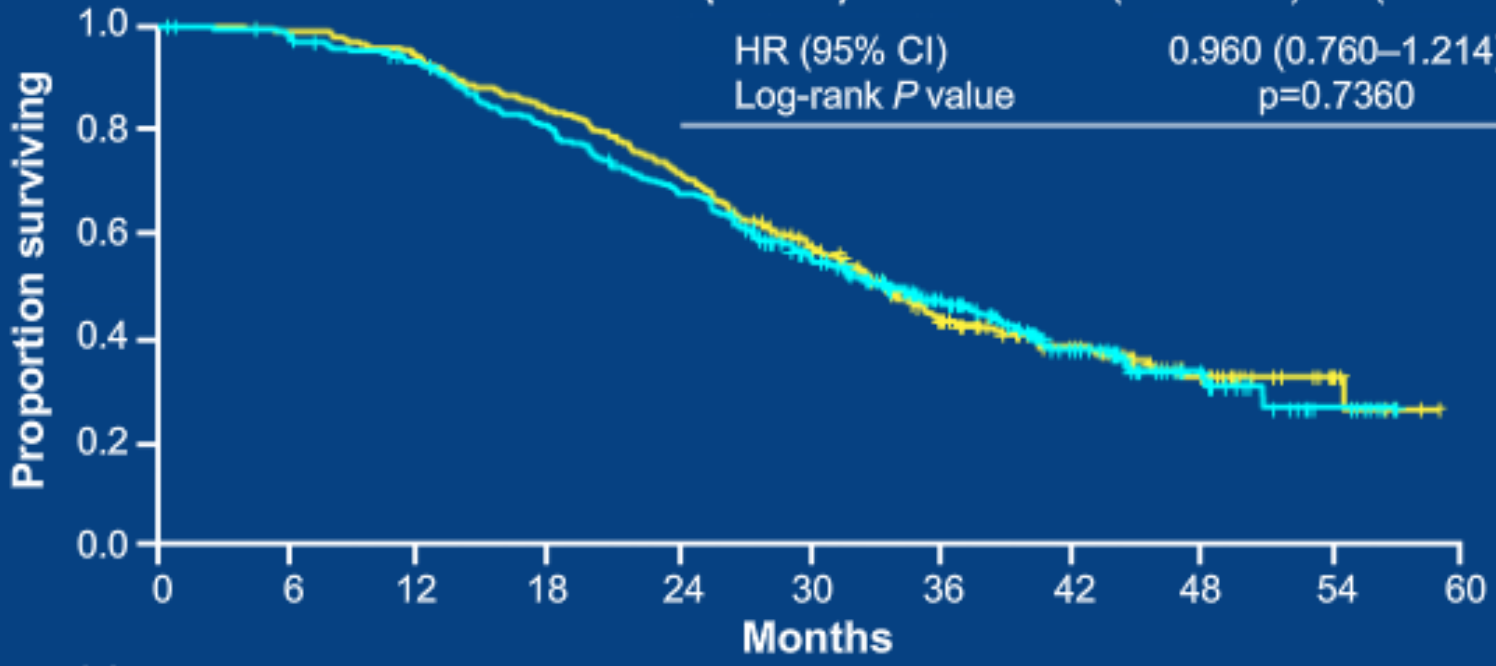
No. at risk

CG + PL	242	177	45	11	3	0
CG + BV	242	203	92	33	11	0

Aghajanian C, et al. J Clin Oncol 2012

OCEANS: Third Interim OS Analysis[a]

	GC + PL (n=242)	GC + BV (n=242)
Events, n (%)	142 (58.7)	144 (59.5)
Median OS, months (95% CI)	33.7 (29.3–38.7)	33.4 (30.3–35.8)
HR (95% CI)	0.960 (0.760–1.214)	
Log-rank *P* value	p=0.7360	



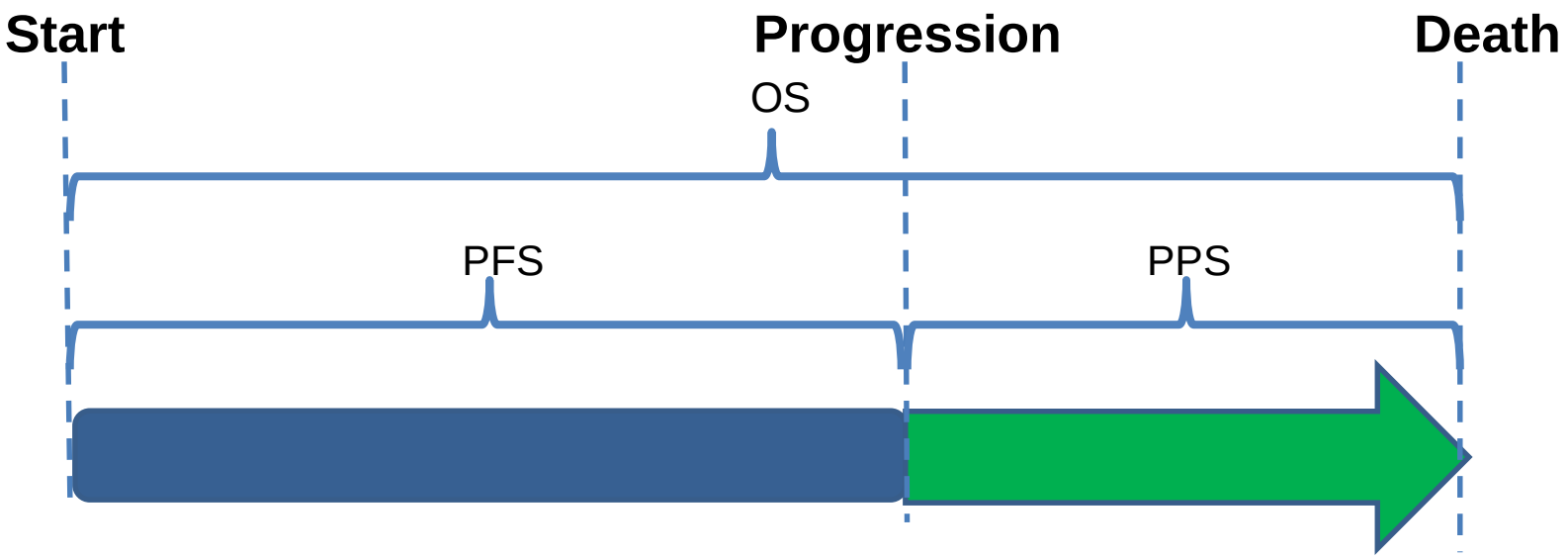
Number at risk:

GC + PL	242	235	221	190	159	117	77	44	23	7	0
GC + BV	242	239	226	201	171	127	78	48	27	7	0

[a]Data cutoff date: March 30, 2012. Median follow-up 41.8 months in PL arm and 42.3 months in BV arm, with 286 deaths (59.1% of patients)

What is Post Progression Survival (PPS)?

Post Progression Survival: Time from disease progression till death



AGO/NCIC/EORTC and OCEANS

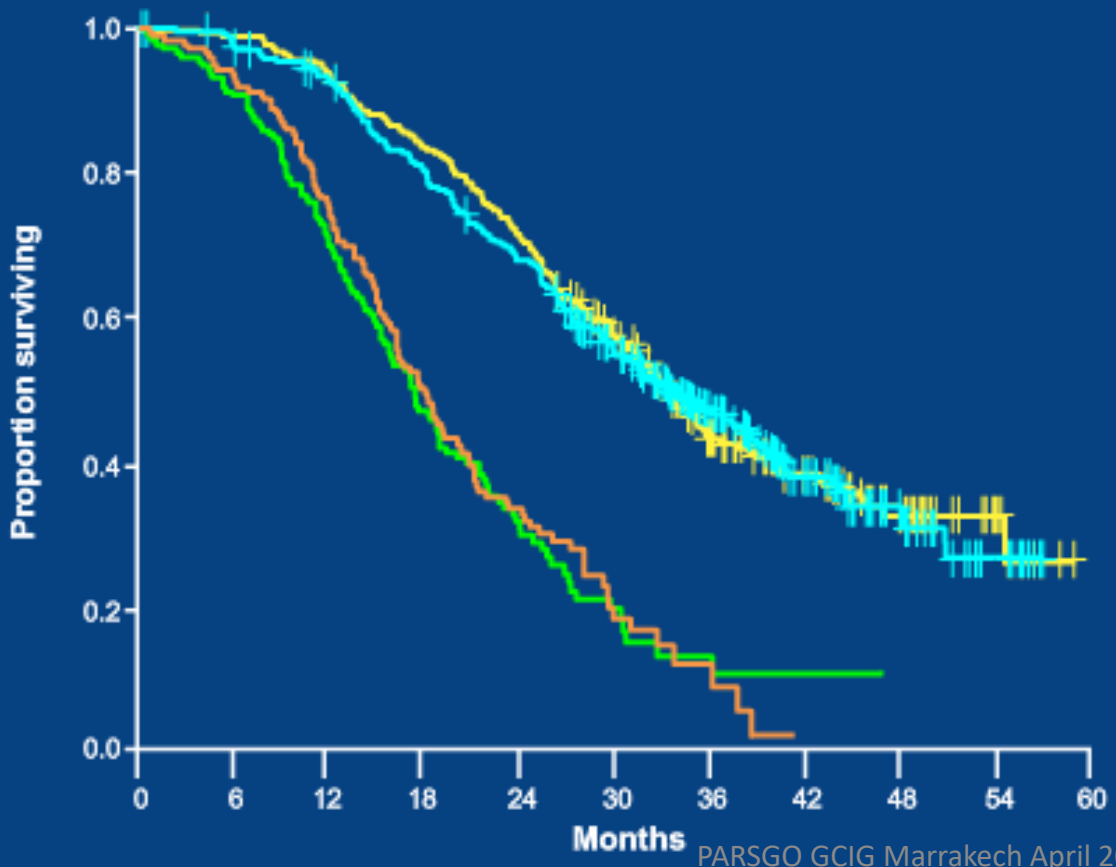
Overall survival and subsequent treatment

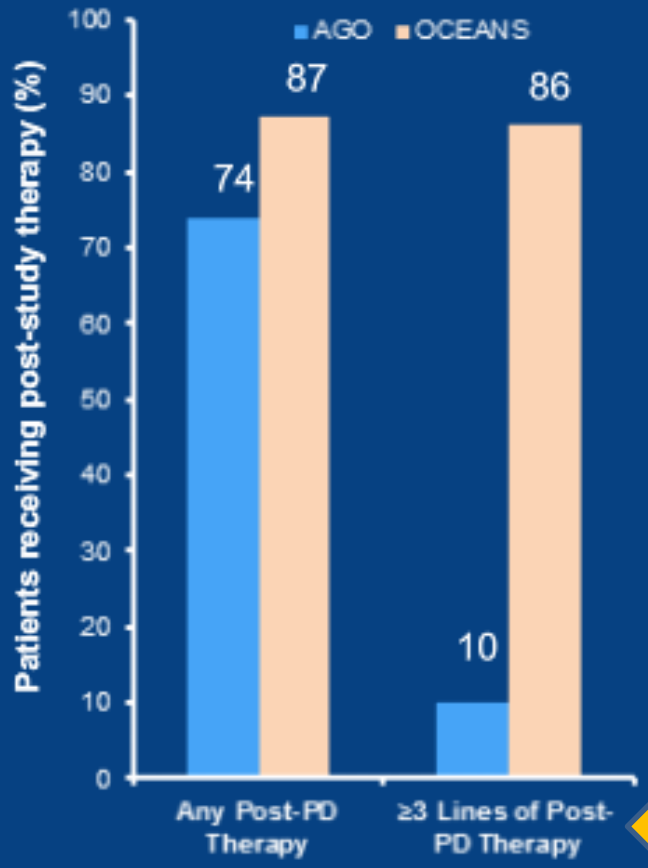
AGO/NCIC/EORTC: OS[1]

	C (n=178)	GC + PL (n=178)
Median OS, mo	17.3	18.0
HR (95% CI)	0.96 (0.75 – 1.23)	
Log-rank *P* value	.7349	

OCEANS: 3rd Interim OS Analysis

	GC + PL (n=242)	GC + BV (n=242)
Median OS, mo	33.7	33.4
HR (95% CI)	0.960 (0.760–1.214)	
Log-rank *P* value	.7360	

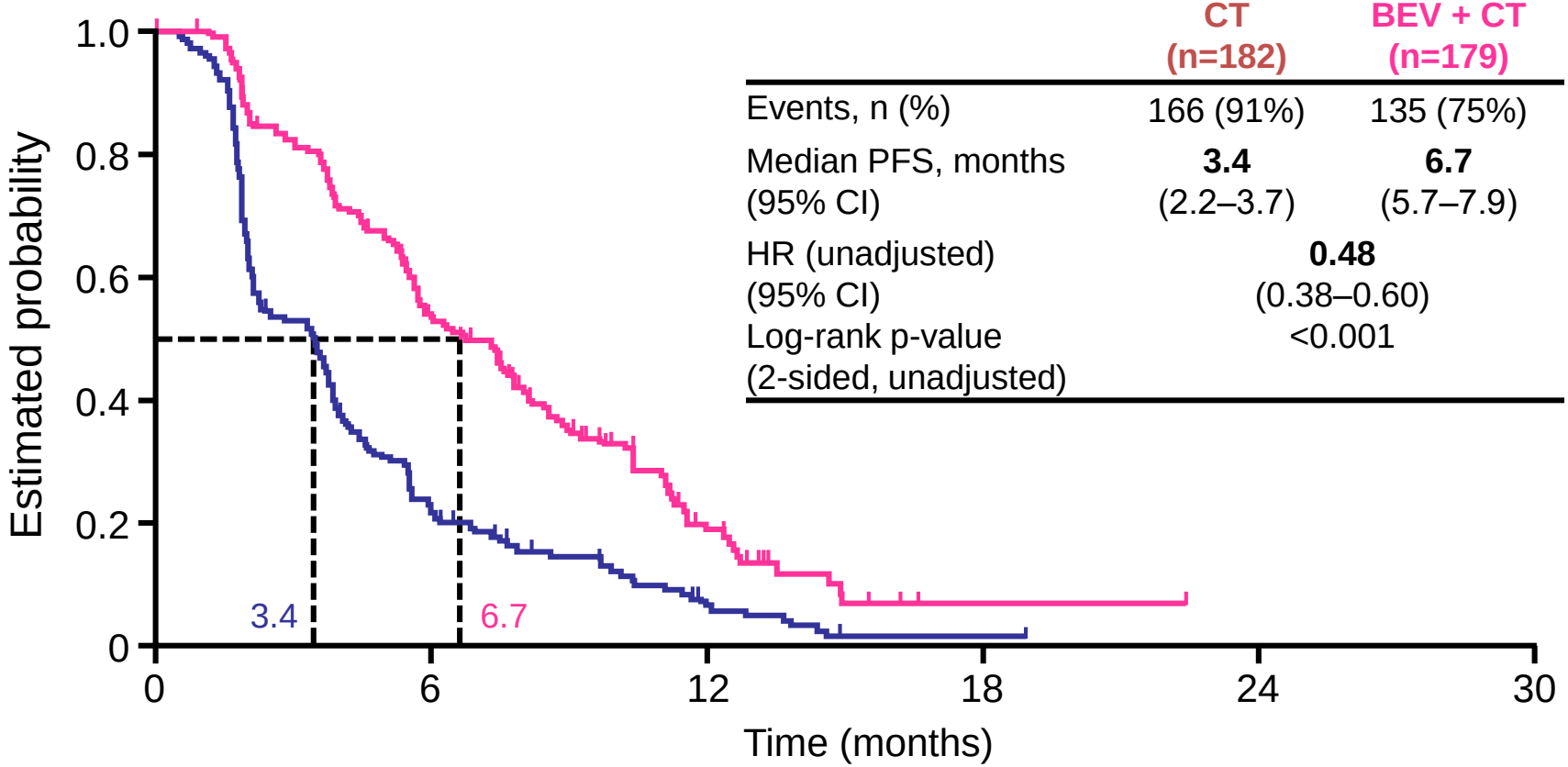




[1]Pfisterer et al. *J Clin Oncol*. 2006

AURELIA trial in **resistant disease**

Progression-free survival



	CT (n=182)	BEV + CT (n=179)
Events, n (%)	166 (91%)	135 (75%)
Median PFS, months (95% CI)	**3.4** (2.2–3.7)	**6.7** (5.7–7.9)
HR (unadjusted) (95% CI)	**0.48** (0.38–0.60)	
Log-rank p-value (2-sided, unadjusted)	<0.001	

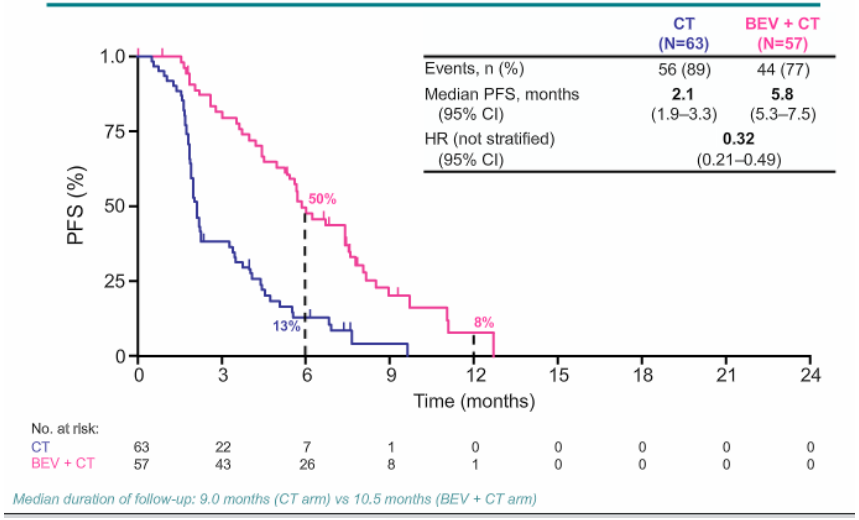
No. at risk:

CT	182	93	37	20	8	1	1	0	0
BEV + CT	179	140	88	49	18	4	1	1	0

Pujade-Lauraine E et al, JCO 2013

ASCO Annual '12 Meeting

PFS: Cohort treated with topotecan



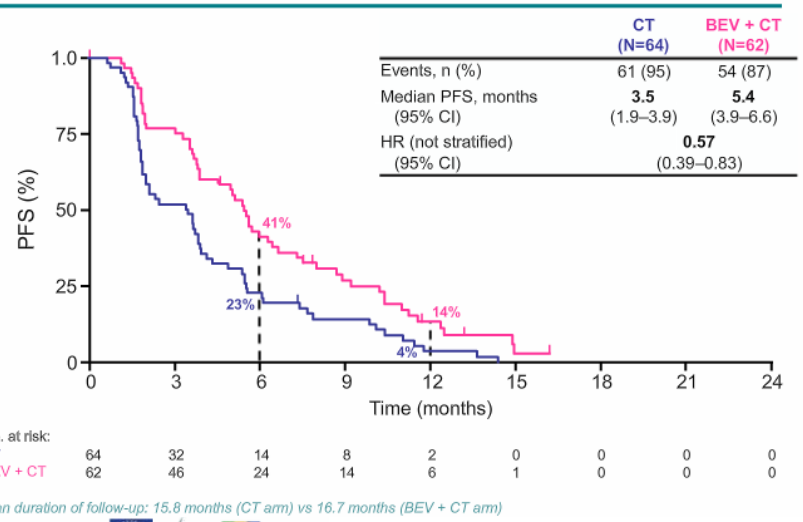
	CT (N=63)	BEV + CT (N=57)
Events, n (%)	56 (89)	44 (77)
Median PFS, months (95% CI)	**2.1** (1.9–3.3)	**5.8** (5.3–7.5)
HR (not stratified) (95% CI)	**0.32** (0.21–0.49)	

No. at risk:

CT	63	22	7	1	0	0	0	0	0
BEV + CT	57	43	26	8	1	0	0	0	0

Median duration of follow-up: 9.0 months (CT arm) vs 10.5 months (BEV + CT arm)

PFS: Cohort treated with PLD



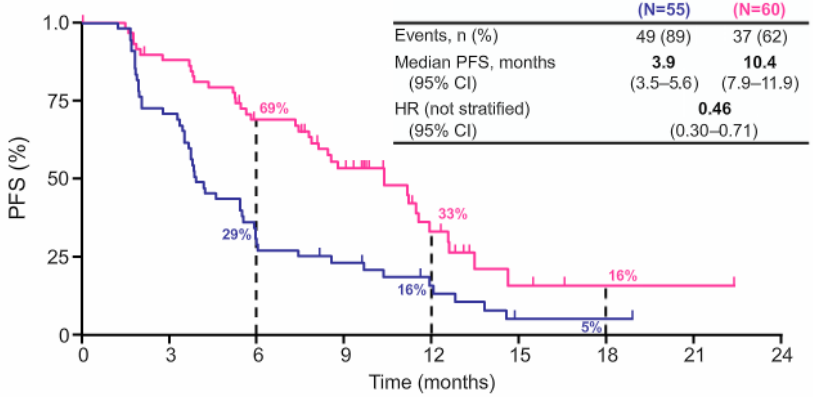
	CT (N=64)	BEV + CT (N=62)
Events, n (%)	61 (95)	54 (87)
Median PFS, months (95% CI)	**3.5** (1.9–3.9)	**5.4** (3.9–6.6)
HR (not stratified) (95% CI)	**0.57** (0.39–0.83)	

No. at risk:

CT	64	32	14	8	2	0	0	0	0
BEV + CT	62	46	24	14	6	1	0	0	0

Median duration of follow-up: 15.8 months (CT arm) vs 16.7 months (BEV + CT arm)

PFS: Cohort treated with paclitaxel



	CT (N=55)	BEV + CT (N=60)
Events, n (%)	49 (89)	37 (62)
Median PFS, months (95% CI)	**3.9** (3.5–5.6)	**10.4** (7.9–11.9)
HR (not stratified) (95% CI)	**0.46** (0.30–0.71)	

No. at risk:

CT	55	39	16	11	6	1	1	0	0
BEV + CT	60	51	38	27	11	3	1	1	0

Median duration of follow-up: 12.7 months (CT arm) vs 12.8 months (BEV + CT arm)

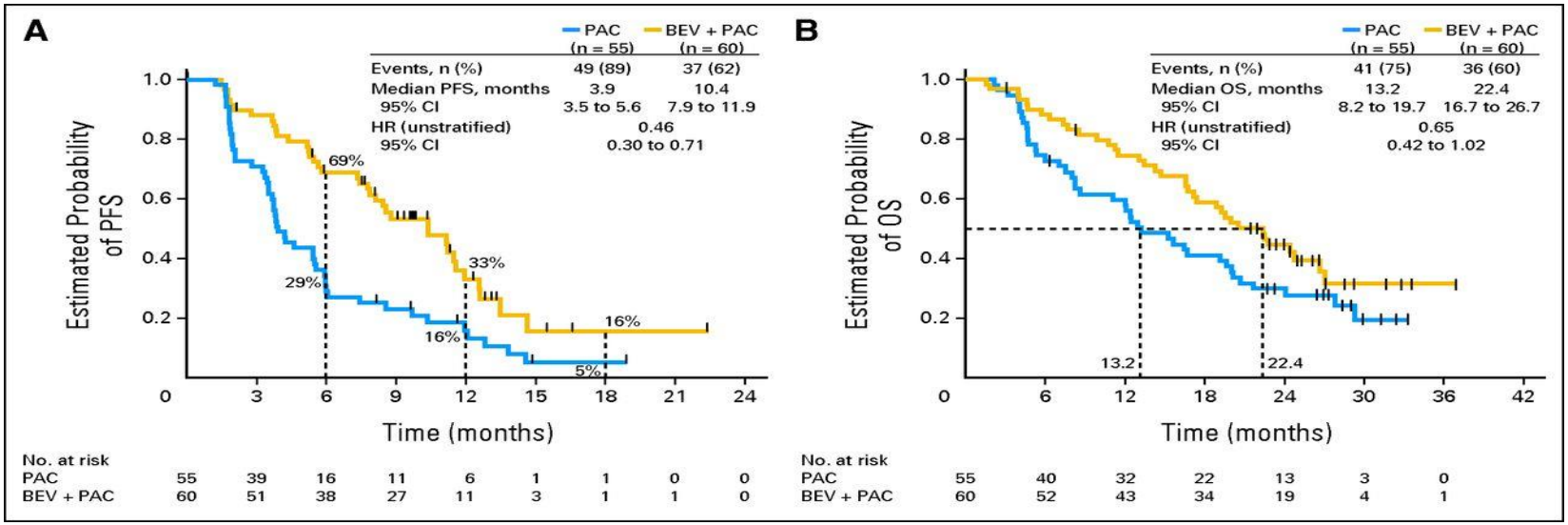
Poveda A et al Ann Oncol 2012

JOURNAL OF CLINICAL ONCOLOGY

AURELIA Study

OS at Weekly paclitaxel (PAC) cohort.

Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: Analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial



Poveda et al. JCO 2015. Vol 33

JOURNAL OF CLINICAL ONCOLOGY ASCO

Angiogenesis as a Target in Ovarian Cancer

- Anti-vascular endothelial growth factor (VEGF) therapy improves progression-free survival (PFS)
  - **GOG 218** — **Front-line**: **Bevacizuma**b
    HR = 0.72; 95% CI, 0.63–0.82[1]
  - **ICON 7** — **Front-line: Bevacizumab**
    HR = 0.81; 95% CI, 0.70–0.94[2]
  - **AGO-OVAR12** — **Front-line: Nintedanib**
    HR = 0.84; 95% CI, 0.72, 0.98[3]
  - **AGO-OVAR16** — **Maintenance: Pazopanib**
    HR = 0.77; 95% CI, 0.64–0.91[4]
  - **AURELIA** — **Platinum-resistant, recurrent** / 1 or 2 prior regimens: **Bevacizumab**
    HR = 0.48; 95% CI, 0.38–0.60[5]
  - **OCEANS** — **Platinum-sensitive, recurrent** / 1 prior regimen: **Bevacizumab**
    HR = 0.48; 95% CI, 0.388–0.60[6]
  - **ICON6** — **Platinum-sensitive, recurrent** / 1 prior regimen: **Cediranib**
    HR = 0.57; 95% CI, 0.44–0.74[7]
  - **TRINOVA1** — **Platinum-PPS + resistant recurrent** / 1 prior regimen: **Trebananib**
    HR = 0.66; 95% CI, 0.56–0.76[8]

1. Burger RA et al. *N Engl J Med*. 2011;365:2473–2483.
2. Perren TJ et al . *N Engl J Med*. 2011;365:2484–2496.
3. du Bois A et al. *J Clin Oncol*. 2013;31(18suppl):LBA5503.
4. du Bois A et al. LBA ESGO 2013 Liverpool, UK. . *J Clin Oncol* 2014
5. Pujade-Lauraine E et al. *J Clin Oncol.* 2013.
6. Aghajanian C et al. *J Clin Oncol*. 2013
7. Ledermann JA et al . *Eur J Cancer.* 2013;*49*(suppl):LBA
8. Monk BJ et al. *Lancet Oncol* 2014

HR = hazard ratio; 95% CI = confidence interval

Adapted from Prof Monk

MOLECULAR AGENTS AND TARGETED THERAPY

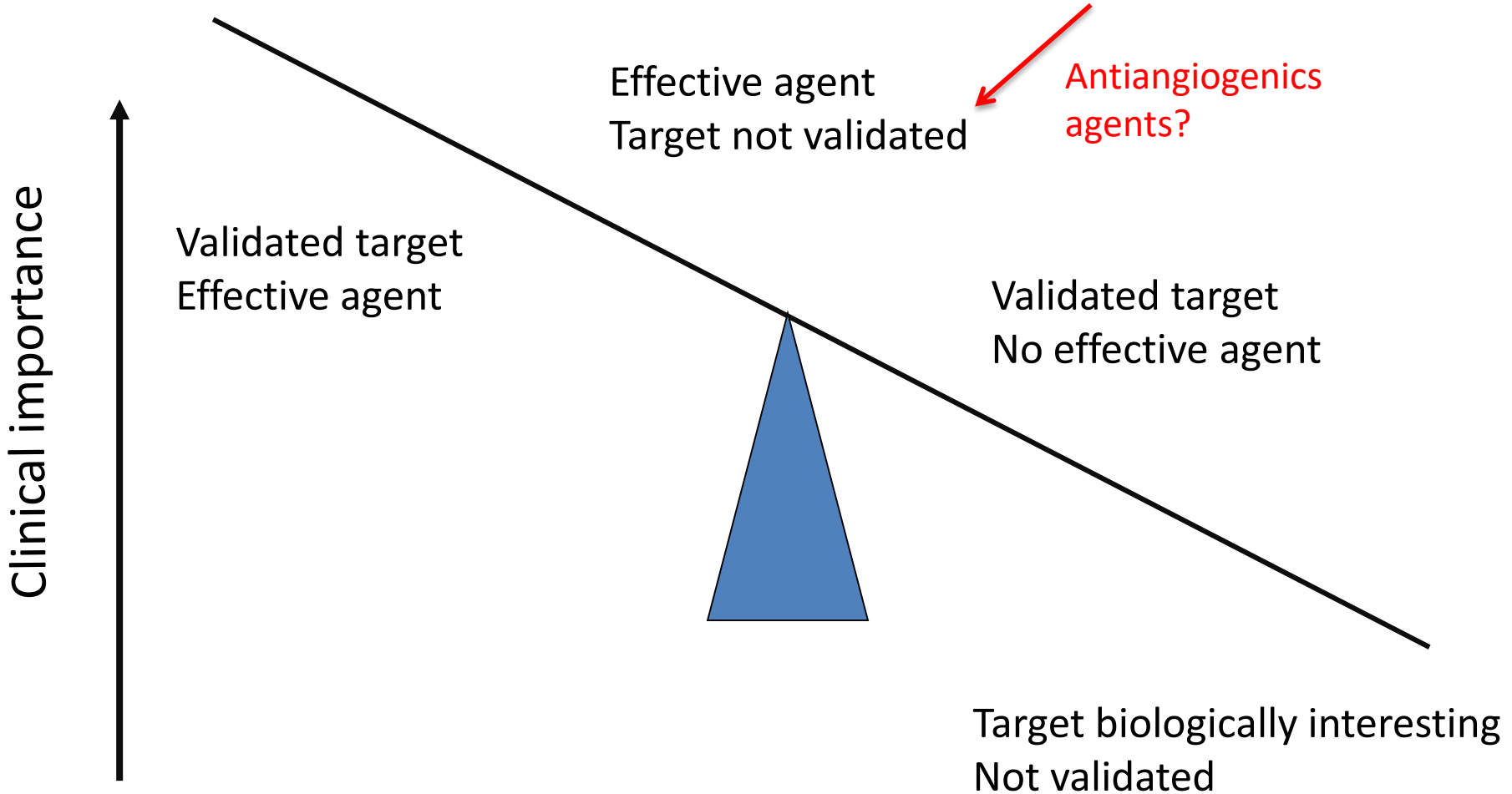
- To select patients for trials investigating these targets, **predictive biomarkers are required**. Understanding mechanisms of resistance is a priority.

4th Ovarian Cancer Consensus Conference *Int J Gynecol Cancer 2011*.

ANTI ANGIOGENIC STUDIES IN OVARIAN CANCER

STUDY	Line	N	Obj	Duration	Drug	HR	Histo-types	Clinical Factors	BMK
GOG218	1st	1873	PFS	12m	Bev	0,72	No dif	Yes	No
ICON7	1st	1528	PFS	15m	Bev	0,81	No dif	Yes	No
AGOOV16	1st	940	PFS	24m	Pazo	0,77	No dif	Yes?	No
AGOOV12	1st	1386	PFS	24m	Ninde	0,84	No dif	Yes	No
GOG262	1st	692	PFS	UP	Bev	DDvsSt	No dif	Yes	??
OCEANS	2nd	484	PFS	UP	Bev	0,53	No dif	Yes?	No
TRINOVA1	2nd	919	PFS	UP	Treb	0,66	No dif	Yes	??
ICON 6	2nd	456	PFS	UP	Cedir	0,57	N.S	N.S.	??
AURELIA	2nd	361	PFS	UP	Bev	0,48	No dif	No	No
TOTAL		**8.639**							**NO**

Therapeutic Targets in Ovarian Cancer



Courtesy of Dr M Birrer

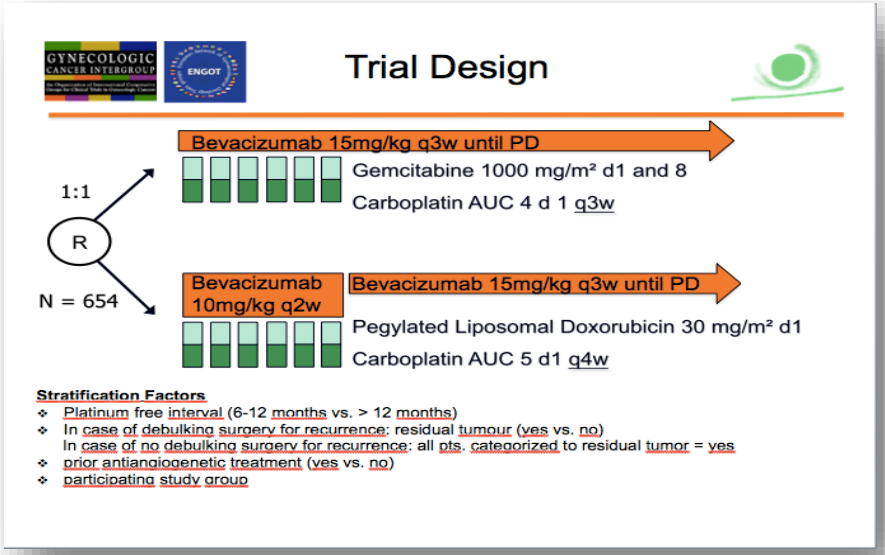
Anti-Angiogenic Therapies
Summary

- Increase tumour response
- Increase PFS
- Have not been shown to increase OS
- Are unselective - no predictive marker

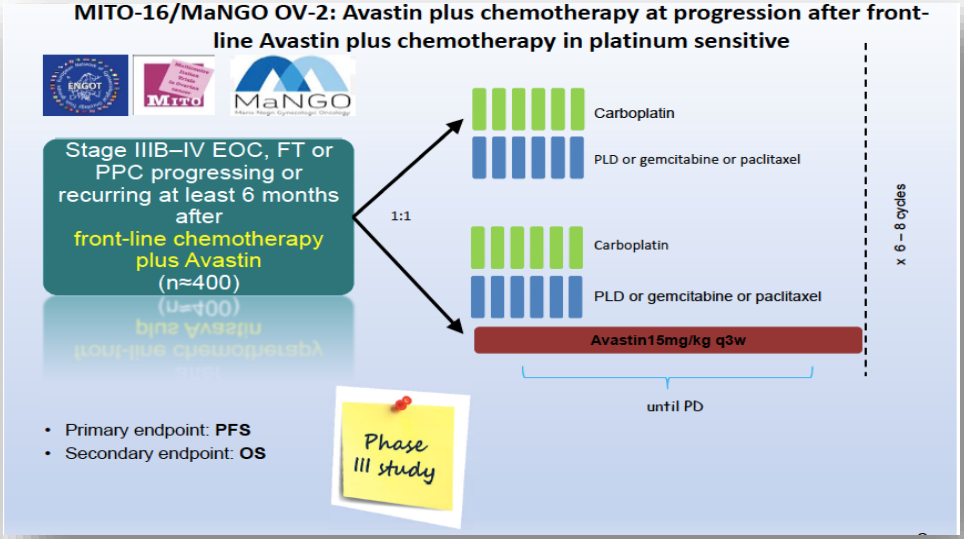
- Combination with other targeted therapies is a **challenge**

Future for bevacizumab in patients with platinum as option

CARBO-PLD-BEVACIZUMAB
ENGOT OV-18 /AGO OVAR 2.21



BEVACIZUMAB AFTER BEVACIZUMAB
ENGOT OV-17/ MITO 14-MANGO OV-2



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- The most promising targets in clinical trials are **angiogenesis and homologous recombination deficiency**.
- Other promising targets currently being studied based on ovarian cancer biology include:
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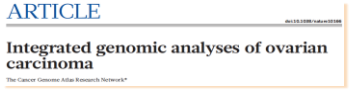
  - Folate receptor

4th Ovarian Cancer Consensus Conference *Int J Gynecol Cancer 2011*.

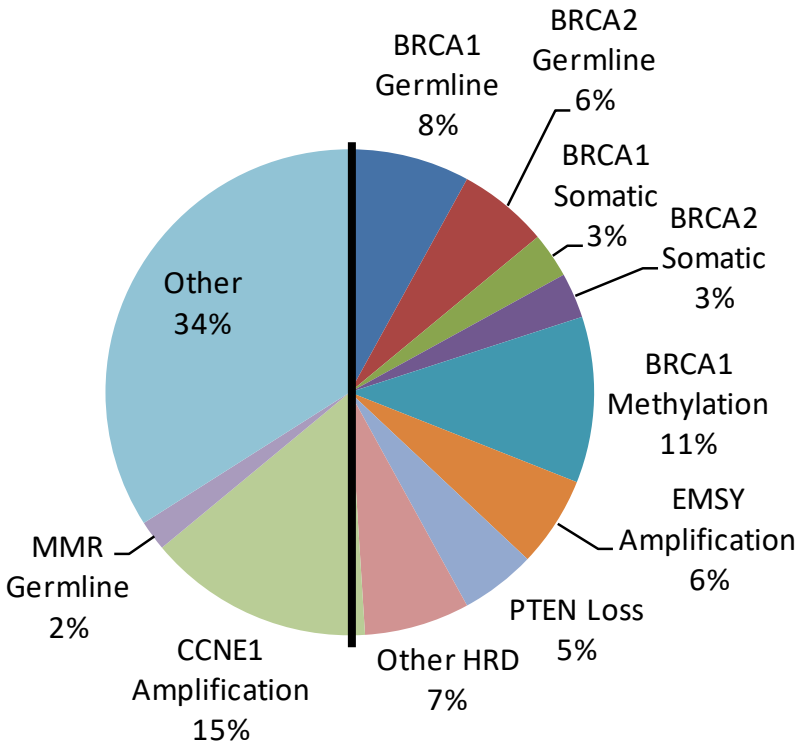
Potential of PARP Inhibitors in Sporadic Ovarian Cancer


ARTICLE

Integrated genomic analyses of ovarian carcinoma

The Cancer Genome Atlas Research Network*

The Cancer Genome Atlas, Molecular profiling of serous ovarian cancer, D. Levine 2011



SUMMARY

TCGA provides a large-scale integrative view of the aberrations in HGS-OvCa.

Mutations in TP53 predominated, occurring in at least 96% of HGS-OvCa samples.

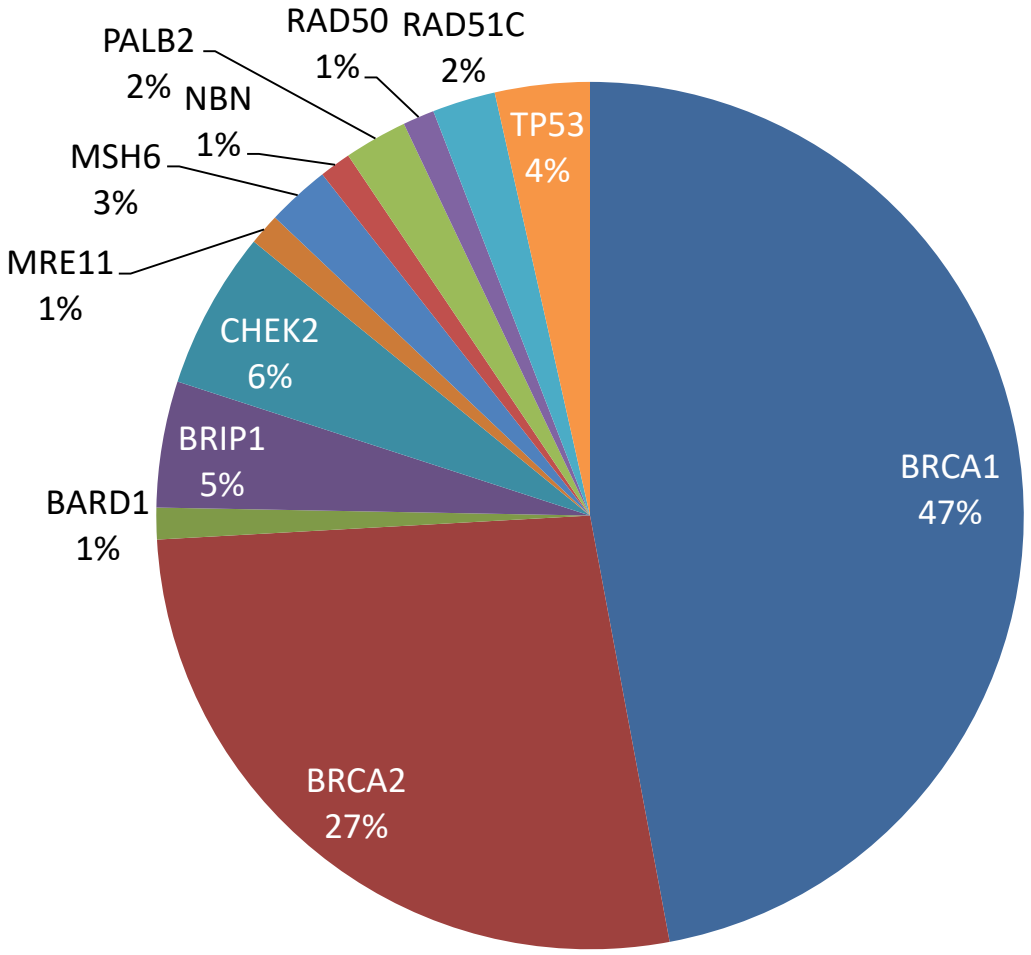
BRCA1 and BRCA2 were **mutated in 21%** of tumours, owing to a combination of germline and somatic mutations.

Seven other significantly mutated genes were identified, **but only in 2–6% of HGS-OvCa samples.**

50% of HGS-OvCa tumours with **homologous recombination defects** may benefit from **PARP inhibitors.**

BRCA mutations are the most common mutations in patients with ovarian cancer

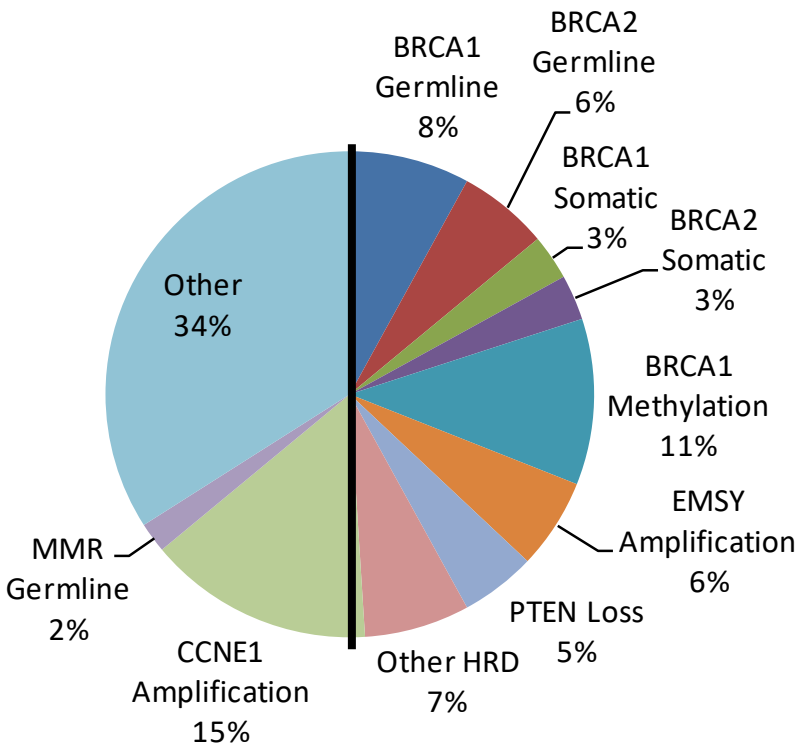
Mutation rate: 24%
(18% *BRCA*,
6% other genes)



Walsh T et al., Proc Natl Acad Sci, 2011

Potential of PARP Inhibitors in Sporadic Ovarian Cancer

The Cancer Genome Atlas, Molecular profiling of serous ovarian cancer, D. Levine 2011



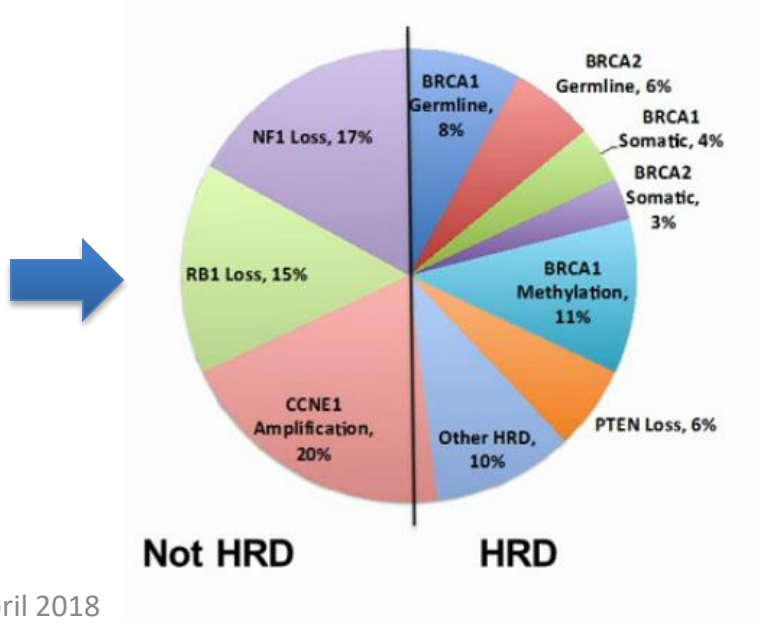
Should all HGS ovarian cancer patients have *BRCA* testing?

Approximately 50% of patients with high-grade serous ovarian cancer predicted to be candidates for PARPi therapy

What are the clinical data?

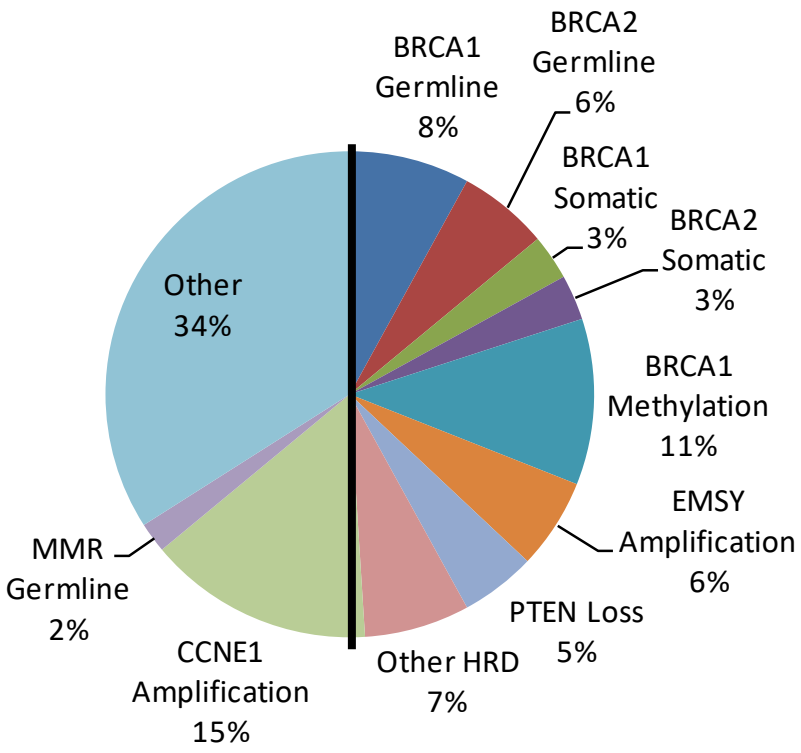
Patient selection for PARP inhibition

- **Clear rationale for PARP inhibition of germline-BRCA mutated tumours** .
    - Mostly high grade serous and endometrioid ovarian cancer
    - Repeated response to platinum-based chemotherapy
    - Prolonged survival (>5 years).
- **Emerging evidence that the HRD phenotype is present in up to 50 % HGSOC**
    - BRCA-1/2 1 germline and somatic events are common.
    - Epigenetic silencing of BRCA1 is common.
    - Potential of PARP inhibitors in sporadic Ovarian Cancer



Potential of PARP Inhibitors in Sporadic Ovarian Cancer

The Cancer Genome Atlas, Molecular profiling of serous ovarian cancer, D. Levine 2011



Not Homologous Recombination (HR) Deficient **HR Deficient**

Should all HGS ovarian cancer patients have *BRCA* testing?

Approximately 50% of patients with high-grade serous ovarian cancer predicted to be candidates for PARPi therapy

What are the clinical data?

PARP Inhibitors in Clinical Trials

PF-01367 (Rucaparib)	Clovis/Pfizer	IV/oral
Olaparib	AZ	Oral
MK 4827 (Niraparib)	Tesaro	Oral
BMN 673	BioMarin	Oral
ABT 888 (Veliparib)	Abbott	Oral
INO-1001	Inotek	IV
GP1201	Eisai	Oral
CEP 9722	Cephalon	Oral

Platinum combination followed by iPARP

Olaparib study design and patient selection

Study-19 aim and design

265 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

Olaparib 400 mg po bid

Randomized 1:1

Placebo po bid

Primary end point : PFS

Ledermann J, et al. N Engl J Med 2012

SOLO-2 aim and design

295 patients

- *BRCA1/2* mutation
- Platinum-sensitive relapsed ovarian cancer
- At least 2 prior lines of platinum therapy
- CR or PR to most recent platinum therapy

Randomized 2:1

Olaparib 300 mg bid n=196

Placebo n=99

Primary endpoint: Investigator-assessed PFS

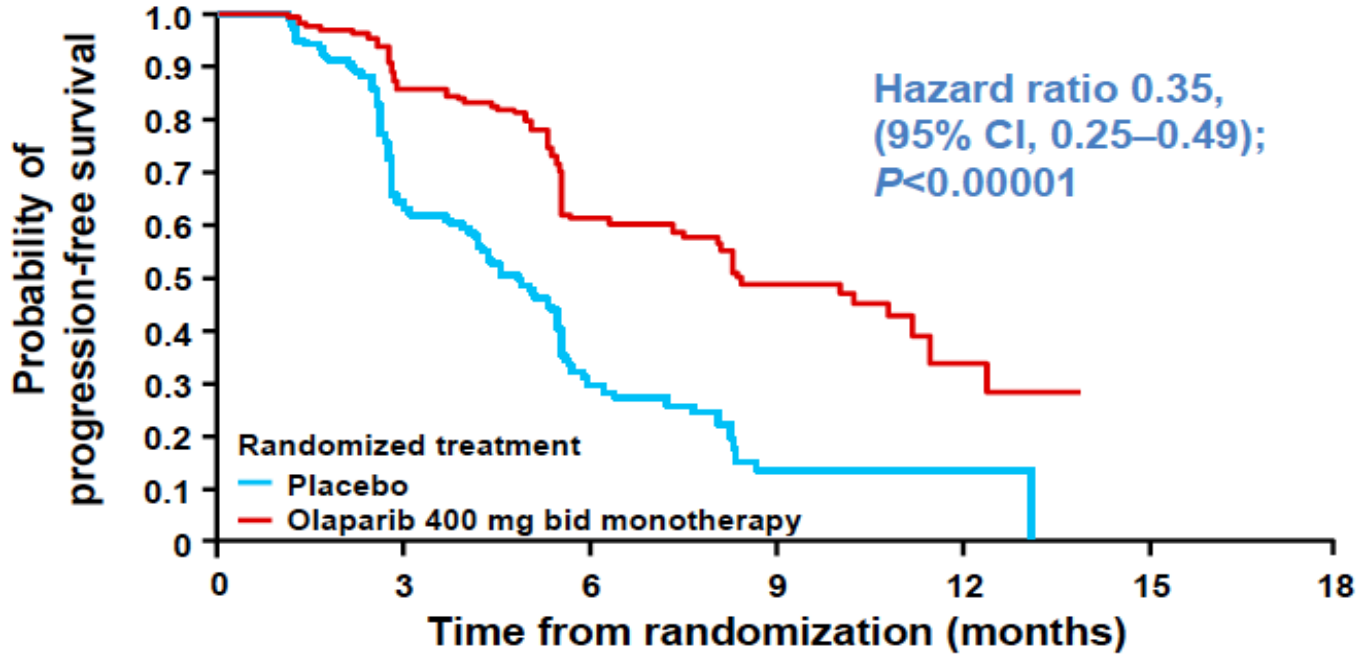
Pujade-Lauraine et al. Lancet Oncol 2017

Study-19

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer



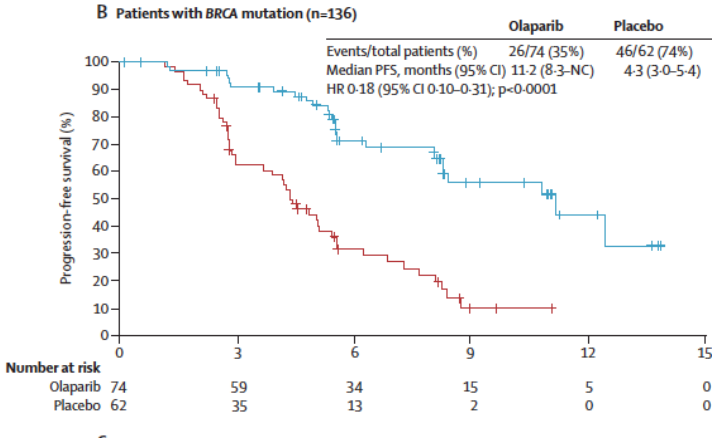
- Statistically significant PFS improvement (HR 0.35, *P*<0.00001)
- Interim OS analysis: HR=0.94; 95% CI, 0.63–1.39; *P*=0.75

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

Platinum combination followed by iPARP

Olaparib data on primary endpoint

Study-19 PFS

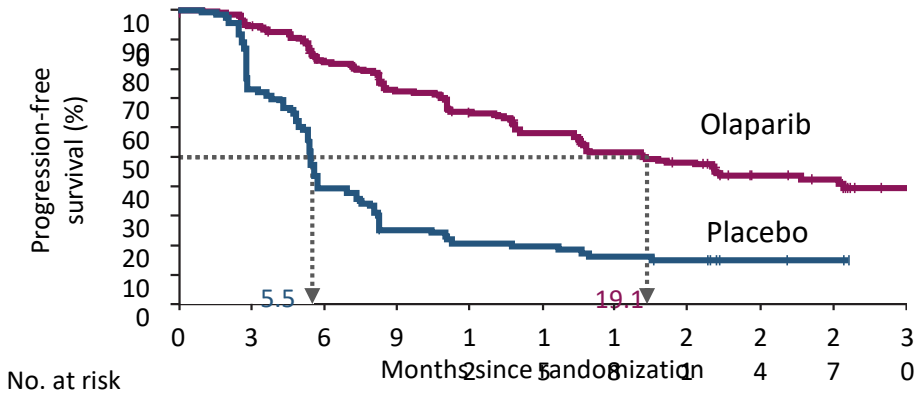


11.2 vs 4.3 months

HR 0.18 (95% CI: 0.10-0.31)

Ledermann et al. Lancet Oncol 2014

SOLO-2 PFS



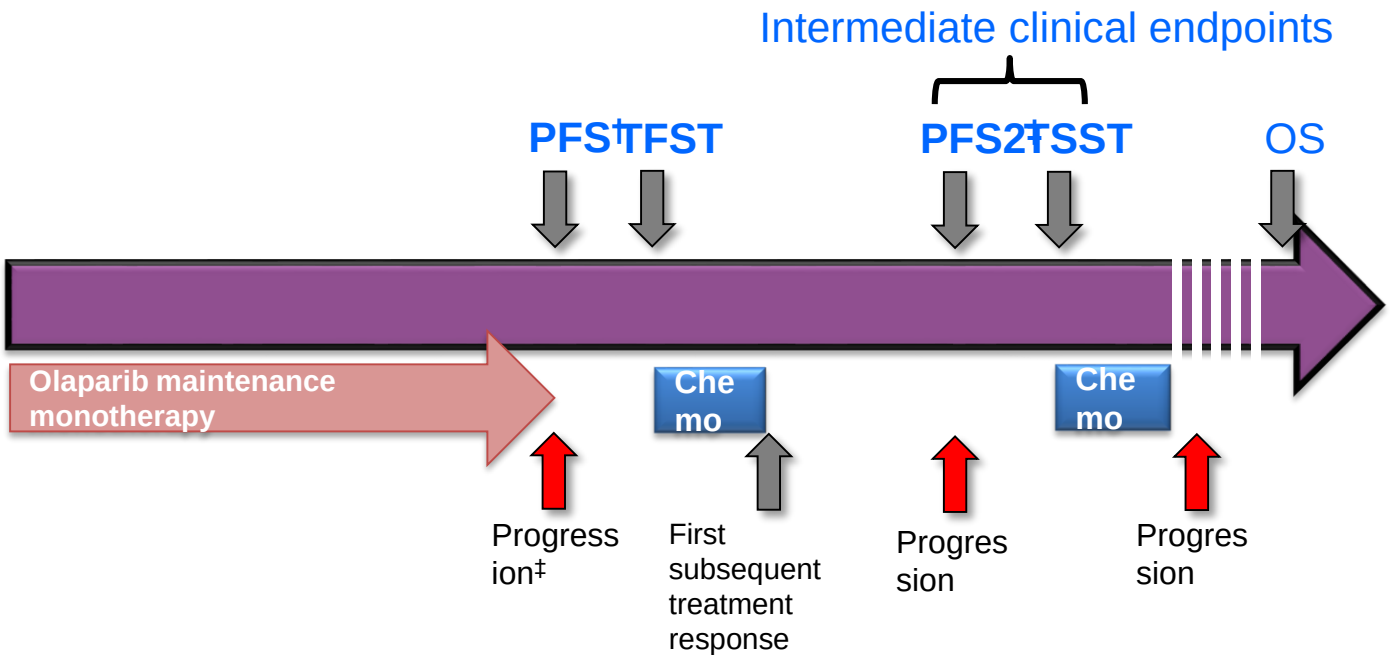
19.1 VS 5.5 months

HR 0.3 (95% CI: 0.22-0.41)

Pujade-Lauraine et al. Lancet Oncol 2017

Time to first/second subsequent therapy: new exploratory endpoints*

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



All patients who received treatment were included in exploratory endpoint analyses

*Endpoints determined retrospectively; †could not be determined for all patients in this trial since the date of progression was not collected for patients who had not progressed by 30 June 2010 (the cut-off for the primary analysis); ‡could not be determined in this trial since the date of subsequent progressions was not collected; **PFS2 is a surrogate for TSST;***Pre-specified exploratory objective

Ledermann J et al. Lancet Oncol 2014;15:852–861

Platinum combination followed by iPARP

Olaparib data on secondary end-points

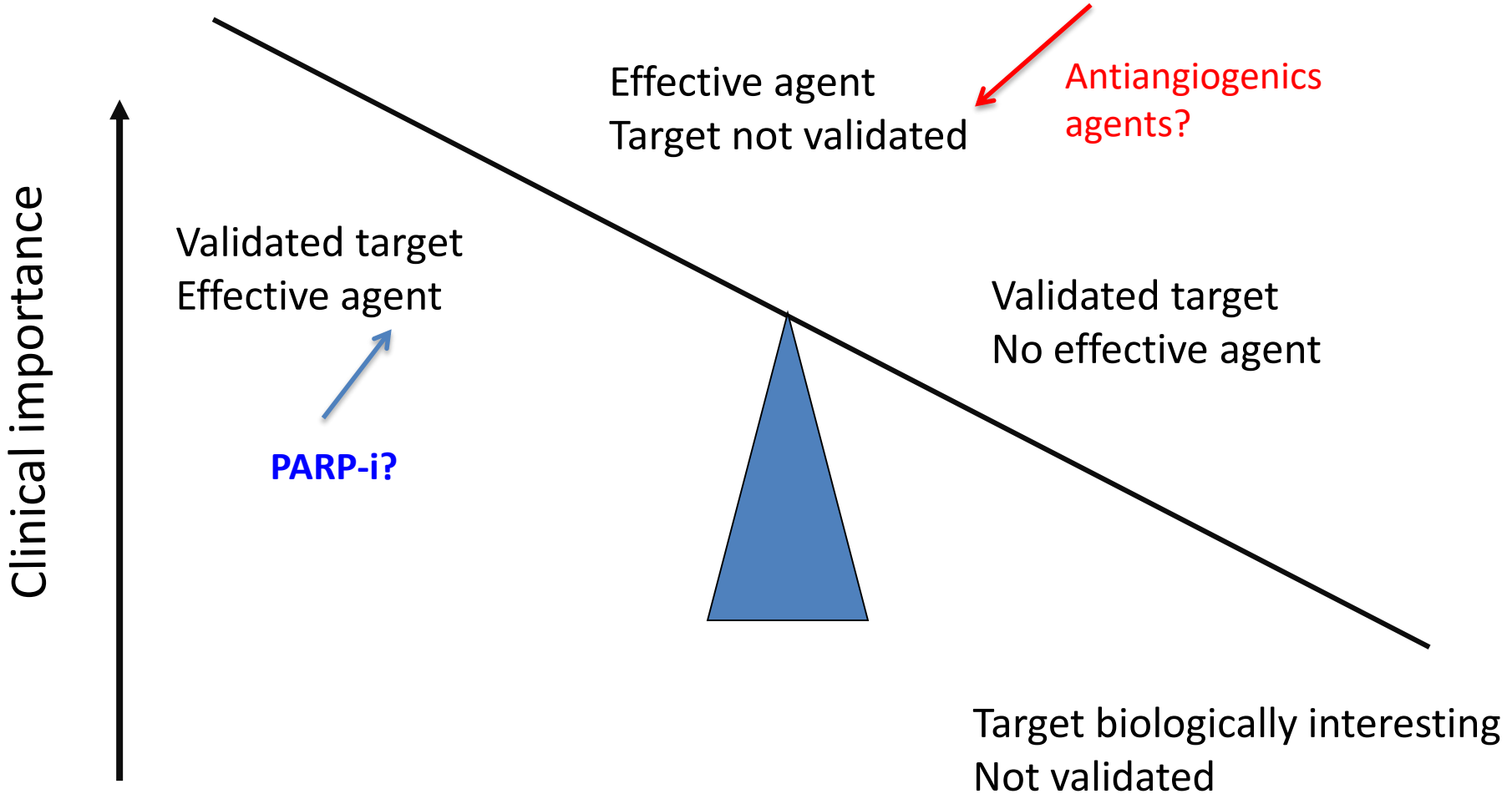
	Study 19[1]		SOLO-2[2]	
	Olaparib 400mg/12	**Control**	**Olaparib 300 mg/12**	**Control**
BRCA	germline & somatic		germline	
N	62	74	99	196
TFST	15 vs 6.2 (HR 0.32; 0.22-0.48)		27.9 vs 7.1 (HR 0.28; 0.21-0.38)	
TSST	22 vs 15.3 (HR 0.41; 0.26-0.62)		NR vs 18.2 (HR 0.37; 0.26-0.53)	

1. Ledermann et al. Lancet Oncol. 2014;15(8):852–861
2. Pujade-Lauraine et al. Lancet Oncol 2017

TFST: Time to first subsequent therapy

TSST: Time to second subsequent therapy

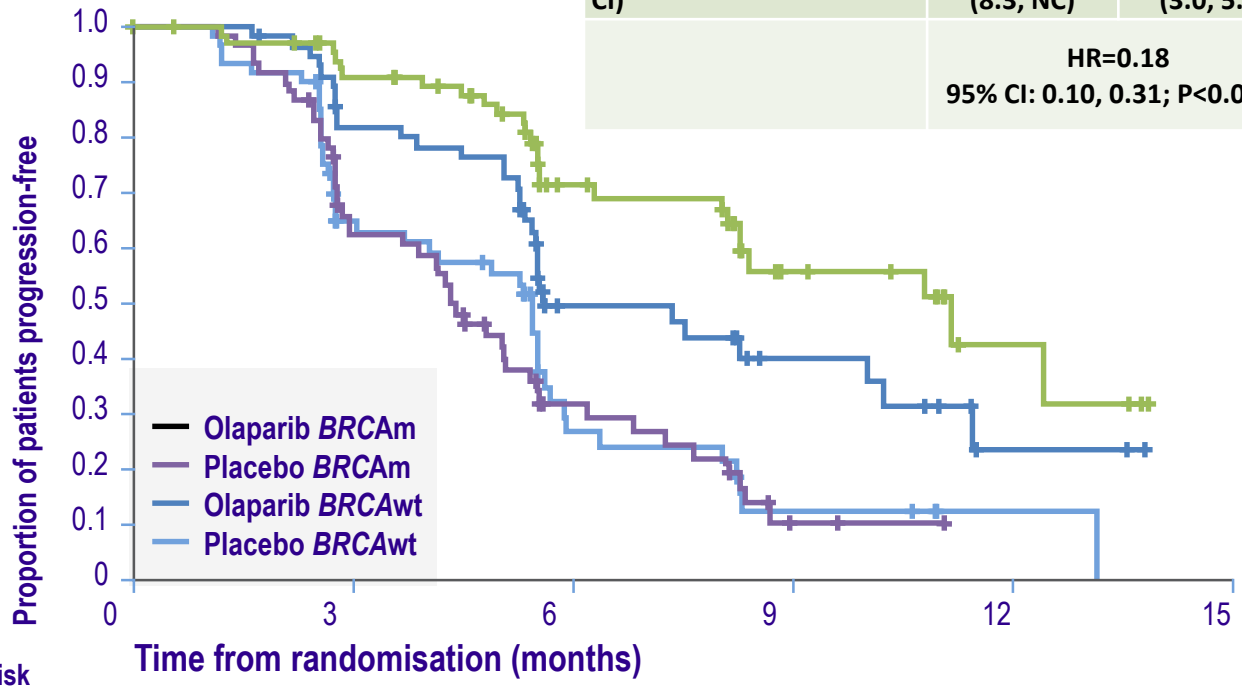
Therapeutic Targets in Ovarian Cancer



Courtesy of Dr M Birrer

STUDY 19: PFS BY *BRCA* MUTATION STATUS

	BRCAm (n=136)		BRCAwt (n=118)	
	Olaparib	Placebo	Olaparib	Placebo
Events/total patients (%)	26/74 (35%)	46/62 (74%)	32/57 (56.%)	44/61 (72%)
Median PFS, months (95% CI)	11.2 (8.3, NC)	4.3 (3.0, 5.4)	7.4 (5.5, 10.3)	5.5 (3.7, 5.6)
	HR=0.18 95% CI: 0.10, 0.31; P<0.0001		HR=0.54 95% CI: 0.34, 0.85; P=0.0075	

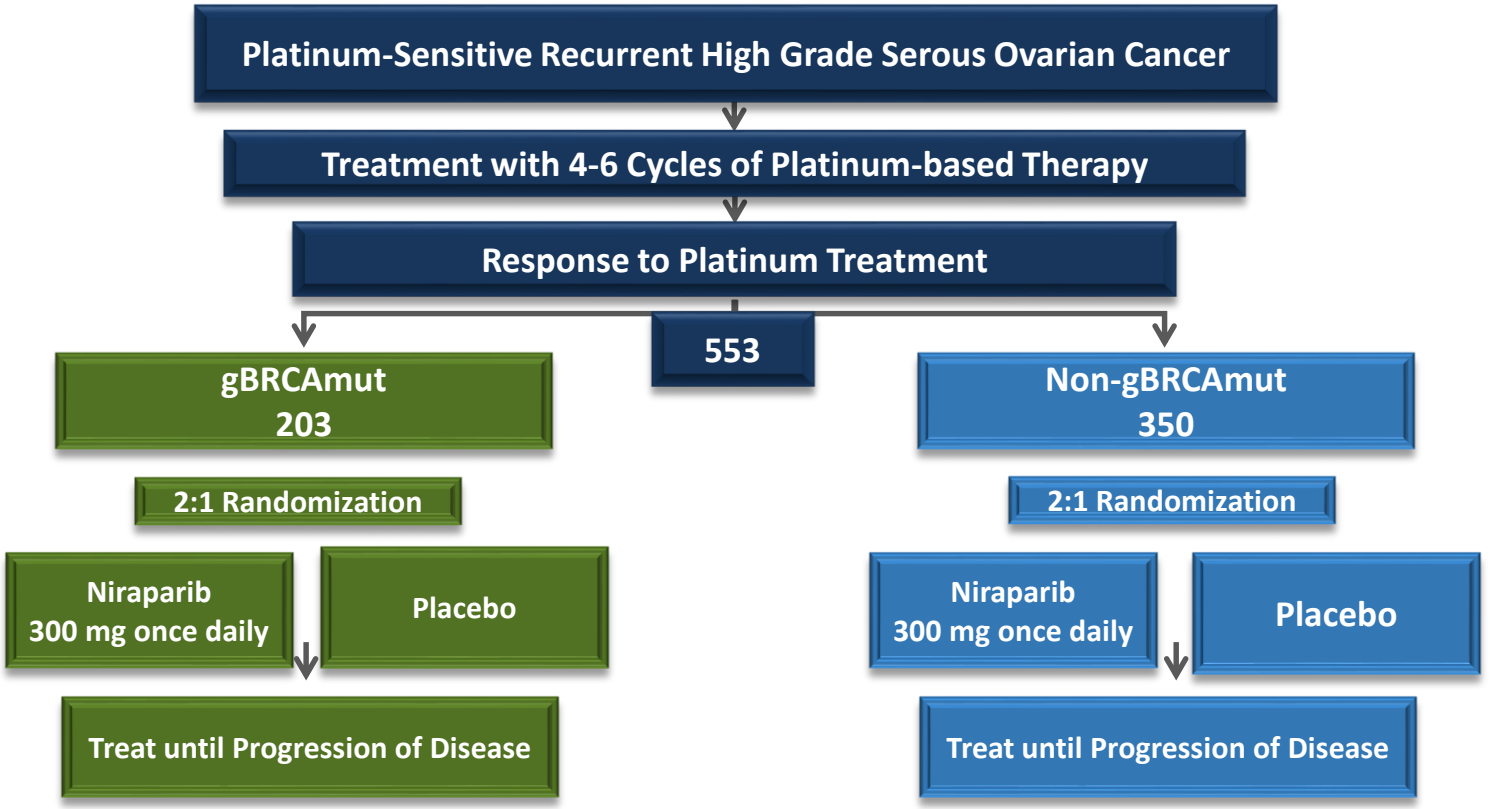


Number at risk						
Olaparib *BRCA*m	74	59	34	15	5	0
Placebo *BRCA*m	62	35	13	2	0	0
Olaparib *BRCA*wt	57	45	18	9	2	0
Placebo *BRCA*wt	61	35	10	4	1	0

Ledermann J et al. Lancet Oncol 2014;15:852–861

Platinum combination followed by iPARP

Niraparib: ENGOT ov16-NOVA study design

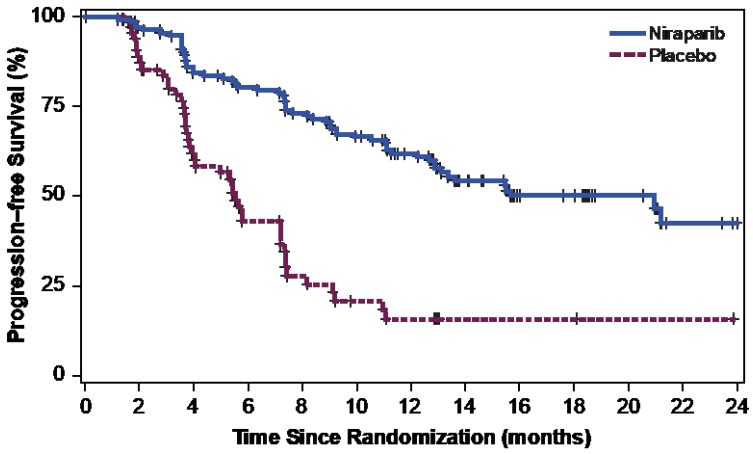


Mirza MR et al. NEJM 2016

Platinum combination followed by iPARP

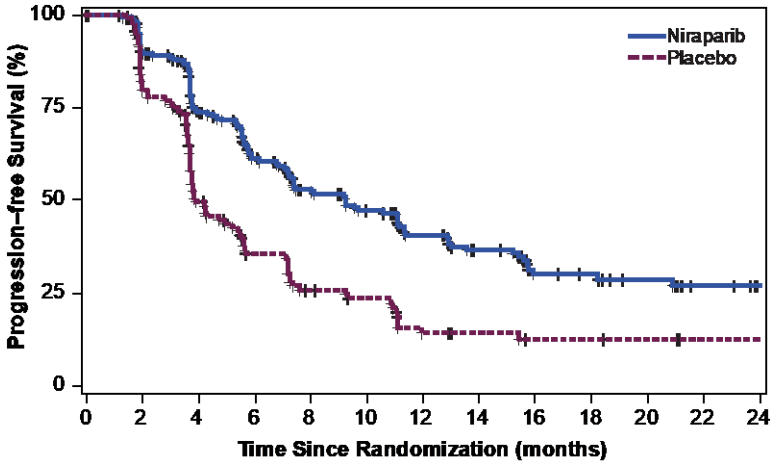
Niraparib: ENGOT ov16-NOVA primary end-point

PFS: gBRCAmut



Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value
Niraparib (N=138)	**21.0** (12.9, NR)	**0.27** (0.173, 0.410) p<0.0001
Placebo (N=65)	**5.5** (3.8, 7.2)	

PFS: non-gBRCAmut



Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value
Niraparib (N=234)	**9.3** (7.2, 11.2)	**0.45** (0.338, 0.607) p<0.0001
Placebo (N=116)	**3.9** (3.7, 5.5)	

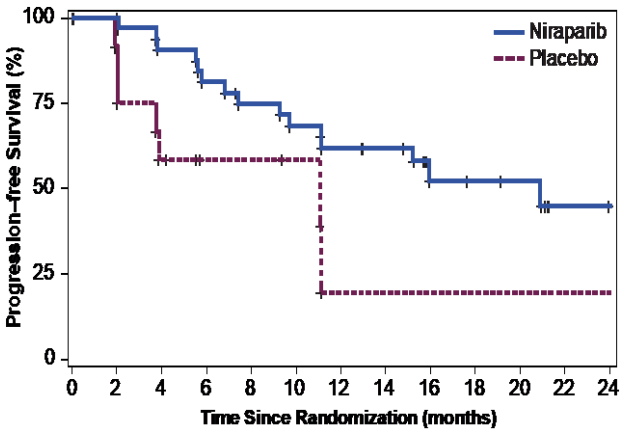
Mirza MR et al. NEJM 2016

Platinum combination followed by iPARP
Niraparib: ENGOT ov16-NOVA exploratory analyses

HRD-positive

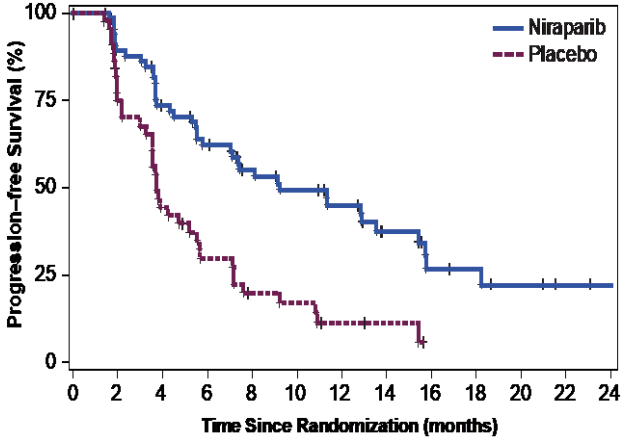
sBRCAmut

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=35)	**20.9** (9.7, NR)	**0.27** (0.081, 0.903) p=0.0248	62%	**52%**
Placebo (N=12)	**11.0** (2.0, NR)		19%	19%



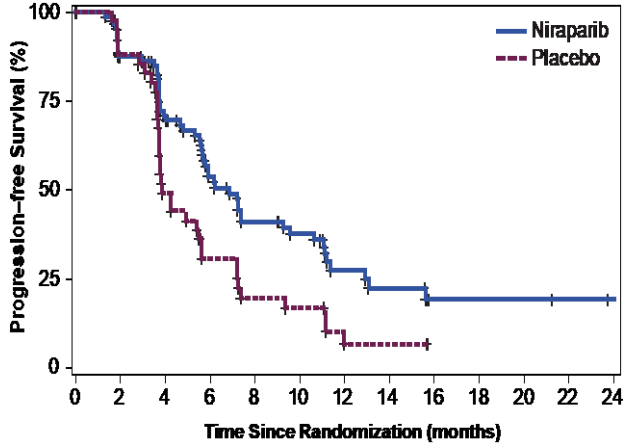
BRCAwt

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=71)	**9.3** (5.8, 15.4)	**0.38** (0.231, 0.628) p=0.0001	45%	**27%**
Placebo (N=44)	**3.7** (3.3, 5.6)		11%	6%



HRD-negative

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=92)	**6.9** (5.6, 9.6)	**0.58** (0.361, 0.922) p=0.0226	27%	**19%**
Placebo (N=42)	**3.8** (3.7, 5.6)		7%	7%



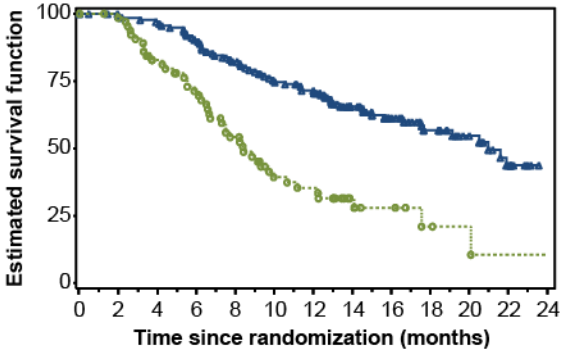
Mirza MR et al. NEJM 2016

Platinum combination followed by iPARP

Niraparib: ENGOT ov16-NOVA secondary end-point

Time to First Subsequent Therapy (TFST)

g*BRCA*mut



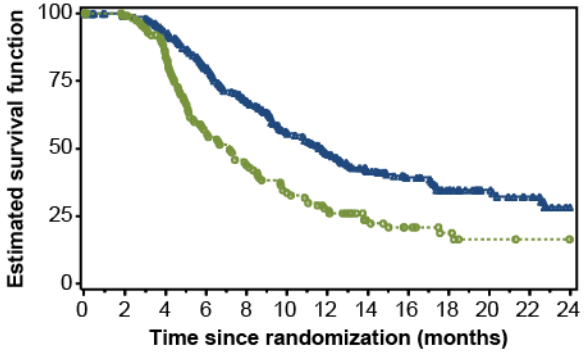
HR=0.31, P<0.0001

Median TFST (months)

Niraparib: **21.0**

Placebo: **8.4**

Non-g*BRCA*mut Overall



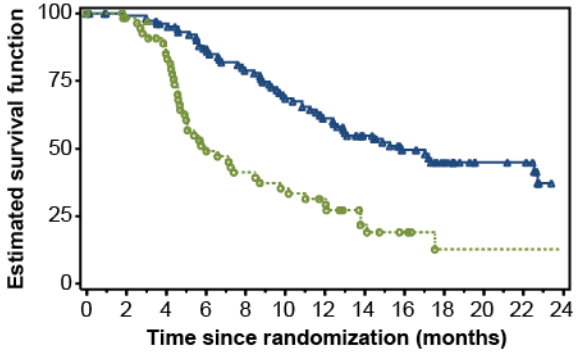
HR=0.55, P<0.0001

Median TFST (months)

Niraparib: **11.8**

Placebo: **7.2**

Non-g*BRCA*mut HRDpos

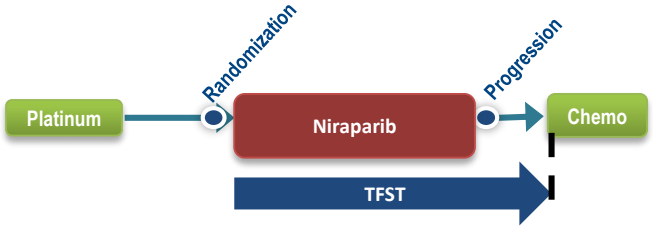


HR=0.36, P<0.0001

Median TFST (months)

Niraparib: **15.9**

Placebo: **6.0**



D. Manher et al. SGO 2017

ARIEL3: Study Design

Rucaparib

Patient eligibility

- High-grade serous or endometrioid epithelial OC, primary peritoneal, or fallopian tube cancers
- ≥2 prior lines of platinum-based treatments
- No prior PARP inhibitors
- Sensitive to penultimate platinum
- Responding to most recent platinum (CR or PR)*
  - Excludes patients without assessable disease following surgery before more recent platinum-based therapy
- ECOG PS ≤1
- CA-125 within normal range
- No restriction on size of residual tumour

Randomisation 2:1

Stratification

- HRR status by NGS mutation analysis
  - Mutation in *BRCA1*, *BRCA2*, or non-*BRCA* HRR gene†
  - No mutation in *BRCA* or HRR gene
- Response to recent platinum
  - CR
  - PR
- Progression-free interval after penultimate platinum
  - 6 to <12 months
  - ≥12 months

Rucaparib 600 mg BID n=375

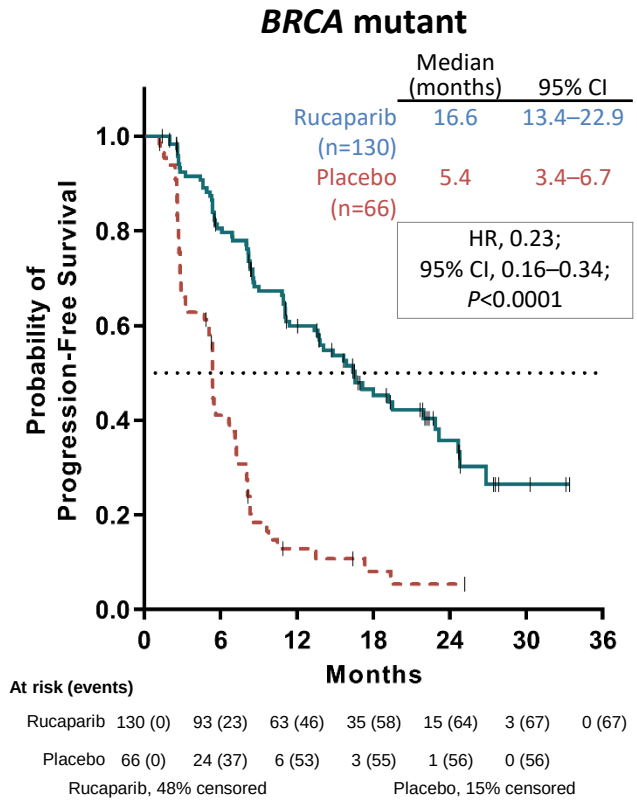
Placebo BID n=189

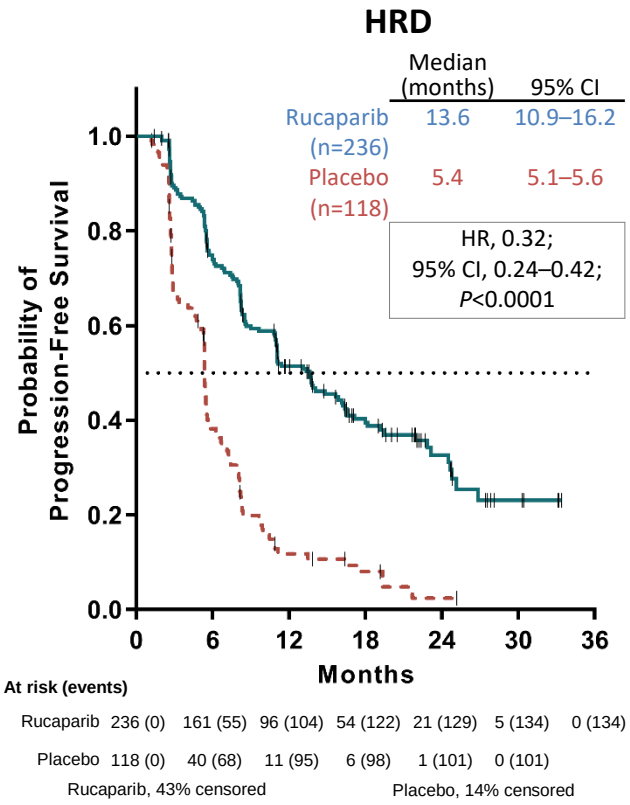
Primary endpoint: Investigator-assessed PFS (per RECIST)

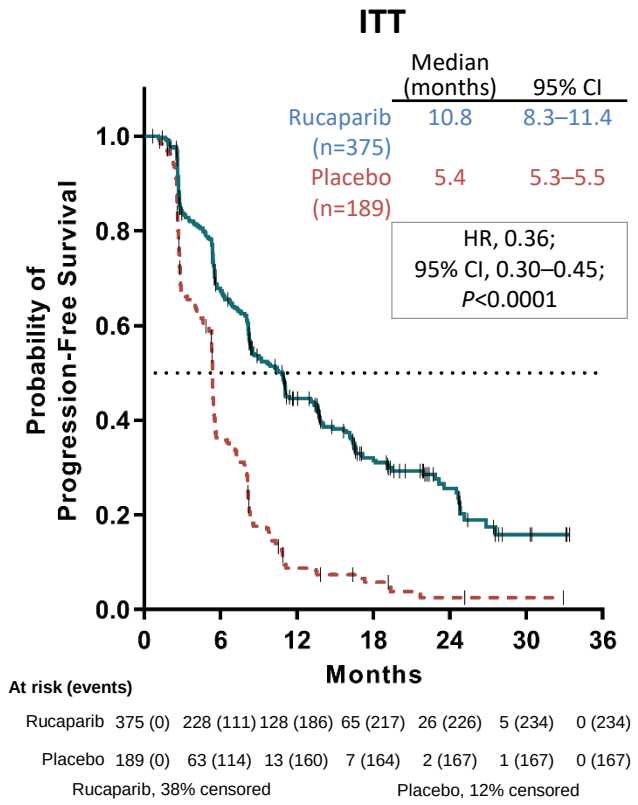
Ledermann J, ESMO 2017

ARIEL3: Investigator-Assessed Progression-Free Survival

Rucaparib



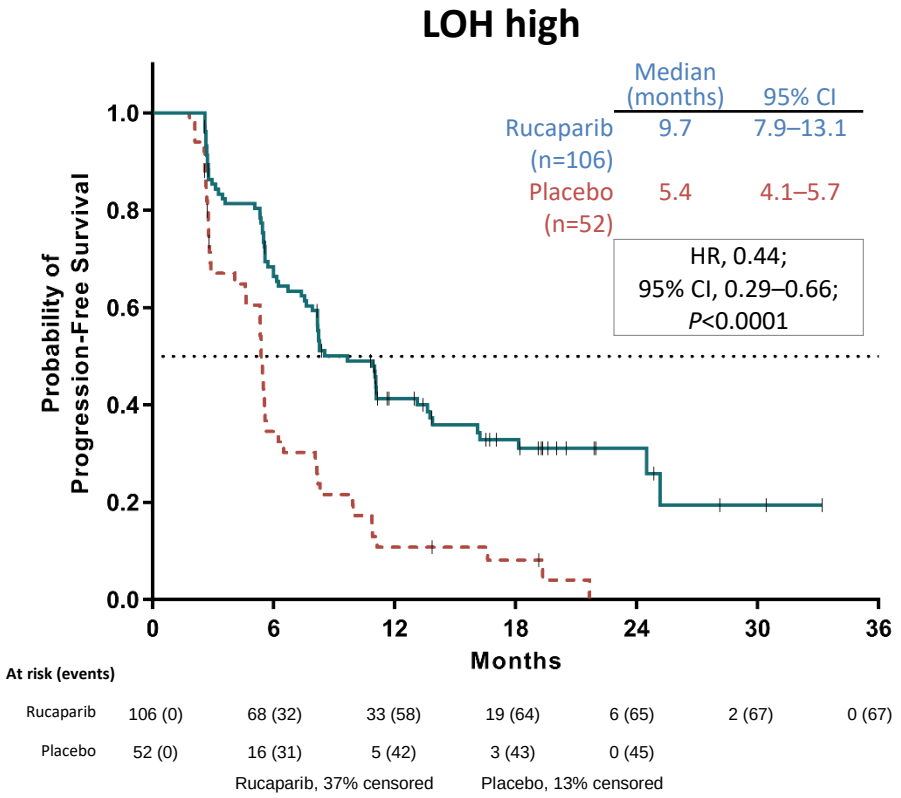


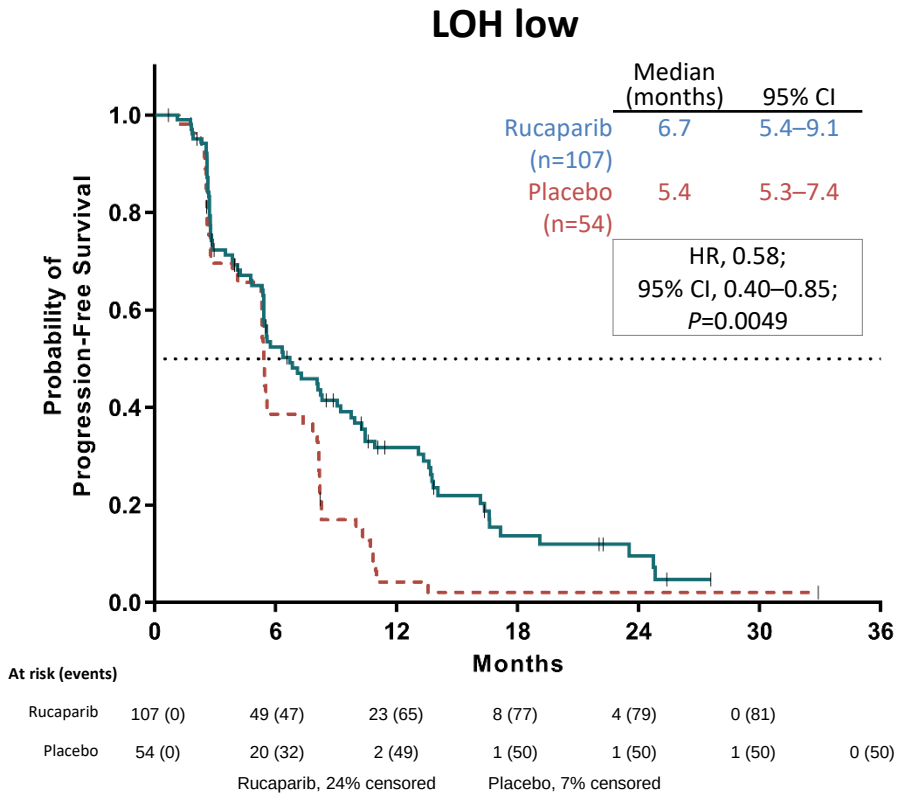


PARSGO GCIG Marrakech April 2018

Ledermann J, ESMO 2017

ARIEL3: Investigator-Assessed Progression-Free Survival: Patients with *BRCA* Wild-Type OC (exploratory analysis)





Ledermann J, ESMO 2017

Tumors with *RAD51C* alterations are BRCA-like (high genomic LOH) and responded to **Rucaparib**

HR-pathway gene	Genetic alteration type	Germline/somatic inference	HRD molecular subgroup	RECIST response	CA-125 response
NBN	Truncation	Germline	Biomarker-negative	Partial Response	Yes
RAD51C	Truncation	Germline	BRCA-like	Partial Response	Yes
RAD51C	Homozygous Del	Somatic	BRCA-like	Partial Response	Yes
RAD51C	Splice	Germline	BRCA-like	Partial Response	Yes
RAD51C	Splice	Germline	BRCA-like	Stable Disease	Yes
ATM	Homozygous Del	Somatic	Indeterminate	Stable Disease	Yes
RAD51L3	Truncation	Indeterminate	BRCA-like	Stable Disease	Yes
BRIP1	Splice	Germline	Biomarker-negative	Stable Disease	No
BRIP1	Truncation	Germline	Biomarker-negative	Stable Disease	No
CHEK2	Splice	Indeterminate	Biomarker-negative	Stable Disease	No
CHEK2	Truncation	Germline	BRCA-like	Stable Disease	No
RAD51L1	Truncation	Indeterminate	Biomarker-negative	Stable Disease	No
NBN	Truncation	Germline	Indeterminate	Stable Disease	Not evaluable
RAD54L	Truncation	Somatic (subclonal)	Biomarker-negative	Stable Disease	Not evaluable
FANCA	Homozygous Del	Somatic	BRCA-like	Stable Disease	Not evaluable
FANCI	Truncation	Germline	Biomarker-negative	Progressive Disease	No
ATM	Truncation	Somatic	Indeterminate	Not evaluable	Not evaluable

Safety profile of iPARP

	Olaparib (SOLO-2)	Niraparib (ENGOT OV-16 / NOVA)	Rucaparib (ARIEL 3)
Discontinuation	11%	14.7%	13.4%
Dose reduction	25%	66,5%	54.6%
Related SAE	17.9%	16,9%	-
Nausea /Vomiting G>3	2.6%	3%	7.8%
Fatigue G>3	4.1%	8%	6.7%
Anemia G>3	19,5%	25 %	18.8%
Thrombopenia G>3	1%	33 %	5.1%
Neutropenia G>3	5.1%	19%	6.7%
MDS	4 (2.1%)	5 (1.4%)	3 (0.8%)
GOT/GPT G>3	-	-	10.5%

General recommendations
on the platinum-combination followed by
iPARP option

- It should the **preferred choice for BRCA mutated** (germ-line or somatic) patients, if no contraindication.
- None HRD test is good enough to exclude benefit of iPARP in BRCAwt
- Also the preferred option in **BRCA wild-type in the following scenarios**
  - High-grade serous or endometrioid sub-type **or**
  - More than 2 prior lines **or**
  - No need for a rapid or higher response due to severe ascites and/or pleural effusion (bev-combination may be preferred in this case)
- Toxicity profile is generally favorable (rate of discontinuation 11-15%) but a leaning curve is needed to manage specific side effects of each iPARP

CONCLUSION

- Very optimistic about new treatments for the first time in 20 years.
  - AA and PARP inhibition are already a reality, with positive data from randomized trials
  - First positive results without chemotherapy (Monk, IGCS 2014, Liu ASCO 2014)

- Patient selection, using robust predictive biomarkers, will be key to success.


SHUKRAAN