Anti-angiogenesis, PAPR inhibitors, CDK 4/6 inhibitors, Fusion protein

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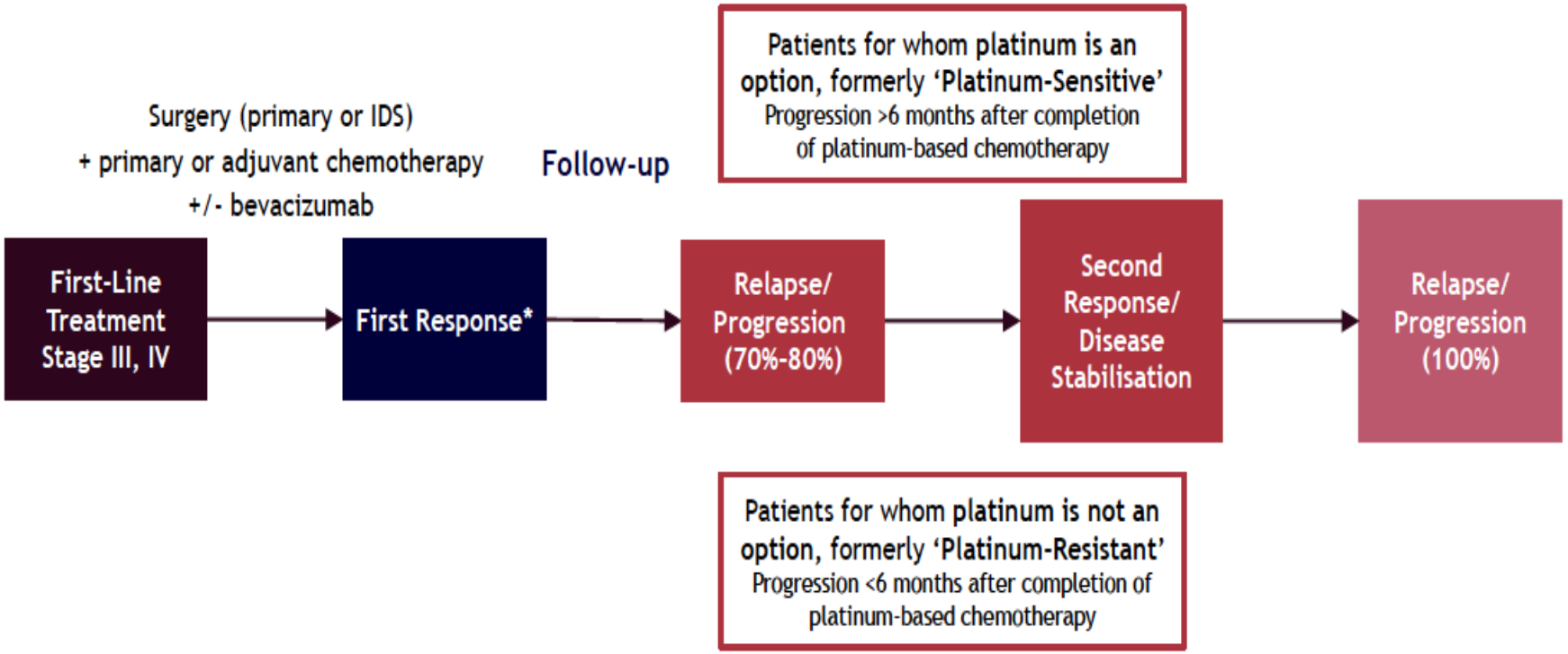
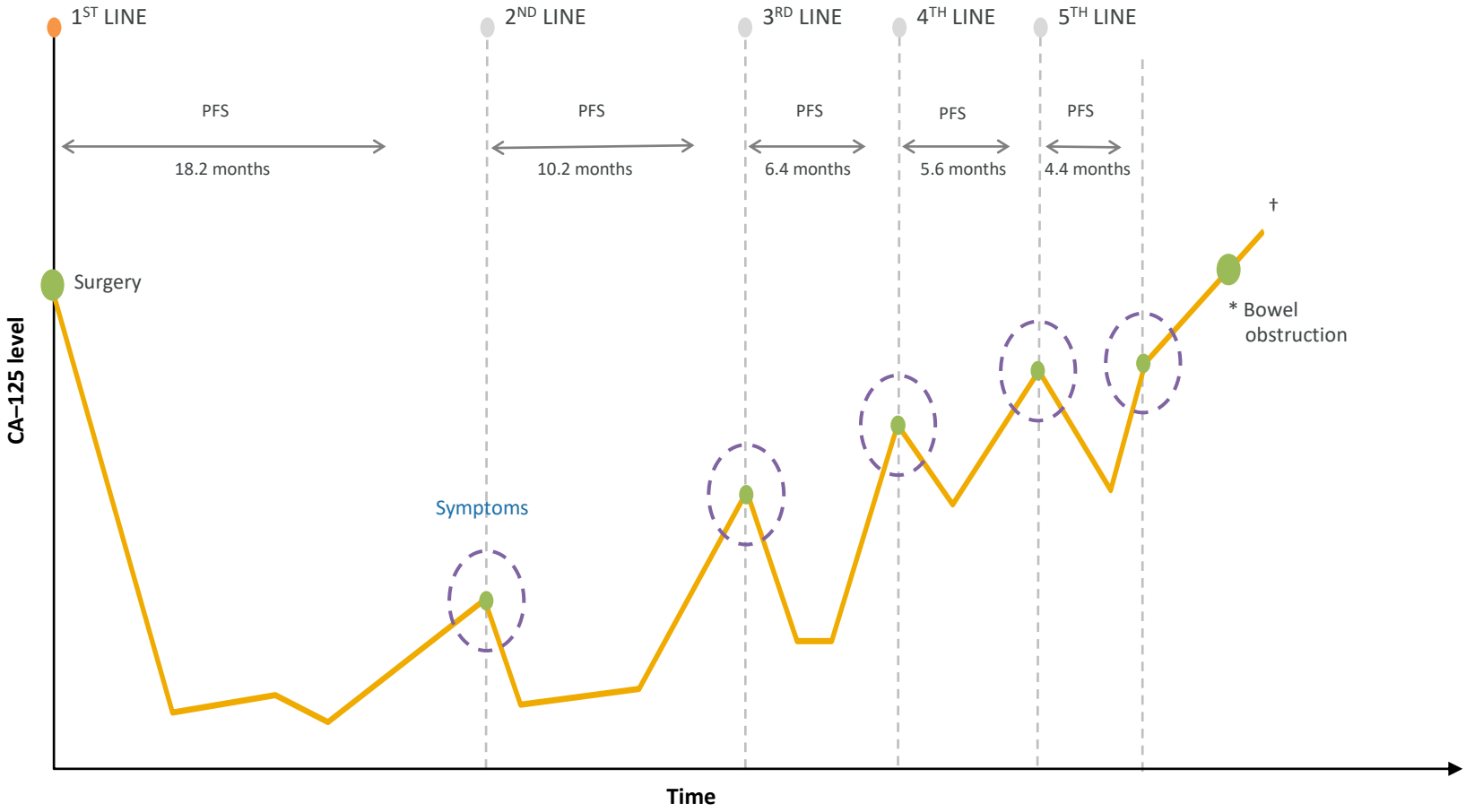
The Typical Course of Advanced Ovarian Cancer[1-5]



*Around 5% of patients are primary treatment-refractory, meaning disease progressed during therapy or within 4 weeks after the last dose.
IDS=interval debulking surgery.

1. Ledermann JA et al. *Ann Oncol*. 2013;24(Suppl 6):vi24-vi32. 2. Giornelli GH. *Springerplus*. 2016;5(1):1197. 3. Pignata S et al. *Ann Oncol*. 2017;28(suppl_8):viii51-viii56. 4. du Bois A et al. *Cancer*. 2009;115(6):1234-1244. 5. Wilson MK et al. *Ann Oncol*. 2017;28(4):727-732.

The majority of patients receive multiple lines of cytotoxic chemotherapy which is associated with cumulative toxicity and decreasing periods of remission[1-4]

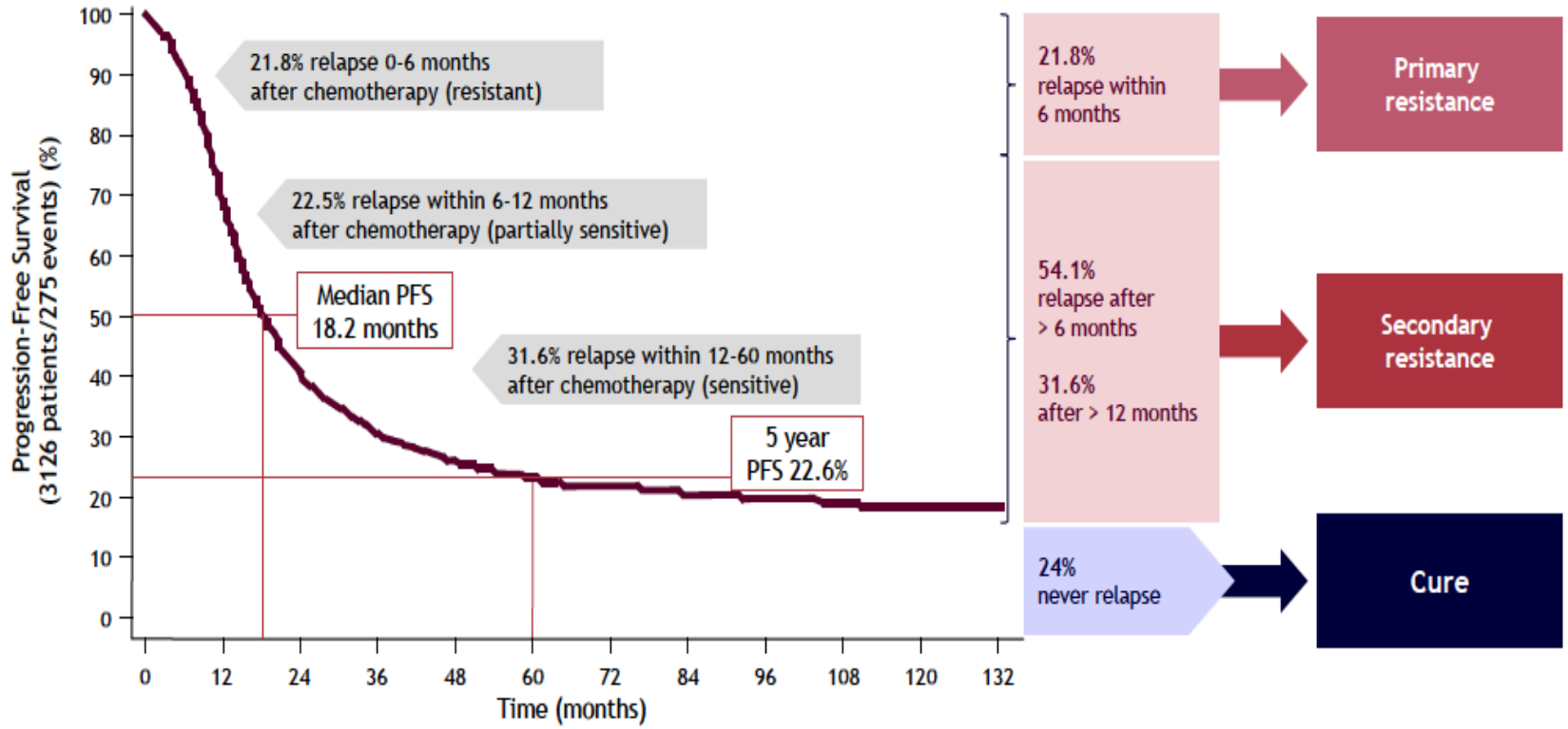


PFS = progression-free survival; CA-125 = cancer antigen 125; † = Common indicator of fatality

1. Markman, M. et al. The Oncologist. 2000;5(1):26–35; 2. Hanker LC, et al. Ann Oncol. 2012;23(10):2605–2612; 3. Armstrong, D. K. The Oncologist 7, 20–28 (2002); 4.Fotopoulou, C. Eur. J. Cancer Suppl. 12, 13–16 (2014)

Ovarian Cancer: Course of Disease

FIGO IIB-IV: Individual patient data meta-analysis of three AGO phase 3 first-line trials (AGO Ovar 3, 5, 7)[1,2]

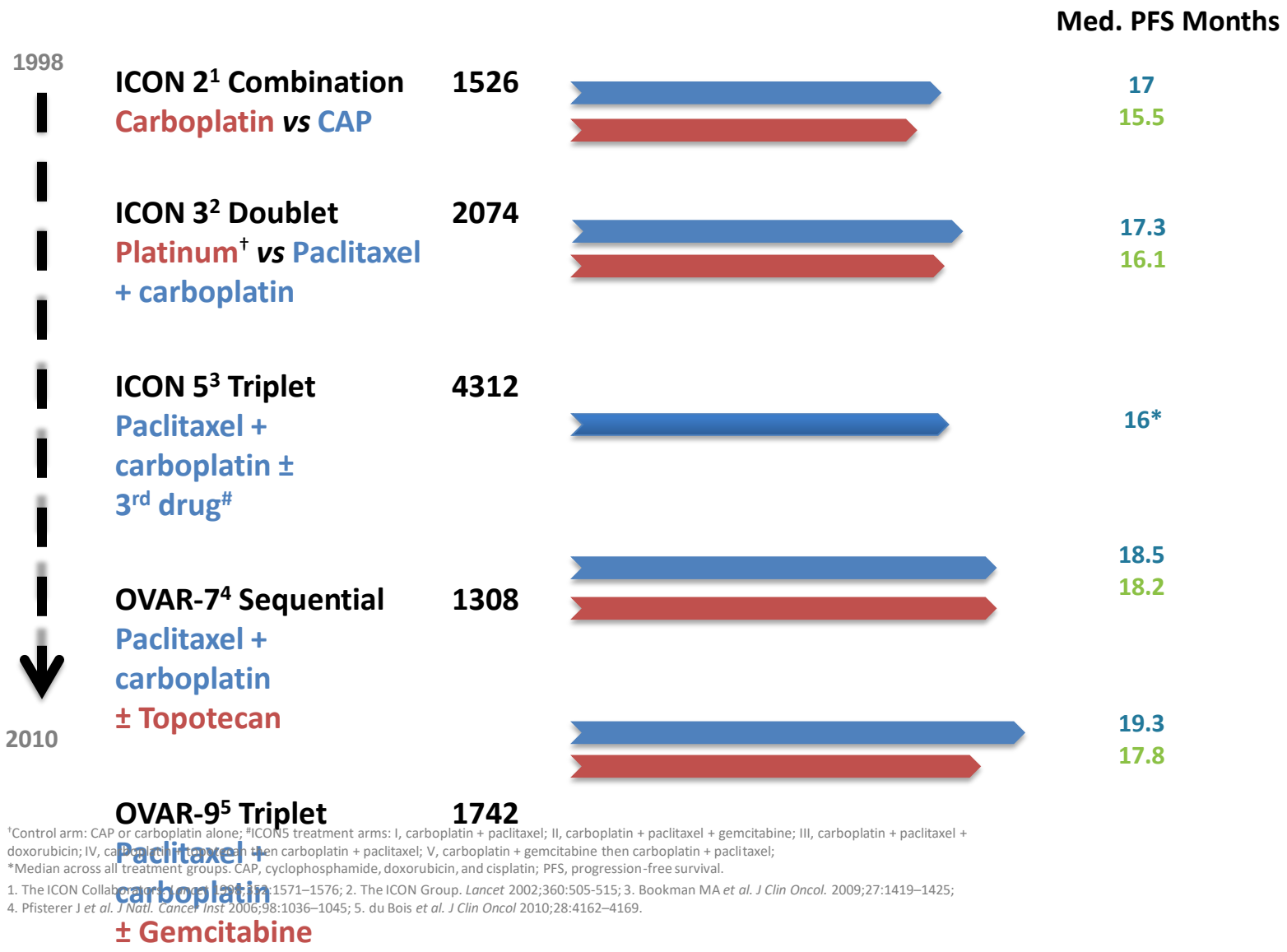


AGO=Arbeitsgemeinschaft Gynäkologische Onkologie; FIGO=International Federation of Gynecology and Obstetrics; PFS=progression-free survival.

1. du Bois A et al. *Cancer*. 2009;115(6):1234-1244. 2. Data from the AGO Study Group.

Adapted from a slide curtesy of Prof Frederik Marmé.

Progression Free survival- First-line Ovarian Cancer Trials



- †Control arm: CAP or carboplatin alone; #ICON5 treatment arms: I, carboplatin + paclitaxel; II, carboplatin + paclitaxel + gemcitabine; III, carboplatin + paclitaxel + doxorubicin; IV, carboplatin + paclitaxel then carboplatin + paclitaxel; V, carboplatin + gemcitabine then carboplatin + paclitaxel;
  *Median across all treatment groups. CAP, cyclophosphamide, doxorubicin, and cisplatin; PFS, progression-free survival.
- 1. The ICON Collaborative Group. *Lancet* 1998;352:1571–1576; 2. The ICON Group. *Lancet* 2002;360:505-515; 3. Bookman MA *et al. J Clin Oncol.* 2009;27:1419–1425; 4. Pfisterer J *et al. J Natl. Cancer Inst* 2006;98:1036–1045; 5. du Bois *et al. J Clin Oncol* 2010;28:4162–4169.

First – line anti-angiogenic treatment

Anti-angiogenic therapy improved progression-free survival (PFS) but not overall survival

Study	Agent	Setting	Median PFS	HR-PFS (95% CI)	HR-OS (95% CI)
GOG 218[1]	Bevacizumab	Front-line/Maintenance	14.7	0.72 (0.63-0.82)	0.89 (0.75-1.04)
ICON7[2]	Bevacizumab	Front-line/Maintenance	19.8	0.81 (0.70-0.94)	0.99 (0.85-1.14)
AGO-OVAR12[3]	Nintedanib	Front-line/Maintenance	17.2	0.84 (0.72-0.98)	NR
AGO-OVAR16[4]	Pazopanib	Primary Maintenance	17.9	0.77 (0.64-0.91)	0.99 (0.75-1.32)

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. LBA ESGO 2013 Liverpool, UK
4. du Bois A et al. J Clin Oncol. 2013;31(18suppl):LBA5503.

First-line GOG-0218 and ICON7: carboplatin/paclitaxel ± bevacizumab → bevacizumab

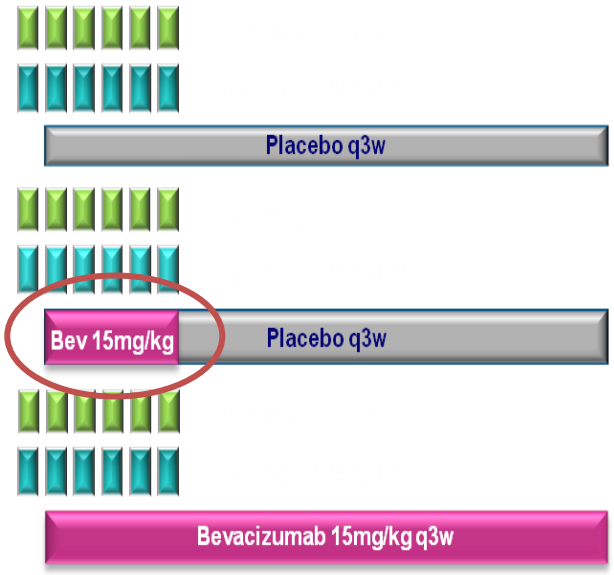
GOG-0218
Stage III or IV
65% R1 resection

Front-line: epithelial OV, PP or FT cancer

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

N=1,873

RANDOMISE



PFS benefit 3.8 mo
OS= NS

15 months

ICON 7
High risk Stage I–IIA
Stage IIB–IV
27% R1 resection

Stage I–IIa (grade 3 or clear cell) or
Stage IIb–IV (all grades/ histologic types) debulked ≤1 cm or >1 cm OC, PP, FTC
(n=1,528)

RANDOMISE

PFS benefit 3.8 mo
OS= NS (HR=0.89)

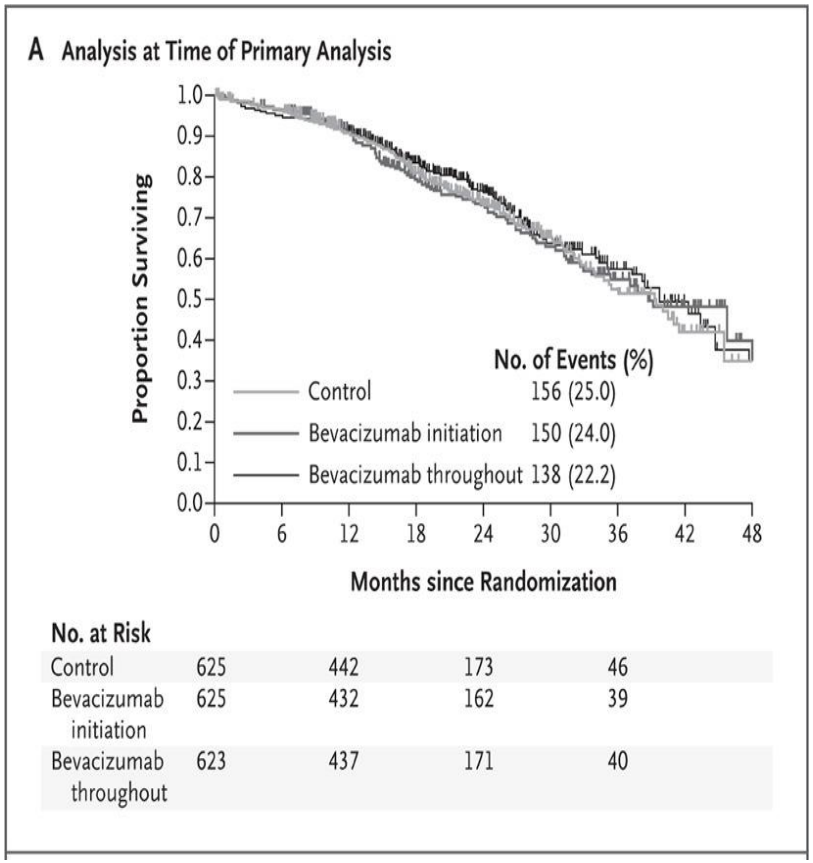
12 months

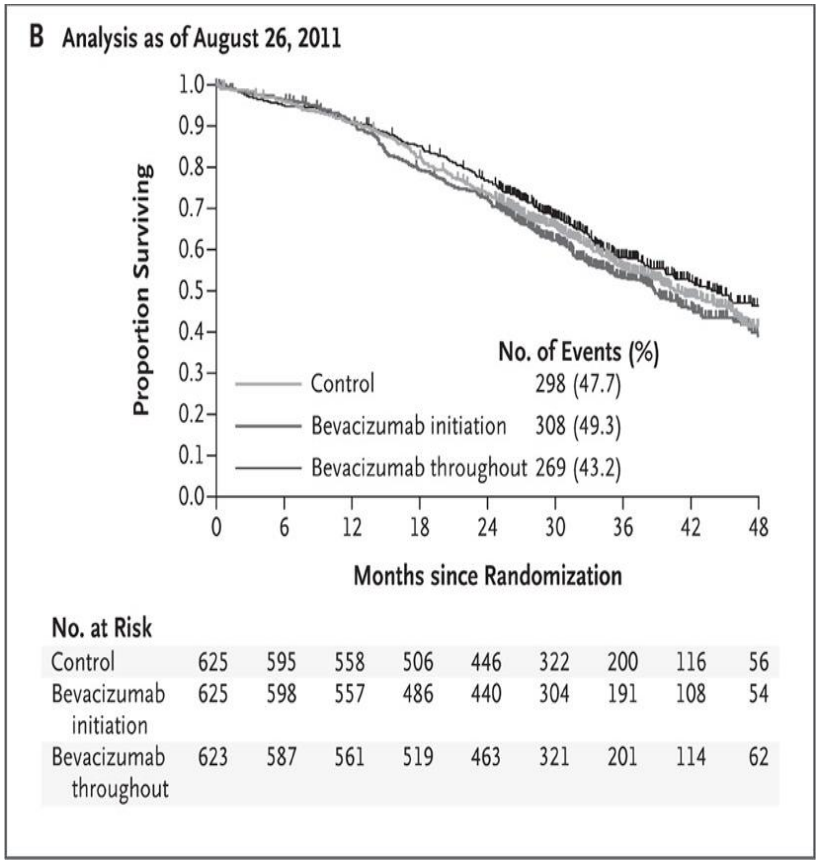
Burger R, et al. N Engl J Med 2011;365(26):2473–2483.
Perren T, et al. N Engl J Med 2011;365(26):2484–2496.

OC, ovarian cancer; OV, ovarian; FT, fallopian tube; PP, primary peritoneal

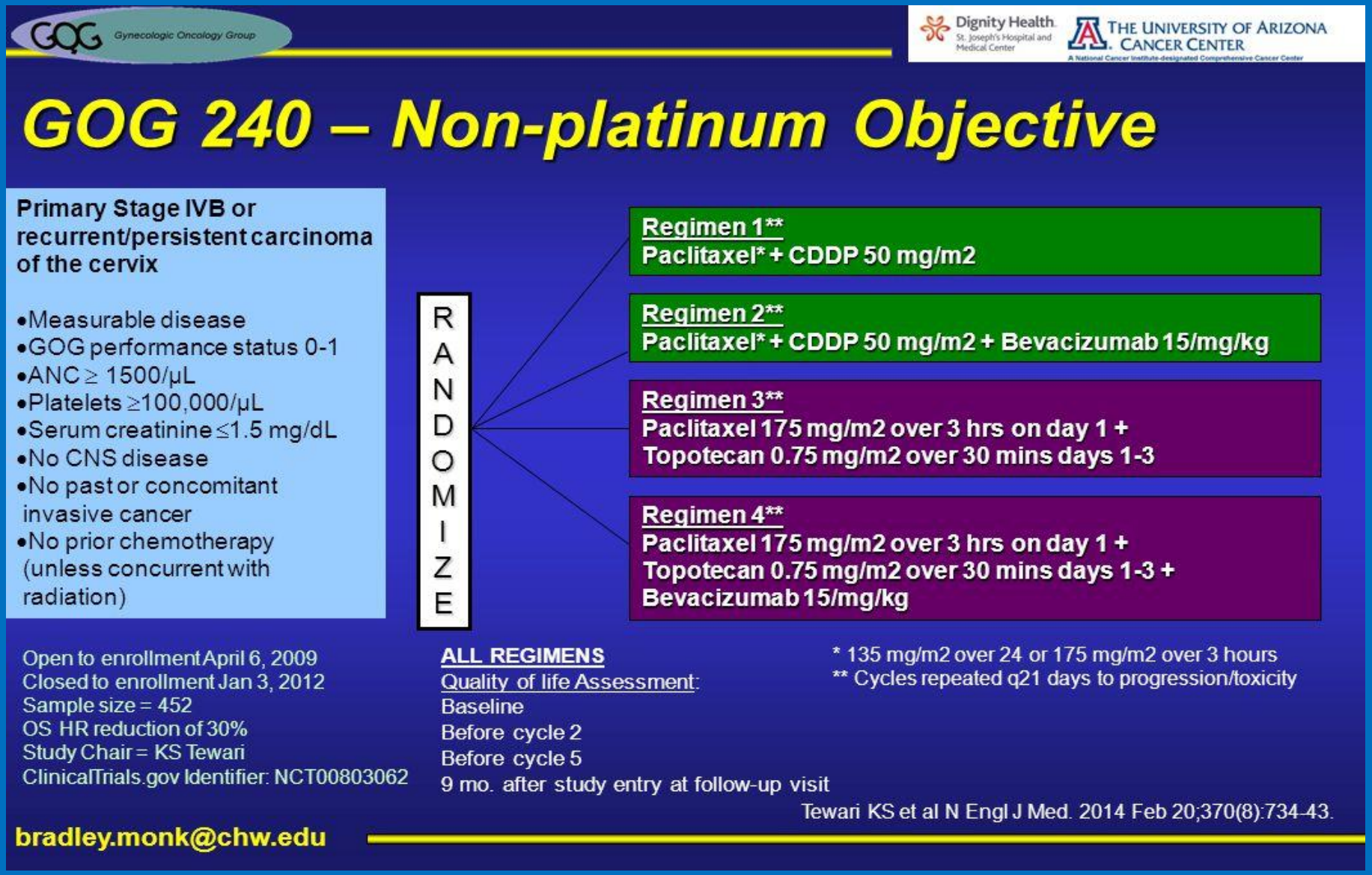
GOG 218 OS

- No significant difference among 3 arms
- Survival benefit in patients with stage IV or with ascites in post hoc analysis





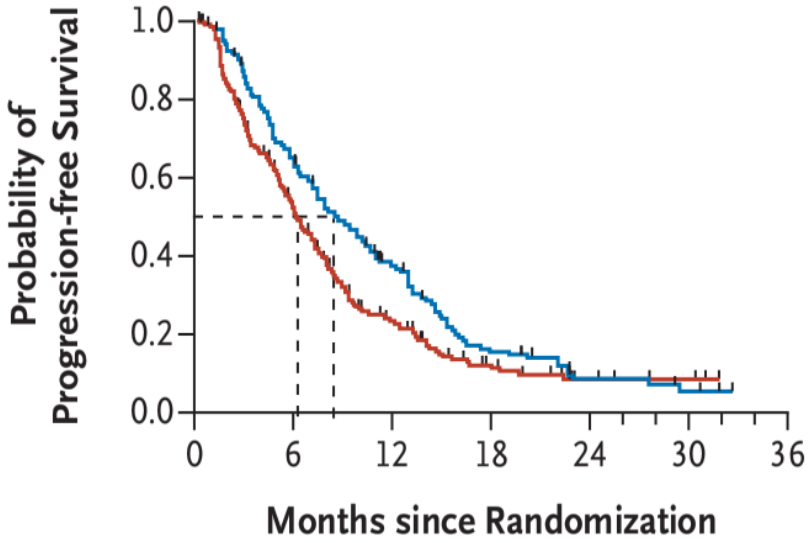
What's the standard therapy ?



How much does Bevacizumab add ?

	Events no. (%)	Median Progression-free Survival mo
Chemotherapy (N=225)	184 (82)	5.9
Chemotherapy+Bev (N=227)	183 (81)	8.2

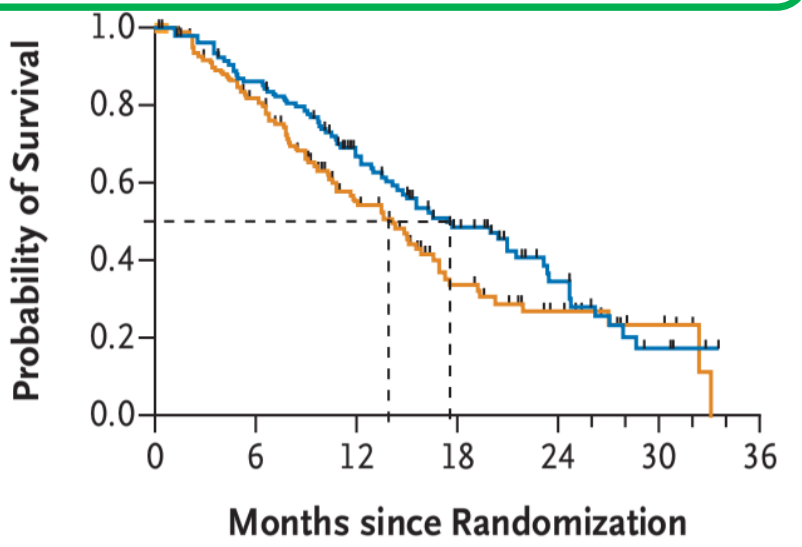
Hazard ratio, 0.67 (95% CI, 0.54–0.82); two-sided P=0.002



No. at Risk						
Chemotherapy	225	103	40	14	6	3
Chemotherapy +bev	227	132	70	22	6	3

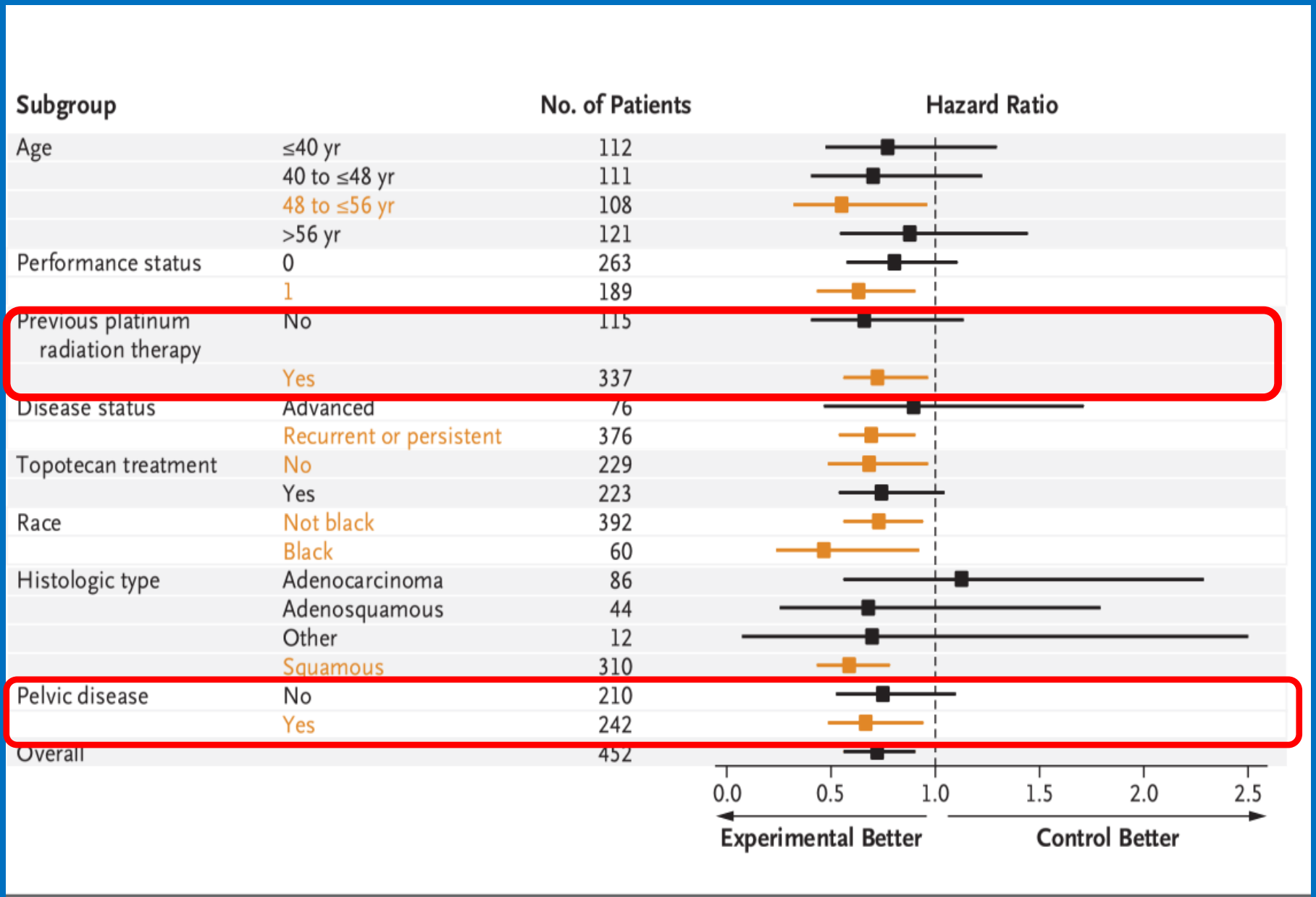
	Events no. (%)	Median Overall Survival mo
CP (N=114)	69 (61)	14.3
CP+Bev (N=115)	66 (58)	17.5

Hazard ratio, 0.68 (95% CI, 0.48–0.97); one-sided P=0.04



No. at Risk						
CP	114	89	50	22	12	5
CP+bev	115	94	63	37	17	5

Does it benefit all?



Bevacizumab- Adding months and toxicity!

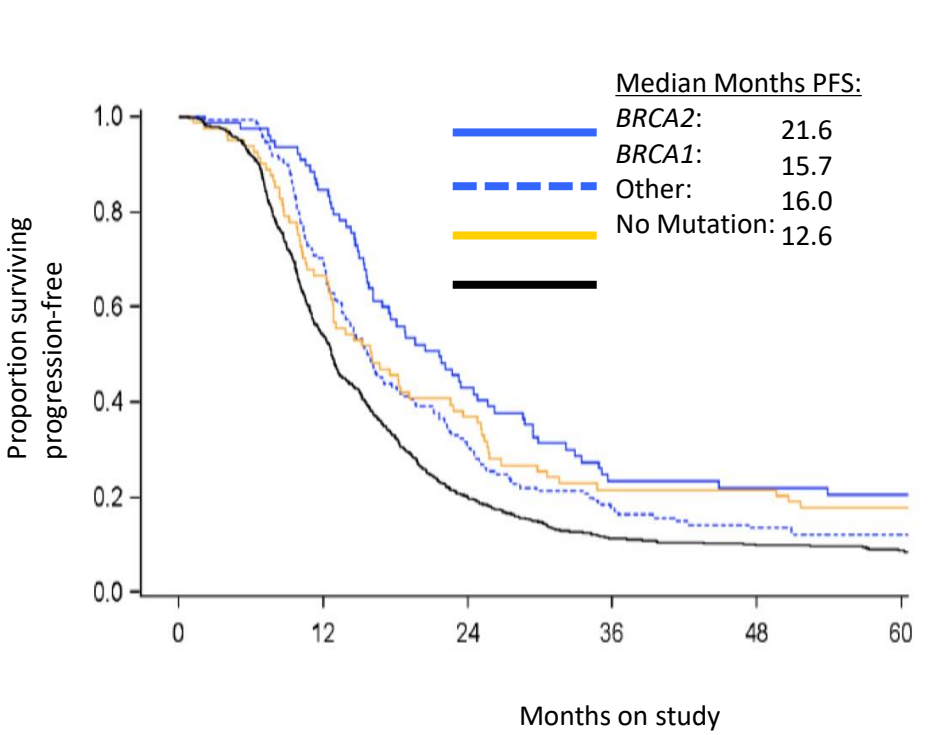
Table 1. Selected Adverse Events among the Study Patients, According to Treatment Group.*

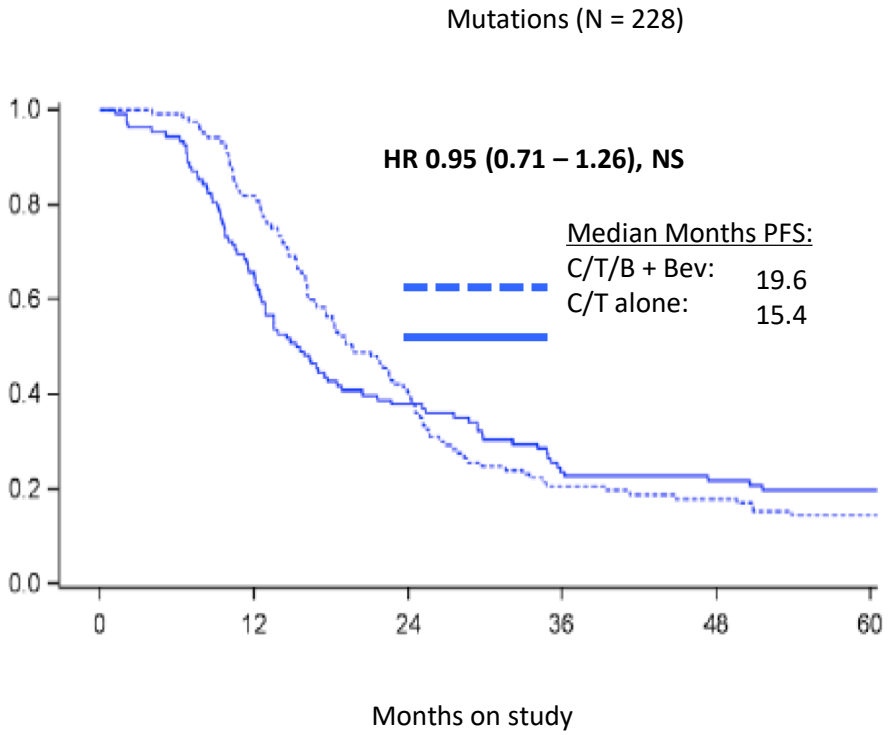
Event	Chemotherapy Alone (N=219)	Chemotherapy plus Bevacizumab (N=220)	Odds Ratio (95% CI)	P Value
	no. of patients (%)			
Gastrointestinal events, excluding fistulas (grade ≥2)	96 (44)	114 (52)	1.38 (0.93–2.04)	0.10
Fistula (grade ≥3)				
Gastrointestinal	0	7 (3)	NA (1.90–∞)	0.02
Genitourinary	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12
Total†	1 (<1)	13 (6)	13.69 (2.01–584.00)	0.002
Hypertension (grade ≥2)‡	4 (2)	54 (25)	17.50 (6.23–67.50)	<0.001
Proteinuria (grade ≥3)	0	4 (2)	NA (0.90–∞)	0.12
Pain (grade ≥2)	62 (28)	71 (32)	1.21 (0.79–1.85)	0.41
Neutropenia (grade ≥4)	57 (26)	78 (35)	1.56 (1.02–2.40)	0.04
Febrile neutropenia (grade ≥3)	12 (5)	12 (5)	1.00 (0.40–2.48)	1.00
Thromboembolism (grade ≥3)	3 (1)	18 (8)	6.42 (1.83–34.4)	0.001
CNS bleeding (grade ≥3)	0	0	NA	
Gastrointestinal bleeding (grade ≥3)§	1 (<1)	4 (2)	4.04 (0.39–200.00)	0.37
Genitourinary bleeding (grade ≥3)§	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12

BRCA mutations confer a better prognosis – what is the outcome of these patients with 'standard of care' chemotherapy and bevacizumab?

GOG 218 : Carboplatin/paclitaxel versus carboplatin/paclitaxel+ bevacizumab with bevacizumab maintenance

- There was no additional statistically significant benefit seen with the addition of Bev to BRCA mutated patients in GOG218



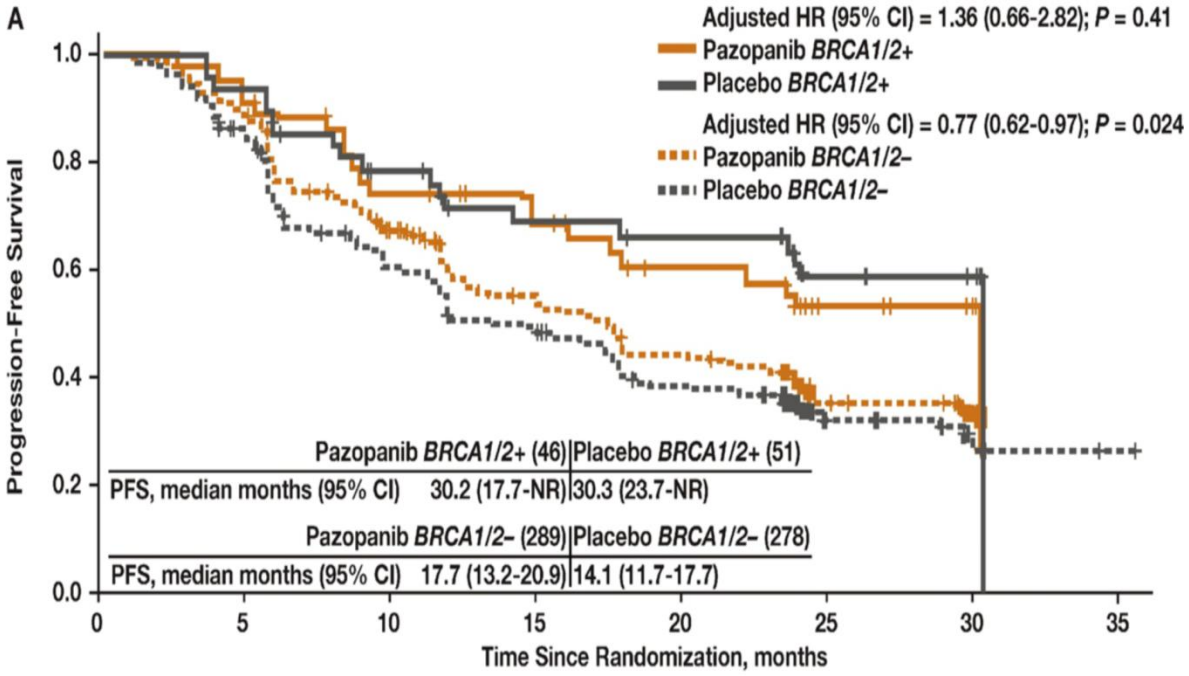


Norquist et al SGO 2016

Maintenance therapy post chemotherapy with pazopanib in patients with a BRCA mutation

AGO-OVAR-16: Carboplatin/paclitaxel followed by maintenance Pazopanib or placebo

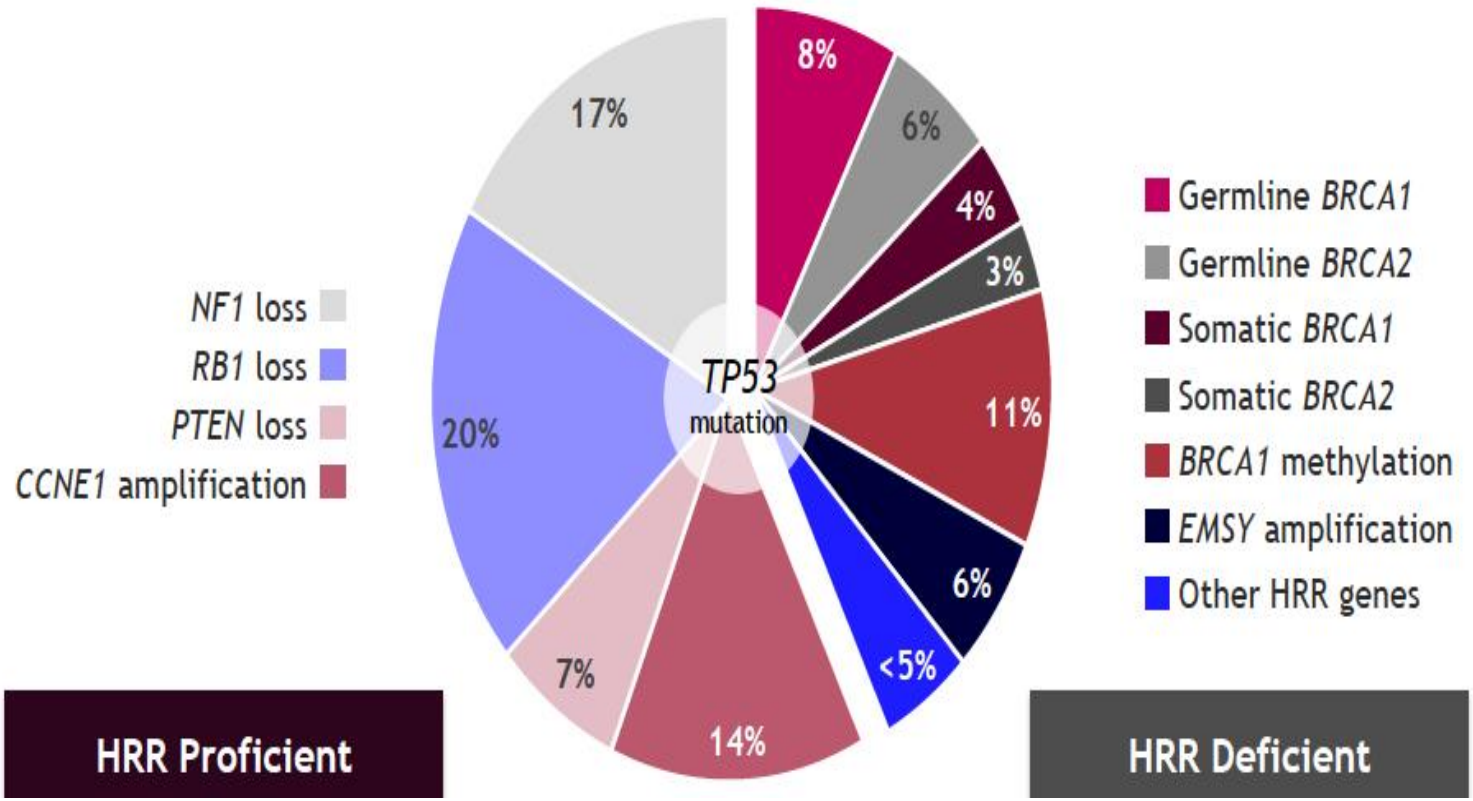
– *No advantage of using Pazopanib in BRCA mutated patients over placebo*



- 664 patients sequenced for BRCA
- 15% BRCA^{mut}
  - 70 % upfront surgery
  - 92% stage III/IV patients
- Median PFS in patients with BRCA^{mut}
  - Pazopanib 30.2 months
  - Placebo 30.3 months

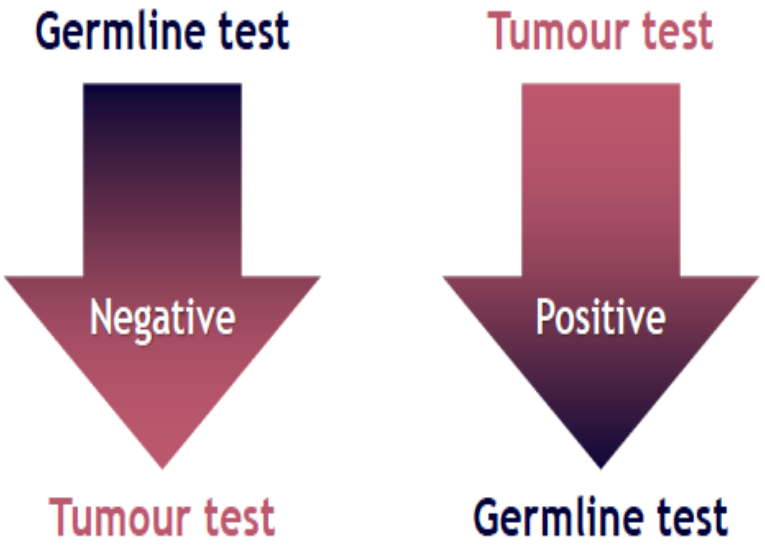
Harter et al Gyn Oncol 2016

Rationale for PARP Inhibitors in Ovarian Cancer: High-Grade Serous Ovarian Cancer Biology



BRCA Testing (Germline or Tumour): Standard of Care[1-5]

A patient with ovarian cancer who is *BRCA* Wild type on germline testing would need a subsequent tumour testing to establish whether or not she has a somatic *BRCA* mutation to access olaparib



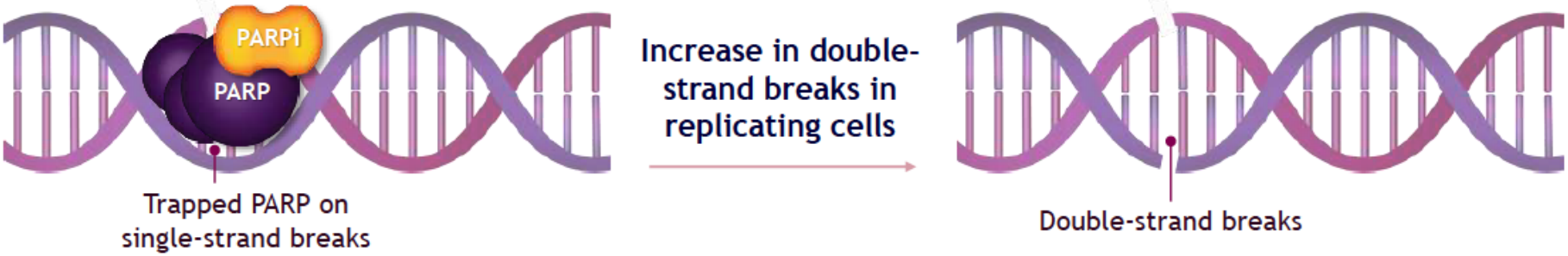
A patient with ovarian cancer who has a *BRCA* mutation identified from tumour testing would need subsequent germline testing to determine whether there are implications for her relatives

Beginning with a tumour test rather than a germline test:

- Fewer patients will require two rounds of *BRCA* testing (a greater number of women with ovarian cancer will test negative on germline testing than will test positive on tumour testing). More cost-effective?
- Consent may be perceived as more straightforward
- Potential risk of not obtaining an accurate result (technical issues): missing a *BRCA* mutation

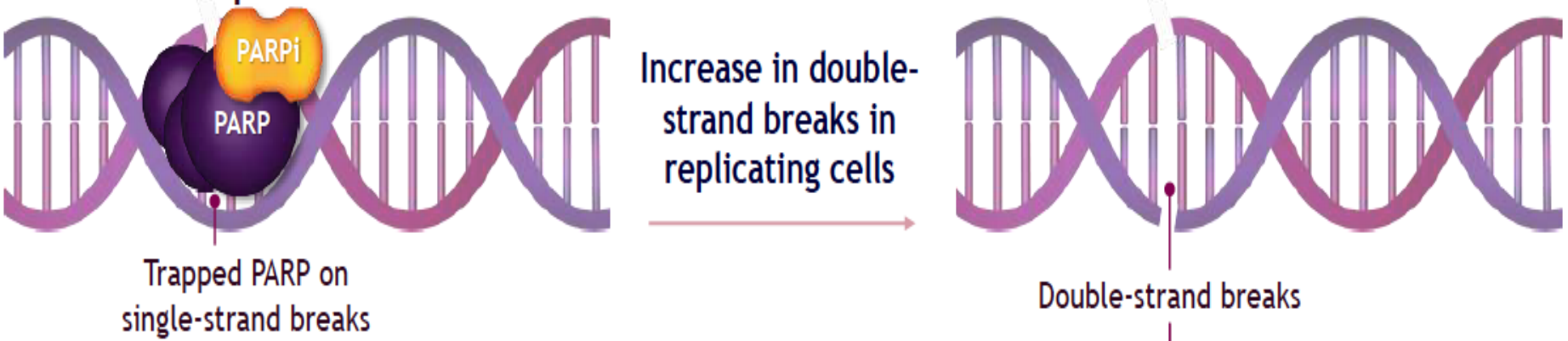
Current perspectives on recommendations for BRCA genetic testing in ovarian cancer patients.
1. Vergote I et al. *Eur J Cancer*. 2016;69:127-134. 2. NCCN Guidelines. https://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf. Accessed 24 September 2018. 3. SGO. https://www.sgo.org/clinical-practice/guidelines/genetic-testing-for-ovarian-cancer/. Accessed 24 September 2018. 4. ASCO. https://www.asco.org/practice-guidelines/cancer-care-initiatives/genetics-toolkit/assessing-your-patient%E2%80%99s-hereditary. Accessed 24 September 2018. 5. Ledermann JA et al. https://www.esmo.org/Guidelines/Gynaecological-Cancers/Newly-Diagnosed-and-Relapsed-Epithelial-Ovarian-Carcinoma/eUpdate-Treatment-Recommendations. Accessed 24 September 2018.

PARP Inhibitors Trap PARP, Preventing the Repair of SSBs Which Are Then Converted to DSBs



DSB=double-strand break; PARPi=PARP inhibitor; SSB=single-strand break.
O'Connor MJ. *Mol Cell*. 2015;60(4):547-560.

In HRD Cells, Where Deficiencies in DSB Repair Exist, the Cells Cannot Cope With the Increase in DSBs and This Leads to Cell Death



HRR-deficient cancer cell

Reliance on error-prone pathways leads to DNA damage accumulation and cell death ✗

Normal cell

Repair of double-strand breaks via the HR pathway and cell survival ✓

SOLO1: Study design

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic *BRCA*m
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete response or partial response after platinum-based chemotherapy

Olaparib 300 mg bd (N=260)

2:1 randomization

Stratified by response to platinum-based chemotherapy

Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints

- PFS using BICR
- PFS2
- Overall survival
- Time from randomization to first subsequent therapy or death
- Time from randomization to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

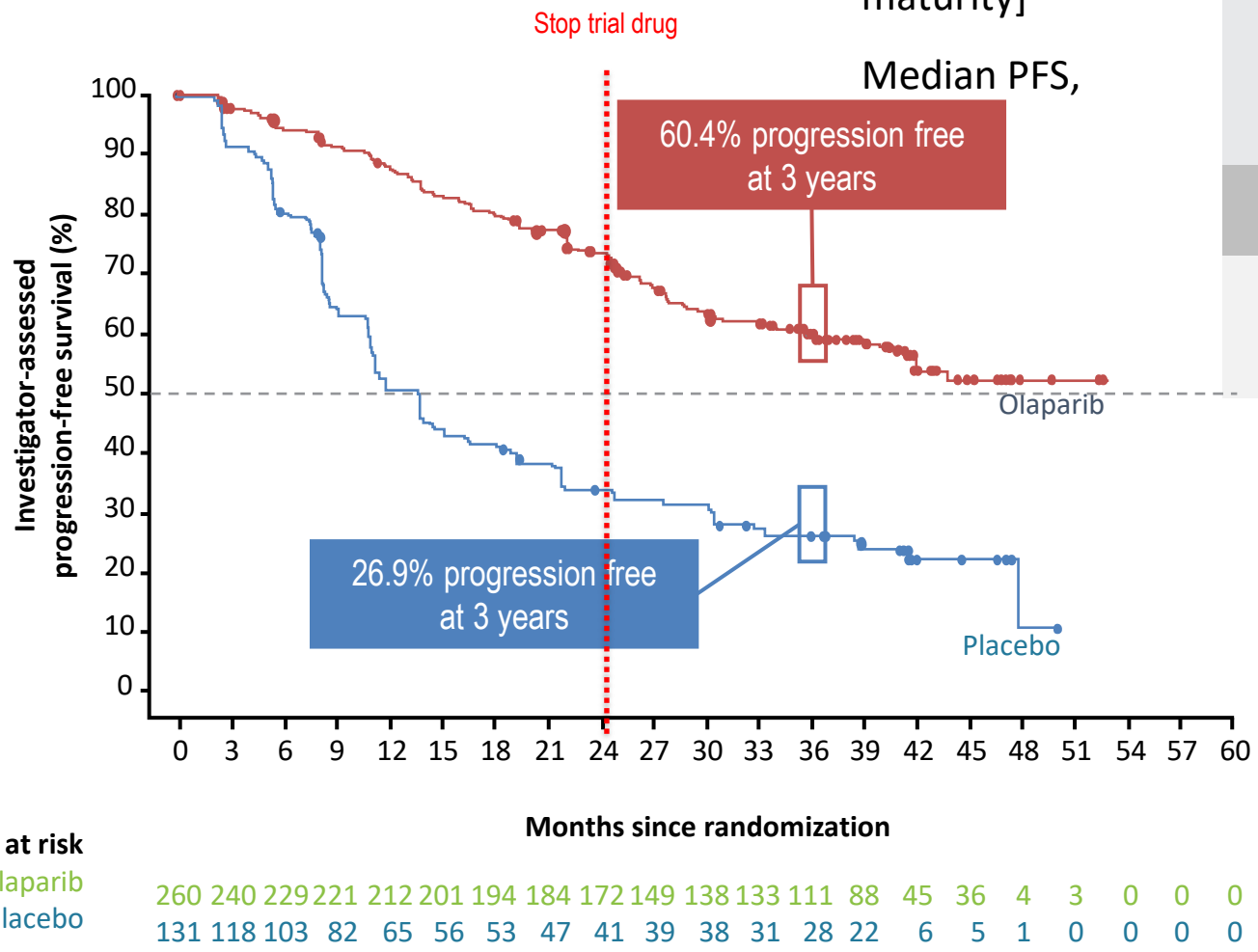
2 years' treatment if no evidence of disease

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease. BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; FACT-O, Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO, International Federation of Gynecology and Obstetrics; HRQoL, health-related quality of life; PFS, progression-free survival; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TOI, Trial Outcome Index

Moore K et al NEJM 2018

PFS by investigator assessment

	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS,	NR	13.8
HR 0.30		
95% CI 0.23, 0.41; *P*<0.0001		



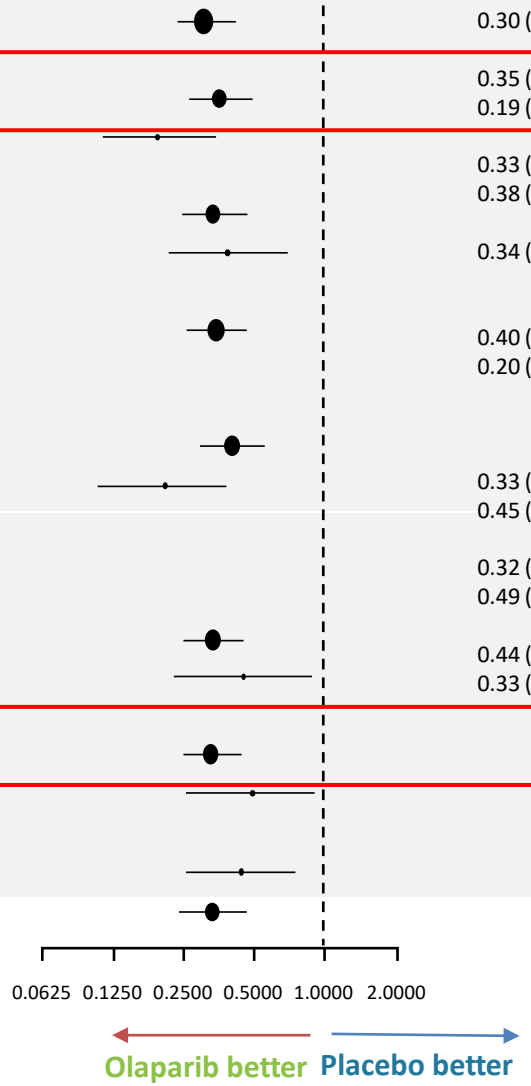
No. at risk

Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

CI, confidence interval; NR, not reached

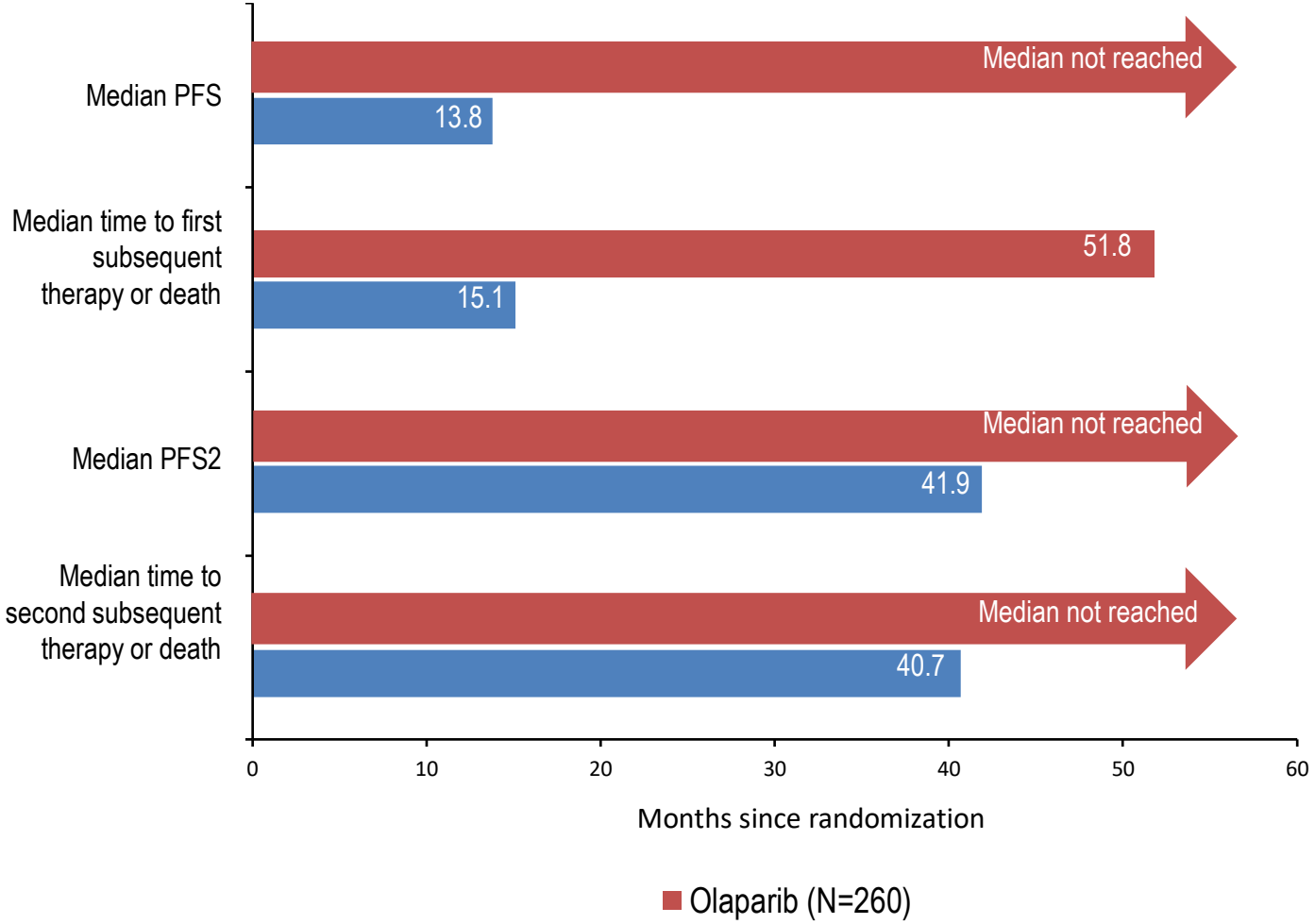
PFS subgroup analysis

Subgroup	Olaparib 300 mg bd	Placebo bd	HR (95% CI)
	Number of patients with events/total number of patients (%)		
All patients	102/260 (39.2)	96/131 (73.3)	0.30 (0.23, 0.41)
Response after surgery/platinum-based chemotherapy			
Clinical complete response	73/213 (34.3)	73/107 (68.2)	0.35 (0.26, 0.49)
Partial response	29/47 (61.7)	23/24 (95.8)	0.19 (0.11, 0.34)
ECOG performance status at baseline			
Normal activity	75/200 (37.5)	76/105 (72.4)	0.33 (0.24, 0.46)
Restricted activity	27/60 (45.0)	20/25 (80.0)	0.38 (0.21, 0.68)
Baseline CA-125 value			
≤ULN	92/247 (37.2)	89/123 (72.4)	0.34 (0.25, 0.46)
>ULN	10/13 (76.9)	7/7 (100.0)	NC
g*BRCA* mutation type by Myriad testing			
BRCA1	84/188 (44.7)	69/91 (75.8)	0.40 (0.29, 0.56)
BRCA2	15/62 (24.2)	26/39 (66.7)	0.20 (0.10, 0.38)
BRCA1/2 (both)	0/3	0/0	NC
Negative	3/7 (42.9)	1/1 (100.0)	NC
Age			
<65 years	85/225 (37.8)	82/112 (73.2)	0.33 (0.24, 0.45)
≥65 years	17/35 (48.6)	14/19 (73.7)	0.45 (0.22, 0.92)
Stage of disease at initial diagnosis			
Stage III	83/220 (37.7)	79/105 (75.2)	0.32 (0.24, 0.44)
Stage IV	19/40 (47.5)	17/26 (65.4)	0.49 (0.25, 0.94)
Following debulking surgery prior to study entry			
Residual macroscopic disease	29/55 (52.7)	23/29 (79.3)	0.44 (0.25, 0.77)
No residual macroscopic disease	70/200 (35.0)	69/98 (70.4)	0.33 (0.23, 0.46)



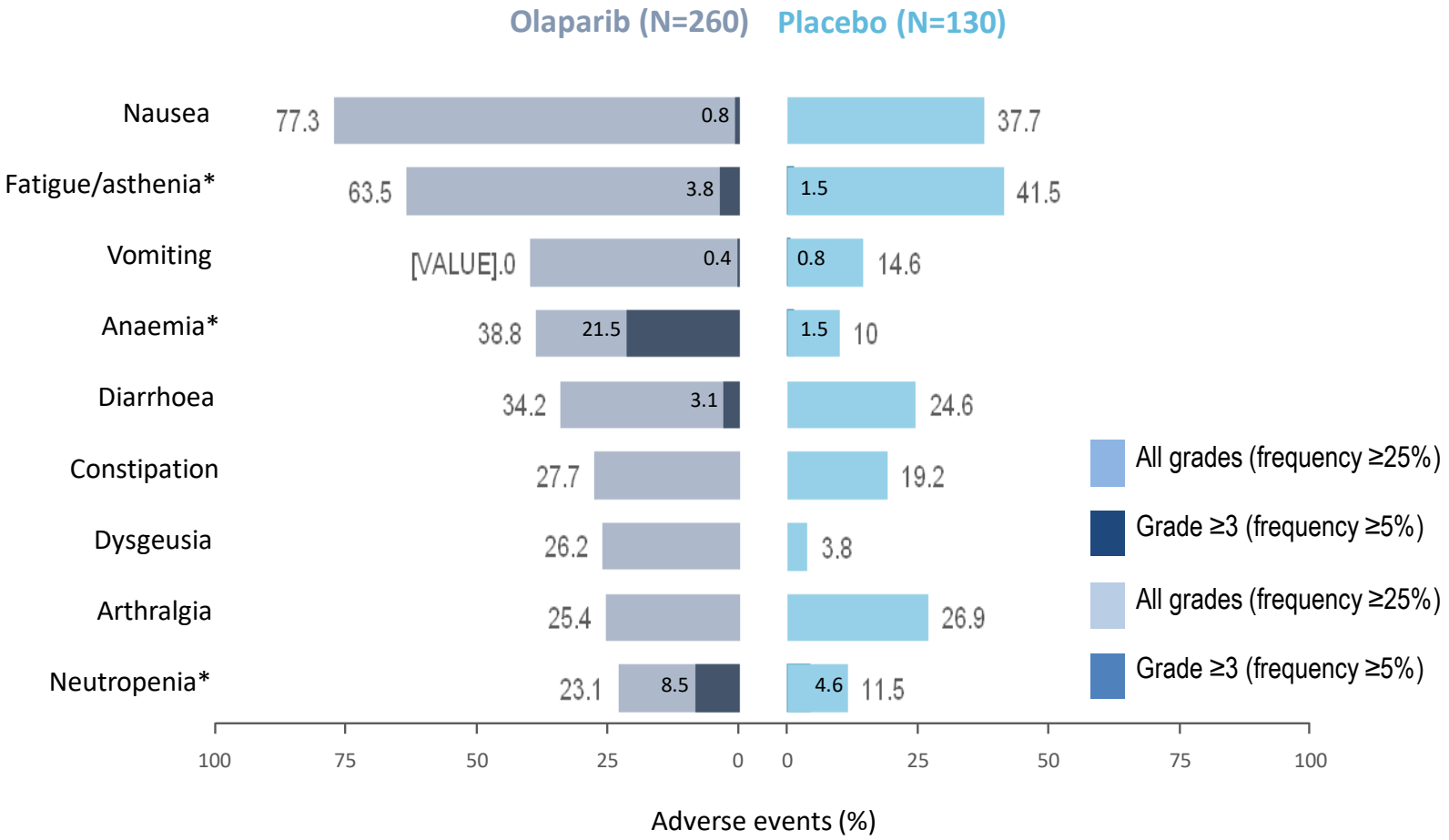
ULN, upper limit of normal

Summary of efficacy endpoints



HR 0.30	95% CI 0.23, 0.41; *P*<0.0001
HR 0.30	95% CI 0.22, 0.40; *P*<0.0001
HR 0.50	95% CI 0.35, 0.72; *P*=0.0002
HR 0.45	95% CI 0.32, 0.63; *P*<0.0001

Most common treatment-emergent adverse events



*Grouped terms. All-grade thrombocytopenia (grouped term) occurred in 11.2% of patients in the olaparib group and 3.8% of patients in the placebo group and grade ≥3 thrombocytopenia (grouped term) occurred in 0.8% and 1.5%, respectively.

TWO other PARPi in first Line maintenance EOC

Niraparib (PRIMA trial)

- All comers (BRCA+/-, HRD+/-)
- 50% HRD (30% BRCA,20 non BRCA)

- All Stage III/IV ,advanced EOC serrous / endometriod

Randomization after completion of chemotherapy (2:1)

Maintenance Niraparib versus placebo

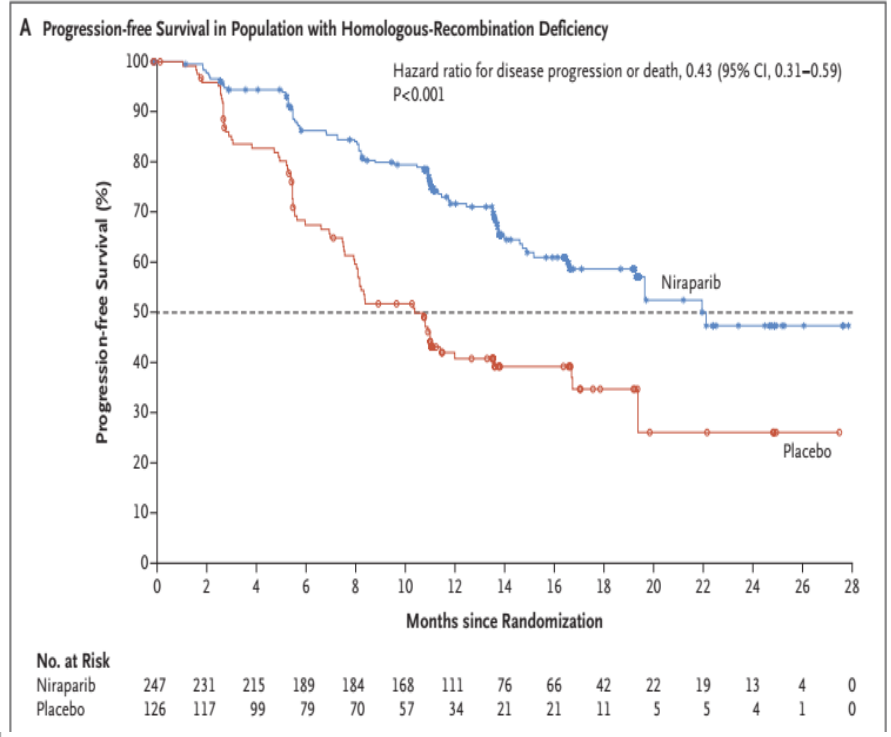
Niraparib 300mg OD – 36 months

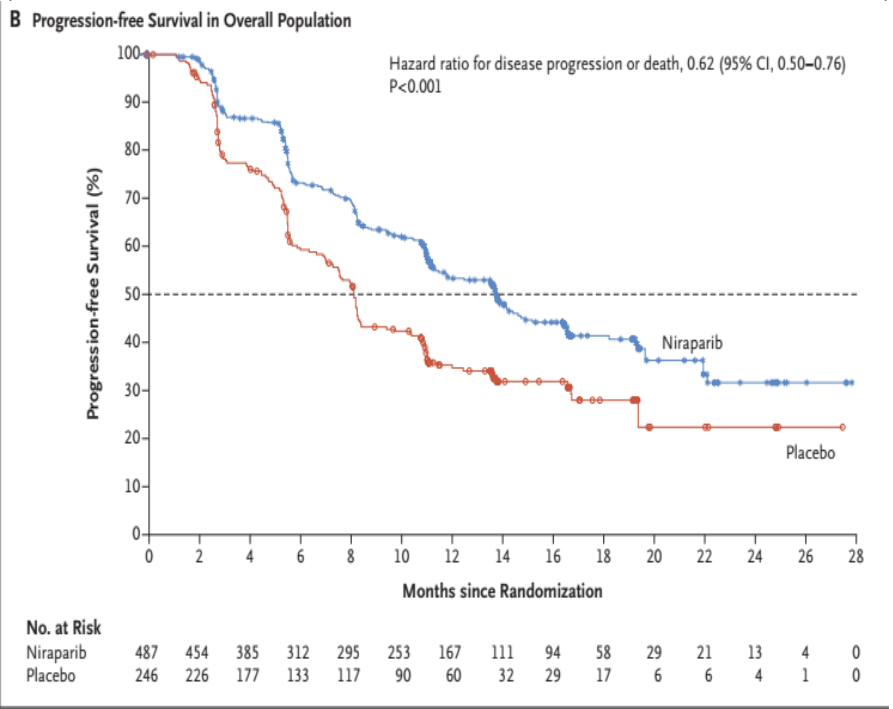
VELAPARIB (GOG 3005/VELIA)

- All comers (BRCA+/-, HRD+/-)
- 50 % HRD (20% BRCA, 30% HRD)
- In BRCA 15% germline, 5% somatic)

- All Stage III/IV ,advanced EOC serrous / endometriod
- Randomization before chemo
- 1:1:1
- **Chemo+ placebo------placebo**
- **Chemo+ velaparib-------placebo**
- **Chemo+ velaparib--------velaparib**

- **Velaparib 150 BD daily with chemo**
- **Velarib 400 mg BD in maintenance 30 months**





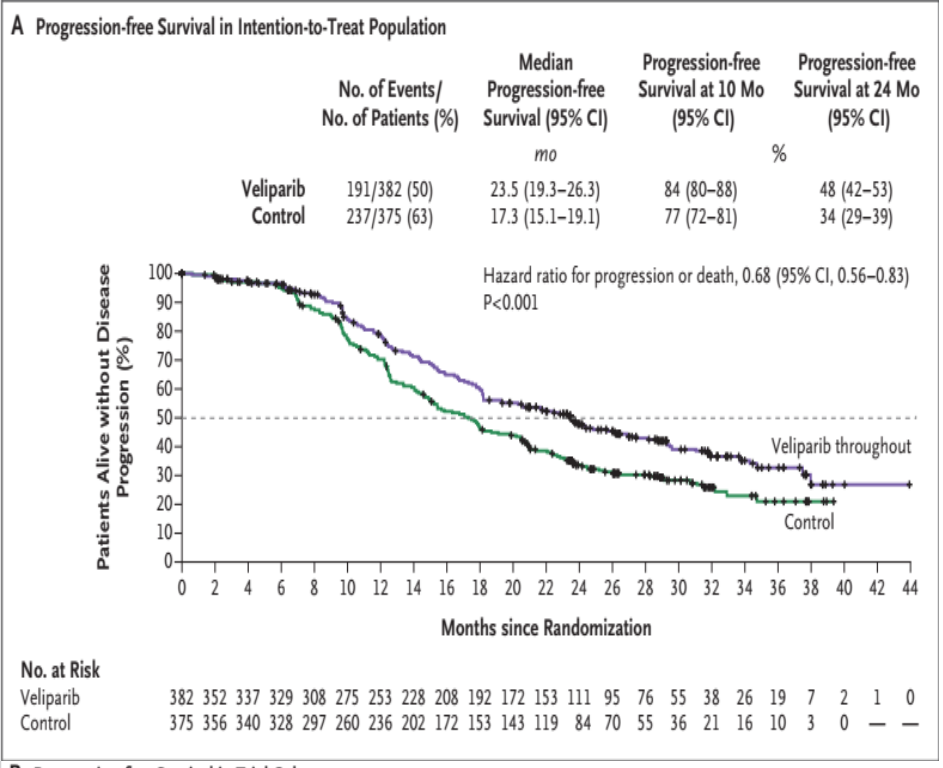
PRIMA – Niraparib

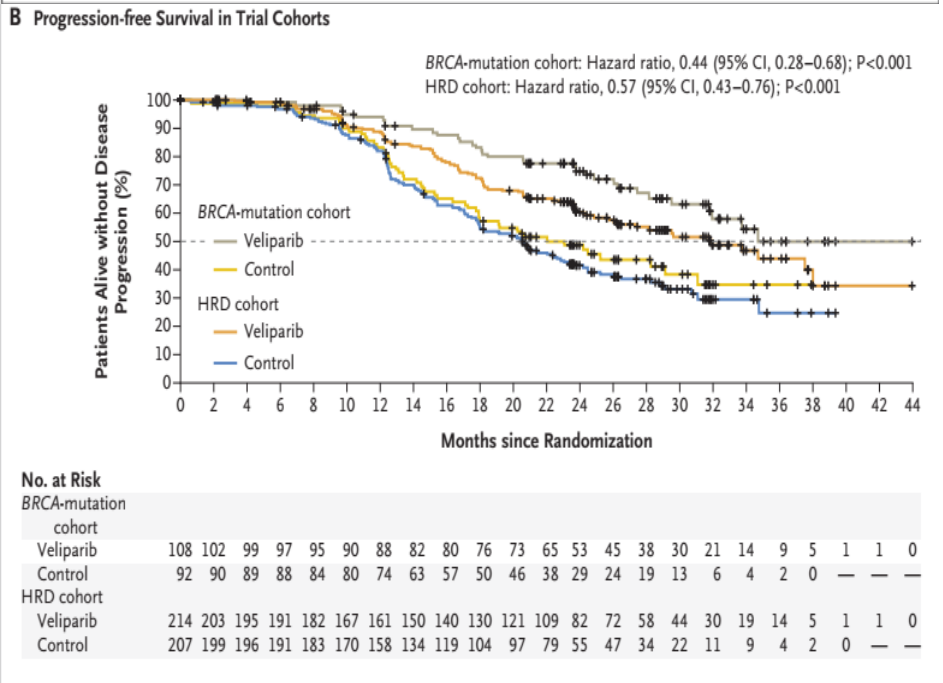
Overall population 13.8 Vs 8.2 months,HR 0.62 (0.32- 0.87)

PFS in BRCA 21 vs 10 months , HR 0.43 (0.27-0.68)

PFS in non BRCA HRD 19 vs 8 months. HR 0.5 (0.3-0.8

PFS in HR proficient 8.1 vs 5.4 months HR 0.68 (0.49 -0.94)





VELIA – Velaparib

PFS BRCA mutation 35 vs 22 HR 0.44 (0.28-0.61)

PFS HRD – 32 vs 20 HR 0.57 (0.34-0.69)

PFS others – 23.5 vs 17.5, HR 0.68 (0.56-0.83)

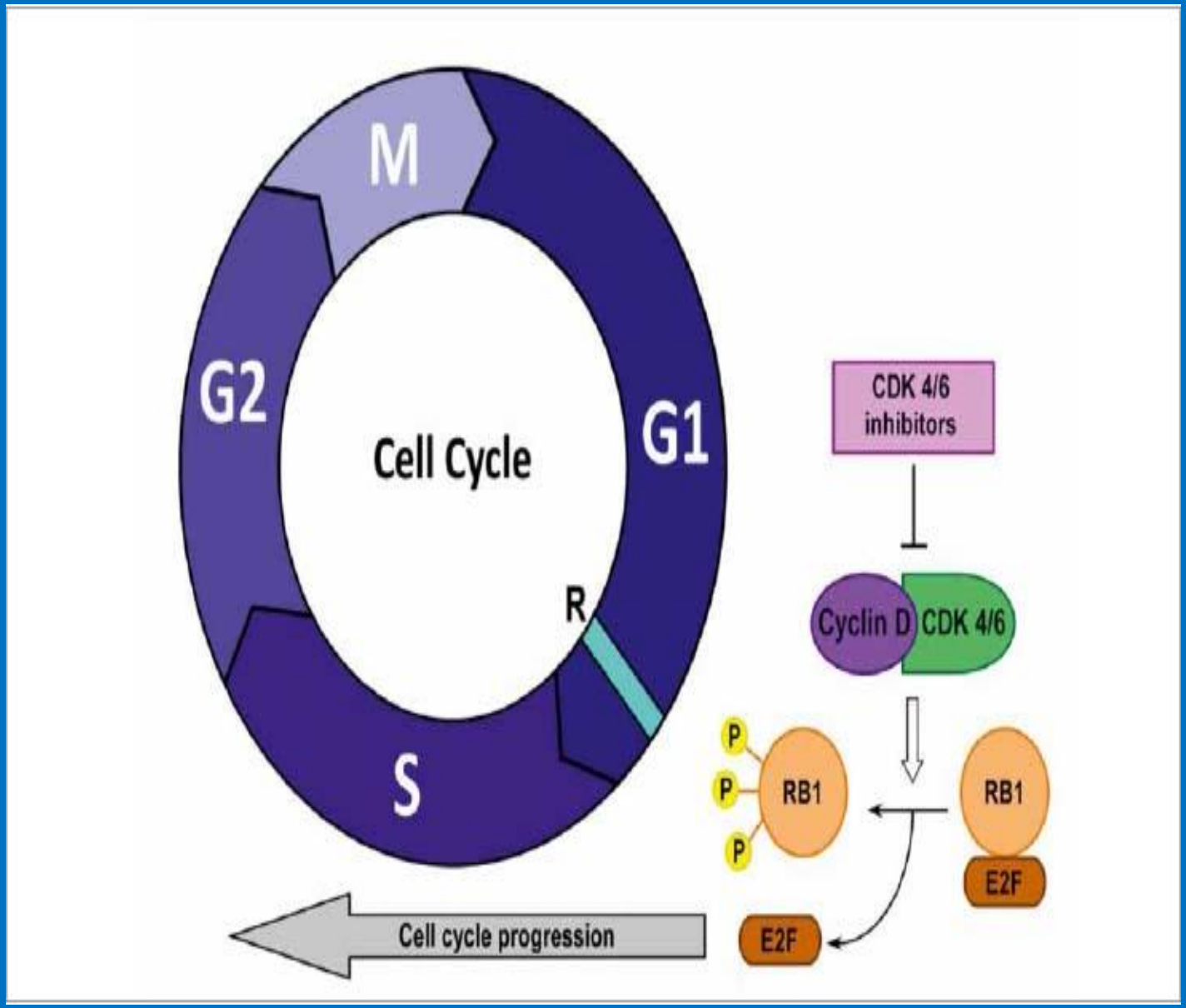
Independent value of adding velaprib with chemotherapy
is less clear as only 4 % patients progressed during chemo

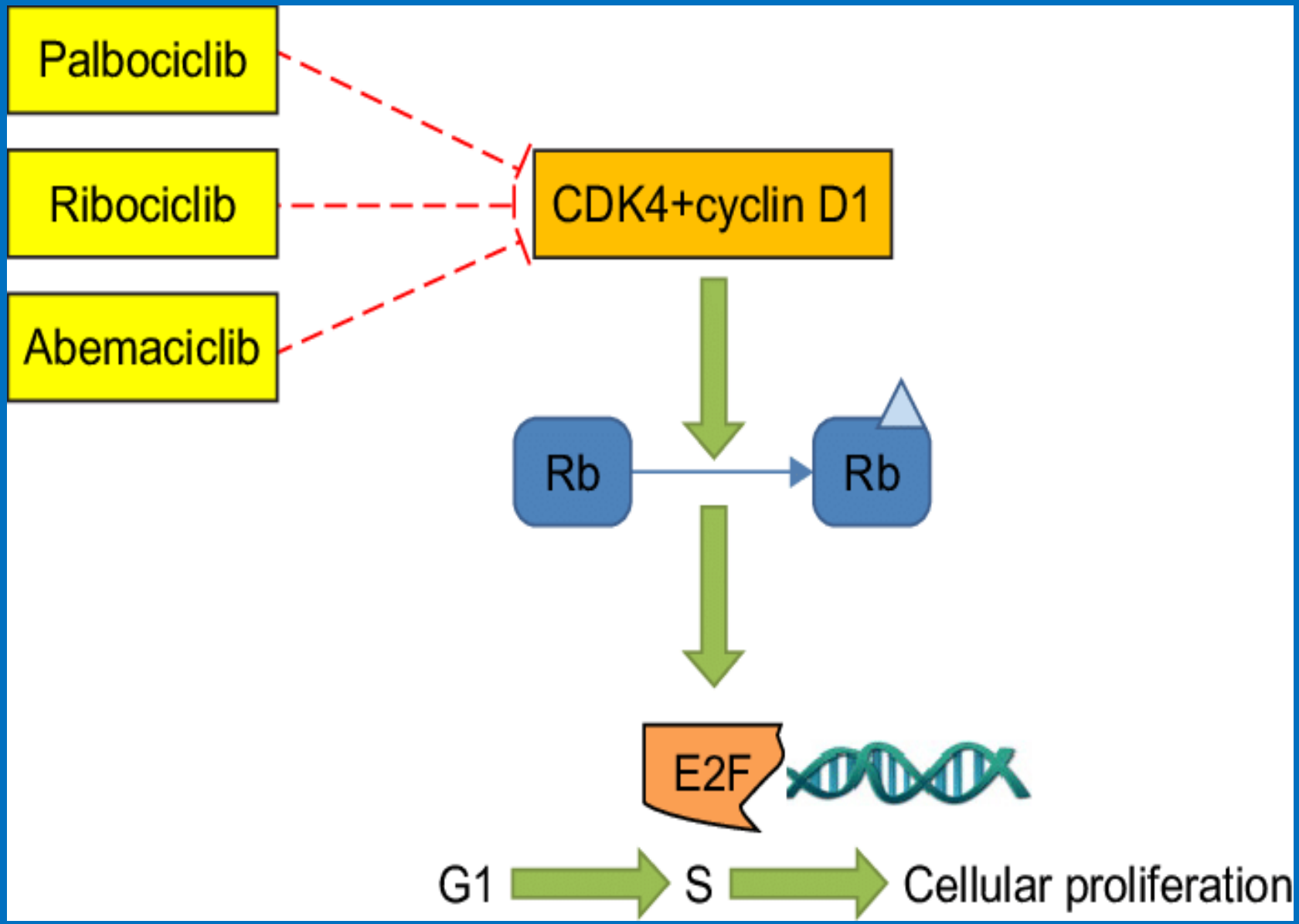
SUMMARY

- Paclitaxel+ Carboplatin +/- bevacizumab- maintenance bevacizumab is standard first line management option for EOC. (No OS)

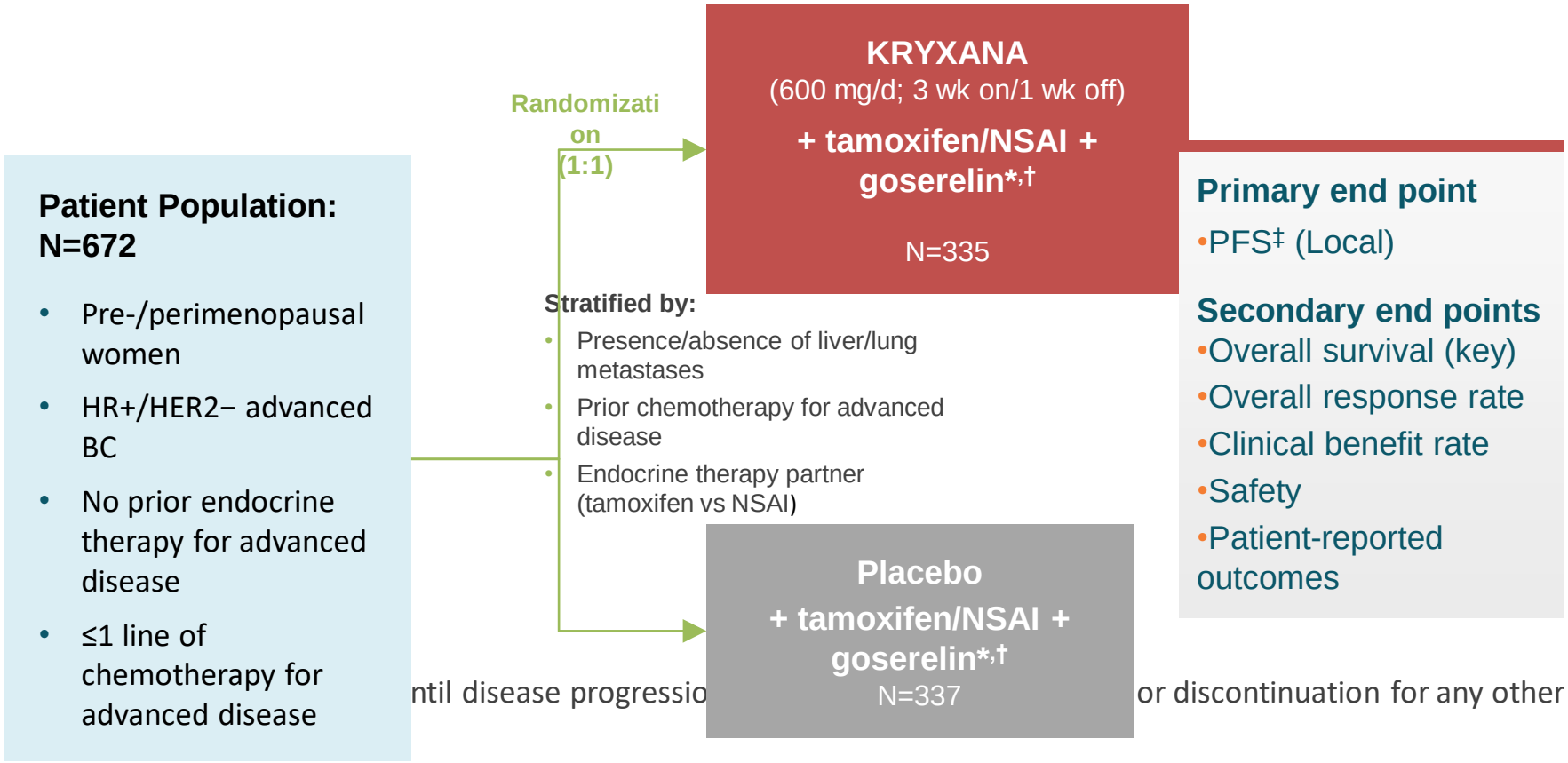
- Maintenance Olaparib (SOLO-1) significantly improves PFS (HR=0.3) ,time to first and subsequent therapy in germline/somatic BRACA1/2 mutation

- BRCA mutation testing should be offered to patients upfront to select patients for olaparib maintenance.


M
G2
Cell Cycle
G1
R
S
CDK 4/6
inhibitors
Cyclin D
CDK 4/6
P
P
P
RB1
RB1
E2F
E2F
Cell cycle progression


Palbociclib
Ribociclib
Abemaciclib
CDK4+cyclin D1
Rb
Rb
E2F
G1
S
Cellular proliferation

MONALEESA-7: Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of KRYXANA + Tamoxifen/NSAI + Goserelin[14]



- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter

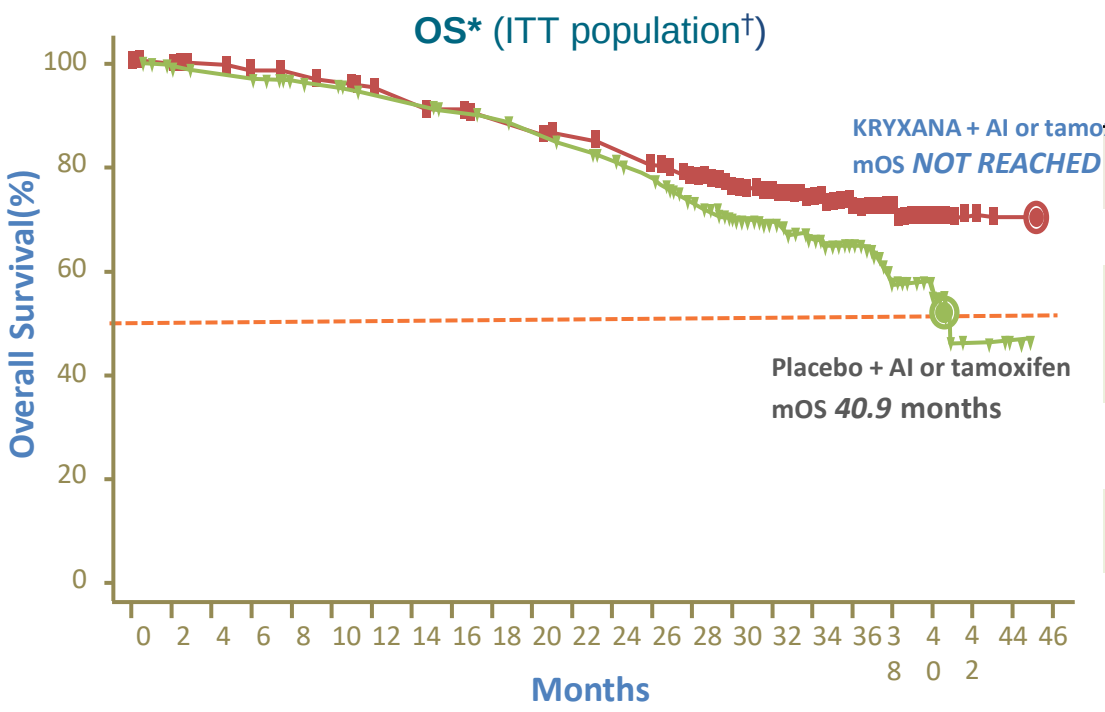
BC, breast cancer; HER2, human epidermal growth factor 2; HR, hormone receptor; NSAI, non-steroidal aromatase inhibitor; PFS, progression free survival; wk, week.

*Starting dosage for tamoxifen was 20 mg/d, for anastrozole was 1 mg/d, for letrozole was 2.5 mg/d, and for goserelin was 3.6 mg every 28 d.

†Goserelin is a luteinizing hormone-releasing hormone (LHRH) agonist.

‡ Locally assessed per RECIST v1.1.

KRYXANA Significantly Improved Overall Survival as First-Line Treatment in Combination With Endocrine Therapy in Patients With HR+/HER2− MBC[10]



	KRYXANA + **AI or tamoxifen** (n=335)	Placebo + **AI or tamoxifen** (n=337)
Events-no. of patients (%)	83 (24.8)	109 (32.3)
Censored	252 (75.2)	228 (67.7)
Hazard Ratio (95% CI)	**0.712 (0.535-0.948)**	
P value	**0.00973**	
Median OS- mo (95% CI)	**NOT REACHED**	**40.9 (37.8-NR)**
OS- Kaplan-Meier estimate (95%CI)		
36 months	71.9 (66.0-77.0)	64.9 (58.7-70.4)
42 months	**70.2 (63.5-76.0)**	**46.0 (32.0-58.9)**

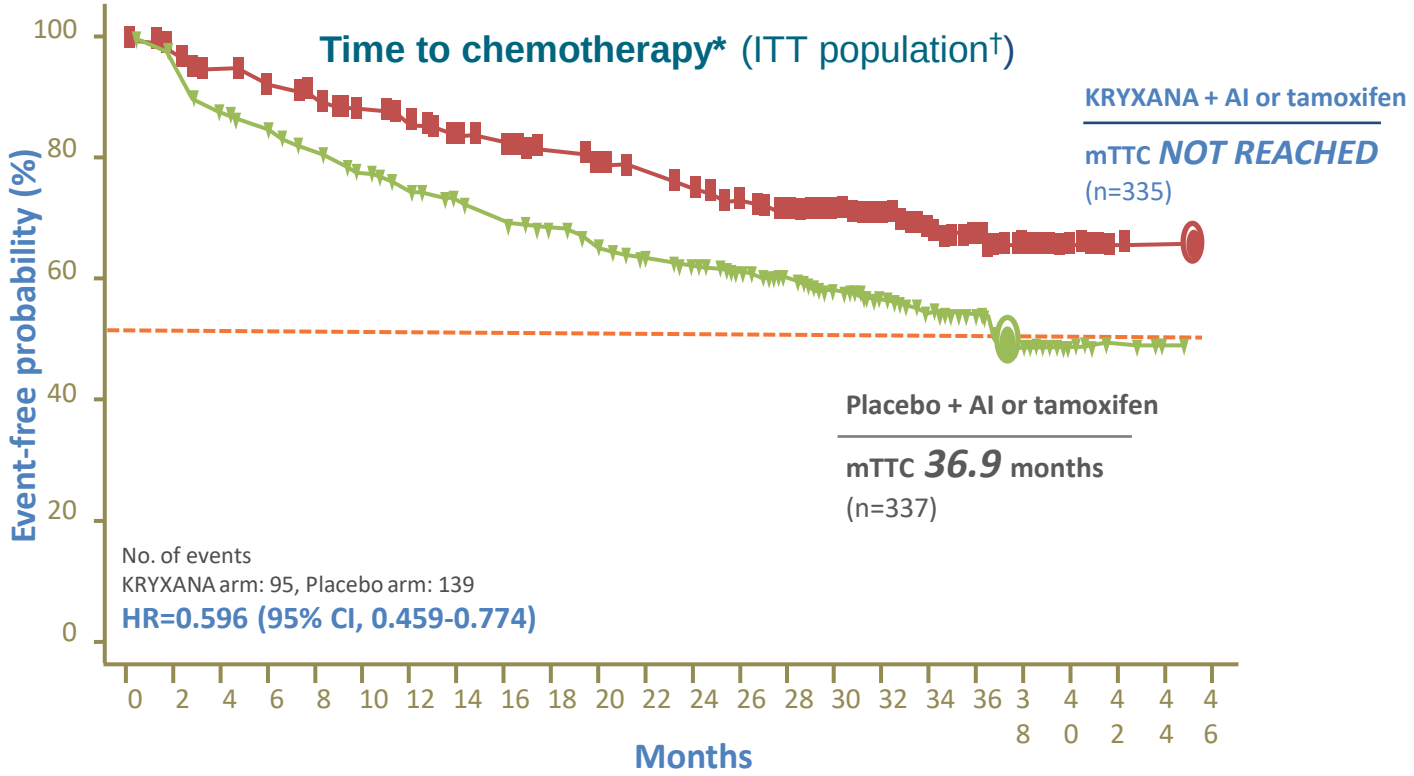
- ***With KRYXANA, a statistically significant improvement in OS was achieved at interim analysis with a 29% risk in reduction of death (HR=0.71, [95% CI, 0.535-0.948], P = 0.00973)***
- ***At 42 months, the survival rate was 70% with KRYXANA†***

KRYXANA is not indicated for concomitant use with tamoxifen.

- 177 of 672 total patients were randomized to receive tamoxifen as a combination partner, including 87 patient who received KRYXANA + tamoxifen.

AI, aromatase inhibitor; CI, confidence interval; HER2, human epidermal growth factor 2; HR, hazard ratio; HR+, hormone receptor positive; ITT, intention-to-treat; MBC, metastatic breast cancer; NR, not reached; OS, overall survival.
*Overall survival was reported based on investigator assessment. †Evaluation of OS at 42 months was part of a landmark analysis without accompanying statistics.

Time to Subsequent Chemotherapy Was Significantly Delayed Following First-Line KRYXANA[10]

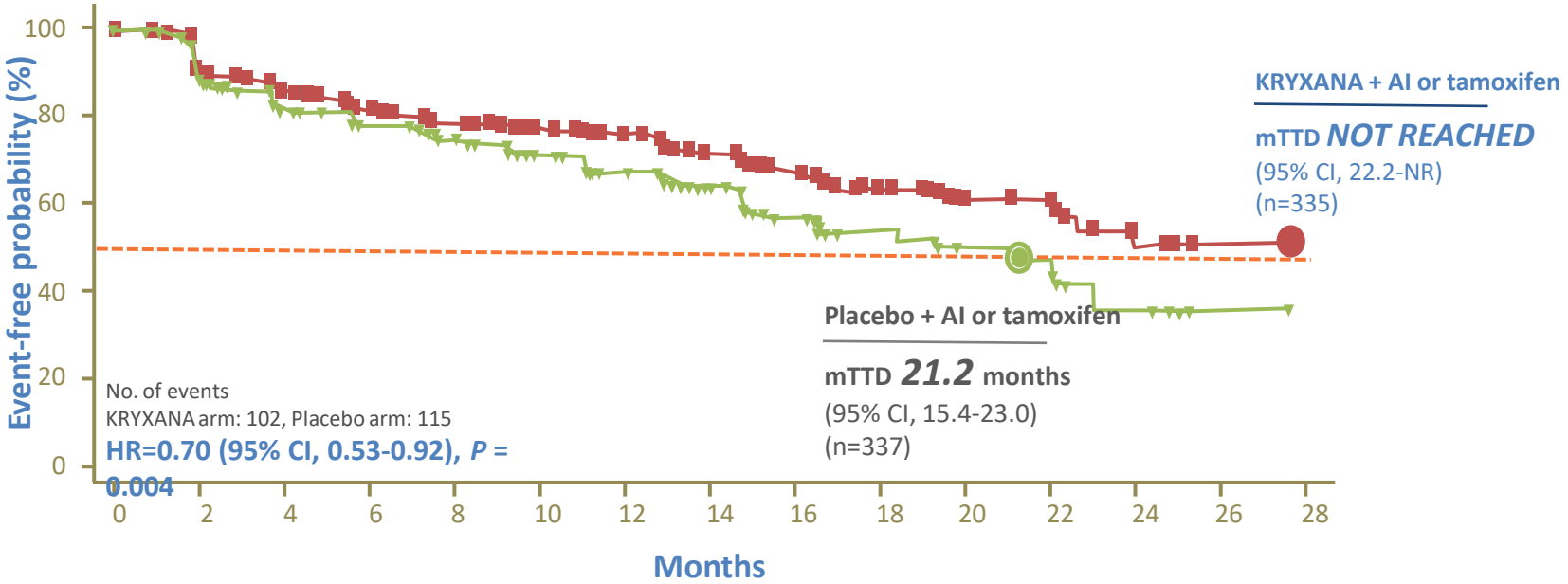


Chemotherapy use in patients with breast cancer is associated with long-term adverse events and has been shown to negatively impact patient QoL.[15,16]

AI, aromatase; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mTTC, median time to chemotherapy; QoL, quality of life.
*Time to chemotherapy was an exploratory end point and was defined as the time from randomization to the beginning of the first chemotherapy after discontinuing study treatment. Time to chemotherapy was reported as part of the second planned interim analysis along with overall survival results. †KRYXANA is not indicated for concomitant use with tamoxifen. 177 of 672 total patients were randomized to receive tamoxifen as a combination partner, including 87 patient who received KRYXANA + tamoxifen.

Time to Deterioration in Overall QoL Was Significantly Delayed With First-Line KRYXANA[18]

TTD ≥10% in global health status/QoL score of EORTC QLQ-C30 (ITT population)*,†



- In the AI only population: TTD ≥10% with KRYXANA was 24.0 months vs placebo 19.4 months (HR = 0.759 [95% CI, 0.561-1.028])[19]

KRYXANA is the only CDK4/6 inhibitor to show a significant improvement in overall QoL in the first-line setting.[18,23]

AI, aromatase inhibitor; CDK, cyclin-dependent kinase; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; MBC, metastatic breast cancer; NR, not reached; QoL, quality of life; TTD, time to deterioration.

*QoL reported as part of the primary PFS analysis with a data cutoff of August 20, 2017.[18] †KRYXANA is not indicated for concomitant use with tamoxifen. 177 of 672 total patients were randomized to receive tamoxifen as a combination partner, including 87 patient who received KRYXANA + tamoxifen.[10]

With 3 Available CDK4/6 Inhibitors: Are They Really All the Same?

	KRYXANA	Abemaciclib	Palbociclib
Preferential inhibition of CDK4 vs CDK6[25]* IC_{50} (µM)	**x8**	x6	x1
Free drug concentration (fold difference)[24]†	**x22**	x1	x1

KRYXANA exhibits more specificity for CDK4 vs CDK6, with more drug available to penetrate and act on tumor cells[25,26]†

†Based on preclinical activity. Preclinical activity does not necessarily correlate with clinical outcomes. The data above is not presented to discuss the efficacy and safety information of the mentioned products.

CDK, cyclin-dependent kinase.

*Free drug concentration is based upon unbound C_{ave} values, determined in human pharmacokinetic studies. Values are normalized to palbociclib.[24,25]

Achieving a Statistical Significant Difference in OS in MBC Clinical Trials Has Been a Challenge

- In nearly 25 years, 5-year survival rates for MBC have improved by less than 5%[4,5]

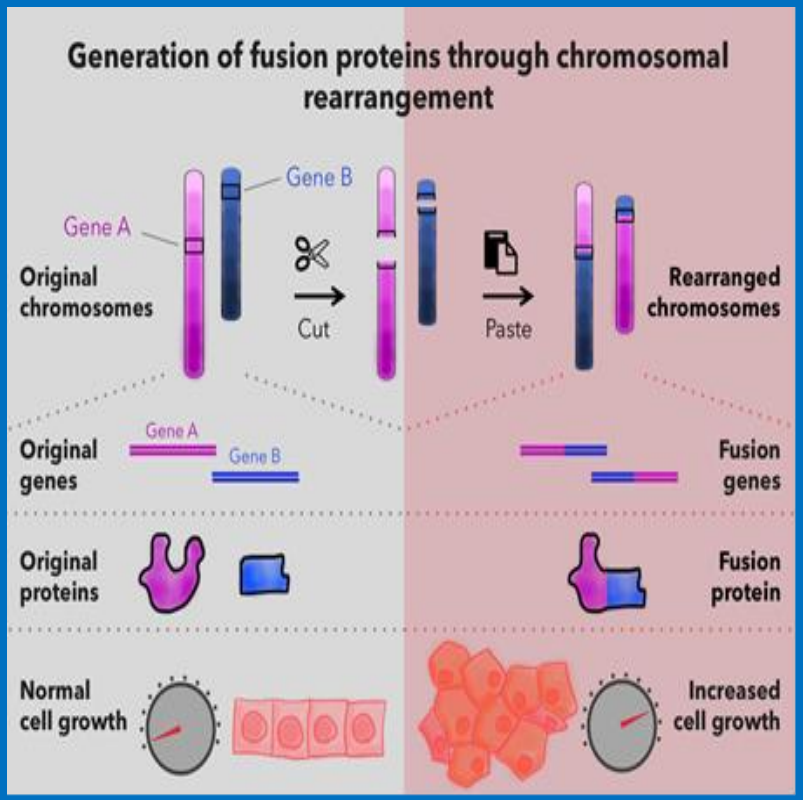
- Over the past decade, few studies with targeted therapies have reported statistically significant improvements in OS[6-8]
  - In a recent analysis of 79 randomized clinical trials in HR+/HER2− MBC, only 1 study of those with endocrine therapy as a control arm (9 studies) reported statistical improvements in OS[6]
    - Everolimus + tamoxifen significantly reduced risk of death by 55% (*P* = 0.007) in a first-line, phase II study of 111 patients compared to tamoxifen alone[6,7]
  - Recently, in a first-line study of 707 patients, fulvestrant + anastrozole in the first line was shown to significantly reduced risk of death by 18% (*P* = 0.03) compared with anastrozole alone [8]

***Up until MONALEESA-7, no CDK4/6 inhibitor had reported a statistically significant OS result.*[6,9-11]**

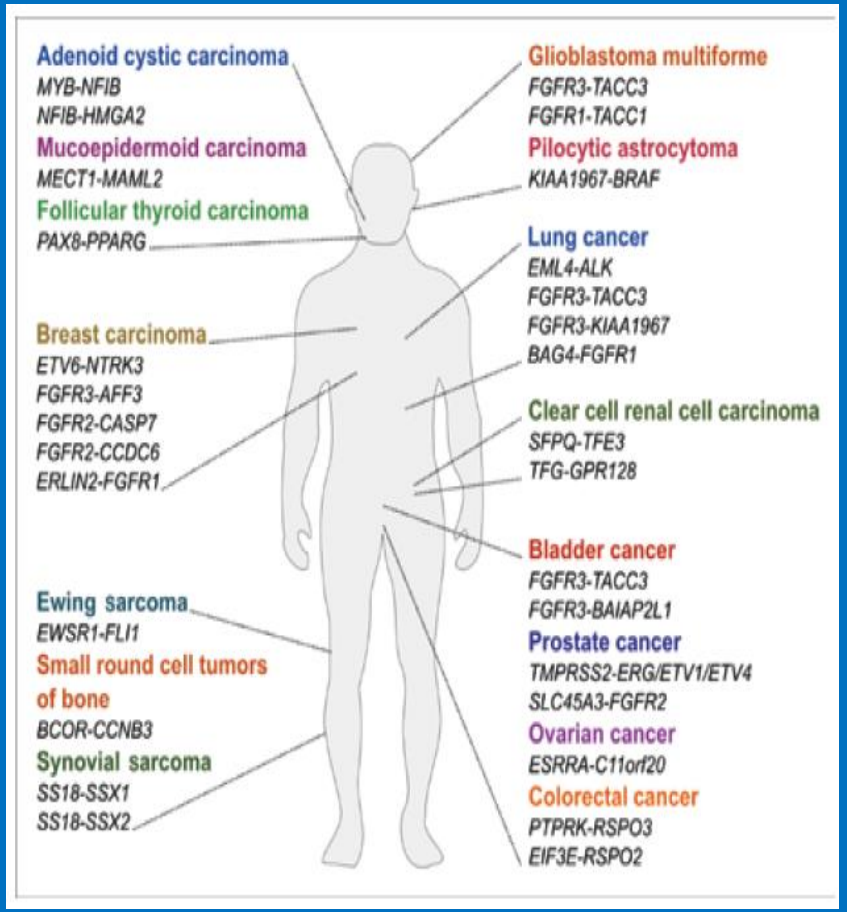
CDK, cyclin-dependent kinase; HER2, human epidermal growth factor 2; HR, hormone receptor; MBC, metastatic breast cancer; OS, overall survival.

Fusion Gene in Solid Tumors

Fusion Genes



Types of Cancer



Chin J Cancer. 2013 Nov; 32(11): 594–603.

Fusion Protein Inhibitors (Solid Tumors & Hematological Malignancy

Solid tumors: Fusion target					
Drug	**Disease Indication**	**Line of Therapy**	**Aberrant gene**	**Number of studies****	**Response Rate (%)****
Alectinib	NSCLC	2+	*ALK*	1	79%
Brigatinib	NSCLC	2+	*ALK*	1	53%
Ceritinib	NSCLC	2+	*ALK*	1	73%
Crizotinib	NSCLC	1	*ALK/ROS1*	2	56%
Entrectinib	Solid tumors	1+	*NTRK/ROS1/ALK*	1	78%
Larotrectinib	Solid tumors	1+	*NTRK*	1	75%
Hematologic malignancies: Fusion Target					
Drug	**Disease Indication**	**Line of Therapy**	**Aberrant gene**	**Number of studies****	**Response Rate (%)**
All trans-retinoic acid	APL	1+	*PML-RARA*	1	72%
Bosutinib	CML	2+	*BCR-ABL*	2	31%
Dasatinib	CML	1+	*BCR-ABL*	2	63%
Imatinib	CML	1	*BCR-ABL*	1	73%
Nilotinib	CML	1+	*BCR-ABL*	1	84%
Ponatinib	CML	2+	*BCR-ABL*	1	46%

Cancer. 2020 March 15; 126(6): 1315–1321

Conclusion

- Responses and outcomes have reached a plateau with conventional chemotherapy in metastatic and adjuvant therapy.
- Novel therapy targeting cell cycle, DNA repair pathways, Anti angiogenesis can further improve outcomes.
- With novel therapies comes novel toxicities – learning curve
- Introduction of Indian low cost generics are making such novel therapy affordable.