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PARP inhibitors in DNA Repair-Associated Cancers

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COI

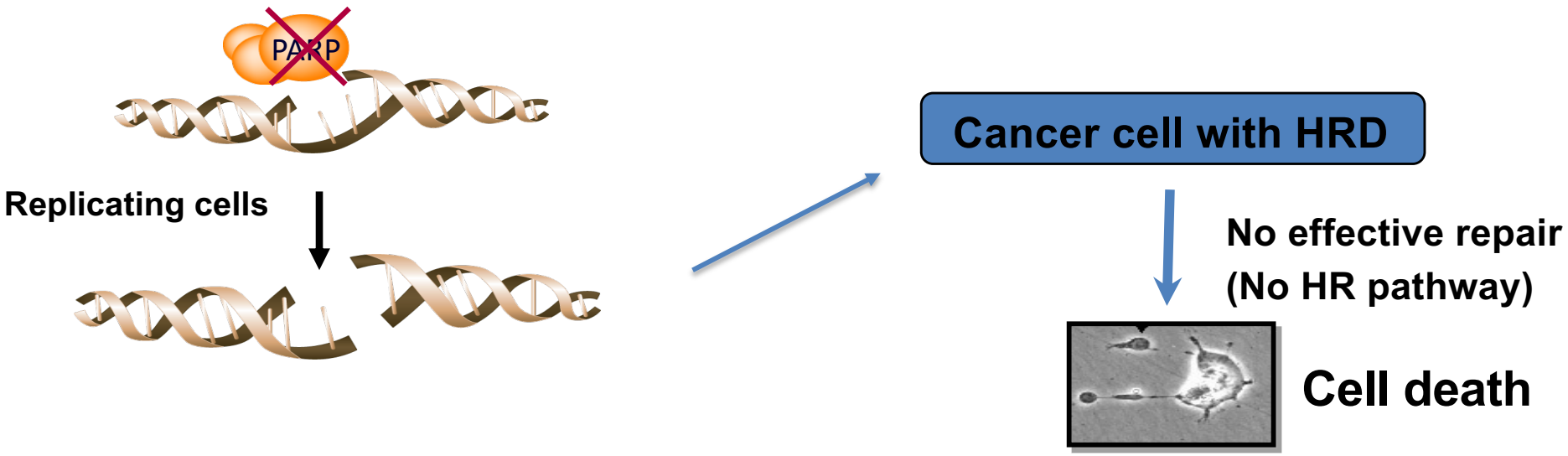
- Honoraria: Curio Science
- Advisory Board: GSK
- Research IP supply: Corcept
- PI of Industry sponsored trial
  - Corcept, Abbvie, Roche, GSK (Tesaro), Syndax, 47inc, Iovance, Syros,Astex, Merck, Sanofi, Sermonix, Compugen, Incyte, Eisai

PARP inhibitors

- Introduction
- Predictors of Benefit
  - g*BRCA*m or tumor *BRCAm*
  - Platinum sensitivity
- Mechanisms of Resistance
  - Reversion *BRCA* mutations
- Combinations
  - Combinations with cytotoxic chemotherapy limited by myelotoxicity

PARPi “synthetic lethality”

- PARP inhibitors inhibit base excision repair, leading to induction of double-stranded breaks after stalling of DNA replication forks
- Double strand DNA breaks are repaired primarily by the high fidelity Homologous Recombination (HR) repair pathway
- Cells with BRCA deficiency lack HR repair and have increased sensitivity to PARP inhibitors



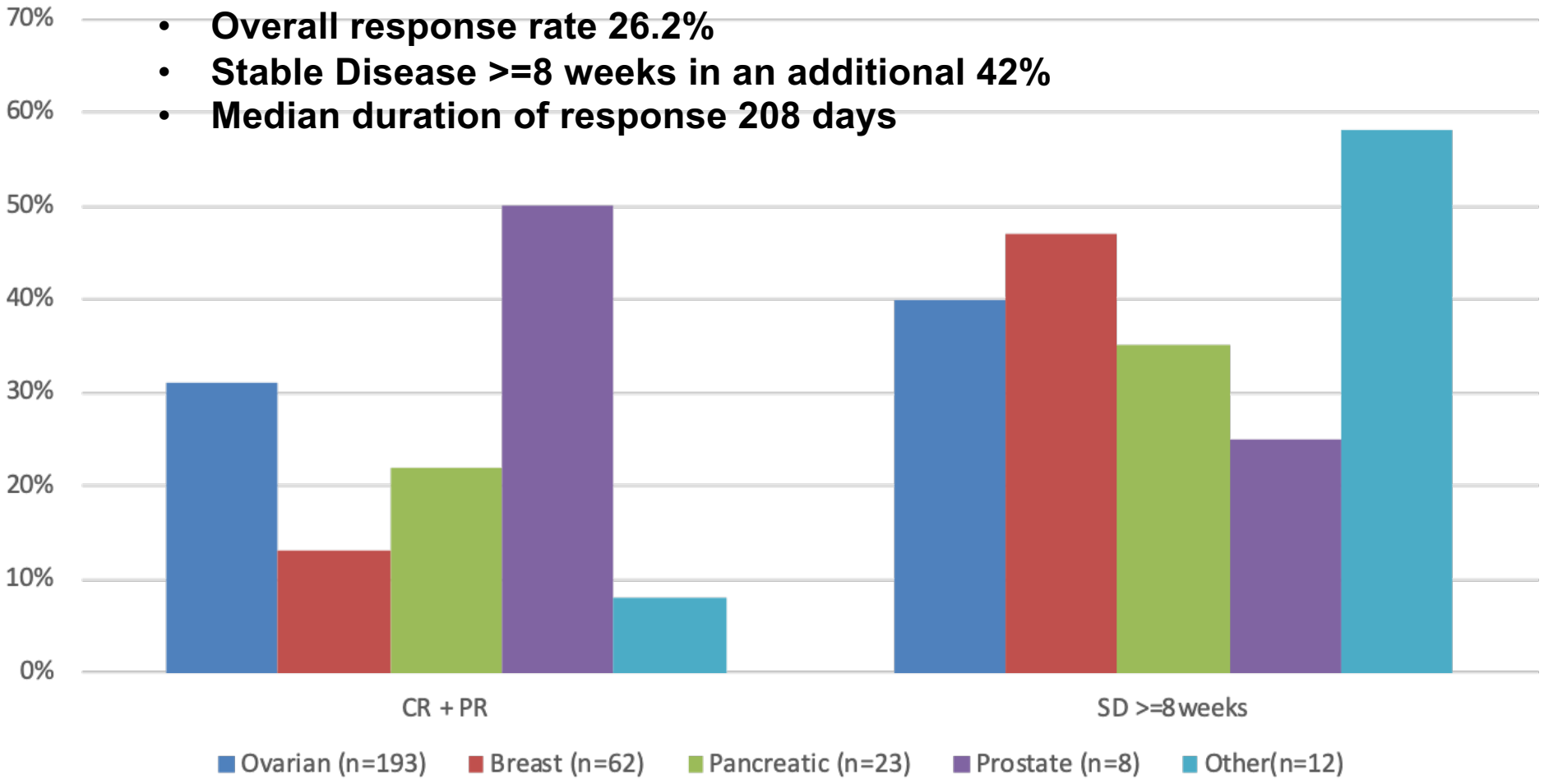
PARP inhibitor in Patients with Advanced Cancer and a Germline *BRCA1/2* mutation

- Multicenter open-label phase II study
- Germline *BRCA1/2* mutation
  - **Ovarian Cancer** resistant to prior platinum
  - **Breast cancer** with at least 3 chemotherapy regimens for metastatic disease
  - **Pancreatic cancer** with prior gemcitabine treatment
  - **Prostate cancer** with progression on hormonal and one systemic therapy
- Olaparib 400 mg bid*
- Primary endpoint = response rate

*recommended dosage with current tablet formulation for most indications is 300 mg bid

Olaparib Monotherapy in Patients with g*BRCA1/2* mutation

- **Overall response rate 26.2%**
- **Stable Disease >=8 weeks in an additional 42%**
- **Median duration of response 208 days**



Kaufman et al J Clin Oncol 33:244, 2015

Current FDA-approved PARP Inhibitors

Agent	Indication
Olaparib	**Ovarian Cancer** -g*BRCA*; ≥3 prior regimens -g/t*BRCA* front-line maintenance -recurrent disease with PR or CR to platinum therapy (regardless of BRCA status) **Breast Cancer** -g*BRCA* HER2(-) metastatic with prior chemo **Pancreatic Cancer** -g*BRCA*m nonprogressed on platinum therapy
Rucaparib	**Ovarian Cancer** -g*BRCAm* OR somatic *BRCAm*; ≥2 prior regimens -recurrent disease with PR or CR to platinum therapy (regardless of BRCA status)

Current FDA-approved PARP Inhibitors

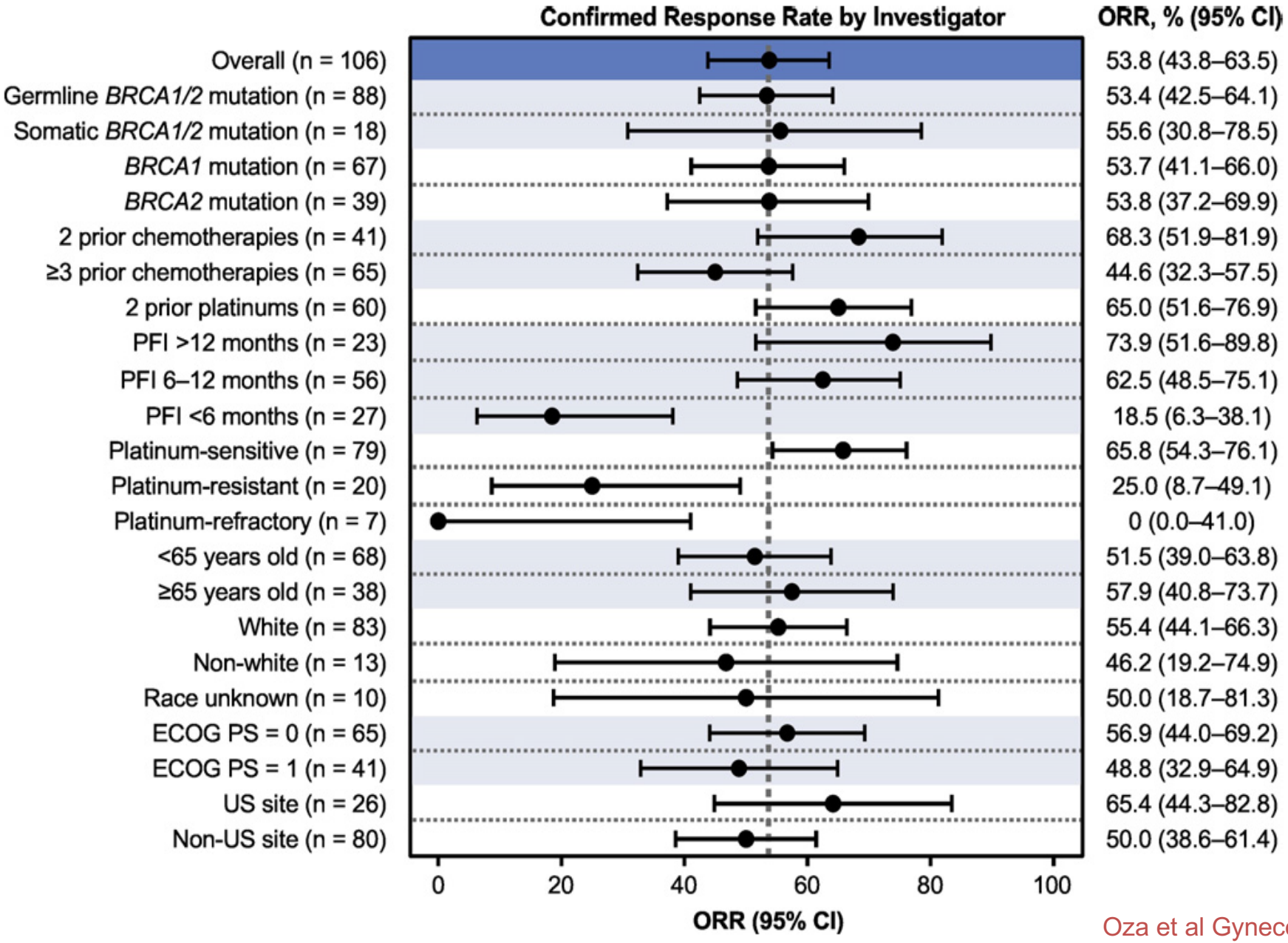
Agent	Indication
Niraparib	**Ovarian Cancer** -t/g*BRCA*m with >= 2 prior regimens -recurrent disease with PR or CR to platinum therapy (regardless of BRCA status)
Talazoparib	**Breast Cancer** g*BRCA*m HER2(-) metastatic disease

PARP inhibitors

- Introduction
- Predictors of Benefit
  - g*BRCA*m or tumor *BRCAm*
  - *?other HRR genes?*
  - In OC: Platinum sensitivity
  - HRD assay?
- Mechanisms of Resistance
  - Reversion *BRCA* mutations
- Combinations
  - Combinations with cytotoxic chemotherapy limited by myelotoxicity

Rucaparib monotherapy Ovarian g/t*BRCA1/2*m

Study 10 + ARIEL2 Trials: Role of platinum-sensitivity



Oza et al Gynecol Oncol 20

Comparing PARPi to non-platinum therapy-ovary

In gBRCAm carriers

Ovarian Cancer			
TRIAL	Population	Design	Results
Kaye et al 2011 n=97	g*BRC*A1/2m recurred within 12 mos of platinum (resistant or "intermediate sensitive")	Open label 1:1:1 Olaparib 200 bid vs Olaparib 400 bid vs PLD 50 mg/m2	PFS 6.5 mos vs 8.8 mos vs 7.1 mos p=NS
SOLO 3 2020 n=266	g*BRC*A1/2m Platinum sensitive >=2 prior platinum regimens	Open-label 2:1 Olaparib vs Non-platinum chemo (50% PLD)	ORR 72% vs 51% PFS 13 vs 9 mos OS immature

Kaye et al JCO 2011;30:372
Penson et al JCO 2020

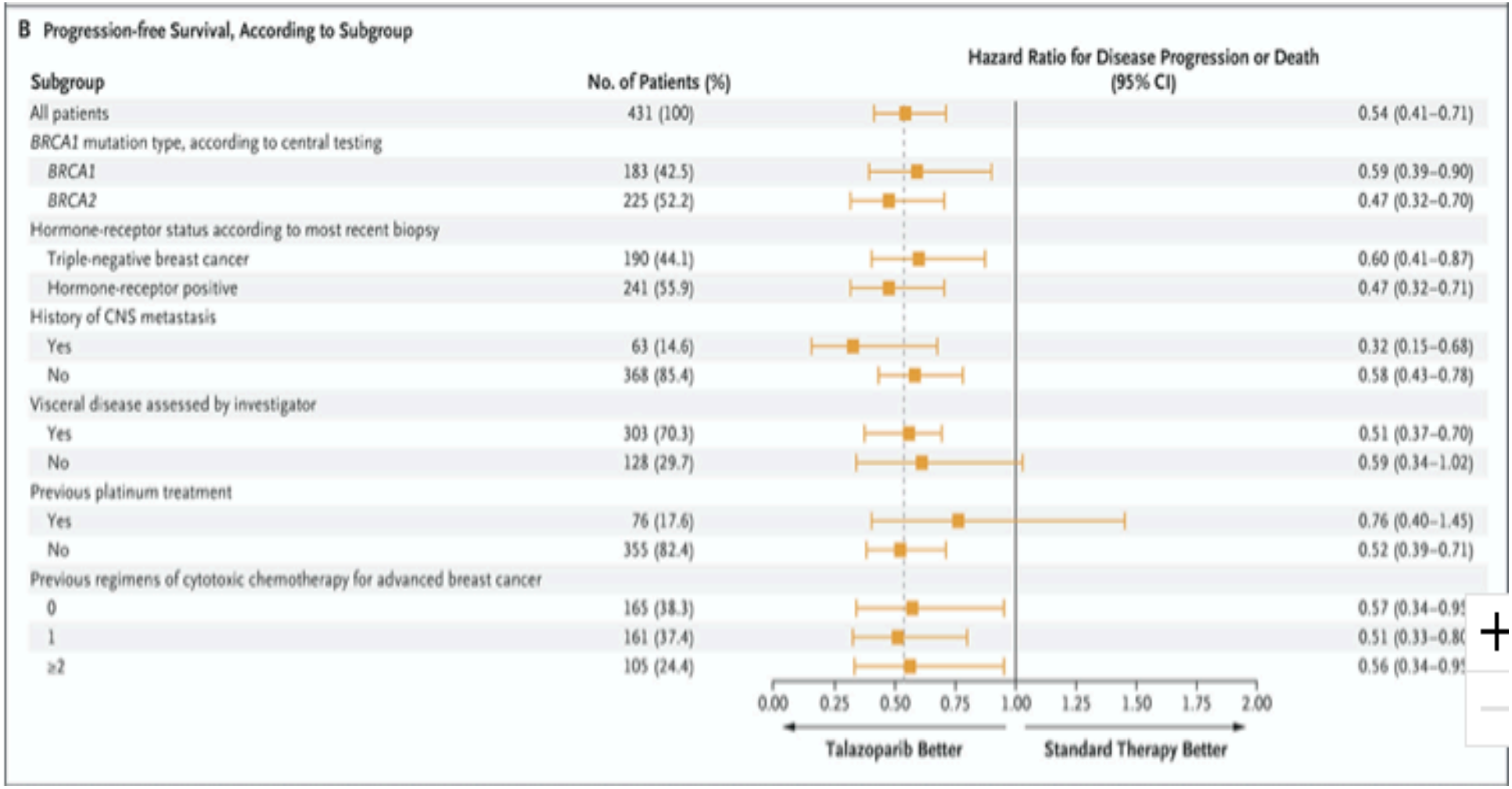
Comparing PARPi to non-platinum therapy

Breast Cancer

Metastatic Breast cancer			
TRIAL	Population	Design	Results
OlympiAD 2017 n=302	g*BRCA1/2*m HER2 (-) <=2 prior regimens No PD on platinum	Open label 2:1 Olaparib vs Non-platinum chemo	RR 60% vs 28% PFS 7 vs 4.2 mos OS no difference HR TNBC 0.43 HR ER+ 0.82
EMBRACA 2018 n=431	g*BRCA1/2*m <=3 prior regimens no PD on platinum	Open label 2/1 Talazoparib vs non-platinum chemo	RR 63 %vs 27% PFS 8.6 vs 5.6 mos

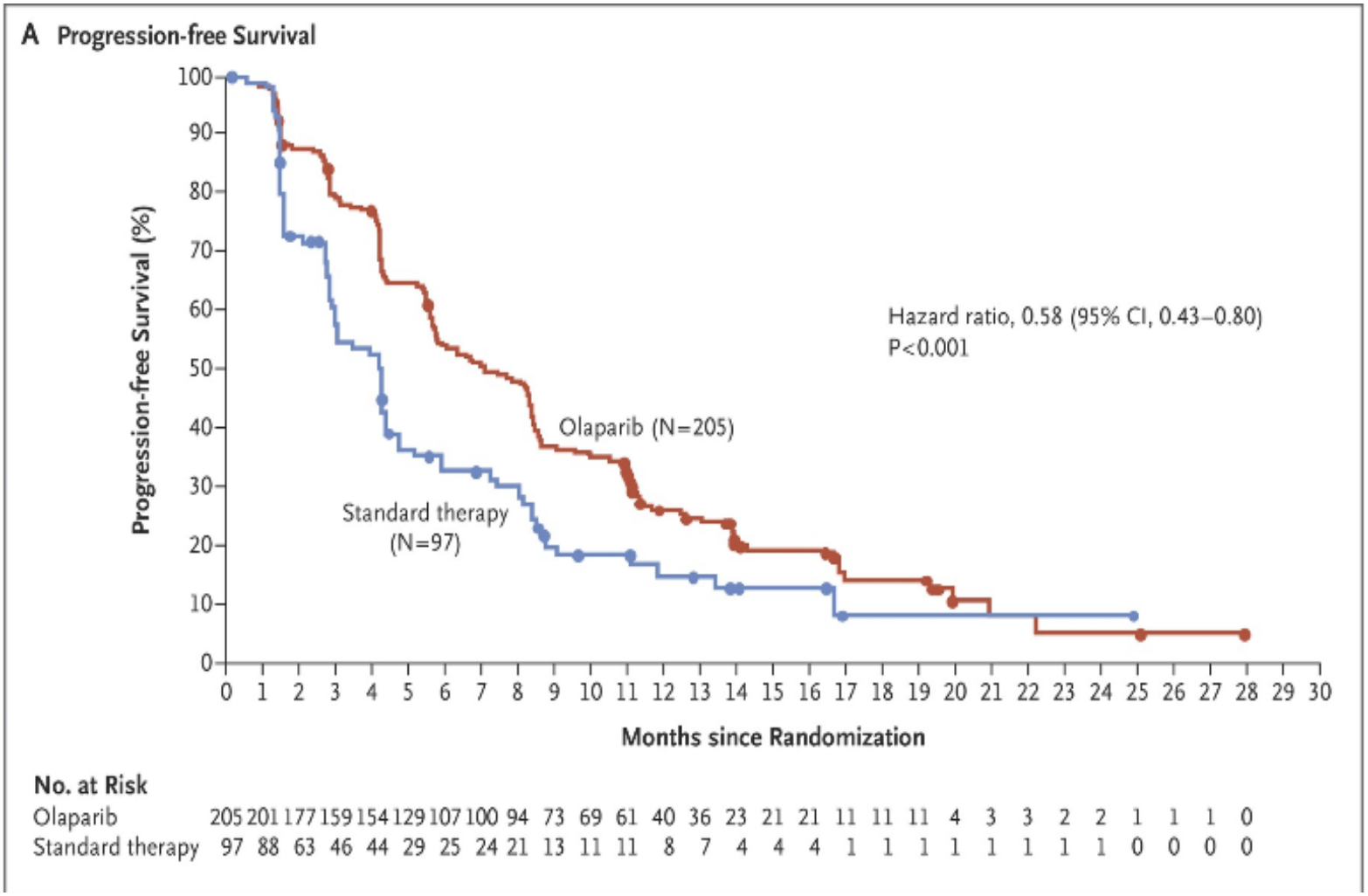
Litton et al NEJM 2018 379:753
Robson et al NEJM 2017; 377:523

Talazoparib Breast Cancer



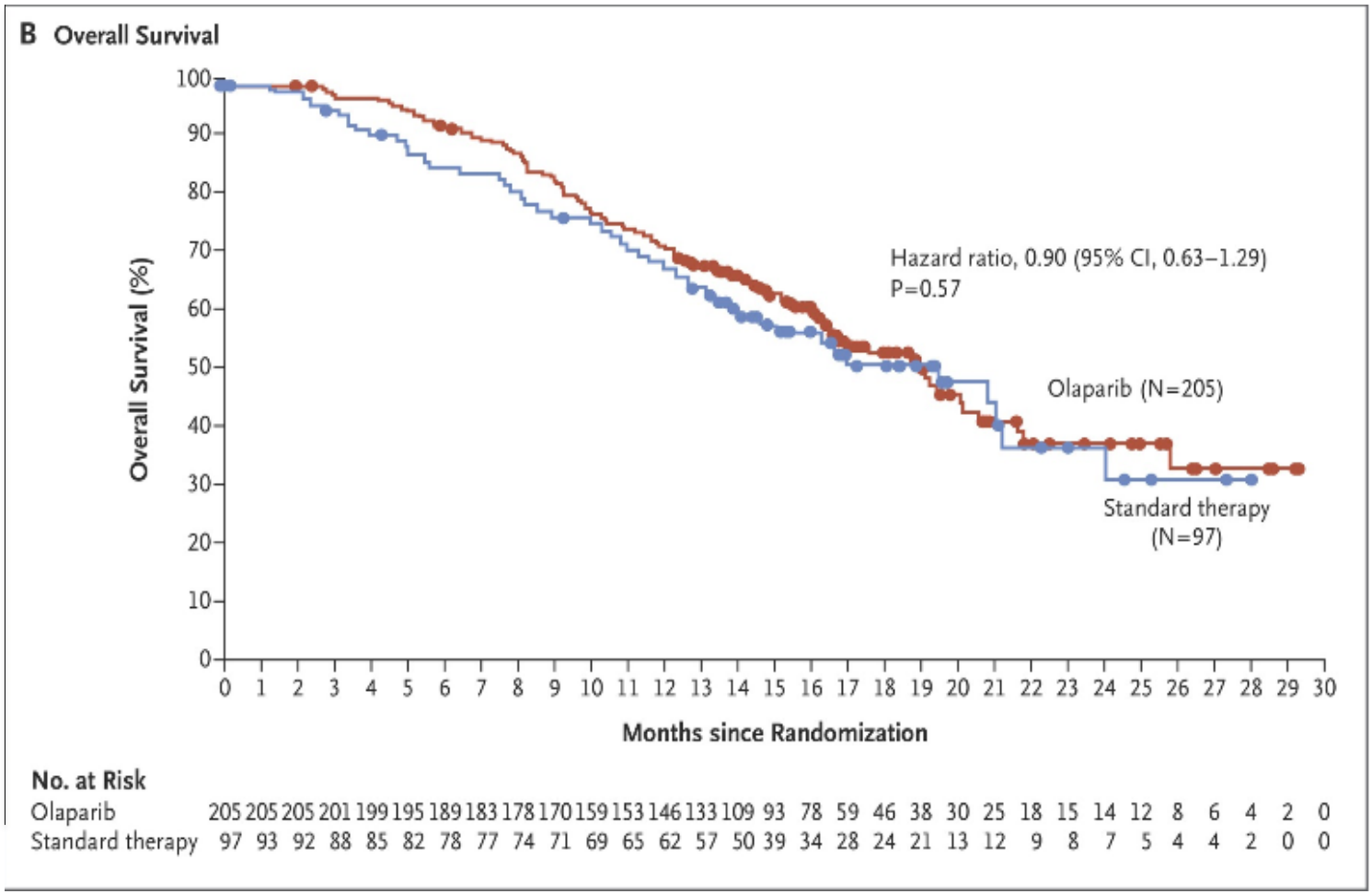
Litton et al NEJM 2018 379:753

Olaparib-Breast Cancer



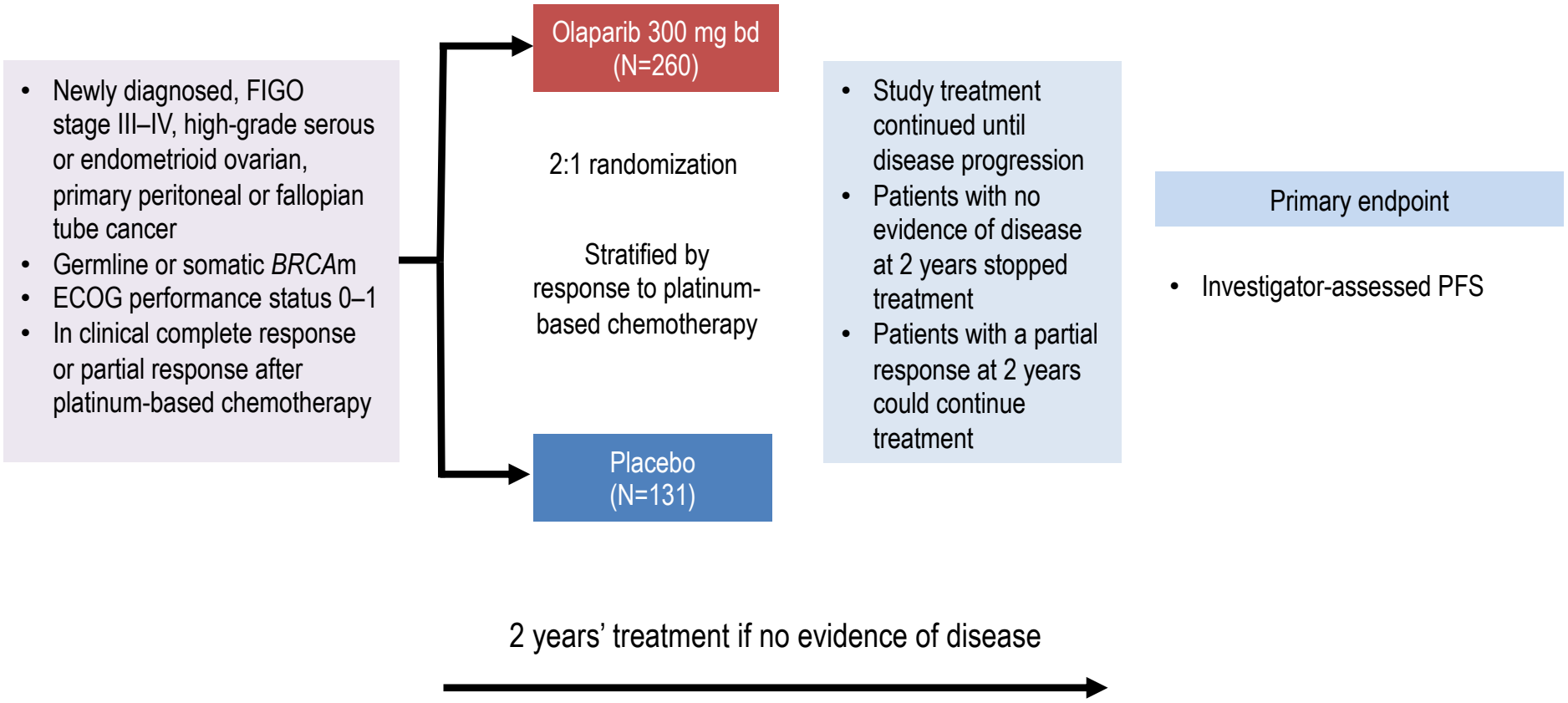
Robson et al NEJM 2017 377:523

Olaparib-Breast Cancer



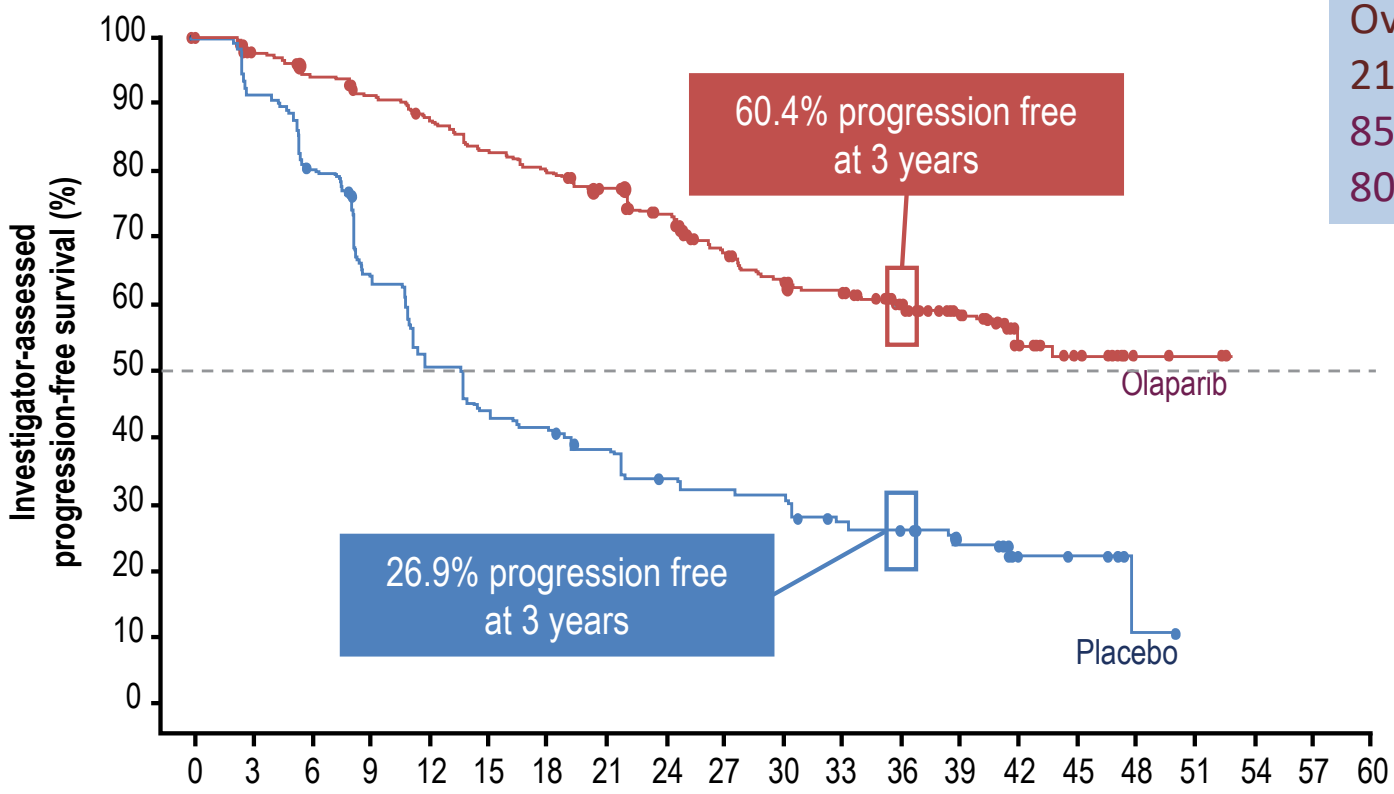
Robson et al NEJM 2017 377:523

Moving PARPi earlier: comparing to placebo
Solo 1 Study: g/t*BRCA*m Ovarian Cancer



Moore et al NEJM 2018

SOLO 1 PFS by Investigator Assessment

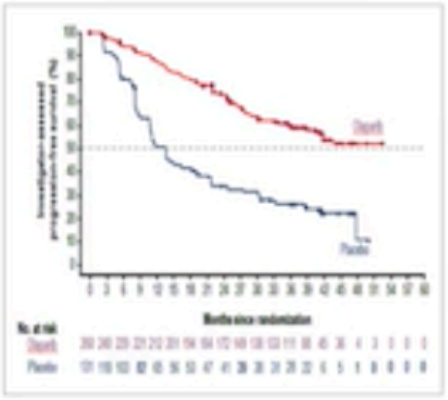
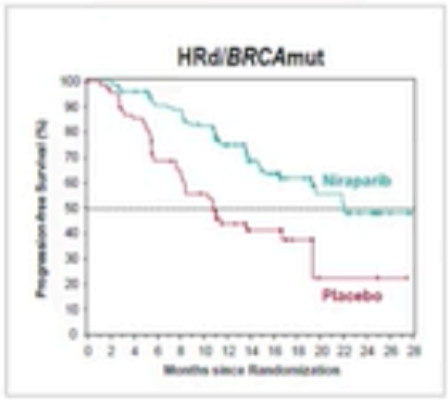
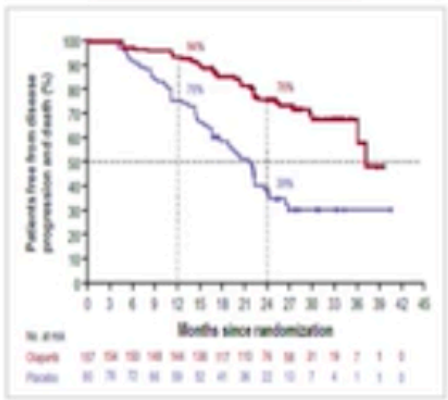
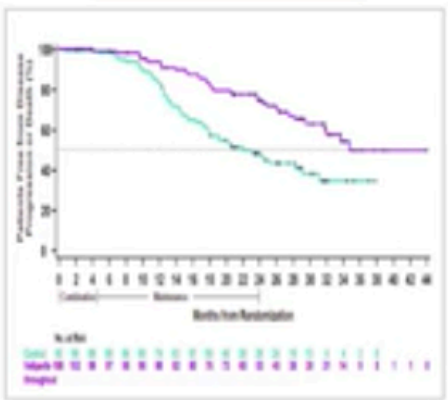


No. at risk																				
Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

Overall survival @ 3 years;
21% data maturity:
85% olaparib
80% placebo

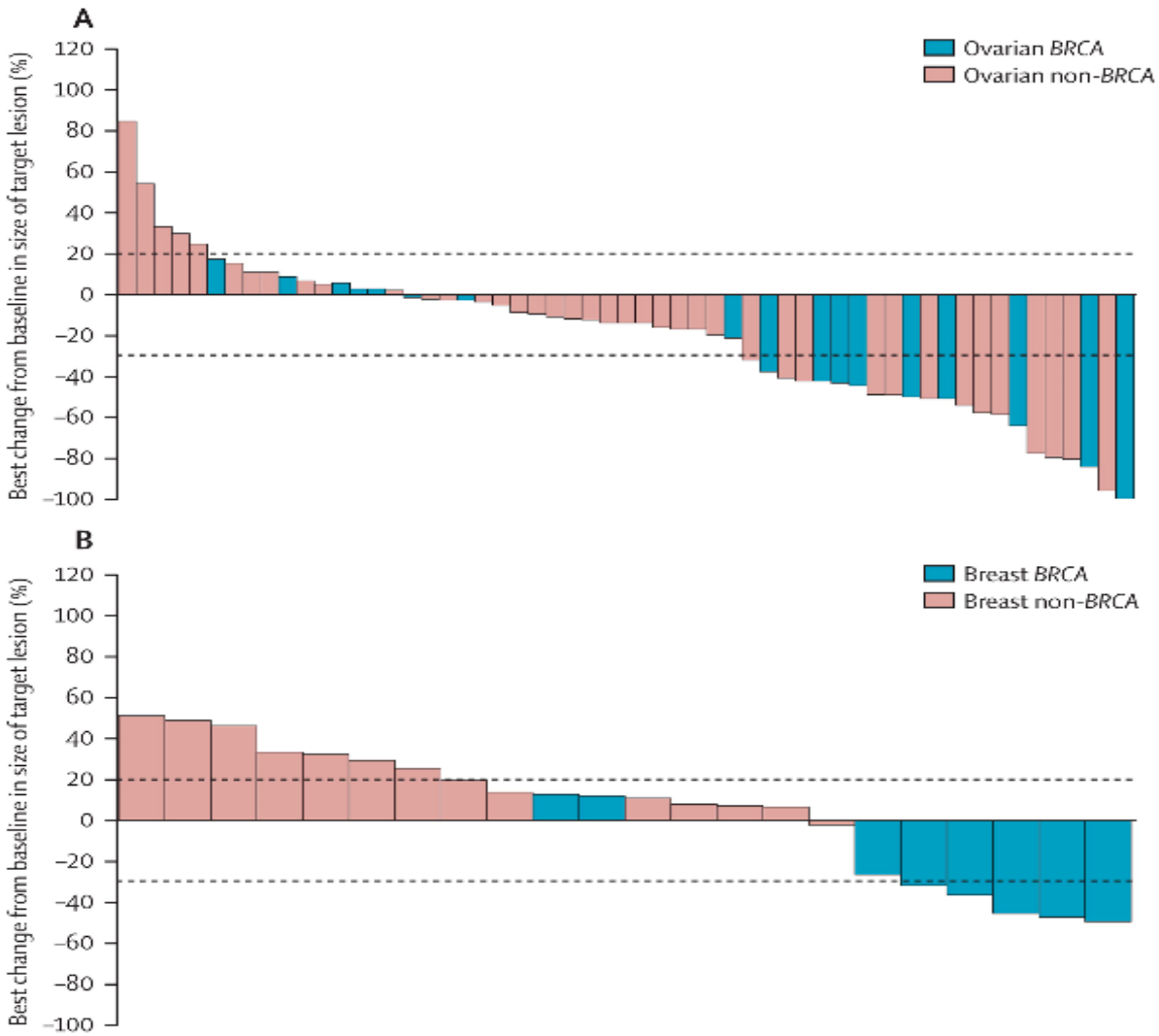
Moore et al NEJM 2018

Newly diagnosed ovarian cancer: BRCAm

SOLO1	PRIMA	PAOLA1	VELIA
			
N = 391	**N = 223**	**N = 235**	**N = 200**
HR 0.30 95% CI 0.23-0.41	**HR 0.40** 95% CI 0.27-0.62	**HR 0.31** 95% CI 0.20-0.47	**HR 0.44** 95% CI 0.28-0.68
13.8 mos vs NR	10.9 vs 22.1 mos	21.7 vs 37.2 mos	22.0 vs 34.7 mos

Moore NEJM 2018; Gonzalez-Martin NEJM 2019; Ray-Coquard ESMO 2019; Coleman NEJM 2019

PARP inihibitors in tumors without gBRCAm



Olaparib

-Single agent therapy 400 mg bid

-High grade serous ovarian cancer or triple negative breast cancer

-Median 3 prior chemotherapy regimens

Gelmon et al Lancet Oncol 2011; 12:852

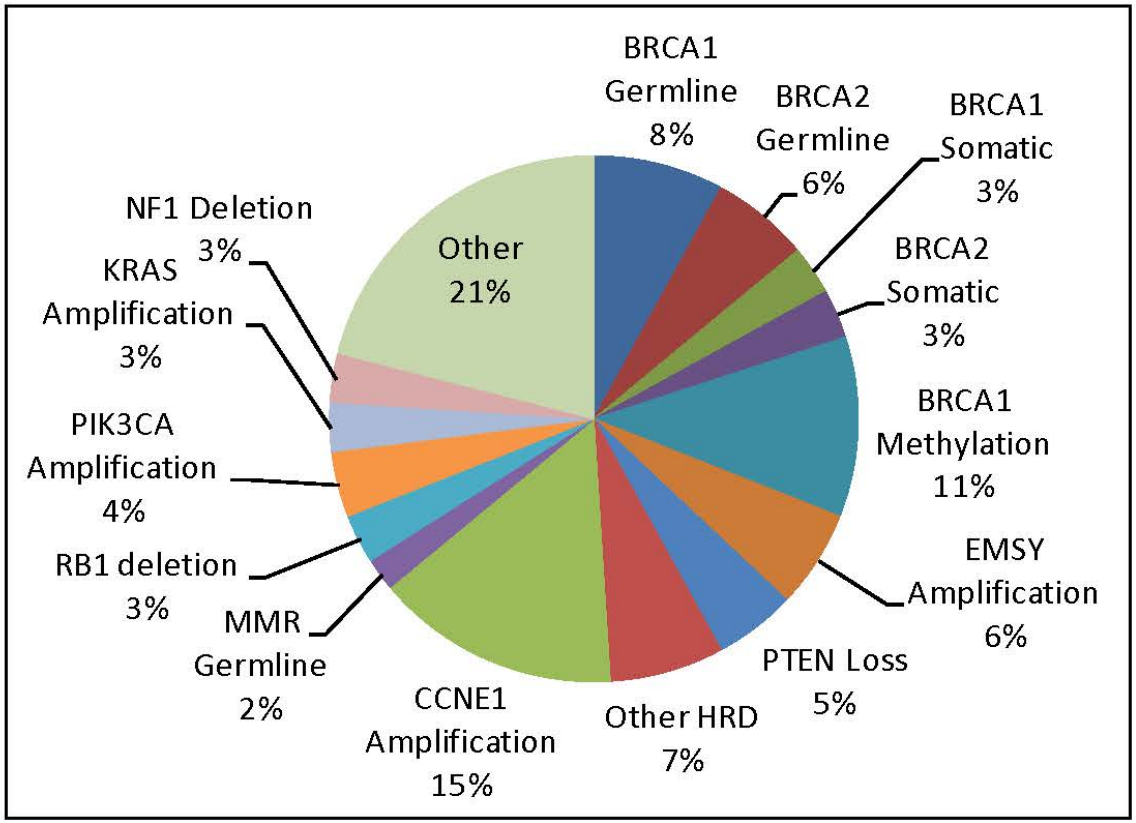
Case Presentation

- 60 y/o woman
  - T3N1 high grade serous ovarian cancer
  - Surgery followed by carboplatin/paclitaxel with CR (and significant neuropathy)
- Three years later, rising CA125
  - Mediastinal biopsy shows recurrent disease
  - Carboplatin/paclitaxel with CR
- Six months later rising CA125
  - Radiation to mediastinum complicated by significant pneumonitis
- One year later rising CA125
  - New right paratracheal lymph node and new liver lesion

Case Presentation

- Enrolled on clinical trial of carboplatin/gemcitabine+veliparib followed by veliparib
  - PR; had resection of liver lesion (showed high grade carcinoma)
  - Required daily antiemetics with veliparib
  - Remained NED for seven years and then elected to stop veliparib
- Germline genetic testing negative

TCGA



Mutually exclusive potential driver events in HGS-Ovarian Cancer

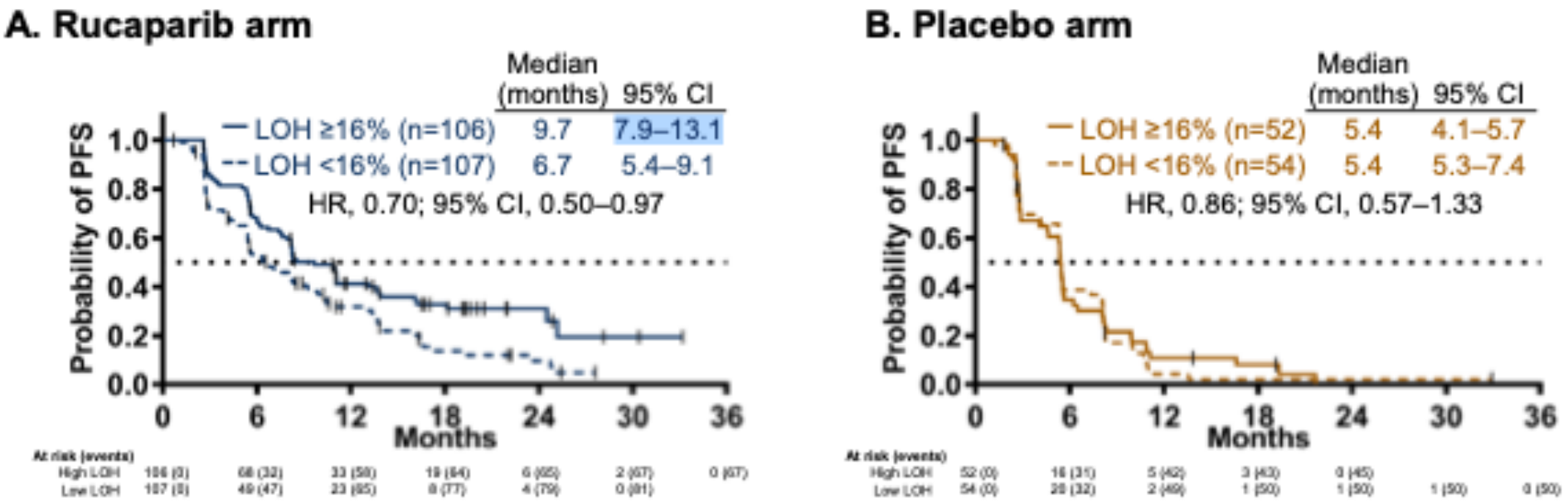
Data provided by Douglas Levine, MD, MSKCC on behalf of tcga.cancer.gov

“BRCA-ness”: HRD testing

- Commercially approved companion assays for response to PARPi therapy
- Reflect ”genomic scarring”
- Foundation Focus CDxBRCA LOH (approved companion for Rucaparib)
  - Tumor *BRCA1/2*
  - % of genomic loss of LOH
- Myriad MyChoice HRD (approved companion for niraparib)
  - Tumor *BRCA1/2*
  - High genomic instability score using three biomarkers associated with homologous recombination deficiency (HRD)
    - LOH (loss of heterozygosity)
    - LST (large-scale state transitions)
    - TAI (telomeric allelic imbalance).

ARIEL 3: platinum-sensitive recurrence

Figure 5. Investigator-Assessed PFS (LOH ≥16% vs LOH <16%) in Patients with a *BRCA* Wild-Type Carcinoma in the (A) Rucaparib and (B) Placebo Arms



Visit cutoff date: April 15, 2017. CI, confidence interval; HR, hazard ratio; LOH, loss of heterozygosity; PFS, progression-free survival.

Oaknin et al ASCO 2018 abstr #5545

HRD testing for Ovarian Cancer upfront Maintenance

TRIAL	Eligibility	HRD assay	Results
Velia n=532 (veliparib throughout and control arms)	Enrolled prior to start of therapy, regardless of BRCA status	Myriad MyChoice Cutoff >=33 for HRD+	PFS for Veliparib use Within *BRCAwt* HRD+ HR 0.77 non HRD HR 0.76 results unchanged with different cutoff
PRIMA n=733 (2:1 niraparib vs placebo)	Enrolled after response to initial platinum-based chemotherapy regardless of BRCA status	Myriad MyChoice HRD= cutoff >=44 OR *BRCA*m	PFS for niraparib use HRD = 0.43 BRCAm = 0.40 BRCAwt = 0.50 non HRD = 0.68

Swisher et al SGO abstr LBA 6 2020 online
Monk et al SGO abstr #31 2020 online

PARP inhibitors

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- Predictors of Benefit
  - g*BRCA*m or tumor *BRCAm*
  - Platinum sensitivity
  - HRR assay?
- Mechanisms of Resistance
  - Reversion *BRCA* mutations
- Combinations
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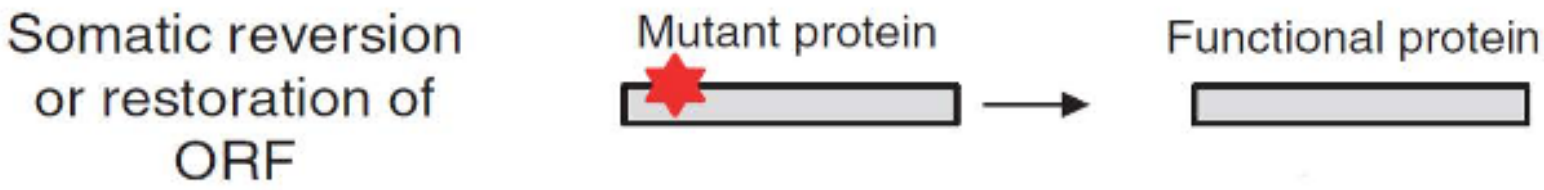
PARPi Resistance: *BRCA* Reversion Mutations

- Somatic base substitutions or insertions/deletions that restore the open reading frame (ORF) of gene and functional protein
- Have been reported in multiple Homologous Recombination Repair pathway genes, including *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *PALB2*
- Reported in ovarian, prostate, and breast carcinomas as a mechanism of acquired resistance to both platinum-based chemotherapies and PARP inhibitors



Lin et al Cancer Discovery Feb 2019

BRCA Reversion Mutations:

ARIEL2 (Rucaparib monotherapy ovarian cancer)

- Cell-free DNA collected pre and post-single agent rucaparib therapy from 112 patients with tumor or germline *BRCA* mutant OC
- As *TP53* is ubiquitously mutated in HGS OC, presence of *TP53* used as indicator of neoplastic DNA
- 107/112 had *TP53* cfDNA detected; 97/107 had a primary deleterious *BRCA* mutation detected
- 8 patients had baseline reversion mutation

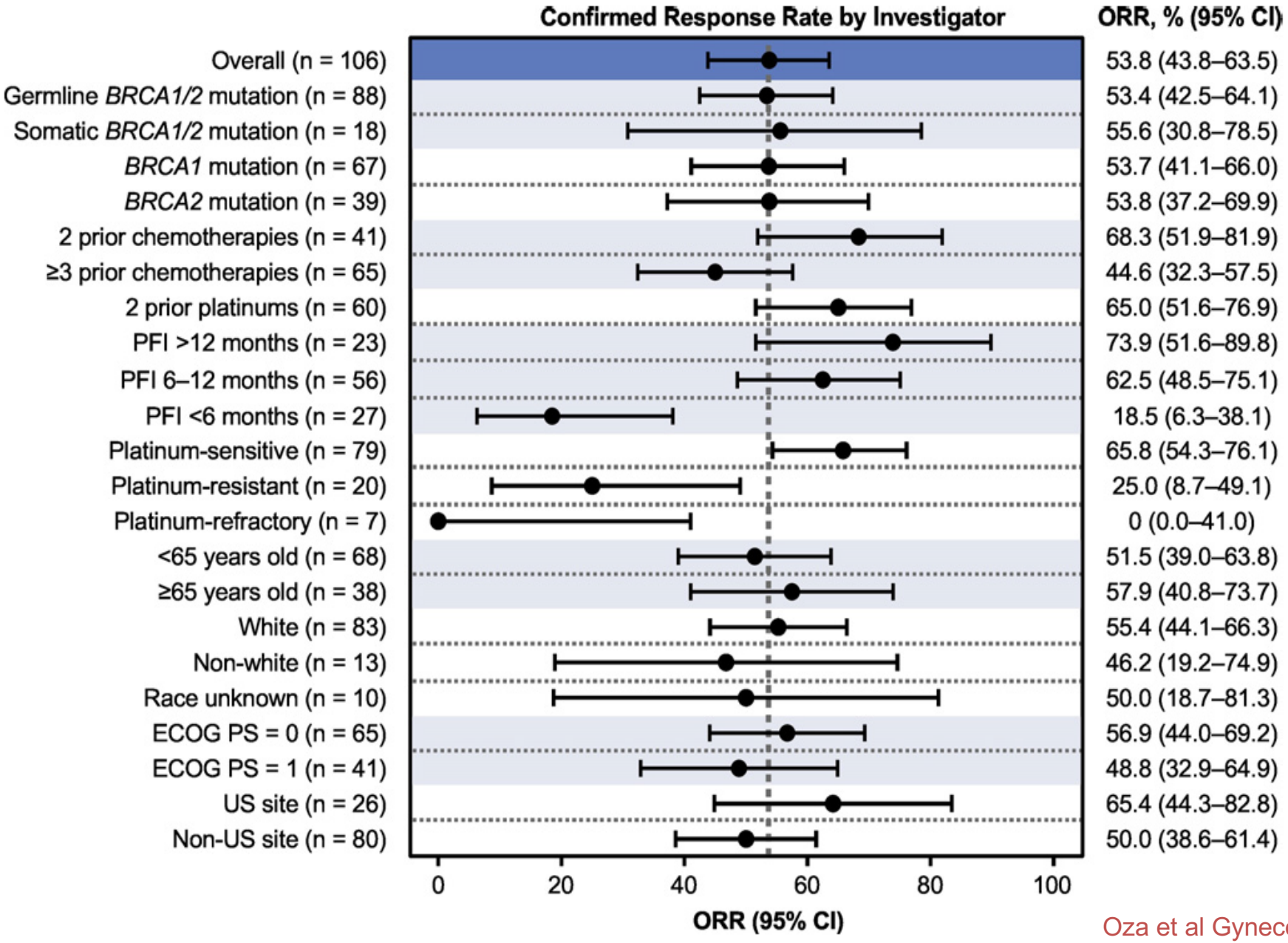
Baseline *BRCA* Reversion Mutations: ARIEL2

- Only platinum resistance status was associated with baseline reversion mutation

	n	n(%) with reversion mutation
Platinum-refractory	11	2(18%)
Platinum-resistant	38	5(13%)
Platinum-sensitive	48	1(2%)
BRCA1		4
BRCA2		4
Original gBRCAm		5
Original tBRCAm		3

Rucaparib monotherapy Ovarian g/t*BRCA1/2*m

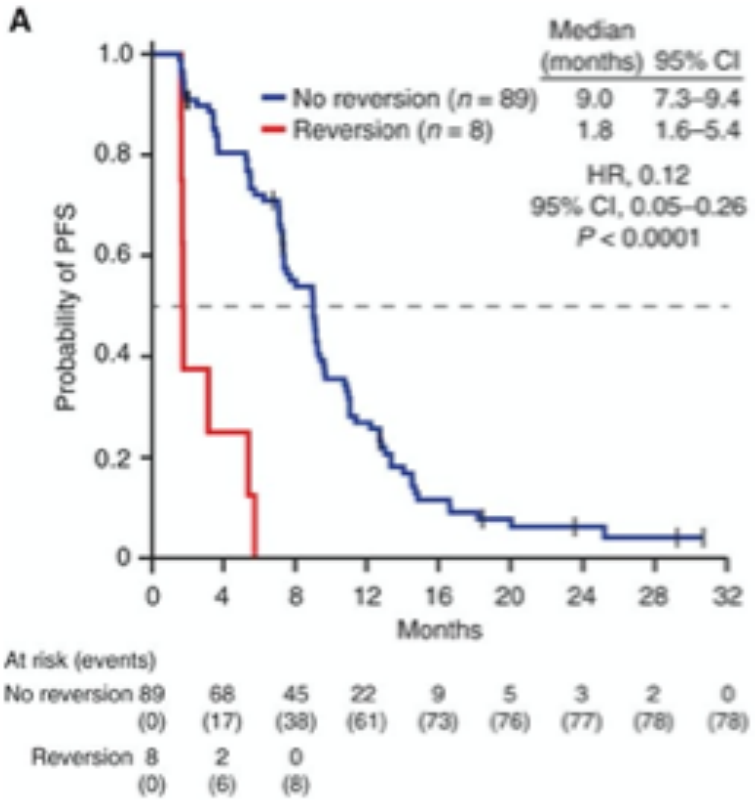
Study 10 + ARIEL2 Trials



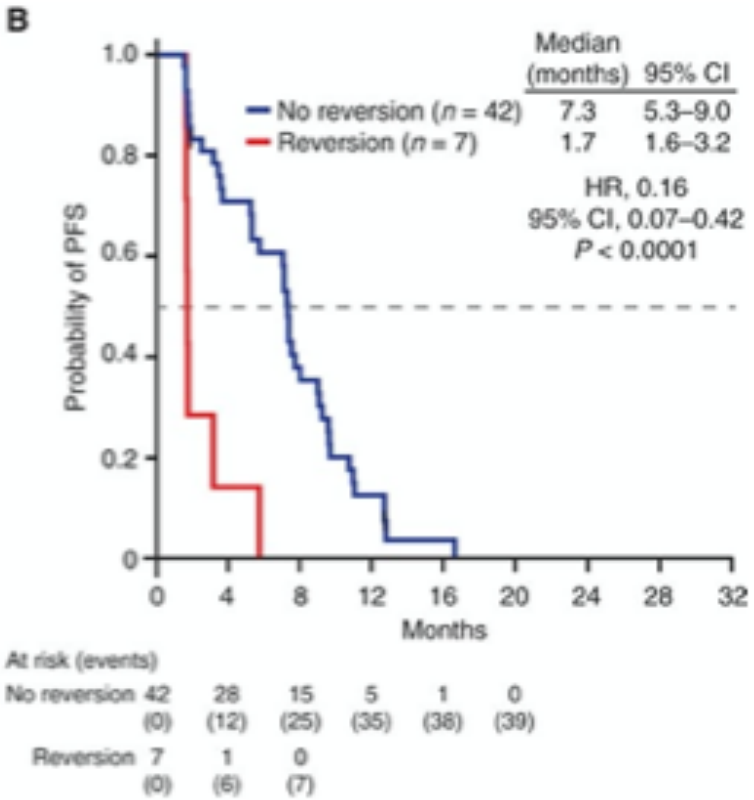
Oza et al Gynecol Oncol 20

ARIEL2 Effect of baseline BRCA reversion mutation

All cases



Platinum resistant/refractory cases



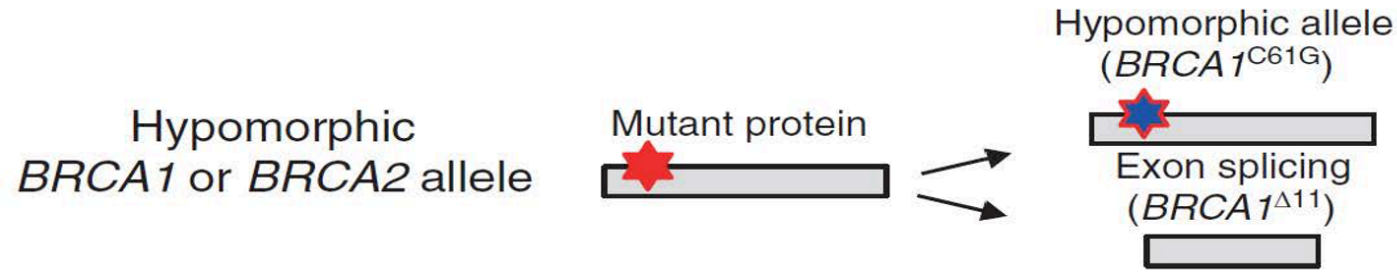
Lin et al Cancer Discovery Feb 2019

ARIEL2 post-progression reversion mutations

- 63/78 post-progression cfDNA samples had both *TP53* and *BRCA* mutations detected
- Eight patients with no baseline *BRCA* reversion mutation developed one (all in germline mutation carriers)
- All eight patients had actual or imminent (median 3.4 months) disease progression at the time reversion mutation noted
- Patients with baseline reversion mutations could develop additional mutations:
  - e.g. a patient with platinum resistant cancer and a primary somatic BRCA1 mutation (c.2679delG;p.K894fs) the reversion mutation (c.2740_2750del11) increased from a relative (to *TP53*) mutation allele frequency of 7.2% to 25.9%, and seven additional BRCA reversion mutations were detected.
- .

BRCA Reversion Mutations

- Multiple other mechanisms of resistance to platinum and PARPi exist
  - Cancers with *BRCA1* mutation in exon 11 can increase expression of a naturally occurring alternative splice isoform that lacks exon 11 but still has residual *BRCA1* activity



- Response rate to platinum-based chemotherapy in patients with g*BRCA1/2*m after progression on PARPi reported at 40%
- Nucleotide Excision Repair (NER) defects are found in 8% of OC
  - Enhanced sensitivity to platinum therapy
  - Do *not* confer sensitivity to PARPi therapy

Wang et at Cancer Res 2016 76:2778
Patch AM et al Nature 2015 521:489
Ceccaldi et al Cancer Res 2015

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BrightNess: Addition of veliparib/carboplatin vs carboplatin alone to neoadjuvant chemotherapy in TNBC

- 2:1:1 randomization, placebo controlled
  - Stratified for g*BRCA*m
  - All arms followed by AC

- Paclitaxel 80 mg/m2 weekly+carbo AUC6 q 3 wk+veliparib 50 mg bid
  - pCR 53%
- Paclitaxel 80 mg/m2 weekly+carbo AUC6 q 3 wk
  - pCR 58%
- Paclitaxel 80 mg/m2 weekly
  - pCR 31%

Loibl et al Lancet Oncology 2018

Ovarian Cancer: platinum + PARPi

Study Design: VELIA/GOG-3005 (NCT02470585)

Patient Population

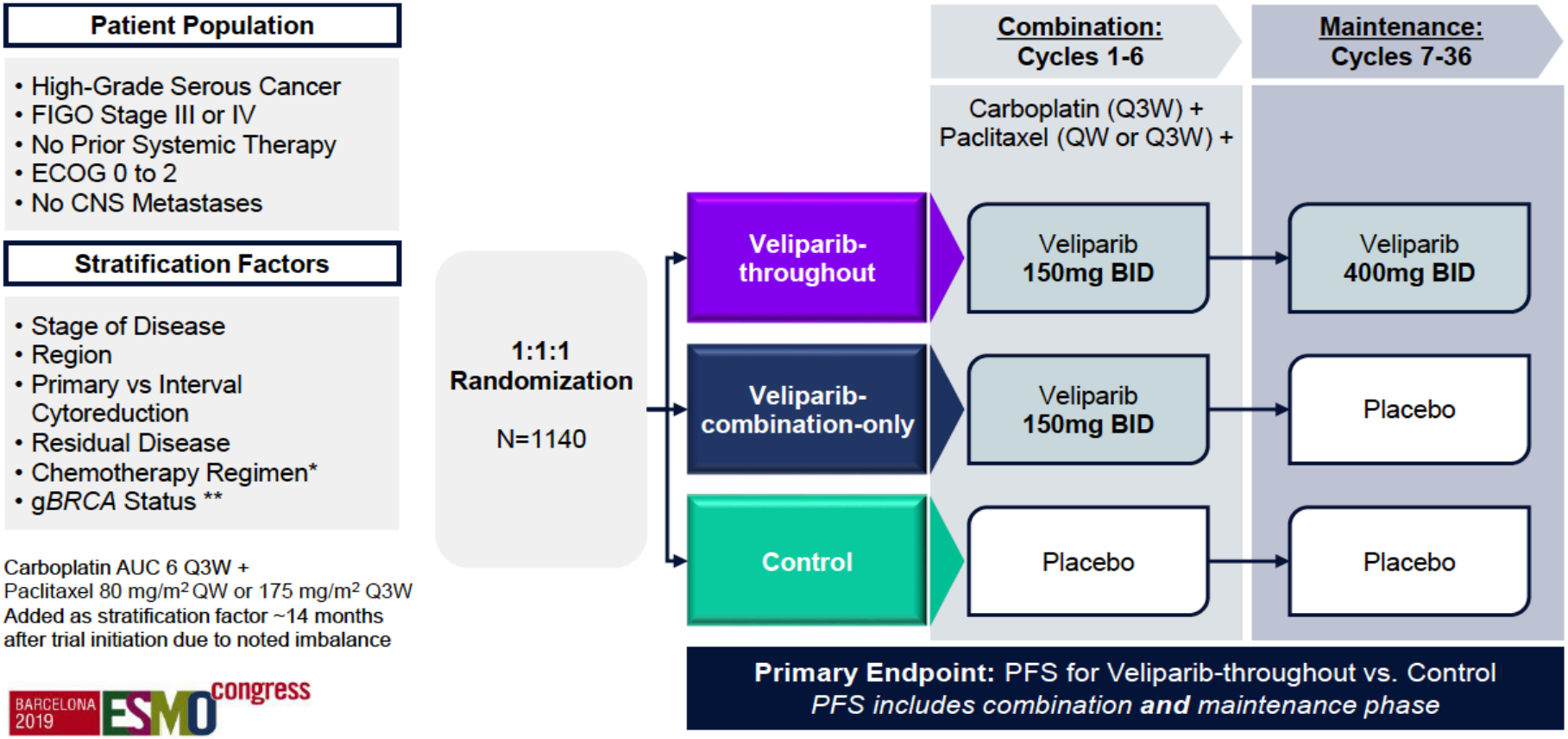
- High-Grade Serous Cancer
- FIGO Stage III or IV
- No Prior Systemic Therapy
- ECOG 0 to 2
- No CNS Metastases

Stratification Factors

- Stage of Disease
- Region
- Primary vs Interval Cytoreduction
- Residual Disease
- Chemotherapy Regimen*
- g*BRCA* Status **

* Carboplatin AUC 6 Q3W + Paclitaxel 80 mg/m² QW or 175 mg/m² Q3W

** Added as stratification factor ~14 months after trial initiation due to noted imbalance



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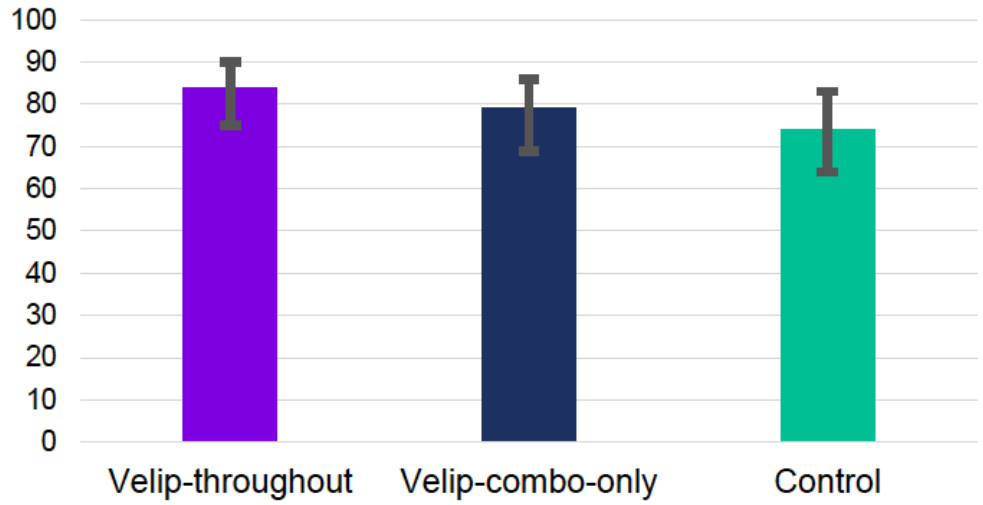
VELIA

Objective Response Rates at End of Combination Phase

ORR at End of Combination Phase in ITT Patients with Primary Surgery and Measurable Disease



ORR (CR+PR), n / N %, [95% CI]		
Veliparib-throughout	**Veliparib-combo-only**	**Control**
82/98	78/99	69/93
84% [75, 90]	**79%** [69, 86]	**74%** [64, 83]

For both veliparib-containing arms, numerically higher response rates were observed at the end of chemotherapy

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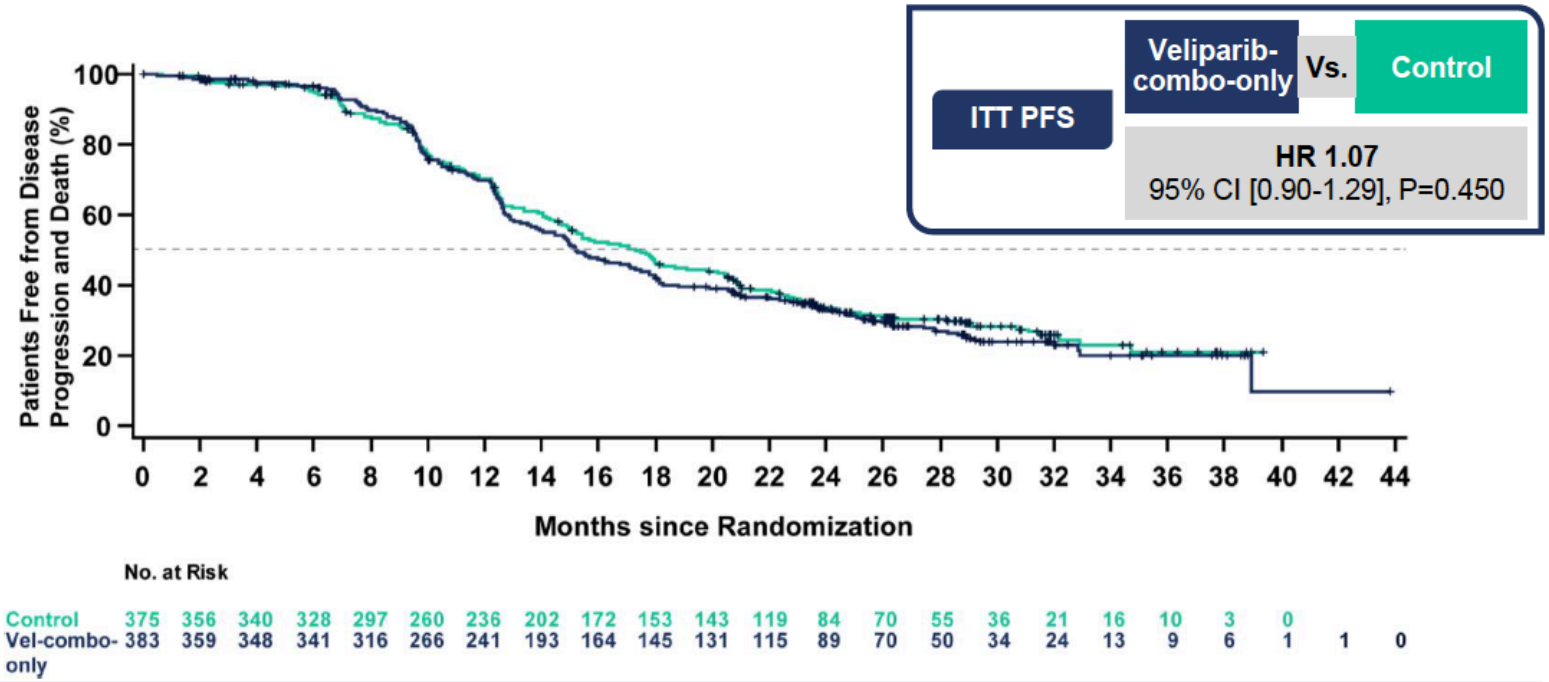
VELIA

PFS for Veliparib-combo-only vs. Control



Across *BRCA*m, HRD, and ITT, the veliparib-combo-only arm and the control arm demonstrated similar PFS

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PARP inhibitors

- Future Directions
  - Overcoming mechanisms of resistance (Wee1 inhibitors?)
  - Better patient selection (new HRD assays?)
  - Combinations that are effective in HRD proficient cancers (AKT inhibitors? Antiangiogenics?)