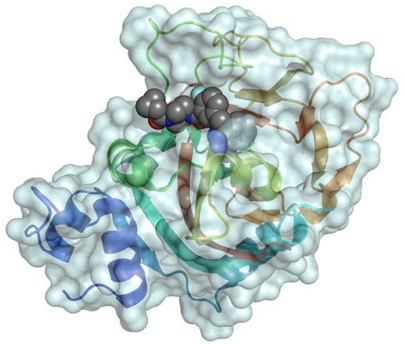
The Evolution of PARP-inhibitors

ד"ר רינת ברנשטיין מולכו

המכון האונקולוגי - מרכז רפואי שיבא



BRCA1/2 mutation probabilities based on single feature

- Among Ashkenazi Jewish individuals, the likelihood of having any *BRCA* mutation is:
  - General Ashkenazi Jewish population: 1 in 40 (2.5%)
  - Women with breast cancer (any age): 1 in 10 (10%)
  - Women with breast cancer (younger than 40 years): 1 in 3 (~30%)
  - Men with breast cancer (any age): 1 in 5 (19%)
  - Women with ovarian cancer or primary peritoneal cancer (all ages): 1 in 3 (36%–41%)
  - Patient with pancreatic caner (all ages): 10-15%
  - Ashkenazi Jewish patient negative for founder mutations – 2-3% chance for rare / private mutation

- In non-AJ population, the likelihood of having any *BRCA* mutation is as follows:
  - General population (excluding Ashkenazim): about 1 in 400 (~0.25%)
  - Women with breast cancer (any age): 1 in 50 (2%)
  - Women with breast cancer (younger than 40 years): 1 in 10 (10%)
  - Men with breast cancer (any age): 1 in 20 (5%)
  - Women with ovarian cancer (any age): 1 in 8 to 1 in 10 (10%–15%)

Issues of testing

- Family history is frequently insufficient

- Testing for multiple germline mutations
  - ✓Increased awareness of other inherited mutations

- Tumor testing
  - ✓Can detect germline mutations without family history
  - ✓Somatic alterations which may predict response

PARP inhibitors as monotherapy

Breast and Ovarian Cancers

Olaparib – heavily pretreated g*BRCAm* OC

December 19, 2014 – The US FDA approved Lynparza (olaparib) for women with advanced ovarian cancer who have been treated with three or more types of chemotherapy and who have a deleterious or suspected deleterious germline BRCA mutation, as detected by a companion diagnostic test - BRACAnalysis CDx (approved by the FDA at the same time as olaparib)

Response status, n (%)	Tumour type					
	Ovarian (n=193)	Breast (n=62)	Pancreas (n=23)	Prostate (n=8)	Other (n=12)	Total (n=298)
Tumour response rate	60 (31.1)	8 (12.9)	5 (21.7)	4 (50.0)	1 (8.3)	78 (26.2)
CR*	6 (3.1)	0	1 (4.3)	0	0	7 (2.3)
PR*	54 (28)	8 (13)	4 (17)	4 (50)	1 (8.3)	71 (23.8)
SD ≥8 weeks	78 (40)	29 (47)	8 (35)	2 (25)	7 (58)	124 (42)
SD	64 (33)	22 (36)	5 (22)	2 (25)	6 (50)	99 (33)
Unconfirmed PR†	12 (6)	7 (11)	3 (13)	0	1 (8.3)	23 (8)
PD‡	41 (21)	23 (37)	9 (39)	2 (25)	3 (25)	78 (26)
RECIST progression	33 (17)	16 (26)	6 (26)	1 (13)	3 (25)	59 (20)
Early death§	8 (4)	7 (11)	3 (13)	1 (13)	0	19 (6)
Not evaluable	14 (7)	2 (3)	1 (4)	0	1 (8.3)	18 (6)
No follow-up assessments	12 (6)	2 (3)	1 (4)	0	0	15 (5)
SD <8 weeks	2 (1)	0	0	0	1 (8.3)	3 (1)

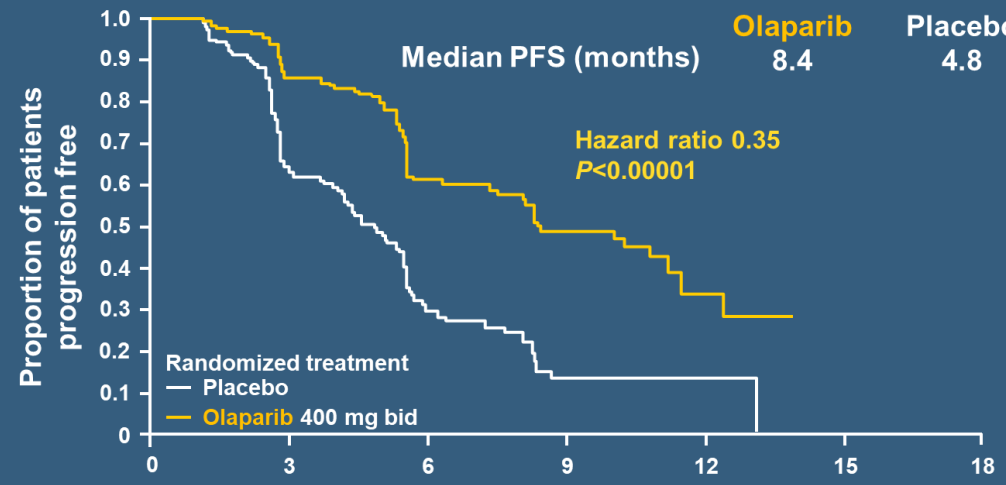
Kaufman B, et al. *J Clin Oncol*. 2015;33(3):244-250.

Olaparib – maintenance in OC

Study 19 - randomized, double-blind, placebo-controlled, phase 2 study

- Platinum-sensitive high-grade serous OC
- ≥2 previous platinum regimens
- Maintained PR or CR after last platinum regimen

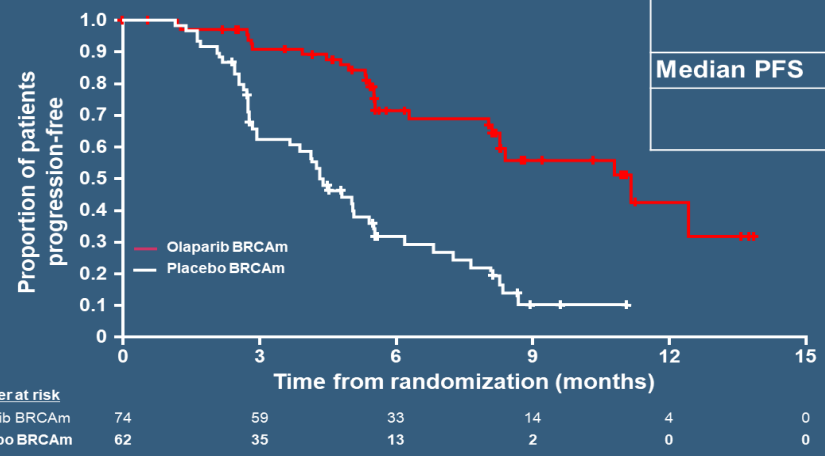
Study 19: Progression-free survival



At risk (n)							
Olaparib	136	104	51	23	6	0	0
Placebo	129	72	23	7	1	0	0

Ledermann et al. *Proc ASCO* 2011;Abstract 5003; *N Engl J Med* 2012;366(15):1382-92.

Study 19: PFS for patients with BRCA mutation (BRCAm)



	BRCAm (n = 136)	
	Olaparib	Placebo
Median PFS	11.2 mo	4.3 mo
	HR = 0.18 $p < 0.00001$	

Number at risk						
Olaparib BRCAm	74	59	33	14	4	0
Placebo BRCAm	62	35	13	2	0	0

- 82% reduction in risk of disease progression or death with olaparib

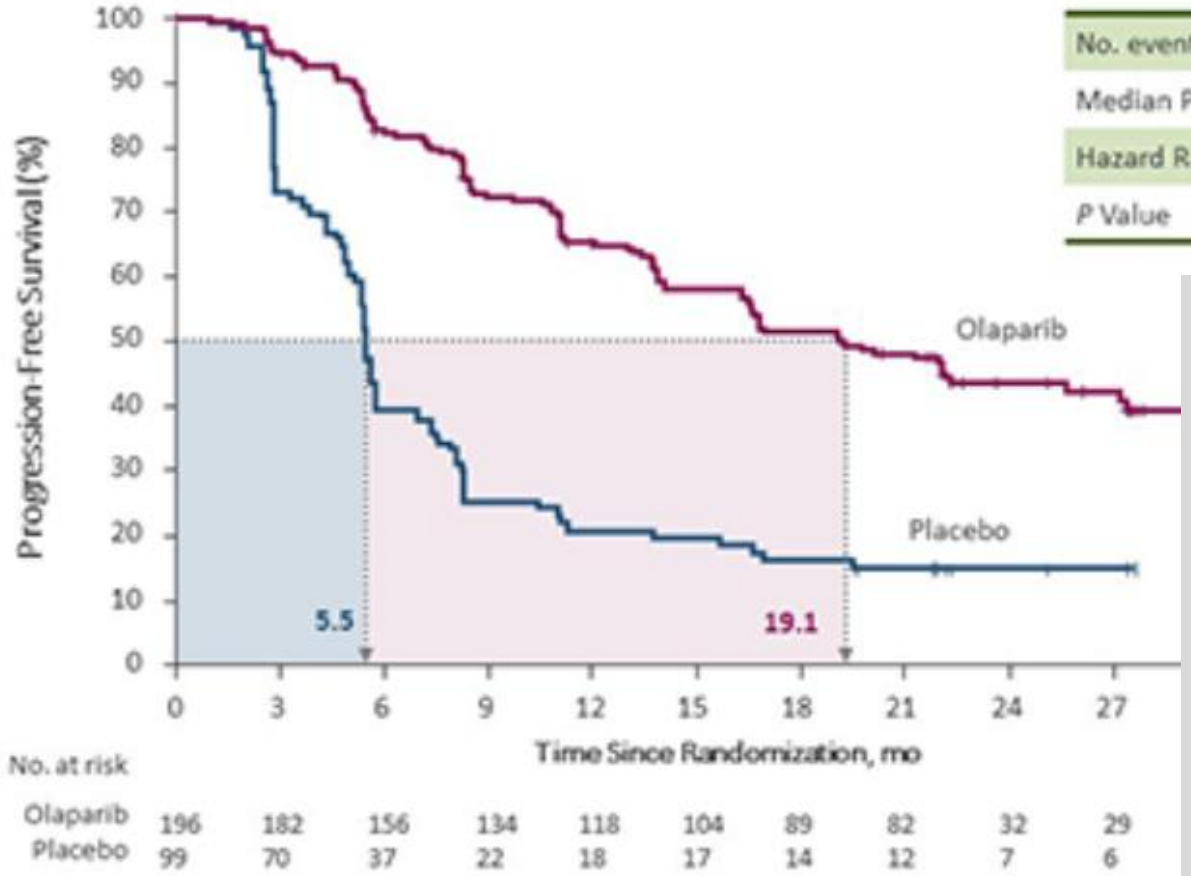
Presented by Jonathan Ledermann et al at ASCO 2013; *Lancet Oncol* 2014;15(8):852-61.

Olaparib – maintenance in OC

SOLO2 trial- randomized, double-blind, placebo-controlled, phase 3 study

- Platinum-sensitive relapsed ovarian ca / PPC
- ≥2 previous platinum regimens, PR or CR after last platinum regimen
- gBRCAm patients

	Olaparib (N=196)	Placebo (N=99)
No. events (%)	107 (54.6)	80 (80.8)
Median PFS, mo	19.1	5.5
Hazard Ratio (CI)	0.30 (0.22, 0.41)	
P Value	< .0001	



Aug. 17, 2017 - The U.S. FDA granted regular approval to olaparib tablets for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy

מעודכן לתאריך : 25/2/2018

מאגר התרופות

פרטי מסגרת הכללה בסל

שם תרופה:	LYNPARZA
הגבלות:	תרופה מוגבלת לרישום ע'י רופא מומחה או הגבלה אחרת
תאריך החלה	21/01/2016 00:00:00

הערות לאריזה\לחוזק

Class Effect

מסגרת הכללה בסל

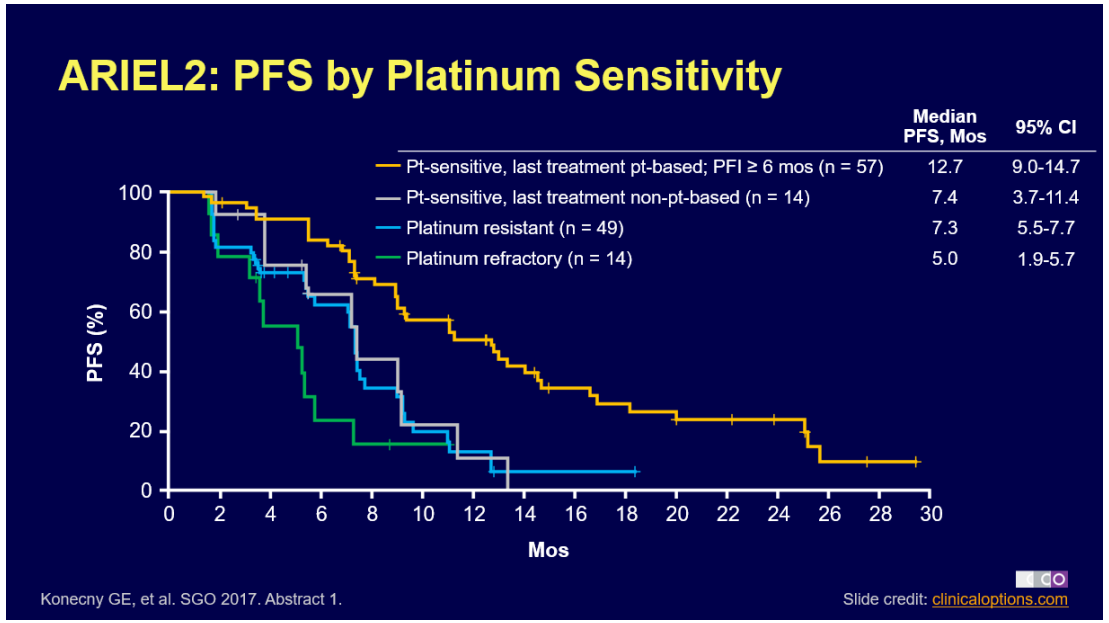
התרופה תינתן כמונותרפיה כטיפול אחזקה בחולות בגירות הסובלות מסרטן שחלה חוזר רגיש לפלטינום מסוג BRCA (breast cancer susceptibility gene) mutatedבחולות עם מוטציה מסוג germlineאו מוטציה סומטית של הגידול.מתן התרופה ייעשה לפי מרשם של רופא מומחה באונקולוגיה או רופא מומחה בגינקולוגיה המטפל באונקולוגיה גינקולוגית.

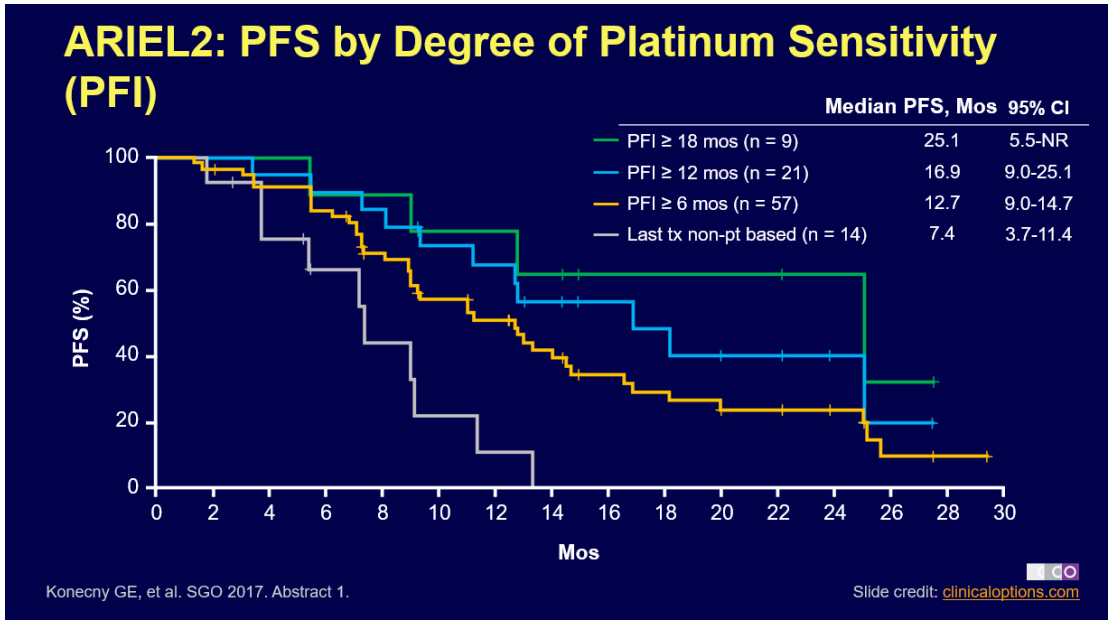
התוויות שהיו רשומות בעת ההכללה בסל

Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian cancer, (including fallopian tube, or primary peritoneal) cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Rucaparib– pretreated g/s*BRCAm* OC

- Dose: 600 mg BID
- Pt population: N = 106 (from phase II ARIEL2 and a phase I/II Study 10 trial)
  - Recurrent ovarian cancer
  - 2+ prior lines of treatment
  - Platinum sensitive and resistant
  - Germline or somatic *BRCA* mutations
- ORR: 54%

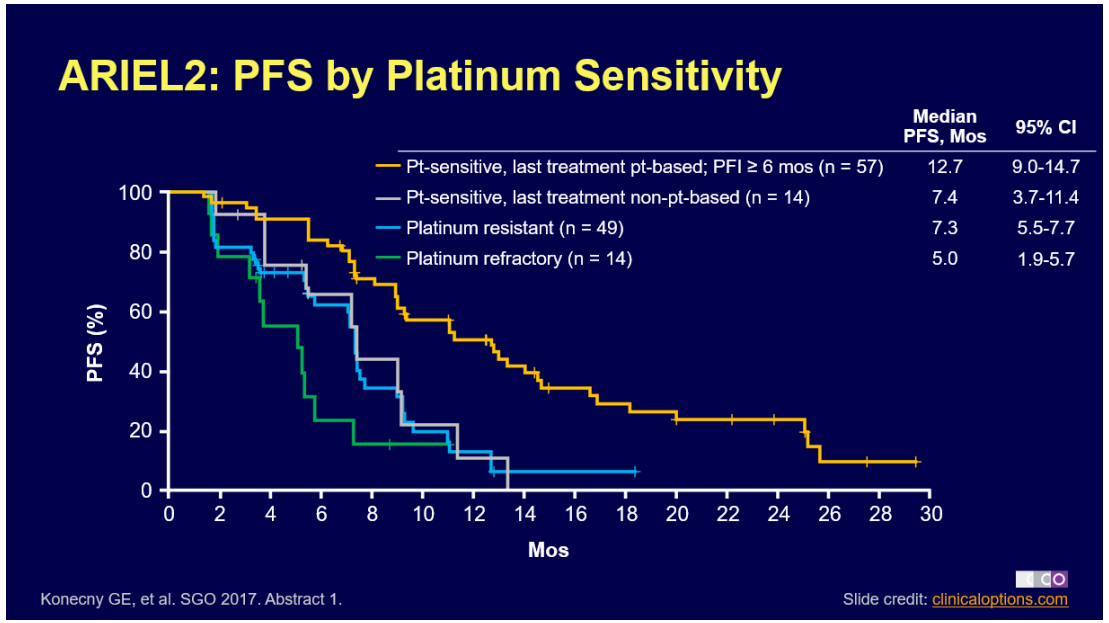


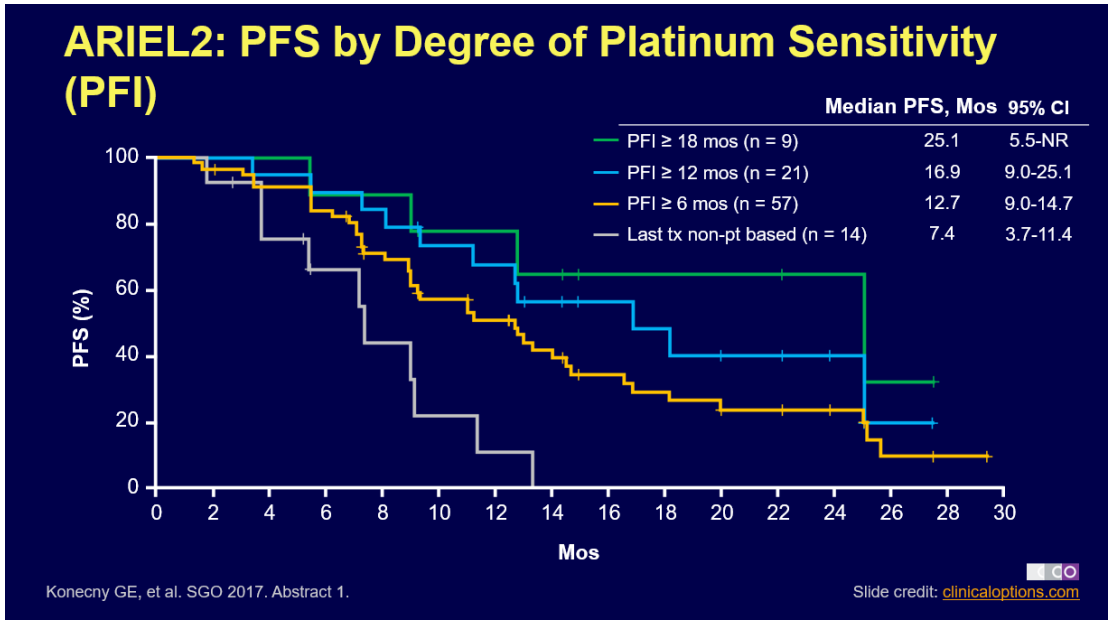


Rucaparib– pretreated g/s*BRCAm* OC

December 19, 2016 – The U.S. Food and Drug Administration granted accelerated approval to Rubraca (rucaparib) as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies as identified by an FDA-approved companion diagnostic test

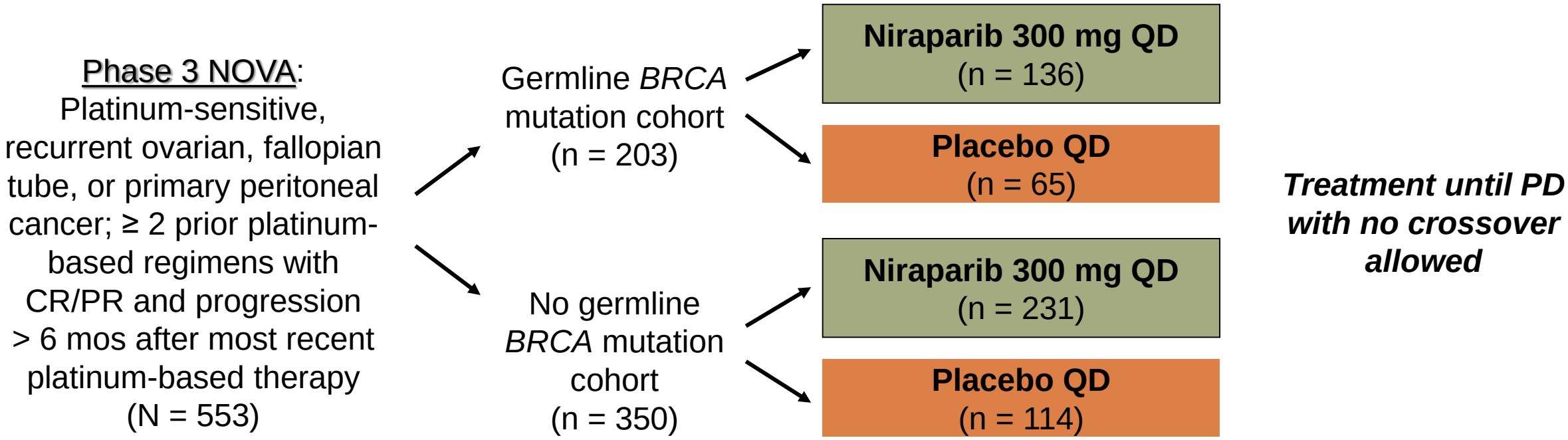
In conjunction with the drug approval, FDA approved the FoundationFocus CDx_{BRCA} test (Foundation Medicine Inc.), the first FDA-approved NGS-based companion diagnostic to identify patients with advanced ovarian cancer eligible for treatment with rucaparib





fda.gov/drugs/informationondrugs/approveddrugs/ucm533891.htm

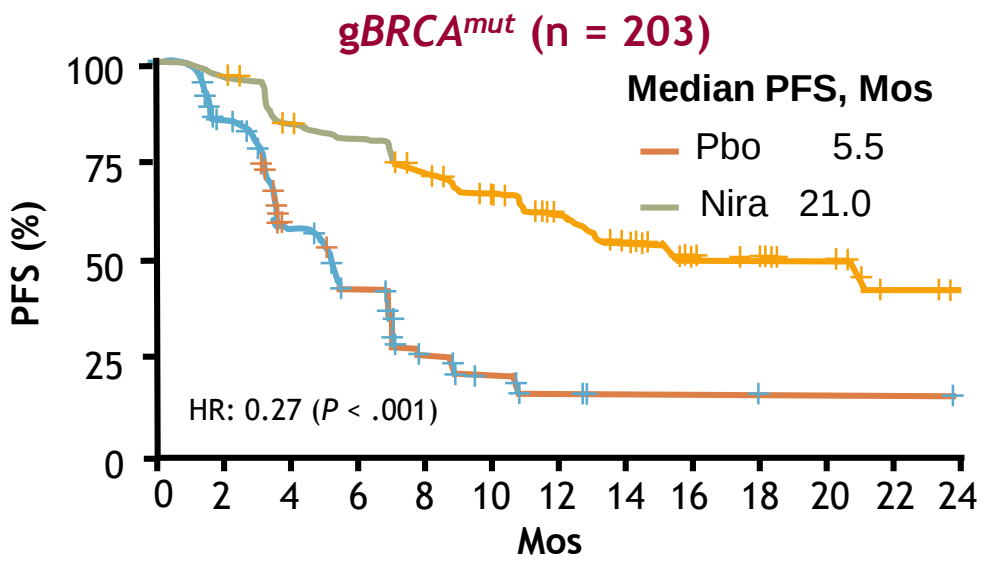
Niraparib Maintenance in Platinum-Sensitive OC

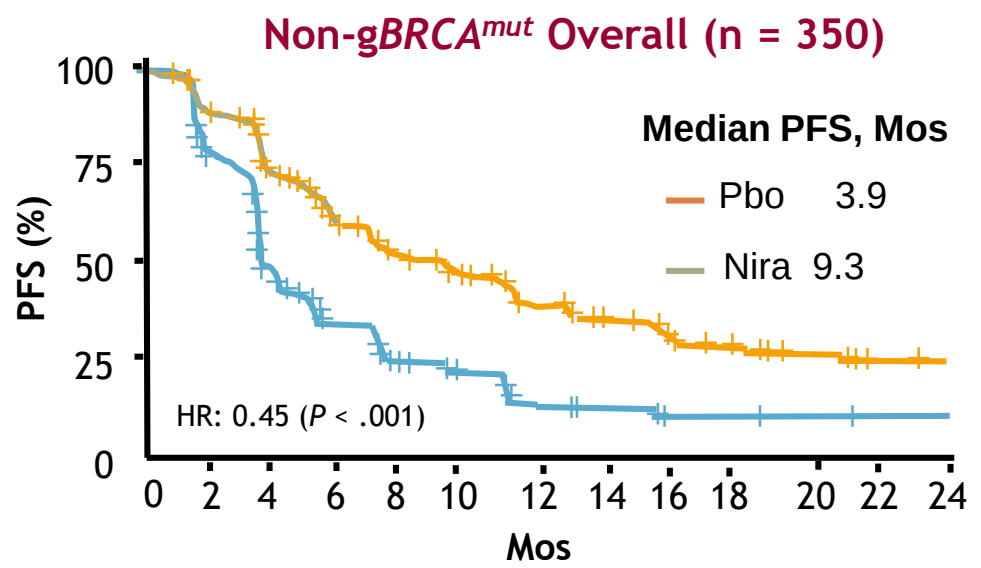


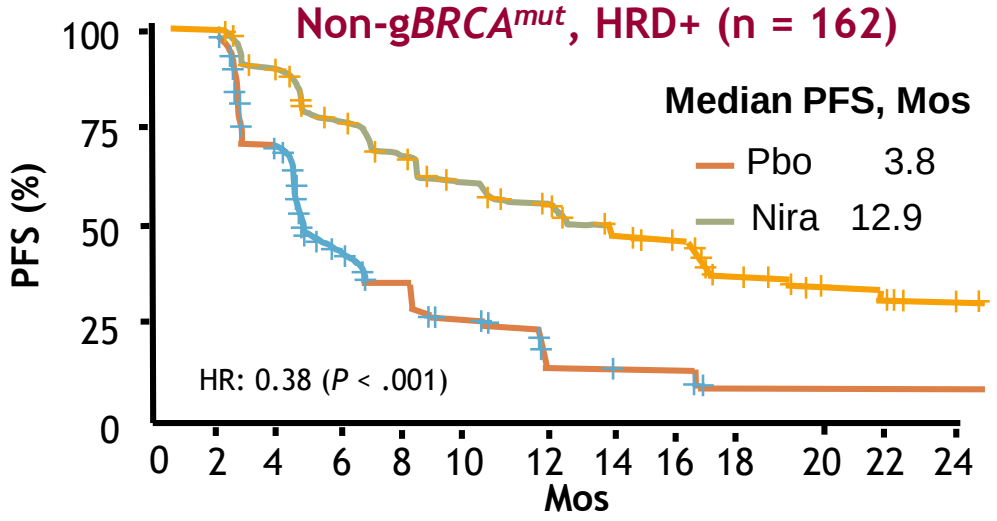
- Primary endpoint: PFS
- Secondary endpoints: chemotherapy-free interval, time to first subsequent therapy, PFS2, time to second subsequent therapy, OS
- Maintenance therapy initiated within 8 wks of last dose of platinum chemotherapy

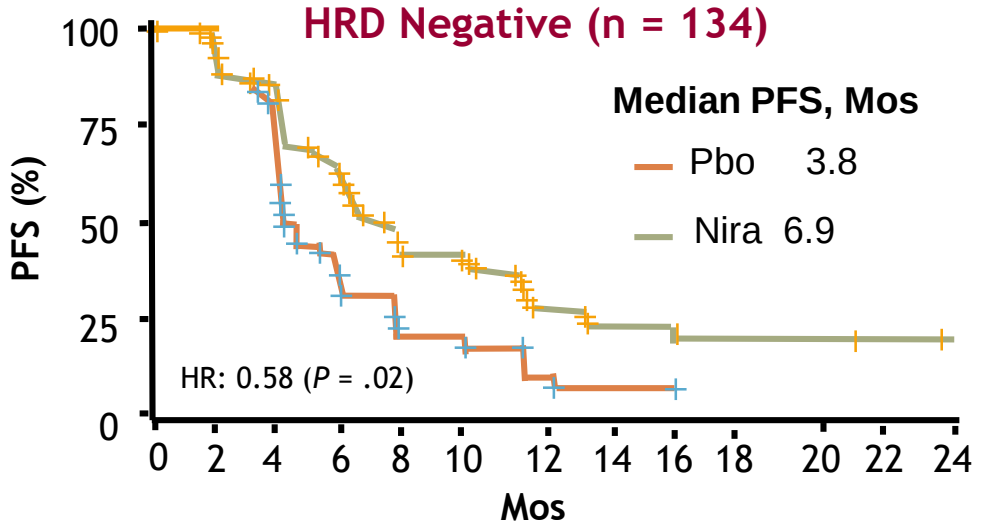
Mahner S, et al. SGO 2017. Abstract 8084.

Niraparib Maintenance in Platinum-Sensitive OC









Mahner S, et al. SGO 2017. Abstract 8084. Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

Niraparib Maintenance in Platinum-Sensitive OC

March 28, 2017 – The FDA approved Tesaro's once-daily, oral PARP inhibitor Zejula™ (niraparib) for the maintenance treatment of women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who demonstrated a partial or complete response to platinum-based therapy.

The drug is the only FDA-approved PARP inhibitor that doesn't require *BRCA* mutation or other biomarker testing.

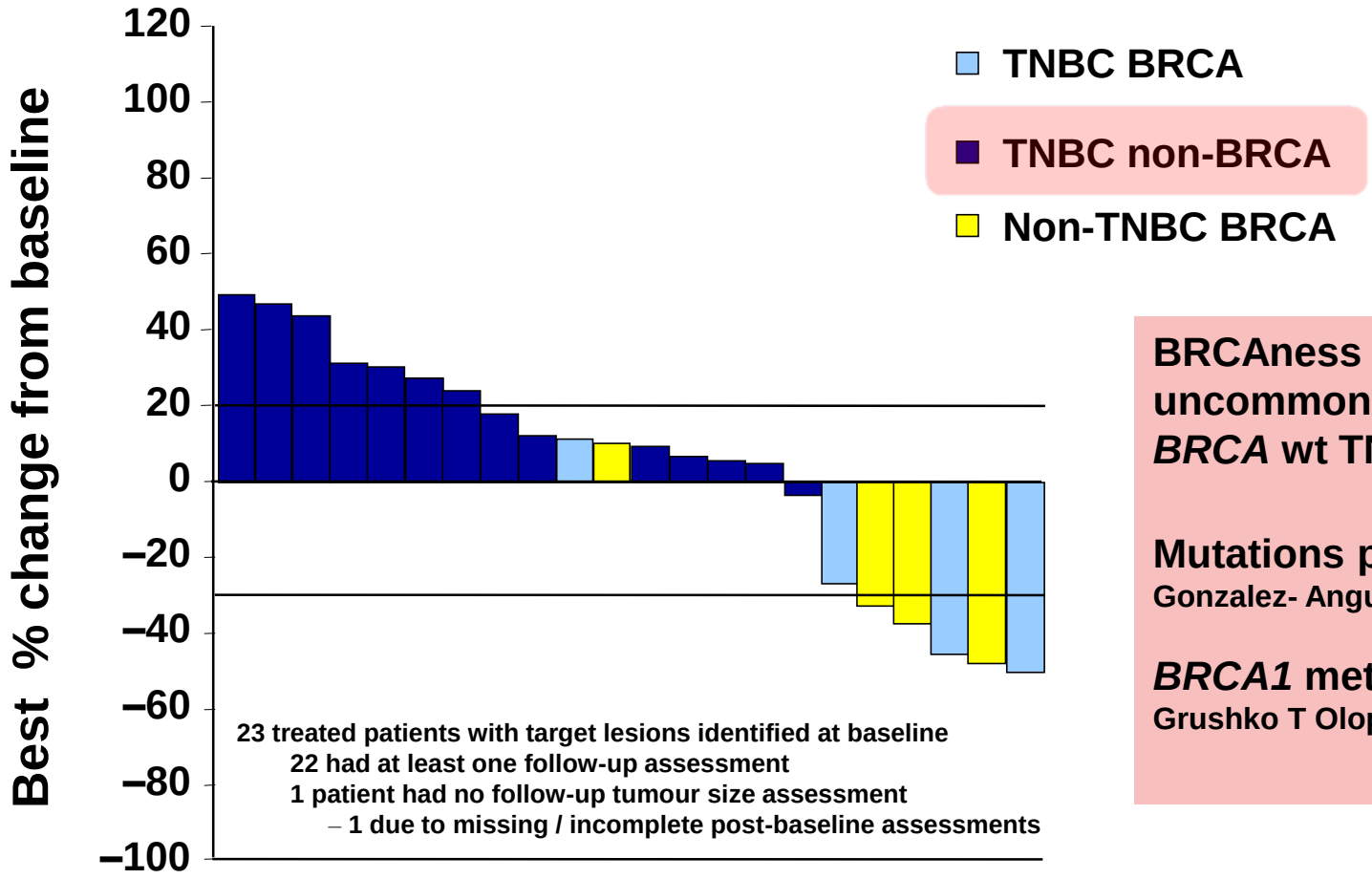
Open questions in ovarian cancer treatment

- No current head-to head studies of PARP inhibitors
- Differences in study populations precluded formal indirect comparisons:
  - Different patients populations – e.g. BRCA mutation type, number of prior chemotherapies, platinum sensitivity
  - Evaluation protocols for tumor assessment – e.g. different intervals between scheduled measurements of response, assessment by investigator vs blinded independent central review
- No OS benefit
- Efficacy in platinum-resistant disease?
- Efficacy in earlier setting (SOLO1 / PRIMA / ATHENA)?

Active / recruiting phase 3 studies in ovarian cancer

- ***OPINION***: A phase 3 clinical trial of Olaparib maintenance monotherapy in platinum sensitive relapsed non-g*BRCA* ovarian cancer patients
- ***OReO*:** A phase 3 clinical trial of Olaparib maintenance re-treatment in patients with relapsed non-mucinous EOC, who have had disease progression following maintenance therapy with PARPi and a complete or partial radiological response to subsequent treatment with platinum-based chemotherapy.
- ***OvCa 3000-03-003:*** A Phase 3 clinical trial of Niraparib in combination with an anti-PD-1 antibody in comparison to niraparib in first-line maintenance treatment of patients with advanced ovarian cancer who have responded to platinum induction therapy.
- ***OvCa 3000-03-002:*** A Phase 3 clinical trial of Niraparib in combination with bevacizumab in comparison to standard of care in patients with a first recurrence of ovarian cancer.
- ***PRIMA:*** A Phase 3 clinical trial of Niraparib in patients with advanced ovarian cancer who have responded to platinum induction therapy.
- ***QUADRA:*** A registration trial of Niraparib for the treatment of patients with recurrent ovarian cancer who have received three or four regimens of therapy.
- ***ARIEL4*** confirmatory study: a Phase 3 multicenter, randomized study of Rucaparib versus chemotherapy in relapsed ovarian cancer patients with *BRCA* mutations who have failed two prior lines of therapy.
- ***ATHENA:*** A randomized, double-blind, placebo-controlled study of Nivolumab and Rucaparib in advanced ovarian cancer in the first-line maintenance treatment setting evaluating rucaparib plus nivolumab (anti-PD1), rucaparib, nivolumab and placebo in newly-diagnosed patients who have completed platinum-based chemotherapy.

Olarapib monotherapy is not active in heavily pretreated sporadic TNBC in contrast to gBRCAm BC



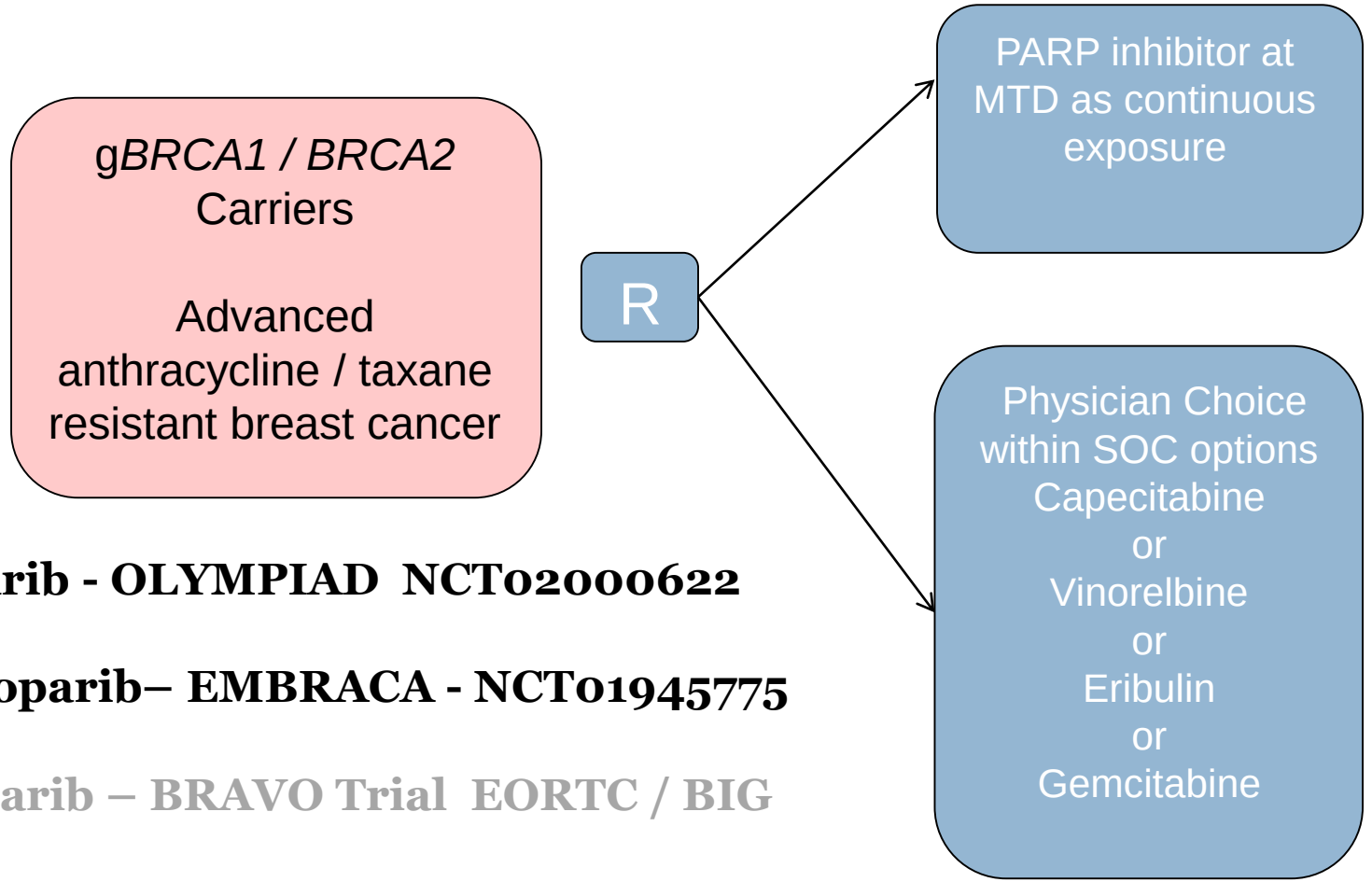
BRCAness sufficient for synthetic lethality uncommon in advanced heavily treated *BRCA* wt TNBC?

Mutations present in 20% TNBC
Gonzalez- Angulo Clin Cancer Res; 17(5) 2011

***BRCA1* methylation in 30 - 40%**
Grushko T Olopade F ASCO 2010

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

PARP inhibition compared to SoC in metastatic *gBRCAm* Breast Cancer



Primary endpoint PFS

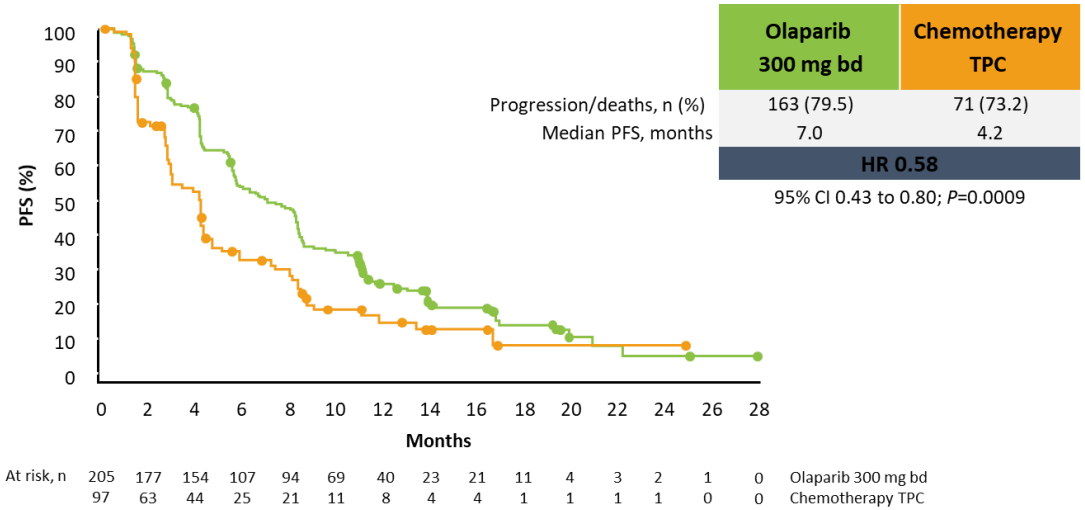
Olaparib - OLYMPIAD NCT02000622

Talazoparib– EMBRACA - NCT01945775

Niraparib – BRAVO Trial EORTC / BIG

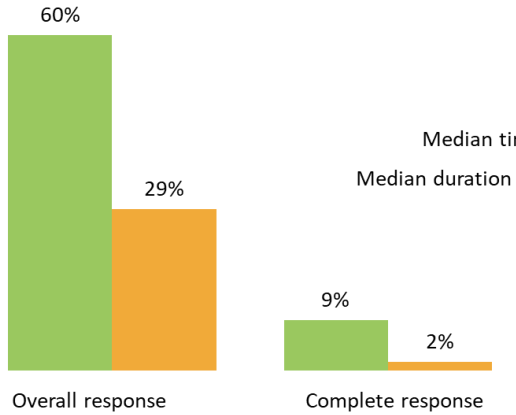
National Institutes of Health, Available at: https://clinicaltrials.gov/ct2/results?term=NCT01945775 and https://clinicaltrials.gov/ct2/results?term=NCT02000622 . Accessed: September 27, 2015.

OlympiAD: Phase III trial of olaparib monotherapy versus chemotherapy for patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation

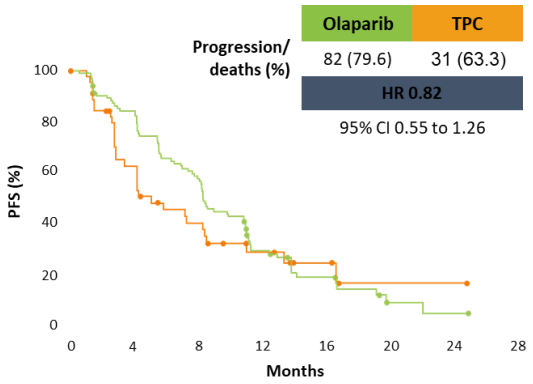


	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		

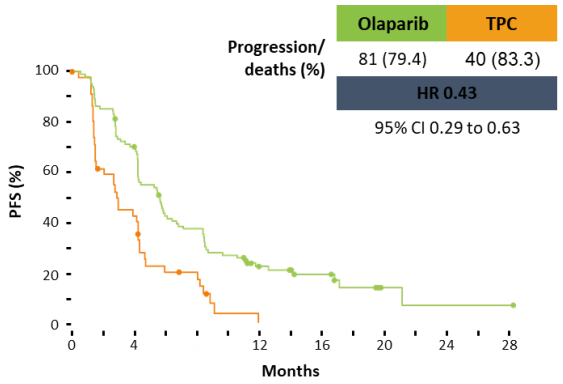
95% CI 0.43 to 0.80; *P*=0.0009



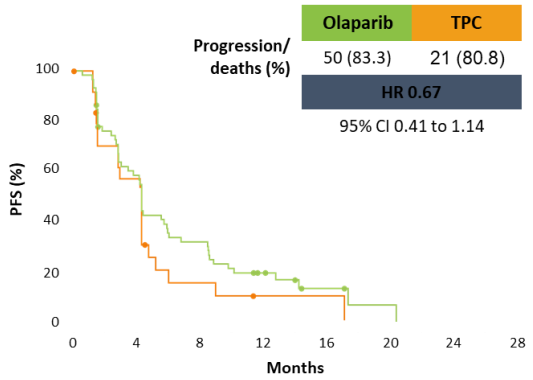
	Olaparib 300 mg bd	Chemotherapy TPC
n	167	66
Median time to response, days	47	45
Median duration of response, months	6.2 (4.6–7.2)	7.1 (2.8–12.2)



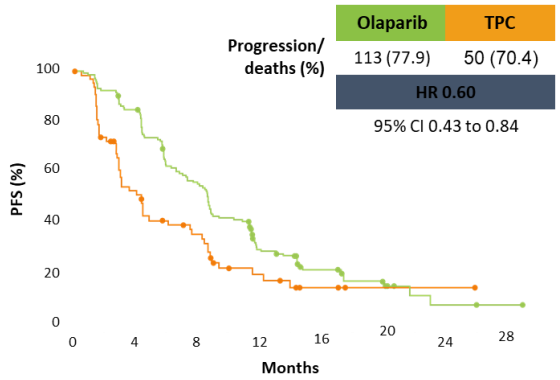
ER+ and/or PR+



TNBC



Prior platinum



No prior platinum

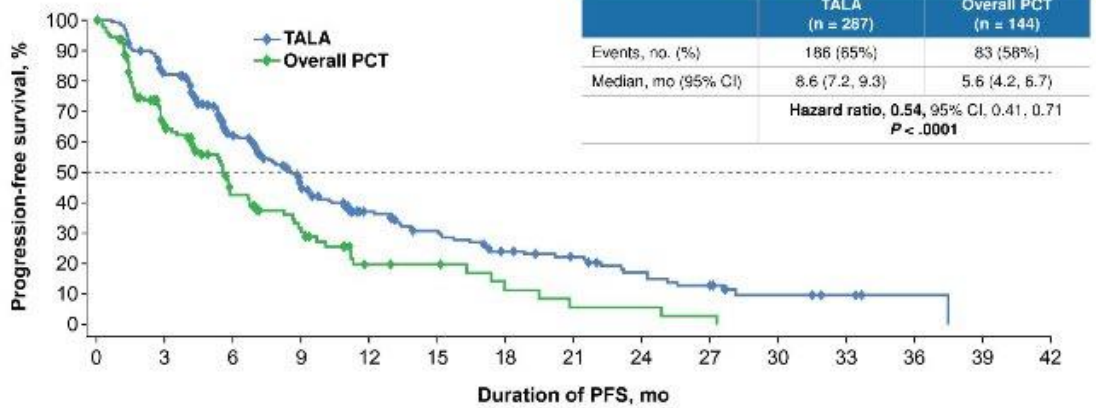
Olabarib in breast cancer

The trial did not find a difference in overall survival (OS) between the groups, but it was not powered to do so.
Patients in the chemotherapy group were more likely to receive PARP inhibitors, platinum-based treatment, or cytotoxic chemotherapy after disease progression, which could also confound analyses of this endpoint

January 12, 2018 – The FDA granted regular approval to olaparib tablets (Lynparza), for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting

Talazoparib in breast cancer

Primary Endpoint: PFS by Blinded Central Review



	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 *P* < .0001	

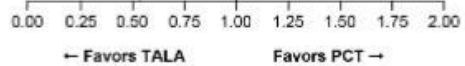
No. at risk (events/cumulative events)

TALA	287 (0/0)	229 (58/58)	149 (33/103)	81 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
PCT	144 (0/0)	68 (4/41)	34 (2/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

1-Year PFS 37 vs 20% Median follow-up time: 11.2 months

PFS: Subgroup Analysis

Subgroup	Patients, no. (%)	Hazard ratio (95% CI)
All randomized patients (ITT)	431 (100)	0.54 (0.41-0.71)
Patients with central testing available	408 (94.7)	0.53 (0.40-0.70)
BRCA status by central testing		
BRCA1	183 (42.5)	0.59 (0.39-0.90)
BRCA2	225 (52.2)	0.47 (0.32-0.70)
Hormone receptor status		
TNBC based on most recent biopsy	190 (44.1)	0.60 (0.41-0.87)
HR+ based on most recent biopsy	241 (55.9)	0.47 (0.32-0.71)
History of CNS metastasis		
Yes	63 (14.6)	0.32 (0.15-0.68)
No	368 (85.4)	0.58 (0.43-0.78)
Prior platinum treatment		
Yes	76 (17.6)	0.76 (0.40-1.45)
No	355 (82.4)	0.52 (0.39-0.71)
Prior regimens of cytotoxic chemo for aBC		
0	165 (38.3)	0.57 (0.34-0.95)
1	161 (37.4)	0.51 (0.33-0.80)
≥ 2	105 (24.4)	0.56 (0.34-0.95)



Select ongoing clinical trials of PARPi in breast cancer

- ***OlympiA***: A phase 3 trial of Olaparib as adjuvant treatment in patients with germline BRCA mutated high risk Her2-negative primary breast cancer
- ***PARTNER***: A phase 2/3 trial of Olaparib and platinum-based chemotherapy as neoadjuvant therapy in TNBC or *gBRCA* breast cancer
- ***TNBC 3000-03-004:*** A Phase 3 clinical trial of Niraparib in combination with anti-PD-1 antibody in comparison to standard of care in patients with advanced triple negative breast cancer.
- ***TOPACIO:*** A Phase 2 clinical trial to evaluate the safety and efficacy of Niraparib plus KEYTRUDA® in patients with triple negative breast cancer and patients with platinum resistant recurrent ovarian cancer
- ***RUBY***: A phase 2 trial to Assess the Efficacy of Rucaparib in Metastatic Breast Cancer Patients With a BRCAness Genomic Signature

PARP inhibitors as monotherapy

Other Cancers

Olaparib Monotherapy in Patients With Advanced Cancer and Germline *BRCA1/2* Mutation – Study 42

An open-label non-comparative trial to determine whether olaparib monotherapy (400 mg bid) is effective against *BRCA1/2* mutant tumors, regardless of tumor type (''basket study'')

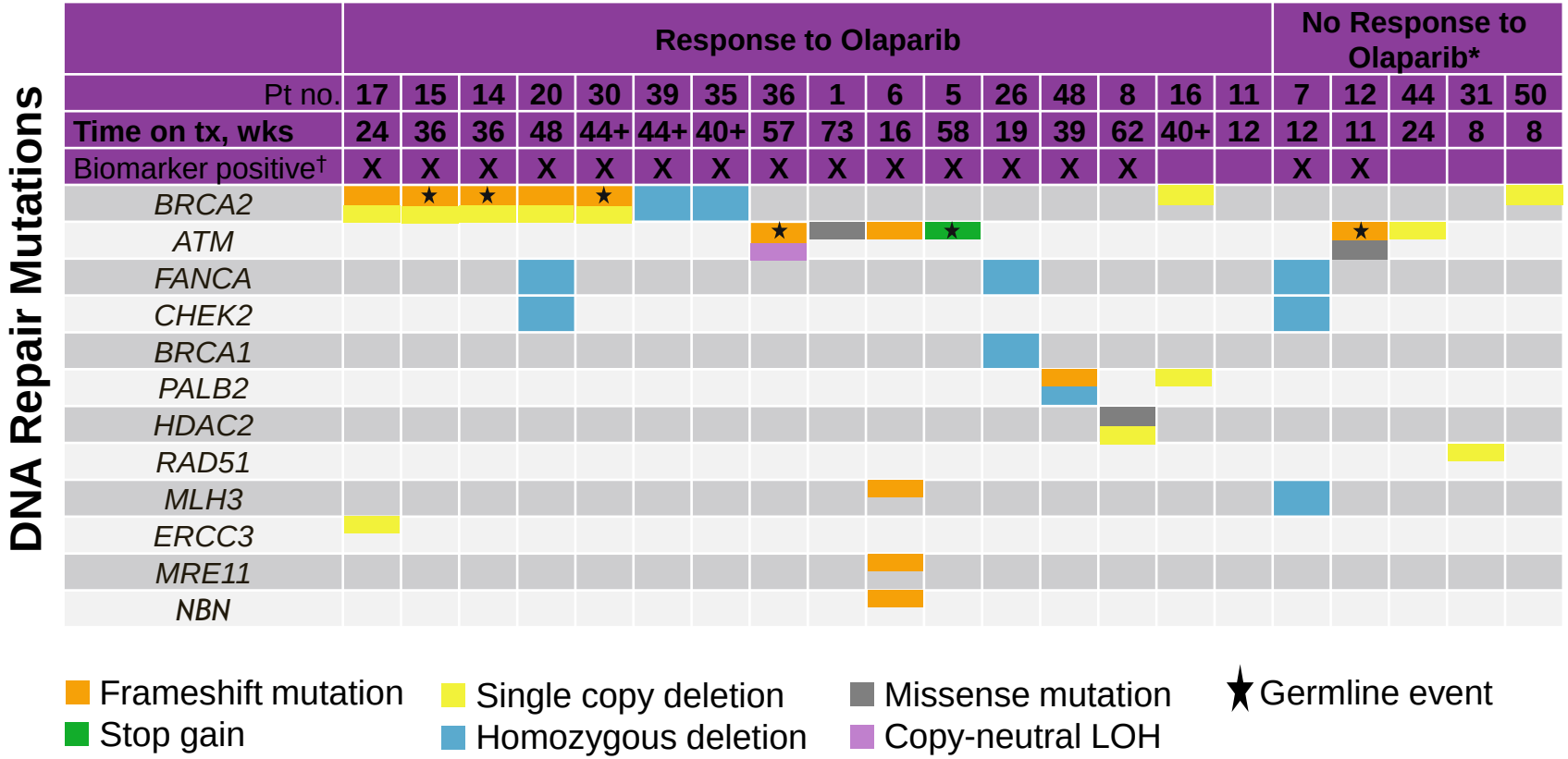
- Tumor types included ovarian, breast cancer, prostate cancer and pancreatic cancer
- All patients were heavily pretreated
- 298 patients, responses across all tumor type, ORR was 26.2%

Response status, n (%)	Tumour type					
	Ovarian (n=193)	Breast (n=62)	Pancreas (n=23)	Prostate (n=8)	Other* (n=12)	Total (n=298)
Tumour response rate	60 (31.1)	8 (12.9)	5 (21.7)	4 (50.0)	1 (8.3)	78 (26.2)
CR*	6 (3.1)	0	1 (4.3)	0	0	7 (2.3)
PR*	54 (28)	8 (13)	4 (17)	4 (50)	1 (8.3)	71 (23.8)
SD ≥8 weeks	78 (40)	29 (47)	8 (35)	2 (25)	7 (58)	124 (42)
SD	64 (33)	22 (36)	5 (22)	2 (25)	6 (50)	99 (33)
Unconfirmed PR†	12 (6)	7 (11)	3 (13)	0	1 (8.3)	23 (8)
PD‡	41 (21)	23 (37)	9 (39)	2 (25)	3 (25)	78 (26)
RECIST progression	33 (17)	16 (26)	6 (26)	1 (13)	3 (25)	59 (20)
Early death§	8 (4)	7 (11)	3 (13)	1 (13)	0	19 (6)
Not evaluable	14 (7)	2 (3)	1 (4)	0	1 (8.3)	18 (6)
No follow-up assessments	12 (6)	2 (3)	1 (4)	0	0	15 (5)
SD <8 weeks	2 (1)	0	0	0	1 (8.3)	3 (1)

* Includes biliary tract (n = 4), bladder (n = 2), colorectal (n = 1), lung (n = 3), mediastinal (esophagus; n = 1), and uterus (n = 1)

Kaufman B, et al. *J Clin Oncol*. 2015;33(3):244-250.

Olaparib in prostate cancer



16 of 49 evaluable pts responded to olaparib

- 14 of 16 (88%) biomarker-positive pts
- 2 of 33 (6%) biomarker-negative pts

*28 additional biomarker-negative pts without a response to olaparib.
†Biomarker positive: homozygous deletions, deleterious mutations, or both in DNA-repair genes.

Mateo J, et al. N Engl J Med. 2015;373:1697-1708.

Select ongoing clinical trials of PARPi in prostate cancer

- ***PROfound***: A phase 3 study of Olaparib compared to Enzalutamide or Abiraterone acetate in men with metastatic castration-resistant prostate cancer and a deleterious homologous recombination DNA repair aberration
- ***TRITON3***: a randomized open-label Phase 3 study evaluating the effects of Rucaparib compared to physician's choice of therapy for patients with mCRPC with specific gene alterations including *BRCA1/2* and *ATM*.

Active / recruiting phase 2/3 studies in pancreatic cancer

- ***POLO***: a phase 3 randomised, double blind, placebo controlled trial of maintenance Olaparib monotherapy in patients with *gBRCA* mutated metastatic pancreatic cancer whose disease has not progressed on first line platinum based chemotherapy
- A Phase 2, open label study of Rucaparib in patients with advanced pancreatic cancer and a known deleterious germline or somatic *BRCA* or *PALB2* mutation
- A Phase 2 study of Cediranib in combination with Olaparib in advanced solid tumors (including breast cancer, non-small cell lung cancer, small cell lung cancer, and pancreatic cancer)

So… Which patients?

- In ovarian cancer, there is clearly evidence of efficacy beyond *BRCA*m patients
  - It remains challenging to prospectively identify these patients
  - Outside of North America, the license is currently restricted to *BRCA*m patients
- Beyond ovarian cancer, the main signal of efficacy is in *BRCA*m patients (so far)
  - This might change as our understanding improves
- There is interest in using PARP inhibitors in individuals who have inherited mutations in DNA damage repair genes other than *BRCA1/2*, such as *PALB2*, *CHEK2*, *RAD51C/D*, *others?*
- Biomarkers?
  - DNA repair: BRCAness, HRD, others?
- Combinations?
  - Feasibility
  - Patient selection
- When?!?
  - Maintenance seems a very effective setting; it is possible that giving as early as possible (in the context of minimal residual disease) may be the best way to avoid resistance, although this remains to be proven

תנדה והמשך יום פורה!