Year in Review

A Multitumor Regional Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Saturday, February 24, 2018, 8:00 AM – 4:00 PM
Charlotte, North Carolina

Faculty

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Moderator

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Research To Practice®

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Disclosures

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Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Roche Laboratories Inc

Select Recently Approved Agents in Ovarian Cancer

Agent	Approval date	Indication
Niraparib	3/27/17	Maintenance for recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer after CR or PR to platinum chemotherapy
Rucaparib	12/19/16	Deleterious BRCA-mutant (germline and/or somatic) advanced ovarian cancer after two or more chemotherapies

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

Ovarian Cancer — Drs Birrer and Moore

Chemotherapy with or without bevacizumab in ovarian cancer

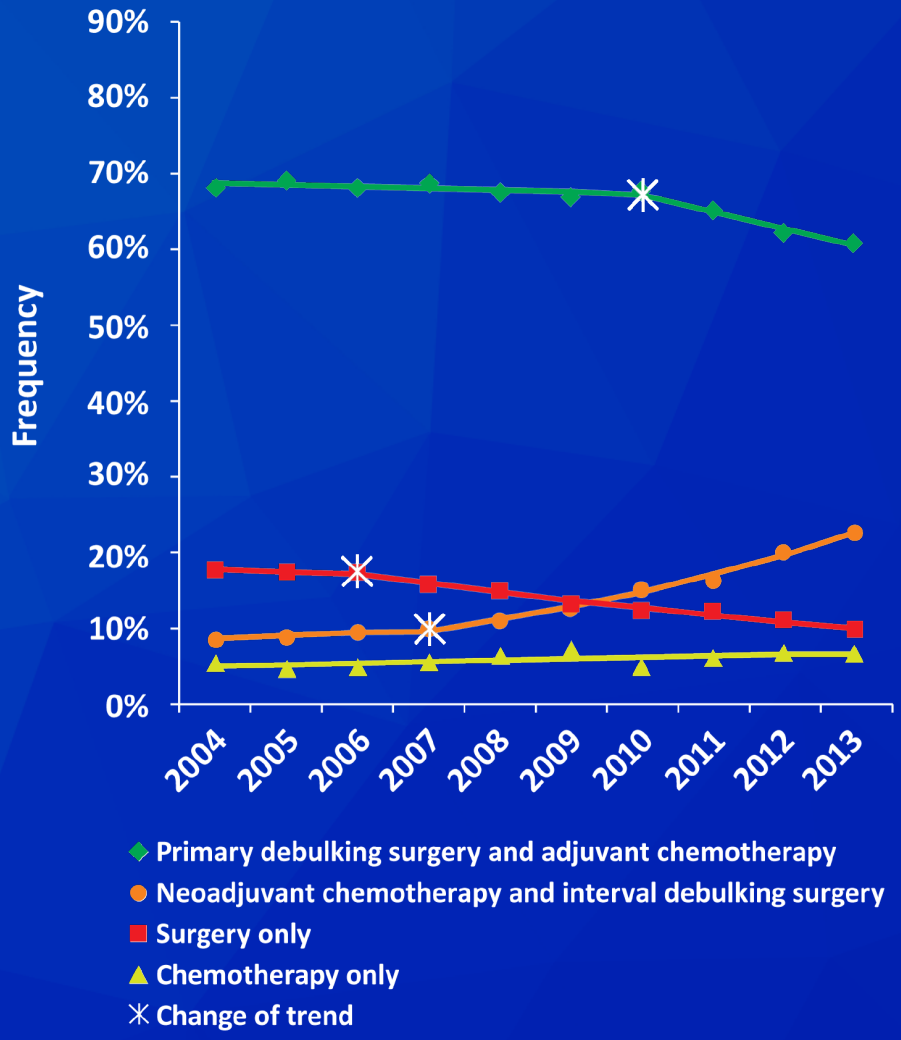
Germline and somatic mutations in ovarian cancer

PARP inhibitors: Efficacy, toxicity and ongoing trials

Novel investigational agents

Trends in the Use of NACT for Advanced Ovarian Cancer in the United States

- Time trend analysis of the National Cancer Data Base
- Women with Stage IIIC and IV epithelial ovarian cancer diagnosed between 2004 and 2013 (N = 40,694)
- The proportion of women receiving neoadjuvant chemotherapy and surgery increased from 8.6% to 22.6% between 2004 and 2013 ($p < 0.001$)

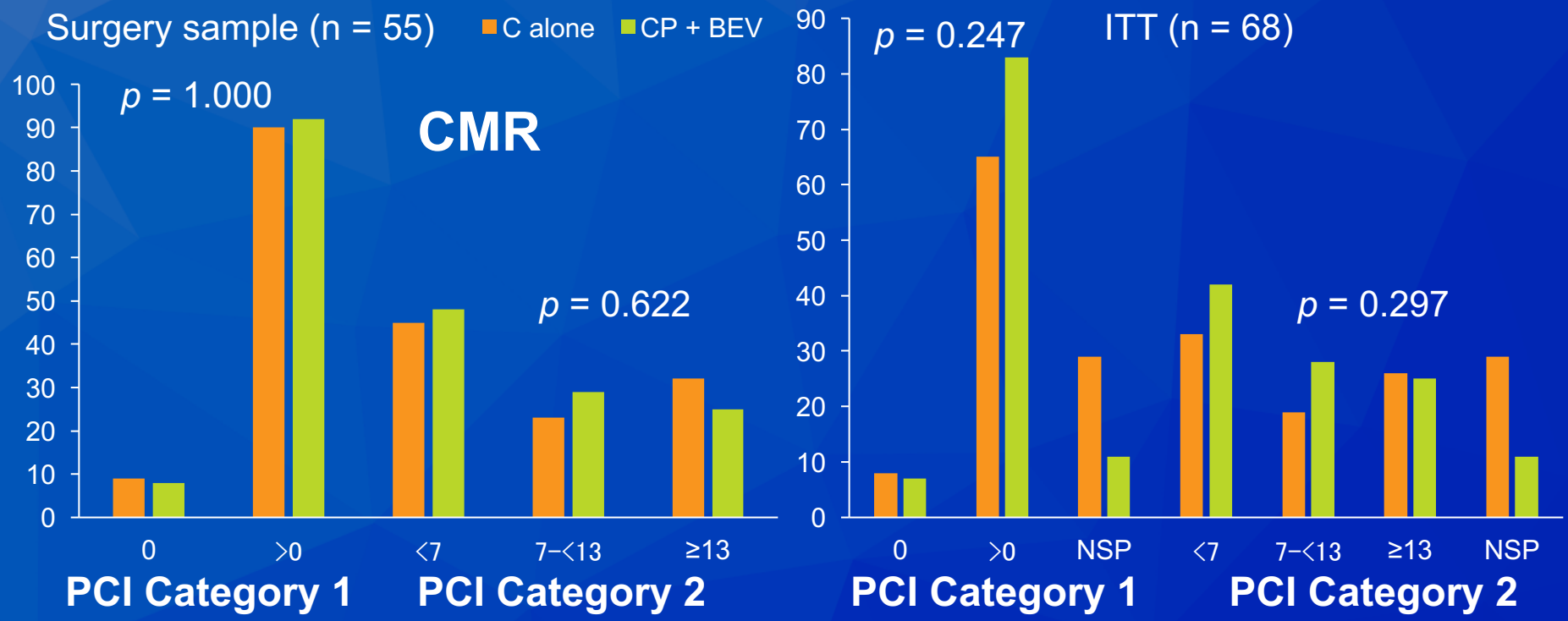


Melamed A et al. *Gynecol Oncol* 2016;143:236-40.

Phase II Randomized Trial of Neoadjuvant (NA) Chemotherapy (CT) with or without Bevacizumab (Bev) in Advanced Epithelial Ovarian Cancer (EOC) (GEICO 1205/NOVA TRIAL)

Garcia Garcia Y et al.
Proc ASCO 2017;Abstract 5508.

GEICO 1205/NOVA: Complete Macroscopic Response (CMR) and Survival Outcome



Outcome	CP alone (n = 33)	CP + bev (n = 35)	HR	*p*-value
Median PFS	20.1 mo	20.4 mo	1.13	0.664
IDS surgical feasibility	22 (67%)	31 (89%)	—	0.029

Garcia Garcia Y et al. *Proc ASCO* 2017;Abstract 5508.

Editorial — Dr Matulonis

Dr Yolanda Garcia presented results from a randomized phase 2 study evaluating neoadjuvant chemotherapy with or without bevacizumab. Patients in this study were initially considered unresectable, and therefore required treatment with neoadjuvant chemotherapy; 68 pts were evaluable. Patients received 4 cycles of neoadjuvant treatment. The first arm received carboplatin and paclitaxel, and the second arm received carboplatin, paclitaxel and bevacizumab on cycles 1, 2, and 3. Bevacizumab was not administered during cycle 4, just before surgery. Among all patients, surgery was followed by an additional 3 cycles of carboplatin and paclitaxel plus bevacizumab for 15 months.

Editorial — Dr Matulonis (continued)

The study found no difference in the primary endpoint of complete macroscopic response rate. The addition of bevacizumab improved surgical feasibility at interval surgery (66.7% vs 88.6%, $p = 0.029$) but no differences were found in the rate of optimal cytoreduction (63.6 versus 65.7%, $p = 0.858$) or PFS (20.3 months in both arms). There were lower rates of serious adverse events in the Bev arm (69.7 versus 42.9%, $p = 0.026$).

Key Phase III Studies of Intraperitoneal Therapy for Up-Front Therapy

Study	N	Eligibility	Median OS	Hazard ratio	*p*-value
SWOG 8501/ GOG 104[1]	546	Stage III, ≤2 cm residual	IP: 49 mo IV: 41 mo	0.76	0.02
GOG 114/ SWOG 9227[2]	462	Stage III, ≤1 cm residual	IP: 63.2 mo IV: 52.2 mo	0.81	0.05
GOG 172[3]	415	Stage III, ≤1 cm residual	IP: 65.6 mo IV: 49.7 mo	0.75	0.03

[4] Retrospective analysis of GOG 114 and 172

- N = 876, median follow-up 10.7 years
- Median OS for IP vs IV **61.8 mo vs 51.4 mo**, HR = 0.77, *p* = 0.002

[5] GOG 252

- Patients with Stage II-IV, ≤1 cm residual (n = 1560)
- Median PFS for IP carbo vs IP cis vs IV bev: 28.7 mo vs 27.8 mo vs 26.8 mo
- IP therapy did not confer a significant PS advantage over IV only

[1] Alberts DS et al. *N Engl J Med* 1996;335:1950-5; [2] Markman M et al. *J Clin Oncol* 2001;19:1001-7; [3] Armstrong DK et al. *N Engl J Med* 2006;354:34-43; [4] Tewari D et al. *J Clin Oncol* 2015;33:1460-6; [5] Walker JL et al. *Proc SGO* 2016;Abstract LBA6.

Phase III GOG-0252

Trial Identifier: NCT00951496
Enrollment: 1,526 (Active, not recruiting)

Eligibility

- Epithelial ovarian, fallopian tube or peritoneal carcinoma
- Stage II-IV
- Optimal or suboptimal disease

Primary endpoint: Progression-free survival

Cycles 1-6

Paclitaxel 80 mg/m^2 IV D1, 8, 15
Carboplatin AUC 6 IV D1
Bevacizumab 15 mg/kg q3wk

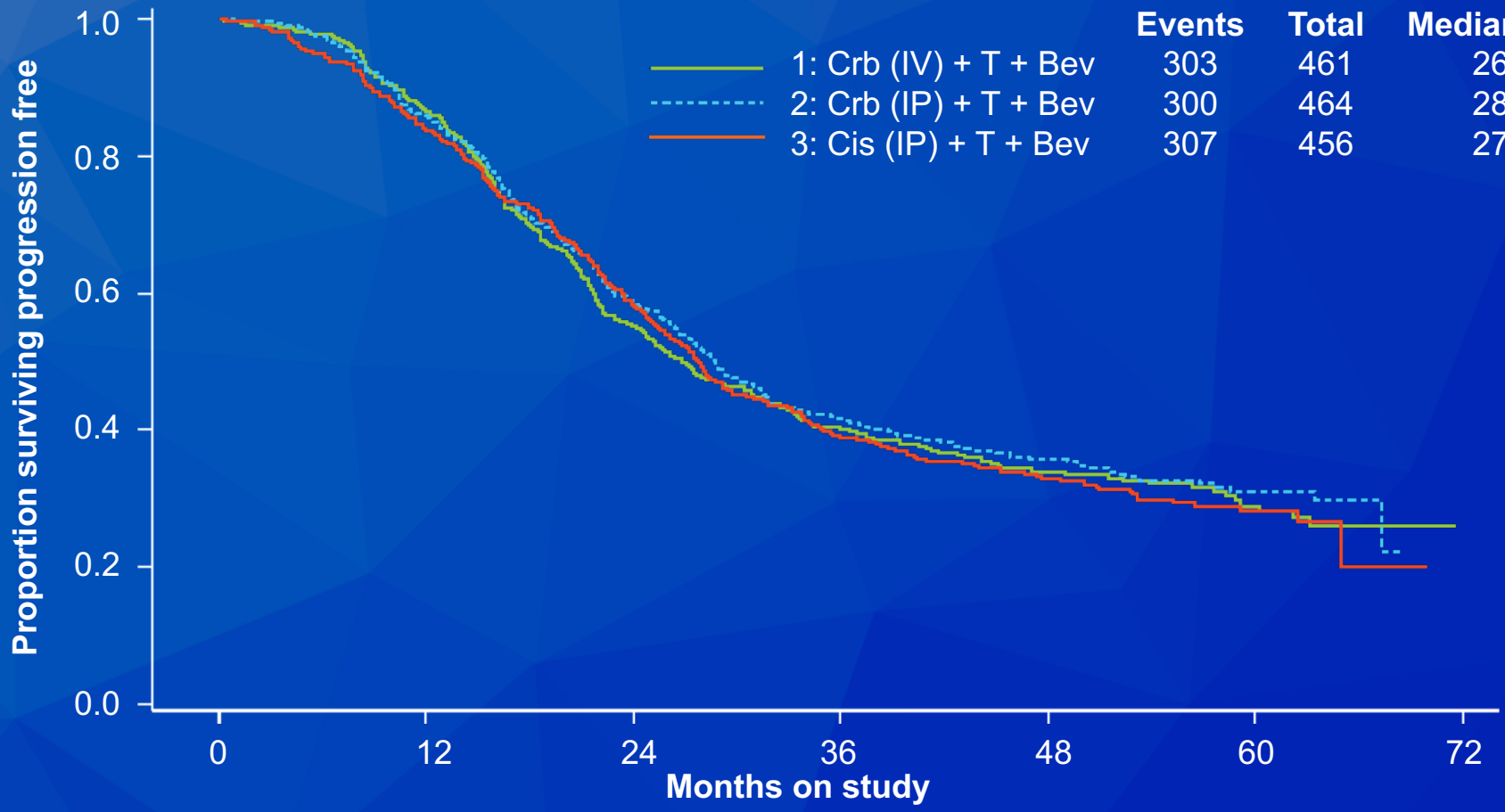
Paclitaxel 80 mg/m^2 IV D1, 8, 15
Carboplatin AUC 6 IP D1
Bevacizumab 15 mg/kg q3wk

Paclitaxel 135 mg/m^2 IV D1
Cisplatin 75 mg/m^2 IP D2
Paclitaxel 60 mg/m^2 IP D8
Bevacizumab 15 mg/kg q3wk

Cycles 7-22:
Bevacizumab 15 mg/kg q3wk

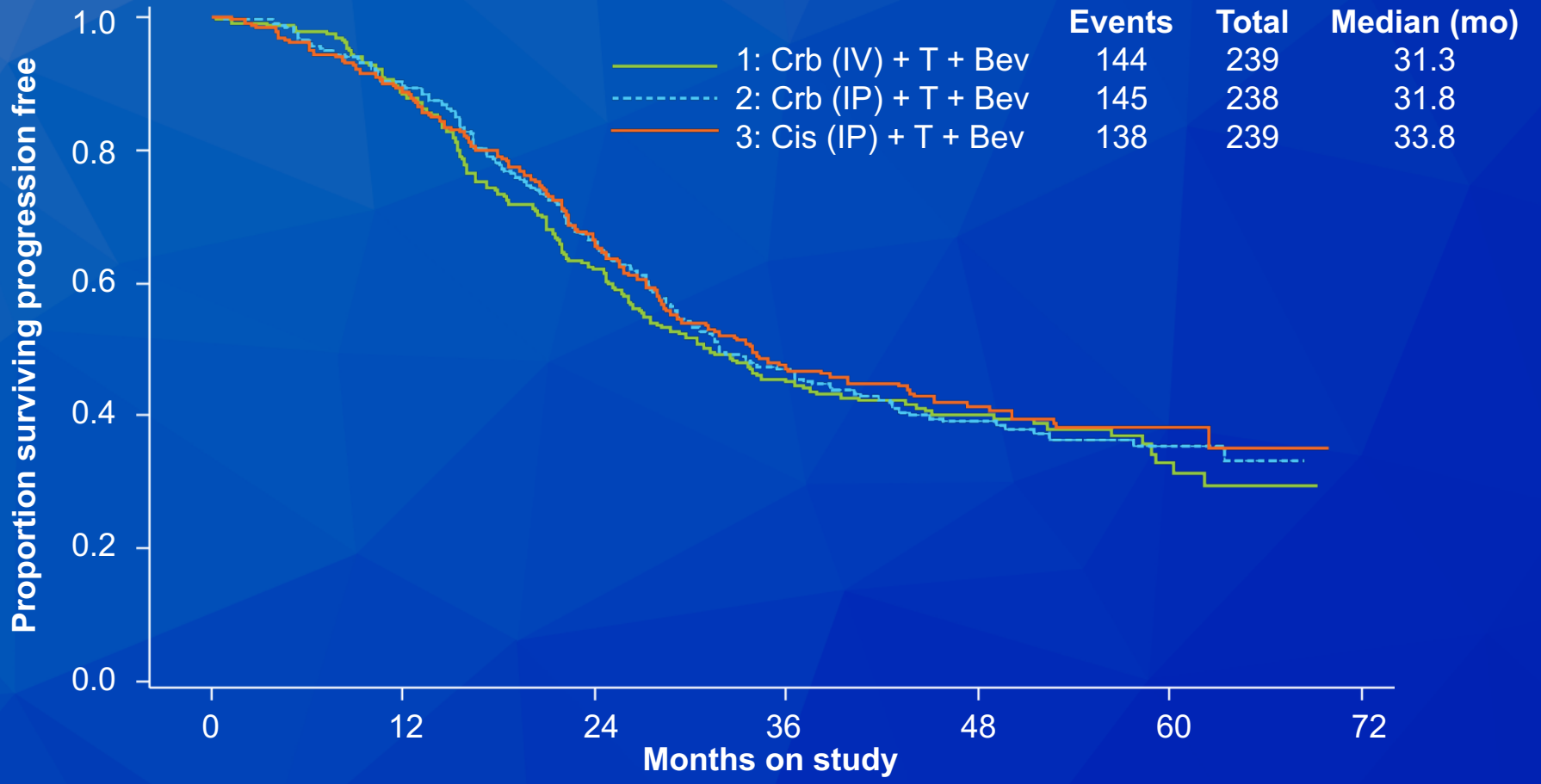
www.clinicaltrials.gov. Accessed January 2017.

GOG Protocol 0252: PFS (<1 cm) by Treatment Group



Walker J et al. Society of Gynecologic Oncology, San Diego, CA March 2016.

GOG Protocol 0252: PFS (R0) by Treatment Group



Walker J et al. Society of Gynecologic Oncology, San Diego, CA March 2016.

GOG Protocol 0252: Toxicity

Event	IV carboplatin		IP carboplatin		IP cisplatin	
	Grade 2	Grade ≥3	Grade 2	Grade ≥3	Grade 2	Grade ≥3
Feb/neut	—	2.5%	—	2.6%	—	3.3%
Neut	—	71%	—	68%	—	64%
Platelets	—	17.6%	—	15.1%	—	6.1%
HTN	—	11.9%	—	13.8%	—	20.5%
Thromb	—	6.3%	—	8.4%	—	9.0%
N/V	—	5.1%	—	4.7%	—	11.2%
Fistula	—	5.3%	—	3.7%	—	4.3%
Urine prot	—	2.7%	—	3.1%	—	1.6%
Sens neur	24.1%	5.7%	22.6%	4.5%	21.3%	5.5%

Walker J et al. Society of Gynecologic Oncology, San Diego, CA March 2016.

Survival Analyses: Dose-Dense versus Conventional Paclitaxel/Carboplatin

	JGOG 3016[1]		GOG-0262[2]	
	3-wks P/C	Wkly P/C	3-wks P/C	Wkly P/C
mPFS	17.5 mo	28.2 mo	10.3 mo	14.2 mo
	HR = 0.76, p = 0.0037		HR = 0.62, p = 0.03	
mOS	62.2 mo	100.5 mo		
	HR = 0.79, p = 0.039		Not reported	

[3] **Meta-analysis of the 3 studies**

- OS, no difference: HR = 0.95, p = 0.06
- Severe acute toxicity, no difference

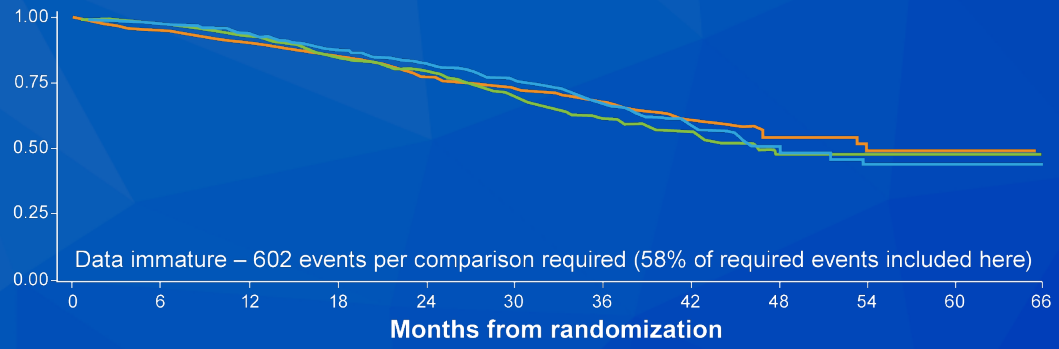
[1] Katsumata N et al. *Lancet Oncol* 2013;14:1020-6; [2] Chan JK et al. *N Engl J Med* 2016;374:738-48; [3] Marchetti C et al. *Oncotarget* 2016;7(36):58709-15.

ICON8: A GCIG Phase III Randomised Trial Evaluating Weekly Dose-Dense Chemotherapy Integration in First-Line Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Carcinoma (EOC) Treatment: Results of Primary Progression-Free Survival (PFS) Analysis

Clamp AR et al.
Proc ESMO 2017;Abstract 929O_PR.

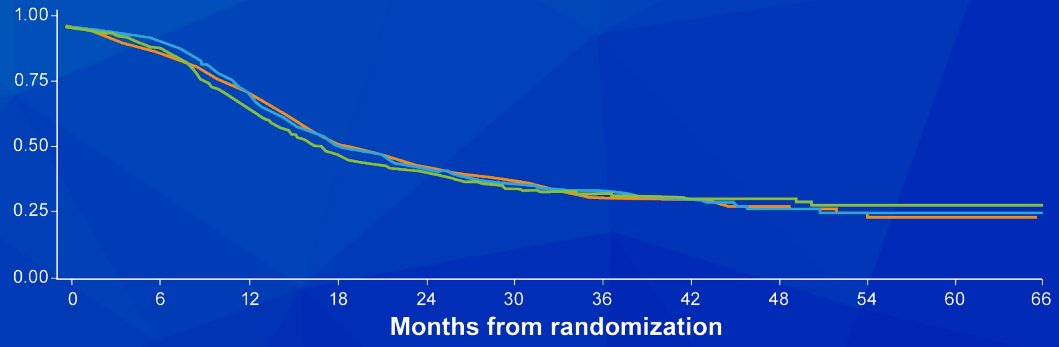
ICON8: Primary Endpoints (OS and PFS)

OS



Total Patients	Arm 1 Standard n = 522	Arm 2 Weekly paclitaxel n = 523	Arm 3 Weekly carbo-paclitaxel n = 521
No. of deaths	183 (35%)	167 (32%)	166 (32%)
Log rank (vs Arm 1 only)		*p* = 0.21	*p* = 0.3
Median OS	46.5 months	48.1 months	54 months

PFS



Total Patients	Arm 1 Standard n = 522	Arm 2 Weekly paclitaxel n = 523	Arm 3 Weekly carbo-paclitaxel n = 521
Progressions	330 (63%)	335 (64%)	338 (65%)
Median PFS	17.9 months	20.6 months	21.1 months
Log rank (vs Arm 1)		*p* = 0.45	*p* = 0.56
HR vs Arm 1		0.92	0.94

Clamp AR et al. *Proc ESMO* 2017;Abstract 920O_PR.

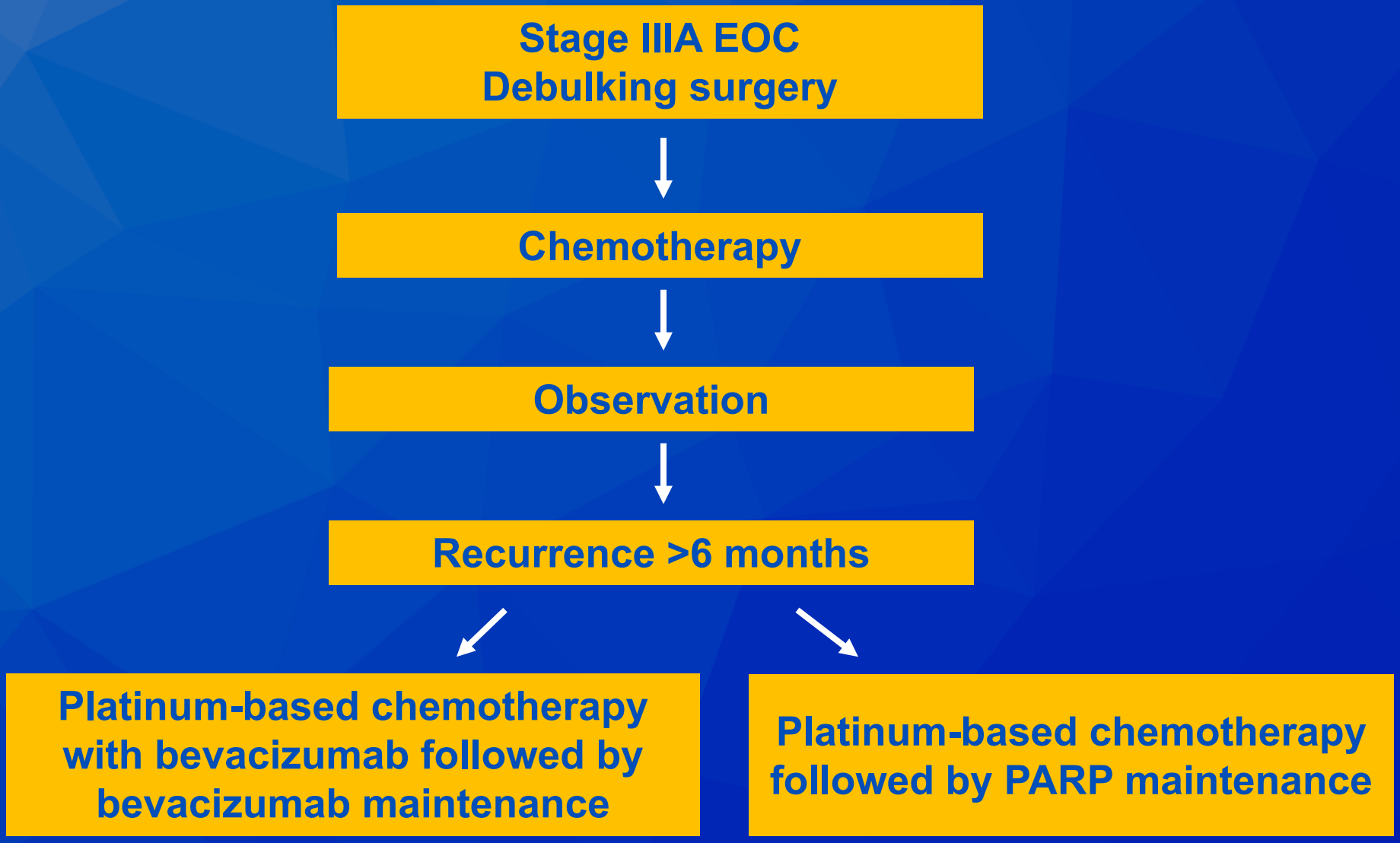
Editorial — Dr Matulonis

This is a phase III trial of arm 1 (carbo AUC 5 and paclitaxel 175 mg/m^2), arm 2 (carbo AUC 5 and paclitaxel 80 mg/m^2 qweek) and arm 3 (carbo AUC 2 and paclitaxel 80 mg/m^2 both weekly). Co primary outcomes are PFS and OS. 1,566 women recruited into the study. The majority of patients had advanced cancer. Patients who completed 6 cycles of treatment defined by the protocol: arm 1 72%, arm 2 60%, and arm 3 63%. Grade 3 and 4 toxicities: arm 1 42%, arm 2 63%, and arm 3 53%. FN and neuropathy appeared comparable for all 3 arms; anemia differed though. Grade 2: arm 1 26%, arm 2 52%, and arm 3 36%. Grade 3 and 4 anemia: arm 1 5%, arm 2 13%, arm 3 5%. Carboplatin hypersensitivity reactions occurred much more frequently in arm 3.

Editorial — Dr Matulonis (continued)

PFS was 17.9 mos (arm 1), 20.6 mos (arm 2), 21.1 mos (arm 3) – no differences. OS also not different amongst the arms: 46.5 mos (arm 1), 48.1 mos (arm 2), and 54 mos (arm 3). These results contradict the JGOG study as well as GOG 262 (pts who did not receive bev) and question the use of weekly paclitaxel and every 3 week carboplatin.

Management of Platinum-Sensitive Recurrent Ovarian Cancer



Phase III Studies of Bevacizumab in Combination with Chemotherapy for Ovarian Cancer: Platinum-Sensitive, Recurrent Setting

Study	Randomization	N	Median PFS (mo)	HR, *p*-value	Median OS (mo)	HR, *p*-value
OCEANS[1]	C/gem + placebo C/gem + bev until progression	242 242	8.4 12.4	HR = 0.48 <0.0001	32.9 33.6	HR = 0.952 0.6479
GOG-0213[2]	C/P C/P + bev	374 374	10.4 13.8	HR = 0.61 <0.0001	37.3 42.2	HR = 0.827 0.056

[1] Aghajanian C et al. *J Clin Oncol* 2012;30(17):2039-45; *Gynecol Oncol* 2015;139(1):10-6; [2] Coleman RL et al. *Proc SGO* 2015;Abstract 3.

Phase III Studies of Bevacizumab in Combination with Chemotherapy for Ovarian Cancer: Platinum-Resistant, Recurrent Setting

Study	Randomization	N	Median PFS	Hazard ratio	*p*-value	Survival advantage
AURELIA	Chemo* Chemo* + bev	182 179	3.4 6.7	0.48	<0.001	No

* Weekly paclitaxel, topotecan or pegylated liposomal doxorubicin

Pujade-Lauraine E et al. *J Clin Oncol* 2014;32(13):1302-8.

Phase III PAOLA-1

Trial Identifier: NCT02477644
Planned Enrollment: 786

Eligibility

- Stage IIIb-IV ovarian, fallopian tube or primary peritoneal cancer with high grade serous/endometrioid or non-mucinous germline BRCAm
- CR or PR to platinum-taxane chemotherapy
- ≥ 3 cycles bevacizumab

R

2:1

Bevacizumab 15 mg/kg q3wk for 15 months

Olaparib 300 mg BID for 2 years

Bevacizumab 15 mg/kg q3wk for 15 months

Placebo for 2 years

Primary endpoint: Progression-free survival

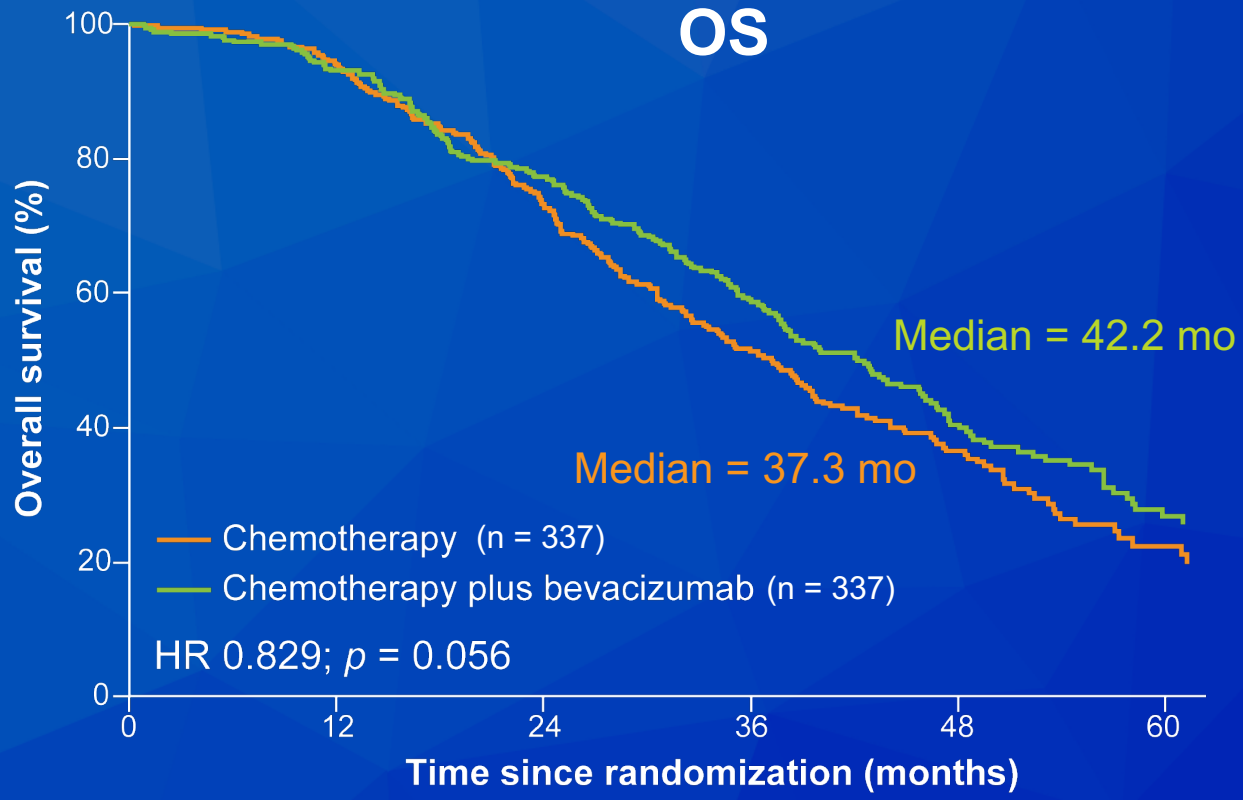
www.clinicaltrials.gov. Accessed October 2017.

Bevacizumab and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial

Robert L Coleman, Mark F Brady, Thomas J Herzog, Paul Sabbatini, Deborah K Armstrong, Joan L Walker, Byoung-Gie Kim, Keiichi Fujiwara, Krishnansu S Tewari, David M O'Malley, Susan A Davidson, Stephen C Rubin, Paul DiSilvestro, Karen Basen-Engquist, Helen Huang, John K Chan, Nick M Spirtos, Raheela Ashfaq, Robert S Mannel

Lancet Oncol 2017;18(6):779-91.

GOG-0213: Survival Outcomes



Due to incorrect treatment-free interval (TFI) stratification data for 45 (7%) pts (equally balanced between treatment groups), a sensitivity analysis of OS based on the audited TFI stratification data gave an adjusted HR of 0.823; $p = 0.0447$.

- Median PFS (N = 674) = 13.8 mo (chemo/bev) vs 10.4 (chemo)
  - HR = 0.628; $p < 0.0001$

Coleman RL et al. *Lancet Oncol* 2017;18(6):779-91.

Editorial — Dr Matulonis

674 women with platinum sensitive recurrent ovarian cancer were randomized 1:1 carboplatin AUC 5 and paclitaxel 175 mg/m^2 versus carbo/paclitaxel + bev (15 mg/kg) and bev maintenance until either disease progression and/or toxicity. This was an open label nonblinded study. Median OS was 42.2 months for the bev arm and 37.3 months in the chemotherapy only arm (p = 0.056). Six cycles were planned and an additional 2 cycles could be given if there was a PR or CR. Disease was assessed by CT or MRI after cycles 3 and 6 (and 8, if administered) of study treatment, every 3 months for 2 years and then every 6 months thereafter. Progression was defined as RECIST 1.0 PD, GCIG CA125 criteria, global deterioration of health or death.

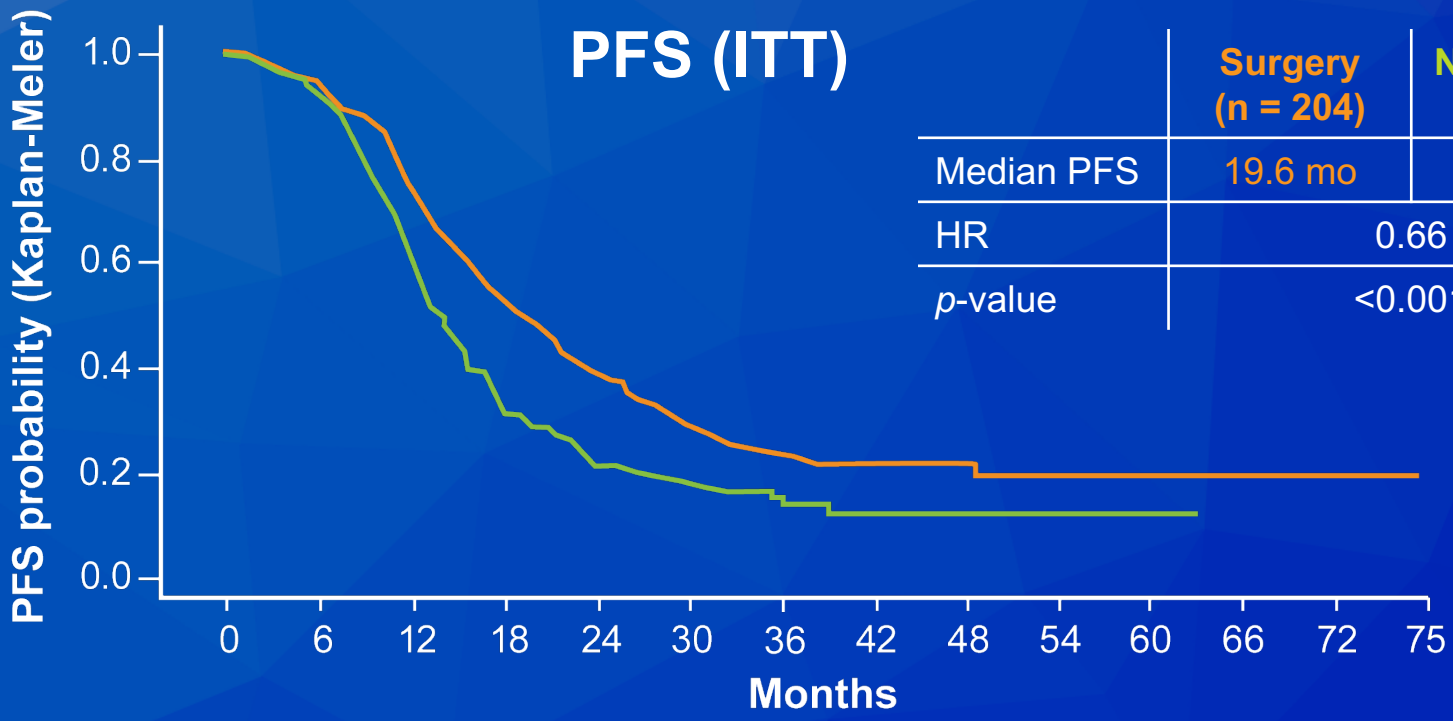
Editorial — Dr Matulonis (continued)

Stage, histology, and previous treatment appeared similar between the 2 groups. Median PFS (measured from time of randomization to date of progression) was longer for the bev arm 13.8 mos versus 10.4 months, p <0.0001). RR was higher in the chemo + bev arm, 78% versus 59%. SAE's occurred in 28% of the bev group versus 11% of the chemotherapy alone group. Toxicities (grade 3 or higher) that were more common with the bev arm was abd pain, nausea, SBO, HTN, proteinuria, and dyspnea. There was an error in the calculation of the platinum free interval in 7% of the patients (balanced between the 2 groups). QOL measures were not different amongst the 2 groups. The addition of bevacizumab to carboplatin and paclitaxel improved OS non-significantly, PFS significantly, overall RR but did not impact QOL scores.

Randomized Controlled Phase III Study Evaluating the Impact of Secondary Cytoreductive Surgery in Recurrent Ovarian Cancer: AGO DESKTOP III/ENGOT ov20

Du Bois A et al.
Proc ASCO 2017;Abstract 5501.

AGO DESKTOP III.ENGOT ov20: Interim Analysis



	Surgery (n = 204)	No surgery (n = 203)
Median PFS	19.6 mo	14.0 mo
HR	0.66	
p-value	<0.001	

- A planned interim analysis after 122 OS events did not reach the local significance level, which was set to alpha = 0.0052 for 2-sided test.
- Median time to start of first subsequent therapy = 21 mo (surgery) vs 13.9 mo (no surgery)
  - HR = 0.61; $p < 0.001$

Du Bois A et al. *Proc ASCO* 2017;Abstract 5501.

Editorial — Dr Matulonis

The AGO DESKTOP III study presented by Andreas DuBois at ASCO is a randomized study of patients with platinum-sensitive recurrent ovarian cancer who also needed to have a positive AGO score. A positive AGO score meant ECOG 0, ascites <500 mL and complete resection at initial surgery. 407 enrolled patients were randomized to either 2nd-line chemotherapy alone (no surgery) versus cytoreductive surgery followed by chemotherapy. Most of the enrolled patients had a platinum-free interval of more than 12 months. Primary endpoint was OS, and secondary endpoint was PFS. Most patients (>90%) received platinum-based chemotherapy and ~20% a bevacizumab combination.

Editorial — Dr Matulonis (continued)

For the patients randomized to surgery, there was a 72.5% macroscopic complete resection rate (R0). OS results are not available yet. PFS results were presented: 19.6 months for surgery arm and 14 months for nonsurgery arm (HR 0.66, 0.52-0.83), so about a 5-month extension of PFS with surgery. The time to next subsequent therapy (time to 3rd line) was 21 months for surgery and 13.9 months for no surgery. The patients who benefited and who went to surgery were those who had an R0 resection.

Editorial — Dr Matulonis (continued)

For patients with platinum-sensitive recurrence who have a platinum-free interval of 12 months or greater and have a positive AGO score (ie, ECOG 0, small-volume ascites and complete resection at surgery), secondary cytoreductive surgery followed by chemotherapy affords a 5-month PFS benefit and further delay of next treatment compared to chemotherapy alone. This is a reasonable option to consider in selected patients.

Ovarian Cancer — Drs Birrer and Moore

Chemotherapy with or without bevacizumab in ovarian cancer

Germline and somatic mutations in ovarian cancer

PARP inhibitors: Efficacy, toxicity and ongoing trials

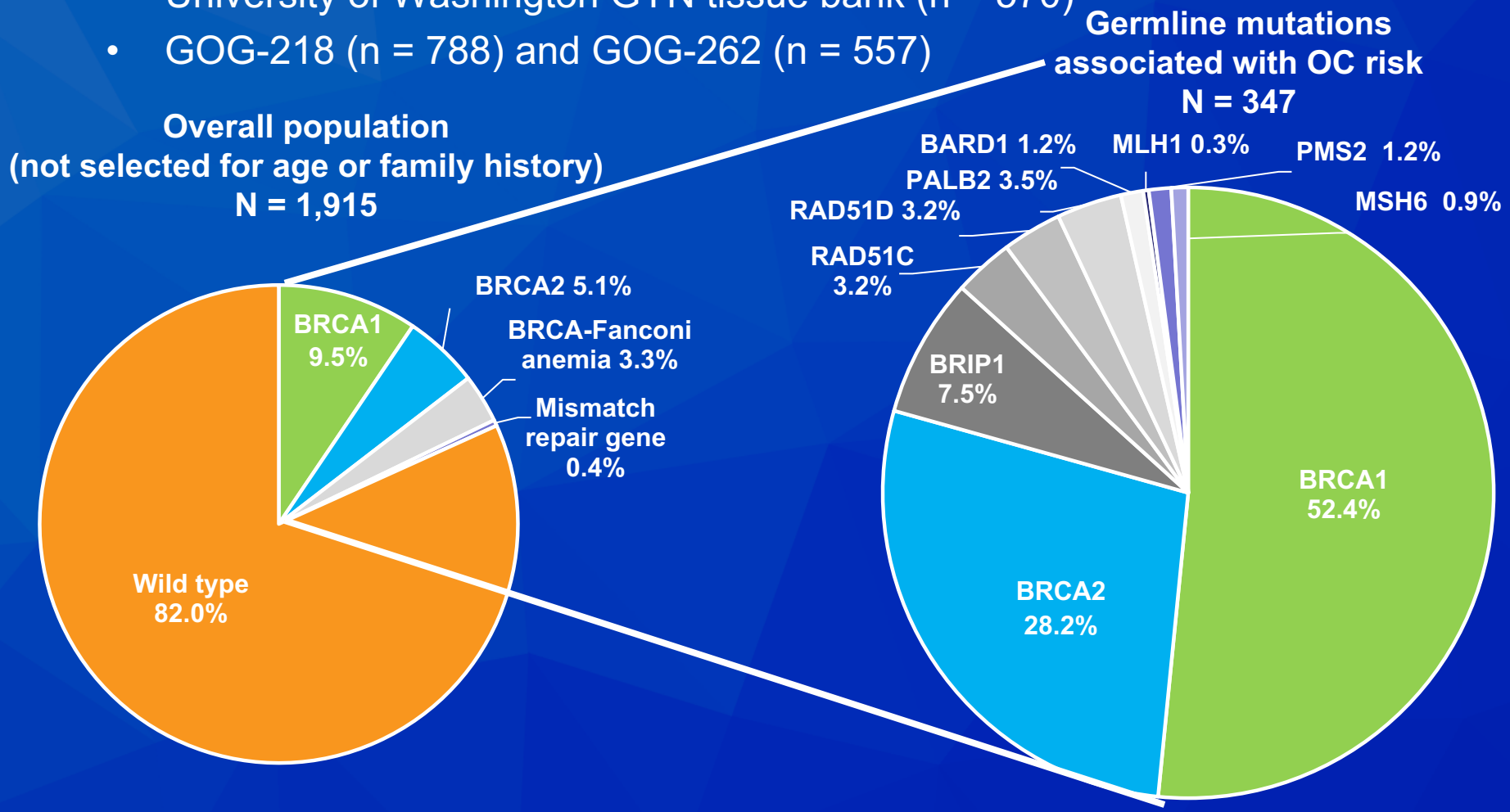
Novel investigational agents

When you do BRCA testing for your patients with ovarian cancer who have no family history of breast or ovarian cancer, do you generally send them to a genetic counselor prior to ordering the test?

a. Yes
b. No

Summary of Germline DNA Mutations in OC

- Germline DNA sequenced from women with OC (N = 1,915) using a targeted capture and multiplex sequencing assay
- University of Washington GYN tissue bank (n = 570)
- GOG-218 (n = 788) and GOG-262 (n = 557)



Norquist BM et al. *JAMA Oncol* 2016;2(4):482-90.

Examples of Assays for Genetic Testing

Test	Companion diagnostics	Turnaround time
BRACAnalysis CDx®	Olaparib companion diagnostic test	2 weeks
FoundationFocus™ CDxBRCA test	Rucaparib companion diagnostic test — somatic and germline BRCA1/2	2 weeks
	Breast/ovarian panels	
Ambry Genetics BRCAplus™	6-gene panel	1-2 weeks
Ambry Genetics OvaNext™	25-gene panel	2-4 weeks
Invitae Breast/Gyn Guidelines-based panel	19-gene panel	1-3 weeks
Color Genomics™	19-gene panel	4-8 weeks
GeneDx Breast/Ovarian	21-gene panel	3 weeks
	Comprehensive panels	
Ambry Genetics CancerNext™	32-gene panel	2-3 weeks
GeneDx Comprehensive	32-gene panel	3 weeks
Myriad myRisk®	25-gene panel	2-4 weeks
Invitae Multi-Cancer	79-gene panel	1-3 weeks

GeneTests (www.genetests.org); Lynce F, Isaacs C. ASCO 2016 Education Book

Panel Testing

Advantages:

- More “diagnoses”
- Often cost effective

Disadvantages:

- Unexpected results
  - Noncorrelative high-penetrant gene(s)
  - Mosaicism
- Low and moderate penetrance genes
- High uncertain variant rate
- Slower turnaround time

Courtesy of Kathleen N Moore, MD

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/ysonc

Guidance Statement On *BRCA1/2* Tumor Testing in Ovarian Cancer Patients

Ettore Capoluongo[a], Gillian Ellison[b], José Antonio López-Guerrero[c], Frederique Penault-Llorca[d], Marjolijn J.L. Ligtenberg[e], Susana Banerjee[f], Christian Singer[g], Eitan Friedman[h], Birgid Markiefka[i], Peter Schirmacher[j], Reinhard Büttner[i], Christi J. van Asperen[k], Isabelle Ray-Coquard[l], Volker Endris[j], Suzanne Kamel-Reid[m], Natalie Percival[f], Jane Bryce[n], Benno Röthlisberger[o], Richie Soong[p], David Gonzalez de Castro[q,*]

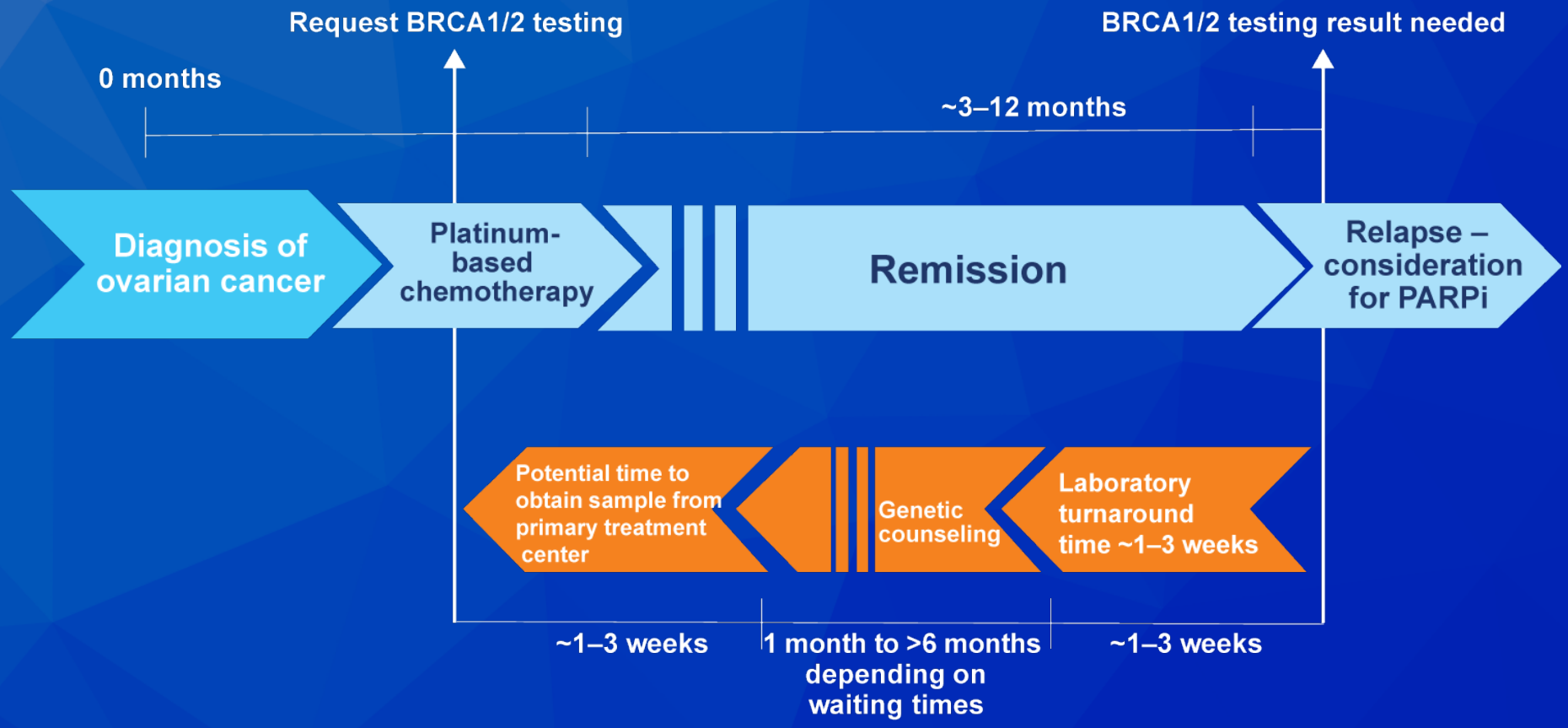
Semin Oncol 2017;44(3):187-97.

BRCA Genetic Testing: Considerations and Key Recommendations

Category	Recommendation
Sample type appropriate for BRCA testing	Use tissue sample from either primary HGS carcinomas or related metastases; FFPE or Fresh-frozen specimens
DNA extraction from tumor samples	Use a validated protocol that ensures sufficient quality & quantity of DNA for the particular methodology
Methodologies for tumor testing	NGS is highly recommended
Avoid false positives/negatives	Use duplicate or repeat analysis from the same starting genomic DNA
Bioinformatics considerations	It varies from lab to lab and should be validated on all BRCA1/2 mutation types
Informed consent/ethical considerations	Use written and personal discussion procedures for the patient and families on the test results
Timing of testing	In such a way that results are available when clinically relevant to the patient

Capoluongo E et al. *Semin Oncol* 2017;44(3):187-97.

BRCA Genetic Testing: Timeline of Factors to Consider



Capoluongo E et al. *Semin Oncol* 2017;44(3):187-97.

Evaluation of BRCA1/2 and Homologous Recombination Defects in Ovarian Cancer and Impact on Clinical Outcomes[1]

Comprehensive Genomic Profiling (CGP) with Loss of Heterozygosity (LOH) Identifies Therapeutically Relevant Subsets of Ovarian Cancer (OC)[2]

[1] Yates MS et al.
Proc ASCO 2017;Abstract 5511.

[2] Elvin JA et al.
Proc ASCO 2017;Abstract 5512.

BRCA1/2 and HRD Impact on Clinical Outcomes

All patients	Surgery (n = 129)	NACT (n = 170)	*p*-value
Median OS	65.8 mo	45.2 mo	0.0032
Median EFS	24.8 mo	15.6 mo	0.0003

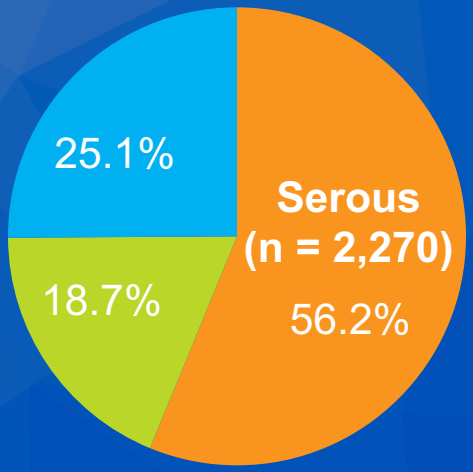
gBRCA1/2 mutation status	Negative (n = 227)	Positive (n = 44)	*p*-value
Median OS	46.1 mo	65.3 mo	0.0331
Median EFS	16.4 mo	27.0 mo	0.0050

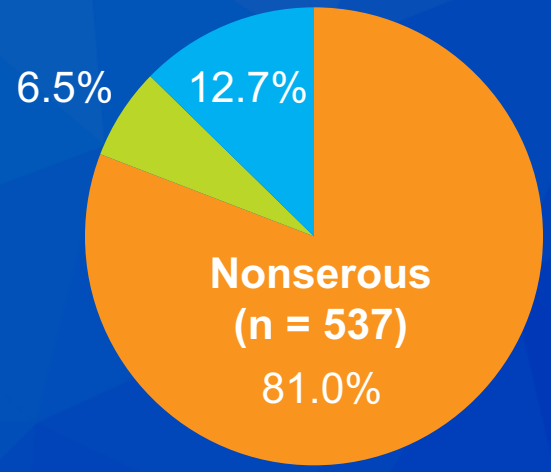
Any germline HR mutation	No (n = 104)	Yes (n = 35)	*p*-value
Median OS	36.7 mo	50.2 mo	0.0236
Median EFS	13.9 mo	20.4 mo	0.0019

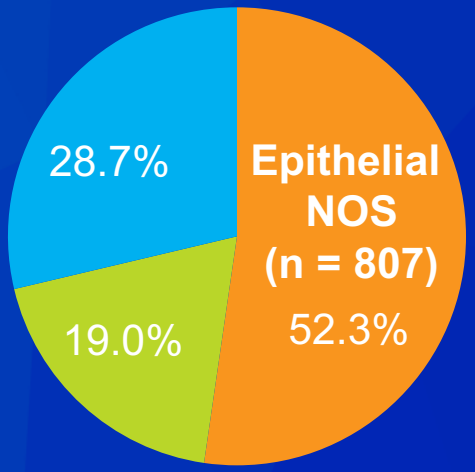
HR = homologous recombination; EFS = event-free survival; OS = overall survival

Yates MS et al. *Proc ASCO* 2017;Abstract 5511.

Molecular Category Prevalence by Histology and Treatment Information

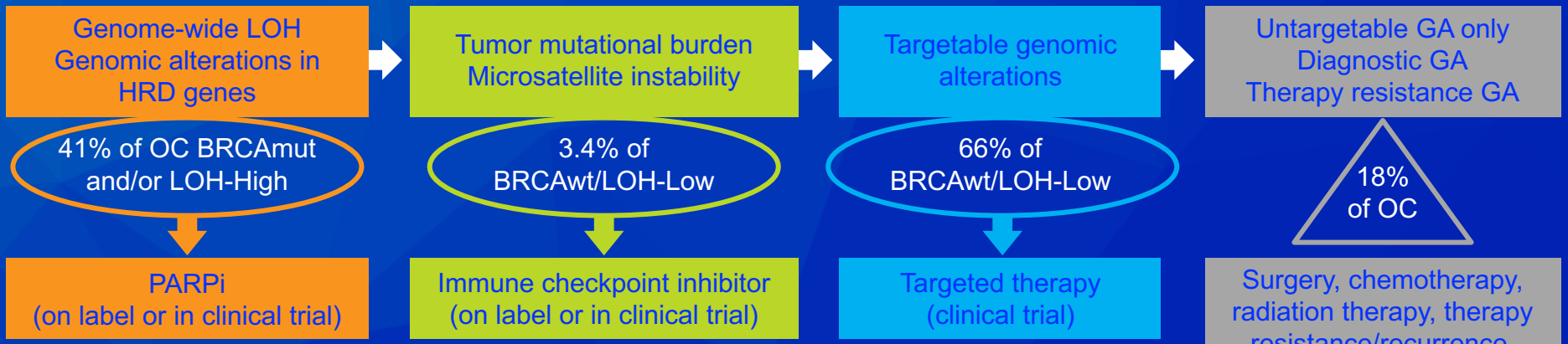






BRCAmut BRCAwt/LOH-H BRCAwt/LOH-L

NOS – Carcinoma not otherwise specified



Ovarian tumor treatment paradigms

LOH = loss of heterozygosity; GA = genomic alterations;
ICPI = immune checkpoint inhibitors; HRD = homologous recombination deficiency

Elvin JA et al. *Proc ASCO* 2017;Abstract 5512.

Editorial — Dr Secord

These studies demonstrate that biomarkers beyond germline BRCA mutations may be prognostic for survival outcomes and tools for treatment decisions.

Yates et al evaluated 229 chemo-naïve patients with advanced ovarian cancer (OC) who underwent neoadjuvant chemotherapy (NACT) vs primary debulking surgery (PDS). HRD+ was defined as germline or somatic BRCA mutations, BRCA1 methylation, HRD score ≥42, or germline mutation in other homologous recombination genes. Those undergoing PDS had better overall survival (OS) and event-free survival compared to NACT. HRD+ status and BRCA mutations were prognostic for survival outcomes. When stratified by NACT vs PDS, the association was specifically seen in those undergoing NACT.

Editorial — Dr Secord (continued)

Elvin et al evaluated 4,114 advanced OC tumor specimens using comprehensive genomic profiling (CGP) for all classes of genomic alterations (GA) by hybrid-capture, next-generation sequencing of up to 315 genes, microsatellite instability (MSI), tumor mutation burden (TMB), and LOH. Serous cancers were significantly more likely to have a BRCA mutation (18.7% vs 4.4%), higher median LOH (12.8 vs. 5.8). LOH was high in the majority of serous and non-serous cancers (86% and 75%). BRCAwt LOH-low cancers had several GA of interest, including CCNE1 (19.7%), KRAS (19%), PIK3CA (16.2%), AKT2 (7.4%), ERBB2 (4.7%), or BRAF (3.3%) GA.

Editorial — Dr Secord (continued)

TMB high was 2.5% and MSI high 1%. CGP revealed molecularly distinct subsets that may benefit from PARPi (46.2% BRCAmut or LOH high), targeted therapy (>50% BRCAwt LOH low) or immunotherapy (3.5% TMB high or MSI high).

Biomarkers have both prognostic and predictive associations that can be used clinically for counseling purposes and treatment decisions.

Ovarian Cancer — Drs Birrer and Moore

Chemotherapy with or without bevacizumab in ovarian cancer

Germline and somatic mutations in ovarian cancer

PARP inhibitors: Efficacy, toxicity and ongoing trials

Novel investigational agents

Press Release — March 27, 2017
FDA Approval of Niraparib as Maintenance Therapy

"The US Food and Drug Administration today approved niraparib for the maintenance treatment (intended to delay cancer growth) of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, whose tumors have completely or partially shrunk (complete or partial response, respectively) in response to platinum-based chemotherapy."

The approved administration of niraparib maintenance therapy is not dependent on the presence of a specific genetic mutation.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm548948.htm

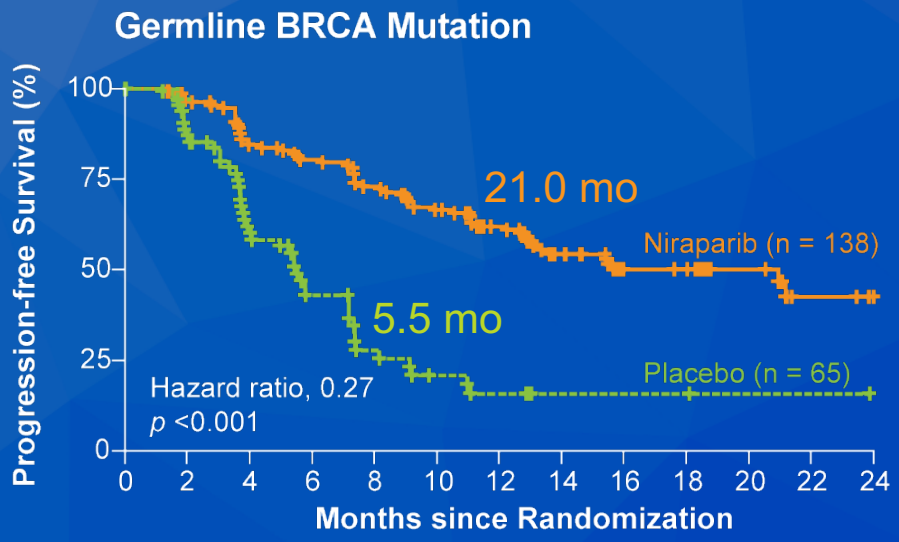
ORIGINAL ARTICLE

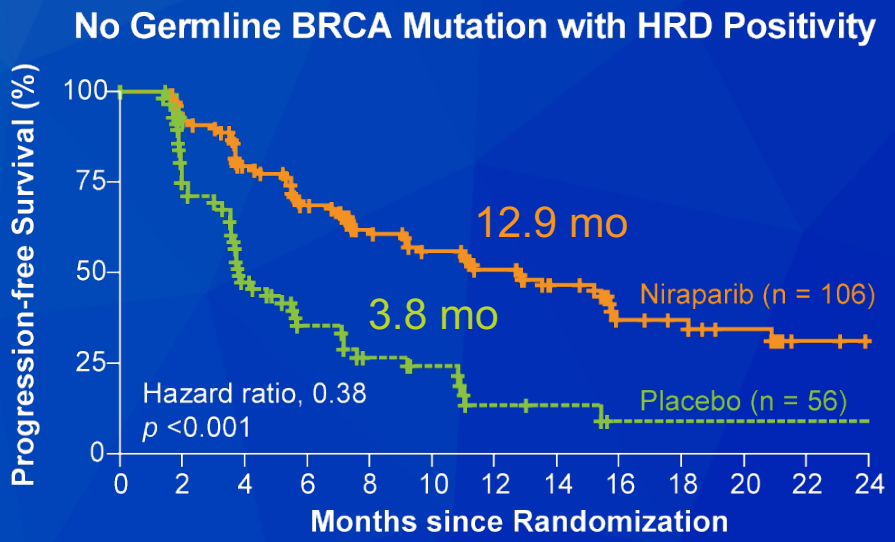
Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

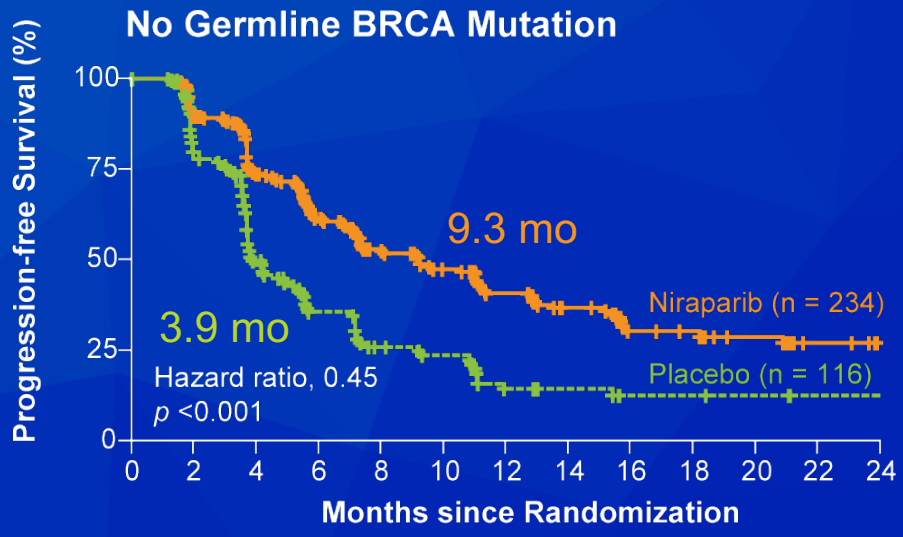
M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, M. Fabbro, J.A. Ledermann, D. Lorusso, I. Vergote, N.E. Ben-Baruch, C. Marth, R. Mądry, R.D. Christensen, J.S. Berek, A. Dørum, A.V. Tinker, A. du Bois, A. González-Martín, P. Follana, B. Benigno, P. Rosenberg, L. Gilbert, B.J. Rimel, J. Buscema, J.P. Balser, S. Agarwal, and U.A. Matulonis, for the ENGOT-OV16/NOVA Investigators*

N Engl J Med 2016;375(22):2154-64.

ENGOT-OV16/NOVA: PFS Results







Mirza MR et al. *N Engl J Med* 2016;375(22):2154-64.

ENGOT-OV16/NOVA: Select Adverse Events (AEs)

Event	Niraparib (n = 367)		Placebo (n = 179)	
	All	Grade 3/4	All	Grade 3/4
Nausea	73.6%	3.0%	35.2%	1.1%
Thrombocytopenia	61.3%	33.8%	5.6%	0.6%
Fatigue	59.4%	8.2%	41.3%	0.6%
Anemia	50.1%	25.3%	6.7%	0%
Neutropenia	30.2%	19.6%	6.1%	1.7%
Dyspnea	19.3%	1.1%	8.4%	1.1%
Hypertension	19.3%	8.2%	4.5%	2.2%
Urinary tract infection	10.4%	0.8%	6.1%	1.1%

Mirza MR et al. *N Engl J Med* 2016;375(22):2154-64.

Editorial — Dr Secord

ENGOT-OV16/NOVA is a randomized, double-blind phase III trial of maintenance niraparib vs placebo for platinum-sensitive, recurrent ovarian cancer following complete or partial response to platinum-based chemotherapy. Niraparib is an oral poly(adenosine diphosphate–ribose) polymerase inhibitor (PARPi). Participants were categorized on germline BRCA mutation (gBRCA cohort, non-gBRCA cohort) and type of non-gBRCA mutation and received either niraparib (300 mg) or placebo once daily. 553 patients were enrolled in the gBRCA (n=203) and non-gBRCA (n=350) cohorts.

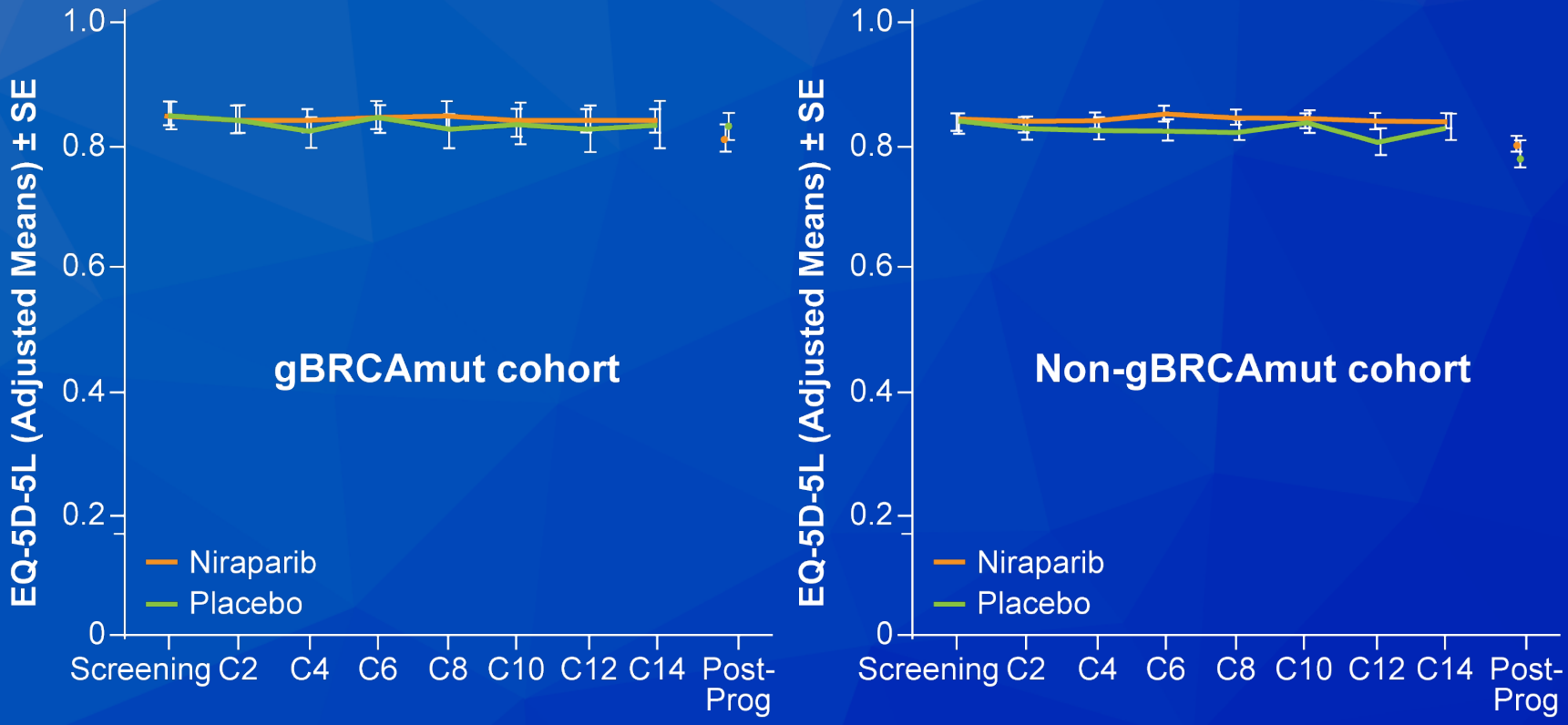
Editorial — Dr Secord (continued)

Patients treated with niraparib had a significantly longer median progression-free survival compared to placebo in all groups (gBRCA: 21.0 vs. 5.5 months, HR=0.27, CI=0.17-0.41; non-gBRCA: 9.3 vs 3.9 months, HR=0.45, CI=0.34-0.61). On subgroup analysis, the non-gBRCA cohort with homologous recombination deficiency (HRD) had improved progression-free survival with niraparib compared to placebo (12.9 vs 3.8 months, HR=0.38, CI=0.24-0.59). The least benefit was in the non-gBRCA/HRD-negative group (3.1 month improvement, HR=0.58). Therapy was well tolerated. The most common grade ≥3 adverse events in the niraparib group were thrombocytopenia (in 33.8%), anemia (in 25.3%), and neutropenia (in 19.6%).

Editorial — Dr Secord (continued)

These findings supported PARPi maintenance therapy, seen in olaparib studies, and extended the use of maintenance PARPi therapy to all comers with platinum-sensitive, recurrent ovarian cancer regardless of biomarker status. However, the greatest magnitude of benefit from maintenance niraparib was in women with BRCA mutations (somatic and germline), followed by those with tumor HRD. Maintenance niraparib is FDA approved for platinum-sensitive recurrent ovarian cancer and represents a new standard of care in the treatment of ovarian cancer.

ENGOT-OV16/NOVA: Quality of Life (QoL)



- Baseline QoL was similar between the niraparib and placebo groups
- QoL scores during treatment were similar between groups
- There was a trend toward less pain in the niraparib group
- Hematologic AEs decreased over time and did not affect QoL

Oza A et al. *Proc ESMO* 2017;Abstract 930O.

Editorial — Dr Secord

This abstract reports the patient-reported outcomes (PROs) and quality of life of women with platinum-sensitive, recurrent ovarian cancer treated on the NOVA trial, a randomized, double-blind, phase III trial with niraparib versus placebo as maintenance treatment. Several PROs tools were evaluated, including the Functional Assessment of Cancer Therapy Ovarian Symptoms Index (FOSI) and European Quality of Life Scale 5-Dimensions (EQ-5D-5L), and adjusted EQ-5D-5L health utility index (HUI) scores. A disutility analysis of hematologic adverse events was also performed.

There was no significant difference in mean PRO scores between the niraparib and placebo arms. Baseline HUI scores were similar in both arms.

Editorial — Dr Secord (continued)

However, average adjusted HUI pre-progression scores trended higher in the niraparib arm (0.812 vs 0.803 in gBRCAmut cohort; 0.845 vs 0.828 in non-gBRCAmut). Hematologic toxicities had no detrimental effect on overall health utility. The findings suggest that women with recurrent OC treated with maintenance niraparib following complete response or partial response to platinum-based chemotherapy have no quality-of-life detriment while on treatment, and hematologic side effects do not lead to adverse clinically significant toxicity.

Press Release — August 17, 2017
Approval of Olaparib Tablets

"The US Food and Drug Administration 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."

The approved administration of olaparib maintenance therapy is not dependent on the presence of a specific genetic mutation.

Olaparib **tablets** are also now approved for adult patients with deleterious or suspected deleterious germline BRCA mutation-positive advanced ovarian cancer who have received 3 or more prior lines of chemotherapy.

"The recommended olaparib **tablet dose** for both the maintenance therapy and later line treatment setting is 300 mg (two 150 mg tablets) taken orally twice daily."

https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm572143.htm

Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial

*Eric Pujade-Lauraine, Jonathan A Ledermann, Frédéric Selle, Val Gebski, Richard T Penson, Amit M Oza, Jacob Korach, Tomasz Huzarski, Andrés Poveda, Sandro Pignata, Michael Friedlander, Nicoletta Colombo, Philipp Harter, Keiichi Fujiwara, Isabelle Ray-Coquard, Susana Banerjee, Joyce Liu, Elizabeth S Lowe, Ralph Bloomfield, Patricia Pautier, the SOLO2/ENGOT-Ov21 investigators**

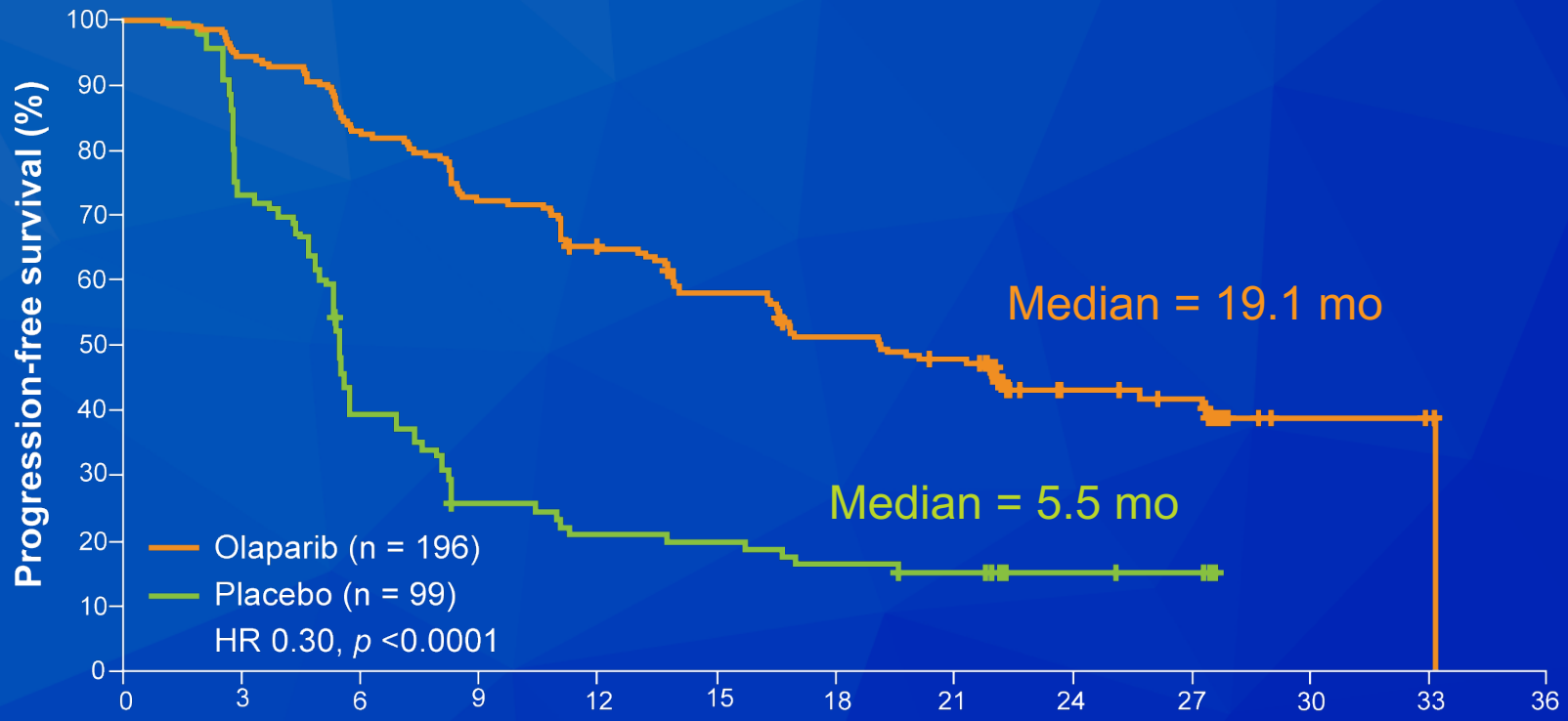
Lancet Oncol 2017;18(9):1274-84.

Efficacy of Olaparib Maintenance Therapy in Patients (pts) with Platinum-Sensitive Relapsed Ovarian Cancer (PSROC) by Lines of Prior Chemotherapy: Phase III SOLO2 Trial (ENGOT Ov-21)

Penson R et al. *Proc ESMO* 2017;Abstract 932PD.

SOLO2: PFS and QoL Results

PFS by Investigator Assessment



- Median PFS (by blinded independent central review):
  - Olaparib (30.2 mo) vs placebo (5.5 mo)
- Olaparib tablet maintenance showed no detrimental effect on quality of life in patients.

Pujade-Lauraine E et al. *Lancet Oncol* 2017;18(9):1274-84.

SOLO2: Select Adverse Events

Event	Niraparib (n = 195)		Placebo (n = 99)	
	All	Grade3/4	All	Grade3/4
Nausea	76%	3%	33%	0%
Fatigue or asthenia	66%	4%	37%	2%
Anemia	43%	19%	6%	2%
Neutropenia	19%	5%	2%	4%
Thrombocytopenia	14%	1%	3%	1%
Dyspnea	12%	1%	1%	0%
Urinary tract infection	10%	1%	10%	0%

- The rate of hypertension was not increased with olaparib vs placebo.

Pujade-Lauraine E et al. *Lancet Oncol* 2017;18(9):1274-84.

SOLO2: PFS Analysis by the Number of Prior Lines of Platinum-Based Chemotherapy (PBC)

Median PFS	Olaparib	Placebo	HR	95% CI
2 prior lines (n = 110, 62)	22.1 mo	5.7 mo	0.38	0.26 – 0.57
3 prior lines (n = 60, 20)	16.9 mo	5.1 mo	0.24	0.13 – 0.42
≥4 prior lines (n = 25, 17)	17.0 mo	5.4 mo	0.26	0.13 – 0.51

- Pts who had received 2 prior lines of PBC were more likely to have had a platinum-free interval of >12 months at baseline vs pts who had received ≥3 prior lines
  - Olaparib: 70.9% (2 prior lines) vs 48.3% (3 prior lines) vs 40.0% (≥4 prior lines)
  - Placebo: 69.4% (2 prior lines) vs 60.0% (3 prior lines) and 23.5% (≥4 prior lines)
- Pts who had received 2 prior lines of PBC were more likely to have had a complete response at baseline vs pts who had received ≥3 prior lines

Penson R et al. *Proc ESMO* 2017;Abstract 932PD.

Editorial — Dr Secord

SOLO2 is a double-blind, randomized, placebo-controlled, phase III trial of olaparib versus placebo maintenance treatment for ovarian cancer patients with somatic or germline BRCA mutation with platinum-sensitive, recurrent ovarian cancer following complete response or partial response to platinum-based chemotherapy. Olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, capsule formulation, had previously shown improved progression-free survival to all-comer patients with platinum-sensitive, relapsed ovarian cancer. 295 patients were randomly assigned to receive olaparib (n=196) or placebo (n=99).

Median progression-free survival was significantly longer with olaparib (19.1 vs 5.5 months, HR=0.30, CI=0.22-0.41, p<0.0001).

Editorial — Dr Secord (continued)

A PFS subgroup analysis was performed to assess effect of prior therapy on olaparib efficacy. Treatment with olaparib improved progression-free survival in all groups (2 priors: 22.1 vs 5.7 months, HR=0.38; 3 priors: 16.9 vs 5.1 months, HR=0.24; ≥4 priors, 17.0 vs 5.4 months, HR=0.26). The most common grade >3 adverse events in the olaparib group were anemia (38%), fatigue (4%), and neutropenia (5%).

These findings confirmed the anti-tumor activity of olaparib tablet maintenance in BRCA-mutation associated platinum-sensitive, relapsed ovarian cancer irrespective of the number of prior lines of platinum-based chemotherapy. The trial reinforced data from other maintenance olaparib and PARPi trials in recurrent ovarian cancer.

Editorial — Dr Secord (continued)

Overall toxicities with olaparib were low grade and/or manageable with dose modification. As with other PARPi, combinations with chemotherapy, anti-angiogenic agents, and immunotherapy are being explored.

Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by *BRCA* status in a randomised phase 2 trial

Jonathan Ledermann, Philipp Harter, Charlie Gourley, Michael Friedlander, Ignace Vergote, Gordon Rustin, Clare L Scott, Werner Meier, Ronnie Shapira-Frommer, Tamar Safra, Daniela Matei, Anitra Fielding, Stuart Spencer, Brian Dougherty, Maria Orr, Darren Hodgson, J Carl Barrett, Ursula Matulonis

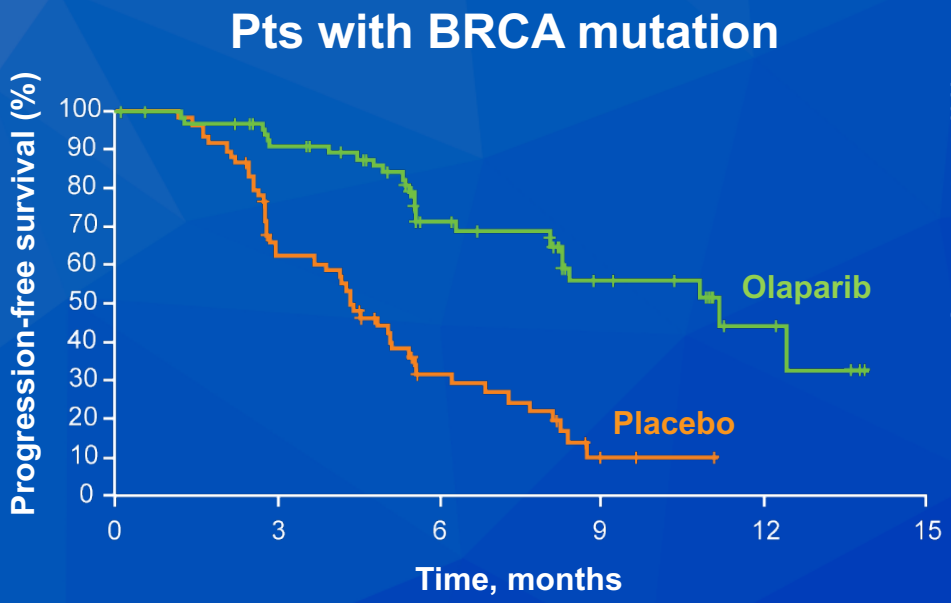
Lancet Oncol 2014;15(8):852-61.

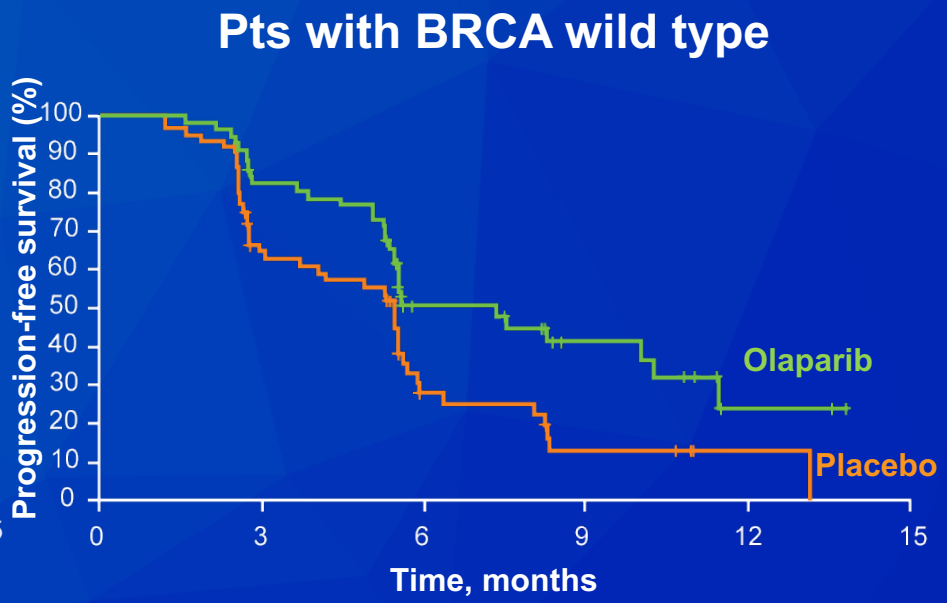
Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial

Jonathan A Ledermann, Philipp Harter, Charlie Gourley, Michael Friedlander, Ignace Vergote, Gordon Rustin, Clare Scott, Werner Meier, Ronnie Shapira-Frommer, Tamar Safra, Daniela Matei, Anitra Fielding, Stuart Spencer, Philip Rowe, Elizabeth Lowe, Darren Hodgson, Mika A Sovak, Ursula Matulonis

Lancet Oncol 2016;17(11):1579-89.

Phase II Trial: PFS by BRCA Mutation Status

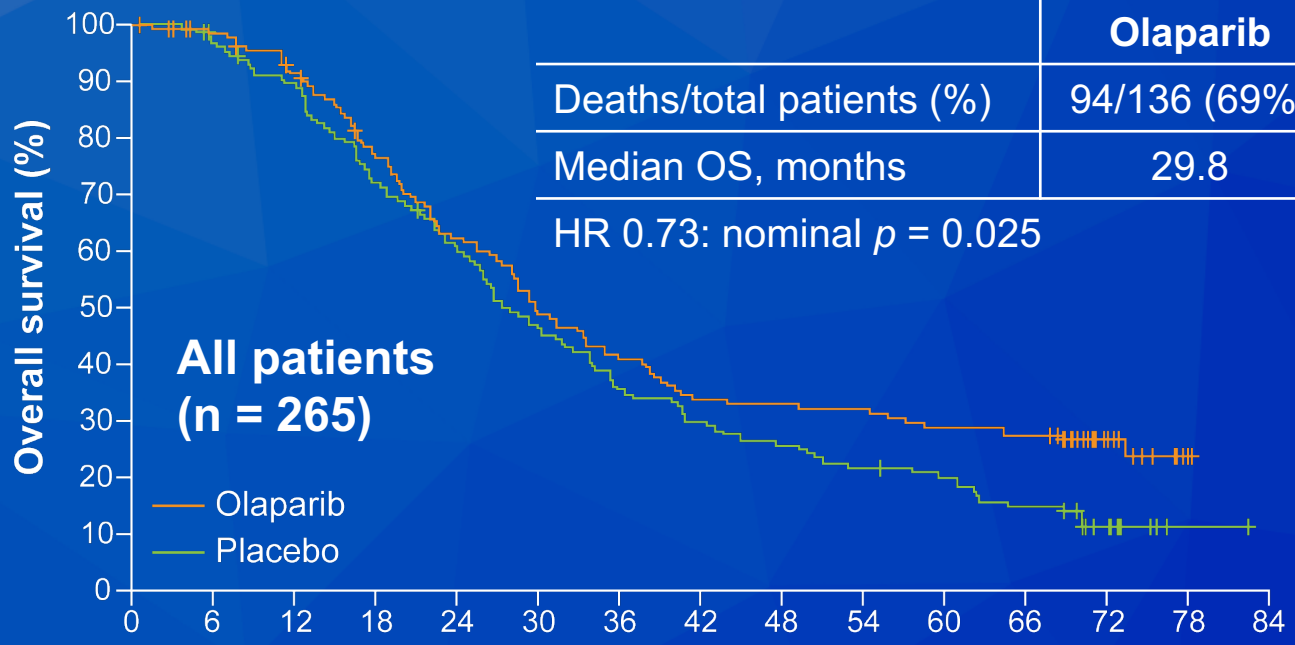




Median PFS	Olaparib	Placebo	HR	*p*-value
BRCAm (n = 74, 62)	11.2 mo	4.3 mo	0.18	<0.0001
BRCAwt (n = 57, 61)	7.4 mo	5.5 mo	0.54	0.0075

Ledermann J et al. *Lancet Oncol* 2014;15(8):852-61.

Phase II Trial: Updated OS Results



	Olaparib	Placebo
Deaths/total patients (%)	94/136 (69%)	109/129 (84%)
Median OS, months	29.8	27.8

HR 0.73: nominal $p = 0.025$

- For all patients, the nominal *p*-value of 0.025 did not meet the required threshold for statistical significance ($p < 0.0095$).

Median OS	Olaparib	Placebo	HR	*p*-value
BRCAm (n = 74, 62)	34.9 mo	30.2 mo	0.62	0.025
BRCAwt (n = 57, 61)	24.5 mo	26.6 mo	0.83	0.37

Ledermann JA et al. *Lancet Oncol* 2016;17(11):1579-89.

Editorial — Dr Secord

An update from the Study 19 randomized, placebo-controlled, double-blind Phase II trial of olaparib maintenance in women with platinum-sensitive recurrent serous ovarian cancer evaluated overall survival outcomes, a secondary endpoint, from the third data analysis after more than 5 years' follow-up. 265 patients were randomly assigned to olaparib (n=136) or placebo (n=129), and 136 had deleterious BRCAm.

A nonsignificant overall survival advantage was seen with maintenance olaparib versus placebo in all patients (median overall survival was 29.8 vs 27.8 months, HR 0.73, CI=0.55-0.96, nominal p=0.025) but did not meet the required threshold for statistical significance ($p<0.00950$).

Editorial — Dr Secord (continued)

The greatest improvement in overall survival was seen in the BRCAm cohort (34.9 vs 30.2 months, HR 0.62, CI=0.41-0.94, nominal p=0.025). There was no overall survival advantage in patients with BRCA wild type treated with olaparib (24.5 *vs* 26.6 months, HR 0.83, CI=0.55-1.24, nominal p=0.37). Fifteen percent of 74 patients with BRCAm received maintenance olaparib for ≥5 years. Adverse events were similar to prior reports, including low-grade nausea, fatigue, vomiting, and anemia. AML was very rare.

These results support the benefit and safety of long-term olaparib. This is the first study to suggest an overall survival benefit with PARPi maintenance in BRCA-mutated platinum-sensitive recurrent serous ovarian cancer.

Editorial — Dr Secord (continued)

Long-term exposure to olaparib appears safe and well tolerated. Olaparib has been FDA approved for maintenance therapy in all women with platinum-sensitive recurrent ovarian cancer.

Press Release — December 19, 2016
Accelerated approval for rucaparib

"The US Food and Drug Administration today granted accelerated approval to rucaparib for women with advanced ovarian cancer who have been treated with two or more chemotherapies and whose tumors have a specific gene mutation (deleterious BRCA) as identified by an FDA-approved companion diagnostic test.

"…the FDA also approved the FoundationFocus CDxBRCA companion diagnostic for use with rucaparib, which is the first next-generation-sequencing (NGS)-based companion diagnostic approved by the agency. The NGS test detects the presence of deleterious BRCA gene mutations in the tumor tissue of ovarian cancer patients."

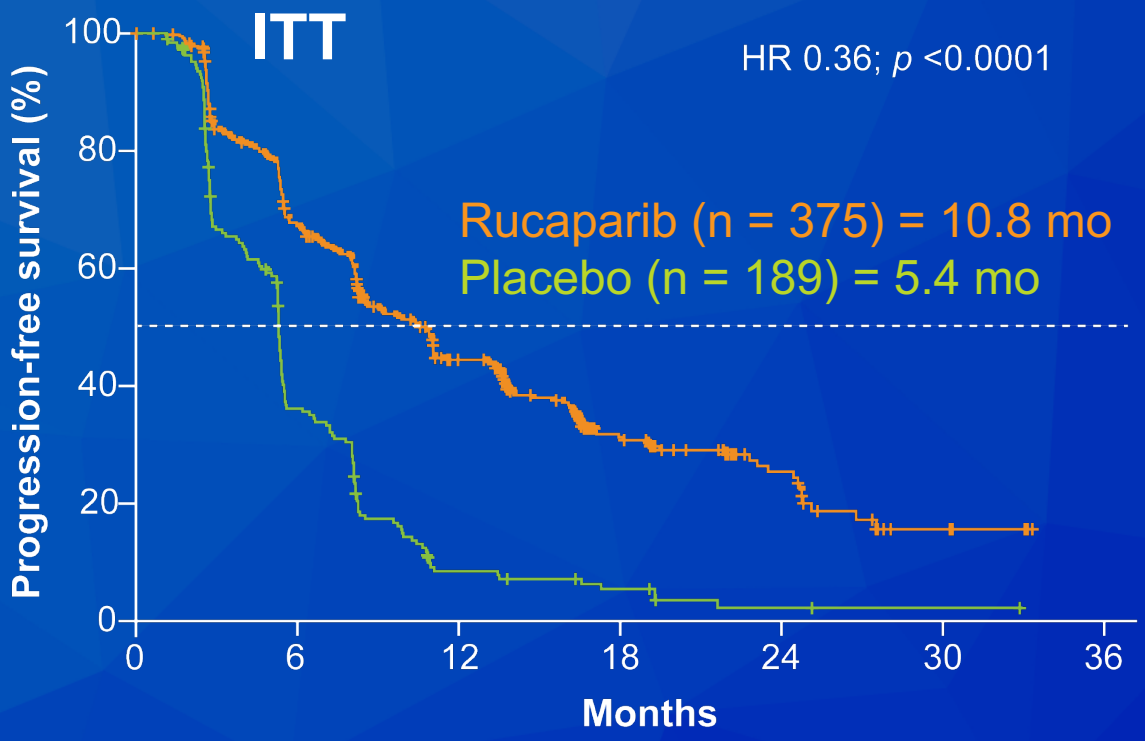
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm533873.htm

Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial

Robert L Coleman, Amit M Oza, Domenica Lorusso, Carol Aghajanian, Ana Oaknin, Andrew Dean, Nicoletta Colombo, Johanne I Weberpals, Andrew Clamp, Giovanni Scambia, Alexandra Leary, Robert W Holloway, Margarita Amenedo Gancedo, Peter C Fong, Jeffrey C Goh, David M O'Malley, Deborah K Armstrong, Jesus Garcia-Donas, Elizabeth M Swisher, Anne Floquet, Gottfried E Konecny, Iain A McNeish, Clare L Scott, Terri Cameron, Lara Maloney, Jeff Isaacson, Sandra Goble, Caroline Grace, Thomas C Harding, Mitch Raponi, James Sun, Kevin K Lin, Heidi Giordano, Jonathan A Ledermann*, on behalf of the ARIEL3 investigators†*

Lancet 2017;390(10106):1949-61.

ARIEL3: PFS by Investigator Assessment (INV)



Subgroup analysis of PFS by INV	Rucaparib	Placebo	HR	*p*-value
Pts with BRCAm dx (n = 130, 66)	16.6 mo	5.4 mo	0.23	<0.0001
Pts with HRD dx (n = 236, 118)	13.6 mo	5.4 mo	0.32	<0.0001

HRD = homologous recombination deficient carcinoma; dx = disease

Coleman RL et al. *Lancet* 2017;390(10106):1949-61.

ARIEL3: Select Adverse Events

Event	Rucaparib (n = 372)		Placebo (n = 189)	
	All	Grade 3/4	All	Grade 3/4
Nausea	75%	4%	37%	1%
Fatigue/asthenia	69%	7%	44%	3%
Vomiting	37%	4%	15%	1%
Anemia	37%	19%	6%	1%
Increased ALT/AST	34%	10%	4%	0%
Thrombocytopenia	28%	5%	3%	0%
Neutropenia	18%	7%	5%	2%
Dyspnea	13%	0%	7%	0%

Coleman RL et al. *Lancet* 2017;[Epub ahead of print].

Editorial — Dr Secord

ARIEL3 is a double-blind, randomized, placebo-controlled, phase III trial of rucaparib (600 mg twice daily) versus placebo as maintenance treatment for ovarian cancer patients with platinum-sensitive, recurrent ovarian cancer following complete response or partial response to platinum-based chemotherapy. Rucaparib, a poly(ADP-ribose) polymerase inhibitor, has FDA approval for treatment in women with recurrent ovarian carcinoma harboring a tumor BRCA mutation. Progression-free survival was evaluated using an ordered step-down procedure for three nested cohorts: patients with germline or somatic BRCA mutations, patients with homologous recombination deficiencies (HRD: BRCA mutant or BRCA wild type and high loss of heterozygosity), and the intention-to-treat population.

Editorial — Dr Secord (continued)

564 eligible patients were randomly assigned to receive rucaparib (n=375) or placebo (n=189).

Median progression-free survival was significantly longer with rucaparib in all cohorts: 16.6 vs 5.4 months, HR=0.23, CI=0.16-0.34, p<0.0001 in women with BRCA-mutant carcinoma; 13.6 vs 5.4 months, HR=0.32, CI=0.24-0.42, p<0.0001 in women with HRD; and 10.8 vs 5.4 months, HR=0.36, CI=0.30-0.45, p<0.0001 in the intention-to-treat population. The most common grade >3 adverse events in the rucaparib group were anemia (19%) and increased alanine or aspartate aminotransferase concentration (10%).

Similar to the other reported PARPi maintenance therapy trials, rucaparib improves disease control in women with platinum-sensitive, relapsed ovarian cancer.

Editorial — Dr Secord (continued)

The findings confirm that maintenance PARPi is a standard-of-care option for all women with platinum-sensitive cancer. The greatest magnitude of benefit is seen in those with a tumor BRCA1/2 mutation and HRD+ disease. Overall toxicities with rucaparib were manageable with dose modification.

Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial

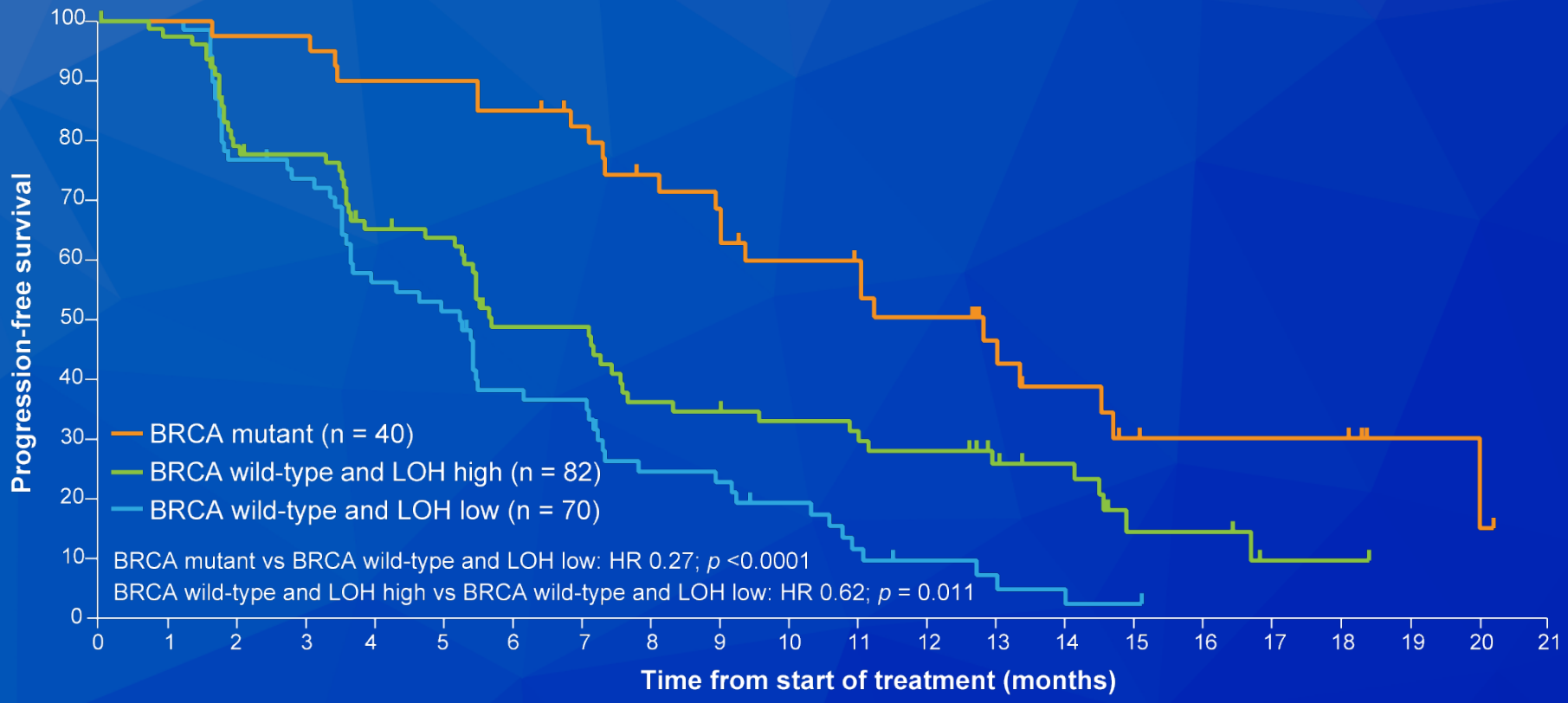
Elizabeth M Swisher, Kevin K Lin*, Amit M Oza, Clare L Scott, Heidi Giordano, James Sun, Gottfried E Konecny, Robert L Coleman, Anna V Tinker, David M O'Malley, Rebecca S Kristeleit, Ling Ma, Katherine M Bell-McGuinn, James D Brenton, Janiel M Cragun, Ana Oaknin, Isabelle Ray-Coquard, Maria I Harrell, Elaina Mann, Scott H Kaufmann, Anne Floquet, Alexandra Leary, Thomas C Harding, Sandra Goble, Lara Maloney, Jeff Isaacson, Andrew R Allen, Lindsey Rolfe, Roman Yelensky, Mitch Raponi, Iain A McNeish**

Lancet Oncol 2017;18(1):75-87.

Rucaparib in Patients with Relapsed, Primary Platinum-Sensitive High-Grade Ovarian Carcinoma with Germline or Somatic *BRCA* Mutations: Integrated Summary of Efficacy and Safety from the Phase II Study ARIEL2

Konecny GE et al. *Proc SGO* 2017;Abstract 1.

ARIEL2 Part 1: PFS After Rucaparib Therapy

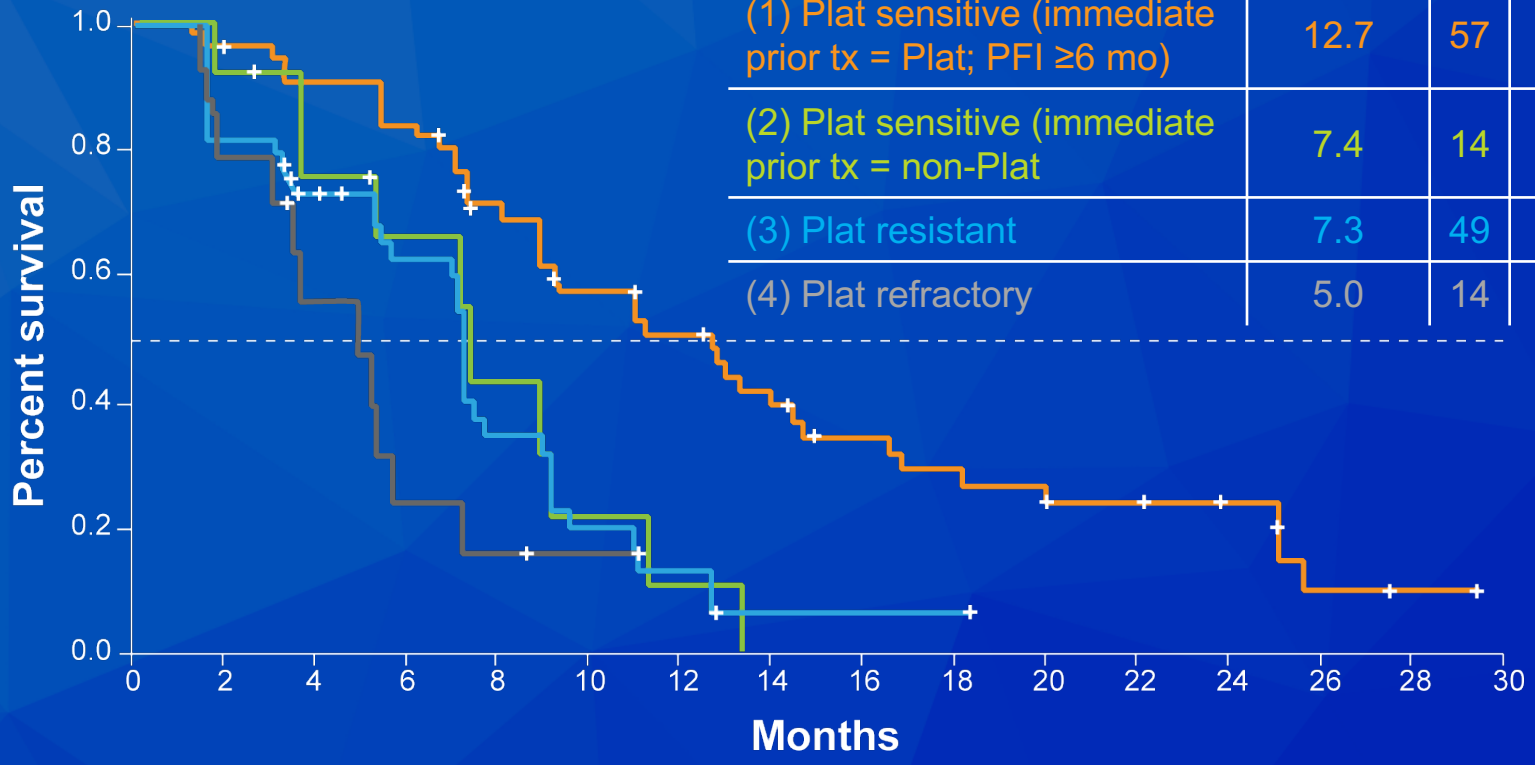


After rucaparib therapy	BRCAm (n = 40)	BRCAwt and LOH-high (n = 82)	BRCAwt and LOH-low (n = 70)
Median PFS	12.8 mo	5.7 mo	5.2 mo

LOH = loss of heterozygosity

Swisher EM et al. *Lancet Oncol* 2017;18(1):75-87.

ARIEL2: PFS in Patients with BRCA-Mutant Ovarian Cancer



Subgroup	Median, mo	n	+ Censored, %
(1) Plat sensitive (immediate prior tx = Plat; PFI ≥6 mo)	12.7	57	30%
(2) Plat sensitive (immediate prior tx = non-Plat	7.4	14	29%
(3) Plat resistant	7.3	49	27%
(4) Plat refractory	5.0	14	21%

PFI = progression-free interval; Plat = platinum; tx = treatment

- The ORR in patients with *BRCA*m (germline or somatic) relapsed high-grade ovarian cancer was greatest in platinum-sensitive patients
  - Range 52%-86% depending on the number of prior therapies

Konecny GE et al. *Proc SGO* 2017;Abstract 1.

Editorial — Dr Secord

ARIEL2 is a two-part, phase 2 study of rucaparib (600 mg BID), an oral PARPi, in women with recurrent platinum-sensitive ovarian cancer (OC). ARIEL2 assessed tumor genomic loss of heterozygosity (LOH) to predict rucaparib response. Patients were classified based on tumor mutational analysis: BRCA mutant (deleterious germline or somatic), BRCA wild type and LOH-high (LOH-high), or BRCA wild type and LOH-low (LOH-low). In ARIEL2, part 1, 206 were enrolled and 192 patients could be classified into the prespecified subgroups.

Median progression-free survival after rucaparib treatment was 12.8, 5.7, and 5.2 months in the BRCA mutant, LOH-high, and LOH-low subgroups, respectively.

Editorial — Dr Secord (continued)

Progression-free survival was significantly longer in the BRCA mutant and LOH-high subgroups compared with the LOH-low subgroup. An update of the study, part 2, included patients who received 3-4 prior lines of chemotherapy. Fifty-eight patients who enrolled in ARIEL2 part 1 (n=41) or part 2 (n = 17) who had somatic or germline BRCA mutations were assessed for objective response rate (ORR). The ORR was 69.0%; median duration of response was 9.2 months. The most common grade ≥3 toxicities were anemia and elevations in alanine aminotransferase or aspartate aminotransferase.

The results suggest that biomarkers beyond BRCA mutations, such as LOH, can identify patients with BRCA wild-type platinum-sensitive OC who may benefit from PARPi.

Editorial — Dr Secord (continued)

Rucaparib demonstrated high anti-tumor activity in OC with tumor BRCA mutations. The results led to FDA approval of rucaparib in conjunction with a companion biomarker for women with recurrent OC and tumor BRCA mutations after 2 prior chemotherapies.

Select Hematologic and Gastrointestinal Adverse Events Associated with PARP Inhibitors

Hematologic toxicity	Grade	Olaparib[1]	Rucaparib[2]	Niraparib[3]
Anemia	All grades	90%	67%	50%
	Grades 3 and 4	15%	23%	25%
Thrombocytopenia	All	30%	39%	61%
	Grades 3 and 4	3%	6%	34%
Neutropenia	All	25%	35%	30%
	Grades 3 and 4	7%	10%	20%
Gastrointestinal toxicity	**Grade**	**Olaparib[1]**	**Rucaparib[2]**	**Niraparib[3]**
Nausea	All grades	64%	77%	74%
	Grades 3 and 4	3%	5%	3%
Constipation	All	21%[4]	40%	40%
	Grades 3 and 4	0%[4]	2%	0.5%
Vomiting	All	43%	46%	34%
	Grades 3 and 4	4%	4%	2%

[1] FDA package insert; [2] FDA package insert; [3] Mirza MR et al. *N Engl J Med* 2016;
[4] Ledermann J et al. *Lancet Oncol* 2014;15(8):852-61.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

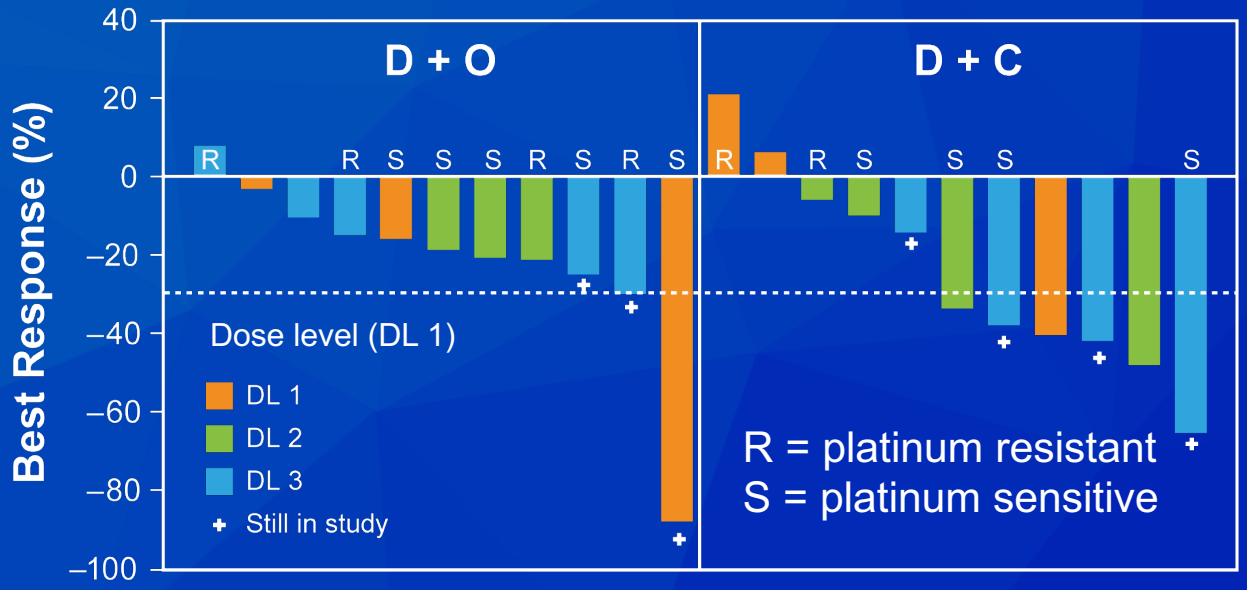
Safety and Clinical Activity of the Programmed Death-Ligand 1 Inhibitor Durvalumab in Combination With Poly (ADP-Ribose) Polymerase Inhibitor Olaparib or Vascular Endothelial Growth Factor Receptor 1-3 Inhibitor Cediranib in Women's Cancers: A Dose-Escalation, Phase I Study

Jung-Min Lee, Ashley Cimino-Mathews, Cody J. Peer, Alexandra Zimmer, Stanley Lipkowitz, Christina M. Annunziata, Liang Cao, Maria I. Harrell, Elizabeth M. Swisher, Nicole Houston, Dana-Adriana Botesteanu, Janis M. Taube, Elizabeth Thompson, Aleksandra Ogurtsova, Haiying Xu, Jeffers Nguyen, Tony W. Ho, William D. Figg and Elise C. Kohn

J Clin Oncol 2017;35(19):2193-202.

Phase I Dose-Escalation Study: Efficacy

Response	Durvalumab (D) + olaparib (O) (n = 12)	D + cediranib (C) (n = 12)
ORR	2 (17%)	6 (50%)
DCR at ≥4 mo	10 (83%)	Not reported



DL 1 = 10 mg/kg every 2 wks D + 200 mg bid O or 20 mg once daily C;
DL 2 = 10 mg/kg every 2 wks D + 300 mg bid O or 30 mg once daily C;
DL 3 = 1,500 mg every 4 wks D + 300 mg bid O or 20 mg (5 d on/2 d off) C – RP2D

Lee JM et al. *J Clin Oncol* 2017;35(19):2193-202.

Phase I Dose-Escalation Study: Select Adverse Events

All grade (n)	D + O (n = 12)	D + once daily C (n = 8)	D + intermittent C (n = 6)
Lymphopenia	9	6	0
Fatigue	9	6	4
Anemia	5	5	0
Abdominal pain	5	3	0
Diarrhea	4	7	3
Thrombocytopenia	3	6	1
Neutropenia	1	0	0
Pulmonary hypertension	0	1	0

No dose-limiting toxicity was recorded with D + O.

Lee JM et al. *J Clin Oncol* 2017;35(19):2193-202.

Editorial — Dr Secord

This phase I study assessed a programmed death-ligand 1 inhibitor, durvalumab, combined with either olaparib (PARPi) or cediranib (vascular endothelial growth factor receptor inhibitor). Durvalumab was administered at 10 mg/kg every 2 weeks or 1,500 mg every 4 weeks with either olaparib tablets twice daily or cediranib. The primary endpoint was the recommended phase II dose (RP2D). 26 women were enrolled.

No dose-limiting toxicity was recorded with durvalumab plus olaparib. Durvalumab plus olaparib demonstrated an 83% disease control rate (two partial responses [≥15 and ≥11 months] and eight stable diseases [≥4 months]). The RP2D was durvalumab 1,500 mg every 4 weeks with olaparib 300 mg twice a day.

Editorial — Dr Secord (continued)

Combination durvalumab and cediranib was more challenging to administer. The cediranib intermittent schedule was examined because of significant toxicity on the daily schedule. Treatment-emergent AEs included hypertension, diarrhea, pulmonary embolism, pulmonary hypertension, and lymphopenia.

Durvalumab exposure increased cediranib area under the curve and maximum plasma concentration on the daily, but not intermittent, schedules. Durvalumab plus intermittent cediranib yielded a 75% disease control rate (six partial responses [≥5 to ≥8 months] and three stable diseases [≥4 months]).

Editorial — Dr Secord (continued)

The RP2D was durvalumab 1,500 mg every 4 weeks with cediranib 20 mg 5 days on/2 days off. Response to therapy was independent of PD-L1 expression. In conclusion, durvalumab combined with either olaparib or cediranib is tolerable and active in recurrent gynecologic cancer. Phase II studies with biomarker evaluation are ongoing.

JOURNAL OF CLINICAL ONCOLOGY

BIOLOGY OF NEOPLASIA

Somatic *BRCA1/2* Recovery as a Resistance Mechanism After Exceptional Response to Poly (ADP-ribose) Polymerase Inhibition

Stephanie Lheureux, Jeff P. Bruce, Julia V. Burnier, Katherine Karakasis, Patricia A. Shaw, Blaise A. Clarke, S.Y. Cindy Yang, Rene Quevedo, Tiantian Li, Mark Dowar, Valerie Bowering, Trevor J. Pugh, and Amit M. Oza

J Clin Oncol 2017;35(11):1240-9.

Genomic Analysis of High-Grade Serous Ovarian Cancer (HGSOC) After PARP Inhibitor Therapy

- Pts with HGSOC without germline BRCA1/2 mutations who experienced responses to olaparib (n = 3)
- Somatic disruption of BRCA1/2 was observed in all 3 patients at diagnosis
  - This was followed by subsequent BRCA recovery upon progression by copy number gain and/or upregulation of the remaining functional allele in 2 pts.
  - 1 pt who had a tumor at diagnosis with biallelic somatic deletion and loss-of-function mutation experienced ongoing response (>7 y).
- Data suggest that biallelic loss of BRCA1/2 in cancer cells may be a potential marker of long-term response to PARP inhibitors and that the restoration of homologous repair function may be a mechanism of disease resistance.

Lheureux S et al. *J Clin Oncol* 2017;35(11):1240-9.

Editorial — Dr Secord

Responses to PARPi have been observed in ovarian cancer patients without BRCA-mutation associated disease. In addition, despite initial response to PARPi, eventually resistance may be observed. This retrospective study sought to determine mechanisms of durable response and resistance to olaparib therapy. Extensive analysis of high-grade serous cancers from three patients without germline BRCA mutations who experienced exceptional responses to olaparib was performed. Analysis included integrated exome, low-pass genome, and RNA sequence analysis of the cancers at diagnosis and relapse. The patients had recurrent platinum-sensitive high-grade serous cancer and had been treated >5 years with olaparib therapy as a single agent.

Editorial — Dr Secord (continued)

All three patients had somatic disruption of BRCA1/2 at diagnosis, followed by subsequent BRCA recovery upon progression by copy number gain and/or upregulation of the remaining functional allele in two patients. The third patient with ongoing response (>7 years) had a tumor at diagnosis with biallelic somatic deletion and loss-of-function mutation, thereby lacking a functional allele for recovery of BRCA1 activity and indicating a potential cure.

These findings indicate the importance of tumor testing beyond germline genetic testing to identify patients who may benefit from PARPi as well as identify mechanisms of recurrence. Biallelic loss of BRCA1/2 may be a potential biomarker of long-term response to PARP inhibition.

Editorial — Dr Secord (continued)

While restoration of homologous repair function may be a mechanism of disease resistance, that could be exploited with novel therapies in conjunction with PARPi.

A 65-year-old woman with advanced ovarian cancer is started on standard-dose niraparib. Her pretreatment platelet count is 220,000 but drops to 90,000 after 10 days of treatment. What would be your most likely approach?

a. Discontinue niraparib
b. Continue niraparib at a reduced dose
c. Hold niraparib until platelet count returns to normal and restart at the same dose
d. Hold niraparib until platelet count returns to normal and restart at a reduced dose
e. Other

A 60-year-old woman with recurrent high-grade serous ovarian cancer is started on rucaparib (600 mg BID). During the second cycle, serum creatinine increases from 0.8 mg/dL to 1.83 mg/dL. What is the most likely cause of the increase in creatinine?

a. Renal dysfunction
b. Increase in creatinine without renal dysfunction
c. I don’t know

Ovarian Cancer — Drs Birrer and Moore

Chemotherapy with or without bevacizumab in ovarian cancer

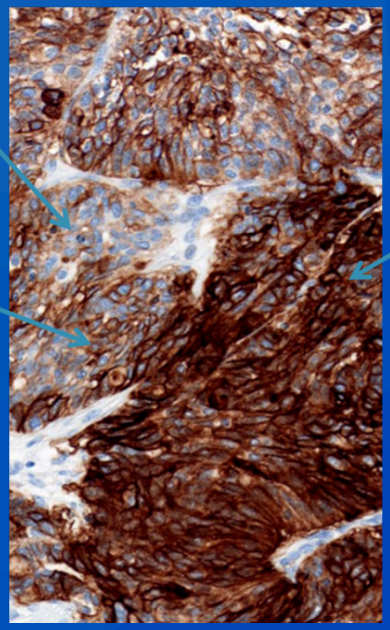
Germline and somatic mutations in ovarian cancer

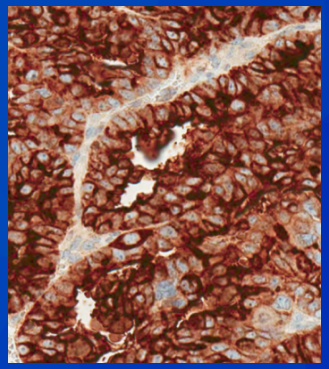
PARP inhibitors: Efficacy, toxicity and ongoing trials

Novel investigational agents

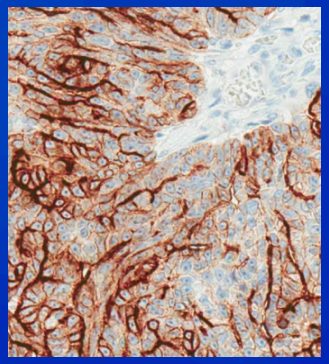
Folate Receptor Alpha Expression Distribution

Staining & Scoring

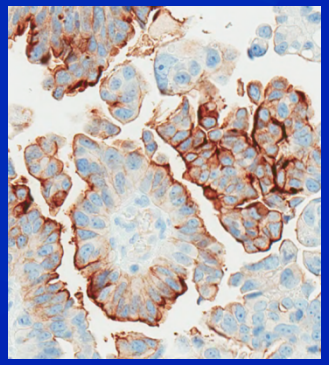




High



Medium



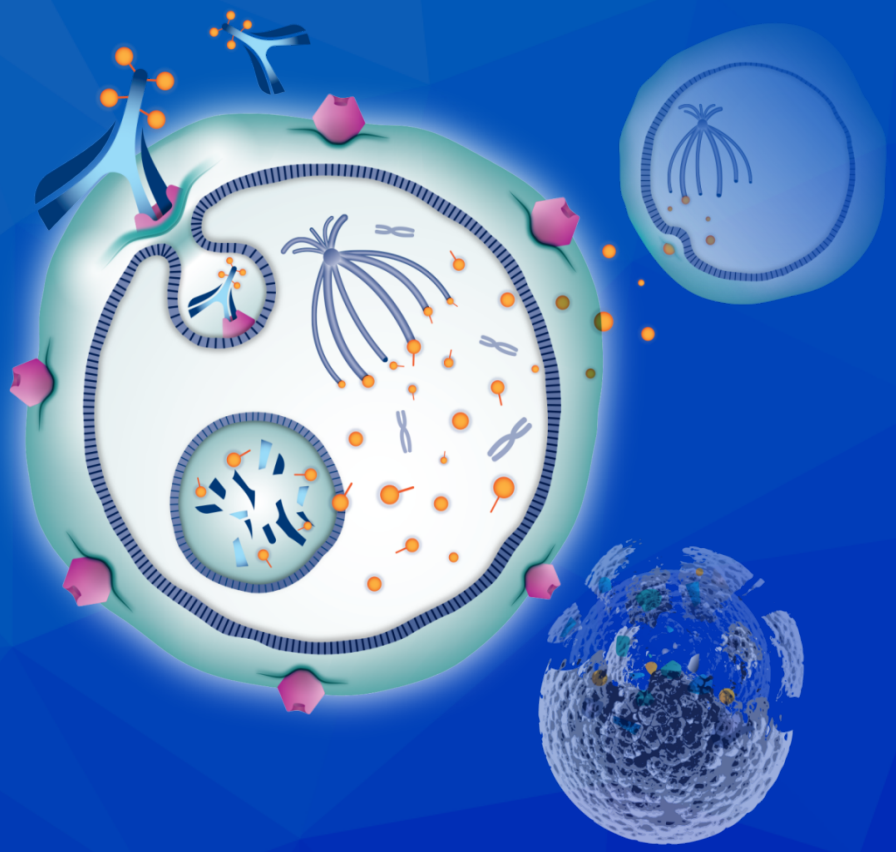
Low

Membrane staining	Intensity score	Percentage of cells (%)
Strong	3	60
Moderate	2	25
Weak	1	10
Negative	0	5

hscore = 240/high expression

Courtesy of Michael J Birrer, MD, PhD

Mirvetuximab Soravtansine (IMGN853) Mechanism of Action



AN INTEGRATED SYSTEM

Linker

- Cleavable linker stable in the blood stream
- Bystander killing of neighboring cancer cells

Ultra-potent anticancer agent

- DM4 — a potent tubulin-targeting agent

Antibody (Ab)

- A folate receptor α (FRα)-binding antibody

Target

- Highly expressed in ovarian and other cancers

Martin LP et al. AACR/EORTC/NCI 2015;Poster C47.

JOURNAL OF CLINICAL ONCOLOGY

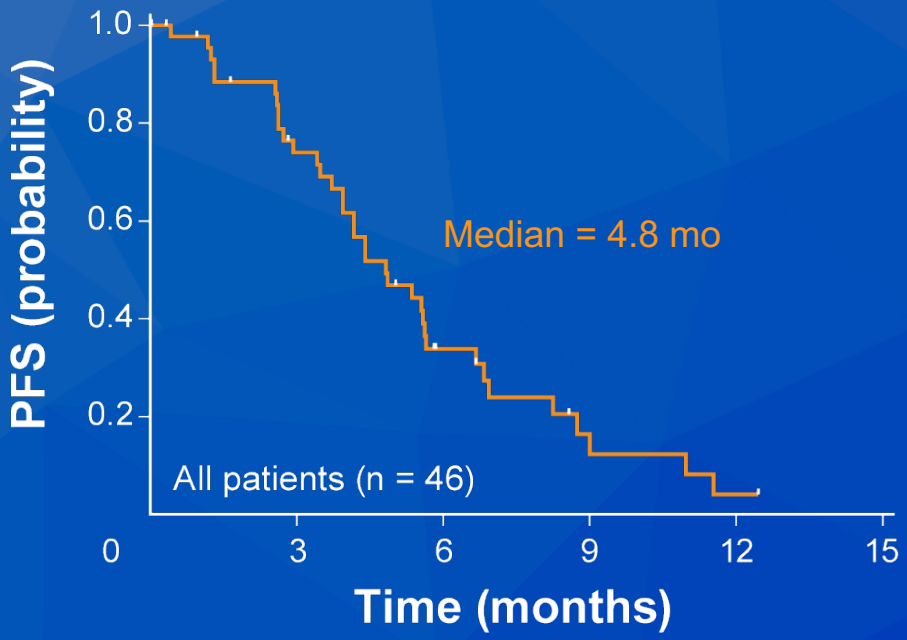
ORIGINAL REPORT

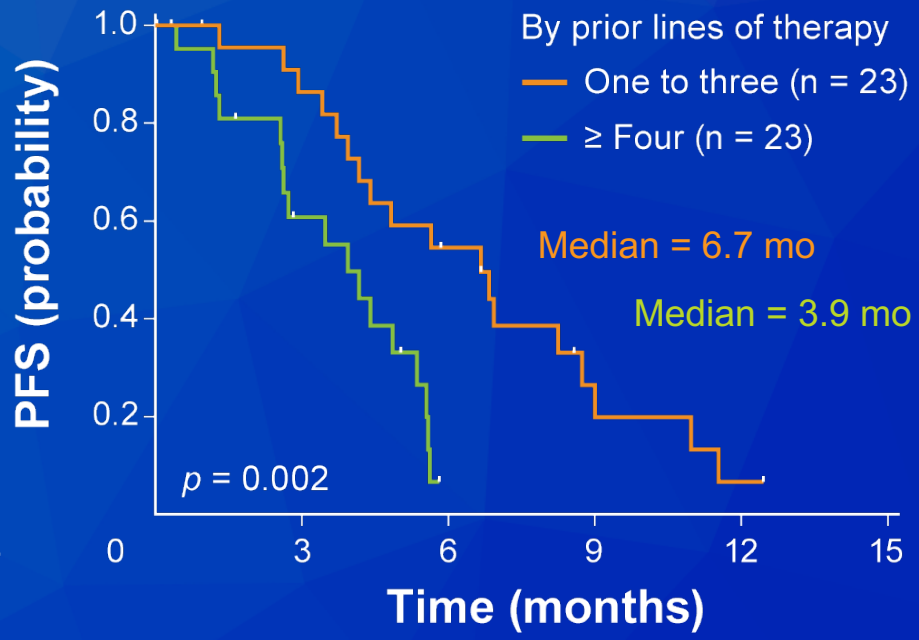
Safety and Activity of Mirvetuximab Soravtansine (IMGN853), a Folate Receptor Alpha–Targeting Antibody–Drug Conjugate, in Platinum-Resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer: A Phase I Expansion Study

Kathleen N. Moore, Lainie P. Martin, David M. O'Malley, Ursula A. Matulonis, Jason A. Konner, Raymond P. Perez, Todd M. Bauer, Rodrigo Ruiz-Soto, and Michael J. Birrer

J Clin Oncol 2017;35(10):1112-8.

Phase I Trial of Mirvetuximab Soravtansine





Response	ORR	CR	PR
All patients (n = 46)	12 (26.1%)	1 (2.2%)	11 (23.9%)
Frα low (n = 9)	2 (22.2%)	0	2 (22.2%)
Frα medium (n = 14)	4 (28.6%)	0	4 (28.6%)
Frα high (n = 23)	6 (26.1%)	1 (4.3%)	5 (21.7%)

FR = folate receptor

Moore KN et al. *J Clin Oncol* 2017;35(10):1112-8.

Phase I Trial of Mirvetuximab Soravtansine: Select Adverse Events

Event (n = 46)	Grade 1	Grade 2	Grade 3
Diarrhea	11 (23.9%)	8 (17.4%)	1 (2.2%)
Nausea	11 (23.9%)	5 (10.9%)	1 (2.2%)
Blurred vision	9 (19.6%)	10 (21.7%)	0
Increased AST	8 (17.4%)	2 (4.3%)	1 (2.2%)
Neuropathy	7 (15.2%)	5 (10.9%)	1 (2.2%)
Keratopathy	6 (13.0%)	6 (13.0%)	0
Fatigue	6 (13.0%)	6 (13.0%)	2 (4.3%)
Hypokalemia	4 (8.7%)	0	1 (2.2%)
Anemia	2 (4.3%)	3 (6.5%)	1 (2.2%)

1 pt experienced Grade 4 febrile neutropenia and septic shock, which resolved after withdrawal from the study; no fatalities resulting from related AEs observed.

Moore KN et al. *J Clin Oncol* 2017;35(10):1112-8.

Editorial — Dr Matulonis

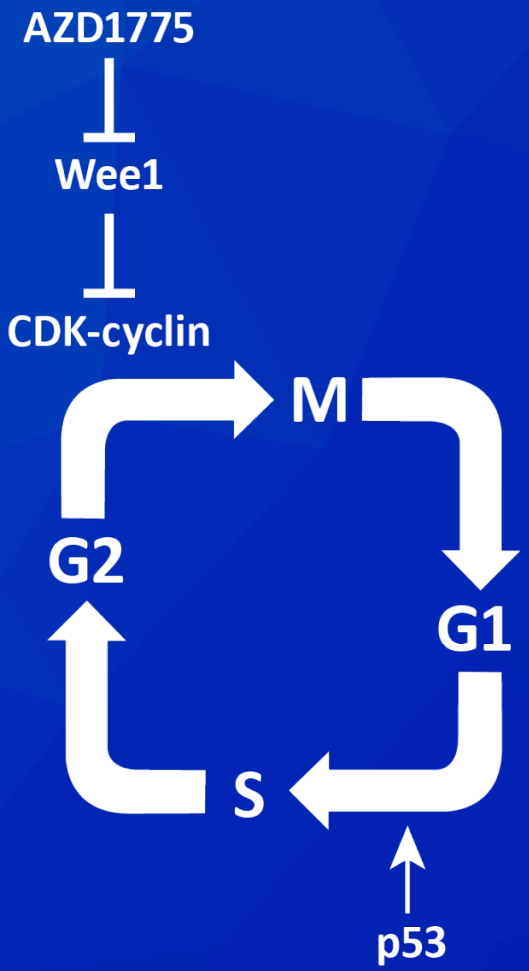
This paper represents the expansion cohort testing the 6 mg/kg IV every 3 weeks in patients with platinum resistant ovarian cancer, folate receptor alpha (FRA) positivity as defined as ≥25% of tumor cells with at least 2+ staining intensity and PS 0 or 1. Most patients had high grade serous cancer; 50% had between 1-3 prior lines and 50% had ≥4 lines. The most common toxicities (all grades) were diarrhea (44%), blurred vision (41.3%), nausea (37%), fatigue (30.4%), neuropathy (28.3%), keratopathy (26.1%). Keratopathy included corneal cysts, corneal disorders, corneal epithelial microcysts, keratitis, keratopathy, limbal stem cell deficiency, and punctate keratitis.

Editorial — Dr Matulonis (continued)

The recognition of this toxicity led to the use of daily lubricating eye drops and also use of corticosteroid drops. The most frequent grade 3 toxicities were fatigue and hypotension (both 4%) – one pt had grade 4 FN and sepsis. No deaths occurred on study. Overall RR was 26% with one CR and 11 PRs. RR for pts with 1-3 prior lines was 39% and 4 or more, 13%. For 1-3 prior line pts, PFS was 6.7 months, and 3.9 months for 4 or more prior therapies. For FRA expression low pts, RR was 22.2%, FRA medium 28.6% and FRA high 26.1%. The results of this study, especially those of the less heavily pretreated patients, led to the phase III study FORWARD I randomizing pts with platinum resistant ovarian cancer to either mirva vs MD's choice; pts have to have 3 or fewer previous treamtents and medium or high FRA expression.

AZD1775 Sensitizes TP53-Mutant Cancers to DNA-Damaging Agents

- TP53 is mutated in ~97% of high-grade serous ovarian cancer cases, which results in loss of regulation of the G1/S cell cycle checkpoint
- To repair damaged DNA, TP53-mutant tumors are therefore more dependent on the G2/M cell cycle checkpoint, which is regulated by Wee1 kinase
- AZD1775 is a small-molecule Wee1 inhibitor and is predicted to sensitize TP53-mutant cancer to genotoxic agents through deregulation of the G2/M checkpoint



Oza A et al. *Proc ASCO* 2015;Abstract 5506.

JOURNAL OF CLINICAL ONCOLOGY

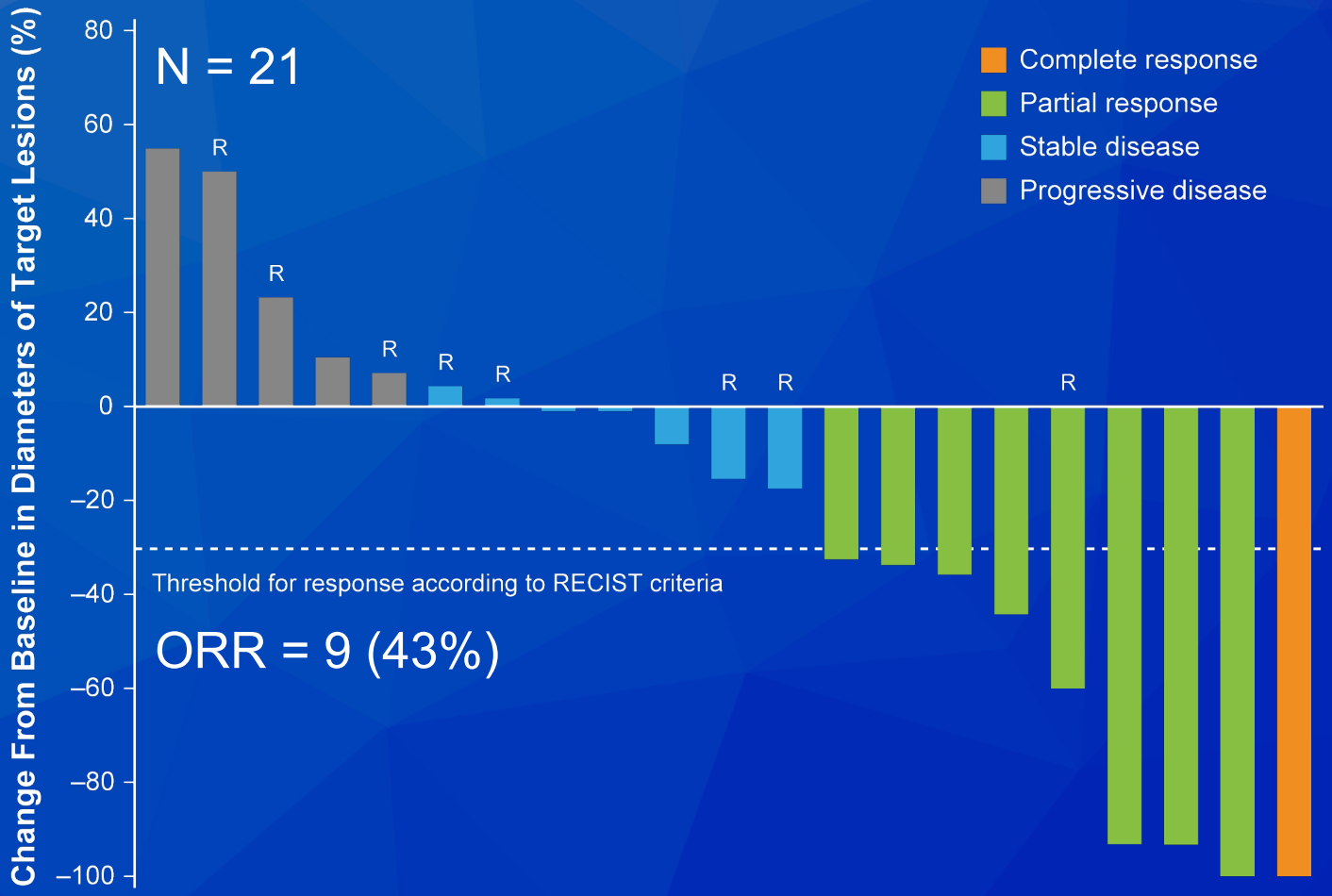
ORIGINAL REPORT

Phase II Study of WEE1 Inhibitor AZD1775 Plus Carboplatin in Patients With *TP53*-Mutated Ovarian Cancer Refractory or Resistant to First-Line Therapy Within 3 Months

Suzanne Leijen, Robin M.J.M. van Geel, Gabe S. Sonke, Daphne de Jong, Efraim H. Rosenberg, Serena Marchetti, Dick Pluim, Erik van Werkhoven, Shelonitda Rose, Mark A. Lee, Tomoko Freshwater, Jos H. Beijnen, and Jan H.M. Schellens

J Clin Oncol 2016;34(36):4354-61.

Phase II Trial of the WEE1 Inhibitor AZD1775



- Median PFS = 5.3 mo
- Median OS = 12.6 mo

Leijen S et al. *J Clin Oncol* 2016;34(36):4354-61.

AZD1775: Select Adverse Events

Event (n = 23)	All	Grade 3	Grade 4
Fatigue	20 (87%)	1 (4%)	0
Nausea	18 (78%)	1 (4%)	0
Thrombocytopenia	16 (70%)	0	11 (48%)
Diarrhea	16 (70%)	1 (4%)	0
Anemia	14 (61%)	2 (9%)	0
Vomiting	11 (48%)	0	0
Hypomagnesemia	11 (48%)	2 (9%)	0
Neutropenia	10 (43%)	4 (17%)	5 (22%)
Peripheral sensory neuropathy	5 (22%)	0	0

Leijen S et al. *J Clin Oncol* 2016;34(36):4354-61.

Editorial — Dr Matulonis

Phase II study of AZD1775 plus carboplatin in pts with TP53 mutated ovarian cancer refractory or resistant to first line therapy within 3 months. Primary objective was RR of carboplatin and AZD1775. Carboplatin AUC 5 and AZD1775 225 mg BID for 2.5 days every 21 days. 23 pts enrolled and all pts had one line of prior therapy; 39% pts were refractory to first line treatment and 61% were platinum resistant. 96% of patients had a p53 mutation; 83% missense, 13% frameshift, 4% nonsense and 4% deletion. 21 Evaluable pts: 24% (5 pts) had PD, 33% (7 pts) had SD, 38% (8 pts) had a PR and one pt (5%) had a CR.

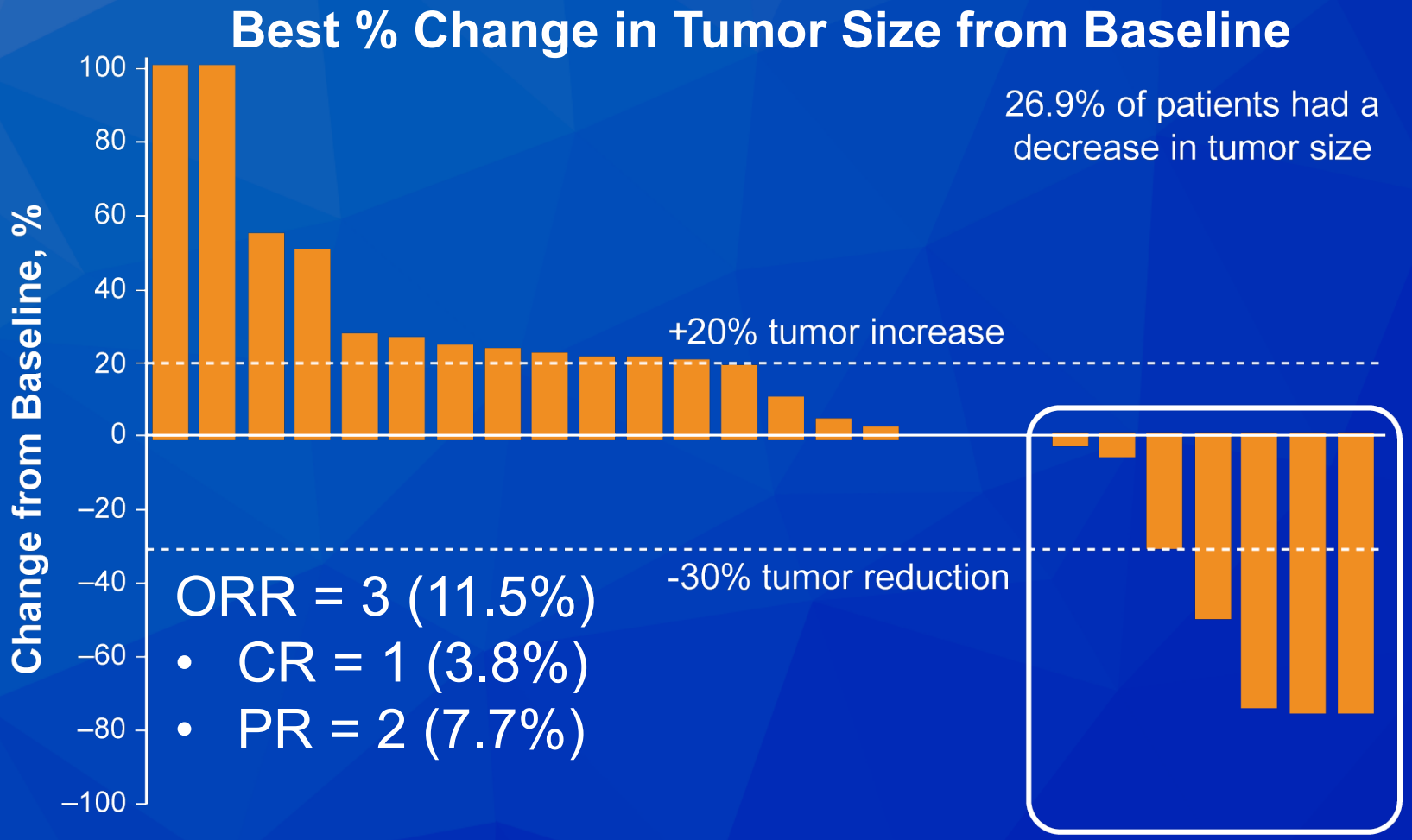
Editorial — Dr Matulonis (continued)

Primary Refractory ovarian cancer is a huge unmet need: 8 pts in this study had primary refractory cancer – 3 pts (38%) had PD, 4 pts (50%) had stable disease and one pt (12%) had a PR. Median PFS for all pts was 5.3 months. Median OS was 12.6 months. The 2 pts with the prolonged responses of >31 and 42 months had mutations in cyclin E and in BRCA1, MYC and cyclin E resp. Grade 3 toxicities: 17% neutropenia, 9% anemia, 4% each of diarrhea, vomiting and fatigue, 9% low magnesium. Grade 2 toxicities: 52% anemia, 39% fatigue, 26% diarrhea, 13% each of thrombocytopenia, nausea, vomiting and neuropathy. These are intriguing results but this regimen will need to be further validated in additional trials.

Pembrolizumab in Patients with PD-L1–Positive Advanced Ovarian Cancer: Updated Analysis of KEYNOTE-028

Varga A et al.
Proc ASCO 2017;Abstract 5513.

KEYNOTE-028: Updated Efficacy Results (N = 26)



- Median PFS = 1.9 mo
- Median OS = 13.8 mo

Varga A et al. *Proc ASCO* 2017;Abstract 5513.

KEYNOTE-028: Select Adverse Events

Event (n = 26)	All Grade
Arthralgia	5 (19.2%)
Nausea	4 (15.4%)
Pruritus	4 (15.4%)
Diarrhea	3 (11.5%)
Asthenia	2 (7.7%)
Hypothyroidism	2 (7.7%)
Onychomadesis	2 (7.7%)
Thrombocytopenia	2 (7.7%)

- Grade 3 treatment-related adverse event (n = 1): Increased transaminase
- No ≥Grade 4 treatment-related adverse event
- No discontinuations due to toxicity

Varga A et al. *Proc ASCO* 2017;Abstract 5513.

Editorial — Dr Matulonis

The abstract from Varga et al presented data for ovarian cancer patients enrolled in the KEYNOTE-028 trial (Study of Pembrolizumab [MK-3475] in Participants With Advanced Solid Tumors). The KEYNOTE trials have been evaluating pembrolizumab in multiple different tumor types. This phase 1b trial KEYNOTE-28 provided data for 26 patients with PD-L1–positive ovarian cancer. Nearly 40% of the patients had received 5 or more lines of therapy. Pembrolizumab was administered at a dose of 10 mg/kg IV every 2 weeks. Disease was assessed by RECIST1.1 every 8 weeks for the first 6 months and then every 12 weeks thereafter. The overall response rate was 11.5%.

Editorial — Dr Matulonis (continued)

The complete response rate was 3.8%, and the partial response rate was 7.7%; all 3 patients who responded completed 2 years of treatment, and the median duration of response was not reached (range, 24.9+ to 26.5+ months). The overall median PFS was 1.9 months. Approximately 60% of patients developed progressive disease, and 27% of patients had stable disease. The safety profile was comparable with other trials of single agent pembrolizumab in other cancer trials. The phase 2 KEYNOTE-100 trial of pembrolizumab in women with advanced ovarian cancer was recently completed.

Ongoing Investigations of Anti-PD-1/PD-L1 Checkpoint Inhibitors in Ovarian Cancer

- 31 ongoing studies specific to ovarian, fallopian tube and peritoneal cancers
- Anti-PD-1/PD-L1 antibodies: Atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab
- Most studies in the platinum-resistant, recurrent setting
- Most studies in combination with bevacizumab, chemotherapy ± bevacizumab, targeted therapy or other immunotherapy
- Several front-line studies in combination with chemotherapy
- 5 Phase III studies identified
  - ATALANTE: Atezolizumab + platinum-containing chemo + bev in late relapse
  - NCI-2016-01081: PLD/atezolizumab ± bevacizumab vs PLD/bevacizumab in platinum-resistant, relapsed
  - JAVELIN Ovarian 200: Avelumab, PLD or the combination in platinum relapsed
  - IMagyn050: Carbo/paclitaxel/bev ± atezolizumab in newly diagnosed Stage III-IV
  - JAVELIN Ovarian 100: Chemo ± avelumab maintenance, chemo → avelumab followed by avelumab maintenance

www.clinicaltrials.gov. Accessed October 2017.

Early Palliative Care is Associated with Improved Quality of End-of-Life Care for Women with High Risk Gynecologic Malignancies

Nevadunsky NS et al.
Proc SGO 2017;Abstract 46.

Early Palliative Care in Women with High-Risk Gynecologic Malignancies (GMs)

- Pts enrolled on study over a 12-month period (n = 96)
  - Pts who received palliative care: 65 (68%)
  - Historical rate for women who received palliative care but died from GMs: 49%
    - $p = 0.014$
- At the time of analysis 28 (29%) were deceased and 24 (25%) had enrolled in hospice.
- Aggressive care at end of life (ACE) scores were significantly higher for women who did not participate in early palliative care:
  - Median = 2.5 vs 0; $p < 0.05$
- Early palliative care is feasible in an ethnically and racially diverse population of women with GMs.

Nevadunsky NS. *Proc SGO* 2017;Abstract 46.

Editorial — Dr Matulonis

Single institution study, 96 pts enrolled with “high risk gyn malignancies” (defined as 5 year prognosis, <30%) were offered a palliative care consult within 12 weeks of cancer diagnosis. 68% of these patients had a palliative care medical consult – compared to historical rate of 49%. Palliative care at the time of cancer dx was associated with decreased aggressive care at the end of life scores, i.e. <3 days of hospice enrollment, death in the ICU etc. This study which ideally would be replicated in a randomized manner is nonetheless important showing the feasibility of offering patients a palliative care consult at new diagnosis and use of less aggressive measures at the end of life.