# Year in Review

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

**October 28, 2017, 8:00 AM – 4:00 PM**
**Orlando, Florida**

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# Disclosures

| | |
|---|---|
| **Contracted Research** | AstraZeneca Pharmaceuticals LP, Eisai Inc, Exelixis Inc, Pfizer Inc |

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# Disclosures

| | |
|---|---|
| **Advisory Committee** | 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 Armstrong

**Current use of chemotherapy with or without bevacizumab in ovarian cancer**

**Germline and somatic mutations in ovarian cancer**

**PARP inhibitors: Efficacy, toxicity and ongoing trials**

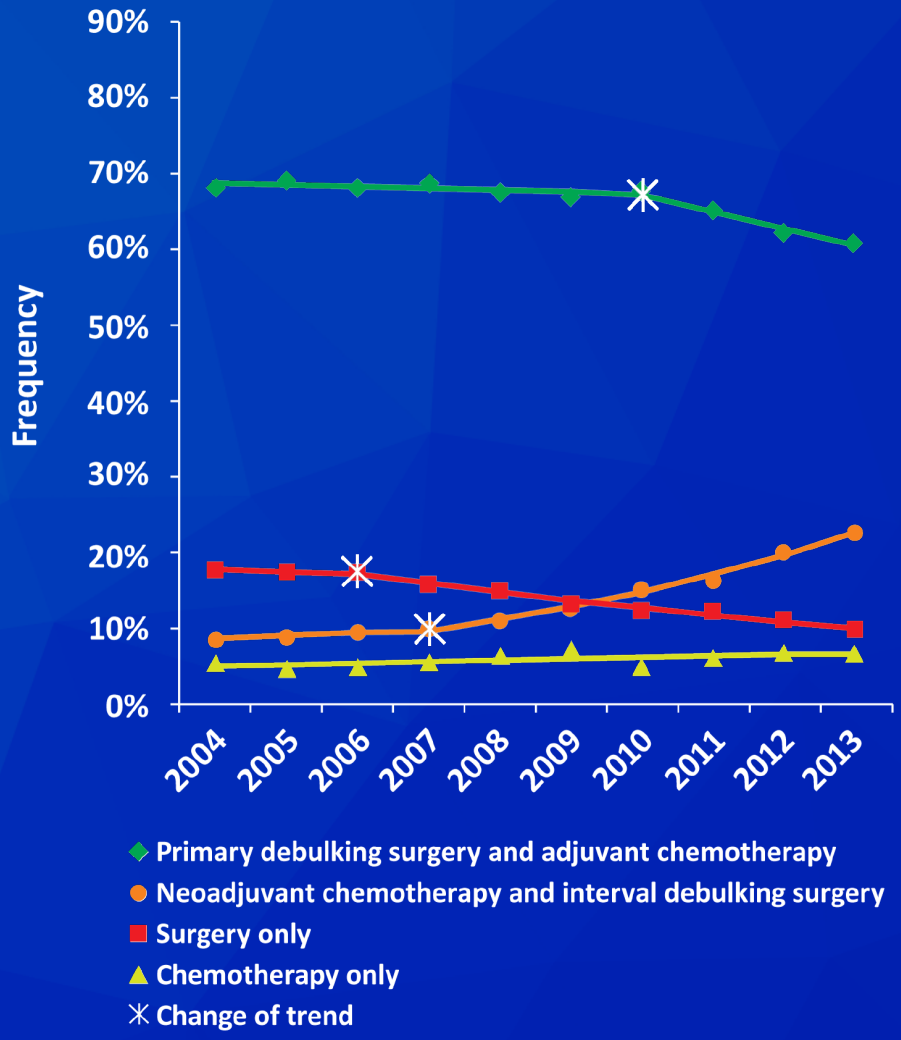
**Novel investigational agents**

**A 50-year-old woman (PS = 0) with Stage IIIA epithelial ovarian cancer (EOC) is s/p primary debulking surgery with no gross residual disease (<1 cm).**
**In general, would you recommend intraperitoneal/intravenous chemotherapy?**

a. Yes
b. No

# 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 ($p < 0.001$)

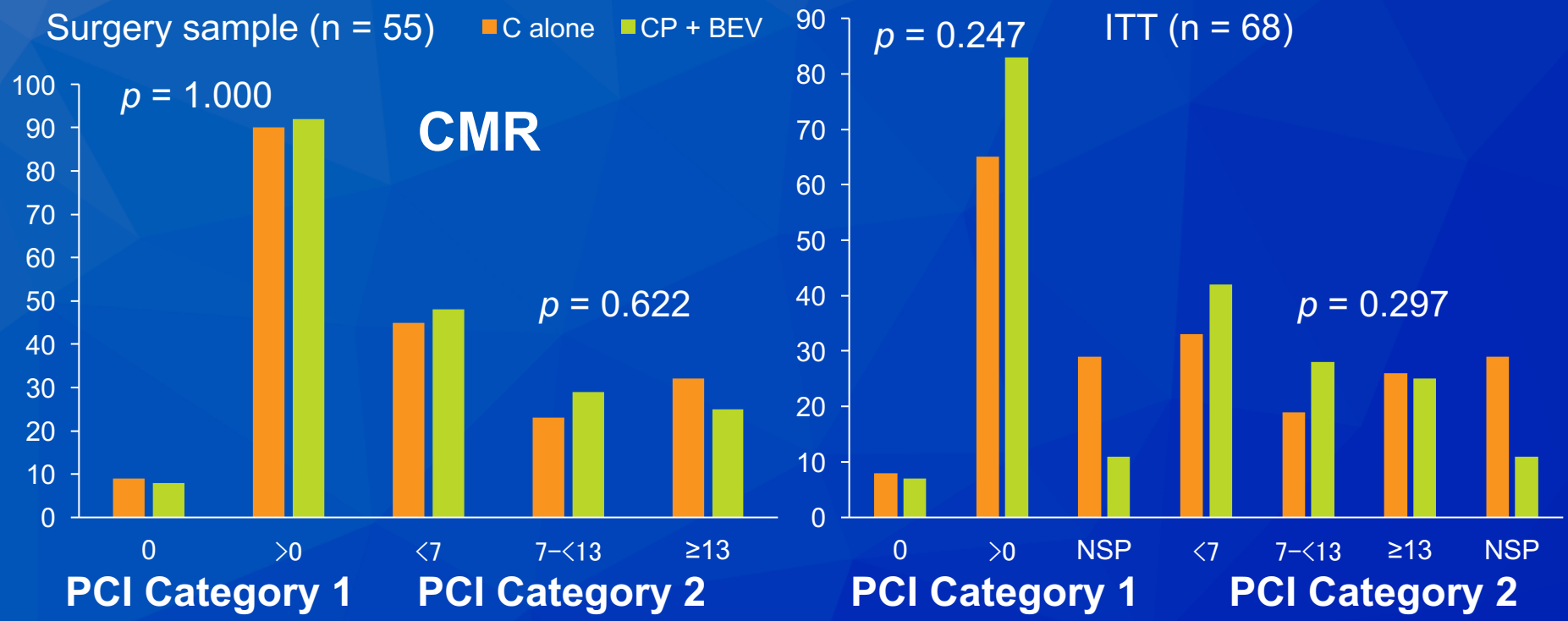



Melamed A et al. *Gynecol Oncol* 2016;143:236-40.

# 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 Armstrong

ICON7 and GOG-0218 showed that bevacizumab with and after front line chemo improves PFS by about two months but has no significant impact on survival. Subgroup analysis of ICON7 suggested that poor-prognosis patients (stage IV and those with bulky disease) may have a benefit from bevacizumab inclusion, but the GOG-0218 population was almost all poor prognosis and did not confirm the finding. Nonetheless, bevacizumab is commonly used with initial chemo, particularly in Europe and Australia. There is now a move toward more neoadjuvant chemotherapy (NACT) in these poor-prognosis patients, but there were concerns about use of bevacizumab, particularly regarding poor wound healing if interval debulking surgery (IDS) was done after NACT with bevacizumab.

# Editorial — Dr Armstrong (continued)

This trial compared NACT alone or with bevacizumab in 68 patients. All patients received bevacizumab with chemo given after IDS. They found that surgery feasibility was greater in those who had bevacizumab but optimal debulking rate was not greater and PFS was not impacted. It is possible that there might have been an impact on PFS if bevacizumab wasn't given to everyone after IDS and the comparison was purer: bevacizumab or no bevacizumab throughout all chemo cycles. Furthermore, this is a small study and may not have been powered sufficiently to see a difference (for the better or for the worse) between the arms.

# Editorial — Dr Armstrong (continued)

The take home message is that if you are a believer in the use of bevacizumab with initial chemotherapy you can probably still use it with NACT without a significant rate of surgical complications.

# 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<br>IV: 41 mo | 0.76 | 0.02 |
| GOG 114/ SWOG 9227[2] | 462 | Stage III, ≤1 cm residual | IP: 63.2 mo<br>IV: 52.2 mo | 0.81 | 0.05 |
| GOG 172[3] | 415 | Stage III, ≤1 cm residual | IP: 65.6 mo<br>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**

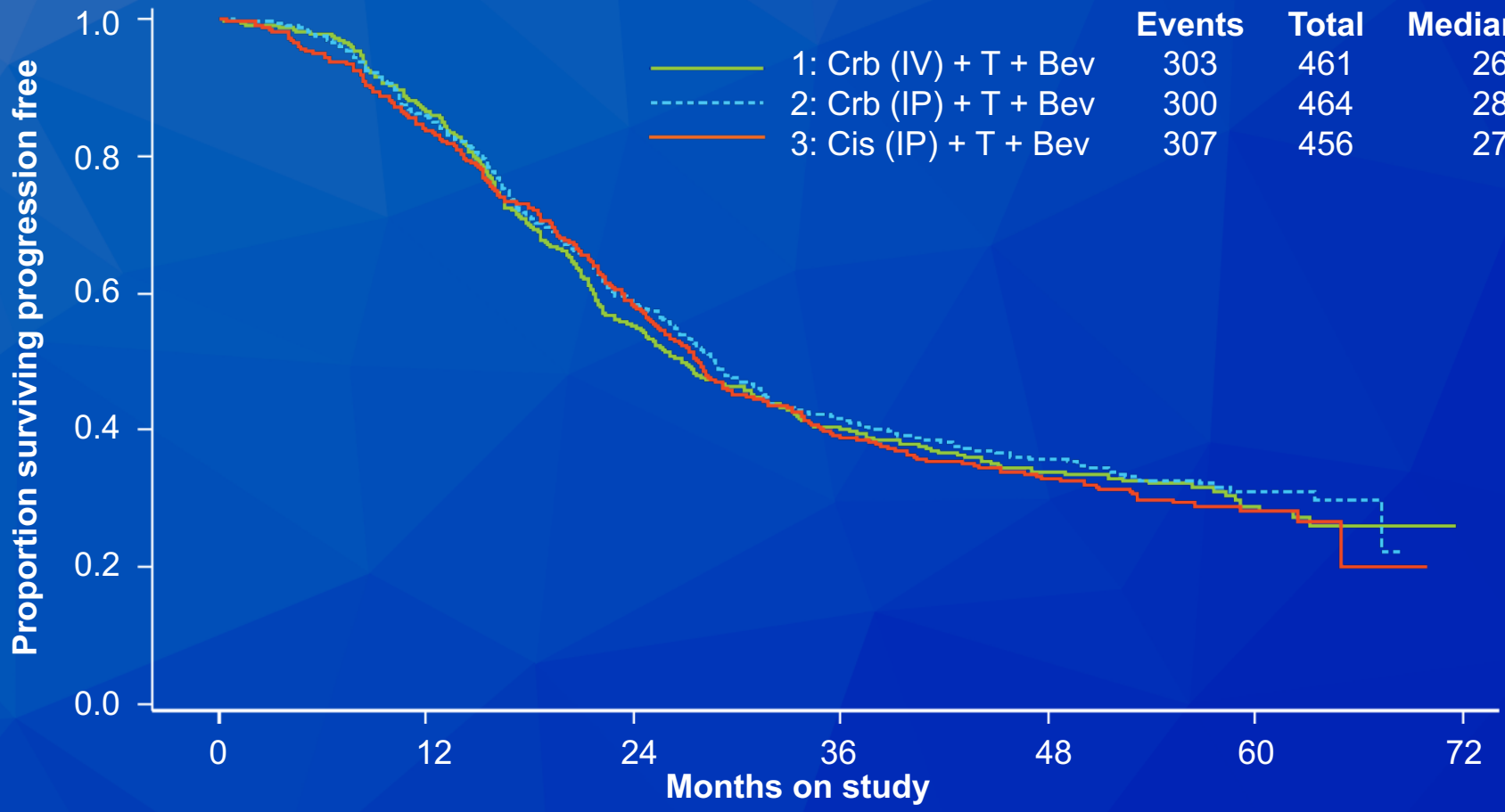
**Paclitaxel 80 mg/m$^2$ IV D1, 8, 15**
**Carboplatin AUC 6 IP D1**
**Bevacizumab 15 mg/kg q3wk**

**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.

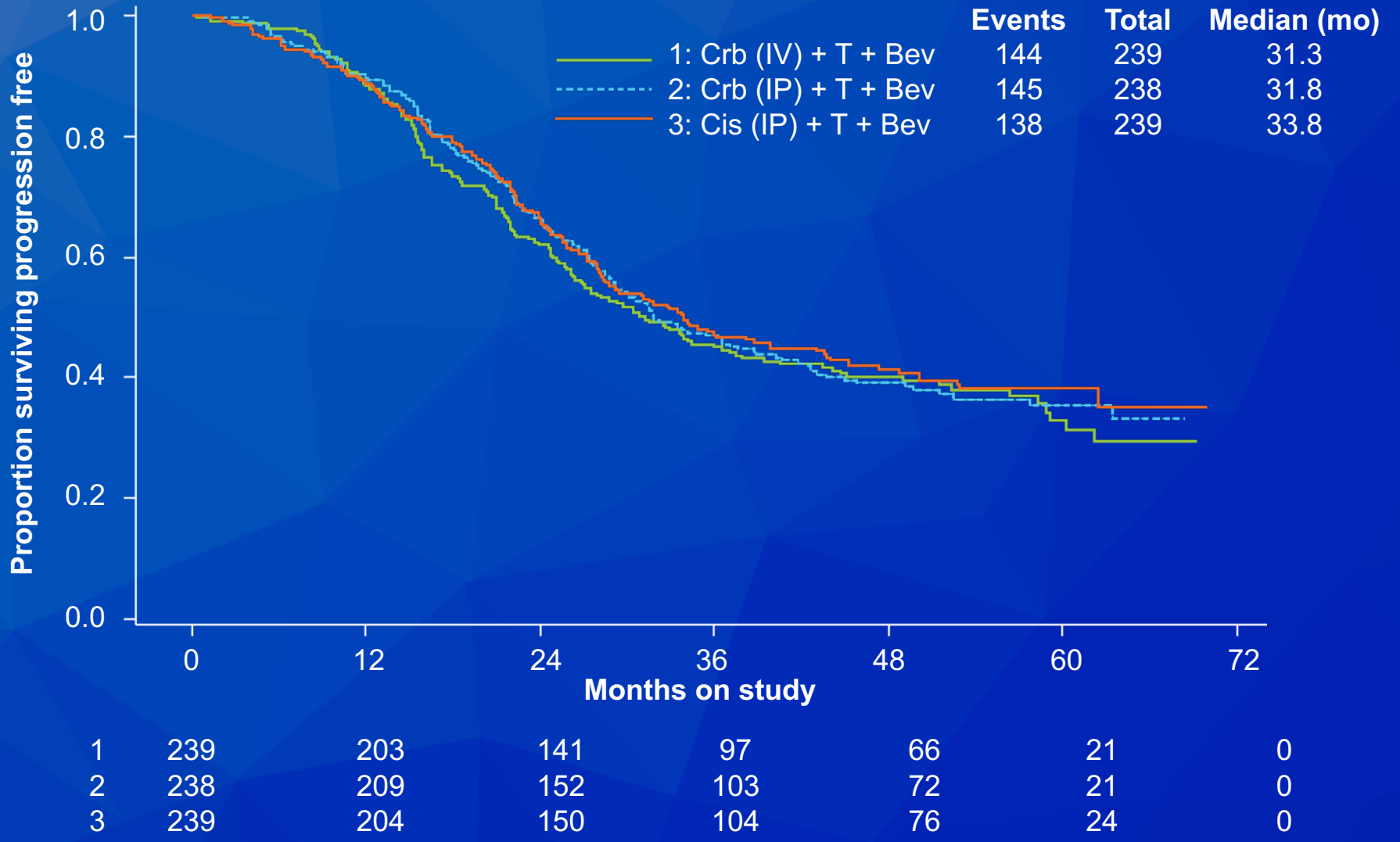
# GOG Protocol 0252: PFS (<1 cm) by Treatment Group




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 | 461 | 387 | 244 | 169 | 111 | 37 | 0 |
| 2 | 464 | 391 | 262 | 177 | 125 | 39 | 0 |
| 3 | 456 | 372 | 255 | 168 | 120 | 34 | 0 |

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

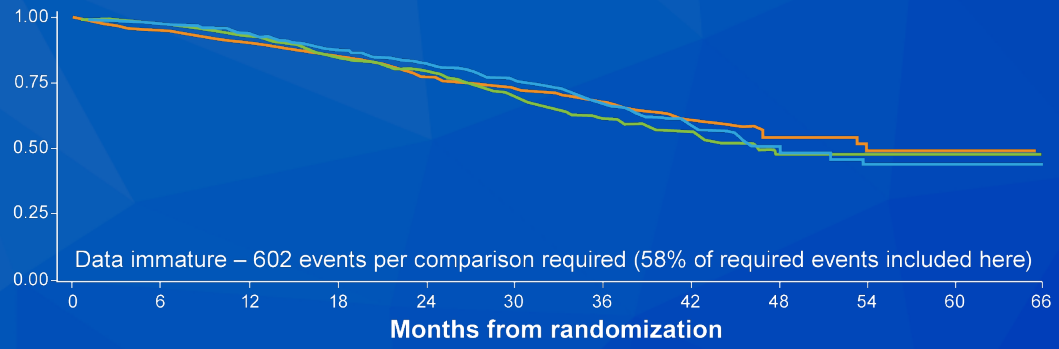
[1] Katsumata N et al. *Lancet Oncol* 2013;14:1020-6; [2] Chan JK et al. *N Engl J Med* 2016;374:738-48; [3] Marchetti C et al. *Oncotarget* 2016;7(36):58709-15.

# 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.

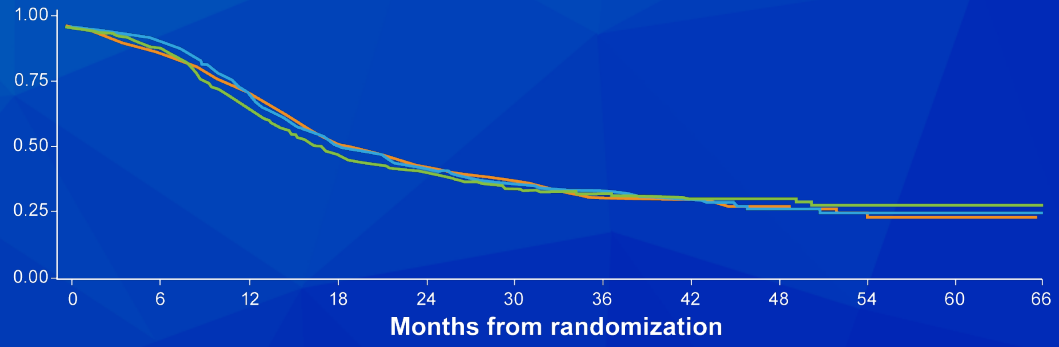
# ICON8: Primary Endpoints (OS and PFS)

## 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 Armstrong

The Japanese GOG trial comparing weekly, dose-dense paclitaxel (80 mg/m$^2$) with standard, every 3-week paclitaxel (180 mg/m$^2$), both with 3-weekly carboplatin (AUC 6), demonstrated an improved PFS and OS. GOG-0262 did a similar comparison but allowed bevacizumab by patient/physician selection. There was no difference in the overall outcomes, but the PFS was improved (14.2 versus 10.3 months) in the 16% of patients who did not choose bevacizumab. One hypothesis was that weekly paclitaxel has antiangiogenic properties and that those benefits were not apparent when bevacizumab was used.

# Editorial — Dr Armstrong (continued)

MITO-7 compared lower dose weekly paclitaxel (60 mg/m$^2$) with fractionated weekly carboplatin (AUC 2) to standard 3-weekly carboplatin and paclitaxel, demonstrating no difference in outcome but better tolerability of the all-weekly regimen. Many now use the all-weekly regimen in poor PS patients.

ICON8 was a randomized phase III 3-arm trial comparing standard 3-weekly paclitaxel and carboplatin to weekly paclitaxel with 3-weekly carboplatin and to an all-weekly regimen. The study showed no significant difference between the three arms in median PFS (17.9, 20.6, and 21.1 months, respectively), 2 year survival (80%, 82% and 78%, respectively) or median OS (46.5, 48.1 and 54 months, respectively).

# Editorial — Dr Armstrong (continued)

The conclusion was that weekly dose-dense chemotherapy is safe and well-tolerated and did not affect ability to perform timely interval cytoreductive surgery but did not improve surgical outcomes, and that 3-weekly carboplatin-paclitaxel remains the standard of care for first-line ovarian cancer treatment.

This was a largely European population with 95% of patients from England, Ireland or Australia/New Zealand. The JGOG study showed a better outcome for their patients treated with standard 3-weekly paclitaxel and carboplatin compared to US GOG outcomes. This is despite approximately 30% of their patients having clear cell histology, which is a poor prognostic histologic type in GOG studies.

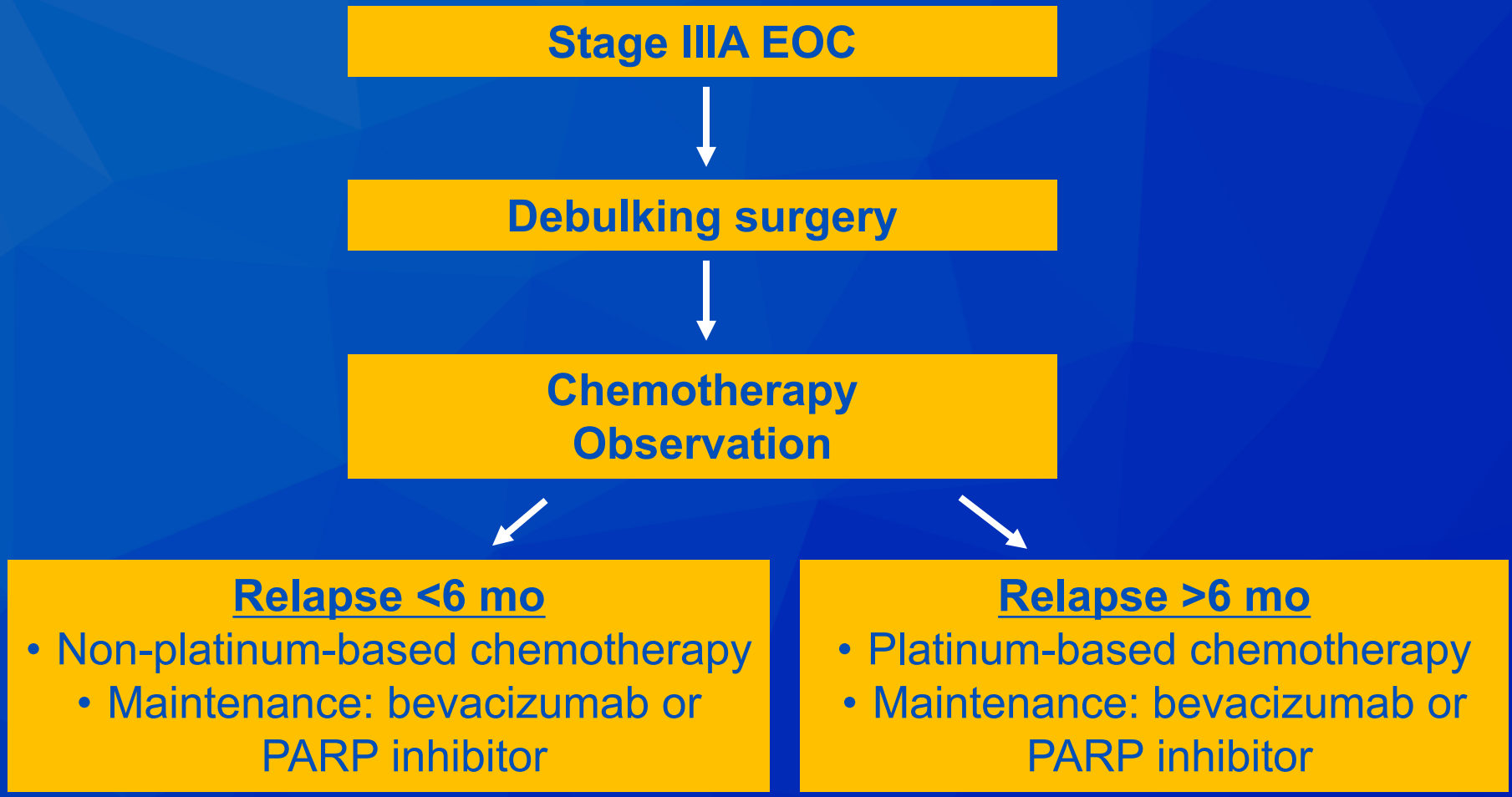
# Editorial — Dr Armstrong (continued)

These data suggest that there are differences between disease prognosis and treatment response in different ethnicities.

# Management of Platinum-Sensitive and Resistant Recurrent EOC

- Is 6 months the optimal definition of platinum sensitivity?
- Choice of chemotherapy regimen
- Role of bevacizumab

# Management of Platinum-Sensitive and Resistant Recurrent EOC



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

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

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

* Weekly paclitaxel, topotecan or pegylated liposomal doxorubicin

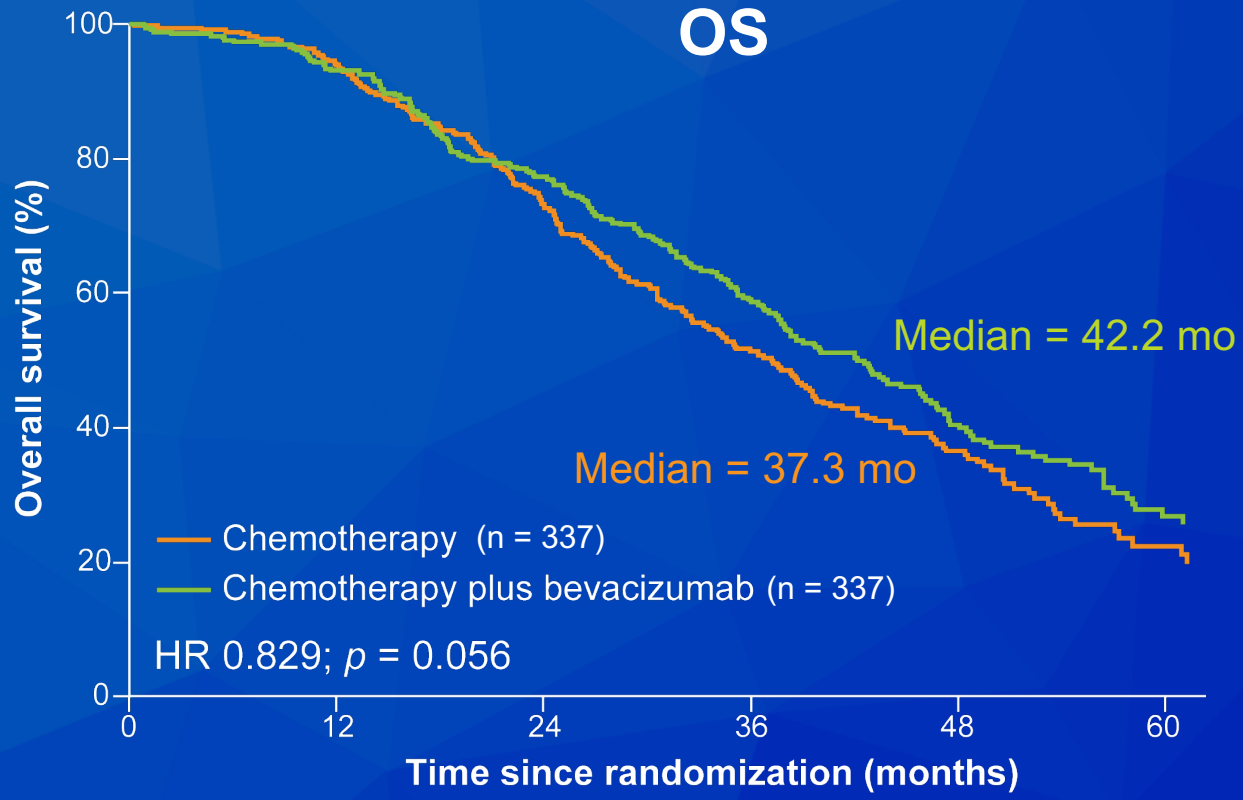
Pujade-Lauraine E et al. *J Clin Oncol* 2014;32(13):1302-8.

# 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 Armstrong

Bevacizumab has significant single agent activity in recurrent ovarian cancer, but the addition of bevacizumab to initial chemotherapy provided only a small improvement in PFS. In the recurrent platinum resistant setting, the addition of bevacizumab to single agent chemotherapy in the AURELIA trial nearly doubled the response rates for all of the chemotherapy agents used.

In the OCEANS study the addition of bevacizumab to gemcitabine and carboplatin for treatment of recurrent platinum sensitive disease improved median PFS from 8.4 to 12.4 months but did not provide a survival advantage (OS 33.3 months for Bev, 35.2 months for placebo).

# Editorial — Dr Armstrong (continued)

This study examined the addition of bevacizumab to paclitaxel and carboplatin for recurrent platinum sensitive disease and showed a median PFS of 10.4 versus 13.8 months and median OS of 37.3 versus 42.2 months ($p = 0.056$) for chemo compared to chemo plus bevacizumab, respectively.

Although the survival outcomes are favorable, there are several questions raised. First, most no longer use paclitaxel and carboplatin for platinum sensitive patients, preferring the less neurotoxic regimens of PLD carbo or gem carbo and using weekly paclitaxel for platinum resistant patients. Second, we now have approval of two PARP inhibitors for maintenance therapy after chemo for platinum sensitive disease.

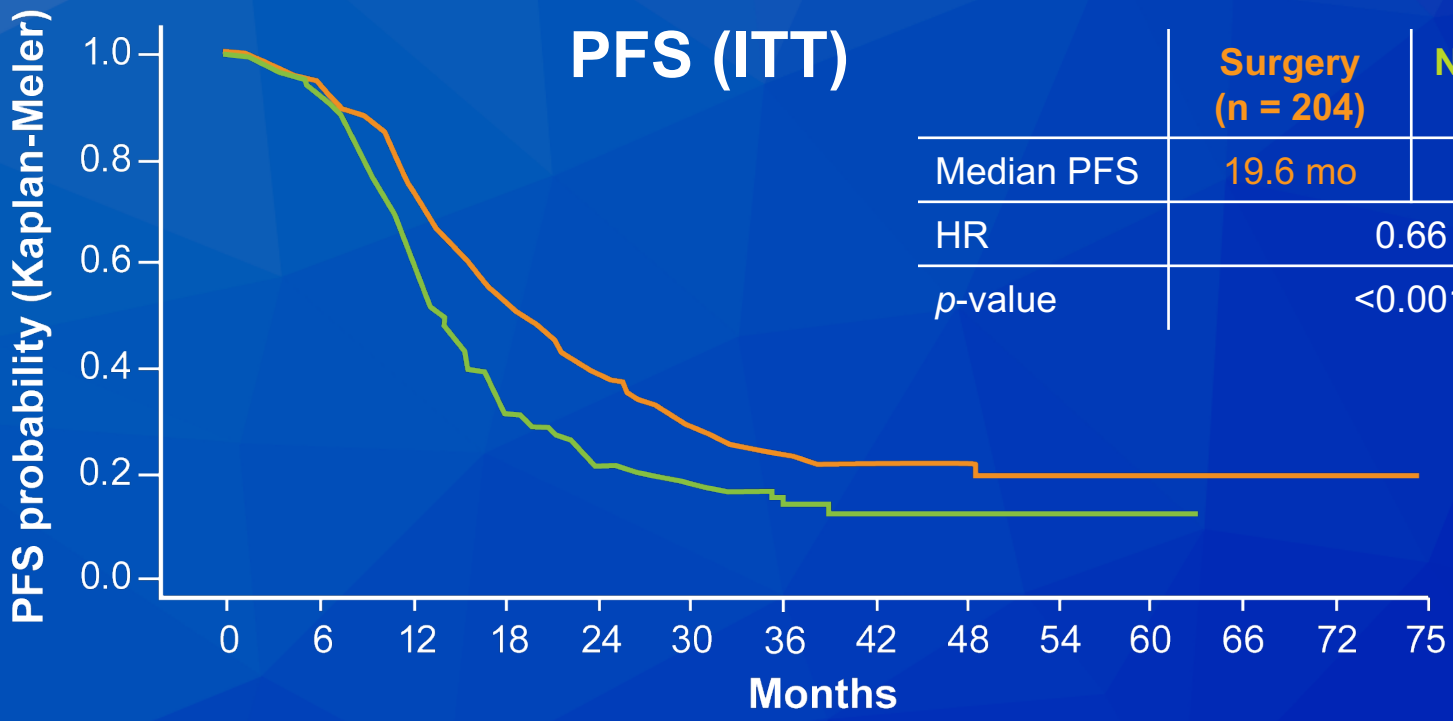
# Editorial — Dr Armstrong (continued)

What do we do with bevacizumab maintenance in this setting? That question may be answered in part by the PAOLA-1 study examining chemo plus bevacizumab, followed by either bevacizumab alone or bevacizumab plus olaparib maintenance after first line chemotherapy. Molecular profiling suggests that a significant subgroup of ovarian cancer may have a worse outcome with bevacizumab. BRCA mutation status and HRD assays can identify subjects who get the greatest benefit from PARP inhibition. We need a biomarker to identify subjects who derive the greatest benefit from bevacizumab to select the best maintenance treatment.

# 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 Armstrong

It is not typical for aggressive surgical cytoreduction to have a significant impact on survival in the setting of metastatic solid tumors. Yet in ovarian cancer, it has been recognized for decades that the degree of cytoreduction with initial surgery is the most important prognostic factor in survival for those with advanced disease. What has been less clear is what impact surgical debulking has in the setting of recurrence. Most have focused this on patients with late recurrence, usually platinum sensitive subjects who recur more than 6-12 months from completion of initial chemotherapy with low volume disease and no evidence of carcinomatosis. Retrospective observational studies have suggested a benefit for this “secondary debulking,” but the potential for patient selection was clearly an issue.

# Editorial — Dr Armstrong (continued)

This third DESKTOP study randomized good-prognosis platinum sensitive patients to cytoreductive surgery followed by chemo, versus chemo without surgery. Nearly 75% of the surgical group were completely resected with no visible residual, and the surgical group had a better than expected 2 year survival rate of 83%. PFS favored the surgery arm (19.6 vs 14 months) and was best for those who could have complete resection (21.2 vs 13.7 months for those with some residual). It should be noted that these patients had a good prognosis and were required to have ECOG PS 0, a history of complete resection with first surgery and less than 500 ml ascites at recurrence. The median platinum-free interval was over 18 months for patients on the protocol.

# Editorial — Dr Armstrong (continued)

Nonetheless, these results complement retrospective data and emphasize the importance of experienced gyn onc surgical assessment and complete resection if secondary debulking is done. Of note, there is a surgical arm of GOG-0213 with a similar design that is awaiting maturation, so we should have some data from a similar North American population.

# Ovarian Cancer — Drs Birrer and Armstrong

Current use of chemotherapy with or without bevacizumab in ovarian cancer

Germline and somatic mutations in ovarian cancer

PARP inhibitors: Efficacy, toxicity and ongoing trials

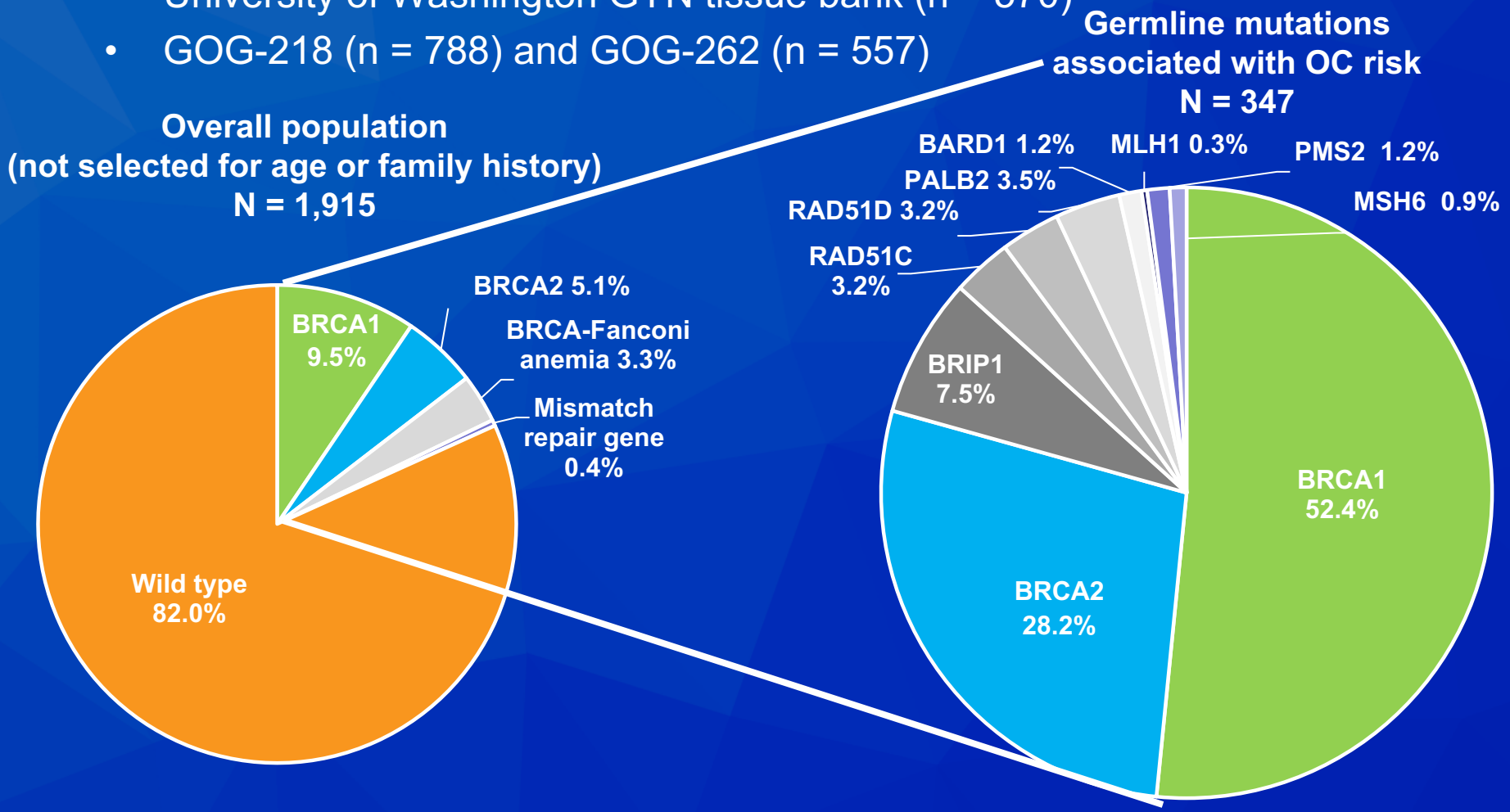
Novel investigational agents

**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

**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 |

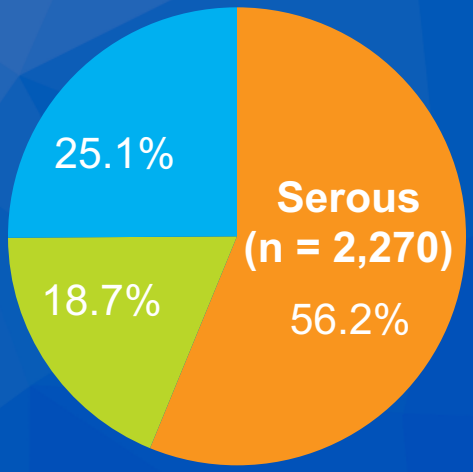
| gBRCA1/2 mutation status | Negative (n = 227) | Positive (n = 44) | *p*-value |
|---|---|---|---|
| Median OS | 46.1 mo | 65.3 mo | 0.0331 |
| Median EFS | 16.4 mo | 27.0 mo | 0.0050 |

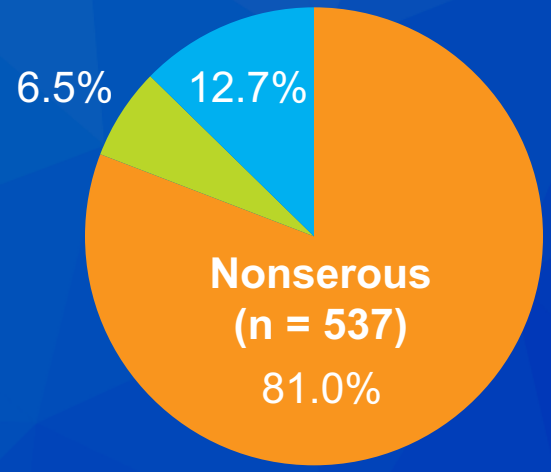
| Any germline HR mutation | No (n = 104) | Yes (n = 35) | *p*-value |
|---|---|---|---|
| Median OS | 36.7 mo | 50.2 mo | 0.0236 |
| Median EFS | 13.9 mo | 20.4 mo | 0.0019 |

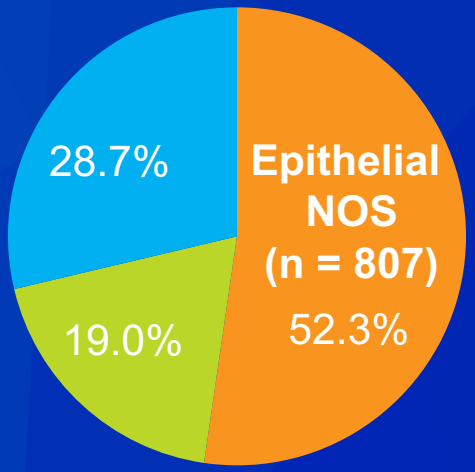
HR = homologous recombination; EFS = event-free survival; OS = overall survival

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

# Molecular Category Prevalence by Histology and Treatment Information

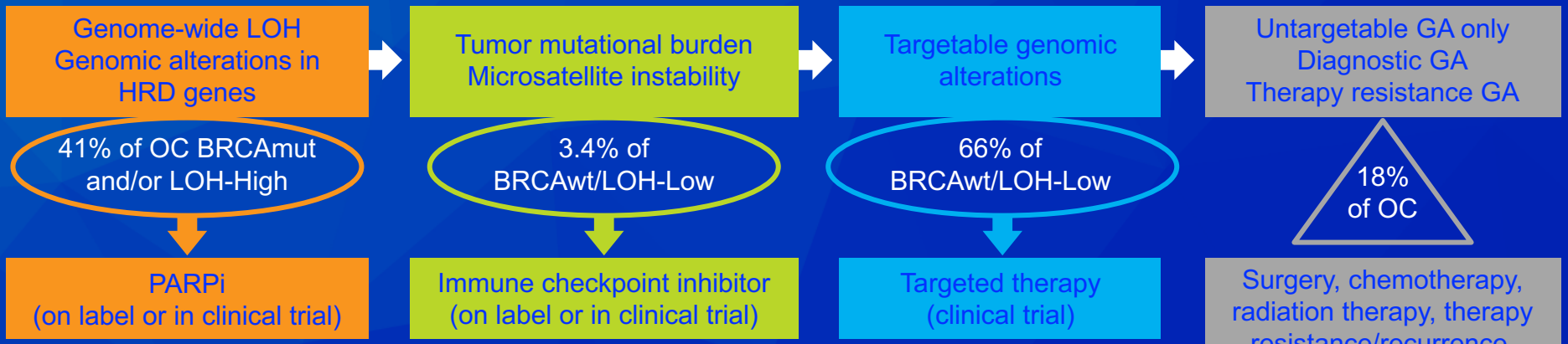



BRCAmut BRCAwt/LOH-H BRCAwt/LOH-L

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 Birrer

The study by Yates et al entitled “Evaluation of BRCA1/2 and homologous recombination defects in ovarian cancer and impact on clinical outcomes” describes the germline and somatic molecular abnormalities in patients newly diagnosed with ovarian cancer. 299 patients were entered on the study and underwent both germline and tumor BRCA1/2 mutations testing along with methylation analysis. Mutations in an additional 21 hereditary genes were also determined, and HR status was scored by LOH, telomeric allelic imbalance and large-scale state transition.

# Editorial — Dr Birrer (continued)

The clinical impact of these abnormalities was reported. Event free survival was significantly longer in HRD-positive patients compared to HRD-negative (20.5 versus 16.3 months, $p = .0268$), and overall survival (OS) was significantly longer for patients with germline or somatic BRCA1/2 mutations versus wildtype BRCA1/2 (65.3 versus 46.1 months, $p = .04$). The study examined the effects of HRD on surgical treatment and demonstrated that HRD had a larger impact on patients undergoing neoadjuvant chemotherapy versus up-front surgical debulking (USD). This was also true for OS in these two groups, and importantly there was no statistically significant impact of HRD on USD patients.

# Editorial — Dr Birrer (continued)

This data adds to a large body of literature demonstrating a PFS and OS improvement for patients with HRD abnormalities in their ovarian cancer (whether it is somatic or germline). The analysis according to surgical approach is unique and suggests a differential impact of HRD based upon the treatment approach. The mechanism behind this remains unclear, and given the small numbers one should be careful about its interpretation.

Elvin et al conducted a study entitled “Comprehensive genomic profiling (CGP) with loss of heterozygosity (LOH) to identify therapeutically relevant subsets of ovarian cancer (OC).”

# Editorial — Dr Birrer (continued)

DNA for 4,114 advanced stage OC (tumors) were analyzed by hybrid capture next-gen sequencing of 315 genes in serous (OC-S), non-serous (OC-NS), and “difficult” to classify (OC-NOS), and algorithms for microsatellite instability, tumor mutation burden and LOH were used for correlation. 17.2% of OC had a BRCA abnormality with serous cancers having a higher frequency of them compared to non-serous or difficult to classify tumors. LOH (as a potential measure of homologous recombination deficiency) is similar in BRCA-mutated OC-S and OC-NS but different in BRCA wildtype tumors.

# Editorial — Dr Birrer (continued)

Specific gene mutations were similar across groups and included the following: myc 27%, NF1 19%, CCNE 20%, KRAS 19%, PIK3CA 16%, AKT2 7%, ERBB2 5%, BRAF 3%, tumor mutation burden high 2.5% and MSI-high 1%.

This is an interesting analysis of a cohort of FFPE samples of OC specimens. There are limitations to its interpretation in that little clinical data is provided in relation to the samples analyzed. Significant clinical elements were not provided. The molecular analysis appears solid, reflecting frequencies found in The Cancer Genome Atlas, and, of importance, provides little information relevant to clinical management of patients.

# Ovarian Cancer — Drs Birrer and Armstrong

Current use of 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

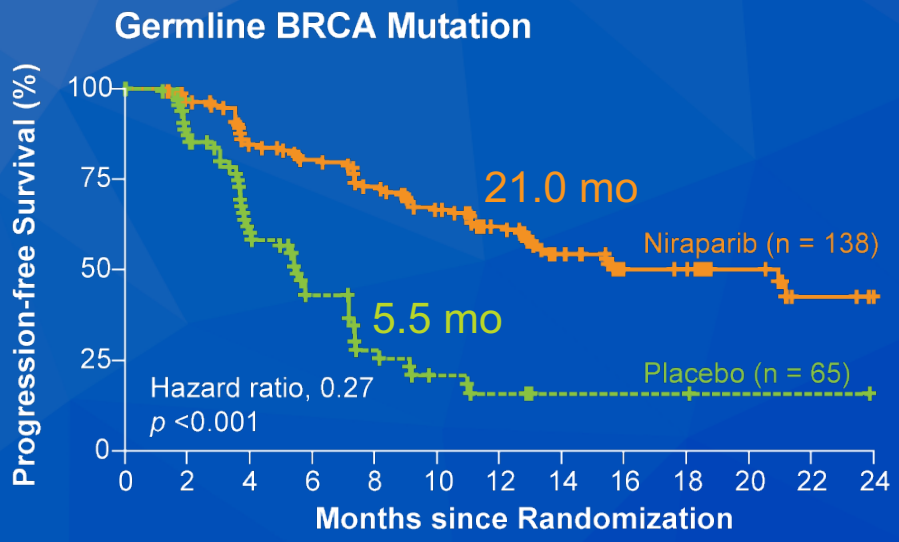
ORIGINAL ARTICLE

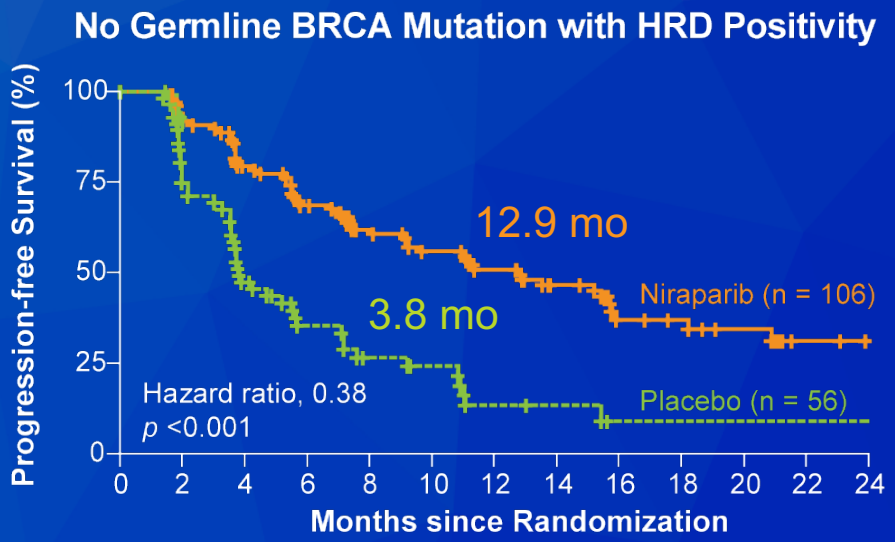
# Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

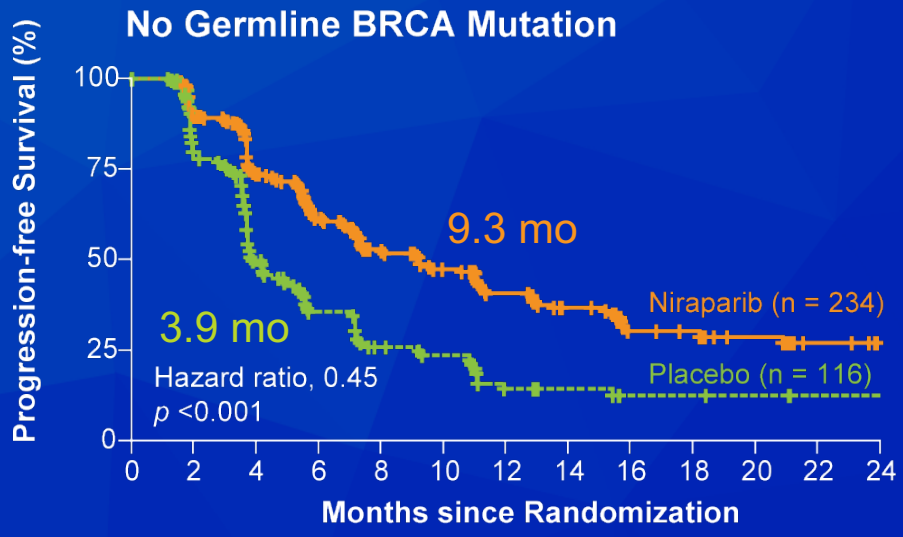
M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, M. Fabbro, J.A. Ledermann, D. Lorusso, I. Vergote, N.E. Ben-Baruch, C. Marth, R. Mądry, R.D. Christensen, J.S. Berek, A. Dørum, A.V. Tinker, A. du Bois, A. González-Martín, P. Follana, B. Benigno, P. Rosenberg, L. Gilbert, B.J. Rimel, 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



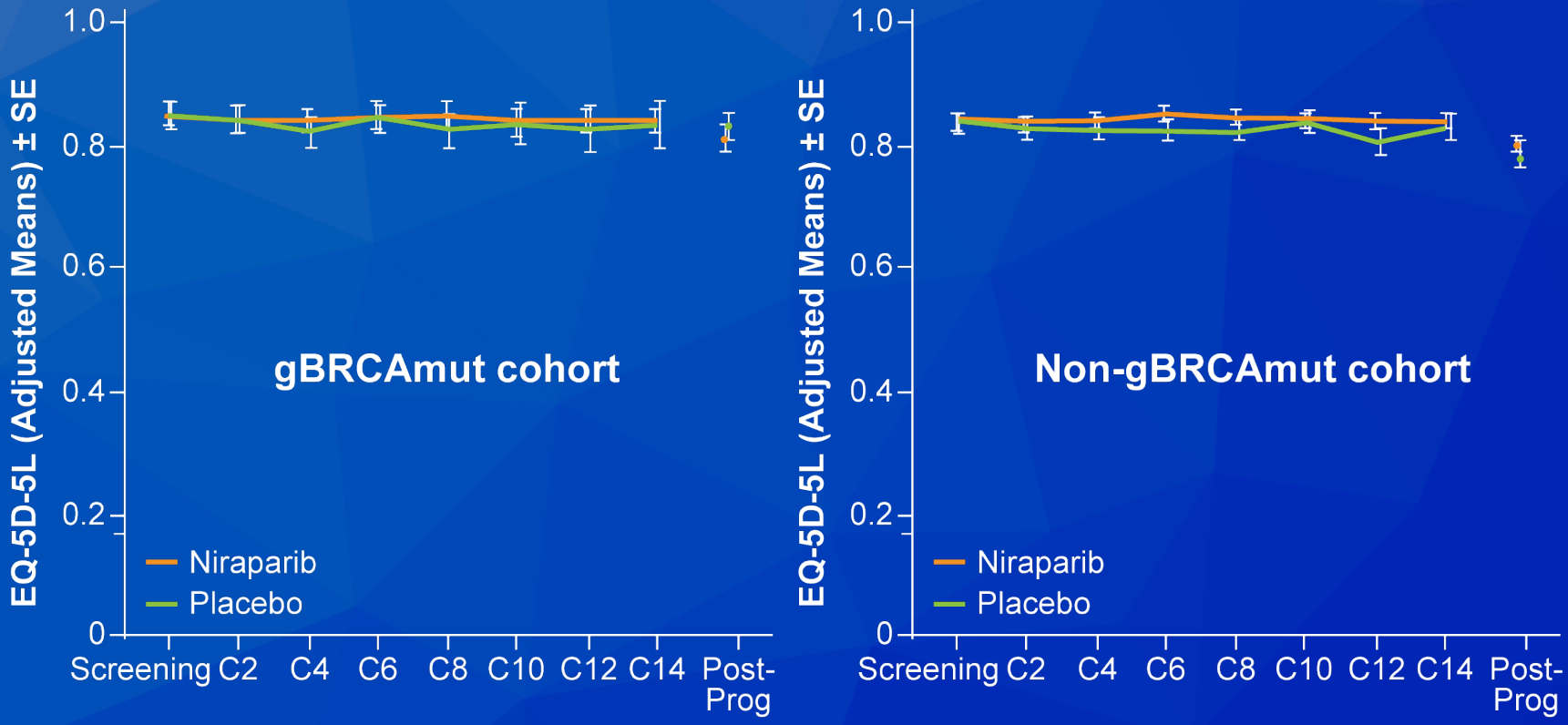

Mirza MR et al. *N Engl J Med* 2016;375(22):2154-64.

# 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.

# 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.

# 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

# Editorial — Dr Birrer

The NOVA trial was a randomized phase III trial testing the impact of niraparib maintenance after platinum treatment for platinum-sensitive recurrent ovarian cancer. This trial is actually two trials testing niraparib maintenance against placebo in ovarian cancers that have had a PR or CR to platinum therapy in 1.) gBRCA mutated patients and 2.) patients who did not have a gBRCA mutation. There were 203 patients with a gBRCA mutation and 350 without mutation randomized 2:1 niraparib versus placebo.

Patients in the niraparib group had statistically significant longer median duration of progression free survival than those in the placebo group (gBRCA 21.0 versus 5.5 months; non-gBRCA 9.3 versus 3.9 months).

# Editorial — Dr Birrer (continued)

In addition, this study employed an HRD assay (utilizing LOH, telomeric imbalance and large state transitions), and those patients with non-gBRCA but HRD positive (by assay) have a prolongation of disease free survival in favor of niraparib, 12.9 months compared to 3.8 months. The regimen was well tolerated, and the major toxicity was hematologic with grade 3 and 4 adverse events including thrombocytopenia (33.8%), anemia (25.3%) and neutropenia (19.6%), all of which were managed with dose modifications.

# Editorial — Dr Birrer (continued)

There are several important features of this trial. First, it needs to be recognized that the patients entered on this trial were patients with recurrent ovarian cancer whose tumors had responded to a platinum based regimen; and second, all patients benefited from the use of niraparib, even those without gBRCA.

This is a pivotal trial, which clinicians need to know and appreciate. It has led to the FDA approval for niraparib for maintenance for all patients with platinum-sensitive recurrent ovarian cancer that has responded to platinum therapy. The HRD assay is considered to be a complementary assay and not required for treatment with niraparib.

# Editorial — Dr Birrer (continued)

The study by Oza et al entitled “Quality of life in patients with recurrent ovarian cancer (OC) treated with niraparib: Results from the ENGOT-OV16/NOVA trial” examines the impact of the PARP inhibitor on quality of life. The study quantified the patient-reported outcomes (PROs) associated with quality of life and individual patient-reported symptoms using the Functional Assessment of Cancer Therapy — Ovarian Symptoms Index (FOSI) and European Quality of Life-5 Dimensions scale in patients who were treated with niraparib.

The relationship between health status and PROs was evaluated through a cross sectional analysis of adjusted health utility scores (HUI).

# Editorial — Dr Birrer (continued)

No significant differences were found in mean PRO scores between niraparib and placebo. Adjusted HUI scores were similar at baseline, but there was a trend for higher HUI scores pre-progression in favor of niraparib.

These findings are reassuring that treating patients with niraparib will not affect QOL despite the hematologic toxicities.

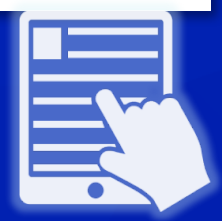
# Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial

*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.

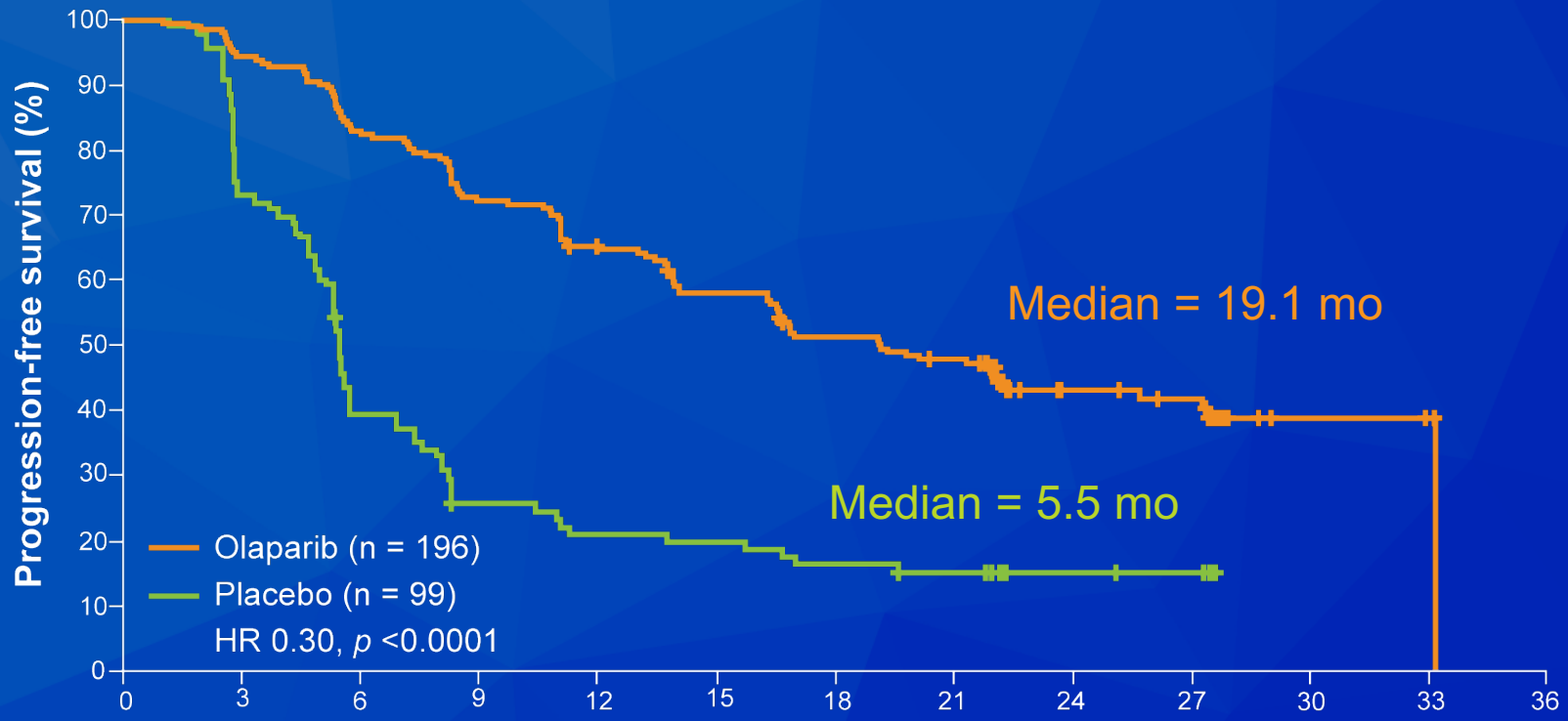
# Efficacy of Olaparib Maintenance Therapy in Patients (pts) with Platinum-Sensitive Relapsed Ovarian Cancer (PSROC) by Lines of Prior Chemotherapy: Phase III SOLO2 Trial (ENGOT Ov-21)

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 Birrer

The SOLO2 trial is a double blind, randomized phase III trial testing olaparib tablets as a maintenance therapy in platinum-sensitive relapsed ovarian cancer patients with a gBRCA mutation who had received at least 2 prior lines of chemotherapy. This study is essentially identical to Study 19, which led to EMA approval of olaparib for maintenance in relapsed ovarian cancer in gBRCA patients.

The results of SOLO2 demonstrated statistically significant prolongation of PFS in the olaparib arm (19.1 months) compared to placebo (5.5 months). The most common grade 3 adverse event was anemia (19% versus 2%). The results of this trial are important in that they validate Study 19 results, have led to approval of the drug in the US and provide a greater safety signal.

# Editorial — Dr Birrer (continued)

A follow-up analysis of the SOLO2 trial was published in abstract form in the *Annals of Oncology* and described a continued evaluation of the data from the trial according to lines of previous therapy. 43% of patients on the olaparib arm and 37% of patients on the placebo arm had greater than 3 prior lines. The analysis showed that olaparib was beneficial regardless of prior lines but that patients with more limited prior line exposure had longer PFS regardless of treatment.

# 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*

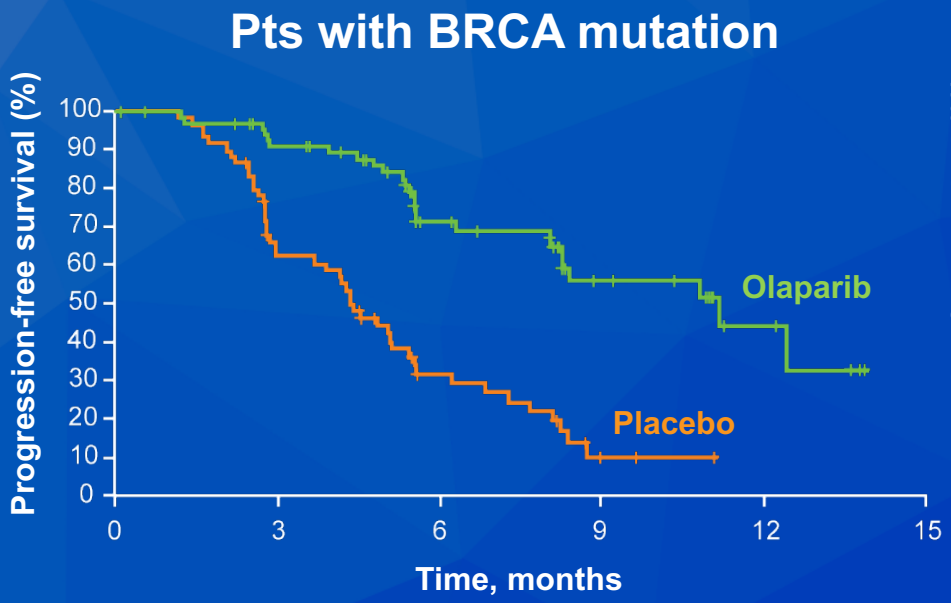
*Lancet Oncol* 2014;15(8):852-61.

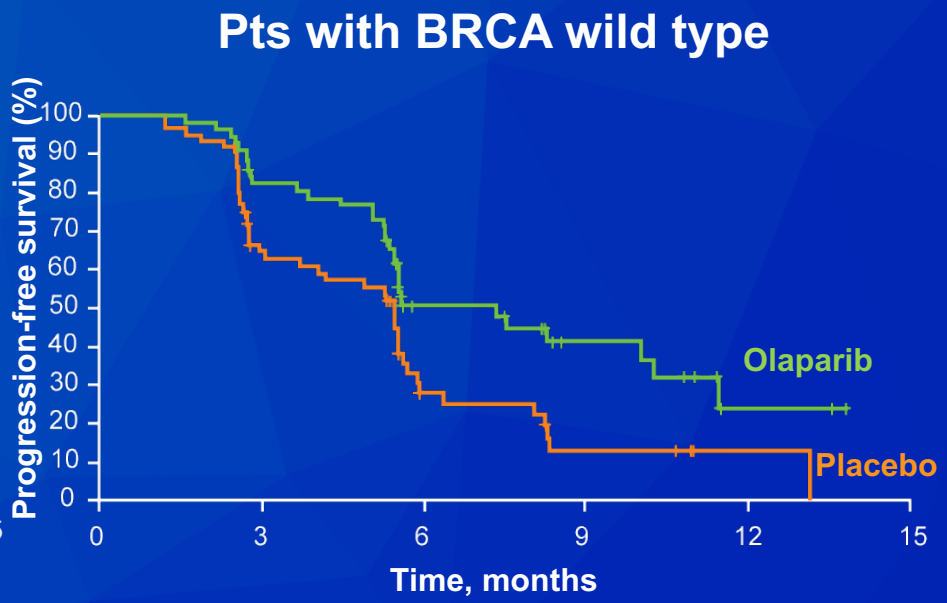
# Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial

*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

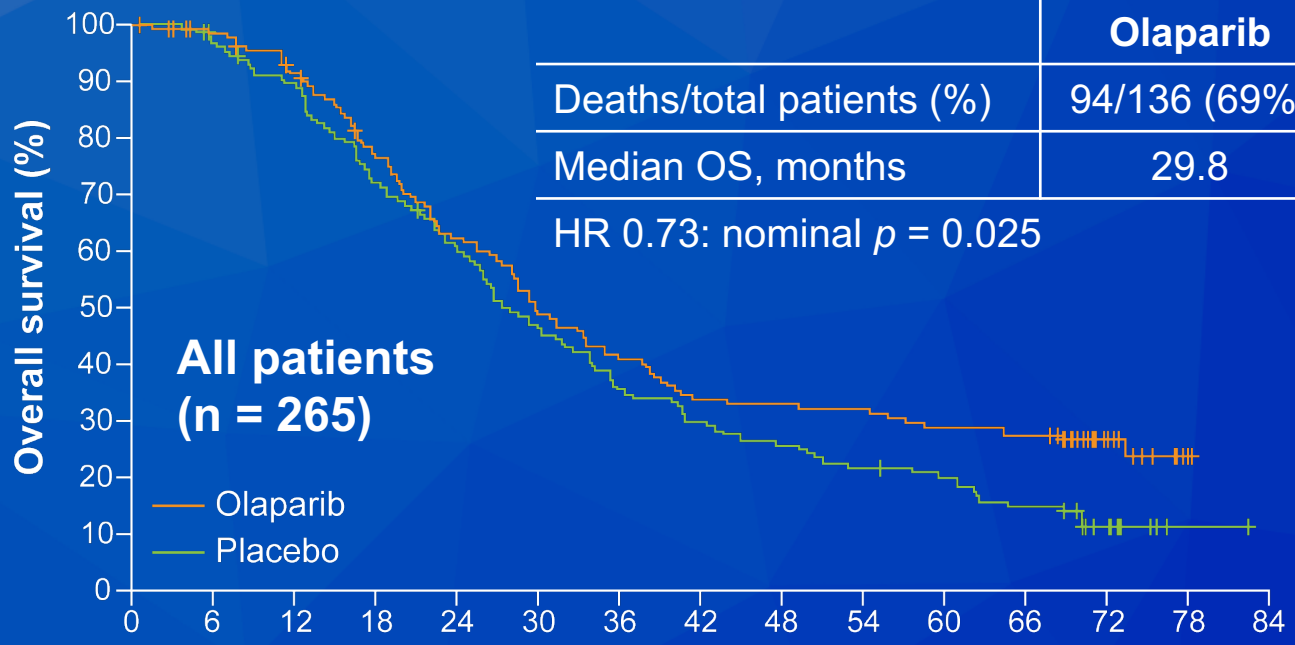



| Median PFS | Olaparib | Placebo | HR | *p*-value |
|---|---|---|---|---|
| BRCAm (n = 74, 62) | 11.2 mo | 4.3 mo | 0.18 | <0.0001 |
| BRCAwt (n = 57, 61) | 7.4 mo | 5.5 mo | 0.54 | 0.0075 |

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.

# 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

# Editorial — Dr Birrer

The paper by Ledermann et al entitled “Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomized, placebo-controlled, double-blind, phase 2 trial” described the overall survival impact of treatment with a PARP inhibitor in Study 19. Although not statistically significant, olaparib maintenance did extend overall survival and supported the statistically significant prolongation of progression free survival. In addition, the paper provides additional long-term safety data reassuring physicians of its tolerability.

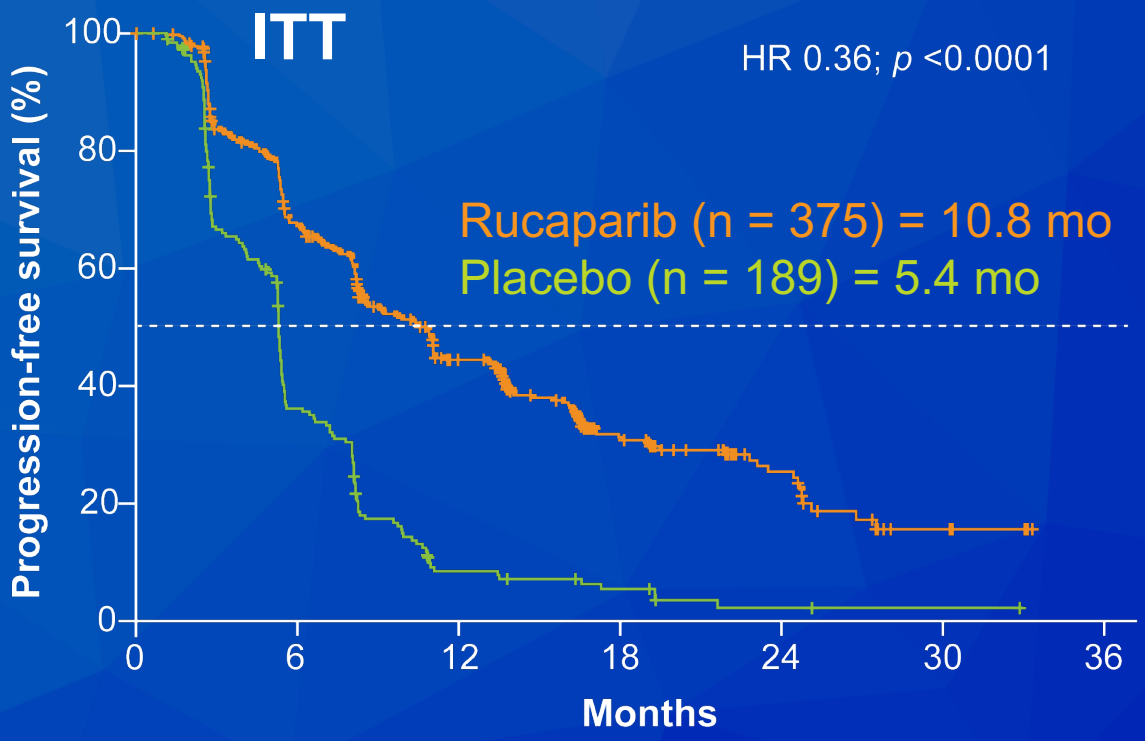
While not providing substantial new data or conclusions, this paper does provide additional support for the benefits of maintenance therapy with olaparib.

# 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;[Epub ahead of print].

# 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;[Epub ahead of print].

# 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 Birrer

Ariel3 is a randomized, double-blind, placebo-controlled phase 3 trial testing the use of rucaparib maintenance treatment for recurrent ovarian cancer after response to platinum therapy. 564 patients were randomized to rucaparib (66%) versus placebo (34%). In the intent-to-treat group, the median progression free survival was 10.8 months in the rucaparib group versus 5.4 in the placebo group.

# Editorial — Dr Birrer (continued)

Subset analysis shows median progression free survival 1.) in patients with a BRCA mutation as 16.6 months in the rucaparib group versus 5.4 months in the placebo group; 2.) in patients with homologous recombination deficient carcinoma (BRCA mutated and BRCA wildtype with high LOH) as 13.6 months versus 5.4 months; and 3.) in patients with BRCA wildtype and low LOH as 6.7 months with rucaparib and 5.4 months with placebo. Treatment-related adverse events of grade 3 or higher were reported in 56% of the rucaparib group versus 28% in the placebo group, the most common being anemia (19% versus 1%) and increased transaminases (10% versus none).

# Editorial — Dr Birrer (continued)

This is an important trial as it definitely demonstrates the activity and safety of rucaparib in the maintenance treatment of recurrent ovarian cancer. Of note, the results are remarkably similar to the NOVA trial and will likely lead to FDA approval of the drug in the maintenance setting.

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

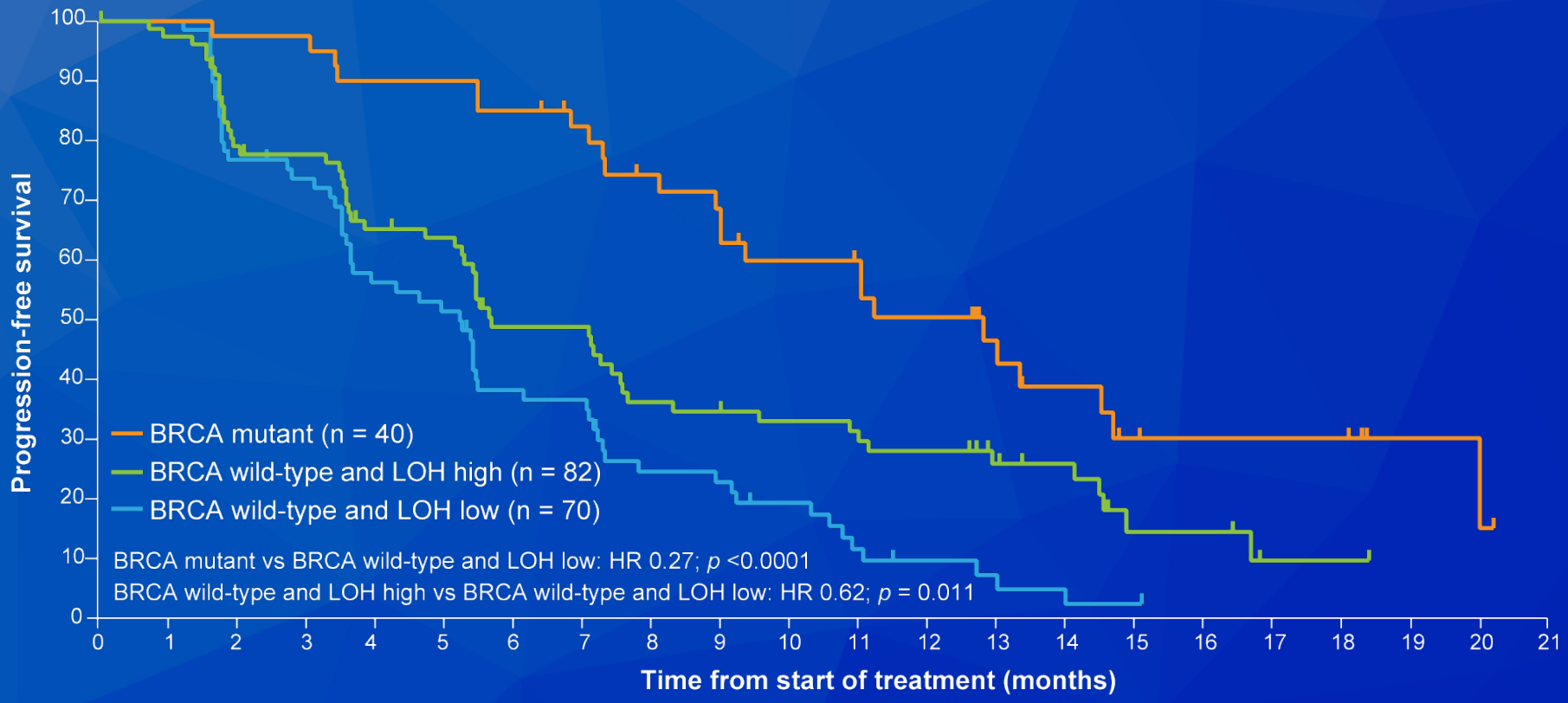
*Elizabeth M Swisher*, Kevin K Lin*, Amit M Oza, Clare L Scott, Heidi Giordano, James Sun, Gottfried E Konecny, Robert L Coleman, Anna V Tinker, David M O'Malley, Rebecca S Kristeleit, Ling Ma, Katherine M Bell-McGuinn, James D Brenton, Janiel M Cragun, Ana Oaknin, Isabelle Ray-Coquard, Maria I Harrell, 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

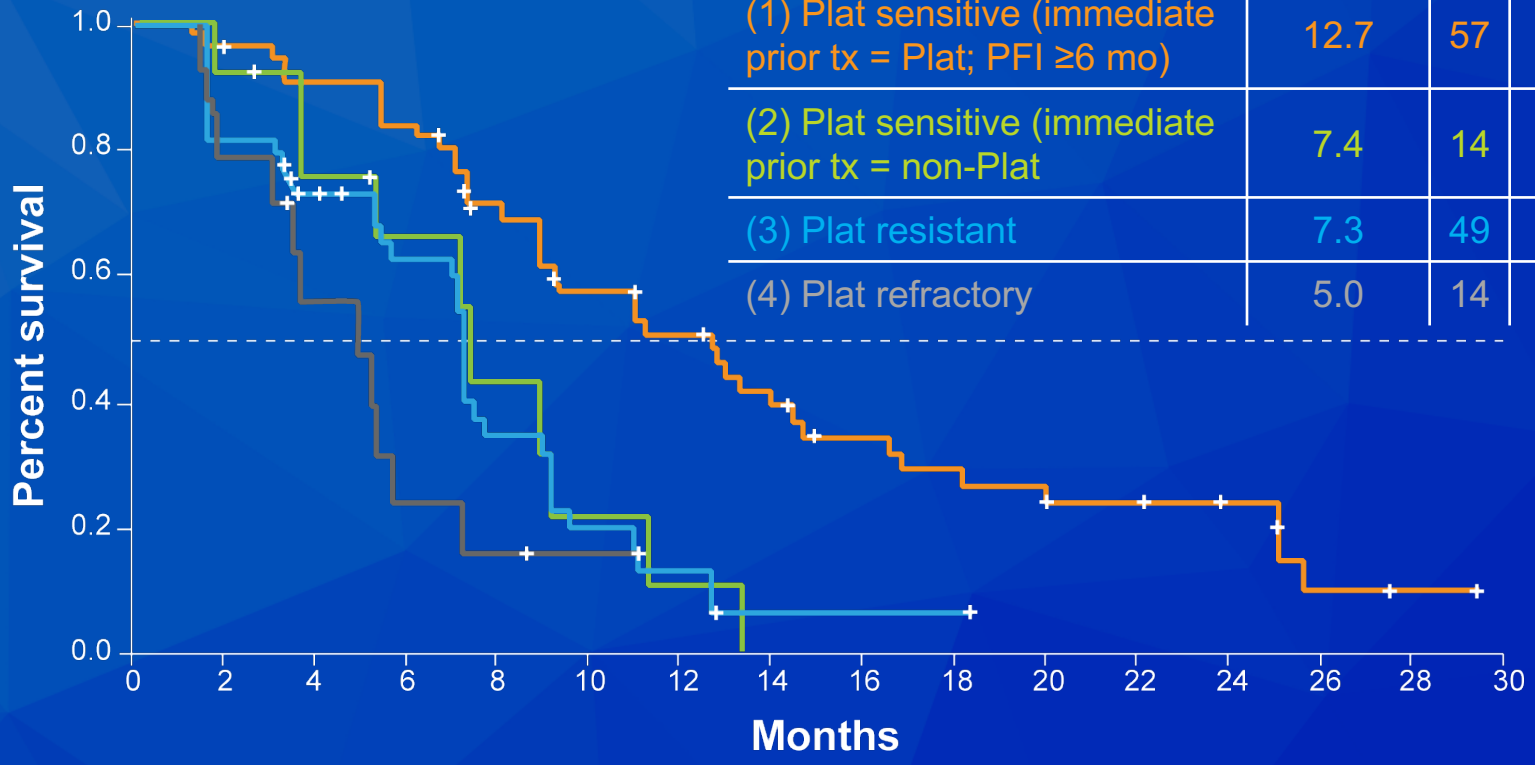



| After rucaparib therapy | BRCAm (n = 40) | BRCAwt and LOH-high (n = 82) | BRCAwt and LOH-low (n = 70) |
|---|---|---|---|
| Median PFS | 12.8 mo | 5.7 mo | 5.2 mo |

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.

# 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.

# Editorial — Dr Birrer

Ariel2 is a multicenter, two-part phase 2 open-label study. In part 1, patients with recurrent platinum-sensitive, high-grade ovarian cancer were classified into one of three predefined homologous recombination deficient subgroups on the basis of tumor mutational analysis: BRCA mutant (germline or somatic), BRCA wildtype and LOH high (LOH high group), or BRCA wildtype and LOH low (LOH low group). Part 2 is an extension of part 1.

206 patients were enrolled with 204 receiving rucaparib. Median progression free survival after rucaparib treatment was 12.8 months in the BRCA mutant group, 5.7 months in the LOH high group and 5.2 months in the LOH low group.

# Editorial — Dr Birrer (continued)

Objective response by RECIST criteria showed an 80% response rate in BRCA mutant tumors (85% germline versus 74% somatic), 29% response in BRCA wild-type and LOH high, and 10% in BRCA wild-type and LOH low. The most common grade 3 adverse events were anemia (22%) and elevations in transaminases (12%). No treatment-related deaths were reported.

This is an important study in that it provided critical results which when combined with additional data led to the FDA approval of rucaparib for the treatment of recurrent ovarian cancer after 2 lines or more. In addition, the indication included both germline and somatic mutations of BRCA 1 and 2.

# Editorial — Dr Birrer (continued)

It also demonstrated that rucaparib was well tolerated and that the increase in liver enzymes was not reflective of liver toxicity. Finally, this was one of the first studies to attempt to identify patients who would benefit from PARP inhibition using a functional “genomic scratch” assay. The results were not conclusive that the assay was of value, and it was not included as a companion diagnostic. In addition, the assay specifications were changed when it was applied to Ariel3.

In the report by Konecny et al, updated data for Ariel2 part 1 and 2 were presented. 58 patients were eligible for this analysis, investigator assessed, with an ORR of patients with a progression free interval of 6-9 months, >12-18 months, and >18 months of 61.5%, 90%, and 60% respectively.

# Editorial — Dr Birrer (continued)

Common treatment-emergent adverse events included nausea (84%), asthenia/fatigue (79%), vomiting (50%), and anemia (47%).

This study extended the results for Ariel2 and demonstrated that rucaparib has activity and an acceptable safety profile in patients with relapsed, platinum-sensitive, high-grade ovarian cancer with germline or somatic mutated tumors.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

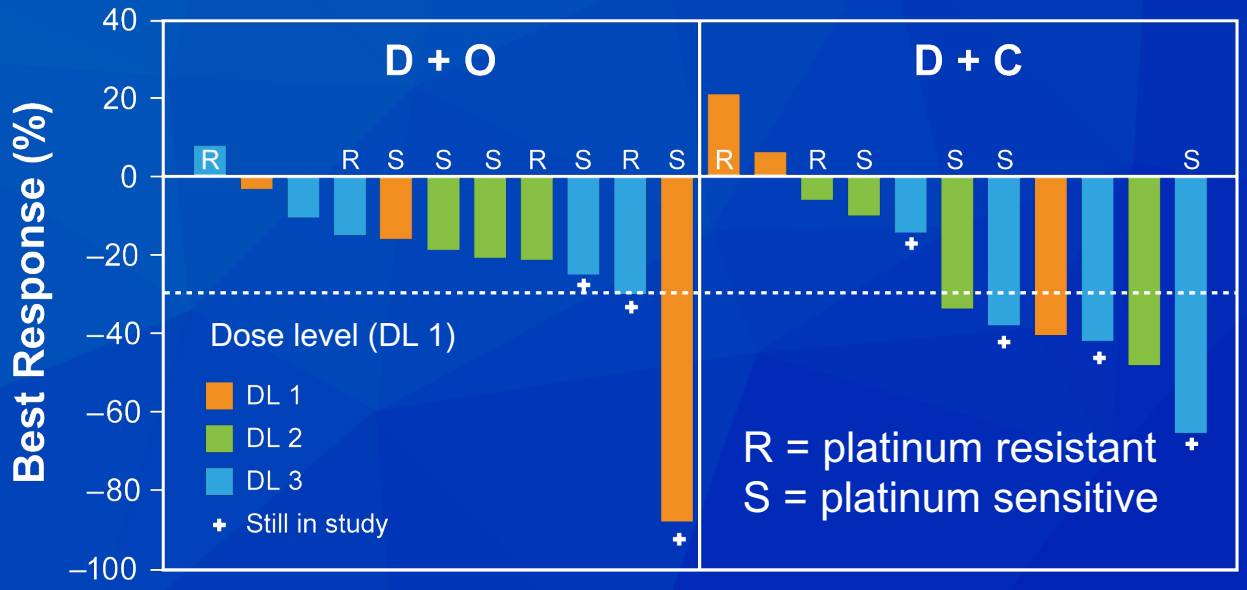
# Safety and Clinical Activity of the Programmed Death-Ligand 1 Inhibitor Durvalumab in Combination With Poly (ADP-Ribose) Polymerase Inhibitor Olaparib or Vascular Endothelial Growth Factor Receptor 1-3 Inhibitor Cediranib in Women's Cancers: A Dose-Escalation, Phase I Study

*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 Birrer

The paper by Lee et al entitled “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 1 Study” describes the safety and activity of programmed death-ligand inhibitor, PARP inhibitors and vascular endothelial growth factor receptor inhibition combinations. The Phase I trial demonstrated that the combination of durvalumab plus olaparib had no dose limiting toxicity. The combination of durvalumab and cediranib had considerable toxicity.

# Editorial — Dr Birrer (continued)

The daily dosing regimen of cediranib was not tolerable and intermittent dosing had to be used. Toxicity included hypertension, diarrhea, pulmonary embolism, and pulmonary hypertension. The intermittent dosing resulted in only hypertension and fatigue.

While this is an early drug development trial, it provides an important signal for future combinations.

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 Birrer

The mechanism of PARP inhibition resistance remains unknown, although reversion mutations in BRCA have been documented. The paper by Lheureux et al describes the molecular characteristics of the tumor from three patients who had platinum sensitive recurrent ovarian cancer treated with olaparib maintenance therapy. In two patients recovery of BRCA function occurred by copy number gain or increased expression, and this corresponded to tumor progression. A third patient with biallelic deletion of BRCA remains progression free and potentially cured.

This is a limited but important study demonstrating the relationship of BRCA mutation/expression status and PARP response.

**A 65-year-old woman with a BRCA1 germline mutation is started on olaparib, and after 6 weeks her hemoglobin has dropped from 11.0 to 8.8 g/dL with no evidence of hemolysis or bleeding. CA125 has decreased from 350 to 150. In addition to supportive measures such as erythropoiesis-stimulating agents and transfusion, what would be your most likely management approach?**

a. Continue olaparib at the same dose
b. Continue olaparib at a lower dose
c. Hold olaparib until hemoglobin increases and restart at the same dose
d. Hold olaparib until hemoglobin increases and restart at a lower dose
e. Switch to another therapy
f. Other

**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 Armstrong

Current use of chemotherapy with or without bevacizumab in ovarian cancer

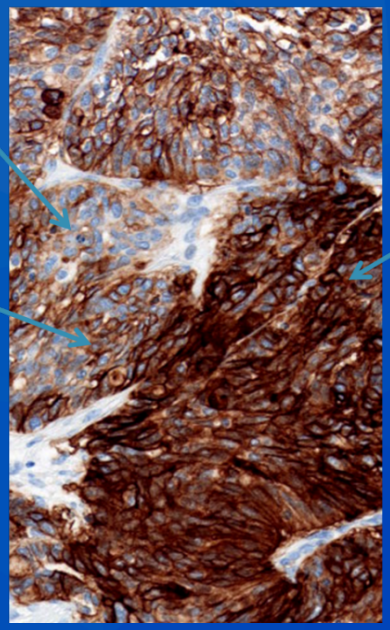
Germline and somatic mutations in ovarian cancer

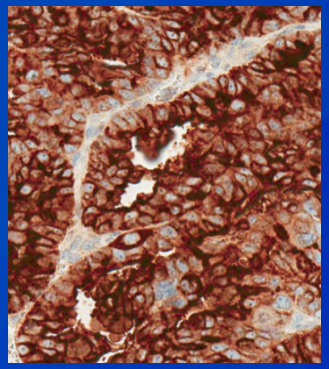
PARP inhibitors: Efficacy, toxicity and ongoing trials

Novel investigational agents

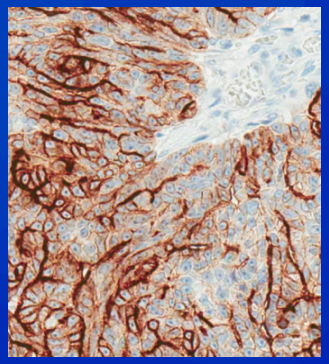
# Folate Receptor Alpha Expression Distribution

**Staining & Scoring**

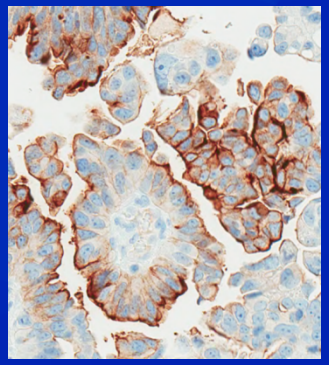


**High**



**Medium**



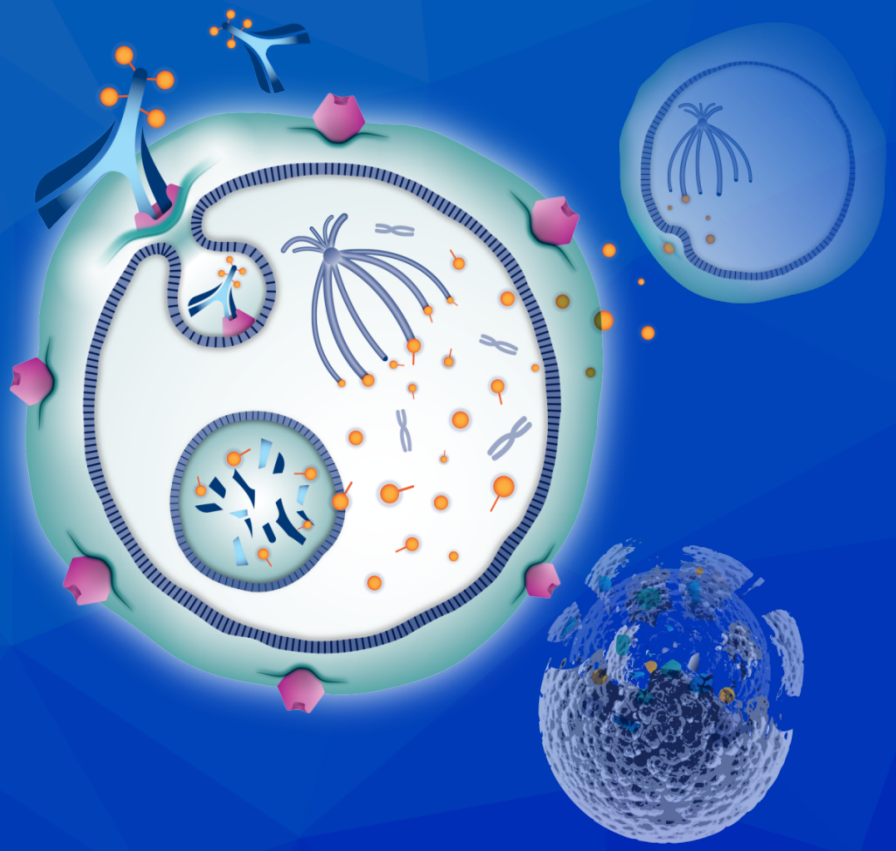
**Low**

| 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

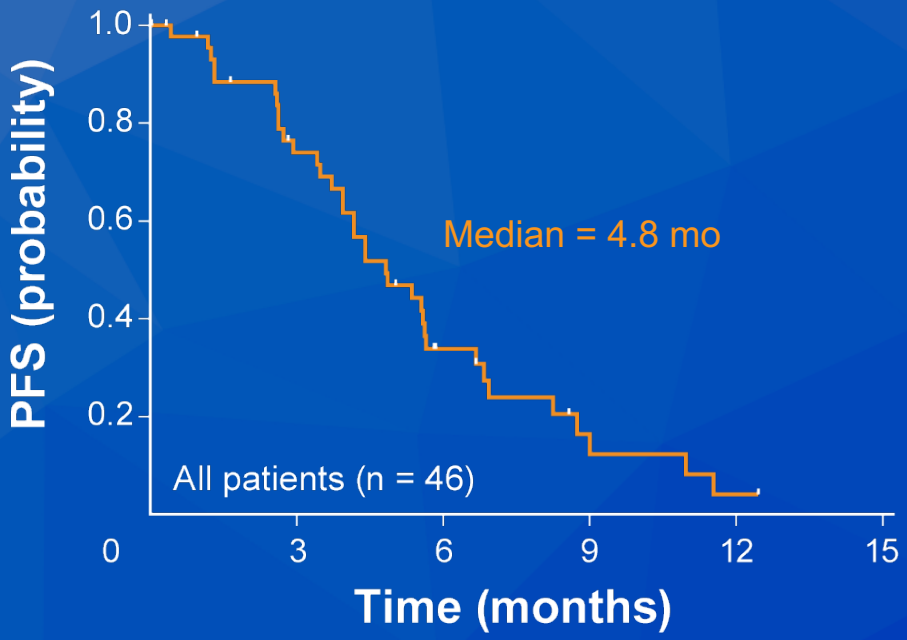
ORIGINAL REPORT

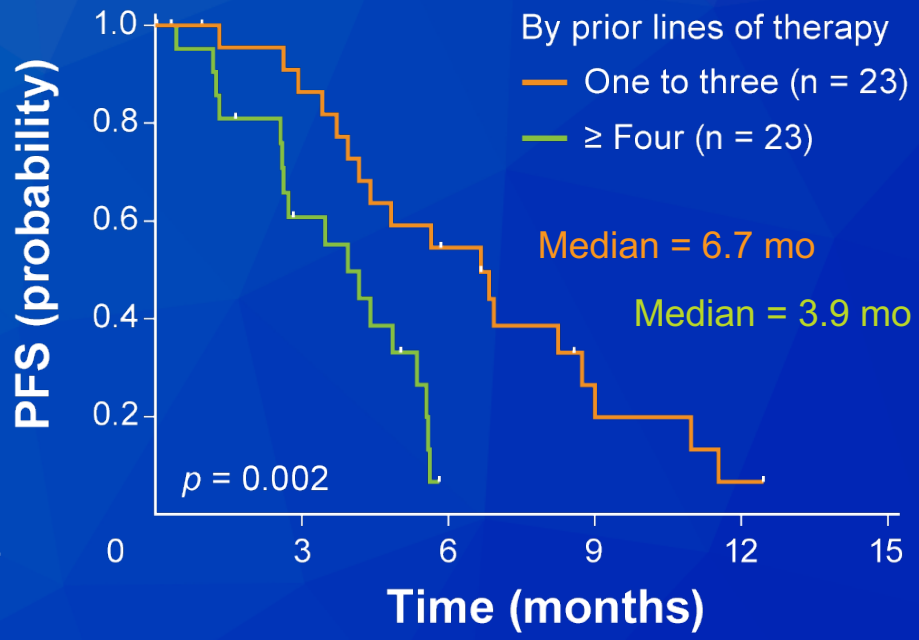
# Safety and Activity of Mirvetuximab Soravtansine (IMGN853), a Folate Receptor Alpha–Targeting Antibody–Drug Conjugate, in Platinum-Resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer: A Phase I Expansion Study

*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 Armstrong

Folate receptor alpha (FRA) is highly expressed in epithelial ovarian cancer (EOC). Prior studies of FRA targeting in EOC have used farletuzumab, a moAb to FRA, and the folate–chemotherapy conjugate vintafolide. FAR-131, a phase III trial of platinum/taxane alone or with two doses of farletuzumab, did not demonstrate an improved PFS for the arms with farletuzumab. A phase II study in patients with low-CA125 platinum-sensitive recurrent ovarian cancer is currently under way. The phase II PRECEDENT trial demonstrated a PFS of 5 months for pegylated liposomal doxorubicin (PLD) with vintafolide compared to 2.7 months with PLD alone. However, the phase III PROCEED study was stopped in 2014 when a futility analysis demonstrated that vintafolide plus PLD did not meet the pre-specified PFS outcomes.

# Editorial — Dr Armstrong (continued)

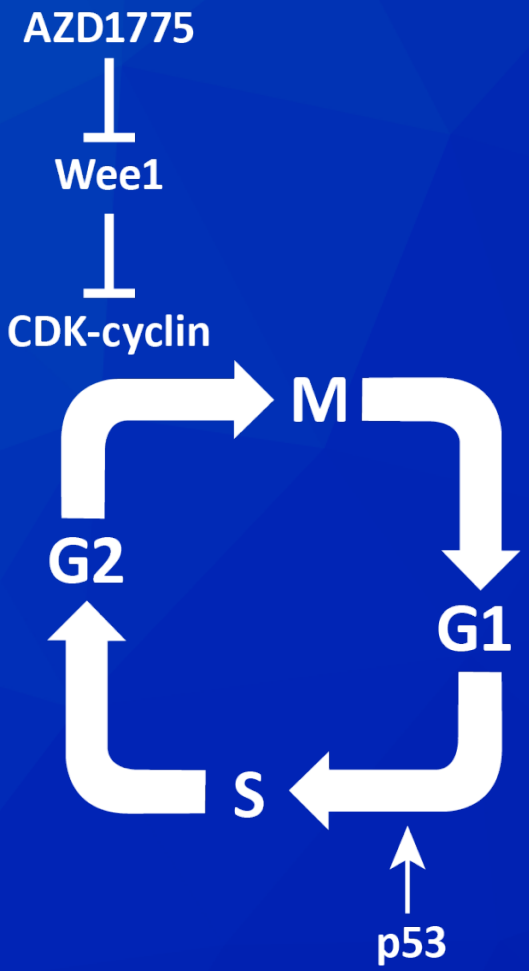
Mirvetuximab soravtansine (IMGN853) is an antibody-drug conjugate consisting of a humanized anti-FRA antibody linked to the tubulin-disrupting maytansinoid DM4. This phase I expansion study treated 46 platinum-resistant FRA-expressing EOC patients and demonstrated an ORR of 26% (1 CR, 11 PR), 39% ORR in 23 patients who had received ≤3 lines of therapy. The drug is currently being compared to investigator choice in recurrent platinum-resistant, FRA-expressing EOC in the FORWARD 1 study and in combination with gemcitabine, bevacizumab, carboplatin, PLD and pembrolizumab in Phase I studies.

# Editorial — Dr Armstrong (continued)

The best marker for FRA expression remains to be determined, whether IHC (and which Ab) or functional imaging. Of note, FRA can be targeted without resulting in folate depletion because most cellular folate uptake is via the alternate reduced folate carrier.

# 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

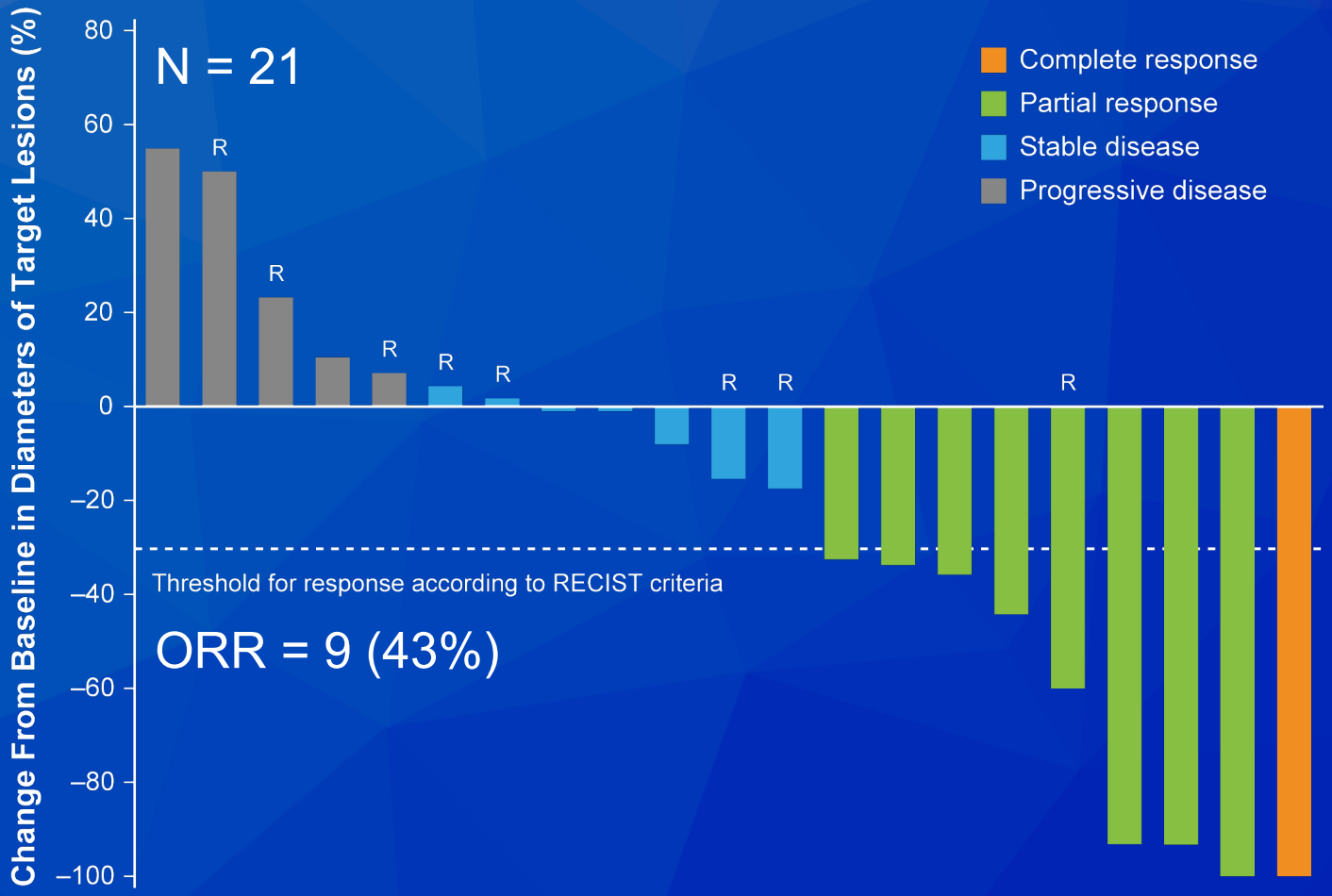
ORIGINAL REPORT

# 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 Armstrong

Platinum agents are the backbone of treatment for ovarian cancer, and finding a means to increase platinum sensitivity or overcome platinum resistance is the holy grail in ovarian cancer. This phase II trial tested the oral WEE1 TKI AZD1775 in combination with carboplatin in 23 highly resistant patients whose disease progressed during, or recurred within 3 months of completing, first line platinum taxane treatment. The ORR in 21 evaluable patients was 43%, including one patient with a prolonged CR and two patients with ongoing response for more than 31 and 42 months.

# Editorial — Dr Armstrong (continued)

Although studies in platinum resistant disease (AURELIA and others) have shown ORR up to 50%-60%, particularly with weekly paclitaxel combinations, some excluded primary resistant disease and most had predominantly late-recurrent patients with a platinum-free interval of >3 months. These results, if confirmed, are thus considered highly significant.

p53 is the key regulator of the G1 checkpoint. Cells with deficient or mutated p53 rely on the G2 checkpoint for DNA repair to damaged cells. WEE1 is a tyrosine kinase that normally inhibits cell cycle progression by phosphorylation of CDK1, resulting in G2 cell cycle arrest that allows for repair of DNA damage.

# Editorial — Dr Armstrong (continued)

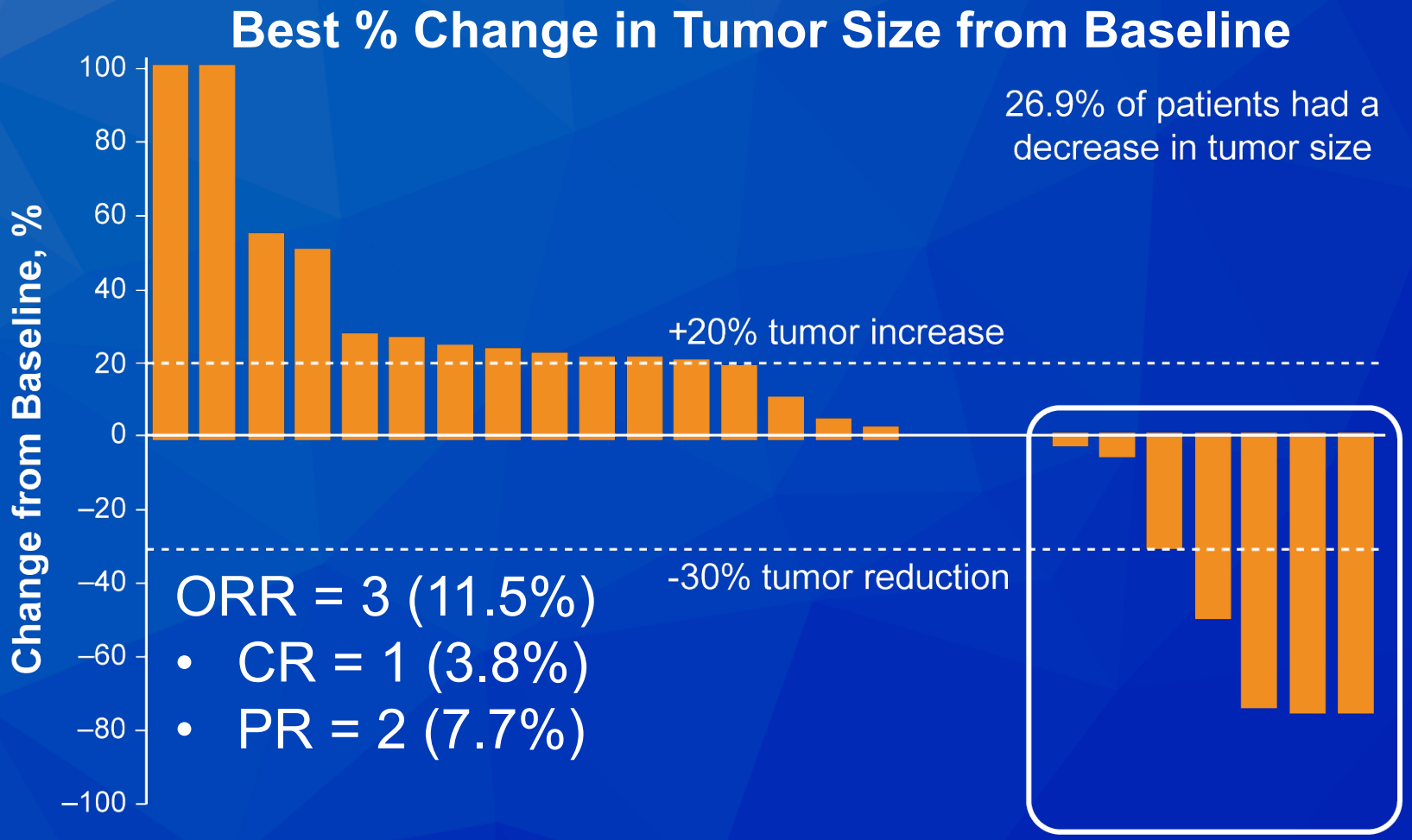
By allowing CDK1 to bind to cyclin B, inhibition of WEE1 impairs the G2 damage checkpoint, allowing mitosis to proceed without DNA repair, resulting in apoptotic cell death in TP53 mutated cells. Perhaps a kind of “synthetic lethality” for cells with TP53 mutations.

Trial eligibility included TP53 mutation, a common event in ovarian cancer, particularly in high grade serous histology, 70% of the patients in this study. What is not clear is whether the combination of carboplatin and AZD1775 is truly synergistic or if the responses are due to single agent activity of AZD1775.

# 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.

# 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.

# Editorial — Dr Armstrong

In lung cancer, PD-L1 positivity predicts response to and efficacy of PD-1 targeting with pembrolizumab or nivolumab. In contrast, efficacy of pembrolizumab in endometrial cancer is related to MSI from deleted or damaged DNA mismatch repair (MMR) proteins, and PD-L1 expression does not appear to predict response.

In this updated report of the KEYNOTE-028 study, patients with PD-L1 positive recurrent ovarian cancer were treated with pembrolizumab. This was a heavily pretreated population with nearly 40% having had five or more lines of therapy. Of 26 patients there were 3 responses (ORR 11.5%, 1 CR, 2 PR) and 6 (23%) patients with SD or a minor response. While response rate was low, median duration of response was over 24 months.

# Editorial — Dr Armstrong (continued)

Overall response of ovarian cancer to immune checkpoint inhibition has been low, ranging from 10% to 15% across multiple trials using different agents, including the 11.5% ORR in this trial. However, it should be pointed out that this rate is similar to the rate seen in unselected patients with NSCLC. Given the prolonged responses seen when the agent does work, it is critical to identify biomarkers of response. For this trial, the definition of PD-L1 positivity was ≥1% membrane staining on tumor cells or TILs. In the KEYNOTE-024 trial of pembrolizumab versus chemotherapy in NSCLC, the criteria for PD-L1 positivity was >50% staining, thus the cutoff in this trial may have been too low.

# Editorial — Dr Armstrong (continued)

The presence of MSI is highest in endometrial and GI cancers, resulting in high levels of neoantigen production that can be recognized with immune stimulation. In a recent analysis of over 12,000 tumors for MMR deficiency we showed that less than 2% of epithelial ovarian cancers show deficiency in MMR.

# 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 Armstrong

It is clear from multiple studies that early institution of palliative care improves patient and family satisfaction with end of life care, decreases inappropriate use of aggressive medical interventions, improves rates of death outside of the acute care setting and decreases health care costs. This study examined the effects of a very early intervention with palliative care consultation within 12 weeks of diagnosis in women with gynecologic malignancies who had a less than 30% 5-year life expectancy. Not surprisingly, ACE scores, reflecting aggressive care interventions at the end of life, were significantly lower in women with early palliative care intervention.

# Editorial — Dr Armstrong (continued)

A major issue is access to palliative care services and provision of services that are focused on the needs of cancer patients. Not all institutions have such services, although more and more do; however, the provision of these services in the community is, I expect, more scarce. As providers most of us are pretty good at knowing when the end is near, but we sometimes hold out for the rare possibility of a response, particularly in the young patient or those who are desperate to live longer.

I would have liked to have known more about the patient population in this study. Median survival is 12-18 months for a patient with stage IV cervical cancer but is 2-3 times that (about 3 years) for a stage IV ovarian cancer patient, who might even have a window of time in complete remission.

# Editorial — Dr Armstrong (continued)

Early palliative care interventions will have variable meaning and benefits for different groups. I have generally referred my ovarian cancer patients to palliative care when they develop platinum resistant disease. I think this helps them and me.