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 8, 2020, 8:00 AM – 4:00 PM
Charlotte, North Carolina

Faculty

Jeremy Abramson, MD
Deborah K Armstrong, MD
Johanna Bendell, MD
Courtney D DiNardo, MD, MSCE
Charles E Geyer Jr, MD
Ian E Krop, MD, PhD
Ann S LaCasce, MD, MMSc
Corey J Langer, MD
Joyce F Liu, MD, MPH
John L Marshall, MD
William K Oh, MD
Daniel P Petrylak, MD
Gregory J Riely, MD, PhD
Mitchell R Smith, MD, PhD
Richard M Stone, MD
Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

Research To Practice®

Agenda

Module 1 — Lung Cancer: *Drs Langer and Riely*

Module 2 — Acute Leukemias: *Drs DiNardo and Stone*

Module 3 — Lymphomas and Chronic Lymphocytic Leukemia: *Drs Abramson, LaCasce and Smith*

Module 4 — Gastrointestinal Cancers: *Drs Bendell, Marshall and Wainberg*

Module 5 — Genitourinary Cancers: *Drs Oh and Petrylak*

Module 6 — Gynecologic Cancers: *Drs Armstrong and Liu*

Module 7 — Breast Cancer: *Drs Geyer and Krop*

Deborah K Armstrong, MD
Professor of Oncology
Professor of Gynecology and Obstetrics
Skip Viragh Outpatient Cancer Building
Johns Hopkins Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland

Disclosures

Advisory Committee	Cue Biopharma, Eisai Inc
Contracted Research	Advaxis Inc, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Pfizer Inc, Syndax Pharmaceuticals Inc, Tesaro, A GSK Company
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP

Joyce F Liu, MD, MPH
Assistant Professor of Medicine
Harvard Medical School
Director of Clinical Research
Division of Gynecologic Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Clovis Oncology, Mersana Therapeutics, Tesaro, A GSK Company

Gynecologic Cancers — Drs Armstrong and Liu

Ovarian Cancer

Endometrial Cancer

Cervical Cancer

Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline

Konstantinopoulos PA et al.
J Clin Oncol 2020;[Epub ahead of print].

ASCO Recommendations for Genetic and Somatic Tumor Testing for Patients Diagnosed with Epithelial Ovarian Cancer (OC)

- Germline genetic testing for BRCA1/2 and other OC susceptibility genes should be performed at the time of diagnosis; if results are positive, patients should be offered FDA-approved treatment options in up-front and recurrent settings
  - Somatic tumor testing for BRCA1/2 pathogenic or likely pathogenic variants should be performed for patients without germline BRCA 1/2 mutations
- Women diagnosed with clear cell, endometrioid or mucinous OC should be offered somatic tumor testing for mismatch repair deficiency (dMMR)
  - Those with identified dMMR should be offered FDA-approved treatment based on these results
- Genetic evaluations should be conducted in conjunction with healthcare providers familiar with the diagnosis and management of hereditary cancer
- First- or second-degree blood relatives of a patient with OC with a known germline pathogenic cancer susceptibility gene variant should be offered individualized genetic risk evaluation, counseling and genetic testing
- Clinical decision-making should not be based on a variant of uncertain significance

Konstantinopoulos PA et al. *J Clin Oncol* 2020;[Epub ahead of print].

Editorial — Dr Armstrong

Welcome to the future! We have seen data on PARP inhibitors with chemo, with bevacizumab, with chemo and bevacizumab, so it should not be surprising that the world wants to combine PARP inhibitors with immunotherapy. We have to acknowledge that the overall response of ovarian cancer to IO has been disappointingly low. However preclinical data have shown that PARP inhibitors can upregulate PD-L1 expression, enhance intratumoral T-cell infiltration and upregulate the activity of interferon, activities that have the potential to increase response to immune checkpoint inhibitors. In a phase I/II study of niraparib and pembrolizumab, Panos Konstantinopoulos documented an ORR of 18% in 62 ovarian cancer patients but a promising disease control rate of 65%.

Editorial — Dr Armstrong (continued)

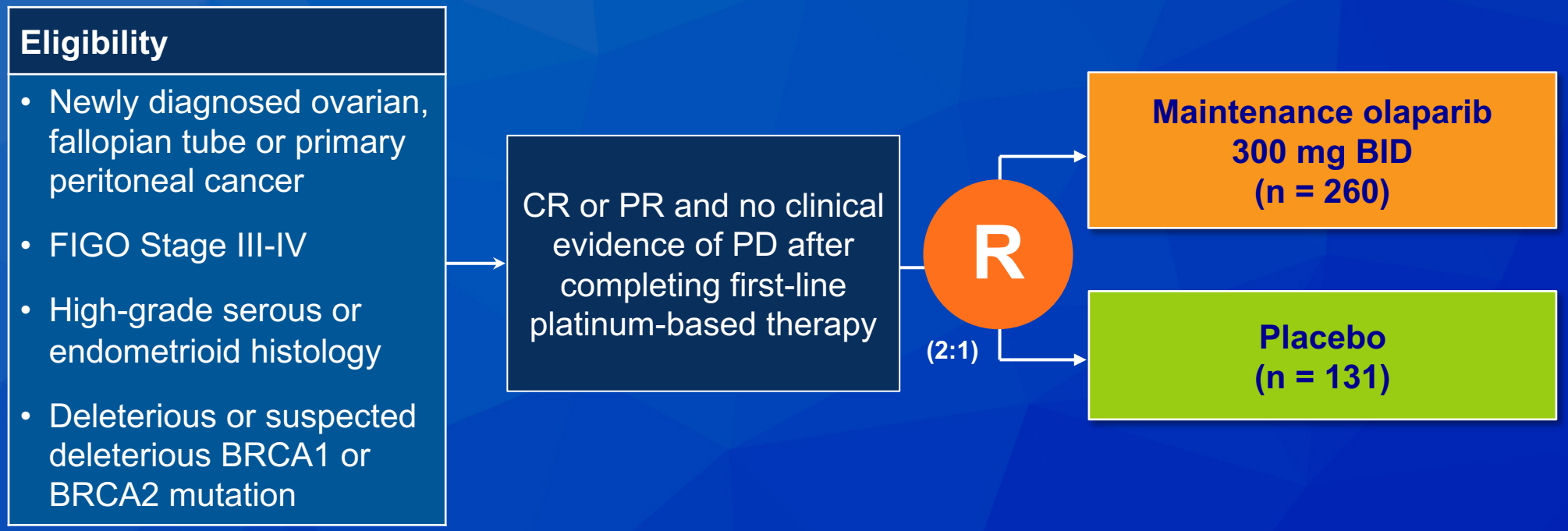
There are now multiple ongoing clinical trials in newly diagnosed and recurrent platinum-sensitive ovarian cancer examining platinum-based chemotherapy with an immune checkpoint inhibitor followed by PARP inhibitor maintenance, many continuing immunotherapy as part of maintenance, and some including bevacizumab with and after chemotherapy. Ka-ching!

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

Moore K et al.
N Engl J Med 2018;379(26):2495-505.

SOLO-1: A Phase III Trial of Maintenance Olaparib for Ovarian Cancer with BRCA Mutation

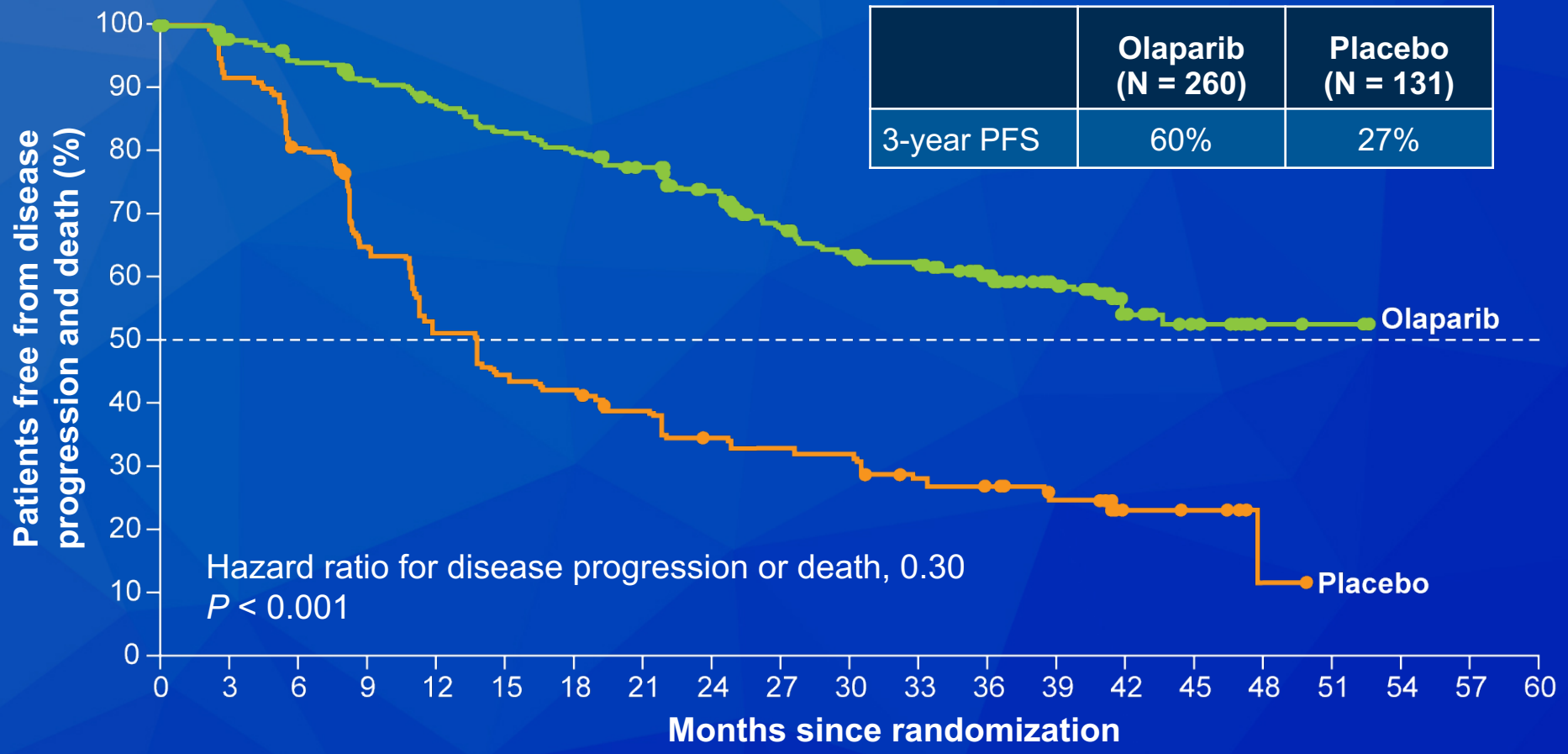
NCT01844986



Primary endpoint: Investigator-assessed progression-free survival

www.clinicaltrials.gov; Moore KN et al. *Proc ASCO* 2014;Abstract TPS5616; Moore K et al. *N Engl J Med* 2018;379(26):2495-505.

SOLO-1 Primary Endpoint: Progression-Free Survival (Investigator Assessed)

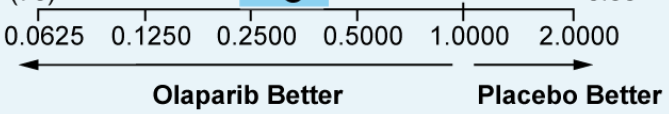


	Olaparib (N = 260)	Placebo (N = 131)
3-year PFS	60%	27%

Moore K et al. *N Engl J Med* 2018;379(26):2495-505.

SOLO-1: PFS Subgroup Analyses

Subgroup	Olaparib	Placebo	Hazard Ratio for Disease Progression or Death
	no. of patients with disease progression or death/total no. (%)		
All patients	102/260 (39)	96/131 (73)	0.30
Clinical response after chemotherapy			
Complete response	73/213 (34)	73/107 (68)	0.35
Partial response	29/47 (62)	23/24 (96)	0.19
ECOG performance status at baseline			
Normal activity	75/200 (38)	76/105 (72)	0.33
Restricted activity	27/60 (45)	20/25 (80)	0.38
CA-125 level at baseline			
≤ULN	92/247 (37)	89/123 (72)	0.34
>ULN	10/13 (77)	7/7 (100)	NC
Germline BRCA mutation according to testing at Myriad			
BRCA1	84/188 (45)	69/91 (76)	0.40
BRCA2	15/62 (24)	26/39 (67)	0.20
BRCA1 and BRCA2	0/3	0/0	NC
None	3/7 (43)	1/1 (100)	NC
Age at baseline			
<65 yr	85/225 (38)	82/112 (73)	0.33
≥65 yr	17/35 (49)	14/19 (74)	0.45
International FIGO stage at initial diagnosis			
Stage III	83/220 (38)	79/105 (75)	0.32
Stage IV	19/40 (48)	17/26 (65)	0.49
Presence of residual macroscopic disease after debulking surgery performed before trial entry			
Yes	29/55 (53)	23/29 (79)	0.44
No	70/200 (35)	69/98 (70)	0.33



Moore K et al. *N Engl J Med* 2018;379(26):2495-505.

Editorial — Dr Armstrong

While it is clear that nearly all patients with advanced, high-grade ovarian cancer will benefit from PARP inhibitors at some point in their therapy, the group that has the greatest benefit are those with a BRCA mutation. The SOLO-1 study examined the use of olaparib maintenance after completion of initial chemotherapy in BRCA-associated advanced ovarian cancers. Patients had to demonstrate a response to chemotherapy. Those in a CR were treated for 2 years while those in a PR could continue past two years if they had further response demonstrated with the olaparib. The 3-year PFS was highly significant: 60% in the olaparib treated group compared to 27% in the placebo group. Although the study allowed both germline (gBRCA) and somatic (sBRCA), there were only 2 patients in the study with sBRCA. However, since prior studies examining PARP inhibitors in BRCA-associated ovarian cancer had demonstrated similar benefits in sBRCA and gBRCA, the FDA approved maintenance olaparib in both groups.

Editorial — Dr Armstrong (continued)

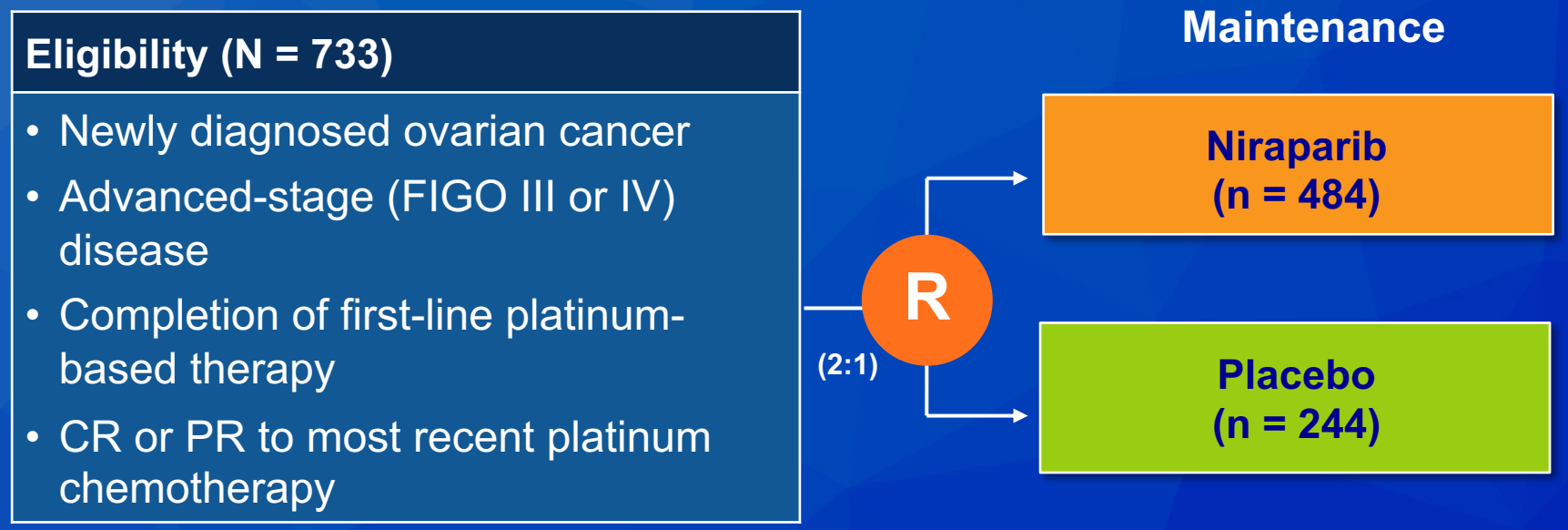
There were no new toxicity signals, with nausea, vomiting, fatigue, anemia and neutropenia predominating. Most of these toxicities were low grade and rarely required discontinuation or prolonged dose interruption. However, there were 3 cases of AML in the 260 pts on olaparib (1.2%), all fatal, a rate similar to that reported in other PARP inhibitor studies, but still sobering. The onset was 1.5–2.5 years after initiation of olaparib. One important point of data that is in the supplementary information was that 17/341 (~5%) Foundation Medicine tumor tests did not confirm the documented germline BRCA mutations. These discordances between germline *BRCA* results and tumor *BRCA* results are probably explained by technical differences in the areas of the gene covered by the test, variant classification, and detection of large rearrangements, but it does suggest that we should still do germline BRCA testing even if tumor testing is negative.

Niraparib Therapy in Patients with Newly Diagnosed Advanced Ovarian Cancer

González-Martín A et al.

Proc ESMO 2019;Abstract LBA1;
N Engl J Med 2019;[Epub ahead of print].

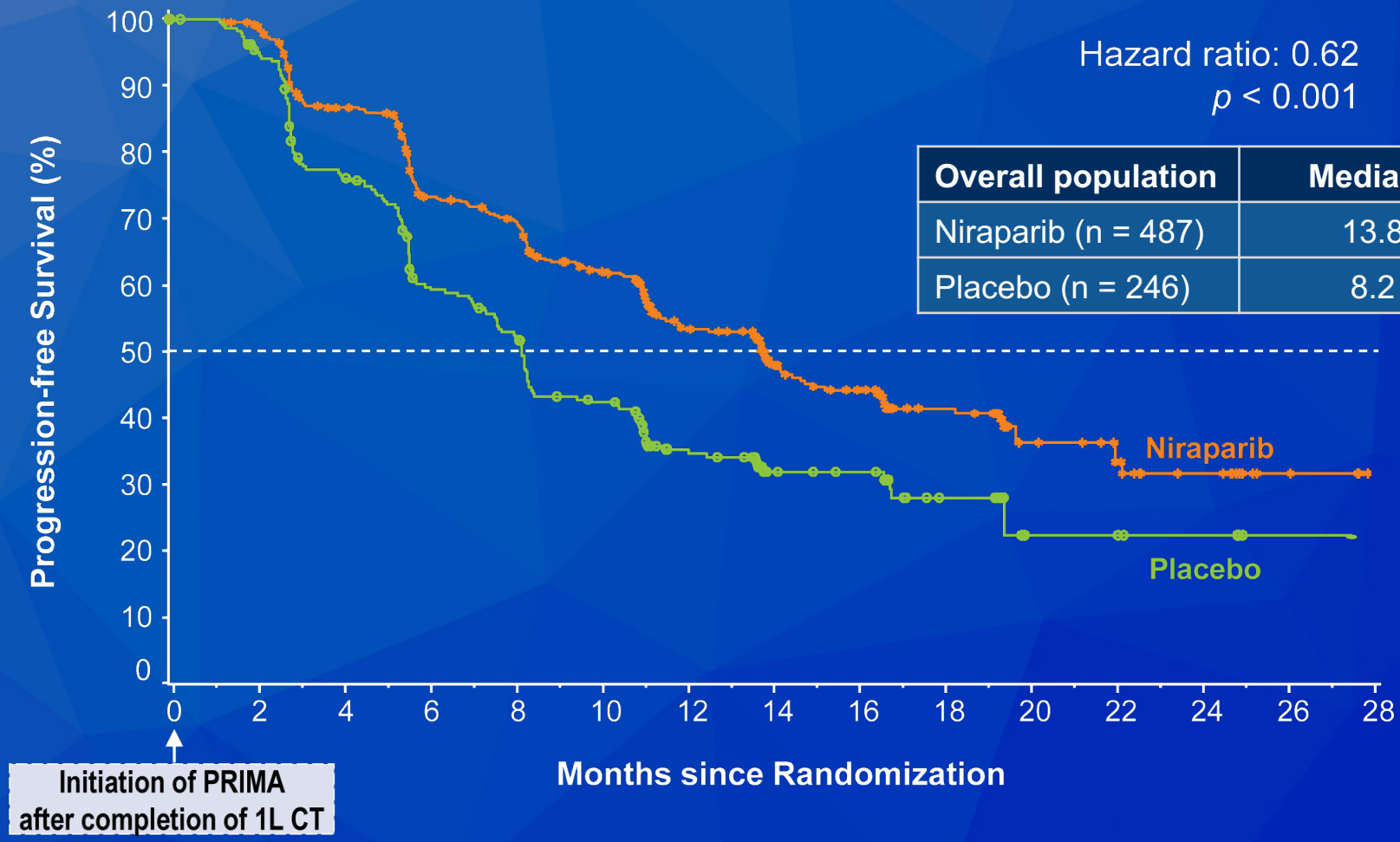
PRIMA: Phase III Trial Schema



Primary endpoint: Progression-free survival

González-Martín A et al. *Proc ESMO* 2019;Abstract LBA1; *N Engl J Med* 2019;[Epub ahead of print].

PRIMA Primary Endpoint: Progression-Free Survival



- Median PFS in the HR-deficient population was 21.9 months for niraparib and 10.4 months for placebo (HR 0.43, $p < 0.001$)
- No new safety signals were identified for niraparib

González-Martín A et al. *Proc ESMO* 2019;Abstract LBA1; *N Engl J Med* 2019;[Epub ahead of print].

PRIMA: Progression-Free Survival by Homologous Recombination (HR) Status

HR status	N	Hazard ratio
HR deficient, BRCA mutation	31	0.40
HR deficient, BRCA wild type	20	0.50
HR proficient	35	0.68
HR not determined	15	0.85

González-Martín A et al. *Proc ESMO* 2019;Abstract LBA1; *N Engl J Med* 2019;[Epub ahead of print].

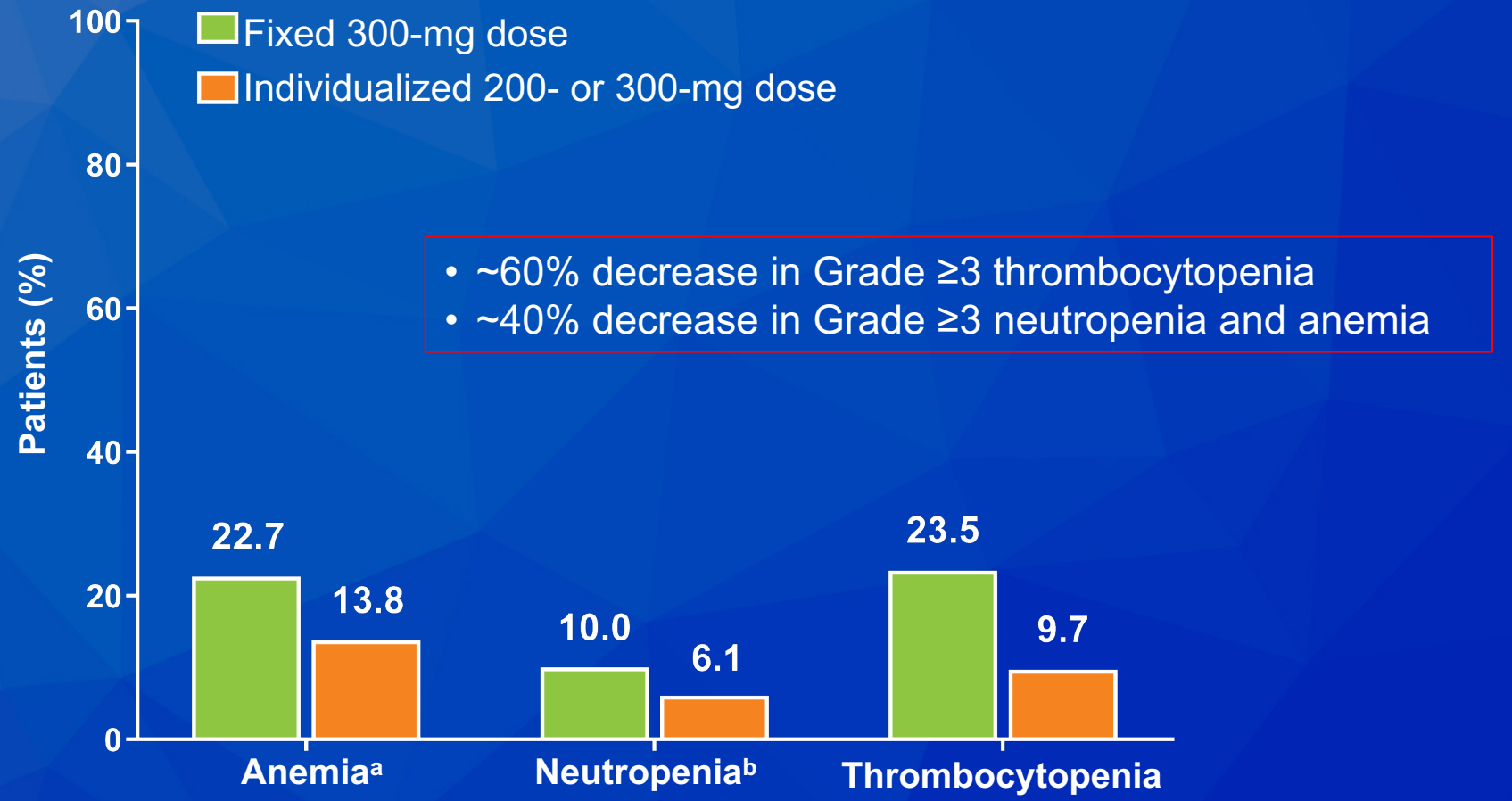
A Prospective Evaluation of Tolerability of Niraparib Dosing Based Upon Baseline Body Weight and Platelet Count: Blinded Pooled Interim Safety Data from the ENGOT-OV26/PRIMA Study

Monk BJ et al.

Proc SGO 2019;Abstract 3.

Grade ≥3 Hematologic Toxicities Decreased with Individualized Dosing Regimen

A Prospective Evaluation of Tolerability of Niraparib Dosing Based Upon Baseline Body Weight and Platelet Count: Pooled Interim Safety Data From the PRIMA Study



[a] Anemia events included anemia and hemoglobin decrease.
[b] Neutropenia events included neutropenia, febrile neutropenia and neutrophil count decrease.

Monk BJ et al. *Proc SGO* 2019;Abstract 3 (Plenary).

Editorial — Dr Armstrong

The PARP inhibitor niraparib is approved for maintenance therapy in recurrent ovarian cancer patients responsive to platinum-based therapy. Similar to olaparib it has been tested as maintenance after initial treatment of advanced ovarian cancer but in patients unselected for BRCA mutation status. The results of the Phase III PRIMA (ENGOT-OV26) study have been released but have not yet been presented at a scientific meeting. It is reported that niraparib demonstrated a statistically significant improvement over placebo in PFS, regardless of patient biomarker status. Brad Monk presented safety results at the 2019 SGO meeting. Although FDA-approved dosing is 300 mg daily, it had previously been shown that body weight and platelet count predicted niraparib toxicity. Therefore PRIMA was amended to modify the starting dose to 200 mg daily in patients with baseline weight <77 kg or platelet count <150 K/μL and 300 mg in all other patients (individualized dosing).

Editorial — Dr Armstrong (continued)

Overall, ~1/3 of patients in the study had individualized dosing. Almost 75% of the individualized patients (181/247) started at the 200-mg dose. As expected, there were fewer AEs and less toxicity in the individualized-dosing group, including a lower rate of serious AEs and of AEs leading to treatment discontinuation. PRIMA will be presented 9/28 at ESMO. It will be interesting to see the magnitude of the benefit of maintenance PARP inhibitor therapy in the non-BRCA group and to see if there are sufficient subjects with BRCA mutations to compare with the SOLO-1 olaparib front-line maintenance data.

Phase III PAOLA-1/ENGOT-ov25: Maintenance Olaparib with Bevacizumab in Patients with Newly Diagnosed, Advanced Ovarian Cancer Treated with Platinum-Based Chemotherapy and Bevacizumab as Standard of Care

Ray-Coquard I et al.

Proc ESMO 2019;Abstract LBA2.

PAOLA-1: Olaparib or Placebo Combined with Bevacizumab as Maintenance Therapy for Patients with Advanced Ovarian Cancer

Study design

- FIGO Stage III–IV high-grade ovarian cancer (serous or endometrioid)* or nonmucinous BRCAm
- No evidence of disease or CR or PR following first-line platinum-based chemotherapy plus bevacizumab
- A minimum of 3 cycles of platinum-based chemotherapy plus bevacizumab (2 after interval debulking)
- ECOG PS 0–1

BRCA testing prior to randomisation

Randomise 2:1

Stratify by:
- tBRCA status
- CR/PR/NED

Olaparib
300 mg† *po* bid +
Bevacizumab
15 mg/kg Q3W
15 months

Placebo
+
Bevacizumab
15 mg/kg Q3W
15 months

Primary endpoint
- PFS1 (RECIST 1.1)

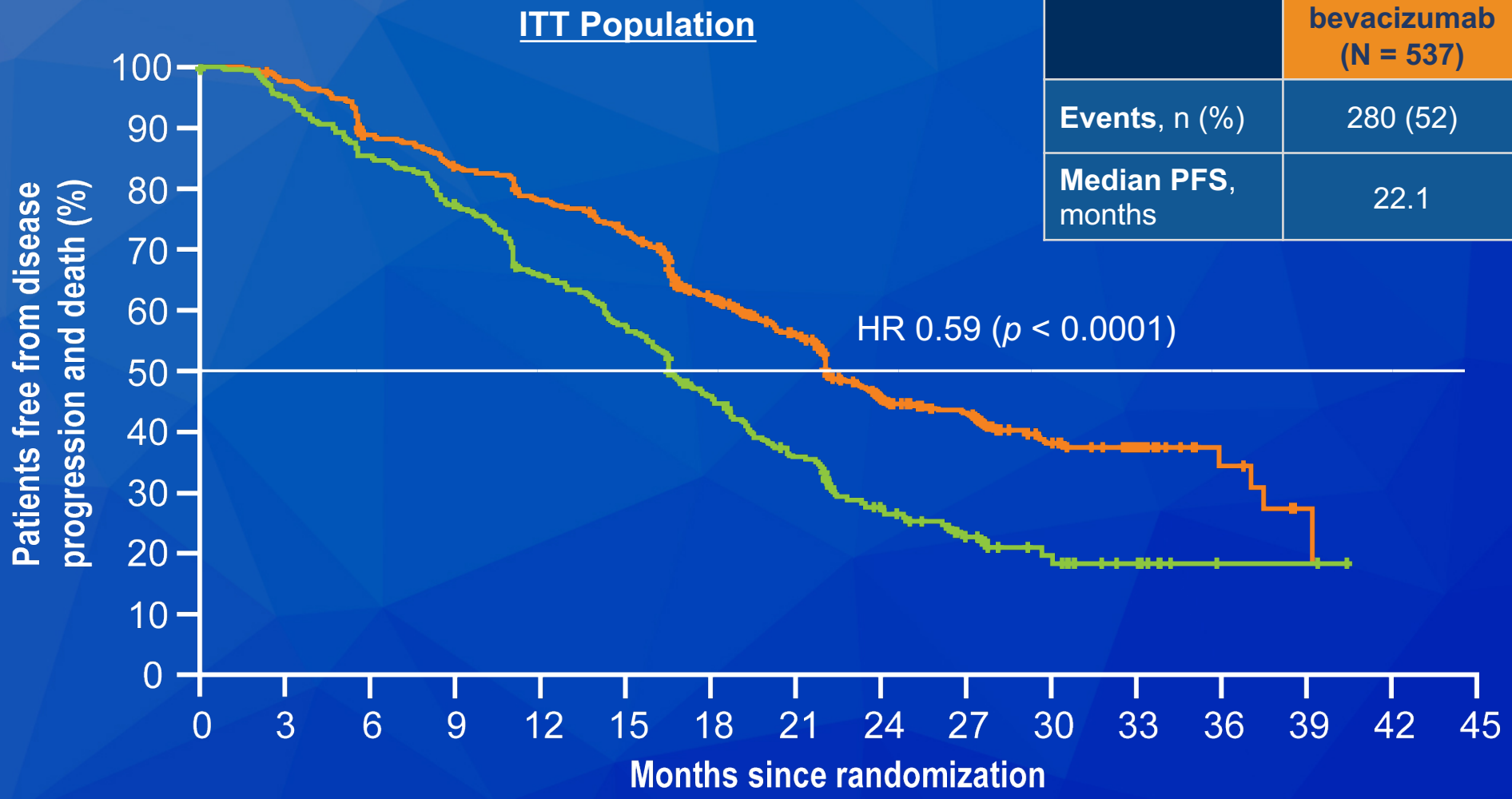
Secondary endpoints
- PFS2
- TSST
- OS
- Safety
- PRO/HRQoL

Status: Completed enrolment

*Includes patients with primary peritoneal and/or fallopian tube cancer
†Tablet formulation (2 tablets twice daily)
ECOG=Eastern Cooperative Oncology Group; OS=overall survival; po=by mouth; PFS=progression-free survival; PFS2=time to second progression; HRQoL=Health-related quality of life; TSST=time to second subsequent therapy; Q3W=every 3 weeks; PRO=patient reported outcome
Ray-Coquard I et al. *J Clin Oncol* 34, 2016 (suppl; abstr TPS5607 and poster presentation); Clinicaltrials.gov identifier: NCT02477644; Closed Aug 2017 N=806

PAOLA Primary Endpoint: Progression-Free Survival

	Olaparib + bevacizumab (N = 537)	Placebo + bevacizumab (N = 269)
Events, n (%)	280 (52)	194 (72)
Median PFS, months	22.1	16.6



Ray-Coquard I et al. *Proc ESMO* 2019;Abstract LBA2.

PAOLA: Progression-Free Survival Biomarker Subgroup Analyses

Median PFS	Olaparib + bev	Placebo + bev	HR
Detected tBRCAm (n = 157; 80)	37.2 mo*	21.7 mo	0.31
No detected tBRCAm (n = 380; 189)	18.9 mo	16.0 mo	0.71
HRD-positive (including tBRCAm) (n = 255; 132)	37.2 mo*	17.7 mo	0.33
HRD-positive (excluding tBRCAm) (n = 97; 55)	28.1 mo*	16.6 mo	0.43

tBRCAm = BRCA tumor mutation

* Median is unstable due to lack of events – less than 50% maturity

Ray-Coquard I et al. *Proc ESMO* 2019;Abstract LBA2.

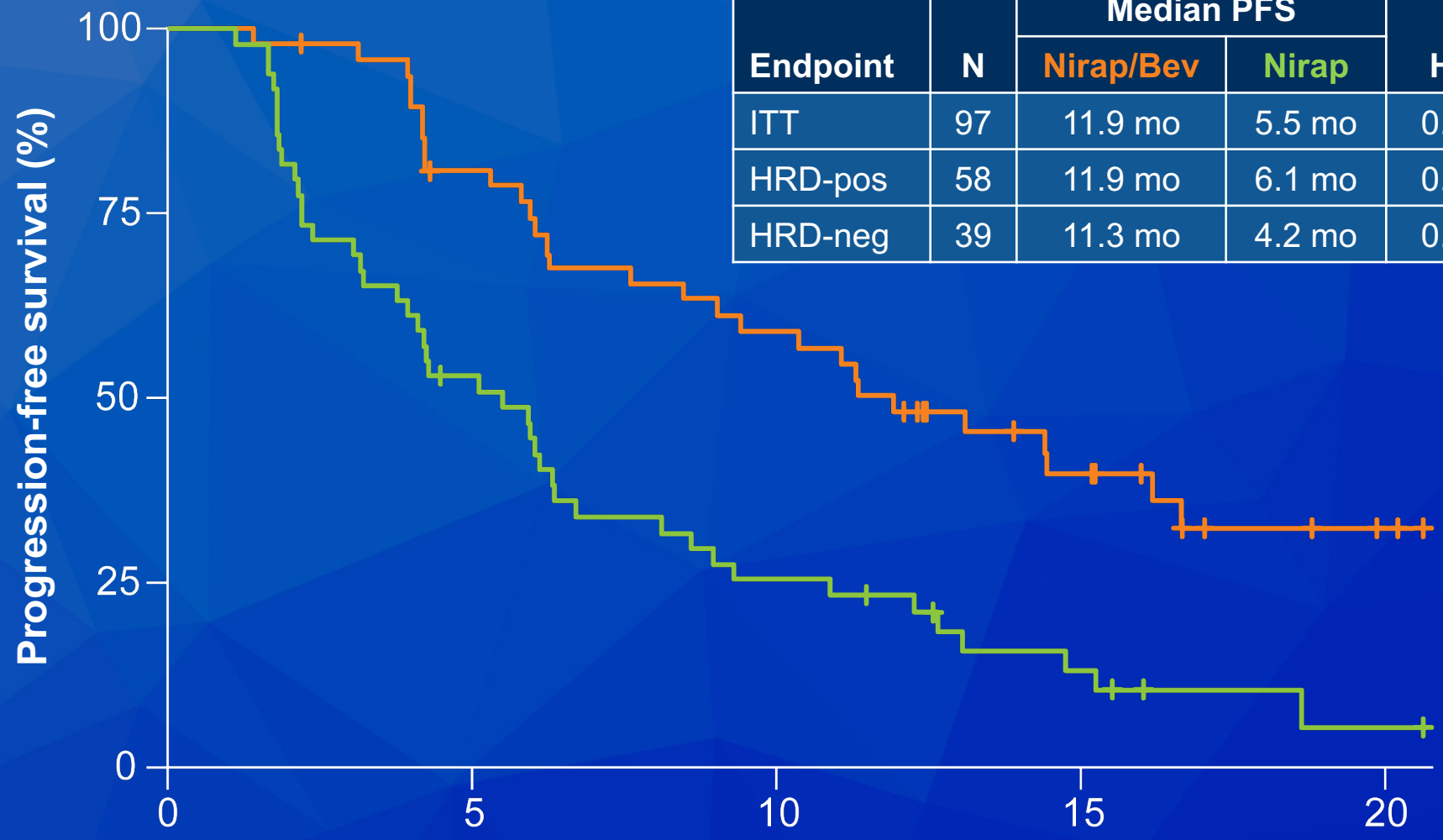
Niraparib plus Bevacizumab versus Niraparib Alone for Platinum-Sensitive Recurrent Ovarian Cancer (NSGO-AVANOVA2/ENGOT-ov24): A Randomised, Phase 2, Superiority Trial

Mirza MR et al.

Lancet Oncol 2019;20(10):1409-19.

NSGO-AVANOVA2/ENGOT-ov24: Progression-Free Survival (ITT)

Endpoint	N	Median PFS		HR	*P*-value
		Nirap/Bev	Nirap		
ITT	97	11.9 mo	5.5 mo	0.35	<0.0001
HRD-pos	58	11.9 mo	6.1 mo	0.38	—
HRD-neg	39	11.3 mo	4.2 mo	0.40	—



Mirza MR et al. *Lancet Oncol* 2019;20(10):1409-19.

Editorial — Dr Liu (continued)

Mirza et al.

A Phase 2 study comparing cediranib and olaparib to olaparib alone in relapsed platinum-sensitive ovarian cancer suggested that anti-angiogenic/PARP inhibitor combinations could have synergistic activity in this patient population. In the AVANOVA2 study, Mirza and colleagues found similar results with the combination niraparib and bevacizumab regimen, with a median PFS of 11.9 months compared to 5.5 months with niraparib monotherapy. In subgroup analyses by HRD status, increased activity of the niraparib/bevacizumab combination was seen regardless of whether tumors were HR deficient or HR proficient. The population in this study was slightly different than in the prior cediranib/olaparib study, as in general they were slightly less heavily pretreated and more platinum sensitive, and the proportion of BRCA1/2 carriers in the study was smaller.

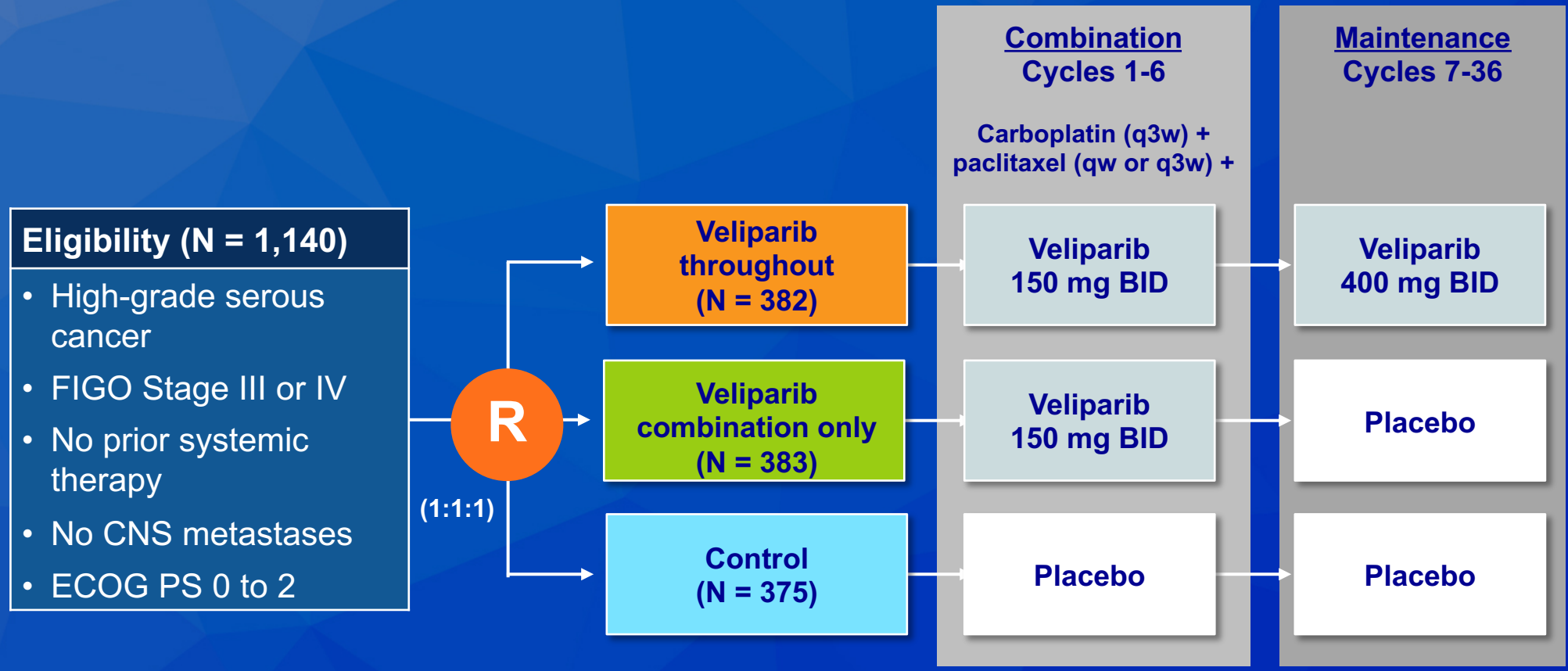
Editorial — Dr Liu (continued)

The regimen did have increased toxicity compared to niraparib monotherapy, with higher hypertension and proteinuria, but overall appears to have better tolerability than the cediranib/olaparib combination. Like the cediranib/olaparib study, the AVANOVA2 study does not have a standard-of-care chemotherapy arm, and comparison against platinum-based chemotherapy will be needed before we can say that an anti-angiogenic/PARP inhibitor chemotherapy-free regimen is an appropriate alternative in these patients. However, this study is exciting, as it is the second randomized study that has now demonstrated potential synergism between anti-angiogenics and PARP inhibitors.

VELIA/GOG-3005: Integration of Veliparib with Front-Line Chemotherapy and Maintenance in Women with High-Grade Serous Carcinoma of Ovarian, Fallopian Tube, or Primary Peritoneal Origin

Coleman RL et al.
Proc ESMO 2019;Abstract LBA3.

VELIA/GOG-3005: Phase III Trial Schema



Primary endpoint: Progression-free survival for "veliparib throughout" versus control

Coleman RL et al. *Proc ESMO* 2019;Abstract LBA3.

VELIA/GOG-3005: Progression-Free Survival by Investigator Assessment

Median PFS	Veliparib throughout	Control	HR (*p*-value)
ITT population (n = 382; 375)	23.5 mo	17.3 mo	0.68 (<0.001)
BRCAm population (n = 108; 92)	34.7 mo	22.0 mo	0.44 (<0.001)
HRD population (n = 214; 207)	31.9 mo	20.5 mo	0.57 (<0.001)
BRCA wt/HRD population (n = 106; 115)	22.9 mo	19.8 mo	0.74 (NR)
Non-HRD population (n = 125; 124)	15.0 mo	11.5 mo	0.81 (NR)

NR = not reported

Coleman RL et al. *Proc ESMO* 2019;Abstract LBA3.

Editorial — Dr O'Malley

VELIA compared three arms of veliparib with chemotherapy plus maintenance versus with chemotherapy without maintenance versus chemotherapy alone. VELIA met its primary PFS endpoint for the entire population when comparing veliparib with chemotherapy plus maintenance versus chemotherapy alone (HR=0.68). VELIA was most impactful as the first phase III trial to show we could combine a PARP inhibitor with standard chemotherapy safely, which results in a significant impact in these front-line patients. Though it impacted the entire intent-to-treat population, the greatest impact appeared to be in the *BRCA*- (HR=0.44) and HRD-positive (HR=0.57) patients. The ability to combine chemotherapy with a PARP inhibitor could potentially move PARP inhibitors ahead of bevacizumab in the adjuvant and maintenance setting of first-line ovarian cancer.

FDA Approves Niraparib for Previously Treated Advanced Ovarian Cancer with HRD-Positive Status

Press Release – October 23, 2019

"The Food and Drug Administration approved niraparib for patients with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD)-positive status. HRD is defined by either a deleterious or suspected deleterious *BRCA* mutation, or genomic instability in patients with disease progression greater than six months after response to the last platinum-based chemotherapy. Efficacy was investigated in 98 patients with advanced ovarian cancer with HRD-positive tumors in the single-arm QUADRA (NCT02354586) trial.

The recommended niraparib dose is 300 mg taken once daily with or without food. Patients should be selected for therapy based on an FDA-approved companion diagnostic for niraparib."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-niraparib-hrd-positive-advanced-ovarian-cancer

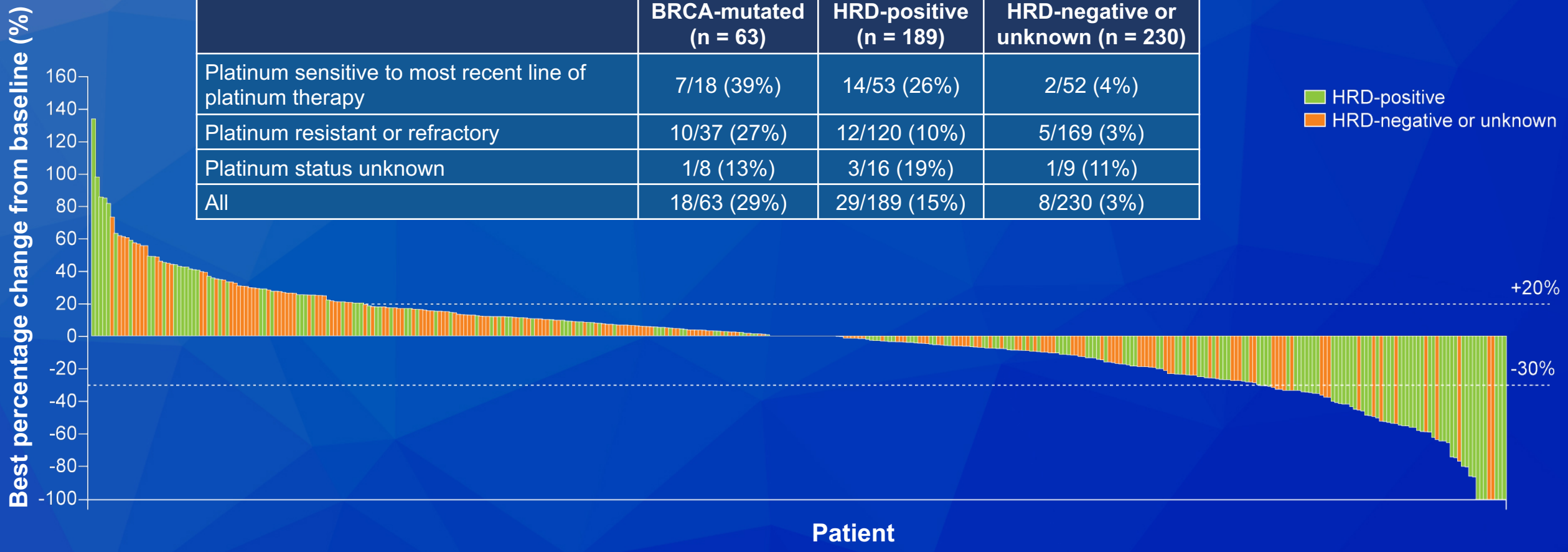
Niraparib Monotherapy for Late-Line Treatment of Ovarian Cancer (QUADRA): A Multicentre, Open-Label, Single-Arm, Phase 2 Trial

Moore KN et al.
Lancet Oncol 2019;20(5):636-48.

QUADRA: Tumor Response by HRD Status

Confirmed Objective Response

	BRCA-mutated (n = 63)	HRD-positive (n = 189)	HRD-negative or unknown (n = 230)
Platinum sensitive to most recent line of platinum therapy	7/18 (39%)	14/53 (26%)	2/52 (4%)
Platinum resistant or refractory	10/37 (27%)	12/120 (10%)	5/169 (3%)
Platinum status unknown	1/8 (13%)	3/16 (19%)	1/9 (11%)
All	18/63 (29%)	29/189 (15%)	8/230 (3%)



Moore KN et al. *Lancet Oncol* 2019;20(5):636-48.

OReO Trial: PARPi After PARPi (Olaparib Maintenance Re-treatment)

Two cohorts independently powered for PFS, one for BRCAm and one for BRCAwt (HRD pos and HRD neg)

All epithelial ovarian cancer*

1 prior PARP inhibitor maintenance period

Known *BRCA* status

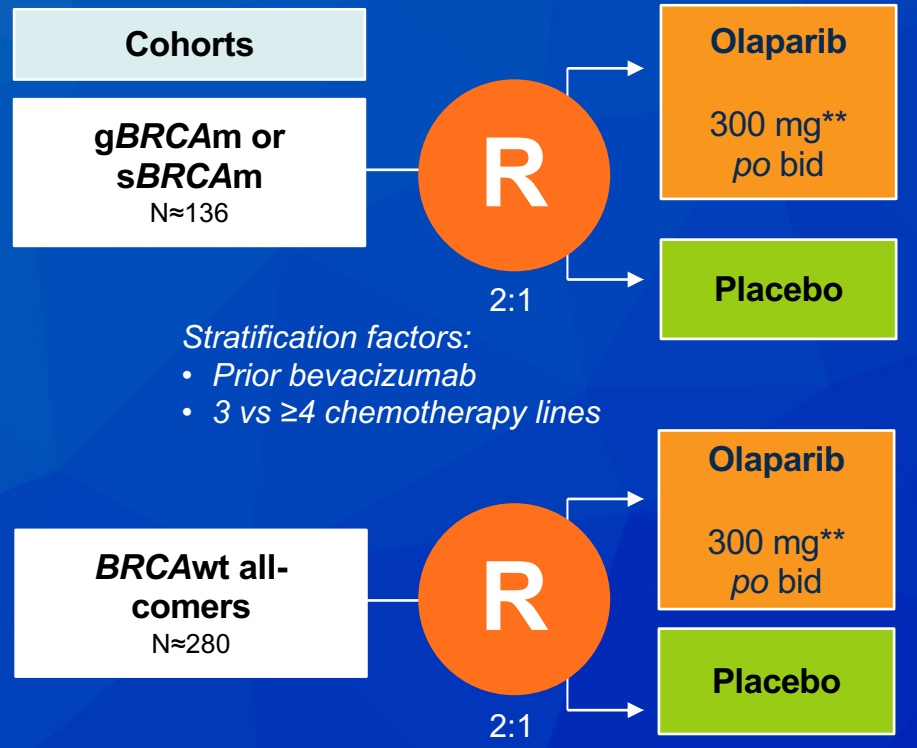
PLUS

Response ≥PR to most recent platinum CT (not bevacizumab)

Entry based on length of first PARP inhibitor exposure

*BRCA*m →
- PARP inhibitor ≥18 mo (after first-line CT)
- PARP inhibitor ≥12 mo (after second-line CT)

*BRCA*wt →
- PARP inhibitor ≥12 mo (after first-line CT)
- PARP inhibitor ≥6 mo after second- or later-line CT



Primary outcome
- PFS

Secondary outcomes
- TFST
- TSST
- FACT-O
- Safety and AEs
- OS

FSI 2Q 2017

PFS readout: BRCAm 4Q 2020
BRCAwt 2Q 2021

CSR 3Q 2022

*Not restricted to high-grade serous ovarian cancer

**Tablet formulation

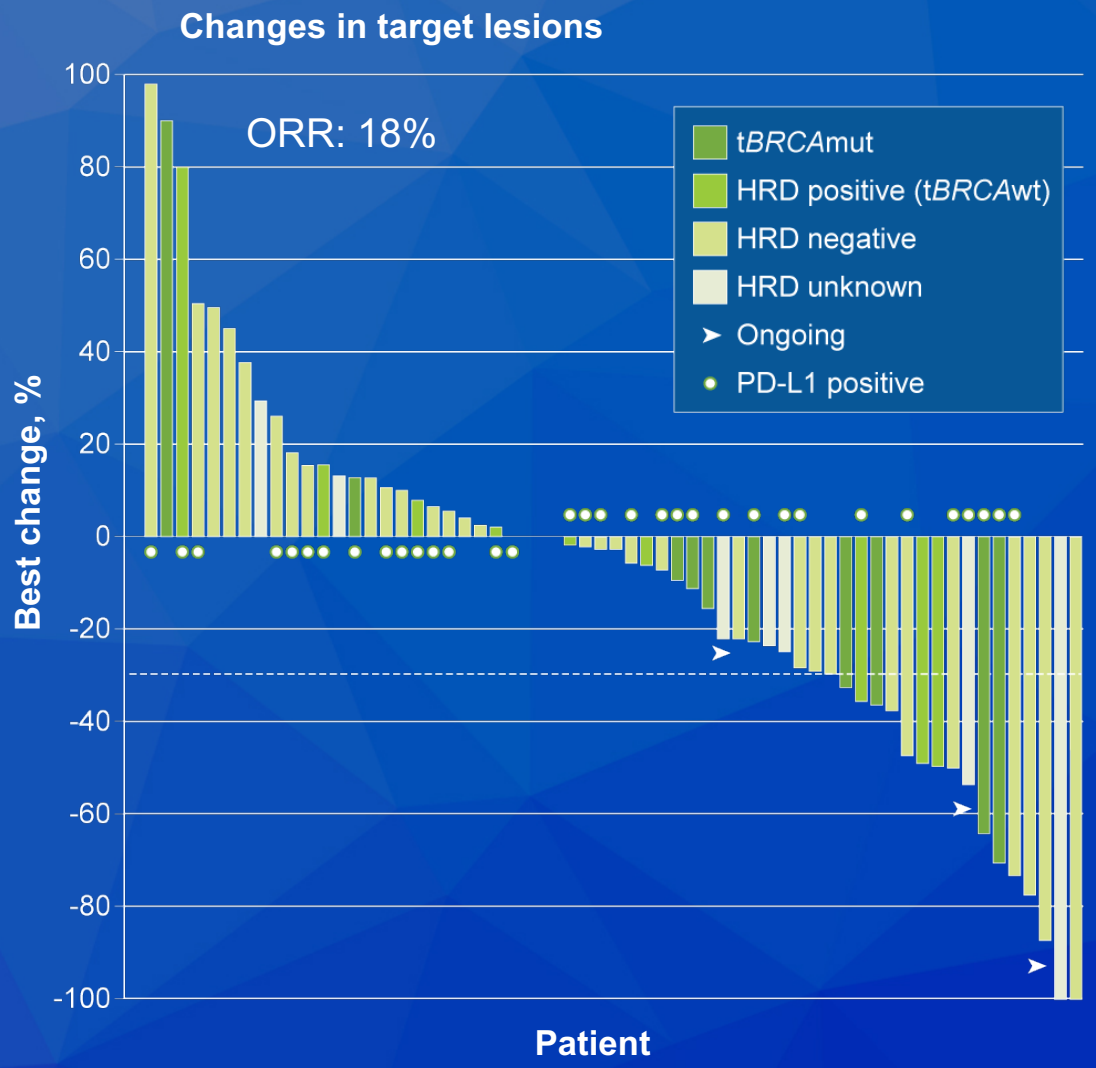
AEs=adverse events; bid=twice daily; CSR=clinical study report; CT=chemotherapy; FACT-O=Functional Assessment of Cancer Therapy-Ovarian; FSI=first subject in; HRD=homologous recombination deficiency; mo=months; OS=overall survival; PARP=poly ADP ribose polymerase; PFS=progression-free survival; po=by mouth; PR=partial response; TFST=time to first subsequent therapy; TSST=time to second subsequent therapy; wt=wild type

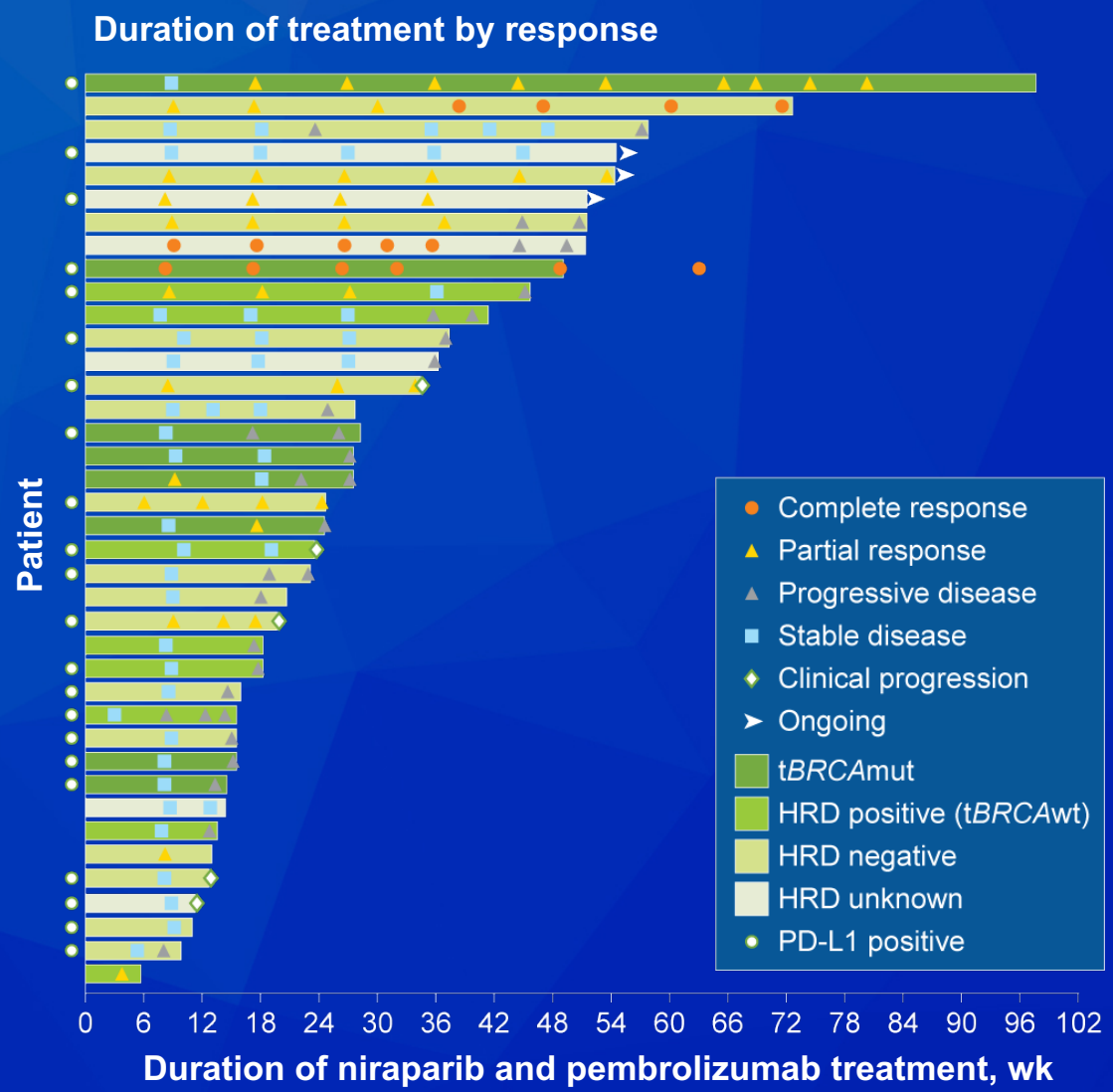
Powered 80% for PFS primary endpoint (*BRCA*m HR=0.5 [74 events]; BRCAwt HR=0.65 [191 events]), Patients followed to OS for long-term safety

Single-Arm Phases 1 and 2 Trial of Niraparib in Combination with Pembrolizumab in Patients with Recurrent Platinum-Resistant Ovarian Carcinoma

Konstantinopoulos PA et al.
JAMA Oncol 2019;[Epub ahead of print].

Single-Arm Phase I/II Trial of Niraparib/Pembrolizumab for Recurrent Platinum-Resistant OC: Response





Konstantinopoulos PA et al. *JAMA Oncol* 2019;[Epub ahead of print].

Editorial — Dr Armstrong

FDA approval for PARP inhibitors as primary therapy for advanced, recurrent disease has been limited to patients with germline or somatic BRCA mutations. Not surprisingly, there have been multiple studies examining PARP inhibitors in a broader ovarian cancer population, including patients unselected for BRCA or HRD status and more heavily pretreated patients. The QUADRA study was a single-arm phase 2 trial of niraparib in 463 relapsed, high-grade serous ovarian cancer patients treated with 3 or more prior chemotherapy regimens with 68% platinum resistant or refractory. The ORR was 8% in the ITT population. However, platinum sensitivity, BRCA positivity, and, to a lesser degree, HRD positivity selected for higher ORR. The authors conclude that their data support expansion of the indication for PARP inhibitor therapy to include patients with HRD positivity.

Editorial — Dr Armstrong (continued)

However, the nesting of BRCA-mutated patients within the HRD-positive group (63 of the 189 HRD+) makes it difficult to support that recommendation since the HRD+, BRCA-negative group is not separately reported.

In the SOLO-3 trial olaparib was compared to chemotherapy in 266 subjects with germline BRCA-mutated, platinum-sensitive recurrent ovarian cancer. Unfortunately (and inexplicably), the chemotherapy arm did not include platinum. Thus the improved ORR (72% with olaparib vs 51% with chemotherapy) and PFS are not frankly meaningful.

The phase II CLIO study compared olaparib vs chemotherapy in 100 BRCA-unselected platinum-resistant ovarian cancer. The ORR was 18% (12/67) for olaparib and 6% (2/33) for chemotherapy. The ORR for olaparib was 38% (5/13) in gBRCAm and 13% (7/54) in gBRCAwt patients. It is hard to know if the difference in response of gBRCAwt patients to chemo (6%) and to olaparib (13%) is clinically meaningful.

Assessment of Combined Nivolumab and Bevacizumab in Relapsed Ovarian Cancer: A Phase 2 Clinical Trial

Liu JF et al.
JAMA Oncol 2019;[Epub ahead of print].

Best Response: Overall and by Platinum Status

Best response	No. (%)		
	Platinum sensitive (n = 20)	Platinum resistant (n = 18)	Overall (N = 38)
Unevaluable	0	1 (5.6)	1 (2.6)
Partial response			
Confirmed	8 (40.0)	3 (16.7)	11 (28.9)
Unconfirmed	1 (5.0)	0	1 (2.6)
Stable disease, wk			
≥24	6 (30.0)	3 (16.7)	9 (23.7)
<24	3 (15.0)	7 (38.9)	10 (26.3)
Progressive disease	2 (10.0)	4 (22.2)	6 (15.8)
Overall confirmed response rate	8 (40.0)	3 (16.7)	11 (28.9)
Total clinical benefit rate	15 (75.0)	6 (33.3)	21 (55.3)

Liu JF et al. *JAMA Oncol* 2019;[Epub ahead of print].

Editorial — Dr Liu

Liu et al.

Liu and colleagues examined the activity of combining nivolumab and bevacizumab in a mixed population of platinum-resistant (recurrence <6 months) and partially platinum-sensitive (recurrence 6-12 months) ovarian cancer patients. This is a single-arm study in a small number (38) of patients. The population ended up being about half platinum resistant (18 patients) and half platinum sensitive (20 patients). The overall response rate was encouraging (28.9%) compared to single-agent activity reported with PD-1 inhibitors to date (10-15% at best), but it's important to note that this is not a randomized study and there is no control arm, so this may be a result of a selected population.

Editorial — Dr Liu (continued)

Notably, in this study, the response rate in platinum-sensitive patients was much better at 40% compared to that in platinum-resistant patients at 16.7%, which is not that different from what one might expect from bevacizumab by itself and raises questions of whether this combination really gives added or synergistic benefit in the platinum-resistant setting. As in other trials of immuno-oncology agents in ovarian cancer, PD-L1 expression was not correlated to activity.

Gynecologic Cancers — Drs Armstrong and Liu

Ovarian Cancer

Endometrial Cancer

Cervical Cancer

FDA Accelerated Approval of Pembrolizumab with Lenvatinib for Advanced Endometrial Carcinoma

Press Release – September 17, 2019

"The Food and Drug Administration granted accelerated approval to the combination of pembrolizumab plus lenvatinib for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation.

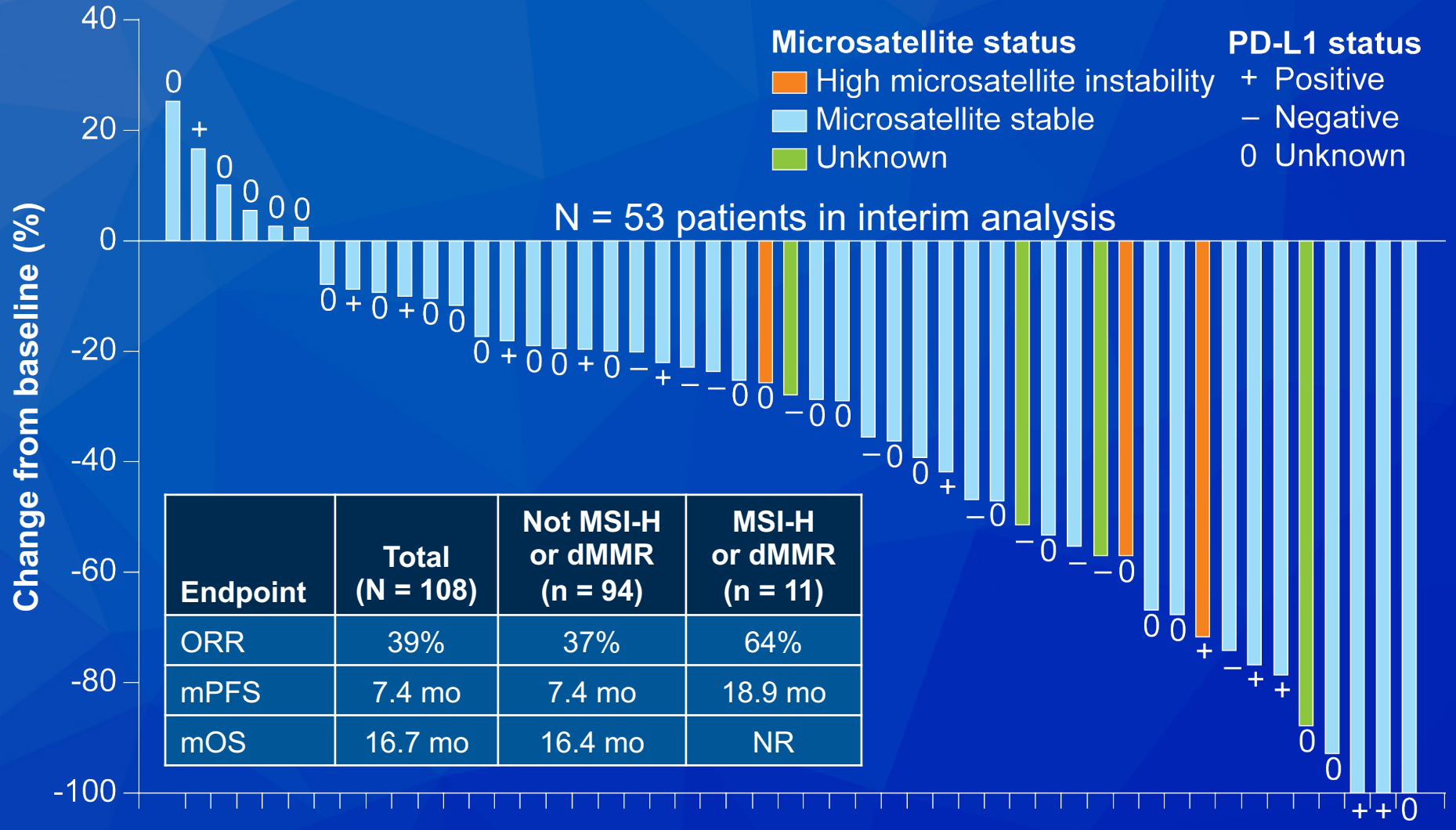
Efficacy was investigated in Study 111/KEYNOTE-146 (NCT02501096), a single-arm, multicenter, open-label, multi-cohort trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting."

https://www.fda.gov/drugs/resources-information-approved-drugs/simultaneous-review-decisions-pembrolizumab-plus-lenvatinib-australia-canada-and-us

Lenvatinib plus Pembrolizumab in Patients with Advanced Endometrial Cancer: An Interim Analysis of a Multicentre, Open-Label, Single-Arm, Phase 2 Trial

Makker V et al.
Lancet Oncol 2019;20(5):711-8.
Proc ESMO 2019;Abstract 994O.

Phase II Trial of Lenvatinib/Pembrolizumab: Response and Survival



Endpoint	Total (N = 108)	Not MSI-H or dMMR (n = 94)	MSI-H or dMMR (n = 11)
ORR	39%	37%	64%
mPFS	7.4 mo	7.4 mo	18.9 mo
mOS	16.7 mo	16.4 mo	NR

Makker V et al. *Lancet Oncol* 2019;20(5):711-8. Makker V et al. *Proc ESMO* 2019; Abstract 994O.

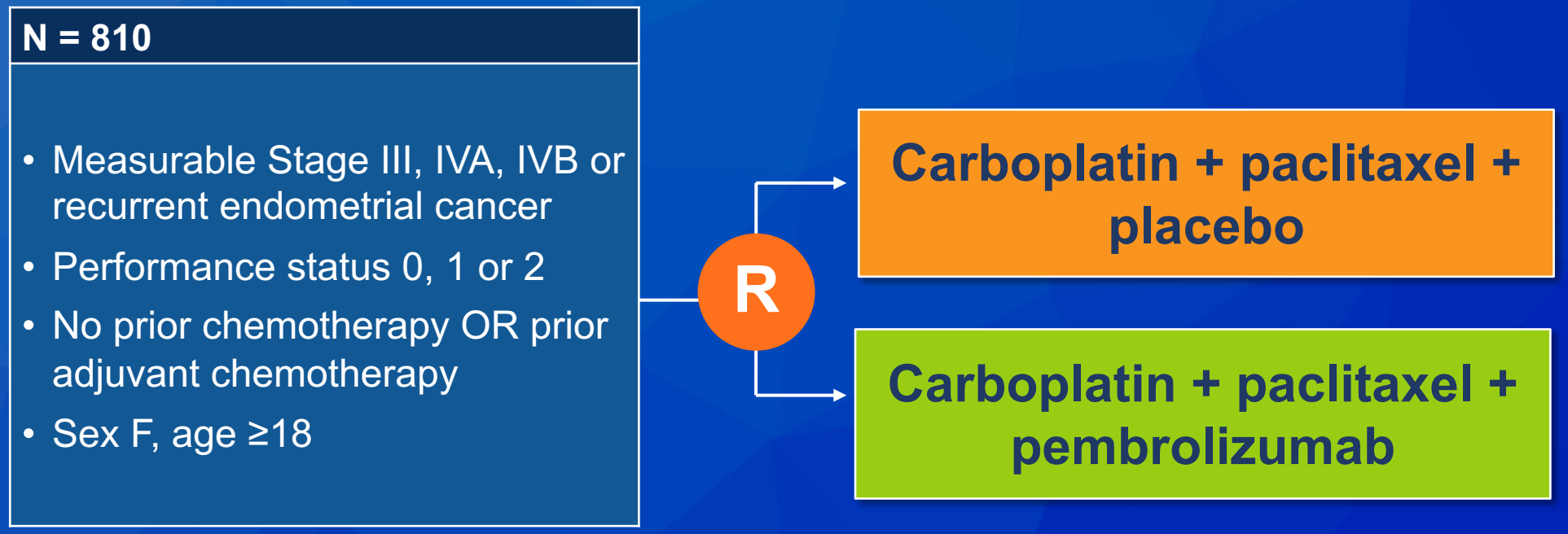
Editorial — Dr Matulonis

The US FDA recently approved the combination of lenvatinib and pembrolizumab for the treatment of recurrent endometrial cancer based on the 2019 *Lancet Oncology* paper by Makker et al. In this study, 53 patients with recurrent endometrial cancer, regardless of tumor histology or microsatellite status, received the combination of lenvatinib 20 mg per day and pembrolizumab 200 mg IV every 3 weeks. 85% of the enrolled patients had microsatellite-stable cancer. 41% of pts had endometrioid histology and 38% had serous histology, 2% clear cell and the rest were other. 39.6% of patients exhibited a response at week 24 of the study and median PFS was 7.4 months. Of the responders, 83% of patients had a duration of response of at least 6 months, and 65% had a duration of response that lasted at least 12 months.

Editorial — Dr Matulonis (continued)

The combination is active but is also toxic. 34% of patients had grade 3 or higher hypertension, 8% grade 3 or higher diarrhea. 50% of patients reported fatigue, mostly grade 1 or 2, 6% grade 3 or higher PPE. 53% of patients required a dose reduction of lenvatinib. Though a regimen that appears toxic, the ORR of this combination is quite impressive and is regardless of MMR status.

Phase III Trial of Standard Chemotherapy with or without Pembrolizumab for Stage III or IV or Recurrent Endometrial Cancer



Primary endpoint: Progression-free survival

www.clinicaltrials.gov (NCT03914612). Accessed October 2019.

AtTEnd: A Phase III Trial of Chemotherapy with or without Atezolizumab for Advanced or Recurrent Endometrial Cancer

N = 550

- Newly diagnosed endometrial cancer with residual disease after surgery OR inoperable Stage III/IV disease OR
- Recurrent endometrial cancer not yet treated for recurrent disease
- Performance status 0-2
- Sex F, age ≥18

R

Atezolizumab + carboplatin + paclitaxel

Carboplatin + paclitaxel + placebo

Primary endpoints

- Overall survival
- Progression-free survival

www.clinicaltrials.gov (NCT03603184). Accessed October 2019.

Preliminary Safety, Efficacy, and Pharmacokinetic/ Pharmacodynamic Characterization from GARNET, a Phase I/II Clinical Trial of the Anti-PD-1 Monoclonal Antibody TSR-042 in Patients with Recurrent or Advanced MSI-H and MSS EC

Oaknin A et al.
Proc SGO 2019;Abstract 33.

GARNET: A Phase I/II Trial of Dostarlimab (TSR-042) for Patients with Recurrent or Advanced MSI-H and MSS Endometrial Cancer

	All evaluable patients (N = 94)	MSI-H	MSS
ORR	27.7%	50.0%	19.1%
Disease control rate	48.9%	NR	NR
Patients with ongoing responses	88.4%	NR	NR

NR = not reported

- Grade ≥3 TRAEs: 13 patients (11.8%)
- Most common Grade ≥3 TRAE: increased aspartate aminotransferase (2.7%)

Oaknin A et al. *Proc SGO* 2019;Abstract 33.

Editorial — Dr Liu (continued)

Oaknin et al.

The activity of PD-1/PD-L1 agents in microsatellite instability (MSI)-high/mismatch repair (MMR)-deficient uterine cancers has been established, with response rates of ~25-40% reported in trials of avelumab, durvalumab, and pembrolizumab. Dostarlimab is a monoclonal PD-1 antibody; it differs from other PD-1/PD-L1 antibodies in administration in that, after a loading period, it can be administered once every 6 weeks. In the MSI-H cohort, a response rate of 48.8% was observed, while in microsatellite stable (MSS) patients, the response rate was 20.3%. The response rate in MSS patients is notable, as every other study of single-agent PD-1/PD-L1 agents in this population has reported response rates in the <10% range. Responses were durable with most patients on treatment for over 6 months.

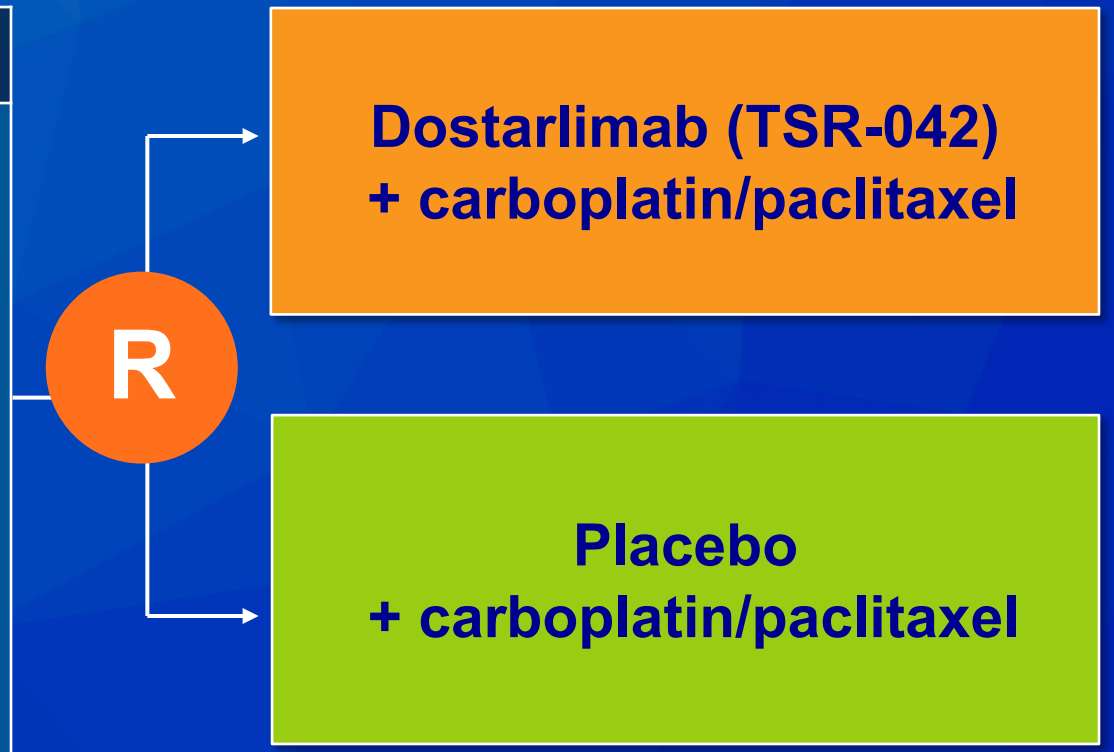
Editorial — Dr Liu (continued)

We are awaiting the full publication for this study; questions that remain outstanding are how MSS was defined (there are some studies that suggest that classification by PCR alone may misclassify some patients who would be considered MMR deficient by IHC) as well as what mechanistically sets dostarlimab apart from the other PD-1 agents that this degree of activity was observed in MSS patients, given the consistent lack of activity with all of the other PD-1/PD-L1 agents.

RUBY: A Phase III Trial Design

Eligibility (N = 470)

- Recurrent or advanced endometrial cancer
- Primary Stage III or IV disease or first recurrent endometrial cancer with a low potential for cure by radiation and/or surgery
- ECOG PS 0-1
- No (neo)adjuvant systemic chemotherapy for primary Stage III/IV disease



Primary endpoint: Progression-free survival

www.clinicaltrials.gov;NCT03981796;Accessed September 2019.

Gynecologic Cancers — Drs Armstrong and Liu

Ovarian Cancer

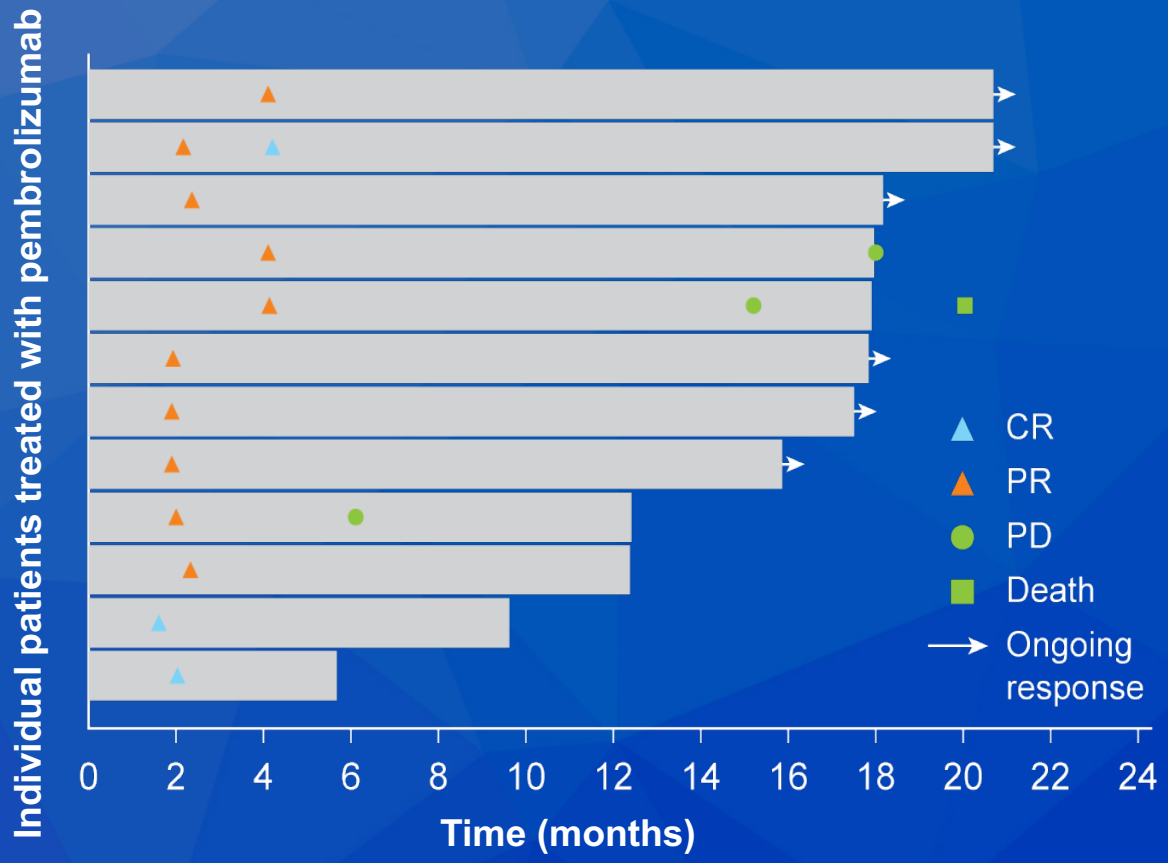
Endometrial Cancer

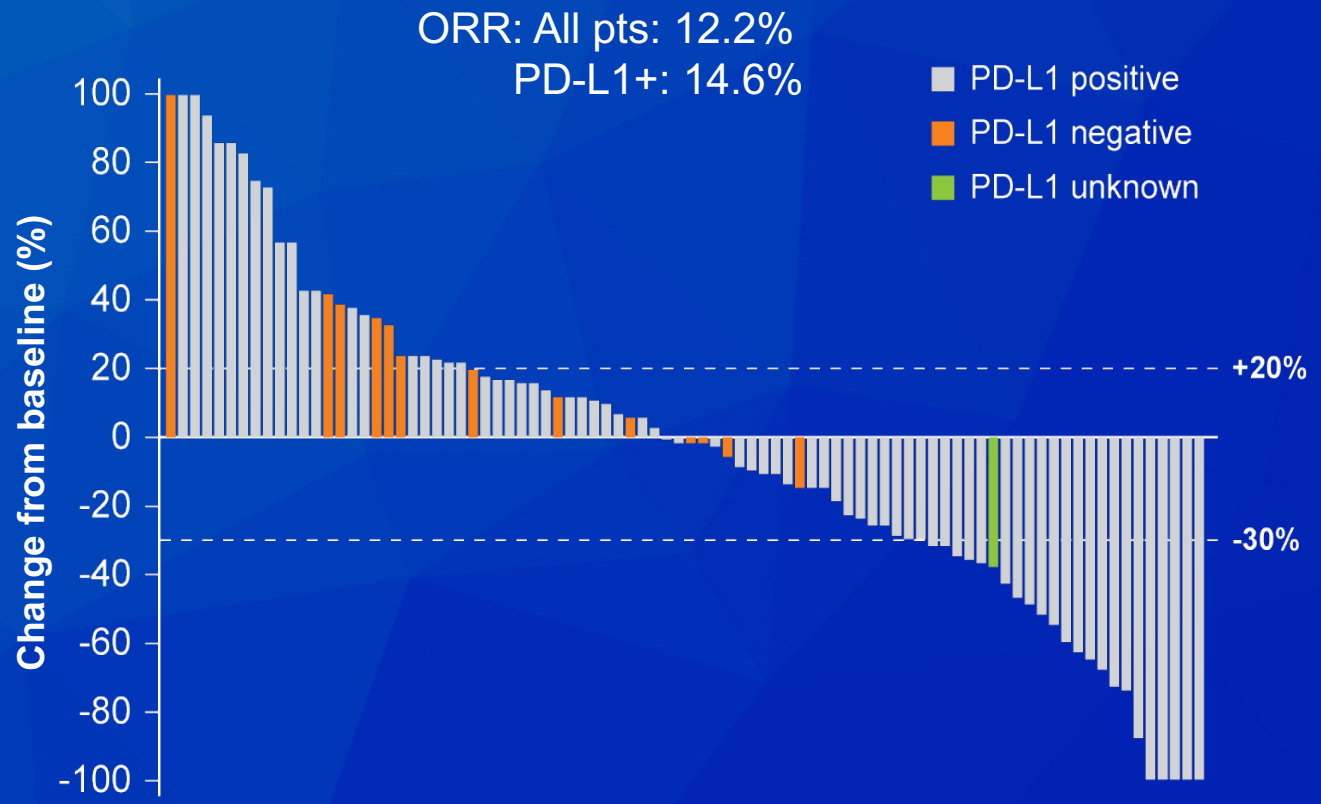
Cervical Cancer

Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results from the Phase II KEYNOTE-158 Study

Chung HC et al.
J Clin Oncol 2019;37(17):1470-8.

KEYNOTE-158: Pembrolizumab for Pretreated Cervical Cancer — Objective Response





Chung HC et al. *J Clin Oncol* 2019;37(17):1470-8.

Editorial — Dr Matulonis

In this KEYNOTE-158 study, 98 patients with recurrent cervical cancer were treated with single-agent pembrolizumab. Patients received pembrolizumab 200 mg every 3 weeks for 2 years or until progression, intolerable toxicity, or physician or patient decision. The primary endpoint was ORR assessed by independent central radiologic review. PD-L1 status was assessed on all tumors, and 82 pts (83.7%) had PD-L1-positive tumors (defined as a combined positive score ≥1), 77 having previously received one or more lines of chemotherapy for recurrent or metastatic disease. ORR was 12.2% (95% CI, 6.5% to 20.4%), with 3 complete and 9 partial responses. All 12 responses occurred in PD-L1-positive tumors, for an ORR of 14.6%; there were no responses in PD-L1-negative cancers.

Editorial — Dr Matulonis (continued)

The median DOR was not reached (range, ≥3.7 to ≥18.6 months). 5% had adenocarcinomas and 94% of patients had squamous cell cancers. The 5 adenocarcinomas and the single adeno-squamous cell carcinoma were PD-L1 positive. These results led to the FDA approval of single-agent pembrolizumab in patients with recurrent cervical cancer that is PD-L1 positive. Pembro does not have significant efficacy in PD-L1-negative cervical cancer.

Tisotumab Vedotin in Patients with Previously Treated Recurrent or Metastatic Cervical Cancer: Updated Safety and Efficacy Results from the Full Cervical Cohort of the Phase II InnovaTV 201 Study

Hong DS et al.
Proc SGO 2019;Abstract 19.

Updated Safety and Efficacy Results from the Phase II InnovaTV 201 Study

- Investigator-assessed ORR (among the first 34 patients enrolled): 32%
- Median duration of response: 5.5 months
- Most common all-grade adverse events:
  - Conjunctivitis
  - Epistaxis
  - Fatigue
  - Alopecia
  - Nausea

Hong DS et al. *Proc SGO* 2019;Abstract 19.

InnovaTV 204: A Phase II Single-Arm Trial Design

Eligibility (N = 102)

- Extra-pelvic metastatic or recurrent cervical cancer, including squamous cell, adenocarcinoma or adenosquamous histology
- Disease progression on standard chemotherapy in combination with bevacizumab
- 2 or fewer prior lines of systemic therapy
- ECOG PS 0-1

→ **Tisotumab vedotin (IV)**
2 mg/kg (q3wk)

Primary endpoint: Objective response rate

www.clinicaltrials.gov;NCT03438396;Accessed September 2019.

Editorial — Dr Liu (continued)

de Bono et al.

Tisotumab is an antibody-drug conjugate (ADC) directed against tissue factor, which has been reported to be expressed in a number of tumor types, including cervical cancer. This was a Phase 1/2 trial, with Phase 2 dose expansion across a number of tumor types, including cervical, endometrial, and ovarian cancers. The activity of tisotumab was most notable in cervical cancers, where a response rate of 26.5% was reported (a follow-up report across the full expansion cohort of 55 patients reported a 24% response rate – Hong et al, *CCR*, published online 01/29/20), while lesser activity was seen in other gyn cancers (7.1% and 13.9%, endometrial and ovarian, respectively). In context, this degree of monotherapy activity in cervical cancer is quite impressive, where traditional chemotherapies have response rates in the ~10% or less range, and pembrolizumab was approved in PD-L1-positive cervical cancer based upon a response rate of 14.6% in PD-L1-positive patients.

Editorial — Dr Liu (continued)

Notable side effects of tisotumab were similar to what have been reported with other ADCs, including neuropathy (43%) and conjunctivitis (43%) or ocular events (7%). Epistaxis was also a noted side effect, potentially due to the targeting of tissue factor. A Phase 2 study, InnovaTV 204, to validate the activity of tisotumab in recurrent/metastatic cervical cancer in the second-line setting, completed enrollment last year, and results are awaited.

InnovaTV 205: A Phase I/II Trial Design

Eligibility (N = 140)

- Patients with squamous, adenosquamous or adenocarcinoma of the cervix **and disease progression on or after** standard treatments or who are ineligible or intolerant for standard therapy for recurrent or Stage IVB cervical cancer **(dose-escalation phase: increasing tisotumab + fixed dose of pembro or carbo)**

Tisotumab vedotin + BEV (Arm A)

Tisotumab vedotin + Pembrolizumab (Arm B)

Tisotumab vedotin + Carboplatin (Arm C)

Pts with squamous, adenosquamous or adenocarcinoma of the cervix **who have not** received prior systemic therapy for recurrent or Stage IVB disease (Arms D and E) or whose disease has progressed on or after standard therapy (Arm F) **(dose-expansion phase)**

Tisotumab vedotin + Carboplatin (Arm D)

Tisotumab vedotin + Pembrolizumab (Arm E)

Tisotumab vedotin + Pembrolizumab (Arm F)

Primary endpoints: DLTs (dose escalation), objective response (dose expansion)

www.clinicaltrials.gov;NCT03786081;Accessed September 2019.

Editorial — Dr Matulonis

Hong et al:
Full 55 patient cohort with cervical cancer was presented. Median duration of response in confirmed responders was 5.5 months (95% CI 3.0–9.6). Confirmed ORR was concordant between INV and independent imaging review (IIR) (26% and 24%). Responses were observed in heavily pretreated (≥3 prior lines of therapy) and refractory patients. The most common all-grade adverse events were conjunctivitis, epistaxis, fatigue, alopecia, and nausea. Compared to the initial cohort of patients, the ORR of the full 55 patient cohort was lower and was now ~24%-26%.