Year in Review

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

Saturday, January 11, 2020, 8:00 AM – 4:00 PM
Houston, Texas

Faculty

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Stephen V Liu, MD, PhD
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Gregory J Riely, MD, PhD
Sonali M Smith, MD

Moderator

Neil Love, MD

Research To Practice®

Agenda

Module 1 — Lymphomas and Chronic Lymphocytic Leukemia: *Drs Cheson, Nastoupil and Smith*

Module 2 — Breast Cancer: *Drs Hamilton and Hurvitz*

Module 3 — Acute Leukemias: *Drs Erba and Levis*

Module 4 — Gastrointestinal Cancers: *Drs Bekaii-Saab, Bendell and Philip*

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

Module 6 — Lung Cancer: *Drs Liu and Riely*

Module 7 — Gynecologic Cancers: *Drs Coleman and Moore*

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Disclosures

Advisory Committee and Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Genentech, GlaxoSmithKline, Janssen Biotech Inc, ImmunoGen Inc, Novocure, Merck, Roche Laboratories Inc, Tesaro, A GSK Company, Takeda Oncology
Contracted Research	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Genentech, Janssen Biotech Inc, Merck, Roche Laboratories Inc
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP, VBL Therapeutics

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Advisory Committee	Aravive Inc, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Genentech, ImmunoGen Inc, Janssen Biotech Inc, Merck, OncoMed Pharmaceuticals Inc, Pfizer Inc, Roche Laboratories Inc, Samumed, Tesaro, A GSK Company, VBL Therapeutics
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Gynecologic Cancers — Drs Coleman and Moore

Ovarian Cancer

Endometrial Cancer

Cervical Cancer

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

Eligibility

- Newly diagnosed ovarian, fallopian tube or primary peritoneal cancer
- FIGO Stage III-IV
- High-grade serous or endometrioid histology
- Deleterious or suspected deleterious BRCA1 or BRCA2 mutation

CR or PR and no clinical evidence of PD after completing first-line platinum-based therapy

R

(2:1)

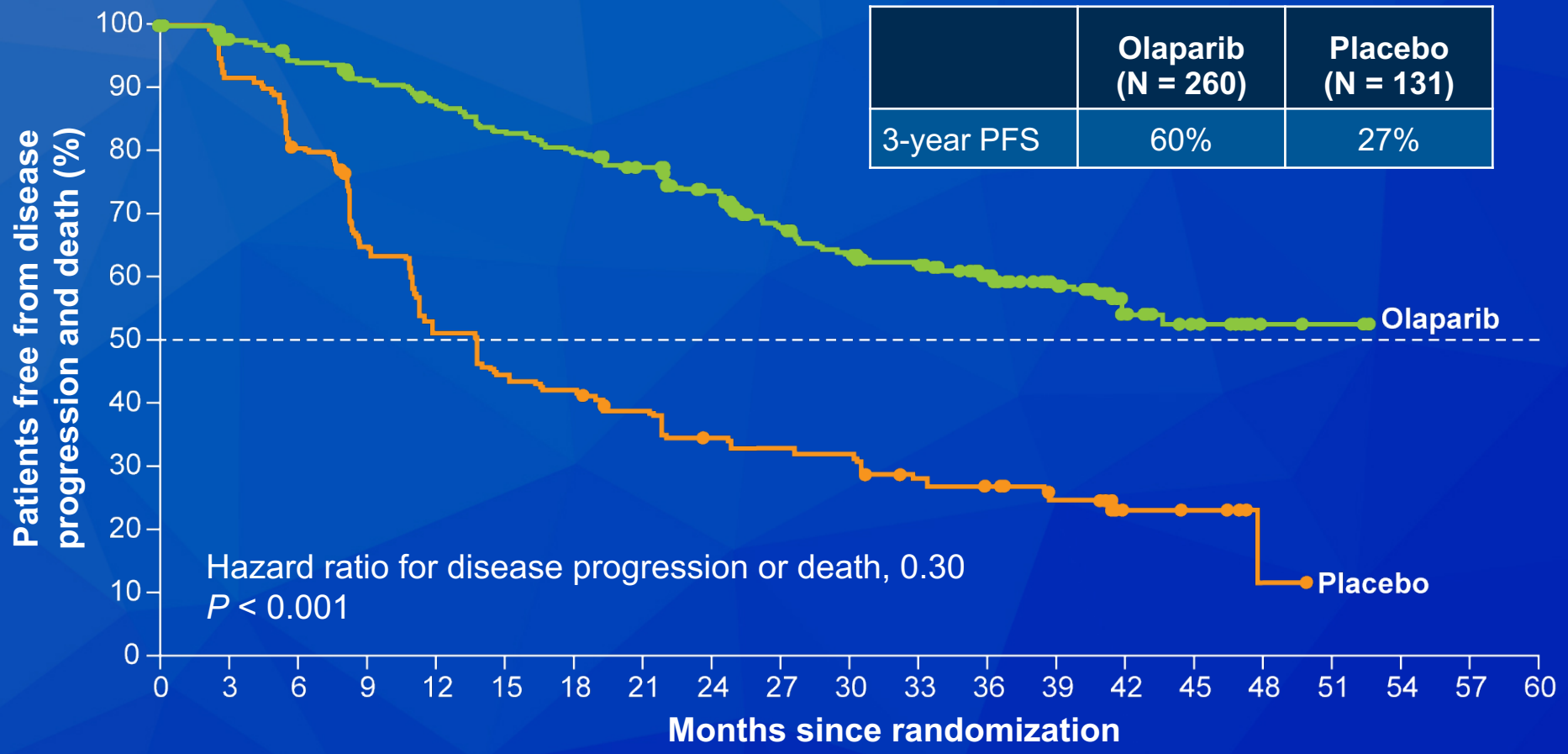
Maintenance olaparib 300 mg BID (n = 260)

Placebo (n = 131)

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)

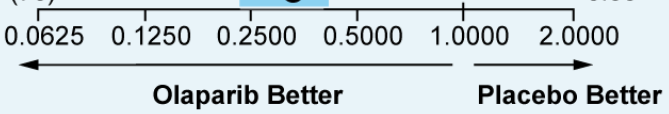


	Olaparib (N = 260)	Placebo (N = 131)
3-year PFS	60%	27%

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 O'Malley

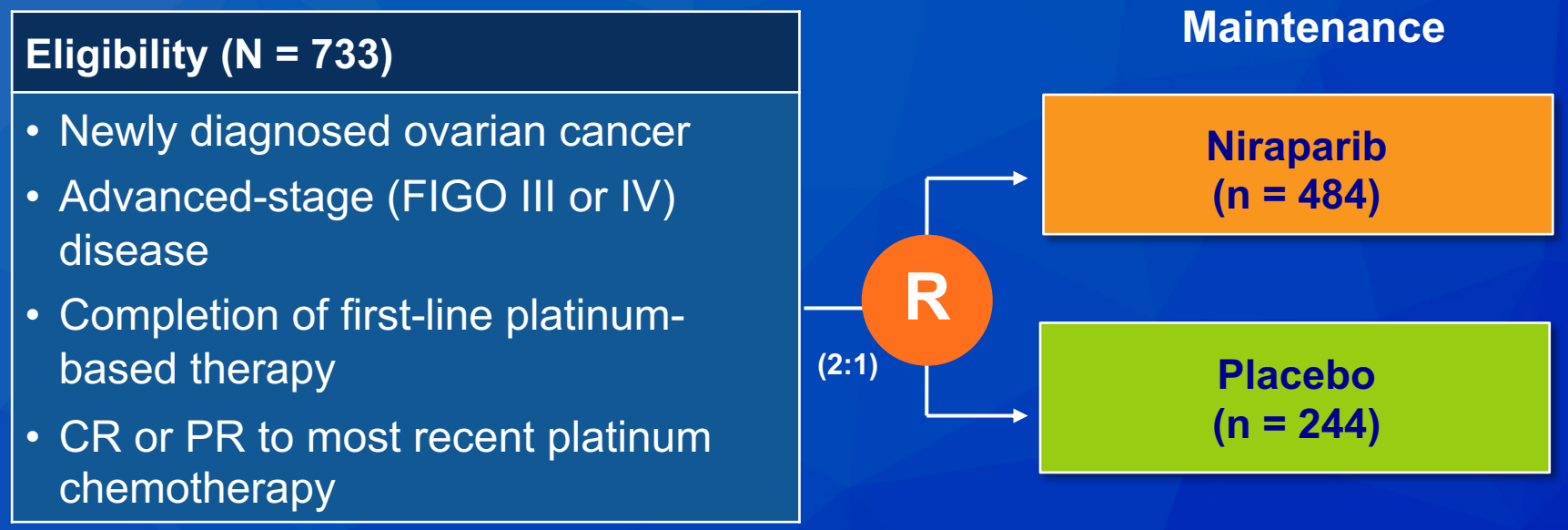
SOLO-1 is likely the most impactful study in ovarian cancer in recent memory. Olaparib is approved in the treatment for third line or more in patients with germline mutations. It is also approved in all patients with platinum-sensitive recurrence for maintenance therapy after a response to platinum therapy. SOLO-1 treated patients with BRCA mutations in the first-line setting after a response to first-line therapy as a maintenance strategy. The most impactful finding was the more than doubling of the patients who were progression free at 3 years (60% vs. 27%). Median PFS had not been reached for the olaparib arm at 48 months of follow-up. It is possible a much larger number of patients have been cured due to the treatment with olaparib. The impact of these findings is far reaching. The most important implication may be that all patients with ovarian cancer should be tested for BRCA mutation during first-line therapy without debate.

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].

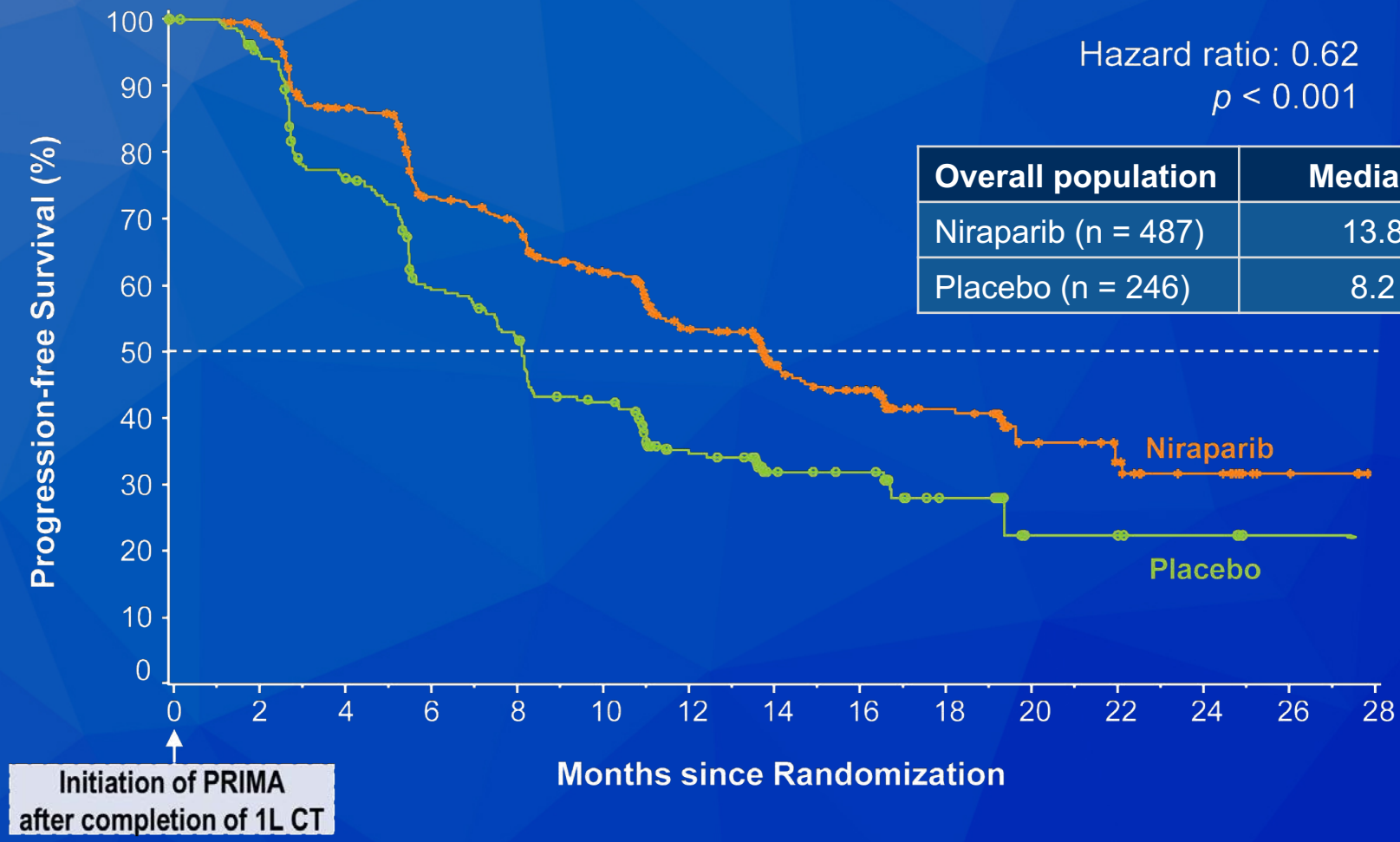
PRIMA: Phase III Trial Schema



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



Overall population	Median PFS
Niraparib (n = 487)	13.8 mo
Placebo (n = 246)	8.2 mo

- 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].

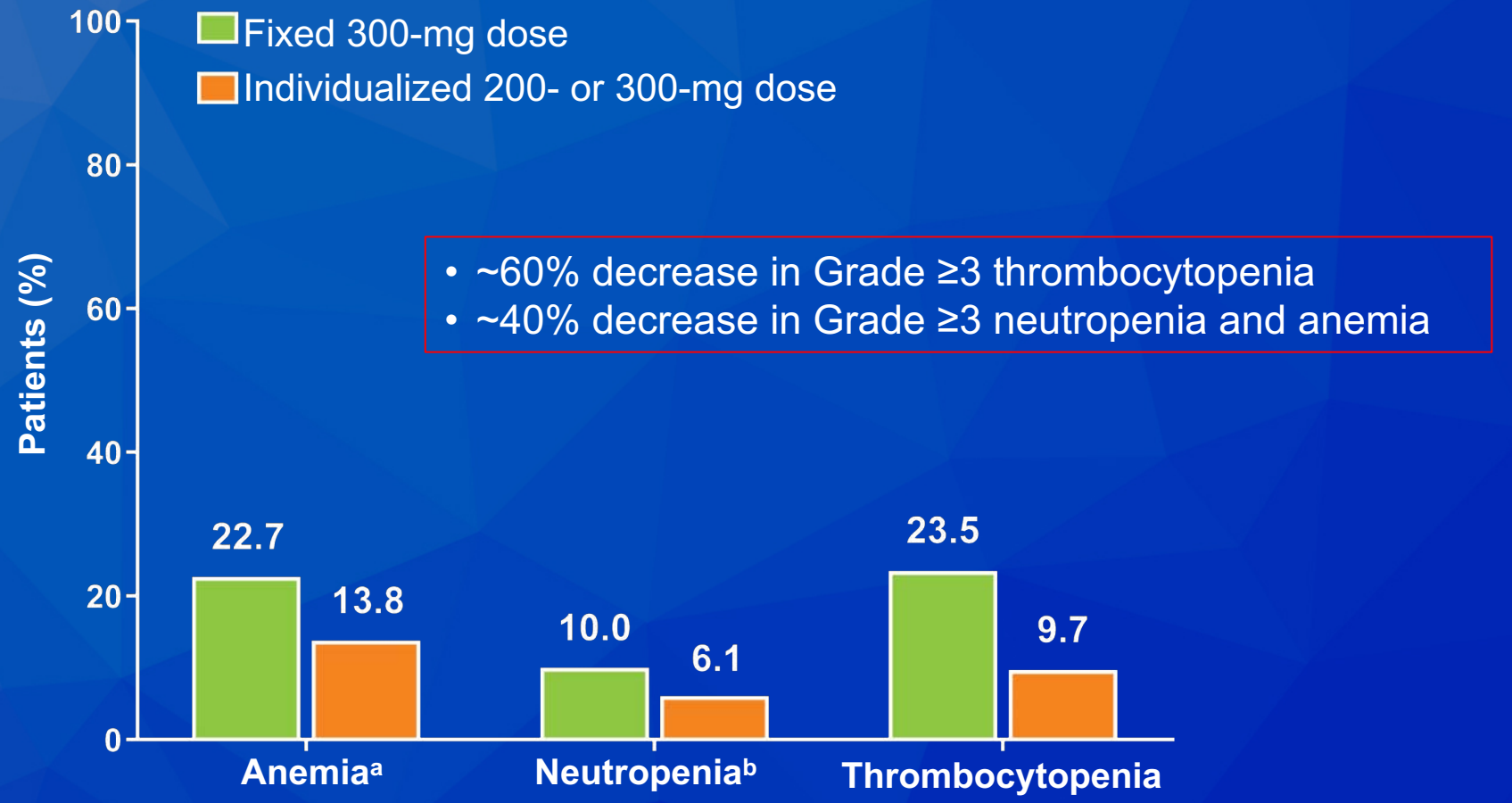
A Prospective Evaluation of Tolerability of Niraparib Dosing Based Upon Baseline Body Weight and Platelet Count: Blinded Pooled Interim Safety Data from the ENGOT-OV26/PRIMA Study

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 O'Malley

Niraparib is already approved in all patients with platinum-sensitive recurrence for maintenance therapy after a response to platinum therapy. PRIMA studied niraparib maintenance in all patients after response to first-line platinum therapy as a maintenance strategy. The groups are organized by BRCA mutations, defined by a homologous recombination deficiency (HRD, HRD was defined as the presence of a BRCA deleterious mutation, a score of at least 42 on the myChoice® test, or both) positive status and the intent-to-treat population (all comers). The trial was amended for the dosing of niraparib to "weight and platelets" individual dosing where approximately 1/3 of patients received this modified dosing. In turn, the thrombocytopenia and hematologic toxicity was improved with the modified dosing, though still high for Grade 3 or higher thrombocytopenia as compared to other PARPi agents. PRIMA was positive for the overall population (HR=0.62).

Editorial — Dr O’Malley (continued)

In an exploratory analysis, the greatest benefit was in the BRCAm (HR=0.4) followed by BRCAwt, HRD deficient (HR=0.5) followed by more modest benefit in the HR proficient (HR=0.68). Clearly the benefit is highest in those HRD deficient.

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)

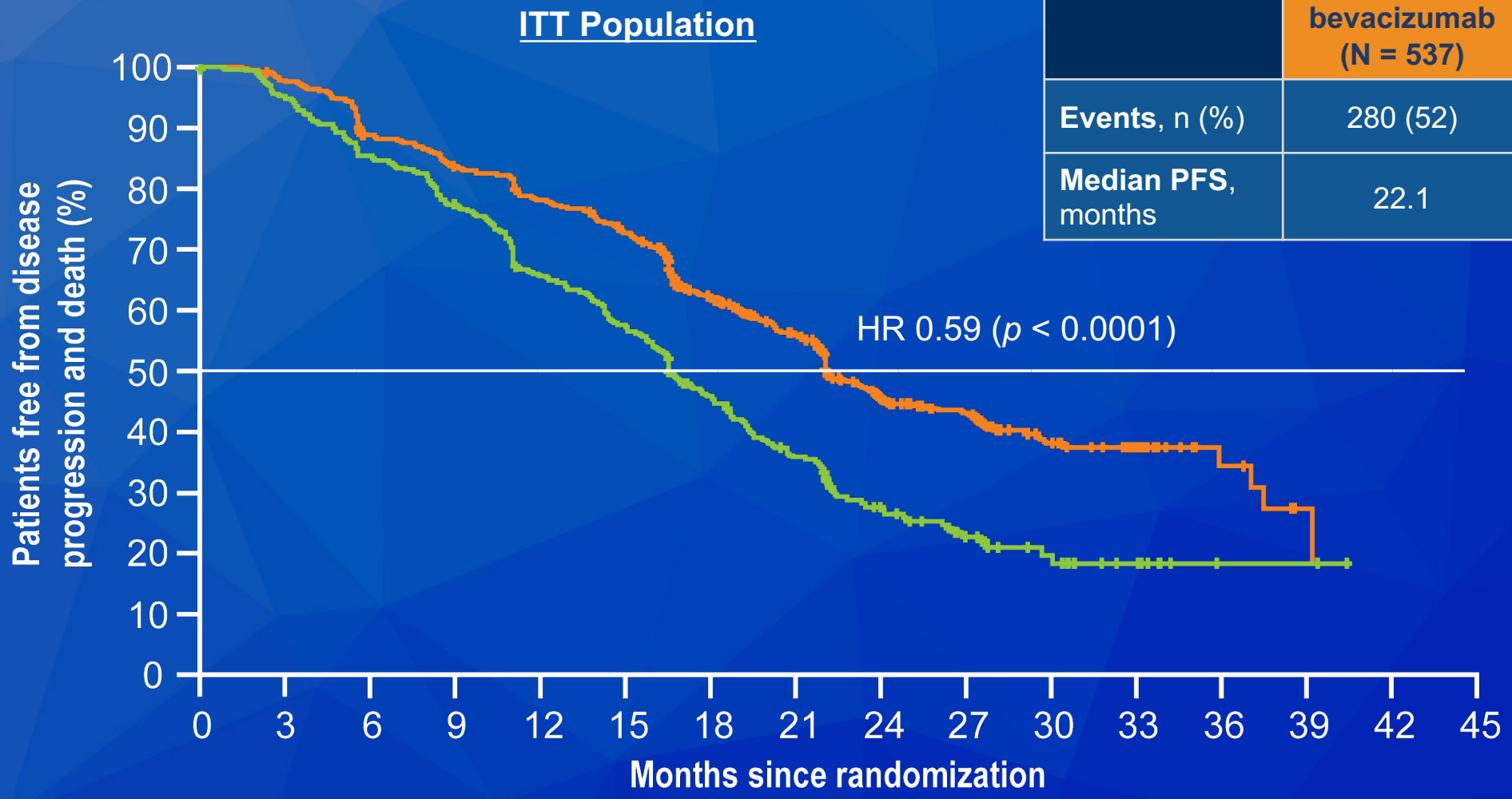
Secondary endpoints
- PFS2
- TSST
- OS
- Safety
- PRO/HRQoL

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.

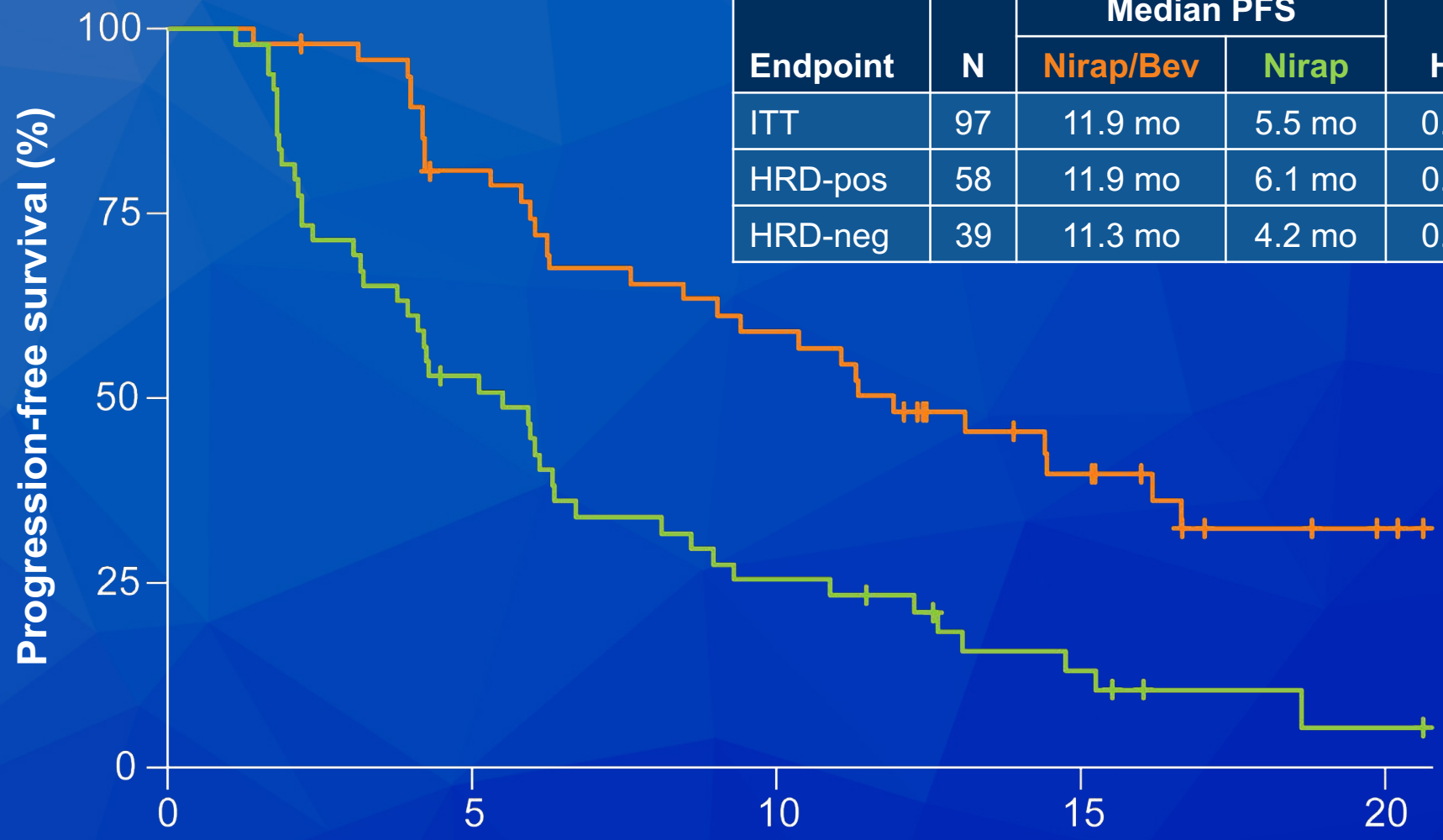
Niraparib plus Bevacizumab versus Niraparib Alone for Platinum-Sensitive Recurrent Ovarian Cancer (NSGO-AVANOVA2/ENGOT-ov24): A Randomised, Phase 2, Superiority Trial

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 O'Malley

The phase III PAOLA-1 trial randomized newly diagnosed patients with advanced ovarian cancer to receive either bevacizumab/olaparib or placebo. PAOLA-1 in the up-front maintenance setting met its primary endpoint of PFS in all patients. This is the first trial to show that PARP inhibitors and bevacizumab when combined as a first-line treatment was beneficial as compared with bevacizumab alone. This is the first phase III trial to show the benefit of PARP inhibitor maintenance compared to an active therapy, bevacizumab, rather than a placebo. The subanalysis was very interesting and thought provoking, especially regarding the differences in outcomes of biomarker-positive (BRCA/HRD) versus biomarker-negative patients. The benefit in PFS by HRD status was analyzed. The benefit in the HRD-positive group (including BRCA) was similar to what we would expect with a single-agent PARPi. The HRD-negative group did not seem to benefit from the combination therapy while the HRD-positive/BRCA-negative (20% of the population) was the group that may have benefited the most.

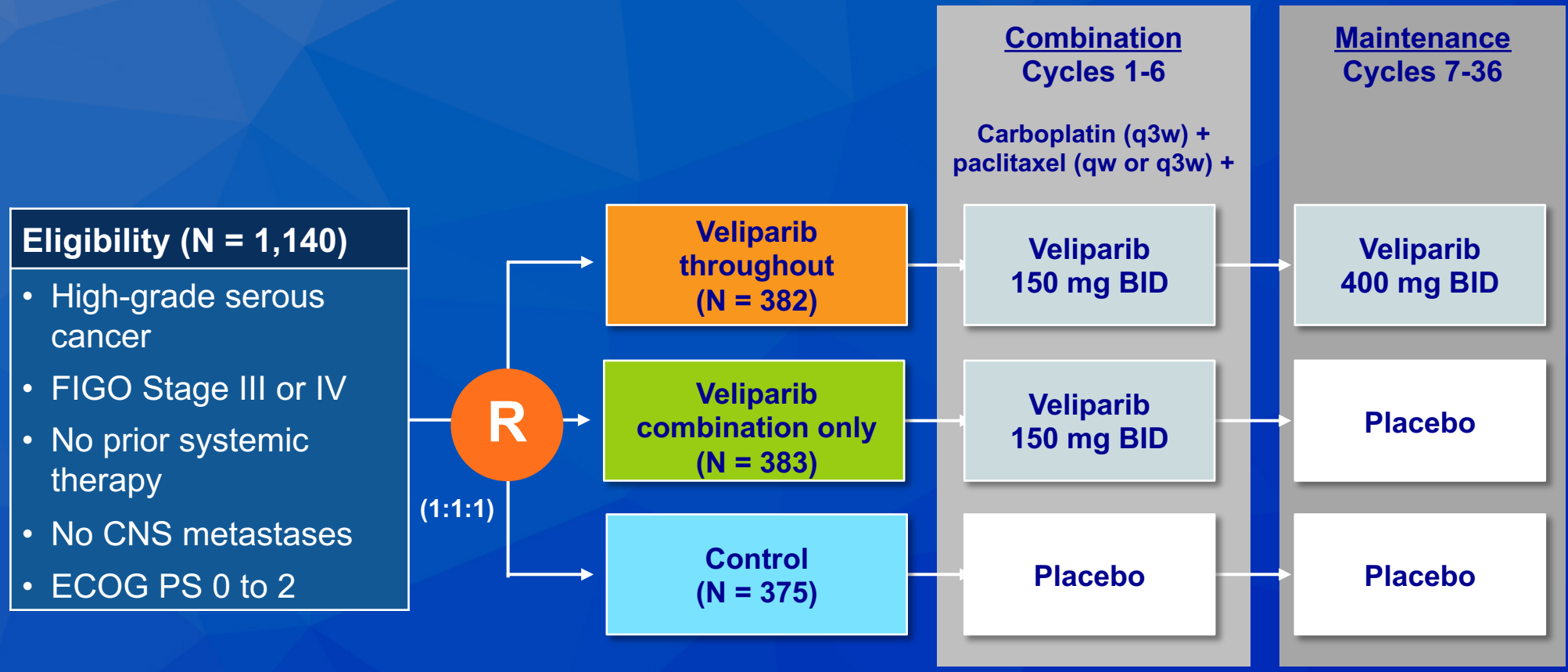
Editorial — Dr O'Malley (continued)

AVANOVA is a small (97 pts) phase II (open label) in the platinum-sensitive maintenance population comparing niraparib to niraparib plus bev. The combination benefited the entire population, but in in the BRCA-mutant subpopulation there was no benefit to the combination but there was marked benefit to BRCAwt. These results justify the proof of principle of moving forward with a larger trial, which should help further clarify the populations who will benefit from the combination of bevacizumab with PARPi.

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

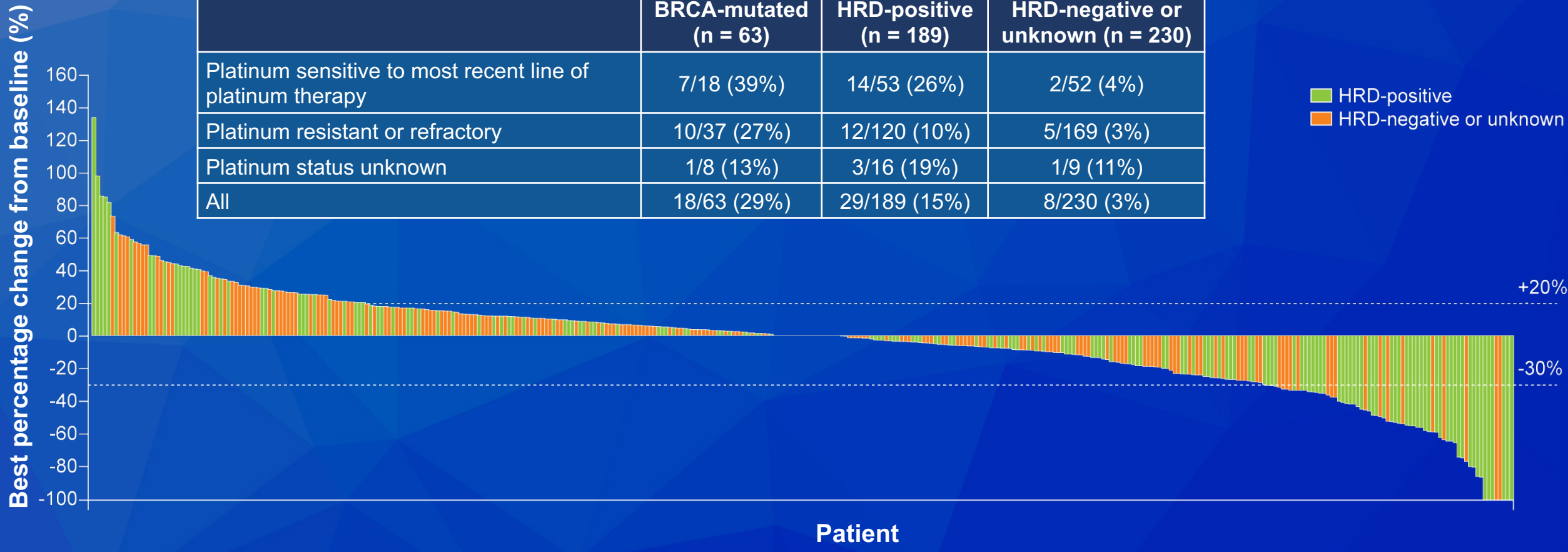
Niraparib Monotherapy for Late-Line Treatment of Ovarian Cancer (QUADRA): A Multicentre, Open-Label, Single-Arm, Phase 2 Trial

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

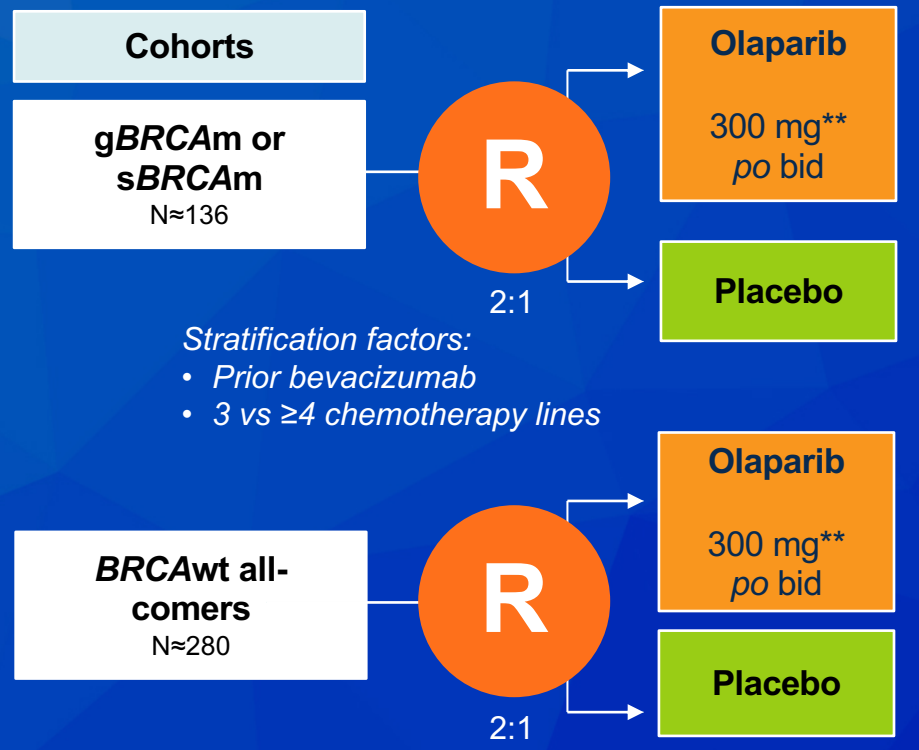
PLUS

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

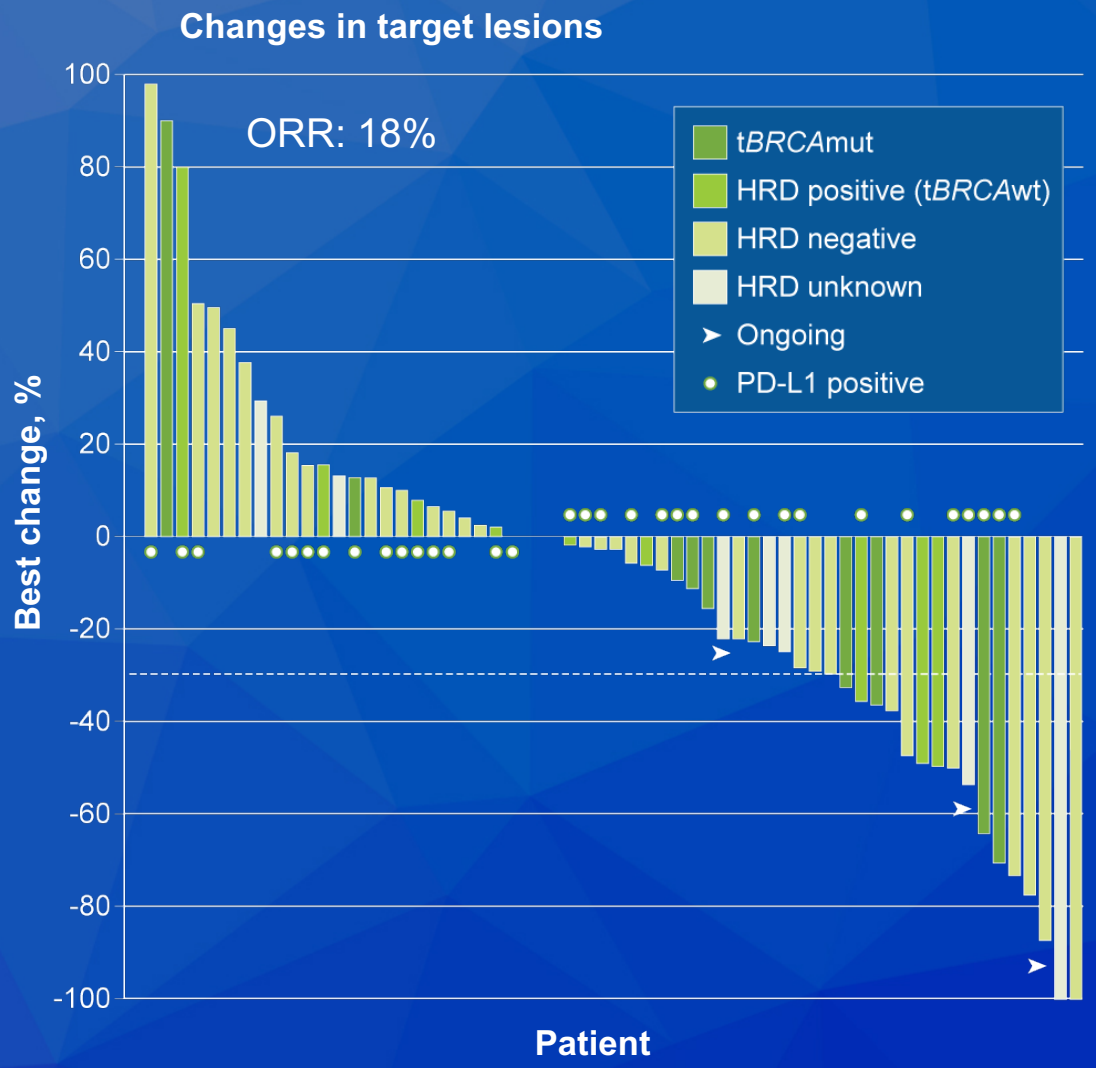
AEs=adverse events; bid=twice daily; CSR=clinical study report; CT=chemotherapy; FACT-O=Functional Assessment of Cancer Therapy-Ovarian; FSI=first subject in; HRD=homologous recombination deficiency; mo=months; OS=overall survival; PARP=poly ADP ribose polymerase; PFS=progression-free survival; po=by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

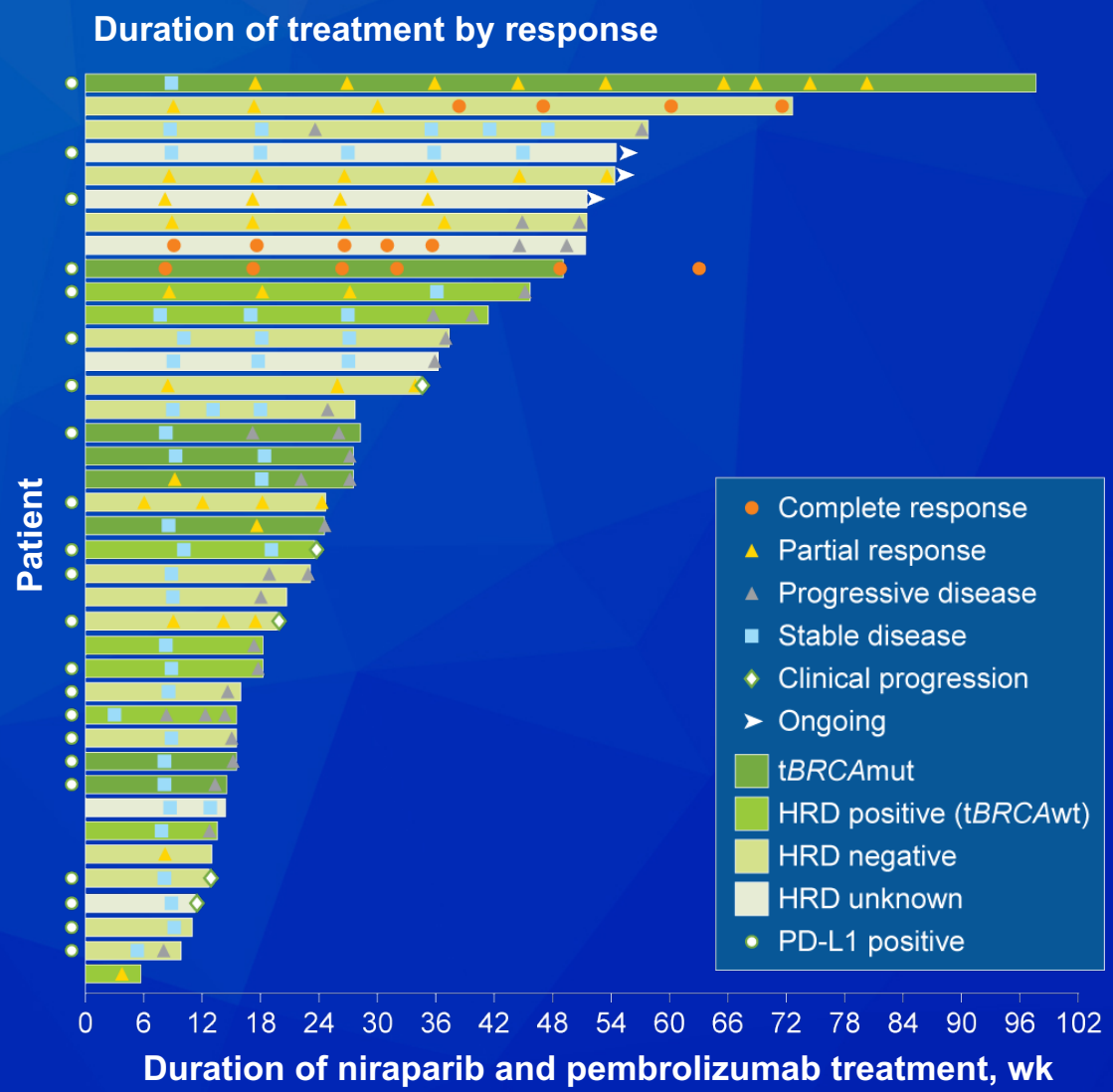
Powered 80% for PFS primary endpoint (*BRCA*m HR=0.5 [74 events]; BRCAwt HR=0.65 [191 events]), Patients followed to OS for long-term safety

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 O'Malley

TOPACIO (KEYNOTE-162) was a small (60 evaluable patients) single-arm phase I/II trial combining niraparib with pembro. Some results are interesting (5% CR; 31% 6m PFS), but with an 18% ORR in the entire population and an 18% ORR in the BRCAm patients, there are still many questions. Does the I-O improve the ORR of PARPi in BRCAm patients? Are there more sustained responses (12% 12m PFS) than you would expect for this population, especially in BRCAwt? Do PARPi increase the immunogenicity of ovarian cancer tumors? TOPACIO raised more questions than it answered.

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 Moore

Owing to the development of novel, active therapeutics, maintenance and better supportive care, we are currently in an era with the highest prevalence of women surviving with ovarian cancer than ever before. This necessitates continuous development of novel therapeutics to continue to provide these women with incremental survival benefit. With the exception of PARP inhibition in BRCA-associated cancers, monotherapy use of targeted agents or immunotherapies have not been overwhelmingly effective. Liu et al. seeks to combine two agents, bevacizumab, a monoclonal antibody targeting VEGF, and nivolumab, a monoclonal antibody targeting PD-1 in the treatment of recurrent platinum-resistant and platinum-sensitive (PFI < 12 months) ovarian cancer. The rationale for this combination comes from studies in renal cell, NSCLC and HCC, where it is felt bevacizumab aided T-cell trafficking to the tumors where the anti-PD-1 antibody could be more effective.

Editorial - Dr Moore

In the Liu trial, there was a reasonable overall response rate — especially among patients considered to have intermediate platinum sensitivity (ORR 40%), but the duration of response was fairly low. Among platinum-resistant patients, the ORR was low (16.7%) and not too dissimilar to what you would expect for monotherapy bevacizumab, but the duration of response (for 3 patients) was over a year, which is an interesting signal.

As a single-arm study, this paper is signal-finding only and suggests a reasonable response rate in patients 6-12 months from their last platinum and if proven in a randomized fashion could be considered another treatment option.

Gynecologic Cancers — Drs Coleman and Moore

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.

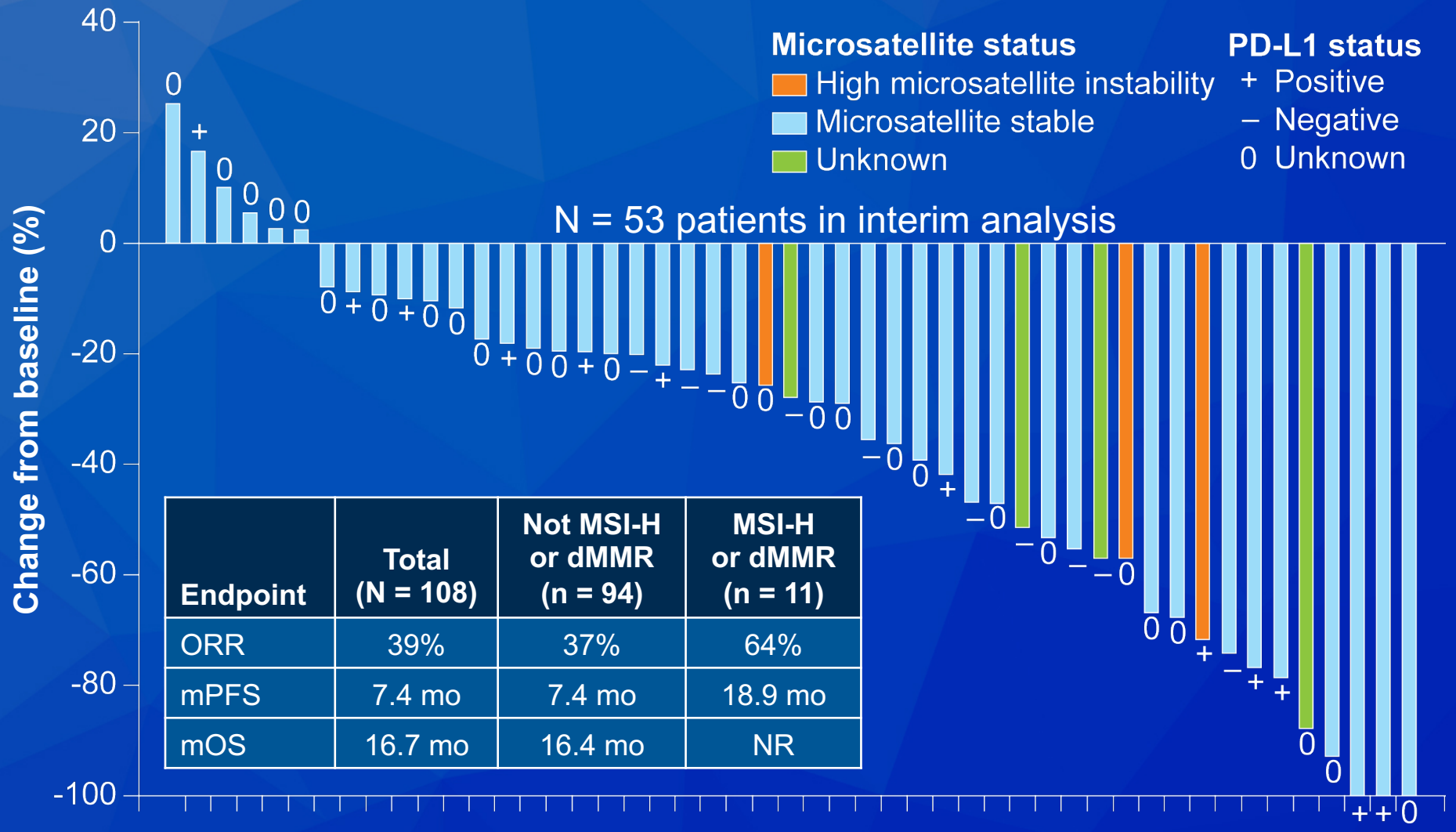
Efficacy was investigated in Study 111/KEYNOTE-146 (NCT02501096), a single-arm, multicenter, open-label, multi-cohort trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting."

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.

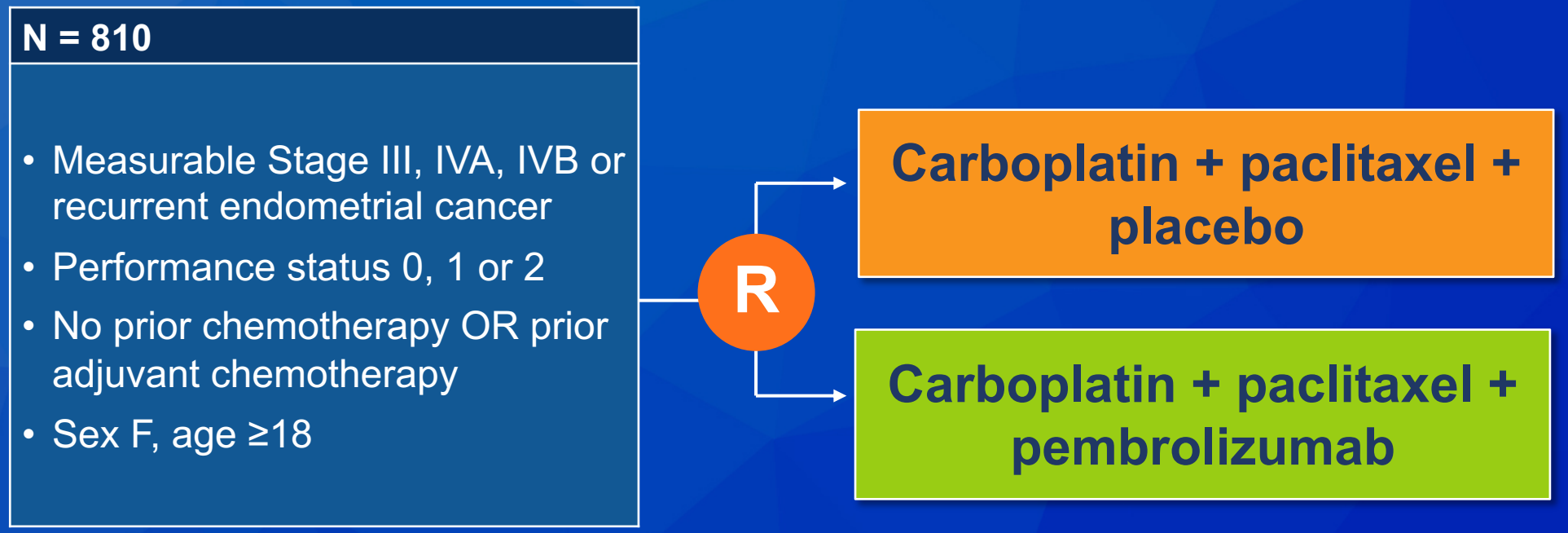
Editorial — Dr Matulonis

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.

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

R

Dostarlimab (TSR-042) + carboplatin/paclitaxel

Placebo + carboplatin/paclitaxel

Primary endpoint: Progression-free survival

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

Editorial — Dr Matulonis

In the GARNET study, patients with recurrent endometrial cancer were enrolled. 65 patients with MSI-high cancers and 125 patients with MSS endometrial cancer were enrolled. Patients could have only received up to 2 prior lines of treatment. In the MSI-high cohort, 78% of patients had endometrioid tumors and 22% others. In the MSS cohort, 39% of patients had endometrioid, 27% had serous, 5% clear cell and 29% other. ORR with TSR-042 was 49% in the MSI-high cancers and 20% in patients with MSS tumors. ~50% of responders remained on treatment for >1 year.

Several ongoing phase 3 studies in the high-risk patient endometrial cancer population are currently focused on the addition of immune checkpoint blockade to carboplatin and paclitaxel chemotherapy; trials are ongoing testing pembrolizumab (NCT03914612), TSR-042 (NCT 03981796, PROs included), as well as atezolizumab (NCT03603184).

Editorial — Dr Matulonis (continued)

These studies are testing the addition of the IO agent to carboplatin and paclitaxel chemotherapy, which will be given either as primary treatment or after radiation therapy. The primary endpoint of these studies is progression-free survival. I just wrote up the GOG-0258 QOL experience, and besides examining PFS and other efficacy endpoints, understanding the QOL and toxicity impact of adding an immune checkpoint inhibitor to chemotherapy will be critical. GI toxicities may be particularly significant in patients who receive radiation therapy and go on to receive chemotherapy and immune checkpoint blockade. PRO measurement with a focus on GI toxicities as well as other immune-related toxicities will be critical to measure.

Gynecologic Cancers — Drs Coleman and Moore

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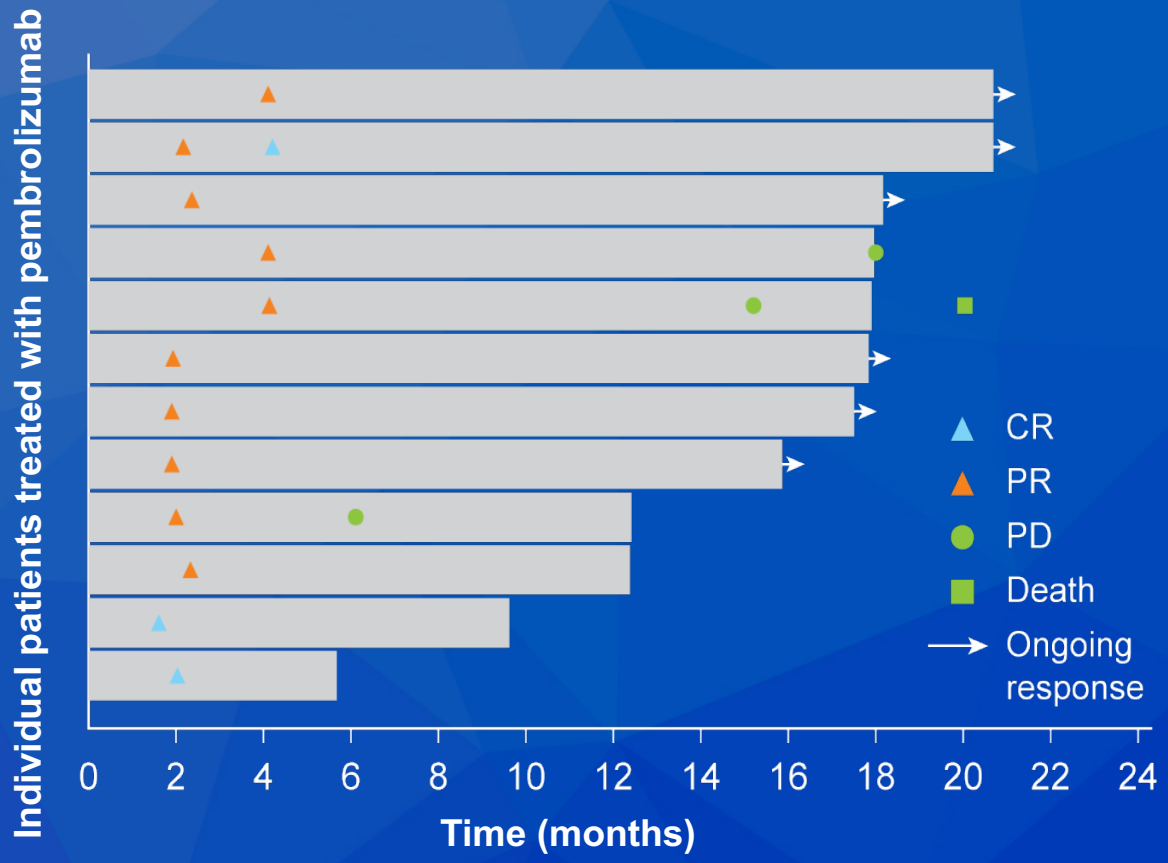
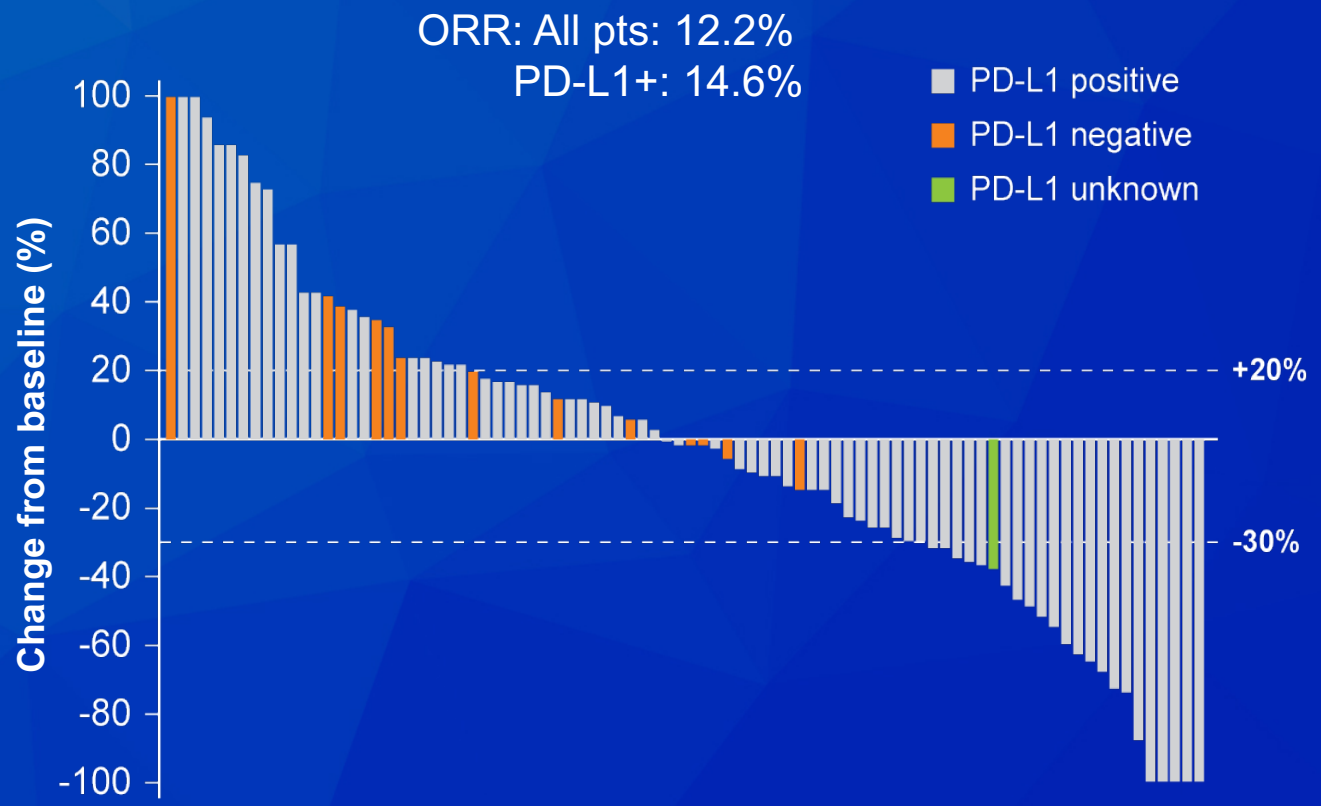
Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results from the Phase II KEYNOTE-158 Study

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.

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%.