TARGETED THERAPY IN GYNECOLOGIC CANCERS

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WE NEED TO DO BETTER….

Little improvement in disease-specific mortality rates
High disease prevalence - successes of contemporary management
opportunity for discovery of new active agents.

TABLE 15.1 Mortality Rates[a] of Major Gynecologic Malignancies Over 30 Years

	1975	1985	1995	2005	2008–2012	2014–2018
Cervical	5.55	3.82	3.24	2.42	2.3	2.2
Endometrial	5.28	4.61	4.15	4.12	4.4	4.9
Ovarian	9.84	9.08	9.12	8.66	7.7	6.7

[a]Mortality rates presented as per 100,000 women.

THE TARGET

Novel therapeutic options - focused on targeting molecular pathways critical to the survival of cancer cells.

CHEMOTHERAPY VS TARGETED THERAPY

- Cytotoxic chemotherapy acts primarily on any rapidly dividing cells.
- Do not discriminate between tumor cells and normal host cells
- Targeted therapies selectively acts on targets in tumor cells or in the TME.
- Targets are members of the pathways involved in tumorigenesis.
- Normal tissues could be spared, and adverse events may be minimized.

- Monoclonal antibody (mAb) - bind cancer-associated antigens /ligands or cell surface molecules that participate in pathways of tumorigenesis.
- Small molecule inhibitors- oral drugs that inhibit molecular receptors through the blockage of tyrosine kinase enzymes (key to an array of normal and abnormal cellular functions).
- Antisense oligonucleotides (ASOs) and short interfering RNAs (siRNAs) – interfere with expression of specific genes involved in tumorigenesis.
- ADCs-Antibody-Drug Conjugate- combine a highly toxic cytotoxic agent (or agents) with a specific immunoglobulin.

Other unique agents

- Decoy receptors that bind key ligands of carcinogenic pathways
- Virus-based gene therapies deliver a functional transgene designed to selectively kill cancer cells

KEY PATHWAYS IN GYNECOLOGIC MALIGNANCIES

CELL CYCLE TARGETS

- The progression through cell cycle is regulated by proteins - cyclin-dependent kinases (CDK – of serine and threonine kinases family.)
- CDK alterations can lead to unregulated growth, genomic instability, and ultimately, malignant transformation.
- HPV oncoproteins (E5, E6, E7) interfere with the cyclins and CDKS in addition to their effect on tumor suppressor proteins p53 and pRb.

CYCLIN-DEPENDENT KINASE (CDK) INHIBITORS

- HUMAN PAPILLOMA VIRUS (HPV)associated malignancies- cervical, vulvar, or vaginal cancers
- High-grade Serous Ovarian Cancer (HGSOC) & Serous uterine cancer -somatic mutation in TP53
- CDK inhibitors are actively being studied as monotherapy and in combination with other treatment modalities.

DNA SYNTHESIS/ REPLICATION

- Unchecked mistakes in DNA replication are key drivers in cancer development.
- Mutations in genes responsible for maintaining fidelity of DNA replication are associated with human cancer syndromes
- Two commonly encountered gynecologic cancer syndromes are associated with

➢ mutations in breast cancer gene 1 and 2 (BRCA1 and BRCA2).

➢ Homologous recombination (HR) repair and DNA mismatch repair (MMR) pathways.

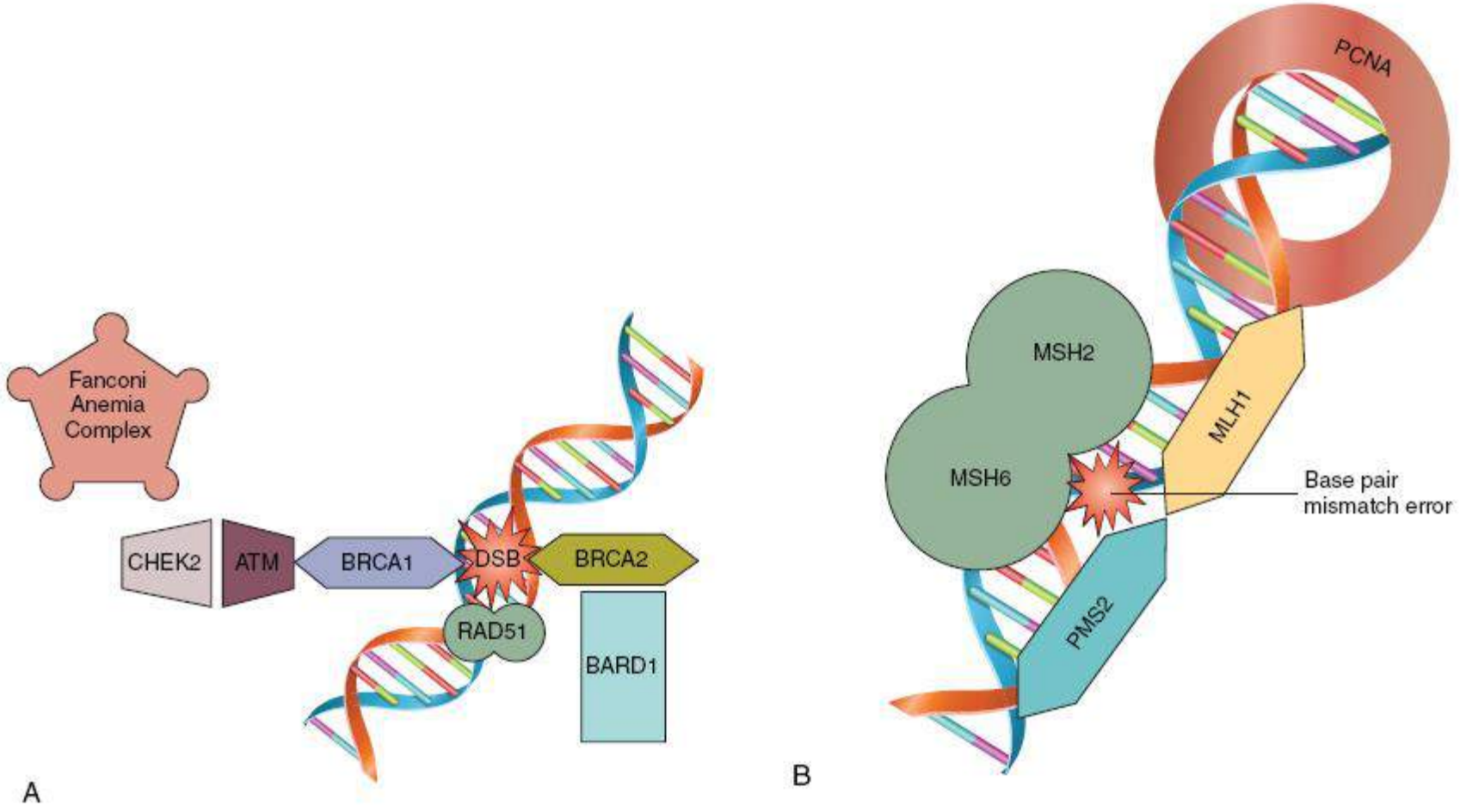


Figure 16.3 **A,** Proteins involved in the homologous recombination repair pathway. **B,** Proteins involved in DNA mismatched repair. *DSB,* Double stranded breaks.

HOMOLOGOUS RECOMBINATION (HR) REPAIR DEFICIENCY

- Mutations in BRCA 1 & BRCA 2 genes - 15% & 40% lifetime risk of developing ovarian cancer.
- Other genes within the Fanconi Anemia pathway, (partner and localizer of BRCA2 (PALB2), BRCA1 interacting protein 1 (BRIP1), and RAD51 paralog C (RAD51C))also increase a female's risk of developing ovarian cancer
- HR deficiency can also occur due to somatic mutations within the tumor.
- Genes related to HR, such as RAD51, checkpoint kinase 2 (CHEK2), ataxia telangiectasia mutated (ATM), and BRCA1 associated ring domain 1 (BARD1), when altered, cause defects in DNA repair leading to genomic instability.

LYNCH SYNDROME

- Autosomal-dominant syndrome, predisposes individuals to an increased risk of developing a variety of tumors.
- Caused by mutations in DNA Mismatch repair MMR genes
- MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), MutS homolog 6 (MSH6), and PMS1 homolog 2 (PMS2)
- Significant risk of acquiring colon cancer at a young age,
- 40% to 60% risk of endometrial cancer, & 12% risk of ovarian cancer.

TARGETED THERAPIES

- VEGF inhibitors,
- PARP inhibitors
- Immunotherapies,

have established their place in treatment paradigm for Gynecologic cancers

- Antibody-drug conjugates (ADCs) are being developed

TARGETING ANGIOGENESIS

Agents Targeting the Vascular Endothelial Growth Factor Pathway

BEVACIZUMAB-HUMANIZED MAB TO HUMAN VEGF

- First FDA-approved drug targeting angiogenesis
- First success in the platinum-resistant recurrent ovarian cancer setting
- Several phase II trials in the upfront setting
- Five major phase III trials in Ovarian Cancer

KEY CHARACTERISTICS

TABLE 16.3 Randomized Control Trials Investigating Bevacizumab Use in Ovarian Cancer

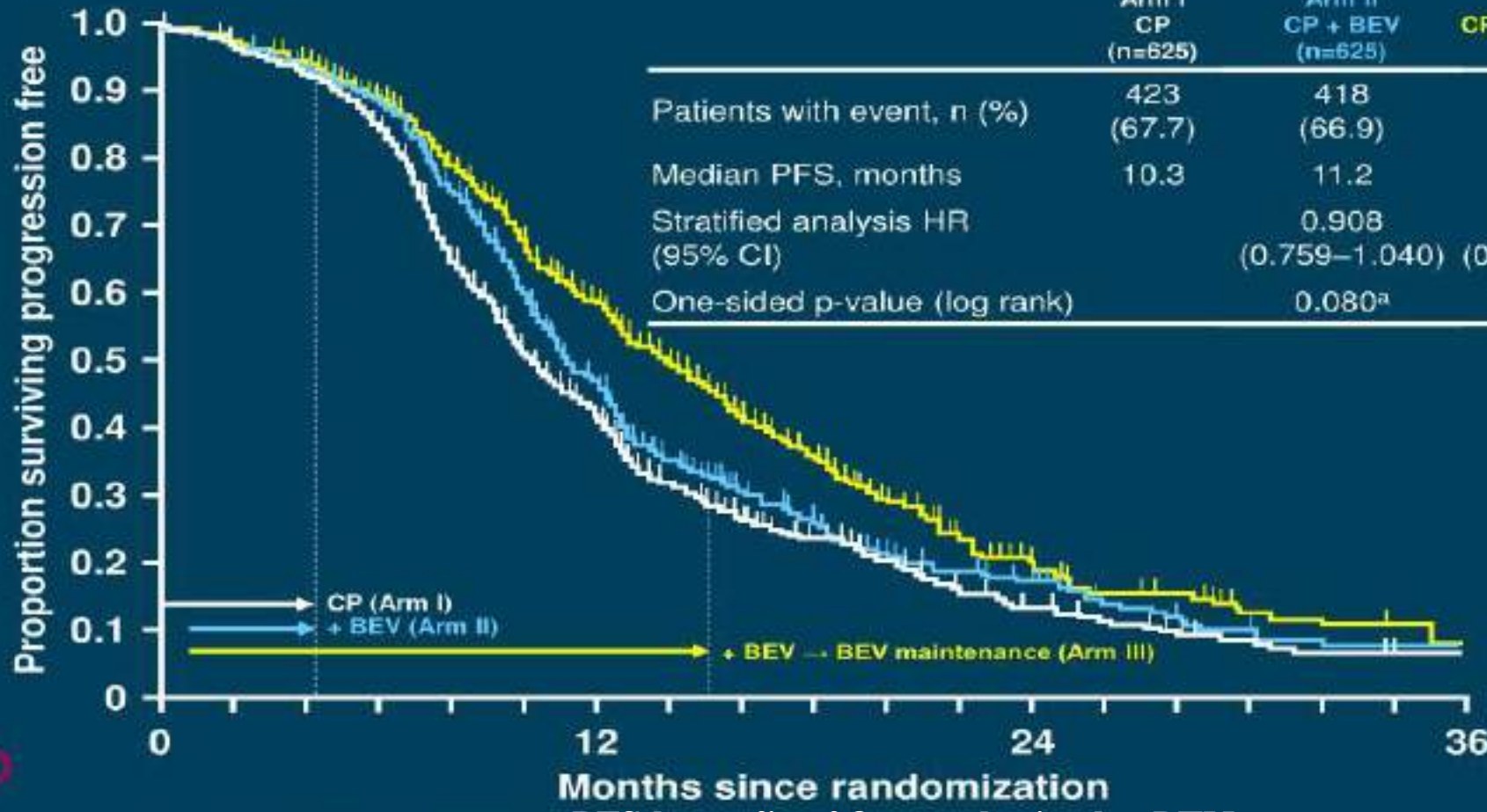
	GOG 213	GOG 218	ICON 7	OCEANS	AURELIA	PAOLA
Total Patients	674	1873	1528	484	361	806
Study Arms	Arm 1: Carbo AUC 5 + paclitaxel 175 mg/m^2 q3 weeks Arm 2: Carbo AUC 5 + paclitaxel 175 mg/m^2 + Bev 15 mg/kg q3weeks followed by Bev maintenance	Arm 1: Carbo AUC 6 + paclitaxel 175 mg/m^2 Arm 2: Carbo AUC 6 + paclitaxel 175 mg/m^2 + Bev 15 mg/kg Arm 3: Carbo AUC 6 + paclitaxel 175 mg/m^2 + Bev 15 mg/kg followed by Bev maintenance	Arm 1: Carbo AUC 5 or 6 + paclitaxel 175 mg/m^2 Arm 2: Carbo AUC 5 or 6 + paclitaxel 175 mg/m^2 + Bev 7.5 mg/kg followed by Bev maintenance	Arm 1: Gem 1000 mg/m^2 day 1 and 8 + Carbo AUC 4 q3weeks + placebo followed by placebo maintenance Arm 2: Gem 1000 mg/m^2 day 1 and 8 + Carbo AUC 4 q3weeks + Bev 15 mg/kg followed by Bev maintenance	Arm 1: Investigator's choice chemo[a] Arm 2: Investigator's choice chemo[a] + Bev 10 mg/kg 15 mg/kg q3weeks	Arm 1: Olaparib 300 mg BID + Bev 15 mg/kg q3weeks Arm 2: Placebo + Bev 15 mg/kg
Primary Endpoint	OS	OS	PFS	PFS	PFS	PFS
Secondary Endpoints	PFS, QoL, Hypersensitivity	Toxicity, QoL, Translational data	OS, RR, QoL	ORR, OS, DoR	ORR, OS, QoL	PFS2, OS, TSST, QoL
Primary or Recurrent Disease	PS Recurrent	Primary	Primary	PS Recurrent	PR Recurrent	Maintenance

[a]Investigator's choice chemo options: Paclitaxel 80 mg/m^2 day 1, 8, 15, 22 q4weeks; Topotecan 4 mg/m^2 day 1, 8, 15 q4weeks; Pegylated Doxorubicin 40 mg/m^2 q4weeks.

Bev, Bevacizumab; *Carbo*, carboplatin; *Gem*, gemcitabine; *ORR*, objective response rate; *OS*, overall survival; *PFS*, progression free survival; *PFS2*, progression free survival to second progression; *PR*, platinum resistant; *PS*, platinum sensitive; *QoL*, quality of Life; *RR*, response rate; *TSST*, time to second subsequent therapy.

MAJOR PHASE III OVARIAN CANCER TRIALS

GOG-0218: Investigator-Assessed PFS



	Arm I CP (n=625)	Arm II CP + BEV (n=625)	Arm III CP + BEV → BEV (n=623)
Patients with event, n (%)	423 (67.7)	418 (66.9)	360 (57.8)
Median PFS, months	10.3	11.2	14.1
Stratified analysis HR (95% CI)		0.908 (0.759–1.040)	0.717 (0.625–0.824)
One-sided p-value (log rank)		0.080[a]	<0.0001[a]

ASCO | Annual '10 Meeting

PFS benefit of 3 months in the BEV concurrent plus maintenance arm (14.1 vs. 11.2 months; hazard ratio [HR], 0.72; P , .001).

[a]p-value boundary = 0.0116

FDA APPROVAL

- 2018- US FDA approved bevacizumab for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with carboplatin and paclitaxel, followed by single-agent bevacizumab, for stage III or IV disease after initial surgical resection.
- The recommended dose is 15 mg/kg every 3 weeks with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single- agent, for a total of up to 22 cycles.

FINAL OVERALL SURVIVAL GOG 0218

PUBLISHED AT JCO.ORG ON JUNE 19, 2019

- Median follow-up 102.9 months.
- Bevacizumab concurrent (n = 625), the hazard ratio (HR) of death was 1.06 (95% CI, 0.94 to 1.20);
- for concurrent plus maintenance (n = 623), the HR was 0.96 (95% CI, 0.85 to 1.09).
- Disease-specific survival was not improved in any arm.
- No survival advantage was observed after censoring patients who received bevacizumab at crossover or as second line.
- Median OS for stage IV bevacizumab-concurrent plus maintenance was 42.8 v 32.6 months in control (HR, 0.75; 95% CI, 0.59 to 0.95).

ICON 7

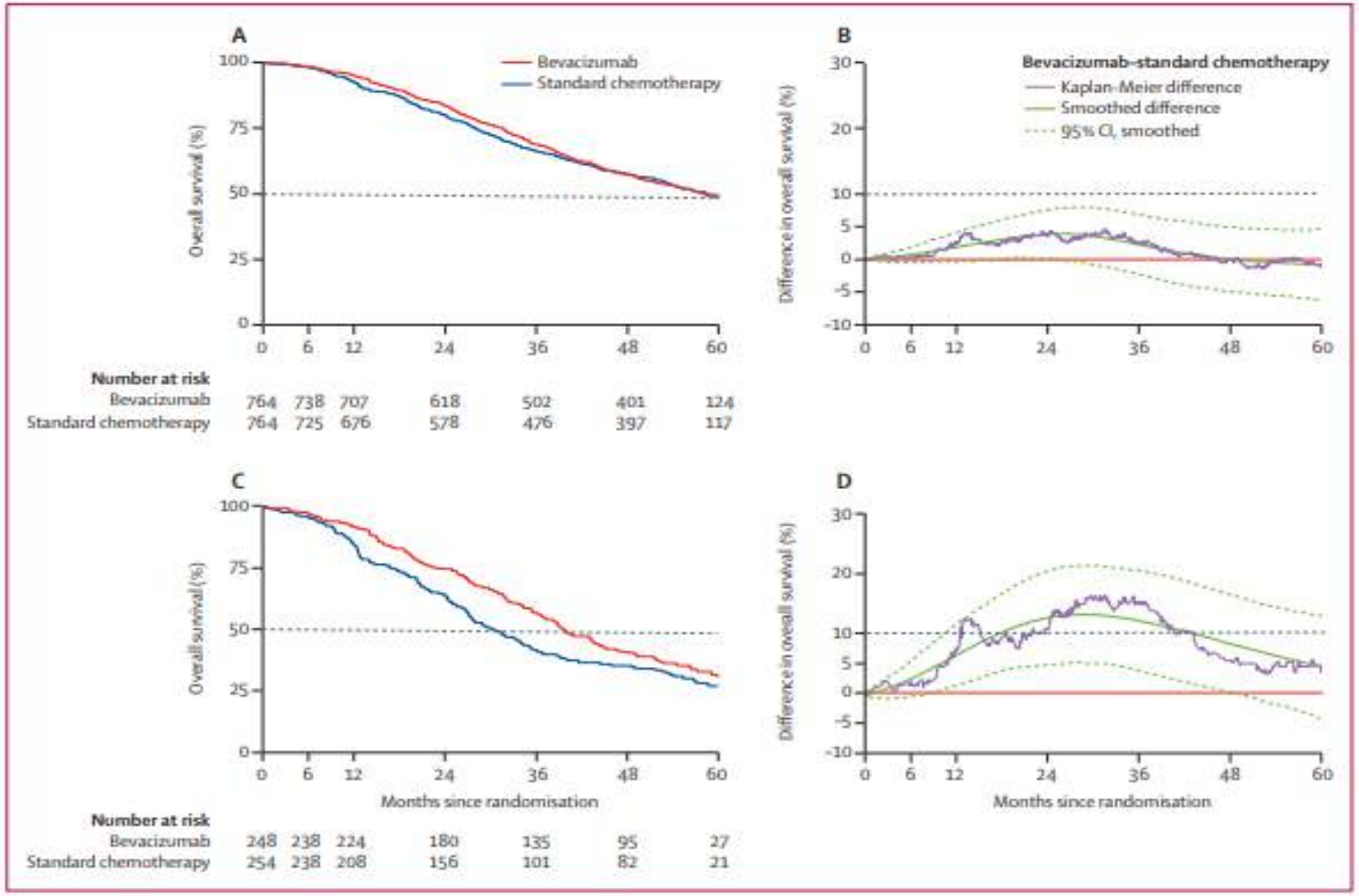


Figure 2: **Overall survival**
(A) Overall survival in all patients. (B) Difference in overall survival between all patients in the two groups. (C) Overall survival in high-risk patients. (D) Difference in overall survival between high-risk patients in the two groups.

- PFS time was improved by 1.7 months

(24.1 vs. 22.4 mo);

- HR, 0.87; P .04).
- OS was similar between the arms.

(ICON7)
OVERALL SURVIVAL RESULTS *LANCET ONCOL* 2015; 16: 928–36

- Dec 18, 2006 - Feb 16, 2009; 1528 women
- Median follow-up as on March 31, 2013 - 48·9 months (IQR 26·6–56·2).
- No overall survival benefit for bevacizumab

  44·6 months [95% CI 43·2–45·9] in the standard chemotherapy group

vs

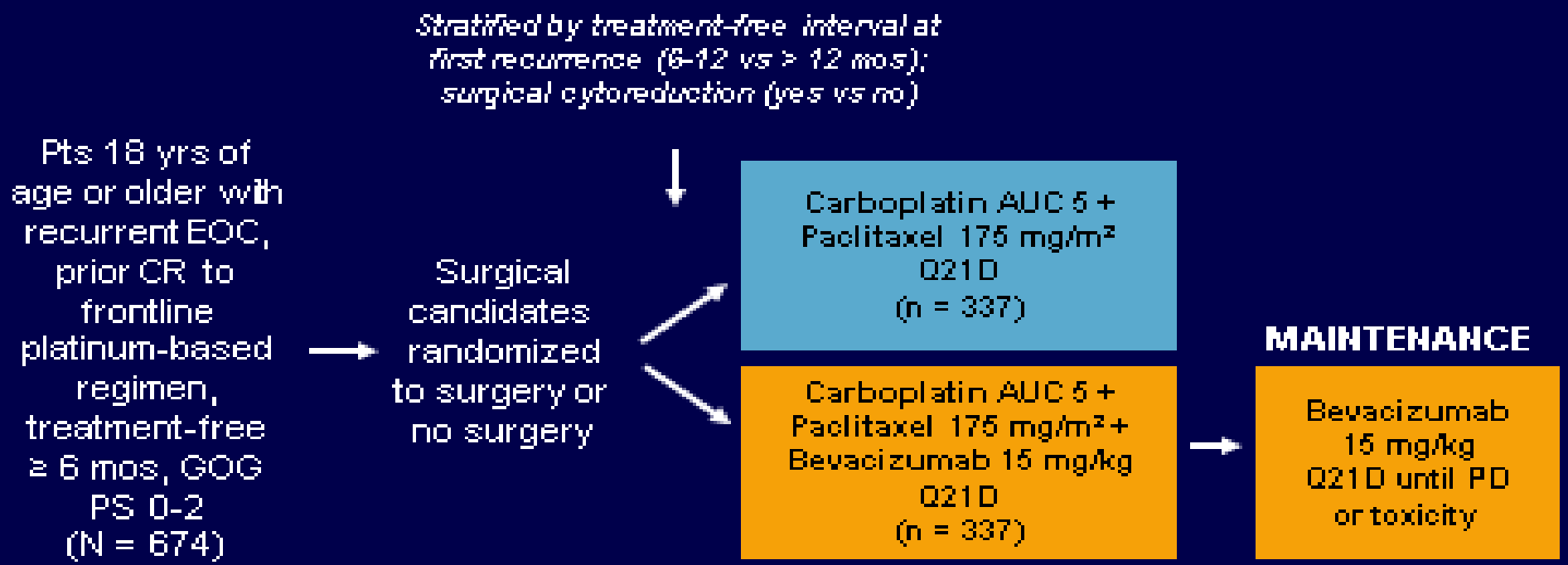
45·5 months [44·2–46·7] in the bevacizumab group; log-rank p=0·85).

➢ Significant OS difference in predefined subgroup of 502 patients with poor prognosis disease, 34·5 months with standard chemotherapy vs 39·3 months with bevacizumab; log-rank p=0·03)

RECURRENT SETTING- PHASE III TRIALS

GOG0213: Study Design

- Bifactorial, randomized phase III trial



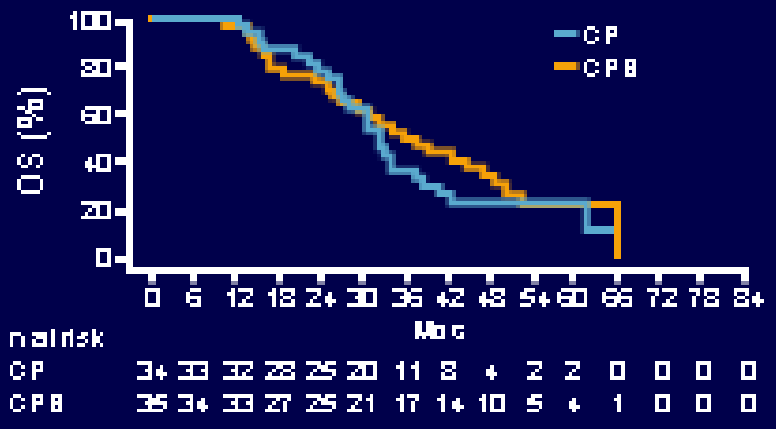
Coleman RL, et al. ASCO 2016. Abstract 5523.

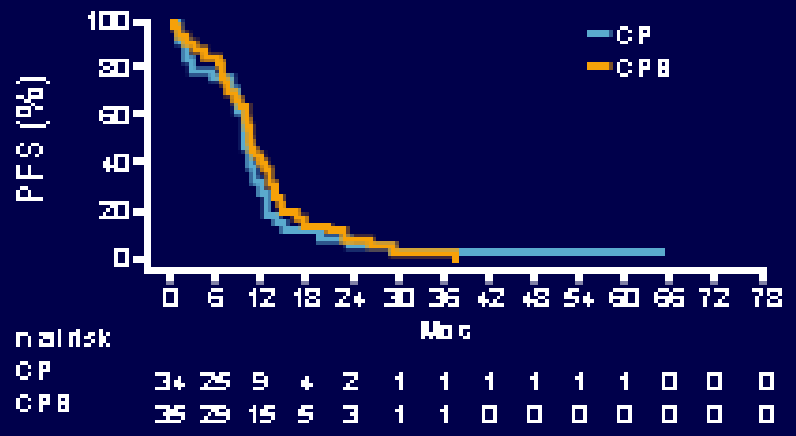
Slide credit: clinicaloptions.com

Prior Bevacizumab Subgroup of GOG0213: Outcomes

Outcome	Carboplatin/ Paclitaxel (n = 34)	Carboplatin/ Paclitaxel + Bevacizumab (n = 35)	HR (95% CI)	P Value
Median OS, mos	32.0	36.8	0.76 (0.44-1.34)	
Median PFS, mos	9.8	10.7	0.84 (0.52-1.37)	
ORR,* %	54	82		.044
CR*, %	11	32		< .02

*n = 28 evaluable in each arm.



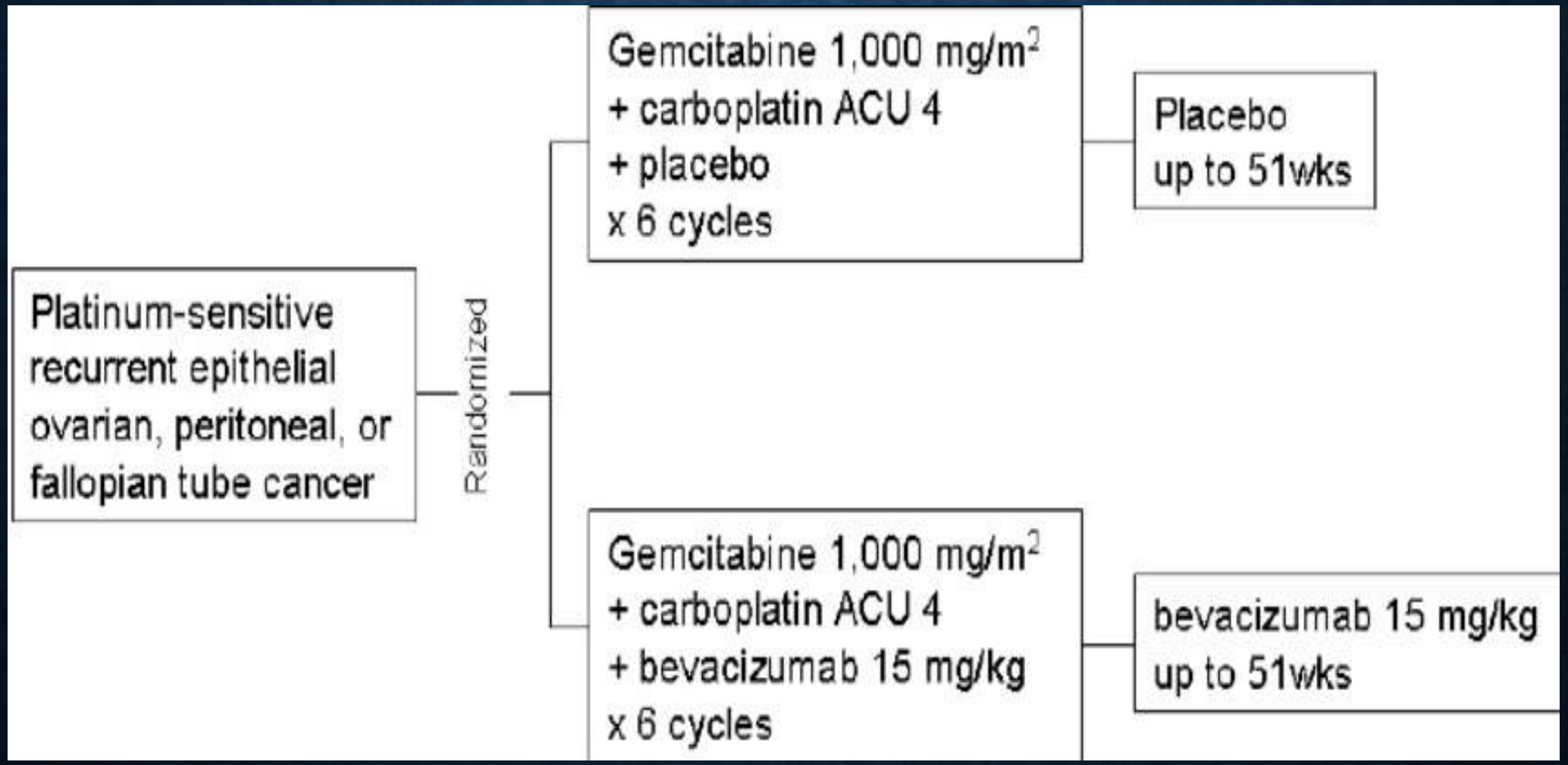


Coleman RL, et al. ASCO 2016. Abstract 5523.

Slide credit: clinicaloptions.com

Significant improvement in PFS as well as a trend toward improved OS in the arm containing bevacizumab.

OCEANS TRIAL



OCEANS: Response

Patients, %	CG + PL (n = 242)	CG + bev (n = 242)	Hazard ratio	*p*-value
Objective response	57%	78%	NR	<0.0001
Complete response	9%	17%		
Partial response	48%	61%		
Median duration of response (n = 139, 190)	7.4 mo	10.4 mo	0.534	<0.0001

Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

OCEANS: Progression-Free Survival

	CG + PL (n = 242)	CG + bev (n = 242)
Events, n (%)	187 (77)	151 (62)
Median PFS, months (95% CI)	8.4 (8.3–9.7)	12.4 (11.4–12.7)
Stratified analysis HR (95% CI) Log-rank *p*-value	0.484 (0.388–0.605) <0.0001	

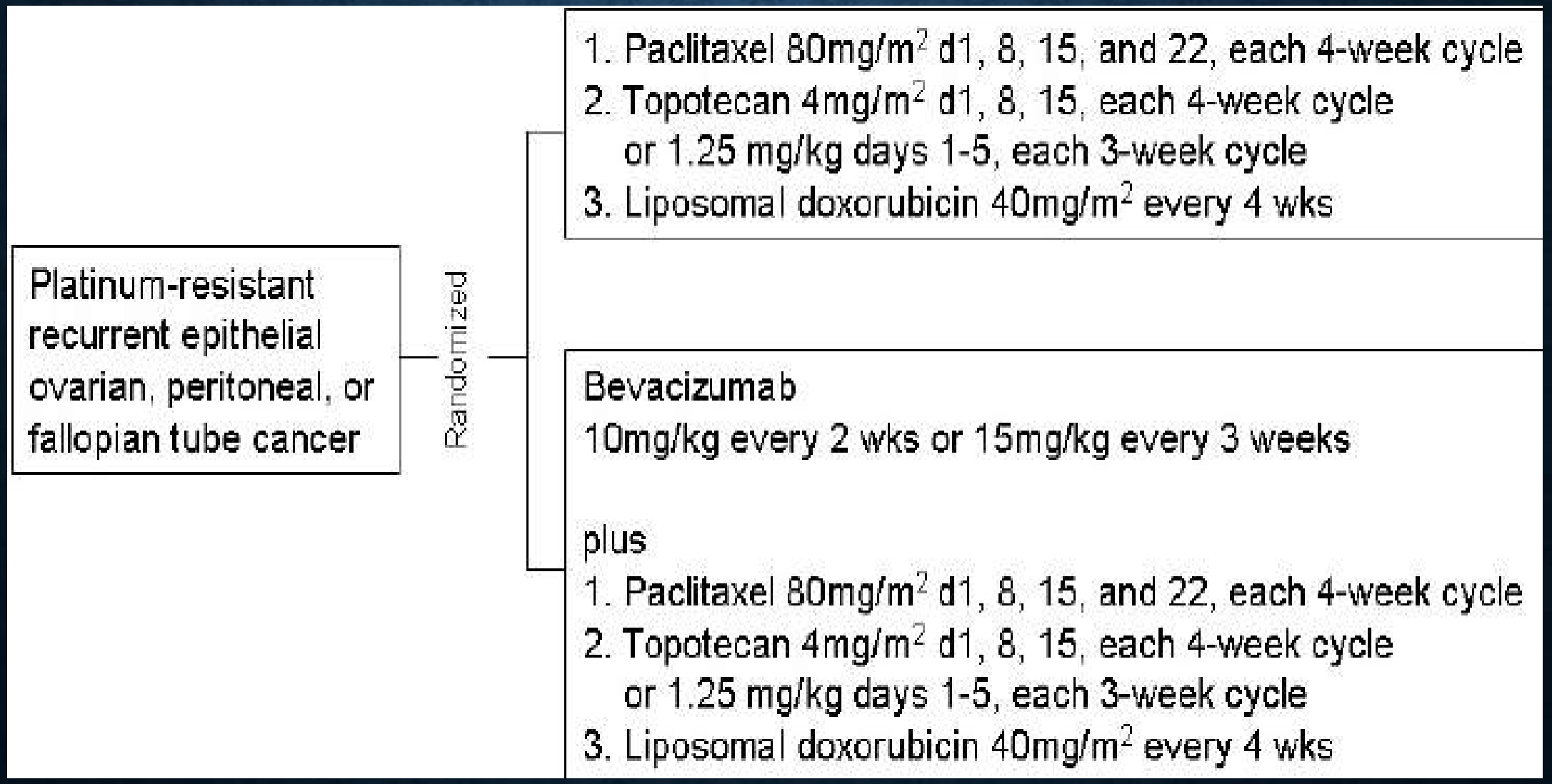
Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

RESULTS

- The study met its primary endpoint, demonstrating improved progression-free survival.
- Bevacizumab improved PFS by 4 months.
- Median OS was comparable between arms (GC + bevacizumab: 33.6 months; GC + PL: 32.9 months; hazard ratio = 0.95; log-rank p = 0.65),
- was consistent across all examined patient subgroups.

AURELIA TRIAL

Bevacizumab with a physician-choice chemotherapy agent



RESULT

- Median PFS was 6.7 months with bevacizumab plus chemotherapy versus 3.4 months with chemotherapy alone.
- Objective response rate (secondary endpoint) was also significantly improved with bevacizumab (30.9% versus 12.6%, P <0.001).
- Greatest PFS benefit (6 months) was found in the cohort that combined weekly paclitaxel with bevacizumab.
- The high crossover to bevacizumab after trial participation likely influenced the lack of OS difference noted in this trial.

IN NONEPITHELIAL OVARIAN CANCER

- Bevacizumab in Recurrent Sex Cord-stromal Ovarian Tumors:

➢ results of a phase 2 trial of the Gynecologic Oncology Group. *Cancer. 2014 Feb* . Among 36 patients treated, 16.7% had a partial response and 77.8% achieved SD.

- Promising results for a chemo resistant disease.

➢ A retrospective review of eight patients with Recurrent Granulosa Cell Tumors demonstrated a partial response rate of 38% and SD rate of 25%.

RECENTLY PUBLISHED STUDIES

Optimal Treatment Duration of Bevacizumab maintenance as Front-Line Therapy for Advanced Ovarian Cancer

AGO-OVAR17/BOOST TRIAL

- 927 women from 161 centers with stage IIb to IV epithelial ovarian (84%), fallopian tube, or peritoneal cancer.
- After induction, randomly assigned to receive maintenance bevacizumab for standard 15 months or 30 months, which was the experimental arm.
- The study found no significant benefit to extending bevacizumab maintenance beyond 15 months

TABLE 1: Outcomes With Bevacizumab Maintenance in ENGOT/GCIG Trial

Endpoint	BEV15 (n = 464)	BEV30 (n = 463)	Hazard Ratio/*P* Value
Progression-free survival	72%	73%	–
Median progression-free survival	24.2 months	26.0 months	HR = –0.99 *P* = .90
Overall survival	55%	59%	HR = 1.04
Median overall survival	54.3 months	60.0 months	*P* = .68

BEV15 = bevacizumab (15 mg/kg every 3 weeks) for 15 months; BEV30 = bevacizumab (15 mg/kg every 3 weeks) for 30 months.

MITO-16B

second line chemotherapy ± bevacizumab in patients with platinum sensitive epithelial ovarian cancer recurrence after bevacizumab/chemotherapy first line

- Recurrent, platinum-sensitive ovarian cancer and prior treatment with bevacizumab,
- Rechallenge with bevacizumab prolongs PFS, but not OS.
- 11.8 versus 8.8 months, for 6 cycles of a platinum-based doublet with and without BEV HR 0.51, 95% CI 0.41-0.65).
- OS results were similar (27 months in both groups).

PREDICTING RESPONSE TO BEVACIZUMAB

- GOG-0218 study analyzed the predictive value of intra-tumor chemo sensitivity, assessed by the KELIM score (which is based on the CA 125 kinetics model)
- The outcome demonstrated a significant benefit of bevacizumab for patients with unfavorable KELIM compared to placebo.

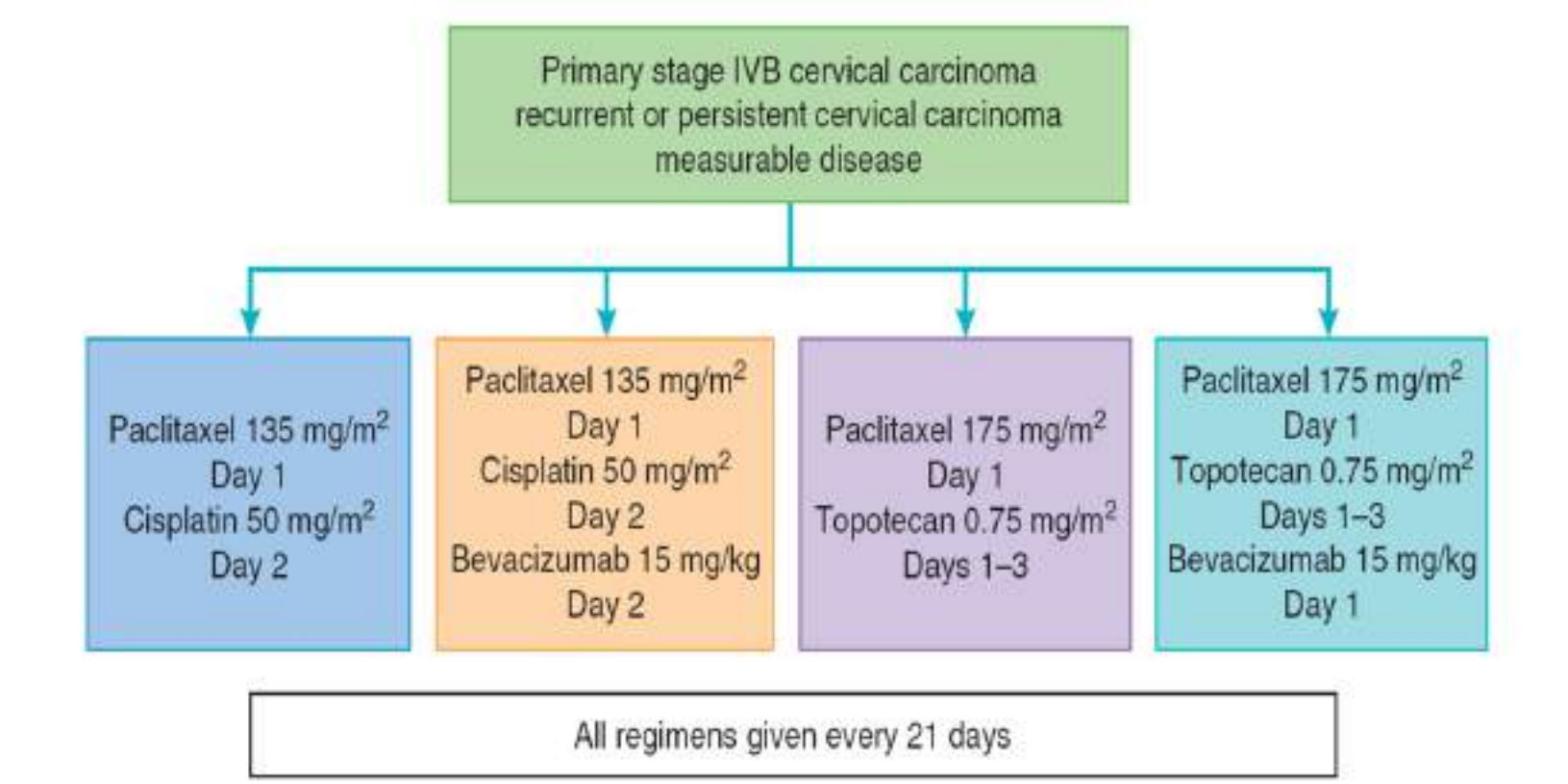
The results reconcile the 2 phase III studies with Bevacizumab ICON 7 and GOG 0218,

➢ Bevacizumab has to be prioritized in high-risk patients with unfavorable KELIM score and poorly chemo- sensitive tumors.

CERVICAL CANCER

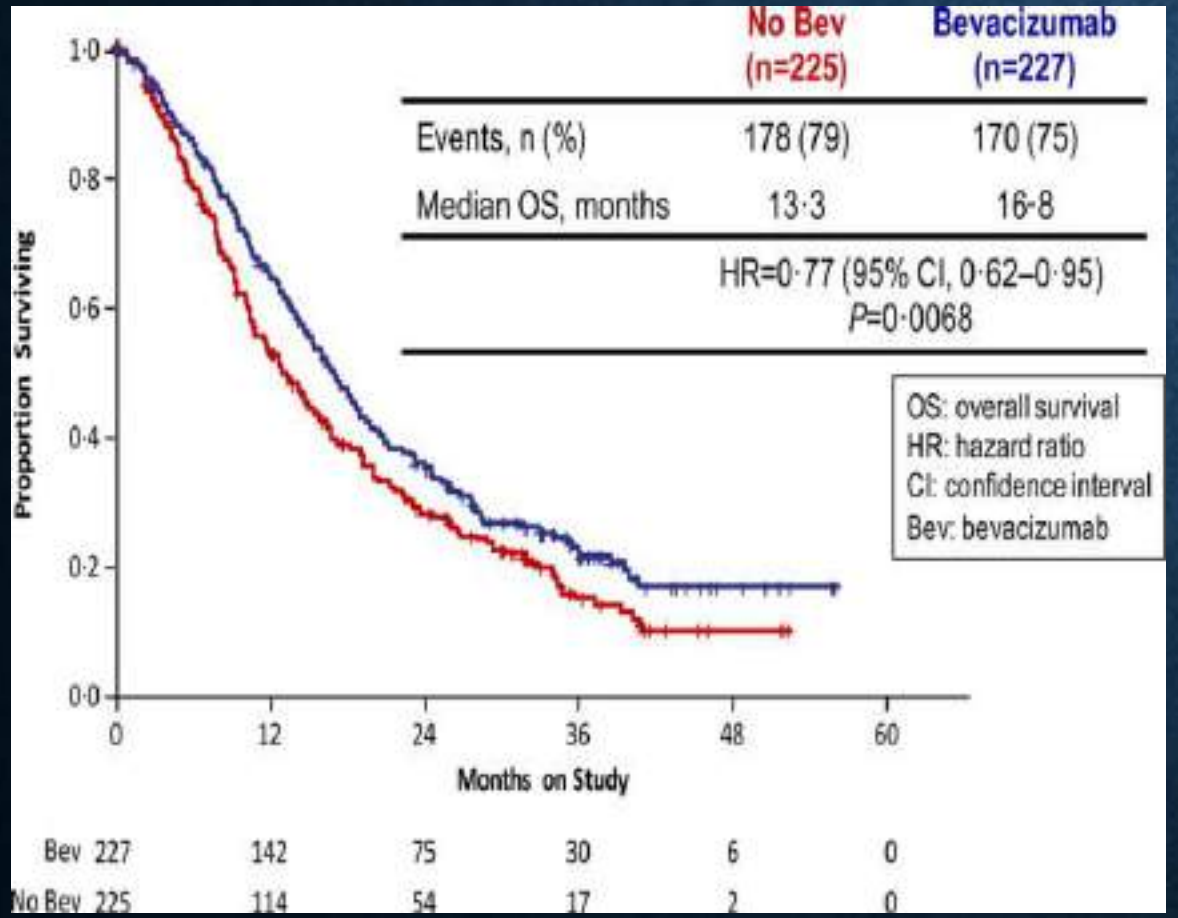
Bevacizumab is the first targeted agent to demonstrate activity in recurrent cervical cancer.

GOG 240

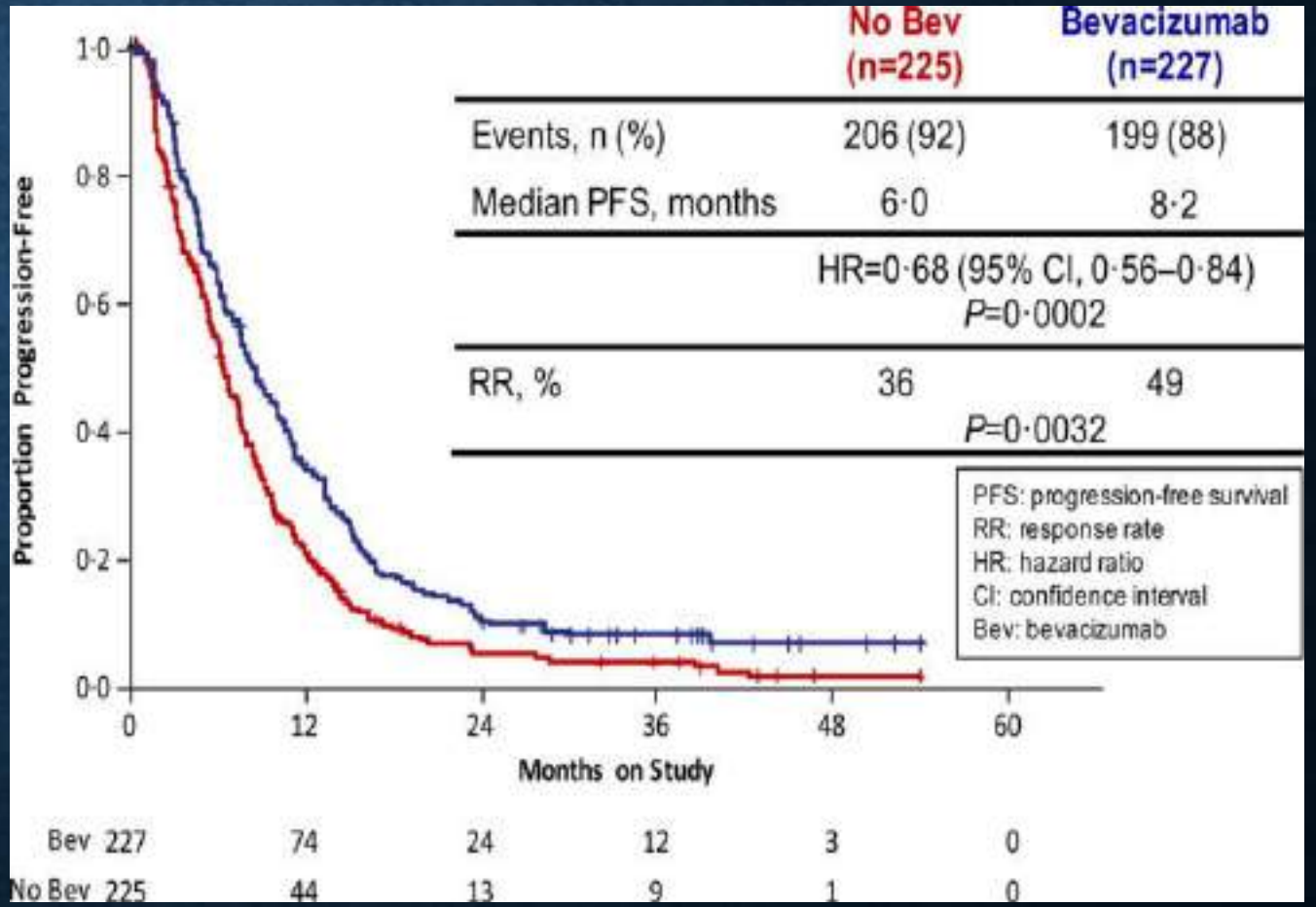


Bevacizumab combined with standard chemotherapy (4 regimens) for Primary stage IVB cervical carcinoma/recurrent or persistent cervical carcinoma with measurable disease.

Kaplan-Meier curves intent-to-treat final protocol-specified overall survival comparing chemotherapy alone to chemotherapy plus bevacizumab.



Kaplan-Meier curves depicting the intent-to-treat updated progression-free survival c



FINAL OVERALL SURVIVAL GOG 240

LANCET. 2017 OCT 7; 390(10103): 1654–1663.

- Regimens administering bevacizumab continued to demonstrate significant improvement in OS: 16.8 vs 13.3 mos (HR 0.77;95% CI 0.62–0.95;p=0.0068).
- Updated progression-free survival also favored bevacizumab (HR 0.68;95% CI 0.56–0.84;p=0.0002).

➢ led to an FDA approval for bevacizumab in combination with chemotherapy for advanced and recurrent cervical cancer.

UTERINE CANCER.

VEGF expression has been correlated with adverse outcomes in endometrial cancer.

Bevacizumab demonstrated encouraging results in early-phase clinical settings

GOG-86P & MITO-END-2 STUDY

- The addition of Bevacizumab to chemotherapy in advanced or recurrent endometrial cancer did not yield an improvement in PFS.

- Interestingly, the presence of p53 mutation was associated with better PFS and OS in GOG-86P.
- May be a potential biomarker to select combination therapy.

BEVACIZUMAB WITH (IMRT) AND CISPLATIN IN HIGH-RISK ENDOMETRIAL CANCER.

- The addition of bevacizumab to intensity-modulated radiation therapy (IMRT) with cisplatin.
- Overall, toxicity was reasonable.
- OS rate for the cohort was 96.7% at 2 years.

POLY-ADENOSINE DIPHOSPHATE-RIBOSE POLYMERASE PATHWAY

PARPi in gynecologic cancer

PARPI IN GYNECOLOGIC CANCER
SYNTHETIC LETHALITY

- Approximately 20% of ovarian cancer patients have a BRCA mutation,
- 50% have some genomic aberration that confers homologous repair deficiency.
- PARP inhibitors extensively investigated in ovarian cancer

➢ PARP inhibitors have US Food and Drug Administration (FDA) approval in both the upfront and recurrent setting

OLAPARIB

FIRST PARP INHIBITOR STUDIED IN CLINICAL TRIALS.

- Study 19 - phase II trial - Olaparib as maintenance therapy in platinum-sensitive relapsed ovarian cancer patients.
- Median PFS was 8.4 months for Olaparib compared to 4.8 months in placebo arm (hazard ratio [HR] 0.35; P , .001).
- Patients with BRCA mutations received the biggest benefit (PFS of 11.2 months vs. 4.3 months).

DOSAGE - STUDY 24

- originally approved olaparib formulation was 400 mg b.i.d
- study 24 determined that the olaparib 300 mg b.i.d. (2 × 150 mg) tablet formulation matched or exceeded the exposure of 400 mg b.i.d. capsules
- 300 mg b.i.d. tablet regimen - non-inferior to 400 mg b.i.d. capsules in terms of tumour shrinkage

SOLO2 PHASE III TRIAL
OLAPARIB IN RECURRENT OVARIAN CANCER

- Patients- BRCAm, PSR ovarian cancer,

in complete or partial response to their most recent platinum-based regimen.

- Maintenance Olaparib therapy resulted in a significantly increased PFS (19.1mo vs. 5.5 mo ; HR: 0.30; P , .0001).

INDICATIONS FOR PARP INHIBITORS

- Initial approval(December 2014 FDA) Olaparib as monotherapy in patients with deleterious or suspected deleterious germ-line BRCAm in advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy
- European Medicines Agency (EMA)- Olaparib monotherapy as maintenance in recurrent ovarian cancer for patients who had a complete response (CR) or partial response (PR) to their most recent line of platinum-based chemotherapy.
- August 2017 FDA approval expanded to include 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, irrespective of their BRCAm status and the number of prior lines of platinum-based chemotherapy received.
- In May 2018, EMA also updated Olaparib indication to maintenance regardless of BRCAm status

SOLO-1 TRIAL
OLAPARIB IN THE UPFRONT SETTING

- BRCA-mutated, newly diagnosed, advanced, high-grade serous or endometrioid ovarian cancer with a complete or partial clinical response after platinum-based chemotherapy.
- Patients were randomly assigned (2:1) to receive olaparib (300 mg twice daily) or placebo tablets orally as maintenance monotherapy for up to 2 years.
- 260 patients were randomly assigned to olaparib and 131 to placebo.
- With olaparib median progression-free survival was **56·0 months** (95% CI 41·9–not reached) versus **13·8 months** (11·1–18·2) with placebo (hazard ratio 0·33 [95% CI 0·25–0·43]).
- Drastic improvement in patients treated with Olaparib maintenance therapy compared to placebo.

PAOLA-1 (PLATINE, AVASTIN, AND OLAPARIB IN 1ST LINE)

- Olaparib and bevacizumab maintenance compared to bevacizumab alone following completion of chemotherapy.
- In the intention to treat (ITT) analysis, PFS improved by almost 6 months (22.1 vs. 16.6 months; HR: 0.59; P , .0001).
- The largest magnitude of benefit was in patients with homologous recombination deficiency (HRD) including BRCA mutation (PFS 37.2 vs. 17.7 months; HR: 0.33).

OLAPARIB ON-GOING TRIALS

- OPINION phase IIIb trial - Olaparib maintenance monotherapy in PSR non-germline BRCAm ovarian cancer patients)
- L-MOCA phase III trial - olaparib maintenance monotherapy in ovarian cancer patients after complete or partial response to platinum (a Chinese study)]
- OReO- olaparib retreatment in patients with or without a BRCAm.
- LIGHT phase II study - olaparib monotherapy treatment in ovarian cancer patients with different HRD tumour status.

RUCAPARIB- STUDY 10

- Rucaparib is a potent inhibitor of both PARP-1 and PARP-2.
- Study 10
- three-part phase I/II trial of Rucaparib in recurrent ovarian cancer.
- Objective response rate in 42 patients with platinum-sensitive HGSOC carrying a germline BRCA mutation was 59.5%
- Median duration of response of 7.8 months.

ARIEL2 PHASE II OPEN LABEL TRIAL

- Rucaparib in women with platinum-sensitive recurrent ovarian cancer.
- BRCA-mutant tumors had overall response rate of 69% and median PFS of 9.4 months.
- Conversely, BRCA-wild type tumors had the lowest evidence of activity with response rate and median PFS of 13% and 3.7 months, respectively
- BRCA-like tumors (homologous recombination deficient) - response rates of 30% and median PFS of 7.1 months

ARIEL 3-PHASE III PLACEBO-CONTROLLED TRIAL

- Maintenance Rucaparib in platinum-sensitive disease
- Three nested cohorts studied:
- (1) patients with germline or somatic BRCA mutations
- (2) HRD including patients with BRCA mutations and LOH high
- (3) the intent to treat population.
- Maintenance Rucaparib significantly improved PFS in all three cohorts with acceptable toxicity.

ARIEL 4 TRIAL

- Rucaparib versus physician- choice platinum-based chemotherapy in
- BRCA-mutant recurrent ovarian cancer.
- Patients treated with rucaparib achieved improved PFS as compared with the standard therapy.

APPROVALS

- 1) as monotherapy in patients with recurrent ovarian cancer and a germline or somatic BRCA mutation after at least two lines of prior chemotherapy.
- (2) maintenance therapy in platinum-sensitive recurrent ovarian cancer after a CR or PR to most recent platinum-based chemotherapy.

NIRAPARIB

- Niraparib inhibits PARP-1 and PARP-2
- Phase II recommended dose of 300 mg/day.
- Phase III NOVA trial- platinum-sensitive recurrent ovarian cancer randomized to niraparib maintenance versus placebo.
- PFS was 21.5 months with niraparib use compared to 5.5 months in the placebo arm in patients with BRCA mutation.
- In patients without a BRCA mutation, PFS improved by 5.4 months with niraparib (9.3 vs. 3.9 months; HR: 0.45; P , .001).

QUADRA
OPEN-LABEL, SINGLE-ARM, PHASE II TRIAL

- Niraparib in heavily pre-treated patients(3+ previous lines of chemotherapy).
- 27.5% of patients achieved an objective response and 68.6% disease control rate in HRD and platinum-sensitive group
- FDA approval Niraparib in homologous recombination deficient ovarian cancer in the fourth line or greater.

PRIMA

- Niraparib maintenance in the upfront setting.
- Patients included advanced HGSOC or endometrioid ovarian carcinoma with a CR or PR to first-line platinum-based chemotherapy.
- In the intention to treat group, PFS improved by 5.6 months with niraparib maintenance (13.8 vs. 8.2 months; HR: 0.62; P , .001).
- In homologous recombination deficient group- PFS improved by 11.5 months (21.9 vs. 10.4 months; HR: 0.43; P .001).
- In homologous recombination proficient group niraparib improved PFS by 3 months (8.1 vs. 5.4 months; HR 0.68).

VELIPARIB

- Veliparib is an inhibitor of PARP-1 and PARP-2 with lower levels of PARP trapping activity & reduced potency of the drug.
- Phase II data 26% response rate in patients with BRCA mutations.
- Unique advantage
- Veliparib can be combined with systemic chemotherapy with an acceptable side effect profile.

VELIA TRIAL

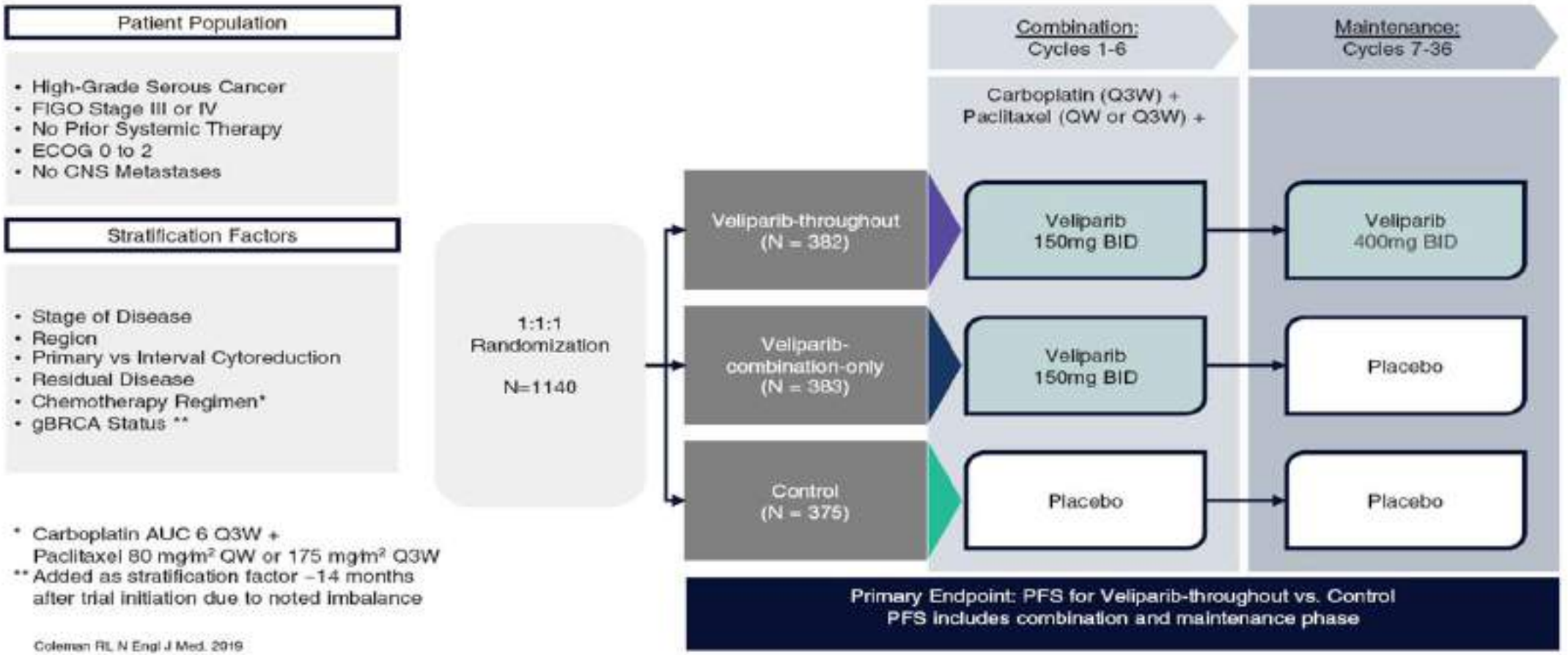


Figure 16.6 Study schema for VELIA trial (GOG 3005). (Maintenance dose initiated at 300 mg BID for 2 weeks and then increased to 400 mg BID if no limiting side effects).

VELIA TRIAL

- Veliparib concurrent followed by maintenance yielded PFS benefit of 6.2-months (23.5 vs. 17.3 months; HR: 0.68; P , .001).
- PFS in BRCAm patients was 34.7 months compared to 22.0 months (HR: 0.44; P , .001)
- 31.9 months in HRD patients compared to 20.5 months (HR: 0.57; P , .001).
- However, the lack of a veliparib maintenance alone arm hampered interpretation of this study

IMMUNE THERAPY

The ability of tumor cells to evade targeting by host immune systems has been deemed a hallmark of malignant transformation.

Therapeutics that target processes involved in the immune response in an effort to either augment host response or block tumor immune evasion

IMMUNE CHECKPOINT INHIBITORS PD-1/PD-L1 PATHWAY

- PD-L1 - overexpressed in a significant proportion of cervical cancer patients leading to the inclusion of cervical cancer patients in the Keynote-028 trial
- Pembrolizumab is an anti-PD-1 humanized monoclonal antibody that blocks the interaction between PD-1 and PD-L1.

KEYNOTE-028 TRIAL

- Phase I trial assessing the safety and efficacy of pembrolizumab in various solid tumors with PD-L1 positivity.
- There were 24 patients in the advanced cervical cancer cohort.
- Overall response rate was 17%
- 6-month PFS rate of 66.7% in patients with PD-L1 positivity.
- Keynote-158 - Phase II basket trial of Pembrolizumab in solid tumors.
- All objective responses were demonstrated in patients with PD-L1 positivity.
- Pembrolizumab - FDA approved for use in patients with advanced and recurrent cervical cancer that are PD-L1 positive.

ENDOMETRIAL CANCER PATIENTS

- Tumors deficient in mismatch repair are associated with increased tumor mutational burden and tumor-associated antigens leading to increased response from TILs.
- Phase II study Fader et al with single agent pembrolizumab

Recurrent endometrial cancer with MMR deficiency demonstrated a 56% ORR.

- Pembrolizumab as monotherapy is approved in solid tumors with microsatellite instability, including endometrial cancer.

COMBINATION TREATMENTS

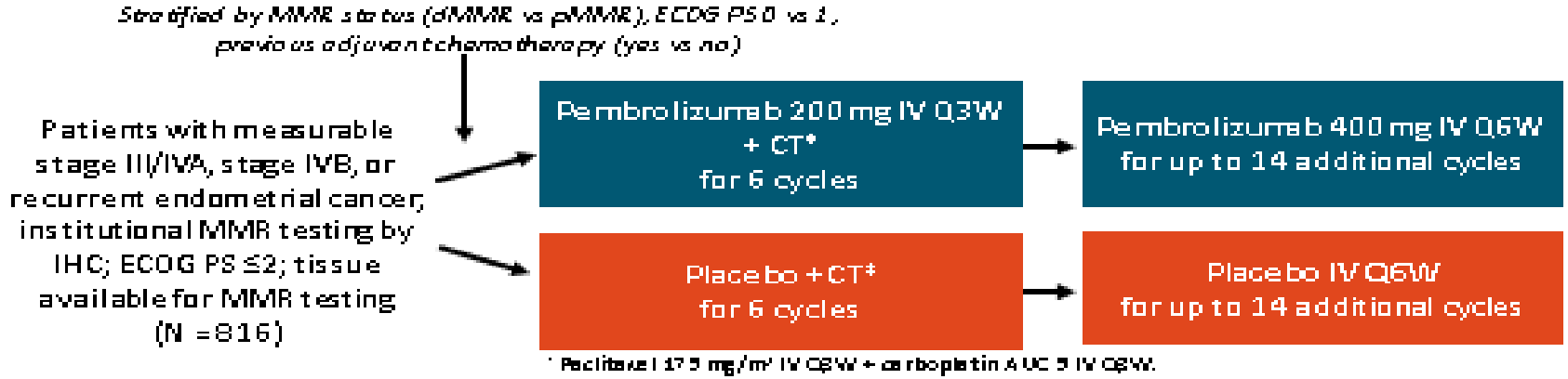
- Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4).
- Keynote-146 - combines lenvatinib and pembrolizumab in metastatic endometrial carcinoma with progressive disease following at least one prior line of systemic therapy
- The ORR in patients without evidence of microsatellite instability was 38.3% with 10 CR and 26 PR.
- Twenty-five patients demonstrated a response greater than 6 months.

➢ FDA approved lenvatinib and pembrolizumab in patients with non-MSI high, advanced endometrial cancer who are not candidates for surgery or radiation and have progressed following one prior line of systemic therapy

CARBOPLATIN + PACLITAXEL ± PEMBROLIZUMAB AS FRONTLINE TREATMENT FOR PATIENTS WITH EC (NRG GY018)

Carboplatin + Paclitaxel ± Pembrolizumab as Frontline Treatment for Patients With EC (NRG GY018): Study Design

- Randomized phase III study in patients with endometrial cancer



* Paclitaxel 175 mg/m² IV Q3W + carboplatin AUC 5 IV Q3W.

- Primary endpoints: PFS per RECIST v1.1 by investigator in pMMR and dMMR
- Secondary endpoints: safety, ORR/DoR per RECIST v1.1 by BICR or investigator by treatment arm and MMR IHC status, OS in pMMR and dMMR, PRO/QoL in pMMR, and concordance of institutional vs central MMR IHC testing

NCT03914612. Eskander. SGO 2023. Abstr 338166. Eskander. NEJM. 2023;[Epub].

Slide credit: clinicaloptions.com

NRG GY018: Baseline Characteristics

Characteristic	dMMR Cohort	
	Placebo* (n = 113)	Pembrolizumab* (n = 112)
Median age, yr (range)	66 (37-85)	67 (38-81)
Histology,† n (%)		
▪ Serous	1 (0.9)	4 (3.6)
▪ Clear cell	0	1 (0.9)
Previous chemotherapy, %		
▪ Yes/no	7.1/92.9	4.5/95.5
No prior radiotherapy, n (%)	58 (51.3)	71 (63.4)
Previous surgery, n (%)	105 (92.9)	98 (87.5)
ECOG PS, %		
▪ 0/1	64.6/31.0	64.3/34.8
Race, n (%)		
▪ White	86 (76.1)	92 (82.1)
▪ Black	9 (8.0)	11 (9.8)
▪ Asian	4 (3.5)	3 (2.7)
Hispanic/Latino/a, n (%)	6 (5.3)	5 (4.5)

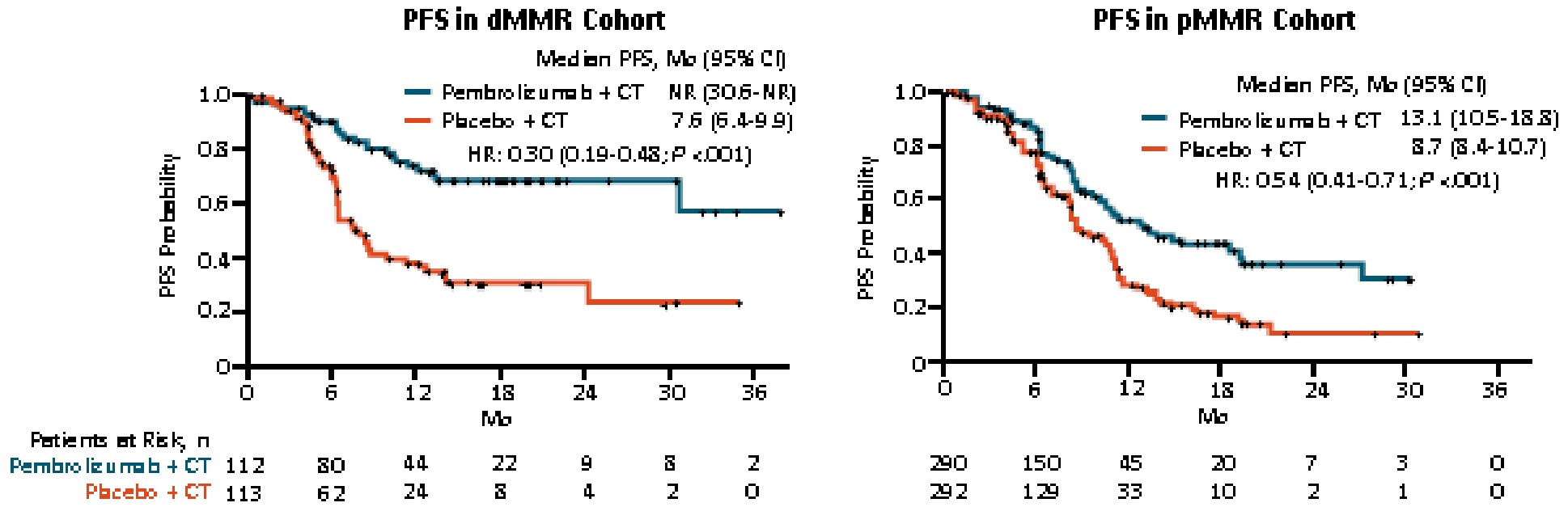
Characteristic	pMMR Cohort	
	Placebo* (n = 295)	Pembrolizumab* (n = 293)
Median age, yr (range)	65 (29-90)	66 (31-93)
Histology,† n (%)		
▪ Serous	72 (24.4)	78 (26.6)
▪ Clear cell	20 (6.8)	17 (5.8)
Previous chemotherapy, %		
▪ Yes/no	26.1/73.9	24.6/75.4
No prior radiotherapy, n (%)	176 (59.7)	179 (61.1)
Previous surgery, n (%)	261 (89.0)	245 (83.0)
ECOG PS, %		
▪ 0/1	67.1/29.8	66.9/30.0
Race, n (%)		
▪ White	212 (71.9)	212 (72.4)
▪ Black	51 (17.3)	45 (15.4)
▪ Asian	14 (4.7)	17 (5.8)
Hispanic/Latino/a, n (%)	16 (5.4)	21 (7.2)

* Plus paclitaxel and carboplatin. Most patients enrolled in the pMMR and dMMR cohorts had endometrioid histology (with 30 to 70% being G1/G2).

Eskander. SGO 2023. Abstr 338166. Eskander. NEJM. 2023;[Epub].

Slide credit: clinicaloptions.com

NRG GY018: PFS (per RECIST v1.1) in dMMR and pMMR Cohorts



- Addition of pembrolizumab to standard-of-care chemotherapy followed by pembrolizumab maintenance resulted in 70% and 46% reduction in risk of disease progression or death in patients with dMMR and pMMR, respectively

Eskander. SGO 2023. Abstr 338166. Eskander. NEJM. 2023;[Epub].

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DOSTARLIMAB + CT IN PRIMARY ADVANCED OR RECURRENT EC

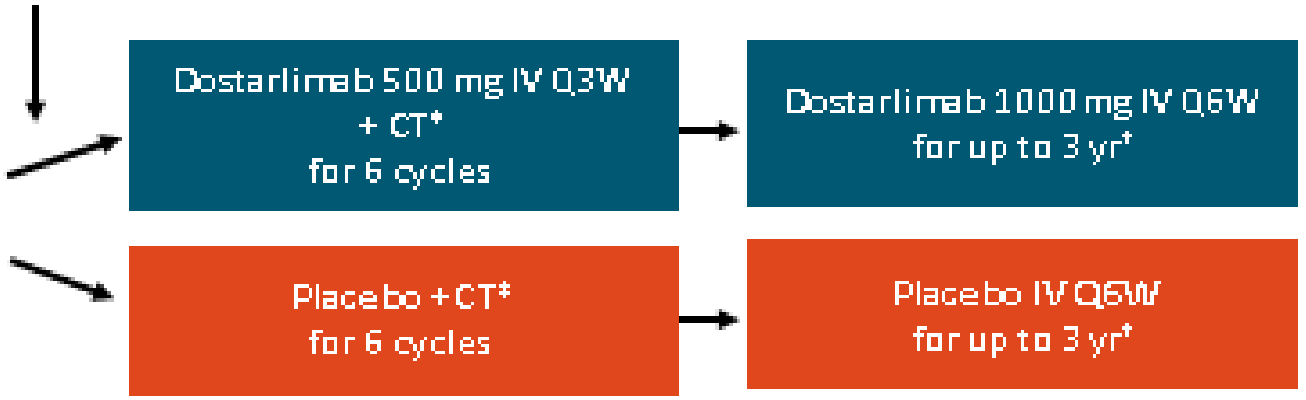
Dostarlimab is an antibody to anti-programmed cell death receptor-1 (PD-1) which is used for the treatment of adults with mismatch repair-deficient (dMMR) advanced solid tumors

Dostarlimab + CT in Primary Advanced or Recurrent EC (ENGOT-EN6/GOG-3031/RUBY): Study Design

- Randomized, placebo-controlled phase III study of chemotherapy + dostarlimab in patients with histologically/cytologically advanced or recurrent endometrial cancer

Stratified by MMR status (deficient vs proficient) and previous external pelvic radiotherapy (yes vs no)

Patients with stage III/IV disease or first recurrence with low potential for cure by radiation, surgery, or both; treatment naive to systemic therapy, with recurrence or progression ≥6 mo after completing treatment; ECOG PS ≤1 (N = 494)



*Paclitaxel 175 mg/m² IV Q3W + carboplatin AUC 5 IV Q3W.
†Treatment may end after 3 yr, disease progression, toxicity, withdrawal of consent, investigator's decision, or death.

- Primary endpoints: PFS by investigator, OS
- Secondary endpoints: PFS by BICR, PFS2, ORR, DoR, DCR, HRQoL/PRO, and safety

Mirza. SGO 2023. Abstr 12. Mirza. NEJM 2023;[Epub].

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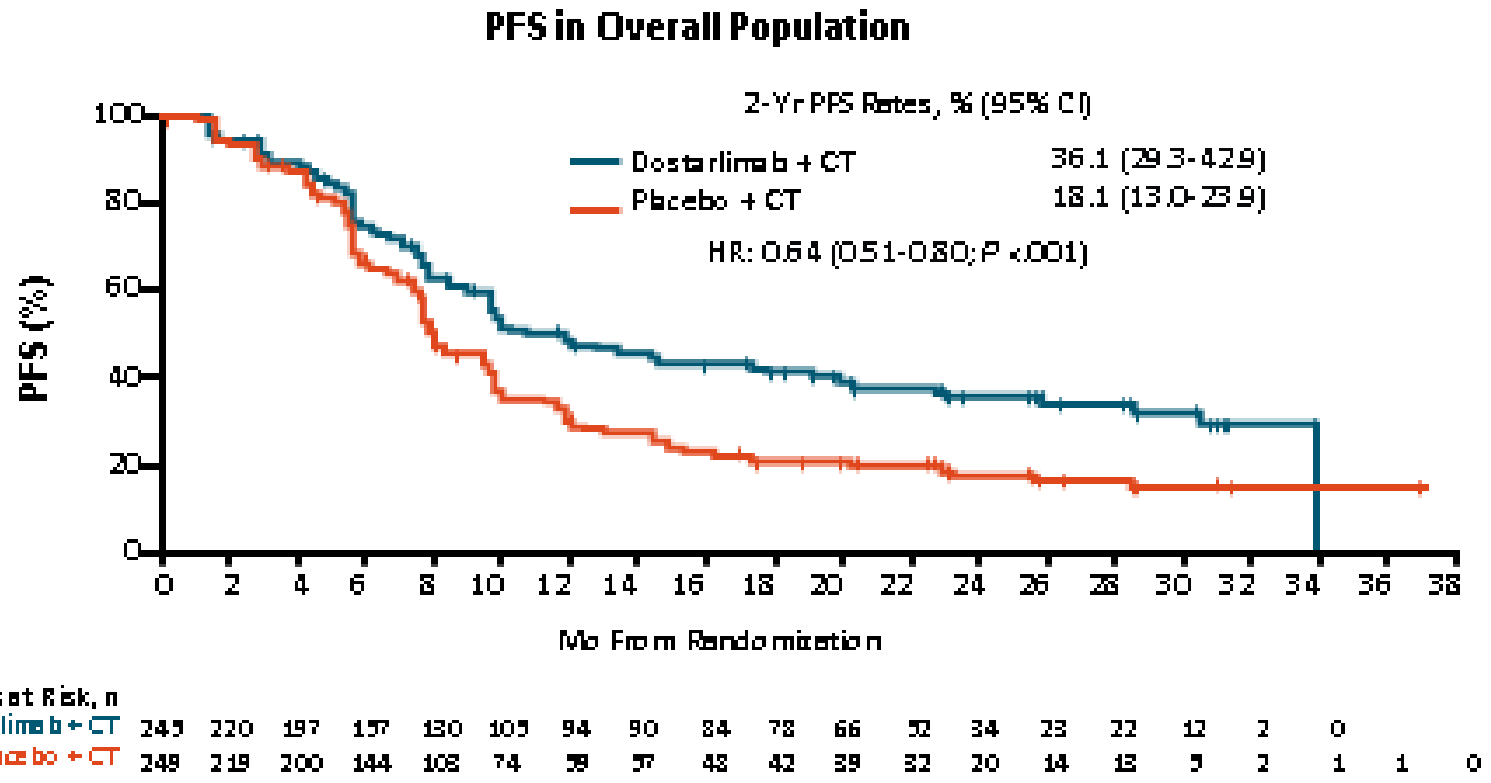
ENGOT-EN6/GOG-3031/RUBY: PFS in Overall Population (Primary Endpoint)



Mirza. SGO 2023. Abstr 12. Mirza. NEJM 2023;[Epub].

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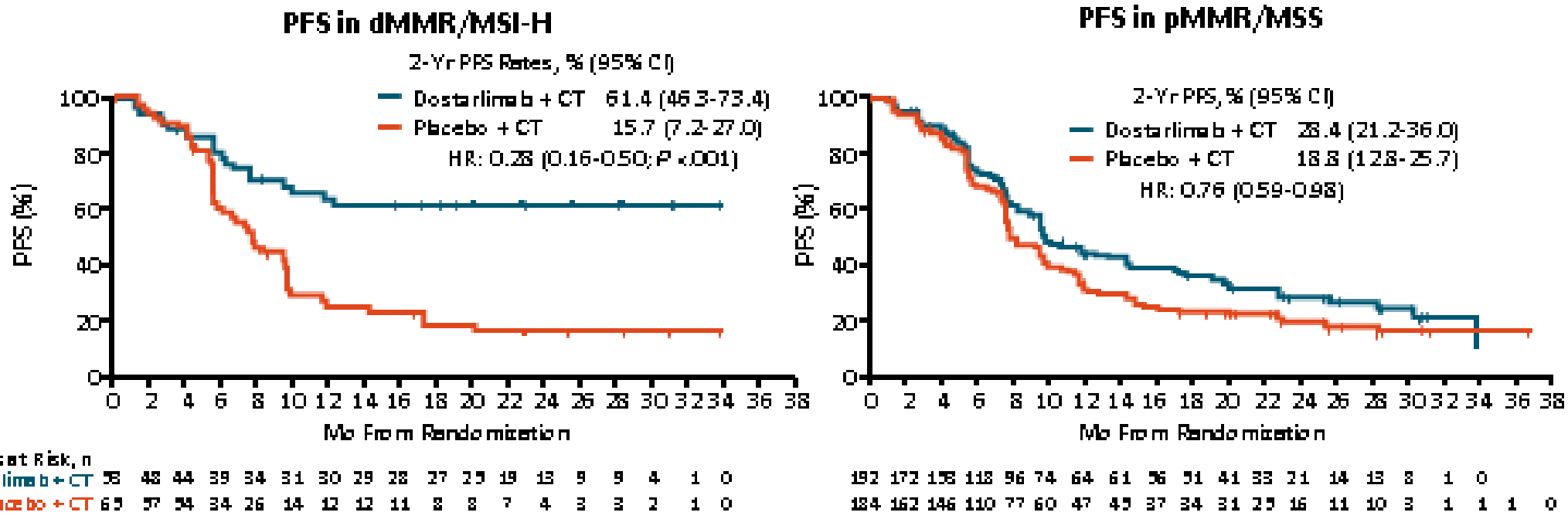
ENGOT-EN6/GOG-3031/RUBY: PFS in dMMR/MSI-H (Primary Endpoint) and pMMR/MSS



- Statistically significant and clinically meaningful PFS seen in patients with dMMR/MSI-H status; benefit also was seen in patients with pMMR/MSS status

Mirza. SGO 2023. Abstr 12. Mirza. NEJM 2023;[Epub].

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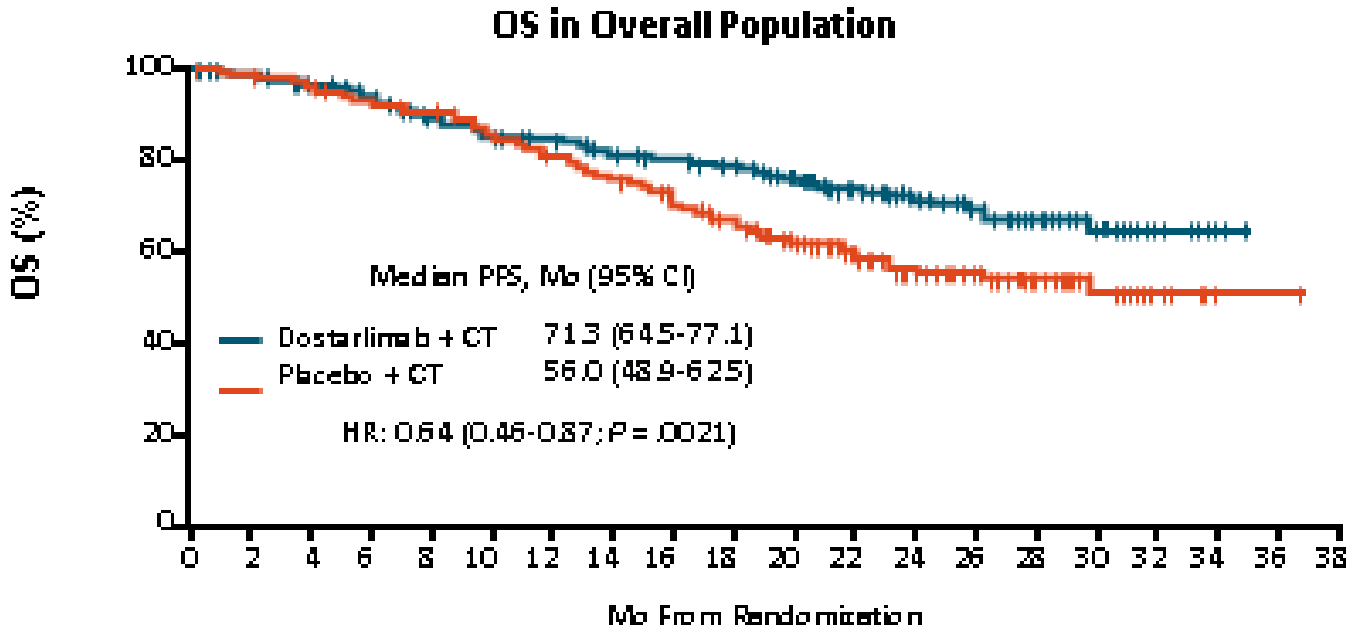
ENGOT-EN6/GOG-3031/RUBY: OS in Overall Population



Patients at Risk, n																			
Dostarlimab + CT	249	235	224	214	198	190	183	174	169	162	14	110	83	64	45	25	7	2	0
Placebo + CT	249	242	237	226	219	208	189	177	162	147	125	88	65	48	33	15	6	1	1	0

Mirza. SGO 2023. Abstr 12. Mirza. NEJM 2023;[Epub].

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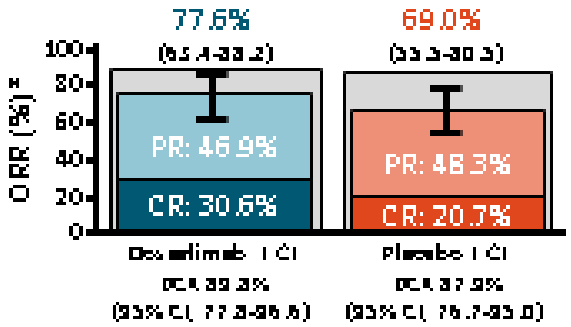
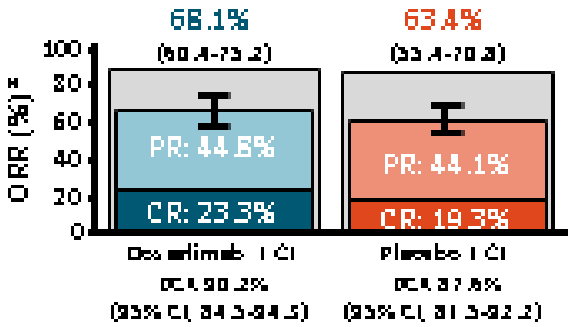
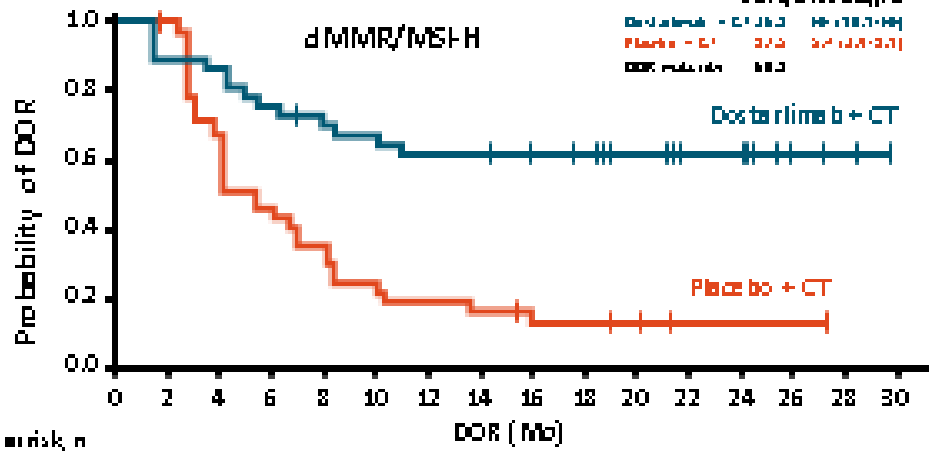
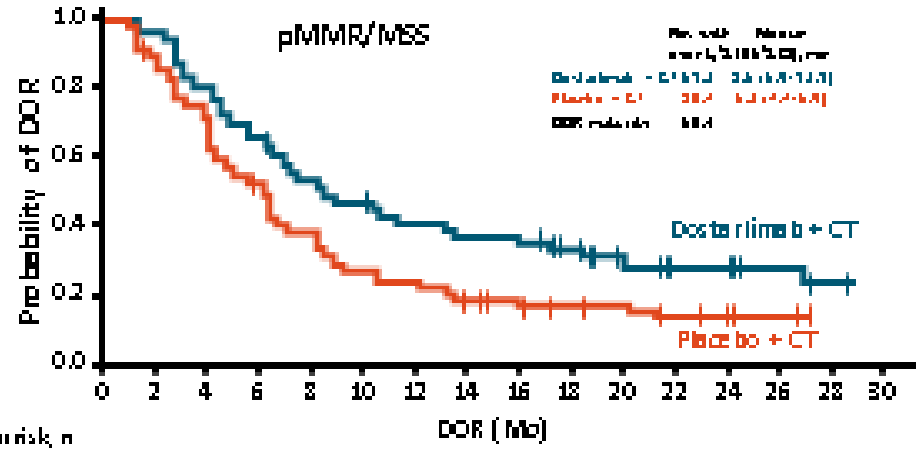
ENGOT-EN6/GOG-3031/RUBY: ORR and DoR





Duration of Response†





*ORR assessed in patients with evaluable disease at baseline in dMMR/MSI-H and pMMR/MSS populations.
†DoR analysis in dMMR/MSI-H population was prespecified and in pMMR/MSS population was post hoc.

Mirza. SGO 2023. Abstr 12. Mirza. NEJM 2023;[Epub].

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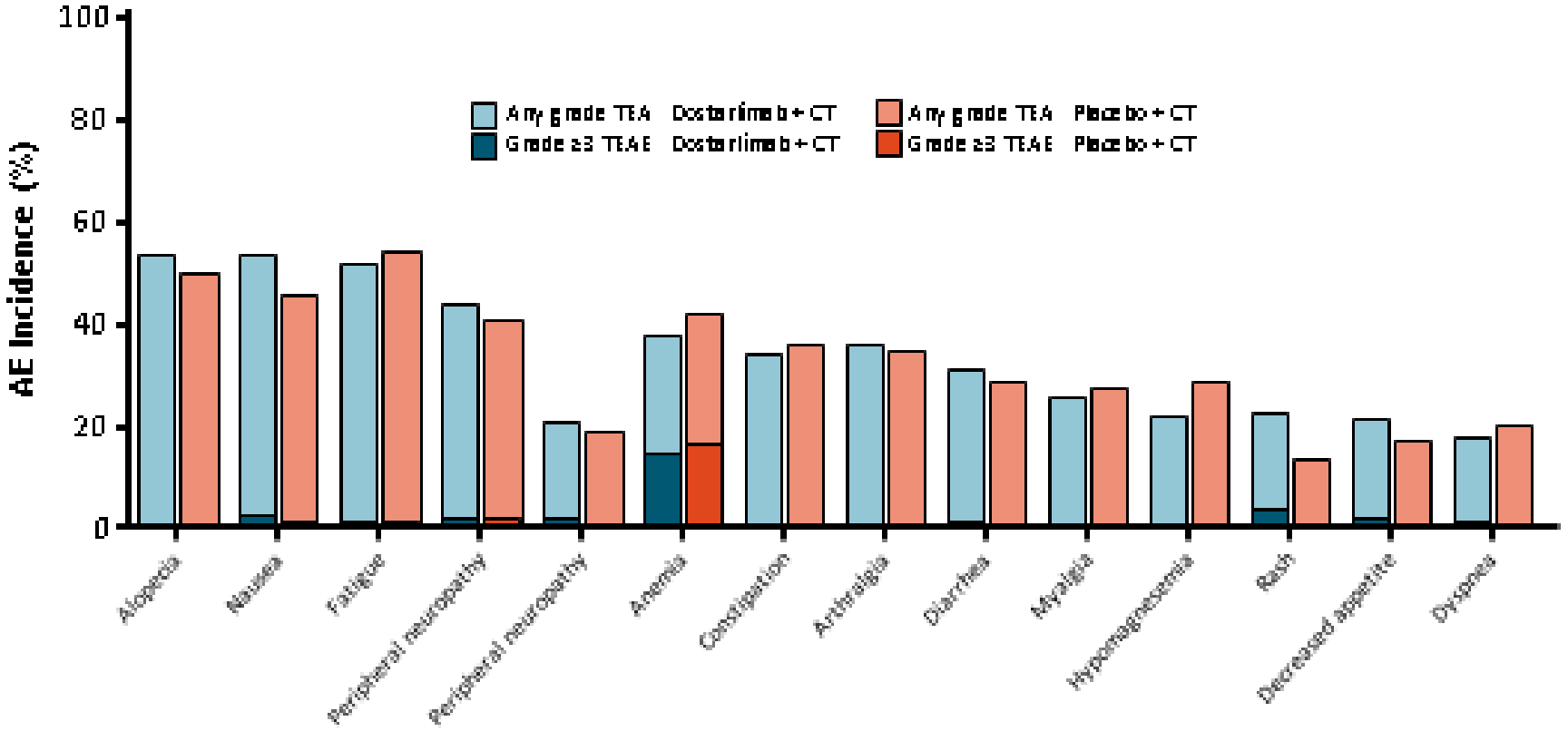
ENGOT-EN6/GOG-3031/RUBY:
TEAEs in ≥20% of Either Arm



Mirza. SGO 2023. Abstr 12.

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Endometrial Cancer Studies: Summary

- **NRG GY018:** Addition of pembrolizumab to SoC chemotherapy followed by pembrolizumab maintenance for 2 years yielded significant reduction in risk of progression or death in dMMR (HR: 0.30)
  and pMMR (HR: 0.54) populations[1]
  - Trend was observed for early benefit during treatment, and separation of Kaplan-Meier curves was seen throughout evaluation period
  - Addition of pembrolizumab to SoC chemotherapy did not increase chemotherapy-related AEs, and incidence of irAEs was not greater than in other studies of pembrolizumab monotherapy in EC[2]
- **ENGOT-EN6/GOG-3031/RUBY:** Addition of dostarlimab to SoC carboplatin and paclitaxel and subsequent maintenance for 3 years yielded statistically significant and clinically meaningful benefit for PFS and trend for OS improvement in overall population[3]
  - Substantial, unprecedented benefit seen in patients with dMMR/MSI-H status, and long-term clinical benefit also seen in patients with pMMR/MSS status
  - Safety profile for dostarlimab + carboplatin and paclitaxel was manageable and consistent with that of individual drugs

1. Eskander. SGO 2023. Abstr 338166. 2. O'Malley. JCO. 2022;40:752. 3. Mirza. SGO 2023. Abstr 12.

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MONOCLONAL ANTIBODY TARGETING PD-1

NIVOLUMAB

- Phase I trial- platinum-resistant ovarian cancer treated with dose escalation cohorts.
- The ORR for these patients was 15% with a median PFS of 3.5 months and overall survival (OS) of 20 months.
- A phase II trial evaluated the combination of nivolumab with bevacizumab in patients with recurrent ovarian cancer.
- Eleven patients (28.9%) demonstrated an objective response.
- Benefit was greatest in patients with platinum-sensitive disease.

CHECKMATE 358

- Phase I/II study evaluating nivolumab in HPV-related cancers including cervical, vulvar, and vaginal cancer.
- ORRs were 26.3% in cervical cancer and 20% in vaginal and vulvar cancer.

- Javelin 100 and 200
- Avelumab is a monoclonal antibody targeting PD-L1.
- Studied in both the upfront and platinum-resistant recurrent setting in ovarian cancer patients.
- Neither trial demonstrated a benefit with avelumab therapy.

STUDIES IN CERVICAL CANCER

Cervical Cancer Studies: Summary

- **Phase I NRG-GY017:** neoadjuvant administration of atezolizumab in LACC leads to early systemic expansion of tumor-associated T-cell receptor clones, suggesting early systemic tumor-specific immune response[1]
  - Chemoradiation results in contraction of tumor-associated T-cell receptor clones, potentially causing deleterious consequences for systemic immune response
  - Investigators concluded that data from NRG-GY17 support additional studies of neoadjuvant sequencing strategies for evaluating PD-1/PD-L1–targeted therapies in LACC
- **Phase II Trial of CRT + Pembrolizumab:** Combination of chemoradiation with pembrolizumab concurrently or sequentially was safe and tolerable in patients with LACC[2]
  - No difference in ratio of CD8+/T_{reg} between sequencing modalities; higher HPV E7 CD8+ T-cells observed with concurrent therapy
  - Trend was observed for IHC increased expression of PD-L1 at 6 wk with sequential therapy
- Other studies[1] have noted differences with immunotherapy priming vs concurrent treatment with chemoradiation
- Ongoing analyses are evaluating blood samples and tissue for immunologic parameters

1. Zamarin. SGO 2023. Abstr 4.2. Duska. SGO 2023. Abstr 29.

Slide credit: clinicaloptions.com

ADCS IN GYNECOLOGIC ONCOLOGY

ADCS- ANTIBODY-DRUG CONJUGATE

- ADCs combine a highly toxic cytotoxic agent (or agents) with a specific immunoglobulin
- spares normal tissues that lack expression of the selected target.
- Current ADCs in development in gynecologic malignancies are leveraging targets, including HER2/neu, tissue factor, folate receptor a, mesothelin, MUC16, and NaPi2B.

- 2 ADCs having received accelerated approval by the FDA in gynecologic oncology:
- Tisotumab Vedotin for adult patients with recurrent or metastatic cervical cancer who have had disease progression on or after chemotherapy
- Mirvetuximab soravtansine for adult patients with FRα-positive, platinum-resistant epithelial ovarian cancer who have received 1–3 prior lines of therapy

TISOTUMAB VEDOTIN

- Tisotumab Vedotin targets TISSUE FACTOR (TF-011) also called thromboplastin, factor III, or CD142 highly prevalent in multiple solid tumors, including cervical cancer.
- Tisotumab vedotin binds to TF on target cells and, upon ligand internalization, releases monomethyl auristatin E (MMAE).
- MMAE, a microtubule-disrupting agent inhibits cell proliferation resulting in apoptotic cell death in tumor cells.

PREVIOUSLY TREATED METASTATIC OR RECURRENT CERVICAL CANCER INNOVATV 204

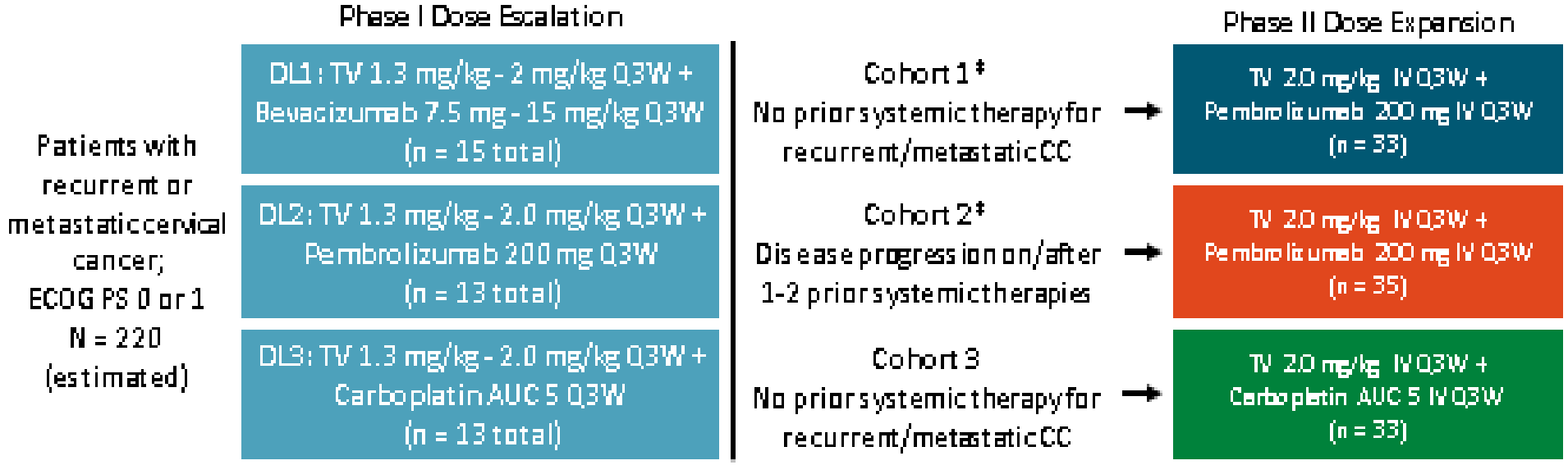
- Achieved mean objective response of around 24% (95% CI 16–33)
- 7 patients (7%) had complete response
- Median duration of response of 8.3 months
- ORR with tisotumab vedotin represented a considerable improvement over chemotherapy agents (15%)
- 53% of patients had treatment-related ocular AEs, predominately conjunctivitis
- FDA fast approval in the second-line setting.

INNOVATV 205 STUDY

- Patients with recurrent or stage IVB cervical cancer
- Tisotumab vedotin combined with pembrolizumab (PEM), bevacizumab (BEVA), or carboplatin (CBP) in first and second-line treatment
- Cohorts 1 and 3 include patients with no prior systemic therapy received
- Cohorts 1 - TV (2.0 mg/kg) +Pembrolizumab (200 mg up to 35 cycles)
- Cohorts 3 - along with Carboplatin (AUC 5 IV)

ENGOT Cx8/GOG 3024/innovaTV 205: Study Design

- Global, open-label phase Ib/II trial



- **Phase I results:** No DLTs, MTD was not reached, acceptable safety profile, evident anti-tumor activity
  - RP2D: TV 2.0 mg/kg + bevacizumab 15 mg/kg Q3W; TV 2.0 mg/kg + pembrolizumab 200 mg Q3W; TV 2.0 mg/kg + carbo AUC 5 Q3W

- **Primary endpoint (phase II):** ORR per RECIST v1.1
- **Secondary endpoints:** AEs and laboratory parameters, DoR, time to response, PFS, OS

‡Pembrolizumab is administered for up to 35 cycles.

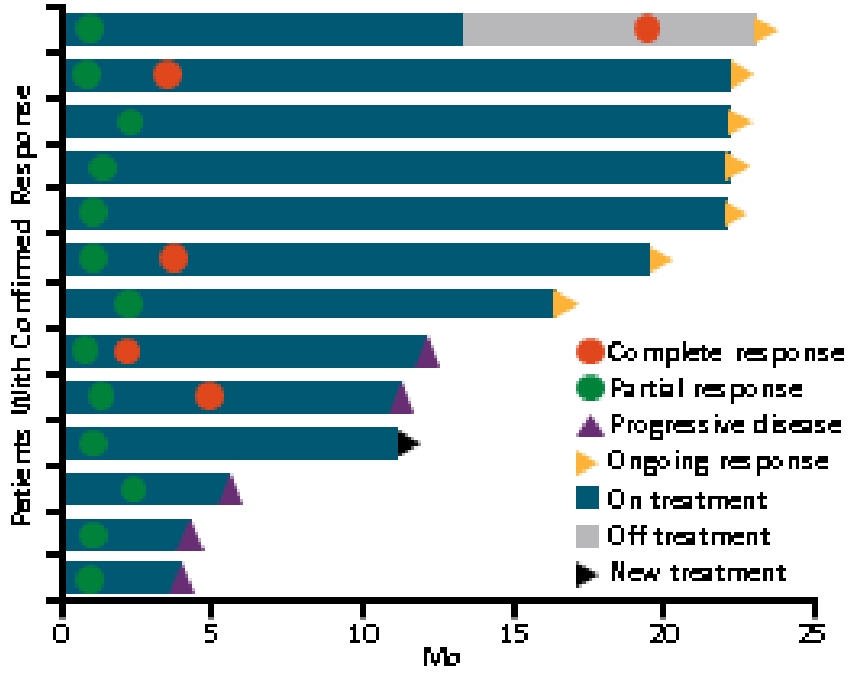
Monk. IGCS 2021. Abstr OO12. NCT03786081. Lorusso. ASCO 2022. Abstr 5507.

Slide credit: clinicaloptions.com

ENGOT Cx8/GOG 3024/innovaTV 205: Response Rates for 1L TV + Pembrolizumab

Parameter	1L TV + Pembro (n = 32)
Confirmed ORR, % (95% CI)	40.6 (23.7-59.4)
▪ CR, n (%)	5 (15.6)
▪ PR, n (%)	8 (25.0)
▪ SD, n (%)	14 (43.8)
▪ PD, n (%)	1 (3.1)
▪ NE, n (%)	4 (12.5)
DCR, % (95% CI)	84.4 (67.2-94.7)
Median DoR,* mo (range)	NR (2.8-21.9+)
Median time to response, mo (range)	1.4 (1.2-2.8)
Median PFS,† mo (95% CI)	5.3 (4.0-12.2)
Median OS,‡ mo (range)	NR (0.5-24.9+)

*8 patients censored. †12 patients censored. ‡19 patients censored.



- At a median follow-up of 18.8 mo, >50% of responders in 1L TV + pembrolizumab cohort have an ongoing response

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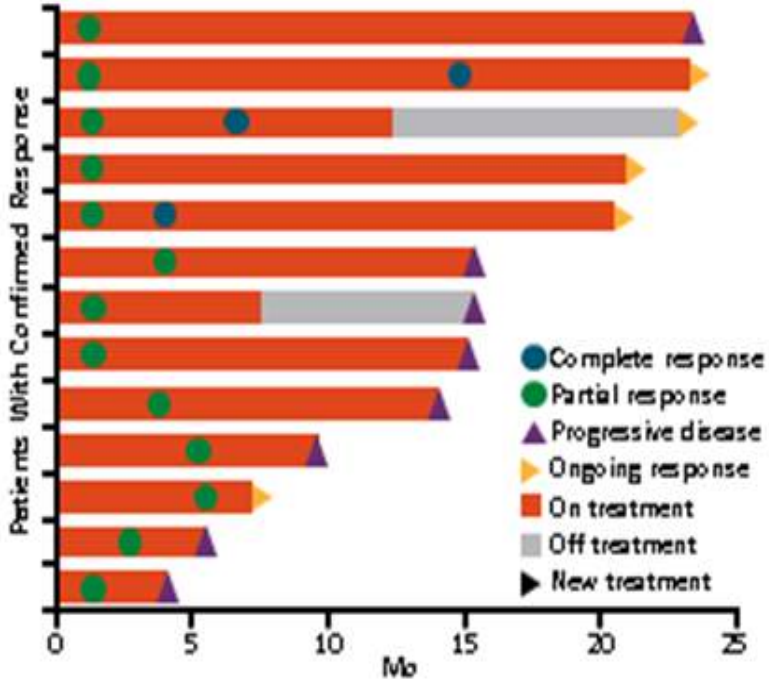
1st line OR of 40.6% (95% CI 23.7–59.4)

ENGOT Cx8/GOG 3024/innovaTV 205: Response Rates for 2L/3L TV + Pembrolizumab

Parameter	2L/3L TV + Pembro (n = 34)
Confirmed ORR, % (95% CI)	38.2 (22.2-56.4)
▪ CR, n (%)	3 (8.8)
▪ PR, n (%)	10 (29.4)
▪ SD, n (%)	12 (35.3)
▪ PD, n (%)	7 (20.6)
▪ NE, n (%)	2 (5.9)
DCR, % (95% CI)	73.5 (55.6-87.1)
Median DoR,* mo (95% CI)	14.0 (2.8-NR)
Median time to response, mo (range)	1.4 (1.3-5.8)
Median PFS,† mo (95% CI)	5.6 (2.7-14.2)
Median OS,‡ mo (95% CI)	15.3 (9.9-NR)

*5 patients censored. †10 patients censored. ‡14 patients censored.



- At a median follow-up of 15.0 mo, 40% of responders in 2L/3L TV + pembrolizumab cohort have an ongoing response

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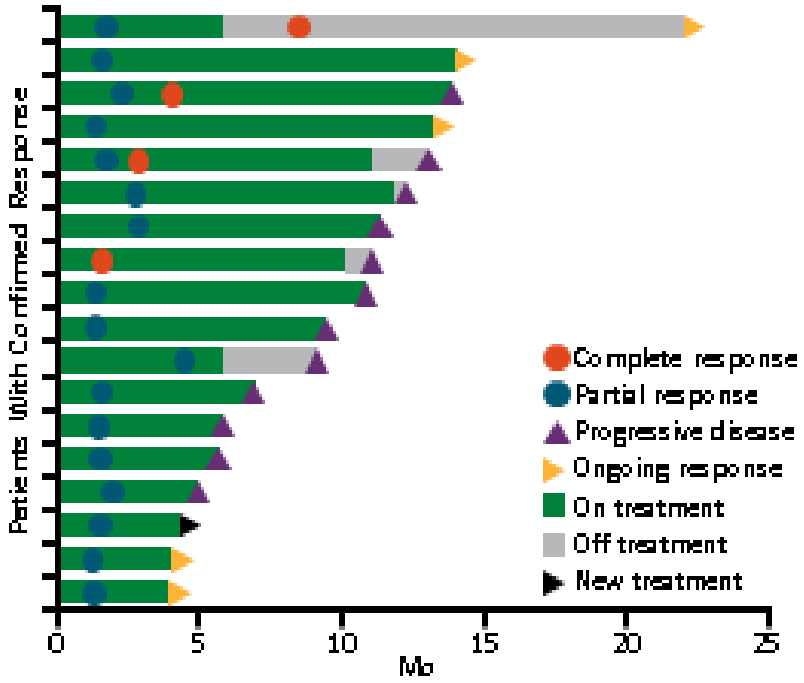
OR of 38.2 (95% CI 22.2–56.4) in 2nd and 3rd line

ENGOT Cx8/GOG 3024/innovaTV 205: Response Rates for 1L TV + Carboplatin

Parameter	1L TV + Carbo (n = 33)
Confirmed ORR, % (95% CI)	54.5 (36.4-71.9)
▪ CR, n (%)	4 (12.1)
▪ PR, n (%)	14 (42.4)
▪ SD, n (%)	12 (36.4)
▪ PD, n (%)	2 (6.1)
▪ NE, n (%)	1 (3.0)
DCR, % (95% CI)	90.9 (75.7-98.1)
Median DoR,* mo (95% CI)	8.6 (4.2-11.5)
Median time to response, mo (range)	1.4 (1.1-4.4)
Median PFS,† mo (95% CI)	6.9 (4.0-11.1)
Median OS,‡ mo (range)	NR (0.8+ to 22.1+)

*4 patients censored. †9 patients censored. ‡22 patients censored.



- At a median follow-up of 14.6 mo, >50% of responders in 1L had a response with a >90% DCR

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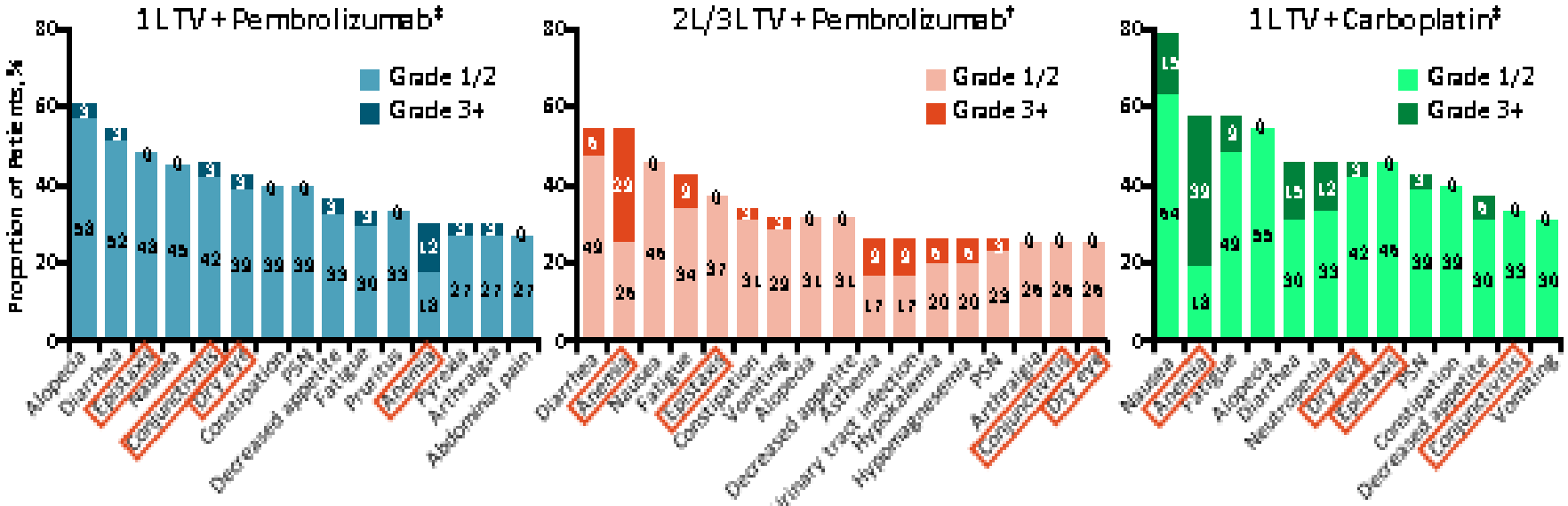
OR of 54.5% (95% CI 36.4–71.9) with CBP 1st line

ENGOT Cx8/GOG 3024/innovaTV 205: Adverse Events in >25% of Patients

- Most TEAEs were grade 1/2; AEs consistent with those of each agent
- 1 grade 5 AE with 1L TV + pembro considered related to treatment by investigator due to disseminated intravascular coagulation



‡24.2% of patients (n = 8) discontinued TV due to AEs. †34.3% of patients (n = 12) discontinued TV due to AEs. ‡21.2% of patients (n = 7) discontinued TV due to AEs; ocular AEs and peripheral neuropathy were associated with treatment discontinuation.

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ENGOT CX8/GOG 3024/INNOVATV 205: CONCLUSIONS

- TV + pembrolizumab demonstrated promising, durable antitumor activity with a tolerable safety profile in recurrent or metastatic CC
  - 41% confirmed ORR and median DoR not reached for 1L TV + pembrolizumab
  - 38% confirmed ORR for 2L/3L TV + pembrolizumab
  - 55% confirmed ORR for 1L TV + carboplatin
- Investigators concluded that these data suggest potential for TV to be included in a combination regimen to improve clinical outcomes in 1L recurrent or metastatic CC
- This trial is ongoing (NCT03786081), and a new cohort will be added to investigate the combination of TV + carboplatin and pembrolizumab ± bevacizumab as 1L treatment for recurrent or metastatic CC

Lorusso. ASCO 2022. Abstr 5507.

MIRVETUXIMAB SORAVTANSINE

- comprises an antibody against FRα
- Phase III single arm SORAYA study, established clinical activity in 106 patients with FRα-positive, platinum-resistant high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancers.
- Overall,32% of patients achieved objective responses, with 5 (5%) complete responses and 29 (28%) partial responses.
- Based on results from SORAYA, in 2022, mirvetuximab soravtansine was granted accelerated approval by the United States FDA for patients with FRα-positive platinum-resistant ovarian cancer who have received 1–3 prior therapies

RAS/RAF/MITOGEN-ACTIVATED PROTEIN KINASE PATHWAY

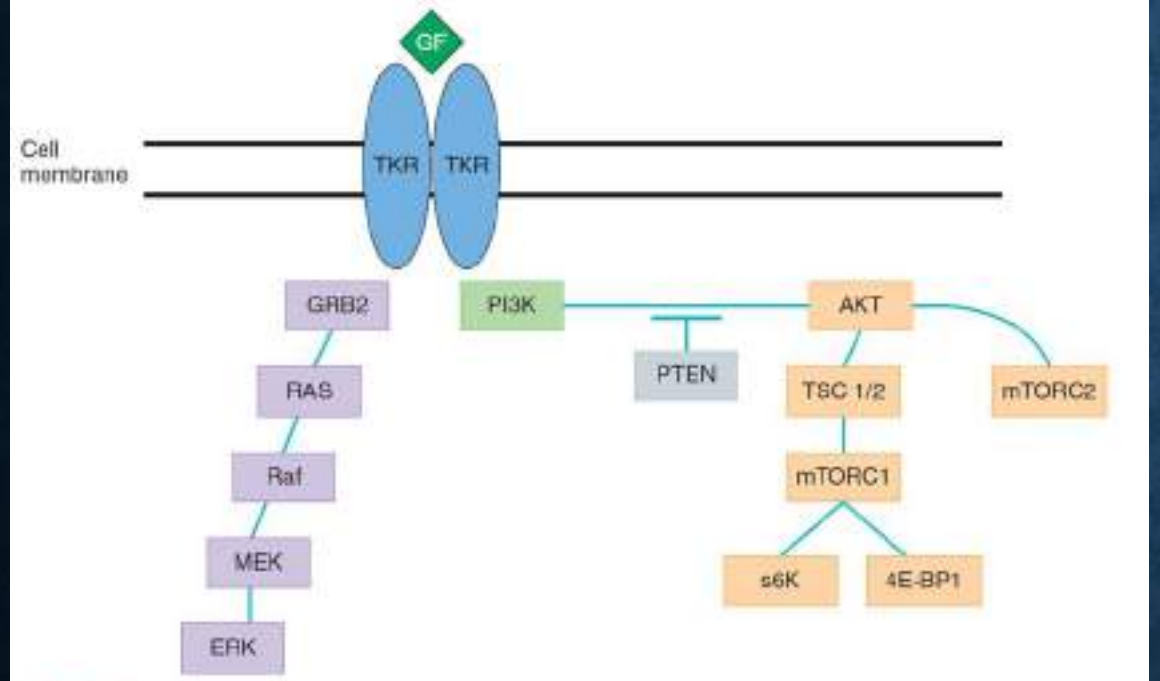


Figure 16.5 PI3K/AKT pathway. *GF*, Growth factor; *GRB2*, growth factor receptor-bound protein 2; *PTEN*, phosphatase and tensin homolog; *TKR*, tyrosine kinase receptor.

TABLE 16.4 Incidence of Genetic Mutations Within the PI3K/AKT/mTOR Pathway in Ovarian and Endometrial Cancer

	Ovarian Cancer	Endometrial Cancer	Reference
PTEN	5.5%	45%	84
PIK3CA	6%	39%	85
AKT1	2%	4%	86
AKT2	13.3%	3.1%	87

PI3K, Phosphoinositide-3-kinase; *PTEN*, phosphatase tensin homolog on chromosome 10.

MEK INHIBITORS

- The highest rates of Ras/Raf pathway aberrations are found in low-grade serous and mucinous ovarian cancer and in endometrial cancer.
- MEK inhibitors have been quite successful for the treatment of low-grade ovarian cancer.
- Selumetinib was explored in a phase II trial by the GOG, yielding a 15% objective response rate and a 65% SD rate in this notoriously chemoinsensitive disease.

STUDIES

- GOG-0281, single-agent trametinib yielded improved PFS and response as compared with physician-choice treatment, including hormonal agents.
- MILO study explored binimetinib in a similar patient population but did not find an improved PFS in the broader population.
- However, there was an improvement in PFS among women with a KRAS mutation
- In recurrent endometrial cancer, single-agent results for MEK inhibition have been limited

CYCLIN KINASE INHIBITORS

Ribociclib is a selective cyclin-dependent kinase inhibitor,

inhibits cyclin-dependent kinase 4 and 6 (CDK4/6).

Phase II Trial of Letrozole + Ribociclib in Women With Recurrent LGSOC (GOG 3026): Study Design

Patient ≥18 yr of age with central pathology histologic confirmation of recurrent LGSC of ovary, fallopian tube, or peritoneum; any number of previous therapies; measurable disease per RECIST v1.1

(N = 51)

→ **Ribociclib*** 600 mg PO QD + **Letrozole** 2.5 mg oral QD
28-day cycle

*3 wk on, 1 wk off.

- Laboratory every cycle
- Radiographic assessment every 3 cycles

→ Treatment until PD; EoT follow-up every 3 cycles (± 7 days)

- **Primary endpoint:** ORR

- **Primary endpoint:** CBR, PFS, OS, DoR, AEs
- **Statistical consideration:** 44-51 patients required to exclude ≤10% ORR (futility)

NCT03673124. Slomovitz. SGO 2023. Abstr 14.

Phase II Trial of Letrozole + Ribociclib in Recurrent LGSOC: Response

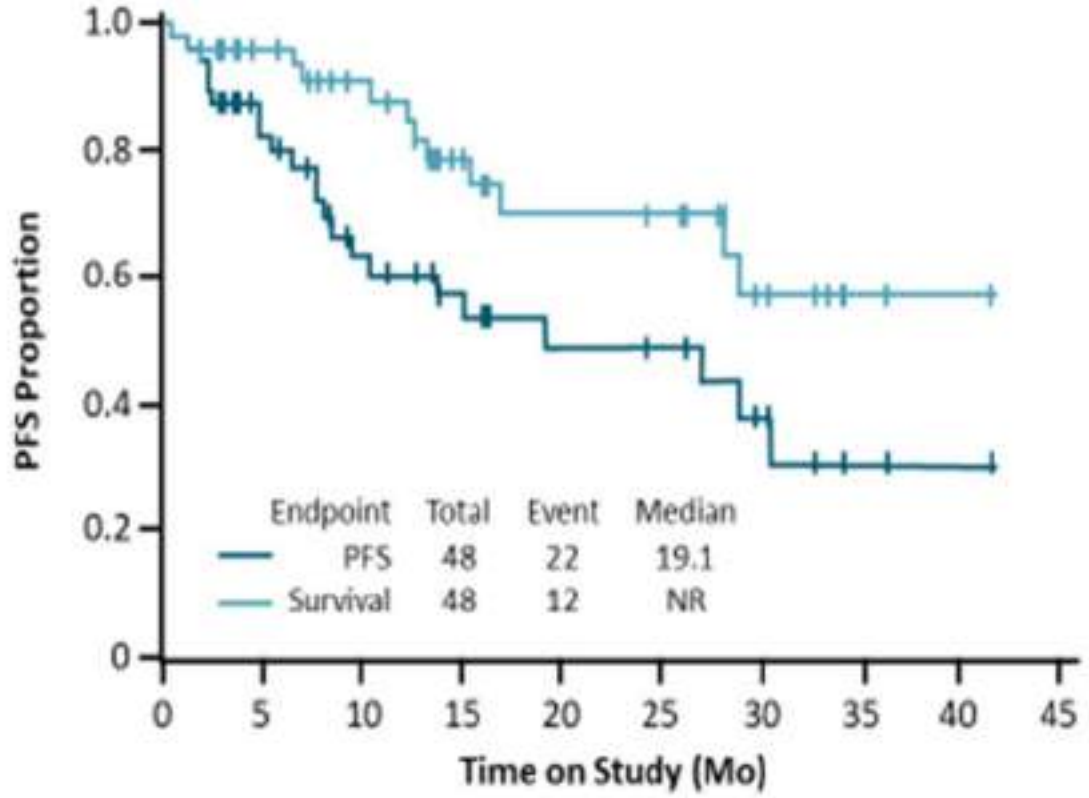
Response	Ribociclib + Letrozole (N = 48)
ORR, n (%) (90% CI) ▪ PR, n (%)	11 (23) (13.4-35.1) 11 (23)
ORR in patients with 2 previous chemotherapy regimens, %	26
Responders ▪ No. of cycles (range)	32 (11-45)
Median DoR, mo (range)	19.1 (4.8-35.8)
CBR, n (%) (90% CI)	38 (79) (67.2-88.2)
CBR in patients with 2 previous chemotherapy regimens, %	90
No. of cycles, CBR (range)	10.5 (3-45)

Of 48 patients treated:

- 18 (38%) remain on study
- Reason for coming off study
  - PD: 17
  - Patient withdrawal: 5
  - Death: 3
  - Other 3
  - Toxicity: 2
- Median cycle to coming off study was 8 (range: 1-45)

Slomovitz. SGO 2023. Abstr 14

Phase II Trial of Letrozole + Ribociclib in Recurrent LGSOC: Time to Event Endpoints



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Phase II Trial of Letrozole + Ribociclib in Recurrent LGSOC: Comparative Efficacy With Alternative Therapies

Agent	PFS, Mo	Response Rate, %	SD Rate, S	CBR, %	DOR, Mo
281 Control Arm	7.2	6	71	77	5.9
281 Letrozole	10.6	14	70	84	--
281 Trametinib	13.0	26	59	85	13.6
MILO Control (CT)	10.6	13	60	73	6.7
MILO Binimetinib	9.1	16	60	76	8.0
Anastrozole PARAGON	11.1	14	50	64	--
GOG 3026	**19.1**	**23**	**56**	**79**	**19.1**

Slomovitz. SGO 2023. Abstr 14.

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Ovarian Cancer Studies: Summary

- **Phase II Trial of Letrozole + Ribociclib in Recurrent LGSOC:** Ribociclib + letrozole is active combination in LGSOC
  - ORR, PFS, and DoR compare favorably with most active agents previously investigated in this setting
  - No new safety signals were observed

Slomovitz. SGO 2023. Abstr 14.

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EPIDERMAL GROWTH FACTOR RECEPTOR PATHWAY

The rate of EGFR mutations in gynecologic malignancies is quite low. The potential for success of these compounds as a single agent is unclear

RANDOMIZED PHASE II TRIAL OF CARBOPLATIN-PACLITAXEL COMPARED TO CARBOPLATIN-PACLITAXEL-TRASTUZUMAB IN ADVANCED (STAGE III-IV) OR RECURRENT UTERINE SEROUS CARCINOMAS THAT OVEREXPRESS HER2/NEU (NCT01367002): UPDATED OVERALL SURVIVAL ANALYSIS

- 61 patients , median-follow-up of 25.9-months
- PFS favor the T-arm, medians of 8.0 in the control versus 12.9-months in T-arms, (HR 0.46, 90%CI 0.28–0.76; P=0.005
- 41 patients with stage III-IV disease primary treatment Median-PFS was 9.3 versus 17.7months (HR 0.44, 90%CI 0.23–0.83; P=0.015)
- 7.0 versus 9.2-months among 17 patients with recurrent disease (HR 0.12, 90%CI 0.03–0.48; P=0.004).
- The benefit was most notable in stage III-IV disease, survival median not reached in the T-arm versus 24.4-months in the control arm (HR 0.49, 90%CI 0.25–0.97; P=0.041).
- Toxicity was not different between arms.