Algorithmen beim fortgeschrittenen Ovarial-, Zervix und Endometriumkarzinom

Kathrin Strasser-Weippl

1. Medizinische Abteilung
Zentrum für Onkologie und Hämatologie
mit Ambulanz und Palliativstation

1. MEDIZINISCHE ABTEILUNG
Zentrum für Onkologie und Hämatologie
mit Ambulanz und Palliativstation

WCRI Wilhelminen Cancer Research Institute

VCC Vienna Cancer Center

Wiener Gesundheitsverbund
Klinik Ottakring

Für die Stadt Wien

Disclosures

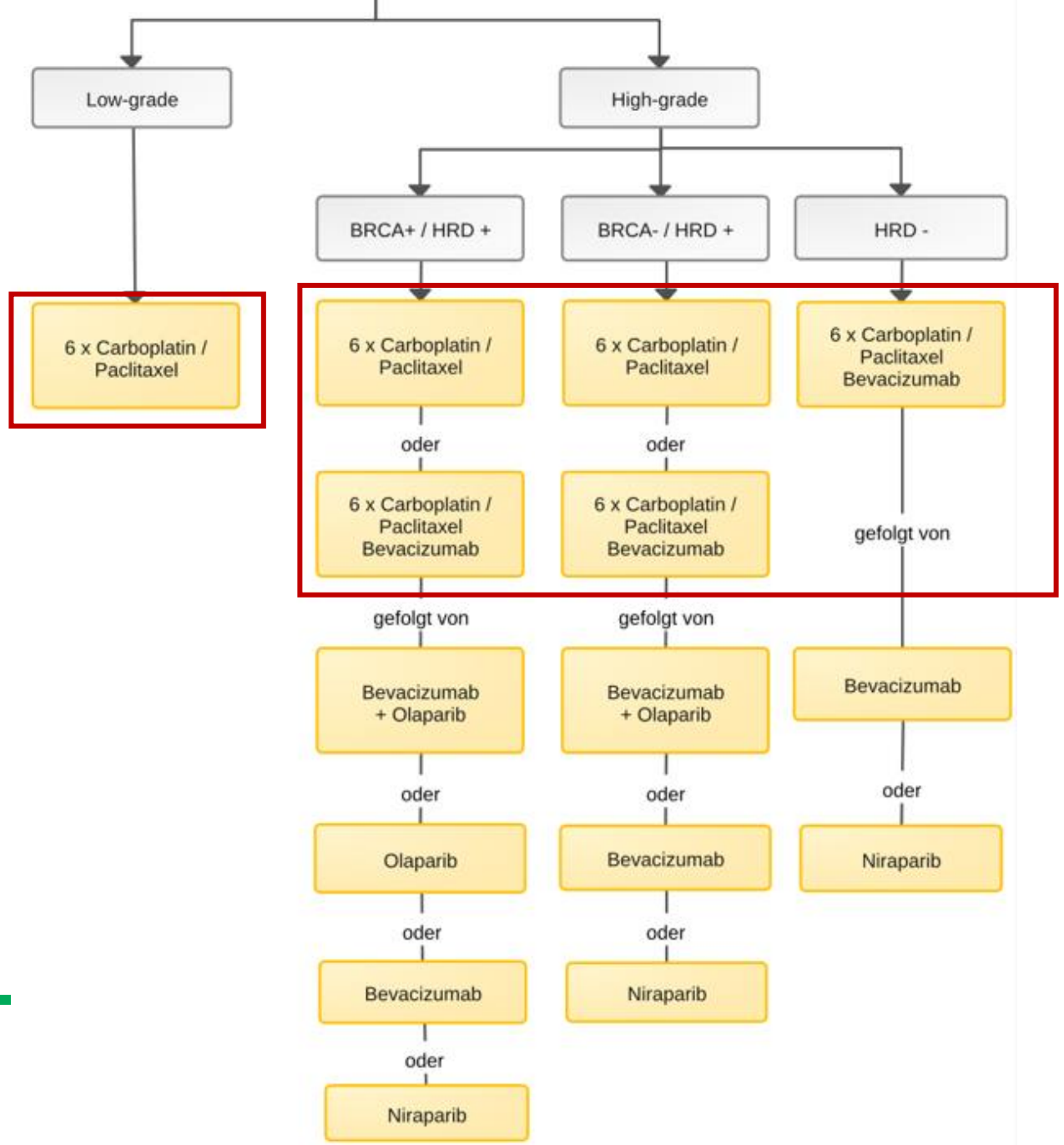
- Kongressunterstützung: Roche, Pfizer, MSD
- Sprecherhonorare/Advisory Boards: Roche, Pfizer, Novartis, Lilly, Daiichi, Myriad, Seagen, MSD, Astra Zeneca

Fortgeschrittenes Ovarialkarzinom

Ovarial-Karzinom

- **Primär fortgeschrittenes Ovarialkarzinom**
  - **Primärtherapie**
  - Erhaltungstherapie
- Rezidiviertes Ovarialkarzinom
  - Erstlinientherapie
  - Erhaltungstherapie
- Platinresistente Erkrankung – zukünftige Optionen

Onkopedia: Primär fortgeschrittenes Ovarialkarzinom



Ovarial-Karzinom

- **Primär fortgeschrittenes Ovarialkarzinom**
  - Primärtherapie
  - **Erhaltungstherapie**
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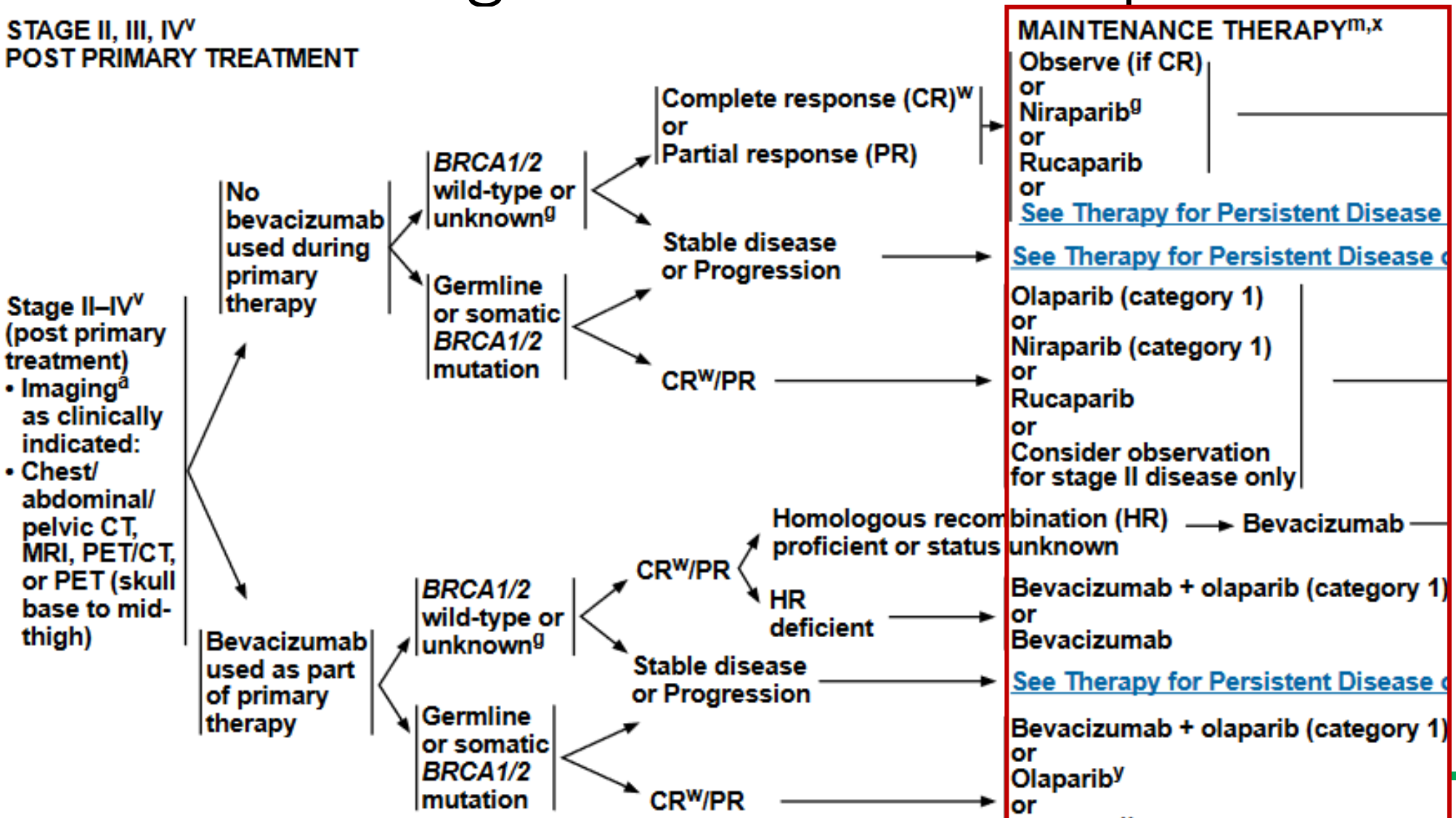
NCCN: Erhaltung nach Primärtherapie



Imaging performed with oral and IV contrast (unless contraindicated) and rectal contrast as needed.
In the absence of a *BRCA1/2* mutation, HRD status may provide information

Key Points

- All women with newly diagnosed ovarian cancer should undergo genetic and tumor testing.
- Focus on PARP inhibitors in first line treatment (curative intent).
- Only treat in the maintenance settings (post platinum-therapy).

2022 Update: 1st Line Maintenance

Updated Recommendation 2.1. Patients with newly diagnosed stage III-IV EOC who are in complete or partial response to first-line platinum-based chemotherapy should be offered PARPi maintenance therapy in high-grade serous or endometrioid ovarian cancer.

For those with germline or somatic pathogenic or likely pathogenic variants in *BRCA*1 or *BRCA*2 genes, options should include **olaparib** (300 mg orally every 12 hours for 2 years), **niraparib** (200-300 mg orally daily for 3 years) or **rucaparib** (600 mg twice a day for 2 years). Longer duration could be considered in selected individuals after discussion of risks.

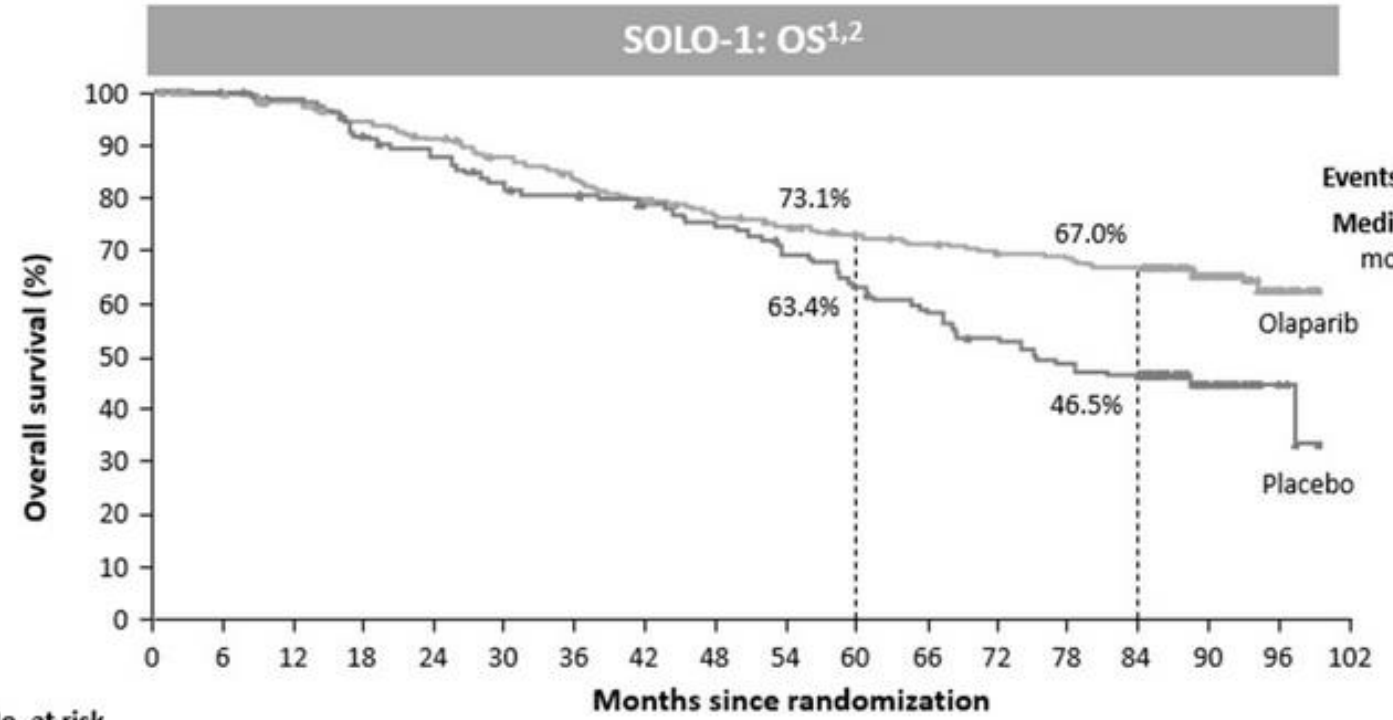
For those who are HRD positive, determined using FDA-approved companion diagnostic tests, rucaparib and niraparib are options. Niraparib or rucaparib may be offered for non-*BRCA*mut/HRDneg patients.

(Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.)

- PFS in Athena Mono (Rucaparib) Monk BJ, et al: Presented at: ASCO Annual Meeting 2022.
- Update OS in SOLO1 (Olaparib) DiSilvestro P et al. Presented at: ESMO Annual Meeting 2022.
- Update OS in PAOLO1 (Olaparib) Ray-Coquard I et al. Presented at: ESMO Annual Meeting 2022

Tew WP, Kohn E, et al: PARP inhibitors in the management of ovarian cancer: ASCO guideline rapid recommendation update. J Clin Oncol 2022

SOLO-1 – BRCA mutation - 1st Line Maintenance olaparib provided a marked survival benefit



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	NR	75.2

HR 0.55 (95% CI 0.40–0.76); *P*=0.0004*

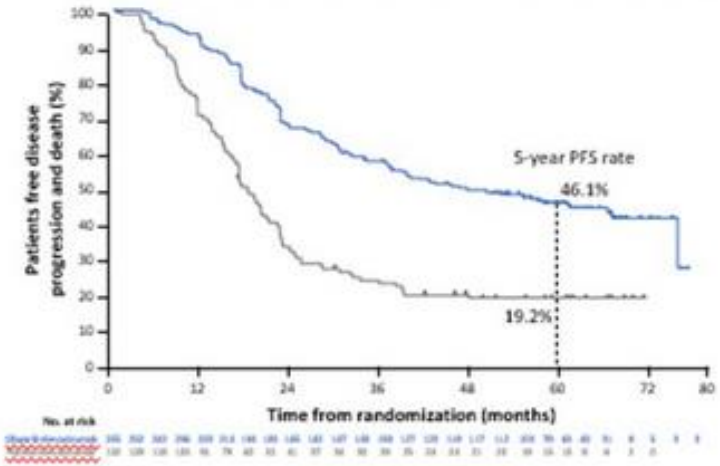
44.3% of patients in the placebo group **received subsequent PARPi therapy**, compared with **14.6%** of patients in the olaparib group

*HR for median OS was not statistically significant due to the alpha assignment of 0.0001 (P<0.0001 required to declare statistical significance)

Di Silvestro.P, et al. 2022 J Clin Oncol.

HRD-score Positive - PFS Benefit (1st Line Maintenance Trials)

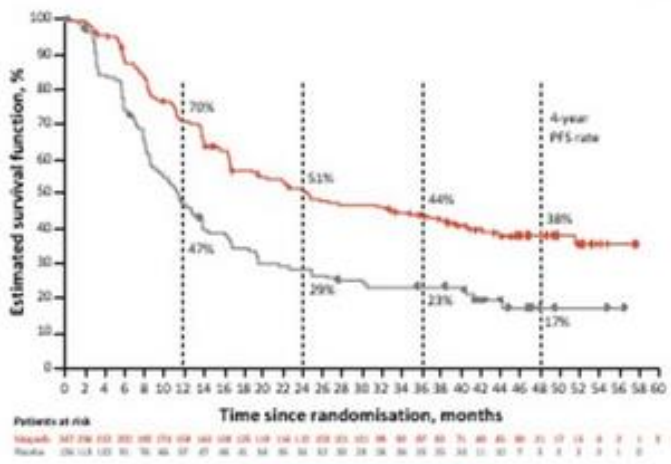
PAOLA-1 (PFS, HRD-positive)[1]



	Olaparib + bevacizumab	Placebo + bevacizumab
mPFS, months	46.8	17.6

HR 0.41 (95% CI 0.32–0.54)

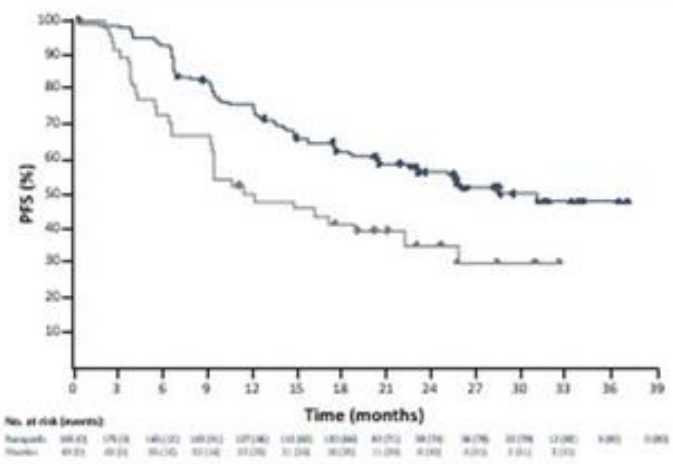
PRIMA (PFS, HRD population)[2]



	Niraparib	Placebo
mPFS, months	24.5	11.2

HR 0.52 (95% CI 0.40–0.68)

ATHENA (PFS, HRD population)[3]



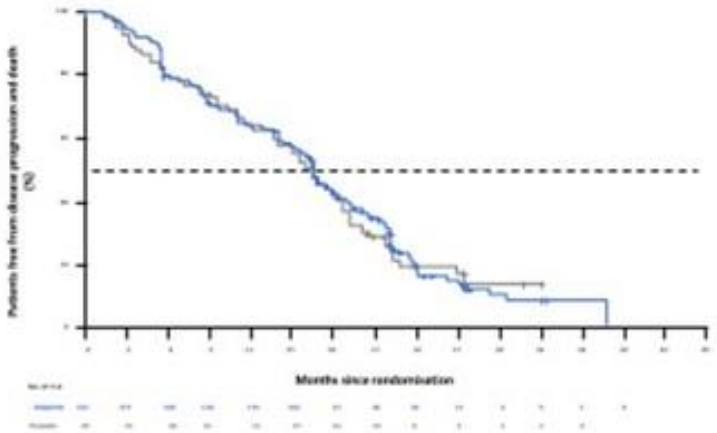
	Rucaparib	Placebo
mPFS, months	28.7	11.3

HR 0.47 (95% CI 0.31–0.72)

1. Ray-Coquard I, et al. Presented at: ESMO Congress 2022; September 2022; Paris, France.2. Gonzalez-Martin A, et al. Presented at: ESMO Congress 2022; September 2022; Paris, France.3. Monk, BJ, et al.. J Clin Oncol. Published online June 6, 2022:JCO2201003.

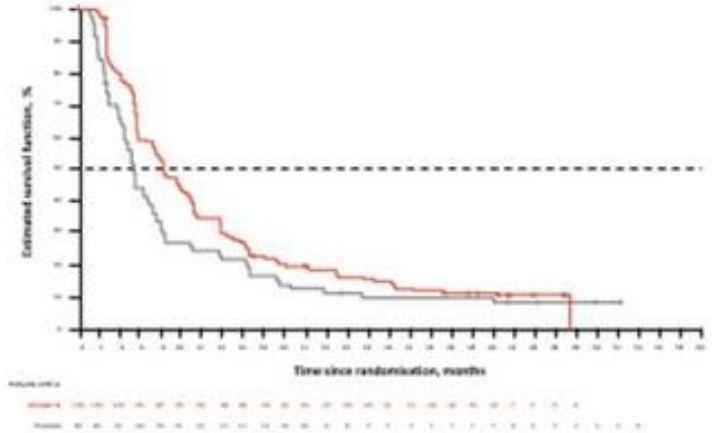
HRD-score negative - Low PFS Benefit (1st Line Maintenance Trials)

PAOLA-1 (PFS, HRD-negative)[1]



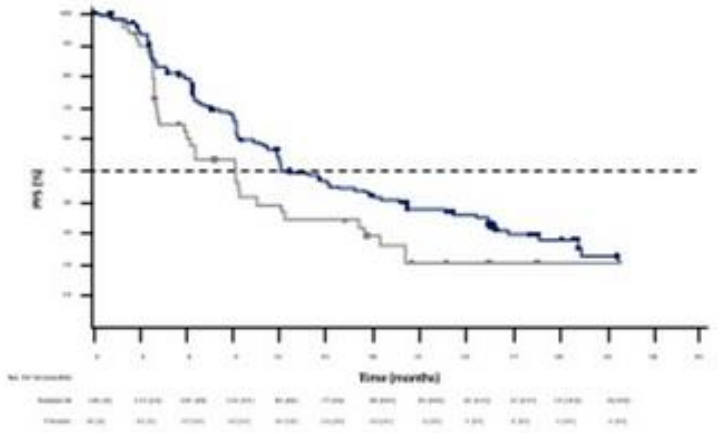
PAOLA-1[1]		
Median PFS, months	Olaparib + bev 16.6	Placebo + bev 16.2
HR 1.00 (95% CI 0.75–1.35)		

PRIMA (PFS, HRD-negative)[2]



PRIMA[2]		
Median PFS, months	Niraparib 8.4	Placebo 5.4
HR 0.65 (95% CI 0.49–0.87)		

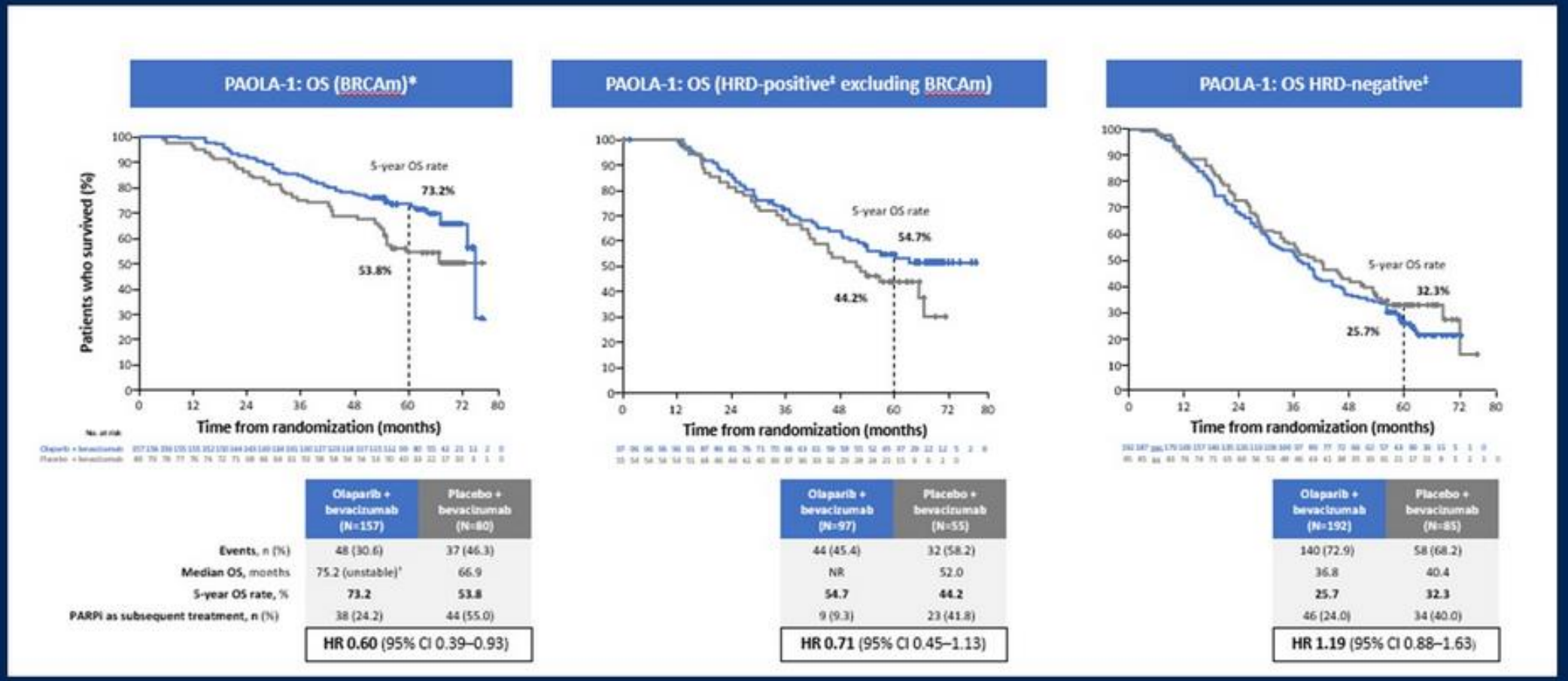
ATHENA (PFS, HRD-negative)[3]



ATHENA[3]		
Median PFS, months	Rucaparib 12.1	Placebo 9.1
HR 0.65 (95% CI 0.45–0.95)		

1. Ray-Coquard I, et al. N Engl J Med 2019;381:2416–2428,.2. Gonzalez-Martin A, et al. Presented at: ESMO Congress 2022; September 2022; Paris, France.3. Monk, BJ, et al.. J Clin Oncol. Published online June 6, 2022:JCO2201003.

Recommendation 2.2: The addition of **olaparib to bevacizumab maintenance** may be offered to patients who have stage III-IV HGS or endometrioid ovarian cancer and germline or somatic pathogenic or likely pathogenic variants in ***BRCA*1 or *BRCA*2 genes and/or genomic instability**, as determined by Myriad myChoice CDx, and who have had a partial/complete response to chemotherapy plus bevacizumab.
(Type: evidence based, benefits outweigh harms; Evidence quality: strong; Strength of recommendation: strong).



	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)†	66.9
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)

HR 0.60 (95% CI 0.39–0.93)

	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
	44 (45.4)	32 (58.2)
	NR	52.0
	54.7	**44.2**
	9 (9.3)	23 (41.8)

HR 0.71 (95% CI 0.45–1.13)

	Olaparib + bevacizumab (N=192)	Placebo + bevacizumab (N=85)
	140 (72.9)	58 (68.2)
	36.8	40.4
	25.7	**32.3**
	46 (24.0)	34 (40.0)

HR 1.19 (95% CI 0.88–1.63)

Ray-Coquard I et al. Presented at: ESMO Annual Meeting 2022

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  - Erhaltungstherapie

DUO-O Studie

- Rezidiviertes Ovarialkarzinom
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- Platinresistente Erkrankung – zukünftige Optionen

2023 ASCO ANNUAL MEETING

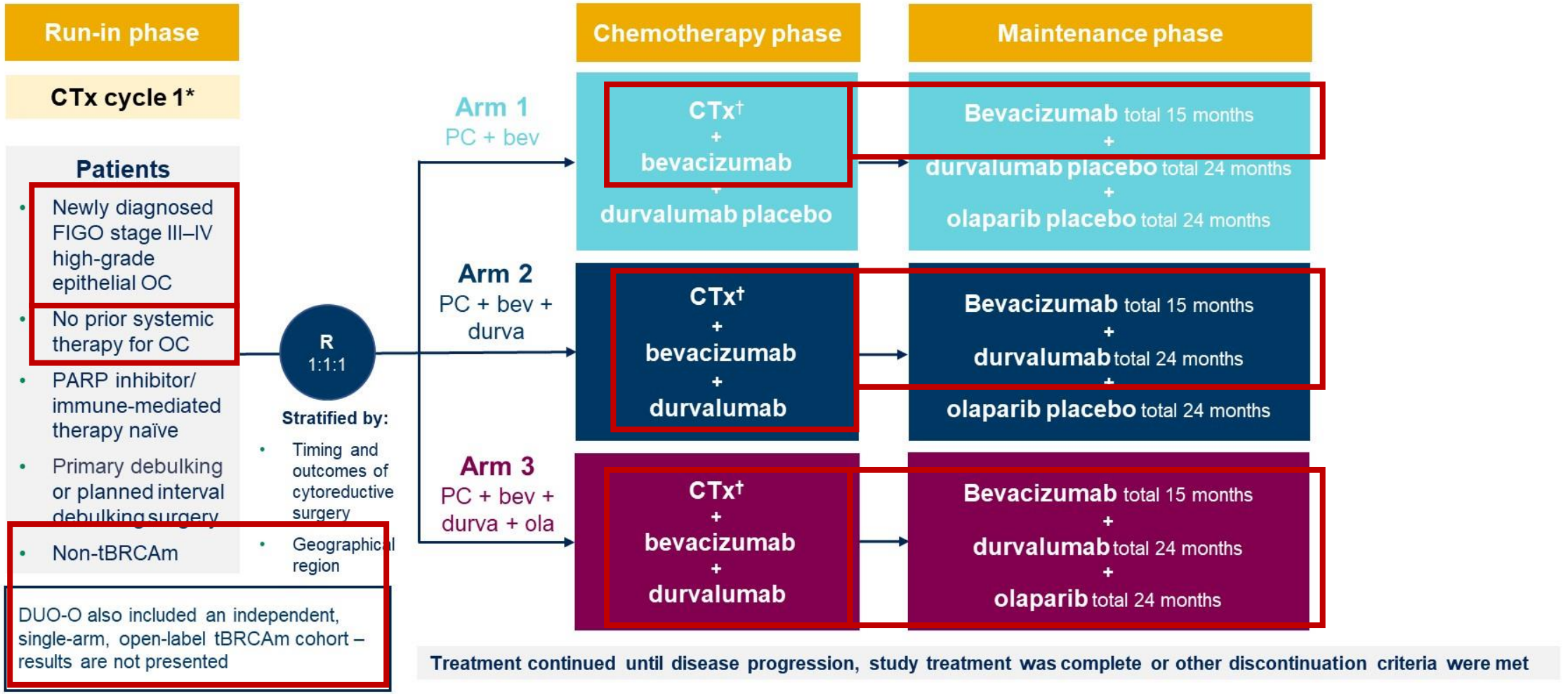
Durvalumab with paclitaxel/carboplatin and bevacizumab followed by maintenance durvalumab, bevacizumab and olaparib in patients with newly diagnosed advanced ovarian cancer without a tumor *BRCA1/BRCA2* mutation: results from the randomized, placebo-controlled Phase III DUO-O/ENGOT-ov46/AGO-OVAR 23/GOG-3025 trial

Philipp Harter,[1] Fabian Trillsch,[2] Aikou Okamoto,[3] Alexander Reuss,[4] Jae-Weon Kim,[5] Maria Jesús Rubio-Pérez,[6] Mehmet Ali Vardar,[7] Giovanni Scambia,[8] Olivier Trédan,[9] Gitte-Bettina Nyvang,[10] Nicoletta Colombo,[11] Anita Chudecka-Głaz,[12] Christoph Grimm,[13] Stephanie Lheureux,[14] Els Van Nieuwenhuysen,[15] Florian Heitz,[16] Robert M. Wenham,[17] Kimio Ushijima,[18] Emily Day,[19] Carol Aghajanian[20]

[1]Kliniken Essen-Mitte, Essen, and AGO, Germany; [2]University Hospital, LMU Munich, Munich, and AGO, Germany; [3]The Jikei University School of Medicine, Tokyo, and JGOG, Japan; [4]Coordinating Center for Clinical Trials of the Philipps-University of Marburg, Marburg, and ENGOT, Germany; [5] Seoul National University Hospital, Seoul, and KGOG, South Korea; [6]Reina Sofia University Hospital, Cordoba, and GEICO, Spain; [7]Medical Faculty, University of Cukurova, and Balcalı Hospital, Adana, and TRSGO, Turkey; [8]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, and MITO, Italy; [9]Centre Léon Bérard, Centre de Recherche en Cancérologie de Lyon, Lyon, and GINECO, France; [10] Odense Universitetshospital, Odense, and NSGO, Denmark; [11]University of Milan-Bicocca and Istituto Europeo di Oncologia IRCCS, Milan, and MANGO, Italy; [12]SPSK Nr 2, Pomeranian Medical University, Szczecin, and PGOG, Poland; [13]Gynecologic Cancer Unit, Medical University Vienna, and AGO-Au, Austria; [14]Princess Margaret Hospital, Toronto, ON, and PMHC, Canada; [15]UZ Leuven, Leuven, and BGOG, Belgium, [16]Ev. Kliniken Essen-Mitte, Essen, and Charité Campus Virchow-Klinikum, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, and AGO, Germany; [17]Moffitt Cancer Center, Tampa, FL, and GOG-F, USA; [18]Kurume University School of Medicine, Kurume, and JGOG, Japan; [19]Oncology Biometrics, AstraZeneca, Cambridge, UK; [20]Memorial Sloan Kettering Cancer Center, New York, NY, and GOG-F, USA

ClinicalTrials.gov identifier: NCT03737643
This study was sponsored by AstraZeneca

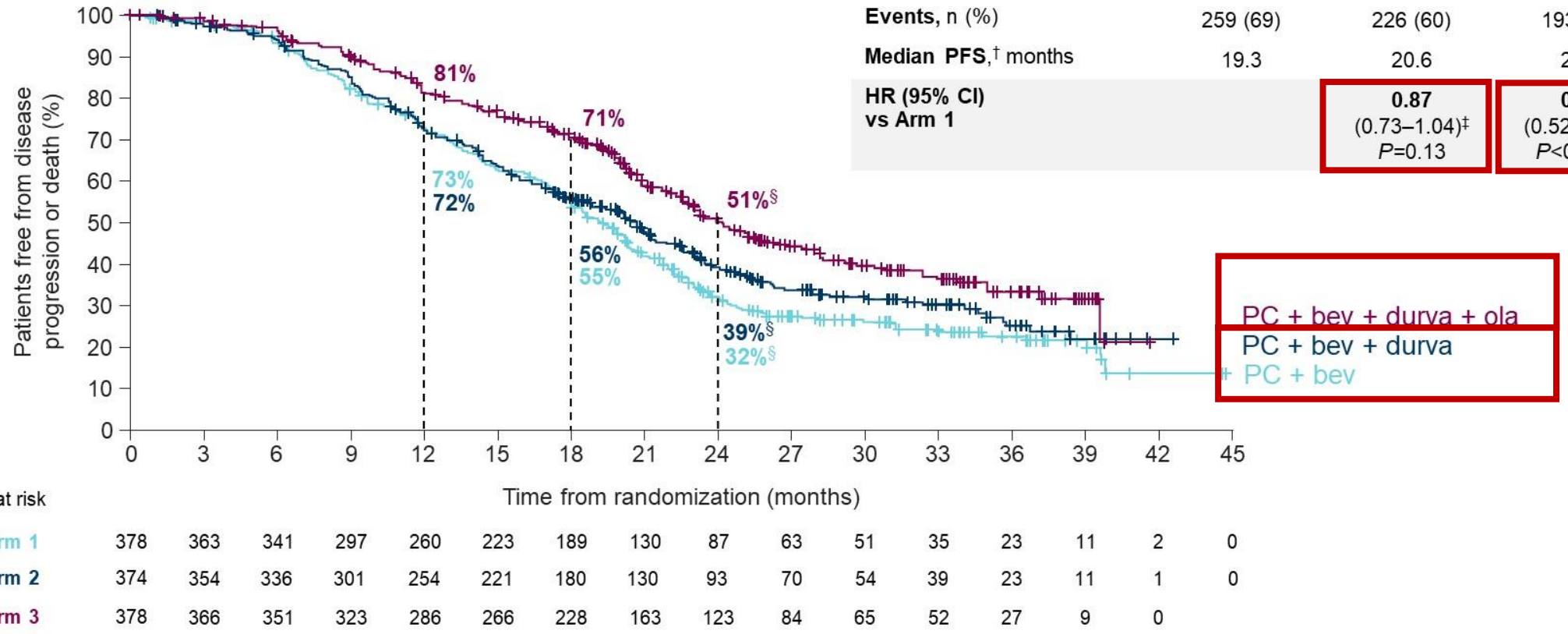
DUO-O study design



Dosing and schedule: bevacizumab (15 mg/kg IV q3w); durvalumab (1120 mg IV q3w); olaparib (300 mg po bid); chemotherapy: paclitaxel 175 mg/m² IV q3w and carboplatin at AUC5 or AUC6 IV q3w. PFS interim analysis DCO: December 5, 2022.
*With or without bevacizumab according to local practice; †Cycles 2–6; ‡Genomic instability score ≥42 assessed prospectively by Myriad MyChoice CDx assay.
AUC, area under the curve; bev, bevacizumab; bid, twice daily; CTx, chemotherapy; DCO, data cutoff; durva, durvalumab; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; IV, intravenous; ola, olaparib; OS, overall survival; PC, paclitaxel/carboplatin; po, by mouth; q3w, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria for Solid Tumors.

PFS: ITT population

	Arm 1 PC + bev N=378	Arm 2 PC + bev + durva N=374	Arm 3 PC + bev + durva + ola N=378
Median follow-up,* months	25.5	23.1	23.3
Events, n (%)	259 (69)	226 (60)	193 (51)
Median PFS,† months	19.3	20.6	24.2
HR (95% CI) vs Arm 1		**0.87** (0.73–1.04)‡ *P*=0.13	**0.63** (0.52–0.76)‡ *P*<0.0001



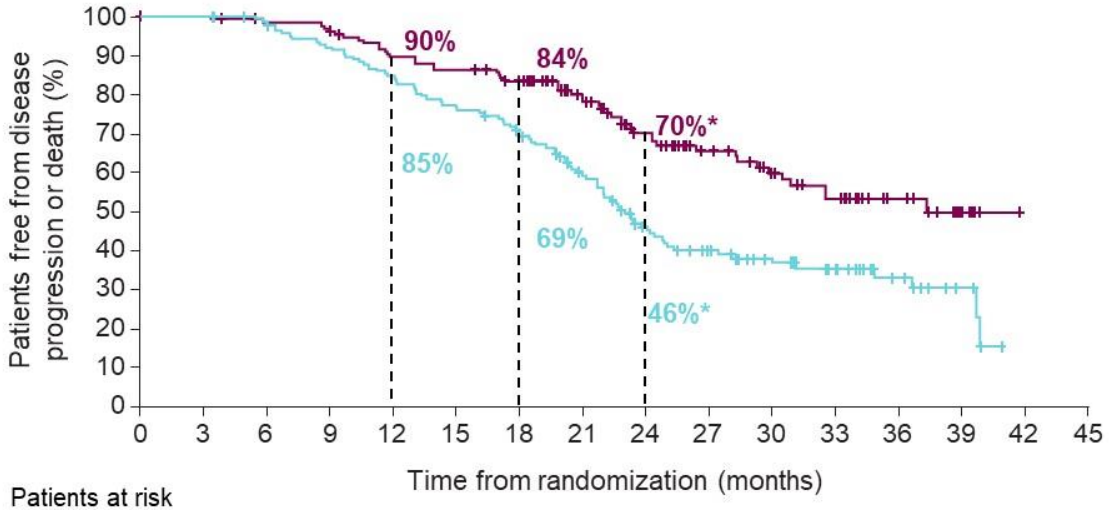
Patients at risk

Arm 1	378	363	341	297	260	223	189	130	87	63	51	35	23	11	2	0
Arm 2	374	354	336	301	254	221	180	130	93	70	54	39	23	11	1	0
Arm 3	378	366	351	323	286	266	228	163	123	84	65	52	27	9	0	

*In censored patients; †Medians and rates were estimated by KM method; ‡HR and CI were estimated from a stratified Cox proportional hazards model. Model stratified by timing and outcome of cytoreductive surgery and geographical region. *P* value from a stratified log rank text; §24-month PFS rates unstable.

Subgroup analysis of PFS by HRD status

Non-tBRCAm HRD-positive

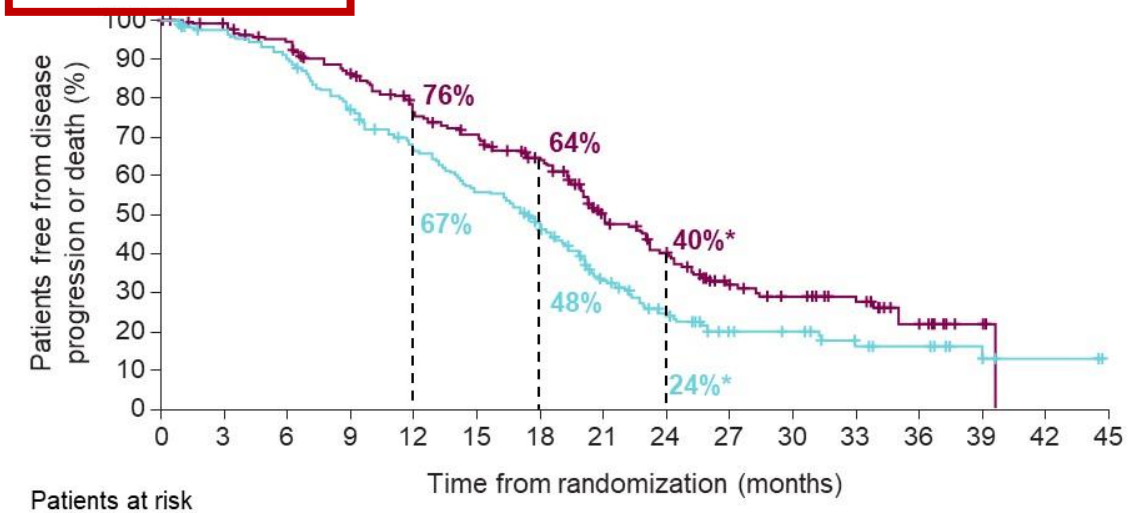


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	49 (35)
Median PFS, months†	23.0	37.3‡
HR (95% CI) vs Arm 1		**0.51** (0.36–0.72)§

HRD-negative



Patients at risk

Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

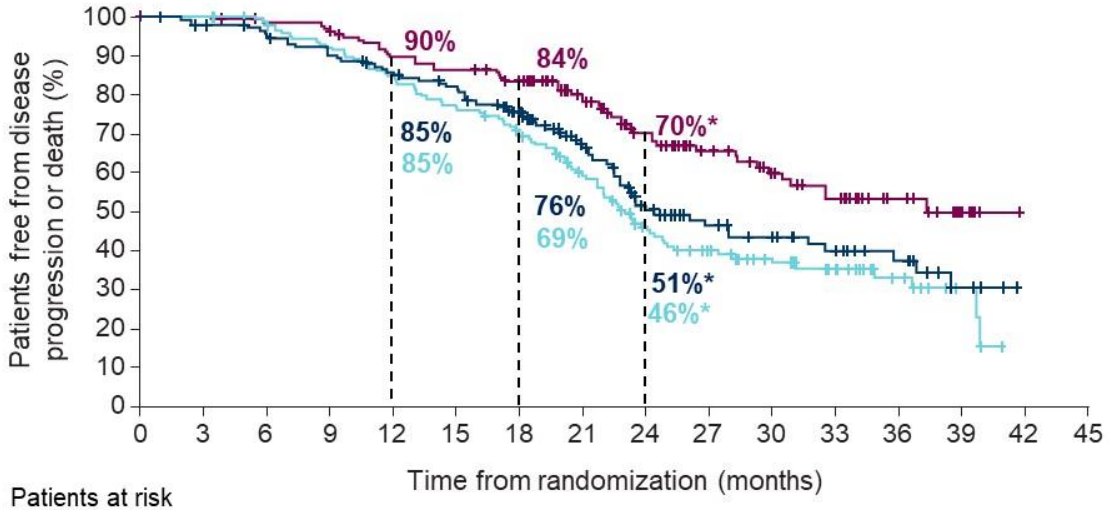
	Arm 1 PC + bev N=216	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	127 (60)
Median PFS, months†	17.1	29.0
HR (95% CI) vs Arm 1		**0.68** (0.54–0.86)§

!

*24-month PFS rates unstable; †Medians and rates were estimated by KM method; ‡Median PFS in HRD-positive subgroup Arm 3 and Arm 2 unstable; §HR and CI were estimated from an unstratified Cox proportional hazards model.

Subgroup analysis of PFS by HRD status

Non-tBRCAm HRD-positive

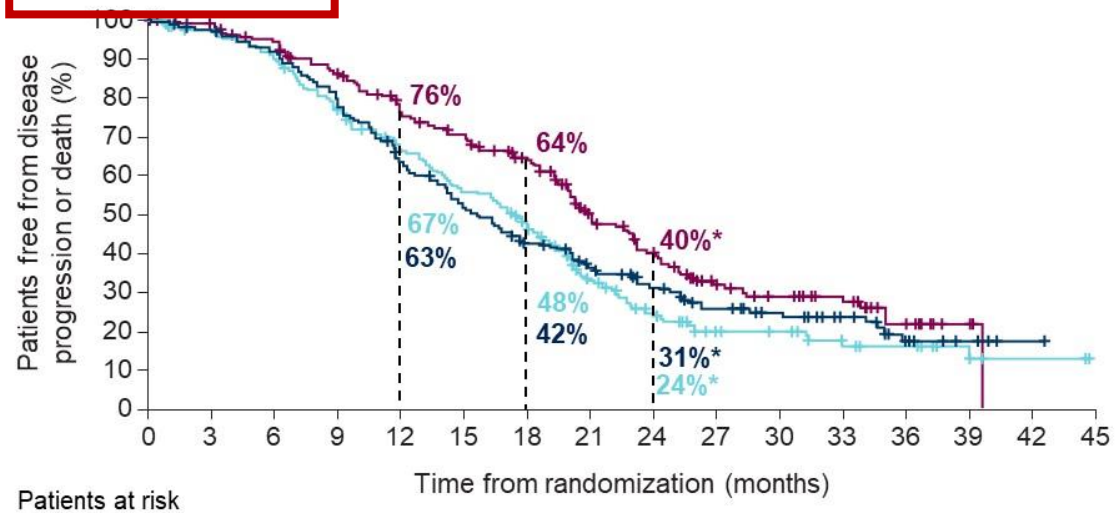


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0	
Arm 2	148	142	137	128	118	112	94	66	45	34	28	21	15	7	0	
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0	

	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	69 (47)	49 (35)
Median PFS, months†	23.0	24.4‡	37.3‡
HR (95% CI) vs Arm 1		**0.82** (0.60–1.12)§	**0.51** (0.36–0.72)§

HRD-negative



Patients at risk

Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 2	199	189	177	153	120	97	76	59	45	33	25	17	8	4	1	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

	Arm 1 PC + bev N=216	Arm 2 PC + bev + durva N=199	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	142 (71)	127 (60)
Median PFS, months†	17.4	15.4	20.9
HR (95% CI) vs Arm 1		**0.94** (0.75–1.18)§	**0.68** (0.54–0.86)§

*24-month PFS rates unstable; †Medians and rates were estimated by KM method; ‡Median PFS in HRD-positive subgroup Arm 3 and Arm 2 unstable; §HR and CI were estimated from an unstratified Cox proportional hazards model.

DISCUSSANT:

First positive phase III IO trial in OC – *even more so in the HRD negative population*

- After 2 negative immunotherapy trials in OC (Javelin 100 and Imagyn 50) DUO-O is the first positive immunotherapy trial in OC –*why? – Studys' design doesn't clearly allow identification of the individual contributions of olaparib vs durvalumab*
- The first study to show a benefit in HRD negative patients against an active standard arm *(Paola neg and PRIMA against placebo)*
- In comparison to PAOLA and PRIMA, in the DUO-O the randomisation occurred already at the beginning of 1st line chemotherapy and proceeded to maintenance also at SD and not just PR/CR: can this be the reason for the effect in the HRD neg population?
- Eagerly awaited results of other IO studies (FIRST, Athena, ENGOT-OV43/ KEYLYNK-001) to establish (?) role of IO in ovarian ca

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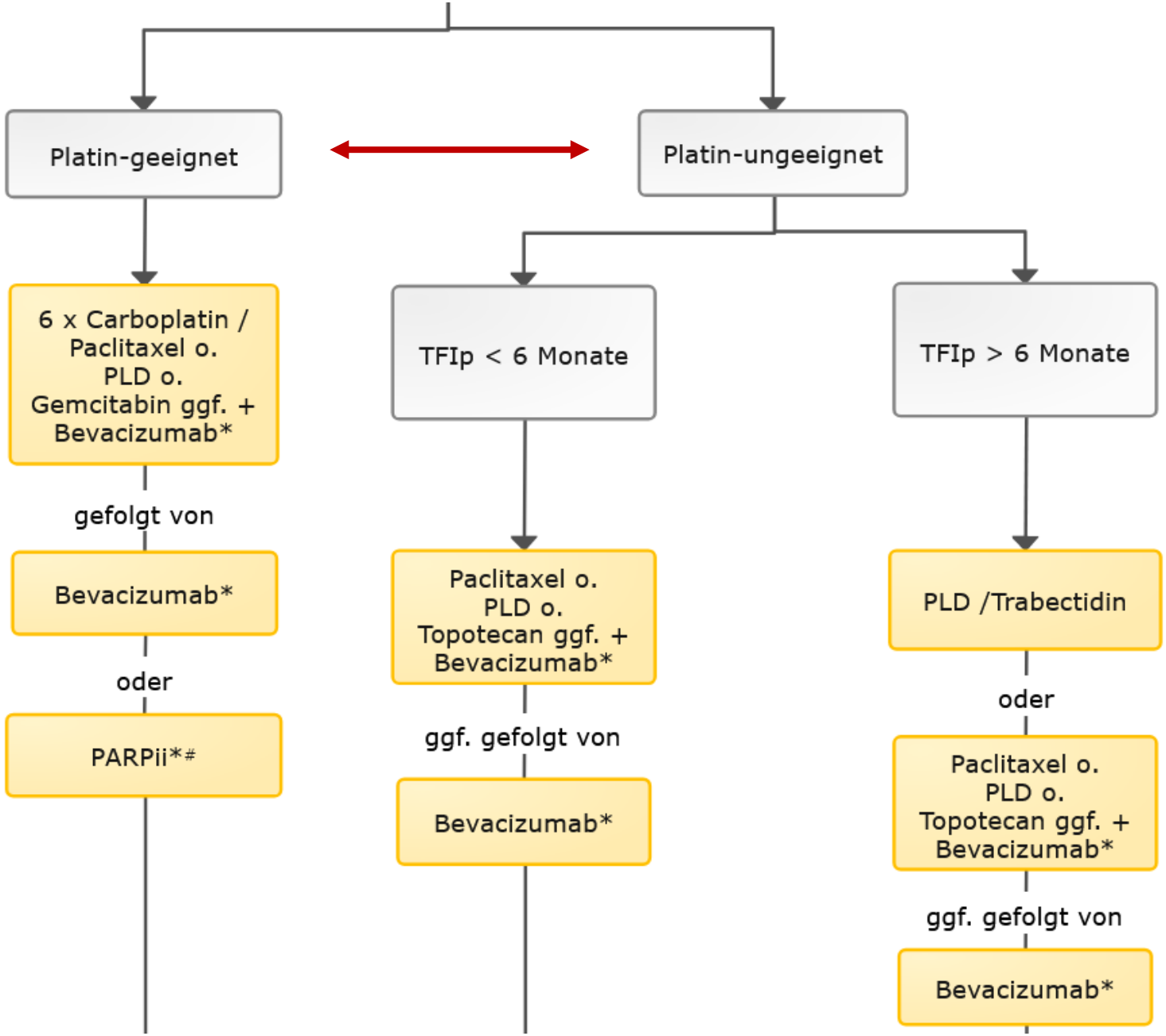
Onkopedia: Rezidiviertes Ovarialkarzinom (nach ggf sekundärem Debulking)



S3-Leitlinie Diagnostik, Therapie und Nachsorge maligner Ovarialtumoren

Version 5.1 - Mai 2022
AWMF-Registernummer: 032/035OL

9.2.2. Rezidivtherapie basierend auf einer erneuten platin-haltigen Therapie (platin-sensitives Rezidiv)

9.6.	Konsensbasierte Empfehlung	Geprüft 2021
EK	Patientinnen mit platinsensitivem Ovarialkarzinomrezidiv sollen, wenn eine Indikation zur Chemotherapie besteht, eine platinhaltige Kombinationstherapie erhalten. Folgende Kombinationen können in Betracht gezogen werden*: • Carboplatin/Gemcitabin • Carboplatin/Gemcitabin/Bevacizumab** • Carboplatin/Paclitaxel • Carboplatin/Paclitaxel/Bevacizumab** • Carboplatin/pegyliertes liposomales Doxorubicin * Reihenfolge alphabetisch **bei Patientinnen mit erstem Rezidiv und ohne vorherige VEGF gerichtete Therapie	

9.2.1. Rezidivtherapie, wenn eine Platin-haltige-Therapie keine Option ist (platin-resistentes Rezidiv)

9.4.	Evidenzbasierte Empfehlung	Geprüft 2021
Empfehlungsgrad A	Patientinnen mit platinresistentem und/oder -refraktärem Ovarialkarzinomrezidiv sollen, wenn eine Indikation zur Chemotherapie besteht, eine nicht platinhaltige Monotherapie erhalten. Folgende Zytostatika können in Betracht gezogen werden: • Pegyliertes liposomales Doxorubicin, • Topotecan, • Gemcitabin, • Paclitaxel wöchentlich.	
Level of Evidence 1+	Leitlinien: NHS TA91 [379] Primärstudien: [459, 460, 462, 468-475]	

9.5.	Evidenzbasierte Empfehlung	Geprüft 2021
Empfehlungsgrad 0	Bevacizumab kann in Kombination mit Paclitaxel, Topotecan oder pegyliertem liposomalen Doxorubicin zur Behandlung von Patientinnen mit platinresistentem Rezidiv angewendet werden.	
Level of Evidence 1+	Primärstudien: [476]	

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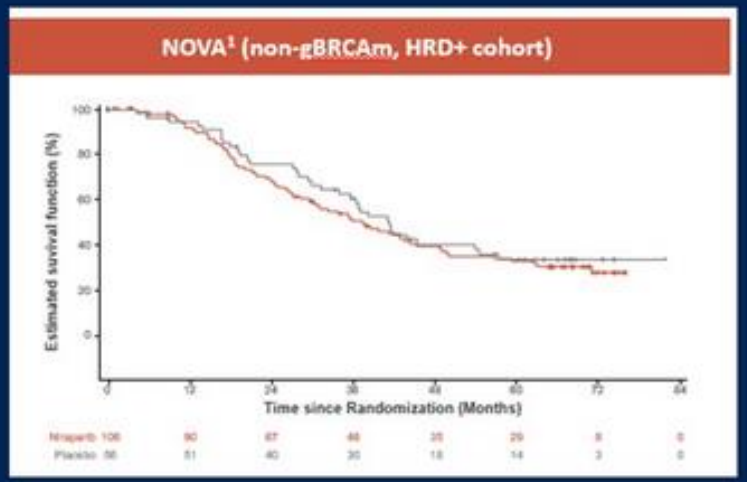
- Platinresistente Erkrankung – zukünftige Optionen

2022 Update: Recurrent Maintenance

Updated Recommendation 3.0. PARPi monotherapy maintenance (second-line or more) may be offered to patients with EOC who have not already received a PARPi and who have responded to platinum-based therapy regardless of *BRCA* mutation status; treatment is continued until progression of disease or toxicity despite dose reductions and best supportive care. Options include olaparib 300 mg every 12 hours, rucaparib 600 mg every 12 hours or niraparib 200-300 mg once daily. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.) **Maintenance treatment with niraparib for patients without germline or somatic *BRCA* mutation should weigh potential PFS benefit against possible OS decrement.** (Type: Evidence-based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Moderate.)



NOVA¹ (non-gBRCAm, HRD+ cohort)

	NOVA¹	
Median OS, months	Niraparib **37.3**	Placebo **41.4**
	HR 1.32 (95% CI 0.84–2.06)	

Tew WP, Kohn E, et al: PARP inhibitors in the management of ovarian cancer: ASCO guideline rapid recommendation update. J Clin Oncol 2022
Matulonis et al. Gynecologic Oncology, August 202; GSK Dear Health Care Provider Letter (Niraparib), May 2022.

2022 Update: Treatment

Updated Recommendations 3.1/3.2. PARPi monotherapy **should not** be routinely offered to patients for the treatment of recurrent platinum sensitive EOC. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate.) *Evidence on PARPi use in this setting is evolving and data are continuing to emerge. Any decision to proceed with PARPi treatment in select populations* (BRCA *mutation, No prior PARPi use, Platinum Sensitive, Advanced Lines of Treatment) should be based on individualized patient and provider assessment of risks, benefits, and preferences*.

- OS in SOLO3 (Olaparib), Penson et al. Gynecol Oncol,August 2022
- OS in ARIEL4 (Rucaparib), Oza AM, et al: Presented at ESMO 2022, (abstr 5180)
- Dear Health Care Provider Letters / FDA Withdrawal of Indications
  - ARIEL4 (Rucabarib, 2+ priors, BRCA-mut)
  - SOLO3 (Olaparib, 3+ priors, BRCA-mut)
  - QUADRA (Niraparib, 3+ priors, HRD positive score)

ASCO Guidelines

PARP INHIBITORS IN THE MANAGEMENT OF OVARIAN CANCER

RAPID RECOMMENDATION UPDATE AT-A-GLANCE SUMMARY

PARPi	First remission: maintenance	Second or greater remission: maintenance *(Indications for patients with no prior PARPi)*
Olaparib	g/sBRCA	g/sBRCA; HRD
Olaparib combined with bevacizumab	g/sBRCA*; HRD	No
Niraparib	g/sBRCA; HRD; wt	g/sBRCA; HRD; wt
Rucaparib	g/sBRCA; HRD; wt	g/sBRCA; HRD; wt

Color Key: should; may; caution.

Notes. *After completion of upfront chemotherapy, continue bevacizumab (1 year) and olaparib (2 years).

1. PARPis are not recommended for use in combination with chemotherapy, nor is it recommended for monotherapy treatment.
2. HRD score companion diagnostic (Myriad MyChoice for niraparib and olaparib; FoundationOne CDx for rucaparib).

asco.org/gynecologic-cancer-guidelines

Abbreviations. g/s *BRCA*, germline or somatic *BRCA*1/2 mutation; HRD, homologous recombination deficiency; PARPi, poly(ADP-ribose) polymerase inhibitor; wt, *BRCA*1/2 wild-type

Ovarial-Karzinom

- Primär fortgeschrittenes Ovarialkarzinom
  - Primärtherapie
  - Erhaltungstherapie
- Rezidiviertes Ovarialkarzinom
  - Erstlinientherapie
  - Erhaltungstherapie
- **Platinresistente Erkrankung – zukünftige Optionen**

2023 ASCO ANNUAL MEETING

Phase III MIRASOL (GOG 3045/ENGOT-ov55) Study: Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancers with High Folate Receptor-Alpha (FRα) Expression

Kathleen N. Moore[1], Antoine Angelergues[2], Gottfried E. Konecny[3], Susana Banerjee[4], Sandro Pignata[5], Nicoletta Colombo[6], John Moroney[7], Casey Cosgrove[8], Jung-Yun Lee[9], Andrzej Roszak[10], Shani Breuer[11], Jacqueline Tromp[12], Diana Bello Roufai[13], Lucy Gilbert[14], Rowan Miller[15], Tashanna Myers[16], Yuemei Wang[17], Anna Berkenblit[17], Domenica Lorusso[18], Toon Van Gorp[19]

[1]Stephenson Cancer Center University of Oklahoma College of Medicine, Oklahoma City, OK, USA; [2]Groupe Hospitalier Diaconesses Croix Saint Simon, Paris, France; [3]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [4]The Royal Marsden NHS Foundation Trust - Royal Marsden Hospital, London, UK; [5]Istituto Nazionale Tumori- G. Pascale, Naples, Italy; [6]European Institute of Oncology IRCCS, Milan, Italy and University of Milan-Bicocca, Milan, Italy; [7]The University of Chicago, Chicago, IL, USA; [8]The Ohio State University, Columbus, OH, USA; [9]Severance Hospital, Seoul, South Korea; [10]Wielkopolskie Centrum Onkologii, Poznan, Poland; [11]Hadassah Ein Kerem – Sharett, Jerusalem, Israel; [12]Amsterdam UMC, Amsterdam, The Netherlands; [13]Hopital Rene Huguenin, Institut Curie, Saint-Cloud, France; [14]McGill University Health Centre, Montreal, Canada; [15]University College London Hospital, London, UK; [16]Baystate Medical Center, Springfield, MA, USA; [17] ImmunoGen, Inc., Waltham, MA, USA; [18]Fondazione Policlinico Universitario A. Gemelli, IRCCS and Catholic University of Sacred Heart, Rome, Italy; [19]University Hospital Leuven Leuven Cancer Institute, Leuven, Belgium

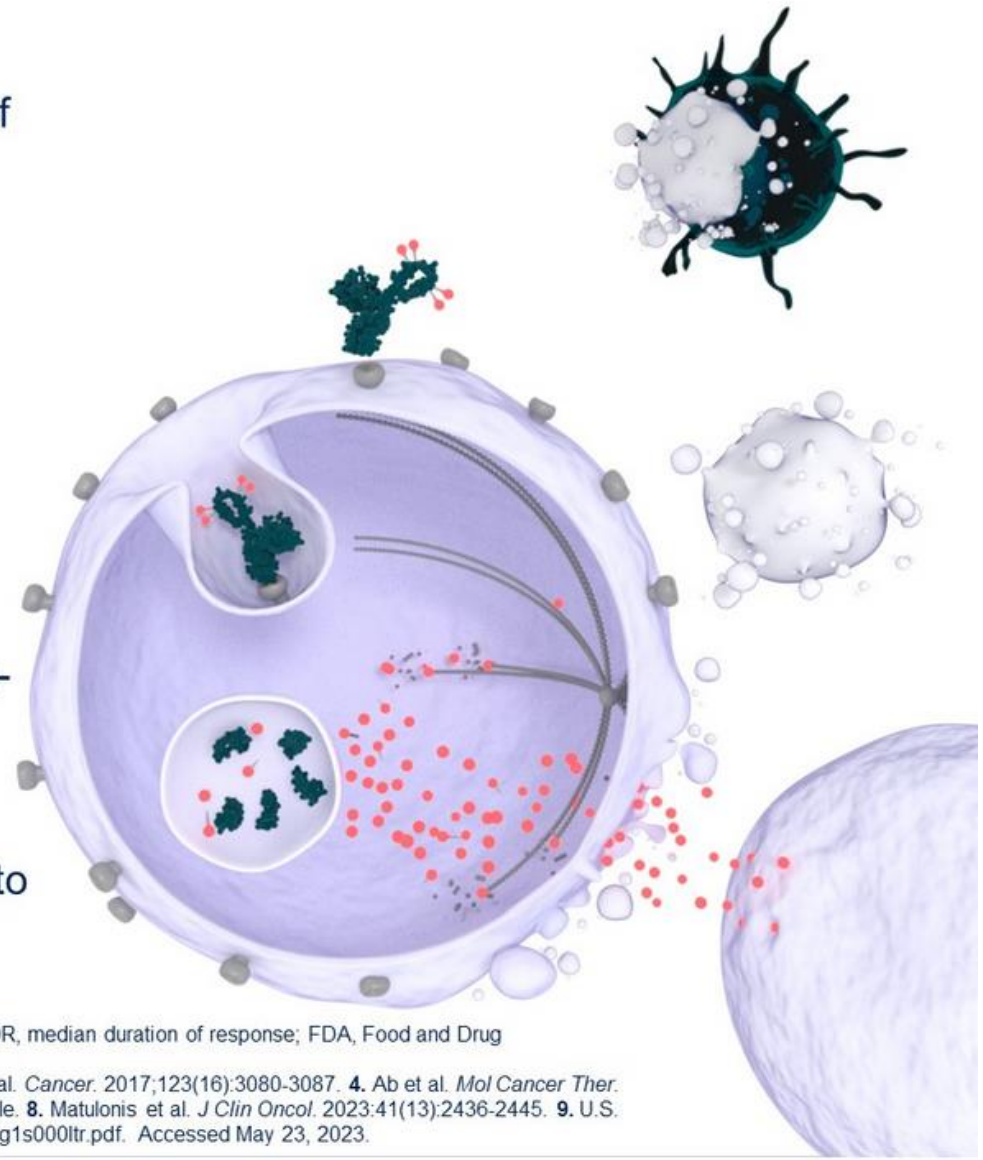
ENGOT European Network of Gynaecological Oncological Trial groups

GOG FOUNDATION® Transforming the standard of care™

PRESENTED BY: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

Background

- No randomized phase 3 trial has shown an overall survival (OS) benefit of a novel therapy in platinum-resistant ovarian cancer (PROC)[1, 2]
- Mirvetuximab soravtansine (MIRV) is an ADC comprising a FRα-binding antibody, cleavable linker, and maytansinoid DM4, a potent tubulin-targeting agent[3,4]
- FRα is expressed in ~90% of ovarian carcinomas,[5, 6] with 35-40%[7] of PROC tumors exhibiting high FRα expression (≥75% of tumor cells positive with ≥2+ intensity)[8]
- MIRV demonstrated an ORR of 32% and mDOR 6.9 months in the single-arm study SORAYA[8] of BEV pre-treated PROC to support accelerated approval by the FDA[9]
- MIRASOL is the confirmatory, randomized, global phase 3 trial designed to support approval worldwide



PFS, progression-free survival; OS, overall survival; FRα, folate receptor alpha; ORR, objective response rate; ADC, antibody-drug conjugate; mDOR, median duration of response; FDA, Food and Drug Administration; BEV, bevacizumab; US, United States; EU, Europe.

1. Pujade-Lauraine et al. *J Clin Oncol*. 2014;32(13):1302-1308. **2.** Richardson et al. *JAMA Oncol*. 2023;10.1001/jamaoncol.2023.0197. **3.** Moore et al. *Cancer*. 2017;123(16):3080-3087. **4.** Ab et al. *Mol Cancer Ther*. 2015;14(7):1605-1613. **5.** Markert et al. *Anticancer Res*. 2008;28(6A):3567-3572. **6.** Martin et al. *Gynecol Oncol*. 2017;147(2):402-407. 7. Data on file. **8.** Matulonis et al. *J Clin Oncol*. 2023:41(13):2436-2445. **9.** U.S. FOOD & DRUG ADMINISTRATION. BLA ACCELERATED APPROVAL. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/761310Orig1s000ltr.pdf. Accessed May 23, 2023.

MIRASOL (NCT04209855) – Study Design[1,2]

An open-label, phase 3 randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer

Patient Population
(N=453)

Enrollment and Key Eligibility
Platinum-resistant disease
(PFI ≤6 mo)

FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells

High-grade serous histology

1º platinum-refractory disease excluded (primary PFI <3 mo)

1-3 prior lines of therapy

Prior BEV and PARPi allowed

Patients with BRCA mutations allowed

1:1 Randomization

Treatment Regimen-Experimental

MIRV
(6 mg/kg AIBW Q3W)

Treatment Regimen-Control

Investigator's Choice Chemotherapy
(Paclitaxel, PLD, or Topotecan)

Stratification Factors
IC chemo: paclitaxel, PLD, or topotecan
Prior lines of therapy: 1 vs 2 vs 3

Primary Endpoint
PFS by INV
(BICR sensitivity analysis)

Key Secondary Endpoints
1) ORR by INV
2) OS
3) PROs[a]

Secondary Endpoints
Safety and tolerability
DOR
CA-125 response[b]
PFS2

AIBW, adjusted ideal body weight; BEV; bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.
[a]PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument.
[b]Gynecological Cancer InterGroup (GCIG) criteria.

1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855
2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

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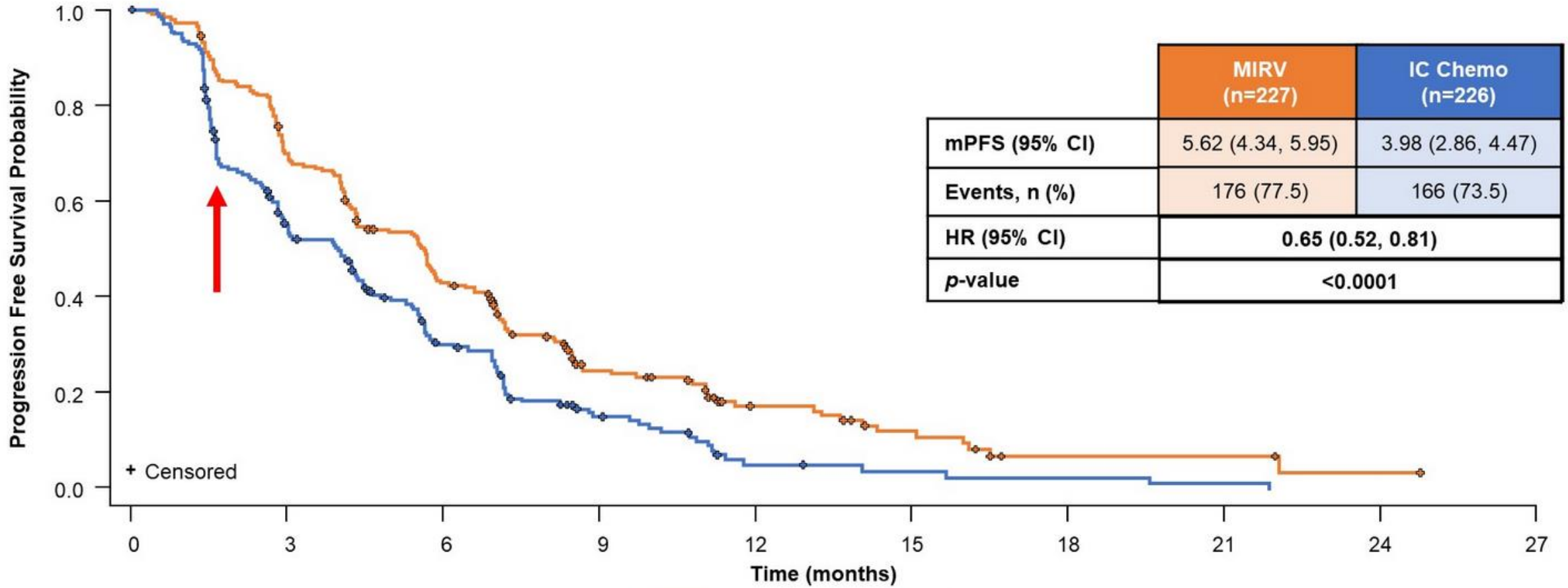
Primary Endpoint: Progression-Free Survival by Investigator



	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	**0.65 (0.52, 0.81)**	
p-value	**<0.0001**	

No. Participants at Risk

MIRV	227	151	89	38	18	10	3	3	1	0
IC Chemo	226	98	48	19	5	3	2	1	0	

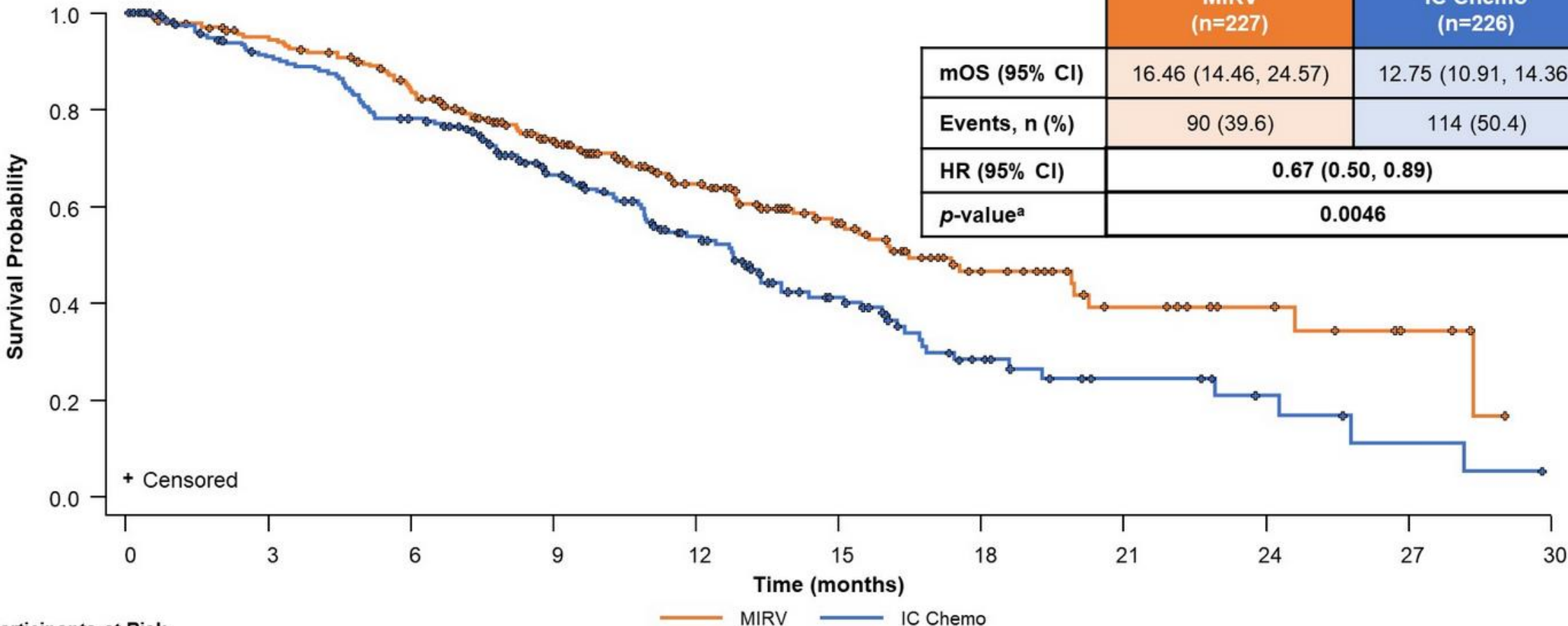
Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio.

PRESENTED BY: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

Overall Survival

	MIRV (n=227)	IC Chemo (n=226)
mOS (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	0.67 (0.50, 0.89)	
p-value[a]	0.0046	



No. Participants at Risk

MIRV	227	204	175	128	82	53	28	15	9	4	0
IC Chemo	226	185	157	107	68	39	18	9	5	2	0

Data cutoff: March 6, 2023; median follow-up time: 13.11 months
MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mOS, median overall survival; CI, confidence interval; HR, hazard ratio.
[a]Overall survival is statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313

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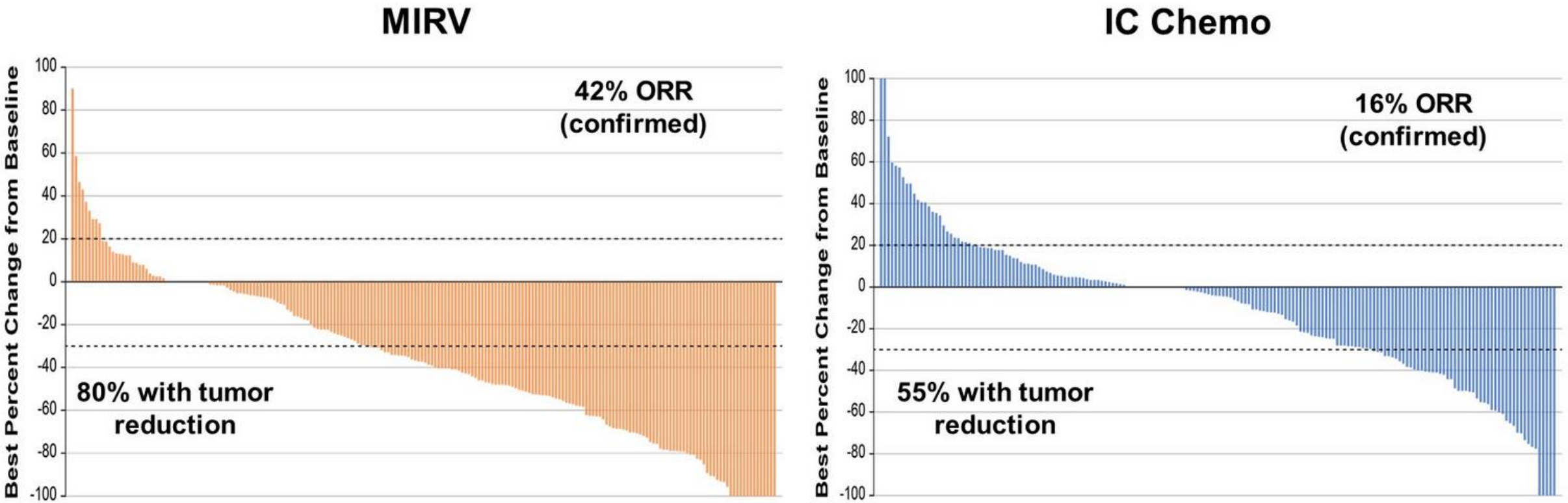
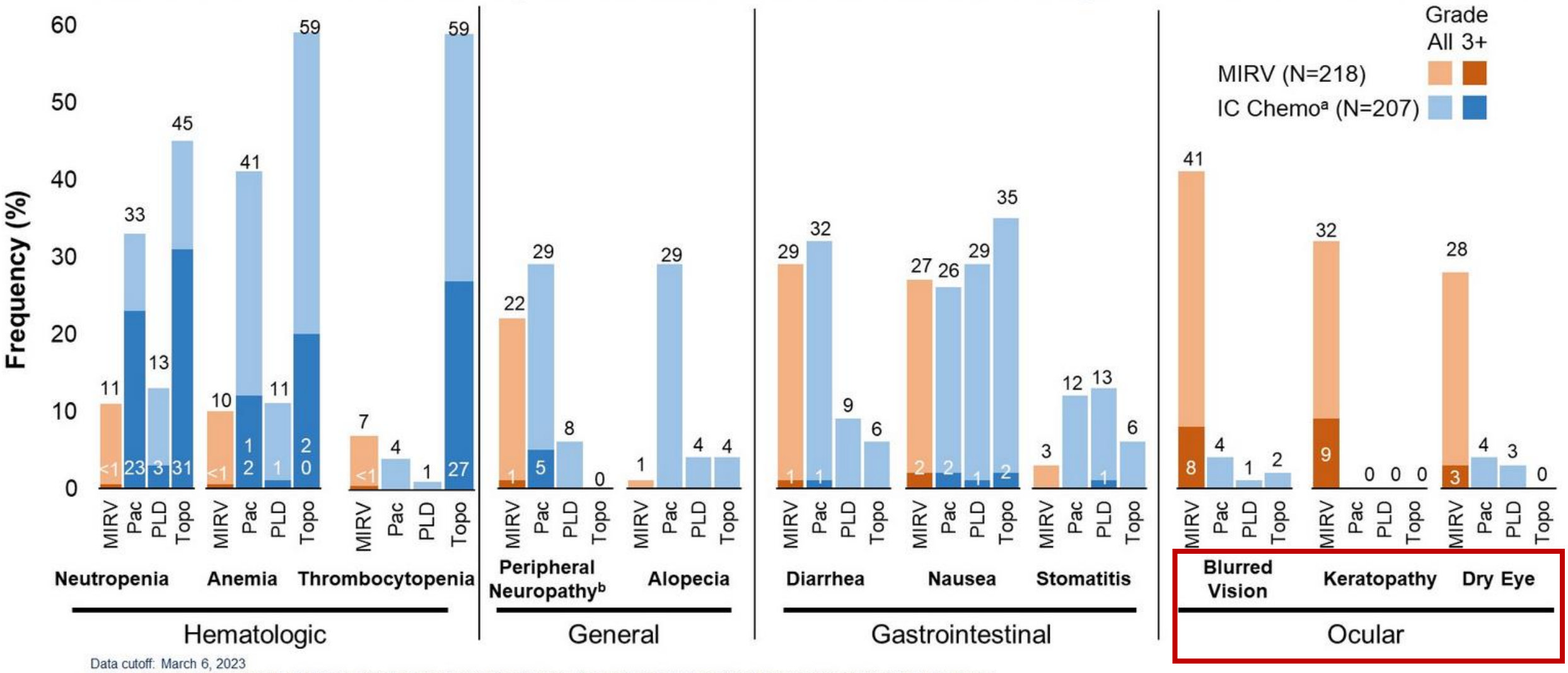
Maximum Percentage Change in Target Lesion Size from Baseline by Investigator (N=453)



Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC chemo, investigator's choice chemotherapy; ORR, objective response rate.

Differentiated Safety Profile: Treatment-Emergent Adverse Events



Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo: investigator's choice chemotherapy; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan.

[a]Pac n=82 (39%), PLD n=76 (37%), Topo n=49 (24%). [b]Grade 2+ peripheral neuropathy events were observed in 12% and 16% of patients that received MIRV or paclitaxel, respectively.

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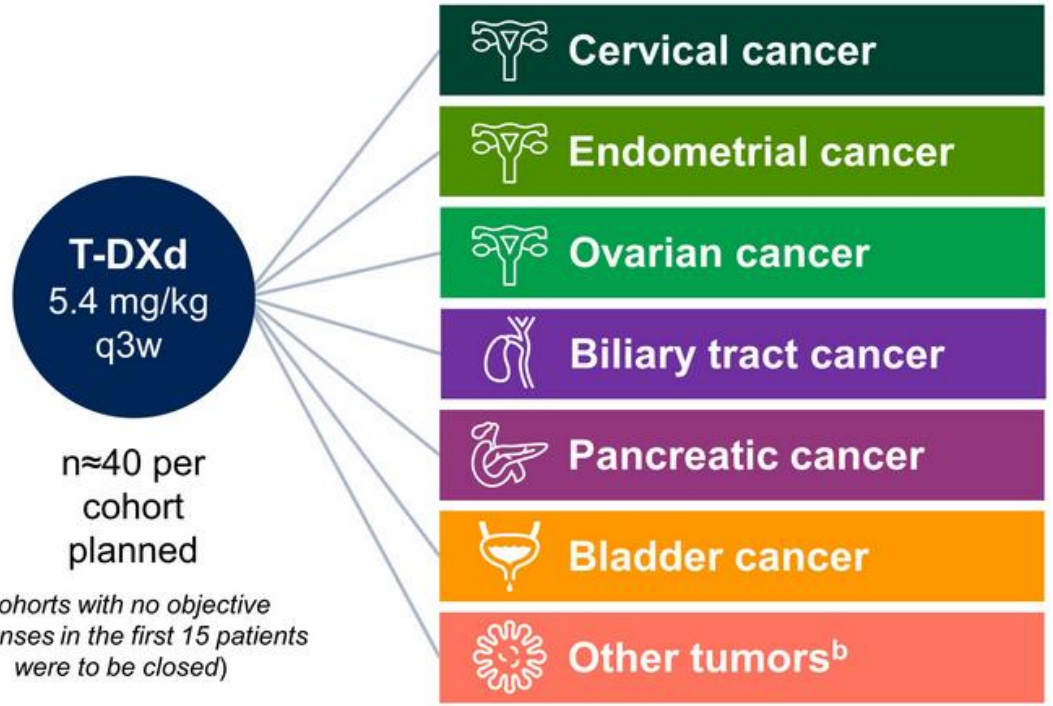
DESTINY-PanTumor02: A Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors

An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)[1]
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

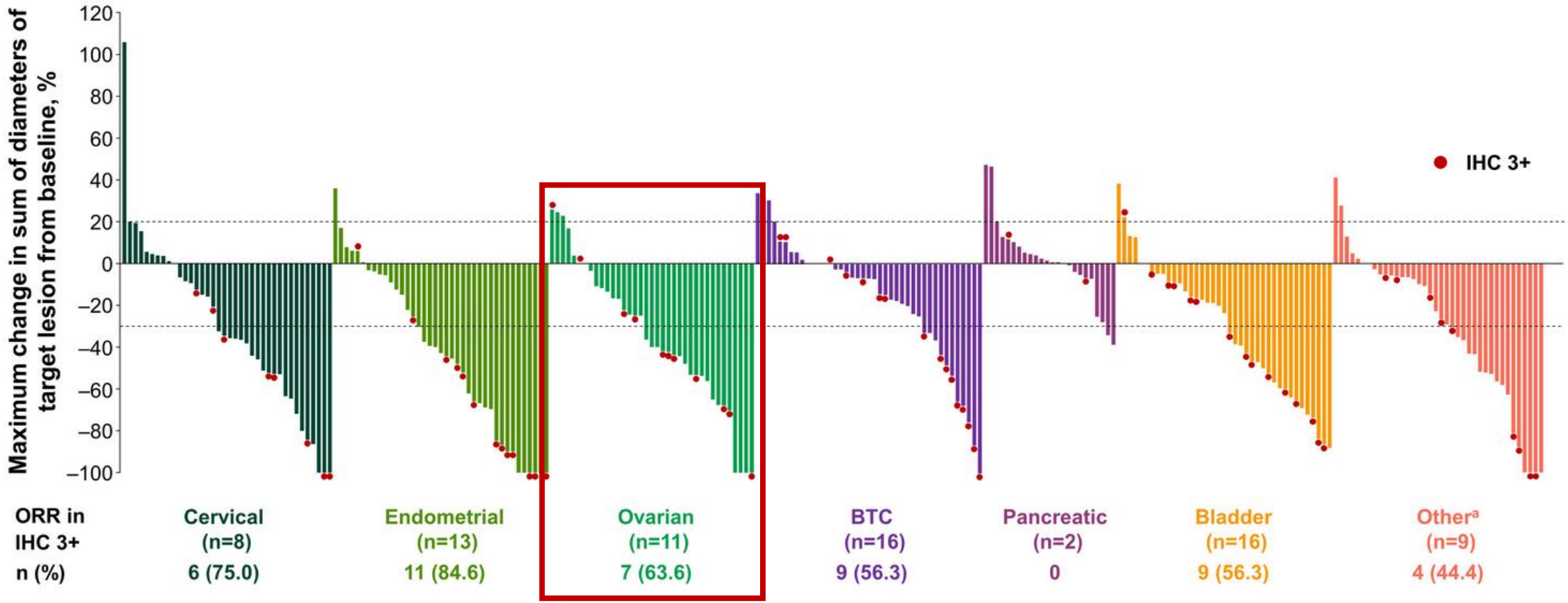
Data cut-off for analysis:

- Nov 16, 2022

[a]Patients were eligible for either test. All patients were centrally confirmed. [b]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer.
[c]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.
2L, second-line; ASCO, American Society of Clinical Oncology; DCR, disease control rate; CAP, College of American Pathologists; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

1. Hofmann M, et al. *Histopathology 2008*;52(7):797–805.

Best Percentage Change in Target Lesion From Baseline



Analyses were performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of ORR in IHC 3+ was performed in patients with centrally confirmed HER2 status (n=75).
[a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; IHC, immunohistochemistry; ORR, objective response rate.

Fortgeschrittenes Zervixkarzinom

Fortgeschrittenes Zervix-Karzinom

- **Erstlinientherapie**
  - **Bisheriger Standard**
  - KEYNOTE-826-Studie
- Spätere Therapielinien

S3-Leitlinie Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom

Langversion 2.2 – März 2022
AWMF-Registernummer: 032/033OL

18.3.5. Medikamentöse Therapiearten in der metastasierten Situation

18.4	Evidenzbasierte Empfehlung	Modifiziert 2021
Empfehlungsgrad **0**	Nach einer Radio(chemo)therapie mit Cisplatin als „Radiosensitizer" kann eine erneute Cisplatingabe erfolgen. Bei Rezidiv/Metastasen nach vorangegangener Chemotherapie mit Cisplatin kann eine erneute Gabe von Cisplatin kombiniert mit Topotecan, Paclitaxel, Gemcitabine oder Vinorelbin oder die Gabe von Carboplatin mit Paclitaxel erfolgen.	

18.5	Evidenzbasiertes Statement	Geprüft 2021
Level of Evidence **1+**	Kombinationstherapien haben eine höhere Morbidität und Toxizität als die Monotherapie. Kombinationstherapien haben eine höhere Ansprechrate. In Bezug auf das Gesamtüberleben konnte bisher nur für die Kombination Cisplatin mit Topotecan ein geringer absoluter Überlebensvorteil gezeigt werden.	

18.6	Evidenzbasierte Empfehlung	Neu 2021
Empfehlungsgrad: **0**	Alternativ zu Cisplatin kann auch Carboplatin in der Mono- und Kombinationstherapie eingesetzt werden.	

18.7	Evidenzbasierte Empfehlung	Neu 2021
Empfehlungsgrad: **B**	Bei Cisplatin-naiven Patientinnen sollte Cisplatin bevorzugt werden.	

18.8	Evidenzbasierte Empfehlung	Modifiziert 2021
Empfehlungsgrad **B**	Patientinnen mit metastasiertem oder rezidiviertem/persistierendem Zervixkarzinom sollten simultan Bevacizumab – unabhängig von einer Vorbehandlung mit einer Radio(-chemo)therapie – zur palliativen first-line Chemotherapie mit Cisplatin/Paclittaxel oder Topotecan/Paclitaxel erhalten.	

Fortgeschrittenes Zervix-Karzinom

- **Erstlinientherapie**
  - Bisheriger Standard
  - **KEYNOTE-826-Studie**
- Spätere Therapielinien

S3-Leitlinie Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom

Langversion 2.2 – März 2022
AWMF-Registernummer: 032/033OL

18.9	Konsensbasiertes Statement	Neu 2021
EK	Bei Patientinnen mit PD-L1 positivem metastasiertem Zervixkarzinom sind Checkpointinhibitoren eine weitere Therapiemöglichkeit.	
	Konsens	

KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study

Key Eligibility Criteria

- Persistent, recurrent, or metastatic cervical cancer not amenable to curative treatment
- No prior systemic chemotherapy (prior radiotherapy and chemoradiotherapy permitted)
- ECOG PS 0 or 1

Stratification Factors

- Metastatic disease at diagnosis (yes vs no)
- PD-L1 CPS (<1 vs 1 to <10 vs ≥10)
- Planned bevacizumab use (yes vs no)

R 1:1

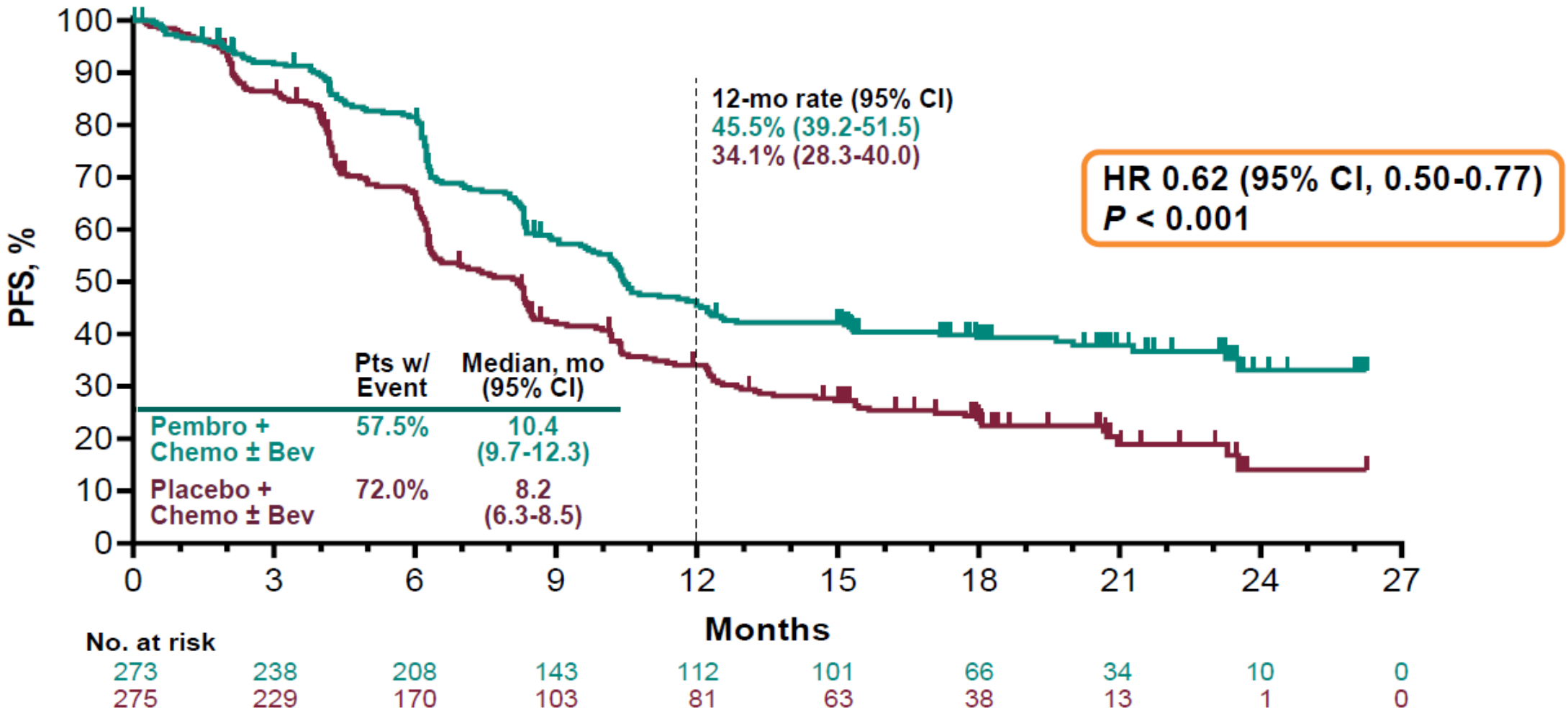
Pembrolizumab 200 mg IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

Placebo IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

End Points

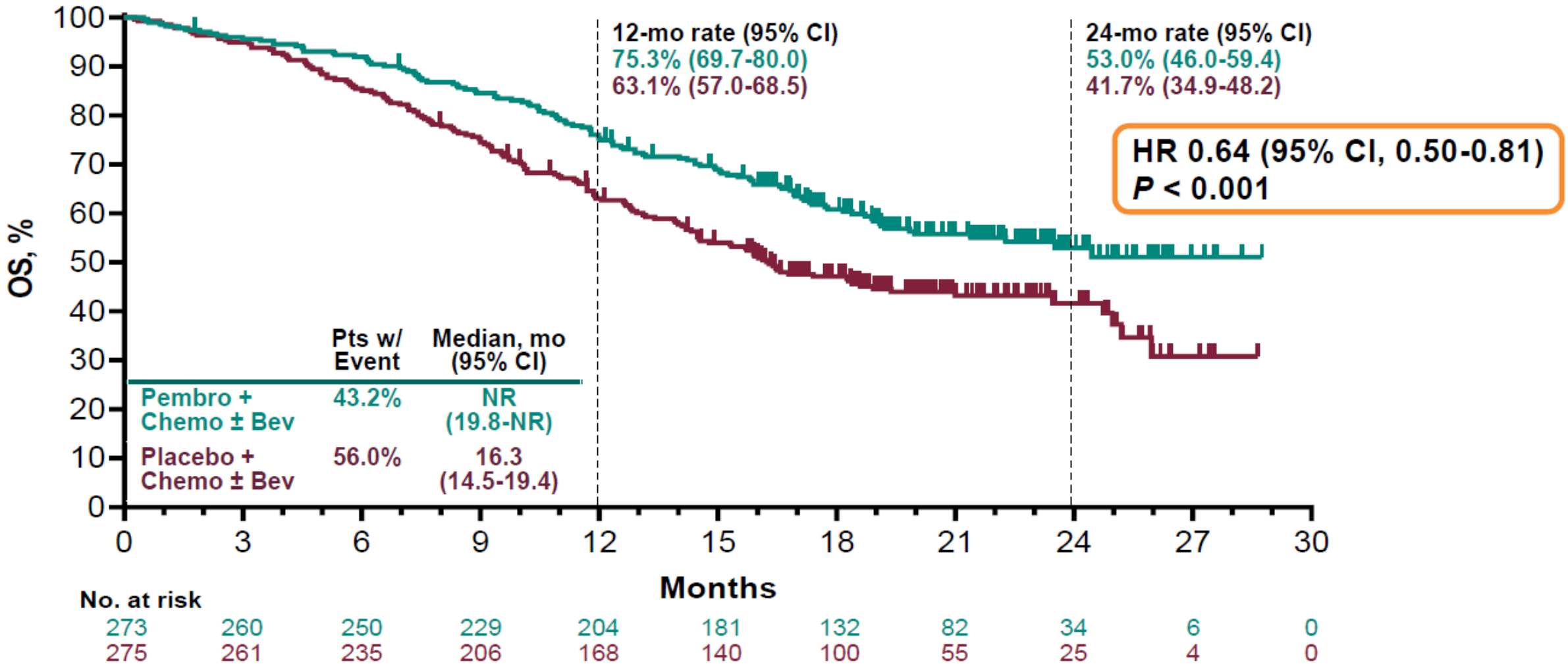
- **Dual primary:** OS and PFS per RECIST v1.1 by investigator
- **Secondary:** ORR, DOR, 12-mo PFS, and safety
- **Exploratory:** PROs assessed per EuroQol EQ-5D-5L VAS

PFS: PD-L1 CPS ≥1 Population



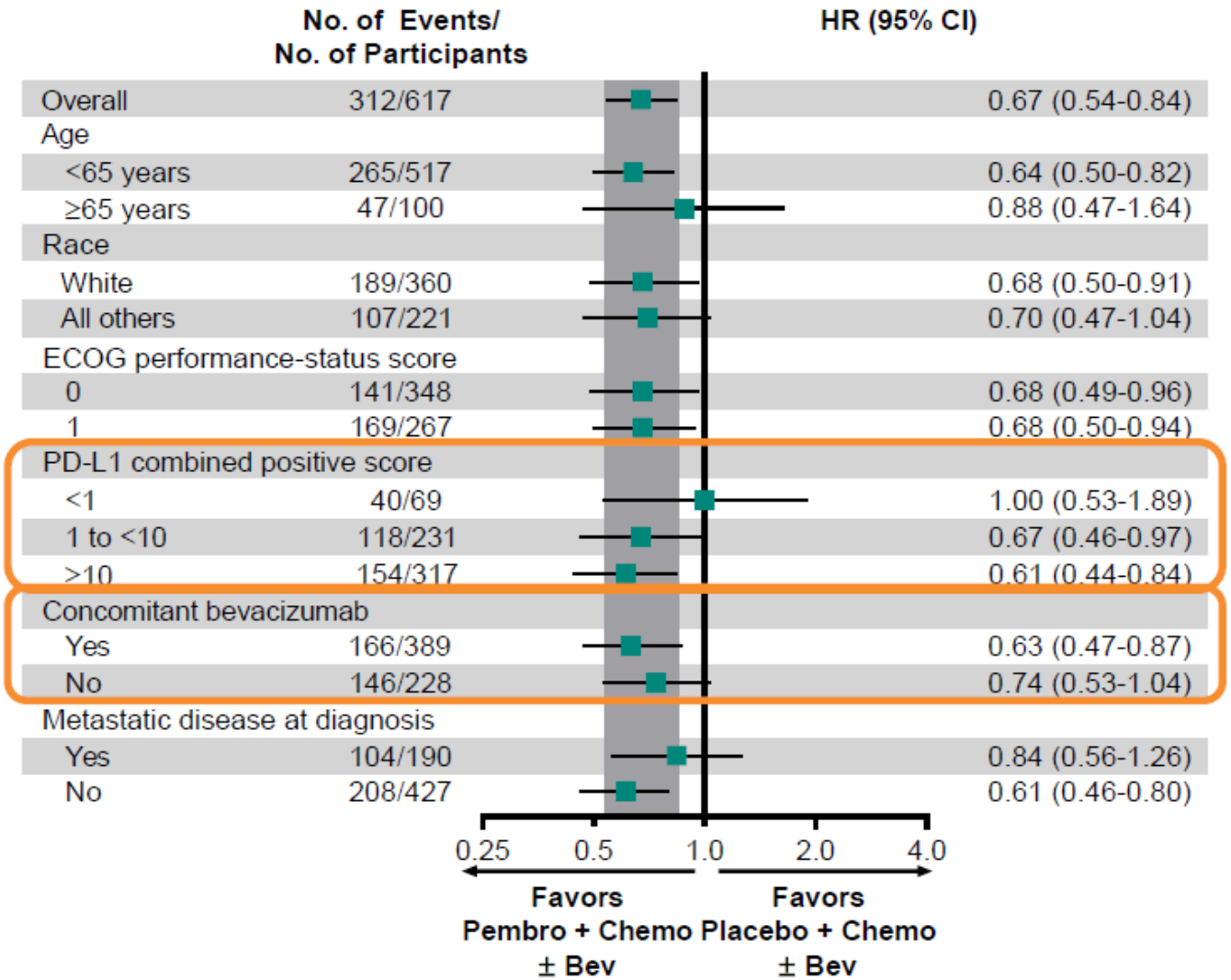
Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

OS: PD-L1 CPS ≥1 Population



Data cutoff date: May 3, 2021.

OS: Protocol-Specified Subgroups, All-Comer Population



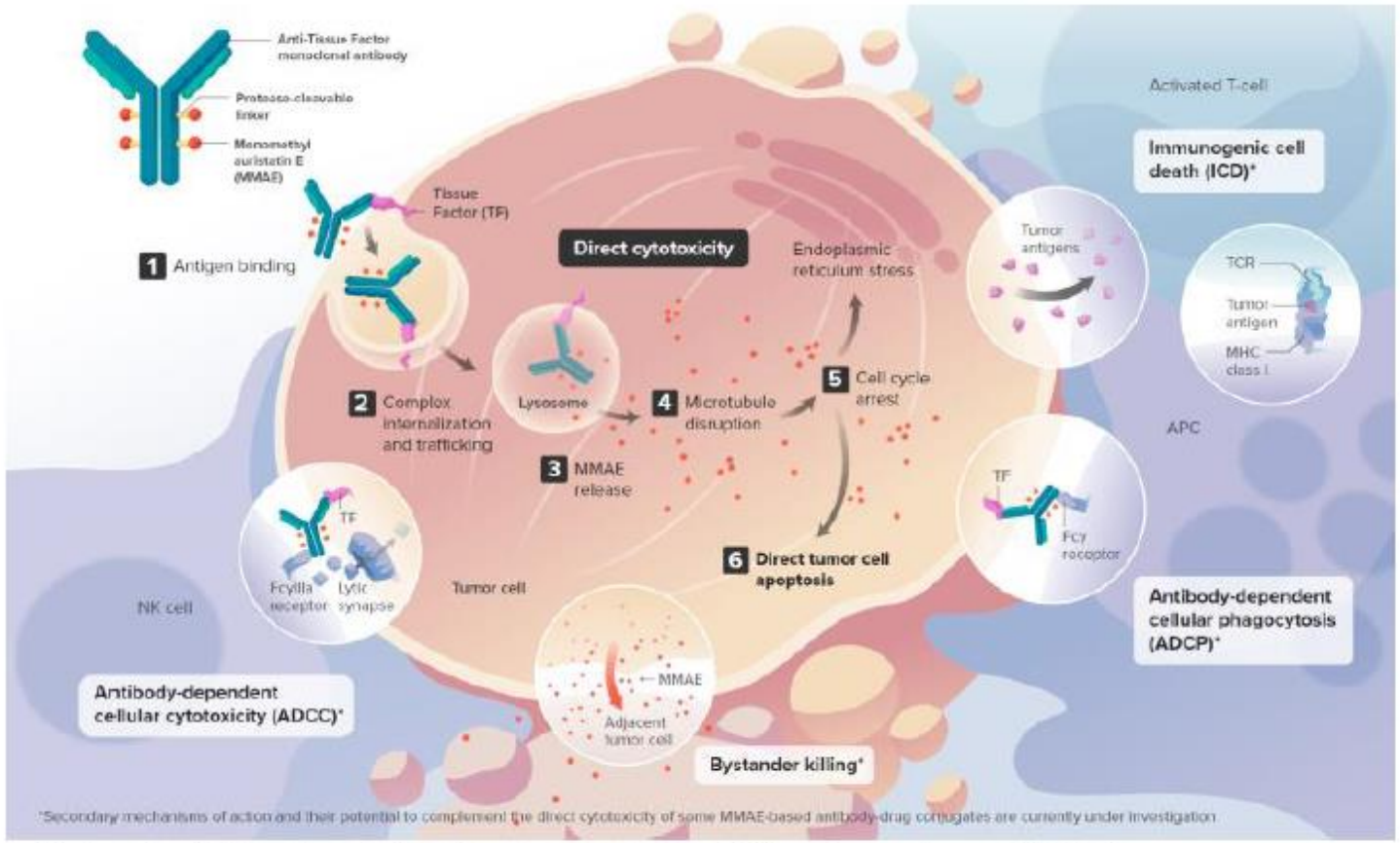
Data cutoff date: May 3, 2021.

Fortgeschrittenes Zervix-Karzinom

- Erstlinientherapie
  - Bisheriger Standard
  - KEYNOTE-826-Studie
- **Spätere Therapielinien**
  - Keynote 158 (Pembro)
  - EMPOWER Cervical/GOG-3016 (Cemiplimab)
  - InnovaTV-Studien (Tisotumab Vedotin)
  - DESTINY-PanTumor02 (Trastuzumab Deruxtecan)

Proposed MOA of Tisotumab Vedotin

- Tisotumab vedotin is an investigational antibody-drug conjugate directed to tissue factor (TF) and covalently linked to the microtubule-disrupting agent MMAE via a protease-cleavable linker[1,2]
- TF is highly prevalent in cervical cancer and other solid tumors and is associated with cancer pathophysiology and poor prognosis[3-5]
  - TF is co-opted by tumor cells to promote tumor growth, angiogenesis, and metastasis[6]
  - In normal physiology, TF's primary role is to initiate the coagulation cascade after vascular injury[6]
- Tisotumab vedotin has multiple anti-tumor effects[1,2,7]



Tisotumab vedotin is an investigational agent, and its safety and efficacy have not been established.

1. Breij EC et al. *Cancer Res.* 2014;74(4):1214-1226. 2. De Goeij BE et al. *Mol Cancer Ther.* 2015;14(5):1130-1140. 3. Pan L et al. *Mol Med Rep.* 2019;19:2077-2086. 4. Cocco E et al. *BMC Cancer.* 2011;11:263. 5. Zhao X et al. *Exp Ther Med.* 2018;16:4075-4081. 6. Forster Y et al. *Clin Chim Acta.* 2006;364:12-21 7. Alley SC et al. American Association for Cancer Research Annual Meeting; March 29 – April 3, 2019; Atlanta, GA, USA; Abstract #221.
ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; MMAE, monomethyl auristatin E; MOA, mechanism of action; TF, tissue factor.

innovaTV 204 Study Design

innovaTV 204 (NCT03438396) is a pivotal phase 2 single-arm, multicenter (United States and Europe) study evaluating tisotumab vedotin in patients with previously treated recurrent and/or metastatic cervical cancer

Key Eligibility Criteria

- Recurrent or extrapelvic metastatic cervical cancer
- Progressed during or after doublet chemotherapy[a] with bevacizumab (if eligible)
- Received ≤2 prior systemic regimens[b]
- ECOG PS 0-1

Enrolled: 102[c]
Treated: 101*

Tisotumab vedotin
2.0 mg/kg IV Q3W

Until PD or unacceptable toxicity

Tumor responses assessed using CT or MRI at baseline, every 6 weeks for the first 30 weeks, and every 12 weeks thereafter

*Study sample size calculated assuming a confirmed ORR of 21% to 25% with tisotumab vedotin and to provide ≥80% power to exclude an ORR of ≤11%[e]

Primary Endpoint

- ORR[d] per RECIST v1.1, by independent imaging review committee (IRC)

Secondary Endpoints

- ORR[d] per RECIST v1.1, by investigator
- DOR, TTR, and PFS by IRC and investigator
- OS
- Safety

Exploratory Endpoints

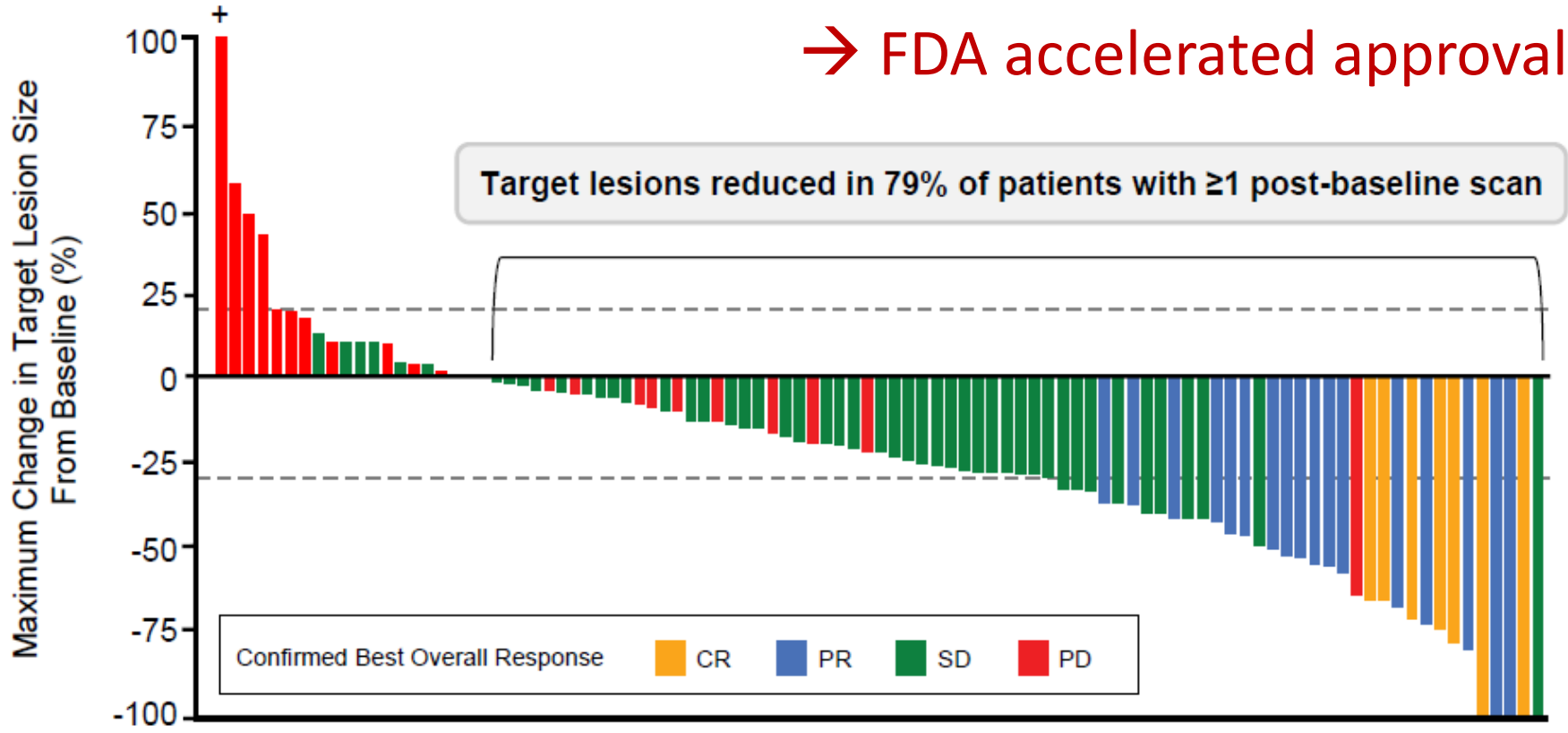
- Biomarkers
- HRQoL

[a]Paclitaxel plus platinum (cisplatin or carboplatin) or paclitaxel plus topotecan. [b]Adjuvant or neoadjuvant chemotherapy or if administered with radiation therapy, was not counted as a prior systemic regimen. [c]June 2018 to April 2019. [d]Responses were confirmed by subsequent repeat imaging performed ≥4 weeks after initial response assessment. [e]Using one-sided exact binomial test at 0.025 significance level.
CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IRC, independent review committee; IV, intravenous; MRI, magnetic resonance imaging; OS, overall survival; PD, progressive disease; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; TTR, time to response.

VIRTUAL 2020 ESMO congress

Maximum Change in Target Lesion Size by IRC Assessment

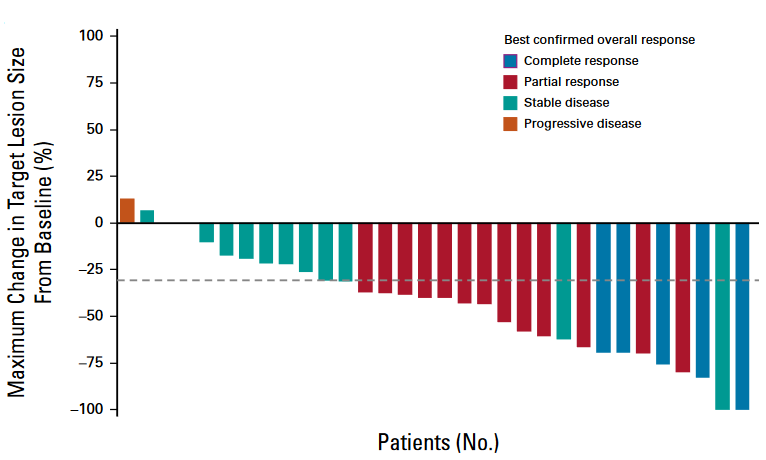
→ FDA accelerated approval 2021



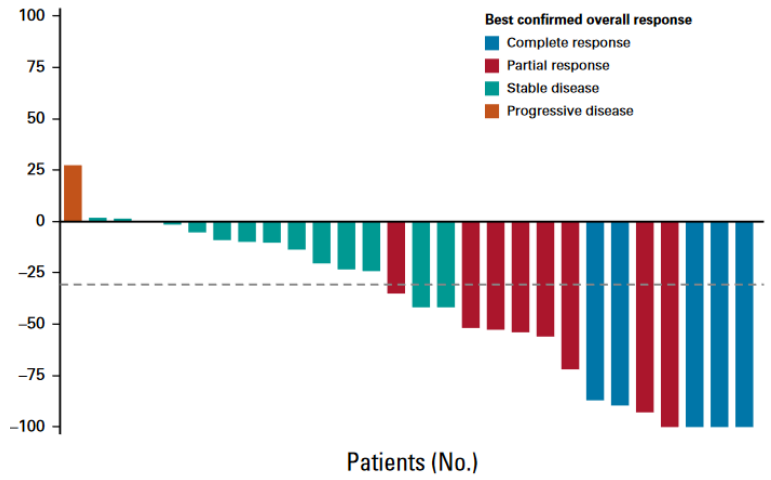
Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. + indicates a change greater than 100%. Horizontal dashed lines indicate 20% increase and 30% decrease in target lesion diameters from baseline for RECIST v1.1 assessment. Colored bars represent the best overall confirmed response. CR, PR, SD, and PD were based on RECIST v1.1 as evaluated by IRC.
CR, complete response; IRC, independent review committee; PD, disease progression; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SD, stable disease.

innovaTV 205/GOG-3024

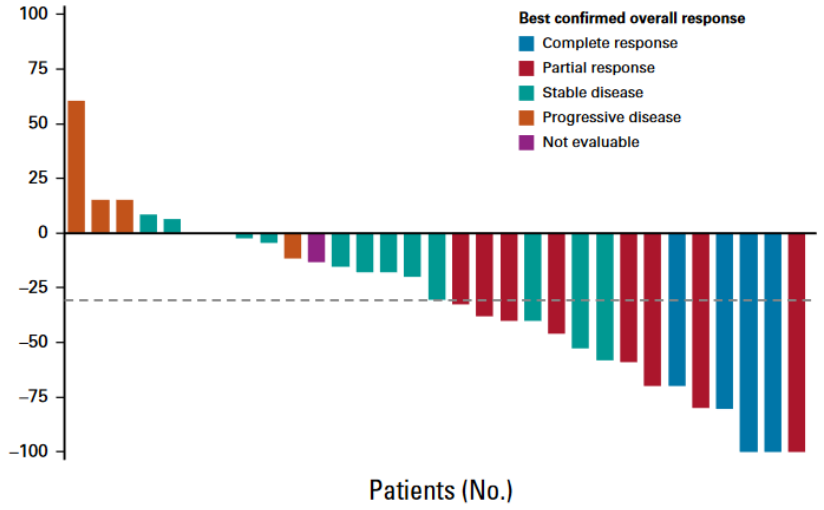
1st Line TV + Carboplatin



1st Line TV + Pembrolizumab

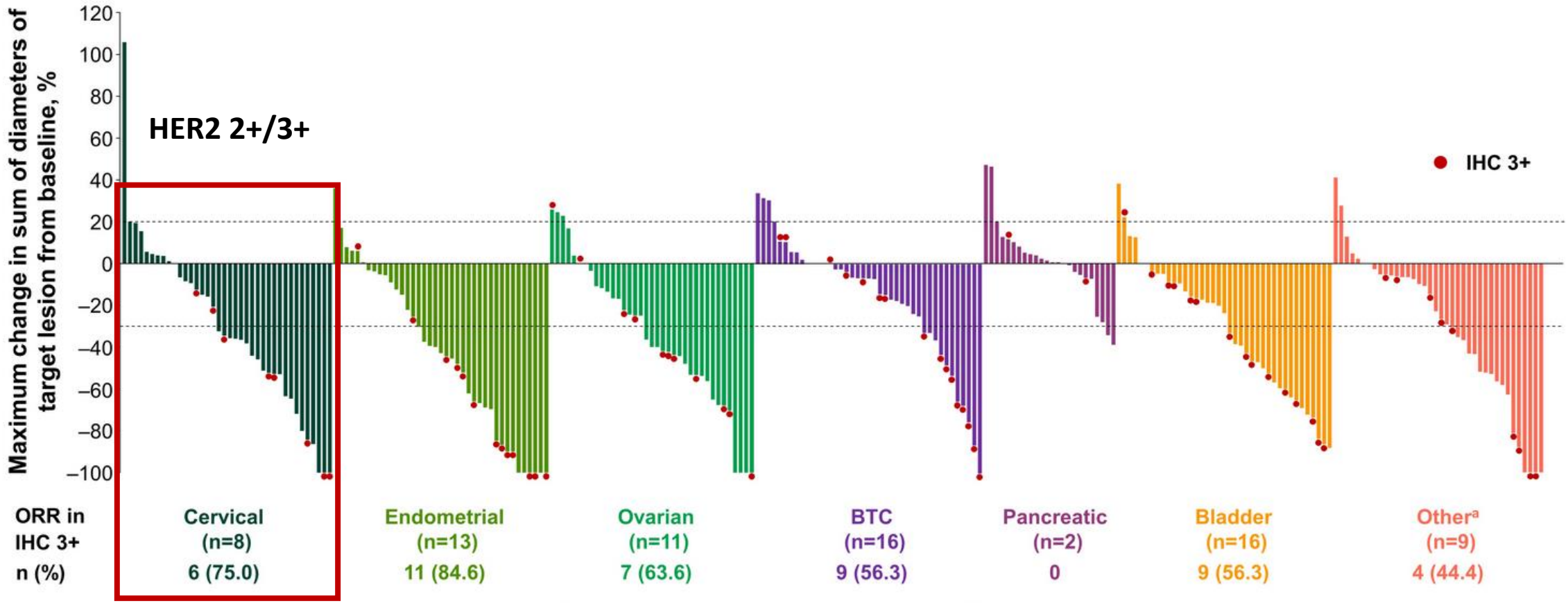


2nd/3rd Line TV + Pembrolizumab



Vergote et al, JCO 2023 Aug 31:JCO2300720

Best Percentage Change in Target Lesion From Baseline



Analyses were performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of ORR in IHC 3+ was performed in patients with centrally confirmed HER2 status (n=75).
[a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; IHC, immunohistochemistry; ORR, objective response rate.

Fortgeschrittenes Endometriumkarzinom

Fortgeschrittenes Endometrium-Karzinom

- **Immuntherapie in der Erstlinie**
- Immuntherapie in späteren Linien
- Anti-HER2-Therapie

EVIDENCE BLOCKS FOR SYSTEMIC THERAPY FOR RECURRENT DISEASE

FIRST-LINE THERAPY FOR RECURRENT DISEASE	
Preferred Regimens	
Carboplatin/paclitaxel	
Carboplatin/paclitaxel/trastuzumab (for recurrent HER2-positive uterine serous carcinoma)	
Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma)	
Carboplatin/paclitaxel/dostarlimab-gxly	
Carboplatin/paclitaxel/trastuzumab (for HER2-positive uterine serous carcinoma)	
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Other Recommended Regimens	
Carboplatin/docetaxel	
Carboplatin/paclitaxel/bevacizumab	
Useful in Certain Circumstances (Biomarker directed: after prior platinum-based therapy including neoadjuvant and adjuvant)	
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Pembrolizumab for TMB-H or MSI-H/dMMR tumors	
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SECOND-LINE OR SUBSEQUENT THERAPY	
Other Recommended Regimens	
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Cisplatin/doxorubicin/paclitaxel	
Cisplatin	
Carboplatin	
Doxorubicin	
Liposomal doxorubicin	
Paclitaxel	
Albumin-bound paclitaxel	
Topotecan	
Bevacizumab	
Temsirolimus	
Cabozantinib	
Docetaxel	
Ifosfamide (for carcinosarcoma)	
Ifosfamide/paclitaxel (for carcinosarcoma)	
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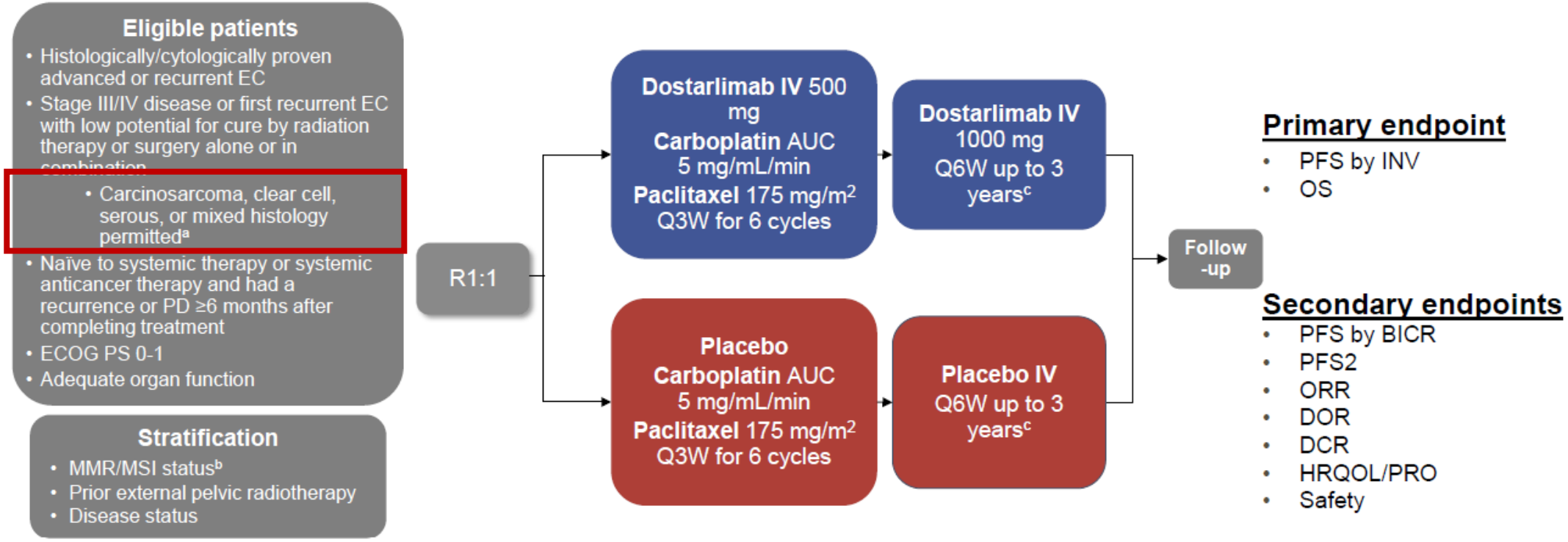
Avelumab for dMMR/MSI-H tumors	
Nivolumab for dMMR/MSI-H tumors	

*Evidence Block development in progress

RUBY: Chemotherapie +/- Dostarlimab

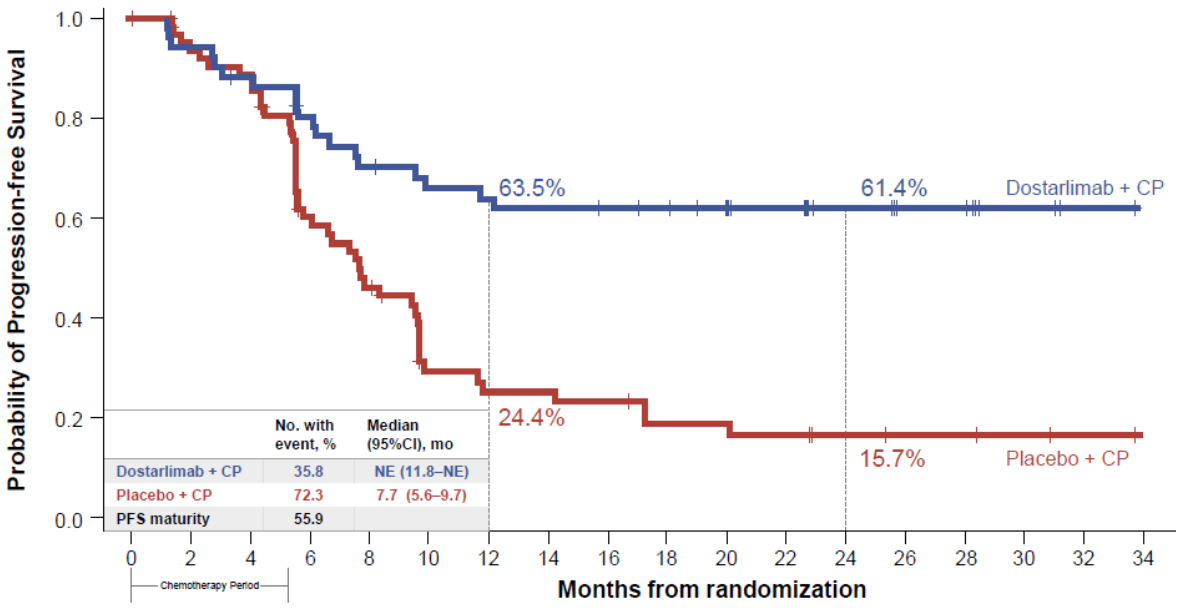
ENGOT-EN6-NSGO/GOG-3031/RUBY (NCT03981796)

Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin/paclitaxel in patients with primary advanced or recurrent EC

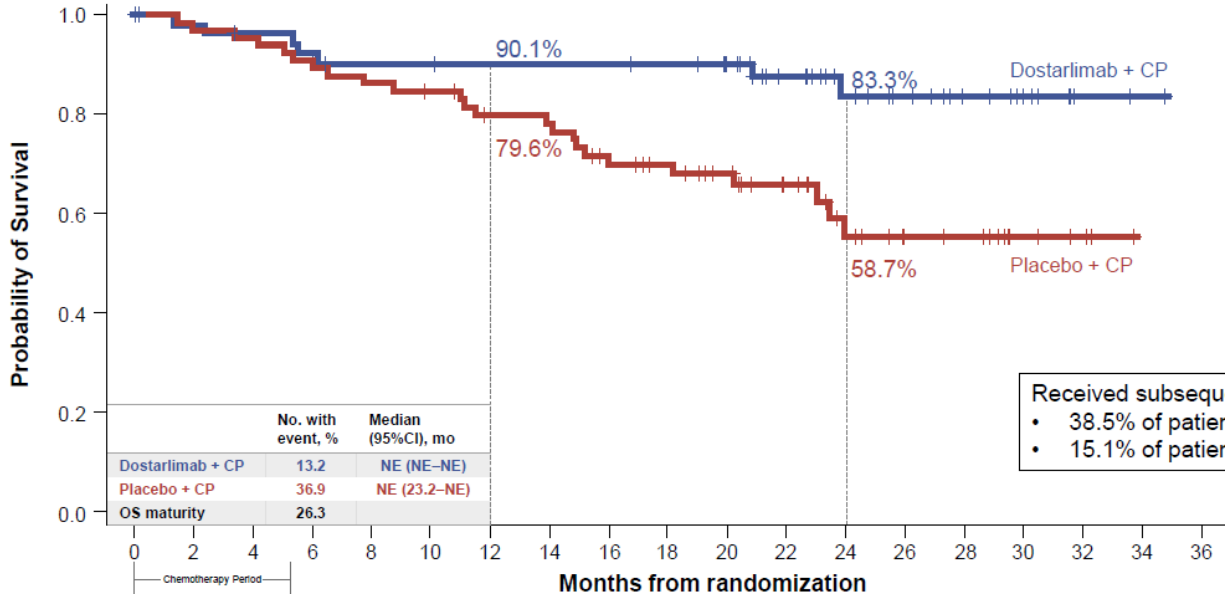


RUBY: 1st-Line Immuntherapie bei dMMR

PFS: HR 0,28; P <0,0001

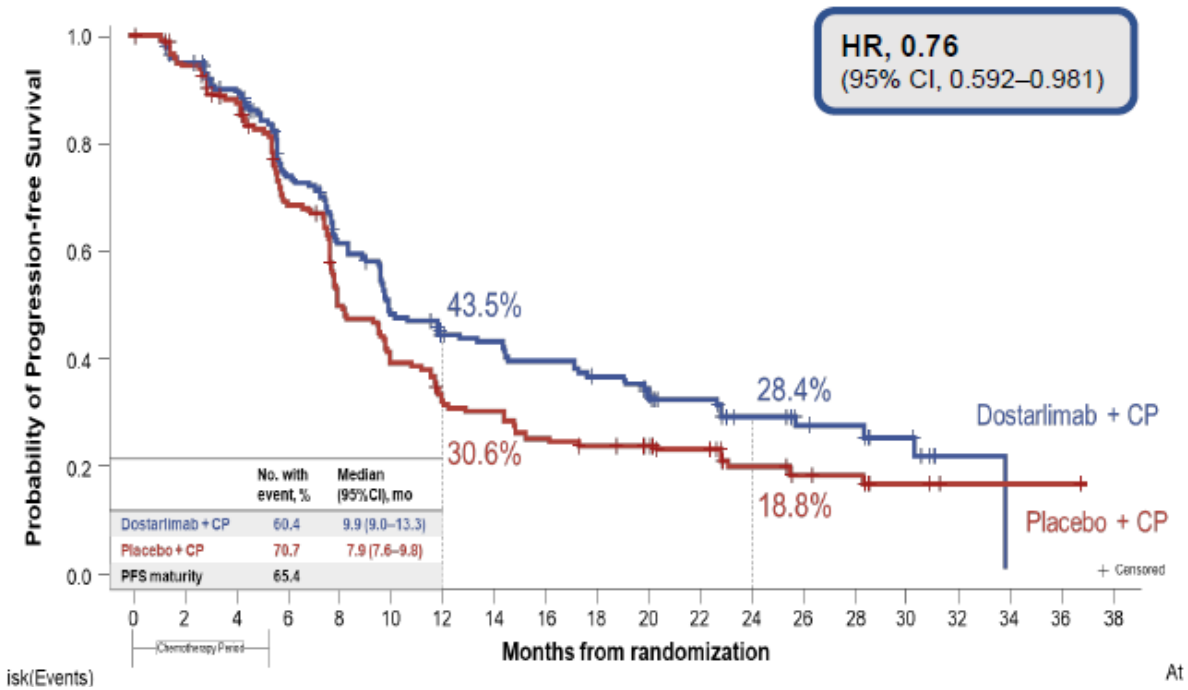


OS: HR 0,3 (CI 0,13-0,70)

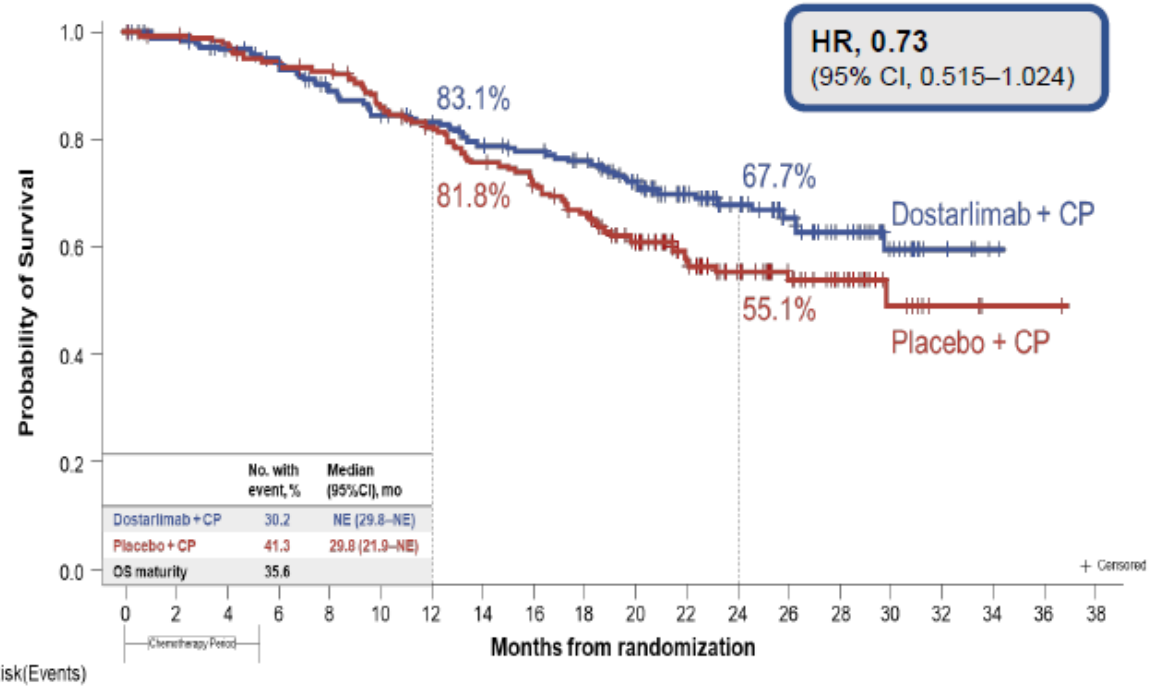


RUBY: 1st-Line Immuntherapie bei pMMR

PFS: HR 0,76 (CI 0,60-0,98)

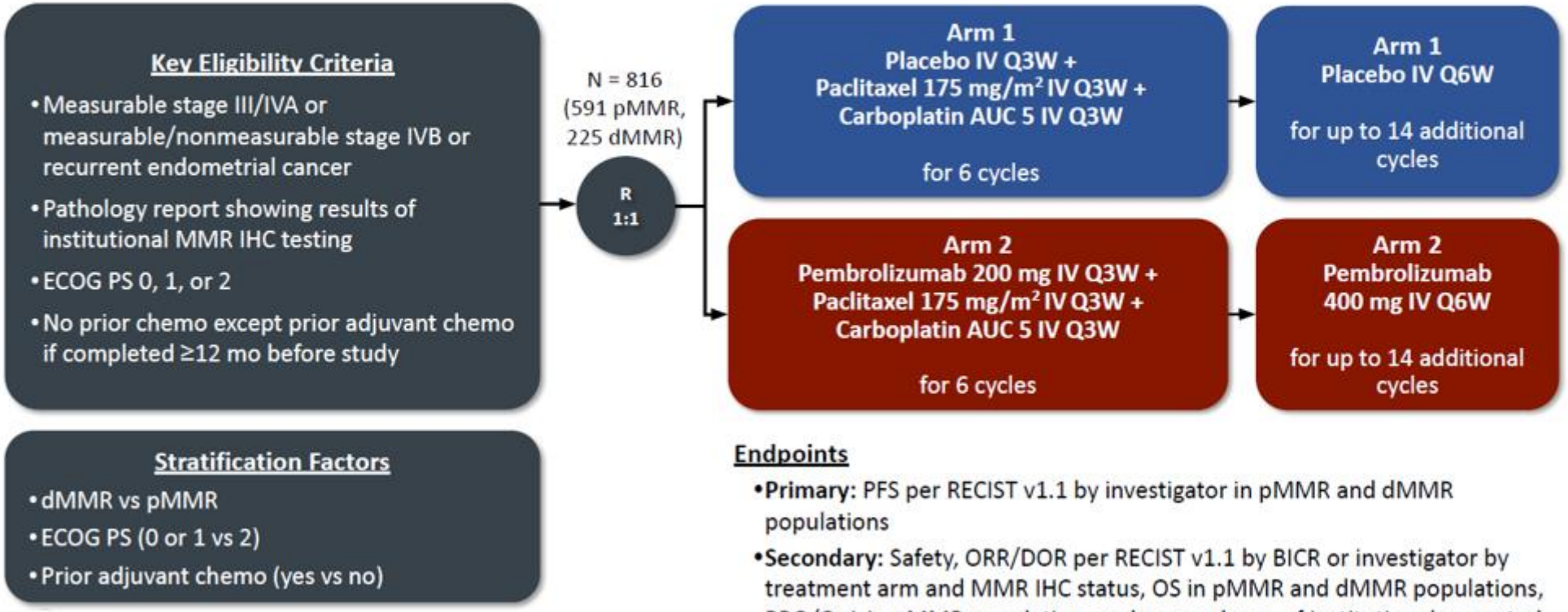


OS: HR 0,73 (CI 0,52-1,02)



KEYNOTE-868: Chemotherapie +/- Pembrolizumab

NRG-GY018/KEYNOTE-868 (NCT03914612)



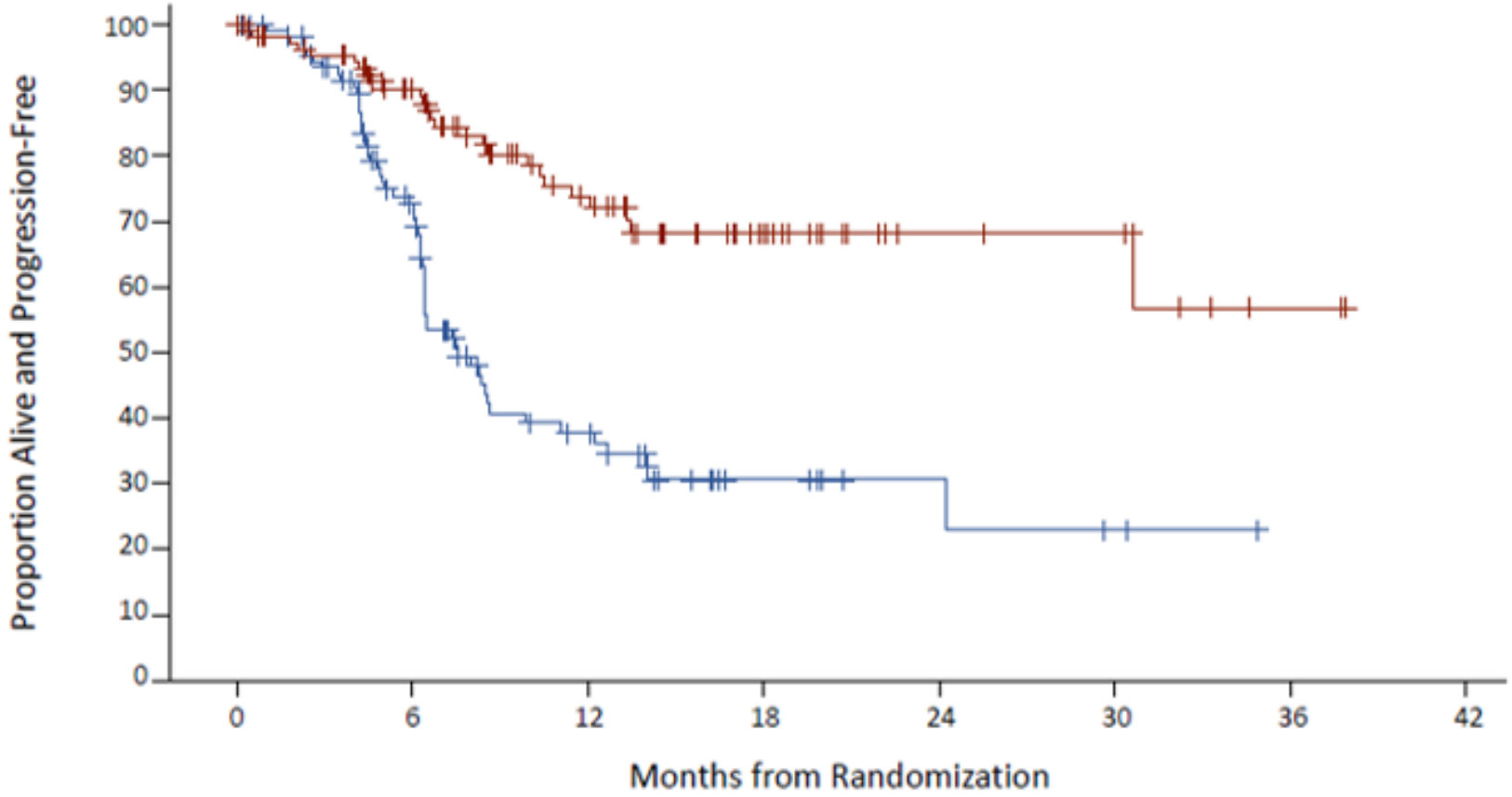
Endpoints

- **Primary:** PFS per RECIST v1.1 by investigator in pMMR and dMMR populations
- **Secondary:** Safety, ORR/DOR per RECIST v1.1 by BICR or investigator by treatment arm and MMR IHC status, OS in pMMR and dMMR populations, PRO/QoL in pMMR population, and concordance of institutional vs central MMR IHC testing results

R.N. Eskander et al. SGO 2023

KN 868: 1st-Line Immuntherapie bei dMMR

PFS: HR 0,30; P <0,00001

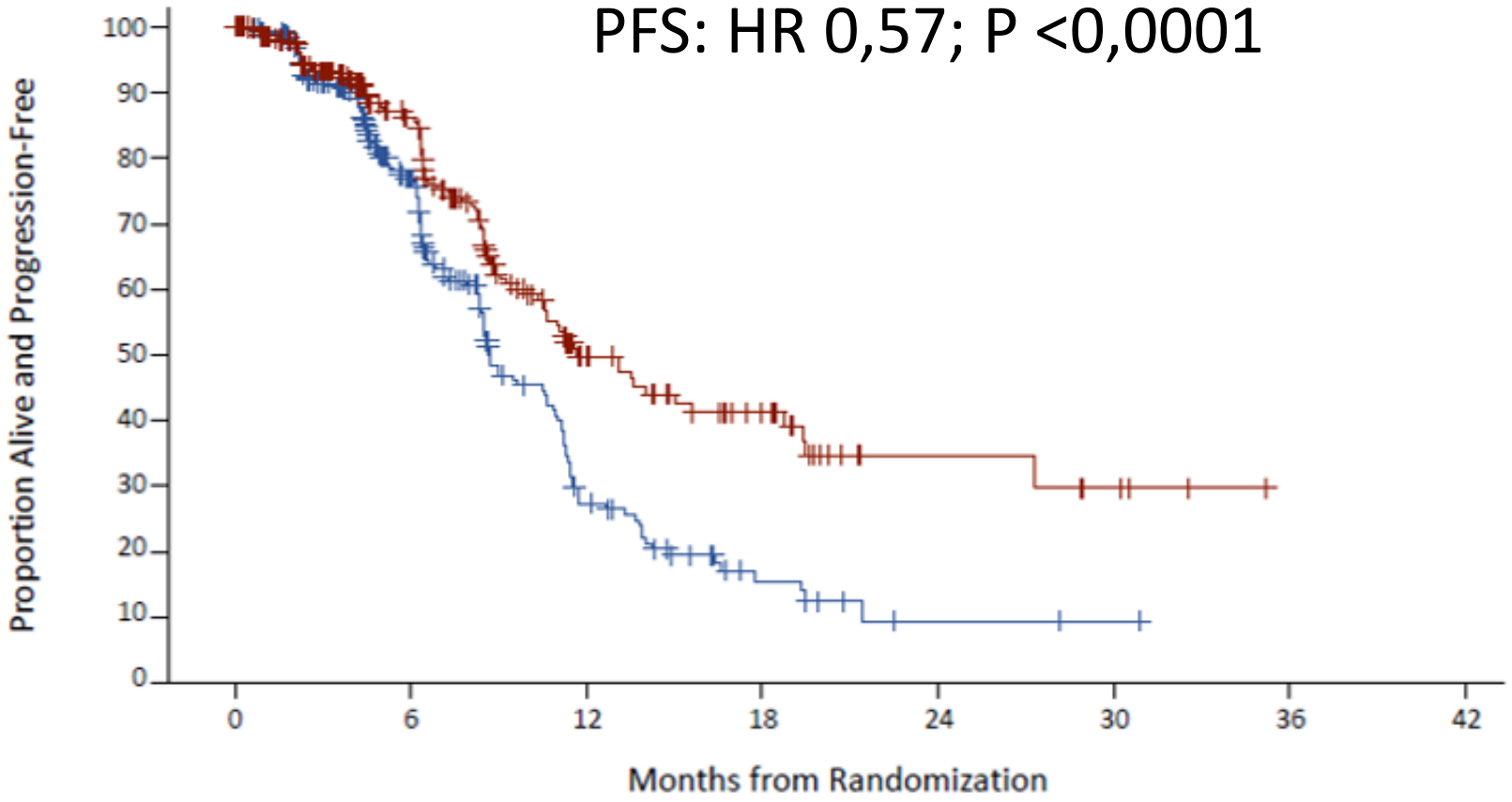


Keine OS-Daten

R.N. Eskander et al. SGO 2023

KN 868: 1st-Line Immuntherapie bei pMMR

PFS: HR 0,57; P <0,0001



Keine OS-Daten

R.N. Eskander et al. SGO 2023

Dostarlimab oder Pembrolizumab?

	RUBY – DOSTARLIMAB	KN 868 - PEMBROLIZUMAB
Karzinosarkome	10%	-
Nicht-endometrioide Histologie	45%	20%
ECOG	0-1	0-2
Zeit seit adjuvanter Chemotherapie	≥ 6 Monate	≥ 12 Monate
Therapiedauer	3 Jahre	2 Jahre
PFS (HR)	dMMR: 0,28 pMMR: 0,76	dMMR: 0,30 pMMR: 0,50
OS (HR)	dMMR: 0,30 pMMR: 0,73	

Fortgeschrittenes Endometrium-Karzinom

- Immuntherapie in der Erstlinie
- **Immuntherapie in späteren Linien**
- Anti-HER2-Therapie

Immuntherapie beim EC ≥ Zweitlinie

Studie	Medikament	N	RR (%)	N	RR (%)
		dMMR		pMMR	
Keynote 158	Pembrolizumab	49	57%	107	11%
GARNET	Dostarlimab	143	46%	156	15%
PHAEDRA	Durvalumab	35	43%	36	3%
Konstantinopoulos	Avelumab	15	27%	16	6%

Marabelle et al. JCO2019; Oaknin, ASCO 2022; Antill ASCO 2019 ; Konstantinopoulos ASCO 2019, Makker NEJM 2022

Immuntherapie beim EC ≥ Zweitlinie

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PHAEDRA	Durvalumab	35	43%	36	3%
Konstantinopoulos	Avelumab	15	27%	16	6%
Keynote 775	Pembrolizumab + Lenvatinib	65	42%	346	32%

Marabelle et al. JCO2019; Oaknin, ASCO 2022; Antill ASCO 2019 ; Konstantinopoulos ASCO 2019, Makker NEJM 2022

Study Design

Keynote 775

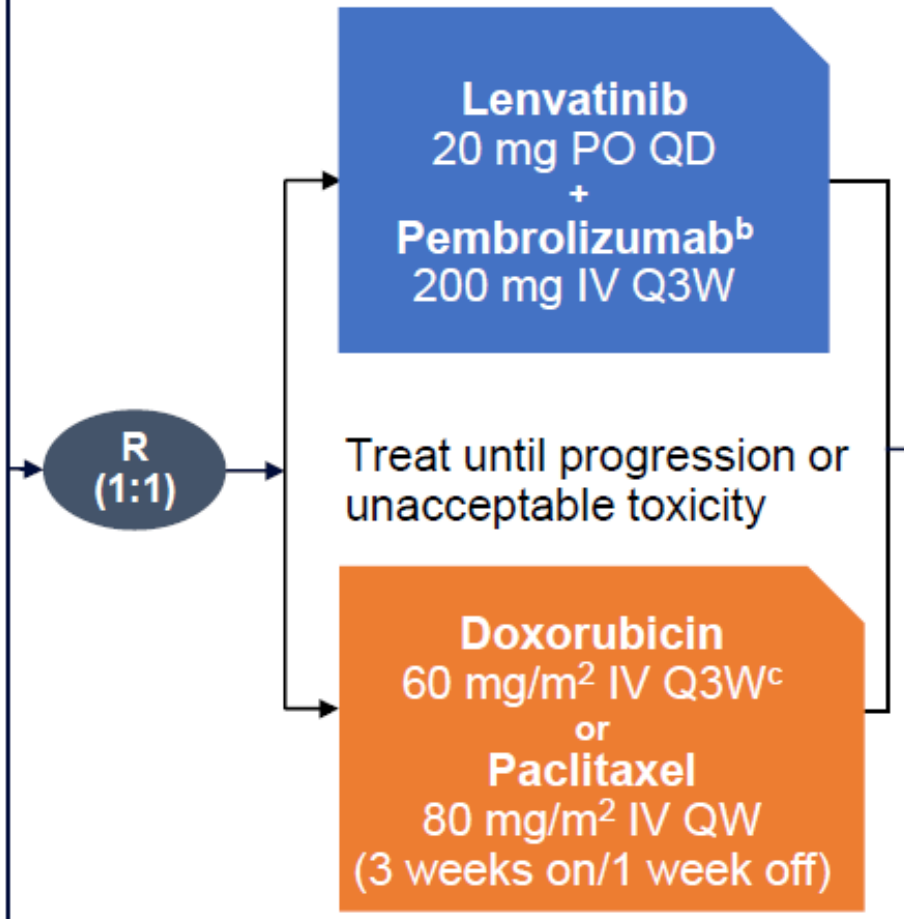
Key eligibility criteria

- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- 1 Prior platinum-based CT[a]
- ECOG PS 0-1
- Tissue available for MMR testing

Stratification factors

MMR status (pMMR vs dMMR) and further stratification within pMMR by:

- Region (R1: Europe, USA, Canada, Australia, New Zealand, and Israel, vs R2: rest of the world)
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (Y vs N)



Primary endpoints

- PFS by BICR
- Overall survival

Secondary endpoints

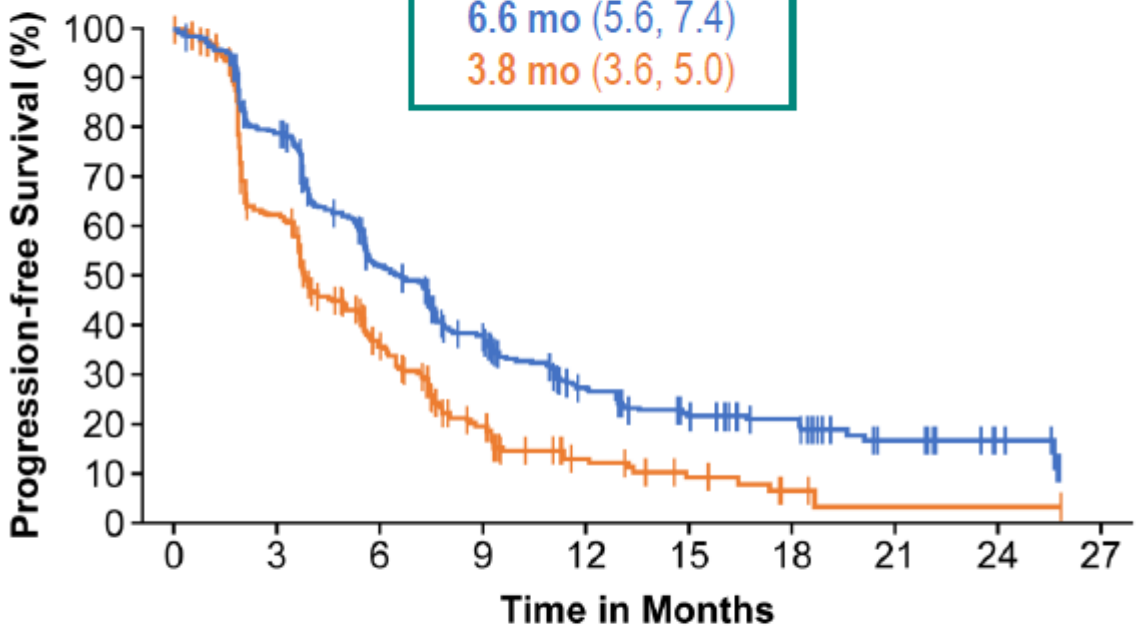
- ORR
- HRQoL
- Pharmacokinetics
- Safety

Key exploratory endpoint

- Duration of response

Progression-free Survival[a]

pMMR

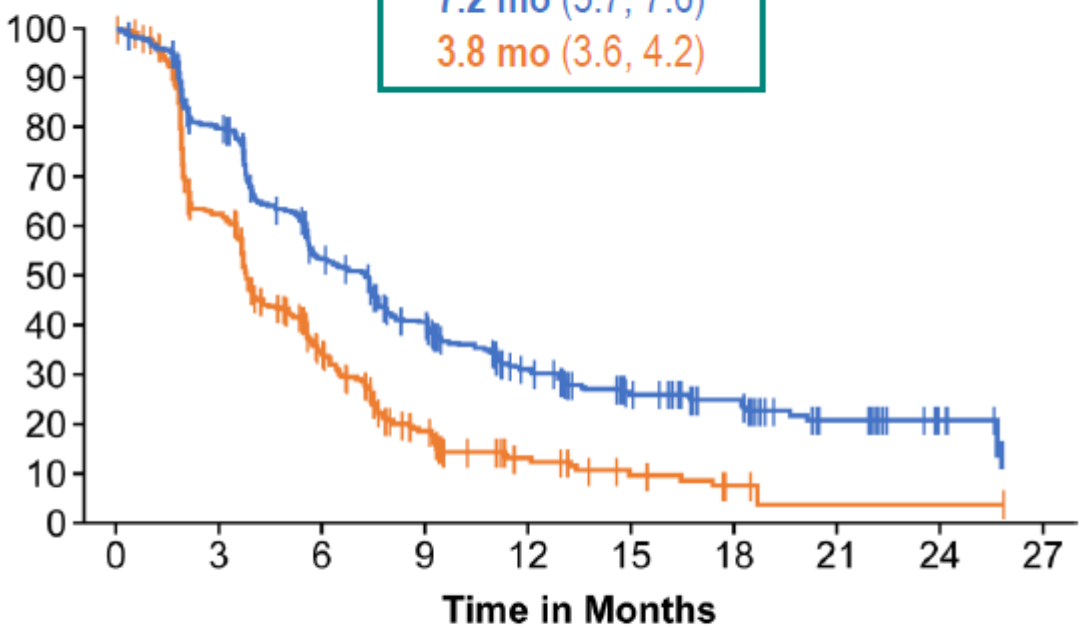


No. at risk

346	264	165	112	60	39	30	12	5	0
351	177	83	37	15	8	3	1	1	0

	Events	HR (95% CI)	*P*-value
LEN + pembro	247	**0.60** (0.50, 0.72)	< 0.0001
TPC	238		

All-comers



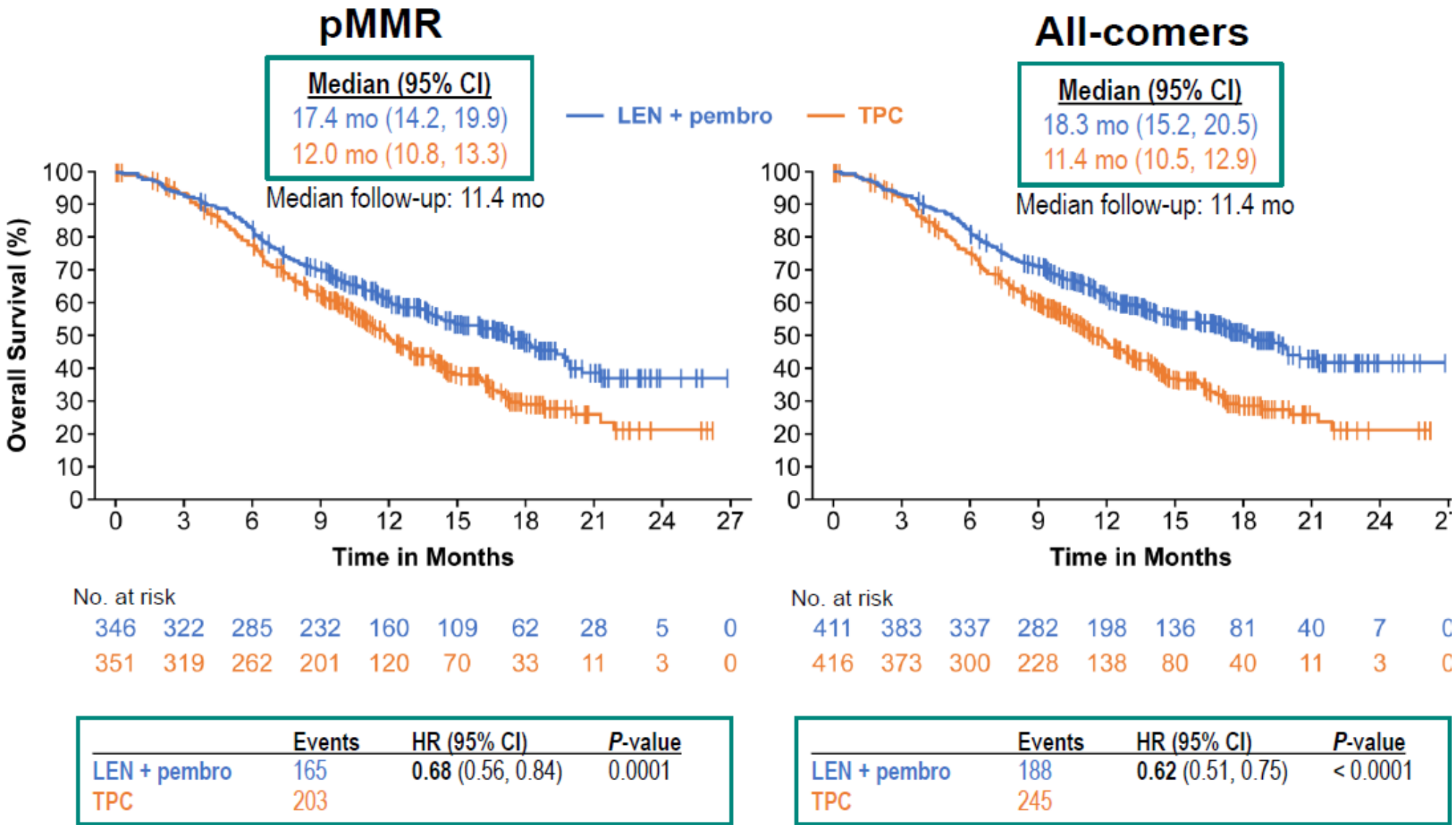
No. at risk

411	316	202	144	86	56	43	17	6	0
416	214	95	42	18	10	4	1	1	0

	Events	HR (95% CI)	*P*-value
LEN + pembro	281	**0.56** (0.47, 0.66)	< 0.0001
TPC	286		

Makker NEJM 2022

Overall Survival



	Events	HR (95% CI)	*P*-value
LEN + pembro	165	**0.68** (0.56, 0.84)	0.0001
TPC	203		

	Events	HR (95% CI)	*P*-value
LEN + pembro	188	**0.62** (0.51, 0.75)	< 0.0001
TPC	245		

Fortgeschrittenes Endometrium-Karzinom

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Albumin-bound paclitaxel	
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Nivolumab for dMMR/MSI-H tumors	

S3-Leitlinie Endometriumkarzinom

Kurzversion 2.0 – September 2022
AWMF-Registernummer: 032/034-OL

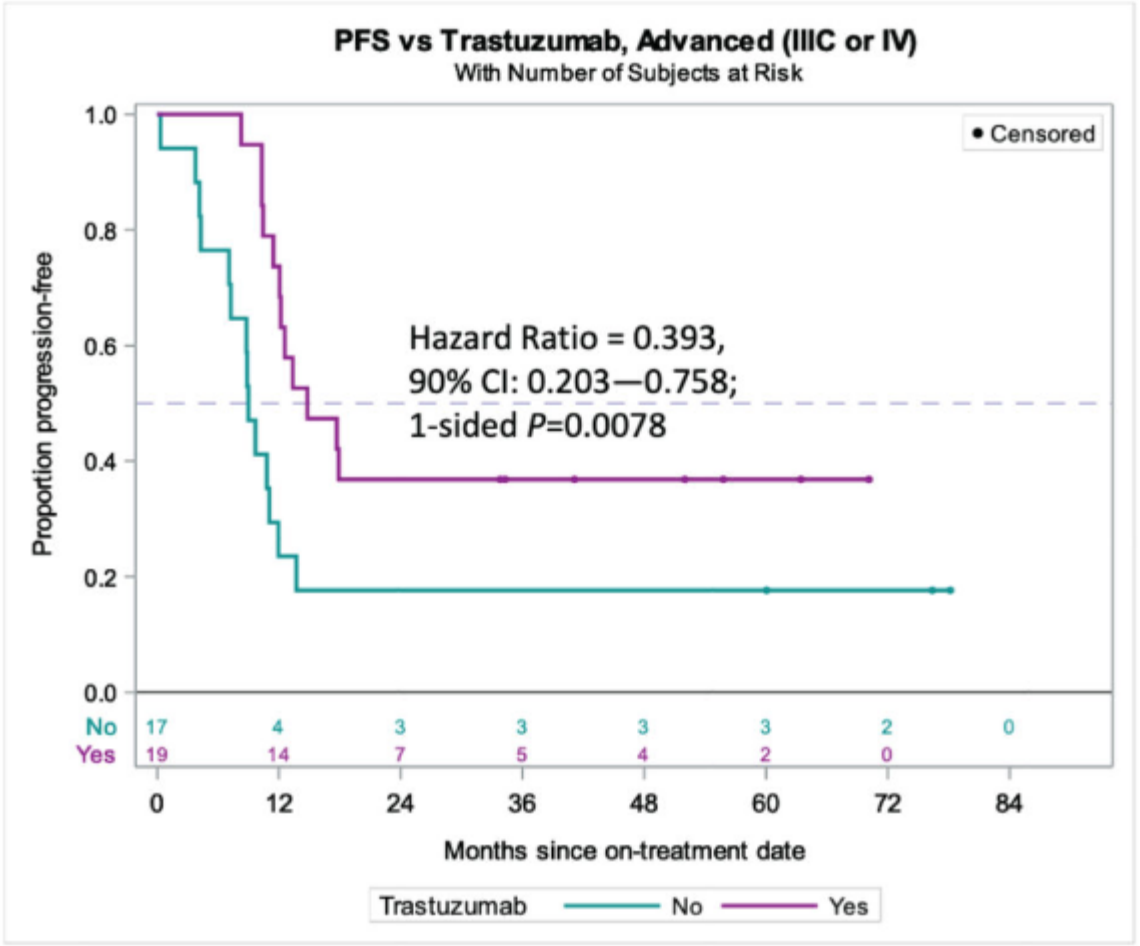
9.5 Chemotherapie beim Rezidiv

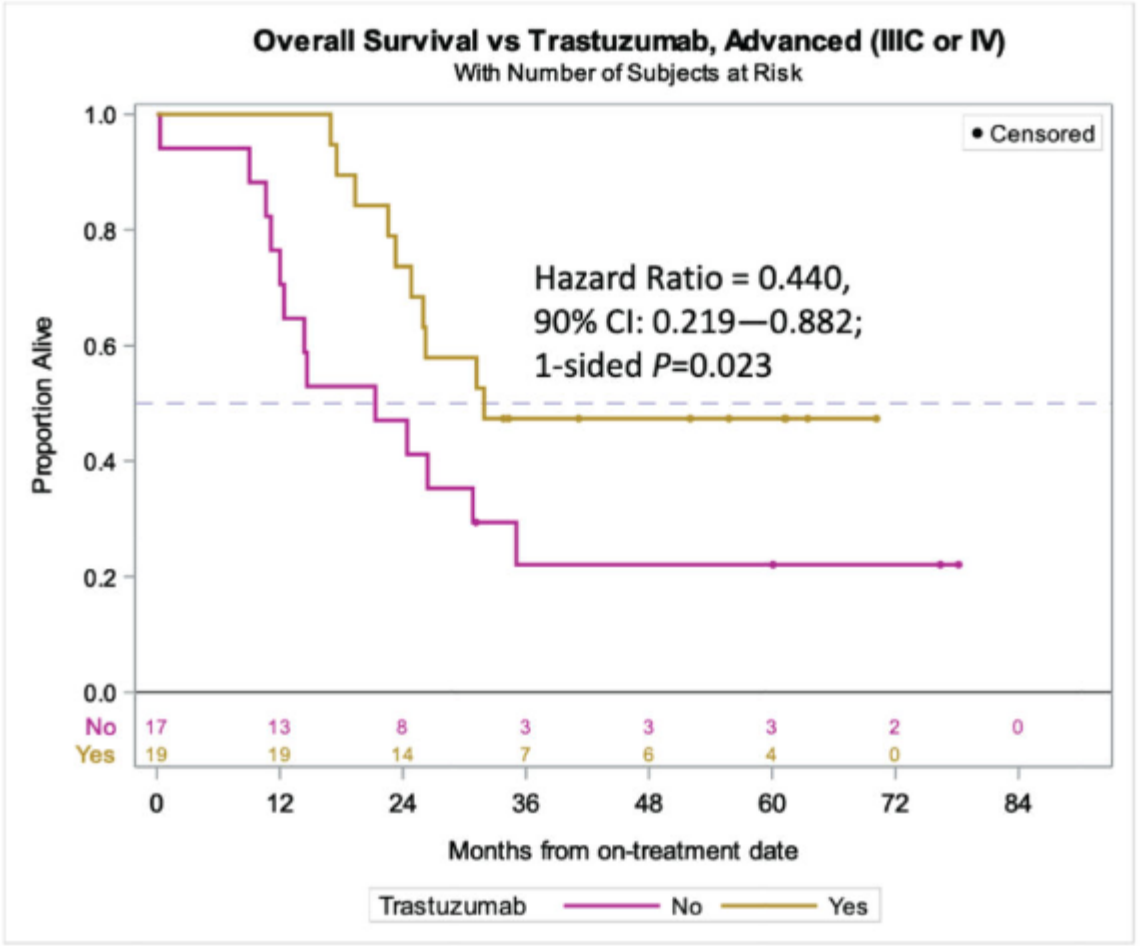
Nr.	Empfehlungen/Statements	GoR	LoE	Quellen
9.16	Eine Chemotherapie kann bei Frauen mit lokal nicht therapierbarem EC-Rezidiv oder bei Fernmetastasierung durchgeführt werden.	0	1	[80]; [188]
9.17	Die Überlegenheit eines bestimmten Chemotherapieregimes bei Frauen mit Rezidiv nach Endometriumkarzinom ist nicht erwiesen. Als äquieffektive Substanzen zur chemotherapeutischen Therapie eines fortgeschrittenen oder rezidivierten Endometriumkarzinoms haben sich die Kombinationen Carboplatin/Paclitaxel und Doxorubicin/Cisplatin/Paclitaxel erwiesen. Aufgrund der besseren Verträglichkeit soll Carboplatin (AUC 6) mit Paclitaxel (175 mg/m2) verwendet werden.	A	2	[188]; [166]

9.6 Immuntherapie beim Rezidiv des Endometriumkarzinoms

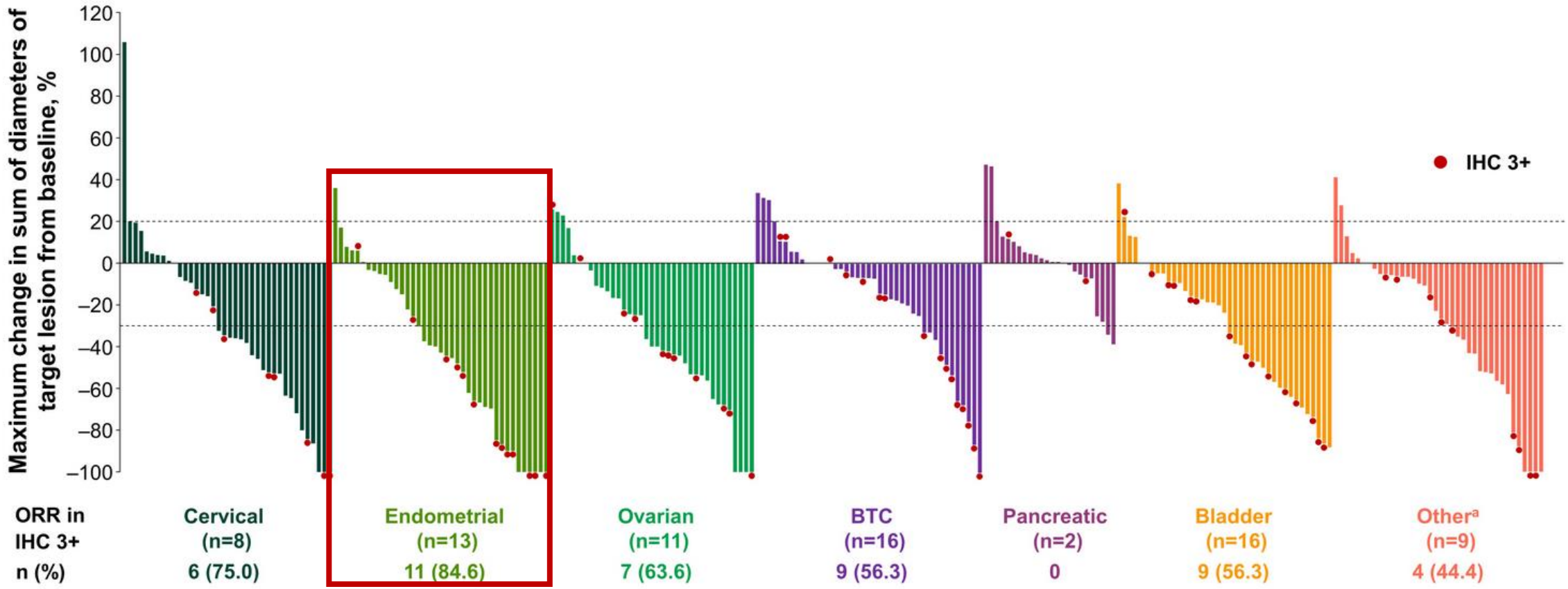
Nr.	Empfehlungen/Statements	GoR	LoE	Quellen
9.18	Bei Patientinnen mit lokal fortgeschrittenem oder rezidiviertem serösen Endometriumkarzinom mit her2/neu-Überexpression kann eine systemische Chemotherapie mit Carboplatin (AUC 5) und Paclitaxel (175 mg/m2) kombiniert mit Trastuzumab (8 mg/kg als Erstdosis, gefolgt von 6 mg/kg als Erhaltungstherapie) durchgeführt werden.	0	2	[189]
9.19	Bei Patientinnen mit rezidiviertem oder primär fortgeschrittenem Endometriumkarzinom mit mikrosatelliten-stabilem/mismatch-repair-funktionellem Tumorgewebe und Progression nach mindestens einer Linie Chemotherapie sollte eine kombinierte Immun- und Multikinase-Inhibitortherapie mit Pembrolizumab (200 mg i.v. d1, q21 oder 400 mg i.v. d1, q42) und Lenvatinib (20 mg p.o. 1 x tgl.) durchgeführt werden. Die hohe Toxizität ist zu beachten.	B	2	[190]; [191]
9.20	Bei Patientinnen mit rezidiviertem oder primär fortgeschrittenem Endometriumkarzinom mit mikrosatelliten-instabilem/mismatch-repair-defizientem Tumorgewebe (MSI-H oder dMMR) kann nach einer Vorbehandlung durch eine platinbasierte Chemotherapie eine Immuntherapie mit Dostarlimab (4 Zyklen 500mg i.v. d1, q3w gefolgt von 1000mg i.v. d1, q6w) oder mit Pembrolizumab (200 mg i.v. d1, q21 oder 400 mg i.v. d1, q42) durchgeführt werden.	0	3	[192]; [193]; [194]; [195]

Carbo/Taxol +/- Trastuzumab (Phase II)





Best Percentage Change in Target Lesion From Baseline



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BTC, biliary tract cancer; IHC, immunohistochemistry; ORR, objective response rate.

Vielen Dank!

1. MEDIZINISCHE ABTEILUNG
Zentrum für Onkologie und Hämatologie
mit Ambulanz und Palliativstation

WCRI Wilhelminen Cancer Research Institute

VCC Vienna Cancer Center

Wiener Gesundheitsverbund
Klinik Ottakring

Für die Stadt Wien