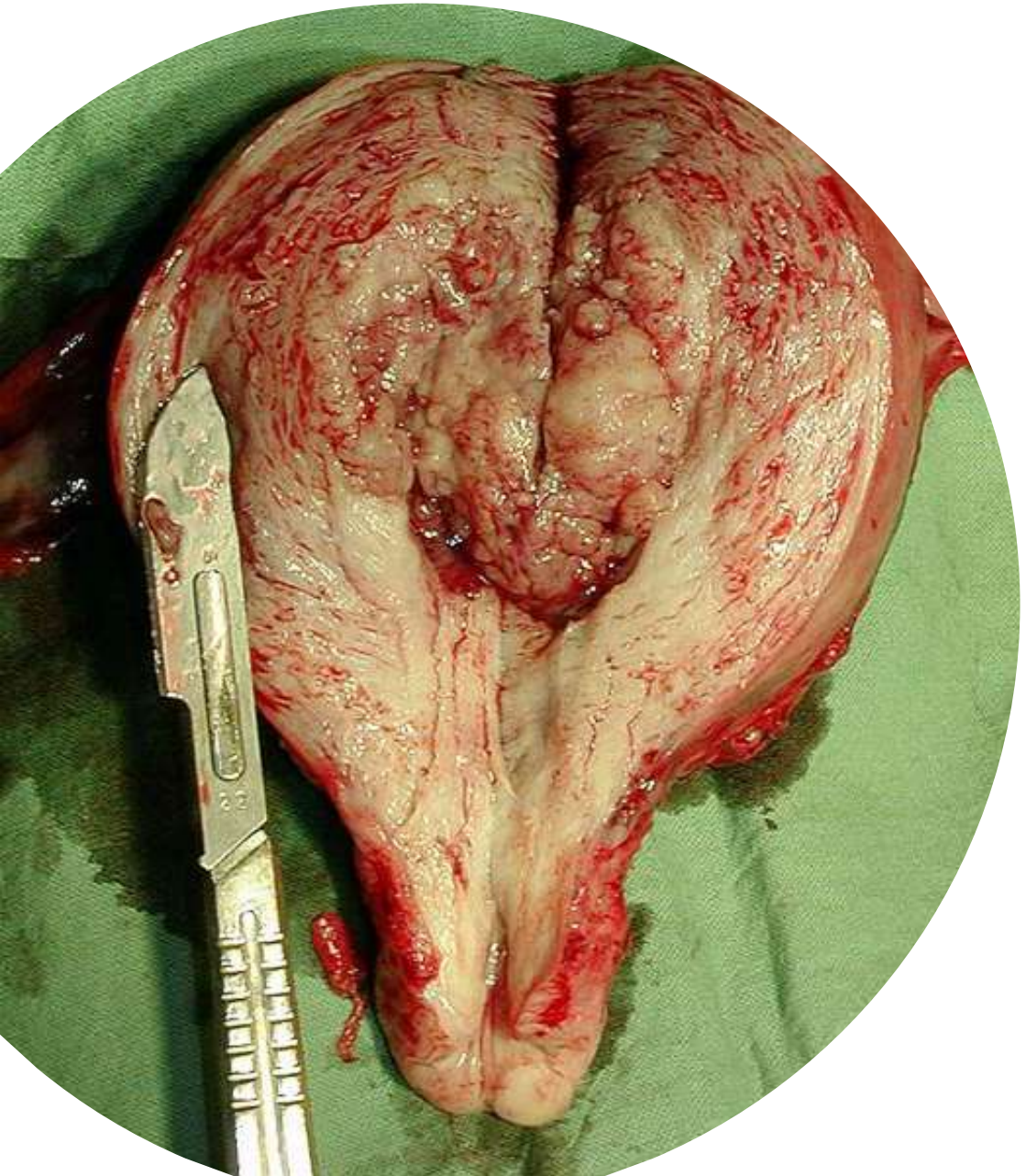
Pokroky v léčbě gynekologických nádorů

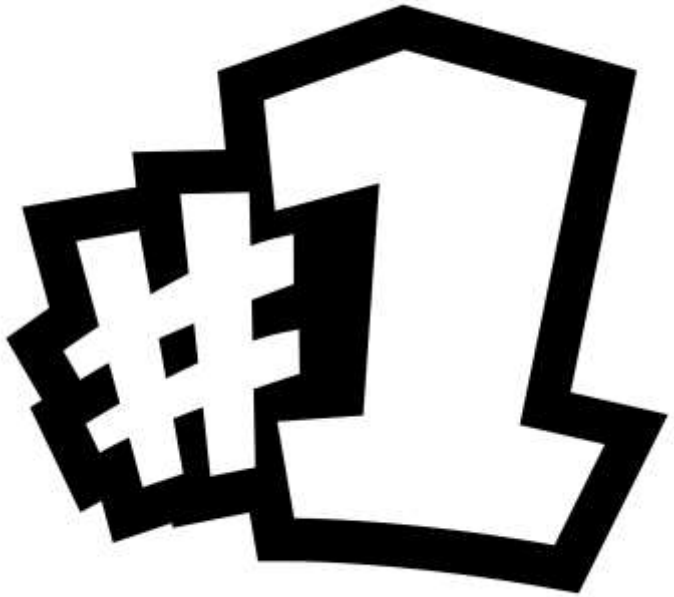
Igor Sirák, FN Hradec Králové

Disclosure:

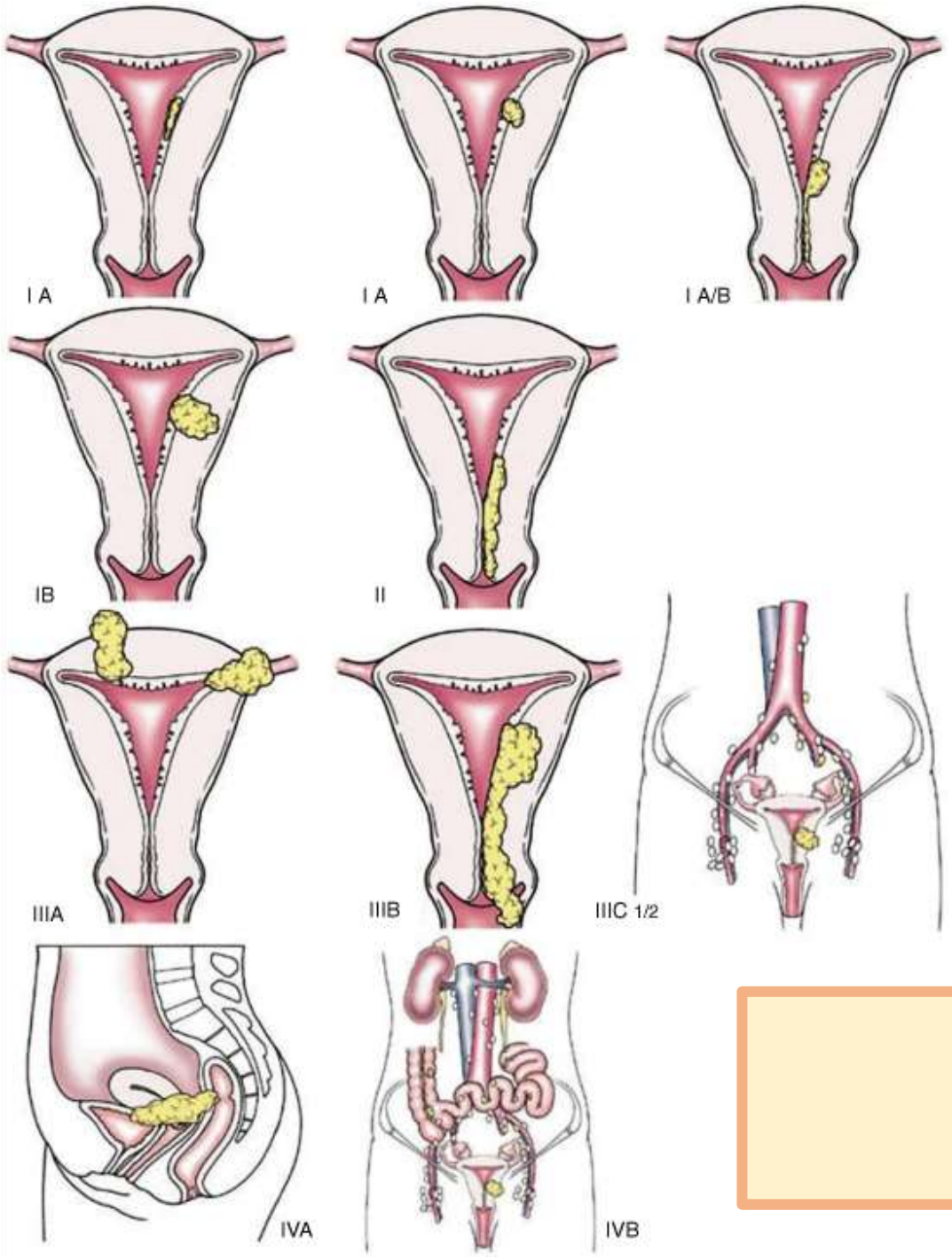
- budu zde vyzdvihovat účinky nových a drahých léků

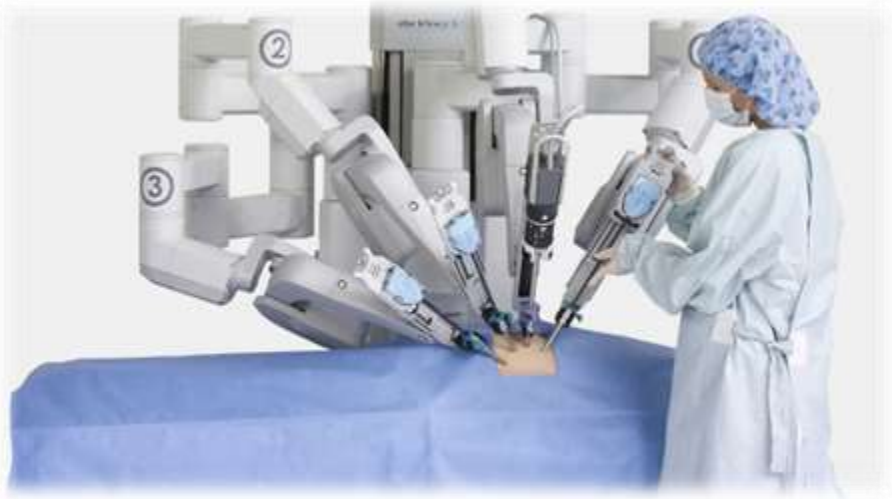
(a nedostal jsem za to ani korunu)

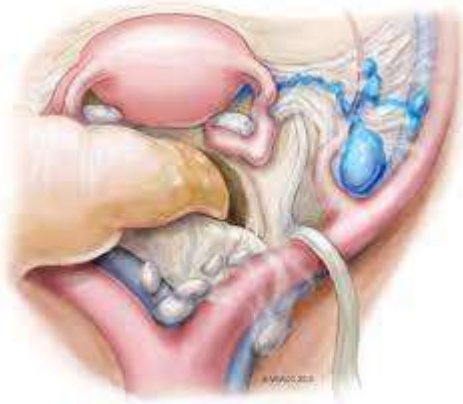




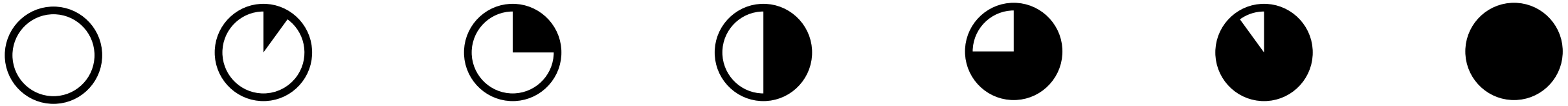
Karcinom endometria







Adjuvantní terapie



Histologie | Grade | Hloubka invaze | LVSI | Velikost Tumoru | Postižení dolního segmentu | Věk

Nízké riziko:

- stadium IA, G1-2, endometroidní → Operace samotná

Střední riziko:

- stadium IB, grade 1-2, endometroidní
- stadium IA, grade 3, endometroidní

→ Vaginální brachyterapie

Vyšší střední riziko: + rizikové faktory (LVSI) → Radioterapie pánve

Vysoké riziko:

- stadium IB, grade 3, endometroidní
- stadium II a III, endometroidní
- stadium I-III serózní a světlobuněčné

→ Radioterapie +/- chemoterapie

Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer – A pooled analysis of PORTEC 1 and 2 trials

Bosse et al European Journal of Cancer 2015

- N=926
- LVSI seen in 13.9%, substantial LVSI in 4.8%
- Therapeutic decisions should be based on the presence of substantial, not 'any' LVSI.

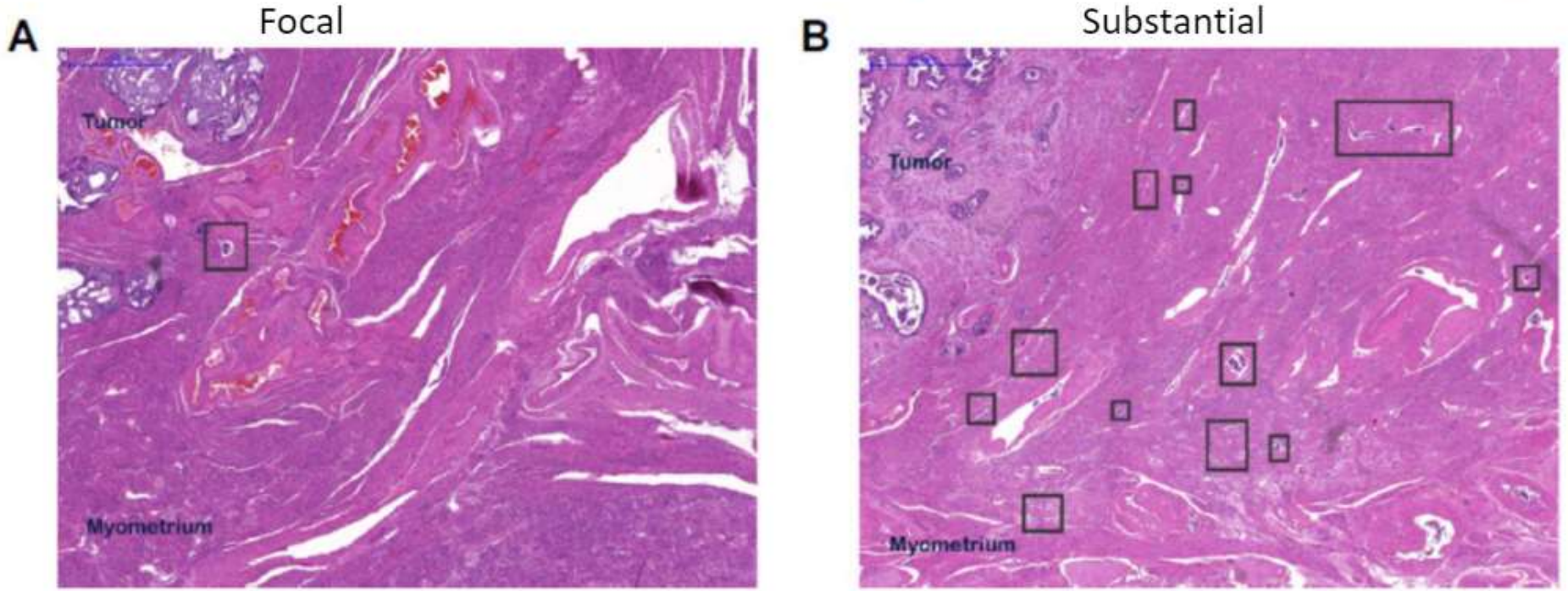
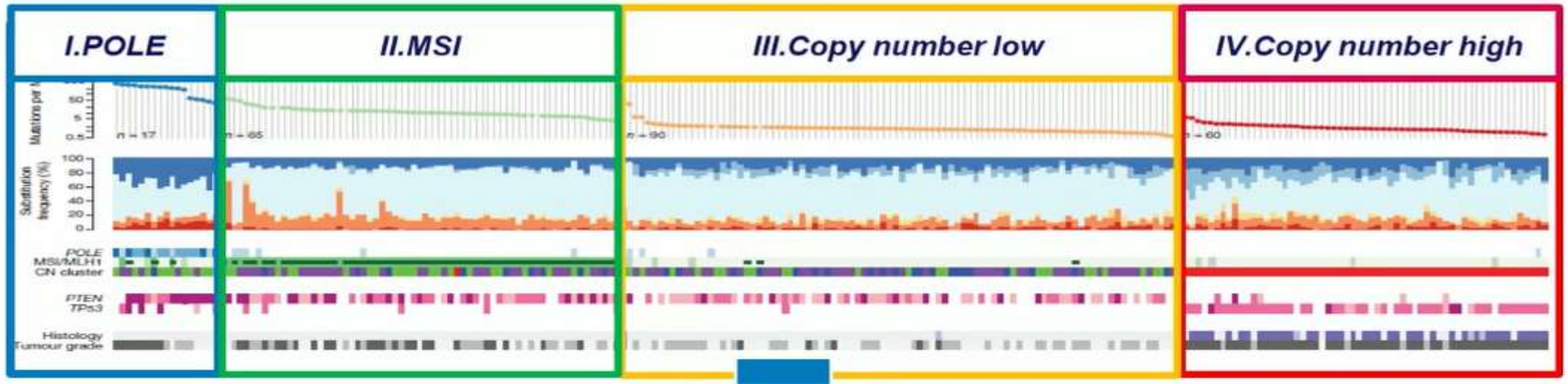
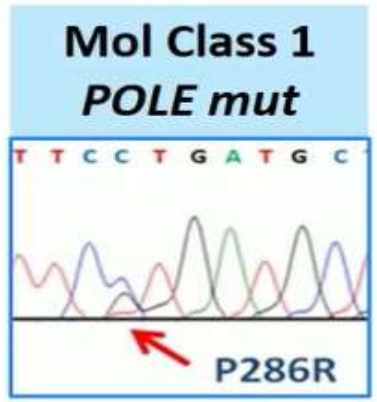


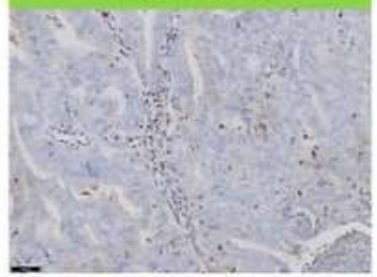
Fig. 1. Representative pictures of haematoxylin & eosin (H&E) stained slides (magnification 2.5×) illustrating how the 3-tiered scoring was applied. Representative examples of focal (A) and substantial (B) Lymph-vascular space invasion (LVSI). Black boxes indicate foci of LVSI.

ProMisE molecular classifier

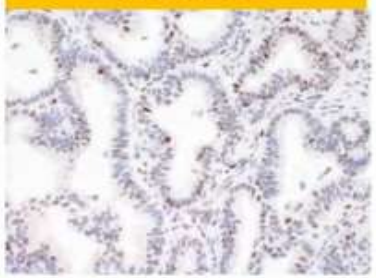




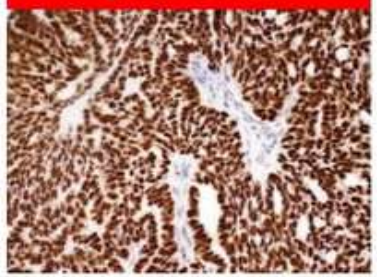
Mol Class 1
POLE mut



Mol Class 2
MMRd



Mol Class 3
NSMP



Mol Class 4
p53*abn*

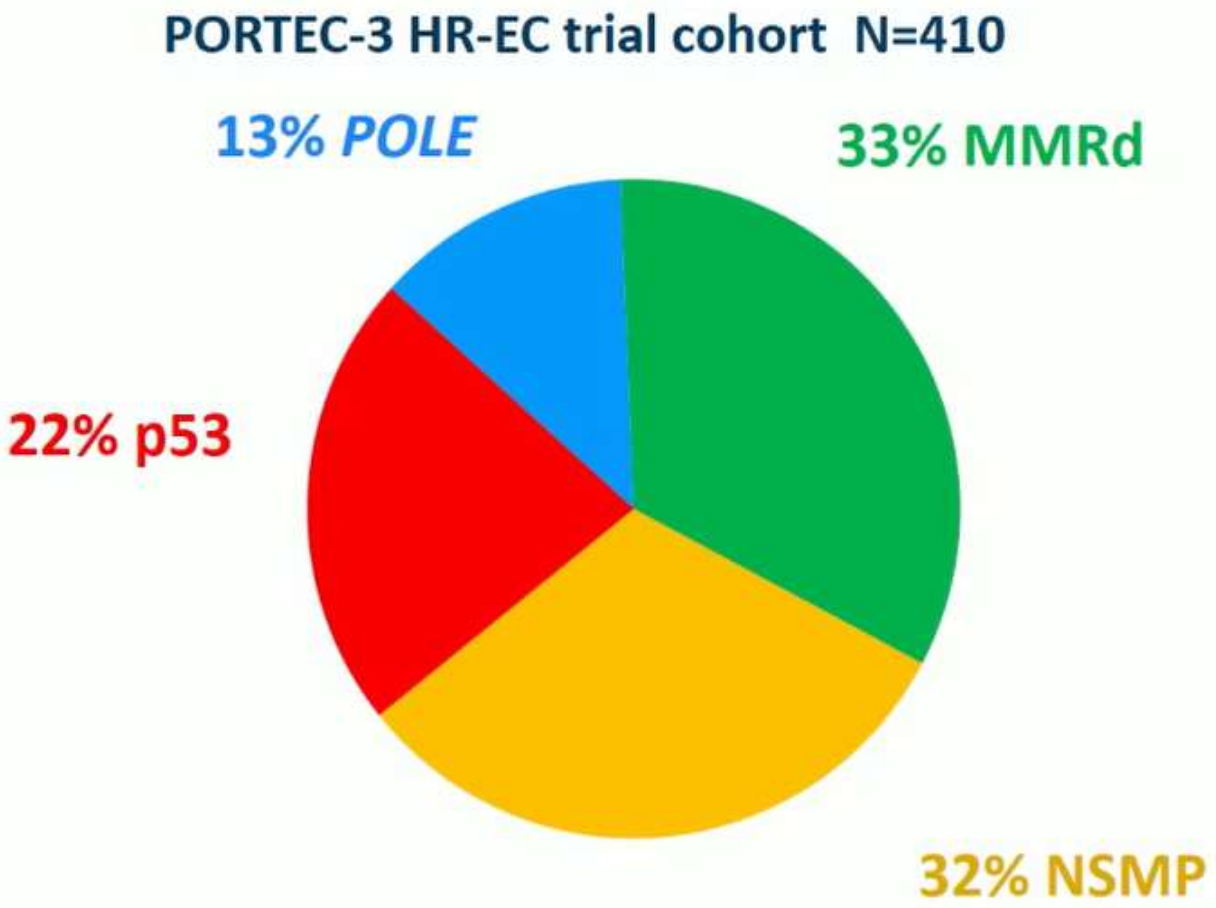
Ultramutated	Hypermutated	Several mutations	p53

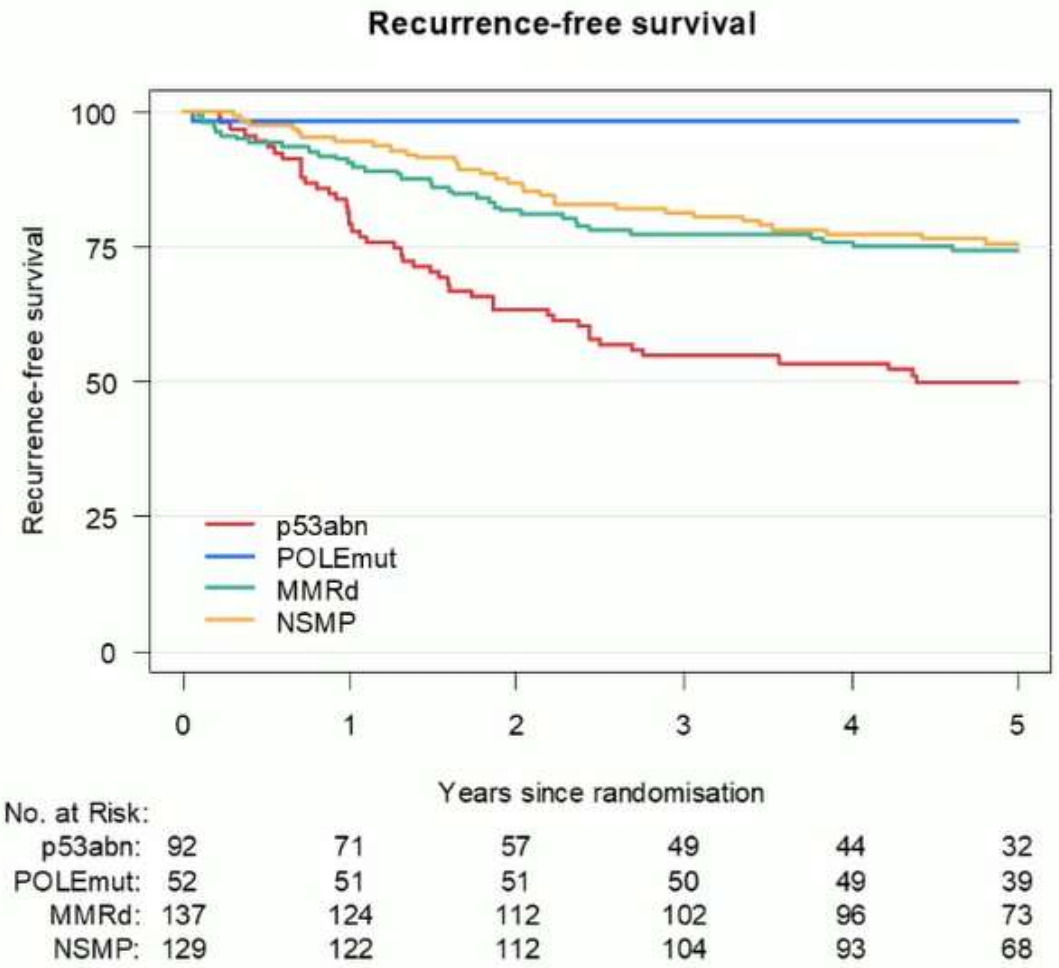
Tumor grade

1	2-3	1	2-3	1	2-3	1	2-3

Prognosis

PORTEC 3 (post-hoc analysis)

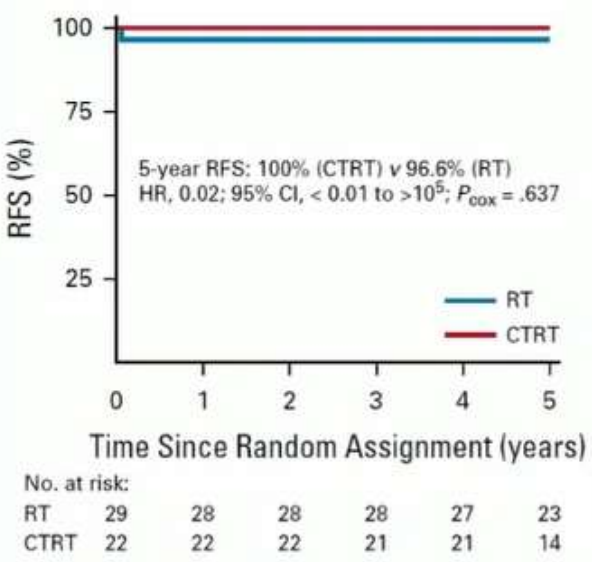




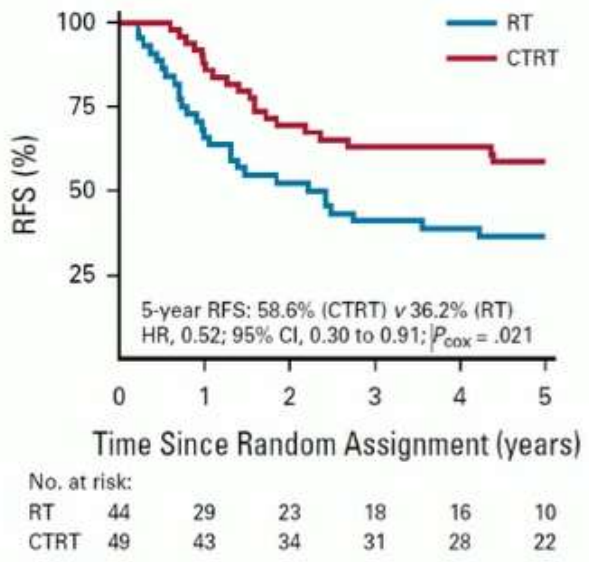
Leon-Castillo, JCO 2020

PORTEC 3 (post-hoc analysis)

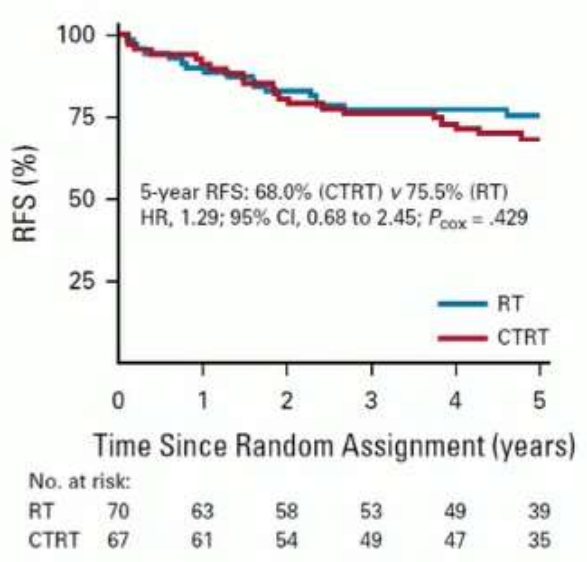
*POLE*mut



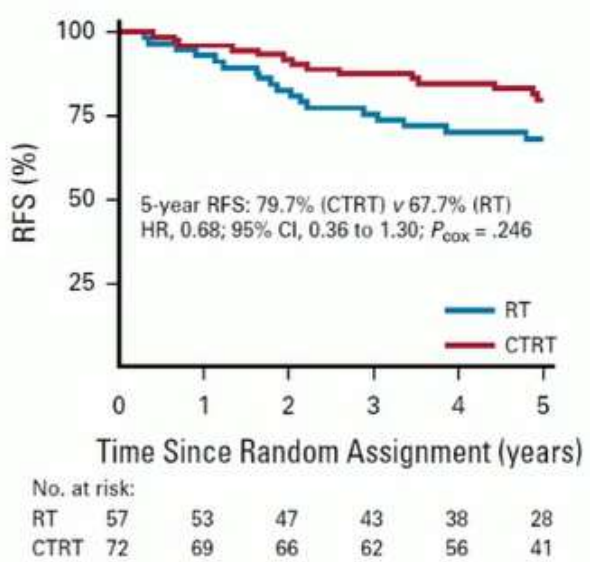
p53abn



MMRd



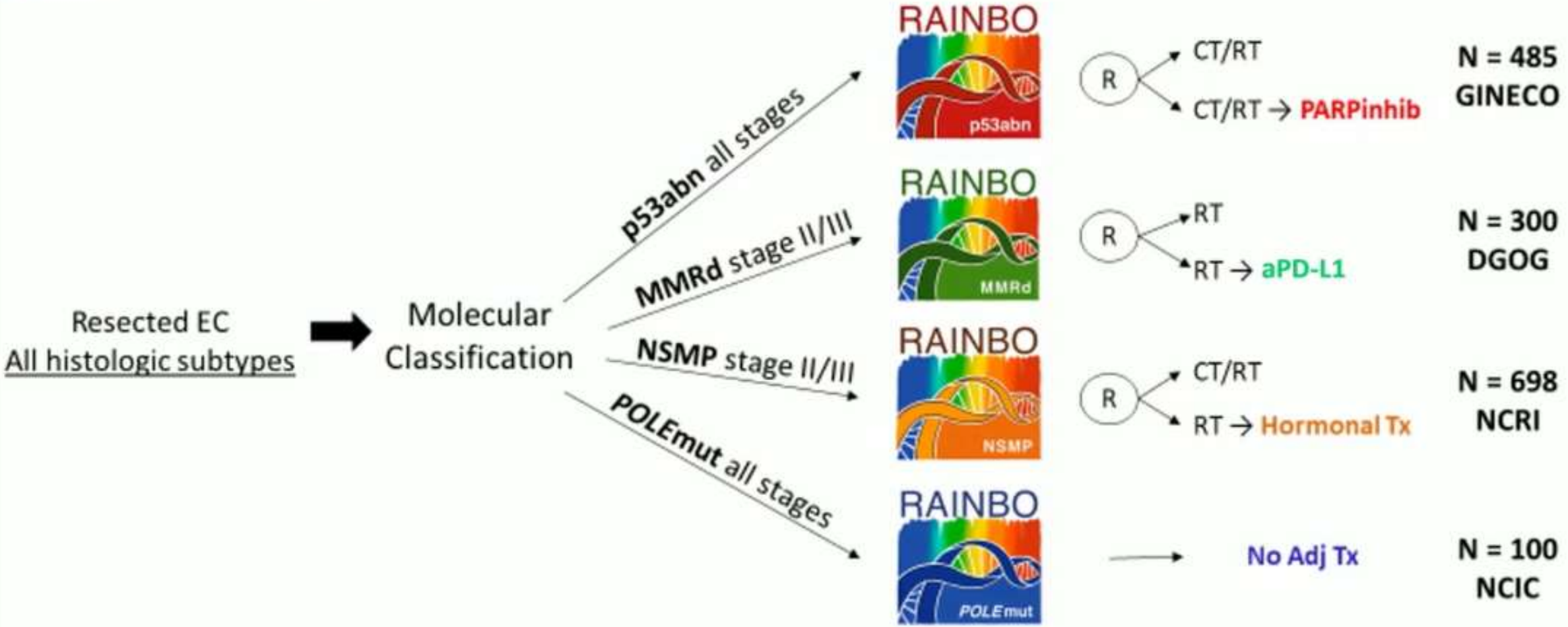
NSMP



Leon-Castillo, JCO 2020

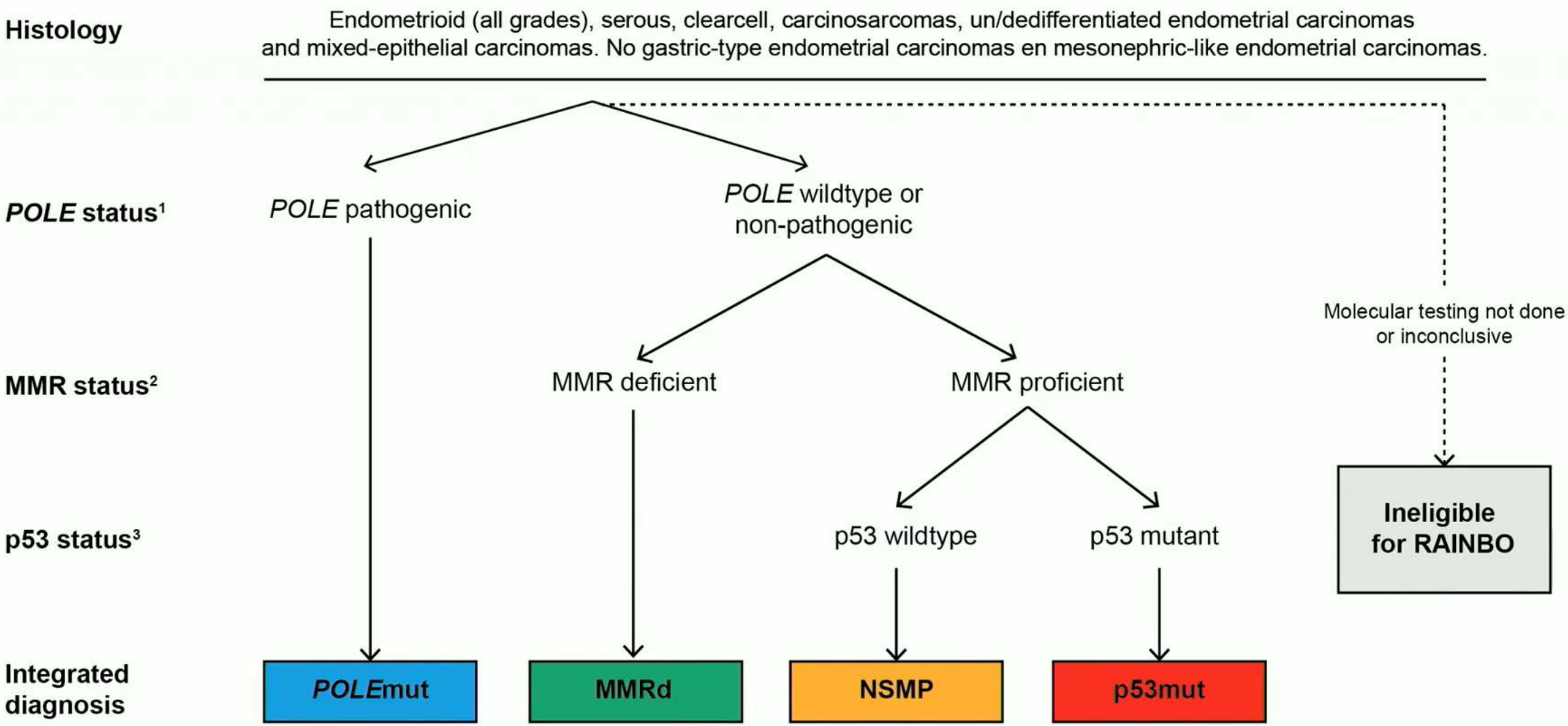
RAINBO

Overview of program



RAINBO program supported by GCIG and coordinated by *Trans*PORTEC will allocate EC pts to 4 international academic sub-trials each led by one Gyn-Onc national clinical trial group

Endometrial cancer molecular classification for inclusion in the RAINBO program

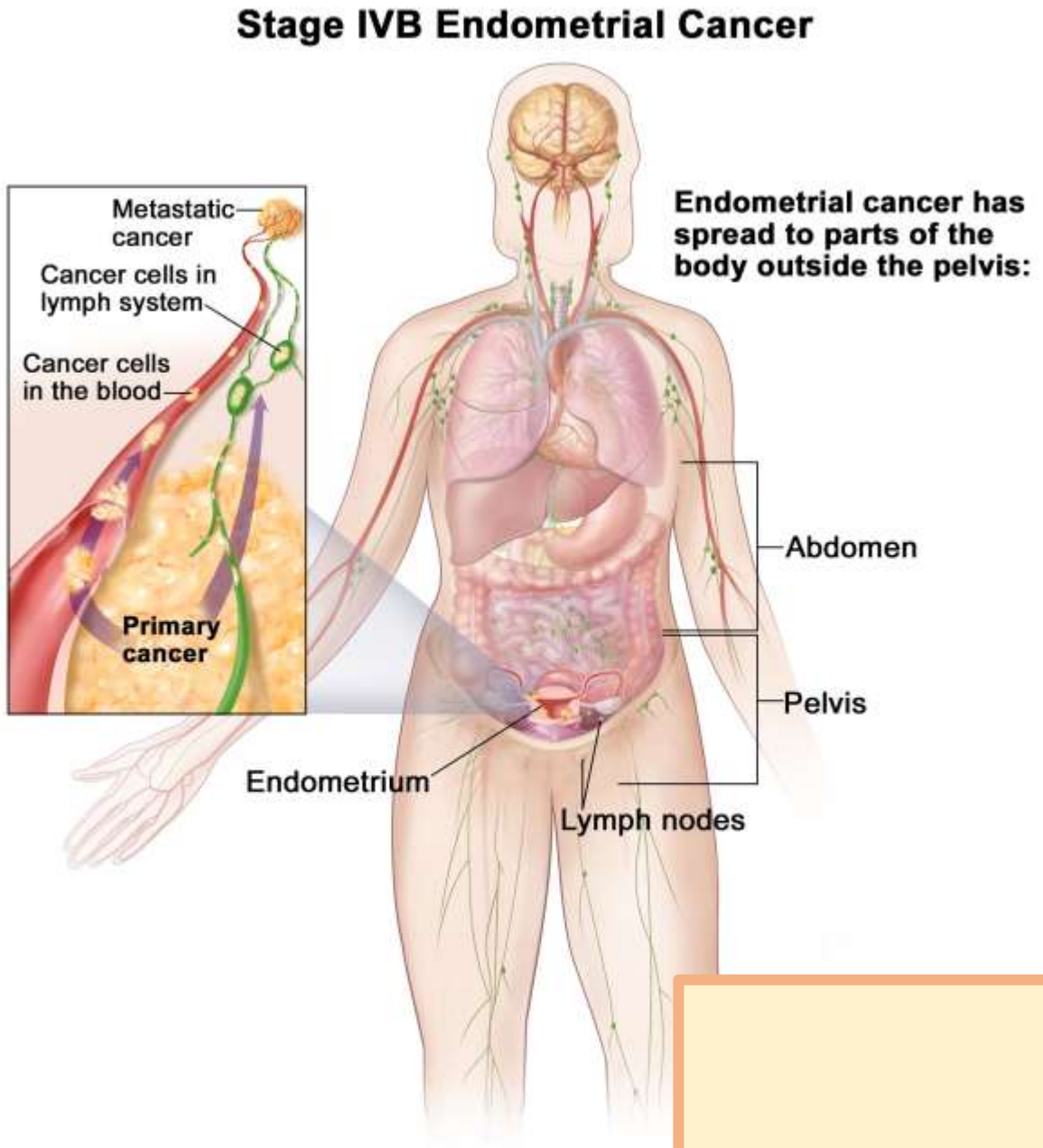


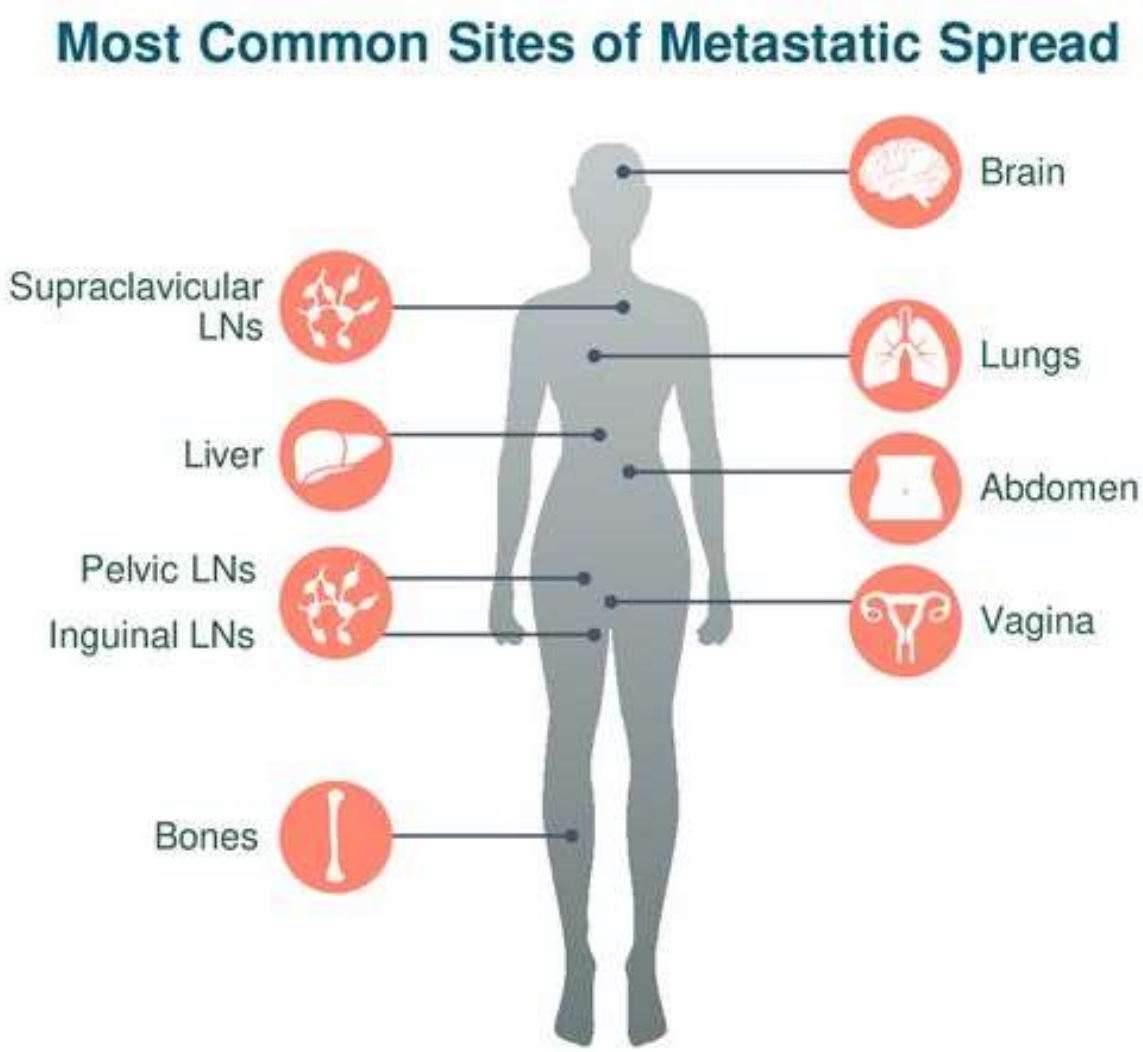
What type of molecular testing is performed routinely for patients with endometrial cancer at your institution?

a. No molecular testing. Histology only.	13	30%	
b. IHC including MMR proteins (MLH1, PMS2, MSH2, MSH6) + p53	28	64%	
c. POLE sequencing + IHC for MMR + p53	2	5%	
d. Genomic mutation panel	1	2%	

Scan With Phone

ASTRO 2022

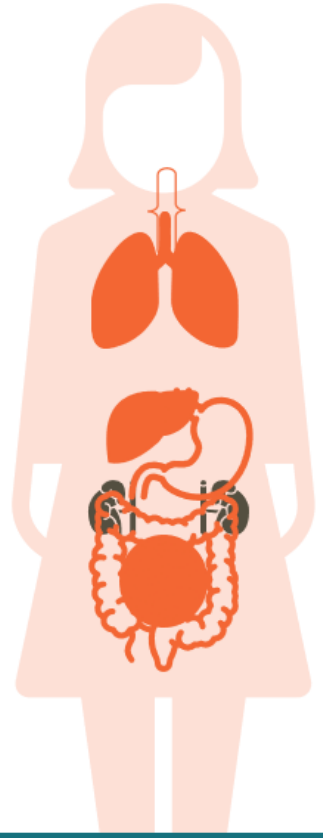




Paliativní terapie

MMR deficience

- Cancer types with the highest prevalence are **Lynch-syndrome-associated tumor types**[1]
- Lynch syndrome is a common hereditary disease characterized by germline mutations in MMR genes, and is associated with multiple cancers[1]
- Non-Lynch syndrome tumor types may also be affected[1]



Stomach: 9%–19.1%
Liver: 1%–3%

Endometrial: 17%–31.4%
Uterine: 3%–3.5%
Cervical: 2.6%–4%
Ovarian: 1.4%–2%

Esophageal: 1.6%
Mesothelioma: 2.4%

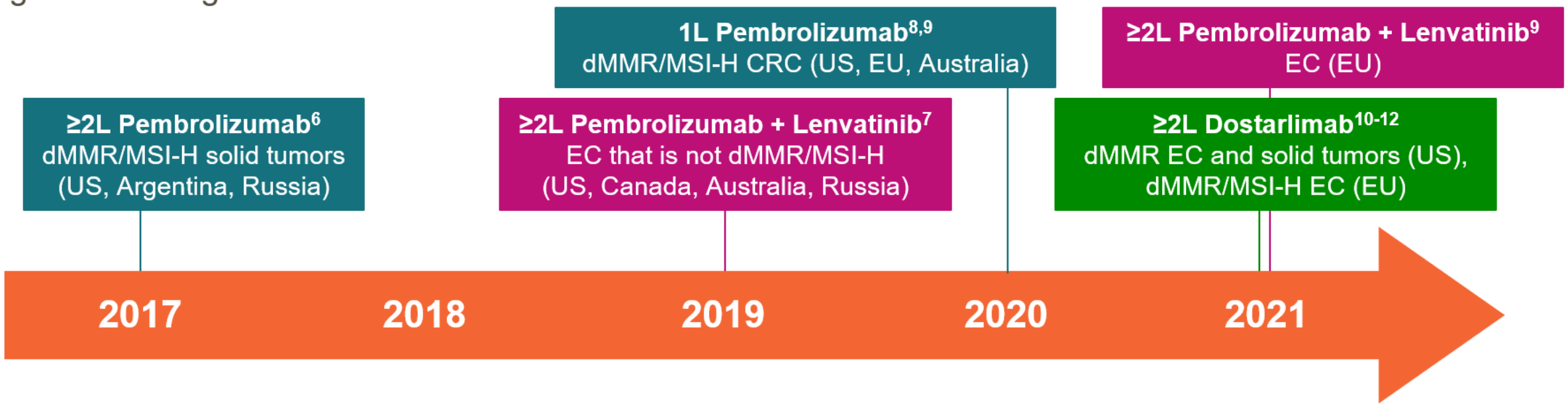
Adrenocortical: 4%

Colon: 6%–19.7%
Rectal: 6%

Not shown
Wilms tumor: 2.4%
Cholangiocarcinoma: 1.4%–3%

A meta-analysis of the prevalence of MSI-H/dMMR among tumor types with at least 5 publications showed that **endometrial cancer had the highest pooled MSI-H and dMMR prevalence (26% and 25% all stages, respectively)**[2]

- Treatment guidelines recommend platinum-based chemotherapy (carboplatin + paclitaxel) as preferred first-line treatment of advanced/recurrent EC[a,1,2]; in second line, guidelines recommend PD-1 regimens based on biomarker (MMR/MSI) status[2]
- Guideline recommendations are based on recent approvals of PD-1 agents in the second-line or greater setting[3-5]



KEYNOTE-158: multikohorotová studie fáze II, která hodnotila účinnost a bezpečnost pembrolizumabu u pokročilého endometriálního MSI-H karcinomu[1]

Pacienti

- ≥18 let věku
- MSI-H/dMMR pokročilý endometriální karcinom
  - kohorta D: endometriální karcinom, bez ohledu na stav MSI a s vyloučením sarkomů a mesenchymálních tumorů
  - kohorta K: jakýkoli MSI-H/dMMR solidní tumor, kromě kolorektálního
- Progrese nebo intolerance ≥1 linie standardní léčby neresekovatelné a/nebo metastázující choroby
- Měřitelná choroba podle RECIST v1.1
- ECOG PS 0 nebo 1
- Poskytnutí vzorku nádoru k vyhodnocení biomarkerů

→

Pembrolizumab
200 mg i.v. každé 3 týdny až 35 cyklů nebo do progrese onemocnění, nesnesitelné toxicity, rozhodnutí zkoušejícího nebo odstoupení pacienta

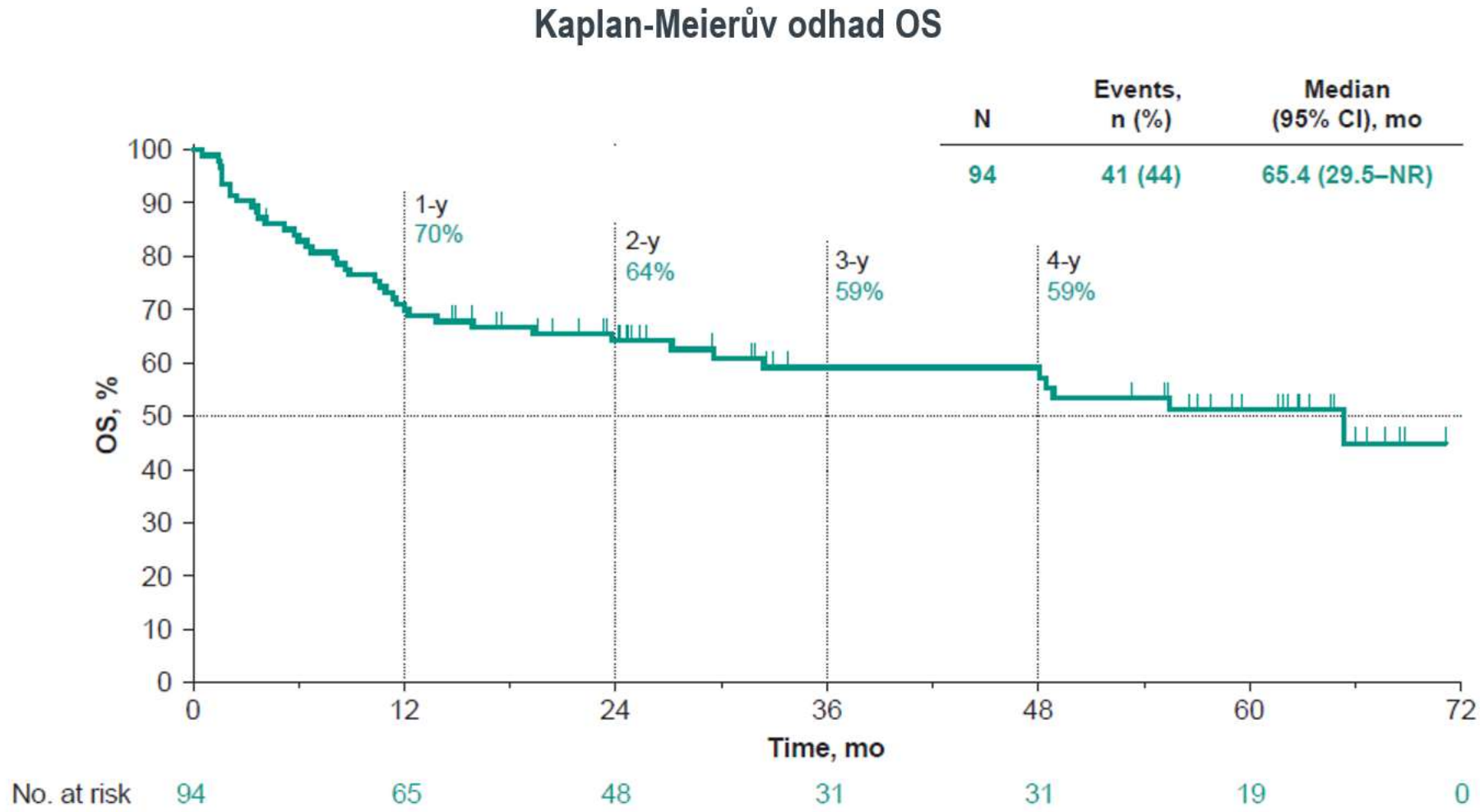
Kritéria hodnocení

- **Primární:** ORR (RECIST v1.1, nezávislá centrální revize), včetně podskupin zvolených podle biomarkeru
- **Sekundární:** DOR, PFS (RECIST v1.1, nezávislá centrální revize), OS a bezpečnost

Pacienti, kteří pembrolizumab vysadili s kompletní odpovědí, částečnou odpovědí nebo stabilizovaným onemocněním, byli po progresi onemocnění vhodní k podání až 17 cyklů (přibližně 1 rok) opakované léčby (druhá kúra) pembrolizumabem, pokud byla splněna kritéria bezpečnosti.

O'Malley et al. Prezentováno na ESMO 2022

KEYNOTE-158: Kaplan-Meierova analýza celkového přežití podle RECIST v1.1[1]



O'Malley et al. Prezentováno na ESMO 2022

KEYNOTE-775: randomizované, otevřené klinické hodnocením fáze III hodnotícím pembrolizumab + lenvatinib versus paklitaxel nebo doxorubicin dle volby lékaře u pacientů s pokročilým endometriálním karcinomem[1]

Populace pacientů (N=827)

- Progrese onemocnění po 1 předchozím režimu systémové, na platině založené chemoterapie u pacientů s pokročilým recidivujícím nebo metastazujícím endometriálním karcinomem
- Diagnoza histologicky potvrzená
- 1 předchozí systémová protinádorová léčba
- Bez předchozí léčby cílené proti VEGF nebo jakékoli anti PD-1, PD-L1, PD-L2 léčby
- K dispozici je archivní nebo čerstvý vzorek nádoru z biopsie ke stanovení stavu MMR

Stratifikační faktory

- pMMR vs dMMR
- V případě pMMR: ECOG PS, zeměpisná oblast, ozařování pánve v anamnéze (ano vs ne)

R
1:1

n=411

Pembrolizumab
200 mg i.v. každé 3 týdny
+
lenvatinib
20 mg p.o. každý den

n=416

Volba lékaře:
Doxorubicin
60 mg/m^2 i.v. každé 3 týdny
NEBO
paklitaxel
80 mg/m^2 i.v.
(28denní cyklus: 3 týdny podávání + 1 týden bez)

Primární kritéria hodnocení

- PFS stanovené BICR podle RECIST v1.1
- OS

Klíčová sekundární kritéria hodnocení

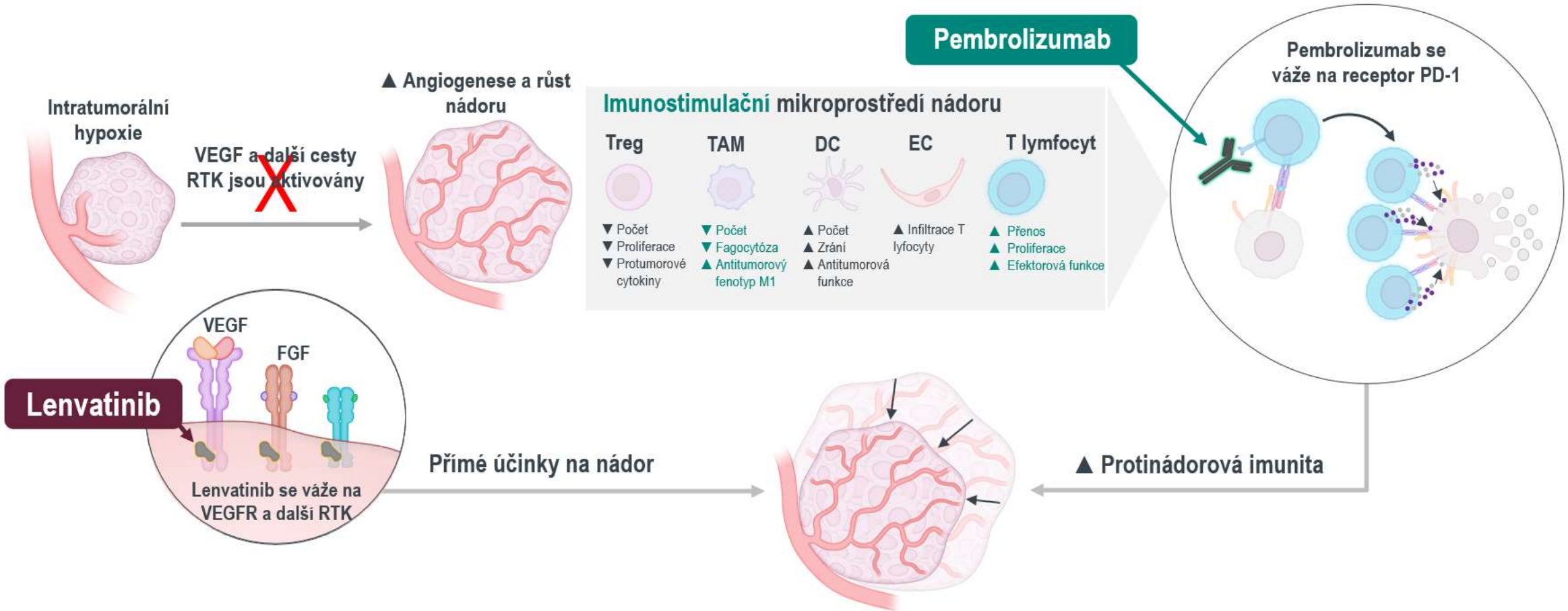
- ORR stanovené BICR podle RECIST v1.1
- Se zdravím související kvalita života
- Bezpečnost

[a]Rovněž označováno jako nikoli MSI-H nebo dMMR. [b]Stanoveno BICR podle RECIST v1.1.

Makker V et al. *N Engl J Med* 2022; 386:437-448

Pembrolizumab + lenvatinib

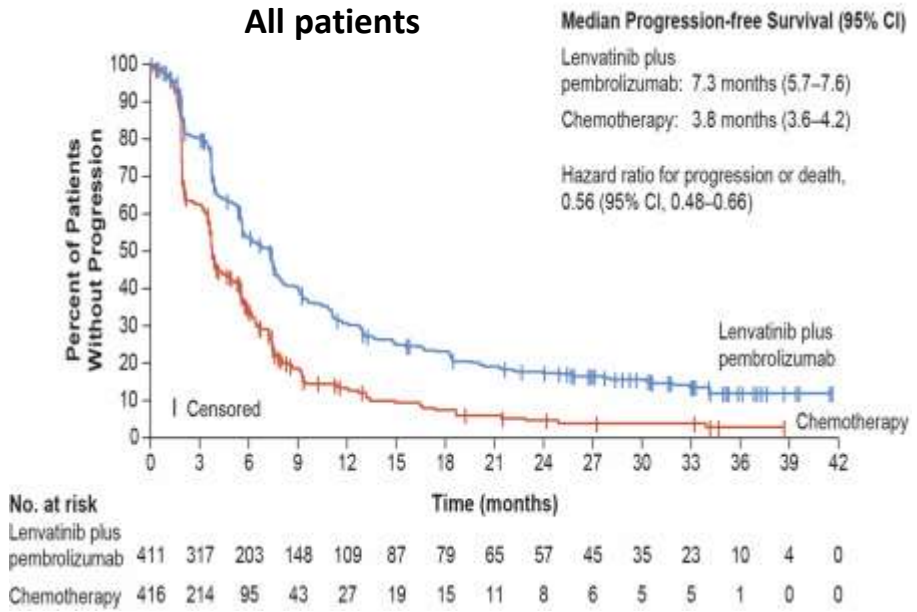
Lenvatinib kromě antiangiogenního a přímého protinádorového účinků rovněž pomáhá prostřednictvím inhibice VGEF měnit mikroprostředí nádoru z imunosupresivního na imunostimulační, čímž doplňuje mechanismus účinku pembrolizumabu, který pomáhá reaktivovat protinádorovou imunitní aktivitu prostřednictvím PD-1 signalizace.[1–3]

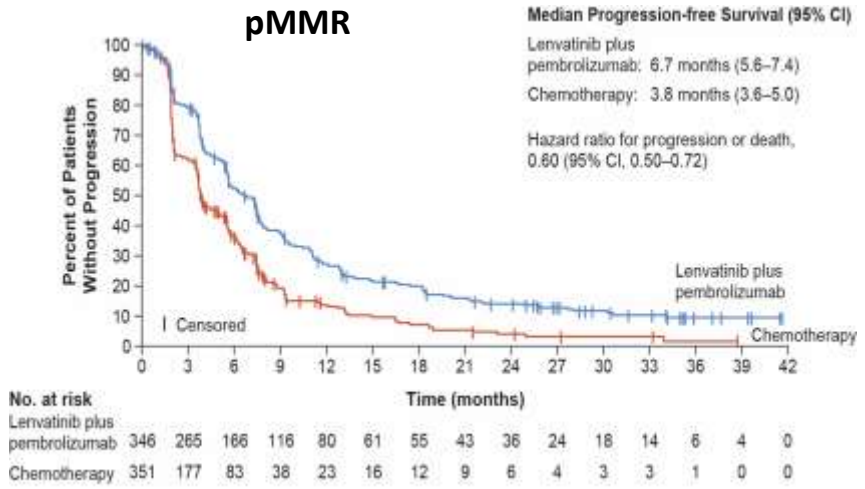


1. Ott P et al. *Front Oncol.* 2015;5:202. **2.** Fukumura D et al. *Nat Rev Clin Oncol.* 2018;15(5):325–340. **3.** Grünwald V et al. *Future Oncol.* 2019;15(9):929–941.

KEYNOTE-775: klíčové výchozí charakteristiky[1]

Charakteristika	Populace pMMR		Všichni pacienti	
	Lenvatinib + pembrolizumab n=346	Doxorubicin nebo paklitaxel n=351	Lenvatinib + pembrolizumab n=411	Doxorubicin nebo paklitaxel n=416
Věk				
Medián (rozmezí) — roky	65 (30 až 82)	66 (35 až 86)	64 (30 - 82)	65 (35 - 86)
≥65 let — počet (%)	171 (49,4)	165 (47,0)	206 (50,1)	204 (49,0)
Rasa[a]				
Bělošská	220 (63,6)	211 (60,1)	261 (63,5)	246 (59,1)
Černošská	15 (4,3)	9 (2,6)	17 (4,1)	14 (3,4)
Asijská	74 (21,4)	80 (22,8)	85 (20,7)	92 (22,1)
Zeměpisná oblast — počet (%)[b]				
Oblast 1	202 (58,4)	204 (58,1)	234 (56,9)	240 (57,7)
Oblast 2	144 (41,6)	147 (41,9)	177 (43,1)	176 (42,3)
Stav MMR — počet (%)				
pMMR			346 (84,2)	351 (84,4)
dMMR			65 (15,8)	65 (15,6)
Výkonnostní stav dle ECOG — počet (%)[c]				
0	212 (61,3)	207 (59,0)	246 (59,9)	241 (57,9)
1	133 (38,4)	144 (41,0)	164 (39,9)	175 (42,1)
Ozařování pánve v anamnéze — počet (%)	142 (41,0)	148 (42,2)	174 (42,3)	186 (44,7)
Histologie počáteční diagnózy — počet (%)				
Endometrioidní karcinom			243 (59,1)	254 (61,1)
Vysokého stupně	73 (21,1)	77 (21,9)	94 (22,9)	90 (21,6)
Nízkého stupně	50 (14,5)	41 (11,7)	59 (14,4)	54 (13,0)
Nespecifikováno[d]	65 (18,8)	80 (22,8)	90 (21,9)	110 (26,4)
Serózní karcinom	99 (28,6)	112 (31,9)	103 (25,1)	115 (27,6)
Světlobuněčný karcinom	29 (8,4)	17 (4,8)	30 (7,3)	17 (4,1)
Smíšené rysy	18 (5,2)	13 (3,7)	22 (5,4)	16 (3,8)

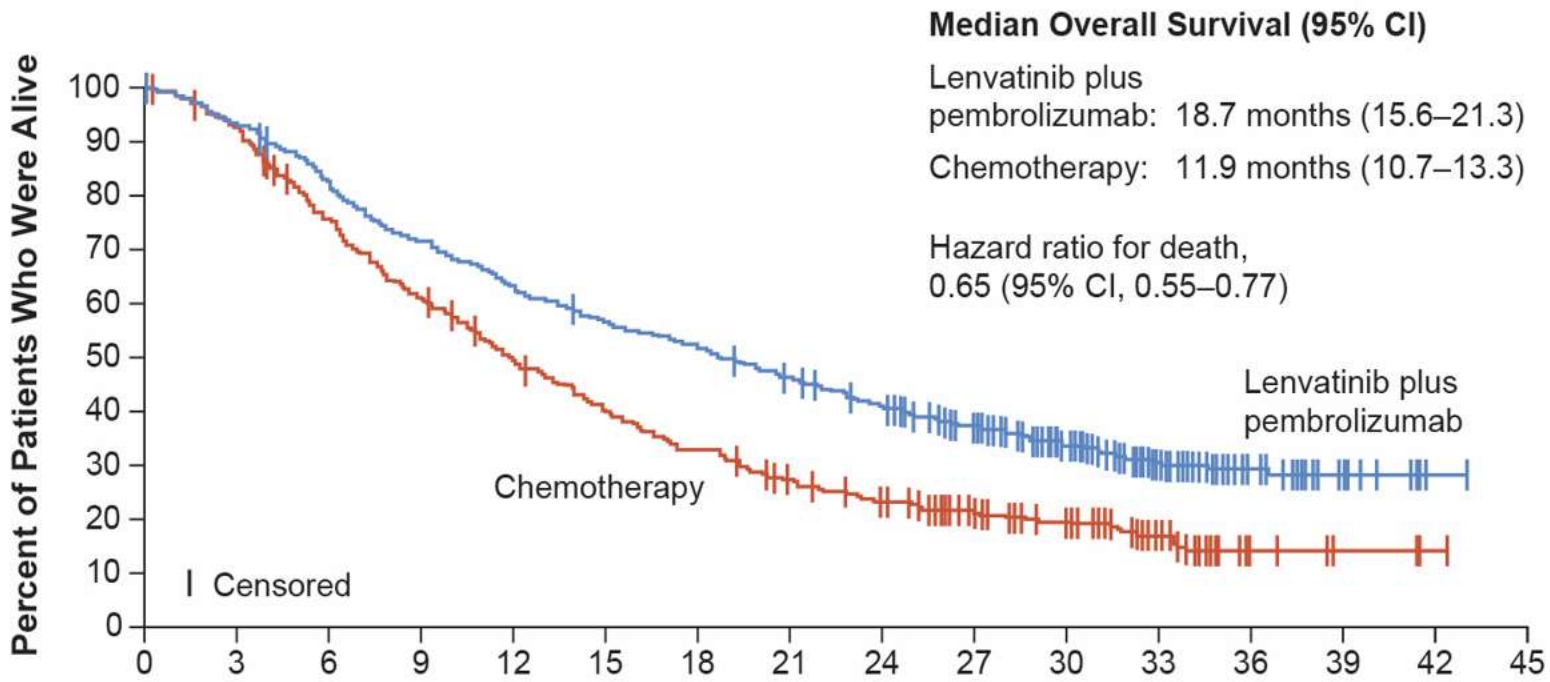




Makker V et al. *N Engl J Med* 2022; 386:437-448

KEYNOTE-775: primární kritérium hodnocení - OS (všichni pacienti)[1]

(medián sledování 14,7 měsíce; datum uzávěrky údajů 1. březen 2022)



No. at risk

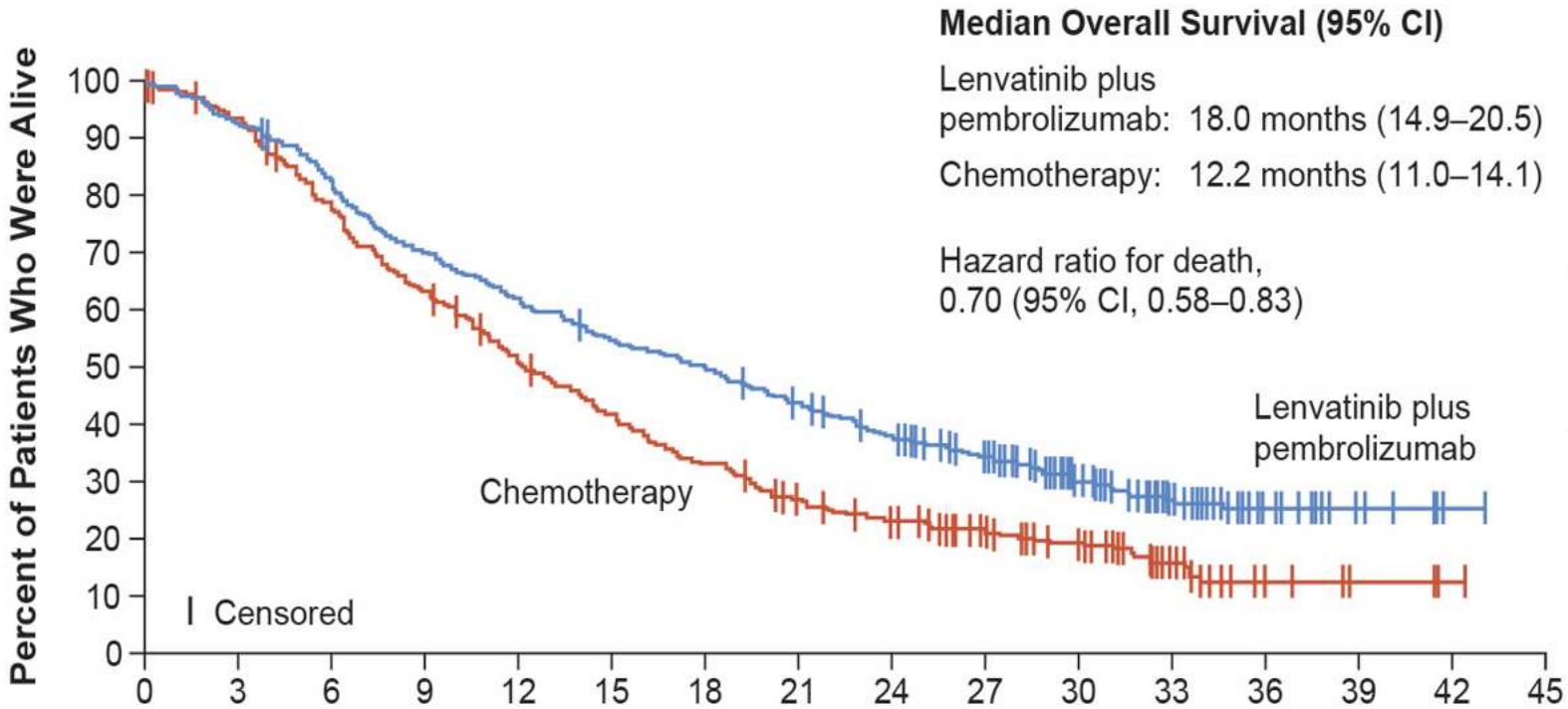
Lenvatinib plus pembrolizumab	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
Chemotherapy	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1

- Ve skupině léčené chemoterapií 8,7 % pacientů v populaci „all-comers“ následně dostávalo lenvatinib plus pembrolizumab.
- Po vyloučení těchto pacientů byl poměr rizik pro OS při pMMR 0,60 (95% CI, 0,51–0,71).

Makker V et al. Prezentováno na ESMO 2022

KEYNOTE-775: primární kritérium hodnocení - OS (pMMR)[1]

(medián sledování 14,7 měsíce; datum uzávěrky údajů 1. březen 2022)



No. at risk

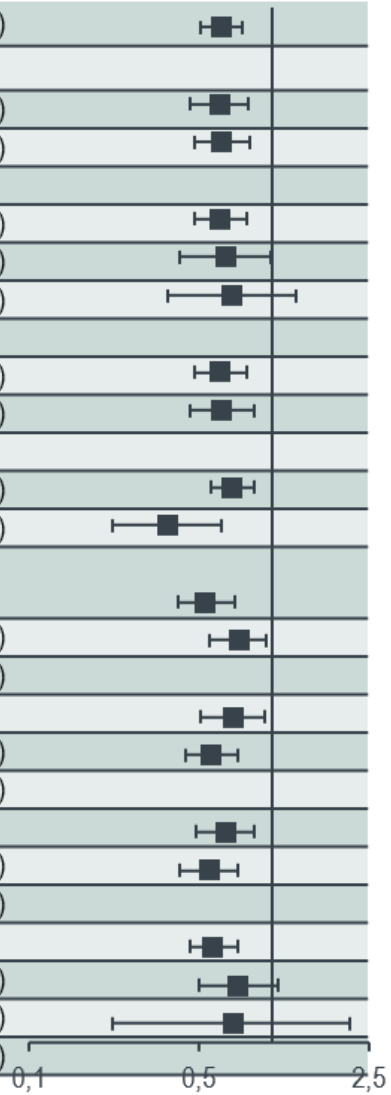
Lenvatinib plus pembrolizumab	346	322	285	242	214	188	171	148	124	95	65	41	20	7	2
Chemotherapy	351	324	267	217	171	138	111	86	71	53	40	21	6	3	1

- Ve skupině léčené chemoterapií 10,0 % pacientů z populace pMMR následně dostávalo lenvatinib plus pembrolizumab.
- Po vyloučení těchto pacientů byl poměr rizik pro OS při pMMR 0,64 (95% CI, 0,54–0,76).

Makker V et al. Prezentováno na ESMO 2022

KEYNOTE-775: analýza OS u podskupin (všichni pacienti)[1]

Podskupina	Lenvatinib + pembrolizumab Výskyt/N	Doxorubicin nebo paklitaxel Výskyt/N	HR (95% CI)
Celkem	188/411	245/416	0,62 (0,51-0,75)
Věk			
<65 let	89/206	116/204	0,61 (0,46-0,80)
≥65 let	99/205	129/212	0,62 (0,48-0,81)
Rasa			
Bělošská	117/261	141/246	0,61 (0,48-0,79)
Asijská	36/85	51/92	0,65 (0,42-0,99)
Jiná	19/29	25/34	0,68 (0,37-1,26)
Oblast*			
Oblast 1	110/234	145/240	0,61 (0,48-0,79)
Oblast 2	78/177	100/176	0,62 (0,46-0,84)
Stav MMR			
pMMR	165/346	203/351	0,68 (0,56-0,84)
dMMR	23/65	42/65	0,37 (0,22-0,62)
Skóre výkonnostního stavu dle ECOG			
0	91/246	131/241	0,53 (0,41-0,70)
1	96/164	114/175	0,73 (0,55-0,95)
Ozařování pánve v anamnéze			
Ano	77/174	99/186	0,69 (0,51-0,93)
Ne	111/237	146/230	0,56 (0,44-0,72)
Histologie			
Endometrioidní	95/243	127/254	0,65 (0,49-0,84)
Neendometrioidní	93/168	118/162	0,55 (0,42-0,72)
Předchozí linie léčby			
1	136/297	172/277	0,57 (0,46-0,72)
2	47/103	65/126	0,72 (0,50-1,06)
≥3	5/11	8/13	0,69 (0,22-2,10)



Makker V et al. *N Engl J Med* 2022; 386:437-448

The NEW ENGLAND JOURNAL of MEDICINE

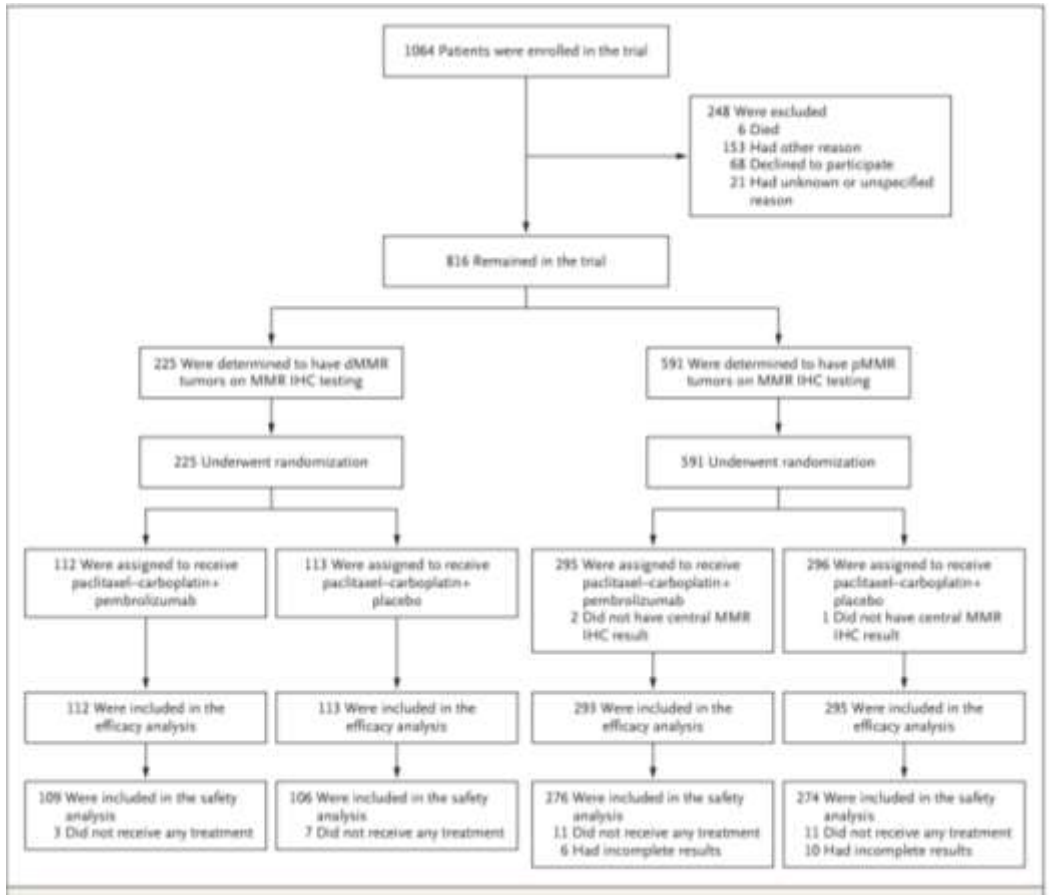
published on March 27, 2023, at NEJM.org

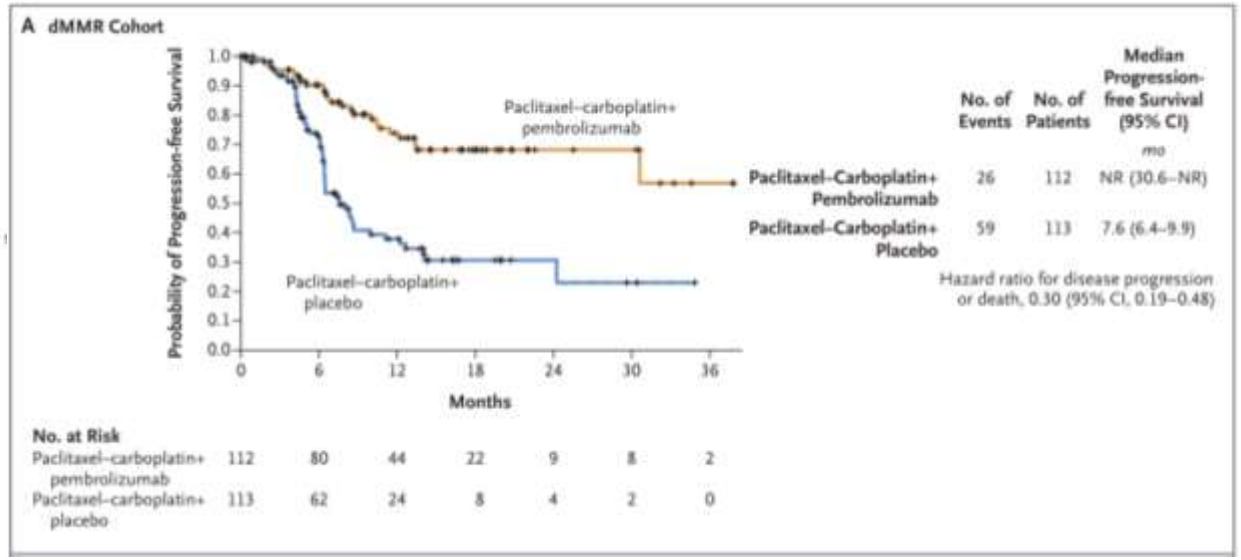
1st Line

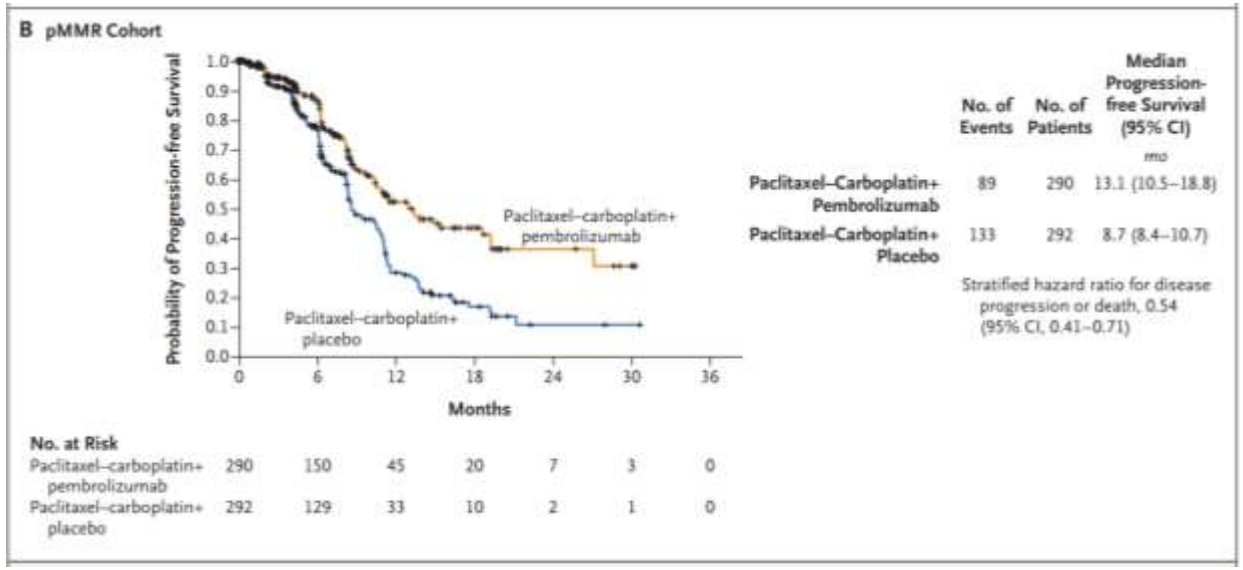
ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D.,







RUBY | Dostarlimab + Chemotherapy

Phase 3, two-part, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel in patients with recurrent or primary advanced endometrial cancer

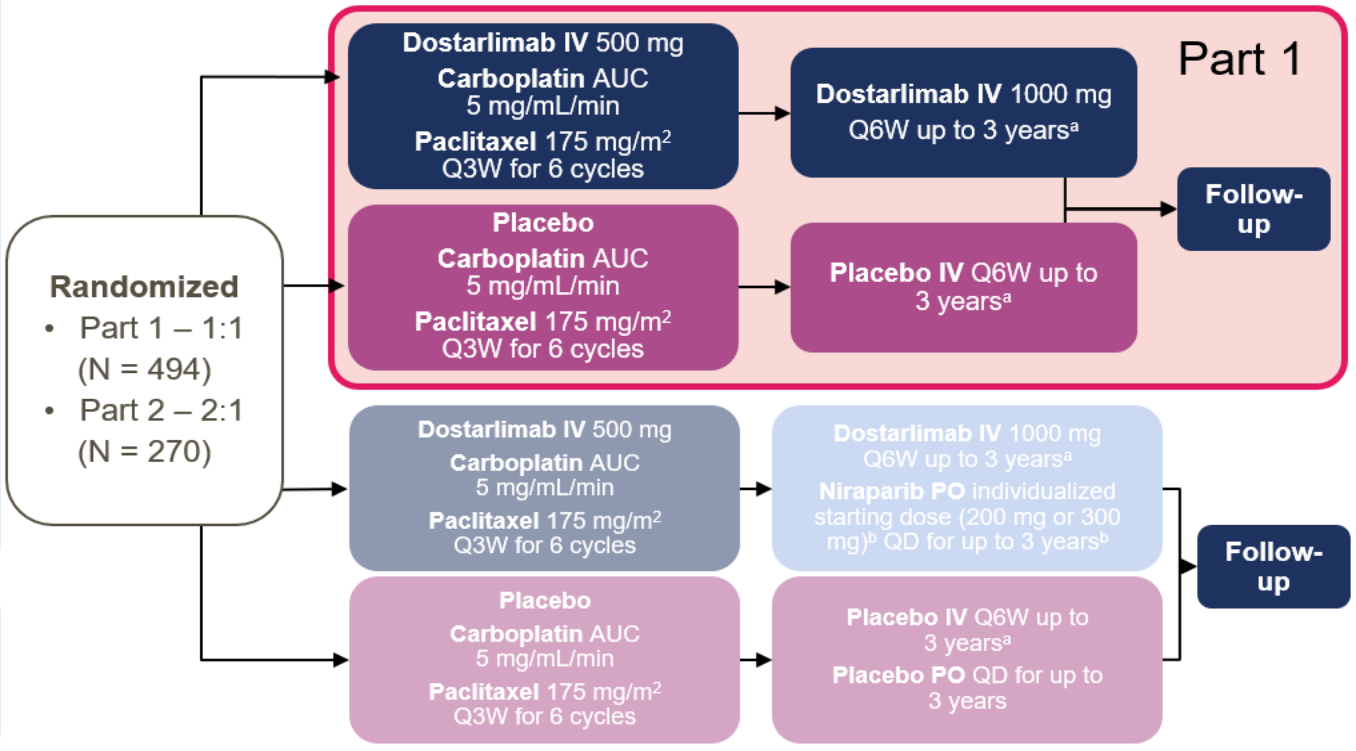
Eligible patients:

- Histologically or cytologically proven EC with recurrent or primary advanced disease
- Stage III or IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
- Naïve to systemic therapy or systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment
- ECOG PS 0-1
- Adequate organ function

Stratification:

- MMR/MSI status
- Prior radiotherapy
- Disease status

Overview of study design



Endpoints[2]

Part 1

Primary endpoint: PFS,[c] OS

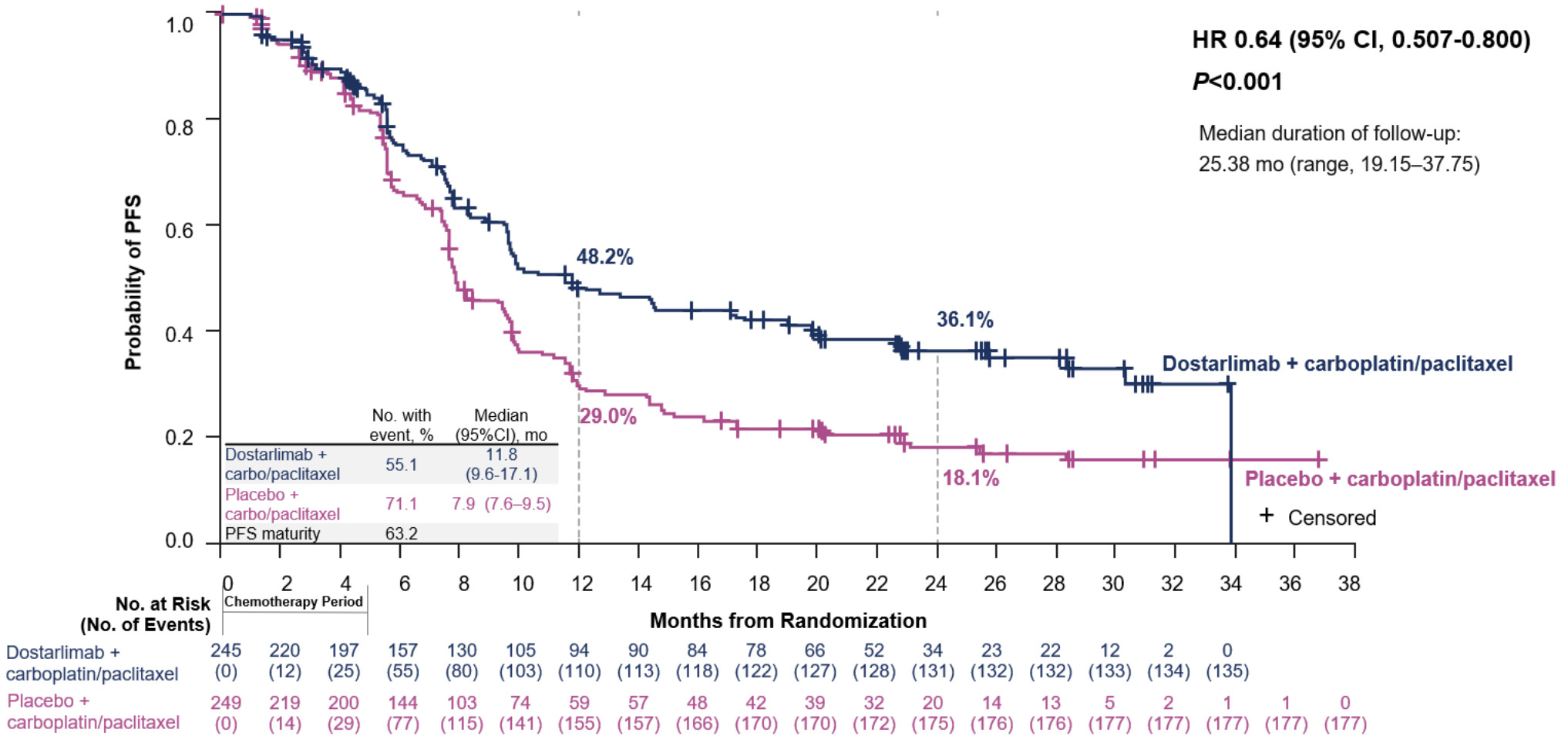
Secondary end points: PFS,[d] PFS2, ORR,[e] DOR,[f] DCR,[g] QoL, pharmacokinetics and immunogenicity, safety[h]

RUBY Part 1

Data cutoff: Sept 28, 2022

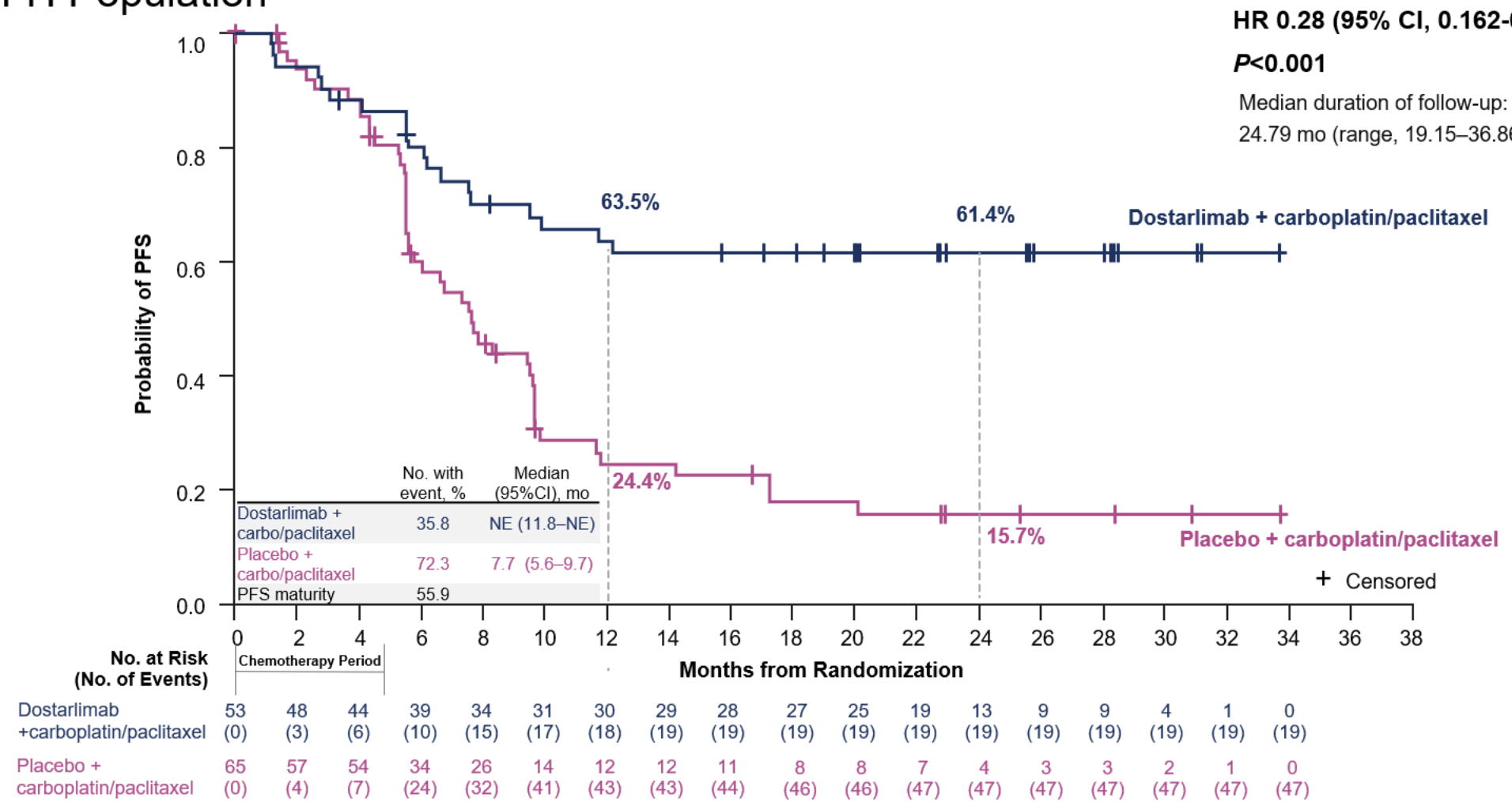
PFS per Investigator Assessment – Primary Endpoint

Overall Population (dMMR/MSI-H and pMMR/MSS)



PFS per Investigator Assessment – Primary Endpoint

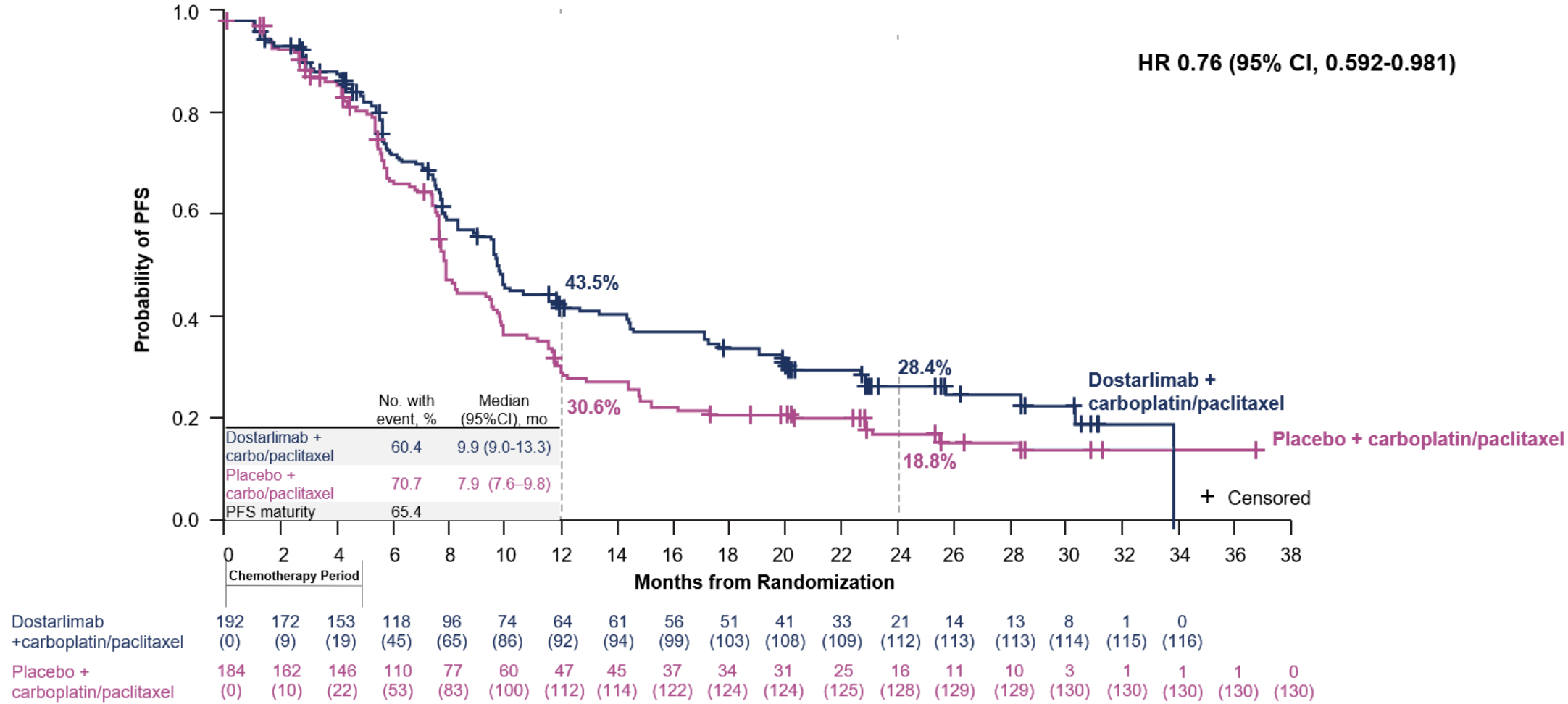
dMMR/MSI-H Population



Link to sensitivity analysis results

PFS per Investigator Assessment – Prespecified Exploratory Endpoint

pMMR/MSS Population



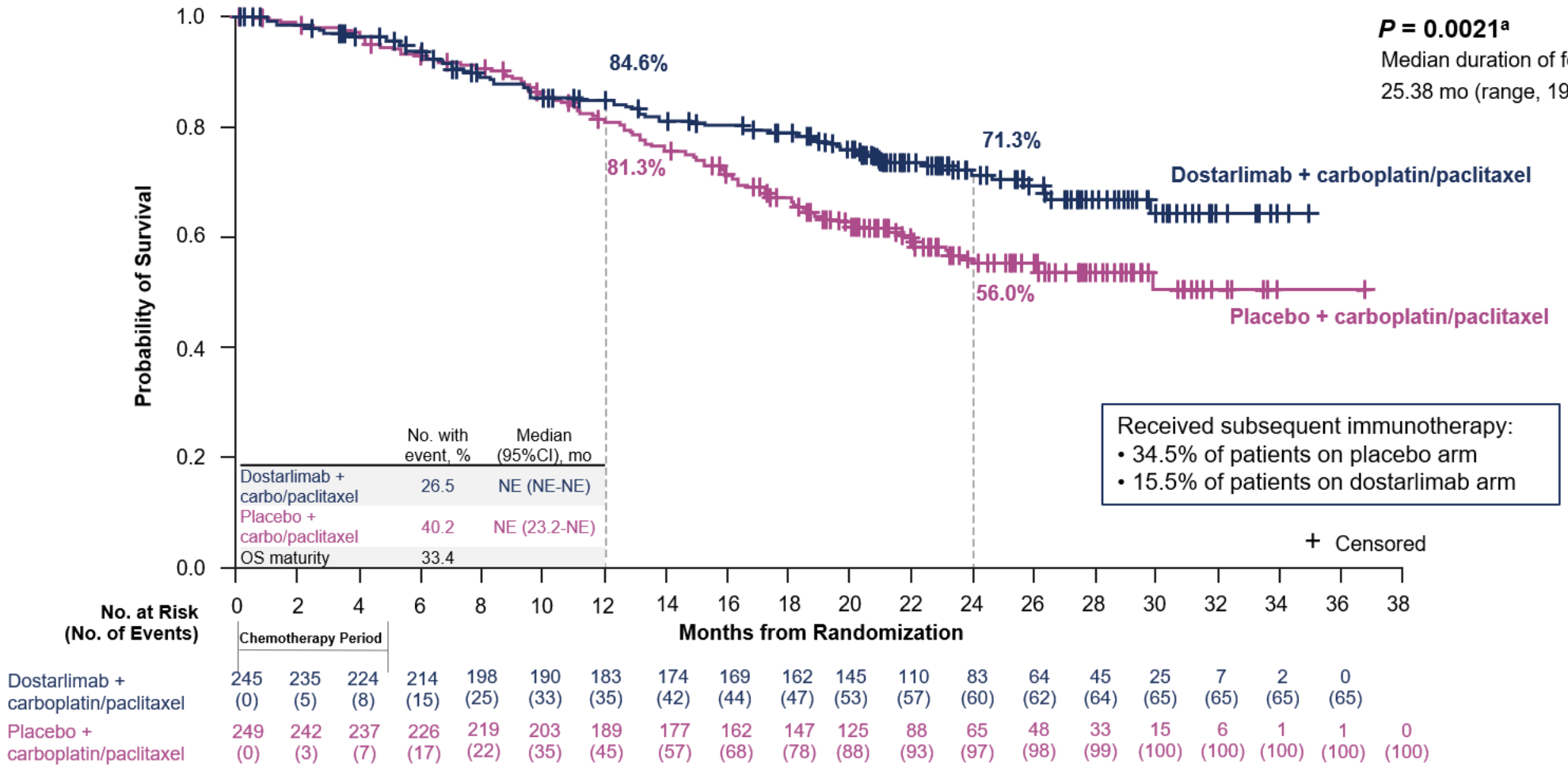
Overall Survival – Primary Endpoint

Overall Population (dMMR/MSI-H and pMMR/MSS)

HR 0.64 (95% CI, 0.464-0870)

***P* = 0.0021[a]**

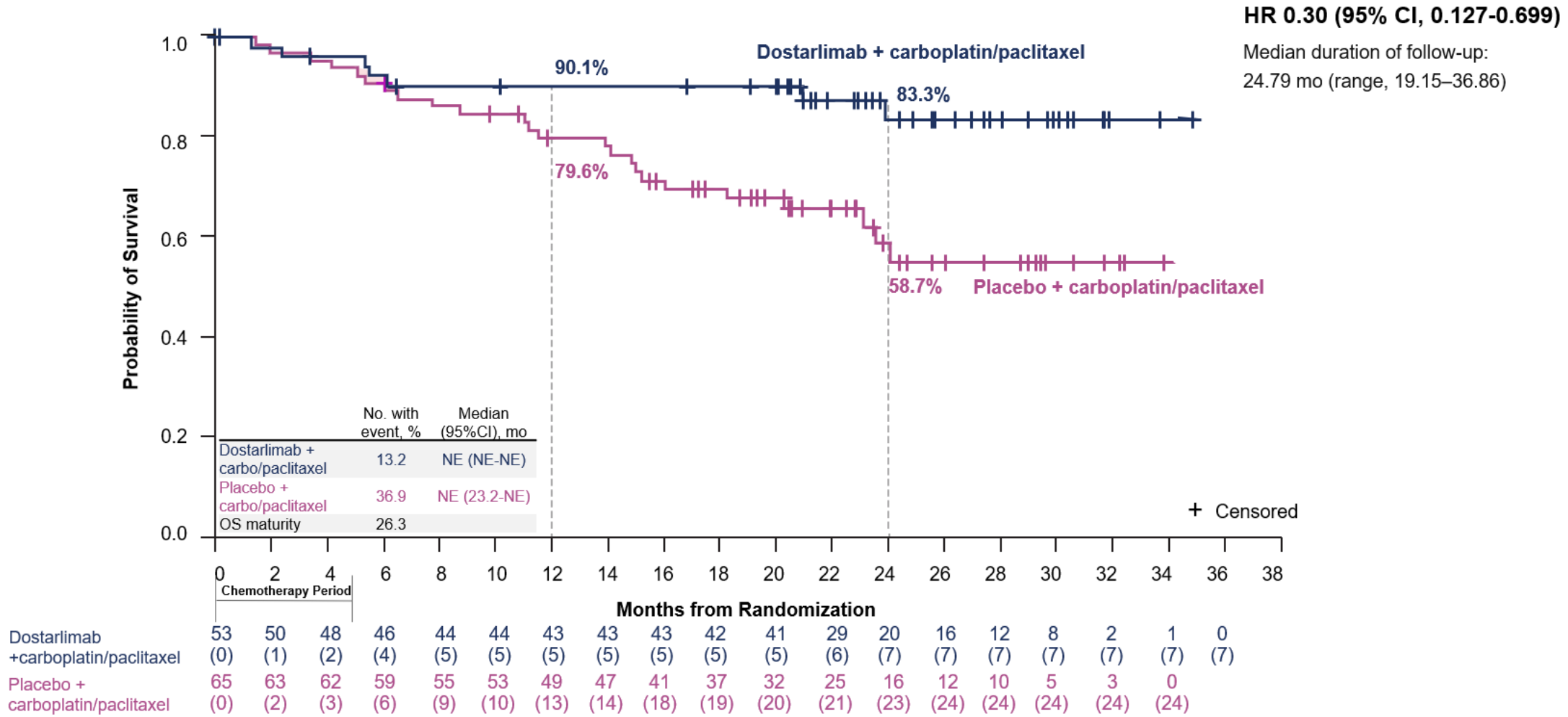
Median duration of follow-up:
25.38 mo (range, 19.15–37.75)



[a]P≤0.00177 required to declare statistical significance at first interim analysis.

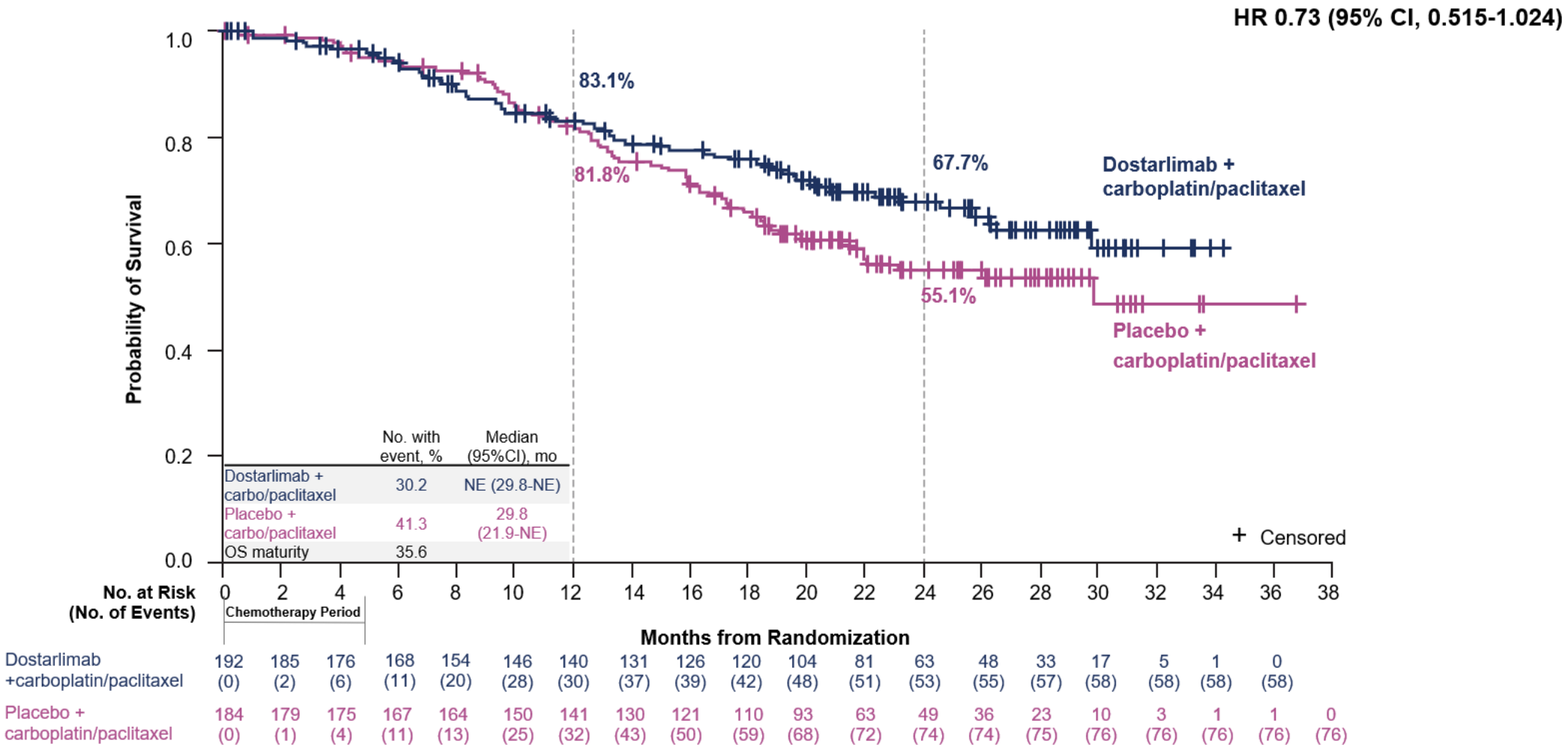
Overall Survival – Prespecified Subgroup Analysis

dMMR/MSI-H Population



Overall Survival – Prespecified Subgroup Analysis

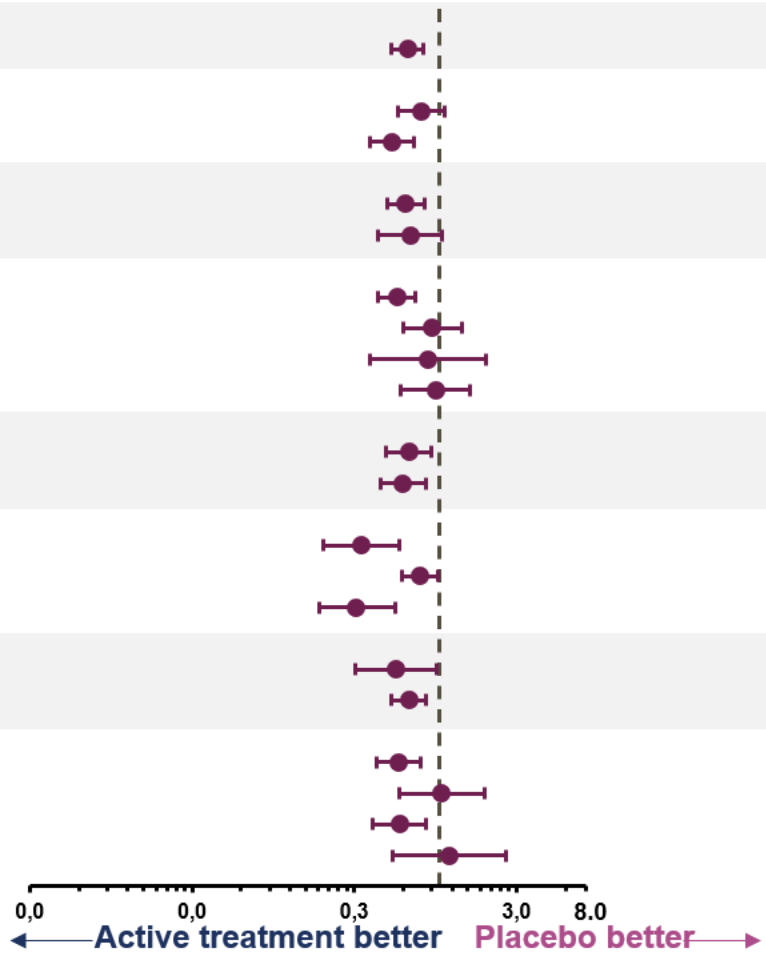
pMMR/MSS Population



PFS per Investigator Assessment – Prespecified Subgroups

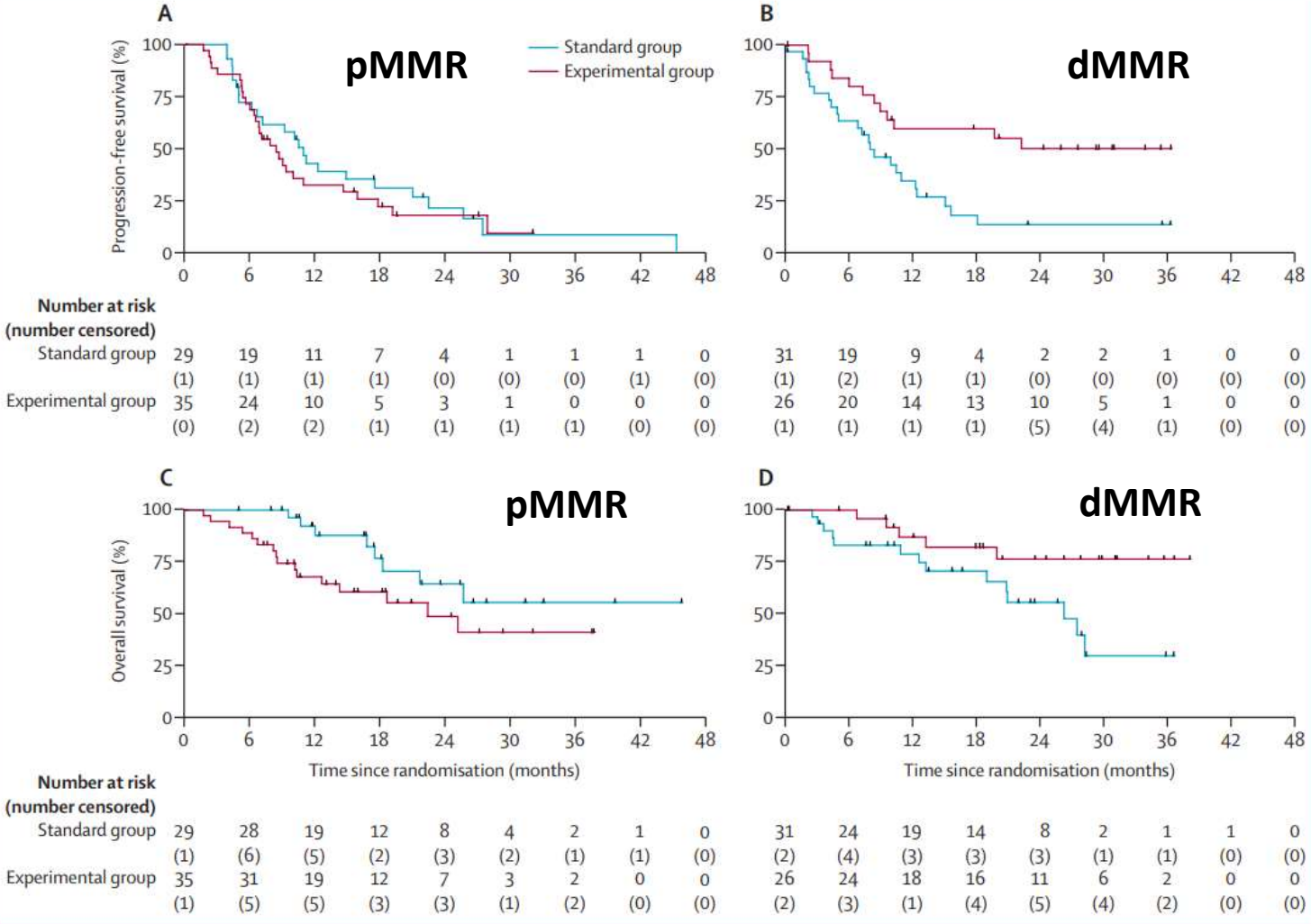
Overall population (dMMR/MSI-H and pMMR/MSS)

Category	Dostarlimab plus carboplatin/paclitaxel (no. events / no. patients)	Placebo plus carboplatin/paclitaxel (no. events / no. patients)	Hazard ratio (95% CI)
All patients	135/245	177/249	0.64 (0.507-0.800)
Age			
<65 years	69/127	72/144	0.78 (0.559-1.083)
≥65 years	66/118	105/135	0.51 (0.376-0.704)
Race			
White	101/189	135/191	0.62 (0.481-0.808)
Other	34/56	42/58	0.67 (0.422-1.050)
Region			
North America	91/171	133/187	0.55 (0.419-0.718)
Europe	44/74	44/62	0.91 (0.602-1.390)
Eastern Europe	11/16	12/14	0.86 (0.377-1.959)
Western Europe	33/58	32/48	0.95 (0.581-1.539)
Histology category			
Endometroid carcinoma	64/130	89/136	0.65 (0.473-0.902)
Other	71/115	88/113	0.60 (0.439-0.823)
MMR/MSI status			
dMMR/MSI-H	19/53	47/65	0.33 (0.192-0.566)
pMMR/MSS	116/192	130/184	0.76 (0.595-0.982)
dMMR status (derived)	19/53	47/63	0.31 (0.182-0.539)
Prior external pelvic RT			
Yes	21/41	31/45	0.54 (0.303-0.956)
No	114/204	146/204	0.65 (0.508-0.831)
Disease status			
Recurrent	68/117	89/119	0.56 (0.408-0.775)
Primary stage III	21/45	21/47	1.03 (0.563-1.891)
Primary stage IV	46/83	67/83	0.57 (0.392-0.836)
No disease at baseline	12/33	12/30	1.16 (0.520-2.590)



Carboplatin and paclitaxel plus avelumab compared with carboplatin and paclitaxel in advanced or recurrent endometrial cancer (MITO END-3): a multicentre, open-label, randomised, controlled, phase 2 trial

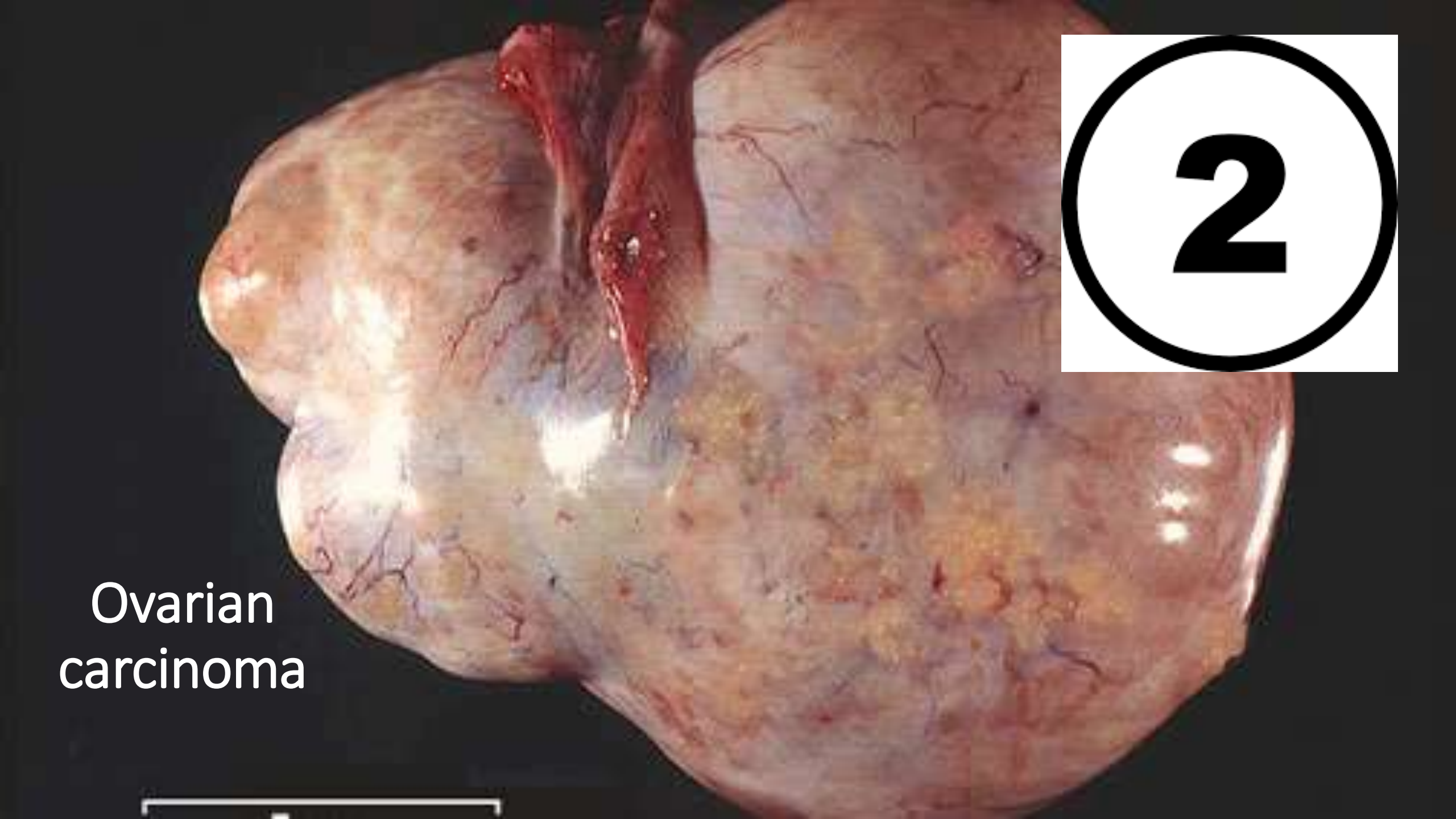
Lancet Oncol 2023; 24: 286–96



	Standard group (n=62)	Experimental group (n=63)
Age, years	65 (56–70)	66 (61–72)
FIGO stage at diagnosis		
I	18 (29%)	15 (24%)
II	6 (10%)	5 (8%)
III	22 (35%)	23 (37%)
IV	16 (26%)	20 (32%)
Stage at study entry		
Recurrent	30 (48%)	30 (48%)
Advanced at diagnosis	32 (52%)	33 (52%)
ECOG performance status		
0	52 (84%)	49 (78%)
1	10 (16%)	14 (22%)
Tumour histology		
Endometrioid	46 (74%)	44 (70%)
Clear cell	1 (2%)	3 (5%)
Mucinous	0 (0%)	1 (2%)
Serous papillary	9 (15%)	10 (16%)
Undifferentiated	3 (5%)	4 (6%)
Mixed	3 (5%)	1 (2%)
Histological grading		
1	1 (2%)	5 (8%)
2	23 (37%)	17 (27%)
3	38 (61%)	41 (65%)
Microsatellite instability		
dMMR	31 (50%)	26 (41%)
pMMR	29 (47%)	35 (56%)
Missing	2 (3%)	2 (3%)
Combined positive score for PD-L1 expression		
Negative	35 (56%)	39 (62%)
Positive	24 (39%)	23 (37%)
Missing	3 (5%)	1 (2%)

Data are median (IQR) or n (%). Data on race or ethnicity was not collected. dMMR=mismatch repair deficient. ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynecology and Obstetrics. pMMR=mismatch repair proficient.

Table 1: **Baseline patient characteristics**



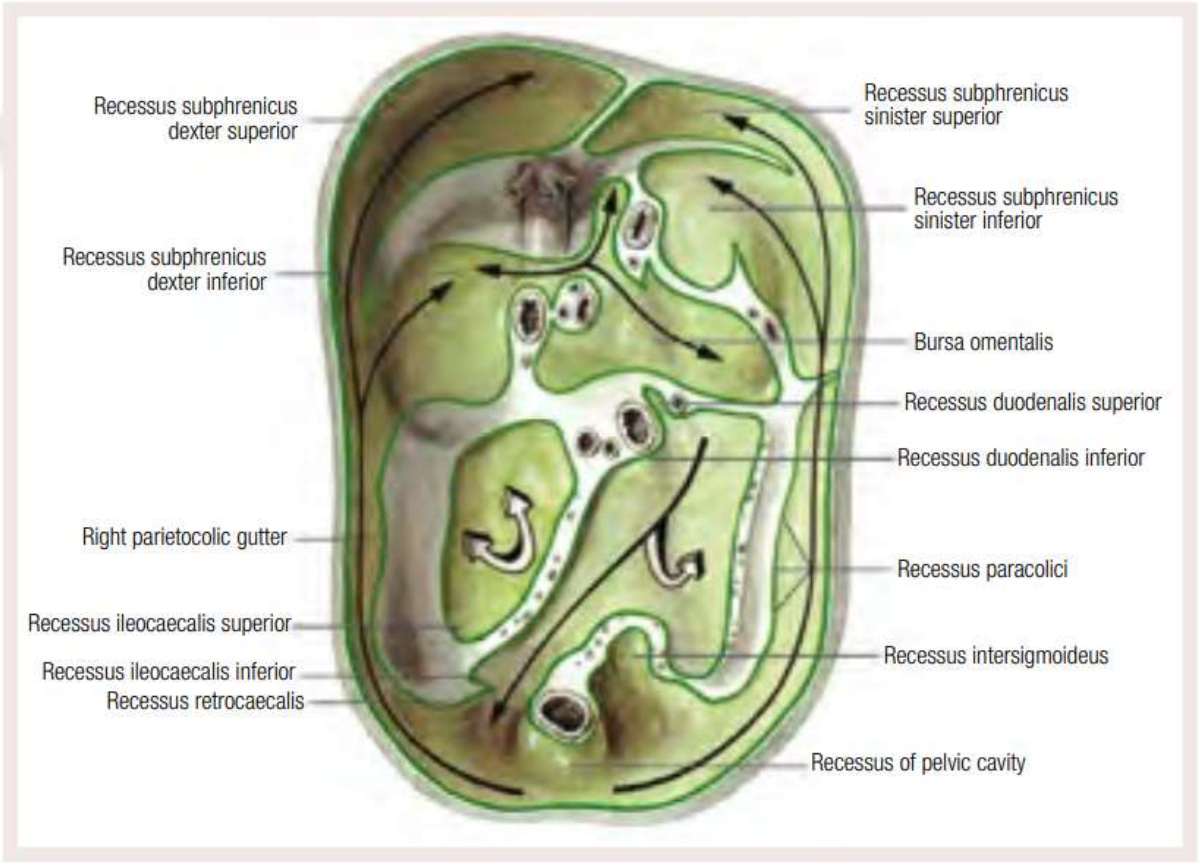
Ovarian carcinoma

Mechanism of tumor spread (peritoneal fluid stream)

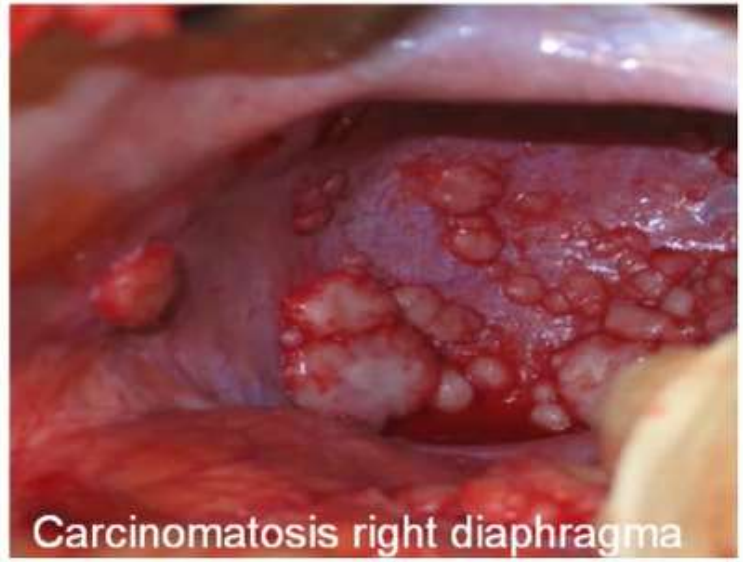
Tumour cells and subsequent peritoneal carcinomatosis can spread throughout the abdomen with the peritoneal fluid stream.

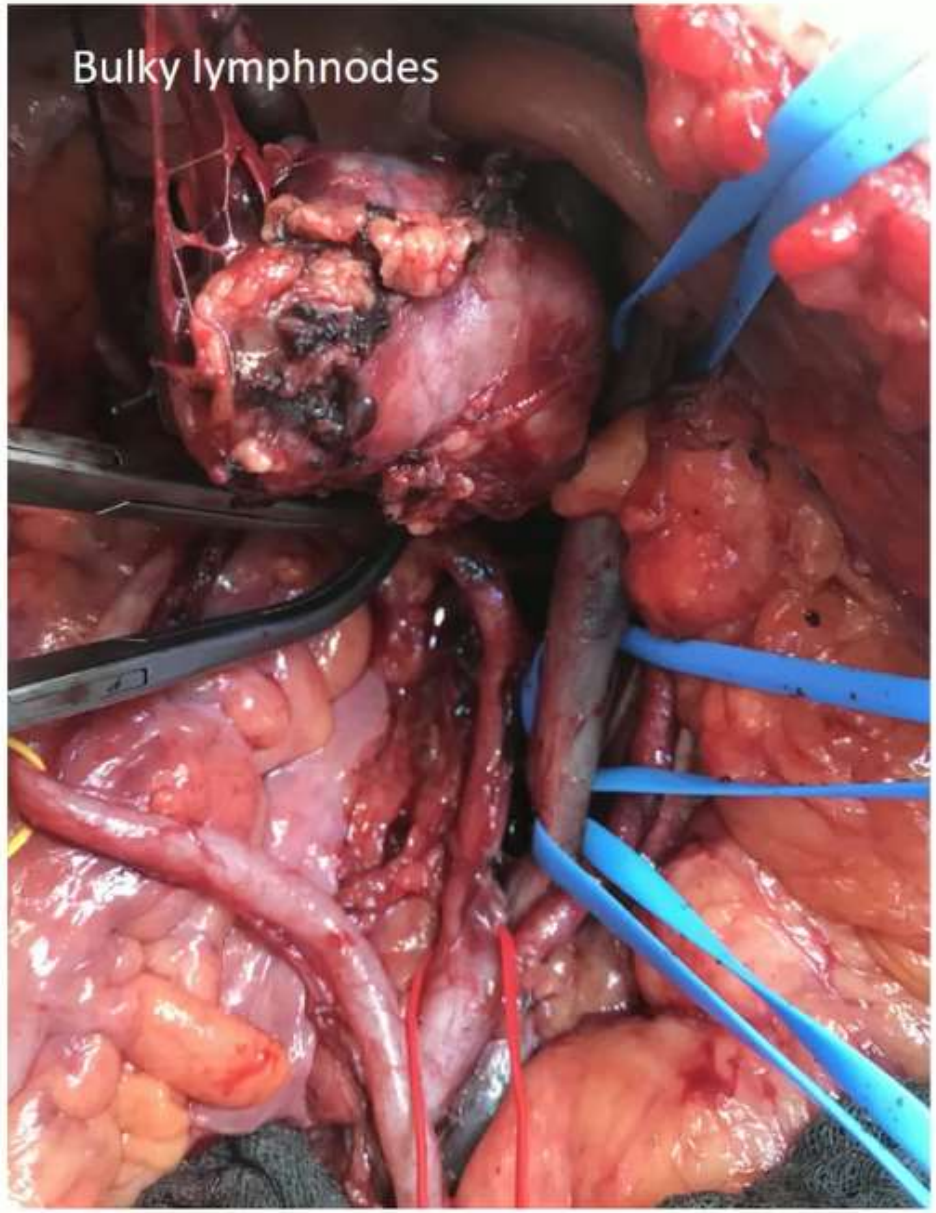
All the areas highlighted in green need to be checked for tumour involvement during surgery and removed if affected.

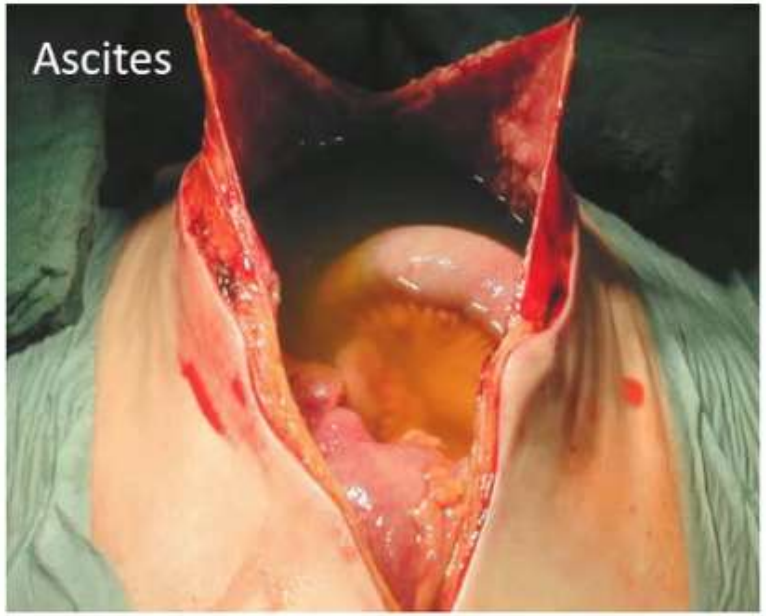
This again illustrates why open access surgery is the only adequate way to approach ovarian cancer.



Heterogeneity of epithelial ovarian cancer reflected by pattern of spread

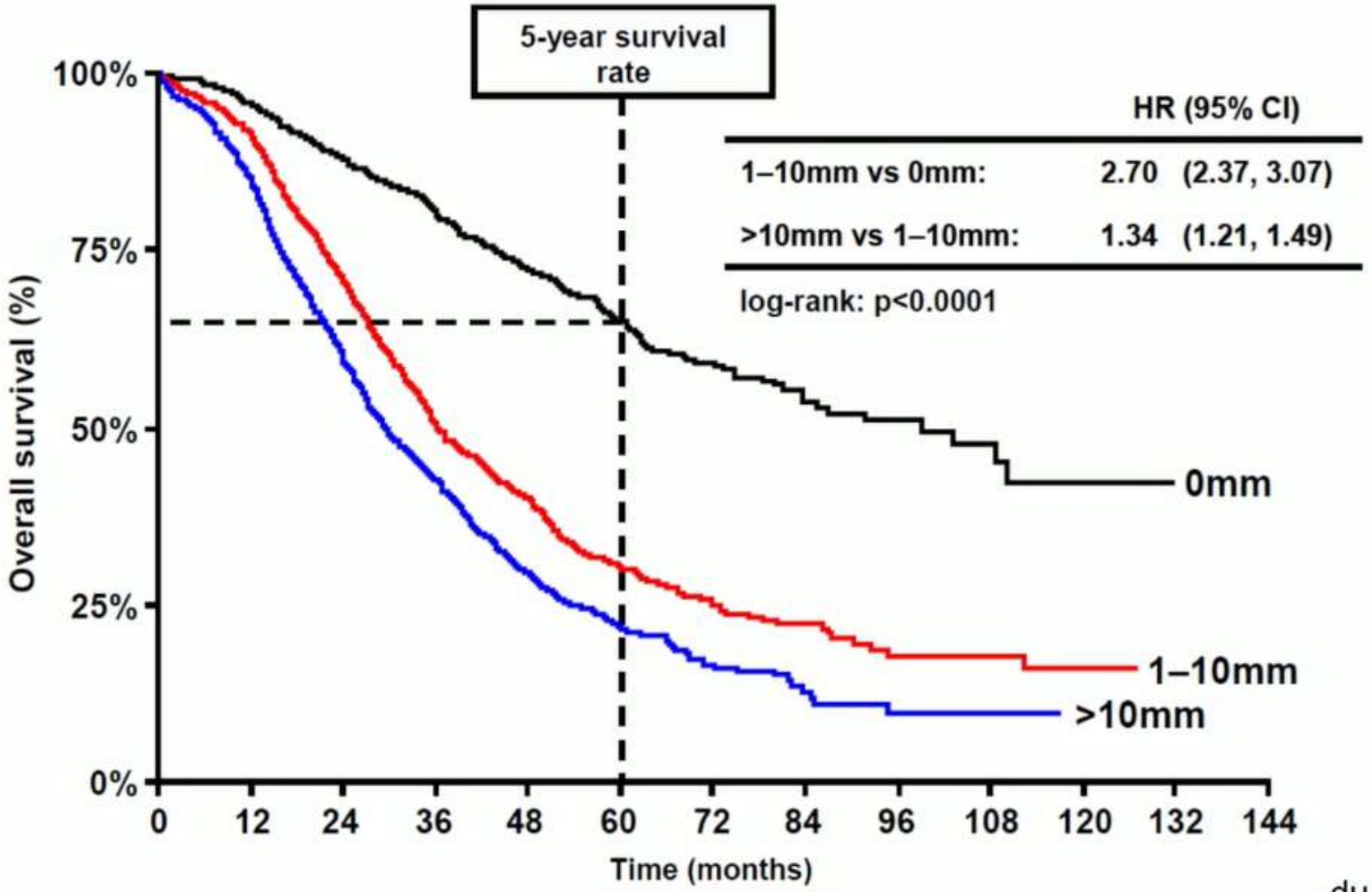






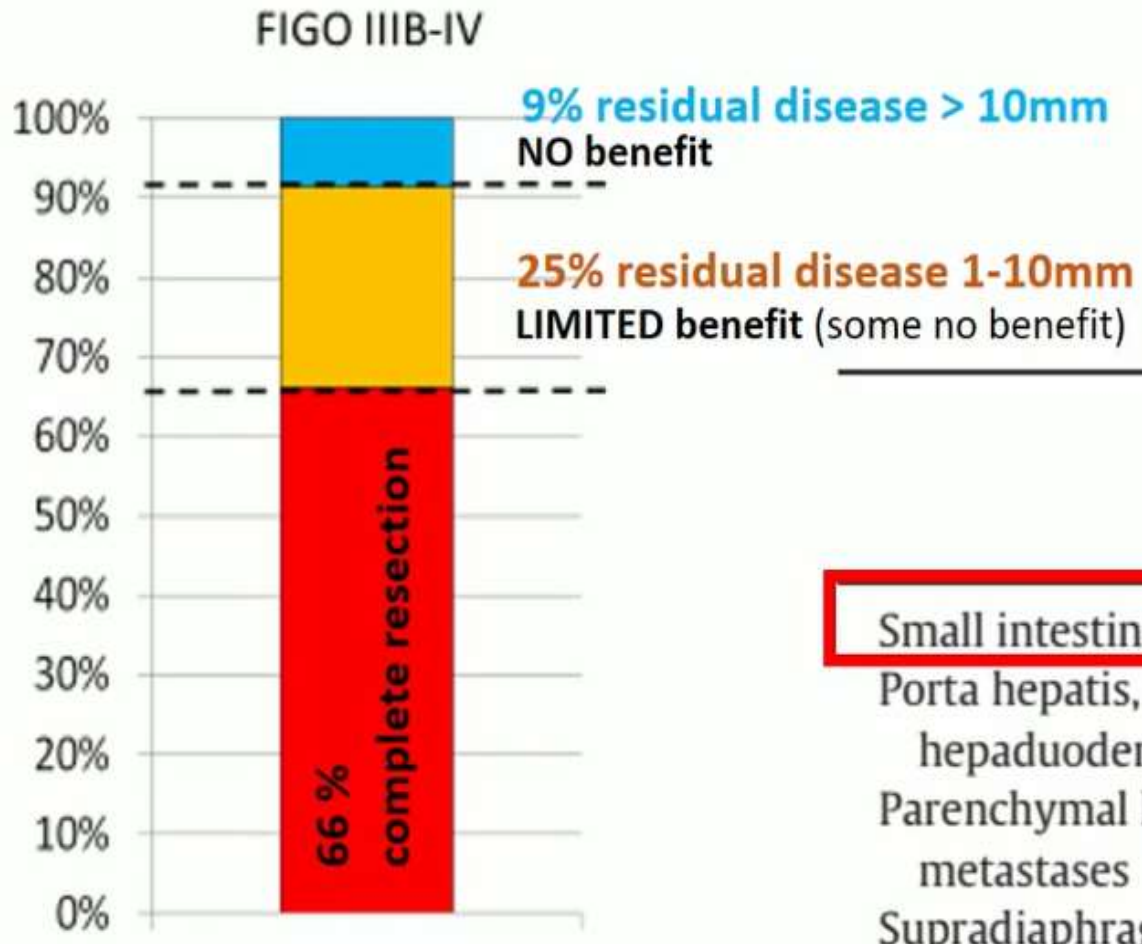
Impact of postoperative residual disease on outcome in advanced ovarian cancer

Data from an individual patient meta-analysis of **three randomised frontline phase III trials** (AGO-OVAR 3, 5, and 7) with **3126 patients**



du Bois et al. *Cancer 2009*

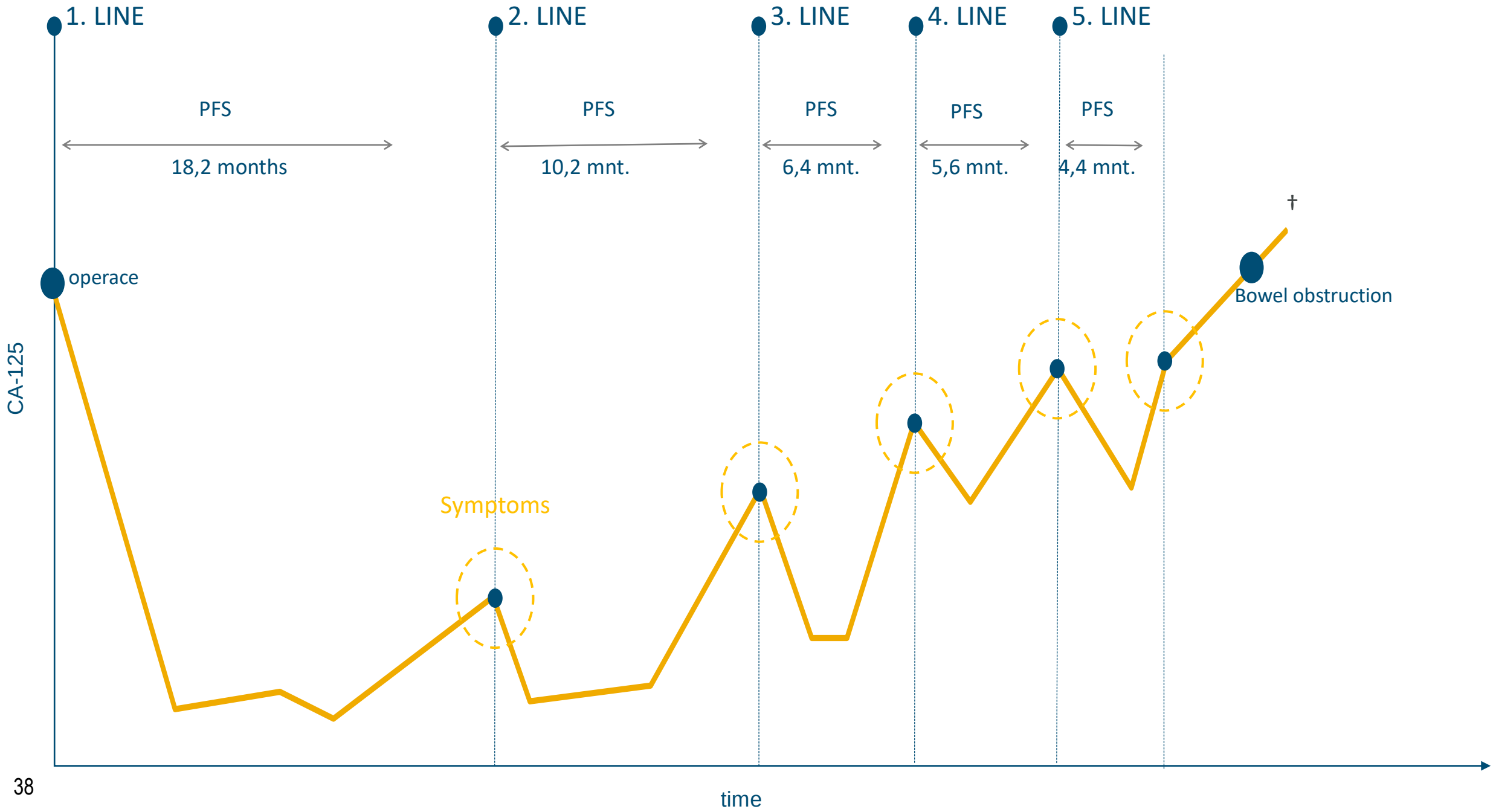
Location of residual disease after initial debulking surgery: reflecting tumour biology?



Gynaecologic Oncology Centers Wiesbaden&Essen, Germany
Heitz et al, *Gynecol Oncol 2016*

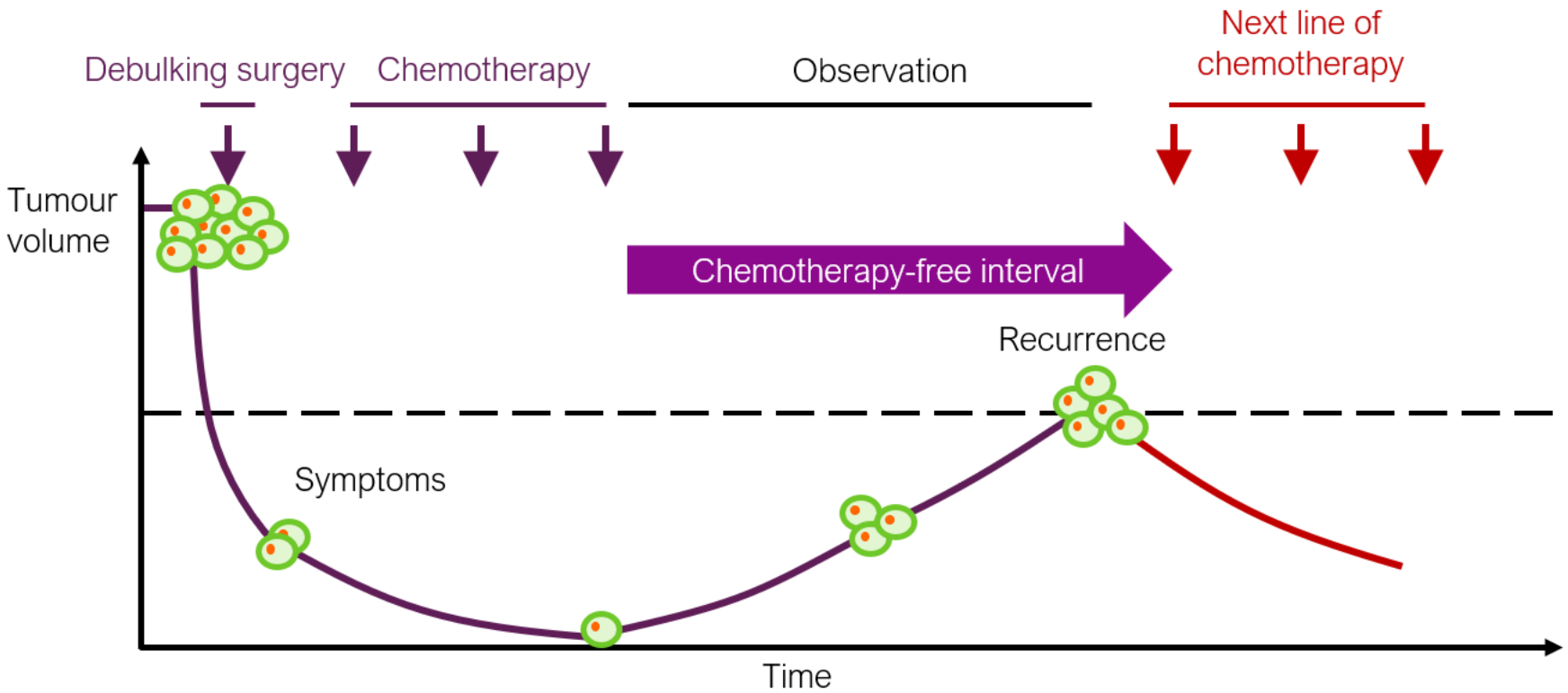
Location of residual disease

	All N = 191	TR 1–10 mm N = 144 (75.4%)	TR > 10 mm N = 47 (24.6%)	*p*-Value‡
Small intestine*	150 (79.8%)	124 (87.9%)	26 (55.3%)	<0.001
Porta hepatis, lig. hepaduodenale	19 (10.1%)	7 (5.0%)	12 (25.5%)	<0.001
Parenchymal liver metastases	8 (4.3%)	1 (0.7%)	7 (14.9%)	<0.001
Supradiaphragmatic†	28 (14.9%)	21 (14.9%)	7 (14.9%)	1.000
Pancreas	15 (8%)	4 (2.8%)	11 (23.4%)	<0.001
Stomach	6 (3.2%)	2 (1.4%)	4 (8.5%)	0.035
Truncus coeliacus	5 (2.7%)	2 (1.4%)	3 (6.4%)	0.101


1. LINE
2. LINE
3. LINE
4. LINE
5. LINE
PFS
18,2 months
PFS
10,2 mnt.
PFS
6,4 mnt.
PFS
5,6 mnt.
PFS
4,4 mnt.
†
operace
Bowel obstruction
Symptoms
CA-125
time

OC is challenging to treat; despite excellent responses to chemotherapy, disease recurrence is typical

Management of OC:[1]

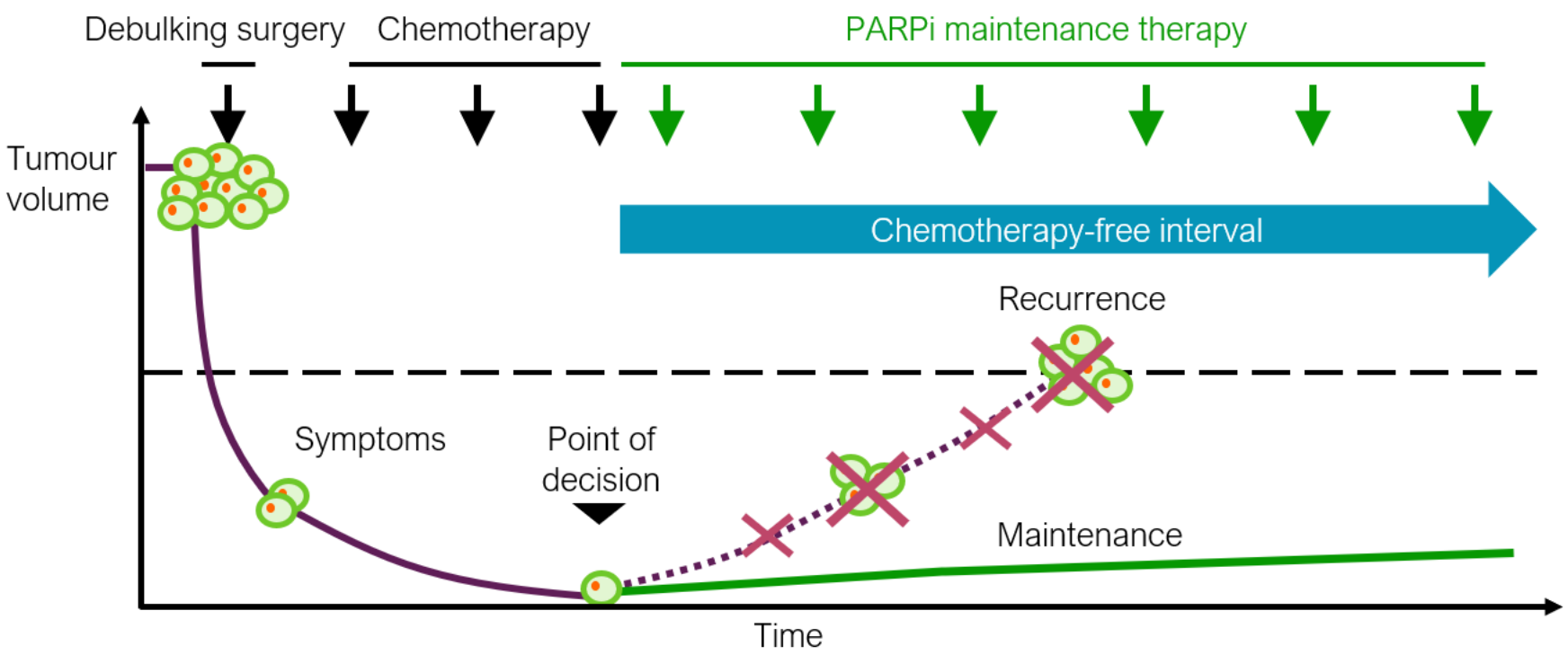


>70% of patients with advanced OC will recur within 3–5 years in the absence of 1L maintenance therapy[2,3]

Figure is for illustrative purposes only.
1L, first line; OC, ovarian cancer.
1. DiSilvestro P, Alvarez Secord A. Cancer Treat Rev 2018;69:53-65; 2. Ledermann JA, et al. Ann Oncol 2013;24:vi24–vi32; 3. du Bois A, et al. Cancer 2009;115:1234–44.

Maintenance therapy with PARPis have brought forward a paradigm shift, altering the natural course of disease in ovarian cancer by extending PFS

Management of OC:[1]

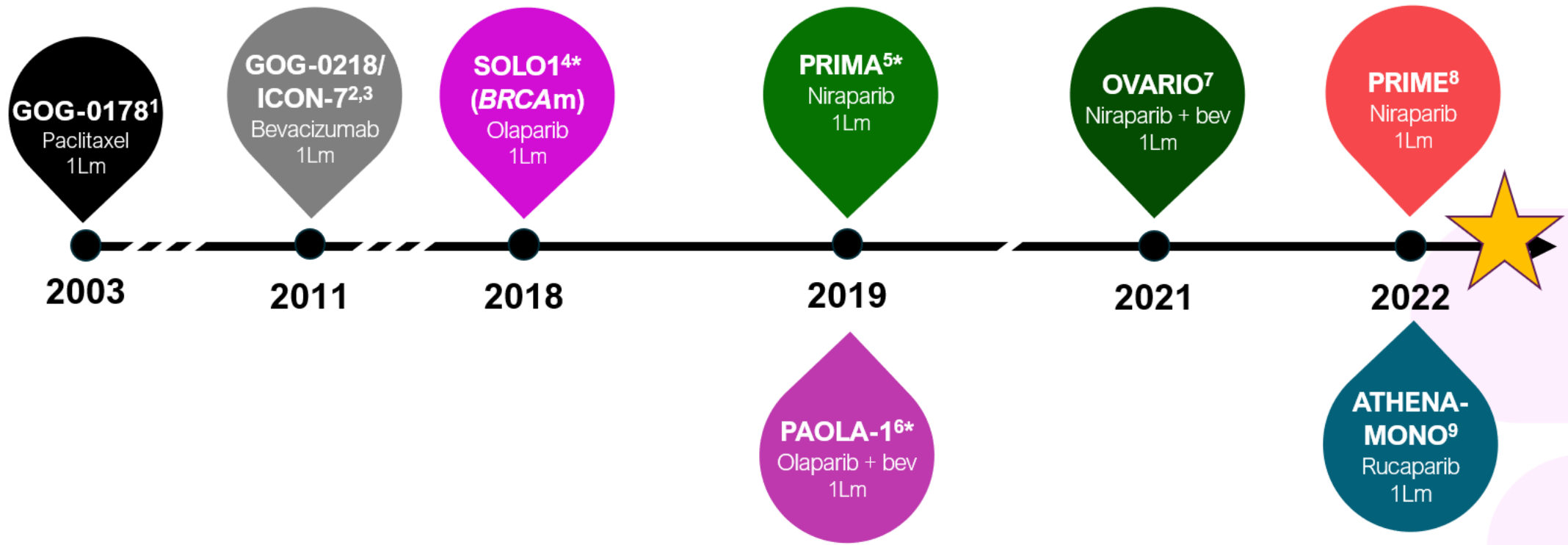


Goals of maintenance therapy

1. Prolong benefit following surgery and chemotherapy
2. Improve survival (PFS and hopefully OS)
3. Manageable toxicity and no negative effects on QoL

Figure is for illustrative purposes only.
OC, ovarian cancer; OS, overall survival; PARPi, poly(ADP-ribose)polymerase inhibitor; PFS, progression-free survival; QoL, quality of life.
1. DiSilvestro P, Alvarez Secord A. Cancer Treat Rev 2018;69:53-65.

Milestones in the evolution of maintenance therapy have advanced the standard of care for ovarian cancer

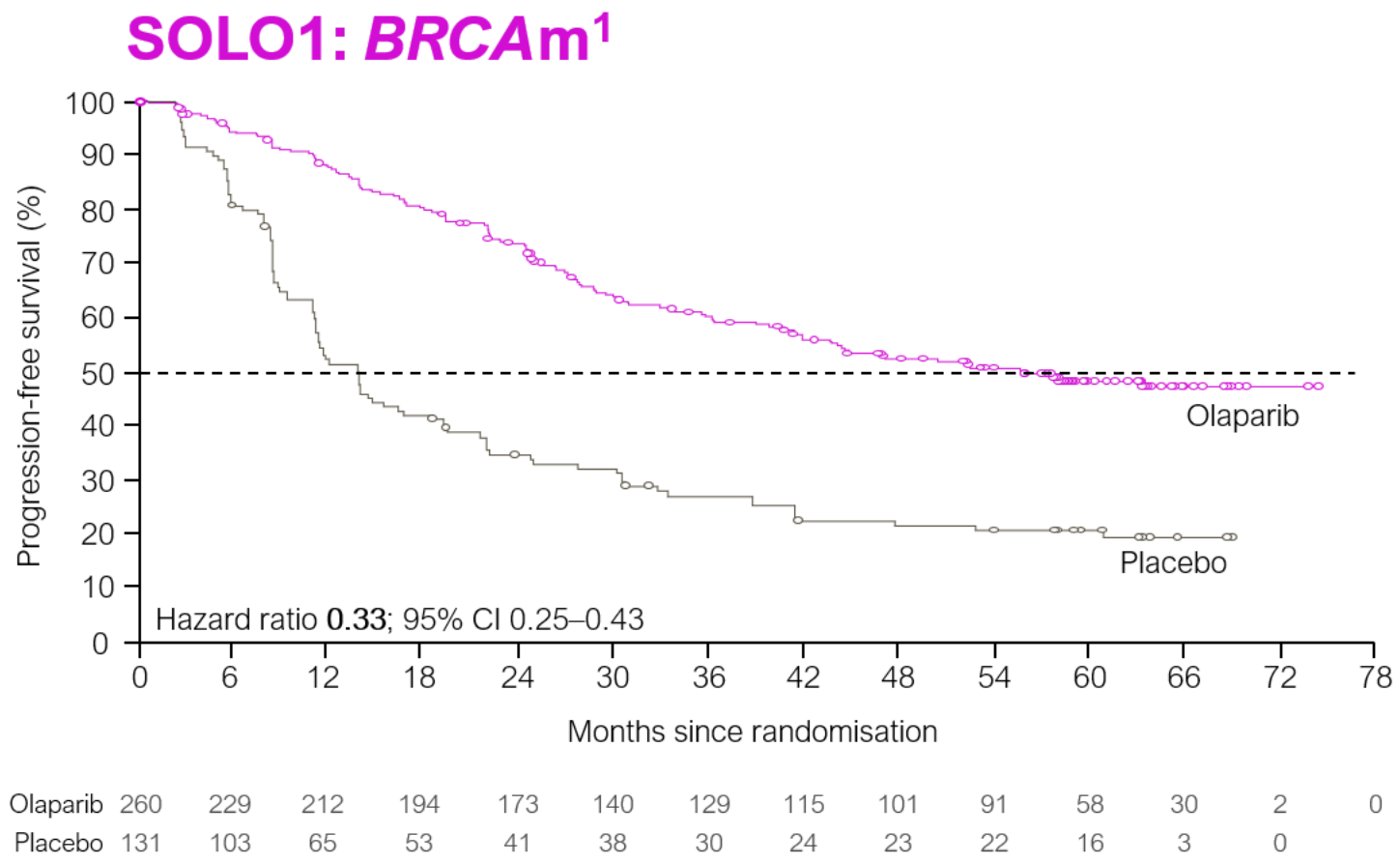


Long-term data readouts for PRIMA, SOLO1 and PAOLA-1 in 2022

PRIME was sponsored by Zai Lab (Shanghai) Co., Ltd. 1Lm, first-line maintenance; bev, bevacizumab; *BRCA*m, breast cancer gene mutant.

1. Markman M, et al. J Clin Oncol 2003;21:2460–5; 2. Burger RA, et al. N Engl J Med 2011;365:2473–83; 3. Perren TJ, et al. N Engl J Med 2011;365:2484–96; 4. Moore K, et al. N Engl J Med 2018;379:2495–505; 5. González-Martín A, et al. N Engl J Med 2019;381:2391–402; 6. Ray-Coquard I, et al. N Engl J Med 2019;381:2416–28; 7. Hardesty MM, et al. Gynecol Oncol 2022;166:219-29; 8. Li N, et al. presented at SGO 2022, 18–21 Mar, Phoenix, AZ; 9. Monk BJ, et al. J Clin Oncol 2022; https://doi.org/10.1200/JCO.22.01003.

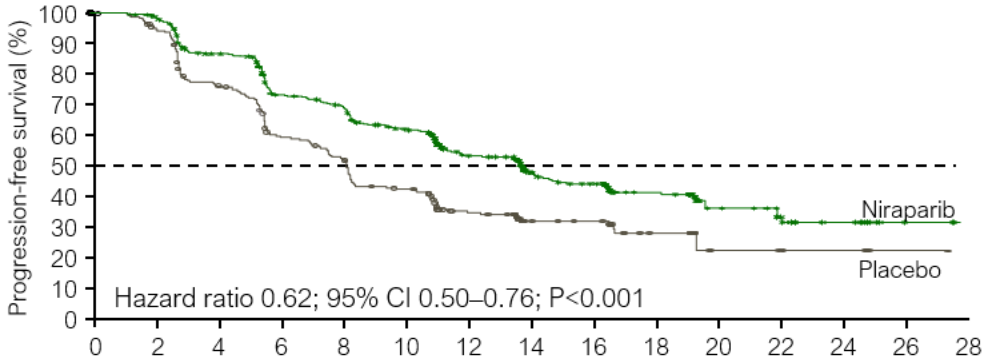
SOLO1: PFS benefit derived from maintenance with olaparib was sustained substantially beyond the end of treatment (5-year follow-up)



*Data cut-off: March 2020; Median follow-up: olaparib, 4.8 years, placebo, 5.0 years.
*BRCA*m, breast cancer gene mutant; CI, confidence interval; PFS, progression-free survival.
1. Banerjee S, et al. Lancet Oncol 2021;22:1721–31.

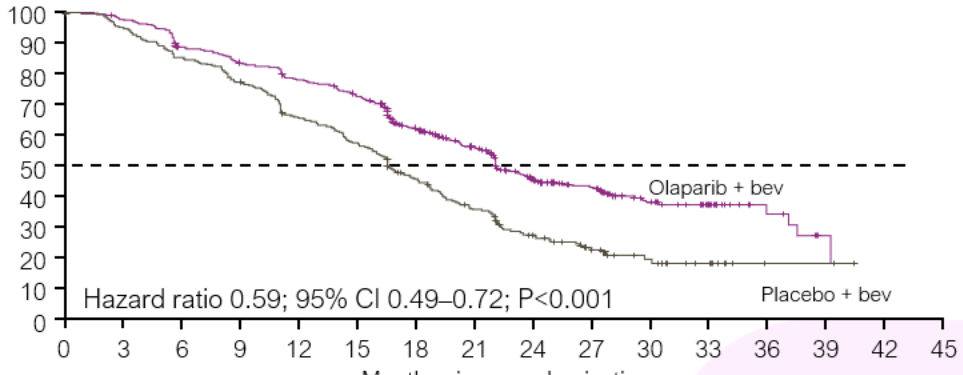
PARPi maintenance improves PFS in newly diagnosed advanced OC patients in pivotal trials

PRIMA: ITT (all biomarker subgroups)[1]



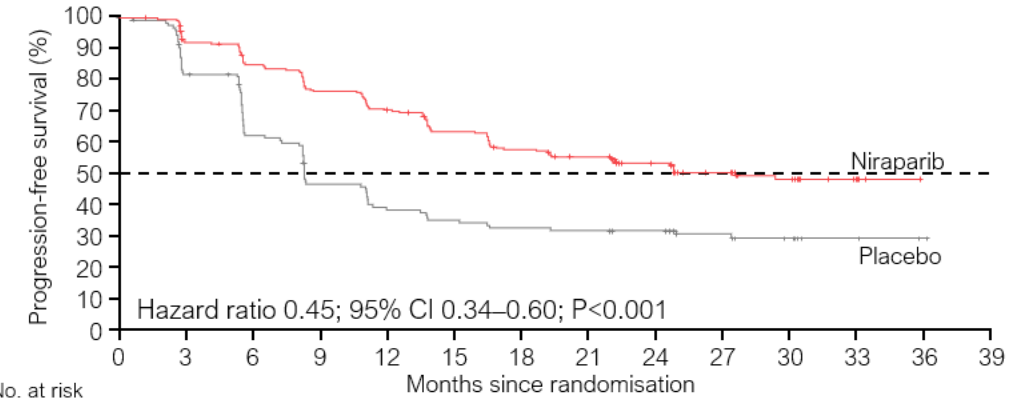
No. at risk															
Niraparib	487	454	385	312	295	253	167	111	94	58	29	21	13	4	0
Placebo	246	226	177	133	117	90	60	32	29	17	6	6	4	1	0

PAOLA-1: ITT (all biomarker subgroups)[4]



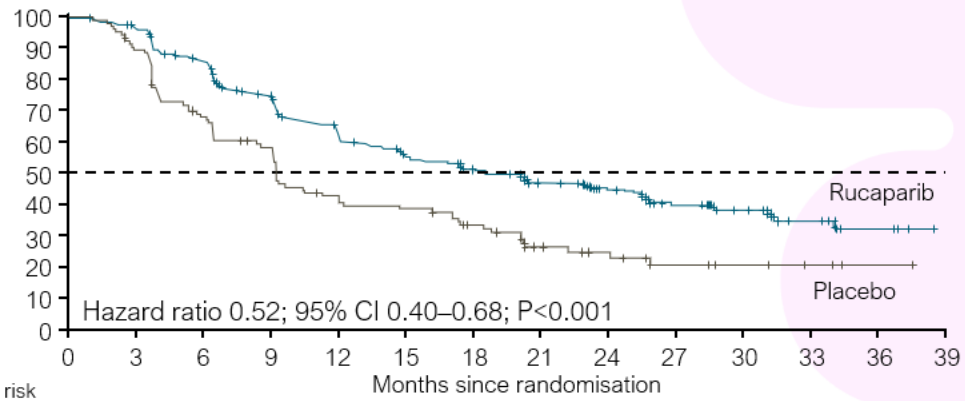
No. at risk															
Olaparib + bev	537	513	461	433	403	374	279	240	141	112	55	37	12	3	0
Placebo + bev	269	252	226	205	172	151	109	83	50	35	15	9	1	1	0

PRIME: ITT (all biomarker subgroups)[2]



No. at risk														
Niraparib	255	227	207	186	170	151	136	125	103	72	41	13	0	0
Placebo	129	101	74	54	44	40	37	36	32	24	17	4	1	0

ATHENA-MONO: ITT (all biomarker subgroups)[3]



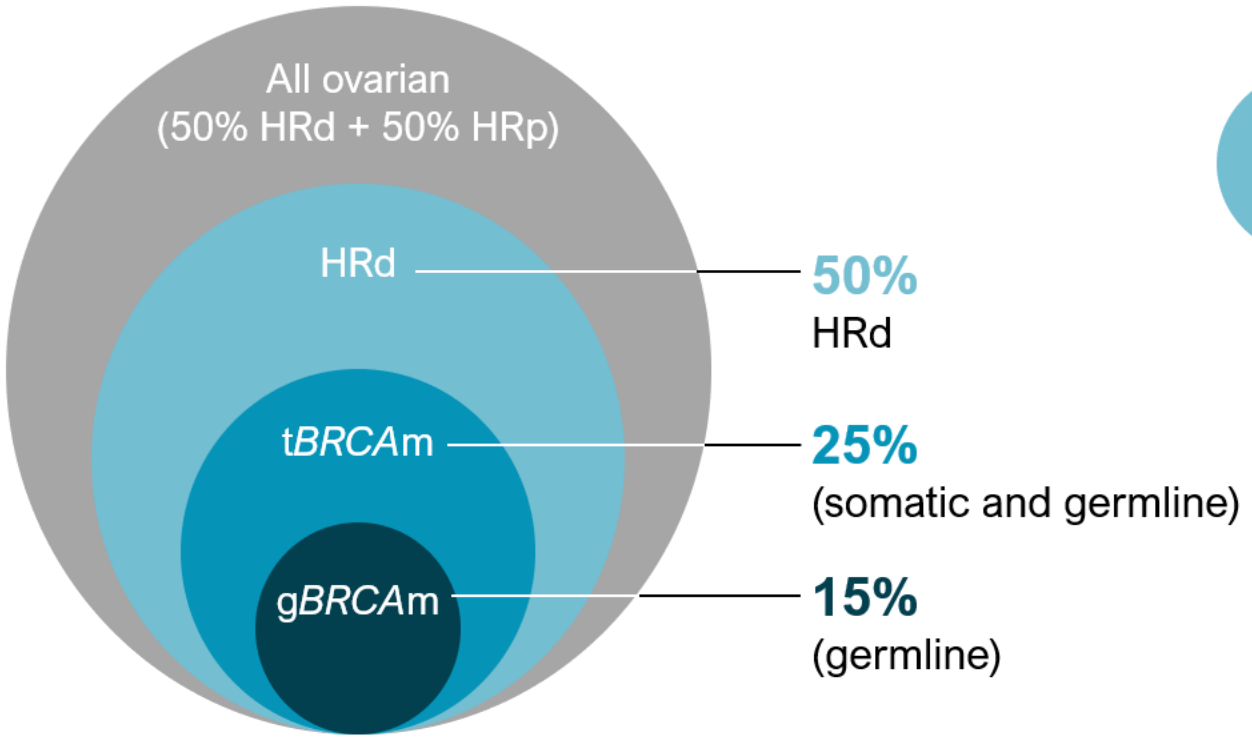
No. at risk														
Rucaparib	427	398	351	298	245	213	190	151	114	67	42	23	7	0
Placebo	111	97	72	60	42	39	31	18	14	8	5	3	1	0

There are no completed direct head-to-head-trials of these products. These data are from different clinical trials, and since there are inherent limitations in cross-study comparisons, caution should be exercised in interpreting these data. These data are for information purposes only and are not intended to imply or infer the noninferiority or superiority of either product, in terms of efficacy or safety.

PRIME was sponsored by Zai Lab (Shanghai) Co., Ltd. Bev, bevacizumab; CI, confidence interval; ITT, intention-to-treat; OC; ovarian cancer; PARPi, poly(ADP-ribose)polymerase inhibitor; PFS, progression-free survival. 1. Figure from N Engl J Med, González-Martín et al, Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer, Volume 381, Pages 2391–402. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; 2. Li N, et al. presented at SGO 2022, 18–21 Mar, Phoenix, AZ; 3. Monk BJ, et al. J Clin Oncol 2022; https://doi.org/10.1200/JCO.22.01003; 4. Figure adapted from N Engl J Med, Ray-Coquard et al, Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer, Volume 381, Pages 2416–28. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Biomarkers play an important role in diagnosing and defining patient populations in ovarian cancer

Half of high-grade serous OC exhibits a high degree of genomic instability due to deficiencies in homologous recombination



50% are HRd including *BRCA*m, *BRCA*1/2 and RAD51 promoter methylation, BRIP1, and other genes involved in homologous recombination[1,2]

25% are t*BRCA*m at diagnosis[1,2]

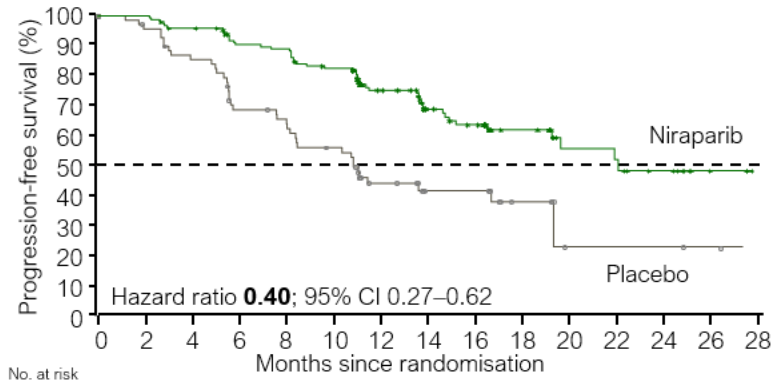
15% are g*BRCA*m at diagnosis[1,2]

BRCA, breast cancer gene; BRIP1, *BRCA*1-interacting protein; g*BRCAm*, germline *BRCA* mutant; HRd, homologous recombination deficient; HRp, homologous recombination proficient; OC, ovarian cancer; t*BRCA*m, tumour *BRCA* mutant.

1. Abkevich V, et al. Br J Cancer 2012;107:1776–82; 2. The Cancer Genome Atlas Research Network. Nature 2011;474:609–15.

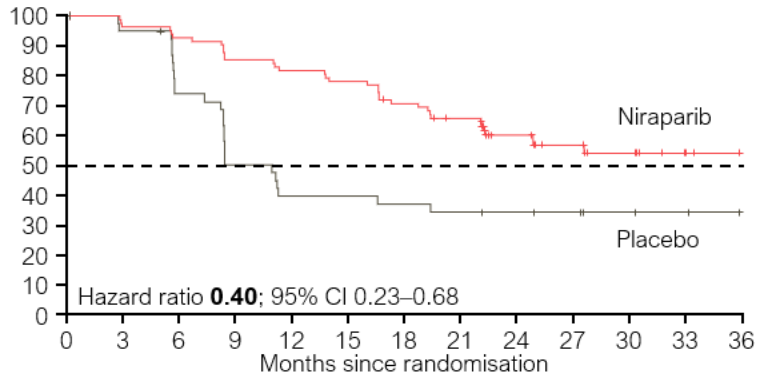
1L trials show substantial PFS benefit with PARPi maintenance therapy in patients with *BRCA*m tumours

PRIMA: *BRCA*m[1,2]



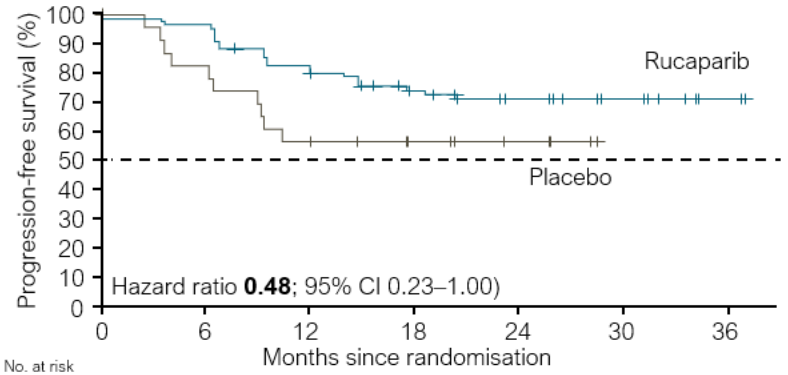
No. at risk															
Niraparib	152	148	140	127	125	113	77	55	48	29	15	14	10	4	0
Placebo	71	65	57	44	41	34	21	14	14	7	2	2	2	1	0

PRIME: *BRCA*m[3]



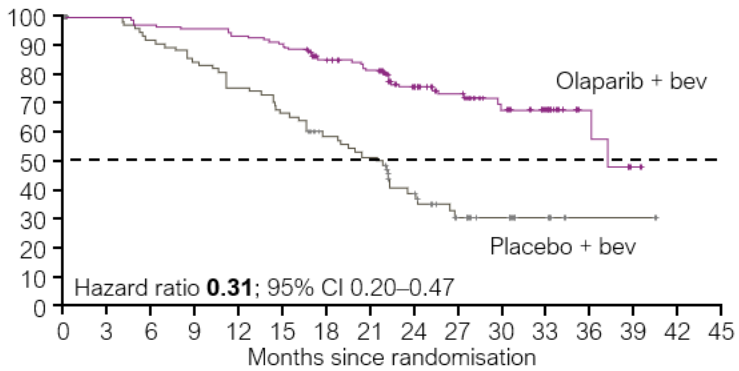
Niraparib	85	79	76	70	67	64	57	51	39	26	13	4	0	
Placebo	40	37	28	19	15	15	14	13	11	8	6	3	0	

ATHENA-MONO: *BRCA*m[4]



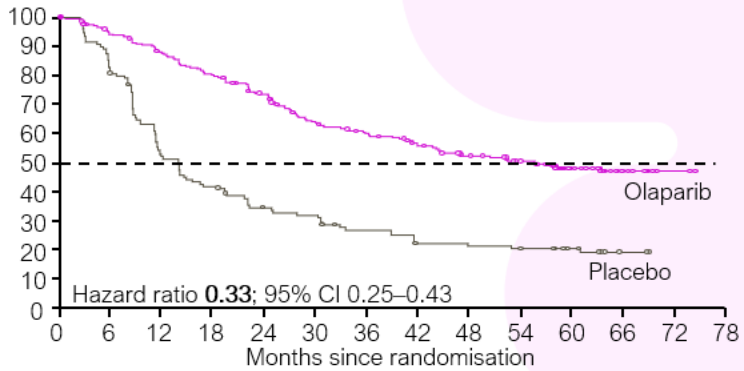
No. at risk							
Rucaparib	91	84	67	57	31	13	2
Placebo	24	19	12	9	4	0	

PAOLA-1: *BRCA*m[5]



Olaparib + bev	157	154	150	148	144	138	117	110	76	58	31	19	7	1	0
Placebo + bev	80	78	72	66	59	52	41	36	22	13	7	4	1	1	0

SOLO1: *BRCA*m[6]



Olaparib	260	229	212	194	173	140	129	115	101	91	58	30	2	0											
Placebo	131	103	65	53	41	38	30	24	23	22	16	3	0												

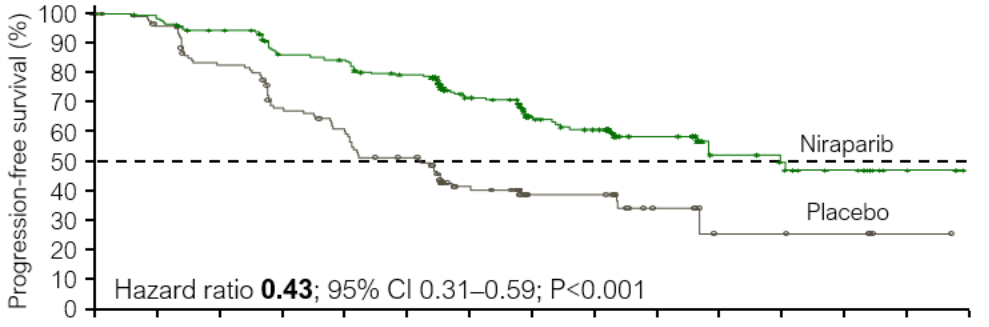
There are no completed direct head-to-head-trials of these products. These data are from different clinical trials, and since there are inherent limitations in cross-study comparisons, caution should be exercised in interpreting these data. These data are for information purposes only and are not intended to imply or infer the noninferiority or superiority of either product, in terms of efficacy or safety.

PRIME was sponsored by Zai Lab (Shanghai) Co., Ltd. 1L, first-line; Bev, bevacizumab; *BRCA*m, breast cancer gene mutant; CI, confidence interval; PARPi, poly(ADP-ribose)polymerase inhibitor; PFS, progression-free survival.

1. Figure from N Engl J Med, González-Martín et al, Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer, Volume 381, Pages 2391–402. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; 2. Korach J, et al. presented at ESGO SoA 2020, 14–16 Dec (virtual); 3. Li N, et al. presented at SGO 2022, 18–21 Mar, Phoenix, AZ; 4. Monk BJ, et al. J Clin Oncol 2022; https://doi.org/10.1200/JCO.22.01003; 5. Figure adapted from N Engl J Med, Ray-Coquard et al, Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer, Volume 381, Pages 2416–28. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; 6. Banerjee S, et al. Lancet Oncol 2021;22:1721–31.

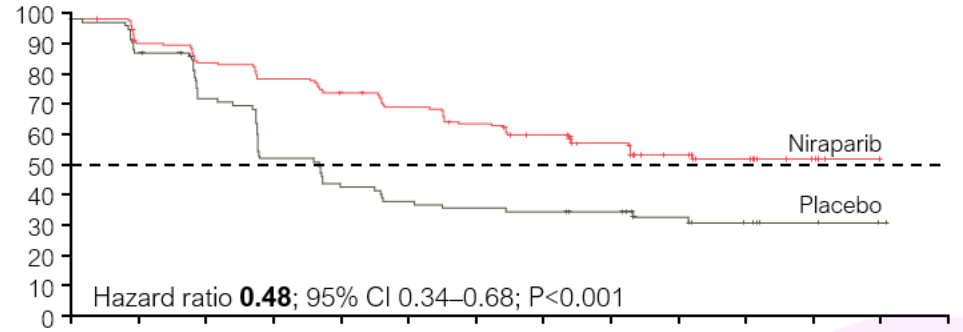
1L trials show substantial PFS benefit with PARPi maintenance therapy in patients with HRd tumours

PRIMA: HRd[1]



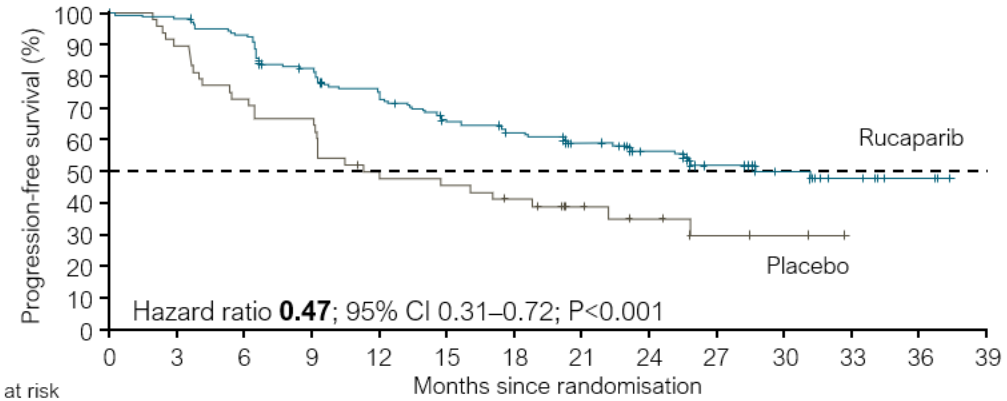
No. at risk														
Niraparib	247	231	215	189	184	168	111	76	66	42	22	19	13	4	0
Placebo	126	117	99	79	70	57	34	21	21	11	5	5	4	1	0

PRIME: HRd[2]



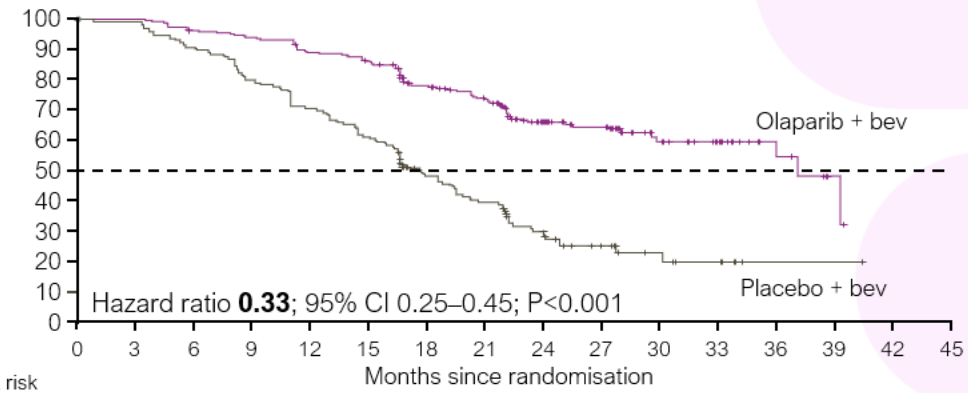
No. at risk														
Niraparib	170	150	139	130	121	112	102	93	75	51	26	10	0	0
Placebo	87	76	60	43	35	31	29	28	24	16	12	4	1	0

ATHENA-MONO: HRd[3]



No. at risk														
Rucaparib	185	175	165	143	127	110	100	82	59	36	22	12	3	0
Placebo	49	43	35	32	22	21	18	11	8	4	2	0		

PAOLA-1: HRd[4]



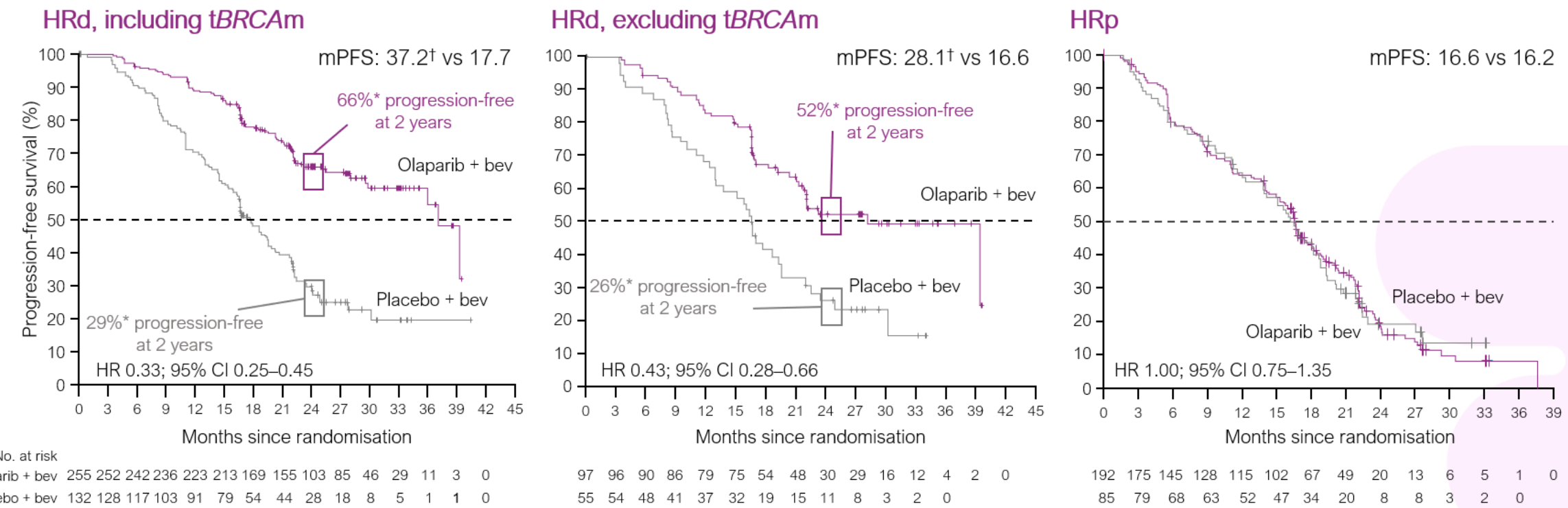
No. at risk															
Olaparib + bev	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

There are no completed direct head-to-head-trials of these products. These data are from different clinical trials, and since there are inherent limitations in cross-study comparisons, caution should be exercised in interpreting these data. These data are for information purposes only and are not intended to imply or infer the noninferiority or superiority of either product, in terms of efficacy or safety.

PRIME was sponsored by Zai Lab (Shanghai) Co., Ltd. 1L, first-line; Bev, bevacizumab; CI, confidence interval; HRd, homologous recombination deficient; PARPi, poly(ADP-ribose)polymerase inhibitor; PFS, progression-free survival. 1. Figure from N Engl J Med, González-Martín et al, Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer, Volume 381, Pages 2391–402. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; 2. Li N, et al. presented at SGO 2022, 18–21 Mar, Phoenix, AZ; 3. Monk BJ, et al. J Clin Oncol 2022; https://doi.org/10.1200/JCO.22.01003; 4. Figure adapted from N Engl J Med, Ray-Coquard et al, Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer, Volume 381, Pages 2416–28. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Why are initial treatment decisions so important?

Subgroup analysis of PAOLA-1 suggests no benefit for addition of olaparib to bevacizumab maintenance in HRp patients



No. at risk

Olaparib + bev	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo + bev	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

Olaparib + bev	97	96	90	86	79	75	54	48	30	29	16	12	4	2	0
Placebo + bev	55	54	48	41	37	32	19	15	11	8	3	2	0		

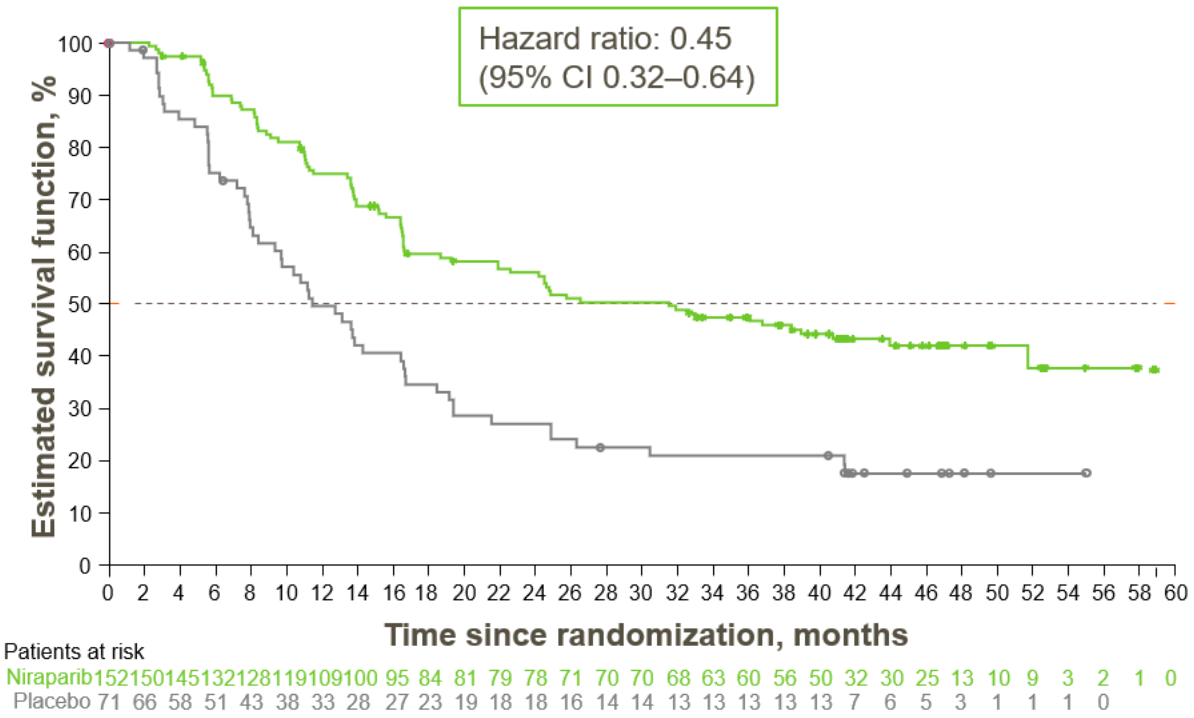
Olaparib + bev	192	175	145	128	115	102	67	49	20	13	6	5	1	0	
Placebo + bev	85	79	68	63	52	47	34	20	8	8	3	2	0		

These subgroup analyses were not powered to detect statistically significant treatment effect; therefore results should be interpreted with caution.

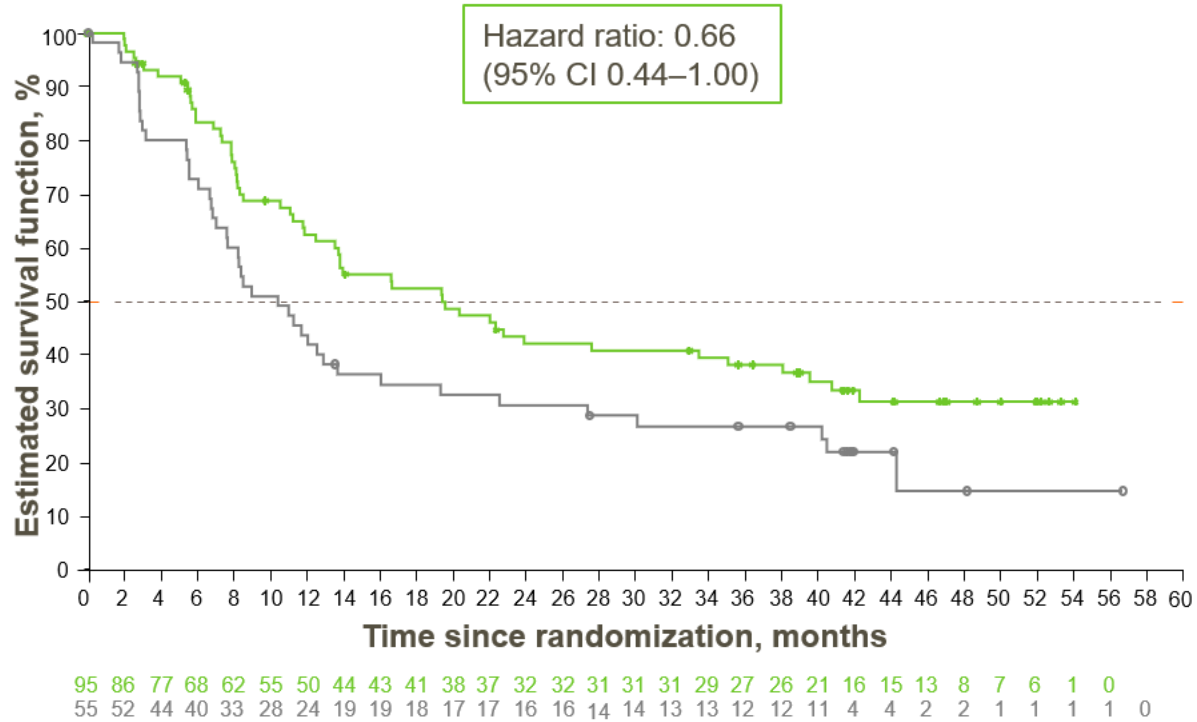
*Based on Kaplan-Meier estimates. †This median is unstable due to a lack of events – less than 50% maturity. HRd is an HRD score ≥42.
bev, bevacizumab; *BRCA*, breast cancer gene; CI, confidence interval; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRp, homologous recombination proficient; mPFS, median progression-free survival; t*BRCA*m, tumour *BRCA* mutation. Figures adapted from N Engl J Med, Ray-Coquard et al, Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer, Volume 381, Pages 2416–28 and the Supplementary Appendix.

Niraparib treatment increased PFS* duration compared with placebo across biomarkers, with greatest treatment benefit in patients with HRd *BRCA*m tumors

HRd *BRCA*m



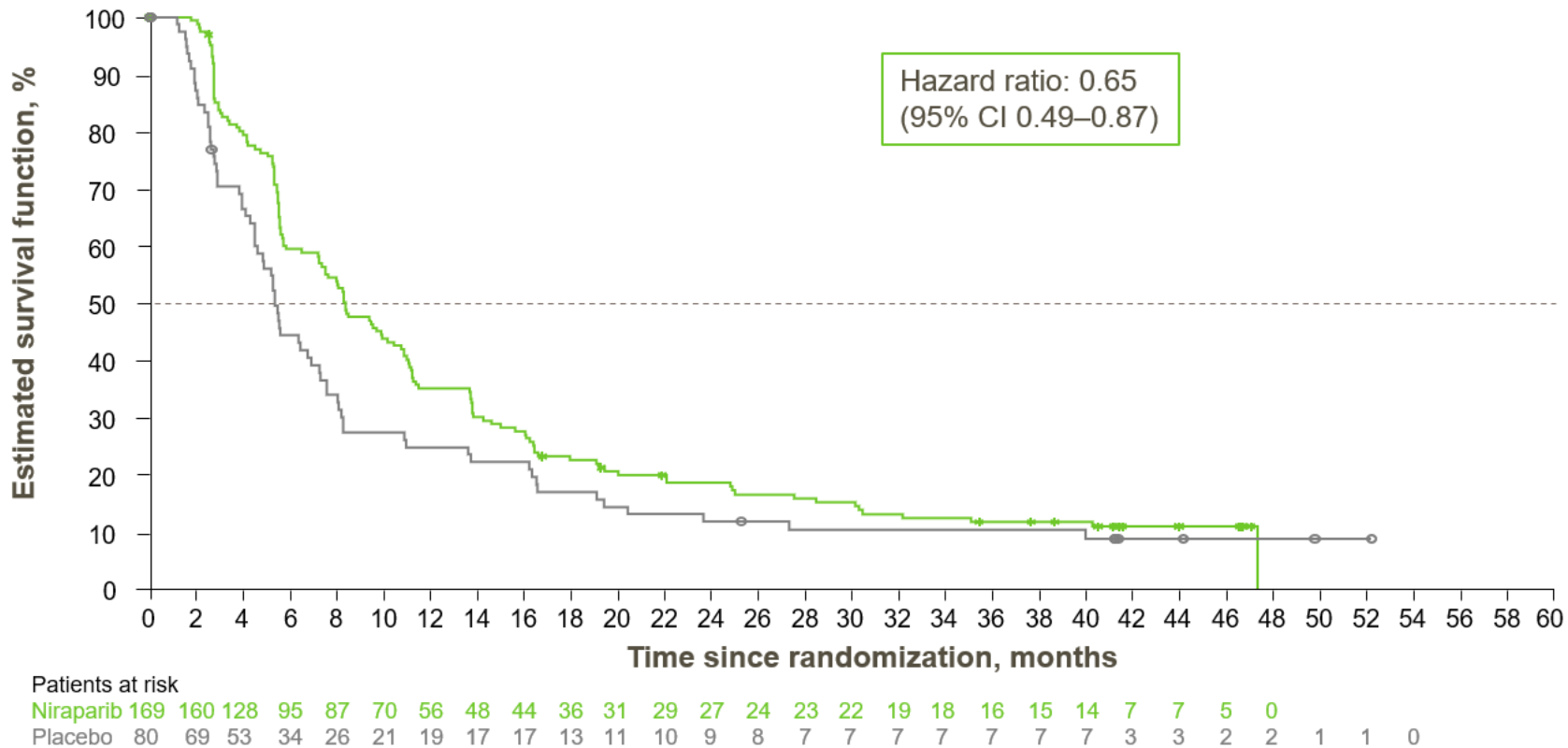
HRd *BRCA*wt



These prespecified subgroup analyses were not powered to detect statistically significant treatment effect; therefore results should be interpreted with caution.

Data cut-off: 17 Nov 2021. *PFS by investigator assessment.
*BRCA*m, breast cancer gene mutated; *BRCA*wt, breast cancer gene wild-type; CI, confidence interval; HRd, homologous recombination deficient; mPFS, median progression-free survival; PFS, progression-free survival.
González-Martín A, et al. Presented at ESMO 2022 (Poster #530), 9–13 Sep, Paris, France.

In the HRp population, a clinically meaningful 35% reduction of the risk of progression or death was observed



These prespecified subgroup analyses were not powered to detect statistically significant treatment effect; therefore results should be interpreted with caution.

Data cut-off: 17 Nov 2021. *PFS by investigator assessment.
CI, confidence interval; HRp, homologous recombination proficient; mPFS, median progression-free survival; PFS, progression-free survival.
González-Martín A, et al. Presented at ESMO 2022 (Poster #530), 9–13 Sep, Paris, France.

Ongoing randomised trials of PARPi monotherapy and treatment combinations will address additional gaps in the care of newly diagnosed OC patients

	Niraparib			Olaparib		Rucaparib	
	FIRST[1]	NIRVANA-1*[2]	AGO-OVAR 28*[3]	DUO-O[4]	KEYLYNK-001[5]	ATHENA-COMBO[6]	MITO-25[7]
Treatment arms	Dostarlimab concurrent with CT followed by niraparib + dostarlimab maintenance ± bevacizumab	CT ± bevacizumab followed by niraparib ± bevacizumab (vs CT followed by niraparib)	CT ± bevacizumab followed by niraparib ± bevacizumab (vs CT followed by niraparib)	Durvalumab concurrent with CT and bevacizumab followed by durvalumab + bevacizumab ± olaparib	Pembrolizumab concurrent with CT and continuation ± olaparib maintenance	CT followed by rucaparib + nivolumab maintenance	CT ± bevacizumab followed by rucaparib maintenance ± bevacizumab or bevacizumab alone
Patient population	Biomarker unselected			Non-*BRCA*m		Biomarker unselected	
Biomarker stratification	HRD status	*BRCA*m		Not available	PD-L1	*BRCA*m, LOH	HRD status
Estimated primary completion date	July 2023	January 2024	February 2028	June 2023	October 2023	December 2024	March 2025

There are no completed direct head-to-head-trials of these products. These data are from different clinical trials, and since there are inherent limitations in cross-study comparisons, caution should be exercised in interpreting these data. These data are for information purposes only and are not intended to imply or infer the noninferiority or superiority of either product, in terms of efficacy or safety.

*Investigator-sponsored study. *BRCA*m, breast cancer gene mutant; CT, chemotherapy; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; OC, ovarian cancer; PARPi, poly(ADP-ribose)polymerase inhibitor; PD-L1, programmed death-ligand 1.

1. https://clinicaltrials.gov/ct2/show/NCT03602859; 2. https://clinicaltrials.gov/ct2/show/NCT05183984; 3. https://clinicaltrials.gov/ct2/show/NCT05009082; 4. https://clinicaltrials.gov/ct2/show/NCT03737643; 5. https://clinicaltrials.gov/ct2/show/NCT03740165; 6. https://clinicaltrials.gov/ct2/show/NCT03522246; 7. https://clinicaltrials.gov/ct2/show/NCT03462212 (All accessed: Jun 2022).

2023 ASCO ANNUAL MEETING

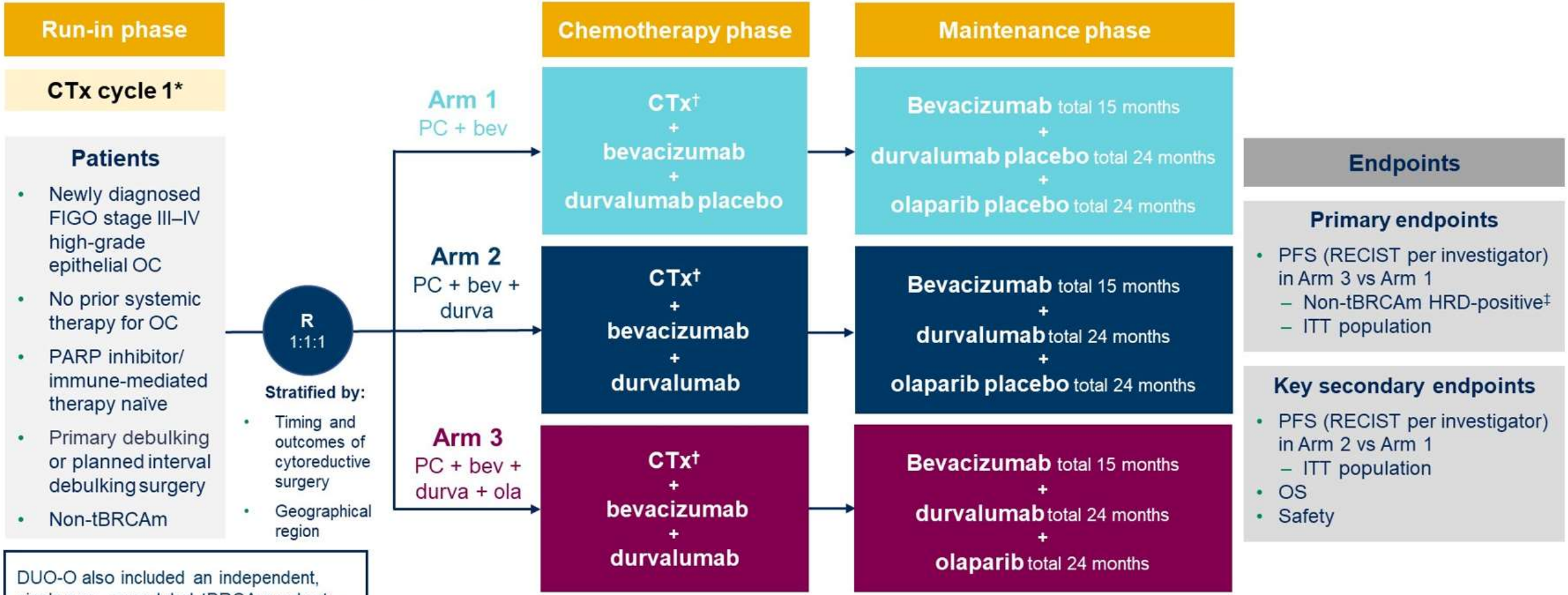
Durvalumab with paclitaxel/carboplatin and bevacizumab followed by maintenance durvalumab, bevacizumab and olaparib in patients with newly diagnosed advanced ovarian cancer without a tumor *BRCA1/BRCA2* mutation: results from the randomized, placebo-controlled Phase III DUO-O/ENGOT-ov46/AGO-OVAR 23/GOG-3025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

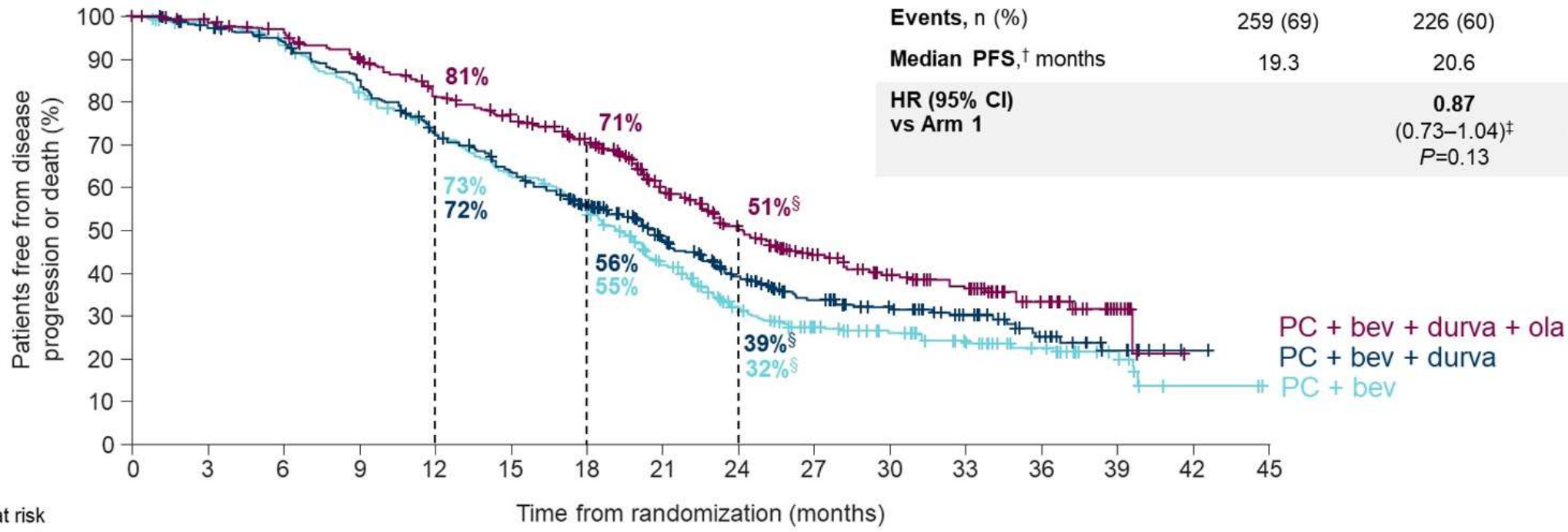
DUO-O study design



Dosing and schedule: bevacizumab (15 mg/kg IV q3w); durvalumab (1120 mg IV q3w); olaparib (300 mg po bid); chemotherapy: paclitaxel 175 mg/m^2 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



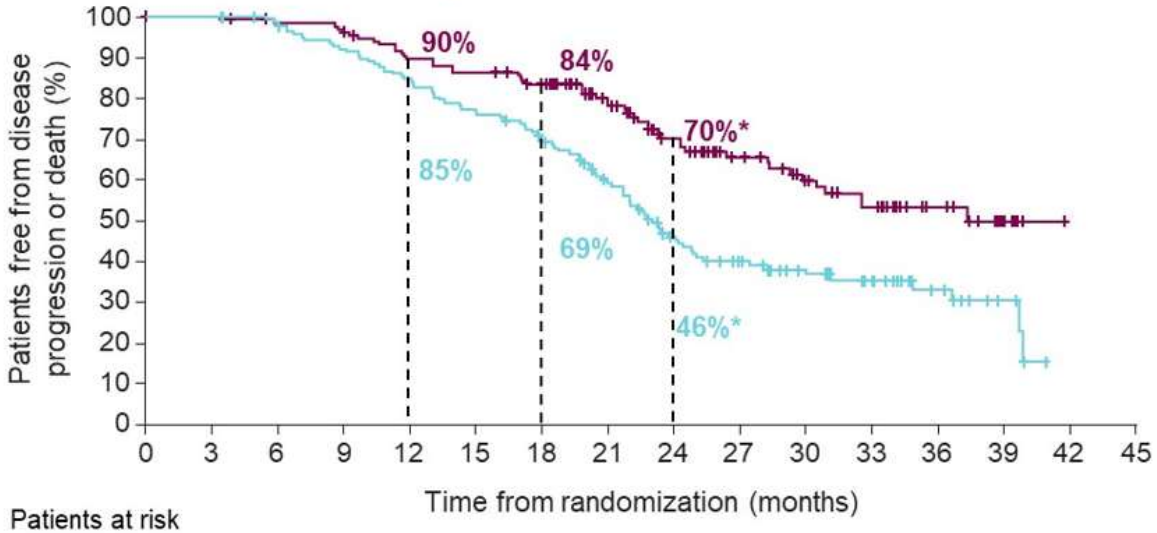
Patients at risk

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

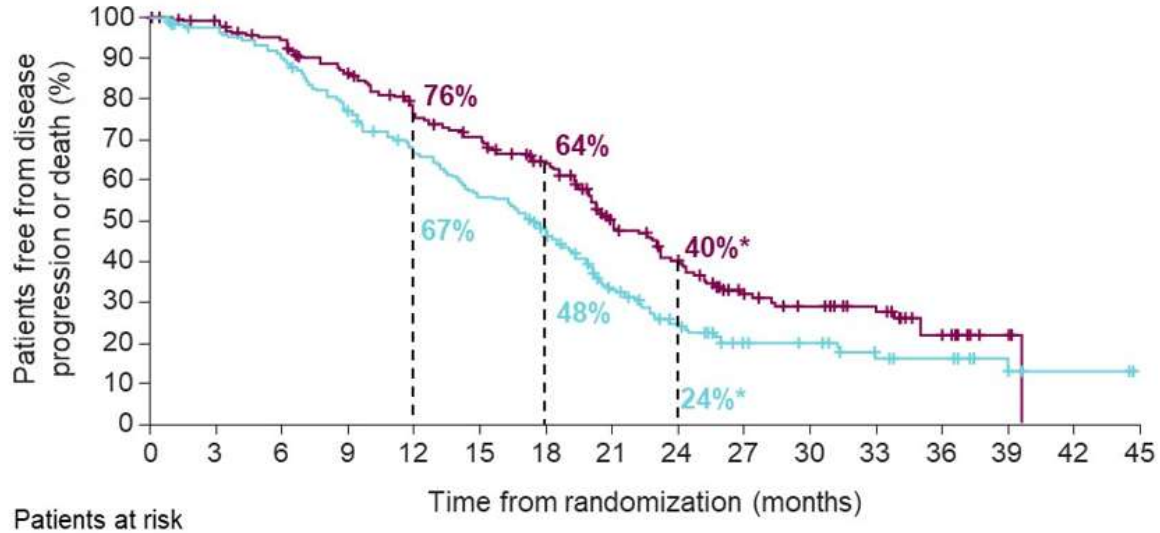


Patients at risk

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

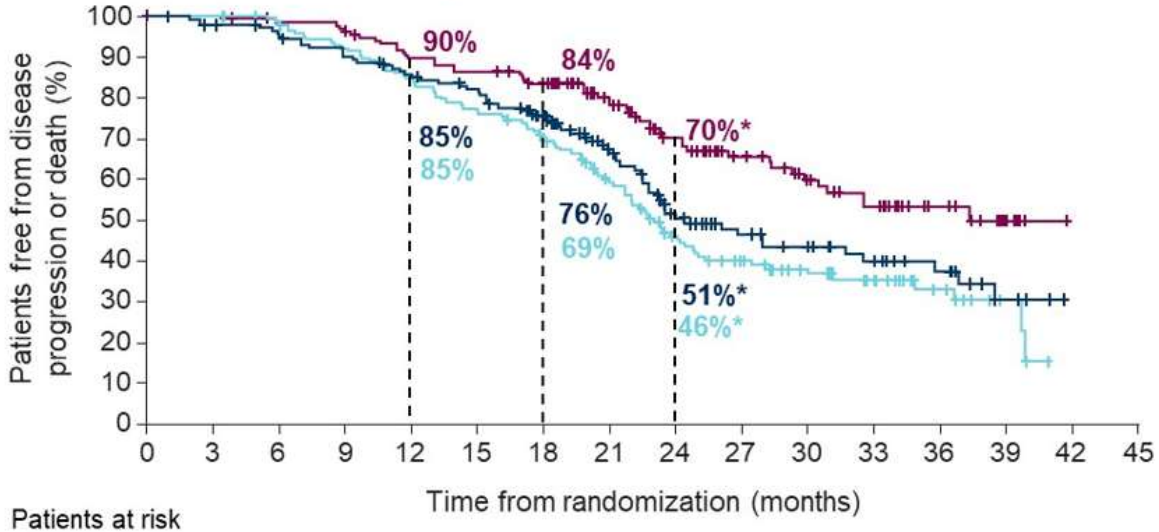
Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

	Arm 1 PC + bev N=216	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	127 (60)
Median PFS, months†	17.4	20.9
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

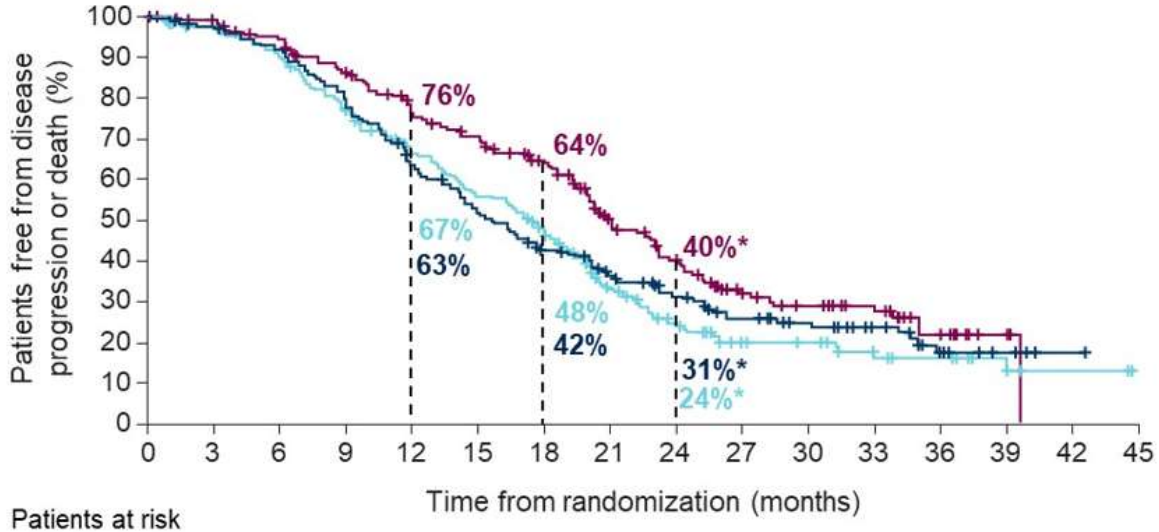


Patients at risk

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.

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

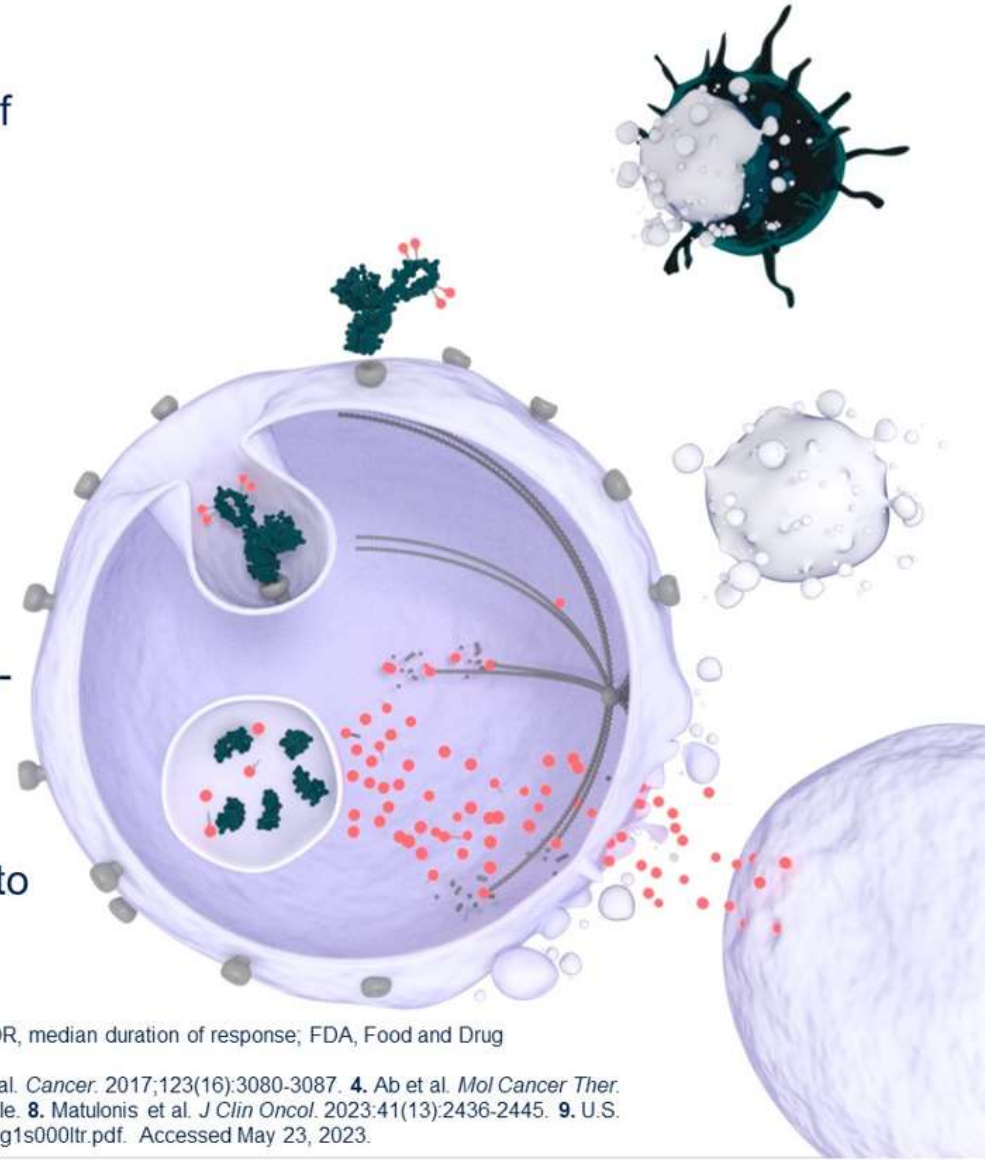
ENGOT European Network of Gynaecological Oncological Trial groups

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



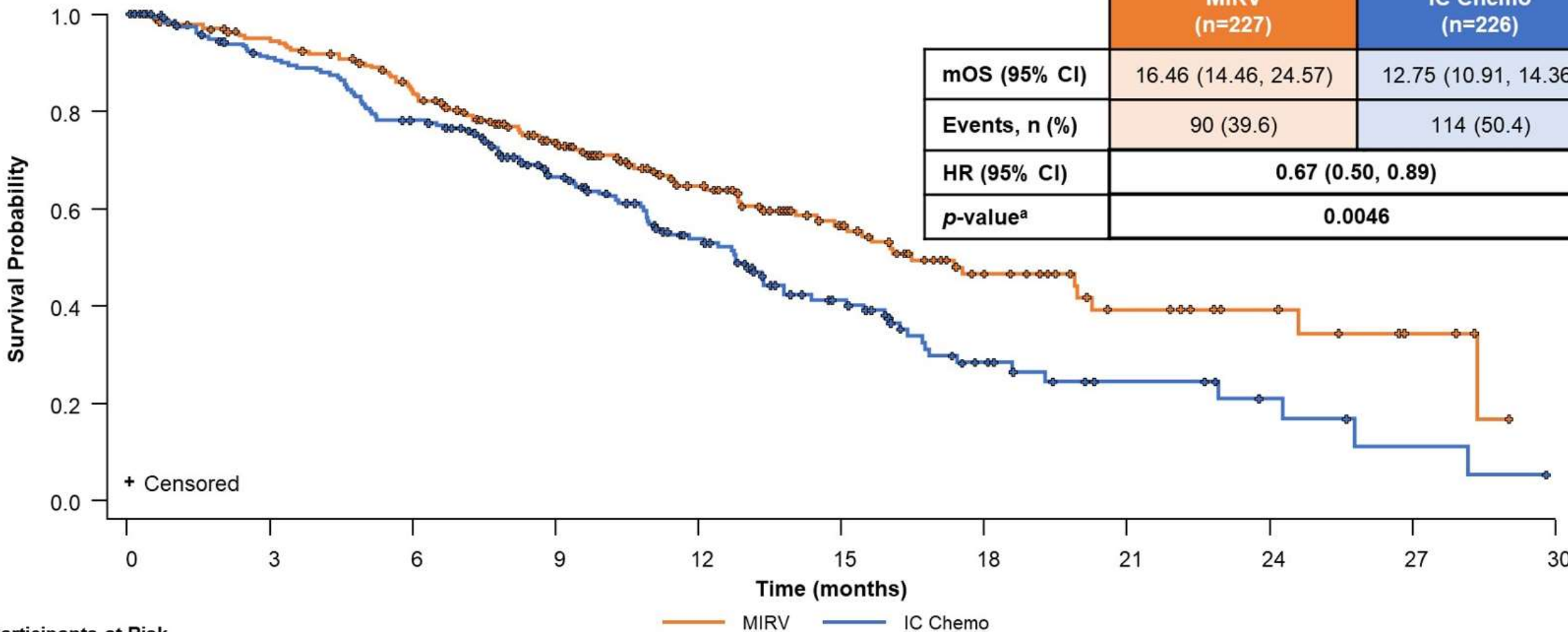
PFS, progression-free survival; OS, overall survival; FRα, folate receptor alpha; ORR, objective response rate; ADC, antibody-drug conjugate; mDOR, median duration of response; FDA, Food and Drug Administration; BEV, bevacizumab; US, United States; EU, Europe.

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.

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

Overall Survival

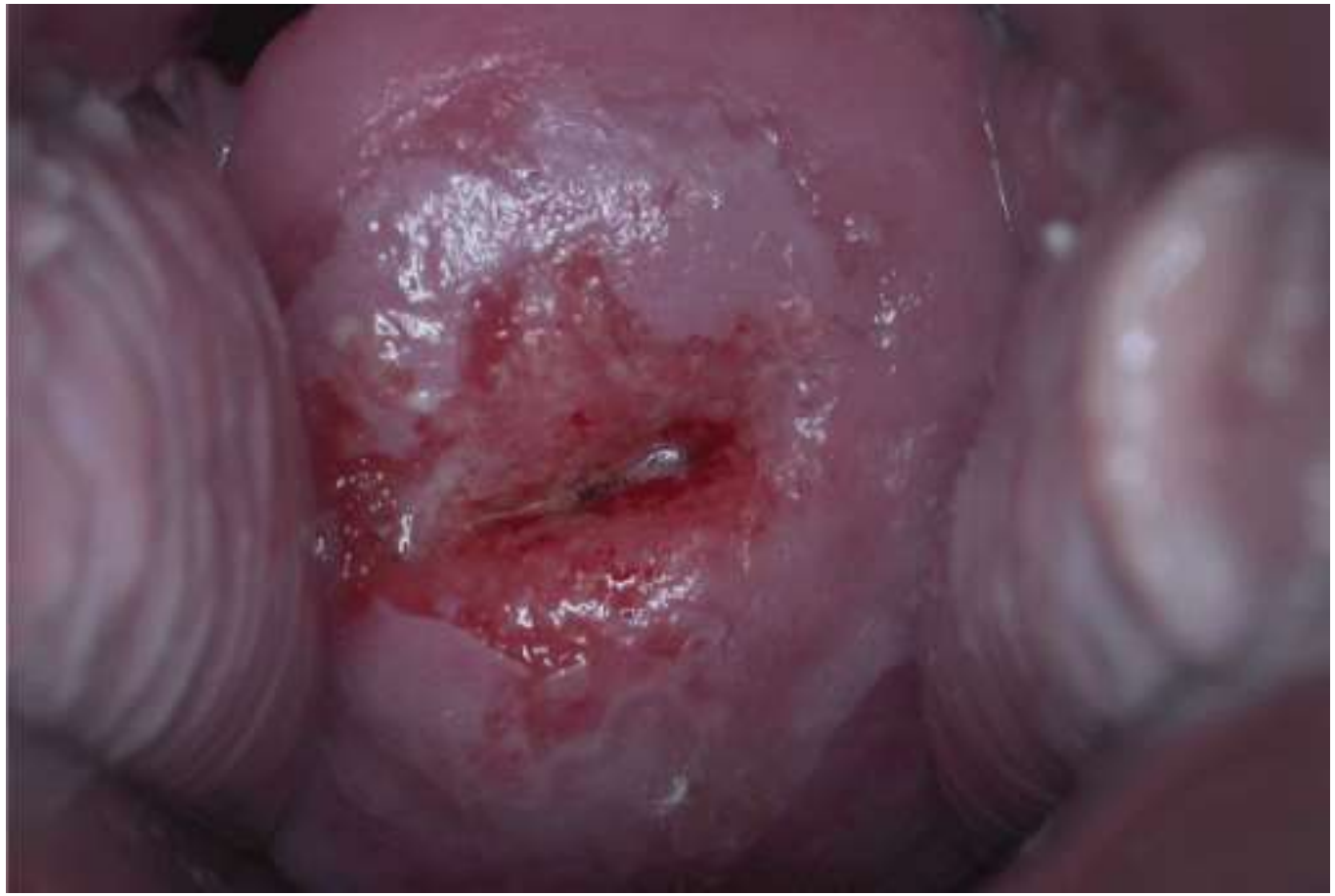
	MIRV (n=227)	IC Chemo (n=226)
mOS (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	**0.67 (0.50, 0.89)**	
***p*-value[a]**	**0.0046**	



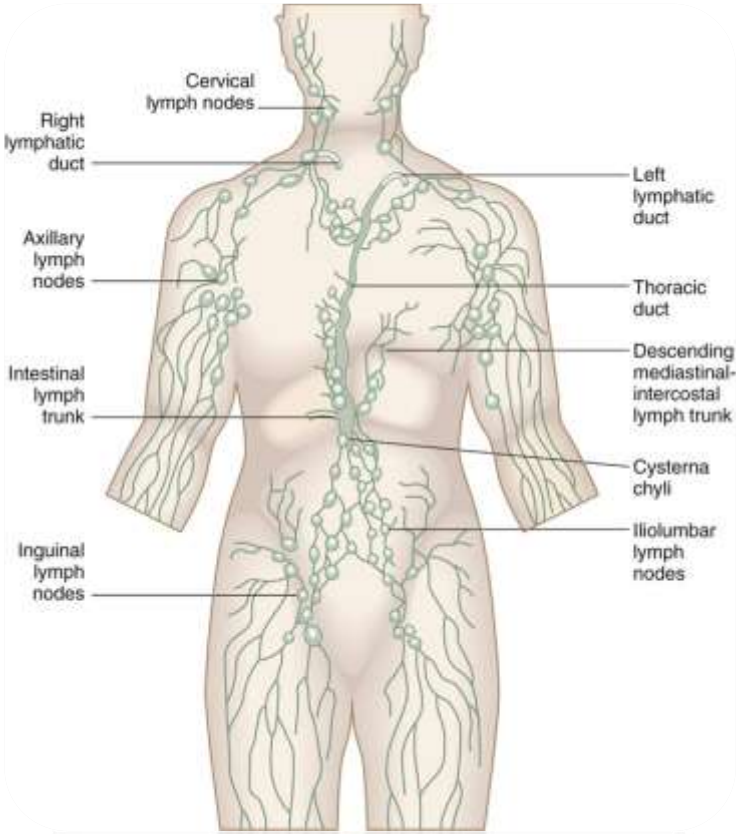
No. Participants at Risk

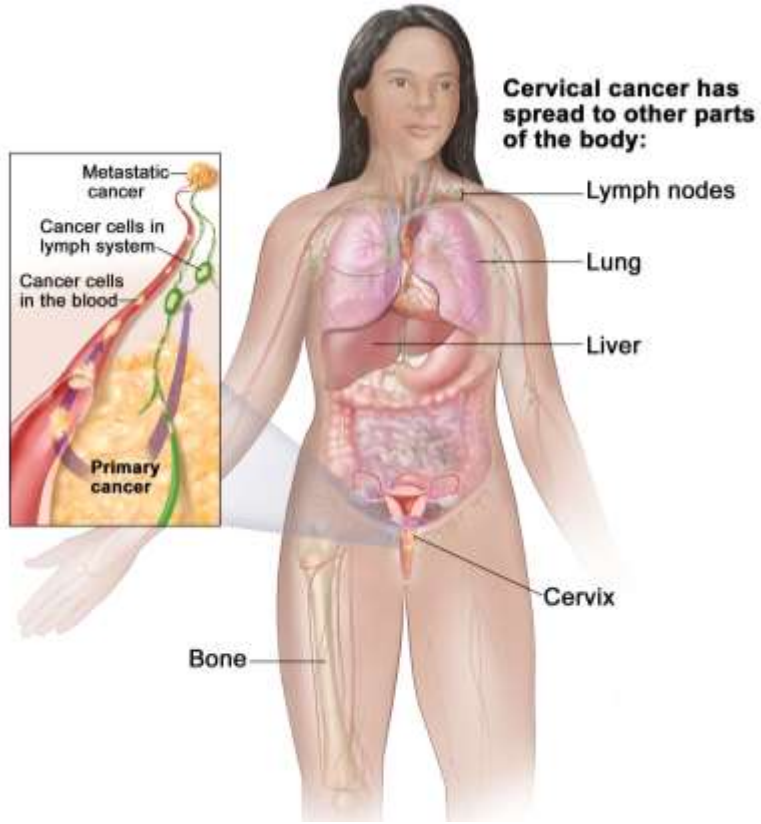
MIRV	227	204	175	128	82	53	28	15	9	4	0
IC Chemo	226	185	157	107	68	39	18	9	5	2	0

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



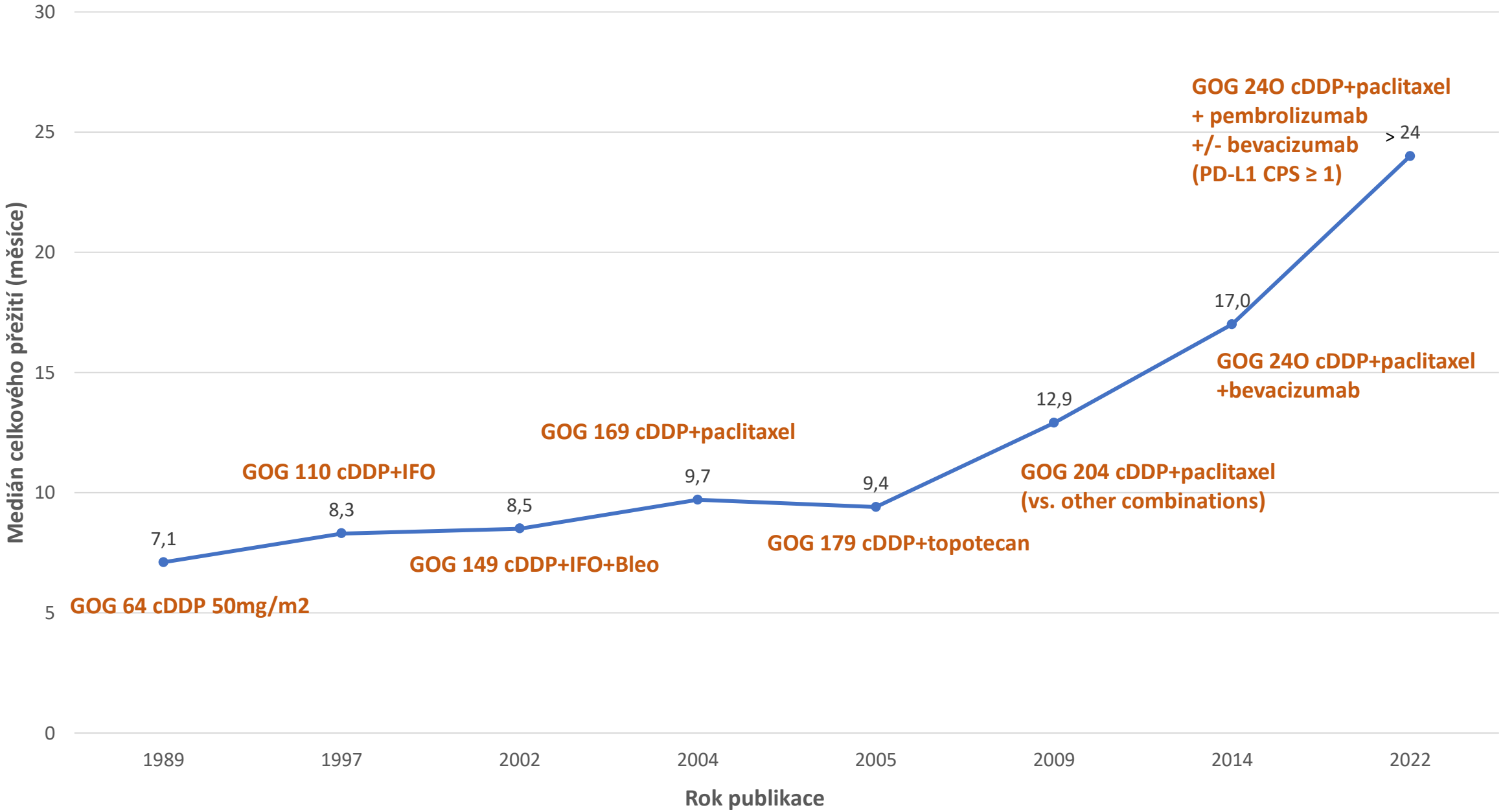
Karcinom hrdla dělohy





Persistant, recurrent, metastatic

Trials in recurrent, persistent or metastatic Cervical Carcinoma (1st line)



KEYNOTE-826: Phase III Trial Pembrolizumab + Chemotherapy as 1L Treatment for Persistent, Recurrent, or Metastatic Cervical Cancer

Patients (N=617)

- Persistent, recurrent, or metastatic cervical cancer not amenable to curative treatment
- No prior systemic chemotherapy
- Prior radiation ± radiosensitizing chemotherapy allowed
- ECOG PS 0–1
- Available archival/fresh tumor tissue

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

Continue treatment until:

- **Disease progression**
- **Unacceptable toxicity**
- **Voluntary patient withdrawal**
- **Up to 35 cycles (~2 years)**
  - Patients with a CR could discontinue treatment if they had received ≥8 cycles of pembrolizumab, including ≥2 cycles beyond a CR

Stratification Factors

- Metastatic status at diagnosis (yes or no)
- Planned bevacizumab use (yes or no)
- PD-L1 status (CPS <1, 1 to <10, or ≥10)

Primary Endpoints

- PFS[b]
- OS

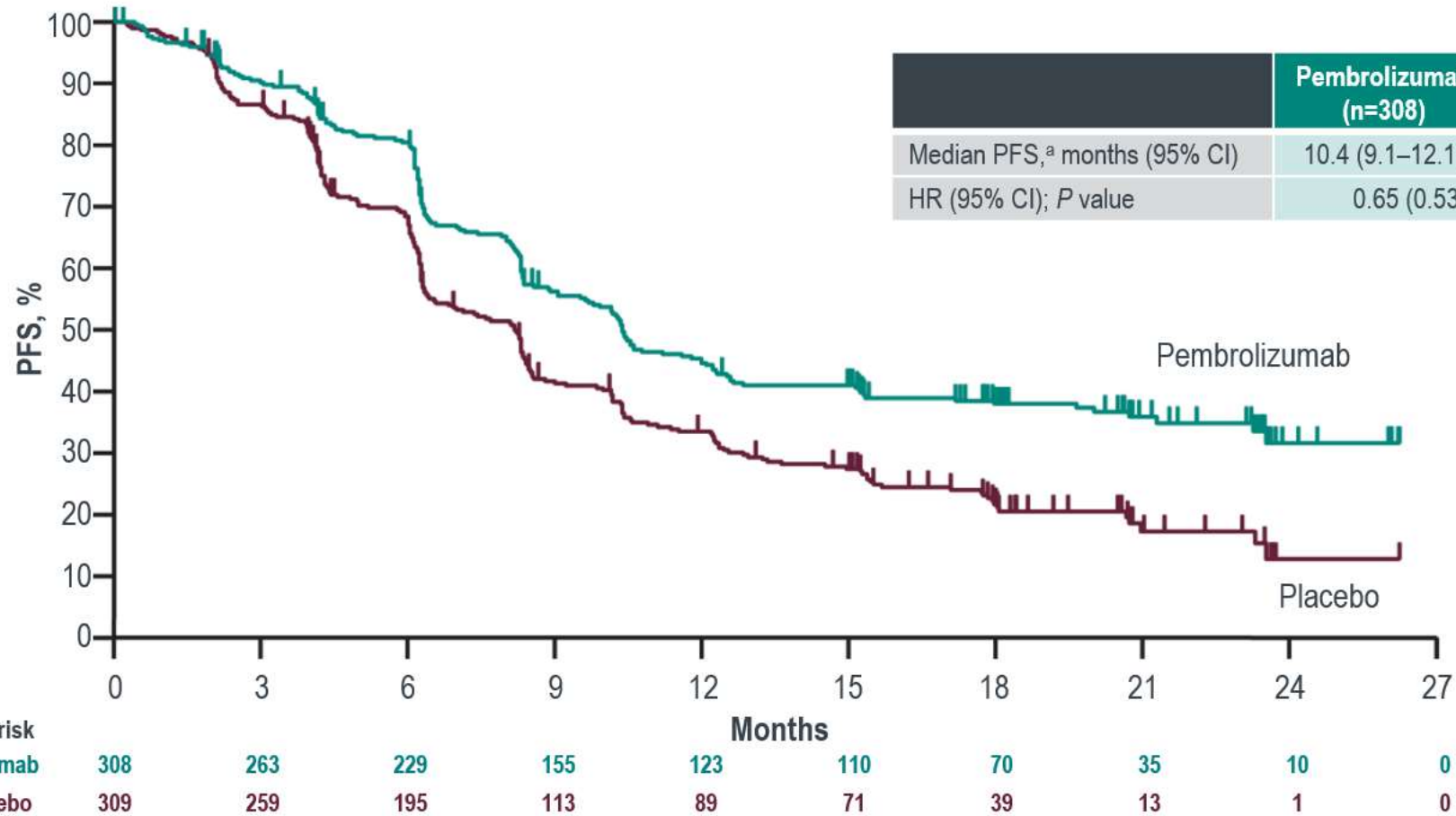
Secondary Endpoints

- ORR[b]
- DOR[b]
- 12-month PFS rate[c]
- PFS[c]
- HRQoL
- Safety and tolerability

[a]Paclitaxel: 175 mg/m^2. Cisplatin: cisplatin 50 mg/m^2. Carboplatin: AUC5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although participants with ongoing clinical benefit who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation. [b]As assessed by investigator per RECIST v1.1. [c]As assessed by BICR per RECIST v1.1.

Colombo N et al. *N Engl J Med*. 2021;385(20):1856–1867.

KEYNOTE-826: PFS in the ITT Population (Primary Endpoint)



	Pembrolizumab (n=308)	Placebo (n=309)
Median PFS,[a] months (95% CI)	10.4 (9.1–12.1)	8.2 (6.4–8.4)
HR (95% CI); *P* value	0.65 (0.53–0.79); *P* <0.001	

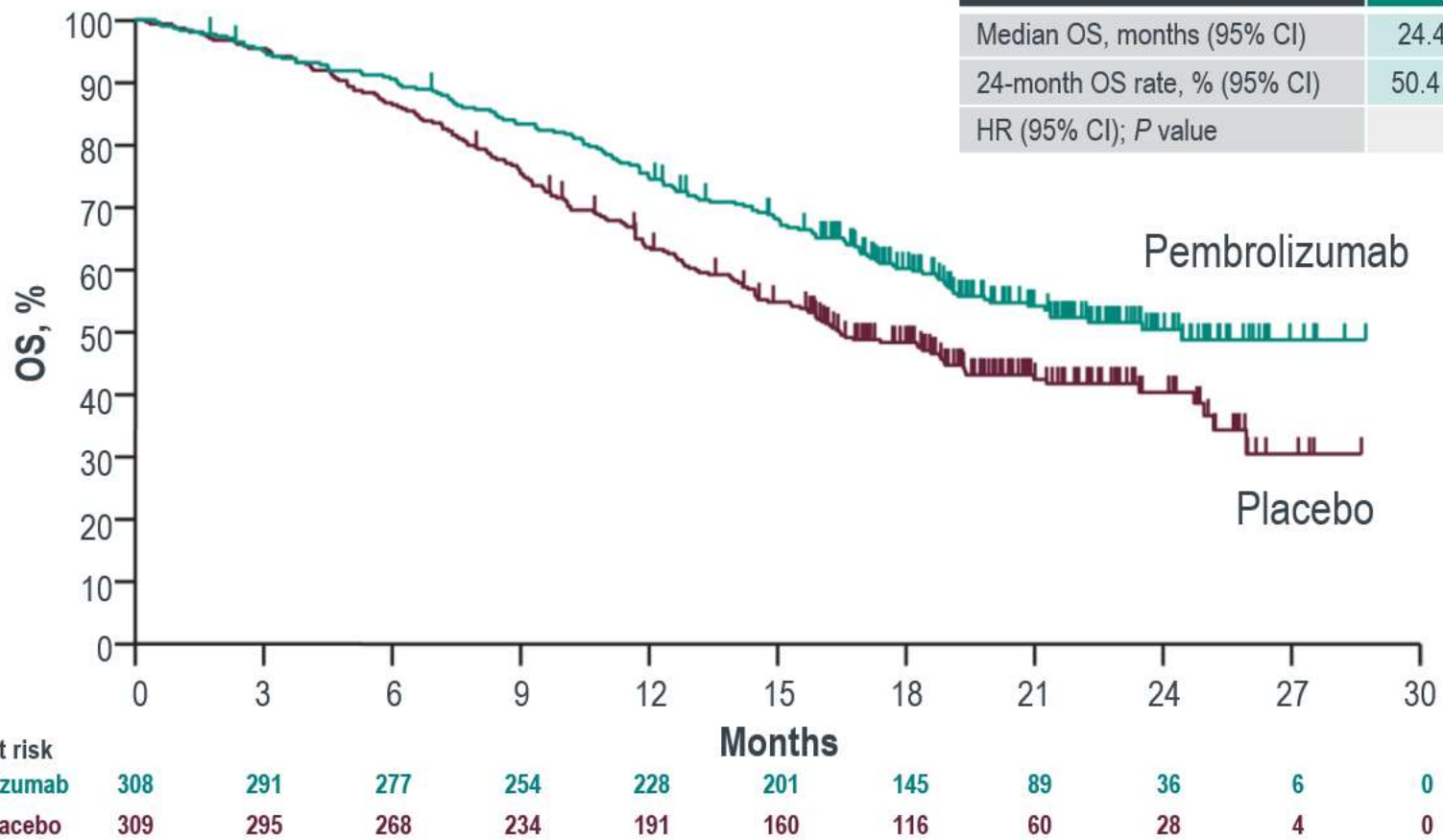
Data cutoff date: 3 May 2021.

[a]As assessed by investigator per RECIST v1.1.

Colombo N et al. *N Engl J Med*. 2021;385(20):1856–1867.

KEYNOTE-826: OS in the ITT Population[1,2] (Primary Endpoint)

	Pembrolizumab (n=308)	Placebo (n=309)
Median OS, months (95% CI)	24.4 (19.2–NR)	16.5 (14.5–19.4)
24-month OS rate, % (95% CI)	50.4 (43.8–56.6)	40.4 (34.0–46.6)
HR (95% CI); *P* value	0.67 (0.54–0.84); *P* <0.001	

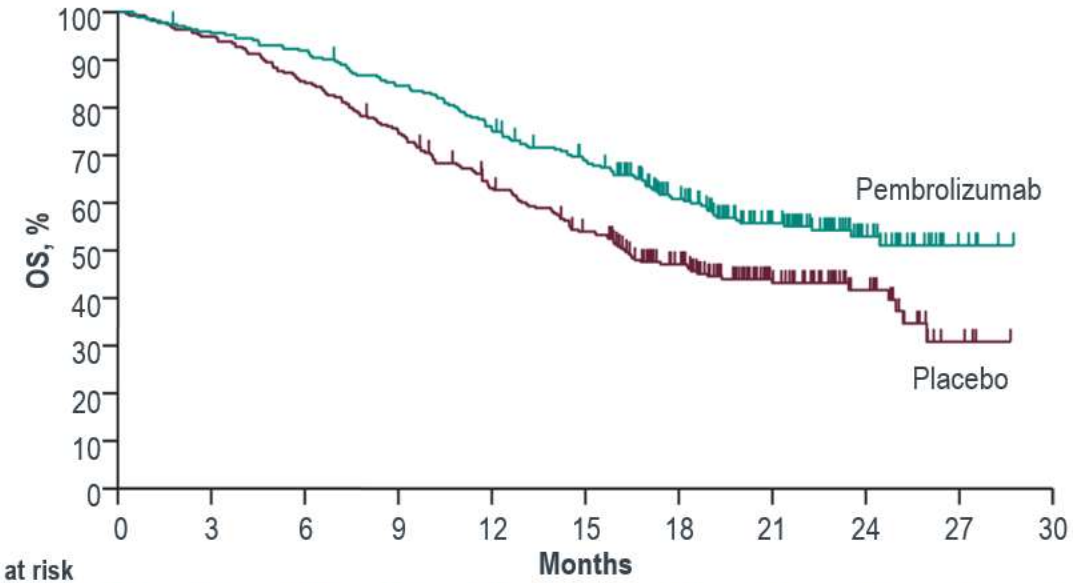


Data cutoff date: 3 May 2021.

1. Colombo N et al. Presented at ESMO 2021; abstract LBA2_PR. **2.** Colombo N et al. *N Engl J Med*. 2021;385(20):1856–1867.

KEYNOTE-826: OS by CPS Population[1,2] (Exploratory Analysis)

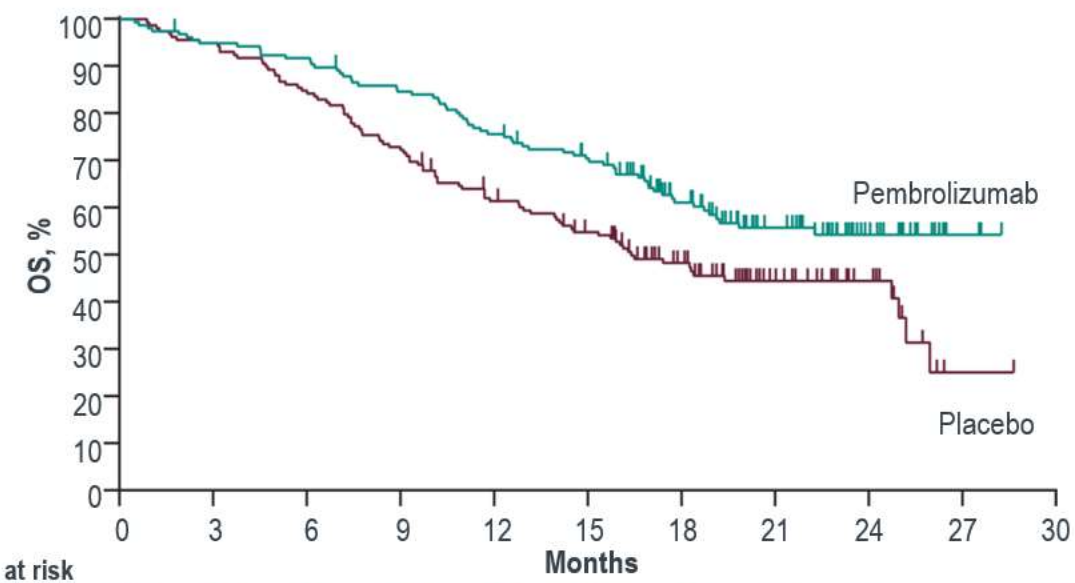
PD-L1 CPS ≥1



No. at risk											
Pembro	273	260	250	229	204	181	132	82	34	6	0
Placebo	275	261	235	206	168	140	100	55	25	4	0

	Pembrolizumab (n=273)	Placebo (n=275)
Median OS, months (95% CI)	NR (19.8–NR)	16.3 (14.5–19.4)
24-month OS rate, % (95% CI)	53.0 (46.0–59.4)	41.7 (34.9–48.2)
HR (95% CI); *P* value	0.64 (0.50–0.81); *P* <0.001	

PD-L1 CPS ≥10



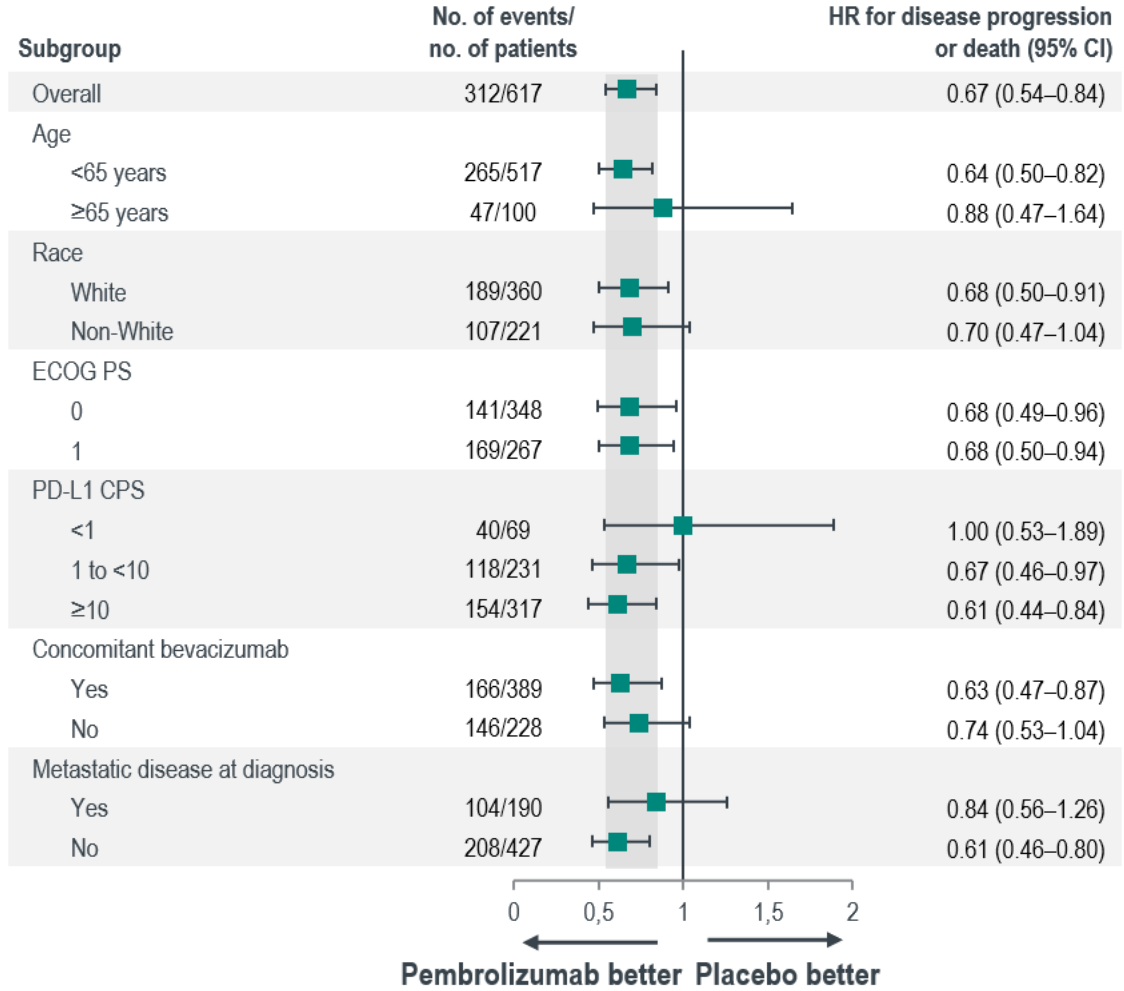
No. at risk											
Pembro	158	149	144	132	118	106	76	46	21	3	0
Placebo	159	151	135	116	95	81	56	31	15	1	0

	Pembrolizumab (n=158)	Placebo (n=159)
Median OS, months (95% CI)	NR (19.1–NR)	16.4 (14.0–25.0)
24-month OS rate, % (95% CI)	54.4 (45.5–62.4)	44.6 (36.3–52.5)
HR (95% CI); *P* value	0.61 (0.44–0.84); *P* = 0.001	

Data cutoff date: 3 May 2021.

1. Colombo N et al. Presented at ESMO 2021; abstract LBA2_PR. **2.** Colombo N et al. *N Engl J Med*. 2021;385(20):1856–1867.

KEYNOTE-826: OS Subgroup Analysis in the ITT Population (Exploratory Analysis)

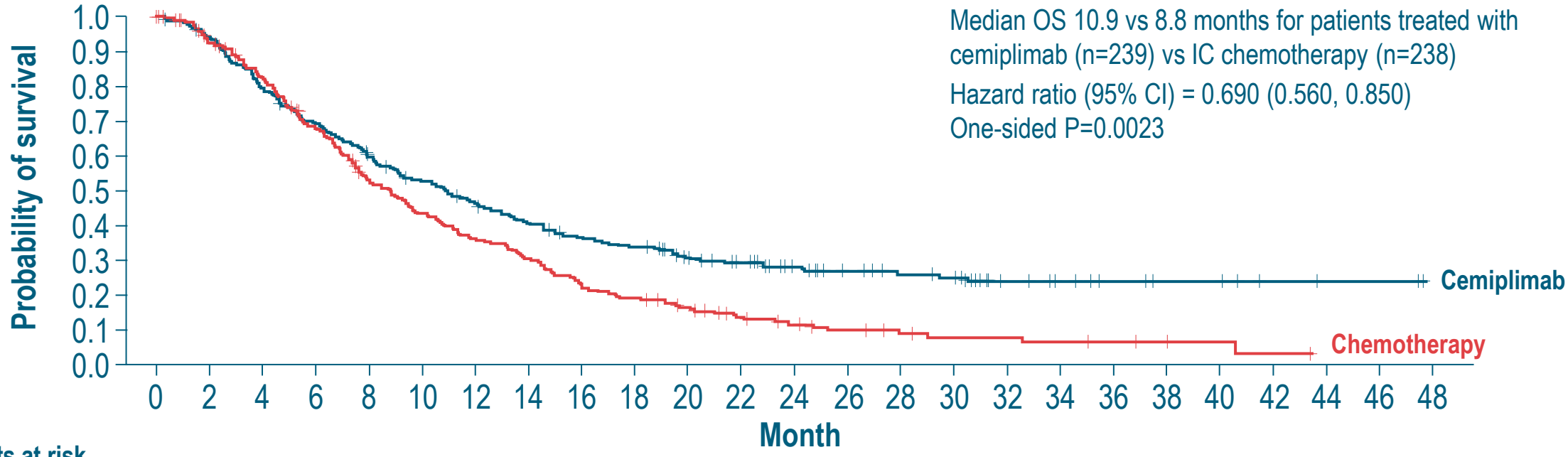


Data cutoff date: 3 May 2021.

Colombo N et al. *N Engl J Med*. 2021;385(20):1856–1867.

Cemiplimab monotherapy significantly improved OS vs chemotherapy in patients with squamous cell histology

Median follow-up time: 30.2 (18.0–50.2) months



Median OS 10.9 vs 8.8 months for patients treated with cemiplimab (n=239) vs IC chemotherapy (n=238)

Hazard ratio (95% CI) = 0.690 (0.560, 0.850)

One-sided P=0.0023

Patients at risk

Cemiplimab	239	223	188	163	140	120	105	91	80	74	60	53	43	35	30	28	17	14	8	6	6	3	2	2	0
Chemotherapy	238	209	182	149	113	92	77	65	50	41	32	22	16	12	9	7	7	6	5	3	2	1	0	0	0

Kaplan–Meier curves of overall survival in the full analysis set.

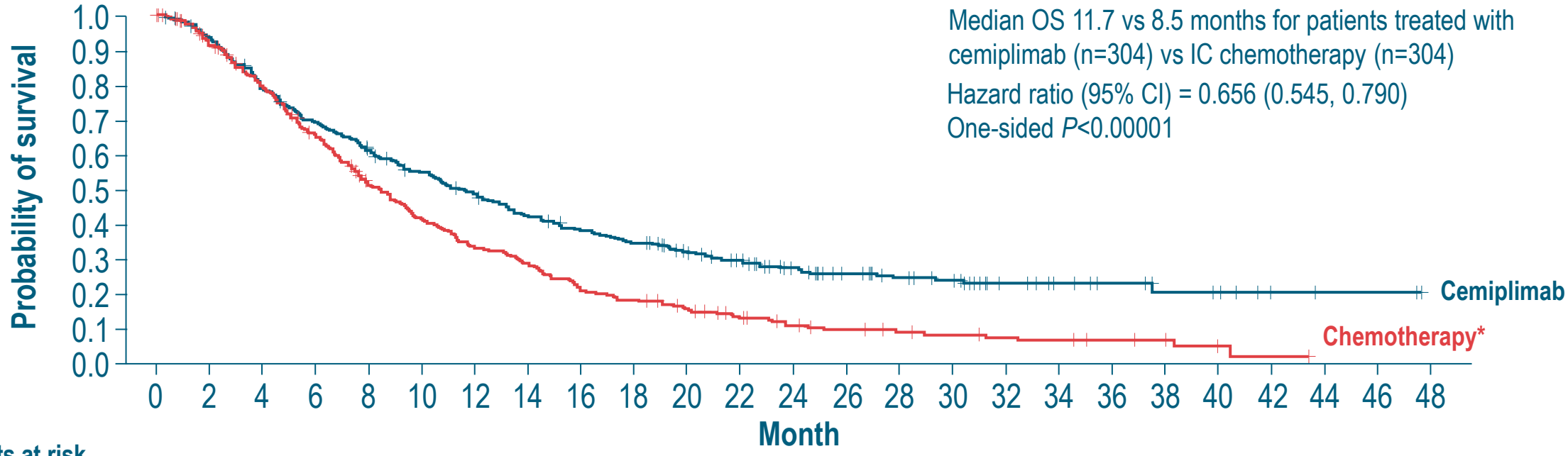
CI, confidence interval; IC, investigator's choice; OS, overall survival. **Data cutoff date: 4 Jan 2022**

PARIS 2022 ESMO congress

Tewari KS and Monk BJ et al. *N Engl J Med.* 2022;386(6):544–55

Cemiplimab monotherapy significantly improved OS vs chemotherapy in the overall population

Median follow-up time: 30.2 (18.0–50.2) months



Patients at risk

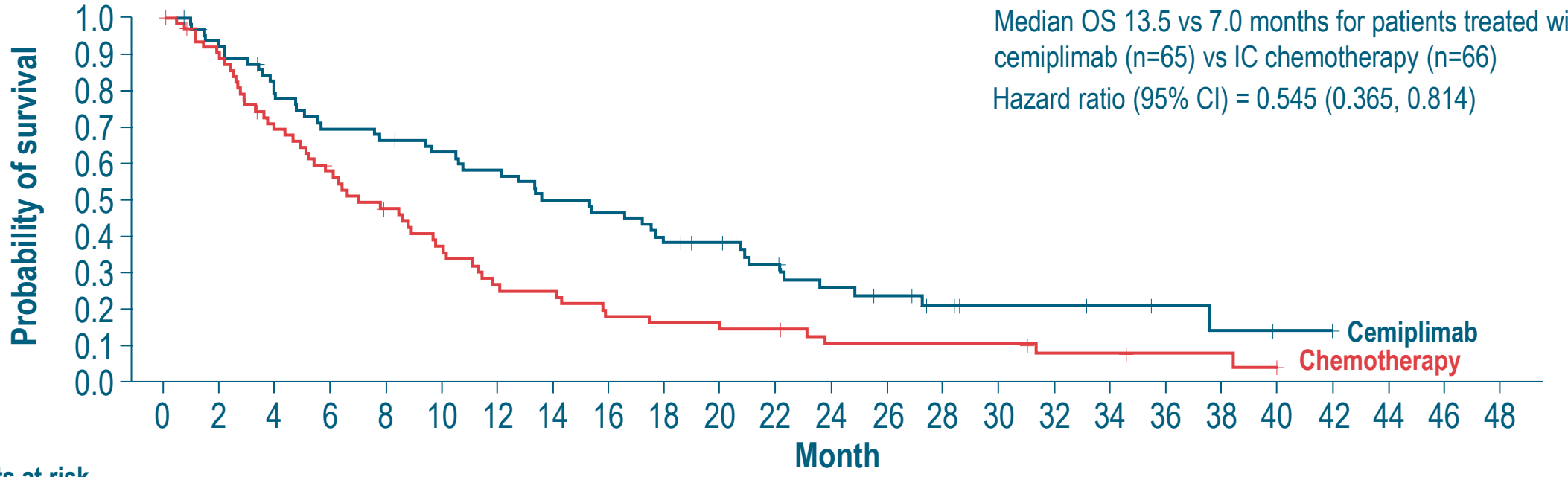
Cemiplimab	304	281	236	206	181	158	140	121	108	97	81	69	55	45	37	33	22	18	11	8	7	3	2	2	0
Chemotherapy	304	264	224	183	140	113	92	79	60	50	40	30	21	17	14	12	10	9	7	5	2	1	0	0	0

Kaplan–Meier curves of overall survival in the full analysis set.
CI, confidence interval; IC, investigator's choice; OS, overall survival. **Data cutoff date: 4 Jan 2022**

* 8/304 chemotherapy patients crossed over to IO, 7 due to PD, 1 due to patient choice

Cemiplimab monotherapy significantly improved OS vs chemotherapy in patients with adenocarcinoma or adenosquamous carcinoma histology

Median follow-up time: 30.2 (18.0–50.2) months



Median OS 13.5 vs 7.0 months for patients treated with cemiplimab (n=65) vs IC chemotherapy (n=66)

Hazard ratio (95% CI) = 0.545 (0.365, 0.814)

Patients at risk

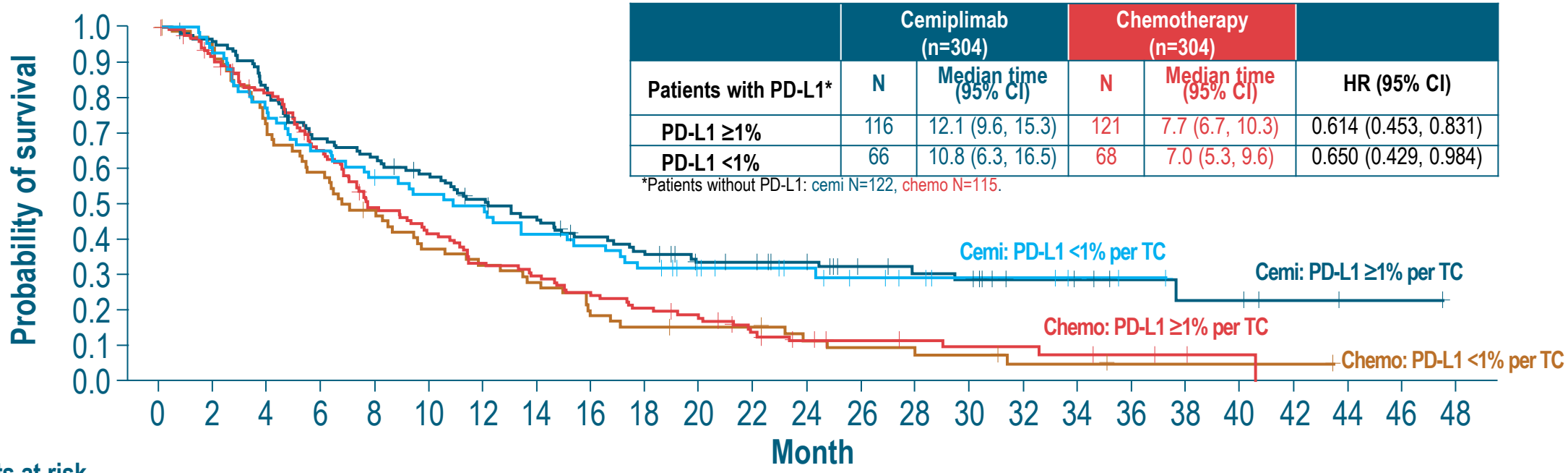
Cemiplimab	65	58	48	43	41	38	35	30	28	23	21	16	12	10	7	5	5	4	3	2	1	0	0	0	0
Chemotherapy	66	55	42	34	27	21	15	14	10	9	8	8	5	5	5	5	3	3	2	2	0	0	0	0	0

CI, confidence interval; IC, investigator's choice; OS, overall survival. **Data cutoff date: 4 Jan 2022**

Cemiplimab monotherapy significantly improved OS vs chemotherapy regardless of PD-L1 status

	Cemiplimab (n=304)		Chemotherapy (n=304)		
Patients with PD-L1*	N	Median time (95% CI)	N	Median time (95% CI)	HR (95% CI)
PD-L1 ≥1%	116	12.1 (9.6, 15.3)	121	7.7 (6.7, 10.3)	0.614 (0.453, 0.831)
PD-L1 <1%	66	10.8 (6.3, 16.5)	68	7.0 (5.3, 9.6)	0.650 (0.429, 0.984)

*Patients without PD-L1: cemi N=122, chemo N=115.



Patients at risk

Cemi: PD-L1 ≥1% per TC	116	110	93	77	71	63	55	48	41	36	30	29	25	20	17	16	10	9	5	4	4	2	1	1	0
Cemi: PD-L1 <1% per TC	66	61	49	43	36	33	30	26	24	20	16	14	12	9	7	5	5	3	1	0	0	0	0	0	0
Chemo: PD-L1 ≥1% per TC	121	107	92	73	54	46	37	33	27	23	19	13	9	7	6	5	5	4	3	2	1	0	0	0	0
Chemo: PD-L1 <1% per TC	68	60	46	39	30	24	21	18	12	10	9	9	6	5	4	4	2	2	1	1	1	1	0	0	0

Kaplan–Meier curves of overall survival in the full analysis set. **Data cutoff date: 4 Jan 2022**

Cemi, cemiplimab; Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death-ligand 1; TC, tumour cell; PD-L1 expression was detected with the SP263 monoclonal antibody (Ventana; Tewari et al., NEJM, 2022)


25
Happy
Anniversary!


Congratulations
1oz 9999 SILVER
P
JWW