SIDNEY KIMMEL CANCER CENTER

Immunotherapy in Gynecologic Malignancies: State of the Art in 2023

Mark S. Shahin, MD, FACOG, FACS

Professor, Sidney Kimmel Cancer Center of Thomas Jefferson University

Jefferson Abington Hospital

Jefferson Health
HOME OF SIDNEY KIMMEL MEDICAL COLLEGE

Goals and Objectives

- Understand the scope of Immunotherapy applications in Gynecologic Cancers
- Explore future areas of study for molecular-based treatment

Endometrial Cancer

How Common Is Endometrial Cancer?[1]

Across all cancer types in the US, uterine cancer represents

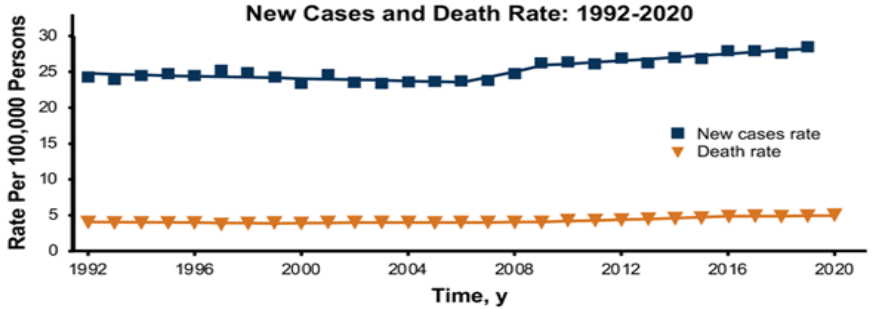
3.4% of new cases

2.1% of deaths

Estimates for 2022

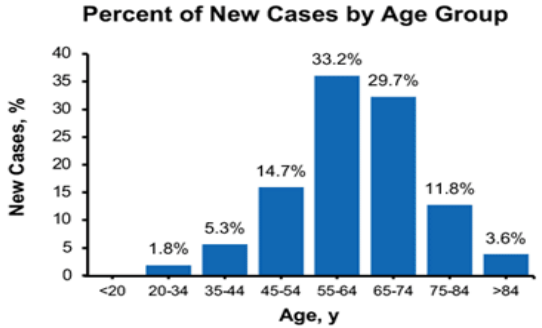
65,950 new cases

12,550 deaths



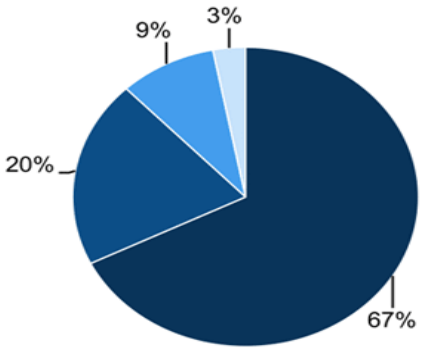
1. https://seer.cancer.gov/statfacts/html/corp.html.

63
median age at diagnosis



Endometrial Cancer Staging Snapshot[1]

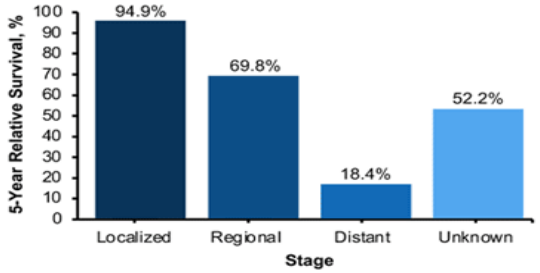
Percent of Cases by Stage



- **Localized (67%)** Confined to primary site
- **Regional (20%)** Spread to regional lymph nodes
- **Distant (9%)** Cancer has metastasized
- **Unknown (3%)** Unstaged

81.3%
5-year relative survival (2012-2018)

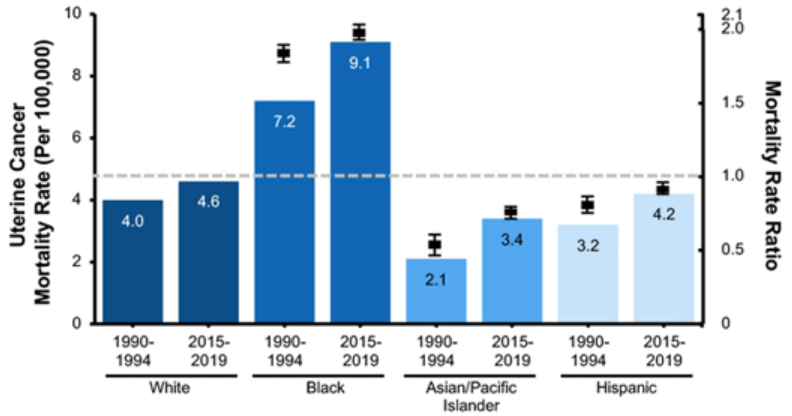
5-Year Relative Survival by Stage

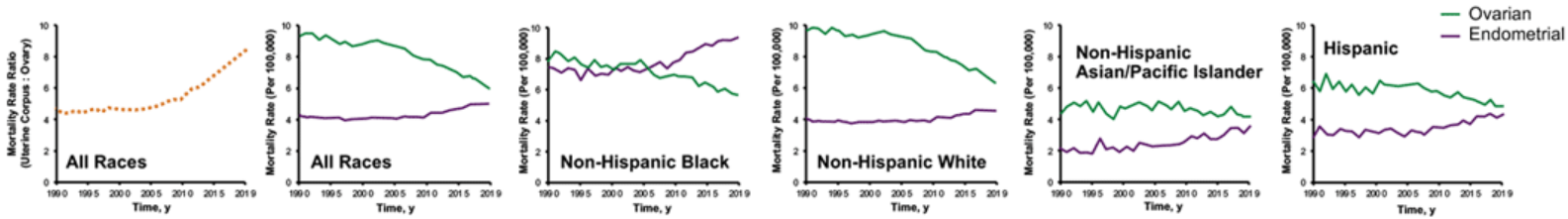


1. https://seer.cancer.gov/statfacts/html/corp.html.

Survival Disparities: Endometrial vs Ovarian Cancers[1-3]

- **Overall, mortality rates for endometrial cancer are now comparable to ovarian cancer**
  - This change comes from declining rates for ovarian cancer and increasing rates for endometrial cancer (2% annually 2008-2018)
- **However, the burden for Black women has increased disproportionately and now represents one of the largest racial disparities in cancer settings**

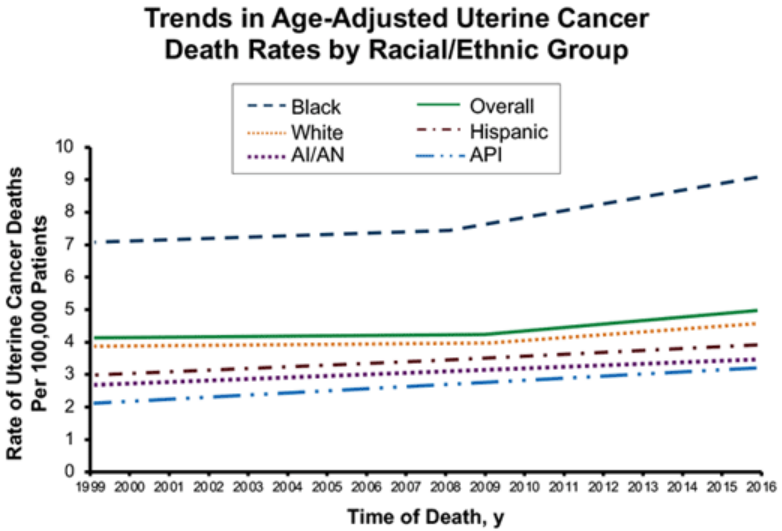




1. Giaquinto AN et al. *Obstet Gynecol.* 2022;139:440-442. 2. Siegel RL et al. *CA Cancer J Clin.* 2021;71:7-33.
3. Monk BJ et al. *Gynecol Oncol.* 2022;164:325-332.

Survival Disparities: Within Endometrial Cancer[1,2]

- **Among patients with endometrial cancer, Black women have a higher mortality rate than White women**
- Racial disparities cannot solely be explained by histologic subtype and stage at diagnosis
- It is imperative to widen diversity of enrollment in clinical trials



Death rates increased 21%
in the US from 1999 to 2016

1. Henley SJ et al. *MMWR Morb Mortal Wkly Rep*. 2018;67:1333-1338. 2. Clarke MA et al. *JAMA Oncol*. 2022;8:895-903.

Risk Stratification for Adjuvant Treatment

Risk Group	Description
Low	• **Stage I endometrioid, grade 1-2, < 50% myometrial invasion, LVSI negative**
Intermediate	• Stage I endometrioid, grade 1-2, **≥ 50% myor** … egative
High-intermediate	• Stage I endometrioid, **grade 3, < 50% myometrial invasion, regardless of LVSI status** • Stage I endometrioid, **grade 1-2, LVSI unequ** … **rdless of depth of myometrial invasion**
High	• Stage I endometrioid, **grade 3, ≥ 50% myometrial invasion regardless of depth of myometrial invasion** • **Stage II** • **Stage III endometrioid, no residual disease** • **Non-endometrioid (serous, clear cell or undifferentiated carcinoma)**
Advanced	• Stage III with residual disease • Stage IVA
Metastatic	• Stage IVB

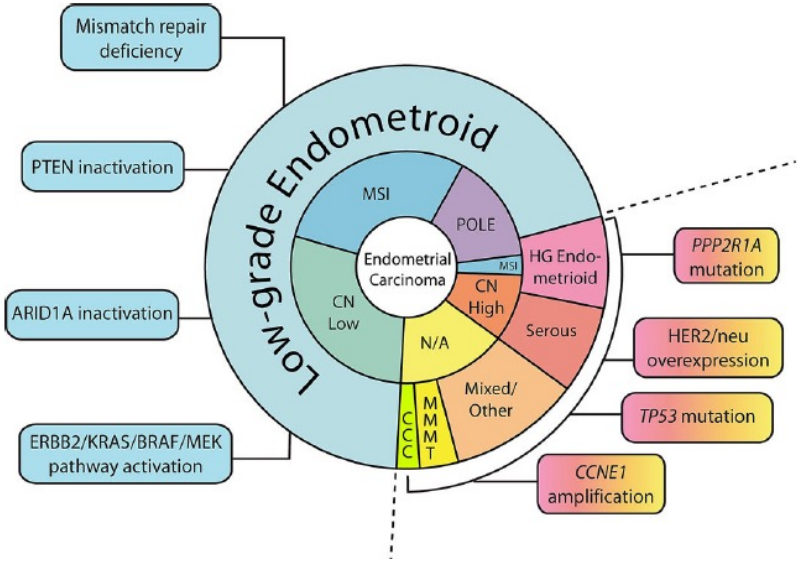
OBSERVATION

RADIATION

CHEMO +/- RADIATION

Limitations of the Current System

- Diagnostic overlap between histology subtypes
- Histologic classification is less objective than molecular classification
- Several molecular categories within subtypes

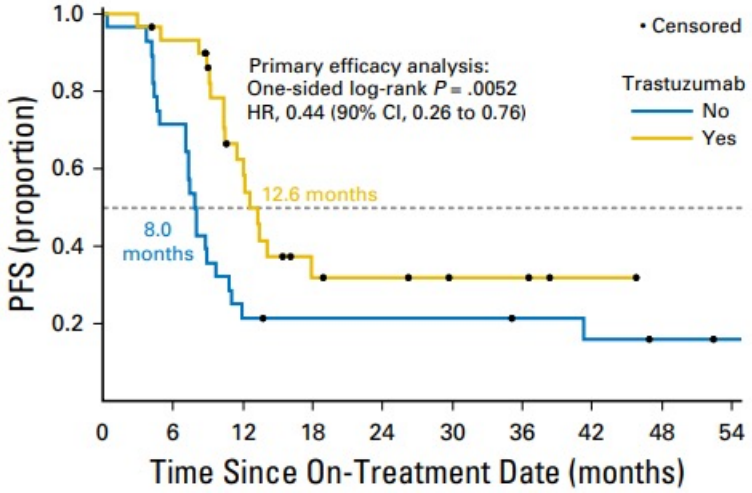


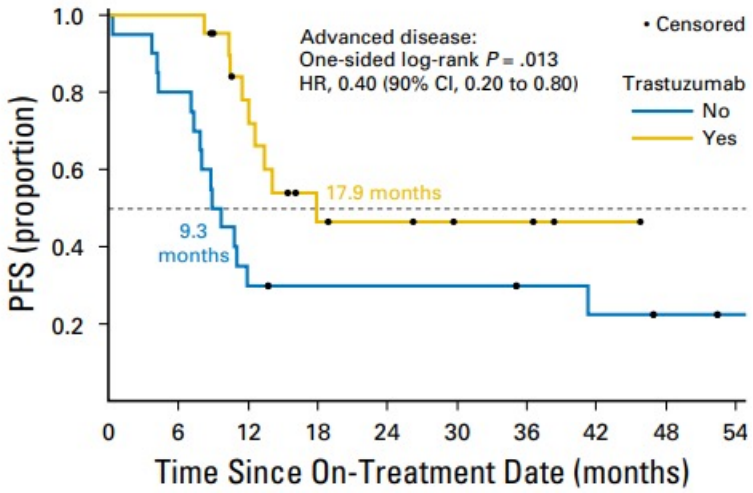
Recent Additions to Standard Treatments

- Trastuzumab
- Pembrolizumab
- Dostarlimab
- Lenvatinib

Trastuzumab – Fader et al (2018)

- 61 patients with advanced or recurrent endometrial cancer
- Randomized to standard cytotoxic chemo +/- trastuzumab

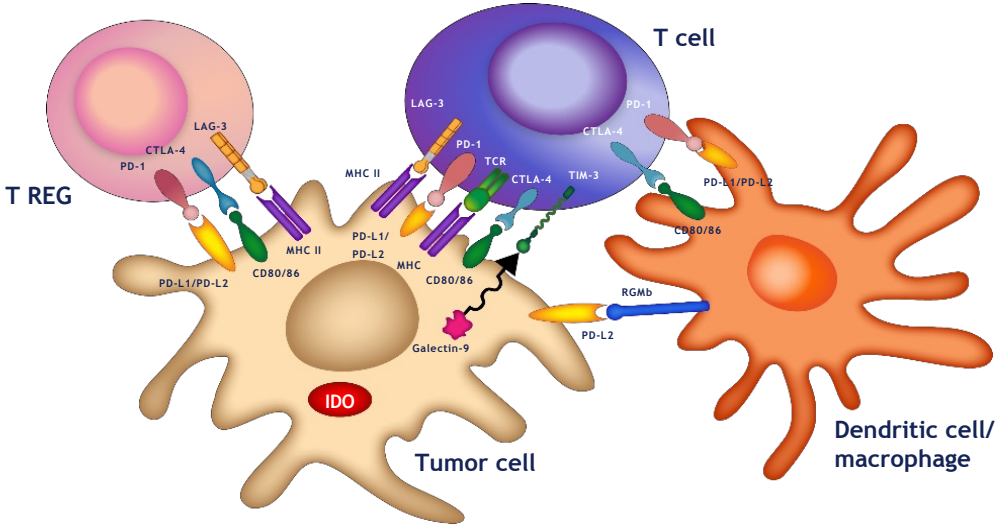




Immunotherapy and Mismatch Repair Deficiency

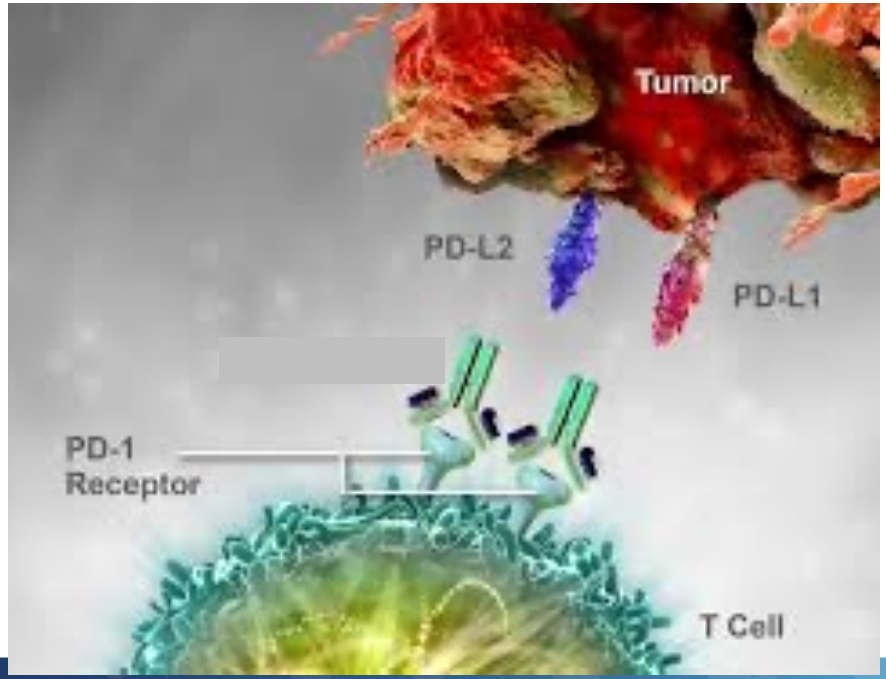
- 4 distinct “caretaker” proteins maintain the integrity of the genome
- Loss of one or more of these: dMMR
- Leads to high rates of repetitive DNA sequences (or microsatellites)

- MMR deficient tumors have strong expression of PD-1, PDL-1
- Notable increase in:
  - T lymphocytes
  - T lymphocyte invasion
  - Chemokines
- Immunogenic environment

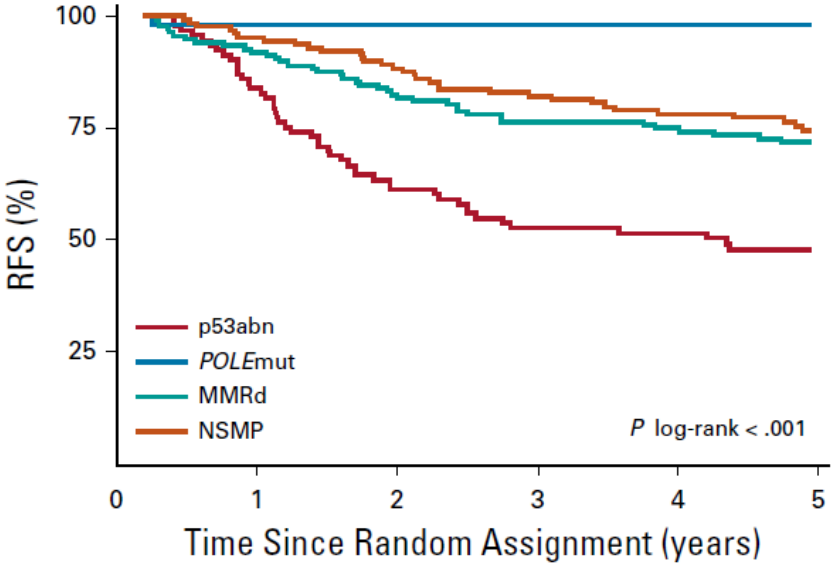


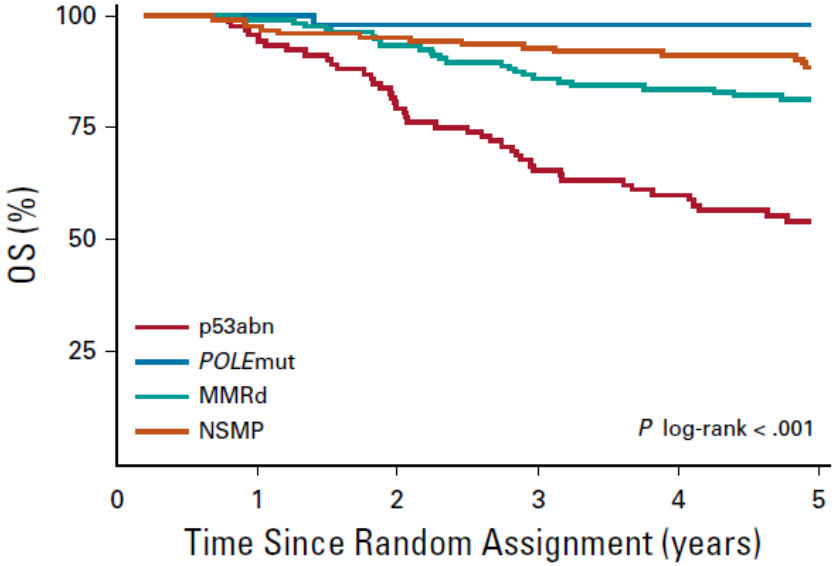
Immunotherapy

- Blocks interaction between T cell and tumor cell at the PD-1 receptor
- Currently FDA-approved
  - Pembrolizumab
  - Dostarlimab

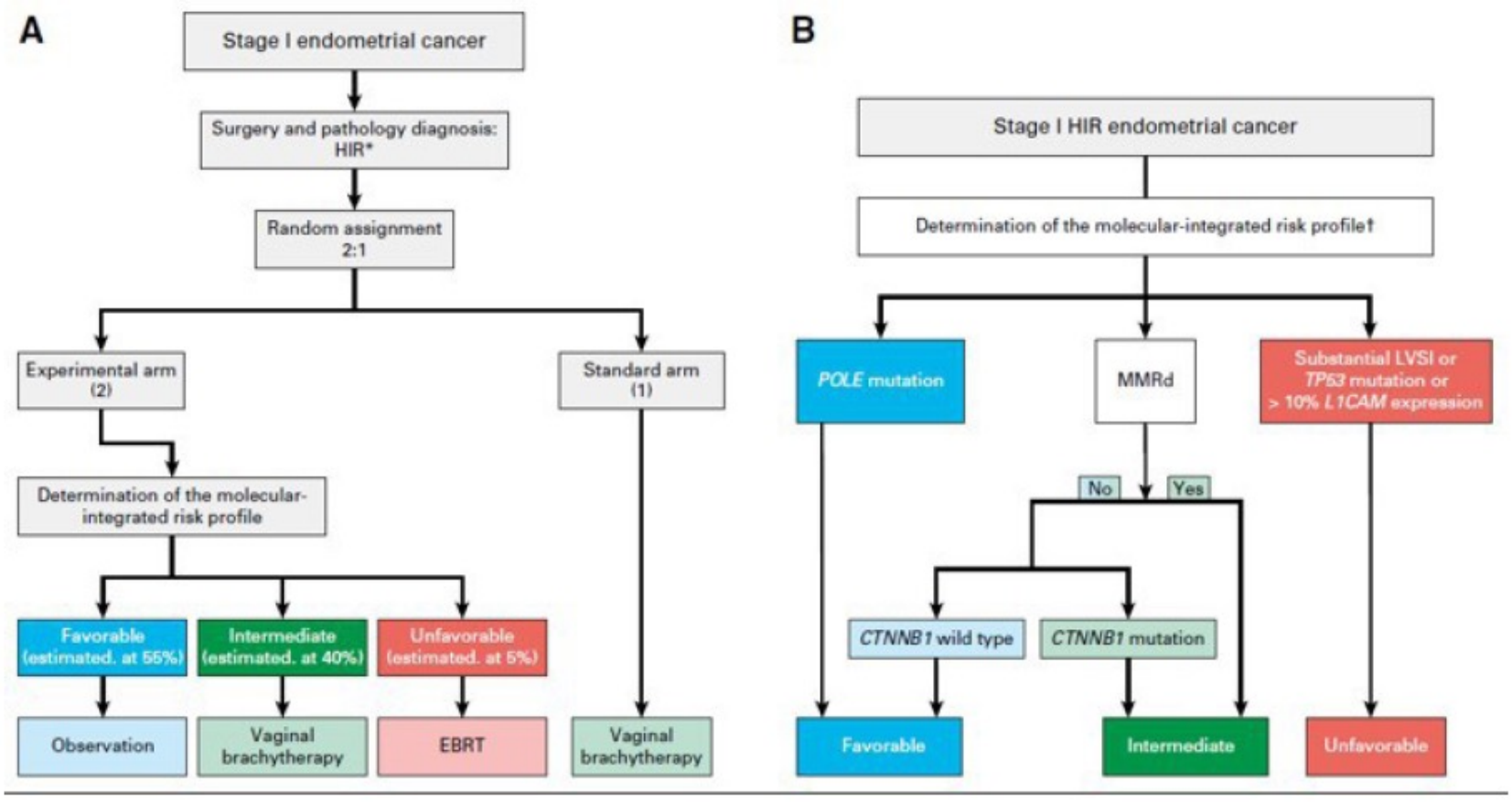


Molecular Classification from PORTEC 3





Future Directions - PORTEC 4a



Single Agent Immunotherapy Approaches

Monotherapy immune checkpoint inhibition is an effective strategy, especially for biomarker-selected patients with advanced or recurrent endometrial cancer

Phase 2 KEYNOTE-158: Pembrolizumab Monotherapy for Advanced Endometrial Cancer[1,2]

Phase 2
KEYNOTE-158
Pembrolizumab

Key Eligibility Criteria

- ≥18 years of age
- MSI-H/dMMR advanced endometrial cancer
  - Cohort D: endometrial cancer, regardless of MSI status and excluding sarcomas and mesenchymal tumors
  - Cohort K: any MSI-H/dMMR advanced solid tumor except colorectal
- Progression on or intolerance to ≥1 line of standard treatment for unresectable and/or metastatic disease
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1
- Provision of a tumor sample for biomarker assessment

Pembrolizumab
200 mg IV Q3W

For 35 cycles (approximately 2 y) or until disease progression, intolerable toxicity, investigator decision, or patient withdrawal

- **Primary endpoint:** ORR per RECIST v1.1 by ICR
- **Secondary endpoints:** DOR and PFS per RECIST v1.1 by ICR, OS, and safety

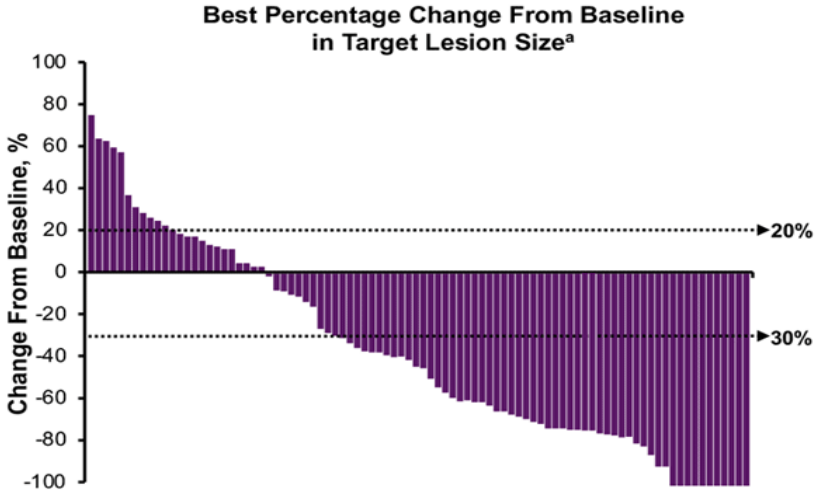
FDA Approval	Indication
2017	Tissue-agnostic approval for the treatment of unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment
2020	Tissue-agnostic approval for TMB-H tumors
2022	Approval for advanced endometrial carcinoma that is dMMR following progression on prior treatment

1. https://clinicaltrials.gov/ct2/show/NCT02628067.
2. (pembrolizumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s127lbl.pdf.

Phase 2
KEYNOTE-158
Pembrolizumab

KEYNOTE-158: Improved Responses With Pembrolizumab in dMMR Endometrial Cancer[1,2]

Variable	dMMR EC (n = 94)
Median follow-up, mo	54.5
ORR, %	50
CR, %	16
PR, %	34
SD, %	18
PD, %	28
mDOR, mo	63.2
Estimated DOR at 4 y, %	66
mPFS, mo	13.1
Estimated PFS at 4 y, %	37
mOS, mo	65.4
Estimated OS at 4 y, %	59



[a] As assessed per RECIST v1.1 by independent central radiologic review.

1. O'Malley DM et al. *J Clin Oncol*. 2022;40:752-762. 2. O'Malley DM et al. European Society for Medical Oncology Congress 2022 (ESMO 2022). Abstract 546P.

Phase 1 GARNET Dostarlimab

Phase 1 GARNET: Dostarlimab Monotherapy in Multiple Tumor Types[1,2]

Part 1: Dose finding → **Part 2A: Fixed-dose safety run-in** → **Part 2B: Expansion cohorts**

Key Inclusion Criteria
Patients with recurrent or advanced EC that progressed on or after treatment with a platinum-containing regimen
- dMMR status by IHC testing
- Patients must have received ≤2 prior lines of treatment for recurrent or advanced disease

Part 2B: Expansion cohorts
- A1: dMMR/MSI-H EC
- A2: pMMR/MSS EC
- E: NSCLC
- F: Nonendometrial dMMR/MSI-H basket
- G: PROC

- **Dosing:** 500 mg IV Q3W for 4 cycles, then 1000 mg Q6W
- **Primary endpoints:** ORR, DOR

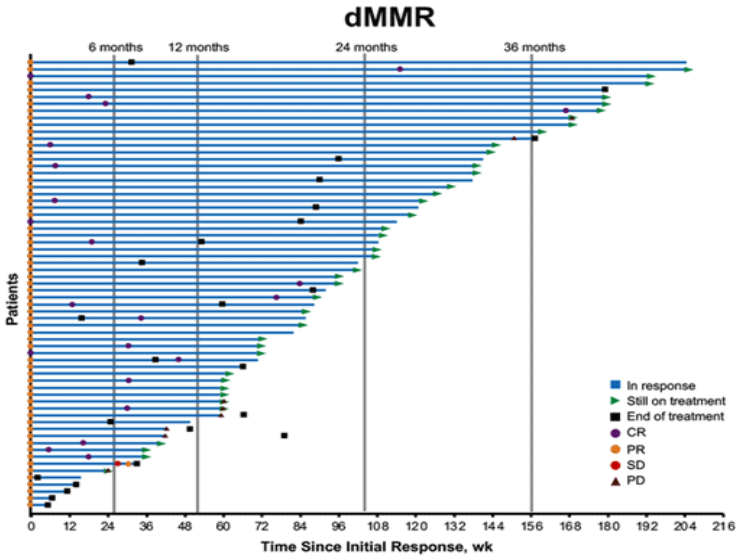
FDA Approval	Indication
2021	Approval for recurrent or advanced endometrial cancer that is dMMR following progression or prior treatment
2021	Tissue-agnostic approval for dMMR recurrent or advanced solid tumors that have progressed on or following prior treatment

1. https://clinicaltrials.gov/ct2/show/NCT02715284.
2. (dostarlimab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761174s002lbl.pdf.

Phase 1
GARNET
Dostarlimab

GARNET: Dostarlimab Showed Durable Antitumor Activity in dMMR Endometrial Cancer[1,2]

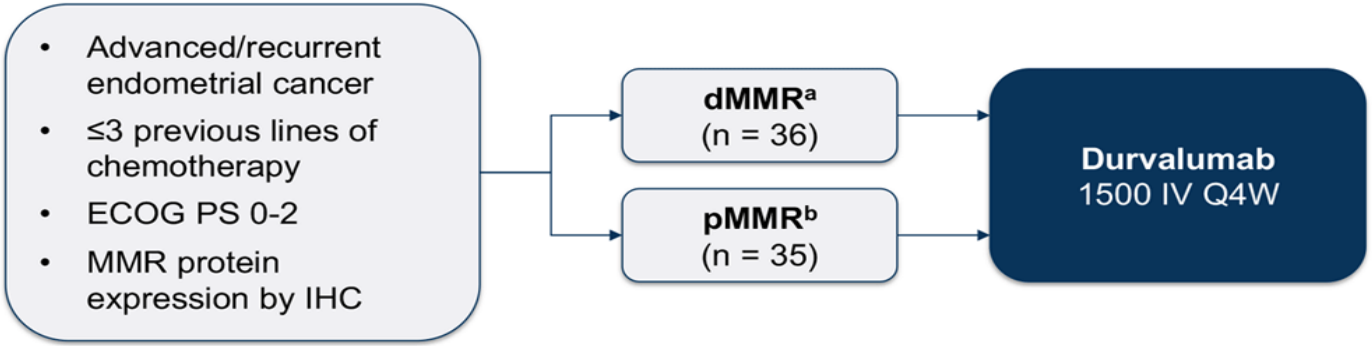
Variable	dMMR EC (n = 143)	pMMR EC (n = 156)
Median follow-up, mo	27.6	33.0
ORR, %	45.5	15.4
CR, %	16.1	2.6
PR, %	29.4	12.8
SD, %	14.7	18.6
PD, %	35.7	56.4
mDOR, mo	NR	19.4
Estimated DOR at 2 y, %	83.7	44.2
mPFS, mo	6.0	2.7
Estimated PFS at 3 y, %	40.1	6.8
mOS, mo	NR	16.9
Estimated OS at 3 y, %	58.4	22.2



1. Oaknin A et al. 2022 American Society of Clinical Oncology Annual Meeting (ASCO 2022). Abstract 5509. 2. Tinker AV et al. ESMO 2022. Poster 548.

Phase 2
PHAEDRA
Durvalumab

Phase 2 PHAEDRA: Durvalumab in Advanced dMMR or pMMR Endometrial Cancer[1]



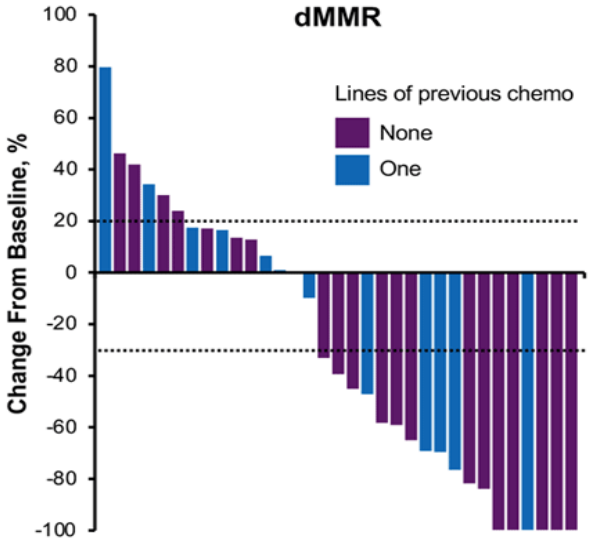
- **Primary endpoint:** OTR by iRECIST
- **Secondary endpoints:** PFS, OS, ORR by RECIST 1.1, safety, QOL

[a] Progression after 0-3 lines of chemotherapy. [b] Progression after 1-3 lines of chemotherapy.
1. https://clinicaltrials.gov/ct2/show/NCT03015129.

Phase 2
PHAEDRA
Durvalumab

PHAEDRA: Durvalumab Monotherapy for Advanced Endometrial Cancer[1]

Variable	dMMR EC (n = 36)	pMMR EC (n = 35)
Median follow-up, mo	19	21
ORR, %	47	3
CR, %	17	0
PR, %	31	3
SD, %	17	29
PD, %	36	66
mPFS, mo	8.3	1.8
Estimated PFS at 6 mo, %	53	14
mOS, mo	NR	12.1
Estimated OS at 1 y, %	71	51



1. Antill Y et al. *J ImmunoTherapy Cancer*. 2021;9:e002255.

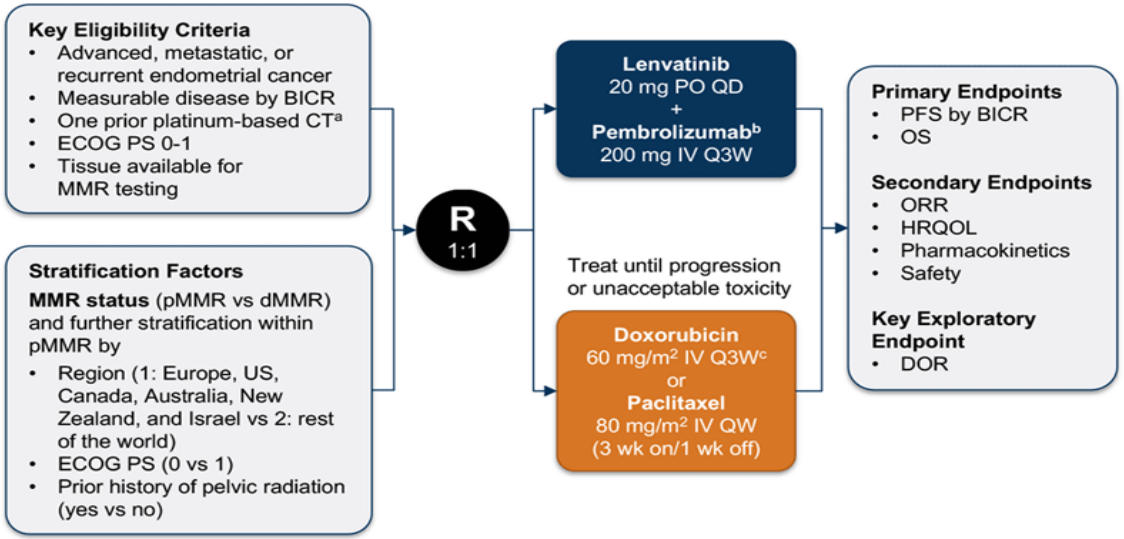
Combination Approach: Pembrolizumab + Lenvatinib[1-3]

FDA Approval	Indication
2019 accelerated approval **2021 full approval**	For the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation

The initial approval was based on data from the **Phase 2 KEYNOTE-146** single-arm trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting and showed promising antitumor activity with the combination regimen

1. (pembrolizumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s127lbl.pdf.
2. Makker V et al. *Lancet Oncol.* 2019;20:711-718. 3. Makker V et al. *J Clin Oncol.* 2020;38:2981.

Phase 3 KEYNOTE-775: Lenvatinib Plus Pembrolizumab[1]



PFS, OS, and ORR were statistically significantly improved with lenvatinib plus pembrolizumab vs chemotherapy at the primary analysis

pMMR:
Len + pembro vs TPC

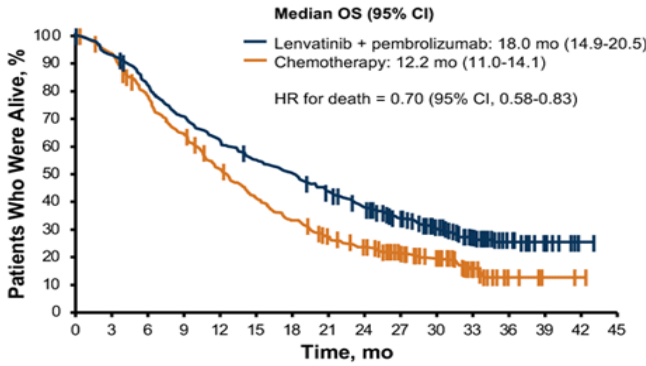
- **ORR**
  30.3% vs 15.1%
- **mPFS**
  6.6 mo vs 3.8 mo
  (HR 0.60)
- **mOS**
  17.4 mo vs 12.0 mo
  (HR 0.56)

[a] Patients may have received up to 2 prior platinum-based CT regimens if 1 was given in the neoadjuvant or adjuvant treatment setting.
[b] Maximum of 35 doses. [c] Maximum cumulative dose of 500 mg/m².

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

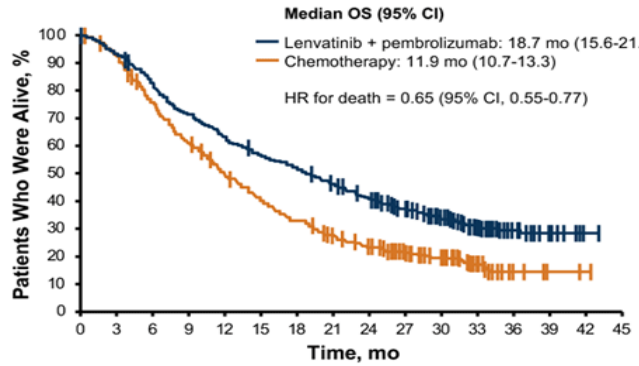
Continued OS Benefit of Lenvatinib + Pembrolizumab vs Chemotherapy With Follow-Up Extended by >16 Months[1,a]

pMMR Population



No. at Risk															
Lenvatinib + 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

All-Comer Population



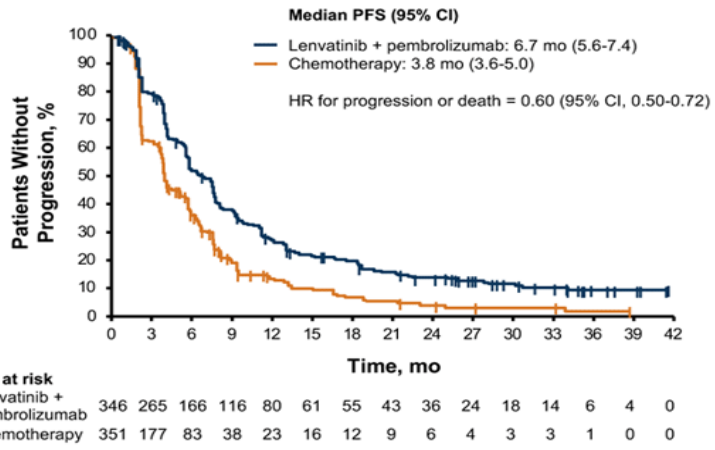
No. at Risk															
Lenvatinib + pembrolizumab	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
Chemotherapy	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1

[a] In the chemotherapy arm, 10.0% of pts in the pMMR population and 8.7% of pts in the all-comer population received subsequent lenvatinib plus pembrolizumab. After excluding these patients, the pMMR OS HR was 0.64 (95% CI, 0.54, 0.76); the all-comer OS HR was 0.60 (95% CI, 0.51, 0.71). Median follow-up time: 14.7 months (data cutoff date: 1 March 2022; >16 months of additional follow-up).

1. Makker V et al. ESMO 2022. Abstract 525MO.

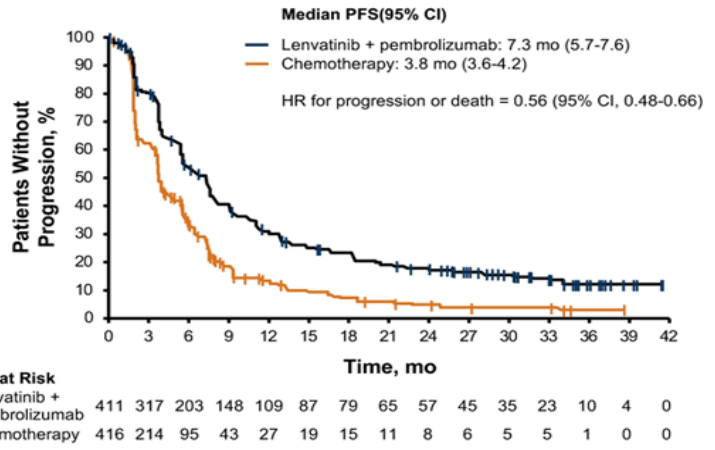
Continued PFS Benefit of Lenvatinib + Pembrolizumab vs Chemotherapy With Follow-up Extended by >16 Months[1,a]

pMMR Population



No. at risk														
Lenvatinib + pembrolizumab	346	265	166	116	80	61	55	43	36	24	18	14	6	4	0
Chemotherapy	351	177	83	38	23	16	12	9	6	4	3	3	1	0	0

All-Comer Population



No. at Risk														
Lenvatinib + pembrolizumab	411	317	203	148	109	87	79	65	57	45	35	23	10	4	0
Chemotherapy	416	214	95	43	27	19	15	11	8	6	5	5	1	0	0

[a] Median follow-up time: 14.7 months; data cutoff date: 1 March 2022; >16 months of additional follow-up. PFS by BICR per RECIST v1.1.

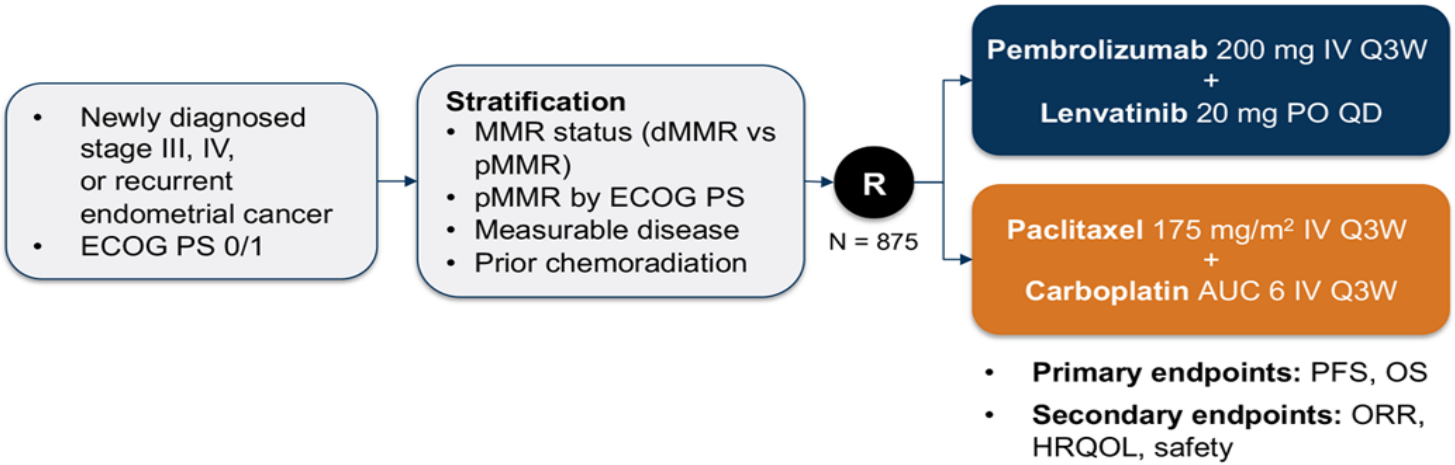
1. Makker V et al. ESMO 2022. Abstract 525MO.

Phase 3 KEYNOTE-775: Response Rates[1]

	pMMR		All-Comer Population	
	LEN + Pembro (n = 346)	Chemotherapy (n = 351)	LEN + Pembro (n = 411)	Chemotherapy (n = 416)
ORR, % (95% CI)	32.4 (27.5, 37.6)	15.1 (11.5, 19.3)	33.8 (29.3, 38.6)	14.7 (11.4, 18.4)
ORR difference in %, estimate (95% CI)	17.2 (11.0, 23.5)		19.2 (13.4, 24.9)	
BOR, % (95% CI)				
Complete response	5.8 (3.6, 8.8)	2.6 (1.2, 4.8)	7.5 (5.2, 10.5)	2.6 (1.3, 4.7)
Partial response	26.6 (22.0, 31.6)	12.5 (9.3, 16.5)	26.3 (22.1, 30.8)	12.0 (9.1, 15.5)
Stable disease	46.5 (41.2, 51.9)	39.6 (34.4, 44.9)	45.0 (40.1, 50.0)	40.1 (35.4, 45.0)
Progressive disease	15.6 (11.9, 19.9)	30.8 (26.0, 35.9)	14.8 (11.5, 18.7)	29.6 (25.2, 34.2)
Not evaluable	0.6 (0.1, 2.1)	2.0 (0.8, 4.1)	1.2 (0.4, 2.8)	1.9 (0.8, 3.8)
No assessment	4.9 (2.9, 7.8)	12.5 (9.3, 16.5)	5.1 (3.2, 7.7)	13.7 (10.5, 17.4)
Disease control rate, % (95% CI)	72.0 (66.9, 76.6)	46.4 (41.1, 51.8)	72.3 (67.7, 76.5)	46.6 (41.8, 51.6)
Median DOR, mo (range)	9.3 (1.6+ to 39.5+)	5.7 (0+ to 37.1+)	12.9 (1.6+ to 39.5+)	5.7 (0+ to 37.1+)
Median TTR, mo (range)	2.1 (1.5 to 23.0)	3.5 (1.0 to 7.4)	2.1 (1.5 to 23.0)	2.1 (1.0 to 7.4)

1. Makker V et al. ESMO 2022. Abstract 525MO.

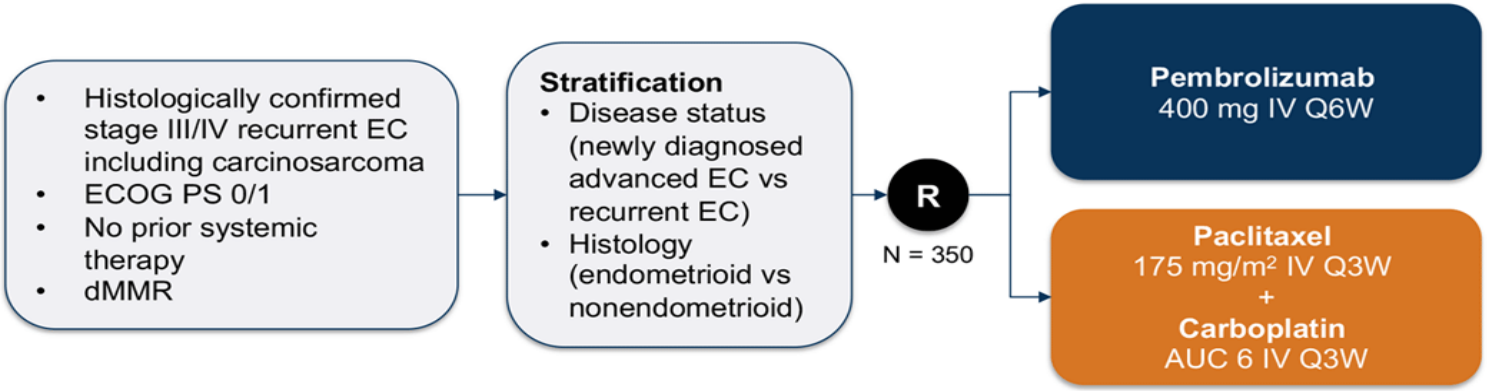
Phase 3 LEAP-001: First-Line Pembrolizumab + Lenvatinib vs Chemotherapy[1]



- **Primary endpoints:** PFS, OS
- **Secondary endpoints:** ORR, HRQOL, safety

1. https://clinicaltrials.gov/ct2/show/NCT03884101.

Phase 3 KEYNOTE C93: First-Line Pembrolizumab vs Chemotherapy in dMMR[1]



- **Primary endpoints:** PFS, OS
- **Secondary endpoints:** ORR, DCR, DOR

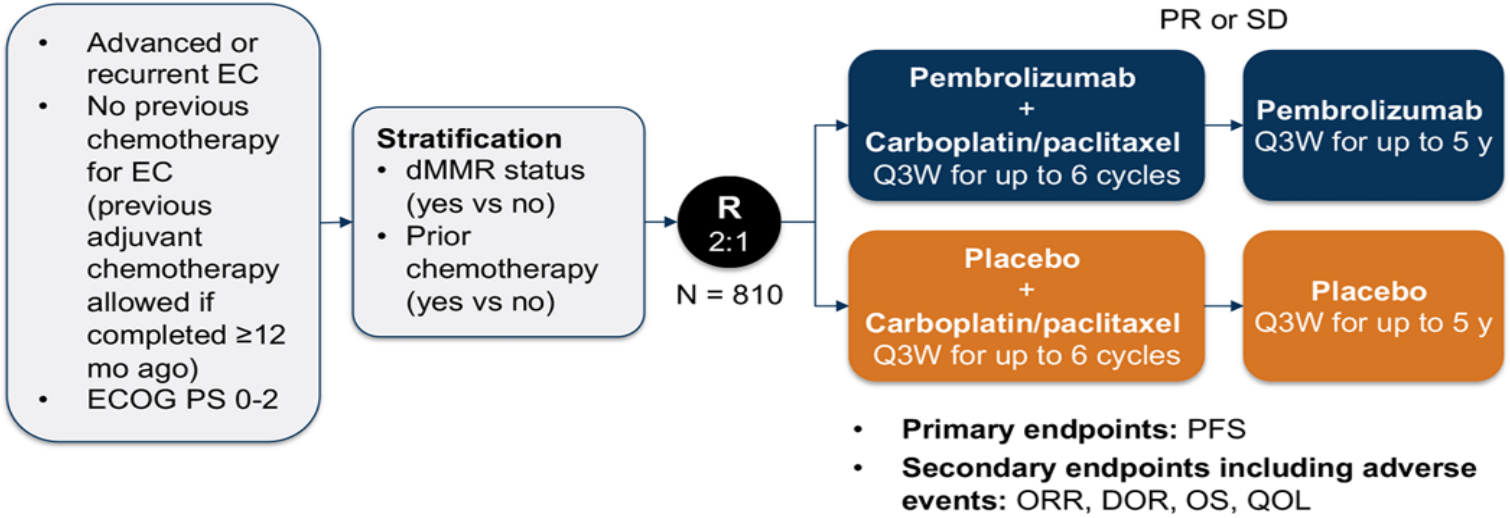
1. https://clinicaltrials.gov/ct2/show/NCT05173987.

Is There Synergy With Combination Approaches?[1]

Trial Name	Treatment Arms
NRG-GY018 *	Pembrolizumab + carboplatin/paclitaxel **vs** placebo + carboplatin/paclitaxel
AtTEnd	Atezolizumab + carboplatin/paclitaxel **vs** placebo + carboplatin/paclitaxel
RUBY *	*Part 1:* Dostarlimab + carboplatin/paclitaxel **vs** placebo + carboplatin/paclitaxel *Part 2:* Dostarlimab + carboplatin/paclitaxel followed by dostarlimab ± niraparib
DUO-E	Durvalumab + carboplatin/paclitaxel followed by durvalumab (± olaparib) maintenance

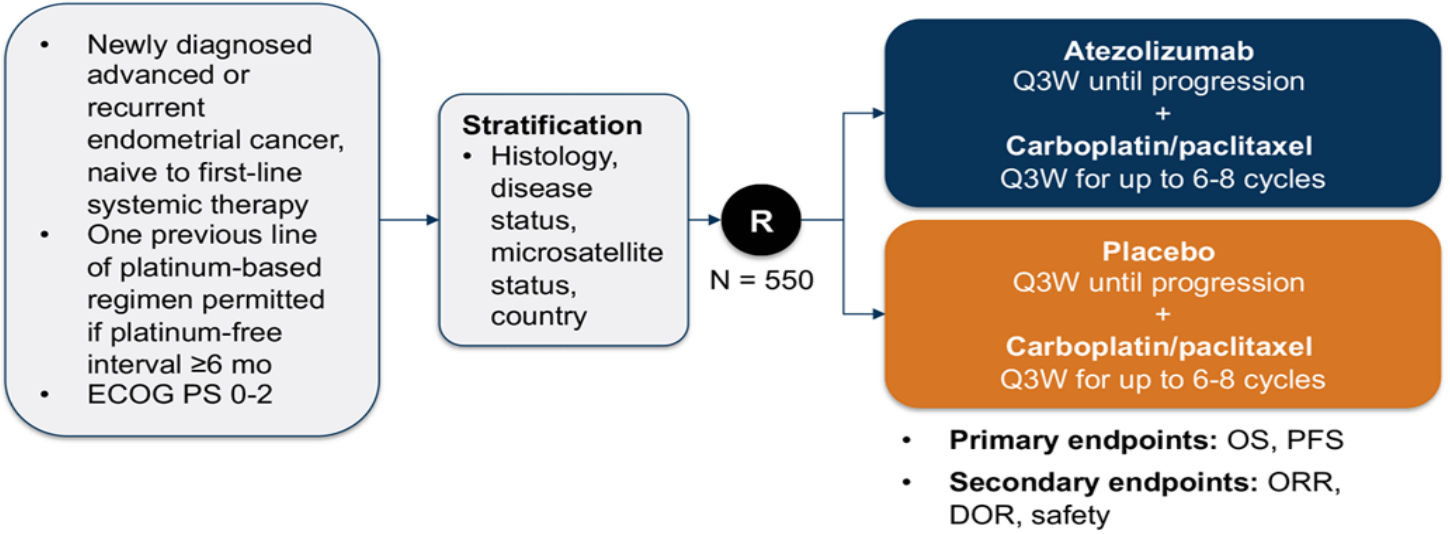
Treatment sequences may change if these combinations are effective and ultimately approved for the 1L setting

Phase 3 NRG-GY018: Pembrolizumab Plus Chemotherapy[1]

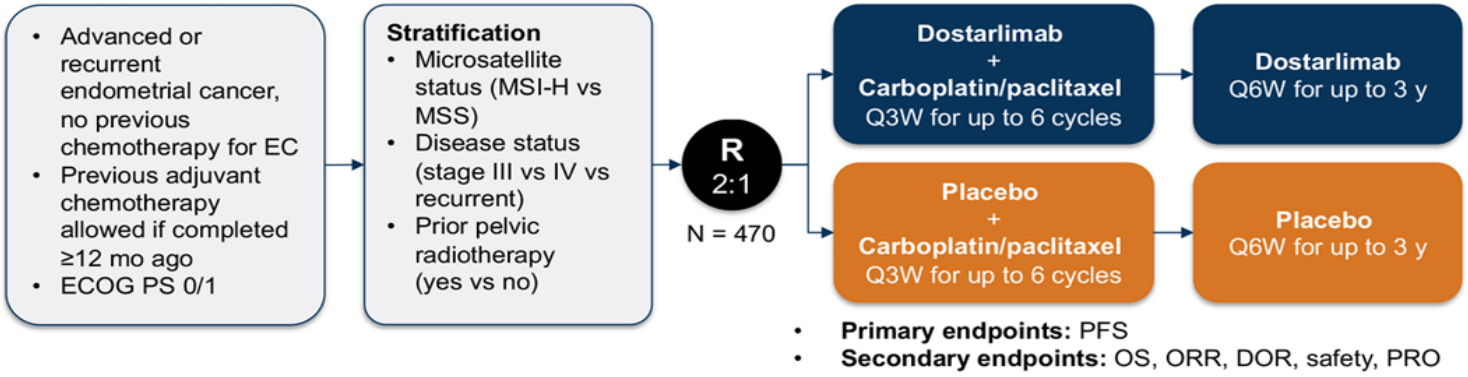


- **Primary endpoints:** PFS
- **Secondary endpoints including adverse events:** ORR, DOR, OS, QOL

Phase 3 AtTEnd: Atezolizumab Plus Chemotherapy



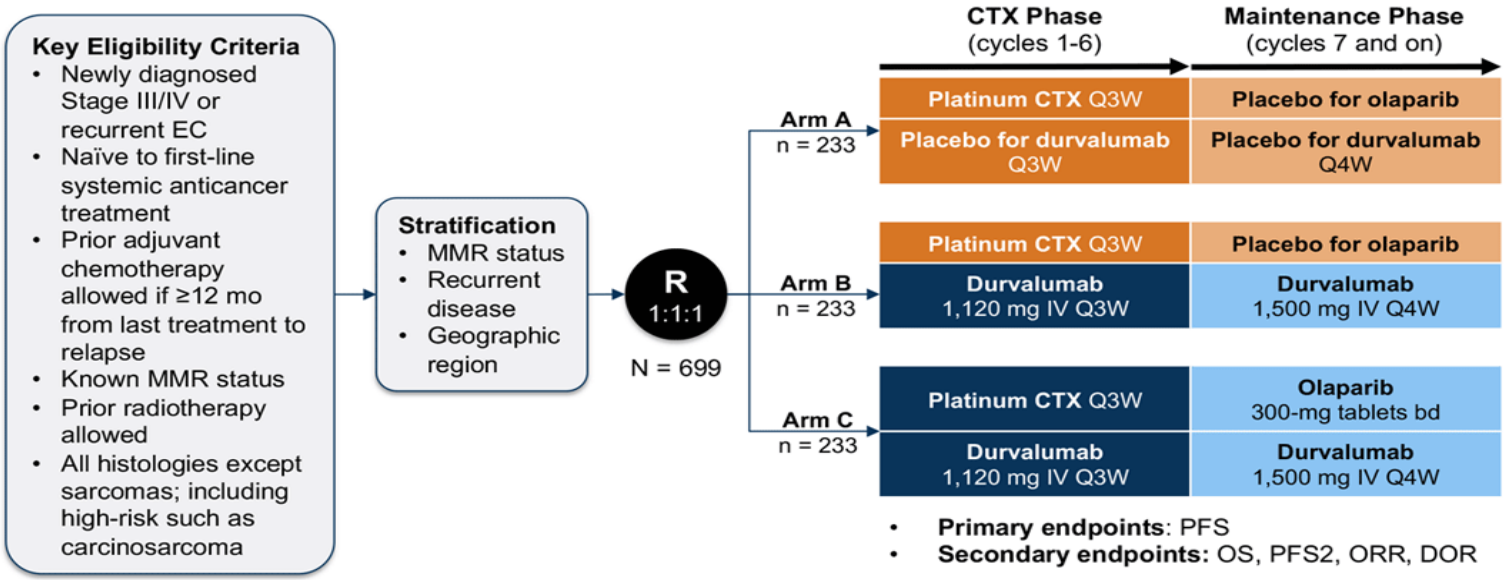
Phase 3 RUBY (Part 1): Dostarlimab Plus Chemotherapy[1]



Results from Part 1 (via press release)

- Met primary endpoint of INV-assessed PFS in a planned interim analysis; showed a statistically significant and clinically meaningful benefit in the prespecified dMMR/MSI-H patient subgroup and in the overall population; a clinically relevant benefit in PFS was also observed in the pMMR/MSS patient subgroup
- Part 2 will assess dostarlimab + carboplatin/paclitaxel followed by dostarlimab ± niraparib

Phase 3 DUO-E: Durvalumab Plus Chemotherapy[1]



1. https://clinicaltrials.gov/ct2/show/NCT04269200.

Recent Announcements
(To be presented at SGO 2023)

- **RUBY Trial**

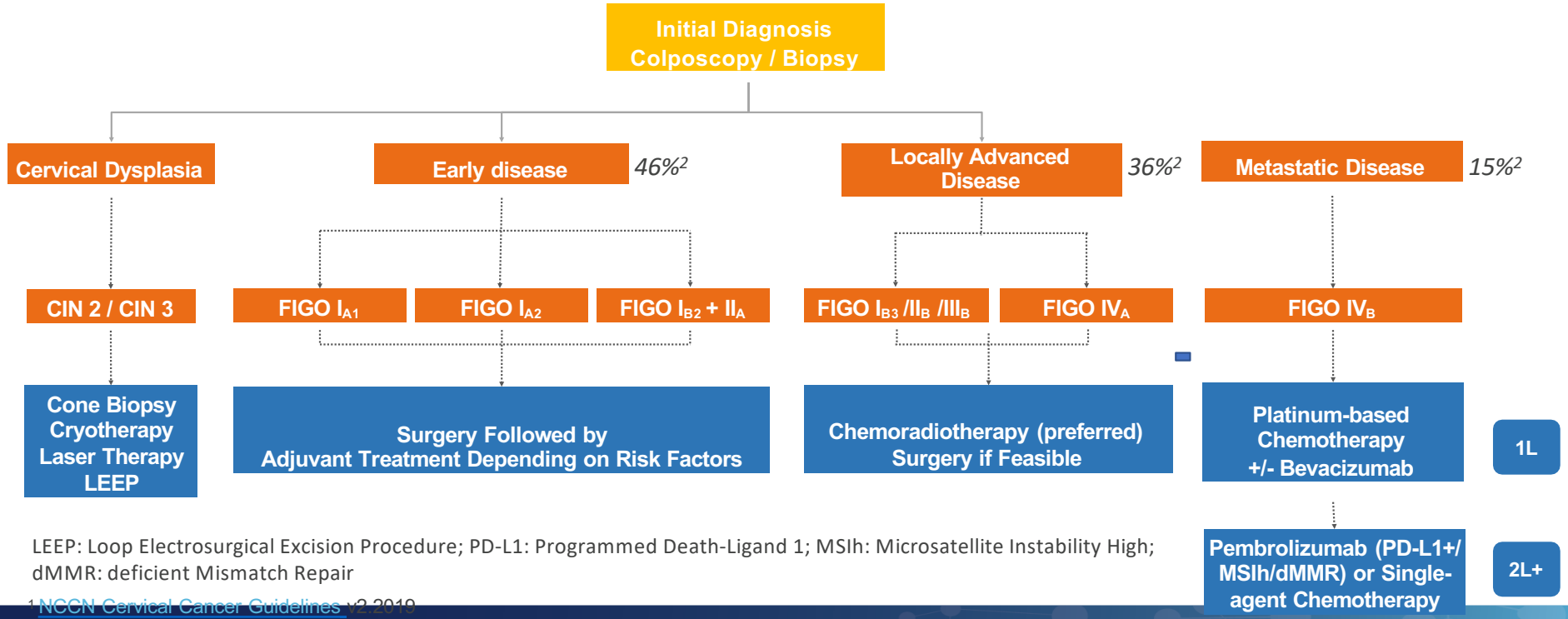
- Phase 3 RCT comparing Dostarlimab + chemo vs chemo alone
- Advanced or recurrent disease
- **Dostarlimab plus chemo** demonstrates significant improvement in PFS in all cohorts

NRG GY018

- Phase 3 RCT comparing pembrolizumab + chemo vs chemo alone
- advanced or recurrent disease
- **Pembrolizumab plus chemo** demonstrates significant Improvement in progression-free survival in all cohorts (dMMR & pMMR)

Cervical Cancer

Cervical Cancer: Summary of Treatment



LEEP: Loop Electrosurgical Excision Procedure; PD-L1: Programmed Death-Ligand 1; MSIh: Microsatellite Instability High; dMMR: deficient Mismatch Repair

1 NCCN Cervical Cancer Guidelines v2.2019
2 SEER Cancer Stat Facts: Cervical Cancer. National Cancer Institute. Bethesda, MD

KEYNOTE-158 (NCT02628067): Phase II basket study, single-agent pembrolizumab, cervical cancer cohort

- Advanced cervical squamous cell carcinoma with progression on/intolerance to ≥1 prior line of standard therapy
- ECOG PS 0/1

- 84% PD-L1-positive; 77/98 (79%) had CPS ≥1
- 65% ≥2 prior therapies for recurrent/metastatic CC)

Primary endpoint: IRC-assessed ORR (RECIST v1.1)

Secondary endpoints: DoR, IRC-assessed PFS, OS, safety

FDA approval June 2018: recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test

Response	All patients (n=98)	PD-L1 positive (n=82)	PD-L1-negative (n=15)
ORR (95% CI)	12.2%	14.6% (8–24)	0% (0–22)
CR	3%	4%	0%
PR	9%	11%	0%
SD	18%	18%	20%

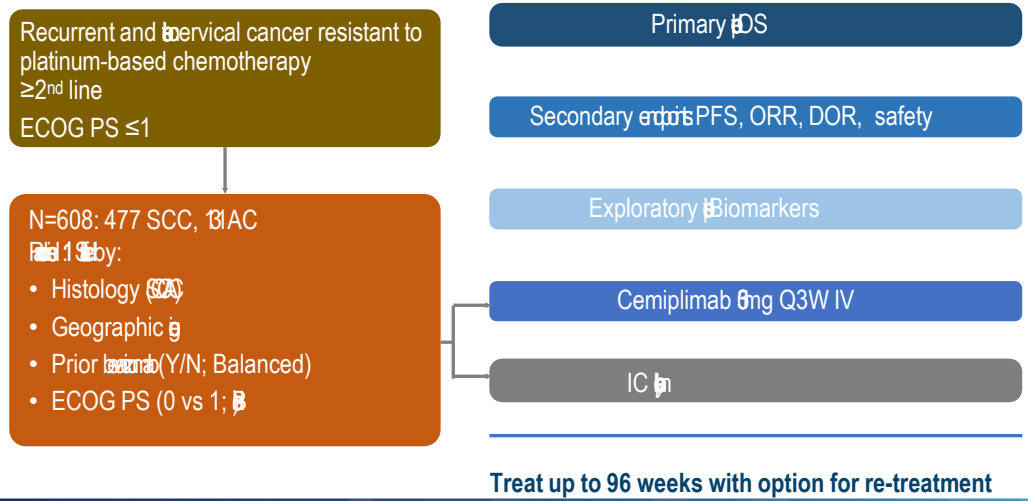
- Median time to response: 2.1 months (range 1.6–4.1)
- Median DoR: not reached (range 3.7+–18.6+)
- 6/12 responses ongoing at data cut-off

Pembrolizumab 200 mg q3w for 2 years or until PD, intolerable toxicity, patient withdrawal or investigator decision

Published in: Hyun Cheol Chung; Willeke Ros; Jean-Pierre Delord; Ruth Perets; Antoine Italiano; Ronnie Shapira-Frommer; Lyudmila Manzuk; Sarina A. Piha-Paul; Lei Xu; Susan Zeigenfuss; Scott K. Pruitt; Alexandra Leary; *Journal of Clinical Oncology*. Ahead of Print
DOI: 10.1200/JCO.18.01265

Background and Design

- EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9: Randomised, Phase 3 study of cemiplimab versus investigator's choice (IC) of chemotherapy in patients with recurrent or metastatic cervical carcinoma following platinum failure and regardless of programmed cell death-ligand 1 (PD-L1) tumour expression.
- Results from second interim analysis: significantly improved overall survival (OS) in patients with cervical cancer receiving cemiplimab monotherapy.[1]
- Per protocol, the final analysis for the OS endpoint was when 340 events were observed in SCC patients.
- Here, we present the final survival analysis after 363 observed OS events in SCC patients, at a median follow-up of 30 months.

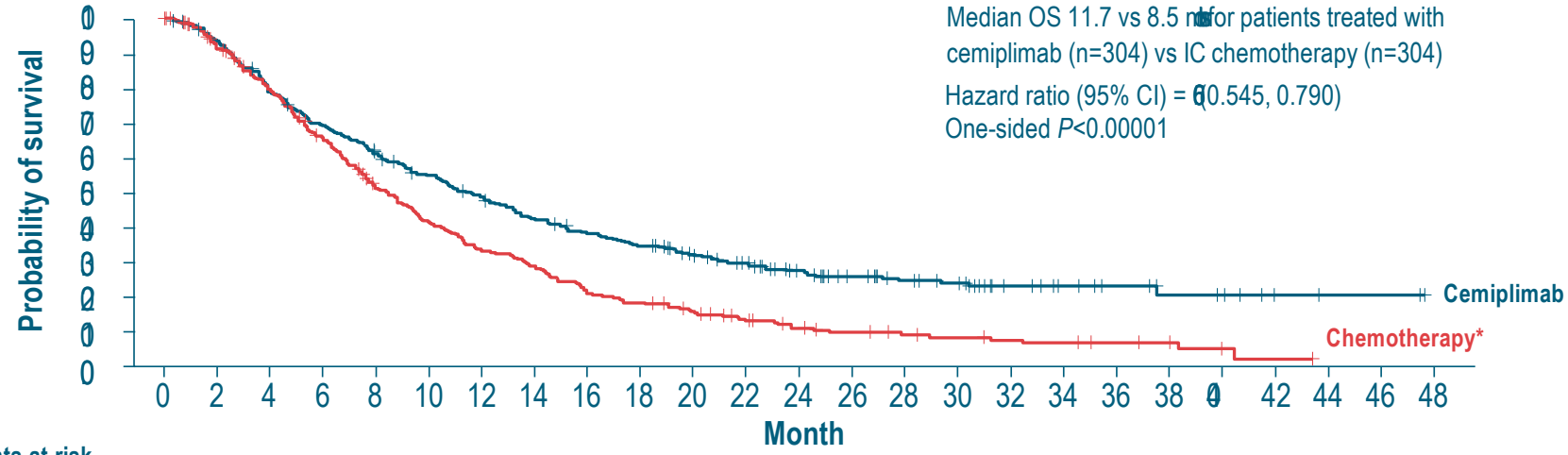


AC, adenocarcinoma or adenosquamous carcinoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, investigator's choice of chemotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; SCC, squamous cell carcinoma.

1. Tewari et al. *N Engl J Med* 2024;390:1655.

Cemiplimab monotherapy significantly improved OS vs chemotherapy in the overall population

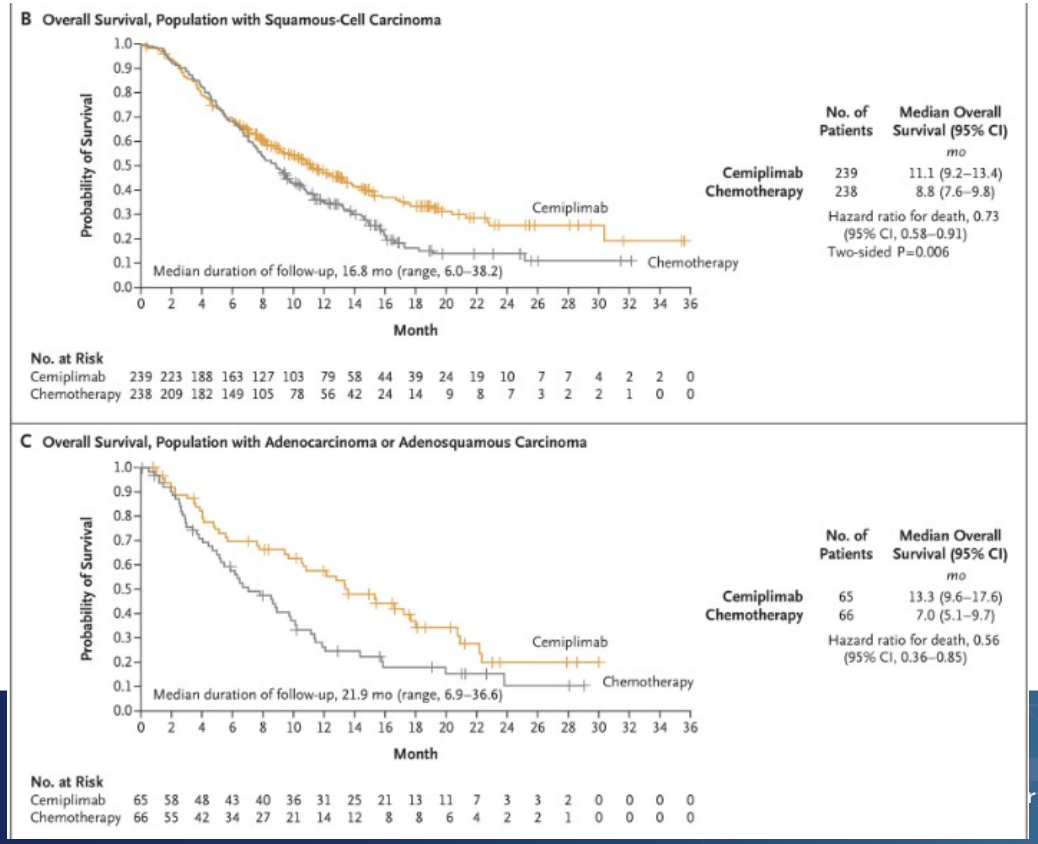
Median follow-up time: 30.2 (18.0–50.2) months



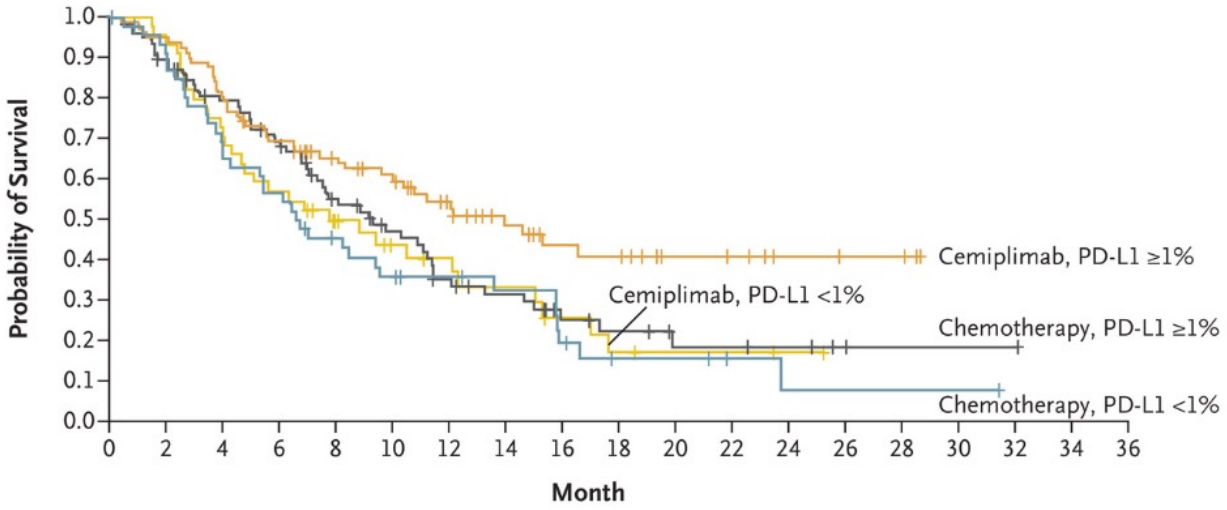
Kaplan–Meier curves of overall survival in the full analysis set.
CI, confidence interval; IC, investigator's choice; OS, overall survival. Data cutoff date: 4 Jan 2022.

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

Cemiplimab monotherapy significantly improved OS vs chemotherapy regardless of histology



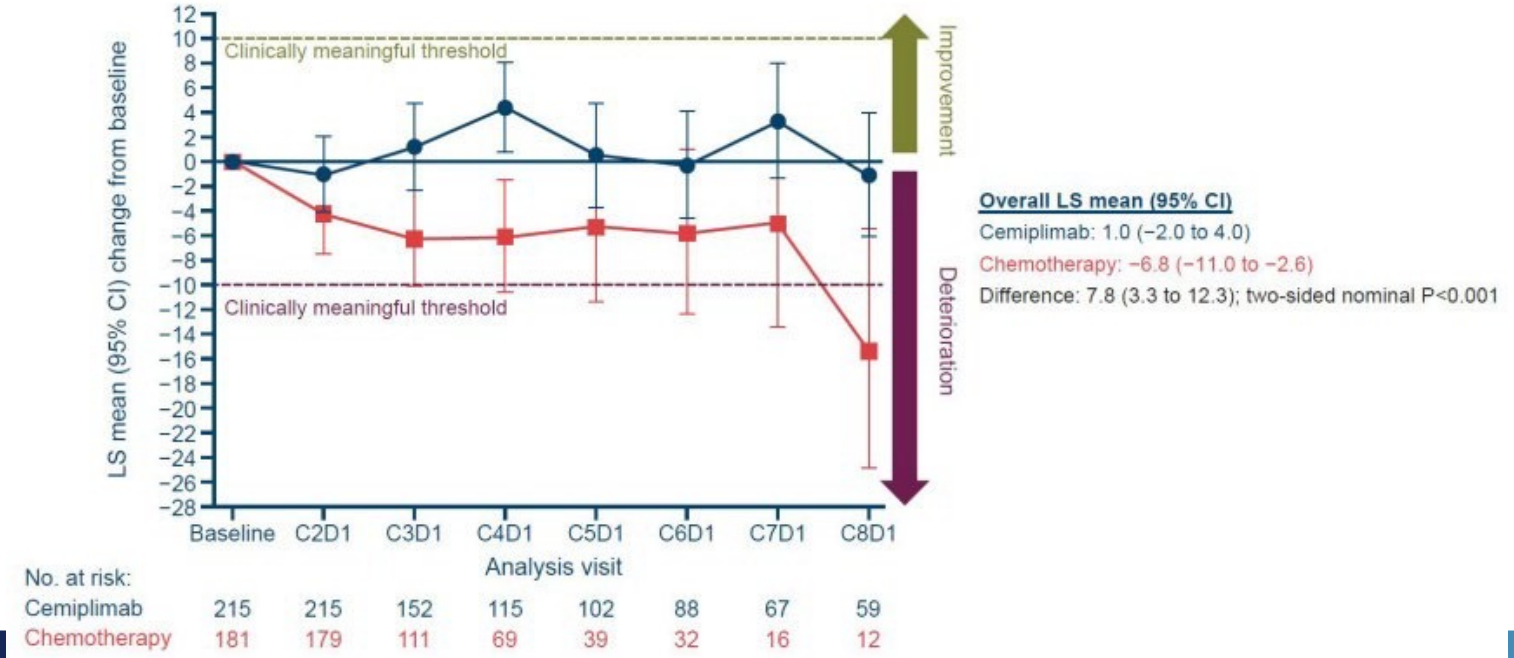
Cemiplimab monotherapy significantly improved OS vs chemotherapy regardless of PD-L1 status



No. at Risk																			
Cemiplimab, PD-L1 ≥1%	82	78	65	55	45	39	30	22	16	15	10	9	4	3	3	0	0	0	0
Cemiplimab, PD-L1 <1%	44	41	30	25	18	13	11	9	6	4	3	3	1	0	0	0	0	0	0
Chemotherapy, PD-L1 ≥1%	80	69	58	50	36	28	20	16	10	8	5	5	4	2	1	1	1	0	0
Chemotherapy, PD-L1 <1%	48	40	30	26	19	15	12	10	6	4	4	2	1	1	1	1	0	0	0

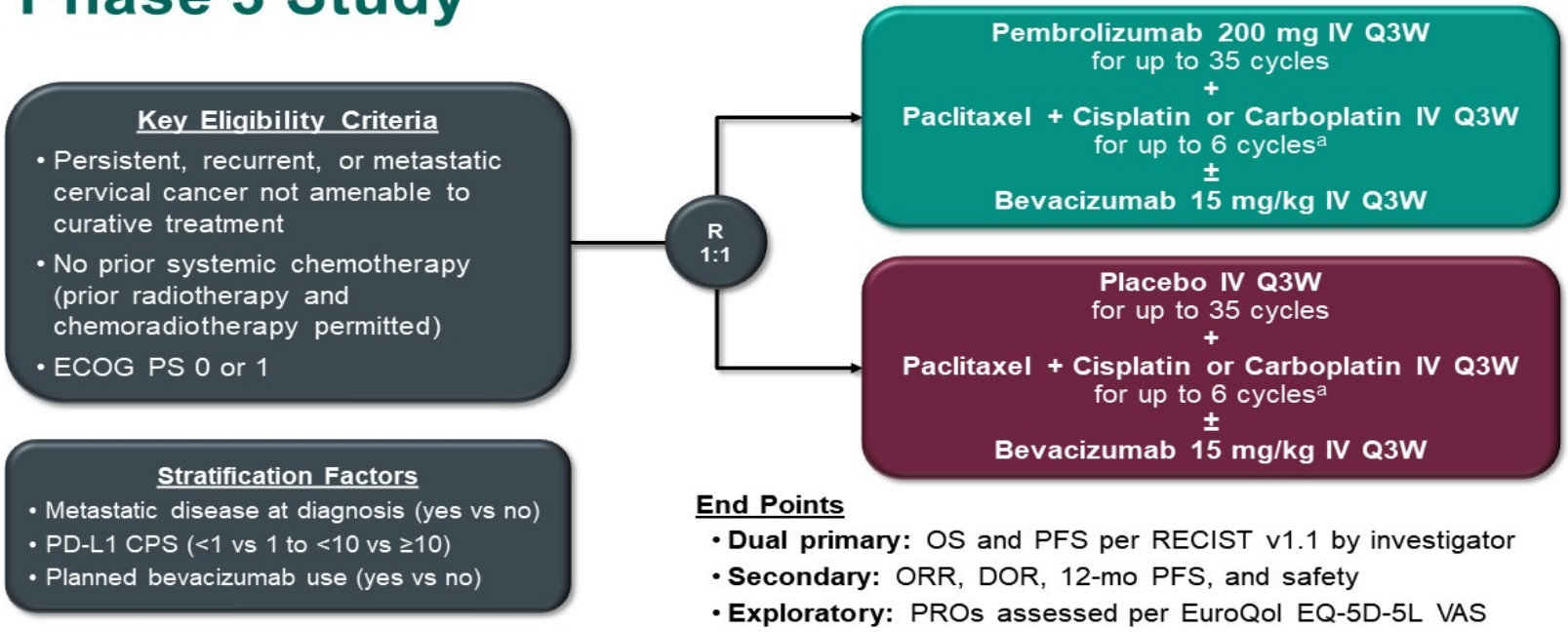
QoL/PROs with cemiplimab in GOG 3016/ENGOT cx9/ EMPOWER cervical

Figure S5. Change from Baseline in GHS/QoL Score in the Overall Population



Tewari KS et al. NEJM 2022

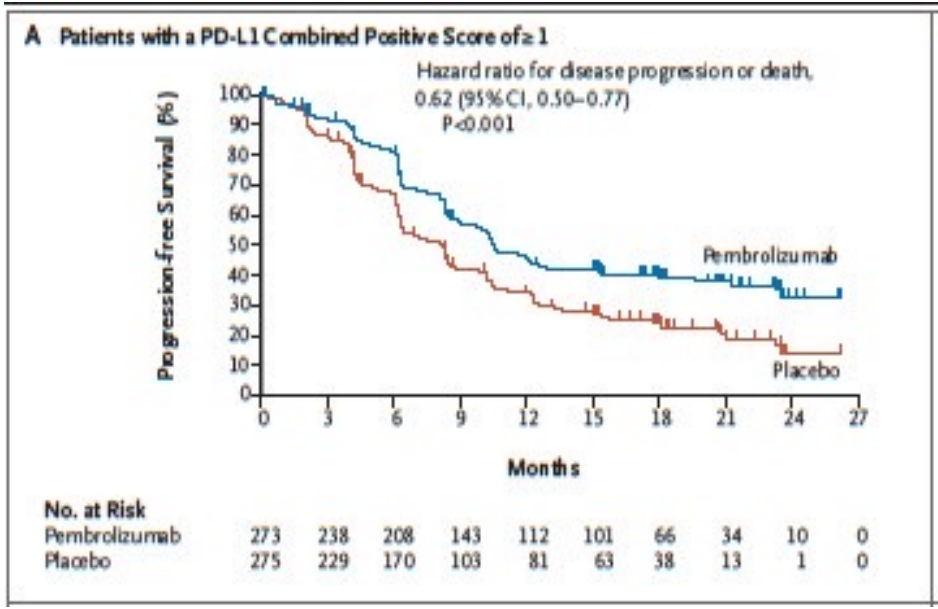
KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study

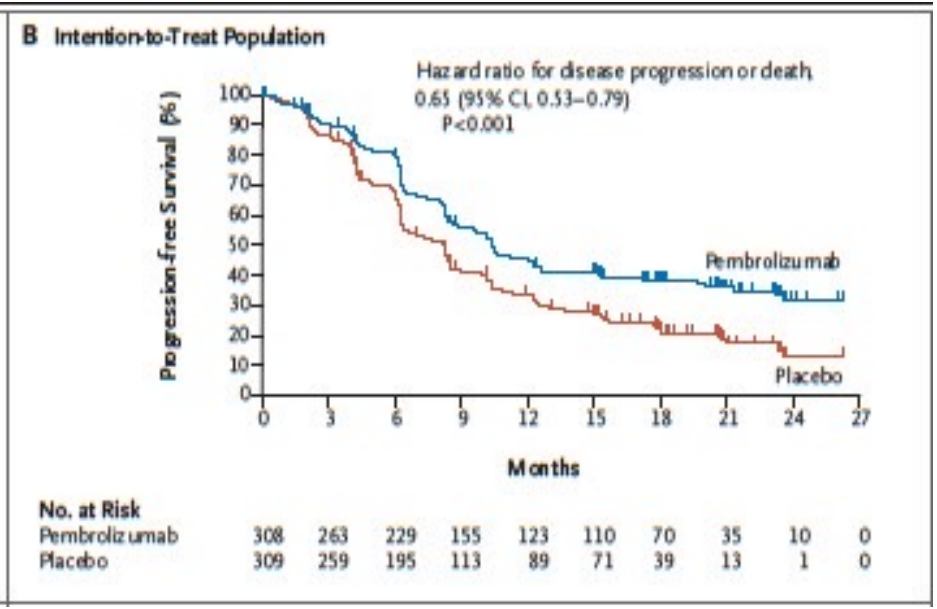


End Points

- **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

[a]Paclitaxel: 175 mg/m^2. Cisplatin: cisplatin 50 mg/m^2. Carboplatin: AUC 5 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.
CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100); PROs, patient-reported outcomes; VAS, visual analog scale. KEYNOTE-826 ClinicalTrials.gov identifier, NCT03635567.



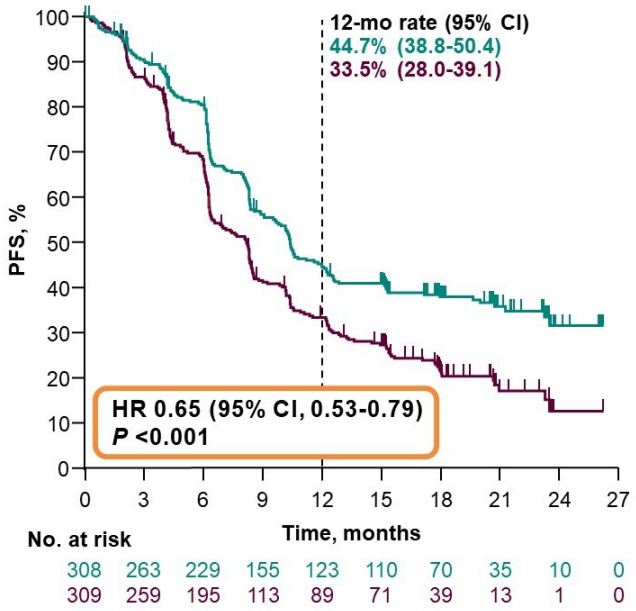


Biomarker group (n)	HR PFS
ITT* (617)	0.67
PDL1 ≥ 1* (231)	0.64
PDL1 ≥ 10 (317)	0.61
PDL1 ≤ 1 (69)	1.00 (95% CI 0.53-1.04)

Dual Primary Endpoints: All-Comer Population

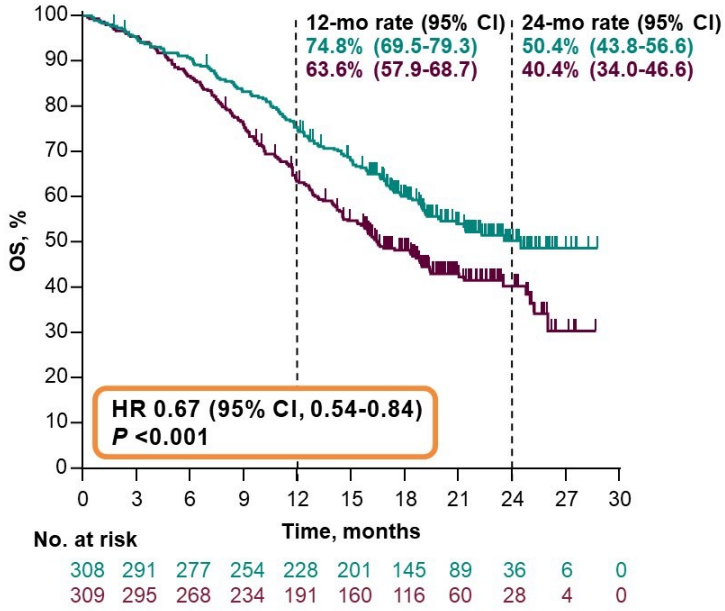
PFS[a]

	Pts w/Event	Median, mo (95% CI)
Pembro + Chemo ± Bev	58.4%	10.4 (9.1-12.1)
Pbo + Chemo ± Bev	73.1%	8.2 (6.4-8.4)



OS

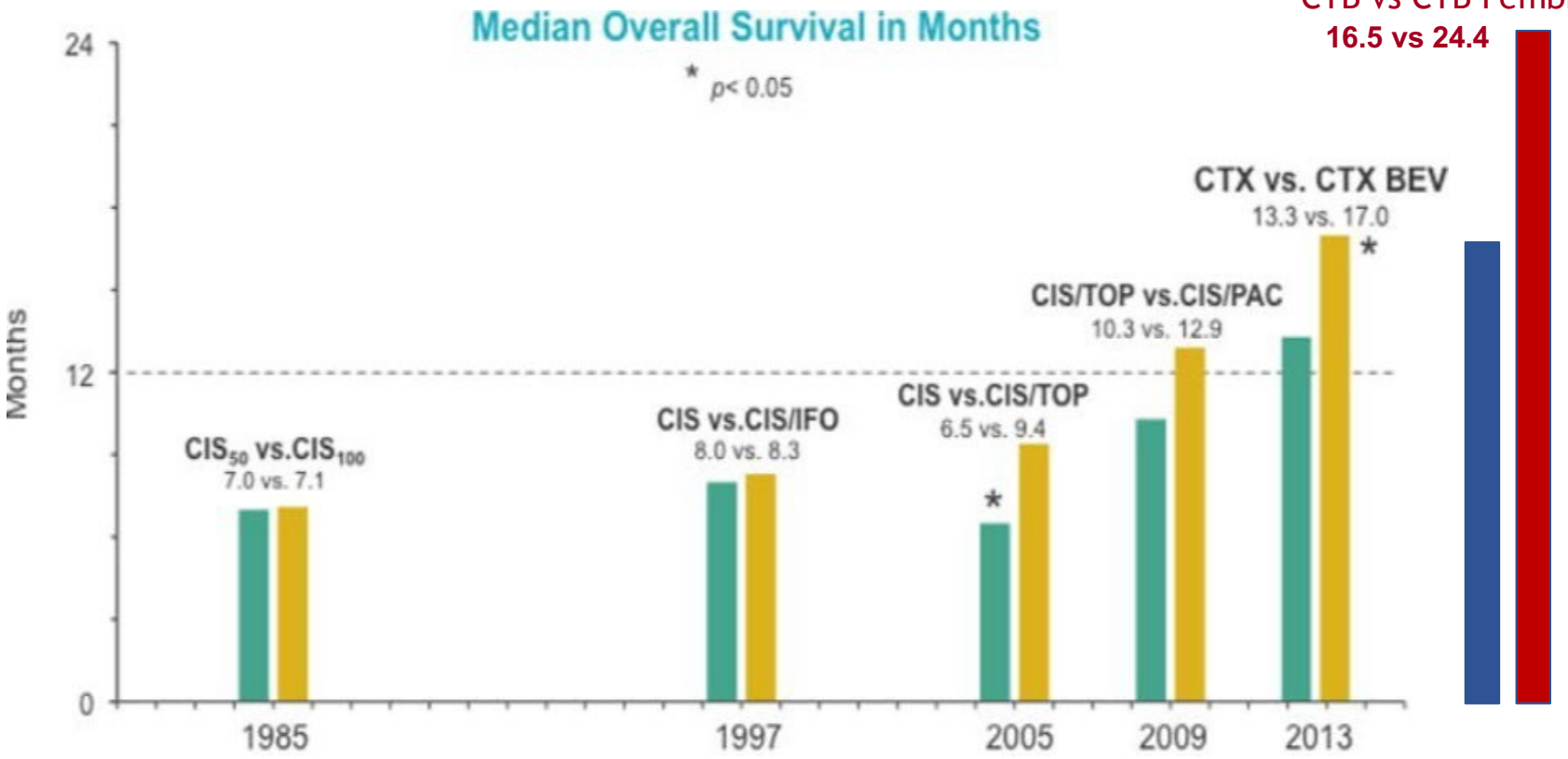
	Pts w/Event	Median, mo (95% CI)
Pembro + Chemo ± Bev	44.8%	24.4 (19.2-NR))
Pbo + Chemo ± Bev	56.3%	16.5 (14.5-19.4)



Colombo N et al. *N Engl J Med* 2021;385:1856-67.
[a]Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

CTB vs CTB Pembro

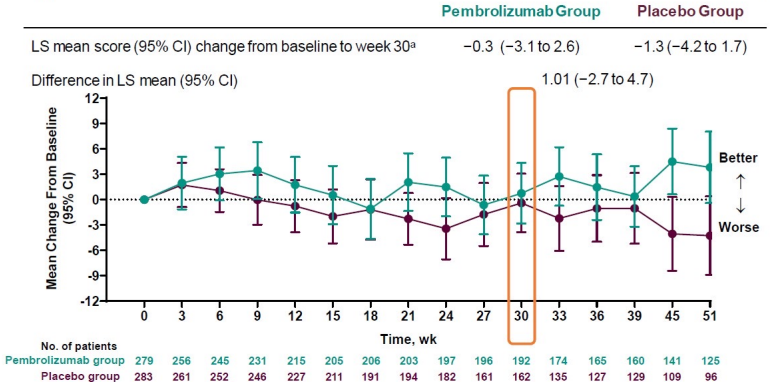
16.5 vs 24.4



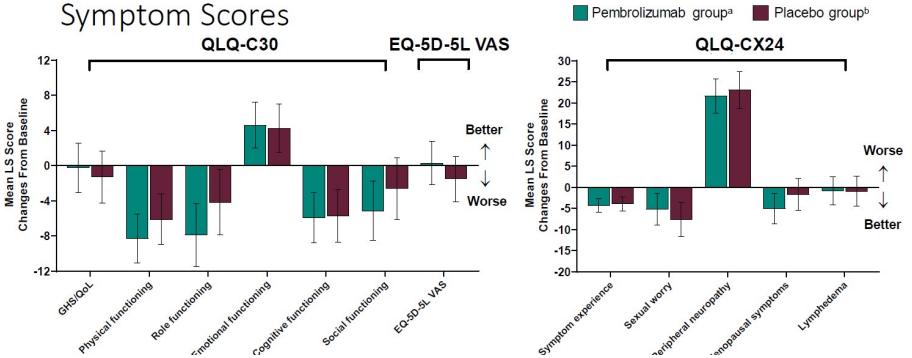
Tewari et al. Clin Cancer Res. 2015; 21(24): 5480-7. Columbo N et al NEJM 2021

IMPROVED QoL/PROs with pembrolizumab

Change From Baseline in EORTC QLQ-C30 GHS/QoL



Change From Baseline to Week 30 in QLQ-C30 Functional Scales, EQ-5D-5L VAS, and QLQ-CX24 Cervical Symptom Scores



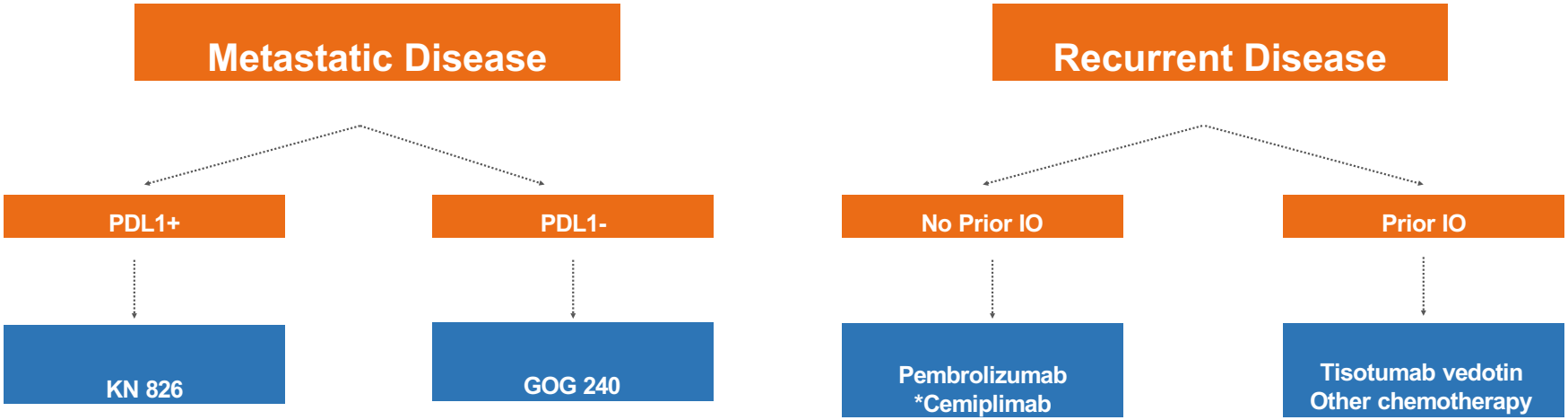
Monk B et al. SGO 2022 Abstract 23

I/O combinations in the pipeline, 2L+

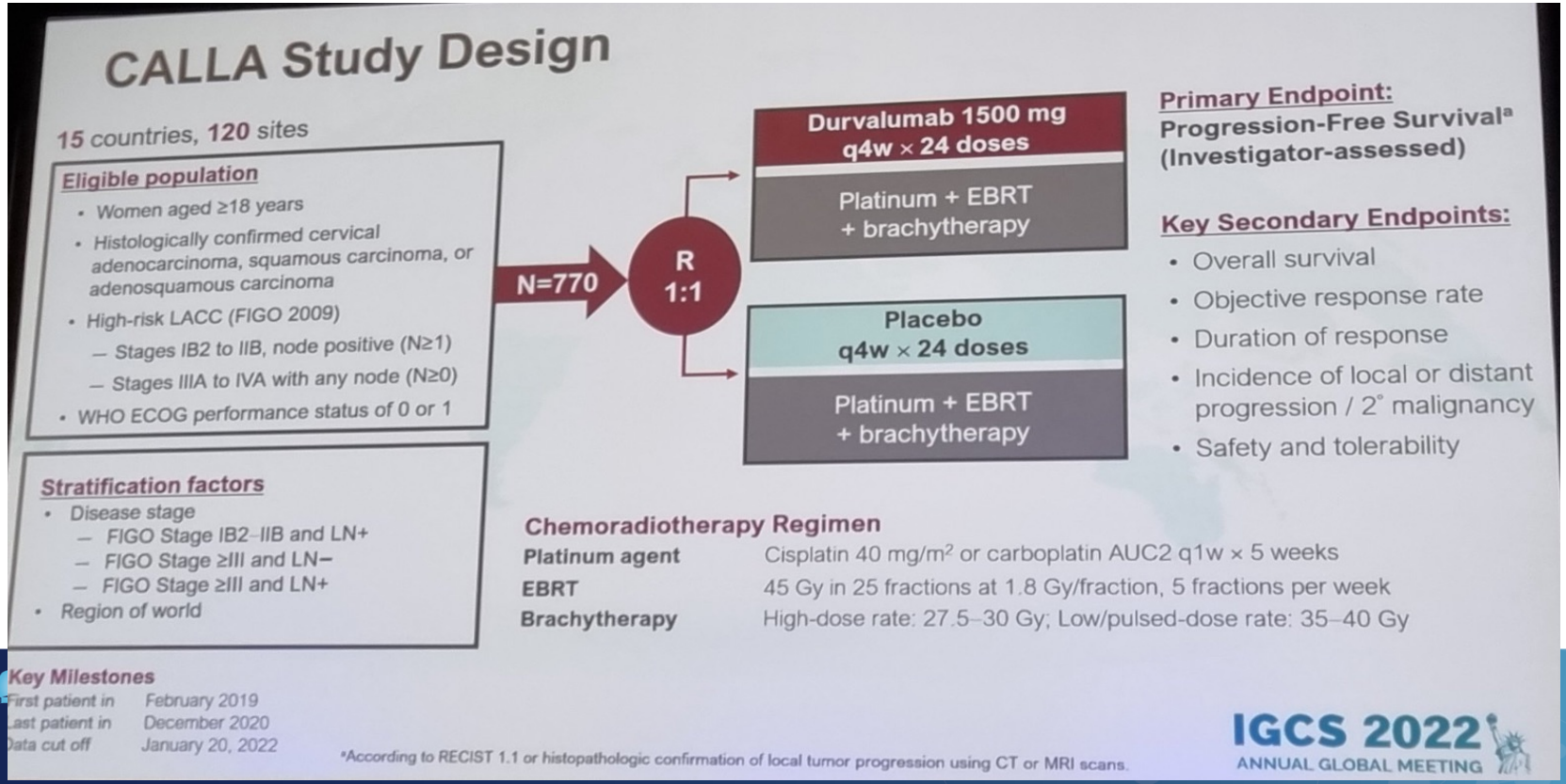
	N	ORR (95% CI)	ORR PD-L1+ (95% CI)	ORR PD-L1- (95% CI)
Nivolumab3 + ipilimumab1[1]	26	23% (9-43.6)	40% (12.2-73.8)	9.1% (0.2-41.3)
Nivolumab1 + ipilimumab3[1]	22	36% (17.2-59.3)	16.7% (2.1-48.4)	57.1% (18.4-90.1)
Balstilimab + Zalifrelimab[2]	125	25.6%	32.8%	9.1%
AK-104 (PD1i/CTLA4i bispecific)[3]	40	--	--	--
Bintrafusp alfa (PDL1i/TGFbi bispecific)[4]	39	28.2% (15-44.9)		
Tiragolumab +atezolizumab[5]	160	--	--	--
Tisotumab vedotin +pembro[6]	35	38% (22-56)	--	--

1. Oaknin. ESMO 2021. 2. O'Malley DM et al. Virtual ESMO 2021 3. https://clinicaltrials.gov/ct2/show/NCT04380805 4. Strauss et al. JCO 39, 2021 abstr 3011. 5. https://clinicaltrials.gov/ct2/show/NCT04300647. 6. Vergote et.al Virtual ESMO 2021.

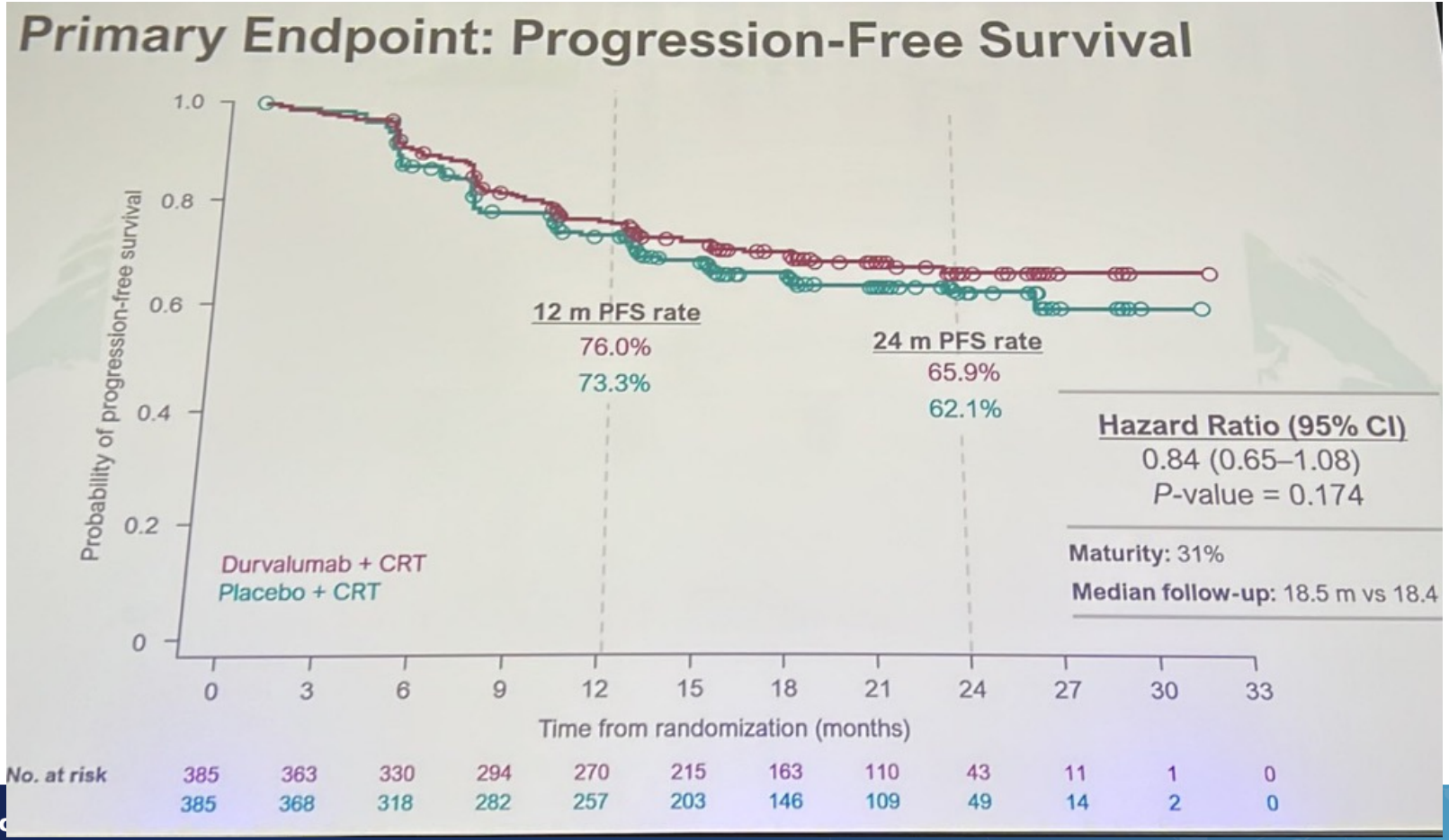
Cervical Cancer: Evolving Treatment



Durvalumab in combination and following chemoradiation for locally advanced cervical cancer



Primary Endpoint: Progression-Free Survival



Conclusions

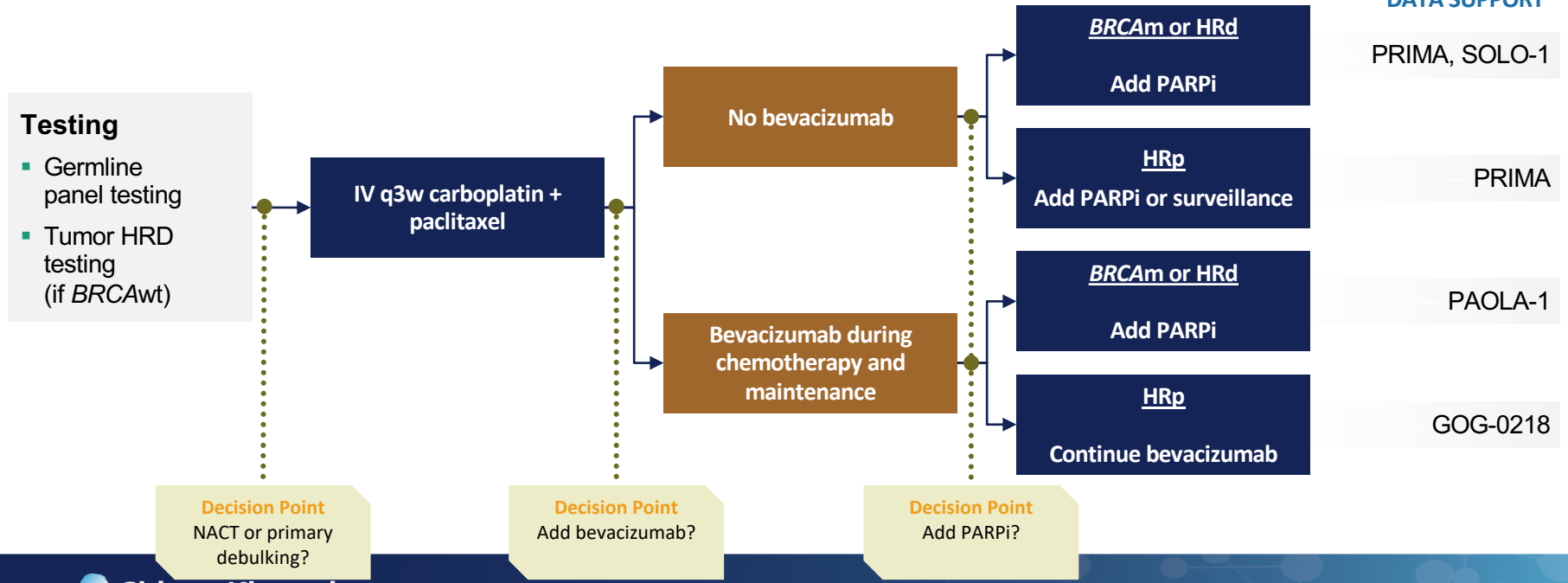
- *Durvalumab, in combination with and following CRT, did not significantly improve PFS in patients with high-risk LACC compared with CRT alone in CALLA*
- *Safety was similar for both arms, without new or unexpected toxicity*
- *Improvements over standard CRT remain a challenge in LACC, and further research is needed to optimize patient outcomes*

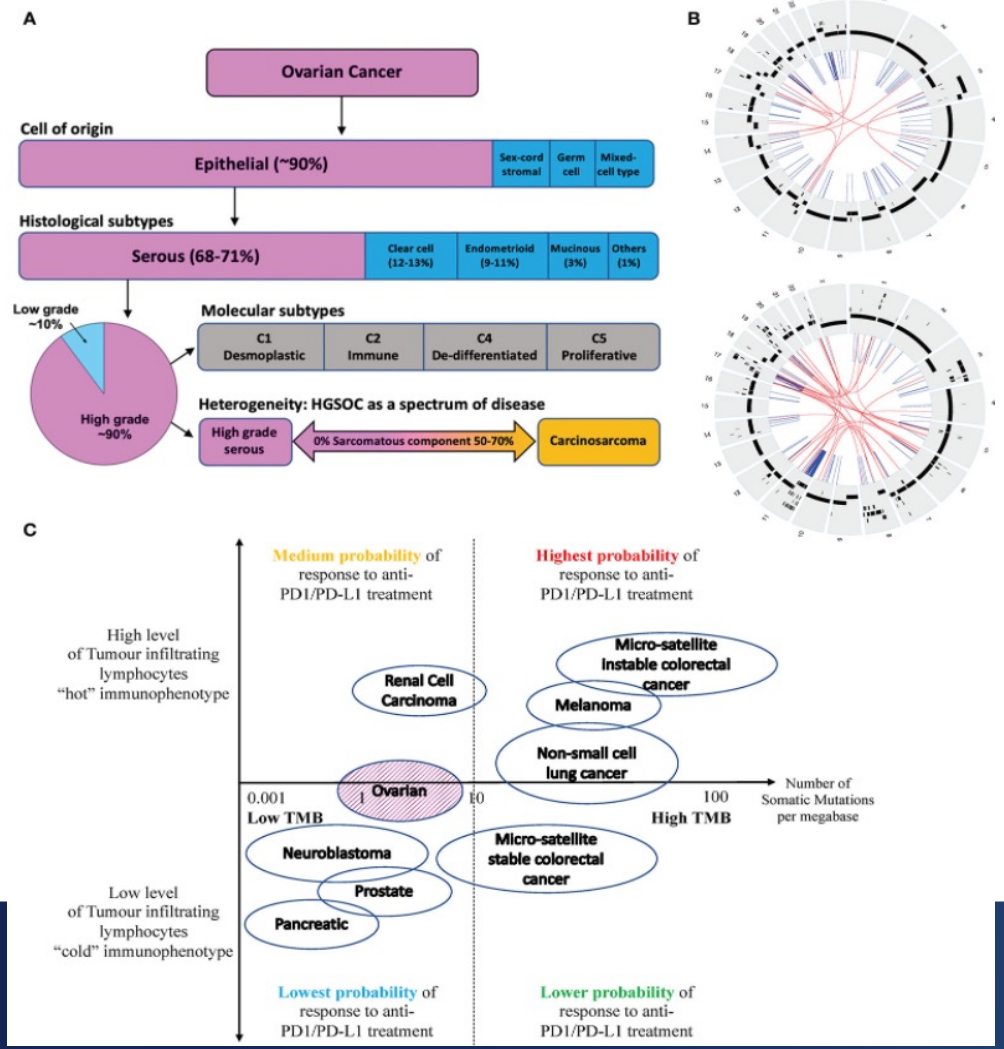
Ovary/Fallopian tube Cancer

Options for treatment of advanced ovarian cancer

A recently published consensus of US physicians outlines one algorithmic approach

Adapted from: Chan JK et al. *Gynecol Oncol*. 2020;159(3):604-606 and Ledermann JA. *Ann Oncol*. 2013;24(suppl 6):vi24-vi32.



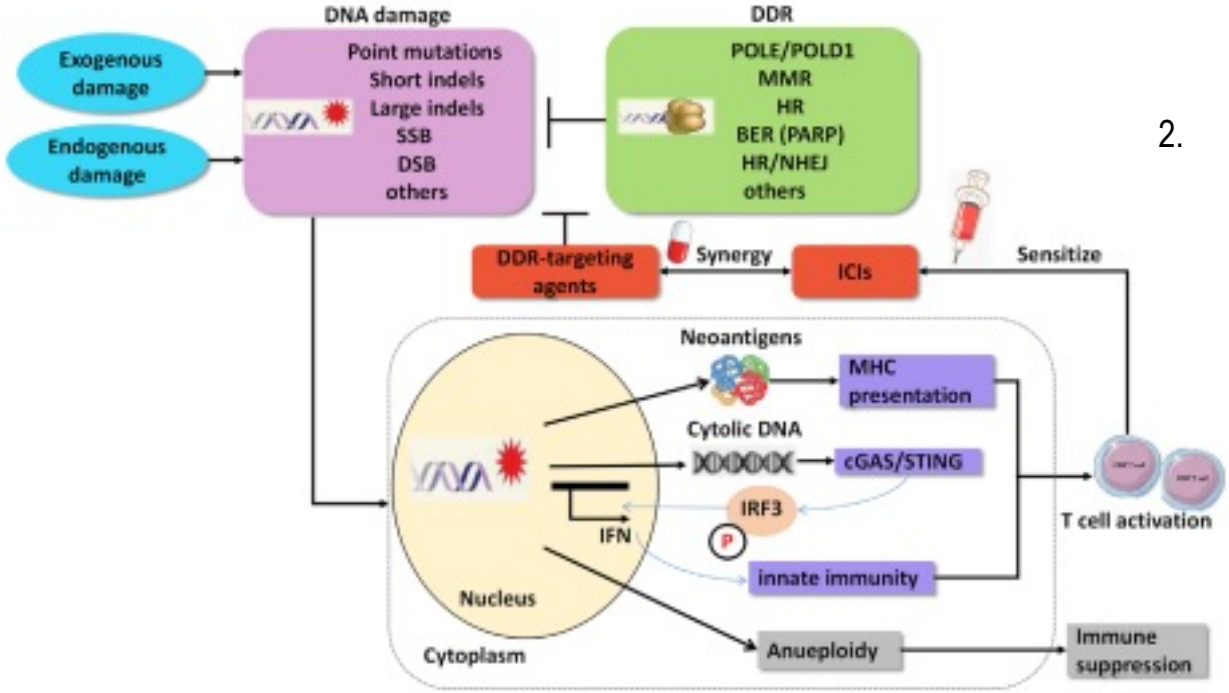


Randomized Phase 3 Trials of Immune Checkpoint Inhibitors in Front Line Ovarian Cancer: A Tale of Two Trials

- At baseline, the majority of epithelial ovarian cancer has a lower probability of responding to immunotherapy
- Over expression of Fas ligand, VEGF and may impair T cell trafficking, although if this were major obstacle, IMagyn050 should have worked
- No biomarkers for patient selection
- **How about Combinations?**

Wu et al. Frontiers in Immunology 2021

Is all hope for immune check point inhibitors lost? Can PARPi save the day?



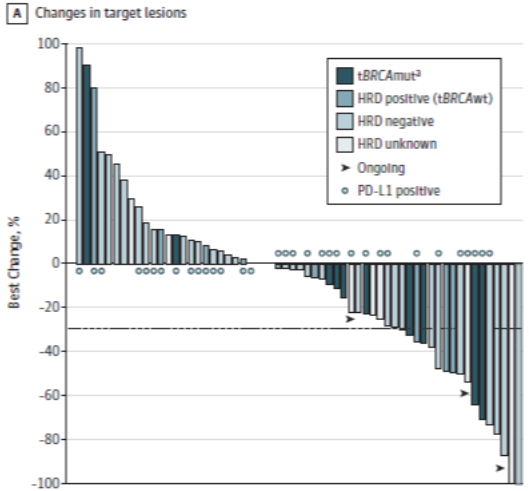
Why would this work?

1. DDR deficiency leads to somatic mutations and neoantigens which can lead to an immune response
2. Damaged DNA which transfers from the nucleus to the cytoplasm = cytosolic DNA. This can activate stimulator of interferon genes (STING) which can trigger an immune response

Sun W et al. frontiers in oncology. 2021

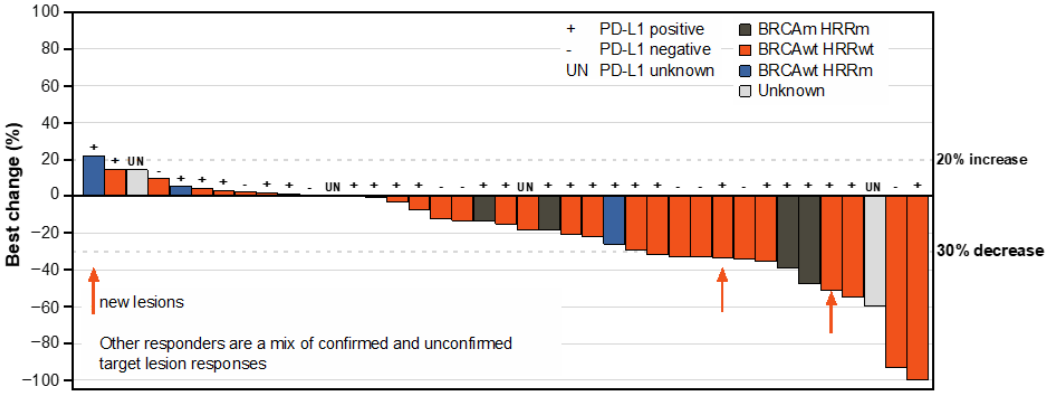
Early Reports of Combination PARPi and Immune Checkpoint Inhibitors Have Demonstrated Modest Efficacy in platinum resistant ovarian cancer

Topacio
Niraparib + Pembrolizumab



ORR 18% (11-29%)
DOR NR

OPAL
Niraparib + Dostarlimab + Bevacizumab

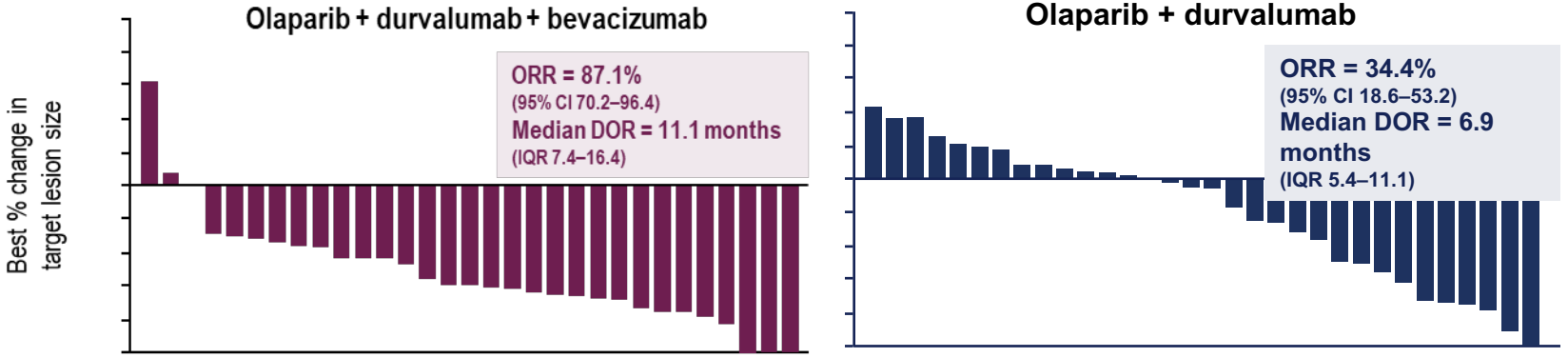


ORR 17.9% (8.7-31.3)

Konstantinopoulos et al. *JAMA Oncol*. 2019;5(8):1141-1149; Liu et al. Society of Gynecologic Oncology Annual Meeting 2021

Is this more a platinum sensitive strategy?

Mediola



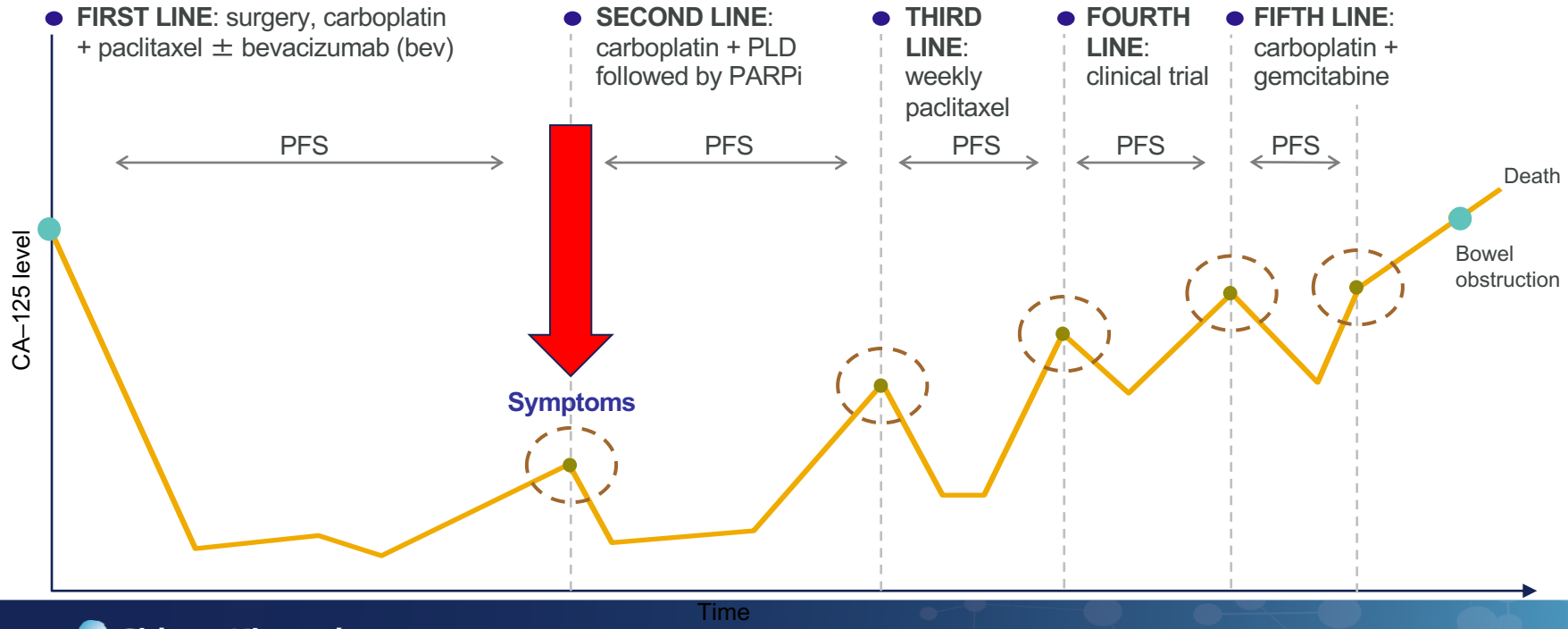
Genomic instability status* subgroup	Olaparib + durvalumab + bevacizumab		Olaparib + durvalumab	
	ORR (95% CI), %	n/N patients	ORR (95% CI), %	n/N patients
GIS-positive	100.0 (69.2–100.0)	10/10	50.0 (18.7–81.3)	5/10
GIS-negative	75.0 (34.9–96.8)	6/8	16.7 (0.4–64.1)	1/6
GIS-unknown	84.6 (54.6–98.1)	11/13	31.3 (11.0–58.7)	5/16

Future Directions in the Front Line: What is Potentially Exciting?

Trial	Size	Anti-angiogenic	PARPi	ICI	Start	Estimated Primary Completion
FIRST[a] ENGOT OV-44	1405	± Bevacizumab	Niraparib	Dostarlimab	Oct 2018	Jan 2023
DUO-O[b] ENGOT OV-46	~1254	Bevacizumab	Olaparib	Durvalumab	Jan 2019	June 2023
ATHENA[c] GOG-3020 ENGOT OV-45	~1000	-	Rucaparib	Nivolumab	May 2018	Dec 2024
ENGOT OV-43[d] **KEYLYNK-001**	~1086	± Bevacizumab	Olaparib	Pembrolizumab	Dec 2018	Aug 2025

- a. ClinicalTrials.gov. NCT03602859; b. ClinicalTrials.gov. NCT03737643
- c. ClinicalTrials.gov. NCT03522246; d. Clinical Trials.gov NCT03740165.

Now that we may be using all our best agents “up front” what do we do here?….

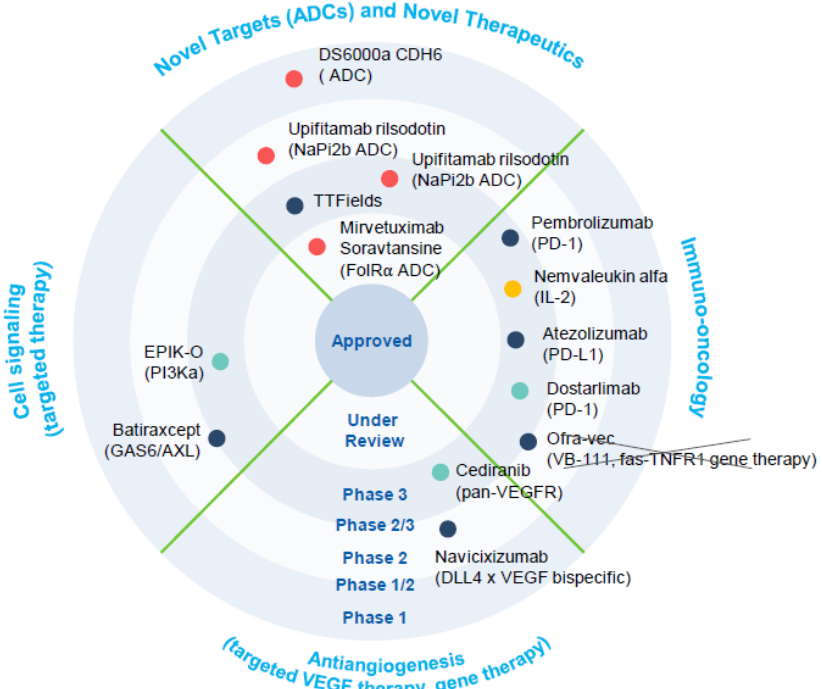


PARPi, PARP inhibitor; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; SOC, standard of care.

Ledermann JA et al. *Ann Oncol.* 2013;24(Suppl 6):vi24-vi32.

Bullseye Overview: Pivotal PROC Trials

Updated Jan 2023



Regimen
- Monotherapy
- Chemo combo
- IO combo
- PARP inhibitor combo

ADC, antibody-drug conjugate; DLL4, delta-ligand 4; TNFR1, tumor necrosis factor receptor 1; GAS6, growth arrest specific 6; IL, interleukin; IO, immuno-oncology; NCI, National Cancer Institute; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; PROC, platinum-resistant ovarian cancer; TTFields, tumor treating fields; VB-111, ofranergene obadenovec.

Emerging Ph3 Treatment Landscape: PROC

▲ Primary completion date (Based on CT.gov unless noted)

▲ Study completion date (Based on CT.gov unless noted)

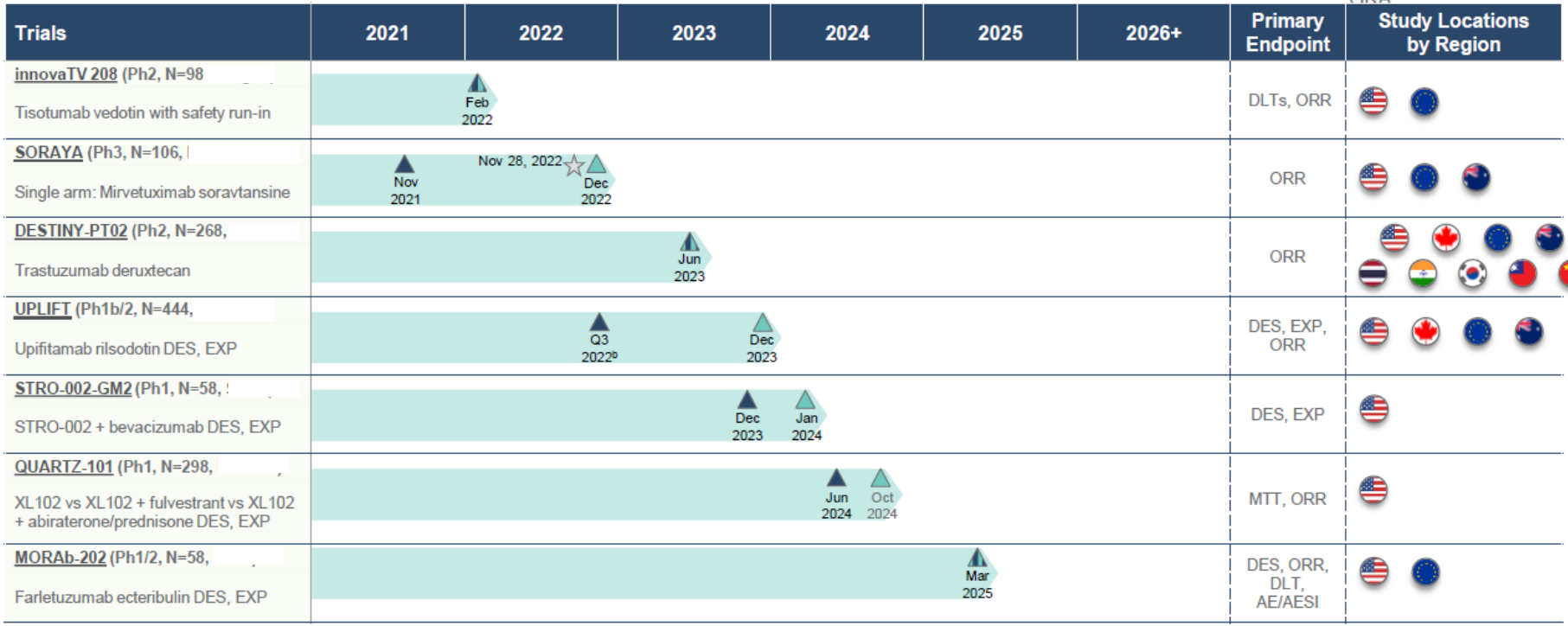
PD-1/PD-L1
IL-2 Cytokine
ADC
AXL decoy protein
TTFields
GRA

Trials	2021	2022	2023	2024	2025	2026+	Primary Endpoint	Study Locations by Region[a]
INNOVATE-3 (Ph3, N=540, NovoTTF-100L(O) + PAC vs. PAC			Sep 2023				OS	
MIRASOL (Ph3, N=430, Mirvetuximab soravtansine vs. IC chemo		Dec 2022		Apr 2024			PFS	
AXLerate-OC (Ph3, N=350 Batiraxcept + PAC vs. placebo + PAC			Jul 2023	Jul 2024			PFS	
AGO-OVAR 2.29 (Ph3, N=550, Bev + chemo + placebo vs. bev + chemo + atezo				Jan 2024	Dec 2024		OS, PFS	
ROSELLA (Ph3, N=360, RELA + nab-PAC vs. nab-PAC				Jun 2024	Jun 2025		PFS	
ARTISTRY-7 (Ph3, N=376, Nemvaleukin alfa + pembro vs. pembro mono vs. nemvaleukin alfa vs. IC chemo					Dec 2025	Dec 2026	PFS	
KEYNOTE B96 (Ph3, N=616, Pembro + PAC ± bev vs. placebo + PAC ± bev					Jun 2025	Aug 2027	PFS	

Emerging ADC Treatment Landscape in OVC

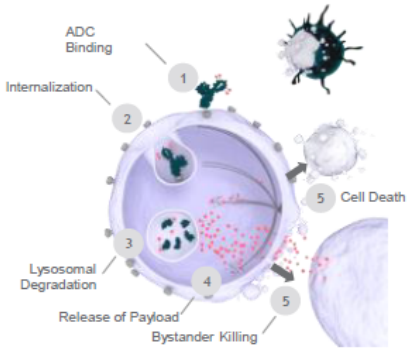
▲ Primary completion date (Based on CT.gov unless noted)
▲ Study completion date (Based on CT.gov unless noted)
☆ PDUFA date

PD-1/PD-L1
IL-2 Cytokine
ADC
AXL decoy protein
TTFields
GRA



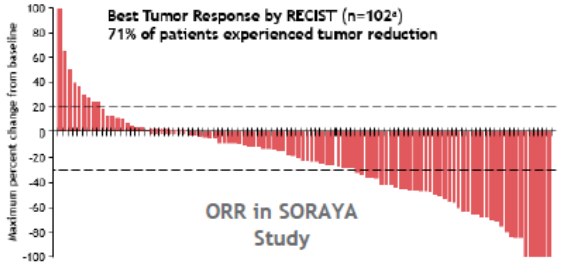
Antibody Drug Conjugates (ADCs) Are Emerging as Highly Active Therapeutics in Gynecologic Cancers

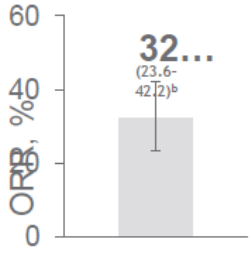
Mirvetuximab Soravtansine: MOA



ADC targeting folate receptor alpha conjugated to DM4 – a microtubule toxin

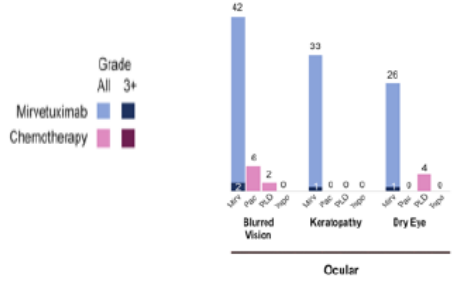
Efficacy





Matulonis et al. SGO Annual Meeting 2022.

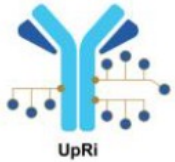
Key TRAEs



Adverse event	Integrated Safety Population (N=464)		SORAYA[a] (N=106)	
	All Grades, n (%)	Grade ≥3, n (%)	All Grades, n (%)	Grade ≥3, n (%)
Alopecia	3 (<1)	0	1 (<1)	0
Neuropathy peripheral	64 (14)	4 (<1)	14 (13)	0
Peripheral sensory neuropathy	36 (8)	4 (<1)	4 (4)	2 (2)
Peripheral motor neuropathy	4 (<1)	1 (<1)	2 (2)	1 (<1)
Paresthesia	21 (5)	0	5 (5)	0
Anemia	43 (9)	4 (<1)	8 (8)	1 (<1)
Thrombocytopenia	43 (9)	1 (<1)	10 (9)	2 (2)
Neutropenia	35 (8)	2 (<1)	14 (13)	2 (2)

Antibody Drug Conjugates (ADCs) Are Emerging as Highly Active Therapeutics in Gynecologic Cancers

Upifiamab Rilsdotin

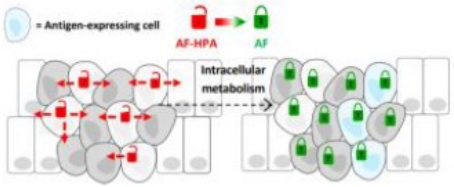


Antibody: Humanized monoclonal anti-NaPi2b[1]

Linker: Polymer scaffold; cleavable ester linker[2]

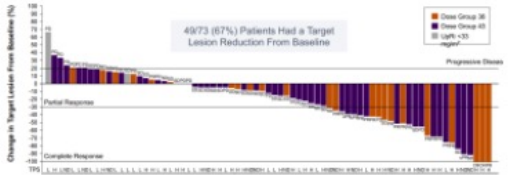
Payload: AF-HPA (DolaLock-controlled bystander effect)[1]

Drug-to-Antibody Ratio: ~10



ADC targeting the sodium gated phosphate channel conjugated with AF-HPA (Dola-Lock controlled bystander effect)

Efficacy

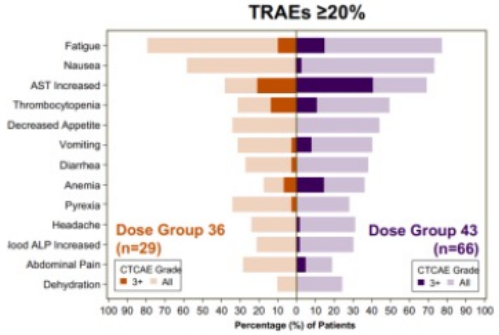


		All Dose Levels	Dose Group 36	Dose Group 43
NaPi2b-High (TPS ≥75)	N	38	16	22
	ORR, n (%)	**13 (34)**	**7 (44)**	**6 (27)**
	CR, n (%)	2 (5)	2 (13)	0
	PR, n (%)	11 (29)	5 (31)	6 (27)
	DCR, n (%)	33 (87)	12 (75)	21 (95)
All NaPi2b Levels	N	75	25	48
	ORR, n (%)	**17 (23)**	**9 (36)**	**8 (17)**
	CR, n (%)	2 (3)	2 (8)	0
	PR, n (%)	15 (20)	7 (28)	8 (17)
	DCR, n (%)	54 (72)	18 (72)	35 (73)

- **Median DoR in patients (all dose levels) with NaPi2b-high ovarian cancer (n=13): 5 months**

Richardson et al. SGO 2022

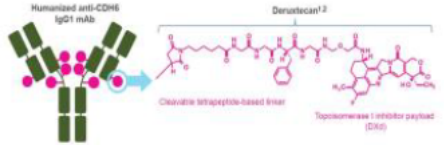
Key TRAEs



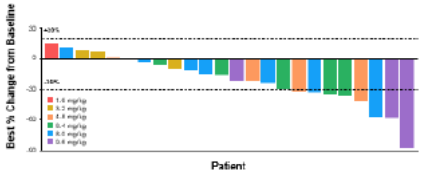
Pneumonitis:
43mg/m²: G1-2 (5); G3+ (4)
36mg/m²: G1-2 (2); G3+ (0)

Antibody Drug Conjugates (ADCs) Are Emerging as Highly Active Therapeutics in Gynecologic Cancers

DS-6000



- A humanized anti-CDH6 IgG1 monoclonal antibody covalently linked to
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker



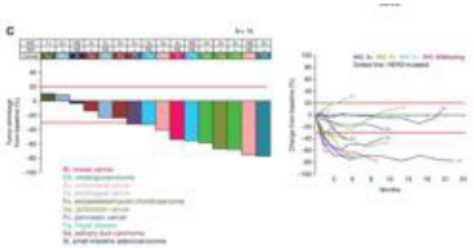
TRAEs:
G3 neutrophils
G2 pneumonits (both appear dose related)

Hamilton et al. ASCO 2022

Trastuzumab deruxtecan

Trastuzumab deruxtecan (T-DXd)[1]

ADC targeting ERBB2 (HER2) conjugated to a topoisomerase inhibitor. DAR =8



Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

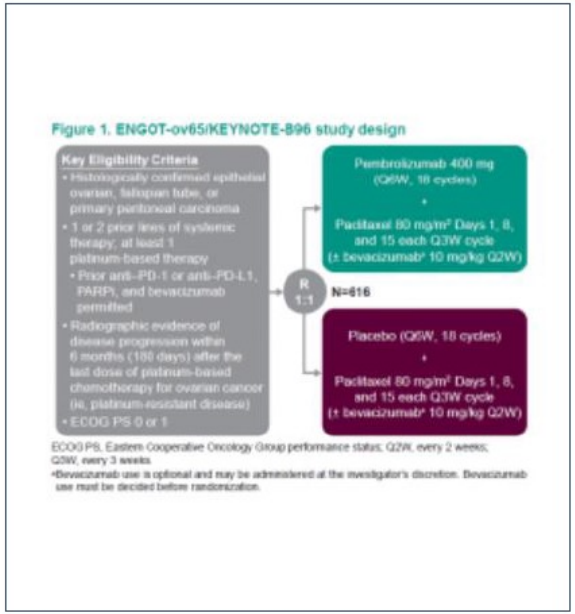
LVEF decrease, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

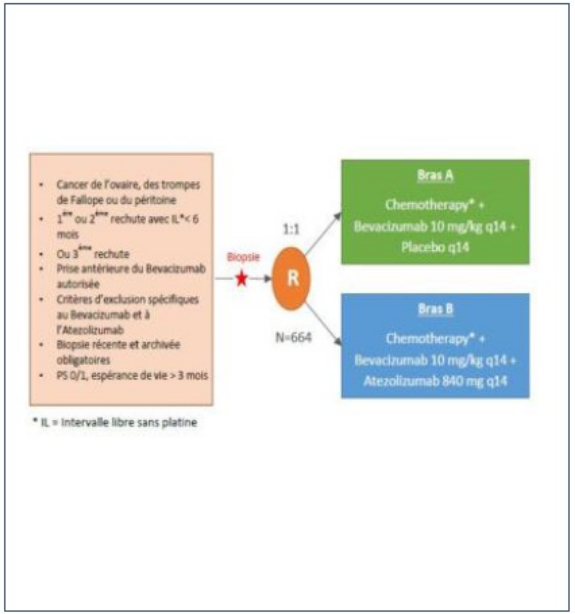
79% nausea
29% diarrhea
All grades

Does Immunotherapy Have a Role in Ovarian Cancer? So Far - No

Keynote B96
NCT05116189



AGO OVAR 2.29



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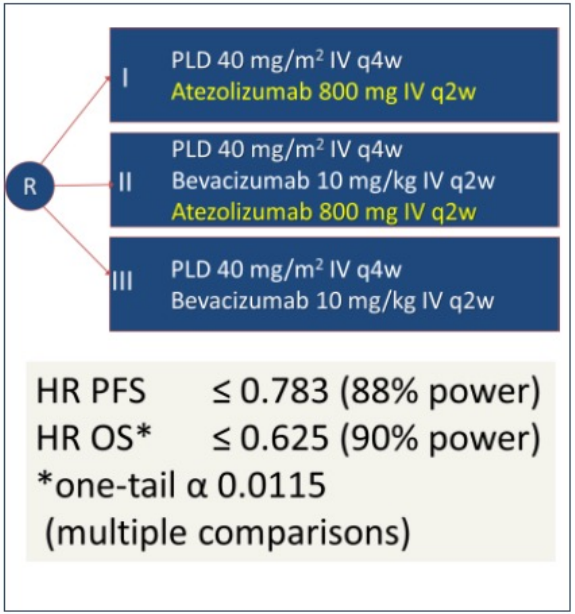
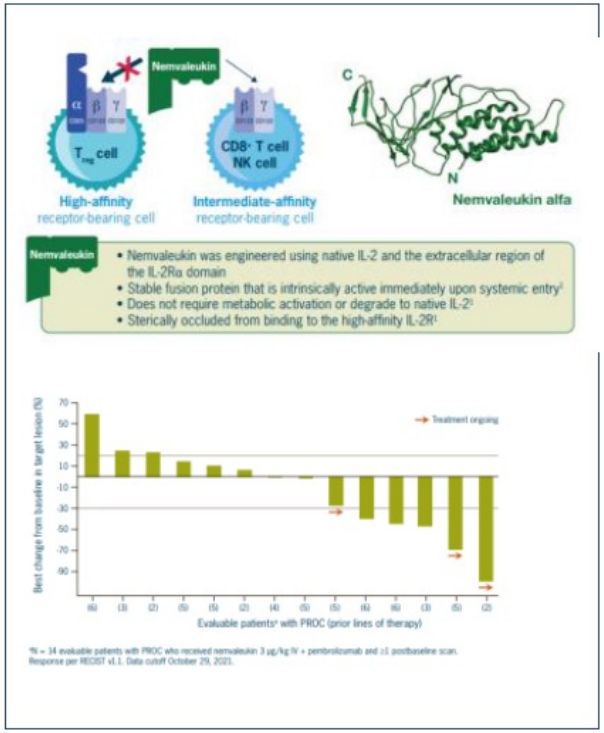
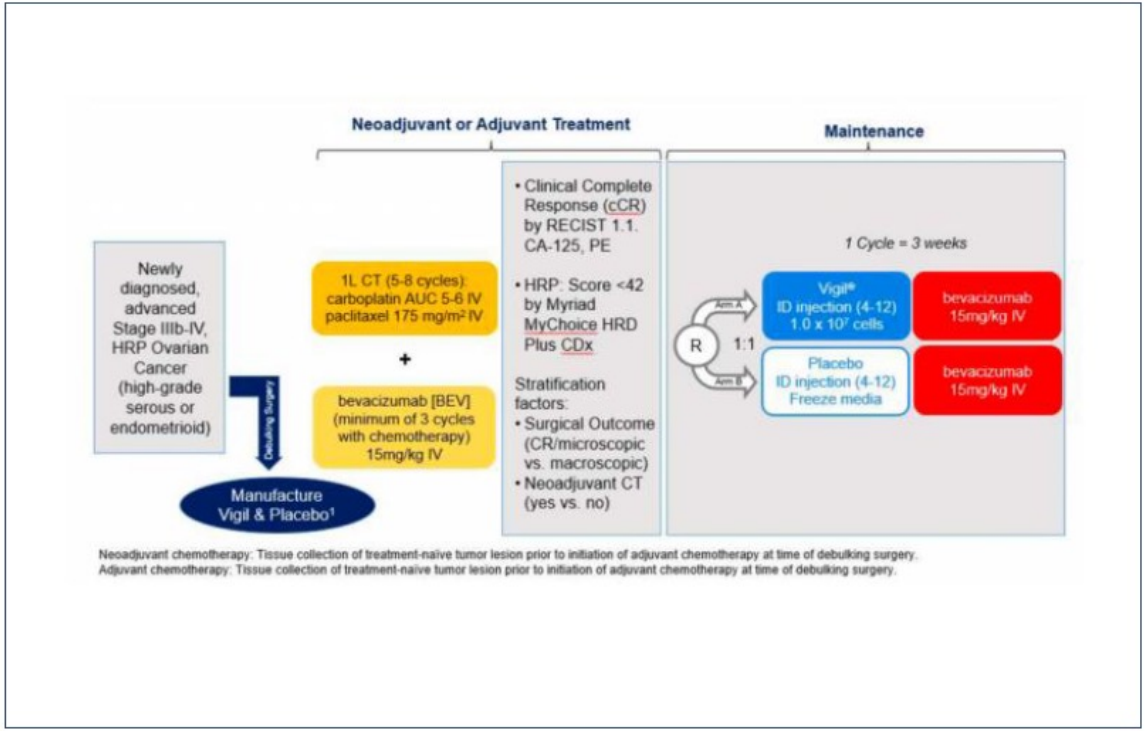


Novel Immunotherapy Approaches in Ovarian Cancer

Alkemeres/ARTISTRY 7



Gemogenovatucel-T (GEM): VIGIL Study



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NCI – designated

Until every cancer is cured

THANK YOU