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Radiation Oncology: Bridging the Care Gap

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The cervix and endometrial cancer journey: what have we not to forget?

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Declaration of Interests

Financial Interests

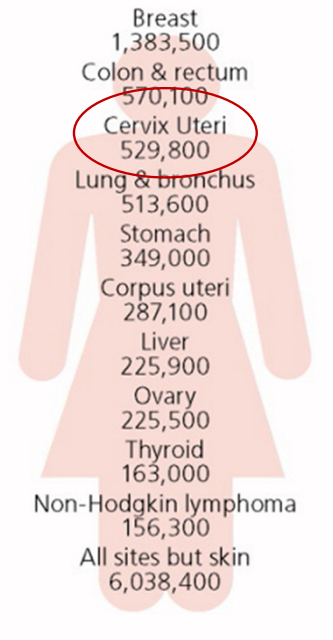
- Consultancy Role: AstraZeneca, Clovis Oncology, GSK, PharmaMar, MSD, AstraZeneca, Novartis, Merck Serono,
- Institutional Financial Support for Research: PharmaMar, GSK, MSD, Clovis Oncology, Roche, Immunogen, Genmab, AstraZeneca, Incyte

Non-Financial Interest

- GCIG, Board of Director
- GCA (Engot), Chair
- ESGO, Board of Director

The global burden of cancer on women worldwide

Estimated New Cases

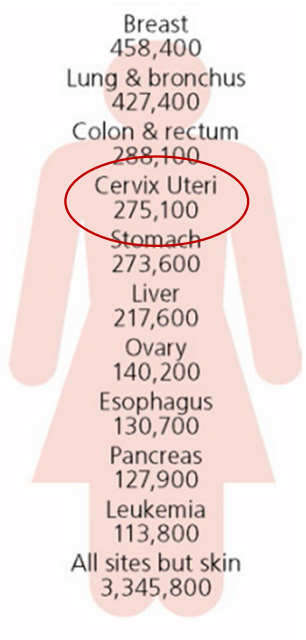


9% of all new cancer cases
>58,000 new cases every year

8% of total cancer deaths
>24,000 deaths every year

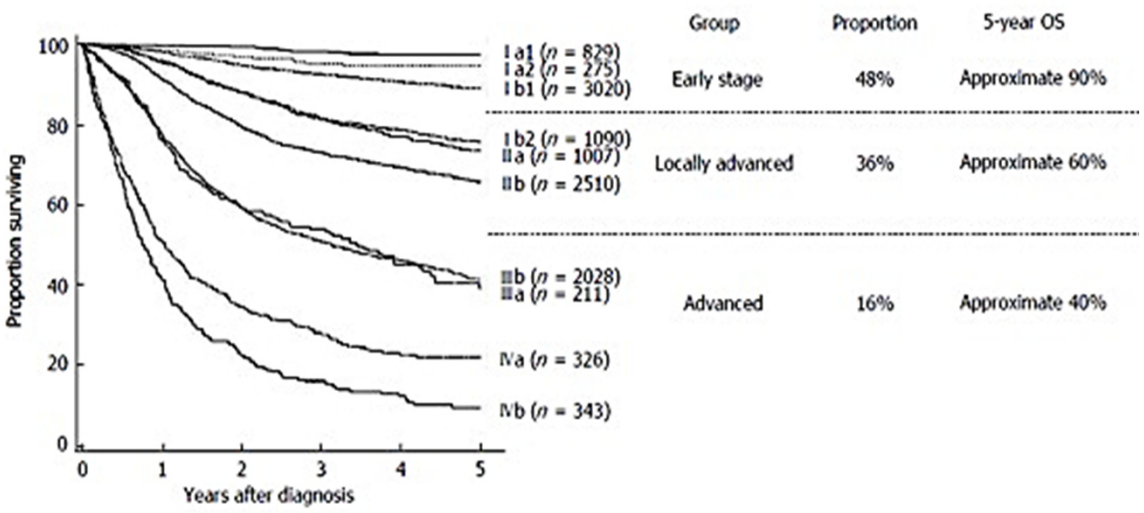
85% of new cases
87% of deaths occur
in developing countries

Estimated Deaths



Jemal A et al. *CA Cancer J Clin* 2011;61:69–90.

Cervical cancer: 5-year survival according to stage



- Early-stage CC may be cured by radical surgery with tailored adjuvant therapy
- Patients diagnosed with locally advanced disease (FIGO IB2-IVA) despite radical chemoradiation experience 5-year DFS and OS of 47–80%
- The management of women with advanced (FIGO stage IVB) and recurrent disease has represented an unmet clinical need for decades.

OS, overall survival; PFS, progression-free survival.

Cancer Stat Facts: Cervical Cancer. https://seer.cancer.gov/statfacts/html/cervix.html. Accessed 21 March 2022.

What is the Rationale to Pursue ICI in Cervical Cancer?

1. Cervical Cancer is a Virally Driven Cancer:

- Almost all cases are driven by **HPV infection.** The virus has evolved many ways of evading the immune system

2. Immune-Privilege State: PD-L1 expression and Tumour Infiltrating Lymphocytes(TILs)

- **PD-L1 i**s not expressed in normal cervical tissue, but is **overexpressed in SCC(19% to 88%) and Adenocarcinoma(14%)**
- The tumour microenvironment(the composition of) has an impact on survival rates:
  - Patients w negative LN have higher numbers of intraepithelial CD8+ cells than positive LN patients

3. Cervical Cancers Have an Increased Tumor Mutational Burden(TMB) Rate

- The rate of **TMB in cervical cancers is about 5-6 mutations per megabase** (behind melanoma, lung, bladder, oesophageal and colorectal cancers)
- Increased TMB lead to the presence of more neoantigens that then stimulate the immune system

Smola, S, et al. *Ther Adv Vaccines.* 2017;5(3):69-82.Dyer et al JNCCN; Volume 17 Number 1 January 2019
S.J. Otter et al. / Clinical Oncology 31 (2019) 834e843; J. Otter et al. / Clinical Oncology 31 (2019) 834e843; Piersma SJ et al; Cancer Res 2007; 67: (1). January 1, 2007Alexandrov LB et al Nature 2013;500:415e421; S.J. Otter et al. Clinical Oncology 31 (2019) 834e843

CALLA Study Design

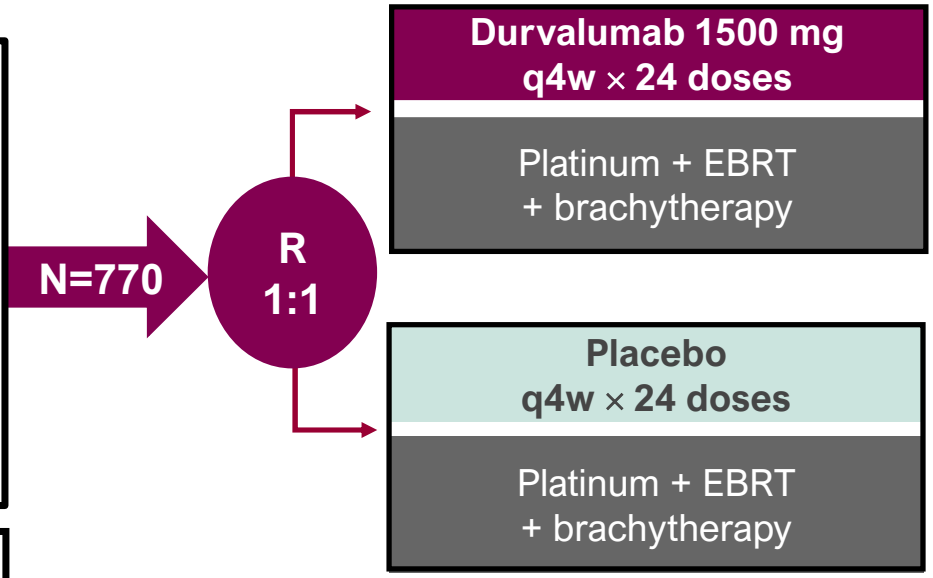
15 countries, **120** sites

Eligible population

- Women aged ≥18 years
- Histologically confirmed cervical adenocarcinoma, squamous carcinoma, or adenosquamous carcinoma
- High-risk LACC (FIGO 2009)
  - Stages IB2 to IIB, node positive (N≥1)
  - Stages IIIA to IVA with any node (N≥0)
- WHO ECOG performance status of 0 or 1

Stratification factors

- Disease stage
  - FIGO Stage IB2–IIB and LN+
  - FIGO Stage ≥III and LN−
  - FIGO Stage ≥III and LN+
- Region of world



Primary Endpoint:

Progression-Free Survival[a] (Investigator-assessed)

Key Secondary Endpoints:

- Overall survival
- Objective response rate
- Duration of response
- Incidence of local or distant progression / 2° malignancy
- Safety and tolerability

Chemoradiotherapy Regimen

Platinum agent	Cisplatin 40 mg/m^2 or carboplatin AUC2 q1w × 5 weeks
EBRT	45 Gy in 25 fractions at 1.8 Gy/fraction, 5 fractions per week
Brachytherapy	High-dose rate: 27.5–30 Gy; Low/pulsed-dose rate: 35–40 Gy

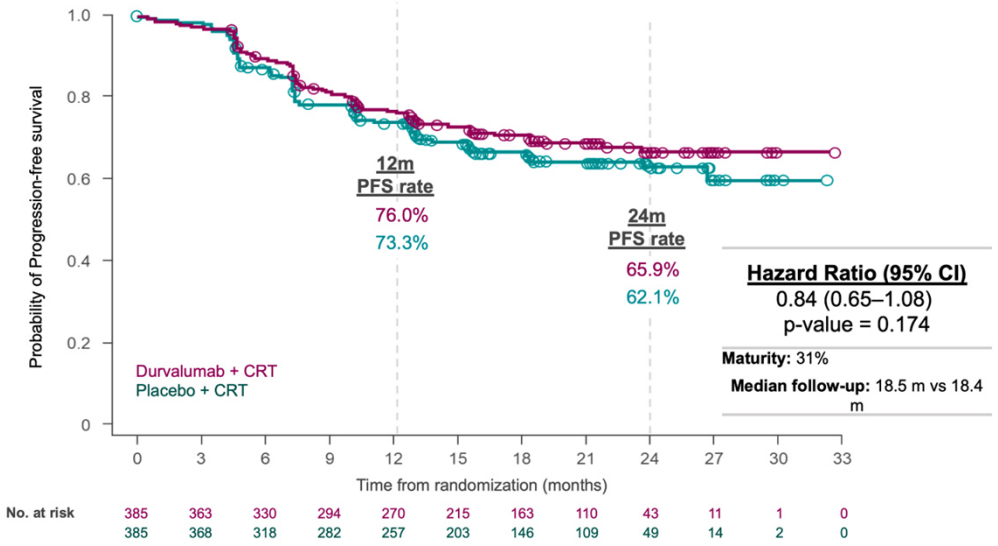
Key Milestones

First patient in	February 2019
Last patient in	December 2020
Data cut off	January 20, 2022

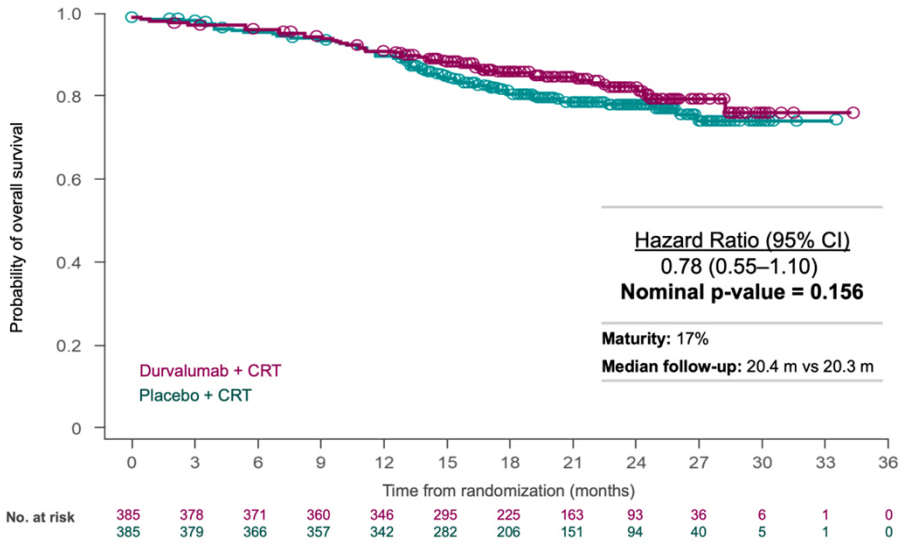
[a]According to RECIST 1.1 or histopathologic confirmation of local tumor progression using CT or MRI scans.

Progression-Free and Overall Survival

PFS



OS



Secondary Efficacy Endpoints

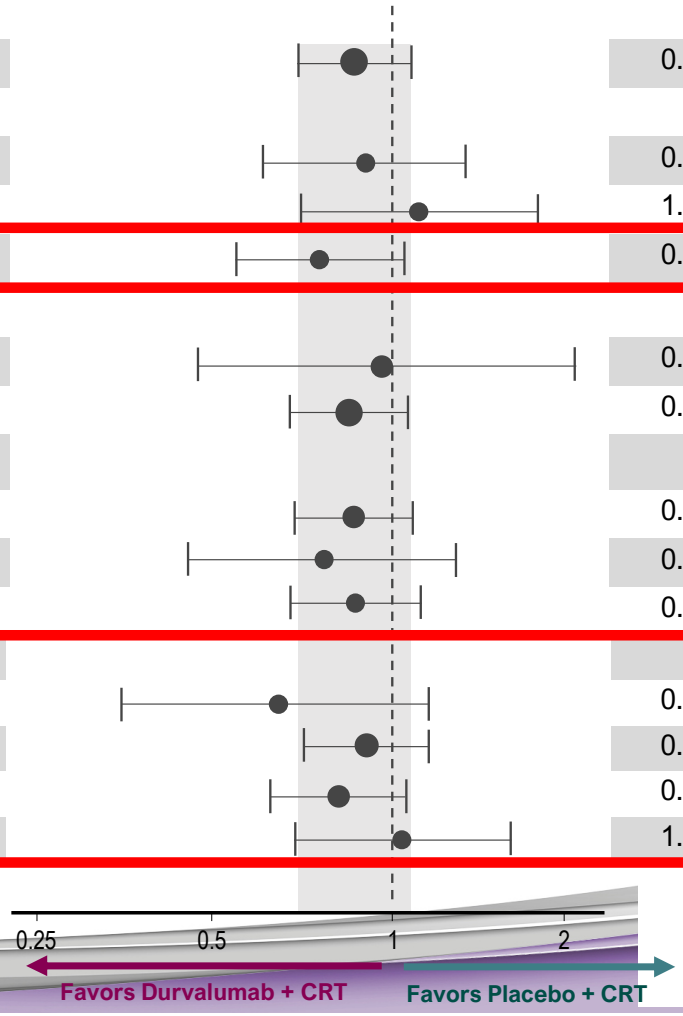
	Durvalumab + CRT (n = 385)	Placebo + CRT (n = 385)
Objective Response Rate[a] , n (%)	318 (82.6)	310 (80.5)
CR, n (%)	165 (42.9)	155 (40.3)
PR, n (%)	153 (39.7)	155 (40.3)
Local Disease Progression Events, n (%)	42 (10.9)	40 (10.4)
Hazard Ratio (95% CI), 2-sided p-value	**1.06 (0.69–1.63), *P*=0.795**	
Local Disease Progression, % (95% CI)		
12 months	8.2 (5.7–11.3)	8.2 (5.7–11.3)
24 months	13.1 (9.3–17.6)	12.7 (9.0–17.1)
Distant Disease Progression Events, n (%)	52 (13.5)	69 (17.9)
Hazard Ratio (95% CI), 2-sided p-value	**0.75 (0.53–1.06), *P*=0.103**	
Distant Disease Progression, % (95% CI)		
12 months	12.3 (9.1–15.8)	15.7 (12.2–19.6)
24 months	16.1 (12.4–20.2)	21.0 (16.8–25.5)

[a]By blinded independent central review using RECIST v1.1; includes unconfirmed complete or partial response.

PFS Subgroup Analysis

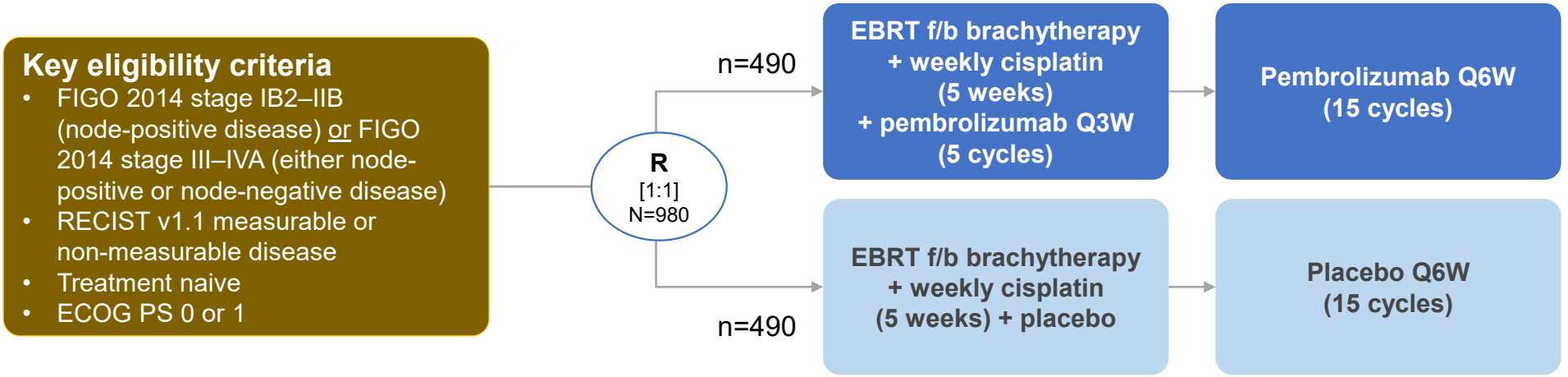
Are there some patients that seem to benefit more? Hypothesis generating

	Durvalumab + CRT (Events/Total)	Placebo + CRT (Events/Total)	Hazard Ratio (95% CI)
All patients	112/385	128/385	0.84 (0.65–1.08)
Disease stage (FIGO 2009)			
Stage IB2-IIB, node positive	35/134	39/133	0.87 (0.55–1.38)
Stage ≥III, LN-	28/108	26/107	1.11 (0.65–1.91)
Stage ≥III, LN+	49/143	63/145	0.71 (0.49–1.03)
Chemotherapy received			
Carboplatin	14/26	9/20	0.94 (0.41–2.27)
Cisplatin	98/359	118/363	0.82 (0.62–1.07)
PD-L1 expression status			
≥1%	102/356	117/352	0.83 (0.64–1.09)
<5%	19/60	25/64	0.73 (0.40–1.32)
≥5%	85/311	95/300	0.84 (0.63–1.13)
Lymph nodes			
Para-aortic lymph node	15/47	20/38	0.60 (0.30–1.17)
No para-aortic lymph node	97/338	108/347	0.89 (0.68–1.17)
Pelvic lymph node	75/246	97/268	0.79 (0.58–1.06)
No pelvic lymph node	37/139	31/117	1.04 (0.64–1.68)



ENGOT-CX11/GOG 3047/KEYNOTE-A18: Study Design

A randomized, Phase 3, double-blind study of chemoradiotherapy with or without pembrolizumab for the treatment of high-risk, LACC



Stratification factors

- IMRT or VMAT versus non-IMRT and non-VMAT
- Stage at initial diagnosis of cervical cancer (FIGO 2014 Stage IB2–IIB [node-positive disease] vs FIGO 2014 Stage III–IVA [either node-positive or node-negative disease])
- Planned total radiotherapy dose (EBRT + brachytherapy dose) of <70 Gy vs ≥70 Gy

Endpoints

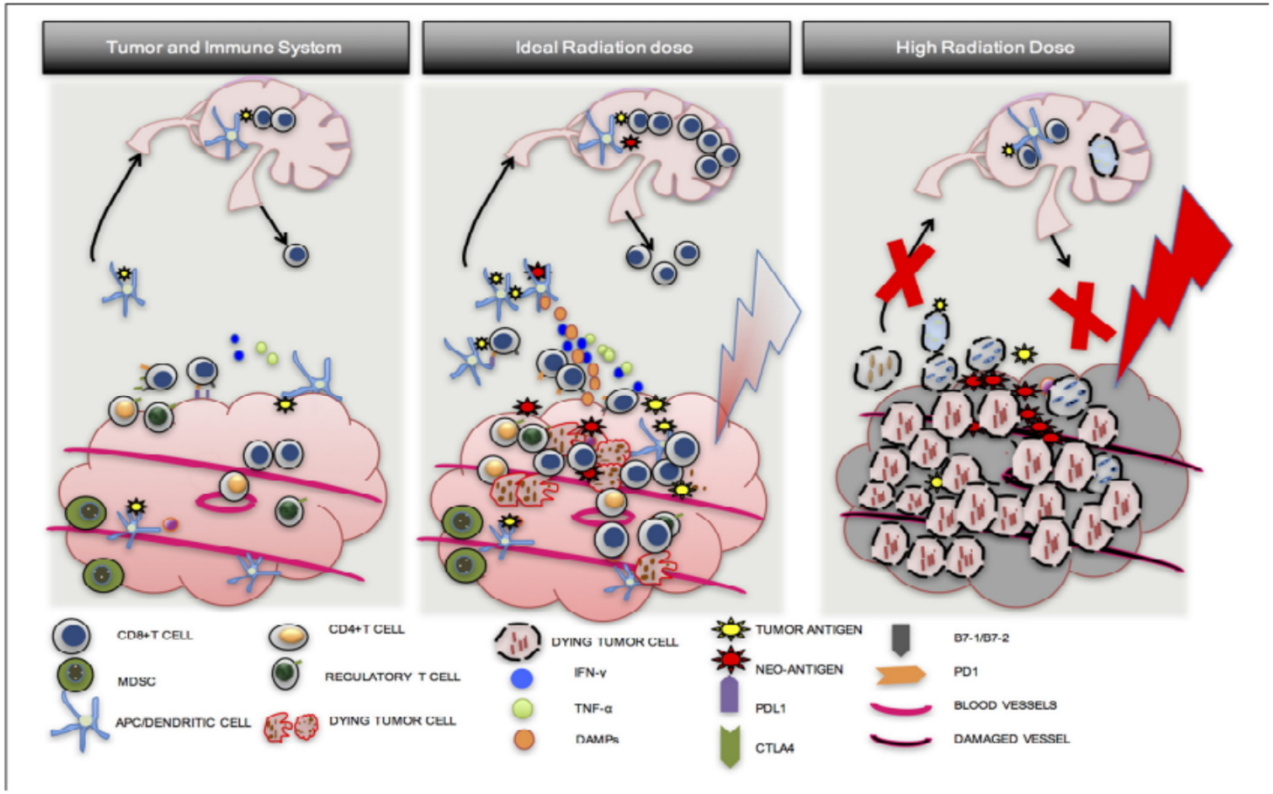
- **Dual primary:** PFS, OS

EBRT, external beam radiation therapy; ECOG PS, European Cooperative Oncology Group performance status; f/b, followed by; FIGO, International Federation of Gynecology and Obstetrics; IMRT, intensity-modulated radiation therapy; LACC, locally advanced cervical cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; VMAT, volumetric modulated arc therapy.

NCT04221945. https://clinicaltrials.gov/ct2/show/NCT04221945. Accessed 7 March 2022; 2. Lorusso D et al. Presented at the European Society for Medical Oncology (ESMO) 2020, 19–21 September. Abstract 254TiP.

Biological hypothesis

- RT is a double-edged sword regarding immune effects: it has both an immunostimulatory effect but also an immunosuppressive effect and a relationship between RT dose and fractioning and immune system exists

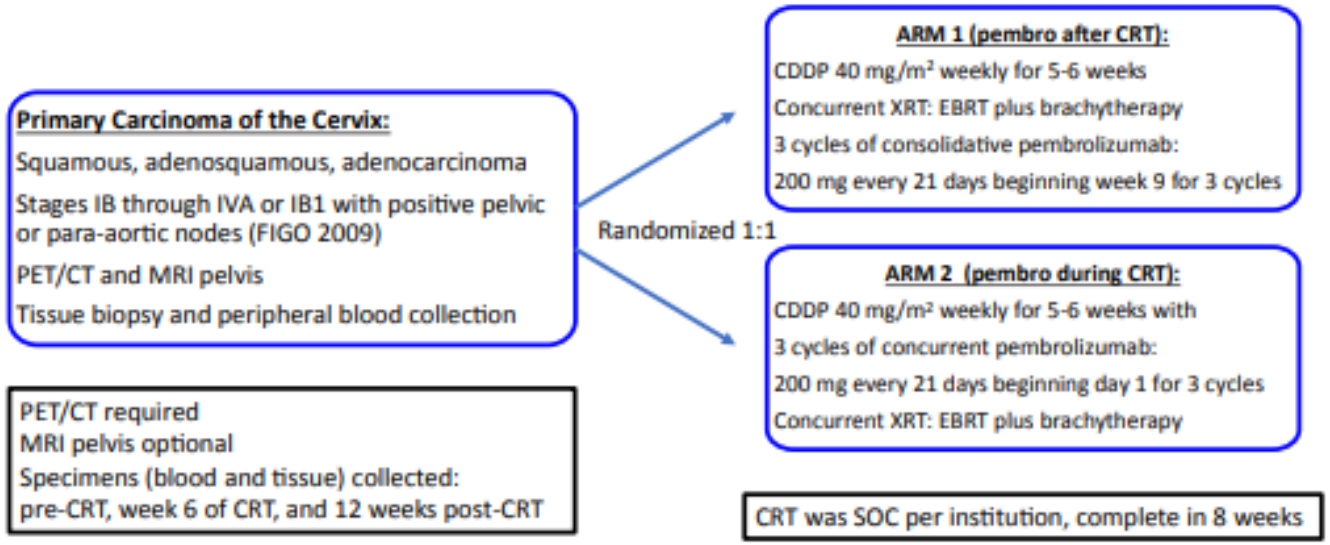


An ideal dose of radiation will induce inflammatory tumor cell death and activate an anti-tumor T-cell response via APC maturation

A high dose of radiation may induce tumor cell death but may also damage blood vessels and induce more CD8 T cell apoptosis. Local control from the direct effects of RT may be good, but effective immune priming and distant control may be compromised

Buchwald et al. Fontiers in Oncology 2018

Results of an Early Safety Analysis of a Study of the Combination of Pembrolizumab and Pelvic Chemoradiation in Locally Advanced Cervical Cancer



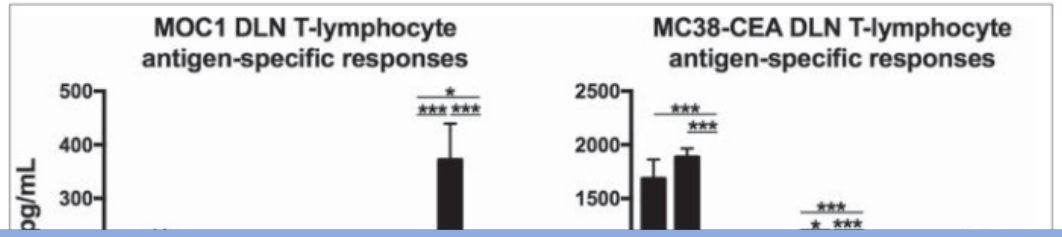
96 patients

No safety nor efficacy issue anticipated

Translational research designed to estimate immunologic effects on tissue and blood ongoing

Biological hypothesis

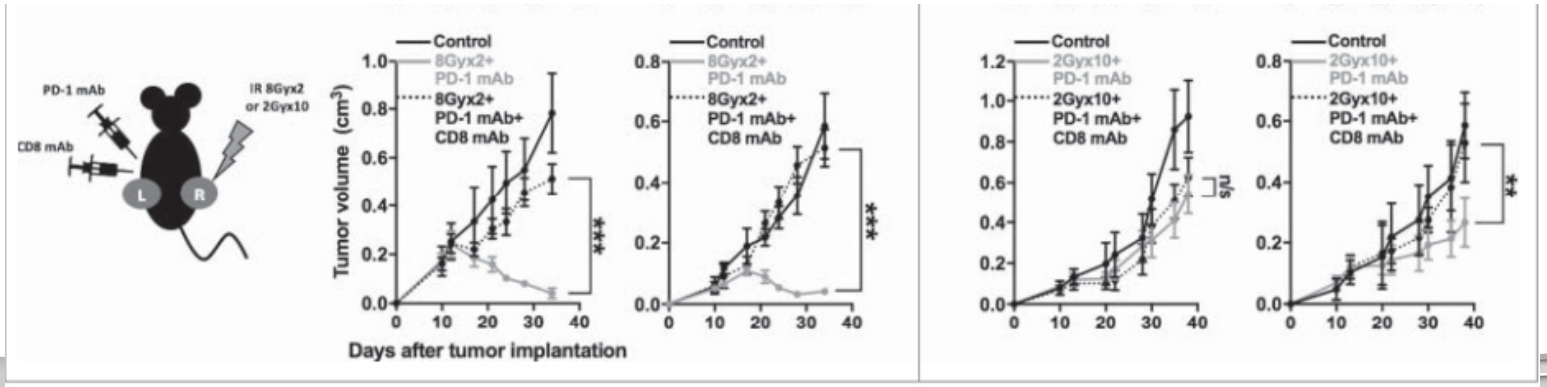
- Elective irradiation of draining lynphnodes (where antigen presenting cells (APC) migrate for T-cell priming) may hinder T-Cell priming



In draining lymph node tumor-specific T-lymphocyte responses is suppresed by longer, conventionally

Adaptation of RT treatment plan and schedule in terms of timing, fields, dose and fractioning may provide different results

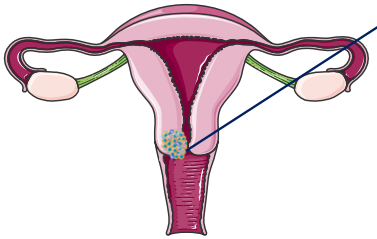
Caution!!! RT is a crucial component of the treatment in this setting providing up to 75% cure rate



2Gyx10 significantly enhances primary tumor control and survival

Morisada M, Oncoimmunology 2017

COLIBRI inclusion criteria & Study design



Cervical cancer
- Women aged ≥18 years
- Histologically confirmed cervical (adeno)squamous carcinoma
- LACC (FIGO 2018) stage IB3-IVA
- ECOG performance status of 0 or 1
- Multicentric single arm pilot study

MRI/PET — MRI/PET — MRI/PET — Surgery of residual disease (optional) — MRI/PET

Screening <28d	Neo-adjuvant phase	RTCT* 5-8 weeks	Delay of 4-6 weeks	Maintenance with nivolumab (6 months)	EOT	Follow-up

*1 *2

D1C1 — D15C1 — D-1 of RTCT — 4 weeks post RTCT — D1C4

Nivolumab 3mg/kg
Ipilimumab 1mg/kg

Nivolumab 480mg, q4w

***1** optional *cervical tumor sample during the surgery*
***2** *mandatory blood sample and optional biopsy at progression*

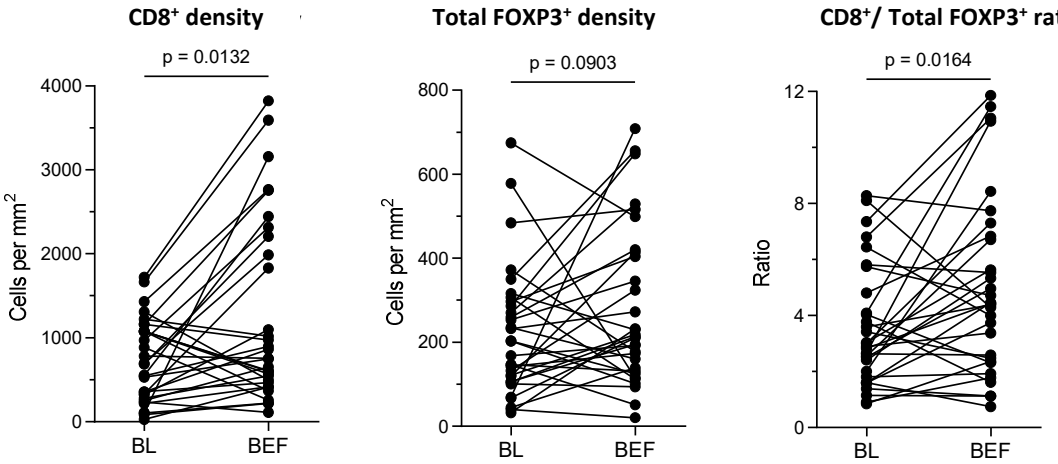
Tumor biopsy
Blood sample

*Chemoradiotherapy Regimen

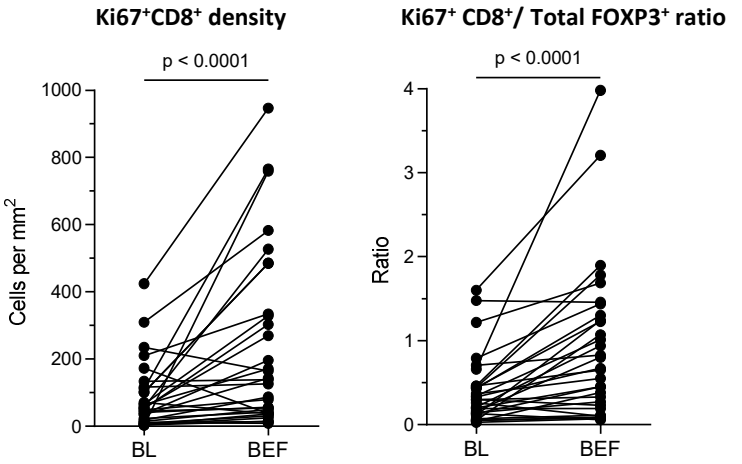
Platinum agent	Cisplatin 40 mg/m² or carboplatin AUC2 q1w × 5 weeks
EBRT	45 Gy in 25 fractions at 1.8 Gy/fraction, 5 fractions per week
Brachytherapy	High-dose rate: 27.5–30 Gy; Low/pulsed-dose rate: 35–40 Gy

Relative changes before/after ICB by multi-IF

Neo-adjuvant dual ICB significantly increases tumor-associated CD8⁺T cells and CD8⁺/FOXP3⁺ ratio

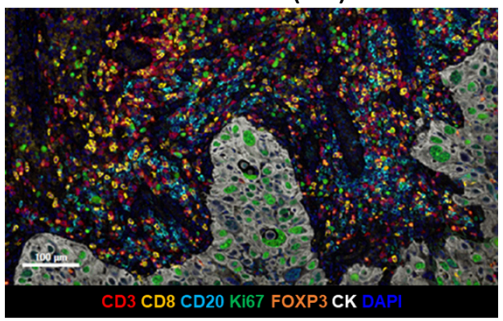


Similar results with **proliferative** CD8⁺ T cells & CD8⁺/FOXP3⁺ ratio



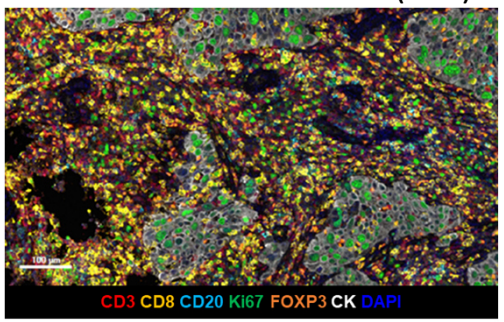
009-04

Baseline (BL)



Ipi + Nivo

After ICB = Before RTCT (BEF)



Efficacy by response rate
After neo-adjuvant ICB, post RTCT and end of maintenance

RESPONSE	RR	Before RTCT N (%)		Post RTCT N(%)		End of maintenance	
Local control	CR	-		27	(68)	34	(85)
	PR	**6**	**(15)**	12	(30)	3	(8)
	SD	32	(80)	1	(2)	1	(2)
	PD	**2**	**(5)**	-		2	(5)
Global response	CR	-		26	(65)	31	(78)
	PR	5	(13)	13	(33)	5	(12)
	SD	33	(82)	1	(2)	-	
	PD	2	(5)	-		**4**	**(10)**

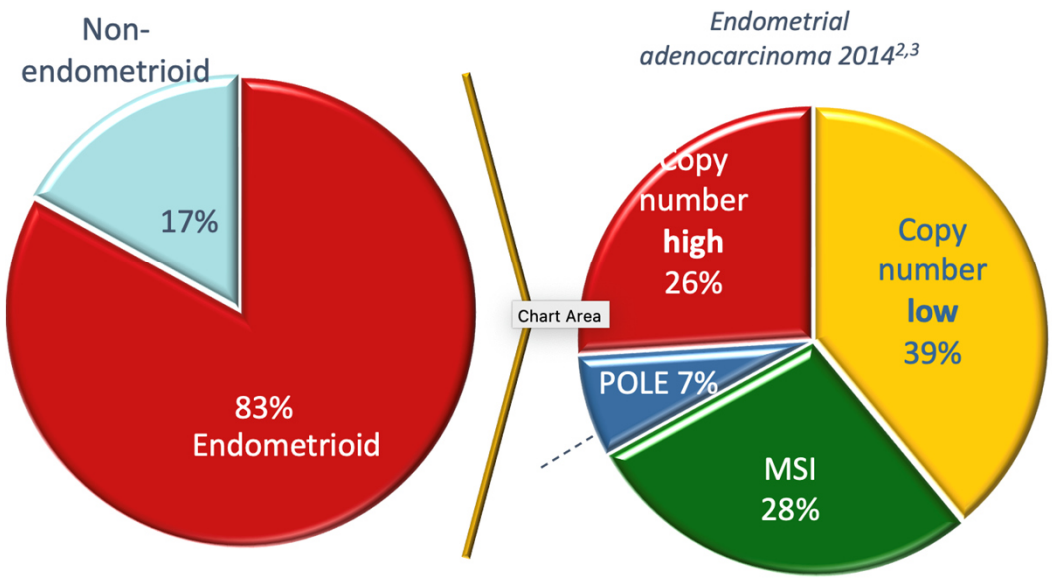
3 pts with initial FIGO IIIC
4 pts have no change before/after ICB for:
- CD8+ infiltrate
- CD8+/Foxp3 ratio
- Cold 'HOT' score

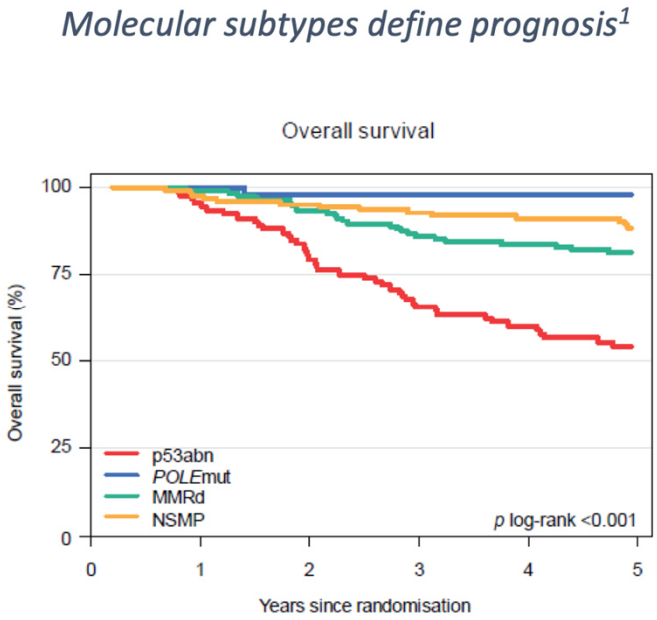
RESPONSE	FIGO STAGE	COMPLETE RESPONSE RATE
Global response	FIGO I/II	81%
	FIGO III/IV	74%

CR complete response, PR partial response, SD stable disease, PD progressive disease

TGCA project: New opportunities in EC

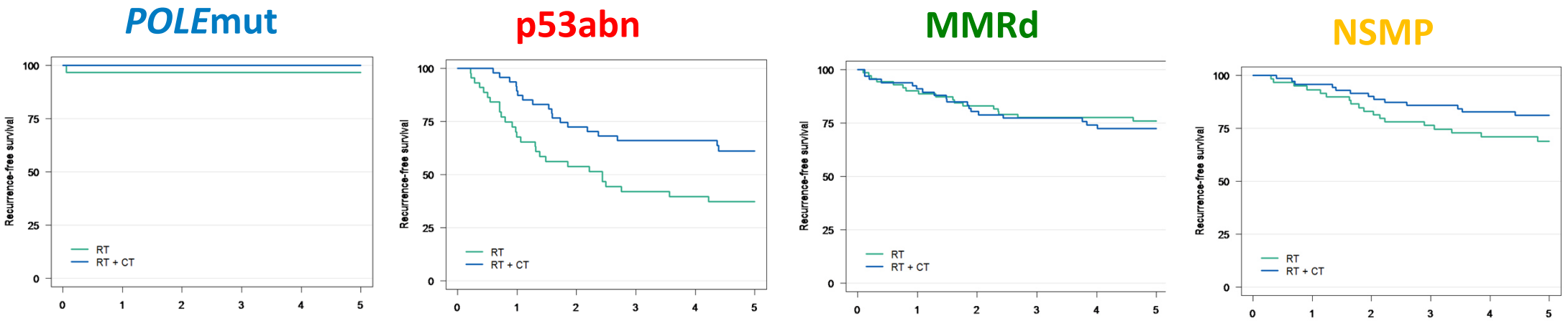
Molecular subtyping: prognostic and predictive value





MacKay. Oncotarget. 2017;8:84579. León-Castillo. JCO. 2020;38:3388.

Differential response to adj. chemotherapy in PORTEC-3



p=0.015, HR 0.50 (95%CI 0,28-0,88)

- *POLE*mut: Excellent prognosis, regardless of adj. treatment
- p53abn: Worst prognosis; greatest benefit from adj chemotherapy
- MMRd: Intermediate prognosis, no benefit from Adj chemotherapy;
- NSMP: Intermediate prognosis, maybe some benefit (ns)

Leon-Castillo et al, Journal of Clinical Oncology 2020

Clinical management guidelines

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Nicole Concin [1,2] Xavier Matias-Guiu,[3,4] Ignace Vergote,[5] David Cibula,[6] Mansoor Raza Mirza,[7] Simone Marnitz,[8] Jonathan Ledermann [9] Tjalling Bosse,[10] Cyrus Chargari,[11] Anna Fagotti,[12] Christina Fotopoulou [13] Antonio Gonzalez Martin,[14] Sigurd Lax,[15,16] Domenica Lorusso,[12] Christian Marth,[17] Philippe Morice,[18] Remi A Nout,[19] Dearbhaile O'Donnell,[20] Denis Querleu [12,21] Maria Rosaria Raspollini,[22] Jalid Sehouli,[23] Alina Sturdza,[24] Alexandra Taylor,[25] Anneke Westermann,[26] Pauline Wimberger,[27] Nicoletta Colombo,[28] François Planchamp,[29] Carien L Creutzberg[30]

Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ],*
Low	• Stage IA endometrioid + low-grade** + LVSI negative or focal	• Stage I-II ***POLE*mut** endometrial carcinoma, no residual disease • Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal
	• Stage IB endometrioid + low-grade** + LVSI negative or focal • Stage IA endometrioid + high-grade** + LVSI negative or focal • Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	• Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal • Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade** + LVSI negative or focal • Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High-intermediate	• Stage I endometrioid + substantial LVSI, regardless of grade and depth of invasion • Stage IB endometrioid high-grade**, regardless of LVSI status • Stage II	• Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI, regardless of grade and depth of invasion • Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade**, regardless of LVSI status • Stage II **MMRd/NSMP** endometrioid carcinoma
High	• Stage III-IVA with no residual disease • Stage I-IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and no residual disease	• Stage III-IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease • Stage I-IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease • Stage I-IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Metastatic	• Stage III-IVA with residual disease • Stage IVB	• Stage III-IVA with residual disease of any molecular type • Stage IVB of any molecular type

[Δ]For stage III-IVA ***POLE*mut** endometrial carcinoma, and stage I-IVA MMRd or NSMP clear cell carcinoma with myometrial invasion, insufficient data are available to allocate these patients to a prognostic risk-group in the molecular classification. Prospective registries are recommended

* see text on how to assign double classifiers (e.g. patients with both *POLE*mut and p53abn should be managed as *POLE*mut)

** according to the binary FIGO grading, grade 1 and grade 2 carcinomas are considered as low-grade, and grade 3 carcinomas are considered as high-grade.

p53abn: p53 abnormal, MMRd: Mismatch Repair Deficient, NSMP: nonspecific molecular profile, *POLE*mut: polymerase Ɛ mutated

TGCA Classification

Potential Therapeutic Impact on Endomentrial Cancer

	POLE	MSI	Copy Number Low	Copy Number High
MSI/MLH methylation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
Molecular profile	*POLE* (100%) *PTEN* (94%) *PIK3CA* (71%) *FBXW7* (82%) *ARID1A* (76%) *KRAS* (53%) PD1/PD-L1 overexpression	*PTEN* (88%) *RPL22* (37%) *KRAS* (35%) *PIK3CA* (54%) *ARID1A* (37%) PD-1/PD-L1 overexpression	*PTEN* (77%) *CTNNB1* (52%) *PIK3CA* (53%) *ARID1A* (42%) *FGFR2* (10.9%)	*TP53* (92%) *PPP2R1A* (22%) *FBXW7* (22%) *PIK3CA* (47%) *PTEN* (11%) *FGFR* (7%) *HER2* (25%)
Potential drugs	• PI3K/PTEN/AKT/ mTOR pathway • Anti-PD-1/PD-L1 • Hormones	• PI3K/PTEN/AKT/mTOR pathway • Anti-PD-1/PD-L1 • Hormones	• PI3K/PTEN/AKT/mTOR pathway • Hormones • FGFR-I	• **HER2- I** • PI3K- I • PARP-I • Wee-1 I • FGFR-I

Stelloo E, et al. *Clin Cancer Res.* 2016;22;4215-4224.

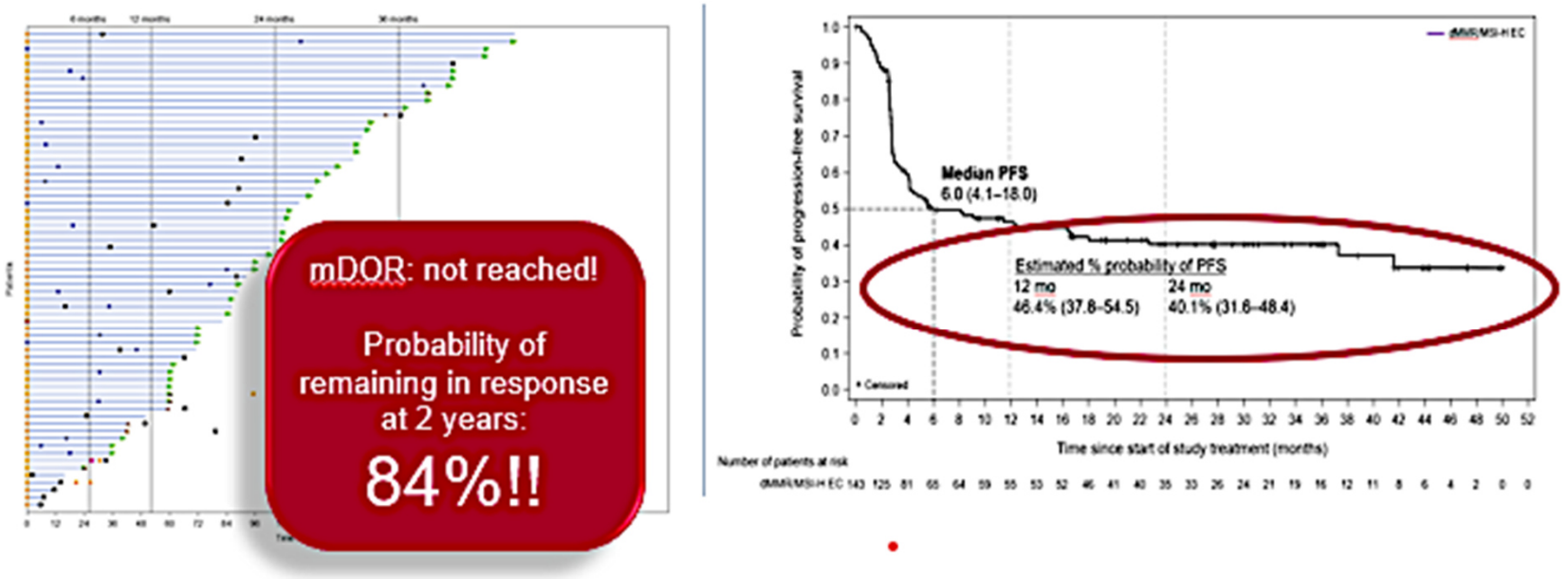
Single agent IO efficacy in biomarker selected Endometrial Cancer

Study	Drug	N	Patient Selection	ORR(%)
Keynote 158:	Pembrolizumab	49	Advanced/metastatic dMMR	57%
Garnet :Oaknin (2020)	Dostarlimab	71	Previously treated Recurrent/advanced d-MMR	45%
PHAEDRA: Antill (2019)	Durvalumab	35	Advanced /metastatic p-MMR	43%
Konstantinopoulos (2019)	Avelumab	15	Advanced /metastatic d-MMR	27%

Marabelle et al. JCO2019; Oaknin, SGO 2020; Antill ASCO 2019 ; Konstantinopoulos ASCO 2019

GARNET study: Dostarlimab in dMMR/MSI-H EC Cohort

Updated Analyses & Long-Term Follow-up



Oaknin et al., ASCO 2022; Courtesy Stephanie Gaillard

pMMR/MSS disease

Response to anti-PD-1 therapy

	KEYNOTE-028[1]	NCT01375842[2]	GARNET[3]	NCT02912572[4]	PHAEDRA[5]
Treatment	Pembrolizumab	Atezolizumab	Dostarlimab	Avelumab	Durvalumab
Phase	1b	1a	1/2	2	2
Cohort	Previously treated locally advanced or metastatic PD-L1+ EC	Incurable or metastatic EC	Previously treated recurrent/advanced pMMR EC	pMMR recurrent EC	Recurrent pMMR EC
Patients, n	23 in efficacy analysis	15 (5 PD-L1high)	142	16	35
ORR, %	13.0*	13**	13.4	6	3
mPFS	1.8 mo	1.4 mo	—	1.9 mo	—
mOS	NR	9.6 mo	—	6.6 mo	—

NR, not reached
* Of the 3 responders, 1 had *POLE*mt disease; the 1 MSI-H patient had progressive disease as best response
** Of the 2 responders, 1 had MSI-H disease

Ott PA, et al. *J Clin Oncol*. 2017;35(22):2535-2341; 2. Fleming GF, et al. Presented at ASCO Annual Meeting. 2017. Abstract 5585; 3. Oaknin A, et al. Presented at ESMO, 2020. 4 Konstantinopoulos et al. *J Clin Oncol*. 2019;37:2786-2794, 5. Antill et al. ASCO 2019

Dostarlimab in Combination with Chemotherapy for the Treatment of Primary Advanced or Recurrent Endometrial Cancer: a Placebo-Controlled Randomized Phase 3 Trial (ENGOT-EN6-NSGO/GOG-3031/RUBY)

Mansoor R. Mirza,[1] Dana Chase,[2] Brian Slomovitz,[3] René DePont Christensen,[4] Zoltán Novák,[5] Destin Black,[6] Lucy Gilbert,[7] Sudarshan Sharma,[8] Giorgio Valabrega,[9] Lisa M. Landrum,[10] Lars C. Hanker,[11] Ashley Stuckey,[12] Ingrid Boere,[13] Michael A. Gold,[14] Sarah E. Gill,[15] Bradley J. Monk,[16] Zangdong He,[17] Shadi Stevens,[18] Robert L. Coleman,[19] Matthew A. Powell[20]

[1]Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, and Nordic Society of Gynaecologic Oncology-Clinical Trial Unit, Copenhagen Denmark; [2*]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [3]Department of Gynecologic Oncology, Mount Sinai Medical Center, and Department of Obstetrics and Gynecology, Florida International University, Miami Beach, FL, USA; [4]Research Unit for General Practice, University of Southern Denmark, Institute of Public Health, Odense, Denmark; [5]Department of Gynecology, Hungarian National Institute of Oncology, Budapest, Hungary; [6]Department of Obstetrics and Gynecology, LSU Health Shreveport, and Willis-Knighton Physician Network, Shreveport, LA, USA; [7]Division of Gynecologic Oncology, McGill University Health Centre, Montreal, Quebec, Canada; [8]Department of Obstetrics/Gynecology, AMITA Adventist Hinsdale Hospital, Hinsdale, IL, USA; [9]University of Torino, AO Ordine Mauriziano, Torino, Italy; [10]Indiana University Health and Simon Cancer Center, Indianapolis, IN, USA; [11]Department of Gynecology and Obstetrics, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; [12]Women and Infants Hospital, Providence, RI, USA; [13]Department of Medical Oncology, Erasmus MC Cancer Centre, Rotterdam, The Netherlands; [14]Oklahoma Cancer Specialists and Research Institute, Tulsa, OK, USA; [15]Division of Gynecologic Oncology, Nancy N. and J.C Lewis Cancer and Research Pavilion, Savannah, GA, USA; [16]HonorHealth Research Institute, University of Arizona College of Medicine, Phoenix, and Creighton University School of Medicine, Phoenix, AZ, USA; [17]GSK, Collegeville, PA, USA; [18]GSK, London, UK; [19]US Oncology Research, The Woodlands, TX, USA; [20]National Cancer Institute sponsored NRG Oncology, Washington University School of Medicine, St Louis, MO, USA;

*Current affiliation. Affiliation at time of study Arizona Center for Cancer Care, Creighton University School of Medicine Phoenix, AZ, USA

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

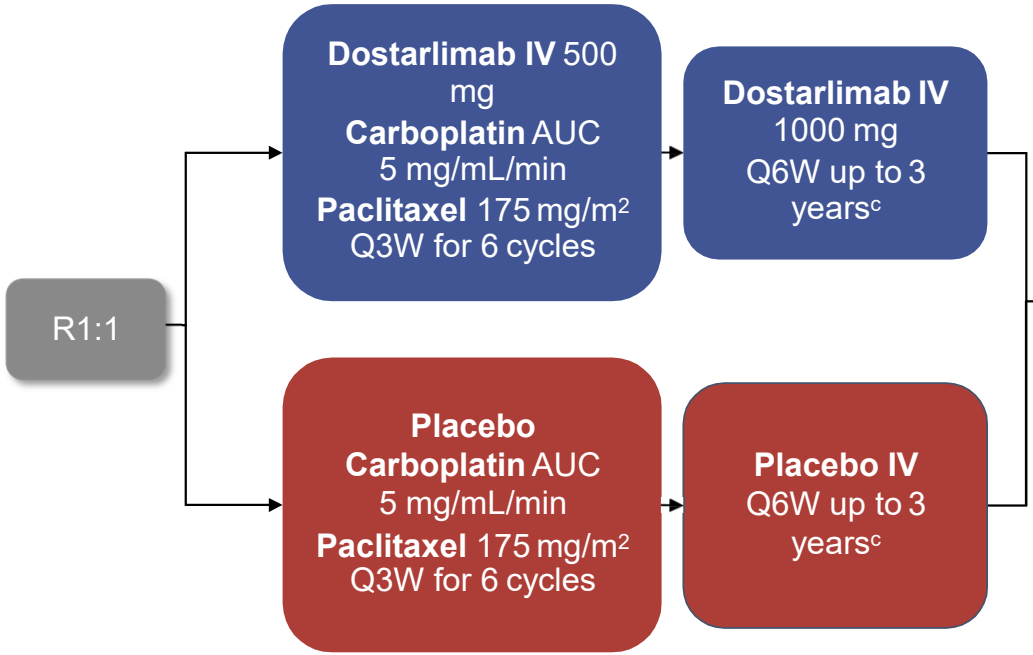
Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin/paclitaxel in patients with primary advanced or recurrent EC

Eligible patients

- Histologically/cytologically proven advanced or recurrent EC
- Stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
  - Carcinosarcoma, clear cell, serous, or mixed histology permitted[a]
- 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[b]
- Prior external pelvic radiotherapy
- Disease status



Primary endpoint

- PFS by INV
- OS

Secondary endpoints

- PFS by BICR
- PFS2
- ORR
- DOR
- DCR
- HRQOL/PRO
- Safety

On-study imaging assessments are to be performed Q6W (±7 days) from the randomization date until Week 25 (Cycle 8), followed by Q9W (±7 days) until Week 52. Subsequent tumor imaging is to be performed every 12 weeks (±7 days) until radiographic PD is documented by Investigator assessment per RECIST v1.1 followed by one additional imaging 4-6 weeks later, or subsequent anticancer therapy is started, whichever occurs first. Thereafter, scans may be performed per standard of care.

[a]Mixed histology containing at least 10% carcinosarcoma, clear cell, or serous histology. [b]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used with local results were not available. For local determination of MMR/MSI status, IHC, next generation sequencing, and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx panel was used. [c]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the Investigator. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response, EC, endometrial cancer; IV, administered intravenously; INV, investigator assessment; MMR, mismatch repair; MSI, microsatellite instability; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome.

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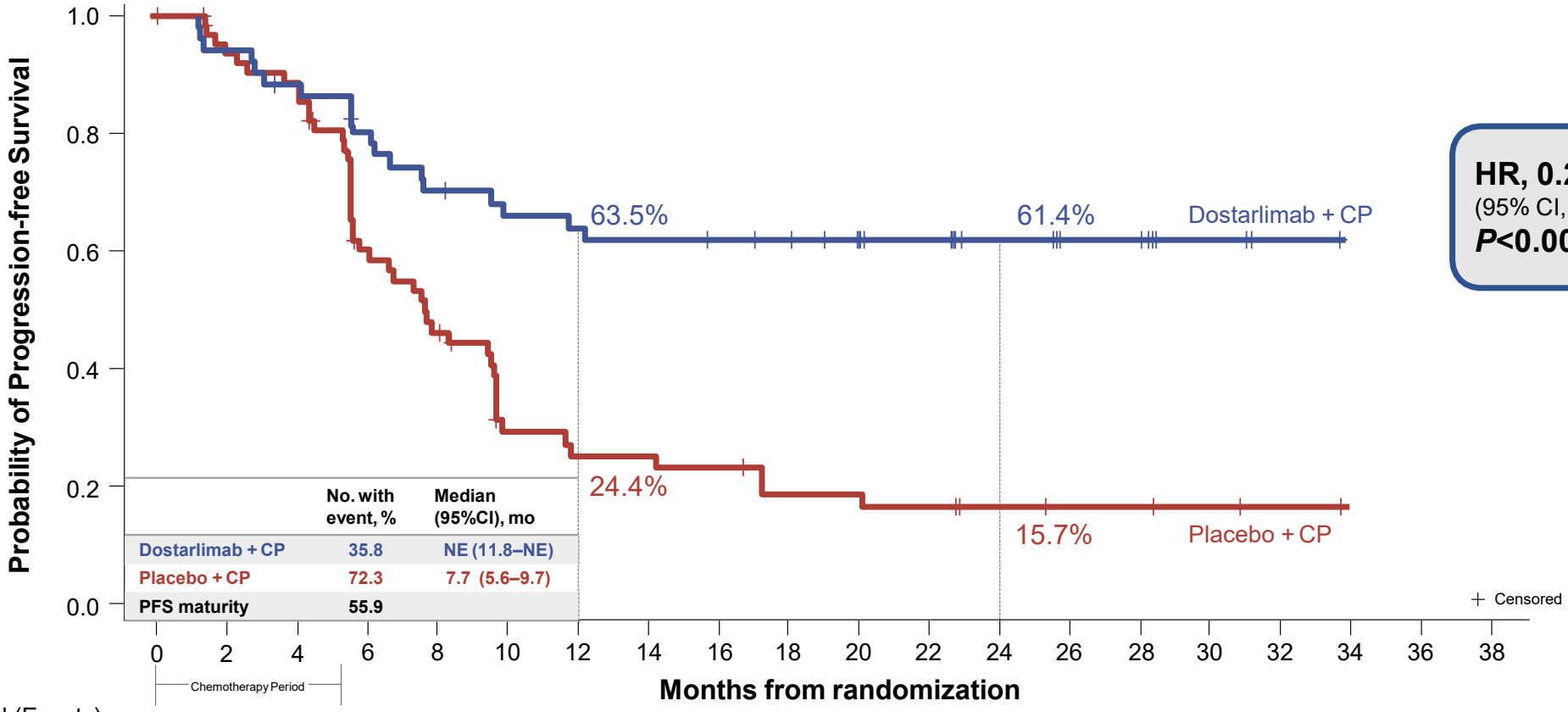
ENGOT-EN6-NSGO/GOG-3031/RUBY presented by Mansoor R Mirza

Primary Endpoint: PFS in dMMR/MSI-H Population



HR, 0.28
(95% CI, 0.162–0.495)
***P*<0.0001**

At Risk(Events)

Dostarlimab + CP	53(0)	48(3)	44(6)	39(10)	34(15)	31(17)	30(18)	29(19)	28(19)	27(19)	25(19)	19(19)	13(19)	9(19)	9(19)	4(19)	1(19)	0(19)
Placebo + CP	65(0)	57(4)	54(7)	34(24)	26(32)	14(41)	12(43)	12(43)	11(44)	8(46)	8(46)	7(47)	4(47)	3(47)	3(47)	2(47)	1(47)	0(47)

Median duration of follow-up 24.79 months.

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; PFS, progression-freesurvival.

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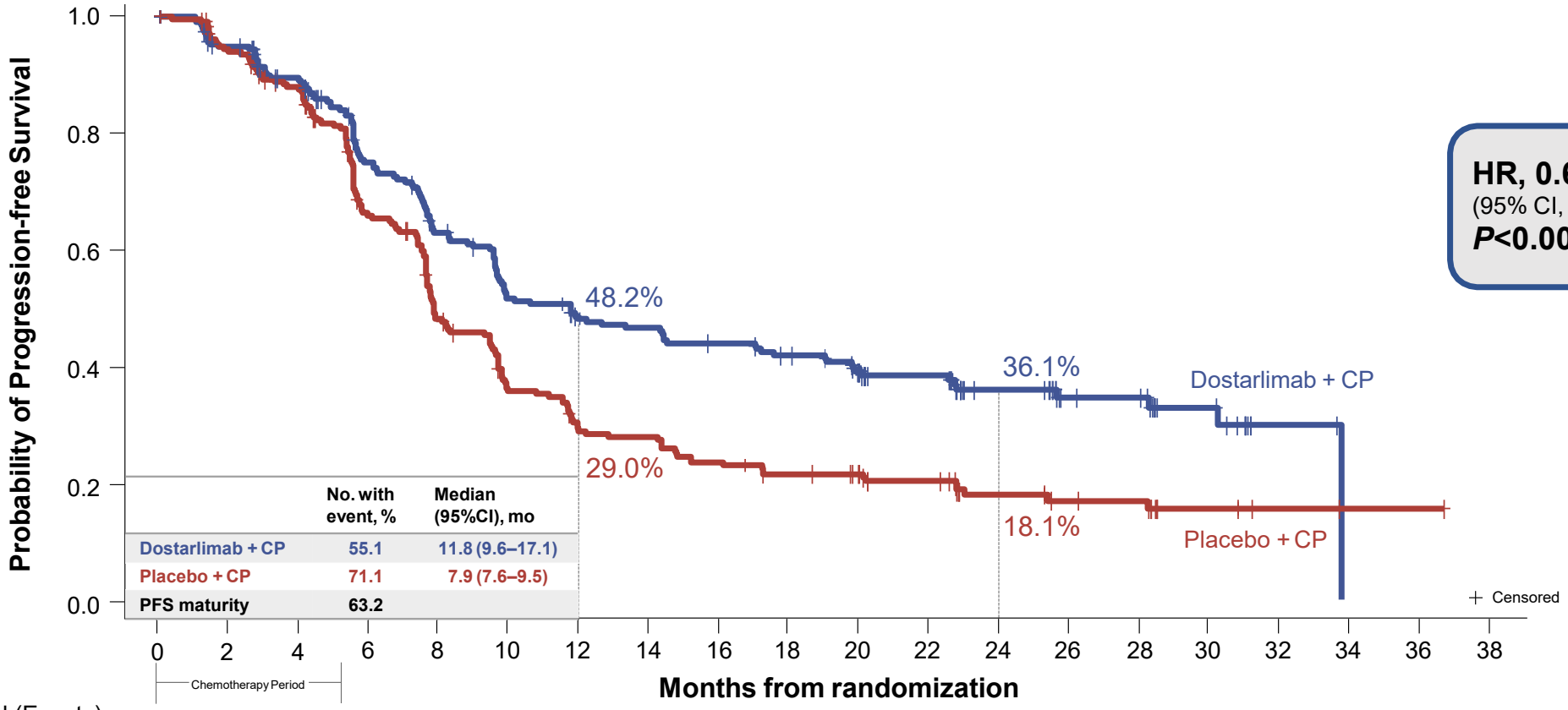
Primary Endpoint: PFS in Overall Population



HR, 0.64
(95% CI, 0.507–0.800)
***P*<0.0001**

At Risk(Events)

Dostarlimab + C	P	220(12)	197(25)	157(55)	130(80)	105(103)	94(110)	90(113)	84(118)	78(122)	66(127)	52(128)	34(131)	23(132)	22(132)	12(133)	2(134)	0(135)
Placebo + CP	245(0) 249(0)	219(14)	200(29)	144(77)	103(115)	74(141)	59(155)	57(157)	48(166)	42(170)	39(170)	32(172)	20(175)	14(176)	13(176)	5(177)	2(177)	1(177)	1(177)	0(177)

Median duration of follow-up 25.38 months.

CP, carboplatin/paclitaxel; HR, hazard ratio; PFS, progression-free survival.

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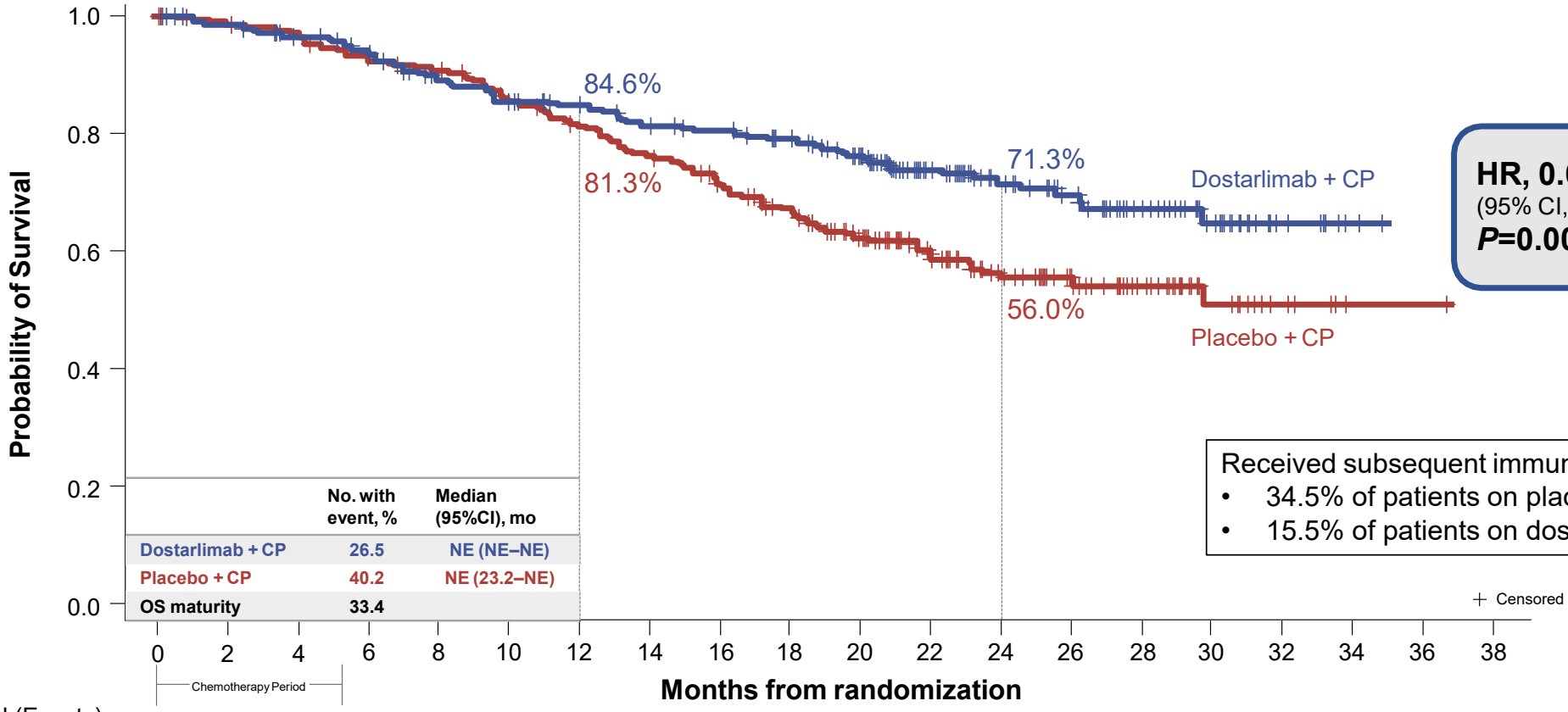
Primary Endpoint: OS in Overall Population (33% maturity)



HR, 0.64
(95% CI, 0.464–0.870)
***P*=0.0021**[a]

Received subsequent immunotherapy:
- 34.5% of patients on placebo arm
- 15.5% of patients on dostarlimab arm

At Risk(Events)

Dostarlimab + C	P	235(3)	224(8)	214(15)	198(25)	190(33)	183(35)	174(42)	169(44)	162(47)	145(53)	110(57)	83(60)	64(62)	45(64)	25(65)	7(65)	2(65)	0(65)
Placebo + CP	245(0) 249(0)	242(3)	237(7)	226(17)	219(22)	203(35)	189(45)	177(57)	162(68)	147(78)	125(88)	88(93)	65(97)	48(98)	33(99)	15(100)	6(100)	1(100)	1(100)	0(100)

Median duration of follow-up 25.38 months.

[a]P≤0.00177 required to declare statistical significance at first interim analysis.
CP, carboplatin/paclitaxel; HR, hazard ratio; NE, not estimable; OS, overall survival.

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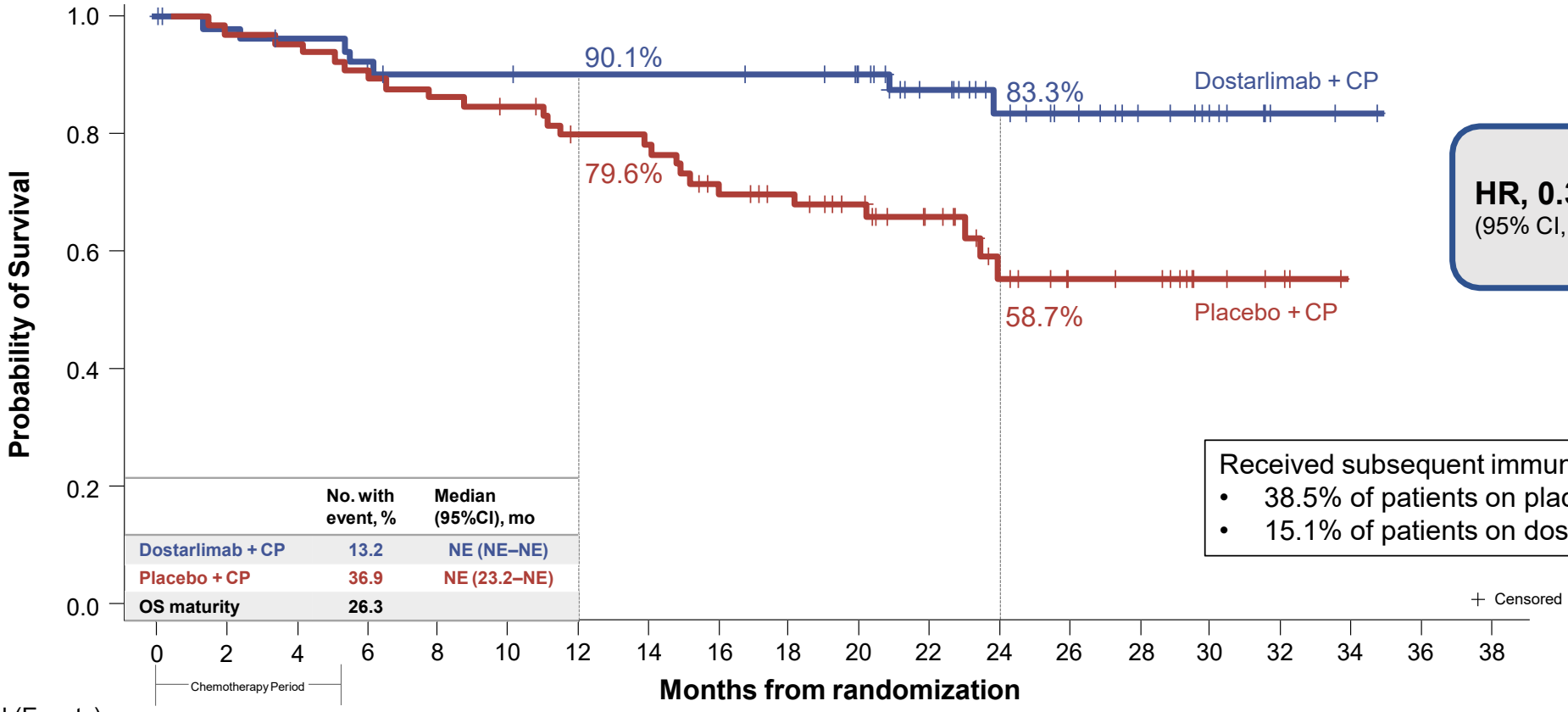
OS in dMMR/MSI-H Population



HR, 0.30
(95% CI, 0.127–0.699)

Received subsequent immunotherapy:
- 38.5% of patients on placebo arm
- 15.1% of patients on dostarlimab arm

At Risk(Events)

Dostarlimab + CP	53(0)	50(1)	48(2)	46(4)	44(5)	44(5)	43(5)	43(5)	43(5)	42(5)	41(5)	29(6)	20(7)	16(7)	12(7)	8(7)	2(7)	1(7)	0(7)
Placebo + CP	65(0)	63(2)	62(3)	59(6)	55(9)	53(10)	48(13)	47(14)	41(18)	37(19)	32(20)	25(21)	16(23)	12(24)	10(24)	5(24)	3(24)	0(24)	

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; OS, overall survival.

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Pembrolizumab Versus Placebo in Addition to Carboplatin and Paclitaxel for Measurable Stage III or IVA, Stage IVB, or Recurrent Endometrial Cancer: The Phase 3, NRG GY018 Study

Ramez N. Eskander, MD, Michael W. Sill, PhD, Lindsey Beffa, MD, Richard G. Moore, MD, Joanie Mayer Hope, MD, Fernanda B. Musa, MD, Robert Mannel, MD, Mark S. Shahin, MD, Guilherme H. Cantuaria, MD, Eugenia Girda, MD, Cara Mathews, MD, Juraj Kavecansky, MD, Charles A. Leath, III, MD, MSPH, Lilian T. Gien, MD, Emily M. Hinchcliff, MD, MPH, Shashikant B. Lele, MD, Lisa M. Landrum, MD, Floor Backes, MD, Roisin E.O'Cearbhaill, MD, Tareq Al Baghdadi, MD, Emily K. Hill, MD, Premal H. Thaker, MD, MS, Veena Susan John, MD, Stephen Welch, MD, Amanda N Fader, MD, Matthew A. Powell, MD, Carol Aghajanian, MD

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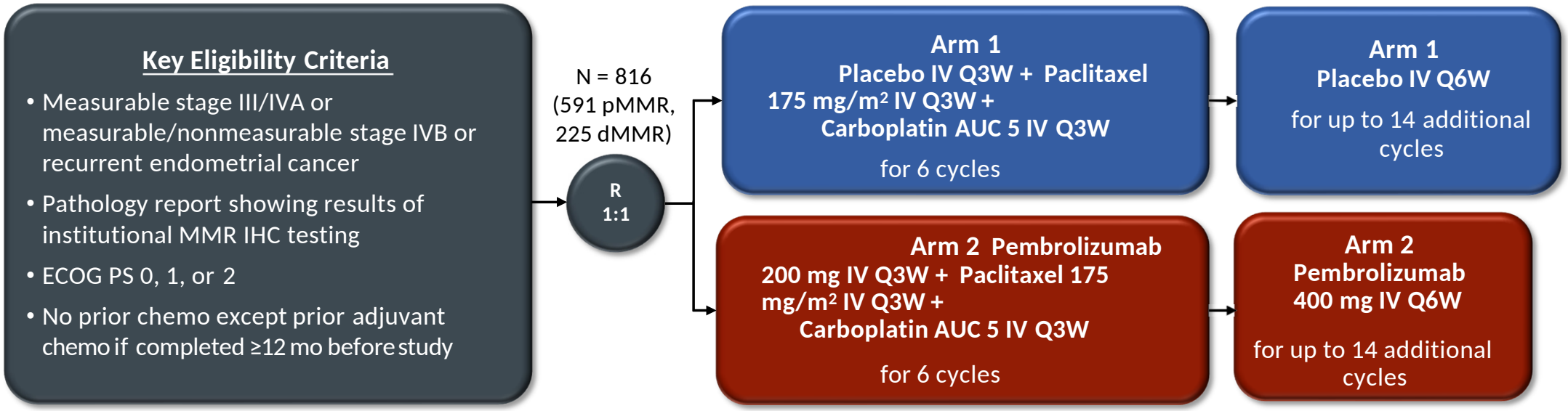
NRG-GY018 (NCT03914612)



Stratification Factors

- dMMR vs pMMR
- ECOG PS (0 or 1 vs 2)
- Prior adjuvant chemo (yes vs no)

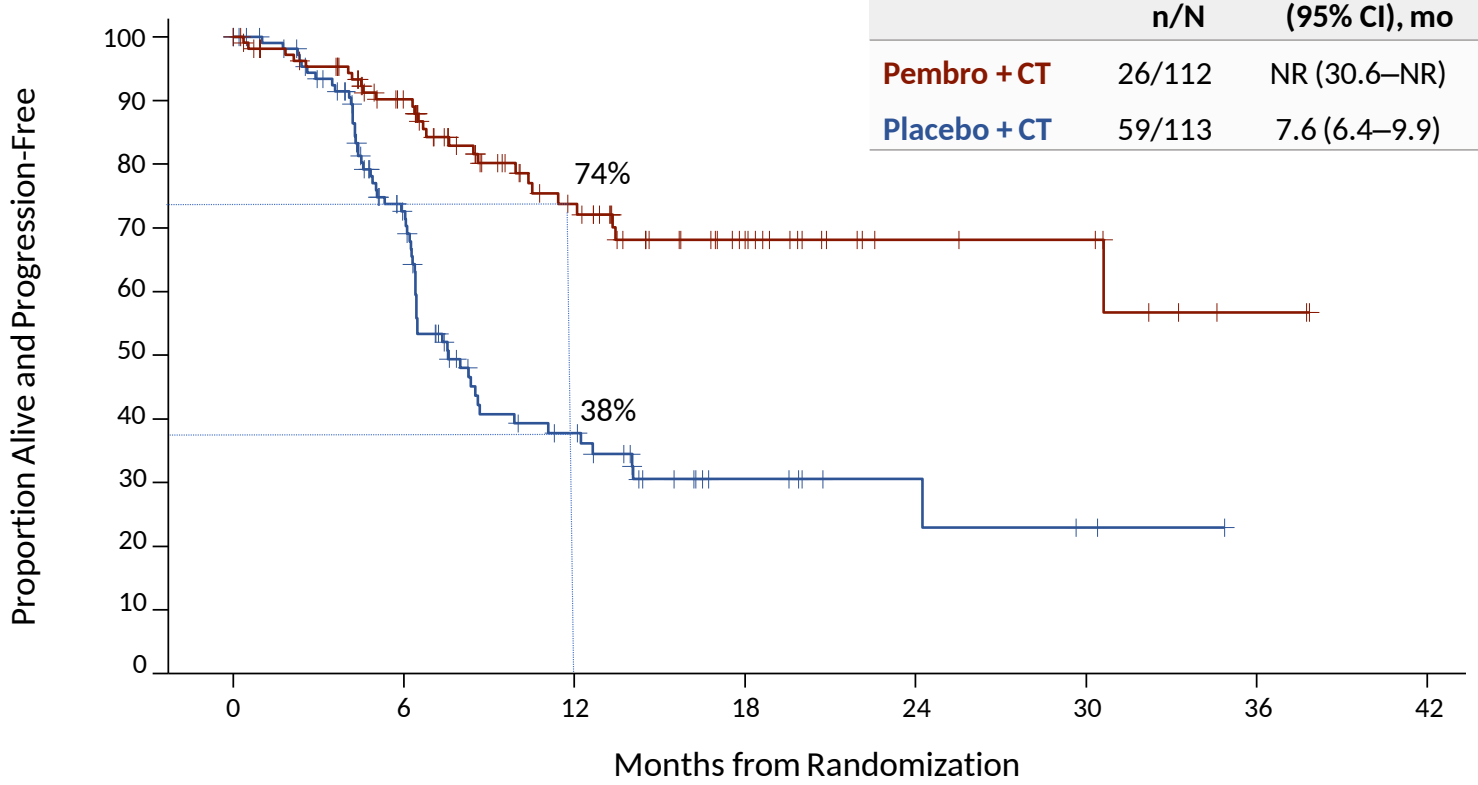
Endpoints

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

BICR, blinded independent central review; dMMR, mismatch repair deficient; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; PRO, patient-reported outcomes; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.

PFS per RECIST v1.1: dMMR Population

	Events, n/N	Median (95% CI), mo	HR (stratified; 95% CI)
Pembro + CT	26/112	NR (30.6–NR)	**0.30 (0.19–0.48)**
Placebo + CT	59/113	7.6 (6.4–9.9)	***P* = <0.00001**

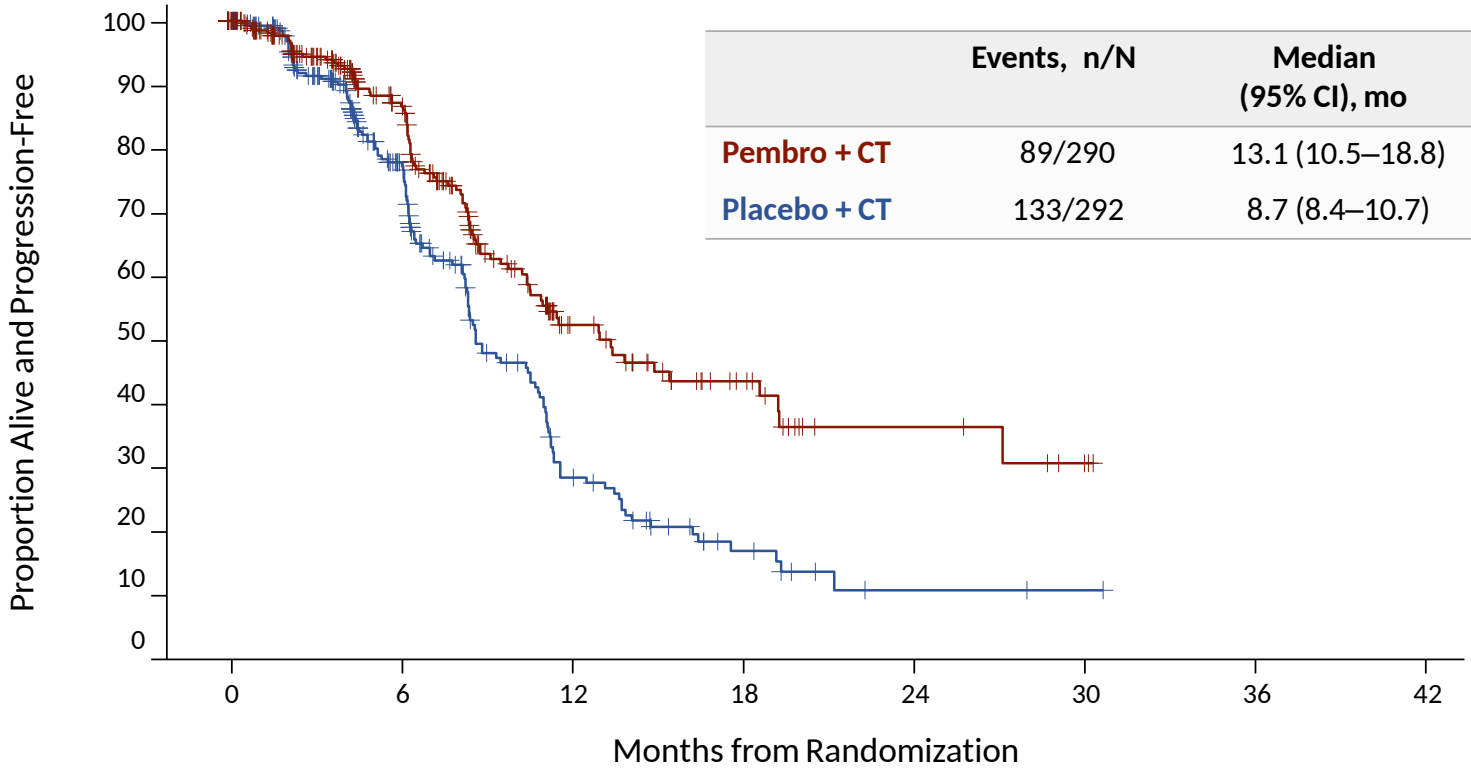


Number at Risk (Cumulative number censored)

Placebo + CT	113 (2)	62 (24)	24 (35)	8 (47)	4 (51)	2 (52)	0 (54)	
Pembro + CT	112 (1)	80 (22)	44 (46)	22 (65)	9 (78)	8 (79)	2 (84)	0 (86)

Data cutoff date: December 16, 2022.

PFS per RECIST v1.1: pMMR Population



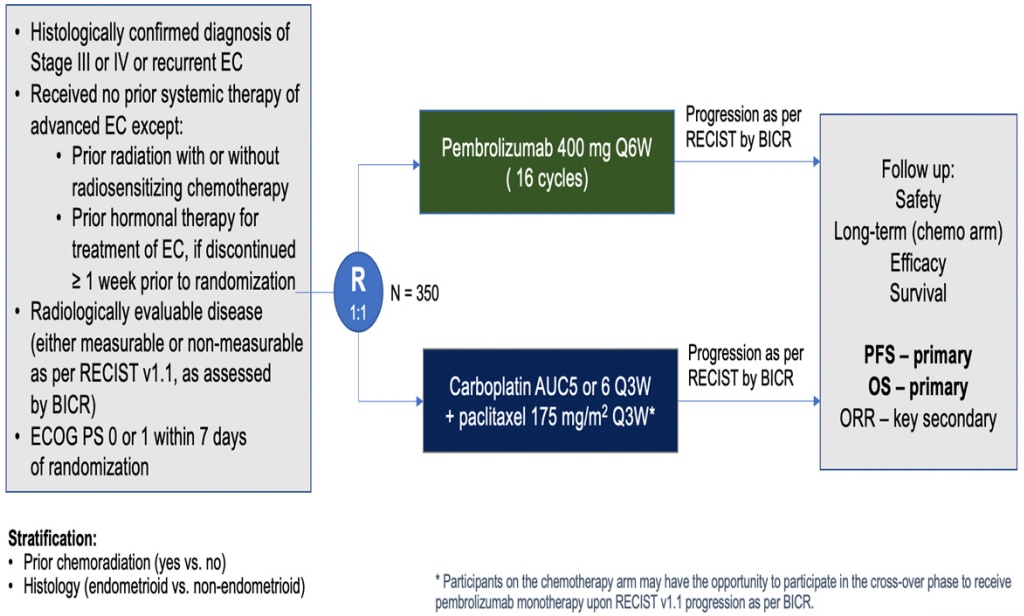
	Events, n/N	Median (95% CI), mo	HR (stratified; 95% CI)
Pembro + CT	89/290	13.1 (10.5–18.8)	0.54 (0.41–0.71)
Placebo + CT	133/292	8.7 (8.4–10.7)	*P* < 0.00001

Number at Risk (Cumulative number censored)

Placebo + CT	292 (14)	129 (115)	33 (141)	10 (152)	2 (157)	1 (158)	0 (159)
Pembro + CT	290 (15)	150 (112)	45 (167)	20 (185)	7 (195)	3 (198)	0 (201)

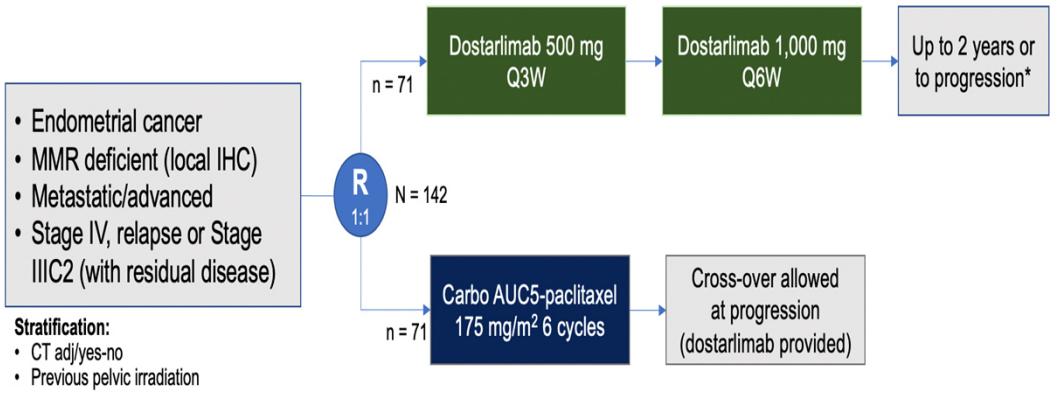
KEYNOTE-C93/GOG-3064/ENGOT-en15
Study design

Phase III randomized trial of pembrolizumab vs platinum doublet chemotherapy in first-line dMMR advanced or recurrent EC



ENGOT-en13/GINECO/DOMENICA
Study design

Phase III randomized trial comparing chemotherapy alone vs dostarlimab in first-line dMMR advanced/metastatic EC



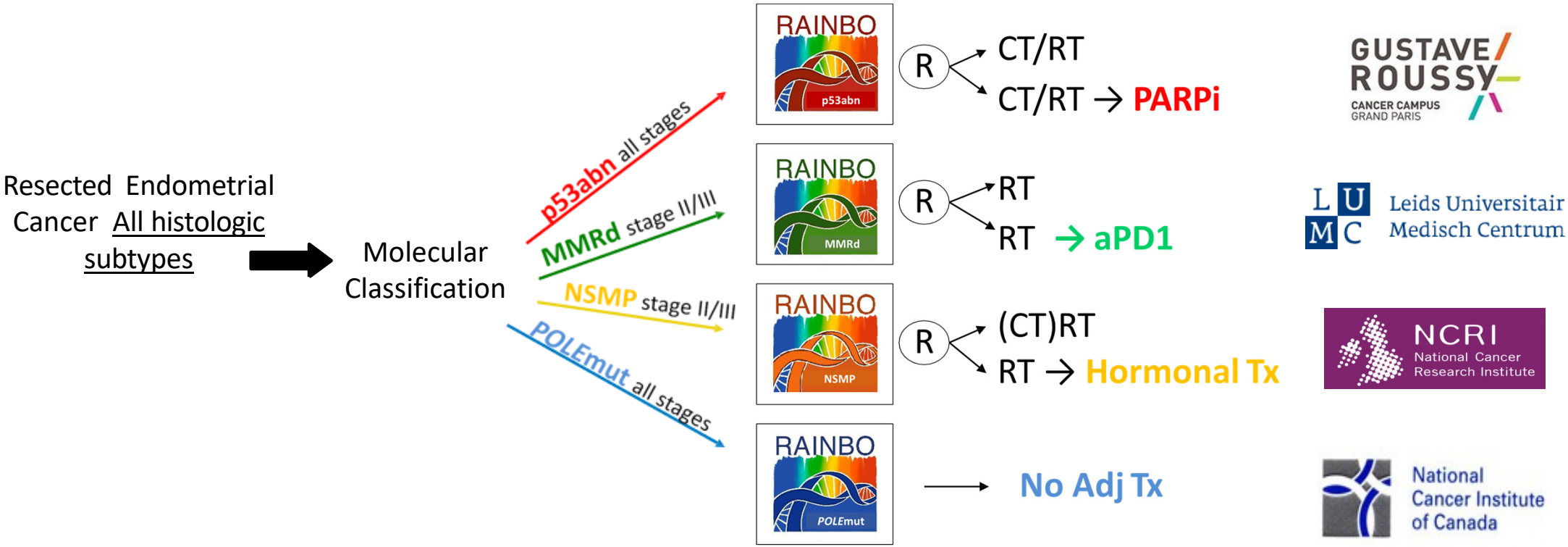
Primary endpoint: Investigator-assessed PFS by RECIST v1.1

Secondary endpoints: OS and PROs (key secondary endpoints), ORR, DoR, PFS2, TFST, safety and tolerability, central MMR

Exploratory endpoints: Translational (MSI, PD-1/-L1 status, immune signature); PFS according to iRECIST

https://clinicaltrials.gov/ct2/show/NCT05173987; https://clinicaltrials.gov/ct2/show/NCT01244789

RAINBO: Refining Adjuvant treatment IN endometrial cancer Based On molecular profile

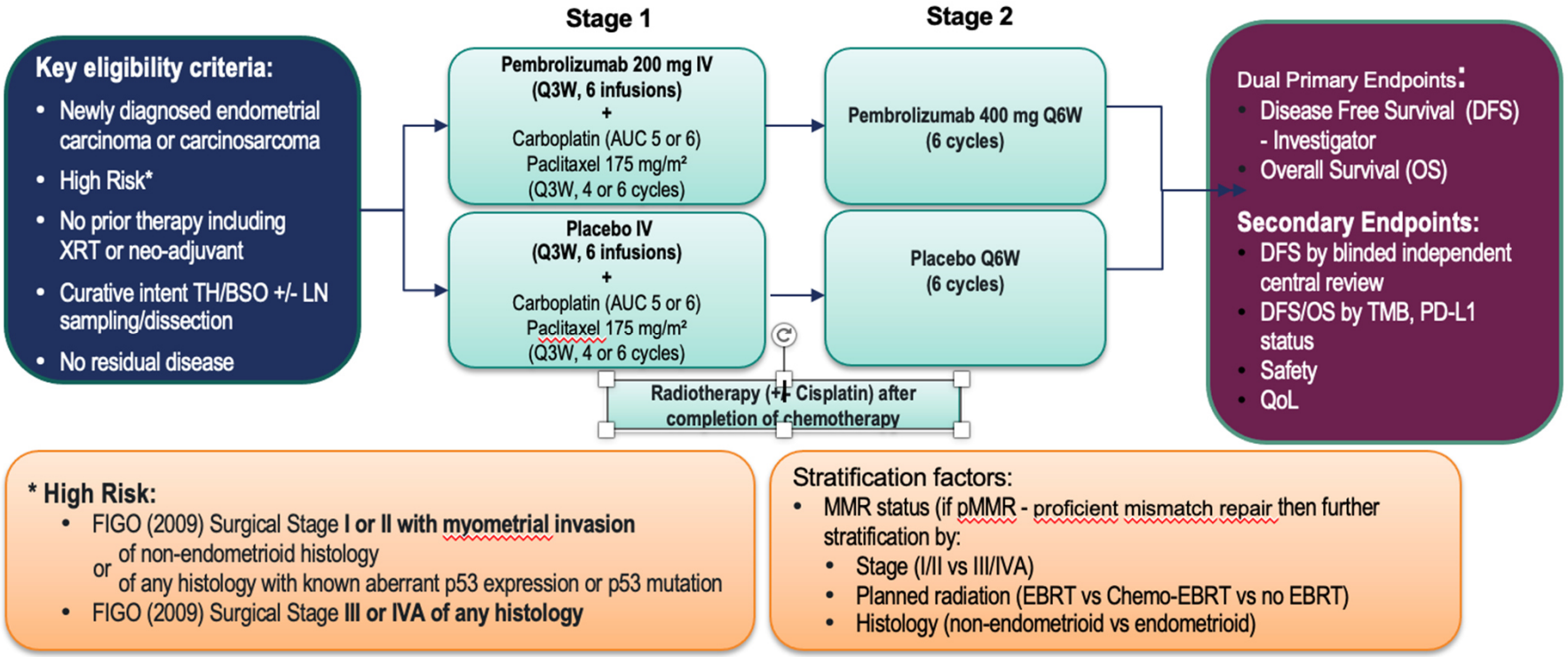


RAINBO umbrella program coordinated by *Trans*PORTEC consortium will allocate EC pts to 4 international academically sponsored trials

Adj, adjuvant; CT, chemotherapy; EC, endometrial; MMRd, MMR-deficient; NSMP, noNspecific molecular profile; p53abn, p53 abnormal; PARPi, Poly (ADP-ribose) polymerase inhibitor; POLEmut, polymerase and mutated; PORTEC-3, Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer; RT, radiotherapy; TX, therapy.
Jamieson A et al. *Ther Adv Med Oncol* 2021;13:17588359211035959.

MK-3475-B21/ENGOT-en11/GOG-3053: Study design

- Phase 3, randomized, double-blind study of pembrolizumab versus placebo in combination with adjuvant chemotherapy with or without radiotherapy for the treatment of newly diagnosed, high-risk endometrial cancer after surgery with curative intent



AUC, area under the curve; BSO, bilateral Salpingo Oophorectomy; ebrt, external beam radiotherapy; FIGO, International Federation of Gynaecology and Obstetrics; IV, intravenous; LN, lymph node; MMR, mismatch repair; PD-L1 programmed cell death ligand 1; pMMR, proficient mismatch repair; QoL, quality of life; Q3W, every 3 weeks; Q6W, every 6 weeks; TH, total hysterectomy, tumour mutational burden; XRT, radiotherapy.

Clinicaltrials.gov. NCT04634877. Available at: https://clinicaltrials.gov/ct2/show/NCT04634877.

RT in Cervical and Endometrial Cancer: Open Question?

What is the best way to combine Radiotherapy and Immunotherapy in LACC?

Is there a role for RT in the adjuvant treatment of (MSI-H) endometrial cancer?