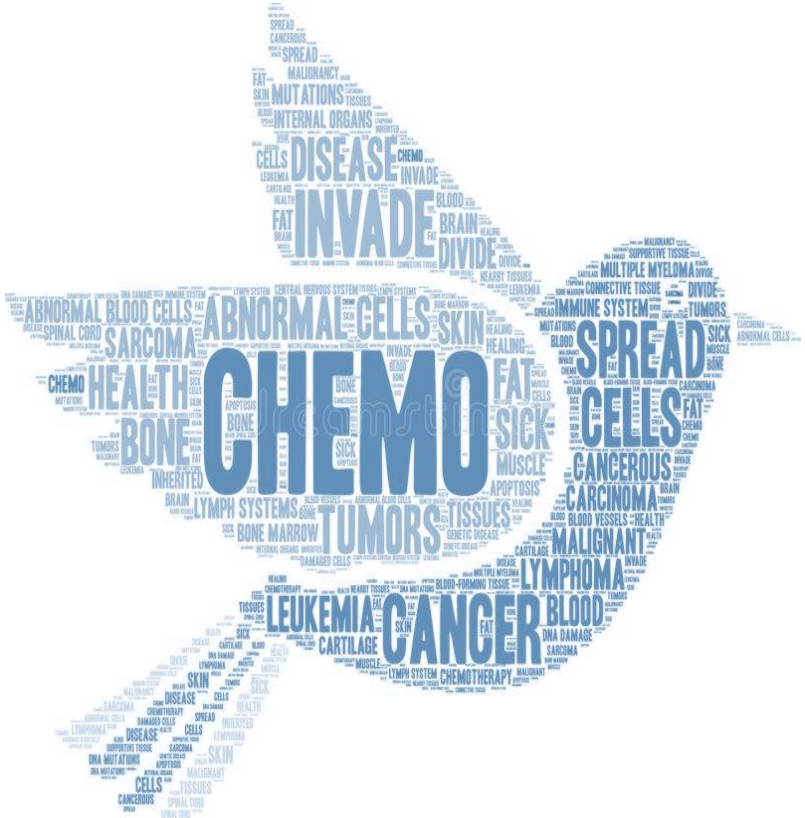

Christian Marth

- Replacing chemotherapy in first line

Replacing chemotherapy in the first line

Christian Marth

Department of Obstetrics and Gynecology
Medical University Innsbruck

AGO AUSTRIA

ENGOT
European Network of
Gynaecological Oncological Trial groups

DISCLOSURE INFORMATION

Funded Research: EU, FWF, Astra Zeneca, Roche

Honoraria/Expenses: Roche, Novartis, Amgen, MSD, Pharmamar, Astra Zeneca, Tesaro, GSK

Consulting/Advisory Board: Roche, Novartis, Amgen, MSD, Astra Zeneca, Pfizer, Pharmamar, Cerulean, Vertex, Tesaro, GSK

Immune Checkpoint Inhibitor Efficacy in Endometrial Cancer

		MMR-d		MMR-p	
Study	Drug	N	ORR(%)	N	ORR(%)
KEYNOTE 158: Marabelle (2019)	Pembrolizumab	79	48%	107	11%
GARNET: Oaknin (2022)	Dostarlimab	143	46%	156	15%
PHAEDRA: Antill (2019)	Durvalumab	35	43%	36	3%
Konstantinopoulos (2019)	Avelumab	15	27%	16	6%

O'Malley et al. ESMO 2019. JCO2022; Oaknin, ASCO 2022; Antill ASCO 2019 ; Konstantinopoulos ASCO 2019, Makker NEJM 2022

Immune Checkpoint Inhibitor Efficacy in Endometrial Cancer

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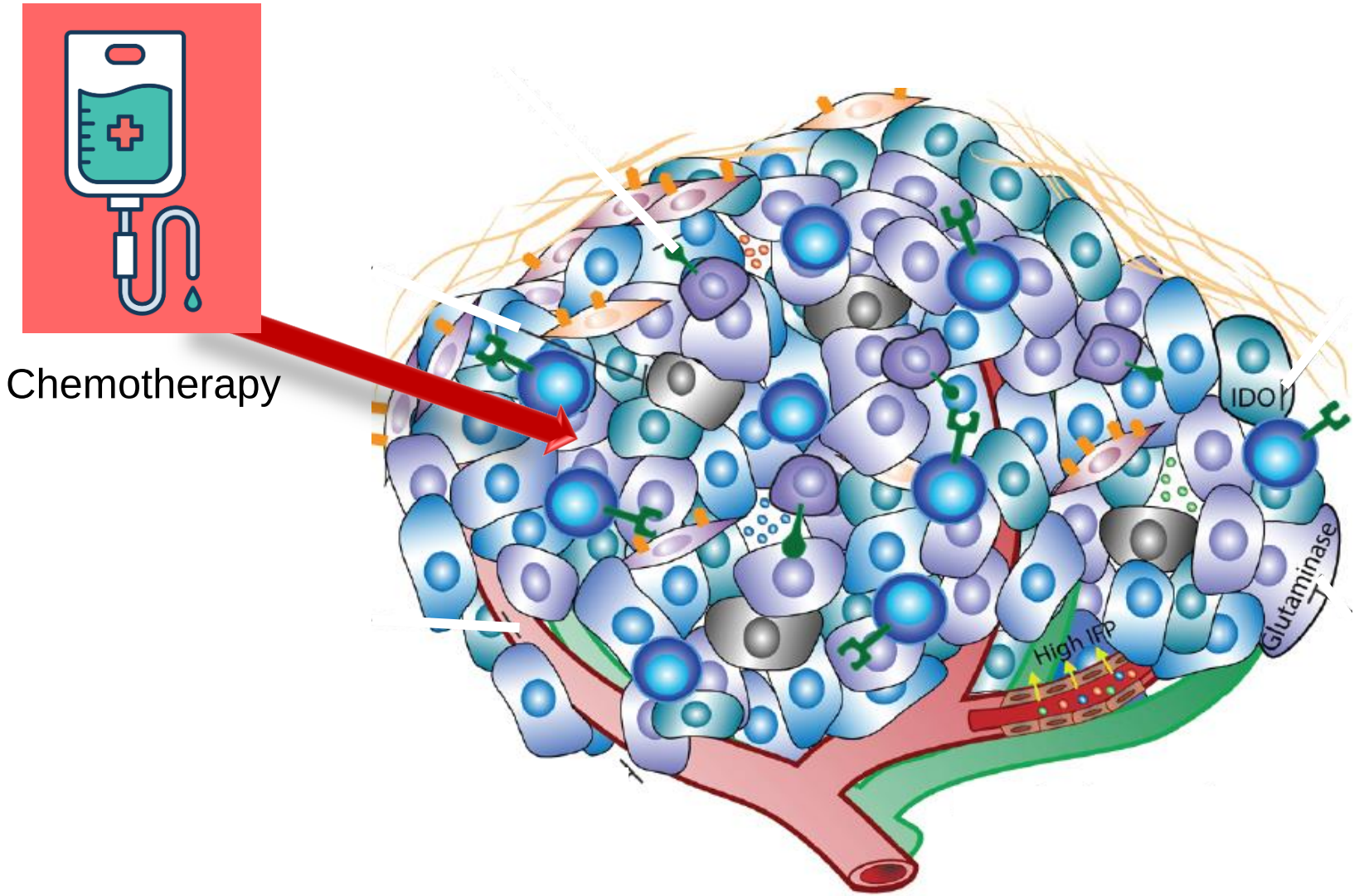
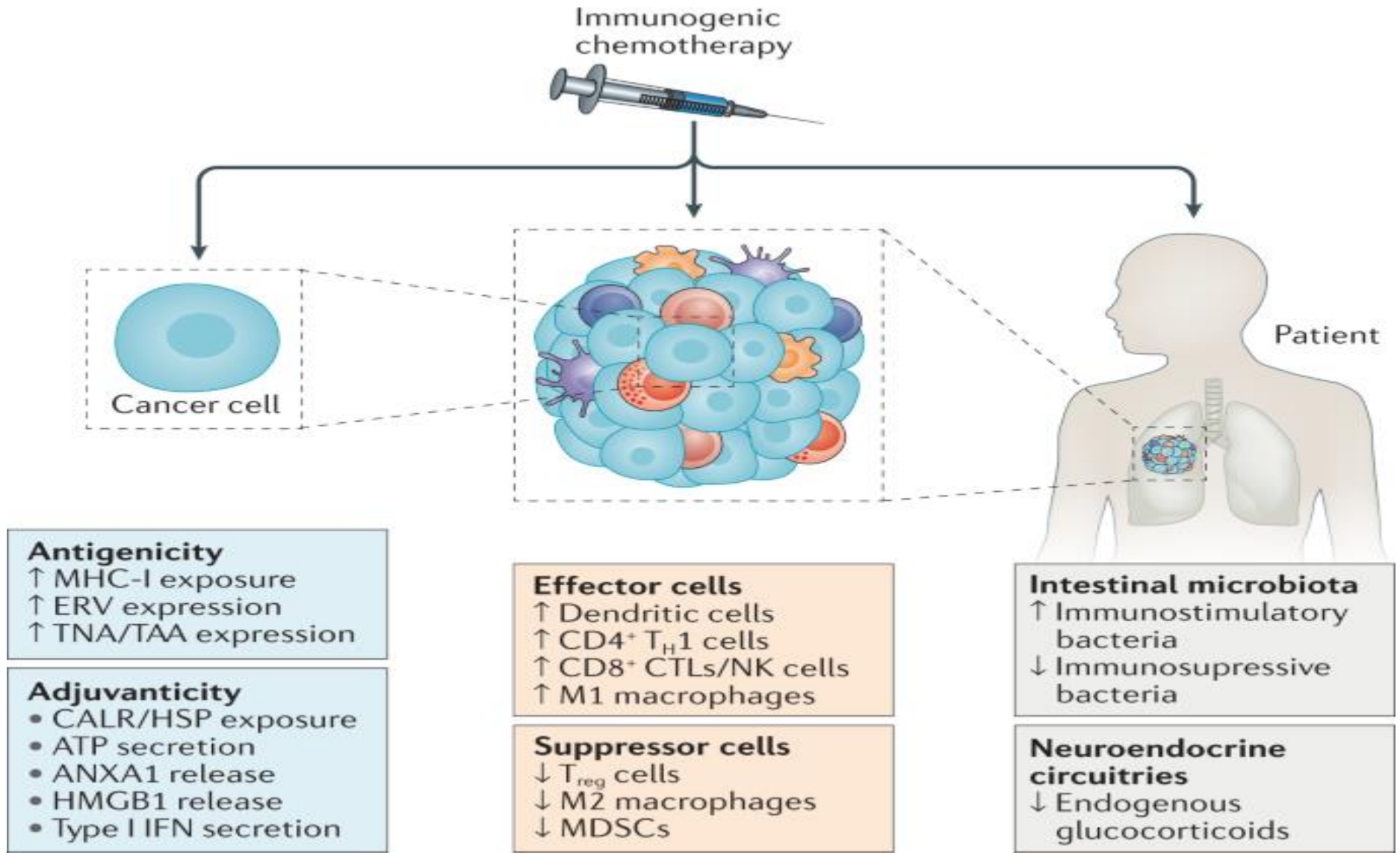
Konstantinopoulos (2019)	Avelumab	15	27%	16	6%
KEYNOTE 775 Makker (2022)	Pembrolizumab + Lenvatinib	65	42%	346	32%

O'Malley et al. ESMO 2019. JCO2022; Oaknin, ASCO 2022; Antill ASCO 2019 ; Konstantinopoulos ASCO 2019, Makker NEJM 2022

Microenvironment, Immunotherapy and Combination



Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors



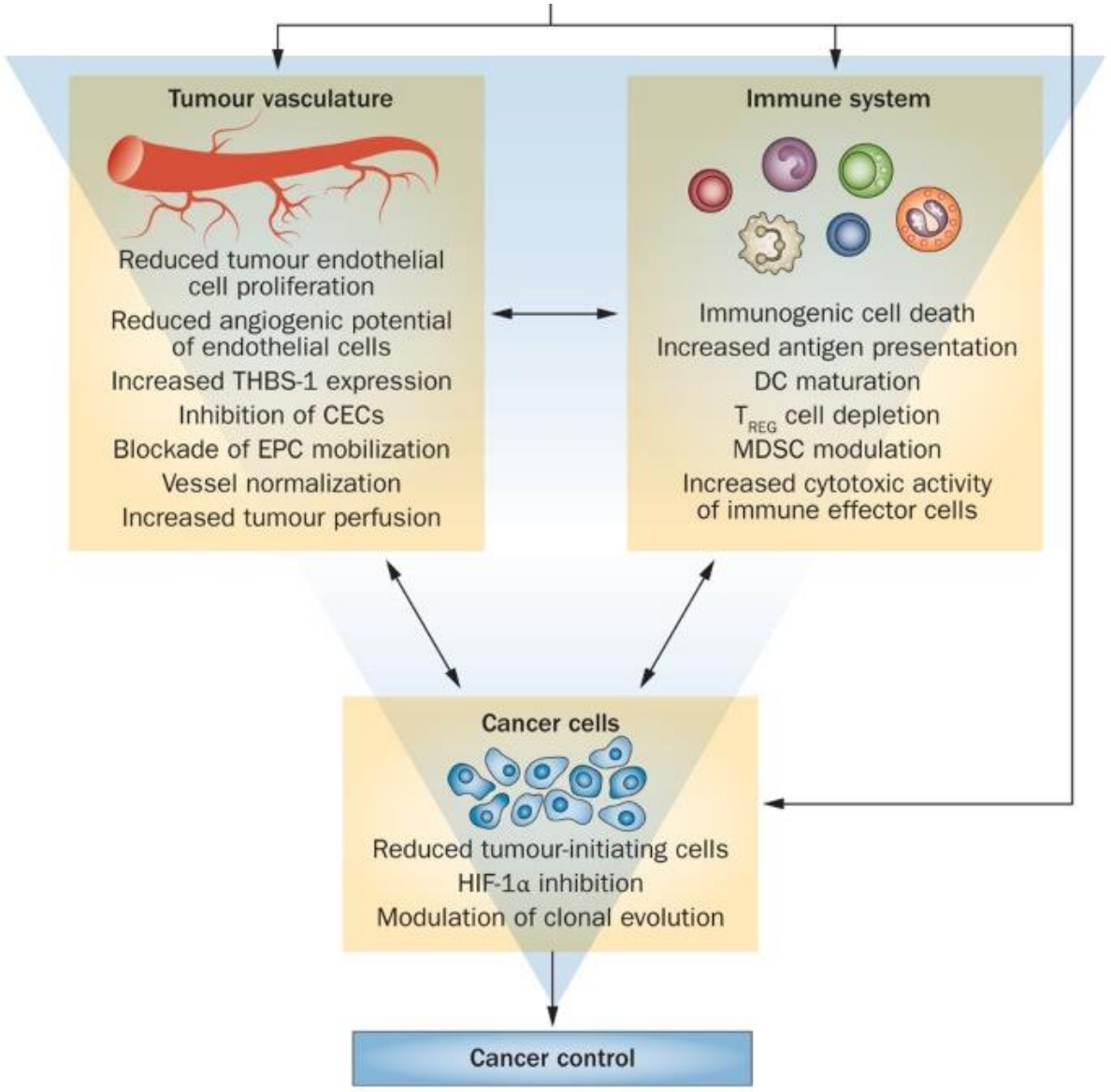
Galluzzi L, et al. Nat Rev Clin Oncol. 2020

Inducers of immunogenic cell death

Agent	Main cytokines	Immune infiltrate
Radiotherapy	↑IL-17 , type I IFNs, IFNγ, TGFβ	↑DCs, CD8+ CTLs
Anthracyclines	↑IL-1β, IL-6, IL-12, IL-17, CXCL10, type I IFNs, IFNγ	↑DCs, CD8+ CTLs, γδ TH17 cells; ↓Treg cells, MDSCs
Cyclophosphamide	↑Type I IFNs, IFNγ, IL-17	↑DCs, CD8+ CTLs, NK cellsb, NKT cells; ↓MDSCs, Treg cells
Lurbinectedin	↑Type I IFNs	ND
Cis/carboplatin	↑Type I IFNs, IFNγ	↑DCs, CD8+ CTLs, CD4+ T cells; ↓Treg cells, MDSCs
Gemcitabine	↑IL-17	↑DCs, CD8+ CTLs, NKb, and NKT cells; ↓MDSCsb,Treg cell
Paclitaxel	↑IL-1β, IL-12, TNF	↑DCs, M1 macrophages; ↓Treg cells
Tumor treating fields	↑Type I IFNs, IFNγ	↑DCs, CD8+ CTLs

Modified from Galluzzi L, et al. Nat Rev Clin Oncol. 2020 and Voloshin T, et al. Cancer Immunol Immunother. 2020

Metronomic Chemotherapy



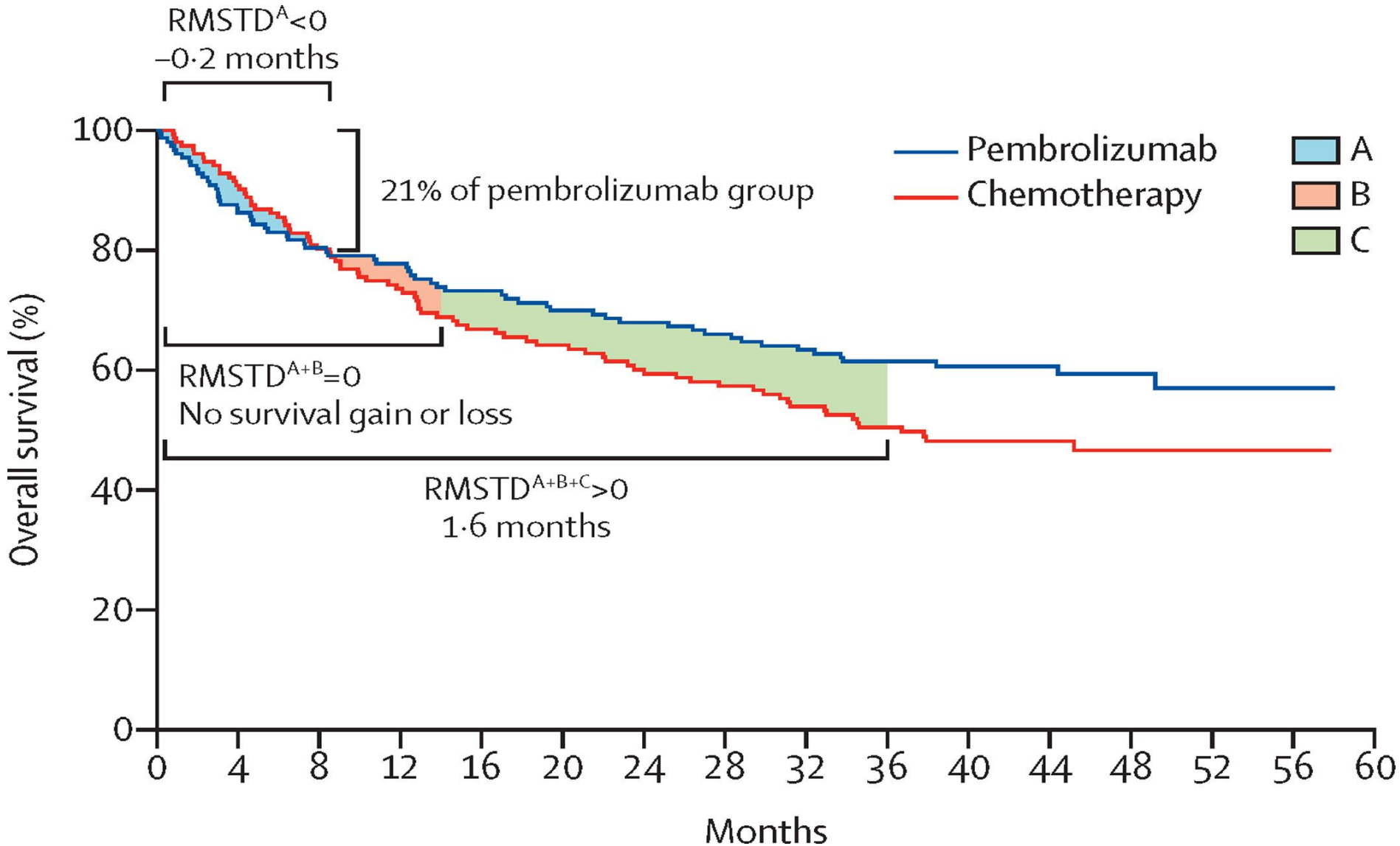
- Metronomic chemotherapy relies on frequent administration of a low dose of chemotherapy
- Initially considered as an antiangiogenic therapy, metronomic chemotherapy is now regarded as a multi-target therapy with immunological properties, and direct effect on cancer stem cells
- Many clinical studies have demonstrated activity in relapsed and/or refractory disease and several randomized studies are ongoing
- Combined with tumour molecular analysis, metronomic chemotherapy is poised to move towards personalized chemotherapy
- Metronomic therapy is a non-toxic, inexpensive strategy well-suited for global oncology

Nicolas André, Manon Carré & Eddy Pasquier Nature Reviews Clinical Oncology 2014

Chemotherapy and IO: Antagonistic activity

- Impair the proliferative and/or effector functions of peripheral T cells
- Immunosuppression by massive tumor-antigen release. The sudden and systemic release of numerous dying tumour cells resulting from chemotherapy might have deleterious consequences on subsequent tumour-specific immune responses
- Glucocorticoids suppress the production of proinflammatory Cytokines and impair the differentiation of and antigen presentation by dendritic cells

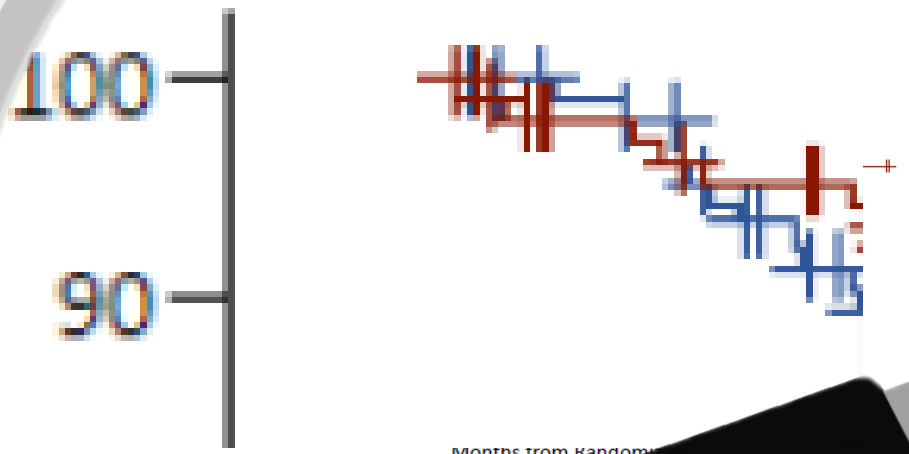
Crossing survival curves of KEYNOTE-177 in MSI-high or MMR-deficient metastatic colorectal cancer illustrate the rationale behind combining immune checkpoint inhibition with chemotherapy



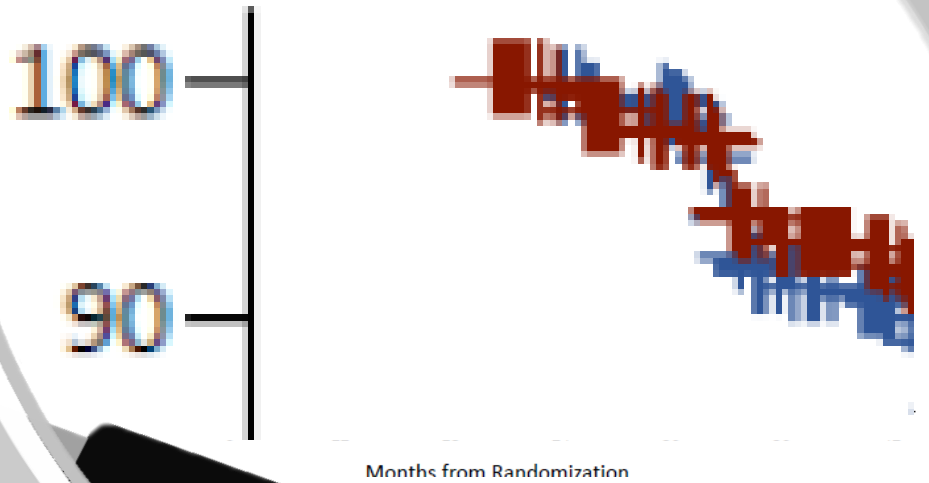
Bomze D, et al. Lancet Oncol. 2022

NRG-GY018/KEYNOTE-868 (NCT03914612)

MMRd



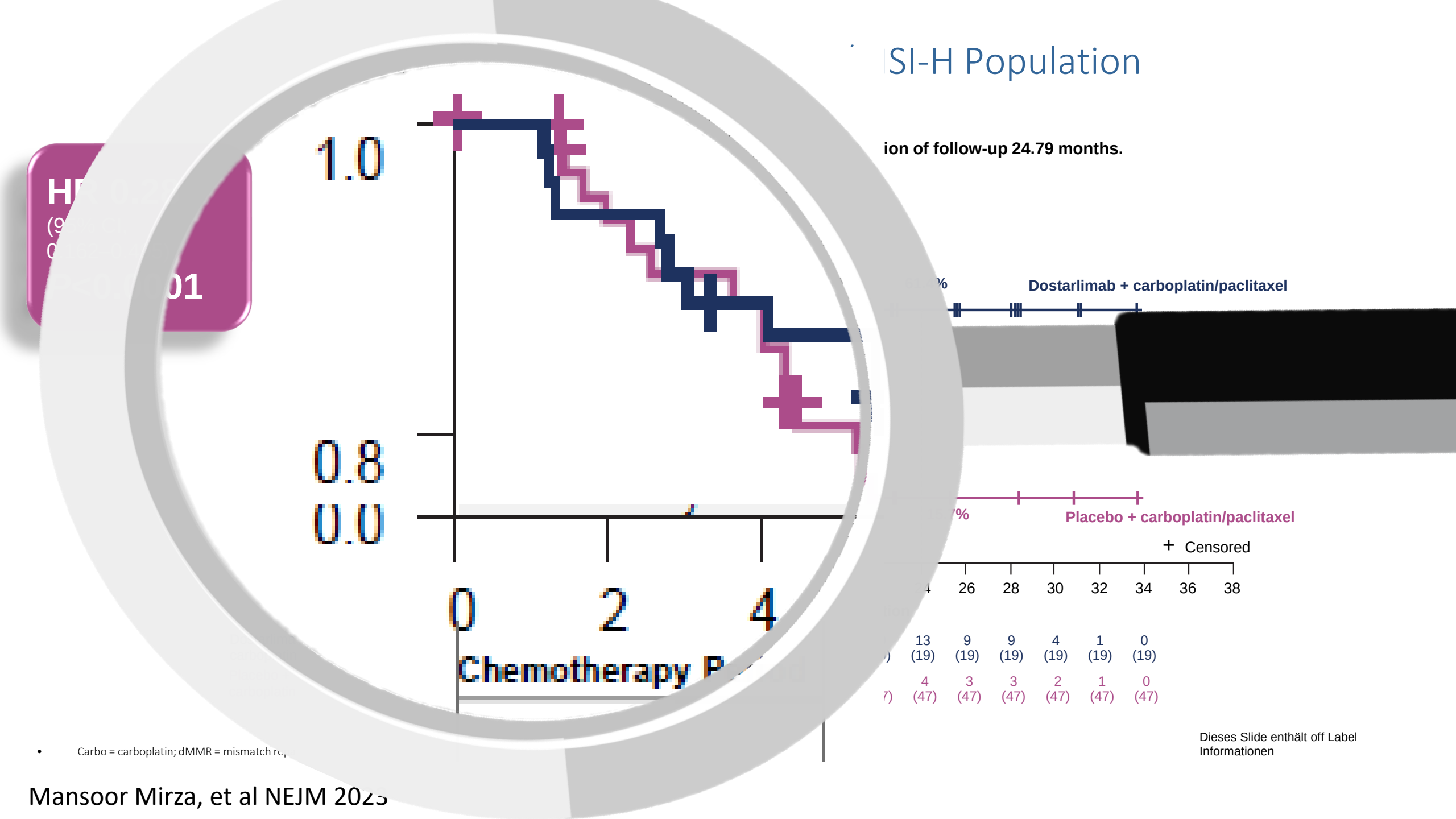
MMRp



R.N. Eskander et al. SGO

SI-H Population

ion of follow-up 24.79 months.



- Carbo = carboplatin; dMMR = mismatch re

Mansoor Mirza, et al NEJM 2023

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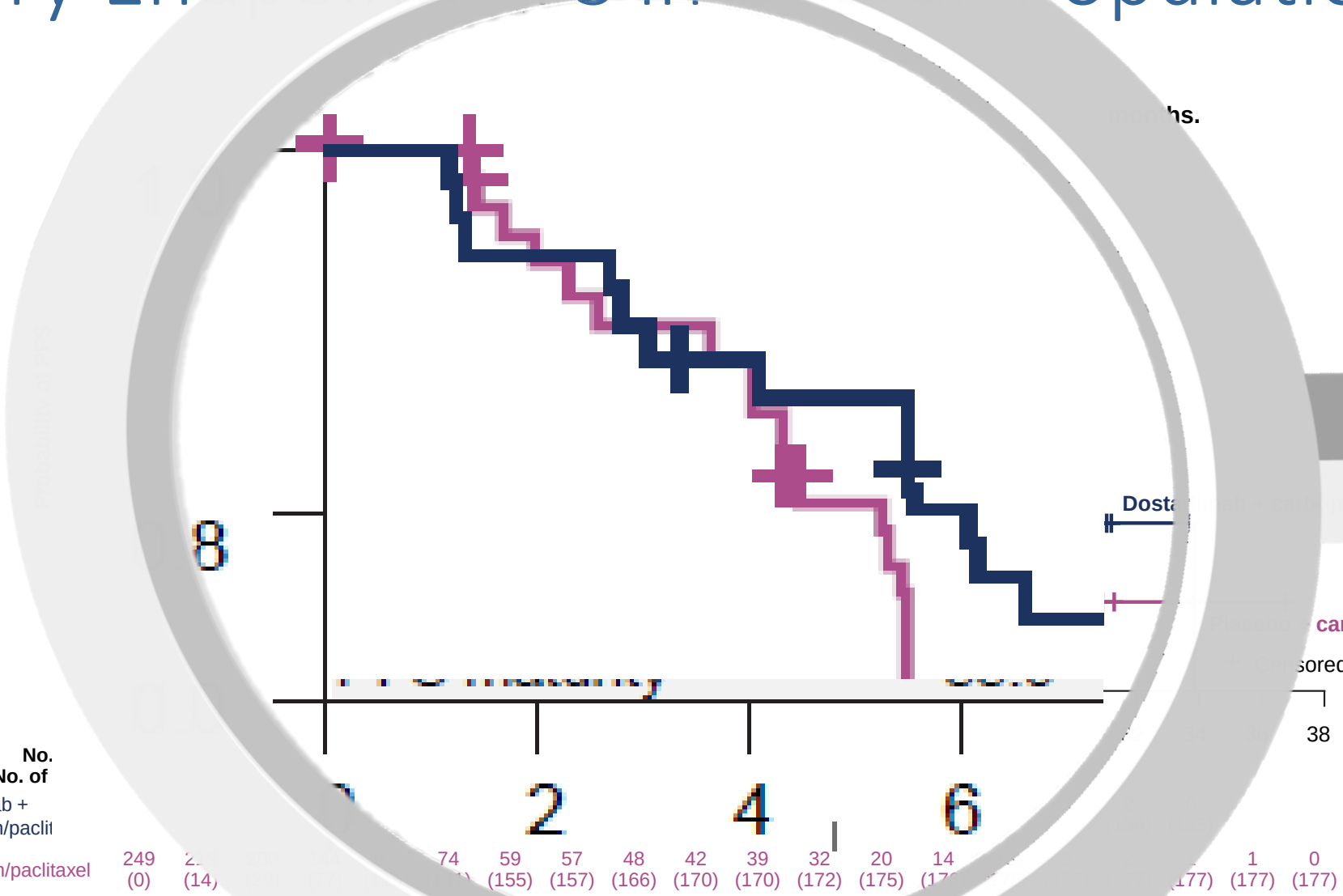
Primary Endpoint: PFS in the Overall Population

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



- Carbo = carboplatin; HR = hazard ratio; PFS = progression-free surviv

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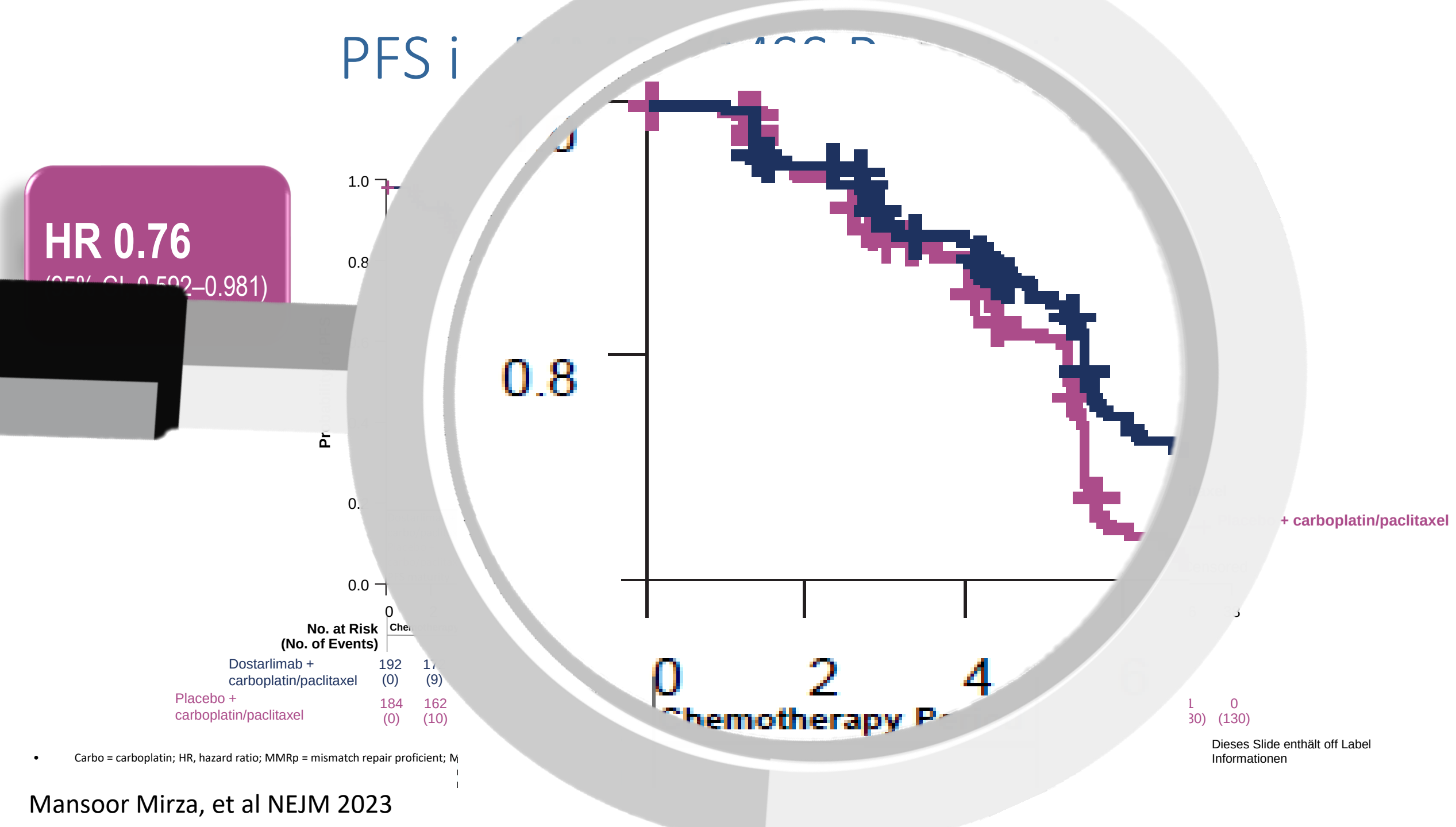
Mansoor Mirza, et al NEJM 2023

PFS i

HR 0.76
(95% CI, 0.592–0.981)



- Carbo = carboplatin; HR, hazard ratio; MMRp = mismatch repair proficient; M

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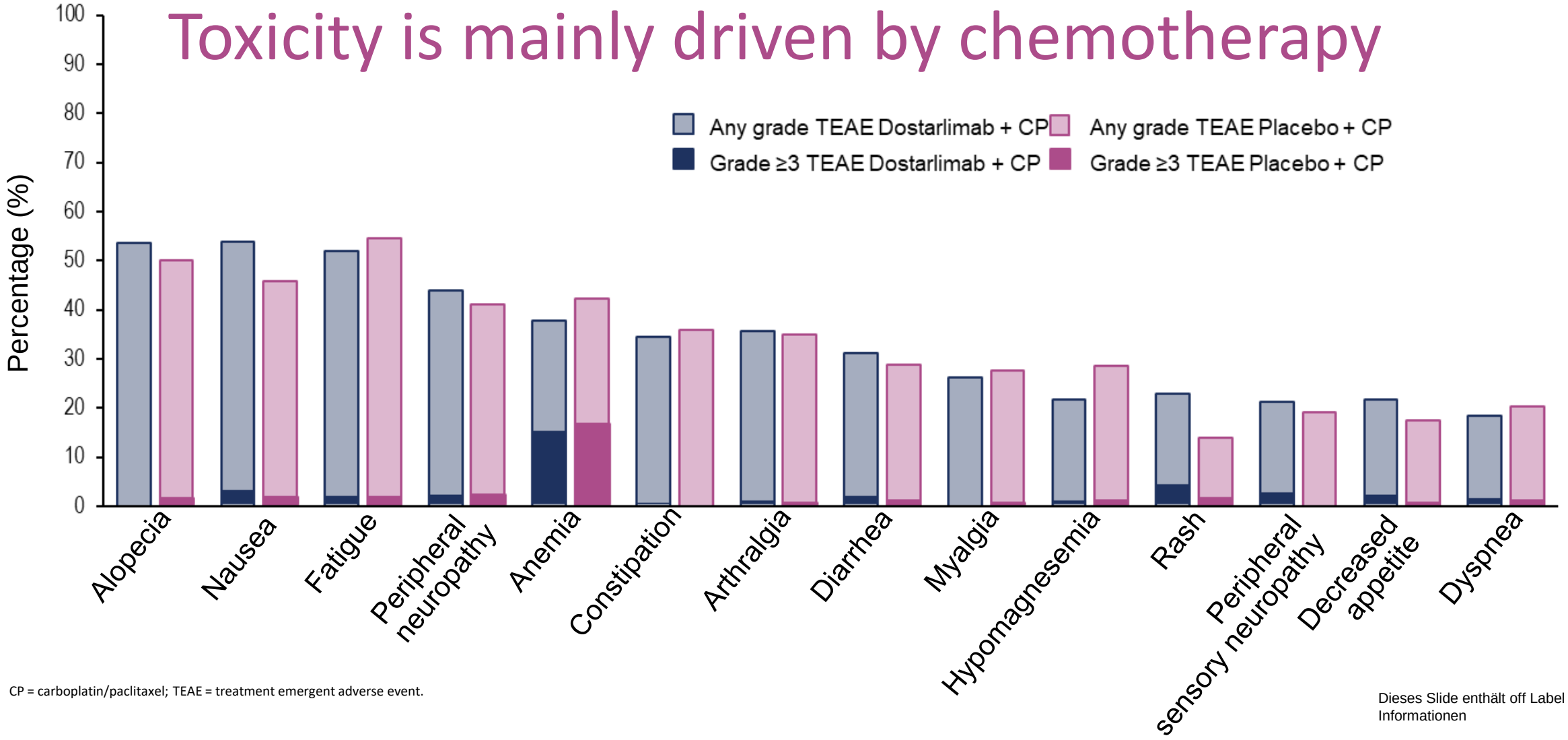
Mansoor Mirza, et al NEJM 2023

TEAEs in ≥20% of Either Arm

Toxicity is mainly driven by chemotherapy



CP = carboplatin/paclitaxel; TEAE = treatment emergent adverse event.

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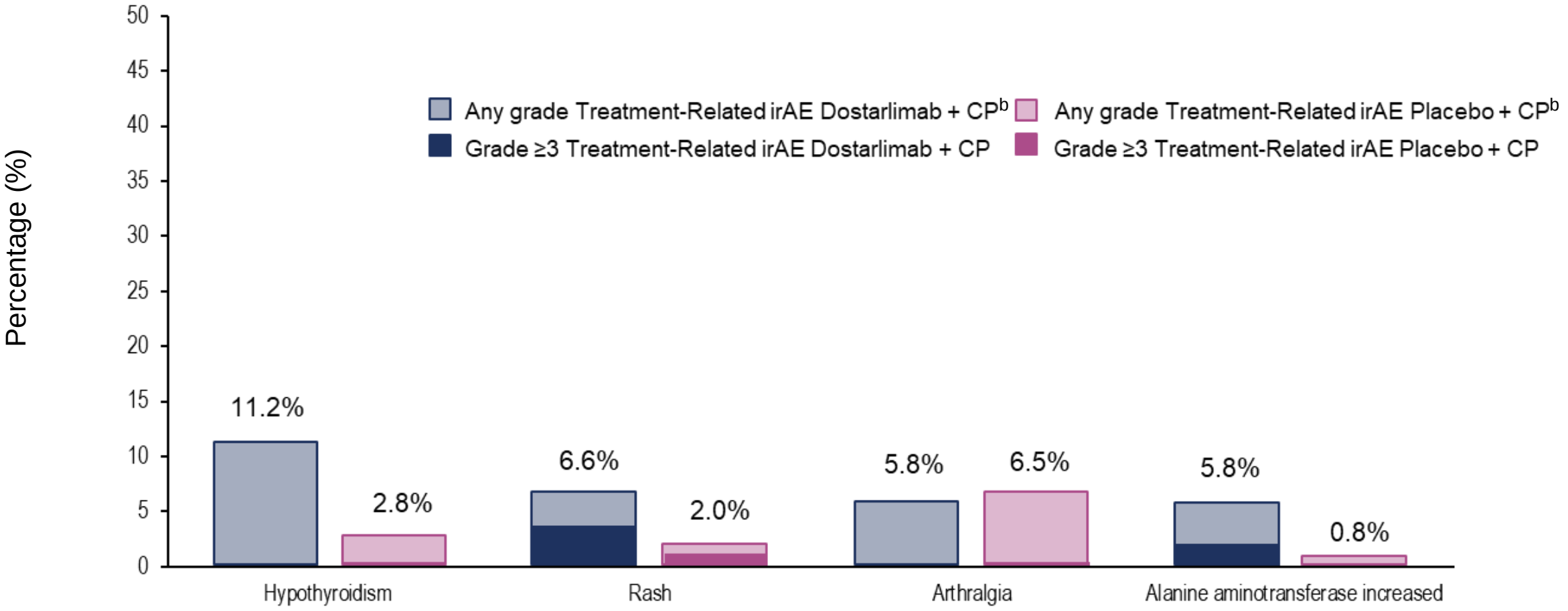
Mansoor Mirza, et al NEJM 2023

Treatment-Related irAEs in ≥5% of Either Arm[a]



[a]Allother irAEs that occurred did so at a frequency below 5% in either arm. [b]Immune-related AEs are defined as grade 2 and above from a predefined list.
AE = adverse event; ir = immune-related.

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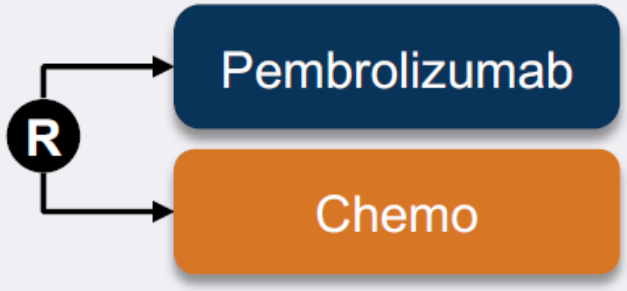
Mansoor Mirza, et al NEJM 2023

Moving Efforts to the Frontline: Immunotherapy vs. Chemotherapy

ENGOT-en15 KN-C93



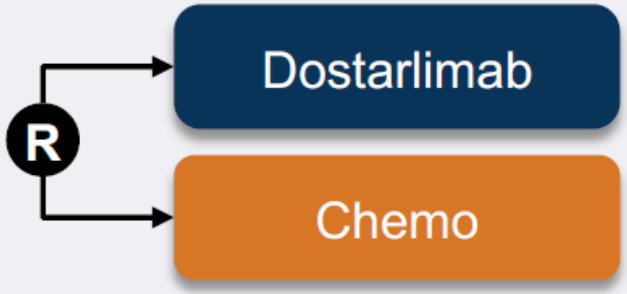
Primary endpoints:
PFS, OS

Key secondary endpoints:
ORR, DCR, DOR

Recruitment ongoing

dMMR patient population

ENGOT-en13 DOMENICA



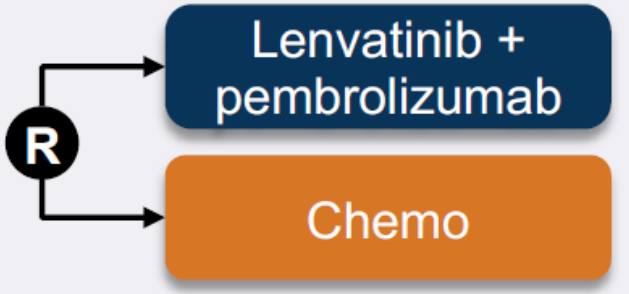
Primary endpoint:
PFS

Key secondary endpoints:
OS, PROs, ORR, DOR

Recruitment ongoing

dMMR patient population

ENGOT-en9 LEAP-001



Primary endpoints:
PFS, OS

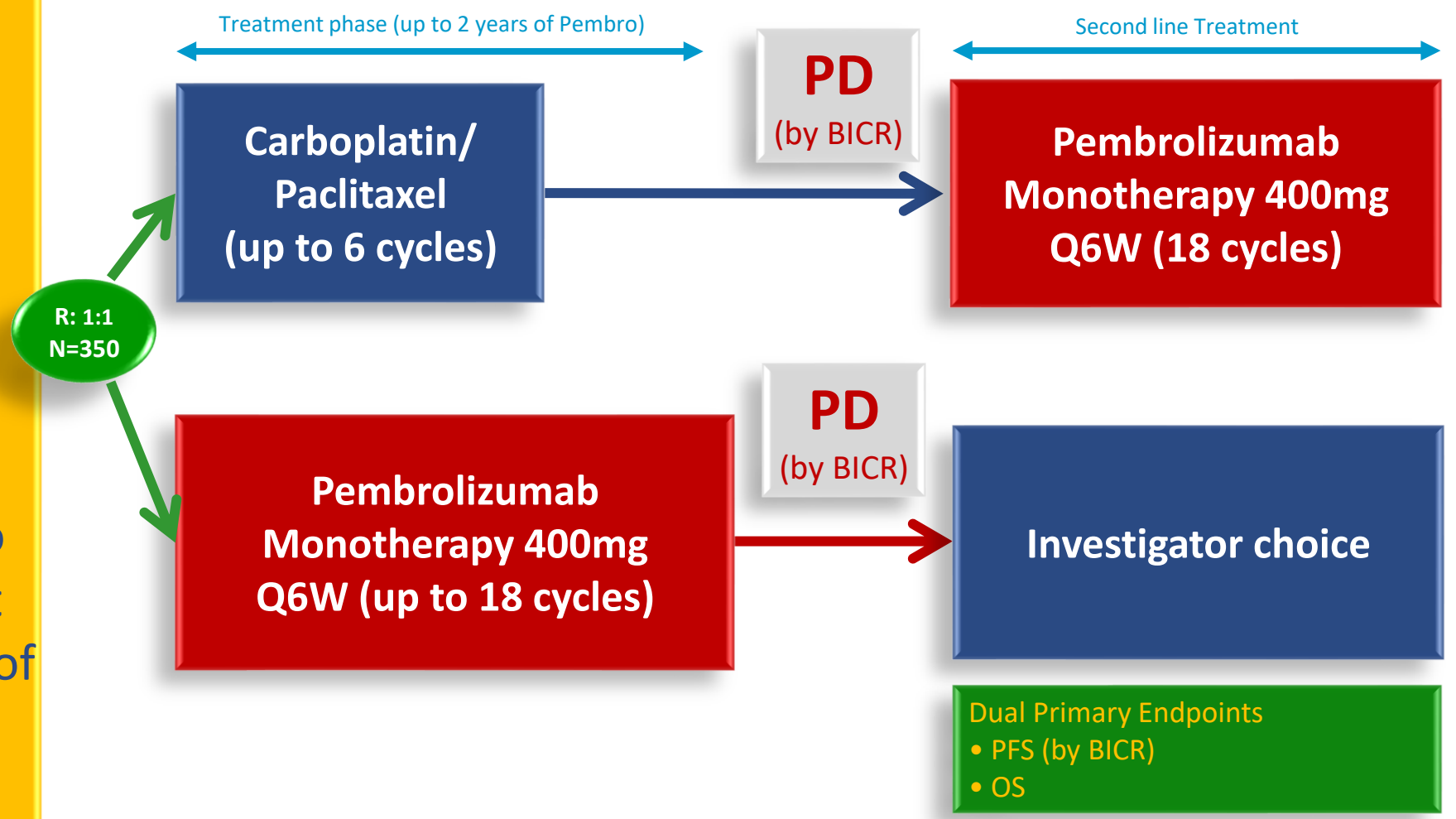
Key secondary endpoints:
ORR, HRQOL, safety

Completed enrollment

dMMR and pMMR patient populations

MK-3475-C93/KEYNOTE-C93/GOG-3064/ENGOT-en15
1L dMMR platinum doublet chemotherapy vs pembro with cross over

- Stage III or IV, persistent/ recurrent, or metastatic EC
- Measurable/non-measurable disease
- **dMMR**
- No previous chemo for adjuvant or first line except as part of radiosensitizing
- ECOG 0-1



ClinicalTrials.gov Identifier: NCT05173987

Domenica– Trial design and endpoints

Phase III Trial

ENGOT-en13

- Endometrial cancer
- MMR deficient (local IHC)
- Metastatic/ advanced
- Stage IV, Relapse or stage IIIC2 (with residual disease)

R 1:1

n= 142

n=71 — Dostarlimab 500 mg Every 3W / Dostarlimab 1000 mg every 6W — Up to 2 years or to progression*

n=71 — Carbo AUC5-Paclitaxel 175mg/m², 6 cycles → *Cross over allowed at progression (dostarlimab provided)*

Stratification factors:
- *CT adj/ yes– no*
- *Previous pelvic irradiation*

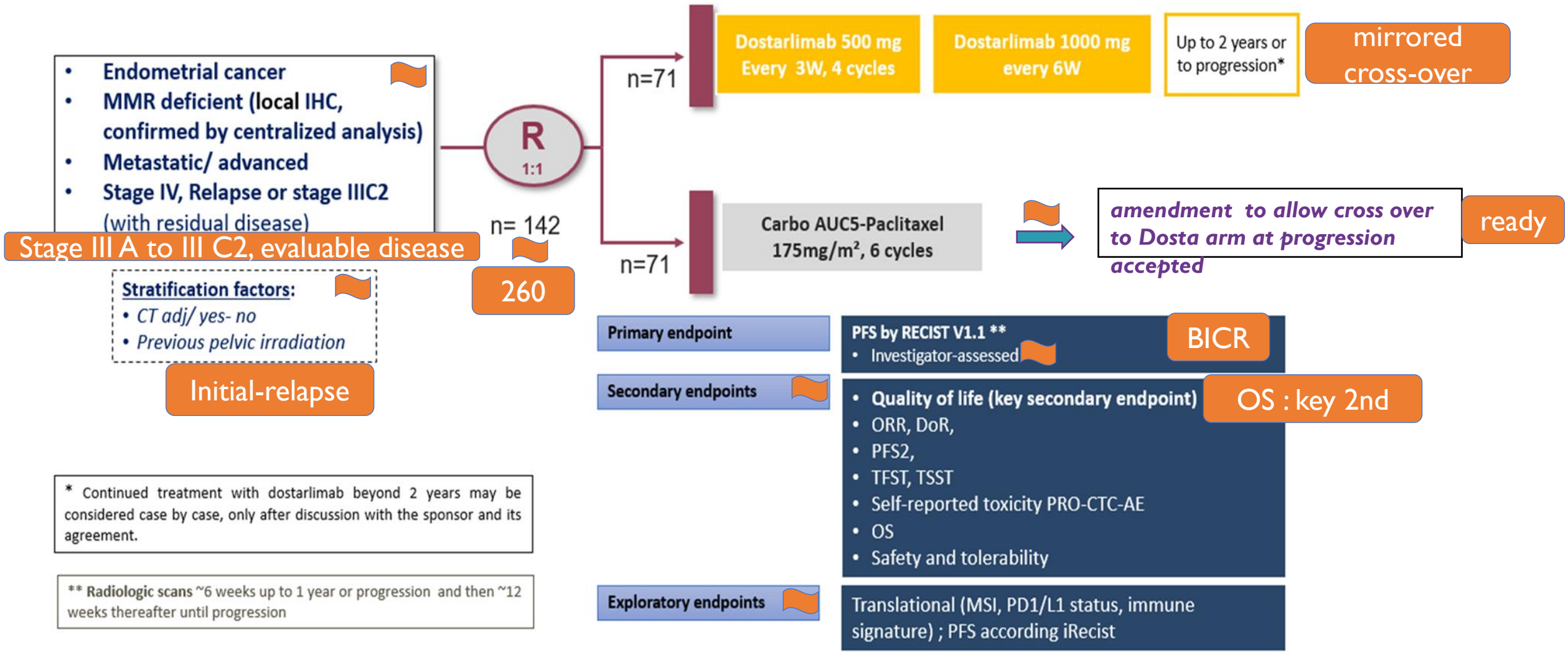
Primary endpoint	**PFS by RECIST V1.1 *** • Investigator–assessed
Secondary endpoints	• **OS and PROs** (key secondary endpoints) • ORR, DoR, • PFS2, • TFST, TSST • Safety and tolerability • Central MMR
Exploratory endpoints	Translational (MSI, PD1/L1 status, immune signature) ; PFS according iRecist

* **Radiologic scans** ~6 weeks up to 1 year or progression and then ~12 weeks thereafter until progression

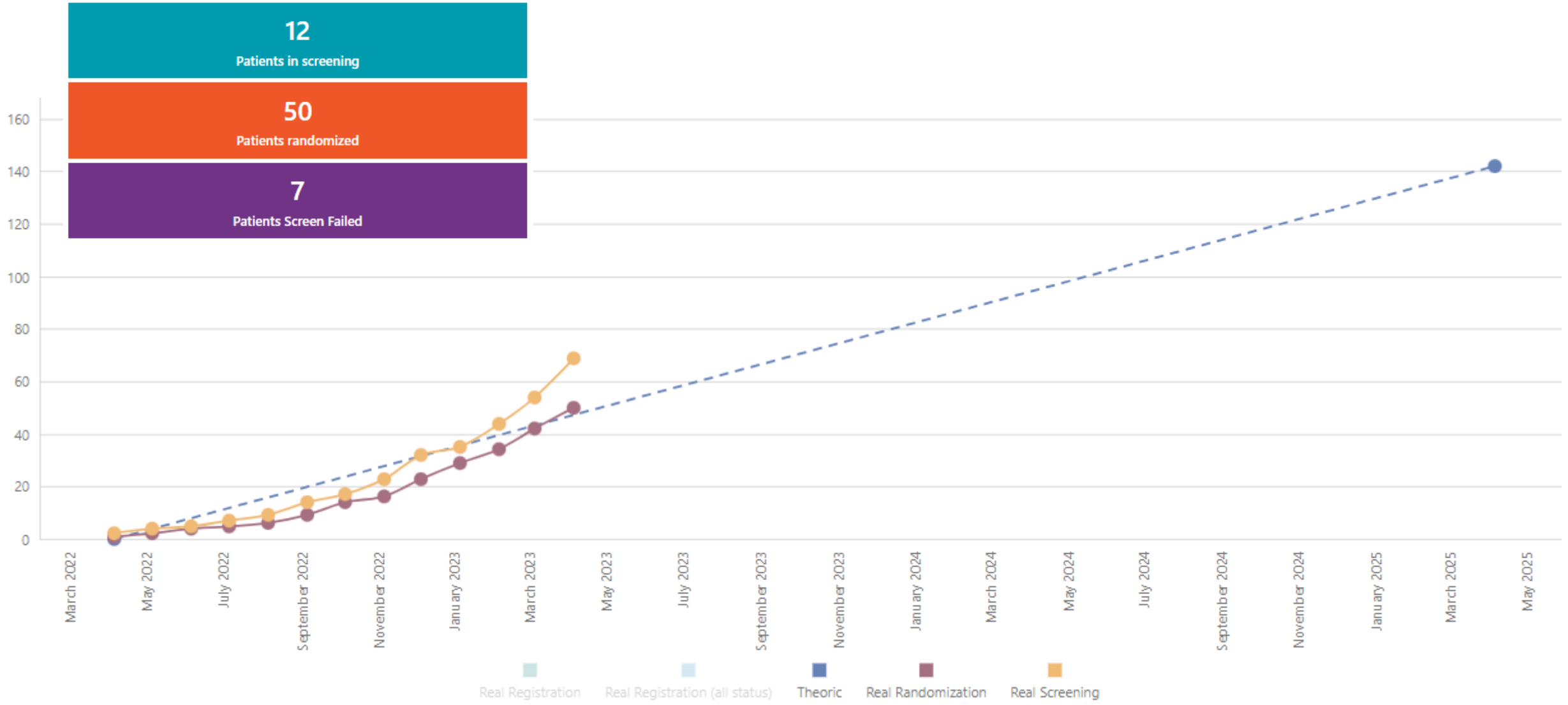
GINECO

New amendment under approval

Phase III Trial : initial design; new amendment : = In modification



Recruitment



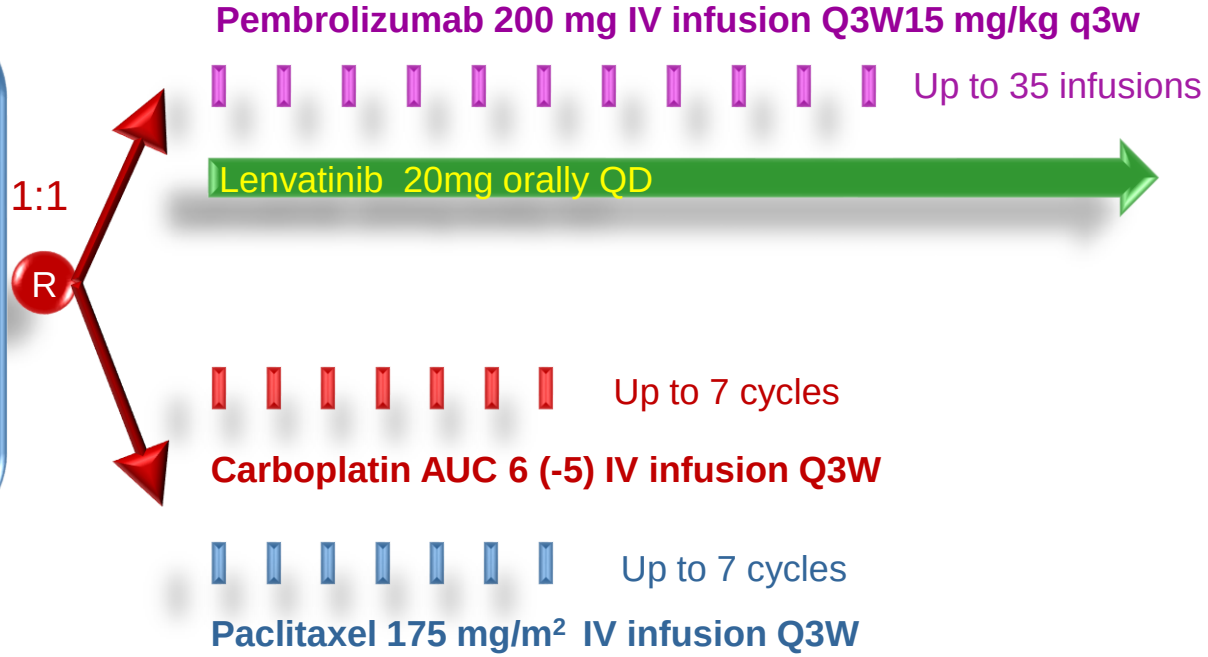
Global study progress

Group/country	Nb sites	Submission status	Nb patients screened	Nb patients randomised
GINECO / France	42	Initial approval received in Dec2021 Amdt 1 v2.0 approval received in Aug2022	68	49
AGO / Germany	8	Submitted in Dec2022	_	_
BGOG / Belgium	3	Migration to CTIS	_	_
GEICO / Spain	8	Initial approval received in Jul2022	1	1
MITO / Italy	11	Approval received in Apr2023	_	_
MaNGO/ Italy	10	Approval received in Apr2023	_	_
NCRI/ UK	10	In preparation	_	_
PMC / Canada	5	1st EC approval on Jan2023	_	_
ANZGOG / Australia	15	In preparation	_	_
GCGS / Singapore	2	In preparation	_	_
KGOG / S. Korea	7	In preparation	_	_
SAAK / Switzerland	10	In preparation	_	_
TRSGO / Turkey	6	Feasibility ongoing	_	_

ENGOT-en9/A-AGO: A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Persistent, Recurrent, or Metastatic Endometrial Carcinoma (LEAP-001)

Model C

- Stage III, IV or recurrent endometrial carcinoma
- No prior chemotherapy (except chemoradiation)
- ECOG 0 or 1
- 888 randomized patients



Stratify:

- MMR status (pMMR vs. dMMR)
  - If pMMR,
    - EGOG (0 versus 1)
    - Measurable disease (yes vs. no)
    - prior chemoradiation (yes vs. no)

Christian Marth et al. Int J Gynecol Cancer 2021

ENGOT-en9/A-AGO: A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Persistent, Recurrent, or Metastatic Endometrial Carcinoma (LEAP-001)

Model C

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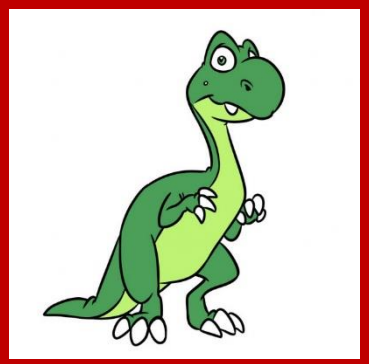
- No prior chemotherapy (except chemoradiation)
- ECOG 0 or 1
- 888 randomized patients

1:1

R

Chemotherapy-free

Immuntherapy + aAngio



Chemotherapy

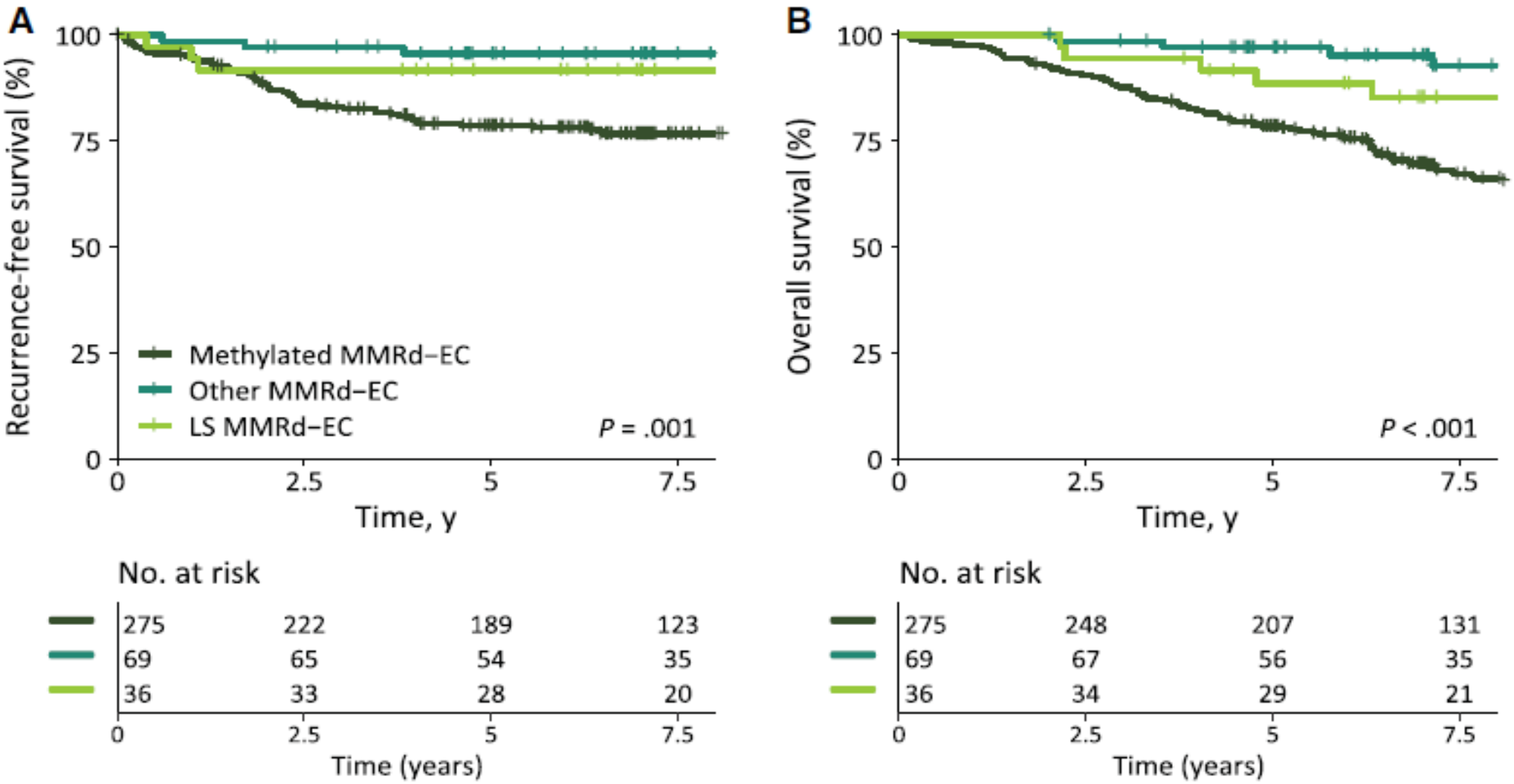
Stratify:

- MMR status (pMMR vs. dMMR)
  - If pMMR,
    - EGOG (0 versus 1)
    - Measurable disease (yes vs. no)
    - prior chemoradiation (yes vs. no)

ENGOT
European Network of Gynaecological Oncological Trial groups

Christian Marth et al. Int J Gynecol Cancer 2021

Prevalence and Prognosis of Lynch Syndrome and Sporadic Mismatch Repair Deficiency in Endometrial Cancer

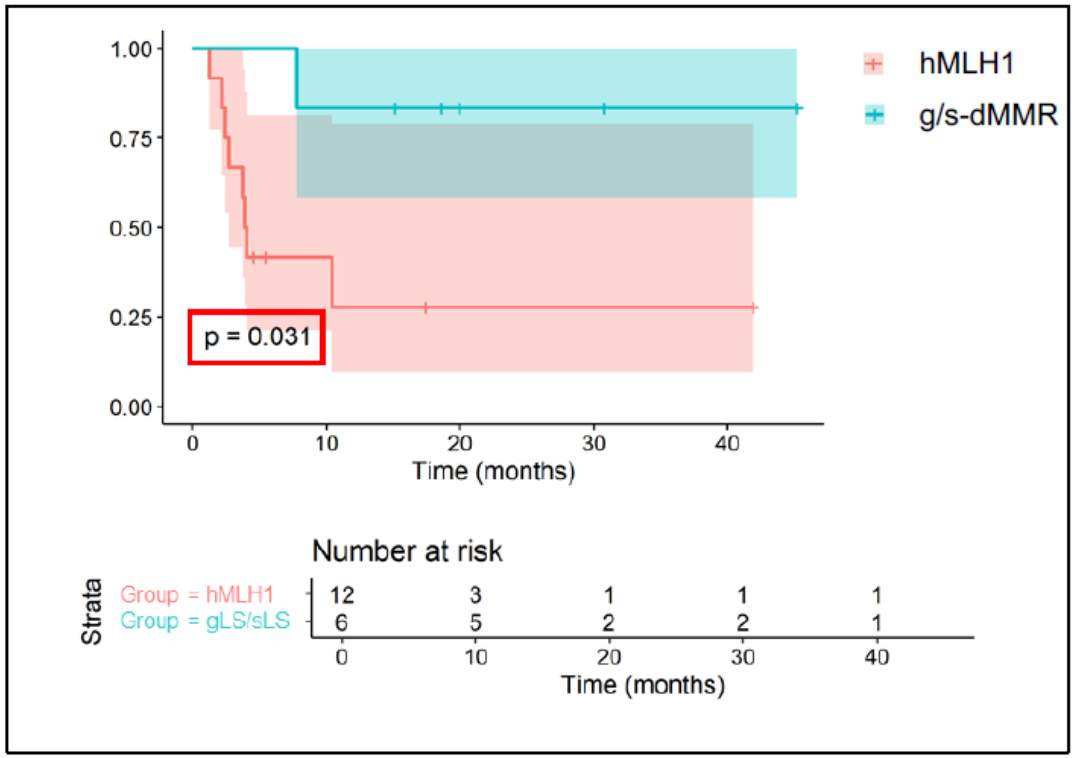


Note: Kaplan-Meier survival curves for recurrence-free survival (A) and overall survival (B) for patients with methylated mismatch repair deficient (MMRd), other MMRd and Lynch syndrome (LS) associated MMRd endometrial cancer (EC). All cases with MMRd phenotype are included in this analysis, including cases with a concurrent POLE variant affecting function (POLEmut-MMRd-EC). P values reflect 2-sided log-rank test.

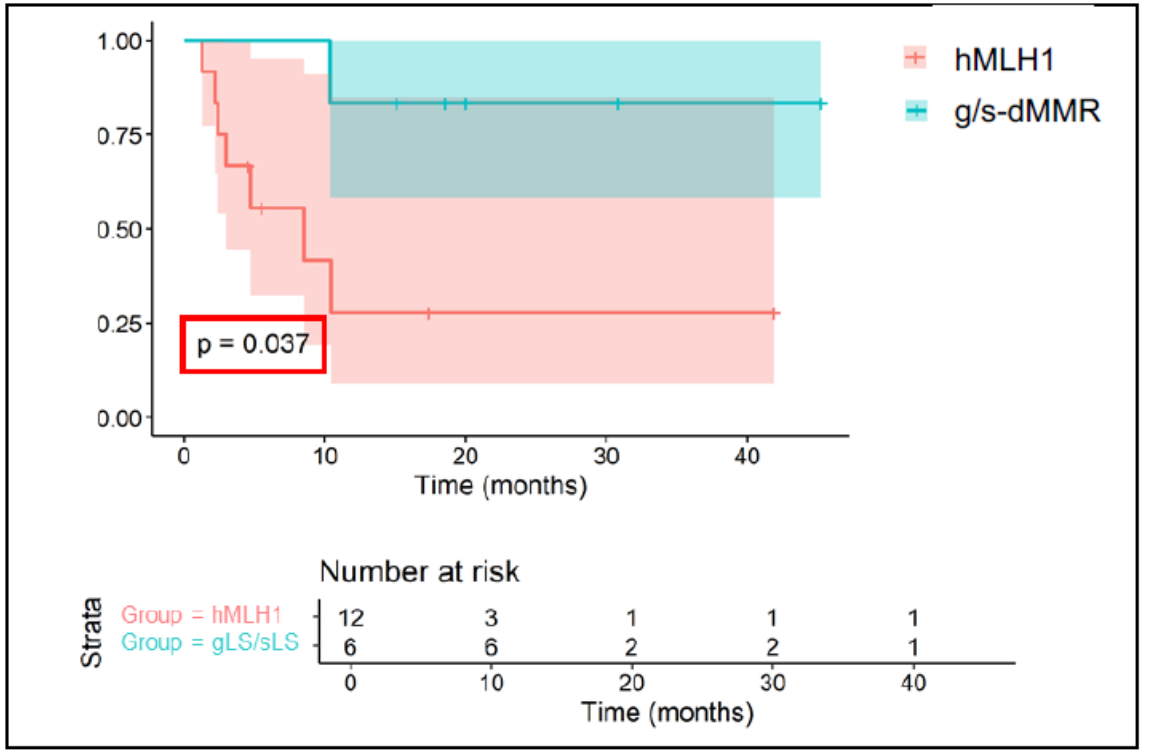
Cathalijne C.B.Post et al .JNCI J Natl Cancer Inst 2021

MLH1 hypermethylation predicts poor outcomes with pembrolizumab in recurrent endometrial cancer

Recurrence-free survival



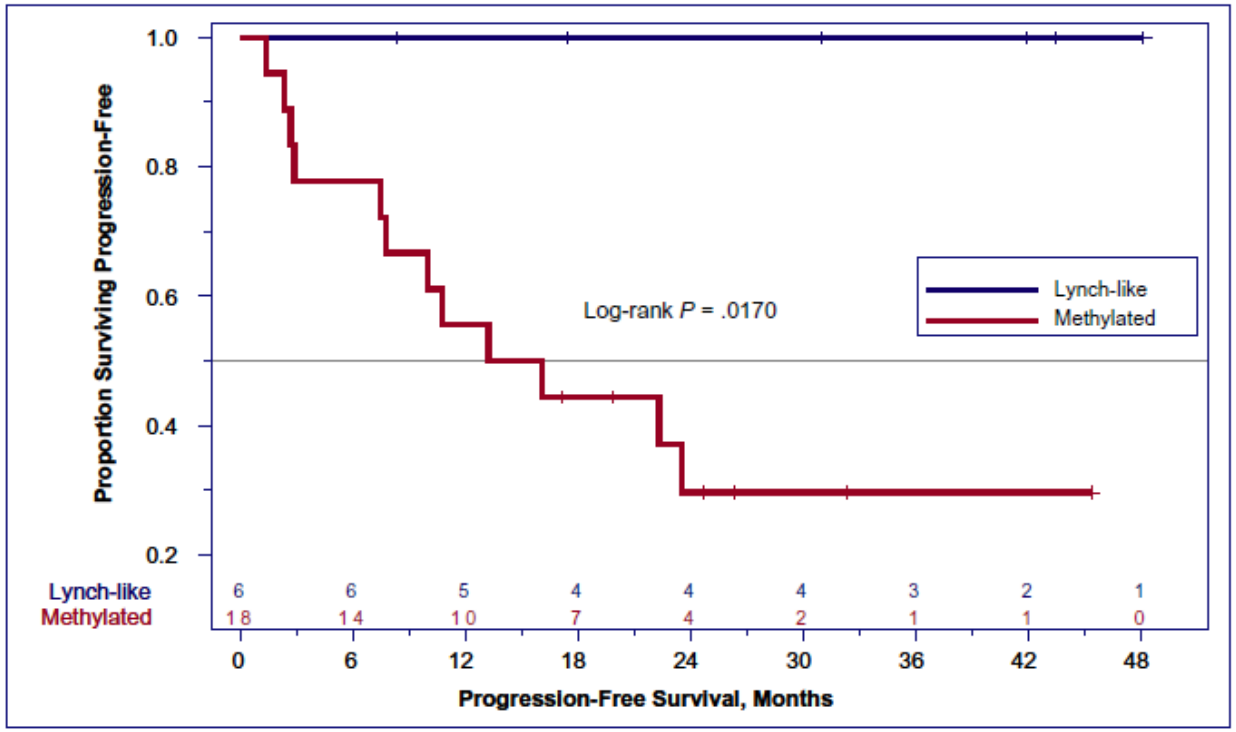
Overall survival

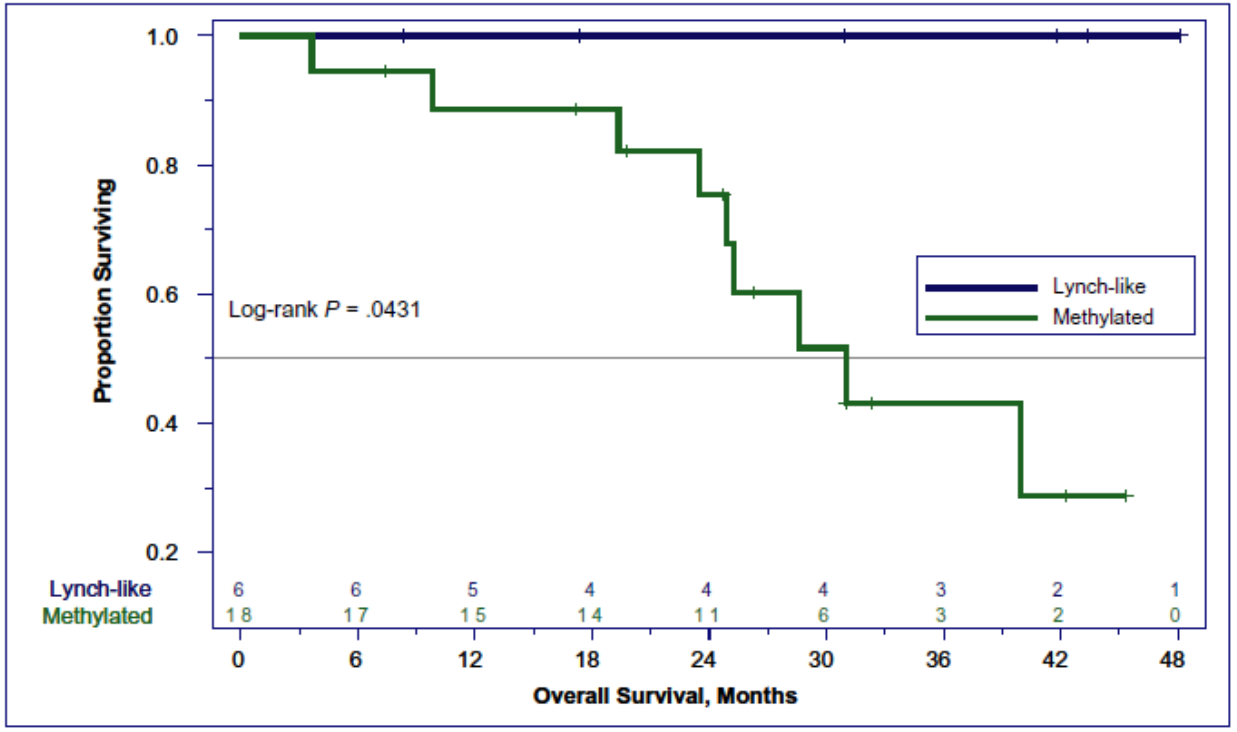


- MMRd endometrial cancer are a heterogenous group
- hMLH-1 tumors may not respond as robustly to immune checkpoint inhibitor single agent therapy

Lindsay Borden SGO 2022

A phase 2 evaluation of pembrolizumab for recurrent Lynch-like versus sporadic endometrial cancers with microsatellite instability





- 25 patients (24 evaluable) were treated with pembrolizumab . 6 (25%) harbored Lynch/Lynch-like tumors, whereas 18 (75%) had sporadic EC
- TMB was higher in Lynch-like (median 2939) versus sporadic tumors (median 604) (P <0.0076).

S Bellone et al. ***Cancer* 2022;128:1206-1218**

Post Hoc Analysis of Objective Response Rate by Mismatch Repair Protein Dimer Loss/Mutation Status in Patients with Mismatch Repair Deficient Endometrial Cancer Treated with Dostarlimab

- Most MLH1 loss was not accompanied by mutations, consistent with the estimated rate in the dMMR population[1-4]

	Patients, N	Responders, n	ORR, % (95% exact CI)	DOR median (95% CI), mo
Cohort A1 (dMMR/MSI-H EC)	143	65	45.5 (37.1–54.0)	NR (38.9–NR)
Cohort A1 patients with available mutation data	101	—	—	—
MLH1 loss by IHC (any pattern)[a]	78	31	39.7 (28.8–51.5)	NR (38.9–NR)
MLH1 loss by IHC (any pattern) and mutation in *MLH1* or *PMS2* genes	7 (9%)	3	42.9 (9.9–81.6)	NR (NR–NR)
MLH1 loss by IHC (any pattern) and no mutation in *MLH1* or *PMS2* genes	71 (91%)	28	39.4 (28.0–51.7)	NR (38.9–NR)

[a]Other: any other pattern of loss that is not exclusively MLH1–PMS2 or MSH2–MSH6 dimer loss. This group includes 17 patients with loss of expression of 1 MMR protein, 13 with loss of 3 proteins, 1 with loss of 2 proteins that are not a canonical dimer, and 2 with MMR unknown/MSI-H status. [b]This group includes 66 patients with loss of the MLH1–PMS2 dimer and 12 with another pattern.

dMMR, MMR deficient; EC, endometrial cancer; IHC, immunohistochemistry; MMR, mismatch repair; MSI-H, microsatellite instability–high.

1. Pasanen, A, et al. *Mod Pathol* 2020:33;1443–1452. 2. Kurpiel B et al. *Int J Gyn Path* 2022;41:1-11. 3. Buchanan DD, et al. *J Clin Oncol* 2014;32:90-100. 4. Kahn RM et al. *Cancer* 2019;125:3172-3183.

Tinker AV et al. Presented at the International Gynecologic Cancer Society (oral poster). September 29 - October 1, 2022; New York, USA

Conclusions

- Concept of chemo-free is appealing
- Avoidance of chemo toxicity: alopecia, neurotoxicity…
- Chemo-free immunotherapy for MMRd?
- POLE?
- Excluding MLH-1 promoter-hypermethylation?
- Combination with Lenvatinib for MMRp?
- Ongoing trials wrong control arm


. . . a bright future for endometrial cancer patients
christian marth

Thank you

NSGO