MEETING THE CHALLENGE AHEAD: PROGRESS AND UPDATES IN ENDOMETRIAL CANCER

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DDHO

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EMORY UNIVERSITY SCHOOL OF MEDICINE
Department of Gynecology and Obstetrics

DISCLOSURES

No relevant disclosures

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TALK OVERVIEW

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- Changing Landscape of Endometrial Cancer
- Unmet Need for Novel Therapies in Advanced Disease
- Immune Checkpoint Inhibitors in 1st Line and Beyond
- Targeted/ADC approaches
- Current Trials

ENDOMETRIAL CANCER ON THE RISE

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2026 Estimates

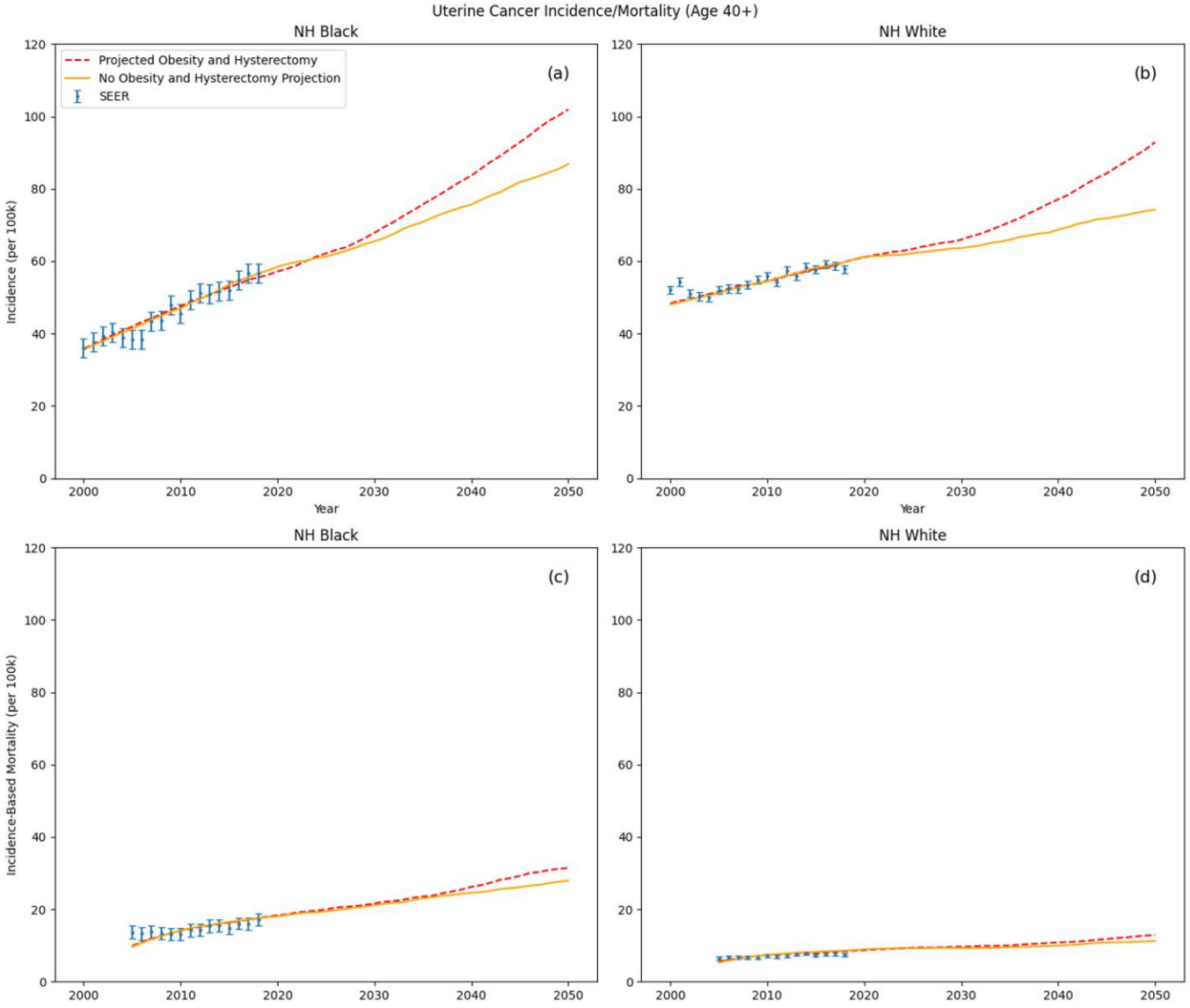
Female

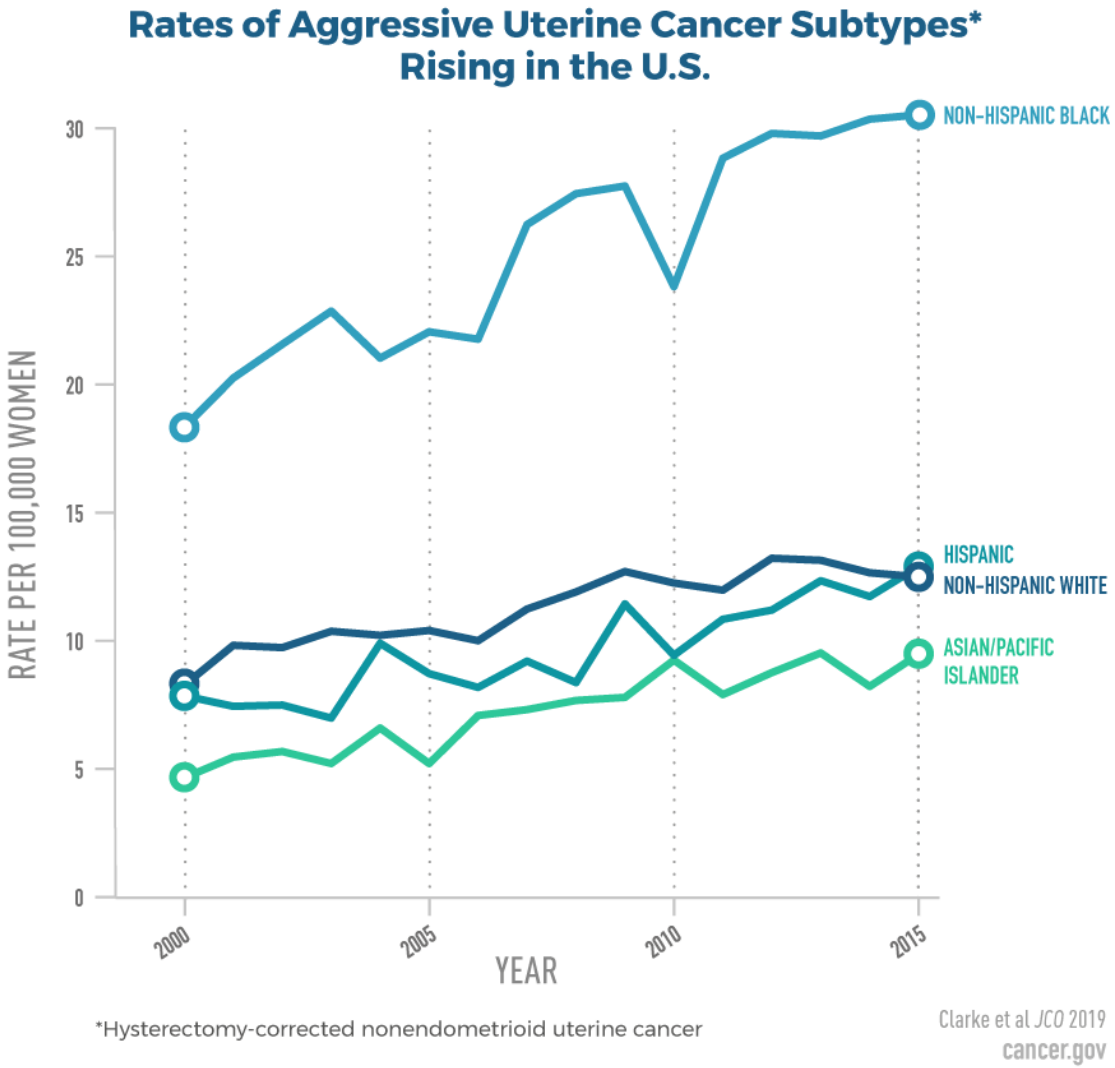
Breast	321,910	32%
Lung & bronchus	118,500	12%
Colon & rectum	74,690	7%
Uterine corpus	68,270	7%
Melanoma of the skin	46,600	5%
Non-Hodgkin lymphoma	35,550	3%
Pancreas	32,340	3%
Thyroid	32,000	3%
Kidney & renal pelvis	29,680	3%
Leukemia	28,720	3%
All sites	**1,020,780**	

Female

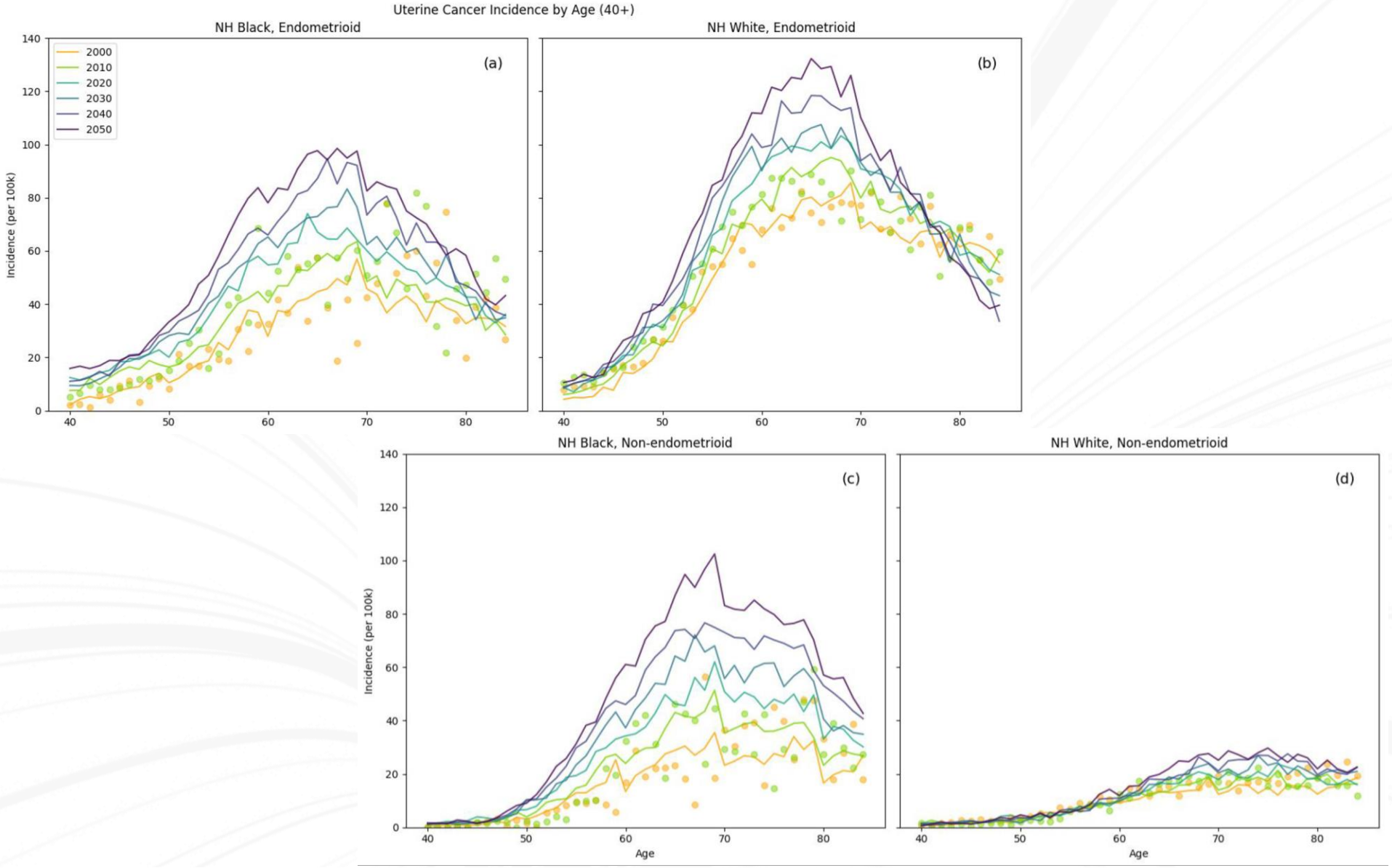
Lung & bronchus	61,950	21%
Breast	42,140	14%
Pancreas	25,510	9%
Colon & rectum	25,120	8%
Uterine corpus	14,450	5%
Ovary	12,450	4%
Liver & intrahepatic bile duct	11,330	4%
Leukemia	10,010	3%
Brain & other nervous system	8,380	3%
Non-Hodgkin lymphoma	8,260	3%
All sites	**298,850**	

ENDOMETRIAL CANCER ON THE RISE





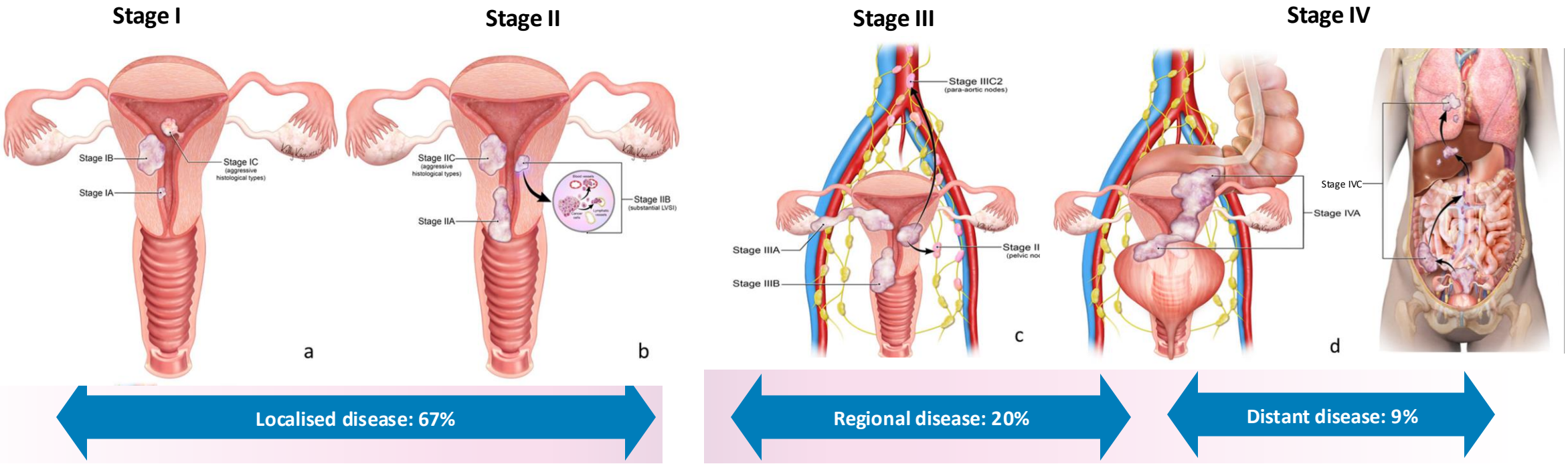
ENDOMETRIAL CANCER ON THE RISE



HETEROGENEITY AND CLASSIFICATION OF ENDOMETRIAL CANCER

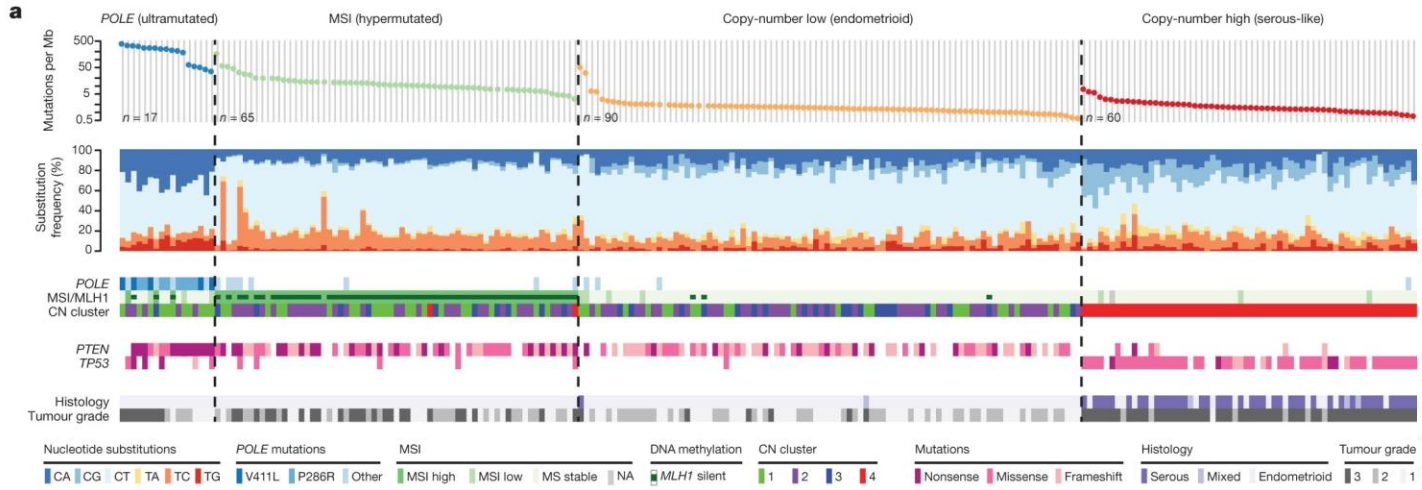
HISTORICAL STAGING CLASSIFICATIONS (TNM AND FIGO) DIFFERENTIATE TUMOR STAGE ACCORDING TO ANATOMIC RISKS: DEPTH OF INVASION AND PRESENCE OF METASTASES

Endometrial cancer staging is a powerful indicator of prognosis, with good outcomes for those diagnosed with local or regional disease but poor outcomes for those with distant disease



5-year relative survival by stage at diagnosis

MOLECULAR CLASSIFICATION OF ENDOMETRIAL CANCER DEFINED



Levine et. al Integrated genomic characterization of endometrial carcinoma 2013

1 POLE-mutated	2 MSI-high (MMRd)	3 CN-low (NSMP; P53wt)	4 CN-high (P53abn)
• POLE exonuclease domain variation • Ultra-mutated • Tumours have brisk lymphocytic infiltration • Highly responsive to IO • Excellent prognosis with low rates of recurrence	• Hypermutated: *PTEN, ARID1A, PIK3CA, PIK3R1* and *RPL22* commonly mutated • MMR defects • Unusual histological morphology but are uniformly endometrioid tumours • Extensive tumour-infiltrating lymphocytes • Highly responsive to IO	• Variants common in *PTEN, CTNNB1, PIK3CA, KRAS* and *ARID1A* • MSS • Uniformly contains endometrioid tumours of generally low grade • *CTNNB1* mutations are associated with a worse outcome than expected from these tumours with favourable histopathological features	• *TP53* mutations common • *CCNE1* amplification common • High-grade, aggressive cancers including uterine serous carcinomas and ~25% of high-grade endometrioid tumours • Higher relapse rate • Poor overall survival

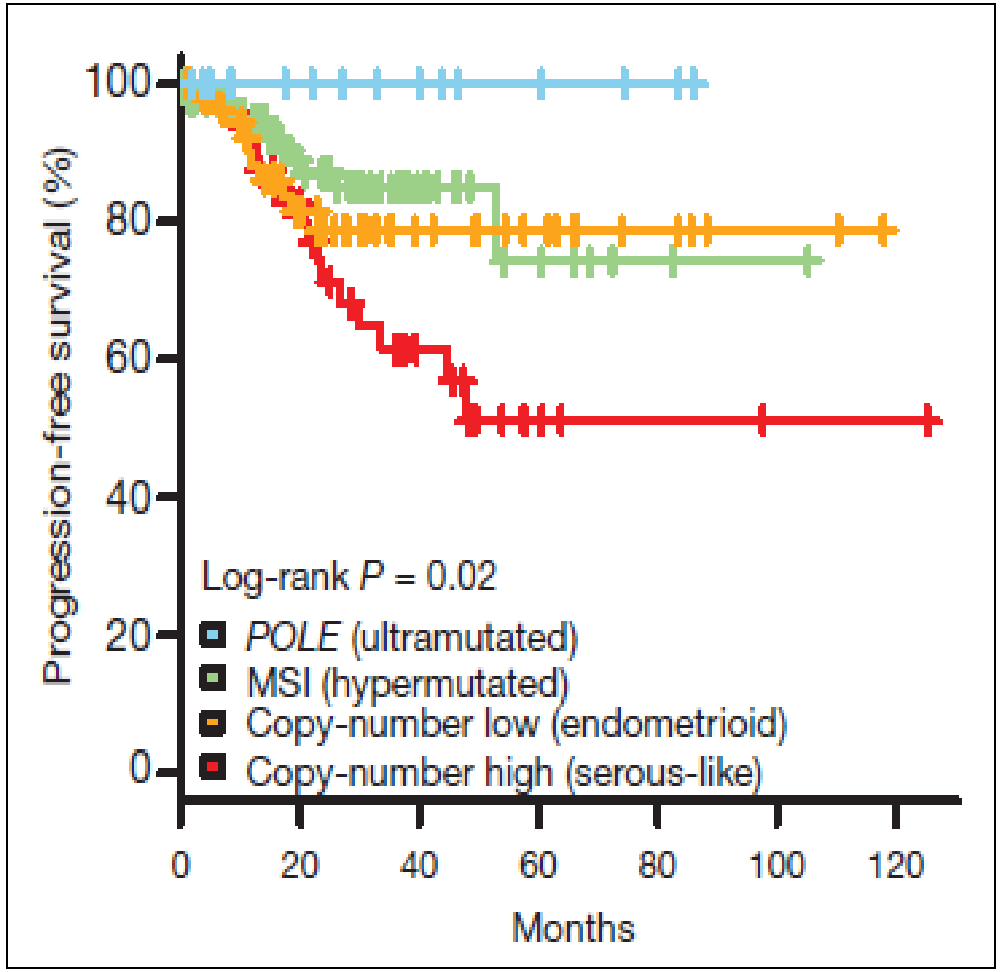
CN=copy number; IO=immuno-oncology; MMR(d)=mismatch repair deficient; MSI=microsatellite instability; MSS=microsatellite stable; NSMP=no specific molecular profile; *P53abn=P53* abnormal; TCGA=The Cancer Genome Atlas.

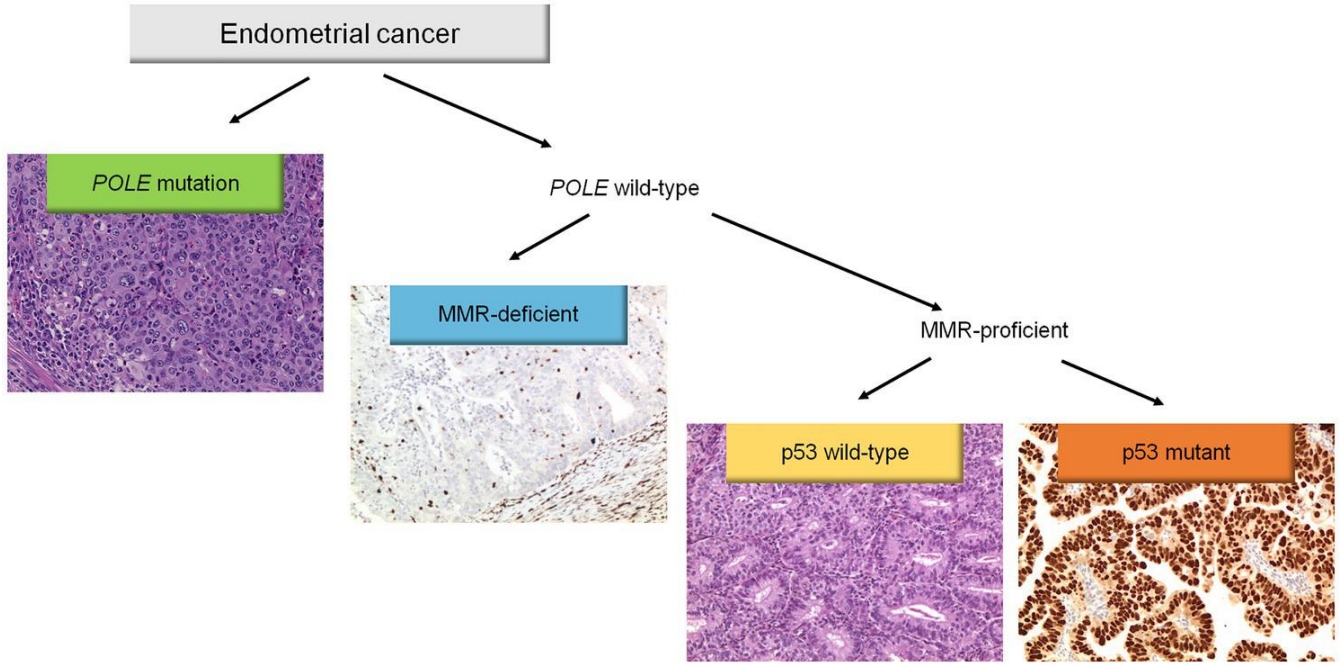
1. Openshaw M & McVeigh T. *Front Digit Health*. 2020;2:573010; 2. Makker V, et al. *Nature Rev Dis Primers*. 2021;7:88; 3. Slomovitz B. Presented at ESMO Gynaecological Cancers Annual Congress. 23–24 February 2023. Barcelona, Spain.

MOLECULAR CLASSIFICATION OF ENDOMETRIAL CANCER DEFINED

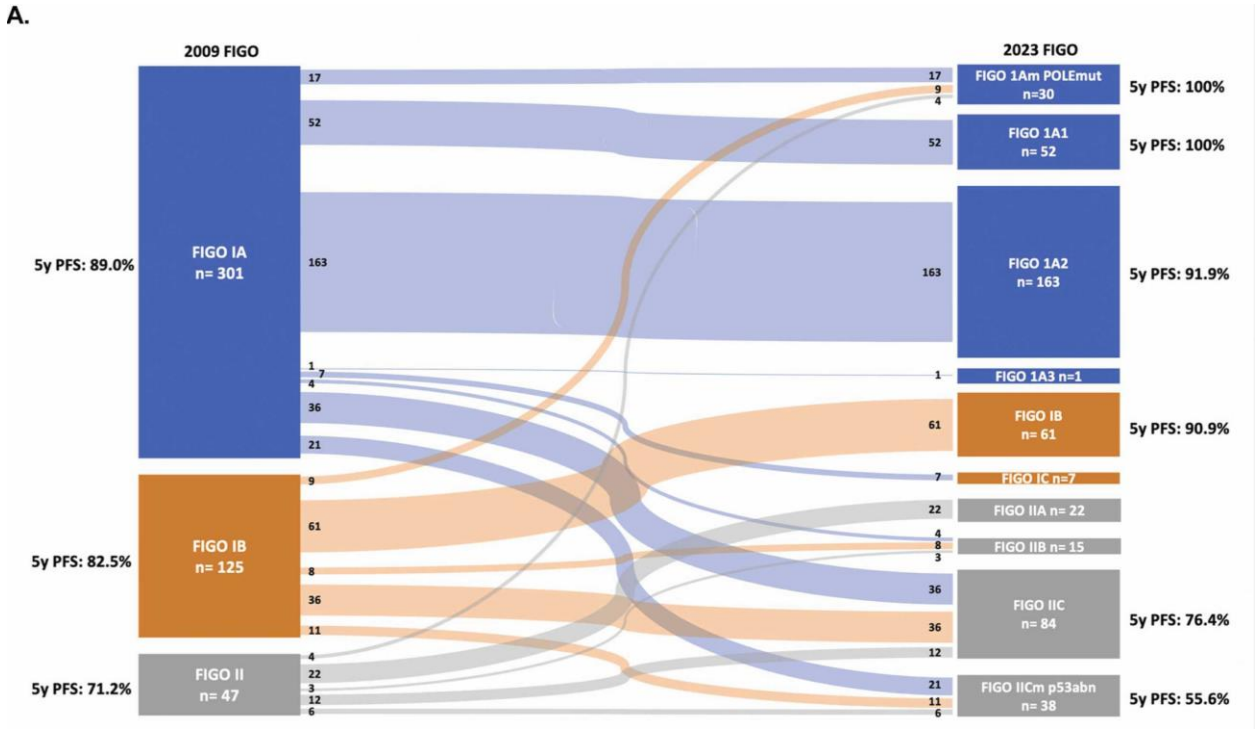
Molecular subtypes correlate with clinical outcome and are being used on and off trial to triage different treatment strategies

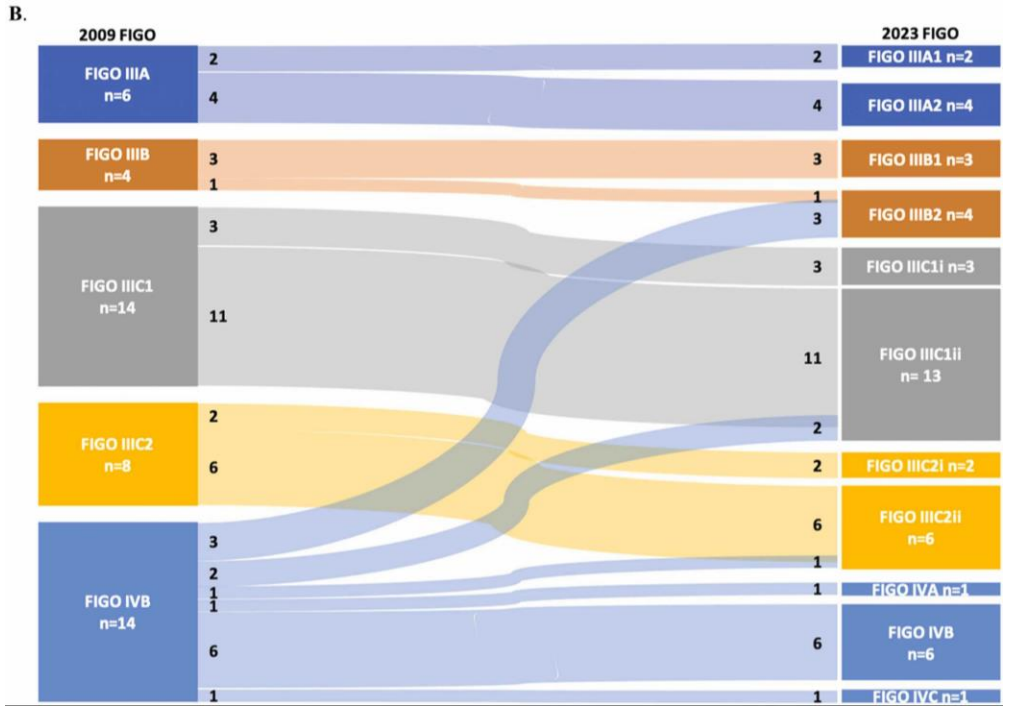
TCGA Group Nature 2011





STAGE MIGRATION WITH INCORPORATION OF MOLECULAR CLASSIFICATION





People are classed as low, intermediate, high-intermediate, or high-risk of relapse, based on FIGO stage and grade, depth of myometrial invasion, presence of LVSI* and molecular grouping1

IMMUNOTHERAPY IN ENDOMETRIAL CANCER

Recent Phase III trials

- NRG GY-018: Advanced/Recurrent, Chemo + Dostarlimab
- RUBY 1: Advanced/Recurrent, Chemo + Pembrolizumab
- Keynote B21: Early High-Risk, surgically resected, Chemo + Pembrolizumab

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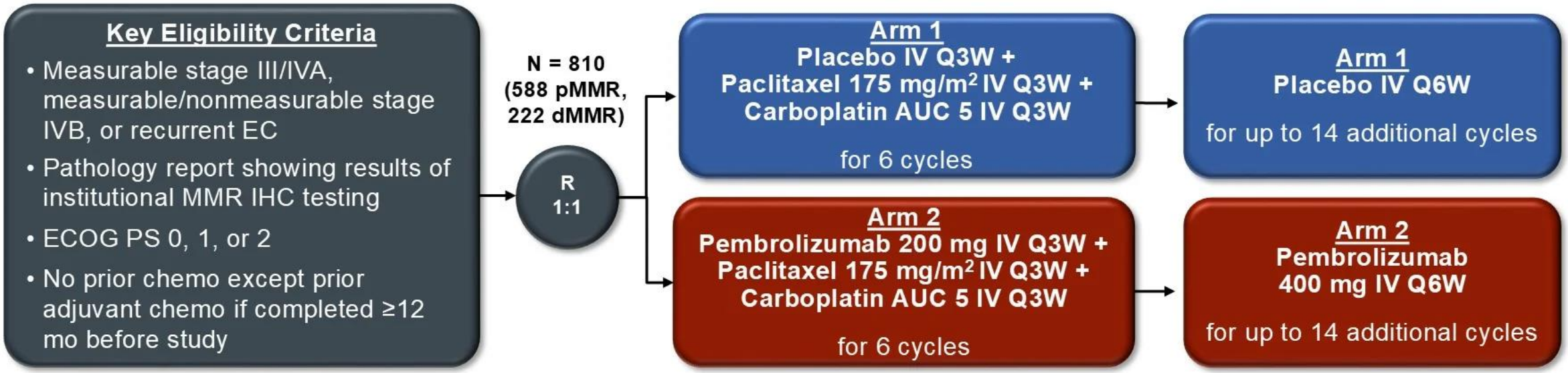
Study Design of NRG-GY018 (NCT03914612): Phase 3, Randomized, Placebo-Controlled



Stratification Factors

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

Unblinding

- Occurred at PD, for safety concerns due to COVID-19, and at interim analysis data presentation
- There was near ubiquitous availability of pembrolizumab and lenvatinib + pembrolizumab for all participants

Endpoints

- **Primary:** PFS per RECIST v1.1 by investigator in pMMR and dMMR cohorts
- **Focus of current long-term follow-up analysis:**
  - Updated OS in dMMR and pMMR cohorts[a]
  - Poststudy ICI therapy in dMMR and pMMR cohorts[a]

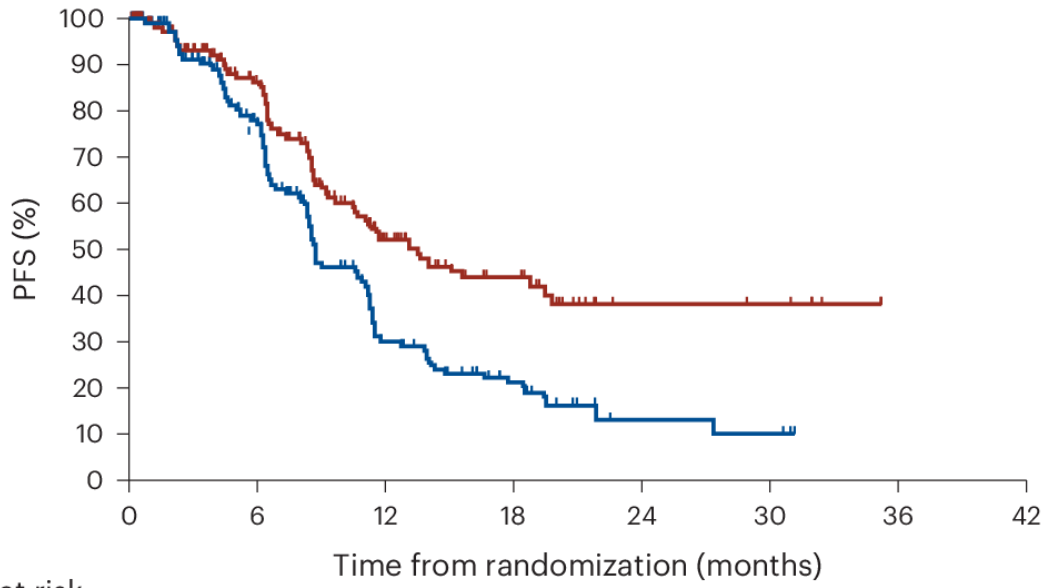
[a]MMR status as randomized.

THE ROLE OF IMMUNOTHERAPY IN ENDOMETRIAL CANCER: NRG GY-018

GY-018: a,**b**, PFS per RECIST v.1.1 in the pMMR (**a**) and dMMR (**b**) populations.

a

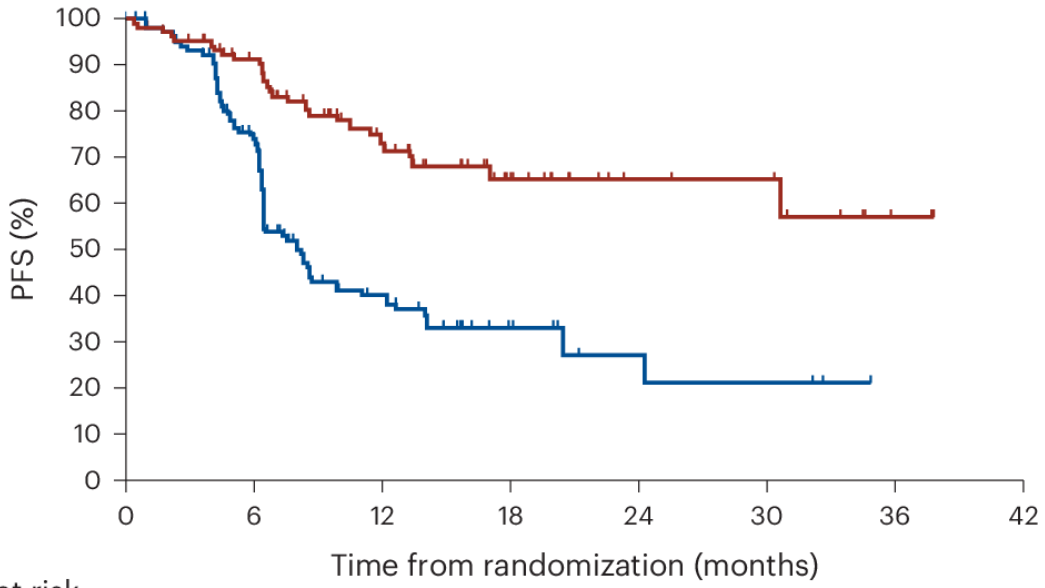
	Events, *n*/*N*	Median PFS (95% CI), months	HR (95% CI)[a], *P* value[b]
Pembrolizumab + CT	95/294	13.1 (10.6–19.5)	0.57 (0.44–0.74)
Placebo + CT	138/294	8.7 (8.4–11.0)	*P* < 0.0001



Number at risk								
Pembrolizumab + CT	294	162	57	29	7	6	0	0
Placebo + CT	294	144	36	15	4	3	0	0

b

	Events, *n*/*N*	Median PFS (95% CI), months	HR (95% CI)[a], *P* value[b]
Pembrolizumab + CT	29/110	NR (30.7–NR)	0.34 (0.22–0.53)
Placebo + CT	60/112	8.3 (6.5–12.3)	*P* < 0.0001

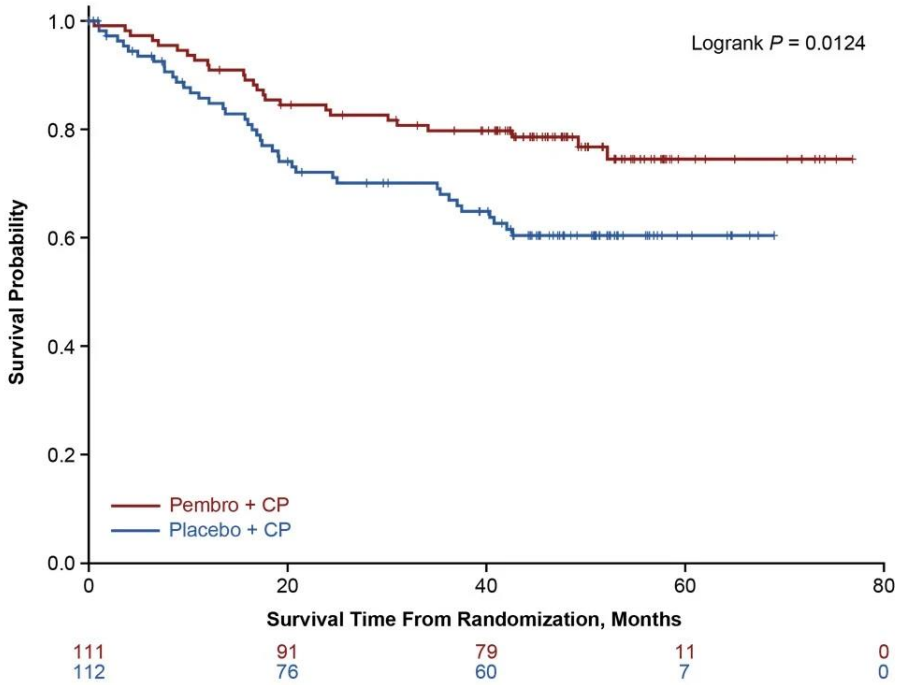


Number at risk								
Pembrolizumab + CT	110	85	45	24	10	9	2	0
Placebo + CT	112	69	25	9	4	3	0	0

Eskander, R.N., Sill, M.W., Beffa, L. *et al*. Pembrolizumab plus chemotherapy in advanced or recurrent endometrial cancer: overall survival and exploratory analyses of the NRG GY018 phase 3 randomized trial. *Nat Med* **31**, 1539–1546 (2025). https://doi.org/10.1038/s41591-025-03566-1

THE ROLE OF IMMUNOTHERAPY IN ENDOMETRIAL CANCER: NRG GY-018

Extended Follow-Up Suggests OS Benefit for Pembrolizumab + CP in the dMMR Cohort



	Pembro + CP	Placebo + CP
Events, n/N	25/111	40/112
Median OS	**Not reached**	**Not reached**
Survival at 24 mo (95% CI), %	83.5 (75.2–89.3)	72.1 (62.4–79.7)
Survival at 36 mo (95% CI), %	79.7 (70.9–86.2)	68.0 (58.0–76.1)
Survival at 48 mo (95% CI), %	78.6 (69.6–85.2)	60.4 (50.0 – 69.2)
HR (95% CI)[a]	**0.56 (0.34–0.92)**	

- Information fraction of 43.3%
- Median follow-up across both treatment arms was 49 months
- Amongst participants receiving poststudy therapy, **93.2% of patients in the control arm received an ICI**

[a]Based on Cox regression model stratified by ECOG PS and prior adjuvant chemo.

Proportion of participants who withdrew study consent: Pembro + CP = 5.4%; Placebo + CP = 7.1%

PRESENTED BY: Ramez N. Eskander, MD

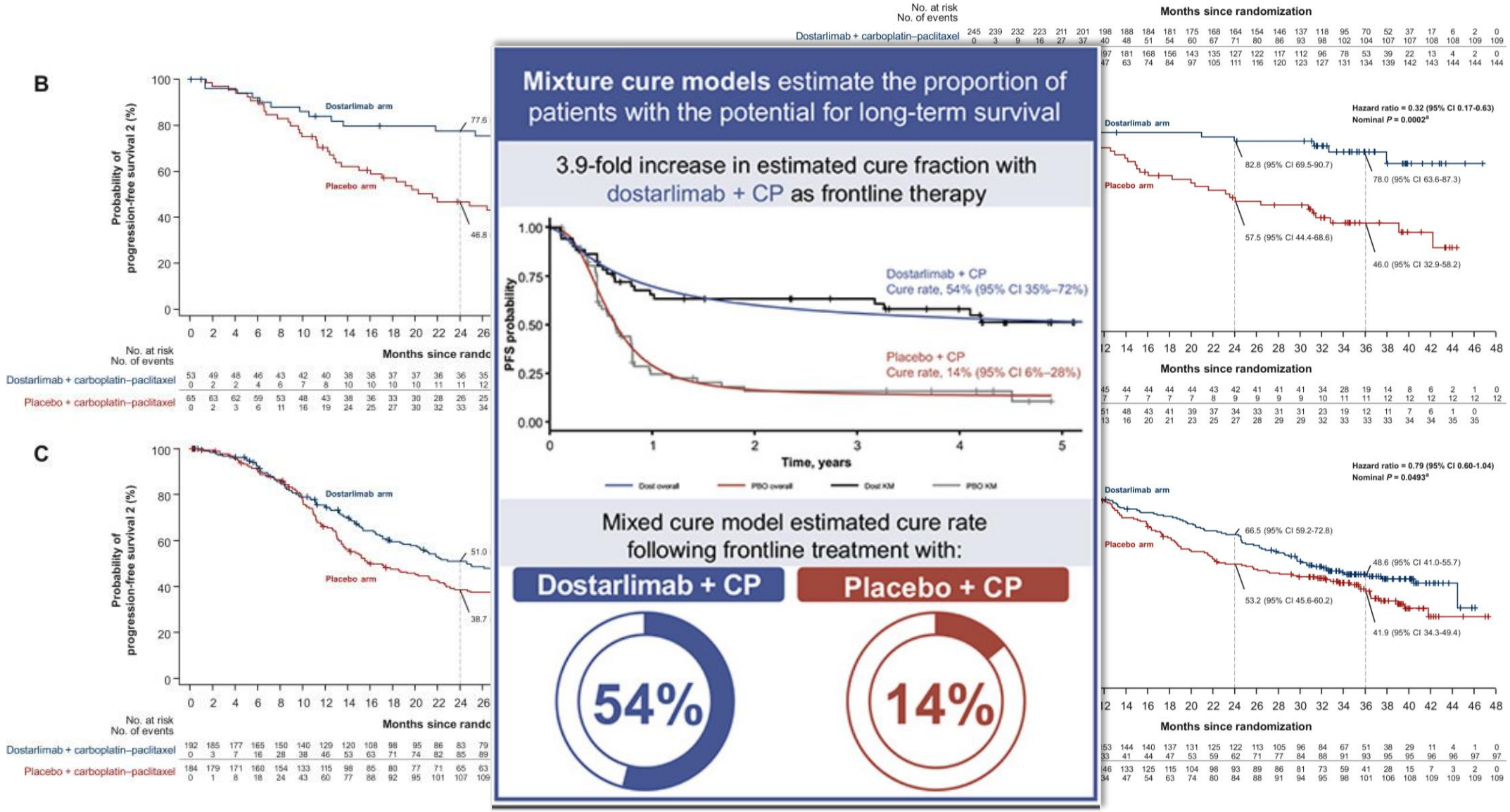
THE ROLE OF IMMUNOTHERAPY IN ENDOMETRIAL CANCER: NRG GY-018

pMMR: pembrolizumab OS advantage- not statistically significant

- Median OS: 46.9 versus 35.1 months
  - 11.8-month difference favoring pembrolizumab + CP
- HR: 0.86 (95% CI, 0.69–**1.08**)

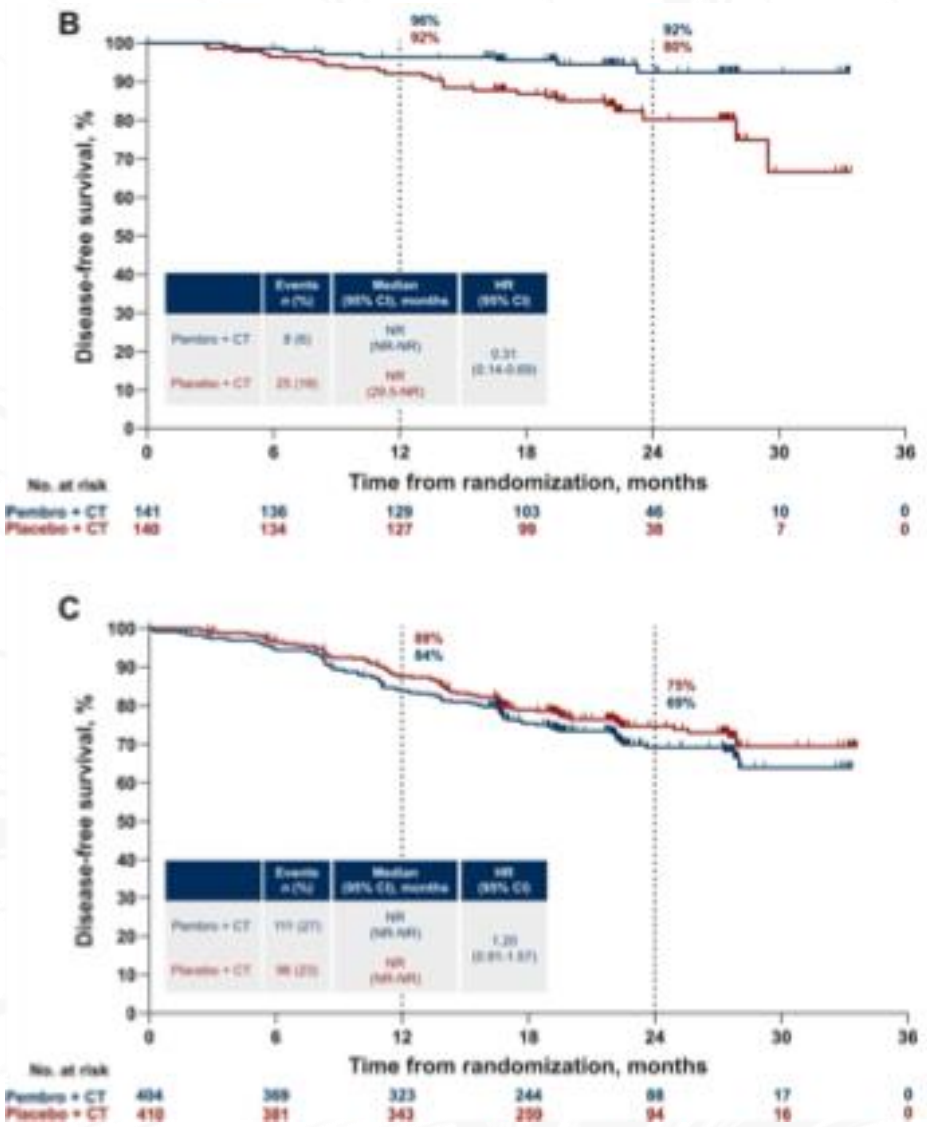
- Advantage persists despite heavy crossover
  - 93% of control-arm patients received post-study ICI — most commonly lenvatinib + pembrolizumab
  - Not effective as “salvage”- curves remain separate
  - Biological differences- immunogenicity

THE ROLE OF IMMUNOTHERAPY IN ENDOMETRIAL CANCER: RUBY PART 1



Powell M, Bjørge L, Willmott L et.al. **Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin–paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial.** Annals of Oncology, 2024; 35, 728-738

THE ROLE OF IMMUNOTHERAPY IN ENDOMETRIAL CANCER: B21 TRIAL



High-risk, early-stage endometrial cancer:

- Newly diagnosed endometrial cancer, including carcinosarcoma
- Surgery with complete resection
- Stage I-II myoinvasive non-endometrioid
- Stage I-II myoinvasive endometrioid with p53 abnl
- Stage III/IV
- Optional Radiation (EBRT or brachy, decide prior to randomization)

- ❑ Benefit in MMRd
- ❑ Radiation did not significantly impact outcomes in MMRd
- ❑ No benefit to adding ICI in MMRp (regardless of RT)

THE ROLE OF IMMUNOTHERAPY IN ENDOMETRIAL CANCER

- Magnitude of OS benefit smaller for specific sub-populations:
  - Prior chemotherapy
  - Prior radiation
  - **No measurable disease** at baseline (vs. measurable disease at baseline)

- Use of immunotherapy in advanced endometrial cancer delivers sustained benefit when added to carboplatin/paclitaxel backbone
  - Controls received post-trial immunotherapy
  - Benefit most pronounced in MMRd
  - MMRp: PFS advantage, OS not significant

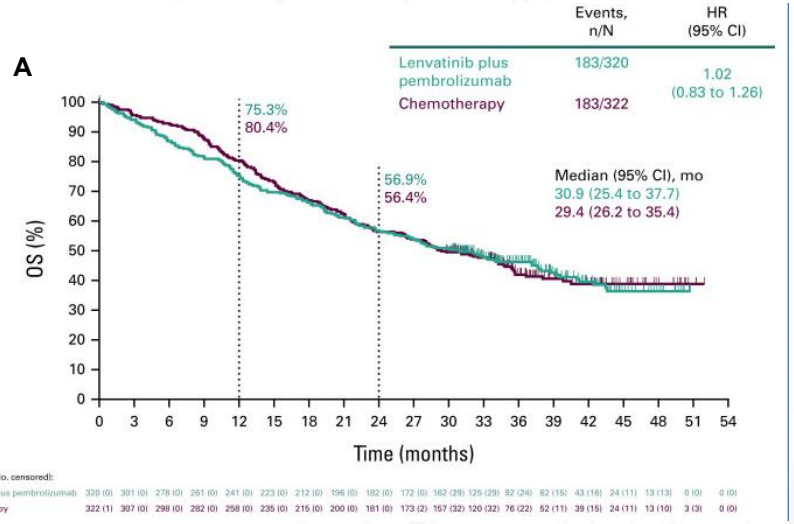
THE ROLE OF IMMUNOTHERAPY IN ENDOMETRIAL CANCER

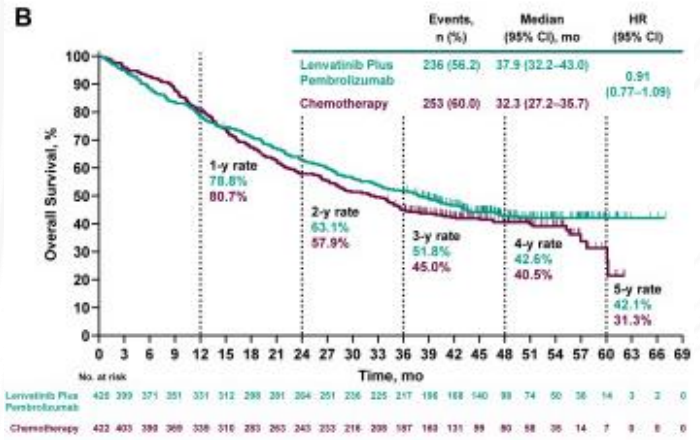
Measurable vs. Non-measurable disease

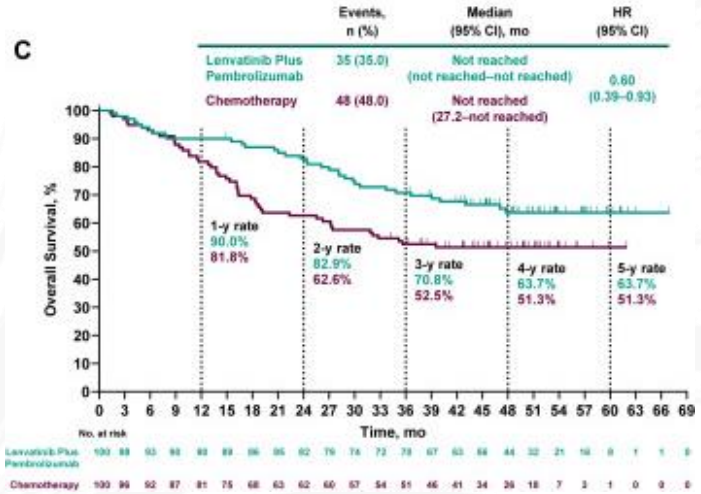
- **NRG-GY018:** statistically significant effect by subgroup for OS for measurability at baseline
  - Patients with no measurable disease at baseline → meaningfully smaller OS benefit
- **RUBY:** NEJM publication: patients with stage III or no measurable disease at baseline
  - Results "not consistent" with the rest of the trial population —absent PFS benefit
- **KEYNOTE-B21:** Exclusively patients with no residual disease post-surgery —
  - No DFS benefit in pMMR patients (HR 1.20), and no benefit overall
  - Only dMMR patients benefit even in the adjuvant setting

IS PEMBROLIZUMAB + LENVATINIB SUPERIOR TO CHEMOTHERAPY?

Overall survival in the (**A**) pMMR, (**B**) all-comer, and (**C**) dMMR populations







Lenvatinib + Pembrolizumab vs. chemotherapy as first-line treatment for advanced or recurrent endometrial cancer-
- did not meet PFS or OS endpoints

EMERGING STRATEGIES: HER2- TARGETED THERAPY

Trastuzumab- Deruxtecan: the only ADC currently approved for use in endometrial cancer

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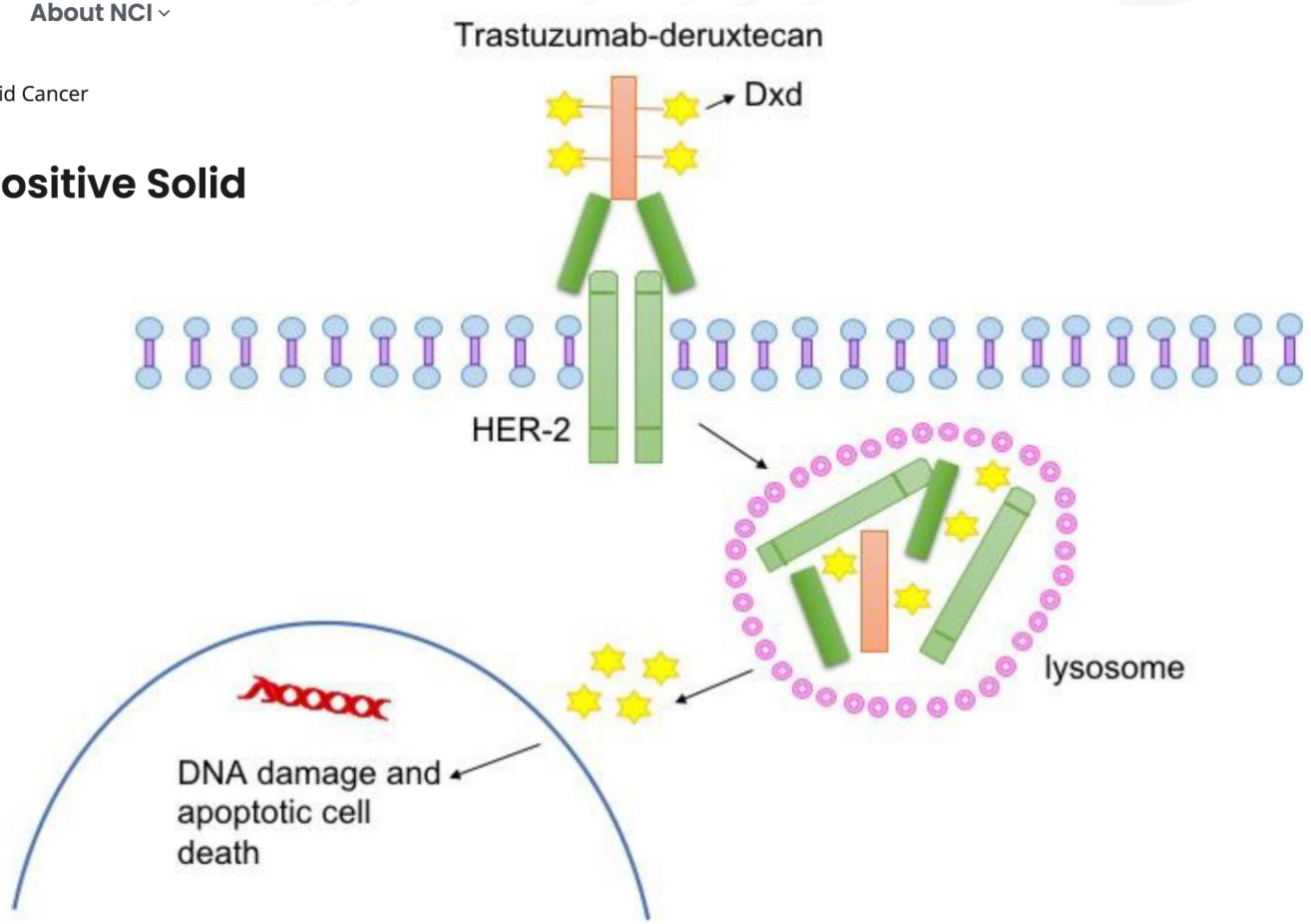
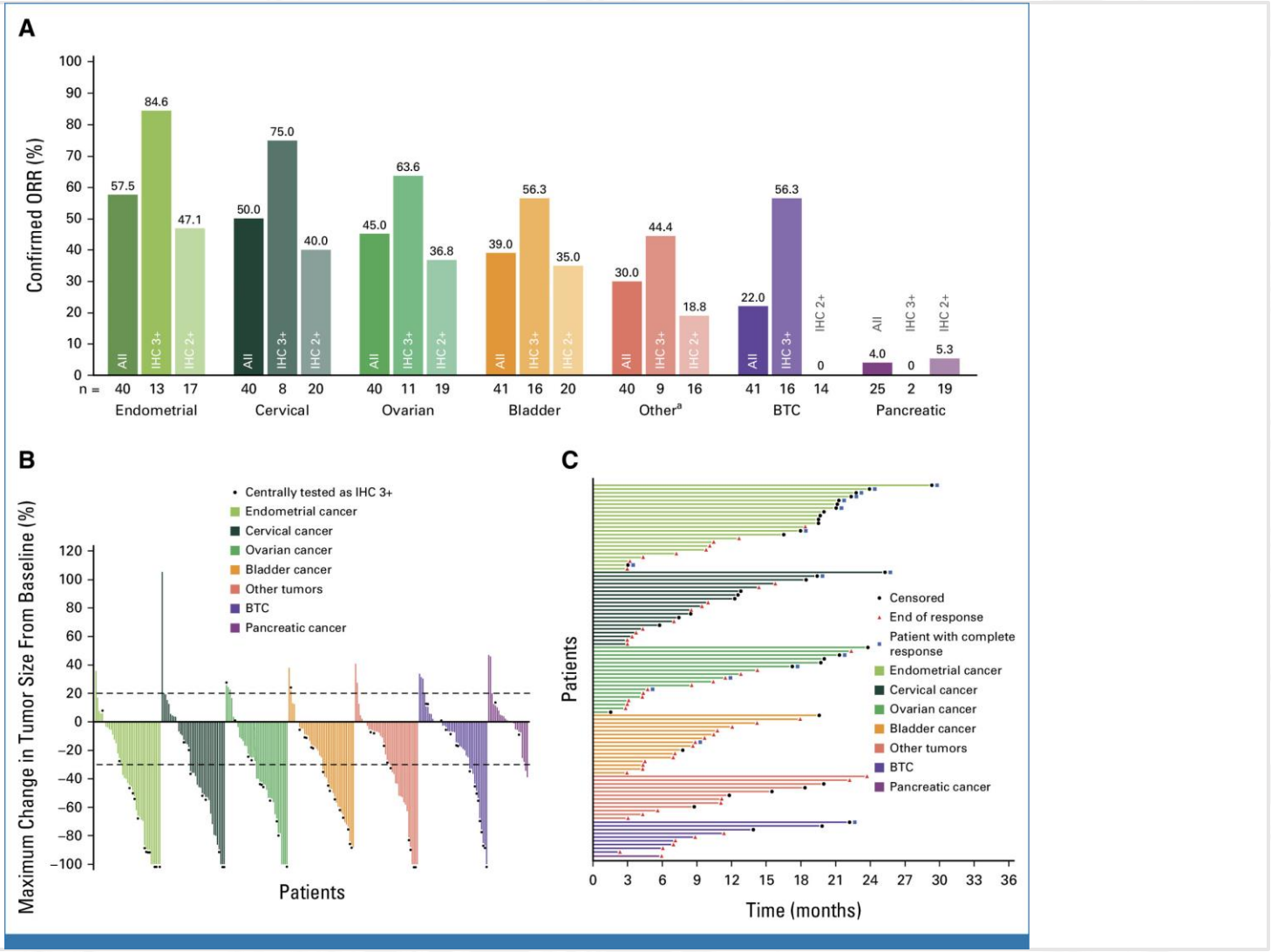
FDA Approves Trastuzumab Deruxtecan for Any HER2-Positive Solid Cancer

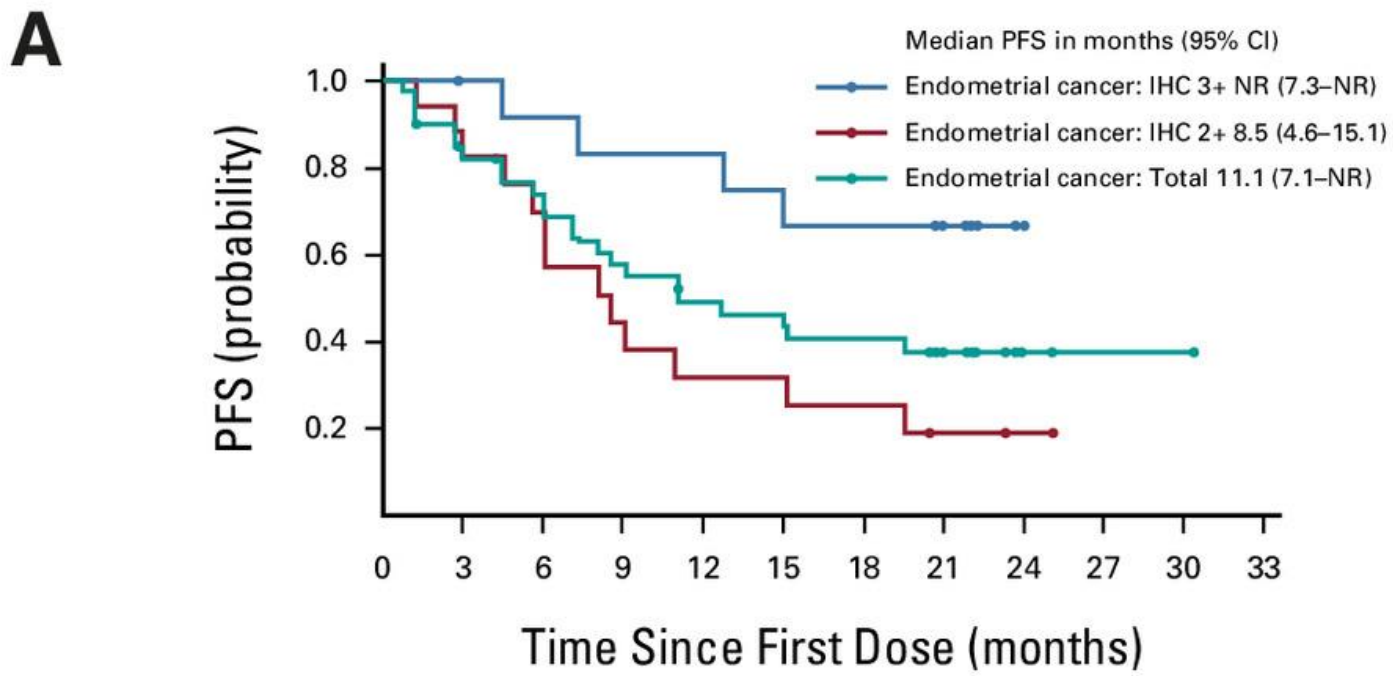


HER2 ADC TRASTUZUMAB DERUXTECAN: PAN-TUMOR-02 TRIAL



- Remarkable responses in HER2 2+/3+
- ORR 57.5% in Endometrial Cancer
- Median DOR was not reached in the endometrial cohort

HER2 ADC TRASTUZUMAB DERUXTECAN: PAN-TUMOR-02 TRIAL



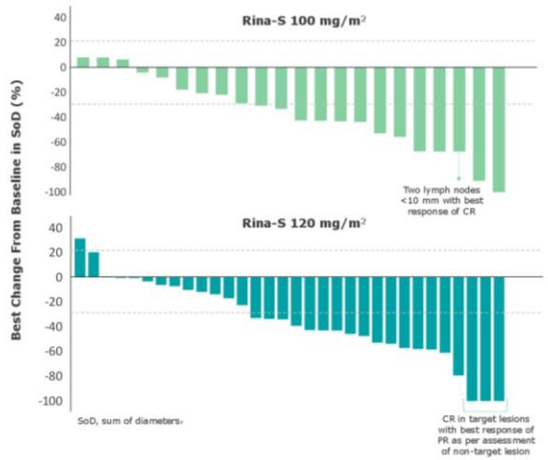
- PFS 3+: NR
- PFS 2+: 8.5 mo
- Compared to PFS of 4-6 months typically observed in 2nd line/beyond chemotherapy
- Watch for ILD: 10-15%, mostly mild, occasionally severe
- 60 ADCs currently in development, ~30 making strong progress/in clinical trials

FOLATE RECEPTOR ADC RINABART- SESUTECAN: RAINFOL-01 TRIAL

Changes in Target Lesion Tumor Burden

- Most efficacy-evaluable patients showed a reduction in tumor burden with Rina-S 100 mg/m² and 120 mg/m² (**Figure 3**)

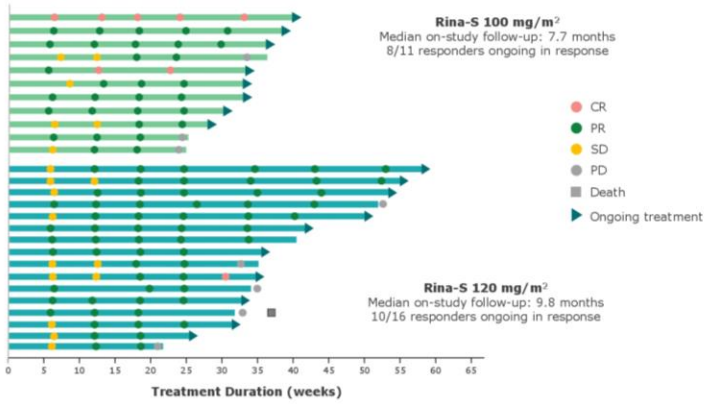
Figure 3. Best Percent Change from Baseline in Target Lesion Tumor Burden



Responses Over Time

- Responses occurred early with median time to response of 6 weeks (time of first disease assessment) (**Figure 4**)
- Most responses were ongoing at data cutoff (**Figure 4**)

Figure 4. Responses With Rina-S 100 mg/m² and 120 mg/m²

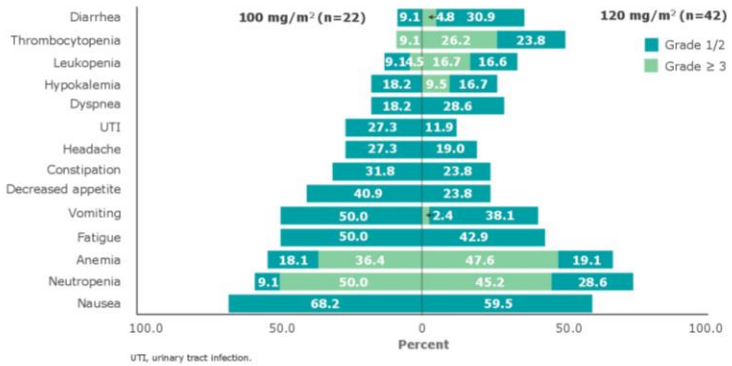


Overall safety

- Rina-S treatment-emergent adverse events (TEAEs) consisted primarily of cytopenias and low-grade gastrointestinal events which were similar across doses (**Figure 5**)
- TEAEs of any grade and ≥ grade 3, respectively, occurred in 100% and ~76% of patients across both dose cohorts
- TEAEs led to dose reductions in 18.2% and 16.7% patients and Rina-S discontinuation in 4.5% and 14.3% with Rina-S 100 mg/m² and 120 mg/m², respectively
- Serious TEAEs occurred in 31.8% and 50.0% of patients with Rina-S 100 mg/m² and 120 mg/m², respectively
- There were two fatal TEAEs in the 120 mg/m² cohort and none in the 100 mg/m² cohort
  - One Grade 5 TEAE of septic shock at 120 mg/m² confounded by comorbidities (related to Rina-S by investigator assessment)
  - One Grade 5 TEAE of acute kidney injury (unrelated to Rina-S by investigator assessment)
- No signals of ocular toxicity, neuropathy, or ILD were observed consistent with prior reports of Rina-S

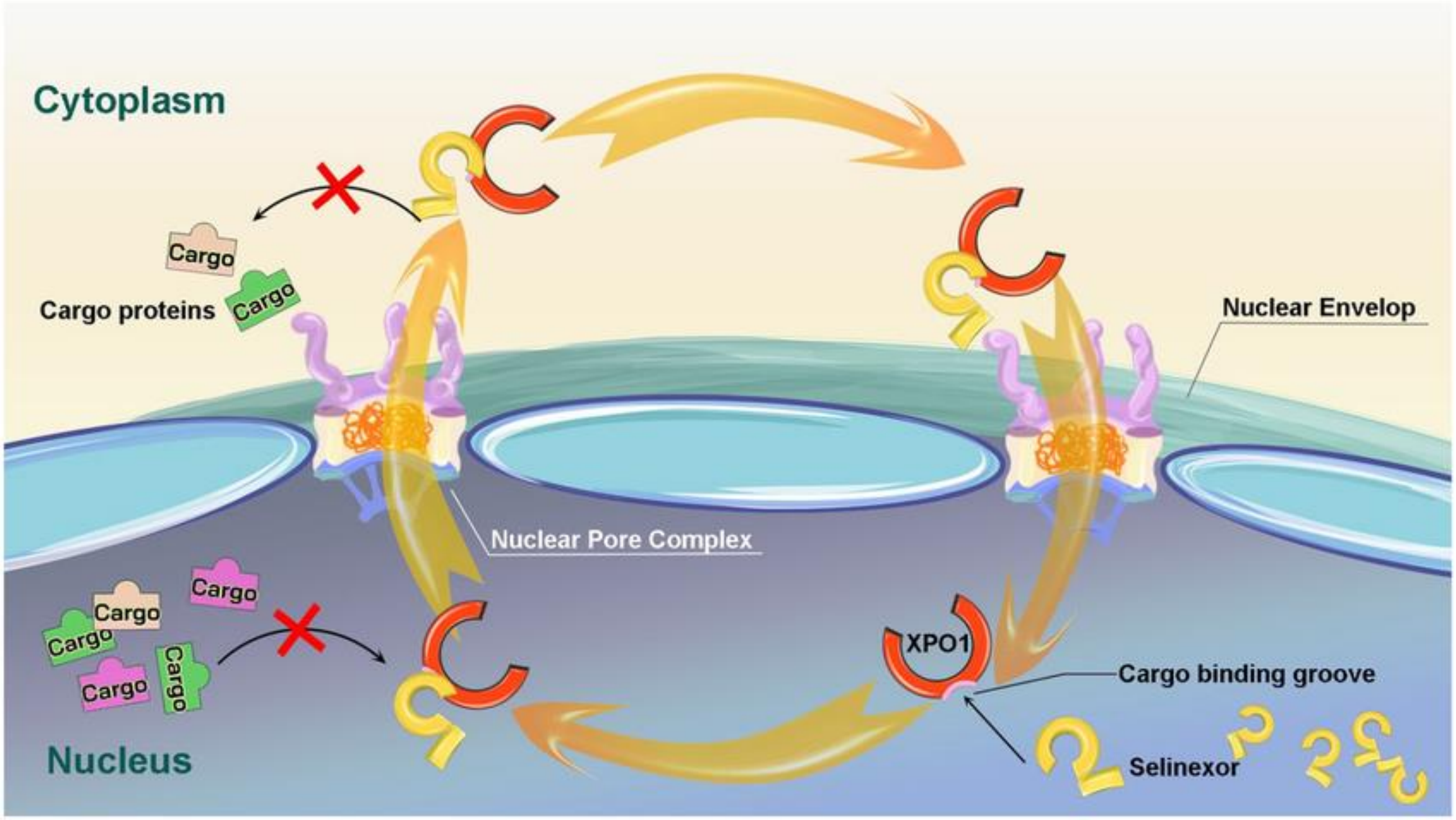
Note: Reasons for treatment-related discontinuation in the 120 mg/m² cohort was citrobacter sepsis; there were none in 100 mg/m² cohort. Granulocyte colony-stimulating factor (GCSF) was used per ASCO and protocol guidance by 77% and 55% for 100 and 120 mg/m² doses, respectively.

Figure 5. Common TEAEs Occurring in ≥25% of Patients



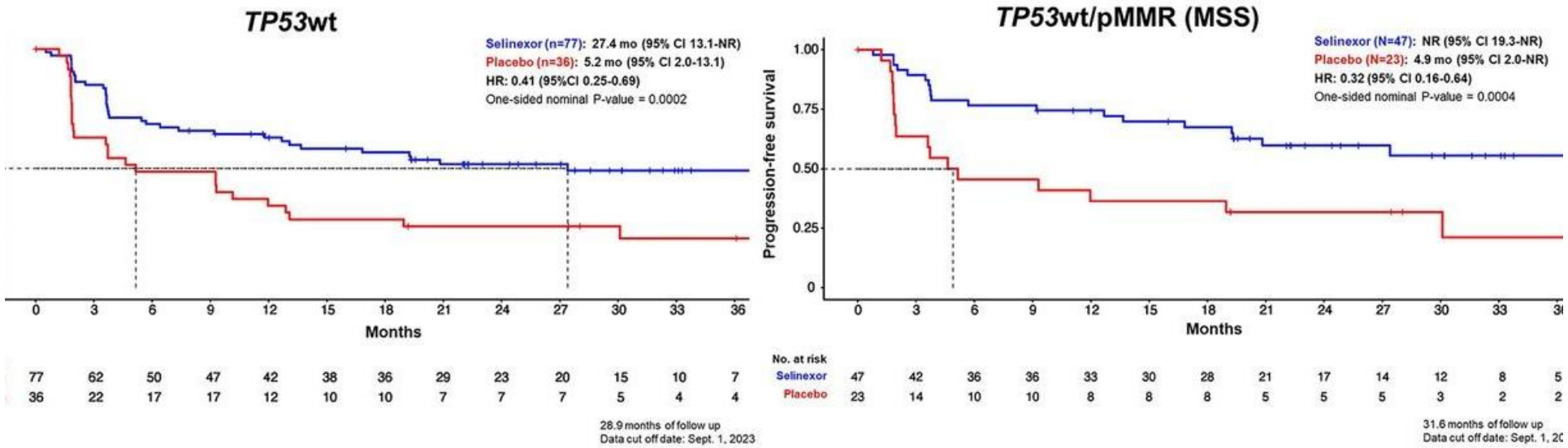
- ADC targeting FOLR1 in advanced/recurrent endometrial cancer
- Topoisomerase I–inhibitor payload
- Heavily pretreated advanced/recurrent, prior ICI
- ORR 50% and 47% at each dose level
- Phase III RCT recently completed accrual
- No ocular toxicity, neuropathy, or interstitial lung disease reported
- Several other FOLR1 ADCs currently in development

SELINEXOR: EXPORTIN-1 (XPO1) INHIBITION



SELINEXOR: EXPORTIN-1 (XPO1) INHIBITION

Long-term Follow up: Progression-free survival



Preliminary Overall Survival

	No. with events (%)	Overall Maturity (%)	Median (95% CI), months	HR (95% CI)	Nominal one-sided p-value	Median follow up (months)
***TP53*wt**						
Selinexor (n=77)	23.4%	26.6%	NR (NR, NR)	**0.76** (0.36-1.59)	0.24	28.9
Placebo (n=36)	33.3%		NR (35.19, NR)			
***TP53*wt/pMMR (MSS)**						
Selinexor (n=47)	23.4%	30.0%	NR (NR, NR)	**0.57** (0.24-1.35)	0.098	31.6
Placebo (n=23)	43.5%		35.19 (28.68, NR)			
***TP53*wt/dMMR (MSI-H)**						
Selinexor (n=20)	10.0%	10.3%	NR (NR, NR)	**0.62** (0.06-6.81)	0.35	27.3
Placebo (n=9)	11.1%		NR (NR, NR)			

Data cut off date: Sept. 1, 2023

P53wt is a robust predictive biomarker for selinexor efficacy in EC- particularly p53wt/MMRp

CURRENT ENDOMETRIAL CANCER TRIALS

NRG GY026: A Phase 2/3 Study of Paclitaxel/Carboplatin Alone or Combined with Trastuzumab and Herceptin Hylecta or Phesgo in Newly Diagnosed HER2+ Stage I-IV Endometrial Serous Carcinoma or Carcinosarcoma

- For upfront treatment/maintenance of HER2+ endometrial carcinoma, all stages.
- Stage I/II HER2+ patients can get HER2-directed treatment

NRG GY-035: A Randomized Phase III Trial of Carboplatin, Paclitaxel, and Pembrolizumab versus Carboplatin, Paclitaxel, and Bevacizumab versus Carboplatin, Paclitaxel, Pembrolizumab and Bevacizumab in the Treatment of PMMR, TP53 Mutated Advanced or Recurrent Endometrial Cancer

- Upfront/first recurrent treatment/maintenance
- Must have surgery first. They do not permit EBRT/Brachytherapy once on trial
- Arms:
  - Carbo/Taxol/Pembrolizumab/Bevacizumab + dual maintenance
  - Carbo/Taxol/ Pembrolizumab + Pembrolizumab maintenance
  - Carbo/Taxol/ Bevacizumab + Bevacizumab maintenance

CURRENT ENDOMETRIAL CANCER TRIALS

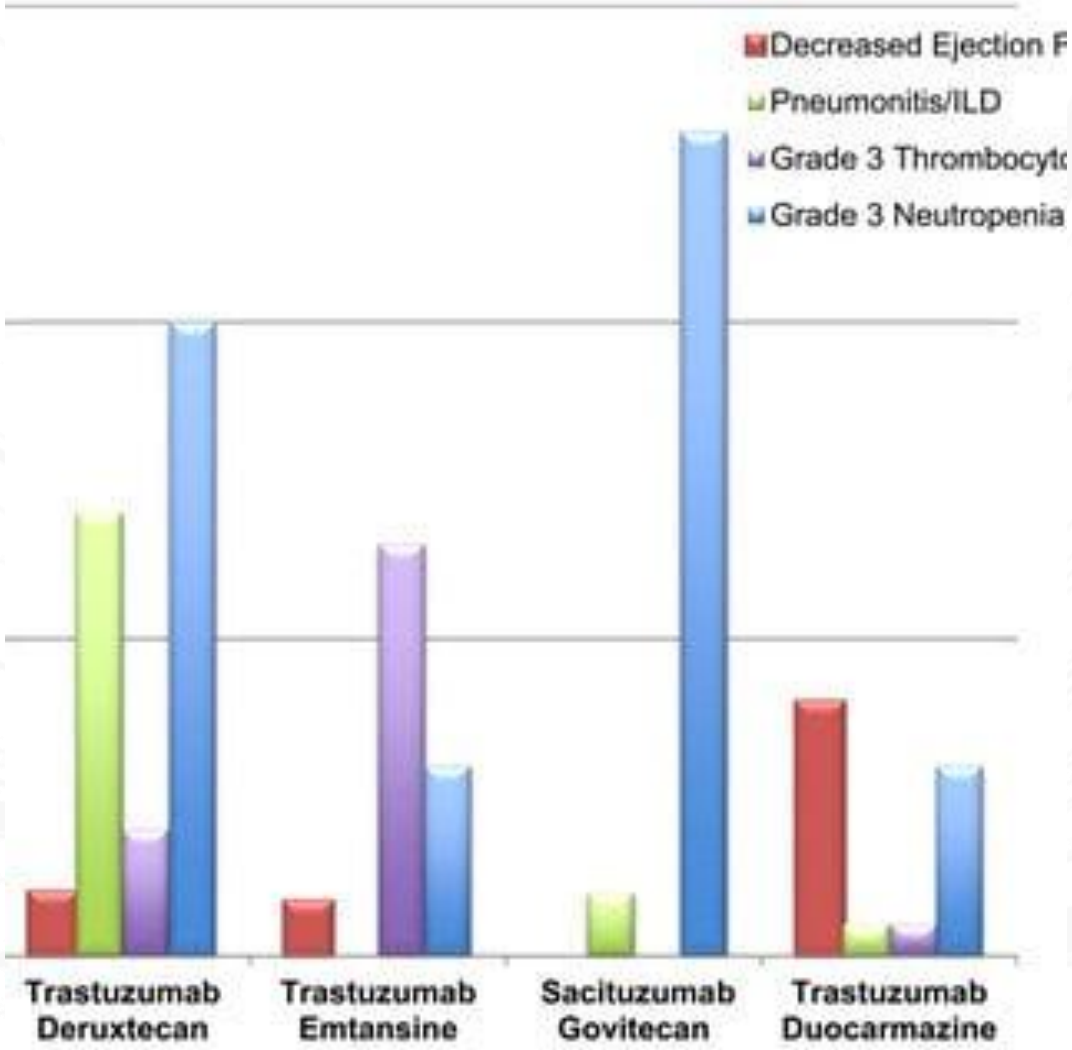
A Phase II Study of ACR-368, a CHK1/2 Inhibitor, in Subjects With Endometrial Cancer
- Fast-track FDA designation in high-grade serous endometrial cancer

Study to Assess the Efficacy and Safety of Rina-S Compared to Treatment of Investigator's Choice in Participants With Endometrial Cancer (RAINFOL-03)
- Rina-S vs investigator-choice chemotherapy in recurrent endometrial cancer
- Allows high-grade histology except neuroendocrine tumors, carcinosarcoma

A Phase 1, First-in-human, Open-label Study to Evaluate the Safety, Tolerability, PK, and Preliminary Anti-tumor Activity of the Novel Oral CDK2 Degrader NKT3964 in Adults With Advanced/Metastatic Solid Tumors
- Proteolysis-targeting chimera (PROTAC) that selectively degrades the **CDK2** protein
- CCNE1 amplification in endometrioid subtype

A Phase I First-in-human, Open-label, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of SIM0505 in Adult Participants With Advanced Solid Tumors
- Cadherin-6 targeting ADC; Proprietary topoisomerase I inhibitor (CPT116)
- FDA Fast-track designation for platinum-resistant ovarian cancer
- 55% objective response rate (ORR) in HG serous ovarian/endometrial cancers

ADC PRECAUTIONS:



Linehan A.S. et. al. 2021; DOI: 10.2147/BCTT.S245024

- Balancing the risks and benefits of new therapies
- Patient selection
- Counseling on side-effects

THE PATH TO PROGRESS IN ENDOMETRIAL CANCER

- Strategies to mitigate toxicities
- Improving therapeutic profiles
- Application of treatment algorithms
- Identification of more/refined biomarkers
- Development of novel/different payloads

THANK YOU