



The Evolving Landscape of Endometrial Cancer

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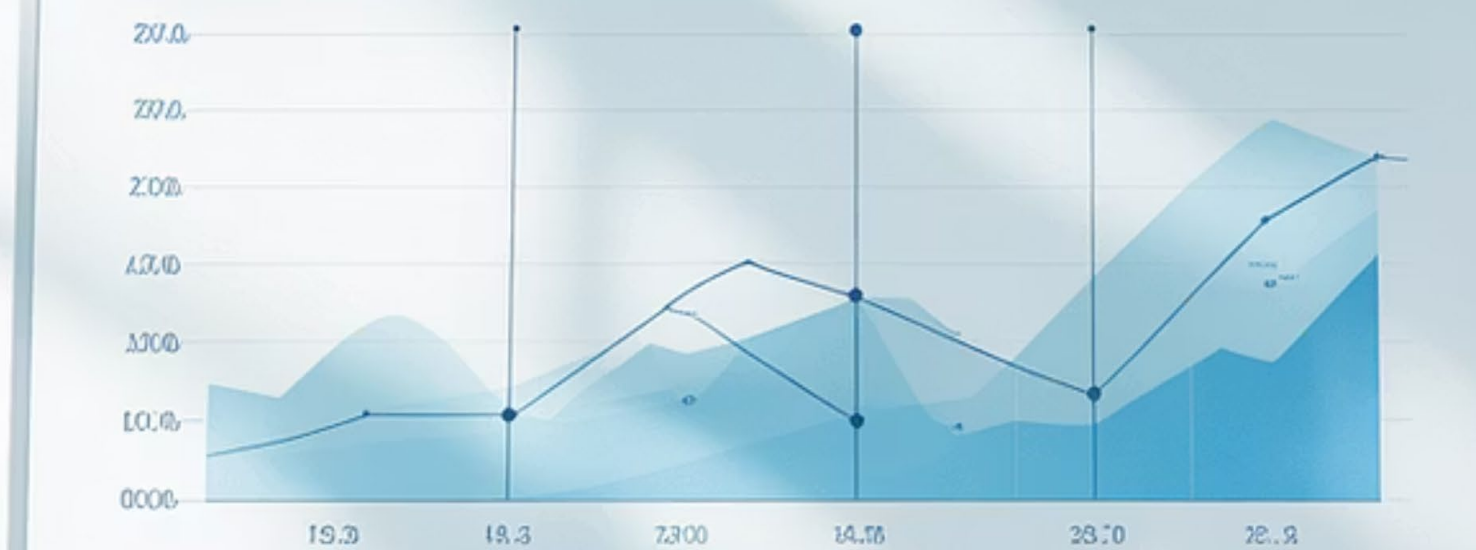
Ochsner Health System

Multidisciplinary Cancer Conference | October 3, 2025

Disclosures

Financial Disclosures

I have no relevant financial disclosures or conflicts of interest



A Growing Crisis: Deaths Overtaking Ovarian Cancer

13,000+

Deaths in 2025

Uterine cancer now deadliest gynecologic malignancy in US

2x

Higher mortality

Non-Hispanic Black women face disproportionate death rates

Rising incidence correlates directly with obesity epidemic

Today's Objectives

1 Molecular Classification Advances

Beyond histology to genomic insights

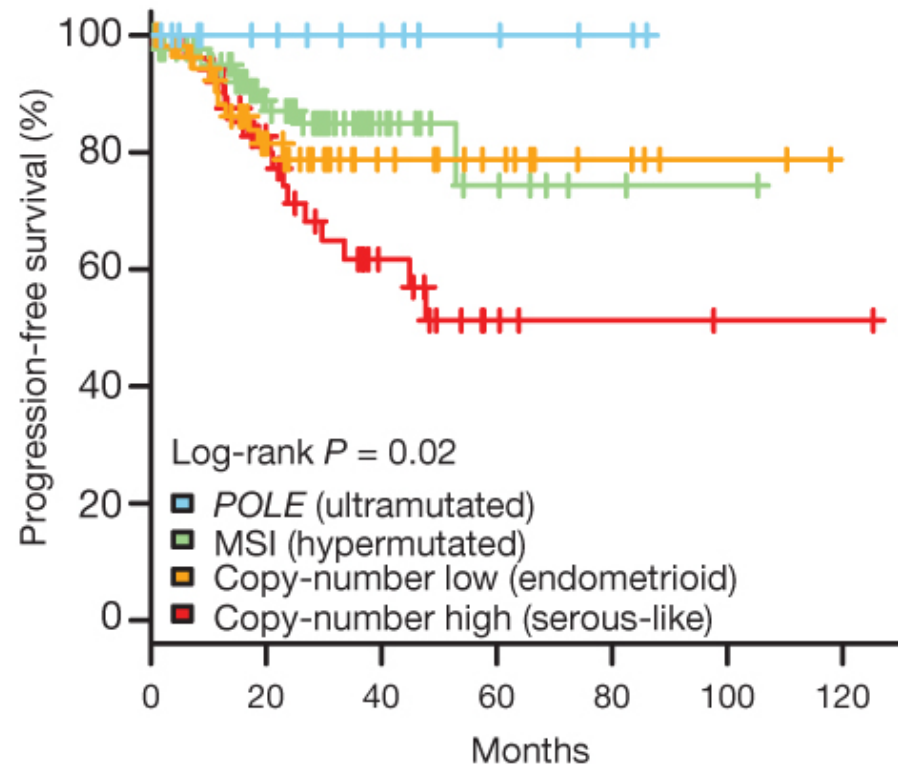
2 Updated FIGO 2023 Staging

Paradigm shift from anatomic to risk-based

3 Treatment Breakthroughs

Focus on advanced and recurrent disease

TCGA Classification: The Foundation



POLE Ultramutated

Excellent prognosis despite high-grade features

Microsatellite Instability

Intermediate prognosis, highly immunogenic

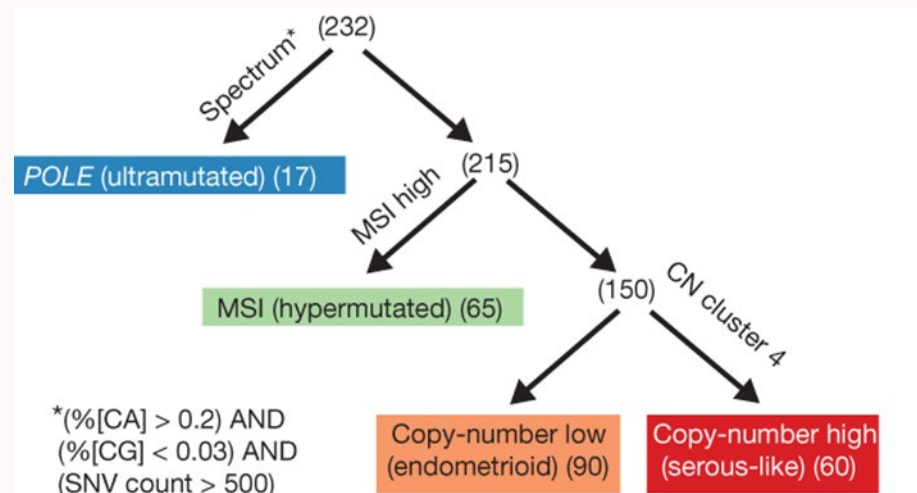
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Endometrioid, hormone-responsive

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Serous-like, poor prognosis

Genomic insights transformed trial design and therapeutic innovation



Controversial Staging Changes

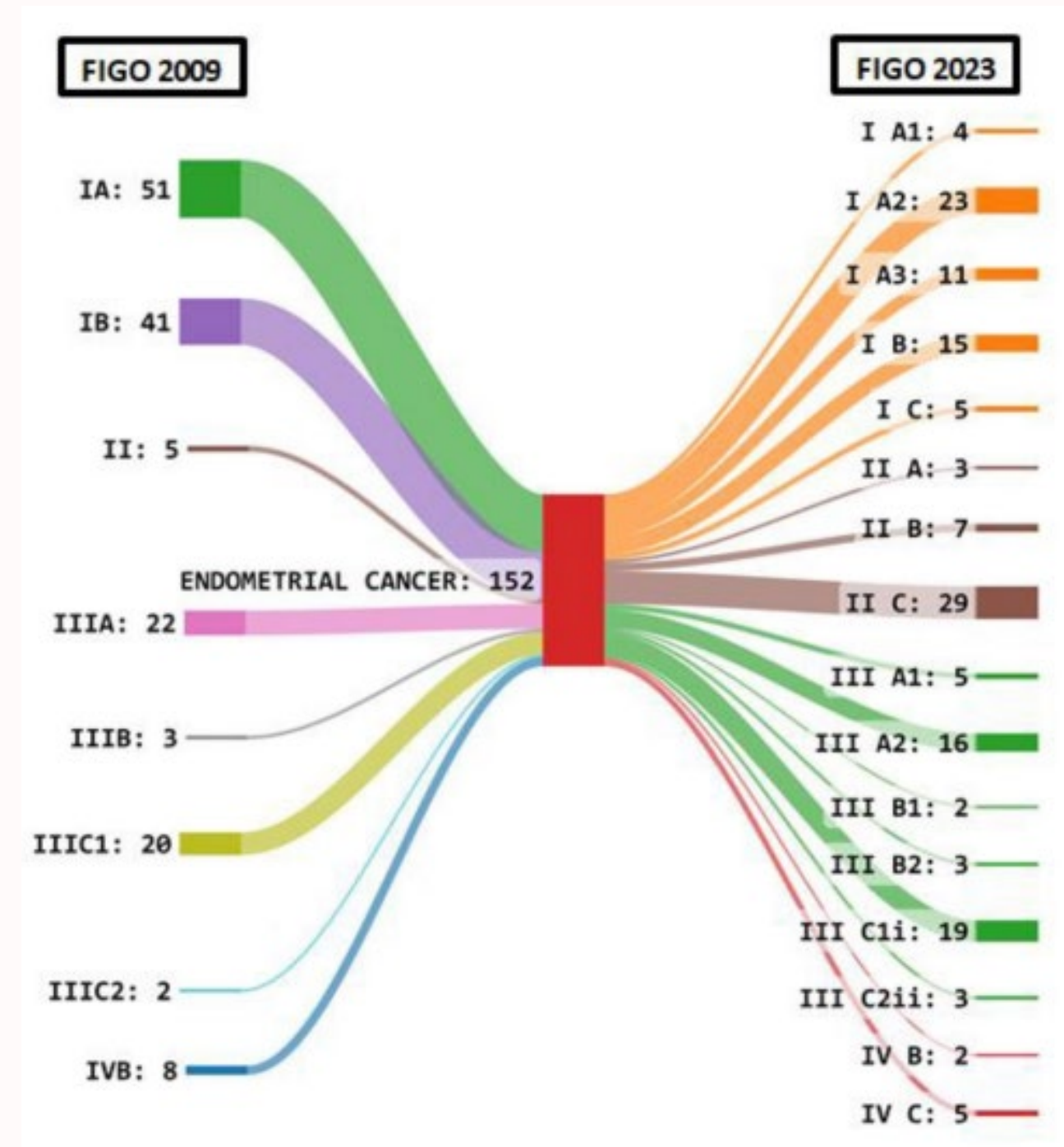
FIGO 2009

- Purely anatomic classification
- Simple, straightforward approach

FIGO 2023

- Risk-factor integration
- Histology, LVSI, node size
- Optional molecular classification

Improved prognostic discernment but increased complexity



My Take on the New Staging System

✓ Ovarian Involvement Distinction

Better separation of old IIIA into risk categories based on involvement pattern

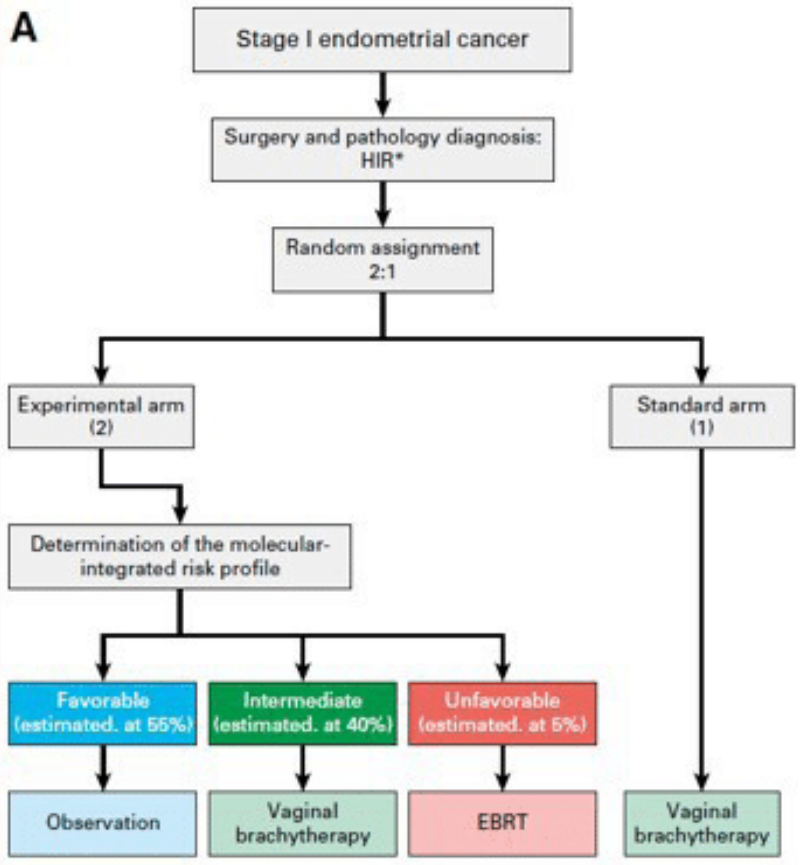
✓ Stage IV Granularity

Differentiates between pelvic, abdominal, and extraperitoneal mets

✗ LVSI Inclusion Concerns

Differential application
Prognostic, but necessary?
Invites confusion

Molecular-Guided Trials: Early Results

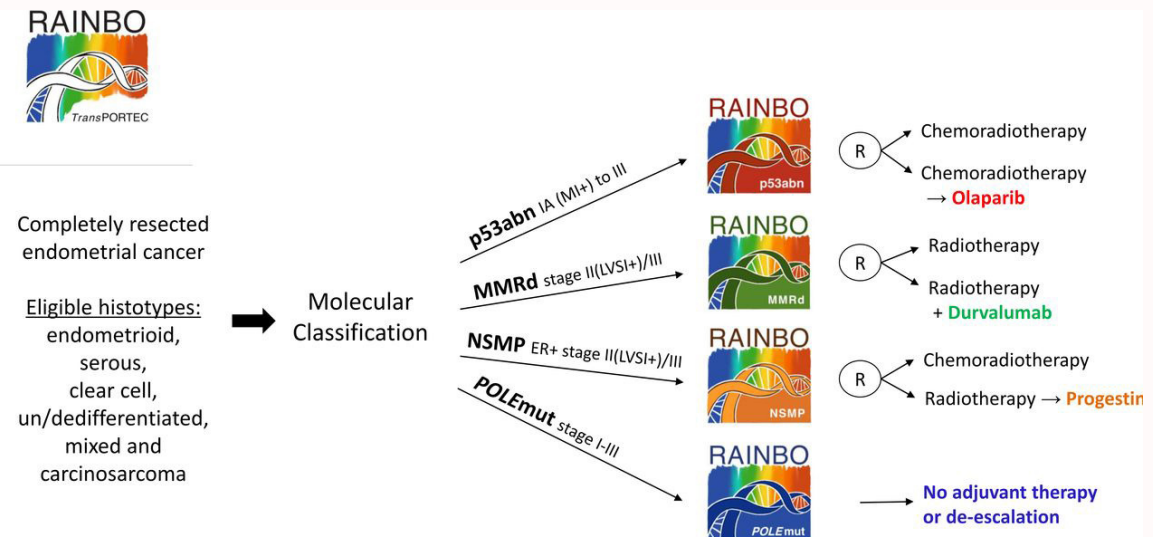


1 — PORTEC 4a Results

Tailored radiation vs standard brachytherapy. No survival differences but proves feasibility of molecular-guided design

2 — RAINBO Trial

Molecular classification informing adjuvant treatment. Results expected 2028



The Immunotherapy Advantage

RUBY

Carbo/Taxol + Dostarlimab

PFS benefit in dMMR and overall population

OS benefit overall population

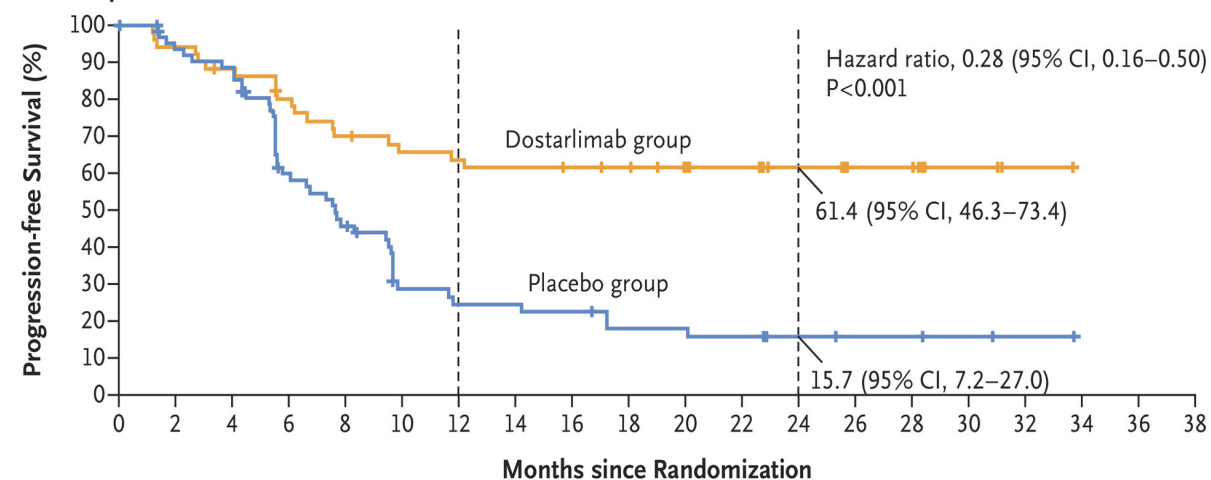
Most pronounced in dMMR

GY018

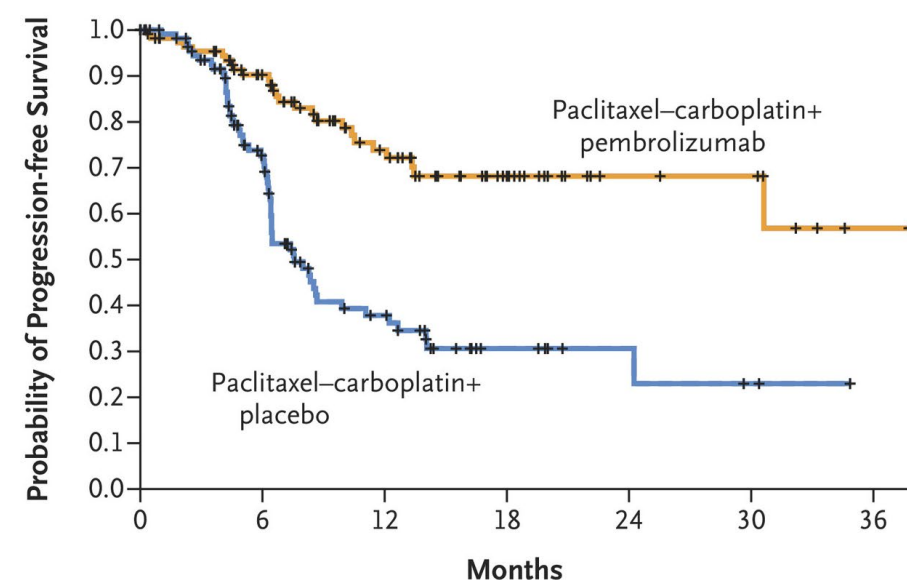
Carbo/Taxol + Pembrolizumab

PFS benefit in dMMR and pMMR groups

dMMR-MSI-H Population



dMMR Cohort



Both trials demonstrated checkpoint inhibitor efficacy in advanced/recurrent disease

2024: Momentum Continues

1

DUO-E Trial

Durvalumab ± Olaparib

Improved PFS vs chemotherapy alone

Potential PARP synergy in pMMR tumors

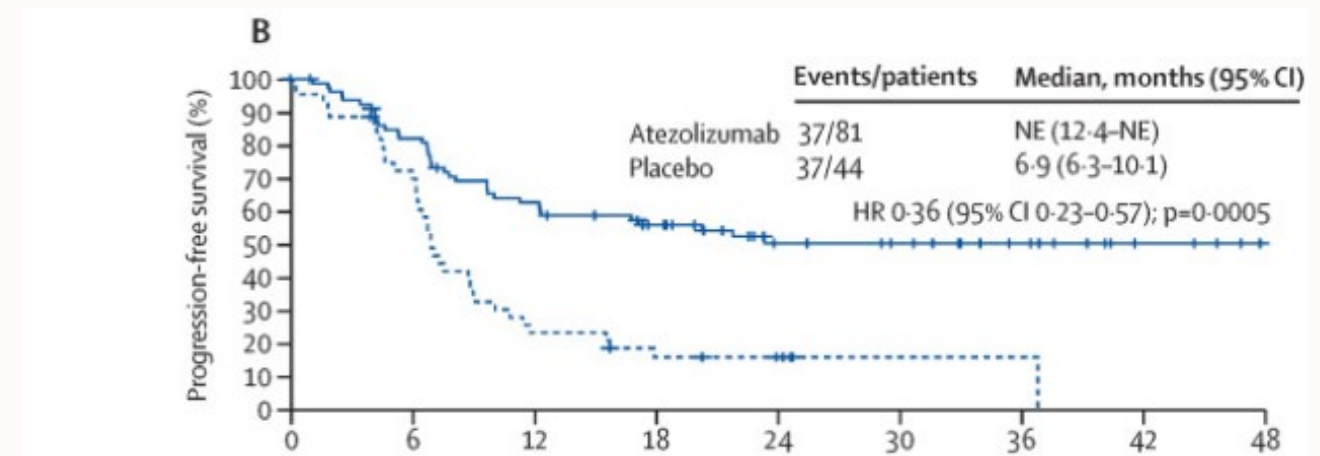
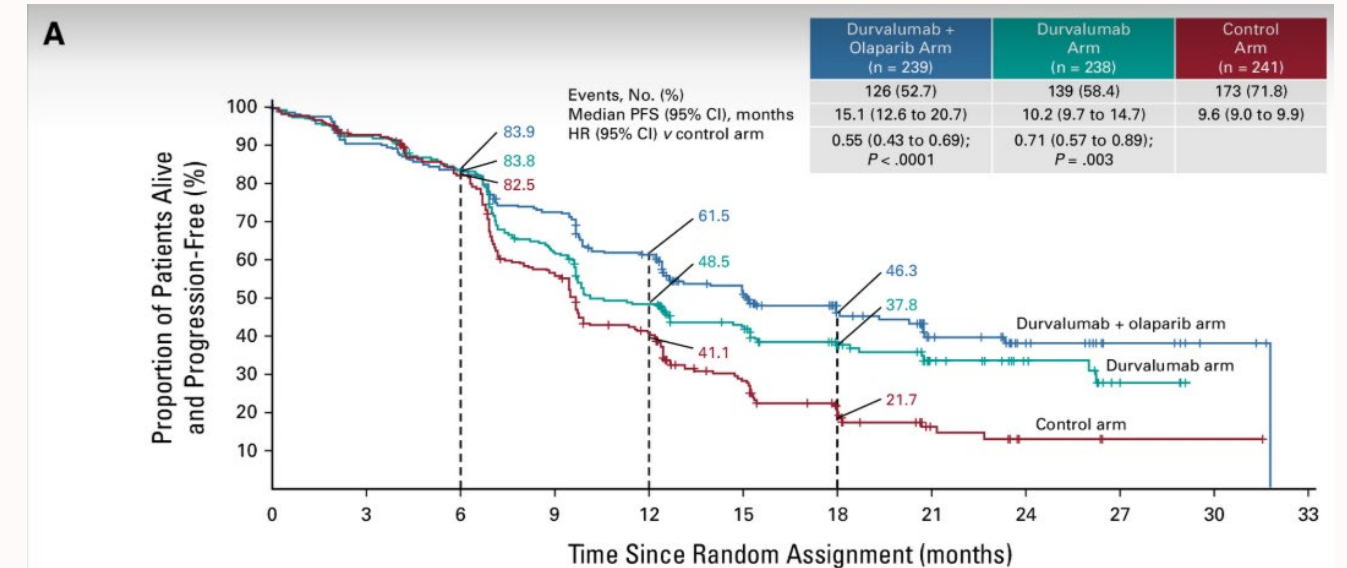
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AtTend Trial

Atezolizumab + Chemotherapy

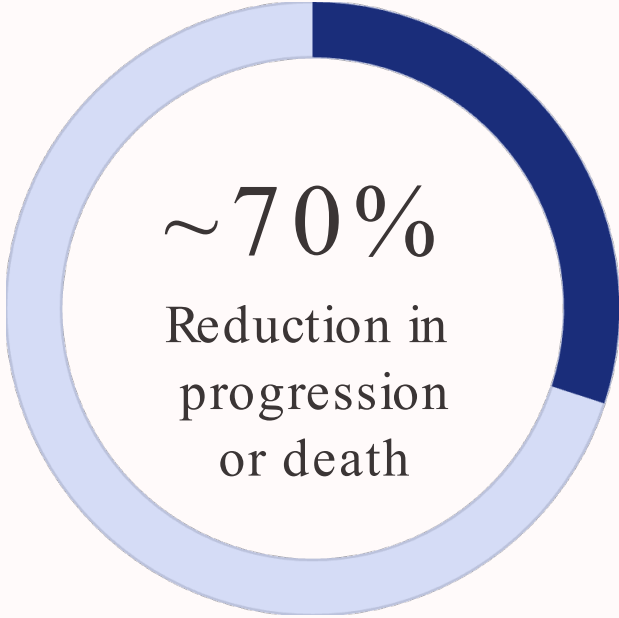
Consistent PFS benefit pattern

Validates immunotherapy approach



Four Trials, Consistent Message

| RUBY Dostarlimab | GY018 Pembrolizumab | DUO-E Durvalumab +/- olaparib | AtTEnd Atezolizumab |
|----------------------|------------------------|--|------------------------|
| dMMR: PFS HR 0.28 | dMMR PFS HR 0.3 | dMMR PFS HR 0.42, 0.42 | dMMR PFS HR 0.36 |
| Overall: PFS HR 0.64 | pMMR PFS HR 0.54 | Overall: PFS HR 0.71, 0.55 pMMR PFS HR 0.77, 0.57 | Overall PFS HR 0.74 |



For patients with dMMR tumors

Clear indication: checkpoint inhibitors deserve frontline role in dMMR tumors

Learning from "Negative" Trials

1

LEAP-001

Lenvatinib/Pembrolizumab missed non-inferiority.

But patients >6 months from adjuvant chemo benefited from Len/Pemb

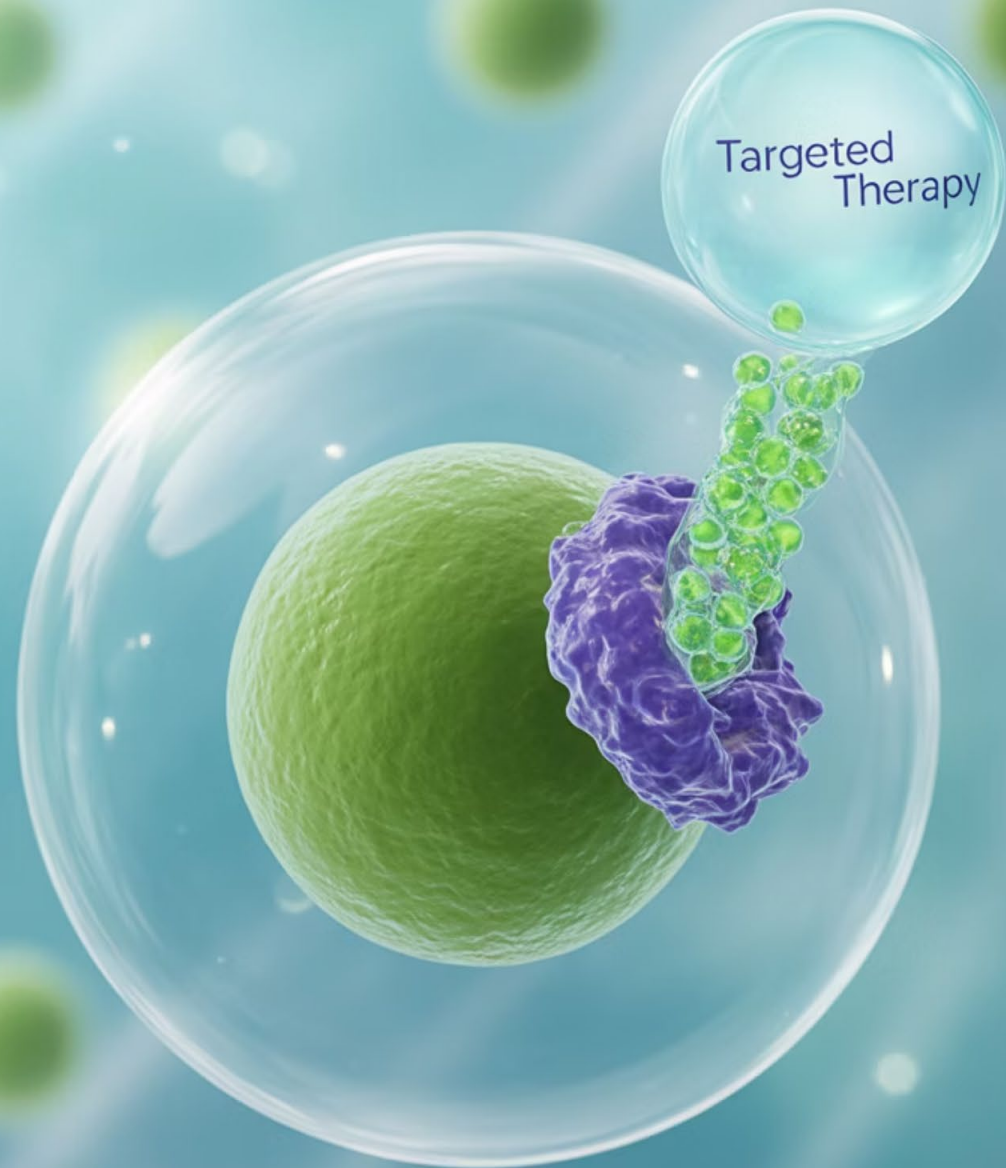
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Keynote B-21

No DFS benefit in adjuvant setting overall.

dMMR subgroup showed 0.3 HR favoring pembrolizumab

Question: does tumor volume influence immune response?



Beyond dMMR: Wild-Type p53 Targeting



XPORT Trial

Selinexor (oral exportin-1 inhibitor) in wild-type p53 patients



SIENDO Signal

Phase III negative overall, but strong benefit signal in p53 wild-type

Results anticipated next year - expanding molecular targeting options

The Second-Line Conundrum



Frontline immunotherapy success creates new vacuum for 2L treatment:
What comes next after checkpoint inhibitor progression?

01

Old Standard

Pembrolizumab for dMMR, Len/Pemb
for pMMR

02

New Reality

Post-immunotherapy treatment
landscape undefined

03

Potential solution

Antibody-drug conjugates entering the field



ADCs: The Trojan Horse Strategy



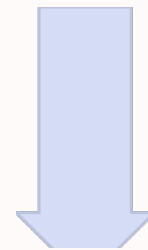
Target Recognition

Antibody binds highly expressed antigen



Cellular Entry

Internalization via receptor-mediated endocytosis



Payload Release

Cytotoxic agent delivers targeted cell death

Like Greeks emerging from the horse - targeted destruction from within

HER2-Targeted Success: Trastuzumab Deruxtecan

57%

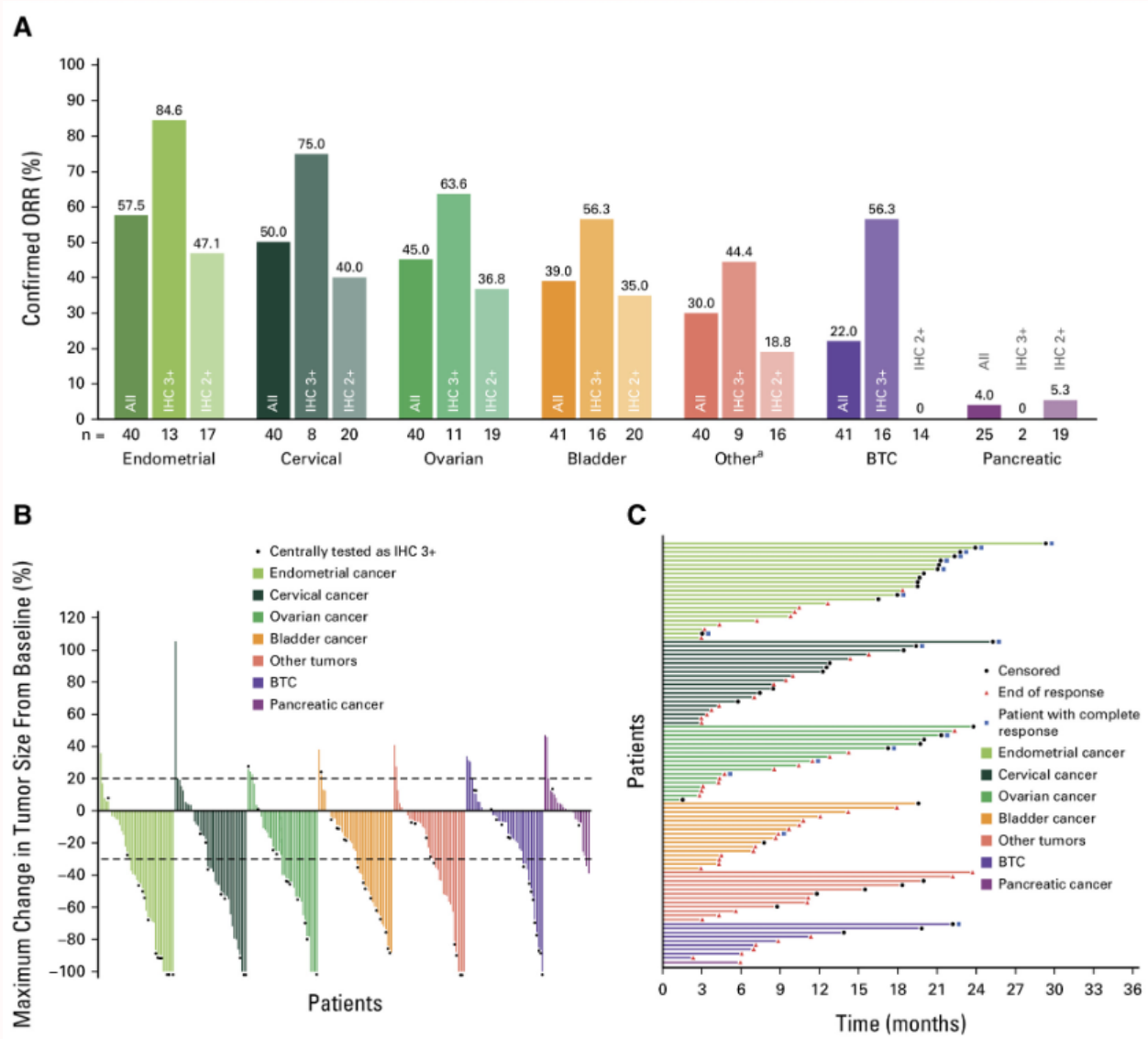
84.6%

Overall Response

HER2 3+ Response

Heavily pretreated patients

Responses seen irrespective of prior trastuzumab therapy





Managing ADC Toxicity: T-DXd



Interstitial Lung Disease

10-20% incidence, mostly mild and reversible with discontinuation



Surveillance Protocol

Baseline CT chest/PFTs, repeat scans every 9 weeks, symptom monitoring

Vigilant monitoring warranted for rare but serious pulmonary complications

Expanding ADC Pipeline



Sacituzumab Govitecan

Trop-2 targeting with camptothecin payload.
ASCENT GYN 01 Phase III trial actively enrolling



Mirvetuximab

Folate receptor alpha targeting with maytansinoid payload.
Proven in ovarian cancer



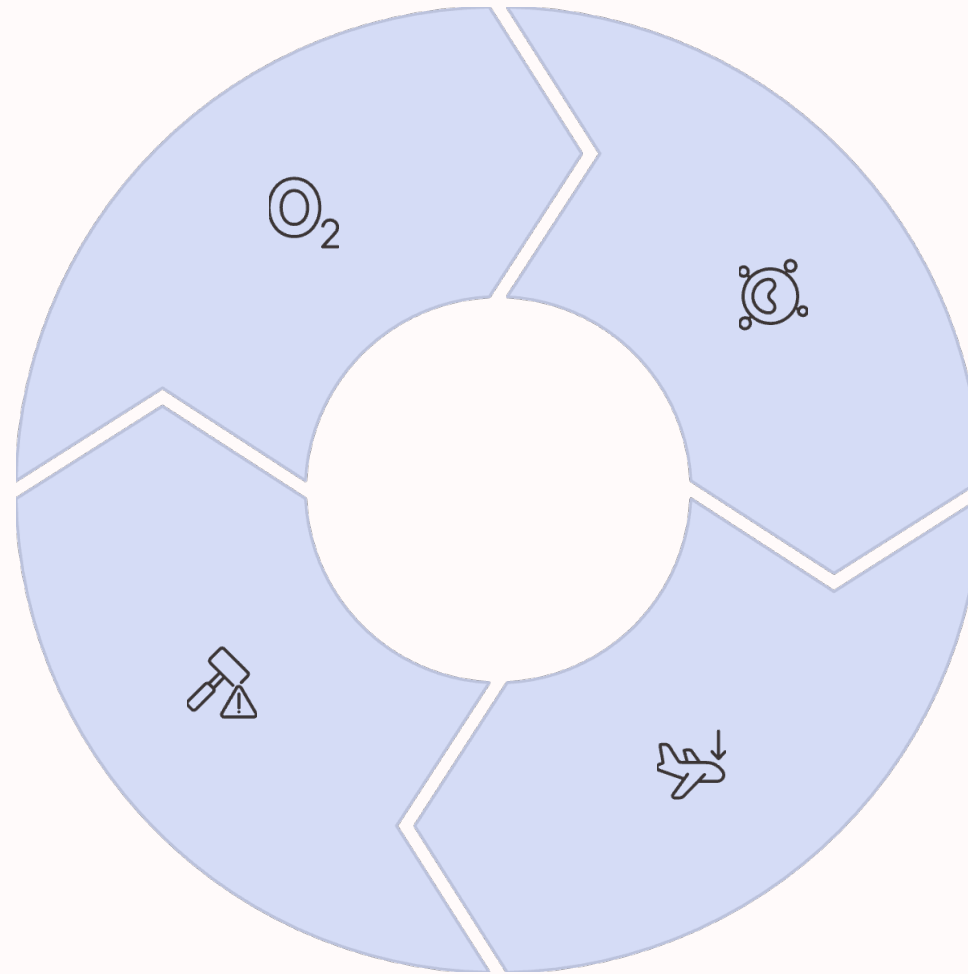
Rinatabart Sesutecan

FDA breakthrough designation.
~50% response rate in RAINFOL-01 trial

Innovation at Unprecedented Pace

Molecular Insights
TCGA classification driving precision
medicine

Trial Innovation
Biomarker-driven study designs



Immunotherapy Success
Checkpoint inhibitors transforming
outcomes

ADC Revolution
Trojan horse delivery of cytotoxic
payloads

Continuous evolution

Rising Challenge

Increasing incidence and lethality
demand urgent action

Unprecedented Innovation

Molecular insights, immunotherapy,
and ADCs reshaping treatment

Thank You

Questions & Discussion

