



7th Annual
LEAD2025
Enriching Experiences for Women in Hematology & Oncology



Updates in Gynecologic Cancer

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Learning Objectives

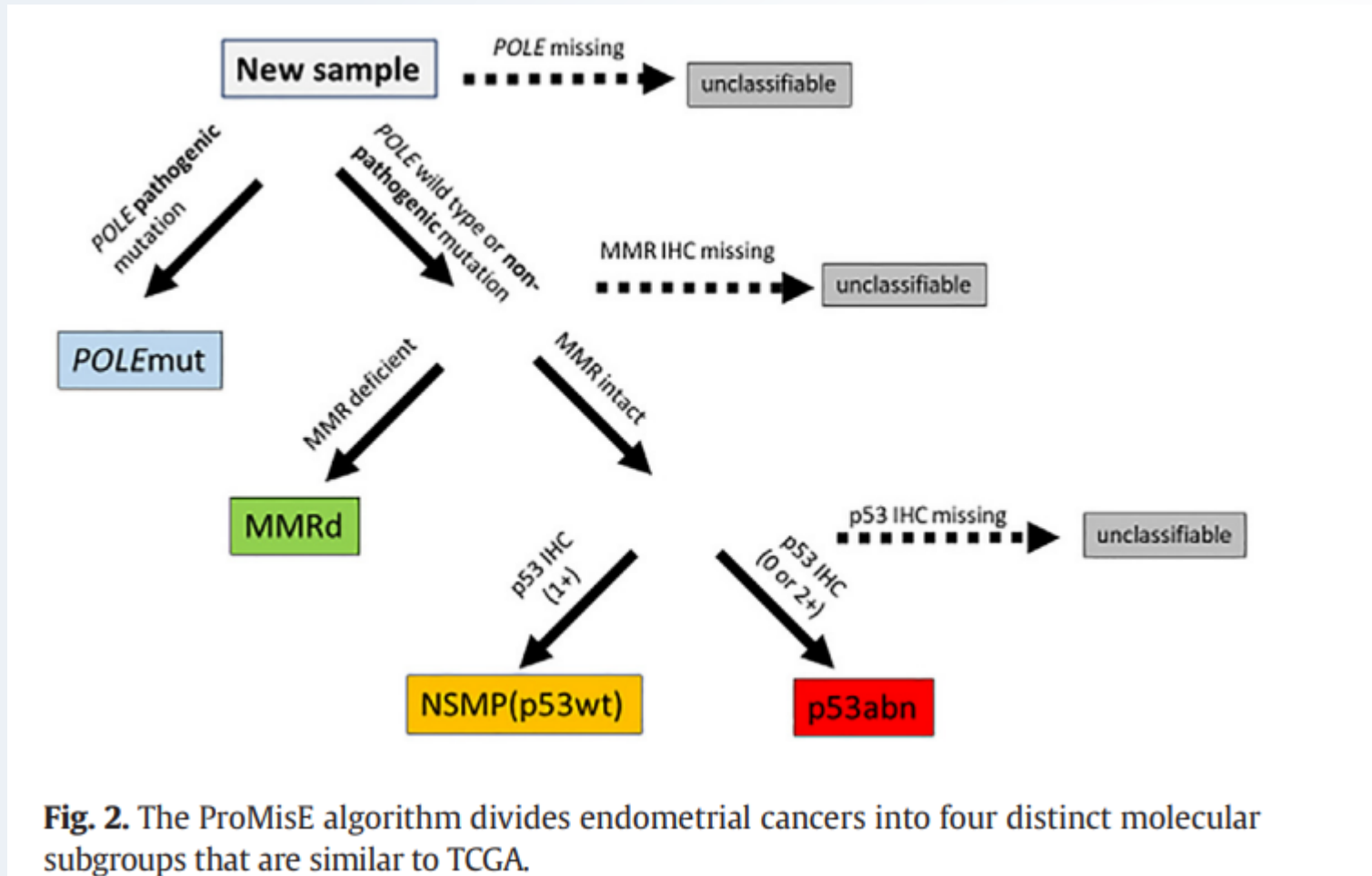
- Summarize key recent clinical updates and FDA approvals in endometrial, ovarian and cervical cancers
- Describe the role of antibody-drug conjugates (ADCs) and immunotherapy in current practice
- Recognize how biomarker testing guides the use of new therapies in gynecologic cancer
- Apply these updates to treatment decision-making in clinical practice

Endometrial Cancer

Updates in Endometrial Cancer

- Molecular classifications
- Immunotherapy (IO) + chemotherapy (followed by IO maintenance) in newly diagnosed stage III-IV disease is the new standard
- Growing role of antibody-drug conjugates (trastuzumab deruxtecan)

Endometrial Cancer Molecular Classifications



Risk Stratification Categories

Table 2. EC risk groups

Risk group	Description ^a
Low risk	Stage IA (G1-G2) with endometrioid type (dMMR ^b and NSMP) and no or focal LVSI Stage I/II <i>POLE</i> mut cancer; for stage III <i>POLE</i> mut cancers ^c
Intermediate risk	Stage IA G3 with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage IA non-endometrioid type (serous, clear-cell, undifferentiated carcinoma, carcinosarcoma, mixed) and/or p53-abn cancers without myometrial invasion and no or focal LVSI Stage IB (G1-G2) with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage II G1 endometrioid type (dMMR and NSMP) and no or focal LVSI
High-intermediate risk	Stage I endometrioid type (dMMR and NSMP) any grade and any depth of invasion with substantial LVSI Stage IB G3 with endometrioid type (dMMR and NSMP) regardless of LVSI Stage II G1 endometrioid type (dMMR and NSMP) with substantial LVSI Stage II G2-G3 endometrioid type (dMMR and NSMP)
High risk	All stages and all histologies with p53-abn and myometrial invasion All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion All stage III and IVA with no residual tumour, regardless of histology and regardless of molecular subtype ^b

dMMR, mismatch repair deficient; EC, endometrial cancer; G1-G3, grade 1-3; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MSI-H, microsatellite instability high/hypermethylated; NSMP, no specific molecular profile; p53-abn, p53-abnormal; *POLE*mut, polymerase epsilon-ultramutated.

^aStage III-IVA if completely resected without residual disease; table does not apply to stage III-IVA with residual disease or for stage IV.

^bdMMR and MSI-H: Both terms identify a similar EC population. Identification of a defective mismatch repair pathway by IHC (i.e. dMMR) or sequencing to determine microsatellite instability (i.e. MSI-H).

^c*POLE*mut stage III might be considered as low risk. Nevertheless, currently there are no data regarding safety of omitting adjuvant therapy.

Portec-4a Clinical Trial

Clinical trial

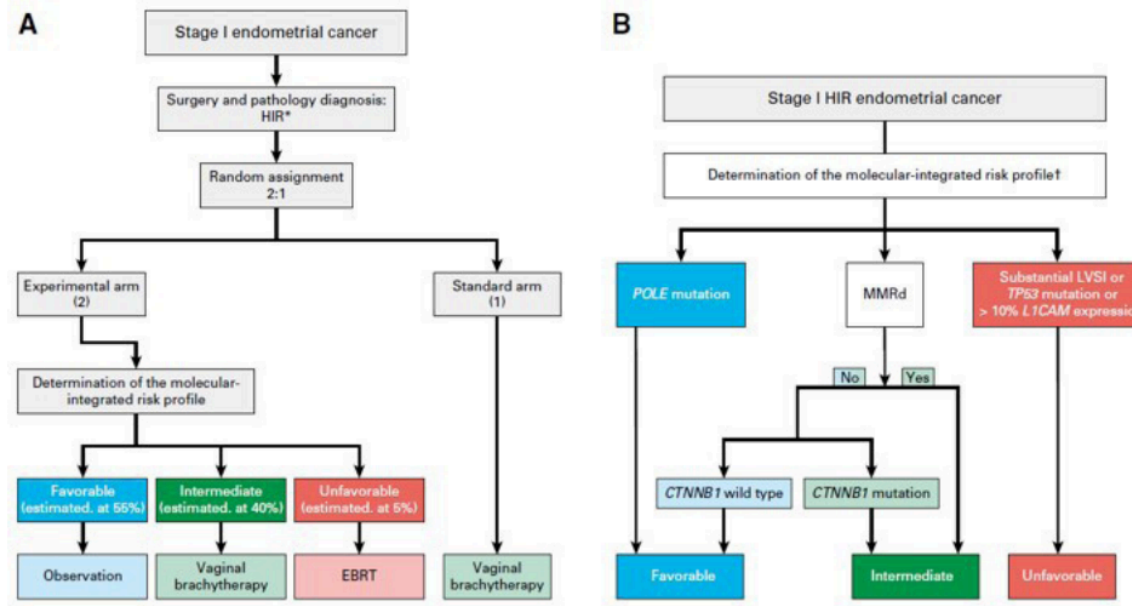


Figure 1 Study design PORTEC-4a trial. Reprinted from 'Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: evaluation of the pilot phase of the PORTEC-4a trial' by Wortman et al., 2018, *Gynecologic Oncology* 151; 69–75. A: trial design of the PORTEC-4a trial; B: decision tree for the molecular-integrated profile; *CTNNB1*, β -catenin; EBRT, external beam radiotherapy; LVSI; lymph-vascular space invasion; HIR, high-intermediate risk; L1-CAM, L1-cell adhesion molecule; *POLE*, polymerase- ϵ * stage I (with invasion) disease, grade 3 tumor; stage IB disease, grade 1 or 2 tumor, with either age 60 years or older or substantial LVSI; stage IB disease, grade 3 tumor, without LVSI; or stage II (microscopic) disease, grade 1 tumor.



Key Findings from PORTEC-4a

The randomised PORTEC-4a trial enrolled 592 women across eight European countries with (high-)intermediate risk endometrial cancer. Molecular testing classified tumours into risk categories, allowing treatment to be adapted accordingly:

- ✓ 46% of patients in the molecular-profile arm safely avoided radiotherapy.
- ✓ Patients with an unfavourable molecular profile received a more intensive radiation approach, pelvic radiotherapy instead of vaginal brachytherapy and the results suggest better locoregional control, with a recurrence rate of 8.4% compared to 30.5% in those who received standard treatment without molecular profiling.

RAINBO Program

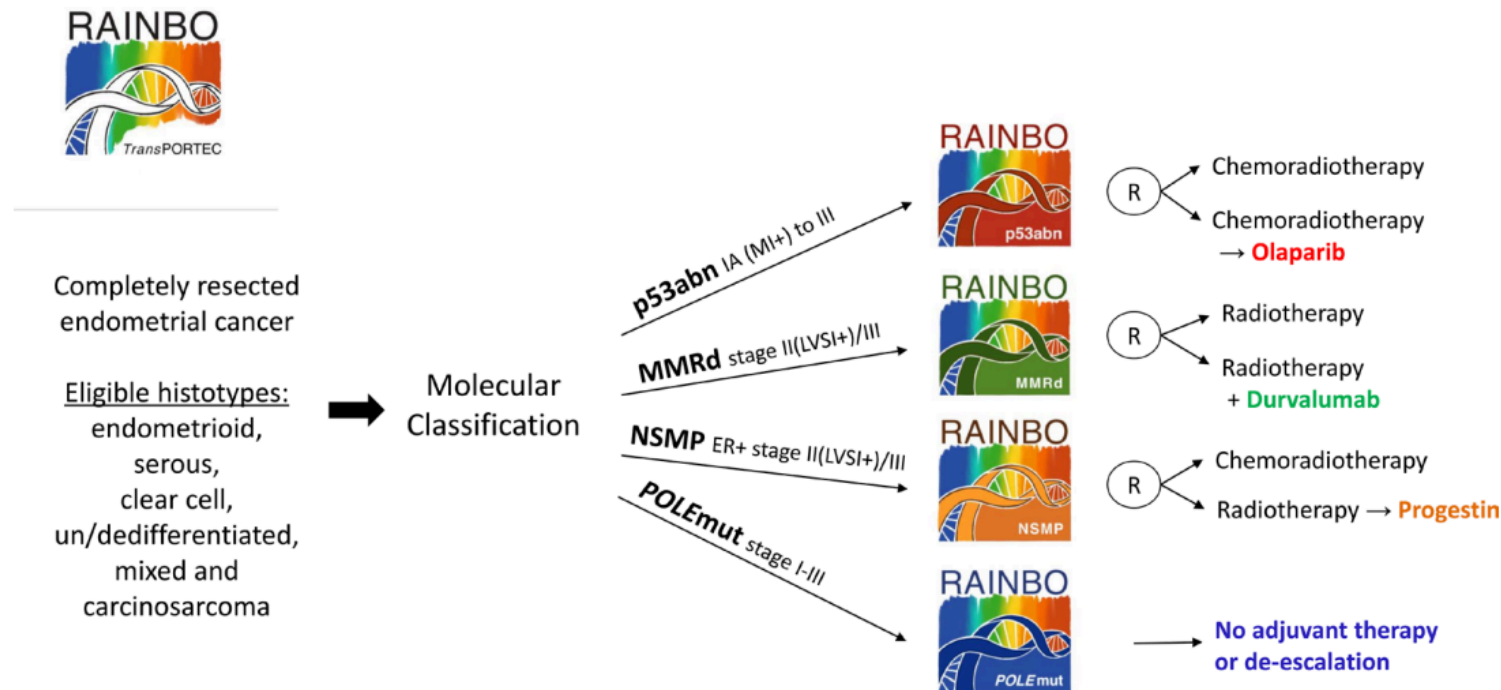


Figure 1 Design of the RAINBO program. ER, estrogen receptor status; LVSI, lymphovascular space invasion; MMRd, mismatch repair deficient; NSMP, no specific molecular profile; p53abn, p53 abnormal; POLEmut, DNA polymerase-ε mutated; R, randomization; RAINBO, Refining Adjuvant treatment IN endometrial cancer Based On molecular features.

Systemic Therapy in Endometrial Cancer



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NCCN Guidelines Version 3.2025 Endometrial Carcinoma

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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA^a

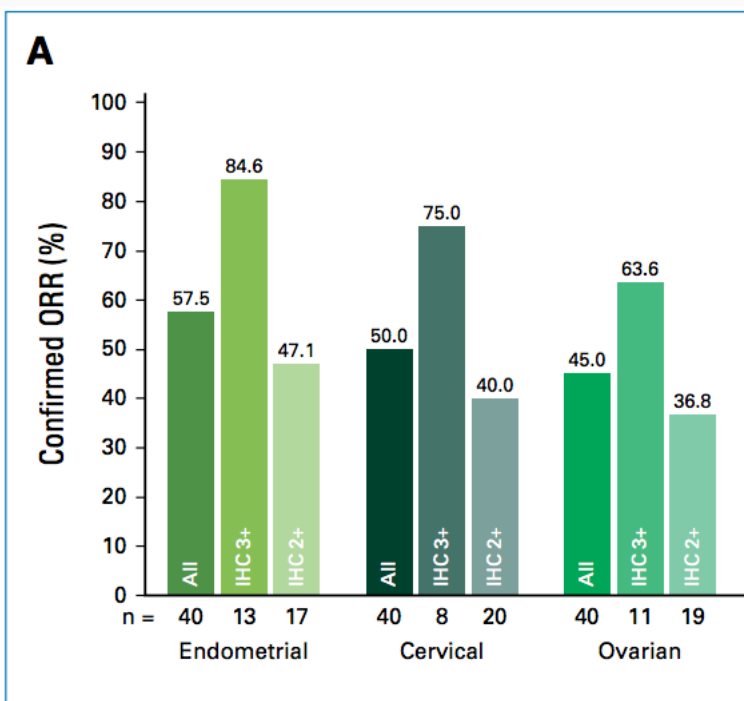
Primary or Adjuvant Therapy (Stage I–IV)	
Chemoradiation Therapy	Systemic Therapy
Preferred Regimen • Cisplatin plus RT followed by carboplatin/paclitaxel^{1,2} Other Recommended Regimens (if cisplatin and carboplatin are unavailable) • Capecitabine/mitomycin³ (category 2B) • Gemcitabine⁴ (category 2B) • Paclitaxel^{5,6} (category 2B)	Preferred Regimens • Carboplatin/paclitaxel/pembrolizumab (for stage III–IV tumors, except for carcinosarcoma) (category 1)^{b,c,d,7,8} • Carboplatin/paclitaxel/dostarlimab-gxly (for stage III–IV tumors) (category 1)^{c,d,e,9} • Carboplatin/paclitaxel/durvalumab (for stage III–IV dMMR tumors only) (category 1)^{c,d,f,10} • Carboplatin/paclitaxel/trastuzumab (for stage III–IV HER2-positive uterine serous carcinoma or carcinosarcoma)^{d,g,11} • Carboplatin/paclitaxel/bevacizumab (stage III–IV with measurable disease)^{d,12,13} • Carboplatin/paclitaxel¹⁴

IO + chemo moves up front for stage III=IV disease, regardless of MMR status (greater benefit from dMMR)

⑧ Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

Funda Meric-Bernstam, MD¹ ; Vicky Makker, MD^{2,3} ; Ana Oaknin, MD⁴ ; Do-Youn Oh, MD⁵ ; Susana Banerjee, PhD⁶ ; Antonio González-Martín, MD⁷ ; Kyung Hae Jung, MD⁸ ; Iwona Ługowska, MD⁹; Luis Manso, MD¹⁰ ; Aránzazu Manzano, MD¹¹; Bohuslav Melichar, MD¹²; Salvatore Siena, MD¹³ ; Daniil Stroyakovskiy, MD¹⁴ ; Anitra Fielding, MBChB¹⁵; Yan Ma, MSc¹⁶; Soham Puvvada, MD¹⁵; Norah Shire, PhD¹⁵; and Jung-Yun Lee, MD¹⁷ 

DOI <https://doi.org/10.1200/JCO.23.02005>



FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors

Meric-Bernstam F et al. J Clin Oncol 2024; 42(1)L 47-58.

Ovarian Cancer

Updates in Ovarian Cancer

- Antibody-drug conjugates
 - Mirvetuximab – overall survival and progression free survival benefit in FR alpha-high platinum resistant disease (standard of care)
 - Ongoing studies with MIRV in platinum sensitive disease
 - Raludotatug deruxtecan in clinical trials
- Targeted therapy – relacorilant (ROSELLA)
- Immunotherapy – pembrolizumab (KEYNOTE B96)
- Avutometinib and defactinib for KRAS-mutated recurrent low grade serous ovarian cancer
- Prevention trials: WISP and SOROCK

ADCs: Mirvetuximab

- MIRASOL: Mirvetuximab soravtansine-gynx (MIRV), ADC targeting folate receptor alpha (FR alpha) in platinum-resistant ovarian cancer
- 30.5 median f/u – OS 16.85 months (MIRV) vs 13.34 months (chemo) (HR 0.68 [95% CI: 0.54, 0.84])
- ORR 41.9% vs 15.9%

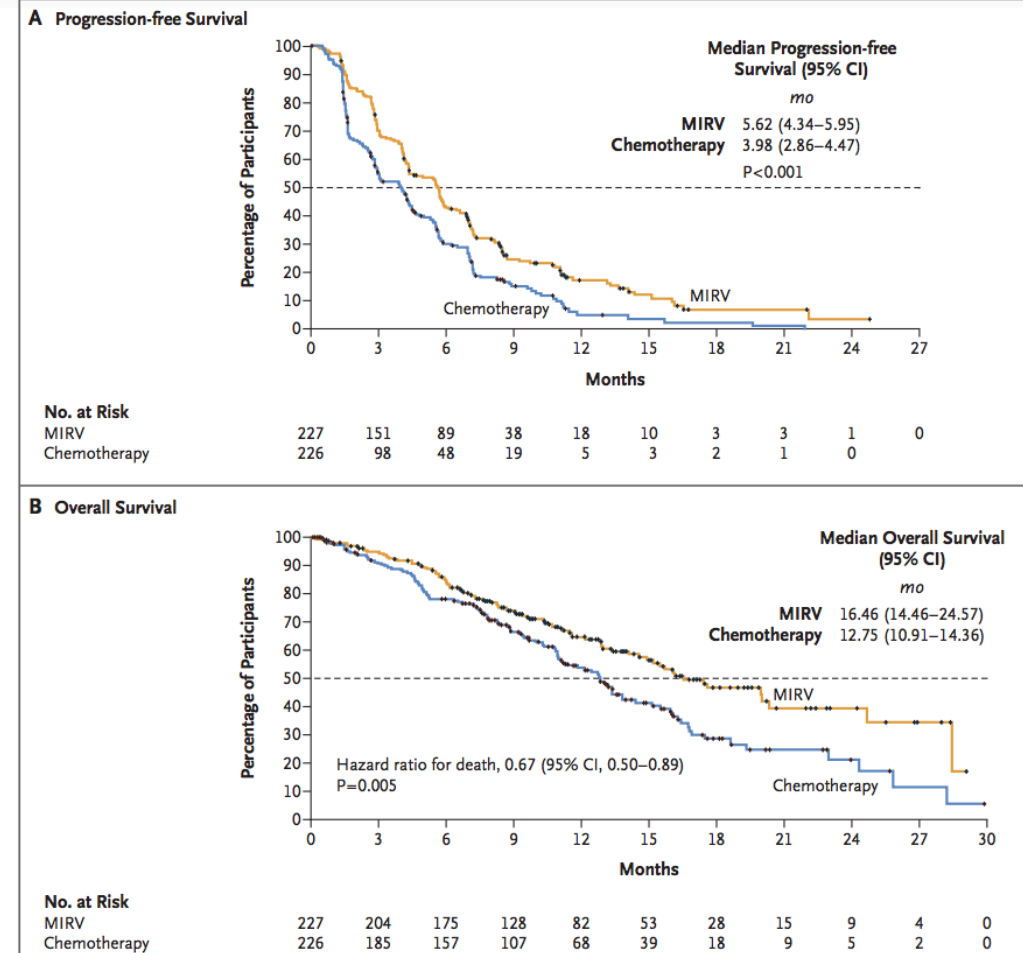


Figure 1. Efficacy Findings with MIRV as Compared with the Investigator's Choice of Chemotherapy.

Shown are the Kaplan–Meier estimates of investigator-assessed progression-free survival (the primary end point [Panel A]) and of overall survival (a key secondary end point [Panel B]) in the mirvetuximab soravtansine-gynx (MIRV) group and the chemotherapy group. The restricted mean progression-free survival at 12 months was 6.13 months (95% CI, 5.62 to 6.64) in the MIRV group and 4.72 months (95% CI, 4.21 to 5.23) in the chemotherapy group. Analyses were performed in the intention-to-treat population.

Moore K et al. NEJM 2023; 389:2162-2174; Van Gorp T et al. 2025 SGO Annual Meeting- Abstract 939696.

GLORIOSA Trial

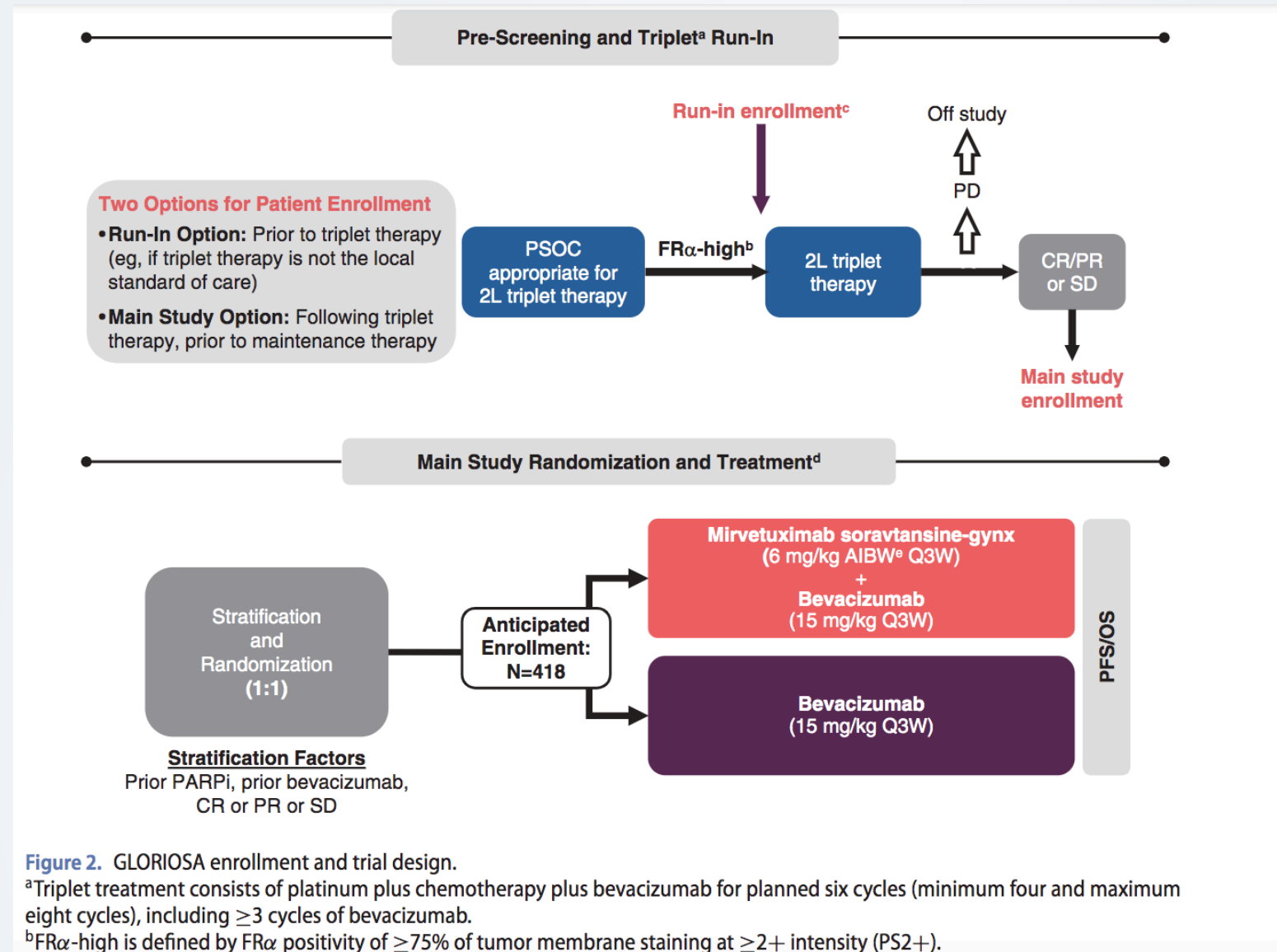


Figure 2. GLORIOSA enrollment and trial design.

^aTriplet treatment consists of platinum plus chemotherapy plus bevacizumab for planned six cycles (minimum four and maximum eight cycles), including ≥ 3 cycles of bevacizumab.

^bFR α -high is defined by FR α positivity of $\geq 75\%$ of tumor membrane staining at $\geq 2+$ intensity (PS2+).

Relacorilant- ROSELLA Trial

- Investigational, oral, selective glucocorticoid receptor antagonist that increases tumor sensitivity to chemotherapy induced apoptosis
- Randomized, controlled, open- label global study
- Relacorilant + nab-paclitaxel vs nab-paclitaxel monotherapy in patients with platinum resistant ovarian cancer
- Relacorilant is administered as 150 mg day before, day of, and day after nab-paclitaxel
- Presented at ASCO 2025: Median PFS 6.5 vs 5.5 months (P=0.008, HR 0.70, 95% CI 0.54-0.91)
- Median OS 16.0 vs 11.5 months, P=0.01 (HR 0.69, 95% CI 0.52-0.92)
- No new safety signals with addition of relacorilant

Raludotatug Deruxtecan (R-DXd)

- Granted FDA Breakthrough Designation September 2025 for the treatment of adult patients with platinum resistant epithelial ovarian, primary peritoneal or fallopian tube cancers expressing CDH6 who have received prior treatment with bevacizumab
- First in class CDH6 directed DXd ADC
- Sub-group analysis of phase 1 in ovarian cancer: 48.6% ORR, 48.6% stable disease, 97.4% disease control rate, CBR lasting ≥ 180 days was 50% (95% CI, 33.4-66.6). Median DOR 11.2 months (95% CI, 3.1-NE)
- Median PFS 8.1 months (95% CI, 5.3-NE)
- REJOICE Ovarian 01 – Phase 2/3 Randomized Study of R-DXd in platinum resistant ovarian cancer

Efficacy and Safety of Avutometinib ± Defactinib in Recurrent Low-Grade Serous Ovarian Cancer: Primary Analysis of ENGOT-OV60/GOG-3052/RAMP 201

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DOI <https://doi.org/10.1200/JCO-25-00112>

Avutometinib is a rapidly accelerated fibrosarcoma/mitogen-activated extracellular signal-regulated kinase clamp)

Defactinib is a focal adhesion kinase inhibitor

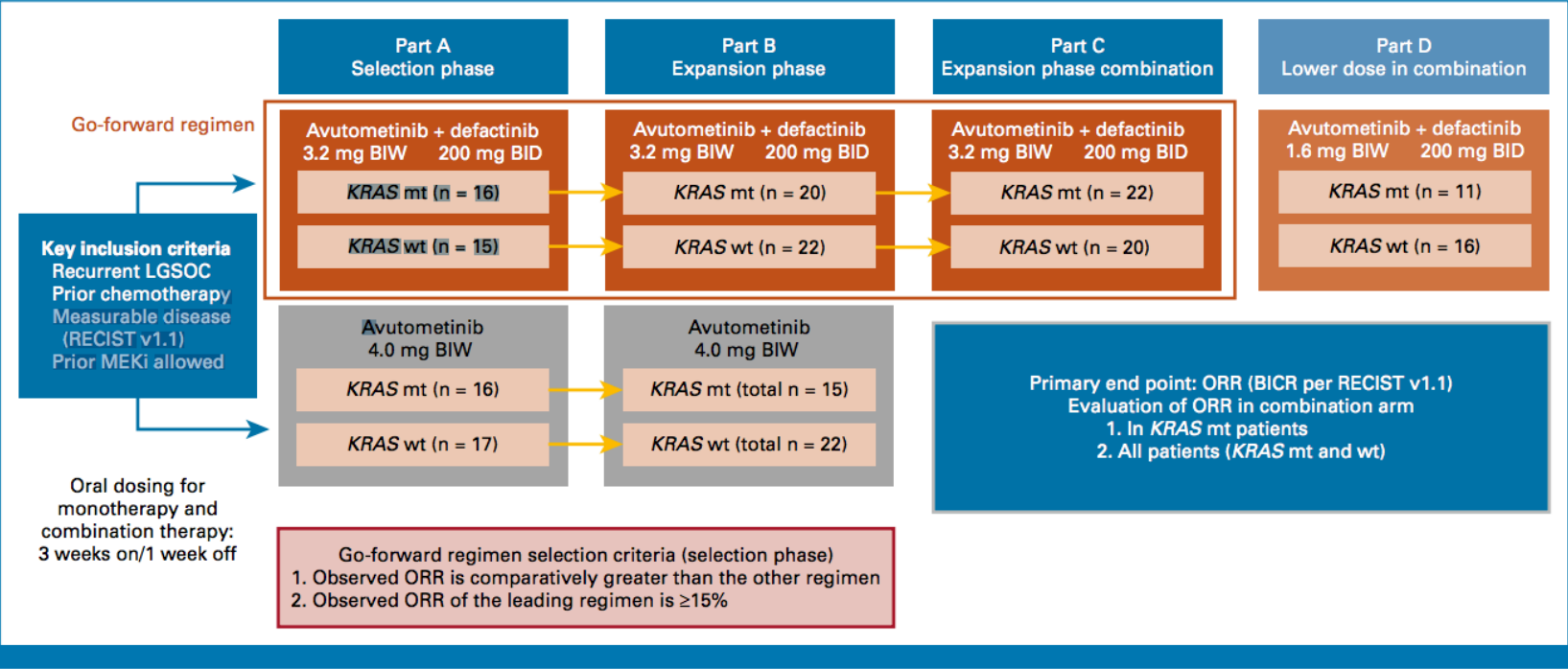
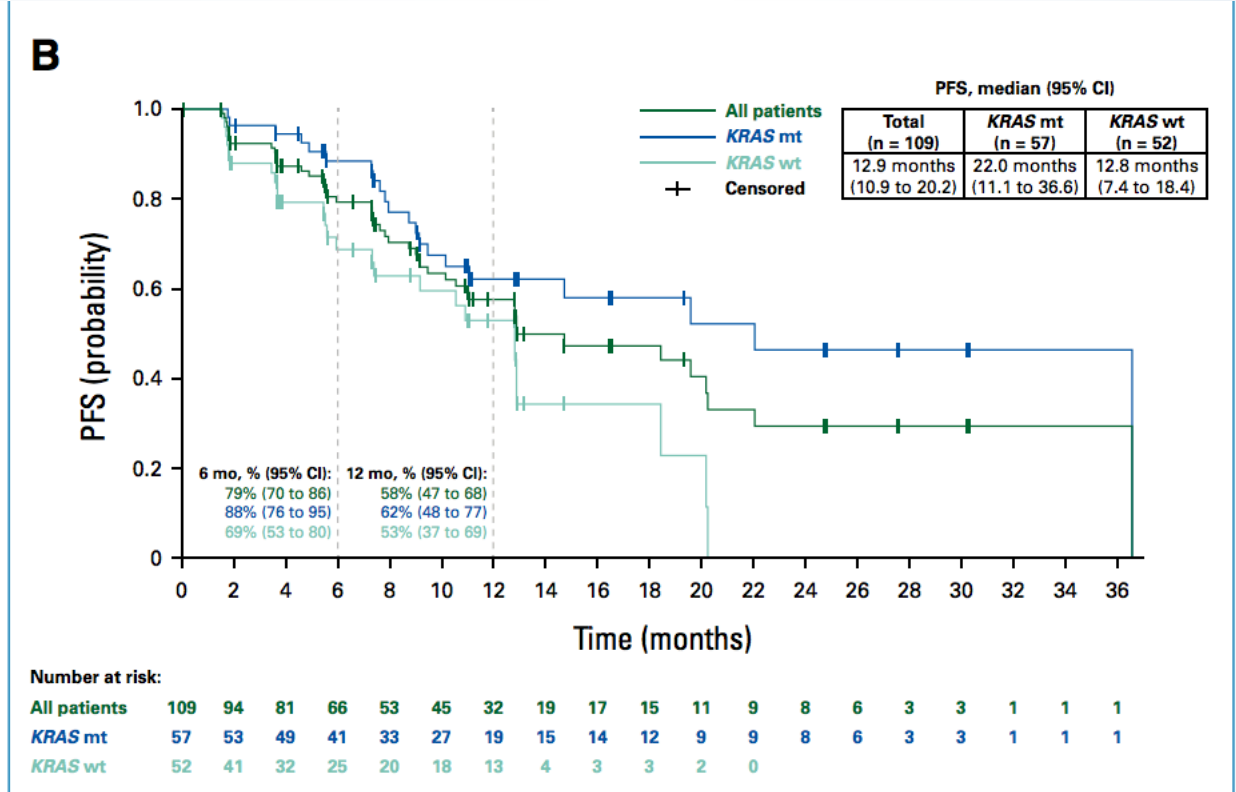
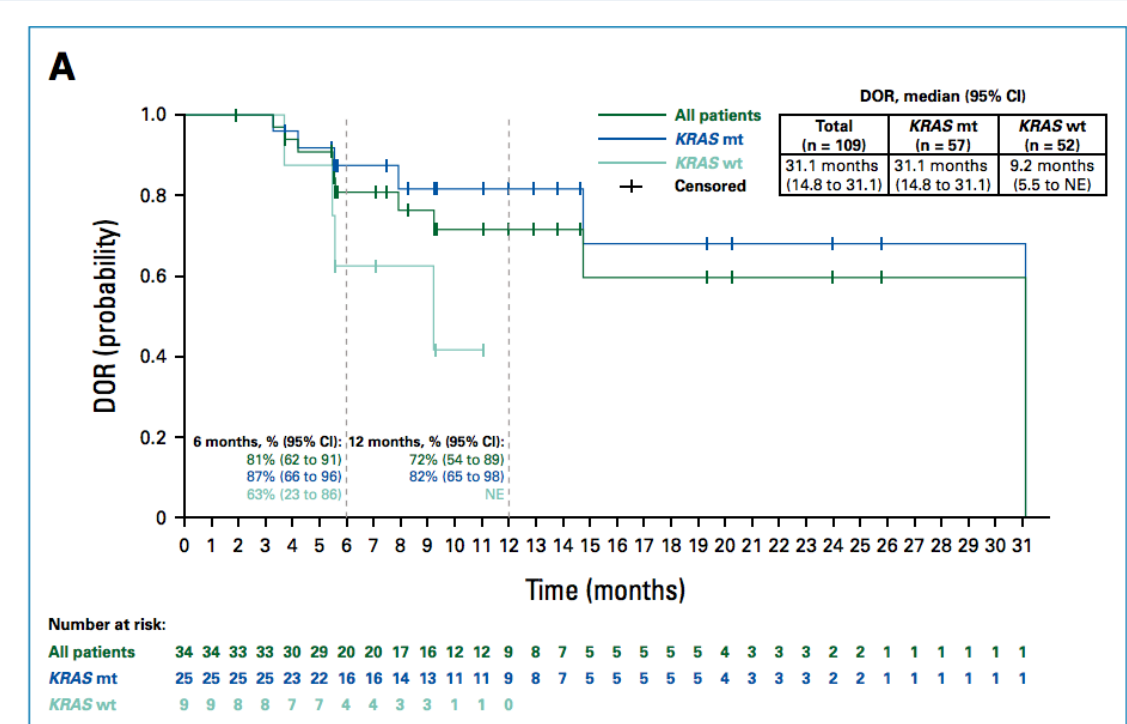


FIG 1. Study design. n values represent patients treated in the study. BICR, blinded independent central review; BID, two times per day; BIW, two times per week; LGSOC, low-grade serous ovarian cancer; KRAS, Kirsten rat sarcoma virus; MEKi, mitogen-activated extracellular signal-regulated kinase inhibitor; mt, mutant; ORR, objective response rate; wt, wild-type.

Results from RAMP 201



FDA approved in May 2025 - This approval marks the first-ever treatment for this specific subtype of ovarian cancer!

Updates in Ovarian Cancer Prevention

- Bilateral salpingo-oophorectomy (BSO) is the most effective way to reduce ovarian cancer risk.
- In BRCA mutation carriers, BSO is associated with 80% reduction in ovarian cancer risk and 68% reduction in all cause mortality
- Some hesitation for oophorectomy due to menopause/concerns re eligibility for menopausal hormone therapy
- Increasing role of opportunistic salpingectomy while preserving ovaries can reduce ovarian cancer risk

ACOG 2019 Clinical Opinion; Crum CP et al. Curr Opin Obstet Gynecol 2007; Yoon SH et al. Eur J Cancer 2016; Rebbeck TR et al. J Natl Cancer Inst 2009; Eleje GU et al. Cochrane Database Syst Rev 2018.

SOROCK Trial

SOROCK: Comparing the Effects of Two Surgical Procedures in Ovarian Cancer Risk Reduction in Women with BRCA1 Mutations

Currently Available for Patients

About This Study

NRG-CC008, also known as the SOROCK Trial, is a clinical trial available to a particular group of individuals with inherited BRCA1 mutations. For these pre-menopausal individuals, the study is testing whether removal of just the fallopian tubes, with the plan to remove the ovaries at a later time, can reduce the risk of ovarian cancer to the same degree as the usual standard of care of removing both the ovaries and fallopian tubes. Surgical removal of both ovaries and fallopian tubes very effectively reduces the risk of ovarian cancer in most individuals. Researchers believe that most “ovarian” cancers first begin in the fallopian tubes, suggesting that removing only the fallopian tubes may be as good as removing both the fallopian tubes and ovaries in preventing the development of ovarian cancer, while avoiding surgically induced menopause. This has never been formally tested in a clinical trial. The study will also look at how individuals on the study feel about their quality of life.

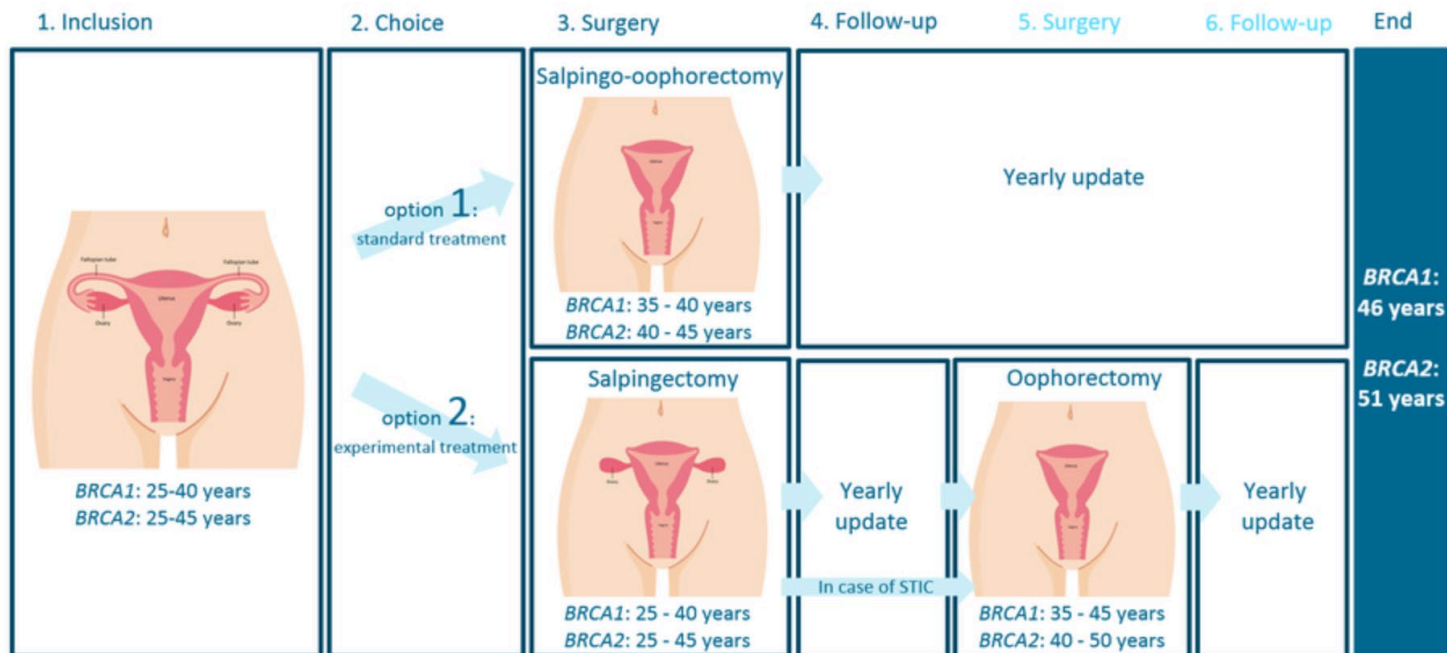
<https://www.nrgoncology.org/SOROCK>

TUBA-WISP II Study



Of the 2,000 patients selected, 1,035 (51.7%) had a BRCA1 pathologic variant, and 916 had the BRCA2 pathologic variant. In addition, 15 RAD51C carriers, seven RAD51D carriers, 21 BRIP1 carriers, and five PALB2 carriers were included. Most participants (75.9%) chose RSS surgery with DO over the standard RRSO (24.1%). Thus far, eight high-grade serious carcinomas (HGSCs) have been diagnosed at first surgery: four in the RSS/DO group and four in the RRSO group. In addition, seven isolated serous tubal intraepithelial carcinomas have been diagnosed in the RRS/DO group, with three in the RRSO group.

Study flowchart



Updates from 2025 SGO Meeting

Cervical Cancer

Surgical Updates

- Early stage cervical cancer
 - LACC Trial: OS between open and minimally invasive radical hysterectomy for early stage cervical cancer: 90.6% for minimally invasive and 96.2% for open surgery approach at 4.5 years (HR for death of any cause =2.71 [95% CI, 1.32 to 5.59], p=0.007) (DFS: 85% in minimally invasive vs 96% open group)
 - SHAPE Trial: Simple hysterectomy not inferior to radical hysterectomy with respect to 3 year incidence of pelvic recurrence (2.17% in rad hyst vs 2.52% simple hyst) and associated with lower risk of urinary incontinence or retention.

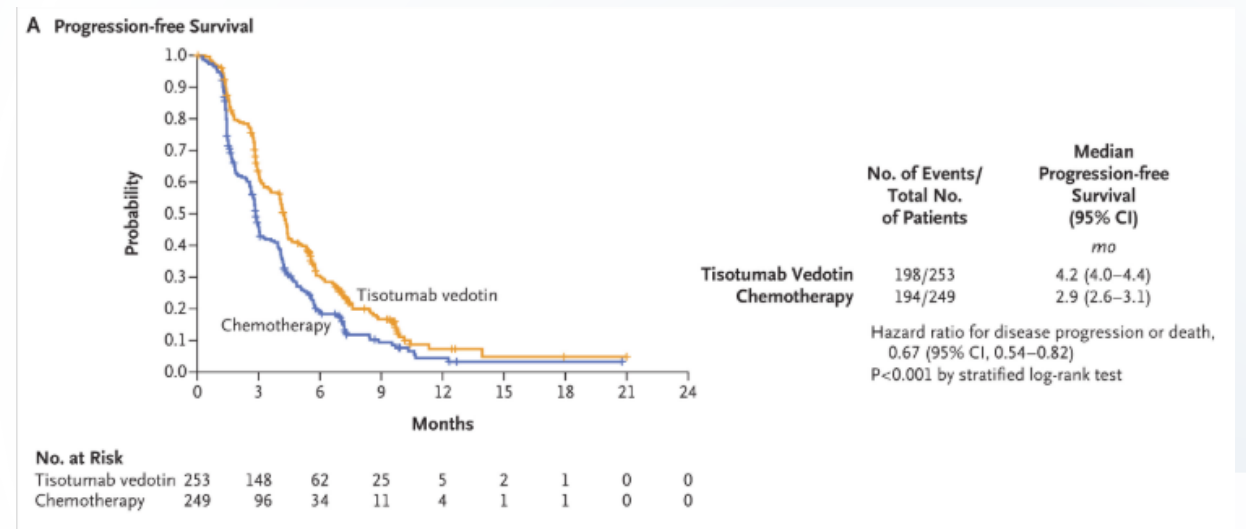
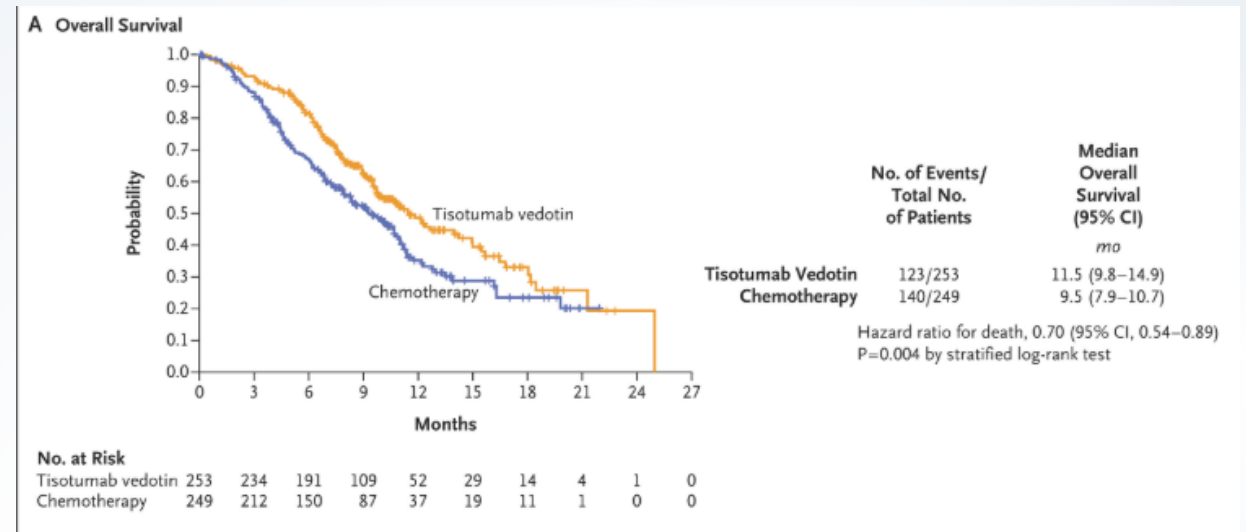
Updates in Locally Advanced Cervical Cancer

- **INTERLACE** - LACC (Stage IB1 with nodal involvement, IB2-IVA) randomized to CCRT with weekly cisplatin or induction chemo (weekly carbo AUC 2/paclitaxel 80 mg/m² for 6 weeks) followed by cisplatin based chemoradiotherapy.
 - Median f/u 67 months 5 year PFS 72% induction group vs 64% chemoRT group alone (HR 0.65, 95% CI 0.46-0.91); 5 year OS 80% induction group vs 72% chemoRT group alone (R 0.60, 95% CI, 0.4-0.91)
- **KEYNOTE A-18**- Newly diagnosed, previously untreated high risk stage IB2-IIIB with node positive disease or stage III-IVA regardless of lymph node status, randomized to CCRT + pembrolizumab or placebo → maintenance pembro or placebo (regardless of PD-L1 status)
 - 36 month OS 81.8% (pembro) vs 74.4%, HR 0.73 (0.57-0.94); Median PFS 47.6 mo vs 47.5 mo; 24 month PFS 70.6% vs 59.7% (HR 0.72, 0.59-0.87)
- **CALLA** – durvalumab concurrent with chemoRT in LACC did not improve PFS (KEYNOTE A18 higher risk population)
- How to integrate INTERLACE and KEYNOTE A18 is evolving

Duska L et al. JCO 2025; 43(17_suppl); Lorusso D et al. Lancet 2024; 403(10434):1341-1350; McCormack M et al. Lancet 2024; 404 (10462): 1525-1535; Monk B et al. Lancet Oncology 2023; 24(12): 1334-1348.

Tisotumab vedotin-tftv in cervical cancer

- Monoclonal antibody directed against the cell surface protein, tissue factor (TF) linked to the cytotoxic agent, monomethyl auristatin E (MMAE) which is a potent microtubular disruptor
- TF elevated in several solid tumors including recurrent cervical cancer
- InnovaTV 301 Trial: phase 3 open label trial of tisotumab vedotin (vs chemo) as second- or third-line therapy in recurrent or metastatic cervical cancer
- Pay attention to ocular toxicities



Management of Ocular Toxicities for Mirvetuximab soravtansine and Tisotumab vedotin

- **Prophylaxis**
 - Preservative-free artificial tears or lubricating eye drops
 - Ophthalmic topical corticosteroids before and during treatment
 - Vasoconstrictor eye drops before each infusion and using cooling eye pads during infusion (Tisotumab vedotin)
 - Avoid contact lenses unless directed by ophthalmologist
- **Monitoring**
 - Ophthalmic examination (visual acuity and slit lamp) prior to initiation
 - Regular ophthalmic examinations
 - Advise patients to report any visual changes
- **Management**
 - Ophthalmic examination promptly for worsening symptoms
 - For moderate or severe ocular AEs, withhold treatment until improvement, restart at same or reduced dose, or consider permanent discontinuation for worsening symptoms that are unresponsive

Conclusions

- Molecular profiling and biomarker testing are essential for every patient, are the standard of care and critical for therapy selection
- ADCs are reshaping gynecologic cancer care
- Toxicity considerations: ADCs require ocular prophylaxis and monitoring (mirvetuximab, tisotumab), ILD/pneumonitis for T-DXd, immune related adverse events for IO therapy
- Prevention and de-escalation trials will continue to refine care in the coming years
- Thank you!