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SGO ANNUAL MEETING ON WOMEN'S CANCER
SAN JUAN, PR
APRIL 10-13, 2026

Results of a Randomized Phase III Trial of Letrozole Alone Versus Paclitaxel and Carboplatin Followed by Letrozole as Initial Treatment for Patients with Stage II-IV Ovarian, Fallopian Tube, or Primary Peritoneal Low-Grade Serous Carcinoma (NRG-GY019, NCT04095364)

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Unlabeled/Investigational Uses

- I will be discussing an unlabeled use of a pharmaceutical product (letrozole) studied within a Phase III trial.

Disclosures

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- I have the following financial relationships with ACCME-defined ineligible companies to report over the past 24 months: GSK.

- This work was supported by grants U10CA180868 (NRG Oncology Operations) and U10CA180822 (NRG Oncology SDMC)

-Amanda Nickles Fader, MD

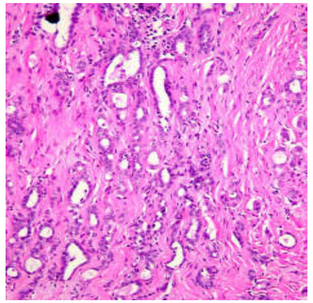
Background

- Low-grade serous ovarian carcinoma (LGSOC) accounts for 2-5% of all epithelial ovarian carcinomas and ~10% of serous ovarian carcinomas

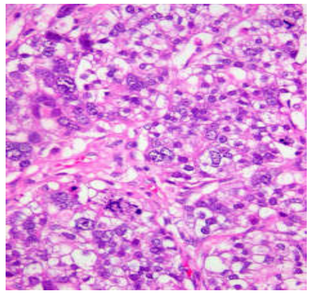
- Epidemiologically, pathologically, molecularly, and clinically distinct from high-grade serous ovarian carcinoma (HGSOC)

- Historically, patients with LGSOC and HGSOC have been treated similarly despite clear biologic differences and treatment responses

Variable	LGSOC (Grade 1)	HGSOC (Grade 2/3)
Nuclear atypia	Uniform round to oval with little variation	Marked variation
Mitotic Index	<12 mitosis per 10 hpf	>12 mitoses per 10 hpf
Chromatin and variation in size of nucleus	Little	Marked (nuclear size ratio ≥3)
Mutation/ Protein Expression	KRAS NRAS BRAF ER/PR	TP53
Precursor	Serous borderline tumor	Tubal intraepithelial neoplasia



LGSOC



HGSOC

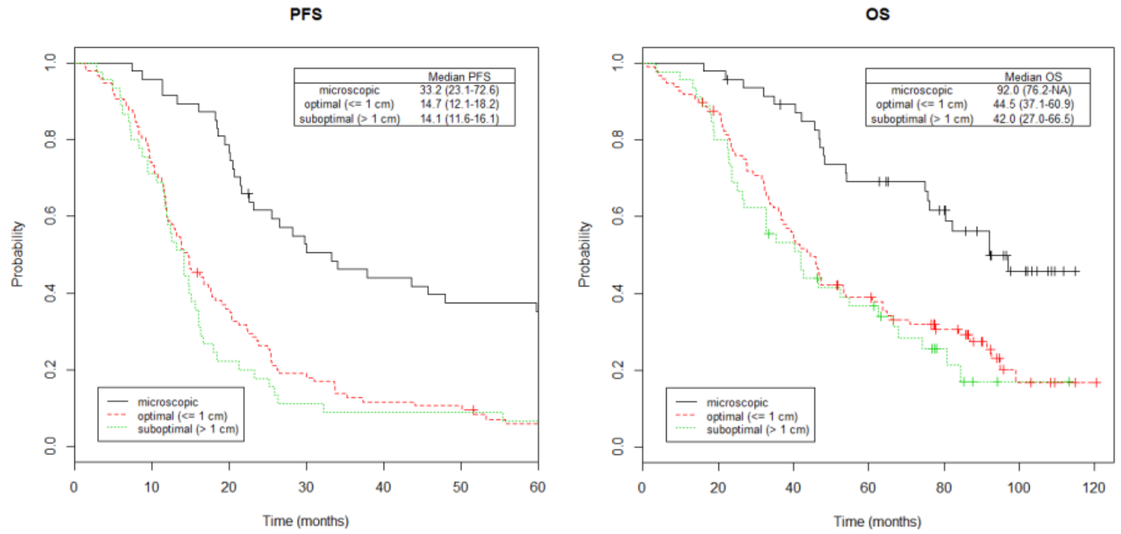
Malpica et al, Am J Path, 2007
Kurman et al, Am J Path, 2007

Background

- Indolent growth rate and relative chemoresistance to platinum/taxane therapy compared with HGSOC

- High recurrence risk; persistent disease after primary cytoreductive surgery linked strongly to worse survival in a Phase III GOG 182 ancillary analysis

GOG 182 Ancillary Analysis of Grade 1 Serous Ovarian Carcinoma Cohort



Fader et al, Obstet Gynecol, 2013; Gershenson et al, J Clin Oncol, 2016; Fader et al, Gynecol Oncol, 2016

Background

- LGOSC expresses estrogen receptors in ~85–90% of cases and progesterone receptors in ~50% of cases

- **MD Anderson:** 1º cytoreductive surgery->chemotherapy +/- endocrine maintenance therapy
  - **Median PFS C/P/Observation vs. C/P/endocrine therapy was 26.4 vs. 64.9 months (p<0.001)**

- **JHH/CCF:** 1º cytoreductive surgery->endocrine therapy
  - Only 22% recurred after a median follow-up of 41 months
  - **Median PFS and OS not reached; At 3 years, PFS 79.0% and OS 92.6%**

- **MGH/MD Anderson:** 1º cytoreductive surgery-> chemotherapy +/-endocrine therapy or endocrine therapy only
  - **Endocrine therapy associated with a reduction in risk of death (HR: 0.60; 95%CI 0.38–0.94)**

NCCN National Comprehensive Cancer Network®

In 2017, the guidelines endorsed treating advanced LGSOC with either chemotherapy followed by endocrine therapy OR endocrine monotherapy (letrozole, anastrozole, tamoxifen, or leuprolide) — a Category 2B recommendation.

Gershenson et al, J Clin Oncol, 2016;
Fader et al, Gynecol Oncol, 2016;
Armstrong D et al, J Compr Canc Network,
Barakzai, et al, Gynecol Oncol, 2024

Unanswered Clinical Questions:

What should be the practice standard for the frontline treatment of advanced LGSOC?

Can chemotherapy be safely omitted in this patient population?

NRG-GY019 Study Objectives:

To demonstrate non-inferiority of Letrozole alone (L) versus paclitaxel and carboplatin followed by L (CP/L) as initial treatment for patients with stage II-IV, low-grade serous carcinoma of the ovary, fallopian tube, or peritoneum.

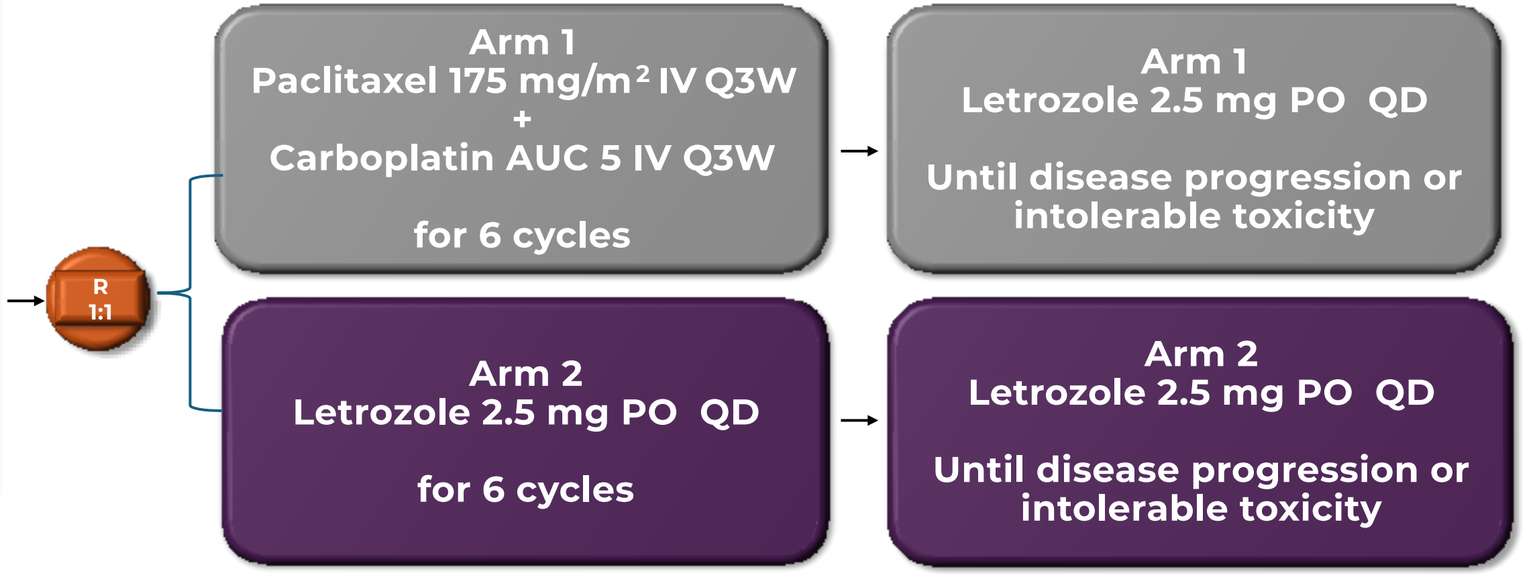
NRG-GY019 (NCT04095364)

Key Eligibility Criteria

- Stage II-IV LGSOC
- Pathology report showing results of institutional p53 wildtype IHC testing
- ECOG PS 0, 1, or 2
- Attempt at maximal cytoreductive surgery
- No prior chemo

Stratification Factors

- Residual disease status
- Country



Endpoints

- **Primary:** PFS by investigator
- **Secondary:** Safety, OS, ORR/DOR per RECIST v1.1

Statistical Considerations

Analysis

- Efficacy: Intent-to-treat
- Safety: All treated patients

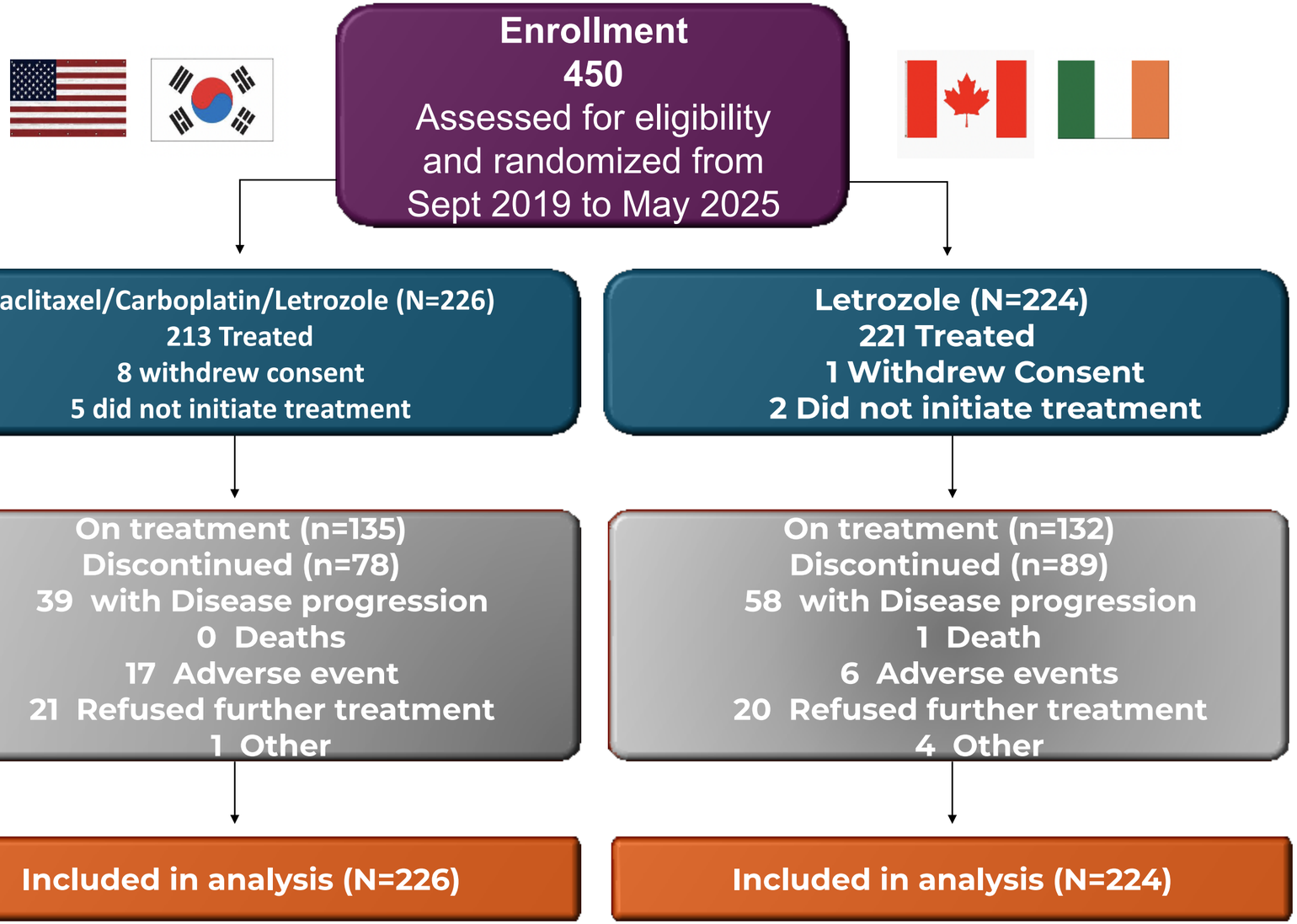
Power calculations for PFS (primary endpoint)

- NI Margin hazard ratio (HR) = 1.18; 1-sided α=0.1, Power=0.8, 222 PFS events
- Two interim analyses planned

• Prespecified exploratory analysis

- Residual disease status, country, race, ECOG performance status

Patient Disposition



Patient Characteristics

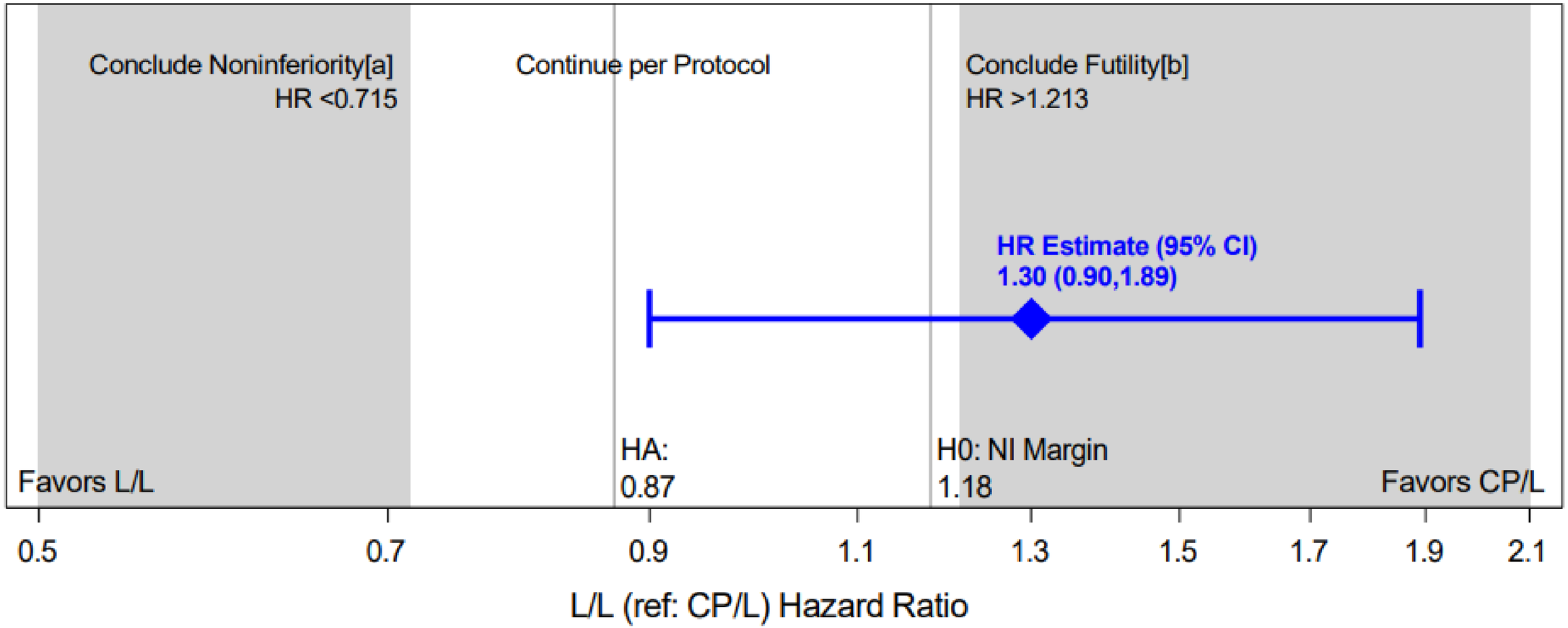
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N = 450			
Age		**Country**	
Median	51.9	US/Canada	432 (96%)
Min/Max	19.3-81.7	Rest of World	18 (4%)
Race		**Stage**	
Am Indian/Alaska Native	5 (1.1%)	I	3 (0.7%)
Asian	19 (4.2%)	II	32 (7.1%)
Black/African American	13 (2.9%)	III	353 (78.2%)
Native Hawaiian	1 (0.2%)	IV	62 (13.8%)
White	386 (85.8%)	Unknown	1. (. 0.2%)
Multiple	1 (0.2%)		
Not Reported/Unknown	25 (5.6%)		
Ethnicity		**Residual Disease**	
Hispanic or Latino	39 (8.7%)	No Gross	286 (63.6%)
Not Hispanic or Latino	396 (88.0%)	</=1 cm	123 (27.3%)
Not Reported or Unknown	15 (3.3%)	>1 cm	41 (9 1%)
ECOG Status			
0 Fully Active	321 (71.3%)		
1 Restr Activity	120 (26.7%)		
2 Ambulatory	7 (1.4%)		
Missing	2. (0.4%)		

PFS-Noninferiority Margin Plot

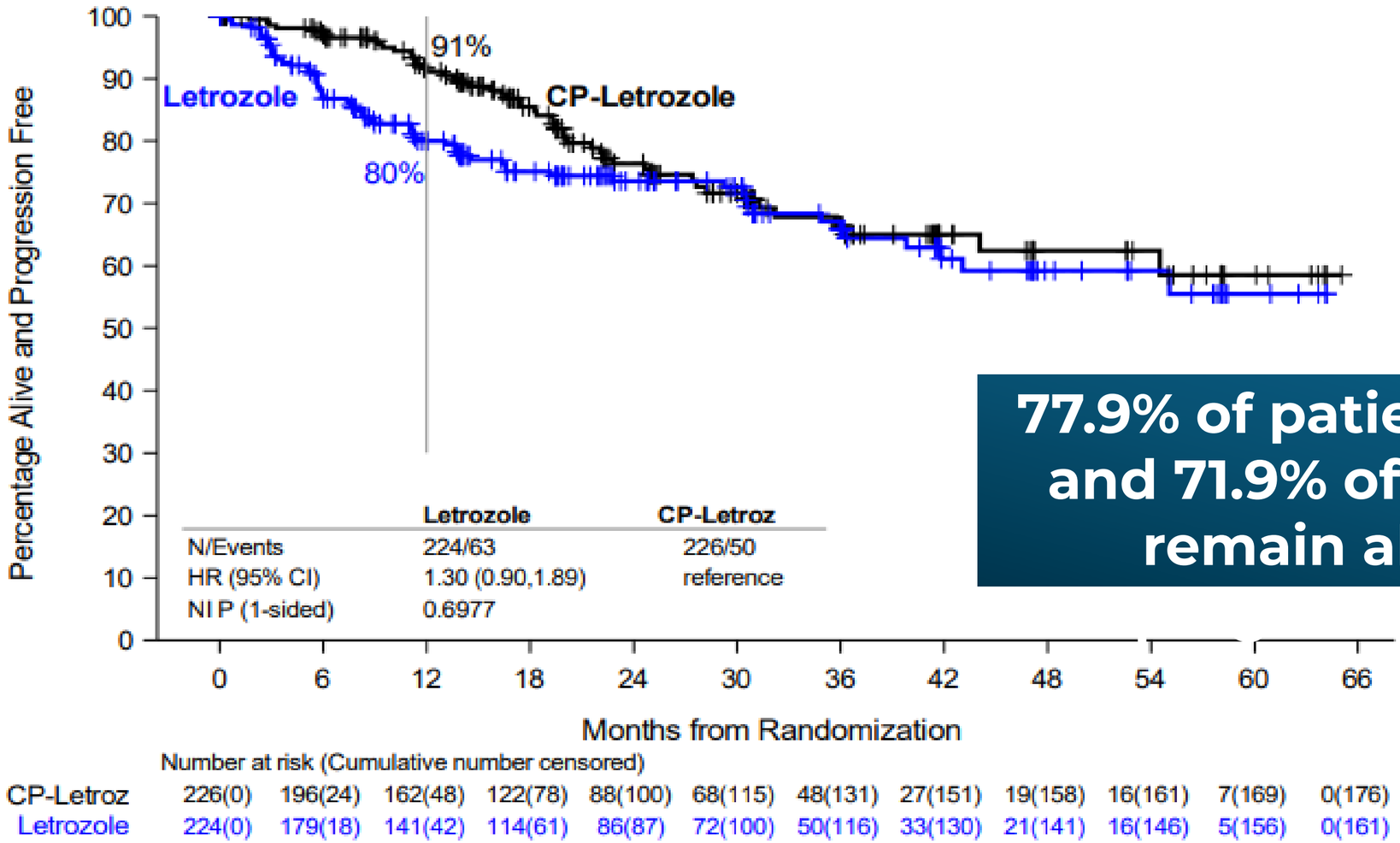
- Interim analysis #2 margins

1. /Analysis4_Fi



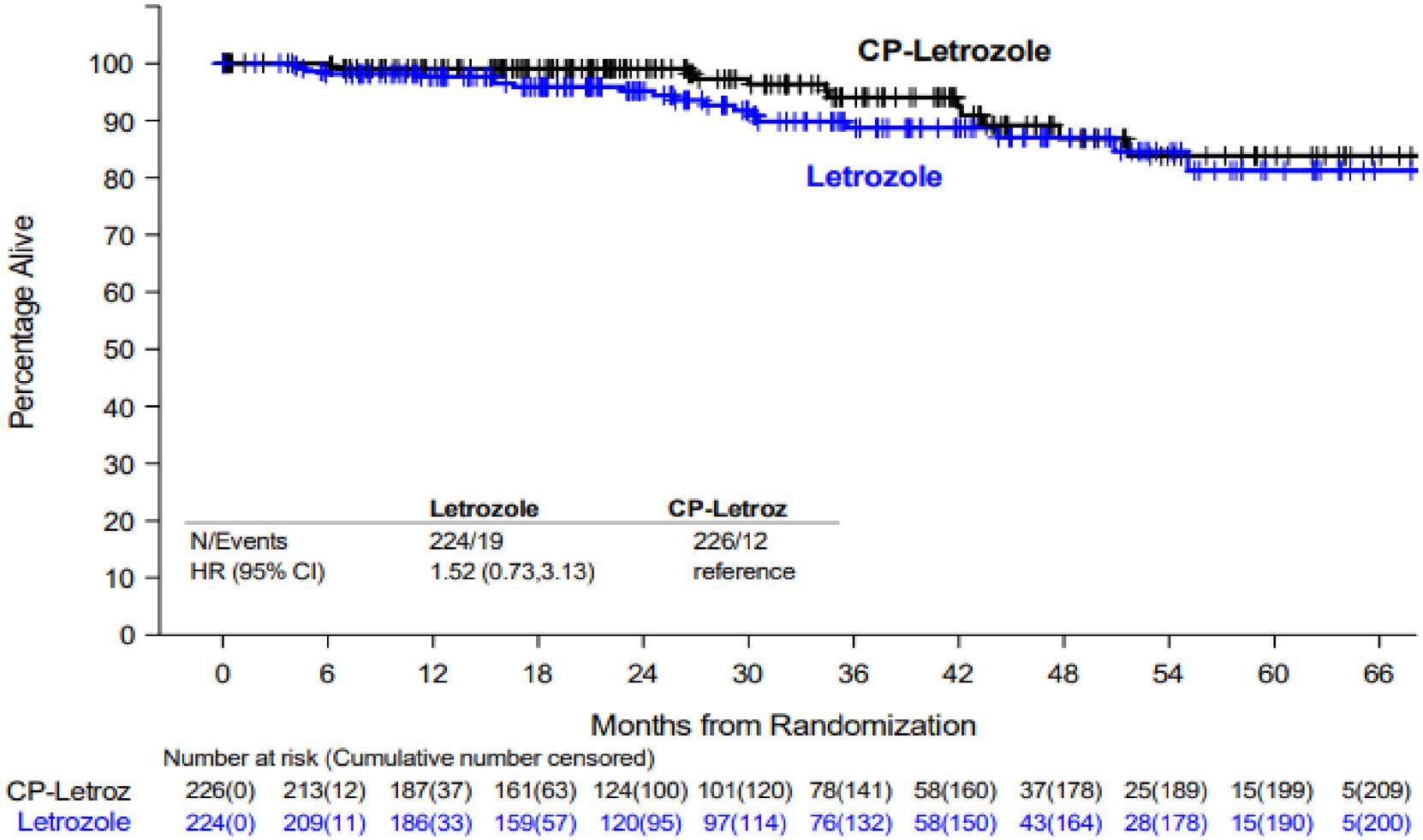
[a] Conclude L/L is not inferior to CP/L.
[b] Conclude L/L is not likely to demonstrate noninferiority at the end of the trial.

Progression-Free Survival (PFS)



77.9% of patients on CP/L and 71.9% of those on L remain alive and

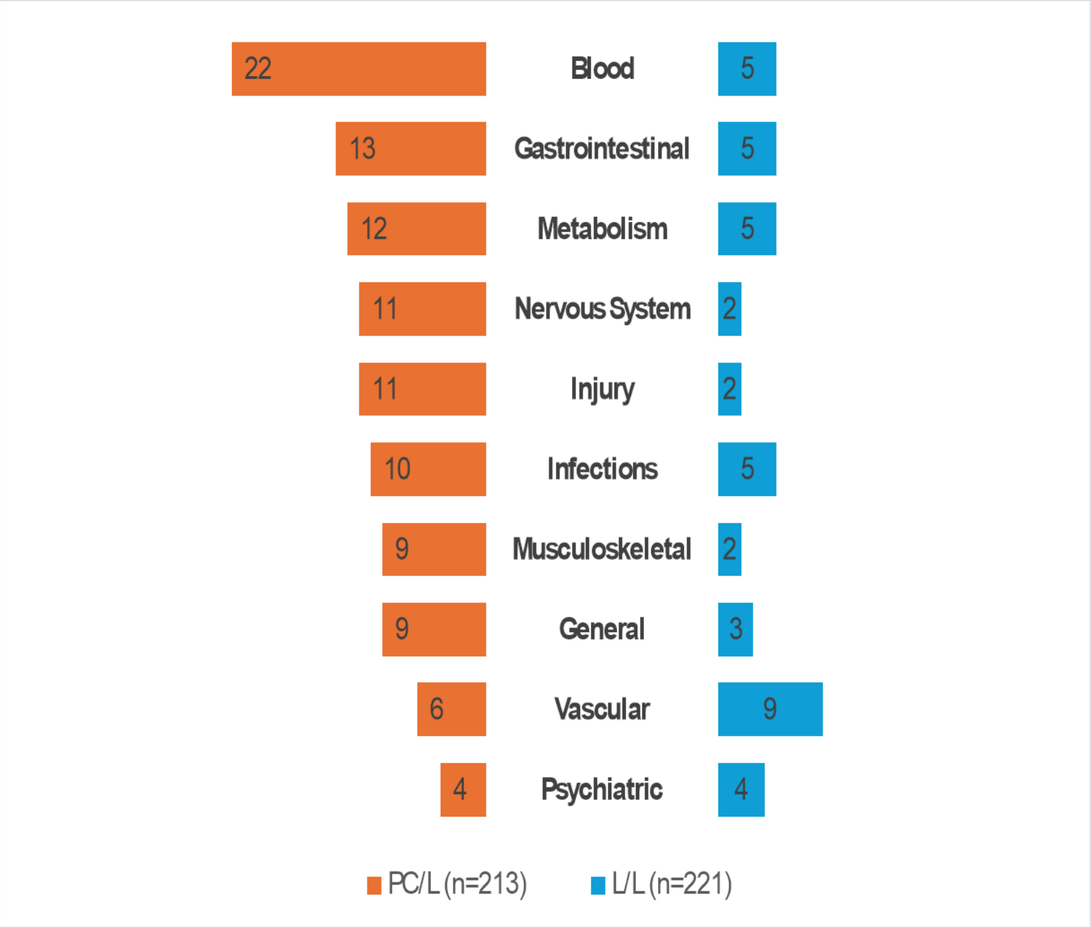
Overall Survival (OS)



Adverse Event Summary

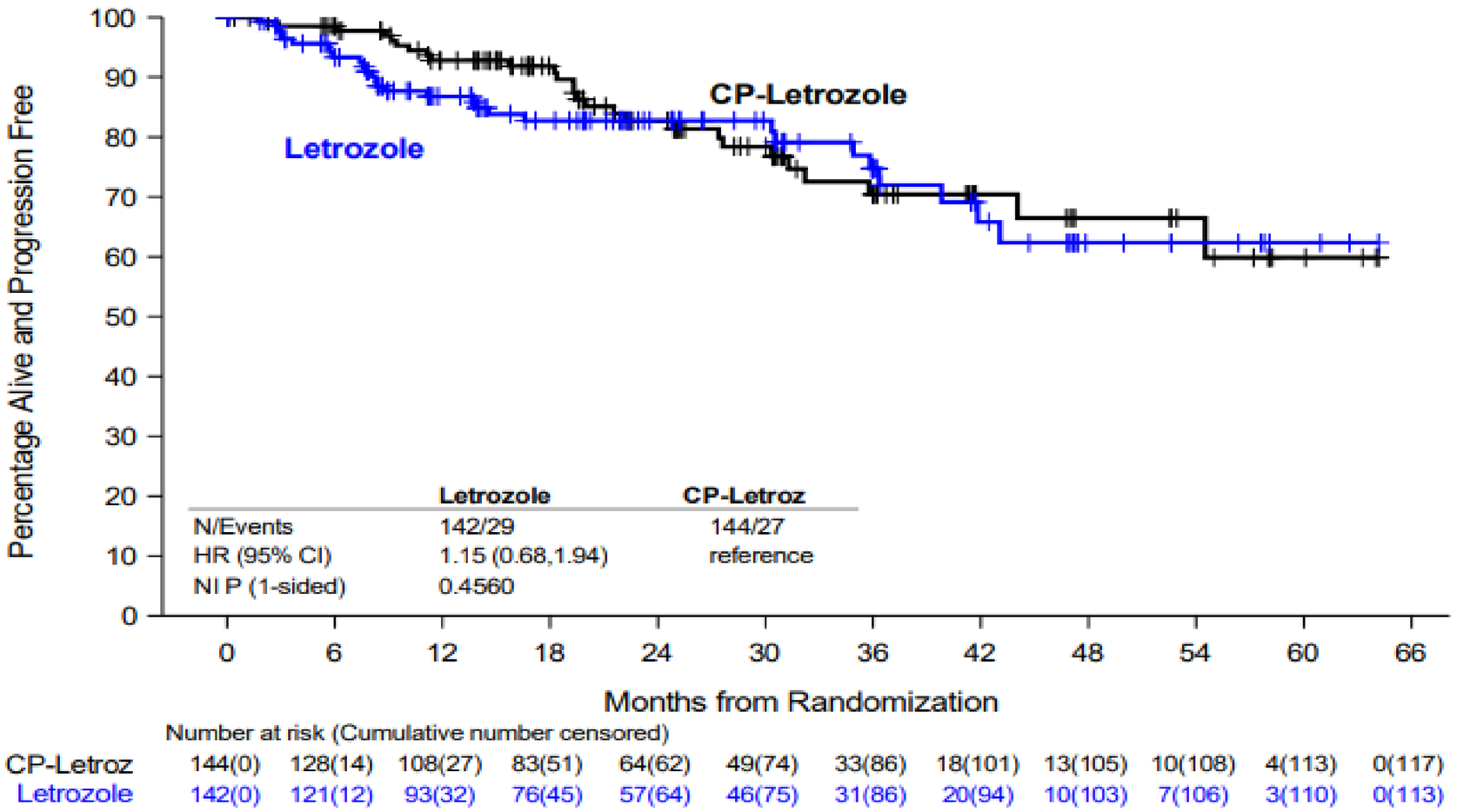
	Cycle 1-6		Cycle 7+	
Adverse Event	PC/L (n=213)	L/L (n=221)	PC/L (n=191)	L/L (n=189)
Any Adverse Event	213 (100)	214 (96.8)	191 (100)	189 (100)
Grade 3-5	100 (46.9)	39 (17.6)	79 (41.4)	66 (34.9)
Leading to death	0 (0)	1 (0.5)	0 (0)	1 (0.5)

During cycles 1-6, the odds of observing at least 1 grade 3/4 adverse event was **3.99 (95%CI: 2.57, 6.18 p<0.001)** higher in the patients on the CP/L than the patients on the L arm.



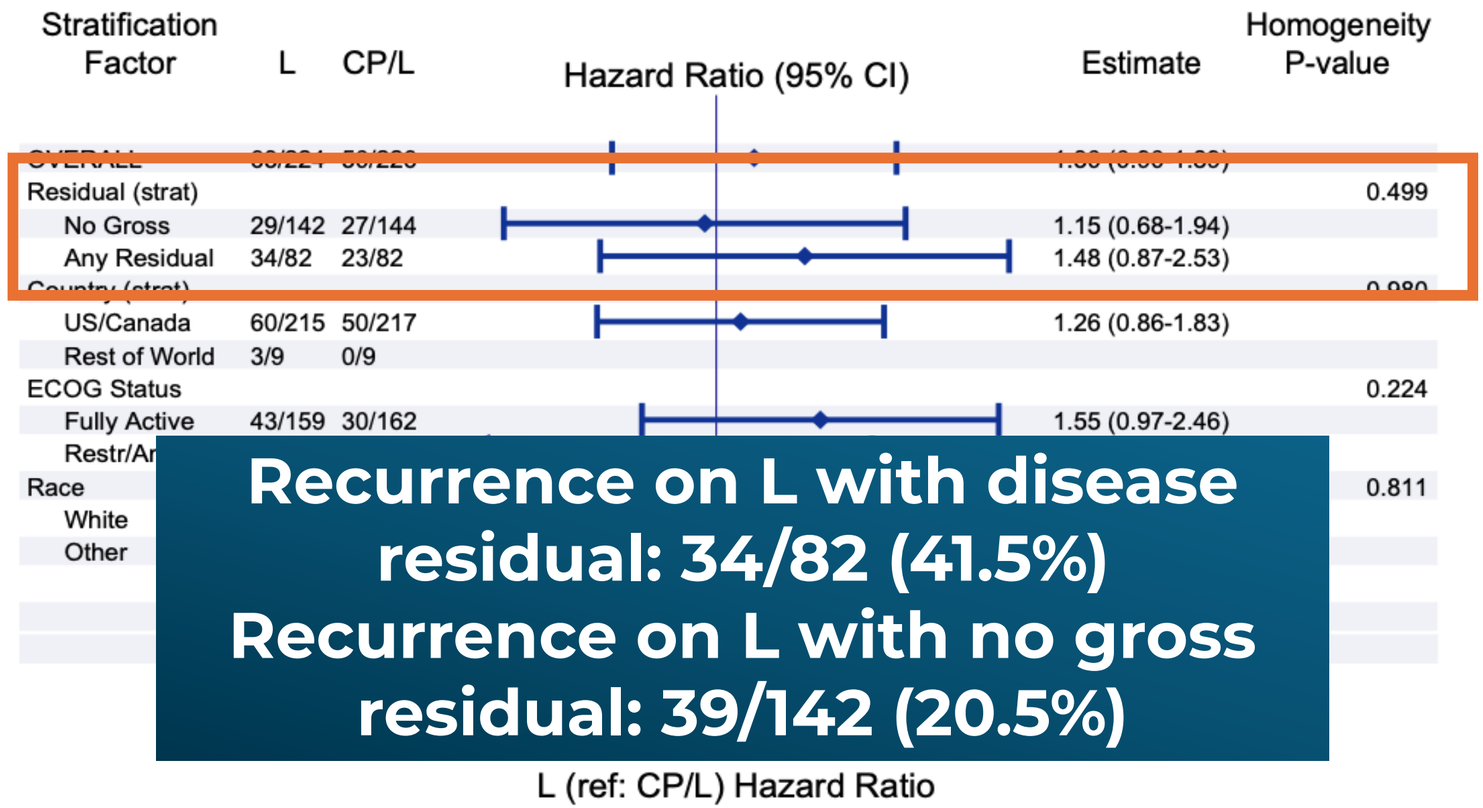
PFS in Patients with No Gross Residual Disease After Cytoreductive Surgery

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1. ./Analysis4_FinalAnalysis/Figs/GY019_PFS_KM_IA3_Nogross4.pdf

PFS: Subgroup Analysis



Recurrence on L with disease residual: 34/82 (41.5%)
Recurrence on L with no gross residual: 39/142 (20.5%)

1. K:\Protocols\NRG\GY019\Analyses\Analysis4_FinalAnalysis\Figs\GY019_pPFS_ForestPlot_20260218.pdf

Conclusions

- In the intent-to-treat population, the study met the pre-specified futility stopping criteria and did not demonstrate non-inferiority of letrozole monotherapy versus chemotherapy followed by letrozole.
- This is a practice-defining trial and establishes carboplatin/paclitaxel and letrozole as the standard of care.
- In a hypothesis-generating, prespecified analysis of patients who achieved NGR disease, PFS did not differ significantly between treatment arms, with a HR of 1.15 for disease progression on letrozole monotherapy.
- Although exploratory, this finding is provocative and raises the possibility that a clinically relevant subset of patients may be appropriate candidates for letrozole monotherapy.
- Ongoing clinical follow-up and planned correlative tumor molecular profiling are essential to better contextualize these observations, clarify which patients derive the greatest benefit from chemotherapy/letrozole, and determine whether letrozole alone may be a reasonable alternative in select patients.

Conclusions

- NRG-GY019 is the first Phase III frontline trial in low-grade serous ovarian carcinoma and the first Phase III rare epithelial ovarian cancer study to complete enrollment—milestones that underscore the ability of clinicians, research teams, and cooperative group networks to successfully conduct rigorous trials in rare tumor patient populations.

- The trial design was shaped by substantial and meaningful input from patient advocates, ensuring alignment with the priorities and lived experiences of the patients it was intended to serve.

Acknowledgments

We gratefully acknowledge the patients and their families who enrolled in this international trial, and the investigators and site teams at 925 sites across 8 countries whose commitment and effort made this study possible.

Study Design:
- A. Miller (Statistician)
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- C. Aghajanian (NRG Gynecologic Oncology Committee Chair)

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