BERLIN 2025 ESMO congress

Risk of Recurrence (ROR) After Neoadjuvant Ribociclib Plus Endocrine Therapy in Clinically High-Risk ER+/HER2− Breast Cancer: First Interim Analysis of the SOLTI-UNICANCER RIBOLARIS Trial

Paul H. Cottu

Department of Medical Oncology & Institute of Women Cancers, Institut Curie, Paris
Université Paris Cité, Paris
UNICANCER UCBG, Paris

On behalf of

Aleix Prat, Tomás Pascual, Huilin Hu, Estelle Roux, Francisco Javier Salvador Bofill, Joana Mourato Ribeiro, Isabel Blancas, Thomas Bachelot, Jerôme Lemonnier, Juan Manuel Ferrero-Cafiero, Pablo Tolosa-Ortega, Antonio Mulero-Sánchez, Thayane Antoniolli Crestani, Roisin M. Connolly, Cynthia X Ma, Antonio C. Wolff, Guillermo Villacampa, Thibault de La Motte Rouge and Joaquin Gavilá Gregori

October 17th 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Declaration of interests

Daichi Invited Speaker, Institutional

Gilead Invited Speaker, Institutional

Lilly Invited Speaker, Institutional

Lilly Invited Speaker, Personal

Pfizer Advisory Board, Personal

Pfizer Invited Speaker, Personal

Roche Expert Testimony, Personal

Novartis Funding, Institutional, No financial interest

Novartis, Roche, Pfizer, travel grants

Paul H. Cottu

Background

- The results from the **NeoPAL (n=52)**[1] and **CORALLEEN (n=51)**[2] trials suggest that **ET+CDK4/6 inhibition** is at least as effective as chemotherapy in patients with **high-risk HR+/HER2- breast cancer in the neoadjuvant setting**.

- The **PAM50-derived ROR score** has been identified as a biomarker of interest **beyond tumor burden** after neoadjuvant CDK4/6i-ET[2-4].

- CDK4/6 inhibitors such as **ribociclib** and **abemaciclib** have shown a benefit in relapse-free survival for early-stage, high-risk HR+/HER2− breast cancer, mostly **in patients who have received prior chemotherapy**.

- **Hypothesis**: Molecular downstaging with ET + CDK4/6i may enable the identification of patients with high-risk ER+/HER2– early breast cancer who can safely avoid chemotherapy

1. Cottu et al, Ann Oncol 2018; 2. Prat et al, L Oncol 2020, 3. Pascual et al, NPJ BC 2024; 4. Cottu et al, Cell Rep Med, in review
Paul H. Cottu

Study Design NCT05296746

N = 1100

- Pre/post-menopausal/male
- HR+/HER2-negative
- ER+ cells > 10%
- Clinical Stage II
- Grade 2 or 3
- Ki67 ≥20% or high-genomic risk platform

24 weeks

Ribociclib 600 mg
3w ON/ 1w OFF
+
Letrozole +/- LHRH

SURGERY

N ~ 400

ROR Low COHORT
ROR-low after 24 weeks of Letrozole + Ribociclib

(defined by: If N0: ROR ≤ 30 points; If N1mi: ROR ≤ 20 points; If N1: ROR ≤ 10 points; N2-3: NA)

2.5 years	≥2.5 years
Ribociclib 400 mg + **Letrozole +/- LHRH**	**ET +/- LHRH**

Primary objective

DMFS in ROR-Low COHORT

A 5-year DMFS of >90.6% will be considered clinically relevant. This estimate is based on a historical cohort from the MINDACT trial, where patients with high-risk HR+/HER2- disease (by both clinical and genomic criteria) received adjuvant multi-agent chemotherapy[5]

N ~ 600

ROR Med/High COHORT
ROR-med/high after 24 weeks of Letrozole + Ribociclib

Chemo-therapy

2.5 years	≥2.5 years
Ribociclib 400 mg + Letrozole +/- LHRH	**ET +/- LHRH**

LHRH: Luteinizing hormone-releasing hormone
HR: Hormone receptor
ET: Endocrine Therapy
ROR: Risk of Recurrence
DMFS: Distant metastasis-free survival

5. Piccart et al. Lancet, 2021

Paul H. Cottu

Statistical Considerations

- Based on **NeoPAL**[1] and **CORALLEEN**[2] results, we estimated that **40%** of patients should achieve a **ROR-low score** at surgery.

- **Sample size calculation**
  - Estimated 5y DMFS: 96%
  - Statistical power 90%, Type I error 1-sided a=5%,
  - A precision estimation +/-2% in the 95%CI of the 5-year DMFS rate in the final analysis.
  - 10% drop-out rate
  - 400 patients with a ROR-low response are needed **=> 1100 patients to be included**

- A **first pre-specified interim analysis** was scheduled when reaching **300** patient-years-of-follow-up in the ROR-low cohort. This interim analyses is not focused on the primary endpoint (DMFS) but included **686** surgical outcomes performed at the data cut-off, out of 750 patients.

1. Cottu et al, Cell Rep Med, in review; 2. Prat et al, L Oncol 2020,

Paul H. Cottu

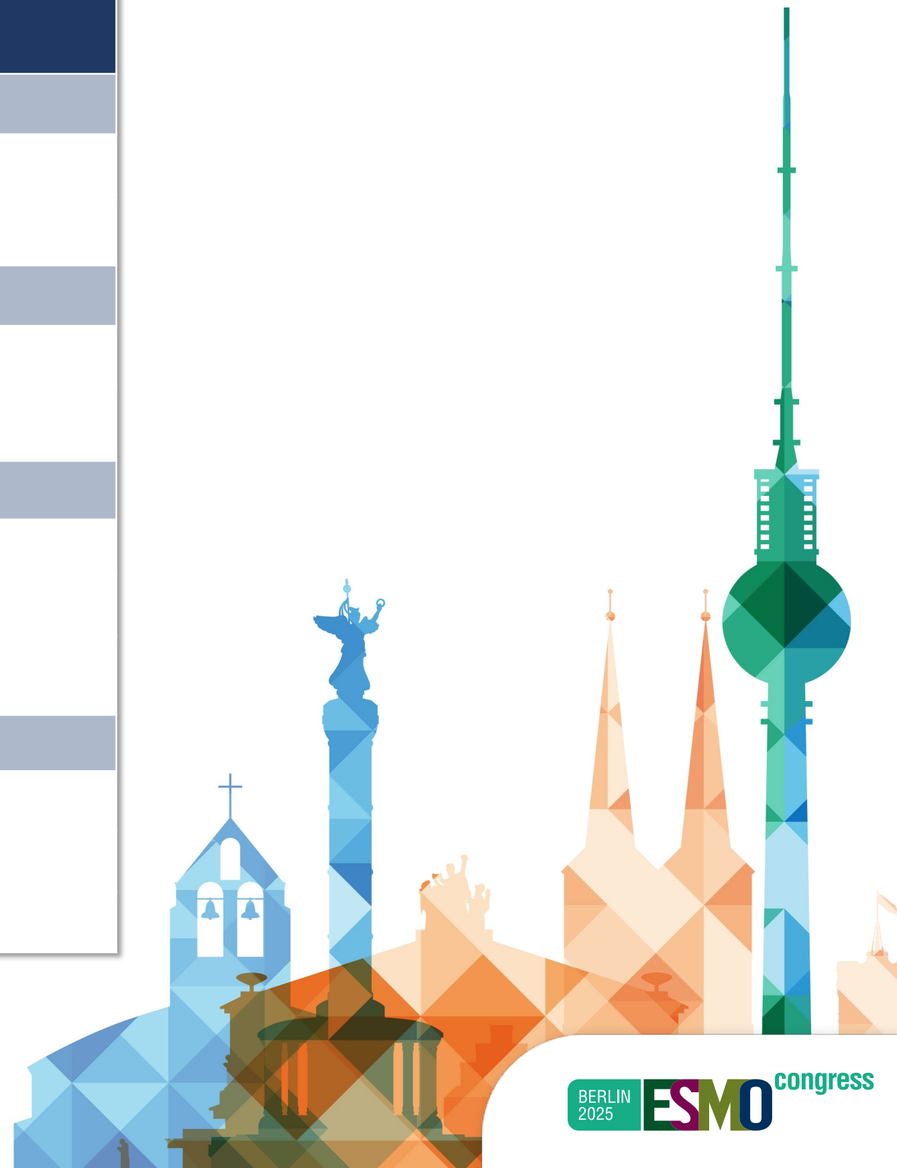
Continuous clinical monitoring in the neoadjuvant phase

- A Quality Limit Threshold (QLT) analysis was established to monitor the tumor progression rate in the neoadjuvant phase.
- The QLT is based on RECIST 1.1 criteria, by monitoring disease status at baseline, cycle 3 and prior to surgery.
- This analysis was performed monthly.
- The 95% CI was calculated using the Clopper-Pearson method. **The QLT was fixed at 2.7% for the lower boundary of the 95% CI.**

Paul H. Cottu

Baseline Characteristics

Demographics	Study Population (N=686/1100)
Age (years)	
N	686
Median (IQR 25-75)	**57.0 (48; 66)**
Sex	
Female	681 (99.3%)
Male	5 (0.7%)
Menopausal status	
N	681
Postmenopausal	421 (61.8%)
Pre/perimenopausal	**260 (38.2%)**
Ki-67 Expression (%)	
N	686
Mean (SD)	33.6 (14.9)
95% CI	(32.5 ; 34.7)



Paul H. Cottu

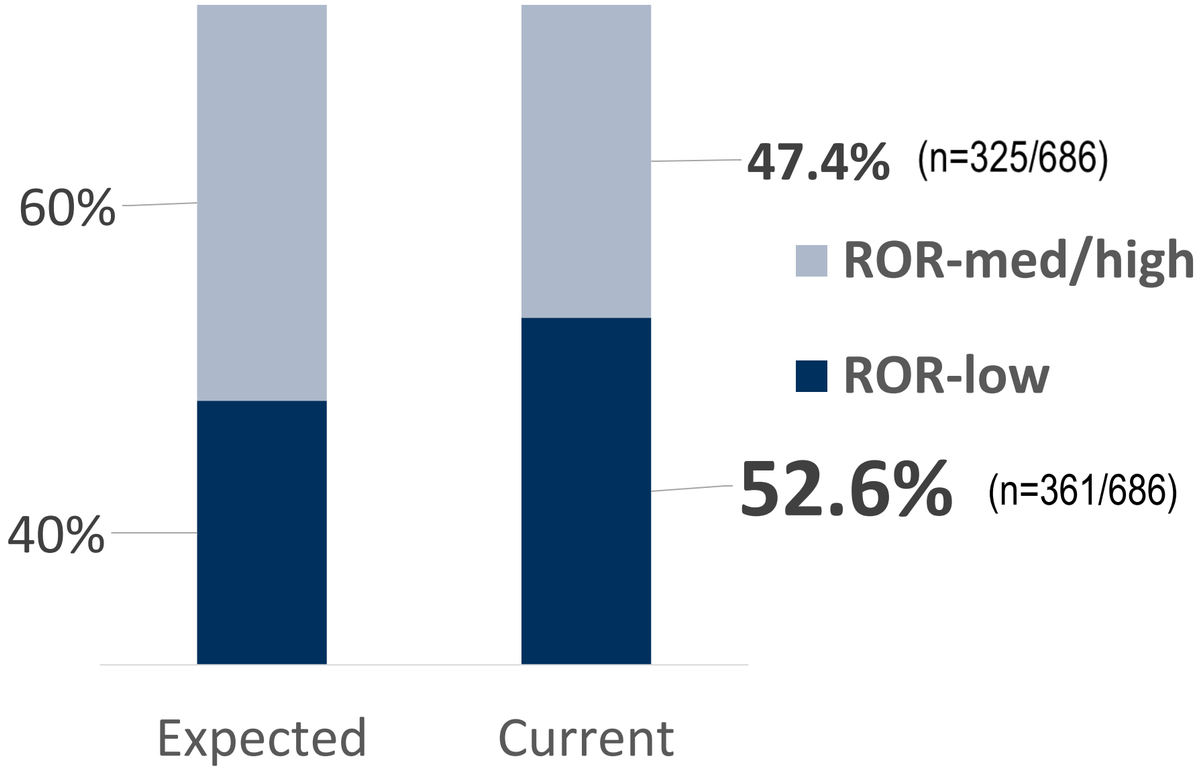
Baseline Characteristics

TNM & Stage at Baseline	Study Population (N=686)
Histological subtype	
Ductal	**596 (86.9%)**
Lobular	78 (11.4%)
Tubular	3 (0.4%)
Other	9 (1.3%)
Primary tumor (T)	
cT1	66 (9.6%)
cT2	**558 (81.4%)**
cT3	62 (9.0%)
Regional lymph nodes (N)	
cNx	1 (0.1%)
cN0	409 (59.6%)
cN1	**276 (40.2%)**
Stage	
IIA	**414 (60.3%)**
IIB	**272 (39.7%)**
Histological grade	
Gx Differentiation cannot be assessed	4 (0.6%)
G1 Well differentiated	1 (0.1%)
G2 Moderately differentiated	510 (74.4%)
G3 Poorly differentiated / Undifferentiated	**171 (24.9%)**

Ki-67 Expression (%)	
N	686
Mean (SD)	33.6 (14.9)
95% CI	(32.5 ; 34.7)

Paul H. Cottu

Results: ROR at surgery



	ROR-low	ROR-med/high
Expected	40%	60%
Current results (IC95 %)	**52.6%** (48.8% ; 56.4%)	**47.4%** (43.6% ; 51.2%)

Paul H. Cottu

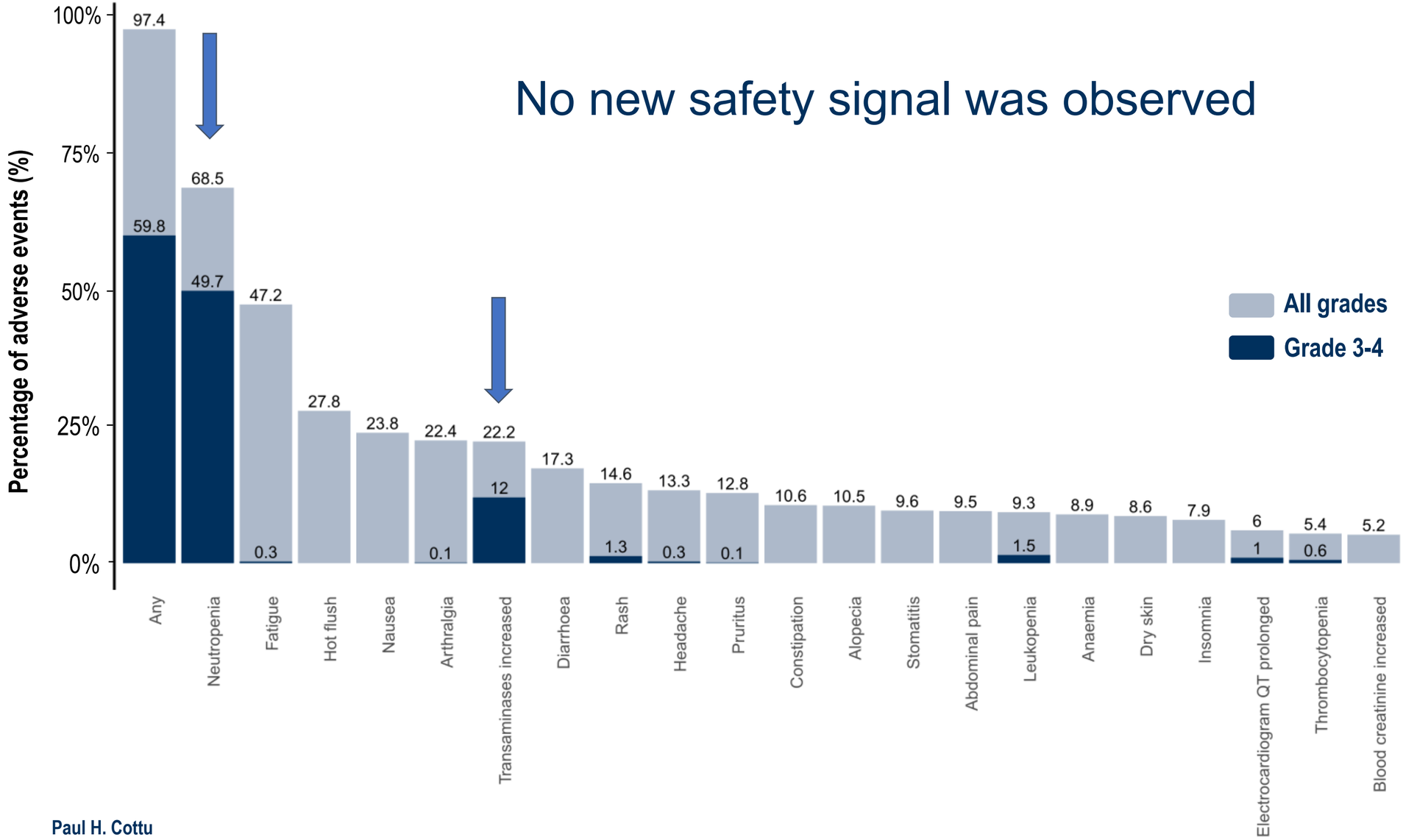
Results: ROR at surgery

Surgery results	ROR-low	ROR-med/high
Age (years)		
Median (IQR 25-75)	55 (47; 64)	59 (50; 67)
Menopausal status		
Postmenopausal	203 (56.4%)	218 (67.9%)
Pre/perimenopausal	**157 (43.6%)**	**103 (32.1%)**
ROR Score		
Mean [IC 95%]	**11.3** [10.5 ; 12.2]	**36.9** [34.2 ; 39.5]
Pathological T status		
ypT0	12 (3.3%)	0 (0.0%)
ypTis	5 (1.4%)	2 (0.6%)
ypT1	**238 (65.9%)**	159 (48.9%)
ypT2	98 (27.1%)	141 (43.4%)
ypT3	8 (2.2%)	23 (7.1%)
Pathological N status		
ypNx	1 (0.3%)	1 (0.3%)
ypN0	**251 (69.5%)**	80 (24.6%)
ypN1mi	39 (10.8%)	18 (5.5%)
ypN1	70 (19.5%)	144 (44.3%)
ypN2	0 (0.0%)	68 (20.9%)
ypN3	0 (0.0%)	14 (4.3%)
Type of surgery		
Breast-conserving surgery	**278 (77.0%)**	**228 (70.2%)**
Unilateral mastectomy	77 (21.3%)	90 (27.7%)
Bilateral mastectomy	6 (1.7%)	7 (2.2%)

Paul H. Cottu

Safety

No new safety signal was observed



Paul H. Cottu

Treatment discontinuations

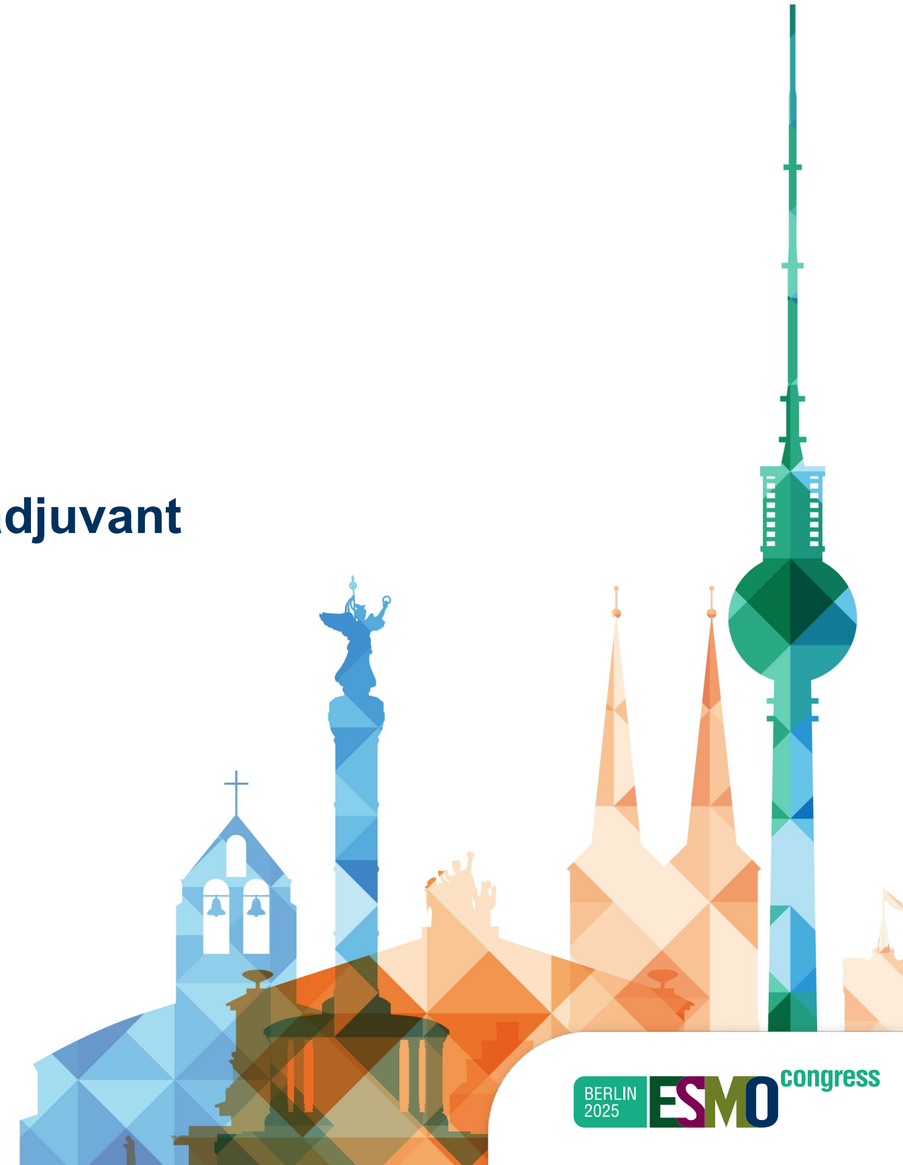
Most common reasons for treatment discontinuation

1) **16.8% (n=126/750)** of patients discontinued due to **any toxicity**

2) **1.9% (n=14/750)** investigator/sponsor's decision

3) 15 Disease progressions have been observed during **neoadjuvant** treatment at data cut-off in the 686 patients**:**

QLT (**lower** boundary of the 95 % CI [**> 2.7**]) **:** 2.19 % (**1.23**-3.58)



Paul H. Cottu

Take-home messages

- These preliminary results from the RIBOLARIS trial suggest that an ***important subset*** of patients with high-risk, early-stage HR+/HER2− breast cancer could achieve ROR-low disease after neoadjuvant ribociclib plus letrozole and may be candidate to **avoid adjuvant chemotherapy**.

- These results confirm and extend the findings from CORALLEEN and NeoPAL trials (total **n=103**), and no new safety signal was observed.

- RIBOLARIS has **successfully completed recruitment**.

Acknowledgments

Ribolaris

Thanks to all the patients, the SOLTI and UNICANCER teams and everyone involved in this project.

Paul H. Cottu

BERLIN 2025 ESMO congress