Elacestrant alone or in combination with triptorelin in premenopausal women with ER+/HER2– early breast cancer: primary analysis from the phase 2 SOLTI-2104- PremiÈRe trial

Meritxell Bellet[1], Pablo Tolosa[2], Cristina Hernando[3], Maria Vidal[4], Vanesa Ortega[5], Marta Tapia[6], Santiago González-Santiago[7], Pilar Sánchez[8], Yolanda Fernández[9], Mara Cruellas[10], Manuel Alva[11], Eduard Mension[12], Martín Espinosa-Bravo[13], Tomàs Cortadellas[14], Sofía Aragón[15], Mariangela Gaudio[16], Esther Sanfeliu[17], Patricia Galván[18], Rubén Olivera-Salguero[19], Guillermo Villacampa[19], Milana Bergamino[4], Naiara Santos[19], Sara Cano-Crespo[19], Xavier González-Farré[20], Aleix Prat[4], Juan M Ferrero-Cafiero[19], Antonio Hurtado[21], Tomás Pascual[4]

(1) Medical Oncology Department, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Barcelona, Spain / Medicine Department, Autonomous University, Barcelona, Spain / SOLTI Breast Cancer Research Group, Barcelona, Spain. **(2)** Medical Oncology Department, University Hospital 12 de Octubre, Madrid, Spain/ Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain / SOLTI Breast Cancer Research Group, Barcelona, Spain. **(3)** Medical Oncology Department, Valencian Institute of Oncology (IVO), IVO Hospital, Valencia, Spain. **(4)** Medical Oncology Department, Hospital Clínic de Barcelona, Barcelona, Spain / Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain / Medicine Department, University of Barcelona, Barcelona, Spain / SOLTI Breast Cancer Research Group, Barcelona, Spain. **(5)** Breast Cancer Unit, Instituto Oncológico Rosell (IOR), Hospital Universitari General de Catalunya, Barcelona, Spain. **(6)** Medical Oncology Department, Hospital Clínico Universitario de Valencia, Valencia, Spain. **(7)** Medical Oncology Department, Hospital Universitario San Pedro de Alcántara, Cáceres, Spain. **(8)** Medical Oncology Department, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain. **(9)** Medical Oncology Department, Central University Hospital of Asturias, Oviedo, Asturias, Spain. **(10)** Medical Oncology Department, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain. **(11)** Medical Oncology Department, University Hospital 12 de Octubre, Madrid, Spain / Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain. **(12)** Department of Gynecology, Hospital Clínic de Barcelona, Barcelona, Spain / Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain. **(13)** Breast Surgical Unit, Breast Cancer Center, Hospital Universitari Vall d'Hebron, Barcelona, Spain / International Breast Cancer Center (IBCC), Pangaea Oncology, Centro Médico Teknon. QuirónSalud, Barcelona, Spain. **14** Breast Cancer Unit, Hospital Universitari Dexeus, Universitat Internacional de Catalunya, Barcelona, Spain. **(15)** Gynecology and Obstetrics Department, University Hospital 12 de Octubre, Madrid, Spain / Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain. **(16)** Medical Oncology Department, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Barcelona, Spain. **(17)** Department of Pathology, Hospital Clínic de Barcelona, Barcelona, Spain / Medicine Department, University of Barcelona, Barcelona, Spain / Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain. **(18)** Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain. **(19)** Clinical Research, SOLTI Breast Cancer Research Group, Barcelona, Spain. **(20)** Breast Cancer Unit, Hospital Universitari General de Catalunya, Universitat Internacional de Catalunya, Barcelona, Spain / SOLTI Breast Cancer Research Group, Barcelona, Spain. **(21)** IACUS Research Group, Cancer Research Center (CIC), University of Salamanca, Spain

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Première Focused in premenopausal women

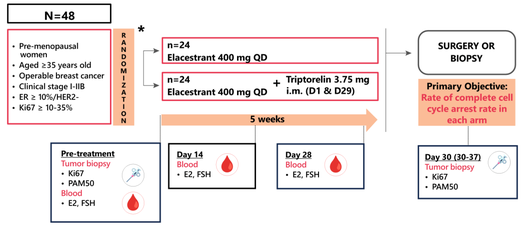
Background

- **Premenopausal women** account for ~30% of patients (pts) with ER+/HER2– early breast cancer (EBC). Ovarian function suppression (OFS) with tamoxifen or aromatase inhibitors improves invasive disease-free survival, distant disease free survival and even overall survival in women at high risk of recurrence. However, its use is limited by toxicity, earlier discontinuations and potential suboptimal supression[1-7].
- **Elacestrant (ELA)**, an oral selective estrogen receptor degrader (SERD), showed superior efficacy versus standard endocrine therapy in pretreated postmenopausal women and men with ER+/HER2– metastatic BC, particularly in *ESR1*^{mut} population[8].
- Mechanistically, **ELA degrades ER while maintaining agonistic activity in non-breast tissues** such as bone, supporting its **potential for the adjuvant setting**[9].
- In the **SOLTI-ELIPSE trial**, a 4-week preoperative ELA led to a 53% Ki67 reduction and 27% complete cell-cycle arrest (CCCA) rate in a postmenopausal endocrine-naïve population, **warranting ELA evaluation with or without OFS in premenopausal pts with EBC**[10].

Methods

- **SOLTI-2104-PremiÈRe (NCT05982093)** is a phase 2, non-comparative, open-label, randomized trial assessing ELA ± triptorelin (T) in premenopausal pts with stage I-IIB ER+/HER2– EBC, age ≥35 years, cT>1 cm, and Ki67 10–35% by local assessment.
- Pts were **stratified by PAM50 subtype (Luminal A vs Non-luminal A)** and randomized to ELA 345 mg (= 400 mg elacestrant dihydrochloride) daily until surgery/biopsy at day 30 (+7), alone or with T 3.75 mg on days 1 and 29.
- **Primary endpoint:** CCCA rate (central Ki67 ≤2.7%) after treatment.
- **Secondary endpoints:** CCCA rate by PAM50 subtype; changes in central Ki67, ER and PgR expression; changes in gene expression (192 gene analysis; paired analysis; FDR-corrected); safety; and estradiol (E2) dynamics measured by LC-MS/MS.

Fig 1. SOLTI-2104 PremiÈRe study design



*Stratification factor: Research-based PAM50 (Luminal A versus Non-Luminal A)

Results

Fig 2. CONSORT diagram

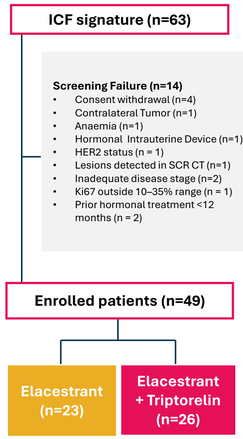


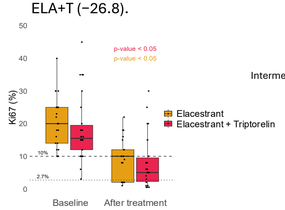
Table 1. Baseline Patient Characteristics (n=49)

	Elacestrant n = 23	Elacestrant + Triptorelin n = 26	Overall n = 49
Age (years), median (range)	47 (39–54)	47 (40–52)	47 (39–54)
Clinical tumor stage, n (%)			
T1	13 (57)	10 (38)	23 (47)
T2	10 (43)	14 (54)	24 (49)
T3	0	2 (8)	2 (4)
Regional lymph node metastasis, n (%)			
N0	22 (96)	24 (92)	46 (94)
N1	1 (4)	2 (8)	3 (6)
Histologic type, n (%)			
Ductal	21 (91)	21 (81)	42 (86)
Lobular	2 (9)	5 (19)	7 (14)
Histologic grade, n (%)			
G1	6 (26)	5 (19)	11 (22)
G2	15 (65)	20 (77)	35 (71)
G3	2 (9)	0	2 (4)
NA	0	1 (3)	1 (2)
Allred ER score [a] median (Q1–Q3)	8 (7-8)	8 (7-8)	8 (7-8)
Allred PgR score [a] median (Q1–Q3)	8 (8-8)	8 (8-8)	8 (8-8)
Ki67%,[a] median (Q1–Q3)	20 (14–25)	16 (12–20)	18 (12–25)
PAM50 Subtype,[a] n (%)			
Luminal A	17 (74)	20 (77)	37 (76)
Non-luminal A*	6 (26)	6 (23)	12 (24)

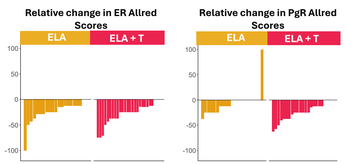
[a]By central assessment; * All non-Luminal A tumors at baseline were classified as Luminal B; ER: Estrogen receptor; PgR: Progesterone receptor

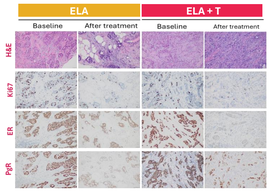
Fig 3. Change in Ki67, ER and PgR levels from baseline

- CCCA rates were similar between arms (29% vs 27%).
- Ki67 decreased comparably in both groups. After treatment Ki67 <10% was reached in 67% (ELA) and 77% (ELA+T).
- ELA±T reduced ER expression to a similar extent (Allred ER: −42.6 vs −32.8). In contrast, PgR changes diverged, increasing with ELA (+16.8) but decreasing with ELA+T (−26.8).



	ELA (n = 21)	ELA + T (n=26)
	n (%)	
CCCA (Ki67 <2.7)	**6 (29)**	**7 (27)**
Intermediate (Ki67 >2.7–10%)	8 (38)	13 (50)
Resistant (Ki67 >10%)	7 (33)	6 (23)
	Δ Geometric mean , % (95% CI)	
Ki67	−62.0 (−74.7 to −43.0)	−71.9 (−82.7 to −54.2)
Allred ER	−42.6 (−69.9 to −9.2)	−32.8 (−42.5 to −21.4)
Allred PgR	+16.8 (−34.8 to 109)	−26.8 (−34.7 to -18)

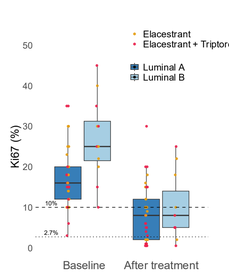


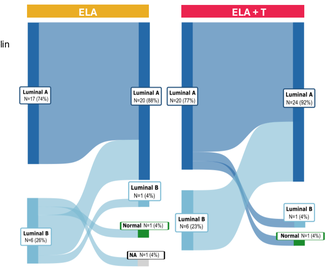


ER: Estrogen receptor; PgR: Progesterone receptor

Fig 4. Change in Ki67 levels between baseline and post-treatment by PAM50 Intrinsic Subtype.

- CCCA rates were higher in Luminal A than in Luminal B tumors across both arms.
- Ki67 levels decreased in both subtypes, with greater suppression in Luminal B.
- Most Luminal B tumors shifted to Luminal A after treatment (9/12).

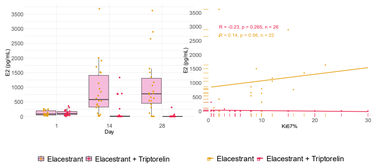




	Luminal A (n = 36)	Luminal B (n = 11)
CCCA after treatment, n (%)	11 (31)	2 (18)
Geometric mean change in Ki67, % (95% CI)	−66.3 (−76.8 to −50.9)	−73.0 (−87.1 to −43.4)

Fig 5. Dynamics of E2 levels

- E2 decreased with ELA + T and increased with ELA alone, with no significant impact of E2 levels on post-treatment Ki67 levels in either arm.
- In combined arm, 88% of women had post-treatment E2 levels <10 pg/mL.



	ELA		ELA + T	
	Day 14 (n = 22)	Day 28 (n = 22)	Day 14 (n = 26)	Day 28 (n= 26)
E2*	+341.4 (100.6 to 871.3)	+367 (91.2 to 1039)	-79.8 (-92.1 to -47.9)	-94.8 (-97.3 to -89.9)

* pg/mL; Geometric mean change from Day 1; % (95% CI)

Fig 6. Differential gene expression from baseline

- 192-gene analysis showed differential expression in 53% of genes with ELA and 62% with ELA+T.
- Proliferation-related genes were consistently downregulated in both arms.
- 41 genes were commonly suppressed, indicating a core elacestrant effect.

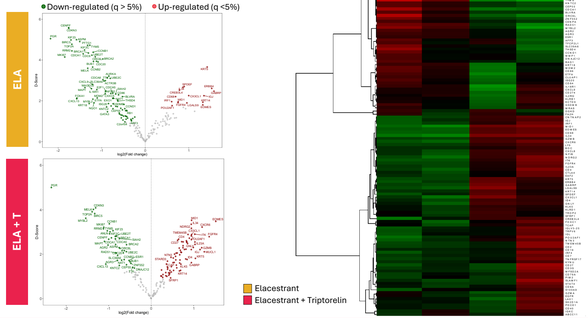
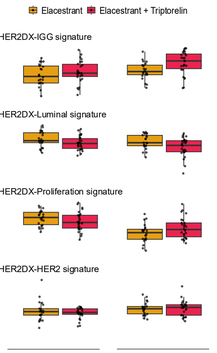
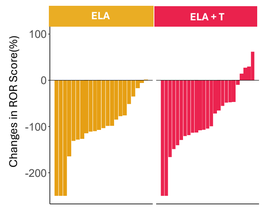


Fig 7. Changes in HER2DX signatures from baseline

- Proliferation signature significantly decreased after treatment in both arms.
- IGG and HER2 signatures increased significantly with ELA + T.
- PAM50 ROR scores showed an overall decline in both treatment arms.





	ELA	ELA + T
	p-value	
HER2DX- IGG	0.140	0.006
HER2DX- Luminal	0.275	0.081
HER2DX- Proliferation	<0.001	0. 019
HER2DX- HER2	0.390	0.010
PAM50-ROR	<0.001	<0.001

Conclusions

- **This study provides the first evidence that ELA elicits antiproliferative and molecular responses in premenopausal women with ER+/HER2– EBC as single agent or in combination with OFS.**
- **Both regimens had comparable and significant reductions in Ki67, CCCA, ROR-P scores, and proliferation gene expression.**
- **PremiÈRe trial support the potential role of ELA as a novel ET in this population, potentially sparing the need for OFS.**

References and acknowledgements: [1]Francis et al. N Engl J Med 2015, [2]Pagani et al. N Engl J Med 2014, [3]Fleming et al. J Clin Oncol 2025, [4]Kim et al. J Clin Oncol 2020, [5]Saha et al. J Clin Oncol 2017, [6]Bellet et al. J Clin Oncol 2016, [7]Bellet et al. J Clin Oncol 2014, [8]Bidard et al. J Clin Oncol 2022, [9]Bihani et al. Clin Cancer Res 2017, [10]Vidal et al. Clin Cancer Res 2025. **Funding:** This study is sponsored by SOLTI and has the financial Support and elacestrant provision of Menarini-Stemline. **We thank the patients, their families, and their caregivers for their participation.**

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