GRUPPO DI LAVORO A

Coordinatori: C. Angiolini; F. Miglietta; G. Pappagallo

In pazienti con carcinoma mammario HR-positivo/HER2-negativo, metastatico, con mutazione *ESR1*, dopo almeno una linea di ormonoterapia (comprendente CDK4/6i),
un trattamento con elacestrant vs fulvestrant è raccomandabile?

Sintesi delle evidenze e problematiche emerse dal lavoro di gruppo

Federica Martorana

SICILIAE STVDIVM GENERALE 1434

HUMANITAS
ISTITUTO CLINICO CATANESE

QUESITO + PICO

Should elacestrant vs. fulvestrant be used for patients with ER–Positive, HER2–Negative, Advanced Breast Cancer with detectable ESR1 mutations?	
POPULATION:	patients with ER–Positive, HER2–Negative, Advanced Breast Cancer with detectable ESR1 mutations, progressed on prior CDK4/6 inhibitor in combination with an AI
INTERVENTION:	elacestrant
COMPARISON:	fulvestrant
MAIN OUTCOMES:	Progression-free survival; Overall Survival; Any Adverse Event of CTC-AE Grade 3-4; Nausea (every CTC-AE Grade); Vomiting (every CTC-AE Grade); Any Adverse Event leading to Discontinuation of elacestrant/fulvestrant
SETTING:	outpatient

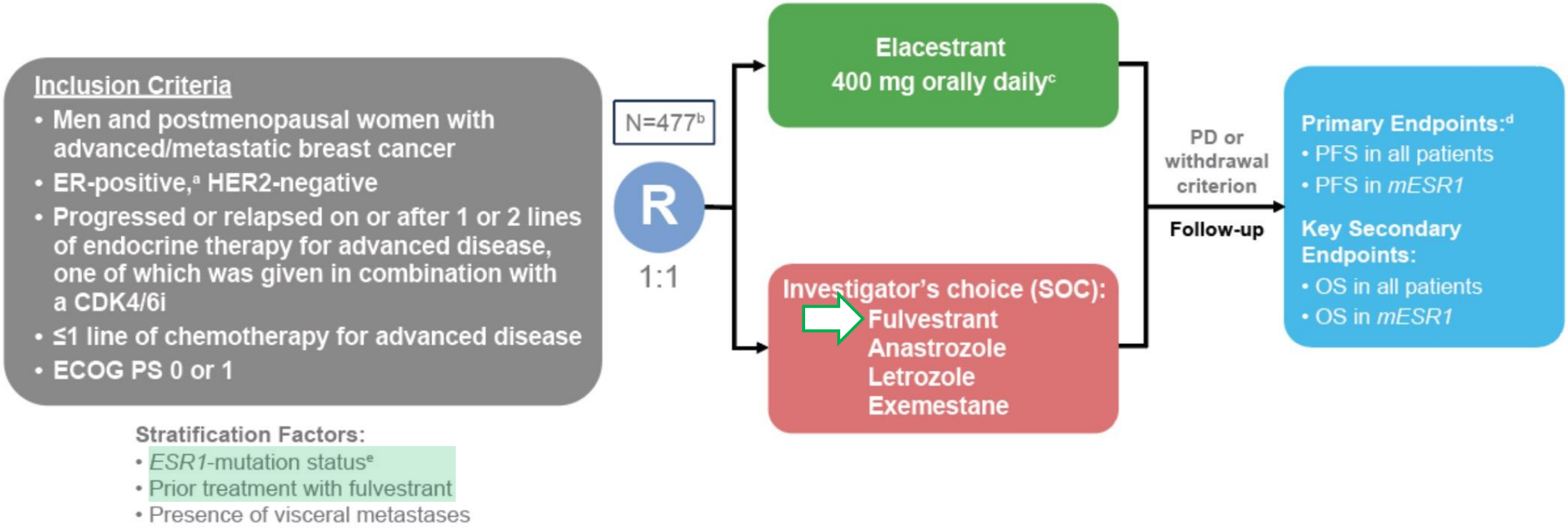
STUDIO EMERALD

Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial

Francois-Clement Bidard, MD[1,2]; Virginia G. Kaklamani, MD[3]; Patrick Neven, MD[4]; Guillermo Streich, MD[5]; Alberto J. Montero, MD[6]; Frédéric Forget, MD[7]; Marie-Ange Mouret-Reynier, MD[8]; Joo Hyuk Sohn, MD[9]; Donatienne Taylor, MD[10]; Kathleen K. Harnden, MD[11]; Hung Khong, MD[12]; Judit Kocsis, MD[13]; Florence Dalenc, MD[14]; Patrick M. Dillon, MD[15]; Sunil Babu, MD[16]; Simon Waters, MD[17]; Ines Deleu, MD[18]; José A. García Sáenz, MD[19]; Emilio Bria, MD[20]; Marina Cazzaniga, MD[21]; Janice Lu, MD[22]; Philippe Aftimos, MD[23]; Javier Cortés, MD[24,25,26,27]; Shubin Liu, MS[28]; Giulia Tonini, PhD[29]; Dirk Laurent, MD[30]; Nassir Habboubi, MD[31]; Maureen G. Conlan, MD[32]; and Aditya Bardia, MD[33]

J Clin Oncol 40:3246-3256.

STUDIO EMERALD



[a]Documentation of ER-positive tumor with ≥1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Blinded independent central review. [e]*ESR1*-mutation status was determined by cell-free circulating DNA analysis using Guardant360® CDx (Guardant Health, Redwood City, CA)

Bidard F.C. et al. *J Clin Oncol* **2022** 40(28):3246-56; supplementary materials

Valutazione Effetti Desiderabili

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ○ Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	With fulvestrant	With elacestrant	Difference	Relative effect (95% CI)
Progression-free survival assessed with: Kaplan-Meier product limit estimate follow-up: median 15.1 months	90 per 100	**68 per 100** (54 to 82)	**22 fewer per 100** (36 fewer to 8 fewer)	**HR 0.50** (0.34 to 0.74)
Overall Survival assessed with: Kaplan-Meier product limit estimate follow-up: median 15.1 months	41 per 100	**27 per 100** (17 to 40)	**14 fewer per 100** (24 fewer to 1 fewer)	**HR 0.59** (0.36 to 0.96)

Valutazione Effetti Desiderabili

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	

Outcomes	With fulve[illegible]	With	Difference	Relative effect (95% CI)
Progression-free survival assessed with: Kaplan-Meier product limit estimate follow-up: median 15.1 months	90 per 100	**68 per 100** (54 to 82)	**22 fewer per 100** (36 fewer to 8 fewer)	**HR 0.50** (0.34 to 0.74)
Overall Survival assessed with: Kaplan-Meier product limit estimate follow-up: median 15.1 months	41 per 100	**27 per 100** (17 to 40)	**14 fewer per 100** (24 fewer to 1 fewer)	**HR 0.59** (0.36 to 0.96)

NNT: 1/0.22 = 4.5

NNT: 1/0.14 = 7.1

Valutazione Effetti Desiderabili

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Trivial ○ Small ○ Moderate ☒ Large ○ Varies ○ Don't know	

Outcomes	With fulvestrant	With elacestrant	Difference	Relative effect (95% CI)
Progression-free survival assessed with: Kaplan-Meier product limit estimate follow-up: median 15.1 months	90 per 100	**68 per 100** (54 to 82)	**22 fewer per 100** (36 fewer to 8 fewer)	**HR 0.50** (0.34 to 0.74)
Overall Survival assessed with: Kaplan-Meier product limit estimate follow-up: median 15.1 months	41 per 100	**27 per 100** (17 to 40)	**14 fewer per 100** (24 fewer to 1 fewer)	**HR 0.59** (0.36 to 0.96)

Valutazione Effetti Non Desiderabili

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	With fulvestrant	With elacestrant	Difference	Relative effect (95% CI)
Any Adverse Event of CTC-AE Grade 3-4 assessed with: cumulative incidence	20 per 100	**27 per 100** (19 to 39)	**7 more per 100** (2 fewer to 19 more)	**RR 1.32** (0.91 to 1.91)
Nausea (every CTC-AE Grade) assessed with: cumulative incidence	16 per 100	**35 per 100** (24 to 52)	**19 more per 100** (7 more to 36 more)	**RR 2.17** (1.46 to 3.21)
Vomiting (every CTC-AE Grade) assessed with: cumulative incidence	7 per 100	**19 per 100** (10 to 35)	**12 more per 100** (3 more to 27 more)	**RR 2.55** (1.39 to 4.66)
Any Adverse Event leading to Discontinuation of elacestrant/fulvestrant assessed with: cumulative incidence	4 per 100	**6 per 100** (2 to 16)	**3 more per 100** (1 fewer to 12 more)	**RR 1.70** (0.67 to 4.28)

Valutazione Effetti Non Desiderabili

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Trivial
- ☒ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	With fulvestrant	With elacestrant	Difference	Relative effect (95% CI)
Any Adverse Event of CTC-AE Grade 3-4 assessed with: cumulative incidence	20 per 100	**27 per 100** (19 to 39)	**7 more per 100** (2 fewer to 19 more)	**RR 1.32** (0.91 to 1.91)
Nausea (every CTC-AE Grade) assessed with: cumulative incidence	16 per 100	**35 per 100** (24 to 52)	**19 more per 100** (7 more to 36 more)	**RR 2.17** (1.46 to 3.21)
Vomiting (every CTC-AE Grade) assessed with: cumulative incidence	7 per 100	**19 per 100** (10 to 35)	**12 more per 100** (3 more to 27 more)	**RR 2.55** (1.39 to 4.66)
Any Adverse Event leading to Discontinuation of elacestrant/fulvestrant assessed with: cumulative incidence	4 per 100	**6 per 100** (2 to 16)	**3 more per 100** (1 fewer to 12 more)	**RR 1.70** (0.67 to 4.28)

Valutazione Qualità delle Prove

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ⊗ Low ○ Moderate ○ High ○ No included studies	

Outcomes	Importance	Certainty of the evidence (GRADE)
Progression-free survival	CRITICAL	⨁⨁⨁⨁ **High** [a,b,c,d,e]
Overall Survival	CRITICAL	⨁⨁◯◯ **Low** [c,d,f,g,h]
Any Adverse Event of CTC-AE Grade 3-4	CRITICAL	⨁⨁◯◯ **Low** [b,c,d,i,j,k]
Any Adverse Event leading to Discontinuation of elacestrant/fulvestrant	CRITICAL	⨁⨁◯◯ **Low** [b,c,d,i,j,k]

a. low risk of detection bias (BICR assessment)
b. previous treatment with fulvestrant as stratification factor
c. a single study
d. fulvestrant as adequate comparator
e. wide 95%CI of absolute effect, but consistent with a unique clinical interpretation
f. low risk of detection bias for the OS outcome
g. patients with SOC of AI included
h. 95%CLs of absolute effect consistent with both greater and comparable efficacy
i. independently of ESR1 mutation status; may not be downgraded
j. 95%CLs of absolute effect consistent with opposite clinical interpretations
k. serious risk of performance bias in open-label trial