Roma, 21 aprile 2023

PRO

# NUOVI FARMACI → NUOVO ALGORITMO

Mattia Garutti – CRO Aviano

CRO AVIANO

PRO

# NUOVI FARMACI → NUOVO ALGORITMO

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CRO AVIANO

# disclosures

- Novartis
- Eli Lilly
- PierreFabre
- Roche
- Organon
- Daichii Sankyo

Irina



# AI + CDK4/6i

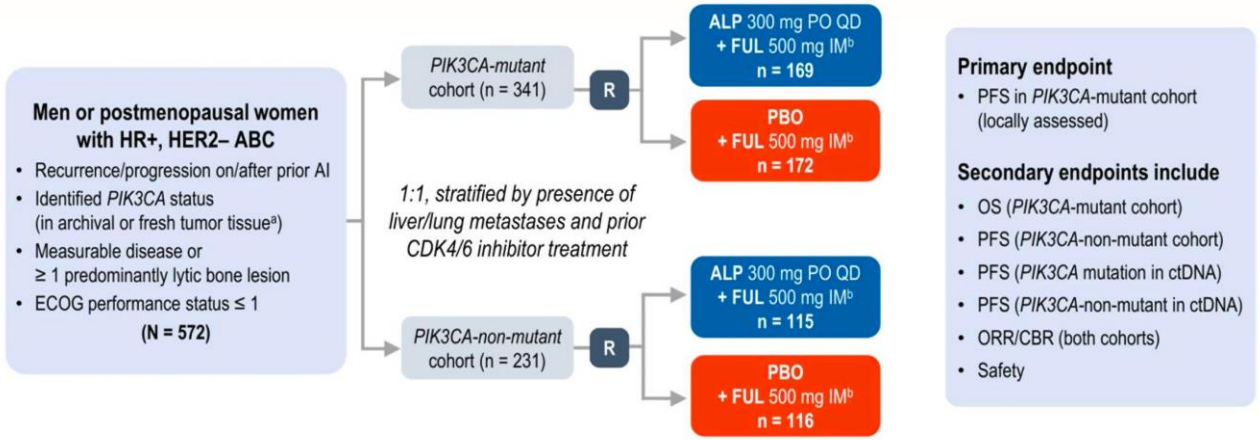
everolimus + exemestane

fulvestrant

# CHEMIO

# SOLAR1

## PIK3CA mutant

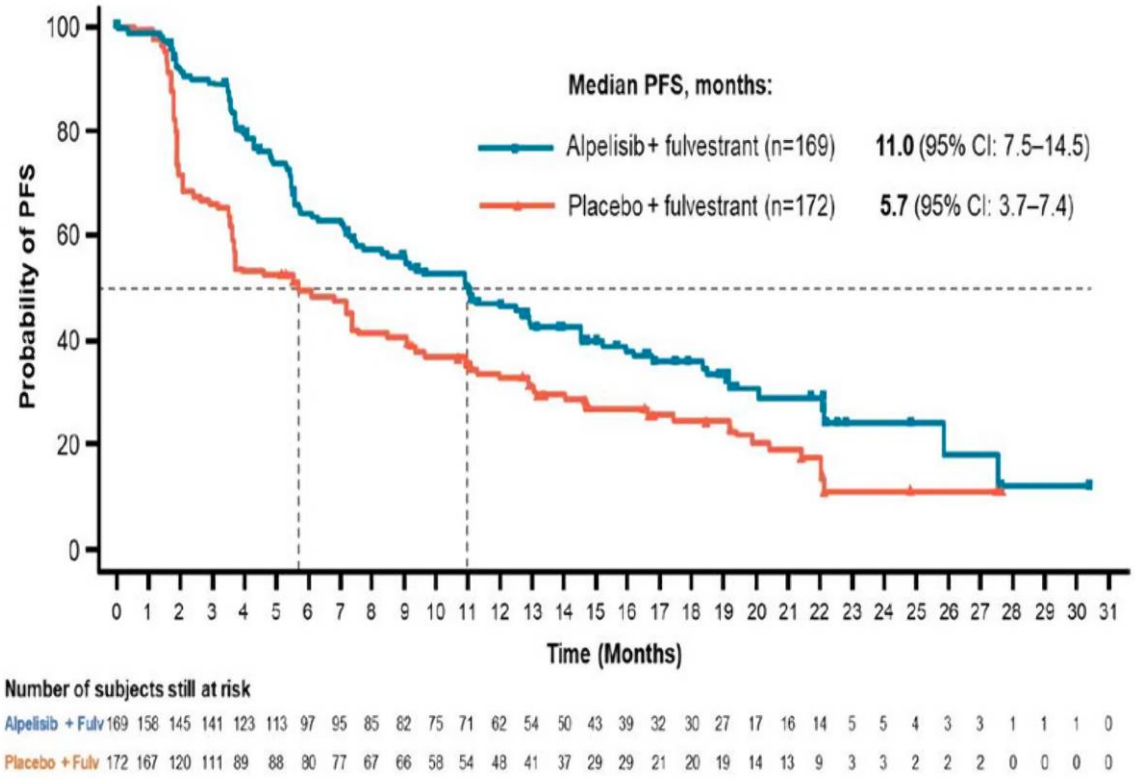



**Primary endpoint**

- PFS in *PIK3CA*-mutant cohort (locally assessed)

**Secondary endpoints include**

- OS (*PIK3CA*-mutant cohort)
- PFS (*PIK3CA*-non-mutant cohort)
- PFS (*PIK3CA* mutation in ctDNA)
- PFS (*PIK3CA*-non-mutant in ctDNA)
- ORR/CBR (both cohorts)
- Safety

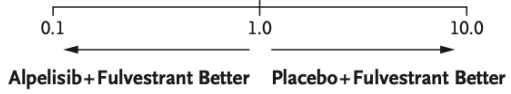



Andrè F et al. NEJM, 2019

# SOLAR1

## PIK3CA mutant

| Subgroup | No. of Patients | Hazard Ratio for Progression or Death (95% CI) |
|---|---|---|
| All patients | 341 | 0.65 (0.50–0.85) |
| Lung or liver metastases | | |
| Yes | 170 | 0.62 (0.44–0.89) |
| No | 171 | 0.69 (0.47–1.01) |
| Bone-only disease | | |
| Yes | 77 | 0.62 (0.33–1.18) |
| No | 264 | 0.66 (0.49–0.88) |
| Previous CDK4/6 inhibitor treatment | | |
| Yes | 20 | 0.48 (0.17–1.36) |
| No | 321 | 0.67 (0.51–0.87) |
| Previous chemotherapy | | |
| Neoadjuvant | 46 | 0.37 (0.17–0.80) |
| Adjuvant | 161 | 0.63 (0.42–0.95) |
| None | 133 | 0.87 (0.58–1.29) |
| Endocrine status | | |
| Primary resistance | 45 | 0.64 (0.31–1.32) |
| Secondary resistance | 247 | 0.66 (0.49–0.90) |
| Sensitivity | 39 | 0.87 (0.35–2.17) |
| Line of treatment in advanced disease | | |
| First line | 177 | 0.71 (0.49–1.03) |
| Second line | 161 | 0.61 (0.42–0.89) |
| No. of metastatic sites | | |
| <3 | 234 | 0.59 (0.43–0.83) |
| ≥3 | 107 | 0.77 (0.50–1.20) |
| *PIK3CA* mutation subtype | | |
| E542K | 60 | 0.60 (0.29–1.23) |
| E545X | 105 | 0.61 (0.37–1.00) |
| H1047X | 193 | 0.68 (0.48–0.95) |
| Geographic region | | |
| Europe | 173 | 0.56 (0.39–0.81) |
| North America | 43 | 0.41 (0.19–0.91) |
| Asia | 70 | 0.76 (0.42–1.37) |
| Latin America | 31 | 1.43 (0.54–3.79) |
| Other | 24 | 0.93 (0.25–3.45) |




Andrè F et al. NEJM, 2019

# CAPITELLO-291

## ITT analysis

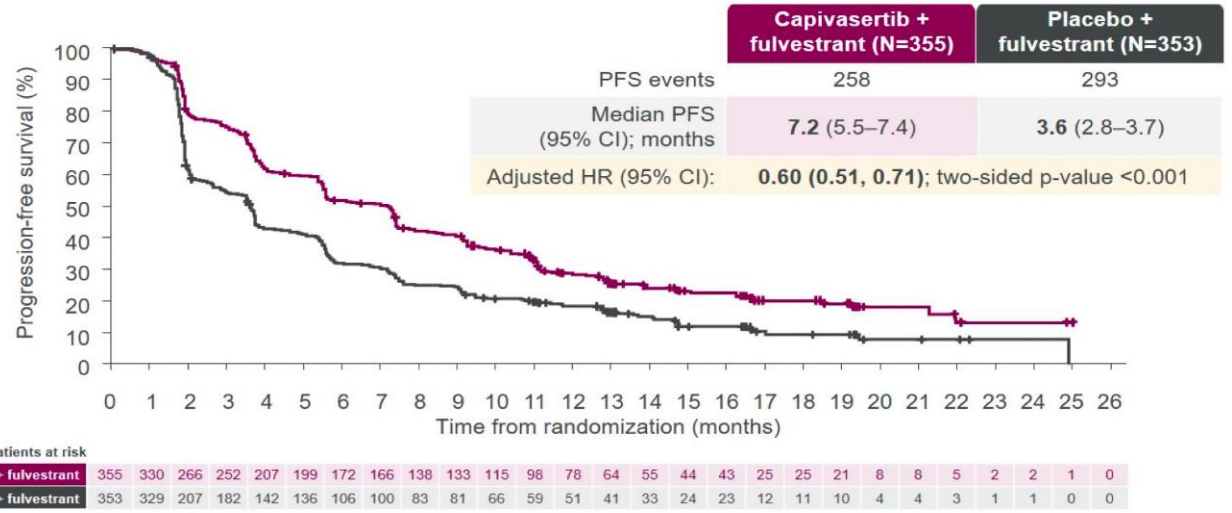
**Patients with HR+/HER2– ABC**

- Men and pre-/post-menopausal women
- Recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

| | |
|---|---|
| **Capivasertib** | 400 mg twice daily, 4 days on, 3 days off |
| **Fulvestrant** | 500 mg: cycle 1, days 1 & 15; then every 4 weeks |
| **Placebo** | Twice daily, 4 days on, 3 days off |
| **Fulvestrant** | 500 mg: cycle 1, days 1 & 15; then every 4 weeks |

**Stratification factors:**
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*



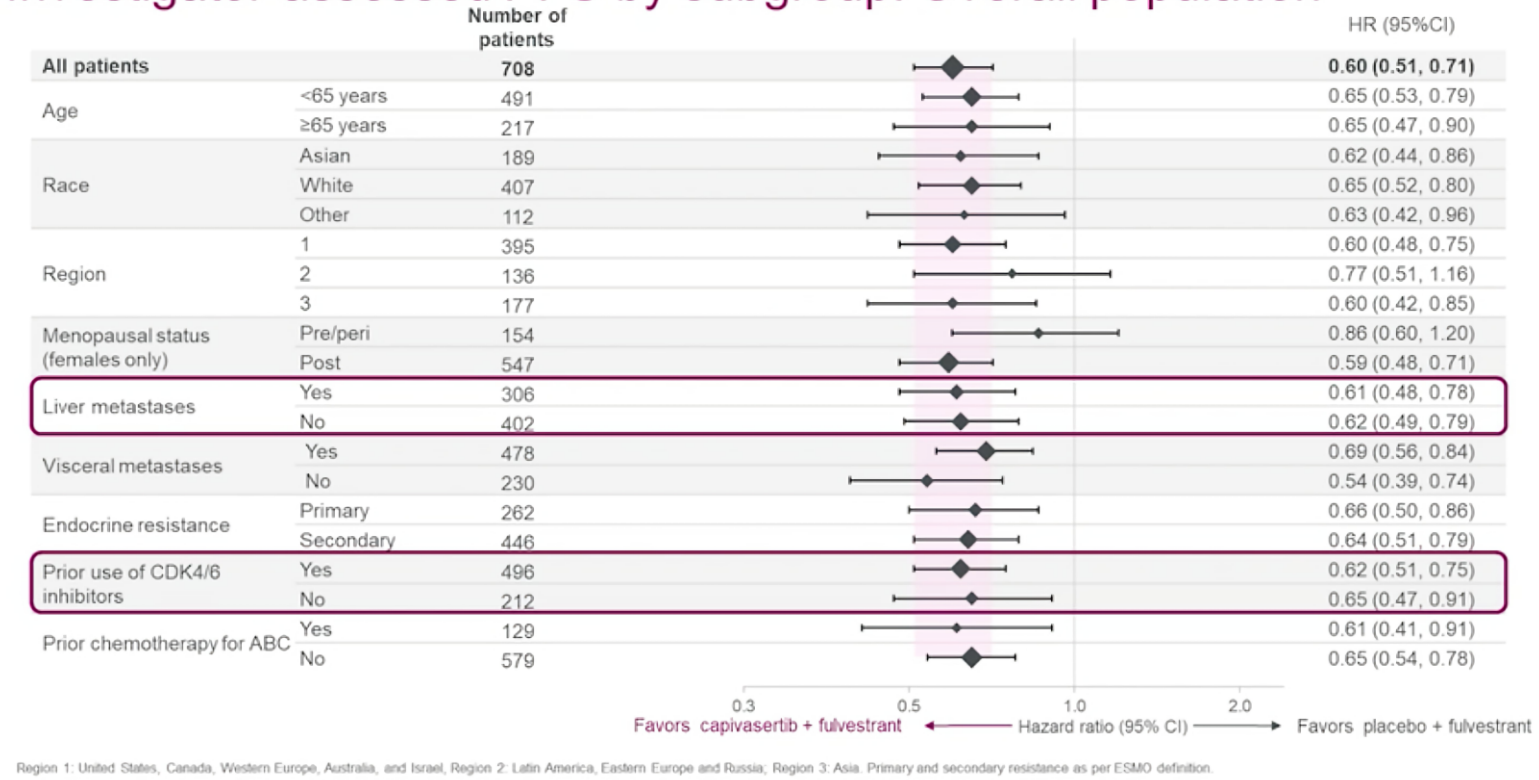

benefit in AKT-altered (wt apparent benefit)

Turner NC et al. SABCS 2022

# CAPITELLO-291

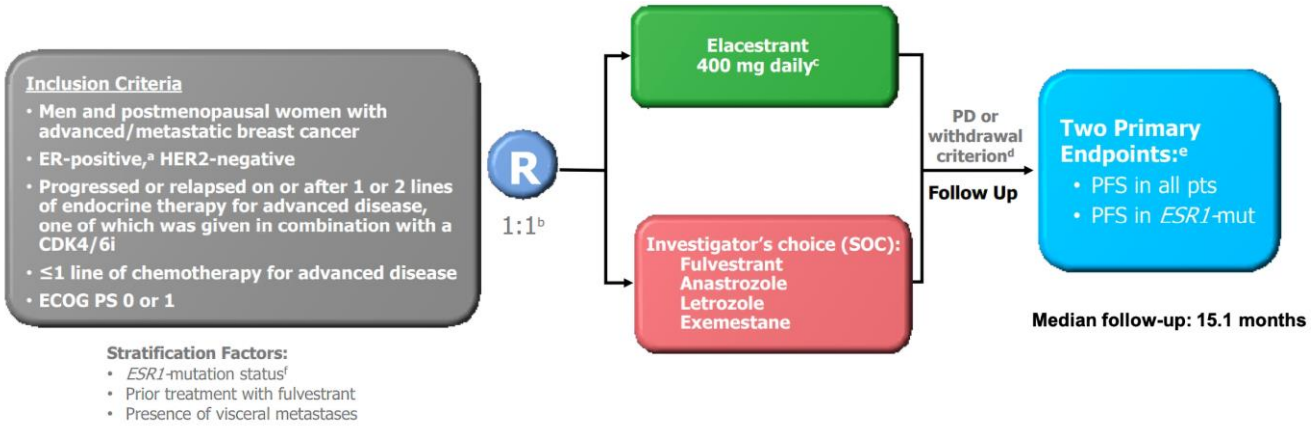
## ITT analysis

### Investigator-assessed PFS by subgroup: Overall population

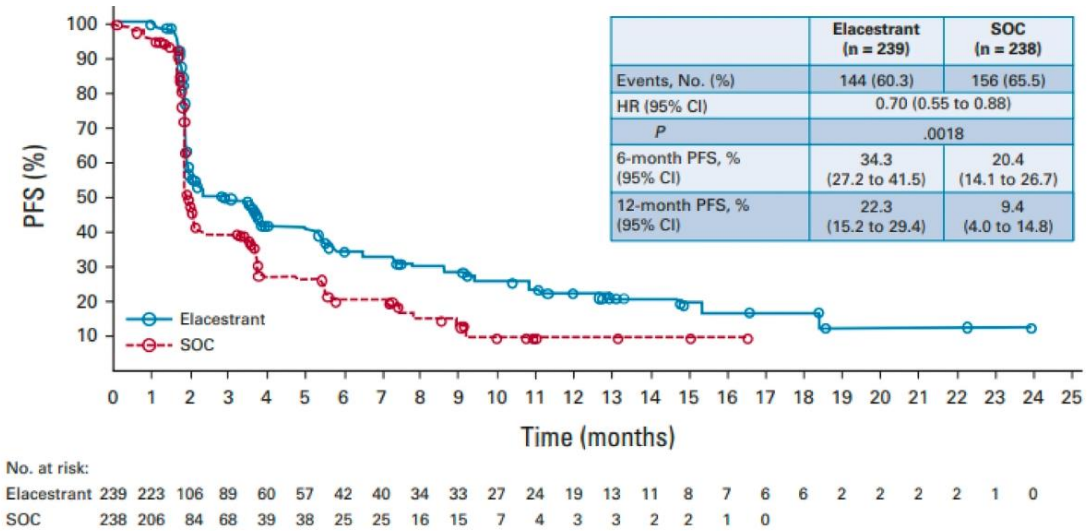



Region 1: United States, Canada, Western Europe, Australia, and Israel; Region 2: Latin America, Eastern Europe and Russia; Region 3: Asia. Primary and secondary resistance as per ESMO definition.

# EMERALD

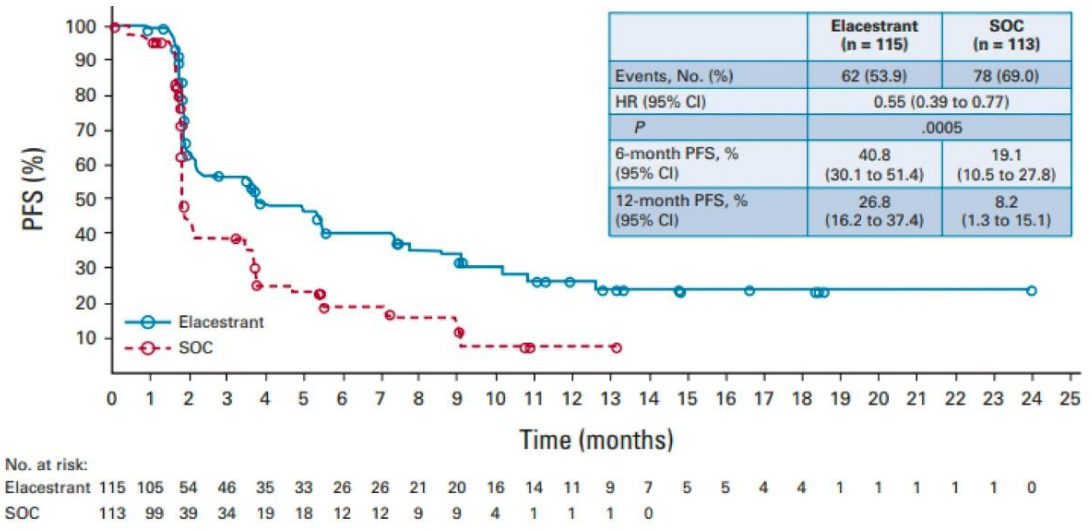



## ITT




| | Elacestrant (n = 239) | SOC (n = 238) |
|---|---|---|
| Events, No. (%) | 144 (60.3) | 156 (65.5) |
| HR (95% CI) | 0.70 (0.55 to 0.88) | |
| *P* | .0018 | |
| 6-month PFS, % (95% CI) | 34.3 (27.2 to 41.5) | 20.4 (14.1 to 26.7) |
| 12-month PFS, % (95% CI) | 22.3 (15.2 to 29.4) | 9.4 (4.0 to 14.8) |

## ESR1mut

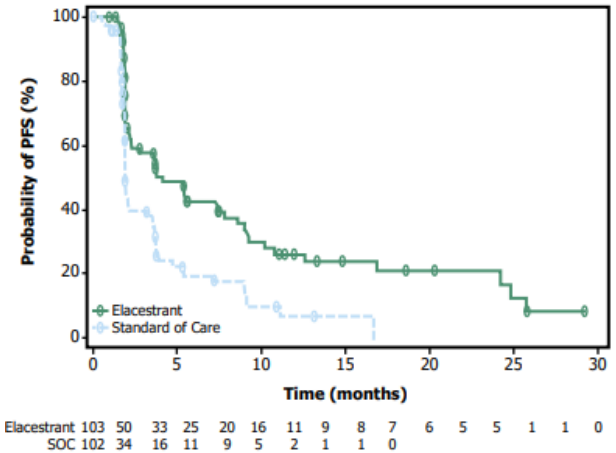



| | Elacestrant (n = 115) | SOC (n = 113) |
|---|---|---|
| Events, No. (%) | 62 (53.9) | 78 (69.0) |
| HR (95% CI) | 0.55 (0.39 to 0.77) | |
| *P* | .0005 | |
| 6-month PFS, % (95% CI) | 40.8 (30.1 to 51.4) | 19.1 (10.5 to 27.8) |
| 12-month PFS, % (95% CI) | 26.8 (16.2 to 37.4) | 8.2 (1.3 to 15.1) |

Bidart FC et al. JCO 2022

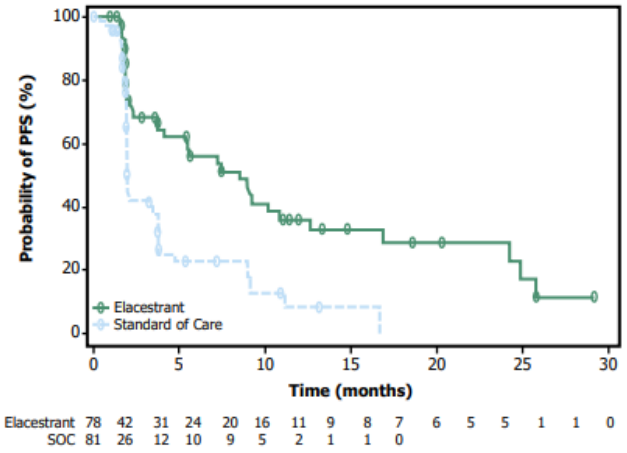
# EMERALD

## At least 6 mo CDK4/6i



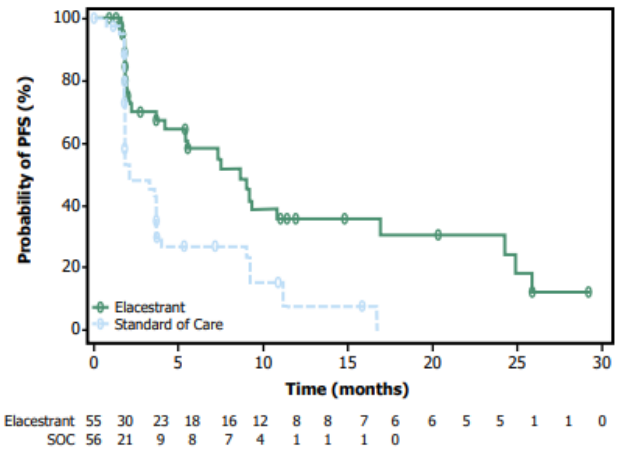

| | Elacestrant | SOC Hormonal Therapy |
|---|---|---|
| Median PFS, months (95% CI) | **4.14** (2.20 - 7.79) | **1.87** (1.87 - 3.29) |
| PFS rate at 12 months, % (95% CI) | 26.02 (15.12 - 36.92) | 6.45 (0.00 - 13.65) |
| Hazard ratio (95% CI) | **0.517** (0.361 - 0.738) | |

## At least 12 mo CDK4/6i




| | Elacestrant | SOC Hormonal Therapy |
|---|---|---|
| Median PFS, months (95% CI) | **8.61** (4.14 - 10.84) | **1.91** (1.87 - 3.68) |
| PFS rate at 12 months, % (95% CI) | 35.81 (21.84 - 49.78) | 8.39 (0.00 - 17.66) |
| Hazard ratio (95% CI) | **0.410** (0.262 - 0.634) | |

## At least 18 mo CDK4/6i

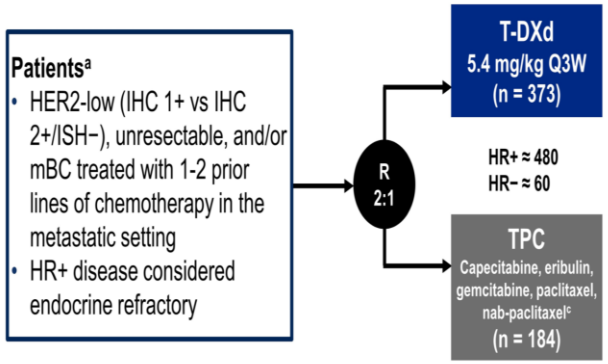



| | Elacestrant | SOC Hormonal Therapy |
|---|---|---|
| Median PFS, months (95% CI) | **8.61** (5.45 - 16.89) | **2.10** (1.87 - 3.75) |
| PFS rate at 12 months, % (95% CI) | 35.79 (19.54 - 52.05) | 7.73 (0.00 - 20.20) |
| Hazard ratio (95% CI) | **0.466** (0.270 - 0.791) | |

Bidart FC et al. JCO 2022

| | EMERALD[1] | SERENA-2[2] | EMBER-3[3] | AMEERA-3[4-6] | acelERA[6-9] |
|---|---|---|---|---|---|
| **Treatment** | **Elacestrant** | **Camizestrant** | **Imlunestrant** +/- abemaciclib | **Amcenestrant** | **Giredestrant** |
| **Control Arm** | fulvestrant / AIs | fulvestrant | fulvestrant / exemestane | fulvestrant / AIs / tamoxifen | fulvestrant / AIs |
| **Phase (n)** | Phase 3 (478) | Phase 2 (240) | Phase 3 (800) | Phase 2 (367) | Phase 2 (303) |
| **Patients** | Men or postmenopausal women | Postmenopausal women | Men or postmenopausal women | Men or women (any menopausal status) | Men or women (any menopausal status) |
| **Prior CDK4/6i** | **Required (100%)** | Permitted | Permitted | Permitted (79.7%) | Permitted (42%) |
| **Allowed Prior Fulvestrant** | **YES** | NO | NO | YES | YES |
| **Allowed Prior Chemotherapy in mBC** | **YES** | YES | NO | YES | YES |
| **Data readout** | **Positive (Registrational)** | Positive (Non-Registrational) | Ongoing | Negative | Negative |

# DESTINY-Breast04

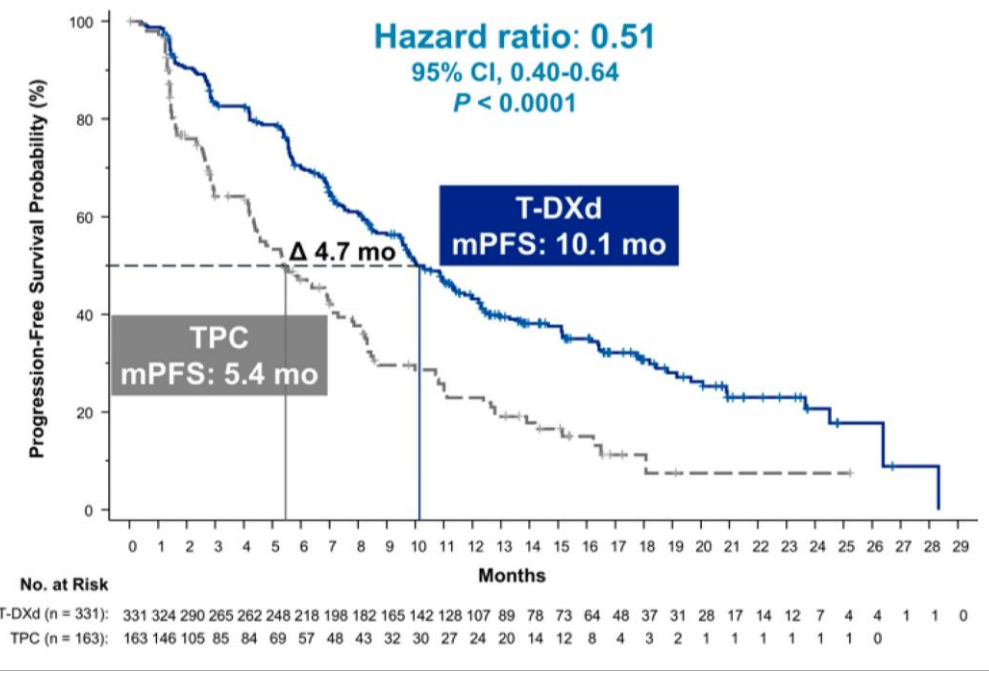


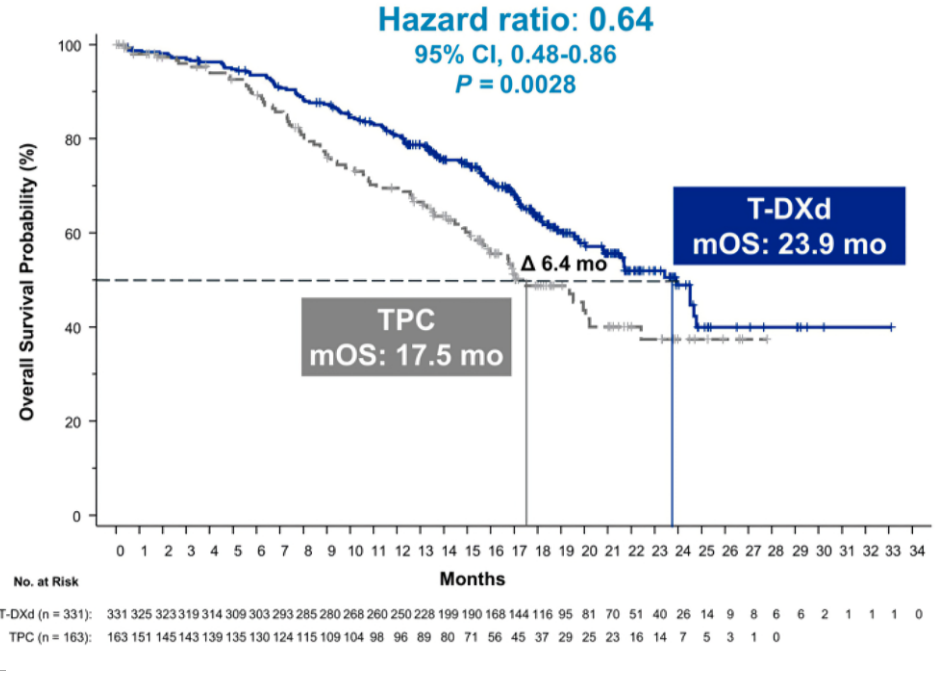

**Primary endpoint**
- PFS by BICR (HR+)

**Key secondary endpoints[b]**
- PFS by BICR (all patients)
- OS (HR+ and all patients)

**Hierarchical testing**

PFS in HR+ → PFS in all patients → OS in HR+ → OS in all patients




Modi S et al. NEJM 2022

# TROPiCS-02

NCT03901339

**Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]:**

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- Measurable disease by RECIST 1.1

N=543

R 1:1

*Treatment was continued until progression or unacceptable toxicity*

**Sacituzumab govitecan 10 mg/kg IV days 1 and 8, every 21 days n=272**

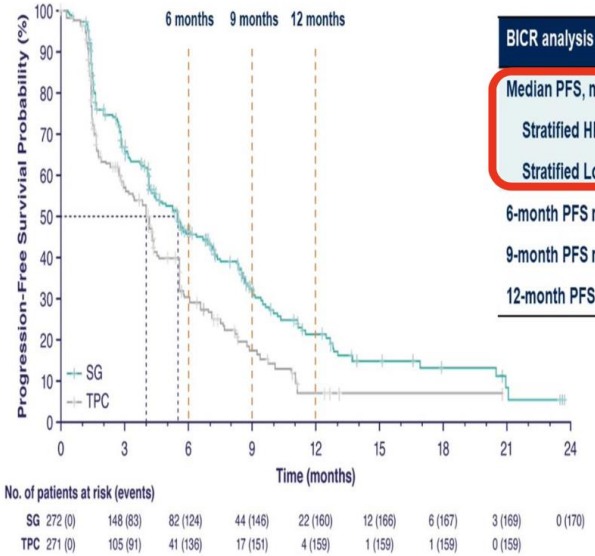
**Treatment of physician's choice[b] (capecitabine, vinorelbine, gemcitabine or eribulin) n=271**

**Endpoints**

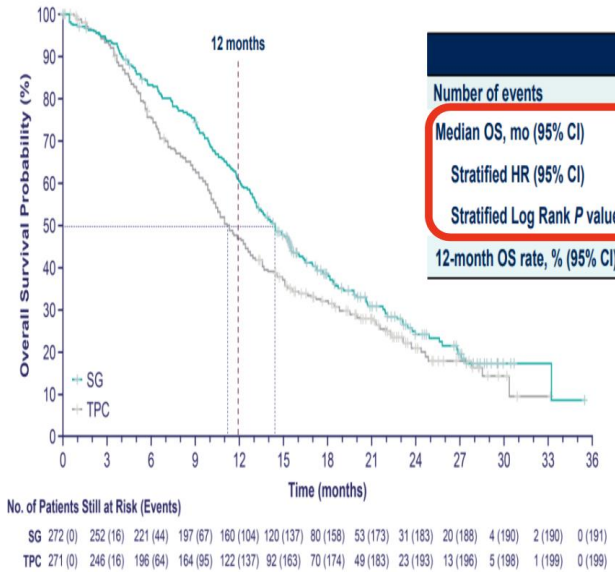
**Primary**
- PFS by BICR

**Secondary**
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

**Stratification:**
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)




| BICR analysis | SG (n=272) | TPC (n=271) |
|---|---|---|
| Median PFS, mo (95% CI) | 5.5 (4.2–7.0) | 4.0 (3.1–4.4) |
| Stratified HR (95% CI) | **0.66** (0.53–0.83) | |
| Stratified Log Rank *P* value | 0.0003 | |
| 6-month PFS rate, % (95% CI) | 46.1 (39.4–52.6) | 30.3 (23.6–37.3) |
| 9-month PFS rate, % (95% CI) | 32.5 (25.9–39.2) | 17.3 (11.5–24.2) |
| 12-month PFS rate, % (95% CI) | 21.3 (15.2–28.1) | 7.1 (2.8–13.9) |




| | SG (n=272) | TPC (n=271) |
|---|---|---|
| Number of events | 191 | 199 |
| Median OS, mo (95% CI) | 14.4 (13.0–15.7) | 11.2 (10.1–12.7) |
| Stratified HR (95% CI) | **0.79** (0.65–0.96) | |
| Stratified Log Rank *P* value | *P*=0.020 | |
| 12-month OS rate, % (95% CI) | 61 (55–66) | 47 (41–53) |

Rugo H et al. ESMO 2022

# EMBRACA

**Phase 3, international, open-label study randomized 431 patients in 16 countries and 145 sites**

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation*†

<=3 chemotherapies containing a Taxane and antracycline

Stratification factors:

- Number of prior chemo regimens (0 or ≥1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

R 2:1

**Talazoparib**
1 mg PO daily

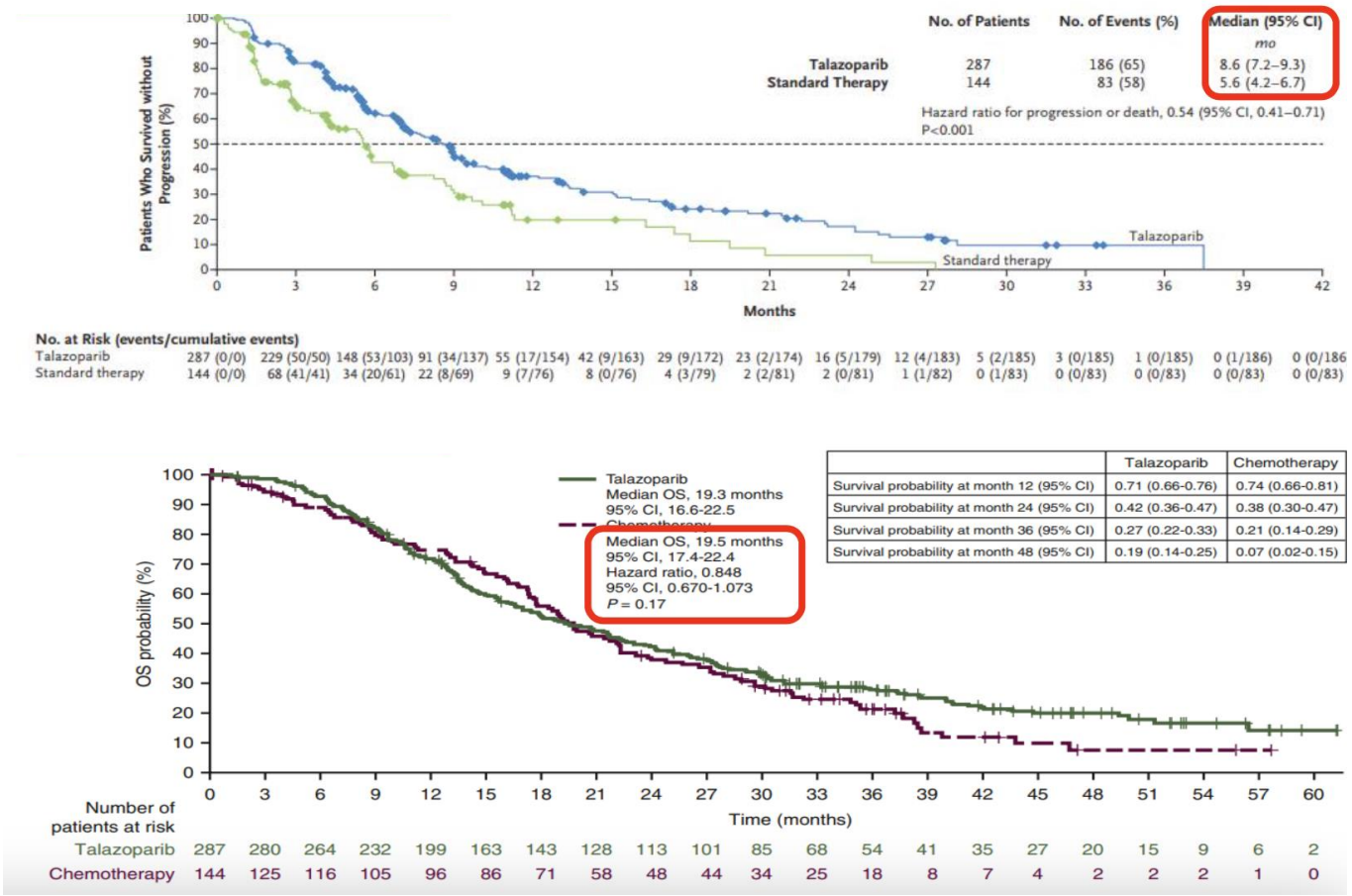
Treatment (21-day cycles) continues until progression or unacceptable toxicity

**Physician's choice of therapy (PCT)‡:**
- Capecitabine
- Eribulin
- Gemcitabine
- Vinorelbine

**Primary endpoint**
- Progression-free survival by RECIST by blinded central review

**Key secondary efficacy endpoints**
- Overall survival (OS)
- ORR by investigator
- Safety

**Exploratory endpoints**
- Duration of response (DOR) for objective responders
- Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)

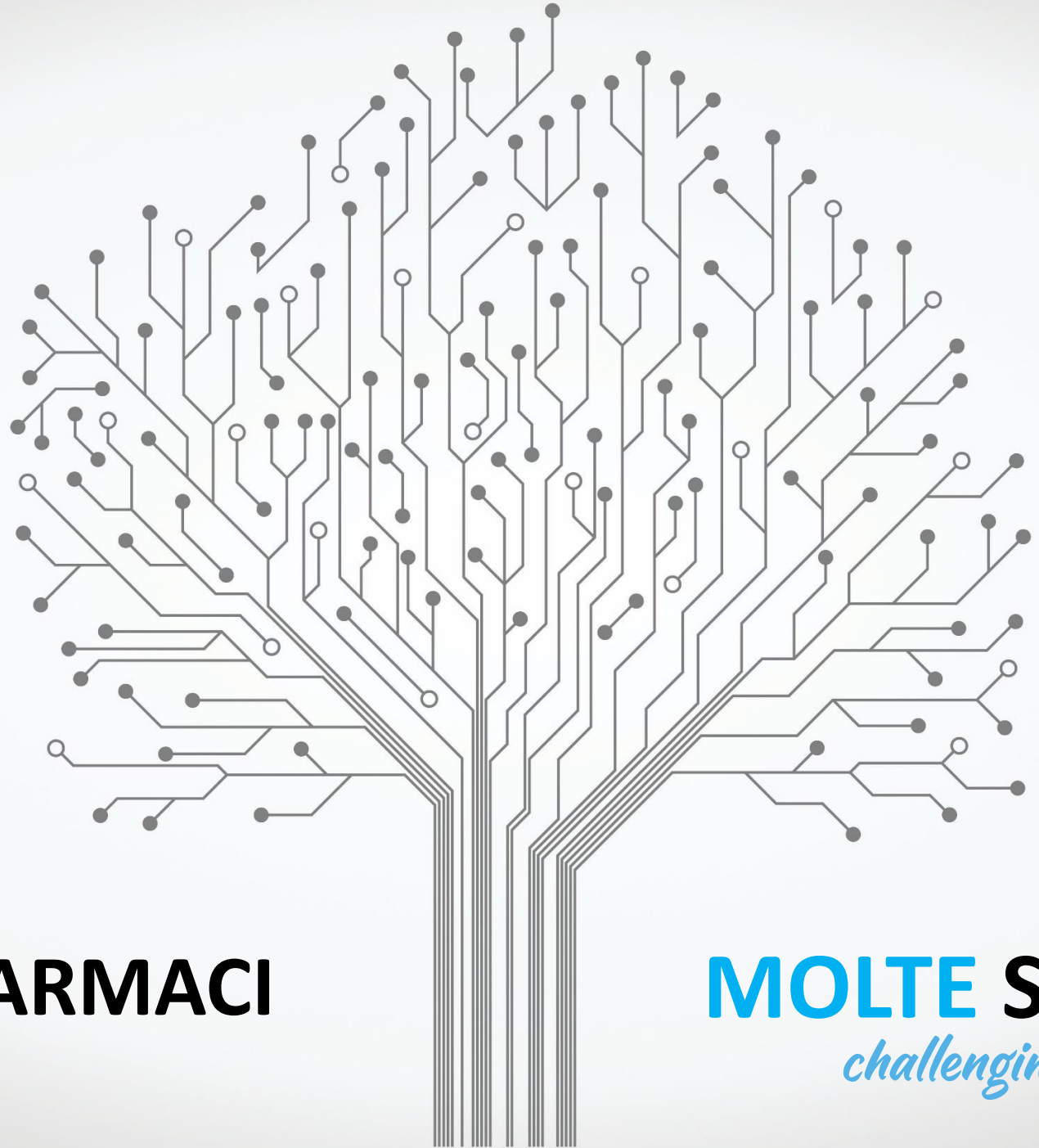



Rugo H et al. ESMO 2022

**POCHI FARMACI**

**POCHE SCELTE**

*easy, no?*



**MOLTI FARMACI**

**MOLTE SCELTE**

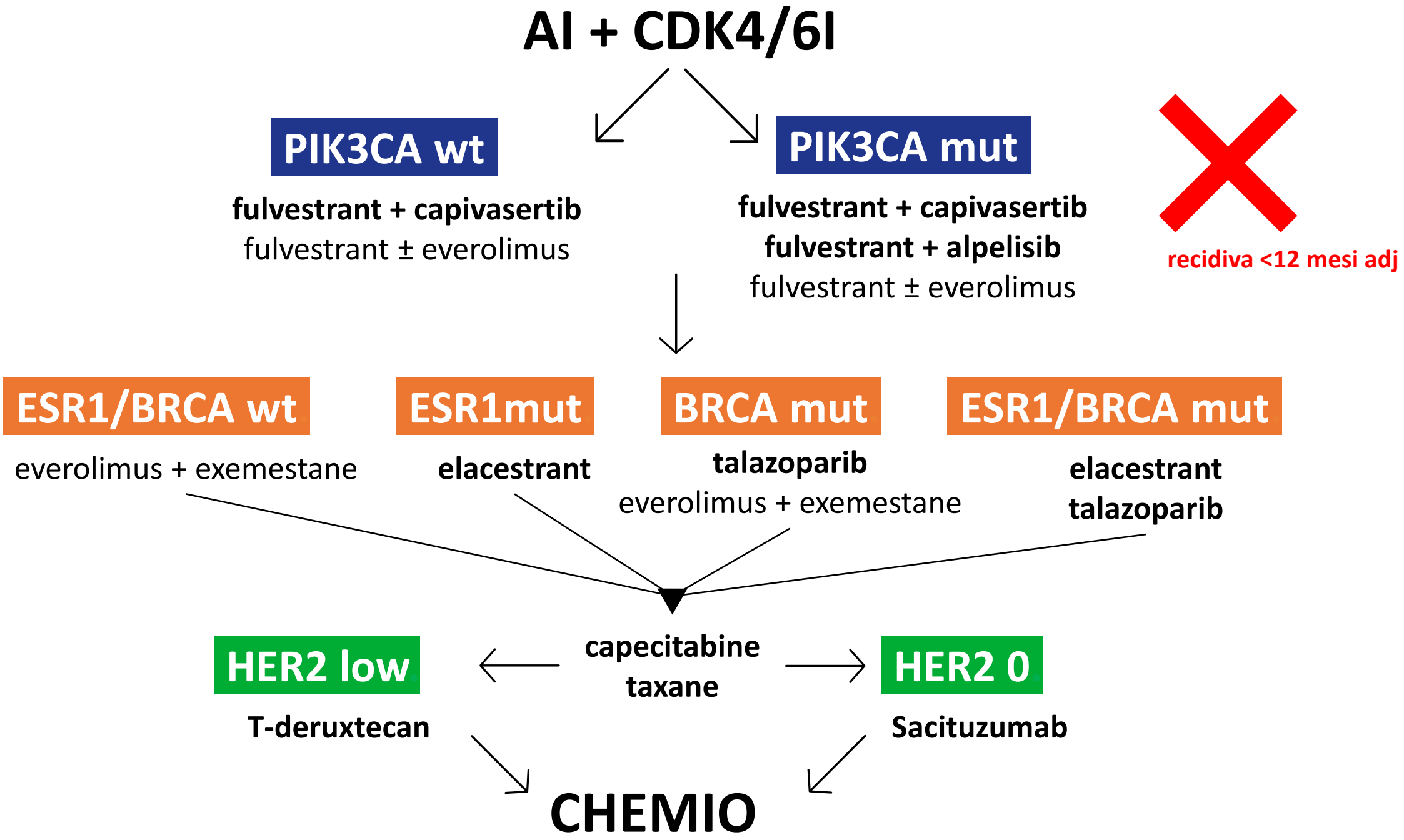
*challenging enough, baby?*

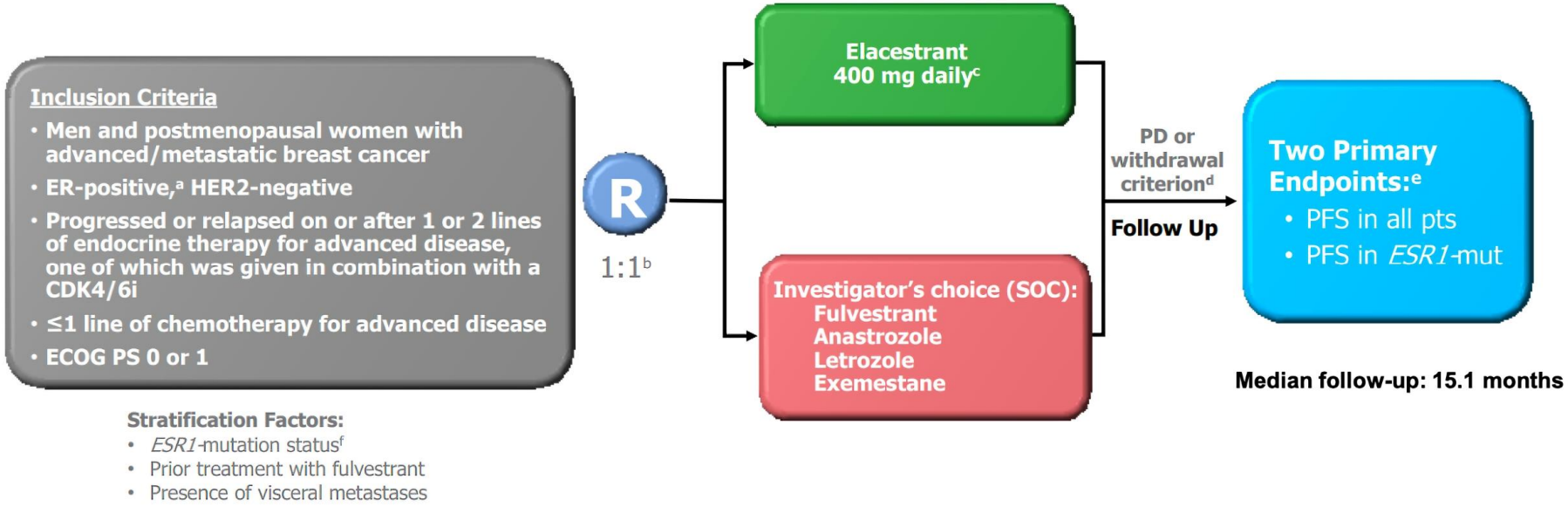
# AI + CDK4/6i

everolimus + exemestane

fulvestrant

# CHEMIO


AI + CDK4/6I
PIK3CA wt
fulvestrant + capivasertib
fulvestrant ± everolimus
PIK3CA mut
fulvestrant + capivasertib
fulvestrant + alpelisib
fulvestrant ± everolimus
recidiva <12 mesi adj
ESR1/BRCA wt
everolimus + exemestane
ESR1mut
elacestrant
BRCA mut
talazoparib
everolimus + exemestane
ESR1/BRCA mut
elacestrant
talazoparib
capecitabine
taxane
HER2 low
T-deruxtecan
HER2 0
Sacituzumab
CHEMIO




ESR1/BRCA wt

everolimus + exemestane

ESR1mut

**ELACESTRANT**

BRCA mut

talazoparib

everolimus + exemestane

ESR1/BRCA mut

**ELACESTRANT**

talazoparib

capecitabine
taxane

HER2 low

T-deruxtecan
Sacituzumab

HER2 0

Sacituzumab

CHEMIO

AGENZIA ITALIANA DEL FARMACO

*Indicazione rimborsata:*

*Talzenna è indicato come monoterapia per il trattamento di pazienti adulti con mutazioni germinali BRCA1/2, affetti da carcinoma mammario HER2-negativo localmente avanzato o metastatico. I pazienti devono essere stati precedentemente trattati con una antraciclina e/o un taxano nel contesto (neo)adiuvante, localmente avanzato o metastatico, ad eccezione dei pazienti non idonei per tali trattamenti (vedere paragrafo 5.1).*

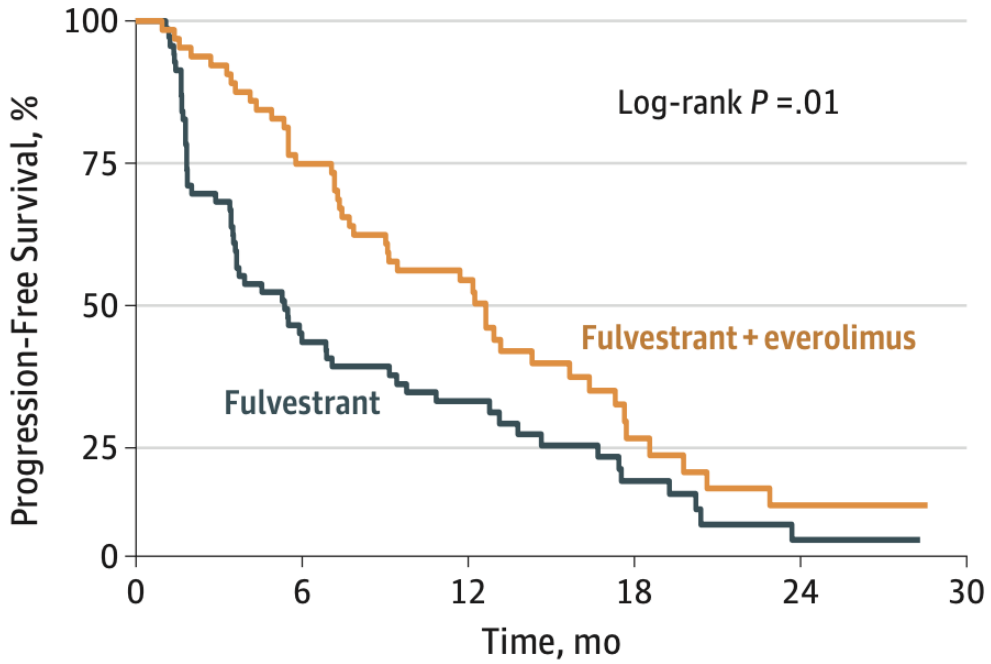
*I pazienti con carcinoma mammario positivo ai recettori ormonali (HR) devono essere stati precedentemente trattati con terapia endocrina o ritenuti non idonei alla terapia endocrina e devono aver ricevuto una linea di trattamento con inibitori delle chinasi ciclina-dipendenti (CDK4/6).*

*I pazienti con carcinoma mammario negativo ai recettori ormonali (HR) devono essere stati precedentemente trattati con chemioterapia a base di platino, ad eccezione dei pazienti non idonei per tale trattamento.*

**massimo 3 linee per M+**

**TALAZOPARIB** **TALAZOPARIB**

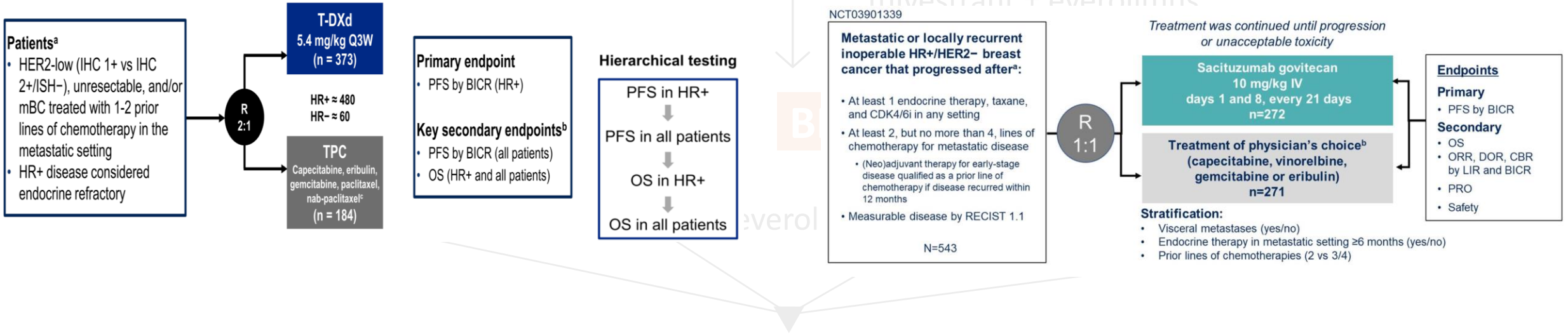
# FULVESTRANT ± EVEROLIMUS




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Fulvestrant | 66 | 29 | 14 | 6 | 1 | 0 |
| Fulvestrant + everolimus | 64 | 45 | 26 | 8 | 2 | 0 |

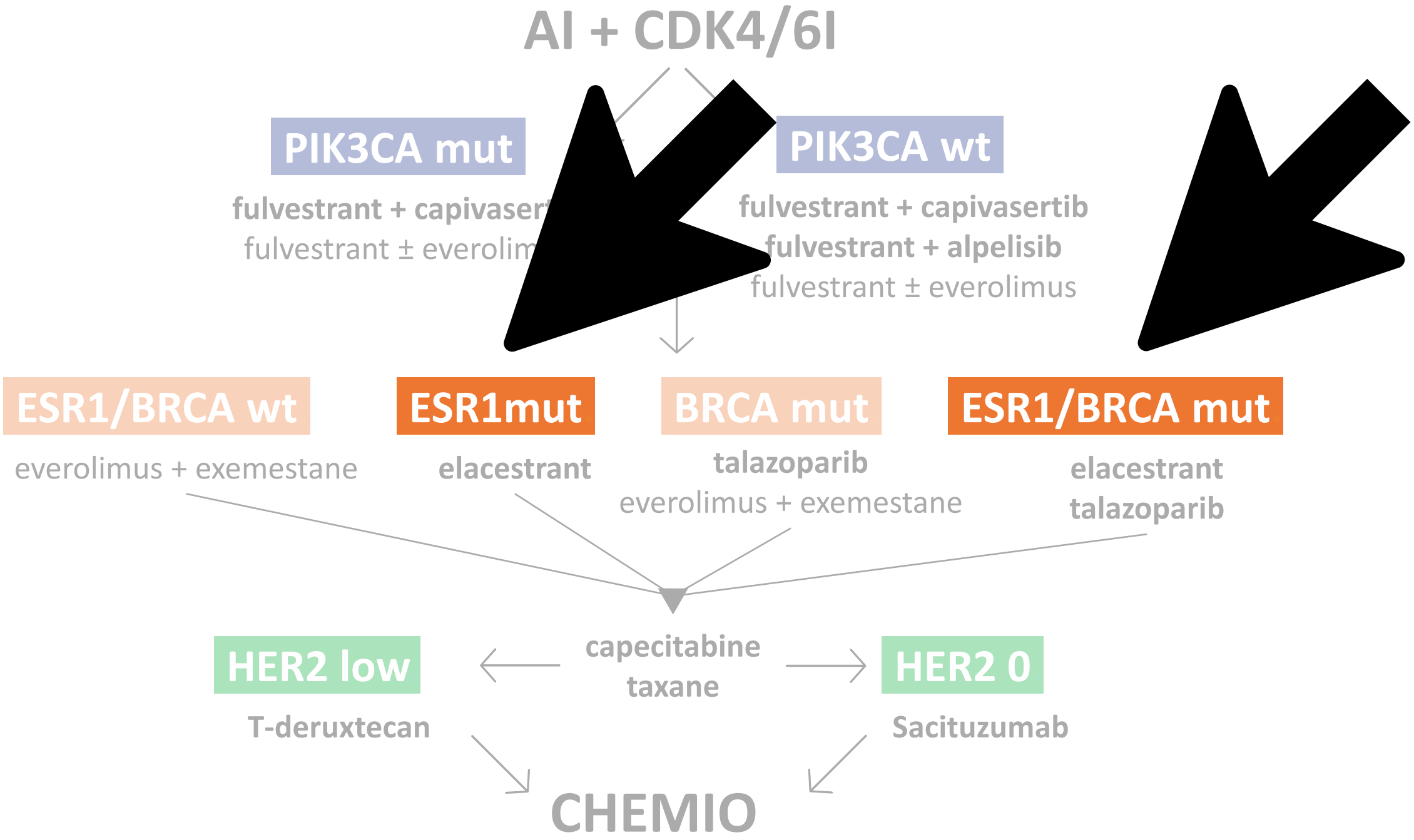
**MANTA TRIAL**

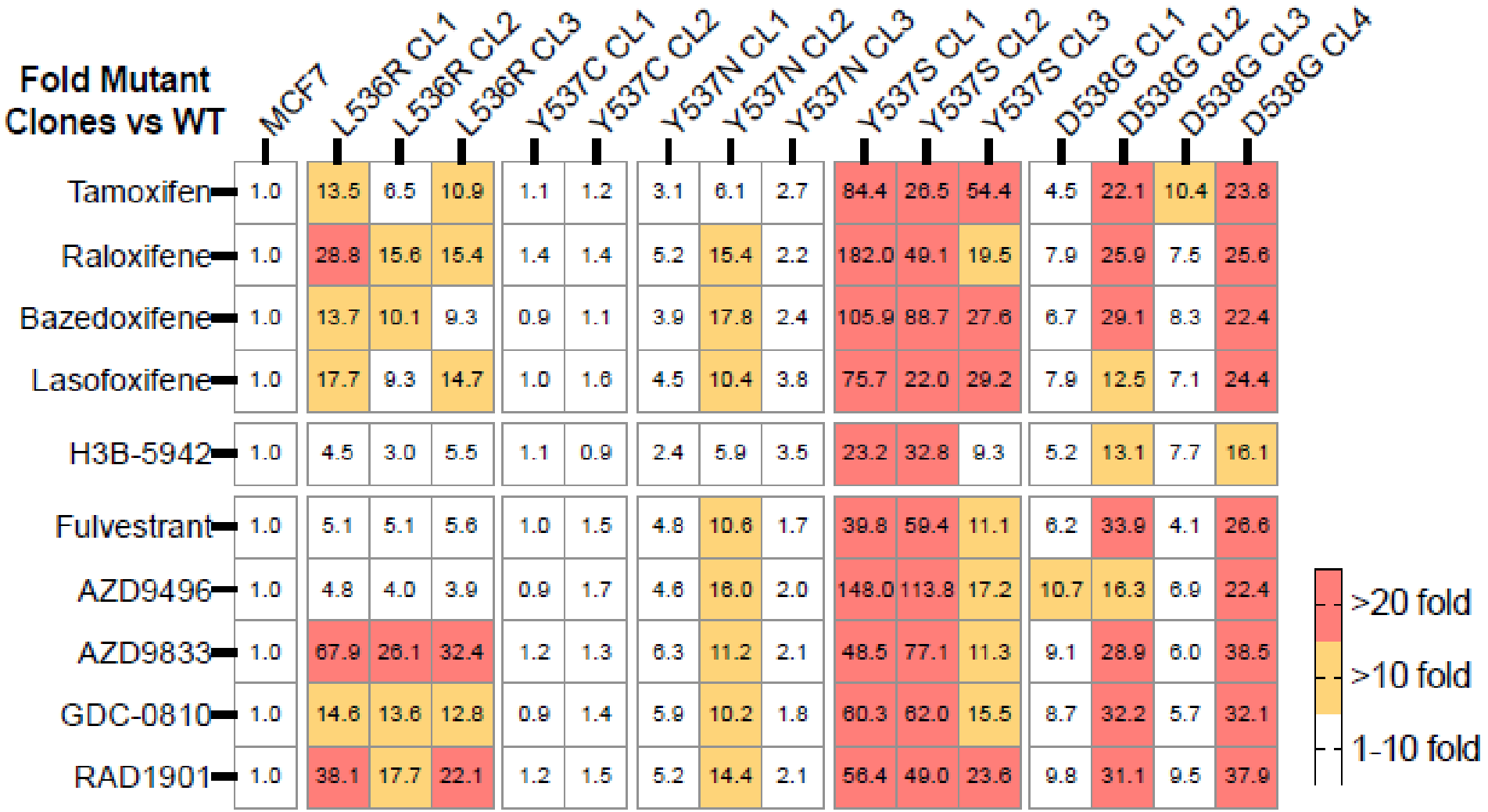
Schmid P et al, JAMA Onc 2019



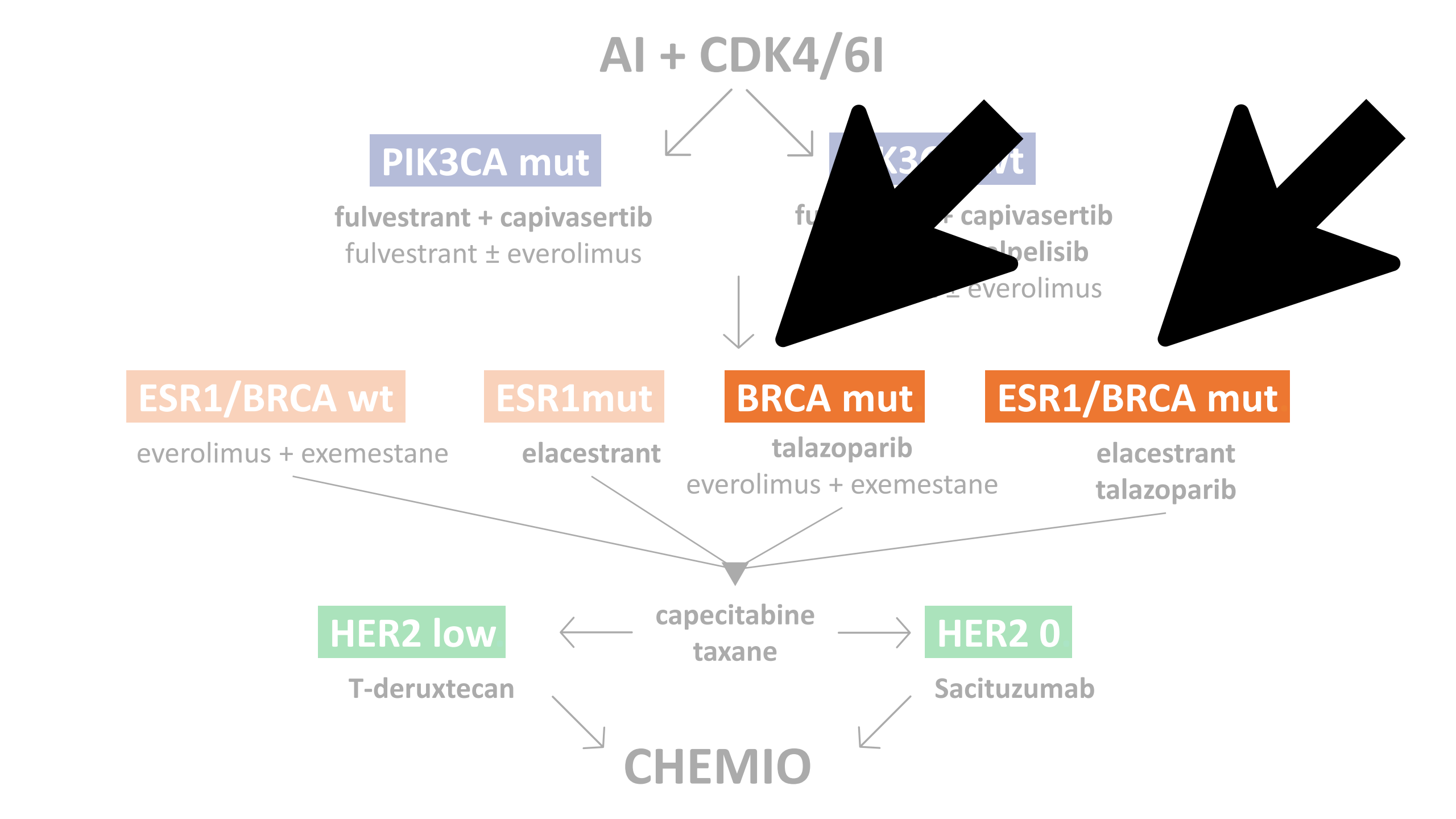

cross-resistenza?

**T-DERUXTECAN** → **SACITUZUMAB**


AI + CDK4/6I
PIK3CA mut
fulvestrant + capivasert
fulvestrant ± everolim
PIK3CA wt
fulvestrant + capivasertib
fulvestrant + alpelisib
fulvestrant ± everolimus
ESR1/BRCA wt
everolimus + exemestane
ESR1mut
elacestrant
BRCA mut
talazoparib
everolimus + exemestane
ESR1/BRCA mut
elacestrant
talazoparib
capecitabine
taxane
HER2 low
T-deruxtecan
HER2 0
Sacituzumab
CHEMIO




Harrod A. et al, Oncogene 2017

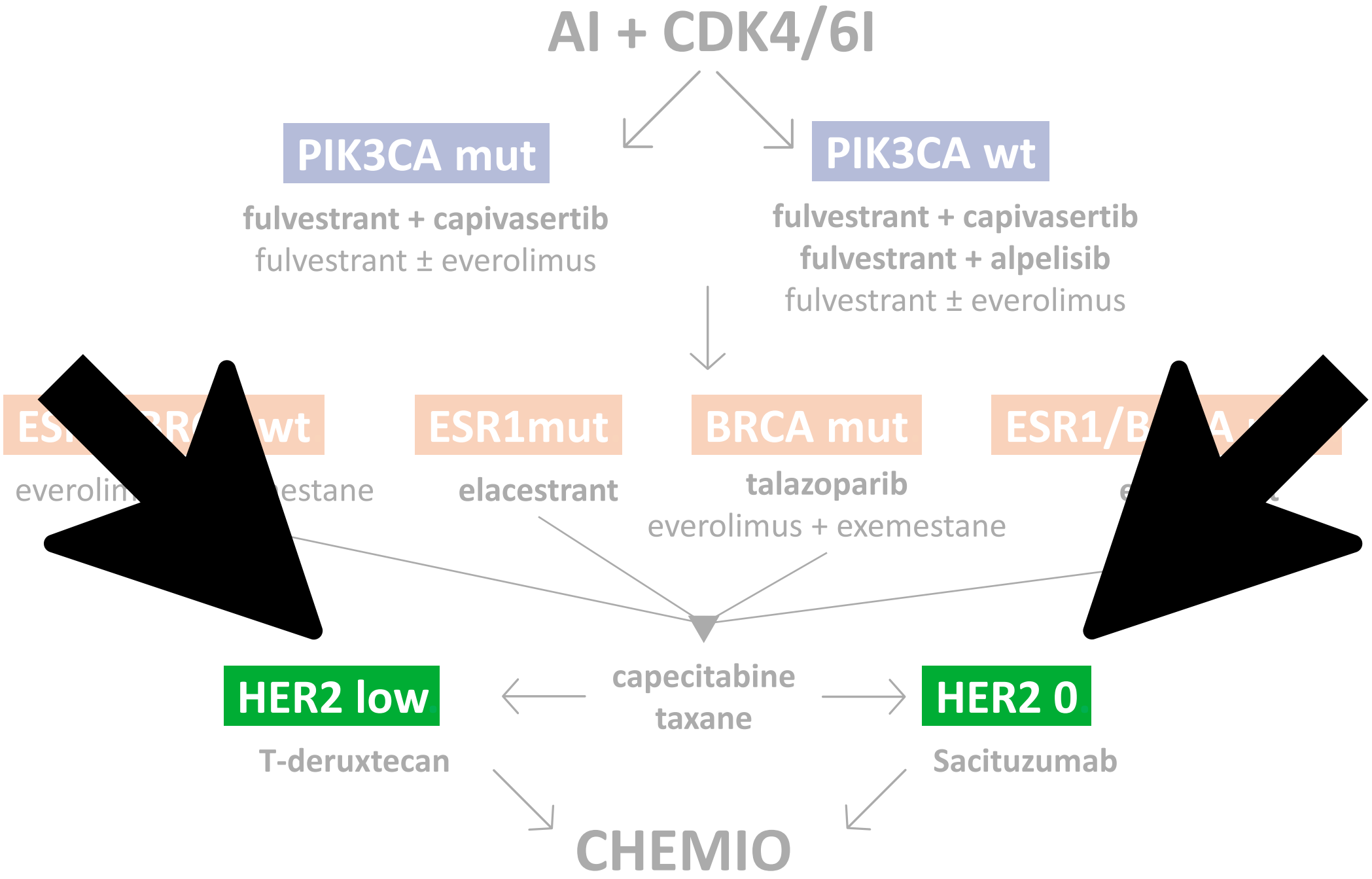

AI + CDK4/6I
PIK3CA mut
fulvestrant + capivasertib
fulvestrant ± everolimus
+ capivasertib
alpelisib
± everolimus
ESR1/BRCA wt
everolimus + exemestane
ESR1mut
elacestrant
BRCA mut
talazoparib
everolimus + exemestane
ESR1/BRCA mut
elacestrant
talazoparib
capecitabine
taxane
HER2 low
T-deruxtecan
HER2 0
Sacituzumab
CHEMIO

# gPALB2 e sBRCA1/2

## unitevi al party!

| | Cohort 1 (germline) | | Cohort 2 (somatic) | |
|---|---|---|---|---|
| **Response** | **All** | **gPALB2 Mutations** | **All** | **sBRCA1/2[a] Mutations** |
| Best response | | | | |
| (Confirmed) CR | 0 | 0 | 0 | 0 |
| (Confirmed) PR | 9 | 9 | 8 | 8 |
| SD | 8 | 2 | 10 | 6 |
| PD | 10 | 0 | 8 | 2 |
| ORR, % (90% CI) | 33 (19 to 51) | 82 (53 to 96) | 31 (15 to 49) | 50 (28 to 72) |
| CBR, % (90% CI) | 50 (33 to 67) | 100 (74 to 100) | 48 (30 to 66) | 66 (42 to 85) |
| DOR, months, median (90% CI) | 9 (7.5 to NA) | 9 (7.5 to NA) | 6.3 (3.1 to NA) | 6.3 (3.1 to NA) |
| PFS, months, median (90% CI) | 4.5 (1.7 to 12) | 13.3 (12 to NA) | 4.1 (2.8 to 6.3) | 6.3 (4.4 to NA) |
| Time to onset of response, weeks, median (90% CI) | 12.1 (11.4 to 20.8) | 12.1 (11.4 to 20.8) | 10.3 (8.4 to 11.9) | 10.3 (8.4 to 11.9) |

Tung NM et al., JCO 2020


AI + CDK4/6I
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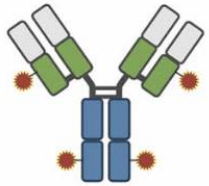
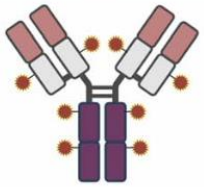
fulvestrant + capivasertib
fulvestrant + alpelisib
fulvestrant ± everolimus
ESR1mut
elacestrant
BRCA mut
talazoparib
everolimus + exemestane
capecitabine
taxane
HER2 low
T-deruxtecan
HER2 0
Sacituzumab
CHEMIO

**Datopotamab Deruxtecan**



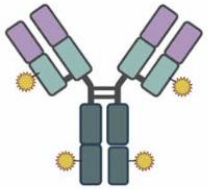
**Target**: Trop-2 (TACSTD2)
**Payload**: Deruxtecan (extecan derivative)
**Payload class:** Topoisomerase I inhibitor
**DAR**: 4:1
**Linker**: cleavable

**Patritumab Deruxtecan**

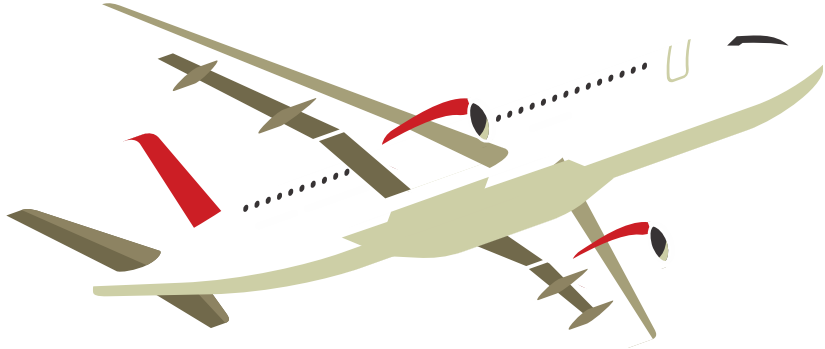


**Target**: HER3 (ERBB3)
**Payload**: Deruxtecan (extecan derivative)
**Payload class:** Topoisomerase I inhibitor
**DAR**: 8:1
**Linker**: cleavable

**Ladiratuzumab Vedotin**



**Target**: LIV-1 (CLC39A6)
**Payload**: Vedotin (MMAE derivative)
**Payload class**: Microtubule inhibitor
**DAR**: 4:1
**Linker**: cleavable



# i 3 EMERGENTI dell'ADC

adapted from Nicolò E. et al., The Cancer Journal 2022

| Biomarker | Trial | Phase |
|---|---|---|
| **Mesothelin** | NCT04175847 (Recruiting) | I |
| **Tissue Factor** | NCT04925284 (JEWEL-101) (Recruiting) | I |
| **Nectin-4** | NCT04225117 (EV-202) (Recruiting) | II |
| **cMet** | NCT03859752 (Active, not recruiting) | I |
| | NCT04617314 (Recruiting) | I |
| **5 T4** | NCT04202705 (Recruiting) | I |
| | NCT04410224 (Recruiting) | I |
| **FRα** | NCT04300556 (Active, not recruiting) | I-II |
| **ROR1** | NCT04441099 (Recruiting) | I-II |
| **ROR2** | NCT03504488 (Recruiting) | I-II |
| **B7-H3** | NCT03729596 (Recruiting) | I-II |

| Biomarker | Trial | Phase |
|---|---|---|
| **B7-H4** | NCT05194072 (Recruiting) | I |
| | NCT05123482 (Recruiting) | I-II |
| **CEACAM5** | NCT04659603 (Recruiting) | II |
| | NCT02187848 (Active, not recruiting) | I-II |
| **STING** | NCT05070247 (Recruiting) | I |
| **FOLR1;PSMA** | NCT04928612 (Active, not recruiting) | I |
| **Globo H** | NTC04084366 (Recruiting) | I |
| **KAAG1** | NCT04972981 (Recruiting) | I |
| **CD205/Ly75** | NCT04064359 (Recruiting) | I |

adapted from Nicolò E. et al., The Cancer Journal 2022

I nuovi farmaci sono un punto di svolta nella creazione di un **nuovo algoritmo** che vada oltre l'**endocrinoresistenza**

# Nuovo algoritmo?

*spoiler: si* 🤫

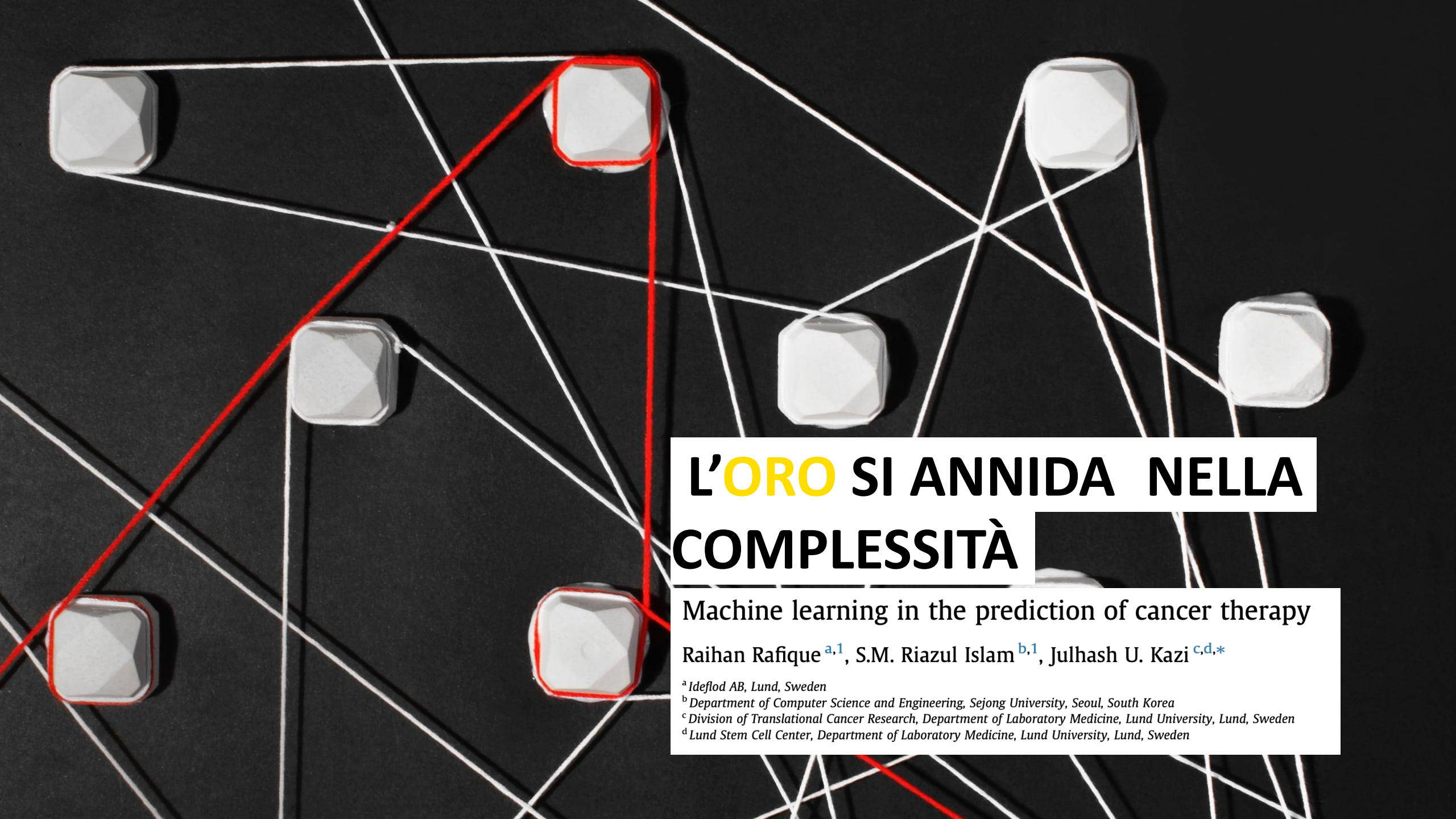
**Elacestrant**

**Capivasertib/Alpelisib**

**Talazoparib, T-Deruxtecan, S-Govitecan**

# Oltre l'endocrinoresistenza?

*spoiler: si* 🤫



# L'ORO SI ANNIDA NELLA COMPLESSITÀ

## Machine learning in the prediction of cancer therapy

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[b] *Department of Computer Science and Engineering, Sejong University, Seoul, South Korea*
[c] *Division of Translational Cancer Research, Department of Laboratory Medicine, Lund University, Lund, Sweden*
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