Universität Zürich[UZH]

Epidemiology, Biostatistics and Prevention Institute (EBPI)



Observance à l'hormonothérapie adjuvante du cancer du sein et survie

Enseignements issus de l'extraction SNDS du Registre national des cancers

Registre National des Cancers inca

Elise Dumas

Journée scientifique du Registre national des cancers, Novembre 2026

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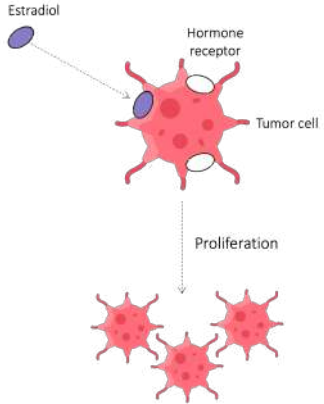
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Survival benefit of ET persistence in young patients

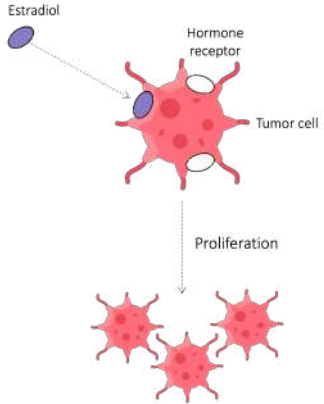
Endocrine therapy for hormone-receptor positive breast cancer

— Around 70-80% of breast tumors express hormone receptors.



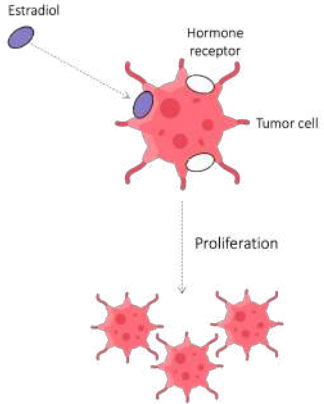
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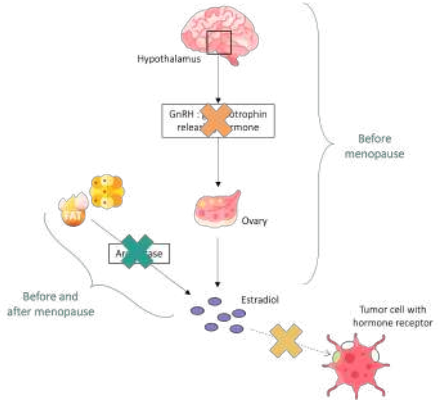
Endocrine therapy for hormone-receptor positive breast cancer

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- Treated with 5 to 10 years of endocrine therapy.
- Endocrine therapy leads to quite severe and distressing side effects : many patients struggle to take endocrine therapy continuously.



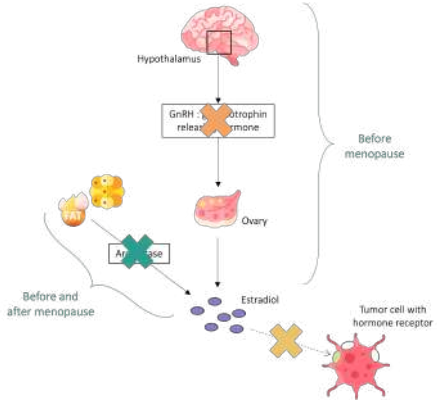
Endocrine therapy regimen (in summary)

— In **post-menopausal** women:
  — 5 years of an aromatase inhibitor (AI) : anastrozole, letrozole, or exemestane



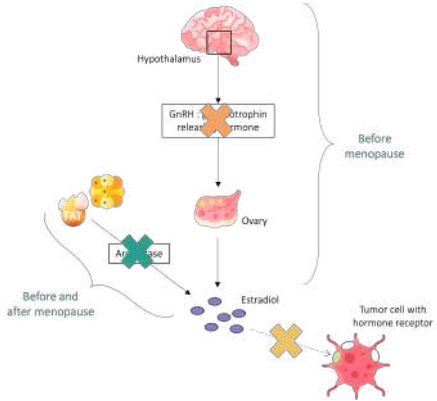
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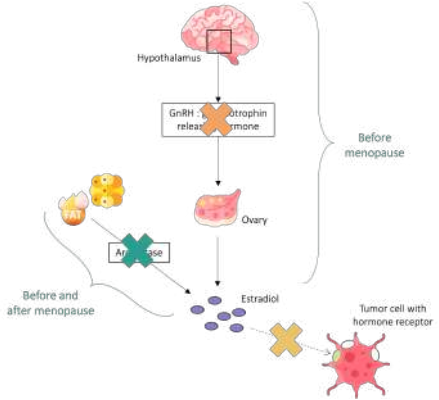
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Tamoxifen and AIs : One pill a day for at least five years

The FRESH cohort

— Data comes from Système National des Données de Santé (SNDS), stored in the **Registre National des Cancers**.

[1] Dumas, Laot u. a., “The French Early Breast Cancer Cohort (FRESH)”.

The FRESH cohort

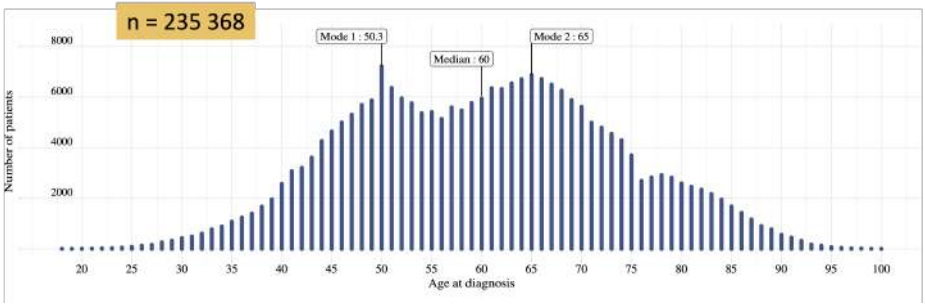
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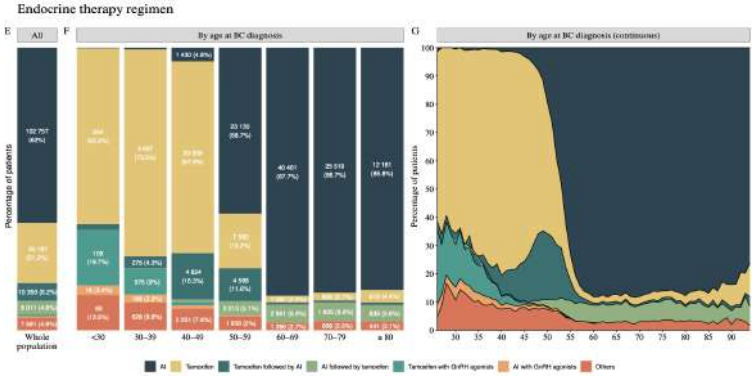


Now: n=376,913 patients.

[1] Dumas, Laot u. a., “The French Early Breast Cancer Cohort (FRESH)”.

Endocrine therapy data

— Pharmacy deliveries of endocrine therapy (number of boxes, doses).



Monthly endocrine therapy coverage : at least one day of treatment in the given month.

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Three aromatase inhibitors

- In post-menopausal women, three aromatase inhibitor molecules are approved as endocrine therapy:
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  - One steroidal : **exemestane**

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- One clinical trial (FATA-GIM3)De Placido u. a., “Adjuvant anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, in endocrine-sensitive breast cancer (FATA-GIM3)” has compared the molecules upfront.
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- Concluded that : "None of the three aromatase inhibitors was superior to the others in terms of efficacy."
- However :
  - The clinical trial was not powered to detect "small" differences.
  - Adherence in the clinical trial may not be representative of real-life adherence.

Target trial emulation

Target trial : Initiation + natural adherence

Randomized 1:1:1 to initiate anastrozole, letrozole, or exemestane

Target trial emulation

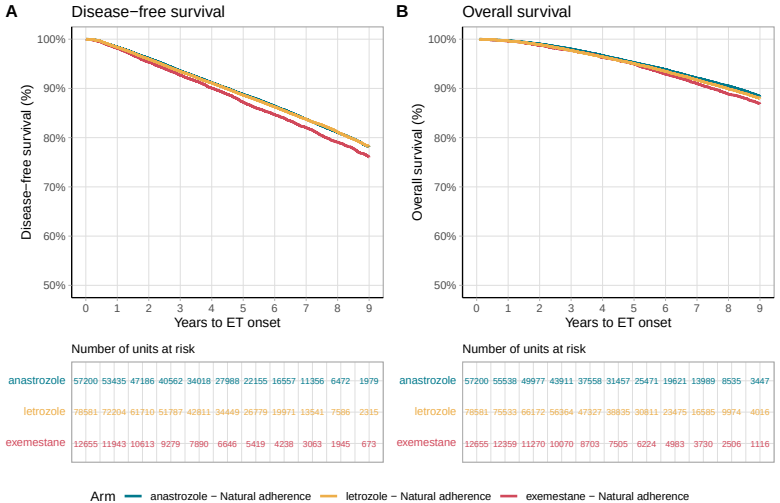
Target trial : Initiation + natural adherence

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— Outcome : disease-free survival and overall survival

— The emulation requires adjustment on **baseline confounding factors** (inverse probability of treatment weights).

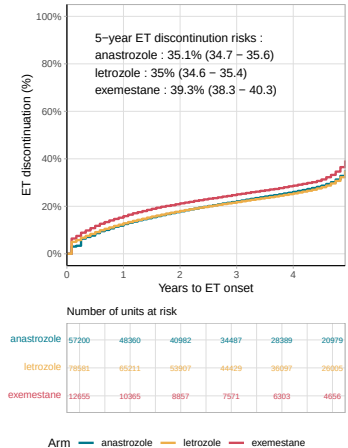
Initiation + natural adherence



Risk of discontinuation

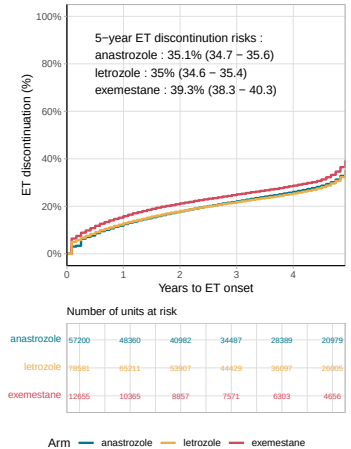
— After adjustment for baseline confounding factors.

— The risk of treatment discontinuation (= one month without coverage) was slightly higher for exemestane compared with anastrozole and letrozole.



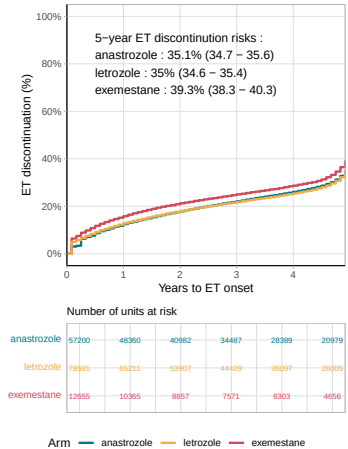
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- A natural hypothesis: the lower survival observed in patients initiating exemestane could be due to a lower adherence.
- Let's emulate the outcome we would have observed under perfect adherence.



Target trial emulation 2

Target trial : initiation + perfect persistence

Randomized 1:1:1 to initiate anastrozole, letrozole, or exemestane. Then should remain persistent to endocrine therapy for five years. Switches to another aromatase inhibitor or to tamoxifen are authorized.

Target trial emulation 2

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Roughly, the estimation method consists in :

— **Artificially censoring** patients whenever they discontinue treatment

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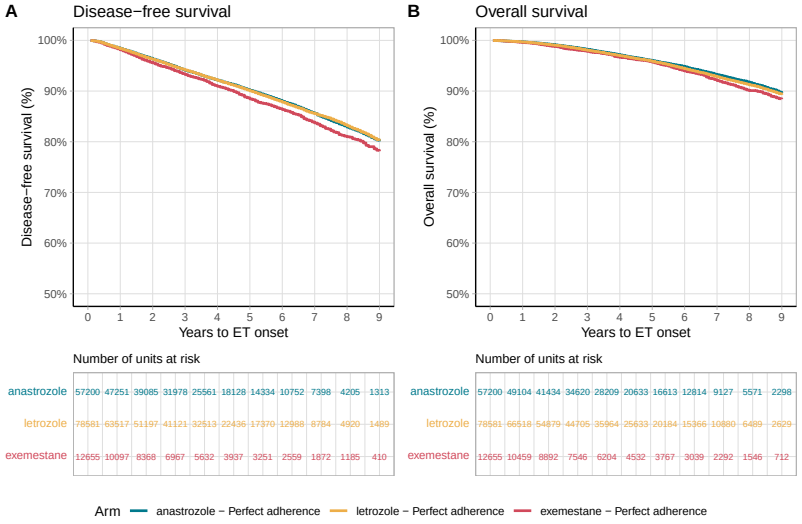
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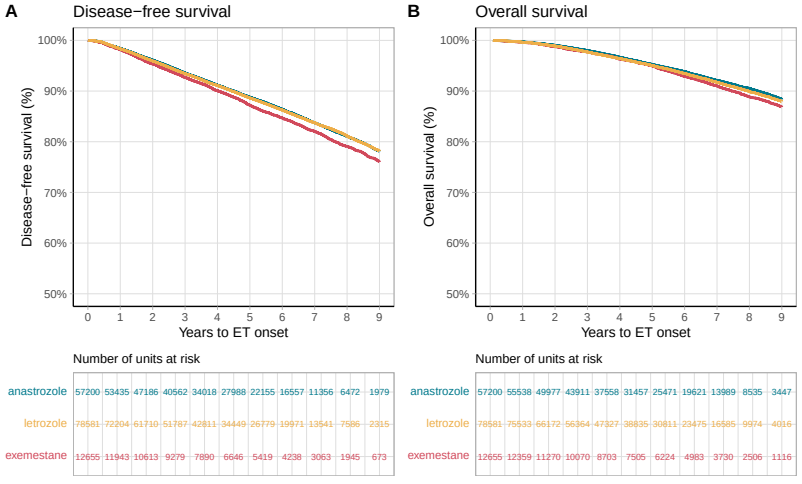
Roughly, the estimation method consists in :

- **Artificially censoring** patients whenever they discontinue treatment
- **Re-weighting** patients by (i) the inverse probability of initiating the molecule they initiated based on baseline confounders (IPTW) and (ii) the inverse of the probability of remaining uncensored every month based on baseline and time-varying covariates (IPCW)

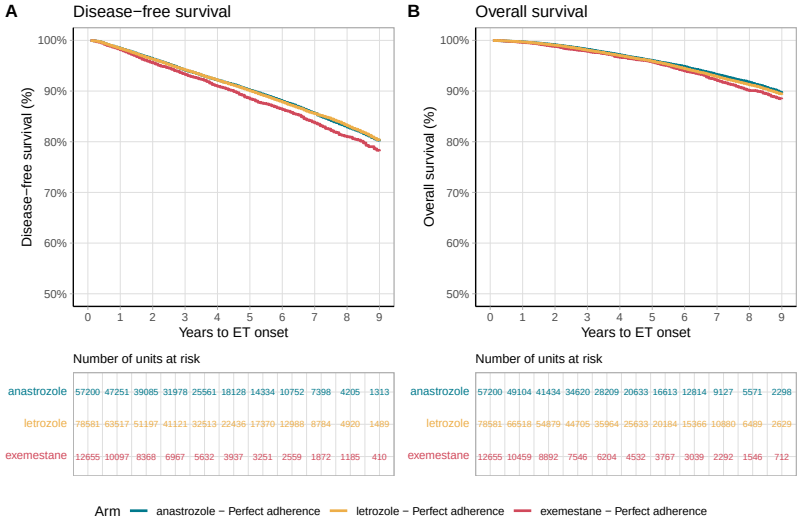
Under perfect adherence



Under natural adherence



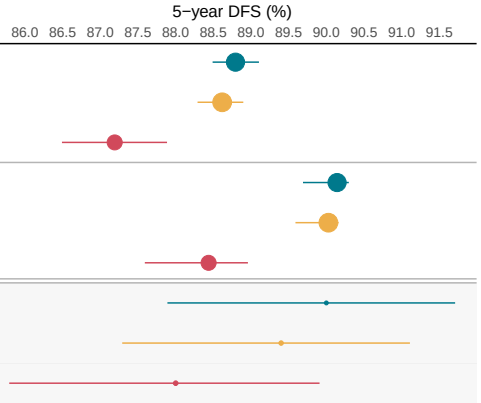
Under perfect adherence



Results.

Comparison between FATA-GIM3 RCT (De Placido et al.[2]) with our estimates[3]:

Strategy	Molecule	No patients	No events	5−year DFS (95% CI)
Natural adherence	anastrozole	57,200	4,977	88.8 (88.5 − 89.1)
	letrozole	78,581	6,755	88.6 (88.3 − 88.9)
	exemestane	12,655	1,313	87.2 (86.5 − 87.9)
Perfect adherence	anastrozole	57,200	3,627	90.1 (89.7 − 90.3)
	letrozole	78,581	4,907	90 (89.6 − 90.2)
	exemestane	12,655	939	88.4 (87.6 − 88.9)
FAGA−GIM3 RCT	anastrozole	1,226	124	90 (87.9 − 91.7)
	letrozole	1,233	129	89.4 (87.3 − 91.1)
	exemestane	1,238	148	88 (85.8 − 89.9)

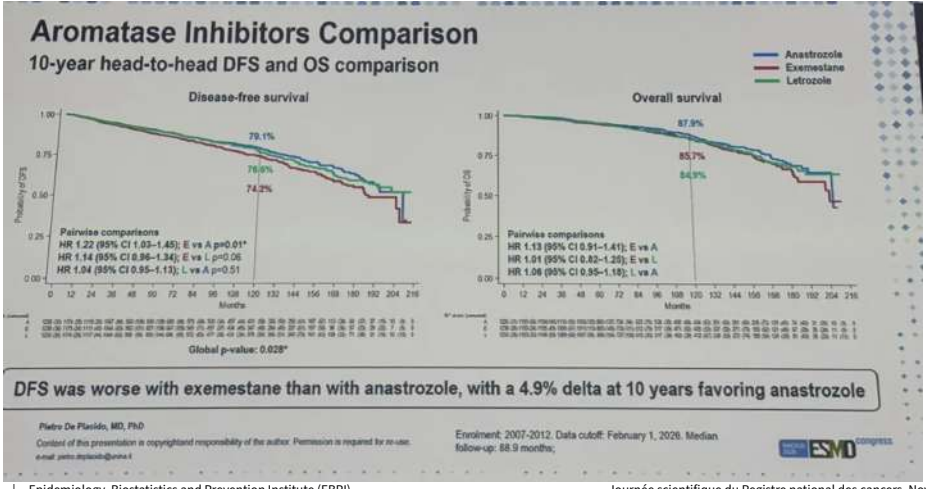


[2] De Placido u. a., “Adjuvant anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, in endocrine-sensitive breast cancer (FATA-GIM3)”.

[3] Dumas, Hamy u. a., “Outcomes of Anastrozole, Letrozole, and Exemestane in Patients With Postmenopausal Breast Cancer”.

An update

At ESMO 2026 : results of FATA-GIM3 at 10 years :



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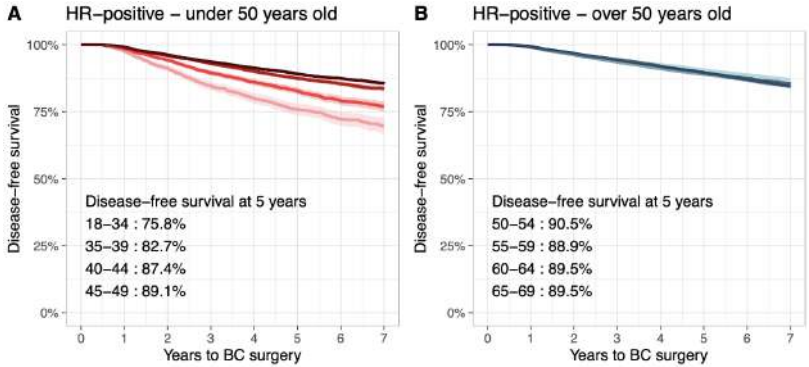
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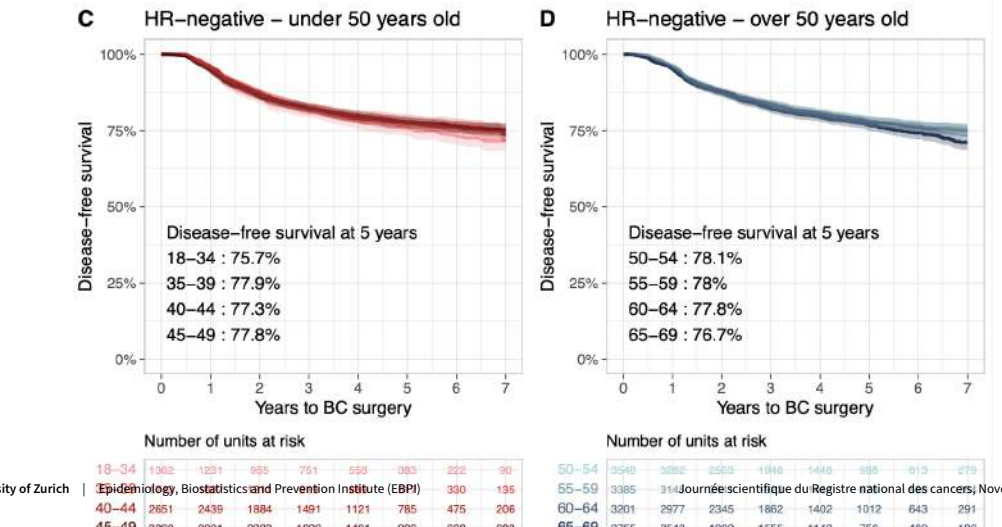
Young age is associated with bad prognosis in patients with HR-positive disease.

— Disease-free survival (DFS) by age in patients with *HR*-positive disease:



But not in patients with HR-negative disease.

— Disease-free survival (DFS) by age in patients with *HR*-negative disease:



Role of adherence to endocrine therapy in young patients

— In patients with *HR*-positive disease, young age is associated with low adherence and persistence to endocrine therapy.
— The poor survival observed in young patients might be partly due to imperfect endocrine therapy intake.
— Can we evaluate the potential survival benefits of improving persistence to endocrine therapy in young patients?

Perfect adherence may not be manageable for certain patients

— Interventions that allow breaks of treatment, as long as they do not exceed a certain length of time.[4]

[4] Wanis u. a., “Grace periods in comparative effectiveness studies of sustained treatments”.

Perfect adherence may not be manageable for certain patients

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Target trial

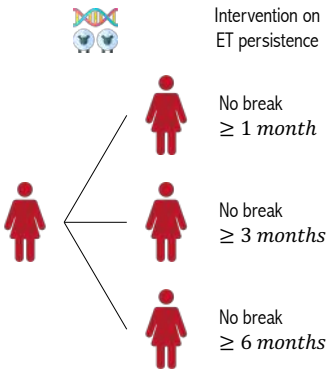
Randomized 1:1:1:1 to

1. No endocrine therapy break $\geq$ 1 month
2. No endocrine therapy break $\geq$ 3 months
3. No endocrine therapy break $\geq$ 6 months
4. Natural adherence **(control arm)**

[4] Wanis u. a., "Grace periods in comparative effectiveness studies of sustained treatments".

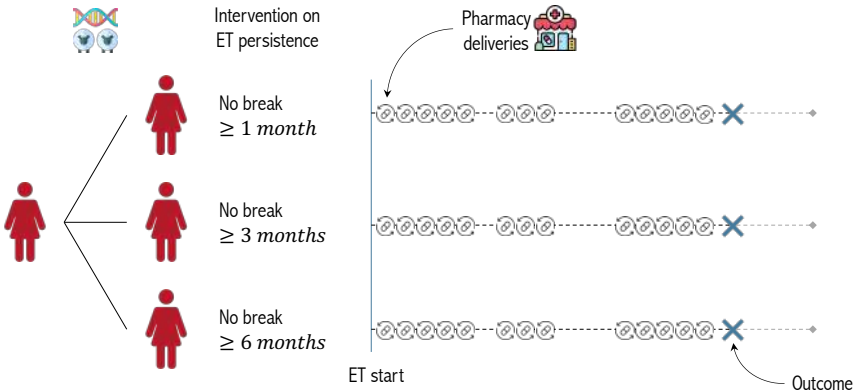
Step 1 : Cloning

Clone each patient and assigning one clone to each of the endocrine therapy persistence regimen (no 1-month, 3-month, and 6-month break)



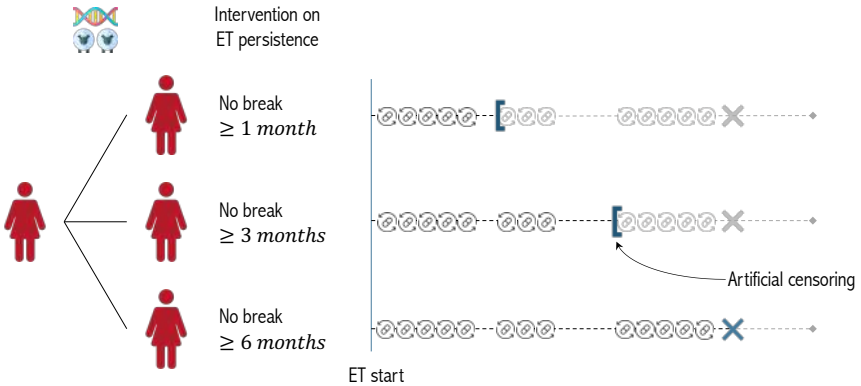
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Step 2 : Censoring

Censor the clones at the first endocrine therapy discontinuation according to the definition used (if any)



Step 3 : Weighting

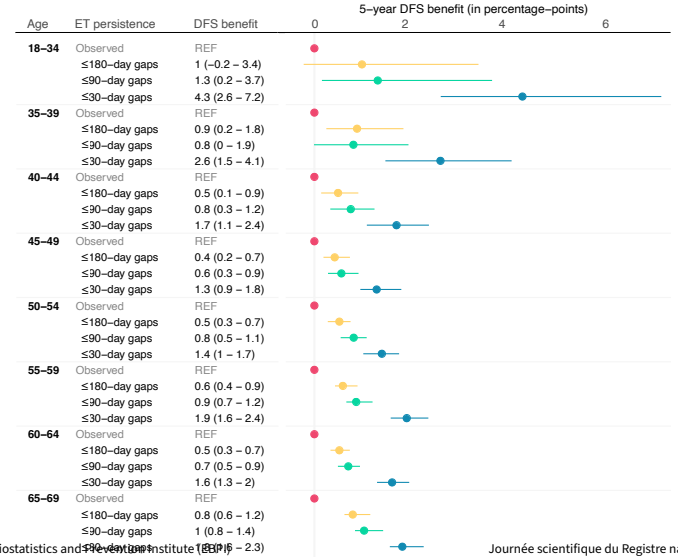
— Artificial censoring is informative : selection bias.
— Inverse Probability of Censoring Weights (IPCW)
— But artificial censoring cannot occur at every month during follow-up (natural grace period, Cf Wanis *et al.*[5])

[5] Wanis u. a., “Grace periods in comparative effectiveness studies of sustained treatments”.

Survival under g_m for $m \in 1, 3, 6$ months



Survival benefits under g_m for $m \in 1, 3, 6$ months



More details



Original Reports | Breast Cancer

Explaining the Relationships Between Age, Endocrine Therapy Persistence, and Risk of Recurrence in Hormone Receptor–Positive Early Breast Cancer: A Nationwide Cohort Study

Elise Dumas, PhD[1,2]; Floriane Jochum, MD, PhD[2,3]; Florence Coussy, MD, PhD[2,4]; Anne-Sophie Hamy, MD, PhD[2,4]; Alena Majdling, MD[5]; Sophie Houzard, MD[6]; Christine Le Bihan-Benjamin, MD[6]; Fabien Reyal, MD, PhD[2,7,8]; Paul Gougis, MD, PhD[2]; and Mats Julius Stensrud, MD, PhD[1]

Original Investigation | Oncology

Outcomes of Anastrozole, Letrozole, and Exemestane in Patients With Postmenopausal Breast Cancer

Elise Dumas, PhD[1,2]; Anne-Sophie Hamy, MD, PhD[2,3]; Kerollos Nashat Wanis, MD, PhD[4]; et al

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