

# Nouvelles thérapeutiques dans le cancer du sein de la femme âgée (cas cliniques)

16 juin 2023

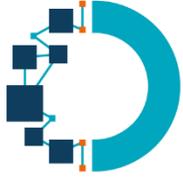
Angoulême

Pr Nicolas ISAMBERT

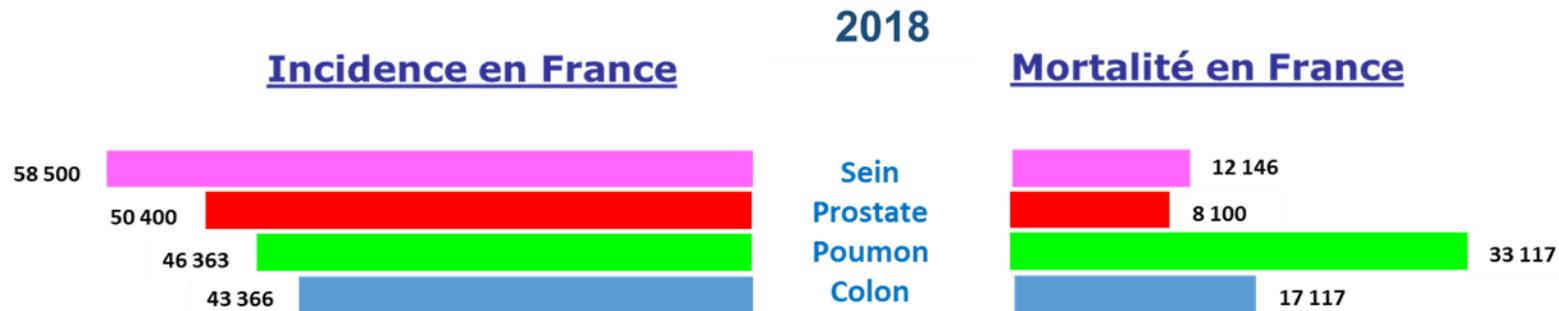


3<sup>ème</sup> rencontre d'Oncogériatrie en Nouvelle-Aquitaine

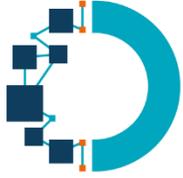




# Généralités



- 1<sup>er</sup> cancer chez la femme en terme d'incidence et de mortalité : 58 000 nouveaux cas/an et 12 000 décès/an
- 2<sup>ème</sup> cancer le plus fréquent tous sexe confondus
- Age médian au diagnostic (2018) : 63 ans; 28% après 69 ans
- Age médian au décès : 74 ans



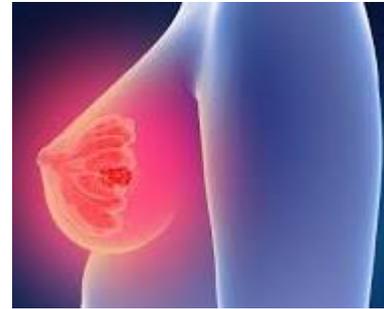
# Généralités

chirurgie

chimiothérapie

radiothérapie

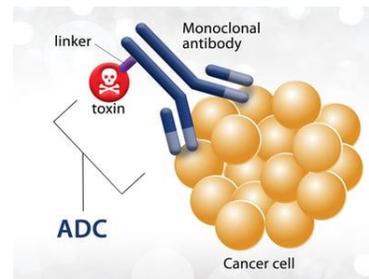
hormonothérapie



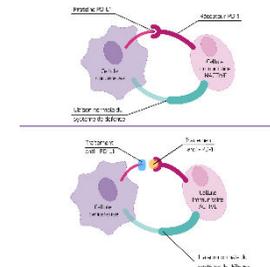
Thérapies ciblées



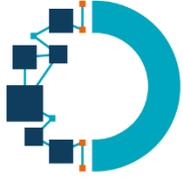
ADC



Immunothérapie

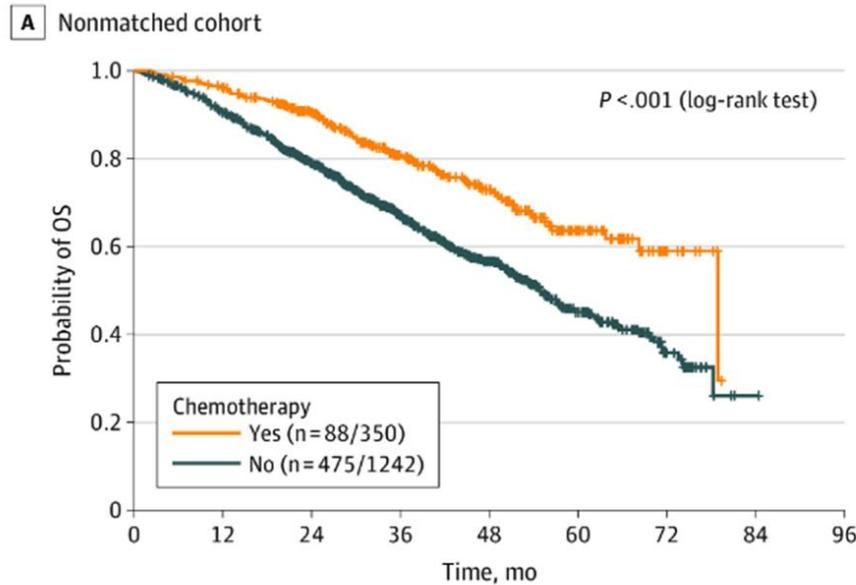


=> peu de données de tolérance et d'efficacité dans la population > 65 ans

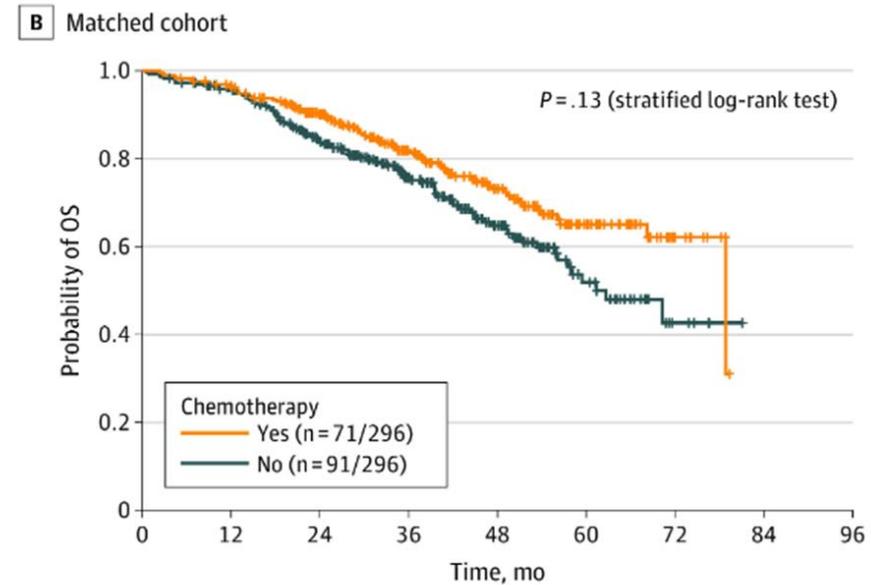


# Chimiothérapie et sujet âgé > 70 ans

Etude de cohorte rétrospective, âge moyen: 77,5 ans avec plusieurs co-morbidités, cancer RH+

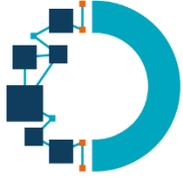


| No. at risk  |      |      |     |     |     |     |    |   |   |  |  |
|--------------|------|------|-----|-----|-----|-----|----|---|---|--|--|
| Chemotherapy |      |      |     |     |     |     |    |   |   |  |  |
| No           | 1242 | 1086 | 823 | 493 | 272 | 116 | 24 | 1 | 0 |  |  |
| Yes          | 350  | 331  | 272 | 175 | 116 | 48  | 11 | 0 | 0 |  |  |



| No. at risk  |     |     |     |     |    |    |    |   |   |  |  |
|--------------|-----|-----|-----|-----|----|----|----|---|---|--|--|
| Chemotherapy |     |     |     |     |    |    |    |   |   |  |  |
| No           | 296 | 273 | 208 | 136 | 77 | 29 | 5  | 0 | 0 |  |  |
| Yes          | 296 | 280 | 226 | 149 | 98 | 45 | 11 | 0 | 0 |  |  |

=> bénéfique adjuvante sur la survie globale, même après ajustement sur l'âge, les co-morbidités, le stade T et N, la réalisation ou non d'une hormonothérapie, et/ou d'une radiothérapie adjuvante



# Cancer du sein RH+, HER2-

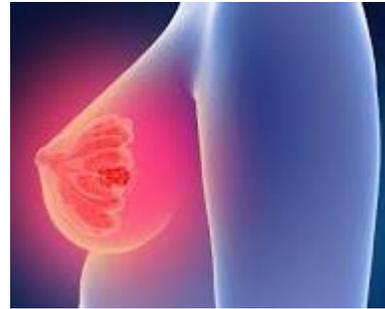
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chirurgie

chimiothérapie

radiothérapie

hormonothérapie



Thérapies ciblées



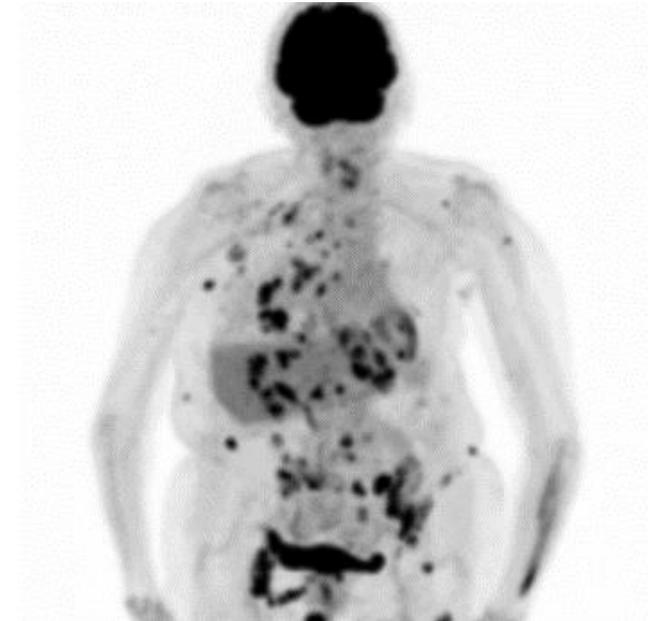
# Cas clinique RH+, HER2-



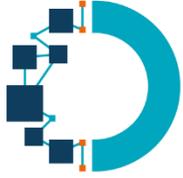
- Mme Q... Claudine née le 24/05/1928, mère au foyer, 3 enfants
- ATCD : HTA, arthrose diffuse
- TTT : aldactazine, celiprolol, diffu K, omeprazole, noctamide, lamaline
- ATCD familiaux : cancer de l'utérus chez sa mère
- Autonome à domicile, veuve, maison à étages, femme de ménage

- **2009** : adénocarcinome canalaire infiltrant du sein gauche de grade I, 24 mm, RH+, HER2 -, traité mastectomie totale + curage (1 N+/15), radiothérapie adjuvante et anastrozole jusqu'en **2014**

- **2020** : apparition d'un nodule SC péri-ombilical dont la biopsie confirme une métastase d'un carcinome mammaire non spécifique, Her2-, RH +



Nodules SC multiples, atteinte ganglionnaire et osseuse diffuse

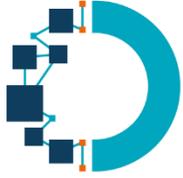


# Cas clinique RH+, HER2-

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Concernant la prise en charge thérapeutique de cette patiente, vous proposeriez?

- A. Traitement par inhibiteur de l'aromatase seule
- B. Traitement par inhibiteur de l'aromatase + inhibiteur de CDK4/6 à dose optimale
- C. Traitement par inhibiteur de l'aromatase + inhibiteur de CDK4/6 à dose diminuée
- D. Chimiothérapie
- E. Prise en charge purement palliative

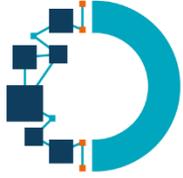


# Cas clinique RH+, HER2-

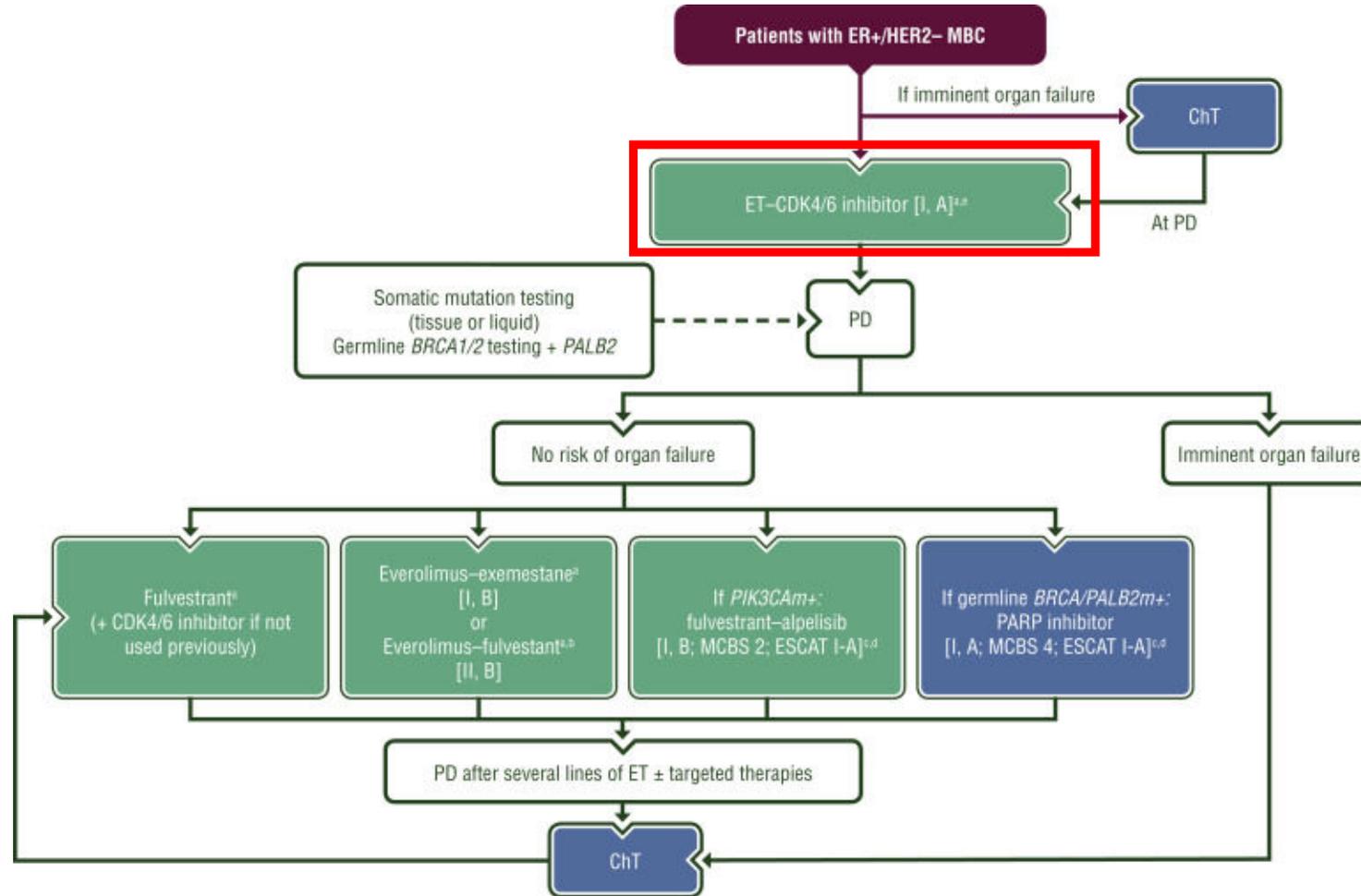
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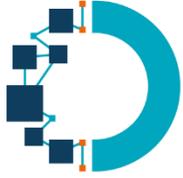
# Guidelines ESMO 2023



# Cancer du sein RH+, HER2-



|                    | Ribociclib                                     |  |   | Abémaciclib  |  | Palbociclib                                    |   |
|--------------------|--|--|---|--|--|--|---|
| Trial              | MONALEESA-2                                    | MONALEESA-3  | MONALEESA-7   | MONARCH-2  | MONARCH-3  | PALOMA-2                                       | PALOMA-3  |
| Line of therapy    | 1L   | 1L & 2L  | 1L  | 1L & 2L  | 1L   | 1L   | 1L & 2L   |
| Menopausal status  | Post (N=668)                                   | Post (N=726)   | Pre (N=672 [ITT])<br>(N=495 [NSAI])   | Post (N=666)   | Post (N=413)<br>Pre (N=108)  | Post (N=493)                                   | Post (N=551)<br>Pre (N=114)                                       |
| Endocrine partner  | AI   | Fulvestrant  | AI  | Fulvestrant  | AI   | AI   | Fulvestrant   |
| Patient population | No prior systemic therapy for advanced disease | No prior therapy for advanced disease; progressed after ET   | No prior ET for advanced disease; 1L of chemotherapy for advanced disease allowed | No prior systemic therapy for advanced disease           | Progressed on or after prior ET; 1L of chemotherapy for advanced disease allowed | No prior systemic therapy for advanced disease | Progressed on or after prior ET                                   |
| Significant OS     | ✓  | ✓  | ✓   | ✓  | Pending ✓  | ✗  | ✓ ✗   |
|                    | G.N. Hortobagyi, et al., ESMO® 2021, Abs LBA17 | ASCO 2021 - D'après Slamon DJ et al., abstr. 1001, actualisé | UPDATE Lu et al. Clin Can Res décembre 2021                                       | Sledge JAMA ONCOL 2020: Sledge Jr GW, et al., SABCS 2022 | Goetz ESMO 2022  | Finn et al ASCO 2022                           | ASCO 2021 - D'après Cristofailli M et al., abstr. 1000, actualisé |



# Etude PalomAGE

Traitement par palbociclib des patientes âgées de 70 ans et plus atteintes d'un cancer du sein avancé

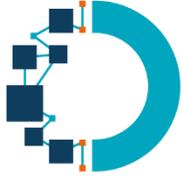
- Résultats de la cohorte A (ET sensitive): taux d'arrêt du palbociclib à 18 mois

| Baseline characteristics | CohortA (n=362) |                        |
|--------------------------|-----------------|------------------------|
|                          | median or n     |                        |
| Median age (years)       | 78.0            | 70.0-94.0 <sup>#</sup> |
| 70-80                    | 199             | 55.1%                  |
| 80-85                    | 112             | 31.0%                  |
| >85                      | 50              | 13.9%                  |
| ECOG PS                  |                 |                        |
| 0                        | 99              | 28.3%                  |
| I                        | 179             | 51.1%                  |
| ≥2*                      | 66              | 18.9%                  |
| Not done                 | 6               | 1.7%                   |
| G8 scores                |                 |                        |
| ≤14 (potentially frail)  | 242             | 68.2%                  |
| >14 (not frail)          | 113             | 31.8%                  |
| DIALOG G-CODE - ADL      |                 |                        |
| Alteration (≤ 5)         | 47              | 15.5%                  |
| No alteration (> 5)      | 256             | 84.5%                  |
| DIALOG G-CODE - IADL     |                 |                        |
| Alteration (≤ 3)         | 89              | 29.4%                  |
| No alteration (> 3)      | 214             | 70.6%                  |

Table 2. Treatment characteristics for patients enrolled in Cohort A

| Treatment characteristics | CohortA (n=362) |       |
|---------------------------|-----------------|-------|
|                           | median or n     |       |
| ET combined with PAL      |                 |       |
| Aromatase inhibitor       | 338             | 93.6% |
| Fulvestrant               | 23              | 6.4%  |
| PAL initiation dose       |                 |       |
| 125 mg                    | 288             | 80.0% |
| 100 mg                    | 52              | 14.4% |
| 75 mg                     | 20              | 5.6%  |

For each variable reported, percentages are calculated on the total of the categories filled of the variable



# Etude PalomAGE

- Taux d'arrêt à 18 mois était de 41,8% (20,8% pour PD, 7,7% pour toxicité, 4,6% pour décès...)

Figure 1. 18-months discontinuation rate according to the initiation dose

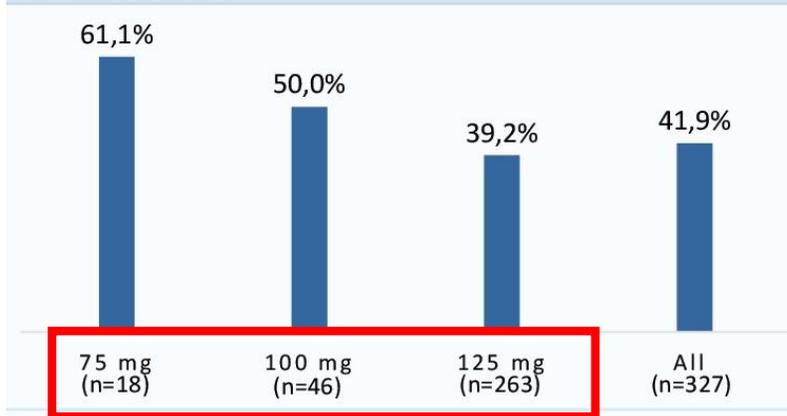
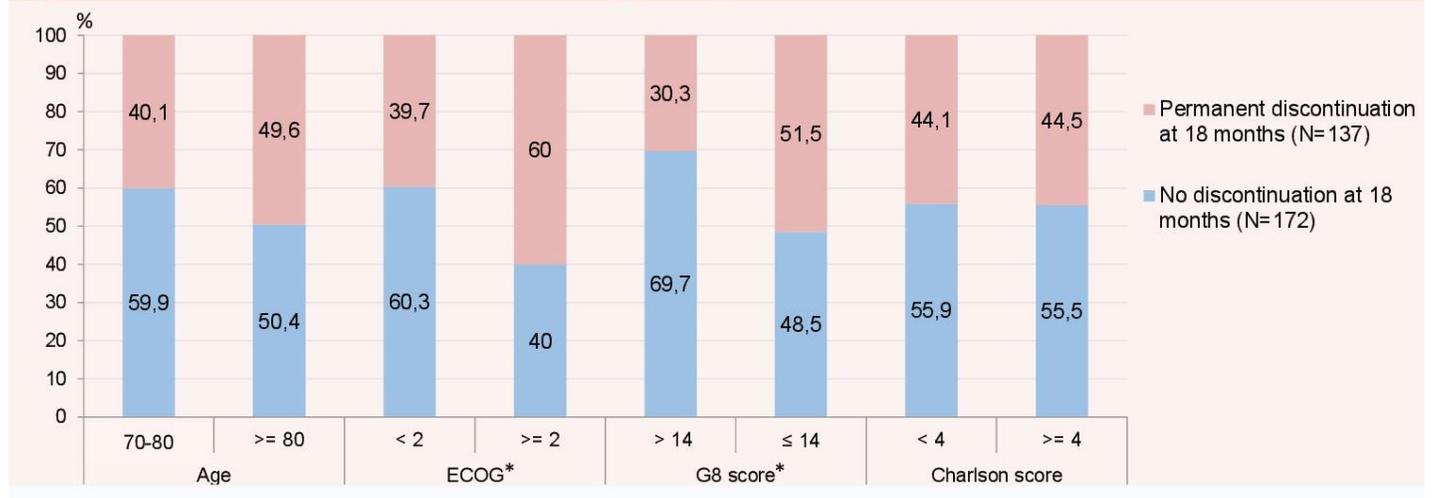
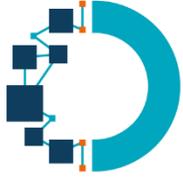


Figure 2. 18-months discontinuation rate according to frailty factors



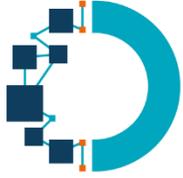


# Etude PalomAGE

Table 3. AEs most frequently report and of special interest\*

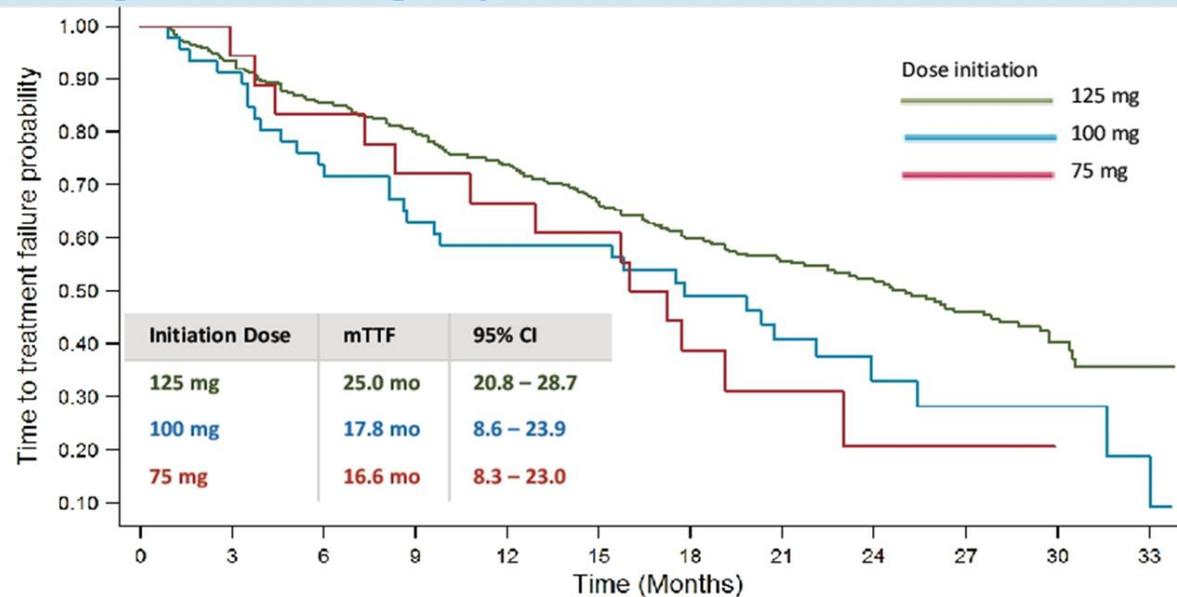
| Preferred term             | Cohort A (n=360) |       |              |       |            |       |
|----------------------------|------------------|-------|--------------|-------|------------|-------|
|                            | Grade 2          |       | Grade 3 or 4 |       | All grades |       |
|                            | n                | %     | n            | %     | n          | %     |
| Neutropenia                | 65               | 18,1% | 148          | 41.1% | 196        | 54.4% |
| Asthenia                   | 35               | 9.7%  | 6            | 1.7%  | 80         | 22.2% |
| Anemia                     | 28               | 7.8%  | 15           | 4.2%  | 68         | 18.9% |
| Thrombocytopenia           | 13               | 3.6%  | 3            | 0.8%  | 43         | 11.9% |
| Alopecia                   | 7                | 1.9%  | 1            | 0.3%  | 42         | 11.7% |
| Arthralgia                 | 7                | 1.9%  | 0            | 0%    | 32         | 8.9%  |
| Leukopenia                 | 15               | 4.2%  | 14           | 3.9%  | 32         | 8.9%  |
| Dyspnea                    | 7                | 1.9%  | 2            | 0.6%  | 24         | 6.7%  |
| Fatigue                    | 5                | 1.4%  | 0            | 0%    | 24         | 6.7%  |
| Diarrhea                   | 4                | 1.1%  | 0            | 0%    | 22         | 6.1%  |
| Lymphopenia                | 11               | 3.1%  | 2            | 0.6%  | 22         | 6.1%  |
| Nausea                     | 5                | 1.4%  | 0            | 0.0%  | 20         | 5.6%  |
| Interstitial lung disease* | 2                | 0.6%  | 1            | 0.3%  | 5          | 1.4%  |
| Febrile neutropenia*       | 0                | 0.0%  | 4            | 1.1%  | 4          | 1.1%  |

AE: adverse event.



# Etude PalomAGE

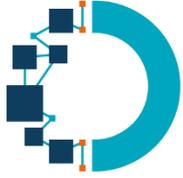
Figure 3. Kaplan-Meier plots of time to treatment failure according to the starting daily dose of PAL



At risk (Events)

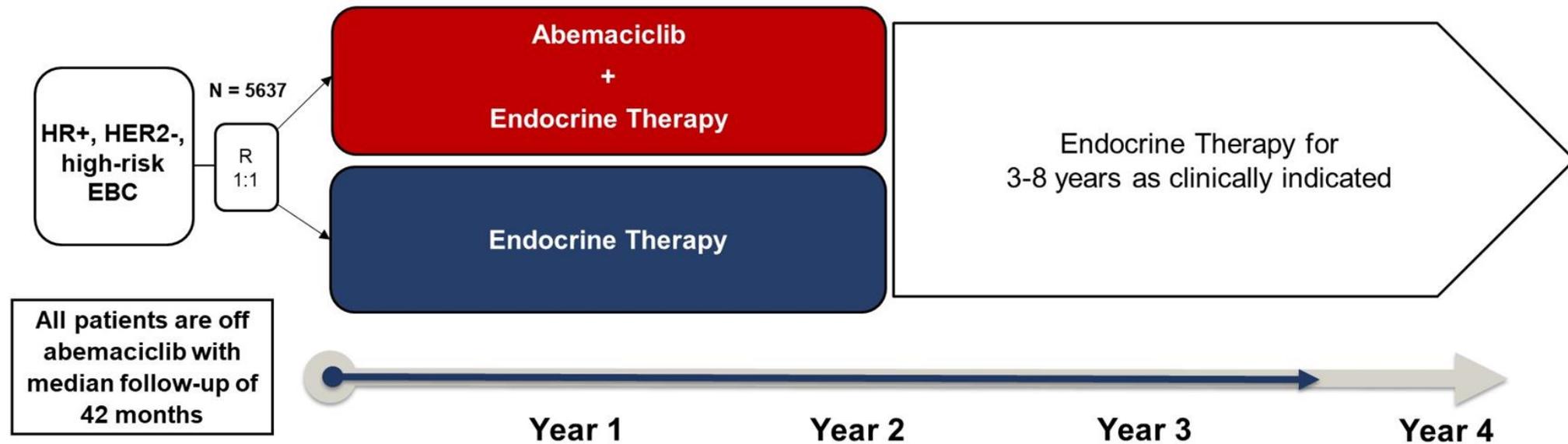
|     |          |          |          |          |          |          |          |         |          |        |        |   |
|-----|----------|----------|----------|----------|----------|----------|----------|---------|----------|--------|--------|---|
| 125 | 263 (17) | 246 (21) | 224 (14) | 207 (16) | 189 (18) | 169 (17) | 148 (10) | 122 (7) | 104 (11) | 74 (7) | 30 (3) | 2 |
| 100 | 46 (4)   | 42 (8)   | 34 (5)   | 29 (2)   | 25 (0)   | 25 (4)   | 19 (3)   | 14 (2)  | 7 (1)    | 6 (0)  | 3 (1)  | 2 |
| 75  | 18 (1)   | 17 (2)   | 15 (2)   | 13 (1)   | 12 (1)   | 11 (4)   | 6 (1)    | 4 (1)   | 2 (0)    | 1 (0)  | 0 (0)  | 0 |

- Taux d'arrêt permanent à 18 mois : 41,9%
- Médiane de PFS : 28,1 mois (27,2 mois PALOMA-2)
- Score G8 < 15 et ECOG > 1 semble associés à un taux d'arrêt prématuré plus important
- Pas de modification de la qualité de vie

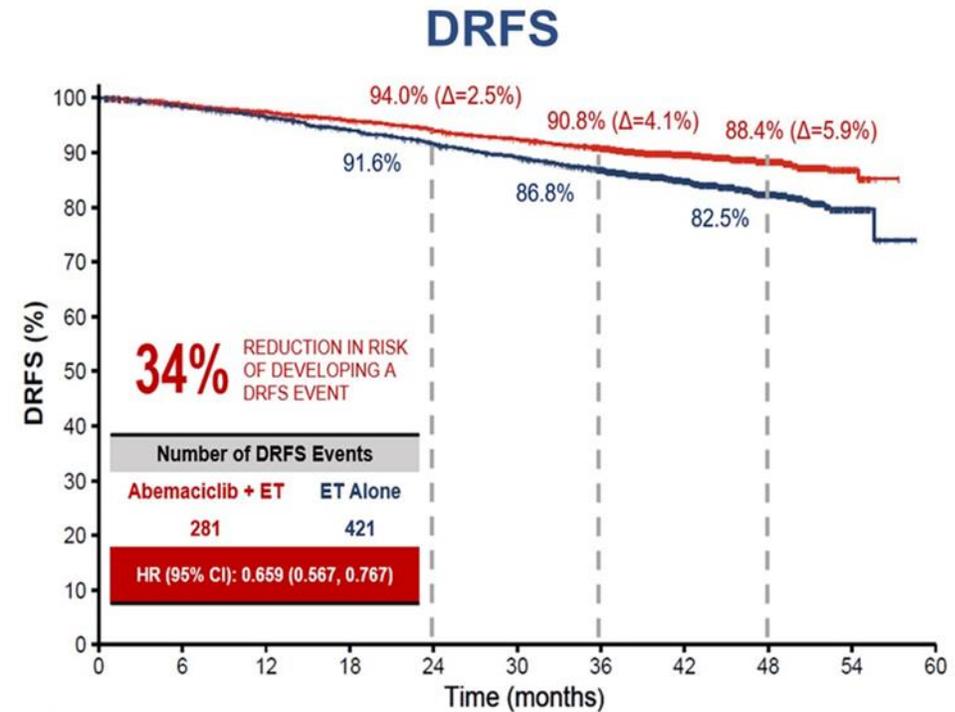
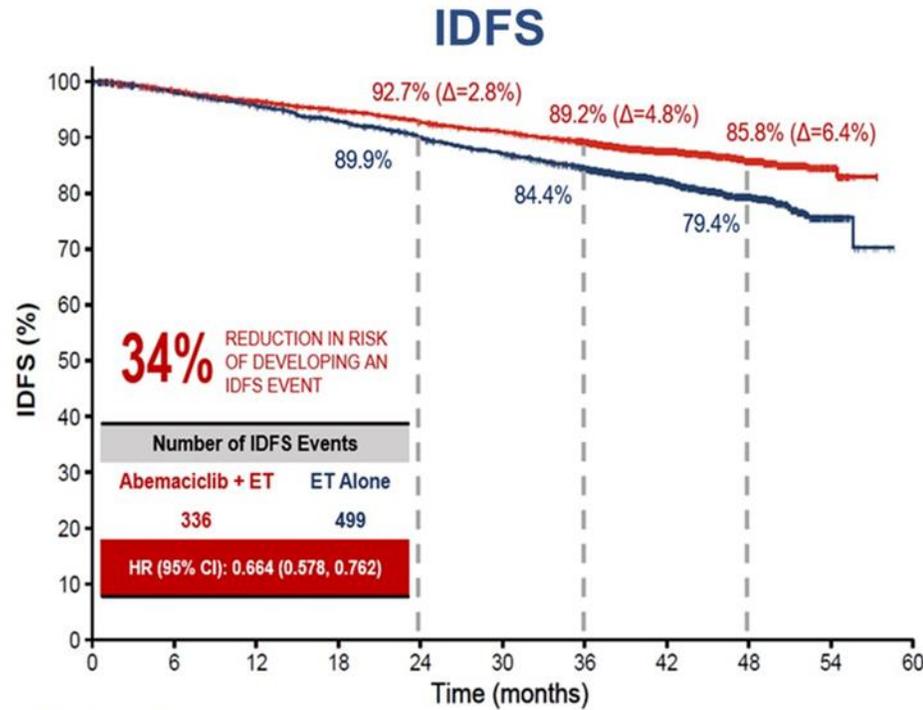
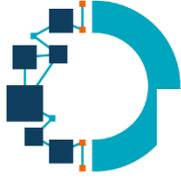


# Etude MonarchE

**Efficacy and Safety Results by Age in monarchE: Adjuvant Abemaciclib Combined with Endocrine therapy (ET) in Patients with HR+, HER2-, Node-Positive, High-Risk Early Breast Cancer (EBC).**



# Etude MonarchE



Number at risk

|      |      |      |      |      |      |      |      |     |    |   |
|------|------|------|------|------|------|------|------|-----|----|---|
| 2808 | 2620 | 2548 | 2478 | 2407 | 2345 | 2214 | 1229 | 521 | 79 | 0 |
| 2829 | 2652 | 2572 | 2474 | 2374 | 2281 | 2103 | 1201 | 512 | 82 | 0 |

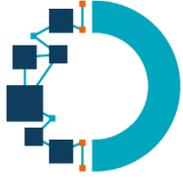
Number at risk

|      |      |      |      |      |      |      |      |     |    |   |
|------|------|------|------|------|------|------|------|-----|----|---|
| 2808 | 2629 | 2567 | 2500 | 2434 | 2374 | 2244 | 1251 | 535 | 81 | 0 |
| 2829 | 2659 | 2589 | 2499 | 2410 | 2327 | 2151 | 1231 | 526 | 85 | 0 |

\*From ITT analysis

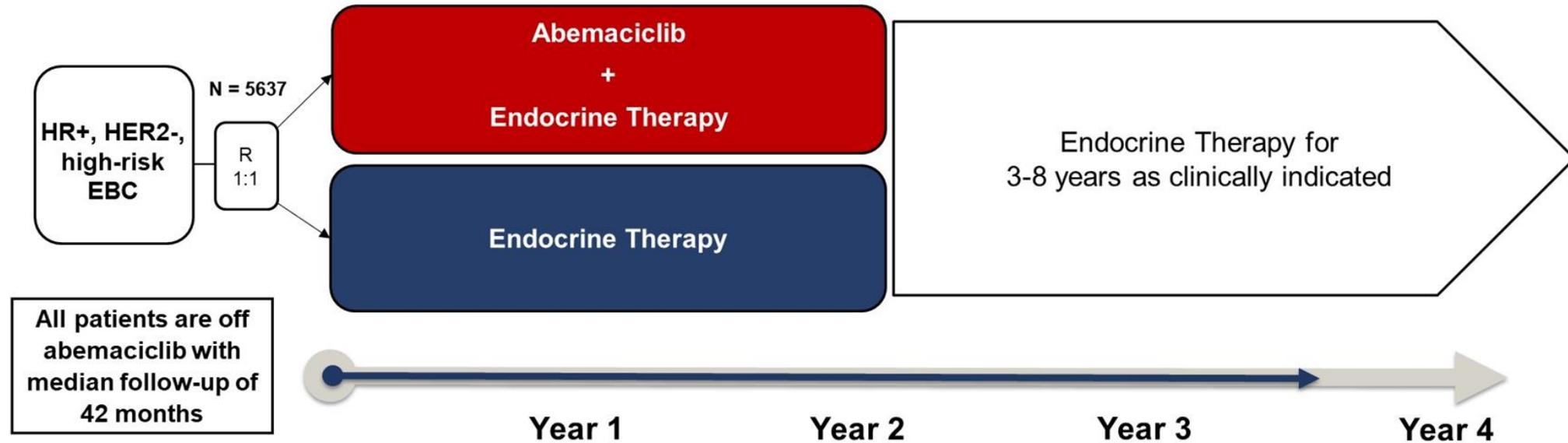
<sup>3</sup>Johnston SRD et al. 2023 The Lancet Oncol;24(01):77-90

=> amélioration de l'IDFS et de la DRFS après 2 ans d'abemaciclib se prolongeant au delà

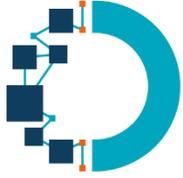


# Etude MonarchE

**Efficacy and Safety Results by Age in monarchE: Adjuvant Abemaciclib Combined with Endocrine therapy (ET) in Patients with HR+, HER2-, Node-Positive, High-Risk Early Breast Cancer (EBC).**



=> Analyse de l'efficacité et de la tolérance de l'abemaciclib adjuvant chez les sujets inclus dans cette étude:  
analyse en sous-groupe < 65 ans ou > ou égal 65 ans

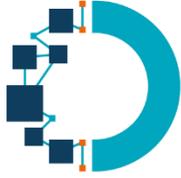


# Etude MonarchE

| <b>Baseline factors, %</b>            |                      | <b>Overall</b><br>n=5637 | <b>&lt;65</b><br>n=4787 | <b>≥65</b><br>n=850 |
|---------------------------------------|----------------------|--------------------------|-------------------------|---------------------|
| Pathological tumor size (mm)          | <20                  | 27                       | 28                      | 23                  |
|                                       | 20-<50               | 50                       | 48                      | 57                  |
|                                       | ≥50                  | 22                       | 22                      | 19                  |
| No. positive lymph nodes <sup>a</sup> | 1-3                  | 40                       | 41                      | 36                  |
|                                       | ≥4                   | 60                       | 59                      | 64                  |
| Histopathological grade               | G1                   | 8                        | 8                       | 7                   |
|                                       | G2                   | 49                       | 49                      | 52                  |
|                                       | G3                   | 38                       | 38                      | 37                  |
| Prior (neo) adjuvant chemotherapy     | Yes                  | 94                       | 97                      | 82                  |
|                                       | No                   | 6                        | 3                       | 18                  |
| ECOG PS <sup>b</sup>                  | 0                    | 85                       | 86                      | 77                  |
|                                       | 1                    | 15                       | 14                      | 23                  |
| <b>Treated patients, %</b>            |                      | <b>n=5591</b>            | <b>n=4751</b>           | <b>n=840</b>        |
| No. pre-existing comorbidities        | 0                    | 17                       | 19                      | 6                   |
|                                       | 1-3                  | 48                       | 48                      | 44                  |
|                                       | ≥4                   | 35                       | 33                      | 51                  |
| Initial endocrine therapy             | Aromatase inhibitors | 68                       | 64                      | 95                  |
|                                       | Tamoxifen            | 31                       | 36                      | 5                   |

Values that do not add up to 100% are due to rounding or missing data; <sup>a</sup>n=14 patients with 0 positive lymph nodes were inadvertently enrolled; <sup>b</sup>n=3 patients with an ECOG PS score of >1 were inadvertently enrolled

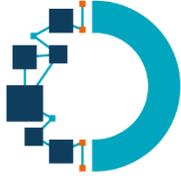
=> patients âgés avec plus de comorbidités, un score ECOG élevé, et moins de chimiothérapie (néo) adjuvante



# Etude MonarchE

|                            | IDFS                           |                                |                                | DRFS                           |                                |                                |
|----------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
|                            | ITT                            | <65                            | ≥65                            | ITT                            | <65                            | ≥65                            |
| <b>Events/N</b>            |                                |                                |                                |                                |                                |                                |
| <b>Abemaciclib + ET</b>    | <b>336/2808</b>                | <b>270/2371</b>                | <b>66/437</b>                  | <b>281/2808</b>                | <b>230/2371</b>                | <b>51/437</b>                  |
| <b>ET alone</b>            | <b>499/2829</b>                | <b>414/2416</b>                | <b>85/413</b>                  | <b>421/2829</b>                | <b>353/2416</b>                | <b>68/413</b>                  |
| <b>HR (95% CI)</b>         | <b>0.664</b><br>(0.578, 0.762) | <b>0.646</b><br>(0.554, 0.753) | <b>0.767</b><br>(0.556, 1.059) | <b>0.659</b><br>(0.567, 0.767) | <b>0.647</b><br>(0.548, 0.764) | <b>0.748</b><br>(0.520, 1.077) |
| <b>Interaction p-value</b> | NA                             | 0.35                           |                                | NA                             | 0.49                           |                                |
| <b>4-year rate, %</b>      |                                |                                |                                |                                |                                |                                |
| <b>Abemaciclib + ET</b>    | <b>85.8</b>                    | <b>86.5</b>                    | <b>82.0</b>                    | <b>88.4</b>                    | <b>88.8</b>                    | <b>86.1</b>                    |
| <b>ET alone</b>            | <b>79.4</b>                    | <b>79.8</b>                    | <b>76.8</b>                    | <b>82.5</b>                    | <b>82.6</b>                    | <b>81.5</b>                    |
| <b>Absolute benefit</b>    | <b>6.4</b>                     | <b>6.7</b>                     | <b>5.2</b>                     | <b>5.9</b>                     | <b>6.2</b>                     | <b>4.6</b>                     |

=> bénéfice dans la population âgée similaire à la population en ITT

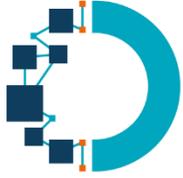


# Etude MonarchE

| AE, %                   | Grade | Abemaciclib + ET  |               |               |
|-------------------------|-------|-------------------|---------------|---------------|
|                         |       | Overall<br>n=2791 | <65<br>n=2361 | ≥65*<br>n=430 |
| Any AE                  | Any   | 98                | 98            | 99            |
|                         | G≥3   | 50                | 49            | 54            |
| Clinically relevant AEs |       |                   |               |               |
| Diarrhea                | G1    | 45                | 46            | 37            |
|                         | G2    | 31                | 31            | 30            |
|                         | G3    | 8                 | 7             | 12            |
| Fatigue                 | G1    | 23                | 23            | 21            |
|                         | G2    | 15                | 14            | 20            |
|                         | G3    | 3                 | 2             | 6             |
| Neutropenia             | G1/2  | 26                | 27            | 22            |
|                         | G≥3   | 20                | 20            | 19            |
| ALT increase            | G1/2  | 10                | 10            | 7             |
|                         | G≥3   | 3                 | 3             | 3             |
| VTE                     | Any   | 3                 | 2             | 3             |
|                         | G≥3   | 1                 | 1             | 1             |
| ILD                     | Any   | 3                 | 3             | 3             |
|                         | G≥3   | <1                | <1            | <1            |

\*Patients ≥75 years had higher rates of grade 3 diarrhea and grade 2/3 fatigue

=> tolérance identique dans les populations

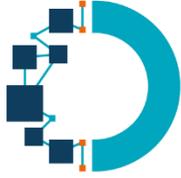


# Etude MonarchE

|   | Abemaciclib + ET |        |       |
|---|------------------|--------|-------|
|   | Overall          | <65    | ≥65*  |
| <b>Abemaciclib dose adjustments due to AEs, %</b> | n=2791           | n=2361 | n=430 |
| Interruptions                                     | 62               | 60     | 68    |
| Reductions  | 44               | 42     | 55    |
| Discontinuations                                  | 18               | 15     | 38    |
| Discontinuations without prior dose reductions    | 10               | 8      | 19    |

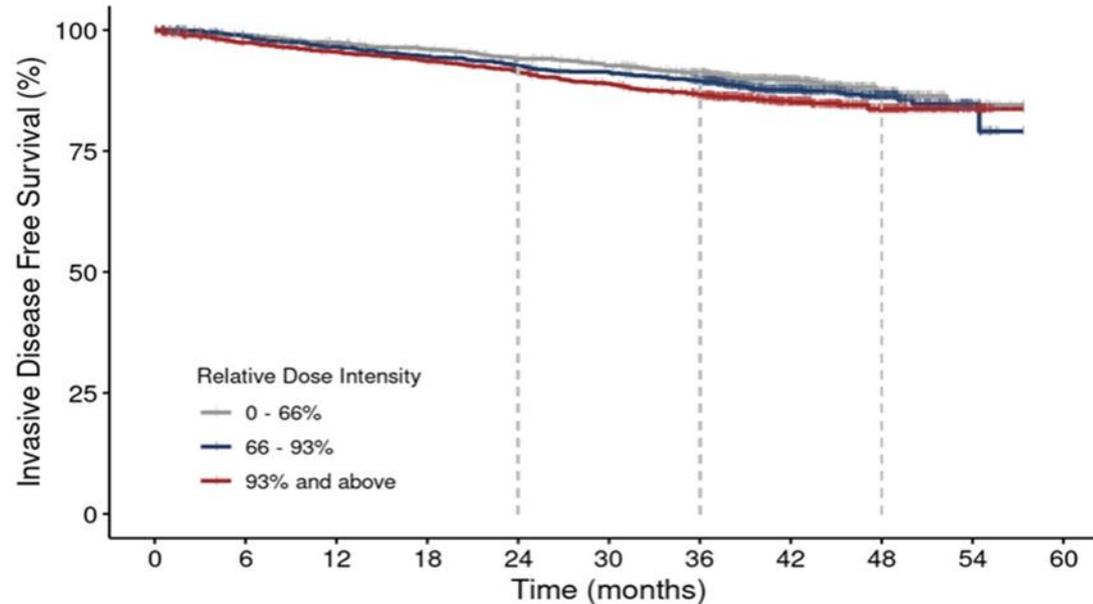
\*Patients ≥75 years had higher rates of abemaciclib dose adjustments and discontinuations due to AEs

=> plus d'ajustement de dose dans la population âgée



# Etude MonarchE

## IDFS according to RDI in patients treated with abemaciclib (all ages included)

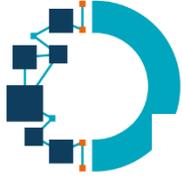


| Number at risk |     | 0   | 6   | 12  | 18  | 24  | 30  | 36  | 42  | 48 | 54 | 60 |
|----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|
| —              | 928 | 879 | 856 | 835 | 809 | 789 | 731 | 388 | 158 | 24 | 0  | 0  |
| —              | 928 | 894 | 868 | 841 | 817 | 801 | 769 | 428 | 181 | 21 | 0  | 0  |
| —              | 927 | 843 | 820 | 798 | 777 | 751 | 710 | 411 | 182 | 34 | 0  | 0  |

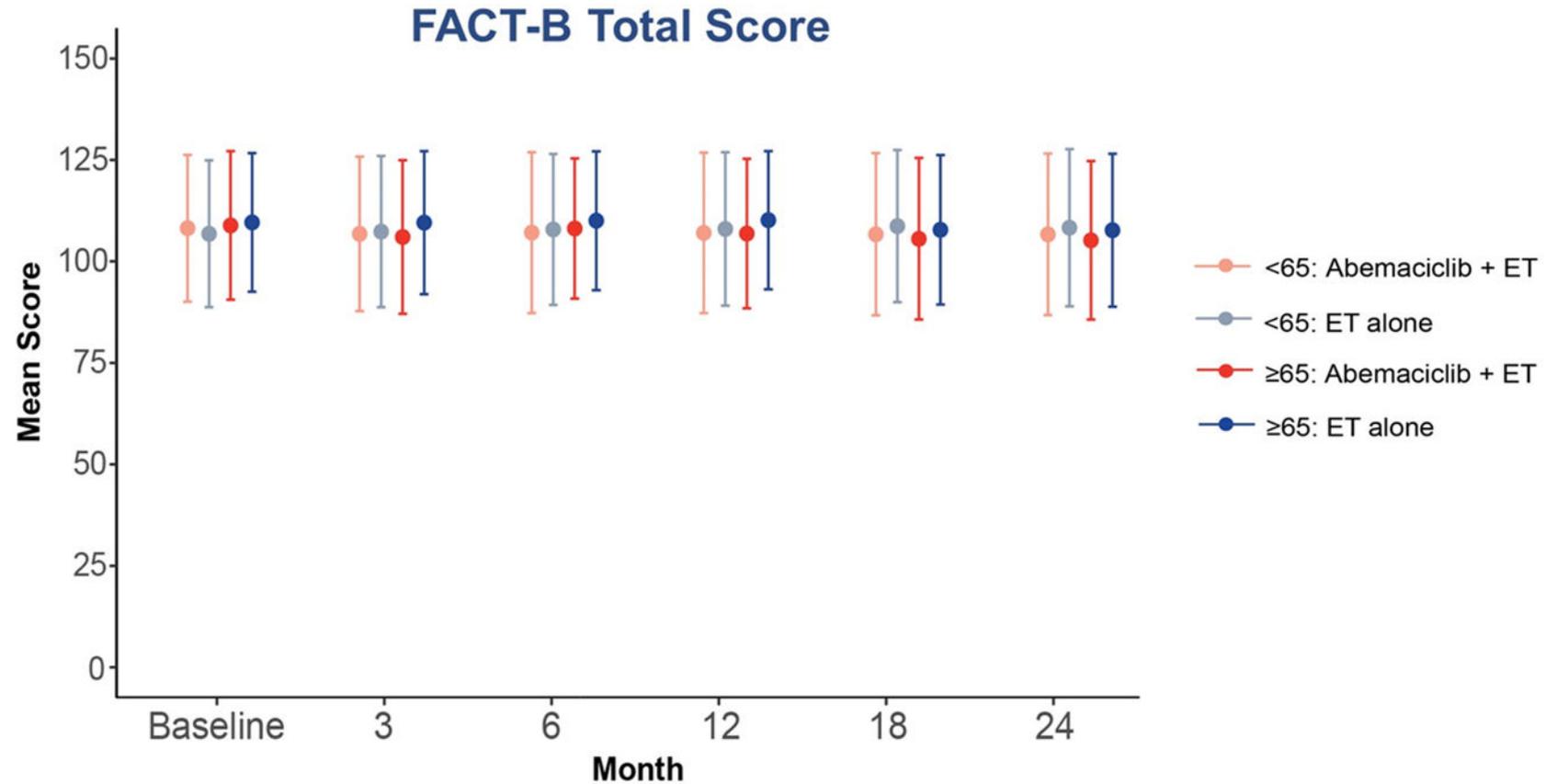
\*RDI is defined as the average daily dose of abemaciclib received over the treatment duration, relative to the full dose (150mg BID)

- Dose adjustments result in lower relative dose intensity (RDI\*). To explore the impact of dose adjustments on abemaciclib efficacy:
  - Patients treated with abemaciclib were classified into 3 equal-sized subgroups according to their RDI
  - IDFS rates were estimated within each subgroup
- 4-year IDFS rates were generally consistent (87.1% vs 86.4% vs 83.7% from the lowest RDI group to the highest)
  - Similar findings were observed in patients treated with abemaciclib in Cohort 1

**=> bénéfice de l'abémaciclib maintenu même en cas de modification de doses**



# Etude MonarchE



=> QoL maintenu dans la population âgée

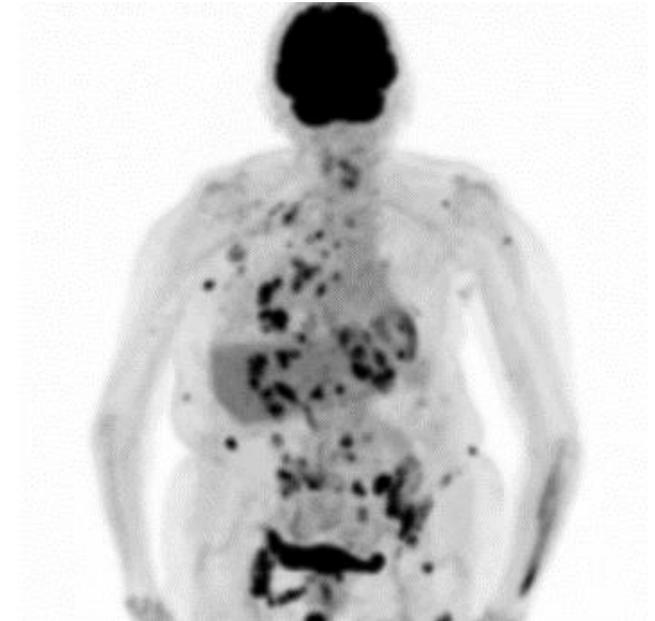
# Cas clinique RH+, HER2-



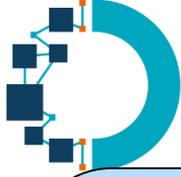
- Mme Q... Claudine née le 24/05/1928, mère au foyer, 3 enfants
- ATCD : HTA, arthrose diffuse
- TTT : aldactazine, celiprolol, diffu K, omeprazole, noctamide, lamaline
- ATCD familiaux : cancer de l'utérus chez sa mère
- Autonome à domicile, veuve, maison à étages, femme de ménage

- **2009** : adénocarcinome canalaire infiltrant du sein gauche de grade I, 24 mm, RH+, HER2 -, traité mastectomie totale + curage (1 N+/15), radiothérapie adjuvante et anastrozole jusqu'en **2014**

- **2020** : apparition d'un nodule SC péri-ombilical dont la biopsie confirme une métastase d'un carcinome mammaire non spécifique, Her2-, RH +



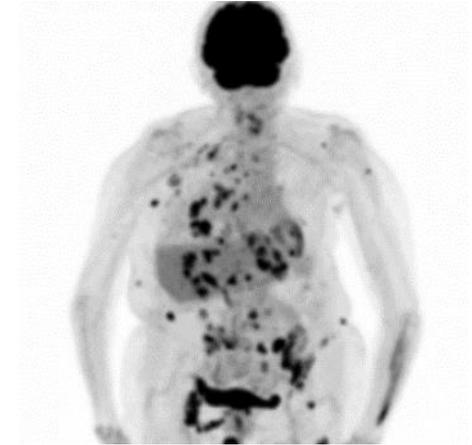
Nodules SC multiples, atteinte ganglionnaire et osseuse diffuse



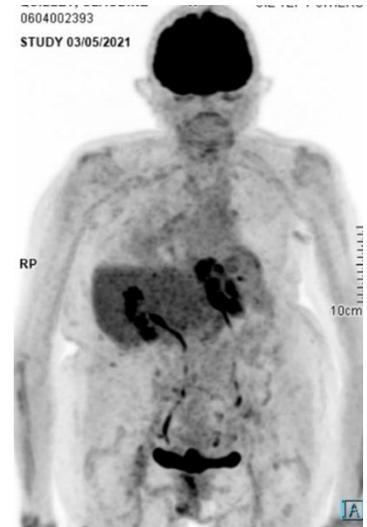
# Cas clinique RH+, HER2-

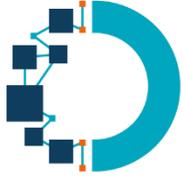
- Traitement par palbociclib 125 mg + letrozole débuté en février 2021
- Après 1 mois de traitement, diminution de la posologie du palbociclib à 100 mg (neutropénie de grade 3)
- Après 3 mois de traitement => RP
- Diminution de la posologie du palbociclib à 75 mg après 6 mois (neutropénie)
- Maintien de la réponse à ce jour mais patiente a souhaité arrêter début 2023 le traitement pour fatigue

- Actuellement une PD est mise en évidence



0604002393  
STUDY 03/05/2021



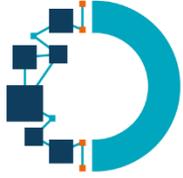


# Cas clinique RH+, HER2-

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Concernant la prise en charge thérapeutique de cette patiente, vous proposeriez?

- A. Traitement par inhibiteur de l'aromatase seule
- B. Traitement par inhibiteur de l'aromatase + inhibiteur de mTOR
- C. Traitement par inhibiteur de l'aromatase + inhibiteur de CDK4/6 à dose diminuée
- D. Chimiothérapie
- E. Prise en charge purement palliative

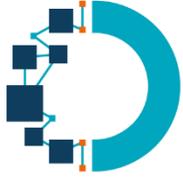


# Cas clinique RH+, HER2-

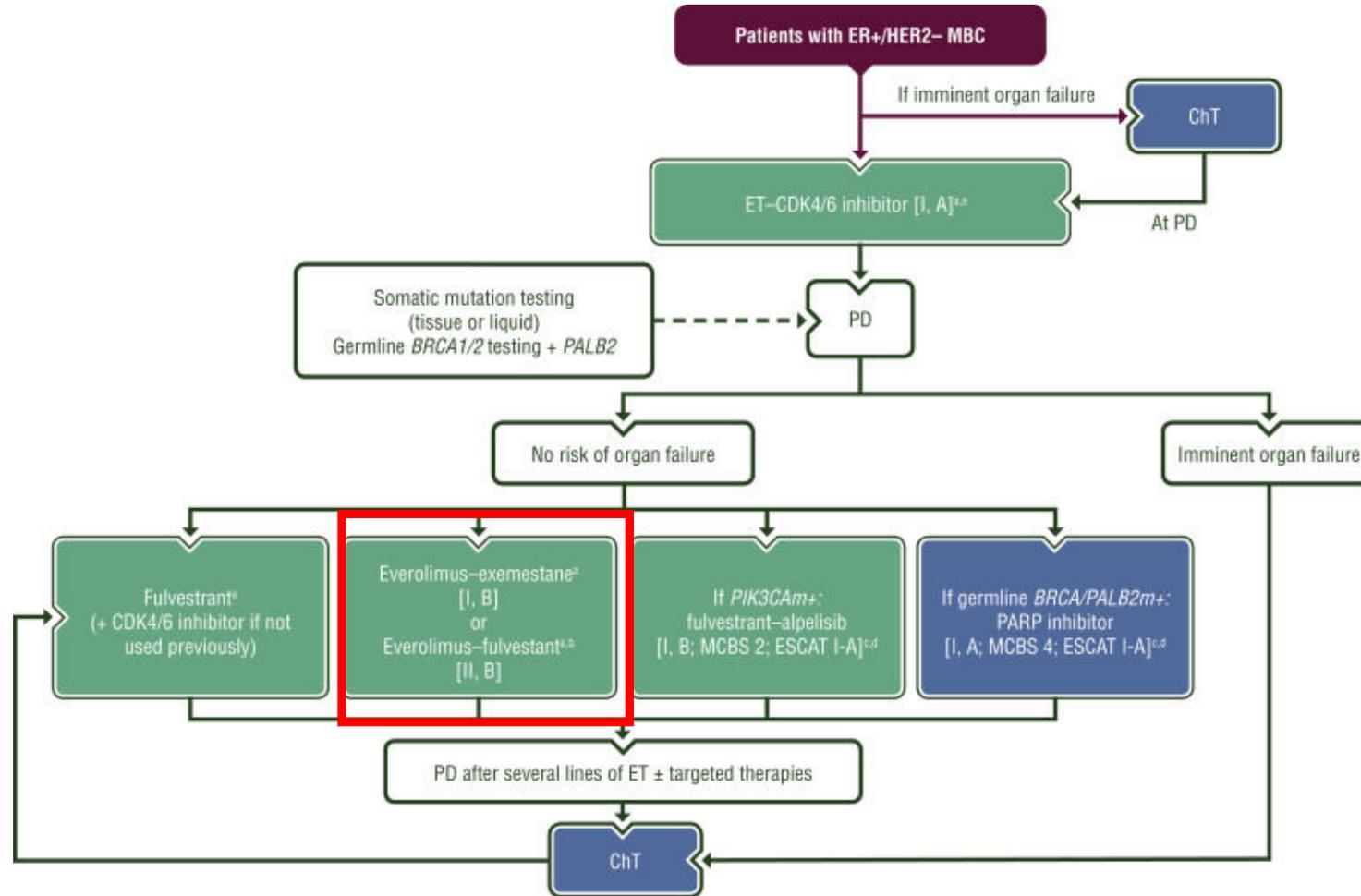
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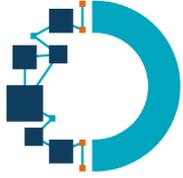
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- A. Traitement par inhibiteur de l'aromatase seule
- B. Traitement par inhibiteur de l'aromatase + inhibiteur de mTOR**
- C. Traitement par inhibiteur de l'aromatase + inhibiteur de CDK4/6 à dose diminuée
- D. Chimiothérapie
- E. Prise en charge purement palliative

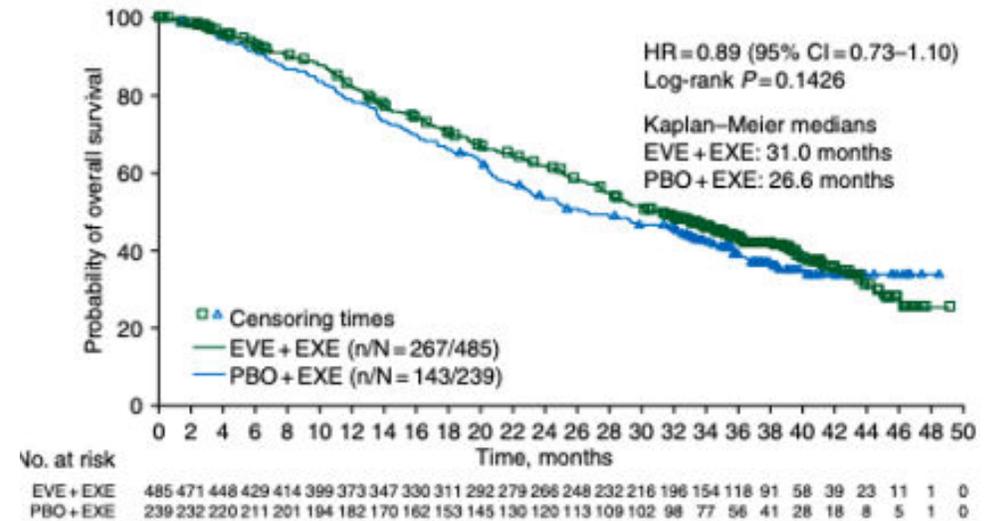
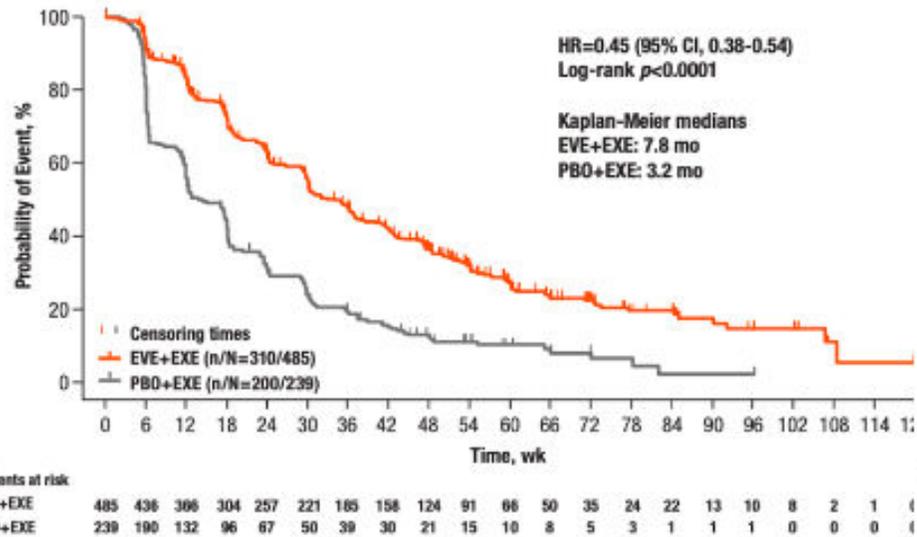
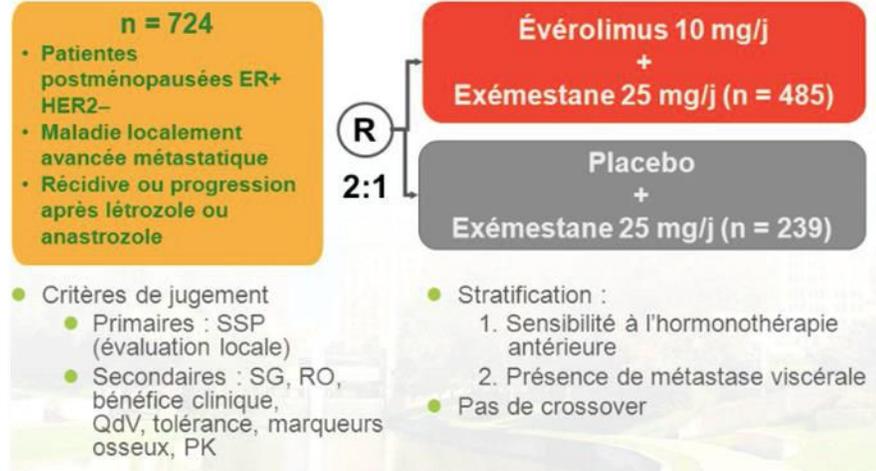


# Guidelines ESMO 2023

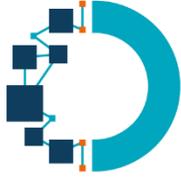




# Etude BOLERO 2

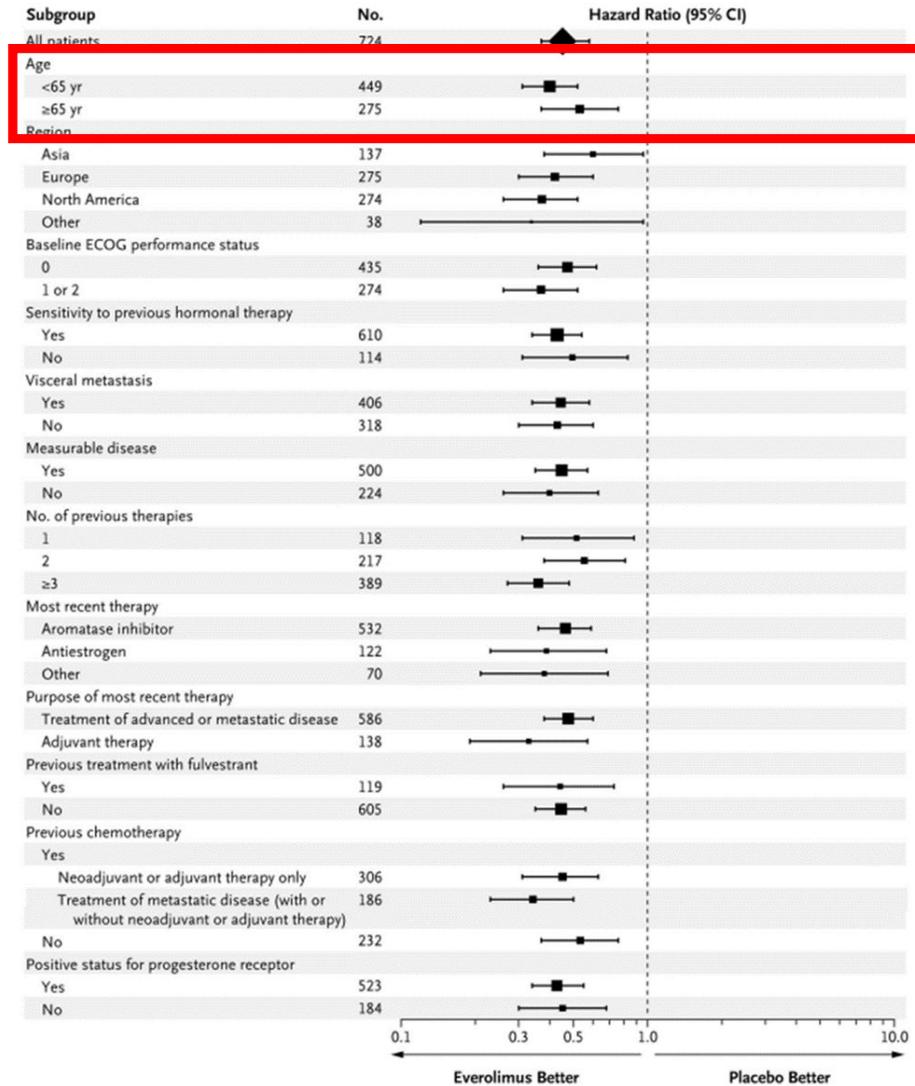


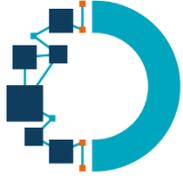
# Etude BOLERO 2



Patient and Tumor Characteristics at Baseline.\*

| Characteristic | Everolimus and Exemestane (N = 485) | Placebo and Exemestane (N = 239) |
|----------------|-------------------------------------|----------------------------------|
| Age (yr)       |                                     |                                  |
| Median         | 62                                  | 61                               |
| Range          | 34–93                               | 28–90                            |





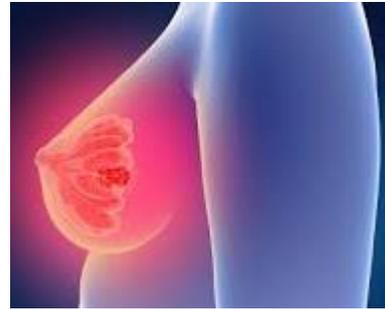
# Cancer du sein HER2 positif

chirurgie

chimiothérapie

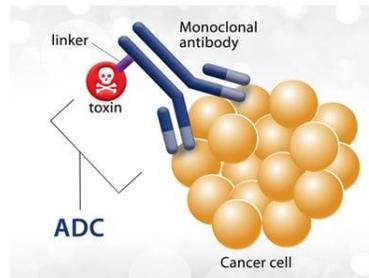
radiothérapie

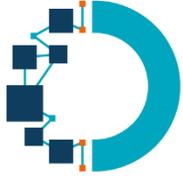
hormonothérapie



Thérapies ciblées

ADC





# Cancer du sein HER2 positif

---

- HER2+  $\approx$  15-20 % des cancers du sein
- RH+ et HER2+  $\approx$  7,5% des cancers du sein
  
- Métastases cérébrales dans 30 à 50 % des cas
- HER2+ métastatiques SG médiane = 50,1 mois (cohorte ESME 2008-2016)

# Cas clinique HER2 positif

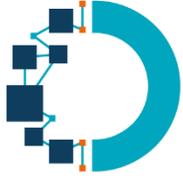


- Mme F... Nicole née le 01/05/1952, ancienne femme de ménage
- ATCD : diabète insulino-réquerant
- ATCD familiaux : cancer ORL chez son frère
- Autonome à domicile, célibataire sans enfant, maison de plein pied

- **Mai 2019** : sein inflammatoire évoluant depuis plusieurs mois
- Biopsie : carcinome mammaire de type non spécifique de grade 3  
RO 70%, RP 50%, Her2 +++, Ki 67 à 40%

- Traitement de 1<sup>ère</sup> ligne par Taxotere + Pertuzumab + Trastuzumab  
(6 cures => RC) puis Pertuzumab + Trastuzumab + AI jusqu'en  
**mars 2021** => atteinte ganglionnaire
- **Avril 2021** : TDM-1 pour 9 cycles => PD



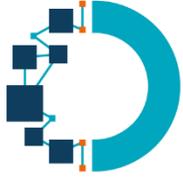


# Cas clinique HER2 positif

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Concernant la prise en charge thérapeutique de cette patiente, vous proposeriez?

- Traitement par inhibiteur de l'aromatase seule
- Chimiothérapie
- Traitement par inhibiteur de l'aromatase + inhibiteur de CDK4/6
- Prise en charge purement palliative
- Traitement par trastuzumab deruxtecan

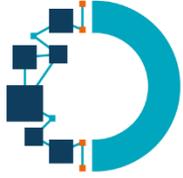


# Cas clinique HER2 positif

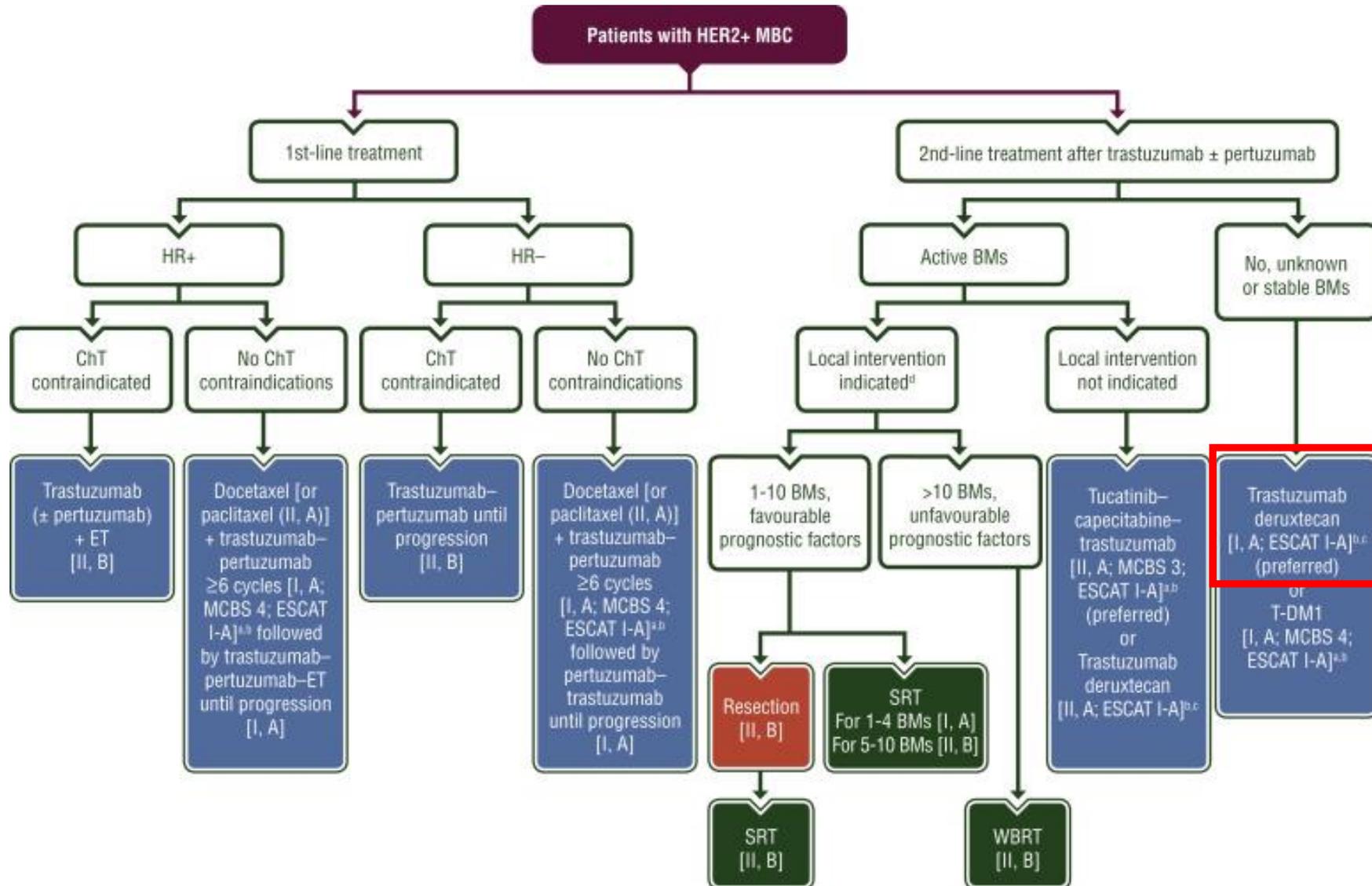
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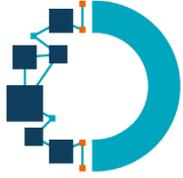
Concernant la prise en charge thérapeutique de cette patiente, vous proposeriez?

- Traitement par inhibiteur de l'aromatase seule
- Chimiothérapie
- Traitement par inhibiteur de l'aromatase + inhibiteur de CDK4/6
- Prise en charge purement palliative
- **Traitement par trastuzumab deruxtecan**



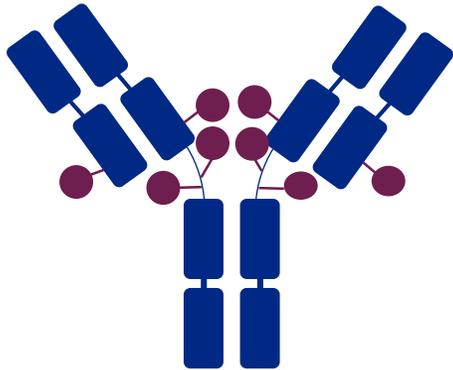
# Guidelines ESMO 2023





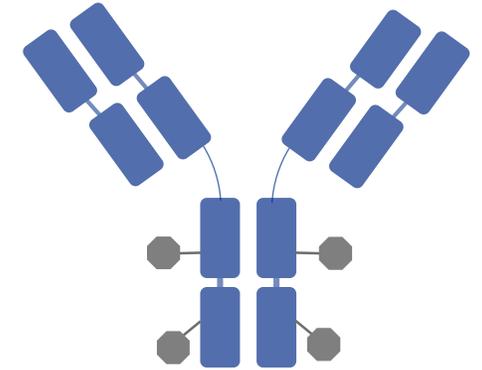
# Trastuzumab Deruxtecan

**Trastuzumab deruxtecan (T-DXd)<sup>1</sup>**

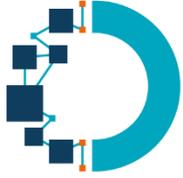


| T-DXd <sup>1-4</sup>          | Caractéristiques ADC                            | T-DM1 <sup>3-5</sup> |
|-------------------------------|---|----------------------|
| Inhibiteur de topoisomerase I | <b>Payload MoA</b>                              | Anti-microtubule     |
| ~8:1                          | <b>Drug-to-antibody ratio</b>                   | ~3.5:1               |
| Oui                           | <b>Tumor-selective cleavable linker?</b>        | Non                  |
| Oui                           | <b>Evidence of bystander anti-tumor effect?</b> | Non                  |

**Trastuzumab emtansine (T-DM1)**



1. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther*. 2018;181:126-42  
4. Ogitani Y et al. *Cancer Sci*. 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47



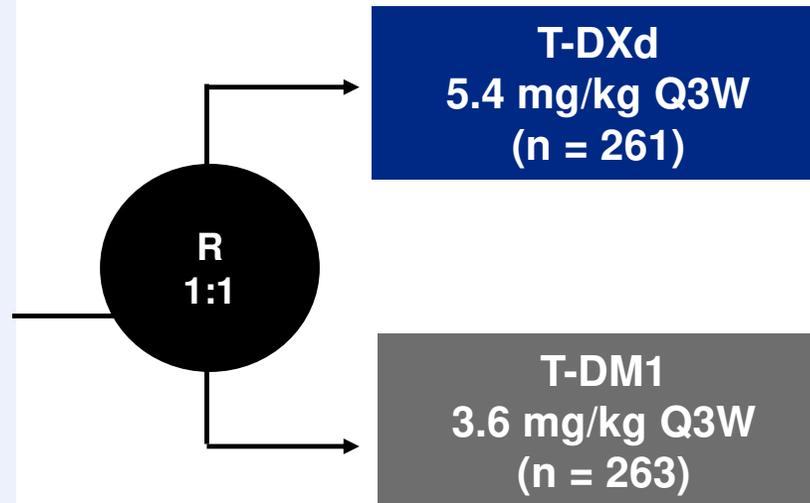
# DESTINY – Breast 03 : study design

## Patients (N = 524)

- Unresectable or metastatic HER2 positive breast cancer that has been previously treated with trastuzumab and taxane
- Could have clinically stable, treated brain metastases
  - $\geq 2$  weeks between end of whole brain radiotherapy and study enrollment

## Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



## Primary endpoint

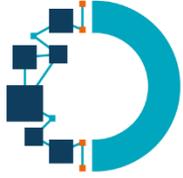
- PFS (BICR)

## Key secondary endpoint

- OS

## Secondary endpoints

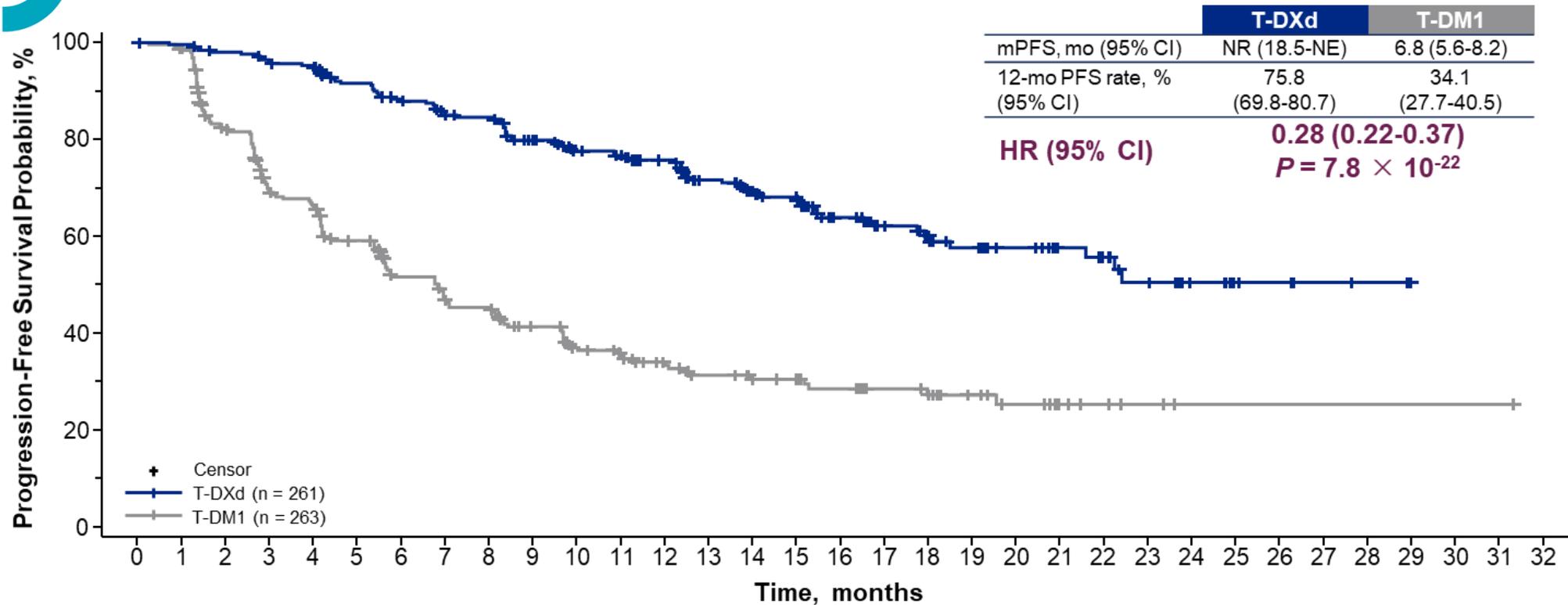
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety



# DESTINY – Breast 03 : caractéristiques patients

| Characteristic                             | T-DXd<br>(n = 261)      | T-DM1<br>(n = 263)      |
|--|-------------------------|-------------------------|
| <b>Age, median (range), years</b>          | 54.3 (27.9-83.1)        | 54.2 (20.2-83.0)        |
| <b>Female, n (%)</b>                       | 200 (99.6)              | 202 (99.6)              |
| <b>HER2 status (IHC), n (%)</b>            |                         |                         |
| 3+   | 234 (89.7)              | 232 (88.2)              |
| 2+ (ISH positive)                          | 25 (9.6)                | 30 (11.4)               |
| 1+   Not evaluable                         | 1 (0.4)   1 (0.4)       | 0   1 (0.4)             |
| <b>ECOG PS<sup>b</sup>, n (%)</b>          |                         |                         |
| 0   1                                      | 154 (59.0)   106 (40.6) | 175 (66.5)   87 (33.1)  |
| <b>Hormone receptor status, n (%)</b>      |                         |                         |
| Positive   Negative                        | 131 (50.2)   130 (49.8) | 134 (51.0)   129 (49.0) |
| <b>History of brain metastases, n (%)</b>  |                         |                         |
| Yes   No                                   | 62 (23.8)   199 (76.2)  | 52 (19.8)   211 (80.2)  |
| <b>Brain metastases at baseline, n (%)</b> |                         |                         |
| Yes   No                                   | 43 (16.5)   218 (83.5)  | 39 (14.8)   224 (85.2)  |
| <b>Visceral disease, n (%)</b>             |                         |                         |
| Yes   No                                   | 184 (70.5)   77 (29.5)  | 185 (70.3)   78 (29.7)  |

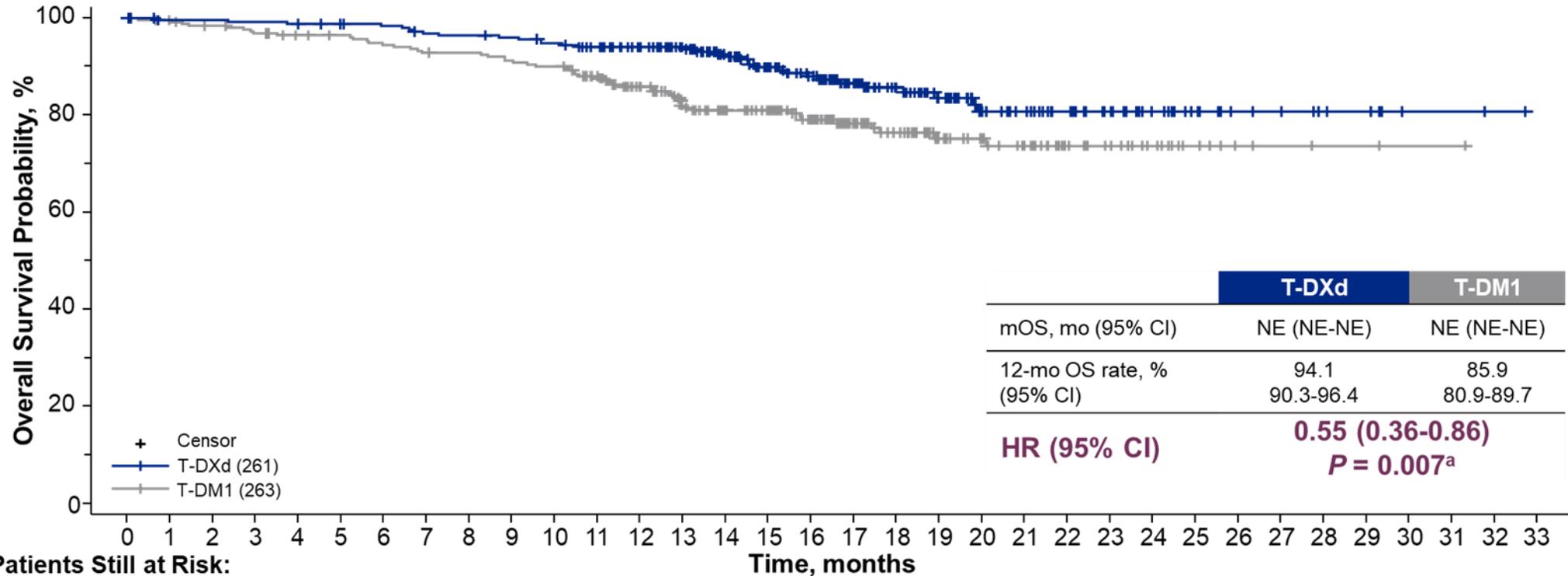
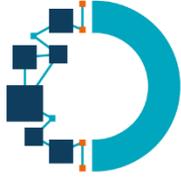
# DESTINY – Breast 03 : efficacité



### Patients Still at Risk:

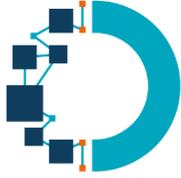
|             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|---|---|---|---|---|---|
| T-DXd (261) | 261 | 256 | 250 | 244 | 240 | 224 | 214 | 202 | 200 | 183 | 168 | 164 | 150 | 132 | 112 | 105 | 79 | 64 | 53 | 45 | 36 | 29 | 25 | 19 | 10 | 6 | 5 | 3 | 2 | 0 |   |
| T-DM1 (263) | 263 | 252 | 200 | 163 | 155 | 132 | 108 | 96  | 93  | 78  | 65  | 60  | 51  | 43  | 37  | 34  | 29 | 23 | 21 | 16 | 12 | 8  | 6  | 4  | 1  | 1 | 1 | 1 | 1 | 1 | 0 |

# DESTINY – Breast 03 : efficacité

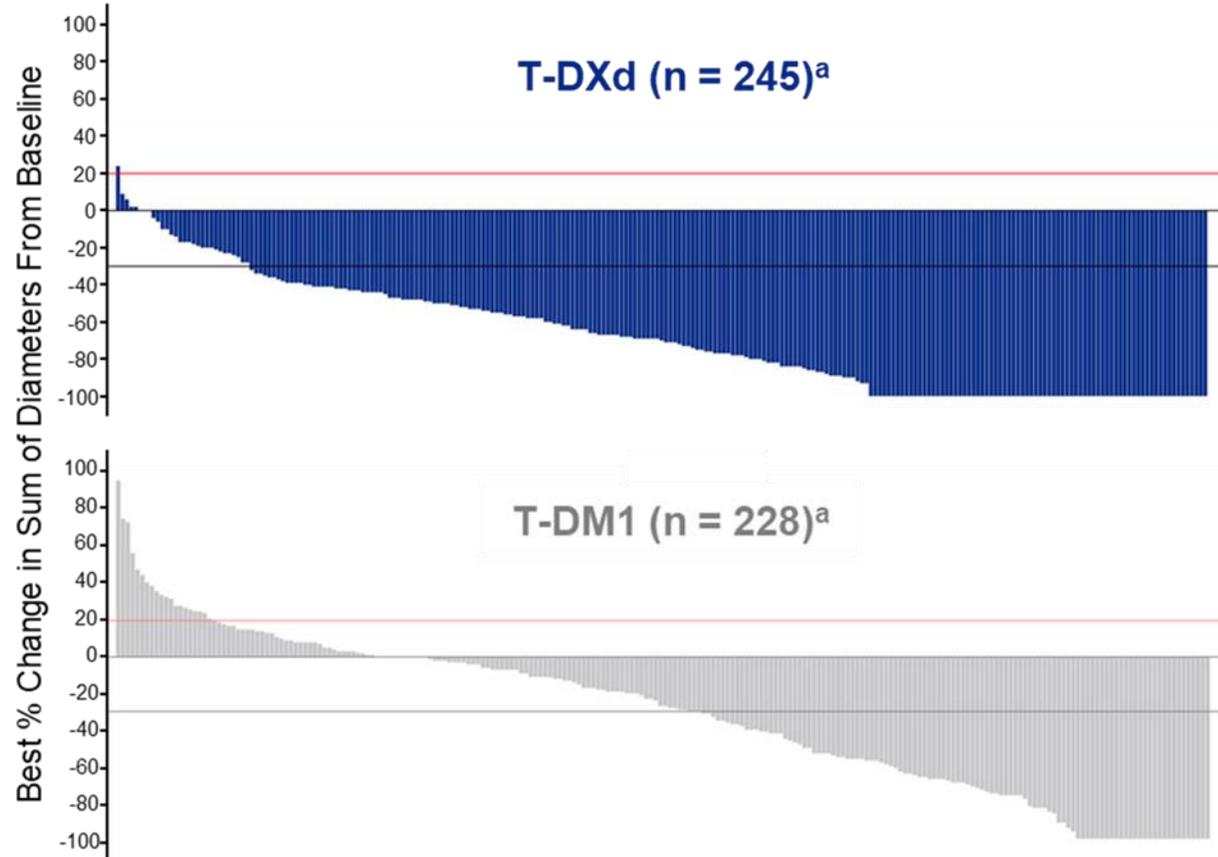


Patients Still at Risk:

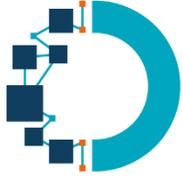
|             | 0   | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  | 17  | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| T-DXd (261) | 261 | 256 | 256 | 255 | 254 | 251 | 249 | 244 | 243 | 241 | 237 | 230 | 218 | 202 | 180 | 158 | 133 | 108 | 86 | 71 | 56 | 50 | 42 | 33 | 24 | 18 | 11 | 10 | 7  | 6  | 2  | 2  | 1  | 0  |
| T-DM1 (263) | 263 | 258 | 253 | 248 | 243 | 241 | 236 | 232 | 231 | 227 | 224 | 210 | 188 | 165 | 151 | 140 | 120 | 91  | 75 | 58 | 52 | 44 | 32 | 27 | 18 | 11 | 5  | 4  | 3  | 3  | 1  | 1  | 0  |    |



# DESTINY – Breast 03 : efficacité



|                               | <b>T-DXd<br/>(n = 261)</b> | <b>T-DM1<br/>(n = 263)</b> |
|-------------------------------|----------------------------|----------------------------|
| <b>Confirmed ORR</b>          |                            |                            |
| n (%)                         | 208 ( <b>79.7</b> )        | 90 ( <b>34.2</b> )         |
| [95% CI]                      | [74.3-84.4]                | [28.5-40.3]                |
|                               | <i>P</i> < 0.0001          |                            |
| <b>CR</b>                     | 42 ( <b>16.1</b> )         | 23 ( <b>8.7</b> )          |
| <b>PR</b>                     | 166 ( <b>63.6</b> )        | 67 ( <b>25.5</b> )         |
| SD                            | 44 (16.9)                  | 112 (42.6)                 |
| PD                            | 3 (1.1)                    | 46 (17.5)                  |
| Not evaluable                 | 6 (2.3)                    | 15 (5.7)                   |
| <b>CR + PR + SD<br/>(DCR)</b> | 252 (96.6)                 | 202 (76.8)                 |

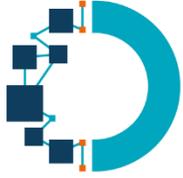


# DESTINY – Breast 03 : tolérance

## Drug-Related TEAEs in ≥20% of Patients

| System Organ Class<br>Preferred term, n (%)                | T-DXd (n = 257) |           | T-DM1 (n = 261) |           |
|--|-----------------|-----------|-----------------|-----------|
|  | Any Grade       | Grade ≥3  | Any Grade       | Grade ≥3  |
| <b>Drug-related blood and lymphatic system disorders</b>   |                 |           |                 |           |
| Neutropenia  | 110 (42.8)      | 49 (19.1) | 29 (11.1)       | 8 (3.1)   |
| Anemia   | 78 (30.4)       | 15 (5.8)  | 37 (14.2)       | 11 (4.2)  |
| Leukopenia   | 77 (30.0)       | 17 (6.6)  | 20 (7.7)        | 1 (0.4)   |
| Thrombocytopenia   | 64 (24.9)       | 18 (7.0)  | 135 (51.7)      | 65 (24.9) |
| <b>Drug-related gastrointestinal disorders</b>             |                 |           |                 |           |
| Nausea   | 187 (72.8)      | 17 (6.6)  | 72 (27.6)       | 1 (0.4)   |
| Vomiting   | 113 (44.0)      | 4 (1.6)   | 15 (5.7)        | 1 (0.4)   |
| Diarrhea   | 61 (23.7)       | 1 (0.4)   | 10 (3.8)        | 1 (0.4)   |
| Constipation   | 58 (22.6)       | 0         | 25 (9.6)        | 0         |
| <b>Drug-related general disorders</b>                      |                 |           |                 |           |
| Fatigue  | 115 (44.7)      | 13 (5.1)  | 77 (29.5)       | 2 (0.8)   |
| <b>Drug-related investigations</b>                         |                 |           |                 |           |
| AST increased  | 60 (23.3)       | 2 (0.8)   | 97 (37.2)       | 13 (5.0)  |
| ALT increased  | 50 (19.5)       | 4 (1.6)   | 71 (27.2)       | 12 (4.6)  |
| <b>Drug-related metabolism and nutrition disorders</b>     |                 |           |                 |           |
| Decreased appetite   | 67 (26.1)       | 3 (1.2)   | 33 (12.6)       | 0         |
| <b>Drug-related skin and subcutaneous tissue disorders</b> |                 |           |                 |           |
| Alopecia   | 93 (36.2)       | 1 (0.4)   | 6 (2.3)         | 0         |

=> Majorité des effets secondaires étaient troubles gastro-intestinaux et hématologiques



# DESTINY – Breast 03 : tolérance

## Adverse Events of Special Interest

### Adjudicated as drug-related ILD/pneumonitis, n (%)

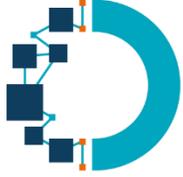
| n (%)           | Grade 1 | Grade 2  | Grade 3 | Grade 4 | Grade 5 | Any Grade |
|-----------------|---------|----------|---------|---------|---------|-----------|
| T-DXd (n = 257) | 7 (2.7) | 18 (7.0) | 2 (0.8) | 0       | 0       | 27 (10.5) |
| T-DM1 (n = 261) | 4 (1.5) | 1 (0.4)  | 0       | 0       | 0       | 5 (1.9)   |

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd
- In the T-DXd arm, 21 patients (8.2%) discontinued treatment due to ILD/pneumonitis
- In the T-DM1 arm, 3 patients (1.1%) discontinued treatment due to ILD/pneumonitis

### LVEF decrease, n (%)

| n (%)           | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any Grade |
|-----------------|---------|---------|---------|---------|---------|-----------|
| T-DXd (n = 257) | 1 (0.4) | 6 (2.3) | 0       | 0       | 0       | 7 (2.7)   |
| T-DM1 (n = 261) | 0       | 1 (0.4) | 0       | 0       | 0       | 1 (0.4)   |

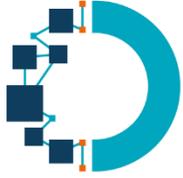
- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred



# Cas clinique HER2 positif

- Traitement de 1<sup>ère</sup> ligne par Taxotere + Pertuzumab + Trastuzumab (6 cures => RC) puis Pertuzumab + Trastuzumab + AI jusqu'en **mars 2021** => atteinte ganglionnaire
- **Avril 2021** : TDM-1 pour 9 cycles => PD
- **Novembre 2021 à avril 2023** : trastuzumab deruxtecan => PD



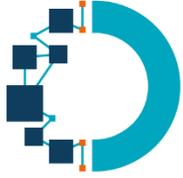


# Cas clinique HER2 positif

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Concernant la prise en charge thérapeutique de cette patiente, vous proposeriez?

- A. Traitement par inhibiteur de l'aromatase seule
- B. Chimiothérapie
- C. Traitement par tucatinib + trastuzumab + capécitabine
- D. Traitement par inhibiteur de l'aromatase + inhibiteur de CDK4/6
- E. Prise en charge purement palliative

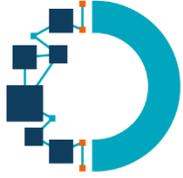


# Cas clinique HER2 positif

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Concernant la prise en charge thérapeutique de cette patiente, vous proposeriez?

- A. Traitement par inhibiteur de l'aromatase seule
- B. Chimiothérapie
- C. **Traitement par tucatinib + trastuzumab + capécitabine**
- D. Traitement par inhibiteur de l'aromatase + inhibiteur de CDK4/6
- E. Prise en charge purement palliative



# Tucatinib

## Tucatinib: A tyrosine kinase inhibitor selective for HER2

1 The small molecule tucatinib diffuses into cells

2 Selectively binds to the kinase domain of HER2

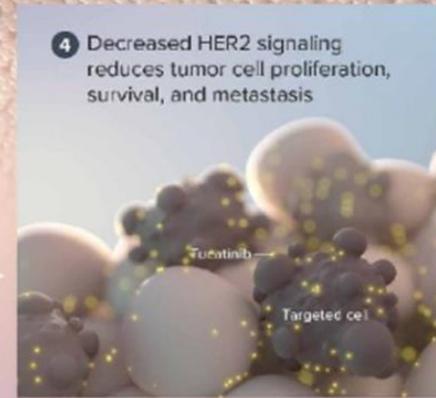
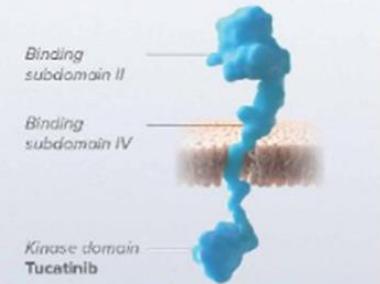
3 Inhibits activation of downstream signaling cascades

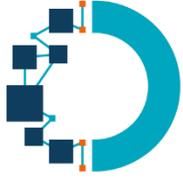
4 Decreased HER2 signaling reduces tumor cell proliferation, survival, and metastasis

EGFR: epidermal growth factor receptor; HER: human epidermal growth factor receptor; MAPK: mitogen-activated protein kinase; PI3K: phosphoinositide 3-kinase

### Dual inhibition of HER2

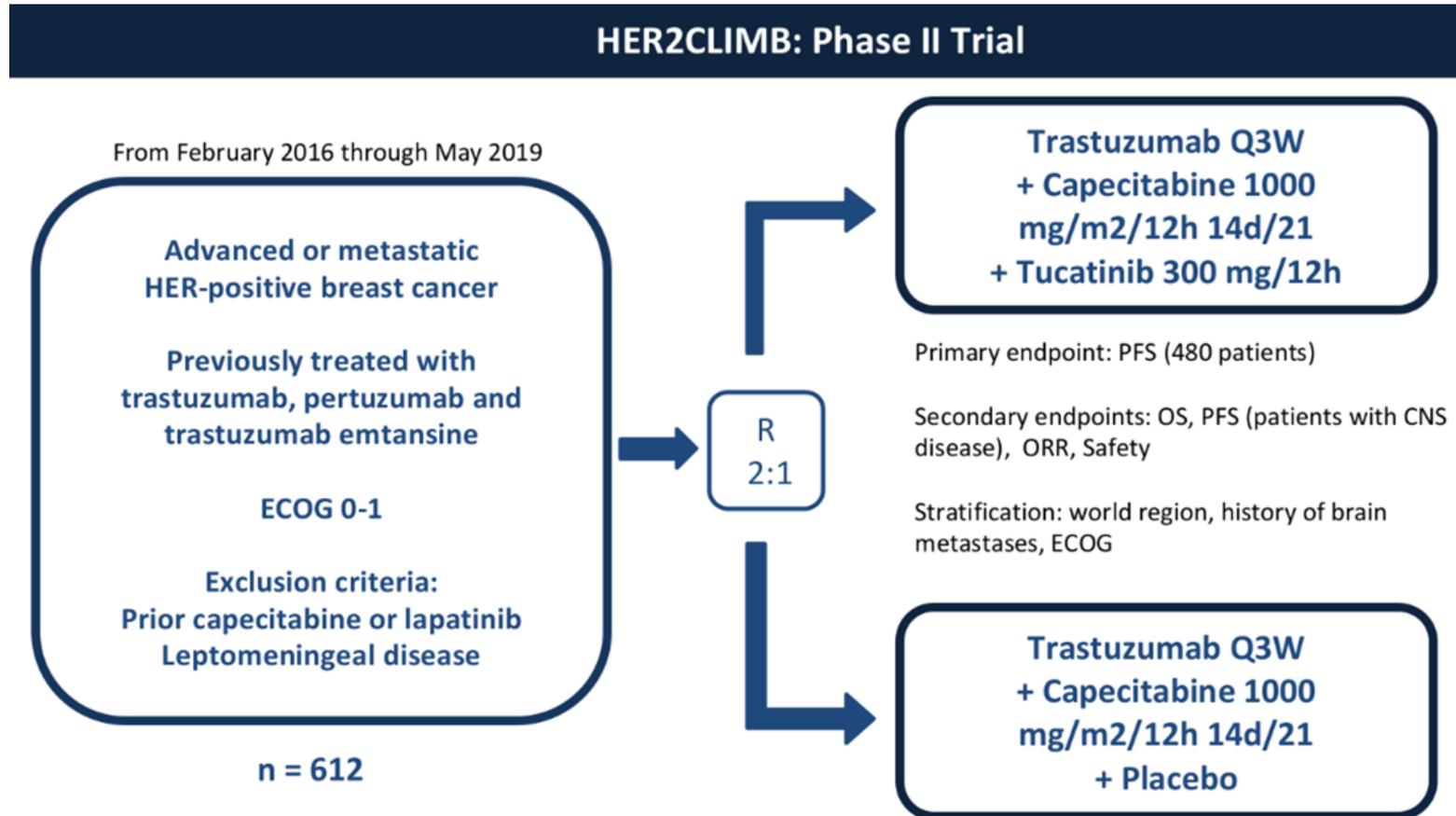
Tucatinib has been combined with other agents that target the extracellular domain of HER2 in clinical trials.

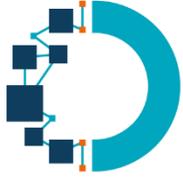




# HER2CLIM

## HER2CLIMB: Phase II Trial

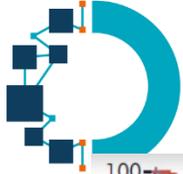




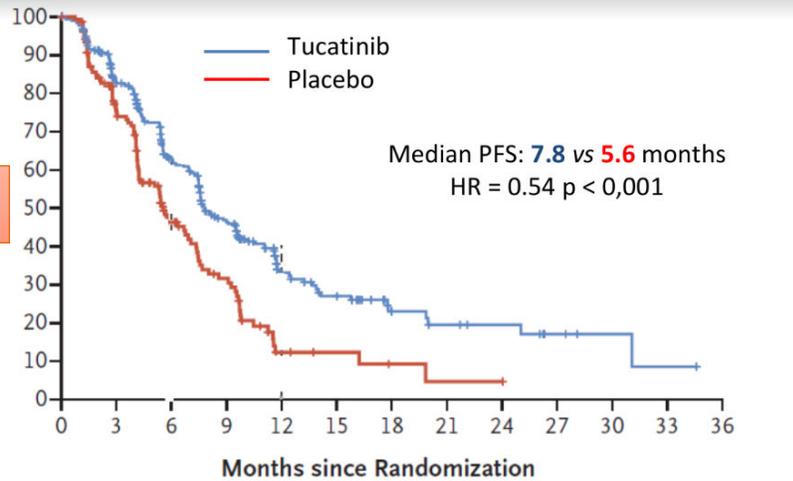
# HER2CLIM

| Characteristic                                    | Primary End-Point Analysis Population<br>(N=480) |                                   | Total Population<br>(N=612)         |                                   |
|---|--|-----------------------------------|-------------------------------------|-----------------------------------|
|   | Tucatinib<br>Combination<br>(N=320)              | Placebo<br>Combination<br>(N=160) | Tucatinib<br>Combination<br>(N=410) | Placebo<br>Combination<br>(N=202) |
| Female sex — no. (%)                              | 317 (99.1)                                       | 158 (98.8)                        | 407 (99.3)                          | 200 (99.0)                        |
| Age — no. (%)                                     |  |                                   |                                     |                                   |
| <65 yr  | 252 (78.8)                                       | 132 (82.5)                        | 328 (80.0)                          | 168 (83.2)                        |
| ≥65 yr  | 68 (21.2)  | 28 (17.5)                         | 82 (20.0)                           | 34 (16.8)                         |
| Median age — yr                                   | 54.0   | 54.0                              | 55.0                                | 54.0                              |
|   | Tucatinib<br>Combination<br>(N=320)              | Placebo<br>Combination<br>(N=160) | Tucatinib<br>Combination<br>(N=410) | Placebo<br>Combination<br>(N=202) |
| Presence or history of brain metastases — no. (%) | 148 (46.2)                                       | 71 (44.4)                         | 198 (48.3)                          | 93 (46.0)                         |
| Location of other metastases — no. (%)            |  |                                   |                                     |                                   |

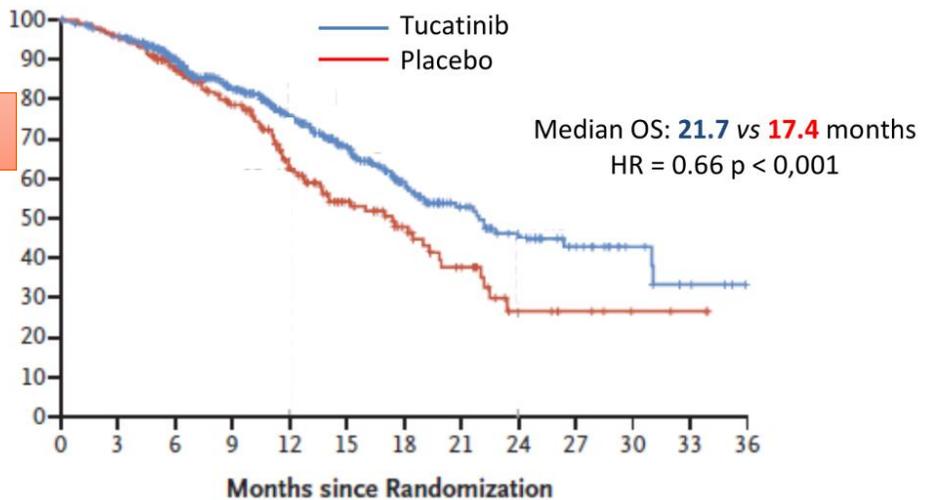
# HER2CLIM



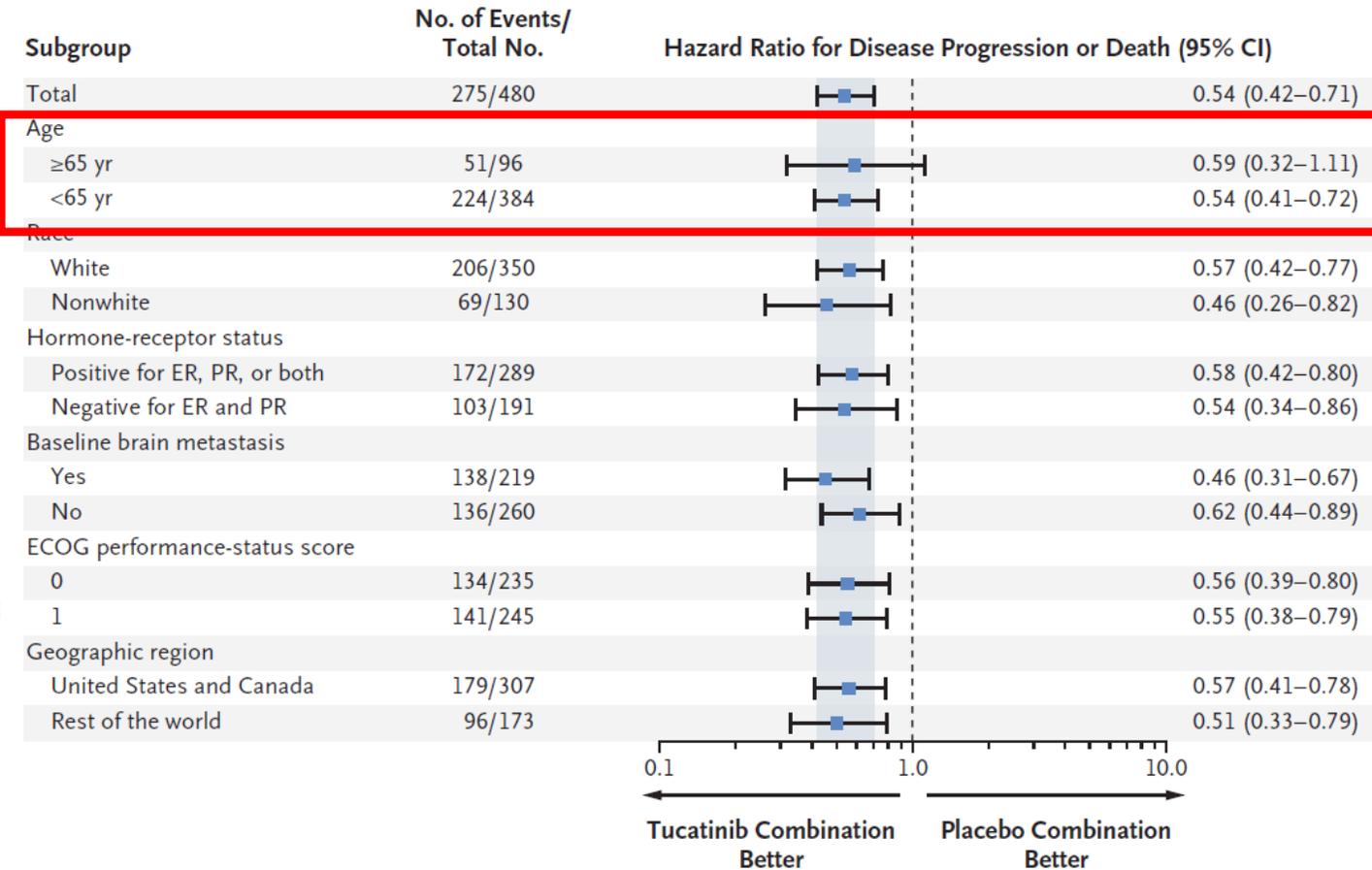
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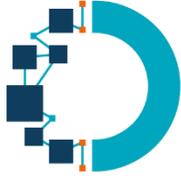


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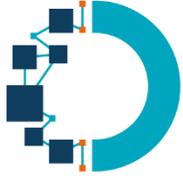
## B Subgroup Analysis of Progression-free Survival





# HER2CLIM

| Event                                | Tucatinib-Combination Group<br>(N= 404) |            | Placebo-Combination Group<br>(N= 197) |           |
|--------------------------------------|---|------------|---------------------------------------|-----------|
|                                      | Any Grade                               | Grade ≥3   | Any Grade                             | Grade ≥3  |
|                                      | <i>number of patients (percent)</i>     |            |                                       |           |
| Any adverse event                    | 401 (99.3)                              | 223 (55.2) | 191 (97.0)                            | 96 (48.7) |
| Diarrhea                             | 327 (80.9)                              | 52 (12.9)  | 105 (53.3)                            | 17 (8.6)  |
| PPE syndrome                         | 256 (63.4)                              | 53 (13.1)  | 104 (52.8)                            | 18 (9.1)  |
| Nausea                               | 236 (58.4)                              | 15 (3.7)   | 86 (43.7)                             | 6 (3.0)   |
| Fatigue                              | 182 (45.0)                              | 19 (4.7)   | 85 (43.1)                             | 8 (4.1)   |
| Vomiting                             | 145 (35.9)                              | 12 (3.0)   | 50 (25.4)                             | 7 (3.6)   |
| Stomatitis                           | 103 (25.5)                              | 10 (2.5)   | 28 (14.2)                             | 1 (0.5)   |
| Decreased appetite                   | 100 (24.8)                              | 2 (0.5)    | 39 (19.8)                             | 0         |
| Headache                             | 87 (21.5)                               | 2 (0.5)    | 40 (20.3)                             | 3 (1.5)   |
| Aspartate aminotransferase increased | 86 (21.3)                               | 18 (4.5)   | 22 (11.2)                             | 1 (0.5)   |
| Alanine aminotransferase increased   | 81 (20.0)                               | 22 (5.4)   | 13 (6.6)                              | 1 (0.5)   |



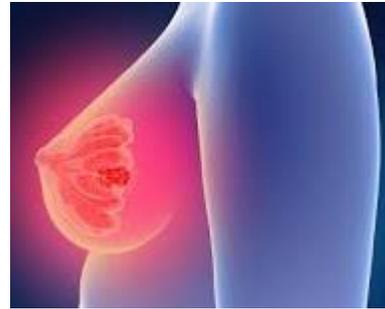
# TNBC

chirurgie

chimiothérapie

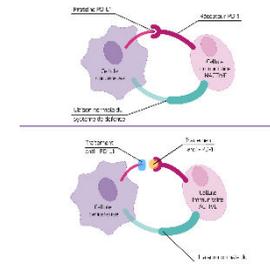
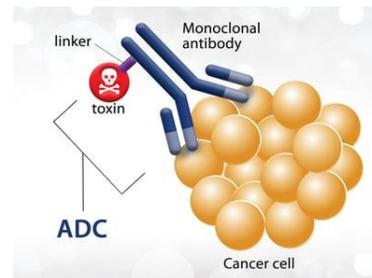
radiothérapie

hormonothérapie



ADC

Immunothérapie



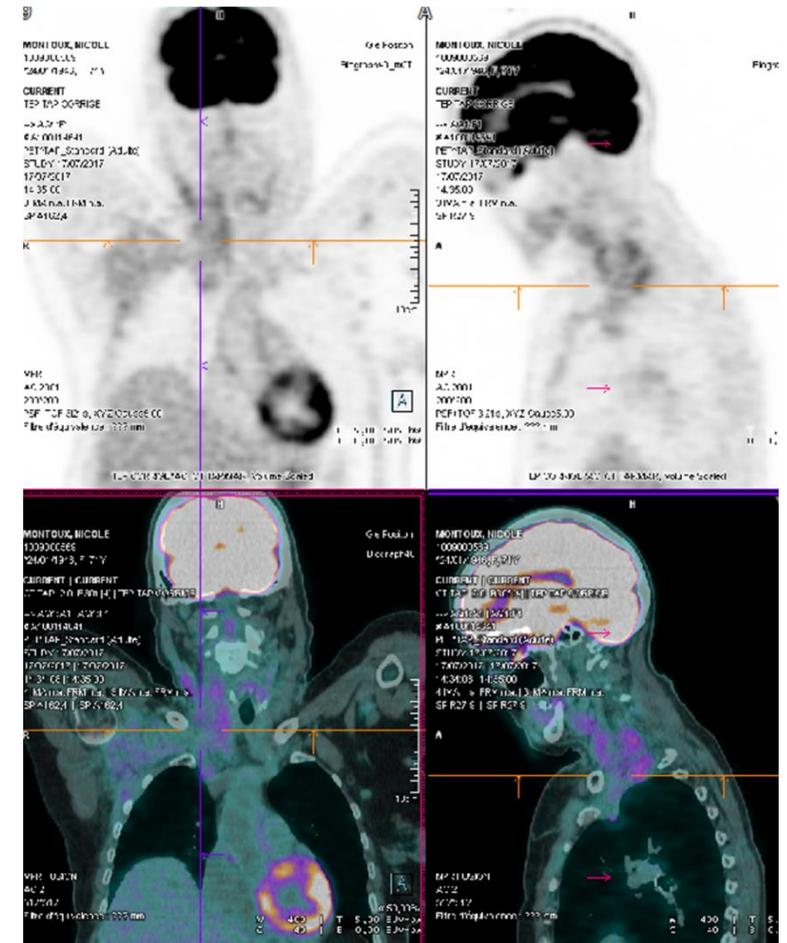
# Cas clinique TNBC

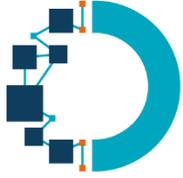


- Mme M... Nicole née le 24/01/1946
- ATCD : HTA
- Autonome à domicile, 1 fils, agricultrice à la retraite

- **Juillet 2010** : mastectomie partielle droite + curage axillaire pour un carcinome lobulaire infiltrant de 42 mm, RO 80%, RP-, HER2-, SBR II, 3 N+/8
- Chimiothérapie (EC, TXT), radiothérapie adjuvante et anastrozole jusqu'en **2016**

- **Juillet 2017** : évolution ganglionnaire et pulmonaire
- Biopsie : carcinome lobulaire infiltrant, RO-, RP-, HE2++ (DDISH négative)
- Paclitaxel bevacizumab, capecitabine, EC, Caelyx, Eribuline



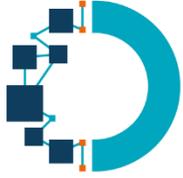


# Cas clinique TNBC

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Concernant la prise en charge thérapeutique de cette patiente, vous proposeriez?

- Prise en charge purement palliative
- Traitement par trastuzumab dexruteacan
- Nouvelle ligne de chimiothérapie avec des sels de platine
- Sacituzumab govitecan
- Radiothérapie localisée

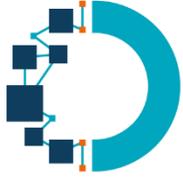


# Cas clinique TNBC

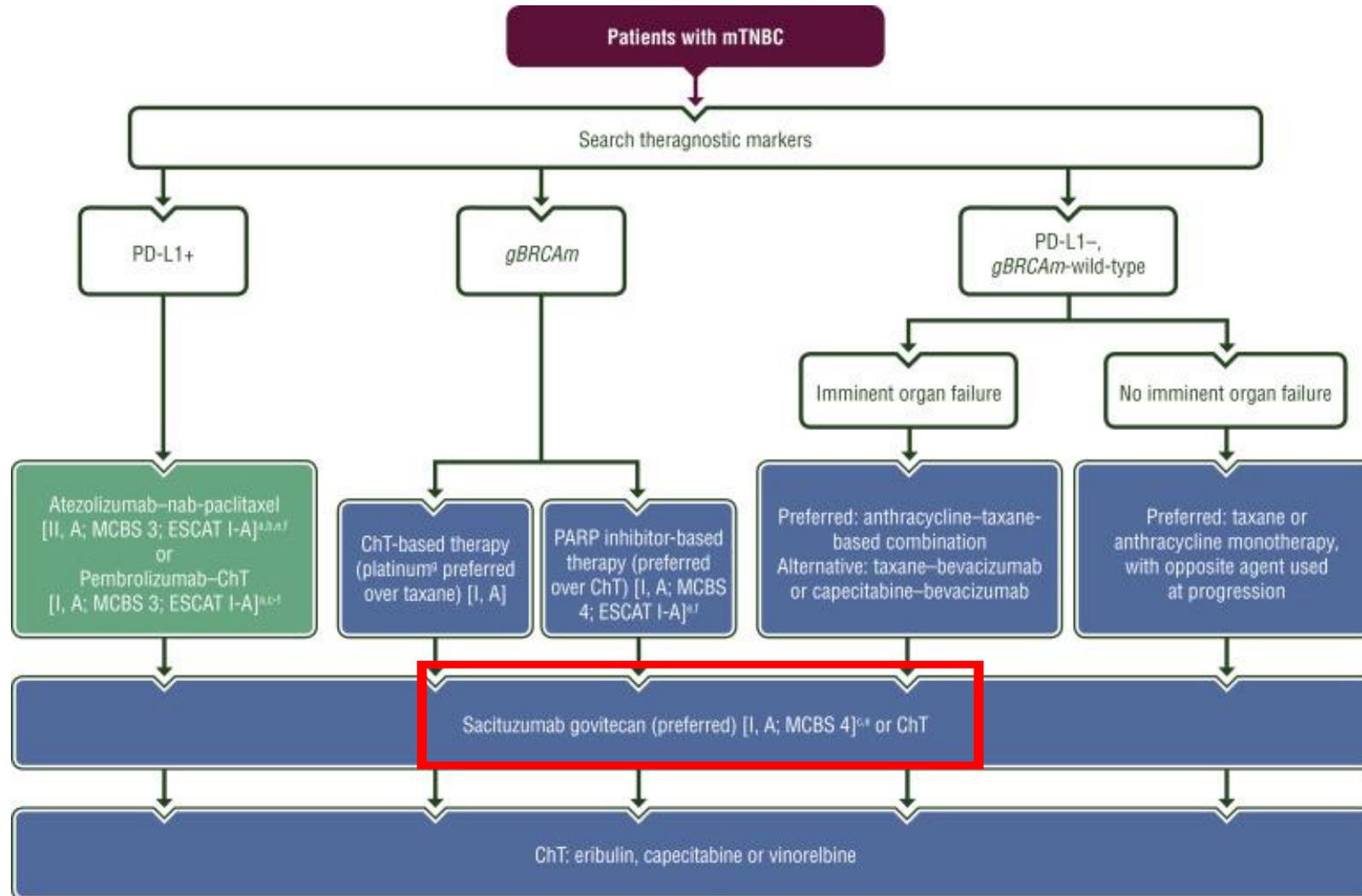
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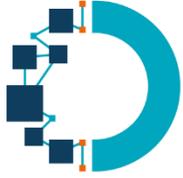
Concernant la prise en charge thérapeutique de cette patiente, vous proposeriez?

- Prise en charge purement palliative
- Traitement par trastuzumab dexruteacan
- Nouvelle ligne de chimiothérapie avec des sels de platine
- **Sacituzumab govitecan**
- Radiothérapie localisée

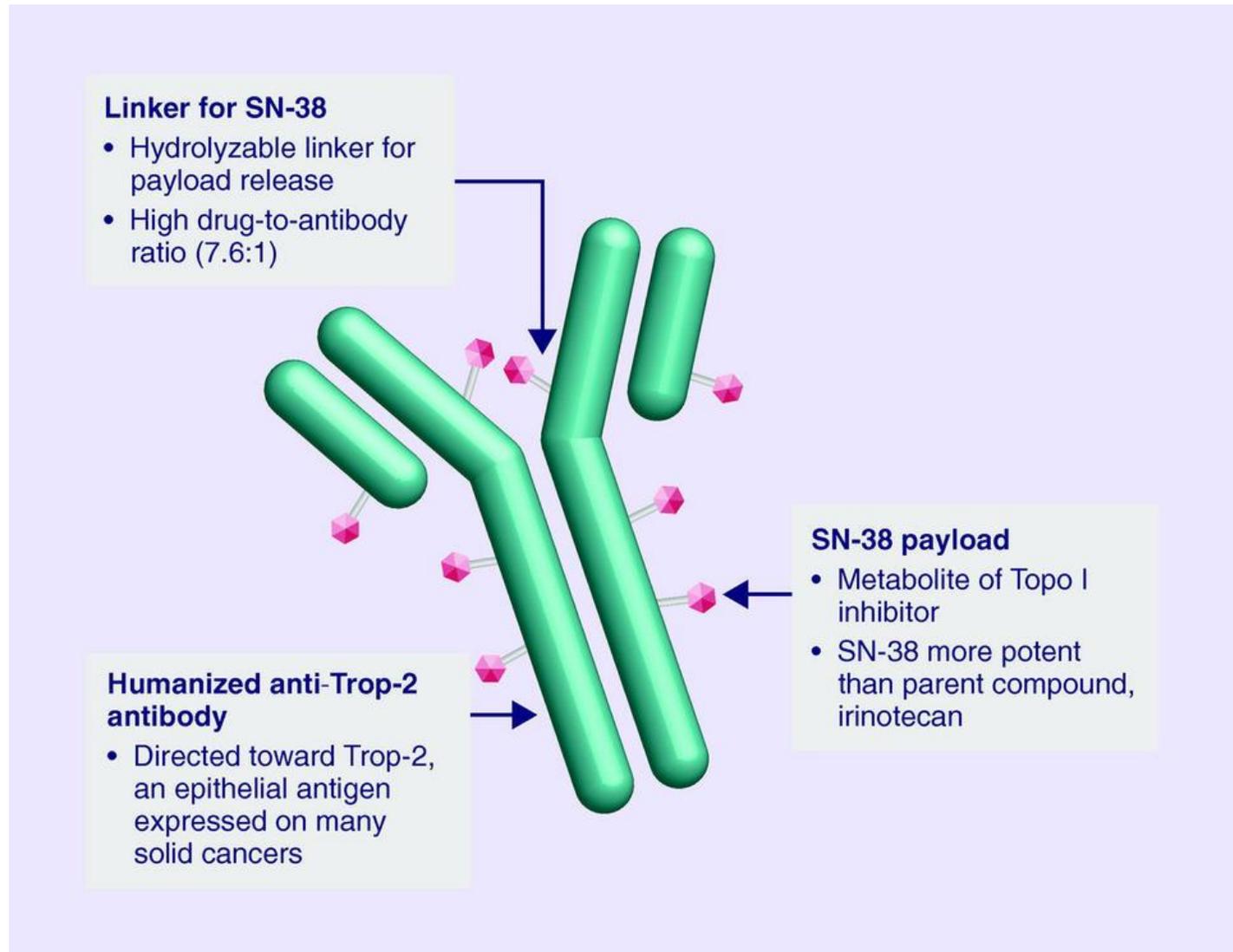


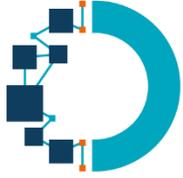
# Guidelines ESMO 2023



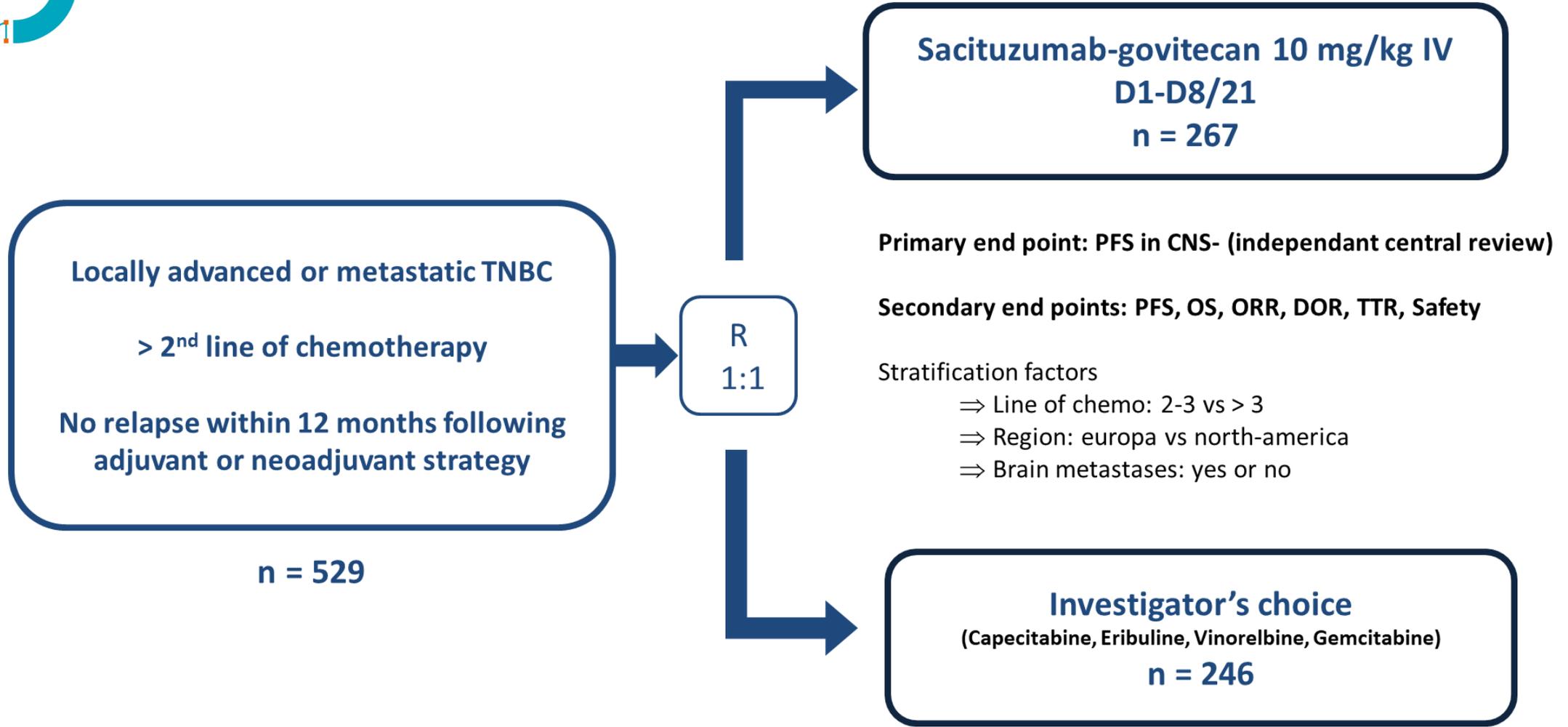


# Sacituzumab govitecan





# Etude ASCENT





# Etude ASCENT

7% avec une mutation BRCA

30% sont devenus TN au cours de l'évolution de la maladie

## Chimiothérapies antérieures

- Taxanes: 100%
- Anthracyclines: 80%
- Cyclophosphamide: 80%
- Capecitabine: 60%
- Sels de platines: 60%

## ASCENT: Demographics and Baseline Characteristics<sup>1,a</sup>

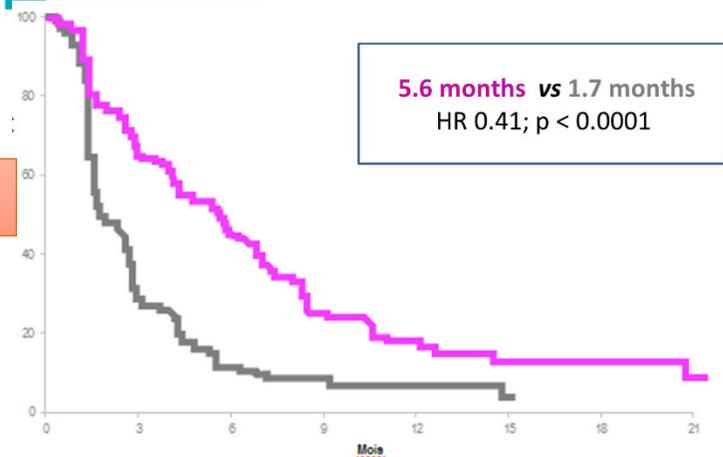
|   | SG (n = 235) | TPC (n = 233) |  | SG (n = 235) | TPC (n = 233) |
|---|--------------|---------------|--|--------------|---------------|
| Female—no. (%)                                  | 233 (99)     | 233 (100)     | Previous anticancer regimens—median no. (range)    | 3 (1-16)     | 3 (1-12)      |
| Median age—yr (range)                           | 54 (29-82)   | 53 (27-81)    | Most common previous chemotherapy—no. (%)          |              |               |
| Race or ethnic group—no. (%)                    |              |               | Taxane <sup>d</sup>                                | 235 (100)    | 233 (100)     |
| White   | 188 (80)     | 181 (78)      | Anthracycline <sup>e</sup>                         | 191 (81)     | 193 (83)      |
| Black   | 28 (12)      | 28 (12)       | Cyclophosphamide                                   | 192 (82)     | 192 (82)      |
| Asian   | 9 (4)        | 9 (4)         | Carboplatin  | 147 (63)     | 160 (69)      |
| Other or not specified                          | 10 (4)       | 15 (6)        | Capecitabine                                       | 147 (63)     | 159 (68)      |
| ECOG PS—no. (%)                                 |              |               | Previous PARP inhibitor—no. (%)                    | 17 (7)       | 18 (8)        |
| 0   | 108 (46)     | 98 (42)       | Previous use of checkpoint inhibitors—no. (%)      | 67 (29)      | 60 (26)       |
| 1   | 127 (54)     | 135 (58)      | Most common sites of disease <sup>f</sup> —no. (%) |              |               |
| BRCA 1/2 mutational status—no. (%)              |              |               | Lung only  | 108 (46)     | 97 (42)       |
| Positive  | 16 (7)       | 18 (8)        | Liver  | 98 (42)      | 101 (43)      |
| Negative  | 133 (57)     | 125 (54)      | Bone   | 48 (20)      | 55 (24)       |
| Unknown   | 86 (37)      | 90 (39)       |  |              |               |
| TNBC at initial diagnosis <sup>g</sup> —no. (%) |              |               |  |              |               |
| Yes   | 165 (70)     | 157 (67)      |  |              |               |
| No  | 70 (30)      | 76 (33)       |  |              |               |

<sup>a</sup>Brain metastases-negative population; <sup>b</sup>Patients on study either had TNBC at initial diagnosis or had hormone receptor-positive disease that converted to hormone-negative at time of study entry; <sup>c</sup>Anticancer regimens refer to any treatment regimen that was used to treat breast cancer in any setting; <sup>d</sup>Includes: Paclitaxel, paclitaxel albumin, and docetaxel; <sup>e</sup>Includes: Doxorubicin, daunorubicin, epirubicin, and variations of those treatment names; <sup>f</sup>Based on independent central review of target and non-target lesions; <sup>g</sup>BRCA, breast cancer gene; ECOG PS, Eastern Cooperative Oncology Group performance status; no., number; PARP, poly-ADP ribose polymerase; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice; yr, year.

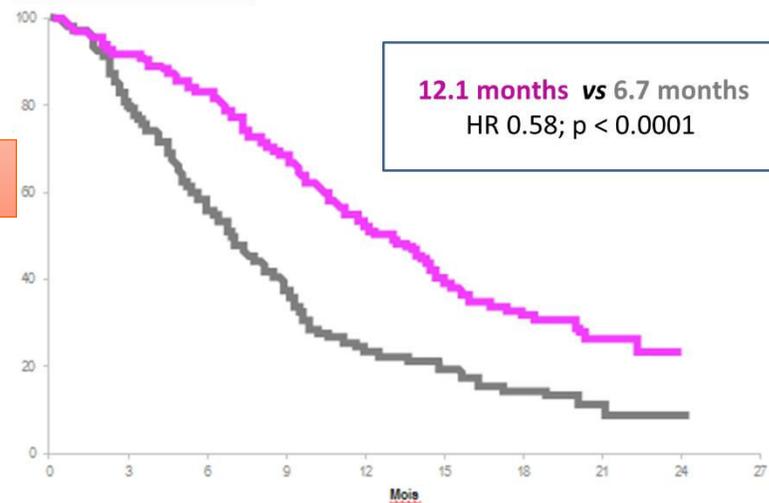
# Etude ASCENT



PFS



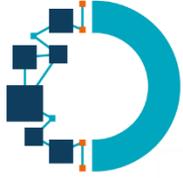
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| Subgroup                                 | No. of Patients | Progression-free Survival            |                             | Hazard Ratio for Disease Progression or Death (95% CI) |             |
|--|-----------------|--------------------------------------|-----------------------------|--|-------------|
|  |                 | Sacituzumab govitecan<br>mo (95% CI) | Chemotherapy<br>mo (95% CI) | HR (95% CI)  | HR (95% CI) |
| All patients                             | 468             | 5.6 (4.3–6.3)                        | 1.7 (1.5–2.6)               | 0.41 (0.32–0.52)                                       |             |
| Age                                      |                 |                                      |                             |  |             |
| <65 yr                                   | 378             | 4.6 (3.7–5.7)                        | 1.7 (1.5–2.5)               | 0.46 (0.35–0.59)                                       |             |
| ≥65 yr                                   | 90              | 7.1 (5.8–8.9)                        | 2.4 (1.4–2.9)               | 0.22 (0.12–0.40)                                       |             |
| Race                                     |                 |                                      |                             |  |             |
| White                                    | 369             | 5.7 (4.3–6.8)                        | 1.7 (1.5–2.6)               | 0.39 (0.30–0.51)                                       |             |
| Black                                    | 56              | 5.4 (2.8–7.4)                        | 2.2 (1.5–2.9)               | 0.45 (0.24–0.86)                                       |             |
| Asian                                    | 18              | NE (1.3–NE)                          | 1.5 (1.2–NE)                | 0.40 (0.08–2.08)                                       |             |
| Previous therapies                       |                 |                                      |                             |  |             |
| 2 or 3                                   | 330             | 5.8 (4.2–7.1)                        | 1.6 (1.5–2.5)               | 0.39 (0.29–0.52)                                       |             |
| >3                                       | 138             | 5.6 (3.0–6.5)                        | 2.5 (1.5–2.8)               | 0.48 (0.32–0.72)                                       |             |
| Geographic region                        |                 |                                      |                             |  |             |
| North America                            | 298             | 4.9 (4.0–6.3)                        | 2.0 (1.5–2.6)               | 0.44 (0.33–0.60)                                       |             |
| Rest of the world                        | 170             | 5.9 (4.2–6.9)                        | 1.6 (1.4–2.7)               | 0.36 (0.24–0.53)                                       |             |
| Previous use of PD-1 or PD-L1 inhibitors |                 |                                      |                             |  |             |
| Yes                                      | 127             | 4.2 (3.2–5.6)                        | 1.6 (1.4–2.3)               | 0.37 (0.24–0.57)                                       |             |
| No                                       | 341             | 6.2 (4.9–7.1)                        | 2.1 (1.5–2.7)               | 0.42 (0.32–0.56)                                       |             |
| Liver metastasis                         |                 |                                      |                             |  |             |
| Yes                                      | 199             | 4.2 (2.8–5.8)                        | 1.5 (1.4–2.4)               | 0.48 (0.34–0.67)                                       |             |
| No                                       | 269             | 6.8 (4.6–8.0)                        | 2.3 (1.6–2.7)               | 0.36 (0.26–0.50)                                       |             |
| Initial diagnosis of TNBC                |                 |                                      |                             |  |             |
| Yes                                      | 322             | 5.7 (4.3–6.9)                        | 1.6 (1.5–2.6)               | 0.38 (0.29–0.51)                                       |             |
| No                                       | 146             | 4.6 (3.7–6.9)                        | 2.3 (1.5–2.8)               | 0.48 (0.32–0.72)                                       |             |

0.06 0.12 0.25 0.50 1.00 2.00 4.00 8.00 16.00

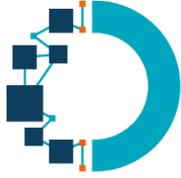
← Sacituzumab Govitecan Better | → Chemotherapy Better



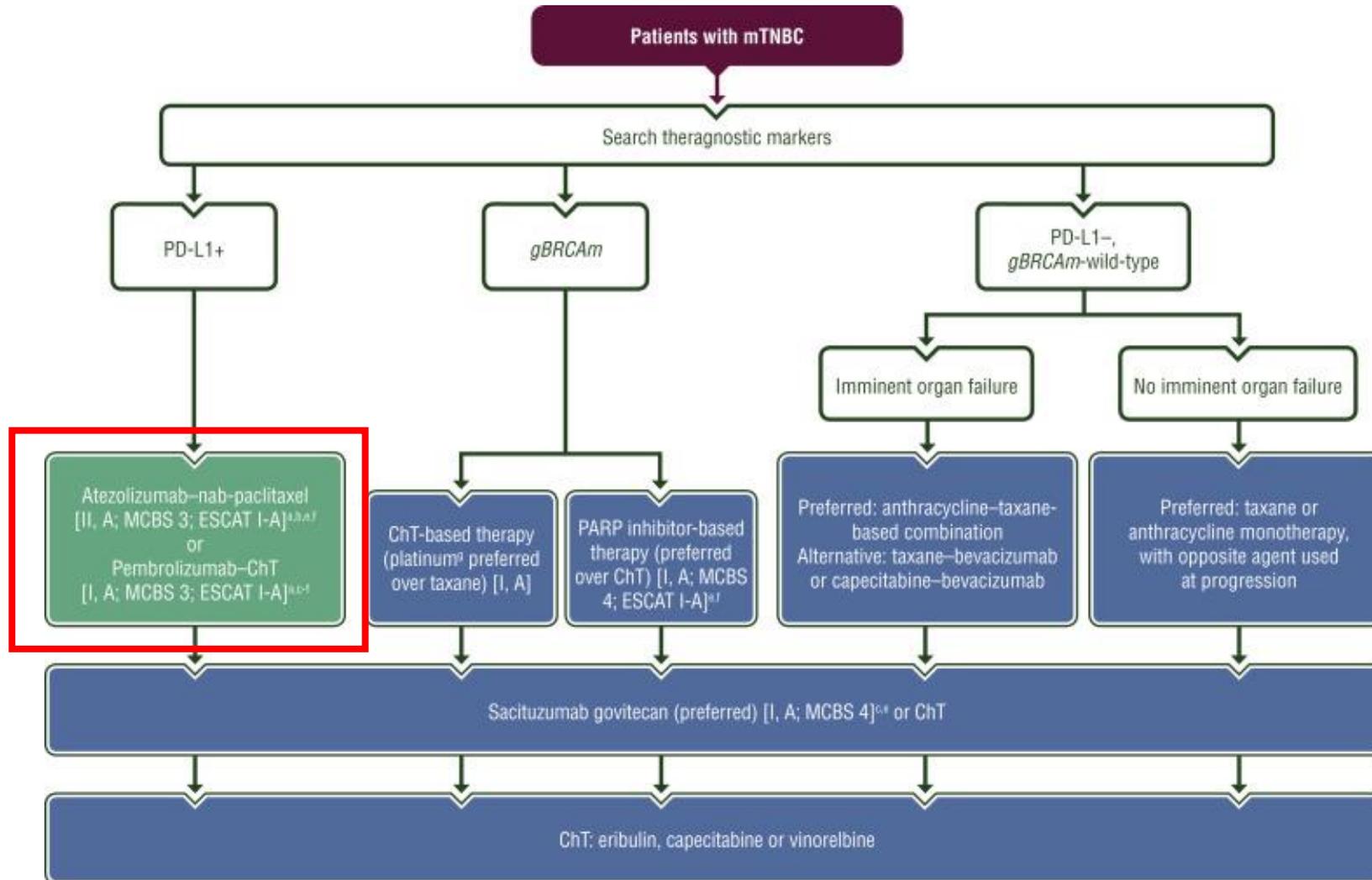
# Etude ASCENT

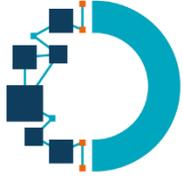
|                      |                          | SG (n=258)   |            |            | TPC (n=224)   |            |            |
|----------------------|--------------------------|--------------|------------|------------|---------------|------------|------------|
|                      |                          | Tous grade % | Grade 3, % | Grade 4, % | Tous grade, % | Grade 3, % | Grade 4, % |
| Hématologique        | Neutropenie <sup>†</sup> | 63           | 46         | 17         | 43            | 27         | 13         |
|                      | Anemie <sup>±</sup>      | 34           | 8          | 0          | 24            | 5          | 0          |
|                      | leucopénie               | 16           | 10         | 1          | 11            | 5          | 1          |
|                      | Neutropenie fébrile      | 6            | 5          | 1          | 2             | 2          | <1         |
| Gastrointestina<br>I | Diarrhée                 | 59           | 10         | 0          | 12            | <1         | 0          |
|                      | Nausée                   | 57           | 2          | <1         | 26            | <1         | 0          |
|                      | Vomissement              | 29           | 1          | <1         | 10            | <1         | 0          |
| autre                | Fatigue                  | 45           | 3          | 0          | 30            | 5          | 0          |
|                      | Alopecie                 | 46           | 0          | 0          | 16            | 0          | 0          |

- Utilisation du G-CSF: 49% (SG) vs 23% (TPC)
- Diminution de la posologie pour toxicité: 22 % (SG) vs 26% (TPC)
- Arrêt pour toxicité : SG et TPC: 4.7% et 5.4%



# Guidelines ESMO 2023





# Etude KEYNOTE 355

From January 2017 through June 2018

**Locally advanced or metastatic TNBC**

**No previous therapy in metastatic setting or completion of previous therapy with curative intent  $\geq 6$  mo**

**ECOG 0-1**

**No active CNS metastases**

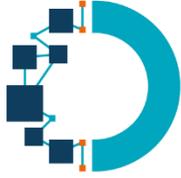
**No active autoimmune disease**

**n = 847**

**R  
2:1**

**Pembrolizumab (up to 35 cycles)  
+ Chemotherapy  
n = 566**

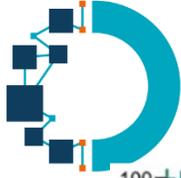
**Placebo (up to 35 cycles)  
+ Chemotherapy  
n = 281**



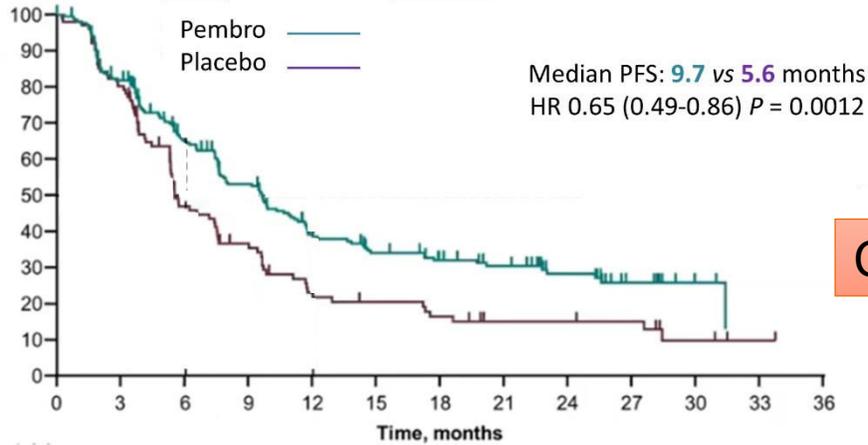
# Etude KEYNOTE 355

| Characteristic, n (%)         | All Subjects, N = 847  |                         |
|-------------------------------|------------------------|-------------------------|
|                               | Pembro + Chemo N = 566 | Placebo + Chemo N = 281 |
| Age, median (range), yrs      | 53 (25-85)             | 53 (22-77)              |
| ECOG PS 1                     | 232 (41.0)             | 108 (38.4)              |
| PD-L1–positive CPS ≥1         | 425 (75.1)             | 211 (75.1)              |
| PD-L1–positive CPS ≥10        | 220 (38.9)             | 103 (36.7)              |
| Chemotherapy on study         |                        |                         |
| Taxane                        | 255 (45.1)             | 127 (45.2)              |
| Gemcitabine/Carboplatin       | 311 (54.9)             | 154 (54.8)              |
| Prior same-class chemotherapy |                        |                         |
| Yes                           | 124 (21.9)             | 62 (22.1)               |
| No                            | 442 (78.1)             | 219 (77.9)              |
| Disease-free interval         |                        |                         |
| de novo metastasis            | 168 (29.7)             | 84 (29.9)               |
| <12 months                    | 125 (22.1)             | 50 (17.8)               |
| ≥12 months                    | 270 (47.7)             | 147 (52.3)              |

# Etude KEYNOTE 355



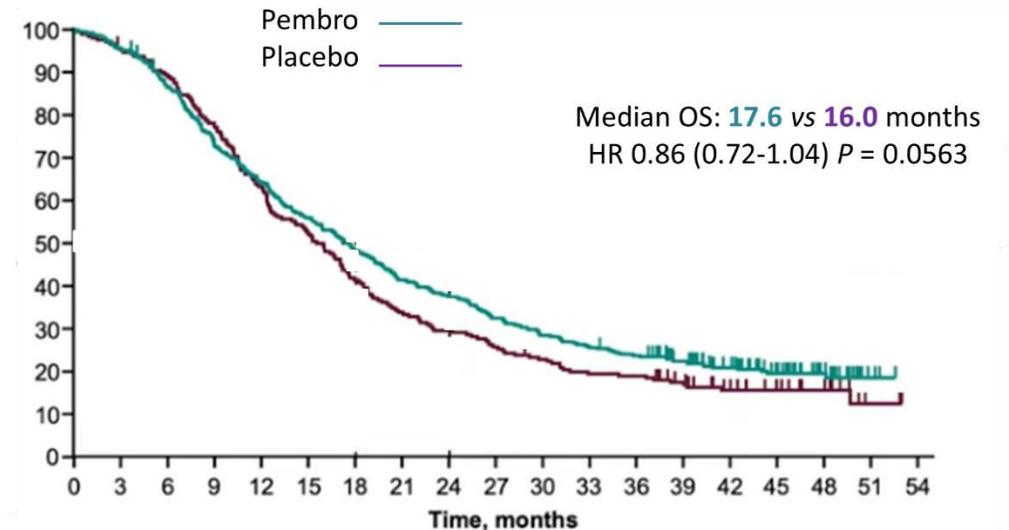
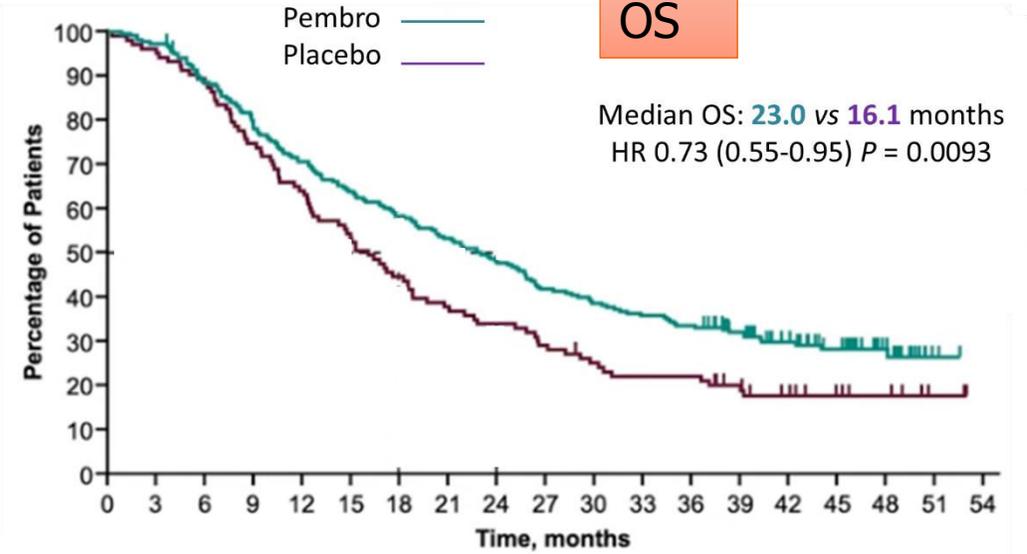
PFS



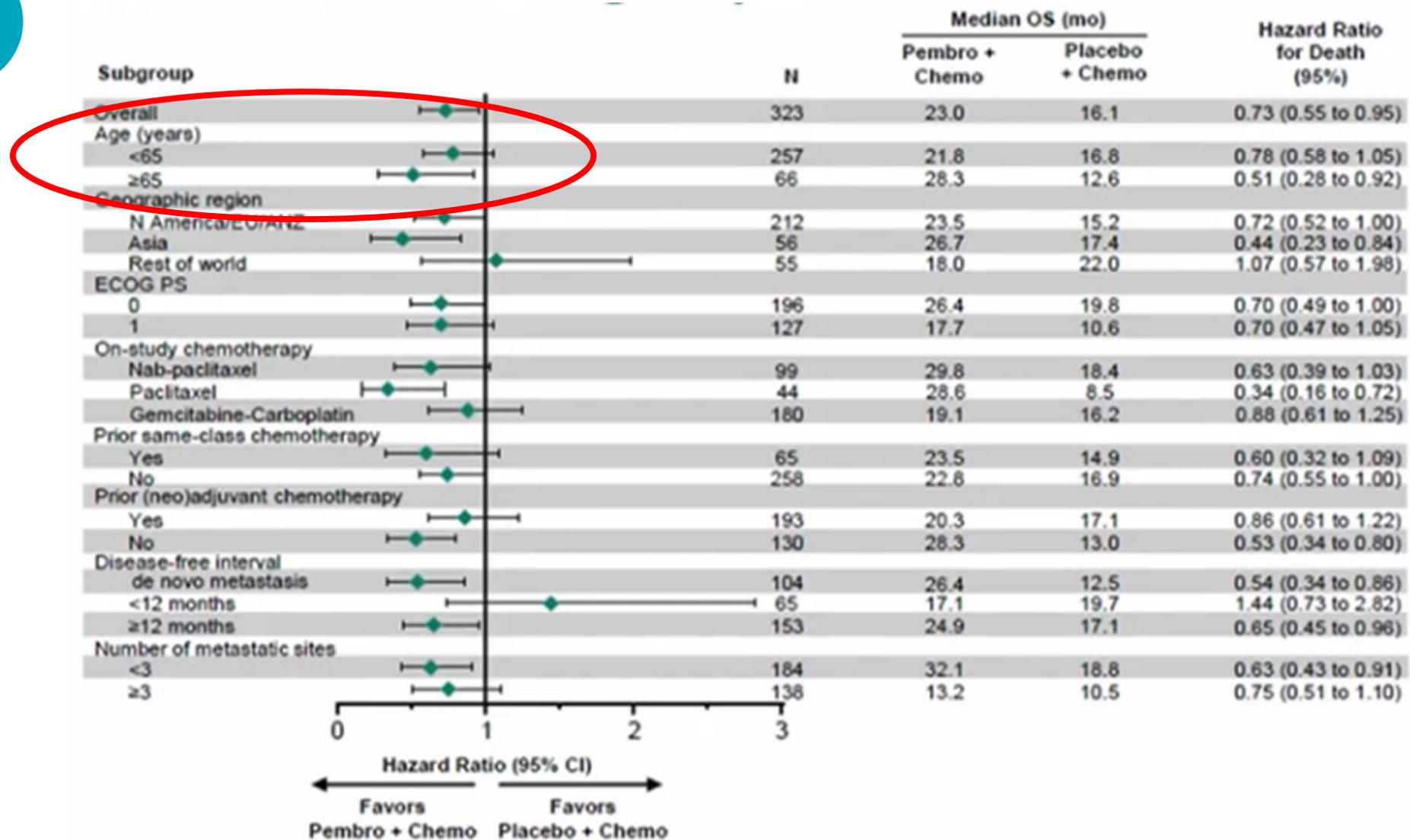
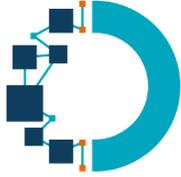
CPS > 10

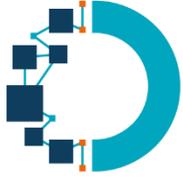
CPS > 1

OS

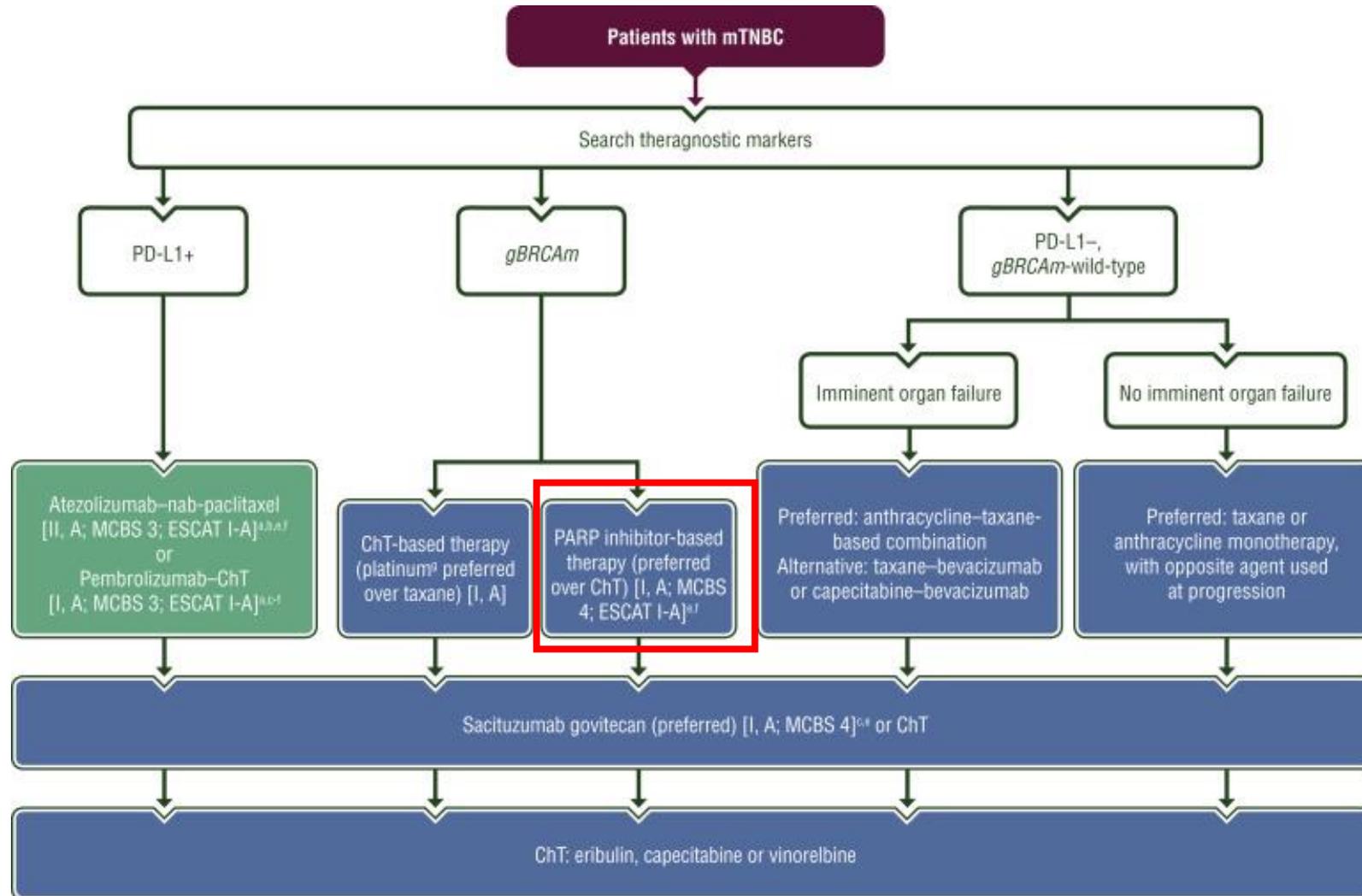


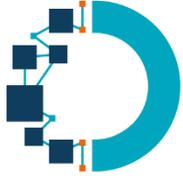
# Etude KEYNOTE 355





# Guidelines ESMO 2023

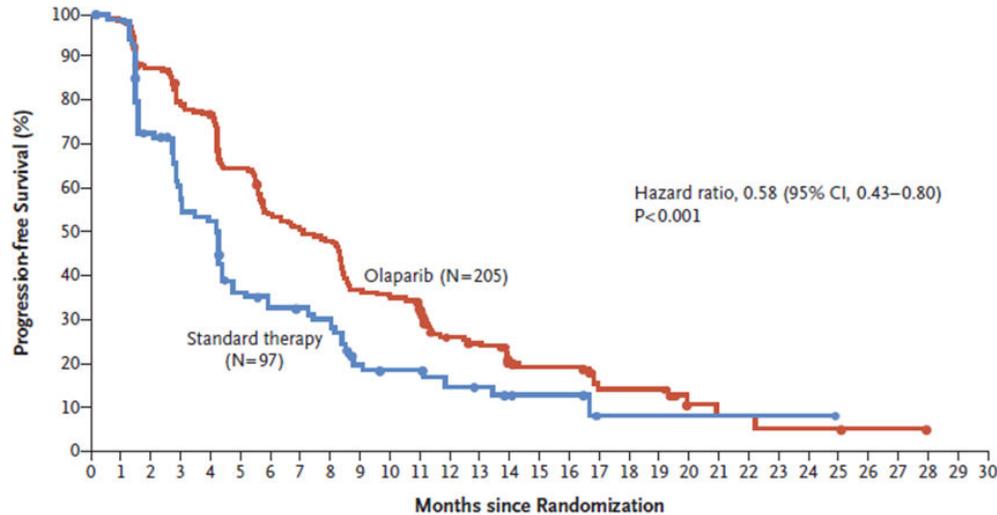




# PARP inhibiteurs

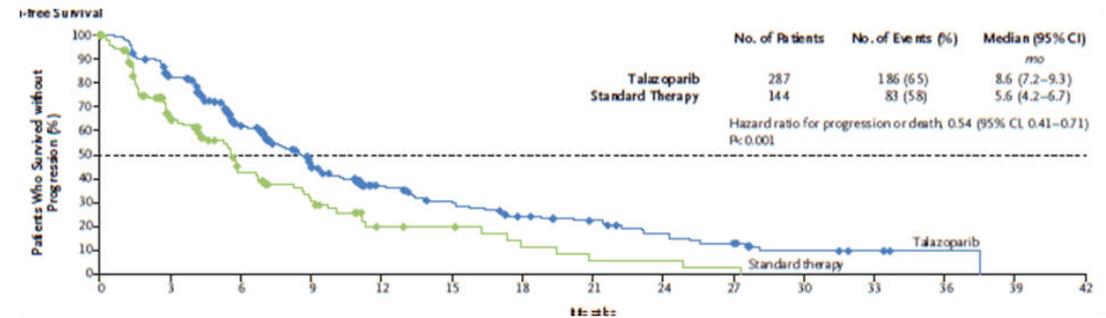
## Olaparib (OlympiAD)<sup>1</sup>

- Population
  - ❑ gBRCA mutation and HER2-
  - ❑ ≤ 2 previous chemo for metastatic disease
- Design: Olaparib vs chemo (capecitabine, eribuline, vinorelbine)



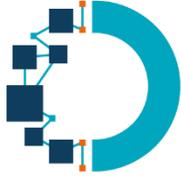
## Talazoparib (EMBRACA)<sup>2</sup>

- Population
  - ❑ gBRCA mutation and HER2-
  - ❑ ≤ 3 previous chemo for metastatic disease
  - ❑ Previous ttt with taxanes and anthracyclines
- Design: Talazoparib vs chemo (capecitabine, eribuline, gemtuzumab, vinorelbine)

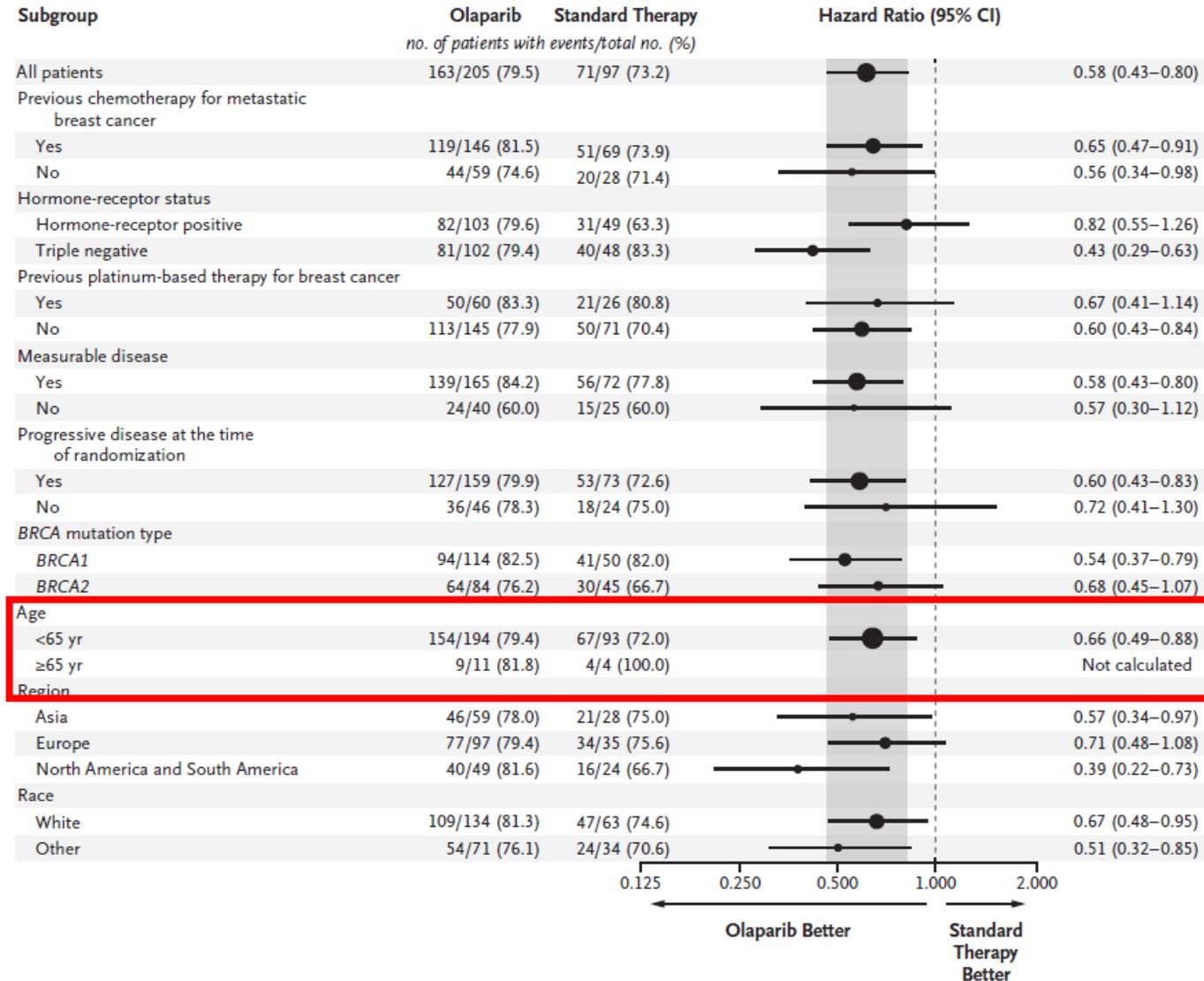


<sup>1</sup>Robson, et al. N Engl J Med, 2017

<sup>2</sup>Litton et al. N Engl J Med 2018



# Etude OlympiAD



<sup>1</sup>Robson, et al. N Engl J Med, 2017  
<sup>2</sup>Litton et al. N Engl J Med 2018

