USE OF REAL WORLD DATA IN THE R&D JOURNEY OF NEW DRUGS

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Disclosure of interest

Suzette Delaloge

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- **Research support (to my institution)**
- AstraZeneca, MSD, BMS, Sanofi, Taiho, Novartis
- European Commission, INCa, Banque des Territoires, Fondation Philanthropia
- **Honoraria for lectures and advisory boards (to my institution)**
- Astra Zeneca, Gilead, Novartis, Elsan, Besins, Sanofi, Exact Sciences, Lilly

- **Travel support**
- Novartis (SPDV)

CASES FOR RWD ANALYSES BY REGULATORS

1 Understand the clinical context

- Disease epidemiology
- Clinical management
- Drug utilisation

2 Support the planning and validity of trials

- Design and feasibility of planned studies
- Representativeness and validity of completed studies

3 (Retrospective) assessment of impact

- Effectiveness and safety studies
- Impact of regulatory actions

FRENCH ESME METASTATIC BREAST CANCER COHORT

ESMÉ
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- 32,598 consecutive metastatic breast cancer patients accrued so far
- 2008 – ongoing
- 19 French Comprehensive Cancer centers
- Over 30% of all MBCs in France

Pérol et al. BJM Open 2019, Ezzalfani PLOS ONE 2021

FRENCH ESME METASTATIC BREAST CANCER COHORT

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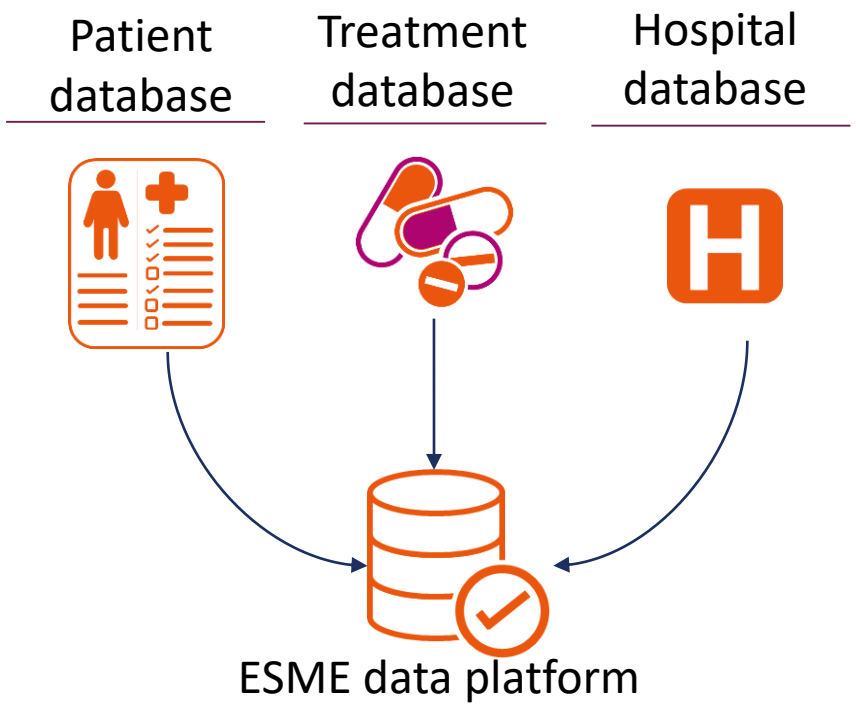

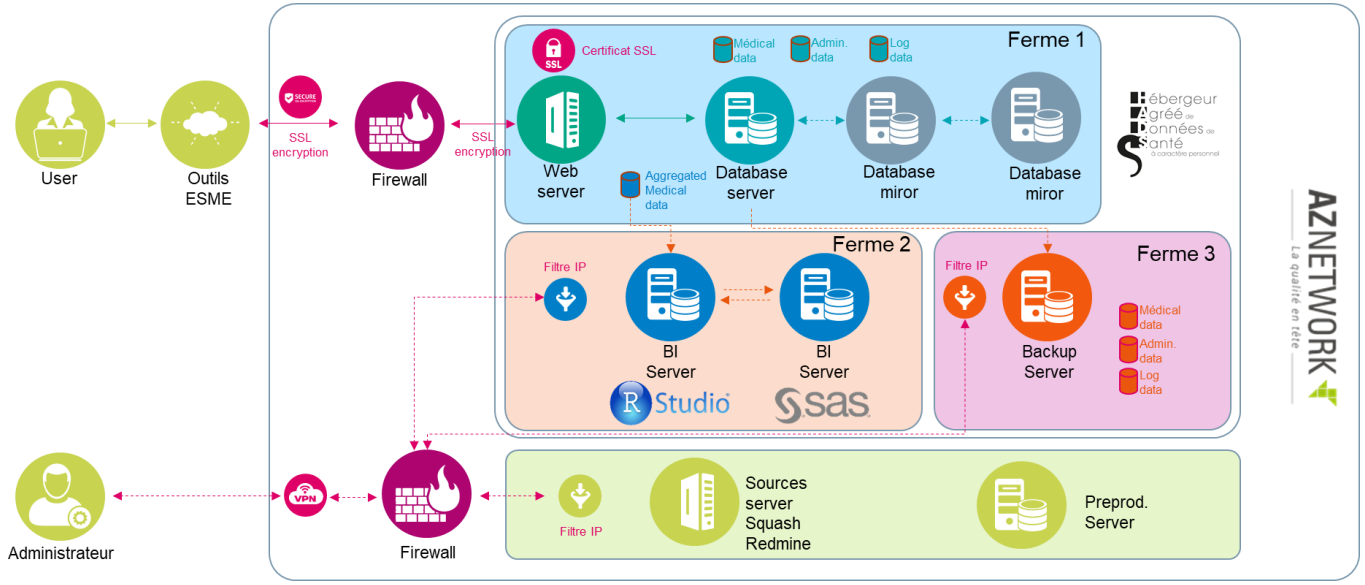

Careful data administration using an Oracle Solution hosted by a « Certified Personal health data hosting » provider

Strictly controlled methodology for data collection and analysis

Pérol et al. BJM Open 2019, Ezzalfani PLOS ONE 2021

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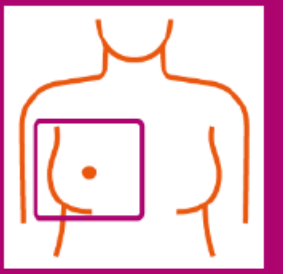
Figures to know about the

2023 metastatic Breast Cancer database



Selection criteria

- Female or male patients
- ≥18 years old
- with mBC whose first metastatic event was treated (completely or partially) in a French Comprehensive Cancer Center

Selection period: 2008-2021

Database extracted in 2023

32 598 patients with **metastatic breast cancer** (mBC)

♂ 281 ♀ 32 317

HR / HER2 profiles

Global IHC profile determined:

- within 3 months from mBC diagnosis or
- at primary tumor if not available at mBC diagnosis

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De novo / relapsed

10 843

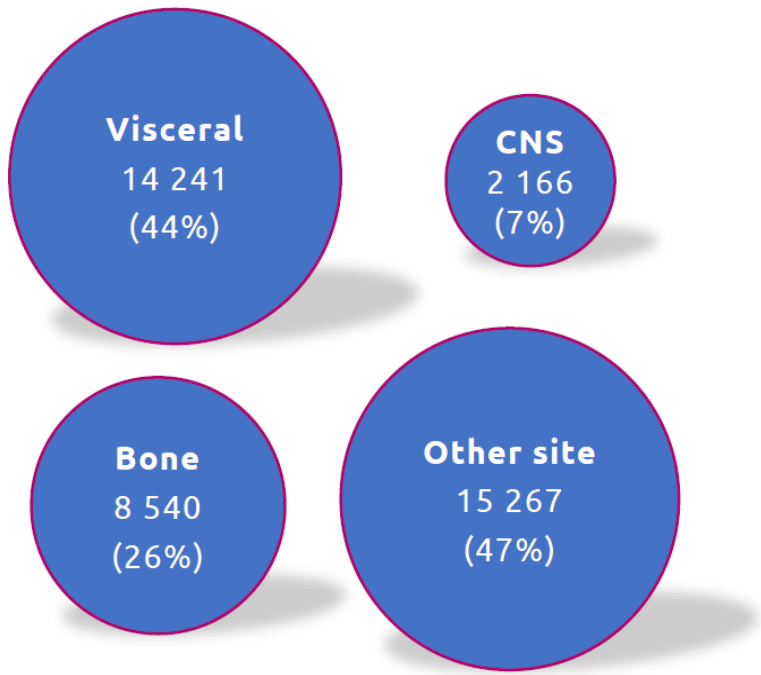
patients with ***de novo*** **mBC**

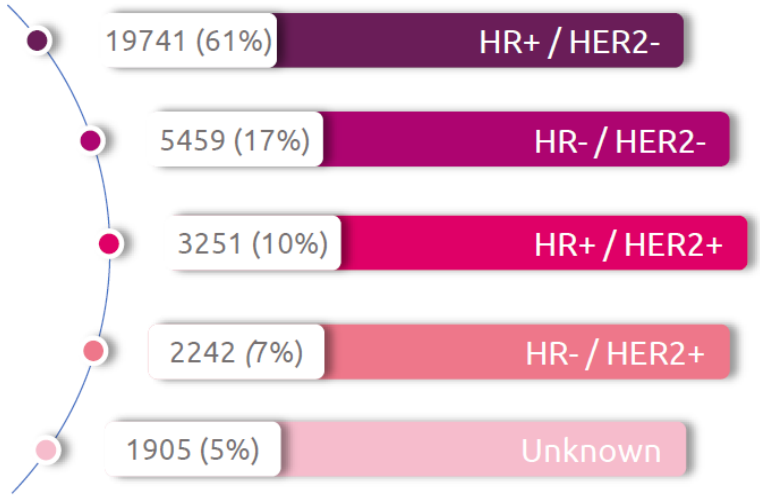
21 755

patients with **relapsed mBC**

Metastatic disease

At mBC diagnosis





BRCA testing

5 845 patients

have undergone ***BRCA*** **testing**

▶ **527** patients with a **germline *BRCA* mutation**

Follow-up

Median follow-up 89.4 months

According to reverse Kaplan-Meier Method

Minimum estimated follow-up

- 36 months for 28 600 patients
- 60 months for 22 900 patients

(Retrospective) assessment of impact

EVOLUTION OF OVERALL SURVIVAL OVER THE PAST 14 YEARS IN ESME-MBC

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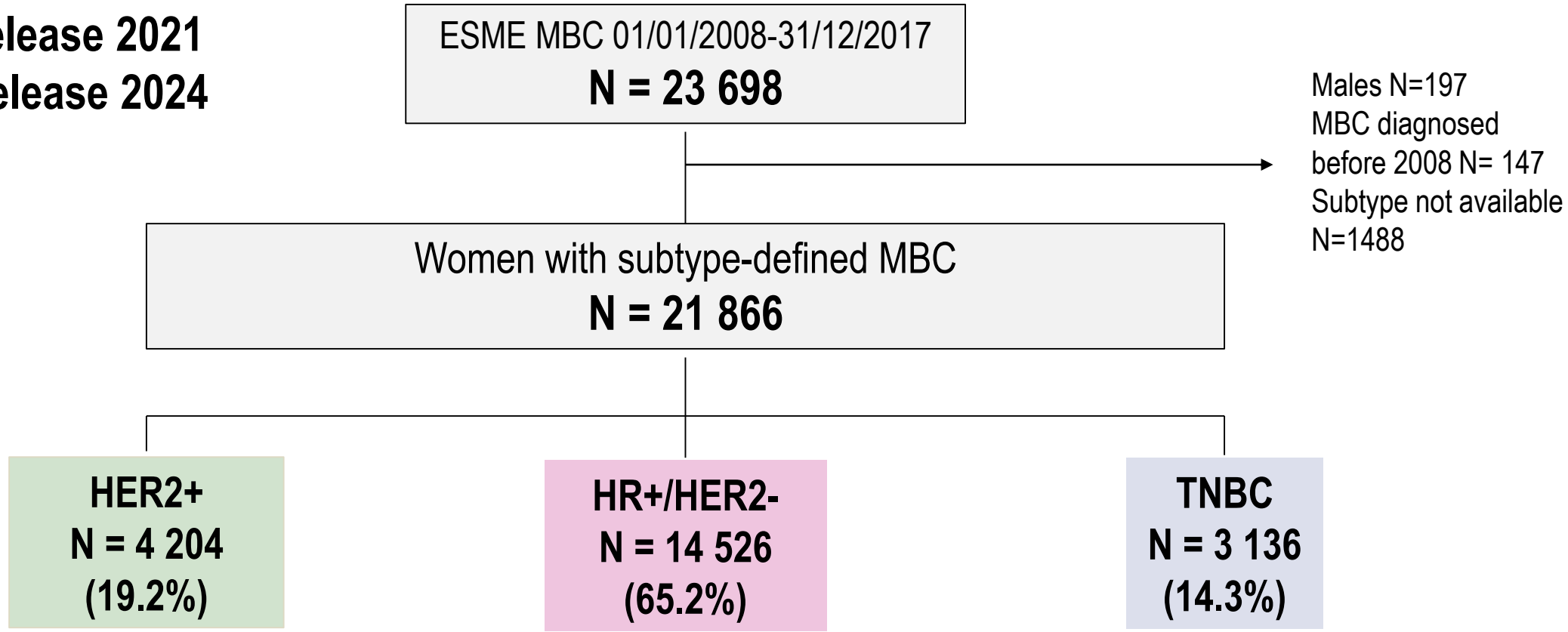
Last release 2021
Next release 2024



HR: Hormone receptor
TNBC: Triple negative breast cancer

Grinda et al ESMO Open 2021

OVERALL SURVIVAL BY SUBTYPE

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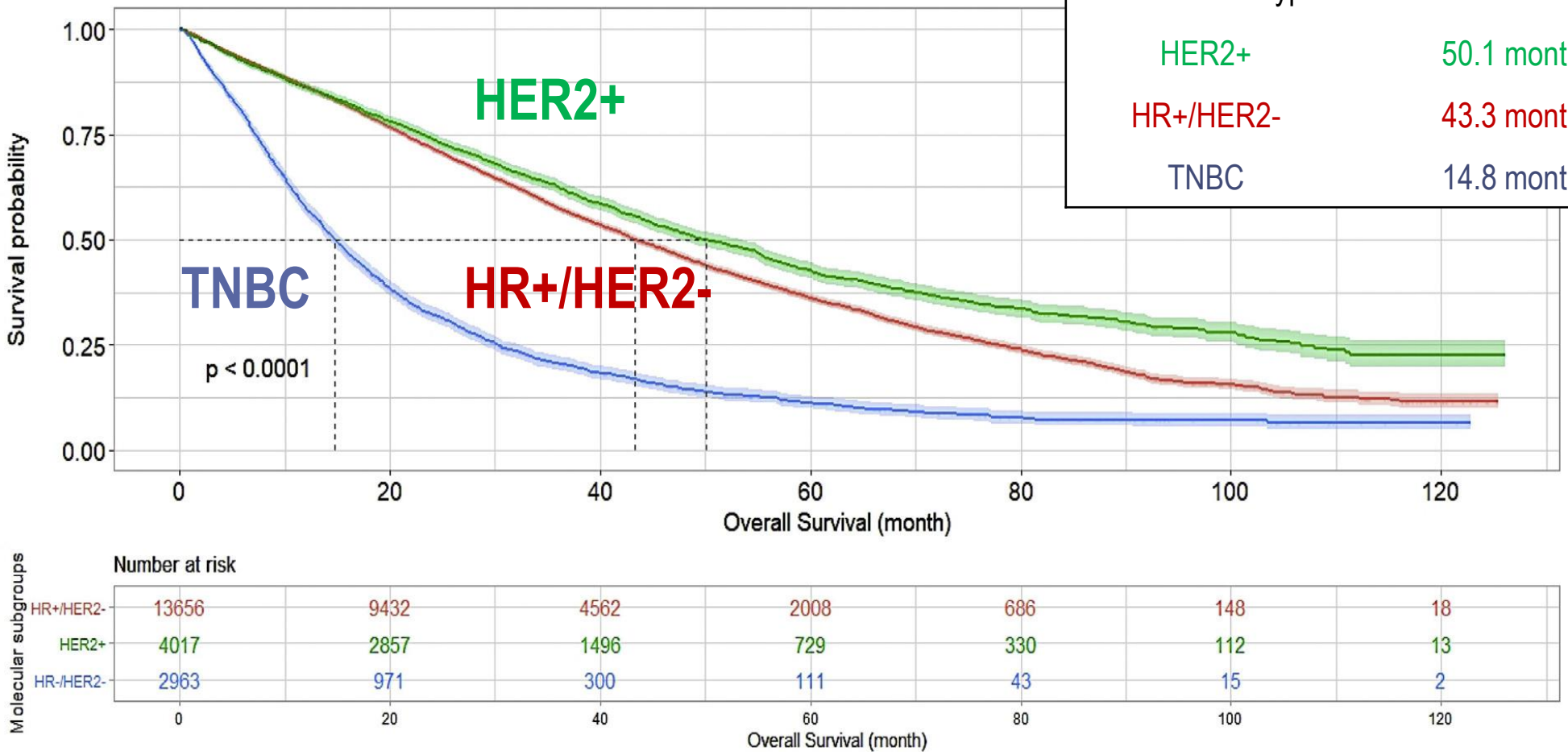
2008-2017 period

Molecular subtype	Median overall survival	95% CI
HER2+	50.1 months	47.6 – 53.1
HR+/HER2-	43.3 months	42.5 – 44.5
TNBC	14.8 months	14.1 – 15.5



Deluche et al. Eur J Cancer 2020

EVOLUTION OF PATIENTS' CHARACTERISTICS AT MBC DIAGNOSIS

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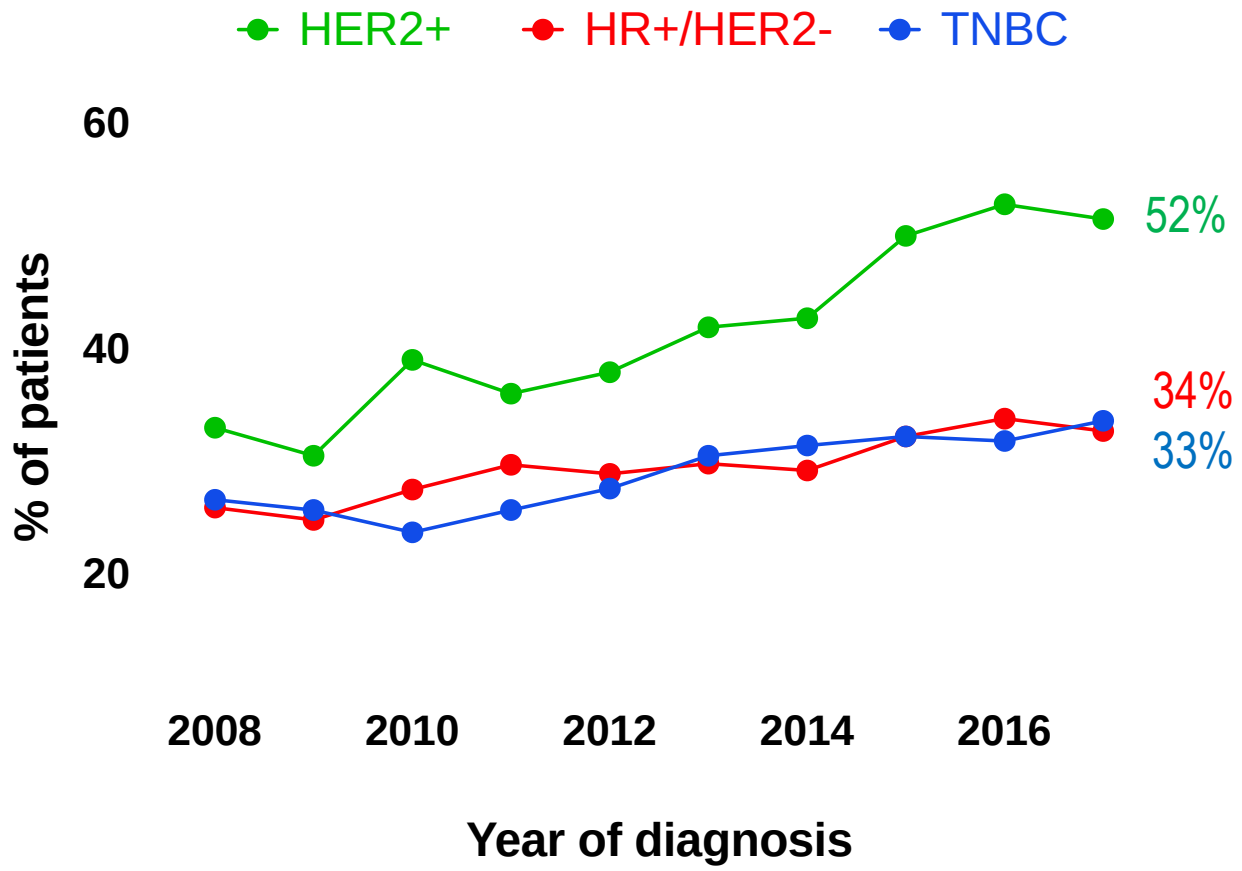
Evolution of the proportion of de novo metastatic breast cancer by year of diagnosis

N= 21 886



The increase of de novo MBCs may be related to:

- → **More patients cured at the localized stage (HER2 +++)**
- → Improved sensitivity of diagnostic tests for better initial staging (all subtypes)

Grinda et al ESMO Open 2021

OUTCOMES IN HER2+ SUBTYPE

Evolution of overall survival in HER2+ subtype by year of diagnosis

Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	39.1 (36.2 - 46.5)
2011	41.1 (35.5 - 48.3)
2013	58.0 (52.0 - 68.4)
2016	NR (NR - NR)

Major improvements in OS by year of diagnosis

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OUTCOMES IN TNBC SUBTYPE

Evolution of overall survival in TNBC subtype by year of diagnosis

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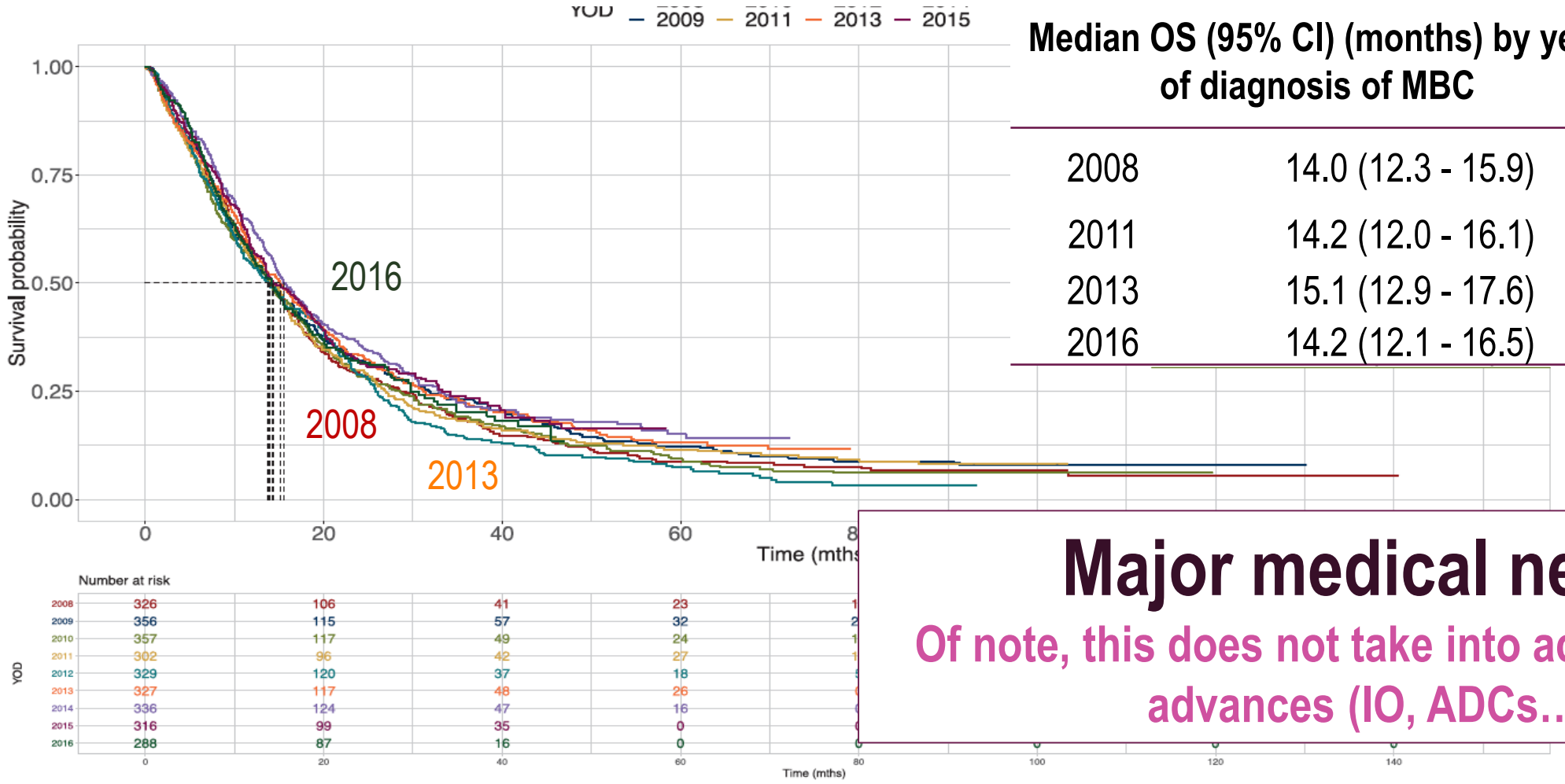


Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	14.0 (12.3 - 15.9)
2011	14.2 (12.0 - 16.1)
2013	15.1 (12.9 - 17.6)
2016	14.2 (12.1 - 16.5)

Major medical need!

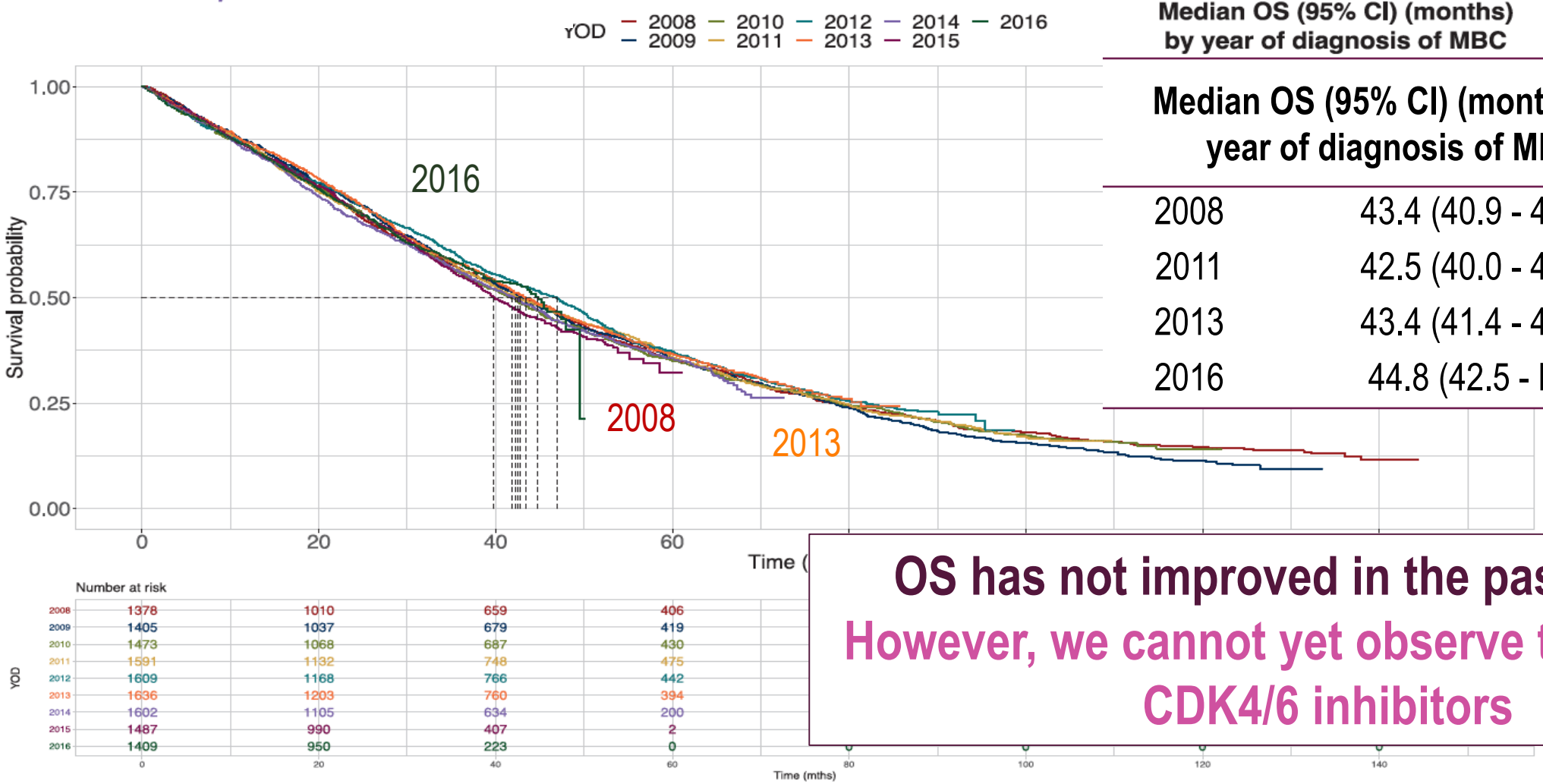
Of note, this does not take into account recent advances (IO, ADCs…)

Grinda et al ESMO Open 2021

OUTCOMES IN HR+/HER2- SUBTYPE

Evolution of overall survival in HR+/HER2+ subtype by year of diagnosis

Based on Kaplan–Meier estimates



Median OS (95% CI) (months) by year of diagnosis of MBC

Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	43.4 (40.9 - 46.5)
2011	42.5 (40.0 - 45.9)
2013	43.4 (41.4 - 46.4)
2016	44.8 (42.5 - NR)

OS has not improved in the past 12 years

However, we cannot yet observe the effects of CDK4/6 inhibitors

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RECEIPT OF NEWLY RELEASED TREATMENTS PER SUBTYPE AND YEAR OF DIAGNOSIS

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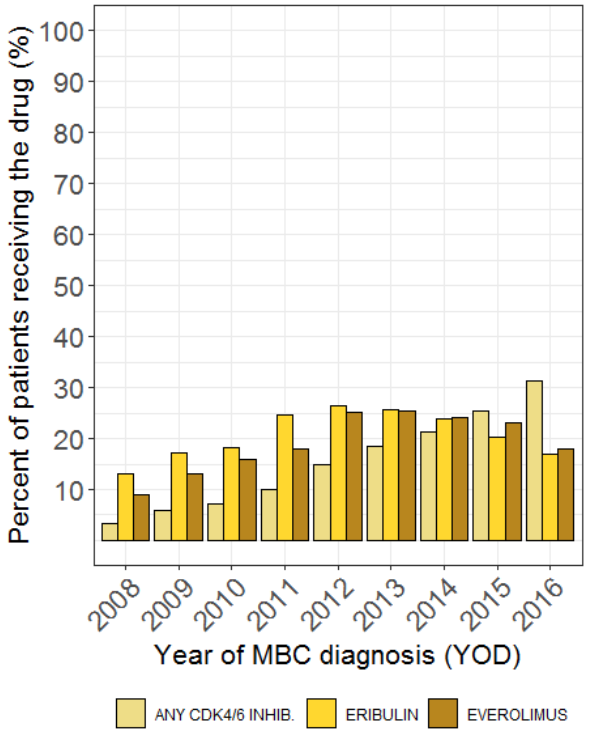
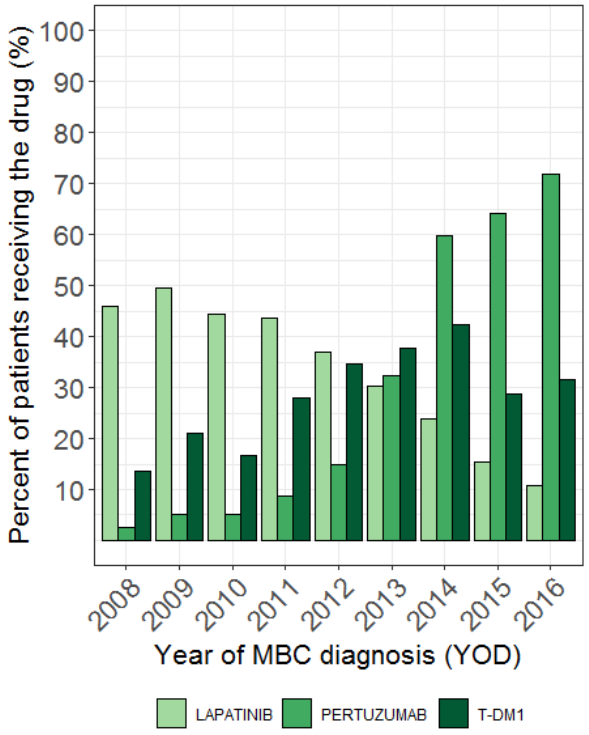
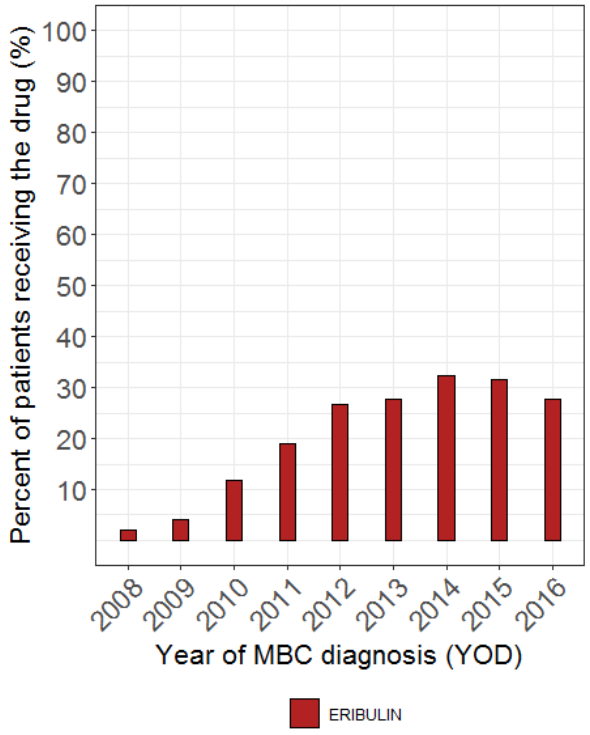
HR+/HER2-



HER2+



TNBC



Any CDK4/6 inh

Eribulin

Everolimus

Lapatinib

Pertuzumab

TDM1

Eribuline

→ More new treatments in HER2 subtype during that period

→ Very high breakthrough of anti-HER2 therapies compared to other new treatments

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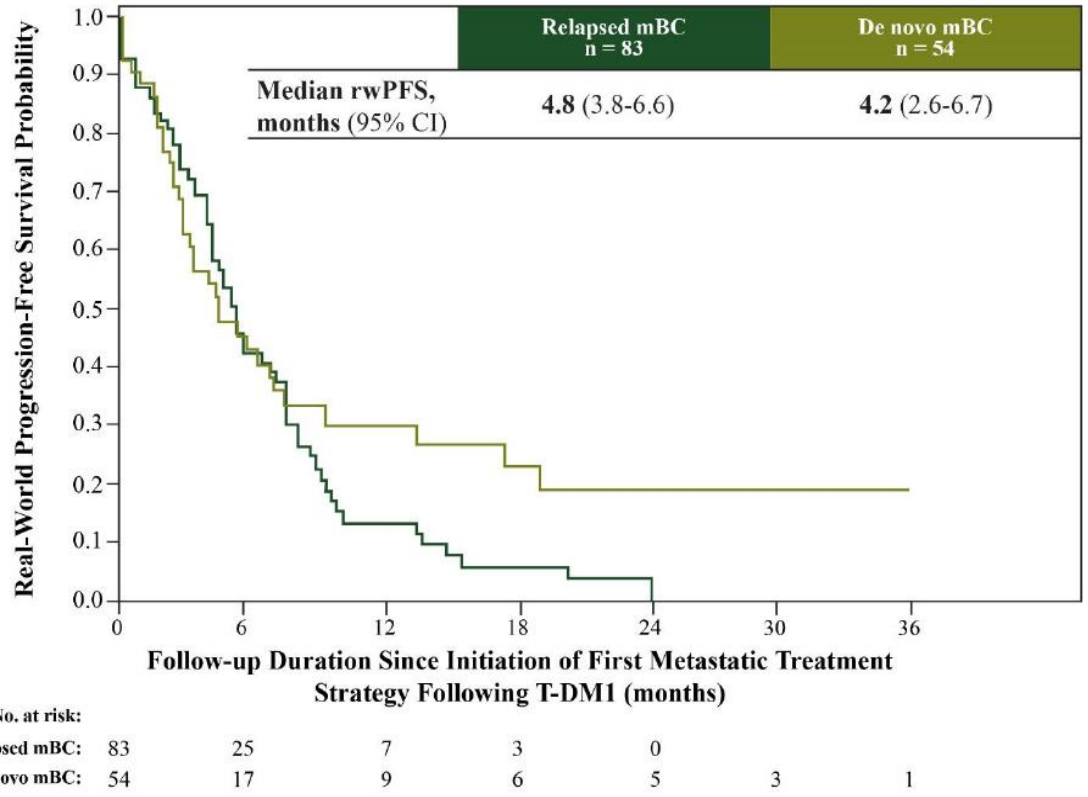
BENCHMARK FOR DESTINY BREAST 01 – TDXD 3RD+ LINE POST TDM1 FOR PATIENTS WITH HER+ MBC: MATCHED COHORT

(UNDER REVISION ESMO RWD AND DIGITAL ONCOL)

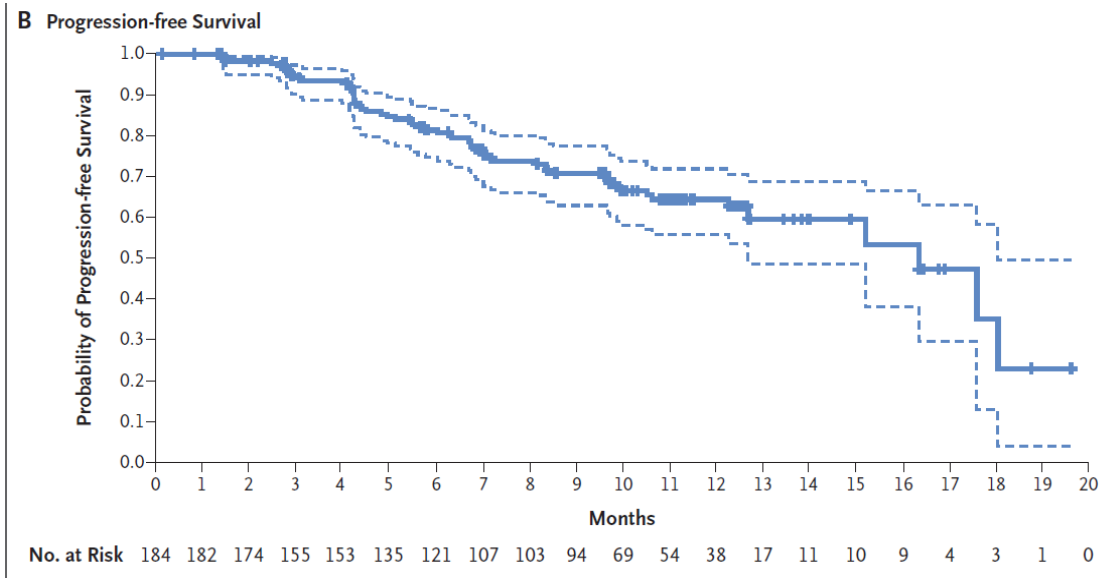
1 Understand the clinical

HER2+ MBC PROGRESSION FREE SURVIVAL in ESME by de novo/not MATCHED



PROGRESSION FREE SURVIVAL IN DESTINY B01 (Modi NEJM 2019)

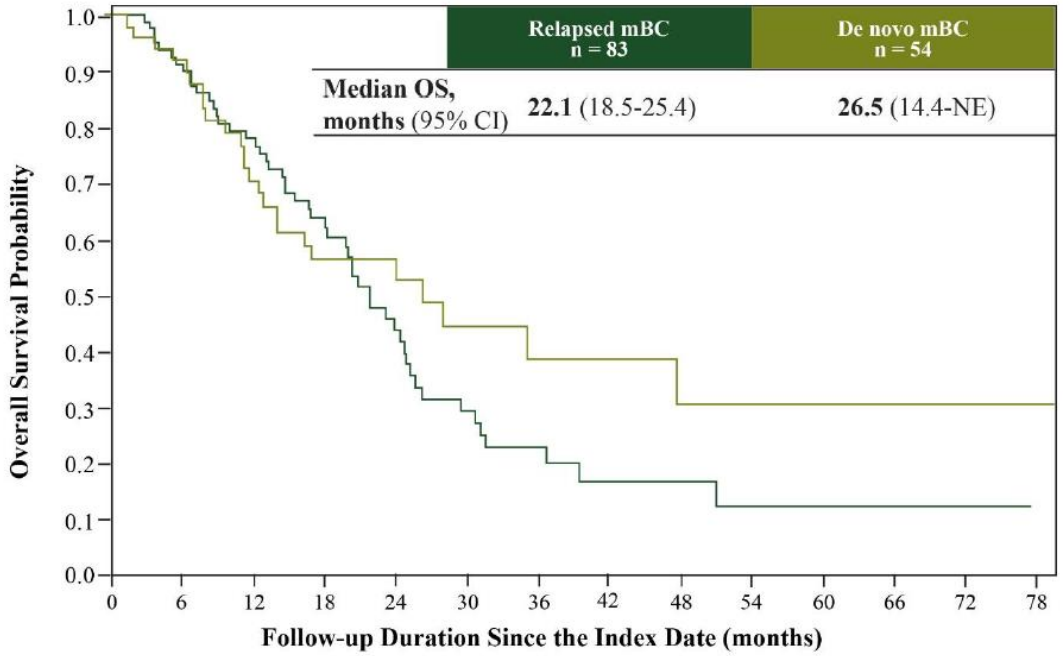
Median progression-free survival 16.4 months (95% CI, 12.-NR)



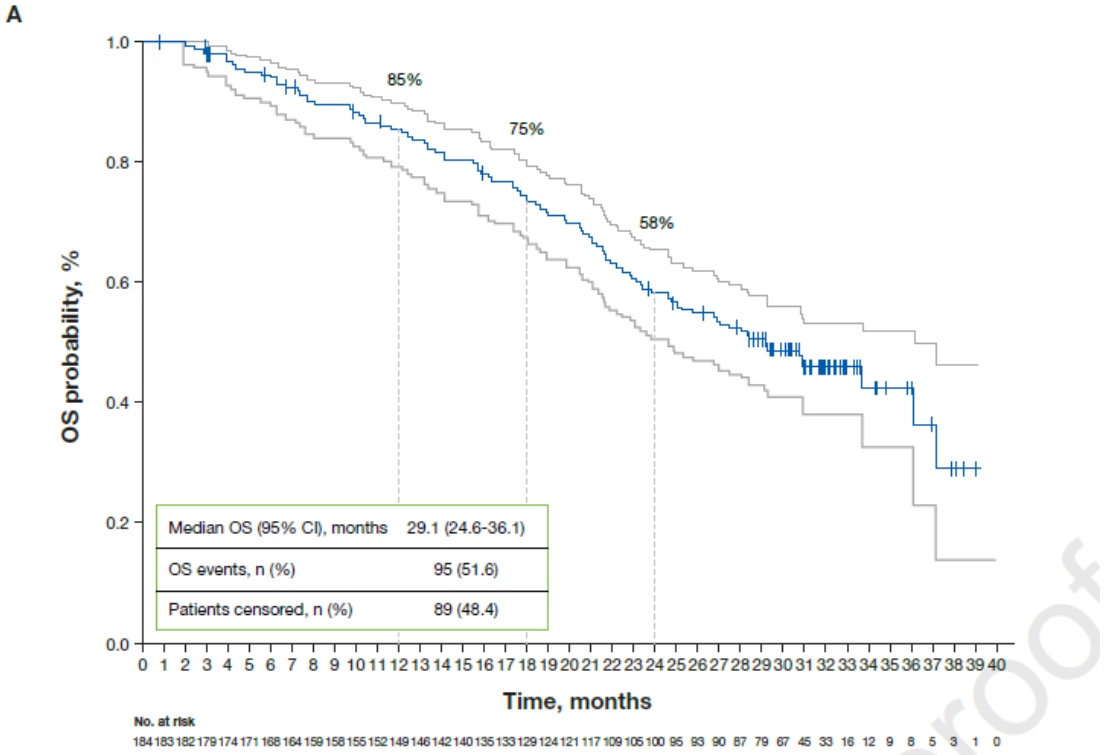
BENCHMARK FOR DESTINY BREAST 01 – TDXD 3RD+ LINE POST TDM1 FOR PATIENTS WITH HER+ MBC: MATCHED COHORT

(UNDER REVISION ESMO RWD DATA AND DIGITAL ONCOL)

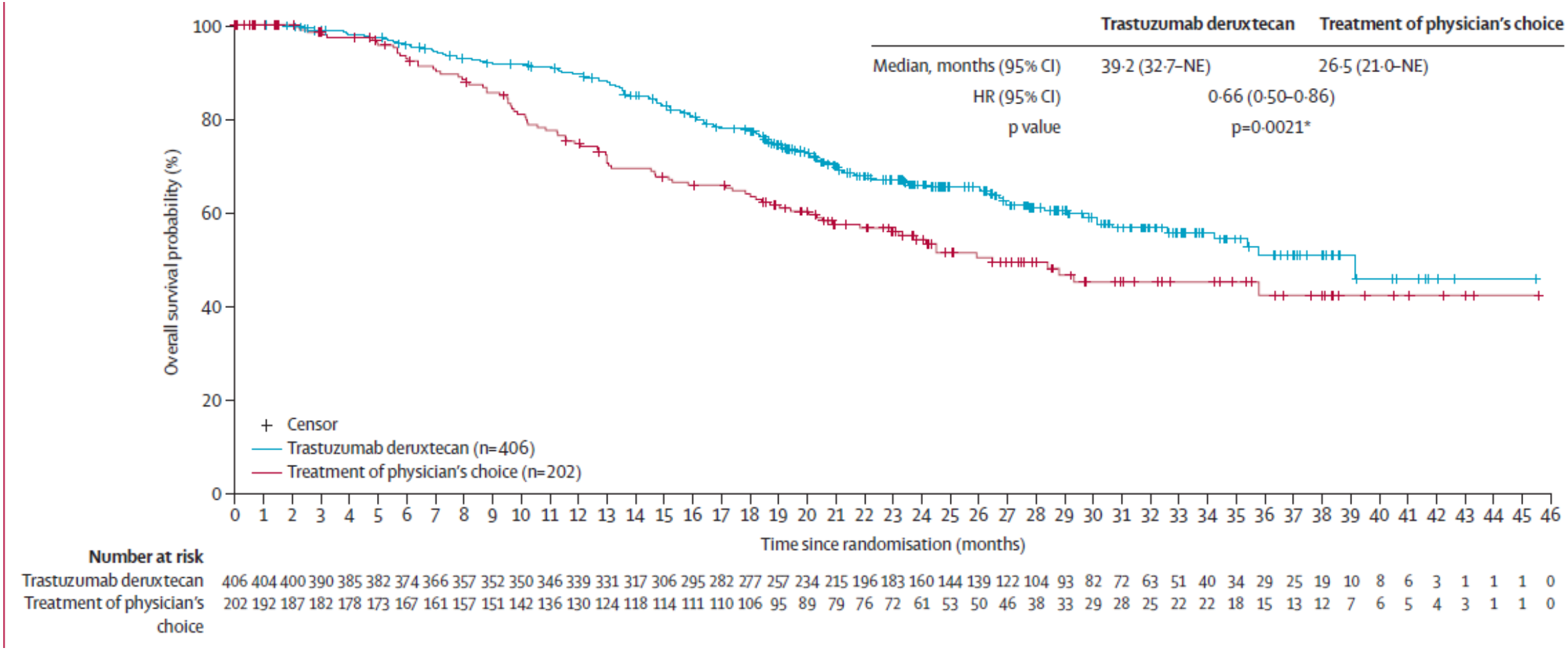
HER2+ MBC OVERALL SURVIVAL in ESME by de novo/not MATCHED



OVERALL SURVIVAL IN DESTINY B01 (Saura Ann Oncol 2023)



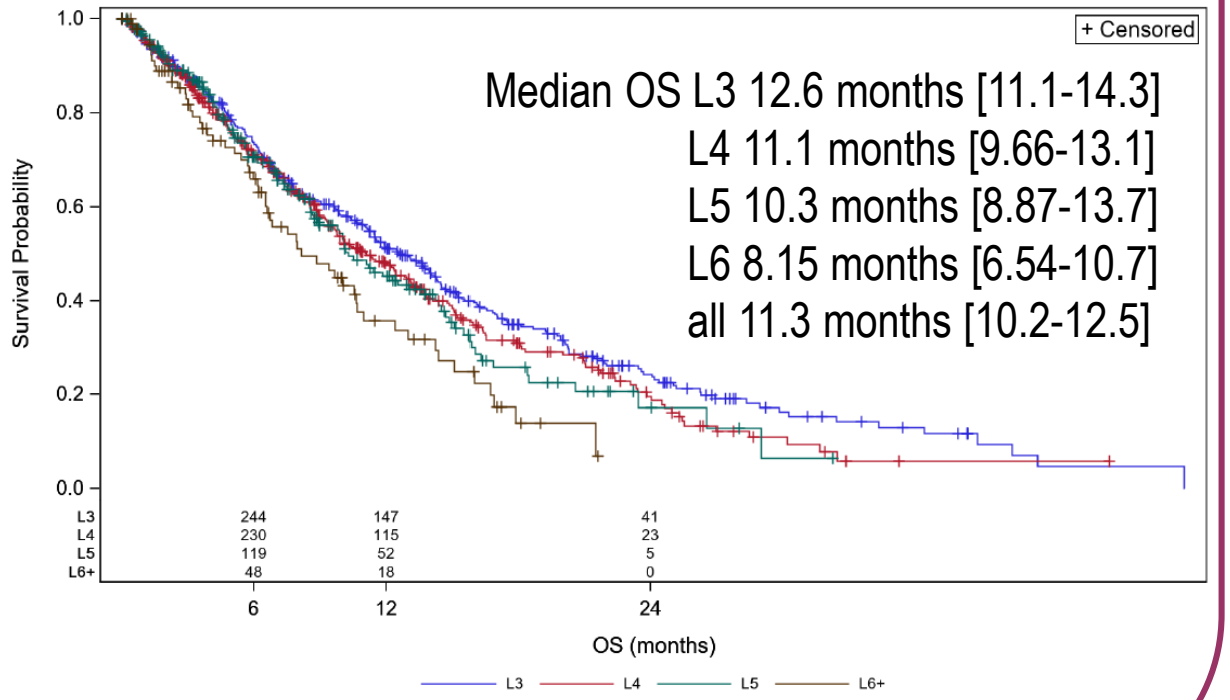
CONFIRMATION IN DESTINY BREAST 02
(ANDRÉ ET AL LANCET 2023)



BENCHMARK FOR TROPICS 2 – SACITUZUMAB GOVITECAN FOR HR+ HER2- MBC, 3RD+ LINE

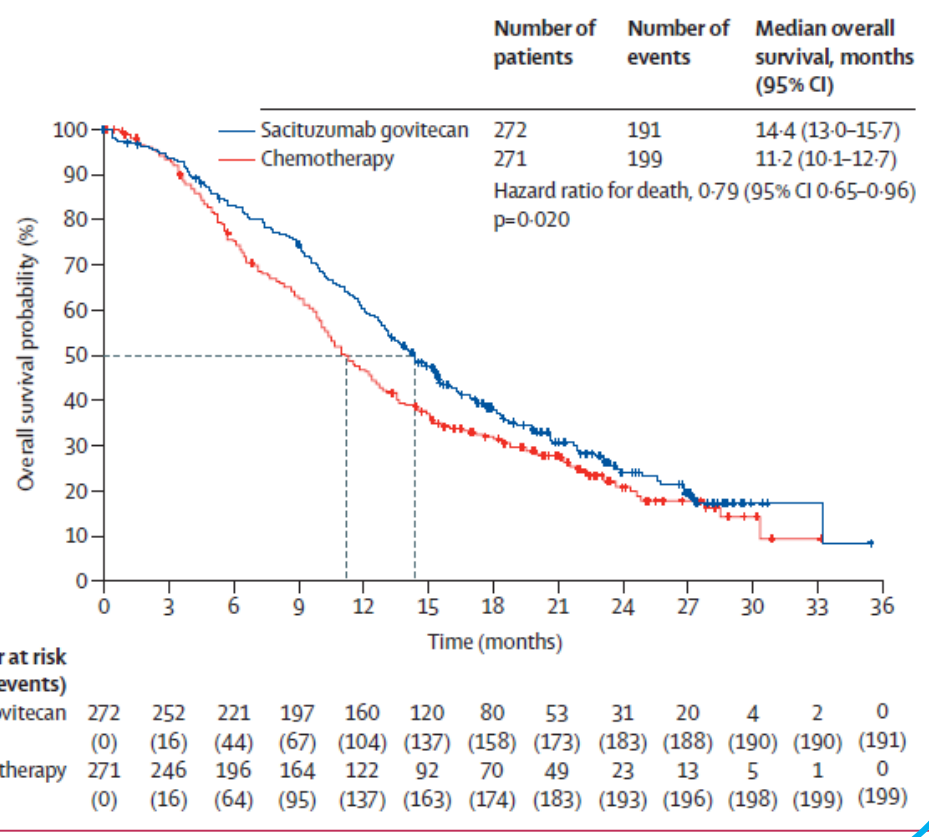
Previous chemotherapy regimens in the metastatic setting, median (IQR)‡	3 (2–3)	3 (2–3)

HR+ HER2- MBC OVERALL SURVIVAL by index line 3+ in ESME



Data extracted from ESME CSM Data Platform on 12-FEB-2021

OVERALL SURVIVAL IN TROPICS 2 Rugo et al Lancet 2023



BENCHMARK FOR TROPICS 2 – SACITUZUMAB GOVITECAN FOR HR+ HER2- MBC, 3RD+ LINE

Progression-free survival by index line 3 and more in ESME

Table 6: Description of PFS according to index line

			L3 (N=363)	L4 (N=404)	L5 (N=235)
Patient's status		Nobs	363	404	235
		Not available	0	0	0
	Alive without progression	n (%)	39 (10.7%)	60 (14.9%)	45 (19.1%)
	Progression including death	n (%)	324 (89.3%)	344 (85.1%)	190 (80.9%)
PFS median from index line (months): x [95%CI]		Median [95%CI]	3.58 [3.09 - 3.94]	3.42 [3.22 - 4.07]	3.25 [2.96 - 3.84]
PFS rate (index line): x% [95%CI]	6 months	% [95%CI]	28.2 [23.4 ; 33.0]	30.2 [25.5 ; 34.9]	25.0 [19.0 ; 31.1]
	12 months	% [95%CI]	10.8 [7.4 ; 14.2]	8.7 [5.5 ; 11.9]	4.2 [1.1 ; 7.4]
	24 months	% [95%CI]	1.9 [0.0 ; 3.8]	1.8 [-0.0 ; 3.5]	3.4 [0.5 ; 6.3]

Progression Free survival in TROPICS 2 Rugo et al LANCET 2023

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

1ST LINE ET + CDK4/6 INHIBITION: STRONG OVERALL SURVIVAL BENEFITS IN CLINICAL TRIALS

	Situation	OS observed
Monaleesa 2 (Hortobagyi NEJM 2022)	Endocrine-sensitive: Letrozole Letrozole + ribociclib	**51.4 months** **63.9 months**
Paloma 2 (Finn ASCO 2022)	Endocrine-sensitive: Letrozole Letrozole + palbociclib	51.2 months 53.9 months
Monarch 3 (ESMO 2022)(**INTERIM)**	Endocrine-sensitive: NSAI NSAI + abemaciclib	**54.5 months** **67.1 months**
Paloma 3 (Turner NEJM 2018, ASCO 2021)	Endocrine-resistant : Fulvestrant Fulvestrant + palbociclib	28.0 months (23.6-34.6) 34.9 months (28.8-40)
Monaleesa 3 (last Neven 2023 exploratory)	Endocrine-mixed : Fulvestrant Fulvestrant + ribociclib	**51.8 months (40.4-61.2)** **67.6 months (59.6 - NA)**
Monarch 2 (Sledge JAMA oncol 2020)	Endocrine-mixed : Fulvestrant Fulvestrant + abemaciclib	**37.3 months** **46.7 months**
Monaleesa 7 (Im NEJM 2019, Lu CCR 2022)	Endocrine-mixed : Letrozole Letrozole + ribociclib	**48 months** **58.7 months**

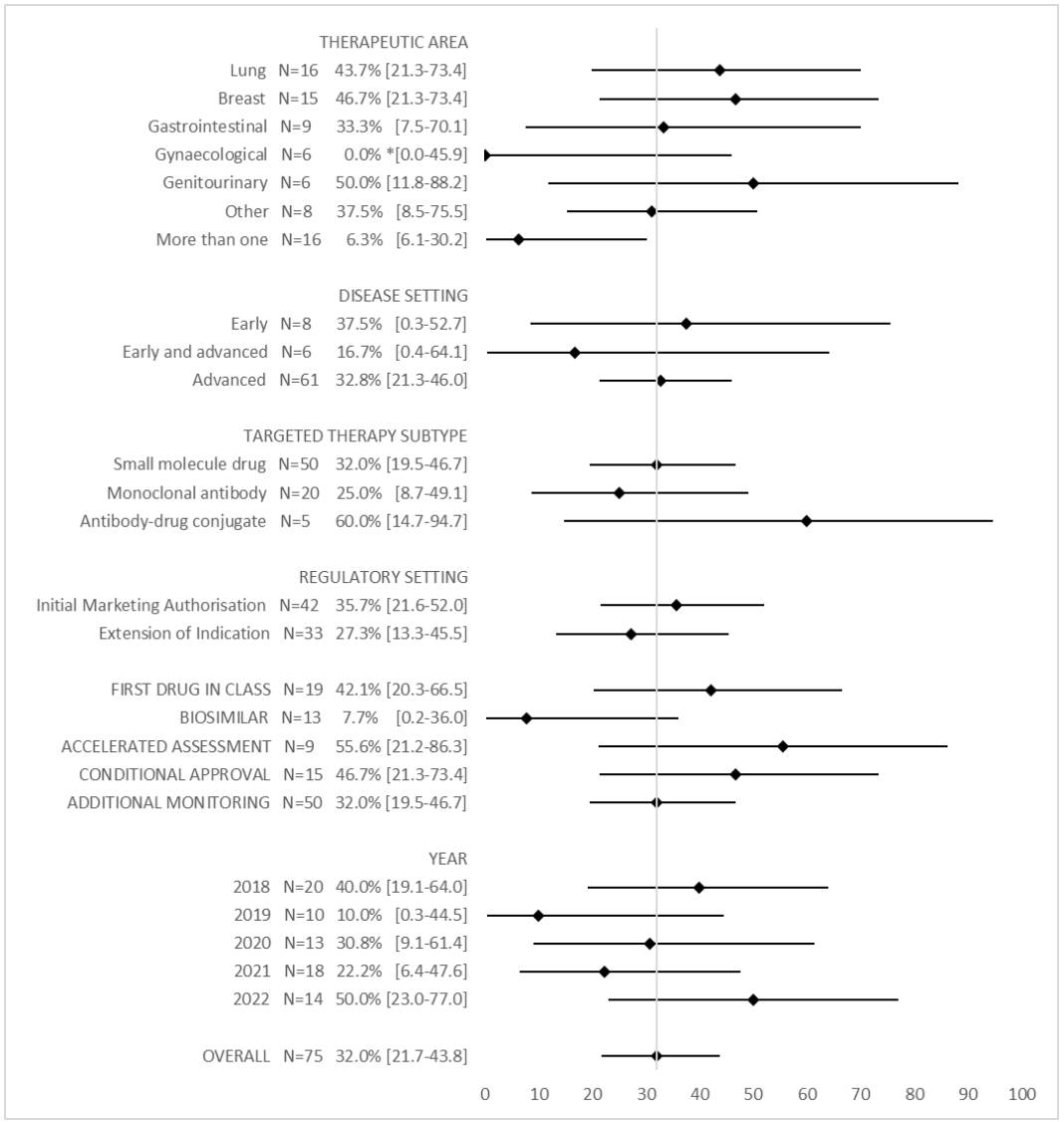
OVERALL SURVIVAL WITH/WITHOUT FIRST LINE PALBO IN RWD

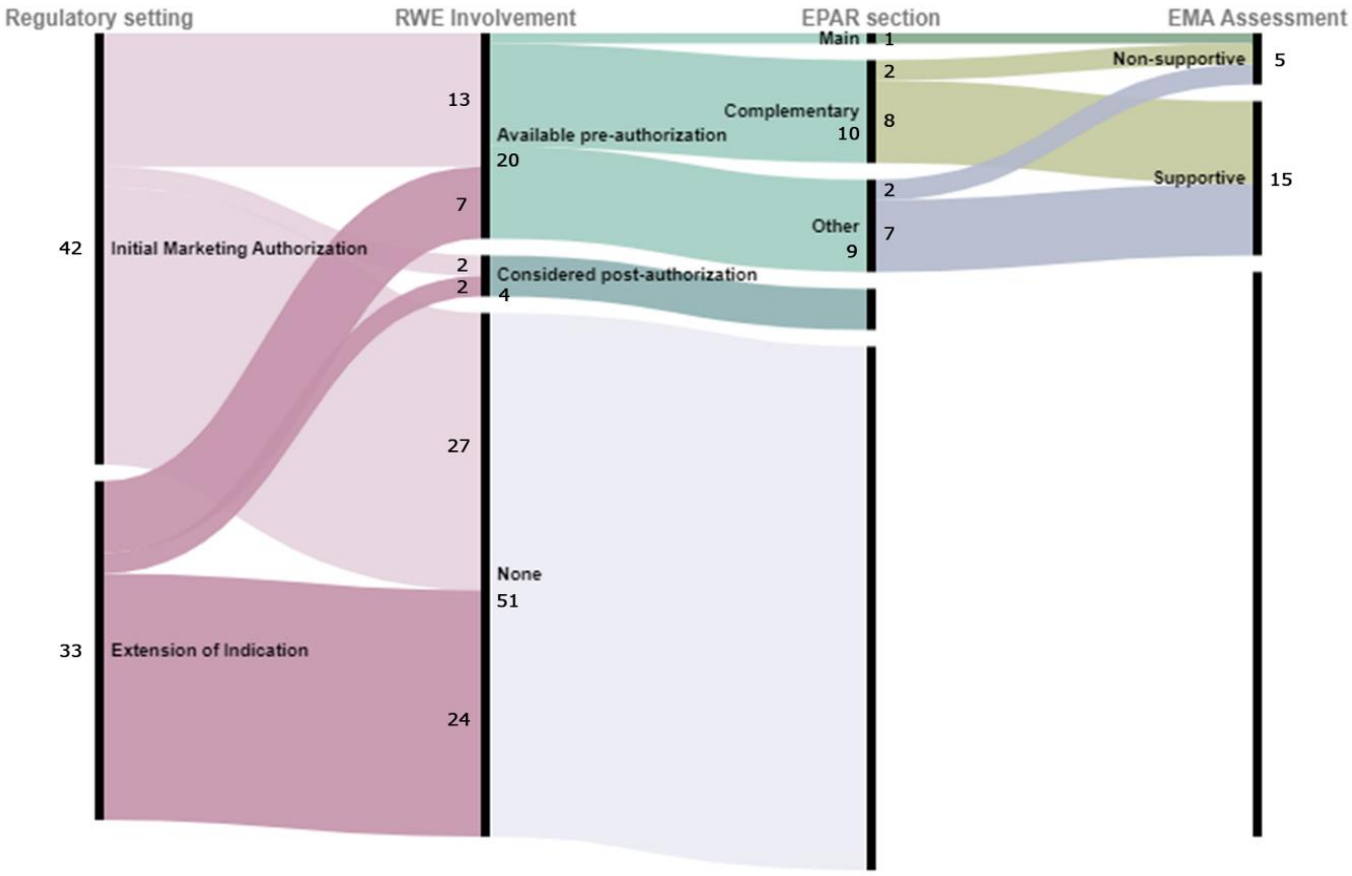
	Situation	OS observed
ESME	HR+ HER2- all comers ET ALONE	39.5 months (95%CI, 38.7-40.3)
ESME (Jacquet 2019 EJC)	Endocrine-sensitive: ET ALONE Chemo +/- ET	**60.78 months** (95% CI, 57.16-64.09) 49.64 months (95% CI, 47.31-51.64)

	Situation	OS observed
Garly et al Acta Oncol 2023	Population-based, Denmark 2017-2020 728 1st line, 423 endocrine-sensitive	OS AI 56.9 months OS fulvestrant 43,6 months
Rugo et al NPJ Breast cancer 2022	Flatiron, insurance-based, USA 2015-2020 N= 2888 patients	OS AI + palbo 49.1 mo [45.2–57.7] OS AI alone 43.2 mo [37.6–48.0]
ESME, unpublished	ESME cohort - 2020	OS AI + Palbo 48.1 mo [46.0 ; NR] Requires more FU

INVOLVEMENT OF RWE IN EMA AUTHORISATIONS FOR TARGETED THERAPIES IN ONCOLOGY IN THE PAST 5 YEARS

Derksen et al (RWD working group ESMO)
Poster ESMO 2023, under submission





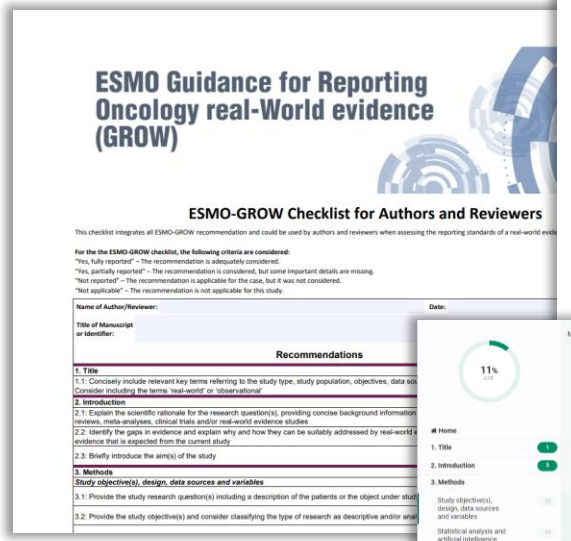
2008-2022
RWD USE IN 32% (24 of 75)
RWE supportive in 15, non supprotive in 5, definitive in 0

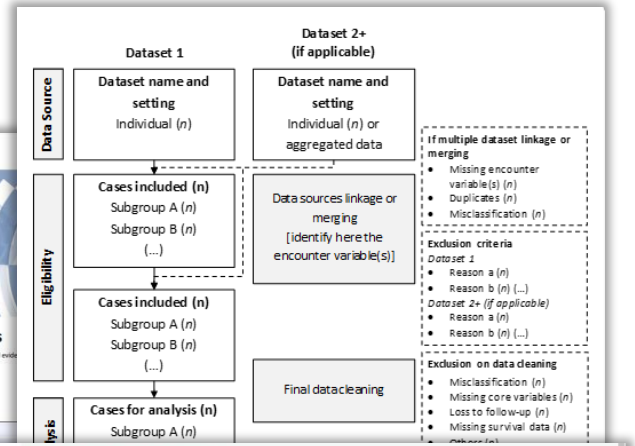
ESMO GROW

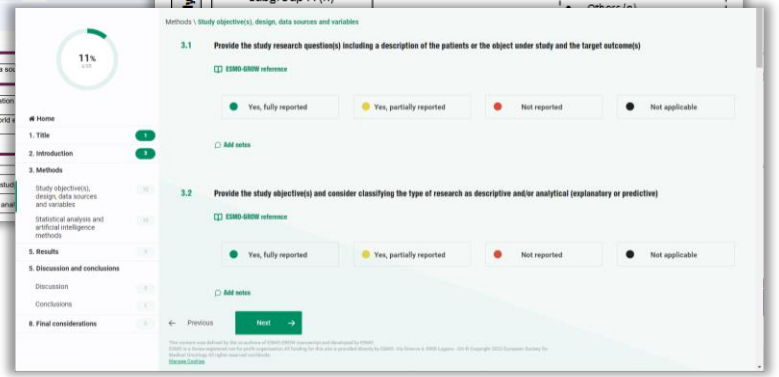
- REPORTING standards
- Checklist informative score

ESMO GUIDANCE FOR REPORTING ONCOLOGY REAL-WORLD EVIDENCE

The first reporting guidance specifically developed for oncology RWE studies







Castelo-Branco L et al. "ESMO Guidance for Reporting Oncology real-World evidence (GROW)". **Ann Oncol** 2023; 34: 10.1016/j.annonc.2023.10.001 and **ESMO Real World Data & Digital Oncol** 2023; 1: 10.1016/j.esmorw.2023.10.001

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