REAL WORLD DATA AND DIGITAL ONCOLOGY

CRACKING THE CODE OF REAL-WORLD DATA REPORTING AND INTERPRETATION IN ONCOLOGY

Karijn Suijkerbuijk and Antonis Valachis

Co-Chairs

ESMO WEBINAR SERIES

INTRODUCTION
Learning Objectives

- To become better equipped for the critical analysis of real-world data and their proper interpretation for clinical practice.

- To familiarize with commonly used concepts and definitions among real-world evidence studies in oncology.

- To recognize common biases in real-world evidence studies and how they can impact the interpretation of study results.

- To understand the importance and benefits of structured reporting of real-world data.

INTRODUCTION

Programme

	23 October 2024

5 min	**Welcome and introduction** Karijn Suijkerbuijk and Antonis Valachis
20 min	**Interpreting real-world data in clinical practice: what clinicians need to know and how reporting guidelines can be helpful** Diogo Martins-Branco
20 min	**Common biases in real-world evidence studies, and how to mitigate them?** David Perol
15 min	**Live Q&A and Discussion** All speakers

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REAL WORLD DATA AND DIGITAL ONCOLOGY

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INTERPRETING REAL-WORLD DATA IN CLINICAL PRACTICE

What clinicians need to know and
how reporting guidelines can be helpful

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DECLARATION OF INTERESTS

Diogo Martins-Branco

Personal financial interests: Full time employment at ESMO since September 1, 2023

Institutional financial interests (funding to *Institut Jules Bordet* as medical research fellow/medical advisor):
Eli Lilly, F. Hoffmann-La Roche Ltd., and Novartis (before September 1, 2023)

Non-financial interest: Board member of *Associação de Investigação e Cuidados de Suporte em Oncologia*

The content of this presentation and opinions expressed do not reflect formal positions of ESMO.

HOW OFTEN IN YOUR CLINICS DO YOU HAVE TO TREAT PATIENTS FOR WHOM YOU DON'T HAVE CLINICAL TRIAL EVIDENCE TO FULLY GUIDE YOUR DECISION?

7 out of

100

patients with cancer participate in therapeutic clinical trials

Unger JM, Shulman LN, Facktor MA, et al. J Clin Oncol. 2024 Jun 20;42(18):2139-2148
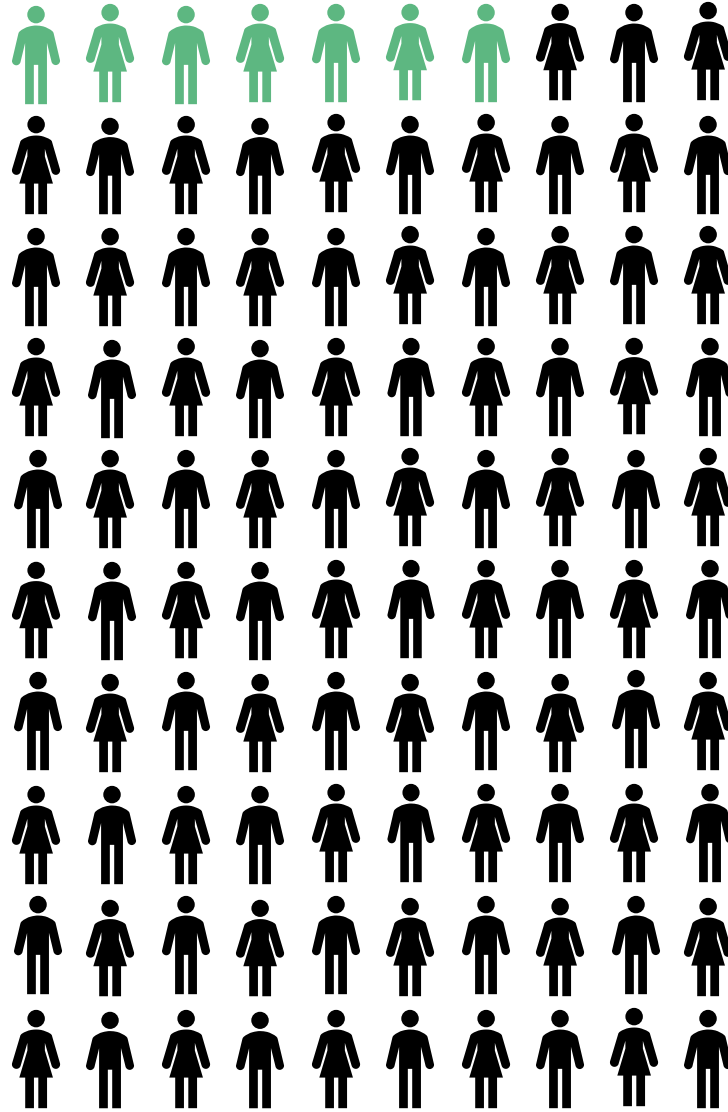
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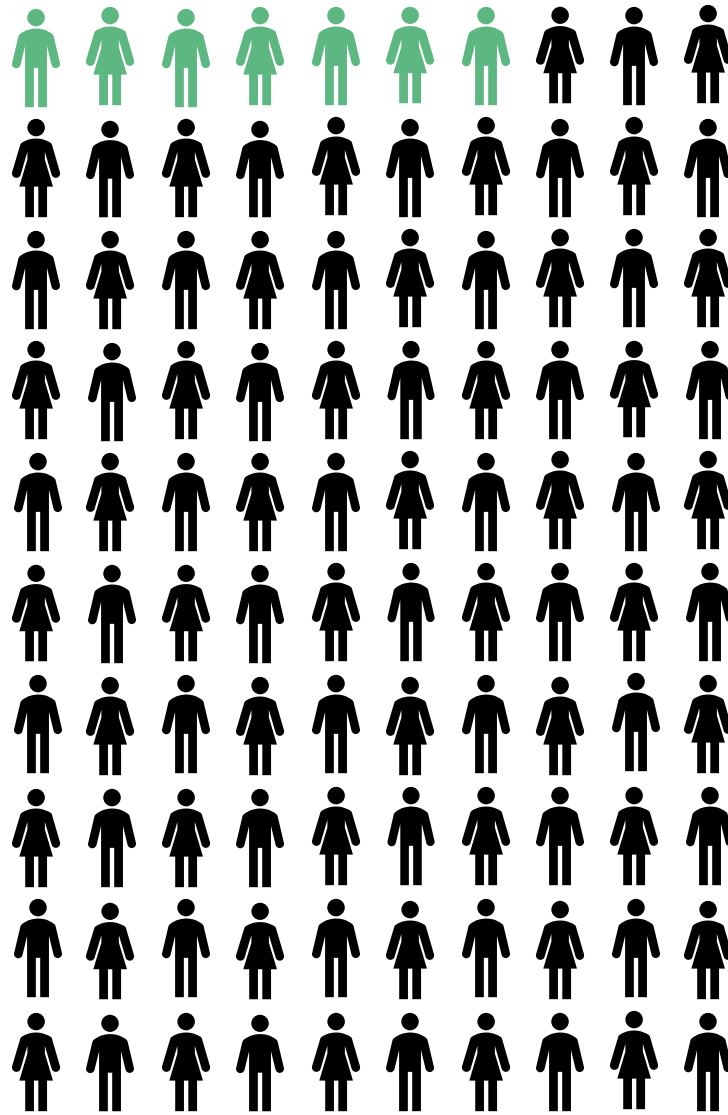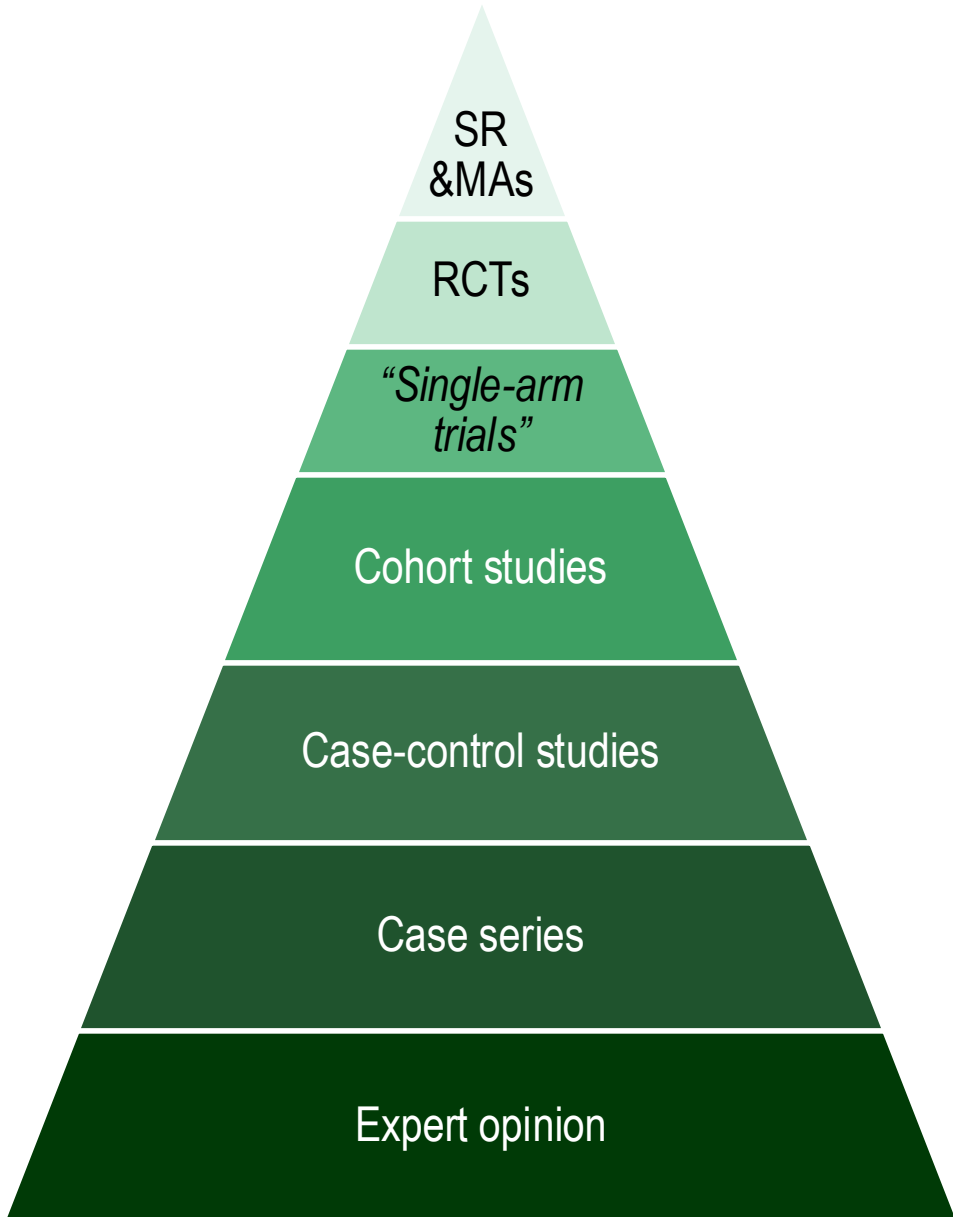# 7 out of 100

patients with cancer participate in therapeutic clinical trials
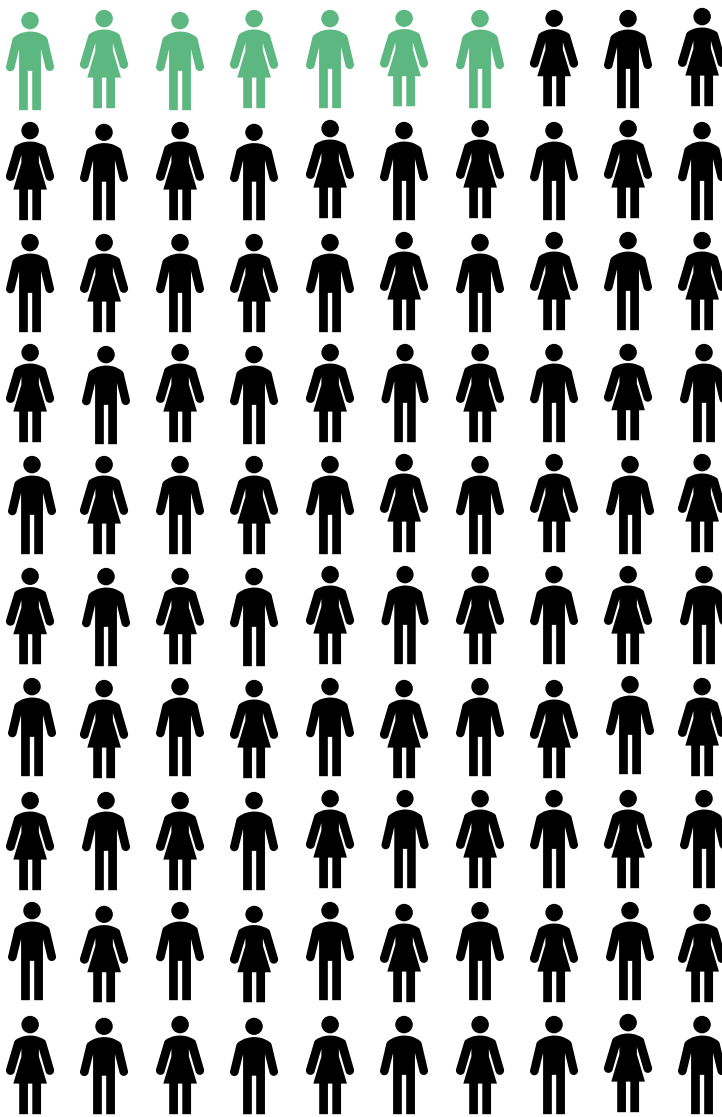
Unger JM, Shulman LN, Facktor MA, et al. J Clin Oncol. 2024 Jun 20;42(18):2139-2148

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RCTs, randomised controlled trials
SR&MAs, systematic review with meta-analysis

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Pyramid levels (top to bottom):

- SR &MAs
- RCTs
- "Single-arm trials"
- Cohort studies
- Case-control studies
- Case series
- Expert opinion

Clinical practice guidelines
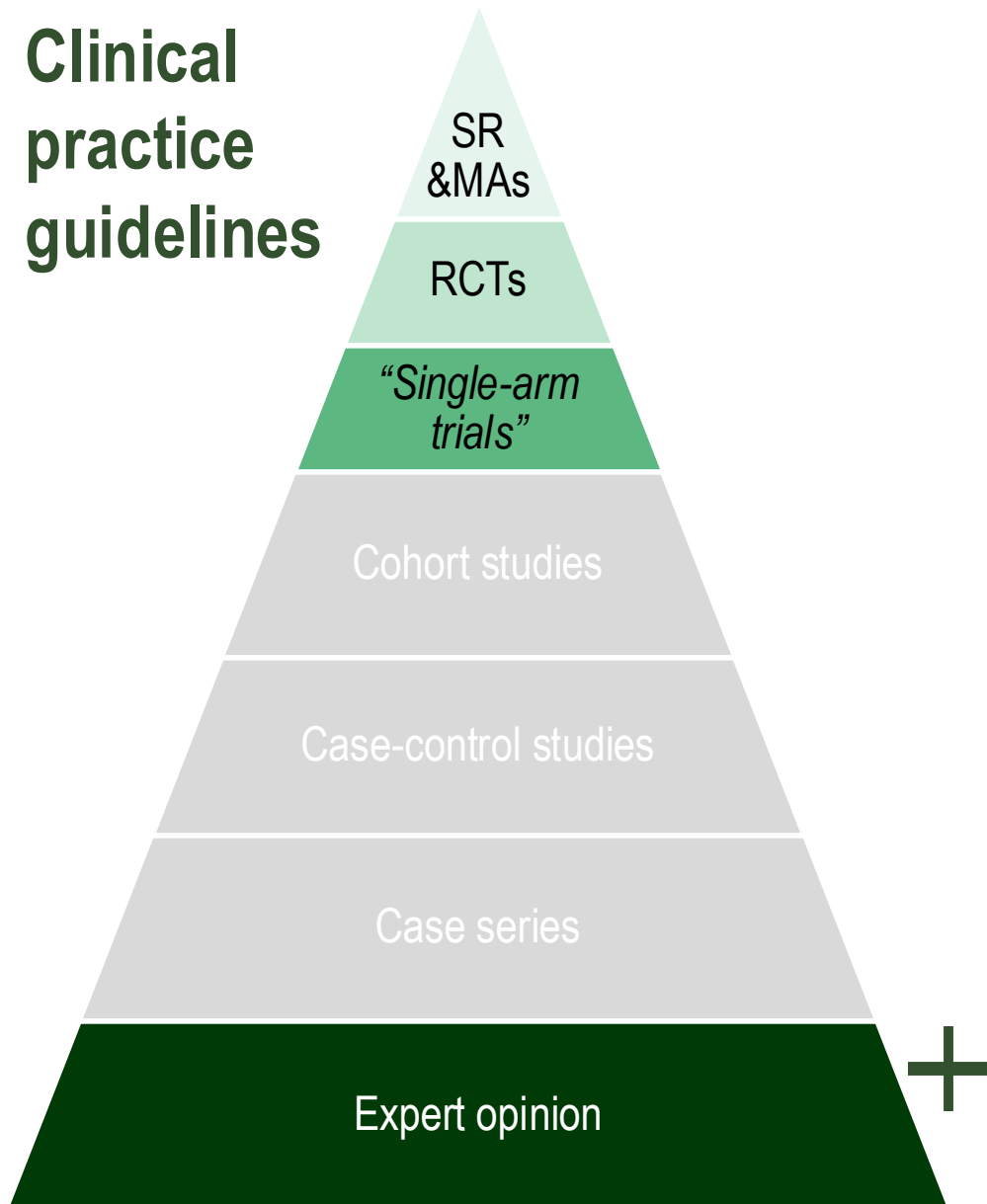
- SR &MAs
- RCTs
- *"Single-arm trials"*
- Cohort studies
- Case-control studies
- Case series
- Expert opinion

REAL WORLD DATA AND DIGITAL ONCOLOGY

RCTs, randomised controlled trials
SR&MAs, systematic review with meta-analysis

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REAL WORLD DATA AND DIGITAL ONCOLOGY

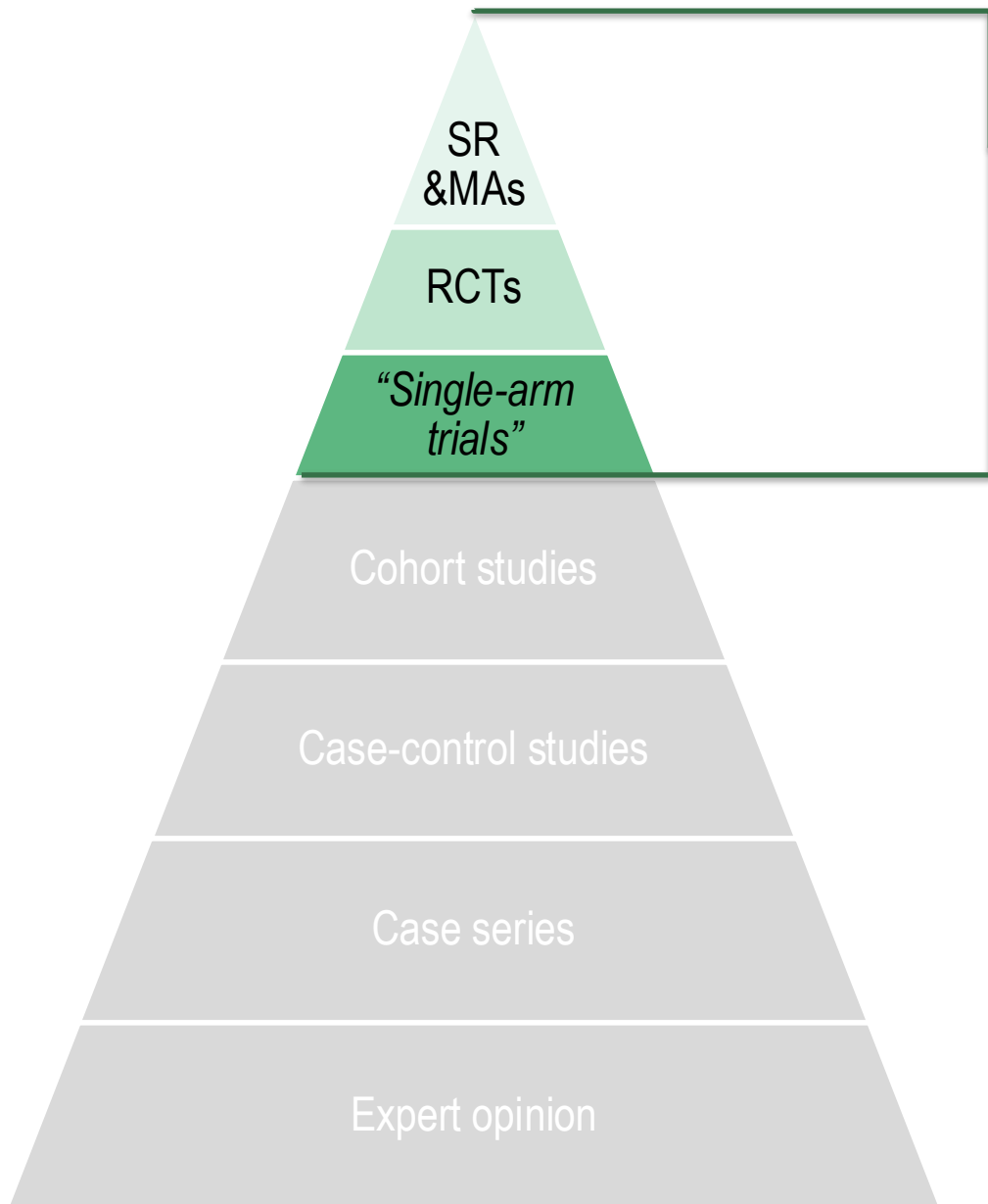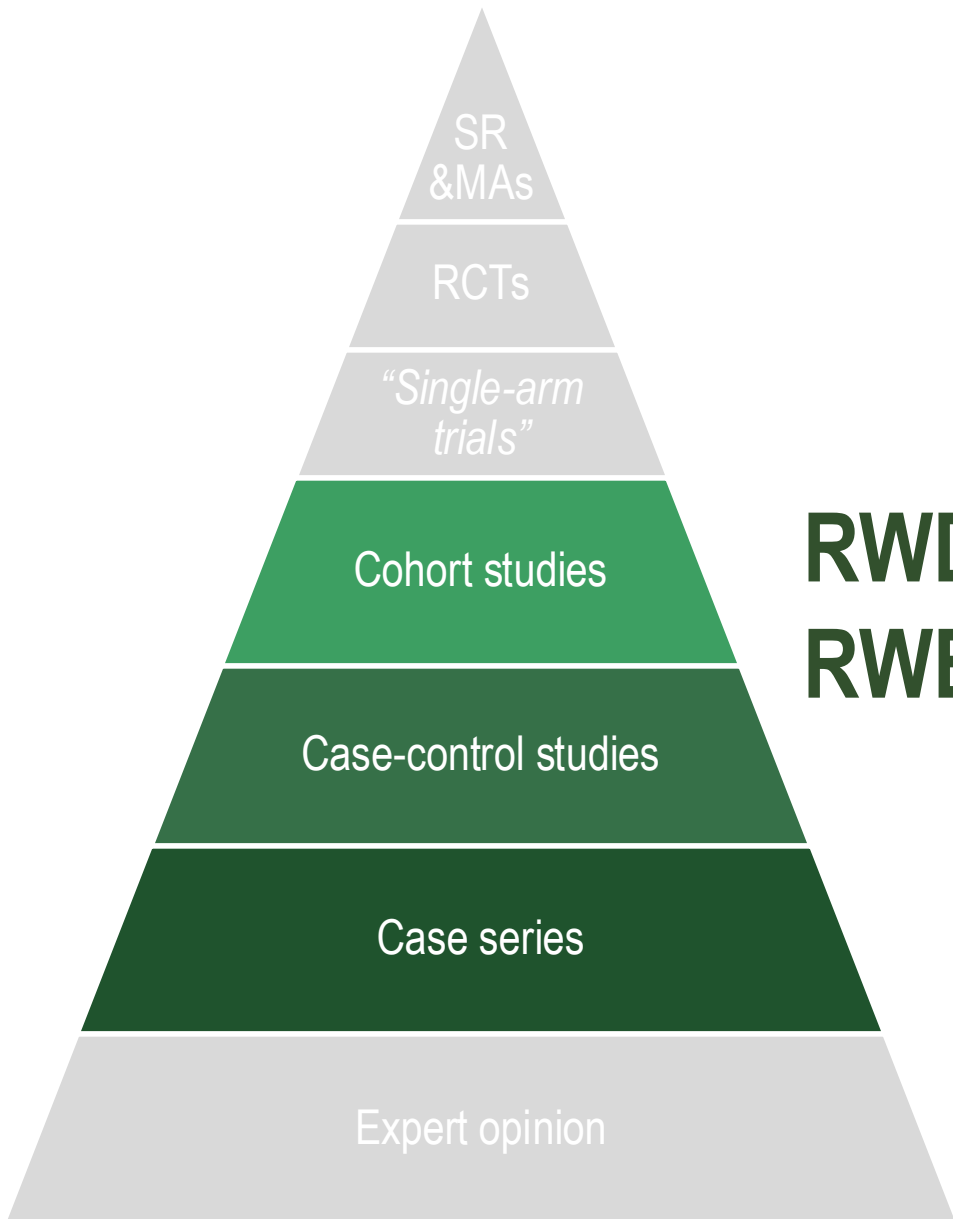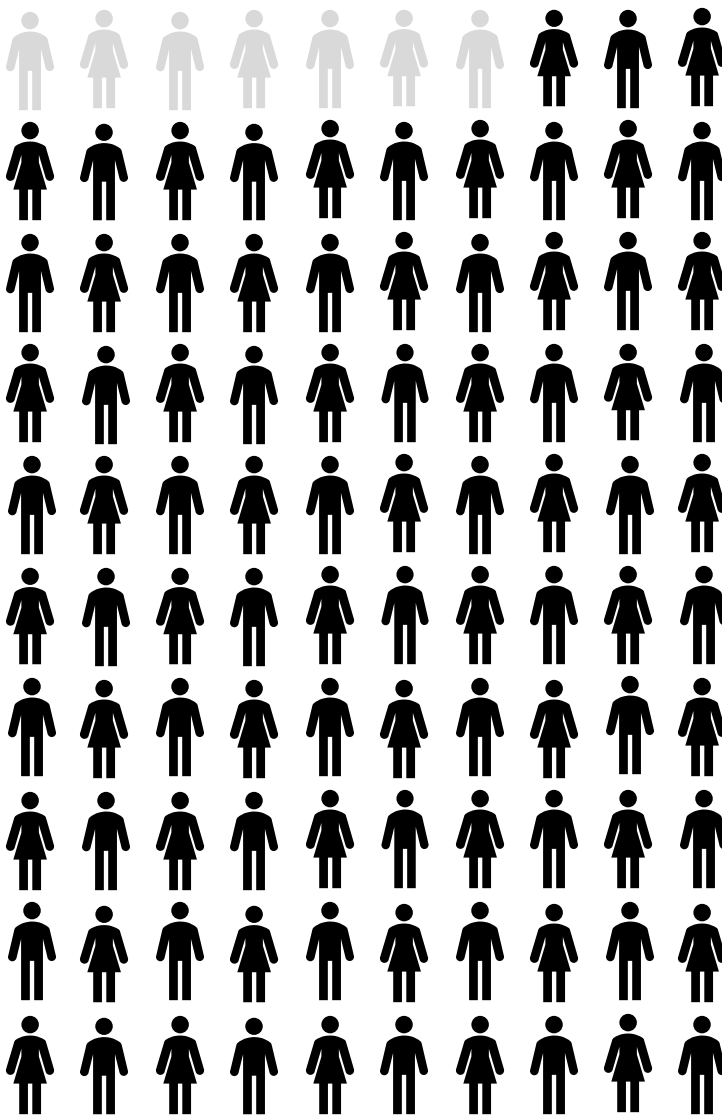RCTs, randomised controlled trials
SR&MAs, systematic review with meta-analysis

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REAL WORLD DATA AND DIGITAL ONCOLOGY

RCTs, randomised controlled trials
SR&MAs, systematic review with meta-analysis

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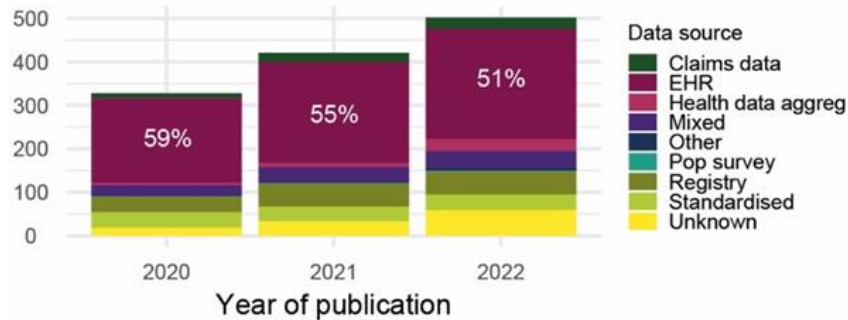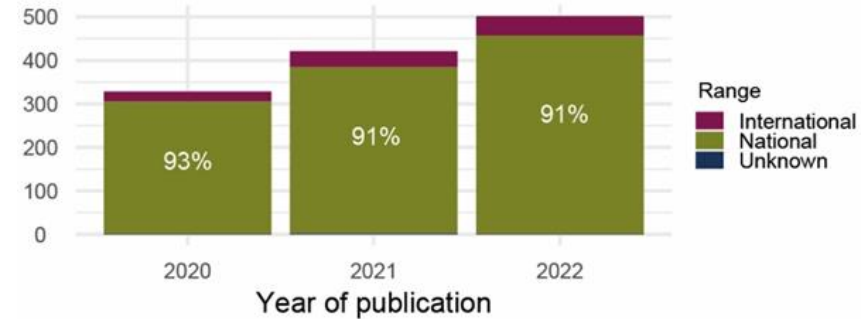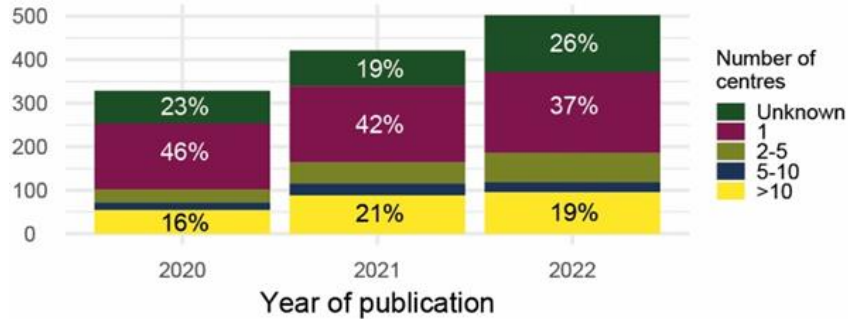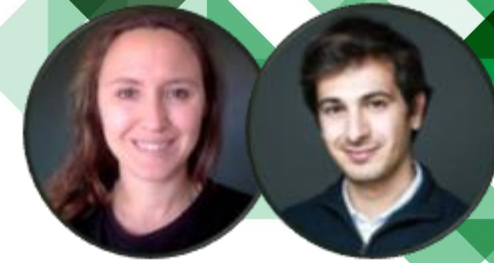
Half of studies were conducted in *Asia*
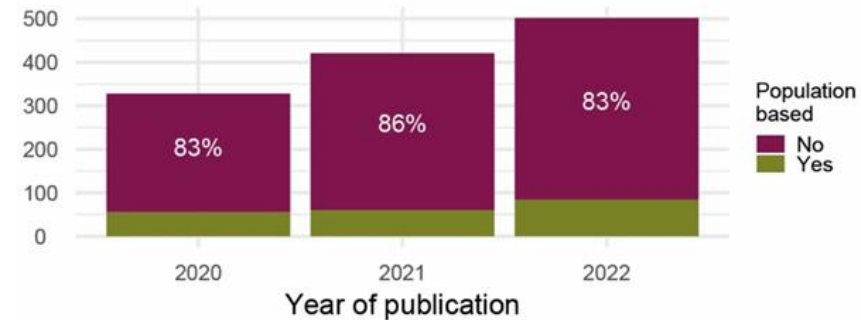
Only 8% in *more than one country*

RWD sources were *medical records* in 60%

87% of studies were *retrospective*

Only 16% were *population-based*

Median of **journal's impact factor** was *4.4 (IQR 3.0, 5.3)*

SCOPE OF THIS PRESENTATION

When and how to use Real-World Data/Evidence for clinical decision making?

✓ RWE studies promise **higher generalisability** than clinical trials, offering the possibility to generate evidence from RWD of *subpopulations under-represented in clinical trials*

AGENDA

When and how to use Real-World Data/Evidence for clinical decision making?

1) Use cases of RWE with direct impact in clinical practice (contextual or therapeutic)

   Disease characteristics and survival

   Treatment effectiveness (non-comparative and comparative)

2) Use cases of RWE for decision making and indirect impact in clinical practice

   Pre-marketing efficacy evaluation

   Health technology assessment (HTA)

3) Why good primary data collection and reporting guidelines are so important?

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What is the **real-life benefit** of new therapies introduced overtime for the treatment of patients with breast cancer?

How was this benefit observed **by disease subtype**?

Which are the **unmet needs to prioritise** research and development?

DISEASE CHARACTERISTICS AND SURVIVAL (*ESME cohort*)
Epidemiological impact of breakthrough therapies & remaining unmet needs

✓ Nationwide high-quality RWD may provide indirect evidence of impact of new treatments and areas of unmet need.

A Overall survival in the whole cohort according to the Year Of Diagnosis (YOD)
Based on Kaplan–Meier estimates

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

YOD	Median OS (95% CI)
2008	36.4 (34.1 - 38.7)
2009	37.7 (35.5 - 40.2)
2010	35.8 (33.8 - 37.8)
2011	37.4 (35.5 - 39.8)
2012	40.6 (37.9 - 43.0)
2013	41.3 (39.1 - 43.3)
2014	39.5 (37.2 - 42.2)
2015	39.4 (37.5 - 41.8)
2016	43.9 (41.7 - 45.9)

C Overall survival in the HER2+ subcohort according to the YOD
Based on Kaplan–Meier estimates

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

YOD	Median OS (95% CI)
2008	39.1 (36.2 - 46.5)
2009	42.1 (38.2 - 50.8)
2010	39.4 (35.9 - 45.4)
2011	41.1 (35.5 - 48.3)
2012	50.8 (45.0 - 55.5)
2013	58.0 (52.0 - 68.4)	← **Pertuzumab**
2014	NR (50.6 - NR)	← **T-DM1**
2015	NR (55.7 - NR)	
2016	NR (NR - NR)	

N=20,446

No real-life OS improvements for ER+/HER2- or TNBC subtypes between 2008 and 2016 !!   **! Selection bias**

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How is **disease stage at presentation** of
early breast invasive lobular carcinoma?

What is the **prognosis** of these patients compared to other subtypes?

DISEASE CHARACTERISTICS AND SURVIVAL *(BE Cancer Registry)*
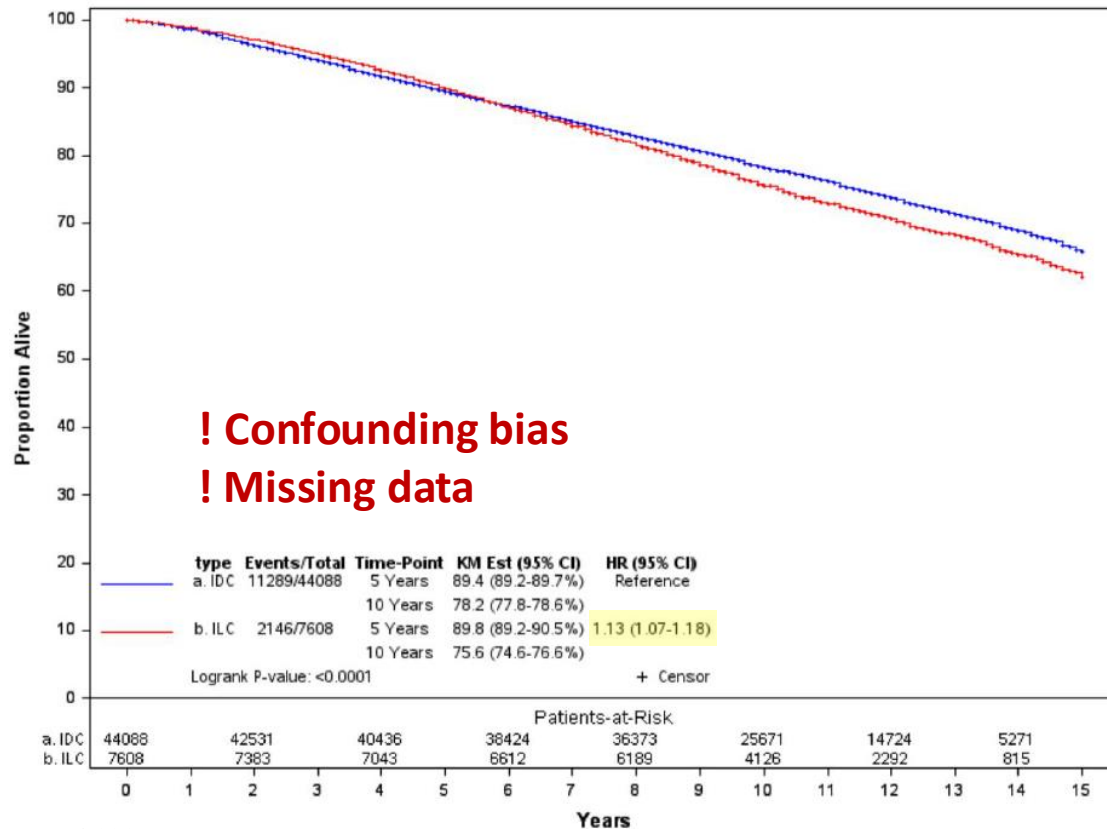## Disease presentation and prognosis of uncommon entities (e.g. lobular EBC)

Figure 1: Unadjusted overall survival curves

! Confounding bias
! Missing data

type	Events/Total	Time-Point	KM Est (95% CI)	HR (95% CI)
a. IDC	11289/44088	5 Years	89.4 (89.2-89.7%)	Reference
		10 Years	78.2 (77.8-78.6%)	
b. ILC	2146/7608	5 Years	89.8 (89.2-90.5%)	1.13 (1.07-1.18)
		10 Years	75.6 (74.6-76.6%)	

Logrank P-value: <0.0001   + Censor

Patients-at-Risk

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
a. IDC	44088		42531		40436		38424		36373		25671		14724		5271	
b. ILC	7608		7383		7043		6612		6189		4126		2292		815	

Years

N=51,696

"Patients with ILC had higher rates of **T3 stage** (14.0% vs 4.4%, p<0.01), **N3 stage** (5.6% vs 2.9%, p<0.0001) (…)" *(when compared to NST)*

Table 4: Overall survival adjusted for T and N

	Events/Total	Hazard Ratio (95% CI)	P-value
Histological type			
NST	10092/40784	Reference	
ILC	1942/7092	1.00 (0.95-1.05)	0.9136
T stage			
1	4552/27504	Reference	
2	5565/16225	2.10 (2.02-2.19)	<.0001
3	1133/2770	2.36 (2.20-2.53)	<.0001
4	782/1341	4.01 (3.70-4.34)	<.0001
N stage			
0	6091/30623	Reference	
1	3728/12696	1.21 (1.16-1.26)	<.0001
2	1320/2978	1.81 (1.70-1.93)	<.0001
3	895/1579	2.51 (2.33-2.70)	<.0001

✓ Population-based RWD sources may provide important evidence of disease behaviour of uncommon entities.

Nader-Marta G, Ameye L, Martins-Branco D, Ann Oncol. 2024;35:S336-7
BE, Belgian; eBC, early breast cancer; ILC, invasive lobular carcinoma; NST, breast cancer of no special type; N, node; T, tumour

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What is the value of **neoadjuvant chemotherapy for stage I TNBC**?

Is **pCR** of patients with **ER-low early breast cancer** treated with neoadjuvant **pembrolizumab** closer to TNBC or ER-positive disease?

TREATMENT EFFECTIVENESS *(Netherlands Cancer Registry)*
Subgroups routinely excluded from clinical trials (neoadj ChT for stage I TNBC)
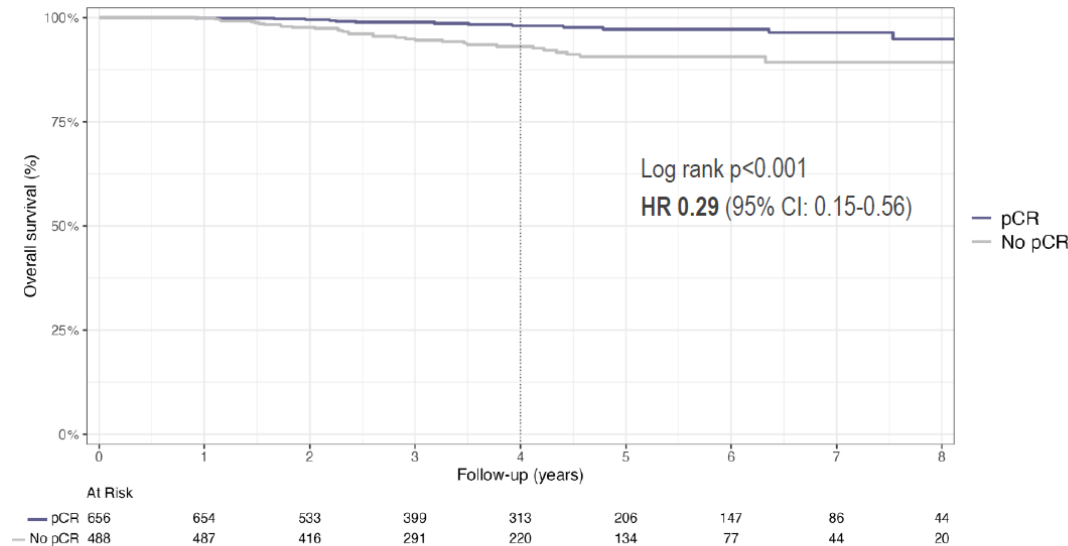
Pathological response:

	N	%
pCR (ypT0/is, N0)	656	57.3%
Residual disease	488	42.7%

Variables **significantly associated** (p < 0.05) with pCR in univariable analysis remained significant in multivariable logistic regression

Younger age (<50 vs ≥50): OR = 1.75 (1.36-2.26)
Higher tumor grade (3 vs 1/2): OR = 2.07 (1.55-2.76)
Lobular (vs ductal): OR = 0.18 (0.03-0.69)

Univariable logistic regression

Subgroup	Patients	pCR (%)	OR (95% CI)	p-value
Age				
Age ≥50	579	49.2%	-	-
Age <50	565	65.7%	1.97 (1.56 to 2.51)	<0.001
Grade				
1/2	274	40.5%	-	-
3	777	61.5%	2.35 (1.77 to 3.12)	<0.001
cT-stage				

Log rank p<0.001
HR 0.29 (95% CI: 0.15-0.56)

— pCR
— No pCR

At Risk

— pCR	656	654	533	399	313	206	147	86	44
— No pCR	488	487	416	291	220	134	77	44	20

N=1,144

Overall survival was defined as the time from diagnosis to death from any cause

Pathologic complete response and survival after neoadjuvant chemotherapy in stage I TNBC: a registry-based study

Manon de Graaf, Robbert C.A.M. Gielen, Sara Balduzzi, Sabine Siesling, Sabine C. Linn & Marleen Kok

Netherlands Cancer Institute, Amsterdam, The Netherlands

	N	4-year OS (95% CI)
pCR	656	98% (97% - 99%)
Residual disease	488	93% (90% - 96%)

Δ 5%

Median follow-up 3.8 years (IQR 2.4-5.6 years)

Total no. events = 39 (3.4%)

pCR is the only significant variable in multivariable Cox proportional hazard model* - **p<0.001**

* Factors considered: age, grade, cT, histology, platinum, radiotherapy & capecitabine

De Graaf M, Gielen RCAM, Balduzzi S, et al. Ann Oncol 2024;35:S309-348
neoadj ChT, neoadjuvant chemotherapy; pCR, pathologic complete response; TNBC, triple-negative breast cancer

TREATMENT EFFECTIVENESS *(Netherlands Cancer Registry)*
Subgroups routinely excluded from clinical trials (neoadj ChT for stage I TNBC)

VOLUME 32 · NUMBER 20 · JULY 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pathologic complete response and survival after neoadjuvant chemotherapy in stage I TNBC: a registry-based study

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Netherlands Cancer Institute, Amsterdam, The Netherlands

Outcomes by Tumor Subtype and Treatment Pattern in Women With Small, Node-Negative Breast Cancer: A Multi-Institutional Study

Ines Vaz-Luis, Rebecca A. Ottesen, Melissa E. Hughes, Rizvan Mamet, Ana M. Gonzalez-Angulo, Beverly Moy, Hope S. Rugo, Richard L. Theriault and Nancy U. Lin

npj | breast cancer

Published in partnership with the Breast Cancer Research Foundation

Brief communication

https://doi.org/10.1038/s41523-024-00634-6
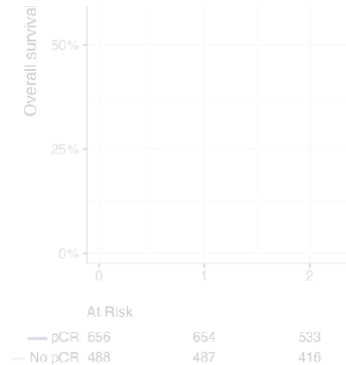
Prognosis and treatment outcomes for patients with stage IA triple-negative breast cancer

Paolo Tarantino [1,2,3,4], Julieta Leone[5], Carlos T. Vallejo[5], Rachel A. Freedman[1,2,3], Adrienne G. Waks[1,2,3], Olga Martínez-Sáez[1,2,6,7], Ana Garrido-Castro [1,2,3], Filipa Lynce [1,2,3], Nabihah Tayob[1,3], Nancy U. Lin[1,2,3], Sara M. Tolaney [1,2,3] & Jose P. Leone [1,2,3]

Lobular (vs ductal): OR = 0.18 (0.03-0.69)

Δ 5%

N=1,144

De Graaf M, Gielen RCAM, Balduzzi S, et al. Ann Oncol 2024;35:S309-348
neoadj ChT, neoadjuvant chemotherapy; pCR, pathologic complete response; TNBC, triple-negative breast cancer

TREATMENT EFFECTIVENESS *(PROMENADE cohort)*
Subgroups routinely excluded from clinical trials (pembrolizumab for ER-low EBC)

% of pCR

- ■ PROMENADE
- ■ KEYNOTE-522
- ■ KEYNOTE 756
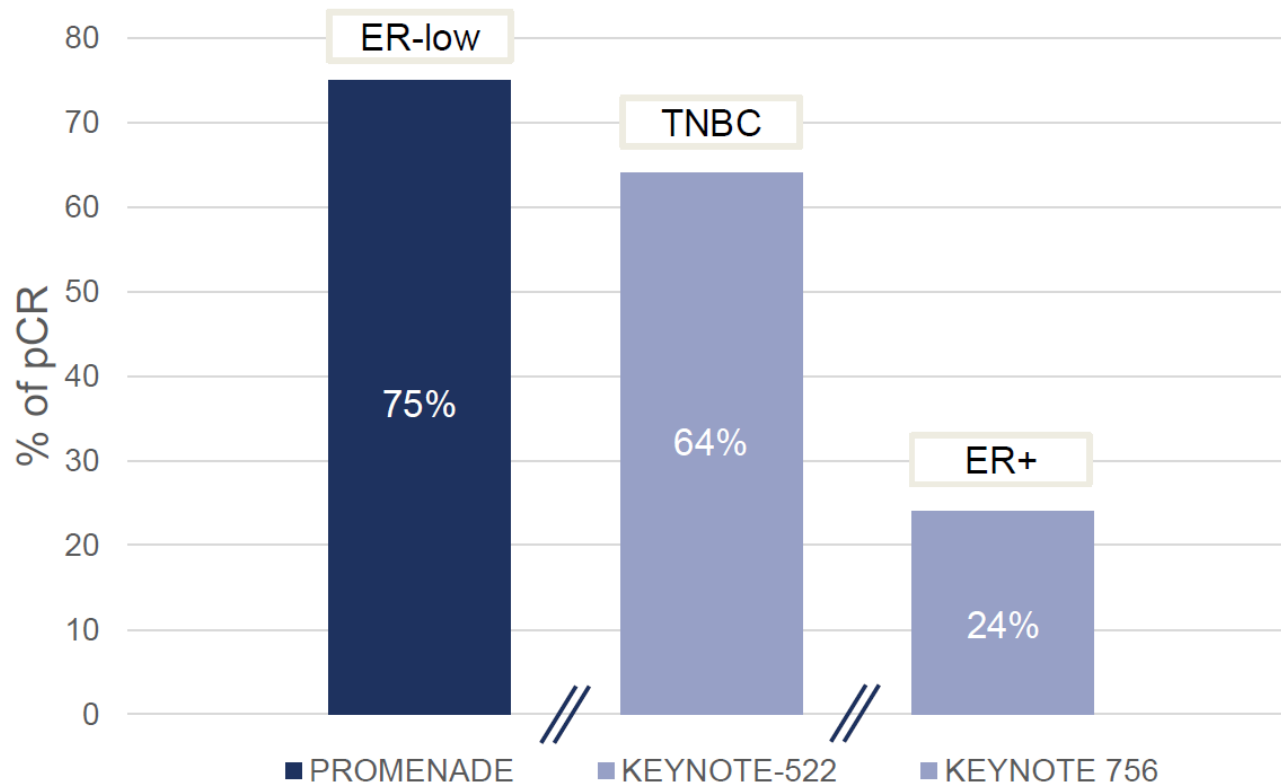
Data are not intended to be directly comparative

N=114

PROMENADE: PembROlizuMab for early ER-low/HER2-breast caNcer, reAlworlD frEnch cohort

F. Cherifi[1], L. Cabel[2], C. Bousrih[3], E. Volant[4], F. Dalenc[5], B. Mery[6], M. Auvray Kuentz[7], M. Alexandre[8], L. Benistant[9], M. Leheurteur[10], C. Bailleux[11], M. Debled[12], J-S. Frenel[13], D. Loirat[2], F.C. Bidard[2], S. Aho[14], A. Glenet[15], J.T.L. Ribeiro Mourato[3], F. Christy[16], G. Emile[1]

RCB	n (%)
0	85 (75 %)
1	9 (8 %)
2	12 (11 %)
3	7 (6 %)
Progressive disease	1 (1 %)

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Cherifi F, Cabel L, Bousrih C, et al. Ann Oncol 2024;35:S309-348

ER, estrogen-receptor; pCR, pathologic complete response; RCB, residual cancer burden; TNBC, triple-negative breast cancer

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What is the value of **surgery of primary tumour** in *de novo* **MBC?**

Is effectiveness of **everolimus** clinically relevant **after CDK4/6i?**
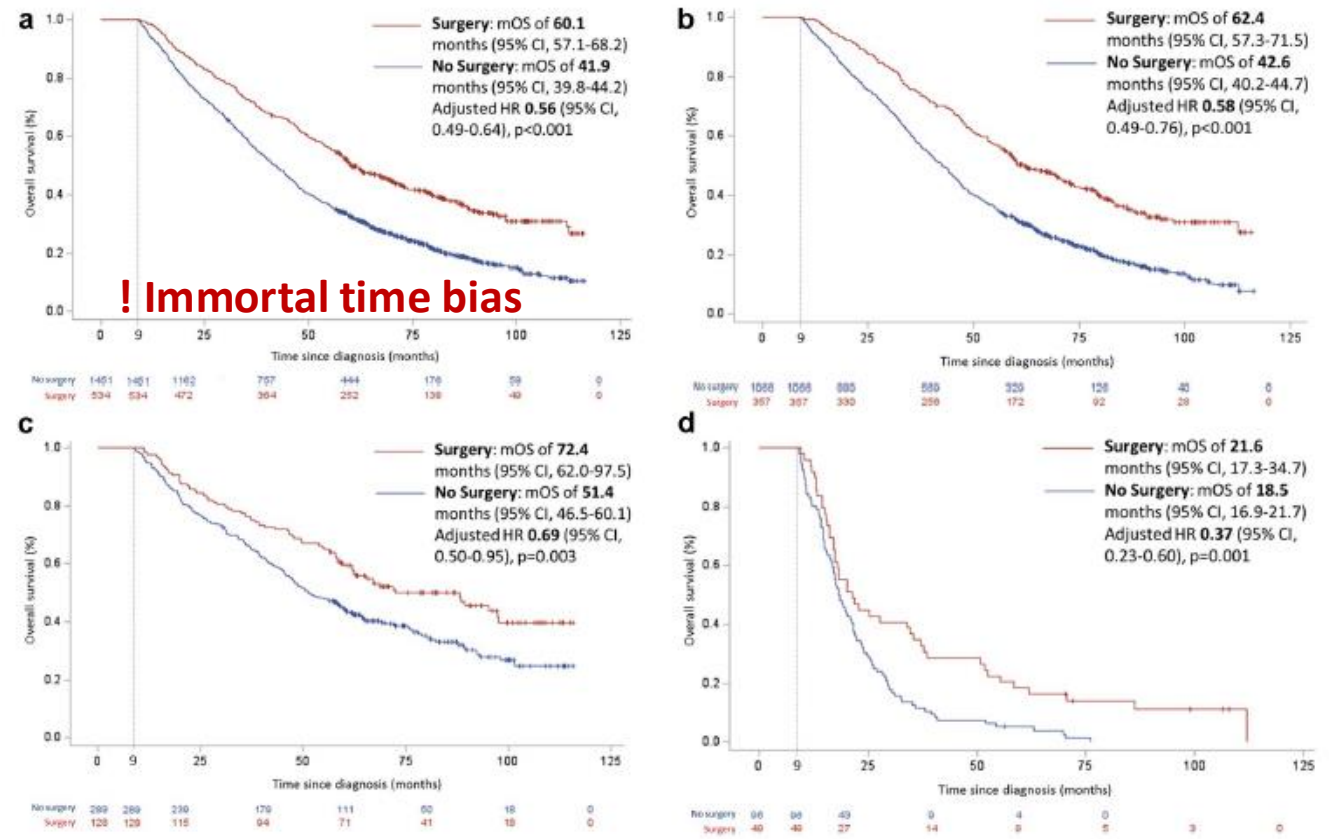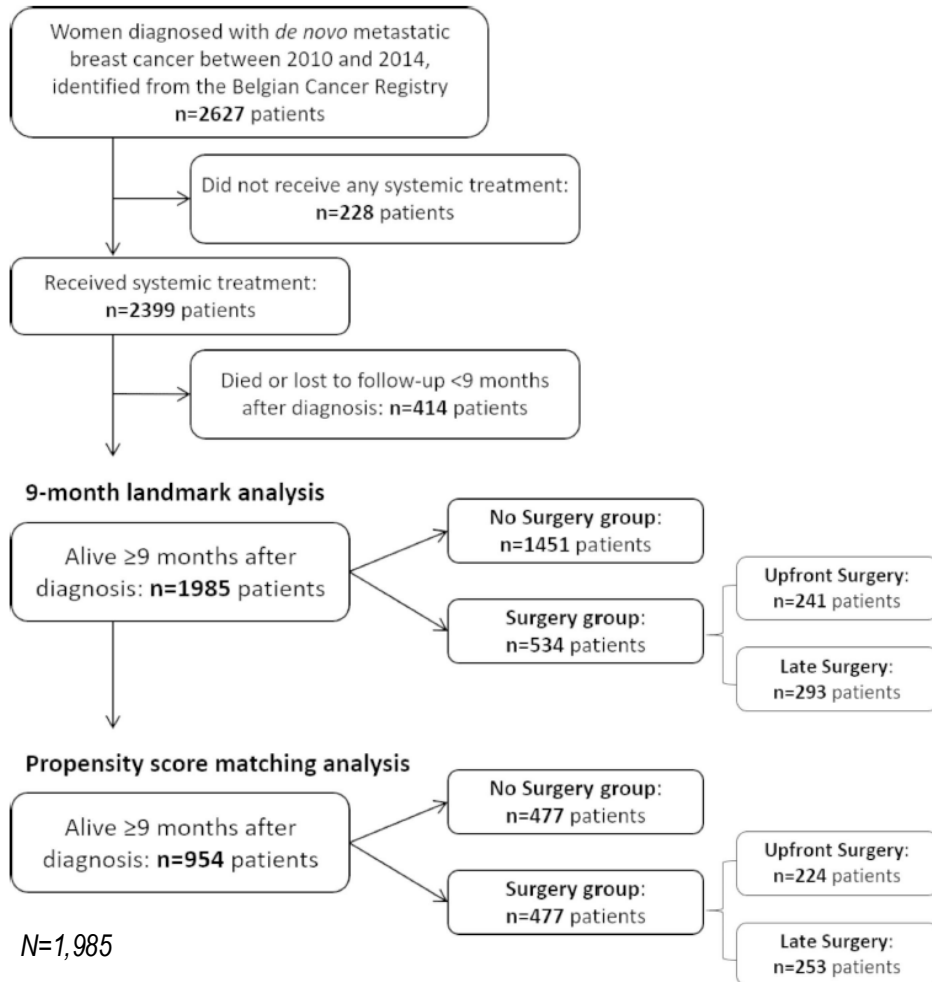
! Immortal time bias

Fig. 2 Kaplan-Meier curves for overall survival in (A) all patients, (B) patients with estrogen receptor (ER)-positive/HER2-negative subtypes, (C) HER2-positive subtype and (D) triple-negative subtype (TNBC); CI: confidence interval; HR: hazard ratio – adjusted for age,

N=1,985

Brandão M, Martins-Branco D, De Angelis C, et al. Breast Cancer Res Treat. 2024;203(2):351-363

1ary, primary; dnMBC, de novo metastatic breast cancer; RCTs, randomised controlled trials

TREATMENT EFFECTIVENESS *(EVERGREEN cohort)*

Interventions with weak magnitude of benefit in RCTs (everolimus for MBC)

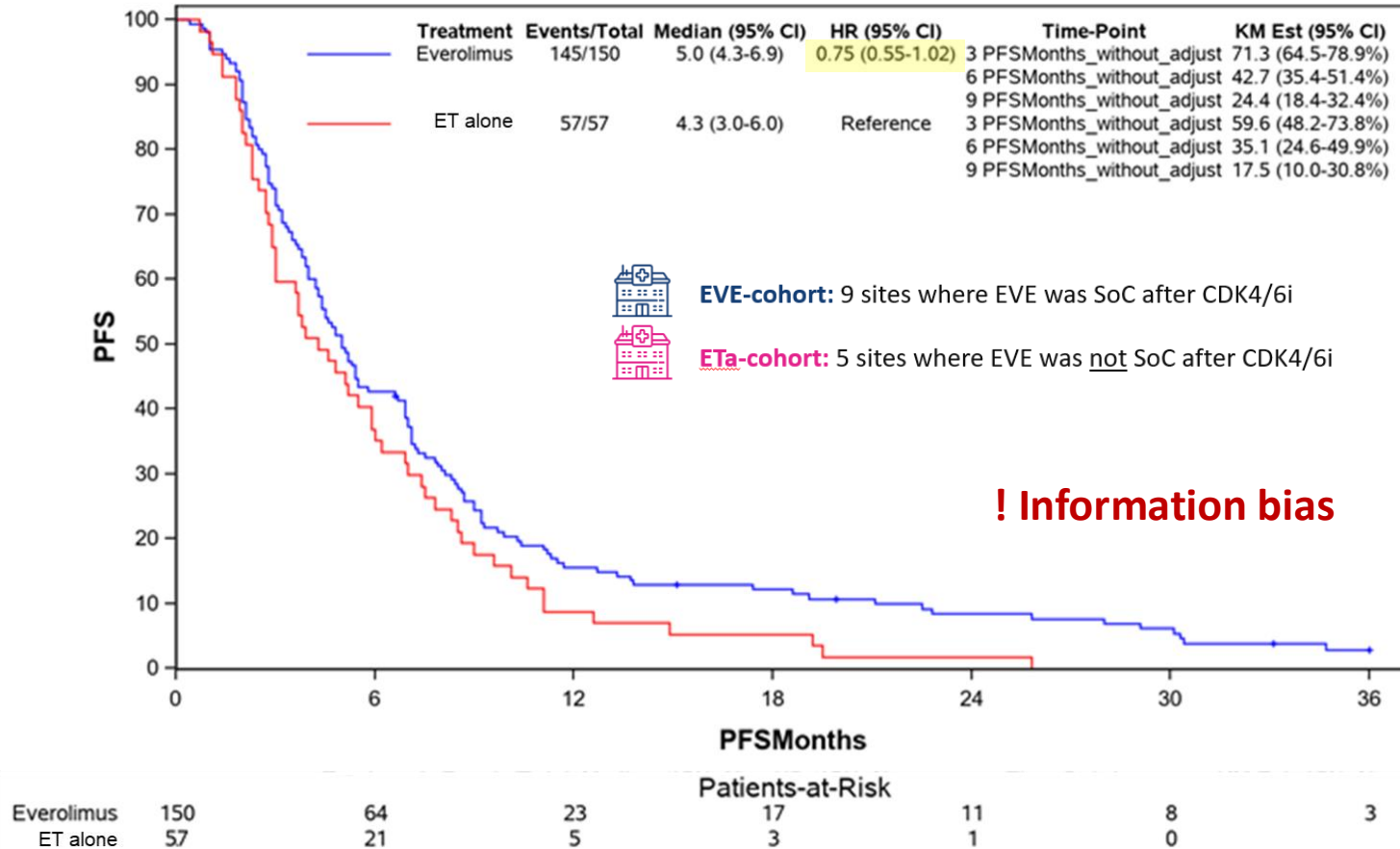**Fig. 1.** Kaplan-Meier curves for rwPFS (*N*=207, 202 events)

Treatment	Events/Total	Median (95% CI)	HR (95% CI)	Time-Point	KM Est (95% CI)
Everolimus	145/150	5.0 (4.3-6.9)	0.75 (0.55-1.02)	3 PFSMonths_without_adjust	71.3 (64.5-78.9%)
				6 PFSMonths_without_adjust	42.7 (35.4-51.4%)
				9 PFSMonths_without_adjust	24.4 (18.4-32.4%)
ET alone	57/57	4.3 (3.0-6.0)	Reference	3 PFSMonths_without_adjust	59.6 (48.2-73.8%)
				6 PFSMonths_without_adjust	35.1 (24.6-49.9%)
				9 PFSMonths_without_adjust	17.5 (10.0-30.8%)

EVE-cohort: 9 sites where EVE was SoC after CDK4/6i

ETa-cohort: 5 sites where EVE was <u>not</u> SoC after CDK4/6i

! Information bias

Table 3. Multivariable analysis for rwPFS (*N*=190, 185 events)

		Events / Total	HR (95% CI)
Treatment	Everolimus	132/137	0.68 (0.47-0.99)
	ET alone	53/53	*Reference*
Age Class (years)	<50	37/37	*Reference*
	50-69	101/104	*0.63 (0.42-0.95)*
	≥70	47/49	0.65 (0.40-1.04)
ECOG PS	0-1	173/177	*Reference*
	2-3	12/13	1.12 (0.57-2.19)
Charlson score	6	141/146	*Reference*
	7	32/32	1.02 (0.67-1.57)
	≥8	12/12	0.88 (0.48-1.62)
***De novo* vs recurrent ABC**	*De novo*	55/57	*Reference*
	Recurrent	130/133	0.86 (0.61-1.22)
Histological subtype	Ductal	129/132	*Reference*
	Lobular	29/30	1.20 (0.78-1.86)
	Mixed/other	27/28	0.65 (0.42-1.01)
Progesterone receptor	Negative	56/56	*Reference*
	Positive	129/134	0.91 (0.65-1.28)
Metastatic sites	Bone only	59/61	*Reference*
	Visceral/CNS	126/129	1.16 (0.83-1.62)
Number of prior lines	1	121/125	*Reference*
	>1	64/65	*1.65 (1.17-2.34)*
Duration of CDK4/6i	≤12 months	81/84	*Reference*
	>12 months	104/106	0.83 (0.60-1.15)

ABC, advanced breast cancer; CDK4/6i, CDK4/6 inhibitor; CI, confidence intervale; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HR, hazard ratio

EVE, everolimus; ETa, endocrine therapy alone; RCTs, randomised controlled trials; rwPFS, real-world progression-free survival

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RWE for clinical efficacy evaluation

was reported in the EPAR of

16 of 75 indications (21.3%)

RWE's role was "**supportive**" in

12 of 16 (75.0%) indications

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Derksen JWG, Martins-Branco D, Valachis A, et al. ESMO RWD&DO 2024;4:100039

EPAR, European Public Assessment Report

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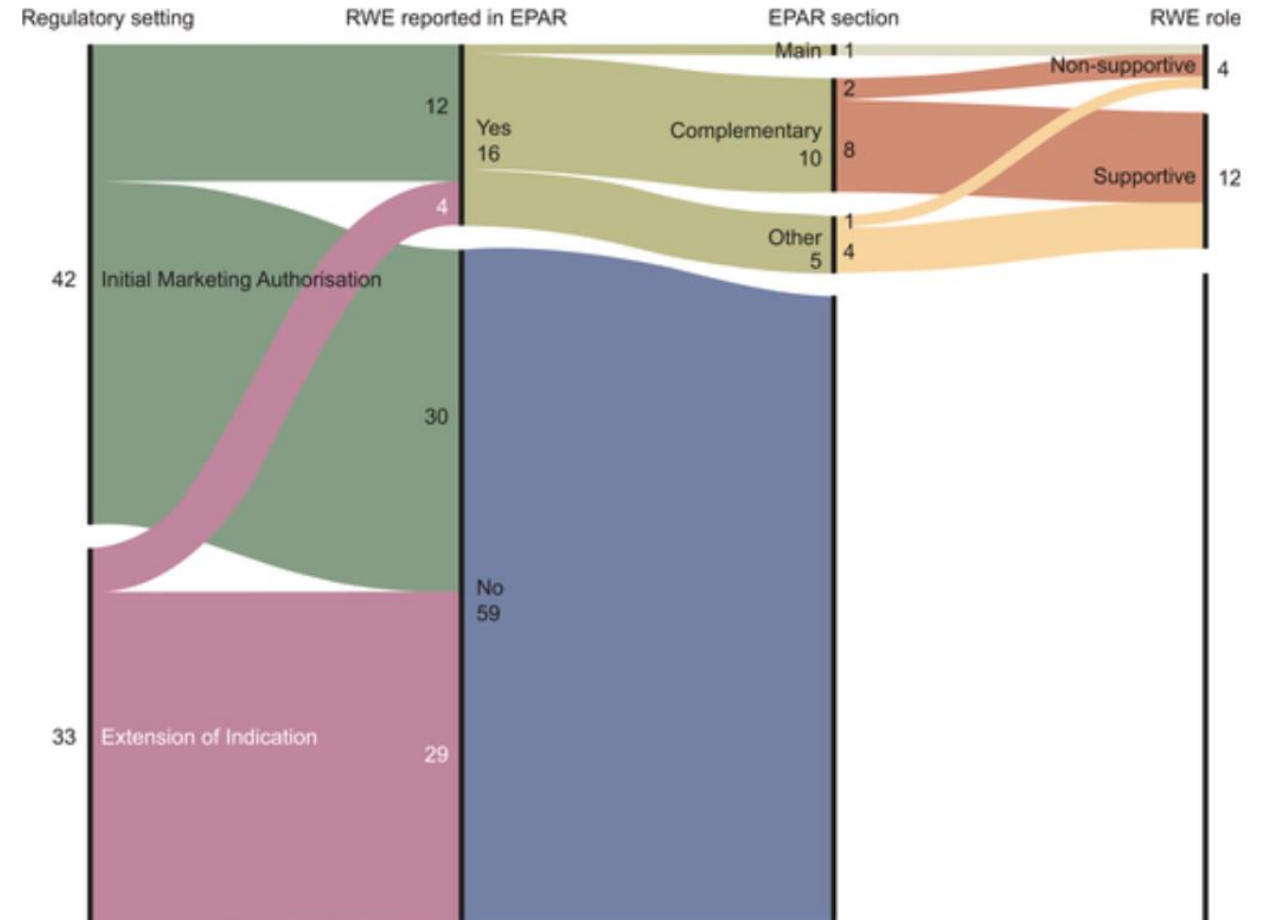
USE OF RWE FOR PRE-MARKETING EVALUATION

Case scenario of supportive complementary study - trastuzumab deruxtecan
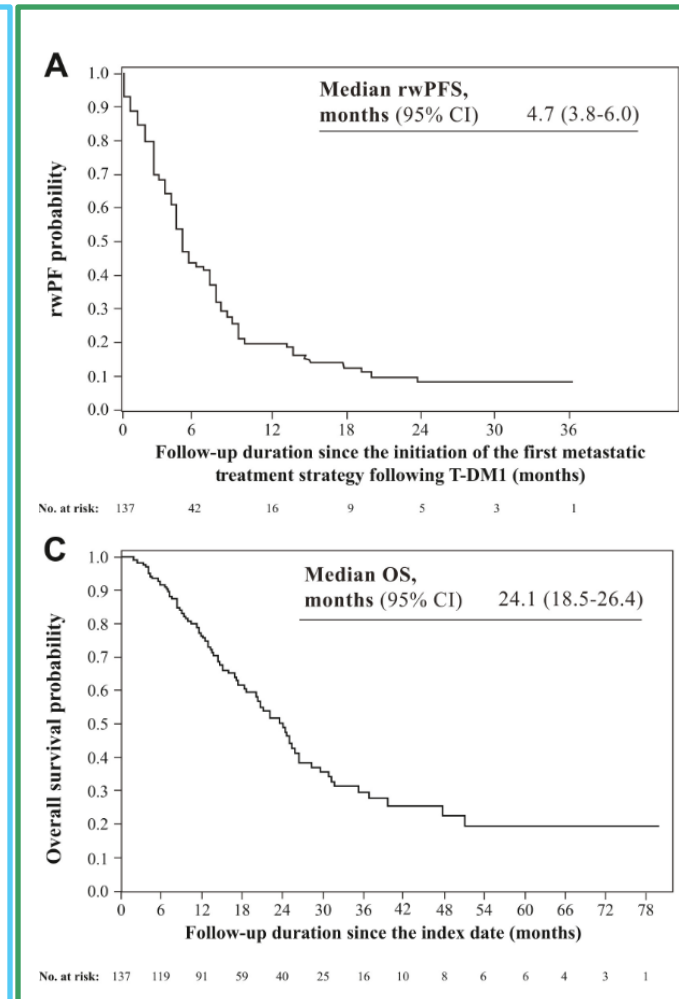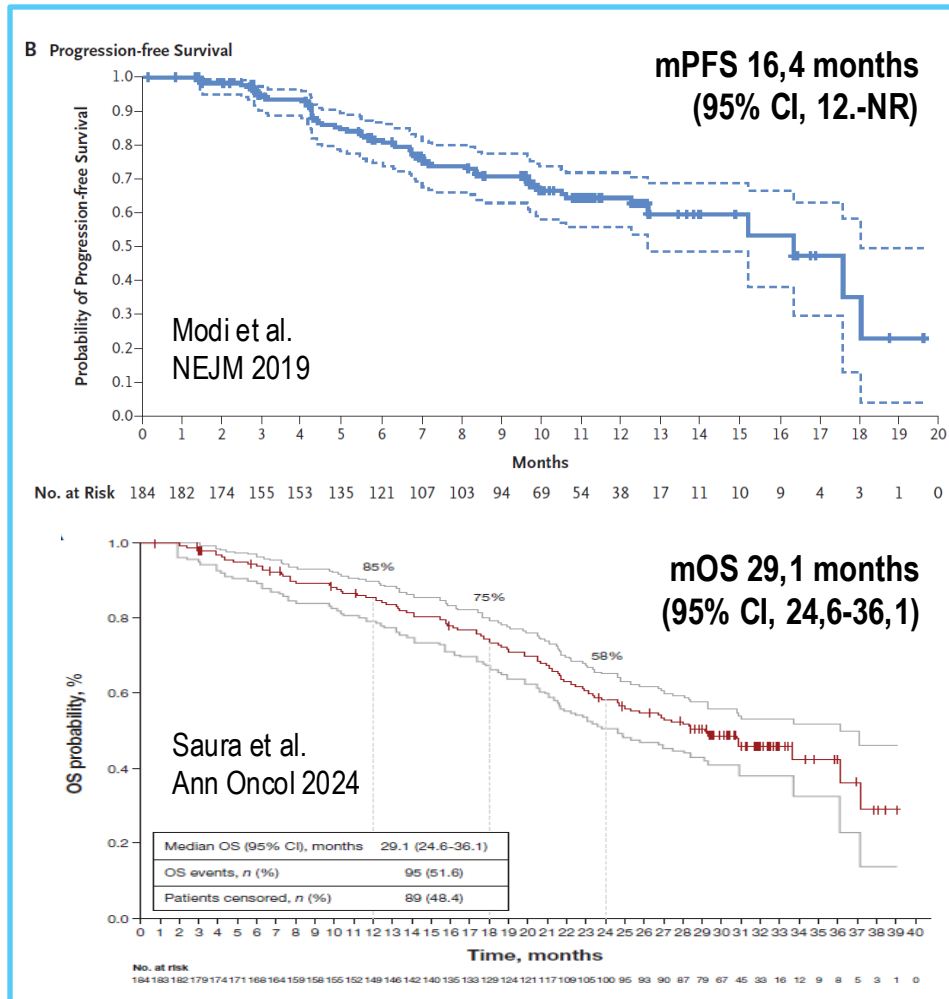
DESTINY B01

ESME DB-01 matched cohort

mPFS 16,4 months (95% CI, 12.-NR)

Modi et al. NEJM 2019

mOS 29,1 months (95% CI, 24,6-36,1)

Saura et al. Ann Oncol 2024

Median OS (95% CI), months	29.1 (24.6-36.1)
OS events, n (%)	95 (51.6)
Patients censored, n (%)	89 (48.4)

Median rwPFS, months (95% CI) 4.7 (3.8-6.0)

Median OS, months (95% CI) 24.1 (18.5-26.4)

Coutinard C, Barbet V, Schiappa R, et al. ESMO RWD&DO 2024;4:100043

THE VALUE OF RWE IN HEALTH ECONOMICS FOR HTA

RWE to support reimbursement decision making

Figure 1: Opinions of RWE use across ten European countries
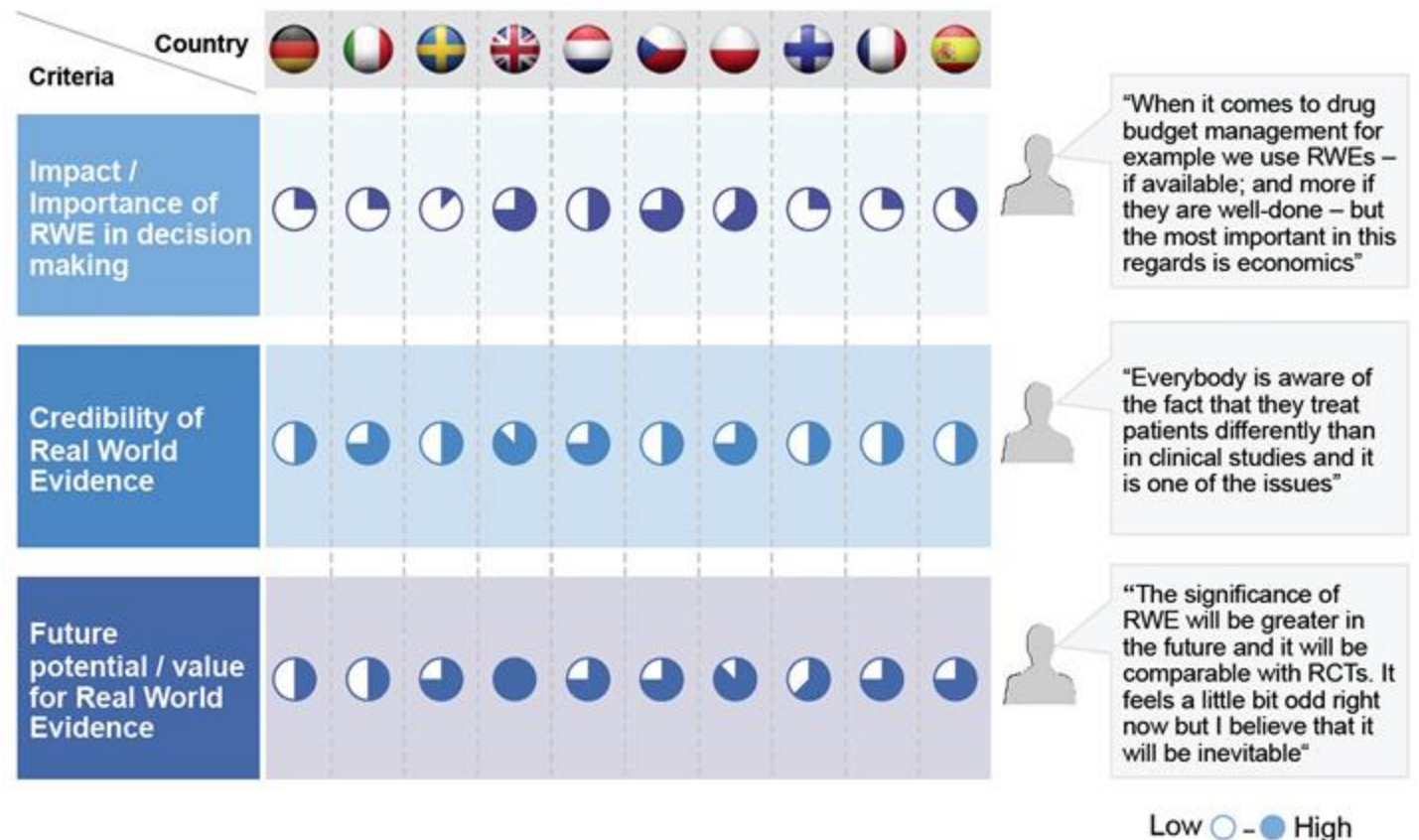
AGENDA

When and how to use Real-World Data/Evidence for clinical decision making?

1) Use cases of RWE with direct impact in clinical practice (contextual or therapeutic)

Disease characteristics and survival

Treatment effectiveness (non-comparative and comparative)

2) Use cases of RWE for decision making and indirect impact in clinical practice

Pre-marketing efficacy evaluation

Health technology assessment (HTA)

3) Why good primary data collection and reporting guidelines are so important?

REAL WORLD DATA AND DIGITAL ONCOLOGY

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RWE QUALITY STANDARDS

3 main dimensions

Reporting quality & study quality are the dimensions more easily assessed in a manuscript

Reporting quality

ESMO RWDD WG developed **ESMO GROW**
To test the compliance with the checklist
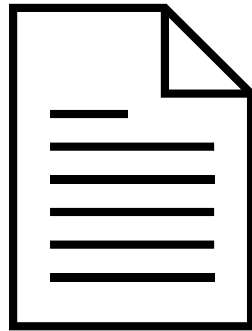
Study quality

Data source quality

Minimum Clinical Dataset

ESMO Guidance for Reporting Oncology real-World Evidence

The first reporting guidance specifically developed for oncology RWE studies

- Detailed **list of recommendations** for authors and reviewers of RWE publications.

- Broad Scope: **Descriptive to Analytical**

- Addresses **new treatments**, **molecular-based epidemiology**, **oncology-specific variables**, and **tech-based RWE research** (AI, machine learning)

- Facilitates **harmonised interpretation** by all stakeholders

- **Related Materials:** Online Tool, Checklist, Flowchart

ESMO GROW

Castelo-Branco L., Pellat A., Martins-Branco D., et al. ESMO Guidance for Reporting Oncology real-World evidence (GROW). Ann Oncol. 2023;34(12):1097–1112.

CONCLUSION - *take home messages*

✓ RWE promises **higher generalisability** than clinical trials, mainly for *subpopulations under-represented in RCTs*

✓ RWE can inform about **disease presentation**, **prognostic factors**, **treatment effectiveness**, and **survival**, playing an important role for clinical practice *whenever clinical trial evidence is not available to guide decision*

✓ Good quality RWE may have an important role in health policy for **regulatory** and **health technology assessment**, *improving access to innovative treatments* in clinical practice

✓ **Reporting quality** is essential for critical appraisal of RWE studies, providing full understanding of main study limitations and strategies to mitigate them – *ESMO-GROW checklist*

✓ The ESMO-RWDD WG aims to develop a **specific tool for assessment of oncology real-world evidence study quality** *AND* to define a **minimum clinical dataset** for primary data collection

✓ There is a need for **optimising RWD collection** for primary and secondary use, generating **good quality RWE** for *supporting clinical practice decision making*

REAL WORLD DATA AND DIGITAL ONCOLOGY

Thank you for your attention

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REAL WORLD DATA AND DIGITAL ONCOLOGY

COMMON BIASES IN REAL-WORLD EVIDENCE STUDIES, AND HOW TO MITIGATE THEM?

David Pérol, MD

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david.perol@lyon.unicancer.fr

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DECLARATION OF INTERESTS

David Pérol

Personal fees and consulting:

AstraZeneca, Bayer, Boehringer-Ingelheim, Brenus Pharma, Bristol-Myers Squibb, Daiichi-Sankyo, Eli-Lilly, Gilead, Ipsen, Janssen, Novartis, Merck Sharp and Dohme, Pfizer and Takeda

Travel funding:

Novartis, Roche

INTRODUCTION

SCOPE OF THIS PRESENTATION

- Is not to provide an exhaustive review of all the biases that can occur when analyzing real-world data (RWD)

SCOPE OF THIS PRESENTATION

- Is not to provide an exhaustive review of all the biases that can occur when analyzing real-world data (RWD)

- But rather to detail the **main biases** that arise when trying to answer the question of (comparative) analysis of the **efficacy of treatments** used in **clinical routine**

  ⇨ Assessing "effectiveness" or "real-world efficacy"

  ⇨ Atypical situations in oncology

ATYPICAL SITUATIONS IN ONCOLOGY
Effectiveness assessment based on RWD

1. **Rare cancers (or subtypes) defined by a molecule defect targeted by a new treatment**

   - Randomized Controlled Trial (RCT) difficult to conduct within a reasonable time frame

     ⇨ **Single Arm uncontrolled Trial (SAT)**

       · Unable to assess relative treatment benefit

ATYPICAL SITUATIONS IN ONCOLOGY
Effectiveness assessment based on RWD

1. **Rare cancers (or subtypes) defined by a molecule defect targeted by a new treatment**

   - Randomized Controlled Trial (RCT) difficult to conduct within a reasonable time frame

     ⇨ **Single Arm uncontrolled Trial (SAT)**

       - Unable to assess relative treatment benefit

     ⇨ **Opportunity to provide an external control arm from RWD to assess the effectiveness of the experimental treatment**

ATYPICAL SITUATIONS IN ONCOLOGY (#2)

Effectiveness assessment based on RWD

2. **RCT completed but questions unresolved:**

- Inappropriate control arm

- Low power for definitive endpoint (overall survival)

- Short duration of follow-up

- Inconclusive RCT in subgroups of interest

ATYPICAL SITUATIONS IN ONCOLOGY (#2)

Effectiveness assessment based on RWD

2. **RCT completed but questions unresolved:**

- Inappropriate control arm

- Low power for definitive endpoint (overall survival)

- Short duration of follow-up

- Inconclusive RCT in subgroups of interest

  ⇨ **Opportunity to use RWD to assess the effectiveness of comparative treatments**

SCOPE OF THIS PRESENTATION

- To detail the **main biases** that arise when trying to answer the question of (comparative) analysis of the **efficacy of treatments** used in **clinical routine**

  ⇨ Assessing "effectiveness" or "real-world efficacy"

  ⇨ Atypical situations

✋ In this context, appropriate methods to mitigate biases require **large cohorts of RWD**, based on EHR, with a **high level of quality** and **granularity** (baseline patient characteristics, outcomes…): ESME (France) [1], FLATIRON (USA) [2]…

---

1. Pérol D et al. BMJ open 2019.   2. Flatiron Health: Real-world evidence, 2023. https://flatiron.com/real-world-evidence/   *EHR: Electronic Health Records*

MAIN BIASES ASSOCIATED WITH THE USE OF RWD

CAUSAL INFERENCE IN TREATMENT EFFECT ASSESSMENT

Randomised Controlled Trial (RCT) (#1)

Randomisation → Treatment A (control)

→ Treatments A + B (experimental)

- **An appropriate and *a priori*-defined protocol:**
  - Eligibility criteria explicitly stated: patient population in the experimental and control groups is similar

CAUSAL INFERENCE IN TREATMENT EFFECT ASSESSMENT

Randomised Controlled Trial (RCT) (#1)

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  - For each patient, **time zero of follow-up (T_0)** = time when 3 things happen: eligibility criteria are met; treatment strategies are assigned; and study outcomes (survival) begin to be counted [1]

1. Hernan MA & Robins JM, Am J Epidemiol. 2016

CAUSAL INFERENCE IN TREATMENT EFFECT ASSESSMENT

Randomised Controlled Trial (RCT) (#1)

Randomisation → Treatment A (control)

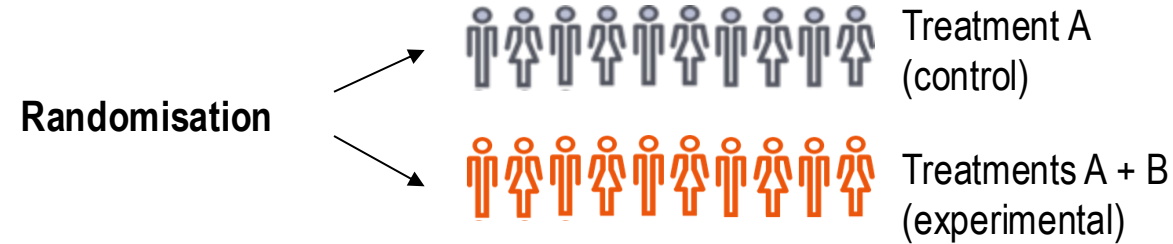→ Treatments A + B (experimental)

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  - For each patient, **time zero of follow-up (T_0)** = time when 3 things happen: eligibility criteria are met; treatment strategies are assigned; and study outcomes (survival) begin to be counted [1]

  - The frequency and methods of tumor assessment are standardized (e.g., tumor progression → RECIST criteria)

1. Hernan MA & Robins JM, Am J Epidemiol. 2016

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CAUSAL INFERENCE IN TREATMENT EFFECT ASSESSMENT

Randomised Controlled Trial (RCT) (#1)

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Randomisation → Treatments A + B (experimental)

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  - The frequency and methods of tumor assessment are standardized (e.g., tumor progression → RECIST criteria)

  - Few or no missing data

1. Hernan MA & Robins JM, Am J Epidemiol. 2016

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CAUSAL INFERENCE IN TREATMENT EFFECT ASSESSMENT

Randomised Controlled Trial (RCT) (#2)

Randomisation

A

A + B

$$Average\ causal\ effect\ \Delta E\ =$$
$$E(arm\ A) - E(arms\ A + B)$$

- **Randomization ensures initial comparability at T_0**

  ⇨ difference in outcomes observed = average causal effect

CAUSAL INFERENCE IN TREATMENT EFFECT ASSESSMENT
Real-World Data (RWD) (#1)

Treatment A
(control)

Treatments A + B
(experimental)

- **No *a priori*-defined protocol:**

  - Eligibility criteria not explicitly stated: characteristics of the patients in experimental group may be different from those in control group → **Selection bias**

CAUSAL INFERENCE IN TREATMENT EFFECT ASSESSMENT
Real-World Data (RWD) (#1)

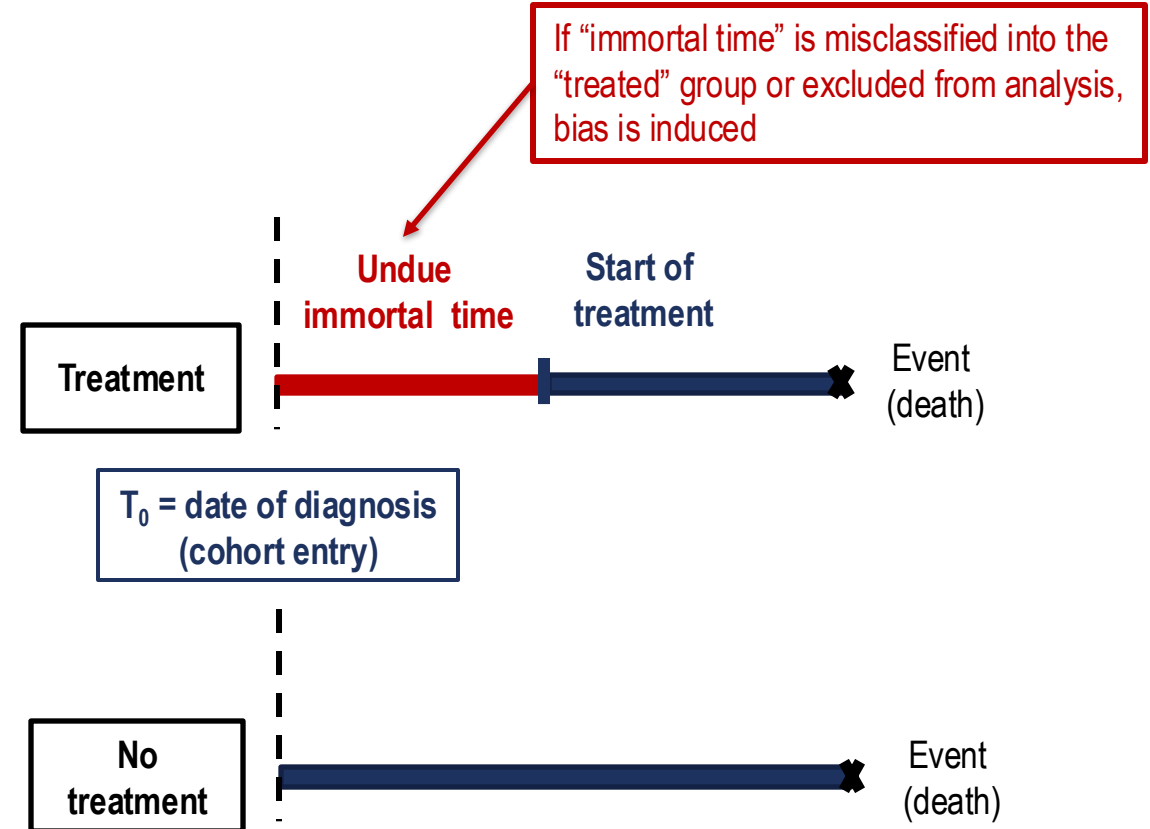Treatment A
(control)

Treatments A + B
(experimental)

- **No *a priori*-defined protocol:**

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  - Misalignment of eligibility criteria and treatment assignment → **Immortal time bias**

IMMORTAL TIME BIAS
Observational study (RWD)

. This bias occurs when there is a period during follow-up where the outcome cannot occur because of study design (e.g., the period between cohort entry and exposure)

. Happens when researchers **assign patients to treated group** by using information that is observed **after the participant enters the study** (after time-zero)

Source: Lèvesque LE et al. BMJ 2010.

If "immortal time" is misclassified into the "treated" group or excluded from analysis, bias is induced

Undue immortal time   **Start of treatment**

Treatment   Event (death)

T_0 = **date of diagnosis (cohort entry)**

No treatment   Event (death)

CAUSAL INFERENCE IN TREATMENT EFFECT ASSESSMENT

Real-World Data (RWD) (#1)

Treatment A
(control)

Treatments A + B
(experimental)

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  - The frequency and methods of tumor assessment are not standardized → **Information bias** (measurement bias in interval-censored outcomes) [1]

1. Siu DHW JCO Precis Oncol 2024.

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CAUSAL INFERENCE IN TREATMENT EFFECT ASSESSMENT

Real-World Data (RWD) (#1)

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  - Misalignment of eligibility criteria and treatment assignment → **Immortal time bias**

  - The frequency and methods of tumor assessment are not standardized → **Information bias** (measurement bias in interval-censored outcomes) [1]

  - RWD studies are more likely to have **missing data** compared with clinical trials [1]

1. Siu DHW JCO Precis Oncol 2024.

CAUSAL INFERENCE IN TREATMENT EFFECT ASSESSMENT

Real-World Data (RWD) (#2)

Treatment A (control)

Treatments A + B (experimental)

- **Absence of randomisation** to ensure equivalent groups for comparison:

  - Heterogeneity of compared groups → **Confusion bias**

    - In routine clinical practice, doctors do not prescribe treatments "at random": implicit or explicit allocation based on patient risk (co-factors) → "confusion" between co-factor effect and treatment effect

    - For example, if more ECOG PS 0-1 patients are assigned to the experimental group than to control, and if PS is independently more likely to be associated with survival, the new treatment may falsely appear to be beneficial

CONFOUNDING BY INDICATION
Observational study (RWD)

PS 0-1   PS 2   PS 3

Treatment A

Treatment B

Treatment C

ECOG PS

Survival
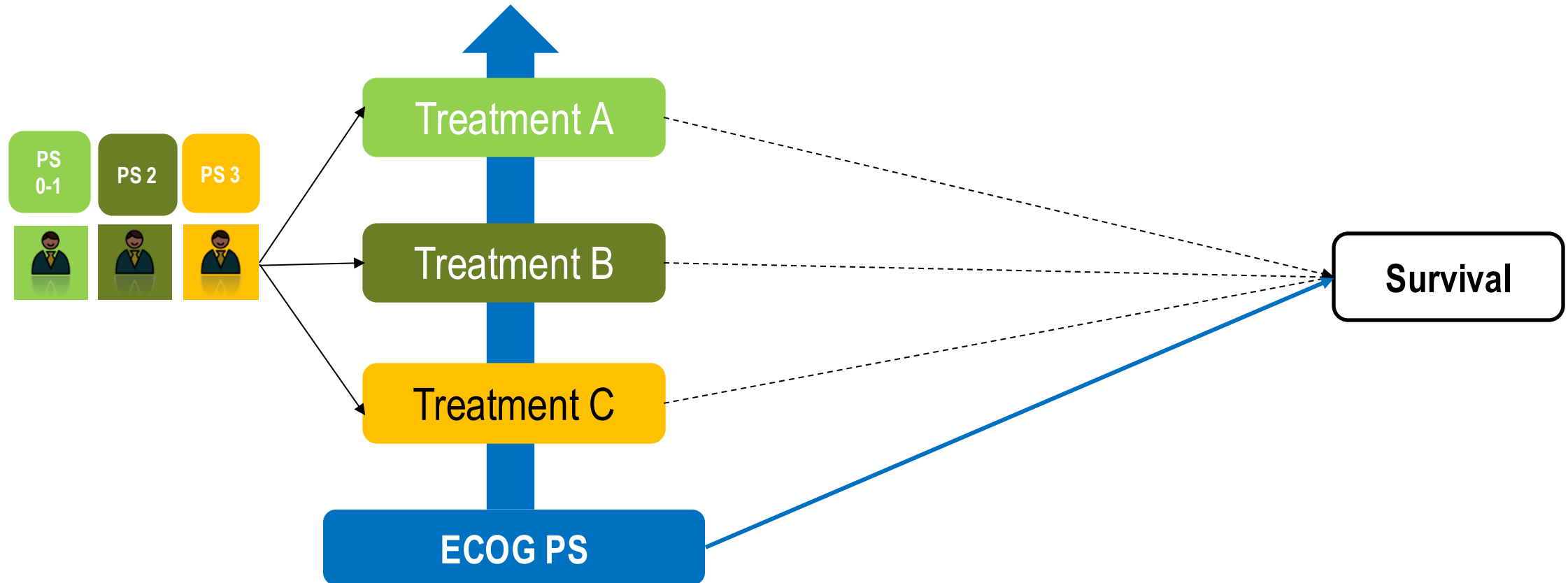
Treatments A, B, C... are in fact prescribed preferentially to patients with a +/- high risk of developing the event

CAUSAL INFERENCE FROM OBSERVATIONAL DATA

Summary

- **In RWD studies, difference in outcomes naively observed is subject to biases:**

  - Selection bias

  - Immortal time bias

  - Information bias

  - Missing data

  - Confounding bias…

$$Average\ causal\ effect\ \Delta E \neq$$
$$E(arm\ A) - E(arms\ A + B)$$

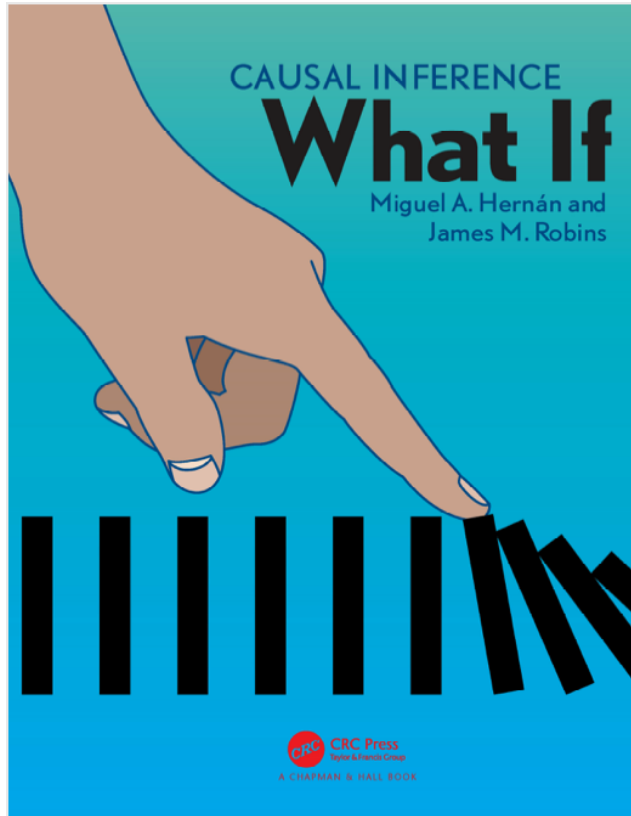⇨ **How to mitigate them?**

HOW TO MITIGATE BIASES?

TARGET TRIAL EMULATION

CAUSAL INFERENCE
What If
Miguel A. Hernán and James M. Robins

CRC Press
Taylor & Francis Group
A CHAPMAN & HALL BOOK

This Issue Views **22,975** | Citations **17** | Altmetric **111**

JAMA Guide to Statistics and Methods

December 12, 2022

Target Trial Emulation
A Framework for Causal Inference From Observational Data

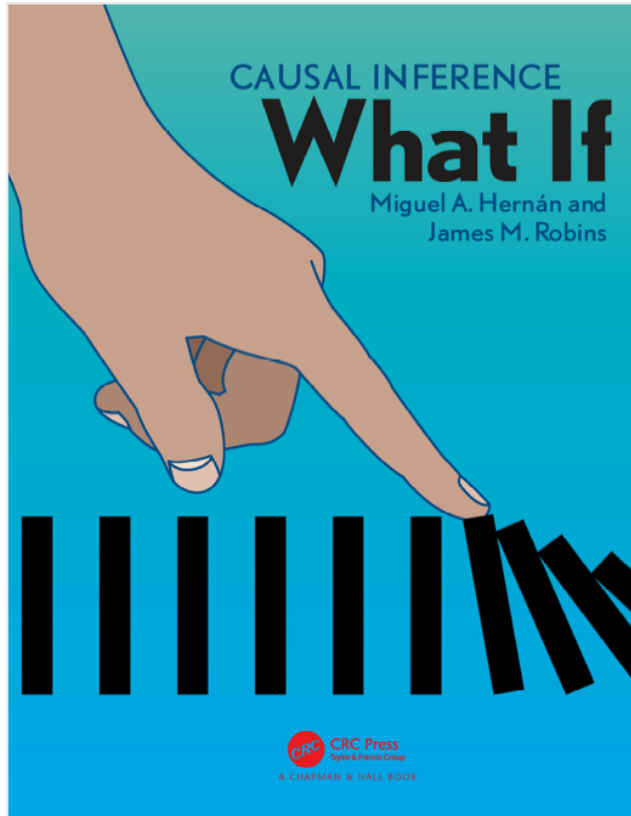Miguel A. Hernán, MD, DrPH[1]; Wei Wang, PhD[2]; David E. Leaf, MD, MMSc[3]

≫ Author Affiliations

JAMA. 2022;328(24):2446-2447. doi:10.1001/jama.2022.21383

CAUSALab | HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

A Center to Learn What Works

Sources: Hernan MA, Robins JM. Causal Inference: What If. Boca Raton. Chapman & Hall/CRC. 2020; Hernan MA et al, JAMA 2022
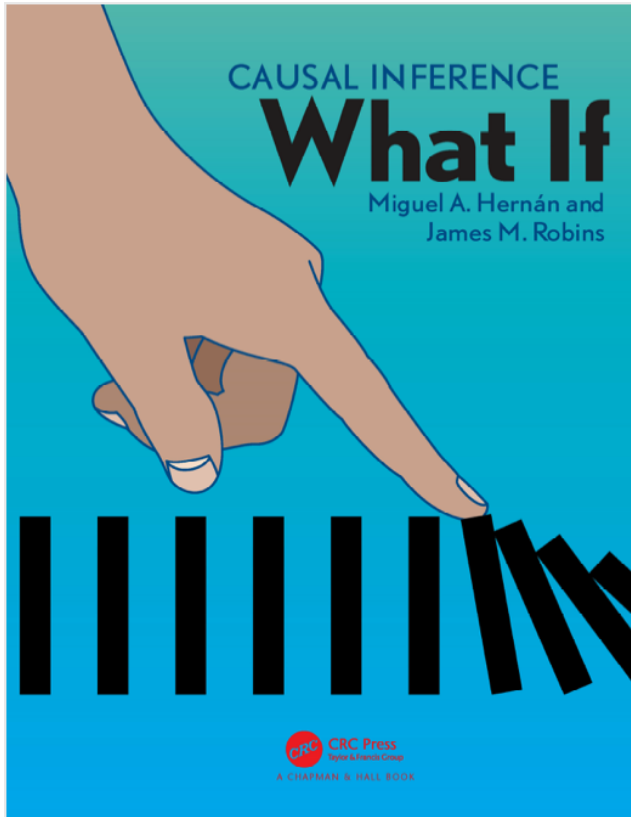
THE TARGET TRIAL

A practical way to ask a causal question in non-interventional studies is to specify a protocol of the target trial

⇨ **The target trial:** the hypothetical randomized trial that we would like to conduct to answer a causal question

Sources: Hernan MA, Robins JM. Causal Inference: What If. Boca Raton. Chapman & Hall/CRC. 2020; Hernan MA et al, JAMA 2022

A practical way to ask a causal question in non-interventional studies is to specify a protocol of the target trial

⇨ **The target trial:** the hypothetical randomized trial that we would like to conduct to answer a causal question

⇨ **Why do we need to explicitly emulate a target trial** for causal inference from observational data?

= because not doing so leads to bias

Sources: Hernan MA, Robins JM. Causal Inference: What If. Boca Raton. Chapman & Hall/CRC. 2020; Hernan MA et al, JAMA 2022

TARGET TRIAL EMULATION
Key concepts

Explicitly emulating the target trial eliminates self-inflicted injuries:

- Selection bias with an explicit application (keys elements) of the protocol to observational data

Sources: Hernan MA & Robins JM, Am J Epidemiol. 2016; Hernan MA et al, JAMA 2022

TARGET TRIAL EMULATION

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- Immortal time-bias with a specification of time zero:

  - T_0 must be synchronized with determination of eligibility and assignment of treatment strategies

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- Information bias by ensuring similarity in the extent and quality of data capture between the arms

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TARGET TRIAL EMULATION

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- Multiple imputation strategies can be applied to handle missing data

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    - T_0 must be synchronized with determination of eligibility and assignment of treatment strategies

- Information bias by ensuring similarity in the extent and quality of data capture between the arms

- Multiple imputation strategies can be applied to handle missing data

    In addition, emulation requires statistical adjustment for confounding due to the lack of randomisation

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TARGET TRIAL EMULATION FRAMEWORK

Applying key methodological & design components of RCT to observational data

Step 1

Designing the target (ideal) trial protocol: explicit description of key elements, *a priori*

- ❏ Eligibility criteria
- ❏ Treatment strategies
- ❏ Treatment assignment: randomization
- ❏ Follow-up
- ❏ Outcome(s)
- ❏ Causal contrast(s) (ITT and/or PP)
- ❏ Analysis plan

Step 2

~~Conducting~~/Emulating the target trial: explicit application of the protocol to observational data

- ❏ Eligibility criteria
- ❏ Treatment strategies
- ❏ Treatment assignment: hypothetical randomization process (confounding adjustment)
- ❏ Follow-up
- ❏ Outcome(s)
- ❏ Causal contrast(s) (ITT and/or PP)
- ❏ Analysis plan

Sources: Hernan MA & Robins JM, Am J Epidemiol. 2016; Hernan MA et al, JAMA 2022

ILLUSTRATION

ESME Metastatic Breast Cancer (MBC)

JNCI: Journal of the National Cancer Institute, 2023, 115(8), 971–980
https://doi.org/10.1093/jnci/djad092
Advance Access Publication Date: May 23, 2023
Article

OXFORD

Target trial emulation to assess real-world efficacy in the Epidemiological Strategy and Medical Economics metastatic breast cancer cohort

Alison Antoine, MSc,[1,2] David Pérol, MD,[1,*] Mathieu Robain, MD, PhD,[3] Suzette Delaloge, MD,[4] Christine Lasset, MD, PhD,[2,5] Youenn Drouet, PhD[2,5]

[1]Clinical Research and Biostatistics Department, Centre Léon Bérard, Lyon, France
[2]UMR CNRS 5558 LBBE, Claude Bernard Lyon 1 University, Villeurbanne, France
[3]Data Direction, UNICANCER, Paris, France
[4]Department of Cancer Medicine, Gustave Roussy, Villejuif, France
[5]Prevention & Public Health Department, Centre Léon Bérard, Lyon, France

*Correspondence to: David Pérol, MD, Clinical Research and Biostatistics Department, Centre Léon Bérard, 28 rue Laennec, 69008 Lyon, France (e-mail: david.perol@lyon.unicancer.fr).

Abstract

Background: Real-world data studies usually consider biases related to measured confounders. We emulate a target trial implementing study design principles of randomized trials to observational studies; controlling biases related to selection, especially immortal time; and measured confounders.
Methods: This comprehensive analysis emulating a randomized clinical trial compared overall survival in patients with HER2-negative metastatic breast cancer (MBC), receiving as first-line treatment, either paclitaxel alone or combined to bevacizumab. We used data from 5538 patients extracted from the Epidemiological Strategy and Medical Economics–MBC cohort to emulate a target trial using advanced statistical adjustment techniques including stabilized inverse-probability weighting and G-computation, dealing with missing data with multiple imputation, and performing a quantitative bias analysis for residual bias due to unmeasured confounders.
Results: Emulation led to 3211 eligible patients, and overall survival estimates achieved with advanced statistical methods favored the combination therapy. Real-world effect sizes were close to that assessed in the existing E2100 randomized clinical trial (hazard ratio = 0.88, P = .16), but the increased sample size allowed to achieve a higher level of precision in real-world estimates (ie, reduced confidence intervals). Quantitative bias analysis confirmed the robustness of the results with respect to potential unmeasured confounding.
Conclusion: Target trial emulation with advanced statistical adjustment techniques is a promising approach to investigate long-term impact of innovative therapies in the French Epidemiological Strategy and Medical Economics–MBC cohort while minimizing biases and provides opportunities for comparative efficacy through the synthetic control arms provided.
Database registration: clinicaltrials.gov Identifier NCT03275311.

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ESMÉ
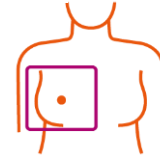
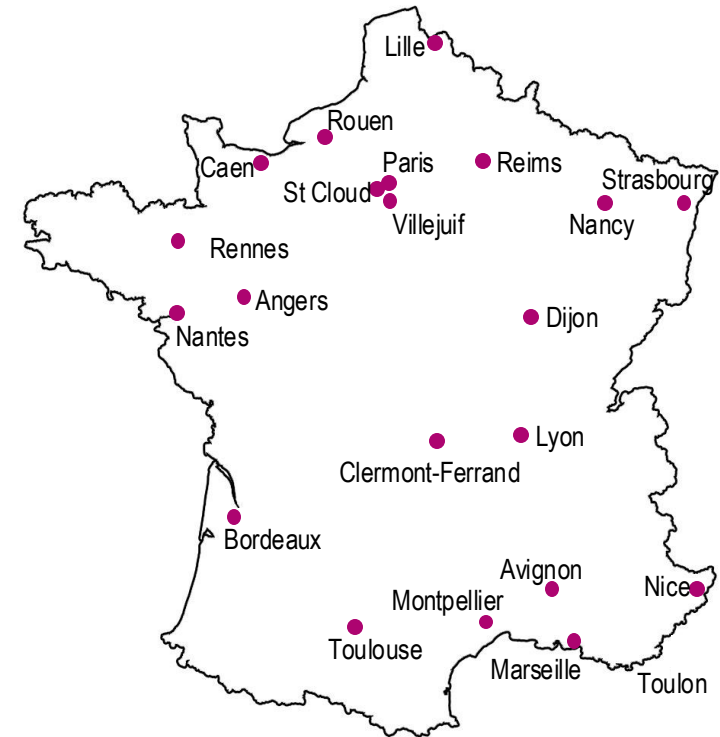## 32 598
Selected patients

Inclusion criteria

○ Male/Female
○ ≥ 18 years
○ MSC* management in a CCC since 2008

Radiotherapy, chemotherapy, targeted therapy or hormone therapy
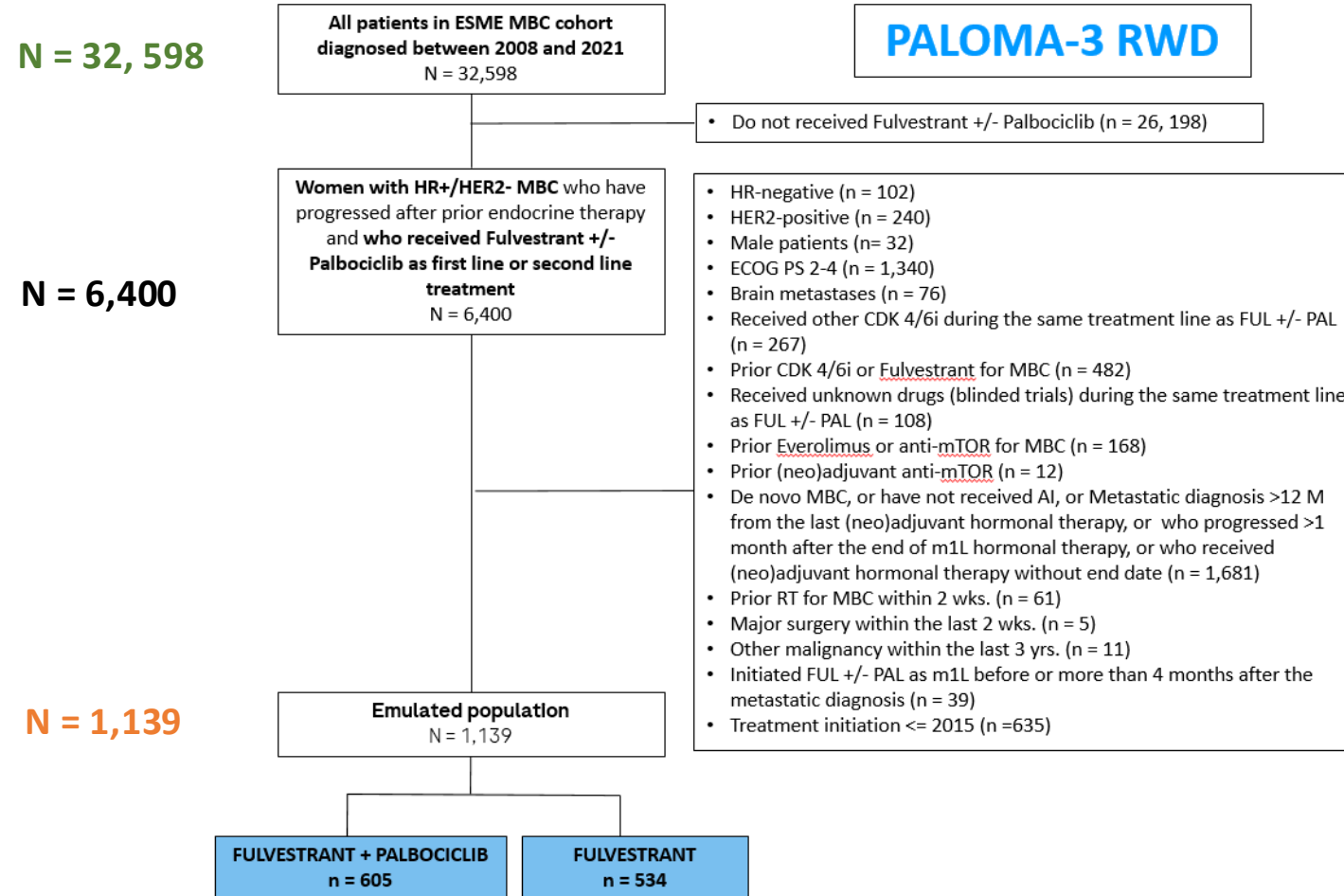
18 contributing centers

18 Comprehensive cancer centers (CCC) over 20 sites
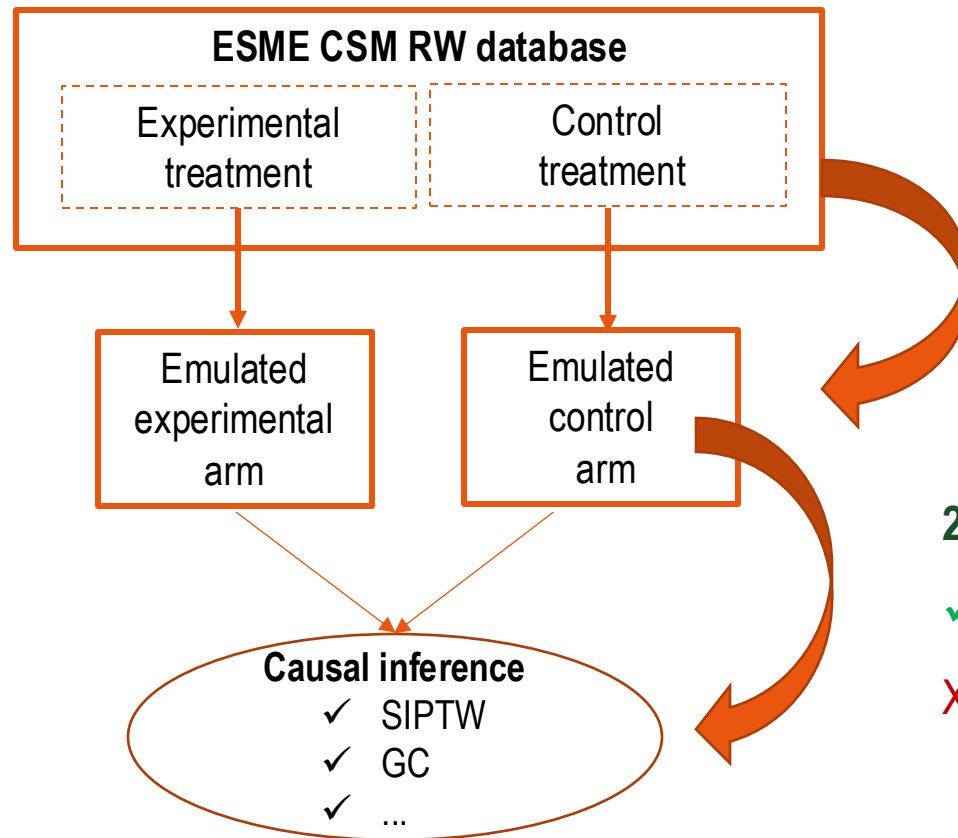
Source: Antoine A et al. J Natl Cancer Inst. 2023.

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ILLUSTRATION (#2)

ESME MBC : PALOMA-3 TRIAL

N = 32, 598

All patients in ESME MBC cohort diagnosed between 2008 and 2021
N = 32,598

PALOMA-3 RWD

- Do not received Fulvestrant +/- Palbociclib (n = 26, 198)

Women with HR+/HER2- MBC who have progressed after prior endocrine therapy and **who received Fulvestrant +/- Palbociclib as first line or second line treatment**
N = 6,400

N = 6,400

- HR-negative (n = 102)
- HER2-positive (n = 240)
- Male patients (n= 32)
- ECOG PS 2-4 (n = 1,340)
- Brain metastases (n = 76)
- Received other CDK 4/6i during the same treatment line as FUL +/- PAL (n = 267)
- Prior CDK 4/6i or Fulvestrant for MBC (n = 482)
- Received unknown drugs (blinded trials) during the same treatment line as FUL +/- PAL (n = 108)
- Prior Everolimus or anti-mTOR for MBC (n = 168)
- Prior (neo)adjuvant anti-mTOR (n = 12)
- De novo MBC, or have not received AI, or Metastatic diagnosis >12 M from the last (neo)adjuvant hormonal therapy, or who progressed >1 month after the end of m1L hormonal therapy, or who received (neo)adjuvant hormonal therapy without end date (n = 1,681)
- Prior RT for MBC within 2 wks. (n = 61)
- Major surgery within the last 2 wks. (n = 5)
- Other malignancy within the last 3 yrs. (n = 11)
- Initiated FUL +/- PAL as m1L before or more than 4 months after the metastatic diagnosis (n = 39)
- Treatment initiation <= 2015 (n =635)

N = 1,139

Emulated population
N = 1,139

FULVESTRANT + PALBOCICLIB
n = 605

FULVESTRANT
n = 534

Antoine A et al. Eur J Cancer 2024. In press.

REAL WORLD DATA AND DIGITAL ONCOLOGY

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ILLUSTRATION (#3)
ESME Metastatic Breast Cancer (MBC)

ESME CSM RW database

Experimental treatment | Control treatment

Emulated experimental arm | Emulated control arm

Causal inference
- ✓ SIPTW
- ✓ GC
- ✓ ...

1. **Selecting the emulated population**

- ✓ Selection bias (by design)
- ✓ Immortality bias (by design)
- ✓ Information bias (by design)...

X Confusion bias

2. **Statistical analysis: estimating the treatment effect**

- ✓ Confusion bias (adjustment)

X Residual confusion?

SIPTW: Stabilized inverse probability of treatment weighting; GC: g-computation

STATISTICAL ADJUSMENT METHODS

- Cox's multivariate regression

- **Stabilized Inverse Probability of Treatment Weighting (SIPTW)**

- **G-computation**

STATISTICAL ADJUSMENT METHODS (#2)

- **Stabilized Inverse Probability of Treatment Weighting (SIPTW)** [1]

  - Weighting method based on the propensity score (PS)

    - PS: defined as the probability of receiving a specific treatment conditional on its observed baseline characteristics

  - The PSs of patients in the experimental arm are weighted against those in the control arm so that baseline characteristics are balanced
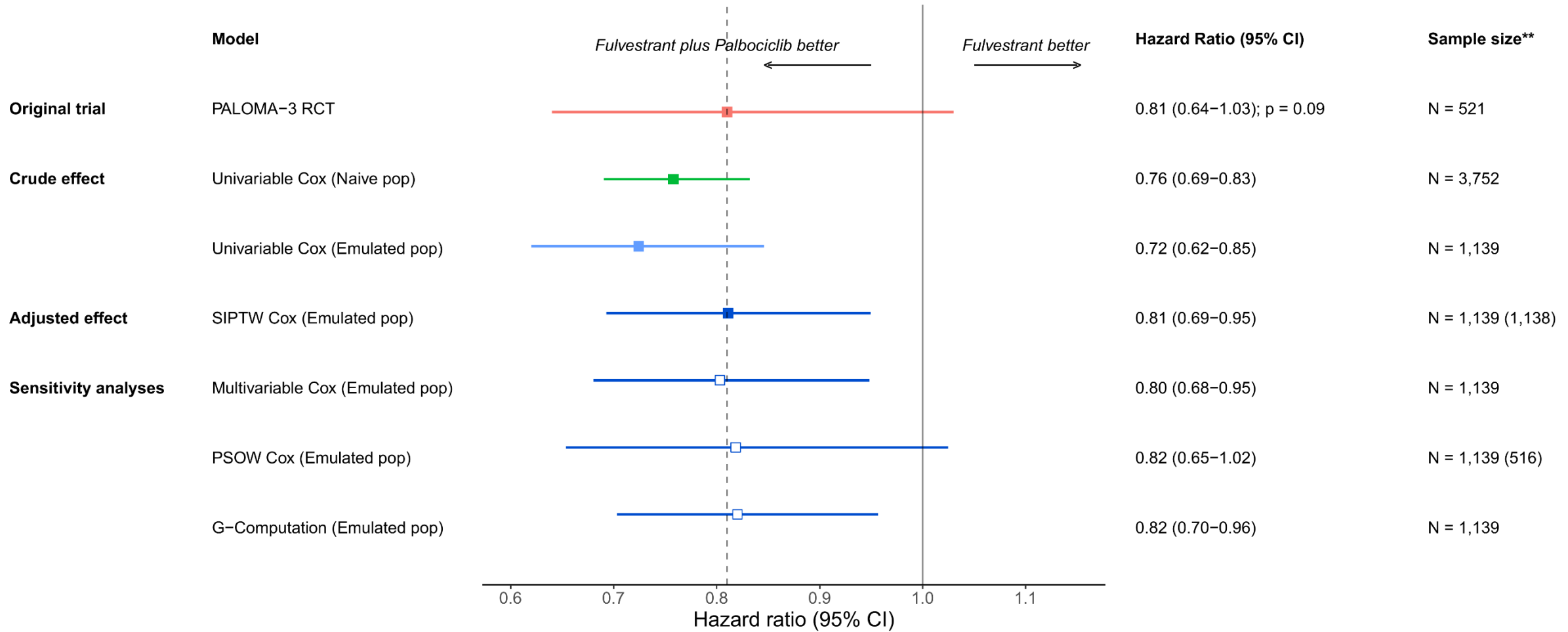
1. Robins, Hernan & Brumback Epidemiology 2000.

STATISTICAL ADJUSMENT METHODS (#3)

- **G-computation** [1,2]

  - Multistage process, modelling outcome as a function of treatment and adjustment covariates under different exposure scenarios

1. Snowden JM, Rose S & Mortimer KM Am J Epidemiol 2011. 2. Chetton A et al. Sci Rep 2020.

REAL WORLD DATA AND DIGITAL ONCOLOGY

PALOMA-3: TRIAL EMULATION USING ESME-MBC COHORT

Model		Hazard Ratio (95% CI)	Sample size**
Original trial	PALOMA−3 RCT	0.81 (0.64−1.03); p = 0.09	N = 521
Crude effect	Univariable Cox (Naive pop)	0.76 (0.69−0.83)	N = 3,752
	Univariable Cox (Emulated pop)	0.72 (0.62−0.85)	N = 1,139
Adjusted effect	SIPTW Cox (Emulated pop)	0.81 (0.69−0.95)	N = 1,139 (1,138)
Sensitivity analyses	Multivariable Cox (Emulated pop)	0.80 (0.68−0.95)	N = 1,139
	PSOW Cox (Emulated pop)	0.82 (0.65−1.02)	N = 1,139 (516)
	G−Computation (Emulated pop)	0.82 (0.70−0.96)	N = 1,139

Fulvestrant plus Palbociclib better ←   → *Fulvestrant better*

Hazard ratio (95% CI)

REAL WORLD DATA AND DIGITAL ONCOLOGY

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APPLICATION

Survival following adjuvant trastuzumab-based treatment among older patients with HER2-positive early invasive breast cancer: A national population-based cohort study using routine data

Melissa Ruth Gannon [a,b,*], David Dodwell [c], Katie Miller [a,b], Jibby Medina [a,b], Karen Clements [d], Kieran Horgan [e], Min Hae Park [a,b], David Alan Cromwell [a,b]
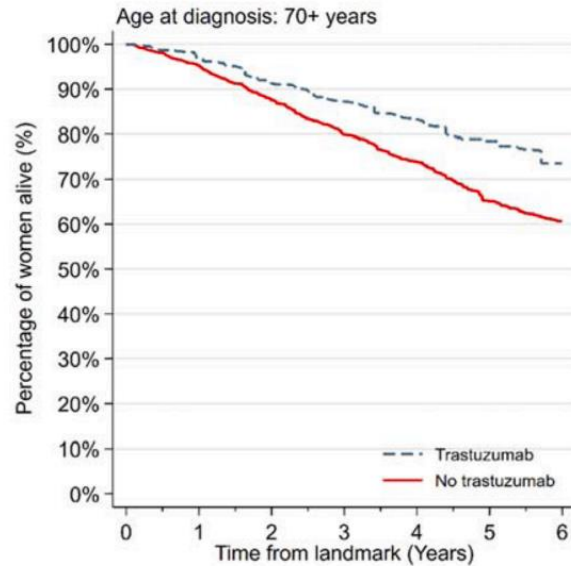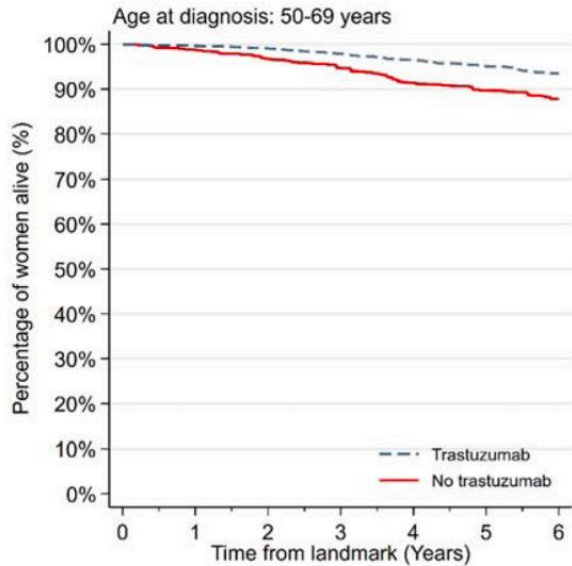
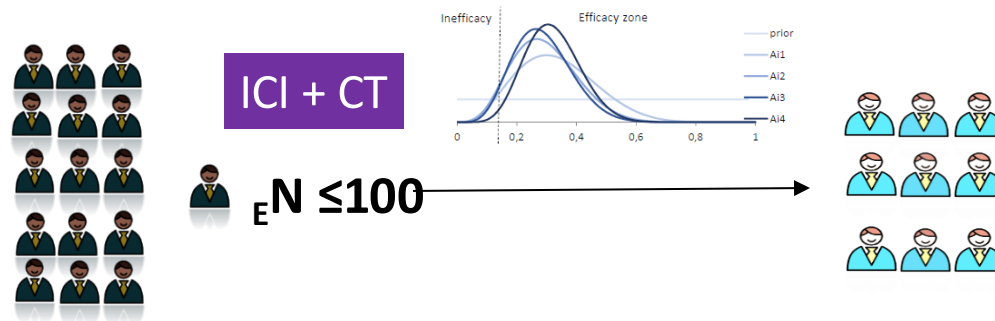*Source : MR Gannon et al. Eur J Cancer 2024.*
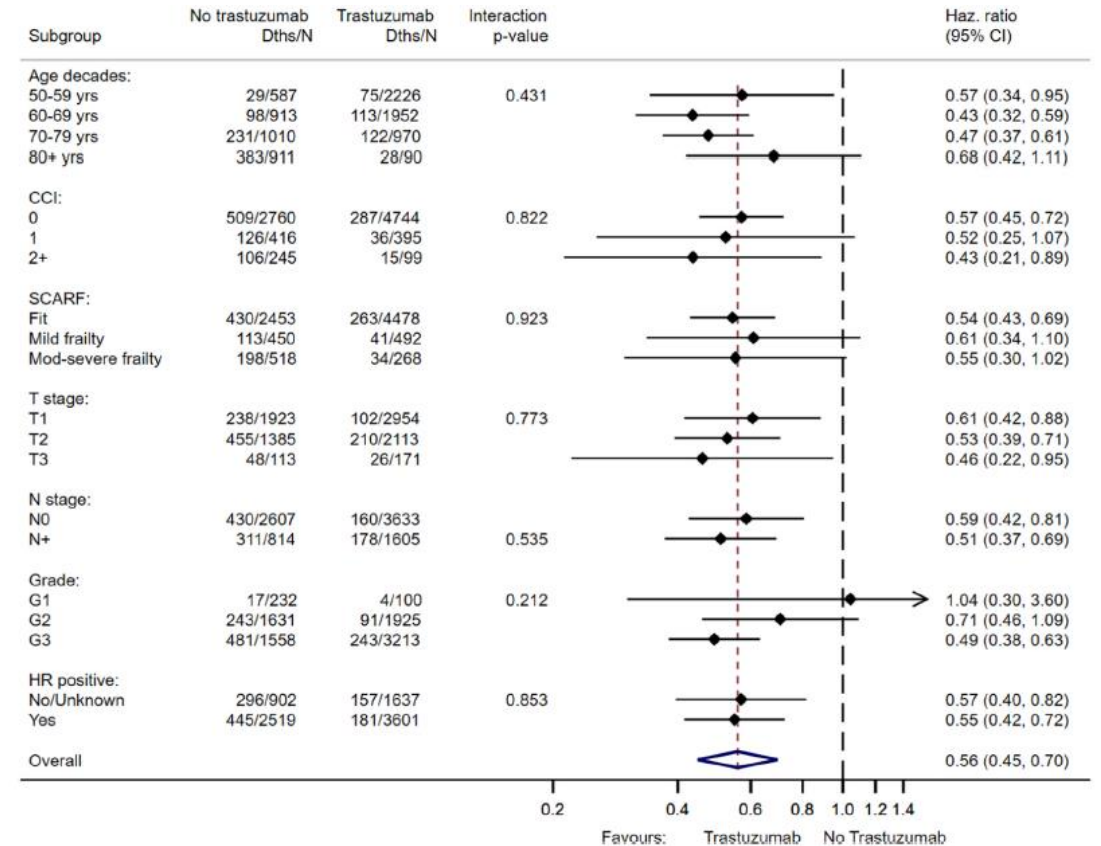
PERSPECTIVE: EXTERNAL CONTROL IN SAT

FIRST-NEC CLINICAL TRIAL (NCT06393816) in large-cell neuroendocrine lung cancer patients

- **Single-Arm Phase II Trial with RW external control (ESME lung cancer cohort)**
  - ⇨ **Emulation of a target trial** to assess the efficacy of standard chemotherapy (CT) $\pm$ immune checkpoint inhibitor (ICI)
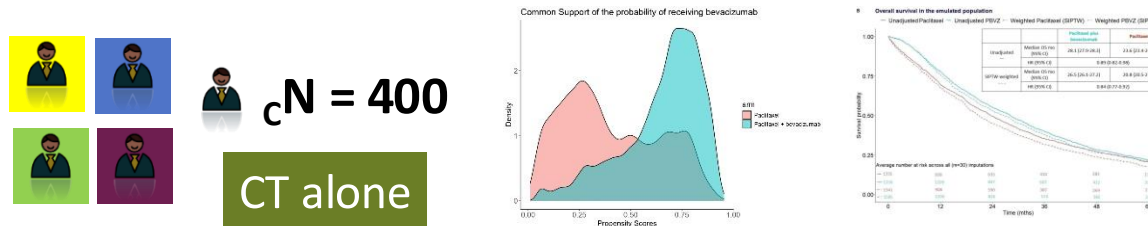

SAT

ICI + CT

$_E$N ≤100

RWD

ESME-LC cohort

$_C$N = 400

CT alone

Endpoints:

PFS and OS

SAT: Single Arm Trial

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GFPC
Groupe Français de Pneumo-Cancérologie
French Lung Cancer Group

ESMÉ

unicancer

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CONCLUSION

- **Trial emulation combined with appropriate adjustment can mitigate biases in RWD**

  - Implementation of eligibility criteria is a critical factor, like adjustment, in limiting biases in RWD studies

  - **Promising in atypical situations:** external control in SAT, RCTs subgroups issues, long-term OS measurement…

- **Constraints and limitations:**

  - Emulation requires **large databases with high quality & granularity**

  - Emulation of placebo and double-blind assignment is not possible

  - Difficulty of emulating contemporaneous arms in some situations

  - **Potential residual bias**: use of sensitivity analyses (simulation, negative controls)

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Thank you for your attention

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