ROPI
RETE ONCOLOGICA PAZIENTI ITALIA

Gemelli

CENTER FOR INTEGRATIVE ONCOLOGY

TERAPIE INTEGRATE IN ONCOLOGIA

1° Incontro

Terapie Integrate e carcinoma mammario

ROMA

27 GENNAIO 2023

Fondazione Policlinico Universitario "A. Gemelli" IRCCS
Aula 617 - 6° Piano - Ala A

Coordinatori Scientifici
Alessandra FABI - Stefania GORI

CON IL PATROCINIO DI

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La qualità di vita come endpoint della ricerca clinica

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Disclosure
as of January 27, 2022

In the last 3 years I received:

- **Personal** honoraria for acting as consultant or participating to advisory boards:
  - Merck Sharp & Dohme
  - AstraZeneca
  - Takeda
  - Eisai
  - Janssen
  - Pfizer
  - Roche
  - Novartis
  - Merck
  - Amgen
- **Institutional** research grant:
  - Tesaro - GlaxoSmithKline

Patient-reported outcomes

- A PRO (*patient-reported outcome*) is a **direct report of a patient's condition**, not interpreted nor modified from a clinician.

- PROs are considered the gold standard for the assessment of **subjective symptoms**, both in clinical practice and clinical trials.

Di Maio M, Basch E et al. Nat Rev Clin Oncol. 2016 May;13(5):319-25.
U.S. Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims.
European Medicines Agency. Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products.

Reasons to include PROs assessment in the clinical development programme for oncology medicinal products may encompass:

• Provide a **patient focused assessment** of the burden and impact of disease, by understanding how a treatment impacts on patient functioning and well-being;

European Medicines Agency, EMA/CHMP/292464/2014

Reasons to include PROs assessment in the clinical development programme for oncology medicinal products may encompass:

• Provide a patient focused assessment of the burden and impact of disease, by understanding how a treatment impacts on patient functioning and well-being;

• Add information on the **clinical benefit** of a therapy by complementing efficacy and safety data with patient-reported evaluation;

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• Provide a patient focused assessment of the burden and impact of disease, by understanding how a treatment impacts on patient functioning and well-being;

• Add information on the clinical benefit of a therapy by complementing efficacy and safety data with patient-reported evaluation;

• Assess the **relationship/ agreement** between clinical reported endpoints and patient-reported endpoints […];

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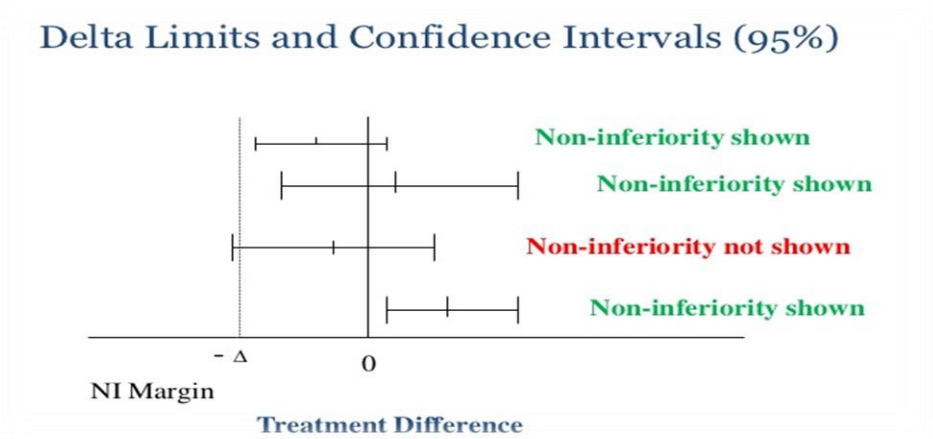
Reasons to include PROs assessment in the clinical development programme for oncology medicinal products may encompass:

- Attempt to differentiate two treatments in the **non-inferiority trial setting**, where the primary endpoint is an objective measure;



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Reasons to include PROs assessment in the clinical development programme for oncology medicinal products may encompass:

- Attempt to differentiate two treatments in the non-inferiority trial setting, where the primary endpoint is an objective measure;

- Provide information to facilitate more accurate future patient-physician **communication** in terms of the quality of the survival time remaining for the patient and the burden of treatment-related morbidities and disease-related patient impacts.

European Medicines Agency, EMA/CHMP/292464/2014

ESMO-Magnitude of Clinical Benefit Scale version 1.1

Quality of Life assessment /grade 3-4 toxicities assessment*

Does secondary endpoint quality of life show improvement	
Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being*	

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Adjustments

1. Upgrade 1 level if improved quality of life and/or less grade 3-4 toxicities impacting daily well-being are shown
2. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 year, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4

Final adjusted magnitude of clinical benefit grade

5	4	3	2	1

N.I. Cherny, et al. Annals of Oncology 2017, 28(10):2340-2366

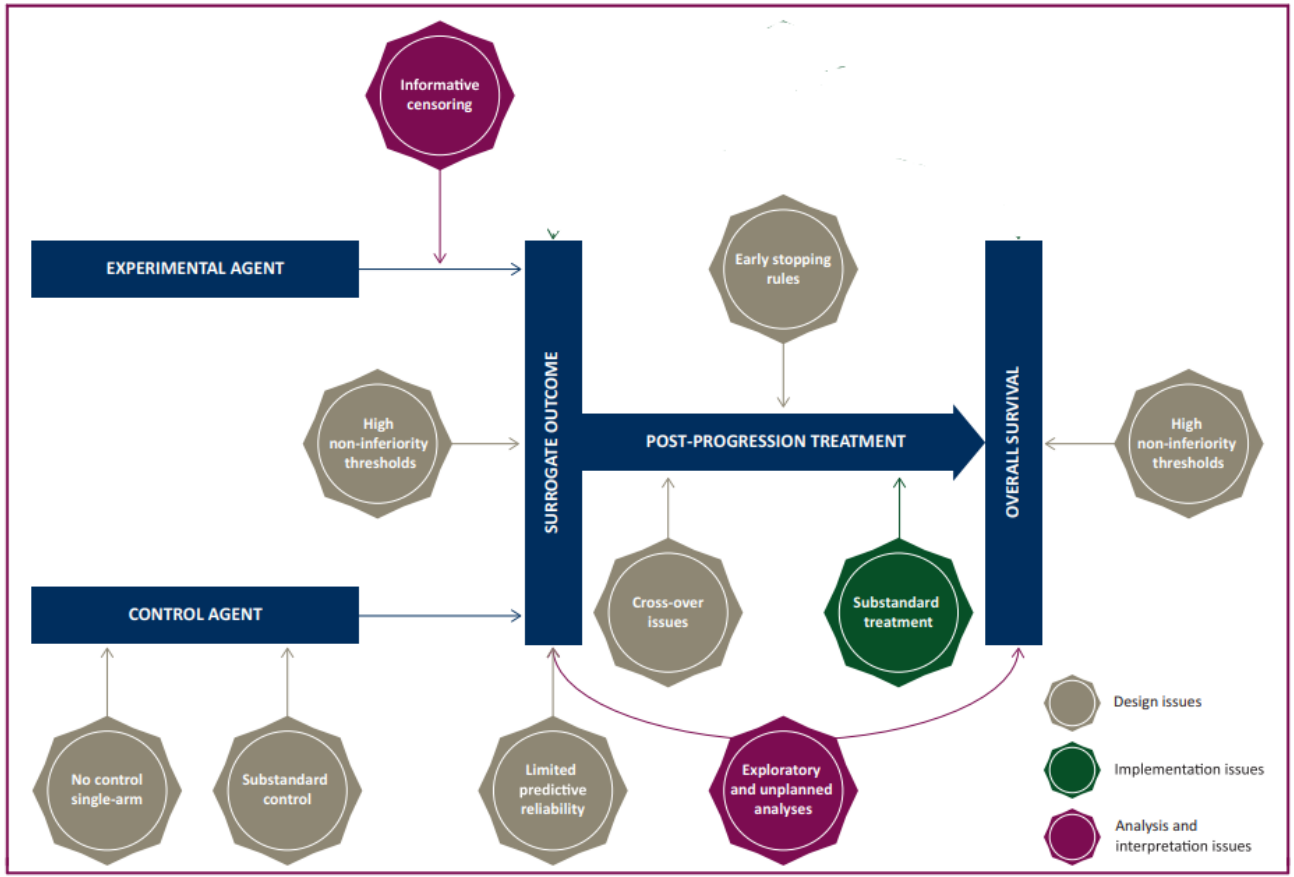
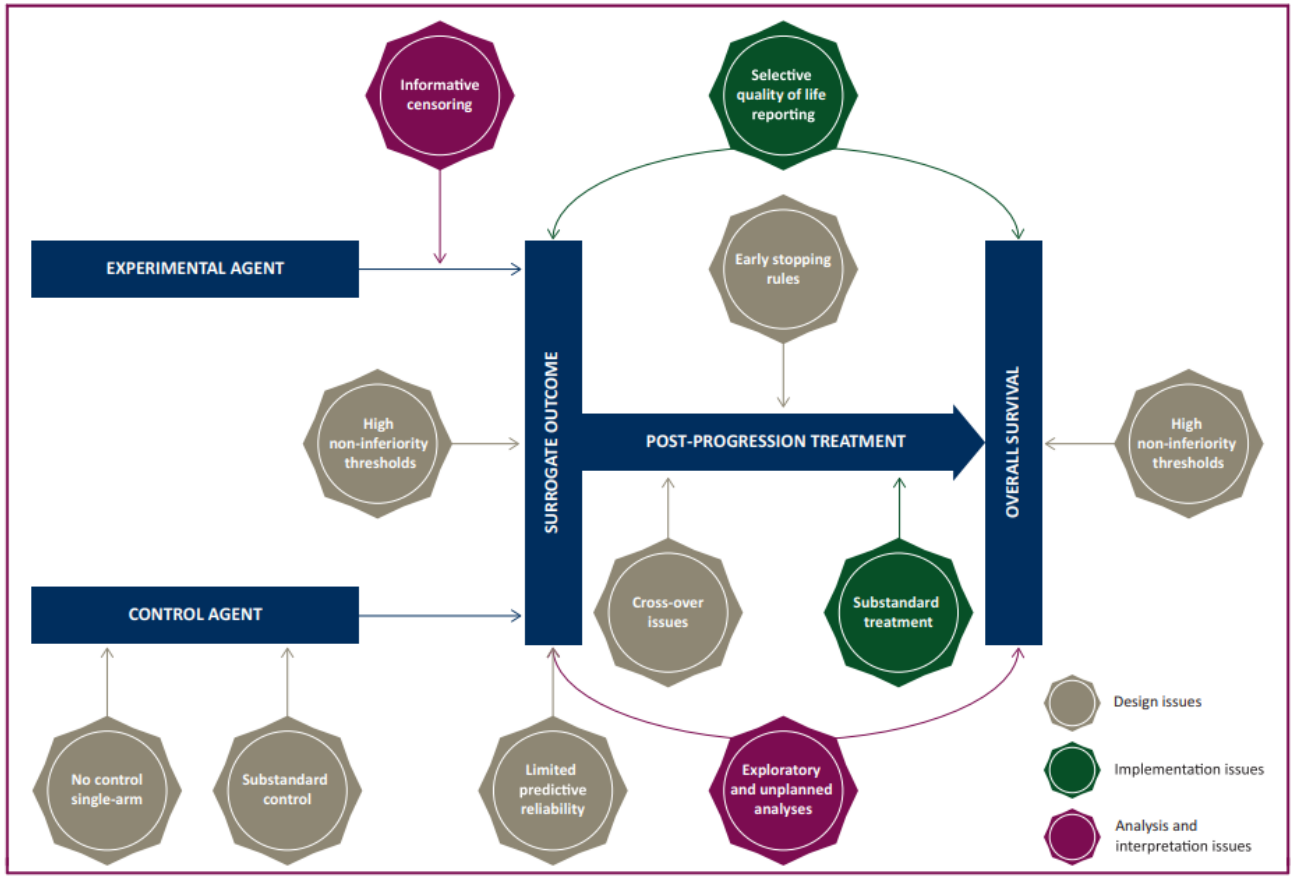


Figure 1. Issues in study design, implementation, and data analysis that may influence study outcomes and compromise the ESMO-MCBS scores.
HR, hazard ratio; NI, non-inferiority; QoL, quality of life.

Gyawali B, et al. ESMO Open. 2021 Jun;6(3):100117.



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Patient-reported outcomes are essential when their availability is prompt

30 Mar 2022 / *Massimo Di Maio - Guest editor*

Patient-reported outcomes provide important information for treatment decision-making but are not generally published alongside primary efficacy and safety data

ESMO Daily Reporter, 30 marzo 2022

Underrating and underreporting of QoL and PROs in oncology

2012-2016

- 446 phase III trials
- 47.1% QoL not included among endpoints
- 38.1% QoL results collected but not presented in primary publications

Marandino et al, Ann Oncol 2018

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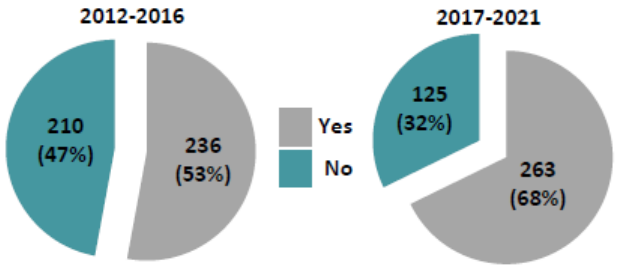
Fig.1 Inclusion of QoL among study endpoints



Marandino et al, ESMO 2022

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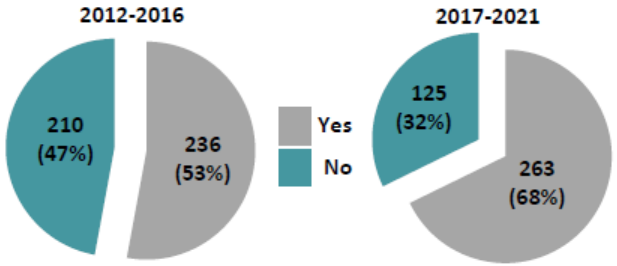
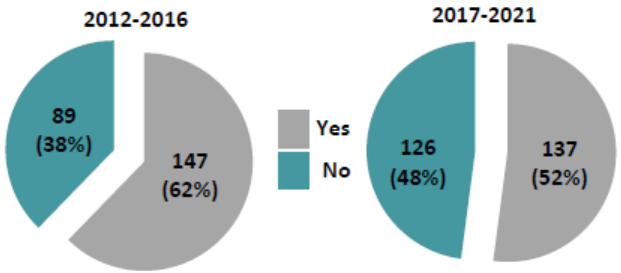


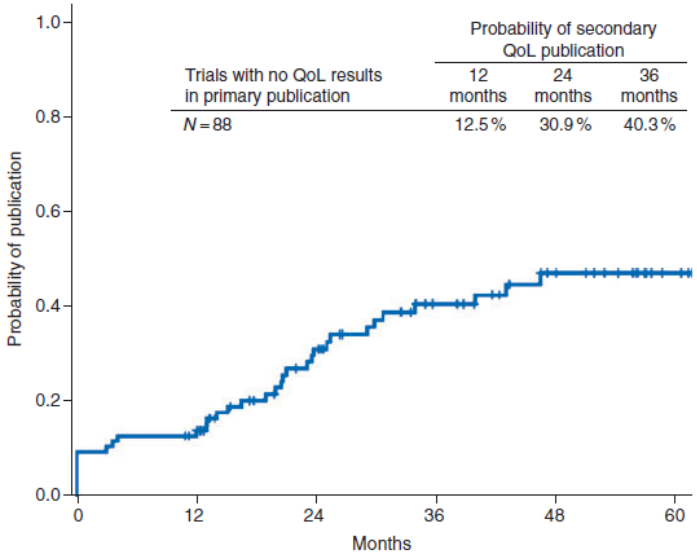
Fig.2 QoL results in primary study publication



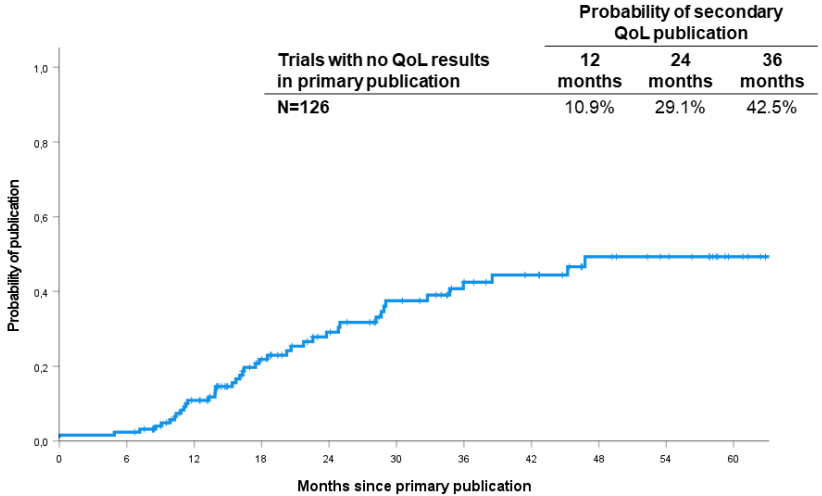
Marandino et al, ESMO 2022

Time to secondary publication of QoL results

2012-2016

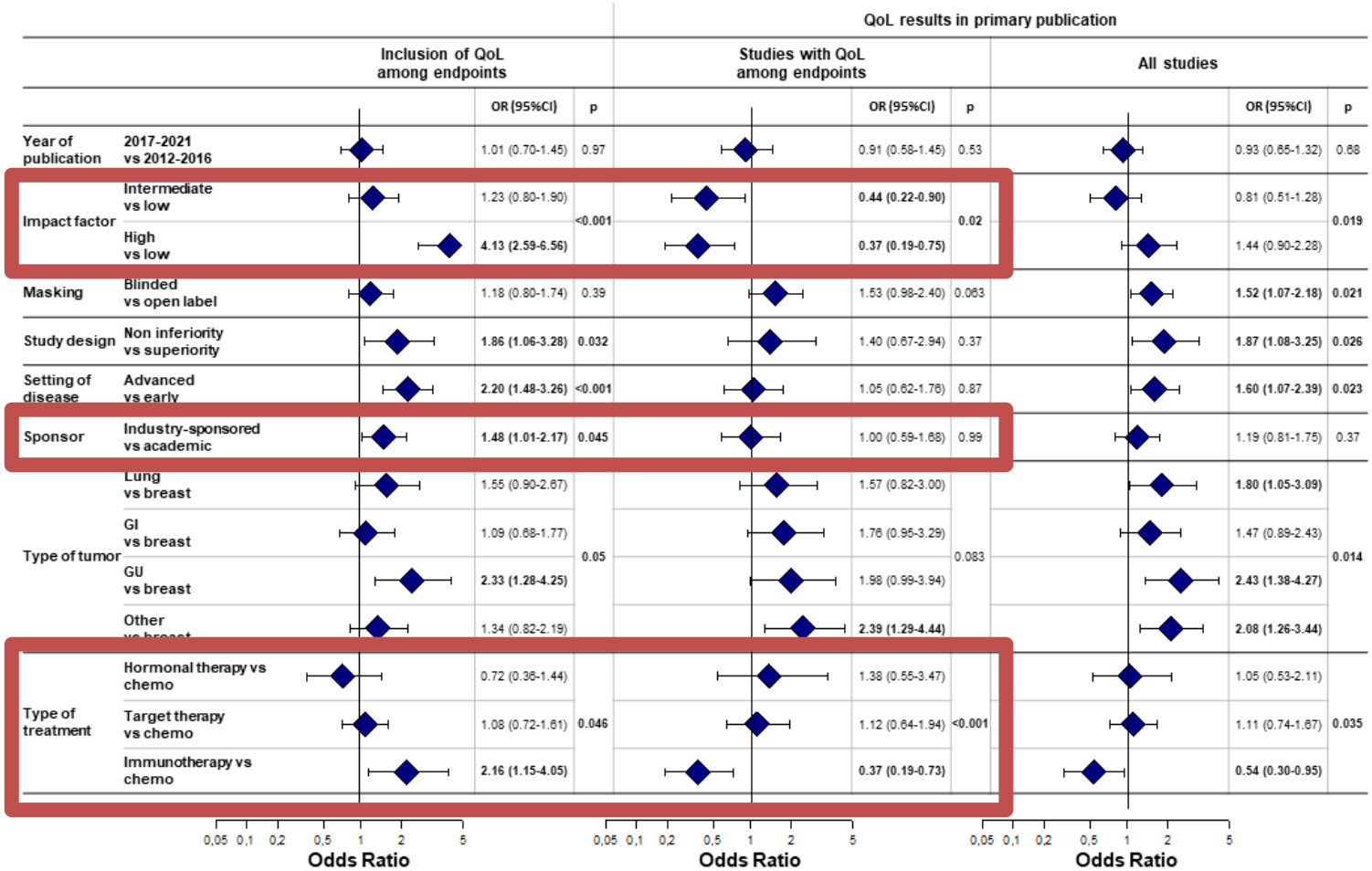


2017-2021



Marandino et al, Ann Oncol 2018

Submitted for publication



Submitted for publication

Perché abbiamo bisogno dei dati di QoL in uno studio positivo su altri endpoints?

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Perché abbiamo bisogno dei dati di QoL in uno studio positivo su altri endpoints?

- In uno studio positivo in OS:
  - La paziente vive meglio oltre a vivere di più?
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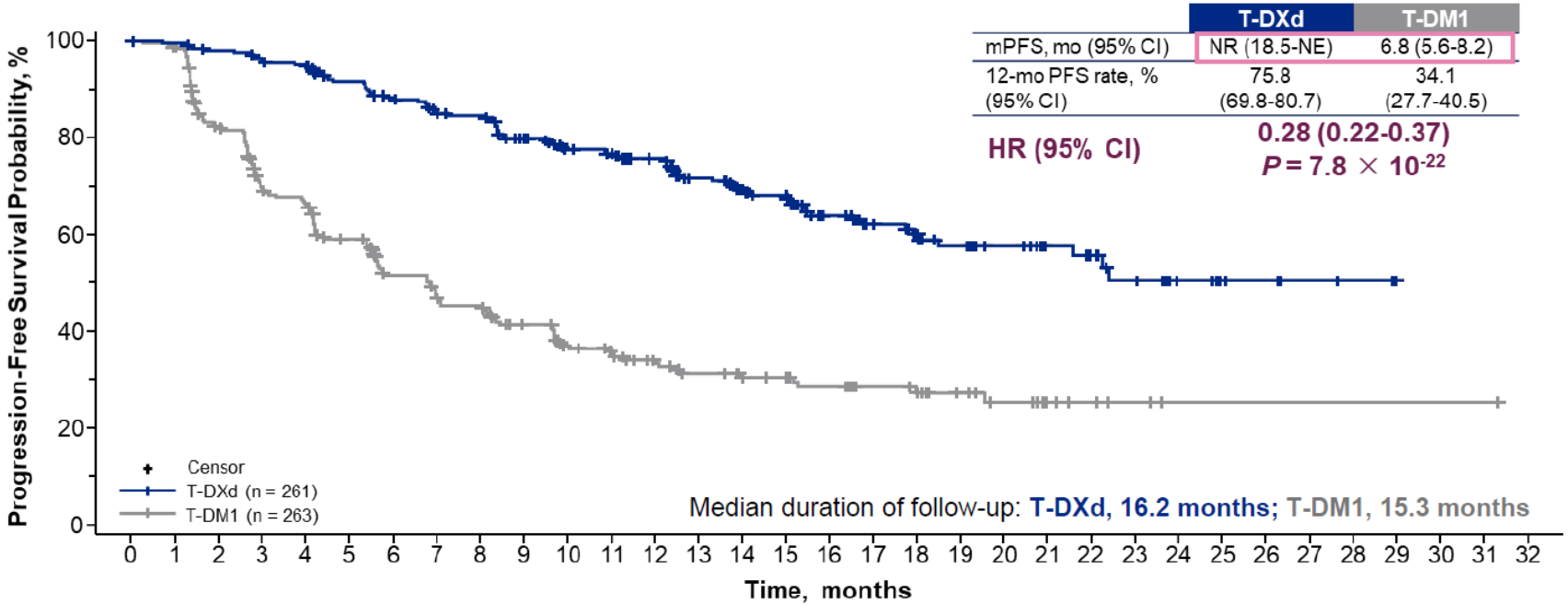
- In uno studio positivo in PFS:
  - Il beneficio è solo strumentale o anche clinico?
  - Che «prezzo» si paga in termini di tossicità / qualità di vita?

DESTINY-Breast03: PFS BY BICR[1-3]



	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

Patients Still at Risk:

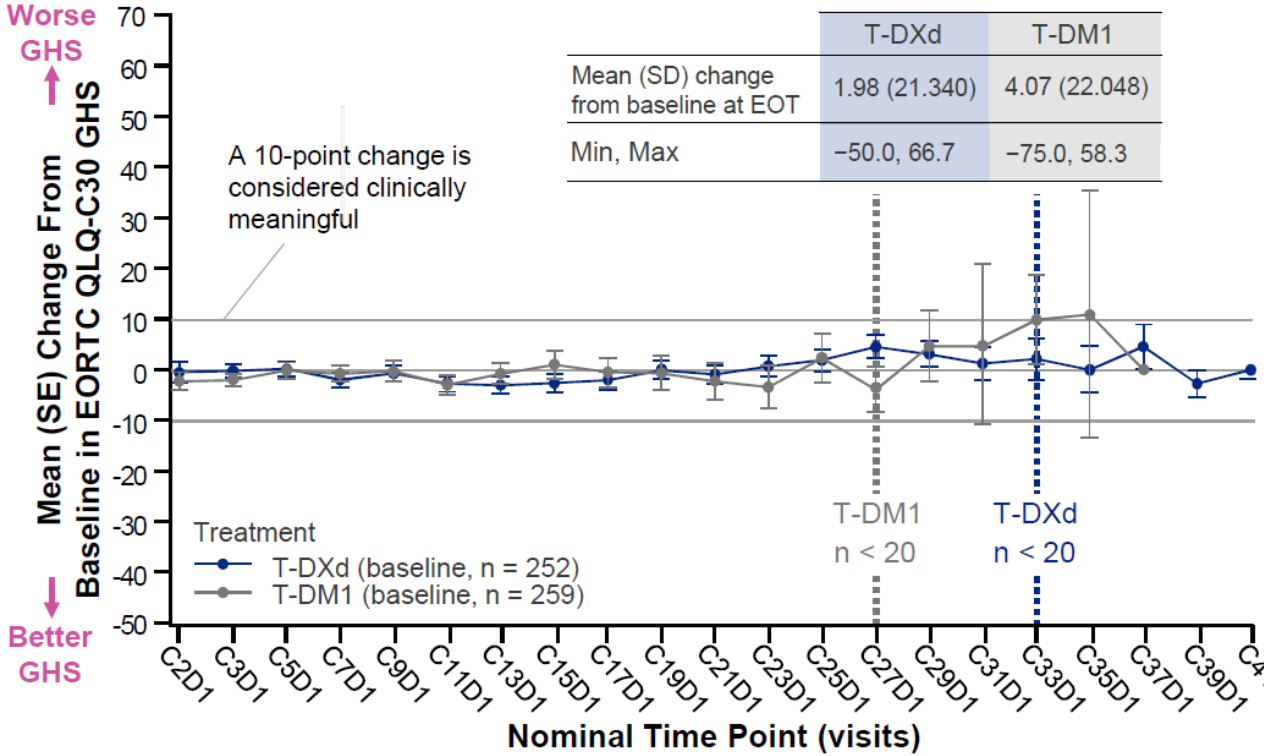
T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0	
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

BICR, blinded independent central review; HR, hazard ratio; mPFS, median progression-free survival; NE, not estimable; NR, not reached; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Cortés J et al. *N Engl J Med.* 2022;386:1143-1154. 2. Cortés J et al. *N Engl J Med.* 2022; 2022;386(supplement). 3. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021. Presentation GS3-01.

ESMO BREAST CANCER

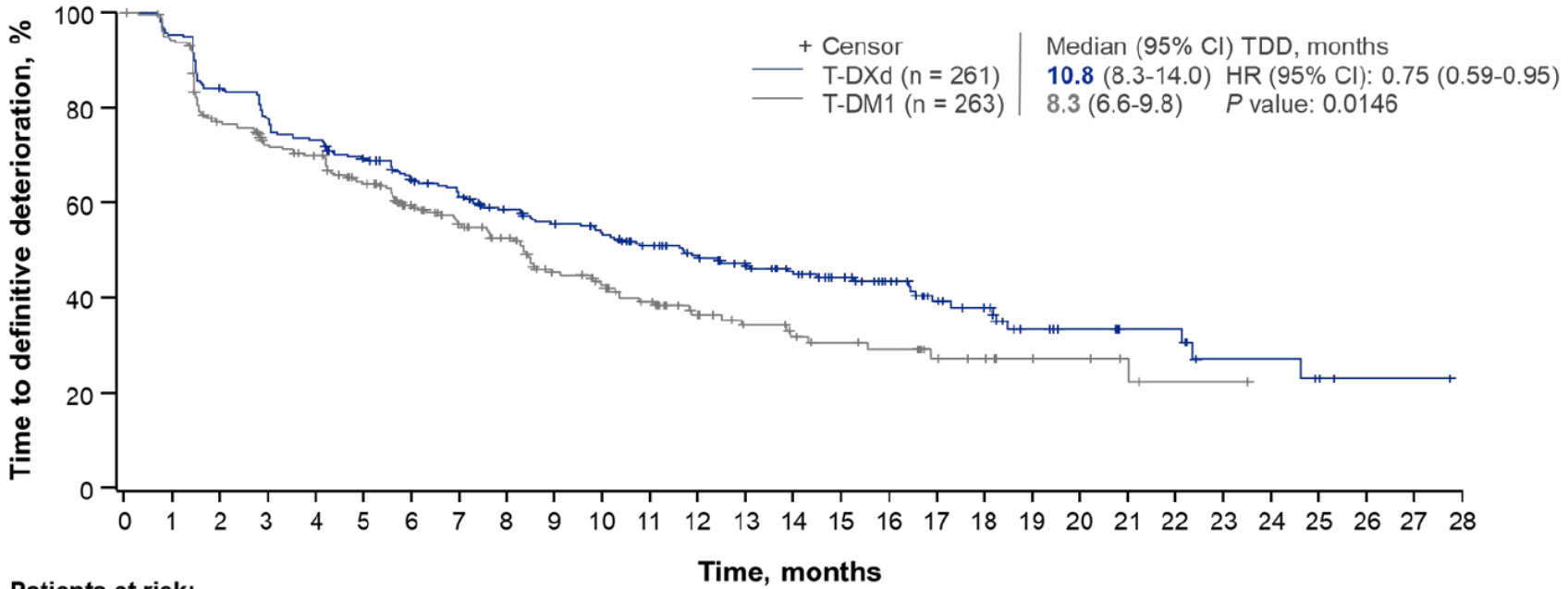
OVERALL HEALTH STATUS AND QOL ON TREATMENT



- As of May 21, 2021, patients still receiving study drug included:[1]
  - **T-DXd: 132 (51.4%)**
  - **T-DM1: 47 (18.0%)**
- Median (range) treatment duration:[2]
  - **T-DXd: 14.3 (0.7-29.8) months**
  - **T-DM1: 6.9 (0.7-25.1) months**
- **Global health was maintained in patients treated with T-DXd** while on treatment (until n < 20 when results are no longer informative)

C, cycle; D, day; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; GHS, global health scale; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Scores range from 0 to 100; a linear transformation was applied to the raw GHS score, thus a higher score represents lower ("worse") GHS/overall QoL
1. Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 16-21, 2021. Presentation 2525. 2. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154.

TDD OF QLQ-C30 PAIN SYMPTOMS



Patients at risk:

T-DXd	261	240	210	193	182	168	152	141	129	120	111	100	89	80	68	58	44	31	26	17	14	11	11	6	6	3	1	1	0
T-DM1	263	237	185	169	161	141	118	100	87	67	59	49	34	28	24	20	18	13	11	7	7	4	3	3	0				

EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; QLQ-C30, Quality of Life Core 30 questionnaire; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
P values are not adjusted for multiple testing. TDD is defined as a >10-point change from baseline.

Ref. Curigliano et al. ESMO BREAST CANCER 2022.

Problemi metodologici
nella valutazione della QoL negli studi clinici

- **Scelta del questionario**

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- **Gestione dei dati mancanti**
- **Molteplicità degli items**
- **Diverse modalità di analisi e presentazione dei risultati**
- **Statisticamente significativo vs clinicamente rilevante**

Take home messages

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- L'attenzione alla QoL è cruciale per una definizione più accurata del valore dei trattamenti antitumorali
- La valutazione della QoL negli studi clinici condotti in ambito oncologico non è priva di importanti sfide metodologiche
- E' importante fare cultura e formazione sull'impiego dei PROs e della QoL negli studi clinici, sulla tempestività e completezza della loro pubblicazione, nonché sulla loro corretta modalità di analisi e di interpretazione.

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