CON IL PATROCINIO

UNIVERSITÀ DI TORINO

Qualità di vita e carcinoma mammario: l'importanza della ricerca

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Disclosure
as of October 13, 2023

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In the last 3 years I received:

- **Personal** honoraria for acting as consultant or participating to advisory boards:
  - MSD; AstraZeneca; Takeda; Eisai; Janssen; Pfizer; Roche; Novartis; Merck; Amgen; Lilly; GSK

- **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:

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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;

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;

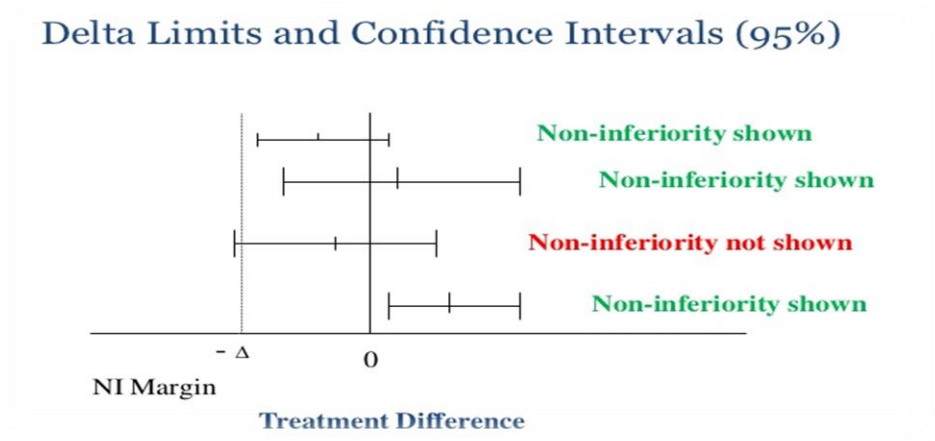
• Add information on the clinical benefit of a therapy by complementing efficacy and safety data with patient-reported evaluation;

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

European Medicines Agency, EMA/CHMP/292464/2014

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

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

Underrating and underreporting of QoL and PROs in oncology

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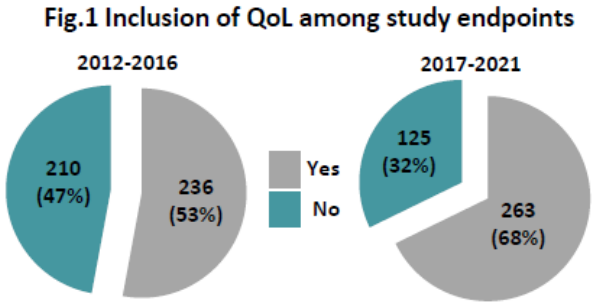
Marandino et al, Ann Oncol 2018

2017-2021

388 phase III trials



Marandino et al, BMJ Oncology 2023;2:e000021

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2017-2021

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Fig.1 Inclusion of QoL among study endpoints

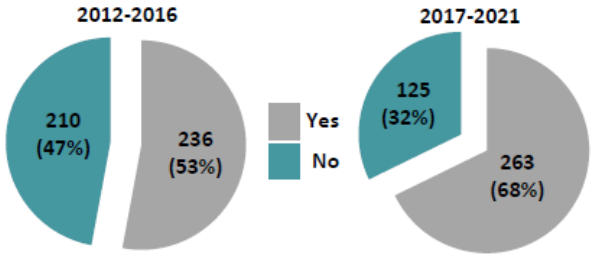
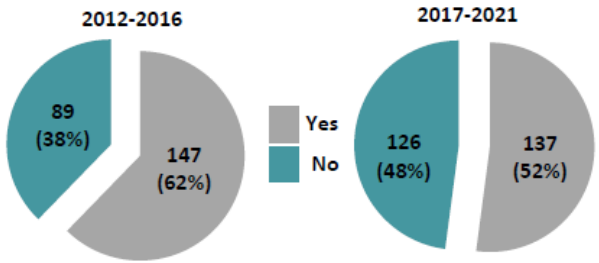
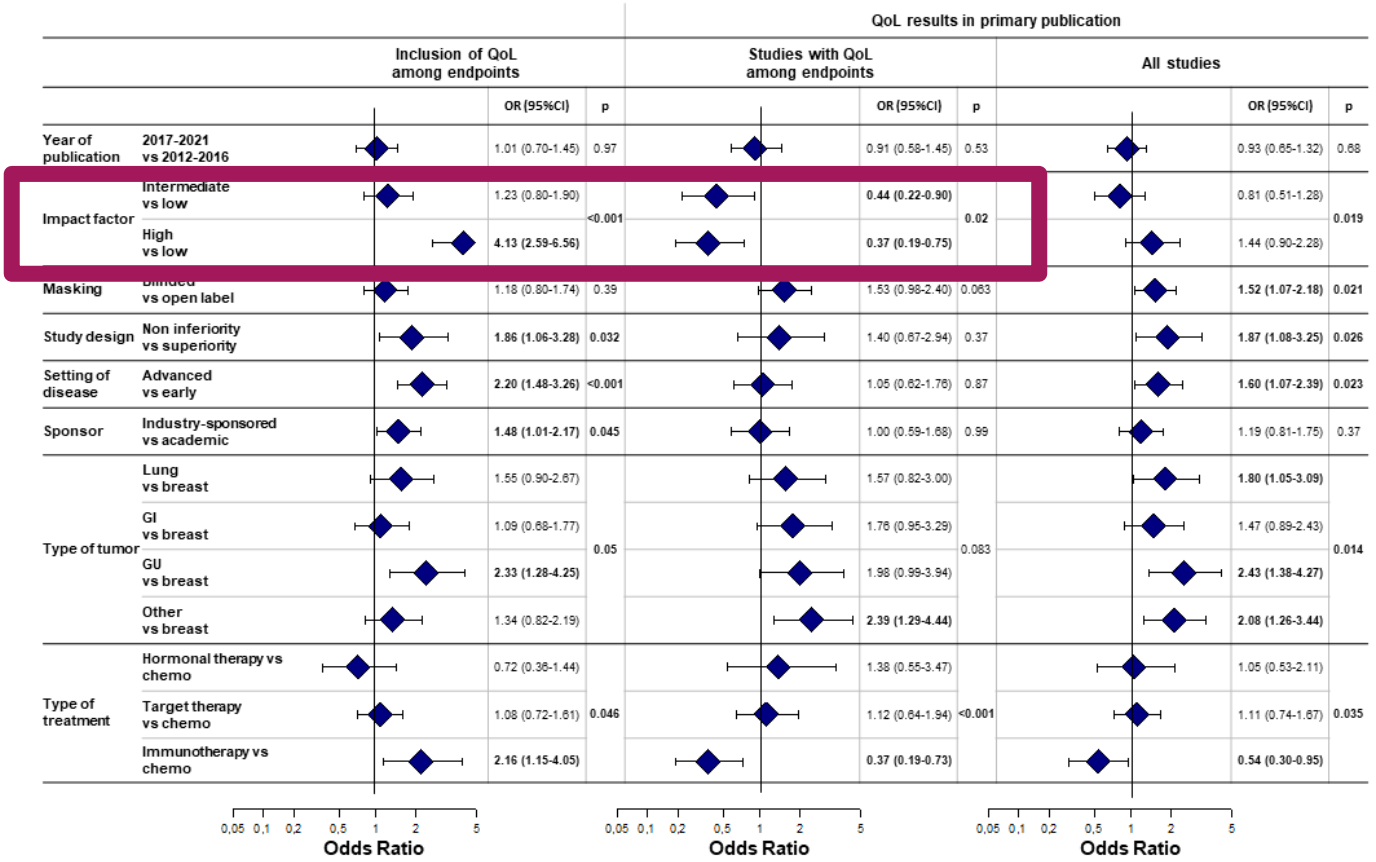


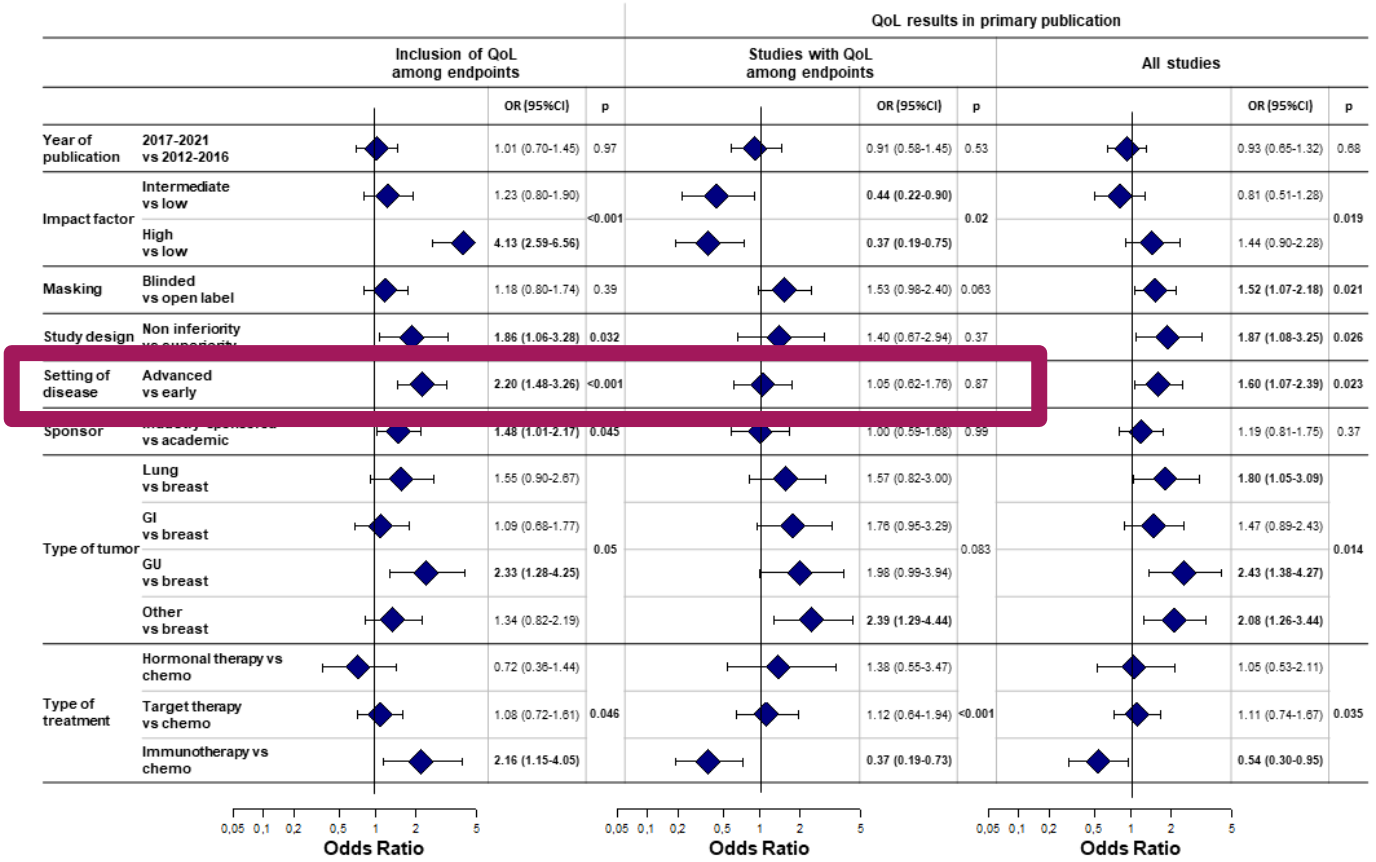
Fig.2 QoL results in primary study publication



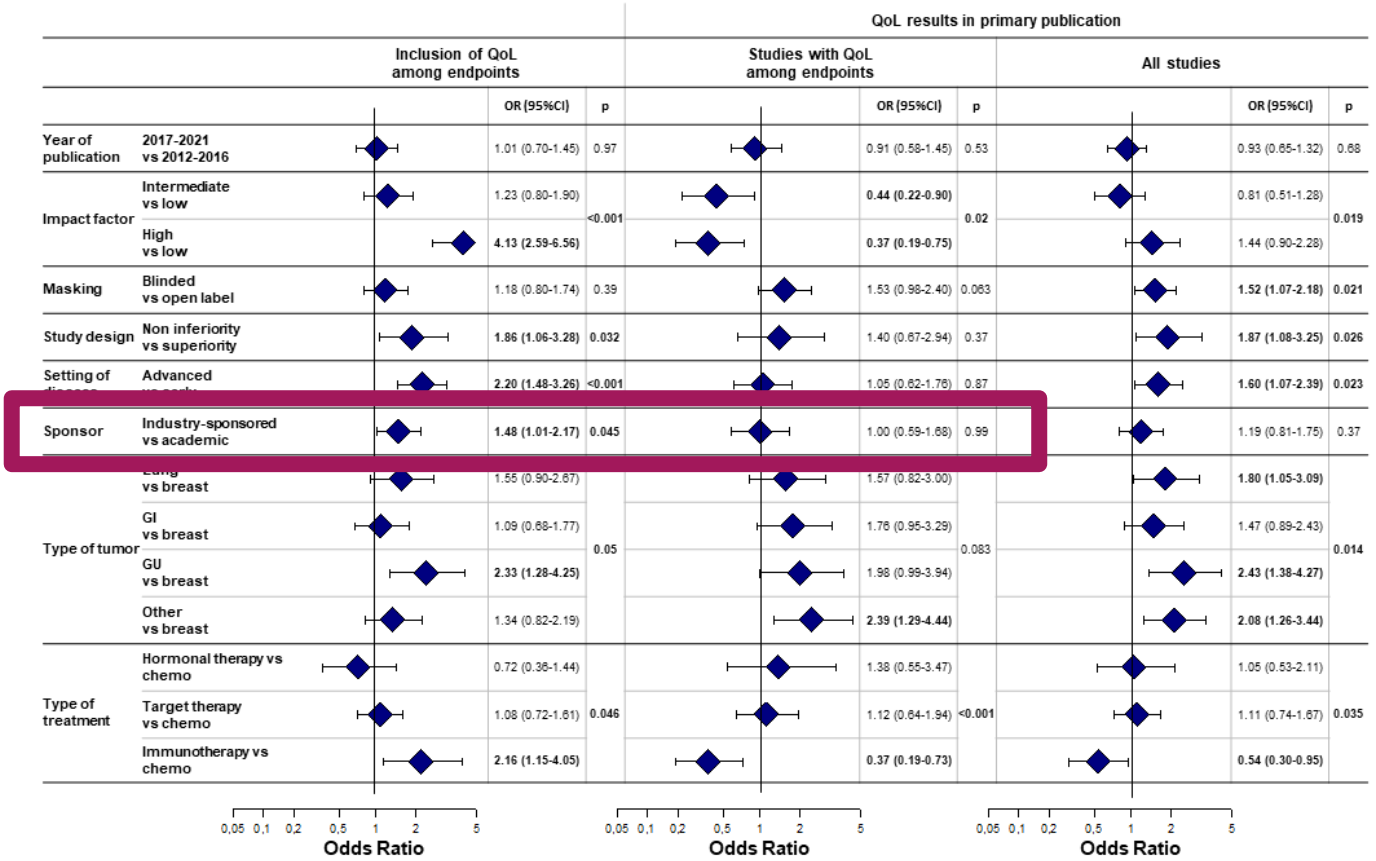
Marandino et al, BMJ Oncology 2023;2:e000021



Marandino et al, BMJ Oncology 2023;2:e000021.



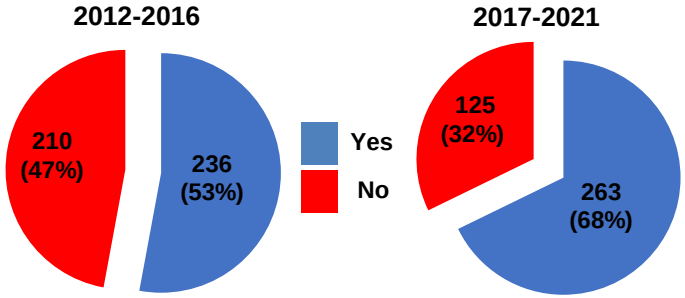
Marandino et al, BMJ Oncology 2023;2:e000021.



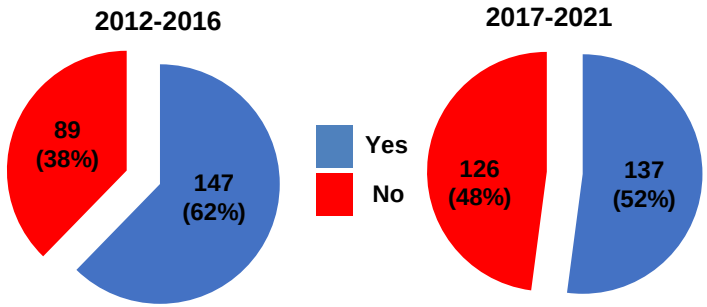
Marandino et al, BMJ Oncology 2023;2:e000021.

All tumors (n= 446 vs. 388)

Inclusion of QoL among study endpoints

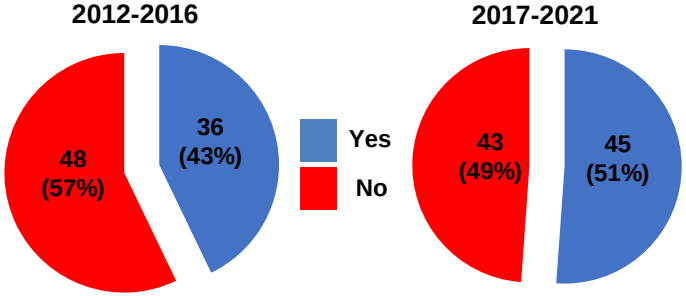


QoL results in primary study publication

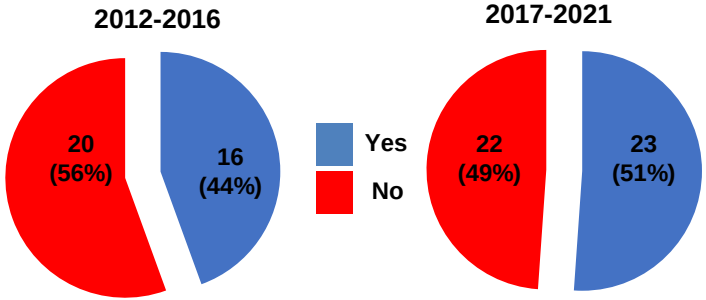


Breast cancer (n= 84 vs. 88)

Inclusion of QoL among study endpoints



QoL results in primary study publication



Marandino et al, BMJ Oncology 2023;2:e000021. (supplemental data)

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

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In uno studio positivo in OS:

La paziente vive meglio oltre a vivere di più?

Che «prezzo» si paga in termini di tossicità / qualità di vita?

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?**
- **Che «prezzo» si paga in termini di tossicità / qualità di vita?**

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?**

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

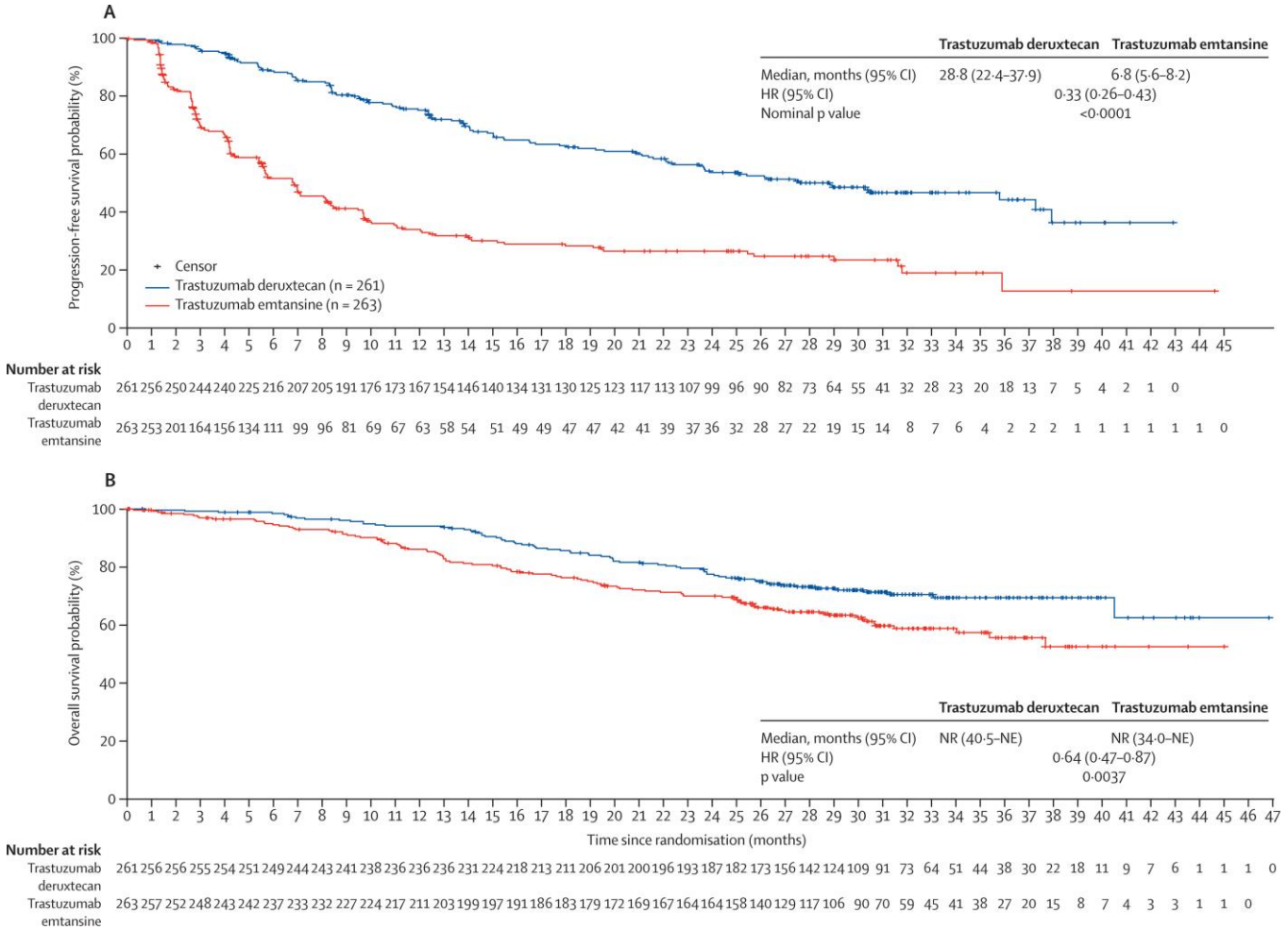
ANNALS OF ONCOLOGY
driving innovation in oncology

EDITORIAL

Trastuzumab deruxtecan for breast cancer: do patients experience a comprehensive benefit?

CHECK FOR UPDATES

Mosele F, Di Maio M.
Ann Oncol. 2023 Jul;34(7):567-568.



Hurvitz SA, et al. Lancet. 2023 Jan 14;401(10371):105-117.

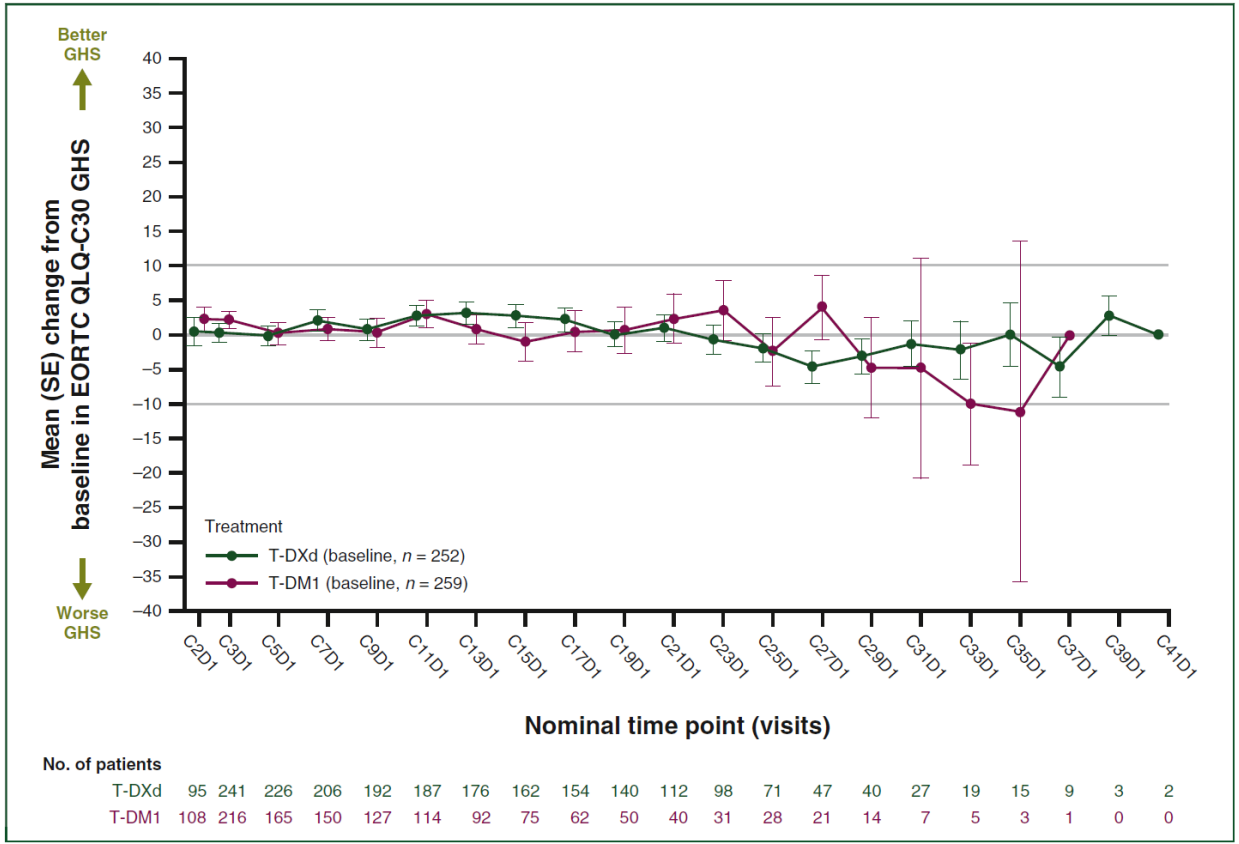


Figure 2. EORTC QLQ-C30 GHS change from baseline over time in patients treated with T-DXd versus T-DM1. Scores range from 0 to 100; a higher score represents higher ('better') GHS/overall QoL. At data cut-off (21 May 2021), the median (range) treatment duration was 14.3 (0.7-29.8) months for patients receiving T-DXd and 6.9 (0.7-25.1) months for patients receiving T-DM1.

C, cycle; D, day; EORTC, European Organization for Research and Treatment of Cancer; GHS, global health scale; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; SE, standard error; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Curigliano G, et al. Ann Oncol. 2023 Jul;34(7):569-577.

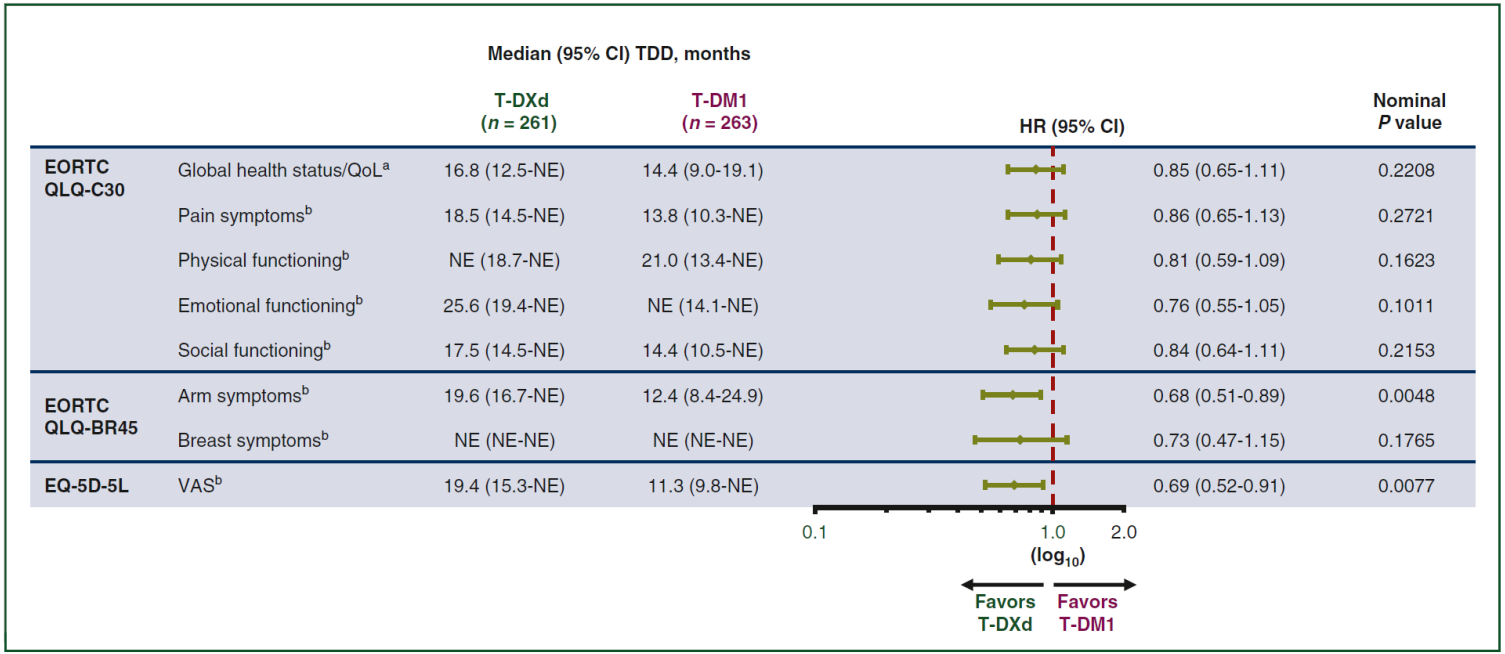


Figure 3. Difference in median TDD between patients treated with T-DXd versus T-DM1 in patient-reported QoL measures. PRO measures are reported such that a high GHS/QoL or VAS score represents a high QoL, a high score on functional scales represents a high level of functioning, and a high score on symptom scales represents a high level of symptomatology. TDD was defined as the number of days between the date of randomization and the date of the assessment at which the definitive deterioration event is first observed (i.e. a change exceeding +10 points for symptom scales, or a change exceeding −10 points for GHS, VAS, and functional scales, with deterioration on two or more consecutive visits or at last visit). *P* values are not adjusted for multiple testing.

CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; GHS, global health scale; HR, hazard ratio; NE, not estimable; PRO, patient-reported outcome; QLQ-BR45, Quality of Life Breast Cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TDD, time to definitive deterioration; VAS, visual analogue scale.

[a]Primary PRO variable of interest.

[b]Secondary PRO variable of interest.

Curigliano G, et al. Ann Oncol. 2023 Jul;34(7):569-577.

QoL in non-inferiority trials

- Phase III non-inferiority trials in adult patients affected by solid tumors, published between 2012 and 2021.
- Trials were classified according to 4 NI strategies:

  (1) different drugs;

  (2) alternative drug administration routes;

  (3) shorter treatment duration;

  (4) “deintensification” of treatment schedule.

Three main endpoints were:

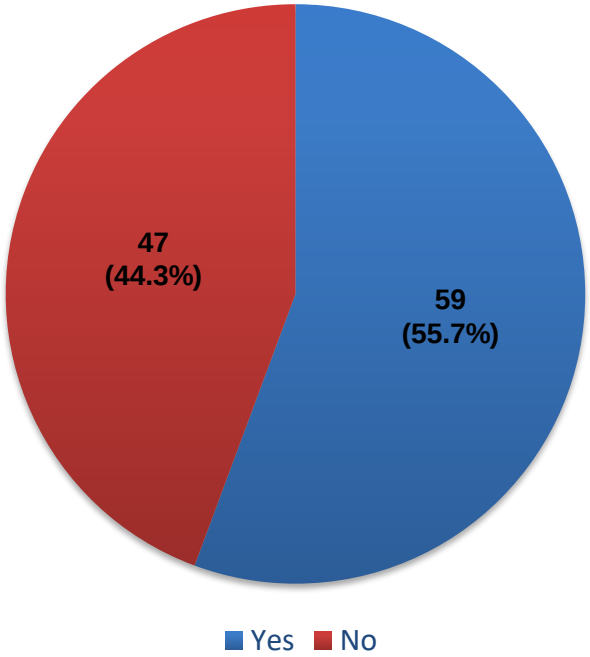
(1) proportion of publications including QoL among endpoints;

(2) proportion of primary publications reporting QoL results;

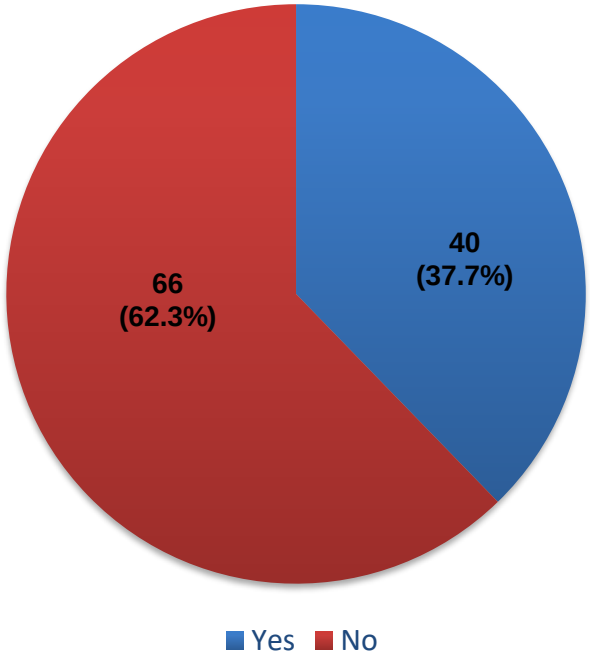
(3) proportion of trials with available QoL results actually favoring the experimental treatment out of trials declaring NI.

Notarnicola, Zumstein, Paparo et al, European Journal of Cancer 2023, October 9

A. QoL included among endpoints



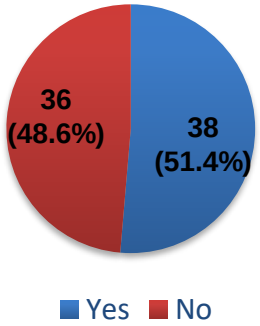
B. QoL results available in primary publication



Notarnicola, Zumstein, Paparo et al, European Journal of Cancer 2023, October 9

Trials demonstrating non-inferiority of the experimental arm (n=74)

A. QoL included among endpoints



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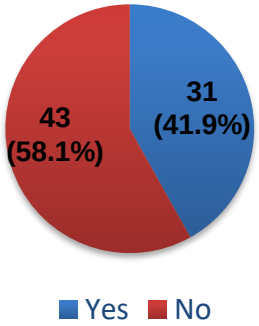
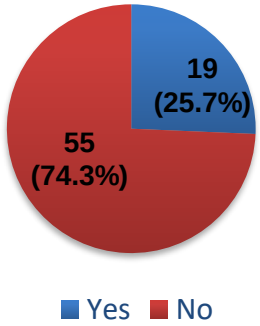


C. QoL results supporting experimental treatment



Notarnicola, Zumstein, Paparo et al, European Journal of Cancer 2023, October 9

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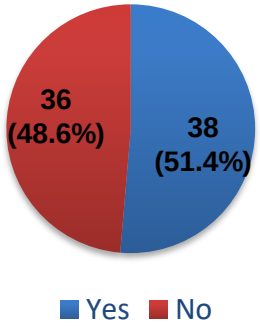

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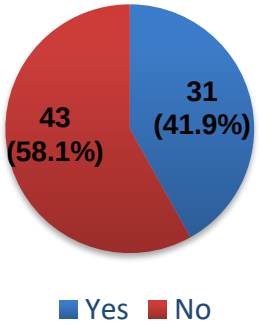

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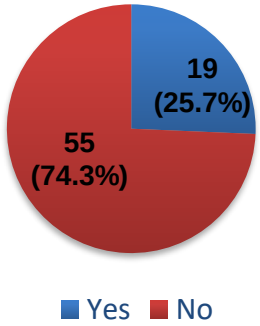
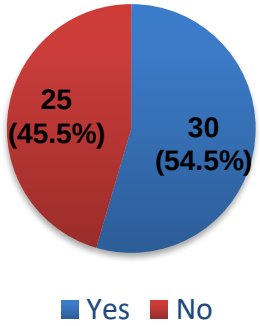
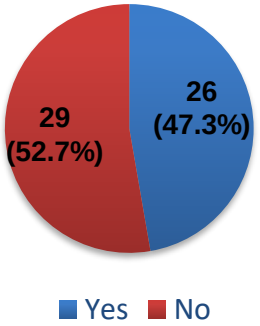


Trials testing the non-inferiority of different drugs, demonstrating non-inferiority of the experimental arm (n=55)

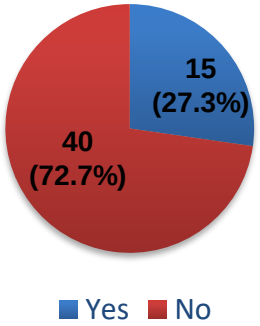
D. QoL included among endpoints



E. QoL results available in primary publication



F. QoL results supporting experimental treatment



Notarnicola, Zumstein, Paparo et al, European Journal of Cancer 2023, October 9

Problemi metodologici nella valutazione della QoL negli studi clinici

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

Take home messages

- 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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Qualità di vita e carcinoma mammario: l'importanza della ricerca

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