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Tailoring the optimal duration of the extended adjuvant endocrine therapy in patients with early-stage breast cancer. A systematic review and meta-analysis of randomized clinical trials☆

Laura Pala [a,1], Tommaso De Pas [a], Eleonora Pagan [b], Isabella Sala [b], Chiara Catania [a], Emma Zattarin [a], Paolo Arnone [c], Massimo M. Grassi [c], Marco Colleoni [d], Antonio C. Wolff [e], Javier Cortes [f,g], Martine Piccart [h], Richard D. Gelber [i], Giuseppe Viale [j,k], Vincenzo Bagnardi [b,1], Fabio Conforti [a,*]

[a] Department of Medical Oncology, Cliniche Humanitas Gavazzeni, Bergamo, 24125, Italy
[b] Department of Statistics and Quantitative Methods, University of Milan-Bicocca, Milan, Italy
[c] Breast Unit, Humanitas Gavazzeni Clinical Institute, Bergamo, Italy
[d] Division of Medical Senology, IEO, European Institute of Oncology IRCCS, Milan, Italy
[e] Johns Hopkins University, Baltimore, MD, USA
[f] International Breast Cancer Center, Pangaea Oncology, Quiron Group, Madrid and Barcelona, Spain
[g] Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain
[h] Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
[i] Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Harvard T.H. Chan School of Public Health, And Frontier Science & Technology Research Foundation, Boston, USA
[j] Department of Pathology, European Institute of Oncology & University of Milan, Milan, Italy
[k] University of Milan, Milan, Italy

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ABSTRACT

Background: Controversy exists regarding the optimal duration of the extended adjuvant endocrine treatment (ET) in patients with early-stage breast-cancer (eBC).
We performed a systematic review and trial-level meta-analysis of all randomized clinical trials (RCTs) comparing a "limited-extended" adjuvant ET (defined as more than 5 but less than 7.5 years of treatment overall) versus a "full-extended" adjuvant ET (defined as more than 7.5 years of treatment overall) in eBC.
Methods: To be eligible, RCTs had to i) compare a "limited-extended" adjuvant ET versus a "full-extended" adjuvant ET in patients with eBC; and ii) report disease-free survival (DFS) hazard ratio (HR) according to the disease nodal-status [i.e., nodal-negative (N-ve) versus nodal-positive (N + ve)].
The primary endpoint was to assess the difference in efficacy of full-versus limited-extended ET, measured in terms of the difference in DFS log-HR, according to the disease nodal-status. Secondary endpoint was the difference in efficacy of full-versus limited-extended ET according to tumor size (i.e., pT1 vs pT2/3/4), histological grade (i.e., G1/G2 vs G3), patients' age (i.e., ≤60 vs > 60 years) and previous type of ET (i.e., aromatase inhibitors vs tamoxifen vs switch strategy).
Results: Three phase III RCTs fulfilled the inclusion criteria. A total of 6689 patients were included in the analysis, of which 3506 (53%) had N + ve disease.
The full-extended ET provided no DFS-benefit as compared with the limited-extended ET in patients with N-ve disease (pooled DFS-HR = 1.04, 95%CI: 0.89 to 1.22; I^2 = 18%).
Conversely, in patients with N + ve disease the full-extended ET significantly improved DFS, with a pooled DFS-HR of 0.85 (95%CI: 0.74 to 0.97; I^2 = 0%).
There was a significant interaction between the disease nodal-status and the efficacy of the full-versus limited-extended ET (p-heterogeneity = 0.048).

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* Corresponding author.
E-mail address: fabio.conforti@gavazzeni.it (F. Conforti).

[1] These authors contributed equally.

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The full-extended ET provided no significant DFS-benefit as compared with the limited-extended ET in all the other subgroups analyzed.
Conclusions: Patients with eBC and N + ve disease can obtain a significant DFS-benefit from the full-extended as compared with the limited-extended adjuvant ET.

1. Introduction

Endocrine therapy (ET) represents the most effective adjuvant treatment for patients with endocrine responsive early-stage breast cancer (BC) [1].

Even after decades of using adjuvant ET as the cornerstone of early-stage BC systemic care and after many trials were conducted, controversy still exists regarding the optimal duration of adjuvant ET [1].

Robust evidence showed that after 5 years of adjuvant endocrine therapy, BC recurrences continued to occur steadily throughout the subsequent decades. The late risk of BC recurrence is mainly affected by nodal stage, and at less extent also by T-stage, histological grade, and patients' age (Table S1) [2].

Several randomized clinical trials (RCTs) showed significantly improved disease-free survival (DFS) for patients treated with ET extended to 10 years as compared with standard 5 years of treatment [3–6].

This holds true when 10 versus 5 years of tamoxifen was compared (i.e., ATLAS and aTTom trials), when 5 years of tamoxifen followed by 5 years of aromatase inhibitor (AI) was compared with 5 years of tamoxifen (i.e., MA17 trial), and when 5 years of extended AI followed 5 years of upfront AI or tamoxifen for ≤3 years then switched to an AI for the remainder of 5 years (i.e., NSABP-42 trial) [3–6].

Another group of RCTs tested the hypothesis that a "full-extended" adjuvant ET (i.e., more than 7.5 years of treatment overall) provided no further benefit as compared with a "limited-extended" ET (i.e., more than 5 but less than 7.5 years of treatment overall) [7–9].

Updated results of all these RCTs seem to support such hypothesis in the intention to treat (ITT) populations [7–9]. Subgroup analyses of the SALSA (ABCSG-16) trial and the IDEAL (BOOG 2006-05) trial failed to show significant benefit from the full-extended adjuvant ET for individual subgroups, but a non-significant trend for potential benefit from the full-extended ET was evident in all trials for patients with higher basal risk of disease relapse, identified by positive nodal disease [8,9]. In the DATA trial, patients with positive nodal status had significant DFS benefit from the full-extended adjuvant ET when compared to limited extended strategy, provided that their tumor was also positive for both hormone receptors [7].

We performed a systematic review and trial-level meta-analysis of RCTs to explore the hypothesis that the lack of significant interaction between the disease nodal-status and the efficacy of the full-versus limited-extended ET reported in each individual trial was due to a limited statistical power. Furthermore, we also explored the efficacy of the full-versus limited-extended ET according to the other clinical-pathological factors affecting the risk of late BC-recurrence.

2. Methods

2.1. Search strategy and selection criteria

We followed PRISMA guidelines for this systematic review and meta-analysis.

We searched PubMed, MEDLINE, Embase, and Scopus for randomized controlled trials published from the inception of each database to September 15, 2022.

Two investigators (FC and LP) independently searched the databases. The search terms were "Extended Adjuvant endocrine therapy", "Early Breast Cancer", "Randomized clinical trials".

We also reviewed abstracts and presentations from all major conference proceedings, including the American Society of Clinical Oncology and the European Society for Medical Oncology, up to September 15, 2022.

To be eligible, randomized trials had to: i) compare a "limited extended" adjuvant ET (defined as more than 5 but less than 7.5 years of treatment overall) versus a "full extended" adjuvant ET (defined as more than 7.5 years of treatment overall) in patients with early-stage BC, and ii) report DFS hazard ratio (HR) according to the nodal status of disease (i.e., negative versus positive).

Two investigators (FC and LP) independently reviewed the list of retrieved articles to choose potentially relevant articles, and disagreements were discussed and resolved with the consensus of all investigators.

Two reviewers (FC and EP) independently extracted data from the studies and all discrepancies were resolved by consensus with all investigators.

2.2. Data analysis

From each included trial, we extracted the study name, first author and year of publication, study design and blinding, study phase, median follow-up time, number of patients, age at randomization, tumor size, histological grade, HER2 status, histology, nodal status of disease, prior endocrine treatment, type of ET and duration for each treatment arm, HR for DFS in overall population, and HR for DFS according to nodal status of disease, age at randomization, tumor size, histological grade, prior endocrine treatment. We included only the most recent and complete report of controlled trials when duplicate publications were identified.

We assessed the methodological quality of studies (to ascertain risk of bias) using the five-point Jadad ranking system [10]. This system assesses the quality of randomization and double-blinding, and the flow of patients (withdrawals and dropouts). A controlled trial could receive a Jadad score of between 0 (poor methodological quality) and 5 (optimal methodological quality).

The primary endpoint was to assess the difference in treatment arms efficacy (i.e., full-versus limited-extended ET), measured in terms of the difference in DFS log-HR, according to disease nodal status.

As secondary endpoint, we explored differences in treatment arms efficacy according to tumor size (i.e., pT1 vs pT2/3/4), histological grade (i.e., G1/G2 vs G3) and patients' age (i.e., ≤60 vs > 60 years).

Additionally, since in the SALSA and IDEAL trials patients could be treated in the first 5 years of treatment with AIs or tamoxifen or switch strategy, we assessed the difference in treatment arms efficacy according to the type of previous endocrine therapy received by patients (the DATA trial was excluded from this last analysis since all patients only received tamoxifen in the first 5 years) [7–9].

We extracted the HRs for disease relapse or death for the full-extended versus limited-extended ET arm, and their 95% CIs from each study, overall and separately for patients of each stratum of the subgroup analyzed. HRs and confidence intervals (CIs) were translated into log-HRs and the corresponding variances. We calculated the pooled HRs of DFS using fixed-effects model. Weights were taken equal to the inverse of the reported within-study variance. We did the Q-test to assess the between-study heterogeneity, and calculated the I^2 statistic, which expresses the percentage of the total observed variability due to study heterogeneity. We assessed the heterogeneity between the strata estimates using a z-test.

When the original publication reported multiple HRs for a specific

subgroup (e.g., separate HRs for G1 and G2 within the G1/G2 subgroup), we applied a two-stage meta-analytic approach. Initially, a fixed-effects model was utilized to combine the multiple estimates into a single pooled estimate, and subsequently, this estimate was included in the between-study meta-analysis.

All reported p-values are two-sided. All analyses were performed using R software (version 3.4.0).

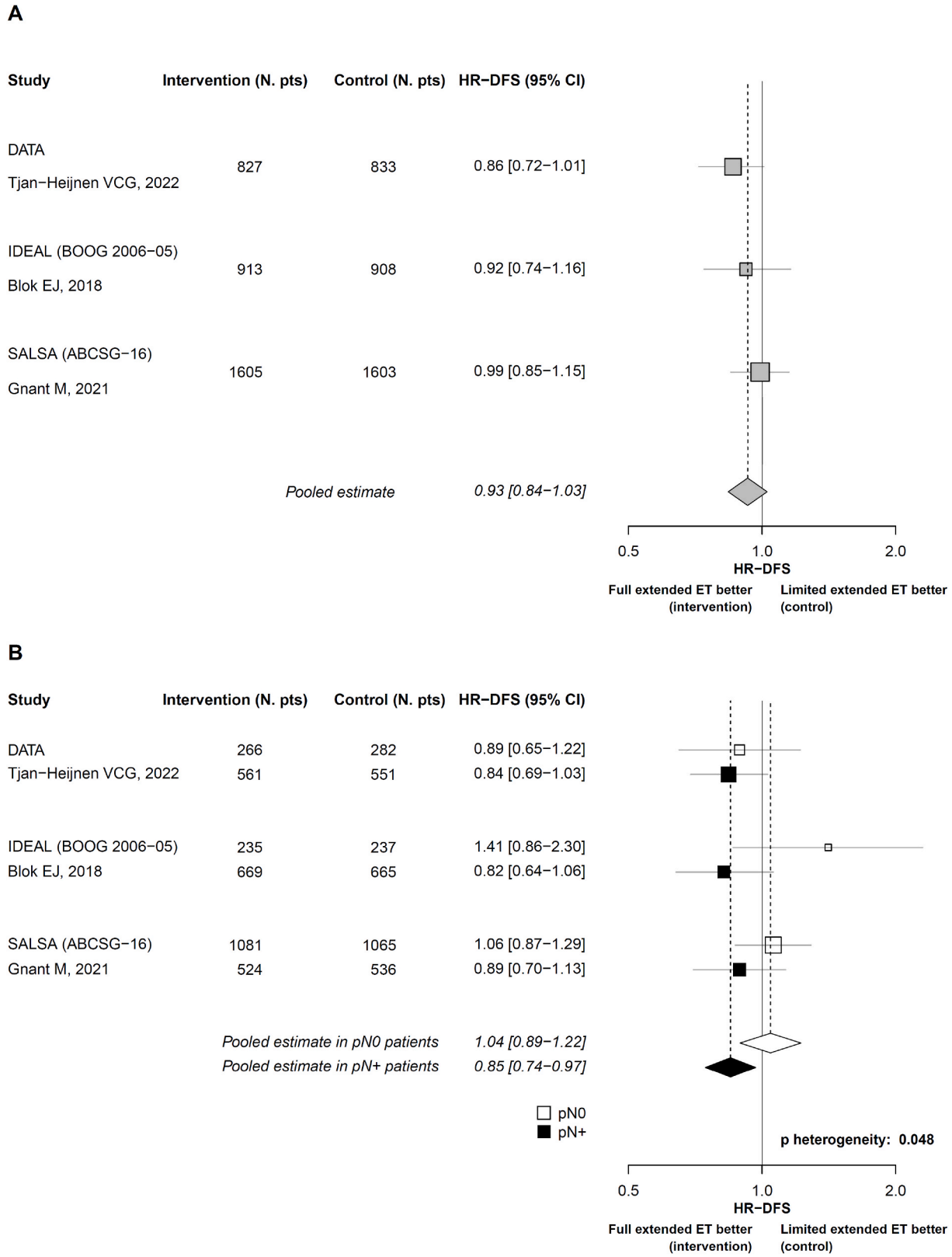

Fig. 1. Efficacy of full versus limited extended adjuvant endocrine treatment (ET), in the ITT population (panel A) and by status of lymph nodes disease (panel B).

3. Results

Three phase III RCTs fulfilled the inclusion criteria: DATA, IDEAL (BOOG 2006-05), and SALSA (ABCSG-16) trials [7–9].

Supp. Fig. 1 shows the study design of the three RCTs included in the analysis. The total duration of ET in the limited extended arm ranged from up to 6 years in the DATA trial to 7.5 years in the IDEAL trial. The total duration of ET in the full extended arm ranged from up to 9 years in the DATA trial to 10 years in the SALSA and IDEAL trials. In all trials, after randomization patients received an AI in both the limited and full extended ET arms. The disease nodal status was a stratification factor in all trials (Table 1).

The median follow-up of the studies, from patients' randomization, ranged from 50 to 118 months.

Risk of bias assessment through the Jadad score is reported in the Supp. Table 2: no trial received a low-quality score [10].

A total of 6689 patients, all post-menopausal women, were included in the analysis (Table 1). Forty-seven percent of patients (N = 3166) had nodal negative (N-ve) disease, while 3506 (52%) had nodal positive (N + ve) disease [2953 (84%) had pN1 disease and only 553 (16%) pN2 or pN3 disease].

The full-extended ET provided no DFS-benefit as compared with the limited-extended ET considering the entire ITT patients' population: the pooled DFS-HR was 0.93 (95% CI: 0.84 to 1.03; $I^2 = 0\%$; Fig. 1A).

Similar result was obtained in the subgroup of patients with N-ve disease, where the pooled DFS-HR was 1.04 (95% CI: 0.89 to 1.22; $I^2 = 18\%$; Fig. 1B).

On the contrary, in all the three RCTs, the subgroup of patients with N + ve disease had reduced relative risk of relapse or death with the full-extended ET as compared with the limited-extended ET, with a pooled DFS-HR of 0.85 (95% CI: 0.74 to 0.97; Fig. 1B). Notably, there was no inter-study heterogeneity across single-study estimates ($I^2 = 0\%$).

There was a significant interaction between the disease nodal status and the efficacy of the full-versus limited-extended ET (p-heterogeneity = 0.048; Fig. 1B).

On the contrary, the full-extended ET provided no significant DFS-benefit as compared with the limited-extended ET in all the other subgroups analyzed, including patients with younger age (Fig. 2A), higher T-stage (Fig. 2B) or histological grade tumors (Fig. 2C).

Finally, also the analysis of the IDEAL and SALSA trials including patients treated with either AI or tamoxifen or switch strategy in the first 5 years of treatment, showed no significant heterogeneity of results

Table 1
Main characteristics of RCTs included in the analysis.

	Trial name		
	DATA [Tjan-Heijnen VCG] (N = 1660)	IDEAL (BOOG 2006-05) [Blok EJ] (N = 1821)	SALSA (ABCSG-16) [Gnant M] (N = 3208)
Treatment arms			
Limited extended arm	3 years of anastrozole (N = 833)	2.5 years of letrozole (N = 908)	2 years of anastrozole (N = 1603)
Full extended arm	6 years of anastrozole (N = 827)	5 years of letrozole (N = 913)	5 years of anastrozole (N = 1605)
Patients characteristics			
Age at randomization			
≤60 years	971 (58%)[a]	510 (28%)[c]	1022 (32%)
>60 years	689 (42%)[b]	1311 (72%)[d]	2186 (68%)
Tumor size			
pT1	759 (46%)	n.a.	2335 (73%)
pT2/3/4	899 (54%)	n.a.	860 (27%)
pTx/Unknown	2 (<1%)	n.a.	13 (<1%)
Histological grade			
G1/G2	1142 (69%)	1060 (58%)	2523 (79%)
G3	467 (28%)	566 (31%)	609 (19%)
Gx/Unknown	51 (3%)	195 (11%)	76 (2%)
HER2 status			
Negative	1493 (90%)	678 (37%)	n.a.
Positive	40 (2%)	159 (9%)	n.a.
Unknown	127 (8%)	984 (54%)	n.a.
Histology			
Lobular	294 (18%)	296 (16%)	n.a.
Other	1366 (82%)	1524 (84%)	n.a.
Unknown	–	1 (<1%)	n.a.
Nodal status			
pN0	548 (33%)	472 (26%)	2146 (67%)
pN1	891 (54%)	1074 (59%)	988 (31%)
N2/N3	221 (13%)	260 (14%)	72 (2%)
Unknown	–	15 (1%)	2 (<1%)
Prior endocrine treatment			
AI	–	524 (29%)	235 (7%)
TAM	1660 (100%)	222 (12%)	1635 (51%)
TAM + AI	–	1075 (59%)	1338 (42%)
Stratification Factors			
Tumor stage	No	No	Yes
Node status	Yes	Yes	Yes
Age at randomization	No	No	No
Histological grade	No	No	No
Others	receptor status; HER2 status; tamoxifen duration.	primary adjuvant endocrine treatment and chemotherapy; time after completion of treatment.	primary adjuvant endocrine and chemotherapy; receptor status; previous trial participation; geographic region.

Abbreviations: n.a., not available; AI, aromatase inhibitor; TAM, tamoxifen.
[a] <60 years.
[b] 60 years.
[c] 55 years.
[d] 55 years.

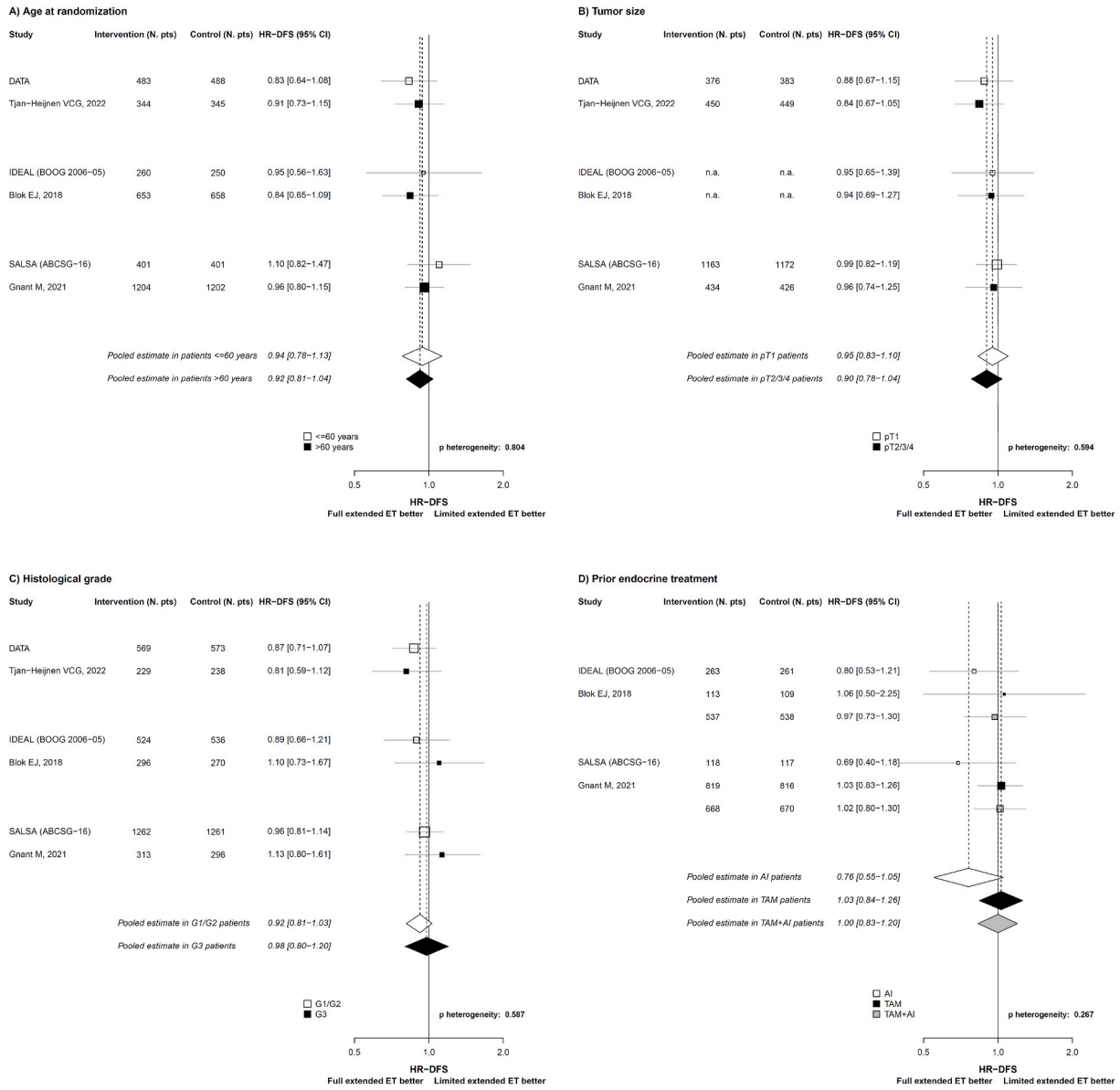

Fig. 2. Efficacy of full versus limited extended adjuvant endocrine treatment (ET), according to age at randomization (panel A), tumor size (panel B), histological grade (panel C), and prior endocrine treatment (panel D).

according to the type of previous endocrine therapy in the ITT patients' population (Fig. 2D).

4. Discussion

These results showed that the full-extended adjuvant ET provides no significant benefit in unselected patients' populations with endocrine sensitive early-stage BC.

However, a more granular and adequately powered analysis revealed that patients with N + ve early-stage BC, burdened with higher predicted risk of relapse, can significantly benefit from longer duration of ET.

It should be noted that the observed pooled DFS benefit from the full-extended adjuvant ET (i.e., 15% of reduction of the relative risk of disease relapse or death) is clinically limited. However, the N + ve subgroup represents a heterogeneous group of patients, including those with only 1 positive lymph node, who likely derive small benefit from the full-extended ET, as well as patients with large nodal involvement, who likely obtain a substantially larger benefit than the average value captured by our meta-analysis.

Furthermore, given the constant risk of relapse of endocrine responsive BC and the long-lasting carry-over effects of the adjuvant endocrine treatments, long-term follow-up substantially longer than that reported in the trials analyzed would be needed to fully capture the ultimate benefit of the prolonged versus shorter duration of ET [2,10]. Actually, ATLAS trial, which is the only RCT with a follow-up long enough to address this issue (77% of patients were still being followed up 15 years after diagnosis), showed a clear and progressive increase of the amount of benefit from the extended ET in the second decade after diagnosis, with no evidence of a rebound increase in the recurrence rate when the extended ET ended [3].

On the contrary, all the other clinical-pathological factors analyzed, including T-stage, histological grade and patients' age, although previously associated with the risk of late BC-recurrence, seem to be not useful to identify patients who benefit from the full-extended ET [2]. Similarly, although limited by the inclusion of only two trials, the results of our analysis do not support the hypothesis that patients treated with tamoxifen or switch strategy in the first five years after diagnosis are

those who benefit the most from the full-extended ET.

The optimal duration of adjuvant treatment for patients with early-stage BC is a complex issue that is understudied by a limited number of small-sized RCTs, with inadequate power and follow-up to identify patient subgroups who can benefit from prolonged treatments [1].

Our meta-analysis shed light on the relevance of taking into account the disease nodal status when choosing between the limited-versus full-extended adjuvant ET.

However, many other relevant questions remain unanswered.

For example, the majority of trials evaluating the efficacy of extended adjuvant ET, including the three RTCs analyzed in our meta-analysis, only included post-menopausal women. Thus, there is still much uncertainty regarding the role and the optimal duration of extended adjuvant ET for pre-menopausal patients, particularly for those treated with 5 years of LH-RH plus exemestane [1].

Furthermore, an intriguing retrospective analysis of the DATA trial suggested that beyond the patients' risk of relapse, other biological features of disease, such as the tumor expression levels of ER and PgR, can be associated with the efficacy of the full versus limited extended adjuvant ET [9].

Moreover, subgroup analyses according to tumor phenotype have rarely been reported in RCTs testing extended adjuvant ET, despite the fact that the tumor phenotype has been long recognized as being associated with the distribution of the risk of disease relapse over time, with lobular cancer having a very long-lasting risk of relapse [11].

In addition, a few tools based on clinicopathologic parameters (i.e., the CTS5) or on gene expression (i.e., 70-gene Mammaprint test or the H/I ratio) could be helpful in individualizing the duration of extended adjuvant ET [12–14].

In the IDEAL trial, patients with tumors characterized as low-risk by Mammaprint test had a significant 9.8% reduction of the absolute risk of distant relapse (DR) when treated with the full-extended ET as compared with limited-extended groups (DR-HR 0.42, 95% CI 0.17–0.99), while patients with high-risk tumors had no benefit [13].

Notably, the H/I ratio has been shown to be potentially useful to calibrate the duration of the extended ET also in the subgroups of patients with nodal positive disease: in the IDEAL trial, patients with node-positive disease and high H/I ratio had a significant absolute RFI-benefit of 11% when treated with 10 versus 7.5 years of letrozole, while node-positive patients with low H/I-ratio derived no benefit from 10 years of treatment [14].

Finally, the recent results of the MonarchE and OlympiA trials showed that 2 years of abemaciclib and 1 year of olaparib during the first years of adjuvant ET improved patient outcomes [15,16]. It is unknown how and if the addition of such new targeted therapies modifies the efficacy of extended ET, as well as the duration of such extension (i.e., full-versus limited-extension). Until specific evidence becomes available, in our opinion, the duration of adjuvant endocrine therapy in such new cohorts of patients treated with abemaciclib or olaparib, should be tailored to the same factors used for the general patients population.

Similarly, since there is no evidence available on the optimal duration of endocrine adjuvant therapy in patients who underwent neoadjuvant treatments, the duration of adjuvant endocrine therapy should be tailored according to the clinical-pathological factors assessed before neoadjuvant therapy.

A possible limitation of our analysis is its derivation from a trial-level meta-analysis of subgroup analyses. However, two considerations strongly support the reliability of our conclusions. First, the straightforward rationale for our finding is that higher absolute DFS-benefit of longer ET is expected in patients with higher baseline risk of relapse. Secondly, we observed a strong consistence of results across all analyzed trials, which was confirmed by the lack of heterogeneity among single-study estimates in the N + ve subgroup [1].

In conclusion, results from our trial-level meta-analysis add a relevant piece of additional evidence regarding the optimal duration of adjuvant ET for early BC, showing that patients with nodal positive disease can obtain a potentially meaningful DFS benefit from the full extended as compared with limited extended.

5. Contributors

Conceptualization, Fabio Conforti, Laura Pala, Tommaso De Pas, Vincenzo Bagnardi, Data Curation, Fabio Conforti, Isabella Sala, Eleonora Pagan, Vincenzo Bagnardi, Formal Analysis, Fabio Conforti, Isabella Sala, Eleonora Pagan, Vincenzo Bagnardi, Funding Acquisition, NA, Investigation, Fabio Conforti, Laura Pala, Tommaso De Pas, Isabella Sala, Eleonora Pagan Vincenzo Bagnardi, Methodology, Fabio Conforti, Laura Pala, Tommaso De Pas, Isabella Sala, Eleonora Pagan Vincenzo Bagnardi, Richard Gelber, Giuseppe, Viale, Project Administration, Fabio Conforti, Resources, NA, Software, Isabella Sala, Eleonora Pagan Vincenzo Bagnardi, Supervision, Richard Gelber, Giuseppe Viale, Validation, All authors, Visualization, All authors, Writing – Original Draft Preparation, All authors, Writing – Review & Editing, Javier Cortes, Antonio Wolf, Martine Piccart.

Data availability statement

Detailed extracted data on all included studies are available upon reasonable request to the corresponding author.

Ethics statements ethical approval

Not required.

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Description: Squares indicate study-specific HRs, overall and by nodal status. Size of the square is proportional to the precision of the estimate (i.e., the inverse of the variance). Horizontal lines indicate the 95% CI. Diamond indicates the meta-analytic pooled HR, with their corresponding 95% CIs. The dashed vertical lines indicate the pooled HR, overall and by nodal status, and the solid vertical line indicates a HR of 1.00 (i.e., no association between type of treatment and risk of recurrence or death).

Description: Squares indicate study-specific HRs, by subgroup strata. Size of the square is proportional to the precision of the estimate (i.e., the inverse of the variance). Horizontal lines indicate the 95% CI. Diamond indicates the meta-analytic pooled HR, with their corresponding 95% CIs. The dashed vertical lines indicate the pooled HR, by subgroup strata, and the solid vertical line indicates a HR of 1.00 (i.e., no association between type of treatment and risk of recurrence or death).

Declaration of competing interest

All other authors declare no conflicts of interest.

The lead author (FC) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2023.02.012.

References

[1] Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KA, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol 2019; 37(5):423–38.

[2] Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med 2017;377(19):1836–46.

[3] Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Adjuvant Tamoxifen: longer against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381(9869):805–16.

[4] Gray RG, Rea D, Handley K, Bowden SJ, Perry P, Earl HM, et al. aTTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. J Clin Oncol 2013;31:5. https://doi.org/10.1200/jco.2013.31.18_suppl.5.

[5] Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349(19):1793–802.

[6] Mamounas EP, Bandos H, Lembersky BC, Jeong JH, Geyer Jr CE, Rastogi P, et al. Ten-year results from NRG Oncology/NSABP B-42: a randomized, double-blinded, placebo-controlled clinical trial of extended adjuvant endocrine therapy with letrozole in postmenopausal women with hormone-receptor+ breast cancer who have completed previous adjuvant therapy with an aromatase inhibitor. San Antonio Breast Cancer Symposium 2019. https://doi.org/10.1158/1538-7445.SABCS19-GS4-01. Abstract GS4-01.

[7] Tjan-Heijnen VCG, Lammers SWM, Geurts SME, Vriens IJH, Swinkels ACP, Smorenburg CH, et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy: final results of the phase III DATA trial. Ann Oncol 2022;33: S599. https://doi.org/10.1016/j.annonc.2022.07.168.

[8] Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, Duijm-de Carpentier M, Putter H, van den Bosch J, et al. Optimal duration of extended adjuvant endocrine therapy for early breast cancer; results of the IDEAL trial (BOOG 2006-05). J Natl Cancer Inst 2018;110(1).

[9] Gnant M, Fitzal F, Rinnerthaler G, Steger GG, Greil-Ressler S, Balic M, et al. Duration of adjuvant aromatase-inhibitor therapy in postmenopausal breast cancer. N Engl J Med 2021;385(5):395–405.

[10] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Contr Clin Trials 1996 Feb;17(1):1–12.

[11] Pestalozzi BC, Zahrieh D, Mallon E, Gusterson BA, Price KN, Gelber RD, et al. Distinct clinical and prognostic features of infiltrating lobular carcinoma of the breast: combined results of 15 International Breast Cancer Study Group clinical trials. J Clin Oncol 2008;26(18):3006–14.

[12] Dowsett M, Sestak I, Regan MM, et al. Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen receptor-positive breast cancer treated with 5 Years of endocrine therapy: CTS5. J Clin Oncol 2018; 36(19):1941–8.

[13] GS5-10 Utility of the 70-gene MammaPrint test for prediction of extended endocrine therapy benefit in patients with early-stage breast cancer in the IDEAL Trial Presented ad SABCS 2022.

[14] Noordhoek I, Treuner K, Putter H, Zhang Y, Wong J, Meershoek-Klein Kranenbarg E, et al. Breast cancer index predicts extended endocrine benefit to individualize selection of patients with HR+ early-stage breast cancer for 10 Years of endocrine therapy. Clin Cancer Res 2021 Jan 1;27(1):311–9. https://doi.org/10.1158/1078-0432.CCR-20-2737.

[15] Harbeck N, Rastogi P, Martin M, Tolaney SM, Shao ZM, Fasching PA, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol 2021;32(12):1571–81.

[16] Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. N Engl J Med 2021;384(25):2394–405. https://doi.org/10.1056/NEJMoa2105215.