Title

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Quality of life in the adjuvant setting: A meta-analysis of US Food and Drug Administration approved anti-cancer drugs from 2018 to 2022

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ABSTRACT

Background: In oncology, quality of life (QoL) questionnaires were historically designed to be used in the advanced or metastatic setting. We sought to determine the effects of contemporary treatments on QoL in the adjuvant setting and to determine if the QoL instruments used in these studies provide a relevant assessment.
Methods: We conducted a systematic identification of all anti-cancer drugs used in the adjuvant setting and approved by the US Food and Drug Administration from January 2018 to March 2022. We conducted a quality evaluation and a meta-analysis of reported QoL results. We used the global QoL results when multiple QoL outcomes were reported.
Results: There were 224 FDA approvals reviewed, of which 12 met the inclusion criteria. The placebo was the control arm in 10 out of 12 trials. Of those, 11 trials (92 %) assessed QoL, and ten (83 %) reported results. In reports with QoL results, a moderate-risk of bias was found in 3 out of 10 (30 %) and a high-risk of bias in 6 out of 10 (60 %) of reports, respectively. No trial reported a meaningful difference between arms. The meta-analysis found an overall detrimental effect on QoL in the experimental arm, though it was not statistically different.
Conclusion: This study identified 12 FDA registration trials in the adjuvant setting between 2018 and 2022. We found a moderate- to high-risk of bias in 90 % of the ten trials reporting QoL data. Our meta-analysis suggested a detrimental effect on QoL in the experimental arm, questioning the relevancy, in the adjuvant setting, of thresholds that were mostly developed in the advanced or metastatic setting.
Policy summary: Future works should focus on specificities of the adjuvant setting when considering QoL evaluation.

1. Background

Quality of life (QoL) is of paramount importance for patients with cancer. Most patients with advanced or metastatic cancer may suffer from physical symptoms related to both the disease and its treatment. In addition to these physical symptoms, aspects such as functional, sociological, psychological, financial, and spiritual health are equally important. Collectively, these aspects can be measured and evaluated using QoL questionnaires. When considering the value of a new therapy for cancer, the United States Food and Drug Administration (FDA) considers impacts on QoL as having at least the same value as overall survival (OS) when it comes to regulatory approval decisions [1]. QoL questionnaires were historically designed for patients in the advanced or metastatic setting [2–4].

Adjuvant cancer therapy is unique from metastatic cancer therapy when it comes to assessing QoL. Patients receiving adjuvant therapy may already be cured, but have a risk of relapse that varies according to many parameters. The goal of adjuvant treatment is to increase the chances of definitive cure by eradicating undetectable disease. Patients in the adjuvant setting do not experience any direct active cancer-related symptoms, and resultant impairment in QoL for patients in the adjuvant setting stem from treatment (e.g., related to side effects from surgery, radiotherapy or systemic treatments). While on treatment and without relapse, adjuvant therapies can theoretically only lower quality of life due to side effects. However, the potential reduction in quality of life may be offset by the benefit of preventing cancer recurrence and its

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associated complications.

In recent years, the US Food and Drug Administration has approved multiple agents, such as immune checkpoint inhibitors and targeted therapies, for the adjuvant treatment of solid tumors. Here we sought to describe the registration trials leading to these approvals and to conduct a meta-analysis of the QoL data from these trials, when available. We sought to determine the overall effects of contemporary adjuvant treatments such as immune checkpoint inhibitors and targeted therapies on QoL in the adjuvant setting and to determine if the traditional QoL instruments used in these studies are relevant in the adjuvant setting.

2. Methods

2.1. Study design and research strategy

Our work was comprised of a two step research strategy. First, we conducted a systematic identification of all anti-cancer drugs used in the adjuvant setting and approved by the US FDA from January 2018 to March 2022.

Second, after identifying the FDA registration trials reporting QoL results, we conducted a meta-analysis of QoL data, following the methodology described by Fayers and Machin [5]. After extraction of the relevant QoL data, we conducted (1) a quality evaluation of QoL data and (2) a statistical meta-analysis. We used the global QoL results instead of the individual QoL components when multiple QoL outcomes were reported.

Because of overlap between Health-related QoL (HRQoL) and QoL definitions, we choose to use the term QoL in our analysis to concurrently describe both types of outcomes [6].

2.2. FDA approvals identification and selection

The research was conducted using the FDA website and a previous work of ours [7]. We reviewed each approval via the official FDA initial announcement and retrieved trial data from the published trial results (identified via the unique NCT identifier). Searches were performed on April 04, 2022. Because we used publicly available data and did not involve human subjects research, in accordance with 45 CFR §46.102(f), we did not submit this study to an institutional review board or require informed consent procedures. We adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.

2.3. FDA approvals inclusion and exclusion criteria

Inclusion criteria were (1) FDA approvals between 2018 and March 2022; (2) drugs of anti-cancer agents (supportive treatments were excluded); and (3) drugs used in the adjuvant setting (drugs that were approved both in the neo-adjuvant setting and the adjuvant setting for the same indication were included). The exclusion criteria were (1) FDA registration trials not evaluating direct anti-cancer interventions, such as those focusing solely on supportive care measures, infection mitigation or prevention, or different stem cell mobilization strategies; and (2) drugs approved in the neoadjuvant setting only. This decision was made to enhance the homogeneity of the trials with regard to the clinical setting being studied – in this case, the adjuvant treatment phase. Supplementary Fig. 1 (Supplementary File) details the approvals selection process.

2.4. Data abstraction

Information abstracted for approval included the registration trial with NCT number; name of the trial (when available); date of approval; tumor type; setting; design (open or double blind); phase of the trial; experimental arm intervention; mechanism of action of the experimental arm; control arm intervention; whether QoL data were collected (yes, no); whether QoL results were reported (yes, no); when reported, the type of report (within the original publication, within an abstract, within a specific QoL report); whether QoL was a primary, coprimary, secondary, exploratory or tertiary endpoint; the type of QoL survey(s) used; mean differences in QoL between baseline and follow-up for both the intervention and control group; and the overall result of the QoL outcome (positive, negative, mixed, null or indeterminate).

Two of the authors (AH, TO) independently reviewed and identified FDA approvals. The same authors independently abstracted data from each article. A third reviewer (VP) adjudicated any discrepancies.

2.5. Quality evaluation of QoL data

This part of the analysis was conducted in trials reporting on QoL. The quality of reporting was assessed following the methodology described by Fayers et Machin [5] and the Cochrane Handbook for Systematic Reviews of Interventions [8].

We assessed 6 types of bias: selection bias, performance bias, detection bias, selective reporting bias, validity instruments evaluation, and missing data. Each item is described in the eMethod (online only).

Based on the evaluation of each item, we attributed an overall *risk of bias* grading as proposed by the Cochrane Collaboration [8]:

- Low (risk of bias) when all quality criteria were met.
- Moderate when $\geq$ 1 criteria were met only partly.
- High risk when $\geq$ 1 criteria were not met (entirely).

This assessment was conducted blindly and independently by two reviewers (TO and AH), and discrepancies were adjudicated between reviewers, and with other authors if any disagreement.

2.6. Review of each identified QoL Instrument

We compiled the following data for each QoL instrument used in selected trials: (1) name of survey; (2) date of initial publication; (3) setting in which it was initially designed; (4) description of the survey. Items 2 and 3 were obtained by reviewing the publication cited by the selected trial to justify such use of the survey, as well as the first publication validating the tool.

2.7. Statistical analysis

Frequencies were calculated for categorical variables throughout. We calculated pooled mean differences for the main outcomes using a random-effects model with the Hartung-Knapp-Sidik-Jonkman method due to the variability in our studies [9]. We used the I^2 index to assess heterogeneity and Egger's test to assess publication bias. The interpretation of I^2 values were based on Cochrane categorization: 30–60 % represents moderate heterogeneity and $>$ 75 % represents considerable heterogeneity [8]. In the primary analysis, we included all studies reporting QoL, using standardized means. We did a separate analysis, pooling reported means, using studies reporting QLQ-C30 results, the most commonly used survey in our database. We conducted an Egger's test to visually inspect publication bias. The pooled effect sizes, forest plots, and corresponding statistical tests were generated using the meta package of R.

Statistical analyses were done using R version 3.6.2 (R Project for Statistical Computing) and a 2-tailed P value less than 0.05 as the level of significance.

3. Results

3.1. Selected trials characteristics

There were 224 FDA approvals reviewed, of which 12 met the inclusion criteria. Supplementary Fig. 1 (Supplementary File) details the

approvals selection process.

Out of 12 trials, ten (83 %) used a placebo as the comparator, while one other trial used best supportive care, which equates to observation. The tumor types involved were breast (n = 3), melanoma (n = 3), NSCLC (n = 3), urothelial (n = 1), renal (n = 1), and esophagus, including the gastro-esophageal junction (n = 1).

Eleven (of 12, 92 %) trials collected QoL data, and ten trials (of 12, 83 %) reported QoL results. Results were reported in the original manuscript alone (n = 1), in a specific publication on QoL or patient-reported-outcome (n = 5), in the original publication and in a meeting abstract (n = 3, CheckMate 577 trial, KEYNOTE-564 trial, and OlympiA), or only in a meeting abstract (n = 1, KEYNOTE-716). Other study qualities are described in Table 1. The mechanism of action of the experimental arm was an anti-PD(L)1 monoclonal antibody in 8 (of 12, 66.7%), kinase inhibitors in 3 (of 12, 25 %) and an antibody-drug conjugate in 1 (of 12, 8.3 %). Among trials with reported QoL data, all (10/10, 100 %) reported no clinically meaningful differences between arms.

3.2. Quality assessment of the QoL data reporting

Six items, relating to bias, were independently coded by two reviewers (TO and AH) for 10 trials. On 60 coded items, there was an overall first-pass agreement in 92 % of them (55/60).

We found no study with selection or validity bias. One study did not met the criteria for performance bias, and the same trial did not met the criteria for detection bias. Selective reporting was present in 2 studies (of 10, 20 %). The risk of bias due to missing data was present in 9 studies (of 10, 90 %). In 3 of these trials, this criterion was considered as partly met, and in 6, it was considered as not met at all.

Overall, we identified one trial with a low risk of bias in the QoL report (of 10, 10 %), 3 trials with a moderate risk of bias (of 10, 30 %), and 6 (of 10, 60 %) trials with a high risk of bias. A “heat-map” representing items evaluation and the overall risk of bias (low, moderate of high) for each trial is provided in Table 2.

3.3. Quality of life metaanalysis

QoL data were reported in 10 trials. No report found a clinically meaningful differences between arms: eight (of 10, 80 %) reported lower QoL values in the experimental arm, and two (of 10, 20 %) reported higher values. The pooled estimation of standardized values found an overall detrimental effect on QoL in the experimental arm, though the difference was not statistically different (Fig. 1). In the overall pooled results, the standardized mean difference in QoL outcomes was − 0.06 (95 % CI = − 0.13 to 0.01), favoring the control arm. The I^2 was 47 %, suggesting moderate heterogeneity.

In order to compare the pooled QoL results with a clinically meaningful threshold, we conducted another meta-analysis selecting studies reporting results from the QLQ-C30 survey (Fig. 2). The pooled estimate showed an overall detrimental effect on QoL in the experimental arm, though it was not statistically or meaningfully different, as it was below the 5-point clinically meaningful threshold. When looking only at studies reporting QLQ-C30 results, the pooled mean difference was − 1.12 (95 % CI = − 2.32 to 0.08), again favoring the control arm. The I^2 was 12 %, suggesting low heterogeneity.

Using the Egger’s test, our analysis suggested the presence of a publication bias, with an asymmetry in the funnel plot (Supplementary Fig. 2 in the Supplementary File).

3.4. Description of QoL Instruments used in the study

Our review of surveys (detailed in eResult and Supplementary Table 1, in the Supplementary File) found that the most common survey used in our selected trials (ie QLQ-C30) was developed in patients in the advanced setting (lung cancer). Most surveys were developed in advanced settings (Supplementary Table 1) and all were developed before the era of targeted therapy and immunotherapy.

Table 1
Characteristics of registration trials leading to an FDA approval in the adjuvant setting between 2018 and 2022 (N = 12).

Trial name	Experimental arm	Mechanism of action (and target)	Control	Design	Phase	Date of approval	Tumor type	Quality of life endpoint and survey(s)
PACIFIC [17]	durvalumab	MAB* (anti-PD(L)1)	Placebo	Blind	3	16.02.2018	Non-small cell Lung Cancer	Secondary QLQ-C30, QLQ-LC13, EQ-5D
COMBI-AD [18]	dabrafenib-trametinib	kinase inhibitor (BRAF, MEK)	Placebo	Blind	3	30.04.2018	Melanoma	Exploratory EQ-5D-3L
KEYNOTE-054 [19]	pembrolizumab	MAB (anti-PD(L)1)	Placebo	Blind	3	15.02.2019	Melanoma	Exploratory QLQ-C30
KATHERINE [20]	trastuzumab emtansine	antibody drug conjugate (HER2)	Trastuzumab	Open	3	03.05.2019	Breast	Secondary QLQ-C30, QLQ-BR23
ADAURA [21]	osimertinib	kinase inhibitor (EGFR)	Placebo	Blind	3	18.12.2020	Non-small cell Lung Cancer	Secondary SF-36
CheckMate 577 [22]	nivolumab	MAB (anti-PD(L)1)	Placebo	Blind	3	20.05.2021	Esophagus or GEJ **	Exploratory EQ-5D-3L, FACT-E
KEYNOTE-522 [23]	pembrolizumab	MAB (anti-PD(L)1)	Placebo	Blind	3	26.07.2021	Breast	Exploratory (not available)
CheckMate 274 [24]	nivolumab	MAB (anti-PD(L)1)	Placebo	Blind	3	19.08.2021	Urothelial	Exploratory QLQ-C30, EQ-5D-3L VAS
IMpower010 [25]	atezolizumab	MAB (anti-PD(L)1)	BSC ***	Open	3	15.10.2021	Non-small cell Lung Cancer	Not an endpoint
KEYNOTE-564 [26]	pembrolizumab	MAB (anti-PD(L)1)	Placebo	Blind	3	17.11.2021	Renal Cell	Secondary QLQ-C30, FKSI-DRS
KEYNOTE-716 [27]	pembrolizumab	MAB (anti-PD(L)1)	Placebo	Blind	3	03.12.2021	Melanoma	Exploratory QLQ-C30, ED-5D-5L
OlympiA [28]	olaparib	kinase inhibitor (PARP)	Placebo	Blind	3	11.03.2022	Breast	Secondary QLQ-C30, FACIT-F

* MAB: monoclonal antibody.
** GEJ: gastroesophageal junction.
*** BSC: best supportive care.

Table 2
Quality assessment of reporting of QoL data.

Trial Name	Experimental arm	Tumor type	Selection bias	Performance bias	Detection bias	Selective reporting bias	Validity bias	Compliance and attrition bias	Overall risk of bias
PACIFIC [17]	durvalumab	Non-Small-Cell Lung Cancer	No	No	No	No	No	Partly	Moderate
COMBI-AD [18]	dabrafenib-trametinib	Melanoma	No	No	No	No	No	Yes	High
KEYNOTE-054 [19]	pembrolizumab	Melanoma	No	No	No	No	No	No	Low
KATHERINE [20]	trastuzumab emtansine	Breast	No	Yes	Yes	No	No	Yes	High
ADAURA [21]	osimertinib	Non-Small-Cell Lung Cancer	No	No	No	No	No	Partly	Moderate
CheckMate 577 [22]	nivolumab	Oesophagus or gatroeosophagus	No	No	No	No	No	Yes	High
CheckMate 274 [24]	nivolumab	Urothelial	No	No	No	No	No	Partly	Moderate
KEYNOTE-564 [26]	pembrolizumab	Renal Cell	No	No	No	No	No	Yes	High
KEYNOTE-716 [27]	pembrolizumab	Melanoma	No	NA	No	Yes	No	Yes	High
OlympiA [28]	olaparib	Breast	No	No	No	Yes	No	Yes	High

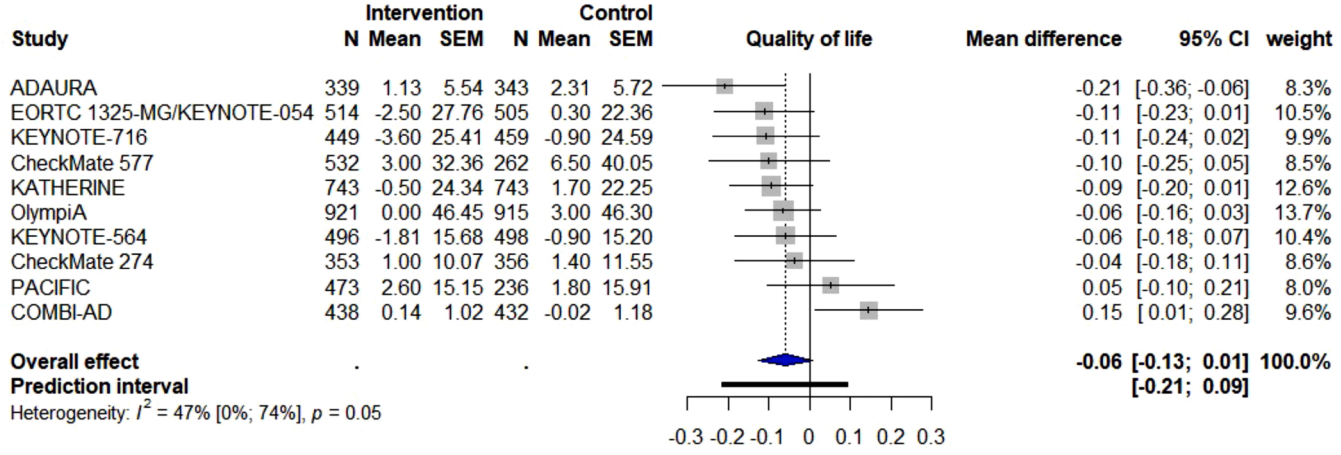

Fig. 1. Meta-analysis of quality of life reported in registration trials for drugs approved in the adjuvant setting (2018–2022, N = 10).

4. Discussion

Since 2018, there have been 12 registration trials leading to US FDA drug approval in the adjuvant setting, with most of them collecting (92 %) and reporting (83 %) QoL data. When QoL data were reported (n = 10), only one report was characterized by a low-risk of bias (10 %), the others reports having moderate to high risk of bias (90 %). Importantly, while no individual trial concluded there was a deterioration in quality of life, our meta-analysis suggests an overall detrimental effect. The lack of deterioration is likely due to these trials not being powered to detect differences in QoL, as it is intuitive that taking a drug with side effects when one has undetectable cancer can only result in loss of quality of life.

The overall quality of reported data was poor. As demonstrated in Fig. 1, this was mainly driven by the risk of biases in compliance and attrition, present at least partly in 90 % of reports. We previously showed that informative censoring due to missing QoL data could not be ruled out in more than 90 % of trials reporting QoL results [10]. When missing data do no occur at random, missing data may be informative, specifically about toxicity. In other words, a patient suffering from toxicity may be less prone to fill out the QoL questionnaire than a patient without such toxicity. If appropriate handling of missing data is not performed, this may introduce major bias in QoL interpretation, potentially missing a detrimental effect on QoL [10,11].

Our meta-analysis demonstrated a trend toward overall detrimental effect on quality of life, depending on the applied clinically meaningful

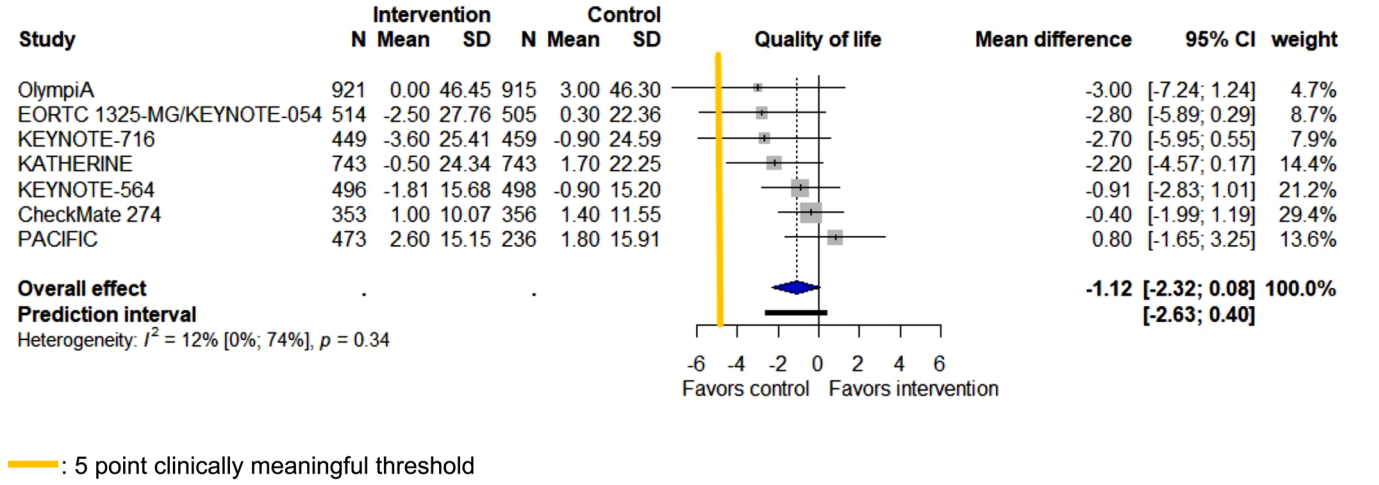

Fig. 2. Meta-analysis in trials with QLQ-C30 results (N = 7).

threshold. While some may argue that we did not prove this deterioration surpassed a threshold for a clinically meaningful difference — this threshold was not derived and validated in the adjuvant setting. What constitutes acceptable loss of quality of life for the metastatic setting may no longer be relevant in the adjuvant setting. In our dataset, the threshold of 10-points in the QLQ-C30 was used in the PACIFIC trial (lung cancer), when a 5-points threshold was considered meaningful in KEYNOTE-054 (melanoma). We contend that many factors may limit the application of usual thresholds into the adjuvant setting.

As a first factor, our review found that most QoL questionnaires were historically designed for patients in the advanced or metastatic setting [2–4], The treatment strategy in the adjuvant setting is entirely different than in the advanced or metastatic setting. In the adjuvant setting, a significant proportion of patients are cured, while only a proportion will eventually relapse. The goal of the adjuvant treatment is to prevent relapse in patients who would have recurred. Unfortunately, in most situations, we are unable to identify specific patients that will benefit from adjuvant therapy. As a result, therapy is administered to a group of patients, according to their risk of relapse, knowing that only a fraction of them will benefit. Therefore, the adjuvant strategy subjects a significant fraction of patients to an unnecessary therapy, in order to prevent the relapse in a smaller fraction of them. QoL data may not have the same significance in the adjuvant setting, because all effects in QoL is due to the drug of interest and is not affected by the disease, as it is in the advanced or metastatic settings. We are then comparing treatment versus no treatment in a fraction of patients that are free from cancer. When compared to a control group who is getting placebo therapy, one might expect QoL to be worse in the treatment arms of adjuvant trials for solid tumors. Indeed, early trials of adjuvant pegylated interferon alfa-2b, which has marked toxicity, in resected stage III melanoma patients showed significant decrements in QoL in the treatment group compared to placebo, despite a benefit in recurrence-free survival [12].

Secondly, specific time-to-event endpoints (e.g. time to deterioration (TTD) of QoL) may be less or not relevant in the adjuvant setting. Patients are not suffering from any active cancer related symptoms when initiating an adjuvant treatment. It is likely that, in the fraction of patients relapsing, this event may be associated with a deterioration in QoL. If the adjuvant treatment prevents or delays the relapse in a fraction of patients, this may prolong the TTD. However, a key question in the adjuvant setting is the QoL of patients before experiencing a relapse. This is because some patients are already cured and will not recur. This is unlike the advanced setting where a delay in QoL deterioration can be significant for the overall population, which consists of individuals with an active disease.

Thirdly, it is possible that patients who are randomized to any treatment over placebo in open-label or poorly-blinded studies will report improved QoL due to a placebo effect. This has been shown in patients assigned to placebo arms of adjuvant trials of targeted or immune therapy, who report and/or experience higher rates of serious adverse events than would be expected, thus minimizing any differences in QoL between arms [13]. The impact of the nocebo effect, or the disappointment of being placed on placebo, also needs to be considered when evaluating patient reported HR QoL, specifically when the patient knows or suspects their assigned allocation arm [14]. However, only two trials included in our analysis had an open-label design.

Fourth and lastly, high drug prices directly harm patients, as increased costs potentially limit patients' compliance, with the risk of less favorable outcomes [15]. The potential impact of financial toxicity on QoL is less of a concern for patients in clinical trials, as most enrolled patients do not have to pay for their care and treatment while on trial [16]. However this is not the case for patients in the real-world. A previous analysis of ours, selecting adjuvant trials over the same time period, found the median cost per treated patient was $158 000. The minimum cost was $118 000 with atezolizumab in the IMpower10 trial, where the higher cost was $440 000 in patients treated with Osimertinib per the ADAURA trial [7]. The impact of financial toxicity on QoL for patients treated in the adjuvant setting outside trials may be massive and entirely uncaptured by QoL data in trials [16].

Our findings question the relevance of current measurement of quality of life in a different setting than where they were initially designed. Future work should focus on considering specific approaches of QoL in the adjuvant setting. Firstly, clinically meaningful thresholds for QoL in the adjuvant setting, where patients are potentially cured, should be reassessed: this setting is entirely different from advanced or metastatic settings of patients with an active disease. Secondly, the fact that undergoing treatment in the adjuvant setting may provide a sense of reassurance to patients must be taken into account. This reassurance could potentially bias their subjective experience of treatment, a dynamic that might differ in the metastatic setting where the comparator is typically not a placebo. Thirdly, studies focusing in refining QoL assessment in the adjuvant setting should include not only patients who were willing to participate in adjuvant trials but also those who chose not to participate. The latter group might have different values or thresholds regarding their QoL. Their perspectives could add invaluable insights to the understanding of patient experience broadly. Fourthly, the time-period which would be considered relevant in the adjuvant setting may be restricted to the period before any event occurs. This would better capture what is related to "treatment-related toxicity" which is, in and of itself, a very important question in QoL assessment in the adjuvant setting, as compared to "disease-related toxicity". Lastly, it

would be essential to integrate financial toxicity into post-marketing requirements, given its significant impact on patient QoL. Taking this comprehensive approach would provide a more nuanced perspective on QoL considerations in the adjuvant setting.

Our work has strengths and limitations. This is the first study to conduct a meta-analysis of recent QoL data in adjuvant oncology trials. Second, we addressed this research question with pre-specified methodology and blinded and independent reviewing of trials. One limitation is that our evaluation was based on study reports, which may not be high-quality reporting, and not on individual data. However, these are the same data provided to clinicians and regulators, and as such, the quality in reporting is of critical importance. Second, our analysis was limited to a small number of trials and a limited time-period. However, we aimed to capture recent trends in adjuvant registration trials, dominated by new and costly treatment. Also, the trials demonstrated rather homogeneous characteristics, allowing for an overall assessment.

5. Conclusion

Our study found 12 registration trials in the adjuvant setting leading to an FDA approval between 2018 and 2022, with 10 of them reporting on QoL data. The overall quality of reporting was poor, with 90% of reports with a moderate to high risk of bias. We argue that clinically meaningful thresholds, mostly developed in the advanced or metastatic setting, may not be relevant in the adjuvant setting, where our meta-analysis showed an overall detrimental effect on QoL in the experimental arm. Financial toxicity is not captured in trials and could have a massive impact in QoL. Future work should focus on specific approaches of QoL in the adjuvant setting.

CRediT authorship contribution statement

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. TO, AA and VP contributed to the conception. TO, AH, and VP contributed to the design of the study and statistical analysis plan. TO, CS and AH collected the data. TO and AH assembled the data and had accessed and verified the data. TO and AH did the statistical analyses. TO and CS wrote first draft of manuscript and all authors reviewed and revised the manuscript. All authors provided final approval of the manuscript.

Role of the funding source

The funders had no role in the design and conduct of the study.

Ethics committee approval

Because we used publicly available data, and this is not human subjects research in accordance with 45 CFR §46.102(f), we did not submit this study to an institutional review board or require informed consent procedures.

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Declaration of Competing Interest

Vinay Prasad's Disclosures: Research funding: Arnold Ventures; Royalties: Johns Hopkins Press, Medscape; Honoraria: Grand Rounds/lectures from universities, medical centers, non-profits, and professional societies; Consulting: UnitedHealthcare; Speaking fees: Evicore; Other: Plenary Session podcast has Patreon backers. Alfredo Addeo's Disclosures: Consulting or Advisory Role: BMS, Astrazeneca, Boehringer-Ingelheim, Roche, MSD, Pfizer, Eli Lilly, Astellas, Takeda, Amgen. Speaker Bureau: Eli Lilly, Astrazeneca, Amgen. All other authors have no financial nor non-financial conflicts of interest to report.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jcpo.2023.100426.

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