Adoption of multiple primary endpoints in phase III trials of systemic treatments in patients with advanced solid tumours. A systematic review

Adoption of multiple primary endpoints in phase III trials of systemic treatments in patients with advanced solid tumours. A systematic review.

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Abstract

Background and aim. Trial designs using multiple primary endpoints (MPEs) are progressively increasing in phase III cancer trials. There are two distinct situations: (i) MPEs correspond to “multiple chances” for the experimental treatment to win, needing adjustment for multiple statistical tests; (ii) a positive result depends on the success in all MPEs. Our objectives were to describe: the incidence of MPEs in recently published phase III trials testing systemic treatments in patients with advanced cancer; the main characteristics of trials adopting MPEs; the presence of mature results for all the endpoints in the primary publication; consistency between results of each endpoint and authors’ conclusions.

Methods. Articles of randomized phase III trials conducted in patients with advanced cancer, published between 2017 and 2020, were retrieved from PubMed. Main outcome was the proportion of trials with MPEs.

Results Out of 235 eligible trials, 27 trials (11.5%) adopted MPE, mostly overall survival (OS) and progression-free survival (PFS). Proportion of trials with MPEs increased over time, from 5.6% in 2017 to 20.0% in 2020 (p=0.025). MPEs were adopted in 15.7% of for-profit trials vs. 3.7% of non-profit trials (p=0.006). Proportion of trials adopting MPEs was particularly high with immunotherapy (52.8%, p<0.00001). Out of 27 trials with MPEs, 10 (37.0%) adopted an explicit definition of “co-primary” endpoints, but only 1/10 declared the positivity of both endpoints critical for interpretation. Most trials (23, 85.2%) planned correction for multiplicity. Of 21 publications with positive conclusions, only 12 had a statistically significant positive result in both primary endpoints. In 4 cases (14.8%), positive conclusions were based on PFS results alone.

Conclusions Adoption of MPEs in randomized trials in oncology is quite common. Despite clear recommendations by regulatory agencies about adoption of MPEs, definition of “co-

primary” endpoints and correction for multiplicity, there is some heterogeneity in applying these rules.

Keywords: cancer; endpoint; randomized controlled trial; overall survival; progression-free survival

Highlights

- We described the incidence of multiple primary endpoints (MPEs) in phase III trials testing systemic anticancer treatments
- Out of 235 eligible trials published between 2017 and 2020, 27 trials (11.5%) adopted MPEs
- Proportion of trials with MPEs increased over time, from 5.6% in 2017 to 20.0% in 2020 (p=0.025)
- Proportion of trials adopting MPEs was particularly high with immunotherapy (52.8%, p<0.00001)
- Despite recommendations by regulatory agencies about MPEs adoption, there is some heterogeneity in applying these rules

Introduction

The primary endpoint of randomized phase III clinical trials is used to define the study hypothesis and to calculate the sample size, and its analysis should be crucial for the interpretation of study results. In fact, failing to demonstrate a statistically significant and clinically relevant benefit in the primary endpoint should imply formally negative conclusions. Usually, a clinical trial is designed with one primary endpoint, corresponding to the measure that is considered to best represent the clinical benefit associated with treatment. However, trial designs including multiple primary endpoints (MPEs) are increasingly used in phase III trials conducted in patients with advanced or metastatic solid tumours, with a growing body of literature discussing the technical aspects of sample size determination and statistical plan[1,2].

In addition, main regulatory agencies have explicitly discussed the issue of MPEs in clinical trials[3,4]. One could argue that if two distinct endpoints are considered both relevant to be chosen as primary endpoints, both should necessarily concur to study interpretation. According to U.S. Food and Drug Administration (FDA), primary endpoints are those "*essential to establish effectiveness for approval*"[3]. However, two distinct situations can be discussed. The first is when study design includes MPEs corresponding to "multiple chances" for the experimental treatment to be "winner"; in this case, the absence of proper statistical adjustment for multiplicity can unduly increase the risk of a false positive result. The second is when determination of efficacy of the experimental treatment (and consequent definition of a positive result) depends on the success of all the two or more primary endpoints. In this latter case, there are no multiple endpoint-related multiplicity issues (because failure of one endpoint implies failure of the whole study, independently of the other), and there is no concern with increased risk of false positivity. Discussing this latter situation, the European Medicines Agency (EMA) states that, when both endpoints

should be satisfied in order to define the study as positive, the endpoints are explicitly defined "*co-primary*"[4].

As a matter of fact, however, most existing designs include formal control of the overall risk of a false positive result due to multiple statistical tests[5], and definition of study positivity does not necessarily imply positivity of both primary endpoints. In other words, a trial with MPEs could be defined positive if either progression-free survival (PFS) or overall survival (OS) analysis (not necessarily both) did show a statistically significant improvement. This methodology has at least two relevant consequences. First, the study can be presented and / or published when only PFS results are available, and OS analysis is still immature (or not presented at all). Second, experimental treatment could be defined "successful" even if OS analysis did not show a significant benefit. This is even more debatable when the PFS benefit is modest in absolute terms, although statistically significant, particularly in clinical settings where prognosis is dismal and improvement of life expectancy should be an indispensable criterion to define a clinically relevant result.

The aim of this systematic review was to describe the incidence of adoption of MPEs (typically - but not exclusively - PFS and OS) in randomized phase III trials testing systemic treatments in patients with advanced / metastatic solid tumours, published in recent years. Further objectives were to describe the main characteristics of trials adopting MPEs; to describe the presence or absence of mature results for both endpoints in the primary publication; to describe the consistency of authors' conclusions with results of each endpoint.

METHODS

Selection of publications

Literature search was performed in July 2020, using PubMed, to identify all primary publications of randomized phase III trials, published in English language between January 2017 and June 2020, conducted in adult patients with locally advanced / metastatic solid tumours.

The following key-words were used in the PubMed search: *random* AND cancer AND ("exten*" OR "previously treated" OR "stage IV" OR "unresectable" OR "advanced" OR "recurren*" OR "metast*") AND ("2017/01/01"[Date - Publication]: "3000"[Date - Publication])*

Trials testing supportive care drugs were excluded, unless their outcome was anticancer efficacy. Trials testing non-pharmacologic interventions were excluded, as well as trials conducted in paediatric patients or in hematologic malignancies. Trials conducted in early stages of disease (adjuvant / neoadjuvant) and trials testing prevention were excluded. Also trials testing biosimilars were excluded.

Data collection

A dedicated electronic database was used to collect data, with one record for each paper. Each selected paper was reviewed by one young investigator, and all doubts and controversies were discussed and settled with one senior investigator. All the trials with MPEs were double checked by one senior investigator.

For each study, information about publication was collected. Information about the clinical trial included: disease setting (locally advanced; first-line treatment for metastatic patients; second line or further treatment for metastatic patients), type of primary tumour (breast; thoracic; gastro-intestinal; urological; gynaecological; other cancers); details of

treatment in both experimental and control arms; study sponsor (for-profit vs. non-profit). Trials were considered for-profit when sponsored by the drug company and as non-profit when sponsored by academic institution / cooperative group, even if receiving drug supply and/or economic support from one or more drug companies. Experimental treatments were classified into 4 main groups: chemotherapy +/- other drugs; targeted agents +/- other drugs; hormonal treatment +/- other drugs; immunotherapy +/- other drugs. According to authors' conclusions, studies were classified into "positive", "negative" or "unclear".

Information about primary endpoints was derived from paper full text (and study protocol when available). Full text was systematically searched for the use of the term "co-primary endpoints". Trials were classified as with MPEs when more than 1 primary endpoint was planned. When multiple primary analyses were planned for the same endpoint in different populations[6-11] (e.g. OS in all patients and OS in a molecularly-selected subgroup), these analyses were not classified as MPEs.

Statistical analysis

Analyses were mostly descriptive of the proportion of trials with MPEs, in the whole series and according to study characteristics.

Chi square test was applied to determine the presence of a statistically significant association between adoption of MPEs and characteristics of publication: study sponsor, type of tumour, treatment setting and type of experimental treatment. A Mantel-Haenszel test was applied to determine the presence of a statistically significant time trend in the adoption of MPEs within the years analyzed (2017-2020).

A p value <0.05 was considered statistically significant. All analyses were performed with SPSS for Windows, version 26.0.

RESULTS

Study characteristics

Overall, 233 eligible publications, corresponding to 235 trials (2 publications included 2 trials each), were identified. The main characteristics of the eligible trials are reported in **Table 1**; 153 (65.1%) were sponsored by drug companies, while 82 (34.9%) were non-profit. Most frequent diseases were gastro-intestinal cancers (70 trials, 29.8%), thoracic cancers (60, 25.5%) and urological cancers (33, 14.0%). Most trials (147, 62.6%) were in patients receiving first-line treatment for metastatic disease, while 78 (33.2%) were in the second- or further line setting. Targeted therapy +/- other drugs (114, 48.5%) and chemotherapy +/- other drugs (74, 31.5%) were the most common experimental treatments.

Adoption of multiple primary endpoints

The adoption of MPEs according to study characteristics is detailed in **Table 1**. In the whole series, 27 trials (11.5%) adopted MPEs[12-38], mostly including OS and PFS (24, 10.2%).

The proportion of trials with MPEs increased significantly within the considered time interval, from 5.6% in 2017 to 20.0% in 2020 (p=0.025) (**Figure 1**). The majority of trials adopting MPEs were sponsored by drug companies: namely, MPEs were adopted in 15.7% of for-profit trials and 3.7% of non-profit trials (p=0.006). The proportion of trials adopting MPEs was not significantly different among different types of tumours, and not significantly different according to treatment setting: namely, MPEs were adopted in 12.9% of trials conducted in the first-line setting of patients with metastatic disease, but also in 7.7% of trials conducted in the second- and further line setting. The proportion of trials

adopting MPEs was particularly high for trials testing immunotherapy (52.8%), compared to other types of treatment (p<0.00001).

The details of the 27 trials adopting MPEs are summarized in **Table 2** (trials testing immunotherapy[12-30]) and **Table 3** (trials testing other treatments[31-38]).

Out of the 27 trials with MPEs, 10 (37.0%) adopted an explicit definition of "co-primary" endpoints[12-14,17,24,25,29,30,33,34]. Of these 10 trials, only 1 explicitly conditioned the interpretation of the trial to the positivity of both endpoints, and correctly did not plan a correction for multiplicity[34]. In the other 9 trials, statistical methods included a formal correction for multiplicity, with alpha adjustment. Conversely, out of 17 trials without explicit definition of "co-primary" endpoints[15,16,18-23,26-28,31,32,35-38], 14 included a formal alpha adjustment for multiplicity, while in 2 cases[32,35] this issue was not specified and 1 case[38] a hierarchical testing was planned for the 3 primary endpoints (PFS, PFS2 and OS).

In 23 trials (85.2%), the results of all MPEs were included in the primary publication. In 4 cases (14.8%), only PFS results were included in the publication while OS results were not available[13,17,23,24]. Although three of these 4 trials[13,17,24] explicitly used the definition of "co-primary" endpoints, which should imply the availability of results of both endpoints to interpret the positivity of the study, all those 4 trials had applied alpha correction for multiplicity, and authors' conclusions presented study results as positive on the basis of PFS positivity alone. In one case, testing durvalumab as consolidation treatment after chemo-radiotherapy in locally advanced non-small cell lung cancer [NSCLC][13], OS results have been subsequently published, and showed a significant OS improvement with durvalumab. In another case, testing nivolumab + ipilimumab as first-line treatment of advanced NSCLC[17], OS results of the subgroup corresponding to PFS co-primary endpoint (patients with high tumor mutation burden [TMB]) were subsequently presented and were statistically not significant. In the remaining 2 cases, testing avelumab + axitinib[23] and atezolizumab + bevacizumab[24] as first-line treatment of advanced renal

cancer, OS results are still not published, respectively 22 and 19 months after primary publication.

Among the 27 publications of trials with MPEs, authors' conclusions were positive in 21[12-14,16-25,27,30-32,35-37], negative in 5[15,26,33,34,38] and unclear (formally negative, but "favourable risk-benefit ratio") in 1 case[28]. In detail, in the 21 publications with positive conclusions, 12 had a positive result in both primary endpoints[13,16,18-20,22,25,29,31,35-37] (including 1 case with positive OS results not available in the primary publication but published later[13]), 5 had a positive result only in PFS[17,21,23,24,30] (including 1 case with negative OS not available in the primary publication but published later[17], and 2 cases with OS results still not available[23,24]), 1 had a positive result only in disease-free survival[32], and 3 had a positive result only in OS, with negative PFS results[12,14,27]. Out of the 5 publications with negative authors' conclusions[15,26,33,34,38], in 3 cases PFS and OS results were both not significant[15,26,33], in 1 case PFS results were statistically significant but clinically not relevant, and OS results were negative[34], and in 1 case PFS results were significant but OS was not formally tested due to negativity of PFS2 within the planned hierarchical testing[38].

Discussion

In this systematic review of randomized phase III trials conducted in patients with advanced cancer, published between 2017 and 2020, we found a non-negligible proportion of trials adopting MPEs, mostly PFS and OS. The proportion of trials with MPEs has significantly increased over time, even within the limited period analysed. The choice of more than one primary endpoint was particularly common in for-profit trials, and in trials testing immunotherapy.

The adoption of MPEs is important for both the design and the interpretation of clinical trials[3,4,39]. The ICH E9 guideline on statistical principles for clinical trials recommends that clinical trials should be designed with one primary variable[39]. In fact, when the treatment-induced change in one endpoint is able to demonstrate a clinically relevant treatment effect, a single endpoint should be considered sufficient. On the other hand, the adoption of more than one primary endpoint might be appropriate when "*a single variable is not sufficient to capture the range of clinically relevant treatment benefits*"[3]. EMA discusses the issue of MPEs, identifying some situations when formal adjustment of the significance level is needed, and other situations when it is not necessary[3]. In fact, when more than one primary endpoint is adopted, one crucial issue is the definition of study success. When it is sufficient that one endpoint has a positive outcome, independently of the others, this should necessarily require appropriate adjustment for multiplicity. Conversely, when MPEs are designated as "co-primary" endpoints, trial success should be subordinated to a positive outcome in all endpoints and, in order to allow study interpretation, the publication should contain results of both endpoints. In this case, correction for multiplicity (i.e. alpha error splitting between the 2 endpoints) is not needed, because if one of the endpoints is not met, the study should be considered negative.

In our series, 10 studies declared that endpoints were “co-primary” [12-14,17,24,25,29,30,33,34], but 9/10 adopted a correction for multiplicity, demonstrating a frequent confusion in the application of MPEs compared to the official documents of regulatory agencies, even in for-profit trials designed to support treatment approval. In 3 cases[13,17,24], despite the explicit definition of “co-primary” endpoints, the publications did not include OS data, and authors’ conclusions defined the study as positive based on PFS results alone. This is conflicting with the definition of “co-primary” endpoints discussed in the EMA guideline[3]. Furthermore, two of the three aforementioned trials received drug approval based on a single “co-primary” endpoint[13,17]. On February and July 2018, FDA and EMA respectively approved durvalumab for locally advanced NSCLC based on the PFS analysis, with immature OS results. On May 2020, nivolumab + ipilimumab combination was approved by FDA as first-line treatment in advanced NSCLC with PD-L1 expression≥1%, based on OS results reported in this population, regardless of the conflicting data on population with high TMB.

Especially in settings characterized by a long post-progression survival, PFS results can be obtained several months (or years) before the maturity of OS analysis. This consideration, together with factors potentially conditioning positivity of OS analysis (e.g. crossover of experimental treatment) and with intrinsic clinical value of a large PFS prolongation, has often led to the choice of PFS as primary endpoint of cancer trials, stimulating a wide scientific debate[40,41]. The increasing adoption of MPEs adds further elements to this debate. As a matter of fact, the correction for multiple testing - that was adopted in the vast majority of the trials with MPEs in our analysis, independently of the use of the term “co-primary” - implies the possibility of a positive study conclusion even in the absence of OS difference, with all the intrinsic limitations in the adoption of PFS as primary endpoint.

The high frequency of both PFS and OS as MPEs in trials testing immunotherapy, in different tumours, characterized by different prognosis and life expectancy, seems to be not casual. From the sponsor's perspective, PFS can be considered a convenient endpoint for early declaration of study positivity. However, due to mechanism of action and difficulty in response evaluation, immunotherapy has often produced more robust results in terms of OS than in PFS[42,43]. The adoption of MPEs would allow to play two cards in the same study, declaring study positivity in the case of PFS improvement, otherwise waiting for OS results in the case of PFS negativity.

Furthermore, we showed that trials with MPEs were often conducted in clinical settings characterized by a limited (in some cases, very limited) life expectancy. In these clinical settings, we strongly believe that trials should be designed to prolong OS, and it is quite difficult to understand the intrinsic value of a PFS benefit, if not translated into a prolongation of OS. Consequently, many of these studies could have been properly designed with OS a single primary endpoint. For instance, the trial comparing pembrolizumab versus chemotherapy with a taxane or vinflunine as second-line treatment for patients with advanced urothelial cancer, after failure of platinum-based chemotherapy, was designed with PFS and OS as co-primary endpoints, with alpha splitting between the two endpoints[12]. With an expected median OS of 8 months in the control arm, it would have been reasonable to design the study to demonstrate an improvement in OS. Actually, trial results showed an improvement in OS with pembrolizumab, without significant difference in PFS. Authors' conclusions were positive, and the treatment has been approved for use in clinical practice. However, in the opposite case (PFS positive and OS negative) the benefit in PFS alone should have been reasonably interpreted as not clinically relevant. Consequently, why to adopt PFS as co-primary endpoint? OS alone could have been a proper primary endpoint. Similar considerations can be made for many other trials adopting PFS and OS in settings with dismal prognosis and limited life

expectancy, like second-line setting of hepatocellular carcinoma[28] or second-line setting of gastric cancer[15].

When PFS is adopted as primary endpoint, demonstration of improvement in instrumental disease control should be accompanied by demonstration of benefit in terms of patients' quality of life, that would make more clinically valuable the interpretation of the PFS result. This would represent a good rational to design clinical trials with MPEs including PFS and patient-reported outcomes. However, our systematic review shows that this concept is never applied to the design of trials for patients with advanced cancer, and interpretation of PFS (even within studies with MPEs) is *de facto* independent of quality of life results.

In conclusion, we have found that adoption of MPEs in randomized phase III trials in oncology is becoming quite common, especially in for-profit trials and in trials testing immunotherapy. Despite regulatory agencies have produced clear methodological recommendations about the adoption of MPEs, the definition of "co-primary" endpoints and the need of correction for multiple statistical testing, this review of the literature demonstrates confusion and heterogeneity in the application of such rules. Furthermore, we believe that adoption of MPEs including PFS and allowing positive interpretation of the results even in the absence of OS improvement, is potentially abused in many clinical settings where prolongation of life expectancy of cancer patients should be the only clinically relevant endpoint.

CRediT author statement

Clizia Zichi, Chiara Paratore, Francesco Perrone: conceptualization, methodology, investigation, writing (original draft), visualization; Piera Gargiulo, Annapaola Mariniello, Maria Lucia Reale, Marco Audisio, Maristella Bungaro, Andrea Caglio, Teresa Gamba: investigation, writing (review and editing); Massimo Di Maio: conceptualization, methodology, investigation, writing (original draft), visualization, supervision.

DISCLOSURE

Maria Lucia Reale had role as consultant for Eli-Lilly.
Francesco Perrone reports grants, personal fees and non-financial support from Bayer, personal fees from Sandoz, grants and personal fees from Incyte, personal fees from Celgene, grants and personal fees from Astra Zeneca, personal fees from Pierre Fabre, personal fees from Janssen Cilag, grants from Roche, grants from Pfizer, outside the submitted work.
Massimo Di Maio received honoraria and had roles as consultant or advisor for AstraZeneca, Pfizer, Novartis, Roche, Takeda, Eisai, Janssen, Astellas; received institutional research grant by Tesaro – GlaxoSmithKline.
All remaining authors declared no conflicts of interest.
As Corresponding author, Massimo Di Maio had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE LEGENDS

Figure 1. Proportion of randomized phase III trials with multiple primary endpoints, scattered by year of publication and by type of study sponsor (light grey: non-profit trials; dark grey: for-profit trials).

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