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Selection of Endpoints in Clinical Trials: Trends in European Marketing Authorization Practice in Oncological Indications

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ABSTRACT

Objectives: To determine the types of endpoints that were the basis for efficacy assessment of medicines used in particular groups of oncological indications. Changes in the endpoints applied in marketing authorization practice were also considered.

Methods: The analysis included marketing authorization applications (MAAs) for medicines used in oncological indications that were first-time approved by the European Medicines Agency (EMA) between 2009 and 2017, and the extensions of the analyzed medicines.

Results: The analysis covered 125 MAAs: first-time approved (62%) and extensions (38%). In the analyzed trials, the endpoints that were reported most frequently included overall survival (OS), progression-free survival (PFS), and overall response rate (in 94.4%, 92.8%, 87.2% of MAAs, respectively). The following trends were observed: decreased significance of OS as a primary endpoint and increased significance of PFS as a primary endpoint (hematological indications). An analysis of MAAs for which the OS results were immature confirms the increased significance of PFS and new efficacy indicators (ie, pathological complete response).

Conclusions: An analysis of EMA's marketing authorization practice proves that the use of surrogate endpoints is becoming increasingly common in evaluating oncological health technologies. EMA's guidelines underline the role played by surrogates in the process of assessing efficacy of new therapies. Results of an analysis demonstrate that protocols of clinical trials define surrogates as primary endpoints more and more often. Furthermore, a positive decision on granting marketing authorization is possible also in situations when only such clinical data are available.

Keywords: European Medicines Agency, marketing authorization practice, overall survival, surrogate endpoints.

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Introduction

The decision on whether to grant a European marketing authorization to new therapies is based on results of clinical trials. The endpoint for a clinical trial is selected not only on the basis of the type of the studied population and the medicine that is the subject of assessment but also on the basis of the study's feasibility, its cost, and the intended goal of treatment.[1] In addition, there should be enough scientific evidence to demonstrate that the selected primary endpoint may represent a current and reliable measure of clinical benefit in the target population.[2] For many years the overall survival (OS) has been considered the "gold standard" and the most important clinical endpoint. Nevertheless, it is being disputed whether treating OS as the key endpoint is justified, particularly in the case of first-line treatment or in crossover studies.[3,4] Under the accelerated assessment procedure, in the absence of results indicating improvement in OS, it becomes necessary to evaluate the efficacy of therapies with the use of time-to-event indicators, for example, progression-free survival (PFS). In line with the position of the Committee for Medicinal Products for Human Use Scientific Advisory Group for Oncology, an improvement in PFS is considered a less significant endpoint than OS, but it is still considered a clinically significant endpoint.[5] It should be emphasized that an improvement in quality of life (QOL) alone, despite being a hard endpoint, is unlikely to be sufficient for the purpose of obtaining marketing authorization (add-on value to conventional efficacy and safety data in benefit-risk assessment).[2,6,7]

Available articles constitute a systematic review of oncological medicines with marketing authorization granted by the European Medicines Agency (EMA) in the years 2009 to 2013; they, however, do not answer the questions about the results and trends observed for particular oncological indications.[8,9] The aforementioned issues seem to be crucial because of the heterogeneity of oncological indications, especially hematological and other oncological indications (solid tumors). The objective of this analysis was to

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determine the types of endpoints that constitute the basis for drawing conclusions on the efficacy of medicines used in specific oncological indications, including hematological ones. The changes that have taken place over recent years in the endpoints applied in registration practice were also considered.

Methods

The European Public Assessment Reports (EPARs) database (www.ema.europa.eu) was searched. The analysis covered marketing authorization applications (MAAs) for medicines used in oncological indications that were first-time approved by the EMA between January 1, 2009, and December 31, 2017. The analysis did not include generic, biosimilar, and hybrid medicines as well as medicines intended for supportive treatment (eg, antiemetics). In addition, the history of EMA's assessment for oncological medicines included in the analysis was searched, whereby it was possible to identify the extension of oncological indications of the analyzed medicines. Accordingly, 2 types of marketing authorizations were distinguished:

1. First-time approved, regarding new active substances that had not been available on the European market before, and
2. Extensions, regarding medicines that had already been available on the European market but their new indications were approved.

Given the broad scope of oncological indications, they were divided into 19 groups. Results are presented by the selected groups of indications in 2 main groups: hematological indications and other oncological indications (solid tumors) or in total.

The analysis covered MAAs approved by the EMA in the years 2009 to 2017, that is, a 9-year period. Because the number of MAAs approved in specific years for a specific group of indications was small because of the limitation of data distribution, it was decided to divide this interval into 2 subperiods. To streamline the analysis, it was decided to analyze full years—the years close to the middle of the analyzed period, that is, 2013 and 2014. After observing the small number of MAAs in the first subperiod, the authors decided to divide the period into 2, with the year 2014 as the cutoff point. The analysis of trends in the marketing authorization practice with regard to the adopted endpoints has been broken down and presented in 2 subperiods—2009 to 2013 and 2014 to 2017—to illustrate the changes that took place in recent years.

The analysis includes primary and secondary endpoints in terms of efficacy, defined in the protocols that clinical trials used for marketing authorization purposes (see the "Main study" section in the EPAR). The endpoints presented in the EPARs, as predefined endpoints, were additionally verified in terms of reported results. That way the analysis covers only primary and secondary endpoints, the results that constituted actual grounds for obtaining marketing authorization. Whenever the decision on granting marketing authorization was based on more than 1 main clinical trial, the endpoints were considered in total as per the given MAA (when the given endpoint constituted a primary endpoint in one study and a secondary endpoint in a different study with regard to the same MAA, for the purpose of an analysis it was assumed that it constituted a primary endpoint).

Results

One hundred twenty-three MAAs regarding oncological indications were approved in the period in question (2009-2017). In the case of 5 applications, because of completely different indications approved in 1 MAA (plerixafor, idelalisib, ibrutinib, ramucirumab, and atezolizumab), it was decided to single them out into adequate groups of indications, which would correspond better to the individual indications included in the MAAs (plerixafor: lymphoma and multiple myeloma; idelalisib: lymphoma and leukemia; ibrutinib: lymphoma and leukemia; ramucirumab: lung cancer and colorectal cancer; and atezolizumab: lung cancer and urothelial cancer; for details, see Appendix Table S1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.007). Furthermore, the analysis did not take into account 3 MAAs that had been approved by the EMA for the treatment of benign neoplasms (propranolol and ulipristal acetate). In this case, no further analyses were conducted (specific endpoints in clinical trials, eg, reduction in uterine bleeding).

The final detailed analysis included 125 MAAs. Of these, 78 applications (62%) were first-time approved and most of them received standard authorization (87%), whereas 10 MAAs received conditional authorization. Forty-seven MAAs (38%) constituted extensions of oncological indications (Table 1; see also Appendix Table S1 in Supplemental Materials).

The largest number of MAAs was approved in the following groups of indications: lung cancer (20 MAAs), leukemia (18 MAAs), skin cancer (15 MAAs), and lymphoma (12 MAAs); they constituted 16%, 14.4%, 12%, and 9.6% of all approved applications, respectively. Single MAAs were approved in the following groups: pancreatic cancer, hepatocellular carcinoma, cancer of the head and neck, and neuroblastoma (Table 1).

An analysis of 125 MAAs indicates that a total of 150 trials constituted the basis for MAAs. The largest number of trials was recorded for the following groups: leukemia (18%), lung cancer (16.7%), skin cancer (12%), lymphoma (8.7%), and multiple myeloma (8%), which is consistent with the largest number of MAAs. More than 77% of all the trials were randomized clinical trials (RCTs) and 30% of all trials used as the basis for MAAs were double-blind trials (nearly 40% of all RCTs). More than one-fifth of all trials were single-arm (SA) studies. The largest percentage of such trials was recorded in the lymphoma (7 of 13 MAAs [54%]), leukemia (11 of 27 MAAs [41%]), urothelial cancer (2 of 5 MAAs [40%]), and neuroblastoma (1 of 2 MAAs [50%]) groups. In the case of 14% of all MAAs (18 MAAs: 6 MAAs, lymphoma; 3 MAAs, leukemia; 6 MAAs, lung cancer; 2 MAAs, skin cancer; and 1 MAA, urothelial cancer), SA studies constituted the main source of information on the efficacy of therapies (no RCTs, eg, brentuximab and idelalisib—lymphoma; blinatumomab—leukemia; and osimertinib and alectinib—lung cancer) (see Appendix Table S2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.007).

EMA's Authorization Practice—Clinical and Surrogate Endpoints in the Trials

The most frequently reported (primary or secondary) endpoints in the trials were OS (in 94.4% of MAAs), PFS (in 92.8% of MAAs), and overall response rate (ORR) (in 87.2% of MAAs). In all applications, OS, PFS, and ORR constituted primary endpoints in 34.4%, 48.8%, and 21.6% of MAAs and secondary endpoints in 60%, 44%, and 65.6% of MAAs, respectively (Table 2).

There were slight differences with regard to the frequency of reporting endpoints (OS, PFS, and ORR)—OS was reported in a similar percentage of first-time approved MAAs (94.9%) as extension MAAs (93.6%). There were also slight differences with regard to the frequency of reporting PFS and ORR in the first-time approval group and the extension group (PFS: 88.5% vs 100%; ORR: 93.6% vs 83.3%).

Table 1. Summary of the MAAs regarding medicinal products in oncological indications registered by the EMA in the years 2009-2017 divided by indications.

Group of indication	Medicines, n	Orphan, n	All MAAs, n (%)	First-time approved, n (%)	Standard approval, n (%)	Conditional approval, n (%)	Extension, n (%)
Lymphoma	8	3	12 (9.6)	5 (6.4)	3 (4.4)	2 (20)	7 (14.9)
Multiple myeloma	7	6	9 (7.2)	7 (9)	6 (8.8)	1 (10)	2 (4.3)
Leukemia	13	11	18 (14.4)	13 (16.7)	10 (14.7)	3 (30)	5 (10.6)
Lung cancer	13	0	20 (16)	9 (11.5)	9 (13.2)	0 (0)	11 (23.4)
Breast cancer	6	0	8 (6.4)	5 (6.4)	5 (7.4)	0 (0)	3 (6.4)
Skin cancer	11	1	15 (12)	11 (14.1)	10 (14.7)	1 (10)	4 (8.5)
Urothelial cancer	4	0	4 (3.2)	2 (2.6)	2 (2.9)	0 (0)	2 (4.3)
Renal cell carcinoma	7	0	7 (5.6)	6 (7.7)	6 (8.8)	0 (0)	1 (2.1)
Prostate cancer	6	0	9 (7.2)	6 (7.7)	6 (8.8)	0 (0)	3 (6.4)
Colorectal cancer	4	0	4 (3.2)	3 (3.8)	3 (4.4)	0 (0)	1 (2.1)
Stomach neoplasm	3	0	3 (2.4)	2 (2.6)	2 (2.9)	0 (0)	1 (2.1)
Pancreatic cancer	1	1	1 (0.8)	1 (1.3)	1 (1.5)	0 (0)	0 (0)
Hepatocellular carcinoma	1	1	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (2.1)
Thyroid cancer	3	2	4 (3.2)	3 (3.8)	1 (1.5)	2 (20)	1 (2.1)
Ovarian neoplasm	2	2	2 (1.6)	2 (2.6)	2 (2.9)	0 (0)	0 (0)
Sarcoma	4	2	4 (3.2)	2 (2.6)	1 (1.5)	1 (10)	2 (4.3)
Neuroendocrine tumor	1	0	2 (1.6)	0 (0)	0 (0)	0 (0)	2 (4.3)
Cancer of the head and neck	1	0	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (2.1)
Neuroblastoma	1	1	1 (0.8)	1 (1.3)	1 (1.5)	0 (0)	0 (0)
Total			125	78	68	10	47

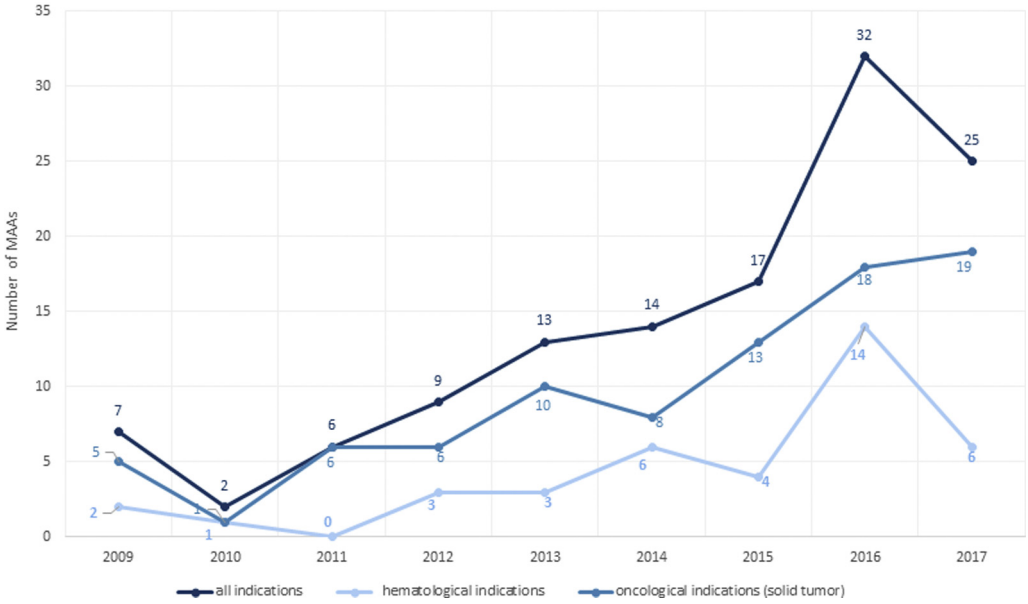
Note. Five MAAs were divided into 2 separate ones because of completely individual indications approved within 1 MAA (plerixafor: lymphoma and multiple myeloma; idelalisib: lymphoma and leukemia; ibrutinib: lymphoma and leukemia; ramucirumab: lung cancer and colorectal cancer; and atezolizumab: lung cancer and urothelial cancer).
EMA indicates European Medicines Agency; MAA, marketing authorization application.

Table 2. Summary of the endpoints used in the clinical trials that were the basis for MAAs for medicinal products in oncological indications registered by the EMA in the years 2009-2017 regarding the type of trials and availability of results.

Endpoint	Primary endpoint				Secondary endpoint			
	All reported MAAs, n (%)*	In SA study, n (%)†	In MA study, n (%)†	NR, n (%)†	All reported MAAs, n (%)*	In SA study, n (%)†	In MA study, n (%)†	NR, n (%)†
OS	43 (34.4)	2 (4.7)	41 (95.3)	1 (2.3)	75 (60)	20 (26.7)	55 (73.3)	35 (46.7)
PFS	61 (48.8)	1 (1.6)	60 (98.4)	1 (1.6)	55 (44)	21 (38.2)	34 (61.8)	2 (3.6)
QOL	0 (0)	0 (0)	0 (0)	0 (0)	44 (35.2)	0 (0)	44 (100)	0 (0)
ORR	27 (21.6)	20 (74.1)	7 (25.9)	0 (0)	82 (65.6)	5 (6.1)	77 (93.9)	0 (0)
DOR	2 (1.6)	2 (100)	0 (0)	0 (0)	60 (48)	14 (23.3)	46 (76.7)	7 (11.7)
TTR	1 (0.8)	1 (100)	0 (0)	0 (0)	25 (20)	9 (36)	16 (64)	0 (0)
DCR	0 (0)	0 (0)	0 (0)	0 (0)	20 (16)	4 (20)	16 (80)	0 (0)
TTP	1 (0.8)	0 (0)	1 (100)	0 (0)	16 (12.8)	2 (12.5)	14 (87.5)	0 (0)
CR	3 (2.4)	1 (33.3)	2 (66.7)	0 (0)	12 (9.6)	6 (50)	6 (50)	0 (0)
Biomarkers	1 (0.8)	0 (0)	1 (100)	0 (0)	11 (8.8)	0 (0)	11 (100)	0 (0)

Note. Data are limited to endpoints that occurred in at least 10 MAAs, which can be considered representative for all singled-out indications.
CR indicates complete response; DCR, disease control rate; DOR, duration of response; EMA, European Medicines Agency; MA, multiarm; MAA, marketing authorization application; NR, not reached (in the treatment and control arms); ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QOL, quality of life; SA, single-arm; TTP, time to progression; TTR, time to response.
*With respect to all the analyzed applications (MAA = 125).
†With respect to the applications reporting given endpoint (all reported).

Figure 1. Number of MAAs approved by the EMA in specific years of the period in question in all indications cumulatively and divided by hematological and other oncological indications.



EMA indicates European Medicines Agency; MAA, marketing authorization application.

The selection of endpoints assessing efficacy of medicines used in cancer therapies depends on the stage of treatment (line of treatment). Although in many cases the indication is complex and it is difficult to divide MAAs by treatment lines, such an attempt was made and 2 such MAA groups were singled out—first-line treatment (untreated patients) and other treatment lines (relapsed/refractory patients or a complex indication for various populations). Of the 125 MAAs, 23 were selected in which the indication was first-line treatment. No differences were observed in the frequency of reporting OS results between the 2 types of MAAs (first-line treatment vs other treatment lines). At the same time, it should be underlined that inference is associated with significant uncertainty because of the small number of MAAs used in first-line treatment.

Reporting results depends on the trials used as the basis for obtaining marketing authorization. In MAAs in which ORR was a primary endpoint, 74.1% (20 MAAs) were based on SA studies. At the same time, relatively high PFS and OS reporting as secondary endpoints was noted in SA studies (38% and 27% of all MAAs in which the aforementioned endpoints were reported, respectively).

Trends in Assessing Efficacy of Oncological Medicines—Changes in the Primary and Secondary Endpoints

It is also worth observing how the adopted endpoints have changed in the studies underlying EMA's marketing authorization decisions over the years. Because of the specificity of the groups of indications, this trend seems to be particularly important when divided into hematological and other oncological indications.

In recent years, an increase in the number of approved MAAs has been observed with regard to oncological indications (Fig. 1). In the period 2009 to 2013, 37 MAAs were approved, whereas in the period 2014 to 2017, more than twice as many applications were approved (88 MAAs).

It should be noted that OS was not a predefined endpoint for 8 MAAs of all applications approved by the EMA in 2009 to 2017 (plerixafor [2 MAAs], asparginase, degarelix, padeliporfin dipotassium, nivolumab [2 MAAs], and pertuzumab). For this type of therapy, prolonging of survival is not an achievable goal, and other indicators are used to assess efficacy (eg, probability of testosterone ≤0.5 ng/mL) (see Appendix Table S1 in Supplemental Materials).

An analysis of endpoints (2009-2017) indicates that the most frequently assessed endpoints were OS, PFS, and ORR (Fig. 2). The performed analysis indicates a decrease in the significance of OS as the primary endpoint for all oncological indications cumulatively (a nearly 13% decrease in MAAs; odds ratio [OR] 1.72; 95% confidence interval [CI] 0.78-3.80; *P*=.180). At the same time, the rate of MAAs reporting OS as a secondary endpoint increased, which was particularly noticeable for hematological indications.

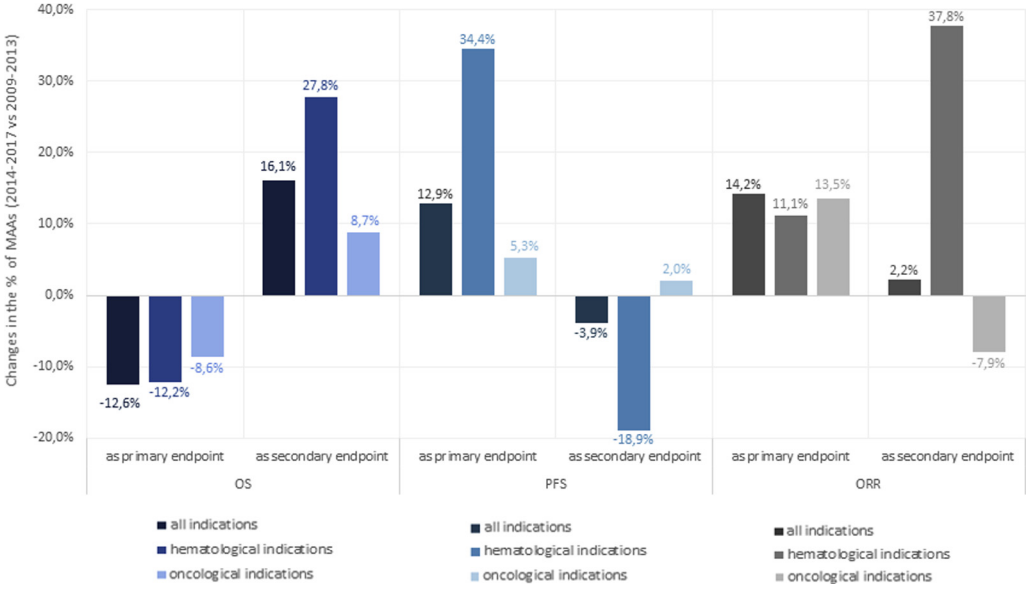
A very clear change in EMA's practice regarding marketing authorization was observed for PFS. For hematological indications, an increase of more than 34% in the rate of MAAs reporting PFS as the primary endpoint (OR 0.22; 95% CI 0.04-1.23; *P*=.080) was noted, with a simultaneous (almost 19%) decrease in reporting it as a secondary endpoint. For the remaining oncological indications, the aforementioned increase was low (about 5%) (Fig. 2).

In terms of response to treatment, all indications demonstrated a 14% increase in the rate of MAAs on the basis of the studies reporting ORR as a primary endpoint. Nevertheless, the change in reporting ORR as a secondary endpoint is distinctly different for various groups of indications—an almost 38% increase was observed for hematological indications, whereas for other oncological indications (solid tumors) there was an approximately 8% decrease (hematological vs other oncological indications: OR 0.38; 95% CI 0.17-0.85; *P*=.020) (Fig. 2).

Trends in Assessment of the Efficacy of Oncological Medicines in Case of Immature OS Results—Significance of PFS and Surrogate Endpoints

A particularly interesting aspect of the marketing authorization practice is the drawing of conclusions on a therapy's efficacy when the OS results are immature. The analyses focused on OS, which is a hard endpoint and, unlike QOL, may constitute the basis for

Figure 2. Changes in the rates of MAAs in which OS, PFS, and ORR were reported as primary or secondary endpoints in all oncological indications cumulatively and broken down into hematological and other oncological indications (2014-2017 vs 2009-2013).



MAA indicates marketing authorization application; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

granting of marketing authorization. Mature results (median achieved) were presented in all the analyzed MAAs for which the OS was a primary endpoint. In contrast, in the MAAs in which OS was predefined as the secondary endpoint, the median was often not reached. In those cases, the decisions on granting marketing authorization were based mainly on results regarding efficacy expressed as PFS or surrogate endpoints.

In the period 2009 to 2013, OS results were immature (with regard to single- and multiple-arm studies) in 7 of 37 MAAs (19%); in comparison, in the period 2014 to 2017, lack of the OS median was recorded in 34 of 88 MAAs (39%) (OR 0.37; 95% CI 0.15-0.94; *P*=.040). The increase in the number of MAAs in which immature OS results were presented can be observed even more distinctively in MAAs regarding hematological indications (2009-2013: 3 MAAs [33%]; 2014-2017: 19 MAAs [63%]).

In the 41 MAAs approved in the period 2009 to 2017, in which immature OS results were reported, the following primary indicators were predefined: PFS, ORR, major cytogenetic response/complete cytogenetic response (MCyR/CCyR), event-free survival (EFS), and pathological complete response (pCR). An analysis of the endpoints used in MAAs in all oncological indications showed that PFS was the primary endpoint in a similar percentage of MAAs in both considered time intervals (2009-2013: 57%; 2014-2017: 59%). In the group of hematological indications, an increase in the significance of the PFS indicator as the primary endpoint was observed (63% of MAAs [2014-2017] compared with 0% [2009-2013]). Nevertheless, an opposite trend was observed for the group of other oncological indications: in the period 2009 to 2013 in 100% of MAAs, PFS was evaluated as the primary endpoint, whereas in the subsequent period the percentage rate dropped to 53%. Nevertheless, in this group there was a visible increase in the importance of ORR as the primary endpoint (33% of MAAs) (Fig. 3).

It should be pointed out that in recent years (2014-2017), new primary endpoints have appeared in both hematological and other oncological indications, constituting the basis for drawing conclusions on the efficacy of the implemented therapy in a precisely defined population of patients, that is, EFS (pegaspargase and dinutuximab beta) and pCR (pertuzumab). In the aforementioned cases, the marketing authorization decisions were based on clinical data expressed as surrogate endpoints.

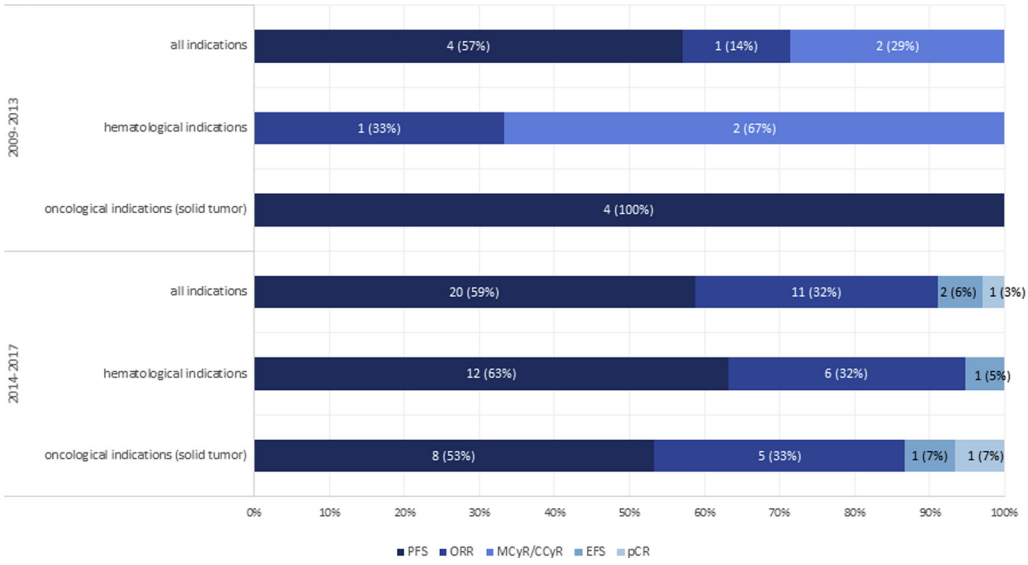
The analysis of MAAs submitted in the period 2009 to 2013, in which immature OS results were reported, indicates that the efficacy assessment was supported by QOL results in only 1 MAA. In turn, in the interval 2014 to 2017, QOL results were reported in 15 MAAs. It is also worth mentioning that new indicators were reported as secondary endpoints in the MAAs in which OS results were not reached. The efficacy analysis was additionally supported with surrogate endpoint results: minimal residual disease (MRD) or PFS for second-line treatment (PFS2) in 4 MAAs and 1 MAA, respectively (in the period 2014-2017) (see Appendix Table S1 in Supplemental Materials).

Discussion

Reporting results in terms of particular endpoints depends on the trials used as the basis for MAAs. An analysis of MAAs approved by the EMA in the years 2009 to 2017 showed that the most frequently reported primary and secondary endpoints were OS and PFS, which occurred in approximately 90% of applications in all oncological indications.

Results of the Liberti 2015 analysis, covering MAAs from the period 2009 to 2013, demonstrate that OS was reported as a primary endpoint in 42% of MAAs and as a secondary endpoint in 52% of MAAs (in total 94%). In contrast, PFS was assessed as a primary endpoint in 33% and as a secondary endpoint in 55% of MAAs (in total 88%).[8] This analysis, covering a wider time interval (2009-2017), shows a similar combined percentage rate of applications that present OS and PFS as a primary or secondary endpoint. At the same time, it indicates changes in the percentage rate of MAAs in the scope of the aforementioned endpoints depending on the endpoint type (as a primary endpoint: OS, 34.4%; PFS, 48.8%). It should be noted that an analysis that would cover the type of adopted research hypothesis (superiority/noninferiority) in

Figure 3. Primary endpoints reported in MAAs, in which immature OS results were presented (the number of MAAs and the percentage rates with regard to the total number of MAAs in a given group—all indications, hematological indications, and other oncological indications).



EFS indicates event-free survival; MAA, marketing authorization application; MCyR/CCyR, major cytogenetic response/complete cytogenetic response; ORR, overall response rate; OS, overall survival; pCR, pathological complete response; PFS, progression-free survival.

clinical trials would contribute greatly to the discussion on the significance of surrogate endpoints in health technology assessment.

The high percentages of applications for which PFS was reported as a primary and secondary endpoint indicate its importance in current clinical trial practice. PFS in some disease entities, that is, leukemia and lymphoma, is an indicator available in a shorter time than OS, which in the aforementioned indications requires a relatively long follow-up. In line with the European network for Health Technology Assessment recommendations, PFS as the endpoint in clinical trials in oncological indications has different values depending on the disease stage. PFS is an acceptable endpoint, in adjuvant indications, in first lines of treatment of chronic indications. In the metastatic stage of the disease, in the last lines of treatment, supporting the application with data in terms of OS and/or QOL is recommended.[10,11] In addition, in line with the position of the Committee for Medicinal Products for Human Use Scientific Advisory Group for Oncology, in certain cases, an improvement in terms of PFS is considered a clinically significant endpoint. Improvement in PFS should be considered as a clinically relevant endpoint per se, even in the absence of a documented improvement in OS, provided that there is no detriment in terms of OS.[5]

The marketing authorization requirements for the selection of endpoints in clinical trials have been evolving for decades—from ORR (1970s), throughout OS, QOL, or endpoints related to tumor evaluation (1980s), to PFS and surrogate endpoints (such as MRD and pCR).[12] Guidelines underline the significance of the OS assessment in most oncological indications. PFS/DFS (disease-free survival) can also serve as primary endpoints, as long as OS is also reported as a secondary endpoint (OS is not always required as a secondary endpoint; reporting it is, however, always recommended). To increase transparency of PFS results, current EMA guidelines recommend the use of an indirect endpoint for PFS and OS, that is, PFS2. In line with EMA's guidelines, ORR may be reported as a primary outcome in SA trials.[2,5]

The results of the analysis support the conclusion that the selection of endpoints for assessing the efficacy of oncological treatment depends on many factors, including the course of the disease (chronic vs acute) and patients' baseline characteristics (naive vs patients after several treatment lines). The EMA has changed its marketing authorization practice regarding medicines for which data on OS can be reached only with a long follow-up.[2,13] An analysis of MAAs in which the OS results presented in the EPAR were immature confirms PFS's increased significance as a primary endpoint (for hematological indications) and new indicators that allow for drawing conclusions on the therapy's efficacy (ie, pCR, MCyR, CCyR, and major molecular response [MMR]). In addition, results of new indicators that emerge as secondary endpoints (such as QOL, MRD, and PFS2) support the assessment of efficacy.

The analysis showed that pCR was the primary endpoint in the case of 1 MAA (pertuzumab). The importance of this endpoint is also underlined by the EMA guidelines (2014), which determine when pCR can constitute a basis for a marketing authorization decision (add-on medicines for the adopted neoadjuvant regimen, used in patients with a high grade of malignancy of early-stage breast cancer, with simultaneous collecting of data on EFS/DFS/OS).[14,15] The marketing authorization was granted in 2015; hence, it was the consequence of the guidelines being published. Furthermore, the updated European Society for Medical Oncology Magnitude of Clinical Benefit Scale provides for a scoring framework for assessing the efficacy of (neo)adjuvant therapies on the basis of pCR.[16]

Another endpoint that is specific to a given disease entity is MRD. The analysis of all MAAs identified 6 applications (2014-2017) for which MRD was reported as a secondary endpoint (4 MAAs in chronic lymphocytic leukemia, 1 MAA in acute lymphoblastic leukemia, and 1 MAA in multiple myeloma). In 2014, the EMA published guidelines referring to the validity of assessing MRD status as an endpoint in chronic lymphocytic leukemia. Differences in terms of MRD response rates may constitute

primary evidence of clinical benefits for the purpose of obtaining early licensure.[17]

In patients with chronic myeloid leukemia (CML), the key factor is response to treatment, which is made up of hematological response (complete hematological response), cytogenetic response (MCyR, CCyR), and molecular response (MMR). Given the significance of the aforementioned endpoints in CML, it is worth indicating that MMR was recorded in 1 MAA, MCyR in 2 MAAs, and CCyR in 1 MAA. The EMA guidelines specify the recommended endpoints in the chronic phase of CML—MMR (as primary endpoint in the superiority trials), MCyR, and CCyR are the criterion standard for efficacy assessment in terms of response.[14]

In connection with molecular response, treatment-free remission is also mentioned as an important endpoint in terms of CML. The European Society for Medical Oncology 2017 guidelines emphasize that treatment discontinuation may be considered in individual patients if proper, high-quality monitoring can be ensured. In the future, treatment-free remission may become a new therapeutic goal in CML.[18,19]

The prostate-specific antigen level is used as a biomarker for different therapies in prostate cancer. EMA guidelines mention that after PFS and OS the prostate-specific antigen level is an important indicator used in clinical trials, regardless of the stage of prostate cancer.[14]

Conclusions

The development of new oncological therapies makes it necessary for regulatory agencies to update their approaches to assessing the efficacy of treatment. The EMA has been updating endpoint guidelines in clinical trials for many years, adapting them to therapeutic progress and knowledge in the field of new efficacy indicators. EMA's guidelines underline the role played by surrogates in the process of assessing efficacy of new therapies, which is reflected in real-world clinical practice. This results in changes in the practice of granting marketing authorizations: the protocols of clinical trials define surrogates as primary endpoints more and more often. Furthermore, a positive decision on granting marketing authorization is possible also in situations when only such clinical data are available. The analysis of EMA's marketing authorization practice confirms the increased significance of surrogate endpoints in efficacy assessment of oncological medicines. This has an impact on the increased availability of new oncological therapies across the European market.

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