



Original Research

# Publicly accessible evidence of health-related quality of life benefits associated with cancer drugs approved by the European Medicines Agency between 2009 and 2015



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## KEYWORDS

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**Abstract Objective:** Health-related quality of life (HRQoL) is one of the most important patient-relevant study end-points for the direct measurement of the benefit of cancer drugs. Therefore, our aim is to detect cancer indications with no published information on HRQoL at the time of European Medicines Agency (EMA) approval and monitor any reported HRQoL evidence updates after at least three years of follow-up.

**Methods:** We included all cancer indications that were approved by the EMA between January 2009 and October 2015. Our main sources of information were the EMA website, [clinicaltrials.gov](http://clinicaltrials.gov) and a systematic literature search in PubMed. Information on HRQoL outcomes was extracted alongside evidence on median overall survival.

**Results:** In total, we identified 110 indications, of which more than half ( $n = 58$ , 53%) were lacking available information on HRQoL assessments at the time of EMA approval. After a monitoring period of at least three years, 24 updates were identified, resulting in 34 (31%) therapies where information on HRQoL was still not available. For the 76 therapies with reported information on HRQoL, cancer-specific instruments were mostly used ( $n = 49/76$ ). Regarding cumulative evidence on median overall survival and HRQoL, 33 ( $n = 33/110$ , 30%) as well as 15 ( $n = 15/110$ , 14%) cancer drugs were lacking information on both study end-points at the time of approval and after monitoring, respectively.

**Conclusion:** Our results demonstrate that there is an urgent need of routine re-evaluation of reimbursed cancer drugs with initially missing information on major outcomes.

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Standardisation of the typology and quality of HRQoL assessments need to be improved to allow better comparability of results.

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## 1. Introduction

Cancer drugs should be clinically meaningful and thus not only prolong but also improve (or at least not worsen) patients' quality of life [1–4]. Due to the increasing number of cancer drugs in the development pipeline and their rapidly increasing costs, it becomes more and more important to assess the overall comparative value of these therapies [5,6]. Therefore, the most essential patient-relevant outcomes that determine the overall value of oncological therapies are overall survival (OS) and health-related quality of life (HRQoL) [7,8]. HRQoL instruments comprise of questions related to the main dimensions of a person's health status [9] and can be understood as multidimensional subjective instruments which cover at least four domains: physical, mental, emotional and social well-being [10]. In contrast, the general term 'quality of life (QoL)' may include broader aspects of well-being such as political and religious freedoms, etc. [7]. Nevertheless, there is no single standard definition available either for HRQoL or for QoL [11].

To support treatment decision-making, cancer societies have developed frameworks to determine the clinical benefit of oncological therapies. These scales not only assess survival improvements, relative benefits (hazard ratio) and absolute benefits (median OS) but also consider toxicities and HRQoL measurements [2,3]. HRQoL can be evaluated via various tools, whereby the most widely used instruments in cancer trials include the non-preference-based cancer-specific European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), the non-preference-based Functional Assessment of Cancer Therapy-General, and the preference-based generic EuroQol five-dimensional questionnaire (EQ-5D) [12–14]. In the case of individual disease-specific instruments, measures for particular malignancies maybe considered, for example the Lung Cancer Symptom Scale (LCSS) [15]. Besides the evaluation of physical and functional domains, disease symptomatology can be measured via the LCSS [16].

Although OS and HRQoL are the only measures that directly correspond to the clinical benefit of cancer therapies, the use of surrogate outcomes in clinical trials is on the rise to allow faster access by provisional approval strategies [7], especially surrogate tumour-related end-points like progression-free survival have been frequently reported [17]. Although these outcomes

often lead to faster access, the risk of misinterpretation of the actual value of these drugs is particularly high [4]. A strong surrogate–survival correlation is essential to avoid potentially toxic cancer drugs with no meaningful clinical benefit entering the market [18]. For example, bevacizumab in combination with paclitaxel had been initially approved for metastatic breast cancer based on progression-free survival evidence but was subsequently withdrawn from the US market due to toxicities and the lack of survival benefit [18,19]. In contrast, this treatment combination is still approved by the European Medicines Agency (EMA); however, it was de-reimbursed in some member states of the EU (e.g. France) [20].

Our aim is to identify cancer indications where no information on HRQoL was publicly available at the time of approval by the EMA. Consequently, we monitored these indications over at least three years after marketing authorisation to detect any published evidence updates (positive/negative/no difference) on HRQoL. In addition, we combined our results with data available on median OS to identify those indications where essential comprehensive patient-relevant outcome information was lacking at the time of approval, as well as at least three years later.

## 2. Methods

### 2.1. Identification of the study cohort

We included novel originator cancer drugs as well as indication extensions for the treatment of adults that received marketing authorisation by the EMA between January 2009 and October 2015 to allow for an at least three years of follow-up period. The patient population was restricted to adult cancer patients because the majority of trials are ineligible for patients younger than 18 and due to the complexity and methodological issues related to the assessment of HRQoL in the paediatric setting [21]. To identify these indications, the EMA website ([www.ema.europa.eu](http://www.ema.europa.eu)) was used. We further obtained information from the European Public Assessment Reports and from the original publications of the approval studies. A previously published study that monitored OS benefit over time was used as our general data basis [22]. In the present study, cancer drugs for indications with missing initial information on HRQoL outcomes at the time of approval were included and selected for monitoring.

## 2.2. Identification of follow-up information and data extraction

Information on HRQoL outcomes was categorised as (1) no information available, (2) statistically significant positive HRQoL outcome difference, (3) no statistically significant HRQoL outcome difference, or (4) statistically significant negative HRQoL outcome difference at follow-up. Regarding two-arm studies, the difference between treatment arms was evaluated, whereby in cases of single-arm studies ( $n = 5$ ) the change from baseline to follow-up was used. If several instruments were applied in one study, the best HRQoL result was taken into account.

To identify potential study updates, we applied a multiple source strategy and scanned three different data sources between 1st June 2018 and 28th January 2019. Our primary source of information was the European Public Assessment Reports from the EMA website. Secondly, data updates (publications or directly posted study results) were identified via the clinical trial registry number (NCT number) from the [ClinicalTrials.gov](https://clinicaltrials.gov) website. Approval studies where no NCT number was accessible were ineligible for inclusion. Thirdly, a systematic search in PubMed was conducted including the following search terms '(name of the active substance) AND (NCT number OR trial name)' with no limitations. The same source strategy was applied to identify information on OS.

EMA approval characteristics were extracted together with general information on the indications together with the applied HRQoL assessment tool(s). Approval characteristics (conditional approval, additional monitoring, and orphan designation) are referred in our analysis as EMA label. Additional information on median OS at the time of approval and after monitoring was also included. Abstracts as well as results sections of peer-reviewed publications were scanned to retrieve information on HRQoL and OS outcomes. We extracted data into a Microsoft Office Excel 2016 data form, which was designed in advance by the study team. Information was primarily extracted by N.G. and double-checked by another co-author (M.R., E.R.). HRQoL instruments were categorised according to Damm *et al.* as generic, cancer specific, or individual disease specific [23].

## 3. Results

### 3.1. Characteristics of EMA-approved cancer drugs

In total, 115 cancer indications were approved by the EMA between January 2009 and October 2015. Out of these, five were ineligible for our analysis because no NCT numbers were accessible. About one-third ( $n = 33/110$ , 30%) of the eligible indications were

approved for the treatment of blood and related tissue cancers, the remaining 70% ( $n = 77/110$ ) were indicated for solid tumours (Table 1). Sixty-two (56%) indications received an EMA label.

Table 1  
Characteristics of EMA-approved cancer indications (January 2009–October 2015).

Characteristics	All approved cancer indications (n = 110)
<b>Indication (ICD-10 category)</b>	
Solid cancer therapies	77 (70.0%)
Gastrointestinal cancer (C15–C26)	15 (13.6%)
Lung cancer (C30–C39)	11 (10.0%)
Melanoma (C43–C44)	12 (10.9%)
Sarcoma (C45–C49)	1 (0.9%)
Breast cancer (C50–C50)	13 (11.8%)
Cervical carcinoma (C51–C58)	2 (1.8%)
Ovarian and peritoneal cancer (C51–C58 & C45–C49)	6 (5.5%)
Prostate cancer (C60–C63)	7 (6.4%)
Renal cell carcinoma (C64–C68)	5 (4.5%)
Thyroid carcinoma and neuroendocrine tumour (C73–C75)	5 (4.5%)
Lymphoid, haematopoietic and related tissue cancer therapies (C81–C96 and D37–D48)	33 (30.0%)
<b>Approval year</b>	
2009	15 (13.6%)
2010	17 (15.5%)
2011	17 (15.5%)
2012	15 (13.6%)
2013	17 (15.5%)
2014	15 (13.6%)
2015	14 (12.7%)
<b>EMA label</b>	
Regular EMA approval	48 (43.6%)
Additional monitoring (AM)	48 (43.6%)
Conditional approval (CA)	17 (15.5%)
Orphan designation (OD)	23 (20.9%)
AM and CA	3 (2.7%)
AM and OD	11 (10.0%)
CA and OD	2 (1.8%)
AM and OD and CA	5 (4.5%)
<b>Information on HRQoL</b>	
Positive difference in HRQoL outcomes	20 (18.2%)
No difference in HRQoL outcomes	32 (29.1%)
Negative difference in HRQoL outcomes	0 (0.0%)
No information on HRQoL outcomes	58 (52.7%)

Data are n (%) unless otherwise specified. Deviation of 100% cumulative percentage may be caused by rounding. EMA, European Medicines Agency; ICD-10, International Classification of Disease (10th Revision); HRQoL, health-related quality of life.

### 3.2. Availability of HRQoL benefit at the time of EMA approval

Among the 52 (n = 52/110, 47%) indications where HRQoL information was available at the time of approval, in 20 (18%) instances a positive HRQoL difference was reported, while 32 (29%) indications showed no difference in HRQoL outcomes (Fig. 1). None of the studies reported a negative difference in HRQoL outcomes at the time of approval. Thirty-five cases were applying one HRQoL instrument from one of the following three categories: generic (n = 2/35), cancer specific (n = 15/35), or individual disease specific (n = 18/35; Fig. 2). More than one instrument was used in 17 studies with the categories cancer and individual disease specific being the most frequently combined ones. Concerning generic HRQoL instruments, all eight trials reported the use of an EQ-5D instrument. Among the studies using cancer-specific instruments (n = 52), 27 applied the EORTC QLQ-C30. Individual disease-

specific HRQoL instruments were applied in a total of 32 studies.

In more than half of the cancer indications (n = 58/110, 53%), no information on HRQoL outcomes was available at the time of EMA approval. Among these 58 therapies, 33 (57%) were approved for the treatment of solid tumours, most commonly for gastrointestinal cancers (n = 10/58, 17%) and melanoma (n = 9, 16%; Table 2). The remaining 25 (43%) therapies were targeting blood and related tissue cancers. More than half of these cancer drugs could be categorised as targeted therapies (n = 32/58, 55%) and received a specific EMA label (n = 36/58, 62%).

### 3.3. Monitoring evidence on HRQoL benefit

After a monitoring period of at least three years following marketing authorisation, updates on HRQoL assessments could be identified in 24 of the 58 instances (Fig. 1). Ten of these updates elucidated no difference in HRQoL outcomes (n = 10/58, 17%), 14 showed a

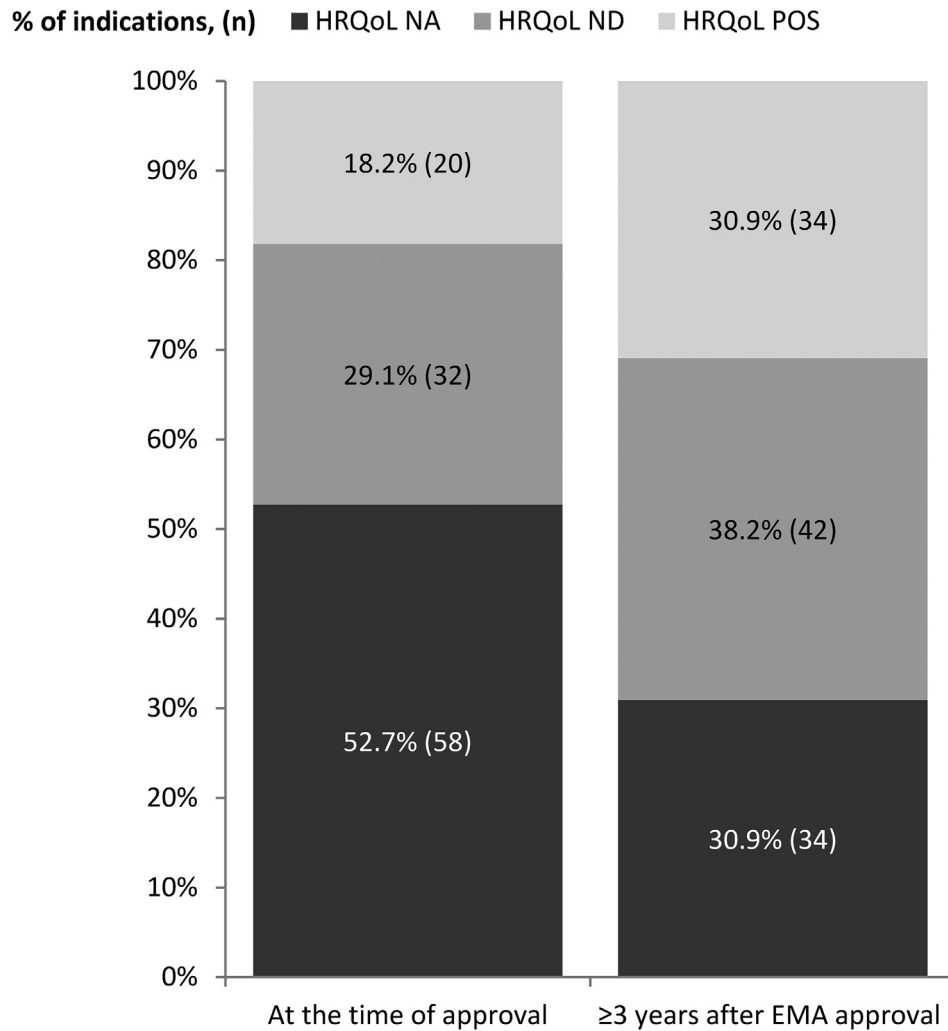


Fig. 1. Evidence on HRQoL benefits at the time of approval and  $\geq 3$  years after approval (n = 110). EMA, European Medicines Agency; NA, not available; ND, no difference, POS, positive difference; HRQoL, health-related quality of life. No evidence on negative differences in HRQoL outcomes could be identified.

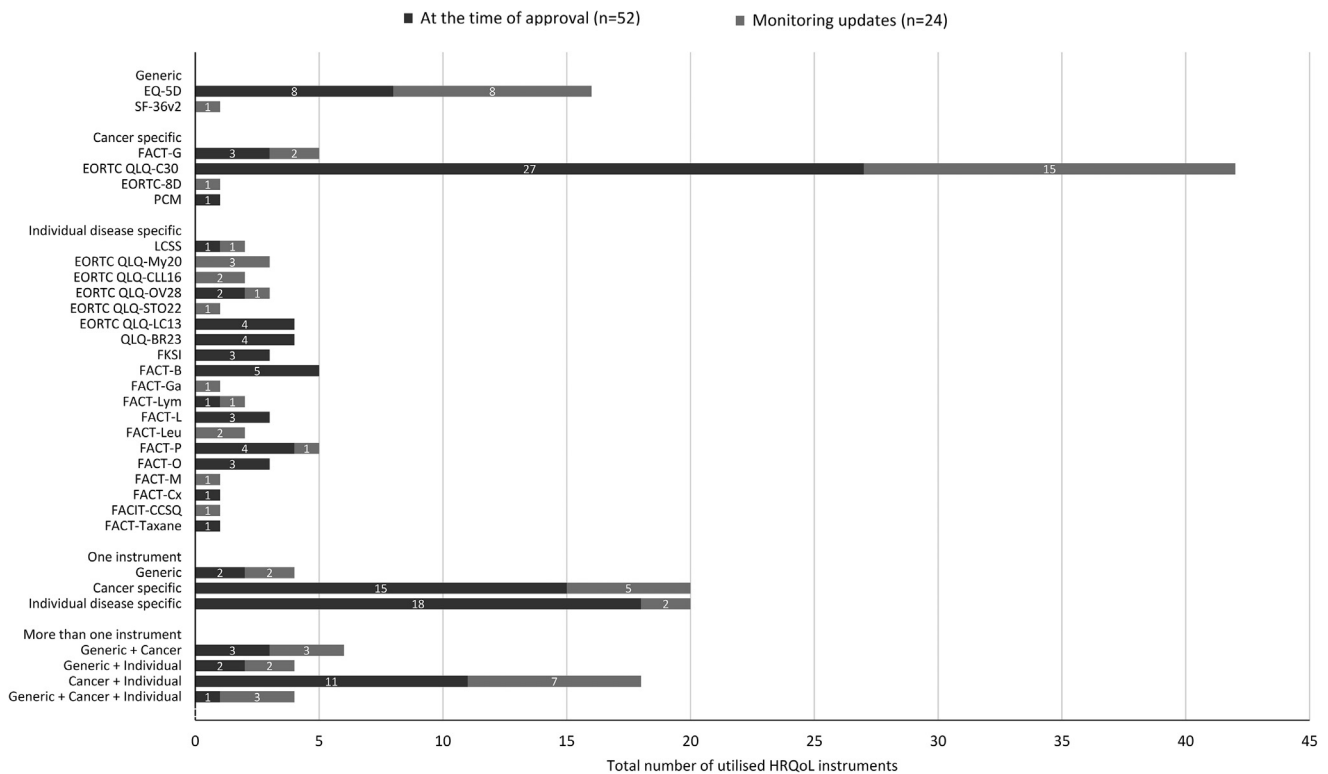


Fig. 2. Applied HRQoL instruments at the time of approval and  $\geq 3$  years after approval.

positive difference (24%), and none showed a negative. All reported HRQoL outcome differences were statistically significant.

Nine monitoring studies were utilising one instrument from the following three HRQoL categories: generic ( $n = 2/9$ ), cancer specific ( $n = 5/9$ ), or individual disease specific ( $n = 2/9$ ). In 15 of the 24 updates, more than one HRQoL instrument was applied (Fig. 2). The EQ-5D was the most frequently applied generic instrument ( $n = 8/9$ ). In six cases the EQ-5D-3L version, and in one case the EQ-5D-5L version was used, while in two studies the version of the EQ-5D was unspecified. Fifteen studies applied the EORTC QLQ-C30 and 15 studies used an individual disease-specific instrument.

For 34 of the 58 indications (59%), information on HRQoL outcomes was still missing after a monitoring period of at least three years following EMA approval. Nineteen ( $n = 19/34$ , 56%) of these therapies were intended for solid tumours and 15 ( $n = 15/34$ , 44%) for blood and related tissue cancers. More than half ( $n = 19/34$ , 56%) have received an EMA label, whereby one-third ( $n = 12/34$ , 35%) were labelled with at least two.

### 3.4. Cumulative evidence on HRQoL and median OS benefits

At the time of approval, 15 ( $n = 15/110$ , 14%) indications showed improvements in HRQoL and median OS (Fig. 3 & supplementary appendix). Positive median OS difference data but no information on HRQoL outcomes were

available for 24 indications ( $n = 24/110$ , 22%). In another 21 cases ( $n = 21/110$ , 19%), HRQoL outcomes showed no statistically significant HRQoL difference but median OS difference was positive. No evidence on HRQoL or median OS outcomes could be found in 33 of 110 instances (30%). In the case of five indications (5%), the median OS difference was negative. Out of these, three showed a negative median OS difference, but statistically significant improvement in HRQoL outcomes. In one instance, there was no statistically significant difference in HRQoL, while for one indication median OS was negative and no information on HRQoL was reported.

After monitoring, 26 (24%) cancer indications showed improved HRQoL outcomes as well as improved median OS. Positive difference in median OS but lacking HRQoL evidence was present in 18 (16%) instances. In one quarter of the cases ( $n = 28/110$ , 26%), a positive median OS difference was observed with no difference in HRQoL outcomes. In 15 (14%) instances, information on these two outcomes was still lacking. Eleven of these therapies received an EMA label. Lastly, for five indications the difference in median OS was negative, including an improvement in HRQoL outcomes in three cases (3%) and no statistically difference in HRQoL in two (2%).

## 4. Discussion

The ultimate aim of cancer therapies should be to prolong patients' lives without negatively impacting their QoL [24]. This study aimed to synthesise publicly



Table 2

Detailed characteristics of the study cohort following a monitoring period of  $\geq 3$  years after EMA approval (n = 58).

Characteristics	At the time of approval		Monitoring evidence on HRQoL <sup>a</sup>					
	HRQoL	NA (n = 58)	NA (n = 34)	ND (n = 10)	POS (n = 14)			
<b>Indication (ICD-10 category)</b>								
All solid cancer therapies	33	(56.9%)	19	(55.9%)	6	(60.0%)	8	(57.1)
Gastrointestinal cancer (C15–C26)	10	(17.2%)	6	(17.6%)	2	(20.0%)	2	(14.3%)
Lung cancer (C30–C39)	2	(3.5%)	1	(2.9%)	1	(10.0%)	–	
Melanoma (C43–C44)	9	(15.5%)	2	(5.9%)	3	(30.0%)	4	(28.6%)
Sarcoma (C45–C49)	–		–		–		–	
Breast cancer (C50–C50)	3	(5.2%)	3	(8.8%)	–		–	
Cervical carcinoma (C51–C58)	–		–		–		–	
Ovarian and peritoneal cancer (C51–C58 & C45–C49)	2	(3.5%)	1	(2.9%)	–		1	(7.1%)
Prostate cancer (C60–C63)	3	(5.2%)	2	(5.9%)	–		1	(7.1%)
Renal cell carcinoma (C64–C68)	–		–		–		–	
Thyroid carcinoma and neuroendocrine tumour (C73–C75)	4	(6.9%)	4	(11.8%)	–		–	
Lymphoid, haematopoietic and related tissue cancer (C81–C96 and D37–D48)	25	(43.1%)	15	(44.1%)	4	(40.0%)	6	(42.9%)
<b>Approval year</b>								
2009	7	(12.1%)	6	(17.6%)	1	(10.0%)	–	
2010	4	(6.9%)	3	(8.8%)	–		1	(7.1%)
2011	10	(17.2%)	6	(17.6%)	2	(20.0%)	2	(14.3%)
2012	8	(13.8%)	6	(17.6%)	–		2	(14.3%)
2013	9	(15.5%)	5	(14.7%)	1	(10.0%)	3	(21.4%)
2014	12	(20.7%)	5	(14.7%)	3	(30.0%)	4	(28.6%)
2015	8	(13.8%)	3	(8.8%)	3	(30.0%)	2	(14.3%)
<b>HRQoL instrument</b>								
One instrument	–		–		5	(50.0%)	4	(28.6%)
More than one instrument	–		–		5	(50.0%)	10	(71.4%)
<b>EMA label</b>								
Regular EMA approval	22	(37.9%)	15	(44.1%)	3	(30.0%)	4	(28.6%)
Additional monitoring (AM)	12	(20.7%)	3	(8.8%)	3	(30.0%)	6	(42.9%)
Conditional approval (CA)	1	(1.7%)	–		1	(10.0%)	–	
Orphan designation (OD)	5	(8.6%)	5	(14.7%)	–		–	
AM and CA	2	(3.5%)	2	(5.9%)	–		–	
AM and OD	13	(22.4%)	7	(20.6%)	3	(30.0%)	3	(21.4%)
CA and OD	–		–		–		–	
AM and OD and CA	4	(6.9%)	3	(8.8%)	–		1	(7.1%)
<b>Mechanism of therapy</b>								
Targeted therapy	32	(55.2%)	22	(64.7%)	2	(20.0%)	8	(57.1%)
Immunotherapy	16	(27.6%)	6	(17.6%)	6	(60.0%)	4	(28.6%)
Chemotherapy	8	(13.8%)	5	(14.7%)	2	(20.0%)	1	(7.1%)
Hormone therapy	2	(3.5%)	1	(2.9%)	–		1	(7.1%)
<b>Line of therapy</b>								
1st-line	15	(25.9%)	7	(20.6%)	5	(50.0%)	3	(21.4%)
$\geq 2$ nd-line	39	(67.2%)	23	(67.6%)	5	(50.0%)	11	(78.6%)
Adjuvant/neoadjuvant	4	(6.9%)	4	(11.8%)	–		–	
<b>Type of therapy</b>								
Combination therapy	25	(43.1%)	11	(32.4%)	5	(50.0%)	9	(64.3%)
Monotherapy	33	(56.9%)	23	(67.6%)	5	(50.0%)	5	(35.7%)
<b>Study design</b>								
Two-arm studies	53	(91.4%)	30	(88.2%)	10	(100.0%)	13	(92.9%)
Single-arm studies	5	(8.6%)	4	(11.8%)	–		1	(7.1%)

Data are n (%) unless otherwise specified. Deviation of 100% cumulative percentage may be caused by rounding.

EMA, European Medicines Agency; ICD-10, International Classification of Disease (10th Revision); NA, not available; ND, no statistically significant difference; OS, overall survival; POS, statistically significant positive difference; HRQoL, health-related quality of life.

<sup>a</sup> No negative differences in HRQoL assessments could be identified.

available evidence on HRQoL in relation to median OS outcomes, to identify those cancer indications with uncertain clinical benefits at least three years later after EMA approval. We found that from the initially identified 110 cancer indications, more than half of them (n = 58/110, 53%) were lacking publicly available

information on HRQoL outcomes at the time of approval and one-third of them after monitoring. A difference between solid tumour drugs and haematologic drugs could be noted. Publicly accessible information on HRQoL was more commonly unavailable in the case of solid tumour drugs, both at the time of

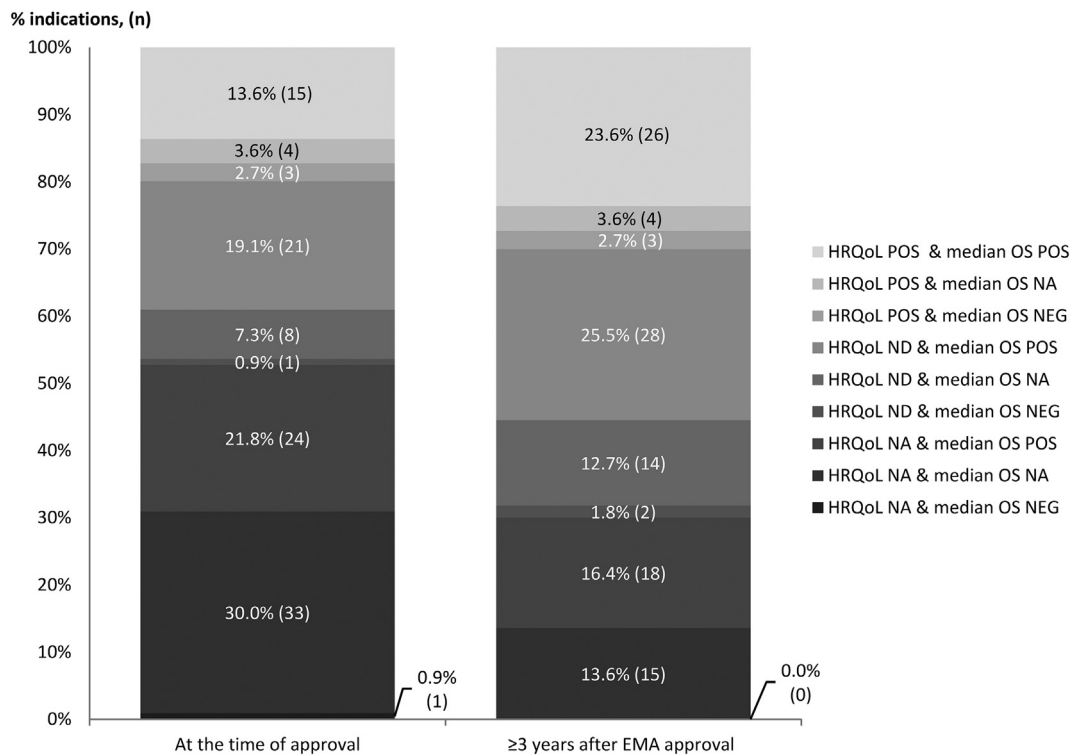


Fig. 3. Evidence on HRQoL and median OS benefits at the time of approval and after  $\geq 3$  years ( $n = 110$ ). EMA, European Medicines Agency; NA, not available, ND, no difference; NEG, negative difference; OS, overall survival; POS, positive difference; HRQoL, health-related quality of life.

approval (57% versus 43%) and after monitoring (56% versus 44%). This may relate to the different courses of disease, because haematologic cancer patients tend to be present with slow-growing indolent diseases, the clinical benefit may be delayed and HRQoL measures are initially of higher importance [25]. The two most commonly applied QoL instruments were the EORTC-QLQ-C30 ( $n = 42/76$ ) and the EQ-5D ( $n = 8/76$ ). Currently, these are also the most commonly validated and thereby the most frequently recommended cancer specific and generic HRQoL instruments by Health Technology Assessment (HTA) agencies [26–28]. Considering cumulative evidence on median OS and HRQoL, we found that 33 of the identified 110 cancer indications (30%) were lacking information initially. After monitoring, there were still 15 indications with no available evidence on either of these two essential outcomes.

Our finding of limited knowledge on HRQoL for approved cancer drugs and after monitoring is in line with other relevant recently published studies [6,8,29,30]. For example, Marandino *et al.* have shown that HRQoL is substantially under-reported in phase III solid tumour cancer trials [31]. Moreover, a study from Smith *et al.* showed that solely 25% of randomised controlled trials in the area of cancer published between 2000 and 2012 applied a methodological design that could be considered as probably robust evidence [32]. This is also in line with a

study from 2010, where they have applied a set of quality criteria to evaluate whether HRQoL results are applicable in clinical practice. They concluded that there is a lack of information in reporting HRQoL results, which made it mostly impossible to utilise results in clinical practice [33]. Our study is the first to attempt monitoring the availability of evidence on multiple major patient-relevant outcomes (median OS and HRQoL) in addition to extensive characterisation of the study cohort including EMA labels and treatment settings.

While the early introduction of cancer drugs onto the European market may improve patient access, it is a substantial challenge for decision-makers, payers and assessors. Post-launch monitoring of these drugs is increasingly important due to data with high uncertainty, healthcare costs, and need for special pricing agreements [34]. This is further strengthened by our current finding indicating that a high rate of indications with provisional approval pathways ( $n = 62/110$ ) still have no comparative outcome evidence on either median OS or HRQoL after three years post-approval ( $n = 15/62$ ). Although some of these approvals are conditional on specific obligations, many of these never fulfilled or delayed as found by Banzi *et al.* [29]. This is also in line with our findings that the complete lack of monitoring evidence on the most important end-points after monitoring has not led to any regulatory consequences (e.g. withdrawal from the market) for any of the relevant 15 indications.

One of the major limitations of our study is the selected time frame for potential study updates. However, the approval years of those therapies with lacking information on HRQoL outcomes after monitoring seem to be balanced (range, 9%–18%) with the lowest proportion of drugs approved in 2010 and 2015. Moreover, our findings are likely to be influenced by publication bias. In particular, our finding of no published evidence on negative difference in HRQoL is indicative of this [35]. Besides – because we have always counted the best HRQoL results – if several instruments were applied in one study, our results must be seen as overoptimistic.

Although we have not assessed the quality of the investigated studies, we are aware that in some HRQoL studies an inappropriate instrument may be applied that would not be eligible to capture the experienced adverse events, or suboptimal assessment schedule was chosen [36]. To be able to interpret trial results in a straightforward manner and thus support evidence-informed clinical as well as political decision-making, there is also need for improved systematic and standardised reporting of HRQoL evidence alongside stricter evidence monitoring requirements in general. In addition, there is a high inconsistency in the current definition and taxonomy of HRQoL outcomes [11]. This was also evident in our analysis, for instance regarding the LCSS instrument which can be considered as a HRQoL measure as well as a symptom scale. However, if we would have not included it in our analysis ( $n = 1$ ), our results would be rather less optimistic.

Costs and markets of cancer drugs have been radically rising, albeit frequently on the basis of more restricted clinical benefit evidence [37]. Currently, regulatory authorities are facing challenges of an increased developmental pipeline with several cancer drugs for rare conditions. The fast introduction of these therapies not only poses potential advantages for patients but also represents potential health hazard, especially if drugs eventually prove to be unsafe or ineffective [5]. Therefore, the evaluation and monitoring of cancer drugs should be of high importance both at national decision-making levels as well as at pan-European regulatory level. To guarantee efficient and fair distribution of limited healthcare resources, the evaluations and re-evaluations of reimbursed cancer drugs urgently need to improve.

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## Conflict of interest statement

None to declare.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2020.01.020>.

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