Implementation rates of PROs/PROMs into European SmPCs of oncologic medicinal products

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Abbreviations

AE:	Adverse Event
CER:	Comparative Effectiveness Research
CHMP:	Committee for Medicinal Products for Human Use
CTCAE:	Common Terminology Criteria for Adverse Events
CTP:	Clinical Trial Protocol
EC:	European Commission
EMA:	European Medicines Agency
EORTC:	European Organisation for Research and Treatment of Cancer
EPAR:	European Public Assessment Report
EU:	European Union
ePRO:	electronic Patient Reported Outcome
ePROM:	electronic Patient Reported Outcome Measure
EQ-5D:	European Quality of Life-5 Dimensions
FDA:	Food and Drug Administration
FACT:	Functional Assessment of Cancer Therapy
FKSI:	FACT - Kidney Symptom Index
FOSI-18:	FACT- Ovarian Symptom Index-18
HER:	Electronic Health Records
HRQL:	Health Related Quality of Life
IVR:	Interactive Voice Response
ISPOR:	International Society for Pharmacoeconomics and Outcome Research
MID:	Minimally Important Difference
NCI:	National Cancer Institute
NME:	New Molecular Entities
OS:	Overall Survival

PedsQL:	Pediatric Quality of Life Inventory
PFS:	Progression Free Survival
PI:	Product Information
PN:	Peripheral Neuropathy
PRO:	Patient Reported Outcome
PROM:	Patient Reported Outcome Measure
PCS:	Prostate Cancer Subscale
QOL CNS:	Quality of Life Central Nervous System
QLG:	Quality of Life Group
QLQ:	Quality of Life Questionnaire
RIR:	Regulatory Intelligence report
SAP:	Statistical Analysis Plan
SmPC:	Summary of Product Characteristics
TA:	Therapetic Area
VAS:	Visual Analogue Scale
WHO:	World Health Organisation

1. Introduction

1.1 PROs and their increasing importance in drug development

Patients can provide unique insights about living with a disease as well as sharing experiences of living with a treatment for a disease. Over the last decades there is an increasing recognition of patients' unique expertise and the importance of incorporating the patients' point of view on their health status both in drug development and clinical care. Such information will be of interest to be provided in the SmPC and may be used in out-lining regulatory conclusions regarding treatment effects. The benefit-risk-balance of a medicinal product is mirrored in all sections of the SmPC. While the therapeutic indications are mentioned in section 4.1, further definition or information on the authorised indication [1] e.g., specific aspirational claims may be included in section 5.1 if they support the underlying indication.

The basis for the approval of a new medicinal product is its efficacy and safety in the given condition. Therefore, in the drug evaluation process, the first step for the regulators is usually to assess efficacy and safety of a given drug by using the established efficacy endpoints. These endpoints usually concern the core symptoms and signs of the condition, and, in general, will support the indication claim.

In addition, a company may decide to study the effect of the medicinal product on the patients' subjective health status. Patient-reported outcomes (PROs) are the gold standard to assess the patients' subjective health status.

In clinical trials, primary endpoints based on PROs may be essential when efficacy of medicines is best assessed or can be measured accurately only by the patient direct report. For example, patient-reported pain intensity would be the primary endpoint in analgesic indications.

PRO-based secondary endpoints can also provide supportive evidence of clinical significance and meaning to a primary endpoint that may or may not be PRO-based. For

example, in cystic fibrosis, efficacy may be assessed by lung function (a biomarker) as a primary endpoint and patient-reported symptom severity as a secondary endpoint. Although labelling based on secondary endpoints is possible, a secondary endpoint may not be appropriate for labelling.

The regulatory authorities EMA and FDA share the view that the patients' perspective is important during the development and approval process for new drugs [2]. The EMA Human Scientific Committees' Working Party with Patients' and Consumers' Organization gives recommendations to the EMA and its committees in the interest of patients regarding medicinal products. Furthermore, the EMA encourages patients' and consumers' organizations to get involved in agency activities [3].

The term "patient reported outcome" was established in 2001 by the PRO Harmonization group as an umbrella term to describe a broad spectrum of disease and treatment outcomes based on data provided by the patient himself [2][4].

The term PRO was quickly adopted by the regulatory agencies.

The EMA defines a PRO as "any outcome directly evaluated by the patient and based on the patient's perception of a disease and its treatment(s)". According to the EMA, a PRO can include both single and multi-dimensional measures of symptoms (e.g., fatigue, insomnia, appetite loss), Health-related quality of life (HRQL), health status, adherence to treatment and satisfaction with treatment. PRO measures (PROMs) are the tools and/or instruments that have been developed to ensure a valid and reliable measurement of these PROs [5, 6].

HRQL:

HRQL is a specific type of the PRO, defined as patient's subjective perception of the effects of the disease and treatment(s) on daily life, well-being, and psychological, physical and social functioning. It is an example of a multi-dimensional PRO measure. The definition of HRQL has as a common basis the definition of health given by the WHO in 1984: "Health is a state of complete physical, mental, and social well-being and not merely the absence of disease". Multidimensionality is a key component of definition of HRQL. A single domain, e.g., physical functioning or fatigue, is not considered as a HRQL. Furthermore, HRQL should

be clearly differentiated from the core symptoms of the disease (like pain, migraine, pyrosis…) which are well accepted primary and secondary efficacy endpoints in registration trials.

HRQL assessment is optional. If a company decides to study the effect of a medicinal product on HRQL, it might provide insight in the interpretation of the observed effect on the primary endpoint in terms of consequences for the daily life and social functioning. In any case, HRQL goes beyond the efficacy and safety assessments, which are the basis for approval.

In chronic, non life-threatening conditions that do not lead to a shortening of life, but require long term treatments, when two drugs have similar efficacy and safety, the information on HRQL have moved into the foreground in the evaluation of therapy and might be important for the choice of one medicinal product over the other in the current clinical practice.

In severe, life-threatening diseases, such as cancer, HRQL may provide an important information for the choice of one medicinal product over another e.g., if overall survival (OS) and progression free survival (PFS) or biomarker measures are similar, and therefore none of the clinical endpoints measured will give a rationale for the recommendation of one or the other drug. In all cases, there must be confidence that the observed HRQL benefit is achieved without any reduction in efficacy (e.g., through reduced toxicity, attained by reducing the dose).

The EMA and the FDA state that only blinded clinical trials are adequate to obtain PRO/HRQL data used to support label claims. Both regulatory agencies assume that patients who are aware that they receive active treatment are biased as they may overestimate the benefit of the treatment.

It is strongly recommended by both agencies to use PRO/HRQL instruments only in randomized, double-blind clinical trials to avoid any bias (of patient or investigator) [6, 7].

Nevertheless, there might be situations, where blinding is not possible for clinical trials with PRO instruments or where there is no acceptable control group. In such cases it is recommended that the sponsor requests scientific advice.

Data about PRO concepts are collected using PRO instruments/measures (PROMs) such as questionnaires, leaflets, and documentation that support their use [8].

Electronic Patient Reported Outcome (ePRO) is one mode of administration that is electronic-based (e.g., computer, tablets, smartphone) [9]. The advantages are, that they are interactive, practical, minimise the risk of data entry errors, provide immediate scoring feedback, offer real-time PRO data transfer and provide the ability for time stamp records. The disadvantages are, that they are cost-intensive (software and/or devices needed), there might be a potential discomfort with technology (especially for older people) and potential problems with accessibility.

The expression ePROMs refers to the electronic assessment of PROMs using different devices or techniques. Typically, ePROMs are interactive voice response (IVR) mobile or computer systems that permit real-time patient assessment and management. There has been increased development of these systems, partially because they are recommended by the FDA and by the EMA at clinical trials, due to the benefit of getting better measures from the patient perspective [10, 11].

1.2 PROs in adult oncology clinical trials

In oncology clinical trials, PROs are an important complement to other clinical endpoints such as survival (OS or PFS) and toxicity, as they may not necessarily capture the full impact of a treatment on how a patient feels and functions. Therefore, they are key measures to understand the overall treatment benefit. PROs help stakeholders to understand the patient experience, particularly the impact of treatment on patients' functioning, and can help differentiate among products that offer similar survival benefits. Furthermore, PROs may provide information to facilitate more accurate the future patient-physician communication in terms of the quality of the survival time remaining for the patient and the burden of treatment-related morbidities and disease-related patient impacts. The use of PROs as endpoints is essential beyond its use in supportive therapy trials, especially, for novel approaches such as targeted therapies and immunotherapies for which the benefits in terms of survival may often not be as significant as the benefit in terms of reduced toxicity and improved quality of life [12, 13].

Definition of Quality of Life (from EORTC homepage):

- the state of well-being that is a composite of two components: the ability to perform everyday activities that reflect physical, psychological, and social well-being; and patient satisfaction with levels of functioning and control of the disease
- the subjective evaluation of the good and satisfactory character of life as a whole
- the gap between the patient's expectations and achievements. The smaller the gap, the higher the quality of life
- represents the functional effect of an illness and its consequent therapy upon the patient as perceived by the patient
- defined as an individual's overall satisfaction with life and general sense of personal well-being
- patient perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns

Oncology clinical trials to support regulatory submissions may include PRO measures as secondary or exploratory endpoints and rarely as primary endpoints [5].

1.3 Description of questionnaires used as PRO measures / instruments

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30): The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. The global health status/QoL, five functional scales (physical, role, cognitive, emotional and social), and three symptom scales (fatigue, pain, nausea and vomiting) and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease will be computed using the

QLQ-C30 scoring procedures. Change scores are defined as change of summary score of EORTC QLQ-C30 from day 1 of first treatment cycle [14]. See Annex II, questionnaire 1 for details.

In addition to this more general questionnaire for all cancer patients, there are further tailored questions for lung cancer patients the *EORTC QLQ Lung Cancer 13 (QLQ-LC13)* regarding e.g., cough and breath [15] (see Annex II, questionnaire 2 for details), the updated version *EORTC QLQ Lung Cancer 29 (QLQ-LC29)* [16, 17] or like the *EORTC QLQ-Myeloma module (MY20)*, which covers disease-specific questions for myeloma patients [18–20]. Further tailored cancer type specific questionnaires are available on the EORTC homepage (see Annex I). Of those, some are already validated, while others are still under development.

Short Form 36 (SF-36): generic instrument for measuring quality of life. It includes 36 items or questions that assess functional health and well-being from the perspective of the patient. The items contribute to eight health domains of physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. The eight domains all contribute to physical component summary (PCS) and mental component summary (MCS) scores [21, 22].

European Quality of Life-5 Dimensions (EQ-5D): a general measure of health status that measures 5 descriptors of current health state - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [23].

Generic EQ-5D-3L questionnaire: The 3-level version of EQ-5D (EQ-5D-3L) essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results into a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state [24].

The *EQ VAS* records the patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement [24].

EQ-5D-5-Levels Health Questionnaire (EQ-5D-5L):

The 5-level EQ-5D version (EQ-5D-5L) was introduced by the EuroQol Group in 2009 to improve the instrument's sensitivity and to reduce ceiling effects, as compared to the EQ-5D-3L. The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). See Annex I, questionnaire 3 for details.

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement [25].

Skindex-16: Together with the Dermatology Life Quality Index, Skindex-16 is the most commonly used dermatology-specific HRQL instruments. It is relatively short, easy to administer and covers following areas of HRQL, such as itching, painful and burning skin, daily activities, work and interpersonal relationships, among others [26, 27].

Functional Assessment of Cancer Therapy - General (FACT-G): a 27-question instrument to measure general HRQL in cancer patients in 4 domains - physical, social/family, emotional, and functional well-being [28].

Functional Assessment of Cancer Therapy-Prostate (*FACT-P) questionnaire*: The FACT–P is a validated multidimensional, self-report questionnaire used to assess HRQL in men with

prostate cancer [29, 30]. FACT–P consists of FACT–G (general), a 27-item self-report questionnaire that measures general HRQL in cancer patients, and a 12-item prostate cancer subscale (PCS). See Annex I, questionnaire 5 for details. The PCS is designed specifically to measure prostate cancer-specific quality of life. The FACT–P Trial Outcome Index (TOI) is based on the physical and functional well-being subscales of the FACT–G and the PCS. The FACT–P total score includes the FACT–G and the PCS. The FACT Advanced Prostate Symptom Index (FAPSI) includes eight items from the FACT–P [31]. A higher overall score indicates better HRQL.

FACT - Kidney Symptom Index (FKSI): The FKSI was developed and validated to enhance treatment decision-making, practice guidelines, symptom management, and treatment efficacy for kidney cancer patients. Thirty-four symptoms related to the disease were identified and tested [32]

FACT - Kidney Symptom Index - Disease Related Symptoms (FKSI-DRS): a 9-question abbreviated version of the FKSI designed to specifically measure kidney cancer-related symptoms [33].

FACT-Ovarian Symptom Index (FOSI)-18: FOSI-18 was developed to provide a clinically meaningful patient-reported symptom index reflecting the symptoms and concerns identified as most important by women with advanced ovarian cancer [34, 35]. Four subscales comprise the 18item index: disease-related symptoms-physical (DRS-P; 9 items), disease-related symptoms-emotional (1 item), treatment side effects (5 items), and general function/well-being (3 items). The recall period is the past 7 days. See Annex I, questionnaire 5 for details.

Wong-Baker FACES Pain Rating Scale (FACES): The FACES Scale is widely used with people ages three and older, not limited to children. This self-assessment tool must be understood by the patient, so they are able to choose the face that best illustrates the physical pain they are experiencing (Fig. 1). It is not a tool to be used by a third person, parents, healthcare professionals, or caregivers, to assess the patient’s pain. There are other tools for those purposes.

Figure 1

Wong-Baker FACES rating scale (Home - Wong-Baker FACES Foundation (wongbakerfaces.org) [36]).

Therapy-Induced Neuropathy Assessment Scale (TINAS) v1.0 scores: It is a valid, reliable and brief patient-reported outcome measure of peripheral neuropathy (PN) to evaluate PN symptom severity and interference on daily functioning and better understand treatment impact, tolerability, and reversibility [37].

1.4 PROs in paediatric oncology clinical trials

Children's daily activities and experiences differ substantially from those of adults and adult PRO measures may not be appropriate for use in paediatric populations, either due to content validity or differences in the measurement process itself. A successful paediatric instrument must adjust for age and take into account the rate and pattern of change, that children experience over time [38]. Recommendations for paediatric PRO instruments in research have been published and are considered to be a useful basis for the approach in children and adolescence [39]. Specific issues to consider are development stage (maturation may also differ because of disease and or experiences) and meaning of self-understanding. As with adult patients, the best information will be received by the patients themselves and it is important to collect as much information directly from the child wherever possible, using creative and age-related approaches e.g., the use of pictures instead of words can be used for children too young to read [38]. However, it is acknowledged that some children will be too young or too sick to contribute to the data

collection and parents or caregivers should be asked to contribute and provide data in situations where the child is unable to provide it directly. These circumstances need to be carefully considered and the differences acknowledged [40]. As for adults, instruments to assess QOL in children and adolescents of a generic as well as disease- or condition-specific nature are being developed and applied in epidemiological surveys, clinical studies, quality assurance and health economics.

Disease-specific measures are typically developed to measure the effects of a specific disease or condition [41] and will reflect disease-specific clinical changes [42]. Generic measures can be used in a wide variety of health conditions and the dimensions or items included apply to diverse conditions and populations [38, 42–44]. Thus, generic measures are able to compare health across different health conditions or populations. Generic measures thus have a wider application and can be used in population health surveys, burden of disease studies, epidemiological studies, screening, describing health status, developing management plans for individual patients, informing clinical policy and resource allocation decisions [42, 45–49]. There are currently over 89 published generic PROMs for children and adolescents younger than 18 years of which the EQ-5D-Y and Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core scale have been frequently cited [50–52].

The EQ-5D-Y was adapted from the EQ-5D, an adult measure, to include youth friendly wording and examples [53]. Respondents aged 8–15 years, can self-report their health, as experienced on that day, across five dimensions and a Visual Analogue Scale (VAS) measuring general health from 0 (worst health) to 100 (best health). The dimensions include mobility, self-care, usual activities, pain or discomfort and emotional state. The original three-level version, EQ-5D-Y-3L (Y-3L), records scores on three levels of severity: no problems, some problems or a lot of problems [53]. The levels of report have recently been expanded to five on the EQ-5D-Y-5L (Y-5L): no/ not, a little bit, some/quiet, a lot/really or cannot/ extreme(ly) [54]. The increase in levels from three to five levels has been shown to improve the discriminatory power and reduce the ceiling effect of the measure [55].

The *Pediatric Quality of Life Inventory (PedsQL)* is a modular instrument designed to measure health-related quality of life (HRQL) in children and adolescents ages 2–18 years. The PedsQL 4.0 Generic Core Scales are multidimensional child self-report and parent

proxy-report scales developed as the generic core measure to be integrated with the PedsQL disease specific modules. The PedsQL Multidimensional Fatigue Scale was designed to measure fatigue in pediatric patients. The PedsQL 3.0 Cancer Module was designed to measure pediatric cancer specific HRQL [56].

The PedsQL™ Cancer Module is a specific module of the PedsQL™.

Existing versions: Acute version and Standard version, for Toddlers (2-4 years of age), Young Child (5-7 years of age), Child (8-12 years of age), Adolescent (13-18 years of age), Young Adult (18-25 years of age) and Adults (>26 years of age) Reference: homepage: ePROVIDE™ - Online Support for Clinical Outcome Assessments (mapi-trust.org)[57].

The 23-item multidimensional PedsQL 4.0 Generic Core Scales encompass 4 scales: 1) physical functioning (8 items), 2) emotional functioning (5 items), 3) social functioning (5 items), and 4) school functioning (5 items). The PedsQL 4.0 Generic Core Scales are comprised of parallel child self-report and parent proxy-report formats. Child self-report includes ages 5–7 years (young child), ages 8–12 years (child), and ages 13–18 years (adolescent). Parent proxy-report includes ages 2–4 years (toddler), 5–7 years (young child), 8–12 years (child), and 13–18 years (adolescent). The parent proxy-report forms are designed to assess the parent's perceptions of their child's HRQL. The items for each of the forms are essentially identical, differing in developmentally appropriate language, or first or third person tense [56].

1.5 Label claims based on PROs

While both the FDA and EMA recommend the use of PROs as endpoints in clinical trials to support claims for medical product labelling, it is not known how often PROs are actually used and implemented into the product label. There are some studies on the implementation of PROs into the label of FDA-approved new drugs that show that the proportion of new molecular entities (NMEs) with PRO-related labelling statements has slightly increased over the years (of all new drugs approved from 2006 to 2015, ~ 20% included PRO-related labelling statements compared with ~ 26% of new drugs approved from 2016 to 2020). Nevertheless, PRO-related statements in drug labelling of new

treatments approved for cancers remained rare [58–60]. Regarding the implementation of PRO-related labelling in the EU, only one study so far analysed to what extent PROs as outcomes in clinical trials of new drugs are reported in European SmPCs [61]. A further study reviewed PRO labelling for oncology drugs approved by FDA and EMA and compared the implementation rate [62]. Those studies show that the EMA grants PRO-labelling to a greater extend then the FDA.

Labelling related to PROs may be more prominent in certain diseases, such as those involving respiratory or digestive systems. Labelling may, however, be less prominent in other diseases such as metabolic or infectious diseases, and cancers. This is because the disease population may not be symptomatic, the assessment of treatment benefit is traditionally based on biomarkers (e.g., infectious diseases), regulatory decisions related to treatment benefit primarily rely on clinicians' evaluation, or interpretation of findings based on PRO endpoints is difficult because of study design characteristics. For example, most cancer studies are carried out in a noncomparative setting, which hinders interpretation of PRO findings [63]

Both FDA and EMA have ongoing initiatives for improving the quality of PROs for use in approvals and in labels.

A claim about improvement in any PRO needs to be supported by data collected by instruments validated for use in the corresponding condition. Proper validation of the PROM is essential to enhance the chance for inclusion into the approved label.

"HRQL improvement" as a claim implies that the most important and clinically relevant health-related domains of functioning that impact patient's quality of life are known and measured. In order to approve a global claim that a product "improves HRQL", it would be necessary to demonstrate robust improvements in all or most of these domains [6].

A company needs to document the change on the predefined HRQL domains of interest, and to provide information about the amount of change that is required to be considered as clinically meaningful. In case of positive/relevant results, a specific claim reflecting domain(s) with improvement might be mentioned in the SmPC. It is recommended that the claim always specifies the changes observed in all HRQL domains for a given condition,

including the domains with the improvement, the domains with no change and the domains with the worsening, if any [6].

Since labelling needs to deliver key safety and efficacy information about drugs concisely, labelling often lack details compared to journal publications and trial documents such as study protocols and clinical study reports. However, such a gap may have significant clinical implications because the labelling should deliver the information required to convey what is best for patients. It is unclear how often information about PROs is excluded in labelling and reasons for exclusion, which may not be solely due to the need for conciseness.

2. Aim

Previous studies suggest that PROs are rarely mentioned in labels of different cancer drugs approved for adults and even less for the paediatric population. They furthermore suggest that PROs may be collected in drug development, but not included in labelling. However, those studies were always performed for the inclusion of PROs into USPIs of medicinal products approved by the FDA. Furthermore, it is unclear how often information about PROs is excluded in labelling as well as reasons for exclusion.

The objective of the present master thesis is to compare the PRO-endpoint data reported in European Public Assessment Reports (EPARs) with that reported in EU SmPCs for oncologic products approved by EMA between 2016 – 2022, and to evaluate to which extend PRO-endpoint data regarding adult patients in comparison to paediatric patients are incorporated into section 5.1. Furthermore, potential reasons for exclusion of PRO data in labelling are identified and the differences in challenges faced for the incorporation of adult vs. paediatric PROMs are discussed.

The focus on oncologic products was chosen due to personal interest in the development of cancer drugs and due to the fact that cancer drugs belong to those kinds of drugs which are usually considered to be non-PRO dependent [58, 59].

3. Methods

Data source:

Using the Cortellis Regulatory Intelligence report (RIR), all medicinal products approved by EMA via the centralised procedure in the EU between November 2016 and March 2022 were identified.

Data extraction and evaluation:

After exporting the data to Excel, the results were filtered for the therapeutic area (TA) „Cancer“ to capture all oncology indications. Only complete submissions according to article 8 (3) of Directive 2001/83/EC [64] were evaluated and all generic and biosimilar applications were not considered. An excerpt of the complete table can be found in Annex III and furthermore captures information whether the products received a paediatric indication, about the respective MAH, the submission date as well as the CHMP and EC opinion date.

For each drug the EPARs (section 2.5 Clinical efficacy) and the respective included EU SmPCs were systematically reviewed for the inclusion of PROs/PROMs, the type of PROM and the reason given by the assessors in the EPAR, why a PRO was not included into the SmPC. The used search terms were: “patient-reported outcome*”, “patient-reported outcome measure*”, “health related quality of life”, and the respective abbreviations. If no hits were retrieved, the section Clinical efficacy in the assessment report was searched for the used endpoints in the clinical trials. It was also assessed if the PRO was described as a primary, secondary or exploratory endpoint in the respective clinical trials mentioned in the EPAR and to what extend the PROs were included into the SmPC section 5.1.

4. Results

The Cortellis Regulatory Intelligence report (RIR) provides an EU medicinal products registration overview and is a list of all centralized products approved since their first EPAR and products withdrawn and suspended since 01 March 2012. In addition, the RIR provides

revision of EPARs published by the EMA since September 2019. It allows a search for general information on each medicinal product, the registration process and some product regulatory information. After retrieving the RIR from Cortellis, the report was screened for medicinal products in the therapeutic area “Cancer”, which revealed 1460 EPARs including all revisions. Subsequently, the list was further narrowed down on full applications and fixed combinations (991 EPARs), approved (EC opinion date) from November 2016 onwards (date for coming into effect of the “Appendix 2 to the guideline of the evaluation of anticancer medicinal products in man – The use of patient-reported outcome (PRO) measures in oncology studies” [5]) until 13 March 2022 (date of retrieving the RIR), revealing 212 EPARs.

4.1 Analysis of reporting rates for PROs in SmPCs

Out of the 212 EPARs, only the current revised EPAR per medicinal product was checked for the description of PROs / PRO measures. The final table of results contains EPARs of 71 products, of which four were not analysed, since they were withdrawn (exerpt see Annex III, Table 1). Of those 67 products six also have a paediatric indication and were thus also checked for the inclusion of PROs in their clinical trials.

PRO data were reported in 52 of the 67 EPARs (77.6%). In total, 128 PROs were described in those 52 EPARs, of which 80 were reported in the CT as secondary endpoints (62.5%) and 41 as exploratory endpoints (32%). The rest of the PROs have not been specified as secondary or exploratory endpoint in the CT. None of the PROs was reported as primary endpoint in the CTs mentioned in the EPARs. 30 of the PROs described as secondary endpoints were included into SmPCs (37.5%), which is only 23.4% of all PROs mentioned in the EPARs. From the exploratory endpoints only two were mentioned within the CT section of the SmPC (4.9%), which is only 1.6% of all PROs mentioned in the EPARs. Overall, there were 16 products (30.8% from the 52 which included PRO data in their EPARs) which received PRO-related language in SmPCs (EMA PRO labelling).

Taken together, in most cases, PROs were not included at all into section 5.1 of the SmPC or were only included partially.

Table 1 presents the specific PROMs referenced in the EPARs of the 52 products with PRO data. The EORTC QLQ-C30 questionnaire was the most commonly used PROM in submissions (41.4%) and was referred to in 51.8% of the approved labels. The EQ-5L questionnaire was included in 18.8% of the EPARs and was referred to in labelling of 15.8% of the approved products. The FACT measure was included in 13.3% of the EPARs and led to a label claim in the SmPC of 11.1% of the approved products. 10.9% of the EPARs only mentioned HRQL or QOL without further specification what has been measured. Surprisingly, this led to inclusion into the label of 18.5% of the products. In 10.2% of the EPARs single-item measures of symptoms were included, which did not lead to inclusion into the label in any of the products.

PRO measure	**EPARs with PRO data (n=52), n (%)**	**EMA PRO labelling (n=16 approvals) n (%)**
EORTC QLQ-C30 (without EORTC disease-specific modules)	31 (24.2)	8 (29.6)
EORTC QLQ-C30 (with disease specific modules)	22 (17.2)	6 (22.2)
EQ-5D (-3L or -5L version)	24 (18.8)	4 (14.8)
HRQL/QOL (not further specified)	14 (10.9)	5 (18.5)
FACT-G (without FACT disease-specific measures)	5 (3.9)	0
FACT-G (with FACT disease-specific measures, e.g., prostate, kidney, melanoma)	12 (9.4)	3 (11.1)
SF-12/36 (general)	3 (2.3)	1 (3.7)
TINAS (general)	2 (1.6)	0
Skindex-16/29 (general)	2 (1.6)	0
Symptoms (general and disease-specific e.g., pruritus, neuropathy, BFI-fatigue, FACES, EI VFQ-25)	13 (10.2)	0

Table 1

Summary of PRO measures included in oncology drug approvals (2016-2022). Total numbers and % were calculated for the PROMs that were mentioned in the 52 EPARs (128 PROMs in total) and for the number of PROMs that were included into the SmPC after approval of 16 products (27 PROMs in total).

The example below shows, first the description of the PROs in the clinical efficacy section of the EPAR of Libtayo and then, what is mentioned in the approved SmPC. Only one PRO (EORTC QLQ-C30) from one study was very shortly described in section 5.1 of the SmPC.

Example Libtayo (cemiplimab):

EPAR, Clinical efficacy section

- study R280-ONC-1540: phase 2 study of REG2810, a fully human monoclonal antibody to programmed death – 1 (PD-1), in patients with advanced cutaneous squamous cell carcinoma

Patient-reported quality of life is measured by the EORTC QLQ-C30: The global health status/QoL, five functional scales (physical, role, cognitive, emotional and social), and three symptom scales (fatigue, pain, nausea and vomiting) and a number of single items assessing additional symptom commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease will be computed using the QLQ-C30 scoring procedures. Change scores are defined as change of summary score of EORTC QLQ-C30 from day 1 of first treatment cycle.

Results:

[…]

Secondary endpoint - Quality of life

[…]

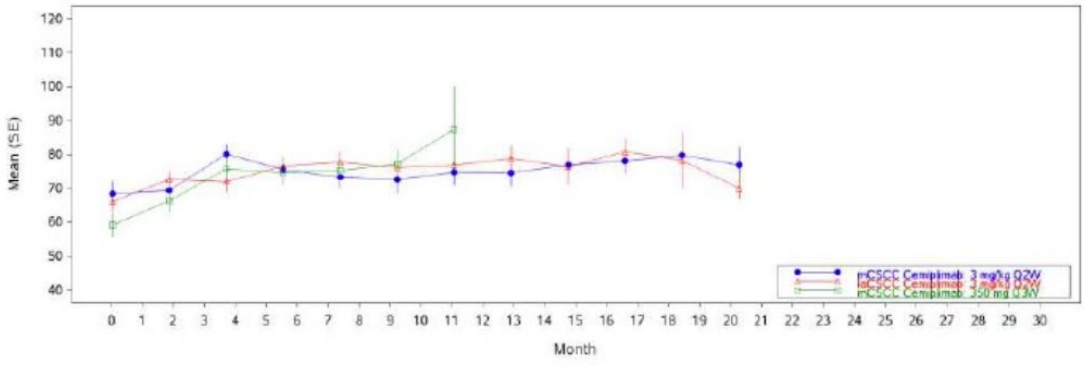
Assessment report:

[…]

Quality of life was assessed using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Changes in mean EORTC

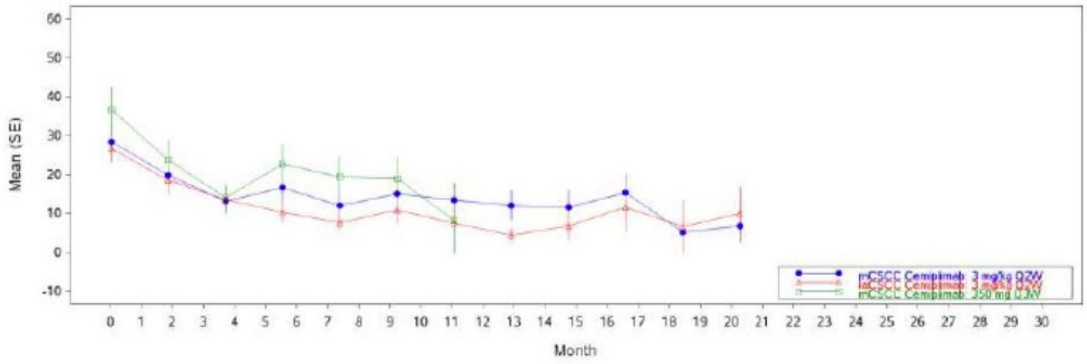
QLQ-C30 scores generally did not indicate consistent changes in quality of life with the exception of the pain symptom subscale:

Table 40: Global health status /QoL - All CSCC patients by group



Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients. Data cut-off as of Oct 10, 2018 for Group 2 patients.

Table 41: Symptom subscale Pain - all CSCC patients by group



Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients. Data cut-off as of Oct 10, 2018 for Group 2 patients.

- study R2810-ONC-1620: A phase 2 study of REGN2810 (cemiplimab) in patients with advanced basal cell carcinoma who experienced progression of disease on hedgehog pathway inhibitor therapy, or were intolerant of prior hedgehog pathway inhibitor therapy

Exploratory objectives:

Assess the impact of cemiplimab on quality of life using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Skindex-16

- **study – Study 1624:** Study 1624 is a randomised, multicentre, global, open-label, pivotal phase 3 study of cemiplimab monotherapy versus platinum-based doublet chemotherapy in patients with stage IIIB, stage IIIC, or stage IV squamous or non-squamous NSCLC who were not candidates for treatment with definitive chemoradiotherapy, whose tumours expressed PD-L1 in ≥50% of tumour cells, with no EGFR, ALK, or ROS1 aberrations, and who had received no prior systemic treatment for their advanced disease

Secondary Objectives:

•To assess the quality of life (QoL) of patients treated with cemiplimab versus patients receiving platinum-based chemotherapies as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQC30) and EORTC QLQ Lung Cancer 13 (LC13)

SmPC, section 5.1: Pharmacodynamic properties

Clinical efficacy and safety:

CSCC

[…]

In study 1540 […], and change in scores in patient reported outcomes on the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30).

4.2 Analysis of reporting rates for paediatric PROs in SmPCs

As mentioned above, six (out of 67) products have been granted a paediatric indication in addition to their adult indication. PRO data were reported in three of those six EPARs. One of those three EPARs described the use of adult PROs in general, but it was not specified, if the PRO measures mentioned, were also applicable for children or if they were used in the

paediatric trials. Only two EPARs specifically reported paediatric PROs (33.3%) (KYMRIAH and VITRAKVI). The total reported number of paediatric PROs was three (one as exploratory endpoint, two as secondary endpoint), of which two were reported in the clinical trial section of an SmPC (KYMRIAH). The implemented PRO measures were the PedsQL and EQ-5D questionnaires completed by patients aged eight years and above. Taken together, this evaluation shows that from the six products with paediatric indications only one product has implemented paediatric PRO data into section 5.1 of its SmPC (16.6%).

4.3 Reasons for not including the PROs/PRO measures into the SmPC

In most cases, PROs were not included at all into section 5.1 of the SmPC. As found in the EPAR assessment reports (products listed in RIR → exerpt see Annex III, Table 1) the following reasons were given by the assessors to exclude the PROs, mentioned in the clinical trial protocols, either in total or partially from the SmPCs:

- The most common reason mentioned by assessors was the open-label **study design** and the lack of controls. "The interpretation of PROs from single-arm open-label studies is generally difficult, due to the non-blinded study design's effect on the patients' experience and the lack of comparator. Also, lack of formal hypothesis testing and the missing data preclude the acceptance of any HRQL claims in the SmPC."
  (VITRAKVI, TECARTUS, SARCLISA, TALZENNA, VIZIMPRO, ALUNBRIG, RUBRACA, RYDAPT, NEXPOVIO)
- The second common reason was, that **no statistical significance** was reached / no meaningful clinical differences between treatment arms could be observed (BESPONSA, INVESTIGATO, PIQRAY, SARCLISA, POLIVY, VIZIMPRO, RUBRACA, OCREVUS).
- Assessors also mentioned as reason, that **no, not sufficient or not the right statistical analysis** has been applied. (TUKYSA, TALZENNA, ERLEADA, ALUNBRIG)
- **Missing data** (claim is not supported by the available data) (ABECMA, GAVRETO, TALZENNA, VITRAKVI, NEXPOVIO, POLIVY)

- **lack of compliance with questionnaire / protocol** (POLIVY, TALZENNA, TECENTRIQ)
- **limited quality of data** (e.g., due to programming issues) (POLIVY, RUBRACA)
- it is not clear why the questionnaire was originally chosen for use in the study (TOOKAD) → **invalid PRO measure**

5. Discussion

Overall, the inclusion rate of PROMs from the EPAR into the respective SmPC of oncologic medicinal products approved in the EU from 2016 until today is low. Only 25% (23.4% as secondary endpoint, 1.6% as exploratory endpoint) of the PROMs mentioned in the EPARS were finally included into section 5.1 of the SmPC. Furthermore, even if PROMs were included into the SmPC, they were only included partially. This means that in the EPARs several PROMs were described, but not all of them have been approved as a label claim in the SmPC or several scores retrieved from the questionnaires were summarized as "HRQL".

The reasons for the non-inclusion of claims derived from PROMs are diverse.

5.1 Possible problems for the inclusion of label claims derived from PROMs into the SmPC

Type of PROM

For example, the specificity of the chosen generic questionnaires may not be sufficiently precise to identify differences specific for the disease or to capture patients' experiences with a particular therapeutic strategy in a meaningful way, e.g., the EQ-5D-5L questionnaire is used across different therapeutic areas like cancer, metabolic diseases or CNS. The lack of sensitivity of PROMs measuring broad concepts such as HRQL may lead to erroneous conclusions [5, 7, 65]. Furthermore, there is the possibility for dilution of important symptoms by irrelevant symptoms [66, 67]. Disease-specific HRQL instruments are conceptualised for certain diagnosed groups or patient populations. They take into account the aspects that are meaningful for these groups or illnesses, for example, the specifics of

the treatment procedures [68]. Disease-specific measurement instruments are generally suitable for the clinical examination of certain therapeutic interventions; however, they might complicate the comparison of HRQL measurements of different diseases. If a questionnaire is too specific and tailored for a certain type of cancer it might also be not applicable in all settings or may be irrelevant for a huge patient population. In connection with health economics investigations, the most important generic measurement instruments are those that assess the broadest possible spectrum of HRQL aspects, and are employable with various illnesses, disabilities, situations, patients and populations [69]. They are meaningfully used in general health investigations, as well as in the comparison of the consequences and courses of various states of illness. Careful choice of the most appropriate measures used for assessment of PROs is one important step during drug development in oncology clinical trials.

In the present analysis, most of the label claims granted by the EMA were based on cancer-specific questionnaires like the EORTC QLQ-C30 (with and without disease-specific modules). However, also a remarkable proportion of label claims were based on the general EQ-5D questionnaire, which is used across indications. For the cancer-specific FACT questionnaire, label claims were only included into the SmPC, when a disease-specific measure, tailored for a certain kind of cancer was used. These findings are comparable to the results from Gnanasakthy et al., 2019 [62], who also showed that most label claims were granted based on the EORTC QLQ-C30 and the EQ-5D.

None of the methods, be it generic or disease-specific can claim universal superiority over the other. Taking into account the specific advantages and disadvantages of the particular methods, each method has its value with regard to specific research aims and research contexts [70]. Even if proper instruments were used with defined change in score (e.g., 10 points or more) and defined minimally important difference (MID), PROs were sometimes not included into SmPCs in the present analysis.

Study design

Often, the reliability of the PRO results was hampered by the single-arm open label study design, and thus inclusion into the SmPC was not granted by the EMA. The assessors

questioned the interpretability of PROs, due to the non-blinded study design's effect on the patients' experience and the lack of comparator. The presence of bias, mainly because of placebo effect from open-label studies, may compromise the ability to draw valid conclusions from clinical trials. Common symptoms of cancer and its treatments may be affected by the placebo or nocebo effect [71, 72]. The absence of a control arm further complicates our ability to draw meaningful conclusions from PRO data, particularly with respect to efficacy, given concerns about an overestimation of benefit when patients are aware of treatment assignment. There is the need to characterise the existence and magnitude of bias in open-label cancer trials [73].

Heightened expectations may also have an impact on reporting of higher order concepts such as HRQL or QoL. For example, patients may consider new or worsening symptoms, such as vitiligo when receiving immunotherapy, to be a marker of treatment efficacy [74, 75]. Even in controlled settings, patients' perception of treatment benefit may be affected when treatment is unblinded because of adverse events (AEs).

On the other hand, single-arm trials are common in (paediatric) oncology drug development because of ethical concerns around placing patients on placebo or wait-listing them in crossover study designs.

Work in patients with cancer suggests that although open-label bias may have a potential effect on PRO assessment completion rates [76], evidence showing that knowledge of treatment assignment has a large effect on PRO responses in the oncology setting is currently limited [73]. Concerns about interpreting PRO findings from single-arm studies can be addressed by using prespecified and appropriate thresholds for clinically meaningful within-patient score change in the concepts of interest.

Comprehensibility

A further problem could be the comprehensibility of labelling statements based on PRO endpoints. Here, two scenarios are possible. First, assessors might find certain label claims to complicated or even not clearly described in the EPAR or CTP what was actually measured and will not grant the inclusion of the respective PROM into the SmPC. Second,

even if the PROM could be included into the SmPC, patients and caregivers might not understand the meaning. Because PRO-related data are intended to reflect the patient experience with a condition or while on treatment, text in the product information (PI) describing the results of a treatment on PROs is often of particular interest to these stakeholders. Of course, labelling (be it the EU SmPC or the USPI) is intended for use by physicians. Nevertheless, because of the expansion of healthcare and better access to information about diseases and treatments, patients are taking a more active role in making their own healthcare decisions [77]. Patients' clear and complete understanding of the benefits and risks of a treatment is an essential component in facilitating effective communication between care providers, regulators, and patients. Although prescribers are the intended audience for PIs, prescribers need access to information in a manner that is consistent, informative, and comprehensible; the information should be simple and clear enough to convey the intended message [78] to enable shared decision making, a process by which the patient and clinician work together to determine what is best for the patient [79].

Hence, to optimise multistakeholder understanding of treatment benefits and risks, PRO data are presented ideally in a way that is understandable to various stakeholders who may review the PI.

5.2 Challenges for the design of paediatric PROMs compared to adult PROMs

The use of PROMs in childhood populations presents methodological challenges compared to applications in adults. Although a broad variety of PROMs is available to assess children's health, only a few PROMs can be used across all age ranges to 18 years.

The International Society for Pharmacoeconomics and Outcome Research (ISPOR) task force has established good research practices for the assessment of PROs of children and adolescents [39] to tackle those challenges:

1. Consider developmental differences and determine age-based criteria for PRO administration:

- Less than five years old: No clear evidence of reliability or validity of child-report measures
- five to seven years old: Child-report is possible, but reliability and validity are often questionable
- eight to 11 years old: Reliability and validity of child-report improves
- 12 to 18 years old: Self-report is preferred

Those age groups are recommended to be used as a starting point when making decisions, but they will not fit all PRO instruments or the developmental stage of every child. Specific age cutoffs should be determined individually for each PRO instrument and tested with cognitive interviews in each new target population.

2. Establish content validity of paediatric PRO instruments:
    - Children and adolescents can be effective content experts.
    - In most cases, children should be included in qualitative research performed to establish content validity of paediatric PROs.
    - Cognitive interviews should be conducted with the intended respondent. Children should be interviewed for child-report instruments, and parents should be interviewed for parent-report instruments.
    - Content validity should be demonstrated within narrow age groupings.
3. Determine whether an informant-reported (parents, clinicians, teachers) outcome instrument is necessary:
    - Informant-reported outcomes include both proxy (require the informant to make inferences about the child's subjective experience, such as emotional state, level of satisfaction, or pain severity) and observational measures (items assessing directly observed behaviour, without interpretation).
    - When children in the target age range are capable of completing a PRO instrument independently, a child-reported measure should be used. A child-reported measure is generally preferred because it is the most direct assessment of the child's experience of disease and treatment, without any bias or interpretation by the informant.
    - When children in the target age range are not capable of completing a PRO measure, an informant-reported measure may be used.

- Informant-reported measures should assess observable content as much as possible, rather than subjective aspects of the child's experience.

4. Ensure that the instrument is designed and formatted appropriately for the target age group:
    - Health-related vocabulary and reading level
    - Response scale: e.g., Likert scale, graphic representations, facial expressions, and visual analogue scale
    - Recall period: Shorter recall periods are preferable for PRO measures used in the regulatory context, and this may be more important for paediatric measures than for adult measures.
    - Length of instrument: Measures that are overly long may cause children to omit items or think less carefully about each item, thus yielding less accurate and reliable data[80]
    - Pictorial representations
    - Formatting
    - Administration approaches
    - Electronic data collection (ePRO)
5. Consider cross-cultural issues:
    - Content validity and measurement approach of a paediatric PRO instrument will need to be reexamined within each new culture. This assessment should focus on all relevant aspects of the instrument including the instructions, items, concepts, vocabulary, and pictorial representations. In sum, cross-cultural PRO instrument development for children is likely to require greater sensitivity and effort than simply following the cross-cultural guidelines set for adult instruments.

The above-mentioned important issues should be considered when designing, validating, or implementing paediatric PRO instruments for use in the context of regulatory submissions and medical product labelling.

Although there are several generic as well as disease-specific PROMs available for children, more work is needed to provide updated PRO instruments and methodological guidance for future studies, as well as to newly design tailored age-appropriate questionnaires for

children. Especially research on optimizing PRO design for younger children is needed, particularly for children younger than eight years for whom self-reported measures often have inconsistent reliability and validity.

When informant-reported outcome instruments must be used, e.g., when parents have to answer on behalf of their children that are too young or too ill to report on their own, there is a growing emphasis on developing truly observational items, rather than proxy measures that require inference into the child's subjective experience. Therefore, it may be useful to update and validate commonly used parent-reported and clinician-reported instruments to reflect this more observational approach.

Another challenge involves the interpretation of data from multiple age groups. Many PROMs for children are developed with multiple versions for different age groups and furthermore with informant-reporter versions for younger children. There might be the problem of comparability in the analysis of so many different versions that might have been used during drug development in clinical studies. This challenge is for example already tackled for the PedsQL questionnaire where the items for each of the forms are essentially identical, differing only in developmentally appropriate language, or first or third person tense [56] to enhance the probability of better comparability.

5.3 Discussion of the use of an adult PROM in paediatric studies (Kymriah)

For Kymriah, which is indicated for the treatment of paediatric and young adult patients with B-cell acute lymphoblastic leukaemia (ALL) and for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy, the sponsor used the EQ-5D and the PedsQL questionnaires. Although there is a special paediatric version available for the EQ-5D, namely the EQ-5D-Y, the sponsor was successful in incorporating the adult PROM for the paediatric indication into the SmPC. The reason for choosing the adult version could be that at the time of the start of the respective study (CCTL019B220, EudraCT no. 2013-003205-25) in April 2015, the EQ-5D-Y was indeed already developed [53], but might not yet have been validated.

5.4 Do PROs lead to changes in the design of clinical trials to enable higher quality of life to patients?

Several studies in adult oncology have shown that PROMS can not only improve patient-physician communication and patient satisfaction [81–85] but may also improve the clinician's awareness of symptoms, better symptom management and continuity of care, ultimately resulting in better overall survival rates during oncological treatment [86–88].

A claim in the SmPC with the respect to HRQL (i.e., in section 5.1) will always be considered depending on the strength of the evidence and the relevance (pertinence and importance) of the finding. The strength of the evidence should be based on the rationale for HRQL assessment in the context of the disease/medicinal product, the justification of the choice of the HRQL questionnaire(s), the objectives of HRQL assessment and the hypotheses of HRQL changes, the evidence of validation (and of cultural adaptation/translation if applicable) of the HRQL questionnaire(s), the adequacy of the statistical analysis plan, and the relevance of observed changes. [6].

The EMA encourages pharmaceutical companies to include PROs into the SmPC. On 31 March 2020, EMA published its Regulatory Science Strategy to 2025 after it was endorsed by EMA's Management Board at its March 2020 meeting [89]. As per this strategic reflection, EMA will continue to work towards systematic incorporation of patient-reported outcomes and patient preferences into drug development and benefit/risk assessments. Core recommendations include:

- Update existing, and develop new EMA guidelines on patient data collection
- Coordinate the approach to patient reported outcomes (PROs)
- Promote use of core health-related quality-of-life PROs

At the moment, there is general guidance on the use of HRQL measures in the evaluation of medicinal products, giving broad recommendations but no methodological requirements for the development, validation and use of PROs [6], and a more specific one

for the use of PRO measures in oncology studies [5]. However, even if the EMA has encouraged the development of new PRO tools for cancers to guide the use of PROs in oncology studies, because the existing ones may not be appropriate or specific enough to measure important outcomes in this population [5], concrete guidance on how to include PROs into the label is missing. Especially for research involving paediatric PRO assessment related to medical product development, limited guidance is available. In addition to the development of new guidelines as mentioned above, the SmPC guideline (2009) should be updated with regards to a concise description about how PROs should be included into section 5.1 and which requirements have to be fulfilled in order to be included. At least it would also be useful to include reference to certain general and TA-specific guidelines regarding the requirements for the inclusion of PROs into the label. In the TA-specific guidelines as such, concrete examples for validated PRO measures/instruments should be included.

On the other hand there are many projects ongoing initiated by the Quality of Life Group (QLG): QLG funded projects - EORTC - Quality of Life : EORTC – Quality of Life e.g. Development of thresholds for the EORTC QLQ-C30 and the EORTC CAT measures to enable their use for symptom screening in daily clinical practice, Development of an interpretation guideline for the EORTC PRO measures.

6. Conclusion

Despite recommendations of regulatory agencies, PRO assessment is extremely rare in adult and especially in paediatric oncology clinical trials and even more rare is the implementation into the label. More efforts should be undertaken by health authorities but also by MAHs to facilitate the implementation of PROs in oncology clinical trials to guarantee patient-centred research and treatments and inclusion of those measures into the product information.

7. Prospect

Common Terminology Criteria for Adverse Events (PRO-CTCAE):

There are a number of validated PRO instruments, including EORTC and FACT measures that aim to capture the consequences of adverse reactions on patient wellbeing. The PRO-CTCAE has been developed by the National Cancer Institute (NCI) to evaluate patient-reported symptom data in oncology clinical trials. It is one way of capturing the patient experience while on treatment in an oncology trial and was designed to be used as a companion to the Common Terminology Criteria for Adverse Events (CTCAE), the standard lexicon for adverse event reporting in cancer clinical trials.

The PRO-CTCAE item library is comprised of 78 symptoms (124 items) that are common in oncology clinical trials and is designed to serve as a flexible toolkit that can be adapted based on the treatment and condition of interest [65, 90].

The instrument has a recall period of 7 days. Symptom items are selected from the PRO-CTCAE library based on anticipated treatment toxicities in the planned study. Patients may be probed sequentially on up to 3 attributes for each symptom; a conditional logic is applied so that a patient's response to the first question determines their access to subsequent items. The PRO-CTCAE is intended to characterize patient-reported symptom data:

- PRO-CTCAE should be administered at baseline in order to understand the impact of treatment on symptoms
- Early-phase trials: PRO-CTCAE used to collect the patient perspective on symptoms experienced while on treatment; assess dose levels and schedules
- Later phase trials: PRO-CTCAE data are used to compare symptoms between regimens
- Post marketing studies, comparative effectiveness research, safety surveillance systems: PRO-CTCAE data are used to detect treatment impacts in targeted or broad populations and/or with long-term treatment [11]

A paediatric module permits self-reporting by children and adolescents ages 7-17 years (Ped-PRO-CTCAE) or caregiver-reporting for children ages 7-17 who are unable to self-report. The paediatric module includes 130 items representing 62 symptomatic toxicities drawn from the CTCAE. PRO-CTCAE has been linguistically validated in more than 30 languages. The Ped-PRO-CTCAE module was developed and tested in English in the US and has been linguistically validated in Italian and Simplified Chinese. Several other languages are in development [91].

It is envisioned that the PRO-CTCAE could enhance the precision and patient centeredness of adverse event reporting in cancer clinical research and ultimately provide a more representative account of patients' treatment experiences.

ePROs:

Even though, the collection of patient data by ePRO instruments has become an important part and widespread methodology in clinical trials during the last decades, ePROs were not mentioned in the analysed description of the trials mentioned in the EPARs in this study. Maybe, they were just not mentioned in the EPAR but have been described in the CTP or the clinical study report. However, the analysis of each and every CTP was not in the scope of this master thesis.

Regarding ePROMS, evidence supports that they enhance patient-clinician communication, provide better documentation of symptoms than clinicians, and decrease symptom distress. Moreover, this electronic collection of symptoms allows the generation of alerts to clinicians for potential toxicities. The use of ePROMs and their integration with electronic health records (EHR) provides clinicians with a longitudinal overview of the patient's symptoms. Therefore, assessment and management of the symptoms have been improved since it is easier to handle and analyse all answers from the different questionnaires electronically. Also, patients found their communication with their health care providers has been enhanced [10, 92, 93].

Especially for older children and adolescents, the use of ePROMs might also be more „interesting" than just filling paper versions of a questionnaire, which could enhance completion compliance during a clinical trial. They would not need to have the paper

versions with them and could just use an app on their smart phone to fill the questionnaire. This will facilitate the use of PROMs for the patients.

Since most PROMs were originally developed and validated in paper form, care is needed when migrating to electronic formats to ensure the instrument measurement properties are unaffected and the electronic PROM features do not limit data validity. As a result, researchers often have to provide evidence demonstrating the equivalence of the original paper version and the electronic version before administering the electronic version in a clinical trial, such as that recommended by the ISPOR ePRO Good Research Practices Task Force, which requires de novo evidence prior to administration in a trial [94].

However, it is concluded by Byrom et al., 2019 [95] that application of best practice recommendations is sufficient to conclude measurement equivalence with paper PROMs. Furthermore, they recommend that previous usability evidence in a representative group is sufficient as opposed to per-study testing. They conclude that this also applies to studies using multiple screen-based devices, including bring-your-own-device (BYOD), if a minimum device specification can be ensured and the instrument is composed of standard response scale types. BYOD promises to provide greater convenience for trial participants, enabling subjects to record PROM data on the device they refer to regularly and are familiar with. This may lead to increased PROM compliance and reductions in missing data. For the MAH, BYOD may also simplify trial logistics if device provisioning is not required and may lower the associated costs of collection of these data.

<u>precedence for a “real” patient-focused approach:</u>

While regulatory agencies move toward an acknowledgment of the value of PRO data—data that patients provide about their own experience that are not subject to interpretation by a third party—drug development cannot be truly “patient-focused” until the results of those patient-reported data are made accessible—without interpretation—to the same groups of people whom we trust to provide it. If, in its current form, FDA approved drug labelling cannot present this information in a way that is comprehensible to patients, it may be time to envision a patient-facing document written specifically for members of the general public. Certainly, there is some precedence for this approach on

the global stage: the European Medicines Agency, for example, publishes “lay summaries” that are intended to provide information for study participants, patients, and other stakeholders who have an interest in clinical study results, but who may have limited health literacy or scientific expertise [96].

8. Summary

PROs can be used as claims in product information texts to inform about the status of a patients’ health condition directly reported from the patient without interpretation of the patients’ response by a clinician or anyone else. Different kinds of PROs exist describing either a symptom, or more complex conditions like HRQL. PRO data are collected in clinical trials via PRO instruments (e.g., questionnaires or diaries) completed by the patient or completed during an interview, provided that the interviewer records only the patient’s response. As several studies suggest that especially in cancer drugs PROs may be collected during drug development in clinical trials, but are not necessarily included into the label, the aim of this master thesis was to evaluate how many oncologic drugs approved between 2016 and 2022 by EMA included PROs as endpoints into their clinical trials described in the EPAR and how many of those were implemented into section 5.1 of the respective SmPCs. For each drug, EPARs and the respective included EU SmPCs were systematically reviewed for the inclusion of PROs/PROMs, the type of PROM and the reason given by the assessors in the EPAR, why a PRO was not included into the SmPC. It was also assessed if the PRO was described as a primary, secondary or exploratory endpoint in the respective clinical trials mentioned in the EPAR and to what extend the PROs were included into the SmPC section 5.1.

Overall, the inclusion rate of PROMs from the EPAR into the respective SmPC of oncologic medicinal products approved in the EU from 2016 until today is low. For the adult indications 25% (23.4% as secondary endpoint, 1.6% as exploratory endpoint) of the PROMs mentioned in the EPARS were finally included into section 5.1 of the SmPC. For the paediatric indications the situation is even worse. Only 16.6% were included as label claim into the SmPC. Furthermore, even if PROMs were included into the SmPC, they were only

included partially. This means that in the EPARs several PROMs were described, but not all of them have been approved as a label claim in the SmPC or several scores retrieved from the questionnaires were summarized as “HRQL”.

The reasons for the non-inclusion of claims derived from PROMs which have been mentioned in the assessment reports are diverse and include: inappropriate study design, no statistical significance, missing data, lack of compliance with protocol, limited quality of data, and use of an inappropriate PROM.

Although one quarter (25%) of adult PROMs mentioned in EPARs have been included as label claim into the SmPC, there is still room for improvement. For the paediatric indications only 16.6% of the PROMs have been included into the SmPC. Those results point at the need for the development of new guidance, especially on paediatric PROs/PROMs and how they should be designed and used to strengthen the likelihood of incorporation of a PRO-related claim into the label to ensure that also the paediatric patients’ voice is heard in order to enable more patient-focused clinical trial designs in the future.

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Annex

Annex I: List of questionnaires (EORTC homepage, [97]).

Code	Name	Category	Phases
QLQ-C30	Quality of Life of Cancer Patients	Core	validated
2054	2054 Immune Checkpoints Inhibitor	Module	II / II - in development
1749	Sarcoma	Module	I / II - in development
1837	Renal Cancer	Module	I / II - in development
1750	Multiple Myeloma (update of MY20)	Module	I / II - in development
M20MMM	Metastatic malignant melanoma	Module	I / II - in development
1841	Male Breast Cancer	Module	I / II - in development
003-2019	Gastric Cancer (update of QLQ-STO22)	Module	I / II - in development
004/2019	Cutaneous T-cell and B-cell lymphomas	Module	I / II - in development
002-2020	Development of an EORTC questionnaire for Children with Cancer (8-14 years)	Module	I / II - in development
Bladder	1942 Bladder cancer (merge of BLM30 and NMIBC24)	Module	I / II - in development
AYA	Adolescents and Young Adults	Core	III - in development
QLQ-ANL27	Anal Cancer	Module	IV - completed
QLQ-BM22	Bone Metastases	Module	validated
QLQ-BN20	Brain	Module	validated
1751	BN20 update	Module	III - in development
QLQ-BR23	Breast	Module	validated
QLQ-BR45	Breast Cancer (update of QLQ-BR23)	Module	IV - in development
QLQ-BRECON23	Breast Reconstruction	Module	validated
QLQ-CAX24	Cancer Cachexia	Module	IV - completed
QLQ-FA12	Cancer related Fatigue	Module	validated
QLQ-CX24	Cervical	Module	validated
QLQ-CIPN20	Chemotherapy-Induced Peripheral Neuropathy	Module	III - completed
QLQ-BIL21	Cholangiocarcinoma and Gallbladder Cancer	Module	validated
QLQ-CLL17	Chronic Lymphocytic Leukaemia	Module	IV - completed
QLQ-CML24	Chronic Myeloid Leukaemia	Module	IV - in development
QLQ-CR29	Colorectal	Module	validated
QLQ-LMC21	Colorectal Liver Metastases	Module	validated

QLQ-COMU26	Communication	Standalone	IV - in development
QLQ-ELD14	Elderly Cancer Patients	Module	validated
MBC	Metastatic Breast Cancer	Module	I / II - in development
QLQ-EN24	Endometrial	Module	validated
1748	Fertility	Module	I / II - in development
QLQ-IN-PATSAT32	Satisfaction with In-Patient Cancer Care	Standalone	validated
QLQ-STO22	Gastric	Module	validated
QLQ-H&N35	Head & Neck	Module	validated
QLQ-H&N43	Head & Neck Cancer (update of QLQ-H&N35)	Module	validated
QLQ-HCC18	Hepatocellular Carcinoma	Module	validated
HCPS	Hereditary Cancer Predisposition Syndrome	Module	I / II - in development
QLQ-HDC29	High-Dose Chemotherapy	Module	III - completed
QLQ-NHL-HG29	High Grade Non-Hodgkin's Lymphoma	Module	IV - in development
QLQ-HL27	Hodgkin's Lymphoma	Module	IV - in development
IADL	IADL in Brain Tumor Patients	Module	IV - in development
QLQ-INFO25	Information	Module	validated
QLQ-NHL-LG20	Low Grade Non-Hodgkin's Lymphoma	Module	IV - in development
QLQ-LC13	Lung	Module	validated
QLQ-LC29	Lung Cancer (update of QLQ-LC13)	Module	validated
QLQ-MEL38	Melanoma	Module	III - completed
QLQ-MY20	Multiple Myeloma	Module	validated
QLQ-BLM30	Muscle Invasive Bladder Cancer	Module	III - completed
QLQ-GINET21	Neuroendocrine Carcinoid	Module	validated

Annex II: Examples of distinct questionnaires

1. EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

SPECIMEN

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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SPECIMEN

2. EORTC QLQ-LC13

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

SPECIMEN

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3. EQ-5D-5L

Health Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- ☐1 I have no problems in walking about
- ☐2 I have slight problems in walking about
- ☐3 I have moderate problems in walking about
- ☐4 I have severe problems in walking about
- ☐5 I am unable to walk about

SELF-CARE

- ☐1 I have no problems washing or dressing myself
- ☐2 I have slight problems washing or dressing myself
- ☐3 I have moderate problems washing or dressing myself
- ☐4 I have severe problems washing or dressing myself
- ☐5 I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- ☐1 I have no problems doing my usual activities
- ☐2 I have slight problems doing my usual activities
- ☐3 I have moderate problems doing my usual activities
- ☐4 I have severe problems doing my usual activities
- ☐5 I am unable to do my usual activities

PAIN / DISCOMFORT

- ☐1 I have no pain or discomfort
- ☐2 I have slight pain or discomfort
- ☐3 I have moderate pain or discomfort
- ☐4 I have severe pain or discomfort
- ☐5 I have extreme pain or discomfort

ANXIETY / DEPRESSION

- ☐1 I am not anxious or depressed
- ☐2 I am slightly anxious or depressed
- ☐3 I am moderately anxious or depressed
- ☐4 I am severely anxious or depressed
- ☐5 I am extremely anxious or depressed

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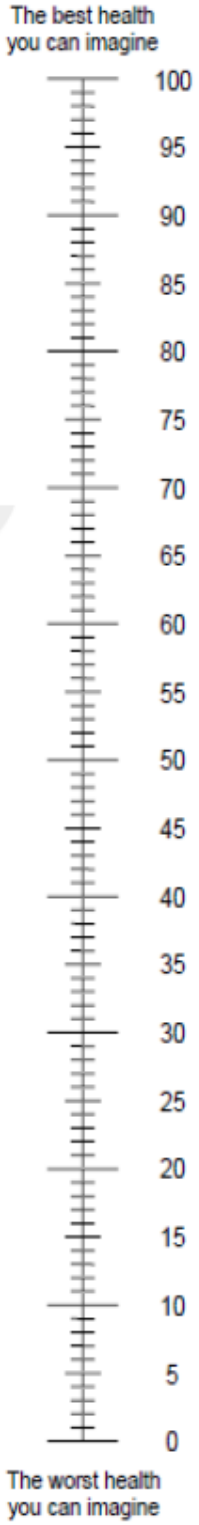
Health Questionnaire (EQ-5D-5L)

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is **TODAY**
- Now, please write the number you marked on the scale in the below.

YOUR HEALTH TODAY = ☐



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4. FACT-P

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

English (Universal)
Copyright 1987, 1997

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

English (Universal)
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5. FACT FOSI-18

NCCN-FACT FOSI-18 (Version 2)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	GP6	I feel ill	0	1	2	3	4
	O3	I have cramps in my stomach area	0	1	2	3	4
	H17	I feel fatigued	0	1	2	3	4
	Cx6	I am bothered by constipation	0	1	2	3	4
	O1	I have swelling in my stomach area	0	1	2	3	4
	C3	I have control of my bowels	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
TSE	B5	I am bothered by hair loss	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	O2	I have been vomiting	0	1	2	3	4
	BMT15	I am bothered by skin problems	0	1	2	3	4
FWB	BMT5	I am able to get around by myself	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

English (Universal)
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03 March 2010
Page 1 of 1

6. PedsQL – report for adolescents

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

TEEN REPORT (ages 13-18)

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DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

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01/00
PedsQL-4.0-Core-A – United States/English – Original version
PedsQL-4.0-Core-A_AU4.0_eng-USorl

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

About My Health and Activities *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

About My Feelings *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

How I Get Along with Others *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

About School *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

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Annex III: Table 1 - Exerpt from Cortellis RIR of oncologic medicinal products approved between November 2016 and March 2022

Active Ingredient	Name	Application Number	TA	Indication(s)	PROs (eg. QoL, symtom) yes/no	PRO in SmPC section	Reason if not in SmPC	CT name	Product Type	Application/ Submission Type	Registration Status	Pediatric Use	Company	Submission Date	CHMP Opinion Date	EC Opinion Date
amivantamab	RYBREVANT	EMEA/H/C/005454	Cancer	RYBREVANT as monotherapy is indicated for treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based therapy.	no	na			Biologic	Complete	Approved	No	Janssen-Cilag International NV	23-Dez-2020	14-Okt-2021	09-Dez-2021
zanubrutinib	BRUKINSA	EMEA/H/C/004978 Rev.1	Cancer	BRUKINSA as monotherapy is indicated for the treatment of adult patients with Waldenströms macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.	no	na			Chemical	Complete	Approved	No	BeiGene Ireland Ltd.	28-Mai-2020	16-Sep-2021	22-Nov-2021
sacituzumab govitecan	TRODELVY	EMEA/H/C/005182	Cancer	TRODELVY as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease.	Quality of life, assessed using the EORTC QLQ-C-30; sec endpoint	no, EPAR only	interpretation of PRO data are hampered by the open-label study design and therefore not included in the SmPC	IMMU-132-05 (ASCENT)	Chemical	Complete	Approved	No	Gilead Sciences Ireland UC	03-Mrz-2021	14-Okt-2021	22-Nov-2021
pralsetinib	GAVRETO	EMEA/H/C/005413 Rev 1	Cancer	GAVRETO is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer	Quality of life, assessed using ?; exploratory objective	no, EPAR only	... important uncertainties that need to be addressed about efficacy in terms of longer follow-up of duration of response and, more importantly, confirmation of an effect on important	?	Chemical	Complete	Approved	No	Roche Registration GmbH	30-Apr-2020	16-Sep-2021	18-Nov-2021

				(NSCLC) not previously treated with a RET inhibitor.			clinical endpoints like PFS, overall survival, or health-related quality of life, and to better characterise the effect in distinct subgroups...									
ripretinib	QINLOCK	EMEA/H/C/005614 Rev 1	Cancer	QINLOCK is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.	no	na			Chemical	Complete	Approved	No	Deciphera Pharmaceuticals (Netherlands) BV	12-Sep-2020	16-Sep-2021	18-Nov-2021
idecabtagene vicleucel	ABECMA	EMEA/H/C/004662 Rev 2	Cancer	ABECMA is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.	PRO (HRQL): EORTC QLQ-C-30 + EORTC QLQ-MY20 (evaluable; sec endpoint) -> potential improvement in quality of life	no, EPAR only	It is acknowledged that patients who achieve a durable response to ide-cel are expected to obtain a significant treatment-free interval that potentially might be accompanied with improvement in quality of life. However, the claim that ide-cel also offers a major contribution to patient care over other approved therapies is currently not considered supported by the available HRQoL data from the pivotal study MM-001. Hence, this argument cannot be used to further support significant benefit of ide-cel in MM. Since no data for comparison of HRQoL in RRMM patient treated with standard of care is provided, contextualisation of the HRQoL data based on this single arm study is limited	MM-001	Biologic	Complete	Approved	No	Bristol-Myers Squibb Pharma EEIG	30-Apr-2020	24-Jun-2021	18-Aug-2021

azacitidine	ONUREG	EMEA/H/C/004761 Rev 1	Cancer	ONUREG is indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT).	HRQoL; sec endpoint (evaluable --> FACIT-Fatigue scale and EQ-5D-3L))	yes, 5.1 HRQoL was similar between Onureg treatment and placebo arms, with no clinically meaningful deterioration over time.		CC-486-AML-001	Chemical	Complete	Approved	No	Bristol-Myers Squibb Pharma EEIG	30-Apr-2020	22-Apr-2021	17-Jun-2021
duvelisib	COPIKTRA	EMEA/H/C/005381 Rev 1	Cancer	COPIKTRA monotherapy is indicated for the treatment of adult patients with: - Relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least two prior therapies. - Follicular lymphoma (FL) that is refractory to at least two prior systemic therapies.	HRQoL; exploratory objective	no, EPAR only		IPI-145-07 (DUO trial)	Chemical	Complete	Approved	No	Secura Bio Limited	25-Nov-2019	25-Mrz-2021	19-Mai-2021

bevacizumab	ABEVMY	EMEA/H/C/005327 Rev.2	Cancer	- ABEVMY in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum. - ABEVMY evmy in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. For further information as to human epidermal growth factor receptor 2 (HER2) status. - ABEVMY in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with ABEVMY in combination with capecitabine. For further information as to HER2 status. - ABEVMY, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous	no	na			Biologic	Complete	Approved	No	Mylan IRE Healthcare Ltd	20-Feb-2020	25-Feb-2021	21-Apr-2021

				cell histology. - ABEVMY, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations - ABEVMY in combination with interferon alfa-2a is indicated for first line treatment of adult patients with advanced and/or metastatic renal cell cancer. - ABEVMY, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics [FIGO] stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer - ABEVMY, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents. - ABEVMY in combination with paclitaxel, topotecan, or pegylated liposomal												

				doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor– targeted agents - ABEVMY, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix												

dostarlimab	JEMPERLI	EMEA/H/C/005204 Rev 2	Cancer	JEMPERLI is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.	yes, secondary objective, the EQ-5D-5L and EORTC QLQ-C30 were used to assess cancer-specific health-related quality of life	no, EPAR only	not described but seems to be not evaluable	4010-01-001 (GARNET), a multicentre, open-label study with expansion cohorts designed to assess the safety, tolerability, PK, PD, and clinical activity of dostarlimab in patients with recurrent or advanced solid tumours who experienced disease progression on or after treatment with available anticancer therapies	Biologic	Complete	Approved	No	GlaxoSmith Kline (Ireland) Limited	06-Mrz-2020	25-Feb-2021	21-Apr-2021
selinexor	NEXPOVIO	EMEA/H/C/005127 Rev. 1	Cancer	NEXPOVIO is indicated in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.	yes, QoL as secondary endpoint	no, EPAR only	lack of a comparative study to confirm an effect on OS, PFS, and health-related quality of life in the claimed indication.; ... In addition, some quantitation of the improvement of the quality of life of patients would have to be provided to further discuss the argument of major contribution to patient care...	Ph 2b (KCP-330-012 "STORM"), Ph2 (KCP-330- 010 SIRRT)	Chemical	Complete	Approved	No	Karyopharm Europe GmbH	09-Jan-2019	28-Jan-2021	26-Mrz-2021

pemigatinib	PEMAZYRE	EMEA/H/C/005266 Rev.2	Cancer	PEMAZYRE monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.	yes, QoL as exploratory objective (EORTC QLQ-C30 and EORTC QLQ-BIL21)	no, EPAR only	Mean and median changes from baseline in EORTC QLQ-C30 and QLQ-BIL21 scores were variable, and no consistent trends were observed --> inconclusive because interpretation of QoL data from uncontrolled trials is mostly not informative; planned 1st line study may help address some of these uncertainties and should include a robust assessment of health-related quality of life.	Ph 2: FIGHT-202 (INCB 54828-202)	Chemical	Complete	Approved	No	Incyte Biosciences Distribution BV	21-Nov-2019	25-Feb-2021	26-Mrz-2021
selpercatinib	RETSEVMO	EMEA/H/C/005375 Rev 2	Cancer	RETSEVMO as monotherapy is indicated for the treatment of adults with: - advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy - advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib. RETSEVMO as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.	yes, collection of patient-reported outcomes (PROs) data to explore disease-related symptoms and health-related quality of life (HRQoL) as exploratory objective	no, EPAR only	Quality of life decreased (Change to ECOG 3 or 4 at any time during treatment)?	Ph 1/2: LIBRETTO-001, LOXO-RET-17001	Chemical	Complete	Approved	Yes	Eli Lilly Nederland BV	20-Dez-2019	10-Dez-2020	11-Feb-2021

tucatinib	TUKYSA	EMEA/H/C/005263 Rev.2	Cancer	TUKYSA is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens.	yes, secondary objective (exploratory): assess HRQoL and health economics based on subject health status collected using the EQ-5D -5L instrument and health care resources utilised in patient care	no, EPAR only	PRO-data concerning hospitalisations and ER visits show no clinically meaningful differences between the treatment arms. Moreover, HRQoL scales measuring anxiety/depression, mobility, pain/discomfort, self-care, and usual activities were done in a subset of the ITT population (n=330) and did not show any meaningful differences, suggesting that tucatinib treatment do not have a detrimental effect on health-related quality of life. Data on the HRQoL has been removed from the SmPC, since there are no formal type I error control.	HER2CLIMB	Chemical	Complete	Approved	No	Seagen BV	09-Jan-2020	10-Dez-2020	11-Feb-2021
trastuzumab deruxtecan	ENHERTU	EMEA/H/C/005124 Rev 3	Cancer	ENHERTU as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.	no	na			Biologic	Complete	Approved	No	Daiichi Sankyo Europe GmbH	22-Mai-2020	10-Dez-2020	18-Jan-2021
tagraxofusp	ELZONRIS	EMEA/H/C/005031 Rev 3	Cancer	ELZONRIS is indicated as monotherapy for the first-line treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).	no	na			Biologic	Complete	Approved	No	Stemline Therapeutics BV	07-Jan-2019	12-Nov-2020	07-Jan-2021

pertuzumab ; trastuzumab	PHESGO	EMEA/H/C/005386 Rev.3	Cancer	PHESGO is indicated for: Early breast cancer (EBC) - PHESGO is indicated for use in combination with chemotherapy in: - the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence - the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence Metastatic breast cancer (MBC) - PHESGO is indicated for use in combination with docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.	yes, 2 secondary endpoint included the assessment of patient-reported global health status, role and physical function, and treatment symptoms using the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires; No statistically significant differences were found between the two treatment groups in Health Related Quality of Life as assessed by FACT-B TOI-PFB scores.	yes, see section 5.1 of SmPC : 1 regarding the APHINITY trial and 1 regarding the CLEOPATRA trial (	na	2 Ph 3 trials: APHINITY (BO25126); CLEOPATRA (WO20698)	Biologic	Fixed combination	Approved	No	Roche Registration GmbH	09-Jan-2020	12-Nov-2020	21-Dez-2020

autologous anti-CD19-transduced CD3+ cells	TECARTUS	EMEA/H/C/005102	Cancer	TECARTUS is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Brutons tyrosine kinase(BTK) inhibitor.	yes, but not mentioned if as secondary endpoint: QoL (EQ-5D questionaire)	no, EPAR only	quality of life data has been collected with the EQ-5D questionnaire throughout the trial. While very welcome on a principle level, interpretation is hampered by lack of control and an open label design	ZUMA 2, an ongoing, uncontrolled open-label, multicentre trial with two treatment cohorts	Biologic	Complete	Approved	No	Kite Pharma EU BV	09-Jan-2020	15-Okt-2020	14-Dez-2020
acalabrutinib	CALQUENCE	EMEA/H/C/005299 Rev.3	Cancer	CALQUENCE as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL). CALQUENCE as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.	yes, as secondary endpoint: PROs by FACIT-Fatigue; as exploratory endpoint: PROs by EORTC QLQ-C30 and EQ-5D-5L	no, EPAR only		Study ASCEND (ACE-CL -309) A Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia	Chemical	Complete	Approved	No	AstraZeneca AB	14-Okt-2019	23-Jul-2020	05-Nov-2020
avapritinib	AYVAKYT	EMEA/H/C/005208 Rev 2	Cancer	AYVAKYT is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation			BLU-285-1303 Ongoing	92 centers/ 17 countries	Efficacy, Safety, PK, and QOL	Phase 3, multi-center, open-label, randomized study of avapritinib vs regorafenib	Approved	No	Blueprint Medicines (Netherlands) BV	01-Jul-2019	23-Jul-2020	24-Sep-2020

belantamab mafodotin	BLENREP	EMEA/H/C/004935 Rev 3	Cancer	BLENREP is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy	National Eye Institute Visual Function Questionnaire (EI VFQ-25) --> PRO-CTCAE (planned in the upcomming PhIII study to receive regular MA (at the moment only conditional MA)	no, EPAR only	not yet performed	DREAMM-3: Phase III Study of Single Agent BLENREP versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) (DREAMM-3)	Biologic	Complete	Approved	No	GlaxoSmith Kline (Ireland) Limited	18-Dez-2019	23-Jul-2020	25-Aug-2020
entrectinib	ROZLYTREK	EMEA/H/C/004936 Rev.2	Cancer	- ROZLYTREK as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, - who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and - who have not received a prior NTRK inhibitor - who have no satisfactory treatment options. - ROZLYTREK as monotherapy is indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously	PROs: QLQ-C30 and the QLQ-LC13 questionnaire 23	no, EPAR only	A trend toward symptoms improvement since cycle 2 is suggested in this subset. An apparent declining in cognitive functioning within the first cycles is of concern, due to the Cognitive Disorders reported in clinical trials with entrectinib	STARTRK-2 study	Chemical	Complete	Approved	Yes	Roche Registration GmbH	07-Jan-2019	28-Mai-2020	31-Jul-2020

				treated with ROS1 inhibitors.												
alpelisib	PIQRAY	EMEA/H/C/004804 Rev.5	Cancer	PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy.	**sec. endpoint:** Time to definitive deterioration defined as an increase in ECOG PS by at least one category from the Baseline score or death due to any cause; change from baseline and time to 10% deterioration in global health status/QoL score of the EORTC QLQ-C30. **Exploratory endpoints**: PROs for HRQoL analysed over time based on theEQ-5D-5L, and BPI-SF.	no, EPAR only	No indication of a detrimental effect on ECOG PS or Global Health Status with alpelisib was observed either. This was also confirmed with recent updated data; however, since the safety profile is considered to have unblinded the investigators, the PRO data could be biased and should not be included in the SmPC. Currently, no important clinical effect has been observed in term of other important endpoints like OS (86% information fraction) and HR-QoL.	Study CBYL719C2301 (SOLAR-1)	Chemical	Complete	Approved	No	Novartis Europharm Ltd.	19-Dez-2018	28-Mai-2020	27-Jul-2020

glasdegib	DAURISMO	EMEA/H/C/004878 Rev.3	Cancer	DAURISMO is indicated, in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy	no	na			Chemical	Complete	Approved	No	Pfizer Europe MA EEIG	29-Apr-2019	30-Apr-2020	26-Jun-2020
isatuximab	SARCLISA	EMEA/H/C/004977 Rev.4	Cancer	SARCLISA is indicated: - in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy. - in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy	yes, as exploratory endpoints, PROs were performed with patient-reported outcome assessments evaluable for C30, MY20, and EQ 5D-5L	no, EPAR only	Health related quality of life was largely maintained during the treatment period as measured by the EORTC QLQ-C30 global health status/quality of life (GHS QoL) score. **no clear or consistent patterns** were observed on the MY20 body image, future perspective, disease symptoms, and side effects of treatment scales/items. No clear or consistent patterns were observed on the on the EQ 5D 5L HSUV and EQ 5D-5L VAS; Several PROs were performed including the disease-specific EORTC QLQ-Myeloma module (MY20). However, **interpretation of PROs in an open label study should be interpreted with caution.** Compliance for all PROs was good. Only grouped averages were provided which had high standard deviation on each datapoint thus further hampering interpretation. Nevertheless it is noted that the median and mean (and SD) are very similar between the treatment groups and remain constant in time, except towards the end of the period (> 22 cycles) when only few patients are at risk. So it	Study EFC14335 – ICARIA; Study EFC15246 (IKEMA)	Biologic	Complete	Approved	No	Sanofi Aventis Groupe	30-Apr-2019	26-Mrz-2020	30-Mai-2020

							seems that there are no differences in health related quality of life between the study arms, and that thus adding I to Kd does not seem to negatively affect quality of life.									
darolutamide	NUBEQA	EMEA/H/C/004790 Rev 3	Cancer	NUBEQA is indicated for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease	yes, exploratory endpoints/objectives: Health-related QoL using FACT-P questionnaire, prostate cancer-specific subscale of the FACT-P questionnaire and generic EQ-5D-3L questionnaire	yes, PRO as evaluated by Brief Pain Inventory-Short Form questionnaire (table in section 5.1: time to pain progression was significantly reduced -> only one parameter out of 3 questionaires in the CTs was incorporated)	For the PRO analyses, statistical tests were performed with a 2-sided type I error of 5%.; reasons for the non-inclusion: Evaluating the QoL is crucial because of patient's good performance status prior to receiving treatment. QoL was not impaired and the delay of time to deterioration in post hoc analysis could be translated as an improvement in patients QoL compared to placebo.Overall, the data presented for the secondary and additional exploratory objectives while encouraging, are too immature to draw any firm conclusions.	Ph3 trial ARAMIS 17712; supportive studies: Phase 1 and 2 studies in the metastatic prostate cancer setting: ARADES 17829, ARADES EXT 18035 and ARAFOR 1783	Chemical	Complete	Approved	No	Bayer AG	07-Mrz-2019	30-Jan-2020	27-Mrz-2020

polatuzumab vedotin	POLIVY	EMEA/H/C/004870 Rev 3	Cancer	POLIVY in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.	yes, PRO (as secondary objective) based on TINAS scores (Evaluate peripheral neuropathy (PN) symptom severity and interference on daily functioning and better understand treatment impact, tolerability and reversibility, as measured by the Therapy-Induced Neuropathy Assessment Scale (TINAS) v1.0)	no, EPAR only	PRO for peripheral neuropathy (PN) was evaluated based on TINAS scores.Missing baseline information was 20.8% in phase Ib and 29.4% in phase II.Less than 50% of patients filled the questionnaire; participation decreased further over time and less than 25% of the few compliant patients continued this assessment after week 29 in the pola+BR, DLBCL arm.No significant change from baseline was identified from pooled pola+BR/BG data in the weekly tables. However, once presented in linear plots, mean TINAS scores appear higher in pola containing arms in DLBCL, vs BR arm whereas comparatively, BR scores remain flat in the linear slots; Patient reports outcome (PRO) for peripheral neuropathy was evaluated based on TINAS scores. Due to programming issues quality of these data was limited	Ph 1b/2 study GO29365	Biologic	Complete	Approved	No	Roche Registration GmbH	20-Dez-2018	14-Nov-2019	16-Jan-2020

gilteritinib	XOSPATA	EMEA/H/C/004752 Rev.2	Cancer	XOSPATA is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation.	yes, Exploratory endpoints : Patient reported outcomes (PRO)The change from baseline in BFI fatigue score, FACIT-Dys-SF and functional limitations subscales scores, FACT-Leu total score and dizziness and mouth sore subscales scores; median EQ-5D-5LVAS change from baseline score; median utility change from baseline score. For each of the 5 EQ-5D-5L dimension scores, the	no, EPAR only	The change from baseline in BFI fatigue score, FACIT-Dys-SF and functional limitations subscales scores, FACT-Leu total score and dizziness and mouth sore subscales scores for cycle 2, day 1 were similar in the gilteritinib arm compared with the salvage chemotherapy arm. The median EQ-5D-5LVAS change from baseline score was 0 for the gilteritinib arm and -3.0 for the salvage chemotherapy arm at cycle 2, day 1. The median utility change from baseline score was 0 for the gilteritinib arm and 0.1 for the salvage chemotherapy arm at cycle 2, day 1. For each of the 5 EQ-5D-5L dimension scores, the majority of patients in both treatment arms reported no problem (score of 1) at baseline and at cycle 2, day 1	phase 3 open-label, multicentre, randomized study of gilteritinibversus salvage chemotherapy in patients with R/RAMLwith FLT3 mutation (ADMIRAL Study/2215-CL-0301)	Chemical	Complete	Approved	No	Astellas Pharma Europe BV	07-Feb-2019	19-Sep-2019	24-Okt-2019

					majority of patients in both treatment arms reported no problem (score of 1) at baseline and at cycle 2, day 1											
larotrectinib	VITRAKVI	EMEA/H/C/004919 Rev.5	Cancer	VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, - who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and - who have no satisfactory treatment options.	yes, PRO) data on HRQoL, exploratory; instruments used were EORTC QLQ-C30, EQ-5D-5L, PedsQL (in several age-appropriate versions), and Wong-Baker FACES Pain Rating Scale (FACES)	no, EPAR only	The interpretation of PROs from single-arm open-label studies is generally difficult, due to the non-blinded study design's effect on the patients' experience and the lack of comparator. In the present case, also lack of formal hypothesis testing and the missing data preclude the acceptance of any HRQoL claims in the SmPC. (It is noted that the Applicant considers that most of the patients without measurements in Study 15002 were missing due to administrative reasons.)	studies 15002 (Phase 2 basket) and 15003 (Paediatric Phase 1/2).	Chemical	Complete	Approved	Yes	Bayer AG	15-Jun-2018	25-Jul-2019	19-Sep-2019

cemiplimab	LIBTAYO	EMEA/H/C/004844 Rev.11	Cancer	LIBTAYO is indicated for: Cutaneous Squamous Cell Carcinoma: - LIBTAYO as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation. Basal Cell Carcinoma: - LIBTAYO as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI). Non-Small Cell Lung Cancer: - LIBTAYO as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have: - locally advanced NSCLC who are not candidates for definitive chemoradiation, or - metastatic NSCLC.	yes, PRO as secondary endpoint (To assess the impact of cemiplimab on quality of life using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)); EORTC QLQ Lung Cancer 13 (LC13); Skindex-16	yes (outcome from study 1540, that lead to first approval), .change in scores in PROs on the EORTC QLQ-C30). --> in section 5.1 als Nebensatz erwähnt	regarding study 1624: The results on quality of life measures are impacted by decreasing sample sizes and consequently very large standard deviations at the later time points. Notable differences between the treatment groups include a significant worsening of alopecia and peripheral neuropathy with chemotherapy, which is entirely in line with its known adverse effect profile	Study R2810-ONC-1624 (Study 1624) is a phase III, open-label, randomised, multicentre trial designed to compare the efficacy and safety of cemiplimab monotherapy vs. platinum doublet chemotherapy in patients with locally advanced or metastatic NSCLC as first line treatmen	Biologic	Complete	Approved	No	Regeneron Ireland DAC	06-Mrz-2018	26-Apr-2019	28-Jun-2019

talazoparib	TALZENNA	EMEA/H/C/004674 Rev.6	Cancer	TALZENNA is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.	yes, PRO were assessed as an exploratory efficacy endpoint using the EORTC QLQ-C30 and EORTC QLQ-BR23 at baseline, Day 1 of each cycle, and at the end of treatment.	no, EPAR only	A statistically significant overall change from baseline favouring talazoparib arm compared with PCT arm was observed for the **symptoms** of fatigue, pain, insomnia, appetite loss, systemic side effects, breast and arm symptoms. Notwithstanding these results, the reliability of the PRO results are hampered by the open label study design, the high proportion of censoring / missing data, the lack of a SAP with type I error control and lack of compliance with HRQoL questionnaires. Therefore, HRQoL data are not considered interpretable	EMBRACA (673-301) a Phase III, Open-Label, Randomized, Parallel, 2-Arm, Multi-Centre Study of Talazoparib (BMN 673) Versus Physician's Choice in Germline BRCA Mutation Subjects With Locally Advanced and/or Metastatic Breast Cancer, Who Have Received Prior Chemotherapy Regimens for Metastatic Disease	Chemical	Complete	Approved	No	Pfizer Europe MA EEIG	27-Apr-2018	26-Apr-2019	20-Jun-2019
lorlatinib	LORVIQUA	EMEA/H/C/004646 Rev.8	Cancer	LORVIQUA as monotherapy is indicated for the treatment of adult patients with anaplastic lymphomakinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with anALK inhibitor. LORVIQUA as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease	yes, PROs based on EORTC QLQ C30 (Version 3.0) and its lung cancer module, QLQ LC13 as secondary objective (exploratory endpoint)	no, EPAR only	Descriptive statistics for absolute scores and change from baseline of the EORTC QLQ-C30 and QLQ-LC13 multiple-item and single-item scale scores. The majority of patients had either improved (42.7%) or stable (39.6%) scores in global QoL during treatment (including all cycles). --> Overall, PRO results is considered to reflect clinical benefit of lorlatinib and no obvious detrimental effect on QoL was observed	Study of PF-06463922 (an ALK Tyrosine Kinase Inhibitor) in Patients With Advanced Non-Small Cell Lung Cancer Harbouring Specific Molecular Alterations (study B7461001)– Phase 2 part	Chemical	Complete	Approved	No	Pfizer Europe MA EEIG	09-Jan-2018	28-Feb-2019	06-Mai-2019

				has progressed after: - alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or - crizotinib and at least one other ALK TKI.												
dacomitinib	VIZIMPRO	EMEA/H/C/004779 Rev.2	Cancer	VIZIMPRO, as monotherapy, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor eceptor (EGFR) activating mutations.	yes, PROs as secondary endpoint; key secondary objective: To compare the PROs of HRQoL and disease/treatment-related symptoms between the 2 treatment arms; To compare the PRO of health status between the 2 treatment arms;	no, EPAR only	PRO questionnaires were completed by more than 90% of patients for almost all cycles. Regarding PROs in the overall population, no differences were observed in time to deterioration between treatment arms. Improvements in most ofthe symptoms were reported in both treatment arms. In the dacomitinib arm, there was no statistically significant change from baseline observed for overall global QoL. In the gefitinib arm, a statistically significant improvement was seen in change from baselines scores (p<0.0001), but did not reach the 10-point threshold of being clinically meaningful. A statistically significant difference in global quality of life was observed between the two treatment groups, favouring gefitinib (P=0.0002). In any case, PRO are considered of limited value considering the open label design of the clinical trial	ARCHER 1050: A Randomized, Open-Label, Phase 3, efficacy and safety study of dacomitinib (PF-00299804) versus gefitinib for the first line treatment of locally advanced or metastatic non-small cell lung cancer in subjects with epidermal growth factor receptor (EGFR) activating mutation(s)	Chemical	Complete	Approved	No	Pfizer Europe MA EEIG	09-Feb-2018	31-Jan-2019	02-Apr-2019

naldemedine	RIZMOIC	EMEA/H/C/004256 Rev.6	Cancer	RIZMOIC is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative	yes, Change form baseline in overall and each domain for patient assessment of constipation symptom/quality of life questionnaires (PAC-SYM/QOL) as exploratory endpoint and secondary efficacy endpoint	no, EPAR only		V9231 and V9232; Trial V9235 is entitled "A randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3 study to evaluate the long-term safety of naldemedine for the treatment of opioid-induced constipation in subjects with non-malignant chronic pain receiving opioid therapy".	Chemical	Complete	Approved	No	Shionogi BV	01-Mrz-2017	13-Dez-2018	18-Feb-2019

ropeginterferon alfa-2b	BESREMI	EMEA/H/C/004128 Rev.2	Cancer	BESREMI is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly.	yes, Quality of Life (EQ-5D) as secondary endpoint; change in QoL (EQ-5D-3L) from baseline over time up to last patient visit.	no, EPAR only		PROUD-PV: open-label, randomized, controlled, parallel-group, non-inferiority study comparing the efficacy and safety of ropeginterferon alfa-2b over hydroxyurea over 12 months; CONTINUATION-PV [2012-005259-18] trial: open-label, multicenter, phase IIIb study assessing the long-term efficacy and safety of ropeginterferon alfa-2b in patients with Polycythemia Vera who participated in the PROUD-PV Study. planned as a follow on study to provide long-term evaluation of ropeginterferon alfa-2b in patients with PV who received …	Biologic	Complete	Approved	No	AOP Orphan Pharmaceuticals GmbH	02-Feb-2017	13-Dez-2018	15-Feb-2019

apalutamide	ERLEADA	EMEA/H/C/004452 Rev.6	Cancer	ERLEADA is indicated: - in adult men for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease. - in adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).	yes, Change from baseline over time in each of the subscales of FACT-P, EQ-5D-5L VAS (QoL), BPI-SF interference subscale and BFI: PRO data for the BPI-SF and BFI were collected as other endpoints for seven days at baseline and every cycle through the end of treatment. The FACT-P and EQ-5D-5L were completed for one day (the last day of the 7 days the BPI-SF and BFI were collected) every	no, EPAR only	Patient-reported outcome results indicated that there was **no detriment to overall health-related quality of life with the addition of apalutamide to ADT.** Similar mean changes from baseline or median time to worsening in the FACT-P were observed in the 2 treatment arms. For nearly all time points, **no differences between apalutamide and placebo were observed in change from baseline across the EQ-5D index or VAS.**However, the Applicant failed to provide the information of improvement of HRQoL in patient in the apalutamide arm. For use of apalutamide in these clinical settings for nonmetastatic cancer, it seems to be important supporting finding that should be analysed and improvement clearly showed. After requesting, the Applicant provided an additional information on differences in HRQoL for patients in apalutamide versus placebo arms. Although the Applicant claims that "There was little to no change observed around the median onset of hypertension, rash, and fatigue compared with baseline across the FACT-P total score and subscales. For all selected TEAEs, the HRQoL scores were similar throughout the TEAE period compared with baseline regardless of treatment arm", the **absence of proper statistical analysis**	ARN-509-003 (SPARTAN): A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of Apalutamide compared with placebo in subjects with high risk Non-Metastatic (M0) Castration-Resistant Prostate Cancer.	Chemical	Complete	Approved	No	Janssen Cilag International NV	08-Feb-2018	15-Nov-2018	14-Jan-2019

					cycle from baseline to Cycle 7, and then every 2 months thereafter until end of treatment. All PROs were collected, in the same way, during the Follow-up Phase at Months 4, 8 and 12.		**providing differences between arms using appropriate tests gives no information for making such a conclusion**. For example, in the Table E8 provided by the Applicant, it can be clearly seen that more selected adverse events (AEs) occur in the apalutamide arm in comparison with placebo. The A**pplicant did not performed analysis of statistical significance providing tables of per cent of distribution of AEs between groups. That makes the proper conclusion on statistical difference impossible.** However, even looking on raw data, the higher prevalence of AEs in apalutamide arm can be mentioned.Furthermore, the Applicant provided the information on participants' QoL with and without AEs for each AE and for each one of the 29 cycles of the study individually. There is still a **lack of statistical information of overall changes in QoL in participants with and without AEs.** The huge amount of information on different parameters of QoL during each one of study cycles, including answers of participants on each one of the study questions, does not allow to perform proper conclusion on differences between study arms									

brigatinib	ALUNBRIG	EMEA/H/C/004248 Rev.7	Cancer	ALUNBRIG is indicated as monotherapy - For the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor. - For the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.	yes, Global health status/quality of life (QoL) and other HRQoL domains were assessed as change in score of the EORTC QLQ C30 (version 3.0) questionnaire. Change in symptoms of lung cancer was evaluated as time to deterioration in dyspnea as assessed by the EORTC lung cancer module, QLQ-LC13 (version 3.0) as secondary endpoint	no, EPAR only	PRO data have been presented and results indicate no detrimental effect of brigatinib (no difference between tretament groiups). However, these data should be interpreted with caution as there was no blinding of the study treatment and biascannot be ruled out. Moreover, the type I error was neither controlled for the multiple secondary endpoints (of which PRO is number 9) nor the multiple symptoms being assessed with the PRO tools.	Study AP26113-13-201: A Randomized Phase 2 Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib; study 301: Phase 3, Randomized Study in TKI-Naïve ALK+ NSCLC	Chemical	Complete	Approved	No	Takeda Pharma AS	03-Feb-2017	20-Sep-2018	22-Nov-2018

mogamulizumab	POTELIGEO	EMEA/H/C/004232 Rev.3	Cancer	POTELIGEO is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sezary syndrome (SS) who have received at least one prior systemic therapy.	yes, QoL (Changes from baseline in Skindex-29, FACT-G, and EQ-5D-3L at other time points- Changes from baseline in Pruritus Evaluation (Likert scale & Itchy QoL) as secondary endpoints	no, EPAR only	The open-label design is also hindering interpretation of the QoL PRO data for demonstration of benefit, although it may be reassuring that some of the parameters showed improvement in QoL. Further, as MF and SS patients can suffer tremendously from symptoms related to their disease (eg, pain, pruritus, fatigue, sleep disturbance) and the social stigma of having obvious unsightly skin lesions, having a durable response could also be interpreted as beneficial to the patient.	Study 0761-010: a Phase 3, randomized, open-label, active controlled study to study evaluate efficacy and safety of mogamulizumab in patients with previously treated CTCL	Biologic	Complete	Approved	No	Kyowa Kirin Holdings BV	06-Okt-2017	20-Sep-2018	22-Nov-2018
abemaciclib	VERZENIOS	EMEA/H/C/004302 Rev 7	Cancer	VERZENIOS is indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy, In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.	yes, Health Outcome /Quality of Life Measures as secondary endpoint	no, EPAR only	Global health status evaluated by EORTC QLQ-C30 questionnaire appeared similar between arms and stable throughout the treatment. The higher difference in global health status is seen at cycle 2 in favour of abemaciclib (possibly due to early diarrhoea), then the curves are overlapping.	trial MONARCH 1 and MONARCH 2: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative …	Chemical	Complete	Approved	No	Eli Lilly Nederland BV	27-Jul-2017	26-Jul-2018	26-Sep-2018

durvalumab	IMFINZI	EMEA/H/C/004771 Rev.9	Cancer	- IMFINZI as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on greater than or equal to 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. - IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).	yes, PRO variables (ORTC QLQ-C30, EORTC QLQ-LC13 and (EQ-5D-5L) Q8W during the treatment period and Q12W until confirmed objective disease	yes, see section 5.1 of SmPC: PROs Patient-reported symptoms, function and HRQoL were collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). The LC13 and C30 were assessed at baseline, every 4 weeks for the first 8 weeks, followed by every 8 weeks until completion of the treatment period or discontinuation of IMFINZI due to toxicity or	na, but in assessment report: Time to deterioration results suggest that delay of patient-reported symptoms was more pronounced in the experimental arm. However, the open-label nature of the study and reduced compliance in the questionnaires challenges definitive conclusions in PRO data.	PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentre study in 713 patients with locally advanced, unresectable NSCLC	Biologic	Complete	Approved	No	AstraZeneca AB	01-Sep-2017	26-Jul-2018	21-Sep-2018

						disease progression. Compliance was similar between the IMFINZI and placebo treatment groups (83% vs. 85.1% overall of evaluable forms completed). At baseline, no differences in patient-reported symptoms, function and HRQoL were observed between IMFINZIand placebo groups. Throughout the duration of the study to Week 48, […]											

binimetinib	MEKTOVI	EMEA/H/C/004579 Rev 6	Cancer	MEKTOVI is indicated in combination with encorafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	yes, PRO measures of 3 HRQoL (FACT-M, QLQ-C30, EQ-5D-5L) as secondary endpoint (time to definitive 10% deterioration in the FACT-M melanoma subscale and global health status score of the EORTC QLQ-C30; change from baseline in the FACT-M melanoma subscale, EQ-5D-5L, and global health status score of the EORTC QLQ-C30; change from baseline in the	yes, see section 5.1: Quality of Life (QoL) (cut-off date: 19 May 2016) The Functional Assessment of Cancer Therapy-Melanoma (FACT-M), the European Organisation for Research and Treatment of Cancer's core quality of life questionnaire (EORTC QLQ-C30) and the EuroQoL-5 Dimension-5 Level examination (EQ-5D-5L) were used to explore patient-	na	COLUMBUS: A 2-part phase III randomized, open label, multicenter study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma	Biologic	Complete	Approved	No	Pierre Fabre Medicament	28-Jul-2017	26-Jul-2018	20-Sep-2018

					other EORTC QLQ-C30 subscales.) The FACT-M melanoma subscale, index score of EQ-5D-5L and global health status/QoL score of the EORTC QLQ-C30 were identified as primary PRO variables of interest. Physical functioning, emotional functioning and social functioning scale scores of the EORTC QLQ-C30 were considered as secondary	reported outcomes (PRO) measures of health-related Quality of Life, functioning, melanoma symptoms, and treatment-related adverse reaction.											

encorafenib	BRAFTOVI	EMEA/H/C/004580 Rev.9	Cancer	Encorafenib is indicated: - in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation - in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer(CRC) with a BRAF V600E mutation, who have received prior systemic therapy.	yes, see above MEKTOVI + PGIC in a ranodmiezd Phase III trial	yes, see above MEKTOVI	na	see above + a Randomized Phase 3	Chemical	Complete	Approved	No	Pierre Fabre Medicament	28-Jul-2017	26-Jul-2018	19-Sep-2018
cytarabine ; daunorubicin	VYXEOS ; VYXEOS LIPOSOMAL	EMEA/H/C/004282 Rev.5	Cancer	VYXEOS LIPOSOMAL is indicated for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).	no	no		na	Chemical	Fixed combination	Approved	No	Jazz Pharmaceuticals Ireland Ltd.	02-Nov-2017	28-Jun-2018	23-Aug-2018
axicabtagene ciloleucel	YESCARTA	EMEA/H/C/004480 Rev 7	Cancer	YESCARTA is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.	no, Assessment of Quality-of-life data was not included within endpoints of ZUMA-1 phase 2; however, outcomes based on EQ-5D are being investigated in cohort 3 of ZUMA-1	na		ZUMA-7 trial is expected to provide further information as evaluation of the treatment on patient reported outcomes (PROs) and quality of life (QoL) compared to SOC is part of the secondary study objectives (see RMP	Biologic	Complete	Approved	No	Kite Pharma EU BV	29-Jul-2017	28-Jun-2018	23-Aug-2018

tisagenlecleucel	KYMRIAH	EMEA/H/C/004090 Rev.9	Cancer	KYMRIAH is indicated for the treatment of: - Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse. - Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy	yes, but not described as primary nor secondary endpoint: adults: QoL assessments were performed with FACT-Lym questionnaire (disease specific) and the SF-36 questionnaire. The QoL instruments were completed by 76 patients (94%) at baseline and 34 patients (42%) at Month 3. Among the 34 patients who reported PRO at 3 months, The PRO results indicate that there is a small increase in QoL	not for adults, but for children: HRQoL was evaluated by PedsQL and EQ-5D questionnaires completed by patients aged 8years and above (n=61). Among patients responding (n=51), the mean(SD) change from baseline in the PedsQLtotal score was 13.1 (13.45) at month3, 15.4 (16.81) at month6 and 25.0 (19.09) at month12, and the mean (SD) change	The PRO results indicate that there is a small increase in QoL after 3 months for patients who responded in terms of ORR to treatment. However,the design of the phase 2 study (uncontrolled, non-randomized, open-label) makes it difficult to conclude ifany clinically relevant symptomatic improvement	study C2201[1] (adults with DLBCL); study C2202 (children < 18 with ALL)	Biologic	Complete	Approved	Yes	Novartis Europharm Ltd.	02-Nov-2017	28-Jun-2018	22-Aug-2018

					after 3 months for patients who responded in terms of ORR to treatment ; children: Secondary endpoint-QoL, HRQoL was evaluated by PedsQL and EQ-5D questionnaires completed by patients aged 8years and above: Patients in the B2202 reported improvements in HRQoL outcomes at 3 and 6 months among responders to therapy. Tisagenlecleucel infusion led to a decrease	from baseline in the EQ-5D VAS score was 16.0 (16.45) at month3, 15.3 (18.33) at month6 and 21.7 (17.14) at month12, indicating overall clinically meaningful improvement in HRQoL following Kymriah infusion.									

					in the severity of problems as measured by the emotional, social, physical, and psychosocial health subscales as well as mobility, self-care, usual activities, pain/discomfort, anxiety/depression as assessed via the EQ-5D questionnaire. Thus, results indicate a meaningful improvement in patients responding to treatment.											

rucaparib	RUBRACA	EMEA/H/C/004272 Rev.7	Cancer	- RUBRACA is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. - RUBRACA is indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.	yes, (PRO), secondary endpoints : both the disease-related symptoms – physical (DRS-P) subscale of National Comprehensive CancerNetwork (NCCN) Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index (FOSI-18) and the complete [total score]; exploratory endpoints : PRO utilizing Euro-Quality of Life 5D (EQ-5D),	no, EPAR only	**There was no statistically significant difference in median time to a 4-point worsening** in the DRS-P subscale for rucaparib compared to placebo-treated patients in the tBRCA population (median time 1.9 vs. 4.2 months, respectively, p= 0.2893) **with the trend favouring placebo**. Therefore, for all subsequent endpoints nominal p values only are presented. The median time to worsening in the DRS-P subscale was shorter for rucaparib compared to placebo in the HRD population (1.9 vs. 4.8 months; HR 1.642, p=0.0024 in favour of placebo) and in the ITT population (1.9 vs 6.4 months, HR 1.817, p<0.0001 in favour of placebo). The **change from baseline in FOSI-18 DRS-P over time is difficult to interpret across the different populations**. The mean change from baseline, although small (<5), is **consistently negative for rucaparib** and is more fluctuant for placebo. The confidence intervals gradually increase over time due to the **limited number of patients remaining on treatment** (in all populations by Cycle 11 there are 8 patients assessed in the placebo arm, with no patients in the non tBRCA LOH unknown population).... consistent with the early toxicity of Rubraca.Selection of the time from randomization to	Study CO-338-014 (ARIEL3)	Chemical	Complete	Approved	No	Clovis Oncology Ireland Ltd	01-Nov-2016	22-Mrz-2018	23-Mai-2018

							a 4-point reduction in the FOSI-18 disease-related symptom score physical (DRS-P) subscale as the first **secondary endpoint in the step down procedure was not carefully planned, given that the patients had all responded to previous treatment at baseline and the first assessment was at 4 weeks when patients would likely experience the toxicity of rucaparib without symptoms of progression on placebo. Poor data quality or chance may have contributed to the results. Therefore, presentation of these data in the SmPC is not recommended.**									
gemtuzumab ozogamicin	MYLOTARG	EMEA/H/C/004204 Rev. 8	Cancer	MYLOTARG is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL)	no	no	na	na	Biologic	Complete	Approved	Yes	Pfizer Europe MA EEIG	01-Dez-2016	22-Feb-2018	19-Apr-2018
ocrelizumab	OCREVUS	EMEA/H/C/004043 Rev 6	Cancer	OCREVUS is indicated for the treatment of adult patients with RMS with active disease defined by clinical or imaging features; OCREVUS is indicated for the treatment of adult patients with early PPMS in terms of disease duration and level of disability, and with imaging features […]	yes, Health Related Quality of Life: SF-36 PCS as secondary endpoint	no	The remainder of the secondary endpoints were met in the hierarchical testing except for change from Baseline in SF-36 PCS Score but MMRM was used to handle missingness. As MMRM was not regarded as being sufficiently conservative method in dealing with missingness, ... statistical significance testing for SF-36 PCS was negative; [...]	WA21093, ITT Population; Study WA25046 (main study in PPMS)	Biologic	Complete	Approved	No	Roche Registration GmbH	25-Apr-2016	09-Nov-2017	08-Jan-2018

niraparib	ZEJULA	EMEA/H/C/004249 Rev.15	Cancer	ZEJULA is indicated: - as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. - as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy	yes, PRO (secondary endpoints): - FOSI (PRO): Validated, 8-item measure of symptom response to treatment for ovarian cancer •EQ-5D-5L (PRO): Validated general preference-based health related QOL instrument in oncology, as well as other conditions, and is intended to compliment other QOL instruments •Neuropathy Questionnaire: As of the prior 7 days, patients provided a	yes, Patient-reported outcome (PRO) data from validated survey tools (FOSI and EQ-5D) indicate that niraparib-treated patients reported no difference from placebo in measures associated with quality of life (QoL)	na	PR-30-5011-C (ENGOT-OV16) (NOVA study); Study PR-30-5017-C (PRIMA)	Chemical	Complete	Approved	No	GlaxoSmith Kline (Ireland) Limited	04-Okt-2016	14-Sep-2017	16-Nov-2017

					response on a scale of 0 (not at all) to 4 (very much), to "My feet feel numb or have prickling/ tingling feelings," "My hands feel numb or have prickling/ tingling feelings" + in a second study: •EORTC-QLQ-C30: validated, 30-item, health-related QoL instrument developed to assess health outcomes from a wide variety of interventions on a common scale •EORTC-QLQ-OV28: assesses ovarian											

					cancer subjects' abdominal/ gastrointestinal symptoms, other chemotherapy side-effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment and sexual functioning											

padeliporfin	TOOKAD	EMEA/H/C/004182 Rev 4	Cancer	TOOKAD is indicated as monotherapy for adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy greater than or equal to 10 years and: - Clinical stage T1c or T2a, - Gleason Score less than or equal to 6, based on high-resolution biopsy strategies, - PSA less than or equal to 10 ng/mL, - 3 positive cancer cores with a maximum cancer core length of 5 mm in any one core or 1-2 positive cancer cores with greater than or equal to 50 % cancer involvement in any one core or a PSA density greater than or equal to 0.15 ng/mL/cm 3.	yes, QoL data (EO5D-5L	no, EPAR only	applicant presented the various facets of the patient reported outcomes for the active surveillance arm split by whether the patient remained on active surveillance or underwent radical therapy (data not shown). There was no difference in quality of life (QoL) reflected by the EQ5D between those that underwent radical treatment (RP) and those that remained on active surveillance. This is in line with QoL at Month 24 that was not influenced by Tookad treatment. However, the applicant states that the QoL criteria evaluated by the EQ5D questionnaire are not known to be impacted by radical treatment for prostate cancer. Therefore, it is not clear why the questionnaire was originally chosen for use in the study. With regards to the IPSS score those that underwent RP had consistently better scores than those that did not. This could be due to chance or the fact that patients with better scores were selected for radical therapy. It is difficult to compare these scores with the scores post Tookad VTP as most radical therapy was undertaken after 12 months so the only follow up available was at 24 months. However, by this time point any decline in IPSS had resolved; there was no difference between patients that underwent […]	?	Chemical	Complete	Approved	No	Steba Biotech SA	07-Jan-2016	14-Sep-2017	10-Nov-2017

lutetium 177 Lu oxodotreotide	LUTATHERA	EMEA/H/C/004123 Rev 5	Cancer	LUTATHERA is indicated for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP NETs) in adults.	yes, QoL: The impact of treatment on health related QoL was assessed using the EORTC QLQ-C30 and the EORTC QLQ-G.I.NET21 questionnaires, which was filled in by the patient prior to knowing the CT scan/MRI result. Changes from baseline were assessed every 12±1 week from the first treatment date until the PFS primary end-point, then until week 72 after randomization, unless	yes, Secondary endpoints included objective response rate (ORR), overall survival (OS), time to tumour progression (TTP), safety and tolerability of the medicinal product and quality of life (QoL)	na	NETTER-1: A multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with 177Lu-Oxodotreotide to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours; Phase I/II Study: Erasmus MC Clinical Study (supportive study)	Chemical	Complete	Approved	No	Advanced Accelerator Applications	26-Apr-2016	20-Jul-2017	26-Sep-2017

					the patient progressed or died. The EORTC QLQ-C30 is a questionnairedeveloped to assess the quality of life of cancer patients. EORTC QLQ-G.I.NET21 questionnaire is a supplemental module for carcinoid/ neuroendocrine tumours. (assessing disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality)											

atezolizumab	TECENTRIQ	EMEA/H/C/004143 Rev.16	Cancer	TECENTRIQ is indicated for: Urothelial carcinoma: TECENTRIQ as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC): - after prior platinum-containing chemotherapy, or - who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression greater than or equal to 5%. Non-small cell lung cancer: - TECENTRIQ, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, TECENTRIQ, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies. - TECENTRIQ, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC. - TECENTRIQ as monotherapy is indicated for the first-line treatment of adult patients with	yes, PROs as secondary endpoint EORTC QLQ-LC13 and QLQ-C30 and SILC	yes, Prolonged time to deterioration of patient-reported pain in chest as measured by the EORTC QLQ-LC13 was observed with atezolizumab compared to docetaxel (HR of 0.71, 95% CI: 0.49, 1.05; median not reached in either arm). The time to deterioration in other lung cancer symptoms (i.e. cough, dyspnoea, and arm/shoulder pain) as measured by the EORTC QLQ-	PRO questionnaire completion rates were high at baseline for the EORTC QLQ-LC13 and QLQ-C30 (>80%), but low for the SILC (50-60%) for both arms.		Biologic	Complete	Approved	No	Roche Registration GmbH	20-Apr-2016	20-Jul-2017	20-Sep-2017

				metastatic NSCLC whose tumours have a PD-L1 expression greater than or equal to 50% tumour cells (TC) or greater than or equal to 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC - TECENTRIQ as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving TECENTRIQ. Small cell lung cancer - TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). Triple-negative breast cancer - […]		LC13 was similar between atezolizumab and docetaxel. These results should be interpreted with caution due to the openlabel design of the study.										

avelumab	BAVENCIO	EMEA/H/C/004338 Rev. 10	Cancer	- BAVENCIO is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC). - BAVENCIO in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).	yes, PRO: Patient reported bladder cancer symptom, functioning, global quality of life (QOL), and Time to Deterioration (TTD) using the NCCN-FACT FBlSI-18; and health status using the EQ-5D -5L as secondary endpoints /PRO endpoints	no, EPAR only	The results for the PRO NCCN/FACT Bladder Symptom Index (NFB1SI-18) and EQ-5D -5L) do not imply that addition of avelumab to BSC conferred a detrimental effect on the quality of life of patients. These results should however be interpreted with caution due to the open label study design and imputation of answers in the analyses for NFB1SI-18. The results from the EQ-5D -5L form do not suggest that the avelumab addition to BSC conferred a detrimental effect of the quality of life for the patients. However, due to the open-label study design the results are open to patient bias, conferring a degree of uncertainty.	Study B9991001A Phase 3, multicentre, multinational, randomized, open-label, parallel-arm study of avelumab (MSB0010718C) plus BSC versus BSC alone as a maintenance treatment in patients with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum-containing chemotherapy	Biologic	Complete	Approved	No	Merck Europe BV	06-Okt-2016	20-Jul-2017	18-Sep-2017
midostaurin	RYDAPT	EMEA/H/C/004095 Rev.6	Cancer	RYDAPT is indicated: - in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by RYDAPT single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive. - as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis	yes, (PRO) / QoL measurements as exploratory endpoints (Memorial Symptom Assessment Scale (MSAS) and the Short Form health survey	no, EPAR only	Patient-reported outcomes were measured as an exploratory endpoint. Updated analyses showed that response according to Valent criteria was associated with superior PROs and provided additional insight into the clinical relevance of the PRO data. The analyses remain, however, considered exploratory, in view of the single-arm open-label nature of the study and of limited value in guiding treatment decisions	Study D2201 was a single arm, phase II, open-label study to determine the efficacy of 100 mg twice daily oral dosing of midostaurin administered to patients with aggressive systemic mastocytosis or mast cell leukaemia	Chemical	Complete	Approved	No	Novartis Europharm Ltd.	22-Jul-2016	20-Jul-2017	18-Sep-2017

				(ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).	(SF-12) questionnaires were used to assess PROs)			with or without an AHNMD								
telotristat	XERMELO	EMEA/H/C/003937 Rev.12	Cancer	XERMELO is indicated for the treatment of carcinoid syndrome diarrhoea in combination with somatostatin analogue (SSA) therapy in adults inadequately controlled by SSA therapy.	yes, QoL as secondary objective (EORTC QLQ-C30 and GI.NET21 scores); … secondary objective was to evaluate changes in patients' quality of life (QOL). Efficacy assessments included patient-reported QOL measures (QLQ-C30, GI.NET21) and subjective global assessment of symptoms associated with CS.	yes, … The secondary objective of this study was to evaluate changes in patients' quality of life (QOL) through week 84. QOL was generally stable over the course of the study	Quality of Life: EORTC QLQ-C30 and GI.NET21 ScoresTreatment differences for mean changes for the EORTC QLQ-C30 scores for Global Health Status/QOL and the individual domain scores of physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea and vomiting, pain, dyspnoea, appetite loss, constipation, and financial difficulties averaged across all visits were not statistically significant.Effects were only seen for the individual subscales of insomnia and diarrhoea. .... The mean change from baseline in the EORTC GI.NET21 scores averaged across all visits for the individual subscales endocrine, GI symptoms, treatment, social function, muscle/bone pain symptom, sexual function, information/communication function, and body image were not statistically significant.The subscale of disease-related worries showed fewer disease-related worries for placebo compared to telotristat etiprate, […]	Study LX1606-301: A Phase 3, randomized, placebo-controlled, parallel-group, multicenter, double-blind study to evaluate the efficacy and safety of telotristat etiprate (LX1606) in patients with carcinoid syndrome not adequately controlled by somatostatin analog (SSA) Therapy; Study LX302	Chemical	Complete	Approved	No	Ipsen Pharma	22-Jun-2016	20-Jul-2017	17-Sep-2017

tivozanib	FOTIVDA	EMEA/H/C/004131 Rev 7	Cancer	FOTIVDA is indicated for the first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC.	yes, QoL as secondary endpoints :• FACT-G: a 27-question instrument to measure general quality of life in 4 domains - physical, social/family, emotional, and functional well-being. • FKSI-DRS: a 9-question abbreviated version of the FKSI designed to specifically measure kidney cancer-related symptoms.• EQ-5D	no, EPAR only	Patient reported outcomes were generally comparable between treatment groups. For this un-blinded study, only limited conclusions can be drawn from patient-reported outcomes.	Study AV-951-09-301	Chemical	Complete	Approved	No	EUSA Pharma (Netherlands) BV	29-Feb-2016	22-Jun-2017	24-Aug-2017

ribociclib	KISQALI	EMEA/H/C/004213 Rev.8	Cancer	KISQALI is indicated: - For the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. - In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.	yes, PRO as secondary endpoint: global QoL scale score of the EORTC QLQ-C30 was the primary PRO variable of interest. Physical functioning, emotional functioning and social functioning sub-scale scores of the EORTC QLQ-C30, the breast cancer symptoms scale of the EORTC QLQ-BR23, and the VAS of the EQ-5D-5L were secondary PRO variables of interest;	The global health status/QoL data showed no relevant difference between the Kisqali plus letrozole arm and the placebo plus letrozole arm.	To evaluate patient-reported outcomes (PROs) for health-related quality of life (QoL) in the two treatment arms was described as a secondary objective in the two clinical studies, with no further specification. The protocols describe the analyses as well as others to be performed, but state that no formal statistical tests will be performed on PRO data and hence that no multiplicity adjustment will be applied. Based on this, the PRO data has not been considered important in determining the benefit/risk for the product in the claimed indication. .... Results of the SAP-specified QoL analyses of change from baseline and time to definitive 10% deterioration in the global health status score indicated a slight benefit for letrozole control arm during treatment, whereas deterioration was somewhat faster in this arm, likely reflecting disease progression. Overall, the global health status/QoL data showed no relevant difference between the Kisqali plus letrozole arm and the placebo plus letrozole arm (see SmPC section 5.1)	Study E2301 – MONALEESA-7 (Phase II); F2301Phase III	Chemical	Complete	Approved	No	Novartis Europharm Ltd.	05-Sep-2016	22-Jun-2017	22-Aug-2017

					as exploratory endpoint: the Work Productivity and Activity Impairment-General Health was used to explore the impact of study treatments on work productivity/productivity loss											

inotuzumab ozogamicin	BESPONSA	EMEA/H/C/004119 Rev.8	Cancer	BESPONSA is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphiachromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatmentwith at least 1 tyrosine kinase inhibitor (TKI).	yes, PRO as secondary endpoint: PROs: Health-related quality of life and health status as measured by the European Organization for Research and Treatment of Cancer questionnaire (EORTC QLQ-C30, and the EuroQol-5 Dimension (EQ-5D) questionnaire were collected	yes, For PROs, most functioning and symptom scores were in favour of BESPONSA compared to Investigator's choice of chemotherapy. PROs measured using the EORTC QLQ-C30, were significantly better for BESPONSA by estimated mean postbaseline scores (BESPONSA and Investigator's choice of chemotherapy, respectively) for role functioning (64.7 versus 53.4, improve	EORTC QLQ-C30:For patient-reported outcomes, most functioning and symptoms scores were in favour of BESPONSA compared to Investigator's choice of chemotherapy. For patient-reported outcomes measured using the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTCQLQ-C30), BESPONSA resulted in significantly better estimated mean postbaseline scores (BESPONSA and Investigator's choice of chemotherapy, respectively) in role functioning (64.7 versus 53.4; p=0.0065), physical functioning (75.0 versus 68.1; p=0.0139), social functioning (68.1 versus 59.8; p=0.0336), and appetite loss (17.6versus 26.3; p=0.0193) compared to Investigator's choice of chemotherapy. Although not reaching statistical significance, BESPONSA resulted in better estimated mean postbaseline scores (BESPONSA and Investigator's choice of chemotherapy, respectively) in global health status/Quality of Life (QoL) (62.1 versus 57.8; p=0.1572), cognitive functioning (85.3 versus 82.5; p=0.1904), dyspnoea (14.7 versus 19.4; p=0.1281), diarrhoea (5.9 versus 8.9; p=0.1534), fatigue (35.0 versus 39.4; p=0.1789), nausea and	Study B1931022	Chemical	Complete	Approved	No	Pfizer Europe MA EEIG	14-Apr-2016	21-Apr-2017	28-Jun-2017

						ment grade small), physical functioning (75.0 versus 68.1, improvement grade small), social functioning (68.1 versus 59.8, improvement grade medium), and appetite loss (17.6 versus 26.3, improvement grade small) compared to Investigator's choice of chemotherapy. There was a trend in favour of BESPONSA, improvement grade small, for estimated mean postbase	vomiting (8.7 versus 10.4; p=0.4578), financial difficulties (29.5 versus 32.0; p=0.4915), insomnia (25.4 versus 27.1; p=0.6207), and pain (21.3 versus 22.0; p=0.8428). Although not reaching statistical significance, BESPONSA resulted in worse estimated mean post-baseline scores (BESPONSA and Investigator's choice of chemotherapy, respectively) in emotional functioning (77.4 versus 79.6; p=0.3307) and constipation (12.1 versus 10.7; p=0.6249) (SmPC section 5.1). EQ-5D Index and EQ-VAS: For patient-reported outcomes measured using the EuroQoL 5 Dimension (EQ-5D) questionnaire, although not reaching statistical significance, BESPONSA resulted in better estimated mean postbaseline scores (BESPONSA and Investigator's choice of chemotherapy, respectively) for the EQ-5D index (0.80 versus 0.76; p=0.1710) and the EQ visual analogue scale (EQ-VAS) (67.1 versus 62.5; p=0.1172) (SmPC section 5.1).									

						line scores (BESPONSA and Investigator's choice, respectively) in global health status/QoL) (62.1 versus 57.8), cognitive functioning (85.3 versus 82.5), dyspnoea (14.7 versus 19.4), diarrhoea (5.9 versus 8.9), fatigue (35.0 versus 39.4). There was a trend in favour of BESPONSA for estimated mean postbaseline scores from the EQ-5D questionnaire,[…]										

fluciclovine 18F	AXUMIN	EMEA/H/C/004197 Rev.14	Cancer	- This medicinal product is for diagnostic use only. - AXUMIN is indicated for Positron Emission Tomography (PET) imaging to detect recurrence of prostate cancer in adult men with a suspected recurrence based on elevated blood prostate specific antigen (PSA) levels after primary curative treatment.	no, diagnostic agent only	no	na	na	Biologic	Complete	Approved	No	Blue Earth Diagnostics Ireland Ltd	04-Dez-2015	23-Mrz-2017	21-Mai-2017
dinutuximab beta	DINUTUXIMAB BETA APEIRON	EMEA/H/C/003918	Cancer	DINUTUXIMAB BETA APEIRON is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures. In patients with a history of relapsed;refractory disease and in patients who have not achieved a complete response after first line therapy, Dinutuximab beta Apeiron should be combined with interleukin-2 (IL-2).	see below				Biologic	Complete	Approved	No	Apeiron Biologics AG	06-Mai-2015	23-Mrz-2017	08-Mai-2017

dinutuximab beta	QARZIBA	EMEA/H/C/003918 Rev 10	Cancer	- QARZIBA is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures; - In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, QARZIBA should be combined with interleukin-2 (IL-2).	no	no	na	na	Biologic	Complete	Approved	Yes	EUSA Pharma (Netherlands) BV	06-Mai-2015	23-Mrz-2017	08-Mai-2017

daratumumab	DARZALEX	EMEA/H/C/004077 Rev 11	Cancer	DARZALEX is indicated: in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant; as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy; in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy;	yes, Functional Status and Well-being: Health-related quality of life (HRQoL), symptoms, functional status and well-being will be assessed using 2 PRO measures, the EORTC-QLQ-C30 and the EQ-5D-5L as secondary endpoint	no, EPAR only	Patient-reported Outcomes Functional status and well-being were assessed using PRO measures, the EORTC-QLQ-C30 and the EQ-5D-5L. Compliance was comparable between treatment groups and baseline scores on all subscales were comparable between treatment Groups. The PRO results indicated no statistically significant difference between DVd and Vd in change from baseline or median time to improvement or worsening in the Global Health Status/QOL subscale of the EORTC-QLQ-C30.For nearly all timepoints, no statistically significant differences between DVd and Vd were observed in change from baseline in the EQ-5D-5L Utility Score or EQ-5D-5L VAS and no statistically significant differences were observed between DVd and Vd in median time to worsening or improvement in the Utility Score or VAS (data not shown).	Study MMY3006; Study MMY 3007	Biologic	Complete	Approved	No	Janssen Cilag International NV	09-Sep-2015	01-Apr-2016	28-Apr-2017
alectinib	ALECENSA	EMEA/H/C/004164 Rev.9	Cancer	- ALECENSA as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). - ALECENSA as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.	yes, HRQoL as secondary endpoint using the EORTC QLQ – C30 and – LC13	no, EPAR only	In terms of HQoL/PRO results, baseline compliance for both treatment arms was moderate (~65 % completing their baseline assessment). PRO results are suggestive of increased tolerability for alectinib compared to crizotinib including commonly reported treatment-related symptoms (e.g. GI-related)although the open-label design should be taken into consideration	NP28761: Phase I/II Study of the ALK Inhibitor alectinib in patients with ALK-rearranged NSCLC previously treated with Crizotinib; JO28928 (J-ALEX)	Chemical	Complete	Approved	No	Roche Registration GmbH	08-Sep-2015	15-Dez-2016	16-Feb-2017

venetoclax	VENCLYXTO	EMEA/H/C/004106 Rev.12	Cancer	VENCLYXTO in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL). VENCLYXTO in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. VENCLYXTO monotherapy is indicated for the treatment of CLL: - in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or - in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor. VENCLYXTO in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.	yes, Fatigue improvement and PRO assessments as secondary endpoints; PRO: Treatment-related symptoms by M.D. symptom inventory (MDASi), EORTC QLQ-C30 and module CLL16. Change from baseline QKQ-C30. Interference of disease symptoms and treatment related symptoms on QoL with MDASI as exploratory endpoints	no, EPAR only	No PRO improvements were observed in the experimental arm	Study M16-043 – venetoclax + LDAC vs placebo + LDAC; Study MURANO	Chemical	Complete	Approved	No	AbbVie Deutschland GmbH & Co. KG	13-Nov-2015	13-Okt-2016	04-Dez-2016

ixazomib	NINLARO	EMEA/H/C/003844 Rev.12	Cancer	NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.	yes, Comparison of change in global health status between baseline and each post-baseline assessment, as measured by the global health scale, functioning, and symptoms of the EORTC QLQ-C30 and MY-20 as secondary endpoint	yes, Quality of life as assessed by global health scores (EORTC QLQ-C30 and MY-20) was maintained during treatment and was similar in both treatment regimens in the Phase 3 study (C16010).	Although no improvement in the quality of life, including pain response, was observed, the addition of ixazomib to the LenDex was not associated with a decrease in QoL scores. The latter observation is considered relevant, since tolerability is usually one of the main issues with triple-drug combinations in relapsedMM.	Phase 3 study (C16010).	Chemical	Complete	Approved	No	Takeda Pharma AS	30-Jul-2015	15-Sep-2016	21-Nov-2016
palbociclib	IBRANCE	EMEA/H/C/003853 Rev.13	Cancer	IBRANCE is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer: - in combination with an aromatase inhibitor - in combination with fulvestrant in women who have received prior endocrine therapy In pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist.	yes, patient-reported symptom as QoL assessed using the EORTC QLQ-C-30 and -BR23 (breast cancer module)	yes, 5.1	na	PALOMA-3	Chemical	Complete	Approved	No	Pfizer Europe MA EEIG	30-Jul-2015	15-Sep-2016	09-Nov-2016

olaratumab	LARTRUVO	EMEA/H/C/004216	Cancer	LARTRUVO is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin.	yes, PRO endpoints such as global Quality of Life (QOL), functioning, breast symptoms, time to deterioration (TTD) in pain, EQ-5D index and general health status as secondary endpoints; EuroQol (EQ 5D) Score as key secondary endpoint!	yes, 5.1: … Secondary efficacy endpoints included […] and change in QoL; Patient-reported symptoms were assessed using the EORTC-QLQ-C30 and its Breast Cancer Module (EORTC QLQ-BR23). A total of 335 patients in the palbociclib plus fulvestrant arm and 166 patients in the fulvestrant only arm completed the questionnaire at baseline and at least 1 postbaseline visit.Time-to-	Patient-Reported OutcomesThe PRO evaluable population was defined as a subset of ITT patients, who had completed a baseline and at least one post–baseline PRO assessment prior to end of study treatment. No update was provided for PROs. Patient–reported outcomes were investigated using the instruments, EORTC QLQ-C30, QLQC30 and EQ-5D. These are considered standard. However, no primary objective and no strategy to protect the type-1 error rational are put forward in the study protocol or SAP. Furthermore, the results indicated emotional functioning as a driver for the overall health related QoL, why the plausibility of results may also be questioned. Unblinding due to the effects of palbociclib on the bone marrow may clearly be present and the results potentially associated with hopes with regard to the benefit of the experimental compound. The claims concerning Global Health Status/QoL were therefore not accepted.Time to Deterioration in PainA time to event analysis was prespecified for pain. Time to Deterioration (TTD) in pain was defined as time from baseline to first occurrence of an increase of at least 10 points in pain on study. This is an established cut-off in QLQ-C30.	Study 1023 (PALOMA-3), Study 1008/PALOMA-2	Biologic	Complete	Withdrawn post approval	No	Eli Lilly Nederland	29-Jan-2016	15-Sep-2016	09-Nov-2016

						Deterioration was prespecified as time between baseline and first occurrence of ≥ 10 points increase from baseline in pain symptom scores. Addition of palbociclib to fulvestrant resulted in a symptom benefit by significantly delaying time-to-deterioration in pain symptom compared with placebo plus fulvestrant (median 8.0 months versus 2.8 months;										

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Weiler, Datum: 06.09.2022

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Unterschrift Dr. Stefanie Pektor