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Indication extensions as part of lifecycle management of cancer medicines: comparison of EMA-approved medicines with and without extensions

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Abstract

Introduction: During the last decade, extensions of therapeutic indications have been one of the most common methods to extend the lifecycle of a medical product in the post-authorization phase and to increase the use and sales of medicines. The aim of this study was to increase comprehensive understanding of the lifecycle of cancer medicines and especially the role of extensions in comparison to first indications.

Materials and methods: We identified all new outpatient cancer medicines approved by the European Medicines Agency (EMA) between 2010 and 2020 and the extensions to their indications. We compared general study design characteristics from the European public assessment reports (EPAR) using critical appraisal tools and clinical added value (CAV) assessments.

Results: We identified altogether 55 new outpatient cancer medicines, 31 of which had one or more extension(s) of indication and 24 were without extension of indication. In total, there were 57 extensions. The most common extension of indication was a change in the treatment line (35%). Compared to first indications, the overall quality of studies supporting extensions was better in terms of study designs. The proportion of medicines providing CAV was higher in extensions compared to first indication of medicines with and without extensions.

Conclusions: Based on different measures and perspectives, we found that extensions of indications are an important part of the strategic plannning regarding cancer medicines. Our findings also suggest that the clinical value of cancer medicines increases with extensions.

Keywords: Cancer medicines, Europe, Study quality, Clinical trials, Clinical added value, Extensions, Level of evidence

Strengths and limitations

- This study provided a comprehensive understanding of the role of extensions of indication in the lifecycle of new cancer medicines by using different measures and perspectives, which is a major strength of this study.
- Cancer medicines without extensions received their MA towards the end of the data set. The median time for a medicine to receive an extension of indication was 2 years and 1 month. However, it is possible that some medicines will receive extensions later.
- We examined EPARs, i.e., official MA documents, and not original research publications. Our interpretation of quality may be affected by the poor reporting of, for example, the design and allocation concealment in many EPARs.
- In the assessments of CAV, we could also have used other indicators, for example ESMO-Magnitude of Clinical Benefit Scale, but in that case some medicines may not have been assessed.
- Our study still provides an integrated understanding of the role of extensions of indications from the European perspective.

Introduction

Cancer medicines have been one of the key medicinal innovations in last decade. In the current niche-buster pharmaceutical market, different methods are used to extend the lifecycle of medicines [1], [2]. Extensions of therapeutic indications are one of the most common methods to extend the lifecycle of a medical product in the post-authorization phase and to increase the use and sales of medicines [3], [4], [5], [6]. In Europe, extensions allow the innovator company an additional period of data exclusivity and market protection lasting at least a year [7], [8]. Nowadays, extensions of indications have become more common than the acceptance of new active substances [9], [10].

Marketing authorization (MA) holders aim to get new cancer medicines approved as soon as possible and expanding indications is common [11]. A study on targeted multi-indication cancer medicines found that medicines are first accepted as monotherapies in rare diseases with less mature evidence often based on single-arm studies and surrogate end-points [4]. Extensions of indications are generally targeted to broader populations and based on more mature evidence. It is important to gain a more comprehensive understanding of the role of extensions compared to cancer medicines in general by using different quality assessments.

The quality of research can be assessed using the critical appraisal tools of the Joanna Briggs Institute (JBI) [12]. In addition to the quality of study designs, it is crucial to assess the clinical added value (CAV) of new medicines. Such work is being done, for example, by the Haute Autorité de Santé (HAS) in France, whose CAV assessments are publicly available [13]. CAV takes into account and compares the efficacy and safety of a medicine with existing treatments.

The aim of the study was to increase the understanding of the lifecycle of cancer medicines and the role of extensions of indication in the European context. More specific aims were (i) to describe and compare the new outpatient cancer medicines and their extensions, (ii) to evaluate and compare the evidence at the MA acceptance phase between the following three groups: first indications for multi-indication medicines, extensions, and medicines without extensions, and (iii) to analyze and compare the CAV between these three groups.

Materials and Methods

Data collection

Our study focuses on new cancer medicines that received MA for the first time in 2010–2020 and possible extensions of indication by the end of 2022, in addition to which they are suitable for outpatient care by their administration route (Supplementary Figure 1), i.e., the active substances are targeted to tumor tissue based on

Anatomical Therapeutic Chemical (ATC) codes L01, L02, L04AX02, L04AX04, and L04AX06 [14]. Data were collected from EMA's website and the European public assessment reports (EPARs). The latest data collection took place in June 2023. We categorized the types of extensions of cancer medicines into five categories (Supplementary Table 1) based on a list by the European Commission [15]. In addition to these categories, we added one more: multiple change. We classified new cancer medicines to 10 groups by the target tissue of their first indication (Table 1). We used level 4 ATC groups (chemical subgroup) [16] to estimate the number of new mechanisms of action.

Quality assessment using the Joanna Briggs Institute (JBI) critical appraisal tools

The quality of the main studies from EPARs was assessed by using the JBI Checklist for randomized controlled trials (RCT), Checklist for quasi-experimental studies, and Checklist for systematic reviews [12]. The JBI checklists were selected due to their comprehensibility and because separate checklists were available for different study settings. The checklists for RCT, quasi-experimental studies, and systematic reviews contain 13, 9, and 11 questions, respectively. Each question can be assessed as *yes*, *no*, *unclear* or *not applicable*.

The quality assessments were conducted separately by two researchers (AMR and TK). Any discrepancies were discussed until a consensus was reached. After all the assessments, the questions were divided into four categories by theme in order to summarize the different checklists and their results.

Clinical added value by the assessment of Haute Autorité de Santé (HAS)

HAS is the independent French National Authority for Health that, among others things, assesses applications for reimbursement of new medicines. HAS will assess the actual clinical benefit (ACB) and decides whether to recommend a medicine for reimbursement. For this study, we utilized the publicly available HAS evaluations of CAV scored on a scale of no improvement, minor, moderate, substantial, and major [18]. We classified medicines with no ACB and no evaluation of the medicine or indication by the HAS under the *No improvement* category. It reflects the overall situation where a new medicine adds no clinical value. We collected assessments for the first indications and subsequent extensions of indications in June 2023.

Results

Characteristics of medicines and extensions

We identified altogether 55 new outpatient cancer medicines approved by EMA between 2010 and 2020 (Supplementary Table 2). The most common indications of these medicines were the treatment of hematological malignancies (24%, n = 13), lung cancer (16%, n = 9), and melanoma and basal cell carcinoma (15%, n = 8) (Table 1). More than half (56%, n = 31) of all new cancer medicines had received at least one extension of indication. The remaining medicines (44%, n = 24) had no extensions of indication. Most commonly, extensions (n = 57) involved a new treatment line (35%, n = 20), a new cancer type (30%, n = 17), or a new combination therapy (18%, n = 10).

A majority (77%) of medicines approved for the treatment of hematological malignancies were launched with a new mechanism of action (Table 1), unlike gynecological cancer medicines, for example, which all had the same mechanism of action. The medicine that was the first in a new ATC group often had the highest number of extensions. In our data, the first active substance in the ATC group had the highest number of extensions in 7 out of 21 different ATC groups (33%) during the follow-up period. Furthermore, most extensions came from other than the first active substance in four (19%) ATC groups, and seven (33%) ATC groups had only one active substance. In the remaining groups (14%), all medicines had the same number of extensions. Medicine-specific characteristics are presented in Supplementary Table 2.

Table 1. Characteristics of new outpatient cancer medicines by cancer type.

First indication	Total number of medicines (of all medicines)	Number of medicines		Total number of extensions	Type of extension(s) of indication					New mechanisms of action*
		with extension	without extension		Treatment line	Cancer type	Combination type	Multiple change	Patient type	
Hematological malignancies - leukemia - multiple myeloma - lymphoma - myelofibrosis	13 (24%)	6 (46%)	7 (54%)	14	2	3	6	3	-	10 (77%)
Lung cancer	9 (16%)	7 (78%)	2 (22%)	10	6	-	-	1	3	3 (33%)
Melanoma & basal cell carcinoma	8 (15%)	3 (38%)	5 (63%)	7	2	3	2	-	-	3 (38%)
Breast cancer	6 (11%)	2 (33%)	4 (67%)	2	1	-	1	-	-	4 (67%)
Prostate cancer	4 (7%)	3 (75%)	1 (25%)	6	6	-	-	-	-	2 (50%)
Colorectal or gastric cancer	4 (7%)	4 (100%)	0 (0%)	5	-	5	-	-	-	2 (50%)
Kidney cancer	3 (5%)	1 (33%)	2 (67%)	1	-	1	-	-	-	2 (67%)
Thyroid cancer	3 (5%)	2 (67 %)	1 (33%)	3	-	2	-	-	1	1 (33%)
Gynecological cancers	3 (5%)	3 (100%)	0 (0%)	9	3	3	1	2	-	1 (33%)
Solid tumors	2 (4%)	0 (0%)	2 (100%)	0	-	-	-	-	-	1 (50%)
Total	55 (100%)	31 (56%)	24 (44%)	57 (100%)	20 (35%)	17 (30%)	10 (18%)	6 (11%)	4 (7%)	

* Based on the number of new different chemical, thus 4th levels in the Anatomical Therapeutic Chemical (ATC) classification maintained by WHO [16].

Of the 31 medicines with extensions of indications, 19 had only one and 12 had two or more extensions (Figure 1). The maximum number of extensions was seven (for olaparib). The timeline in Figure 1 shows when the new active substances received their first MA and when their extensions of indication were approved. On average, the first extension of indication was granted 2 years and 7 months after the first MA (min. 7 months; max. 10 years and 10 months; median 2 years and 1 month). The average time between the first and second extension of indication was 2 years and subsequent extensions were granted in less than 2 years, on average.

Study designs and marketing authorizations

In total, 124 main studies were identified and evaluated. In 13 cases, there were two main studies. Most of the main studies supporting the first MA or extensions of indications were phase III studies with randomized controlled study design (80%, Figure 2). Phase I-II non-controlled single-arm trials were a more common study design for the first indication of medicines with extensions (32%) than for other groups (12% and 17%).

Medicines with extensions were more likely to have a conditional MA application than medicines without extensions (26% and 13%, respectively). Most of the main studies utilized surrogate endpoints (such as PFS or ORR) as the main outcome variable (Figure 2). Overall survival (OS) was rarely used as main endpoint and was more common in the studies on medicines without extensions (21%) than in the other groups (12% and 13%).

The majority of all new cancer medicines (85%, n = 47) were indicated for the treatment of advanced or metastatic disease at the time they received their first MA. Treatment of early-stage condition was more common for extensions of indications than for other groups.

Evaluation of evidence

Based on the JBI assessment, the overall quality of the main studies on extensions and medicines without extensions was better than that of the first indications of medicines with extensions (good and unclear in Figure 3). This is explained by the larger proportion of phase III RCTs in the study designs. When only the studies with good assessments of quality are considered, medicines without extensions received the best rating in three out of four categories.

In many studies, details of the randomization and double-blinding were missing. Double-blinding was well-described in up to a third of the studies. However, almost half of all main studies of all medicines did not have a double-blind design (Figure 3). Medicine-specific assessments are presented in Supplementary Tables 2 and 3.

In the assessment of the similarity between the compared groups, less than half of the studies were evaluated to fill the criteria of good quality. The most common reasons for poor quality of studies were crossover between groups, different follow-up times in different populations, and, in some cases, different previous treatments in the compared groups.

Clinical added value

Overall, extensions of indications had the highest scores in CAV assessment (minor and moderate CAV in 63%; Figure 4). In the other two groups, almost the same proportion of medicines had some CAV (52% vs. 50%). Moderate was the highest CAV estimate of dataset, and it should be noted that none of the indications provided substantial or major CAV. In terms of percentages, the highest moderate ratings were to the first indication for medicines with extension of indication (26%). Moderate assessments focused particularly on products for the treatment of prostate cancer, hematological cancers, and melanoma. Medicine-specific assessments are presented in Supplementary Table 2.

Discussion

According to our study, extensions of indications are an important part of the strategic planning regarding cancer medicines. Firstly, the most common category of extensions was a change in the treatment line, i.e., a tendency to push the use of a cancer medicine to an earlier point in the treatment line and, thus, increase the number of potential users and extend the duration of treatment. Secondly, based on the characteristics of study design and JBI evaluation, extensions of indications are based on improved quality of evidence compared to first accepted indications. In addition, according to CAV assessments, extensions add more clinical value than the first indications. Looking at the different measures and perspectives, it appears that extensions of indication are of higher quality than the first indications of evaluated medicines.

Our study is in accordance with previous findings [4], [11], [19] suggesting that new outpatient cancer medicines are brought to market as early as possible and with less comprehensive clinical evidence, which is to be improved in later indication extension studies. This is linked to, for example, the number of conditional MAs and phase I-II studies. For example, it seems that conditional MA is more common for medicines with extensions than for those without them. Furthermore, the overall CAV evaluation was quite similar between first indication of medicines with later extensions and medicines without extensions. Our study provided a more comprehensive understanding of the European cancer medicine selection by considering medicines with and without extensions and by bringing a broader perspective, beyond the consideration of MA research, to the consideration of CAV assessment.

In our study, the most common type of extension was a change in the treatment line. This was seen, for example, in prostate cancer, where androgen receptor signaling inhibitors (ARSI) abiraterone, enzalutamide, and apalutamide were first indicated to castration-resistant prostate cancer and later extended to earlier hormone-sensitive stages of the disease. This was also seen in metastatic lung cancer and ALK tyrosine kinase inhibitors (crizotinib, alectinib, ceritinib, brigatinib, and lorlatinib), all of which were initially indicated as second- or third-line treatment but received extensions to first-line treatment over time. This reflects the fact that cancer medicines often initially enter the later line and move to an earlier stage of treatment with extensions. The second most common type of extension was a new cancer type, which was particularly common for colorectal and gastric cancer medicines. These medicines (tegafur comb., trifluridine and tipiracil, regorafenib and avapritinib) are not targeted to specific signaling pathways (like androgen receptors in prostate cancer or EML4-ALK translocations in lung cancer), which explains the rationale to investigate their potential in cancers of different origin.

In our data, it is common that the first-to-market products with a new mechanism of action have the highest number of extensions. To our knowledge, there are no previous studies on this. The first entrant can be characterized as a trendsetter, and subsequent entrants will, in most cases, have the same indication(s) as the first entrant. A majority (61%) of medicines with extensions had only one extension, while 32% had two or three extensions. There were two exceptions in the data: ibrutinib with six and olaparib with seven extensions. Both products with multiple extensions entered the market with a new

mechanism of action, and medicines that entered the market later with a similar mechanism of action had fewer extensions.

Looking at the research design and the quality of the evidence, it seems that a new mainstream of medicine approval has emerged over the last decade. For example, previous research [20] suggests that the majority of new cancer medicines from 1995 to 2008 had only one indication. This is the opposite of the current situation with medicines with multiple extensions targeted to larger populations. Medicines with extensions of indications are first accepted with lower evidence and lower requirements overall, and later extensions of the same medicine are targeted to larger populations. The current drive is to provide new treatments to patients as quickly as possible. This trend can also have a negative impact on patient care and outcomes. On the other hand, for some medicines, lighter approval criteria are important for the uptake of medicines and, therefore, for patients [21]. More research with a different setting and design is needed on the strategic planning of medicines. Strategic planning is possible, but trends can also be based on the natural evolution of medicines, their research, and treatments. Distinguishing between the two can be difficult. It is also worth considering whether the extension of indication or the first indication becomes the main indication for a medicine, and what impact it has on the number of medicine users and the resulting costs.

Declarations

Ethics approval and consent to participate: Not applicable
Availability of data and materials: All materials are publicly available. EPARS: https://www.ema.europa.eu/en/medicines. Clinical added value assessments: https://www.has-sante.fr/jcms/pprd_2986129/en/home.
Competing interests: The authors declare that they have no competing interests
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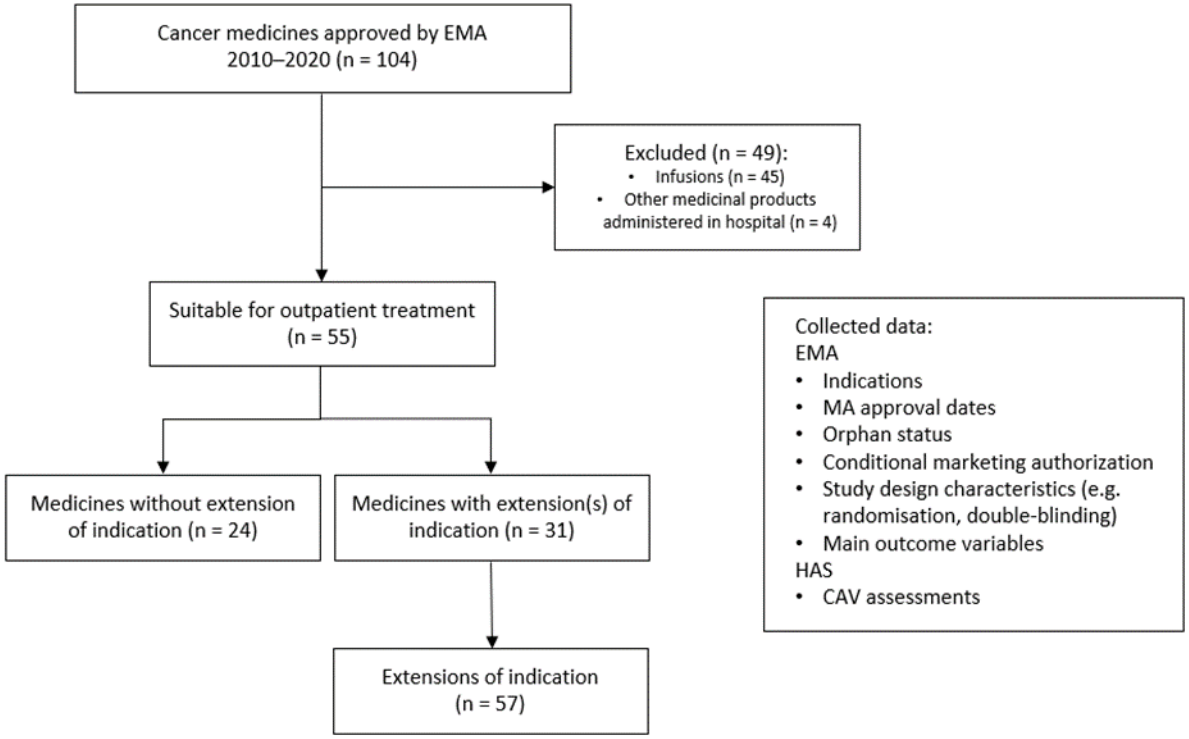
Supplementary figure 1. Flowchart of included medicines and their extensions of indication. Data collected from HAS and EMA documents [13], [17].



EMA= European Medicines Agency, HAS= Haute Autorité de Santé

Supplementary Table 1. The different categories of extensions used in this study [15].

Category of extension	Description of category
Treatment line	The medicine was authorized for a different treatment line or stage of the disease (e.g., the first MA* for metastatic disease and the extension for adjuvant setting).
Cancer type	The medicine was authorized for another cancer type (e.g., the first MA for melanoma and the extension of indication for lung cancer)
Patient type	The medicine was authorized for different patients than previously (e.g., the first MA for certain mutation type and the extension for another mutation type).
Combination type	The medicine was authorized to be used as part of a different combination of medicines (e.g., the first MA only as a monotherapy, the extension as a part of certain combination therapy).
Multiple change	At least two previously introduced categories are met.

*MA=marketing authorization

Supplementary Table 2. Characteristics of cancer medicines. Medicines without extension of indication are marked by purple.

Medicinal product, *active substance*, date	**First indication**	**Conditional marketing authorisation[1]**	**Orphan status[1]**	**Accelerated assessment**	**Additional monitoring**	**Extension(s) of indication according to the type of the extension[2], date**	**HAS**
L01B Antimetabolites							
L01BC Pyrimidine analogues							
Teysuno®, tegafur, gimeracil and oteracil. 14.3.2011	gastric cancer	-	Previously yes, now withdrawn	-	-	1. Cancer type (colorectal cancer), 24.1.2022	Na Insuf.
Lonsurf®, *trifluridine and tipiracil*, 25.4.2016	colorectal cancer	-	-	-	-	1. Cancer type (gastric cancer), 3.9.2019	5 5
L01E Protein kinase inhibitors							

L01EA BCR-ABL tyrosine kinase inhibitors							
Bosulif®, *bosutinib*, 27.3.2013	chronic myelogenous leukaemia	-	Previously yes, now withdrawn	-	-	1. Treatment line, 23.4.2018	5 5
Iclusig®, *ponatinib*, 1.7.2013	leukaemia		Yes	Yes	-	-	5/4/3
L01EB Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors							
Giotrif®, *afatinib*, 25.9.2013	lung cancer	-	-	-	-	1. Patient type (mutation), 31.3.2016	5 5
Tagrisso®, *osimertinib*, 2.2.2016	lung cancer	Previously yes, now full authorisation	-	Yes	Yes	1. Treatment line, 7.6.2018 2. Treatment line + patient type (mutation), 1.2021	5 4 3
Vizimpro®, dacomitinib, 2.4.2019	lung cancer	-	-	-	Yes		5
L01EC B-Raf serine-threonine kinase (BRAF) inhibitors							
Zelboraf®, *vemurafenib*, 17.2.2012	melanoma	-	-	-	-		3
Tafinlar®, *dabrafenib*, 26.8.2013	melanoma	-	-	-	-	1. Combination type, 25.8.2015 2. Cancer type (lung cancer), 29.3.2017 3. Treatment line, 27.8.2018	5 Na 5 3
Braftovi®, *encorafenib*, 20.9.2018	melanoma	-	-	-	Yes	1. Cancer type (colorectal cancer), 2.6.2020	5 3
L01ED Anaplastic lymphoma kinase (ALK) inhibitors							
Xalkori®, *crizotinib*, 23.10.2012	lung cancer	-	-	-	-	1. Treatment line, 23.11.2015 2. Patient type (mutation), 25.8.2016 3. Patient type (adolescents), 28.10.2022	3 4 5 4
Zykadia®, *ceritinib*, 6.5.2015	lung cancer	Previously yes, now full authorisation	-	-	-	1. Treatment line, 23.6.2017	4 4
Alecensa®, *alectinib*, 16.2.2017	lung cancer	-	-	-	-	1. Treatment line, 18.12.2017	4 4
Alunbrig®, *brigatinib*, 22.11.2018	lung cancer	-	-	-	-	1. Treatment line, 1.4.2020	5 4
Lorviqua®, *lorlatinib*, 6.5.2019	lung cancer	Yes	-	-	Yes	1. Treatment line, 27.1.2022	5 4
L01EE Mitogen-activated protein kinase (MEK) inhibitors							
Mekinist®, *trametinib*, 30.6.2014	melanoma	-	-	-	-	1. Combination type, 25.8.2015 2. Cancer type (lung cancer), 27.3.2017 3. Treatment line, 27.8.2018	3 Na 5 3
Cotellic®, *cobimetinib*, 20.11.2015	melanoma	-	-	-		-	3
Mektovi®, *binimetinib*, 20.9.2018	melanoma	-	-	-	Yes	-	5
L01EF Cyclin-dependent kinase (CDK) inhibitors							
Ibrance®, *palbociclib*, 9.11.2016	breast cancer	-	-	-	Yes	-	4
Kisqali®, *ribociclib*, 22.8.2017	breast cancer	-	-	-	Yes	1. Combination type, 17.12.2018	3 4

Verzenios®, *abemaciclib,* 27.9.2018	breast cancer	-	-	-	Yes	1. treatment line, 1.4.2022	5/4 5
L01EH Human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitors							
Nerlynx®, *neratinib,* 31.8.2018	breast cancer	-	-	-	yes	-	Insuf.
L01EJ Janus-associated kinase (JAK) inhibitors							
Jakavi®, *ruxolitinib,* 23.8.2012	myelofibrosis	-	Previously yes, now withdrawn	-	-	1. cancer type (polysytemia vera), 11.3.2015	3 4
L01EK Vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors							
Inlyta®, *axitinib,* 3.9.2012	kidney cancer	-	Previously yes, now withdrawn	-	Yes	-	4
Fotivda®, *tivozanib,* 24.8.2017	kidney cancer	-	-	-	Yes	-	Insuf.
L01EL Bruton's tyrosine kinase (BTK) inhibitors							
Imbruvica®, *ibrutinib,* 27.10.2014	mantle cell lymphoma and chronic lymphocytic leukaemia	-	Previously yes, now withdrawn	-	-	1. cancer type (Walderström's macroglobulinaemia), 3.7.2015 2. treatment line, 26.5.2016 3. combination type, 25.8.2016 4. combination type, 2.8.2019 5. combination type, 28.8.2020 6. combination type, 2.8.2022	3 Na 4 Na Insuf. 3 4
Calquence®, *acalutinib,* 5.11.2020	leukaemia		Previously yes, now withdrawn		Yes	-	Na
L01EM Phosphatidylinositol-3-kinase (Pi3K) inhibitors							
Zydelig®, *Idelalisib,* 18.9.2014	follicular lymphoma and chronic lymphocytic leukaemia	-	-	-	Yes	1. combination type, 19.9.2016 2. combination type, 23.4.2018	5/4 Na Na
Piqray®, *alpelisib,* 27.7.2020	breast cancer	-	-	-	Yes	-	Insuf.
L01EX Other protein kinase inhibitors							
Votrient®, *pazopanib,* 14.6.2010	renal cell carcinoma	Yes	Previously yes, now withdrawn	-	-	1. cancer type (soft-tissue sarcoma), 24.8.2012	5 5
Caprelsa®, *vandetanib,* 16.2.2012	thyroid cancer	Yes	-	-	Yes	1. patient type (paediatric patients), 12.12.2016	4 5
Stivarga®, *regorafenib,* 26.8.2013	colorectal cancer	-	-	-	-	1. cancer type (gastrointestinal stromal tumors), 27.10.2014 2. cancer type (hepatocellular carcinoma), 2.2.2017	5 4 4
Cometriq®, cabozantinib, 21.3.2014	medullary thyroid cancer	-	Yes	-	-	-	4
Lenvima®, *lenvatinib,* 28.5.2015	thyroid cancer	-	Previously yes, now withdrawn	Yes	Yes	1. cancer type (liver cancer), 20.8.2018 2. cancer type (endometrial carcinoma), 26.1.2021	4 Insuf. 3
Vargatef®, *nintedanib,* 21.11.2014	lung carcinoma	-	-	-	-	-	Insuf.
Rydapt®, *midostaurin,* 18.9.2017	acute myeloid leukaemia, mastocytosis	-	Yes	-	Yes	-	4/5
Vitrakvi®, *larotrectinib,* 19.9.2019	solid tumours with NTRK gene fusion	Yes	Previously yes, now withdrawn	-	Yes	-	4

Xospata®, *gilteritinib,* 24.10.2019	acute myeloid leukemia	-	Yes	-	Yes	-	4
Rozlytrek®, *entrectinib,* 31.7.2020	solid tumors with NTRK fusion, lung cancer	Yes	-	-	Yes	-	Insuf.
Ayvakyt®, *avapritinib,* 24.9.2020	gastrointestinal stromal tumours	Yes	Yes	-	Yes	1. cancer type (mastocytosis), 24.3.2022	5 4
L01X Other antineoplastic agents							
L01XG Proteasome inhibitors							
Ninlaro®, *ixazomib,* 21.11.2016	multiple myeloma	yes	yes	-	Yes		5
L01XH Histone deacetylase (HDAC) inhibitors							
Farydak®, *panobinostat,* 28.8.2015	multiple myeloma	-	Yes	-	Yes		5
L01XJ Hedgehog pathway inhibitors							
Erivedge®, *vismodegib,* 12.7.2013	basal cell carcinoma	-	-	-	Yes		4
Odomzo®, *sonidegib,* 14.8.2015	basal cell carcinoma	-	-	-	Yes		4
Daurismo®, *glasdegib,* 26.6.2020	acute myeloid leukaemia		Yes	-	Yes		Na
L01XK Poly (ADP-ribose) polymerase (PARP) inhibitors							
Lynparza®, *olaparib,* 16.12.2014	ovarian, fallopian tube or primary peritoneal cancer	-	Previously yes, now withdrawn	-	-	1. cancer type (breast cancer), 8.4.2019 2. treatment line, 12.6.2019 3. cancer type (pancreatic cancer), 3.7.2020 4. combination type, 3.11.2020 5. cancer type (prostate cancer), 3.11.2020 6. treatment line (breast cancer), 2.8.2022 7. treatment line + combination (prostate cancer), 16.12.2022	4 5 4 5 4 4 3 4
Zejula®, *niraparib,* 16.11.2017	ovarian, fallopian tube or primary peritoneal cancer	-	Yes	-	Yes	1. treatment line, 27.10.2020	4 4
Rubraca®, *rucaparib,* 24.5.2018	ovarian, fallopian tube or primary peritoneal cancer	Yes	Previously yes, now withdrawn	-	Yes	1. treatment line + patient type (mutation), 23.1.2019	Insuf. 4
Talzenna®, *talazoparib,* 20.6.2019	breast cancer	-	-	-	Yes	-	5
L01XX Other antineoplastic agents							
Venclyxto®, *venetoclax,* 5.12.2016	chronic lymphocytic leukaemia	Previously yes, now full authorisation	Previously yes, now withdrawn	-	Yes	1. treatment line + combination type, 29.10.2018 2. treatment line + combination typfe, 9.3.2020 3. cancer type (acute myeloid leukaemia), 22.4.2021	5 4 3 4
L02B Hormone antagonists and related agents							
L02BB Anti-androgens							
Xtandi®, *enzalutamide,* 21.6.2013	prostate cancer	-	-	-	-	1. treatment line, 28.11.2014 2. treatment line, 23.10.2018 3. treatment line, 30.4.2021	3 4 3 3
Erleada®, *apalutamide,* 14.1.2019	prostate cancer	-	-	-	Yes	1. treatment line, 27.1.2020	3 3

Nubeqa®, *darolutamide,* 27.3.2020	prostate cancer	-	-	-	Yes	-	3
L02BX Other hormone antagonists and related agents							
Zytiga®, *abiraterone,* 5.9.2011	prostate cancer	-	-	Yes	-	1. treatment line, 18.12.2012 2. treatment line, 15.11.2017	3 4 3
L04A Immunosuppressants							
L04AX Other immunosuppressants							
Imnovid®, *pomalidomide,* 5.8.2013	multiple myeloma	-	Yes	-	Yes	3. treatment line + new combination, 13.5.2019	5 5

[1] In some stage of the product life cycle

[2]Types of extensions: *Cancer type* = authorised for new cancer type, *Treatment line* = authorised for a different treatment line or for a different stage of the disease, e.g. after a surgery, *Patient type* = authorised for different patients than previously, *Combination type* = authorised to be used as a part of different combination of medicines

HAS= Haute Autorité de Santé

Na= No assessment. HAS has not evaluated the medicine or indication.

Insuf. = The actual clinical benefit is insufficient

3 = moderate clinical added value (CAV), 4 = minor CAV, 5 = no improvement CAV.

Supplementary Table 3. Assessment of cancer medicines with extension of indication by JBI (Joanna Briggs Institute) criteria.

Medicinal product, *active substance*, (ATC-code)						
	Study	**Setting**	**Randomization and concealment of allocation (1–2)**	**Double-blinding (4–6)**	**Similarity of the compared groups (3,7,8)**	**Validity and reliability of the outcome assessment (9-12)**
Lonsurf *Trifluridine and tipiracil* (L01BC59)						
Original MA	TPU-TAS-102-301	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟢	🟢	🟡
1. ext	TAS-102-302	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟡
Bosulif *Bosutinib* (L01EA04)						
Original MA	200-WW	Open, non-controlled, phase I-II	⚫	⚫	⚫	🔴
1. ext	AV001	Randomized, open, active-controlled, phase III	🟡	⚫	🟢	🟢
Giotrif *Afatinib* (L01EB03)						
Original MA	LUX-Lung 3	Randomized, open, active-controlled, phase III	🟡	⚫	🟡	🟢
1. ext	LUX-Lung 8	Randomized, open, active-controlled, phase III	🟡	⚫	🟡	🔴
Tagrisso, *Osimertinib* (L01EB04)						
Original MA	201 & 210	Open, non-controlled, phase I-II (both)	⚫⚫	⚫⚫	⚫⚫	🟡🟡
1. ext	2014-002694-11	Randomized, double-blinded, active-controlled, phase III	🟢	🟢	🔴	🟢
2. ext	D5164C00001/ Adaura	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🔴
Tafinlar *Dabrafenib* (L01EC02)						
Original MA	BRF11368	Randomized, open, active-controlled, phase III	🟡	⚫	🟢	🟢
1. ext	MEK115306	Randomized, double-blinded, active-controlled, phase III	🟢🟡	🟡⚫	🟡🟢	🟢🟢

	MEK116513	Randomized, open, active-controlled, phase III				
2. ext	BRF113928	Open, non-controlled, phase II	●	●	●	●
3. ext	BRF115532	Randomized, double-blinded, placebo-controlled, phase III	●	●	●	●
Braftovi, *Encorafenib* (L01EC03*)*						
Original MA	CMEK162B2301	Randomized, open, active-controlled, phase III	●	●	●	●
1. ext	ARRAY-818-302	Randomized, open, active-controlled, phase III	●	●	●	●
Xalkori, *Crizotinib* (L01ED01)						
Original MA	A8081001	Open, non-controlled, phase I-II	●	●	●	●
1. ext	A8081014	Randomized, open, active-controlled, phase III	●	●	●	●
2. ext	A8081001	Open, non-controlled, phase I-II	●	●	●	●
3.ext	ADVL0912	Open, non-controlled, phase I-II	●	●	●	●
Zykadia, *Ceritinib* (L01ED02)						
Original MA	CLDK378X2101	Open, non-controlled, phase I-II	●	●	●	●
1. ext	ASCEND-4/A2301	Randomized, open, active-controlled, phase III	●	●	●	●
Alecensa *Alectinib* (L01ED03)						
Original MA	NP28761, NP28673	Open, non-controlled, phase I-II Open, non-controlled, phase I-II	●●	●●	●●	●●
1. ext	BO28984	Randomized, open, active-controlled, phase III	●	●	●	●
Alunbrig *Brigatinib* (L01ED04)						
Original MA	AP26113-13-201	Randomized, open, non-controlled, phase II*	●	●	●	●

1. ext	AP26113-13-301	Randomized, open, active-controlled, phase III				
Lorviqua, *Lorlatinib* (L01ED05)						
Original MA	PF-06463922	Open, non-controlled, phase I-II				
1. ext	B7461006	Randomized, open, active-controlled, phase III				
Mekinist, *Trametinib* (L01EE01)						
Original MA	MEK114267	Randomized, open, active-controlled, phase III				
1. ext	MEK115306 MEK116513	Randomized, double-blinded, active-controlled, phase III Randomized, open, active-controlled, phase III				
2. ext	BRF113928	Open, non-controlled, phase I-II				
3. ext	BRF115532	Randomized, double-blinded, placebo-controlled, phase III				
Kisqali *Ribociclib* (L01EF02)						
Original MA	MONALEESA-2	Randomized, double-blinded, placebo-controlled, phase III				
1. ext	MONALEESA-7 MONALEESA-3	Randomized, double-blinded, placebo-controlled, phase III Randomized, double-blinded, placebo-controlled, phase III				
Verzenios *abemaciclib* (L01EF03)						
Original MA	MONARCH 3 MONARCH 2	Randomized, double-blinded, placebo-controlled, phase III, Randomized, double-blinded, placebo-controlled, phase III				
1. ext	monarchE	Randomized, open, active-controlled, phase III				
Jakavi *Ruxolitinib* (L01EJ01)						
Original MA	352 351	Randomized, open, active-controlled, phase III Randomized, double-blinded, placebo-controlled, phase III				

1. ext	B2301	Randomized, open, active-controlled, phase III	🟡	⚫	🟢	🟢
Imbruvica *Ibrutinib* (L01EL01)						
Original MA	PCYC-1112-CA PCYC-1104-CA	Randomized, open, active-controlled, phase III Open, non-controlled, phase II	🟡⚫	⚫⚫	🟢⚫	🔴🟢
1. ext	PCYC-1118E	Open, non-controlled, phase II	⚫	⚫	⚫	🔴
2. ext	PCYC-1115-CA	Randomized, open, active-controlled, phase III	🟡	⚫	🟡	🟢
3. ext	PCI-2765CLL3001	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟡	🟡	🟡
4. ext	1127	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟡
5. ext	E1912	Randomized, open, active-controlled, phase III	🟢	⚫	🟡	🟡
6.ext	CLL3011	Randomized, open, active-controlled, phase III	🟢	⚫	🟡	🟢
Zydelig *Idelalisib* (L01EM01)						
Original MA	GS-US-312-0116 & 101-09	Randomized, double-blinded, placebo-controlled, phase III Open, non-controlled, phase II	🟢⚫	🟢⚫	🟢⚫	🟢🟢
1. ext	GS-US-312-0119	Randomized, open, active-controlled, phase III	🟢	⚫	🟡	🔴
2. ext	GS-US-312-0115	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟢
Votrient *Pazopanib* (L01EX03)						
Original MA	VEG105192	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟢	🟢	🟢
1. ext	VEG110727	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟡	🟡	🟡
Caprelsa *Vandetanib* (L01EX04)						
Original MA	D4200C00058	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟡	🟡	🟢
1. ext	IRUSZACT0098	Open, non-controlled, phase II	⚫	⚫	⚫	🔴

Stivarga, *Regorafenib* (L01EX05)						
Original MA	14387	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟡	🔴	🟡
1. ext	14874	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟡	🟡	🟢
2. ext	15982	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟢
Lenvima, *Lenvatinibi* (L01EX08)						
Original MA	E7080-G000-303	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟡
1. ext	E7080-G000-304	Randomized, open, active-controlled, phase III	🟢	⚪	🟡	🟢
2. ext	E7080-G000-309	Randomized, open, active-controlled, phase III	🟢	⚪	🔴	🟡
Ayvakyt *Avapritinib* (L01EX18)						
Original MA	BLU-285-1101	Open, non-controlled, phase I-II	⚪	⚪	⚪	🔴
1. ext	BLU-285-2202	Open, non-controlled, phase I-II	⚪	⚪	⚪	🟢
Lynparza, *Olaparib (L01EK01)*						
Original MA	D0810C00019	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟢	🟢	🔴
1. ext	D0819C00003	Randomized, open, active-controlled, phase III	🟢	⚪	🔴	🟢
2. ext	D0818C00001	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟡
3. ext	D081FC00001	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟡
4. ext	D0817C00003	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟡	🔴	🟡
5. ext	D081DC00007	Randomized, open, active-controlled, phase III	🟡	⚪	🔴	🔴
6. ext	D081CC00006	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟢
7. ext	D081SC00001	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟡	🟢	🟢

Zejula *Niraparib (L01XK02)*						
Original MA	PR-30-5011-C	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟢	🟡	🟢
1. ext	PR-30-5017-C	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟡
Rubraca *Rucaparib (L01XK03)*						
Original MA	CO-338-010 CO-338-017	Open, non-controlled, phase I-II Open, non-controlled, phase I-II	⚫⚫	⚫⚫	⚫⚫	🔴🔴
1. ext	CO-338-014	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟡	🟡	🟡
Venclyxto, Venetoclax (L01XX52)						
Original MA	M13-982	Open, non-controlled, phase I-II	⚫	⚫	⚫	🔴
1. ext	MURANO	Randomized, open, active-controlled, phase III	🟡	⚫	🟡	🟢
2. ext	BO25323	Randomized, open, active-controlled, phase III	🟢	⚫	🟡	🟢
3. ext	M15-656 M16-043	Randomized, double-blinded, placebo-controlled, phase III (both)	🟡🟡	🟡🟡	🟢🟢	🟡🟢
Xtandi, *Enzalutamide (L02BB04)*						
Original MA	MDV3100	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟡
1. ext	MDV3100-03	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟢
2. ext	MDV3100 14	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟡
3. ext	9785-CL-0335	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟡
Erleada, Apalutamide (L02BB05)						
Original MA	ARN-509-003 (SPARTAN	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟢

1. ext	PCR3002 (TITAN)	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟢
Zytiga *Abiraterone (L02BX03)*						
Original MA	COU-AA-301	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟢	🟢	🟡
1. ext	COU-AA-302	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟡	🟢	🟡
2. ext	212082PCR3011	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟢
Imnovid *Pomalidomide (L04AX06)*						
Original MA	CC-4047-MM-003	Randomized, open, active-controlled, phase III	🟡	⚪	🟡	🟢
1. ext	MM-007	Randomized, open, active-controlled, phase III	🟢	⚪	🟡	🟢
Teysuno, Tegafur, gimeracil and oteracil (L01BC53)						
Original MA	S-1301/FLAGS	Randomized, open, active-controlled, phase III	🟢	⚪	🟢	🟢
1. ext	-	Exploratory and retrospective Meta-analysis	⚪	⚪	⚪	🟡

* Dose comparison,
MA= Marketing authorization,
ext. = Extension of indication

Supplementary table 3. Assessment of cancer medicines without extension of indication by JBI (Joanna Briggs Institute) criteria.

Medicinal product, *active substance*, (ATC-code)						
	Study	**Setting**	**Randomization and concealment of allocation (1–2)**	**Double blinding (4–6)**	**Similarity of the compared groups (3,7,8)**	**Validity and reliability of the outcome assessment (9-12)**
Calquence, Acalabrutinib (L01XE51)						
Original MA	ACE-CL-007, ACE-CL-309	Randomized, open, active-controlled, phase III (both)	🟢🟢	⚪	🔴🔴	🟡🟢
Daurismo, glasdegib (L01XX63)						
Original MA	B1371003	Randomized, open, active-controlled, phase III	🟢	⚪	🟢	🟢
Nubega, darolutamide (L02BB)						
Original MA	ARAMIS 17712	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟡	🟡	🟢
Piqray Alpelisib (L01XE)						
Original MA	C2301 (SOLAR-1)	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟢
Rozlytrek, Entrectinib (L01EX14)						
Original MA	GO40782, STARTRK-2)	Open, non-controlled, phase I-II (basket study)	⚪	⚪	⚪	🔴
Talzenna, Talazoparib (L01E)						
Original MA	673-301 (EMBRACA)	Randomized, open, active-controlled, phase III	🟢	⚪	🟢	🟢
Vitrakvi, Larotrectinib (L01E)						
Original MA	LOXO-TRK-15002 (NAVIGATE)	Open, non-controlled, phase I-II (basket study)	⚪	⚪	⚪	🔴

Vizimpro, Dacomitib, (L01EB07)						
Original MA	ARCHER 1050	Randomized, open, active-controlled, phase III	🟢	⚪	🟢	🟢
Xospata, gilteritinib, (L01EX13)						
Original MA	ADMIRAL (2215-CL-0301)	Randomized, open, active-controlled, phase III	🟢	⚪	🟢	🟢
Mektovi, binimetinib, (L01EE03)						
Original MA	COLUMBUS CMEK162B2301	Randomized, open, active-controlled, phase III	🟢	⚪	🟢	🟡
Nerlynx, neratinib , (L01EH02)						
Original MA	3144A2-3004-WW	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟡	🟢	🟢
Fotivda, tivozanib, (L01EK03)						
Original MA	AV-951-09-301	Randomized, open, active-controlled, phase III	🟢	⚪	🔴	🟢
Rydapt, midostaurin, (L01XE)						
Original MA	RATIFY (A2301)	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟡	🟡	🟢
Ibrance, palbociclib (L01XE)						
Original MA	1023 (PALOMA-3) 1008 (PALOMA-2)	Randomized, double-blinded, placebo-controlled, phase III	🟡🟡	🟡	🟡🟡	🟢🟢
Ninlaro, ixazomib (L01XG03)						
Original MA	C16010	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟡	🟢	🟡
Cotellic, cobimetinib (L01XE38)						

Original MA	GO28141/coBRI	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟡	🟢	🟢
Farydak, panobinostat (L01XH03)						
Original MA	CLBH589D2308 (Panorama I)	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟡	🟡	🟢
Odomzo, sonidegib (L01XJ02)						
Original MA	A2201 (BOLT)	Randomized, double-blinded, non-comparative, phase II	🟢	🟢	🟡	🟢
Cometriq, cabozantinib (L01XE)						
Original MA	XL184-301	Randomized, double-blinded, placebo-controlled, phase III	🟡	🟡	🟡	🟢
Vargatef, nintedanib (L01XE3)						
Original MA	XL184-301	Randomized, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟡
Erivedge, vismodegib (L01XX43)						
Original MA	SHH4476g	Open, non-controlled, phase-II (basket study)	⚪	⚪	⚪	🟡
Iclusig, ponatinib (L01EA05)						
Original MA	AP24534-10-201	Open, non-controlled, phase-II	⚪	⚪	⚪	🟡
Inlyta, axitinib (L01EK01)						
Original MA	A4061032	Randomized, open, active-controlled, phase III	🟡	⚪	🟢	🟢
Zelboraf, vemurafenib (L01XE15)						
Original MA	NO25026 (BRIM 3)	Randomized, open, active-controlled, phase III	🟢	⚪	🟡	🟢

MA= Marketing authorization,
ext. = Extension of indication

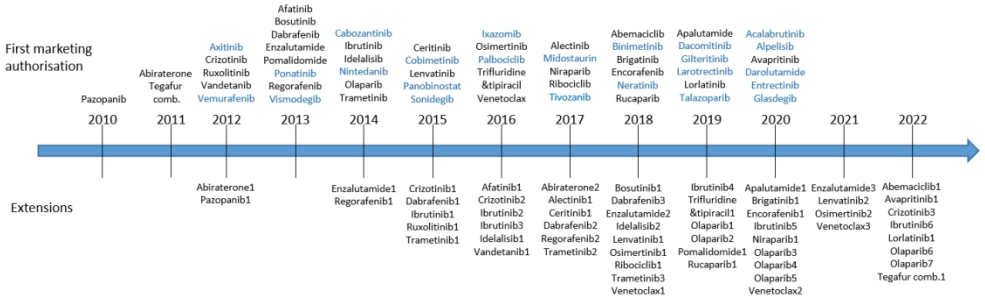


Figure 1.Timeline of the approved medicines with and without extensions of indications. Medicines without extensions are indicated in blue.

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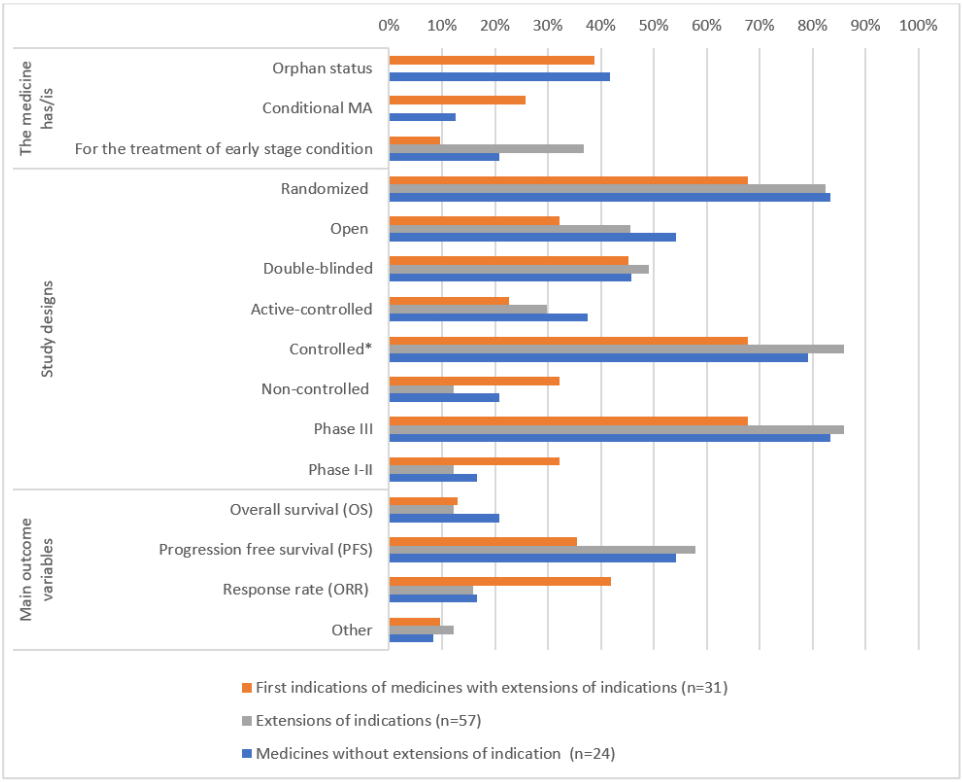

Figure 2.Comparison of study designs and main outcome variables in the main studies leading to marketing authorization or extensions of indications.
* Controlled study design includes both active- and placebo-controlled studies. For two medicines, their extensions were based on the same active-controlled studies.
* In addition to designs presented, one medicine's (tegafur combination) extension is based on a meta-analysis.

688x554mm (38 x 38 DPI)

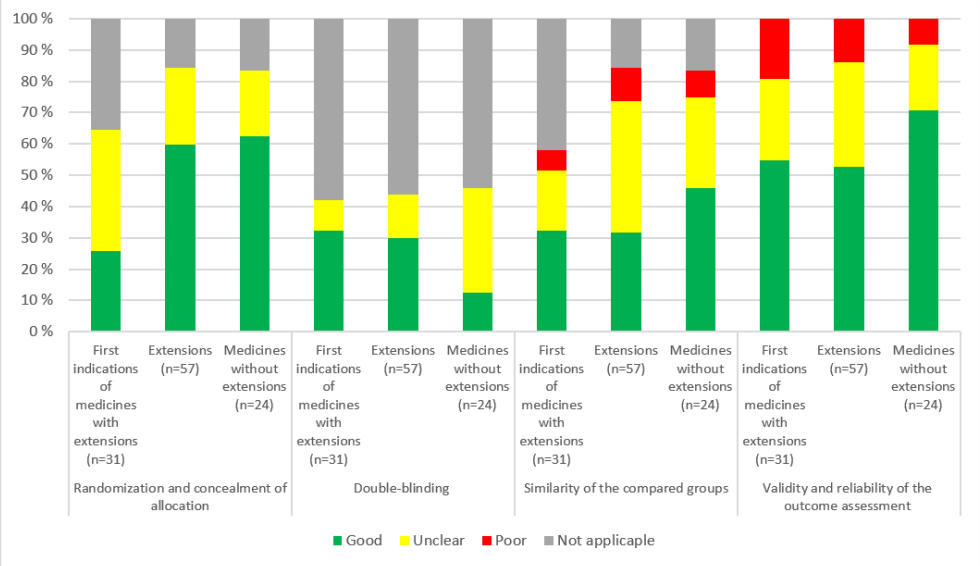

Figure 3. Quality of main studies assessed against JBI-criteria, comparison of the first indication of the medicines with extensions (n=31), the extensions of the indications (n=57) and the medicines without extensions of indications (n=24).

722x421mm (38 x 38 DPI)

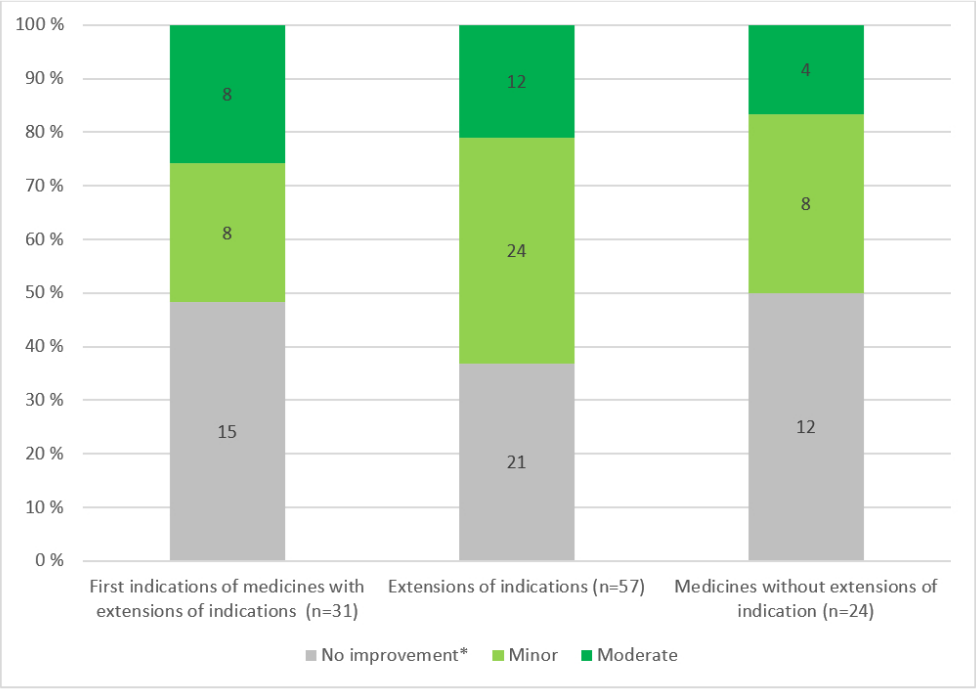

Figure 4. Assessment of clinical added value by HAS. Comparison of the first indication of medicines with extensions of indication (n=31), extensions of the indications (n=57), and medicines without extensions of indication (n=24). No assesment is available (n=9) and actual clinical benefit is insufficient (n=9).
* Includes situations where the actual clinical benefit is insufficient or no assessment is available.

683x516mm (38 x 38 DPI)

Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0)
September 15, 2015

Text Section and Item Name	Section or Item Description
Notes to authors	• The SQUIRE guidelines provide a framework for reporting new knowledge about how to improve healthcare • The SQUIRE guidelines are intended for reports that describe system level work to improve the quality, safety, and value of healthcare, and used methods to establish that observed outcomes were due to the intervention(s). • A range of approaches exists for improving healthcare. SQUIRE may be adapted for reporting any of these. • Authors should consider every SQUIRE item, but it may be inappropriate or unnecessary to include every SQUIRE element in a particular manuscript. • The SQUIRE Glossary contains definitions of many of the key words in SQUIRE. • The Explanation and Elaboration document provides specific examples of well-written SQUIRE items, and an in-depth explanation of each item. • Please cite SQUIRE when it is used to write a manuscript.
Title and Abstract	
1. Title	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient-centeredness, timeliness, cost, efficiency, and equity of healthcare)
2. Abstract	a. Provide adequate information to aid in searching and indexing b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions
Introduction	*Why did you start?*
3. Problem Description	Nature and significance of the local problem
4. Available knowledge	Summary of what is currently known about the problem, including relevant previous studies

5. Rationale	Informal or formal frameworks, models, concepts, and/or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work	✓
6. Specific aims	Purpose of the project and of this report	✓
Methods	*What did you do?*	
7. Context	Contextual elements considered important at the outset of introducing the intervention(s)	✓
8. Intervention(s)	a. Description of the intervention(s) in sufficient detail that others could reproduce it b. Specifics of the team involved in the work	
9. Study of the Intervention(s)	a. Approach chosen for assessing the impact of the intervention(s) b. Approach used to establish whether the observed outcomes were due to the intervention(s)	
10. Measures	a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost c. Methods employed for assessing completeness and accuracy of data	
11. Analysis	a. Qualitative and quantitative methods used to draw inferences from the data b. Methods for understanding variation within the data, including the effects of time as a variable	
12. Ethical Considerations	Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest	✓
Results	*What did you find?*	
13. Results	a. Initial steps of the intervention(s) and their evolution over time (*e.g.*, time-line diagram, flow chart, or table), including modifications made to the intervention during the project b. Details of the process measures and outcome c. Contextual elements that interacted with the intervention(s) d. Observed associations between outcomes, interventions, and relevant contextual elements e. Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s). f. Details about missing data	
Discussion	*What does it mean?*	
14. Summary	a. Key findings, including relevance to the rationale and specific aims b. Particular strengths of the project	

15. Interpretation	a. Nature of the association between the intervention(s) and the outcomes b. Comparison of results with findings from other publications c. Impact of the project on people and systems d. Reasons for any differences between observed and anticipated outcomes, including the influence of context e. Costs and strategic trade-offs, including opportunity costs
16. Limitations	a. Limits to the generalizability of the work b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis c. Efforts made to minimize and adjust for limitations
17. Conclusions	a. Usefulness of the work b. Sustainability c. Potential for spread to other contexts d. Implications for practice and for further study in the field e. Suggested next steps
Other information	
18. Funding	Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting

Table 2. Glossary of key terms used in SQUIRE 2.0. This Glossary provides the intended meaning of selected words and phrases as they are used in the SQUIRE 2.0 Guidelines. They may, and often do, have different meanings in other disciplines, situations, and settings.

Assumptions
Reasons for choosing the activities and tools used to bring about changes in healthcare services at the system level.

Context
Physical and sociocultural makeup of the local environment (for example, external environmental factors, organizational dynamics, collaboration, resources, leadership, and the like), and the interpretation of these factors ("sense-making") by the healthcare delivery professionals, patients, and caregivers that can affect the effectiveness and generalizability of intervention(s).

Ethical aspects
The value of system-level initiatives relative to their potential for harm, burden, and cost to the stakeholders. Potential harms particularly associated with efforts to improve the quality, safety, and value of healthcare services include opportunity costs, invasion of privacy, and staff distress resulting from disclosure of poor performance.

Generalizability
The likelihood that the intervention(s) in a particular report would produce similar results in other settings, situations, or environments (also referred to as external validity).

Healthcare improvement
Any systematic effort intended to raise the quality, safety, and value of healthcare services, usually done at the system level. We encourage the use of this phrase rather than "quality improvement," which often refers to more narrowly defined approaches.

Inferences
The meaning of findings or data, as interpreted by the stakeholders in healthcare services – improvers, healthcare delivery professionals, and/or patients and families

Initiative
A broad term that can refer to organization-wide programs, narrowly focused projects, or the details of specific interventions (for example, planning, execution, and assessment)

Internal validity
Demonstrable, credible evidence for efficacy (meaningful impact or change) resulting from introduction of a specific intervention into a particular healthcare system.

Intervention(s)
The specific activities and tools introduced into a healthcare system with the aim of changing its performance for the better. Complete description of an intervention includes its inputs, internal activities, and outputs (in the form of a logic model, for example), and the mechanism(s) by which these components are expected to produce changes in a system's performance.

Opportunity costs

Loss of the ability to perform other tasks or meet other responsibilities resulting from the diversion of resources needed to introduce, test, or sustain a particular improvement initiative

Problem
Meaningful disruption, failure, inadequacy, distress, confusion or other dysfunction in a healthcare service delivery system that adversely affects patients, staff, or the system as a whole, or that prevents care from reaching its full potential

Process
The routines and other activities through which healthcare services are delivered

Rationale
Explanation of why particular intervention(s) were chosen and why it was expected to work, be sustainable, and be replicable elsewhere.

Systems
The interrelated structures, people, processes, and activities that together create healthcare services for and with individual patients and populations. For example, systems exist from the personal self-care system of a patient, to the individual provider-patient dyad system, to the microsystem, to the macrosystem, and all the way to the market/social/insurance system. These levels are nested within each other.

Theory or theories
Any "reason-giving" account that asserts causal relationships between variables (causal theory) or that makes sense of an otherwise obscure process or situation (explanatory theory). Theories come in many forms, and serve different purposes in the phases of improvement work. It is important to be explicit and well-founded about any informal and formal theory (or theories) that are used.

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New cancer medicines in Europe 2010-2020: comparison of medicines with or without extensions of indications

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New cancer medicines in Europe 2010-2020: comparison of medicines with or without extensions of indications

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Abstract

Introduction: During the last decade, extensions of therapeutic indications have been one of the most common methods to extend the lifecycle of a medical product in the post-authorisation phase and to increase the use and sales of medicines. The aim of this study was to gain understanding of the lifecycle of cancer medicines and especially the role and level of evidence extensions in comparison to first indications.

Materials and methods: We identified all new outpatient cancer medicines approved by the European Medicines Agency (EMA) between 2010 and 2020 and the extensions to their indications. We compared general study design characteristics from the European public assessment reports (EPAR) using critical appraisal tools and clinical added value (CAV) assessments.

Results: We identified altogether 55 new outpatient cancer medicines, 31 of which had one or more extension(s) of indication and 24 had no extension of indication. In total, there were 57 extensions. The most common extension of indication was a change in the treatment line (35%). Compared to first indications, the overall quality of studies supporting extensions was better in terms of study designs. The proportion of medicines providing CAV was higher in extensions compared to first indication of medicines with and without extensions.

Conclusions: Based on different assessments and perspectives, we found that extensions of indications are a very common and important part of extending the lifecycle of outpatient cancer medicines in Europe. Our findings also suggest that the clinical value of cancer medicines increases with extensions.

Keywords: Cancer medicines, Europe, Study quality, Clinical trials, Clinical added value, Extensions, Level of evidence

Strengths and limitations

- We analysed all European Public Assessment reports (EPARs) of new outpatient cancer medicines with or without extensions of indications during 2010–2020
- We used multiple perspectives in the assessment: the characteristics of the medicines and study designs, the quality of clinical studies by Joanna Briggs Institution (JBI) Assessment tools, and the assessment of clinical added value (CAV) using Haute Autorité de Santé evaluations
- It is possible, that we missed some extensions of indications if they were approved after our data collection
- This study was descriptive in its nature and due to the low number of observations we were unable to detect any statistically significant differences between the medicines with or without extensions of indications.
- Our study provides an integrated understanding of the role of extensions of indications from the European perspective.

Introduction

Cancer medicines have been one of the key medical innovations in last decade. In the current niche-buster pharmaceutical market, different methods are used to extend the lifecycle of medicines [1], [2]. Extensions of therapeutic indications are one of the most common methods to extend the lifecycle of a medical product in the post-authorisation phase and to increase the use and sales of medicines [3], [4], [5], [6]. In Europe, extensions allow the innovator company an additional period of data exclusivity and market protection lasting at least a year [7], [8]. Nowadays, extensions of indications have become more common than the acceptance of new active substances [9], [10].

Marketing authorization (MA) holders aim to get new cancer medicines approved as soon as possible and expanding indications is common [11]. A study on targeted multi-indication cancer medicines found that medicines are first accepted as monotherapies in rare diseases with less mature evidence often based on single-arm studies and surrogate endpoints [4]. Extensions of indications are generally targeted to broader populations and based on more mature evidence. On the other hand, extension of indications may have minor clinical importance than the first approved indications [12]. A recent US analysis also revealed the importance of extensions of indications for the so-called partial orphan medicines, thus medicines initially intended to treat both rare and common diseases and how they are turned into block-buster medicines [13]. However, many of the previous findings focusing on the role of extensions of the indications are based on the medicines approved in the USA.

Another major trend in cancer medicine market is the shift towards outpatient cancer care, driven by the desire to use inpatient care resources more rationally, improve cost-efficiency and patient experience and avoid hospitalisation [14]. Although outpatient cancer care has become more important in recent decades, to our knowledge no previous study has focused on outpatient cancer medicines and their extensions of indications. Extensions of indications may be even more important for outpatient medicines than for inpatient medicines, as their potential uptake is indication-based [15].

Many publications have questioned the actual benefits of the new cancer medicines, as their impact and evidence on survival and quality of life is very limited [16], [17], [18]. In order to better understand the value of outpatient cancer medicines and the role of extensions of indications, it is important to gain a more comprehensive understanding of first and later indications of cancer medicines and the quality of the research evidence supporting their approvals.

The quality of research can be assessed with different critical appraisal tools [19]. One of the most common methods is the critical appraisal tools of the Joanna Briggs Institute (JBI) [20], which include comprehensive checklists for different types of study settings [21]. In addition to the quality of study designs, it is crucial to assess the clinical added value (CAV) of new medicines. CAV takes into account and compares the efficacy and safety of a medicine with existing treatments. One validated instrument for this kind of work is the French Haute Autorité de Santé (HAS), whose CAV assessments are publicly available [22].

The aim of the study was to explore the role and the level of evidence of extensions of indications in the European cancer medicine approvals. More specific aims were (i) to describe and compare the new outpatient cancer medicines and their extensions, (ii) to evaluate and compare the evidence at the MA acceptance phase between the following three groups: first indications for multi-indication medicines, extensions, and medicines without extensions, and (iii) to analyze and compare the CAV between these three groups.

Materials and Methods

Data collection

Our study focuses on new cancer medicines that received MA for the first time in 2010–2020 and possible extensions of indication by the end of 2022, in addition to which they are suitable for outpatient care by their administration route (Supplementary Figure 1), i.e., the active substances are targeted to tumor tissue based on Anatomical Therapeutic Chemical (ATC) codes L01, L02, L04AX02, L04AX04, and L04AX06 [23]. Data were collected from EMA's website and the European public assessment reports (EPARs) [24]. The latest data collection took place in June 2023. We categorized the types of extensions of cancer medicines into five categories (Supplementary Table 1) based on a list by the European Commission [25]. In addition to these categories, we added one more: multiple change. We classified new cancer medicines to 10 groups by the target tissue of their first indication (Table 1). We used level 4 ATC groups (chemical subgroup) [26] to estimate the number of new mechanisms of action.

Quality assessment using the Joanna Briggs Institute (JBI) critical appraisal tools

The quality of the main studies from EPARs was assessed by using the JBI Checklist for randomized controlled trials (RCT), Checklist for quasi-experimental studies, and Checklist for systematic reviews [20]. The JBI checklists were selected due to their comprehensibility and because separate checklists were available for different study settings [21]. The checklists for RCT, quasi-experimental studies, and systematic reviews contain 13, 9, and 11 questions, respectively. Each question can be assessed as *yes*, *no*, *unclear* or *not applicable*.

The quality assessments were conducted separately by two researchers (AMR and TK). Any discrepancies were discussed until a consensus was reached. After all the assessments, the questions were divided into four categories by theme in order to summarize the different checklists and their results.

Clinical added value by the assessment of Haute Autorité de Santé (HAS)

HAS is the independent French National Authority for Health that, among others things, assesses applications for reimbursement of new medicines. HAS will assess the actual clinical benefit (ACB) and decides whether to recommend a medicine for reimbursement. For this study, we utilised the publicly available HAS evaluations of CAV scored on a scale of no improvement, minor, moderate, substantial, and major [27]. We classified medicines with no ACB and no evaluation of the medicine or indication by the HAS under the *No improvement* category. It reflects the overall situation where a new medicine adds no clinical value. We collected assessments for the first indications and subsequent extensions of indications in June 2023. Another popular, validated instrument for the assessment of CAV is the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS) [28]. However, at the time of our study, MCBS scales did not include the evaluation of medicines for hematological indications [29]. Because HAS evaluations include also medicines for hematological cancer, we used HAS evaluations in this study.

Patient and public involvement

Patients and members of the public were not involved in the design and conduct of this study.

Results

Characteristics of medicines and extensions of indications

We identified altogether 55 new outpatient cancer medicines approved by EMA between 2010 and 2020 accounting for more than half (53%) of all new cancer medicines approved (Supplementary Table 2). The most common indications of these medicines were the treatment of hematological cancers (24%, n = 13), lung cancer (16%, n = 9), and melanoma and basal cell carcinoma (15%, n = 8) (Table 1). More than half (56%, n = 31) of all new cancer medicines had received at least one extension of indication. The remaining medicines (44%, n = 24) had no extensions of indication. Most commonly, extensions (n = 57) involved a new treatment line (35%, n = 20), a new cancer type (30%, n = 17), or a new combination therapy (18%, n = 10). We found only three extensions of indications to new patient groups (5%) and all were lung cancer medicines. We found six extensions, classified as multiple change (11%) in following medicine groups: hematological cancers (n=3), gynecological cancer (n=2) and lung cancer (n=1).

A majority (77%) of medicines approved for the treatment of hematological cancers were launched with a new mechanism of action (Table 1), while a third of medicines for lung, gynecological and thyroid cancers, had a new mechanism of action. The medicine that was the first in a new ATC group often had the highest number of extensions. In our data, the first active substance in the ATC group had the highest number of extensions in 7 out of 21 different ATC groups (33%) during the follow-up period. Furthermore, most extensions came from other than the first active substance in four (19%) ATC groups, and seven (33%) ATC groups had only one active substance. In the remaining groups (14%), all medicines had the same number of extensions. Medicine-specific characteristics are presented in Supplementary Table 2.

Table 1. Characteristics of new outpatient cancer medicines by cancer type according to the first approved indication of the medicine.

First approved indication	Total number of medicines (of all medicines)	Number (%) of medicines with extension	Total number of extensions	The most common type of extension(s) of indication			New mechanisms of action*
				Treatment line	Cancer type	New combination	
Hematological cancers: - leukemia - multiple myeloma - lymphoma - myelofibrosis	13 (24%)	6 (46%)	14	2		6	10 (77%)
Lung cancer	9 (16%)	7 (78%)	10	6		-	3 (33%)
Melanoma & basal cell carcinoma	8 (15%)	3 (38%)	7	2		2	3 (38%)
Breast cancer	6 (11%)	2 (33%)	2	1	-	1	4 (67%)
Prostate cancer	4 (7%)	3 (75%)	6	6	-	-	2 (50%)
Colorectal or gastric cancer	4 (7%)	4 (100%)	5	-	5	-	2 (50%)
Kidney cancer	3 (5%)	1 (33%)	1	-	1	-	2 (67%)
Thyroid cancer	3 (5%)	2 (67 %)	3	-	2	-	1 (33%)
Gynecological cancers	3 (5%)	3 (100%)	9	3	3	1	1 (33%)
Solid tumors	2 (4%)	0 (0%)	0	-	-	-	1 (50%)
Total	55 (100%)	31 (56%)	57 (100%)	20 (35%)	17 (30%)	10 (18%)	

* Based on the number of new different chemical, thus 4th levels in the Anatomical Therapeutic Chemical (ATC) classification maintained by WHO [26].

Of the 31 medicines with extensions of indications, 19 had only one and 12 had two or more extensions (Figure 1). The maximum number of extensions was seven (for olaparib). The timeline in Figure 1 shows when the new active substances received their first MA and when their extensions of indication were approved. On average, the first extension of indication was granted 2 years and 7 months after the first MA (min. 7 months; max. 10 years and 10 months; median 2 years and 1 month). The average time between the first and second extension of indication was 2 years and subsequent extensions were granted in less than 2 years, on average.

Study designs and marketing authorisations

In total, 124 main studies were identified and evaluated. In 13 cases, there were two main studies. Most of the main studies supporting the first MA or extensions of indications were phase III studies with randomised controlled study design (80%, Figure 2). Phase I-II non-controlled single-arm trials were a more common study design for the first indication of medicines with extensions (32%) than for other groups (12% and 17%).

Medicines with extensions were more likely to have a conditional MA application than medicines without extensions (26% and 13%, respectively). Most (86%) of the main studies utilized surrogate endpoints (such as progression free survival (PFS) or overall response rate (ORR) as the main outcome variable (Figure 2). Overall survival (OS) was rarely used as main endpoint and was more common in the studies on medicines without extensions (21%) than in the other groups (12% and 13%). In addition, ORR was most frequently used as a key outcome variable in the studies (42%) of the first indication of the medicines with extensions while its use was less frequent in the other groups (16% and 17%).

The majority of all new cancer medicines (85%, n = 47) were indicated for the treatment of advanced or metastatic disease at the time they received their first MA. Treatment of early-stage condition was more common for extensions of indications than for other groups.

Evaluation of the quality of evidence

Based on the JBI assessment, the overall quality of the main studies on extensions and medicines without extensions was better than that of the first indications of medicines with extensions (good and unclear in Figure 3). This is explained by the larger proportion of phase III RCTs in the study designs. When only the studies with good assessments of quality are considered, medicines without extensions received the best rating in three out of four categories.

In many studies, details of the randomisation and double-blinding were missing. Double-blinding was well-described in up to a third of the studies. However, almost half of all main studies of all medicines did not have a double-blind design (Figure 3). Medicine-specific assessments are presented in Supplementary Tables 2 and 3.

In the assessment of the similarity between the compared groups, less than half of the studies were evaluated to fill the criteria of good quality. The most common reasons for poor quality of studies were crossover between groups, different follow-up times in different populations, and, in some cases, different previous treatments in the compared groups.

Clinical added value

Overall, extensions of indications had the highest scores in CAV assessment (minor and moderate CAV in 63%; Figure 4). In the other two groups, almost the same proportion of medicines had some CAV (52% vs. 50%). Moderate was the highest CAV estimate of dataset, and it should be noted that none of the indications provided substantial or major CAV. In terms of percentages, the highest moderate ratings were to the first indication for medicines with extension of indication (26%). Moderate assessments focused particularly on products for the treatment of prostate cancer, hematological cancers, and melanoma. Medicine-specific assessments are presented in Supplementary Table 2.

Discussion

Based on different assessments and perspectives, we found that extensions of indications are a very common and important part of extending the lifecycle of outpatient cancer medicines in Europe. Our findings also suggest that the clinical value of cancer medicines increases with extensions. In more detail, firstly, the most common category of extensions was a change in the treatment line, i.e., a tendency to push the use of a cancer medicine to an earlier point in the treatment line and, thus, increase the number of potential users and extend the duration of treatment. Secondly, based on the characteristics of study design and JBI evaluation, extensions of indications are based on improved quality of evidence compared to first accepted indications. In addition, according to CAV assessments, extensions add more clinical value than the first indications. Looking at the different measures and perspectives, it appears that extensions of indication are of higher quality than the first indications of evaluated medicines.

Evidence supporting extensions of indications was of higher quality

Our study is in accordance with previous findings [4], [11], [30] suggesting that new outpatient cancer medicines are brought to market with less comprehensive clinical evidence, which is to be improved in later indication extension studies. This is linked to, for example, the number of conditional MAs and phase I-II studies. It also seems that conditional MA is more common for medicines with extensions than for those without them. Furthermore, we also found that in studies of extensions of indications yielded a higher overall CAV than the studies of those medicines whose indications were subsequently extended and those medicines without extensions. This finding is slightly different from findings of a study utilising ESMO MCBS [31], in which original indications were scored higher than extended indications [31]. This can be explained by the different assessment scale used or by the fact that we included also hematological indications in our study.

Change in treatment line was the most common extension type

In our study, the most common type of extension was a change in the treatment line. This was seen, for example, in prostate cancer, where androgen receptor signaling inhibitors (ARSI) abiraterone, enzalutamide, and apalutamide were first indicated to castration-resistant prostate cancer and later extended to earlier hormone-sensitive stages of the disease. This pattern was similar also in metastatic lung cancer and ALK tyrosine kinase inhibitors (crizotinib, alectinib, ceritinib, brigatinib, and lorlatinib), all of which were initially indicated as second- or third-line treatment but received extensions to first-line treatment over time. This reflects the fact that cancer medicines often initially enter the later line and move to an earlier stage of treatment with extensions. The second most common type of extension was a new cancer type, which was particularly common for colorectal and gastric cancer medicines. These medicines (tegafur comb., trifluridine and tipiracil, regorafenib and avapritinib) are not targeted to specific signaling pathways (like androgen receptors in prostate cancer or EML4-ALK translocations in lung cancer), which explains the rationale to

investigate their potential in cancers of different origin. New combination therapies were particularly common in hematological indications. For other extension types, only a few medicines were included and for instance the extension to new patients was only found in three lung cancer medicines.

Medicines with new mechanism of action had most extensions of indications

According to our data it is common that the first-to-market products with a new mechanism of action have the highest number of extensions. To our knowledge, there are no previous findings on this. A previous North American cross-sectional study [32] showed that only a minority of FDA approved cancer medicines during 2009–2020 were based on a new mechanism of action. Our findings indicate that the first entrant can be characterised as a trendsetter, and subsequent medicines will, in most cases, have the same indication(s) as the first medicine. The importance of new mechanism of action and subsequent extensions should be studied more, also in different therapeutic areas.

Implications for patient care and policy

Looking at the research design and the quality of the evidence, it seems that a new mainstream of medicine approval has emerged over the last decade. For example, previous research [33] suggests that the majority of new cancer medicines from 1995 to 2008 had only one indication. This is the opposite of the current situation with medicines with multiple extensions targeted to larger populations. The current drive is to provide new treatments to patients as quickly as possible. This trend can also have a negative impact on patient care and outcomes. On the other hand, for some medicines, lighter approval criteria are beneficial for the uptake of medicines and, therefore, for patients [34]. Of the beginning of 2025, the new Regulation on Joint Health Technology Assessment (HTAR) at the EU level is applied [35]. One important aspect to consider in the joint evaluation of the evidence is the possible extensions of indications and how they are addressed. The results of this study may increase of the overall understanding among authorities and decisions makers of the role of extensions of indications, which can help in future medicine assessments. For instance, it is worth considering whether the extension of indication or the first indication becomes the main indication for a medicine, and what impact it has on the number of medicine users and the resulting costs.

Strengths and limitations

Although previous analyses [4], [11] have assessed the evidence related to extensions of indications, to our knowledge, our study includes more medicines than previous analyses, with a particular focus on the European outpatient cancer medicines. Our study included also cancer medicines with hematological indications, accounting for almost a quarter of all new outpatient cancer medicines approved. The strength of this study is that it was based on publicly available documents from the European Medicines Agency on all new cancer medicines suitable for outpatient use in Europe between 2010 and 2020 using multiple essential assessment methods. We also provide detailed, medicine level information in the supplementary tables 2 &3. However, our study is not without limitations. First, the median time to first extension was two years and one month. Based on this, we believe that the follow-up period of our study (until spring 2023) is long enough to capture the majority of the potential extensions of the indications. However, it is possible that some of the products have extensions after the data collection period has ended. We used the JBI critical appraisal tools to assess methodological quality because of their comprehensibility [21] and because JBI checklists exist for different types of study settings. In the assessment of CAV, we chose to use HAS assessments because they are performed for most medicines, including hematological indications. It is possible that the assessment tools we used have influenced our results. Finally, due to the low number of observations we were unable to detect any statistically significant differences between the observed medicine groups (first indications, extensions of indications and medicines without extensions). Overall, we consider the utilisation

of the different kinds of assessments and perspectives gives us a comprehensive understanding of the evolvement of the evidence during the lifecycle of the studied medicines and especially the important role of extensions of indications in extending the lifecycle of outpatient cancer medicines in Europe.

Declarations

Ethics approval and consent to participate: Not applicable because the study was based on publicly available documents.

Availability of data and materials: All materials are publicly available. EPARS: https://www.ema.europa.eu/en/medicines. Clinical added value assessments: https://www.has-sante.fr/jcms/pprd_2986129/en/home.

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Author contributions

Concept and design: TK, KS, HK. Acquisition, analysis, or interpretation of data: All the authors. Drafting of the manuscript: AMR, TK. Critical revision of the manuscript for important intellectual content: All authors. Supervision: TK, KS, KK, HK. TK is responsible for the overall content of the manuscript [as guarantor].

Figure legends

Figure 1. Timeline of the approved medicines with and without extensions of indications. Medicines without extensions are indicated in blue.

Figure 2. Study designs and main outcome variables of the main studies, comparison of the first indication of the medicines with extensions (n=31), the extensions of the indications (n=57) and the medicines without extensions of indications (n=24).

* Controlled study design includes both active- and placebo-controlled studies. For two medicines, their extensions were based on the same active-controlled studies.
* In addition to designs presented, one medicine's (tegafur combination) extension is based on a meta-analysis.

Figure 3. Quality of main studies assessed against JBI-criteria, comparison of the first indication of the medicines with extensions (n=31), the extensions of the indications (n=57) and the medicines without extensions of indications (n=24).

Figure 4. Assessment of clinical added value by HAS. Comparison of the first indication of medicines with extensions of indication (n=31), extensions of the indications (n=57), and medicines without extensions of indications (n=24). * The category "no improvement" included also medicines for which no assessment was available (n=9) or actual clinical benefit was insufficient (n=9).

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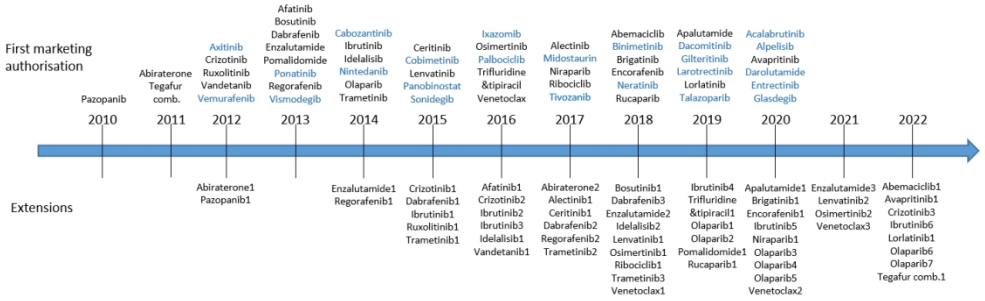

Figure 1.Timeline of the approved medicines with and without extensions of indications. Medicines without extensions are indicated in blue.

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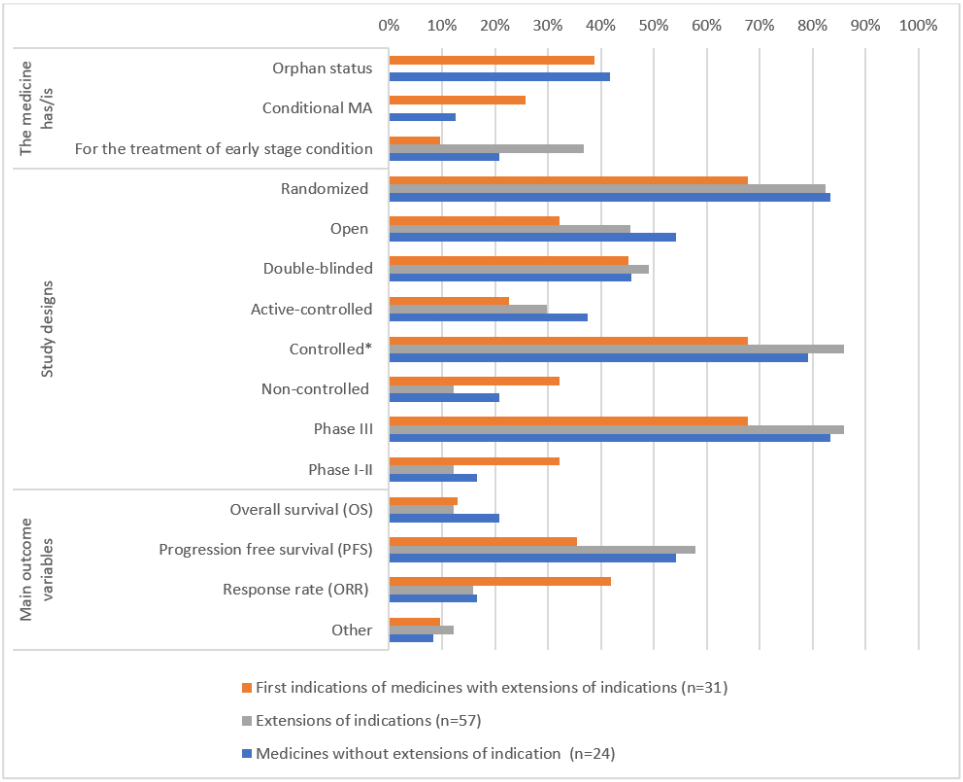

Figure 2.Comparison of study designs and main outcome variables in the main studies leading to marketing authorization or extensions of indications.
* Controlled study design includes both active- and placebo-controlled studies. For two medicines, their extensions were based on the same active-controlled studies.
* In addition to designs presented, one medicine's (tegafur combination) extension is based on a meta-analysis.

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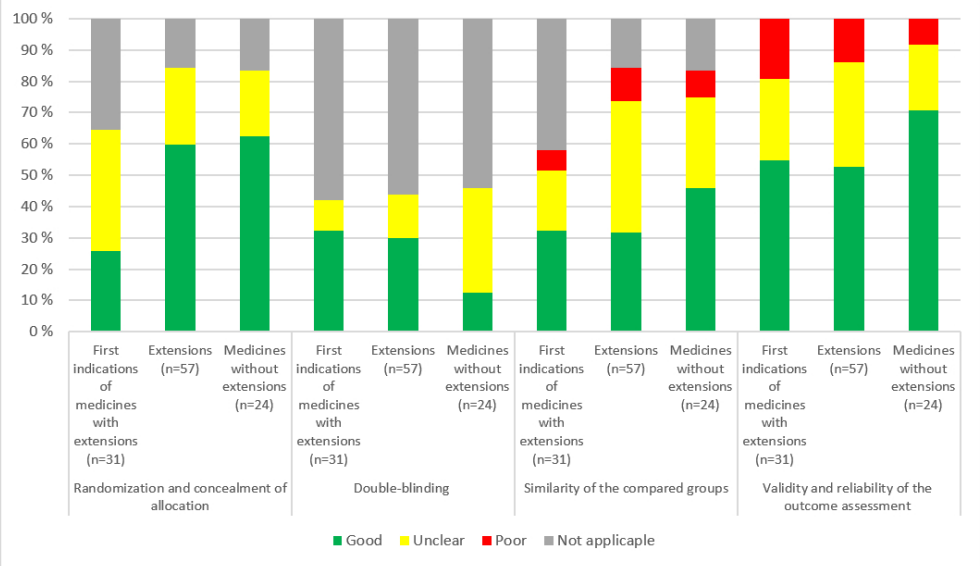

Figure 3. Quality of main studies assessed against JBI-criteria, comparison of the first indication of the medicines with extensions (n=31), the extensions of the indications (n=57) and the medicines without extensions of indications (n=24).

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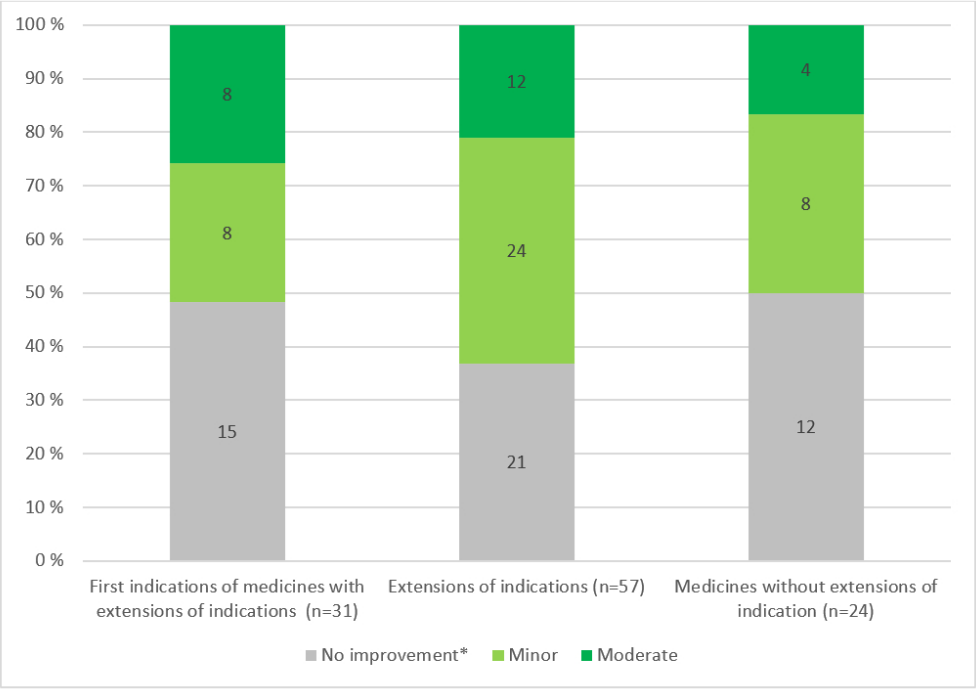

* Includes situations where the actual clinical benefit is insufficient or no assessment is available.

Figure 4. Assessment of clinical added value by HAS. Comparison of the first indication of medicines with extensions of indication (n=31), extensions of the indications (n=57), and medicines without extensions of indication (n=24). No assesment is available (n=9) and actual clinical benefit is insufficient (n=9).
* Includes situations where the actual clinical benefit is insufficient or no assessment is available.

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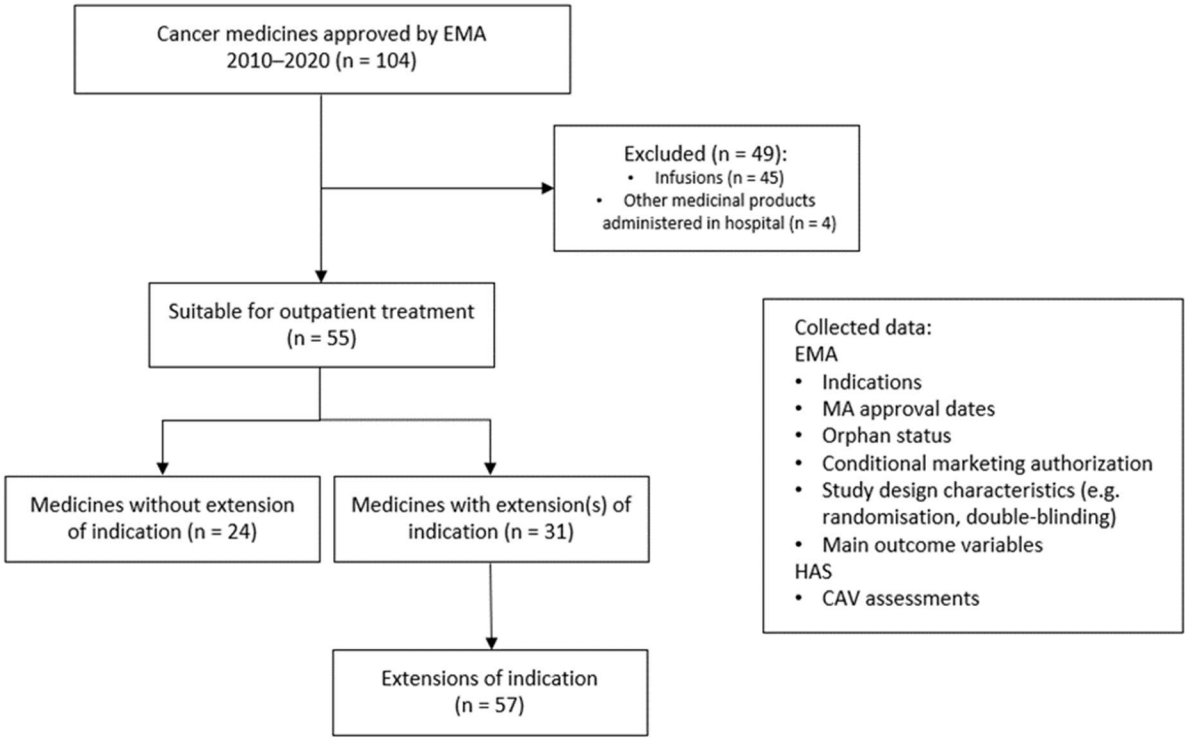

EMA= European Medicines Agency, HAS= Haute Autorité de Santé

Supplementary Figure 1. Flowchart of included medicines and their extensions of indication. Data was collected from HAS and EMA documents [22], [24].

Supplementary Table 1. The different categories of extensions used in this study [25].

Category of extension	Description of category
Treatment line	The medicine was authorised for a different treatment line or stage of the disease (e.g., the first MA* for metastatic disease and the extension for adjuvant setting).
Cancer type	The medicine was authorised for another cancer type (e.g., the first MA for melanoma and the extension of indication for lung cancer)
Patient type	The medicine was authorised for different patients than previously (e.g., the first MA for certain mutation type and the extension for another mutation type).
Combination type	The medicine was authorised to be used as part of a different combination of medicines (e.g., the first MA only as a monotherapy, the extension as a part of certain combination therapy).
Multiple change	At least two previously introduced categories are met.

*MA=marketing authorisation

Supplementary Table 2. Characteristics of the outpatient cancer medicines. Medicines without extension of indication are marked by purple.

Medicinal product, *active substance*, date	First indication	Conditional marketing authorisation[1]	Orphan status[1]	Accelerated assessment	Additional monitoring	Extension(s) of indication according to the type of the extension[2], date	HAS
L01B Antimetabolites							
L01BC Pyrimidine analogues							
Teysuno®, tegafur, gimeracil and oteracil. 14.3.2011	gastric cancer	-	Previously yes, now withdrawn	-	-	1. cancer type (colorectal cancer), 24.1.2022	Na Insuf.
Lonsurf®, *trifluridine and tipiracil*, 25.4.2016	colorectal cancer	-	-	-	-	1. cancer type (gastric cancer), 3.9.2019	5 5
L01E Protein kinase inhibitors							
L01EA BCR-ABL tyrosine kinase inhibitors							
Bosulif®, *bosutinib,* 27.3.2013	chronic myelogenous leukaemia	-	Previously yes, now withdrawn	-	-	1. treatment line, 23.4.2018	5 5
Iclusig®, *ponatinib,* 1.7.2013	leukaemia		Yes	Yes	-		5/4/3
L01EB Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors							
Giotrif®, *afatinib,* 25.9.2013	lung cancer	-	-	-	-	1. patient type (mutation), 31.3.2016	5 5
Tagrisso®, *osimertinib,* 2.2.2016	lung cancer	Previously yes, now full authorisation	-	Yes	Yes	1. treatment line, 7.6.2018 2. treatment line + patient type (mutation), 21.1.2021	5 4 3
Vizimpro®, dacomitinib, 2.4.2019	lung cancer	-	-	-	Yes	-	5
L01EC B-Raf serine-threonine kinase (BRAF) inhibitors							
Zelboraf®, *vemurafenib,* 17.2.2012	melanoma	-	-	-	-	-	3
Tafinlar®, *dabrafenib,* 26.8.2013	melanoma	-	-	-	-	1. combination type, 25.8.2015 2. cancer type (lung cancer), 29.3.2017 3. treatment line, 27.8.2018	5 Na 5 3
Braftovi®, *encorafenib*, 20.9.2018	melanoma	-	-	-	Yes	1. cancer type (colorectal cancer), 2.6.2020	5 3
L01ED Anaplastic lymphoma kinase (ALK) inhibitors							
Xalkori®, *crizotinib,* 23.10.2012	lung cancer	-	-	-	-	1. treatment line, 23.11.2015 2. patient type (mutation), 25.8.2016 3. patient type (adolescents), 28.10.2022	3 4 5 4
Zykadia®, *ceritinib,* 6.5.2015	lung cancer	Previously yes, now full authorisation	-	-	-	1. treatment line, 23.6.2017	4 4
Alecensa®, *alectinib*, 16.2.2017	lung cancer	-	-	-	-	1. treatment line, 18.12.2017	4 4
Alunbrig®, *brigatinib,* 22.11.2018	lung cancer	-	-	-	-	1. treatment line, 1.4.2020	5 4
Lorviqua®, *lorlatinib,* 6.5.2019	lung cancer	Yes	-	-	Yes	1. treatment line, 27.1.2022	5 4
L01EE Mitogen-activated protein kinase (MEK) inhibitors							

Mekinist®, *trametinib,* 30.6.2014	melanoma	-	-	-	-	1. combination type, 25.8.2015 2. cancer type (lung cancer), 27.3.2017 3. treatment line, 27.8.2018	3 Na 5 3
Cotellic®, *cobimetinib,* 20.11.2015	melanoma	-	-	-		-	3
Mektovi®, *binimetinib,* 20.9.2018	melanoma	-	-	-	Yes	-	5
L01EF Cyclin-dependent kinase (CDK) inhibitors							
Ibrance®, *palbociclib,* 9.11.2016	breast cancer	-	-	-	Yes		4
Kisqali®, *ribociclib,* 22.8.2017	breast cancer	-	-	-	Yes	1. combination type, 17.12.2018	3 4
Verzenios®, *abemaciclib,* 27.9.2018	breast cancer	-	-	-	Yes	1. treatment line, 1.4.2022	5/4 5
L01EH Human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitors							
Nerlynx®, *neratinib,* 31.8.2018	breast cancer	-	-	-	yes		Insuf.
L01EJ Janus-associated kinase (JAK) inhibitors							
Jakavi®, *ruxolitinib,* 23.8.2012	myelofibrosis	-	Previously yes, now withdrawn	-	-	1. cancer type (polysytemia vera), 11.3.2015	3 4
L01EK Vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors							
Inlyta®, *axitinib,* 3.9.2012	kidney cancer	-	Previously yes, now withdrawn	-	Yes	-	4
Fotivda®, *tivozanib,* 24.8.2017	kidney cancer	-	-	-	Yes	-	Insuf.
L01EL Bruton's tyrosine kinase (BTK) inhibitors							
Imbruvica®, *ibrutinib,* 27.10.2014	mantle cell lymphoma and chronic lymphocytic leukaemia	-	Previously yes, now withdrawn	-	-	1. cancer type (Walderström's macroglobulinaemia), 3.7.2015 2. treatment line, 26.5.2016 3. combination type, 25.8.2016 4. combination type, 2.8.2019 5. combination type, 28.8.2020 6. combination type, 2.8.2022	3 Na 4 Na Insuf. 3 4
Calquence®, *acalutinib,* 5.11.2020	leukaemia		Previously yes, now withdrawn		Yes	-	Na
L01EM Phosphatidylinositol-3-kinase (Pi3K) inhibitors							
Zydelig®, *Idelalisib,* 18.9.2014	follicular lymphoma and chronic lymphocytic leukaemia	-	-	-	Yes	1. combination type, 19.9.2016 2. combination type, 23.4.2018	5/4 Na Na
Piqray®, *alpelisib,* 27.7.2020	breast cancer	-	-	-	Yes	-	Insuf.
L01EX Other protein kinase inhibitors							
Votrient®, *pazopanib,* 14.6.2010	renal cell carcinoma	Yes	Previously yes, now withdrawn	-	-	1. cancer type (soft-tissue sarcoma), 24.8.2012	5 5
Caprelsa®, *vandetanib,* 16.2.2012	thyroid cancer	Yes	-	-	Yes	1. patient type (paediatric patients), 12.12.2016	4 5
Stivarga®, *regorafenib,* 26.8.2013	colorectal cancer	-	-	-	-	1. cancer type (gastrointestinal stromal tumors), 27.10.2014	5 4

						2. cancer type (hepatocellular carcinoma), 2.8.2017	4
Cometriq®, cabozantinib, 21.3.2014	medullary thyroid cancer	-	Yes	-	-	-	4
Lenvima®, *lenvatinib,* 28.5.2015	thyroid cancer	-	Previously yes, now withdrawn	Yes	Yes	1. cancer type (liver cancer), 20.8.2018 2. cancer type (endometrial carcinoma), 26.01.2021	4 Insuf. 3
Vargatef®, *nintedanib,* 21.11.2014	lung carcinoma	-	-	-	-		Insuf.
Rydapt®, *midostaurin*, 18.9.2017	acute myeloid leukaemia, mastocytosis	-	Yes	-	Yes		4/5
Vitrakvi®, *larotrectinib,* 19.9.2019	solid tumours with NTRK gene fusion	Yes	Previously yes, now withdrawn	-	Yes		4
Xospata®, *gilteritinib,* 24.10.2019	acute myeloid leukemia	-	Yes	-	Yes		4
Rozlytrek®, *entrectinib,* 31.7.2020	solid tumors with NTRK fusion, lung cancer	Yes	-	-	Yes		Insuf.
Ayvakyt®, *avapritinib,* 24.9.2020	gastrointestinal stromal tumours	Yes	Yes	-	Yes	1. cancer type (mastocytosis), 24.3.2022	5 4
L01X Other antineoplastic agents							
L01XG Proteasome inhibitors							
Ninlaro®, *ixazomib,* 21.11.2016	multiple myeloma	yes	yes	-	Yes		5
L01XH Histone deacetylase (HDAC) inhibitors							
Farydak®, *panobinostat,* 28.8.2015	multiple myeloma	-	Yes	-	Yes	-	5
L01XJ Hedgehog pathway inhibitors							
Erivedge®, *vismodegib,* 12.7.2013	basal cell carcinoma	-	-	-	Yes		4
Odomzo®, *sonidegib,* 14.8.2015	basal cell carcinoma	-	-	-	Yes	-	4
Daurismo®, *glasdegib,* 26.6.2020	acute myeloid leukaemia		Yes	-	Yes	-	Na
L01XK Poly (ADP-ribose) polymerase (PARP) inhibitors							
Lynparza®, *olaparib,* 16.12.2014	ovarian, fallopian tube or primary peritoneal cancer	-	Previously yes, now withdrawn	-	-	1. cancer type (breast cancer), 8.4.2019 2. treatment line, 12.6.2019 3. cancer type (pancreatic cancer), 3.7.2020 4. combination type, 3.11.2020 5. cancer type (prostate cancer), 3.11.2020 6. treatment line (breast cancer), 2.8.2022 7. treatment line + combination (prostate cancer), 16.12.2022	4 5 4 5 4 4 3 4
Zejula®, *niraparib,* 16.11.2017	ovarian, fallopian tube or primary peritoneal cancer	-	Yes	-	Yes	1. treatment line, 27.10.2020	4 4
Rubraca®, *rucaparib,* 24.5.2018	ovarian, fallopian tube or primary peritoneal cancer	Yes	Previously yes, now withdrawn	-	Yes	1. treatment line + patient type (mutation), 23.1.2019	Insuf. 4
Talzenna®, *talazoparib,* 20.6.2019	breast cancer	-	-	-	Yes	-	5
L01XX Other antineoplastic agents							

Venclyxto®, *venetoclax,* 5.12.2016	chronic lymphocytic leukaemia	Previously yes, now full authorisation	Previously yes, now withdrawn	-	Yes	1. Treatment line + combination type, 29.10.2018 2. Treatment line + combination typfe, 9.3.2020 3. Cancer type (acute myeloid leukaemia), 22.1.2021	5 4 3 4
L02B Hormone antagonists and related agents							
L02BB Anti-androgens							
Xtandi®, *enzalutamide,* 21.6.2013	prostate cancer	-	-	-	-	1. Treatment line, 28.11.2014 2. Treatment line, 23.10.2018 3. Treatment line, 30.4.2021	3 4 3 3
Erleada®, *apalutamide,* 14.1.2019	prostate cancer	-	-	-	Yes	1. Treatment line, 27.1.2020	3 3
Nubeqa®, *darolutamide,* 27.3.2020	prostate cancer	-	-	-	Yes		3
L02BX Other hormone antagonists and related agents							
Zytiga®, *abiraterone,* 5.9.2011	prostate cancer	-	-	Yes	-	1. Treatment line, 18.12.2012 2. Treatment line, 15.11.2017	3 4 3
L04A Immunosuppressants							
L04AX Other immunosuppressants							
Imnovid®, *pomalidomide,* 5.8.2013	multiple myeloma	-	Yes	-	Yes	1. Treatment line + new combination, 13.5.2019	5 5

[1] In some stage of the product life cycle

[2]Types of extensions: *Cancer type* = authorised for new cancer type, *Treatment line* = authorised for a different treatment line or for a different stage of the disease, e.g. after a surgery, *Patient type* = authorised for different patients than previously, *Combination type* = authorised to be used as a part of different combination of medicines

HAS= Haute Autorité de Santé

Na= No assessment. HAS has not evaluated the medicine or indication.

Insuf. = The actual clinical benefit is insufficient

3 = moderate clinical added value (CAV), 4 = minor CAV, 5 = no improvement CAV.

Supplementary Table 3a. Assessment of cancer medicines with extension of indication by JBI (Joanna Briggs Institute) criteria.

Medicinal product, *active substance*, (ATC-code)						
	Study	**Setting**	**Randomisation and concealment of allocation (1–2)**	**Double-blinding (4–6)**	**Similarity of the compared groups (3,7,8)**	**Validity and reliability of the outcome assessment (9-12)**
Lonsurf *Trifluridine and tipiracil* (L01BC59)						
Original MA	TPU-TAS-102-301	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟢	🟢	🟡
1. ext	TAS-102-302	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟡
Bosulif *Bosutinib* (L01EA04)						
Original MA	200-WW	Open, non-controlled, phase I-II	⚪	⚪	⚪	🔴
1. ext	AV001	Randomised, open, active-controlled, phase III	🟡	⚪	🟢	🟢
Giotrif *Afatinib* (L01EB03)						
Original MA	LUX-Lung 3	Randomised, open, active-controlled, phase III	🟡	⚪	🟡	🟢
1. ext	LUX-Lung 8	Randomised, open, active-controlled, phase III	🟡	⚪	🟡	🔴
Tagrisso, *Osimertinib* (L01EB04)						
Original MA	201 & 210	Open, non-controlled, phase I-II (both)	⚪⚪	⚪⚪	⚪⚪	🟡🟡
1. ext	2014-002694-11	Randomised, double-blinded, active-controlled, phase III	🟢	🟢	🔴	🟢
2. ext	D5164C00001/ Adaura	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🔴
Tafinlar *Dabrafenib* (L01EC02)						
Original MA	BRF11368	Randomised, open, active-controlled, phase III	🟡	⚪	🟢	🟢
1. ext	MEK115306 MEK116513	Randomised, double-blinded, active-controlled, phase III Randomised, open, active-controlled, phase III	🟢🟡	🟡⚪	🟡🟢	🟢🟢

2. ext	BRF113928	Open, non-controlled, phase II	●	●	●	●
3. ext	BRF115532	Randomised, double-blinded, placebo-controlled, phase III	●	●	●	●
Braftovi, *Encorafenib* (L01EC03*)*						
Original MA	CMEK162B2301	Randomised, open, active-controlled, phase III	●	●	●	●
1. ext	ARRAY-818-302	Randomised, open, active-controlled, phase III	●	●	●	●
Xalkori, *Crizotinib* (L01ED01)						
Original MA	A8081001	Open, non-controlled, phase I-II	●	●	●	●
1. ext	A8081014	Randomised, open, active-controlled, phase III	●	●	●	●
2. ext	A8081001	Open, non-controlled, phase I-II	●	●	●	●
3.ext	ADVL0912	Open, non-controlled, phase I-II	●	●	●	●
Zykadia, *Ceritinib* (L01ED02)						
Original MA	CLDK378X2101	Open, non-controlled, phase I-II	●	●	●	●
1. ext	ASCEND-4/A2301	Randomised, open, active-controlled, phase III	●	●	●	●
Alecensa *Alectinib* (L01ED03)						
Original MA	NP28761, NP28673	Open, non-controlled, phase I-II Open, non-controlled, phase I-II	●●	●●	●●	●●
1. ext	BO28984	Randomised, open, active-controlled, phase III	●	●	●	●
Alunbrig *Brigatinib* (L01ED04)						
Original MA	AP26113-13-201	Randomised, open, non-controlled, phase II*	●	●	●	●
1. ext	AP26113-13-301	Randomised, open, active-controlled, phase III	●	●	●	●
Lorviqua, *Lorlatinib* (L01ED05)						

Original MA	PF-06463922	Open, non-controlled, phase I-II	●	●	●	●
1. ext	B7461006	Randomised, open, active-controlled, phase III	●	●	●	●
Mekinist, *Trametinib* (L01EE01)						
Original MA	MEK114267	Randomised, open, active-controlled, phase III	●	●	●	●
1. ext	MEK115306 MEK116513	Randomised, double-blinded, active-controlled, phase III Randomised, open, active-controlled, phase III	●●	●●	●●	●●
2. ext	BRF113928	Open, non-controlled, phase I-II	●	●	●	●
3. ext	BRF115532	Randomised, double-blinded, placebo-controlled, phase III	●	●	●	●
Kisqali *Ribociclib* (L01EF02)						
Original MA	MONALEESA-2	Randomised, double-blinded, placebo-controlled, phase III	●	●	●	●
1. ext	MONALEESA-7 MONALEESA-3	Randomised, double-blinded, placebo-controlled, phase III Randomised, double-blinded, placebo-controlled, phase III	●●	●●	●●	●●
Verzenios *abemaciclib* (L01EF03)						
Original MA	MONARCH 3 MONARCH 2	Randomised, double-blinded, placebo-controlled, phase III, Randomised, double-blinded, placebo-controlled, phase III	●●	●●	●●	●●
1. ext	monarchE	Randomised, open, active-controlled, phase III	●	●	●	●
Jakavi *Ruxolitinib* (L01EJ01)						
Original MA	352 351	Randomised, open, active-controlled, phase III Randomised, double-blinded, placebo-controlled, phase III	●●	●●	●●	●●
1. ext	B2301	Randomised, open, active-controlled, phase III	●	●	●	●
Imbruvica *Ibrutinib* (L01EL01)						

Original MA	PCYC-1112-CA PCYC-1104-CA	Randomised, open, active-controlled, phase III Open, non-controlled, phase II	🟡⚫	⚫⚫	🟢⚫	🔴🟢
1. ext	PCYC-1118E	Open, non-controlled, phase II	⚫	⚫	⚫	🔴
2. ext	PCYC-1115-CA	Randomised, open, active-controlled, phase III	🟡	⚫	🟡	🟢
3. ext	PCI-2765CLL3001	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟡	🟡	🟡
4. ext	1127	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟡
5. ext	E1912	Randomised, open, active-controlled, phase III	🟢	⚫	🟡	🟡
6.ext	CLL3011	Randomised, open, active-controlled, phase III	🟢	⚫	🟡	🟢
Zydelig *Idelalisib* (L01EM01)						
Original MA	GS-US-312-0116 & 101-09	Randomised, double-blinded, placebo-controlled, phase III Open, non-controlled, phase II	🟢⚫	🟢⚫	🟢⚫	🟢🟢
1. ext	GS-US-312-0119	Randomised, open, active-controlled, phase III	🟢	⚫	🟡	🔴
2. ext	GS-US-312-0115	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟢
Votrient *Pazopanib* (L01EX03)						
Original MA	VEG105192	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟢	🟢	🟢
1. ext	VEG110727	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟡	🟡	🟡
Caprelsa *Vandetanib* (L01EX04)						
Original MA	D4200C00058	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟡	🟡	🟢
1. ext	IRUSZACT0098	Open, non-controlled, phase II	⚫	⚫	⚫	🔴
Stivarga, *Regorafenib* (L01EX05)						
Original MA	14387	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟡	🔴	🟡
1. ext	14874	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟡	🟡	🟢

2. ext	15982	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟢
Lenvima, *Lenvatinibi* (L01EX08)						
Original MA	E7080-G000-303	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟡
1. ext	E7080-G000-304	Randomised, open, active-controlled, phase III	🟢	⚫	🟡	🟢
2. ext	E7080-G000-309	Randomised, open, active-controlled, phase III	🟢	⚫	🔴	🟡
Ayvakyt *Avapritinib* (L01EX18)						
Original MA	BLU-285-1101	Open, non-controlled, phase I-II	⚫	⚫	⚫	🔴
1. ext	BLU-285-2202	Open, non-controlled, phase I-II	⚫	⚫	⚫	🟢
Lynparza, *Olaparib (L01EK01)*						
Original MA	D0810C00019	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟢	🟢	🔴
1. ext	D0819C00003	Randomised, open, active-controlled, phase III	🟢	⚫	🔴	🟢
2. ext	D0818C00001	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟡
3. ext	D081FC00001	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟡
4. ext	D0817C00003	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟡	🔴	🟡
5. ext	D081DC00007	Randomised, open, active-controlled, phase III	🟡	⚫	🔴	🔴
6. ext	D081CC00006	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟢
7. ext	D081SC00001	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟡	🟢	🟢
Zejula *Niraparib (L01XK02)*						
Original MA	PR-30-5011-C	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟢	🟡	🟢
1. ext	PR-30-5017-C	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟡
Rubraca *Rucaparib (L01XK03)*						

Original MA	CO-338-010 CO-338-017	Open, non-controlled, phase I-II Open, non-controlled, phase I-II	⚫⚫	⚫⚫	⚫⚫	🔴🔴
1. ext	CO-338-014	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟡	🟡	🟡
Venclyxto, Venetoclax (L01XX52)						
Original MA	M13-982	Open, non-controlled, phase I-II	⚫	⚫	⚫	🔴
1. ext	MURANO	Randomised, open, active-controlled, phase III	🟡	⚫	🟡	🟢
2. ext	BO25323	Randomised, open, active-controlled, phase III	🟢	⚫	🟡	🟢
3. ext	M15-656 M16-043	Randomised, double-blinded, placebo-controlled, phase III (both)	🟡🟡	🟡🟡	🟢🟢	🟡🟢
Xtandi, *Enzalutamide (L02BB04)*						
Original MA	MDV3100	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟡
1. ext	MDV3100-03	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟢
2. ext	MDV3100 14	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟡
3. ext	9785-CL-0335	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟡
Erleada, Apalutamide (L02BB05)						
Original MA	ARN-509-003 (SPARTAN	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟢
1. ext	PCR3002 (TITAN)	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟢
Zytiga *Abiraterone (L02BX03)*						
Original MA	COU-AA-301	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟢	🟢	🟡
1. ext	COU-AA-302	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟡	🟢	🟡

2. ext	212082PCR3011	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟡	🟢
Imnovid *Pomalidomide (L04AX06)*						
Original MA	CC-4047-MM-003	Randomised, open, active-controlled, phase III	🟡	⚫	🟡	🟢
1. ext	MM-007	Randomised, open, active-controlled, phase III	🟢	⚫	🟡	🟢
Teysuno, Tegafur, gimeracil and oteracil (L01BC53)						
Original MA	S-1301/FLAGS	Randomised, open, active-controlled, phase III	🟢	⚫	🟢	🟢
1. ext	-	Exploratory and retrospective Meta-analysis	⚫	⚫	⚫	🟡

* Dose comparison,
MA= Marketing authorization,
ext. = Extension of indication

Supplementary Table 3b. Assessment of cancer medicines without extension of indication by JBI (Joanna Briggs Institute) criteria.

Medicinal product, *active substance*, (ATC-code)						
	Study	**Setting**	**Randomization and concealment of allocation (1–2)**	**Double-blinding (4–6)**	**Similarity of the compared groups (3,7,8)**	**Validity and reliability of the outcome assessment (9-12)**
Calquence, Acalabrutinib (L01XE51)						
Original MA	ACE-CL-007, ACE-CL-309	Randomised, open, active-controlled, phase III (both)	🟢🟢	⚪	🔴🔴	🟡🟢
Daurismo, glasdegib (L01XX63)						
Original MA	B1371003	Randomised, open, active-controlled, phase III	🟢	⚪	🟢	🟢
Nubega, darolutamide (L02BB)						
Original MA	ARAMIS 17712	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟡	🟡	🟢
Piqray Alpelisib (L01XE)						
Original MA	C2301 (SOLAR-1)	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟢
Rozlytrek, Entrectinib (L01EX14)						
Original MA	GO40782, STARTRK-2)	Open, non-controlled, phase I-II (basket study)	⚪	⚪	⚪	🔴
Talzenna, Talazoparib (L01E)						
Original MA	673-301 (EMBRACA)	Randomised, open, active-controlled, phase III	🟢	⚪	🟢	🟢
Vitrakvi, Larotrectinib (L01E)						
Original MA	LOXO-TRK-15002 (NAVIGATE)	Open, non-controlled, phase I-II (basket study)	⚪	⚪	⚪	🔴
Vizimpro, Dacomitib, (L01EB07)						
Original MA	ARCHER 1050	Randomised, open, active-controlled, phase III	🟢	⚪	🟢	🟢

Xospata, gilteritinib, (L01EX13)						
Original MA	ADMIRAL (2215-CL-0301)	Randomised, open, active-controlled, phase III	🟢	⚪	🟢	🟢
Mektovi, binimetinib, (L01EE03)						
Original MA	COLUMBUS CMEK162B2301	Randomised, open, active-controlled, phase III	🟢	⚪	🟢	🟡
Nerlynx, neratinib , (L01EH02)						
Original MA	3144A2-3004-WW	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟡	🟢	🟢
Fotivda, tivozanib, (L01EK03)						
Original MA	AV-951-09-301	Randomised, open, active-controlled, phase III	🟢	⚪	🔴	🟢
Rydapt, midostaurin, (L01XE)						
Original MA	RATIFY (A2301)	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟡	🟡	🟢
Ibrance, palbociclib (L01XE)						
Original MA	1023 (PALOMA-3) 1008 (PALOMA-2)	Randomised, double-blinded, placebo-controlled, phase III	🟡🟡	🟡🟡	🟡🟡	🟢🟢
Ninlaro, ixazomib (L01XG03)						
Original MA	C16010	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟡	🟢	🟡
Cotellic, cobimetinib (L01XE38)						
Original MA	GO28141/coBRI	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟡	🟢	🟢
Farydak, panobinostat (L01XH03)						
Original MA	CLBH589D2308 (Panorama I)	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟡	🟡	🟢

Odomzo, sonidegib (L01XJ02)						
Original MA	A2201 (BOLT)	Randomised, double-blinded, non-comparative, phase II	🟢	🟢	🟡	🟢
Cometriq, cabozantinib (L01XE)						
Original MA	XL184-301	Randomised, double-blinded, placebo-controlled, phase III	🟡	🟡	🟡	🟢
Vargatef, nintedanib (L01XE3)						
Original MA	XL184-301	Randomised, double-blinded, placebo-controlled, phase III	🟢	🟢	🟢	🟡
Erivedge, vismodegib (L01XX43)						
Original MA	SHH4476g	Open, non-controlled, phase-II (basket study)	⚪	⚪	⚪	🟡
Iclusig, ponatinib (L01EA05)						
Original MA	AP24534-10-201	Open, non-controlled, phase-II	⚪	⚪	⚪	🟡
Inlyta, axitinib (L01EK01)						
Original MA	A4061032	Randomised, open, active-controlled, phase III	🟡	⚪	🟢	🟢
Zelboraf, vemurafenib (L01XE15)						
Original MA	NO25026 (BRIM 3)	Randomised, open, active-controlled, phase III	🟢	⚪	🟡	🟢

MA= Marketing authorisation,
ext. = Extension of indication

Research and reporting methodology
Revised **Standards for QUality Improvement Reporting Excellence** (**SQUIRE 2.0**) publication guidelines

Notes to authors

- The SQUIRE guidelines provide a framework for reporting new knowledge about how to improve healthcare.
- The SQUIRE guidelines are intended for reports that describe system level work to improve the quality, safety and value of healthcare, and used methods to establish that observed outcomes were due to the intervention(s).
- A range of approaches exists for improving healthcare. SQUIRE may be adapted for reporting any of these.
- Authors should consider every SQUIRE item, but it may be inappropriate or unnecessary to include every SQUIRE element in a particular manuscript.
- The SQUIRE glossary contains definitions of many of the key words in SQUIRE.
- The explanation and elaboration document provides specific examples of well-written SQUIRE items and an in-depth explanation of each item.
- Please cite SQUIRE when it is used to write a manuscript.

Text section and item name	Page/line no(s). info is located
Title and abstract:	**page 1–2**
1. **Title** : **New cancer medicines in Europe 2010-2020: comparison of medicines with or without extensions of indications**	
Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient-centredness, timeliness, cost, efficiency and equity of healthcare).	Pages 2 lines 75-114
2. **Abstract**	
a. Provide adequate information to aid in searching and indexing.	page 2, lines 35–38
b. Summarise all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions.	page 2, lines 35–50
Introduction: Why did you start?	
3. **Problem description** - Nature and significance of the local problem.	page 3 lines 78–100
4. **Available knowledge** - Summary of what is currently known about the problem, including relevant previous studies.	page 3, lines 76–99
5. **Rationale** - Informal or formal frameworks, models, concepts and/or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s) and reasons why the intervention(s) was expected to work	page 3 lines 75–82 and lines 93–100
6. **Specific aims** - Purpose of the project and of this report.	page 3 lines 110–114
Methods: What did you do?	page 3, lines 118–152
7. **Context** - Contextual elements considered important at the outset of introducing the intervention(s).	page 3, lines 104–109

	page 4 lines 133–153

8. **Intervention(s)**	
a. Description of the intervention(s) in sufficient detail that others could reproduce it.	page 4, lines 133–136
b. Specifics of the team involved in the work.	page 10, lines 322–325
9. **Study of the intervention(s)**	
a. Approach chosen for assessing the impact of the intervention(s).	page 3, lines 131–135; lines 150–152
b. Approach used to establish whether the observed outcomes were due to the intervention(s).	not applicable
10. **Measures**	
a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions and their validity and reliability.	page 4, lines 132–153, also supplementary table 1
b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency and cost.	not applicable
c. Methods employed for assessing completeness and accuracy of data.	Page 4, lines 121–130 and Supplementary Figure 1 and Supplementary tables 2 & 3
11. **Analysis**	
a. Qualitative and quantitative methods used to draw inferences from the data.	Page 4 lines 132–140; lines 142–153
b. Methods for understanding variation within the data, including the effects of time as a variable.	Figure 1, discussion section, page 9, heading strengths and limitations, lines 290–301
12. **Ethical considerations** - Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest.	Page 10, lines 314–315
Results: What did you find?	
13. **Results**	
a. Initial steps of the intervention(s) and their evolution over time (eg, time-line diagram, flow chart or table), including modifications made to the intervention during the project.	Supplementary Figure 1, Supplementary tables 2–3,
b. Details of the process measures and outcomes.	Figure 1–2, text page 5 lines 161–226, Supplementary tables 2–3,
c. Contextual elements that interacted with the intervention(s).	not applicable

d. Observed associations between outcomes, interventions and relevant contextual elements.	Page 7–8, lines 204–227
e. Unintended consequences such as unexpected benefits, problems, failures or costs associated with the intervention(s).	Page 9 lines 304–307
f. Details about missing data.	Page 9, lines 290–300
Discussion: What does it mean?	
14. **Summary**	
a. Key findings, including relevance to the rationale and specific aims.	page 8, lines 230–239
b. Particular strengths of the project.	Page 9, lines 290–297
15. **Interpretation**	
a. Nature of the association between the intervention(s) and the outcomes.	page 8 lines 241–250
b. Comparison of results with findings from other publications.	pages 8–9, lines 241–250; lines 266–269; lines 274–277
c. Impact of the project on people and systems.	Page 8 lines 281–288
d. Reasons for any differences between observed and anticipated outcomes, including the influence of context.	page 8, lines 245–250
e. Costs and strategic trade-offs, including opportunity costs.	Not applicable
16. **Limitations**	
a. Limits to the generalisability of the work.	Pages 9–10, lines 298–308
b. Factors that might have limited internal validity such as confounding, bias or imprecision in the design, methods, measurement or analysis.	Pages 9, lines 297–308
c. Efforts made to minimise and adjust for limitations.	page 9, lines ; 291–298
Conclusions	
a. Usefulness of the work.	Page 9, lines 274–288
b. Sustainability.	Page 9, lines 286–288
c. Potential for spread to other contexts.	Page 9, lines 281–286
d. Implications for practice and for further study in the field.	Page 9 lines 274–288
e. Suggested next steps.	Page 9, lines 272–273
Other information	
18. **Funding** - Sources of funding that supported this work. Role, if any, of the funding organisation in the design, implementation, interpretation and reporting.	Page 10, lines 321