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

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-083549
Article Type:	Original research
Date Submitted by the Author:	21-Dec-2023
Complete List of Authors:	Ruuskanen, Anna-Maria; The Social Insurance Institution of Finland Kurko, Terhi; The Social Insurance Institution of Finland Sarnola, Kati; The Social Insurance Institution of Finland Klintrup, Katariina; The Social Insurance Institution of Finland Koskinen, Hanna; The Social Insurance Institution of Finland
Keywords:	Clinical trials < THERAPEUTICS, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, ONCOLOGY

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Ruuskanen Anna-Maria and Kurko Terhi Sarnola Kati Klintrup Katariina Koskinen Hanna

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.

	Total number of	Number o	of medicines	Total number of extensions	njopen-2023-083649 Type of extension(s) of Tiple					New mechanisms
First indication	medicines (of all medicines)	with extension	without extension		Treatment line	Cancer type	Combina- tion type	Mu g iple change	Patient type	of action*
Hematological malignancies - leukemia - multiple myeloma - lymphoma - myelofibrosis	13 (24%)	6 (46%)	7 (54%)	14	2	3	6	October 2024. Downloaded from http://bmjopen.bmj.com/ on June Enseignement Superieur (ABES)	-	10 (77%)
Lung cancer	9 (16%)	7 (78%)	2 (22%)	10	6	-	-	ownlo	3	3 (33%)
Melanoma & basal cell carcinoma	8 (15%)	3 (38%)	5 (63%)	7	2	3	2	aded fro grieur (A	-	3 (38%)
Breast cancer	6 (11%)	2 (33%)	4 (67%)	2	1	-	1	m http BES)	-	4 (67%)
Prostate cancer	4 (7%)	3 (75%)	1 (25%)	6	6	-	-	//bmjo	-	2 (50%)
Colorectal or gastric cancer	4 (7%)	4 (100%)	0 (0%)	5	-	5	-	bmjopen.bm Al training, a	-	2 (50%)
Kidney cancer	3 (5%)	1 (33%)	2 (67%)	1	-	1	-	com/	-	2 (67%)
Thyroid cancer	3 (5%)	2 (67 %)	1 (33%)	3	-	2	-	i.com/ on June 11, 2025	1	1 (33%)
Gynecological cancers	3 (5%)	3 (100%)	0 (0%)	9	3	3	1	thnolo	-	1 (33%)
Solid tumors	2 (4%)	0 (0%)	2 (100%)	0	-	-	-	<u>.</u> නි	-	1 (50%)
Total Based on the number of r	55 (100%)	31 (56%)	24 (44%)	57 (100%)	20 (35%)	17 (30%)	10 (18%)	Agen£11%)	4 (7%)	

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

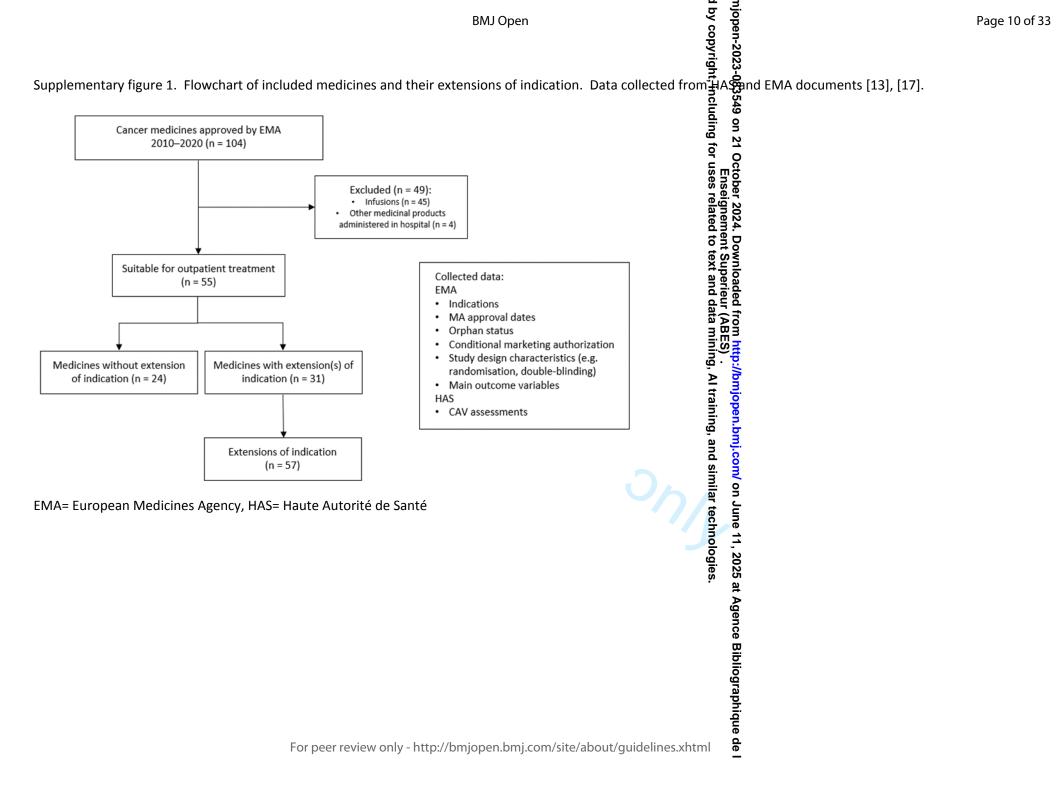
Funding: Not applicable

Acknowledgements: Not applicable

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The medicine was authorized for a different treatment of O
line or stage of the disease (e.g., the first MA* for
metastatic disease and the extension for adjuvant
The medicine was authorized for another cancer type
(e.g., the first MA for melanoma and the extension of
indication for lung cancer)
who was a second with a second
The medicine was authorized for different patients
than previously (e.g., the first MA for certain mutation at 1
type and the extension for another mutation 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).
ories of extensions used in this study [15]. Description of category 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). The medicine was authorized for another cancer type (e.g., the first MA for melanoma and the extension of indication for lung cancer) 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 and the extension for another mutation type and the extension of medicines (e.g., the first MA only as a monotherapy, the extension as a part of certain combination therapy). At least two previously introduced categories are met.
similar technologies. 11, 2005; ancer medicines. Medicines without extension of indication are markers.
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Medicinal product, active substance,	First indication	Conditional marketing	Orphan status ¹	Accelerated	Additional	Extension(s) of indication according to the	HAS
date		authorisation ¹		assessment	monitoring	tyee of the extension ² , date	
L01B Antimetabolites						en	
L01BC Pyrimidine analogues						Се	
Teysuno®, tegafur, gimeracil and	gastric cancer	-	Previously yes, now	-	-	1. oncer type (colorectal cancer), 24.1.2022	Na
oteracil.			withdrawn			<u> </u>	Insuf.
14.3.2011						lio	
Lonsurf®, trifluridine and tipiracil,	colorectal cancer	-	-	-	-	1. Gincer type (gastric cancer), 3.9.2019	5
25.4.2016						a p	5
L01E Protein kinase inhibitors						<u> </u>	

			BMJ Open			njopen-2023-08	
L01EA BCR-ABL tyrosine kinası	e inhibitors					ight, 08	
Bosulif®, bosutinib,	chronic myelogenous	-	Previously yes, now	-	-	1. Gratment line , 23.4.2018	5
27.3.2013 Iclusig®, <i>ponatinib</i> ,	leukaemia		withdrawn Yes	Yes	-	tudin	5
1.7.2013						ng n 21	5/4/3
	receptor (EGFR) tyrosine kinase inhib	oitors		1	1	0	
Giotrif®, <i>afatinib</i> , 25.9.2013	lung cancer	-	-	-	-	1. Attient type (mutation), 31.3.2016	5 5
Tagrisso®, osimertinib, 2.2.2016	lung cancer	Previously yes, now full authorisation	-	Yes	Yes	7 5. Seatment line, 7.6.2018 Freatment line + patient type (mutation),	5 4 3
Vizimpro®, dacomitinib, 2.4.2019	lung cancer	-	-	-	Yes	31emed 22021	5
L01EC B-Raf serine-threonine ki	nase (BRAF) inhibitors					ਰੇ ਤੁੱ D	
Zelboraf [®] , <i>vemurafenib</i> , 17.2.2012	melanoma	-	-	-	-	wn le	3
Tafinlar®, dabrafenib, 26.8.2013	melanoma	Do	-	-	-	description of the content of the co	5 Na 5 3
Braftovi®, encorafenib, 20.9.2018	melanoma	- 60%	-	-	Yes	eancer type (colorectal cancer), 2.6.2020	5 3
L01ED Anaplastic lymphoma kin	nase (ALK) inhibitors					<u>0</u> .	
Xalkori®, <i>crizotinib</i> , 23.10.2012	lung cancer	-	(e),	-	-	1. Treatment line, 23.11.2015 2. Traitient type (mutation), 25.8.2016 3. Traitient type (adolescents), 28.10.2022	3 4 5 4
Zykadia®, <i>ceritinib,</i> 6.5.2015	lung cancer	Previously yes, now full authorisation	- //)-,	-	1. reatment line, 23.6.2017	4 4
Alecensa®, <i>alectinib</i> , 16.2.2017	lung cancer	-	-	1/	-	1. reatment line, 18.12.2017	4
Alunbrig®, <i>brigatinib</i> , 22.11.2018	lung cancer	-	-	-)	1. ceatment line, 1.4.2020	5 4
Lorviqua®, <i>lorlatinib</i> , 6.5.2019	lung cancer	Yes	-	-	Yes	1. reatment line, 27.1.2022	5 4
L01EE Mitogen-activated protein	kinase (MEK) inhibitors			'		c a	
Mekinist®, trametinib, 30.6.2014	melanoma	-	-	-	-	1. combination type, 25.8.2015 2. concer type (lung cancer), 27.3.2017 3. Reatment line, 27.8.2018	3 Na 5 3
Cotellic®, <i>cobimetinib</i> , 20.11.2015	melanoma	-	-	-		at A	3
Mektovi [®] , <i>binimetinib</i> , 20.9.2018	melanoma	-	-	-	Yes	Agence	5
L01EF Cyclin-dependent kinase ((CDK) inhibitors				•	Ö	
Ibrance®, <i>palbociclib</i> , 9.11.2016	breast cancer	-	-	-	Yes	1.@mbination type, 17.12.2018	4
Kisqali [®] , <i>ribociclib</i> , 22.8.2017	breast cancer	-	-	-	Yes	1. combination type, 17.12.2018	3 4

			BMJ Open			by copyrigh 1.1.835met line, 1.4.2022	
Verzenios®, abemaciclib, 27.9.2018	breast cancer	-	-	-	Yes	1.1.00 atment line, 1.4.2022	5/4 5
				1		3549	3
	factor receptor 2 (HER2) tyrosine kir	nase inhibitors	1			dir	
Nerlynx®, <i>neratinib</i> , 81.8.2018	breast cancer	-	-	-	yes	on 21	Insu
L01EJ Janus-associated kinase (JA	AK) inhibitors					9 –	
Jakavi [®] , <i>ruxolitinib</i> ,	myelofibrosis	-	Previously yes, now	-	-	mancer type (polysytemia vera), 11.3.2015	3
23.8.2012	,		withdrawn			es ns	4
L01EK Vascular endothelial grow	th factor receptor (VEGFR) tyrosine	kinase inhibitors				eig eig	
Inlyta [®] , <i>axitinib</i> , 3.9.2012	kidney cancer	-	Previously yes, now withdrawn	-	Yes	To OC The Bracer type (polysytemia vera), 11.3.2015	4
Fotivda®, <i>tivozanib</i> , 24.8.2017	kidney cancer	-	-	-	Yes	Downlent Su	Insu
L01EL Bruton's tyrosine kinase (E						e S e	
Imbruvica®, <i>ibrutinib</i> , 27.10.2014	mantle cell lymphoma and chronic lymphocytic leukaemia	Deer	Previously yes, now withdrawn	-	-	Cancer type (Walderström's Ca	3 Na 4 Na Insu 3 4
Calquence®, <i>acalutinib</i> , 5.11.2020	leukaemia		Previously yes, now withdrawn		Yes	. (b://p	Na
L01EM Phosphatidylinositol-3-kii	nase (Pi3K) inhibitors					<u> </u>	
Zydelig [®] , <i>Idelalisib,</i> 18.9.2014	follicular lymphoma and chronic lymphocytic	-	Vi	-	Yes	1. Sombination type, 19.9.2016 2. Combination type, 23.4.2018	5/4 Na Na
Piqray®, alpelisib, 27.7.2020	leukaemia breast cancer	-	- (7	Yes	.bmj.a	Insi
L01EX Other protein kinase inhib	itors					<u>a</u> .	
Votrient®, pazopanib, 14.6.2010	renal cell carcinoma	Yes	Previously yes, now withdrawn	- 1		1. Sancer type (soft-tissue sarcoma), 24.8.2012	5
Caprelsa®, <i>vandetanib</i> , 16.2.2012	thyroid cancer	Yes	-	-	Yes	1. patient type (paediatric patients), 12.12.2016	4 5
Stivarga®, <i>regorafenib,</i> 26.8.2013	colorectal cancer	-	-	-	- 1	1. @ancer type (gastrointestinal stromal tumors), 27.10.2014 2. cancer type (hepatocellular carcinoma), 2.82017	5 4 4
Cometriq®, cabozantinib, 21.3.2014	medullary thyroid cancer	-	Yes	-	-	s - 5 at	4
Lenvima®, <i>lenvatinib</i> , 28.5.2015	thyroid cancer	-	Previously yes, now withdrawn	Yes	Yes	1. Sencer type (liver cancer), 20.8.2018 2. Sencer type (endometrial carcinoma), 26 1.2021	4 Insi 3
Vargatef®, <i>nintedanib,</i> 21.11.2014	lung carcinoma	-	-	-	-	_ 0	Inst
Rydapt®, <i>midostaurin</i> , 18.9.2017	acute myeloid leukaemia, mastocytosis	-	Yes	-	Yes	Bibliographiqu	4/:
Vitrakvi [®] , <i>larotrectinib</i> , 19.9.2019	solid tumours with NTRK gene fusion	Yes	Previously yes, now withdrawn	-	Yes	raph	4

			BMJ Open			njopen-2023-083549 o	
			_	_		023-(
Xospata [®] , <i>gilteritinib</i> , 24.10.2019	acute myeloid leukemia	-	Yes	-	Yes	; inc	4
Rozlytrek®, <i>entrectinib</i> , 31.7.2020	solid tumors with NTRK fusion, lung cancer	Yes	-	-	Yes	49 o	Insuf.
Ayvakyt [®] , avapritinib, 24.9.2020	gastrointestinal stromal tumours	Yes	Yes	-	Yes	1. Sancer type (mastocytosis), 24.3.2022	5 4
L01X Other antineoplastic agents						ž 0	
L01XG Proteasome inhibitors						Octo er use	
Ninlaro®, <i>ixazomib</i> , 21.11.2016	multiple myeloma	yes	yes	-	Yes	ber 2 seig	5
L01XH Histone deacetylase (HDA0	C) inhibitors					202	
Farydak®, <i>panobinostat</i> , 28.8.2015	multiple myeloma	-	Yes	-	Yes	ober 2024. Dov Enseignement :	5
L01XJ Hedgehog pathway inhibitor	s		•	•	'	e S ≤	
Erivedge®, <i>vismodegib</i> , 12.7.2013	basal cell carcinoma	· -	-	-	Yes	ownloaded from he take the tand data min	4
Odomzo®, sonidegib, 14.8.2015	basal cell carcinoma	<i>i</i> O ₀	-	-	Yes	eur d d da	4
Daurismo®, <i>glasdegib</i> , 26.6.2020	acute myeloid leukaemia	60	Yes	-	Yes	om ABE	Na
L01XK Poly (ADP-ribose) polymer	rase (PARP) inhibitors					nir S)	
Lynparza®, <i>olaparib</i> , 16.12.2014	ovarian, fallopian tube or primary peritoneal cancer		Previously yes, now withdrawn) 	-	1. cancer type (breast cancer), 8.4.2019 2. catment line, 12.6.2019 3. cancer type (pancreatic cancer), 3.7.2020 4. Symbination type, 3.11.2020 5. cancer type (prostate cancer), 3.11.2020 6. catment line (breast cancer), 2.8.2022 7. catment line + combination (prostate cancer), 16.12.2022	4 5 4 5 4 4 3 4
Zejula [®] , <i>niraparib</i> , 16.11.2017	ovarian, fallopian tube or primary peritoneal cancer	-	Yes	-	Yes	1. Reatment line, 27.10.2020	4 4
Rubraca®, <i>rucaparib</i> , 24.5.2018	ovarian, fallopian tube or primary peritoneal cancer	Yes	Previously yes, now withdrawn	-	Yes	1. Seatment line + patient type (mutation), 23 2019	Insuf. 4
Talzenna®, <i>talazoparib</i> , 20.6.2019	breast cancer	-	-	-	Yes	une -	5
L01XX Other antineoplastic agents						70 11	
Venclyxto®, <i>venetoclax</i> , 5.12.2016	chronic lymphocytic leukaemia	Previously yes, now full authorisation	Previously yes, now withdrawn	-	Yes	1. reatment line + combination type, 29 30.2018 2. Reatment line + combination typfe, 9.3.2020 3. Ancer type (acute myeloid leukaemia), 22 2021	5 4 3 4
L02B Hormone antagonists and rela	nted agents					gen	
L02BB Anti-androgens Xtandi®, enzalutamide, 21.6.2013	prostate cancer	-	-	-	-	1. bratment line, 28.11.2014 2. bratment line, 23.10.2018 3. bratment line, 30.4.2021	3 4 3 3
Erleada®, <i>apalutamide</i> , 14.1.2019	prostate cancer	-	-	-	Yes	1. Seatment line, 27.1.2020	3 3

Page 15 of 33				BMJ Open			mjopen-2023-0835	
1	Nubega® darolutamide	nrostate cancer				Ves	righ - 08	3
3	27.3.2020	P					inc 35	
4	L02BX Other hormone antagonist	s and related agents					49	_
5	Zytiga [®] , abiraterone,	prostate cancer	-	-	Yes	-	1. Seatment line, 18.12.2012	$\begin{bmatrix} 3 \\ 4 \end{bmatrix}$
6	3.7.2011						6 2. N atiliciti lilic, 13.11.2017	3
7	L04A Immunosuppressants						<u>- 0</u>	
8	L04AX Other immunosuppressan	multiple myeloma		Vec		Vec	(7) Deatment line + new combination 13 5 2019	5
9	5.8.2013	multiple myeloma	-	168	-	1 65	To be the combination, 13.3.2019	5
10	In some stage of the product li	fe cycle			•		gne at	
11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	type = authorised for different p HAS= Haute Autorité de Santé Na= No assessment. HAS has n Insuf. = The actual clinical bene 3 = moderate clinical added value			CAV.			copyright; including for uses related to the disease, e.g. after a surgery, Parish the disease, e.g. after a surge	itteni

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

	Study	Setting	Randomization and	Double- →	21	Similarity of the	Validity and reliabilit
	Study	Setting	concealment of allocation (1–2)	blinding 4	- 8	compared groups (3,7,8)	of the outcome assessment (9-12)
onsurf <i>Triflui</i>	ridine and tipiracil (L01BC59)		elate	202		
Original MA	TPU-TAS-102- 301	Randomized, double-blinded, placebo-controlled, phase III		d to text	tober 2024. Downloaded from http://bm		
L. ext	TAS-102-302	Randomized, double-blinded, placebo-controlled, phase III		and o	oade		
Bosulif <i>Bosuti</i>	nib (L01EA04)			data I	d from		
Original MA	200-WW	Open, non-controlled, phase I-II		nin in	n hit		
L. ext	AV001	Randomized, open, active-controlled, phase III		g, Al	nd//:c		
Giotrif <i>Afatini</i>	b (L01EB03)			Al training,	njope		
Original MA	LUX-Lung 3	Randomized, open, active-controlled, phase III		ing, a	n.bmj		
L. ext	LUX-Lung 8	Randomized, open, active-controlled, phase III	0	and similar	j.com	•	
Γagrisso, <i>Osin</i>	nertinib (L01EB04)			milar	on .		
Original MA	201 & 210	Open, non-controlled, phase I-II (both)	••		June	••	
L. ext	2014-002694-11	Randomized, double-blinded, active-controlled, phase III		technologies	11, 2	•	
2. ext	D5164C00001/ Adaura	Randomized, double-blinded, placebo-controlled, phase III	•	es.	2025 at Age		
Tafinlar <i>Dabro</i>	afenib (L01EC02)				gence		
Original MA	BRF11368	Randomized, open, active-controlled, phase III			Bibliographiq		
l. ext	MEK115306	Randomized, double-blinded, active-controlled, phase III			iogr		••

33		BMJ Open		by copyright, including	njopen-2023-	
	MEK116513	Randomized, open, active-controlled, phase III		ht, inc	3-0835	
2. ext	BRF113928	Open, non-controlled, phase II		• dudir	49 on	•
3. ext	BRF115532	Randomized, double-blinded, placebo-controlled, phase III		for	21 0	
Braftovi, Enco	rafenib (L01EC03)			Ense uses r	ctob	
Original MA	CMEK162B2301	Randomized, open, active-controlled, phase III		rela	er 20	
1. ext	ARRAY-818-302	Randomized, open, active-controlled, phase III		emen led to	24. D	•
Xalkori, <i>Crizo</i>	tinib (L01ED01)			reignement Superieur (ABES) . related to text and data mining, AI trainir	ownie	
Original MA	A8081001	Open, non-controlled, phase I-II		and o	padeo	•
1. ext	A8081014	Randomized, open, active-controlled, phase III		data r	d from	•
2. ext	A8081001	Open, non-controlled, phase I-II		nininin	n http	
3.ext	ADVL0912	Open, non-controlled, phase I-II		, <u>≽</u>	e.//bm	
Zykadia, Cerit	inib (L01ED02)			traini	Jope	
Original MA	CLDK378X2101	Open, non-controlled, phase I-II		ng, a	.bmj	•
1. ext	ASCEND- 4/A2301	Randomized, open, active-controlled, phase III		Al training, and simila	.bmj.com/ on	•
Alecensa Alec	tinib (L01ED03)				June	
Original MA	NP28761,	Open, non-controlled, phase I-II	••	technologies	<u> </u>	••
	NP28673	Open, non-controlled, phase I-II		ogies	2025	
1. ext	BO28984	Randomized, open, active-controlled, phase III			<u>a</u>	•
Alunbrig Brige	atinib (L01ED04)				Agence	
Original MA	AP26113-13- 201	Randomized, open, non-controlled, phase II*			Bibliograph	

				gh	23		
1. ext	AP26113-13- 301	Randomized, open, active-controlled, phase III		t, includ	083549		-
Lorviqua, Lorl	atinib (L01ED05)			ling f	on 21		
Original MA	PF-06463922	Open, non-controlled, phase I-II		or us	OCT	•	
1. ext	B7461006	Randomized, open, active-controlled, phase III		es re	ober		
Mekinist, Trai	metinib (L01EE01)			lated	2024.		
Original MA	MEK114267	Randomized, open, active-controlled, phase III		to te	Dow		
1. ext	MEK115306 MEK116513	Randomized, double-blinded, active-controlled, phase III Randomized, open, active-controlled, phase III	••	ight, including for uses related to text and data mining, Al training, and similar technologies	nloaded fi		
2. ext	BRF113928	Open, non-controlled, phase I-II		a min	OM h		
3. ext	BRF115532	Randomized, double-blinded, placebo-controlled, phase III		uing,	ttp://		
Kisqali <i>Ribocio</i>	clib (L01EF02)			Al tra	mjo		
Original MA	MONALEESA-2	Randomized, double-blinded, placebo-controlled, phase III		ining	en.b		
1. ext	MONALEESA-7	Randomized, double-blinded, placebo-controlled, phase III	•••	and	mj.cc		••
	MONALEESA-3	Randomized, double-blinded, placebo-controlled, phase III		simi	m/ oi		
Verzenios abe	maciclib (L01EF03)			ar tec	Jun		
Original MA	MONARCH 3	Randomized, double-blinded, placebo-controlled, phase III,	••	hno	e 11,		••
	MONARCH 2	Randomized, double-blinded, placebo-controlled, phase III		ogies	2025		
1. ext	monarchE	Randomized, open, active-controlled, phase III		•	at A		
Jakavi Ruxolit	inib (L01EJ01)				at Agence		
Original MA	352	Randomized, open, active-controlled, phase III	••				••
	351	Randomized, double-blinded, placebo-controlled, phase III			Bibliograph		
					머		

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1. ext	B2301	Randomized, open, active-controlled, phase III		ht, inc		
Imbruvica Ibr	utinib (L01EL01)			Sludir	49 on	
Original MA	PCYC-1112-CA PCYC-1104-CA	Randomized, open, active-controlled, phase III Open, non-controlled, phase II		g for uses	21 Octob	
1. ext	PCYC-1118E	Open, non-controlled, phase II		seigneme related	er 20	•
2. ext	PCYC-1115-CA	Randomized, open, active-controlled, phase III		emen ted to	24. D	•
3. ext	PCI- 2765CLL3001	Randomized, double-blinded, placebo-controlled, phase III	•	nent Superieur (AE d to text and data	ownload	•
4. ext	1127	Randomized, double-blinded, placebo-controlled, phase III		eur (<i>i</i> data	ed fr	•
5. ext	E1912	Randomized, open, active-controlled, phase III		ABES). a mining, Al	<u> </u>	•
6.ext	CLL3011	Randomized, open, active-controlled, phase III		ing, \	#p://r	
Zydelig <i>Idelali</i>	isib (L01EM01)			Al trai	ğ Ö	
Original MA	GS-US-312-0116 & 101-09	Randomized, double-blinded, placebo-controlled, phase III Open, non-controlled, phase II		training, and	mjopen.bmj.co	
1. ext	GS-US-312-0119	Randomized, open, active-controlled, phase III		Similari	m/ on	•
2. ext	GS-US-312-0115	Randomized, double-blinded, placebo-controlled, phase III			n June	
Votrient Pazo	panib (L01EX03)			hnol	e 11 1,	
Original MA	VEG105192	Randomized, double-blinded, placebo-controlled, phase III		ologies	2025	
1. ext	VEG110727	Randomized, double-blinded, placebo-controlled, phase III			<u>a</u>	•
Caprelsa Vand	detanib (L01EX04)				Agence	
Original MA	D4200C00058	Randomized, double-blinded, placebo-controlled, phase III			B b	•
1. ext	IRUSZACT0098	Open, non-controlled, phase II			Bibliographi	•

		BMJ Open		;	njopen-2023-083549 on 2			Pag
Stivarga, Rego	orafenib (L01EX05)				-0835			
Original MA	14387	Randomized, double-blinded, placebo-controlled, phase III			649 on			
1. ext	14874	Randomized, double-blinded, placebo-controlled, phase III	•		→ ''2			
2. ext	15982	Randomized, double-blinded, placebo-controlled, phase III			October 2024. I Enseigneme or uses related t			
Lenvima, <i>Lenv</i>	ratinibi (L01EX08)				oer 20 seign s rela			
Original MA	E7080-G000- 303	Randomized, double-blinded, placebo-controlled, phase III		•)24. Down nement Stated to te			
1. ext	E7080-G000- 304	Randomized, open, active-controlled, phase III		•	Downloaded from http://bmjopen.bmjent Superieur (ABES) . to text and data mining. Al training, a	•	•	
2. ext	E7080-G000- 309	Randomized, open, active-controlled, phase III		•	from htt (ABES) ta minin		•	
Ayvakyt Avap	ritinib (L01EX18)				p://br			
Original MA	BLU-285-1101	Open, non-controlled, phase I-II			mjopen.bn I training.		•	
1. ext	BLU-285-2202	Open, non-controlled, phase I-II		•	n.br		•	
Lynparza, <i>Ola</i>	parib (L01EK01)				nd 🔀			
Original MA	D0810C00019	Randomized, double-blinded, placebo-controlled, phase III			om/ on similar		•	
1. ext	D0819C00003	Randomized, open, active-controlled, phase III				•	•	
2. ext	D0818C00001	Randomized, double-blinded, placebo-controlled, phase III			11,		•	
3. ext	D081FC00001	Randomized, double-blinded, placebo-controlled, phase III			2025 a ogies.		•	
4. ext	D0817C00003	Randomized, double-blinded, placebo-controlled, phase III					•	
5. ext	D081DC00007	Randomized, open, active-controlled, phase III	•		Agence		•	
6. ext	D081CC00006	Randomized, double-blinded, placebo-controlled, phase III			Biblic			
7. ext	D081SC00001	Randomized, double-blinded, placebo-controlled, phase III		•	Bibliographiq		•	

of 33		BMJ Open		by copyright, including	njopen-2023- <mark>08354</mark> 9		
Zejula <i>Nirapa</i>	rib (L01XK02)			nt, ii	-083		
Original MA	PR-30-5011-C	Randomized, double-blinded, placebo-controlled, phase III		cludii	549 on		
1. ext	PR-30-5017-C	Randomized, double-blinded, placebo-controlled, phase III		δ	21 (•	
Rubraca Ruca	parib (L01XK03)			uses	October 2024. Enseigneme		
Original MA	CO-338-010	Open, non-controlled, phase I-II	00	Tela S	er 20 seign	00	••
	CO-338-017	Open, non-controlled, phase I-II		ited to)24. D Iemer		
1. ext	CO-338-014	Randomized, double-blinded, placebo-controlled, phase III		- text	own!		•
Venclyxto, Ve	netoclax (L01XX52)			and	oade berieu		
Original MA	M13-982	Open, non-controlled, phase I-II		data	r (AE		•
1. ext	MURANO	Randomized, open, active-controlled, phase III		<u> </u>	n http BES)		•
2. ext	BO25323	Randomized, open, active-controlled, phase III		, A	o://bm		
3. ext	M15-656 M16-043	Randomized, double-blinded, placebo-controlled, phase III (both)	••	training, and similar	Downloaded from http://bmjopen.bmj.com/ent Superieur (ABES) .		
Xtandi, <i>Enzalu</i>	ıtamide (L02BB04)			milar	on		
Original MA	MDV3100	Randomized, double-blinded, placebo-controlled, phase III			June		
1. ext	MDV3100-03	Randomized, double-blinded, placebo-controlled, phase III	•	technologies	11, 20		•
2. ext	MDV3100 14	Randomized, double-blinded, placebo-controlled, phase III		es.	2025 at		•
3. ext	9785-CL-0335	Randomized, double-blinded, placebo-controlled, phase III			t Agence		•
Erleada, Apalı	utamide (L02BB05)						
Original MA	ARN-509-003 (SPARTAN	Randomized, double-blinded, placebo-controlled, phase III			Bibliographi		

				Jr.	- μ			
1. ext	PCR3002 (TITAN)	Randomized, double-blinded, placebo-controlled, phase III		t, includin				
Zytiga Abiraterone (L02BX03)								
Original MA	COU-AA-301	Randomized, double-blinded, placebo-controlled, phase III		or use	Octor En			
1. ext	COU-AA-302	Randomized, double-blinded, placebo-controlled, phase III	•	<u> </u>	Se			
2. ext	212082PCR3011	Randomized, double-blinded, placebo-controlled, phase III			24. eme			
Imnovid <i>Pomalidomide (L04AX06)</i> සි වි								
Original MA	CC-4047-MM- 003	Randomized, open, active-controlled, phase III		t and da	اج ق			
1. ext	MM-007	Randomized, open, active-controlled, phase III		e ta	from (ABE			
Teysuno, Tegafur, gimeracil and oteracil (L01BC53)								
Original MA	S-1301/FLAGS	Randomized, open, active-controlled, phase III		Al tra				
1. ext	-	Exploratory and retrospective Meta-analysis	20	aining	pen.		•	
					 			

^{*} Dose comparison,

MA= Marketing authorization,

ext. = Extension of indication

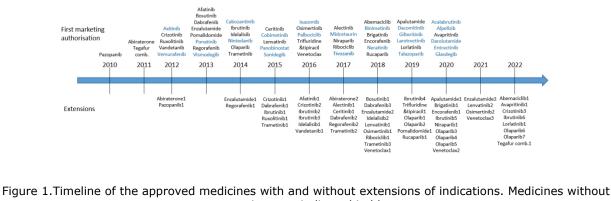
Supplementary table 3. Assessment of cancer medicines without extension of indication by JBI (Joanna Briggs Institute) criteria.

		BMJ Open		njopen-2023-0 d by copyright,		
Medicinal pro	duct, active substa	<i>ince,</i> (ATC-code)		3-0835, ht, inc		
	Study	Setting	Randomization and concealment of allocation (1–2)	Dollading (4–6)	Similarity of the compared groups (3,7,8)	Validity and reliability o the outcome assessment (9-12)
Calquence, Ac	alabrutinib (L01XE	51)		tob Ens		
Original MA	ACE-CL-309	Randomized, open, active-controlled, phase III (both)	••	2024. ignemo	••	•
Daurismo, gla	sdegib (L01XX63)			Downkent Sup		
Original MA	B1371003	Randomized, open, active-controlled, phase III	•	loade perie and		
Nubega, daro	lutamide (L02BB)			ownloaded from http:// t Superieur (ABES) . text and data mining,		
Original MA	ARAMIS 17712	Randomized, double-blinded, placebo-controlled, phase III		BES)		
Piqray Alpelis	ib (L01XE)					
Original MA	C2301 (SOLAR-1)	Randomized, double-blinded, placebo-controlled, phase III		/bmjopen.bmj.com/ on June 11, 2025 Al training, and similar technologies		
Rozlytrek, Ent	rectinib (L01EX14)			mj.co and		
Original MA	GO40782, STARTRK-2)	Open, non-controlled, phase I-II (basket study)		.com/ on June		•
Talzenna, Tala	zoparib (L01E)			ne 11,		
Original MA	673-301 (EMBRACA)	Randomized, open, active-controlled, phase III		, 2025 at logies.		
Vitrakvi, Larot	rectinib (L01E)			Agence		
Original MA	LOXO-TRK- 15002 (NAVIGATE)	Open, non-controlled, phase I-II (basket study)		nce Bibliographiqu		
				aphiq		

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extensions are indicated in blue.

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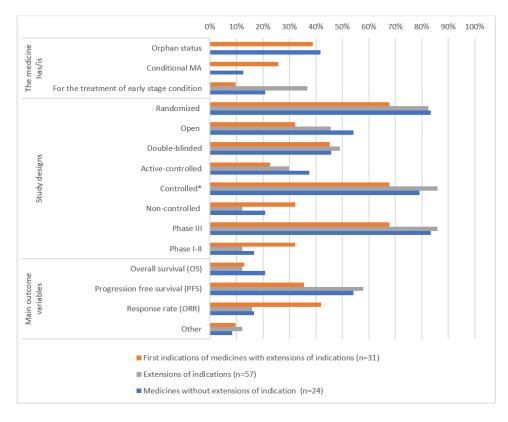


Figure 2.Comparison of study designs and main outcome variables in the main studies leading to marketing authorization or extensions of indications.

- * 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 metaanalysis.

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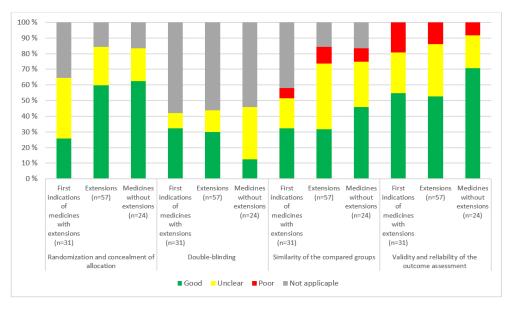
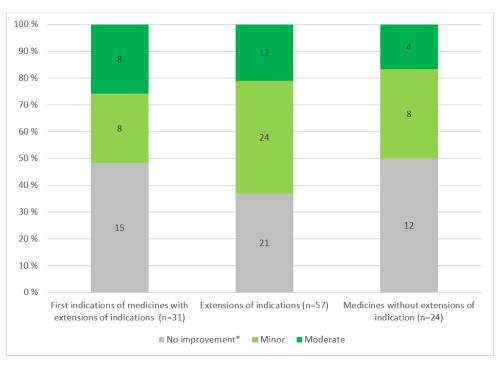


Figure 3. Quality of main studies assessed against JBI-criteria, comparison of the first indication of the medicines with extensions (n=31), the extensions of the indications (n=57) and the medicines without extensions of indications (n=24).

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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 assessment 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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	September 15, 2015
Text Section and Item	Section or Item Description
Name	_
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 <u>initiative</u> 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 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 <u>problem</u>
4. Available knowledge	Summary of what is currently known about the <u>problem</u> , including relevant previous studies

5. Rationale	Informal or formal frameworks, models, concepts, and/or <u>theories</u> used to explain the <u>problem</u> , any reasons or <u>assumptions</u> that were used to develop the <u>intervention(s)</u> , and reasons why the <u>intervention(s)</u> 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. <u>Intervention(s)</u>	 a. Description of the <u>intervention(s)</u> in sufficient detail that others could reproduce it b. Specifics of the team involved in the work 				
9. Study of the Intervention(s)	The Approach used to establish whether the observed outcomes were due				
10. Measures	 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	Qualitative and quantitative methods used to draw <u>inferences</u> from the data D. 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	 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 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 <u>rationale</u> and specific aims Particular strengths of the project				

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 <u>system</u> 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 <u>system</u>-level <u>initiatives</u> 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 <u>opportunity costs</u>, invasion of privacy, and staff distress resulting from disclosure of poor performance.

Generalizability

The likelihood that the <u>intervention(s)</u> 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 <u>system</u> 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 <u>system</u> 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 <u>system's</u> 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 <u>improvement</u> 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 <u>intervention(s)</u> were chosen and why it was expected to work, be sustainable, and be replicable elsewhere.

Systems

The interrelated structures, people, <u>processes</u>, 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 <u>process</u> or situation (explanatory theory). Theories come in many forms, and serve different purposes in the phases of <u>improvement</u> work. It is important to be explicit and well-founded about any informal and formal theory (or theories) that are used.

BMJ Open

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-083549.R1
Article Type:	Original research
Date Submitted by the Author:	12-Aug-2024
Complete List of Authors:	Ruuskanen, Anna-Maria; The Social Insurance Institution of Finland, Research Kurko, Terhi; The Social Insurance Institution of Finland, Research Sarnola, Kati; The Social Insurance Institution of Finland, Research Klintrup, Katariina; The Social Insurance Institution of Finland, Medical Advisory Centre Koskinen, Hanna; The Social Insurance Institution of Finland, Research
Primary Subject Heading :	Oncology
Secondary Subject Heading:	Health policy, Pharmacology and therapeutics
Keywords:	Clinical trials < THERAPEUTICS, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, ONCOLOGY

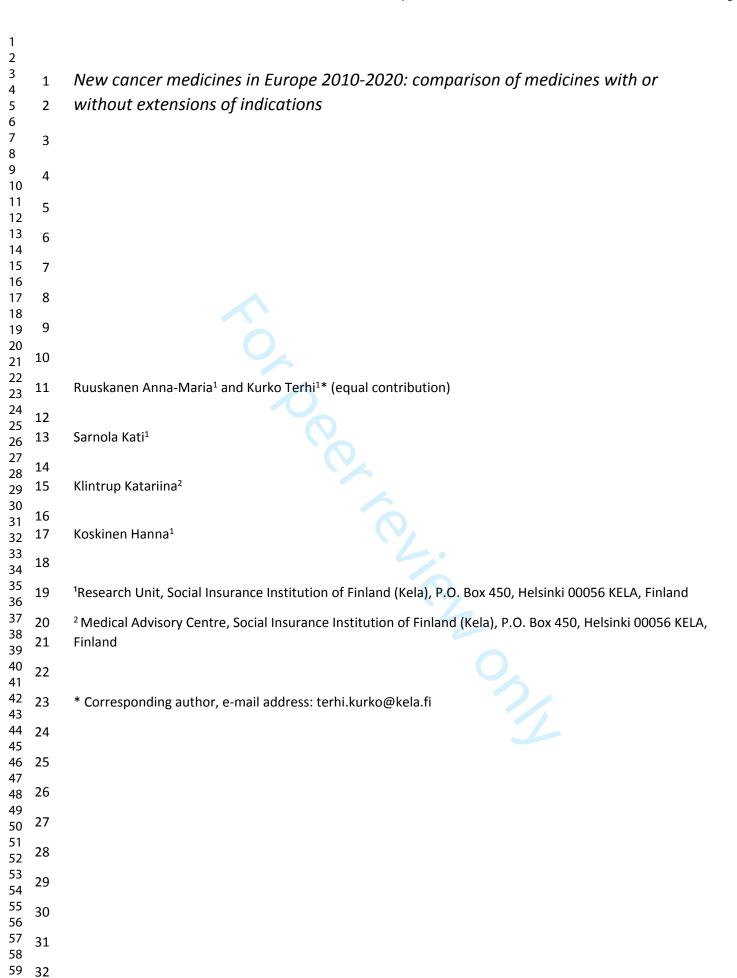
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Abstract

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

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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.

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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.

155 Characteristics of medicines and extensions of indications

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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.



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	Total number of medicines (of all	Number (%) of	Total number of extensions	The most cor	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	extension(s) of indication	New mechanisms of action*	
First approved indication	medicines)	medicines with extension	extensions	Treatment line	Canger type Ens	New combination	- OI action	
Hematological cancers: - leukemia - multiple myeloma - lymphoma - myelofibrosis	13 (24%)	6 (46%)	14	2	October 2024. Downloade Enseignement Superie r uses related to text and	6	10 (77%)	
Lung cancer	9 (16%)	7 (78%)	10	6	ed fron eur (AB data n		3 (33%)	
Melanoma & basal cell carcinoma	8 (15%)	3 (38%)	7	2	wnloaded from http://bmjopen.bmj.com/ on J Superieur (ABES) . text and data mining, Al training, and similar	2	3 (38%)	
Breast cancer	6 (11%)	2 (33%)	2	1	njoper - traini	1	4 (67%)	
Prostate cancer	4 (7%)	3 (75%)	6	6	njopen.bmj.c training, and	-	2 (50%)	
Colorectal or gastric cancer	4 (7%)	4 (100%)	5	-	om/ on J	-	2 (50%)	
Kidney cancer	3 (5%)	1 (33%)	1		June 11, 2025 at 1 2 cechnologies.	-	2 (67%)	
Thyroid cancer	3 (5%)	2 (67 %)	3	-	, 2025 ; 2 logies.	-	1 (33%)	
Gynecological cancers	3 (5%)	3 (100%)	9	3	at Agence	1	1 (33%)	
Solid tumors	2 (4%)	0 (0%)	0	-	nce Bit	-	1 (50%)	
Total	55 (100%)	31 (56%)	57 (100%)	20 (35%)	17 (30%) T	10 (18%)		

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

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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.

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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.

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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.

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> In many studies, details of the randomisation and double-blinding were missing. Double-blinding was welldescribed 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.

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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.

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Clinical added value

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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

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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

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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.

309 **Declarations**

- Ethics approval and consent to participate: Not applicable because the study was based on publicly available documents.
- 13 312 Availability of data and materials: All materials are publicly available. EPARS:
- 15 313 https://www.ema.europa.eu/en/medicines. Clinical added value assessments: https://www.has-
- 16 314 sante.fr/jcms/pprd_2986129/en/home.
- 17 315 Competing interests: The authors declare that they have no competing interests
- Funding: No funding, all the authors are working in the Finnish Social Insurance Institution (Kela)
- 20 317 Acknowledgements: Not applicable

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].

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Figure legends

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

- 340 Figure 2. Study designs and main outcome variables of the main studies, comparison of the first indication 341 of the medicines with extensions (n=31), the extensions of the indications (n=57) and the medicines 342 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 metaanalysis.

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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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> 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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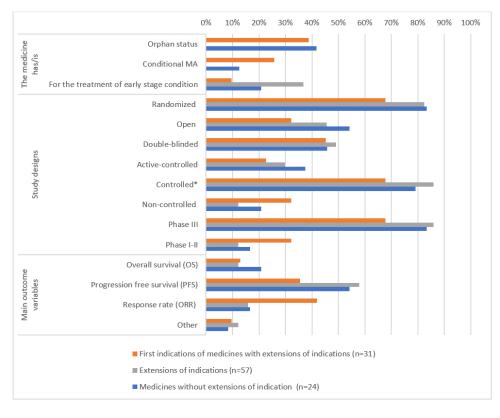


Figure 2.Comparison of study designs and main outcome variables in the main studies leading to marketing authorization or extensions of indications.

- * 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 metaanalysis.

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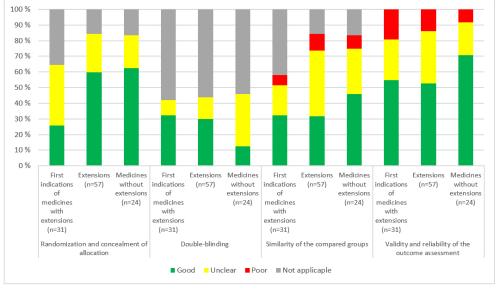
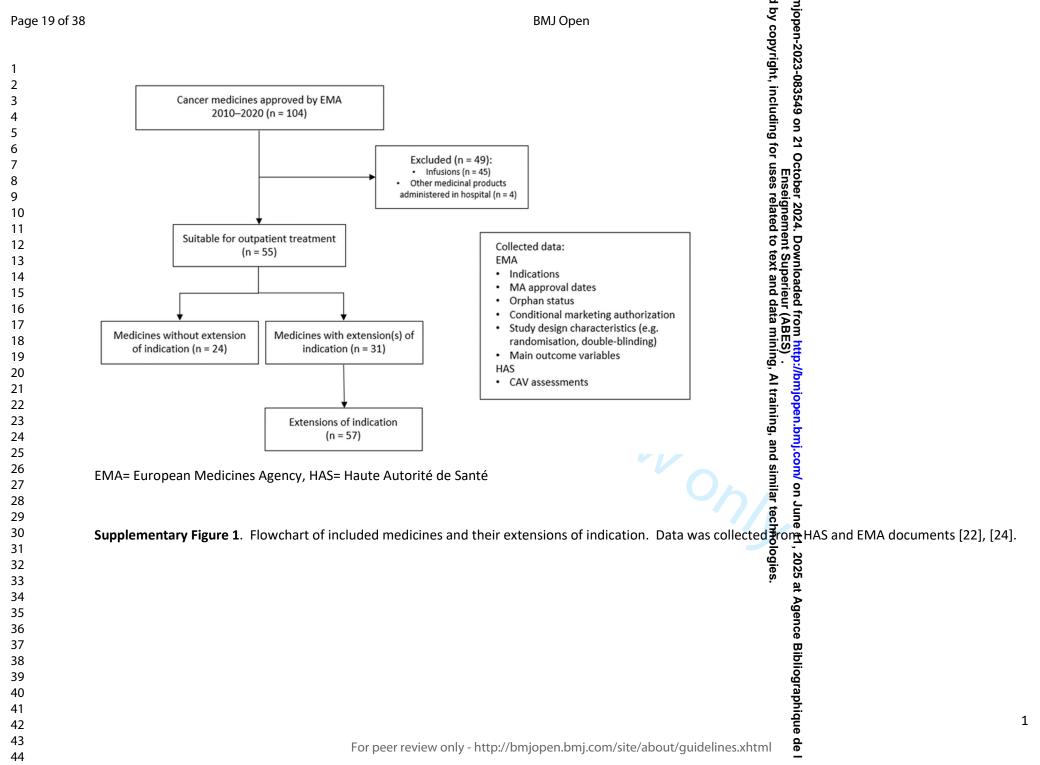


Figure 3. Quality of main studies assessed against JBI-criteria, comparison of the first indication of the medicines with extensions (n=31), the extensions of the indications (n=57) and the medicines without extensions of indications (n=24).

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	BMJ Open
upplementary Table 1. The different categories of	BMJ Open get 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	
For poo	er review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

^{*}MA=marketing authorisation

Supplementary Table 2. Characteristics of the outpatient cancer medicines. Medicines without extension of indications 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				<u>'</u>		0 N	
L01BC Pyrimidine analogues						1 0	
Teysuno®, tegafur, gimeracil and oteracil. 14.3.2011	gastric cancer	-	Previously yes, now withdrawn	-	- 8	1. cancer type (colorectal cancer), 24.1.2022	Na Insuf.
Lonsurf®, <i>trifluridine and tipiracil</i> , 25.4.2016	colorectal cancer	-	-	-	- 9	Gastric cancer), 3.9.2019	5 5
L01E Protein kinase inhibitors						e A	
L01EA BCR-ABL tyrosine kinase inhibi	itors					t en D	
Bosulif®, <i>bosutinib</i> , 27.3.2013	chronic myelogenous leukaemia	-	Previously yes, now withdrawn	-	-	To be catment line, 23.4.2018	5 5
Iclusig®, <i>ponatinib</i> , 1.7.2013	leukaemia	b	Yes	Yes	- 5	n loade Superies	5/4/3
L01EB Epidermal growth factor receptor	r (EGFR) tyrosine kinase inhib	itors			9	<u>유</u> 득 요	
Giotrif®, <i>afatinib</i> , 25.9.2013	lung cancer		-	-		The partient type (mutation), 31.3.2016	5 5
Tagrisso®, osimertinib, 2.2.2016	lung cancer	Previously yes, now full authorisation	- -	Yes	Yes	treatment line, 7.6.2018 Treatment line + patient type (mutation), 215, 2021	5 4 3
Vizimpro®, dacomitinib, 2.4.2019	lung cancer	-	-01	-	Yes	h mjop	5
L01EC B-Raf serine-threonine kinase (B	RAF) inhibitors				5	a C	
Zelboraf®, <i>vemurafenib</i> , 17.2.2012	melanoma	-	- //6	-	-	d'ua	3
Tafinlar®, dabrafenib, 26.8.2013	melanoma	-	-	4	-	1. Sombination type, 25.8.2015 2. Cancer type (lung cancer), 29.3.2017 3. Reatment line, 27.8.2018	5 Na 5 3
Braftovi®, encorafenib, 20.9.2018	melanoma	-	-	-	Yes	1. Sancer type (colorectal cancer), 2.6.2020	5 3
L01ED Anaplastic lymphoma kinase (Al	LK) inhibitors			'		e in	
Xalkori®, <i>crizotinib</i> , 23.10.2012	lung cancer	-	-	-		1. treatment line, 23.11.2015 2. patient type (mutation), 25.8.2016 3. Setient type (adolescents), 28.10.2022	3 4 5 4
Zykadia [®] , <i>ceritinib</i> , 6.5.2015	lung cancer	Previously yes, now full authorisation	-	-	- 3	1. treatment line, 23.6.2017	4 4
Alecensa®, alectinib, 16.2.2017	lung cancer	-	-	-	-	1. deatment line, 18.12.2017	4 4
Alunbrig®, <i>brigatinib</i> , 22.11.2018	lung cancer	-	-	-	-	1. R eatment line, 1.4.2020	5 4
Lorviqua®, lorlatinib, 6.5.2019	lung cancer	Yes	-	-	Yes	1. 5 atment line, 27.1.2022	5 4
L01EE Mitogen-activated protein kinase	(MEK) inhibitors					ic grap	

			BMJ Open		by copy	njopen-2023-	1
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Mekinist [®] , <i>trametinib</i> , 30.6.2014	melanoma	-	-	-		1. Sombination type, 25.8.2015 2. Some fine (lung cancer), 27.3.2017 3. Some atment line, 27.8.2018	3 Na 5 3
Cotellic®, <i>cobimetinib</i> , 20.11.2015	melanoma	-	-	-	Ç.	. 21	3
Mektovi®, binimetinib, 20.9.2018	melanoma	-	-	-	Yes	Octo	5
L01EF Cyclin-dependent kinase (CD	K) inhibitors				i	λ 75 C	
Ibrance®, <i>palbociclib</i> , 9.11.2016	breast cancer	-	-	-	Yes	9. 20mbination type, 17.12.2018	4
Kisqali [®] , <i>ribociclib</i> , 22.8.2017	breast cancer	-	-	-		3 . Sembination type, 17.12.2018	3 4
Verzenios®, a <i>bemaciclib</i> , 27.9.2018	breast cancer	-	-	-	Yes	Atteatment line, 1.4.2022	5/4 5
L01EH Human epidermal growth fac	tor receptor 2 (HER2) tyrosine ki	nase inhibitors			9	lload peri	
Nerlynx [®] , <i>neratinib</i> , 31.8.2018	breast cancer	<i>i</i> O _a	-	-	yes	wmloaded f	Insuf.
L01EJ Janus-associated kinase (JAK)	inhibitors				<u> </u>	n > 0,	
Jakavi [®] , <i>ruxolitinib</i> , 23.8.2012	myelofibrosis		Previously yes, now withdrawn	-	-	meancer type (polysytemia vera), 11.3.2015	3 4
L01EK Vascular endothelial growth	factor receptor (VEGFR) tyrosine	kinase inhibitors			Ū.	3 . 0	
Inlyta [®] , <i>axitinib</i> , 3.9.2012	kidney cancer	-	Previously yes, now withdrawn	-		(mad/)	4
Fotivda®, <i>tivozanib</i> , 24.8.2017	kidney cancer	-	-	-	Yes	- ope	Insuf.
L01EL Bruton's tyrosine kinase (BTk					į.	B :	
Imbruvica®, ibrutinib, 27.10.2014	mantle cell lymphoma and chronic lymphocytic leukaemia	-	Previously yes, now withdrawn	40		1. Sincer type (Walderström's macroglobulinaemia), 3.7.2015 2. Reatment line, 26.5.2016 3. Sombination type, 25.8.2016 4. Sombination type, 2.8.2019 5. Combination type, 28.8.2020 6. Sombination type, 2.8.2022	3 Na 4 Na Insuf. 3 4
Calquence®, acalutinib,	leukaemia		Previously yes, now		Yes	ne 11	Na
5.11.2020 L01EM Phosphatidylinositol-3-kinas	e (Pi3K) inhibitors		withdrawn			,	
Zydelig [®] , <i>Idelalisib</i> ,	follicular lymphoma and				Yes	1. Ambination type, 19.9.2016	5/4
18.9.2014	chronic lymphocytic leukaemia	-	-		i cs	2. combination type, 23.4.2018	Na Na
Piqray [®] , <i>alpelisib</i> , 27.7.2020	breast cancer	-	-	-	Yes	. Age	Insuf.
L01EX Other protein kinase inhibitor	'S					5	
Votrient®, pazopanib, 14.6.2010	renal cell carcinoma	Yes	Previously yes, now withdrawn	-	-	1. Eancer type (soft-tissue sarcoma), 24.8.2012	5 5
Caprelsa®, <i>vandetanib</i> , 16.2.2012	thyroid cancer	Yes	-	-	Yes	1. Tatient type (paediatric patients), 12.12.2016	4 5
Stivarga®, regorafenib, 26.8.2013	colorectal cancer	-	-	-	-	1. nancer type (gastrointestinal stromal tuners), 27.10.2014	5 4

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		T	T	T		ا د	
						2. Soncer type (hepatocellular carcinoma), 2. 3017	4
Cometriq [®] , cabozantinib, 21.3.2014	medullary thyroid cancer	-	Yes	-	-	- 49 o	4
Lenvima [®] , <i>lenvatinib</i> , 28.5.2015	thyroid cancer	-	Previously yes, now withdrawn	Yes	Yes	1. cancer type (liver cancer), 20.8.2018 2. eancer type (endometrial carcinoma),	4 Insu 3
Vargatef®, <i>nintedanib</i> , 21.11.2014	lung carcinoma	-	-	-	-	ctober 2024. D uses related to	Insu
Rydapt [®] , <i>midostaurin</i> , 18.9.2017	acute myeloid leukaemia, mastocytosis	-	Yes	-	Yes	er 20 eign	4/5
Vitrakvi [®] , <i>larotrectinib</i> , 19.9.2019	solid tumours with NTRK gene fusion	Yes	Previously yes, now withdrawn	-	Yes	124. [leme	4
Xospata [®] , <i>gilteritinib</i> , 24.10.2019	acute myeloid leukemia	-	Yes	-	Yes	tement Superior type (mastocytosis), 24.3.2022	4
Rozlytrek®, <i>entrectinib</i> , 31.7.2020	solid tumors with NTRK fusion, lung cancer	Yes	-	-	Yes	ıloac ıperi	Insu
Ayvakyt [®] , <i>avapritinib</i> , 24.9.2020	gastrointestinal stromal tumours	Yes	Yes	-	Yes	Encer type (mastocytosis), 24.3.2022	5 4
L01X Other antineoplastic agents							
L01XG Proteasome inhibitors						3	
Ninlaro [®] , <i>ixazomib,</i> 21.11.2016	multiple myeloma	yes	yes	-	Yes	http://	5
L01XH Histone deacetylase (HDA	<u> </u>					A b	
Farydak [®] , <i>panobinostat,</i> 28.8.2015	multiple myeloma	-	Yes	-	Yes	njope train	5
L01XJ Hedgehog pathway inhibito	ors						
Erivedge [®] , <i>vismodegib</i> , 12.7.2013	basal cell carcinoma	-	-		Yes	, an Jaj	4
Odomzo [®] , <i>sonidegib</i> , 14.8.2015	basal cell carcinoma	-	-		Yes	d sim	4
Daurismo [®] , <i>glasdegib</i> , 26.6.2020	acute myeloid leukaemia		Yes	-	Yes	on J	Na
L01XK Poly (ADP-ribose) polymo	erase (PARP) inhibitors					tec un	
Lynparza [®] , <i>olaparib</i> , 16.12.2014	ovarian, fallopian tube or primary peritoneal cancer	-	Previously yes, now withdrawn	-		1. Cancer type (breast cancer), 8.4.2019 2. Heatment line, 12.6.2019 3. Sancer type (pancreatic cancer), 3.7.2020 4. Symbination type, 3.11.2020 5. Cancer type (prostate cancer), 3.11.2020 6. Heatment line (breast cancer), 2.8.2022 7. Heatment line + combination (prostate cancer), 16.12.2022	4 5 4 5 4 4 3 4
Zejula [®] , <i>niraparib</i> , 16.11.2017	ovarian, fallopian tube or primary peritoneal cancer	-	Yes	-	Yes	1. R eatment line, 27.10.2020	4 4
Rubraca [®] , <i>rucaparib</i> , 24.5.2018	ovarian, fallopian tube or primary peritoneal cancer	Yes	Previously yes, now withdrawn	-	Yes	1. Leatment line + patient type (mutation), 23 ± 2019	Insu 4
Talzenna®, <i>talazoparib</i> , 20.6.2019	breast cancer	-	-	-	Yes	- ogra	5
L01XX Other antineoplastic agent						5	

Venclyxto [®] , <i>venetoclax</i> , 5.12.2016	-1					<u>및 3</u>	
5.12.2016	chronic lymphocytic	Previously yes, now full	Previously yes, now	-	Yes	1. catment line + combination type,	5
	leukaemia	authorisation	withdrawn			2980.2018	4
						2. Statment line + combination typfe, 9.3.2020 3. Sancer type (acute myeloid leukaemia),	3 4
						22.7.2021	7
L02B Hormone antagonists and re	elated agents					fo 1	
L02BB Anti-androgens						- O	
Xtandi [®] , <i>enzalutamide</i> ,	prostate cancer	-	=	-	-	T b eatment line, 28.11.2014	3
21.6.2013						9. Reatment line, 23.10.2018	3
						a no	3
Erleada [®] , <i>apalutamide,</i>	prostate cancer	-	-	-	Yes	3 Leatment line, 27.1.2020	3
14.1.2019						# B D	3
Nubeqa®, darolutamide,	prostate cancer	-	-	-	Yes	A CON	3
27.3.2020 L02BX Other hormone antagonis	ets and related agents					Geatment line, 28.11.2014 Geatment line, 23.10.2018 Geatment line, 30.4.2021 Geatment line, 30.4.2021 Geatment line, 27.1.2020 Geatment line, 27.1.2020 Geatment line, 27.1.2020	
Zytiga [®] , <i>abiraterone</i> ,	prostate cancer		I _	Yes	1_	שממ	3
5.9.2011	prostate cancer		=	105	-	Geatment line, 18.12.2012 Geatment line, 15.11.2017	4
						at C	3
L04A Immunosuppressants						2 2 0 ⊐ ⊞∃	
L04AX Other immunosuppressan			- X7	1	37		
Imnovid®, <i>pomalidomide</i> , 5.8.2013	multiple myeloma	-	Yes	-	Yes	eatment line + new combination, 13.5.2019	5 5
In some stage of the product li	ife cycle			1		ন <u>১</u> ১ ট	3
ypes of extensions: Cancer ty	<i>ype</i> = authorised for new cancer	r type, <i>Treatment line</i> = autl	norised for a different	treatment li	ne or for a differ	t stage of the disease, e.g. after a surgery, Pa	tient
suf. = The actual clinical ben	c. : : cc : .					2 0 <u>-</u> 2.	
1 4 11 1 1 1 1	efit is insufficient	·				nj.co	
= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				nj.com/ and sim	
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= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				nj.com/ on Ju	
= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				nj.com/ on June	
= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				nj.com/ on June 11	
= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				nj.com/ on June 11, 20	
= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	■ no improvement CAV.				nj.com/ on June 11, 2025	
= moderate clinical added val	wpe = authorised for new cance; patients than previously, Combinate the previously of the previously o	no improvement CAV.				nj.com/ on June 11, 2025 at	
= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				nj.com/ on June 11, 2025 at Ag	
= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				nj.com/ on June 11, 2025 at Agen	
= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				Agence	
= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				Agence	
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= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				Agence Bibl	
= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				Agence Bibl	
= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				Agence Bibl	
= moderate clinical added val	efit is insufficient lue (CAV), 4 = minor CAV, 5 =	no improvement CAV.				Agence Bibl	6
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= moderate clinical added val		no improvement CAV.				Agence Bibliographique (6
= moderate clinical added val						Agence Bibliographique (6

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

				ncluc		
Medicinal prod	uct, active substance	?, (ATC-code)		549 on		
	Study	Setting	Randomisation and concealment of allocation (1–2)	1.21 October 2024. Downloaded from http://bi	Similarity of the compared groups (3,7,8)	Validity and reliability of the outcome assessment (9-12)
Lonsurf Triflurio	dine and tipiracil (LO	LBC59)		r 202. igner elate		
Original MA	TPU-TAS-102-301	Randomised, double-blinded, placebo-controlled, phase III	•	4. Doment d to t		-
1. ext	TAS-102-302	Randomised, double-blinded, placebo-controlled, phase III		Supe Supe ext a		
Bosulif Bosutin	ib (L01EA04)			rieur nd da		
Original MA	200-WW	Open, non-controlled, phase I-II		from (ABE ita mi		
1. ext	AV001	Randomised, open, active-controlled, phase III		http://bmj ES) . nining, AI tr		
Giotrif <i>Afatinib</i>	(L01EB03)			Al tr		
Original MA	LUX-Lung 3	Randomised, open, active-controlled, phase III	•	aining	•	
1. ext	LUX-Lung 8	Randomised, open, active-controlled, phase III		bmjopen.bmj.com/ Al training, and sir		
Tagrisso, Osime	ertinib (L01EB04)			sim		
Original MA	201 & 210	Open, non-controlled, phase I-II (both)	••		••	00
1. ext	2014-002694-11	Randomised, double-blinded, active-controlled, phase III		ne 11 chno		
2. ext	D5164C00001/ Adaura	Randomised, double-blinded, placebo-controlled, phase III	•	lune 11, 2025 at technologies.		
Tafinlar <i>Dabraf</i>	enib (L01EC02)					<u></u>
Original MA	BRF11368	Randomised, open, active-controlled, phase III		Agence E		
1. ext	MEK115306	Randomised, double-blinded, active-controlled, phase III		Bibliographiqu	•	••
	MEK116513	Randomised, open, active-controlled, phase III		grapi		
		·		ا م		7

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2. ext	BRF113928	Open, non-controlled, phase II		ght, in	23-0835	
3. ext	BRF115532	Randomised, double-blinded, placebo-controlled, phase III		- udi	99 0	
Braftovi, <i>Encor</i>	afenib (L01EC03)			ng for	21	
Original MA	CMEK162B2301	Randomised, open, active-controlled, phase III	-	us en n	Octor -	•
1. ext	ARRAY-818-302	Randomised, open, active-controlled, phase III		s rela	per 20	
Xalkori, <i>Crizotii</i>	nib (L01ED01)			ted t)24. E	
Original MA	A8081001	Open, non-controlled, phase I-II		Enseignement Superieur (ABI or uses related to text and data m	own	
1. ext	A8081014	Randomised, open, active-controlled, phase III		perie t and	loade	•
2. ext	A8081001	Open, non-controlled, phase I-II		data	d fro	
3.ext	ADVL0912	Open, non-controlled, phase I-II		minir	m htt	
Zykadia, <i>Ceritir</i>	nib (L01ED02)			າg, <u>≯</u>	p://br	
Original MA	CLDK378X2101	Open, non-controlled, phase I-II		BES) . mining, Al training, and sin	njope	•
1. ext	ASCEND-4/A2301	Randomised, open, active-controlled, phase III		ing,	n.bm	
Alecensa <i>Alecti</i>	inib (L01ED03)			and s	J.con	
Original MA	NP28761, NP28673	Open, non-controlled, phase I-II Open, non-controlled, phase I-II		nilar tech	on June	••
1. ext	BO28984	Randomised, open, active-controlled, phase III		nolog	11, 2025	•
Alunbrig <i>Briga</i> r	tinib (L01ED04)			es.)25 at	
Original MA	AP26113-13-201	Randomised, open, non-controlled, phase II*	•		t Agence	•
1. ext	AP26113-13-301	Randomised, open, active-controlled, phase III	•		Се В	•
Lorviqua <i>, Lorla</i>	tinib (L01ED05)				blio	
1. ext Lorviqua, <i>Lorla</i>		Randomised, open, active-controlled, phase III	•		ce Bibliographic)

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Original MA	PF-06463922	Open, non-controlled, phase I-II		ht, inc	0835	0
1. ext	B7461006	Randomised, open, active-controlled, phase III		includin	49 on	•
Mekinist, <i>Tram</i>	etinib (L01EE01)			g ı	Ń	
Original MA	MEK114267	Randomised, open, active-controlled, phase III		US es	Octob	•
1. ext	MEK115306 MEK116513	Randomised, double-blinded, active-controlled, phase III Randomised, open, active-controlled, phase III		Enseignemer or uses related to	er 2024. D	••
2. ext	BRF113928	Open, non-controlled, phase I-II		o text	own!	•
3. ext	BRF115532	Randomised, double-blinded, placebo-controlled, phase III		and o	oade	•
Kisqali <i>Ribocicli</i>	ib (L01EF02)			ur (AE	fror	
Original MA	MONALEESA-2	Randomised, double-blinded, placebo-controlled, phase III		ninin		•
1. ext	MONALEESA-7 MONALEESA-3	Randomised, double-blinded, placebo-controlled, phase III Randomised, double-blinded, placebo-controlled, phase III	••	ent Superieur (ABES) . to text and data mining, Al training,	://bmiope	••
Verzenios <i>aben</i>	naciclib (L01EF03)			ing, s	.b	
Original MA	MONARCH 3	Randomised, double-blinded, placebo-controlled, phase III,	00	and s	bmi.com/	••
	MONARCH 2	Randomised, double-blinded, placebo-controlled, phase III				
1. ext	monarchE	Randomised, open, active-controlled, phase III			on June	•
Jakavi <i>Ruxolitin</i>	nib (L01EJ01)				11. 2	
Original MA	352	Randomised, open, active-controlled, phase III	00		2025 at	••
	351	Randomised, double-blinded, placebo-controlled, phase III		· ·	t Agence Bibliograp	
1. ext	B2301	Randomised, open, active-controlled, phase III			nce	

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Original MA	PCYC-1112-CA PCYC-1104-CA	Randomised, open, active-controlled, phase III Open, non-controlled, phase II	•	by copyright, including for			
1. ext	PCYC-1118E	Open, non-controlled, phase II		ng fo	2	•	
2. ext	PCYC-1115-CA	Randomised, open, active-controlled, phase III		or uses related t			
3. ext	PCI-2765CLL3001	Randomised, double-blinded, placebo-controlled, phase III		s rela		•	
4. ext	1127	Randomised, double-blinded, placebo-controlled, phase III		emer ted to		•	
5. ext	E1912	Randomised, open, active-controlled, phase III		text		•	
6.ext	CLL3011	Randomised, open, active-controlled, phase III		and o			
Zydelig <i>Idelalis</i>	ib (L01EM01)			ur (AE			
Original MA	GS-US-312-0116 & 101-09	Randomised, double-blinded, placebo-controlled, phase III Open, non-controlled, phase II	••	to text and data mining, Al training, and s		••	
1. ext	GS-US-312-0119	Randomised, open, active-controlled, phase III		traini	•	•	
2. ext	GS-US-312-0115	Randomised, double-blinded, placebo-controlled, phase III		— 9, a	•		
Votrient <i>Pazop</i>	anib (L01EX03)			Al training, and similar			
Original MA	VEG105192	Randomised, double-blinded, placebo-controlled, phase III	•	milar		•	
1. ext	VEG110727	Randomised, double-blinded, placebo-controlled, phase III	•	r techi		•	
Caprelsa <i>Vande</i>	etanib (L01EX04)			technologies.			
Original MA	D4200C00058	Randomised, double-blinded, placebo-controlled, phase III	•	ogies.		•	
1. ext	IRUSZACT0098	Open, non-controlled, phase II		Age		•	
Stivarga, Regoi	rafenib (L01EX05)			Agence			
Original MA	14387	Randomised, double-blinded, placebo-controlled, phase III	-	o di april que	•	•	
1. ext	14874	Randomised, double-blinded, placebo-controlled, phase III		9	-		

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2. ext	15982	Randomised, double-blinded, placebo-controlled, phase III		right, inc)23-0835	
Lenvima, <i>Lenva</i>	tinibi (L01EX08)			Cludir	: 49 : on	
Original MA	E7080-G000-303	Randomised, double-blinded, placebo-controlled, phase III		ng for	. 21 0	•
1. ext	E7080-G000-304	Randomised, open, active-controlled, phase III		uses	Dctober :	•
2. ext	E7080-G000-309	Randomised, open, active-controlled, phase III		- Regard	er 2024. seignem	•
Ayvakyt <i>Avapri</i>	tinib (L01EX18)			ted to	emen	
Original MA	BLU-285-1101	Open, non-controlled, phase I-II	•	text	2024. Downloaded from http://bm.gnement Superieur (ABES)	•
1. ext	BLU-285-2202	Open, non-controlled, phase I-II		and o	oadec berieu	•
Lynparza, <i>Olap</i> o	arib (L01EK01)			ata r	ir (AE	
Original MA	D0810C00019	Randomised, double-blinded, placebo-controlled, phase III	•		ES)	•
1. ext	D0819C00003	Randomised, open, active-controlled, phase III		9, <u>></u>	//bm	•
2. ext	D0818C00001	Randomised, double-blinded, placebo-controlled, phase III		Al training,	· jope	•
3. ext	D081FC00001	Randomised, double-blinded, placebo-controlled, phase III		ng, a	jopen.bmj.com/	•
4. ext	D0817C00003	Randomised, double-blinded, placebo-controlled, phase III	•	and similar		-
5. ext	D081DC00007	Randomised, open, active-controlled, phase III	•		: O	•
6. ext	D081CC00006	Randomised, double-blinded, placebo-controlled, phase III		technologies	June	•
7. ext	D081SC00001	Randomised, double-blinded, placebo-controlled, phase III		- lolog	11, 20	•
Zejula <i>Niraparii</i>	b (L01XK02)			es.	2025 at	
Original MA	PR-30-5011-C	Randomised, double-blinded, placebo-controlled, phase III	•		Agen	
1. ext	PR-30-5017-C	Randomised, double-blinded, placebo-controlled, phase III	•		6	-
Rubraca Rucap	arib (L01XK03)				Bibliographi	
					yrapt	

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Original MA	CO-338-010	Open, non-controlled, phase I-II			3-083	
	CO-338-017	Open, non-controlled, phase I-II		cludii	549 on	
l. ext	CO-338-014	Randomised, double-blinded, placebo-controlled, phase III		ng for	23	•
/enclyxto, Ven	etoclax (L01XX52)			uses	Octob	
Original MA	M13-982	Open, non-controlled, phase I-II		re a	er 20	•
1. ext	MURANO	Randomised, open, active-controlled, phase III	•	ted to	24. D	•
2. ext	BO25323	Randomised, open, active-controlled, phase III		text	own!	
3. ext	M15-656 M16-043	Randomised, double-blinded, placebo-controlled, phase III (both)	••	and data minin	October 2024. Downloaded from http://b	
(tandi, <i>Enzalut</i>	amide (L02BB04)			_	nd//s	
Original MA	MDV3100	Randomised, double-blinded, placebo-controlled, phase III		training,	mjopen	-
l. ext	MDV3100-03	Randomised, double-blinded, placebo-controlled, phase III			n.bmj	
2. ext	MDV3100 14	Randomised, double-blinded, placebo-controlled, phase III		nd si	j.com/	-
3. ext	9785-CL-0335	Randomised, double-blinded, placebo-controlled, phase III		and similar		-
Erleada, Apalut	amide (L02BB05)				on June	
Original MA	ARN-509-003 (SPARTAN	Randomised, double-blinded, placebo-controlled, phase III	•	technologies	11, 2025	
L. ext	PCR3002 (TITAN)	Randomised, double-blinded, placebo-controlled, phase III			홛	
Zytiga <i>Abirater</i>	one (L02BX03)				gence	
Original MA	COU-AA-301	Randomised, double-blinded, placebo-controlled, phase III			Agence Bibliographic	•
1. ext	COU-AA-302	Randomised, double-blinded, placebo-controlled, phase III			liogr	

 MA= Marketing authorization,

ext. = Extension of indication

^{*} Dose comparison,

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

viedicinal prod	luct, active substance, (ATC-	code)		549 on		
	Study	Setting	Randomization and concealment of allocation (1–2)	9 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	Similarity of the compared groups (3,7,8)	Validity and reliability o the outcome assessment (9-12)
Calquence, Aca	alabrutinib (L01XE51)			202. gner elate		
Original MA	ACE-CL-007, ACE-CL-309	Randomised, open, active-controlled, phase III (both)	••	nent d to	••	•
Daurismo, glas	degib (L01XX63)			wnlo Supe		
Original MA	B1371003	Randomised, open, active-controlled, phase III		aded Prieur Ind da		
Nubega, darol	utamide (LO2BB)			from (ABI		
Original MA	ARAMIS 17712	Randomised, double-blinded, placebo-controlled, phase III		ining.	0	
Piqray Alpelisi	o (L01XE)			, Al tr		
Original MA	C2301	Randomised, double-blinded, placebo-controlled, phase III	•	/bmjopen.bmj.com/ on J		
	(SOLAR-1)			.bmj.o		
Rozlytrek, Entr	ectinib (L01EX14)			om/ I sim		
Original MA	GO40782, STARTRK-2)	Open, non-controlled, phase I-II (basket study)		on June 11		•
Talzenna, Tala	zoparib (L01E)		'	June 1: techno	'	
Original MA	673-301 (EMBRACA)	Randomised, open, active-controlled, phase III	•	e 11, 2025	•	•
Vitrakvi, Laroti	rectinib (L01E)			· at		
Original MA	LOXO-TRK-15002 (NAVIGATE)	Open, non-controlled, phase I-II (basket study)	•	Agence E		
Vizimpro, Daco	omitib, (L01EB07)			Biblic		
Original MA	ARCHER 1050	Randomised, open, active-controlled, phase III		ibliograph		
				hique		14

ge 33 of 38		BMJ Open		mjopen-2023-083549 on 21 O		
Xospata, gilter	ritinib, (L01EX13)			3-0838 ht, in		
Original MA	ADMIRAL (2215-CL- 0301)	Randomised, open, active-controlled, phase III		549 on 21 cluding fo		
Mektovi, binin	netinib, (L01EE03)			or us		
Original MA	COLUMBUS CMEK162B2301	Randomised, open, active-controlled, phase III	•	October 2024. Dow Enseignement S or uses related to to	•	•
Nerlynx, nerat	tinib , (L01EH02)			Dow lent S		
Original MA	3144A2-3004-WW	Randomised, double-blinded, placebo-controlled, phase III		Downloaded from http:/ent Superieur (ABES) . to text and data mining.		
Fotivda, tivoza	anib, (L01EK03)			ded fr		
Original MA	AV-951-09-301	Randomised, open, active-controlled, phase III		a min		
Rydapt, midos	staurin, (LO1XE)					
Original MA	RATIFY (A2301)	Randomised, double-blinded, placebo-controlled, phase III	•	bmjopen.bi		
Ibrance, palbo	ociclib (L01XE)			ning,		
Original MA	1023 (PALOMA-3)	Randomised, double-blinded, placebo-controlled, phase III	00		00	••
	1008 (PALOMA-2)			and similar		
Ninlaro, ixazor	mib (L01XG03)					
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Cotellic, cobim	netinib (L01XE38)			lune 11, 2025 technologies		
Original MA	GO28141/coBRI	Randomised, double-blinded, placebo-controlled, phase III		<u> </u>		
Farydak, pano	binostat (L01XH03)			yence		
Original MA	CLBH589D2308 (Panorama I)	Randomised, double-blinded, placebo-controlled, phase III		Agence Bibliograph	•	
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Odomzo, sonide	egib (L01XJ02)			ht, i		
				3549 nclu		
Original MA	A2201 (BOLT)	Randomised, double-blinded, non-comparative, phase II		on John		
Cometriq, cabo	ozantinib (L01XE)			21 C g for		
Original MA	XL184-301	Randomised, double-blinded, placebo-controlled, phase III		ctobe Ens uses		
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Original MA	NO25026 (BRIM 3)	Randomised, open, active-controlled, phase III		com/	0	•
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Research and reporting methodology

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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).
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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	Pages 2 lines
and equity of healthcare).	75-114
2. Abstract	
	page 2, lines
a. Provide adequate information to aid in searching and indexing.	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,	page 2, lines
methods, interventions, results, conclusions.	35–50
Thethous, interventions, results, contrastons.	33 30
Introduction: Why did you start?	
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3. Problem description - Nature and significance of the local problem.	78–100
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5. Rationale - Informal or formal frameworks, models, concepts and/or theories used to	page 3 lines
explain the problem, any reasons or assumptions that were used to develop the	75–82 and lines
intervention(s) and reasons why the intervention(s) was expected to work	93–100
intervention(s) and reasons why the intervention(s) was expected to work	page 3 lines
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8. Intervention(s)	
a. Description of the intervention(s) in sufficient detail that others could reproduce it.	page 4, lines 133–136
	page 10, lines
b. Specifics of the team involved in the work.	322–325
9. Study of the intervention(s)	
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a. Approach chosen for assessing the impact of the intervention(s).	150–152
b. Approach used to establish whether the observed outcomes were due to the intervention(s).	not applicable
10. Measures	пот аррпсавле
10. Weasures	page 4, lines 132–153, also
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.	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
	Page 4, lines 121–130 and Supplementary Figure 1 and Supplementary
c. Methods employed for assessing completeness and accuracy of data.	tables 2 & 3
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b. Methods for understanding variation within the data, including the effects of time as a	Figure 1, discussion section, page 9, heading strengths and limitations, lines
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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,
now chart of table), including mounications made to the intervention during the project.	Figure 1–2, text page 5 lines 161–226, Supplementary
b. Details of the process measures and outcomes.	tables 2–3,
c. Contextual elements that interacted with the intervention(s).	not applicable
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d. Observed associations between outcomes, interventions and relevant contextual elements.	Page 7–8, lines 204–227
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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

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..com/ on Jai. Ogrinc G, et al. BMJ Qual Saf 2015;0:1-7. doi:10.1136/bmjqs-2015-004411 Downloaded from http://qualitysafety.bmj.com/ on January 2, 2017