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Original Research

Access to EU-Authorized Nonreimbursed Anticancer Medicines: An Explorative Survey Among Dutch Medical Oncologists

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ABSTRACT

Purpose: Timelines for market authorization and reimbursement for anticancer medicines differ across European countries. Therefore, medical oncologists may face periods when promising anticancer medicines are not reimbursed, prompting ethical concerns about equitable access, particularly in publicly funded healthcare systems, such as the Netherlands. This study explores Dutch medical oncologists' experiences and moral perspectives regarding access to EU-authorized nonreimbursed anticancer medicines and assesses practice variation.

Methods: A survey targeted 378 Dutch medical oncologists from all hospitals to explore their experiences, perspectives, and perceived responsibilities, as well as hospital policies regarding nonreimbursed EU-authorized anticancer medicines and their opinions on out-of-pocket payments and information provision.

Findings: Responses were provided by 132 medical oncologists (response rate of 34.9%), with 104 (78.8%) reporting that they sought access to nonreimbursed medicines in the past three years for one or more patients, primarily through manufacturer-funded "free-of-charge" programs (n = 77/104; 74,0%), clinical trials referral (n = 46/104; 44.2%) or clinical trials at their own hospital (n = 45/104; 43.3%), insurance leniency (n = 45/104; 43.3%), or the Dutch Drug Access Protocol (n = 42/104; 40.4%). While 48.5% felt responsible for seeking access to nonreimbursed medicines, 40.9% did not. Respondents mentioned different hospital policies on drug access. In the past three years, 69.5% (n = 91/131) of respondents had received patient inquiries about out-of-pocket (OOP) payment, but only 3.1% (n = 4/131) had actually prescribed OOP financed medicines. Fewer than half of the respondents (44.7%; n = 59/132) informed patients about nonreimbursed treatment options. Oncologists expressed strong concerns about financial toxicity, inequities in access, and threats to solidarity-based health care.

Implications: The majority of Dutch medical oncologists encounter EU-authorized, nonreimbursed anticancer medicines and report substantial variation in related practices and ethical views. In the absence of a national access framework, availability often depends on individual physicians, leading to potential inequities. National regulation is recommended to ensure consistent and equitable access for all patients.

Introduction

Globally, the number of innovative expensive anticancer medicines entering the market has rapidly increased.[1] The shift toward personalized medicine, with a focus on molecular targeting, has led to the development of highly selective medicines for specific (sub)groups of patients. Patients and healthcare professionals strive for timely access to these innovative medicines, although the evidence of their efficacy could be limited due to the utilization of nonrandomized, single-arm studies and surrogate endpoints.[2] To safeguard the sustainability of pub-

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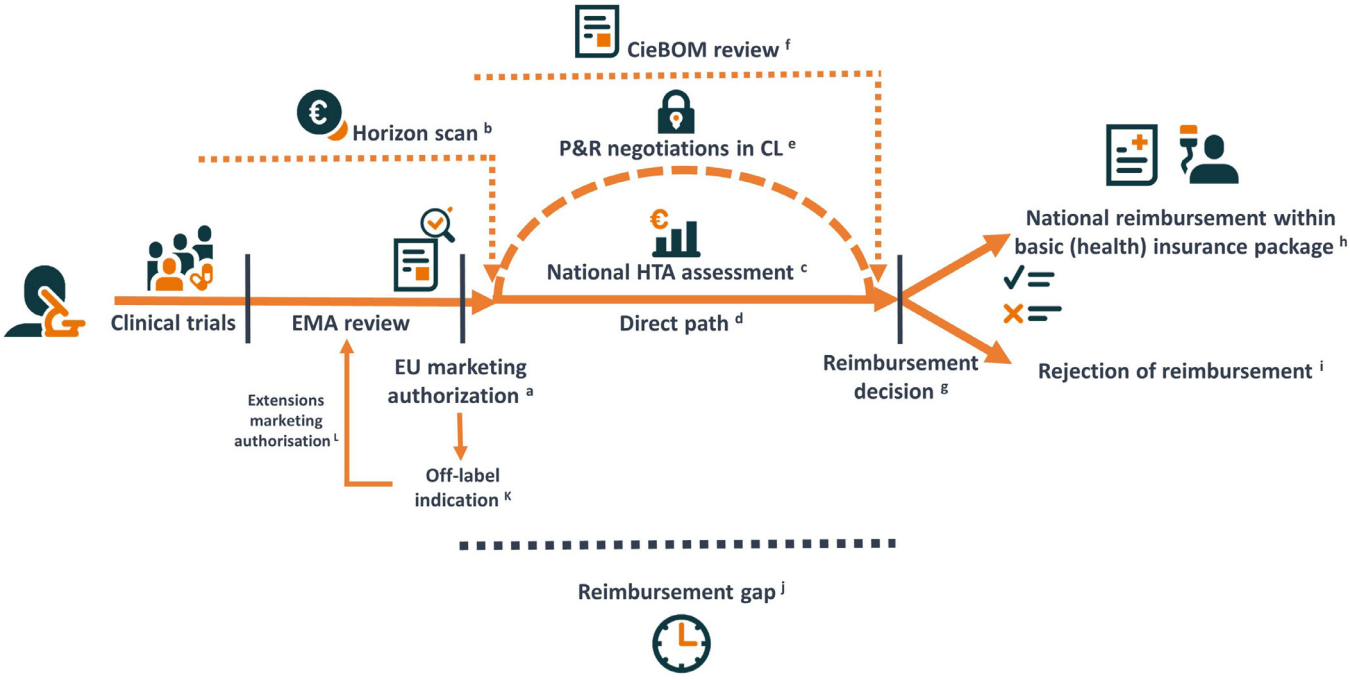

Figure 1. Overview of the timeline from drug development to reimbursement in the Netherlands.
The Netherlands utilizes an open system to integrate medicines into its health insurance package. This process occurs after EU authorization (**a**). Low-risk medicines have a straightforward path to reimbursement. In this process, the CieBAG of the Association of Dutch Health Insurers ("ZN") determines their state-of-the-art status and eligibility for inclusion in the health insurance package (**d**), leading to reimbursement (**g**). EU-authorized high-budget impact medicines* are identified through the Horizon scan for Medicinal Products (**b**), and they are placed in the "Coverage Lock" (CL). Within the CL, the manufacturer submits a dossier. The National Health Care Institute advises their inclusion in the health insurance package on the basis of the assessment of clinical benefits, cost-effectiveness, necessity and feasibility as well as sufficient guarantees for appropriate use. Additionally, the ministry negotiates with the manufacturer to reach a reasonable financial arrangement if deemed feasible. (**e**).[34] The Dutch Committee for the Assessment of Oncological Medicines, known as the CieBOM, provides recommendations regarding the inclusion of these medicines in national clinical guidelines, assessing their clinical value (**f**). This committee collaborates closely with the National Health Care Institute, which then formulates their advice. In addition to the treatments listed in the CL, expanded access, compassionate use, and named patient programs provide routes for accessing treatments not yet reimbursed, addressing the reimbursement gap (j). In 2021, the Dutch Drug Access Protocol, a national platform, was established to harmonize the fragmented utilization of novel treatments not yet reimbursed and to facilitate comprehensive data collection in the Netherlands. To date, seven medicines (cemiplimab, larotrectinib, entrectinib, capmatinib, selpercatinib, tepotinib, and amivantamab) have been included in DAP.[6] Used abbreviations in Figure 1 and its subtitle: EU = European Union; CieBAG = Add-on Drugs Assessment Committee (Commissie ter Beoordeling Add-on Geneesmidden); ZN = Dutch Association of Health Insurers (Zorgverzekeraars Nederland); CieBOM = Dutch Committee for the Assessment of Oncological Medicines (Commissie ter Beoordeling Oncologische Middelen); EMA = European Medicines Agency; HTA = Health Technology Assessment; P&R = Pricing and reimbursement; CL = Coverage lock; DAP = Drug Access Protocol
*If the budget impact exceeds €50,000 per patient and reaches a total of €10 million, or if the total budget impact surpasses €20 million regardless of the budget impact per patient (updated for 2024). The icons in this figure are sourced from the Amsterdam UMC image collection; a previous, different version of this figure has been published earlier[7]. For an overview of medicines included in the Coverage Lock, please refer to the following link: https://www.zorginstituutnederland.nl/over-ons/programmas-en-samenwerkingsverbanden/horizonscan-geneesmiddelen/sluis-voor-dure-geneesmiddelen/overzicht-sluismiddelen-waarover-het-zorginstituut-heeft-geadviseerd.

licly funded healthcare systems, it is crucial to keep healthcare affordable and distribute healthcare funds fairly across various patient groups and healthcare domains.[3] Facing scientific and financial challenges in ensuring unrestricted access to innovative medicines, governments have developed policy instruments to guide access and reimbursement decisions. These decisions follow scientific EMA evaluations, with the European Commission making the final EU authorization decision. These tools often include National Health Authorities' scientific assessment and appraisal, leading to decisions on pricing and reimbursement. In these processes, treatments' effectiveness can be balanced against their costs, and even effective medicines may not be reimbursed in some countries if they are deemed too expensive or insufficiently cost-effective.[4] An illustrative example of regulated access is the Dutch Coverage Lock, a policy in which high-cost medicines are initially excluded from reimbursement[5] (see Figure 1).

Differences in price regulation, market size, expected prices and national policies result in varying timelines for access to and reimbursement for anticancer medicines.[6–8] Even in high-income European countries, the time between authorization and the reimbursement decision of anticancer medicines varies significantly and may often exceed 180 days.[7] This has been studied recently in Nordic countries where average time from authorization to reimbursement of anticancer medicines ranged from 416 to 895 days.[9] In the Netherlands specifically, time between authorization and the reimbursement decision is determined by the coverage lock period.[5] The coverage lock time has more than doubled over time, increasing from an average of 225 days in 2015 to nearly 600 days in 2023.[10,11] In contrast, in the Netherlands, the Dutch Committee for the Assessment of Oncological Medicines (CieBOM) assesses the inclusion of EU-authorized anticancer medicines in national clinical guidelines, irrespective of their cost or reimbursement status. Consequently, EU-authorized anticancer medicines may receive positive reviews from CieBOM but remain pending reimbursement. The protracted processes in national policies raise concerns regarding patient access, especially for cancer patients with urgent unmet medical needs.

Furthermore, the Drug Access Protocol (DAP) was created in the Netherlands to address the gap between EU market approval and access to nonreimbursed medicines due to insufficient data on (cost)effectivity. The Dutch Drug Access Protocol (DAP) is designed to facilitate struc-

tured access to promising novel targeted anticancer medicines for patients with rare cancers and unmet medical needs.[12] Within the DAP study, reimbursement is organized individually, and data on effectiveness and safety are collected. Importantly, the DAP study has, to date, included a limited number of medicines ($n = 7$) for specific indications, and treatment is available in a limited number of hospitals,[12–14] thus bridging the reimbursement gap (only) for those patients with a specific disease. After DAP inclusion is completed, reimbursement is not automatically arranged. Recently, in the case of cemiplimab, real-world data from the DAP study, combined with existing evidence in locally advanced or metastatic squamous cell carcinoma, have resulted in a positive final health technology assessment, leading to reimbursement in the Netherlands.[15]

The delay and inequities in time between authorization and the reimbursement decision across countries may cause unnecessary loss of life years.[6] In addition, variability in clinical oncology practices within one EU member state could lead to inequalities in patient access to treatments, raising ethical concerns regarding justice and solidarity.[3] While previous qualitative research has revealed that practice variation exists,[16] it is not yet clear to what extent this is the case. This study aims to explore medical oncologists' experiences and moral perspectives with EU-authorized anticancer medicines that are currently nonreimbursed, to quantitatively assess the extent to which practice variation exists among Dutch medical oncologists, and to elucidate the principles underlying their actions. These insights may support policymakers and healthcare professionals in developing strategies to ensure equal and faster access to nonreimbursed treatments.

Participants and Methods

Study Population

This study included all hospitals in the Netherlands. Medical oncologists were identified through public hospital websites, and their email addresses were obtained via the investigators' professional networks. We invited all medical oncologists from all 35 general- ($n = 100$), 26 top clinical- ($n = 150$), 7 academic- ($n = 122$), and 2 specialized oncology hospitals ($n = 43$) (Appendix 2). On May 30, 2023, an explanatory letter with a link to a web-based survey in CASTOR was sent via email. Medical oncologists received reminder emails after two and four weeks. Data collection continued for up to six weeks and five days after the initial email was sent (July 16, 2023).

Survey

The survey focused on medical oncologists' experiences and moral perspectives on accessing EU-authorized anticancer medicines not (yet) reimbursed within the healthcare insurance package. The questionnaire, based on a previous interview study among Dutch medical oncologists[16] was developed by CB, CP, TS, and EB, with input from all co-authors to refine its content. It covered medical oncologists' roles and responsibilities, hospital policies, out-of-pocket (OOP) payments and information provision. Two hypothetical cases, (inspired by the cases of sacituzumab-govitecan and trastuzumab subcutaneously which were both not reimbursed at the time) were used to gauge respondents' perspectives on OOP payments for effective innovative nonreimbursed medicines (Case 1, Text Box 1) and OOP payments for alternative treatment options associated with quality-of-life benefits (Case 2, Text Box 1). The draft survey was reviewed by the multidisciplinary research team, which included three ethicists, two medical oncologists, and one internist specializing in metabolic diseases. Additionally, the survey was tested and approved by all the panelists and an oncologist in training before being distributed. While this research focuses exclusively on nonreimbursed EU-authorized anticancer medicines, a distinct and minor section of the questionnaire addressed off-label treatments (ie, treatments used for other indications than those for which they granted EU market authorization), the results of which will be described in a separate manuscript. Notably, terminology used for prereimbursement programs can vary across countries and between pharmaceutical manufacturers. In this context, we refer to the provision of EU-authorized medicines through prereimbursement programs introduced and funded by the manufacturer as "free-of-charge" programs.

Box 1. Two cases included in the survey about out-of-pocket payments

> **Case 1:** Imagine there is a new medicine that offers a 6-month median overall survival benefit compared to standard treatment (HR < 0.6) for metastatic breast cancer. The cost per 3-week cycle is 12,000 euros. The medicine is not currently covered by the health insurance package, and the patient wants to pay for it out-of-pocket. Would you agree with this approach?
> **Case 2:** Suppose a medicine can be administered both subcutaneously and intravenously. Due to cost considerations (subcutaneously being more expensive than intravenously), many medical oncologists opt for intravenous administration. If the patient wishes to pay extra for subcutaneous administration, would you agree with this approach?

Predefined answer choices and provisions for free-text responses were provided for all the questions. For certain questions, respondents had the option to select multiple answers. It was not obligatory to respond to all the questions. The questions were presented in Dutch. The English-translated version of the entire survey is provided in Appendix 1.

Data Analysis

Survey responses were included in the analyses if at least 60% of the questions were completed. In the Netherlands, hospitals are categorized into three categories: general, top clinical and academic hospitals.[17] Given the relatively small population of medical oncologists working in specialized oncology hospitals and their function as reference centers for both top clinical and general hospitals in the Netherlands, their responses were combined with academic centers in one category, called "academic hospitals." Statistical analyses were performed via SPSS (IBM, version 28; Chicago, IL). Univariate regression analyses were used to explore differences between baseline participant characteristics and the outcome variables "wish to prescribe nonreimbursed EU-authorized medicine" (Yes; No), "experience prescribing a nonreimbursed EU-authorized medicine" (Yes; No) and "Considering it your responsibility to find a way to prescribe a nonreimbursed medicine" (Yes; No), reporting hazard ratios (HR) and 95% CI. The open question on OOP payments was thematically analyzed by two researchers independently (CP, CB), by assigning and reassigning codes inductively. Based on thematic analysis, quotes were selected per theme to illustrate the varieties in responses. Any discrepancies between the two researchers were solved through discussions, including two additional members of the research team (TS, EB), and subsequently documented in a mutually agreed-upon codebook (Appendix 2).

Ethical Approval and Informed Consent

This study does not fall within the scope of the "WMO" (Dutch Medical Research Involving Human Subject Act); therefore, ethical review of the study was not needed. Participation in the study was voluntary, and the information provided by the participants was treated as confidential and anonymous. The respondents provided their consent for participation at the start of the online survey.

Table 1
Respondents' characteristics.

Survey respondent characteristics			
	n	%	
Gender (n = 129)	Male	43	33.3%
	Female	86	66.7%
Type of hospital (n = 129)	Academic hospital	39	30.2%
	Specialized oncology hospital	6	4.7%
	Top clinical hospital	44	34.1%
	General hospital	40	31.0%
Age (n = 129)	<40	30	23.3%
	40–50	58	45.0%
	51–60	31	24.0%
	> 60	10	7.8%
Experience as oncologist (n = 129) in years	0–3	19	14.7%
	3–10	43	33.3%
	10–20	42	32.6%
	> 20	25	19.4%
Member of (inter)national guideline working group within medical oncology (n = 129)	No	92	71.3%
	Yes	37	28.7%
Do you recruit and include patients in clinical trials? (n = 129)	No, I do not treat patients in clinical trials	6	4.7%
	Yes, I am a principal investigator in one or more clinical trials	50	38.8%
	Yes, I am a coinvestigator in one or more clinical trials	73	56.6%

Baseline characteristics of 3 participants who were missing (Demographic part of these surveys were not completed by participants).

Results

Participant Demographics

We included all hospitals in the Netherlands in our study, identifying 413 registered medical oncologists, of whom 378 valid email addresses were obtained. These 378 oncologists were invited to participate via email. The distribution of those approached was as follows: 114 out of 122 academic hospital specialists (93.4%), all 43 specialists from specialized oncology hospitals (100%), 131 out of 150 from top-clinical hospitals (87.3%), and 90 out of 100 from general hospitals (90.0%) (see flow diagram in Appendix 3). Sufficiently comprehensive responses (defined as >60% of questions answered) were obtained from 132 medical oncologists, resulting in an overall response rate of 34.9%. The respondents in general hospitals had the highest response rate of 44.4% (n = 40/90), followed by those in top clinical hospitals at 33.5% (n = 44/131). Academic/specialized medical oncologists had a response rate of 28.7% (n = 45/157). The majority of the respondents were medical oncologists with 3–10 years (n = 43; 33.3%) or 10–20 years of experience (n = 42; 32.6%) Respondents reported that a majority of their work involved patient care (median 75%, interquartile range 60–80%) (for additional demographics, see Table 1).

Access to Nonreimbursed EU-Authorized Anticancer Medicines

Most respondents (85.6%; n = 113/132) expressed the wish to prescribe EU-authorized medicines that were not (yet) reimbursed by the health insurance package in the past three years. Among these respondents, a majority (92.0%; n = 104/113) had prescribed nonreimbursed anticancer medicines in the past three years, mainly (69.2%; n = 72/104) for 1 to 5 patients. Most respondents (93.3%; n = 97/104) prescribed nonreimbursed medicines awaiting national scientific assessment and appraisal by the Dutch Healthcare Institute. These medicines were placed within the Coverage Lock (see Figure 1).

Medical oncologists followed various routes to access nonreimbursed medicines (Table 2): reaching out to manufacturers to obtain medication "free-of-charge" (74.0%; n = 77/104), referring patients to other hospitals for study treatment (44.2%; n = 46/104), enrolling patients in their own hospital for study treatment (43.3%; n = 45/104), and enrolling patients in the Dutch Drug Access Protocol (DAP, 40.4%; n = 42/104) (see Figure 1).

Reasons for Pursuing Access to Nonreimbursed Medicines

More than one reason for pursuing access to nonreimbursed medicines could be given. The most frequent answers included the following: perceived effectiveness of the drug (81.8%; n = 108/132), endorsement by the Dutch Committee for the Assessment of Oncological Medicines (CieBOM) (75.0%; n = 99/132) (see Figure 1), perceived superior effectiveness compared with reimbursed alternatives (44.7%; n = 59/132), a specific mechanism of action targeting a tumor characteristic (42.4%; n = 56/132), absence of reimbursed alternatives (40.9%; n = 54/132), and statement in an international guideline (34.8%; n = 46/132) (Table 2).

In response to an open-ended question, additional reasons were cited, advocating for patients' rights to access nonreimbursed treatments, and physicians' perceived duty to provide the highest standard of care (Appendix 2).

When asked at what point in the trajectory of a new medicine from clinical trials to national scientific assessment and appraisal, respondents were ready to prescribe a medicine, they gave various answers. Most respondents preferred prescribing innovative anticancer medicines promptly after a positive assessment by CieBOM (53.0%; n = 70/132). Some indicated a readiness to prescribe the medicine following publication in the peer-reviewed scientific literature (15.2%; n = 20/132) or immediately after EU authorization (11.4%; n = 15/132), whereas others preferred to wait until the medicine was included in the health insurance package (13.6%; n = 18/132).

Perspectives on Medical Oncologists' Roles and Responsibilities

Among respondents, there was a variability in (moral) perspectives on physicians' professional responsibility for pursuing access to nonreimbursed medicines for patients. The largest group believed that they bore this responsibility (48.5%; n = 64/132), whereas a slightly smaller group did not (40.9%; n = 54/132), and a minority remained uncertain (10.6%; n = 14/132) (see Table 2). Compared to respondents in "academic hospitals," oncologists in general hospitals reported less responsibility for pursuing access to nonreimbursed medicines (HR = 0.236; 95% CI: 0.095–0.588; p = 0.002). In addition, members of (inter)national guideline working groups indicated to feel more responsible than nonmembers (HR = 2.623; 95% CI: 1.188–5.794; p = 0.017) (Appendix 5).

Among respondents who did not hold themselves responsible for pursuing access to nonreimbursed anticancer medicines, some provided

Table 2
Summary of responses categorized by type of hospital where the oncologist works.

Survey answers					
		Academic/specialized oncology hospital (n = 45)	Top clinical hospital (n = 44)	General hospital (n = 40)	Total[#]
1. in the past 3 years, considered prescribing a medicine for an EMA-authorized indication that was not reimbursed? (n = 132)[¶]	Total number of medical oncologists answering question	45	44	40	132
	No, this did not happen	9	3	7	19
		20.0%	6.8%	17.5%	14.4%
	Yes, but the medicine was pending pricing and reimbursement approval	33	35	26	97
		73.3%	79.5%	65.0%	73.5%
	Yes, but the medicine was rejected for reimbursement	2	3	2	7
		4.4%	6.8%	5.0%	5.3%
	Yes, but the reason for the medicine not being reimbursed is unknown	1	3	5	9
		2.2%	6.8%	12.5%	6.8%
1.1 For how many patients have you prescribed nonreimbursed medicines? (n = 113)[†]	Total number of medical oncologists answering the question	36	41	33	113
	0 patients	1	2	6	9
		2.8%	4.9%	18.2%	8.0%
	1–5 patients	24	25	21	72
		66.7%	61.0%	63.6%	63.7%
	6–20 patients	9	12	5	26
		25.0%	29.3%	15.2%	23.0%
	> 20 patients	2	2	1	6
		5.6%	4.9%	3.0%	5.3%
1.1.1 Used (one or more) of the following rmethods to prescribe nonreimbursed medicines (n = 104)[‡]	Total number of medical oncologists answering the question	35	39	27	104
	Reaching out to manufacturer for “free-of-charge” program	22	33	19	77
	Referral to another hospital for study treatment	13	19	11	46
	Enrolling for study treatment in own hospital	21	18	5	45
	Leniency application to health insurer[‖]	16	19	7	45
	Enrolling in Dutch DRUG Access Protocol	21	13	7	42
	Covered by hospital	14	7	6	27
	Referring to another Dutch hospital where medicine was available	1	10	8	20
	Patient went for treatment abroad	5	4	1	11
	Referring abroad where this treatment was available	3	4	0	8
	Unknown how reimbursement was arranged	1	0	1	2
	Reimbursement was arranged otherwise (specified)[¶]	1	0	1	2
	OOP payment	0	0	1	1
2. Reasons (one or more) for seeking access (n = 132)	Total number of medical oncologists answering the question	45	44	40	132
	The effectiveness of the medicine	38	38	29	108
	Positive assessment by CieBOM	32	35	30	99
	Superior effectiveness compared to reimbursed alternatives	18	22	18	59
	Specific mechanism of action targeting tumor characteristic	22	17	16	56
	Absence of reimbursed alternative	18	25	10	54
	Statement in an international guideline	15	16	14	46
	No options for study treatment	15	14	9	39
	Patients’ clinical performance/fitness	13	11	8	34
	Patients (young) age	7	12	9	30
	Less toxicity compared to reimbursed medicines	12	8	9	30
	Experience with the medicine abroad	11	6	3	21
	Patients’ wish	4	11	3	18
	Experience with the medicine in another Dutch hospital	1	6	8	15
	Other (specified)[¶]	1	1	0	2
3. From which point in time are you willing to prescribe a medicine? (n = 132)	Total number of medical oncologists answering the question	45	44	40	132
	After a presentation on a scientific meeting	2	2	0	5
	After a scientific publication (peer reviewed)	12	6	2	20
	After approval by FDA	0	0	0	0
	After approval by EMA	7	5	3	15
	After a (preliminary) positive assessment by CieBOM	15	25	29	70
	After reimbursement in the health insurance package	6	5	6	18
	Otherwise (specified)[¶]	3	1	0	4
4. Do you consider it your professional responsibility to seek ways to prescribe nonreimbursed medicines? (n = 132)	Total numbers of medical oncologists answering the question	45	44	40	132
	No	13	18	22	54
	Yes	29	21	12	64
	Do not know	3	5	6	14
6. In the past 3 years, for how many patients have you prescribed a medicine that was provided “free-of-charge” by the manufacturer? (n = 132)	Total number of medical oncologists answering the question	45	44	40	132
	none	9	6	16	31
	1–5 patients	29	27	22	80
	6–10 patients	6	8	1	15
	11–20 patients	1	3	1	5
	>20 patients	0	0	0	1
6.1 On average, how many hours does it take you as a doctor to initiate a “free-of-charge” program? (n = 101)	Total numbers of medical oncologists answering the question	36	38	24	101
	< 2 hours	3	9	2	15
	2–5 hours	16	17	14	48
	5–10 hours	11	8	6	25
	10–20 hours	3	2	1	6
	> 20 hours	3	2	1	7

(*continued on next page*)

Table 2 (*continued*)

Survey answers					
		Academic/specialized oncology hospital (n = 45)	Top clinical hospital (n = 44)	General hospital (n = 40)	Total[#]
7. What is your hospital's policy on prescribing nonreimbursed medicines? (n = 131)	Total number of medical oncologists answering the question	45	44	40	131
	A medicine can be prescribed if a financial arrangement with the manufacturer or health insurance company is set[§]	32	29	18	80
	Only reimbursed medicines can be prescribed	7	15	21	43
	A medicines committee decides which nonreimbursed medicines can be prescribed	9	13	7	30
	I don't know	1	2	6	9
	A specific hospital budget is available	6	1	1	8
	Following national approval by CieBOM regardless of national reimbursement	2	2	1	5
	If the patient pays for it (out-of-pocket)	0	3	0	3
	Other, specified[¶]	6	2	0	8
8. In the past 3 years, how often have patients asked you whether they could pay for a medicine themselves ? (n = 131)	Total number of medical oncologists answering the question	45	44	40	131
	Never	8	13	19	40
	1–5 times	23	28	18	71
	6–10 times	12	3	3	18
	>10 times	2	0	0	2
9. In the past 3 years, have you prescribed nonreimbursed medicines based on OOP payment? (n = 132)	Total number of medical oncologists answering the question	45	44	40	132
	Yes	1	2	1	4
	No, and in our hospital we do not refer patients for this reason	28	24	20	74
	No, and in our hospital we do refer patients to another hospital in the Netherlands	0	5	5	10
	No, and in our hospital we do refer patients to another hospital abroad	5	4	1	10
	Other, specified[¶]	11	9	13	34
14. Do you inform patients about medicines that are EU-authorized but not yet reimbursed? (n = 132)	Total number of medical oncologists answering the question	45	44	40	132
	No	28	23	21	73
	Yes	17	21	19	59
15. Factors influencing informing patients regarding nonreimbursed medicines (n = 59)[D]	Total number of medical oncologists answering the question	17	21	19	59
	Effectiveness of the medicine	16	18	13	49
	There is no alternative reimbursed medicine available	10	13	6	30
	The added value compared to alternative reimbursed medicines	14	14	11	41
	The level of evidence of the medicine	11	14	6	33
	The toxicity compared to reimbursed medicines	8	9	6	24
	The costs of the medicines	2	6	4	12
	The patient's age	1	4	6	12
	The patient's physical condition	7	8	9	26
	Whether the patient ask for it or not	6	11	13	30
	The patient's financial situation	0	0	1	1
	Other, specified[¶]	0	1	1	2

*Question completed by all 132 respondents.
† Question only completed by respondents who had agreed that they wanted to prescribe medicines (yes, ….) without reimbursement in the last 3 years in the previous question.
‡ Question completed by only respondents who had answered that they had prescribed nonreimbursed medicines in the previous question.
§ Only applicable if participant does inform patients about EU-authorized not yet reimbursed medicines
‖ Individual application to patients' health insurance to ask for reimbursement of the medicine
¶ Questions answered with "other" are displayed in Appendix 3.
# Three medical oncologists did not complete the baseline characteristics and were labeled "unknown." This category is not presented separately but is included in the overall number of participants.

reasons in open-text, mentioning a preference for a national policy for accessing nonreimbursed treatments in the healthcare system, a belief that nonreimbursed medicines should be prescribed in academic and top clinical hospitals but not in general hospitals, and concerns about the time and effort associated with pursuing access to nonreimbursed medicines, which could lead to displacement of other care.

One common route for accessing nonreimbursed anticancer medicines in the Netherlands is to request the medicine "free-of-charge" from the manufacturer. Over the last three years, 101 respondents (n = 101/132; 76.5%) had prescribed nonreimbursed anticancer medicines through such a manufacturer-funded program. Respondents in academic hospitals (80.0%; n = 36/45) or top clinical hospitals (86.4%; n = 38/44) more frequently sought access through the manufacturer than did respondents in general hospitals (60.0%; n = 24/40) (Table 2).

The majority of respondents (79.2%; n = 80/101) who utilized manufacturer-funded programs to access anticancer medicines had applied for these programs for 1 to 5 patients. The time and effort required by medical oncologists to initiate patient access through these programs vary considerably, ranging from less than 2 hours to more than 20 hours. Across all types of hospitals, many respondents reported that initiating such a program took 2 to 5 hours (47.5%; n = 48/101) or 5 to 10 hours (24.8%; n = 25/101) (Table 2).

Hospitals' Policies Regarding Access to Nonreimbursed Anticancer Medicines

The respondents reported substantial variation in hospital policies regarding access to nonreimbursed anticancer medicines (see Table 2). Some respondents noted that hospital regulations prohibited the pre-

scription of nonreimbursed medicines, a trend particularly prevalent for general hospitals (52.5%; n = 21/40) but also observed in top clinical hospitals (34.1%; n = 15/44) and academic hospitals (15.6%; n = 7/45). Most respondents indicated that hospitals facilitated the prescription of innovative anticancer medicines when the manufacturer provided the medicine "free-of-charge." This practice was widespread among academic hospitals (71.1%; n = 32/45), top clinical hospitals (65.9%; n = 29/44), and general hospitals (53.2%; n = 21/44). Approximately 22.7% of the respondents (n = 30/132) reported that hospitals had established medicine committees tasked with evaluating and authorizing the prescription of nonreimbursed medicines. Additionally, a minority (3.9%; n = 5/132) indicated adherence to CieBOM advice, regardless of reimbursement status. Only a few respondents (2.3%; n = 3/132) stated that their hospitals permitted support for patients opting for OOP payments. A small proportion (6.9%; n = 9/132) reported being unaware of their hospital's policy.

Experiences With and Perspectives on OOP Payment

A significant number of respondents (69.5%; n = 91/131) reported having received requests from patients willing to pay OOP for nonreimbursed anticancer medicines in the previous three years. Medical oncologists in general hospitals reported less frequently that patients had asked to pay for a medicine themselves, compared to those in academic hospitals (HR = 0.239; 95% CI: 0.089–0.640; p = 0.004) (Appendix 5). Even though the majority had received requests for OOP payment, only four respondents (3.1%; n = 4/131) had actually prescribed medicines at patients' expense, while the large majority (2%; n = 94/132) had not done so. Among these 94 respondents who had not prescribed OOP-funded anticancer medicines, 10.6% (n = 10/94) reported that their hospital's policy was to refer patients to other Dutch hospitals, and another 10.6% (n = 10/94) to foreign hospitals. In contrast the vast majority (78.7%; n = 74/94) indicated that no referrals were offered for OOP requests (Table 2).

When presented with two hypothetical cases (Text Box 1), many respondents expressed their disapproval of OOP payments. The majority rejected OOP payments in both Case 1 (79.5%; n = 105/132) and Case 2 (76.5%; n = 101/132). The reasons for rejecting OOP payments included concerns about undermining solidarity within the Dutch healthcare system, the importance of ensuring equal access to health care for all patients, the potential (financial) burden on patients, and the logistical complexities associated with arranging OOP payments.

Those who supported OOP payments did so because of the perceived therapeutic benefits of treatment (Case 1), a belief in the moral right of patients to allocate their own funds according to their preferences, and concerns about the safety of patients who might seek treatment elsewhere if OOP payments were restricted. Conditions for prescribing OOP treatments included: ensuring safety and efficacy, EU marketing authorization, receiving positive recommendations from CieBOM, receiving support from colleagues for the decision to prescribe the treatment, and the expectation that the time until reimbursement would be limited. A more detailed presentation of respondents' rationales for (not) endorsing OOP payments and the associated ethical values is presented in Table 3 and Appendix 2.

Provision of Information About Nonreimbursed Innovative Anticancer Medicines

Interestingly, over half of the respondents (55.3%; n = 73/132) reported that they did not disclose information about nonreimbursed anticancer medicines to their patients. The reasons for this included a desire to shield patients from emotional and financial burden, the perception that such discussions were inappropriate, and limited during consultations (Appendix 2). Conversely, among respondents who did inform patients about nonreimbursed treatments (44.7%; n = 59/132), motivations included the possibility that patients might seek out or discover this information independently at a later stage, the intention to enable patients to monitor potential future access, and positive assessment by CieBOM (Appendix 2). Furthermore, the most frequently cited factors guiding the decision to inform patients were the perceived effectiveness of the medicine (83.1%; n = 49/59), its added value compared to reimbursed alternatives (69.5%; n = 41/59), a high level of supporting clinical evidence (55.9%; n = 33/59), and the absence of alternative treatment options (50.8%; n = 30/59) (Table 2).

Discussion and Conclusion

This nationwide survey quantitatively and qualitatively explored medical oncologists' experiences and moral perspectives on EU-authorized anticancer medicines that are not currently reimbursed within the publicly funded Dutch healthcare system. We found substantial variation in practices and perspectives, contributing to unequal patient access.[7,18–22] As a national policy regarding access to EU-authorized nonreimbursed medicines in the Netherlands is lacking, patient access depends on the efforts of individual physicians. Our findings revealed considerable variation in both clinical practices and perspectives of medical oncologists regarding their sense of responsibility to secure access to nonreimbursed anticancer medicines. Some reported feeling personally responsible for providing access if the medicine is deemed effective by the individual oncologist or the professionals' advisory body (CieBOM), with an – often implicit – reference to beneficence, one of the four principles of biomedical ethics,[23] or the duty of physicians to act for the benefit of patients, as laid down in the International Code of Medical Ethics of the World Medical Association.[24] Others reported believing that such responsibility lies beyond the tasks of the physician, and that provisions for access to nonreimbursed medicine should be developed not for individual patients, but for the entire patient population, at a national level. The routes used to access nonreimbursed medicines were similar to those previously reported by Canadian medical oncologists.[25] Interestingly, Dutch medical oncologists did not consider OOP payments a viable option for accessing EU-authorized nonreimbursed medicines. While over half of the respondents received inquiries about OOP payments, only a small fraction (<5%) actually prescribed treatments with OOP payments. This practice aligns with the low incidence of OOP payments in the Netherlands.[21] This general disapproval of OOP payments is tied to values such as equitable access, solidarity, which are tied to the medical-ethical principle of justice, or concerns about harms to patients, including emotional and financial burdens, which are tied to the medical-ethical principle of nonmaleficence[23] and practical challenges, including time constraints and logistical complexities, which have been reported previously.[16]

The difficulty of obtaining access to EU-authorized nonreimbursed medicines poses the ethical dilemma of whether to inform patients about these medicines. Nearly half of the respondents chose not to disclose information regarding nonreimbursed medicines. Previous survey studies conducted in Israel and Australia found that 2–41% of physicians chose not to disclose.[26,27] In contrast, in Canada, where access to nonreimbursed medicines is a growing problem, 98% of medical oncologists reported discussing these options with patients.[28] A UK study indicated that 94% of patients expect doctors to inform them about all available anticancer treatments, regardless of public funding.[29] Similarly, between 90% and 98% of Australian respondents wanted to know about expensive anticancer medicines, despite potential affordability concerns.[30] Other studies have also shown that cancer patients prefer having comprehensive information on nonreimbursed treatment options, often turning to various sources, including the internet.[26,31,32] It should be noted that it is not clear whether the provision of information about nonreimbursed treatments will always benefit the patient. Especially when the level of available evidence on the safety and efficacy of the treatment is low and the out-of-pocket costs are high, physicians may experience ethical dilemmas regarding the disclosure of information about nonreimbursed treatments to patients. As reported in previ-

Table 3
Results of the thematic analysis of responses to out-of-pocket payment cases.

Thematic analysis: out-of-pocket payment Case 1 and 2	
Pro OOP payment Case 1 (n = 27; 20.5%); Case 2 (n = 31; 23.5%) Liberty and autonomy Patients should be able to spend their money as they see fit, including on health care Case 1: - *"Everyone has the freedom to decide to spend their money as they see fit – on a new car or prolongation of life"* Case 2: - *"Since the treatment is just as effective and is [available and] reimbursed intravenously for everyone, in my opinion patients can decide for themselves whether they spend their money on this"* - *"They may decide for themselves whether they want to pay for this."*	Con OOP payment Case 1 (n = 105; 79.5%); Case 2 (n = 101; 76.5%) Solidarity OOP payments would undermine the solidarity-based healthcare system Case 1: - *"This would undermine the solidarity underpinning our healthcare system, and I will not be a part of that"* Case 2: - *"Solidarity and equality are a great thing."*
Beneficence Nonreimbursed treatments would provide potential health benefits for patients if OOP payments were allowed Case 1: - *"If the patient is able to afford that, I think the [health] benefit outweighs the costs"* - *"It is in the best interest of the individual patient, who pays for it and there is a benefit"* - *"If the evidence is significant and the patient truly wants it"* Case 2: - *"It is more patient-friendly, and administering a subcutaneous treatment takes much less time than an IV treatment"*	Equality OOP payment would hinder equal access and potentially lead to a class divide. Case 1: - *"If a medicine is available, it must be available to everyone regardless of their income and social status"* - *"Treatment would then depend on financial resources, so [it would lead to] class medicine"* - *"It is a bad thing if only rich people can get treatment"* Case 2: - *"In this case, availability [of the treatment] is not the problem. Therefore, I would stick to one policy and not distinguish between people with and without financial capabilities"* - *"Many patients would prefer subcutaneous treatment, also here [I prefer] equal access regardless of financial capabilities"* - *"I never would never want patients to pay extra. Because of the disparity in treatment between patients with different financial possibilities"*
Nonmaleficence (to do no harm) If OOP payments were not allowed, patients might go elsewhere, which might be less safeCase 1: - *"I would prefer to prescribe the treatment myself, instead of [a scenario in which] the treatment might be prescribed elsewhere and then I could only treat the complications."*	Nonmaleficence (to do no harm) OOP payment could lead to financial harm for individual patients, and prescribing nonreimbursed medicines could lead to displacement of care, which could harm other patients.Case 1: - *"You do not want to get people into (financial) trouble at the end of life"* - *"In addition to the direct costs of the treatment, nurses are also needed. Even if this is paid for, the shortage of nurses could lead to displacement of other care that is included in the health insurance package"* Practical challenges: There are many practical challenges in arranging access to OOP paymentsCase 1: - *"I have not enough time"* - *"I do not know how to organize it"* - *"It is not possible in my hospital"* Case 2: - *"[It would be] too much hassle"* - *"It is just hidden marketing"*

The complete codebook is provided in Appendix 2.

ous research,[16,27,28,33] the decision not to disclose such information can be motivated by a desire to shield patients from the emotional burden of having to consider an out-of-reach treatment option, or a belief that discussing these matters was inappropriate or inconsequential, given the difficulties in accessing nonreimbursed medicines.

Healthcare systems differ across (European) countries, with differences in funding, insurance systems, the prevalence of and support for OOP payments, and the availability of additional reimbursement options. The Netherlands has a publicly funded healthcare system aimed at providing coverage for all essential medical needs for all citizens. Funded through taxes and mandatory health insurance premiums, the Dutch healthcare system is built on principles of solidarity and equal access. In contrast, some European countries have established regulatory frameworks governing access to these medicines through financial arrangements. Examples include France[18] and the UK,[19,20] with supplementary health insurance, or Belgium, with patient funds,[21] all of which support the value of solidarity. Countries with protracted reimbursement timelines are likely to face a higher demand for such access programs, whereas countries with (nearly) immediate access, such as Germany,[7,22] may find the usefulness of access programs limited.

In summary, in healthcare systems with extended time between EU authorization and the reimbursement decision, patients and medical oncologists may explore alternative routes to access promising yet nonreimbursed medicines. However, access to these drugs and information provision can vary, depending on individual medical oncologists' practices and hospital policies. Additionally, assertive patients with higher socioeconomic status may secure earlier access to these medicines, potentially increasing existing health inequalities.[34] While manufacturers strive to provide early access to their products for patients and clinicians through "free-of-charge" programs,[26] the lack of structured information regarding hospitals offering these programs may lead to inequality regarding access.[35,36] Furthermore, the absence of standardization and regulatory oversight can increase these disparities.[37] In addition, a major barrier for medical oncologists regarding access, is that identifying and implementing access programs demands considerable time and resources. These demanding actions further burden an already

strained healthcare system and potentially lead to displacement of care. As medicines may enter the market at an early stage, with limited evidence of effectiveness, and at increasingly high cost, the lengthy period between market authorization and reimbursement is expected to increase in the future. The Dutch medicine coverage lock was created precisely for this purpose. Therefore, it is time to look for alternative solutions, conduct national programs in which medicines are accessed more quickly, are equally accessible for patients, and obtain data in a structured manner. However, alternative solutions are needed, as in the Dutch DAP protocol, medicines can be accessed more quickly but in a controlled manner. However, this overlooks a system adjustment, where promising resources must be assessed early in the process and the opportunity for rapid access must be created. We therefore recommend a framework that enables cyclical health insurance package management by gathering more evidence for effectiveness, accompanied by a price agreement adapted to the development phase of the medicine. Collaborative efforts from all parties—patients, medical oncologists, manufacturers, health insurers, regulatory bodies, and governmental entities—are essential for the success of such a framework.

Strengths and Limitations

This study has several strengths, including a large number of respondents and a significant response rate. Importantly, survey-based studies involving physicians frequently face difficulties in attaining high response rates.[38] Furthermore, the study achieved an equitable distribution of participants among different types of hospitals. Hence, we believe that this sample provides a reasonable representation of medical oncologists in the Netherlands.

Nevertheless, this study has certain limitations. First, there could be response bias due to unintentionally inaccurate responses on topics that are less familiar to respondents. Second, self-reported responses could have introduced social desirability bias. However, we expect this bias to be smaller than in earlier interview studies[16,26] because of the anonymity of responses. The anonymity of responses itself also presents a limitation, as it made hospital-level analysis impossible and may have led to overrepresentation of respondents from a limited number of hospitals, potentially affecting the reported outcomes. Another limitation is the risk of nonresponse bias. Oncologists with little interest in the topic may have been underrepresented, while those with a particular interest in the subject may have been more likely to respond. As a result, the variation in perspectives and practices observed in our sample may underestimate the true heterogeneity within the broader oncologist population. Nevertheless, the aim of this study was to capture a broad range of perspectives by reaching as many individual oncologists as possible. Future research on hospital policies should consider collecting a single response per hospital or aggregating multiple responses at the institutional level to reflect hospital-wide practices more accurately.

Finally, another limitation is the generalizability of the findings to other countries, as the survey was exclusively administered to Dutch medical oncologists. Perceptions and practices may differ across nations with dissimilar healthcare systems. However, comparable attitudes regarding cancer drug costs, cost-effectiveness, and associated policies were observed among medical oncologists in both the United States and Canada, despite differences in their healthcare systems.[29] Furthermore, the structure of our solidarity-based healthcare system, characterized by mandatory universal health insurance, is similar to that of many healthcare systems worldwide, making the findings from this study meaningful for numerous economically stable nations across Europe and worldwide.

List of abbreviations

EU = European union; CieBAG = add-on drugs assessment committee (Commissie ter Beoordeling Add-on Geneesmiddelen); ZN = Dutch Association of Health Insurers (Zorgverzekeraars Nederland); CieBOM = Dutch Committee for the Assessment of Oncological Medicines (Commissie ter Beoordeling Oncologische Middelen); DAP = DRUG access protocol; OOP = out-of-pocket; EMA = European medicines agency; HTA = health technology assessment; P&R = pricing and reimbursement; CL = coverage lock.

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Declaration of competing interest

Besides the membership of H.C.P and C.E.M.H of the platform “Medicines for Society” (see funding), C.E.M.H. reports to be involved in pre-marketing studies with Protalix and Idorsia and is member of advisory committee to the health care package, Health care Institution. H.W.M.L. declared a consultant or advisory role: Amphera, Anocca, Astellas, AstraZeneca, Beigene, Boehringer, Daiichy-Sankyo, Dragonfly, MSD, Myeloid, Servier; Research funding, medication supply, and/or other research support: Auristone, Incyte, Merck, ORCA, Servier; Speaker role: Astellas, Beigene, Benecke, BMS, Daiichy-Sankyo, JAAP, Medtalks, Novartis, Springer, Travel Congress Management B.V. All remaining authors have declared no conflicts of interest.

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Supplementary materials

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