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MARKET ACCESS OF ORAL CANCER DRUGS IN FINLAND:

A patient and patient organization view

Master's Thesis, Health and Business

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ABSTRACT
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The purpose of this thesis is to explore the market access of oral cancer drugs in Finland and take a patient and patient organization view to this process. In order to discover this, the study aims to answer what is the path of oral cancer medicines to Finnish market after its R&D process has been completed, how long is the market access delay of oral cancer drug in Finland and how patients and patient organization views this process.

Based on the previous literature the market access of oral cancer medicines consists from overcoming two barriers that are identified as the regulatory approver and national price and reimbursement decision maker. The successfulness of market access can be measured as market access delay that shows the duration of overcoming these two barriers and making a new oral cancer drug available in the markets. According to the previous literature patients feel that it is unfair that some treatments for life-threatening diseases such as cancer are not reimbursed making them unavailable to all patients.

This study takes on a qualitative phenomenography research approach in exploring the patient and patient organization view toward the markets access of oral cancer drugs in Finland. In-depth semi-structured interviews were conducted with patients and patient organization personnel. The path of oral cancer medicines to market is studied by exploring existing written materials and the market access delay is computed according to the method used in previous literature. In addition, a semi-structured interview was conducted with Pharmaceutical Pricing Board in order to get more in-depth understanding from the price and reimbursement decision making processes.

This study showed that the mean market access delay for oral cancer drugs in Finland was 2,36 years. For drugs granted reimbursement between years 2006–2009 the delay was 1,98 and between years 2014–2016 the delay was 2,77 years. This result implies that the market access delay has prolonged for newer oral cancer drugs. Patients regard that their perspective should be more incorporated into the decision making. Not including new cancer medicines into the Finnish drug reimbursement system is seen to place the patients in an unequal situation based on their wealth. In the eyes of the patients' finances should not be barrier to access for treatments. Further inequalities may arise from the regional differences in administering oral cancer medicines. When new cancer drugs cannot be accessed through the public health care system, the possibilities to access is sought from private sector or from abroad.

TIIVISTELMÄ

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Tämän tutkielman tarkoituksena on selvittää oraalisten syöpälääkkeiden markkinoille tulo Suomessa ja tarkastella sitä potilaan ja potilasjärjestön näkökulmasta. Tutkimuksen tavoitteena on selventää mikä on oraalisten syöpälääkkeiden tie Suomen markkinoille tuotekehitysprosessin jälkeen, kuinka pitkä on oraalisten syöpälääkkeiden markkinoille tulon viive Suomessa ja kuinka potilaat ja potilasjärjestö näkevät tämän prosessin.

Aikaisemman tutkimuksen mukaan oraalisten syöpälääkkeiden markkinoille tulo koostuu kahden esteen ylittämisestä. Nämä esteet ovat määritelty myyntilupaviranomaiseksi ja kansalliseksi hinta ja korvattavuus päätöksentekijäksi. Markkinoille tulon onnistuvuutta voidaan mitata markkinoille tulon viiveenä, joka mittaa aikaa, jolloin nämä kaksi estettä ylitetään ja uusi lääke saadaan markkinoille. Perustuen aikaisempaan tutkimukseen potilaiden mielestä on epäoikeudenmukaista, että jotkut hoidot hengenvaarallisiin sairauksiin kuten syöpään eivät ole saaneet korvattavuutta rajoittaen niiden saatavuutta kaikille potilaille.

Tämä tutkielma soveltaa kvalitatiivista fenomenograafisista tutkimustapaa tutkittaessa, mikä on potilaiden ja potilasjärjestön näkökulma oraalisten syöpälääkkeiden markkinoille tuloon Suomessa. Tutkimuksen aineisto kerättiin käyttäen puolistrukturoituja syvähaastatteluja. Haastateltavina oli potilaita ja potilasjärjestön henkilökunnan jäseniä. Oraalisten syöpälääkkeiden reittiä markkinoille tutkittiin käyttäen aineistona jo olemassa olevia kirjallisia materiaaleja. Lisäksi Lääkkeiden hintalautakunnan kanssa suoritettiin puolistrukturoitu syvähaastattelu, jotta hinta ja korvattavuus päätöksenteon prosesseista saataisiin syvällisempi käsitys.

Tutkimus osoitti, että keskimääräinen oraalisten syöpälääkkeiden markkinoille tulon viive Suomessa on 2,36 vuotta. Vuosina 2006–2009 korvattavuuden saaneiden lääkkeiden viive oli 1,98 vuotta ja vuosina 2014 – 2016 viive oli 2,77 vuotta. Tämä tulos osoittaa, että uusimpien oraalisten syöpälääkkeiden kohdalla markkinoille tulon viive on pidentynyt. Potilaiden mielestä heidän näkökulmaansa pitäisi tuoda enemmän esille päätettäessä lääkkeiden korvattavuudesta. Jos uusia syöpälääkkeitä ei liitetä lääkkeiden korvattavuusjärjestelmään, asettaa se potilaat eriarvoiseen asemaan heidän varallisuuteensa perusteella. Potilaiden mukaan raha ei saisi olla esteenä uusien hoitojen käyttöönottoon. Muita eriarvoisuuteen vaikuttavia tekijöitä voi syntyä alueellisista eroista oraalisten syöpälääkkeiden jakelussa. Jos uusia lääkkeitä ei ole saatavilla julkisen terveydenhuollon kautta, potilaat etsivät mahdollisuuksia saada lääkkeitä yksityiseltä puolelta tai ulkomailta.

Contents

1 INTRODUCTION

1.1 Market access of cancer drugs

Cancer is one of the leading causes of morbidity and mortality worldwide. In 2012 there were 14 million new cancer cases and 8,2 million deaths related to cancer and the number of new cases is expected to rise by 70% over the next two decades. (WHO 2015.) In European Region cancer causes 20% of the deaths, making cancer the second most important cause of morbidity and mortality in Europe. In addition, Europe holds only 1/8 of the total world population but it has 1/4 of the total cancer cases worldwide. (WHO Europe 2016.) These figures highlight the importance of cancer as a societal burden and emphasizes the importance of introducing new effective cancer treatments for curing cancer and prolonging the life of cancer patients.

Although the European Medicines Agency (EMA) is responsible for granting marketing authorization valid across Europe for new cancer drugs (Pignatti et al. 2011) the final implementation of market access for cancer drugs rests on a national responsibility through the national price and reimbursement decisions (Martinalbo et al. 2016; Pauwels at al 2014; McCabe et al. 2009). Furthermore, health care providers keep struggling with new innovations that offer in their view limited benefits at an unjustified high price which further deepens in disease areas such as oncology where medical unmet need still remains (Pauwels et al. 2016). Although cancer drugs accounts for less than 15% of the total health care expenditure for cancer they are easily identified as target for cost-containment (Jönsson & Wilking 2007).

There are significant variations in the level of uptake and speed of uptake for new cancer drugs between countries (Jönsson and Wilking 2007c; Wilking et al. 2009; Jönsson et al. 2016b). Not only between countries with different economic status but also between countries with similar economic power (Jönsson et al. 2016b). A variety of instruments is used for price and reimbursement decision making for cancer drugs across Europe affecting this heterogeneity in accessing new cancer drugs (Pauwels et al. 2014; McCabe et al. 2009). Previous research has shown that in Finland the average time to access for cancer medicines authorized between the time period 2003–2006 in outpatient setting was 259 days after gaining marketing authorization (Wilking et al. 2009). Furthermore, a more recent study showed that for oral cancer drugs authorized before 2012 the mean market access delay was 397 days (Kanninainen et al. 2014). For the intent of managing health care budgets health care decision makers may seek to delay

or restrict access to new innovative drugs although with unintended consequences for patients (Jönsson & Wilking 2007).

Stakeholders should coordinate their views as much as possible to ensure the efficient allocation of scarce resources, sustainable development and access to innovative drugs (Pauwels. 2016). Currently all stakeholders see patients' perspective in decision making as highly important and the paternalistic approach that experts know the best patients' interests has outlived its purpose. Although, there is no universal approach to what extent patients should have the opportunity to choose the treatment that experts would consider more harmful than beneficial. Several methods are used for ranking the benefits and risks each with its own advantages and limitations but without generally accepted gold standard. (Enzmann 2016.)

1.2 Purpose of the study

The purpose of this thesis is two-fold. Firstly, I intend to explore what is the mechanism behind the market access of cancer drugs in outpatient setting in Finland. Therefore, I concentrate on the market access of oral cancer drugs since they are primarily used in outpatient setting. Secondly, I intend to explore how the market access of new cancer drugs is viewed among cancer patients and patient organization.

For the market access of new oral cancer drugs I will explore how the marketing authorization is gained from European Medicines Agency, what is the national decision maker of price and reimbursement decisions and how this decision will be reached. Besides this, I will study what is the current delay in the market access of oral cancer drugs in Finland. Based on this research aim the first research question is the following:

Q1: "How will new oral cancer drugs gain market access in Finland and how long is the duration of process for gaining market access?"

In addition, the second aim of this thesis is to explore how cancer patients and cancer patient organization views the market access of new oral cancer medicine in Finland. Previous research has shown that there is lack of understanding about the drug approval process among patients although patients are eager to gain knowledge about all available treatment options (Kaser et al. 2010). Therefore, I intend to explore how the market access of new oral cancer medicine is viewed among patients in Finland. Additionally, I will study what is the perspective of cancer patient organization as an interest group of the patients' towards market access of new oral

cancer medicines and what kind of information and feedback the organization receives from the patients. Based on this research aim the second research question of this thesis is the following:

Q2: "How cancer patients and patient organization views the market access of new oral cancer drugs in Finland?"

For the research question Q1 I will attempt to answer by exploring the extensive written materials found online from the official websites of European Medicines Agency, Pharmaceutical Pricing Board PPB, the Social Insurance Institution of Finland SII and legislation. Besides this I will conduct an interview with the national price and reimbursement (P&R) decision maker of Finland to capture more in-depth understanding form the process of reaching the P&R decision. For computing the market access delay of oral cancer medicines in Finland I will attempt to identify the dates when the medicinal products have been applied for marketing authorization, gained marketing authorization, applied P&R decision and have been included into the Finnish drug reimbursement system.

For answering the research question Q2 I will conduct semi-structured in-depth interviews with cancer patients and personnel from patient organization. The predetermined entry questions for the interviews will be formed according to the themes emerging from the existing literature.

The study will contribute to the existing literature by exploring what is the current market access delay of oral cancer drugs in Finland, clarify what is the route of these medicines for accessing market in Finnish context and explore what kind of mechanisms are used for the market access. In addition, this study will add more to the existing literature about the patient perspective to the market access of new cancer drugs since this perspective is currently highly valued (Enzmann 2016).

The structure of this thesis is the following. In the next section I will define the key concepts of this study i.e. market access and market access delay. Chapter 2 discusses the literature of market access of new cancer medicine and forms the theoretical framework for this study. Chapter 3 presents the methodological approach for this thesis, methods of data collection and methods of analysis. Chapter 4 will reveal the empirical results of this study and presents a summary of these findings. Chapter 5 will bring this thesis to a closure by summarizing the study, discussing the key empirical results of this thesis, bringing these results to a theoretical discussion and making a conclusion based on the key findings. Additionally, limitations of this study and suggestions for future study will be discussed in the final chapter.

1.3 Key concepts of the study

1.3.1 Market access

Although market access currently determines the success or failure of any new medicinal products the definitions of this concept is varying and multifaceted while sharing same underlying approach. The concept results from the fundamental changes in the market environment of medical and pharmaceutical industries and most prominently from the changes concerning the acceptance of funding new and usually more expensive products by healthcare systems which is then typically referred by using the concept of "market access". (Smith 2012.)

Sendyona (2014) tried to define the concept "market access" by conducting a literature review but came into the conclusion that the concept is hard to define with differing opinions and perspectives. Market access can be thought as either gaining regulatory approval for marketing authorization or successfully achieving reimbursement status for a medicine (Sendyona 2014). The reason behind this forked definition could be that up until the 1990s gaining regulatory approval was the sole hurdle for launching new medicine (McCabe et al. 2008). For this reason, in the 1980s and 1990 the discussion for accessing new drugs focused on the lag time between applying and gaining marketing authorization (Jönsson & Wilking 2007). As a result of gradual development after the 1990s an additional hurdle has appeared in the form of reimbursement authorities (McCabe et al. 2008) who makes the decision concerning the price and reimbursement status of a drug.

Although, these both stakeholders i.e. regulatory approver and reimbursement authority share the same principle of balancing the benefits and risks in deciding the availability of drugs (Sendyona 2014) the intellectual paradigms behind adopting different decision rules are very diverse (McCabe et al. 2008). Furthermore, there is not a consistent agreement what factors influence the successful development and commercialization of medicinal products (Sendyona et al. 2015) and the clear and internationally validated definition of this concept is still lacking (Sendyona 2014). Therefore, further research is needed into this field (Sendyona et al. 2015).

The differing views for defining the concept "market access" can be seen when comparing articles discussing the access to new medicine. For example, Eichler et al. (2008) used market access to denote the granting of marketing authorization or licensing of a drug and separated the decision about reimbursement by third-party payers e.g. national health services under the concept "treatment access" for denoting the access by individual patient. Whereas Russo et al.

(2010) used the concept “patient access” to denote medicines that reached patients and separated that concept from “market access” by noting that not every medicine receiving market access (i.e. plausible P&R decision by national agency) will subsequently be released in every Italian region available for patients. Furthermore, in their study concerning market access for personalized medicine Payne & Annemans (2013) associated three decision making levels under the concept “market access” in addition to gaining regulatory approval: national level, provider level (hospital or primary care) and patient-client level decision.

Jommi et al. (2012) took under a study to explore how “market access” is defined by pharmaceutical companies and the results were differing. Most of the companies associated the phrase with public affair issues while some companies had linked it with commercial activity or with a mix of both of these issues and although some companies had adopted formal definition of market access the definitions varied across companies. Access had been most often referred as “access for patients to drug”, “drugs to market (and patient)” and “actions aimed at removing barriers to access”. But what is common for these definition is the fact that “it is increasingly difficult to gain market access unless the product provides not only clinical advantages over the incumbent product but also significant and demonstrably superior health economic outcomes” as stated by Smith (2012).

The study by Jommi et al. (2012) also made an exploration about what are regarded as the key factors that influence market access from the industry perspective. Monitoring regional regulation and negotiations about price and reimbursement were seen as the central activities affecting the market access. Whereas increasing knowledge of the relevant target and providing evidence about the drug’s value (HTA & economic evaluation) were regarded as the most important tools to benefit the market access. (Jommi et al. 2012) This can be resulting from the fact that authorities responsible for managing healthcare budgets increasingly require evidence on value for money (McCabe et al. 2008). When it comes to evaluating how well a pharmaceutical company has performed in market access the most important criteria to take into consideration are time to national market and introduction in regional formularies (Jommi et al. 2012).

Apart from defining the concept “market access” Smith (2012) conducted a study with qualitative approach to solve what is the definition of “market access strategy” in pursuit of helping the companies operating in pharmaceutical and medical industry to define more targeted outcome for their significant investments made in market access activity. The conclusion was that: “Market access strategy is that pattern of resource allocation and activity decisions about what

health economic value proposition to make to the market and which audiences within the market access decision making process to whom to address that proposition." However, the further exploitation of this definition remains unclear.

From these disorganized and vague definitions of "market access" it can be seen that although the definitions can vary in detail they all share common fundamentals as already stated by Smith (2012). Additionally, based on these descriptions it can be argued that there are different stakeholders involved in the market access of new drugs. By looking first at the company definitions brought up in the study by Jommi et al. (2012) where "access" was referred to "access for patients to drug", "drugs to market (and patient)" and "actions aimed at removing barriers to access" it can be seen that market access can be regarded as a process of delivering new drug from manufacturer to patients. This is done by overcoming hurdles which were identified in the previous paragraphs as the regulator that grants the marketing authorization and national reimbursement authorities that makes the decision concerning the price and reimbursement status of a drug.

1.3.2 Market access delay

Jönsson and Wilking (2007c) studied the market uptake of cancer drugs in 25 different (19 countries in Europe) countries around the world during period 1995–2005 and they concluded their article by saying that there are great variations in level and speed of uptake for new cancer drugs between countries and the ability to access new cancer drugs depends on where the patients live. This highlights the inequality for accessing new cancer treatments. In most cases United States has faster uptake of new cancer drugs and in nearly half of the cases in the study USA was the country of first use. This can be explained by the FDA's comparably short drug approval process, successful development of the country's pharmaceutical industry and economical attractiveness of the United States health care market. The average time from launch to sales for the cancer drugs introduced between 1995-2005 and the number of new cancer drugs approved was 1,3 years and 25 new molecules in USA compared to 2,2 years and 23 new molecules in Finland. (Jönsson and Wilking 2007c.)

An update was made to this report exploring the period 1998–2008 in European setting (22 countries) and still the conclusion was the same that there are great variations in the level and speed of uptake for the cancer drugs. The average time to access for cancer medicines author-

ized between the time period 2003–2006 in outpatient setting in Finland was 259 days computed as the time elapsed between gaining marketing authorization and reimbursement decision. (Wilking et al. 2009.) Recently a further update was made for this report still with a consistent result with the previous papers. Access to cancer drugs varies in Europe mainly due to countries' economic status. Although there are also great variations in access between countries with similar economic power. (Jönsson et al. 2016b.)

Kanniainen et al. (2014) studied the market access delay for oral cancer drugs authorized before 2012 and found that the mean delay for gaining reimbursement in Finland was 397 days. Furthermore, the study showed that the market access delay for newer oral cancer drugs is becoming longer. For six oral cancer drugs authorized after 2011 the mean delay was at the time of the study (December 2013) 500 days and these medicinal products still had not been included into the drug reimbursement system. (Kanniainen et al. 2014)

The European Federation of Pharmaceutical Industries and Associations (EFPIA) has monitored the market access delays between the period 2008–2011 in its "Patients W.A.I.T. Indicator" (Patients waiting to access innovative therapies) to study the whether the access to new drugs is equal in Europe. For the 17 countries included in the indicator the rate of availability and the average time elapsed between EU marketing authorization and the completion of post-marketing authorization administrative processes (including price and reimbursement processes) has been computed. The results on behalf Finland can be seen in Figure 1. The yearly indicator includes the medicine authorized through the centralized procedure in EU from three previous years (e.g. 2008 includes medicines authorized between period 2005–2007). (EFPIA 2008; EFPIA 2009; EFPIA 2010; EFPIA 2011.)

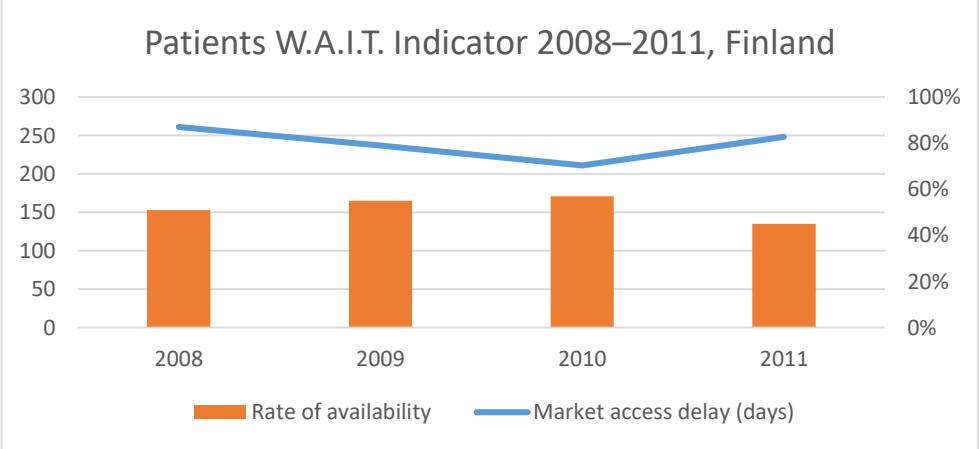

Figure 1: Market access delay of new innovative medicines in Finland

An update for EFPIA reports were made by Flostrand et al. (2014) in their study where they calculated the delay between marketing authorization and first sale date for all marketing authorized non-generic and non-biosimilar product since 2008 in 15 EU countries. The results showed that the delay in 2012 were on average 281 days and the rate of availability of regulatory approved medicines was on average 41% in 2013. However, this study is not fully comparable with the EFPIA indicator since EFPIA (2008; 2009; 2010; 2011) computed the delay as time elapsed between marketing authorization and the completion of post-marketing authorization administrative processes (same as methodology used by Wilking et al. (2009)) where as Flostrand et al. (2014) computed the delay between marketing authorization and first sale (same as methodology used by Jönsson & Wilking (2007c)).

Based on the previous literature it is evident that the market access of new medicine is measured as the delay between gaining marketing authorization and reimbursement or sale. Furthermore, the regulatory process for approving new medicine can be seen as a delay for accessing new drugs although it is necessary in order to assure that the available drugs are both safe and effective (Jönsson & Wilking 2007b). This assumption is consistent with the findings of the study by Jommi et al. (2012) where it was shown that the most important criteria to take into consideration when evaluating the market access in the time elapsed in gaining access to national market.

2 THEORETICAL BACKGROUND

2.1 Regulatory approval and National reimbursement authorization

The European Medicines Agency (EMA) is responsible for the scientific evaluation of drugs granted a marketing authorization valid throughout European Union. Since 2005 EMA has been responsible for the approval of all new cancer drugs in EU due to the mandatory centralized evaluation procedure for these medicine. (Pignatti et al. 2011.)

An important role for the regulator is to provide the first comprehensive and objective assessment of a medicine's benefits and risks. This assessment will subsequently be used by other stakeholders. An inadequate evaluations of the risks would further reflect that the data provided and was insufficient and cannot be used as a basis for informed consent. Contrary an exaggerated evaluation of the risks would be also detrimental as it would make patients to decline an objectively indicated treatment. The ultimate goal would be to form basis for an informed decision on treatment by individual patients and their physicians. Additionally, safeguards need to be set against medicinal products that would more likely be harmful than beneficial. However, the role of the regulator is shifting from ultimate decision maker to just one of the stakeholders taking part in a complex process of decision making. (Enzmann 2016.)

National agencies regulate the final access in every domestic market and national price and reimbursement decisions are critical for covering the new high-priced cancer drugs by health care systems (Russo et al. 2010; Martinalbo et al. 2016). The vast majority of health care system is funded through organizations that have very real budget constraints. In addition, considering the causal relationship between age and demand for health care services and the ageing population suggests that these budget constraints will become more or less stressed in the future. For offering good value for scarce resources medicines have to provide health gain for a price that is considered affordable. (McCabe et al. 2008.) The non-inferiority to a generally accepted comparator treatment is sufficient for gaining marketing authorization. However, the mere non-inferiority is not considered sufficient for justifying the higher cost for the comparator. For justification of a higher price payers will require solid evidence from the additional benefit offered by the treatment compared to preferably the most appropriate comparator. (Enzmann 2016.)

EMA and national reimbursement agencies have slightly different goals. For the EMA the primary concern is the quality, safety and efficacy of the medicinal product i.e. estimate of effect

under ideal circumstances. Whereas for national reimbursement agencies the main focus is on the clinical effectiveness i.e. estimate of effect in typical clinical practice and typical patient population, "the real-life effect" and cost-effectiveness in particular. (McCabe et al. 2009.) The observed survival benefits may often differ between these two approaches for a number of reasons (Howard et. al 2016). However, it should not be necessary to conduct another safety and efficacy appraisal of a new medical product in order to make reimbursement decision once the drug has already received marketing authorization by EMA. Instead the national decision should be whether the drug will or will not be reimbursed and available through national health care systems. (Jönsson & Wilking 2007.)

The different approach of these two decision makers may cause the problem that EMA marketing authorization will not guarantee the access to new drug for the reason that national reimbursement authorities may consider that the cost of new therapy is greater than the health gain received and will not grant reimbursement for the new treatment (McCabe et al. 2009). This poses a significant threat for the equal access to new cancer drugs because the market access of new cancer drugs, especially, is highly dependent on reimbursement decision due to the high price of new innovative cancer drugs and long treatments for cancer (Pauwels et. al 2014).

Canada and Australia were early pioneers to take the approach for assessing the health gain against the price of a drug. Since then reimbursement authorities increasingly recognize that the trade-off between providing a therapy for one person is that the health gain is forgone for others since the resources consumed are no longer available to provide other treatments. Therefore, the true cost of new treatment is the total net health forgone by the community to make the treatment available. (McCabe et al. 2008.) This created the challenge for balancing the interest of different patient groups competing for the limited resources (Enzmann 2016). Thus, price and reimbursement decisions are depending on the ability or willingness of health care systems to pay and the priorities of health care systems. (Martinalbo et al. 2016.) For this reason, the further implementation of market access remains national responsibility leading to heterogeneous accessibility to new cancer drugs across Europe (Pauwels et. al 2014).

Payers face certain pressures when talking about oncology treatment. First of all, the number of oncology drugs being developed and licensed is on the rise, especially targeted therapies. Second, the treatment might be life-long rather than few cycles with well-defined cost. Third, the costs are additive form budgetary perspective with the increase of combination therapies which then increases uncertainty in budgeting. Lastly, there is a need to consider what is the

most efficient and convenient service delivery environment e.g. whether the drug is in the form of intravenous administration or oral administration. (McCabe et al. 2009.)

2.2 Health technology assessments (HTAs) and economic evaluations

The common goal for both the pharmaceutical companies and regulators is to get high-quality, safe and effective drugs to patients as rapidly as possible. Therefore, reimbursement agencies must balance between the expected health gain from expedited access against the risk that future evidence will show that the treatment is not a cost-effective use of health care resources. (McCabe et al. 2009.) The decision makers need sufficient evidence base to reassure them that they are spending the scarce resources in the best possible way. This has stimulated the development and importance of Health technology assessments, HTAs. (Payne & Annemans 2013.)

The European Network for Health Technology Assessment (EUnetHTA) defines HTA as "a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value" (EUnetHTA 2016). Although this definition is generally accepted across Europe there can be seen substantial variation in the technical details used to evaluate treatments, the process of funding and producing HTAs and the intended use of these assessments (O'Donnell et al. 2009). Especially between systems that make the decision based on the drug's relative effectiveness (e.g. France) and cost-effectiveness (e.g. UK) (Martinalbo et al. 2016).

HTAs are intended for those who make decisions about health care options and for this reason HTA assessments can be expected to have strong influence on the market access of new drugs. It is important to have information about the cost-effectiveness of new drug therapies on the basis of decision making and treatment recommendations but it is also important that the requirements for economic evaluations do not delay the access to new drug therapies. (Jönsson & Wilking 2007.) If HTA is not performed in a timely manner it can create delay for the uptake of new drugs but at the same time positive HTA opinion can boost the uptake. Thus, there is a little trade-off between gaining reliable evidence and a fast access to new drugs. (Ades et al. 2014; Jönsson & Wilking 2007.)

The growing activity in publishing HTAs must be seen as a sign of growing importance of cost-effectiveness and economic evaluations for decisions regarding market access. United Kingdom has the leading role in the development of health economics in Europe and in particular the methodology of economic evaluation. (Jönsson & Wilking 2007.) With producing one third of all HTA reports concerning the health economic evaluations of cancer medicine UK is the most active country in producing HTA reports (Ades et al. 2014). Moreover, the HTA process set up by The National Institute for Health and Care Excellence (NICE) in the UK has become the gold standard for using evidence of cost-effectiveness and clinical effectiveness to form national guidelines which are subsequently used by decision makers to choose how best to spend and allocate the scarce health care resources (Payne & Annemans 2013).

The complexity of cancer as a disease complicates the assessment of drug costs and benefits within clinical trials. First of all, the prolonged course of cancer diseases slows down clinical research and results in shift from hard end points (Overall Survival, OS) to surrogate end points (e.g. Progression-Free Survival, PFS) and markers for drug response. Second, specific molecular and genetic profiling of tumor subtypes can limit the proof of evidence to a well-defined patient group. Putting this together with the vast number of cancer diseases this leads to restrictions regarding approved indications of drugs which can then lead to unauthorized drug use. Additionally, significant portion of new cancer medicine are orphan drugs which can create additional clinical and regulatory hurdles. (Pauwels et al. 2014.)

Some concerns have been raised in the use of cost-effectiveness analysis when deciding which new therapies health care systems pay for. Cost-effectiveness analysis may compromise the access to new cancer drug therapies because the robustness and transparency for some cost-effectiveness appraisals are not always obvious. The lack of standardization in threshold value creates variations between analyses (value that is used as an indicator to decide whether the treatment is cost-effective or not). Stakeholders are concerned that post regulatory agencies can take a restrictive perspective with regard to end points used to show cost-effectiveness. In case of new innovative drugs, the post regulatory agencies should take into consideration opportunity costs, morbidity and the marginal benefits to identify which drugs can truly make a difference. (McCabe et al. 2009.) There are only few countries that applies a societal perspective when considering the costs and benefits of health care in cost-effective analysis and e.g. in Sweden there is no predefined threshold values for cost-effectiveness because they are dependent on the severity of disease (Pauwels et al. 2014).

In addition, although economic evaluations and HTAs are useful in assessing the value of new medical products, the real issue is the appropriate allocation of budgetary resources. Patients will not have access to new drug therapies unless budgets are made available. In contrast only few countries require a full economic evaluation for the reimbursement decision. Appropriate funding and resources should be allocated independently regardless whether the drug is financed through the hospital budget, budget for the hospital outpatients or prescribed for self-medication and paid through drug reimbursement system. Moreover, health care systems should ensure that there is adequate funding for innovative cancer medicine included in the health care system. The total cost of therapeutic alternatives should be evaluated and compared to avoid situation where suboptimal decision is made for the reason of economic incentives through specific form of administration. (Jönsson & Wilking 2007.)

2.3 Risk Sharing Agreements

When purchasing new cancer medicine, it is the payers that takes the responsibility and carries the risk in most purchasing decisions. In a situation where new drug does not live up to its expectations it is the payers that have wasted their scarce health care resources without any compensation from the manufacturer. However, payers do have some degree of negotiation power they can exercise when purchasing new medicine. (McCabe et al. 2009.) In making the decision whether a new drug should or should not be reimbursed and should budgetary resources be allocated towards it; one important issue is the uncertainty regarding long-term consequences of the use of new drug. In addition to clinical trial data and deducing long-term consequences on the basis of the data one option to reduce the uncertainty is the concept of 'risk sharing' between the manufacturer and the payer. (Jönsson & Wilking 2007.)

Risk-sharing agreement is a form of conditional coverage between these two parties and it is typically based on a guaranteed outcome resulting from a treatment. This kind of agreements provide access to a drug while minimizing the risk of wasting health care resources. (McCabe et al. 2009; de Pouvourville 2006.) Such agreements are designed to share the costs of uncertainty about a drug's value and volume between payer and manufacturer to expedite the market access to this drug (Pauwels et al. 2014). To monitor the effectiveness and safety compared to resource spend and utilization these agreements are likely to involve some sort of financial and clinical system of measurement in order to assess the contractual performance (Rao 2015). The

effectiveness of risk-sharing agreements in reducing the risk of wasting resources is highly depended on the measurement properties of such scheme and its relationship to actual health gain (McCabe et al. 2009).

The effective evaluations about whether such agreements are effective in promoting access to new drugs or whether they are effective in enhancing the use of health care resources have been rare (McCabe et al. 2009). However, the study by Russo et al. (2010) showed that marketing authorized cancer drugs with risk sharing agreements had very fast accessibility in Italy compared to cancer drugs authorized without such agreement. Generally, risk-sharing agreement are expensive to implement and monitor. There is a possibility that they can become bureaucratic and burdensome processes and they increase the manufacturers uncertainty of future income stream. (McCabe et al. 2009.) In addition, such schemes can increase the introduction of new drugs with only limited data and further facilitate the acceptance of unjustifiably high price stetting of new cancer drugs. (Pauwels et al. 2014). For these reasons they should be regarded as an exception rather than rule and should not be regarded only as a shortcut to market access (McCabe et al. 2009). In order to maximize the benefits of risk-sharing agreements it would be helpful to create legislation or guidelines for such arrangements (Pauwels et al. 2014).

Another form of contractual agreements such as risk-sharing agreements to avoid overspending on health care budgets are payback mechanisms. For example, in 2002 Belgium launched payback mechanism in which pharmaceutical industry had to cover 65 % on the pharmaceutical budget deficit, in 2006 a provisionary fund was created by the industry to payback 100 % of the overspending and since 2008 the pharmaceutical company contributions to the fund are based on the turnover of reimbursed medicinal products. In Italy the expenditures to medicinal products in primary care cannot exceed 11,35 % of the national and regional health care budget and in the case of overspending companies have to cover the whole budget excess. (Pauwels et al. 2014.)

2.4 Expediting access to cancer drugs

Pauwels et al. (2014) studied the market access of cancer drugs in eight European countries and came to the conclusion that when all possibilities for the coverage of cancer drugs are used additional measures are usually taken in order to ensure the access to treatment for patients. In Italy reimbursement can be gained and the cost will be covered by national health system in the absence of therapeutic alternative when the drug is not yet authorized or the drug is marketed

for another therapeutic indication. This arrangement requires data collection to inform HTA (Martinalbo et al. 2016) Besides this, a fund called “Fondo “AIFA 5%” has been established by contributions of the pharmaceutical industry to promote research and access to treatment for rare diseases (Pauwels et al. 2014). In Germany AMHV (Arzneimittel- Härtefall-Verordnung) scheme allows the distribution of drugs without authorization on the base case-by-case reimbursement negotiations (Martinalbo et al. 2016).

In France the ATU (Authorisation Temporaire d'Utilisation) scheme allows temporary use and coverage of innovative drugs without marketing authorization under following conditions: no alternative treatment options, positive benefit-risk ratio, severe disease and public need for drugs (Pauwels et al. 2014). This also requires the evidence generation to later inform HTA. On average the ATU scheme has provided effective access to drugs one year before centralized authorization (Martinalbo et al. 2016). Additionally, “Temporary Recommendations for Use” can be requested by the pharmaceutical company to allow off-label use in cases of serious or rare medical conditions when there is no treatment alternative and a positive benefit-risk ratio can be established. The cost of this off-label use will be covered by pharmaceutical company. (Pauwels et al. 2014.)

The United Kingdom has launched Early Access to Medicines Scheme which gives access to unauthorized medicines for patients with life-threatening or seriously debilitating diseases and a high medical unmet need. The scheme was launched on the basis of public consultation from the Medicines and Health Care Products Regulatory Agency (MHRA). The same agency also gives the scientific opinion on the positive benefit-risk ratio that will be required on the treatments included into the scheme. (Martinalbo et al. 2016; Pauwels et al. 2014.) In 2010 the Department of Health in England established the Cancer Drug Fund for the purpose of providing access to cancer drugs not yet appraised or refused by the NICE. £200 million is made available for the fund annually to ensure that the new cancer treatments can be covered. (Pauwels et al. 2014.)

2.5 Pharmaceutical industry

Gaining marketing authorization is no longer considered as the ultimate goal for pharmaceutical companies in their process for developing new drugs (Enzmann 2016). Taking this into account and considering the finding that after gaining marketing authorization reimbursement authorities may consider that the cost of the drug is greater than the health gain produced has created

uncertainty for pharmaceutical companies planning their research and development (McCabe et al. 2008).

Economic success is dependent additionally on other stakeholders and the return on the large investments made in this area is not necessarily provided (Enzmann 2016; McCabe et al. 2008). Thus, the differences in these requirements by separate bodies have complicated pharmaceutical development (Enzmann 2016). Adding to this is the concern of researchers that the public may not be able to benefit from the rapid expansion of medical knowledge (McCabe et al. 2008; Rawlins 2004). However, the complex situation with centralized marketing authorization on one end and many national price and reimbursement decisions on the other end will not be resolved in the foreseeable future (Enzmann 2016).

In addition, market access of a new drug in a certain country can be a contingent on the market access strategies of pharmaceutical companies in several European countries or their ability to manage the regulatory workload (Russo et al. 2010). McGrath (2010) states in his paper that a pharmaceutical company should implement a market access strategy at least 18 months before launch in order to avoid the failure to reach markets in a timely manner. Failing to do so would create financial loss and more importantly would cause the patients to wait for the access to a new drug. After gaining marketing authorization in EU companies will have to further tailor drug applications according to the individual requirements of each EU member states. This can possibly create frustration in the companies as the objective measures such as efficiency and side effects might not be treated the same way across these member states. (Pauwels et al. 2016.)

The decision for delaying a drugs launch in a specific country can be influenced by the potential global profits (Russo et al. 2010). Considering this, the factors that can affect the decision for delaying drug launch are external price benchmarking by national agencies, parallel trade and the market size of a country (Richter 2008). Pharmaceutical companies may be subject for delaying the launch of new drug in a country with lower drug prices in order avoid the use of these countries as an external price benchmark in other countries (Russo et al. 2010).

Pauwels et al. (2016) studied the pharmaceutical industry perspectives on the market access of innovative drugs and oncology drugs in particular and found out that the industry calls for a broader recognition of value within the assessment of innovative drugs. However, the absence of common value definition across EU and the poor availability and validity of value measures is threating the value based pricing. A well-considered value-framework with attention for patient reported outcomes, societal preferences and dynamic approach on the drugs life cycle

needs to be integrated in assessment and appraisal processes in both the national and the European level in order to coordinate the views of different stakeholders and allow efficient resource allocation. Particularly in expanding areas that face expensive drug therapies such as oncology value is a key determinant. (Pauwels et al. 2016.)

2.6 Price of new cancer drugs

There is ongoing active debate over the value of new cancer drugs and critics of the pharmaceutical industry usually conclude that the prices of new cancer drugs are excessive. Often the opinion leaders of oncology have focused on the price as the main indicator of the costs. (Howard et al. 2016.) Generally pricing of pharmaceuticals considers three factors: production costs, reimbursement level and restrictions on prescriptions (Ades et al. 2014). The complex pricing system of pharmaceuticals comes from the substantial expense associated with the research and development (R&D) of new pharmaceuticals. The significant investment in drug development is considered as a sunk cost at the time marketing authorization is applied, new drug is launched and prices are negotiated. This is in a strong contrast with the relatively low cost for producing additional units after the R&D process has been completed and market access has been gained. (Jönsson & Wilking 2007.)

For cancer drugs the clinical development times tend to be longer than for other drugs. Furthermore, the failure rate of cancer drugs after entering Phase III trials (the last trial phase before marketing authorization) is higher than the failure rate of other drugs reaching this point in development. If all other factors would be equal this alone would imply higher average development costs for cancer drugs. (DiMasi & Grabowski 2007.) It is important to take into account that the prices of the drugs that will reach the market and will be granted marketing authorization also include the R&D costs of the drugs that will fail to reach the market (Ades et al. 2014). This is a way for allowing the industry to amortize the cost of failed therapies through the price of successful treatments (McCabe et al. 2008).

One mean to provide incentives for the research and development of new drug therapies is patent protection which provides a monopoly-like position on the market for a certain time period after launching the new drug allowing the company to recompense the R&D costs before allowing competitors to access the market with generic copy or biosimilar of a drug. Usually competitors entering the market after the patent protection has expired prices their medicine much lower than the original medicinal product thereby lowering drug costs. In relation to this

the prices of many high-priced cancer drugs introduced lately can be expected to reduce considerably as their patents expire. (Jönsson & Wilking 2007.)

Innovative pharmaceuticals including oncology drugs are often exempt from the consequences of budget overspending (Pauwels et. al 2014). An Important notion is that the price of a drug does not necessarily correlate with the health benefit it offers (Ades et al. 2014). Therefore, it remains a burning question how the value of drugs can be measured. Overall, pharmaceutical companies can maintain even unjustifiably high prices for innovative (including cancer) drugs while public health systems are unable to bear them and eventually patients in all disease areas become influenced. In order to obtain a sustainable health care system, the price in terms of the therapeutic value and societal benefit needs to be assessed appropriately. (Pauwels et. al 2014.)

However, in their study Howard et al. (2016) assessed the value of new cancer treatments for patients with metastatic breast, lung or kidney tumors or systematic chronic myeloid leukemia in the period of 1996-2011. They estimated and compared changes in lifetime medical costs and life expectancy. They found out that the increases in the costs of treating patients were accompanied by meaningful improvements in patients' survival. Since they included only patients with metastatic disease most of the increases in survival were likely to be from the benefit of new cancer drugs rather than biased by the fact that nowadays patients are more likely to be diagnosed earlier in the progression of their disease than in the past. This outcome highlights the fact that it is important to consider the overall costs and outcomes in a routine practice to get an accurate measure of the value. (Howard et al. 2016.)

Looking at the total expenditure on cancer in European Union between 1995–2014 the inflation corrected expenditure has risen from 50,5 billion € in 1995 to 83,2 billion € in 2014 which equals the increase of 65 % in the expenditure on cancer. At the same time newly diagnosed cancer cases have increased by 30 % between 1995–2012. Other factors explaining the increasing expenditure are the roll out of mass screening programs, new and more expensive medical equipment for diagnostic and treatment and new cancer therapies that comes with a high price and allows a bigger share of the patients to be treated. Although these can effect on the expenditure in both decreasing and increasing way. The sales of cancer drugs in EU increased from 9,2 billion € in 2005 (2014 prices) to 19,1 billion € in 2014 and cancer drugs accounts for growing share on the total expenditure for cancer in the EU (12 % in 2005 vs. 23 % in 2014). During that time the production loss due to premature mortality caused by cancer has decreased 11 % equaling 40 % of the increase in cancer drug expenditure. (Jönsson et al 2016.)

Despite the absolute increase in the expenditure the cancer-specific share of the total health care expenditure remained almost the same being 5,9 per cent in 1995 and 6,1 per cent in 2014 which implies the increase of total health expenditure in the EU. In Finland the cancer-specific share on total health expenditure has remained the same between 1995 and 2014 (4,4 per cent). (Jönsson et al 2016.) However, defining value and linking this value to an acceptable price level for all stakeholders including reasonable budgetary impact toward health care systems and reasonable profitability for the manufacturer remains problematic (Pauwels. et al 2016).

2.7 Patients perspective

Previous studies show that patients want to know about all possible treatment options regardless whether they can afford it or not (Mileshkin et al. 2009; Kaser et al. 2010). Paternalistic behaviors such as withholding information or making assumptions about patients' treatment options are viewed negatively among patients. Withholding information about all treatment options denies the patients ability to exercise control over their own health which can further cause distress among patients. Evidence has shown that patients want to be active participants in their treatment decision making. (Kaser et al. 2010.)

Patients' usual resource for the information regarding treatment are oncologist. Besides this, patients use internet as an additional resource for information. The information shared by oncologist and the openness and honesty of the oncologist is seen as key element in developing trust between patient and physician. (Kaser et al. 2010.) This is important since patient trust has been identified as central factor in the process constructing shared decision making between patient and physician (Shepherd et al. 2008). If not informed about all treatment options the foundation of patient-physician relationship can be undermined later on during the course of cancer treatment (Kaser et al. 2010).

The demand for drugs treating life-threatening diseases such as cancer is found to high regardless of the costs (Kaser et al. 2010; Goldman et al. 2010). Patients' willingness to pay for treatment option can be affected on individual's diagnosis, values and social circumstances. (Kaser et al. 2010). Treatments that increase life-expectancy at a late stage of life are viewed very differently than treatments that lower mortality risks throughout an individual's life (Becker et al. 2007). Patient that feel they are at lower risk are less eager to pay for costly treatment contrary to e.g. patients diagnosed with secondary disease (Kaser et al. 2010). Patients diagnosed with terminal cancer may be willing to spend their entire fortune to prolong their life even for

few weeks (Becker et al. 2007). Individuals facing imminent death places a much higher value for life-extending treatments than individuals for whom the ending of life is a remote risk (Goldman et al. 2010).

When evaluating treatment options patients place high importance on the efficacy of the treatment. Prolonged survival is regarded as important consideration and patients are willing to opt for treatment with high cost if the treatment would prolong their life expectancy or represent a cure. Patients with secondary diagnose places also more emphasis on the side-effects of the treatments than newly diagnosed patients. (Kaser et al. 2010.)

However, despite the general willingness to gain knowledge there have been lack of understanding about the drug approval process. Some patients feel that it is unfair that some treatments for life-threatening disease such as cancer are not reimbursed and therefore not accessible to all patients. There is a strong view among patients that finances should not be barrier to access for treatments although it is understood that there are some inevitable trade-offs concerning the availability of high cost drugs. (Kaser et al. 2010.) From the patients' perspective it is desired that the decision making process regarding the funding and availability of treatments is fair, equal and developed in conjunction with public and patient input. Initiating media campaigns is seen as tool to make an influence if there is no opportunity for patients to participate in this process. (Rosenberg-Yunger et al. 2012.)

2.8 Theoretical framework

The theoretical framework of this thesis is illustrated in Figure 2. The theoretical approach of this study is to explore the importance and role of the two major barriers before new oral cancer drugs are accessible in the markets while examining the role of the other factors influencing the market access in Finnish context. As a result, the current market access delay of these drugs is computed and patient and patient organization perspective towards market access of oral cancer drugs is examined. Additionally, a short synthesis from the previous literature is presented in this subchapter.

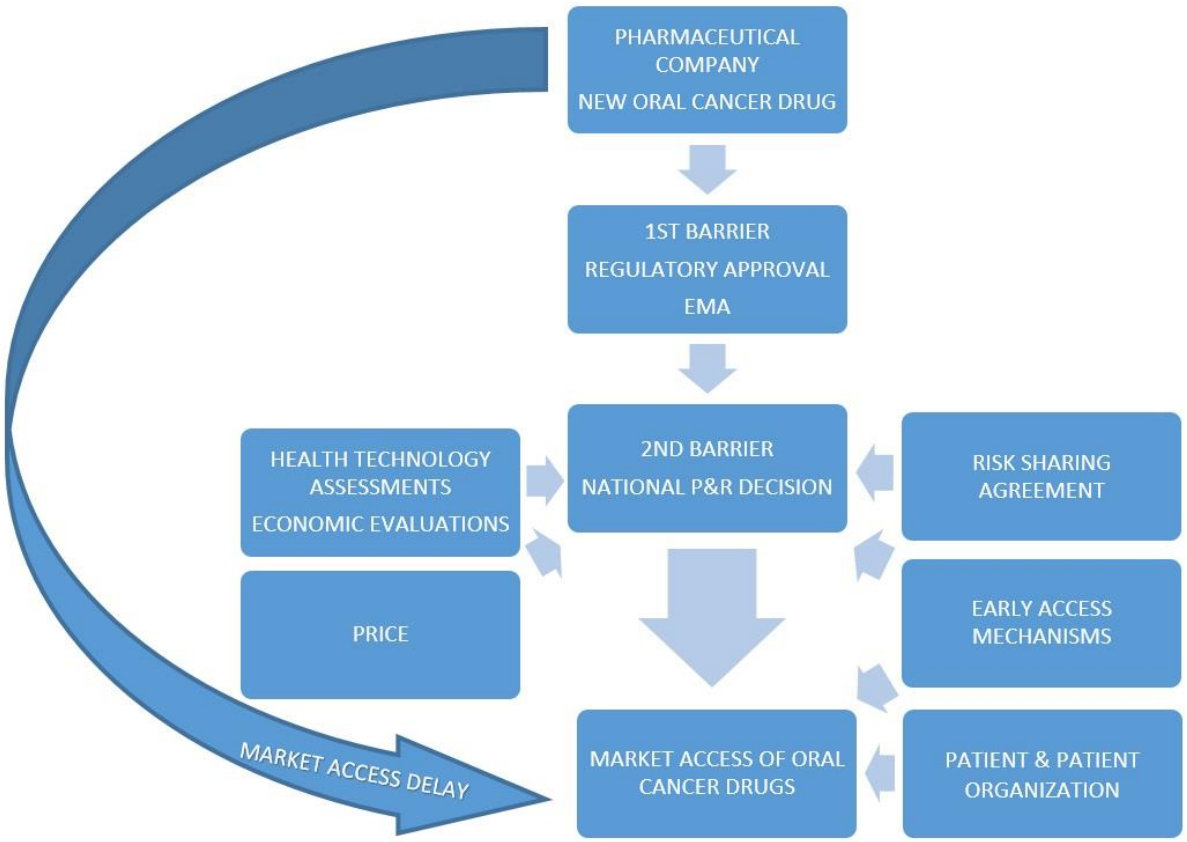

Figure 2: Theoretical framework.

The previous literature shows that the discussion around the market access of cancer medicine focuses on overcoming the two barriers (McCabe et al. 2008) which are identified as the regulatory approver i.e. in Europe the European Medicines Agency (EMA) (Pignatti et al. 2011) and the post-regulatory agencies i.e. national price and reimbursement decision makers (Martinalbo et al. 2016; Pauwels at al 2014; McCabe et al. 2009; Russo et al. 2010; Jönsson & Wilking 2007). In the process of granting marketing authorization EMA focuses on the quality, safety and efficacy of the new medicine excluding economic aspects (McCabe et al. 2009) and the role of the regulator is shifting from the ultimate decision maker toward one of the many stakeholder taking a part in a process of decision making (Enzmann 2016).

Whereas the primary focus for national P&R decision makers is on the estimate of effect in typical clinical practice and typical patient population, "the real-life effect" and cost-effectiveness in particular (McCabe et al. 2009). Thus, after gaining marketing authorization reimbursement authorities may consider that the cost of the drug is greater than the health gain produced (McCabe et al. 2008). Therefore, the final implementation of market access for cancer drugs rests on a national responsibility (Martinalbo et al. 2016; Pauwels at al 2014; McCabe et al.

2009) because the market access of new cancer drugs, especially, is highly dependent on reimbursement decision due to the high price of new innovative cancer drugs and long treatments for cancer (Pauwels et. al 2014).

The price of new cancer drugs is object for an ongoing debate (Howard et al. 2016). Pauwels et al. (2014) stated that pharmaceutical companies can maintain even unjustifiably high prices for innovative (including cancer) drugs while public health systems are unable to bear them and eventually patients in all disease areas become influenced. However, Howard et al. (2016) found out that the increases in the costs of treating patients were accompanied by meaningful improvements in patients' survival. Additionally, the pharmaceutical industry desires for a broader recognition of value within the assessment of innovative drugs (Pauwels et al. 2016).

For justification of a higher price payers will require solid evidence from the additional benefit offered by the treatment compared to preferably the most appropriate comparator (Enzmann 2016). This has stimulated the development and importance of Health technology assessments, HTAs (Payne & Annemans 2013). The growing activity in publishing HTAs must be seen as a sign of growing importance of cost-effectiveness and economic evaluations for decisions regarding market access (Jönsson & Wilking 2007). However, there can be seen substantial variation in the technical details used to evaluate treatments, the process of funding and producing HTAs and the intended use of these assessments (O'Donnell et al. 2009).

In a purchasing decision for new cancer medicine, it is often the payers that takes the responsibility and carries the risk (McCabe et al. 2009). An option to reduce the uncertainty in the purchase decision is the concept of 'risk sharing' between the manufacturer and the payer (Jönsson & Wilking 2007). Risk sharing agreements are designed to share the costs of uncertainty about a drug's value and volume between payer and manufacturer to expedite the market access (Pauwels et al. 2014). In addition to the risk sharing agreements also other mechanisms exists to expedite the access for new medicines such as the Cancer Drug Fund in the UK and ATU scheme in France (Martinalbo et al. 2016; Pauwels et al. 2014).

Patients' perspective in decision making is regarded highly important and the paternalistic approach that experts know the best patients' interests has outlived its purpose (Enzmann 2016). Based on the previous research patients are willing to know about all treatment options for their cancer disease including treatments that would be financially unreachable for them (Mileshkin et al. 2009; Kaser et al. 2010). The demand for drugs treating life-threatening diseases such as cancer is found to high regardless of the costs and patients' willingness to pay for treatment

option can be affected on individual's diagnosis, values and social circumstances (Kaser et al. 2010; Goldman et al. 2010). Patients often gain the information from treatment options from their oncologist. This information shared by the oncologist has an important role in building the trust in doctor-patient relationship. Thus it is important that all available information is shared between the physician and patient. (Shepherd et al. 2008; Kaser et al. 2010.) Despite the general desire for knowledge there have been lack of understanding about the drug approval process among cancer patients and some patients feel that it is unfair that some treatments are not reimbursed and therefore not available to all patients (Kaser et al. 2010).

3 METHODOLOGY

3.1 Methodological approach

As mentioned the research aim of this thesis is two-folded. Thus, the research questions Q1 & Q2 require a different methodological approach while sharing some same elements in the use of interview as part of empirical data collection. For achieving a holistic view about the phenomenon under study here I believe it is important to answer the Q1 in order to find out how oral cancer drugs really gain market access complemented with the answer for Q2 how this is perceived among the end users i.e. patients. The approaches used in this study are discussed in the following sections starting from the methodology used in answering research question Q1 and continuing with the methodology used in answering research question Q2.

3.1.1 Methodological approach for research question Q1

The answer for Q1: "How will new oral cancer drugs gain market access in Finland and how long is the duration of process for gaining market access?" the path of new oral cancer drugs from pharmaceutical company to market access was explored by examining written material online i.e. naturally occurring materials which exists irrespective of the researcher's actions and intentions (Silverman 2011). This decision to choose this approach was based on the transparency assumption that texts are considered to represent directly what is being studied i.e. we believe in their ability tell us about the issues that they represent (Eriksson & Kovalainen 2016).

This is even increasingly correct with the written materials about the market access of drugs in Finnish setting since the operations of the regulatory approver and national P&R decision maker is based on regulations and legislation. Additionally, Eriksson & Kovalainen (2016) notes that existing written materials provides excellent opportunities for research and regulations and laws provide increasingly relevant research data.

An interview is performed with the director of the national P&R decision maker of Finland to gain more in-depth understanding from the processes regarding the decision making for the price and reimbursement of new drugs in Finnish context.

I will study the time to market i.e. market access delay of oral cancer medicine in Finland according to method used in previous research by Russo et al. (2010) who studied the time to patient access in Italy. Here market access delay is defined as the time elapsed between the completion of research and development (R&D) and positive price and reimbursement (P&R)

decision. According to Russo et al. (2010) and as defined by OECD (2016) R&D comprises set of activities: basic research, applied research and experimental research. For this reason, the date that the manufacturer submits the dossier for marketing authorization application (MAA) to EMA can be considered as the last step for R&D and the first step towards market or patient access. Although the regulatory process for approving new medicine is necessary in order to assure that the available drugs are both safe and effective it can be seen as a delay for accessing new drugs (Jönsson & Wilking 2007b). In addition, the time interval between applying and granting the marketing authorization has been traditionally seen as the first barrier for accessing new medicines (Jönsson & Wilking 2007).

Unlike Russo et al. (2010) I will study the time elapsed to market access and not to patient access which would further require including the sequential time phase starting from the P&R decision date and ending to date when the drug in purchased for the first time. I will concentrate on the delay between the completion of R&D and the date when the drug is available for patients to use i.e. accessible in the market. This date is defined as the date when the drug is included into the reimbursement system because market access of new cancer drugs, especially, is dependent on the reimbursement decision and effective market access of a drug requires including the drug into the reimbursement system (Pauwels et al. 2014; Martikainen 2012; Martinaldo et al. 2016). The extensive uptake of a new high priced drug is practically impossible without reimbursement and for this reason the drug reimbursement system has a significant effect on the prescribing policy of drugs (Merikoski & Enlund 2016; Martikainen 2012). By doing this the results of this thesis will show how long it takes for new oral cancer medicine to reach the market access in Finland after its R&D completion.

Therefore, the delay is defined here as the difference between the date when the manufacturer of a drug submits MAA to EMA and the date a drug receives positive P&R decision and is included into the drug reimbursement system in Finland. Furthermore, the P&R decision date is the date when the drug is included in the reimbursement system because the time between actual decision date and the date when the reimbursement is rather standard and regulated by the law. The P&R decision will be in force at the beginning of the second month following the decision date unless otherwise is stated in the decision. (Health Insurance Act (1224/2004).)

The market access delay time span will be divided into three sequential phases adapting the sequential phases used by Russo et al. (2010):

1. European Medicines Agency (EMA) time: interval computed as the difference between the date EMA receives the application for marketing authorization and the date marketing authorization will be granted.
2. Pharmaceutical company time: interval computed as the difference between the date marketing authorization is gained and the date pharmaceutical company submits the application for P&R decision to Pharmaceutical Pricing Board (PPB)
3. Pharmaceutical Pricing Board (PPB) time: interval computed as the difference between the date PPB receives the first application for P&R decision and the date P&R decision is made and the drug is included into the drug reimbursement system.

These phases together are also defined as the overall time.

3.1.2 Methodological approach for research question Q2

The primary stress of this thesis on answering to the research question Q2: "How cancer patients and patient organization views the market access of new oral cancer drugs in Finland?". For answering this question, a qualitative phenomenography research approach was chosen. This decision was based on a previous research by Kaser et al. (2010) where this approach was utilized in order to determine breast cancer patients experiences and attitudes towards high-cost drugs.

Furthermore, the definition for this approach by Marton (1981) highlights its appropriateness for studying the patient and patient organization view for the market access of oral cancer medicine in Finland: "It is research which aims at description, analysis, and understanding of experiences; that is, research which is directed towards experiential description." The ultimate goal for this approach is to "describe the qualitatively different ways a group of people make sense of, experience, and understand phenomena in the world around them" as stated by Barnad et al (1999).

The main purpose to use this approach is the same as the main purpose of phenomenography: to describes the variety of experiences regarding the phenomenon under study (Sjöström & Dahlgren 2002). In addition, phenomenography takes on a secondary perspective to study a phenomenon in answering to the question: "How a thing is perceived?" contrary to the first-

order perspective which answers to the question: “What a thing really is?” (Assarroudi & Heydari 2016; Sjöström & Dahlgren 2002; Marton 1981).

The most well-known classification of what procedural steps have to made for conducting phenomenography research is applied in this study. These steps include the following: defining the subject as well as restricting it, selecting participants and interviewing them, transcribing the interviews, analyzing the interviews and placing the analysis results in categories of description. (Assarroudi & Heydari 2016; Kaapu et al. 2006; Järvinen 1997).

3.2 Data collection

The data collection to answer Q1 was performed in the official websites of the stakeholders taking a part in the market access of oral cancer medicines to ensure the validity of the data collected. Additionally, Regulation (EC) No 726/2004 and Health Insurance Act (1224/2004) was examined since these form the regulative basis for the process of granting marketing authorization and making the P&R decision. To get more in-depth understanding form the processes of the European Medicines Agency academic literature was also explored to find studies evaluating the operation.

A semi-structured interview was performed with the director of the national P&R decision maker of Finland. The main purpose of this interview was to examine the process for achieving the P&R decision more in-depth than it is explained in the Health Insurance Act (1224/2004) that regulates this decision making. The predetermined entry questions used in this interview were based on relevant statements from previous literature. The predetermined entry questions for this interview and the statements they are based on can be seen in Appendix 1

The data for computing the EMA time was acquired from the European public assessment reports (EPARs) published by EMA online (EMA 2016d). The data for the dates when pharmaceutical companies have submitted the first P&R application and the date when medicinal products under study were included into the Finnish reimbursement system was requested and received from the Pharmaceutical Pricing Board (PPB) and used for computing the pharmaceutical company time and PPB time.

This thesis concentrates to study the market access of oral cancer drugs. The two main selection criteria were that the drugs have received marketing authorization after the centralized evaluation procedure became mandatory for oncology medicine in 2005 in the EU and that the drug

is included in the Finnish drug reimbursement system at time of this thesis. These limitations were made because this allows to compute the time elapsed between the date of the application of market authorization and the date that the drug is included into the drug reimbursement system.

In addition, only oral cancer medicine is included into the study because intravenously administered cancer medicines are only administered in hospital settings and the uptake of these medicines doesn't require a separate P&R decision from the Pharmaceutical Pricing Board PPB in order for hospitals to include them into clinical practice after market authorization has been gained from EMA. The price of the medicines administered in hospital settings are included into the daily hospital fee and the decisions for including a medicine into clinical practice are made within the hospital organizations (Merikoski & Enlund 2016). According to these limitations there are 22 cancer drugs that are included in this study. The selected drugs and the date that they have been included into the Finnish drug reimbursement system is shown in Table 1.

Table 1: List of the cancer drugs included in this study.

Product	Active substance	Date of approval into the Finnish drug reimbursement system
Erivedge	Vismodegib	1 April 2016
Zydelig	Idelalisib	1 October 2015
Iclusig	Ponatinib	1 October2015
Stivarga	Regorafenib	1 March 2015
Zelboraf	Vemurafenib	1 November 2014
Xalkori	Crizotinib	1 August 2014
Tafinlar	Dabrafenib	1 August 2014
Gilotrif	Afatinib	1 June 2014
Xtandi	Enzalutamide	1 April 2014
Inlyta	Axitinib	1 February 2014
Bosulif	Bosutinib	1 December 2013
Zytiga	Abiraterone	1 September 2012
Votrient	Pazopanib	1 January 2011
Iressa	Gefitinib	1 November 2010
Afinitor	Everolimus	1 June 2010
Tyverb	Lapatinib	1 March 2009
Revlimid	Lenalidomide	1 November 2008
Tasigna	Nilotinib	1 September 2008
Sprycel	Dasatinib	1 November 2007
Nexavar	Sorafenib	1 June 2007
Sutent	Sunitinib	1 May 2007
Tarceva	Erlotinib	1 March 2006

3.2.1 Semi-structured interviews

Interviews was chosen as a mean for data collection because they are recognized to be an efficient and practical way of collecting information that cannot be found in a published form (Eriksson & Kovalainen 2008). As with the methodology of phenomenography research that is the data collection is often based on a particular group of people and their relation to a phenomenon in a designated context (Barnard et al 1999). I defined the group of people to be cancer patients that are likely to be in a situation that they cannot receive a novel oral cancer treatment for their condition due to market access delay. Besides these participants, patient organization personnel were added to the group of interest since at the beginning of this study it was not clear whether cancer patients in Finland acknowledge the existence of market access delay. Furthermore, patient organization as an interest group for patients should have information if patients in Finland had experienced situation related to market access delay through their consultation service and extensive network of regional and cancer indication specific patient groups.

The patient participants for the interviews were reached through the patient organization. An email about the interview was written on the behalf of the researcher and then sent to the patients belonging to the different patient groups of the patient organization on the behalf of patient organization personnel. The email shortly presented the topic and aim of this thesis and requested the people interested and belonging to the group of interest to take part in the interview to contact the researcher by email for further information. A total of six contacts was received. Four out of these six patients took part in the final interviews. The interviews were held through telephone to overcome the hurdle of geographical distances to participate in the interview. Another advantage of this was to allow the participants to take part in the research in a familiar environment (Eriksson & Kovalainen 2016).

A form of snowball effect was used to identify the personnel from the patient organization with close contacts to patients. An email was sent to the head of the organization explaining the topic and aim of the thesis requesting possible interviews with personnel that might be familiar with the topic and would be in close contact with patients. A total of three employees of the organization was identified this way to participate in this research. All the participants are shown in Table 2.

Table 2: Empirical interview data.

Participant	Duration
Patients	
Interview 1	c.a. 30 min
Interview 2	c.a. 30 min
Interview 3	c.a. 30 min
Interview 4	c.a. 30 min
Patient organization personnel	
Interview 5	c.a. 1 hour
Interview 6	c.a. 1 hour
Interview 7	c.a. 1 hour
Director of PPB	
Interview 8	c.a. 1 hour

Semi-structured interviews were chosen as it is common for phenomenographic approach (Barnard et al 1999; Assarroudi & Heydari 2016; Simoila 1993). The aim of the interviews was to collect information about the phenomenon as experienced by the interviewees. Using semi-structured interviews allowed to construct a liberal interview structure (Barnard et al. 1999) and gave the possibility to vary the wording and the order of questions in each interview (Eriksson & Kovalainen 2008). This allowed the participants to focus on the subjects that they experienced as the most meaningful matters under the predetermined entry questions for the interviews. When applicable interviewees were invited to further explain their understanding.

The predetermined entry questions for the interview was formed according to relevant statements found in previous literature. The entry questions and the statements they are based on are shown in Appendix 2. The questions are based on previous literature since it assures a better design of the main questions and understanding about previous conceptions (Assarroudi & Heydari 2016; Järvinen 1997).

The predetermined questions for the personnel of the patient organization was based to the entry questions of the patients. In these interviews the participants were asked that what kind of information have they received form patients contacting the organization. Besides this, the interviewees were asked what kind of attitude the organization has towards the subjects under discussion. This allowed to also gain the organizations perspective to the phenomenon under study. All the interviews conducted for this study were recorded.

The phenomenon under study can be considered sensitive because the questions issued to the patients considered information about their medical condition. Although some topic can be considered sensitive it is not a barrier for conducting the research itself (Kuula 2011). The avoidance of research concerning sensitive and conflicting topic is not always even responsible as stated by Sieber and Stanley (1988). However, additional attention was given to the participants' anonymity and informing participants about the aim and intention of the interviews. These issues to be taken into account was examined from a research ethics publication by Kuula (2011) and were explained before conducting the interviews in an email that was sent to the participants. The email can be seen in Appendix 3.

3.3 Analysis of the data

All relevant data concerning the Q1 and phenomenon under study was captured from the official websites of the stakeholders and from the regulations. The data was read through carefully together with the data from the interview with the director of PPB in order to capture a holistic view about the phenomena. After reading the data multiple times the most important aspects began to stand out. Next the path of oral cancer medicines to market access in Finland began to from and a caption of this process was written. The time elapsed in the market access and other calculations related to it was computed using Microsoft Excel 2016.

There is no single procedure specified for undertaking phenomenographic analysis (Barnard et al. 1999). The analysis of the empirical material is a phase of reading and re-reading the transcripts of the interviews before ending up with categories and excerpts that communicate the most meaningful information (Sjlsöström & Dahlgren 2002). However, in this thesis I utilized the steps defined by Dahlgren and Fallsberg (1991) who listed seven steps that can discerned in analyzing the collected empirical data in phenomenography studies:

1. Familiarization
2. Compilation
3. Condensation
4. Preliminary grouping or classification of similar answers
5. Preliminary comparison of categories
6. Naming the categories to emphasize their essence
7. Contrastive comparison of categories

The first step is to familiarize with the empirical material collected for the study. This means reading through the transcripts of the interview recordings. This step is also used to correct errors in the transcripts. The next step is to compile answer from all participants to a certain question. The aim of this step is to identify the most significant elements in the responders answers. Condensation is the third step which means finding the central parts form the longer answers or dialogue. The fourth step of the analysis is the preliminary grouping of classification of similar answers. After this step the preliminary comparison of categories is made to establish borders between the categories and can sometimes include revision of the preliminary groups. In the sixth the categories will be named to emphasize their essence. The last step of the analysis is the contrastive comparison of categories where the description of the unique character of each category and the description of the resemblances between categories is made. (Dahlgren & Fallsberg 1991; Sjöstrom & Fallsberg 2002.)

According to definition this the analysis was started by transcribing the recorded interviews. Then the data was read through multiple times to identify the most significant elements embedded in the responders' answers. After which the longer answers were shorten to bring up the central parts of the answers. Next the preliminary classification of these answers were made and compared. This step was rather iterative process going back and forth with the empirical data to ensure that the most significant elements of these interviews were identified and that the classification was made with the utmost precision. After the categories were defined they were named under descriptive concepts. In the next step the categories were shortly descripted and the results of the analysis were presented so that they would reflect the experiences of the participants as closely as possible. To retain the participants' descriptive language in the results relevant statements from the interviews were chosen to be quoted for representing the meanings connected to the phenomena.

4 RESULTS

4.1 Market access of oral cancer medicines in Finland

4.1.1 Regulatory approval and marketing authorization

All drugs in the European Union must be authorized before they can be marketed and made available for EU citizens. This is to ensure the high quality, safety and efficacy of the medicine available in EU. There are two different paths for the authorization of a new medicine: centralized authorization procedure and national authorization procedure. The national authorization procedure comprises mutual-recognition procedure; where medicine that has authorization in one EU country can apply for this authorization to be recognized in other EU member states, decentralized procedure; where manufacturer can apply new medicine that has not been authorized yet to be authorized simultaneously in many EU countries and procedure where new medicine is authorized in one EU country according to its national authorization procedures. (EMA 2016a; EMA 2014.)

The centralized authorization procedure is compulsory for new cancer medicine as well as for most innovative medicine and that is why this thesis concentrates only on this authorization procedure. According to the centralized authorization procedure manufacturer of a new medicine submits a single marketing authorization application to European Medicines Agency, EMA. EMA's Committee for Medicinal products for Human Use (CHMP) is responsible for carrying out the scientific assessment of the application. CHMP then gives the recommendation on whether the medicine should or should not be granted marketing authorization. Once European Commission has granted the centralized marketing authorization it is valid in all EU countries and European Economic Area (EEA) countries Iceland, Liechtenstein and Norway. This procedure allows the manufacturer to make the new drug available and market it in these countries on the basis of only one marketing authorization. (EMA 2016a; EMA 2014.)

EMA opinions are built on balancing the benefits of a drug against its risks. CHMP can recommend the authorization of new medicines which benefits outweighs its risks i.e. the desired medical effects are greater than the undesired effects. (EMA 2016b.) This has been often criticized for slowing down the access to new therapeutic options for cancer patients with high unmet need but the regulators have shown greater flexibility in approval of cancer drugs than

in other therapeutic area. This approval process must therefore resolve the challenge of expediting access to new promising drugs while guaranteeing their safety and efficacy and as far as possible meet the evidence requirements (Martinalbo et al. 2016).

The time limit for CHMP evaluation procedure is 210 days after receipt of valid application. However, on the basis of duly reasoned request the duration of this scientific data analysis can be extended (Regulation (EC) No 726/2004). This evaluation procedure includes two clock stop times which the applicant uses to answer questions raised by CHMP in their assessment process. At day 120 after starting the evaluation CHMP will sent the applicant List of Questions which should be responded within three months and extensions beyond six months is not normally accepted. After receiving the applicants answer the clock starts at day 121. If needed, List of Outstanding issues will be released at day 180 to the applicant and the respond should be given within a month. In exceptional circumstances additional extension time of one month can be granted to applicant. After receiving the applicants answer the clock starts at day 181. Additional clock stops can be grated if there is issues of inspection or need for additional expert input. (EMA 2009.) After CHMP has reached its opinion it will be forwarded to European Commission. The Commission will assess the compliance of marketing authorization application to European laws. The time span of this phase is 67 days. (European Commission 2016; Regulation (EC) No 726/2004.)

The time CHMP uses to evaluate the marketing authorization application is defined as active time. The term scientific time is used when the clock stop times that the applicant uses to answer the questions raised by the CHMP is added together with the active time. The European Commission's decision making phase is defined as administrative time. These times combined is defined as the total assessment time. (Ades et al. 2014.)

In addition to the regular centralized marketing authorization procedure EMA offers regulatory mechanisms to support the early access of promising new medicine: compassionate use opinion, accelerated assessment, conditional marketing authorization and. In order to optimize the use of these tools EMA has launched PRIME scheme. First of all, compassionate use opinion by CHMP allows the use of unauthorized medicine for patients with high unmet medical need. (EMA 2016c.) However, cancer drugs lack the examples in the use of compassionate use opinion by CHMP (Martinalbo et al. 2016).

Secondly, accelerated assessment reduces the timeframe for CHMP assessment from 210 days to 150 days and is applicable for medicinal products of major public health interest and therapeutic innovation (EMA 2016c). In the period 2006-2014 23 cancer drugs was requested accelerated assessment. Twelve of these application was not accepted on the base of uncertain clinical relevance and several were turned back to regular timeframe. (Martinalbo et al. 2016.)

Thirdly, conditional marketing authorization can be granted on the basis of less comprehensive data than regular marketing authorization. It can be applied by medicine for life-threatening or seriously disabling diseases, orphan disease with high unmet medical need or public health emergencies. The benefit-risk balance must also be positive, comprehensive data must be provided after authorization and this authorization must be renewed annually. (EMA 2016c.)

Hoekman et al. (2015) studied conditional marketing authorization (CMA) as pathway for early access of oncology medicine. In the period 2006-2013 11 drug medicine was given a CMA. They found that the assessment timelines for medicines receiving CMA (513 days) were longer when compared to standard marketing authorization (390 days). However, this was due to longer clock stop time rather than longer active assessment time which was created by more frequent request for additional data during the CMA process. In addition, accelerated assessment was never applied for products receiving CMA and most of the CMAs were proposed by the EMA late in the evaluation process. In conclusion, the authors state that CMA is sometimes used as a "rescue option" for medicines that lacks the data required for granting regular marketing authorization rather than a planned pathway to early market access that shows promising efficacy but still lacks the data required for regular marketing authorization. (Hoekman et al. 2015.)

Further concept targeting bringing promising drugs to patients with unmet medical need in a timely manner is EMA approach called "adaptive pathways". This approach seeks to balance timely access with the need to provide adequate evolving information on a drug's risk-benefit balance. Adaptive pathways makes use of existing approval tools in more iterative development plan involving multiple stakeholders which starts off with well-defined patient group and later expands to wider patient population as more data has been gathered. The adaptive pathways pilot project between 2014–2016 showed that this approach can foster a multi-stakeholder dialogue and incorporating the multiple-stakeholder view upfront reduces the need to generate additional studies later in the development. Adaptive pathways can support drug development in therapeutic areas such as rare cancers where evidence generation is challenging and it is

applicable only for drugs developed for patient populations with unmet need. However, adaptive pathways is still a concept under development. (EMA 2016e.)

Marketing authorizations are valid for five years and it may be renewed on the basis of re-evaluation of the risk-benefit balance. In the case of renewal, the holder of the authorization must submit the renewal dossier to EMA at least six months before the authorization expires. Once the authorization has been renewed it is valid for unlimited time period unless the European Commission decides to proceed with an additional five-year authorization. This decision can be made only on justified grounds regarding to pharmacovigilance. (Regulation (EC) No 726/2004.)

4.1.2 National price and reimbursement decision maker

The national price and reimbursement decision maker in Finland is Pharmaceuticals Pricing Board PPB. PPB operates under the Ministry of Social Affairs and Health and its operation and decisions are based on the Health Insurance Act (1224/2004). (Hila 2015.) The Pricing Board decides the following matters concerning medicinal products, clinical nutritional preparations and basic ointments: confirmation of reimbursement status, confirmation of reasonable wholesale price, increase of wholesale price and termination of the reimbursement status and wholesale price. The decisions are based on the applications submitted by manufacturers i.e. the marketing authorization holders (Health Insurance Act (1224/2004); Hila 2015).

The Pharmaceutical Pricing Board and the experts operating under the Board will be appointed for three year terms by the Ministry of Social Affairs and Health. The Board has seven members and must include two members from the Ministry of Social Affairs and Health, one from the National Institute for Health and Welfare, two members from the Finnish Social Insurance Institution (SII) and one from the Finnish Medicines Agency (Fimea). Maximum of seven members can be appointed in the expert group representing expertise from the fields of medicine, pharmacology, health insurance and health economics. (Health Insurance Act (1224/2004).) In addition, the secretariat of the Pharmaceutical Pricing Board is responsible for preparing the applications for decision making. This body consists from the director, principal pharmaceutical officer, chief pharmaceutical officers, senior medical officer, pharmaceutical officers, lawyer and secretaries. (Hila 2015b.)

The Finnish drug reimbursement system includes three reimbursement categories: Basic rate of reimbursement 40%, lower special rate of reimbursement 65% and higher special rate of reimbursement 100% (copayment of 4,5€ is charged per medicine and per purchase). These reimbursements are only available for medicinal products confirmed as reimbursable by the Pharmaceuticals Pricing Board and for reimbursement category decided by the same board. Reimbursements for medicines purchased can be obtained once an initial deductible of 50 € per calendar year has been exceeded (children under the age of 19 years are exempt). An additional reimbursement can be obtained if an annual limit on out-of-pocket costs exceeded. In 2017 this limit is set to 605,13 € and if this limit is exceeded patient only pays 2,50 € copayment for each reimbursable medicine. (Kela 2017; Health Insurance Act (1224/2004).)

The P&R decision making process starts when the application is received. First of all, the application is reviewed and checked that it includes all the required information. Secondly, the expert group and SII will be heard and after the statements from these parties have been received the applicant will present its own statement. If necessary PPB can also request additional statements. After the necessary data have been collected it will be processed by reporting officer and forwarded to the Board for decision making. At this point the Board can request the applicant to submit further clarification for its application which can delay the decision making. If the decision is approving the Social Insurance Institution of Finland will execute the decision and if the decision negative the applicant can appeal the decision to Supreme Administrative Court. (Pelkonen, interview.) This process is illustrated in Figure 3.

The wholesale price and reimbursement application submitted to the Pricing Board should include the proposed wholesale price and a justified explanation from the benefits and costs that will take effect if the medicine is accepted to the reimbursement system. Among other important information, the application should include a comparison from the benefits of the drug compared to other medicines used to treat same illness, evaluation of the expected sales and consumption for the next three years, prices and grounds for reimbursement in other EEA countries. Drugs containing new active substance should include a health economic evaluation in the application. (FMS 2014.) This is also applicable when the application concerns significant extension of the reimbursement e.g. for other indications (Health Insurance Act (1224/2004)).

The assessment of the application takes into account all the aspects and information required in the application and factor listed in the legislation. There is no single thing that would be high-

lighted more than others during the evaluation process. (Pelkonen, interview.) Besides the required information the applicant can also include other information it regards as important relating to the P&R decision (Health Insurance Act (1224/2004)). The final decision is comprehensive evaluation considering all criteria listed in the legislation, what is known, how things seems and should resources be allocated towards it (Pelkonen, interview).

When deciding whether a drug should be granted basic reimbursement the Pharmaceutical Pricing Board assess the therapeutic value of the drug. Basic reimbursement will not be granted if the therapeutic value of the medicinal product is found to be low. (FMS 2014.) However, in Finland the threshold for basic reimbursement is set low. Because of this there are not many marketing authorized drugs which application would not been approved for the reason that it does not fulfill the requirements for basic reimbursement. Thus after fulfilling the requirement for basic reimbursement the focus is on assessing whether the price of the drug is reasonable. If the application is rejected due to price regarded as unreasonable the decision does not question the therapeutic value of the drug. Instead, to put it briefly, the question is that is the added cost related to the health benefits gained. There is no established method to decide if the price is reasonable instead the reasonability of the suggested price varies case by case. This has contributed to the public opinion that PPB is only interested in the price of the drugs. (Pelkonen, interview.)

In the process of deciding the reasonability of the wholesale price PPB takes into assessment the costs of the treatment and benefits gained from both the patients perspective and the perspective of overall health care and social costs. Before making the final decision on the reimbursement PPB will also request an opinion from the Social Insurance Institution of Finland SII to incorporate the perspective of Health Insurance Scheme for the reasonability of the drug's price, costs and reimbursement. (FMS 2014.) The upward price trend of new pharmaceuticals is a challenge and it will challenge the sustainability of funding the new medicine not only in Finland but everywhere. Even if the medicines prove to be efficacious. (Pelkonen, interview.)

One of the factor affecting the assessment on whether a drugs price is reasonable is its price in other EEA countries. In this comparison the price in all EEA countries (where the drug is launched) will be taken into account contrary to the method used by some member states that will include only certain counties into the comparison. Despite the fact that all member states have some type of price control (direct or indirect) it varies between the countries and can affect

the introduction of new drug to national markets. Typically, new drug is launched into the markets that have looser price control. This creates situation where pharmaceutical companies might plan in which schedule a new drug is launched in different countries. Additionally, the extensive utilization of various types of risk sharing agreements in different countries have hindered the knowledge about the current international price level of drugs (Pelkonen, interview.)

One of the basic challenges in the decision making is created when a new drug comes into a situation where there is already an established medicinal treatment option and the price of the drug might be more than tenfold compared to the established drug treatment. There can be high hopes and expectations related to the new drug but the evidence in real-life use is often limited. This makes it hard to evaluate whether the price is reasonable compared to the health outcomes the drug produces and what is the real health benefit in large scale use. However, the limited data poses also a challenge when a drug is in a situation that there is not equivalent treatment alternative. (Pelkonen, interview.)

Uncertainty about the drugs value can lead to the rejection of the application (Pelkonen, interview). If needed, the reimbursement can be restricted only to clearly defined indications (FMS 2014). This can be used in both situations where the uncertainty about a drugs benefits is reduced by approving the drug initially for only restricted patient population and situations where the drug is guided to patient group that would benefit the most from its usage. Another way to deal with the uncertainty is to require the applicant to submit additional information or further clarification with the forthcoming P&R application. (Pelkonen, interview.) Since the decision is only valid for maximum of five years and for three years when the medicine under the application contains new active substance (Health Insurance Act (1224/2004)). Therefore, if the marketing authorization holder wishes the drug to be included into the reimbursement system after this period the required further clarification must be submitted before the validity of the initial P&R decision has expired.

A new tool for reducing the uncertainty related to P&R decisions has been launched in Finland at the beginning of 2017. This system is called “conditional reimbursement” and it is a form of risk sharing agreement. (Health Insurance Act (1224/2004); GP 184/2016.) The aim of the conditional reimbursement scheme is to expedite the market access of new innovative drugs, orphan drugs and high cost drugs, contain costs related to the reimbursement of medicines and improve the possibilities to manage uncertainty regarding the P&R decision of new drugs (GP

184/2016). The conditional reimbursement can be used for an especial reason only. There must be an unmet medical need for the treatment option and considerable uncertainty must be related to factors (e.g. therapeutic value) affecting the assessment of reasonable wholesale price and reimbursement. (Health Insurance Act (1224/2004).) The use of this scheme will allow the collection of data to clarify the uncertainties for further assessment while also grating the access to it (GP 184/2016).

Initially the use of the conditional reimbursement scheme would be limited rather than extensive for evaluating the functionality and effects of it. The further application of the scheme would also remain as a supplement for the current decision making process on special occasions. (GP 184/2016.) Conditional reimbursement is valid for maximum of five years after which the reimbursement will cease if P&R decision has not been made through the conventional process (Health Insurance Act (1224/2004)).

Through this reform Finland is taking a path to an area which is still rather unknown. It can be expected that this reform will create changes. Risk sharing agreements are confidential between the contracting parties and therefore so little is known about the real effects of these agreements. It will create a situation where there is publicly listed price and then there is the real price listed in the agreement that might be achieved thorough discounts or payback mechanisms. This will change the current situation where the wholesale price and reimbursement in only based on a decision towards end result where part of this decision is based on an agreement that is confidential. (Pelkonen, interview.)

During the P&R decision making process patient organization can submit their statement about the therapeutic value of the medicine under the assessment and thus include patient perspective into the process. Patient organization must submit their opinion within a month starting from the date the Pricing Board publishes a list from the pharmaceuticals submitted under assessment during the previous month. (Hila 2016.) However, this can be problematic since the applications submitted to PPB are not public information which means that patient organizations know what drugs are under assessment but they do not know the contents of the applications. Therefore, their statement can only reassert the opinion of the Pricing Board on one direction or another. In addition, the resources of patient organization to produce statements can be scarce and additional information that is not already included into the application e.g. patient experiences concerning new drugs can be difficult to produce. Disregarding these factors overall it is a good thing that this kind of system is in place. (Pelkonen, interview.)

Some of the drugs used to treat serious and chronic diseases can be granted special reimbursement status under the special refund categories. These illnesses are decided by the Finnish Government. When deciding should a drug be granted this special reimbursement status PPB assess the nature of the illness, necessity of the treatment, therapeutic value and cost-effectiveness of the medicine as well as the overall funds available for special reimbursement payments. The reasonableness of the drug's price is also reassessed. The application for the special reimbursement status must be submitted by the manufacturer and drug must have been in the basic reimbursement category for two years before it is eligible for special reimbursement. The special reimbursement status can be granted earlier if sufficient clinical experience and data is available to fulfill the data requirements of special reimbursement application. (FMS 2014.)

The timeline for the price and reimbursement decision is 180 days (Health Insurance Act (1224/2004)). The timeframe is derived from EU regulation. A member state can assess price for 90 days, reimbursement for 90 days and if these are assessed in the same process the timeframe can be combined to 180 days (Pelkonen, interview). If the information included in the application is found to be insufficient the Pharmaceutical Pricing Board will interrupt the assessment and request the applicant to fulfill the information needs. In these situation the decision has to be made within 180 days starting from the submission of the additional data. Before making the final decision the applicant can be requested to submit additional data several times. (FMS 2014.) The process can be suspended on the behalf of the applicants on request to PPB. This can be done e.g. in situations where the applicant knows that they will receive research data in the following months that can be critical for the final P&R decision. In these cases, the timeline is also stopped for the time requested. (Pelkonen, interview.)

The P&R decision will come into effect at the beginning of the second month following the decision date unless otherwise is stated in the decision (Health Insurance Act (1224/2004)). The Social Insurance Institution of Finland is responsible for executing the decision made by the Pharmaceutical Pricing Board (Pelkonen, interview). For example, the P&R decision for Erivedge was made 4th of February 2016 and it came into effect 1st of April 2016 (Hila 2016b). This means that the execution of the decision took 57 days. The timeline and the sequential phases taken before the P&R decision will come into effect is illustrated in Figure 3.

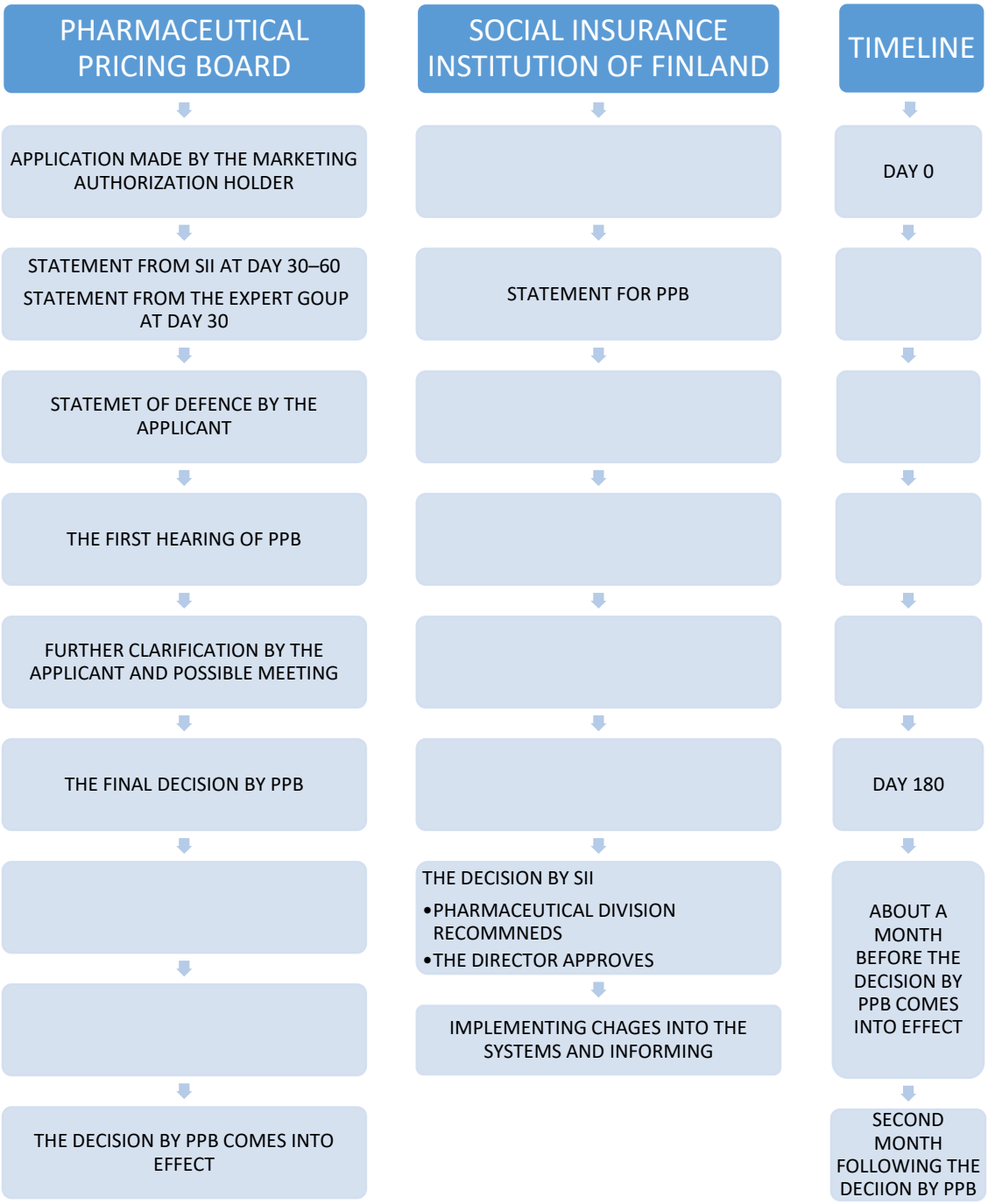

Figure 3: The timeline and sequential phases for the P&R decision making

Source: Pelkonen & Kalliokoski 2016 (adapted); Also referred in the interview with Pelkonen.

Shortening the time frame for making P&R decision has been discussed few years back on the basis of the EU Commissions objectives. However, shortening the timeframe has not been seen very reasonable. Although, the decision making could be made e.g. within 90 days it would cut

off many good aspects of the current system. The current timeframe allows the applicant to supplement its application, add new reports to it, reform it and enables supplementary statements to be taken into the process. Shortening the timeframe would leave such phases out of the process. Thus, this kind regulative expediting would possibly lead to increasing number of negative decision which then would further prolong the delay. Moreover, creating an additional scheme such as the National Cancer Fund in UK to allow the access to medicines that are not found cost-effective in some evaluations is not seen very reasonable or a good option. (Pelkonen, interview.)

In principle the approved reasonable wholesale price cannot be the price that the applicant initially proposes because the applicant might start off by seeking to get higher price for the drug. This will effect on the decision making time on the behalf of the applicant. The main question here is that is the initial application consistent with the desired result of the P&R decision or is there included some room for further negotiations in the application. (Pelkonen, interview.)

It is common that the application goes through changes during the decision making process. The applicant can change its propositions e.g. on the part of the proposed wholesale price or proposed restriction of the reimbursement. This is resulting from the fact that the process is based on gathering statements and then the applicant has its opportunity to make defensive statements. This assures that the applicant can review all the information that affects the decision making. There is a sort of formal dialog going on during the process between the applicant and PPB. The apparent decision making time could be reduced by directly rejecting the application if the proposed price is found to be unreasonable. However, rather than doing this it is seen more appropriate to give the applicant the possibility to come up with a further clarification so that the dialog could be continued and the decision could be reached during the first process. (Pelkonen, interview.)

4.1.3 Market access delay of oral cancer drugs in Finland

The mean overall time for the chosen oral cancer medicines to be included into the Finnish drug reimbursement systems after pharmaceutical company has submitted the application for marketing authorization to EMA is 2,36 years (861 days) with a min-max range of 1,51–4,33 years.

The drugs are listed in Figure 4 with their overall delay. The mean EMA time is 1,17 years (427 days) with a min–max range of 0,72–1,68 years. This phase absorbs on average 49,6% from the

overall time and represents the longest phase in the market access delay. The mean Pharmaceutical company time is 55 days with a min–max of 9–177 days and represents on average only 6,4 % from the overall time. The mean PPB time is 1,04 years (379 days) with a min–max range of 0,42–2,67 years absorbing on average 44% of the overall time. See Table 3 and Figure 4.

Table 3: Results, days.

Phase	Mean	Median	Min–Max range	Coefficient variation %
EMA time	427	404	262–615	25,4
Pharmaceutical company time	55	40	9–177	85,5
PPB time	379	276	152–974	66,2
Overall	861	781	552–1583	29,8

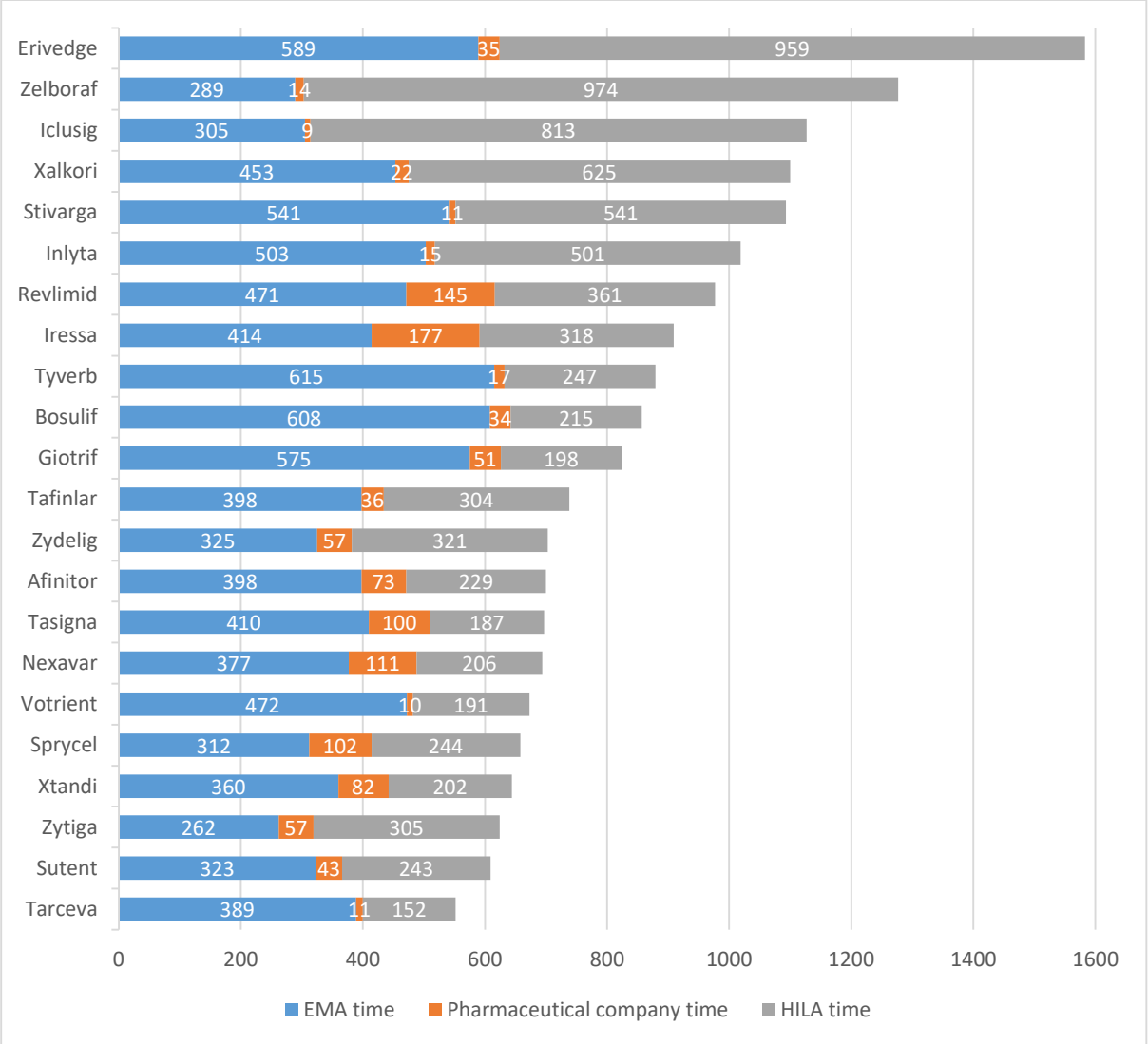

Figure 4: The market access delay for all the drugs. Horizontal axis = days.

If the clock stop times will be taken into account i.e. the times when the CHMP assign the applicant List of Questions and List of Outstanding issues the mean active EMA evaluation time is 332 days with a min–max range of 234–486 days (coefficient variation of 19,2%). This means that the mean time that the applicant takes to answer questions issued by the CHMP during the evaluation process is 95 days with a min–max range of 25–269 days (coefficient variation of 67,5%). See Figure 5.

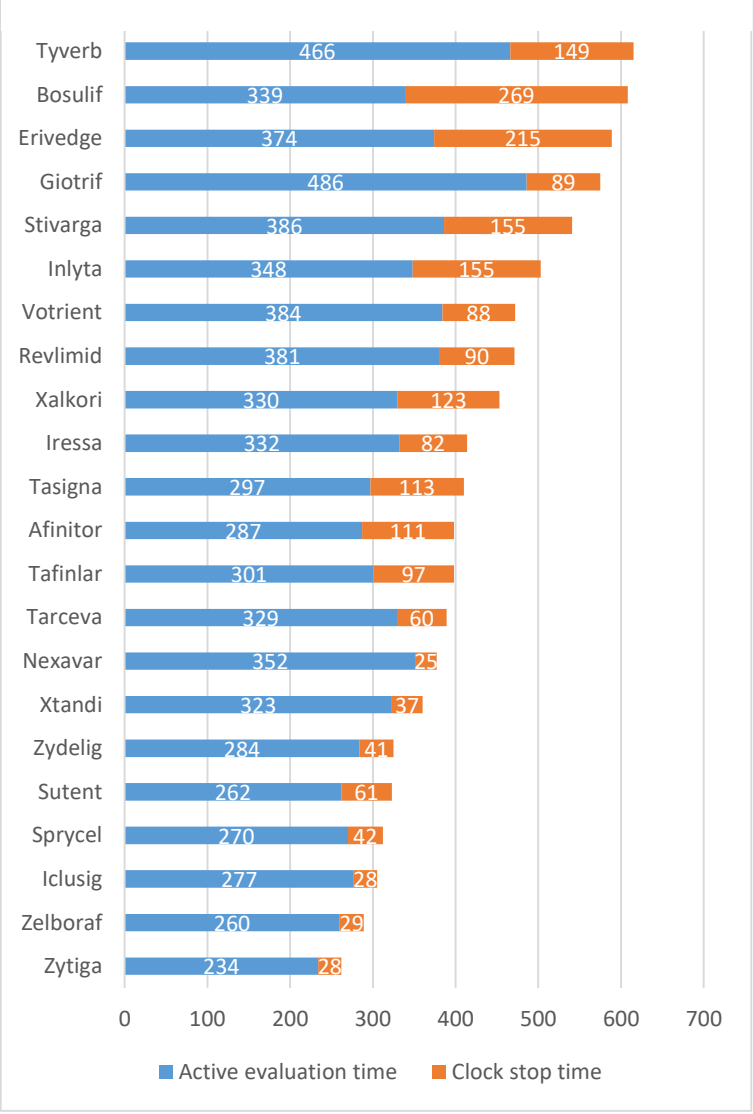

Figure 5: EMA time, active evaluation time and clock stop time separated. Horizontal axis = days.

As mentioned the mean PPB assessment time was 379 days. The application for reimbursement were rejected at the first time for five medicine out of the selected 22 drugs. The mean time for

these medicines to be included into the reimbursement system after the pharmaceutical company had submitted the first application was 1,97 years (720 days) with a min–max range of 1,37–2,67 years (coefficient variation of 31,9%) compared to the mean time of 279 days (min–max range 152–813; coefficient variation 53,6%) for the medicine that received a positive P&R decision for the first application.

Exploring how the year that a drug is included into the Finnish drug reimbursement system affects the market access delay it can be observed that the drugs included between years 2006–2009 have a mean delay of 1,98 years (724 days) with a min–max range of 1,43–2,67 years (coefficient variation of 20,9%). The drugs approved between 2010–2013 have a mean delay of 2,06 years (753 days) with a min–max range of 1,71–2,49 years (coefficient variation of 16,4%) and the latest drugs included into the reimbursement system between years 2014 – 2016 has a mean delay of 2,77 years (1011 days) with a min–max range of 1,76–4,33 years (coefficient variation of 28,8%). This would imply that the market access delay has prolonged for newer drugs. The prolongation is even rather apparent between the group consisting form drugs granted reimbursement between years 2010–2013 and drugs granted reimbursement between years 2014–2016 being 34,3 %. This can be seen in Figure 6.

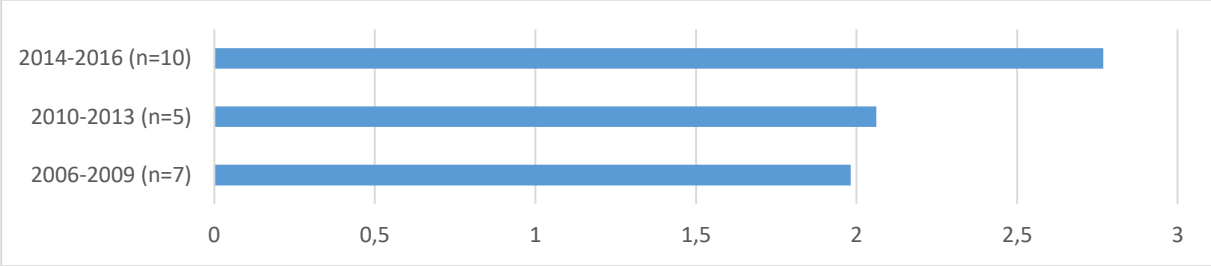

Figure 6: Mean market access delay categorized based on the year of a drug's approving P&R decision (n= number of entrants). Horizontal axis = years.

4.2 Patient view on market access of oral cancer drugs

As a result of analyzing the patient interviews three overarching categories were found which are associated with the patient view regarding the market access of oral cancer drugs in Finland. The categories were named as: access to new cancer drugs, information regarding cancer drugs and organization of treatment.

First of all, access to new cancer drugs cover the participants' thoughts concerning the current accessibility of new cancer drugs in Finland and their opinions of what effects on this accessibility. Secondly, information regarding cancer drugs covers what kind of attitudes the participants hold toward new cancer treatments and how they receive information about cancer drugs. Thirdly, a large part of the discussion with the interviewees focused on the other aspects affecting the treatment of cancer. Most importantly to the relationship between patient and doctor. This is covered in the organization of treatment part.

4.2.1 Access to new cancer drugs

What was interesting to find out is that all the participants knew that all the newest cancer drugs are not yet accessible in Finland or they haven't been included into the drug reimbursement system. It was noted that patients even search information that in which country the drugs could be accessed and what would be the price to get these drugs or could they be ordered to Finland.

"Well, these new cancer drugs that have been developed, there have been some discussion about them but they are not included into the reimbursement system in Finland yet." (Interview 4)

Most of the participants shared the same opinion that there can be seen a delay in the introduction of new cancer drugs in Finland and all of the participants were consistent that the access to new cancer drugs should be expedited from the current situation. The availability of new cancer treatments is most often compared to other European countries.

"They have (USA) all sorts of drugs in everyday use and then they will arrive to Europe with a delay and then with a further delay to us." (Interview 2)

"…it feels like is the introduction of new medicines to Finnish market somehow extremely slow when it might be in use in elsewhere in Europe and in rest of the world…" (Interview 1)

However, for most of the participants it is not clear how new medicines gain market access in Finland or who makes the decision about the reimbursement status of medicines. A consistent opinion among the participants is that the patient view is not incorporated into the decision making as much as it should. It is thought that at this moment the decision makers cannot include patient perspective into the decision making and the decision making itself is rather closed and conducted only by officials regardless of the patients' opinion.

"I don't know who it is in Finland, is it SII or doctors or decision makers of parliament who obstruct these matters in somehow or is there some sort of "old boy network" who decides what drugs are prescribed…" (Interview 3)

"…you wish that you could get the best drug that can be used for your treatment but for some reason in Finland it is there…that it doesn't get reimbursed." (Interview 1)

"Absolutely the patients' opinion should be asked…they are the ones suffering from this…although the patients don't know every aspect related to these medicine but in the end it is concerning patients themselves." (Interview 4)

Additionally, when the participant had knowledge that the Pharmaceutical Pricing Board makes the decisions concerning the P&R status of cancer drugs it came up that these decisions can be monitored very closely by the patients since they are public and published online in PPB's website.

"I know that the Pharmaceutical Pricing Board has many more drugs under assessment but they haven't been approved yet." (Interview 2)

The general opinion among the participants seemed to be that the underlying reason for the new oral cancer drugs not being reimbursed is because of budgetary constraints. No other reasons were mentioned or then the reasons could not be defined by the participants. Although it was remarked that budgetary constraints could be overcome by better resource allocation This can be related to the knowledge that the new cancer drugs tend to be high priced and patients know that they probably couldn't afford them if they are not included into the drug reimbursement system.

"Yeah, money, it annoys me that it is dependent on money…" (Interview 2)

"Probably no one can afford the high priced unreimbursed treatments." (Interview 1)

It was also brought up that regardless of the means the newest drugs should be made accessible ignoring the budgetary constraints.

"Personally I think that somehow it should be made available if its already coming at the door and not obstruct it any longer." (Interview 3)

Among the interviewees the cost of the drug is usually compared to the value of human life which is then regarded as immeasurable value. Therefore, it cannot be accepted that a drug is not made accessible due its high price since it is used to save something even more valuable.

Furthermore, it was considered that cancer does not only affect the patient itself rather it affects all the patient's close ones and therefore the disease can have deeper effects to its surface e.g. to the welfare of whole family.

"I have understood that the value of human life is immeasurable and anyone that can be kept alive would be salvation for the entire family…" "…the human life is more valuable than some medicine…" (Interview 3)

Although, it is seen that the current treatment options have improved the probabilities for survival in the basis there is the thought that cancer is such a fatal disease that the non-accessibility of the newest treatment options is seen to affect directly to the possibilities of surviving the disease. Additionally, emphasis was placed on possibility to return to normal life when patient could access an effective treatment It was also wondered what benefit the developed cancer research can then offer when the newest treatment options cannot be accessed.

"…it will be paralyzing when you can't access the medicine that would benefit you the most…" (Interview 1)

"Certainly, and it irritates me and it hurts my sense of justice that when you are at your weakest and sick, you become unequal. I call it as a murder." (Interview 2)

As depicted already in the previous statement not including the latest cancer drugs into the reimbursement system is seen to position the patients into unequal situation based on their wealth. It was thought that if you are wealthy enough you can provide the treatments for yourself and if you are not you just have to settle with the current situation. The long treatment cycles of cancer are seen to further unbalance the economic status of patients which further highlight the importance of including drugs into the reimbursement system in order to make them accessible.

"…it is not equal, wealthy will get it and the poor won't. In this situation you know that you are not going to be able to get that treatment." (Interview 4)

The delay for accessing new drugs caused astonishment as well as anger and bitterness. However, anger is not seen only as a negative feeling. It is seen to also give more strength and energy to solve why the treatment cannot be currently accessed. Half of the participants believed that it can also cause some level of depression and anxiety when it is noticeable that the new treatment option is just a passing chance for them. What was consistent with the interviewees is that

this subject evokes many different feelings with patients and it can be hard to process on top of the initial shock of getting diagnosed with cancer.

"It angers me and feels unimaginable that how can it be possible and it causes many feelings…" (Interview 1)

"My grit is only boiling. That just gives me more energy." (Interview 2)

4.2.2 Information regarding new cancer drugs

All the participants expressed a genuine interest towards new cancer drugs and cancer treatments in general. This is well captured in the following answer by one of the interviewees when asked whether the interviewee was acquainted with the different treatment options for cancer.

"Yes, when your own life is in question you will begin to be quite acquainted, yes this is the case." (Interview 2)

Patient groups were seen as an important mean to gain and share information about new cancer drugs. Through peer support patients share their experiences about their treatments, information about what kind of treatments they have received, what kind treatments there are for their condition and what upcoming treatments there might be. These groups can be used e.g. for asking things that the patients forget or didn't think of asking when they visited their doctor. This kind of discussion among the patients is seen to have great impact on the support patients receive. Through these groups patients notice that they are not alone with their disease.

"In our group, we have our own group, others have told…what kind effects the treatments have, what kind of treatments they have received and it is highly individual." "Peer support has huge impact on welfare especially in the beginning. It supports, it supports more than close ones in that stage because at the beginning you try to shelter your close ones…" (Interview 4)

As a secondary source of information participants mentioned media and internet. Newspapers, magazines, television are closely watched for articles and programs concerning the treatment for cancer. Internet is used to further explore this information and information discussed in the patient groups. Additionally, advices and information is sought from patient organization and online doctor services.

"First of all it is media that pretty much gives information. I may have read something form magazines or newspapers and also television has been important channel for information, the

programs covering health issues, and then I have further searched this information online." (Interview 1)

For its part, the knowledge about newer cancer drugs can create distrust for the current or ongoing treatment option. Especially it can have an effect for trusting that the treatment with older i.e. currently available cancer drug has positive survival effect on a patient's disease.

"...I reacted mentally like I don't believe in it one bit. Like I am doing a disservice for myself because always when you receive treatment you should believe that it works." "I said to my doctor that I really don't like about this situation." (Interview 2)

However, in most cases the knowledge about new cancer medicines were seen as positive. Most participants regarded that the information concerning new cancer drugs can give hope for patients. Even if the patients know that at the moment the drugs would be unavailable for them due monetary constraints or something else. In their opinion this can help patients not to give up on their treatments.

"It will bring hope that maybe the drug will become reimbursed in some point during this disease." (Interview 1)

"You should say and tell about them because it is really good for the patient that they are aware of their existence so you don't throw your hope away." (Interview 2)

"...for those who can even the slightest bit or their family can could then get the needed help from elsewhere, seek the help or at least they would gain the knowledge that a drug exists." (Interview 3)

The opinion of the interviewees towards new cancer drugs were favorable. It is seen that patients have great hopes towards new treatment options and although it was acknowledged that new medicines probably would not provide a total cure from cancer it was believed that new medicines could prolong the life-expectancy for years to come or at least make it possible to keep their cancer at more manageable stage.

"(New medicines) They are good, they are good…" (Interview 2)

"With them it is possible to keep cancer under control for years even if it has been recurred." (Interview 1)

A part of the expectations toward new medicines was related to milder side-effects and in general the side-effects of cancer medicines was brought up by most of the interviewees. The experiences of side-effects are shared between patients in their discussion and side-effects can cause concerns before starting treatments. Therefore, new and more targeted cancer therapies can be seen as a long-awaited help for this situation among patients. However, it was recognized that the new cancer medicines will also have side-effects.

"My image is that new drugs don't cause so much side-effects and what information I have come across and found says that the side-effects are milder." "It causes, the cytostatic treatment, that the additional drug burden will be pretty big and I know some who had to take drugs for nausea, constipation, pain and then there can be antidepressants, sleeping pills…" "And then many of these infusions can cause infections and they can require medicinal treatment." (Interview 1)

"Of course you would hope that there would not be side-effects that you wouldn't have to feel sick all the time and you wouldn't get so weak that you wouldn't be able to stay up…and you wouldn't get all kinds of infections…" (Interview 4)

4.2.3 Organization of treatment

Active patient groups and animated discussion in both inside and outside the groups between patients with same diagnosed cancer type gives patients the opportunity to compare what kind of treatment they are receiving and how the treatments are organized between different areas and hospitals in Finland. This has generated the understanding that there are regional differences in the treatment of cancer. The differences have concentrated on what cancer drugs are used for the treatment and how things are told and informed. It was noted that some areas have newer equipment for certain treatment and that university hospitals have more resources for using the latest treatments for cancer.

"You hear it from the others coming from different parts of Finland that different things are emphasized there." "There are regional differences and mainly there are differences in how things are told to patients." (Interview 4)

"There are great regional differences and it is also highly dependent on the trust you have with your doctor and how your cooperation works with your doctor and is the doctor really interested in you." (Interview 3)

As it can be already seen in the previous statement the relationship between patient and doctor plays a major role in patients' satisfaction to their treatment. The individual patient-doctor relationship and the differences in these relationships between patients can have partial effect on the observed regional differences. Thus, the regional differences might also mean differences between these individual relationships depending on the mutual trust between patient and doctor.

"It is totally impossible meaning that if you will be treated with this kind then the quality of care will suffer from it…chemistry or whatever you want to call it just is not there." (Interview 3)

"I am so happy that the treating physician is my doctor… Some people just got the talent and it is like either you have or you don't." (Interview 2)

The change of the treating physician during the treatment cycle is viewed negatively. This hinders the formation of patient-doctor relationship which then further creates uncertainty for the patient. Patients need a continuum on their treatment which then enables them to trust more on their treatment plan.

"…this doctor called me and this doctor haven't called me before and that is the thing, every time the doctor changes there can't form a closer relationship because every time you have to tell these thing all over again." (Interview 4)

Furthermore, the change of treating physician can create distress for patient if the information and the treatment plan is inconsistent with the previous and current doctor. This can require including a third party opinion regarding the diagnosis and treatment plan.

"The physician told me about a moth about the planned treatment and then physician changed and told me that the planed treatment would not be an option any more. I was really amazed that why? Then I requested to consult a different doctor." (Interview 3)

In addition, not including the patient to the decision making process concerning the treatment can be seen negatively. Patients wish to have a certain degree of control over their own treatment. Although, it is acknowledged that doctors have the expertise to decide the treatment option the patients would at least like to be included into the discussion. This would allow the patient to receive more justified and thoroughly explained reasons why the treatment plan has been chosen.

"Patient should be included into the discussion rather than keep the patient outside of this discussion and then later on inform the patient about the chosen treatment plan. It is not humane; you feel like you are some kind of object that someone else can take control over…" (Interview 4)

4.3 Patient organization view on market access of oral cancer drugs

The analysis of the patient organization personnel showed that there were the same overarching categories emerging from the interviews as in the analysis of patient interviews: access to new drugs, information of new drugs and organization of treatment.

4.3.1 Access to new cancer drugs

The patient organizations opinion towards the access of new drugs is that patients should get the needed medicines, the drugs should be available to all patients at the same time, patients should receive the treatments equally and patients should be placed in an equal position. The availability of the drugs should not be depending upon the place where the patient lives, what is the wealth of the patient or how the drug is administered. The organization stands by the concept that with the help of new innovative cancer drugs the disease will become manageable.

"Patients should receive drugs and the drugs should be available to all patients equally." (Interview 5)

"The organization has opinion that the patients should be positioned equally regardless whether the drug of the patient is administered intravenously or orally." (Interview 6)

The consistent opinion of the interviewed patient organization personnel was that the decision making time of the P&R status of new cancer drugs is too long. It was noted that it might even feel random that how long it takes that a new drug is included into the reimbursement system. This creates uncertainty about when a new drug will become accessible. It is desired that the total time this process takes would be more systematic. This delay is viewed as the most common reason for not accessing new drugs. The current situation is regarded as painful for all stakeholders involved, pharmaceutical companies can't access markets, doctors can get familiar with new drugs and patients can't access them. Nevertheless, it was regarded that it is necessary

that there is decision maker like PPB that assess new drugs before they are included into the reimbursement system.

"The process is really long. I wish someone would find the happy medium that would allow us to take a little shortcut but it really is long like hunger year." (Interview 7)

The desire of the patient organization is that the P&R decision making process could be expedited. This can be seen first and foremost as the benefit of cancer patients but also as the benefit of whole society and the health care system. The current situation is seen to consume too much time for patients waiting for the treatments although for some patients even more expedited time can be too long but still improvements has to be made. The ability to access the treatments that could save the patients ability to return to working life is considered as important for the societal perspective and the ability to offer treatments that would benefit patients the most is considered as important for retaining the trust toward the health care system.

"Somehow the reimbursement of these oral prescription cancer drugs should be expedited." "On the account of patients and the whole infrastructure it important that new treatments can be accessed fast." (Interview 6)

"It is inhumane like when this one patient called and said: "There is no other drug than this new drug and now I cannot get it". The patient knows that there is drug that would keep him/her alive but it is not given to him/her because it is too expensive. That is totally absurd that we know that there is drug but it is not prescribed because it is too expensive and the patient passes away." (Interview 7)

The current P&R decision making process should be further developed. It was considered that this system might not be the most suitable system regarding the decision making about new and innovative medicines. Considering drugs for cancer diseases with high unmet medical need and drugs that would offers great health benefit there should be another evaluation option besides the conventional P&R decision. These kind of medicines that could be referred as highly important should have the possibility to reach patients much faster through some sort of accelerated decision making.

"The process of PPB is not exactly appropriate for these innovative and high cost drugs when these medicines should be also accessible." (Interview 6)

"What if we have this new medicine with a dramatic health benefit could they have some kind of fast track system that allows the decision be made with fast procedure." (Interview 5)

Patient organizations have the possibility to influence on the P&R decision of new cancer drugs made by the Pharmaceutical Pricing Board by giving a statement concerning the drug but this possibility is seen to leave on rather general level or the importance of the statement has been left unclear. It is seen that the statement is a document among the others in this decision making process and that the information of the statement can be overlapping with the information presented already in the application or in the expert statement given into the assessment. The main data that could be generated by the patient organization is the experiences by patients but this is seen troublesome how the organization could generate this national data when new drugs has been rarely or at all available to the patients before the P&R decision. Moreover, this would require resources that are at least at the moment non-existent.

"I don't see what kind of data could we generate that is not already included into the application. I don't think that we have that kind resources." (Interview 6)

"I think that it is there among other data." (Interview 5)

However, the participants noted that there have been times that the statements made by the patient organization has really influenced the P&R decision and that statements are given if it is seen that they could truly have the possibility to make difference. From the organization point of view public discussion is seen as more efficient way for influencing the accessibility of new cancer drugs and that patients will have access to treatments that have been found to be effective but inaccessible.

"The way that the organization could influence more and we have influenced is through public discussion." (Interview 5)

The rising price of new medicinal products was also brought up in the interviews. The growing cost of new cancer drugs to society was seen to create additional hurdle for access. However, the medicines share of the total cost in cancer treatment was seen still to be rather small depending on the type of cancer. Compared to other major therapeutic areas like diabetes and cardiovascular diseases the cost of cancer treatment is seen to be more affordable. Considering the long R&D process for medicines the prices can be understandable. Up to date research data was longed for to reveal have the costs really grown since the amount of diagnosed cancer patients have increased, the treatments have developed and the drug offering have expanded.

"…but it is really, we can say that the price of the drugs is problem." (Interview 5)

"Cancer patients just happen to be the ones that has high cost treatments." (Interview 6)

"…but still the treatment of cancer is affordable compared to many: diabetes, blood pressure, heart conditions so it is still affordable but I guess there should some cap for the price that it doesn't…" (Interview 7)

Patient organization receives contacts form patients considering their inability to access some new cancer drugs. Usually the contacts are concerning and questioning whether they receive the best possible treatment for their condition. The knowledge that some new treatments cannot be accessed can be in contradiction with the general opinion that in Finland patients will receive the best world class treatment in health care. This can create more amazement and some stage of distrust towards the health care system. In addition, bitterness and variety of negative emotion can overcome the patient at the moment the information is received.

"It doesn't only raise amaze but anxiety, agony, fear, will the patient become unequal, can some receive the medicine through contacts, how the patients that receives the medicines are chosen, can the patient itself influence this situation that the medicine could be accessed." (Interview 7)

4.3.2 Information regarding new cancer drugs

Patients willingness and need to search for information can be classified according to the stages of cancer. In the initial phase when individual receives the diagnosis patients does not yet have the readiness to look for information on the disease of oneself. Rather in the diagnosis phase patients concentrate on thinking could they overcome this disease and focus on the starting the treatments. It comes in the later stages of the disease that patients start to consider all the aspects connected to the disease and has the ability to take a wider look from their situation. It is until then when the patients have the ability and need to look for information regarding the treatment and medication. Especially if the current treatment does not have effect on the patient's cancer or the patient has already gone through all the treatments listed in clinical guidelines.

"…in the diagnosis phase patients are not yet aware of anything. After patients have been suffered from cancer for a while they will become more calm and adapted into the situation and starts thinking that maybe I can overcome this. It is until then when the information will be searched." (Interview 7)

It is seen that patients wouldn't have the possibility to get information concerning new cancer drugs without actively searching for it and following up the development of new medicines.

Often the patients' premises for accessing information varies. Some are more educated, some have better lingual skills, some can have better IT skills or some can be more motivated to search information. This creates different possibilities for patient to gain information. Additionally, younger patients tend to be more eager to search for additional data. However, the current trend refers that the family of older patients e.g. their children are eager to familiarize with their parents' disease and then provides this information for the patients themselves. Internet is regarded as the main data source for the patients especially the international websites. Hospitals, other patients or patient groups and media is regarded as the secondary data source. Besides these also the organization receives questions from patients about new cancer medicines.

The main problem with the information that the patients possess is that it might be only one-sided. Patients can discuss about things that they only partly know about. Individual patients might not be able to capture the whole picture of a cancer disease or what kind of effects a medicine has or in what stage it should be used. They might not be able to identify how meaningful a cancer drug could be for the treatment of their disease since they might not know all the medical information that is required to make decisions about treatment plans. The information obtained from the internet and shared between patients can be also incorrect. Drugs can be mistakenly mixed and then causes that the whole picture for a patient about certain drug can become distorted. Essentially the discussion between patients can be compared as an informal discussion over coffee table. Therefore, patients should not jump into conclusion based only on the data that they have succeeded to acquire or trust too much into their self-diagnosis.

"So patients usually have a part of the information but not the whole information concerning the disease that the doctor possess." (Interview 7)

However, it is considered as good thing that the patients are interested and willing to acquire information. If patients do not have any knowledge about their disease they can make wrong conclusions too suddenly and sometimes based on wrong information. Cancer disease can be seen deadly and all hope can be lost although the reality could be totally different i.e. disease could be treatable and maybe even defeated. Additional information allows the patients to ask their physician more specific questions which can help them to better adjust to the situation. The most important thig would be that patients could receive information in a steady pace, they could discuss this information without hurry, outline the information and the come back again with new questions. This is seen to have the possibility to solve many wrong impressions that they patients might get.

"It is really good that patients search for information we think like that also here in our organization because it allows patients to outline their own situation, what is going on and where we are heading." (Interview 7)

"…I would consider it more as a thank you that they are more aware…" (Interview 5)

The increasing amount of available information, the fast movement of the information, social media and the active discussion in patient groups have made it possible to gain vast amount of knowledge without requiring physician or other medical professional to discuss with patient. This has generated changes in the attitude of patients toward health care. Patients can be more demanding and critical about their treatment. It is no longer enough that patients will get into treatment but it is increasingly relevant that how the treatment is organized. Thus, it is increasingly important for the physician to communicate the treatment thoroughly with the patient. What reflects this is the phrase "smart patients get smart care" that was brought up in the interviews meaning that the patients' own activity may also have influence on how the patient is treated.

"…before patient were humbler asking that "Could I get treated?" compared to nowadays when the attitude is different like "What can you offer me?". Nowadays patients can be more demanding." (Interview 7)

4.3.3 Organization of treatment

First of all, it was considered that do we have the same criteria in different parts of Finland in the introduction of oral cancer therapies i.e. regardless of where the patients live does they have the same possibility to access the drugs. Although we have the same rules and clinical guidelines applicable in all areas of Finland the reality might differ. The prescription of a drug can be contingent on the oncologist experience of a drug. Often the big health care clusters e.g. university hospital districts introduce new drugs first to gain more experience of its usage. Especially experiences about what kind of side-effects a drug might have. After experience has gained the drug is then diffused to smaller health care units.

"Another aspect is however the usage of oral drugs that do we have the same criteria in different parts of Finland..." (Interview 5)

Additionally, the regional differences can be resulting from the different criteria of hospitals to administer oral cancer medicines to patients. It was mentioned that can be more willing to give

patients the needed oral medicines if they are not included into the reimbursement. This can be done for the sake that the patients will receive the needed treatments irrespective their reimbursement status. It has come to the patient organizations attention that even arrangements where the patient in taken into the hospital so that the hospital could then give the patient the high cost non reimbursement drug for the price of daily hospital fee have been considered. However, the current situation has evolved into more consistent and stringent state where the oral cancer drugs are not given to the patients out of the hospital.

"They have been distributed pretty well. Depends on the hospital though, has depended, but it has come into my attention that they have been distributed." (Interview 6)

More consistency between different hospital districts is longed for. One possible solution for this can be the upcoming Comprehensive Cancer Center Finland whose planned role would be to give clinical guidelines and give statements concerning new treatments. Not only considering medicinal treatments for cancer but also involving the whole treatment of cancer e.g. surgeries and radiotherapy. This is seen to have the possibility to create more equality among the patients through more consistent clinical guidelines applicable to whole country. The consistency of treatment is important especially in the treatment of rare cancers where clinical guidelines is not as established as in the treatment of larger cancer diseases such as breast cancer. The cancer center could operate as an independent agent that could identify the critical cancer medicines that should be used for treatment and included into the drug reimbursement system.

"In my opinion Comprehensive Cancer Center Finland could be really logical operator in assessment for example in the assessment of medical need." (Interview 5)

The finite resources of health care system will create prioritization in the uptake of new cancer drugs. The resources should be allocated towards new drugs that will truly make the difference. In some cases, the statistical significance of e.g. overall survival found in a drug research does not necessarily correlate with the clinical significance of a drug in real life use. This is consistent with the notion that the newest of most expensive treatments are not necessarily always the best. This is a part that might sometimes be forgotten by patients that health care system cannot function with the mentality of offering the most expensive treatments no matter the costs.

"Altogether the treatment of cancer is ensemble of different parts and unfortunately we have to consider the fact that we will have to make prioritization is cancer drug treatments." (Interview 5)

It was brought up in the interviews that patients can regard that "every single day is important". If patients can't access the treatments through public health care system, they are willing to consider private cancer treatment or search treatment possibilities from abroad. Private sector is also often considered in getting a second opinion for diagnosis. Ways to access the treatment somehow is especially considered in situation where the available treatments do not have effect anymore or the disease in found to be untreatable. Patients can be willing to sell their property or even take loan to cover the cost of non-reimbursed high cost cancer medicine.

"…patients are different; we have them who are willing to sacrifice their entire possessions to be able to live few months longer, we have patients who have taken or their family has taken loan for purchasing medicine…" (Interview 5)

However, Finland is seen as one of the countries with good accessibility to relevant cancer drugs. The international recommendations are followed and usually the drugs that can be considered as minimal clinical recommendations by European society for Medicinal Oncology (ESMO) are accessible for patients. It can be considered that big part of patients receives good cancer treatment and the situation compared globally is good although it is not optimal.

"It could be said that compared to many other European countries in Finland we are in a quite privileged situation." (Interview 5)

4.4 Summary of the research results

Before accessing the markets in Finland new oral cancer medicines have to gain marketing authorization from the European Medicines Agency through centralized authorization procedure and a positive price and reimbursement decision from the Pharmaceutical Pricing Board PPB. Both these processes begin when pharmaceutical company submits an application to the decision maker and both of these processes are based on regulations.

In the first phase of deciding whether a drug should be granted a marketing authorization EMA assess the safety, quality and efficacy of the medicinal product. CHMP is responsible for carrying out the scientific assessment. The assessment is based on balancing the risks of a drug against its benefits and CHMP can recommend the authorization of a drug which benefits outweighs its risks. After CHMP has reached its opinion it will be forwarded to European Commission who will assess the compliance of marketing authorization application to European laws and then grants the marketing authorization valid throughout the EU and EEA countries.

In second phase PPB will confirm the reimbursement status and reasonable wholesale price in deciding whether a new drug should be included into the Finnish drug reimbursement system. This decision is based in evaluating a drugs benefits against its costs and comparing it to other medicinal products used to treat the same therapeutic indication. After the decision has been made the Social Insurance Institution of Finland will execute the decision.

The time frame for the marketing authorization process is 277 days consisting from the 210 days given for the CHMP evaluation procedure and 67 days given for the European Commission decision making process. The time limit for the P&R decision making process is 180 days. These time frames are considered as active evaluation time and they do not include the time that the applicant uses to answer to the question raised by CHMP or further clarifications requested by PPB. Computing these times together and adding the time it takes to execute the decision made by PPB which is less than two months it would mean that in an ideal situation a new oral cancer drug would gain market access in ca 500 days.

In addition to the conventional centralized marketing authorization procedure EMA offers set of regulatory tools to support the early access of promising new drugs. Compassionate use opinion by CHMP allows the use of unauthorized medicine for patients with high unmet medical need, accelerated assessment reduces the CHMP evaluation time to 150 days and conditional marketing authorization can be granted on the basis of less comprehensive data than regular marketing authorization. Besides these mechanisms adaptive pathways is a developing EMA approach that seeks to balance timely access with the need to provide adequate evolving information on a drug's risk-benefit balance. PPB is also implementing a new mechanism to expedite the access to new innovative, orphan and high cost drugs called conditional reimbursement. However, the conditional reimbursement can be used for an especial reason only e.g. unmet medical need or considerable uncertainty regarding the assessment of the P&R status.

The mean market access delay of oral cancer drugs in Finland is 2,36 years (861 day). The European Medicines Agency absorbs almost half of this time in their process for assessing the safety, quality and efficacy of a new medicine (427 days). Almost same share of the delay is absorbed by the Pharmaceutical Pricing Board (379 days). While the Pharmaceutical company only takes about six percent of the delay in their process of applying a new drug to be included into the drug reimbursement system (55 days). See Figure 7. Additionally, it was discovered that the market access delay for medicines that are included into the reimbursement system more recently is greater than for the medicines that have been granted reimbursement earlier.

For drugs included between years 2006–2009 the mean delay is 1,98 years and for drugs included between years 2014–2016 the mean delay is 2,77 years which implies 34,3% longer market access delay for the newer oral cancer drugs.

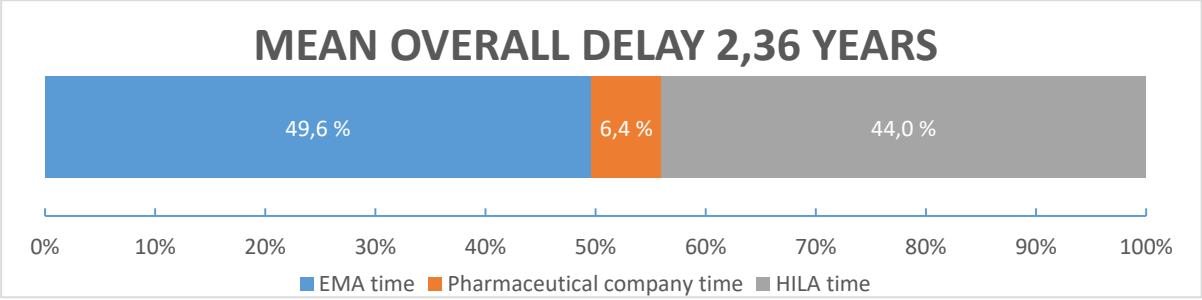

Figure 7: The mean market access delay with sequential phases.

This market access delay is regarded as excessively time consuming by patients and patient organization and viewed as the most common reason for patients not being able to access new medicines. However, it is considered necessary that new drugs are assessed before they are included into the drug reimbursement system. Only the operation of PPB should be further developed to allow the faster access to needed medicines. Especially for medicines that can be referred as highly important. This would benefit the patients and eventually the whole society.

Among the patients the accessibility to new cancer drugs is often compared to other European countries. Patients are active in searching information about new cancer treatments and this information is then actively shared between patients. Patients eagerness to search for information usually rises as they have suffered from a cancer for a while and they have adjusted to their situation. The willingness to acquire information is also affected by the patients' individual skills to search information. Because of this curiosity it has come evident to patients that all the new cancer drugs are not accessible in Finland. The access to these treatments unavailable through public health care system is sought through private cancer treatment or from abroad. If the patient has high unmet need for unreimbursed treatment they can be willing to sell their property or even take loan to cover the costs.

The path of new cancer drugs to market access in Finland is not evident to all patients. Nevertheless, patients share the same point of view that patient perspective should be more incorporated to the decision making about the P&R status of new cancer medicines. Despite the patient organizations possibility to submit their statement into the P&R decision making process public

discussion is seen more efficient way to influence the decision making since the contents of a drugs application is not available for the patient organization to explore.

Budgetary constraints were regarded as the main barrier for cancer drugs to be included into the drug reimbursement system among patients. However, the medicines share of the total cost in cancer treatment was seen still to be rather small by the patient organization personnel and compared to other major therapeutic areas the treatment of cancer is seen to be more affordable. Although it was acknowledged that the new drugs tend to be high priced price itself should not barrier the access since they can save human life which is considered as immeasurable value as noted by the patients. Among the patients the inability to access new medicines due to market access delay caused astonishment, bitterness and anger. It was also considered to divide patients into an unequal situation based on their wealth when only wealthy individuals can access the medicines without reimbursement. This is against the patient organizations principle that all the patients should be placed into an equal position.

The importance of patient groups and peer support was considered to be very high. Through peer support the patients realize that they are not alone with their condition and they can discuss about different aspect linked to the treatment and overcoming cancer. Patient groups were considered also as a relevant source of information about new drugs. Internet and media were considered as the secondary source for information. The main problem with the information gained by patients is that it can be one-sided. Patients might have a part from the information but they rarely do have the complete knowledge about a cancers disease that a doctor has. However, patient organization considers it as a good thing that the patients are enthusiast to search for information. The additional information often helps the patient to better perceive their own situation. The most important thing in acquiring information is that patients have the time to arrange it, ask questions about it and come back to it again after suggesting it in controllable pieces.

The knowledge gained about new medicines was seen to bring hope for the patients although they knew that at the moment they are inaccessible. However, this knowledge can also cause distrust for the ongoing cancer treatment. The general opinion of the patient towards new cancer medicines was favorable and great hopes and expectations are connected to new drugs. Most importantly they are seen to have greater possibility to stop the progression of the disease and milder side-effects. This increasing knowledge about different treatment options have moved patients' attitude towards more demanding and critical about their own treatment. Therefore, it

is increasingly important that the treating physician communicate the treatment thoroughly with a patient. Not including the patient into the decision making process about the treatment plan for the patient is viewed negatively since patient wish to have a certain degree of control over their own treatment. An important factor affecting the treatment and the satisfaction of the patient toward treatment is the patient-doctor relationship. Patients desire a continuing relationship with one treating physician which allows them to build trust between each other

The active discussion between patients have made it possible to compare the treatment of cancer between patients coming from different parts of Finland. On the account of this, patients have discovered that here are regional differences in the treatment of cancer. Patient organization personnel questioned whether we have same criteria in different parts of Finland in the introduction or administering of oral cancer therapies. It was noted that some hospitals can be more permissive to administer the unreimbursed cancer drugs to patients although the current situation is moving towards more stringent and consistent state. A further mean to balance the inconsistencies between different hospital districts can be offered by the upcoming Comprehensive Cancer Center Finland. Especially in the treatment of rarer cancer diseases. This body could also help in identifying the critical cancer medicines that should be included into the drug reimbursement system. Altogether, the patient organization regarded patients access to new cancer medicines as good in Finland and compared to many other European countries the situation is rather privileged although not optimal.

5 CONCLUSION AND DISCUSSION

5.1 Summary of the study

The main goal for this thesis was to answer into two research questions exploring the market access of new oral cancer medicines in Finland. The research question Q1 was: "How will new oral cancer drugs gain market access in Finland and how long is the duration of process for gaining market access?" Based on the previous literature search two major barriers were identified in the form of regulatory approval and national P&R decision maker (Martinalbo et al. 2016; Pauwels at al 2014; McCabe et al. 2009). In addition to these two other factor affecting the market access was found such as HTAs, economic evaluations, risk sharing agreements, national early access mechanisms and the price of the new cancer drugs.

An extensive literature review was conducted on the written materials found on the decision makers' websites in order to discover the path of new cancer medicines to Finnish market. In addition, the regulations that are the base of the operation of these two bodies was inspected and an in-depth interview was conducted with the director of the Pharmaceutical Pricing Board. For computing the market access delay, the EPAR of each medicine was inspected to acquire the needed dates for this process and the P&R application dates were requested from PPB.

EMA is responsible for granting marketing authorization to new cancer drugs in Europe. This is based on assessing the benefit of a medicinal product against its risks. If this benefit-risk paradigm is positive marketing authorization can be granted to new medicine. The timeframe for this process is regulated to be 277 days including only the active assessment time. For oral cancer medicines in this thesis the mean EMA assessment time was 427 days.

After the medicinal product has gained marketing authorization the marketing authorization holder can submit an application for the medicine to be included into the Finnish drug reimbursement system to PPB. The P&R decision is based on a comprehensive assessment on all aspects regulated in Finnish Health Insurance Act. Mainly the health benefit of a medicinal product is assessed against its costs and compared with other medicines used to treat the same therapeutic indication. The regulated timeframe for this decision making process is 180 days including only the active assessment time. The decision made will come into effect at the beginning of the second month after the decision is made. This time will be added to the assessment time in defining when the medicine is accessible in the markets. The mean time for oral cancer medicines in this thesis to be included into the drug reimbursement system was 379 days.

Apart from these two phases the market access in contingent upon the pharmaceutical company. The medicinal products won't be included into the Finnish drug reimbursement system unless the marketing authorization holder will apply this. The mean time for oral cancer medicines to be applied a P&R decision after gaining marketing authorization was 55 days. Combining these three phases gives the mean overall market access delay for new cancer medicines in Finland which was computed to be 861 days (2,36 years). Market access delay for newer oral cancer medicines was found to be longer than for older drugs.

The second part of this thesis constructed form the goal for answering the second research question Q2: "How cancer patients and patient organization views the market access of new oral cancer drugs in Finland?" Based on the previous literature it was expected that patient are eager to gain knowledge about new treatment options even if they are unavailable (Mileshkin et al. 2009; Kaser et al. 2010), the treatments are viewed differently depending on the stage of patient's disease (Goldman et al. 2010; Becker et al. 2007), the oncologists are the main source of information concerning new cancer drugs, there is a lack of understanding how new drugs will become accessible and that it is regarded unfair that all the treatment options are not reimbursed (Kaser et al. 2010).

In addition to the patient view patient organization personnel were added to the group of interest since at the beginning of this study it was not clear to what extent cancer patients in Finland acknowledge the accessibility to new cancer drugs and the existence of market access delay. Phenomenographic research approach was chosen for answering this research question. The research data comprised from four semi-structured in-depth interviews with cancer patients and three semi-structured in-depth interviews with patient organization personnel with close contacts to patients.

The results of the semi-structured interviews showed that patients and patient organizations opinion toward the market access is that is taking excessively long time and it should be expedited somehow. The P&R decision making process should be further developed to allow the faster access to new drugs although it is important that the drugs are assessed before they are included into the reimbursement system. It was regarded that not including the needed medicines into the reimbursement system will place patients in an unequal situation based on their wealth. For accessing the unreimbursed treatment options patients are willing to search their accessibility from private sector or from abroad and the willingness to cover the costs of these

costly drugs can be very high especially when a patient does not have any other treatment options.

Patients are eager to gain knowledge about new cancer drugs and they would like know about the newest treatment options although they could not be accessed. Patient share their knowledge in active discussion inside peer groups. The main problem with the information patients is that it might be only one-side. However, it is regarded as a good thing that patients are active in acquiring knowledge about their disease since it can help them to better adjust into their situation.

Apart from getting the best treatment for their condition patient-doctor relationship plays a major role in patient satisfaction towards their treatment. The regional differences raised concern among the participants especially the administration of oral cancer drugs but it was seen that in the future these differences will become less significant. Overall the accessibility of new cancer treatments was seen to be good in Finland but not optimal.

5.3 Key Findings

This study showed that the mean market access delay for oral cancer drugs in Finland was 2,36 years. This is close to the result 2,3 years that Russo et al. (2010) discovered in their research to be the time to patient access for cancer drugs in Italy although the calculation of this study did not include the sequential phase of further adding the time that is elapsed from the P&R decision date to the date when the drug in purchased for the first time. Besides the regional differences in the introduction of new cancer drugs and this study's concentration on oral entrants only this can imply that the delay of new cancer drugs has further prolonged in the market access of newer cancer medicines as it was already discovered in the results section. An increase of 34,3% was discovered for drugs receiving reimbursement between years 2014–2016 compared to drugs granted reimbursement between years 2006–2009. This is consisted with the study by Kanniainen et al. (2014 where they stated that older oral cancer has been included into the drug reimbursement system significantly faster than newer oral cancer drugs.

Considering only the P&R decision making time i.e. PPB time the mean delay was 379 days. Compared to the average 259 days in the study by Wilking et al. (2009) where they computed the reimbursement delay for cancer drugs included into the reimbursement system between years 2003–2006. This also implies a significant increase in the time used to make the P&R

decision. The prolongation of the P&R decision making time can be already seen when comparing the result of the study by Wilking et al. (2009) to the study by Kanniainen et al. (2014) where this delay was computed to be 397 days. However, it is not apparent from these figures how much of the time consist from active assessment time and what part can be considered as pharmaceutical company time i.e. time which the applicant uses to submit further clarifications requested by the decision maker. In order to extract the true delay that the national P&R decision maker causes it would be important to be able to identify the active assessment time only.

Considering only the drugs that received a positive P&R decision for the first application the mean delay was 279 days which is then much closer to the delay found out by Wilking et al. (2009). Contrary the drugs that were rejected for their first application the mean reimbursement delay was 720 days which is in a stark contrast with the previous figure. This can imply that there was considerable uncertainty related to the approval of these drugs or their price were considered as unreasonable the benefit their offered. Considering that they were after all included into the reimbursement system there were need for these drugs but maybe not at the initial price. Taking the applicant possibility to alter their application during the P&R decision making process they have themselves the possibility to affect this delay. Additionally, the time is contingent to the suggestion made in the initial P&R application i.e. how realistic they are.

The mean pharmaceutical time in the market access delay was 55 days which would imply at least in Finland and in the case of the chosen medicines the companies do not delay themselves the launch for the reason of potentially bigger global profits as stated by Russo et al. (2010). Although the pharmaceutical company time was significantly longer for some of the drugs. As a small country the market size of Finland can be considered as small in global comparison which would refer that companies does not consider this as a major factor in applying for P&R (Richter 2008).

To reduce the uncertainty of new cancer drugs (McCabe et al. 2009) Finland has also introduced a form of risk sharing agreement called conditional reimbursement. The reasons for implementing this reform is consistent with the previous literature. It is used to expedite the access to certain drugs and control the uncertainties related to new drugs (Pauwels et al. 2014). In addition to these on of the aim for this scheme is to control the costs of pharmaceuticals. Additional mechanisms to allow the faster access to new cancer medicines such as the Cancer Drug Fund in the UK and ATU scheme in France (Martinalbo et al. 2016; Pauwels et al. 2014) was not considered as a reasonable choice.

The growing importance of cost-effectiveness (Jönsson & Wilking 2007) is not apparent in the Finnish P&R decision making since the decision is based on a comprehensive assessment of also many other aspects and role of cost-effectiveness analysis cannot be precisely defined. However, the P&R decision making process in Finland is consistent with the previous literature that for justification of a higher price payers will require solid evidence from the additional benefit offered by the treatment compared to preferably the most appropriate comparator (Enzmann 2016).

As with the previous literature the price of new cancer drugs remains as an object for a debate (Howard et al. 2016) since the price of new cancer drugs raised concerns towards the sustainability of funding the new drugs even if they are proven to be efficacious. Although it was found out that the introduction of new cancer medicines can have deeper effects for society and patients e.g. the ability to return to normal life or meaningful incensement in the life expectancy. Which would further imply that there is need for broader recognition of the value of innovative drugs as stated in the study by Pauwels et al. (2016).

By patient organization it was regarded that the treatment of cancer is still affordable compared to other major therapeutic areas and that the share of costs accountable for drugs is rather small. This is consistent with the study by Jönsson et al (2016) where they found out that the cancer-specific share of the total Finnish health care costs was in 2014 only 4,4 % and the share of the cancer treatment costs in EU accountable for cancer drugs was 23% in 2014.

As already mentioned the mean market access delay for new oral cancer drugs is 861 days. This regarded as excessive by patients and patient organization and the consistent opinion was that this should be expedited. However, most of the criticism can be attributed towards the P&R decision making time since the availability of new drugs was often compared to other European countries meaning that the drugs have already gained marketing authorization from EMA. Although, there were also comparison to USA and as it was mentioned that the drugs are usually accessible there first which is then consistent with the study by Jönsson & Wilking (2007c) that showed the USA's lead in the uptake of cancer medicines.

The patients shared the same vision as Enzmann (2016) who stated that the patient perspective is currently highly valued in in their view that patient perspective should be more incorporated into the decision making. Although the patient organization can give their statement into the P&R decision making process the importance of this statement has still remained rather un-

known. Therefore, public discussion was regarded as a convenient tool to affect the P&R decision as already found out by Rosenberg-Yunger et al. (2012). The results of this study was consistent with the study by Kaser et al. (2010) that the understanding of the path of cancer drugs to market access is a bit lacking. However, it was also found out that the operation of the decision makers can be very closely monitored if it is known who makes the decisions.

Similarities to the previous literature (Kaser et al. 2010; Goldman et al. 2010) was found for the part that the demand for drugs used for treatment of cancer is high regardless of the costs and finances should not be barrier to access for treatments. If the new cancer drugs cannot be accessed through the public health care system, the possibilities to access is sought from private sector or from abroad. Furthermore, not granting reimbursement for new cancer medicines are seen to place the patients in an unequal situation based on their wealth. Further inequality can be attributable to the regional differences in administering oral cancer medicines. However, this is seen to be less significant along with the upcoming Comprehensive Cancer Center Finland.

In the previous literature the willingness to pay for treatment option was found to be contingent upon the individual's diagnosis (Kaser et al. 2010), stage of the disease and patients diagnosed with terminal cancer can be willing to spend their entire fortune to prolong their life even for few weeks (Becker et al. 2007). This was also seen in the results of this study where it was found out that patients are even willing to take a loan to cover the expenses of high cost drugs and the willingness to find and begin a new treatment option increased as the patient had experienced all the available cancer treatment from public sector with no effect on his condition.

The patient willingness to gain knowledge found out in this study is consistent with the previous study by Kaser et. al (2010) although the resource of information was primarily the patient groups and discussion with other patients contrary to the primary source of being oncologist. As with the previous researches by Mileshkin et al. (2009) and Kaser et al. (2010) patients want to know about all possible treatment options regardless of their accessibility. In addition to this it was found out that the general opinion towards new cancer medicines was favorable, willingness to search information is affected by the stage of the patient's disease and the main defect of this information is that it can be one-sided. Patients can be unable to take into consideration the entire picture of a cancer disease and usually they do not possess the comprehensive knowledge of a doctor.

5.3 Limitations of the study and future study

The purpose of this thesis was to uncover the path of new oral cancer medicines to market access, compute the market access delay for oral cancer medicines in Finland and explore the patient and patient organization view toward this process. The patient perspective was based on four interviews. Adding more interviews to the data could have produced more variable results or include more aspects of the behalf of patients. However, this would have required more time or coming up with additional plan to reach the patients which under these circumstances could have required unavailable resources most importantly time. In addition, a more experienced research interviewer could have been able to get more in-depth understandings from the participants. Since the interviews were held in Finnish the quotations are translated to English which can have a minor effect on their authenticity.

The director of Pharmaceutical Pricing Board was interviewed to get more in-depth understanding from its operation. In order to get more in-depth understanding from the operation of EMA an interview could have been conducted on their part also. The resulted market access delay does not separate the active assessment time and the time pharmaceutical company uses themselves in P&R decision making process. To get deeper understanding about what causes the delay this would have been important. However, for doing this the documents concerning the decision should have been acquired which could have been troublesome since they are not public for possibly containing trade secrets. In addition, the chosen medicines do not include medicines whose P&R application has been rejected, whose application is under assessment or medicines that are not applied for P&R decision in Finland. An important addition to the study would have been to explore rate of availability of new cancer medicines in Finland for revealing how many of the new cancer drugs are currently accessible in Finland.

This study did not consider the delay to higher rate of special reimbursement category when a drug is reimbursed 100% and only 4,5 € copayment is charged per purchase. Thus, it could be interesting to further compute the delay for the chosen drugs to be included into this reimbursement category since the annual limit on out-of-pocket cost (605,13 € in 2017) can be too high for some patients to pay in the first purchase of a basic reimbursed medicine. Which is usually the case because the 40 % basic reimbursement leaves a major part of a high cost drug's price to be paid and this annual limit of out-of-pocket costs is left to be covered by the patient in the first purchase of a medicine. After which patient is able to purchase the medicine for a 2,5 € copayment per purchase.

For future it would be interesting to study what kind of effects market access delay has on the welfare of Finland. The influence for the welfare of Finnish society could be measured as lost progression-free survival (PFS) time i.e. it could be explored by computing how many patients could have been treated with new and possibly more effective cancer drug during the market access delay and define the deadweight loss as lost PFS time during the market access delay. Furthermore, since many stakeholders are taking a part or are influenced by the market access of new cancer drugs this subject could be studied from other perspectives possibly leading to altering results. For future it could be also interesting to study what kind of effect the conditional reimbursement scheme has on market access delay of oral cancer medicines or on the rate of availability of these drugs.

The study contributes to the existing literature by updating what is the current market access delay of oral cancer drugs in Finland and uncovers the path of these medicines for accessing market in Finland. In addition, this study will add more to the existing literature about the patient perspective to the market access of new cancer drugs and attitudes towards new cancer medicines. This study can be used for referring the Finnish patients view on market access of cancer drugs or for referring their general opinion towards new cancer medicines. In addition, various stakeholders can use this study for updating the current situation on the market access delay of oral cancer medicines.

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Pelkonen, L. Director, Pharmaceutical Pricing Board PPB, Helsinki, 21 November 2016

Appendix 1. Interview frame for the PPB interview

Questions are translated from Finnish.

1. How would you describe the actual progression of the process for making the decision about price and reimbursement?
   "Following the EU-wide authorisation, there is large variability in terms of procedures, timelines, and criteria in the P&R decision-making processes in each individual country, which ultimately determine effective access to new cancer drugs within the national healthcare systems." – Martinalbo et al. 2016

2. What kind of challenges there is in making this decision?
   "Payers, however, face certain pressures when it comes to oncology treatment." – McCabe et al. 2009

3. What are the most important aspects influencing the decision about P&R?
   "Price and reimbursement (P&R) decisions at a national level, increasingly informed by HTA, are critical for coverage of high-priced cancer drugs by public healthcare systems, depending on their priorities, ability/willingness to pay." – Martinalbo et al. 2016

4. What factors influence on the timeline of the decision making process?
   "EMA centralized authorization is not immediately followed by the access in all European markets; in fact, national agencies subsequently regulate the final access in every domestic market." – Russo et al. 2010

5. What are the future aspects and object to improvement for the operation of Pharmaceutical Pricing Board?
   "Therefore, there are clearly opportunities for procedural improvements with regards to access to cancer drug therapies to potentially address some of the current imbalance." – Jönsson & Wilking 2007

6. How great is the importance of the patient organizations statement regarding the P&R decision?
   "Today all stakeholders see patients' participation in decision making as indispensable." – Enzmann 2016

Appendix 2. Interview frame for the patient interviews

Questions are translated from Finnish.

1. What is your opinion about new cancer medicines?
   "A key policy question is whether new anticancer drugs offer value, given their high cost. … We found that there were large increases in medical costs, but also large gains in life expectancy." – Howard et al. 2016

2. Where do you get information about the treatment option and cancer drugs?
   "The majority of women identified their oncologists as the primary source of information regarding treatment. Approximately half the participants reported utilizing the internet as an additional source." – Kaser et al. 2010

3. How do you view the situation that a new treatment option is unreachable because it is not included into Finnish drug reimbursement system?
   "Study participants felt it unfair that some treatments for life-threatening conditions were unsubsidized and therefore not accessible to all patients." – Kaser et al. 2010

4. As a patient how would consider this to affect your wellbeing?
   "In efforts to manage health care or budgetary costs, health care policy and decision makers may seek to delay or restrict access to new innovative drugs, with unintended consequences for patients." – Jönssön & Wilking 2007

5. What would be your desire for accessing new cancer drugs?
   "The goal was to increase all parties' understanding of their counterparts' roles in the development, licensure, and appraisal of new agents for cancer treatment, events guided by an understanding that cancer patients should have rapid and equitable access to life-prolonging treatments." – McCabe et al. 2009

6. Should the patient perspective be more incorporated to the price and reimbursement decision making?
   "Today all stakeholders see patients' participation in decision making as indispensable." – Enzmann 2016

Appendix 3. Email sent to the patients

Copy of the email sent to the patients explaining the aim of the thesis, the use of the interview material and anonymity. Translated from Finnish.

Hi!

Thank you for your reply! It would be great if you could participate in the interview. Below are shown further information about the study.

I study in the University of Eastern-Finland and my Master's thesis concentrates to explore the market access of oral cancer drugs in Finland. In the first part of the study the market access and market access delay of these medicines are examined. The market access for medicines includes the application for marketing authorization from Europan Medicines Agency EMA and application for reimbursement in Finland and duration of this process is defined as market access delay.

In the second part of the study the aim is to bring up the patient and patient organization view concerning the market access of oral cancer drugs in Finland. The main goal is to explore the thoughts, opinions and images of patients about the subject under study.

This is a once-only data collection for my Master's thesis. The interview is voluntary and is performed as a free-formed discussion over telephone under the predetermined themes. The phone call will be recorded.

The thigs uncovered in the interview will be reported in the thesis so that the participant or other persons brought up in the interview cannot be identified. The confidentiality of the interview will be secured by assuring that only the researcher himself process the recoding. The interview will be transcribed and the names of the participants, persons, organizations and areas will be transformed into pseudonyms in this process. When the transcription is complete the names and contact information of the participants will be deleted. After the thesis is complete the recordings and transcriptions will be deleted.

The interviews are planned to take place at the following dates and times:

THU 24.11. 16-20, FRI25.11. 16-20, TUE 29.11. 16-20, THU 1.12. 16-20, FRI 2.12. 16-20

Would you kindly inform me the suitable time for you to participate as soon as you can. The duration of the interview will be approximately 30-40 min. When you inform the date and time

I will call you then and we can perform the interview. You can suggest other date and time if the above times are not suitable for you.