

Background

Chronic Lymphocytic Leukemia (CLL) is the most common type of leukemia found in adults aged over 65 years, it accounts for about 25% of all leukemias and 70% of lymphoid leukemias. In Poland the median age at the time of diagnosis is 72 years. [1] According to epidemiological data 5-year survival rate for people with CLL in Eastern Europe (including Poland) is substantially lower compared to Northern Europe countries (54% vs. 78%). [2]

Although recent therapeutic options (in particular targeted therapy) have notably improved clinical outcomes for patients with contraindications against the use of B-cell receptor inhibitors (BCRi), CLL remains an incurable disease.

Over the last few years several innovative therapies were introduced for CLL treatment. This review will focus on targeted agents: ibrutinib, idelalisib, and venetoclax, currently approved by European Medicines Agency (EMA), and immunotherapies: rituximab, obinutuzumab and ofatumumab.

Objective

The aim of this analysis was to compare the barriers effective treatment of patients with CLL between Polish and British clinical practice.

Methods

Non-systematic search of PubMed, Web of Science and Embase databases was performed to identify relevant publications. Additionally, National Cancer Registry (NCR) database, Cancer Research UK registry, clinical practice recommendations, reimbursement lists of drugs in Poland and the UK, and the list of therapies approved by EMA were searched.

Results

Population

The Polish National Cancer Registry (NCR) reports data regarding lymphoid leukemia (ICD-10 code: C91), but published data are missing information specific to CLL (ICD-10 code: C91.1). In accordance with NCR, CLL accounts for 70% of lymphoid leukemias. [1] Epidemiological data in the UK were retrieved from Cancer Research UK website [3].

In Poland 1 989 newly-diagnosed patients with lymphoid leukemia were reported in 2014, including almost 1.4 thousand new cases of CLL [1] while in the same year in the UK there were 3 515 new cases of CLL [3] (Table 1).

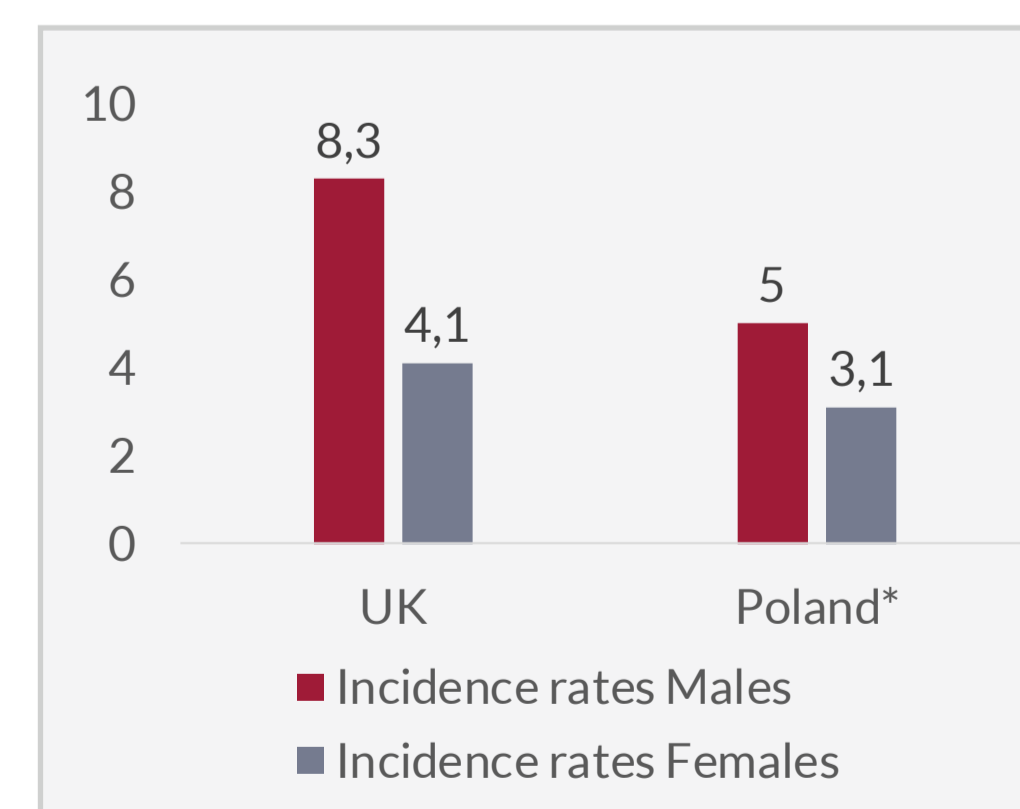
Table 1. Number of new cases of CLL in Poland and in the UK in 2014 [1, 3]

Parameter	UK	Poland
Number of total population in 2014 [4]	64 351 155	38 017 856
Number of new cases of CLL in 2014	3 515	1 392*

* 70% of new cases of lymphoid leukemias

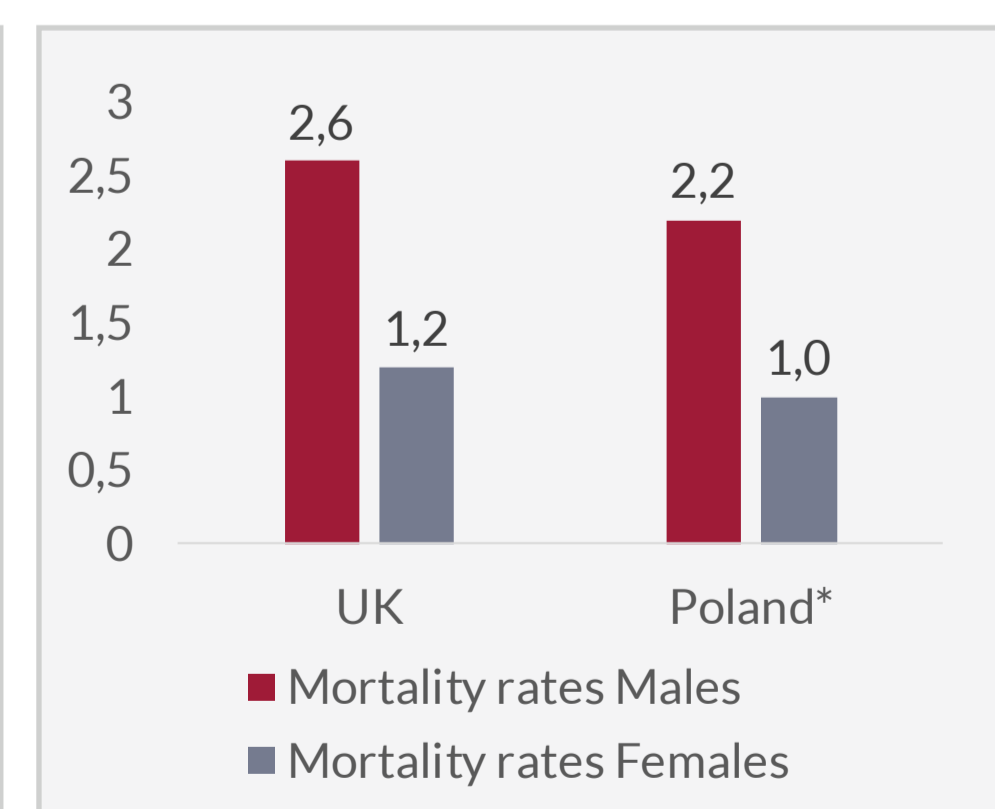
The age-standardized incidence and mortality rates for both males and females are significantly higher in the UK compared with Poland. According to NCR, the incidence rates of lymphoid leukemia in Poland in 2013 were 5.1 and 3.1 per 100 000 for males and females, respectively (Figure 1) and mortality rates in 2014 were 2.2 for males and 1.0 females per 100 000 inhabitants (Figure 2). [1] In the UK in 2014 the incidence rates of CLL were 8.3 and 4.1 per 100 000 for males and females, respectively (Figure 1) and mortality rates were 2.6 and 1.2 per 100 000 for males and females, respectively (Figure 2). [3]

Figure 1. Incidence rates in Poland and in the UK [1, 3]



* the incidence rates of lymphoid leukemia

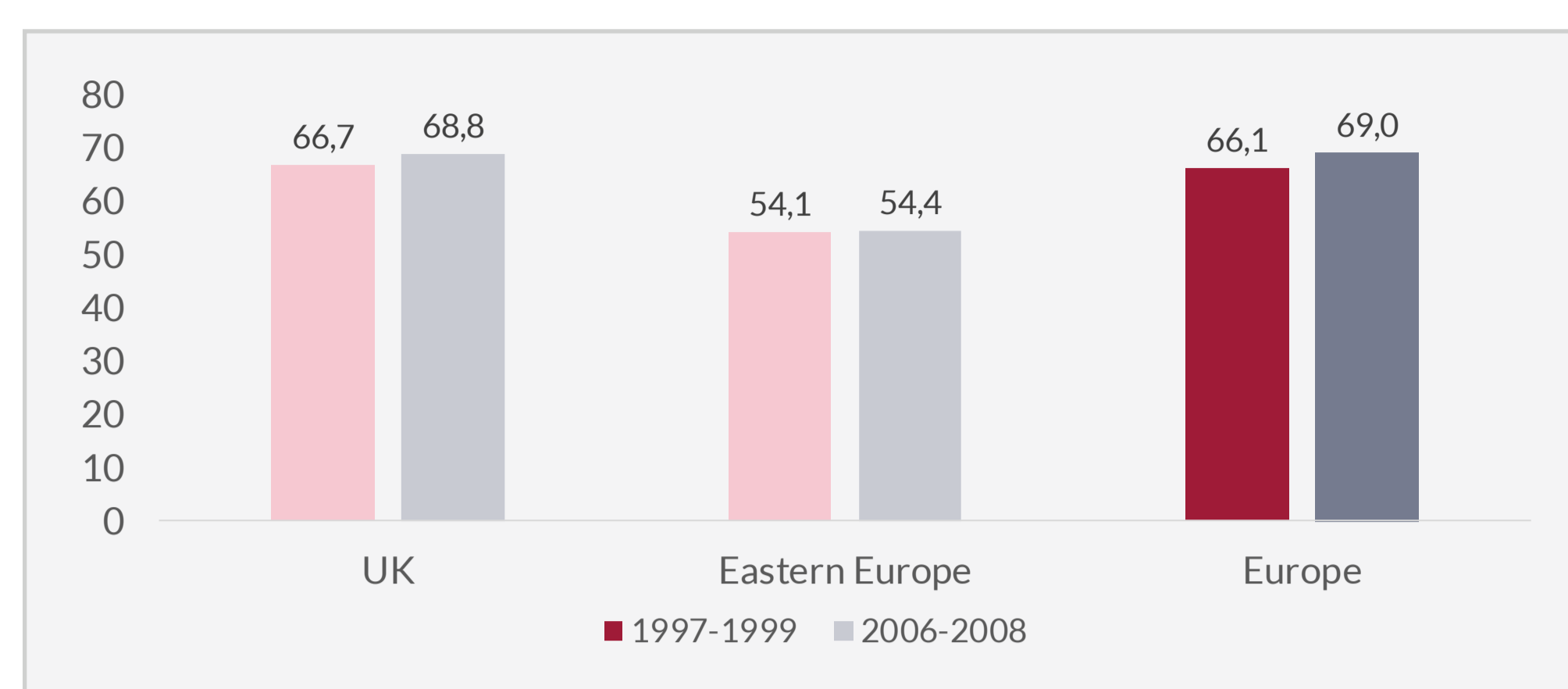
Figure 2. Mortality rates in Poland and in the UK [1, 3]



* the incidence rates of lymphoid leukemia

The Figure 3 presents 5-year survival rate for patients with CLL/SLL between 1997-1999 and between 2006-2008 based on EURO CARE-5 study conducted in Europe. 5-years survival rate for CLL patients in the UK was similar to the average survival in all Europe and was substantially higher compared to Eastern European countries (including Bulgaria, Estonia, Lithuania, Poland and Slovakia). [2]

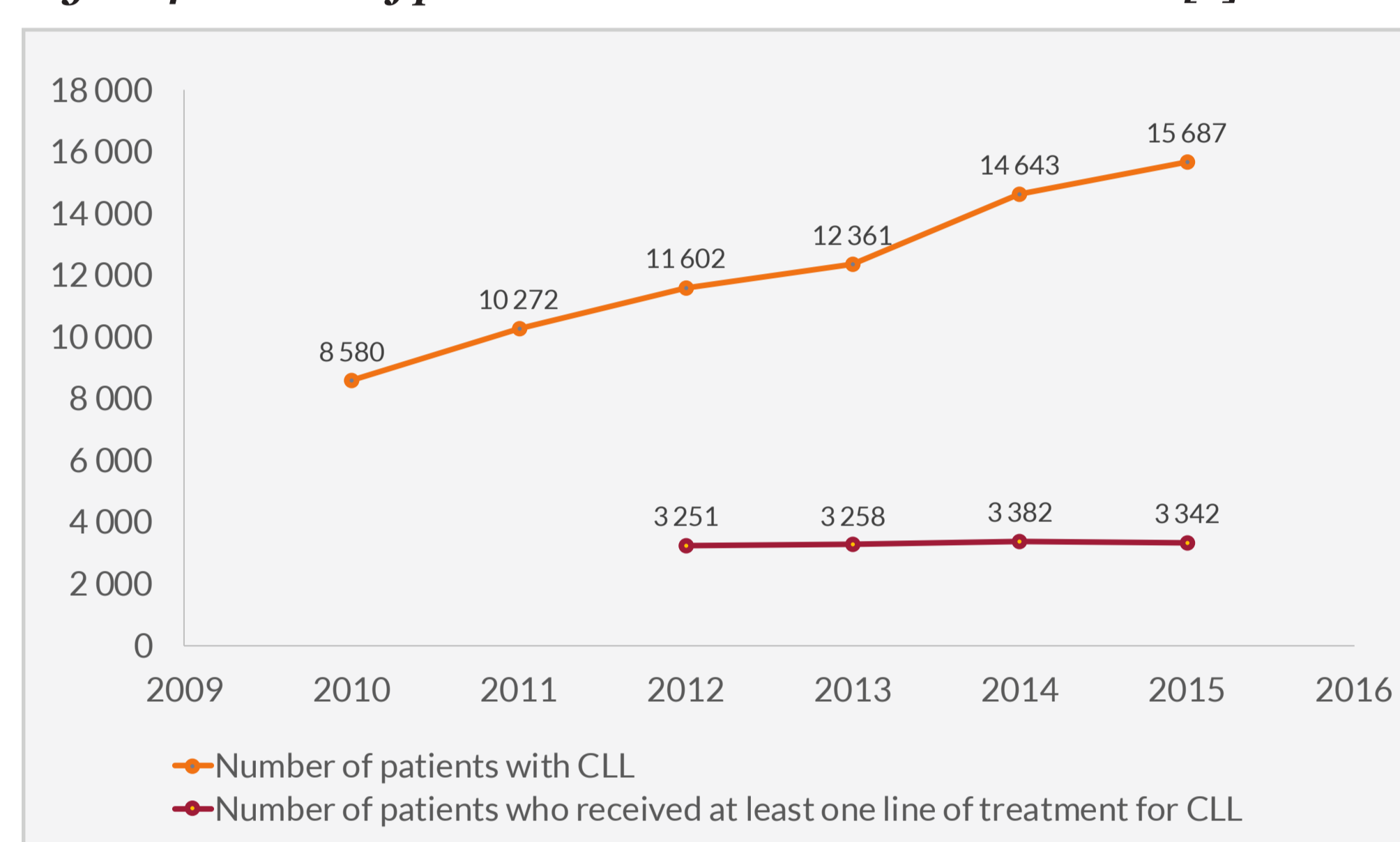
Figure 3. 5-year survival rate based on EURO CARE-5 study [4]



National Health Fund data

Nowadays, the biggest barriers to effective treatment for Polish patients with CLL and involved in therapy health-care professionals is the limited access to the newest, not yet reimbursed therapies. According to National Health Fund (NHF) data, the number of patients with principal or additional diagnosis of CLL increased from around 8.6 thousand in 2010 to 15.7 thousand in 2015. At the same time, approximately 3 300 patients received each year at least one line of treatment for CLL. [5] (Figure 4)

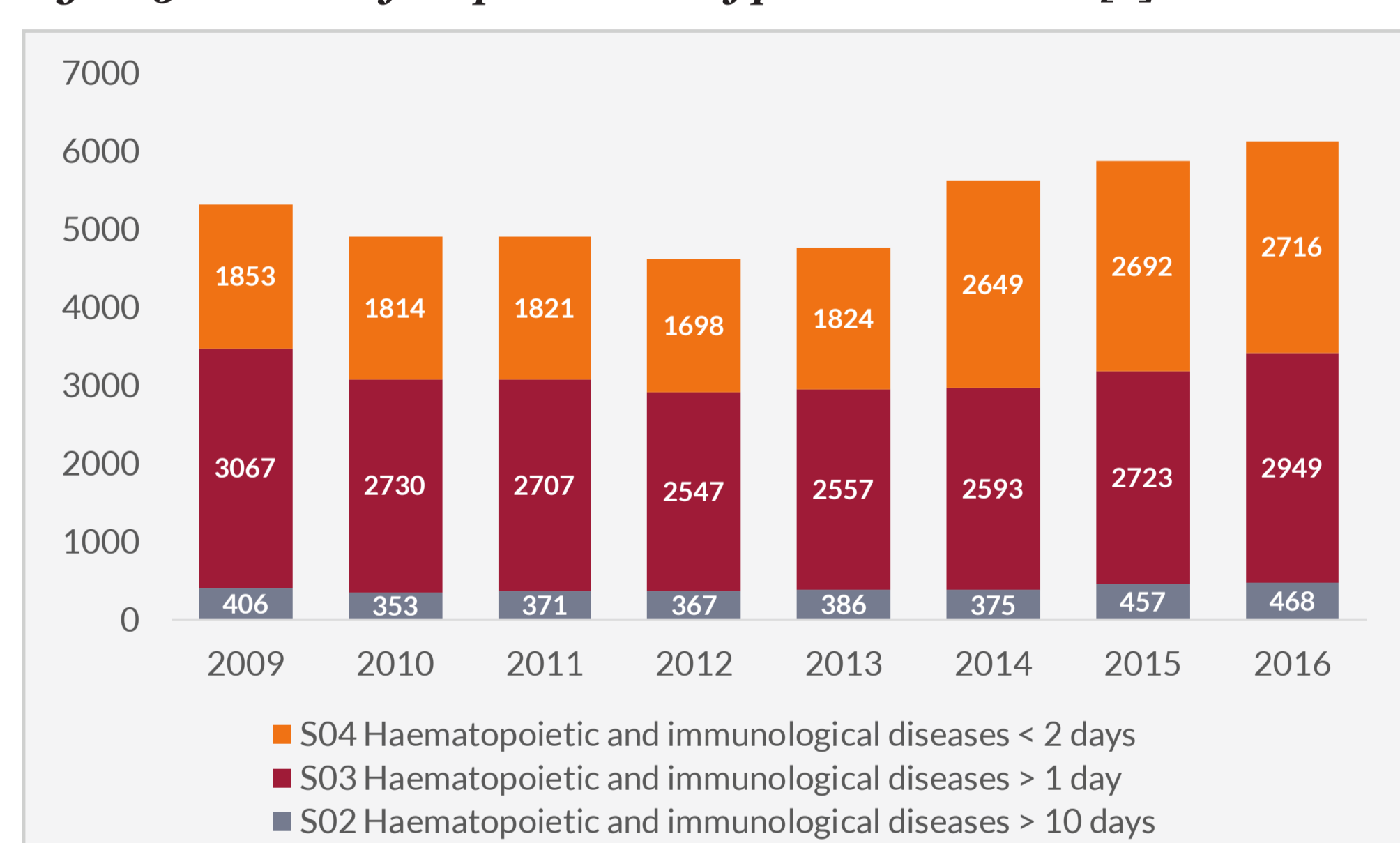
Figure 4. Number of patients with CLL in Poland - NHF data. [6]



Patients with CLL may require hospitalization, which costs in Poland are covered by NHF within JGP groups:

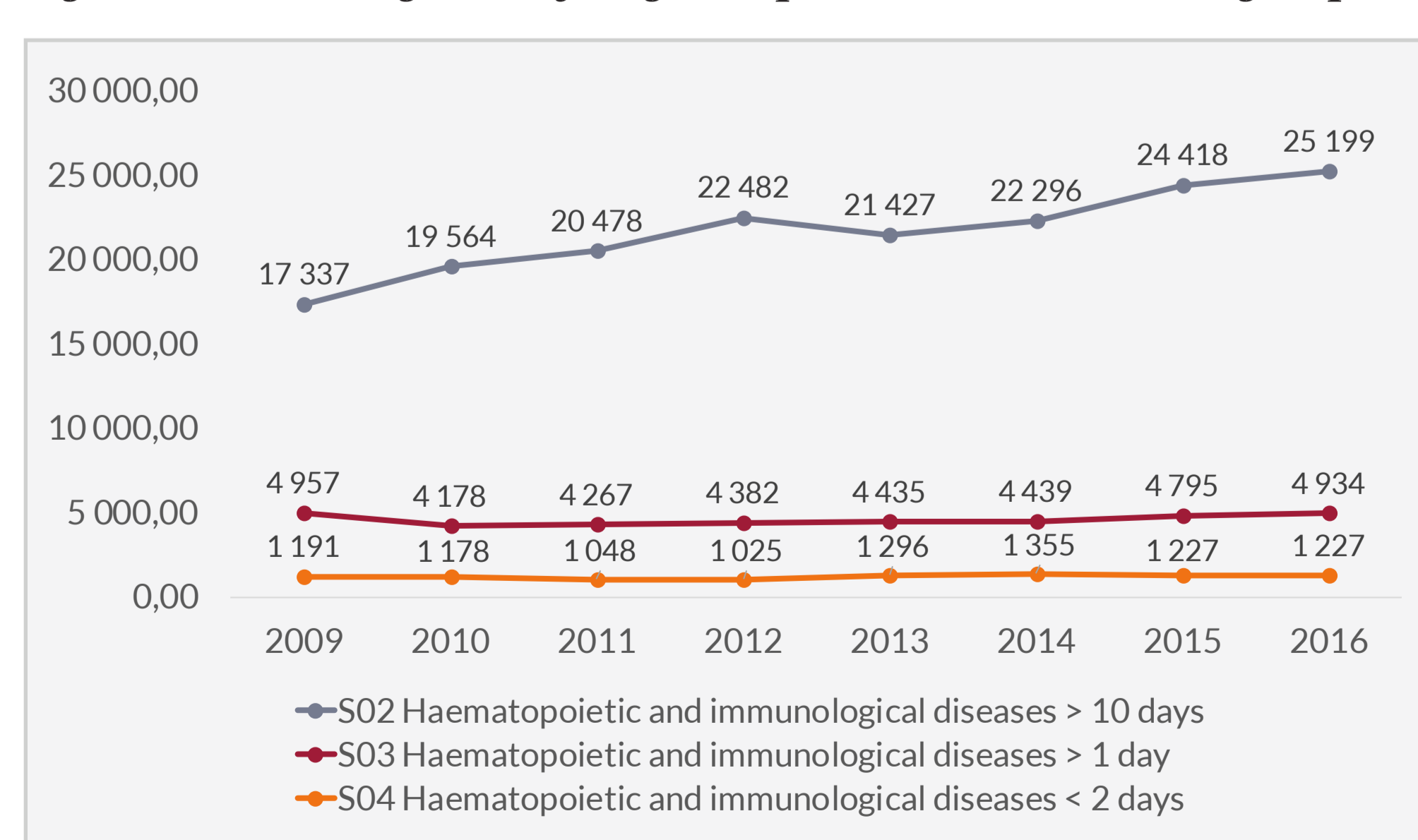
- S02 Haematopoietic and immunological diseases > 10 days,
- S03 Haematopoietic and immunological diseases > 1 day,
- S04 Haematopoietic and immunological diseases < 2 days.

Figure 5. Number of hospitalization of patients with CLL [6]



According to NHF data, the annual number of hospitalizations increased from 5 326 in 2009 to 6 133 in 2016. The highest number of hospitalizations were within group S03 Haematopoietic and immunological diseases > 1 day (Figure 5). The most cost-intensive group was S02 Haematopoietic and immunological diseases > 10 days – the average cost of single hospitalization increased from 17.3 thousand in 2009 to 25.2 thousand in 2016 (Figure 6). [6]

Figure 6. The average cost of single hospitalization within JGP groups [6]



Treatment of patients with CLL

Table 2 and Table 3 presents the summary about registration and reimbursement of substances used in treatment of patients with CLL in Poland and in the UK. In the UK the licensed innovative drugs: ibrutinib, idelalisib, obinutuzumab, ofatumumab, rituximab are reimbursed and venetoclax is recommended by NICE for use within the Cancer Drugs Fund. [7] For comparison, in Poland only three new drugs are reimbursed: ibrutinib (for treatment of relapsed or refractory CLL in patients with presence of 17p deletion or TP53 mutation), obinutuzumab and rituximab. The other two (idelalisib and ofatumumab) are not recommended by President of AOTMiT and venetoclax is under appraisal. Currently, idelalisib is not recommended for reimbursement by President of AOTMiT. President decision is based on the lack of evidence. In case of ofatumumab, the President of AOTMiT taking into account the Transparency Council Statement, available scientific evidences, results of pharmacoeconomic analyses, and national and international guidelines, stated that reimbursement of ofatumumab is unjustified. [8]

In Poland, there is a narrow group of patients requiring special treatment due to contraindications against the use of BCRi: ibrutinib, idelalisib (about 25 – 26% of patients). [9] It is important to ensure alternative, reimbursed therapeutic options for these patients. Venetoclax has a marketing authorization for the treatment of CLL in patients with the presence of 17p deletion or TP53 mutation who are unsuitable for or have failed a BCRi treatment or for the treatment of CLL in patients with the absence of 17p deletion or TP53 mutation who have failed both chemo-immunotherapy and a BCRi treatment.

Table 2. Therapeutic options for CLL in Poland and in the UK – targeted therapy and immunotherapy [9-14]

Substance	Information on registration		Date of registration in CLL indication	Reimbursement date in Poland	Reimbursement in UK
	PBL	del17p and/or mTP53			
Venetoclax	√*	√	05-12-2016	x (Before HTA appraisal)	x (Venetoclax is recommended for use within the Cancer Drugs Fund (NICE))
Ibrutinib	√	√	21-10-2014	01-09-2017	√
Idelalisib*	√	√	18-09-2014	x	√
Alemtuzumab**	Medicinal product no longer authorised for treatment of CLL			x***	x
Obinutuzumab*	√	x	23-07-2014	01-07-2016	√
Ofatumumab*	√	x	19-04-2010	x	√ (conditional approval)
Rituximab**	√	x	23-02-2009	01-05-2012	√

* The substance is a component of complex therapy; ** The substance used in monotherapy or as a component of complex therapy; a) Applies to patients without del17p or mTP53; *** Genzyme developed the Campath Distribution Program to ensure continued access to Campath (alemtuzumab) for appropriate patients. Campath is provided through the Campath Distribution Program free of charge

Table 3. Therapeutic options for CLL in Poland and in the UK – chemotherapy [9-14]

Substance	Reimbursement in Poland	Level of payment in Poland	Reimbursement in UK
Bendamustine**	√	free of charge	√ (in combination with ofatumumab or rituximab)
Chlorambucil**	√	free of charge	√
Cyclophosphamide*	√	free of charge / lump sum payment	√
Dexamethasone*	√	lump sum payment	√
Doxorubicin*	√	free of charge	√
Fludarabine*	√	free of charge	√
Cladribine*	√	free of charge	√
Methylprednisolone*	√	free of charge* / lump sum payment	√
Pentostatin*	x	NA	√
Prednisolone*	√	free of charge	√

* The substance is a component of complex therapy; ** The substance used in monotherapy or as a component of complex therapy; a) The drug used in CLL treatment could also be accounted within hospitalization.

Conclusions

Poland is lagging behind the UK in terms of availability of effective treatment options for patients with CLL. At present, the age-standardized incidence rates of CLL are lower in Poland compared to the UK, however the CLL is a disease of the people aged over 65 years and since the Polish population is aging, we expect that CLL incidence rate will increase in the coming years. Furthermore, 5-years survival rate for patients with CLL in Poland is substantially lower compared to the UK as well as to the average survival in whole of Europe, therefore, it is important for Polish patients gain to access to new therapies to ensure that they are receiving best available treatment.

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- Summary of Products Characteristics included in the tables. Access: February 2017.