Regulatory acceptability of clinical surrogate endpoints for accelerated (US) or conditional (EU) approval of haematological anti-cancer drugs in the light of the new CHMP anti-cancer guideline (CHMP/205/95 Rev. 4 and appendices) and the new FDA draft guidance on expedited programs for serious conditions

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1. INTRODUCTION

One of the main goals of regulatory science is to support the development of novel drugs in a way that leads to a fast access of the drug to the market within the constantly evolving regulatory and scientific framework. Such a fast access is, in particular, in the interest of patients suffering from life-threatening diseases for which few or no treatment options are currently available. In order to ensure fast access of patients to drugs promising relevant improvements of their condition, both Food and Drug Administration (FDA) and European Medicines Agency (EMA) have devised pathways that are intended to speed up the drug approval process or to allow for the approval of drugs based on limited data sets.

In the European Union (EU), these pathways include conditional approval and approval under exceptional circumstances. To a certain extent the development and approval of drugs with orphan designation status may also be considered a pathway to fast approval, since the requirements on the extent of clinical trials conducted for an orphan drug are less extensive compared to those of a non-orphan drug.

In the United States of America (US), accelerated approval, priority review and fast-track designation have been tools leading to fast drug developments and approvals for several years. Recently, FDA devised an additional regulatory path that may lead to fast approvals, namely breakthrough designation.

Haematological malignancies are amongst those diseases which still have a high unmet medical need. Many have a high incidence in elderly patients who present with a large number of comorbidities and may already be treated with a large number of comedications making them a rather frail and, due to the risk of drug-drug interactions, difficult to treat patient population.

This thesis focuses on chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma (MCL), a type of non-Hodgkin's lymphoma (NHL), because the first approvals of compounds with breakthrough designation occurred in these indications and chronic myelogenous leukaemia (CML), because it provides an illustrative example of how surrogate efficacy endpoints may evolve with the increase of scientific understanding of a disease and the development of new diagnostic tools. This thesis provides an overview of how EMA and FDA use the currently available tools for the fast approval of novel drugs. It provides:

- an overview on the recent changes in the regulatory guidelines on the development of drugs treating serious, life-threatening conditions,
- examples on how the guidelines have been interpreted during the last couple of years in both jurisdictions,
- and an outlook on current discussions which may lead to the development and acceptability of novel surrogate efficacy endpoints.

2. OVERVIEW OF HAEMATOLOGICAL MALIGNANCIES

Haematological malignancies are cancers of the blood, the bone marrow and/or the lymphatic system (including lymphatic organs, vessels, and white blood cells). Historically, they were categorized based on whether they occurred in the blood (leukaemias) or in the lymphatic system (lymphomas). Nowadays, they are categorized based on the blood cell lineage they are derived from into myeloid and

lymphoid malignancies. Myeloid malignancies are derived from the blood lineage that normally produces granulocytes, erythrocytes, thrombocytes, macrophages and mast cells. Lymphoid malignancies are derived from the blood cell lineage that normally produces B, T, natural killer (NK) and plasma cells (wikipedia haematological malignancies).

Over the years, various classification systems were established, which were more or less widely used. Examples are the Kiel classification and the Revised European-American Classification of Lymphoid Neoplasms (REAL classification) (Harris 1994), which ultimately resulted in the creation of the nowadays widely accepted World Health Organisation (WHO) classifications. The current versions were revised in 2008. (Vardiman 2009, Campo 2010)

The current 2008 WHO classification of myeloid neoplasms and acute leukemia recognizes eight major categories: myeloproliferative neoplasms, myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of platelet-derived growth factor receptor alpha (PDGFRα), PDGFRβ, or fibroblast growth factor receptor 1, myelodysplastic/myeloproliferative neoplasms, myelodysplastic syndrome (MDS), acute myeloid leukaemia and related neoplasms, acute leukaemias of ambiguous lineage, B lymphoblastic leukaemia/lymphoma and T lymphoblastic leukaemia/lymphoma (Vardiman 2009). The current 2008 WHO classification of tumours of hematopoietic and lymphoid tissues recognizes five major categories: mature B-cell neoplasms, mature T-cell and NK-cell neoplasms, Hodgkin lymphoma, histiocytic and dendritic cell neoplasms and post transplantation lymphoproliferative disorders. These classifications are based on a combination of morphology, immunophenotype, genetic, molecular, and clinical features as well as the diseases' cell lineage and its derivation from precursor or mature lymphoid cells (Campo 2011).

Due to the existence of these different classification systems, it is sometimes not easy to determine exactly for which indication drugs are approved, especially if they have been developed or approved before 2008. Reference to older classification systems is, therefore, made whenever relevant, e.g. when discussing drugs developed for the treatment of NHL. For the purpose of this thesis, drugs are, in general, classified by the indication identified in the respective current label regardless of whether a particular disease entity is recognized by the current classification system or not.

Incidences and mortality rates vary for the different types of haematological malignancies, the most common malignancies being non-Hodgkin's lymphomas (which encompass many types of disease including MCL), myeloma, acute myelogenous leukaemia and CML. Table 1 provides an overview of estimated new cases and estimated deaths for some haematological malignancies in the US in 2013 (American Society of Cancer, 2013).

Table 1 Estimated new cases of and deaths due to haematological malignancies in the US in 2013

Type of malignancy	Estimated new cases	Estimated deaths
Lymphoma, Hodgkin	9,290	1,180
Lymphoma, non-Hodgkin	69,740	19,020
Myeloma	22,350	10,710
ALL	10,710	1,430
AML	14,590	10,370
CLL	15,680	4,580
CML	5,920	610
Other leukaemias	6,350	6,730

Source: American Society of Cancer, Cancer Facts & Figures 2013
Abbreviations: ALL = acute lymphocytic leukaemia, AML = acute myelogenous leukaemia, CLL = chronic lymphocytic leukemia, CML = chronic myelogenous leukaemia

2.1 CHRONIC LYMPHOCYTIC LEUKAEMIA

CLL is a distinct subtype of mature B cell neoplasms which is characterized by a leukaemic component, i.e. tumour cells in the blood. According to the 2011 European Society for Medical Oncology (ESMO) CLL treatment guidelines, it is the most common leukaemia in the Western world with an incidence of 4.2 per 100,000 individuals per year (Altekruse 2010). It is a disease of older adults with a median onset at 72 years. Diagnosis of CLL is confirmed by detecting at least 5000 monoclonal B-cells for at least 3 months in peripheral blood by flow cytometry (Hallek 2008). According to the WHO classification, small lymphocytic leukaemia and CLL are the same entity. Median survival varies between 18 months and more than 1 year from time of diagnosis.

Two staging systems are being used that are of prognostic value: the Binet system and the Rai system (Binet 1981, Rai 1975). In addition, the following prognostic cytogenetic markers are known: 17p and 11q deletions (del17p and del11q) as well as p53 mutations (p53mut) confer the poorest prognosis, however, patients with del11q are successfully treated with chemoimmunotherapy, in particular fludarabine, cyclophosphamide and rituximab (FCR) (Hallek 2010). Other mutations are known, however, their prognostic value is not yet understood. Following treatment, minimal residual disease (MRD) is of prognostic value in so far as patients who are MRD negative after treatment have a longer duration of response and a longer survival. (Moreton 2005) However, currently MRD status does not have an impact on treatment decisions and is not generally assessed.

2.1.1 Current treatment options

Although both EU and US clinical treatment guidelines recommend a large number of medicinal products as single agents or as part of combination therapy, there are only few which are licensed for this indication as shown in Table 2.

Treatment options depend on the stage of the disease and the prognostic risk factors. If a patient presents with early stage disease, a “watch and wait” strategy is adopted until the disease becomes

more advanced. Treatment options for various stages and prognostic factors are summarized in Table 2, however, the only curative treatment is allogeneic stem cell transplantation (alloSCT). (Dreger 2007)

Over many decades, the therapy for CLL has mainly been chemotherapy, often as combination chemotherapy. Over the last 15 years immunochemotherapy, especially with the addition of rituximab, an anti-CD20 antibody, to the chemotherapy, has improved the response rates, progression-free survival (PFS) and overall survival significantly. However, CLL remains a largely incurable disease and the majority of patients will through the course of the disease require several lines of therapy.

Table 2 Current treatments options for CLL

Indication	**US approved**	**EU approved**	**NCCN recommended**	**ESMO recommended**
Leukaemia, unspecified, 1st line	N/A	Cyclosporine (also maintenance)	N/A	N/A
CLL, unspecified	Chlorambucil Cyclophosphamide Bendamustine hydrochloride Rituximab (CD20+)	chlorambucil Fludarabine phosphate (B-cell, sufficient bone marrow reserve) Vincristine Sulfate	N/A	N/A
CLL, 1st line	Obinutuzumab (CD20+, in combination with chlorambucil)	Bendamustine hydrochloride (when fludarabine combination chemotherapy is not appropriate) Fludarabine phosphate (advanced stage) Rituximab (CD20+)	**<70 years or nor significant comorbidities:** Chemo immunotherapy, (e.g., FCR, FR, PCR, benda +/- R, obi +/- clb) **>=70 years or comorbidities:** Obi + clb, R + clb, benda +/- R, cyclophosphamide + prednisone +/- R, R, F +/- R, cladribine, clb **Frail patients (not able to tolerate purine analogs):** Obi + clb, R + clb, pulse corticosteroids, clb **Del17p:** Alemtuzumab +/- R, FCR, FC, HDMP + R, obi + clb	**Fit, no del17p:** FCR Cladribine or pentostatin instead of fludarabine **Fit, del 17p:** Alemtuzumab or FA + alloSCT **Unfit:** PCR chlorambucil **Del17p or p53 mut:** alemtuzumab + alloSCT

Indication	US approved	EU approved	NCCN recommended	ESMO recommended
CLL, relapsed	Fludarabine phosphate (B-cell) Ofatumumab (refractory to fludarabine and alemtuzumab) ibrutinib	Ofatumumab (refractory to fludarabine and alemtuzumab) Rituximab (CD20+)	**<70 years or no significant comorbidities:** Ibrutinib, ofa, Lenalidomide +/- R, Alemtuzumab +/- R, HDMP + R, Chemo immunotherapy (e.g., FCR, PCR, benda +/- R, F +/- R, RCHOP, OFAR) **>=70 years:** Ibrutinib, ofa, lenalidomide +/- R, alemtuzumab +/- R, dose-dense R, chemo immunotherapy (e.g., reduced-dose FCR or PCR, benda +/- R, HDMP + R, R + clb) **Del17p:** Alemtuzumab +/- R, RCHOP, CFAR, HDMP +/- R, ibrutinib, lenalidomide +/- R, ofa, OFAR	Repeat first-line tx **Fit, no del17p:** Refractory to 1st line tx w/ an alkylating agent: FCR benda + R, **With or without del17p:** alemtuzumab or F+alemtuzumab -> alloSCT **Physically non-fit without del17p:** FCR, benda, A, Ofa, R + HD steroids **subsequent relapses:** HD ofa or R + HD steroids **del17p:** alemtuzumab-containing regimen

Sources: FDA website, EMA website, List of medicinal products approved in the EU by ATC code, NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas Version I.2014, ESMO Clinical Practice Guidelines CLL published in Annals of Oncology 22 (Supplement 6): vi50–vi54, 2011

Abbreviations: benda = bendamustine; CFAR = cyclophosphamide, fludarabine, alemtuzumab, rituximab; clb = chlorambucil; FA = fludarabine, alemtuzumab; FCR = fludarabine, cyclophosphamide, rituximab; FR =fludarabine, rituximab; R = rituximab; HD = high-dose; HDMP = high-dose methyl prednisone; obi = obinutuzumab; ofa = ofatumumab; OFAR = oxaliplatin, fludarabine, cytarabine, rituximab; PCR = pentostatin, cyclophosphamide, rituximab; RCHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

Both FDA and EMA acknowledge that many compounds are commonly used for the treatment of first line CLL – either as mono- or combination therapy – and that not all of them are necessarily approved in this indication. This is illustrated by the medical review of obinutuzumab in 2013, where the FDA considered the following compounds to be FDA-approved for the treatment of CLL: chlorambucil (line not specified), cyclophosphamide (line not specified), fludarabine (after 1st line failure of alkylating agent), alemtuzumab (line not specified), bendamustine (unspecified), ofatumumab (refractory to fludarabine and alemtuzumab) and rituximab (1st line, CD20+, in combination with fludarabine and cyclophosphamide). In addition, the FDA acknowledged that many more compounds and combinations are currently commonly used in the clinic, albeit not approved, for treatment of first line CLL in the US. The list of mono- and combination therapy options listed in the medical review of obinutuzumab is very similar to the current recommendations of the National Comprehensive Cancer Network (NCCN) treatment guidelines. It is, therefore, assumed that they reflect the recommendations of these guidelines at the time of review of the obinutuzumab biologics license application (BLA). (Obinutuzumab FDA Medical Review 2013)

Similarly, in 2009 the European public assessment report (EPAR) of the rituximab variation EMEA/H/C/165/II/0060 for the inclusion of CLL in the summary of product characteristics (SmPC) summarizes: "There is no universally accepted standard treatment for previously untreated patients with CLL. Single alkylating agents (chlorambucil, cyclophosphamide) are widely established; single purine-analogues such as fludarabine or cladribine may also be used. Despite initial response with single agent therapies, most patients progress and require further therapy within 1-2 years after single agent therapy. Based on synergistic activity between purine analogues, alkylating agents and monoclonal antibodies, new active combination therapies for CLL were introduced over the last years." And although by 2010 both rituximab and alemtuzumab were approved in the EU for the treatment of CLL, the 2010 EPAR of ofatumumab pointed out that nearly all patients with CLL relapse, even if they responded initially. It further acknowledged limited response to therapy in patients with del17p and del11q and indicated that double-refractory patients (to both fludarabine and alemtuzumab) were a patient population with unmet medical need, which subsequently was alleviated to a certain extent by the approval of ofatumumab (for double-refractory patients).

2.2 CHRONIC MYELOGENOUS LEUKAEMIA

CML belongs to the group of so-called myeloproliferative disorders. The majority of CML patients (95%) are positive for the Philadelphia chromosome (Ph+), the cytogenetic manifestation of the bcr-abl fusion kinase, which is causing CML. (Kurzrock 2003, Goldman 2003, Deininger 2000) The median age of onset for Ph+ CML is 67 years. (Lee 1998) Prior to the availability of bcr-abl inhibitors, such as imatinib mesylate, the median survival used to be 4 to 6 years. Median survival is expected to nearly reach normal life expectancy for most patients, although currently there are no data available corroborating this. (National Cancer Institute [NCI] PDQ® on CML 2013)

CML progresses from the so-called chronic phase (CP) to the accelerated phase (AP) or the blast phase (BP). The main difference of these phases consists in the percentage of blasts present either in the peripheral blood or in the bone marrow, which increases from less than 10% blasts and promyelocytes in the chronic phase, to 10% to 19% blasts in the accelerated phase and, finally, to 20% or more blasts. (Cortes 2006) The phase determines the treatment regimen.

Response to treatment is monitored by assessing the molecular response at regular intervals, i.e. by measuring the number of bcr-abl fusion genes present in peripheral blood using quantitative polymerase chain reaction (qPCR). The criteria of this response are outlined in the Committee of Human Medicinal Products (CHMP) Anticancer guideline (see Section 3.1.3.4.1).

2.2.1 Current treatment options

Since tyrosine kinase inhibitors (TKIs) targeting the bcr-abl fusion protein have become available, they are the mainstay of CML treatment, regardless of the disease stage. Patients who are intolerant or develop resistance to a certain TKI usually get switched to another for further treatment. And an increasingly smaller patient population undergoes alloSCT, mainly in case of blast phase CML. Table 3 summarizes the current treatment options for CML.

Table 3 Current treatment options for CML

Indication	**US approved**	**EU approved**	**NCCN recommended**	**ESMO recommended**
CML, unspecified	Cytarabine (blast phase) Recombinant Interferon Alfa-2b Cyclophosphamide	Recombinant Interferon Alfa-2b Vincristine Sulfate (blast crisis)	N/A	N/A
CML, palliative	Mechlorethamine Busulfan	Busulfan (CP)	N/A	N/A
CP CML, 1st line	Dasatinib Imatinib mesylate (adult and paediatric) Nilotinib	Dasatinib Imatinib mesylate (adult and paediatric, ineligible for SCT) Nilotinib	Dasatinib Imatinib mesylate Nilotinib HSCT	Dasatinib Imatinib mesylate Nilotinib
CP CML, 2nd line	Bosutinib Dasatinib (TKI resistant/intolerant) Imatinib mesylate (after failure of interferon-alpha therapy) Nilotinib (prior tx resistant/intolerant) Ponatinib hydrochloride (TKI resistant/intolerant)	Dasatinib (TKI resistant/intolerant) Imatinib mesylate (after failure of interferon-alpha therapy) Ponatinib hydrochloride (TKI resistant/intolerant, imatinib not appropriate or T315I)	assessment of response at 3- and 6-months follow-up same or alternate TKI: Bosutinib Dasatinib Imatinib mesylate Nilotinib HSCT	same or alternate TKI: Dasatinib Nilotinib Imatinib mesylate alloSCT
CP CML, ≥3rd line	Omacetaxine mepesuccinate	Bosutinib (when imatinib, nilotinib and dasatinib are not appropriate)	assessment of response at 12-months follow-up same or alternate TKI: Bosutinib Omacetaxine mepesuccinate Dasatinib Imatinib Nilotinib HSCT	alloSCT
AP CML, 1st line	N/A	N/A	N/A	N/A

Indication	**US approved**	**EU approved**	**NCCN recommended**	**ESMO recommended**
AP CML, 2nd line	Bosutinib Dasatinib (TKI resistant/intolerant) Imatinib mesylate (after failure of interferon-alpha therapy) Nilotinib (prior tx resistant/intolerant) Ponatinib hydrochloride (TKI resistant/intolerant)	Dasatinib (TKI resistant/intolerant) Imatinib mesylate (after failure of interferon-alpha therapy) Ponatinib hydrochloride (TKI resistant/intolerant, imatinib not appropriate or T315I)	Bosutinib Dasatinib Imatinib mesylate Nilotinib Omacetaxine mepesuccinate HSCT	TKI naïve: Dasatinib Imatinib mesylate Nilotinib alloSCT TKI pretreated: switch to another TKI chemotherapy alloSCT
AP CML, ≥3rd line	Omacetaxine mepesuccinate	Bosutinib (when imatinib, nilotinib and dasatinib are not appropriate)	Clinical trial	N/A
BP CML, 1st line	Cytarabine	Cytarabine	N/A	N/A
BP CML, 2nd line	Ponatinib hydrochloride (TKI resistant/intolerant) Bosutinib Dasatinib (TKI resistant/intolerant) Imatinib mesylate (after failure of interferon-alpha therapy)	Ponatinib hydrochloride (TKI resistant/intolerant, imatinib not appropriate or T315I) Dasatinib (TKI resistant/intolerant) Imatinib mesylate (after failure of interferon-alpha therapy)	ALL- or AML-type induction therapy + TKI (choice based on mutations) followed by HSCT or TKI followed by HSCT	TKI naïve: Dasatinib Imatinib mesylate Nilotinib alloSCT TKI pretreated: switch to another TKI chemotherapy alloSCT
BP CML, ≥3rd line	N/A	Bosutinib (when imatinib, nilotinib and dasatinib are not appropriate)	Clinical trial	N/A

Sources: FDA website, EMA website, List of medicinal products approved in the EU by ATC code, NCCN Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia, Version 3.2014 , ESMO Clinical Practice Guidelines CML published in Annals of Oncology 23 (Supplement 7): vii72–vii77, 2012

Abbreviations: alloSCT = allogeneic haematopoetic stem cell transplantation; AP = accelerated phase; BP = blast phase; CP = chronic phase; ESMO = European Society of Medical Oncology; EU = European Union; HSCT = haematopoetic stem cell transplantation; N/A = not applicable; NCCN = National Comprehensive Cancer Network; T315I = mutation of amino acid 315 changing threonine to isoleucine; TKI = tyrosine kinase inhibitor; US = United States of America

The current NCCN treatment guidelines also provide guidance on how to select TKIs based on resistance to prior TKI therapy as illustrated below:

1st line treatment	**2nd line treatment**	**3rd line treatment**	**4th line treatment**
Imatinib – >	Dasatinib or – >	Nilotinib or bosutinib – >	Clinical trial or
	Nilotinib or – >	Dasatinib or bosutinib – >	Ponatinib or
	Bosutinib – >	dasatinib or nilotinib – >	HSCT or
			Omacetaxine
Dasatinib – >	Nilotinib or – >		
	Bosutinib – >	Clinical trial or	
		Ponatinib or	
Nilotinib – >	Dasatinib or – >	HSCT or	
	Bosutinib – >	Omacetaxine	

In contrast to CLL, only approved compounds were considered "available therapy" by FDA at the time of omacetaxine New Drug Application (NDA) approval in 2012 as summarized in Table 4. At this point of time, imatinib, nilotinib and dasatinib were considered standard of care in 1st line CML according to the NCCN Guidelines. Nothing was approved for the treatment of AP or CP CML after failure of two TKIs. (omacetaxine mepesuccinate FDA Medical Review 2012)

Table 4 Available therapy for CML in the US at time of omacetaxine approval (2012)

CML Phase	1st line	resistant/intolerant after imatinib	after failure of IFN
Chronic phase	Interferon 2-alpha Imatinib Nilotinib (AA) Dasatinib (AA)	Nilotinib Dasatinib Bosutinib	Imatinib
Accelerated phase	N/A	Nilotinib Dasatinib Bosutinib	Imatinib
Blast phase	Cytarabine	Dasatinib Bosutinib	Imatinib

Source: Omacetaxine mepesuccinate FDA Medical Review 2012

Abbreviations: AA = accelerated approval; CML = chronic myelogenous leukaemia; IFN = interferon 2-alpha; N/A = not applicable

In the 2012 FDA Medical Review of the ponatinib NDA, which was submitted approximately 3 months after the omacetaxine NDA, the FDA also indicated that mechlorethamine, busulfan and cyclosphosphamide were approved for the treatment of CML, however, not commonly used anymore. In addition, the recently approved omacetaxine mepesuccinate was added to the list of "available" therapies for CML treatment after failures of two TKIs. (Ponatinib FDA Medical Review 2012)

Similar to the FDA, in 2013 the CHMP considered imatinib, dasatinib and nilotinib to be available therapy for the treatment of CML at the time of approval of ponatinib. However, they pointed out that, at that point of time, limited treatment options existed for patients after failure or intolerance of 2nd line treatment with dasatinib or nilotinib and that patients with the T315I mutation were resistant to all TKIs available at the time. (Ponatinib EPAR 2013)

2.3 MANTLE CELL LYMPHOMA

MCL, a type of NHL, is a rare mature B-cell lymphoma that is characterized by cyclin D1 expression and a t(11;14) translocation. (Swerdlow 2008) A cyclin D1 negative variant has been described, however, it is quite rare. (Fu 2005) Median age of onset is 60 to 65 years. The disease is not curable. (NCI PDQ NHL 2013)

The natural course of the disease is variable, however, proliferative activity of the tumour measured, e.g., as the mitotic Ki-67 index, has been identified as a prognostic factor indicating aggressive disease. (Jares 2008) However, no consistent histopathological scoring system is available yet. (De Jong 2007) Most MCL patients suffer from the aggressive form of MCL and have a median survival of 3 to 5 years. (Herrmann 2009)

A prognostic index, the MCL International Prognostic Index, has been established. (Hoster 2008) This index is based on age, performance status, lactate dehydrogenase concentrations and leukocyte count. It is of prognostic value with regard to median OS. Prognostic value has also been shown for MRD negative disease with regard to long-term survival, however, consensus criteria for its assessment have not yet been established. (Pott 2010; Dreyling 2013)

2.3.1 Current treatment options

Treatment of young (<65 years) and fit patients consists of induction chemotherapy, which frequently is followed by autologous stem cell transplantation (autoSCT). Elderly, unfit patients are usually treated with less aggressive combination chemotherapy. (Dreyling 2013) A plethora of drug combinations are recommended in the 2013 ESMO and, in particular, in the 2014 NCCN treatment guidelines as shown in Table 5, however, only few compounds are actually approved for this indication.

Table 5 Current treatment options for MCL

Indication	US approved	EU approved	NCCN recommended	ESMO recommended
MCL, induction	N/A	N/A	**Aggressive therapy:** R + methotrexate + aug. CHOP, etoposide + cytarabine + R, carmustine + etoposide + cyclophosphamide followed by autoSCT Hyper CVAD + R NORDIC regimen Alternating RCHOP/RICE **Less aggressive therapy:** Benda + R R-CHOP followed by consolidation with rituximab Cladribine + R Modified R-hyper CVAD	**Elderly, frail:** mild chemotherapy (e.g., clb + R) **Elderly, fit:** RCHOP FCR **Younger:** R-containing induction chemotherapy (e.g., R-CHOP) or HD-cytarabine-contain regimen followed by autoSCT
MCL, maintenance	N/A	N/A	Rituximab	**Elderly, frail:** rituximab
MCL, 2nd line	Bortezomib Ibrutinib	Temsirolimus (R/R)	Benda +/- R, bortezomib +/- R, cladribine + R, FC +/- R, FCMR, FMR, ibrutinib, lenalidomide +/- R, PCR, PEPC +/- R **Consolidation:** alloSCT	Temsirolimus Bortezomib Lenalidomide
MCL, 3rd line	Lenalidomide (after bortezomib failure)	N/A	N/A	N/A

Sources: FDA website, EMA website, List of medicinal products approved in the EU by ATC code, NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas Version I.2014 , ESMO Consensus Conferences: guidelines on malignant lymphoma published in Annals of Oncology 00: 1–21, 2013

Abbreviations: alloSCT = allogeneic stem cell transplantation; autoSCT = autologous stem cell transplantation; aug. = augmented; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CVAD = cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high-dose methotrexate and cytarabine; ESMO = European Society of Medical Oncology; FC = fludarabine, cyclophosphamide; FCMR = fludarabine, cyclophosphamide, mitoxantrone, rituximab; FMR = fludarabine, mitoxantrone, rituximab; HD = high-dose; N/A = not applicable; NCCN = National Comprehensive Cancer Network; NORDIC regimen = dose-intensified induction immunotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone (maxi-CHOP) alternating with rituximab + high-dose cytarabine; PCR= pentostatin, cyclophosphamide, rituximab; PEPC = prednisone, etoposide, procarbazine, cyclophosphamide; R = rituximab; R/R = relapsed/refractory; RCHOP/RICE = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone/ rituximab, ifosfamide, carboplatin, etoposide

In the 2013 FDA Medical Review of the ibrutinib NDA for MCL, the FDA acknowledged that no one generally accepted and approved 1st line treatment exists for MCL. However, the review takes note of the NCCN recommendations. The only approved compounds at the time of the ibrutinib NDA review, bortezomib and lenalidomide, were approved for 2nd and 3rd line treatment, respectively.

In the EU, no treatment was approved for MCL at the time the variation of temsirolimus received approval for MCL in 2009. Although the CHMP recognized that treatment guidelines recommend various chemotherapy regimens, it stated clearly that an unmet medical need existed for this patient population. (Temsirolimus variation EPAR, EMEA/H/C/000799/II/0001, 2009)

3. REGULATORY REQUIREMENTS FOR EFFICACY ENDPOINTS FOR APPROVAL

3.1 EUROPEAN UNION

3.1.1 Regulatory pathways leading to approval

Article 6 of Directive 2001/83/EC, as amended, states that "no medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued". As laid out in Article 26 of Directive 2001/83/EC, "the marketing authorisation shall be refused if […] the risk-benefit balance is not considered to be favourable; or […] its therapeutic efficacy is insufficiently substantiated by the applicant […]". The risk-benefit balance is defined in Article 1 (28 and 28a) of this directive as "an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks […]", which include "any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health".

In line with the directive, Article 3(1) of the European Commission Regulation (EC) 726/2004, as amended, which is governing the centralized procedure, lays out that medicinal products for human use require a marketing authorisation before they may be placed on the market, if they are covered by the Annex of this regulation. This Annex lists, amongst others, medicinal products that are intended for the treatment of cancer. As a consequence, all anticancer drugs fall within the scope of the centralized procedure. Marketing authorisations, however, "shall be refused if, […] the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product" as stated in (EC) 726/2004 Article 12.1. No details are provided on how to demonstrate efficacy in this regulation, though. Guidance may instead be found in disease-specific guidelines, such as the CHMP Anticancer guideline (see Section 3.1.3).

In addition to a "traditional" approval according to Regulation (EC) 726/2004, there also exist possibilities for the CHMP to grant a so-called conditional approval or an approval under exceptional circumstances. The requirements for these approvals are summarized in Section 3.1.1.1 and in Section 3.1.1.2.

3.1.1.1 Conditional approval

In the EU, it is possible to grant a conditional approval as laid out in Article 14(7) of Regulation (EC) 726/2004 and Regulation (EC) 507/2006. Such an approval is valid for one year, renewable and subject to specific obligations. Medicinal products according to Article 3(1) and (2) of Regulation (EC) 726/2004 may be eligible for this procedure, if they are:

- intended for the treatment, prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;

- to be used in emergency situations, World Health Organisation or by the Community in the framework of Decision No 2119/98/EC;

- orphan medicinal products.

As specified in Article 3 of Regulation (EC) 507/2006, a conditional marketing authorisation may be granted although clinical safety and efficacy data may be "less complete", as long as the benefit-risk evaluation is positive. Additional prerequisites for a conditional marketing authorisation are that it is likely that comprehensive data can be provided, that unmet medical needs will be fulfilled and that there is a benefit to public health. In this context "unmet medical need" is defined as the lack of a satisfactory method of diagnosis, prevention or treatment for a specific disease. At the time of approval, the CHMP specifies the conditions which will need to be fulfilled by the sponsor in order to keep the marketing authorisation. As mentioned above, the fulfilment of these obligations are reviewed annually. Once all obligations have been fulfilled, it can become a "traditional" marketing authorisation.

3.1.1.2 Approval under exceptional circumstances

In certain cases, a marketing authorisation may be granted under exceptional circumstances. Such an authorisation is reviewed annually to reassess the risk-benefit balance. The legal basis is provided by Article 14(8) Regulation (EC) No 726/2004 and Directive 2001/83/EC Annex 1. The latter provides the grounds based on which such an approval may be granted, namely: comprehensive efficacy and safety data cannot be generated because the indication for which the product is being developed is so rare it cannot reasonably be expected that comprehensive evidence will be generated or, in the present state of scientific knowledge, comprehensive information cannot be provided, or it would be considered unethical to collect such data. These grounds need to be justified based on current epidemiological and scientific data. Nevertheless, specific obligations may be connected with such an approval, such as, the completion of certain clinical trials within a certain time period, the requirement to distribute the medicinal product by medical prescription only and the requirement to highlight the limitation of the available data in the SmPC and patient information leaflet (PIL). In general, approval under exceptional circumstances is not granted if conditional approval is more appropriate. Since it is not expected that comprehensive efficacy and safety data can be generated, a marketing authorisation that was granted under exceptional circumstances cannot be transformed into a "regular" marketing authorisation.

3.1.2 Orphan designation

Since many of the haematological malignancies, especially when only subpopulations are considered, occur in very few patients, the EU legislation on orphan drugs is summarized here. According to Article 3(1) of Regulation (EC) 141/2000, "a medicinal product shall be designated as an orphan medicinal product if […] it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made" or if it is unlikely that the revenue generated with the marketed drug will compensate the development cost and that either no satisfactory diagnosis, prevention or treatment options exist or that the to be licensed drug provides a significant benefit to the patients.

In spite of the small number of patients affected, i.e. the small number of patients who potentially could be included in clinical trials, the recitals of this regulation still point out that "patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients" and "orphan medicinal products should therefore be submitted to the normal evaluation process", i.e. according to Regulation (EC) 726/2004. Nevertheless, some methodological challenges of generating

data in small patient populations are acknowledged, and measures to address these are described in the CHMP guideline on the conduct of trials in small populations summarized in Section 3.1.2.1

3.1.2.1 Conducting trials in small populations

When conducting trials in small populations, it may be difficult to accrue patient numbers that would be sufficient to demonstrate superiority on "hard" clinical endpoints, such as overall survival (OS) or PFS, in randomized, controlled trials. As a consequence, the CHMP has issued its guideline on clinical trials in small populations (CHMP/EWP/83561/2005) in 2007. This guideline acknowledges the difficulties in obtaining robust data in small populations and provides suggestions on how to collect relevant data using different approaches in trial design or in the choice of clinical efficacy endpoints.

Although the guideline reinforces that randomized controlled studies (or meta-analyses thereof) provide the highest level of evidence, it recognizes that these may not always be feasible and shows the openness of regulators to accept even case reports or data from non-randomized trials if properly documented and justified. Such data should be supported by a robust preclinical rationale. If clinical studies can be conducted, but would require large numbers of patients or a very long time to reach statistically significant improvement of a "hard" clinical endpoint, alternative endpoints, such as validated surrogate endpoints may lead to initial regulatory approval, which would eventually need to be supported by additional efficacy and safety data collected in larger trials.

According to this guideline, a surrogate endpoint is a biomarker that is "reasonably likely – based on epidemiologic, pathophysiologic, or other evidence – to predict benefit". This definition is in line with the FDA definition of a surrogate endpoint as laid out in 21 Code of Federal Regulation (CFR) 314 Subpart H Section 314.510 (see Section 3.2.1.2). The CHMP guideline points out that it is important that the surrogate endpoint has been validated, i.e. that it has shown to be correlated with a generally accepted clinical efficacy endpoint, such as OS or PFS, and that it is not considered final proof of clinical benefit and long-term benefit. As a consequence, a plan to obtain such data (on long-term benefit) needs to be in place at the time of a marketing authorisation application (MAA) submission based on a surrogate endpoint. The same approach is taken by FDA when granting accelerated approvals (see Section 3.2.1.2).

3.1.3 Requirements according to the new CHMP anticancer guideline

Both the old and the new revision of the CHMP anticancer guideline emphasize the need for confirmatory trials to demonstrate clinical benefit. However, while Revision 3 describes acceptable efficacy endpoints in more general terms, Revision 4 includes more detailed guidance for different settings, such as: treatment administered with curative intent (with different levels of toxicity expected) and palliative treatment. (CPMP/EWP/205/95/Rev.3/Corr.2, EMA/CHMP/205/95/Rev.4) Such detailed information had previously been provided in the now superceded Appendix 2 on haematological malignancies (EMA/CHMP/EWP/520088/2008). In the following paragraphs, the current requirements are outlined and changes to the previous revision are indicated.

3.1.3.1 Main guidance text

3.1.3.1.1 Acceptable endpoints for confirmatory trials

Acceptable endpoints for confirmatory trials are discussed in Section 7.5 of Revision 4 (previously Section III.1.3). According to this guideline, cure rate, PFS and OS are acceptable efficacy endpoints.

However, OS data are considered most persuasive, but may be difficult to obtain if survival is expected to be long, if cross-over is permitted or if subsequent therapies may affect OS. In general, if OS is to be the primary efficacy endpoint of a trial, PFS should be secondary and vice versa. The current version of the guideline clarifies that, if OS is the secondary endpoint, a trend towards superiority should be demonstrated in addition to an absence of a detrimental effect on this outcome. Emphasis is put on a consistency of the results, including sensitivity analyses, and the importance of an overall positive benefit-risk evaluation.

As an alternative to OS and PFS, event rate at a pre-specified point of time may be acceptable as primary efficacy endpoint if progression events occur so rarely that very long follow-ups would be required. Nevertheless, the CHMP would expect PFS as a secondary endpoint in such a setting as well. Interestingly, the statement indicating that Overall Response Rate (ORR) would not be considered an acceptable primary endpoint without appropriate justification has been removed from this version of the guideline. Nevertheless, it may be assumed that proper justification still is needed, if ORR is to be used as a primary endpoint.

3.1.3.1.2 Endpoints to be chosen depending on the intent of treatment: cure, long-term disease control or palliation

Depending on the line of treatment the main text of Revision 4 now contains more detailed guidance on which efficacy endpoints may be considered appropriate. Although this appears like new information, virtually all guidance had previously been given in the superceded Appendix 2 on haematological malignancies (EMA/CHMP/EWP/520088/2008).

The section on endpoints applicable to **treatments with curative intent** remained virtually unchanged. The only changes are addition of non-haematological indications, and some minor clarification of text. In this setting, the ultimate goal is prolonged OS. When aiming at curing the disease, event-free survival (EFS), PFS or complete response rate (CRR) may be justifiable, especially in case subsequent treatment is scheduled, which may confound the OS outcome. However, in order to support regulatory approval, positive CRR results should be supported by positive trends in EFS or PFS and OS. Both the superceded Appendix 2 and Revision 4 of the Anticancer Guideline recommend collecting supportive evidence of CRR in form of, e.g., absence of MRD (discussed in more detail Section 6.1).

The section on endpoints applicable to **treatments with the intent to achieve long-term disease control** remained virtually unchanged. The only changes are addition of non-haematological indications as well as a clarification that a positive trend on OS is expected, if PFS is the primary endpoint. And although some guidance was removed on seeking scientific advice if non-established surrogate endpoints are to be used, it goes without saying, that scientific advice should still be sought in such situations. If the intent is to improve disease control, PFS is considered an acceptable endpoint in a trial demonstrating non-inferiority, if the drug is expected to be less toxic. If increased toxicity is expected, at least PFS data should be provided from a trial with superiority design and be followed up with OS data post approval. And a trend towards OS improvement is required for approval, if the new treatment is expected to be much more toxic than established therapies. This approach is foreseen, e.g., in early lines of treatment of advanced low-grade lymphoma or chronic leukaemias.

The section on endpoints applicable to **palliative therapy** remained virtually unchanged. The main changes are that Revision 4 requires reduction of bias as much as possible when assessing Health-related Quality of Life (HRQoL) endpoints, whereas the superceded Appendix 2 explicitly required double-blind trials and the requirement of survival data after progression in superiority trials powered

for PFS. In this last line setting, where palliation is to be provided to patients for whom no well-established therapies exist or to patients who are too frail to undergo more intensive, potentially, curative treatment, improvement in terms of OS and/or relevant symptoms, such as reduction of transfusion dependence in patients with MDS, and improvement in HRQoL are considered justifiable by the guideline. In case the new treatment is compared to treatment for which efficacy has been established, superiority in terms of PFS should be demonstrated.

3.1.3.1.3 Endpoints in the context of haematopoetic stem cell transplantation

In a newly added section, the guideline recommends pre-specifying in the protocol how haematopoetic stem cell transplantation (HSCT) is to be handled in a clinical trial evaluating induction therapy. The largest part of this section has simply been transferred from the superceded Appendix 2 (EMA/CHMP/EWP/520088/2008). In line with the text previously included in this appendix, the guideline clarifies that number of patients receiving HSCT is not an appropriate endpoint, since prior treatment may affect the outcome of the HSCT. However, information on censoring approaches has been deleted from the guideline and replaced by a brief statement that intention-to-treat (ITT) principles should be followed as described in the new Appendix 4 (EMA/CHMP/703715/2012). More clarity is provided on the need for following patients undergoing HSCT for OS and EFS in a randomized manner. In addition, more detailed guidance for the development of compounds for individual steps of an HSCT procedure are provided in the new Appendix 4 and are summarized in Section 3.1.3.4.3.

3.1.3.2 Additional guidance and summary of guidance provided in the main text of the Anticancer guideline

The new revision of the Anticancer guideline also provides additional clarification on the methodological approaches to demonstrate efficacy in particularly small populations and emphasises in particular the need for a holistic view of all available efficacy and safety data to enable a benefit-risk assessment. Again, MRD is mentioned as one efficacy endpoint that may add to the evidence of a new drug's efficaciousness. If a new drug is to be developed in a small population (by virtue of the disease's incidence or the number of patients expressing a certain target), the CHMP guideline on clinical trials in small populations (CPMP/EWP/83561/2005) should be taken into consideration (see Section 3.1.2.1). Since a single pivotal trial may form the basis of an MAA, the CHMP points to consider on application with 1. meta-analyses; 2. one pivotal study (CPMP/EWP/2330/99) also need to be taken into account.

In summary, although OS is still considered the most relevant efficacy endpoint in many oncology settings, PFS, CRR or even symptom control may be acceptable for regulatory approval – depending on the line of treatment, the severity of the disease and the number of treatment options available.

3.1.3.3 Appendix 1

The revised Appendix 1 of the anticancer guideline provides detailed guidance on methodological considerations for using PFS or EFS in confirmatory trials (EMA/CHMP/27994/2008/Rev.1). In particular, it provides some clarification on how to define these efficacy endpoints for the statistical analysis. This appendix now contains examples of how inappropriate trial design may lead to incorrect conclusions and provides suggestions for trial design. It further clarifies the two concepts of informative and uninformative censoring and suggests statistical approaches to investigate whether censoring truly is uninformative. It cautions against changes to the statistical analysis plan of open-

label trials while these are on-going or completed, since it would be difficult to demonstrate that the changes made at such a late point of time would not be data driven.

This revision now includes the reasons for conducting sensitivity analyses, namely, assessment of the robustness of the data in spite of deviations and missing data, uninformative censoring, proportional hazards and unscheduled evaluations. In this context, it cross-refers to the 2007 FDA guidance on clinical trial endpoints for the approval of cancer drugs and biologics summarized in Section 3.2.3. It also provides guidance on how to plan for interim analyses, both for demonstrating efficacy early and for futility and caveats are given for the former. It further provides guidance on the frequency of assessments and points out that increasing the frequency rarely increases statistical power. Much room is given to the considerations of central independent blinded data review, which is particularly important for unblinded trials. Scientific advice is recommended to discuss the assessment and analysis of efficacy endpoints. In new sections, this appendix emphasizes that the treatment difference, which is to be shown, needs to be justified prospectively based on current evidence and it emphasizes the need for OS data to further corroborate PFS results.

3.1.3.4 Appendix 4: condition-specific guidance

Appendix 4 of the guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/703715/2012) provides condition specific guidance for non-small cell lung cancer, prostate cancer, CML, MDS and HSCT. It introduces the diagnostic criteria of CML and provides recommendations for clinical study design depending on the stage of the disease. For MDS, the definition, history, diagnosis and classification as well as treatment options are summarized. Much of this information was previously contained in Appendix 2. Finally, it provides guidance on drug development in relation to HSCT, conditioning treatment and peripheral blood stem cell mobilisation. For the purpose of this thesis, only the information and changes on CML, MDS and HSCT are summarized here.

3.1.3.4.1 CML

For CML, much more detailed information is included on the assessments of response that should be performed in the course of a clinical trial in general. In contrast to the old guidance provided in the superceded Appendix 2 (EMA/CHMP/EWP/520088/2008), which considered complete cytogenetic response rate at 1 year an acceptable primary efficacy endpoint in a first line setting, the new Appendix 4, accepts major molecular response at 18 months in a superiority trial compared to a TKI approved in this setting. Cytogenetic response is now considered to be a secondary endpoint. Similarly, compared to the old text, the new Appendix 4 requires longer follow-up in case non-inferiority trials are conducted. This is now specified to be major cytogenetic response after at least 2 years.

As further clarification, the new Appendix 4 now requires the assessment of potential additive toxicities in case two TKIs are combined and that a first-line TKI should be chosen as a comparator for a trial in patients with newly diagnosed accelerated phase CML. The recommendation to seek scientific advice in particular prior to the conduct of trials in small populations with no treatment options replaces the old guidance that single-arm trials may be acceptable for regulatory approval, if a new TKI can demonstrate a sufficiently large effect size and duration of response on cytogenetic response in conjunction with acceptable tolerability. These changes reflect the advances in determining molecular response and qualifying it as an acceptable endpoint as well as the increasing number of treatment options that have become available since the former Appendix 2 came into effect.

3.1.3.4.2 Myelodysplastic syndrome

The guidance on MDS remains virtually unchanged. The only difference is that all recommendations on HRQoL have been transferred to a newly to be created Appendix, which has not been released for comments yet.

3.1.3.4.3 Haematopoetic stem cell transplantation

Most of the guidance on HSCT that had previously been provided in Appendix 2 has been transferred to the main anticancer guideline text where it has remained virtually unchanged. As a consequence, information on HSCT is now provided in two places: Section 7.5.1 of the main anticancer guideline and in Appendix 4. However, these two texts cover different aspects of HSCT. While the main anticancer guideline focuses rather on methodological considerations regarding HSCT in the context of a trial that is investigating induction treatment which may be succeeded by HSCT, the appendix focuses on data to be collected for compounds developed for HSCT, either as conditioning treatment, treatment prior to high-dose therapy or peripheral blood stem cell mobilisation. For each of these settings, recommendations on the trial design and choice of endpoints are given.

3.2 UNITED STATES OF AMERICA

3.2.1 Regulatory pathways leading to approval

3.2.1.1 Full approval

According to 21 CFR 314 Subpart B, a sponsor seeking approval for a new chemical or biological entity needs to provide FDA with “substantial evidence of effectiveness for the claimed indications” and “an integrated summary of all available information about the safety of the drug product”. These data need to be sufficient to support the label, in particular, with regard to dosing recommendations, which may be different for certain subpopulations based on, e.g., age, gender, race, different levels of severity of the disease, reduced renal or hepatic function or comedication. The FDA may deny approval if the data suggest the use of the new drug may not be safe or if there is a lack of evidence to determine whether it is safe or efficacious as described in the proposed label (21 CFR 314 Subpart D Section 314.125). In this context, the FDA refers to the need of substantial evidence in form of “adequate and well-controlled” clinical studies, which are defined in 21 CFR 314.126. Usually, these are randomized, controlled, double-blind studies. 21 CFR 314.126 explicitly states that non-randomized studies are not acceptable as the “sole basis for the approval of claims of effectiveness”.

3.2.1.2 Accelerated approval – concept of surrogate endpoints

The FDA foresee accelerated approval of new drugs for serious and life-threatening illnesses based on adequate and well-controlled trials using a validated surrogate efficacy endpoint that is “reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity” as laid out in 21 CFR 314 Subpart H Section 314.510. The FDA require this surrogate endpoint to be validated, i.e., to be correlated to a clinical efficacy endpoint that is generally accepted to demonstrate clinical benefit. In addition, the FDA require post-marketing data verifying and confirming the clinical benefit. These requirements of validating surrogate endpoints and providing additional data demonstrating clinical benefit are in line with the CHMP requirements laid out in the guideline on

clinical trials in small populations, which possibly were modelled after the FDA legislation (see Section 3.1.2.1).

3.2.2 Orphan designation

In the US, the concept of orphan drugs was established even earlier than in the EU (Regulation [EC] 141/2000) and the designation and incentives connected to it are governed by the Orphan Drug Act of 1983 and in 21 CFR Part 316. According to Section 526 of the Federal Food, Drug and Cosmetic Act, "the term 'rare disease or condition' means any disease or condition which […] affects less than 200,000 persons in the United States" or that, although more than 200,000 persons in the US are affected, it is unlikely that the revenue generated will cover the cost of development. Similar to the European Commission, the FDA require that "safety and effectiveness of a drug must be established through adequate and well-controlled studies" (FDA website accessed on 01 Dec 2013). However, no dedicated guidance exists on how to approach the methodological challenges of generating such data in a small population.

3.2.3 Requirements according to the FDA guidance on clinical trial endpoints for the approval of cancer drugs and biologics

This guidance reiterates the need for efficacy data based on adequate well-controlled studies that would lead to full approval according to 21 CFR 314 Subpart B, while acknowledging the possibility of an accelerated approval based on surrogate endpoints as detailed in 21 CFR 314 Subpart H. Similar to the CHMP anticancer guideline, it considers OS a "universally accepted direct measure of clinical benefit". However, depending on the disease setting and the trial design, other endpoints may be acceptable – at least as surrogate endpoints –, such as symptom improvement, disease-free survival, ORR, CRR or PFS. FDA note, though, that sometimes a correlation between the time-to-event endpoints and clinical benefit in form of improved OS has not yet been established for all indications. And although symptom improvement is listed as a potential endpoint leading to approval of an anticancer drug or biologic, the lack of instruments that are considered validated by FDA limits the use of such endpoints in practice. Of particular note for the development of drugs and biologics for the treatment of haematological malignancies is the fact that the FDA guidance mentions that for leukaemia ORR data have often led to full approvals, even when used in single-arm clinical trials.

3.2.4 Requirements according to the new FDA draft guidance on expedited programs

The June 2013 published FDA draft guidance on "Expedited Programs for Serious Conditions—Drugs and Biologics" provides an overview of all currently available regulatory pathways leading to a fast approval, i.e., fast track designation, breakthrough designation, accelerated approval and priority review. In addition, it provides some clarification on certain concepts that are relevant for the proper implementation of these pathways, i.e., serious condition, available therapy and unmet medical need. The concept of surrogate efficacy endpoints is explained in 21 CFR 314 Subpart H. The final version of this guidance will supercede the previous FDA guidance on fast track drug development programs (FDA guidance on fast track programs, July 2004). An overview of all the expedited programs available for compounds intended for serious conditions is provided in Table 6.

Table 6 Overview of FDA's expedited programmes for drugs for serious conditions

	Fast track	**Breakthrough therapy**	**Accelerated approval**	**Priority review**
Qualifying criteria	A drug that is intended to treat a serious condition and **nonclinical or clinical data** demonstrate the potential to **address unmet medical need**	A drug that is intended to treat a serious condition and **preliminary clinical evidence** indicates that the drug may demonstrate **substantial improvement** on a clinically significant endpoint(s) over available therapies	A drug that treats a serious condition and generally provides meaningful advantage over available therapies and demonstrates an **effect on a surrogate endpoint that is reasonably likely to predict clinical benefit** or on an intermediate clinical endpoint	An application (original or efficacy supplement) for a drug that treats a serious condition and if approved, would provide a **significant improvement in safety or effectiveness**
When to apply	With or during IND Ideally, no later than the pre-BLA or pre-NDA meeting	With or during IND Ideally, no later than the EoP II meeting	The sponsor should ordinarily discuss the possibility of accelerated approval with the review division during development, supporting, for example, the use of the planned endpoint as a basis for approval and discussing the confirmatory trials.	With original BLA, NDA, or efficacy supplement
Features	Actions to expedite development and review Rolling review	All fast track designation features Intensive guidance on efficient drug development during IND, beginning as early as Phase 1 Organizational commitment involving senior managers	Approval based on an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	Shorter clock for review of marketing application (6 months compared to the 10-month standard review)
Additional considerations	Designation may be withdrawn if it no longer meets fast track qualifying criteria	Designation may be withdrawn if it no longer meets breakthrough therapy qualifying criteria	Submission of copies of promotional materials for review Conduct any required post approval trials to verify and describe the anticipated clinical benefit Subject to expedited withdrawal	Designation will be assigned at the time of original BLA, NDA or efficacy supplement filing

	Fast track	**Breakthrough therapy**	**Accelerated approval**	**Priority review**
References	Section 506(b) of the FD&C Act, as added by section 112 of the 1997 FDAMA, and amended by section 901 of the 2012 FDASIA	Section 506(a) of the FD&C Act, as added by section 902 of FDASIA	21 CFR part 314, subpart H 21 CFR part 601, subpart E Section 506(c) of the FD&C Act, as amended by section 901 of FDASIA	Prescription Drug User Fee Act of 1992

Source: FDA Draft Guidance: Expedited Programs for Serious Conditions—Drugs and Biologics, June 2013

Abbreviations: BLA = biologics license application; FDAMA = Food and Drug Administration Modernization Act; FDASIA = Food and Drug Administration Safety and Innovation Act; FD&C Act = Food, Drug & Cosmetic Act; EoPII = end of Phase II meeting; IND = investigational new drug; NDA = new drug application

3.2.4.1 Clarification of “available therapy”, “serious condition” and “unmet medical need”

3.2.4.1.1 “Serious condition”

The definition of “serious condition” in the newly published draft guidance does not differ from the definition used previously be FDA in the context of accelerated approval and fast track designation. In line with these guidances, a “serious condition” is defined as a disease with a morbidity that substantially impacts on everyday functioning and that is, at least, either persistent or recurrent. A life-threatening disease is automatically considered a serious disease. (FDA Guidance on Expedited Programs 2013)

3.2.4.1.2 “Available therapy”

According to this draft guidance, the FDA consider “available therapy” a therapy that has regulatory approval in the indication that is targeted and that is considered relevant to the current standard of care in the US. The guidance points out that therapies which are not approved in a certain indication but are considered standard of care, e.g., based on current treatment guidelines, may be considered “available therapy” only exceptionally. Therapy that has been granted accelerated approval based on a surrogate efficacy endpoint is not considered “available therapy” by FDA according to this draft guideline. (FDA Guidance on Expedited Programs 2013)

3.2.4.1.3 “Unmet medical need”

This guidance clarifies that “unmet medical need” exists, if there is no therapy for a serious condition. In addition, a new therapy addresses an “unmet medical need” in spite of available therapy, if the new therapy:

- is efficacious on serious outcomes that the available therapy does not address,
- shows better efficacy in terms of survival or serious morbidity in a head-to-head comparison or based on historical data,
- is efficacious in patients who relapsed after or are refractory to available therapy,

- has a better side effect profile compared to available therapy while having similar efficacy,
- provides some other benefit that is expected to improve on the serious outcome of the disease, while having similar efficacy and safety compared to available therapy,
- addresses some public health need, such as multidrug resistant microbes.

3.2.4.1.4 Surrogate endpoints

The guidance provides a definition of "surrogate endpoints" that is fully in line with the definition given in 21 CFR 314 Subpart H Section 314.510 (see Section 3.2.1.2). In addition, it provides some examples for both surrogate endpoints and intermediate clinical endpoints, i.e., endpoints that can be measured earlier than "irreversible morbidity and mortality" and are reasonably likely to predict the clinical benefit of the drug. (FDA Guidance on Expedited Programs 2013)

3.2.4.2 Breakthrough designation

Breakthrough therapy designation has been created as part of the FDA Safety and Innovation Act 2012 (FDASIA). It is meant to accelerate development and review time of new therapies for serious and life-threatening diseases for which early clinical evidence indicates a potential "substantial improvement" on a "clinically significant" endpoint compared to available therapies. (FDA Guidance on Expedited Programs 2013)

"Substantial improvement" may be demonstrated either in terms of duration of the effect or increase in effect size. Such an effect may be demonstrated in a direct comparison of the new therapy alone or in combination to available therapy (if there is any), by demonstrating that the new therapy is treating the underlying cause of disease rather than its symptoms, or by showing that it is changing the course of the disease or that it provides a significantly improved safety profile. (FDA Guidance on Expedited Programs 2013)

A "clinically significant" endpoint for the purpose of breakthrough designation is an endpoint that directly measures the morbidity or serious outcome of the disease or that is an established surrogate efficacy endpoint or a surrogate endpoint reasonably likely to predict a clinical benefit. It may also be a pharmacodynamic biomarker that strongly suggests a positive effect on the underlying cause of the disease or a side effect profile with much less toxicity compared to available therapy while being similarly efficacious. (FDA Guidance on Expedited Programs 2013)

The advantages of a breakthrough designation lie in the intensive guidance to be provided by FDA to the sponsor throughout the drug development programme. This guidance is to be provided by a cross-functional team involving senior FDA staff. (FDA Guidance on Expedited Programs 2013) However, more detailed guidance is currently lacking on how this interaction between FDA and the sponsor may occur. In addition, a compound with a breakthrough designation may benefit from all the features of a fast track designation, since a compound meeting the criteria of breakthrough designation would automatically meet all the criteria of fast track designation as well (see Section 3.2.4.4).

3.2.4.3 Priority review designation

A compound may be eligible for priority review designation if it is for the treatment, prevention or diagnosis of a serious condition and if it is expected to provide a significant improvement in safety or efficacy compared to available therapy. In order to benefit from such a designation, data need to be

provided that demonstrate improved efficacy, substantial reduction or elimination of certain treatment-limiting toxicities, improvement of compliance that may have a positive impact on serious outcomes or efficacy and safety in a subpopulation. FDA review timelines for compounds with priority review designation are shortened from ten to six months for initial NDA/BLA submissions. (FDA Guidance on Expedited Programs 2013)

3.2.4.4 Fast track designation

According to Section 506(b) of the Food Drugs & Cosmetics Act, a compound may be eligible for fast track designation "if it is intended […] for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition". In order to qualify for fast track designation data need to be provided suggesting a new compound has this potential. Such data may be derived from preclinical models, if the designation is sought early during development, or they may be based on clinical data. A compound with fast track designation may benefit from more frequent communication with FDA to discuss the development programme. It may also be eligible for a rolling submission where parts of the NDA, usually Module 3 sometimes together with Module 4, would be submitted earlier than the remainder of the dossier. This could enable FDA to start the review of these parts of the NDA earlier, although there is no legal requirement for them to do so. (FDA Guidance on Expedited Programs 2013)

4. HISTORICAL EXAMPLES

Unless indicated otherwise, all information in this section is based on the information provided by FDA and EMA in the respective approval documents of the compounds discussed in this thesis.

4.1 CLL

Table 7 and Table 8 summarize the data that led to approval of fludarabine, ofatumumab and alemtuzumab for the treatment of relapsed/refractory CLL in the US and for ofatumumab and alemtuzumab in the EU, respectively.

Table 7 Pivotal data leading to approval for treatment of relapsed/refractory CLL in the US

Pivotal study(ies)	N	Efficacy	Approval year / type	Comments
Fludarabine (tablets)				
ME96029: OL, Ph II, single-arm	ME96029: 78 Safety: 502; 78 in target indication	1º: ORR (CR+PR): 46.2% (IWCLL criteria, best case), 51.3% (NCI criteria, best case)	2008 / accelerated	Oral formulation; i.v. had been approved in 1991; PMC: PFS data (fludarabine compared to chlorambucil) by 30 Jul 2014
Alemtuzumab				
CAM211 (pivotal): Ph II, OL, single-arm	CAM211: 93 Safety: 149; 92 in target indication	ORR: 33.3% (sponsor; CI 23.4,42.6), 21.9% (FDA); DOR: 8.7m (sponsor, CI 5.9,11.5) 7.1m (FDA); PFS (sponsor): 4.7m (CI 3.7,5.8); OS: 15.9m (CI 11.8,N/A)	2001 / accelerated	PMC: comparative trial providing efficacy, safety and evidence of clinical benefit
Ofatumumab (refractory to fludarabine and alemtuzumab)				
Hx-CD20-406 (pivotal; Ph II, OL, single-arm, interim analysis)	Hx-CD20-406: 154 (primary efficacy based on 59 double-refractory patients) Safety: 648	1º: ORR (1996 IWCLL criteria); 54% (IRC), 42% (Inv); 2º: DOR: 6.5m (Inv; CI 5.8,8.3); OS: 13.7m (CI 9.4,N/A); PFS: 5.7m (CI 4.5,8.0)	2009 / accelerated	Safety database included 1138 pts at time of 4-months safety-update; data cut-off: 27 Nov 2007; PMC: PFS of ofa+clb vs clb in 1st line CLL
Ibrutinib (2nd line)				
Ph I/II, OL, two doses of ibrutinib (NCT01105247)	48 (at marketed dose of 420mg) Safety: at least ˜170; 48 in target indication	ORR: 58.3% (CI 43.2,72.4) 2008 IWCLL criteria (IRC); no CR; mDOR: 5.6 to >24.2m	2013 / accelerated	PMC: Ph III OL trial comparing ibrutinib to ofa in R/R CLL, Ph III DB trial comparing ibrutinib + benda + R to PBO + benda + R

Source: Alemtuzumab FDA Medical Review, Fludarabine FDA Medical Review 2008, Ofatumumab FDA Medical Review, Byrd 2013

Abbreviations: benda = bendamustine; CI = 95% confidence interval; clb = chlorambucil; CR = complete response; DB = double-blind; IRC = independent review committee; Inv = investigator assessment; i.v. = intravenous; IWCLL = international working group on CLL; m = months; mDOR = median duration of response; N = number; N/A = not available; NCI = National Cancer Institute; ofa = ofatumumab; OL = open-label; ORR = overall response rate; PBO = placebo; PFS = progression-free survival; Ph = phase; PMC = post marketing commitment; PR = partial response; R = rituximab; R/R = relapsed/refractory; vs = versus

Table 8 Pivotal data leading to approval for treatment of relapsed/refractory CLL in the EU

Pivotal study(ies)	N	Efficacy	Approval year / type	Comments
Alemtuzumab (3rd line)				
CAM211: Ph II, OL, single-arm	93 Safety: ~700; 149 in target indication	RR (1996 IWCLL): 33.3% (IRC; CI 24,44); DOR: 8.7m (n=35)	2001 / exceptional circumstances	CAM211 was compliant with EMA SA; transformed into full approval in 2008
Ofatumumab (double-refractory to fludarabine and alemtuzumab)				
Hx-CD20-406: Ph II, OL, single-arm	Hx-CD20-406: 154 (primary efficacy based on 59 double-refractory patients) Safety: 648; 362 in CLL pts	1º: ORR (1996 IWCLL criteria); 58% (IRC), 42% (Inv); 2º: DOR: 7.1m (Inv; CI 3.7,7.6)); OS: 13.7m (CI 9.4,N/A); PFS: 5.7m (CI 4.5,8.0)	2010 / conditional approval	interim analysis data cut-off: 19 May 2008; ORR assessed by IRC was specified as 1º efficacy endpoint; Approval was based on investigator assessed ORR; PMC: PFS of ofa+clb vs clb in 1st line CLL

Sources: Alemtuzumab EPAR, Ofatumumab EPAR

Abbreviations: CI = 95% confidence interval; clb = chlorambucil; EMA SA = EMA scientific advice; IRC = independent review committee; Inv = investigator assessment; IWCLL = international working group on CLL; m = months; mDOR = median duration of response; N/A = not available; ofa = ofatumumab; OL = open-label; ORR = overall response rate; PFS = progression-free survival; Ph = phase; PMC = post marketing commitment; pts = patients; RR = response rate; vs = versus

4.1.1 Fludarabine

In 2008, the FDA granted accelerated approval to fludarabine tablets for the treatment of patients with CLL with relapse or lack of response during or after treatment with at least one alkylating-agent containing therapy. This approval was based on ORR according to IWCLL criteria collected in one single-arm Ph II trial. The NDA contained additional five Ph II trials providing supportive evidence of efficacy for both oral and intravenous fludarabine. The safety database provided with this NDA included 502 patients, 78 of which in the target indication. In addition, the compound had been on the market in other countries for several years, so extensive safety data were available at time of approval. In the US, the intravenous formulation had been approved for this indication in 1991. Nevertheless, the FDA required PFS data from a Ph III trial comparing the efficacy of fludarabine to that of chlorambucil in previously untreated CLL patients as post-marketing commitment (PMC). (FDA Medical Review of fludarabine 2008, Application number: 22-273, and approval letter 2008)

In the EU, fludarabine had been approved in 1991 based on Trial CLL 101, in which intravenous treatment with fludarabine resulted in a 70% response rate in treatment-naïve CLL patients. (FDA Statistical Review of fludarabine 2008, Application number: 22-273) The MAA contained three additional supportive trials: CALGB9011 comparing fludarabine to chlorambucil, A00545 comparing fludarabine to chlorambucil + methyl prednisone and the FCGCLL trial comparing fludarabine to cyclophosphamide + adriamycin + prednisone and cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP). (FDA Medical Review of fludarabine 2008, Application number: 22-273)

4.1.2 Alemtuzumab

Although withdrawn due to commercial reasons in 2012, the pivotal data leading to approval of alemtuzumab in the EU (approval under exceptional circumstances in 2001) and the US (accelerated approval in 2001) for the treatment of patients with CLL who have been treated with alkylating agents and who have failed fludarabine phosphate therapy are summarized in Table 7 and Table 8. This is mainly to illustrate the agencies' thinking at the time of approval of alemtuzumab.

The approvals were based on ORR according to the 1996 International Working Group Response Criteria for CLL (Cheson et al, 1996) and mDOR of 8.7 months observed in one single-arm trial. (Alemtuzumab FDA Medical Review 2001, Alemtuzumab EPAR 2001) The design of this trial had been subject to scientific advice in the EU, where a comparative Ph III trial was not considered feasible or necessary, because it was not possible to identify an appropriate comparator and best supportive care was not considered ethical. At the time of approval, the CHMP considered response rate to be an adequate surrogate endpoint for clinical benefit. These considerations led to the granting of an approval under exceptional circumstances. (Alemtuzumab EPAR 2001)

The MAA was supported by a safety database including 700 patients with various indications who had received at least one dose of alemtuzumab. For the benefit-risk evaluation, however, the CHMP focused their review on 149 patients with CLL. The data provided in the MAA were considered sufficient to support a positive benefit-risk ratio, especially since a Ph III trial was already on-going in 1st line CLL comparing alemtuzumab to chlorambucil. (Alemtuzumab EPAR 2001)

The pivotal trial had also been discussed with FDA at the pre-BLA meeting. And although the FDA agreed that a comparative trial was not feasible, they voiced concern on the lack of comparative data at the time of BLA review. This was discussed further at the ODAC held on 14 Dec 2001, which confirmed the acceptability of ORR as a surrogate endpoint and considered the data available sufficient to support the accelerated approval of alemtuzumab in this indication. (Alemtuzumab Oncology Drugs Advisory Committee [ODAC] 14 Dec 2001 transcript)

The BLA was supported by a safety database including 149 CLL patients, of which 92 were in the target indication. Whether safety data from trials in other indications was provided, is not clear based on the information provided in the FDA medical review document. However, it is clear that no safety data obtained in other populations were taken into account by the FDA. Given the fact that this antibody was the first anti-CD52 antibody approved, the size of the safety database appears to be quite small. Since this approval was based on one single-arm trial, no comparative data existed to properly characterize the side effect profile of alemtuzumab. Nevertheless, the FDA found the benefit-risk evaluation of alemtuzumab to be positive and requested PMCs including a randomized Ph III trial comparing alemtuzumab to chlorambucil, which would provide relevant data both for the efficacy and safety of this antibody. (Alemtuzumab FDA Medical Review 2001 and approval letter 2001)

4.1.3 Ofatumumab

Virtually the same data led to accelerated and conditional approval of ofatumumab for the treatment of CLL patients refractory to alemtuzumab and fludarabine in 2009 in the US and in 2010 in the EU, respectively. Approvals were granted based on ORR with mDORs of 6.5 and 7.1 months based on investigator's assessment. The difference in the results is due to the different data cut-off dates used for the submissions in the US and the EU. Both agencies required PFS data comparing the efficacy of ofatumumab + chlorambucil to chlorambucil monotherapy in 1st line CLL as PMC. (Ofatumumab FDA Medical Review and approval letter 2009 and ofatumumab EPAR 2010)

At the time of approval, patients who were refractory to both fludarabine and alemtuzumab were considered a population with high unmet medical need both by the FDA and the CHMP. In the Medical Review, FDA pointed out that durable objective response rate was considered a surrogate endpoint reasonably likely to predict clinical benefit. Since the CHMP was concerned due to the fact that the pivotal trial was uncontrolled and, thus, the efficacy of ofatumumab relative to other treatments virtually impossible to assess, an Oncology Scientific Advisory Group (SAG-O) was consulted prior to approval. The SAG-O "agreed that it is reasonable to assume that this effect will lead to some improvement in disease related symptoms and that this is expected to be of clinical relevance", i.e., they confirmed the surrogacy of ORR in this population. (Ofatumumab FDA Medical Review and ofatumumab EPAR 2010)

Both the BLA and the MAA were supported by a safety database including 648 patients, 362 of which were CLL patients. Since ofatumumab was not the first anti-CD20 antibody to be approved by either Agency, the safety database seems to be quite large. However, the FDA based their safety review primarily on data from 181 CLL patients treated with ofatumumab monotherapy. The FDA reviewer pointed out, though, that the amount of safety data was comparable to that provided for alemtuzumab (see Section 4.1.2). Nevertheless, both FDA and CHMP acknowledged that there was uncertainty in the assessment of the side effect profile of ofatumumab, since only data from one single-arm trial were available and data from the on-going Ph III trial comparing ofatumumab + chlorambucil to chlorambucil were required to characterize both the efficacy and safety of ofatumumab. (Ofatumumab FDA Medical Review and ofatumumab EPAR 2010)

4.1.4 Ibrutinib

The most recent accelerated approval of a compound with breakthrough designation was for ibrutinib on 12 Feb 2014. This approval, again, was based on ORR and mDOR. PMCs consist of two randomized Ph III trials: one comparing ibrutinib to ofatumumab and one comparing ibrutinib in combination with bendamustine and rituximab to placebo in combination with bendamustine and rituximab. Both trials are conducted in patients with relapsed or refractory CLL and have PFS as primary efficacy endpoint. (ibrutinib CLL FDA approval letter 2014)

Unfortunately, no review documentation was available on the FDA website as of 30 Mar 2014, so it is currently impossible to learn more about the discussions that preceded the approval. However, the approval was granted approximately one month after the recommendation of the Data Monitoring Committee to stop the on-going Ph III trial in CLL early due to the fact that statistically significant improvement of PFS and OS had been demonstrated (NCT01578707; Pharmacyclics press release 07 Jan 2014). The fact that this NDA was not discussed at an ODAC suggests that the FDA comparatively easily arrived at an aligned evaluation of the benefits and risks associated with ibrutinib treatment, although the initial NDA included safety data from only approximately 48 patients in the target

indication. According to the 08 Apr 2014 Pharmacyclics press release, an sNDA including data from the Ph III trial mentioned above has been submitted to convert the accelerated approval of ibrutinib for the treatment of CLL to a full approval.

Interestingly, though, the initial NDA submission included both CLL and MCL as target indication. However, during review the procedure was split into two, and approval for MCL was granted approximately 3 months earlier than for CLL (see Section 4.3). It may be speculated that the split of the NDA was due to the fact that data from the interim analysis of the on-going Ph III trial for CLL were expected early 2014. As a consequence, patients with relapsed/refractory MCL, who have very limited treatment options, could already benefit from a new treatment option, while review for CLL was still on-going. (ibrutinib MCL FDA Medical Review 2013)

4.2 CML

Table 9 Pivotal data leading to approval for CML in the US

Pivotal study(ies)	N	Efficacy	Approval year / type	Comments
Imatinib (adult CML, Ph+, 2nd line)				
110 (Ph II, OL, single-arm, CP CML after failed interferon tx) 109 (Ph II, OL, 2 doses imatinib, AP CML) 102 (Ph II, OL, single-arm, BP CML)	Study 110: 532 Study 109: 235 Study 102: 260 Safety: 1027	110: 1º: MCyR: 49%; 2º: CCyR: 30%, CHR: 88% 109: 1º: HR: 63%, 2º: MCyR: 21%, CHR: 26% 102: 1º: HR: 26%; 2º: CHR: 4%, MCyR: 14%	2001/ accelerated, initial approval	PMC: Ph III trial to verify benefit of imatinib compared to interferon + cytarabine (Trial 106)
Imatinib (adult CML, Ph+, 1st line)				
106 (Ph III, OL, imatinib vs interferon + cytarabine)	553 per arm Safety: 1663	1º: HR 0.183 (CI 0.117,0.285); 2º: MCyR: 82.6% vs 39.8% (up to cross-over: 20.2%); CHR: 94.4% (CI 92.1%, 96.2%) vs 54.6% (CI 50.4%, 58.8%)	2002/ accelerated, sNDA	PMC: annual updates of 106
Imatinib (paediatric CML, Ph+, 2nd line)				
0103 (Ph I, OL, dose-finding) 3001 (Ph I, OL, dose-finding)	39 Safety: 39 paediatric patients	1º: safety MCyR or CCyR in 13 of 16 evaluable patients across all doses tested	2003 / accelerated, sNDA	PMC: Ph II trial to verify and describe clinical benefit of imatinib
Imatinib (paediatric CML, Ph+, 1st line)				
Ph II, OL, single-arm	51 Safety: 93 paediatric patients in total	1º: CHR rate (Wk 8): 78%; 2º: CCyR: 65%; PCyR: 16%	2006 / accelerated, sNDA	PMC: provide follow-ups of efficacy and safety of Ph II trial leading to approval
Dasatinib (adult CP, AP, BP CML, 2nd line, resistant or intolerant to prior tx including imatinib)				
CA180013 (Ph II, single-arm, CP) CA180005 (Ph II, single-arm, AP) CA180006 (Ph II, single-arm, myeloid blast) CA180015 (Ph II, lymphoid blast)	CA180013: 186 CA180005: 107 CA180006: 74 CA180015: 42 Safety: 1104; 489 pts w/ CML	CA180013: 1º: MCyR: 45% (CI 37,52) CA180005: 1º: MHR: 59% (CI 49,68) CA180006: 1º: MHR: 32% (CI 22,44) CA180015: 1º: MHR: 31% (CI 18,47)	2006/ accelerated, initial approval	PMC: completion of the trials that formed the basis of approval, Ph III trial vs imatinib mesylate

Pivotal study(ies)	N	Efficacy	Approval year / type	Comments
Dasatinib (CP CML, Ph+, 1st line)				
CA180056 (Ph III, OL, randomized dasatinib vs imatinib)	519 (total) Safety: 519 newly diagnosed CP CML	1º: CCyR (Month 12): 76.8% (CI 71.2,81.8) vs 66.2% (CI 60.1,71.9); 2º: MMR: 52.1% (CI 45.9,58.3) vs 33.8% (CI 28.1,39.9)	2010/ accelerated, sNDA	PMC: completion of Ph III trial which formed the basis of this approval
Nilotinib (adult CP, AP CML, Ph+, 2nd line, resistant/intolerant to prior tx that included imatinib)				
2101 (Ph II, CP and AP CML)	232 (CP CML) 105 (AP CML) Safety: 438 total; 318 CP CML	CP CML: 1º: MCyR 40% (Cl 33,46; unconfirmed, CCyR: 28% , PCyR: 12%); DOR: ≥6 months in 95% of pts w/ MCyR; 2º: CHR: 50% (n = 185) AP CML: 1º: MHR: 26% (CI 18,35) ; DOR: ≥6 months in 95% of pts w/ MHR; 2º: MCyR: 21% (unconfirmed) and 6% (confirmed) (n = 81)	2007/ accelerated, initial approval	PMC: completion of trial 2101
Nilotinib (adult CP CML, 1st line)				
1651-1 (OL, randomized vs imatinib)	283 (imatinib 400 mg) 282 (nilotinib 300 mg bid) Safety: 279 pts in target indication	1º: MMR (Month 12): 44% (CI 38.4,50.3) vs 22% (CI 17.6,27.6); MCyR: 80% (CI 75.0,84.6) vs 65% (CI 59.2,70.6)	2010/ accelerated, sNDA	PMC: completion of 1651-1

Pivotal study(ies)	N	Efficacy	Approval year / type	Comments
Ponatinib (adult CP, AP, BP CML, 2nd line, TKI resistant or T315I)				
10-201 (Ph II, OL, single-arm)	CP CML: TKI res: 203 T315I: 64 AP CML: TKI res: 65 T315I: 18 BP CML: 62 Ph+ ALL: 32 Safety : 530 ; 449 from 10-201	CP CML: 1º: MCyR: 54% (all), 49% (TKI res), 70% (T315I) AP CML: 1º: MHR: 52% (all), 55% (TKI res), 39% (T315I) BP CML / Ph+ALL: 1º: MHR: 31% (BP CML), 41% (Ph+ ALL) DOR MCyR: not reached (CP CML), DOR HR: 9.5m (AP CML), 4.7m (BP CML), 3.2m (Ph+ ALL)	2012/ accelerated, initial approval	PMC: 24-months follow-up of 10-201
Omacetaxine mepesuccinate (adult AP, CP CML, 3rd line, resistant or intolerant to 2 or more TKIs)				
CML-202 (Ph II, OL, single-arm, CP w/ T315I) CML-203 (Ph II, OL, single-arm, CP, AP, BP)	CML-202: 103 CML-203: 100 Safety: 158 in target indication	CP CML: 1º: MCyR: FDA: 18.4% w/ mDOR 12.5 m (CI 3.5,NA); Sponsor: 20.5% w/ mDOR 17.7 m (CI 4.1,NA) AP CML: 1º: MHR: FDA: 14.3% w/ mDOR 4.7 m (CI 3.6,NA); Sponsor: 26.8% w/ mDOR 9.0 m (CI 3.6,14.1)	2012/ accelerated, initial approval	PMC: provide 24 months follow-up for Ph II trials

Sources: dasatinib FDA Medical Review initial approval, dasatinib 28 Oct 2010 FDA approval letter sNDA approval, dasatinib 28 Oct 2010 label, imatinib FDA Medical Review initial approval 2001, imatinib adult 1st line CML sNDA approval 2002, imatinib paediatric 2nd line CML sNDA approval 2003, imatinib paediatric 1st line CML sNDA approval letter and label 2006, nilotinib FDA Medical Review initial approval, nilotinib sNDA approval letter and label 2010, omacetaxine mepesuccinate FDA Medical Review, ponatinib FDA Medical Review

Abbreviations: ALL = acute lymphocytic leukaemia; AP = accelerated phase; BP = blast phase; CHR = complete haematologic response; CI = 95% confidence intervall; CP = chronic phase; CCyR = complete cytogenetic response; FDA = assessment of the FDA; HR = haematologic response; MCyR = major cytogenetic response; mDOR = median duration of response; MHR = major histologic response; MMR = major molecular response; NA = not available; sNDA = supplemental NDA; PCyR = partial cytogenetic response; Ph+ = Philadelphia chromosome positive; PMC = post marketing commitment; pts = patients; T315I = mutation of amino acid 315 changing threonine to isoleucine; TKI res = tyrosine kinase inhibitor resistant; tx = treatment; w/ = with; Wk = Week

Table 10 Pivotal data leading to approval for CML in the EU

Pivotal study(ies)	N	Efficacy	Approval year	Comments
Imatinib (adult CML, Ph+, 2nd line)				
110 (Ph II, OL, single- arm, CP CML after failed interferon tx) 109 (Ph II, OL, 2 doses imatinib, AP CML) 102 (Ph II, OL, single-arm, BP CML)	Study 110: 532 Study 109: 235 (AP CML) Study 102: 260 Safety: 1027	110: 1º: MCyR: 49% (unconfirmed), 38.0% (confirmed); 2º: CCyR: 30% (unconfirmed), 14.7% (confirmed); CHR: 88% 109: 1º: HR: 63%, 2º: MCyR: 21%, CHR: 27.7% 102: 1º: HR: 26%; 2º: CHR: 4%, MCyR: 14%	2001/ exceptional circumstances	PMC: provision of long-term efficacy and safety data
Bosutinib (CML, 2nd line, imatinib, dasatinib and nilotinib not appropriate)				
3160A4-200-WW (Ph I/II, OL, CP CML)	"unmet medical need" subgroup: 52 Safety: 1572 total; 118 in 3160A4-200-WW	CP CML: 9/36 pts w/ MCyR and 2 CMR. 1 MMR. 4 CCyR. 2 PCyR AP CML: 3/5 pts w/ MCyR and 1 CMR. 2 CCyR. 1 MHR BP CML: 2/11 pts w/ MCyR and 2 CCyR, 1 MHR	2013/ conditional approval	PMC: OL, single-arm efficacy and safety study in Ph+ CML pts after tx w/ ≥ 1 TKI for whom imatinib, nilotinib and dasatinib are not appropriate

Sources: imatinib 2001 EPAR, bosutinib 2013 EPAR

Abbreviations: AP = accelerated phase; BP = blast phase; CHR = complete haematologic response; CMR = complete molecular response; CP = chronic phase; CCyR = complete cytogenetic response; HR = haematologic response; MCyR = major cytogenetic response; MHR = major histologic response; MMR = major molecular response; OL = open-label; PCyR = partial cytogenetic response; Ph = Phase; Ph+ = Philadelphia chromosome positive; PMC = post marketing commitment; pts = patients; TKI = tyrosine kinase inhibitor; tx = treatment; w/ = with

4.2.1 Imatinib

One of the prime examples for a compound using surrogate endpoints to achieve accelerated approvals for various lines of CML treatment (and other indications, which are beyond the scope of this thesis) in the US is imatinib mesylate. Since a single molecular cause has been established for CML, it is the example of a disease that lends itself to such an approach.

Already the initial FDA approval of imatinib mesylate in 2001 for the treatment of adult Ph+ CML after failure of interferon therapy was an accelerated approval based on the following surrogate endpoints: major cytogenetic response (MCyR) for CP CML and haematologic response (HR) for AP and BP CML. However, data on duration of response and survival were limited or not available at the time of approval. Nevertheless, precedence existed for approvals for haematological malignancies based on complete response, e.g., pentostatin, cladribine, tretinoin and arsenic trioxide, or partial response, which had led to the approval of fludarabine (note: based on the imatinib review, it is unclear which fludarabine approval is referred to; based on approval dates, it is likely that the original approval

of iv fludarabine in 1991 is referred to, for which no review documents are available on-line.). (imatinib FDA Medical Review 2001)

As indicated in the Medical Review of the initial imatinib NDA, FDA accepted HR as a surrogate efficacy endpoint for the approval for AP and BP CML and complete hematologic response (CHR) or MCyR as surrogate efficacy endpoints for the approval for any phase of CML. And since the efficacy data available for imatinib were at least as good as those of historical examples, the FDA granted accelerated approval while requesting a Ph III trial evaluating the clinical benefit of imatinib compared to interferon + cytarabine, the standard of care at the time, as a PMC. (imatinib FDA Medical Review 2001)

The initial NDA of imatinib was supported by a safety database including 1027 patients, which allowed description of the side effect profile of this first-in-class tyrosine kinase inhibitor, although no comparative data were submitted. Nevertheless, the FDA considered the safety profile of imatinib acceptable to support accelerated approval. (imatinib FDA Medical Review 2001)

The 2002 accelerated approval for 1st line adult Ph+ CML was based on improved HR and MCyR rates of imatinib compared to interferon + cytarabine. In addition, improvements of time to progression and time to AP and BP were demonstrated, although the durability of these effects was not established at the time of approval, and no effect on OS was demonstrated at that time. (imatinib FDA Medical Review 2002)

Approval of imatinib for the 2nd line treatment of paediatric patients with Ph+ CML in 2003 was based on CCyR and MCyR observed in two Ph I dose-escalation trials. Although the efficacy data were very limited, they were found to be consistent with those observed in adults previously. Compared to adults, no difference in the safety profile was detected based on a safety database including 39 paediatric patients. The PMC of this accelerated approval was a Ph II trial in paediatric Ph+ CML patients who were in 1st and 2nd line treatment. (imatinib FDA Medical Review 2003)

The 2006 accelerated approval for 1st line paediatric Ph+ CML was based on CHR rate at Week 8 supported by CCyR and PCyR data, which corresponded to the results seen in the corresponding adult population previously. PMC of this approval were efficacy and safety updates of the Ph II trial that led to this approval. (imatinib FDA approval letter 2006 and label 2006)

In the EU, initial approval of imatinib for 2nd line treatment of Ph+ adult CML in 2001 was based on the same data as the initial approval of imatinib for the same indication in the US. Although the CHMP did not consider the endpoint MCyR to be a validated surrogate endpoint, they approved imatinib under exceptional circumstances because the efficacy observed was similar or better compared to historical controls. (imatinib EPAR 2001)

The MAA of imatinib was supported by a safety database including 1027 patients, which allowed description of the side effect profile of this first-in-class tyrosine kinase inhibitor, although no comparative data were submitted. Nevertheless, the CHMP considered the safety profile of imatinib acceptable to support accelerated approval. In spite of the fact that this was an approval under exceptional circumstances, the CHMP required the provision of long-term efficacy and safety data. (imatinib EPAR 2001)

4.2.2 Dasatinib

In 2006, the FDA granted accelerated approval to dasatinib for 2nd line treatment of adult CP, AP, BP CML patients who were resistant or intolerant to prior treatment including imatinib. This approval was based on data from four single-arm Ph II trials with approximately 6 months of follow-up. Primary efficacy endpoints were MCyR for CP CML and MHR for AP and BP CML. Interestingly, the 2006 dasatinib NDA included data for both CML and ALL. At the time of FDA review, precedence existed for accelerated approvals of compounds for the treatment of CP, AP and BP CML based on response rates (MCyR and MHR) with limited duration, while complete response rate of limited duration was the basis of full approval in ALL. Therefore, the initial NDA was split into two and accelerated approval was granted for CML and full approval for ALL. (dasatinib FDA medical review 2006)

The NDA was supported by a safety database including 1104 patients, 489 of which with CML. Although the FDA found the safety database adequate with regard to number of patients in the target indication, they considered it limited with regard to duration of exposure and the absence of comparative data. These were to be generated in a randomized Ph III trial comparing dasatinib to imatinib. (dasatinib FDA medical review 2006)

In the EU, dasatinib was granted regular approval for the treatment of CP CML (or Ph+ ALL) with resistance or intolerance to prior therapy in 2006 (dasatinib 2006 EPAR). This approval was based on the same data as the original accelerated NDA approval together with an additional Ph II trial (CA180017) which compared dasatinib to imatinib in CP CML. This trial, however, was not powered to demonstrate statistical significance (neither with regard to superiority nor to non-inferiority) and allowed cross-over. Primary efficacy endpoint of this trial was MCyR at 3 months, which was met by 35% of the dasatinib treated patients compared to 29% of the imatinib treated patients. CCyR data supported this result with 21% of the dasatinib treated patients achieving this endpoint compared to 8% of the imatinib treated patients. The MAA was supported by a safety database including 511 patients with CMP or ALL. The main shortcoming of the safety data was the lack of long-term safety data as pointed out by the CHMP. (dasatinib 2006 EPAR)

In 2010, the FDA granted accelerated approval to dasatinib for the treatment of newly diagnosed adult CP CML patients. Since no review documents are published for this nilotinib approval, information on the basis for approval is taken from the label and the approval letter. According to this information, this approval was based on data from a Ph III trial CA180056 comparing dasatinib to imatinib with CCyR at 12 months as primary efficacy endpoint. In addition, MMR, defined as "BCR-ABL ratios $\leq 0.1\%$ by RQ-PCR in peripheral blood samples standardized on the International scale", supported the approval as secondary efficacy endpoint. This sNDA was supported by safety data from 519 patients with newly diagnosed CP CML. The PMC connected with this approval was to provide complete (60 months) data of the Ph III trial. (dasatinib FDA approval letter 2010 and label 2010)

4.2.3 Nilotinib

In 2007, FDA granted accelerated approval to nilotinib for treatment of adult CP and AP CML patients resistant or intolerant to prior therapy including imatinib mesylate. At the time of approval, dasatinib had been granted accelerated approval in the same indication. The nilotinib approval was based on data from a Ph II trial without comparator, since none was available at the time of initiation of this trial. Primary endpoints were MCyR for CP CML and MHR for AP CML and a minimum follow-up of 6 months. The NDA was supported by a safety database including 438 patients, 318 of which with CP CML. The FDA considered the safety profile acceptable, however, since signs of QT prolongation

were detected, FDA required adequate labeling and a medication guide. The PMC requirement for conversion to full approval was 24 months follow-up data from the Ph II trial. (nilotinib FDA Medical Review 2007 and approval letter 2007)

In the EU, nilotinib was granted regular approval in 2007 based on data from the same study as the NDA, albeit with a data cut-off date that occurred approximately one year later. (nilotinib 2007 EPAR) The endpoints were considered to be accepted surrogates and the duration of response sufficient. Although dasatinib was approved for this indication at the time of nilotinib approval, no comparative data were requested by CHMP who considered the nilotinib efficacy data to be "in the range of what [is] described for dasatinib". Although approximately 2740 healthy volunteers and patients with various diagnoses had been exposed to nilotinib by 25 Jul 2007, the MAA was mainly supported by a safety database including 438 patients, 318 of which with CP CML. The safety data were considered acceptable, the main safety concern identified was QT prolongation. (nilotinib EPAR 2007)

In 2010, FDA granted accelerated approval to nilotinib for the treatment of adult patients with newly diagnosed CML. At the time of approval, two compounds were approved in this indication: imatinib with a full approval (converted in 2009) and dasatinib with an accelerated approval. Since no review documents are published for this nilotinib approval, information on the basis for approval is taken from the label and the approval letter. According to this information, this approval was based on a randomized open-label trial comparing nilotinib to imatinib using MMR at 12 months as primary efficacy endpoint. The definition of MMR was the same as the one used for the secondary efficacy endpoint in CA180056, the trial that led to accelerated approval of dasatinib in the same indication. (see Section 4.2.2) This nilotinib approval is the first and only example of MMR supporting a regulatory approval in CML in the US. Evaluation of the safety profile of nilotinib in this indication was primarily based on the pivotal trial including 279 patients. The PMC of this approval was submission of 24 and 60 months follow-up data from the trial leading to accelerated approval. (nilotinib FDA approval letter 2010 and label 2010)

The same data supported a 2010 EU variation for nilotinib that extended the indication to treatment of newly diagnosed adult patients with CML. At the time, MMR was not included as an acceptable efficacy endpoint for newly diagnosed CML in Rev 3 of the anticancer guideline. However, data from an 84 months follow-up of the pivotal imatinib trial CSTI571A0106 supported the use of MMR as a relevant surrogate primary endpoint. Use of this endpoint had been discussed in a scientific advice procedure for nilotinib at which the CHMP accepted MMR at 12 month as an appropriate primary endpoint. In contrast, the current Anticancer guideline requires 18 months MMR data in a superiority trial to support an approval in newly diagnosed CP CML. This approval is currently the only approval for 1st line CML based on MMR in the EU. (nilotinib 2010 variation, EMA/CHMP/678208/2010)

4.2.4 Ponatinib

In 2012, ponatinib was granted accelerated approval by FDA for 2nd line treatment of adult patients with CP, AP or BP CML, who were TKI resistant or carried the T315I mutation. At the time of approval, no treatment options existed for patients with the T315I mutation. The approval was based on the same surrogate efficacy endpoints that had been used for the approvals of imatinib, dasatinib and nilotinib in the 2nd line setting, namely MCyR for CP CML and MHR for AP CML with 6 months follow-up. Also in line with those approvals, the PMC was 24 months follow-up data for conversion to regular approval, although the Medical Reviewer recommended including an additional Ph III trial in newly diagnosed CML comparing ponatinib to imatinib in the PMCs. (ponatinib FDA Medical Review 2012 and approval letter 2012)

The NDA was supported by a safety database including 530 patients, 449 of which from the pivotal trial 10-201. This seems to be quite a large safety database when taking into consideration that several TKIs had been approved previously, so knowledge on class effects already existed. Nevertheless, in their Medical Review of the NDA, the FDA pointed out that they could not adequately evaluate the side effect profile of ponatinib since no comparative data were available. Such an evaluation would only be possible once data were available from the on-going Ph III trial comparing ponatinib to imatinib in patients with newly diagnosed CML. In spite of this shortcoming and of the fact that the safety data submitted with the initial NDA and with the 4-month safety update pointed towards a risk of arterial thrombotic effects with treatment with ponatinib, the FDA did not require a risk evaluation and mitigation strategy (REMS) for the initial approval. However, the initial 14 Dec 2012 label did include a black box warning for this side effect. (ponatinib FDA Medical Review 2012 and ponatinib label 2012)

In the EU, ponatinib was granted regular approval in 2013 based on the same data that supported the NDA. The CHMP considered the treatment effect size to be "very" clinically meaningful and recommended approval, although prior scientific advice had suggested that the trial design may not support regulatory approval at all. However, since CML patients who are resistant or intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation had virtually no treatment options at the time of approval of ponatinib. (ponatinib 2013 EPAR)

Just like the NDA, the MAA was supported by a safety database including 530 patients, 449 of which from the pivotal trial 10-201. Similar to the FDA, the CHMP pointed out that the evaluation of the side effect profile was difficult because no comparative data were available. However, ischemic events were considered a potential risk and routine pharmacovigilance activities were agreed with the sponsor. (ponatinib 2013 EPAR)

4.2.5 Omacetaxine mepesuccinate

In 2012, omacetaxine was granted accelerated approval for the 3rd line treatment of adult patients with AP or CP CML, who are resistant or intolerant to 2 or more TKIs. This approval was based on data from two single-arm Ph II trials with MCyR as primary efficacy endpoint for CP CML and MHR for AP CML. At the time of approval, no drug was approved in the 3rd line setting. (Omacetaxine mepesuccinate FDA Medical Review 2012 and Approval Letter 2012) This NDA was converted to full approval based on the submission of 24 months follow-up data. (Omacetaxine mepesuccinate FDA Approval Letter 2014)

The NDA was supported by a safety database including 158 in target indication. Omacetaxine mepesuccinate was a novel substance that inhibits protein synthesis and that was not assigned to a specific class at time of NDA submission. The amount of safety data was quite small for a compound with a novel mechanism of action. Nevertheless, no major safety concerns were identified by FDA. (Omacetaxine mepesuccinate FDA Medical Review 2012)

In the EU, the application for omacetaxine was withdrawn in 2011 at Day 120 when the Rapporteur and Co-Rapporteur requested longer follow-up, which could not be provided in the time frame of an MAA review in the centralised procedure. Based on the Question & Answer document on the omacetaxine withdrawal published on the EMA website, it may be assumed that only data from CML-202 were considered pivotal by the applicant for this application. In their withdrawal letter, the

sponsor indicated future plans to re-submit the MAA, however, by 06 Apr 2014, no application has been resubmitted. (Omacetaxine mepesuccinate Q&A document 2013, EMA/13310/2011)

4.2.6 Bosutinib

In the EU, bosutinib was granted conditional approval in 2013 based on a post-hoc analysis of 3160A4-200-WW, which was originally submitted as supportive trial. The original aim of the sponsor had been to achieve a label in 1st line CML based on a randomized Ph III open-label trial comparing bosutinib to imatinib. The trial included patients with CP CML, and CCyR rate at 1 year was its primary efficacy endpoint, which was the recommended endpoint based on Rev 3 of the anticancer guideline. According to the current revision, it would be considered a secondary efficacy endpoint in this setting with major molecular response at 18 months being the recommended surrogate endpoint for a superiority trial. However, the trial failed to meet its primary efficacy endpoint, and at 24 months imatinib was numerically better than bosutinib. The secondary efficacy endpoint, MMR, reached statistical significance at 12 months, but not at 24 months follow-up. Therefore, the CHMP considered this trial to be failed. (bosutinib EPAR 2013)

The MAA also contained data that were generated in single-arm Ph II trials, which were considered sufficient for regulatory approval of 3rd line TKIs based on Rev 3 of the anticancer guideline, but not based on the current revision, which requires comparative data. Post-hoc analyses of these Ph II data eventually provided the basis of approval. For these post-hoc analyses, subpopulations of last line patients with “unmet medical need” were identified. Such patients were described as patients who were not eligible for dasatinib or nilotinib treatment due to co-morbidities, TKI intolerance or mutations that would confer resistance to these TKIs. (bosutinib EPAR 2013)

The MAA was supported by a safety database including 1572 patients, 118 of which from the pivotal trial 3160A4-200-WW. Given that bosutinib is a TKI, for which class effects are fairly well-described, this appears to be quite a large safety database. However, since the sponsor originally aimed to base the approval on the Ph III trial in 1st line CML patients, the size is understandable. (bosutinib EPAR 2013)

Based on the same Ph II data, FDA granted full approval of bosutinib for the treatment of CP, AP and BP Ph+ AML resistant or intolerant to prior therapy in 2012. The primary efficacy endpoint was MCyR at 24 weeks for patients with CP CML. At the time of review, imatinib, dasatinib and nilotinib were approved in the US and were considered “available therapy” by the medical reviewer. At this time, the NDA for nilotinib and dasatinib had been converted to full approval. No PMC requesting comparative data were required for bosutinib. (Bosutinib FDA Medical Review 2012)

The NDA was supported by a safety database including 870 patients, 570 of which from the pivotal single-arm Ph II trial. Although bosutinib belongs to the class of TKIs, which have well-understood class effects, the FDA considered the safety data limited, since they based their assessment primarily on data from the single-arm Ph II trial. (Bosutinib FDA Medical Review 2012)

4.3 MCL

Table 11 Pivotal data leading to approval for treatment of 2nd line treatment of MCL

Pivotal study(ies)	N	Efficacy	Approval year / type	Comments
Ibrutinib				
PCYC-1104-CA: Ph II, OL, single-arm	115 Safety: ~170; 120 in MCL	1º: ORR: 65.8% (CI 56.2,74.5; IRC); 2º: mDOR: 17.5m (CI 15.8,NR); PFS: not considered evaluable in a single-arm trial by FDA; mOS: NR	2013 / accelerated	PMC: 24 months follow-up of trial PCYC-1104-CA; Ph III, DB, PBO-controlled trial evaluating ibrutinib + benda + R in newly diagnosed MCL

Source: Ibrutinib MCL FDA Medical Review 2013

Abbreviations: benda = bendamustine; CI = 95% confidence interval; CR=complete response; CRu=complete response unconfirmed; DB = double-blind; FDA = Food and Drug Administration; IA=independent assessment; IAP=independent assessment panel; IC=investigator's choice; IPI=International Prognostic Index; IWRC: International Workshop Criteria; m = months; MCL = mantle cell leukaemia; mDOR = median duration of response; mOS = median overall survival; N = number of patients; NR = not reached; ns=not significant; NR = not reached; OL = open-label; ORR = overall response rate; PBO = placebo; PFS = progression-free survival; Ph = Phase; PMC = post marketing commitment; R = rituximab

Prior to ibrutinib, bortezomib and lenalidomide had been granted full approvals for the treatment of MCL after failure of one or two prior lines of therapy and after failure of two prior therapies, one of which being bortezomib, respectively. The approvals were based on ORR (complete response, unconfirmed complete response and partial response) determined by an Independent Review Committee (IRC) and mDOR in single-arm trials. Bortezomib achieved an ORR of 31% with an mDOR of 15.4 months and lenalidomide an ORR of 26% with an mDOR of 16.6 months. (Ibrutinib MCL FDA Medical Review 2013)

However, at the time of the ibrutinib review, the FDA voiced uncertainty as to the relation of ORR and mDOR to OS, especially since 48% of the patients enrolled in the Ph II trial with ibrutinib experienced progressive disease and 30% of them died because of it. Another point of concern was that the follow-up of patients who responded was relatively short at time of approval, lending additional uncertainty to the true efficacy of ibrutinib. In addition, no quantitative assessments of extranodal disease sites were made and the new 2007 Response Criteria for MCL, which were used in this trial, included ^{18}F fluorodeoxyglucose positron emission tomography (FDG-PET) instead of computer tomography (CT) scans, although it is currently unknown whether FDG-PET negative complete responses confer the same benefit as CT-based complete responses (Cheson et al., 2007). And, lastly, bortezomib and lenalidomide had already been approved for MCL. (Ibrutinib MCL FDA Medical Review 2013)

The NDA was supported by a safety database including at least approximately 170 patients, of which 120 were in the target indication. Although ibrutinib is a first-in-class Bruton's tyrosine kinase inhibitor and although the approval of the NDA was based on a single-arm Ph II trial, the FDA considered the safety data adequate. Still, the FDA reviewer pointed out that results from on-going randomized, controlled trials would provide safety data to better assess certain signals, such as second primary malignancies. (Ibrutinib MCL FDA Medical Review 2013)

In the EU, the MAA for ibrutinib for the treatment of MCL is currently in review. The Day 120 list of questions was to be adopted at the March CHMP meeting (CHMP Meeting Agenda March 2014).

5. EXAMPLES OF DRUGS MOST RECENTLY APPROVED

As of 15 Apr 2014, two drugs with breakthrough designation have been approved by FDA for the treatment of haematological malignancies: obinutuzumab and ibrutinib.

Obinutuzumab was approved on 01 Nov 2013 for the treatment of patients with previously untreated CLL in combination with chlorambucil. This was a regular approval based on PFS collected in a randomized, controlled Ph III trial comparing obinutuzumab in combination with chlorambucil to chlorambucil alone. Breakthrough designation was granted on 09 May 2013, after the pre-BLA meeting with FDA had already been held. The approval was supported by a safety database including 356 patients from the pivotal trial. Obinutuzumab is an anti-CD20 antibody and belongs, therefore, to a class with a well-defined side effect profile. The FDA considered the safety data provided adequate for a safety evaluation. (Obinutuzumab FDA Medical Review 2013)

Ibrutinib was approved on 13 Nov 2013 for the treatment of patients with MCL who have received at least one prior therapy and on 12 Feb 2014 for the treatment of patients with CLL who have received at least one prior therapy. As stated in the product information, “an improvement in survival or disease-related symptoms has not been established” for either indication. Both approvals were granted as accelerated approvals based on ORR. Details are provided in Section 4.1.4 for CLL and in Section 4.3 for MCL.

Ibrutinib was granted breakthrough designation for MCL on 08 Feb 2013 after the EoP II meeting (held on 03 Dec 2012), most likely based on the Ph II trial data that formed the basis of the approval in this indication. (FDA Medical Review of ibrutinib for MCL 2013) In April 2013, it was also granted breakthrough designation for relapsed/refractory CLL with del17p. (Pharmacyclics press release 08 Apr 2013), however, the approval was granted for the entire relapsed/refractory CLL patient population, since the Ph II trial did not detect a difference in efficacy in patients with del17p compared to those without. (Byrd 2013)

In the EU, no approvals have been granted for compounds intended to treat haematological malignancies after Revision 4 of the Anticancer guideline has come into effect.

6. CURRENT REGULATORY DISCUSSIONS OF NOVEL POTENTIAL SURROGATE ENDPOINTS

6.1 MRD IN CLL

In the context of CLL, a potential new surrogate efficacy endpoint is currently attracting attention of both the CHMP and the FDA: MRD, or rather absence thereof. Since CLL is caused by clonal expansion of leukaemia cells, reducing the number of these leukaemia cells below an internationally established threshold, i.e., achieving MRD negativity, has been shown to be correlated with improvement of PFS and OS. (Böttcher 2012) This endpoint had already been suggested as supportive in Revision 3 of the Anticancer guideline, however, to date, no approval has been based on it nor have MRD data been used to strengthen the evidence of benefit provided by a novel compound. Nevertheless, it is being evaluated as secondary or exploratory endpoint in several clinical trials,

including Ph III trials evaluating lenalidomide, ibrutinib, idelalisib either as mono- or combination therapy in 1st line or relapsed CLL (e.g., NCT01556776, NCT01611090, NCT01980888).

6.1.1 CHMP view

In addition to the mentioning of MRD as supportive measure of efficacy in the Anticancer guideline, the CHMP published a concept paper on the need to revise Appendix 4 of the guideline on 16 Jul 2013 (EMA/CHMP/432831/2013). In this concept paper, the CMHP acknowledge that MRD negative status is of prognostic value for PFS and OS, **the** endpoints for clinical trials in cancer. The CHMP refer to data published by clinical groups who conducted prospective trials in CLL as well as international working groups who published criteria for the assessment of MRD in CLL (Cheson 1996; Hallek 2008; Eichhorst 2011; Rawstron 2001, Böttcher 2012). However, although the CHMP acknowledge that MRD negativity is a qualitative predictor of PFS and OS, it requires additional data to allow estimation of a PFS difference based on MRD status. What kind of data would be considered appropriate to provide evidence for a quantitative improvement in PFS based on MRD is not clearly stated. Currently, it also remains unclear what kind of data would be needed to justify use of MRD negativity as primary efficacy endpoint in a clinical trial. Scientific advice should be sought, if a sponsor considered using MRD negativity to support efficacy of a novel compound in clinical trials.

6.1.2 FDA view

Similarly, the FDA are discussing the applicability of MRD negativity as a surrogate efficacy endpoint in CLL. To foster this discussion, FDA held a workshop on this topic on 27 Feb 2013. Unfortunately, no clear decision was made on the applicability of MRD negativity. (FDA workshop on MRD in CLL 27 Feb 2013, transcript) Nevertheless, the FDA indicated interest in this endpoint and advised sponsors to consider central testing for MRD if it were to be used in Ph III registration trials. In addition, so-called proficiency testing should be conducted as outlined in the FDA guidance for industry on the qualification process for drug development tools (Jan 2014). The threshold for MRD negativity was considered reasonable, and based on current data an assessment at end-of-therapy was likely to be the most appropriate. Less consensus seemed to exist with regard to the tissue that should be tested, peripheral blood or bone marrow. And a caveat was raised, since all data currently linking MRD negativity to improved PFS and OS were based on trials with alkylating compounds, purine analogs or chemoimmunotherapy. FDA were not convinced that similar data would be obtained with compounds employing other mechanisms of action. (FDA workshop on MRD in CLL 27 Feb 2013, transcript) Similar to the CHMP, the applicability of MRD as a surrogate endpoint should be discussed with FDA prior to including it in Ph III trials.

7. DISCUSSION

7.1 CLL

As can be seen from the examples for CLL provided in Section 4.1, ORR has been considered a surrogate effect, not a clinical benefit, in relapsed/refractory CLL by both FDA and CHMP in the past. As such, it has been the basis of accelerated and conditional approvals, respectively. However, PFS data were requested as a post-marketing commitment by both the FDA and the CHMP in all instances. With the most recent approvals of ibrutinib based on ORR in form of accelerated and of obinutuzumab based on PFS in form of regular approval in the US, it is expected that this requirement will still be applicable in the future and it is not expected to change with the new FDA guideline on expedited programs. The MAAs of both ibrutinib and obinutuzumab are currently in review – most likely with

the same data that were included in the NDA and the BLA, respectively. It is expected that marketing authorisations will be granted for both of them, since the changes in the Anticancer guideline are not expected to affect the acceptability of ORR and PFS data to support conditional and full approvals in CLL, respectively.

Although discussions of MRD as a potential novel surrogate efficacy endpoint in CLL are on-going both in the EU and the US, it seems unlikely that approvals will be granted on this endpoint soon. As pointed out at the February 2013 FDA workshop, establishing a novel endpoint as a surrogate supporting regulatory decisions takes several steps: Not only does the (MRD) endpoint need to be included in clinical trials to generate data, a validated assay needs to be in place and standardized internationally (e.g., by virtue of an NIH consensus conference). And only once the standardized assay is implemented into clinical trials prospectively, it may be considered to support regulatory decisions. (Deisseroth, presentation at Feb 2013 FDA workshop on MRD in CLL)

7.2 MCL

The recent accelerated approval of ibrutinib for relapsed/refractory MCL is an interesting example of how the FDA's view can change on the acceptability of data to support approvals over time as new treatment options emerge and international response criteria evolve. This approval was based on ORR data obtained in one single-arm Ph II trial. The same type of data had led to full approvals of bortezomib and lenalidomide previously. However, when reviewing the NDA for ibrutinib, the FDA voiced concern on the surrogacy of ORR and on the reliability of the newly revised international response criteria. In spite of these concerns, and although treatment is available in this indication, ibrutinib was granted accelerated approval. Strictly speaking, this is in contradiction to the FDA guidance on expedited programs and illustrates that there is some flexibility in the regulatory decisions taken by FDA.

7.3 CML

In CML, the space for developing novel compounds is becoming increasingly crowded and an increasing number of compounds has been licensed for patients who are resistant or intolerant to prior TKI therapy (see Section 4.2). A common theme in the development of these drugs is to target a highly refractory patient population initially while initiating a large randomized Ph III in treatment naïve patients. Requirements for efficacy endpoints supporting approvals have evolved over the years, from demonstrating major haematological response via major cytogenetic response to major molecular response. However, although the constitutively active bcr-abl kinase has been known to be the single cause of the disease since the 1980s, so far only one compound has been approved based on major molecular response, nilotinib.

Different patterns of approval could be seen for CML treatments in the EU compared to the US: Data that led to accelerated approvals for CML in the US frequently led to full approvals in the EU, e.g., for dasatinib, nilotinib and ponatinib. This suggests that, at least in the context of CML, the CHMP considered the data sufficient to provide evidence of a clinical benefit in patient populations who had no treatment options available, while the FDA still considered them to be a surrogate. In contrast, bosutinib was granted full approval by FDA and conditional approval in the EU based on the same post-hoc analyses of data generated in Ph II trials after failure of a Ph III trial in 1st line CML. Since Revision 4 of the Anticancer guideline requires comparative data to support licensure of a 3rd line TKI, it remains doubtful that an approval based on a similar data package may be granted again.

Another interesting aspect is the fact that accelerated approvals have been granted repeatedly for similar, albeit not identical, 2nd line CML indications over time in spite of the fact that an increasing number of treatments have become available. Although the FDA guidance on expedited programs clarifies that "available therapy" is, strictly speaking, only therapy that has been granted full approval, it still suggests that compendia-listed compounds may be considered "available therapy" as well. Therefore, it is difficult to assess whether this approach of repeatedly granting accelerated approvals will still be observed in the future for late-line CML or whether comparative data may be required to support accelerated approval in the US. Early interaction with the FDA should be sought to ensure that the planned clinical development programme actually does support an approval.

7.4 SAFETY AND BENEFIT-RISK EVALUATION

In the examples provided in Section 4, the size of the safety database available at time of MAA or NDA submission ranged from approximately 150 patients (alemtuzumab initial NDA) to approximately 1660 (imatinib initial NDA) when taking all available safety data into account, also those from non-target indications. When focusing on the target indication and taking into consideration only initial approvals, the size of the safety databases ranged from 78 (oral fludarabine initial NDA) to 570 (bosutinib initial NDA). Although one would assume that, in general, the Agencies would require more extensive safety data for drugs with a novel mechanism of action (MoA) than for those with a well-described MoA, this does not necessarily appear to be the case.

For example, for the initial accelerated approval of ibrutinib data from only 120 patients with MCL enrolled in the pivotal single-arm Ph II trial were considered sufficient by FDA to support its safety evaluation, although ibrutinib is functioning through a novel mode of action. At the time of NDA approval, several randomized, controlled Ph III trials were on-going with ibrutinib in various indications, however, additional data from a Ph III trial comparing ibrutinib to temsirolimus in MCL are not expected before August 2014 (NCT01646021). Therefore, it seems that even quite limited safety data may support the approval of a first-in-class compound in the US.

On the other hand, the safety database for bosutinib, the most recently approved TKI in the US, was considered limited by FDA although it included 870 patients. 570 of these participated in the pivotal single-arm Ph II trial. However, since no comparative safety data were collected in this trial, the FDA considered the safety information limited. Bearing in mind that safety data were also included from a failed randomized, controlled Ph III trial and the fact that TKIs are considered to have a well-understood safety profile, it seems surprising that the FDA would consider the amount of safety data limited for bosutinib.

Similar to the FDA, the CHMP basis the risk-benefit evaluation primarily on data obtained in the target indication. Concerns on the limitations of safety raised by the CHMP are also similar to those raised by FDA. For example, both Agencies considered the safety data supporting the initial approval of dasatinib limited, because long-term safety data were limited at the time. Similarly, both Agencies considered the safety data supporting the ponatinib approval limited, since no comparative data were available. However, they do not always assess data in the same way. While both Agencies considered the safety data supporting the initial approval of dasatinib limited with regard to long-term data, only the FDA found them also to be limited because no comparative data were available.

Regardless of the slightly different view of the Agencies on the data available, generally, safety data tend to be rather limited at the time of an accelerated or conditional approval. As a consequence, the comparatively limited safety data supporting some accelerated or conditional approvals, may lead to

the approval of drugs before their risks are well-described. Emerging safety data from trials that are on-going after initial approval may then lead to label restrictions or withdrawal of the marketing authorisation, if these emerging data are rather concerning. One such example is ponatinib: Ponatinib was granted accelerated approval in the US and full approval in the EU, respectively, with a safety database including 530 patients, 449 of which from the pivotal trial 10-201. Since it is a TKI, one may assume that its safety profile would be similar to that of the class of TKIs. However, even in the safety data supporting this approval, signs suggesting a risk of arterial thrombotic events were detected. Due to the limited data available, the likelihood of this risk could not be fully assessed and no risk evaluation and mitigation strategy (REMS) was required by FDA. However, the initial 14 Dec 2012 label did include a black box warning for this side effect. (Ponatinib FDA Medical Review 2012, Ponatinib US label 2012)

As announced in the 18 Oct 2013 press release by Ariad Pharmaceuticals, an increased incidence of arterial thrombotic events were observed in the Ph III trial that was conducted to convert the accelerated approval into a full approval initially, but that was terminated due to these results. Based on these data, FDA initially required the manufacturer to suspend sales of the drug, which were permitted again after the product information was updated to reflect this risk and its mitigation in a REMS, which had not been required at the time of approval, was implemented. (FDA drug safety information on ponatinib, 2013) In the EU, in addition to changes in the SmPC, a referral is currently on-going according to Article 20 of Regulation (EC) 726/2004. (EMA/745969/2013)

7.5 DIFFERENCES AND SIMILARITIES IN APPROVALS GRANTED BY FDA AND THE CHMP

In general, recent publications, such as those by Hartmann 2013 and Shea 2013, suggest different approval patterns in the US and the EU: Whereas repeated granting of accelerated approvals for similar indications appears to be a regulatory approach taken by the FDA, the CHMP would rather grant conditional approvals to increasingly smaller target indications with high unmet medical needs. Such an approach would be in line with the new FDA draft guideline on expedited programs, especially if compounds already approved for a certain indication have only been granted accelerated approval in a certain indication. According to the new draft guideline for expedited programs such compounds would not be considered “available therapy” (see Section 3.2.4.1.2), so that the unmet medical need still exists in spite of these approvals. As a consequence, the path towards accelerated approval is still available once other compounds have been granted accelerated approvals for the same indication. Alternatively, accelerated approval may be granted, if a “meaningful therapeutic benefit over existing therapies” has been demonstrated. (FDA Guidance on Expedited Programs 2013)

In the EU, Regulation (EC) 507/2006 defines “unmet medical need” as the lack of a satisfactory method of diagnosis, prevention or treatment for a specific disease. Alternatively, the Sponsor may demonstrate that the new compound provides a major therapeutic advantage. Although no definition of “satisfactory method” is available, the CHMP guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 (EMEA/509951/2006) provides some guidance on how to justify that a new compound fulfills an unmet medical need. According to this guideline, such a justification should provide quantitative medical and/or epidemiological data highlighting an unmet medical need. This justification should also include a review of all available methods of treatment of the disease and a justification on how and to what extent the new compound will address this medical need. If treatment options are already available, such a justification should be based on the additional benefit provided by the new compound compared to available therapy. This EU approach of granting conditional approval based on data

comparing a new compound to “available therapy” is similar to one of the two scenarios in which FDA may grant accelerated approval.

A major difference, though, is that the accelerated approval pathway is available both to initial and sNDAs in the US, whereas conditional approval may only be granted for initial MAAs in the EU, no “accelerated” approval pathways are foreseen for variations in the EU. As a consequence, e.g., when comparing Table 9 with Table 10 it appears as if FDA is using the accelerated approvals more often to grant approvals for novel drugs for life-threatening indications than the CHMP. To avoid this bias when looking at the seemingly different approval patterns, one needs to, therefore, focus on initial approvals only to evaluate whether or not there is a difference in the use of accelerated and conditional approvals, respectively, in the US and the EU.

When comparing only initial approvals for the treatment of CML, similar data packages appear to lead to approvals both in the EU and the US (see Table 9 and Table 10). For this indication, it is particularly striking that several examples do exist where FDA granted accelerated approvals only, whereas the CHMP granted full approvals, as illustrated in Table 12. This is despite the fact that the endpoints supporting these approvals were considered appropriate surrogate endpoints in the target indication by both Agencies as indicated in the respective reviews and assessment reports. This is also despite the fact that most sponsors discussed their clinical development programme and regulatory strategy early enough during development to allow for changes made to the design of the pivotal trials based on the feedback from FDA. It appears, therefore, that, despite the fact that seeking and adhering to scientific advice generally is considered to increase the likelihood of obtaining regulatory approval (Regnstrom 2010), this approach does not seem to have increased the chance of obtaining full rather than accelerated approval for the CML indications reviewed here. Overall, the finding that similar data packages led to approvals in both legislations is different from the observations published by Hartmann 2013. However, one needs to bear in mind that the current thesis focuses on a few selected target indications, whereas Hartmann reviewed approval patterns for oncological compounds in general.

Table 12 Approvals granted by FDA and CHMP based on virtually identical data packages

Compound	Indication	US approval	SPA	EU approval	SA
imatinib	2nd line CML	accelerated approval	yes[a]	exceptional circumstances	no
dasatinib	2nd line CML resistant/intolerant to prior tx incl imatinib	accelerated approval	yes[b]	full approval	yes
nilotinib	2nd line CML resistant/intolerant to prior tx incl imatinib	accelerated approval	yes[c]	full approval (data cut ~1 year later)	yes
ponatinib	TKI resistant or T315I mut+ 2nd line CML	accelerated approval	N/A[d]	full approval	protocol assistance
omacetaxine	3rd line CML	accelerated approval	no	negative opinion	N/A
bosutinib	2nd line CML resistant or intolerant to prior tx	full approval	yes[e]	conditional approval	yes[f]

Notes:

a: The FDA Medical Review of imatinib does not specify that the protocol of the pivotal trial was reviewed under a special protocol assessment (SPA). However, the overall clinical development plan was discussed with FDA at multiple occasions and appears to have been modified based on FDA feedback.

b: According to the FDA Medical Review of dasatinib, no SPA was sought. However, the Sponsor discussed the overall clinical development programme at an End of Phase I meeting with FDA.

c: According to the FDA Medical Review of nilotinib, SPAs were sought for CML patients with suboptimal response to imatinib and for a non-haematological indication. However, the overall registration strategy appears to have been discussed at End of Phase I and II meetings.

d: According to the FDA Medical Review of ponatinib, several Type B meetings occurred, however, no information is provided on what was discussed at these meetings.

e: According to the FDA Medical Review of bosutinib, several Agency meetings occurred, in particular, to discuss the path forward after the failure of the Ph III trial in 1st line CML.

f: According to the bosutinib EPAR, scientific advice was sought for this compound by the Sponsor. However, no details are available on the topics discussed.

Sources: bosutinib 2013 EPAR, dasatinib FDA Medical Review initial approval 2010, imatinib FDA Medical Review initial approval 2001, imatinib 2001 EPAR, nilotinib FDA Medical Review 2007, omacetaxine mepesuccinate FDA Medical Review 2012, ponatinib FDA Medical Review 2012

Abbreviations: CML = chronic myelogenous leukaemia; EPAR = European Assessment Report; mut+ = mutation positive; N/A = not available; SA = scientific advice; SPA = special protocol assessment; TKI = tyrosine kinase inhibitor; tx = treatment

7.6 CLINICAL DEVELOPMENT IN A RAPIDLY CHANGING ENVIRONMENT

Over the last decades, our understanding of the underlying causes of many diseases has increased tremendously. As a consequence, new targets have been identified for the treatment of diseases previously inevitable fatal outcome. A prime example of how increased understanding of molecular disease etiology has led to the development of targeted treatment is CML. In 1972, the bcr-abl fusion kinase was detected, which was later on identified as the single molecular cause of the disease. (wikipedia bcr-abl tyrosine kinase inhibitor) Imatinib mesylate was developed to specifically target this fusion protein, which was discovered in 1992. (wikipedia bcr-abl tyrosine kinase inhibitor) In 2001, accelerated and conditional approvals were granted for 2nd line treatment of adult Ph+ CML patients in the US and the EU, respectively.

While originally the fusion protein was detected cytogenetically in form of the so-called Philadelphia chromosome, a more sensitive, PCR-based detection method was developed over time and criteria for the definition of major molecular response were established. In particular, GSK used substantial data generated for imatinib to support the surrogacy of major molecular response as a surrogate for OS in first line treatment of CML. (Nilotinib EPAR 2007) This was the primary endpoint supporting approval of nilotinib in this indication. (Nilotinib EPAR 2007) In spite of the fact that the cause of disease had been well described for decades, it took considerable time and effort to establish MMR as an accepted primary efficacy endpoint for first-line CML. This endpoint is now also included in the CHMP Anticancer guidance and, as a consequence, available for other sponsors as well.

It is expected that quite a large body of evidence may also be needed to establish MRD negativity as a surrogate for OS in (first line) CLL. The current data have not yet convinced either of the agencies, because although the CHMP Anticancer guideline mentions MRD as a potential endpoint, the recently published concept paper suggests that sponsor would need to provide additional data supporting this endpoint. It appears unlikely that the currently published evidence will be sufficient and sponsors may need to consider seeking approval on currently established endpoints, such as response rate and OS while collecting data on MRD in the same trials. Such data could, in the future, be used as supportive evidence for the surrogacy of MRD. Whether data collected for drugs with a certain MoA could be extrapolated to drugs with a different MoAs should be discussed with the Agencies.

Changes may also occur in the diagnostic or response criteria. Such changes may lead to uncertainty, which were reflected in the accelerated approval of ibrutinib for relapsed/refractory MCL. Although clearly an indication with high unmet medical need and in spite of precedence for full approvals based on similar data packages, the FDA reviewer voiced concerns about the assessment of response based on revised, internationally harmonized, response criteria. A Sponsor faced with this challenge of changing response criteria should reach out to the Agencies early to discuss how to ensure the data that are to be generated in a pivotal trial will be considered adequate for approval.

8. CONCLUSIONS

The precedence provided in this thesis suggests that response rates in one single-arm trial in populations with no (or very limited) treatment options may support accelerated or conditional approval, in some cases even full approvals, of compounds treating haematological malignancies. Although the type of approval granted, full or accelerated/conditional, varied in the US and the EU, in most cases similar data led to approvals in both legislations.

When aiming for an initial accelerated or conditional approval, sponsors should bear in mind that the initial approval will be most likely for a niche indication that may only generate limited revenue. In any case, comparative PFS or OS data will need to be generated as a PMC to achieve conversion to full approval, possibly in an earlier line of treatment. While PMCs are followed-up on, safety data may arise that could even further limit the approved indication.

In CLL, MRD appears to be a newly emerging surrogate efficacy endpoint for which data should be collected prospectively in clinical trials. However, since no internationally harmonized criteria exist for its detection, it is not expected that approvals will be based on this endpoint in the near future. However, they may lend supportive evidence to ORR results.

With the availability of the new guidelines, the bar may be raised for certain indications, e.g. for CML in the EU, however, they are expected to still provide a lot of room for discussion with the Agencies, especially in the context of the newly created breakthrough designation in the US. Early interaction with the authorities should be sought, both on the design of the trial leading to accelerated/conditional approval and on the design of the Ph III trial that would be expected as PMC in case of an accelerated or conditional approval.

9. ABBREVIATIONS

AA	accelerated approval
AML	Acute myeloid leukemia
ALL	Acute lymphoid? leukemia
alloSCT	allogeneic stem cell transplantation
AP	accelerated phase
aug.	augmented
autoSCT	autologous stem cell transplantation
BCR/ABL	breakpoint cluster region/Abelson
benda	bendamustine
BLA	Biologics license application
BP	blast phase
BTK	Bruton's tyrosine kinase
CCyR	complete cytogenetic response
CFAR	cyclophosphamide, fludarabine, alemtuzumab, rituximab
CFR	Code of Federal Regulations
CHMP	Committee of Human Medicinal Products
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CHR	complete haematologic response
CI	95% confidence interval
clb	chlorambucil
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukaemia
CMR	complete molecular response
CP	chronic phase
CR	complete response
CRR	Complete response rate
CRu	unconfirmed complete response
CT	computer tomography
CVAD	cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high-dose methotrexate and cytarabine
DB	double-blind

del11q	deletion of 11q
del17p	deletion of 17p
DFS	Disease-free survival
EC	European Commission
EFS	Event-free survival
EMA	European Medicines Agency
EMA SA	EMA scientific advice
EoPII	end of Phase II meeting
EPAR	European Public Assessment Report
ESMO	European Society of Medical Oncology
EU	European Union
FA	fludarabine, alemtuzumab
FCR	fludarabine, cyclophosphamide and rituximab
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FDASIA	Food and Drug Administration Safety and Innovation Act
FD&C Act	Food, Drug & Cosmetic Act
FDG-PET	^{18}F fluorodeoxyglucose positron emission tomography
FGFR	Fibroblast growth factor receptor
FMCR	fludarabine, cyclophosphamide, mitoxantrone, rituximab
FMR	fludarabine, mitoxantrone, rituximab
FR	fludarabine, rituximab
HD	high-dose
HDMP	high-dose methyl prednisone
HR	haematologic response
HRQoL	Health-related quality of life
HSCT	Haematopoetic stem cell transplant
IAP	independent assessment panel
IC	investigator’s choice
IFN	interferon 2-alpha
IND	investigational new drug
Inv	investigator assessment

IPI	International Prognostic Index
IRC	Independent Review Committee
i.v.	intravenous
IWCLL	International Working Group on CLL
IWRC	International Workshop Criteria
m	months
MAA	Marketing authorisation application
MCL	Mantle cell lymphoma
MCyR	major cytogenetic response
mDOR	median duration of response
MDS	Myelodysplastic syndrome
MHR	major histologic response
MMR	major molecular response
MoA	mechanism of action
mOS	median overall survival
MRD	Minimal residual disease
N, n	number (of patients)
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application
NHL	Non-Hodgkin lymphoma
NK cell	Natural killer cell
NORDIC regimen	dose-intensified induction immunotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone (maxi-CHOP) alternating with rituximab + high-dose cytarabine
NR	not reached
ns	not significant
ODAC	Oncoloy Drugs Advisory Committee
obi	obinutuzumab
ofa	ofatumumab
OFAR	oxaliplatin, fludarabine, cytarabine, rituximab
ORR	overall response rate

OS	Overall survival
PCR	pentostatin, cyclophosphamide, rituximab
PCyR	partial cytogenetic response
PDGFR	Platelet-derived growth factor
PEPC	prednisone, etoposide, procarbazine, cyclophosphamide
PFS	Progression-free survival
Ph	Phase
Ph+	Philadelphia chromosome positive
PMC	post marketing commitment
PR	partial response
pts	patients
qPCR	quantitative PCR
R	rituximab
R/R	relapsed/refractory
RCHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
RCHOP/RICE	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone/ rituximab, ifosfamide, carboplatin, etoposide
REAL classification	Revised European-American Classification of Lymphoid Neoplasms
REMS	Risk evaluation and mitigation strategy
sNDA	supplemental NDA
T315I	mutation of amino acid 315 changing threonine to isoleucine
TKI	tyrosine kinase inhibitor
tx	treatment
US	United States of America
vs	versus
w/	with
WHO	World Health Organisation
Wk	Week

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.