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Targeted venetoclax therapy of 11;14 translocated multiple myeloma

PhD thesis

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List of abbreviations

AML – acute myeloid leukemia

Al amyloidosis – amyloid light chain amyloidosis

ASCT – autologous stem cell transplantation

BiTE – bi-specific T-cell engagers

BCL-XL – B-cell lymphoma-extra large

BH3 – Bcl-2 homology domain 3

CAR T-cell – chimeric antigen receptor T-cell

CCND – cyclin D

CLL – chronic lymphoid leukemia

CNS – central nervous system

CSR – class switch recombination

CR – complete response

CyBorDex – cyclophosphamide-bortezomib- dexamethasone

CYP – cytochrome P450

ISS – International Staging System

DNA – deoxyribonucleic acid

ER – endoplasmic reticulum

FDA – Food and Drug Administration

FGFR3 – fibroblast growth factor receptor 3

FISH – fluorescence in situ hybridization

FLC – free light chain

G-CSF – granulocyte stimulating factor

GFR – glomerular filtration rate

IgH – immunoglobulin heavy chain

IMID – immunomodulatory imide drug

IMWG – International Myeloma Working Group

MAF(B) – MAF BZIP Transcription Factor (B)

MCL-1 – myeloid leukemia cell differentiation protein-1

MM – multiple myeloma

MOMP – mitochondrial outer membrane permeabilization

MPV – melphalan-prednisone-bortezomib

NDMM – newly diagnosed multiple myeloma

NEAK – Nemzeti Egészségbiztosítási Alapkezelő (National Health Insurance Fund of Hungary)

NHL – non-Hodgkin lymphoma

NSD2 – nuclear receptor binding SET domain 2

OGYÉI – Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet (National Institute of Pharmacy and Nutrition)

OS – overall survival

ORR – overall response rate

PCL – plasma cell leukemia

PFS – progression free survival

PD – progressive disease

PR – partial response

R/R MM – relapsed/refractory multiple myeloma

SD – stable disease
TLS – tumor lysis syndrome
UPR – unfolded protein response
UPS – ubiquitin-proteasome system
VenKD – venetoclax-carfilzomib-dexamethasone
V(D)J – variable, diversity, and joining
VGPR – very good partial response
VTD – bortezomib thalidomide dexamethasone
VRD – bortezomib lenalidomide dexamethasone

1. Introduction

Multiple myeloma (MM) is one of the most common hematological malignancies, with more than 400 new cases estimated to occur in Hungary each year(1). Its treatment – similar to the treatment of other hematological malignancies – has undergone radical transformation in the past three decades, with therapy shifting from classical chemotherapy to several classes and generations of specific anti-myeloma agents and, nowadays, to more targeted drugs and the beginnings of personalized therapy(2,3). In spite of these advances and the plethora of drugs available, no definitively curative approach has yet been determined – for the majority of patients, the diagnosis of MM therefore means a sequence of therapy lines, remissions and relapses.

Beginning with more effective induction therapy than currently standard is one of the main directions in current myeloma research (e.g. utilizing quadruplet combinations and later generation drugs, such as daratumumab-carfilzomib-lenalidomide-dexamethasone – D-KRD or even BCMA-targeted chimeric antigen receptor (CAR) T-cells or bispecific T cell engagers (BiTE) in the first line(4–6)). In Hungary, bortezomib-thalidomide-dexamethasone - VTD has been standard over the past decade(1), with the option for bortezomib-lenalidomide-dexamethasone - VRd in the first line introduced in recent years. This follows the rationale that achieving a deeper response early on may amount to a cure in a higher number of cases than seen before with less effective combinations. In eligible patients, autologous stem cell transplantation (ASCT) following the induction remains the cornerstone of a curative approach in everyday practice despite near continuous scrutiny as to its necessity(7).

More recent data have also shown that MM is a genetically heterogeneous disease(8). This heterogeneity explains, in part, why standard practices as well as the newer anti-myeloma agents only ever seem to work in a subset of myeloma patients - the underlying disease biology appears to be different enough to require different drug combinations instead of a ‘one size fits all’ approach. Tailoring our therapy to the underlying cytogenetic abnormalities may thus help us to achieve better results, and is one of the directions current myeloma research is exploring(2). For example, the ongoing phase 1/2 study ‘MyDRUG’ (NCT03732703) assigns patients to different treatment arms based on the available cytogenetic data, adding molecularly-targeted drugs (e.g. the MEK inhibitor cobimetinib for RAS mutations, or venetoclax for t(11;14)) to standard MM

combinations(9–11)). It is becoming increasingly clear that t(11;14) myeloma is fundamentally different from other genetic subsets.

1.1. Difficult to treat myeloma populations

As mentioned above, first line therapy in myeloma generally tends to be the most advanced combination available that patient comorbidities and financial restrictions allow. Those patients who are refractory to or progress on this first line therapy, or are unable to proceed to ASCT at all, face a dismal prognosis(12–16). Options in this setting include nevertheless proceeding to ASCT (if at all possible) or attempting a second line salvage to deepen response before the ASCT. While still considered the current standard of care, the former approach has been shown to have 79% overall response rate (ORR), and only 14.4 months of progression-free survival (PFS) post-transplant in the real-world setting(17). The benefit of a second line salvage and subsequent ASCT instead is uncertain; a large randomized trial, Myeloma XI found deeper post-ASCT responses and significantly longer PFS with second line proteasome inhibitor (PI) salvage(15), whereas a different retrospective study showed better outcomes with immediate ASCT(18). Indeed, unlike in other hematological malignancies (e.g. Hodgkin's lymphoma, AML, ALL etc.), where therapy continuation or escalation (in some instances, even de-escalation) are based on the patient's response and the need for salvage in refractory patients is self-evident, in myeloma, no such guidelines have been formed and there is a glaring lack of clinical studies to base treatment changes upon. Evidently, progressing patients need to be changed to the next line therapy - but patients that neither reach a deep response, nor fulfil the criteria for progression, are currently continued on the treatment that is semi-effective, until such a time they become fully refractory and start to progress. Those patients who do progress – after ASCT, or after the induction therapy in ASCT-ineligible cases – initially have many treatment options, with different generations of proteasome inhibitors (PI), immunomodulatory imide drugs (IMID), anti-CD38 antibodies readily available for them. Cell-based therapies, such as CAR T-cells or BiTEs are an innovative, but more costly approach that has been gaining ground in myeloma therapy, moving forward among treatment lines(5,6). However, when these options have been exhausted, and the patient has become triple class refractory (i.e. refractory to PIs, IMIDs and anti-CD38s), treatment choices become more limited, with dire associated

outcomes(19). Possible options consist of pomalidomide combinations, selinexor-dexamethasone, belantamab mafodotin, melflufen, CAR T-cells or BiTEs and, in certain cases, venetoclax - with the caveat that generally speaking, drugs used in the relapsed/refractory setting tend to be less effective the more the patient becomes refractory.

Composing another difficult to treat group are those with certain notable manifestations of MM, such as extramedullary disease (EMD), central nervous system (CNS) myeloma, plasma cell leukemia (PCL) or AL amyloidosis. CNS myeloma (and indeed, the CNS propagation of any hematologic malignancy) poses a challenge because only a few agents are capable of penetrating the blood-brain barrier, limiting treatment options to just a handful of drugs (most prominently daratumumab). Uniquely, venetoclax has also been found to cross the blood-brain barrier and show measurable amounts in CSF(20). Concordantly, effectivity has been described in central CNS manifestations of several hematologic malignancies, among them, multiple myeloma.

PCL is defined as more than $2x10^9$ plasma cells in peripheral blood or more than 5% circulating plasma cells(21) and may manifest at diagnosis (primary PCL) or at a later relapse (secondary PCL). Both are characterized by aggressive disease course, frequent therapy refractoriness and an almost always fatal outcome in the course of just a few months(22).

In contrast, AL amyloidosis has an indolent initial behavior, slowly building up organ damage over the years or even decades preceding the diagnosis. Despite the slow presentation, AL amyloidosis has a poor prognosis, unless discovered very early on. In order to reverse organ damage and improve survival the outlook, the involved light chain levels should be promptly minimized. Response to modern therapies, however, can be unfortunately slow-going. Several case reports demonstrated venetoclax therapy to be effective in both PCL(23–26) and AL amyloidosis(27–30), if the patients harbored t(11;14).

Finally, the majority of MM patients suffer a decrease in renal function at least transiently, with many having overt renal failure and a need for dialysis for a period of time. Late myeloma diagnosis as well as untreated relapses can lead to permanent kidney damage, affecting patients' quality of life as well as complicating therapy, since many anti-myeloma drugs are contraindicated in case of renal failure.

1.2. Venetoclax mechanism of action

Anti-myeloma drugs have traditionally aimed to target processes as specific to plasma cells as possible. Similar to healthy plasma cells, multiple myeloma cells generally produce immense quantities of immunoglobulins – and with them, abnormally high amounts of faulty, misfolded proteins as well(31). The survival of MM cells therefore hinges upon the activation of the unfolded protein response (UPR) and finding effective coping mechanisms to either successfully deal with the abundance of these unfolded proteins or to evade the apoptosis that would be triggered by them(32,33). The UPR employs several strategies to eliminate misfolded immunoglobulins: inducing chaperones to attempt to refold them; expanding the endoplasmic reticulum to store more of them; and activating the ubiquitin-proteasome system (UPS) to shred them(33,34) (Figure 1A). If all these strategies are unsuccessful, the UPR attempts to trigger apoptosis(34) (Figure 1B). Cancer cells, however, often have a coping mechanism for this eventuality as well, by upregulating antiapoptotic proteins belonging to the B-cell lymphoma 2 (BCL-2) family, such as Mcl-1, Bcl-xl and Bcl-2(35,36).

Members of the BCL-2 family regulate the induction of mitochondrial apoptosis in cells and are classed into four categories: effectors (Bak, Bax), BH3 domain only members (activators – Bid, Bim, Puma, and sensitizers – Noxa, Bad, Bik) and antiapoptotic (Mcl-1, Bcl-2, Bcl-xl, Bcl-w) proteins. Apoptosis occurs when effectors can bind activators and thus oligomerize in the mitochondrial membrane to form a transmembrane channel, causing mitochondrial outer membrane permeabilization (MOMP) and letting mitochondrial proteins and cytochrome c escape into the cytoplasm, triggering the caspase cascade and cell death. The activators permitting this process, however, are bound to the antiapoptotic BCL-2 members in healthy cells, to be freed only if molecules with higher affinity – sensitizers or certain drugs – take their place.

Studies are ongoing for the discovery of antiapoptotic BCL-2 protein inhibitors, such as BH3 mimetic compounds. Indiscriminate inhibition by the nonselective drug navitoclax was found beneficial in studies with small cell lung cancer and acute lymphocytic leukemia, but its use is limited by dose-dependent thrombocytopenia(38). This was attributed to Bcl-xl inhibition and raised the need for more selective Bcl-2 inhibitors.

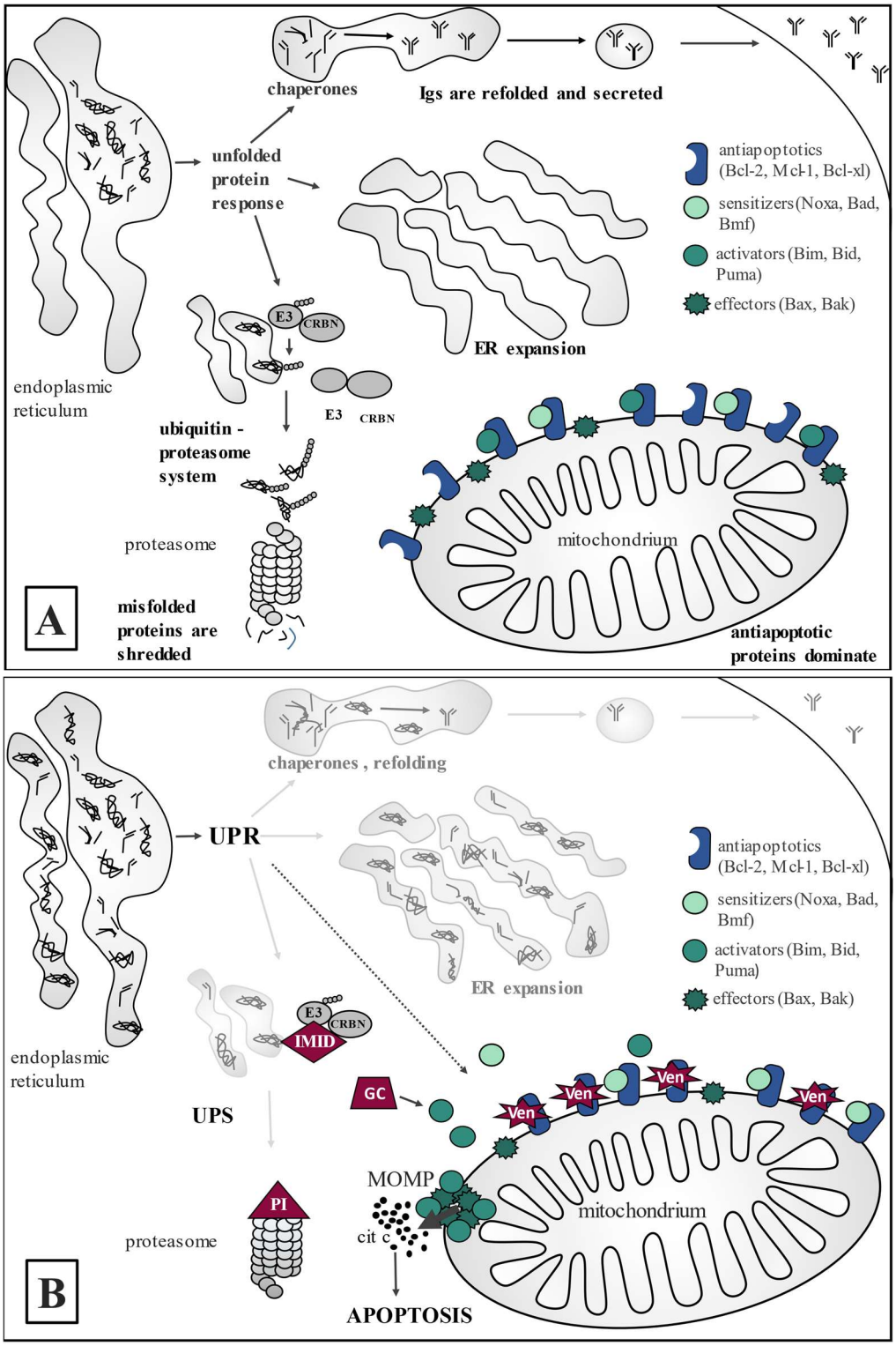

Figure 1. A. Untreated myeloma cell. **B.** Myeloma cell under treatment. (cit c: cytochrome c, E3-CRBN: E3-ligase-Cereblon complex, GC: glucocorticoid, MOMP: mitochondrial outer membrane permeabilization, PI: proteasome inhibitor, Ven: venetoclax, UPR: unfolded protein response, UPS: ubiquitin-proteasome system) - figure adapted (translated) from own published work(37)

While B-cells rely on Bcl-2 itself, plasma cells and myeloma cells in general mainly upregulate Mcl-1 to prevent apoptosis(39–42); one exception, apparently, is t(11;14) MM which depends on Bcl-2. Preclinical, phase I and II studies are underway with several Mcl-1 inhibitors in MM as well as other hematological malignancies and solid tumors despite some concerns about possible cardiotoxicity due to cardiomyocytes' reliance on Mcl-1 for survival.

The selective Bcl-2 inhibitor, venetoclax has been so far more successful. Venetoclax strongly binds to Bcl-2 in order to free trapped pro-apoptotic proteins and thus remove the roadblock from apoptosis. While this in itself may not be enough to induce apoptosis in most myeloma cells, venetoclax can work synergistically with other agents. In vitro studies showed that the glucocorticoids commonly used in MM care increase the expression of proapoptotic proteins (e.g. Bim), boosting the proapoptotic effect of venetoclax. Other classic anti-myeloma drugs mainly target the UPS uniquely activated in myeloma cells: PIs block the degradation of proteins by the proteasomes, while IMIDs change the substrate specificity of ubiquitination(31,32,43). One of the resistance mechanisms to these drugs is the upregulation of antiapoptotic BCL-2 proteins(35,36). In those myeloma cells that rely chiefly on Bcl-2 upregulation to evade apoptosis, venetoclax can promote the cell death induced by PIs(44). Bortezomib and carfilzomib use are associated with higher Noxa (sensitizer) levels which in turn binds Mcl-1, working in tandem with venetoclax to free more proapoptotic activators and effectors. Conversely, in cells with great amounts of Mcl-1 or Bcl-xl, venetoclax may not have any appreciable effect facilitating apoptosis. Clinically, the constellation of Bcl-2 reliance and lower Mcl-1 and Bcl-xl levels best correlates with the presence of t(11;14).

1.3. Clinical studies with venetoclax

Venetoclax has been initially studied and since then licensed for the treatment of several hematological malignancies, such as acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL) and relapsed/refractory non-Hodgkin lymphoma (NHL). Its benefit for the treatment of MM, however, proved less straightforward.

Even early preclinical studies predicted better efficacy in t(11;14) patients(45), as this cytogenetic makeup correlates well with high cellular levels of BCL-2 and low MCL-1 and BCL-XL expressions. This constellation, as detailed above, is essential for the

induction of venetoclax-facilitated apoptosis. This is well demonstrated by a phase 1 study analyzing the efficacy of venetoclax monotherapy vs. placebo(46) in R/R MM: contrary to t(11;14) patients, who showed a 40% ORR to venetoclax monotherapy, none of those confirmed non-t(11;14) responded. Given the preclinical synergy of venetoclax with PIs, most clinical studies have been designed to evaluate the effectiveness of venetoclax-bortezomib combinations. In another early phase 1 study(47), this combination resulted in a favorable, 68% ORR, independent of the patients' cytogenetic makeup. It is noteworthy to mention however, that these studies were performed without control groups, included more t(11;14) patients than generally present in the MM population, and that patients received lower doses of venetoclax than generally considered fully effective in MM(46,47). These aspects might explain why unfavorable effects only surfaced in the later phase 3 clinical study BELLINI.

BELLINI (M14-031) was an open, double blind, randomized phase III study comparing bortezomib-dexamethasone with either venetoclax or placebo in MM patients who had previously received 1-3 treatment lines(48). Although results showed an effectivity in myeloma treatment (PFS 22,4 vs. 11,5 months, ORR 81% vs 68% in favour of venetoclax), an unexpected excess mortality was reported in the venetoclax arm (21.1% vs. 11.3%)(48,49). Following these results, all studies involving venetoclax in myeloma were put on hold by the FDA. Several theories were put forth to explain the increased mortality, with most attributing it to venetoclax predisposing patients to lethal infections(50), although the exact reasons remain unclear. Subsequent subgroup analysis has shown that this excess mortality is not observed in t(11;14) patients. Although quantitative RT/PCR results showed that more than 80% of patients had high Bcl-2 expression, Mcl-1 and Bcl-xl levels had not been measured in the BELLINI study (Bcl-2 measurements are readily available in most pathology departments because of its role in NHL prognostic examinations, conversely, tests for the latter two are not routine). Only 12% of patients in BELLINI had confirmed t(11;14). This latter group showed no increase in mortality with venetoclax use, but rather a survival benefit with median PFS and OS not reached vs 9.9 months PFS in non-t(11;14) patients. Considering the results of the subgroup analysis, studies with t(11;14) myeloma (and *only* t(11;14)) had been authorized going forward.

More and more clinical studies support the use of venetoclax in t(11;14) R/R MM patients, and phase I and II results are promising with pomalidomide(51), carfilzomib(52) and daratumumab(53) combinations as well. Based on these results, venetoclax therapy has been available in Hungary for t(11;14) patients with an OGYÉI 'off label' permission and NEAK financing agreement. It is noteworthy to mention that copy number increases in 1q (gain(1q21)) are associated with higher Mcl-1 expression. Therefore, patients with both t(11;14) and gain or amp(1q21) may respond less favorably to venetoclax.

1.4. Translocation (11;14) in myeloma

Why is t(11;14) myeloma behaviour so different then? To our current understanding, two distinct structural genomic changes may lead to the formation of a malignant plasma cell clone, both occurring during B cell maturation processes; either a hyperdiploid DNA set is acquired through incomplete mitoses, possibly throughout the rapid germinal center proliferation; or recurrent translocations misplace important proto-oncogenes to constitutionally active sites during the class switch recombination process (CSR). The translocations almost exclusively involve the powerfully activated immunoglobulin heavy chain (IgH) locus 14q32, causing pathological activation of cyclin D (CCND1 in t(11;14), CCND2 in t(12;14) and CCND3 in t(6;14)), MAF genes (MAF in t(14;16) and MAFB in t(14;20)) or NSD2 and FGFR3 (in t(4;14)). These foundational structural genomic changes spur on hyperactive growth and the immortalization of the plasma cell clone, leading to overt MM in time by two proposed scenarios: the "static progression model" hypothesizes that the malignant clone is present from the beginning, taking the bone marrow over progressively, whereas the "clonal evolution model" suggests the disease gains momentum with the constant acquisition of more and more oncogenic mutations, epigenetic changes and a facilitative bone marrow microenvironment.

The most common founding translocation, t(11;14)(q13;q32) (commonly abbreviated to t(11;14)) is found in approximately 15-25% of all MM patients, identified at diagnostic FISH examinations. (A similar (11;14) translocation is an important hallmark of mantle cell lymphoma (MCL)(54), but in-depth mutational analyses have shown altogether different breakpoints in MCL(55), that seem to occur at a different time point in B cell development, during the V(D)J recombination. This can explain the development of two very different and distinct diseases with the 'same' genetic background. The prevalence

of t(11;14) is also exceptionally high in two myeloma-related conditions, PCL and AL amyloidosis, in which approximately 50% patients harbor this translocation(22,56). The possibility of targeted therapy in the form of venetoclax focused more attention to t(11;14) in recent years, and more targeted studies highlighted several peculiarities in this translocation, with a somewhat different disease behavior to other founding genetic abnormalities in MM.

Light microscopy of t(11;14) bone marrow samples often reveals a lymphoplasmacytic morphology, with small, round, B-cell-like plasma cells, which could cause great diagnostic difficulty before the immunophenotyping that could definitively identify them as myeloma cells became widely available(57). As recent gene expression studies demonstrated, t(11;14) myelomas are similar to B-cells in more than their appearance, with high expression of mature B-cell markers, such as CD20 and CD79a, but low expression of CD56 and CD38. Fortunately, high expression of CD38 is not imperative for good therapeutic efficacy with anti-CD38 antibodies(53,58,59). Several studies found high PAX5 activity(60–62), a transcriptional factor silenced during B cell maturation to plasma cells, and an overall genetic expression profile more like mature B-cells(60).

Historically, t(11;14) had conferred a good or neutral prognosis with a perhaps sluggish disease course, for instance, smoldering myeloma (SMM) progresses to overt MM significantly slower in t(11;14) patients than in those with t(4;14) (median 55 vs 28 months)(63). After the advent of novel anti-myeloma agents, which greatly improved outcomes in most MM patients (64) but affected survival in t(11;14) much less (65), this trend might have reversed, and the prognosis of t(11;14) has become more controversial. T(11;14) patients seem to benefit less from treatment with PIs (66,67) and more from intensive treatment or ASCT(65,68–70). Some reports suggest that t(11;14) patients may face a worse prognosis now than the general MM population(65,71,72), while other authors found no difference(73,74). Classing t(11;14) as intermediate risk at the moment seems to be most commonly accepted. Naturally, the prognostic implications of genetic subtypes depend on the available treatment landscape: if t(11;14) is shown to respond very favourably to venetoclax due to its unique Bcl-2 dependence, it could then become a good prognostic factor.

1.5. Venetoclax administration and safety

While other hematological malignancies treated with venetoclax utilize lower doses of venetoclax, i.e. 400 mg daily, the effective dose in MM was found to be much higher, between 800-1200mg, to be taken in an oral tablet once daily. Absorption of the drug is significantly affected by food intake: ingestion of venetoclax with high-fat meals versus without food can increase bioavailability three- to fourfold; therefore, patients are advised to take the pills and consume a similar breakfast each day during therapy (75). Venetoclax is metabolised by the liver via the cytochrome P450 (CYP)3A enzymes with minimal excretion in urine; pharmacokinetics were found to be unaffected by renal function and dose reduction is only recommended in the case of severe hepatic impairment(76).

Concerning the adverse effects of venetoclax, case reports, and clinical studies describe patients frequently experiencing gastrointestinal complaints: usually mild, grade 1-2 nausea and diarrhea(47,49,51,53,77). Given the drug's history, more worrisome is the higher incidence of infectious adverse events and neutropenia, including neutropenic fever(49). Blood count checks should be conducted at regular intervals and therapy supported with G-CSF, transfusion or antimicrobial prophylaxis as necessary. Circumspection is needed however, with the prescription of some common antibiotics and antifungal agents (as well as the patients' consumption of grapefruit seeds), as CYP3A inhibitors elevate venetoclax serum levels two to fourfold(76,78). In patients experiencing gastrointestinal toxicity at higher venetoclax doses, direct venetoclax dose may be lowered by the addition of clarithromycin or voriconazole without a change in effective serum level.

2. Objectives

The aim of our study was to evaluate venetoclax use in t(11;14) myeloma patients in the real life setting in Hungary.

We wanted

1. to describe the characteristics of the myeloma patients that have received venetoclax as well as the treatment regimens that were followed, including the dosing of venetoclax and concomitant use of CYP3A inhibitors.
2. to evaluate objective response rates to venetoclax therapy in the relapsed/refractory (R/R) setting.
3. to measure PFS and OS in the R/R setting and see whether it was comparable in length to other possible treatment options for this group.
4. to see whether we would find a survival difference in patients with or without high risk features such as del(17p) or kidney failure.
5. to assess whether early venetoclax salvage was effective in deepening hematological responses and to help eligible patients reach ASCT.
6. to estimate whether venetoclax salvage positively affected OS in t(11;14) patients responding unfavorably to standard therapy.
7. to evaluate PFS as compared to a similar cohort of patients.
8. to assess how venetoclax use impacted OS in t(11;14) patients in our praxis
9. to see how venetoclax performed in patient groups excluded from clinical trials, such as patients with kidney failure and whether renal failure affected the safety profile of venetoclax.
10. to overview how many PCL patients were treated with venetoclax in Hungary and the length of PFS that could be expected with venetoclax treatment.
11. to assess the range and severity of adverse effects associated with venetoclax use in our study population.

3. Methods

We collected data evaluating venetoclax use in t(11;14) myeloma retrospectively, from three sources: from our own praxis at the Department of Internal Medicine and Hematology, Semmelweis University, Budapest; in a countrywide project in 2021 in seven different hematology centers (Department of Hematology and Stem Cell Transplantation, South Pest Central Hospital, National Institute for Haematology and Infectious Diseases, Budapest; 1st Department of Internal Medicine, University of Pécs; Department of Haematology, Teaching Hospital Mór Kaposi, Kaposvár; Jósa András Teaching Hospital, Nyíregyháza; Teaching Hospital Markusovszky, Szombathely and the Department of Haematology, Faculty of Medicine, Clinical Center, University of Debrecen, Debrecen as well as our own praxis); - and, for comparative purposes, a different, previously published dataset(79) from the Department of Hematology and Stem Cell Transplantation, South Pest Central Hospital was used with the authors' help and consent.

For our countrywide project, we requested that all t(11;14) myeloma patients treated with venetoclax in the time period between 2017-2021 at the participating hematological centers be reported. Specific patient data was accessed and extracted from local electronic medical records by the treating physicians and reported to the data collector in anonymized data sets. To avoid patient duplication in the case of a patient's relocation, an annotation was left to mark the change in treating hematological center (applicable in one case). Patients with non-t(11;14) myeloma, and those undergoing treatment for more than one malignancy concurrently, were subsequently excluded from our analysis. In the comparative data set, survival data was collected from all patients diagnosed with t(11;14) myeloma between 2012-2016 in the South Pest Central Hospital(79).

We have also studied the survival of a smaller subgroup of patients, those that received venetoclax in early lines at our praxis (the Department of Internal Medicine and Hematology, Semmelweis University), and compared their survival to both non-t(11;14) patients and t(11;14) patients who did not receive venetoclax salvage in two time periods, between 2012-16 and 2017-21.

Cytogenetic abnormalities were evaluated at the time of diagnosis and at relapse. P53 loss was defined as either del(17p) or p53 mutation demonstrated on FISH. Gain(1q21) was defined as the presence of at least 3 copies of 1q21 in myeloma cells. Diagnosis, ISS

staging and hematological response evaluation were performed according to the IMWG criteria(80), ORR was defined as a hematological response of PR or better. PFS and overall survival (OS) were calculated from the initiation of venetoclax therapy to either the date of last medical contact or the date of progression and death, respectively. Refractoriness was defined based on the patient's response to the last line containing the agent in question – if they failed to reach a PR or progressed on or within 2 months after finishing the protocol.

We collected data about the number of prior therapy lines, including previous ASCT; the presence of AL amyloidosis, PCL or EMD; venetoclax and concurrent CYP3A inhibitor dosage; venetoclax treatment duration and adverse events associated with the venetoclax use. PCL was defined according to the 2013 IMWG criteria(81) as had been the consensus during our study period.

For statistical analyses the software SPSS (version 26.0; SPSS, Chicago, IL, USA) has been utilized. Survival data was analyzed with the Kaplan-Meier method. The comparison of different subgroups was performed with log-rank tests. Median follow-up time was determined via the reverse Kaplan-Meier method. In all cases, a p value of <0.05 was considered statistically significant.

Venetoclax treatment was prescribed with individual OGYÉI 'off label' permissions and NEAK financial support in all cases. The research has been approved by Semmelweis University Regional, Institutional Science and Study Ethic Committee (ethic code: 12/2023) and conducted in accordance with the declaration of Helsinki.

4. Results

Seven Hungarian hematology centers contributed to our data collection, reporting 58 t(11;14) MM patients who received venetoclax treatment from August 2017 to August 2021 and fit our inclusion criteria. Patients could be sorted into two distinct groups, depending on the clinical situation: relapsed/refractory (R/R) or reinduction group. 37 patients were classed as relapsed/refractory: they were refractory to several classes of myeloma drugs and received venetoclax after numerous previous lines of therapy, often as a last resort. We classed 21 patients as the reinduction group, who showed suboptimal response to first line treatment and received venetoclax as a form of salvage in preparation for ASCT.

As patient characteristics and the goals of venetoclax therapy greatly differed between the two groups, we analyzed them separately.

4.1. Patient characteristics

Patient characteristics in the two groups are shown in more detail in Table 1.

4.1.1. Relapsed/refractory group

Relapsed patients were heavily pretreated: 59% of the patients had undergone ASCT; after median 4 prior lines of therapy, the vast majority had also been treated with bortezomib, thalidomide and lenalidomide (95%, 86% and 89%, respectively), as well as anti-CD38 antibodies (almost all of them with daratumumab) in 38%, later generation IMIDs (namely pomalidomide) in 22%, and PIs: carfilzomib and ixazomib in respectively 38% and 22% of cases. Thalidomide treatment was often switched to lenalidomide regimens due to patients exhibiting the early signs of therapy-induced neuropathy. Treatment with later generation IMIDs, PIs and anti-CD38 antibodies was stopped due to refractoriness in all cases: 62% had become double class, 38% triple class refractory by the start of venetoclax treatment. More than half of patients (57%) had ISS stage 3 disease at this time and almost one third (30%) had impaired kidney function, with GFR estimated below 45 ml/min. Not all patients had repeat bone marrow sampling at this juncture, but high-risk cytogenetic features, p53 loss and gain(1q21) were nevertheless confirmed in 32% and 57% of patients, respectively.

Table 1. Patient characteristics

Patient characteristic	**Relapsed/refractory group (n=37)**	**Reinduction group (n=21)**
male gender	17 (46%)	9 (43%)
age at diagnosis (years)	62 (32-86)	64 (50-91)
age at the start of venetoclax therapy (years)	69 (45-89)	65 (50-91)
median time to venetoclax	4.7 years	2.6 months
ISS stage at the start of venetoclax therapy		
1	5 (14%)	11 (52%)
2	6 (16%)	1 (5%)
3	21 (57%)	9 (43%)
Adverse prognostic factors		
loss of p53	12 (32%)	6 (29%)
gain(1q21)	21 (57%)	8 (38%)
GFR <45 ml/min	11 (30%)	5 (24%)
Prior therapy		
median lines of prior treatment	4 (1-12)	1 (1-2)
double class refractory	23 (62%)	5 (24%)
triple class refractory	14 (38%)	0 (0%)

4.1.2. Reinduction group

Unlike in the relapsed/refractory setting, where venetoclax therapy was started at a median of 4.7 years after diagnosis, the reinduction group was switched to a venetoclax-containing regimen after a median of only 2.6 months (Table 1). As expected with VTD having been the standard first line regimen at the time, prior treatment consisted of bortezomib (90%) and thalidomide (71%) for the most part, with a minority of the patients exposed to lenalidomide (14%), mainly after a switch due to thalidomide intolerance. As expected with MM patients, a non-negligible number had impaired kidney function (24%). Adverse cytogenetics, loss of p53 and gain(1q21) were also found during the bone marrow sampling performed at diagnosis in a relatively high percentage of cases, 29% and 38%, respectively.

4.2 Characteristics of venetoclax therapy

Venetoclax doses had been appointed individually for each patient, taking into account the patients' gastrointestinal tolerance, concurrent CYP3A inhibitor use and the results from serum level measurements, where accessible for the treating physician. To decrease the chance of TLS, treatment was started with a three-day ramp-up phase. The majority of patients (86%) received a concurrent CYP3A inhibitor to raise venetoclax levels two- to fivefold: 73% of all patients took clarithromycin, while 12% took fluconazole. Considering the results of preclinical studies, venetoclax was combined with other anti-myeloma agent(s), most commonly bortezomib.

4.1.1. Relapsed/refractory group

Direct venetoclax dose in the R/R setting was higher (mean: 414 mg, range: 200-800 mg); accounting for concurrent CYP3A inhibitor use, expected venetoclax serum levels were comparable to those in published phase 3 studies. 65% of patients received VenVD, 22% venetoclax monotherapy (VenD) and 14% with carfilzomib and dexamethasone (VenKD). Therapy was continued until intolerance, progression or death.

4.1.2. Reinduction group

In the reinduction group, venetoclax doses were slightly lower (mean: 312 mg, range: 150-400 mg); CYP3A inhibitors were also used in this group to reach the therapeutic range of venetoclax exposure. Patients either received venetoclax with bortezomib and dexamethasone (VenVD, 62% of patients), or as an add-on to conventional VTD therapy

(VenVTD, 38%). The length of therapy in this group was fixed as a couple months of bridging, a median of 3 cycles of venetoclax therapy followed by either ASCT, if eligible, or observation, if ineligible.

4.3. Therapy outcomes

4.3.1. Relapsed/refractory group

As shown in Figure 2, the overall response rate was remarkable considering the heavily pretreated population: 92% of patients achieved at least a partial response (PR), with only 3 patients staying in stable disease (SD) or progressing (PD). 38% of patients reached even deeper remission, either very good partial response (VGPR) or complete response (CR). These response rates were associated with 10.0 months progression-free survival and 14.6 months overall survival from the start of venetoclax therapy (Figure 3.).

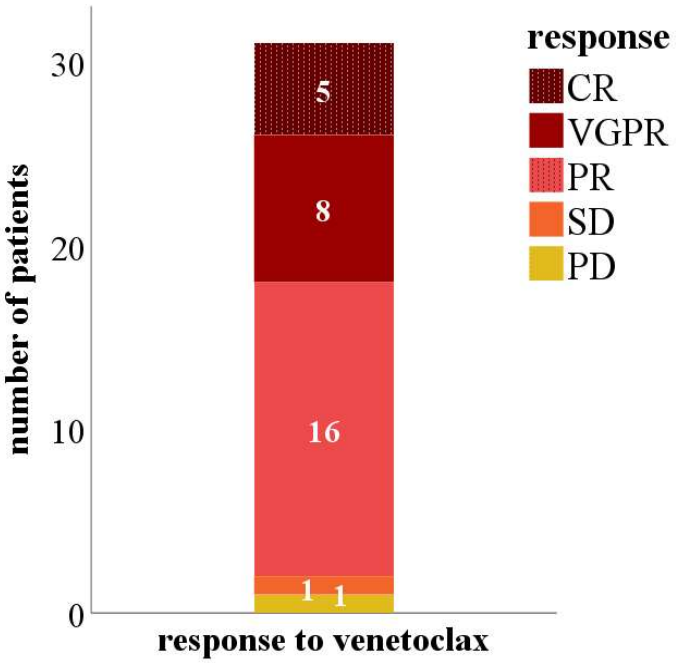

Figure 2. Treatment response rates in the relapsed/refractory group (CR - complete response, VGPR - very good partial response, PR - partial response, SD - stable disease, PD - progressive disease)

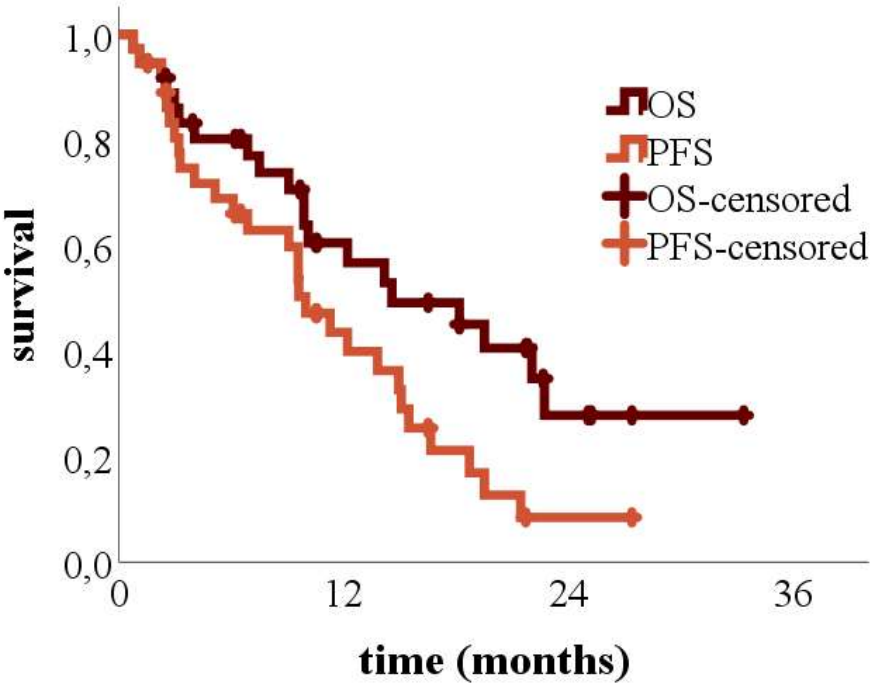

Figure 3. Kaplan-Meier curves showing progression-free survival (PFS) and overall survival (OS) in the relapsed/refractory group

We also compared the survival of those with adverse prognostic factors such as ISS stage, p53 loss or renal failure to those without them; no significant difference was found in any of these subgroups. Across the three ISS prognostic groups, median PFS were 18.7, 12.2 and 9.6 months in ISS 1, 2 and 3, respectively (p=0.377); with median OS not reached, 14.2 and 10.1 months, respectively (p=0.240). Patients with or without renal failure defined as an eGFR < 45 ml/min, showed very similar PFS (median 9.6 vs 10.0 months, p=0.957) and not statistically different OS (median 9.9 vs 18.2 months, p=0.461). Similarly, in patients with or without del(17p), PFS (median 9.6 vs 11.3 months, p=0.499) and OS (median 9.9 vs 19.5 months, p=0.173) was not significantly different, just as the presence or absence of add(1q21) meant no significant difference in either PFS (median 11.3 vs 10.0 months, p=0.507) or OS (median 18.2 vs 12.2 months, p=0.436). The difference in the survival of double-class and triple-class refractory patients was also not statistically different: PFS were 9.6 and 12.2, and OS were 12.2 and 18.2 months in double and triple refractory patients, respectively.

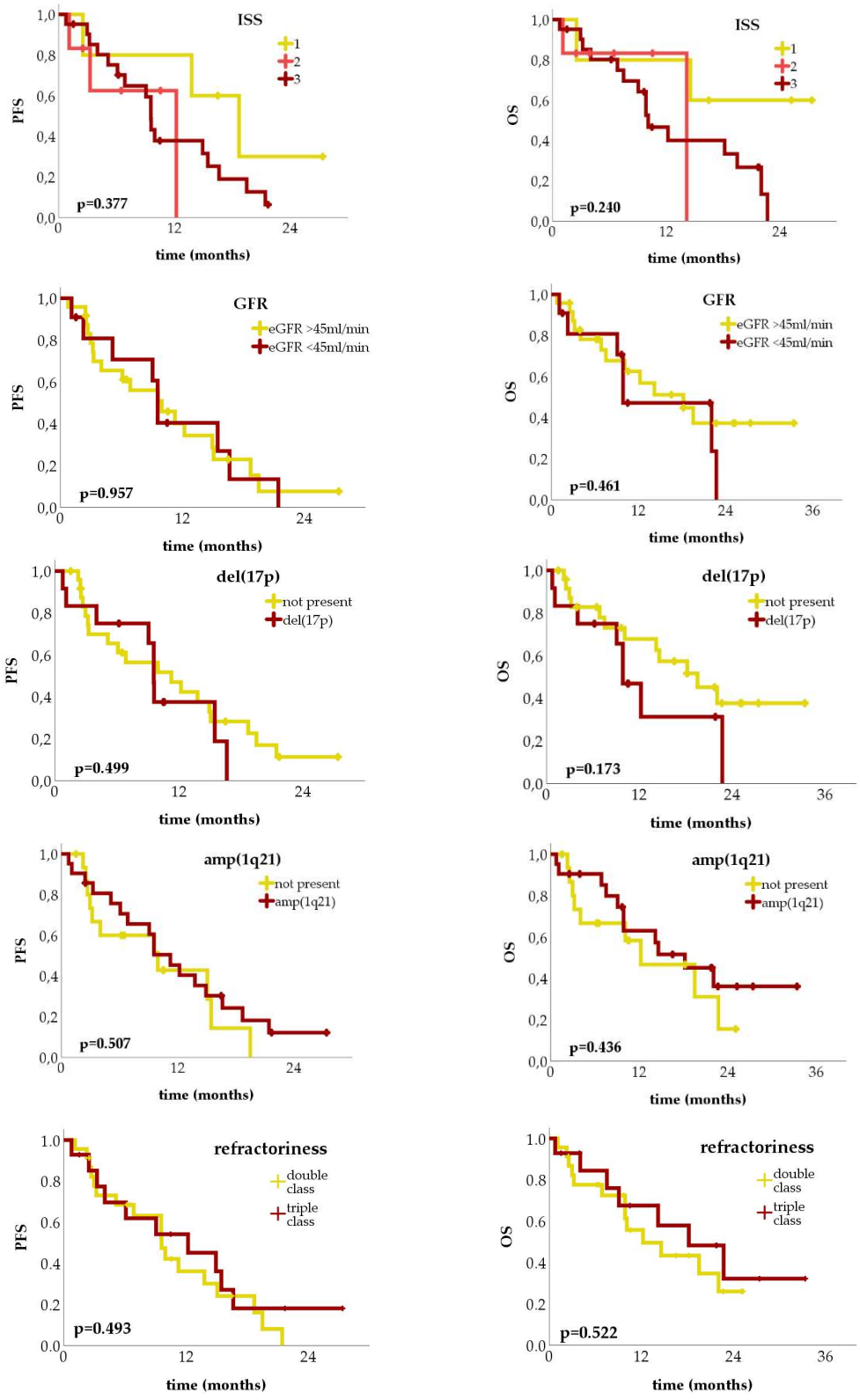

Figure 4. Kaplan-Meier curves showing progression-free and overall survival in the relapsed/refractory setting, depending on International Staging System (ISS) stage, kidney function, del(17p) and amp(1q21) status and refractoriness

4.3.2. Reinduction group

As discussed above, venetoclax therapy in the reinduction group was initiated after suboptimal response to the frontline treatment: following standard frontline therapy, 13 patients had PR, 6 had stable disease (SD) and 2 progressive disease (PD)(Figure 5); 5 patients already became double class refractory. After a median three months of venetoclax therapy, response rates improved dramatically: every single patient had responded, and reached at least VGPR, i.e. a minimum of 90% drop in M protein or FLC values compared to the measurements at the time of diagnosis. 16 of the 21 patients in this group were eligible for ASCT, which could be carried out in all cases. Response rates further improved for these latter patients, with the majority achieving CR. After a median 55.2 months observation (95% CI 42.7-67.6 months), neither the median PFS nor the median OS were reached in this group (Figure 6).

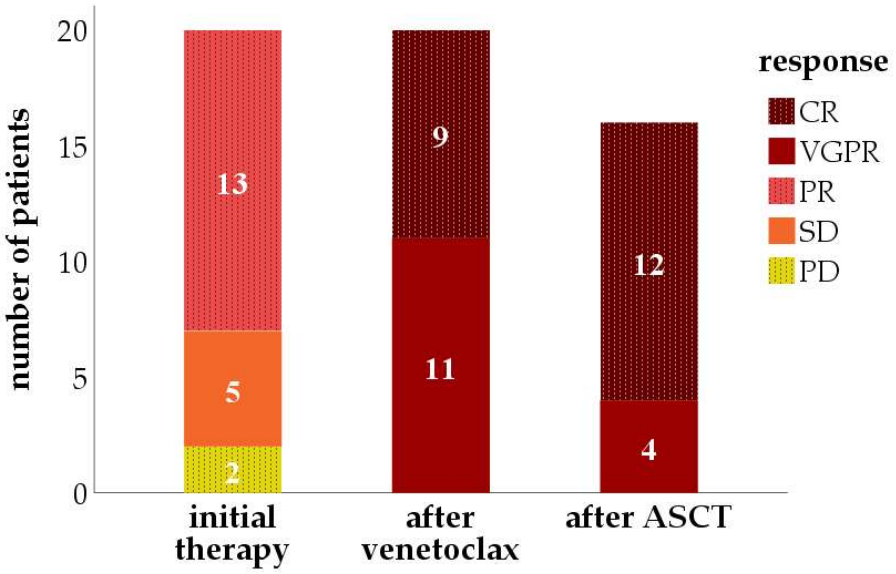

Figure 5. Treatment response rates in the reinduction group (CR - complete response, VGPR - very good partial response, PR - partial response, SD - stable disease, PD - progressive disease)

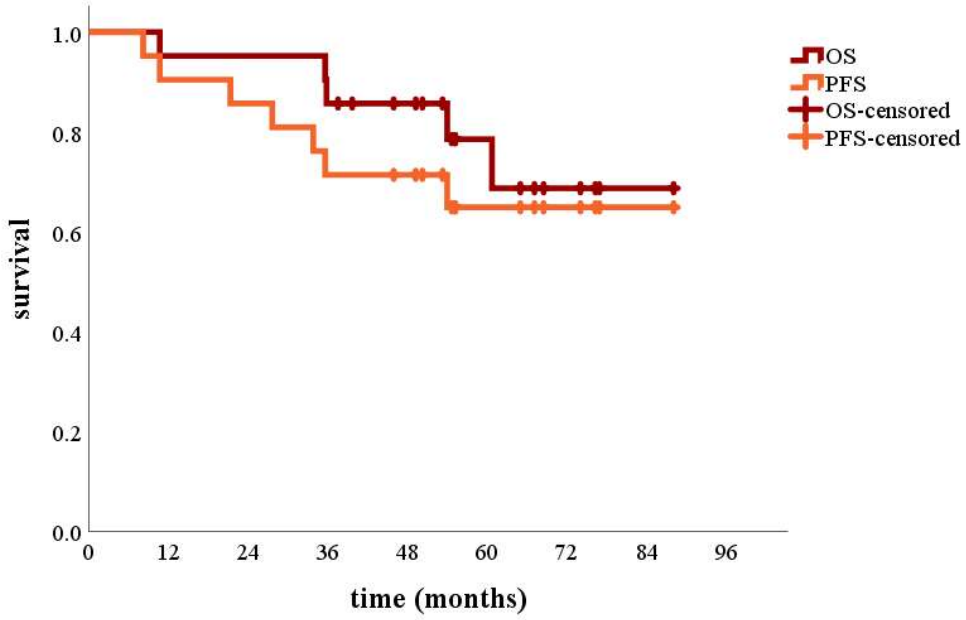

Figure 6. Kaplan-Meier curve showing progression-free survival (PFS) and overall survival (OS) in the reinduction group

4.3.2.1. Comparison with a historical cohort

To aid the correct interpretation of these survival results, we compared our results to those from a large historical dataset(79). The basis of our historical comparison group was a large group of t(11;14) MM cases. To form a similar cohort to ours, we selected those 43 patients who only reached PR or less after receiving an IMID and/or PI containing induction regimen. 30 of these patients had reached PR (70%), 8 had SD (19%) and 5 PD (11%) after initial therapy, which was comparable to (or slightly better than) what we saw in our venetoclax study group (62, 29% and 9%, respectively). The 13 nonresponders (SD or PD) in the historical cohort received salvage: best available therapy of the physician's choice, but not venetoclax (as it had not been available at the time). Of these 13 salvage patients, 7 responded (54% vs 100% in our venetoclax cohort). 21 of the 43 historical patients had been ASCT eligible (49% vs 76% in the venetoclax group), 11 of whom (52%) could proceed to ASCT, all of them in PR. As mentioned above, all ASCT eligible patients in our venetoclax group could proceed to ASCT and all of them had reached at least VGPR.

When we first published our results, although a positive tendency had been observed, follow-up time had been insufficient to prove that the venetoclax group would have better survival compared to those treated five years earlier. In an unpublished update to our dataset (Figure 7), after median 55.2 months follow-up in the venetoclax group, we found both significantly better PFS (median not reached vs 13.6 months p=0.000007) and OS (median not reached vs 39.1 months p=0.037).

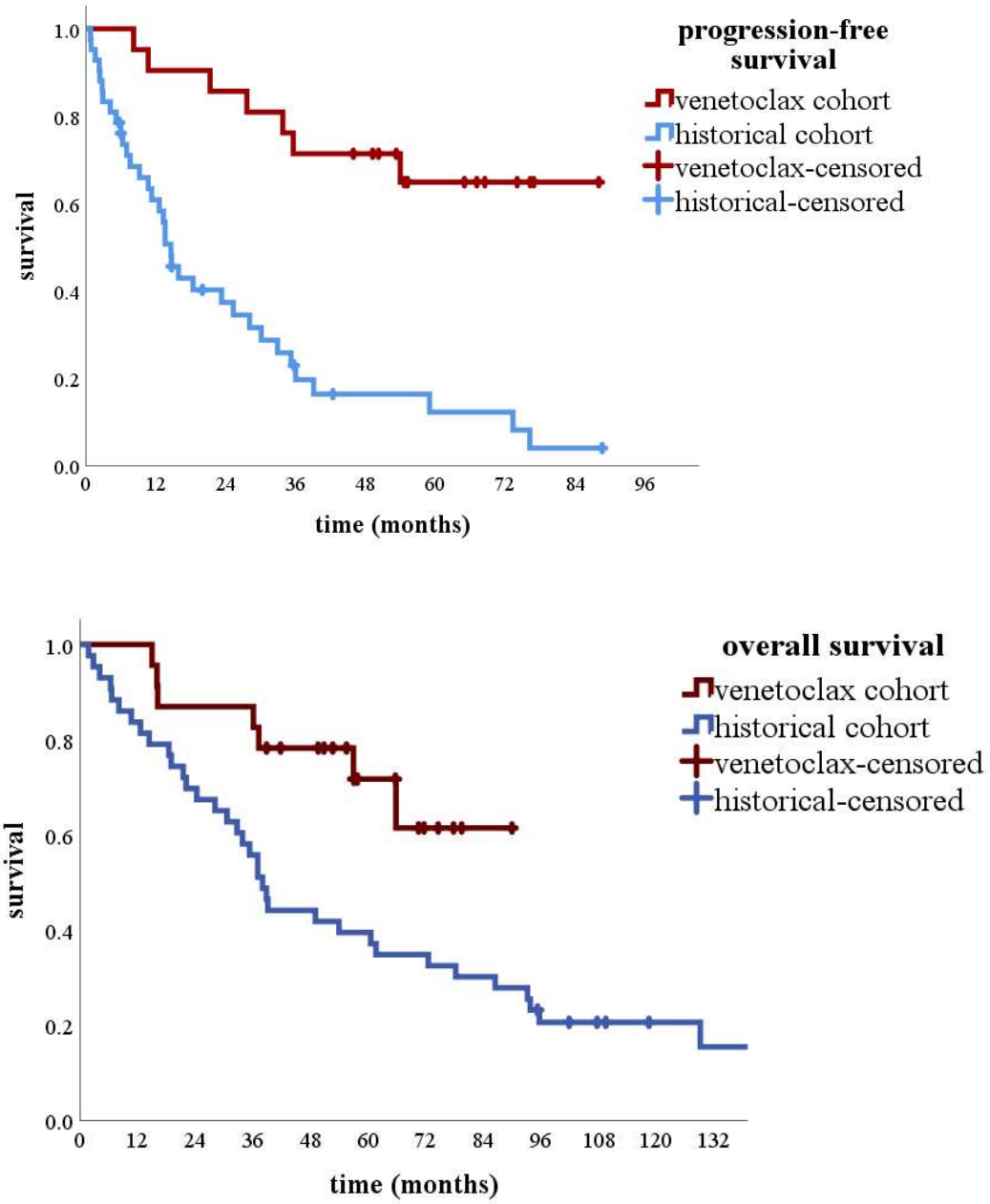

Figure 7. Progression-free survival (PFS) and overall survival (OS) in the venetoclax-treated reinduction group and the historical cohort

4.3.2.1. Comparison with other myeloma subgroups in our praxis

We studied the survival of both t(11;14) and non-t(11;14) patients in the 2012-21 time period at our praxis in the Department of Hematology and Internal Medicine. In the earlier period, between 2012-16, we have treated 13 t(11;14) and 73 non-t(11;14) myeloma patients, whereas between 2017-21, we identified 10 patients with t(11;14) that did not and 13 with t(11;14) that did receive venetoclax as well as and 130 patients with no t(11;14) found during cytogenetic analysis. Although in the course of the two time periods, median overall survival has numerically improved in both the non-t(11;14) general population (median 57 vs 45 months) and the conventionally treated t(11;14) group (median 36 vs 32 months), this change was not significant overall (p=0.252). Survival of t(11;14) and non-t(11;14) myeloma was not statistically different in the 2012-16 time period (p=0.504). In contrast, the survival of venetoclax-treated t(11;14) patients was much more favorable, not reaching the median (Figure 8). Their overall survival was significantly better, both compared to the t(11;14) patients in the same period who did not receive venetoclax (p=0.045), and to t(11;14) patients in the earlier 2012-16 era (p=0.028). The venetoclax-treated t(11;14) patients also showed an improved survival compared to the general myeloma population in both time periods (p=0.039 in both cases). When comparing the survival of t(11;14) patients overall, whether they received venetoclax treatment or not, the improvement between the two time periods did not reach statistical significance (p=0.120).

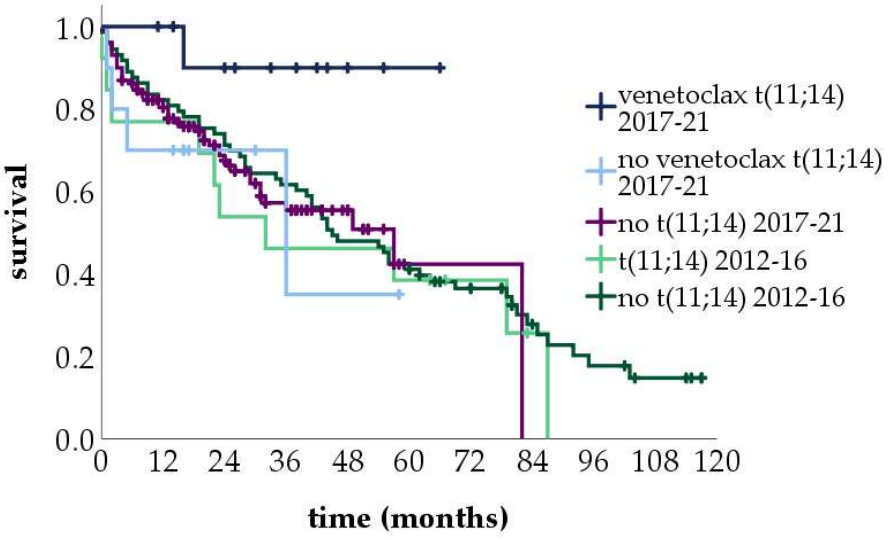

Figure 8. Kaplan-Meier curves of overall survival in the different subgroups and study periods

4.4. Patient subpopulations of special interest

4.4.1. Patients with impaired kidney function

As already stated above, patients with renal failure (in this case defined as having an eGFR < 45 ml/min) were excluded from clinical trials. More than a quarter of patients in our study group, 28% had impaired kidney function at the initiation of venetoclax treatment (Table 1), slightly more in the R/R group (30%) than in the reinduction setting (24%). During venetoclax therapy, we observed clinically relevant improvement in kidney function in five of these patients (45% of those with initial kidney failure). Three of the patients had required regular dialysis at the beginning, but during the course of therapy, all three of them had enough improvement in kidney function for dialysis to be stopped altogether.

Twice as many patients in this subgroup reported adverse events, however, than patients with normal kidney function, 83% vs 37% of patients, respectively.

4.4.2. Plasma cell leukemia

We analyzed the prevalence of special disease manifestations, such as myeloma-associated AL amyloidosis, PCL and extramedullary disease in our cohorts (Table 4).

Table 4. Number of plasma cell leukemia, extramedullary disease and amyloidosis cases in our study

	All patients	**Relapsed/refractory**	**Reinduction**
Plasma cell leukemia	6	5	1
Extramedullary disease	4	3	1
Amyloidosis	5	1	4

Given the high prevalence of t(11;14) in plasma cell leukemia, the limited available treatment options, and the typically dismal outcomes, we decided to analyze PCL patients in our study separately. In our study, six patients were reported to have PCL. Two of these patients had primary PCL detected at diagnosis, four of them had secondary PCL. Venetoclax treatment had been initiated shortly after the primary PCL diagnosis in one patient, with all others receiving venetoclax at a later relapse. Compared to our overall study population, PCL patients were slightly younger at diagnosis (mean 63 years), had

fewer, median 3.5 previous treatment lines, and a shorter time period between the diagnosis and venetoclax treatment (the latter differences were partly due to the inclusion of the reinduction group PCL patient). Most patients had a high-risk cytogenetic abnormality present, p53 loss in three cases and gain(1q) in 2 cases.

Each patient responded to venetoclax, with 1 reaching PR, 4 VGPR and 1 CR. Despite the remarkable hematological response rate, all relapsed/refractory patients eventually progressed after a median of 10.0 months PFS and passed away after a median of 12.2 months after the start of venetoclax therapy (Figure 9).

The primary PCL patient that had been treated in an early line, did not progress and continues to be in CR 74 months after the diagnosis.

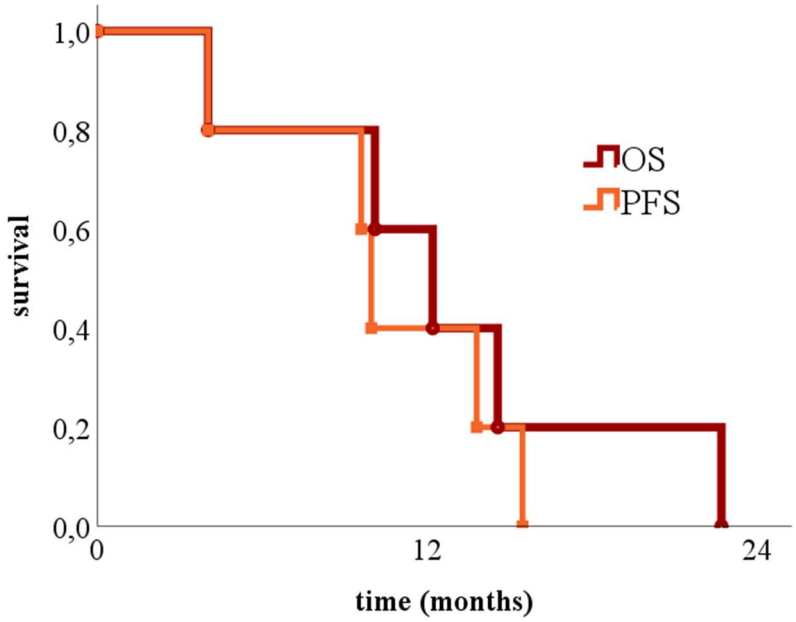

Figure 9. Kaplan-Meier curves showing progression-free survival (PFS) and overall survival (OS) among the R/R PCL patients.

4.5. Safety

Clinical studies and case reports previously listed tumor lysis syndrome, infections, cytopenias and GI symptoms as adverse events during venetoclax treatment. In our study, 60% and 38% of patients reported adverse events during venetoclax therapy in the relapsed and reinduction groups, respectively. Details are presented in Table 5.

Table 5. The incidence of adverse events in our study population

Adverse event	**Relapsed/refractory group (n=37)**	**Reinduction group (n=21)**
reported any adverse event	22 (59%)	8 (38%)
gastrointestinal complaints (nausea/diarrhea)	6 (16%)	5 (24%)
cytopenia	10 (27%)	1 (5%)
infections	11 (30%)	2 (10%)
tumor lysis syndrome	1 (3%)	0 (0%)
acute myocardial infarction	4 (11%)	0 (0%)

Despite concerns about severe TLS necessitating careful monitoring and a ramp-up phase, as is common with CLL patients, we only observed one mild case of TLS, in a patient with PCL. Infections were monitored vigilantly, with patients receiving detailed instructions in case of fever and infectious symptoms; infections occurred in almost a third of R/R patients, proving fatal in four cases (two of which were COVID-related). Only two patients had infections in the reinduction cohort, neither of which was fatal.
Cytopenia of one or more cell lines was also more prevalent in the R/R setting, affecting almost a third of patients, with only one case in the reinduction group. Gastrointestinal complaints, nausea and diarrhea were reported by more patients in the latter group, and prompted dose reduction in several cases. Full discontinuation of therapy did not become necessary in any of the cases.

More vulnerable patients, those with renal failure or PCL experienced more adverse events. PCL patients were especially prone to cytopenia (83% of PCL patients) and infections (67% of PCL patients, the infection was fatal in one case).
Previously unreported as an adverse event, 4 patients in the R/R group suffered ischemic coronary events during the course of venetoclax therapy, one of which was fatal.

5. Discussion

5.1. Relapsed/refractory group

In the relapsed/refractory myeloma setting, heavily pretreated double and triple class refractory patients had a 92% ORR to venetoclax treatment, giving patients a median PFS 10.0 and OS of 14.6 months after the start of venetoclax therapy. This compares favourably with the outcomes for double-class (PFS 5, OS 13 months) (71) and triple-class refractory patients (PFS 3.4, OS 8.6 months) (19). Our data are also very similar to a more recent retrospective study conducted at the Mayo Clinic, which found 11.8 months median PFS in venetoclax-treated t(11;14) patients(82). Further, this gain in PFS may benefit patients not only by itself, but also by bridging for more time-sensitive approaches such as transplantation or CAR T-cell therapy. In our study, PFS and OS were remarkably close; this was likely due to a combination of factors: firstly, in the majority of these patients, venetoclax was given as an ultimum refugium and no further treatment option remained for them at the relapse, this was especially true for the five PCL patients included; and secondly, venetoclax-therapy was associated with lethal infections (i.e. Covid-19 pneumonia, sepsis) as well as myocardial infarction in non-relapsing patients.
Analyzing different subgroups in our study, we have found that conventional prognostic factors such as ISS stage, kidney failure or del(17p) had no significant effect on either PFS or OS. These results seem to indicate that patients with adverse prognostic factors may especially benefit from venetoclax therapy, but we must keep in mind that this has not been a non-inferiority analysis and therefore we cannot make this conclusion with any certainty. There is evidence that add(1q21) confers worse prognosis in patients treated with different regimens, including PIs, IMiDs and ASCT(8,82–85). Venetoclax-treated t(11;14) patients with gain/amp(1q21) may also fare worse, since this cytogenetic aberration is associated with elevated MCL-1 levels and offers myeloma cells an alternative antiapoptotic mechanism independent of venetoclax effect(86,87). The presence of gain/amp(1q21) was however not associated with worse prognosis in our study.

5.2. Reinduction group

As discussed in the introduction, NDMM patients that fail to respond to initial therapy, only reach a suboptimal response or are unable to proceed to ASCT, usually have poor

ORR to second line therapy and subsequently have shorter survival. Compared to literature data, where second line ORR tends to be around 50%, each of our patients reached VGPR or better after venetoclax salvage, ORR was 100% - double of what may be expected from other drugs in this setting. As the median OS is reported to be between 5-10 years for NDMM (depending on the cytogenetics, therapy regimens and geographical region), not reaching median OS or PFS in our study group is by itself unsurprising. Observing the PFS and OS curves, however, they run noticeably closer than would be expected in an early line myeloma setting, where there should still be numerous treatment possibilities available for a relapsing patient. In order to clarify this, we reviewed these progression-death cases in further detail. In some instances, the mortality rapidly following the evolution of venetoclax resistance was due to the aggressive disease course, such as CNS myeloma; in many cases however, this was due to mortality without myeloma progression, the cause of death COVID-19 infection during the pandemic, myocardial infarction and sepsis among others. That having been said, our study cohort's overall survival is nevertheless remarkably far from reaching the median.

In order to gain better insight into whether this might translate to actual, measurable survival benefit, but lacking a predefined, prospective control group, we have used two different approaches for the sake of comparison.

In the first approach, we have used a historical cohort containing a set of similar patients, as detailed above. In the historical cohort, salvage had only been used in overt non-responders (SD or PD after first line therapy), partial responders continued on the initial therapy or proceeded to ASCT, if possible, receiving the next line of treatment only when they overtly relapsed. Therefore, the observed PFS benefit of venetoclax could ostensibly show a similar survival trajectory in the two groups, where only the timing of the second line therapy differed without real survival benefit to the patients. Longer follow-up, however, showed a significant OS benefit with venetoclax, proving that early salvage was beneficial for these patients, partially via the venetoclax therapy itself, but also by enabling ASCT (all eligible patients could proceed to transplant with venetoclax vs half of them with conventional therapy) as well as the lower tumour burden (as evidenced by better hematological responses) probably enhancing the ASCT effectivity. It is also noteworthy to mention that although historical group patients could not receive

venetoclax as second line salvage, as it became available later on, a significant portion of long term survivors likely received it in later lines.

In the second approach, we have included only the 13 patients treated in our praxis and compared them to other t(11;14) and non-t(11;14) patients in our praxis at the same and earlier time periods. In the 2012-16 time period, cytogenetic analysis had not been routine for all NDMM patients (approximately one third of patients had no available FISH results in this period, as opposed to 5 to 10% in more recent years). Studying those patients that were shown to have either t(11;14) or non-t(11;14) myeloma in 2012-16 therefore inherently skews for better survival - those that died early on would not have cytogenetic analyses done later in the disease course. This change also accounts in part for the doubling of cases in the later study period; the proportion of t(11;14) in all diagnoses has remained constant, 15% in both periods.

Across all time periods and cytogenetic groups, t(11;14) myeloma patients treated with venetoclax in the reinduction setting fared significantly better than others. If this was due to selection bias (e.g. the patients that die shortly after diagnosis can obviously not receive venetoclax in the second line, venetoclax treatment may be deemed too risky for very frail patients etc.), the remainder of t(11;14) patients in the time period would show worse survival, however, this is not the case. Rather, we saw almost the opposite: not statistically different, 36 vs 32 months median survival in 2017-21 vs 2012-16, respectively.

It is also important to also keep in mind that barring those we lost in the very first month after the myeloma diagnosis, we have actually recommended venetoclax treatment to the t(11;14) patients that we considered to have the worst prognosis – and these are the patients that went on to have remarkable survival. This survival improvement was not enough to become statistically significant when comparing 2012-16 t(11;14) patients to all 2017-21 t(11;14) patients – what we have to keep in mind, however, is that long term survivors in the 2012-16 group either went on to live without myeloma or in the case of relapse, most of them also received venetoclax (as part of the R/R group), blunting the apparent survival benefit of early line venetoclax therapy in the statistic.

5.3. Renal failure

Clinical trials evaluating venetoclax excluded patients with impaired kidney function from participation. Previous pharmacokinetic studies have found that there is only minimal renal excretion of venetoclax(75), but little clinical experience has been reported(88). Our study found that although patients with impaired renal function had higher rates of adverse events, their PFS and OS after venetoclax treatment did not significantly differ from patients whose eGFR was above 45 ml/min. Importantly, venetoclax therapy was able to reverse myeloma-related renal failure in 42% of cases, overcoming dialysis dependence in three patients which would contribute to much higher quality of life.

5.4. Plasma cell leukemia

Our study had a disproportionately high number of plasma cell leukemia cases. Although case reports of successful venetoclax treatment of primary(23,24,89) and secondary(25,26) plasma cell leukemia had been published, the study providing the backbone of this thesis presented the highest number of cases available in literature at the time of publication. Plasma cell leukemia confers a prognosis significantly worse than MM in itself: OS in secondary PCL is reported to be 1-4 months(22,90), largely unchanged in recent years despite the introduction of novel agents. In our relapsed group, we observed remarkably good PFS (10 months) and OS (12.2 months), suggesting that this population may benefit substantially from venetoclax treatment.

5.5. AL amyloidosis

As with PCL, our cohorts included several patients with AL amyloidosis. Unlike with PCL, we opted not to attempt any kind of statistical analysis in this subgroup, as AL amyloidosis manifests as a very heterogeneous disease palette with differing outcomes depending on stage and organ involvement. Due to this, clinical studies in myeloma typically exclude AL amyloidosis patients and clinical trials focusing on AL amyloidosis select patients without myeloma and with a distinct organ involvement (i.e. renal or cardial amyloidosis). The patients in our study had both myeloma and AL amyloidosis concurrently; in this setup, the presence of AL amyloidosis confers a prognosis equal to or worse than the prognosis of MM alone and thus we felt justified in including them in

our main survival analysis. Multiple published case studies have already described venetoclax use in AL amyloidosis, and concordantly, among our five patients, we observed very similar adverse events or drug reactions to those patients who had myeloma without amyloidosis.

5.6. Dosing and co-administration with CYP3A inhibitors

There is uncertainty concerning optimal venetoclax dosage in MM. Clinical trials utilized doses higher than that recommended in AML or CLL, e.g. 800 mg to even 1200 mg once daily(48). Following recent study results, this recommendation has been lowered to around 400 mg daily in an effort to stem the excess mortality and infectious complications. As detailed above, venetoclax administration in our study showed both interpatient and intercenter variance. In part due to the gastrointestinal intolerance caused by larger direct doses, and in part because of financial constraints associated with the off label use of this drug, many physicians in our study combined venetoclax with moderate or strong CYP3A inhibitors. This takes advantage of the dose reduction necessary due to the CYP metabolisation of venetoclax. Most centers utilized clarithromycin, and some used voriconazole, according to local experience with either drug. Adding clarithromycin to patients' regimen, venetoclax dose must be reduced by 50-75%. Previous studies of venetoclax use in AML have shown that complying with the recommended 50% and 75% dose reductions kept venetoclax exposure comparable to the normal administration(91); and co-administration had no effect on long term outcomes(78). Patients were closely monitored during initial administration and in the centers where it was possible, serial serum level measurements were carried out. Despite lower direct doses in our practice, venetoclax exposure in our patients was similar to that in the BELLINI study(75,92).

5.7. Adverse events

Over half of the patients in our study encountered side effects or adverse events during treatment. The more serious of these were infections and cytopenias, events not uncommon in the general myeloma population. Their higher incidence in the relapsed group and disparately high rate in patients with kidney failure or plasma cell leukemia patients may be due to the more aggressive disease itself, however caution must be exercised in these more vulnerable patients. The lower incidences in the reinduction

cohort might be explained by the overall better fitness of these patients as well as the shorter length of venetoclax therapy.

Although previous studies with venetoclax had listed acute coronary events among observed adverse events, an association had not been published(93). In our study we have found four cases of myocardial infarction. One patient was 56 years old, two of these patients were 64 years of age at the time of the event, whereas the patient we lost was 76 years old; three were male; two events were unexpected, with the other two patients were known to have had severe ischemic heart disease. Although this is a higher number than would be expected based on Hungarian epidemiological data of the general population(94), myeloma patients have been shown to have a higher risk of arterial thromboses and ischemic cardiac events(95). Studies have published the rate of ischemic cardiac events and myocardial infarction to be between 0.1% and 5.9% of patients, depending on drug combinations and patient characteristics(95–97). Nevertheless, this rate was nevertheless very high in our studied population and further research is warranted to exclude a causative relationship with venetoclax-based therapy.

5.8. The place of venetoclax in the treatment landscape today

Despite an illustrious and successful career in other hematological malignancies, venetoclax faced several calamities during trials in myeloma, so much so that it may now even be called unsuccessful. The initial Bellini study has not been limited to t(11;14) patients and the subsequent failure has set the tone for the drug's development for the subsequent several years. Another major trial, the CANOVA study comparing VenDex to pomalidomide has failed to reach its primary endpoint, better PFS. As it was later shown, this was mainly due to informative censoring that resulted from the badly thought out study design: light chain increases were not accepted as progression in the trial design, which explains why treating physicians may have advised patients on the pomalidomide arm to withdraw from the study, causing censoring but no official data about their progression.

In the interim, daratumumab - which does have license, and is not limited to t(11;14) MM - has gained reimbursement for use in the second line (or, in the case of many countries in our region, even in first line), diminishing the importance of venetoclax.

Although some studies are still ongoing, none of them however seem promising enough to truly redeem the drug. The protected license for venetoclax is close to its end, and due to the consequent nonprofitability, pharmaceutical company trials will not be forthcoming either - elevating the importance of real world data.

5.9. The limitations of our study

While the results of our study are very suggestive, there are several limitations and caveats that must be kept in mind to form an unbiased opinion about its reliability and impact. As our study was retrospective and not randomized, patient selection had been subject to the treating physicians' conscious or unconscious biases, as well as the patients' choice. This is especially true in the case of the reinduction group - as discussed before, the concept of salvage, though logical, is not a widespread consensus in myeloma and it lacks clear clinical definition and guidelines.

In order to avoid recollection bias (long term survivors visiting the clinic regularly would be more easily remembered than those that died shortly after diagnosis), patient reporting was based on a systematic retrospective audit, rather than physician recall. For similar reasons, however, adverse events (especially adverse events of lower grade) are probably under-reported in our study compared to prospective trials, where real time reporting is mandated.

Even though the measurement of minimal residual disease (MRD) would have been a good substitute for longer term follow-up and OS results, it is yet unavailable for the treatment of the general myeloma population outside of clinical trials due to both a lack of funding and a lack of the relevant infrastructure in Hungary.

Another limitation is that due to the constant and rapid evolution in both treatment protocols and funding, the therapy landscape has changed majorly since our study period, making our results difficult to apply to current patients' needs.

6. Conclusions

1. We have collected real life data from a large number of hematological centers in Hungary and characterized venetoclax use in t(11;14) myeloma throughout the 2017-21 time period, including the use of CYP3A inhibitors and venetoclax dosing.
2. In the relapsed/refractory setting, the t(11;14) patients in our study showed much better response rates to venetoclax than studies have reported for other agents possibly used in this population.
3. In the relapsed/refractory setting, although venetoclax therapy was not effective indefinitely and progression could be expected after a median 10 months, the length of PFS and OS were nevertheless comparable or better to other treatment options for this group.
4. We found no significant difference in the survival of patients with high risk features such as del(17p) or kidney failure compared to patients without them.
5. We found that venetoclax salvage deepened the hematological response in t(11;14) patients to VGPR or CR reliably. After venetoclax therapy, all our eligible patients could proceed to ASCT, which could be carried out in either VGPR or CR.
6. We could not prove that early venetoclax therapy would have a significant effect on long term overall survival in t(11;14) patients responding unfavorably to standard therapy.
7. We found that the addition of venetoclax did lengthen progression-free survival and thus the time to further treatment in this group.
8. We found that among the patients in our praxis, early venetoclax use in t(11;14) patients was associated with significantly better OS than the use of conventional therapy.
9. We found that venetoclax was as effective in patients with renal failure (even if concurrently dialyzed) as in the normal kidney function population investigated in clinical trials, however, these patients were more prone to adverse events.
10. Our study article reported the highest number of PCL patients successfully treated with venetoclax in the literature at the time. We found that PCL patients treated with venetoclax had 10 months PFS, significantly better than would be expected with other agents.

11. Venetoclax treatment had an acceptable safety and toxicity profile in t(11;14) multiple myeloma patients, but attention should be paid to the possibility of coronary artery events.

7. Summary

Despite the introduction of more and more novel agents, multiple myeloma remains incurable for the majority of patients; treatment options that are reliably curative are an unmet need. Venetoclax, a selective BCL-2 inhibitor was shown to be contraindicated in the general myeloma population due to excess mortality, but demonstrated promising results in patients with translocation t(11;14). Its optimal application however remains in question. We evaluated venetoclax use in t(11;14) myeloma in a country-wide data collection in Hungary as well as in a more in depth analysis among our own patients at the Department of Internal Medicine and Hematology, Semmelweis University. Seven hematology centers participated, reporting 58 patients who we divided into two groups based on their history: 37 patients were treated in the relapsed/refractory setting with few or no other therapeutic options available; and 21 patients started venetoclax as salvage after failing to achieve satisfactory response to first line therapy. In the relapsed/refractory setting objective response rate (ORR) was 94%, median progression-free survival (PFS) 10.0 months and median overall survival (OS) 14.6 months. In reinduction patients, ORR was 100%, median PFS and OS were not reached, and all eligible patients could proceed to ASCT. Importantly, we found high risk features such as deletion 17p or renal failure had no adverse effect on survival, moreover, renal failure ameliorated after venetoclax therapy in 42% of the cases, including three patients who became dialysis independent. Our study also reported the highest number of plasma cell leukemia cases successfully treated with venetoclax published in literature at the time, with refractory plasma cell leukemia patients achieving a median PFS of 10.0 and a median OS of 12.2 months.

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9. Bibliography of the candidate's publications

9.1. Publications that provide the basis of the thesis

1.

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9.2. Other publications by the candidate

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