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The role of minimal residual disease (MRD) and fixed time duration (FTD) on the example of venetoclax in chronic lymphocytic leukemia (CLL) - clinical and systemic perspective

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Abstract

In recent years, haematologic treatment has undergone significant progress associated with the introduction of new drug technologies characterised by significant efficacy expressed by a deep response. At the same time the need for conducting and standardising MRD (minimal residual disease) evaluation, which can be used as an indicator for treatment discontinuation, is being debated. The aim of this paper is to indicate the significance of MRD in the assessment of treating CLL (chronic lymphocytic leukaemia) and discussing FTD (fixed time duration) treatment from a clinical and systemic perspective.

Current evidence confirms that a negative end-of-treatment MRD status is a strong predictive factor for PFS (progression-free survival) and OS (overall survival) regardless of the type of first-line treatment used and the risk factors. Some new technologies used in CLL treatment (such as venetoclax) are characterised by very high efficacy and can lead to obtaining a deep response, and thus the possibility of using the treatment for a FTD. Obtaining MRD(-) means reducing the number of cancer cells, which decreases the risk of clonal resistance, and thus gives the patients a better prognosis. Administration of the most effective therapy at disease onset is particularly important in CLL treatment. It is underlined that the adopted therapeutic regimen can impact subsequent treatment lines. The greatest benefits of using highly efficacious therapies are reported in first-line treatment, which increases the chances of longer PFS and helps delay the use of subsequent treatment regimens. FTD therapies constitute a beneficial (clinical and systemic) perspective of CLL treatment.

Introduction

PFS is currently considered the appropriate primary endpoint used to demonstrate clinically relevant benefits for the patient in randomised phase III trials in CLL. [1]. The importance of surrogate endpoints in assessing the long-term efficacy of therapy is also increasing. This plays a special role in the case of first-line and high-efficacy drug technologies. The possibility of conducting an evaluation of a therapy's efficacy based on surrogate endpoints is particularly important in indications for which five-year survival rates are anticipated to be high. One example of such indication is chronic lymphocytic leukaemia. The development of efficacious treatment methods constituting a response to the unmet medical needs of CLL patients necessitates the search for alternatives to the currently used time-to-event endpoints. A changed attitude taking into account the use of surrogate endpoints allows for determining treatment efficacy at an earlier time point and making therapy accessible to patients faster.[2]

Thanks to the development of diagnostic methods, improved detection methods and better understanding of leukaemia pathogenesis, over the last 20 years, much attention was devoted to the MRD (minimal residual disease) ratio. Minimal residual disease regards a very small number of cancer cells remaining in the patient's body after end of treatment. An MRD-positive status means that the disease is still detectable after end of treatment. An MRD-negative status means that the disease has not been detected after end of treatment. Currently MRD is assessed in trials conducted on patients with chronic lymphocytic leukaemia and constitutes a tool used to evaluate and monitor response to treatment.[2, 3]

At the same time, CLL therapy, which usually requires constant treatment until disease progression, is associated with the occurrence of many adverse reactions, which significantly contributes to a reduction in the patients' quality of life and at the same time constitutes a significant financial burden for the healthcare system.[4, 5] That is why researchers have been increasingly focused on fixed time duration therapies which allow for obtaining a deep response to treatment[6] and can lead to in clinical and systemic benefits.

Given the increasing significance of MRD in assessing efficacy of CLL treatment[3, 7], as well as in view of the occurrence of highly efficacious fixed time duration therapies, this paper includes an analysis of:

- the approach adopted by regulatory authorities towards using MRD as a treatment efficacy ratio,
- the correlation of MRD with hard endpoints,
- the role of MRD as a fixed time duration therapy indicator

as well as presents evidence on the benefits of using fixed time duration therapies in CLL.

The analysis was performed using venetoclax as an example, a selective inhibitor of the Bcl-2 protein used in chronic lymphocytic leukemia. The clinical trials indicate that the application of venetoclax in earlier lines of treatment allows for deeper MRD responses and shortens the duration of therapy, while ensuring a long progression-free time after treatment completion.

Methods:

The position of regulatory authorities with regard to MRD as the efficacy indicator has been verified by way of a search of materials published on websites of those organisations, in particular The European Medicines Agency (EMA) and The Food and Drug Administration (FDA), as the key bodies responsible for the creation of guidelines associated with the development and marketing of drugs.

In the course of identifying evidence on the use of MRD in assessing efficacy of haematologic therapies and indicating trends and directions in haematologic treatment, in particular using fixed time duration (FTD) therapies, PubMed database was searched using the following keywords: "*fixed time therapy*"; "*time fixed therapy*"; "*fixed time duration*", "*FTD*","*MRD*"; "*minimal residual disease*" connected with "*OR*".

Approach of regulatory authorities to the use of MRD in assessing efficacy of CLL treatment

Using MRD as a surrogate endpoint was reflected in guidelines published by the EMA and FDA. In 2014, the EMA published a document entitled: Guideline on the use of minimal residue disease as an endpoint in chronic lymphocytic leukaemia studies[3], while in 2020, the FDA published their guidelines entitled: Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment.[7] Both the European and the US agencies underline the significant part played by MRD as a prognostic factor and treatment efficacy indicator.

In line with the EMA 2014 guidelines, MRD constitutes an objective measure of the disease status. The EMA guidelines clearly indicate that available qualitative evidence is convincing enough for the negative status of residual disease to be used as a surrogate endpoint in randomised controlled clinical trials. Differences in terms of the obtained response indicators in patients with negative status of residual disease may constitute primary evidence of clinical benefits and may constitute the basis for obtaining early marketing authorisation.[3]

The merits of using MRD in assessing efficacy of CLL treatment

Based on Buckley 2013, present the concept of MRD. According to author, lower level of residual disease, generally associated with longer time to progression (i.e. less likely to relapse) (Figure 1).[8]

Table 1. THE USE OF MRD IN THE DEVELOPMENT OF DRUGS AND BIOLOGICAL PRODUCTS IN HEMATOONCOLOGICAL INDICATIONS ACCORDING TO FDA GUIDELINES[7]

MRD as biomarker according to FDA guidelines (2020)	
Diagnostic biomarker	A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.
Prognostic biomarker	A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest. A prognostic biomarker informs about the natural history of the disease in that particular patient in the absence of a therapeutic intervention
Predictive biomarker	A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a drug product.
Efficacy-response biomarker	A biomarker that is used to show that a response has occurred in an individual who has been exposed to a drug product.
Monitoring biomarker	A biomarker measured serially and used to detect a change in degree or extent of the disease.

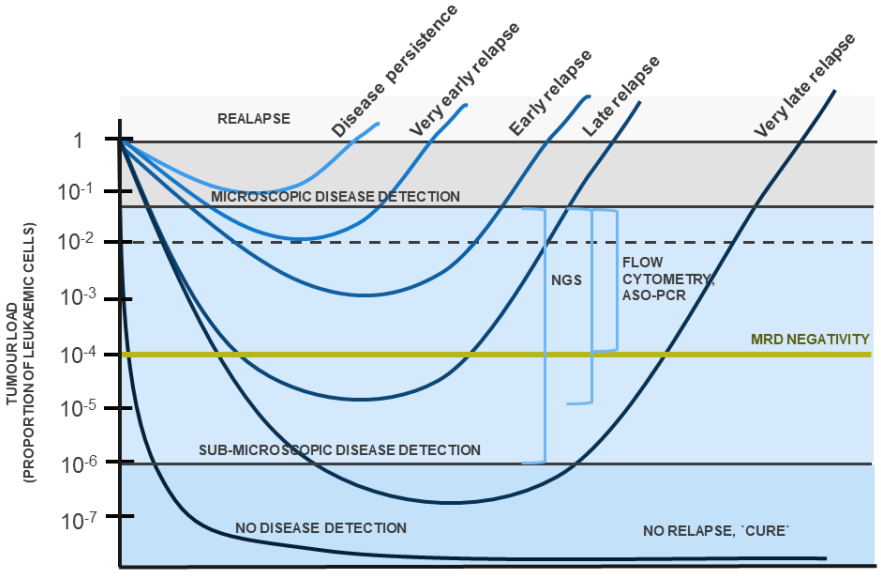

Figure 1. HYPOTHETICAL SCENARIOS OF LEUKEMIA CELL BURDEN CHANGES IN RESPONSE TO THERAPY, ADAPTED FROM BUCKLEY 2013 [8]

The merits of using MRD in assessing efficacy of therapies used in clinical trials has been confirmed by relevant evidence. It has been demonstrated in Owen (2017)[9] that assessment of the MRD status as an independent variable is the most important predictive factor of PFS and OS, regardless of whether CR was obtained, the type of therapy used, other predictive factors and the patient's baseline characteristics.[10, 11, 12] Similar conclusions have been published in Thompson et al. (2017), where it was demonstrated that MRD (-) is associated with more favourable PFS and OS prognoses, and that at the same time the greatest benefits were achieved in patients with a complete response to treatment.[13]

Pursuant to data published in Kovacs 2016[12] [Table S1], there were no significant differences between the MRD(-) CR and MRD(-) PR arms within terms of progression-free survival (HR 1.24; 95%CI: [0.87; 1.78], p=0.228); however, the study demonstrated longer PFS for MRD(-) PR than MRD(+) CR (p=0.48) and for MRD(+) CR compared to MRD(+) PR (p=0.002). Compared to MRD(-) CR, only MRD(+) PR patients have a significantly shorter OS (p=0.01). It has been determined that quantitative MRD status measurement allows for better PFS anticipation both in PR and CR patients, and hence using MRD in all types of obtained response to treatment is justified. Current clinical evidence suggests that PFS results can be forecast using the MRD response measurement.

MRD as the indicator for possible treatment discontinuation

New technologies are characterised by very high efficacy resulting from deep responses reaching beyond clinical response criteria. Hence, a decision on treatment discontinuation can be taken in the event a deep response to treatment, i.e. eradication of the minimal residual disease, has been achieved.[4] The above is confirmed by results of studies on venetoclax (MURANO and CLL14), which suggest that the idea of fixed time duration therapies is feasible and allows for treatment discontinuation in CLL patients by eliminating MRD.[14, 15, 16] It has been demonstrated that the use of venetoclax in combination with first-line obinutuzumab treatment: for a period of 12 months was associated with achieving a very high PFS percentage rate and obtaining MRD (-) in 76% of patients.[14] With regard to the population of patients with refractory/relapsed CLL, where venetoclax was administered in combination with rituximab for a period of 24 months (the median observation time was 9 months), a negative MRD status was obtained in over 60% of patients.[16]

It should be stressed that treatment duration depends on the specific treatment line. In the case of patients with an advanced form of the disease who have undergone 2 or more treatment lines, VEN is used until disease progression or death. At the same time, the use of VEN in earlier treatment lines allows for obtaining good results in terms of MRD (-) and thus a deep response to treatment. (Figure 2)

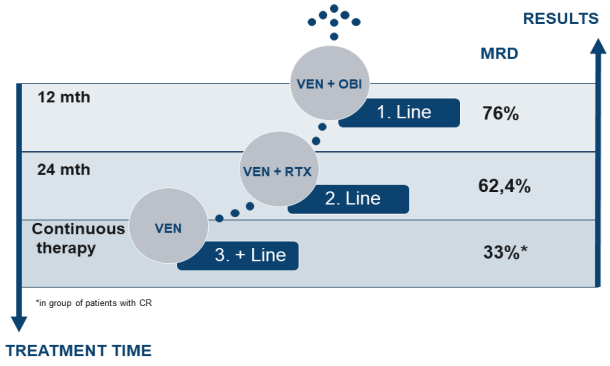

Figure 2. VENETOCLAX IN CLL THERAPY – TREATMENT TIME VARIOUS LINES AND RESPONSE [14, 15, 16, 17]

Fixed time duration therapy (clinical and systemic perspective)

The use of fixed time duration therapies is not limited solely to CLL and can be applied to other indications as well. In recent years, and increasing number of such treatment regimens have been used in other haemato-oncologic indications. (Table S2) Regard to CLL, an example of FTD is venetoclax applied in the 1st and 2nd lines of treatment.

Due to innovative mechanism of action, venetoclax is a potent, selective inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL cells where it mediates tumour cell survival and has been associated with resistance to chemotherapeutics. Venetoclax binds directly to the BH3-binding groove of BCL-2, displacing BH3 motif-containing pro-apoptotic proteins like BIM, to initiate mitochondrial outer membrane permeabilization (MOMP), caspase activation, and programmed cell death. Venetoclax allows to obtain good results of MRD. The high proportion of patients achieving a deep response confirms efficacy of the drug's and thus allows the decision to discontinue therapy. [14, 15, 16, 18]

In Cuneo 2019,[6] fixed time duration therapies are discussed and their high efficacy is confirmed, which allows for achieving a deep and lasting response to treatment and improved survival of patients with relapsed/refractory CLL. (Table S1)

Adopting FDT as a parameter can bring benefits both to the patient and to the entire healthcare system.[4, 5] (Figure 3)

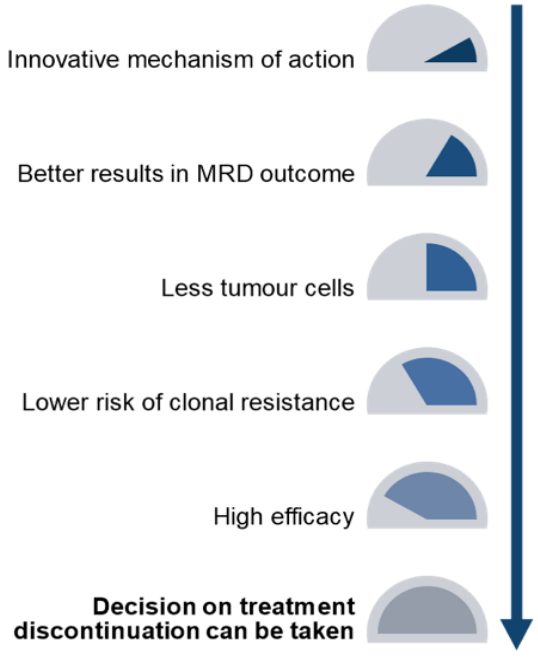

Figure 3. INDICATORS FOR POSSIBLE TREATMENT DISCONTINUATION – VENETOCLAX

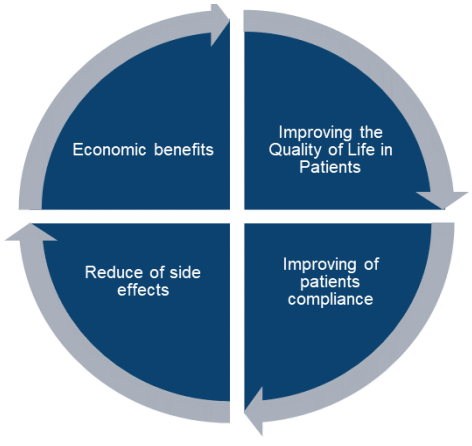

Figure4. BENEFITS OF FIXED TIME THERAPY [3,4]

Setting out a limited treatment duration is particularly significant from the patient's perspective, as the therapy can be applied for a specified time, and not until disease progression, as is usually the case. Furthermore, adverse effects of the treatment are also limited in time.[4, 5]

Apart from the benefits to the patient, the use of these types of therapy is associated with benefits to the healthcare system. Authors of Sail 2017 assessed the difference in direct medical costs for CLL patients taking into account the response to treatment status: (MRD (-) (negative MRD status) / CR, MRD (-) / PR, MRD (+) (positive MRD status) / CR

and MRD (+) / PR). On the basis of the conducted analysis, it has been demonstrated that low-risk patients undergoing first-line treatment with MRD (-) generated on average 30% lower costs than MRD (+) patients. The same effect was also observed in CR patients who achieved MRD (-)/ CR, on average the costs where lower by 19% compared to MRD (+)/CR patients. A comparison of costs after second-line treatment has demonstrated that low-risk patients achieving MRD (-) have generated on average 24% lower costs than MRD (+) patients. A similar effect has also been observed in CR patients, where patients achieving MRD (-)/ CR generated on average 18% lower costs compared to MRD (+)/CR patients. Conclusions of Sail 2017 suggest that the MRD (-) status is correlated with lower direct costs in CLL, regardless of the clinical response (either CR or PR). The results suggest that patients achieving MRD (-) will also generate lower costs throughout the entire treatment duration.[19]

Another publication – Davids 2019 – presents a cost-effectiveness analysis on the use of venetoclax in combination with obinutuzumab in naive CLL patients, carried out from the payer's perspective. The following costs were taken into account in the set-out time horizon (20 years): costs of CLL treatment, costs of routine care and treatment monitoring, costs of AEs, costs of disease progression, as well as costs of subsequent treatment and palliative care. Pursuant to the publication, the use of a 12-month venetoclax + obinutuzumab combination therapy (i.e. fixed time duration therapy) is the dominant therapy in relation to the other comparators included in the model (lower total costs and higher efficacy).[20] The advantage results from the fixed time duration of the therapy compared to other continuous therapies (i.e. until time to progression or death).

Conclusions

FDA and EMA guidelines confirm the significance of a negative MRD status as a prognostic factor and indicator of treatment efficacy. The published evidence clearly demonstrates the correlation between a negative MRD status and improved PFS and OS results. In recent years, an increased number of clinical trials using MRD as one of the endpoints have also been observed. Using MRD as an indicator makes it possible to get a better understanding of remission and the risk of relapse, including to estimate the duration of the response to treatment. The efficacy of fixed time duration therapies, such as venetoclax, allows for obtaining a deep response to treatment (expressed as an MRD parameter), and thus the possibility of administering treatment for a limited period of time. Using fixed time duration therapies offers benefits to both the patients and the healthcare system. It contributes to reducing the occurrence of adverse effects, allows for an improvement of patients' quality of life and brings significant pharmacoeconomic benefits (reducing expenditure from the state budget by limiting the therapy duration in time).

Authors declare none potential conflicts of interest.

Supplementary materials

Table S1. PFS and OS by Clinical Response and MRD Assessments in CLL

MRD and Clinical Response Cohort	Patients, No (%)	PFS				OS			
		Median (months)	HR	95%CI	p	Median (months)	HR	95%CI	p
MRD(-) CR	186 (33,6)	60,7	-			NR	-		
MRD(-) PR	161 (29,1)	54,2	-			NR	-		
MRD(+) CR	39 (7,0)	35,4	-			NR	-		
MRD(+) PR	168 (30,3)	20,7	-			72,1	-		
Comparison with MRD(-) CR									
MRD(-) PR	-	-	1,24	0,87; 1,78	0,228	-	0,85	0,45; 1,61	0,612
MRD(+) CR	-	-	1,99	1,25; 3,18	0,004	-	0,92	0,37; 2,26	0,853
MRD(+) PR	-	-	4,27	3,14; 5,81	<0,001	-	2,38	1,44; 3,94	0,001
Comparision with MRD(+) CR									
MRD(-) PR	-	-	0,63	0,39; 1,00	0,048	-	0,93	0,36; 2,39	0,882
MRD(+) PR	-	-	2,00	1,30; 3,08	0,002	-	2,56	1,09; 6,00	0,031

CR, complete remission; HR, hazard ratio; MRD, minimal residual disease; MRD2, minimal residual disease negative; MRD+, minimal residual disease positive; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response.

Table S2. FIXED DURATION THERAPIES- HEMATO-ONCOLOGICAL INDICATIONS

Name (Substance)		Indication	Duration of therapy
Venetoclax [18]		VEN + OBI for the treatment of adult patients with previously untreated CLL.	12 months
		VEN + RTX for the treatment of adult patients with CLL who have received at least one prior therapy.	24 months
Obinutuzumab [21]		OBI + CHL for the treatment of adult patients with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy	6 treatment cycles (duration of cycle: 28 days).
CAR-T [22, 23]	Tisagenlecleucel	Paediatric and young adult patients up to and including 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse.	Single use
		Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after ≥2 lines of systemic therapy.	
	Axicabtagene ciloleucel	For the treatment of adult patients with relapsed or refractory DLBCL and PMBCL, after ≥2 lines of systemic therapy.	
Inotuzumab ozogamicin [24]		As monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor ALL.	For patients proceeding to HSCT, the recommended duration of treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve a CR or CRi and MRD negativity after 2 cycle. For patients not proceeding to HSCT, a maximum of 6 cycles may be administered. Any patients who do not achieve a CR/Cri within 3 cycles should discontinue treatment. Cycle 1 is 3 weeks in duration but may be extended to 4 weeks Subsequent cycles are 4 weeks in duration.
Panobinostat [25]		In combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory MM who have received at least two prior regimens including bortezomib and an immunomodulatory agent.	Patients should be treated initially for eight cycles. It is recommended that patients with clinical benefit continue the treatment for eight additional cycles. The total duration of treatment is up to 16 cycles (48 weeks).
Bortezomib [26]		Monotherapy; MM after at least 1 prior therapy.	It is recommended that patients receive 2 cycles of treatment following a confirmation of a CR (after first cycle, duration of cycle: 3 weeks). It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of therapy.
		BOR+DEX; MM after at least 1 prior therapy.	Patients achieving a response or a stable disease after 4 cycles of this combination therapy can continue to receive the same combination for a maximum of 4 additional cycles.
		BOR+MEL+PRE; adult patients with previously untreated MM who are not eligible for high-dose chemotherapy with HSCT.	9 treatment cycles of this combination therapy are administered (duration of cycle: 6 weeks).
		BOR+DEX; adult patients with previously untreated MM who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation (induction therapy).	4 treatment cycles of this combination therapy are administered (duration of cycle: 3 weeks).
		BOR+DEX+TAL; adult patients with previously untreated MM who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation (induction therapy).	4 treatment cycles of this combination are administered (duration of cycle: 4 weeks). It is recommended that patients with at least partial response receive 2 additional cycles.
		BOR+RTX+CYC+DOK+PRE; adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.	6 cycles of treatment are recommended, although for patients with a response first documented at cycle 6, two additional cycles of treatment may be given.
Brentuximab vedotin [27]		BRE+DOK+WIN+DAC: previously untreated CD30+ Stage IV HL.	28-day cycle for 6 cycles.
		Adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.	Patients should receive up to 16 cycles.
		Adult patients with relapsed or refractory CD30+ HL.	Treatment should be continued until disease progression or unacceptable toxicity.
		BRE+CYC+DOX+PRE: adult patients with previously untreated sALCL.	Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year).
		Adult patients with CD30+ CTCL after at least 1 prior systemic therapy.	Patients should receive up to 16 cycles.
Blinatumomab [28]		Adults with Philadelphia chromosome negative CD19 positive relapsed or refractory B-precursor ALL. Adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.	Patients may receive 2 cycles of treatment. Patients who have achieved complete remission (CR/CRh*) after 2 treatment cycles may receive up to 3 additional cycles of consolidation treatment, based on an individual benefits-risks assessment. Patients may receive 1 cycle of induction treatment followed by up to 3 additional cycles of consolidation treatment.

VEN+OBI – venetoclax in combination with obinutuzumab, VEN+RTX – venetoclax in combination with rituximab, CLL – chronic lymphocytic leukaemia, OBI+RTX – obinutuzumab in combination with chlorambucil, CML - chronic myeloid leukemia, ALL - acute lymphoblastic leukemia, DCBCL - diffuse large B-cell lymphoma, PMBCL - primary mediastinal large B-cell lymphoma, HSCT - hematopoietic stem cell transplantation CR - complete response, CRi - complete response with incomplete hematopoietic recovery, MM – muliple myeloma, BOR+DEX – bortezomib in combination with dexamethasone, BOR+MEL+PRE – bortezomib in combination with melphalan and prednisone, BOR+DEX+TAL- bortezomib in combination with thalidomide, BOR+RTX+CYC+DOK+PRE – bortezomib in combination with rituximab, cyclophosphamide, doxorubicine and prednisoen, HL – Hodgkin lymphoma, ASCT - autologous stem cell transplant, CTCL - cutaneous T-cell lymphoma, sALCL - systemic anaplastic large cell lymphoma, BRE+CYC+DOX+PRE - brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisone

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