



Novel Approaches for the Treatment of Patients with Richter's Syndrome

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Opinion statement

In the last 10–15 years, the way to treat cancers has dramatically changed towards precision medicine approaches. These treatment options are mainly based on selective targeting against signaling pathways critical for or detrimentally activated in cancer cells in cancer cells, as well as exploiting molecules that are specifically expressed on neoplastic cells, also known as tumor-associated antigens. These considerations hold true also in the hematological field where a plethora of novel targeted agents have reached patients' bedside, significantly improving clinical responses. Chronic lymphocytic leukemia (CLL) is an example of how targeted therapies, such as BTK, PI3K, or Bcl-2 inhibitors as well as anti-CD20 antibodies, have improved patients' management, even when adopted as frontline treatment. However, these advancements do not apply to Richter's syndrome (RS), the transformation of CLL into a very aggressive and fatal lymphoma, occurring in 2–10% of patients. RS is usually a fast-growing lymphoma of the diffuse large B cell or the Hodgkin's variant, with a dismal prognosis. Despite advancements in depicting and understanding the genetic background of RS and its pathogenesis, no significant clinical results have been registered. In the last couple of years, several studies have started to investigate the impact of novel drugs or drug combinations and some of them have opened for clinical trials, currently in phase I or II, whose results will be soon available. This review will present an overview of current and most recent therapeutic options in RS, discussing also how results coming from xenograft models may help in designing and identifying novel treatment opportunities to overcome the lack of effective therapies.

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Introduction

The landscape of lymphomas is currently rapidly changing and becoming more complex, both because of novel subtype classifications based on the genetic and transcriptomic profiles of neoplastic cells [1–5], and due to more treatment options, that are progressively available. These two paths are paving the way for the transition towards personalized approaches where patients will be cured based on cancer cell characteristics to achieve the best response while minimizing side effects.

RS is defined by the WHO classification of tumors of hematopoietic and lymphoid tissues as the development of a high-grade aggressive lymphoma in a previous or concomitant background of CLL [1]. RS is typically a diffuse large B-cell lymphoma (DLBCL) [6, 7], with only a minority of cases (0.5–5%) presenting a Hodgkin's variant [8, 9]. Even though the prognosis of RS is generally poor, a significant difference is registered when considering the clonal relatedness to the CLL phase. Indeed, clonally related cases show a median survival of approximately 12 months, while clonally unrelated RS are characterized by a median survival of 65 months [10]. Beside the aggressiveness of the disease, an element of poor survival for RS patients is the lack of effective therapies. Indeed, while treatment options for CLL patients have significantly increased with the introduction of targeted agents, such as rituximab, ibrutinib, or

venetoclax [11•], resulting in improved OS and different treatment regimens to be adopted depending on the genetic and molecular features of CLL cells, almost nothing has changed for RS patients. In the last couple of years, this gap has started to close with novel agents or drug combination strategies being tested in clinical trials, also thanks to the availability of representative pre-clinical models.

The incidence rate of RS has been estimated 0.5–1% per year, with an overall incidence in CLL patients of 5–16% [12, 13]. However, a still open point regarding RS incidence is whether treatment regimens adopted in the CLL phase may somehow exert a selective pressure, finally pushing toward RS transformation. Epidemiological results are still controversial, depending also on patient cohorts analyzed. Recent analyses considering treatment-naïve CLL patients who underwent only novel agent therapies showed no increase in the number of RS transformation. On the contrary, when considering relapsed/refractory CLL patients, the incidence raised up to 2–15% following ibrutinib, venetoclax, or idelalisib treatments [14–18].

Results coming from large and prospective cohorts will clarify in the next future the impact of these novel therapies in potential selection of more aggressive clones that can eventually transform into RS.

Treatment options

Currently, RS patients are treated with the same therapeutic regimens commonly adopted for aggressive B-cell non-Hodgkin lymphomas or de novo DLBCL, mainly based on chemo-immunotherapy and stem cell transplantation (SCT), depending on the fitness of the patients. However, in the former case, only limited efficacy with frequent relapses are registered [19], while SCT can be adopted only in fit RS patients [20, 21]. These limitations require additional investigation of alternative and more effective therapeutic strategies. In the last years, different trials have started with the aim of testing the clinical efficacy of novel compounds or drug combinations. Moreover, generation of RS patient-derived xenograft models has been of help for the designing and pre-clinical validation of selective therapeutic approaches.

Here, we present a brief overview of the currently available (mainly chemo-immunotherapy and SCT) treatment options for RS patients, moving then to novel agents that are presently under investigation.

Current treatments

Chemo-immunotherapy

Different chemotherapy or chemo-immunotherapy regimens are adopted to treat RS patients. Chemotherapy alone, mainly based on cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) administration, results in limited overall response rate (ORR; approximately 20–30%) and a median overall survival (OS) of few months (4–8 months) [22, 23]. Its efficacy is slightly improved when combined with rituximab (R), a human/murine chimeric anti-CD20 monoclonal antibody (mAb). R-CHOP resulted in an ORR of 67% and a median OS of 21 months, three-time longer than CHOP alone [22–24]. On the contrary, no significant clinical improvements compared to chemotherapy alone have been obtained by the CHOP-O treatment, where rituximab was replaced by ofatumumab, another humanized mAb anti-CD20 [25, 26], R-EPOCH (rituximab, etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone) [27], or R-hyper-CVXD/R-MA regimens, an intensive treatment scheme based on fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone in combination with rituximab alternated to methotrexate and cytarabine plus rituximab [28, 29].

Despite the unsatisfactory results obtained and apart from the ongoing clinical trials (Table 1), the use of chemo-immunotherapy for RS patients remains the frontline therapy, underlining the urgent need for novel and more effective therapeutic strategies.

Stem cell transplantation

An alternative approach to chemo-immunotherapy is either the autologous or allogenic-SCT, which however can only be adopted in fit RS patients, who generally represent a minority of patients (10–15%) [30]. Clinical data showed that RS patients who underwent allogenic-SCT as post remission therapy had longer survival compared to patients who received no additional therapy or SCT as salvage therapy, with some difference in terms of OS depending on the cohort analyzed (estimated 3-year OS of 36% for allogenic-SCT and 59% for autologous-SCT) [20, 23, 30]. These results have been recently confirmed in different studies, revealing a 5-year OS of 58% and confirming the long-term efficacy of SCT [22, 31, 32, 33]. Moreover, a meta-analysis of the existing medical literature focused on the clinical efficacy of allogenic-SCT, performed in 2020, highlighted an encouraging ORR of 79%, including 33% of complete responses, and an OS rate of 49% [34].

Novel therapeutic approaches

Antibody-based therapies

Naked antibodies

The programmed death 1 (PD-1) pathway plays a crucial role in tumor host immunity evasion and its blockade has emerged as an effective anti-cancer immunotherapy [35]. Preclinical studies suggested that PD-1 or PD-ligand

Table 1. Clinical trials enrolling RS patients and evaluating single or combined therapeutic agents

Trial ID	Status	Disease	N° of patients	Treatments	Phase	References
NCT03054896	Recruiting	RS	67	Venetodax, DA-R-EPOCH, R-CHOP	Phase II	[102•]
NCT03899337	Not yet recruiting	CLL, RS	105	Acalabrutinib, R-CHOP	Phase II	[100]
NCT04939363	Recruiting	RS	15	Obinutuzumab, ibrutinib, venetoclax	Phase II	
NCT01171378	Completed	CLL, RS	43	Ofatumumab	Phase II	[25]
NCT03931642	Recruiting	RS	35	R-CHOP, blinatumomab	Phase II	
NCT02576990	Completed	PMBCL, RS	80	Pembrolizumab	Phase II	[41]
NCT04679012	Recruiting	CLL, RS	20	Polatuzumab vedotin, DA-R-EPOCH	Phase II	
NCT04992377	Not yet recruiting	RS	30	R-EPOCH, ibrutinib	Phase II	
NCT04271956	Recruiting	RS	48	Tislelizumab, zanubrutinib	Phase II	
NCT03121534	Active, not yet recruiting	RS	10	Blinatumomab, dexametason	Phase II	
NCT02846623	Recruiting	CLL, RS	65	Atezolizumab, obinutuzumab, venetoclax	Phase II	
NCT04082897	Recruiting	RS	28	Obinutuzumab, atezolizumab, venetoclax	Phase II	
NCT00309881	Completed	CLL, RS	75	R-CHOP	Phase II	[19]
NCT02420912	Active, not yet recruiting	R/R CLL, RS	72	Ibrutinib, nivolumab	Phase II	
NCT04305444	Recruiting	R/R CLL, DLBCL, FL, RS	120	DTRM-555	Phase II	
NCT02530515	Completed	CLL, RS, PLL	8	Ex vivo-activated autologous lymph node lymphocytes	Phase II	
NCT02332980	Active, not yet recruiting	NHL, CLL, MZL, FL, CLL, RS	65	Ibrutinib, idealisib, [embrolizumab	Phase II	[40]
NCT00452374	Completed	R/R CLL, RS	48	OFAR	Phase I/II	[105]
NCT03534323	Recruiting	CLL, RS	67	Duvelisib, venetoclax	Phase I/II	[106]
NCT04623541	Recruiting	R/R CLL, RS	102	Epcoritamab	Phase I/II	
NCT00304005	Completed	R/R CLL, RS	35	Laromustine	Phase I/II	
NCT00472849	Completed	R/R CLL, RS	92	OFAR	Phase I/II	[107]
NCT02029443	Active, not yet recruiting	CLL, RS	306	Acalabrutinib	Phase I/II	[80]
NCT01217749	Completed	CLL, RS	71	Ibrutinib, ofatumumab	Phase I/II	[98]
NCT05025800	Recruiting	NHL, FL, MZL, MCL, RS	52	ALX148, lenalidomide, rituximab	Phase I/II	
NCT04491370	Recruiting	BL, DLBCL, FL, MCL, MZL, RS	20	ASCT, polatuzumab vedotin	Phase I/II	
NCT02362035	Active, not yet recruiting	FL, CLL, RS, MCL, NHL, MM, BL, MZL	161	Acalabrutinib, pembrolizumab	Phase I/II	
NCT03010358	Completed	FL, MCL, MZL, R/R CLL, RS	24	Entospletinib, obinutuzumab	Phase I/II	
NCT03162536	Recruiting	CLL, MCL, DLBCL, RS, FL, MZL	190	Neutabrutinib	Phase I/II	
NCT03892044	Recruiting	CLL, DLBCL, RS	44	Duvelisib, nivolumab	Phase I	
NCT04978779	Recruiting	R/R CLL, RS	54	VIP152	Phase I	
NCT04781855	Not yet recruiting	R/R CLL, RS	50	Ibrutinib, ipilimumab, nivolumab	Phase I	

Table 1. (Continued)

Trial ID	Status	Disease	N° of patients	Treatments	Phase	References
NCT03884998	Recruiting	RS, NHL, FL, LPL, MZL	15	Copanlisib, nivolumab	Phase I	
NCT03778073	Recruiting	NHL, RS	72	Cosibelimab, ublituximab, bendamustina	Phase I	
NCT03113695	Active, not yet recruiting	RS	10	Obinutuzumab, lenalidomide, HDMP	Phase I	
NCT02535286	Completed	CLL, RS	27	Umbralisib, ublituximab, TG-1501	Phase I	
NCT03263637	Completed	AML, ALL, CLL, RS, NHL, MM	44	AZD4573	Phase I	
NCT03321643	Recruiting	DLBCL, NHL, RS	24	Atezolizumab, gemcitabine, oxaliplatin, rituximab	Phase I	
NCT05176691	Not yet recruiting	CLL, NHL, MCL, MZL, LPL, FL, DLBCL, RS	168	HMPL-760	Phase I	
NCT05107674	Recruiting	Solid tumors, RS	336	NX-1607	Phase I	
NCT04892277	Not yet recruiting	R/R NHL, R/R CLL, RS	25	CAR-T, cyclophosphamide, fludarabine	Phase I	
NCT03479268	Recruiting	CLL, DLBCL, FL, MCL, MZL, NHL, RS	30	Ibrutinib, pevonedistat	Phase I	
NCT01254578	Completed	CLL, RS, AML, APL, ALCL & other lymphomas	17	Lenalidomide	Phase I	
NCT04771572	Recruiting	NHL, RS, MM, AML, ALL	100	LP-118	Phase I	
NCT04806035	Recruiting	CLL, RS, FL, MZL, DLBCL, MCL	60	TG-1801, ublituximab	Phase I	
NCT03833180	Recruiting	CLL, MCL, FL, MZL, DLBCL, RS, BL, ALL		Zilvertamab vedotin	Phase I	

ALL, anaplastic large cell lymphoma; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BL, Burkitt lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PLL, prolymphocytic leukemia; PMBCL, primary mediastinal B-cell lymphoma; R/R, relapse/refractory; RS, Richter's syndrome

1 (PD-L1) blocking antibodies have efficacy in selected hematological malignancies, including DLBCL and other NHLs, all expressing high levels of these surface antigens [36, 37]. In addition, RS patients are characterized by a high expression of both PD-1 and PD-L1 [38, 39], opening for their targeting exploiting selective naked antibodies, capable of interfering with this signaling pathway (Fig. 1A).

Pembrolizumab is a PD-1 blocking antibody whose safety and clinical activity were initially evaluated in a phase II clinical trial that enrolled a small cohort of RS patients, most of them (approximately 70%) having been previously treated with ibrutinib, resulting in a 44% of ORR and 11 months of OS. This efficacy was associated to an acceptable safety profile, with only 20% of patients presenting severe hematologic toxicity [40].

These promising results were not overlapping the ones obtained by the KEYNOTE-170 multicenter phase II trial (NCT02576990) that enrolled relapsed/refractory RS patients. Indeed, in this subset of patients, pembrolizumab monotherapy resulted in a reduced clinical efficacy, with only 1 complete and 2 partial responses, leading to a 13% ORR [41].

Nivolumab is another PD-1-binding immune checkpoint inhibitor, capable of potentiating T-cell activity, that has already showed efficacy in several solid tumors [42–44]. The clinical impact of this humanized mAb, administered either alone or in combination with targeted agents (ibrutinib or venetoclax), has been evaluated in a small cohort of RS patients. Results were not encouraging with 90% of patients experiencing treatment failure, disease progression, and a median OS from the first dose of only 2 months [45].

Despite the low clinical efficacy observed with anti-PD-1 inhibitors in RS, different clinical trials are currently ongoing testing the impact of co-targeting strategies, where checkpoint inhibitors are administered together with molecules targeting critical signaling pathways for B cells, such as BTK or PI3K (NCT04271956, NCT02535286; Table 1).

Drug-conjugated antibodies

A promising therapeutic strategy for cancer treatment is based on antibody-drug conjugates (ADCs), engineered therapeutics combining the selectivity of a mAb, that recognizes a tumor-associated antigen, to the cytotoxicity of a payload. Their success depends on their effectiveness and the lack of off-target toxicities [46, 47]. Several ADCs are currently approved by FDA or in late-stage clinical development for treatment of both solid tumor and hematological malignancies [48•].

The clinical impact of ADCs in RS has been recently explored by our group, taking advantage of four RS patient-derived xenograft models [49], and targeting two molecules that are highly and selectively expressed by these neoplastic cells. Firstly, we explored the effects of VLS-101, an ADC comprising UC-961, a mAb targeting the extracellular domain of receptor tyrosine kinase-like orphan receptor 1 (ROR1) [50], linked to the anti-microtubule agent monomethyl auristatin E (MMAE). ROR1 is expressed by CLL cells and other cancers but not by healthy adult tissues, making it an attractive tumor-specific therapeutic target [51, 52]. Once VLS-101 is bound to its target, the complex is internalized and delivered to lysosomes, where

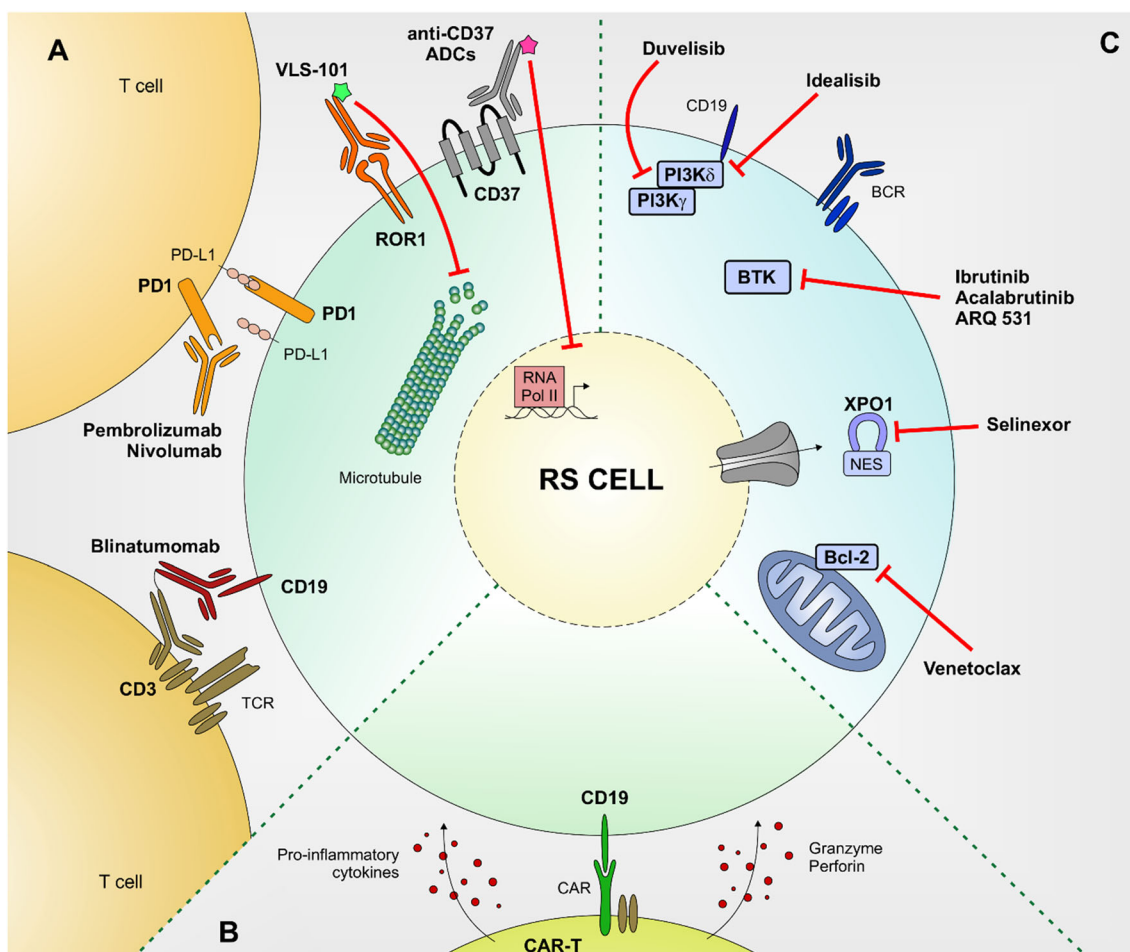


Fig. 1. Schematic representation of novel therapeutic approaches to treat RS patients. The main novel therapeutic approaches to treat RS patients are summarized. Small molecules targeted therapies (**A**), antibody-based therapies (**B**), and CAR-T (**C**). Bcl-2 (B-cell lymphoma 2), XPO1 (exportin 1), BTK (Bruton tyrosine kinase), BCR (B-cell receptor), PI3K (phosphoinositide 3-kinase), ADC (antibody-drug conjugate), ROR1 (receptor tyrosine kinase-like orphan receptor 1), PD1 (programmed death 1), PD-L1 (programmed death 1 Ligand), TCR (T-cell receptor), RNA Pol II (RNA polymerase 2), CAR (chimeric antigen receptor), NES (nuclear export signal).

MMAE is released via proteolytic cleavage and free to inhibit cell-cycle progression and to induce apoptosis of the target cell. VLS-101 has shown promising efficacy to treat RS, resulting in cell-cycle arrest and apoptosis *ex vivo*, and significantly reducing tumor burden *in vivo* resulting in a prolonged animal survival. Moreover, VLS-101 was characterized by a high selectivity since no clinical effects were registered in a ROR1-negative model and no adverse toxic effects showed in treated mice [53]. Based on these promising results, a phase I clinical trial testing VLS-101 in RS and other aggressive hematological malignancies is currently ongoing (NCT03833180).

The second target we explored in RS to be targeted with ADC is CD37, a surface molecule belonging to the tetraspanin family, showing a peculiar pattern of expression. Indeed, it is expressed by mature B and transformed

leukemic/lymphoma cells, but not on normal T, NK, pro-B, and plasma cells. Given this expression profile, CD37 has been recently proposed as an actionable target for the treatment of CLL and non-Hodgkin lymphomas [54–58].

RS cells, both primary samples and PDX models, are characterized by CD37 surface expression, comparable to the one detected in DLBCL and follicular lymphoma cells. Three different anti-CD37 ADCs were tested, all generated using amanitin as a payload, a toxin that once internalized in the target cell is released from the mAb and free to localize to the nucleus where it binds to the RNA polymerase II, finally inhibiting messenger RNA synthesis. These compounds showed high selectivity and specificity as no targeting and toxic effects were highlighted in CD37-negative cells. Treatment of RS cells with these compounds, both *ex vivo* and *in vivo*, induced apoptosis and significantly prolonged survival of treated mice, after a single-dose administration of these ADCs, making CD37 an interesting target for RS patients (Fig. 1A) [59].

Bispecific antibodies

Bispecific monoclonal antibodies (bsAbs) are designed to bind two different epitopes or antigens, frequently expressed by distinct cells, and have been largely explored to drive an effector to a target cell [60•]. This approach has been recently adopted for the treatment of different B-cell malignancies [61•], including RS, where a refractory patient underwent a rapid and complete response following therapy with the bispecific anti-CD19/CD3 antibody blinatumomab, opening the way for a clinical trial (NCT03121534) with the aim of testing its efficacy and safety in RS (Fig. 1A) [62].

Chimeric antigen receptor T-cell therapy (CAR-T)

An innovative approach that has recently entered in the onco-hematological field is the targeting of CD19, an antigen exclusively expressed on normal and pathological B cells, via CAR-T [63, 64]. CAR-T cell therapy is designed to get T cells to fight against cancer prior *ex vivo* genetic manipulation of the receptor to better identify cancer antigens (Fig. 1B).

The first attempts of RS treatment with this approach were conducted few years ago in 2 patients with poor responses, including disease progression [65] and evolution to plasmablastic lymphoma [66]. Additional studies performed in relapsed patients who underwent hematopoietic stem cell transplantation and chemo-immunotherapy showed only partial responses [67, 68]. More recently, different trials based on larger cohorts of RS patients obtained quite satisfactory results, reaching an ORR of 71% and 56%, 4 weeks after cell therapy. Despite these results, a lower antitumor activity was registered in the subset of patients presenting large lymph node burden compared to those with a lower lymph node bulk [69–71]. In one of this study, CAR-T therapy was administered in combination with ibrutinib resulting in an increased clinical efficacy [71]. In line with these encouraging data, in a recent study that included 9 RS patients, heavily pretreated with chemo-immunotherapy, ibrutinib or ibrutinib in combination with venetoclax, an ORR of 90% with 5 patients

showing a complete response in a median follow-up of 6 months was obtained [72].

Taken together, these results are encouraging, but prospective studies with larger cohorts of patients are needed to better understand how CAR-T can be combined with the available targeted therapies, which the patients who can benefit the most from this approach.

Small molecules–targeted therapy

Chemotherapy is one of the most effective therapeutic options against cancer, even though it is accompanied by several side effects. A breakthrough in this field has been the introduction of targeted therapies, which are based on pharmacological agents capable of selectively interfering with proteins involved in tumorigenesis. Focusing on molecular changes that are uniquely associated to a specific type of cancer may lead to improved therapeutic benefits, accompanied by a more safety profile, tailoring treatments to an individual patient's tumor. Besides mAbs and ADCs, targeted therapy may involve the use of small molecule inhibitors, drugs capable of recognizing and block kinases, epigenetic regulatory proteins, and DNA damaged repair enzymes and proteasome [73].

Hematological malignancies have been an example of how small molecule inhibitors can be successfully adopted in the clinics [74] and treatment of CLL has been revolutionized by the introduction of BTK, PI3K, and Bcl-2 inhibitors [75].

These small molecule inhibitors have started to be translated in the clinic for the treatment of RS patients, even though results are still limited and sometimes discouraging (Fig. 1C).

Ibrutinib, a BTK inhibitor, has shown well tolerability in small cohorts of patients but poor clinical effects with only partial responses and a complete response obtained only in one patient [76–79]. Similar limited results have been obtained also with acalabrutinib, an irreversible BTK inhibitor, that showed a good tolerability profile, but poor responses when used as monotherapy [80]. Clinical data in RS patients are still missing for ARQ 531, another reversible non-specific BTK inhibitor, that has been tested in murine models of CLL and aggressive B-cell lymphomas [81], resulting in a prolonged survival of mice compared to animals treated with ibrutinib [82]. An ongoing phase I trial (NCT03162536) is enrolling patients, including RS patients, for testing safety, tolerability, and efficacy of ARQ 531 [83, 84].

AKT, another element of the BCR signaling cascade downstream to the PI3K kinase, has been shown to be active in RS and its constitutive activation in the E μ -TCL1 CLL model can induce an aggressive lymphoma that mimics the clinical features of RS, suggesting that PI3K/AKT kinases play a key role in RS transformation [85, 86]. Idelalisib is a PI3K δ inhibitor that has shown great clinical activity in CLL despite a significant toxicity, even in relapsed/refractory patients, when combined either with rituximab or with bendamustine regimens [75]. When administered to RS patients in a small cohort trial (4 patients), it has demonstrated some activity with no disease progression in all patients, one complete response and two partial responses [87]. Moreover, an independent case report confirmed idelalisib efficacy in RS, with a complete response achieved in 3 weeks, even though patient relapsed rapidly after drug discontinuation due to severe side effects [88].

More recently, our group has shown preclinical efficacy of duvelisib, a dual PI3K δ/γ inhibitor, in PI3K expressing RS-PDX models [85]. Inhibition of the PI3K signaling pathway resulted in AKT downregulation and GSK3 β activation, leading to ubiquitination and subsequent degradation of both c-Myc and Mcl-1, finally resulting in an increased apoptotic rate of RS cells. Moreover, treatment of RS-PDX mice resulted in a significant reduction of tumor volume and in a prolonged survival of mice, while no effects were obtained in RS cells with a reduced PI3K γ expression underlining the high selectivity of this compound [85]. These encouraging results opened for further investigation on PI3K inhibition in RS patients and provided a rationale for a clinical trial (NCT03892044) investigating the clinical activity of duvelisib together with the anti-PD1 nivolumab. Moreover, given the selective activity in PI3K expressing cells, these data prompt in favor of a molecular profiling of RS patients prior to treatment decision to identify in advance those who will benefit the most from a specific targeted drug administration.

Another interesting molecular target is represented by the anti-apoptotic protein Bcl-2, whose targeting by Venetoclax, an orally bioavailable BH3 mimetic, in CLL patients have shown high percentage of durable responses, even in patients carrying the chromosome 17p deletion [18, 89]. When tested in RS-PDX models, venetoclax showed efficacy in Bcl-2-expressing cells, inducing apoptosis and prolonging mice survival [85]. However, clinical trials testing its efficacy in RS patients as monotherapy resulted only in partial responses [90, 91].

Lastly, one of the small molecule inhibitors that has increasingly gained attention in cancer treatment in the last years is selinexor, a selective inhibitor of nuclear export protein XPO1 [92]. Indeed, protein transport across nuclear membrane is often dysregulated in cancers [93] and *XPO1* has been shown to be overexpressed and/or mutated in several hematological malignancies, including CLL and RS, thus representing an interesting target [94, 95]. In a phase I pilot study, including 6 refractory/relapsed RS patients, selinexor used in monotherapy was generally well tolerated and induced partial response in 2 out of 5 patients [96]. However, no additional studies are available thus its efficacy in RS remains to be determined and better explored (Fig. 1C).

Combination strategies

CLL therapy and clinical responses have radically changed since the introduction of small molecules replacing traditional chemo-immunotherapy approaches [75]. However, as discussed above, many of these novel compounds are associated with poor or partial responses in RS, likely due to a more aggressive behavior of these cells even because of a more complex karyotype or genetic background. Therefore, combination of drugs targeting different molecules or molecular pathways can be envisaged as an effective strategy to overcome resistance.

Ibrutinib has been already tested in combination with several other agents. In 2015, Lamar and colleagues reported of a RS patient, heavily treated with chemo-immunotherapy before and after transformation, who experienced a significant, but unfortunately temporary, reduction of tumor burden in almost all infiltrated lymph nodes within 1 month of ibrutinib and rituximab treatment [97]. Similar results have been obtained in 3 patients treated with ibrutinib and ofatumumab, another anti-CD20 monoclonal antibody

(NCT01217749). Two of them had a stable disease for a median time of 10 months, while the other had a partial response, before undergoing disease progression 5 months later [98]. Finally, BTK inhibition has been tested in combination with the anti-PD-1 agent nivolumab, in a trial that included patients with different relapsed/refractory B-cell hematological malignancies along with 20 RS cases. The best clinical responses were obtained in the RS cohort, with an ORR of 65% and two patients experiencing complete remission. Due to adverse events in a significant proportion of patients, treatment was discontinued, but the promising results support for further clinical assessment [99].

Similar combination trials have been proposed for acalabrutinib and other BTK inhibitors. In 2019, Appleby and colleagues has started the STELLAR trial protocol (NCT03899337), a prospective phase II randomized study of R-CHOP alone or in combination with acalabrutinib in a large cohort of RS patients. Results from this trial will highlight the safety, feasibility, and clinical activity of the addition of acalabrutinib to standard R-CHOP for RS [100]. Recently, the novel BTK inhibitor DTRM-12 has been tested in combination with the mTOR inhibitor everolimus and pomalidomide in RS, exploring the potential synthetic lethality of this therapeutic setting (NCT04305444). This combination had an acceptable safety profile and resulted in an ORR of 45%, and it is now investigated in a phase II expansion study [101].

In the last couple of years, preliminary results on combination strategies including the Bcl-2 inhibitor venetoclax are coming to the stage for RS treatment. In a phase II trial (NCT03054896), Davids and colleagues evaluated the therapeutic response of venetoclax in combination with chemotherapy regimen based on R-EPOCH. On a cohort of 26 patients, 13 achieved CR and 3 a partial response, with an ORR of 62% and a median OS of 19.6 months, with neutropenia and thrombocytopenia as major toxic effects [102•].

Encouraging data are also coming from preclinical model of RS. We have recently showed that the dual targeting of Bcl-2 and PI3K, through the combination of venetoclax and duvelisib, synergistically induced apoptosis in target expressing cells both *ex vivo* and *in vivo* in RS-PDX models, blocking tumor growth and significantly prolonging mice survival, even compared to each drug alone. The molecular mechanism beneath this effect relies on the concomitant inactivation of Mcl-1, c-Myc, and Bcl-2, via GSK3 β activation [85]. Similar results were obtained combining venetoclax with other BH3 mimetics or with bromodomain extra-terminal (BET) protein targeting chimera (PROTAC), bi-functional molecules capable of hijacking the ubiquitin-proteasome system to induce degradation of BET proteins [103], suggesting that the simultaneous targeting of key molecular players within RS cells may represents a winning strategy [104].

Understanding the genetics and biology of RS are necessary steps in deciphering the critical pathways these cells rely on and identifying target(s). Despite advancements in the treatment options, based on different targeting approaches, RS remains a disease asking for effective therapies. Novel insights for therapeutic opportunities are expected to come in the next years when results from several clinical trials as well as from experimental models will be available and will finally reach patients' bedside.

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Declarations

Conflict of Interest

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Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

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