Chapter 4
Chronic Lymphocytic Leukemia with Alterations in *TP53*

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Introduction

Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia in the Western world. In the United States, there are approximately 20,000 new cases diagnosed annually [1]. The disease generally occurs in older individuals with a median age of 70 years and is more commonly seen in men than women. CLL presents heterogeneously, with most patients being diagnosed incidentally after routine blood work demonstrates an elevated white blood cell count. However, other patients can present more dramatically with advanced disease, manifesting as bulky lymphadenopathy, hepatosplenomegaly, symptomatic bone marrow failure, or constitutional symptoms such as fevers, weight loss, or night sweats. The diagnosis of CLL can generally be made from peripheral blood flow cytometry demonstrating a characteristic immunophenotype (CD5+, CD19+, CD23+, with dim CD20) in more than 5000/L clonal B-cells. However, given that mantle cell lymphoma can rarely mimic CLL [2], cytogenetic testing excluding the presence of an (11;14) translocation is necessary for full confirmation. In patients with lymphadenopathy and pathology showing the same immunophenotype as above, but who have less than 5000/L circulating clonal B-cells, the diagnosis would be more accurately called small lymphocytic lymphoma (SLL), which is considered the same disease as CLL. Computed tomography (CT) scans are not routinely indicated in patients with early-stage CLL given that imaging does not improve survival and can detect

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incidental findings leading to costly and risky interventions [3]. In the absence of cytopenias, a bone marrow biopsy and aspirate at the time of diagnosis is not necessary.

Recurrent cytogenetic abnormalities are demonstrated in CLL; the most common aberrations are 13q deletions, trisomy 12, 11q deletions, and 17p deletions (listed from most favorable to least favorable prognostically) [4]. A normal karyotype carries a prognosis intermediate between an isolated 13q deletion(s) and trisomy 12. Demonstration of cytogenetic abnormalities is ideally performed with both fluorescence in situ hybridization (FISH) testing and karyotyping, given that the latter can detect complex karyotypic abnormalities not included in routine CLL FISH panels and which lead to an independent adverse effect on prognosis [5–7]. Stimulation of CLL cells in vitro leads to improved reliability of conventional karyotyping [8]. 17p deletions are only present in 5–10% of patients at initial diagnosis and thus constitute a rare, but clinically important, subset of CLL patients [4, 9].

Recent data also support the utility of molecular testing, with either Sanger-based sequencing or next-generation sequencing, to detect *TP53* mutations that would not be detected on cytogenetic analysis. Detected variants should be cross-referenced with locus-specific databases to ensure pathogenic variants are being reported [10]. *TP53* mutations, in absence of 17p deletions, occur in approximately 5% of treatment-naïve patients [11, 12]. Most commonly, patients have biallelic inactivation of *TP53*, usually with a 17p deletion on one allele and a *TP53* mutation on the other allele, though monoallelic inactivation carries a similarly poor prognostic impact [12, 13]. Even small *TP53*-mutated subclones present at the time of diagnosis have been linked with poorer survival [14, 15].

TP53 aberrations, as detected both by conventional cytogenetic and molecular testing, are significantly more common in the relapsed/refractory setting and may be present in up to half of patients [16]. This emphasizes the need to repeat both cytogenetic and molecular testing at the time of each new therapy in patients who did not have previously documented *TP53* aberrations. These changes arise due to clonal evolution leading to the acquisition of new abnormalities [17, 18] and/or outgrowth of small, previously undetectable clones [19].

IGHV mutation testing and B2-microglobulin are useful tests to send at time of diagnosis, as these can allow for calculation of the patient's CLL International Prognostic Index (CLL-IPI) score (Table 4.1). This is a prognostic model that stratifies patients into one of four risk groups (low, intermediate, high, and very high), developed based on 3472 treatment-naïve patients and validated by other groups [20–22]. Prognosis for patients in the lowest-risk group is excellent, with 93% of patients being alive at 5 years, compared to 23% for patients in the highest-risk group. The survival estimates from this model were generated from data in a pre-novel small-molecule inhibitor setting, so the model may overestimate the impact on survival for adverse features in setting of newer, effective therapies [23]. Note that presence of a *TP53* aberration places a patient at a minimum in the high-risk group given the weight assigned to presence of a 17p deletion or *TP53* mutation [20].

Prior to recent introduction of novel small-molecule inhibitors, which will be discussed at length in this chapter, treatment outcomes for *TP53*-aberrant CLL have

Table 4.1 CLL International Prognostic Index (CLL-IPI) score

Variable	**Adverse factor**	**Points**
Age	>65	1
Clinical stage	Rai I–IV or Binet B–C	1
B_2-microglobulin	>3.5 mg/L	2
IGHV mutation status	Unmutated (<2% difference with germline)	2
Deletion of 17p and/or *TP53* mutation	Present	4
Risk	**Score**	**5-year OS (%)**
Low	0–1	93.2
Intermediate	2–3	79.3
High	4–6	63.3
Very high	7–10	23.3

OS overall survival

been dismal. Standard cytotoxic chemotherapy and chemoimmunotherapy in patients with *TP53*-aberrant CLL are associated with low overall response rates (ORR), near absent attainment of complete remission (CR), short progression-free survival (PFS), and poor overall survival (OS) [24–26].

Non-cytotoxic Treatment Approaches

Agents Available Prior to Novel Small-Molecule Inhibitors

Alemtuzumab

Alemtuzumab, a humanized monoclonal antibody against CD52, was first noted to demonstrate activity in *TP53*-aberrant CLL as a monotherapy in a single patient [27] and in a series of patients [28], suggesting a mechanism of action independent of *TP53*. This was followed by a phase 3 study (CAM307) comparing alemtuzumab to chlorambucil in 297 relapsed/refractory CLL patients, where it showed an improved ORR among the 21 patients with 17p deletions [64% (7/11) vs. 20% (2/10)], although this was not statistically significant for this small subset ($p = 0.08$) [29]. Alemtuzumab has also been combined with rituximab in both the upfront and relapsed/refractory settings, though with a paucity of *TP53*-aberrant patients in these studies [30, 31]. One frontline patient had a partial response (PR) followed by Richter's transformation and death, while another achieved a minimal residual disease (MRD)-negative CR. The one relapsed patient with 17p deletion had a PR. Alemtuzumab has significant toxicities including, though not limited to, infusion-related events, neutropenia, and cytomegalovirus (CMV) reactivation [29–32].

High-Dose Steroids plus Rituximab

The combination of high-dose methylprednisone and rituximab achieved an impressive ORR (96%) when studied in the frontline setting [33]. However, only one patient in this study had a 17p deletion, achieving a PR. The single 17p-deleted patient in a study of relapsed/refractory CLL did not respond [34], though another relapsed/refractory study enrolled one 17p patient, who achieved a nodular PR [35]. Overall, with the paucity of 17p patients treated with this regimen, it is unlikely to play an extensive role in the therapeutic armamentarium in light of multiple effective novel small-molecule inhibitors.

Lenalidomide

Lenalidomide is an immunomodulatory agent that has been studied extensively in CLL. In the frontline setting, single-agent lenalidomide was associated with an increased risk of death when compared to chlorambucil, leading to discontinuation of the phase 3 study (the ORIGIN trial) [36]. In the relapsed/refractory setting, it has been studied in combination with rituximab, demonstrating an ORR of 66%, with a 53% ORR (8/15) in patients with 17p deletions [37]. In a pooled series of 208 patients on lenalidomide-based trials (both frontline and relapsed/refractory), Strati et al. demonstrated that among patients who discontinued lenalidomide due to toxicity (43 out of 208 patients), prolonged responses can be seen with median time to next treatment of 40 months (despite median time of lenalidomide exposure of 11 months), suggesting that this agent may lead to sustained responses [37]. However, only 3 of the 43 patients reviewed had 17p deletions [37]. Lenalidomide can be associated with tumor lysis syndrome (TLS) and tumor flare reactions, in addition to hematologic toxicity, which is most significant at higher doses [38]. Further, a recent study demonstrated a worse ORR to lenalidomide-based regimens in patients with *TP53* aberrations [39].

Novel Small-Molecule Inhibitors

Following several pivotal clinical trials, the CLL field has potent novel small-molecule inhibitors available for both frontline treatment and the treatment of relapsed/refractory disease, with multiple Food and Drug Administration (FDA) approvals in the last few years. Specifically, ibrutinib, a first-in-class oral covalent inhibitor of Bruton's tyrosine kinase (BTK), was approved for patients with relapsed/refractory disease in February 2014 and in patients with 17p deletions in the frontline setting in July 2014. The approval was extended to all patients with CLL, regardless of age or line of treatment, in March 2016. Idelalisib, an oral, selective small-molecule inhibitor of the

delta isoform of phosphatidylinositol 3-kinase (PI3Kδ), was FDA approved for treatment of relapsed/refractory CLL in combination with rituximab in July 2014. Lastly, venetoclax, an oral small-molecule inhibitor of B-cell lymphoma 2 (BCL2), was FDA approved for the treatment of relapsed/refractory CLL in patients with 17p deletions in April 2016. In June 2018, the FDA granted regular approval to venetoclax for patients with or without 17p, who have received at least one prior therapy. The details of the studies leading to these FDA approvals, in addition to ongoing studies, will be the subject of the remainder of this chapter.

Frontline Approaches

Ibrutinib

The BTK inhibitor ibrutinib is the only novel small-molecule inhibitor that has been FDA approved for the frontline treatment of CLL. The initial FDA approval for frontline use only included patients with 17p deletions, though this has subsequently been extended to all patients. Ibrutinib was first examined in the frontline setting in a phase 1b/2 study enrolling untreated elderly patients (>65 years of age) [40]. Of the 29 treatment-naïve patients, 2 had 17p deletions, both of whom had a response to ibrutinib [40]. A phase 2 study using ibrutinib was conducted in patients with *TP53* aberrations, the majority having 17p deletions ($n = 47$) and 4 having *TP53* mutations in the absence of 17p deletions [41]. Ninety-seven percent (32 of 33 evaluable patients) of the treatment-naïve patients attained a response; most responses were PRs or PRs with lymphocytosis [41]. PR with lymphocytosis is a common response in patients with CLL receiving kinase inhibitors and is not a sign of treatment failure [42, 43].

The RESONATE-2 trial, which led to the FDA approval in CLL for all patients, was a phase 3 study comparing ibrutinib to chlorambucil in treatment-naïve patients age 65 and older [44]. Notably, the trial did not enroll patients with 17p deletions, given the known inefficacy of chlorambucil in this population. This trial demonstrated an improved progression-free survival (PFS), ORR, and overall survival (OS) for ibrutinib as compared to chlorambucil.

Ibrutinib toxicity includes diarrhea (seen in 42% of ibrutinib patients in RESONATE-2), atrial fibrillation (seen in 10–16% of patients) [45, 46], bleeding (most often grade 2 or less though can be severe) [47], rash [48], hypertension [49], and rarely ventricular arrhythmias [50].

Ibrutinib has also been combined with chemoimmunotherapy, and there is an ongoing clinical trial combining ibrutinib with fludarabine, cyclophosphamide, and rituximab (FCR) chemotherapy in the frontline setting (NCT02251548). Notably, this trial excludes patients with 17p deletions, likely due to the fact that such patients are often refractory to FCR.

Idelalisib

Idelalisib, a PI3Kδ-inhibitor, has been studied in the frontline setting as well. A phase 2 study of idelalisib plus rituximab in patients 65 and older showed promising efficacy, especially in patients with *TP53* aberrations (100% ORR) [51]. However, further development of this drug in the frontline setting led to concerns regarding increased risks for multiple adverse events, including immune-mediated hepatotoxicity, pneumonitis, and colitis [52]. As a result, this drug is not currently recommended in the frontline setting, and its development in the frontline setting is not currently being pursued.

Venetoclax

The BCL2 inhibitor venetoclax is actively being studied in the frontline setting, though no completed studies have been published at time of this chapter. One study, CLL14, has published the findings from a lead-in phase administering venetoclax and obinutuzumab to 13 previously untreated CLL patients (2 with *TP53* aberrations) with significant comorbid conditions [53]. ORR at 3 months was 100% and 92% rate of peripheral blood MRD negativity at 3 months post completion of treatment. The regimen was tolerated well except with one patient with a grade 4 infusion-related reaction that discontinued study treatment [53].

Relapsed/Refractory Approaches

Ibrutinib

In patients who have not already received frontline ibrutinib, this agent is highly effective in the relapsed/refractory setting. Ibrutinib demonstrated a 71% ORR in a phase 1b/2 trial, with responses occurring in 68% (19/28) of patients with 17p deletions [54]. The PFS and OS at 26 months were 57% and 70%, respectively. Based on these findings, a phase 2 study of ibrutinib was conducted, enrolling 144 relapsed patients, all with 17p deletions (RESONATE-17) [55]. This study showed a 64% ORR at median follow-up of 11.5 months and 83% at 27.6 months. A phase 3, open-label, randomized study (RESONATE) was conducted to compare ibrutinib to ofatumumab in patients with previously treated CLL, where ibrutinib demonstrated improved PFS, OS, and ORR compared to ofatumumab [54].

With 5 years of follow-up for trials enrolling both treatment-naïve elderly patients and patients with *TP53* aberrations, the depth of response has increased over time, and the majority of patients remain progression-free. Specifically, Ahn et al. reported a 58.2% 5-year PFS for patients with *TP53* aberrations; 16 of 50

patients were relapsed/refractory and had a more rapid progression than the treatment-naïve *TP53* patients [56]. Similarly, O'Brien et al. reported a 92% 5-year PFS among treatment-naïve patients and 44% in relapsed/refractory patients, with a median PFS of 26 months in patients with 17p deletions (*TP53* mutation status not reported) [49].

Idelalisib

Idelalisib was examined as a monotherapy in a phase 1 trial of 54 heavily pretreated CLL patients, 24% of whom had *TP53* aberrations, and produced a 72% ORR, with most responses being PRs and PRs with lymphocytosis [57]. Subsequently, a phase 3 randomized study was performed in relapsed CLL patients with significant coexisting medical comorbidities, comparing rituximab with idelalisib to rituximab with placebo [58]. The idelalisib arm outperformed the placebo arm with respect to PFS (not reached vs. 5.5 months, $p < 0.001$), ORR (81% vs. 13%, $p < 0.001$), and OS at 12 months (92% vs. 80%, $p = 0.02$) [58]. The PFS benefit of idelalisib was seen in the 96 patients with 17p deletions and/or *TP53* mutations [HR for disease progression or death = 0.12 (CI of 0.05–0.32)] [58]. A phase 3 randomized study was conducted to compare idelalisib with bendamustine and rituximab (BR) to BR alone in relapsed CLL patients who were candidates for intensive chemotherapy [59]. The idelalisib arm demonstrated superior PFS (20.8 months vs. 11.1 months), (hazard ratio [HR] 0.33, 95% CI 0.25–0.44; $p < 0.0001$) though with an increased number of infections, serious adverse reactions, and deaths in the idelalisib arm [59]. The improved response rate was seen in the 137 patients with *TP53* aberrations, with median PFS for idelalisib arm of 11.3 months vs. 8.3 months for the BR arm (HR, 0.47; 95% CI, 0.31, 0.72; $p < 0.0001$) [59]. Idelalisib has also been studied in combination with ofatumumab, demonstrating improved median PFS when compared to ofatumumab alone (16.3 months vs. 8.0 months, adjusted HR 0.27, 95% CI 0.19–0.39, $p < 0.0001$) [60]. Recent recommendations suggest patients getting treated with idelalisib-containing regimens should receive prophylaxis against *Pneumocystis jirovecii* pneumonia and be monitored for CMV reactivation.

Venetoclax

The phase 1 study evaluating venetoclax monotherapy in relapsed CLL patients led to an encouraging 79% ORR, with a 71% ORR and 16% CR rate in patients with 17p deletions [61]. However, TLS was a significant toxicity in this study, occurring in 10 of 56 patients (18%). TLS led to serious clinical sequelae in two patients: one required emergent hemodialysis for renal failure (after a single 50 mg dose) and another experienced sudden death (on 2nd day of stepping up to 1200 mg dose) [61].

An open-label phase 2 study of venetoclax was conducted in relapsed CLL patients with 17p deletions, which demonstrated a 79% ORR and an 8% CR/CRi rate [62]. Venetoclax has also been studied in combination with rituximab, with an 86% ORR and 51% CR rate [63]. Further, 20 of 25 of the patients attaining a CR achieved MRD negativity on bone marrow biopsies [63]. There was one death from TLS in this study after a patient was administered starting dose of 50 mg. Subsequently, patients began receiving 20 mg as a starting dose [63]. As a result of these studies, a ramp-up protocol has been designed with administration recommendations based upon the patient's TLS risk, as measured by baseline computed tomography (CT) and circulating absolute lymphocyte count (Table 4.2). Venetoclax appears to be effective in patients who have progressed on both ibrutinib and idelalisib [64, 65].

A phase 3 trial compared the efficacy of venetoclax plus rituximab (VR) to BR (MURANO trial). The VR regimen comprises the traditional 5-week venetoclax ramp-up period followed by six cycles of rituximab and then 2 years of venetoclax

Table 4.2 Tumor lysis syndrome (TLS) risk stratification and monitoring recommendations for patients initiating venetoclax [105]

Tumor burden assessment		
Low risk	All nodes <5 cm and ALC $<25\times10^9$/L	
Medium risk*	Any node 5–10 cm or ALC $\geq25\times10^9$/L	
High risk	Any node >10 cm or	
	Any node >5 cm and ALC $\geq25\times10^9$/L	
Prophylaxis/monitoring recommendations		
Low risk	Oral hydration (1.5–2 L/day) and allopurinol	Pre-dose: TLS labs prior to every dose
		Post-dose: TLS labs 6–8 and 24 h post the 20 and 50 mg doses
Medium risk	Oral hydration (1.5–2 L/day) and allopurinol	Pre-dose: TLS labs prior to every dose
	*If a patient has a creatinine clearance of <80 mL/min, consider following "high-risk" recommendations for prophylaxis and hospital monitoring for the 20 and 50 mg doses	Post-dose: TLS labs 6–8 and 24 h post the 20 and 50 mg doses
High risk	Oral hydration (1.5–2 L/day) and IV hydration with 150–200 mL/h, as tolerated	Pre-dose: TLS labs prior to every dose
	Allopurinol and consider rasburicase if the baseline uric acid level is elevated	Post-dose instructions depend on dose level: Inpatient monitoring for the 20 and 50 mg doses Post-dose: TLS labs at 4, 8, 12, and 24 h Outpatient monitoring for subsequent dose levels Post-dose: TLS labs at 6–8 and 24 h

*A subset of patients with medium TLS risk should be treated as "high risk" if their creatinine clearance is <80

TLS labs include potassium, uric acid, phosphorus, calcium, and creatinine. Any baseline abnormalities should be corrected prior to proceeding with treatment

ALC absolute lymphocyte count, *IV* intravenous, *TLS* tumor lysis syndrome

monotherapy. Findings demonstrated that VR was superior to BR with respect to 2-year PFS (HR for progression or death, 0.17; 95% CI, 0.11–0.25; $p < 0.001$), with a high rate of MRD negativity among VR-treated patients compared to BR (62.4% vs. 13.3%, respectively, for patients achieving MRD negativity in peripheral blood at the 9-month time point) [66]. Notably, VR was superior for patients with 17p deletions and/or *TP53* mutations with median PFS not reached for both groups, compared to 15.4 months and 12.9 months for the 17p-deleted patients and *TP53*-mutated patients receiving BR, respectively [66, 67]. Based upon the MURANO study, in June 2018, the FDA granted regular approval for venetoclax for patients with and without 17p deletions, who have received at least one prior therapy. In Europe, venetoclax's approval is wider, indicated as a frontline therapy for patients with *TP53* aberrations who are unsuitable for a B-cell receptor pathway inhibitor and to patients in the relapsed setting regardless of *TP53* status.

How to Best Sequence Novel Small-Molecule Inhibitors in the Relapsed Setting

With the availability of multiple effective novel agents, a natural question that has arisen is how to best sequence these therapies [68]. Ibrutinib is the only novel small-molecule inhibitor indicated in the frontline setting at this time, but what is the best approach for patients who progress on, or are intolerant to, ibrutinib? Both retrospective and prospective data have indicated an excellent response to venetoclax following ibrutinib therapy [64, 69]. The response rate for idelalisib following ibrutinib seems lower, though numbers are too small to draw firm conclusions (venetoclax ORR of 79% versus idelalisib ORR of 46%, PFS HR 0.6 with $p = 0.06$) [69]. In absence of an appropriate clinical trial, my approach for *TP53*-aberrant CLL includes treatment with ibrutinib in the frontline setting. In the setting of progression on ibrutinib, I generally select a venetoclax-based regimen, preferably VR given the high response rate, general tolerability, and limited treatment course with this approach. Venetoclax monotherapy has a high response rate, but the current treatment paradigm includes indefinite therapy rather than a limited treatment course. Further details regarding treatment approaches are outlined in Figs. 4.1 and 4.2.

Selected Early-Phase Agents in Development

Though ibrutinib, venetoclax, and idelalisib have revolutionized the CLL field, patients can still progress and/or develop intolerance to these agents, necessitating consideration of alternative therapies. Though ibrutinib has shown a relatively low discontinuation rate within its clinical trials [70], real-world studies have demonstrated a higher rate of discontinuation (42%), most often due to toxicity/intolerance [71]. Another study showed a 51% rate of discontinuation

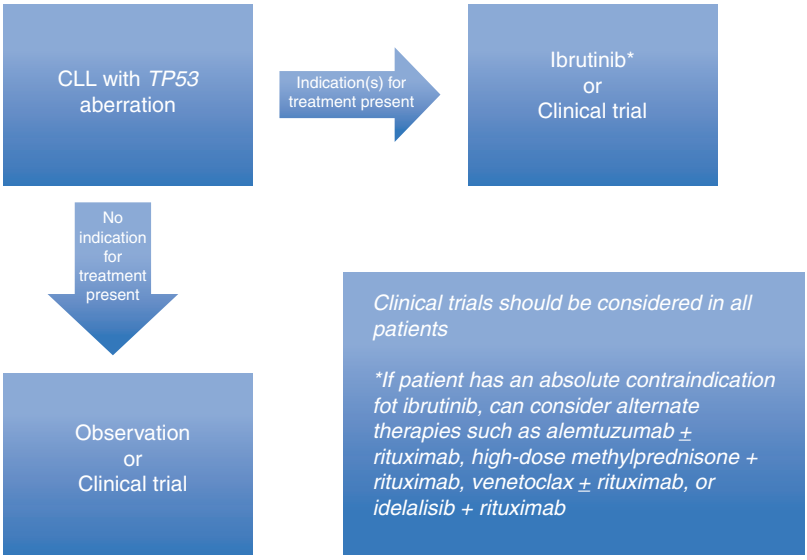

Fig. 4.1 Recommended treatment approach for untreated CLL patients with *TP53* aberrations

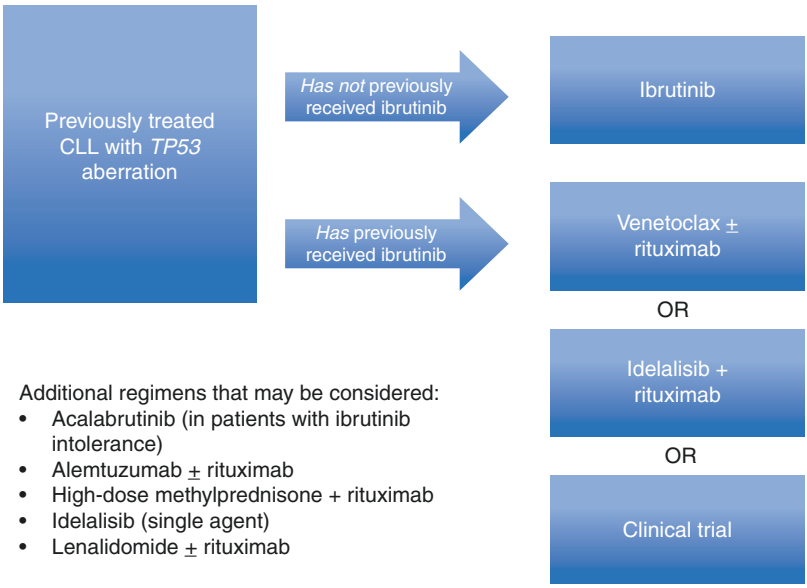

Fig. 4.2 Recommended treatment approach for previously treated CLL patients with *TP53* aberrations

due to toxicity upon reviewing patients treated with ibrutinib or idelalisib [72]. Outcomes following ibrutinib discontinuation are generally poor, with the poorest outcomes among patients who discontinue due to Richter's transformation as opposed to disease progression or intolerance [73, 74]. Ibrutinib resistance has been linked to acquired mutations in *BTK* and *PLCG2*, as demonstrated by multiple studies [75–77]. Mechanisms of idelalisib resistance have not yet been described in the literature. The mechanism behind venetoclax resistance is more variable based on limited studies to date. In a cohort of eight patients, acquired mutations in *BTG1* and *CDKN2A/B* were identified in two and three patients, respectively [78].

Newer BTK Inhibitors

Acalabrutinib

Acalabrutinib is a more selective, irreversible second-generation inhibitor of BTK that was designed to improve on the safety and efficacy of ibrutinib, given that it does not irreversibly target alternative kinases such as ITK, EGFR, and TEC. It was studied in a phase 1–2 trial in patients with relapsed CLL and led to a 95% ORR, with 85% PR and 10% PR with lymphocytosis, with a 100% ORR in patients with 17p deletions [79]. The safety profile of this agent is encouraging with no episodes of grade ≥3 bleeding and 3% of patients with atrial fibrillation in an updated analysis [80]. The agent is currently only FDA approved for mantle-cell lymphoma. A randomized, open-label non-inferiority phase 3 study comparing acalabrutinib to ibrutinib (NCT02477696) in previously treated CLL patients is currently active, but no results have been reported. An additional phase 3 study comparing acalabrutinib to investigator's choice of idelalisib with rituximab or bendamustine with rituximab, in previously treated CLL patients, is currently recruiting (NCT02970318).

ONO/GS-4059/Tirabrutinib

ONO/GS-4059/tirabrutinib is a selective BTK inhibitor, which has been tested in patients with relapsed/refractory B-cell lymphoid malignancies in a phase 1 study; 8 of 25 CLL patients had 17p deletion, and another 4 had a *TP53* mutation in absence of 17p deletion. There was a 96% ORR in the evaluable CLL patients [81]. There was one treatment-related grade 3 bleeding event among the CLL patients. Tirabrutinib is being further developed in combination with other agents including idelalisib, obinutuzumab, and entospletinib (NCT02968563, NCT02457598, and NCT02983617).

Newer PI3K Inhibitors

Duvelisib is a novel oral dual PI3K-δ and γ inhibitor that has been studied in multiple hematologic cancers, including CLL. In the phase 1 study of this compound, a 56% ORR was noted among the 55 relapsed/refractory CLL patients, including one CR [82]. Its toxicity profile appears similar to idelalisib. The drug continues to be developed, and we are currently awaiting results from a phase 3 trial comparing it to ofatumumab in relapsed/refractory CLL (NCT02004522, patients must be naïve to PI3K and BTK inhibitors).

SYK Inhibitors

Entospletinib (GS-9973) is an oral selective inhibitor of spleen tyrosine kinase (SYK), which is constitutively activated and essential for cell proliferation and survival in multiple B-cell malignancies. This agent was studied in a phase 2 trial including 41 relapsed/refractory CLL patients (ten of whom had 17p deletions or *TP53* mutations) and demonstrated a 24-week PFS of 70% (median PFS of 13.8 months) and an ORR of 61% (predominantly PRs, no CRs), with response not being statistically significantly lower among patients with 17p deletions and *TP53* mutations [83]. This study has completed enrollment though final results have not yet been reported (NCT01799889). Entospletinib has also been combined with idelalisib, though this combination was limited by a high incidence of pneumonitis (18% patients), most of which were severe [84].

CAR-T Cells

Chimeric antigen receptor-modified T-cells (CAR-T) have been an active area of clinical research for many cancer types, including CLL [85–87]. A phase 1/2 open-label clinical trial of anti-CD19 CAR-T cells in refractory CLL was performed by Turtle et al., demonstrating an ORR of 74% including 21% CR rate in a highly pretreated cohort, which included 14 patients with 17p deletions [88]. Similar findings including an ORR of 57% were obtained in a smaller study of 14 patients [89]. Toxicity of CAR-T cells can be severe, including cytokine-release syndrome and neurotoxicity [90–92].

Allogeneic Hematopoietic Stem Cell Transplantation

In this era of effective novel small-molecule inhibitors, allogeneic hematopoietic stem cell transplantation (alloHSCT) has been utilized less frequently [93, 94], including in patients with *TP53* aberrations [95]. AlloHSCT can be an effective

and reasonably safe approach for younger patients with high-risk disease, including patients with *TP53* aberrations. Ten-year follow-up from CLL3X, a trial from the German CLL group [96], evaluating reduced-intensity conditioning alloHSCT in patients with HR-CLL has recently been reported [97]. This demonstrated sustained disease control in a subset of patients, with 34% disease-free survival rate at 10 years, though with a significant rate of non-relapse mortality (20%) [97]. Patients with *TP53* aberrations did not fare worse than patients without *TP53* abnormalities [97].

Richter's transformation, the transformation of CLL most often to a diffuse large B-cell lymphoma, carries a poor prognosis though patients can achieve long-term survival following alloHSCT [98]. Richter's syndrome may be more common in patients with poor-risk genetic features including 17p deletion, mutations in *TP53* and *NOTCH1*, and complex karyotype [99, 100].

Ongoing Clinical Trials Utilizing Novel Small-Molecule Inhibitors

Treatment of Asymptomatic CLL

Prior work has suggested that early treatment for patients with asymptomatic CLL does not improve survival, which is why the standard approach is close observation until an indication for treatment develops [101]. However, in the setting of less toxic, novel small-molecule inhibitors, this paradigm is being revisited (NCT0251855 and NCT01351896 are active but not recruiting, with additional studies currently in various stages of development) [102].

Current Clinical Trials Including Patients with TP53-Aberrant CLL

There are many clinical trials combining novel small-molecule inhibitors in both the frontline and relapsed/refractory setting, though the most commonly utilized combinations generally include ibrutinib, venetoclax, and/or obinutuzumab (Table 4.3). Preclinical work is suggestive of synergy between ibrutinib and venetoclax, with BTK inhibition leading to increased mitochondrial BCL-2 dependency [103, 104]. In absence of an available clinical trial, suggestions for treatment approaches for the frontline and relapsed/refractory setting are outlined in Figs. 4.1 and 4.2, respectively.

Table 4.3 Trials utilizing novel small-molecule inhibitor combinations in the (a) frontline and (b) relapsed/refractory settings

Trial	Agents	Schedule	Population	Status[a]
(a)				
Captivate NCT02910583	Ibrutinib Venetoclax	Ibrutinib monotherapy for first 3 cycles followed by combination treatment for at least 12 cycles If MRD negative: treatment is followed by either ongoing ibrutinib or ibrutinib placebo capsules If MRD positive: treatment is followed by continuous combination therapy with ibrutinib and venetoclax or ibrutinib only	Ages 18–70	Active, not recruiting
NCT02756897	Ibrutinib Venetoclax	Ibrutinib monotherapy for three cycles. At start of cycle 4, venetoclax is added as a weekly escalation. The combination continues for an additional 24 cycles	Ages 18 and older High-risk CLL (17p or 11q deletion, mutated *TP53*, unmutated IGHV, or age ≥65)	Recruiting
NCT03128879	Ibrutinib Venetoclax	Patients who have already been on ibrutinib for at least 12 months can enroll on study, where venetoclax is added as a weekly escalation while continuing ibrutinib	Ages 18 and older High-risk CLL (17p and 11q deletions, TP53 mutation, or complex karyotype) have a known ibrutinib resistance mutation without progression on ibrutinib or have not achieved B2-microglobulin normalization after a year on ibrutinib. Patients must have received at least 12 months of ibrutinib and have measurable disease	Recruiting
CLL2-GiVe NCT02758665	Ibrutinib Venetoclax Obinutuzumab	Obinutuzumab is administered for cycles 1–6. Ibrutinib is given for cycles 1–15. Venetoclax is given in cycles 1–12, introduced in escalating doses. The full dose of venetoclax (400 mg) is administered for cycles 3–12	Ages 18 and older, there are arms for both physically fit and unfit patients Patients must have 17p deletion and/or *TP53* mutation	Recruiting
(b)				
NCT02756897	Ibrutinib Venetoclax	Ibrutinib monotherapy for three cycles. At start of cycle 4, venetoclax introduced by a weekly escalation. The combination continues for an additional 24 cycles	Ages 18 and older Relapsed and/or refractory to at least one prior therapy No prior ibrutinib or venetoclax	Recruiting

Bloodwise TAP Clarity study ISCRTN13751862	Ibrutinib Venetoclax	8 weeks of ibrutinib monotherapy followed by venetoclax introduced by a weekly escalation. Patients continue on the combination for the same duration of time that it takes them to achieve MRD negativity	Relapsed within 3 years of FCR or BR or had 17p deletion and failed at least one line of therapy	Active, not recruiting[b]
NCT02427451	Ibrutinib Venetoclax Obinutuzumab	Patients receive obinutuzumab on day 1 for up to eight cycles. Cycle 2, ibrutinib is added. Cycle 3, venetoclax is initiated. Treatment continues up to 14 cycles in absence of disease progression or toxicity	Ages 18 and older Received at least one prior therapy Cannot have known BTK mutation or CLL refractory to or progressed during ibrutinib	Active, not recruiting
NCT03422393	Ibrutinib Venetoclax	Patients receive either 420, 560, or 840 mg of ibrutinib in addition to introduction of increasing doses of venetoclax	Ages 18 and older Patients must have been on ibrutinib monotherapy and experienced disease progression. Primary ibrutinib resistance is excluded	Not yet recruiting
NCT03045328	Ibrutinib Venetoclax	Patients receive ibrutinib on week 1, day 1. Venetoclax begins on week 9, day 1, and continues until week 61, day 7	Ages 18 and older No prior treatment with ibrutinib or venetoclax	Recruiting
NCT03226301	Ibrutinib Venetoclax	Patients receive ibrutinib for two cycles followed by venetoclax, which is initiated as a weekly ramp-up beginning in cycle 3 and continued through cycle 15. MRD-positive patients continue on ibrutinib monotherapy until progression/ relapsed. MRD-negative patients are randomized to either continuous ibrutinib monotherapy or observation. For patients who relapse on observation period, treatment is reinitiated with ibrutinib and venetoclax for 12 cycles	Ages 18 and older Refractory to or in relapse after initial therapy No prior treatment with ibrutinib or venetoclax	Recruiting

Studies excluding patients with 17p deletions and/or TP53 mutations are not listed
MRD minimal residual disease, *BTK* Bruton's tyrosine kinase
[a]Clinical trial status was obtained from https://www.clinicaltrials.gov on March 21, 2018
[b]This study is not listed on clinicaltrials.gov though the abstract presented at the 2017 American Society of Hematology meeting indicated that all planned 50 CLL patients had been enrolled

Conclusions

The introduction of novel small-molecule inhibitors, including ibrutinib, idelalisib, and venetoclax, has changed the treatment landscape for CLL patients with *TP53* aberrations. This subset of CLL patients previously had few, if any, effective options but now has the choice of several effective agents. The prognosis of patients with *TP53* aberrations is likely improved as compared to what is predicted using the CLL-IPI model; their specific prognosis may be more clearly elucidated by incorporation of patients treated with such agents into newer prognostic models. At this time, novel agents are continued indefinitely, provided that the patient's disease is responding and the agent is being tolerated without significant toxicity. Ongoing research will help determine the role of combination therapy with novel agents, most promisingly ibrutinib and venetoclax, with many ongoing trials utilizing attainment of MRD negativity as a benchmark by which treatment discontinuation can be evaluated.

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