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IBRUTINIB IN THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): FIVE YEARS ON.

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ABSTRACT

A major revolution in the treatment of chronic lymphocytic leukemia (CLL) began with the approval of ibrutinib, a first-in-class oral inhibitor of Bruton tyrosine kinase (BTK), for the treatment of relapsed/refractory (R/R) and/or TP53 mutated patients with CLL. However, 5 years later, some issues relating to this disorder still remain including the fact that with ibrutinib only a relatively small proportion of patients achieve complete remission and that ibrutinib-resistant CLL clones can develop in about 20% of patients. In addition, therapy must still be given continuously, and toxicities leading to drug discontinuation occur in about 30% of patients. In the meantime second-generation BTK inhibitors have already aroused considerable interest and gathered momentum. A possible strategy to overcome some of these obstacles is to combine ibrutinib with other targeted agents especially in high-risk disease, such as previously treated refractory patients or those with TP53 aberrations or complex karyotypes, in whom rapid eradication of disease is most desirable. Therapy with single agent ibrutinib should be part of a sequential approach for patients with low risk disease, especially in older patients (aged >70 years) with a higher burden of comorbidities. Long-term results of ongoing studies combining ibrutinib with (chemo)- immunotherapy or other targeted agents are eagerly awaited. Future clinical trials are indeed still needed to provide answers to these open questions.

Background

The landscape of treatment of chronic lymphocytic leukemia (CLL) has changed dramatically with the introduction of several targeted therapeutic strategies (1-5). In this paradigm shift ibrutinib, the first-in-class oral inhibitor of Bruton tyrosine kinase (BTK), has played a pioneering role. The history of ibrutinib in CLL started with publication of the results of the pivotal PCYC-1102/1103 phase 2 study (1). Later results of RESONATE phase 3 clinical trial enabled the Food and Drug Administration (FDA), in February 2014, to approve ibrutinib for the treatment of patients with CLL who had received at least one prior therapy (1-2). A few months later, ibrutinib also received breakthrough therapy designation for its use in CLL patients with del 17p. Thereafter, in 2016, on the basis of results of the RESONATE-2 clinical trial ibrutinib was approved by FDA as first-line therapy for older patients with CLL or small lymphocytic lymphoma (SLL), regardless of their cytogenetic profile and risk status (6).

Three recent landmark trials have suggested in turn, that ibrutinib alone or in combination with an anti-CD20 monoclonal antibody would become the new standards of care for upfront therapy of CLL (7-12). However, while many issues still remain unsolved with ibrutinib, (including the fact that only a relatively small proportion of patients achieve complete remission [CR], emergence of resistant clones, the need for continuous therapy and drug toxicities), second-generation BTK inhibitors have already aroused considerable interest and have gathered momentum (13-15).

This review focuses on the effectiveness of ibrutinib in relapsed /refractory (R/R) patients as well as in the frontline setting and takes into account the fact that the therapeutic landscape of CLL is rapidly changing under the pressure of recent progress in the understanding of the biology of this disease.

Early trials of ibrutinib single agent in the setting of R/R CLL

When results of early studies of ibrutinib were published clinical benefits were impressive for patients with CLL/SLL, with an acceptable safety profile (1). The overall response rate (ORR) was 71% with an additional 20% achieving partial response (PR) with lymphocytosis (PR-L).

Responses were observed in patients with poor prognostic features including those with del17p.

Of note, estimated PFS was 75% and OS 83% at 26 months. There were 15% grade 3–4

neutropenia events but these did not lead to any treatment discontinuations (1). The follow-up

data at up to 7-years of this phase Ib/II trial ibrutinib trial continues to look promising (16-17).

Similarly to results reported after 5-year follow-up, the median PFS and OS were shortest (26 and

57 months), in R/R patients with del(17p) when compared with those obtained in lower-risk

cytogenetic groups (16-17). The most common grade ≥ 3 AEs, included hypertension (32% TN,

25% R/R), pneumonia (10% TN, 27% R/R), neutropenia (3% TN, 21% R/R), thrombocytopenia

(3% TN, 11% R/R), and AF (6% TN, 9% R/R)(17).

The phase 3 RESONATE trial compared ibrutinib to ofatumumab in R/R CLL or SLL patients who had received one or more previous therapies. Median PFS was not reached in the ibrutinib

group while it was 8.1 months in the ofatumumab group ($p < .0001$). Adverse events of grade 3 or

higher occurred more frequently in the ibrutinib group and included diarrhea (4%) and atrial

fibrillation (3%). An additional four patients in the ibrutinib group and one patient in the

ofatumumab group had grade 1 or 2 atrial fibrillation. Also bleeding-related adverse events of

any grade (most commonly, petechiae, and including ecchymoses) were more common in the

ibrutinib group than in the ofatumumab group (44% vs. 12%). Major hemorrhage (any

hemorrhagic event of grade 3 or higher or resulting in transfusion of red cells or in

hospitalization) was reported in two patients (1%) in the ibrutinib group (including one patient

with a subdural hematoma) and three patients (2%) in the ofatumumab group (2). An integrated

safety analysis of the RESONATE and RESONATE-2 trials based on ibrutinib treatment duration of up to 43 months suggests that the most common adverse events (AEs) encountered were diarrhea (52% any-grade; 5% grade 3) and fatigue (36% any-grade; 3% grade 3) while the most common grade 3/4 AEs were neutropenia (18%) and pneumonia (12%). Prevalence of AEs (diarrhea, fatigue, grade 3 infection, bleeding, and neutropenia) tended to decrease over time while the rate of hypertension eventually increased despite an early initial decrease seen after the first year. The most common AEs contributing to drug discontinuation were pneumonia (n=4), anemia (n=3), and atrial fibrillation (n=3)(18). Of note, PFS benefit with ibrutinib remained in the final analysis after 6-year of follow-up (20). Patients with ≥ 2 prior therapies and those with TP53 or SF3B1 mutations had shorter PFS (18-20).

Several reports have described the efficacy and toxicity of ibrutinib in patients in a real-world setting (21-23). In this respect Mato et al (23) found that the median PFS was 35 months which is shorter than that reported in the final 6-year follow-up analysis of the RESONATE study (median PFS 44.1 months)(20). An indirect comparison between 2908 patients with CLL from 30 countries enrolled in the named patient program (NPP) and patients enrolled in the RESONATE trial, suggests that PFS of R/R patients receiving ibrutinib in clinical practice is similar to that seen in the randomized controlled trial setting (i.e., 12-month PFS 77.3% in the NPP and 81.5% in the RESONATE trial) (24). NPP enrollment criteria were similar to those used in RESONATE™ which could explain the similarity in outcome.

Resistance to ibrutinib

Despite durable responses in the majority of cases, approximately 20% of CLL patients who receive ibrutinib, still develop disease progression on current follow-up (25-26). In the majority of patients progressing on ibrutinib, BTK or phospholipase C γ 2 (PLCG2) resistance mutations

predate clinical progression by up to 15 months (25). Resistance to ibrutinib generally correlates with progressive CLL or Richter transformation(RT). Early progression (i.e., < 12 months) is generally due to RT while beyond 12 months RT is less frequent and progression is more likely to be determined by BTK or PLCG2 mutations (25). These observations have important and relevant clinical implications. In absence of RT the logical approach is to shift to a BCL2 inhibitor (eg, venetoclax) because several patients can be rescued with this therapy (27). In contrast, treatment of RT remains largely ineffective and prognosis is dismal (28).

Data from 4 sequential trials of ibrutinib in CLL at Ohio State University suggest that in patients who relapsed on ibrutinib, 85% had acquired BTK or PLCG2 mutations at a median time of 9.3 months prior to relapse (29). Ahn et al (30) recently reported updated results of a phase 2 trial enrolling 85 CLL patients (52 treatment naïve and 33 R/R) treated with ibrutinib as single-agent . RT occurred in 6% and was limited to the first 15 months on ibrutinib while progression due to CLL occurred in 10 patients

(11.9%) at a median of 38 months on study. At the time of progression, BTK (Cys481) and/or PLCG2 mutations were found in 8 of 10 patients with progressive CLL, and in 1 patient with prolymphocytic transformation (30).

BTK- and PLCG2-mutations in a real-life setting, evaluated by next-generation sequencing (NGS), have been reported by the French Innovative Leukemia Organization (FILO), respectively in 57% and 13% patients who received ibrutinib (31). This finding was significantly associated with subsequent CLL progression at a median of 8.5 months after sample collection. In the light of the above observations it would be important to consider future clinical trials aimed at evaluating the clinical impact of an early switch to another treatment in patients carrying BTK mutations and trials of agents capable of overcoming ibrutinib resistance caused by acquired BTK or PLCG2 mutations are already in progress (35-37). A phase 1 dose escalation study provided compelling clinical proof-of- concept for ARQ-531, a novel class of reversible BTK inhibitors and similar trials have also been conducted with GDC-0853 and SNS-510, both reversible BTK inhibitors (32-34). Also agents that do not target BTK are of interest and include newer heat shock protein 90 (HSP90) inhibitors, histone deacetylase (HDAC) inhibitors, and XPO1 inhibitors (35-37). However, despite the availability of robust data supporting clinical implications of ibrutinib resistance, mutation testing still essentially remains a research issue, since many major academic centers still do not have facilities to carry out the test in-house as yet.

Adherence to ibrutinib: still an open issue

Sustained adherence to TKI has been shown to be an important factor in achieving efficacy of treatment in chronic myeloid leukemia (CML)(38). In CLL, however, it is still unclear whether intermittent interruption of ibrutinib therapy influences clinical outcomes (39-43). In the

RESONATE trial a mean ibrutinib dose intensity <95% was associated with inferior PFS, but had no effect on OS (39). A real life study by the UK CLL Forum reported that treatment

interruptions >14 days within the first year of ibrutinib therapy were associated with inferior OS (40). Among 84 CLL patients (52 treatment-naïve and 32 R/R) enrolled in a phase II study (NCT01500733), there was no evidence that clinically-justified ibrutinib dose reductions or interruptions impacted on long-term outcome (41). A retrospective analysis of patients with CLL receiving ibrutinib at the Roswell Park Comprehensive Cancer Center showed that there was no statistically significant difference in ORR, PFS, and OS between dose-reduced and standard-dose groups (42). In a real-world experience of reduced dose ibrutinib in CLL (n=197pts) Mato et al (43) demonstrated that ibrutinib dose reduction does not affect clinical outcomes. Given that ibrutinib irreversibly binds to its target, the rate of BTK saturation might have minimal effect on drug efficacy; this is of particular interest during the period of treatment when the amount of ibrutinib required to achieve the same target occupancy may be less (44). In a pilot study of ibrutinib dose reduction performed by Chen and co-workers (45) showed that lower doses of ibrutinib given after one full dose cycle are enough to maintain biological activity. However, until prospective studies demonstrating equivalent clinical outcomes for patients receiving lower or standard doses of ibrutinib are reported, sustained adherence is recommended.

Ibrutinib versus chemo-immunotherapy as first-line therapy

The study that led to approval of ibrutinib for previously untreated patients with CLL was the phase III RESONATE-2 trial, randomizing 269 patients aged 65 years or older to ibrutinib or chlorambucil (6). Patients with del17p were excluded, since chlorambucil was not considered an appropriate alternative in this subgroup. After long-term follow-up of a median of 5 years, PFS continued to favor ibrutinib over chlorambucil (HR, 0.15; 95% CI, 0.10-0.22). This was also evident in CLL

patients with unmutated IGHV (HR, 0.11; 95% CI, 0.06-0.19) and 11q deletion (HR, 0.03; 95% CI, 0.01-0.11). OS also favored ibrutinib (HR 0.45; 95% CI, 0.266-0.761), with crossover to ibrutinib after clinical progression on chlorambucil (in 57% of patients). No new safety indications have emerged during long-term ibrutinib treatment. The most commonly reported grade ≥ 3 AEs were neutropenia (13%), pneumonia (12%), hypertension (8%), anemia (7%), hyponatremia (6%), atrial fibrillation (5%), and cataract (5%). The above findings provide the longest follow-up observation period of a phase III study of BTK-inhibitors given as frontline therapy for CLL (46).

In the large ECOG-ACRIN Cancer Research Group study, the combination of ibrutinib and rituximab (IR) was shown to be superior to the current gold standard therapy of fludarabine, cyclophosphamide and rituximab (FCR) used for young, fit patients with untreated CLL in terms of PFS ($P < 0.0001$) and OS ($P = 0.0003$)(7). A subset analysis dealing with mutational IGHV status showed that patients with mutated IGHV had a trend towards improved outcome with IR ($P = 0.07$), while those with unmutated IGHV status experienced a significantly improved PFS with IR ($P < .00001$) (7). Treatment-related grade 3 and 4 adverse events occurred in 58% of patients receiving IR therapy and in 72% who received FCR ($P = 0.0042$). In particular, both neutropenia (23% vs 44%, $P < 0.0001$) and infectious complications (7.1% vs 17.7%, $P < 0.0001$) were significantly less common in patients receiving IR , than in those treated with FCR (7). According to the results of ALLIANCE study, ibrutinib monotherapy or IR were both superior to the combination of bendamustine-rituximab (BR) in elderly patients ≥ 65 years with CLL (8-9). The rate of grade 3,4 or 5 hematological AEs was statistically higher in the BR group (61%) than in the IR (39%) or ibrutinib alone arm (41%). In contrast, the rate of grade 3,4 or 5 non-hematological AEs was lower in the BR arm (63%) than with the ibrutinib-containing regimens (74% for IR or ibrutinib alone). An industry-sponsored study, the phase 3 iLLUMINATE trial, indicated that the combination of ibrutinib and obinutuzumab provided a 77%

reduction in the risk of progression or death compared to chlorambucil and obinutuzumab (10-11) (Table 1).

Although the results of the above studies are most informative, practical problems exist and some questions still remain unanswered . It is unclear whether the data of non-inferiority of ibrutinib versus combined IR in older patients is applicable to the entire population of CLL patients. In a single center study comparing ibrutinib monotherapy versus IR , mostly in patients with R/R CLL, estimates of PFS were 86% for those receiving ibrutinib and 86.9% for patients receiving IR (47). What we can perhaps forecast is that FCR will probably be used less in the future, despite the fact that it is still the more appropriate choice for patients with mutated IGVH disease. In contrast, in patients with unmutated IGHV, ibrutinib (+/- Rituximab) seems to be a reasonable choice (Fig 1). Elderly/unfit patients with mutated IGHV should be considered for upfront ibrutinib or chemo-immunotherapy and the choice between these approaches should be based on the potential toxicities that a given patient may develop to either CIT or ibrutinib. An indirect comparative analysis of ibrutinib-related toxicity in patients enrolled in the ECOG-ACRIN and ALLIANCE trials suggests that there is a difference in the rate of the commonest side effects of ibrutinib in younger and older CLL patients, respectively (Table 2), and this should be taken into consideration when decisions on therapy are taken.

Can we improve the depth of response using ibrutinib in combination with chemo-immunotherapy?

The combination of ibrutinib with chemo-immunotherapy regimens has been safely tested in early phase 1b trials (48). In the pivotal HELIOS study R/R CLL/SLL patients were randomized to receive ibrutinib or placebo, in combination with 6 cycles of BR, followed by ibrutinib or placebo

alone (49). After a median follow-up of 34.8 months median PFS was not reached for ibrutinib+BR, versus 14.3 months for placebo+BR. Of note, minimal residual disease (MRD)-negative response rates were 26.3% for ibrutinib+BR and 6.2% for placebo+BR ($P < 0.0001$)(50). Currently the interest in combinations of ibrutinib with chemotherapy has focused on previously untreated young fit patients. In this subgroup three different studies have reported that FCR can achieve long-term PFS in more than 50% of patients with mutated IGHV, suggesting that many of these patients could perhaps eventually be cured (51-53).

In the phase II MD Anderson Cancer Center (MDACC) trial 42 younger fit patients with mutated IGHV were treated with a combination of 3 cycles of FC, ibrutinib and obinutuzumab (GA101) .

When the chemotherapy was stopped these patients continued to receive ibrutinib and obinutuzumab for a variable number of cycles depending on their MRD status. Overall, 17 of 42 (40.4%) patients achieved CR/CRi with undetectable MRD (uMRD) at 3 months.

All 28 patients who reached the 12 month time-point had uMRD and stopped ibrutinib according to protocol design. These patients maintained uMRD status at a median follow-up of 10.1 months after stopping ibrutinib (54). Interestingly, an indirect comparison with FCR suggests that the association of ibrutinib,FC and obinutuzumab significantly improved the depth of response in patients with mutated IGHV (Table 3).

A similar multicenter phase 2 study of ibrutinib plus FCR (iFCR) as frontline treatment for 85 young, fit CLL patients was reported by Davids et al. (55). At median follow-up of 16.5 months a CR rate (with BM uMRD 2 months after the last cycle of ibrutinib plus FCR) was achieved in 33% of patients which is higher than the CR rate of historical FCR (20%; $P=0.0035$). The most common all-grade toxic effects were hematological, including thrombocytopenia in 63 (74%) patients, neutropenia in 53 (62%), and anemia in 41 (49%). Grade 3 or 4 non-hematological serious adverse events included grade 3 atrial fibrillation in three (4%) patients and grade 3

Pneumocystis jirovecii pneumonia in two (2%)(54).

In conclusion, this strategy designed to increase the cure rate should be retained for small number of CLL patients.

Can we improve the efficacy of ibrutinib through combination using time-limited targeted therapy?

CR is only achieved in 9-26% of patients with CLL treated with ibrutinib (56). Recent results of combinations of ibrutinib with other targeted agents, especially venetoclax, suggest that deeper response can be achieved (14,57)(Table 4). CLARITY is a phase II trial that combines ibrutinib with venetoclax in patients with R/R CLL with primary end point the eradication of MRD after 12 months of combined therapy (57). Ibrutinib plus venetoclax led to uMRD condition in the blood of 28 (53%) and the marrow of 19 (36%). Of note, the combination was well tolerated and only a single case of biochemical tumor lysis syndrome (TLS) was recorded (57). Recently, Jain et al. (14) reported results of an investigator-initiated study on the combination of ibrutinib and venetoclax given as first line therapy in 80 patients with CLL. After 12 cycles of combined treatment, 88% of patients had CR or CRi and 61% achieved remission with uMRD. The adverse-event profile was similar to that reported for ibrutinib and venetoclax administered as single agents. Accordingly, after 24 cycles, therapy in patients with uMRD was stopped, while those who still had detectable MRD continued on ibrutinib. More recently, fixed-duration, targeted treatment with venetoclax–obinutuzumab has also been shown to be effective in previously untreated patients with CLL and coexisting morbidities (median age, 72 years; median Cumulative Illness Rating Scale [CIRS] score, 8; median creatinine clearance, 66.4 ml per minute). In this pioneering phase 3 trial venetoclax–obinutuzumab achieved longer PFS than chlorambucil–obinutuzumab (2-year PFS 88.2 versus 64.1%)(58).

This progress in CLL therapy has encouraged additional efforts to use more than two highly effective targeted agents, thereby testing the concept that a deeper response might allow discontinuation of all treatment (59). A recent phase 1b study demonstrates that combination therapy with obinutuzumab, ibrutinib, and venetoclax is feasible in patients with CLL (15).

Other active agents such as phosphoinositide-3-kinase (PI3K) inhibitors have also been used in combination with ibrutinib and novel anti-CD20 monoclonal antibodies (60).

On the basis of these preliminary reports, it is indeed tempting to hypothesize that combining ibrutinib with other targeted agents could be very useful in selected patients with high-risk disease (eg, pretreated patients, those with TP53 aberrations or complex karyotypes) in whom rapid eradication of disease is essential in order to prevent the emergence of resistant clones (61).

Finally, the appropriate duration of treatment with targeted agents such as venetoclax combined with ibrutinib or obinotuzumab has not yet been defined and ongoing trials have been specifically designed to address the issue (ClinicalTrials.gov numbers, NCT02910583 and NCT03462719; and EudraCT number, 2013 -001944-76)

Can we Improve safety of ibrutinib by using a different BTK inhibitor?

AEs which has led to discontinuation of ibrutinib in 9% -14% of patients in clinical studies and about 22% of patients in routine clinical practice (22). In this respect it is of interest to note that with acalabrutinib , a potent, highly selective covalent BTK inhibitor, toxicities which are associated with ibrutinib, were not observed (62). In this study including 33 R/R CLL patients who had discontinued ibrutinib because of intolerance no acalabrutinib dose reductions were needed, although treatment grade 3/4 AEs occurred, most commonly neutropenia (12%) and thrombocytopenia (9%)(62).

The phase III ASCEND trial compared acalabrutinib monotherapy in patients with previously-treated CLL to the physician's choice which consisted of rituximab in combination with either idelalisib or bendamustine (63). Acalabrutinib significantly prolonged PFS ($P < .0001$), with a 69% reduction in risk of progression or death. Discontinuation due to AEs occurred in 11% of patients in the acalabrutinib arm versus 49% of patients in the physician's choice arms. Typical AEs of BTK inhibition were encountered less frequently (e.g bleeding in 25% of patients receiving acalabrutinib and atrial fibrillation in about 5%) (63). A prospective phase 2 study of acalabrutinib in patients with CLL intolerant to ibrutinib is still ongoing (NCT02717611) to confirm safety and assess efficacy of acalabrutinib in this patient population, while another randomized safety study comparing acalabrutinib with ibrutinib (NCT02477696), will probably provide final answers to the above questions. Other second-generation irreversible BTK inhibitors (i.e., zanubrutinib, tirabrutinib) are also being studied now, in particular, a phase 3 study comparing zanubrutinib to ibrutinib (NCT03734016), which will further assess the safety and efficacy of this novel second generation irreversible BTK inhibitor in R/R CLL Results of the above studies are eagerly awaited in this exciting time of new therapeutic options in CLL .

Conclusions

Despite headway made in CLL treatment in the last few years, many questions remain. CLL is mostly a disease of the elderly, so if we have therapies that provide durable control of the disease for many years, such as ibrutinib, a large number of patients will not succumb to CLL.

Venetoclax allows the achievement of uMRD status in a substantial proportion of patients and this condition may translate into durable remissions even after stopping therapy (64). This suggests that venetoclax should be part of next-generation fixed duration combination therapy possibly MRD-driven. Since ibrutinib and venetoclax have a complementary compartmental activity in CLL (ibrutinib on lymph node and venetoclax on peripheral blood and bone marrow) association of these agents appears particularly useful for younger patients and those with high-risk molecular characteristics (65-66). However, also using the association of ibrutinib and venetoclax we do not know as yet if any of these patients are cured. In this population, we are hopeful that using novel agents in combination and continued improvements in CAR T-cell therapy approaches will provide better results (67).

Finally, ibrutinib has been the first targeted treatment tested in early stage CLL patients at risk to progress towards an active form of disease requiring treatment. Results of the placebo-controlled double-blinded CLL12 trial allow to conclude that ibrutinib significantly improves event-free survival (EFS), PFS, and time to next treatment (TNT) in patients with treatment-naïve early-stage CLL when compared to placebo (68). However, while waiting for survival analysis, a *watch and wait* strategy for early stage patients with increased risk of progression is recommended.

References

1. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(1):32-42.
2. Byrd JC, Brown JR, O'Brien S, et al. RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223
3. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014; 370(11):997- 1007.
4. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):311-322.
5. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2016;17(6):768-778.
6. Burger JA, Tedeschi A, Barr PM, et al. RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25): 2425-2437.
7. Shanafelt TD, Wang V, Kay NE, , et al. A randomized phase III study of ibrutinib (PCI-32765)-based therapy vs. standard fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy in untreated younger patients with chronic lymphocytic leukemia (CLL): a trial of the ECOG-ACRIN Cancer Research Group (E1912). *Blood* 2018, 132 (Suppl. 1), abstract LBA-4.
8. Shanafelt TD, Wang XV, Kay NE, et al Ibrutinib- Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. *N Engl J Med*. 2019 Aug 1;381(5):432-443.

9. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib alone or in combination with rituximab produces superior progression free survival (PFS) compared with bendamustine plus rituximab in untreated older patients with chronic lymphocytic leukemia (CLL): results of Alliance North American Intergroup Study A041202. *Blood* 2018, 132 (Suppl. 1), abstract 6.
10. Woyach JA, Ruppert AS, Heerema NA, et al Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. *N Engl J Med*. 2018 Dec 27;379(26):2517-2528.
11. Moreno C, Greil R, Demirkan F, et al. Ibrutinib + obinutuzumab versus chlorambucil + obinutuzumab as first-line treatment in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL): results from phase 3 iLLUMINATE. *Blood* 2018, 132 (Suppl. 1), abstract 691.
12. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicenter, randomized, open-label, phase 3 trial. *Lancet Oncol*. 2019 Jan;20(1):43-56.
13. Sarraf Yazdy M, Mato AR, Cheson BD. Combinations or sequences of targeted agents in CLL: is the whole greater than the sum of its parts (Aristotle, 360 BC)? *Blood*. 2019;133(2):121-129.
14. Jain N, Keating MJ, Thompson PA, et al. Ibrutinib and Venetoclax for First-Line Treatment of CLL. *N Engl J Med*. 2019 May 30;380(22):2095- 2103.
15. Rogers KA, Huang Y, Ruppert AS, et al. Phase 1b study of obinutuzumab, ibrutinib, and venetoclax in relapsed and refractory chronic lymphocytic leukemia. *Blood*. 2018;132(15): 1568-1572.

16. Byrd JC, Furman RR, Coutre S, et al. Up to 7 years of follow-up of single-agent ibrutinib in the Phase 1b/2 PCYC-1102 trial of first line and relapsed/refractory patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. *Blood* 2018, 132 (Suppl. 1), abstract 3133.
17. O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. *Blood*. 2018;131(17):1910-1919.

18. Coutre SE, Byrd JC, Hillmen P, et al. Long- term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies. *Blood Adv*. 2019 Jun 25;3(12):1799-1807.
19. Byrd JC, Hillmen P, O'Brien S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib versus ofatumumab. *Blood*. 2019;133(19):2031-2042.
20. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: up to 6 years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019 Sep 11. doi: 10.1002/ajh.25638. [Epub ahead of print].
21. Winqvist M, Asklid A, Andersson PO, et al Real-world results of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia: data from 95 consecutive patients treated in a compassionate use program. A study from the Swedish Chronic Lymphocytic Leukemia Group. *Haematologica*. 2016 Dec;101(12):1573- 1580.
22. Dimou M, Iliakis T, Pardalis V, et al Safety and efficacy analysis of long-term follow up real-world data with ibrutinib monotherapy in 58 patients with CLL treated in a single-center in Greece. *Leuk Lymphoma*. 2019 Jun 11:1-7. doi: 10.1080/10428194.2019.1620944. [Epub ahead ofprint]
23. Mato AR, Hill BT, Lamanna N, et al. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. *Ann Oncol*. 2017;28(5):1050-1056.
24. Hillmen P, Diels J, Healy N, et al. Ibrutinib for chronic lymphocytic leukemia: international experience from a named patient program. *Haematologica* 2018 ;103(8):e345-e347.
25. Woyach JA. How I manage ibrutinib-refractory chronic lymphocytic leukemia.

26. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia. *JAMA Oncol.* 2015;1(1):80-7.
27. Jones JA, Mato AR, Wierda WG, et al Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2018;19(1):65-75.
28. Rossi D, Spina V, Gaidano G. Biology and treatment of Richter syndrome. *Blood.* 2018 ;131(25):2761-2772.
29. Woyach JA, Ruppert AS, Guinn D ,et al. BTKC^{481S}- Mediated Resistance to Ibrutinib in Chronic Lymphocytic Leukemia. *J Clin Oncol.* 2017;35(13):1437-1443.
30. Ahn IE, Underbayev C, Albitar A,et al. Clonal evolution leading to ibrutinib resistance in chronic lymphocytic leukemia. *Blood.* 2017;129(11):1469- 1479.
31. Quinquenel A, Fornecker LM, Letestu R, et al Prevalence of BTK and PLCG2 mutations in a real-life CLL cohort still on ibrutinib after three years: a FILO group study. *Blood.* 2019 Jun 26. pii: blood.2019000854. doi: 10.1182/blood.2019000854. [Epub ahead of print].
32. Woyach J, Stephens DM, Flinn I, et al A Phase 1 dose escalation study of ARQ 531 in patients with relapsed or refractory B-cell lymphoid malignancies. 24th Congress of the European Hematology Association (EHA), June 12- 16,2019; abst 2631
33. Byrd JC, Smith S, Wagner-Johnston N, et al First-in-human phase 1 study of the BTK inhibitor GDC-0853 in relapsed or refractory B-cell NHL and CLL. *Oncotarget* 2018 Jan 22;9(16):13023-13035.
34. Allan JN, Patel K, Mato AR, et al Preliminary results of a phase 1b/2 dose-

escalation and cohort-expansion study of the noncovalent reversible Bruton's Tyrosine Kinase inhibitor (BTKi) ibrutinib in B-cell malignancies.

24th Congress of the European Hematology Association (EHA), June 12-16,2019; abst 1148.

35. Jacobson C, Kopp N, Layer JV, et al. HSP90 inhibition overcomes ibrutinib resistance in mantle cell lymphoma. *Blood*. 2016 Nov 24;128(21):2517- 2526
36. Bottoni A, Rizzotto L, Tzung-Huei L, et al. Targeting BTK by a microRNA mechanism in chronic lymphocytic leukemia. *Blood*. 2015;126(23). Abstract 1232.
37. Ming M, Wu W, Xie B, et al. XPO1 inhibitor selinexor overcomes intrinsic ibrutinib resistance in mantle cell lymphoma via nuclear retention of I κ B. *Mol Cancer Ther*. 2018 Dec;17(12):2564-2574.
38. Marin D, Bazeos A, Mahon FX, et al.
Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol*. 2010;28(14):2381-2388.
39. Barr PM, Brown JR, Hillmen P, et al. Impact of ibrutinib dose adherence on therapeutic efficacy in patients with previously treated CLL/SLL. *Blood*. 2017;129(19):2612-2615.
40. Forum UC. Ibrutinib for relapsed/refractory chronic lymphocytic leukemia: a UK and Ireland analysis of outcomes in 315 patients. *Haematologica*. 2016;101(12):1563-1572.
41. Ahn IE, Basumallik N, Tian X, et al. Clinically-indicated ibrutinib dose interruptions and reductions do not compromise long-term outcomes in CLL. *Blood*. 2019 May 30;133(22):2452-2455.
42. Akhtar OS, Attwood K, Lund I, et al. Dose reductions in ibrutinib therapy are not associated with inferior outcomes in patients with chronic lymphocytic leukemia (CLL).

43. Mato AR, Timlin C, Ujjani C, et al. Comparable outcomes in chronic lymphocytic leukaemia (CLL) patients treated with reduced-dose ibrutinib: results from a multi-centre study. *Br J Haematol*. 2018;181(2):259-261.
44. Advani RH, Buggy JJ, Sharman J, et al Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol*. 2013;31, 88–94.
45. Chen LS, Bose P, Cruz ND, et al. A pilot study of lower doses of ibrutinib in patients with chronic lymphocytic leukemia. *Blood*. 2018;132(21):2249- 2259.
46. Tedeschi A, Burger J, Barr PM, et al. Five-year follow-up of patients receiving ibrutinib for first-line treatment of chronic lymphocytic leukemia. Presented at: 2019 European Hematology Association Congress; June 13-16, 2019; Amsterdam, Netherlands. Abstract S107.
47. Burger JA, Sivina M, Jain N, et al. Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. *Blood*. 2019;133(10):1011-1019.
48. Brown JR, Barrientos JC, Barr PM, et al. The Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, with chemoimmunotherapy in patients with chronic lymphocytic leukemia. *Blood* 2015; 125 (9): 2915–2922.
49. Chanan-Khan A, Cramer P, Demirkan F, et al Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol*. 2016 ;17(2):200-211.

50. Fraser G, Cramer P, Demirkan F, et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leukemia*. 2019 Apr;33(4):969-980.
51. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood*. 2016;127(3):303-309.
52. Rossi D, Terzi-di-Bergamo L, De Paoli L, et al. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukemia. *Blood*. 2015;126(16):1921-1924.
53. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood*. 2016;127(2):208-215.
54. Jain N, Thompson PA, Burger JA, et al. Ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (GA101) (iFCG) for previously untreated patients with chronic lymphocytic leukemia (CLL) with mutated IGHV and non-del (17p). *J Clin Oncol* 2017; 35 (Suppl. 1), abstract 7522.
55. Davids MS, Brander DM, Kim HT, et al. Ibrutinib plus fludarabine, cyclophosphamide, and rituximab as initial treatment for younger patients with chronic lymphocytic leukaemia: a single-arm, multicentre, phase 2 trial. *Lancet Haematol*. 2019 Aug;6(8):e419-e428. doi: 10.1016/S2352-3026(19)30104-8. Epub 2019 Jun 14]
56. Strati P, Sivina M, Kim E, et al. Achievement of complete remission (CR) as an endpoint for patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib. *J Clin Oncol* 2018 (Suppl 1), abstract 7522.
57. Hillmen P, Rawstron AC, Brock K, et al. Ibrutinib Plus Venetoclax in

Relapsed/Refractory Chronic Lymphocytic Leukemia: The CLARITY Study. J Clin
Oncol. 2019 Jul 11;JCO1900894. doi: 10.1200/JCO.19.00894. [Epub ahead of print]

58. Fischer K, Al-Sawaf O, Bahlo J, et al Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. *N Engl J Med*. 2019 Jun 6;380(23):2225-2236.
59. Wierda WG, Siddiqi T, Flinn I, et al. Phase 2 CAPTIVATE results of ibrutinib (ibr) plus venetoclax (ven) in first-line chronic lymphocytic leukemia (CLL). *J Clin Oncol* 2018, 36 (Suppl 1), abstract 7502.
60. Nastoupil LJ, Lunning MA, Vose JM, et al. Tolerability and activity of ublituximab, umbralisib, and ibrutinib in patients with chronic lymphocytic leukaemia and non-Hodgkin lymphoma: a phase 1 dose escalation and expansion trial. *Lancet Haematol*. 2019 Feb;6(2):e100-e109.
61. Molica S, Montserrat E. Novel pathway inhibitors for the treatment of chronic lymphocytic leukaemia. *Lancet Haematol*. 2019 Feb;6(2):e65-e66.
62. Awan FT, Schuh A, Brown JR, et al Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. *Blood Adv*. 2019 May 14;3(9):1553-1562.
63. Ghia P, Pluta A, Wach M, et al. ASCEND phase 3 study of acalabrutinib vs investigator's choice of rituximab plus idelasib (IDR) or bendamustine (BR) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). Presented at: 2019 European Hematology Association Congress; June 13-16, 2019; Amsterdam, Netherlands. Abstract LB2606.
64. Kater AP, Seymour JF, Hillmen P, et al. Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study. *J Clin Oncol*. 2019 Feb 1;37(4):269-277
65. Roberts AW, Ma S, Kipps TJ, et al. Efficacy of venetoclax in relapsed chronic

lymphocytic leukemia is influenced by disease and response variables. Blood.

2019;134(2):111-122.

66. Rossi D. Quest of biomarkers for venetoclax-treated CLL. Blood 2019 134:97-98

67. Bair SM, Porter DL. Accelerating chimeric antigen receptor therapy in chronic lymphocytic leukemia: The development and challenges of chimeric antigen receptor T-cell therapy for chronic lymphocytic leukemia. *Am J Hematol*. 2019 May;94(S1):S10-S17.
68. Langerbeins P, Bahlo J, Rhein C, et al. Ibrutinib versus placebo in patients with asymptomatic, treatment-naïve early stage chronic lymphocytic leukemia (CLL): primary endpoint results of the phase 3 double-blind randomized CLL12 trial. Presented at 2019 EHA Congress; June 13-16, 2019; Amsterdam, The Netherlands. Abstract LB2602.

Legend of figure 1

Suggested approach to the upfront therapy of chronic lymphocytic leukemia (CLL) patients which takes into account results of ALLIANCE, ECOG-ACRIN Cancer Research Group (E1912), iLLUMINATE and CLL14 trials.

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All authors contributed equally to this manuscript

Table 1
Inclusion criteria and progression-free survival (PFS) in trials of ibrutinib given in upfront.

Clinical trial	Inclusion criteria	Ibrutinib arm	CIT arm	3-year PFS (Ibrutinib arm)	3-year PFS (CIT arm)
ECOG-ACRIN ⁽⁷⁻⁸⁾	<ul style="list-style-type: none"> • Able to tolerate FCR • Not included 17p deleted • Patient age < 70 years 	Ibrutinib + Rituximab	FCR	92%	73%
ALLIANCE ⁽⁸⁻⁹⁾	<ul style="list-style-type: none"> • Patient age > 65 years • Included 17p deleted 	Ibrutinib + Rituximab	BR	85%	60%
ILLUMINATE ⁽¹⁰⁻¹¹⁾	<ul style="list-style-type: none"> • Patient age > 65 yrs • < 65 yrs unfit • Included 17p deleted or TP53 mutated 	Ibrutinib + Obinotuzumab	CLB + Obinotuzumab	70%	32%

FCR= Fludarabine, Cyclophosphamide, Rituximab; BR= Bendamustine, Rituximab; CLB=Chlorambucil

Table 2

Grade 3-5 Treatment Related Adverse Events ECOG-ACRIN E1912 & Alliance

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Adverse event	IR Arm ECOG-ACRIN E1912 ⁽⁷⁻⁸⁾ N=352	IR Arm Alliance ⁽⁸⁻⁹⁾ n=181	Ibrutinib Arm Alliance ⁽⁸⁻⁹⁾ n=180
Median Age (range)	57 yrs (31-70)	71 yrs (65-86)	71yrs (65-89)
Infection	5%	20%	21%
Atrial fibrillation	3%	6%	9%
Bleeding	1%	3%	2%

Hypertension	7%	34%	29%
Deaths during active treatment +30 days	1%	7%	7%

IR, Ibrutinib + Rituximab

Table 3

Responses in terms of complete remission (CR) and undetectable minimal residual disease (U-MRD) in mutated M- *IGHV* patients after 6 cycles of FCR. Results obtained with ibrutinib, FC, and GA101 (iFCG) in the same setting of patients are also presented.

Trial	Regimen	N. pts	**CT scan	CR/CRI (%)	BM U-MRD(%)
MDACC ⁽⁵⁾ ₁₎	FCR x 6	88	No	83	51
MDACC ⁽⁵⁾ ₁₎	FCR x 6	82	No	66	56
CLL8 ⁽⁵³⁾	FCR x 6	113	No	50	50
CLL10 [§]	FCR x 6	123	Yes	39	62
MDACC ⁽⁵⁾ ₂₎	Ibrutinib + FC+GA101 x 3 followed by ibrutinib + GA101 x3	42	Yes	74%	*100%

*Patients who reached the 12 month time-point were undetectable MRD (U-MRD) and stopped ibrutinib

** CT scan, Computed Tomography scan

§ Eichhorst B, et al Lancet Oncol. 2016 Jul;17(7):928-942

Table 4

Trials of ibrutinib in combination with other targeted agents

Regimen	Study phase	Disease setting	No. patients	CR	U-MRD rate
Ibrutinib + venetoclax (CLARITY) ⁽⁵⁷⁾	2	R/R	50 (25 completed 6 mo.)	60 %	BM, 28% PB, 93% (after 12 mo.)
Ibrutinib + venetoclax (CAPTIVATE) ⁽⁵⁹⁾	2	TN	163 (14 completed 12 mo.)	36 %	BM, 36% (after 12 mo.)
Ibrutinib + venetoclax (MDACC) ⁽¹⁴⁾	2	TN	80 (25 completed 12 mo.)	92 %	BM, 68% (after 12 mo.)
Obinotuzumab + ibrutinib + venetoclax ⁽¹⁵⁾	1b/2	TN	25 (24 completed 8 mo.)	50 %	PB, 58% BM, 58%
Ublituximab, umbralisib, and ibrutinib ⁽⁶⁰⁾	1	R/R	23	36 %	NA

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