Ibrutinib (Imbruvica™), a first-in-class Bruton’s tyrosine kinase (BTK) inhibitor, has been approved for previously treated patients with chronic lymphocytic leukemia (CLL) and for patients with del(17p) CLL. Primary analysis of the phase II RESONATE™-17 (PCYC-1117-CA) study is designed to evaluate the efficacy and safety of single-agent ibrutinib for treatment of patients with relapsing/remitting (R/R) del(17p) CLL or small lymphocytic lymphoma (SLL). Patients with del(17p) CLL or SLL who failed at least 1 therapy were enrolled to receive 420 mg oral ibrutinib once daily until progression. All patients receiving at least 1 dose of ibrutinib were included in the analysis. The primary endpoint was overall response rate (ORR) per an independent review committee (IRC). Other endpoints included duration of response (DOR), progression-free survival (PFS), and safety of ibrutinib.

Results: Among 144 treated patients (137 with CLL, 7 with SLL), the median age was 64 (48% 65 years or older) and all had del(17p). Baseline characteristics included 63% of patients with Rai stage III or IV disease, 49% with bulky lymphadenopathy of at least 5 cm, and 10% with lymphadenopathy of at least 10 cm. The median baseline absolute lymphocyte count (ALC) was 32.9 x 10⁹/L, with 57% of patients with a baseline ALC at least 25.0 x 10⁹/L. Baseline beta-2 microglobulin levels were at least 3.5 mg/L in 78% of patients (range 1.8–19.8 mg/L), and lactate dehydrogenase levels were at least 350 U/L in 24% of patients (range 127–1979 U/L). A median of 2 prior therapies (range 1–7) was reported. Investigator-assessed ORR was 82.6%, including 17.4% partial response (PR) with lymphocytosis (PR-L). Complete response (CR)/complete response with incomplete bone marrow recovery (CRi) were reported in 3 patients. IRC-assessed ORR is pending. At a median followup of 13.0 months (range 0.5–16.7 months), the median PFS and DOR by investigator determination had not been reached. At 12 months, 79.3% were alive and progression-free, and 88.3% of responders were progression-free. Progressive disease was reported in 20 patients (13.9%). Richter transformation was reported in 11 of these patients (7.6%), 7 of the cases occurring within the first 24 weeks of treatment. Prolymphocytic leukemia was reported in 1 patient. Most frequently reported grade 3–4 adverse events (AEs) were neutropenia (14%), anemia (8%), pneumonia (8%) and hypertension (8%). Major hemorrhage was reported in 7 patients (4.9%, all grade 2 or 3). Study treatment was discontinued in 16 patients (11.1%) due to AEs, with 8 eventually having fatal events (pneumonia, sepsis, myocardial or renal infarction, health deterioration). At the time of data cut, the median treatment duration was 11.1 months, and 101 of 144 patients (70%) continued treatment with ibrutinib.
In the largest prospective trial dedicated to the study of del(17p) CLL/SLL, ibrutinib demonstrated marked efficacy in terms of ORR, DOR and PFS, with a favourable risk-benefit profile. At a median followup of 13 months, the median DOR had not yet been reached; 79.3% of patients remained progression-free at 12 months. These results support ibrutinib as an effective therapy for patients with del(17p) CLL/SLL.

Commentary: The last several years have seen significant advancements in treatment options for patients with chronic lymphocytic leukemia (CLL), with the introduction of novel targeted agents. The first of these novel agents to be approved by the US Food and Drug Administration (FDA), ibrutinib, is a first-in-class selective inhibitor of Bruton’s tyrosine kinase (BTK). BTK plays a central role in B-cell receptor signaling and was found to be involved in activating several pathways key to CLL-cell survival. Inhibition of BTK proved to be highly effective for CLL, leading to very high response rates in early studies of relapsed and refractory CLL patients. This BTK inhibition is also specific to B cells while sparing healthy T cells, making infectious complications rare. Ibrutinib is orally administered, unlike most traditional chemotherapeutics, making it highly desirable for most patients.

In the landmark phase 1b-2 study published by Byrd and colleagues in the New England Journal of Medicine, ibrutinib was very potent, with a high frequency of durable remissions in a heavily pretreated population. The study included many patients with high-risk features including deletion of the short arm of chromosome 17 (del(17p)), a chromosomal aberration associated with chemotherapy resistance and very poor survival for CLL patients. Patients with del(17p) were seen to respond as well as the rest of the population to ibrutinib; however, proportionally more of those patients eventually progressed on therapy, indicating that del(17p) was still a poor prognostic factor even in the era of novel agents.

The RESONATE study aimed to directly examine the efficacy and safety of ibrutinib in the del(17p) CLL population. Patients were included after failure of at least 1 prior therapy, with a median of 2 prior therapies, and all had del(17p). Three patients obtained a CR or CRi, a response that would not be expected for relapsed patients with del(17p), who typically fail to respond to most therapies. At the time of the assessment, with a median followup of 13 months, the median PFS was not yet reached, with 79.3% of patients still progression-free at 12 months. This is a very impressive PFS for this population and suggests that ibrutinib is an excellent treatment option for del(17p) patients. Importantly, ibrutinib was also very well tolerated in this population, with very low rates of grade 3-4 AEs. The only notable AE was atrial fibrillation, which has been reported in several recent ibrutinib studies. Of the progressive disease events reported in the study, several were Richter’s transformation events that appeared to occur early in the course of treatment, indicating that ibrutinib is not effective against transformation of CLL to a high-grade lymphoma. These early results support ibrutinib as an effective treatment for CLL patients with del(17p).

What this study showed:
- ibrutinib is effective for patients with del(17p) with very high response rates and a median progression-free survival (PFS) not yet reached at 13 months.

Next steps:
- Await final results to determine the median PFS for single agent ibrutinib.
- Determine if combination studies (ex. with an anti-CD20 mAb) can improve on these results for patients with del(17p) and other high-risk patients.

**In Brief**

**Already known:**
- Traditional chemotherapy including intensive chemoinmunotherapy (with fludarabine-cyclophosphamide-rituximab [FCR]) is not effective in patients with del(17p) who have a very short survival in all previous studies.

**What this study showed:**
- ibrutinib is effective for patients with del(17p) with very high response rates and a median progression-free survival (PFS) not yet reached at 13 months.

**Next steps:**
- Await final results to determine the median PFS for single agent ibrutinib.
- Determine if combination studies (ex. with an anti-CD20 mAb) can improve on these results for patients with del(17p) and other high-risk patients.

**References:**

**Trial Summary: Interim analysis of Mabtenance trial**

This study aimed to assess the efficacy of rituximab maintenance after chemoimmunotherapy induction. Patients (pts) were recruited at the end of any rituximab-containing induction treatment in first or second line that achieved at least a PR. Randomization was stratified by country, line of treatment, induction response and type of induction regimen. The primary endpoint is PFS. This interim analysis was undertaken after half of the planned events (46) were observed. It includes 263 pts enrolled into the trial: 134 randomized to rituximab maintenance and 129 to the observation arm. Patients had a median age of 63 years, 28.9% were female and 80.6% were enrolled after first induction treatment. Hierarchical fluorescence in situ hybridization (FISH) cytogenetic risk was available in 221 pts: del(17p) 3.1%, del(11q)
27.6%, trisomy 12 10.8%, del(13q) 36.2%, and normal FISH karyotype 21.2%. Immunoglobulin variable region heavy chain (IgVH) mutation state was available in 161 pts at time of interim analysis; 67% were unmutated. The induction regimen was fludarabine-cyclophosphamide-rituximab (FCR) in 73.5% and bendamustine-rituximab (BR) in 20.2%. The response to induction treatment was complete response (CR)/complete response with incomplete bone marrow recovery (CRi) in 58% and PR in 41.8% of pts, and 57% scored negative in an 8-colour minimal residual disease (MRD) flow-cytometric analysis after induction.

Results: Median observation time at interim analysis was 17.3 months. Severe adverse event (SAE) causes were well balanced between arms, with the exception of infectious SAEs (32 in the rituximab, including 1 death, and 22 in the observation arm, including 2 deaths) and secondary malignancies: 8 in the rituximab arm (including 4 localized nonmelanoma skin cancers and 1 death from melanoma) and 1 in the observation arm (including 1 death from melanoma). At the time of interim analysis, disease progression was evident in 27.9% in the observation arm and in 14.9% in the rituximab arm. Ten pts died in the observation arm and 7 in the rituximab arm.

The primary endpoint (PFS) is significantly in favour of rituximab maintenance, with a p-value of 0.007 and a PFS at 17.3 months of 85.1% in the rituximab group vs 75.5% in the observation arm. To account for toxicities and secondary neoplasms, an event-free survival (EFS) was calculated counting secondary malignancies, termination of treatment due to toxicities, progression and death. In this analysis, the benefit was preserved, albeit with a lower p-value of 0.03. The observed benefit seemed independent of response after induction (CR vs PR), but was associated with positive MRD state after induction. Further factors that influenced the benefit in exploratory subgroup analyses were sex, cytogenetics, IgVH and B-symptoms at diagnosis.

Conclusions: Rituximab maintenance after chemotherapy induction in CLL seems feasible and shows signs of efficacy, although with an increase in infectious complications. Exploratory analyses suggest that with longer followup it may be possible to define subpopulations with larger benefit from extended immunotherapy.

TRIAL SUMMARY: Interim analysis of ofatumumab maintenance study

Ofatumumab, a human anti-CD20 monoclonal antibody, has proven efficacy as a monotherapy in refractory CLL. PROLONG is an open-label, 2-arm randomized study of ofatumumab versus observation for pts in remission after induction treatment for relapsed CLL. Results were presented from interim analysis for the key primary and secondary endpoints of the study. Pts in CR or PR after second- or third-line treatment for CLL were randomized 1:1 to receive ofatumumab (300 mg followed 1 week later by 1000 mg, every 8 weeks for up to 2 years) or observation. Pts on ofatumumab received premedication with acetaminophen, antihistamine and glucocorticoid. Pts were stratified by number and type of prior therapy, and by remission status (CR or PR) after induction treatment. The primary endpoint was PFS from randomization, as assessed by investigator. The predefined interim analysis of efficacy occurred at 2/3 study events (minimum 187), with a p<0.001 required for a positive analysis. The interim analysis was reviewed by an independent data monitoring committee. Secondary endpoints included duration of response, overall survival (OS) and safety.

Results: 474 pts were randomized prior to the interim analysis. Baseline characteristics were similar between arms. The median duration of ofatumumab treatment was 12.5 months, with median followup was 26.1 months for ofatumumab and 24.0 months for observation. The median PFS was 28.6 months for ofatumumab and 15.2 months for observation (HR=0.48; p<0.0001). Time to start of next therapy was significantly longer in the ofatumumab arm compared to the observation arm (median 38.0 vs 27.4 months, HR=0.63; p=0.0076). At the time of interim analysis, there were no differences in OS (HR=0.92; p=0.74). AEs during the study occurred in 87% ofatumumab pts vs 75% observation pts. Ofatumumab pts had 25% grade 3–4 AEs vs 17% in observation pts. Grade 3–4 infection rates were 18% in the ofatumumab group vs 13% in the observation arm, the most common (>5% of all pts) being neutropenia (22% ofatumumab vs 9% observation) and pneumonia (7% ofatumumab vs 4% observation). The death rate was similar in both arms (14%). AEs that led to permanent discontinuation of treatment occurred in 8% of ofatumumab pts.

Conclusions: Ofatumumab maintenance provided significant clinical benefit for pts with relapsed CLL; it was well tolerated with no unexpected toxicities. Additional data analyses are ongoing and efficacy outcomes according to patient subgroups will be presented.

COMMENTARY: The development of the anti-CD20 monoclonal antibody (mAb) rituximab has greatly optimized the treatment of B-cell lymphoproliferative disorders, including CLL. Rituximab combined with chemotherapy is the standard frontline therapy for all B-cell malignancies, based on several studies showing survival advantages in diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL) and other indolent non-Hodgkin lymphomas (iNHL) and, most recently, in CLL.1,4 Early studies of rituximab in CLL demonstrated disappointing response rates, much inferior to those noted in most other subtypes of NHL, thought to result from reduced drug levels of rituximab caused by altered pharmacokinetics and/or due to the low density of CD20 expression on CLL cells.5 Despite these concerns, in the German CLL Study Group (GCLLSG) CLL8 study, the addition of rituximab to intensive chemotherapy with fludarabine and cyclophosphamide resulted in an OS advantage for CLL patients. An OS advantage was
also demonstrated in the GCLLSG CLL11 study with the addition of obinutuzumab, a novel anti-CD20 mAb, to chlorambucil, compared to chlorambucil monotherapy, in older patients with CLL. Based on these results, it has become clear that all patients with CLL should receive an anti-CD20 mAb in combination with chemotherapy, at least as a part of their frontline therapy.

Following the initial studies of immunochemotherapy for B-cell malignancies, several trials investigated the value of maintenance therapy in responding patients. The value of maintenance therapy has been clearly demonstrated in FL and other iNHLs, and has become a routine part of primary therapy. The question of whether a similar maintenance therapy approach would also be beneficial in CLL has not yet been answered, but is being investigated in 2 large randomized studies, with interim analyses of each presented at the American Society of Hematology meeting in December 2014.

The first study, reported by Greil and colleagues, entitled the Mabtenance trial (AGMT-CLL8 study), investigated the impact of rituximab maintenance after first- or second-line chemoimmunotherapy in patients with CLL. The included patients were younger than the average CLL patients (median age 63 years) and most had received FCR as their chemoimmunotherapy, implying that they were also a fit population. Otherwise, the clinical characteristics of the patients appeared representative, with 67% having unmutated IgVH status, a cohort predicted to experience earlier relapse after therapy. After a median observation time of 17.3 months, the PFS was significantly longer in the rituximab maintenance group compared to those who received only observation. However, this PFS advantage was not without toxicity, with more severe infections noted in the rituximab maintenance group.

The second study, reported by van Oers and colleagues, entitled the PROLONG study, investigated the impact of ofatumumab maintenance versus observation in patients with relapsed CLL (i.e. after second- or third-line therapy). Ofatumumab has demonstrated efficacy in a phase 2 study as monotherapy for relapsed CLL, making it appear a good choice for maintenance in CLL patients. Again, the PFS was significantly improved with ofatumumab maintenance compared to observation in this population, but there was more neutropenia noted in the ofatumumab group (24% versus 10%). However, despite the higher incidence of neutropenia in the ofatumumab maintenance cohort, there was only a moderate increase in infections, that was not statistically significant. The authors also reported an improvement in the time to next treatment but no difference in OS at the time of the analysis.

Based on these interim analyses, it is clear that maintenance therapy is feasible for CLL patients following chemoimmunotherapy and that the side effects are typical for anti-CD20 mAb therapy (infections and neutropenia). The final results of these studies will be very interesting, though it may be difficult to determine where anti-CD20 maintenance therapy will fit into the therapeutic options for CLL patients, given the recent availability of novel oral agents, like ibrutinib and idelalisib, which themselves are provided with an extended duration of therapy (treatment until disease progression).

References