TABLE 1

	N=60
Overall response rate (≥ PRL), n (%)	46 (77)
95% CI	64, 87
CR	1 (2)
PR	42 (70)
PRL	3 (5)
Median PFS	Not reached
21-month PFS rate, % (95% CI)	76 (61, 86)

Abbreviations: CR, complete response; PFS, progression-free survival; PR, partial response; PRL, partial response with lymphocytosis.

Background: In patients with chronic lymphocytic leukemia (CLL) treated with the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, intolerance was the most common reason for discontinuation (50% to 63%; Mato AR, et al. *Haematologica.* 2018). This Phase 2 trial evaluated acalabrutinib, a highly selective, potent, covalent BTK inhibitor, in ibrutinib-intolerant patients with relapsed/refractory CLL.

Methods: Patients with relapsed/refractory CLL (≥1 prior therapy) who discontinued ibrutinib due to Grade 3/4 adverse events or persistent/recurrent Grade 2 adverse events and had progressive disease after ibrutinib discontinuation were eligible. Acalabrutinib was given orally at 100 mg twice daily in 28-day cycles until progressive disease or unacceptable toxicity. The primary endpoint was overall response rate.

Results: Sixty patients were treated. The median age was 70 years (range, 43 to 88). Patient characteristics included bulky disease ≥5 cm (33%), Rai stage III/IV (47%), del17p (28%), del11q (23%), and unmutated *IGHV* (79%). Fifty-two of 55 patients (95%) with available baseline samples were wild type for*BTK* and *PLCG2*. The median number of prior therapies was 2 (range, 1 to 10). The median duration of prior ibrutinib therapy was 6 months (range, <1 to 55); common adverse events that led to ibrutinib discontinuation were atrial fibrillation/flutter (25%), diarrhea (12%), arthralgia (10%), and rash (12%). At a median follow-up of 19 months (range, 1 to 31), 67% of patients remain on acalabrutinib; discontinuations were mostly due to progressive disease (13%) and adverse events (10%; pneumonia [n=2], diarrhea, headache, ascites, arthralgia, subdural hematoma [all n=1]). Efficacy outcomes are in the **Table**. Common adverse events (any grade) were diarrhea (48%), headache (40%), contusion (35%), and dizziness (32%). Serious adverse events (≥2 patients) were pneumonia (10%), anemia (3%), and syncope (3%). Atrial fibrillation occurred in 3 patients (5%; all Grade 1/2) and major hemorrhage in 2 (3%; Grade 3 hematuria and Grade 2 subdural hematoma). Grade 5 adverse events were pneumonia (n=2), bronchopulmonary aspergillosis (n=1), and ventricular fibrillation (n=1); all were considered not related to treatment.

Conclusions: Acalabrutinib is tolerable and effective in ibrutinib-intolerant patients, providing a viable strategy for continuing BTK inhibitor therapy.

Keywords: BTK inhibitors.

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030
RAPID AND DURABLE RESPONSES WITH THE SYK/JAK INHIBITOR CERDULATINIB IN A PHASE 2 STUDY IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA—ALONE OR IN COMBINATION WITH RITUXIMAB

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Background: Despite recent advances, follicular lymphoma (FL) remains incurable for most patients (pts). Relapsed/refractory (r/r) FL is associated with decremental treatment responses, accumulating toxicity, and poor survival among early failures of 1st line chemo-immunotherapy. Underscored by the recent approvals of idelalisib, copanlisib, and duvelisib, targeting B-cell receptor (BCR) signaling produces ORR of ~50% in r/r pts; however, new agents with a better therapeutic index over long-term administration are needed.

SYK is a key regulator of BCR signaling (upstream of BTK and PI3K), and its inhibition results in clinical activity in FL. Compared with unaffected nodes, lymph nodes from FL pts have greater numbers of follicular helper T cells that express high levels of IL-4, which may support the tumor via the JAK1/3 pathway.

Cerdulatinib, an oral, reversible inhibitor of SYK and JAK kinases (JAK1, JAK3, TYK2), previously reported a ~45% ORR in r/r FL as a single agent. Xenograft studies suggest cerdulatinib may combine with rituximab to enhance antitumor activity. We report updated results from a Ph2a study of single-agent cerdulatinib and initial results in combination with rituximab in r/r FL.

Methods: This Ph2a study confirmed the safety and efficacy of cerdulatinib 30 mg BID in r/r B- and T-cell lymphoma pts. Dose reductions were permitted to 15 mg BID. Response was assessed by Lugano criteria.

Results: As of Jan 2019, enrollment was 40 pts in the single-agent cohort and 11 in the rituximab combination cohort. Median (range) age was 64 (42-81) and median prior therapies was 3 (1-8). Fifty (98%) pts had prior anti-CD20 therapy, and 8 (16%) had prior PI3K or BTK inhibitors. The most common AEs of any grade were diarrhea (47%), nausea (37%), lipase increase (29%), and amylase increase (22%). Grade 3+ AEs in ≥5% pts were lipase increase (24%), diarrhea (12%), amylase increase (10%), nausea (8%), hypertension (8%), and neutropenia (6%). Grade 3+ infections occurred in 6 (12%) pts. One pt had grade 5 multi-organ failure potentially related to study drug. Amylase and lipase increases generally were not associated with abdominal pain or pancreatitis. The safety profile appeared similar in both cohorts.

The ORR was 46% as a single agent (5 CRs, 13 PRs in 40 pts) and 67% in the combination cohort (4/6 PRs; 2 pts with SD had a >40% reduction in tumor volume at 1st re-scan). Responses typically occurred after 2 cycles and were durable in the single-agent cohort, with 10 pts on drug for >1 year. Enrollment in the combination cohort is ongoing. Updated safety and efficacy will be presented.

Conclusion: The recommended cerdulatinib Ph2 dose of 30 mg BID was tolerable and efficacious in heavily pretreated r/r FL. The cerdulatinib + rituximab combination appears to be well tolerated, with tumor reductions in all evaluable pts. The safety profile and unique MOA of cerdulatinib support further combination studies in FL.

Keywords: follicular lymphoma (FL); JAK/STAT; SYK.

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031
A PHASE 2B STUDY OF SELINEXOR IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)