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To the editor:

Efficacy and safety of dinaciclib vs ofatumumab in patients with relapsed/refractory chronic lymphocytic leukemia

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Novel approaches targeting molecules involved in intracellular pathways that are crucial for the survival and proliferation of the leukemic clone have been recently approved for the treatment of chronic lymphocytic leukemia (CLL) patients. Nevertheless, CLL remains incurable outside of allogeneic stem cell transplant, and novel treatment options for relapsed/refractory patients remain an unmet clinical need. Cyclin-dependent kinases (CDKs), key regulators of cell cycle progression, have become attractive therapeutic targets in oncology and hematology,[1,2] given the role of aberrant cell cycle regulation in the pathogenesis of many cancers, including leukemias. CDK inhibitors offer the potential of simultaneous blockade of cell cycle progression and transcription, facilitating the induction of apoptosis and reactivation of the TP53 tumor suppressor mechanism. These agents have shown potent activity in patients with CLL.[3] The pan-CDK inhibitor flavopiridol demonstrated clinical efficacy[4,5] but was associated with tumor lysis syndrome (TLS), which occurred in 25% of patients, some of whom required hemodialysis.[6]

Dinaciclib is a novel, potent, small-molecule CDK inhibitor that selectively inhibits CDK1, 2, 5, and 9 at 50% inhibitory concentration values in the 1- to 4-nM range.[7,8] In in vitro studies, dinaciclib induced apoptosis and/or cell growth arrest in various solid and hematopoietic tumor cell models.[9-11] Additionally, dinaciclib produces caspase-independent downregulation of messenger RNA and protein expression of the antiapoptotic protein myeloid cell leukemia 1 (MCL1), which is essential for CLL cell survival.[12] In murine xenograft models, dinaciclib exhibited a superior therapeutic index compared with flavopiridol.[9] Phase 1 studies of dinaciclib demonstrated acceptable toxicity, with typical adverse events (AEs) represented by cytopenias, transient laboratory abnormalities, and TLS.[13,14] A phase 1 study of dinaciclib in patients with CLL showed a partial response rate of ~63% in pretreated subjects at the recommended phase 2 dose (14 mg/m^2),[13] including responses in high-risk subgroups, such as patients with deletion of 17p (del17p).[13]

Ofatumumab is a fully humanized type I anti-CD20 monoclonal antibody,[15,16] which binds to a different epitope of CD20 than rituximab.[17] A phase 1/2 study in relapsed/refractory CLL demonstrated that ofatumumab had an overall response rate (ORR) of 50% and was generally well tolerated, even at high doses.[18] Ofatumumab has shown activity in subjects with fludarabine- and alemtuzumab-refractory and bulky fludarabine-refractory CLL, irrespective of prior treatment with rituximab.[19] However, the phase 3 RESONATE trial demonstrated a remarkably lower ORR in patients with relapsed/refractory CLL treated with ofatumumab (4.1%; used as control arm vs ibrutinib).[20]

Here, we present the results of a randomized, open-label, phase 3 trial designed to compare the efficacy and tolerability of dinaciclib with ofatumumab in patients with relapsed/refractory CLL (registered at www.clinicaltrials.gov as #NCT01580228; study P012). At the time of study initiation, ofatumumab was the only therapy specifically approved for refractory CLL patients and was therefore selected as the comparison arm. Patients with confirmed CLL, as defined by the 2008 International Workshop on CLL criteria,[21] and no response or disease relapse within 6 or 24 months after fludarabine or chemoimmunotherapy, respectively, were enrolled. Dinaciclib was administered IV at escalating doses of 7 to 10 to 14 mg/m^2 (on days 1, 8, and 15, respectively) in cycle 1 and 14 mg/m^2 in cycle 2 and thereafter (1 cycle = 28 days) for 12 cycles. Ofatumumab was administered IV once weekly for 8 weeks starting in cycle 1 on day 1, followed by 9 monthly doses as follows: 300 mg in cycle 1 on day 1; 2000 mg in cycle 1 on days 8, 15, and 22 and cycle 2 on days 1, 8, 15, and 22, and every 4 weeks starting from 5 weeks later on day 1 of cycles 4 to 12.

Table 1. Baseline demographics and disease characteristics

	Dinaciclib (n = 20)	Ofatumumab (n = 22)	Total (n = 42)
Sex (male)	15 (75.0)	17 (77.3)	32 (76.2)
Age, mean ± SD, y	60.1 ± 8.6	62.3 ± 9.1	61.2 ± 8.8
Race			
White	19 (95.0)	20 (90.9)	39 (92.9)
Other	1 (5.0)	2 (9.0)	3 (7.2)
Rai stage			
I	1 (5.0)	2 (9.1)	3 (7.1)
II	4 (20.0)	8 (36.4)	12 (28.6)
III	1 (5.0)	5 (22.7)	6 (14.3)
IV	13 (65.0)	7 (31.8)	20 (47.6)
Missing	1 (5.0)	0 (0.0)	1 (2.4)
Number of prior therapies, median (range)	2 (1-6)	3 (1-20)	3 (1-20)
Prior fludarabine	18 (90.0)	21 (95.5)	39 (92.9)
Prior rituximab	19 (95.0)	22 (100.0)	41 (97.6)
Bulky disease*	12 (60.0)	12 (54.5)	24 (57.1)
ECOG <1	18 (90.0)	22 (100.0)	40 (95.2)
Del17p	7 (35.0)	9 (40.9)	16 (38.1)
Refractory/relapse			
Chemoimmunotherapy ≤6 mo	14 (70.0)	13 (59.1)	27 (64.3)
Fludarabine refractory	3 (15.0)	3 (13.6)	6 (14.3)
Chemoimmunotherapy >6 to 24 mo	3 (15.0)	6 (27.3)	9 (21.4)

Data are presented as n (%) of patients, unless otherwise indicated.
ECOG, Eastern Cooperative Oncology Group.
*Defined as any lymph node >5 cm by physical exam or computed tomography scan.

Table 2. Progression-free survival and response to treatment

	Dinaciclib (n = 20)	Ofatumumab (n = 24)
PFS		
PFS events*	11 (55.0)	17 (70.8)
Person-months	213	135
Event rate/100 person-months, %	5.2	12.6
Median PFS, months (95% CI)†	13.7 (10.3, 21.2)	5.9 (2.1, 9.4)
Response to treatment‡		
Complete	0 (0.0)	0 (0.0)
Partial	8 (40.0)	2 (8.3)
Overall response	8 (40.0)	2 (8.3)
Stable disease	7 (35.0)	11 (45.8)
Progressive disease	1 (5.0)	1 (4.2)
Not evaluable§	4 (20.0)	10 (41.6)

Data are presented as n (%) of patients, unless otherwise indicated. Small sample sizes due to early study termination precluded testing of statistical significance.

CI, confidence interval.

*PFS is defined as the time from randomization to disease progression or death, whichever occurred first.

†From product-limit (Kaplan-Meier) method for censored data.

‡Patients' best response to therapy, according to investigator assessment across time points per the 2008 International Workshop on CLL criteria.

§Patients were required to have at least 2 postbaseline scans for an evaluable response.

The trial was designed to evaluate progression-free survival (PFS) as the primary end point (ORR, partial response + complete response) and overall survival (OS) in patients with relapsed/refractory CLL treated with dinaciclib compared with ofatumumab. Safety and tolerability were assessed by clinical review of all relevant parameters, including AEs, laboratory tests, vital signs, and electrocardiographic measurements. Complete details regarding trial methodology are provided in supplemental Materials (available on the *Blood* Web site).

Early termination of the study due to program prioritization and unrelated to safety or efficacy issues occurred, but collected data are reported here. Overall, 44 patients were randomized (intention to treat) and 42 were treated (supplemental Figure 1). Approximately 284 to 466 subjects (186 del17p; 98 to 280 non-del17p) were originally planned for enrollment. Patient characteristics at baseline are presented in Table 1. The median follow-up duration (range) was 16.7 (0.4-26.1) months.

The results informing PFS, ORR, and OS signaled promising antileukemia activity with dinaciclib relative to ofatumumab (Table 2), although the limited sample size precluded the conduct of planned statistical analyses. Median PFS was 13.7 and 5.9 months for patients receiving dinaciclib and ofatumumab, respectively. The ORR was 40.0% for patients receiving dinaciclib and 8.3% for those receiving ofatumumab; all were partial responses. Stable disease was achieved by 35.0% of dinaciclib and 45.8% of ofatumumab patients. Median OS was 21.2 and 16.7 months for patients receiving dinaciclib and ofatumumab, respectively.

Interestingly, dinaciclib was similarly effective in the del17p subgroup of patients (n = 7) compared with the overall study population. In this subgroup, median PFS was 17.2 and 2.4 months and median OS was 21.2 and 5.4 months in patients receiving dinaciclib and ofatumumab, respectively. Del17p has consistently been associated with poor response to chemotherapy, decreased OS,[22] and earlier relapse despite treatment with novel B-cell receptor inhibitors.[23]

Dinaciclib had an acceptable safety and tolerability profile in patients with relapsed/refractory CLL (supplemental Tables 1 and 2). The observed AEs were consistent with those previously identified in patients with relapsed/refractory CLL,[13] especially considering that the study population received a median of 3 previous lines of treatment before enrollment into the study. The most common grade ≥3 AEs with dinaciclib and ofatumumab, respectively, were neutropenia (35.0% vs 9.1%), thrombocytopenia (20.0% vs 9.1%), decreased neutrophil count (20.0% vs 4.5%), pneumonia (5.0% vs 13.6%), sepsis (5.0% vs 13.6%), and febrile neutropenia (10.0% vs 4.5%). TLS has been observed with other CDK inhibitors in the treatment of CLL and may be the result of sensitivity of the CLL cells to this class of agents.[24] Only 1 patient in the dinaciclib group developed a laboratory TLS[25]; this event was deemed not treatment related by the study investigator.

This study provides important insight into the potential antileukemic activity and signals an acceptable safety and tolerability profile of dinaciclib compared with ofatumumab in patients with relapsed/refractory CLL, even among high-risk subgroups. The tolerability of dinaciclib appears to be strongly improved in comparison with first-generation CDK inhibitors, especially with respect to the occurrence of TLS. Whereas these data are encouraging, the efficacy results from this small, terminated trial are insufficient to definitively conclude that dinaciclib provides superior anticancer activity vs ofatumumab in patients with relapsed/refractory CLL. Nevertheless, based on these results and given the distinct mechanism of action directed against CDK while allowing for downregulation of MCL1, further studies investigating dinaciclib are warranted. In particular, combinations with other novel agents for the treatment of CLL are currently being explored in clinical trials.

*P.G. and L.S. contributed equally to this study.

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Contribution: P.G., S.P., M.D., and K.S. designed or planned the study; S.P. and N.P. acquired the data; P.G., L.S., S.P., K.P., and M.D. analyzed the data; P.G., L.S., S.P., K.P., K.S., C.M.S., and N.P. interpreted the data; P.G., K.P., and C.M.S. drafted the manuscript; and all authors critically revised the manuscript for important intellectual content. All authors have reviewed the submitted version of the manuscript and agree with its content and submission, had access to all relevant study data, vouch for the accuracy and completeness of the data presented, agree to be accountable for all aspects of the work, and will ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict-of-interest disclosure: P.G. received personal fees from Merck & Co., Inc. (during the conduct of the study), as well as personal fees from AbbVie, Adaptive Biotechnologies, Janssen, and Pharmacyclics; grants from GSK and Celgene; and grants and personal fees from Roche and Gilead (outside the submitted work). L.S. received personal fees from Janssen, Gilead, and Roche (outside the submitted work). S.P., K.P., M.D., K.S., and C.M.S. are current employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and hold stock and stock options in the company. N.P. declares no competing financial interests.

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To the editor:

Overall survival among older US adults with ALL remains low despite modest improvement since 1980: SEER analysis

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Over the past 4 decades, outcomes have improved dramatically among pediatric patients with acute lymphoblastic leukemia (ALL), with observed cure rates now >80% in developed countries.[1] This progress can be attributed, in part, to large cooperative group studies, advances in combination chemotherapy, monitoring of minimal residual disease, and use of tyrosine kinase inhibitors (TKIs) for Philadelphia chromosome–positive (Ph^+) ALL. Recent series have reported excellent outcomes among adolescents and younger adults with ALL who have been treated with pediatric-inspired regimens.[2-4] Despite these advances, 5-year overall survival (OS) remains dismal (~20%) among adults age ≥60 years treated at academic centers and on multi-institutional clinical trials by using established first-line regimens.[5,6] European population-based analyses have similarly revealed suboptimal outcomes in this population.[7-10] Emerging novel agents provide substantial antileukemic effect with manageable toxicity and may represent attractive therapeutic strategies for older patients with ALL, either as components of initial therapy or as treatment at relapse.[11-15] There remains a paucity of data reflecting clinical outcomes in older US adults with ALL, particularly outside clinical trials, which provides historical context for evaluating novel approaches. Therefore, we used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to describe secular trends of median OS and long-term clinical outcome over the past 4 decades in US adults age ≥60 years with ALL.

We identified 12 891 patients with ALL from SEER-9 registries by using the International Classification of Diseases for Oncology, third revision (ICD-O-3) codes (http://seer.cancer.gov/siterecode/icdo3_dwhoheme/index.html). Of 1707 patients age ≥60 years diagnosed in 1980 or later, 1675 had known survival time and were included for analysis of characteristics associated with OS. OS was defined as months from diagnosis until death or study cutoff (December 31, 2012).