Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience

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Key Points

- Toxicity was the most common reason for discontinuation of ibrutinib or idelalisib in treated patients with CLL.
- KI-intolerant patients, but less so those with CLL progression, can be successfully treated with an alternate KI.

B-cell receptor kinase inhibitor (KI) therapy represents a paradigm shift in chronic lymphocytic leukemia (CLL) management, but data on practice patterns after KI discontinuation and optimal sequencing are limited. We conducted a multicenter, retrospective, comprehensive analysis on 178 patients with CLL (ibrutinib = 143; idelalisib = 35) who discontinued KI therapy. We examined responses, toxicity, post-KI therapies, and overall survival (OS). Patients had a median of 3 prior therapies (range 0-11); del17p (34%), p53 mutation (27%), del11q (33%), and complex karyotype (29%). Overall response rate (ORR) to first KI was 62% (complete response 14%). The most common reasons for KI discontinuation were toxicity (51%), CLL progression (29%), and Richter transformation (RT) (8%). Median progression-free survival (PFS) and OS from KI initiation were 10.5 and 29 months, respectively. Notably, initial KI choice did not impact PFS or OS; however, RT portended significantly inferior OS ($P = .0007$). One hundred fourteen patients received subsequent salvage therapy following KI discontinuation with an ORR to subsequent KI at 50% and a median PFS of 11.9 months. Median PFS in KI-intolerant patients treated with an alternate KI was not reached vs 7 months for patients with CLL progression. In summary, these data demonstrate that toxicity was the most common reason for KI discontinuation, that patients who discontinue KI due to toxicity can respond to an alternate KI, and that these responses may be durable. This trial was registered at www.clinicaltrials.gov as #NCT02717611 and #NCT02742090. (Blood. 2016;128(18):2199-2205)

Introduction

Inhibition of B-cell receptor signaling represents a paradigm shift in treating chronic lymphocytic leukemia (CLL) where high rates of durable responses have been achieved in relapsed/refractory and in previously untreated disease.1-4 Two kinase inhibitors (KI), ibrutinib and idelalisib, are US Food and Drug Administration approved for the treatment of CLL and are being increasingly prescribed in practice.5,6 The majority of published clinical data on these new KIs are from the initial clinical trials that predominantly enrolled patients with relapsed/refractory CLL. In addition, there are limited data on the optimal sequencing of these novel therapeutics and outcomes for patients who discontinue a KI and are subsequently treated with another KI.

In the absence of clear guidelines and randomized data, the unique toxicity profile for each agent and clinicians’ preference with either compound likely guide which agent is used first.7,8 Furthermore, whether patients who discontinue 1 of these 2 agents derive any therapeutic benefit, if the alternate KI is prescribed, has not been adequately studied. Data from landmark clinical trials suggest a discontinuation rate for ibrutinib or idelalisib as high as 35%. However, patients’ characteristics and treatment approaches following discontinuation have not been reported.9

Given the rapid adoption of ibrutinib and idelalisib into clinical practice, we studied KI discontinuation among a large cohort of patients with CLL treated across US-based centers. We studied reasons for KI...
discontinuation, outcomes after stopping therapy, and the impact that KI sequencing had on outcomes. To our knowledge, this is the largest series of patients with CLL who have received and discontinued ibrutinib- or idelalisib-based therapies.

**Methods**

We conducted a multicenter, retrospective cohort study to describe the characteristics and outcomes of patients with CLL who discontinued ibrutinib- or idelalisib-based therapies between 2013 and 2015. Medical chart review of patients with CLL was performed to identify all patients with CLL at each institution who discontinued ibrutinib- or idelalisib-based therapies. Ten US academic cancer centers participated in this study, which was approved by the institutional review board of each institution, with informed consent in accordance with the Declaration of Helsinki. Additional patients were provided by the Connect CLL Registry. Data points for patients with CLL treated with either ibrutinib- or idelalisib-based therapies were collected, including patients’ demographics, number of prior therapies, clinical and genetic characteristics, KI therapy (indication for therapy, initial dose, combination vs monotherapy, treatment discontinuations, treatment interruptions, best response to KI), and reason for KI discontinuation. Duration of KI exposure was calculated from the start of KI to the time of discontinuation, including interruptions.

Reasons for KI discontinuation were categorized as follows: CLL progression, KI toxicity intolerance, Richter transformation (RT) to diffuse large B-cell lymphoma or to Hodgkin lymphoma, planned cellular therapy (alloimmune hematopoietic stem cell transplantation or chimeric antigen receptor genetically modified T-cell therapy), sudden death, or other.

Progression-free survival (PFS) and overall survival (OS) from the time of first KI initiation were estimated using the Kaplan-Meier method. We stratified outcomes by reasons of discontinuation and KI choice (ibrutinib vs idelalisib). We further described subsequent therapies, response rates, and survival outcomes (PFS and OS), stratified by reason for discontinuation and KI choice. In addition, we performed exploratory analyses to study KI sequencing practices and whether these affected patient outcomes. Disease progression was defined based on the International Workshop on Chronic Lymphocytic Leukemia criteria. PFS was defined as the time in months from the initiation of a therapy to the time of documented CLL progression, transformation, or death. OS was defined as the time in months from the initiation of KI to death (all causes). The log rank (LR) test was used to compare differences between Kaplan-Meier curves. Univariate Cox regression analyses were used to estimate hazard ratios (HR). All other analyses were descriptive. All tests were 2-sided at the 5% level. Statistical analyses were performed using Stata version 10.1 (Stata Statistical Software: Release 10. 2007; StataCorp LP, College Station, TX).

**Results**

**Patients’ characteristics**

We identified 178 patients with CLL who discontinued KI therapy. Of these, 143 discontinued ibrutinib-based and 35 discontinued idelalisib-based therapy. Baseline characteristics for the entire cohort stratified by first KI choice are included in Table 1. Patients generally had high-risk features with a median of 3 prior therapies (range 0-11, 8% untreated) and del17p, p53 mutation, del11q, and complex karyotype (≥3 abnormalities) in 34%, 27%, 32%, and 29% of patients, respectively.

**Response rates**

In the ibrutinib cohort, the reported overall response rate (ORR) was 58% (15% complete response [CR]), 22% stable disease (SD), and 20% progressive disease (PD). In the idelalisib cohort, ORR was 76% (11% CR), SD 12%, and PD 12%. Responses to therapy following KI discontinuation are reported in Table 2. Notably, the ORR was 50% for patients treated with an alternate subsequent KI (ie, ibrutinib → idelalisib and idelalisib → ibrutinib), with an additional 30% of patients...

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**Table 1. Baseline patient characteristics and KI dosing**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result (range)</th>
<th>Ibrutinib as first KI</th>
<th>Idealisib as first KI</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at diagnosis</td>
<td>60 y (33-89)</td>
<td>60 (33-89)</td>
<td>62 (43-79)</td>
<td>178</td>
</tr>
<tr>
<td>Median number prior therapies</td>
<td>3.0 (0-11)</td>
<td>3 (0-11)</td>
<td>2 (0-8)</td>
<td>178</td>
</tr>
<tr>
<td>Elevated LDH at first KI</td>
<td>63%</td>
<td>67%</td>
<td>50%</td>
<td>125</td>
</tr>
<tr>
<td>B symptoms present at first KI</td>
<td>32%</td>
<td>31%</td>
<td>36%</td>
<td>149</td>
</tr>
<tr>
<td>Median WBC at first KI</td>
<td>21 THO/µL (1-549)</td>
<td>21.0 THO/µL (1359)</td>
<td>24.3 THO/µL (2-549)</td>
<td>143</td>
</tr>
<tr>
<td>Median ALC at first KI</td>
<td>18 THO/µL (0.1-359)</td>
<td>18.4 THO/µL (0.1-359)</td>
<td>17.5 THO/µL (0.7-267)</td>
<td>129</td>
</tr>
<tr>
<td>Median Hb at first KI</td>
<td>11.5 g/dL (6-15.8)</td>
<td>11.5 g/dL (6-15.8)</td>
<td>11.2 g/dL (7.9-15.6)</td>
<td>143</td>
</tr>
<tr>
<td>Median Plt at first KI</td>
<td>115 THO/µL (12-368)</td>
<td>116 THO/µL (7-368)</td>
<td>99 THO/µL (15-303)</td>
<td>141</td>
</tr>
<tr>
<td>del17p present (FISH)*</td>
<td>34%</td>
<td>37%</td>
<td>24%</td>
<td>155</td>
</tr>
<tr>
<td>del11q present (FISH)</td>
<td>33%</td>
<td>37%</td>
<td>26%</td>
<td>152</td>
</tr>
<tr>
<td>p53 mutation present</td>
<td>27%</td>
<td>33%</td>
<td>14%</td>
<td>95</td>
</tr>
<tr>
<td>Complex karyotype present (≥3 abnormalities)</td>
<td>29%</td>
<td>33%</td>
<td>18%</td>
<td>128</td>
</tr>
<tr>
<td>IGHV unmutated</td>
<td>69%</td>
<td>70%</td>
<td>69%</td>
<td>49</td>
</tr>
</tbody>
</table>

**ibrutinib/idelalisib dosing information**

| Number (patients) | 143 | 35 |
| Median time from CLL diagnosis to KI start | 84 mo | 81 mo |
| Median time on KI | 5 mo (0.25-41) | 5.5 mo (0.5-38) |
| Median starting dose | 420 mg daily | 150 mg bid |
| Proportion requiring dose modification | 18% (n = 141) | 35% (n = 34) |
| Proportion requiring dose interruption | 43% (n = 96) | 64% (n = 33) |
| KI administered as monotherapy | 85% | 20% |

Where data are available, patients with p53 mutations, 81% are occurring concomitantly with a del17p detected by FISH analysis and 19% are occurring without a concomitant p53 mutation present.
having SD. In Table 2, we further stratified responses by alternate KI choice. With a median time on therapy of 4 months (range 1-11 months), the ORR to idelalisib in patients who failed ibrutinib was 28% with an additional 45% achieving SD. With a median time on therapy of 7.5 months (range 1-20 months), the ORR to idelalisib in patients who failed ibrutinib was 64% with an additional 23% achieving SD. Response rates to chemoimmunotherapy (CIT) (ie, fludarabine- and R-bendamustine-based) and anti-CD20 monoclonal antibody (ofatumumab, obinutuzumab, or rituximab) were 25% and 36%, respectively. Because BCL2-I therapy was administered in the context of clinical research, only “BCL2-I” was captured, as opposed to capturing the names of individual agents such as ABT-199, so as to not report the incomplete results of ongoing clinical trials. We documented significant clinical activity for BCL2-I following KI discontinuation (n = 16 patients, ORR 76%). Responses to alternate KI were also stratified by the reason for discontinuation. In the setting of CLL progression, the ORR to alternate KI was 39.9% (26.6 partial response [PR], 13.3% PR with lymphocytosis, 40% SD), whereas the ORR in the setting of KI intolerance was 56.4% (52.1% PR, 4.3% PR with lymphocytosis, 26% SD).

Toxicities and discontinuation

Available information regarding KI dosing is included in Table 1. The time from CLL diagnosis to KI initiation was similar between both groups (median 84 months, range 1-333 months), as was the median time on KI (median 5 months, range 0.25-41 months). Patients treated with idelalisib required more frequent dose modifications and interruptions compared with ibrutinib. Reasons for dose interruption, duration of interruption, and dose modification were not universally captured. In addition, 85% of patients treated with ibrutinib received monotherapy, whereas 80% of patients treated with idelalisib received it in combination. In terms of initial KI dosing, 30% of subjects initiated idelalisib at 100 mg twice daily while 7% started ibrutinib at 140 mg daily or 4% started ibrutinib at 280 mg daily.

Table 3 lists the 5 most common reasons for KI discontinuation, stratified by KI choice. Treatment-related toxicity, followed by CLL progression, was the most frequent reason for discontinuation of both agents. RT was reported in only 6% and 8% of patients (2 cases of Hodgkin lymphoma, remainder diffuse large B-cell lymphoma), in the idelalisib and ibrutinib groups, respectively. In the setting of toxicity, the most common reason for discontinuing ibrutinib was atrial fibrillation (20%, n = 14), followed by infection (12%, n = 8), and cytopenias (9%, n = 6). The most common toxicity-related reason for discontinuing idelalisib was pneumonitis (33%, n = 6), followed by colitis (28%, n = 6), and rash (17%, n = 3) (supplemental Table 1, available on the Blood Web site). Common terminology criteria for adverse events grading and timing of these events, relative to KI initiation and discontinuation, were not available in this dataset. In addition, management strategies for treatment-related toxicities, such as pneumonitis, colitis, and atrial fibrillation, were not recorded. Toxicities that did not lead to KI discontinuation were not captured.

Outcomes

With a median follow-up of 14 months (range 0.3-51 months), median PFS and OS for the entire cohort (n = 178), from the time of first KI initiation, were 10.5 months and 29 months, respectively (Figure 1). Notably, initial KI choice (ibrutinib vs idelalisib) did not impact PFS (HR 1.2, 95% confidence interval [CI] 0.8-1.8) or OS (HR 0.8, 95% CI 0.4-1.5) (Figure 1B). We further stratified PFS and OS by reason of discontinuation (Figure 2A-B). Patients who discontinued KI for RT had the shortest median PFS (6 months, range 2-25 months), followed by those who discontinued KI due to CLL progression (8 months, range 1-41 months), and KI intolerance (10 months, range 1-40 months) (P = .14, LR test). This pattern was also reflected for OS (Figure 2A), with patients who developed RT experiencing an inferior outcome (P = .0007, LR test).

Patient disposition, stratified by reason for KI discontinuation, and treatment status following discontinuation are depicted in supplemental Figure 1. To date, 64% (114/178) of patients have been treated with a subsequent line of therapy following KI discontinuation, as delineated in Table 4. The most common choice for treatment following KI discontinuation was an alternate KI (39%, 44/114). Sixteen patients were treated with a BCL2-I. Alternate anti-CD20 monoclonal antibodies and CIT combinations were less common treatment choices (supplemental Table 2).

PFS for the combined subset of patients who discontinued KI therapy, and were then treated with a subsequent KI, was estimated to be 11.9 months (Figure 3A). Alternate KI choice (ibrutinib vs idelalisib) did not appear to impact PFS (HR 0.3, 95% CI 0.08-1.2) or OS (HR 0.4, 95% CI 0.08-2.1). We subsequently stratified PFS for patients with CLL treated with an alternate KI by the reason for discontinuation of the first KI. Median PFS in KI-intolerant patients was not reached (range 0.57-20 months), whereas median PFS was 7 months (range 0.76-12 months) in patients with CLL progression on the first KI, and who were subsequently treated with an alternate KI (P = .01, LR test) (Figure 3B).
Discussion

To our knowledge, this is the largest reported series of patients with CLL who discontinued KI therapy due to toxicity, progression, or transformation. Our goal was to gain insight into practice patterns and selection of subsequent therapies for patients following KI discontinuation. We found that alternate KI were the most commonly prescribed therapies following initial KI discontinuation. Notably, we found that alternate KI therapy following initial KI discontinuation could be effective, particularly if the first KI was discontinued due to intolerance. We observed that patients who discontinue KI due to CLL progression achieve less durable responses when treated with an alternate KI. Moreover, outcomes did not appear to differ whether ibrutinib or idelalisib was selected as the first or second KI, suggesting that either sequence is appropriate.

The majority of patients discontinued KI therapy due to toxicity or CLL progression (~80%). RT was a less frequent reason for discontinuation of KI therapy, differing slightly in both frequency and prognosis from previously reported, single-center experiences. The slightly improved outcome of RT patients in our cohort compared with previous reports might be explained by differences in studied patient populations, criteria to define RT, especially in the absence of a confirmatory biopsy, stringency of response criteria, and frequency of response assessments performed in clinical trials compared with routine practice.

Although the rates of KI discontinuations were initially unknown, there is emerging literature to suggest that KI discontinuations are a relatively frequent event. For example, a recent report estimated a cumulative incidence of nonrelapse discontinuation of ibrutinib of 15.6% at 18 months. With the widespread utilization of agents like ibrutinib in clinical practice, the number of patients who discontinue KI therapy due to intolerance, in the setting of responsive disease, is likely to increase, representing an unmet clinical need.

The prognosis, outcomes, and therapeutic options for patients who discontinue KI therapy are not well known. To date, 2 centers have reported on outcomes of patients with CLL participating in clinical trials who discontinued ibrutinib. These series documented poor prognosis, particularly in the subset of patients who develop RT while on ibrutinib (median OS 3.1-3.5 months). Similarly, Martin et al have recently described very poor outcomes for patients with mantle...
cell lymphoma who have discontinued ibrutinib (median time on ibrutinib 4.9 months, median OS 2.9 months).17

Jain et al reported a 26% (33/127) discontinuation rate, with the most common reasons for discontinuation being adverse events/intolerance (42%), CLL progression (21%), and RT (18%).16 The median OS for the entire cohort was 3.1 months, which was largely dominated by the short OS of the RT subset (2.6 months). Maddocks et al reported the experience of 76 patients with CLL (76/308, 24.7% discontinuation rate) who discontinued ibrutinib. The most common reasons for discontinuation were nonrelapse discontinuation (including toxicity/intolerance (59%), RT (24%), and CLL progression (17%).9 With a median follow-up of 20 months, the OS for RT patients was inferior, as compared with patients with CLL progression (3.5 months vs 17.6 months). Data regarding subsequent therapies following CLL progression were not provided.9

Two centers have recently presented data on patients who discontinued ibrutinib treated outside of the context of clinical research.18,19 Sandoval-Sus et al reported outcomes on 22 patients who discontinued ibrutinib, of which 8 discontinued due to toxicity (36%). In this series, the median OS for patients who discontinued ibrutinib due to toxicity was not reached (vs 5.5 months in PD/10.8 months following stem cell transplantation), without data on RT specifically.18 Parikh et al reported outcomes on 23 patients who discontinued commercially prescribed ibrutinib, of which 65% discontinued for a reason other than progression.19 In this series, the cumulative incidence of ibrutinib discontinuation at 12 months was estimated to be 22%. Neither series described subsequent treatment approaches, except for patients who underwent stem cell transplantation.18,19

Outcomes following idelalisib discontinuation are limited. One center reported findings from 38 relapsed/refractory CLL idelalisib-discontinuation patients, demonstrating a median OS of 64 days from the time of discontinuation.20 RT events were rare and occurred in 2% of patients. Barrientos et al suggested that patients who discontinue idelalisib may subsequently respond to ibrutinib.20

Contrary to previous reports of patients treated with ibrutinib as noted above, our findings suggest RT to be an uncommon cause for KI discontinuation. Rather, KI intolerance and progression of CLL without transformation were the 2 major reasons for KI discontinuation. Because patients discontinued KI therapy due to intolerance, analysis of response to subsequent therapies is essential and represents an unmet medical need, and an important area for clinical investigation. Data from next generation KI, such as ACP196 (acalabrutinib; Acerta Pharmaceuticals) and TGR-1202 (TG Therapeutics), suggest these agents may distinguish themselves not only by their clinical activity but more so by their improved toxicity profiles.21-23 In addition, given the recent US Food and Drug Administration approval of venetoclax, there is now availability of an active CLL therapy that exerts its effect in a pathway independent of B-cell receptor signaling.24 Clinical trials of next generation KI, utilizing acalabrutinib (NCT02717611) and TGR-1202 (NCT02742090), are planned specifically for patients who have discontinued a KI due to intolerance.

Although emerging data suggest an increased risk of infection (cytomegalovirus or Pneumocystis carinii pneumonia) for patients treated with idelalisib, particularly in the front-line setting and/or in combination with bendamustine, in our series infection was only noted in 6% of idelalisib patients as a reason for discontinuation. Survival was not different between the ibrutinib- and idelalisib-treated patients in our cohort. However, it should be highlighted that most of the patients in the current series were treated in the relapsed/refractory setting, whereas increased risk of infection with idelalisib/autoimmune toxicities was particularly observed in younger patients, and those treated in the frontline setting.

Understanding the mechanisms of KI resistance is an active area of scientific investigation. Using whole exome sequencing, Woyach et al have identified a point mutation resulting in a cysteine to serine (C481S)
change, affecting ibrutinib-BTK binding and gain of function mutations in PLCγ2 (R665W, L845F) as causes of ibrutinib resistance.25 Subsequent larger series have confirmed these findings.5,6 Analogous data describing resistance mechanisms for idelalisib are not available. In our series, responses to an alternate KI in the setting of CLL progression were obtained following KI discontinuation, although PFS was considerably shorter in this group as compared with those with KI intolerance. These data suggest more definitive therapies, such as clinical trials examining novel agents, cellular therapies, stem cell transplantation, and BCL-2 inhibition with venetoclax, should be considered over switching to an alternate KI in the setting of CLL progression.24,26

The optimal patient selection, and sequence of ibrutinib and idelalisib therapy, remains a challenging clinical question. The decision to initiate ibrutinib or idelalisib, particularly in the relapsed setting, is somewhat arbitrary and may be guided by physicians’ preference, the patient’s medical history, and potential toxicities associated with either agent. As we did not detect a difference in outcomes based on KI sequencing, we suggest that either class of agent is a reasonable initial agent. As we did not detect a difference in outcomes based on KI

Altogether, our data provide a comprehensive analysis on the largest cohort of KI-treated patients who discontinued therapy. We show that many patients who discontinued ibrutinib responded subsequently to idelalisib and vice versa. Furthermore, RT rates were lower than previously described, but the prognosis of RT patients was poor relative to patients with CLL progression or KI intolerance. Because the number of patients who discontinue KI due to toxicity or disease progression within the first 1 to 2 years of initiating therapy is not trivial, understanding the extent of KI toxicity/disease progression, and how these patients can be subsequently treated, is a critical area of research.

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Authorship
Contribution: A.R.M., C.N., and A.M.E. designed research, performed research, analyzed data, and wrote the paper; P.M.B., C.S.U., B.T.H., N.L., A.P.S., C.H., J.J.P., A.R.S., L.E.S., A.V., D.M.F., C.S.Z., T.F., A.G., D.F.C., J.S., S.D.N., D.P., D.J.L., S.J.S., and B.D.C. performed research, analyzed data, and wrote the paper; P.M.B., C.S.U., B.T.H., N.L., A.P.S., C.H., J.J.P., A.R.S., L.E.S., A.V., D.M.F., C.S.Z., T.F., A.G., D.F.C., J.S., S.D.N., D.P., D.J.L., S.J.S., and B.D.C. performed research and wrote/edited the paper; S.H.B. and G.K. performed research; and P.K. performed research and analyzed data. Conflict-of-interest disclosure: A.R.M. received research funding and consultancy fees from Gilead and AbbVie Pharmacys; research funding from Pronai Pharmaceuticals, TG Therapeutics, and Acerta; and consultancy fees from Janssen and Celgene Corporation. C.N. received research funding and Honoraria from Celgene Corporation. P.M.B. received research funding and consultancy fees from Pharmacycics LLC, an AbbVie Company; and consultancy fees from Abbvie and Gilead. C.S.U. maintained membership on an entity’s Board of Directors or advisory committees for Genentech. B.T.H. received Honoraria from and maintained membership on an entity’s Board of Directors or advisory committees for Janssen, Seattle Genetics, and Celgene; and received consultancy fees from Pfizer. N.L. maintained membership on an entity’s Board of

Figure 3. PFS for alternate KI. (A) PFS from start of alternate KI (ibrutinib → idelalisib, idelalisib→ ibrutinib). (B) PFS from start of alternate KI stratified by reason for discontinuation (CLL progression vs KI intolerance).
Directors or advisory committees for and received research funding from Gilead. A.P.S. received Honoraria from and is on the Speakers Bureau for Genentech and Gilead Sciences; and maintained membership on an entity’s Board of Directors or advisory committees for and received Honoraria from Pharmacies. C.H. is on the Speakers Bureau for Genentech. J.J.P. received research funding from Merck, Cyclacel, Medimmune, Ambit, and Astellas; and consultancy fees from Bristol-Myers Squibb (BMS). C.S.Z. received research funding from Genzyme-Sanoﬁ, Biothera, GlaxoSmithKline, and Novartis. T.F. is on the Speakers Bureau and received Honoraria from Celgene, Pharmacyclics/Johnson & Johnson, and Seattle Genetics. A.G. received research funding from Allos, Biogen Idec, Celgene, Genentech, and Millennium; is on the Speakers Bureau for Gilead; and received research funding and consulting fees from and is on the Speakers Bureau for Gilead. D.F.C. received research funding from Cyclacel, Merck, Astellas, Ambit, and Medimmune; and consultancy fees from BMS. J.S. received research funding from Celgene, Celdlex, Immunomedics, and Seattle Genetics. S.D.N. received research funding from BMS and Millennium. D.P. received spouse employment with Genentech; research funding from Novartis; and IP interest licensed to Novartis by the University of Pennsylvania. S.J.S. maintained membership on an entity’s Board of Directors or advisory committees for Nordic Nanovector; received research funding from Janssen, Novartis, Gilead, and Hoffman-LaRoche; received consultancy fees from Genentech; and received research funding and consultancy fees from Celgene and Pharmacies. B.D.C. received research funding and consultancy fees from Celgene, Pharmacies, Gilead, Roche-Genentech, and Seattle Genetics; consultancy fees from Astellas; and research funding from Acerta. The remaining authors declare no competing financial interests.

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References


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