Ibrutinib, lenalidomide, and rituximab in relapsed or refractory mantle cell lymphoma (PHILEMON): a multicentre, open-label, single-arm, phase 2 trial


Summary

Background Regimens based on ibrutinib alone and lenalidomide and rituximab in combination show high activity in patients with relapsed or refractory mantle cell lymphoma. We hypothesised that the combination of all three drugs would improve efficacy compared with previously published data on either regimen alone.

Methods In this multicentre, open-label, single-arm, phase 2 trial, we enrolled patients aged 18 years or older with relapsed or refractory mantle cell lymphoma who had previously been treated with at least one rituximab-containing regimen, an Eastern Cooperative Oncology Group performance status score of 0–3, and at least one site of measurable disease, and who met criteria for several laboratory-assessed parameters. Treatment was divided into an induction phase of 12 cycles of 28 days with all three drugs and a maintenance phase with ibrutinib and rituximab only (cycle duration 56 days), given until disease progression or unacceptable toxicity. In the induction phase, patients received intravenous (375 mg/m²) or subcutaneous (1400 mg) rituximab once a week during cycle 1 and then once every 8 weeks. Oral ibrutinib (560 mg once a day) was given to patients every day in the cycle, whereas oral lenalidomide (15 mg once a day) was given on days 1–21. The primary endpoint was overall response assessed in the intention-to-treat population according to Lugano criteria. Safety analysis included all patients who received the treatment, irrespective of eligibility or duration of treatment. The trial is ongoing, but is no longer accruing patients, and is registered with ClinicalTrials.gov, number NCT02460276.

Findings Between April 30, 2015, and June 1, 2016, we enrolled 50 patients with relapsed or refractory mantle cell lymphoma at ten centres in Sweden, Finland, Norway, and Denmark. At a median follow-up of 17-8 months (IQR 14·7–20·9), 38 (76%, 95% CI 63–86) patients had an overall response, including 28 (56%, 42–69) patients who had a complete response and ten (20%, 11–33) who had a partial response. The most common grade 3–4 adverse events were neutropenia (in 19 [38%] of 50 patients), infections (in 11 [22%] patients), and cutaneous toxicity (in seven [14%] patients). There were three treatment-related deaths during the study, two due to sepsis and one due to embolic stroke.

Interpretation Our results provide preliminary evidence that the triplet combination of ibrutinib, lenalidomide, and rituximab is an active regimen in patients with relapsed or refractory mantle cell lymphoma, and should be evaluated in a prospective randomised controlled trial.

Funding Janssen and Celgene.

Introduction Relapsed or refractory mantle cell lymphoma is associated with poor outcomes. The choice of therapy depends on the efficacy of previous lines of treatment.1 In many cases of disease progression, a non-cross-resistant chemotherapy regimen is the next choice, usually in combination with the anti-CD20 antibody rituximab. In patients with chemorefractory disease or early relapse, non-chemotherapeutic alternatives might be considered. Among such drugs active in relapsed or refractory mantle cell lymphoma are bortezomib, temsirolimus, lenalidomide, ibrutinib, and venetoclax.1,4 Lenalidomide is an immunomodulatory drug with antiangiogenic and antineoplastic properties. In B-cell malignancies, lenalidomide interacts with the ubiquitin E3 ligase cereblon and enhances its enzymatic activity to degrade the transcription factors IKZF1 (DNA-binding protein Ikaros) and IKZF3 (zinc finger protein Atiolos), leading to reduced activity of IRF4 (interferon regulatory factor 4), a downstream target of cereblon. This downregulation of IRF4 leads to proliferation and activation of natural killer cells, thereby enhancing natural killer cell-mediated cytotoxicity and antibody-dependent cellular cytotoxicity.7 In this respect, lenalidomide acts as an immunosensitiser, enhancing the activity of rituximab. The combination of rituximab and lenalidomide has been shown to be active in mantle cell lymphoma, in both relapsed and front-line settings.8,9

The introduction of ibrutinib, an inhibitor of Bruton’s tyrosine kinase, was considered a major step forward in the treatment of mantle cell lymphoma. Its activity is substantially higher than other single drugs used in the...
Research in context

Evidence before this study
We searched PubMed without language restrictions for clinical trials published up to Dec 5, 2013, using the search term “ibrutinib, rituximab, and lenalidomide”. We also searched the EU Clinical Trials Register and ClinicalTrials.gov using the same search term. We found no trials examining the combination of these drugs in the treatment of mantle cell lymphoma. At the annual meeting of the American Society of Hematology in December, 2015, Ujjani and colleagues presented the results of a phase 1 trial of lenalidomide, rituximab, and ibrutinib in previously untreated patients with follicular lymphoma. They found no clear benefit for the triplet regimen over the combination of rituximab and lenalidomide in terms of efficacy, but a high incidence of grade 3 cutaneous toxicity (36%).

Added value of this study
To the best of our knowledge, this study is the first to assess the non-chemotherapeutic combination of lenalidomide, rituximab, and ibrutinib in patients with relapsed or refractory mantle cell lymphoma. Compared with previous studies of ibrutinib alone or in combination with rituximab, the triplet regimen was associated with increased haematological toxicity and infections, but also appeared to be more active in terms of complete responses. The effect of specific mutations and copy-number alterations has not previously been investigated in a prospective clinical trial of a non-chemotherapy regimen for mantle cell lymphoma. We showed that the combination of lenalidomide, rituximab, and ibrutinib might overcome the adverse prognostic effects of TP53 mutations and CDKN2A-TP53 deletions. Additionally, evaluation of minimal residual disease in bone marrow and peripheral blood with real-time PCR has not previously been reported in a trial of a non-chemotherapeutic regimen for mantle cell lymphoma. We found that a molecular remission could be obtained in a high proportion of patients, including in those with TP53 mutation.

Implications of all the available evidence
Our findings indicate that the combination of lenalidomide, rituximab, and ibrutinib might be an active regimen in patients with relapsed or refractory mantle cell lymphoma, particularly in the subset of patients with high-risk genetic features, such as TP53 mutations or combined deletions of TP53 and CDKN2A. For this subset of patients, the triplet regimen might be used as a bridge to allogeneic stem-cell transplantation.

Methods
Study design and participants
We did an open-label, single-arm, multicentre, phase 2 trial at ten centres in Sweden, Finland, Norway, and Denmark (appendix p 8). Eligible patients were older than 18 years; had previously been treated with at least one rituximab-containing regimen, with no upper limit on the number of previous treatments received; and had histologically confirmed mantle cell lymphoma, an Eastern Cooperative Oncology Group performance status score of 0–3, at least one site of measurable disease (>1.5 cm long axis), an absolute neutrophil count of 1000 cells per μL or higher, a platelet count of 100 000 per μL or higher (or ≥50 000 per μL in cases of bone marrow involvement), alanine aminotransferase and aspartate aminotransferase levels three times lower than the upper limit of normal, and serum creatinine concentrations no greater than two times the upper limit of normal. A washout period of 3 weeks since previous therapy was required. Key exclusion criteria included known CNS involvement, HIV infection, active hepatitis B or C virus infection, stroke or intracranial haemorrhage (within 6 months before enrolment), need for anticoagulation with warfarin (or equivalent vitamin K antagonist), or treatment with strong or moderate CYP3A (cytochrome P450 3A4) inhibitors. Previous treatment with ibrutinib or lenalidomide was allowed.

The study was approved by the national ethics committee in each country and done according to the Declaration of Helsinki and International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent.

Procedures
At the time of initiation of this study, a phase 1 trial of the combination of ibrutinib, rituximab, and lenalidomide in patients with follicular lymphoma was ongoing. We selected doses of lenalidomide and ibrutinib on the basis of this previous trial. Treatment was divided into an induction phase of 12 cycles of 28 days with all three drugs and a maintenance phase with ibrutinib and rituximab only (cycle duration 56 days), given until disease progression or unacceptable toxicity. Patients received rituximab once a week for 4 weeks during cycle 1, then every 8 weeks. The initial dose of rituximab
was given intravenously at 375 mg/m²; subsequent doses could then either be given intravenously at the same dose or as a subcutaneous injection of 1400 mg to remove the need for intravenous access. No dose reductions were permitted for rituximab. Ibrutinib was given orally (560 mg once a day) on days 1–28, and lenalidomide was given orally (15 mg once a day) on days 1–21. Doses of lenalidomide and ibrutinib were reduced in cases of grade 3 or 4 neutropenia and thrombocytopenia. In such cases, ibrutinib was reduced from 560 mg per day to 420 mg per day and then to 280 mg per day; lenalidomide was reduced from 15 mg per day to 10 mg per day and then to 5 mg per day.

Study treatment was terminated in cases of progressive disease or grade 4 non-haematological toxicity, if requested by a patient, or if the treating physician thought a change of therapy would be in the best interest of the patient.

To assess minimal residual disease at baseline, DNA was extracted from lymphoma cells in bone marrow with the QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany) and used for design of primers for PCR amplification of patient-specific clonally rearranged immunoglobulin heavy chain genes (IGH) and detection of the CCND1-IGH translocation t(11;14). PCR was done with the TaqMan Gene Expression Master Mix (Thermo Fisher Scientific, Waltham, MA, USA). The sensitivity of the assay for minimal residual disease was one in 10⁵ cells, except for four patients in whom the sensitivity of the assay was one in 10⁴ cells. For patients with less than 1% tumour cells in bone marrow at baseline, a quantitative assay for minimal residual disease was not feasible and, instead, a qualitative nested PCR assay was done, as previously described.16

For genetic analyses, we did next-generation sequencing using Ion Torrent technology (ThermoFisher Scientific, Waltham, MA, USA) to analyse DNA from bone marrow specimens taken at baseline for mutations in selected coding regions, splice sites, and untranslated regions of ATM, KMT2D, CCND1, TP53, WHSC1, BIRC3, NOTCH1, and NOTCH2, as described previously.17 The cutoff for calling a variant was 5% in general and 3% for TP53 mutations. Median coverage for all runs was 2575×, and the limit for calling a variant was 400×. Chromosome 17p13 (TP53) and chromosome 9p21 (CDKN2A) deletions were identified by droplet digital PCR with the QX200 system (Bio-Rad Laboratories, Hercules, CA, USA), as described previously.18 Copy number loss was defined as copy number less than 1·95. Each sample was analysed at least twice and deletions were called with QuantaSoft software version 1·7 (Bio-Rad Laboratories, Hercules, CA, USA). The people who did the genetic analyses were masked to patient characteristics and outcomes.

**Outcomes**

The primary endpoint was overall response assessed according to Lugano criteria,7 with restaging every 12 weeks during the induction phase according to results of CT and bone marrow examination. PET scans were done to confirm complete responses or at the time of maximal tumour regression. During the maintenance phase, CT and bone marrow examination were done every 6 months. Evaluation of CT and PET scans was done at the individual study centres.

Secondary endpoints included proportion of patients who achieved a complete response (assessed with and without PET), response duration (time from date of response to date of disease progression or death), proportion of patients who achieved molecular remission, molecular remission duration (time from date of molecular remission to date of molecular relapse or death), progression-free survival (time from enrolment to date of disease progression, death from any cause, or last available follow-up), and overall survival (time from enrolment to date of death or last available follow-up). In a post-hoc analysis, factors predictive of progression-free and overall survival were evaluated. Safety was also a secondary endpoint, assessed with adverse event monitoring and laboratory analyses. Adverse events were assessed according to the Common Toxicity Criteria for Adverse Events, version 4·03. We also investigated the presence of biomarkers, including specific mutations and chromosomal deletions. Health-related quality of life was assessed with the European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire, although the results of this analysis will be reported elsewhere. Minimal residual disease in blood and bone marrow specimens after cycles 6, 12, 18, and 24 using real-time PCR, according to EuroMRD criteria, was also assessed as a secondary endpoint.19 Genetic analyses were exploratory.

**Statistical analysis**

According to Fleming’s single-stage procedure (type I error α of 0·05 and power of 0·8), to achieve an overall response in more than 85% of patients (chosen to be superior to the 75 [68%] of 111 patients who had an overall response in a previous phase 2 trial of ibrutinib alone; p<0·05), 40 patients would need to be recruited. If 34 or more patients had a response, the null hypothesis could be rejected. The primary analysis was done by intention to treat. The safety analysis included all patients who received the treatment, irrespective of eligibility or duration of treatment. To account for loss of 20% of patients because of ineligibility and early progression, a total sample size of 50 patients was required.

Descriptive statistics were used to summarise patient demographics and baseline characteristics. We used the Kaplan-Meier method to estimate progression-free survival and overall survival. Univariate and multivariate analyses were done with the Cox proportional-hazards regression model. All statistical analyses were done with IBM SPSS version 22·0. This trial is registered with ClinicalTrials.gov, number NCT02460276.
Role of the funding source
The funders were not involved in the protocol writing, data collection, data analysis, data interpretation, or writing of the report, but did review the manuscript before submission. All authors had full access to the raw data and approved the final submitted version. The corresponding author had the final decision to submit for publication.

Results
Between April 30, 2015, and June 1, 2016, we enrolled 50 patients with relapsed or refractory mantle cell lymphoma from ten centres in Sweden, Finland, Norway, and Denmark (figure 1). Table 1 shows the patients’ characteristics at baseline. 44 (88%) of 50 patients were evaluable for response with Lugano criteria. Six patients were not evaluable because of withdrawn consent (n=3) or discontinuation of treatment because of treatment-related toxic effects, including sepsis (n=2) and fatigue (n=1), before response evaluation.

At a median follow-up of 17·8 months (IQR 14·7–20·9), 38 (76%, 95% CI 63–86) of 50 patients had an overall response (table 2). 28 (56%, 42–69) patients had a complete response and ten (20%, 11–33) had a partial response (table 2). Of the 27 patients in whom PET was done for response evaluation, 21 (78%) had a complete response, five (19%) had a partial response, and one (4%) had stable disease.

Median progression-free survival was 16·0 months (95% CI 13·7–20·5) and median overall survival was 22·0 months (19·5–23·8; figure 2); 12-month progression-free survival was 56·9% (95% CI 42·7–71·1) and 12-month overall survival was 77·6% (65·6–89·6). Overall median duration of response was not reached (95% CI not calculable). The 28 patients who achieved a complete response had a longer median duration of response (not reached [95% CI not calculable]) than the ten patients who achieved a partial response (8·9 months [95% CI 6·3–13·8]). Four patients who had disease progression on ibrutinib were included, of whom one achieved a partial response (which is still ongoing after 13 months), one had stable disease, and two progressed early on study treatment. None of the eight patients with a low-risk score in the Mantle Cell Lymphoma International Prognostic Index (MIPI) progressed during the study. In an exploratory post-hoc analysis, MIPI score was the only factor predictive of outcome, in terms of progression-free survival (appendix p 9).

49 (98%) of 50 patients were evaluable for genetic aberrations associated with mantle cell lymphoma. We found no difference in overall response between patients with and without TP53 mutations (eight [73%, 95% CI 39–94] of 11 patients with mutations, including seven [64%, 31–89] with a complete response, vs 30 [79%, 63–90] of 38 patients without mutations, including 21 [55%, 38–71] with a complete response; table 2). Although patients with TP53 mutations appear to have longer progression-free survival, there was no difference in progression-free survival according to the univariate analysis (hazard ratio [HR] 2·0, 95% CI 0·81–4·8, p=0·11; appendix pp 1, 9), even after adjusting for MIPI score, sex, and deletion of CDKN2A and TP53 in the multivariate analysis (2·6, 0·57–11·0, p=0·22; appendix p 9). 14 patients presented with deletion of both CDKN2A and TP53, 12 (86%) of whom responded to treatment. The presence of a deletion in both CDKN2A and TP53 had no effect on progression-free or overall survival (appendix pp 2, 9). Similarly, we found no association between any other specific genetic abnormality and outcome (data not shown).

Table 1: Patient and disease characteristics

<table>
<thead>
<tr>
<th>All patients (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>ECOG performance status score 0–1</td>
</tr>
<tr>
<td>MIPI score</td>
</tr>
<tr>
<td>Low risk (&lt;5·7)</td>
</tr>
<tr>
<td>Intermediate risk (5·7–6·1)</td>
</tr>
<tr>
<td>High risk (&gt;6·2)</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>Ann Arbor stage IV disease</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
</tr>
<tr>
<td>Refractory disease</td>
</tr>
<tr>
<td>Number of previous therapies</td>
</tr>
<tr>
<td>Previous therapy</td>
</tr>
<tr>
<td>Autologous stem-cell transplantation</td>
</tr>
<tr>
<td>Allogeneic stem-cell transplantation</td>
</tr>
<tr>
<td>Ibrutinib</td>
</tr>
<tr>
<td>Lenalidomide</td>
</tr>
</tbody>
</table>

Data are n (%) or median (range). ECOG=Eastern Cooperative Oncology Group. MIPI=Mantle Cell Lymphoma International Prognostic Index.
Of 49 patients with available DNA, 22 (45%) harbourled at least one mutation in genes commonly mutated in mantle cell lymphoma (figure 3). The most common mutations were found in TP53 (in 11 [22%] patients), ATM (in eight [16%] patients), and KMT2D (in seven [14%] patients). Detailed information about the detected mutations can be found in the appendix (pp 6,7).

CDKN2A deletions were detected in 28 (58%) of 48 evaluable patients and TP53 deletions in 17 (35%) of 49 evaluable patients (figure 3). 14 (29%) of 48 patients presented with both deletions.

After 6 months, 28 (56%) of 50 patients were evaluable for minimal residual disease. 22 patients were not evaluable because follow-up samples were not available because of early progression or withdrawal (n=11), no lymphoma cells were detectable in bone marrow (n=7), or no clonal marker could be identified (n=4; figure 1). Primers for IGH rearrangements were used in all cases, and in seven patients with the t(11;14) translocation, primers to the CCND1-IGH rearrangement were used. Eight patients with less than 1% tumour cells in bone marrow at baseline were assessed for molecular remission with qualitative nested PCR. At 6 months, 15 (56%) of 27 patients had molecular remission in peripheral blood and 12 (43%) had molecular remission in bone marrow. 13 (68%) of 19 patients had molecular remission in bone marrow at 12 months (table 3). The median duration of molecular remission was 3 months (IQR 3–9).

Patients who were negative for minimal residual disease in peripheral blood at 6 months had longer progression-free survival (median not reached [95% CI not calculable]) than patients who were positive for minimal residual disease in peripheral blood at 6 months (10·3 months [95% CI 5·6–15·0]; HR 0·14, 95% CI 0·03–0·71; p=0·017; appendix p 3). The estimated 24-month progression-free survival for patients with molecular remission at 6 months was 82% (95% CI 69–96) compared with 42% (13–70) for patients not achieving molecular remission at 6 months. Furthermore, molecular remission in peripheral blood at 6 months was associated with longer overall survival (median not reached [95% CI not calculable]) vs 20·0 months (9·8–31·0) for people who had not achieved molecular remission in peripheral blood at 6 months; HR 0·17, 95% CI 0·03–0·95; p=0·043; the estimated 24-month overall survival for these patients was 67% (95% CI 36–97), compared with 44% (16–72) for patients positive for minimal residual disease at 6 months (appendix p 4). Among four patients with TP53 mutation who were evaluable at 12 months, two were negative for minimal residual disease in bone marrow. All patients in molecular remission were in complete remission, based on Lugano criteria.

At a median follow-up of 17·8 months (IQR 14·7–20·9), treatment was discontinued in 34 (68%) of 50 patients because of progressive disease (in 17 [34%] patients), adverse events led to dose reduction of lenalidomide in

| Table 2: Maximal responses to treatment in all patients and according to presence of TP53 mutation |

<table>
<thead>
<tr>
<th>Overall response</th>
<th>TP53 unmutated (n=28)</th>
<th>TP53 mutated (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>28 (56%, 42–69)</td>
<td>21 (55%, 40–70)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>10 (20%, 11–33)</td>
<td>9 (24%, 13–39)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1 (2%, 0–1)</td>
<td>1 (3%, 0–14)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5 (10%, 4–21)</td>
<td>3 (8%, 3–21)</td>
</tr>
<tr>
<td>Not evaluable*</td>
<td>6 (12%, 6–24)</td>
<td>4 (11%, 4–24)</td>
</tr>
</tbody>
</table>

Data are n (%). *Six patients were not evaluable because of withdrawal of consent (n=3) or treatment discontinution because of treatment-related toxicity before response evaluation (n=3). One patient was not evaluable for TP53 mutation status for technical reasons.

Figure 2: Progression-free survival (A) and overall survival (B)
five (10%) of 50 patients and of ibrutinib in two (4%) patients.

The most common grade 1–2 non-haematological adverse events are reported in table 4. Gastrointestinal toxicity generally occurred in the early phase of treatment, with a median duration of 2 months (IQR 1–3). One patient developed an intracerebral haematoma after 12 months of treatment, leading to termination of ibrutinib; the patient recovered without residual symptoms and is still on maintenance treatment with rituximab. Atrial fibrillation was reported in four (8%) of 50 patients (one was grade 3). The most common grade 3–4 non-haematological adverse events (occurring in >10% of patients) were gastrointestinal toxicity (in six [12%] of 50 patients), infections (in 11 [22%] patients), and cutaneous toxicity (in seven [14%] patients; all grade 3). One patient developed Guillain-Barré syndrome, requiring ventilator support for 3.5 months.

Grade 3–4 haematological adverse events included neutropenia in 19 (38%) patients, thrombocytopenia in six (12%) patients, and anaemia in one (2%) patient.

Discussion

In this study, we showed that the triplet regimen of ibrutinib, rituximab, and lenalidomide was an active combination in patients with relapsed or refractory mantle cell lymphoma. 76% (95% CI 63–86) of patients had an overall response; however, the lower bound of the 95% CI did not exceed the 68% (58–76) overall response with ibrutinib alone in a previous study, suggesting that the triplet regimen might not be superior to ibrutinib alone, although such cross-trial comparisons should be made with caution. In 2016, Wang and colleagues presented data on the combination of ibrutinib and rituximab in a patient population that was similar to our population. The proportion of patients who achieved an overall response in that trial was slightly higher than that in this study (88% vs 76%), although similar when we excluded the six patients who either withdrew informed consent or dropped out because of early toxicity in this study (88% vs 86%). The population in the study by Wang and colleagues was different to our population in terms of the proportion of patients with a low-risk MIPI score (44% in the study by Wang and colleagues vs 16% in our trial) and the proportion of patients with refractory disease (70% in the study by Wang and colleagues vs 16% in our trial).

Addition of lenalidomide to ibrutinib and rituximab might increase the proportion of patients who have complete remission, which was 56% in this study. Previous studies reported complete responses in 44% of patients on ibrutinib and rituximab, in 36% of patients on rituximab and lenalidomide, and in 19% of patients on ibrutinib alone. However, 12-month progression-free
In conclusion, we showed that the combination of ibrutinib, lenalidomide, and rituximab was an active regimen in patients with relapsed or refractory mantle cell lymphoma, with high proportions of complete and molecular responses. However, our data did not support that the triplet regimen is superior to the combination of ibrutinib and rituximab alone in these patients. Unlike chemotherapy-based regimens, this novel triplet combination seemed to overcome the negative prognostic effects of TP53 mutations and CDKN2A-TP53 deletions.

Contributors
MJ, MH, RR, KFW, HK, AL, CHG, and AK designed the trial and wrote the study protocol. CWE, CD, and KG did the sequencing and copy number analyses. LBP and CUN did the minimal residual disease assessment. HT was responsible for trial coordination and data management. All authors had access to the raw data, contributed to the writing of the manuscript, and approved the final version for submission.
Declaration of interests
MJ reports grants and non-financial support from Janssen and Celgene, during the conduct of the study, and grants and non-financial support from AbbVie, grants, personal fees, and non-financial support from Gilead, and personal fees from Janssen, outside the submitted work.
MH reports grants, personal fees, and non-financial support from Janssen, Celgene, Takeda, and Genentech, outside the submitted work.
CUN reports grants from Novo Nordisk Foundation, grants and personal fees from AbbVie, and personal fees from Gilead and Janssen, outside the submitted work.
CHG reports personal fees from Janssen, outside the submitted work.
AK reports grants and personal fees from Nordic Nanovector and grants from Roche and Merckx, outside the submitted work. All other authors declare no competing interests.

References


21 Sagiv-Barfi I, Kohrt HE, Czerwinski DK, Ng PP, Chang BY, Levy R. Therapeutic antitumor immunity by checkpoint blockade is enhanced by ibrutinib, an inhibitor of both BTK and ITK. Proc Natl Acad Sci U S A 2015; 112: E966–72.

