



**HAL**  
open science

## Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma

Michael Wang, Simon Rule, Pier Luigi Zinzani, Andre Goy, Olivier Casasnovas, Stephen D. Smith, Gandhi Damaj, Jeanette K. Doorduijn, Thierry Lamy, Franck Morschhauser, et al.

► **To cite this version:**

Michael Wang, Simon Rule, Pier Luigi Zinzani, Andre Goy, Olivier Casasnovas, et al.. Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma. *Leukemia*, 2019, *Leukemia*, 33, pp.2762-2766. 10.1038/s41375-019-0575-9 . hal-03562576

**HAL Id: hal-03562576**

**<https://hal.univ-lille.fr/hal-03562576>**

Submitted on 9 Feb 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution| 4.0 International License

8. Fernandez-Mercado M, Pellagatti A, Di Genua C, Larrayoz MJ, Winkelmann N, Aranaz P, et al. Mutations in SETBP1 are recurrent in myelodysplastic syndromes and often coexist with cytogenetic markers associated with disease progression. *Br J Haematol.* 2013;163:235–9.
9. Nguyen N, Vishwakarma BA, Oakley K, Han Y, Przychodzen B, Maciejewski JP, et al. Myb expression is critical for myeloid leukemia development induced by Setbp1 activation. *Oncotarget.* 2016;7:86300–12.
10. Fukuda M, Asano S, Nakamura T, Adachi M, Yoshida M, Yanagida M, et al. CRM1 is responsible for intracellular transport mediated by the nuclear export signal. *Nature.* 1997;390:308–11.
11. Ossareh-Nazari B, Bachelier F, Dargemont C. Evidence for a role of CRM1 in signal-mediated nuclear protein export. *Science.* 1997;278:141–4.
12. Hutten S, Kehlenbach RH. CRM1-mediated nuclear export: to the pore and beyond. *Trends Cell Biol.* 2007;17:193–201.
13. Conway AE, Haldeman JM, Wechsler DS, Lavau CP. A critical role for CRM1 in regulating HOXA gene transcription in CALM-AF10 leukemias. *Leukemia.* 2015;29:423–32.
14. Oka M, Mura S, Yamada K, Sangel P, Hirata S, Maehara K, et al. Chromatin-prebound Crm1 recruits Nup98-HoxA9 fusion to induce aberrant expression of Hox cluster genes. *Elife.* 2016;5:e09540.
15. Kosugi S, Hasebe M, Tomita M, Yanagawa H. Nuclear export signal consensus sequences defined using a localization-based yeast selection system. *Traffic.* 2008;9:2053–62.

*Leukemia* (2019) 33:2762–2766

<https://doi.org/10.1038/s41375-019-0575-9>

## Lymphoma

# Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma

Michael Wang<sup>1</sup> · Simon Rule<sup>2</sup> · Pier Luigi Zinzani<sup>3</sup> · Andre Goy<sup>4</sup> · Olivier Casasnovas<sup>5</sup> · Stephen D. Smith<sup>6</sup> · Gandhi Damaj<sup>7</sup> · Jeanette K. Doorduijn<sup>8</sup> · Thierry Lamy<sup>9</sup> · Franck Morschhauser<sup>10</sup> · Carlos Panizo<sup>11</sup> · Bijal Shah<sup>12</sup> · Andrew Davies<sup>13</sup> · Richard Eek<sup>14</sup> · Jehan Dupuis<sup>15</sup> · Eric Jacobsen<sup>16</sup> · Arnon P. Kater<sup>17</sup> · Steven Le Gouill<sup>18</sup> · Lucie Oberic<sup>19</sup> · Tadeusz Robak<sup>20</sup> · Preetesh Jain<sup>1</sup> · Melanie M. Frigault<sup>21</sup> · Raquel Izumi<sup>21</sup> · Dorothy Nguyen<sup>21</sup> · Priti Patel<sup>21</sup> · Ming Yin<sup>21</sup> · Monika Długosz-Danecka<sup>22</sup>

Received: 5 April 2019 / Revised: 17 June 2019 / Accepted: 19 July 2019 / Published online: 26 September 2019

© The Author(s) 2019. This article is published with open access

**Supplementary information** The online version of this article (<https://doi.org/10.1038/s41375-019-0575-9>) contains supplementary material, which is available to authorized users.

✉ Michael Wang  
miwang@mdanderson.org

<sup>1</sup> MD Anderson Cancer Center, University of Texas, Houston, TX, USA

<sup>2</sup> Plymouth University Medical School, Plymouth, UK

<sup>3</sup> Institute of Hematology “Seràgnoli”, University of Bologna, Bologna, Italy

<sup>4</sup> John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA

<sup>5</sup> CHU Dijon - Hôpital d’Enfants, Dijon, France

<sup>6</sup> Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA

<sup>7</sup> Institut d’Hématologie de Basse-Normandie, Caen, France

<sup>8</sup> Erasmus MC, HOVON Lunenburg Lymphoma Phase I/II Consortium, Rotterdam, Netherlands

<sup>9</sup> CHU de Rennes, Rennes, France

<sup>10</sup> Univ. Lille, CHU Lille, EA 7365—GRITA—Groupe de Recherche sur les Formes Injectables et les Technologies Associées, F-59000 Lille, France

<sup>11</sup> Clínica Universidad de Navarra, Pamplona, Spain

<sup>12</sup> Moffitt Cancer Center, Tampa, FL, USA

<sup>13</sup> Cancer Research UK Centre, University of Southampton Faculty of Medicine, Southampton, UK

<sup>14</sup> Border Medical Oncology, Albury, Victoria, Australia

<sup>15</sup> Unité Hémopathies Lymphoïdes, AP-HP Hôpital Henri Mondor, Créteil, France

<sup>16</sup> Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

<sup>17</sup> Cancer Center Amsterdam, Amsterdam University Medical Centers, University of Amsterdam, HOVON Lunenburg Lymphoma Phase I/II Consortium, Amsterdam, Netherlands

<sup>18</sup> CHU de Nantes—Hotel Dieu, Nantes, France

<sup>19</sup> Institut Universitaire du Cancer—Oncopole Toulouse (IUCT-O), Toulouse, France

<sup>20</sup> Copernicus Memorial Hospital, Medical University of Lodz, Lodz, Poland

<sup>21</sup> Acerta Pharma, South San Francisco, CA, USA

<sup>22</sup> Department of Haematology, Jagiellonian University, Krakow, Poland

## To the Editor:

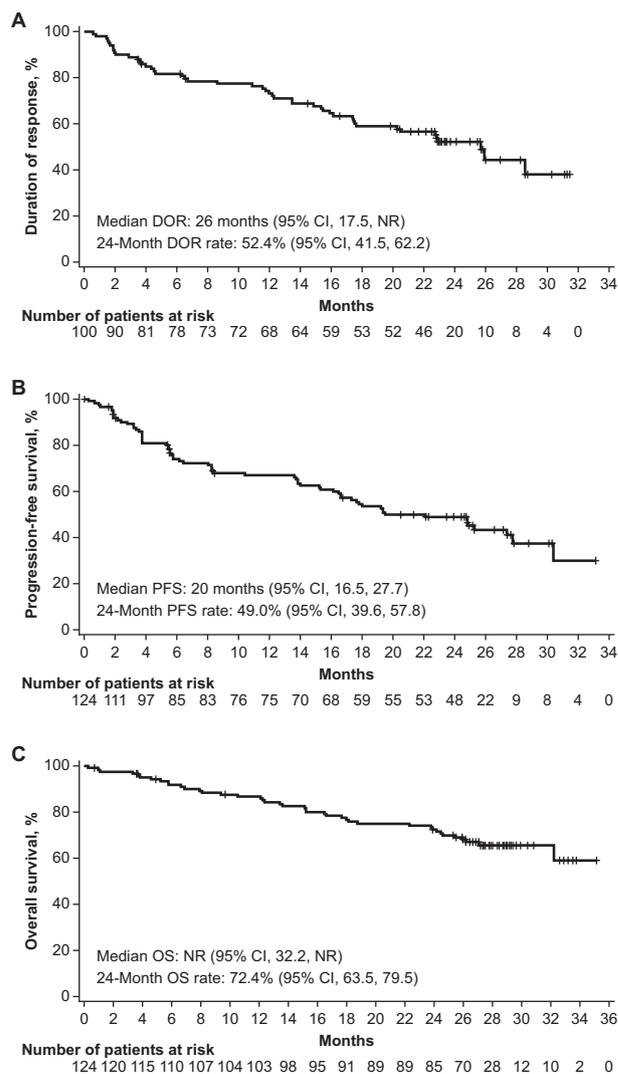
Bruton tyrosine kinase (BTK) inhibitors have greatly improved the spectrum of treatment options in mantle cell lymphoma (MCL) [1–4]. Acalabrutinib is a highly selective, orally administered, and potent BTK inhibitor with limited off-target activity [5]. Acalabrutinib was approved in 2017 by the US Food and Drug Administration for the treatment of relapsed/refractory MCL based on clinical data from the open-label, multicenter, phase 2 ACE-LY-004 study of acalabrutinib 100 mg twice daily [1]. Here, we present updated results from the ACE-LY-004 study after a median 26-month follow-up.

Eligibility criteria and study design were published previously (Supplementary methods) [1]. Analysis of minimal residual disease (MRD) was conducted after complete response (CR) or partial response (PR) was achieved using the quantitative ClonoSEQ next-generation sequencing ( $5 \times 10^{-6}$ ) assay (Adaptive Biotechnologies, Seattle, WA, USA) in consenting patients with available paired archival tumor and whole blood samples. Data are updated as of February 12, 2018.

A total of 124 patients across 40 centers were enrolled and treated; demographic data were previously reported (Supplementary Table 1) [1]. Cytomorphological variants included classical ( $n = 89$  [72%]), blastoid/pleomorphic ( $n = 26$  [21%]), or other ( $n = 9$  [7%]). Ki-67 data were available for 96 patients (77%); 32/96 patients (33%) had a Ki-67 proliferation index  $\geq 50\%$ . The mean Ki-67 proliferation index for blastoid/pleomorphic patients ( $n = 21$ ) was 55.8% (SD: 22.3) vs 34.5% (SD: 22.6) in patients with classical MCL ( $n = 68$ ); seven patients with Ki-67 data were in the other variant category.

The median follow-up was 26 months (range, 0.3–35.1). Forty percent of patients remain on treatment, and 61% remain in follow-up for survival (Supplementary Table 2). After discontinuing acalabrutinib, six patients received allogeneic stem-cell transplants at a median of 19 days after discontinuation (range, 1–95).

Response to acalabrutinib was maintained similar to the original report [1], with an overall response rate (ORR) of 81% and 43% CR rate (Supplementary Table 3). The median duration of response (DOR) was 26 months (95% CI, 17.5, not reached), with an estimated 24-month DOR of 52.4% (95% CI, 41.5, 62.2; Fig. 1a). The median progression-free survival (PFS) was 20 months (95% CI, 16.5, 27.7), and the estimated 24-month PFS rate was 49.0% (95% CI, 39.6, 57.8; Fig. 1b). The median overall survival (OS) was not reached; the estimated 24-month OS rate was 72.4% (95% CI, 63.5, 79.5; Fig. 1c). ORR was consistent across patients with refractory disease and those with blastoid/pleomorphic MCL, despite those patients having a higher mean Ki-67 index  $\geq 50\%$ , suggesting that



**Fig. 1** Kaplan–Meier curves for time-to-event endpoints. Curves shown are duration of response in responding patients (a), progression-free survival (b), and overall survival (c). DOR duration of response, NR not reached, OS overall survival, PFS progression-free survival

some patients with poorer prognosis may also benefit from acalabrutinib (Supplementary Table 4). Prolonged median DOR, median PFS, and 24-month OS rates, however, were observed in patients with low/intermediate Mantle Cell Lymphoma International Prognostic Index scores, classical MCL, and Ki-67 index  $< 50\%$  (Supplementary Figs. 1–4).

Twenty-nine patients (23%) had evaluable samples available for MRD analysis (Supplementary Fig. 5). Seven of 29 patients (24%) had MRD-negative ( $5 \times 10^{-6}$ ) disease in peripheral blood after achieving a response (CR or PR). All seven patients with MRD-negative disease were in CR. Seventeen of 29 patients had a second blood sample approximately 6 months after the first, including five of the seven MRD-negative patients. Sustained MRD negativity was observed in four of the five patients. An additional

**Table 1** Incidence of select adverse events by 6-month intervals

Adverse event, n (%)	1–6 months (n = 124)	7–12 months (n = 99)	13–18 months (n = 74)	19–24 months (n = 65)	>24 months (n = 55)
Headache, any grade	42 (34)	2 (2)	0	0	0
Grade $\geq 3$	2 (2)	0	0	0	0
SAE	1 (1)	0	0	0	0
Diarrhea, any grade	31 (25)	8 (8)	3 (4)	5 (8)	5 (9)
Grade $\geq 3$	3 (2)	1 (1)	0	0	0
SAE	0	0	1 (1)	0	0
Infection, any grade	51 (41)	20 (20)	17 (23)	11 (17)	6 (11)
Grade $\geq 3$	11 (9)	4 (4)	2 (3)	2 (3)	1 (2)
SAE	8 (6)	4 (4)	2 (3)	2 (3)	1 (2)
Bleeding events, any grade	31 (25)	14 (14)	5 (7)	4 (6)	0
Major hemorrhage <sup>a</sup>	1 (1)	0	0	2 (3)	0
Atrial fibrillation, any grade <sup>b</sup>	0	0	0	0	0
Rash, any grade	10 (8)	5 (5)	2 (3)	1 (2)	0
Grade $\geq 3$	1 (1)	0	1 (1)	1 (2)	0
SAE	0	0	0	0	0

SAE serious adverse event.

<sup>a</sup>Defined as grade  $\geq 3$ , SAE and/or any grade or seriousness of central nervous system hemorrhage.

<sup>b</sup>There was one event of atrial fibrillation in a subject with a history of paroxysmal atrial fibrillation (removed by investigator as this preexisting condition did not worsen on study drug).

patient with CR who was MRD positive in the first sample became MRD negative in the second sample. Therefore, a total of 8/29 patients (28%) achieved MRD negativity at any time on acalabrutinib monotherapy. Despite limited samples, these results demonstrate that continued use of acalabrutinib can lead to undetectable MRD in patients with CR. Since most patients with MRD data are still on treatment (27/29), relationships between MRD negativity and durability of response cannot be made at this time.

The adverse event AE profile was largely consistent with earlier reporting [1], with no new safety signals after an additional year of follow-up. The most frequent AEs ( $\geq 20\%$ ) were primarily grade 1/2 and included headache (38%), diarrhea (36%), fatigue (28%), cough (22%), and myalgia (21%; Supplementary Table 5). The most common events, headache and diarrhea, were mostly grade 1/2, occurred early in treatment, and were manageable. Headache events occurred primarily within the first month of treatment and most diarrhea events occurred in the first 6 months of treatment (Table 1 and Supplementary Table 6). The percentage of patients experiencing grade  $\geq 3$  AEs or serious AEs was similar to that previously reported (Supplementary Table 7), indicating that sustained use of acalabrutinib may not lead to cumulative toxicities [1].

Thirteen patients (10%) had cardiac events, including four grade 3/4 events (3%). As previously reported, one patient each had acute coronary syndrome (considered treatment related by investigator), acute myocardial infarction (not treatment related), and cardiorespiratory arrest (not treatment related) [1]; one grade 3 event (coronary artery disease [not treatment related]) occurred during this long-term follow-up.

Consistent with the previous report [1], there were no new atrial fibrillation events (Table 1). One patient with a history of paroxysmal atrial fibrillation was initially assessed as experiencing an AE of atrial fibrillation, but the AE was reconsidered by the investigator since the condition was preexisting and did not worsen on study drug. No new hypertension events occurred with long-term follow-up. As previously reported, four patients had hypertension events (3%), with one grade 3 event [1]. Bleeding events of any grade occurred in 33% of patients, most commonly contusion (13%) and petechiae (9%), and markedly decreased over time (Table 1). All bleeding events were grade 1/2 except for three grade 3 events (gastrointestinal hemorrhage, hematuria, hematoma). Two of the three major hemorrhage events occurred after the previous report, though the rate of major hemorrhage events (2%) remains the lowest reported for a BTK inhibitor with  $\geq 2$  years of follow-up [1, 6]. Anticoagulant use was reported in 57 patients (46%) while on study, but there was no reported use of concurrent anticoagulants in the patients with the three grade 3 hemorrhage events during the events. Consistent with previous reporting, most infections were grade 1/2, were considered unrelated to study treatment, and were not serious. Here, we also show that the frequencies of any grade, grade  $\geq 3$ , and serious infections decreased over time (Table 1). Grade 3/4 infections occurred in 15% of patients, most commonly pneumonia ( $n = 7$  [6%]); no grade 5 infections occurred. As previously reported, there was one case of cytomegalovirus viremia and one case of *Pneumocystis jiroveci* pneumonia (both grade 2), with no *Aspergillus* infections [1]. Mean immunoglobulin levels

did not change much over time (Supplementary Fig. 6). Rashes were infrequent and mostly grade 1/2. Second primary cancers occurred in ten patients (8%; Supplementary Table 8).

Treatment discontinuation was primarily due to progressive disease ( $n = 54$  [44%]) and AEs ( $n = 10$  [8%]). Ten patients discontinued treatment due to AEs; each AE occurred in one patient. AEs leading to discontinuation were aortic stenosis, diffuse large B-cell lymphoma, blood blister and petechiae (both in one patient with grade 3 acute coronary syndrome treated with clopidogrel), dyspnea and leukostasis syndrome (both in one patient), noncardiac chest pain, pulmonary fibrosis, rash, thrombocytopenia, non-small cell lung cancer, and pulmonary embolism. AEs led to dose delays (missed  $\geq 1$  dose) in 39 patients (31%) and dose modification ( $\geq 1$  dose at 100 mg once daily) in two patients (2%; Supplementary Table 9).

There were 43 deaths (35%), most commonly from progressive disease ( $n = 29$  [23%]). Six patients (5%) died due to AEs, including bilateral pulmonary embolism, aortic stenosis (in a patient with a history of aortic stenosis), myelodysplastic syndrome, pneumonia, suicide, and non-small cell lung cancer. Two patients (2%) died of unknown causes  $\geq 198$  days after the last dose, and one patient (1%) died due to multiorgan failure 176 days after the last dose. Five patients (4%) died of “other” causes (secondary acute myeloid leukemia  $\geq 277$  days after last dose [ $n = 2$ ]; intestinal obstruction 63 days after last dose [ $n = 1$ ]; lung cancer 728 days after last dose [ $n = 1$ ]; and graft-vs-host disease 275 days after the last dose [ $n = 1$ ; patient received an allogeneic stem-cell transplant 95 days after last dose]).

Extended follow-up of a median 26 months revealed continued efficacy and favorable safety with single-agent acalabrutinib in relapsed/refractory MCL. Differences between patient populations and staging criteria in the current study and the single-arm study of the other approved BTK inhibitor ibrutinib preclude comparison between studies, regardless of similar follow-up time (27 months in the ibrutinib study) [6]. Nonetheless, the response rates and median DOR based on the Lugano classification in this study are the highest reported among all approved single-agent therapies for the treatment of relapsed/refractory MCL. Moreover, four patients with PR converted to CR with longer follow-up indicating improvement of response (similar to ibrutinib [2, 6]), and most responders maintained a response for over 2 years. Nearly half of all patients remain progression free after 2 years of treatment, with few discontinuations due to AEs (8%). AEs considered associated with BTK inhibition continued to occur at relatively low rates or not at all, including no new onset of atrial fibrillation. Taken together, these findings further support the favorable benefit-risk profile of acalabrutinib monotherapy in relapsed/refractory MCL.

**Acknowledgements** This study was sponsored by Acerta Pharma, a member of the AstraZeneca Group. We thank the patients who participated in this trial and their families and caregivers; the investigators and coordinators at each study site; and the Acerta Pharma study team, including Sofia Wong. Medical writing assistance was provided by Stephanie Morgan of Team9Science and funded by Acerta Pharma.

**Author contributions** RI, SR, and MW designed the study. DN and PP performed the literature search. OC, AD, JDo, JDu, RE, GD, AG, MDD, APK, TL, SLG, FM, LO, CP, DN, PP, TR, BS, SDS, MW, and PLZ collected the data. GD verified the data. EJ, APK, DN, PP, MY, MMF, and MW analyzed the data. AD, RI, MDD, APK, TL, FM, LO, CP, DN, PP, SR, and SDS interpreted the data. MY and MMF produced the figures. MW wrote the first draft. All authors contributed to the writing and reviewing of manuscript content and approved the final version of the manuscript.

### Compliance with ethical standards

**Conflict of interest** MW is a consultant for AstraZeneca, Janssen, and MoreHealth, has received honoraria from Acerta Pharma, Celgene, Dava Oncology, Janssen, and Pharmacyclics, has received research funding from Acerta Pharma, AstraZeneca, Celgene, Janssen, Kite Pharma, Juno, Novartis, and Pharmacyclics, and is a member of the Board of Directors or advisory committees for Celgene and Janssen. SR is a consultant for, a member of the Board of Directors or advisory committees for, and has received honoraria from AstraZeneca, Celgene, Celltrion, Gilead, Janssen, Kite, and Roche, has received research funding from Janssen, and participates in a speakers' bureau for Celgene. PLZ has received honoraria from BMS, Celgene, Celltrion, Gilead, Janssen, MSD, Roche, and Servier, and participates in a speakers' bureau for AstraZeneca, BMS, Gilead, Janssen, MSD, Servier, and Verastem. AG is a consultant for Acerta Pharma, Celgene, Kite/Gilead, Pharmacyclics/J&J, and Takeda, has received honoraria from Celgene, Pharmacyclics/J&J, and Takeda, is a member of the Board of Directors or advisory committees for Acerta Pharma, Celgene, COTA, Kite/Gilead, Pharmacyclics/J&J, and Takeda, has received research funding from Acerta Pharma, Celgene, Genentech, Kite/Gilead, Pharmacyclics/J&J, and Seattle Genetics, and participates in a speakers bureau for Acerta Pharma, Celgene, Pharmacyclics/J&J, and Takeda. OC is a consultant for Gilead, Janssen, Merck, MSD, Roche, and Takeda, has received honoraria from Celgene, Gilead, Janssen, Merck, MSD, Roche, and Takeda, and has received research funding from Gilead and Roche. SDS is a consultant for Merck Sharpe Dohme and Corp, and has received research funding from Acerta Pharma, Genentech, Merck Sharpe Dohme and Corp, Pharmacyclics, Portola, and Seattle Genetics. FM is a consultant for Celgene and Gilead, is a member of the Board of Directors or advisory committees for BMS, Celgene, Gilead, and Roche, and gives scientific lectures for Janssen and Roche. CP is a consultant for Roche, participates in a speakers' bureau for Celgene, Janssen, and Roche, has received research funding from Acerta Pharma, is a member of the Board of Directors or advisory committees for BMS and Janssen. AD is a consultant for Acerta Pharma, Celgene, Janssen, Karyopharma, Kite, Roche, and Takeda, and has received research funding from Acerta Pharma, Celgene, Gilead, GSK, Karyopharma, Pfizer, and Roche. BS reports relationships with Amgen, Incyte, and Pharmacyclics that do not exceed \$5000, nor are relevant to this content. RE is a member of the Ramsay Hospital Medical Advisory Committee. EJ is a consultant for AstraZeneca, Merck, and Seattle Genetics. APK has received honoraria from Abbie, Genentech, and Janssen, and research funding from Abbie, Acerta/AstraZeneca, Genentech, and Janssen. LO is a consultant for Janssen, Sanofi, and Takeda, and has received honoraria from Janssen. TR has received research funding from Acerta Pharma.

DN, MY, and PP are employees of Acerta Pharma and have equity ownership of Acerta and AstraZeneca. RI is an employee of, has equity ownership of and patents at Acerta Pharma, and has equity ownership of AstraZeneca. MMF is an employee of and has equity ownership and patents at AstraZeneca. MDD is a consultant for Janssen, Roche, Servier and Takeda, and gives scientific lectures for Janssen, Servier, and Roche. GD, JD, JKD, SL, and TL declare no competing interests.

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

## References

1. Wang M, Rule S, Zinzani PL, Goy A, Casasnovas O, Smith SD, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *Lancet* 2018;391:659–67.
2. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013;369:507–16.
3. Tam CS, Anderson MA, Pott C, Agarwal R, Handunnetti S, Hicks RJ, et al. Ibrutinib plus venetoclax for the treatment of mantle-cell lymphoma. *N Engl J Med* 2018;378:1211–23.
4. Dreyling M, Jurczak W, Jerkeman M, Silva RS, Rusconi C, Trneny M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet* 2016;387:770–8.
5. Barf T, Covey T, Izumi R, van de Kar B, Gulrajani M, van Lith B, et al. Acalabrutinib (ACP-196): a covalent Bruton Tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. *J Pharm Exp Ther* 2017;363:240–52.
6. Wang ML, Blum KA, Martin P, Goy A, Auer R, Kahl BS, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood* 2015; 126:739–45.