# Clinical activity of abemaciclib in patients with relapsed or refractory mantle cell lymphoma – a phase II study

*Franck Morschhauser,[1] Kamal Bouabdallah,[2] Stephan Stilgenbauer,[3] Catherine Thieblemont,[4] Sophie de Guibert,[5] Florian Zettl,[6] Lawrence M. Gelbert,[7] P. Kellie Turner,[8] Siva Rama Prasad Kambhampati,[8°] Li Li,[8] Lily Q. Li,[8] Sean Buchanan,[8] Susana Barriga,[8] Melissa M. Bear,[8] Martin Wilhelm[9] and Georg Hess[10]*

*[1]Universitè de Lille, CHU Lille, ULR 7365 - GRITA - Groupe de Recherche sur les formes Injectables et les Technologies Associees, Lille, France; [2]Hôpital Haut-Lévêque, Centre Hospitalier Régional Universitaire de Bordeaux, Pessac, France; [3]Internal Medicine III, Ulm University, Ulm, Germany; [4]APHP, Hôpital Saint-Louis, Hemato-Oncology Department, Paris & Diderot University, Paris, France ; [5]Hôpital de Pontchaillou, Rennes, France; [6]Universitätsmedizin Göttingen, Göttingen, Germany; [7]LMG PharmaTech, LLC., Indianapolis, IN, USA; [8]Eli Lilly and Company, Indianapolis, IN, USA; [9]Klinikum Nürnberg Nord, Nürnberg, Germany and [10]Universitätsmedizin Mainz, Mainz, Germany*

*°Current address: Arkos Pharma Inc., Princeton, NJ, USA*

*Correspondence: FRANCK MORSCHHAUSER - franck.morschhauser@chru-lille.fr*

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**Authors**

Franck Morschhauser,[1] Kamal Bouabdallah,[2] Stephan Stilgenbauer,[3] Catherine Thieblemont,[4] Sophie de Guibert,[5] Florian Zettl,[6] Lawrence M. Gelbert,[7] P. Kellie Turner,[8] Siva Rama Prasad Kambhampati,[8*] Li Li,[8] Lily Q. Li,[8] Sean Buchanan,[8] Susana Barriga,[8] Melissa M. Bear,[8] Martin Wilhelm,[9] and Georg Hess[10]

**Affiliations**

[1]Hôpital Claude Huriez, Centre Hospitalier Régional Universitaire, Lille, France
[2]Hôpital Haut-Lévêque, Centre Hospitalier Régional Universitaire de Bordeaux, Pessac, France
[3]Internal Medicine III, Ulm University, Ulm, Germany
[4]Hôpital Saint-Louis, Paris, France
[5]Hôpital de Pontchaillou, Rennes, France
[6]Universitätsmedizin Göttingen, Göttingen, Germany
[7]LMG PharmaTech, LLC., Indianapolis, Indiana, USA
[8]Eli Lilly and Company, Indianapolis, Indiana, USA
[9]Klinikum Nürnberg Nord, Nürnberg, Germany
[10]Universitätsmedizin Mainz, Mainz, Germany
*Current affiliation: Arkos Pharma Inc., Princeton, NJ, USA

**Corresponding Author**

**Franck Morschhauser, MD**
Université Lille, CHU Lille,
EA 7365 - GRITA - Groupe de Recherche sur les formes Injectables et les Technologies Associées, F-59000 Lille, France
Telephone: 03.20.44.57.13
Fax: 03.20.44.47.08
E-mail: franck.morschhauser@chru-lille.fr

## Supplemental Methods

### Patients

Patients ≥18 years of age with R/R MCL to standard therapy were eligible. Additional inclusion criteria included assessable disease based on the Response Criteria for NHL[13], an Eastern Cooperative Oncology Group performance status (ECOG PS) score ≤2 and adequate organ function (absolute neutrophil count ≥1.5 $\times$ $10^9$/L, platelets ≥75 $\times$ $10^9$/L, hemoglobin ≥8 g/dL, bilirubin ≤1.5 times upper limits of normal [ULN], alanine aminotransferase ≤3 times ULN, aspartate aminotransferase ≤ 3 times ULN, and estimated creatinine clearance ≥50 ml/min).[14] Key exclusion criteria included any serious medical condition that precluded participation, symptomatic CNS metastasis, recipient of autologous or allogenic stem-cell transplant ≤75 days prior to receiving treatment, pregnant or lactating female patients, and the presence of any active infection. The institutional review boards of the participating institutions approved the study protocol. Written informed consent was obtained from all participants before entering the study, and ethical principles of the Declaration of Helsinki and Good Clinical Practice were followed.

### Study design

This was a multi-center, open-label, single arm Phase II study of patients with R/R MCL. Patients received the maximum tolerated dose of 200 mg oral abemaciclib Q12H (every 12 hours) on Days 1 through 28 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, or patient or physician withdrawal. Dose adjustments in the form of treatment suspension or reduction were allowed both within a cycle and between cycles. Dose suspensions and reductions were required if a patient experienced grade 3 or 4 nonhematologic or grade 4 hematologic toxicity possibly related to abemaciclib. If patient had

persistent or recurrent grade 2 nonhematologic toxicity that did not resolve to baseline or grade 1 within 7 days with supportive care, dose can be reduced or suspended. Supportive care and concomitant medications were allowed. Any concurring anticancer therapy was not allowed.

**Efficacy and safety measurements**

Radiological tumor assessments were made by computed tomography (CT) and magnetic resonance imaging (MRI) at baseline (≤28 days before the first dosing of abemaciclib) and at the end of every 2 cycles for the initial 6 cycles and thereafter at the end of every 3 cycles until objective progression was observed. Patient's survival status was followed until death or study completion.

**Pharmacokinetics**

For PK evaluations, blood samples were collected on Days 1 and 15 pre-dose and 1, 2, 4, 6, and 8 hours post-dose. Plasma concentrations of abemaciclib and its metabolites were determined using a validated LC-MS method (Charles River Laboratories, Montreal, Canada). Maximum concentration ($C_{max}$), time of maximum concentration ($t_{max}$), steady state trough concentration ($C_{trough}$), area under the concentration-time curve from time zero until the last observed concentration ($AUC_{0\text{-}last}$), and accumulation ratio based on $C_{max}$ were computed by non-compartmental methods using WinNonlin Professional Edition.

**Statistical methods**

The study tested the assumption that the true DCR was significantly different from a pre-specified null DCR (25%). If the observed DCR was 50%, then a sample size of 20 patients was estimated to provide a 95% confidence interval (CI) that the DCR will be between 27% and 73%

excluding a 25% or lower DCR. DCR and its 95% CI were estimated using the Clopper-Pearson method. DoR, PFS, and OS were analyzed using Kaplan-Meier methods.

**Supplemental Table 1. Patient and disease characteristics**

| Characteristic | Abemaciclib treatment (N=28) |
|---|---|
| Age in years, median (range) | 70.0 (53.0-83.0) |
| Male, n (%) | 17 (60.7) |
| Race<br>White, n% | 27 (96.4) |
| MCL Stage at initial diagnosis, n% | |
| I | 2 (7.1) |
| III | 6 (21.4) |
| IV | 20 (71.4) |
| Bulky mass (tumor size ≤10 cm), n (%) | 3 (10.7) |
| ECOG PS, n (%) | |
| 0 | 12 (42.9) |
| 1 | 14 (50.0) |
| 2 | 2 (7.1) |
| Simplified MIPI at baseline, n (%) | |
| Low risk | 6 (21.4) |
| Intermediate risk | 11 (39.3) |
| High risk | 7 (25.0) |
| Not available | 4 (14.3) |
| Number of prior regimens, n (%) | |
| 1 | 6 (21.4) |
| 2 | 5 (17.9) |
| 3 | 8 (28.6) |
| >3 | 9 (32.1) |
| Prior systemic therapies, n (%) | |
| Rituximab | 28 (100.0) |
| Doxorubicin-based therapy | 24 (85.7) |
| Cytarabine-based therapy | 20 (71.4) |
| Temsirolimus | 14 (50.0) |
| Bendamustine | 9 (32.1) |
| Stem cell transplantation (autologous) | 7 (25.0) |
| Bortezomib | 3 (10.7) |

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; MIPI = simplified mantle-cell lymphoma international prognostic index; N = total population size; n = number of patients.

**Supplemental Table 2. Subgroup analysis based on number of prior systemic therapies**

| | **≤3 prior therapies (n=19)** | **>3 prior therapies (n=9)** |
|---|---|---|
| Best Overall Response n (%) (95% CI) | | |
| Disease Control Rate | 16 (84.2) (60.4, 96.6) | 4 (44.4) (13.7, 78.8) |
| Overall Response Rate (CR+CRu+PR) | 9 (47.4) (0.2, 0.7) | 1 (11.1) (0.003, 0.5) |
| Complete Response | 1 (5.3) (0.1, 26.0) | 0 |
| Complete Response Unconfirmed | 1 (5.3) (0.1, 26.0) | 0 |
| Partial Response | 7 (36.8) (16.3, 61.6) | 1 (11.1) (0.3, 48.2) |
| Stable Disease | 7 (36.8) (16.3, 61.6) | 3 (33.3) (7.5, 70.1) |
| Time to Best Overall Response, days (range) | 112 (55, 25) | 109 (109, 109) |
| Median Time to Events (months, 95% CI) | | |
| Duration of Response | 12.39 (3.19, NR) | 6.67 (NR) |
| Time to Progression | 16.16 (5.45, NR) | 5.09 (0.72, 10.2) |
| Disease-free Survival | 14.36 (3.19, NR) | 6.67 (NR) |
| Progression-free Survival | 12.85 (4.34, 16.2) | 5.09 (0.72, 10.2) |
| Overall Survival | NR (6.47, NR) | 8.18 (1.12, 16.3) |
| Event-free Survival | 11.79 (5.45, 16.3) | 10.22 (NR) |
| MCL Stage at diagnosis, n (%) | | |
| Stage I | 0 | 2 (22.2) |
| Stage III | 4 (21.1) | 2 (22.2) |
| Stage IV | 15 (78.9) | 5 (55.5) |

**Supplemental Table 3. Pharmacokinetics of abemaciclib and its metabolites in relapsed or refractory MCL**

| | | Geometric Mean (CV%) | | | | |
|---|---|---|---|---|---|---|
| **Dose** | **Analyte** | **$C_{max}$ ng/mL, (%) (n=26)** | **$t_{max}$[a] (hr) (n=26)** | **$AUC_{(0\text{-last})}$ (hr*ng/mL) (n=26)** | **$C_{trough}$ (ng/mL) (n=21)** | **RA, $C_{max}$ (n=20)** |
| Single | Abemaciclib | 189 (59) | 5.70 (3.92 – 8.00) | 978 (61) | NA | NA |
| | LSN2839567 | 42.6 (58) | 4.06 (3.33 – 8.00) | 221 (59) | NA | NA |
| | LSN3106726 | 54.4 (55) | 6.04 (3.97 – 8.00) | 275 (64) | NA | NA |
| | LSN3106729 | 13.8 (90) | 6.00 (3.92 – 8.00) | 68.0 (97) | NA | NA |
| Multiple[b] | Abemaciclib | 449 (71)[c] | 4.00 (0.00 – 8.00)[c] | 3090 (77)[c] | 364 (85) | 2.14 (74) |
| | LSN2839567 | 198 (42)[c] | 4.00 (1.05 – 8.00)[c] | 1350 (45)[c] | 156 (53) | 3.91 (70) |
| | LSN3106726 | 323 (45)[c] | 2.00 (0.00 – 8.00)[c] | 2280 (48)[c] | 282 (55) | 5.17 (68) |
| | LSN3106729 | 86.2 (60)[c] | 3.97 (0.00 – 8.00)[c] | 585 (61)[c] | 64.9 (71) | 5.02 (79) |

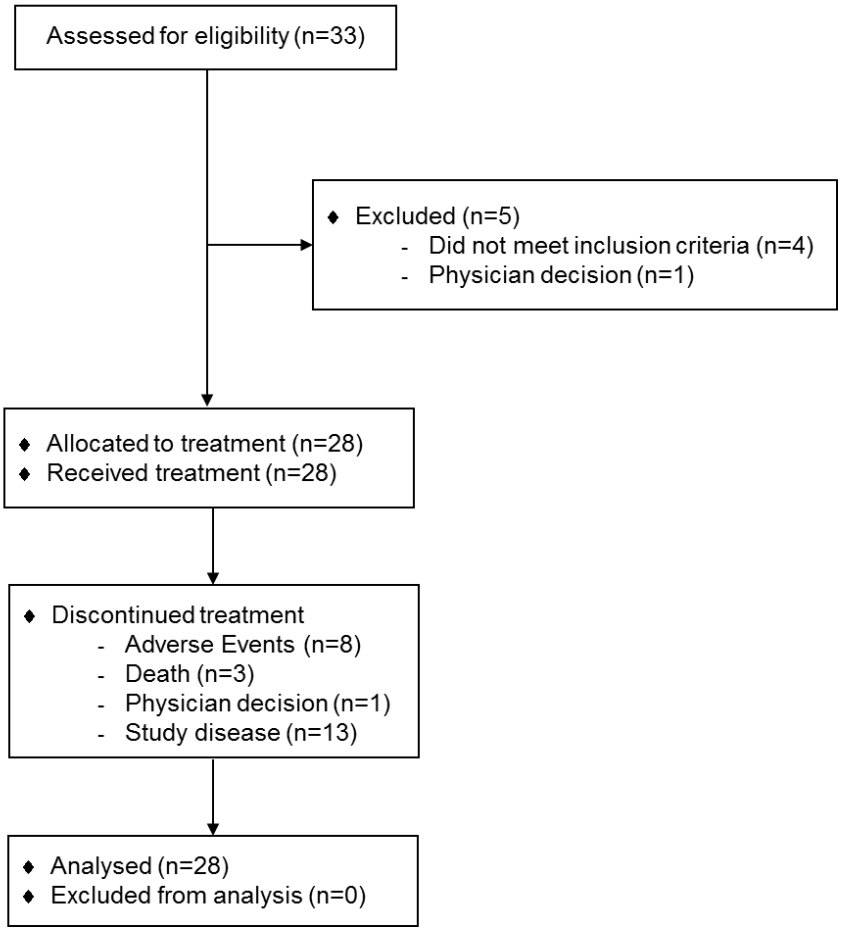
Abbreviations: $C_{max}$ = maximum observed plasma concentration; $t_{max}$ = time of maximum observed drug concentration; AUC(0-last) = area under the concentration time curve from time 0 to last observed concentration; $C_{trough}$ = observed plasma concentration prior to next dose; RA, $C_{max}$ = accumulation ratio based on $C_{max}$; n = number of observations

[a] Median and range

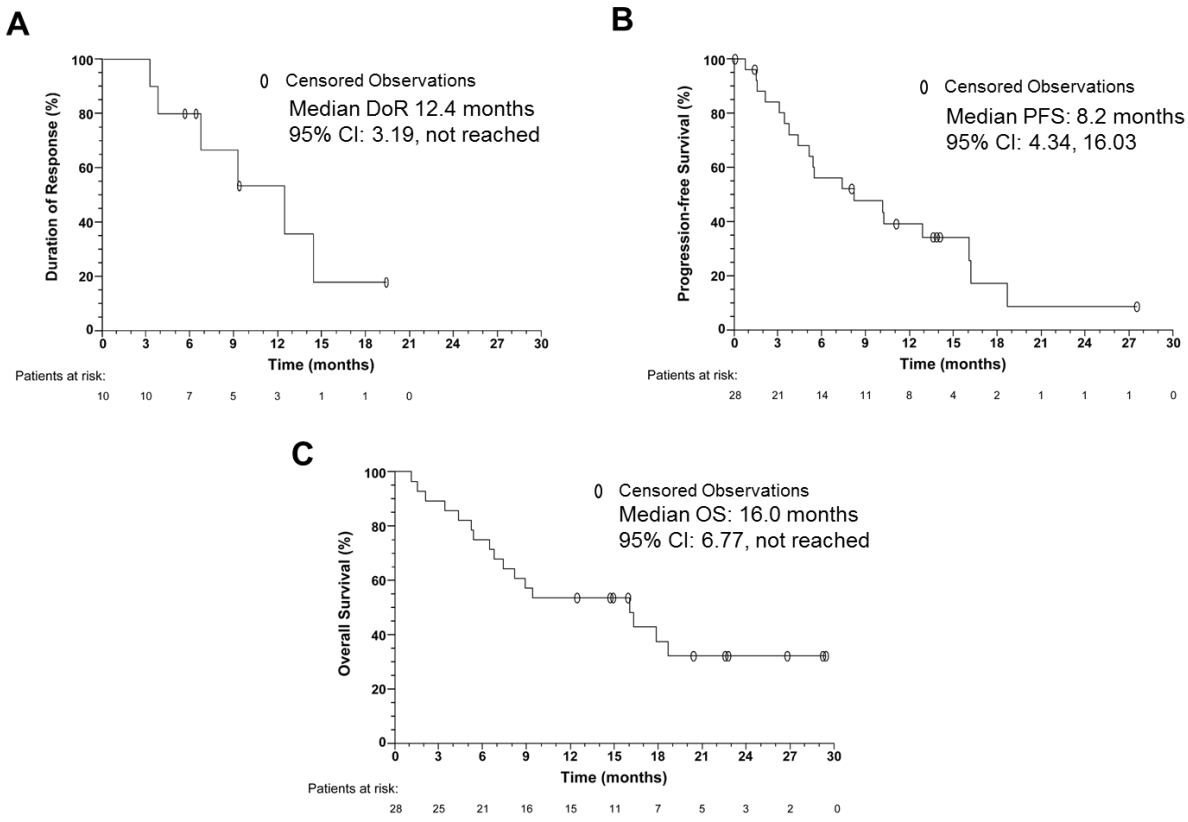
[b] In multiple dose, PK values were calculated on days 12 (n=1), 14 (n=10), 15 (n=9), or 16 (n=1)

[c] n=21

**Supplemental Figure 1.** CONSORT diagram



**Supplemental Figure 2**. Kaplan-Meier curves of duration of response (A), progression-free survival (B) and overall survival (C)



**Supplemental Figure 3.** Duration of treatment and reason for discontinuation by patient