Efficacy and safety of idelalisib in patients with relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study

Gilles Salles,[1] Stephen J. Schuster,[2] Sven de Vos,[3] Nina D. Wagner-Johnston,[4] Andreas Viardot,[5] Kristie A. Blum,[6] Christopher R. Flowers,[7] Wojciech J. Jurczak,[8] Ian W. Flinn,[9] Brad S. Kahl,[10] Peter Martin,[11] Yeonhee Kim,[12] Sanatan Shreay,[12] Matthias Will,[13] Bess Sorensen,[13] Madlaina Breuleux,[13] Pier Luigi Zinzani[14] and Ajay K. Gopal[15]

[1]Hospices Civils de Lyon, University Claude Bernard, Pierre Benite, France; [2]Lymphoma Program, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; [3]Department of Hematology/Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [4]Departments of Oncology and Hematologic Malignancies, Johns Hopkins University, Baltimore, MD, USA; [5]Department of Internal Medicine III, University Hospital of Ulm, Germany; [6]Division of Hematology, Ohio State University Wexner Medical Center, Columbus, OH, USA; [7]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, USA; [8]Department of Hematology, Jagiellonian University, Krakow, Poland; [9]Hematologic Malignancies Research Program, Sarah Cannon Research Institute, Nashville, TN, USA; [10]Department of Medicine, Oncology Division, Washington University School of Medicine, St Louis, MO, USA; [11]Division of Hematology/Oncology, Weill Cornell Medical College, NY, USA; [12]Gilead Sciences Inc., Foster City, CA, USA; [13]At the time of the analyses, Gilead Sciences Inc., Foster City, CA, USA; [14]Institute of Hematology and Oncology, University of Bologna, Italy and [15]Medical Oncology Division, University of Washington School of Medicine, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Correspondence: agopal@u.washington.edu
doi:10.3324/haematol.2016.151738

SUPPLEMENTARY APPENDIX

Efficacy and safety of idelalisib in patients with relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study

Gilles Salles,[1] Stephen J. Schuster,[2] Sven de Vos,[3] Nina D. Wagner-Johnston,[4] Andreas Viardot,[5] Kristie A. Blum,[6] Christopher R. Flowers,[7] Wojciech J. Jurczak,[8] Ian W. Flinn,[9] Brad S. Kahl,[10] Peter Martin,[11] Yeonhee Kim,[12] Sanatan Shreay,[12] Matthias Will,[13] Bess Sorensen,[13] Madlaina Breuleux,[13] Pier Luigi Zinzani,[14] and Ajay K. Gopal[15]

[1]Hospices Civils de Lyon, University Claude Bernard, Pierre Benite, France; [2]Lymphoma Program, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; [3]Department of Hematology/Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [4]Departments of Oncology and Hematologic Malignancies, Johns Hopkins University, Baltimore, MD, USA; [5]Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany; [6]Division of Hematology, Ohio State University Wexner Medical Center, Columbus, OH, USA; [7]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, USA; [8]Department of Hematology, Jagiellonian University, Krakow, Poland; [9]Hematologic Malignancies Research Program, Sarah Cannon Research Institute, Nashville, TN, USA; [10]Department of Medicine, Oncology Division, Washington University School of Medicine, St Louis, MO, USA; [11]Division of Hematology/Oncology, Weill Cornell Medical College, New York, NY, USA; [12]Gilead Sciences Inc., Foster City, CA, USA; [13]Employee of Gilead Sciences Inc, Foster City, CA, USA at the time of the analyses; [14]Institute of Hematology and Oncology, University of Bologna, Bologna,

Italy; [15]Medical Oncology Division, University of Washington School of Medicine, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Supplementary Methods

Study Design

This was a post hoc subgroup analysis of a phase 2, multicenter single-arm, open-label study[1] using a data cutoff date of June 11, 2014 (vs June 25, 2013 for initial data cutoff). Patients received oral idelalisib 150 mg twice daily until progressive disease (PD) or unacceptable toxicity. Based on previous studies with overall response rates (ORR) of ≤20% for bortezomib[2, 3] or lenalidomide,[4] the study was designed to test the null hypothesis of ORR ≤20% (intent-to-treat [ITT] population) against the alternative hypothesis of ORR ≥40%. The protocol was approved by each site's institutional review board or independent ethics committee. The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and Helsinki Declaration. All patients gave written informed consent.

Patients

Eligible patients were aged ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance score[5] of ≤2, diagnosis of B-cell iNHL (WHO 2008 guidelines)[6] with radiographically measurable disease, absolute neutrophil count ≥1.0 × 109/L, and platelet count ≥50 × 109/L. This subgroup analysis included only patients with FL (grade 1, 2, or 3a). Patients must have received ≥2 prior chemotherapy- or immunotherapy-based regimens for FL, with refractoriness to rituximab and an alkylating agent. Main exclusion criteria were histologic transformation, central nervous system lymphoma, history of hepatic dysfunction, and active systemic infection.

Assessments

The primary efficacy endpoint was ORR. An independent review committee (IRC) evaluated responses using the International Working Group criteria.[7] Secondary endpoints included lymph node response rate (response defined as ≥50% decrease in the sum of the products of the diameters [SPD] of index lesions), DOR (from onset of response to disease progression), progression-free survival (PFS), time to response (TTR; from start of treatment to first documented response), and overall survival (OS). Tumor assessments were performed via computed tomography/magnetic resonance imaging, laboratory testing, and physical examination at screening; weeks 8, 16, and 24; and every 12 weeks thereafter. Health-related quality of life (HRQoL) was assessed based on the patient-reported Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym) score and ECOG status at screening (ECOG only); baseline; weeks 4, 8, 12, 16, 20, 24, 30, 36, 42, and 48; and every 12 weeks thereafter. Safety assessments included adverse events (AEs), physical examination, laboratory tests, and electrocardiogram. AEs were coded using Medical Dictionary for Regulatory Activities version 15.1.

Analyses

Analyses were performed in the ITT population (patients who received ≥1 dose of idelalisib).[1] Multivariate analyses of ORR were performed with subgroups based on age (<65 vs ≥65 years), sex, white/nonwhite, US/non-US, presence of bulky disease (yes vs no), suitability for radioimmunotherapy (yes vs no), number of previous therapies (<4 vs ≥4), refractoriness to last treatment (yes vs no), number of times refractory to an alkylating agent (<2 vs ≥2), number of times refractory to rituximab (≤2 vs >2), prior bendamustine use (yes vs no), and refractoriness to bendamustine (yes vs no). DOR, TTR, PFS, OS, and time to symptom

improvement for FACT-Lym scores were estimated using the Kaplan-Meier (KM) method. Safety data were analyzed descriptively.

References

1. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014 Mar 13;370(11):1008-1018.

2. Di Bella N, Taetle R, Kolibaba K, et al. Results of a phase 2 study of bortezomib in patients with relapsed or refractory indolent lymphoma. Blood. 2010 Jan 21;115(3):475-480.

3. Goy A, Younes A, McLaughlin P, et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. J Clin Oncol. 2005 Feb 1;23(4):667-675.

4. Witzig TE, Wiernik PH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J Clin Oncol. 2009 Nov 10;27(32):5404-5409.

5. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-655.

6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas (version 1.2016). 2016 [cited 2016 January 11]; Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site

7. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007 Feb 10;25(5):579-586.

SUPPLEMENTAL TABLES AND FIGURES

Table S1. Time to response and duration of response

Median (Range), mo	Time to Response	Duration of Response
Overall (n=38)	2.6 (1.6–11.0)	10.8 (0–26.9)
CR, first response (n=8)	1.9 (1.8–8.4)	
CR, best response (n=10)	4.5 (1.9–19.2)	13.7 (3.7–26.9)
PR (n=30)	3.3 (1.6–11.0)	5.5 (0–18.6)

CR=complete response; PR=partial response.

Table S2. Treatment-emergent adverse events (≥10%) and key laboratory abnormalities

Event or Abnormality, n (%)	Any	Grade ≥3*
AE	71 (98.6)	47 (65.3)
Diarrhea	37 (51.4)	10 (13.9)
Cough	23 (31.9)	0
Pyrexia	21 (29.2)	3 (4.2)
Fatigue	20 (27.8)	0
Nausea	20 (27.8)	2 (2.8)
Dyspnea	14 (19.4)	2 (2.8)
Rash	14 (19.4)	2 (2.8)
Decreased appetite	13 (18.1)	0
Vomiting	12 (16.7)	2 (2.8)
Night sweats	11 (15.3)	0
Upper respiratory tract infection	11 (15.3)	0
Weight decreased	11 (15.3)	0
Abdominal pain	10 (13.9)	2 (2.8)
Headache	10 (13.9)	1 (1.4)
Back pain	9 (12.5)	1 (1.4)
Asthenia	8 (11.1)	0
Constipation	8 (11.1)	0
Pneumonia	8 (11.1)	5 (6.9)
Hematopoietic laboratory abnormality		
Neutropenia	37 (51.4)	16 (22.2)
Anemia	25 (34.7)	2 (2.8)
Thrombocytopenia	17 (23.6)	4 (5.6)
Chemical laboratory abnormality		
Increased ALT/AST	38 (52.8)	10 (13.9)[†]
Hypokalemia	14 (19.4)	4 (5.6)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*AE severity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, Version 3.0.

[†]Seven patients had both grade ≥3 ALT and grade ≥3 AST elevation.

Table S3. Outcomes of treatment-emergent adverse events of diarrhea and/or colitis and grade ≥3 ALT/AST elevation

	Diarrhea and/or Colitis			ALT/AST Elevation
n (%)*	**Any Grade**	**Grade 1/2**	**Grade ≥3**	**Grade ≥3**
Patients with TEAE	38 (52.8)	35 (48.6)	12 (16.7)	10 (13.9)
Median (range) time to onset of first event, wk	15.2 (0.1–79.9)	15.7 (0.1–84.9)	24.7 (3.7–77.3)	6.1 (3.9–124.1)
Median (range) time from first event onset to resolution, wk	3.0 (0.1–35.7)	4.4 (0.4–12.4)	5.8 (1.4–35.7)	4.4 (0.4–12.4)
Complete resolution of symptoms without treatment interruption[†]	13 (34.2)[‡]	12 (34.3)	1 (8.3)	
Idelalisib treatment interruption and reexposure	6 (15.8)	1 (2.9)	5 (41.7)	7 (70.0)
Event did not recur	5 (83.3)[§]	1 (100)	4 (80.0)[§]	5 (71.4)
Permanent idelalisib discontinuation	15 (39.5)		6 (50.0)	
Due to TEAE	3 (7.9)		3 (25.0)	
Due to other reason before TEAE resolution	12 (31.6)		3 (25.0)	
TEAE began after last dose	4 (10.5)		0	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

*Unless otherwise specified.

[†]Complete resolution=resolution to grade 0.

[‡]Three of these patients were managed for diarrhea, primarily with loperamide (no steroids).

[§]Event of same or higher grade did not recur. One patient had grade 3 diarrhea after reexposure and permanently discontinued idelalisib; 1 patient had grade 2 diarrhea after reexposure followed by another idelalisib dose interruption.

Table S4. Treatment-emergent adverse events leading to dose interruption or reduction, or to study drug discontinuation

Adverse Event	Total N=72
Patients with any TEAE leading to study drug interruption	24 (33.3)
Diarrhea	7 (9.7)
Pneumonia	4 (5.6)
Pyrexia	3 (4.2)
Abdominal pain	2 (2.8)
Pneumonitis	1 (1.4)
Patients with any TEAE leading to study drug reduction	21 (29.2)
Alanine aminotransferase increased	4 (5.6)
Aspartate aminotransferase increased	4 (5.6)
Diarrhea	4 (5.6)
Neutropenia	4 (5.6)
Rash	2 (2.8)
Abdominal discomfort	1 (1.4)
Asthenia	1 (1.4)
Blood bilirubin increased	1 (1.4)
Bronchopneumonia	1 (1.4)
Colitis	1 (1.4)
Dysgeusia	1 (1.4)
Gastroesophageal reflux disease	1 (1.4)
Hepatocellular injury	1 (1.4)
Pneumonia	1 (1.4)
Pneumonitis	1 (1.4)
Renal mass	1 (1.4)
Transaminases increased	1 (1.4)
Patients with any TEAE leading to study drug discontinuation	18 (25.0)
Diarrhea	2 (2.8)
Colitis	1 (1.4)
Enterocolitis	1 (1.4)
Death	1 (1.4)
Pyrexia	1 (1.4)
Mucosal inflammation	1 (1.4)
Pneumonitis	2 (2.8)
Lung infiltration	1 (1.4)
Cytomegalovirus colitis	1 (1.4)

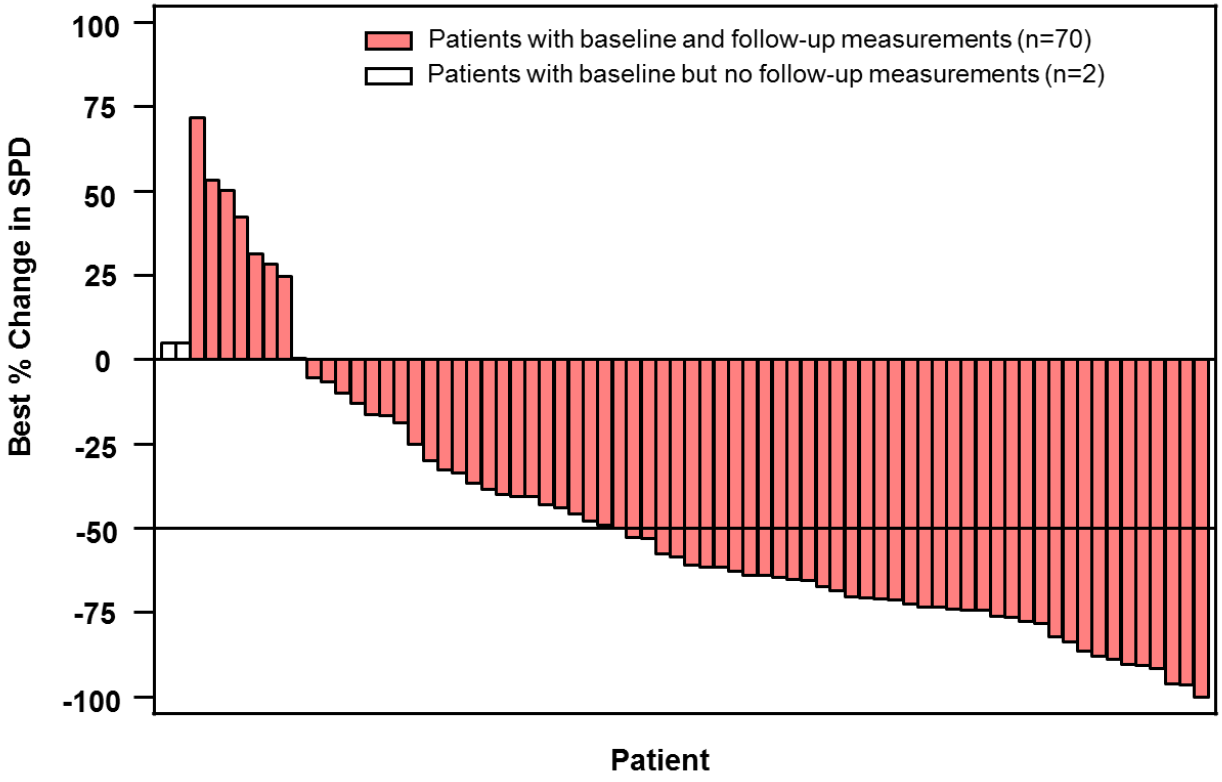
Septic shock	1 (1.4)
ALT increased	2 (2.8)
AST increased	2 (2.8)
Cardiac failure	1 (1.4)
Hepatocellular injury	1 (1.4)
Autoimmune disorder	1 (1.4)
Hydronephrosis	1 (1.4)
Rash	1 (1.4)

Data presented as n (%). TEAEs reported with MedDRA preferred term. TEAE, treatment-emergent adverse event. Patients could be counted in more than one category (e.g. dose reduction and dose interruption).

Supplemental Figure Legend

Figure S1. Best response in change in tumor volume. SPD, sum of the product of the diameters of index lesions.

Figure S1.


Patients with baseline and follow-up measurements (n=70)
Patients with baseline but no follow-up measurements (n=2)
Best % Change in SPD
100
75
50
25
0
-25
-50
-75
-100
Patient