NEW EVIDENCE

Idelalisib monotherapy and durable responses in patients with relapsed or refractory marginal zone lymphoma

Peter Martin, Armando Armas, Ajay K. Gopal, Emmanuel Gyan, Nina D. Wagner-Johnston, Jan Walewski, Steve Abella, Wei Ye, Betsy Philip, Bess Sorenson, Sven de Vos

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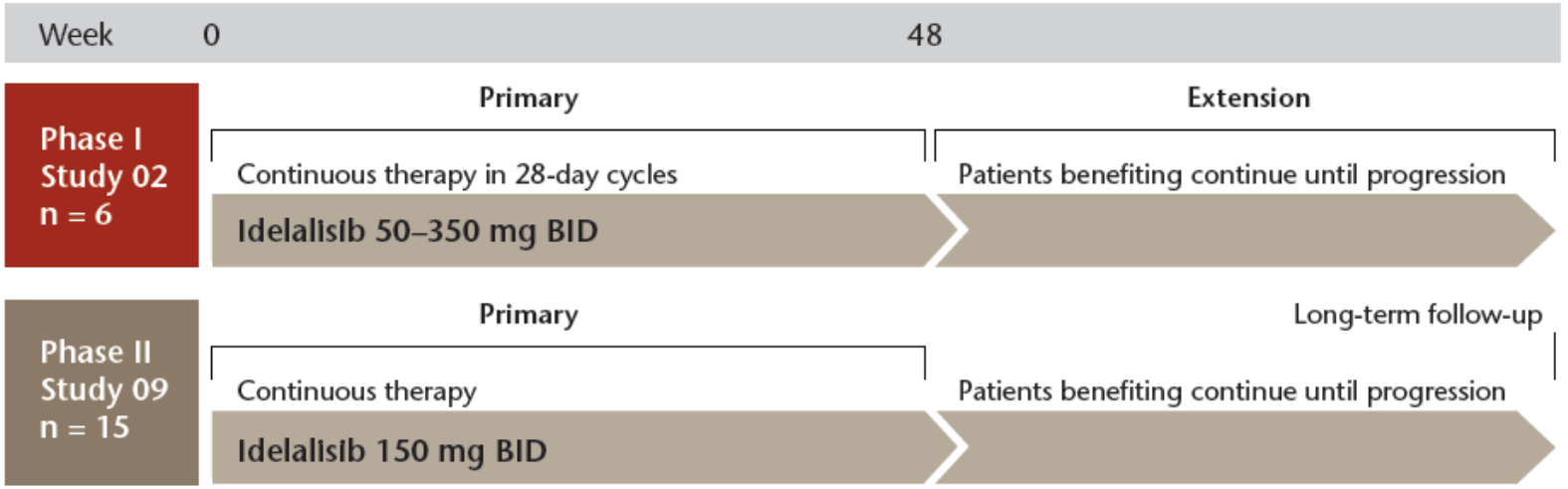
Background

- MZL comprises 5–17% of all adult cases of NHL
- There have been few randomized trials evaluating treatment options in patients with MZL
  - Hence, there is a lack of consensus about best practices
- **Objective:** to evaluate the efficacy and safety of idelalisib in patients with R/R MZL via a post hoc subgroup analysis of two clinical trials.

MZL = marginal zone lymphoma; NHL = non-Hodgkin lymphoma; R/R = relapsed/refractory

Study Design



- Study 02 (NCT00710528): a phase I, single-arm, dose-ranging study
  - Primary study accrual completed in January 2012; extension study is ongoing
  - Tumour assessments were performed at weeks 4, 8, 16, 24, 32, 40, and 48, and every 12 weeks thereafter using standard criteria for lymphoma
  - Primary endpoint: safety; secondary endpoint: ORR
- Study 09 (NCT01282424): a phase II, single-arm study of idelalisib monotherapy
  - Study accrual completed in October 2012
  - Tumour response was assessed at weeks 0, 8, 16, 24, 36, and 48, and every 12 weeks thereafter by an independent review committee of three radiologists and an oncologist/hematologist
  - Primary endpoint: ORR; secondary endpoints: DOR, PFS, safety

BID = twice a day; DOR = duration of response; ORR = overall response rate; PFS = progression-free survival

Key Eligibility Criteria

	Study 02	Study 09
Disease	• Previously treated	• Previously treated
Performance status	• World Health Organization performance status ≤2	• Eastern Cooperative Oncology Group status ≤2 • Karnofsky score >60
Prior therapy	• Refractory to or relapsed after ≥1 prior chemotherapy regimen and received rituximab as single agent or combined with other therapies	• Refractory to rituximab and an alkylating agent • Progression within 6 months of completing therapy • Documented on imaging
Measurable disease minimum requirement	• >2-cm lymph-node enlargement or symptomatic disease needing treatment	• >2-cm lymph-node enlargement
Organ function	• Serum ALT/AST <2 × ULN • Serum bilirubin <2 mg/dL • Serum creatinine <2 mg/dL	• Neutrophils >1,000 cells/μL • Hemoglobin >8 g/dL • Platelets >50,000/μL • Serum ALT/AST <2.5 × ULN • Serum bilirubin <1.5 × ULN • Serum creatinine <1.5 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

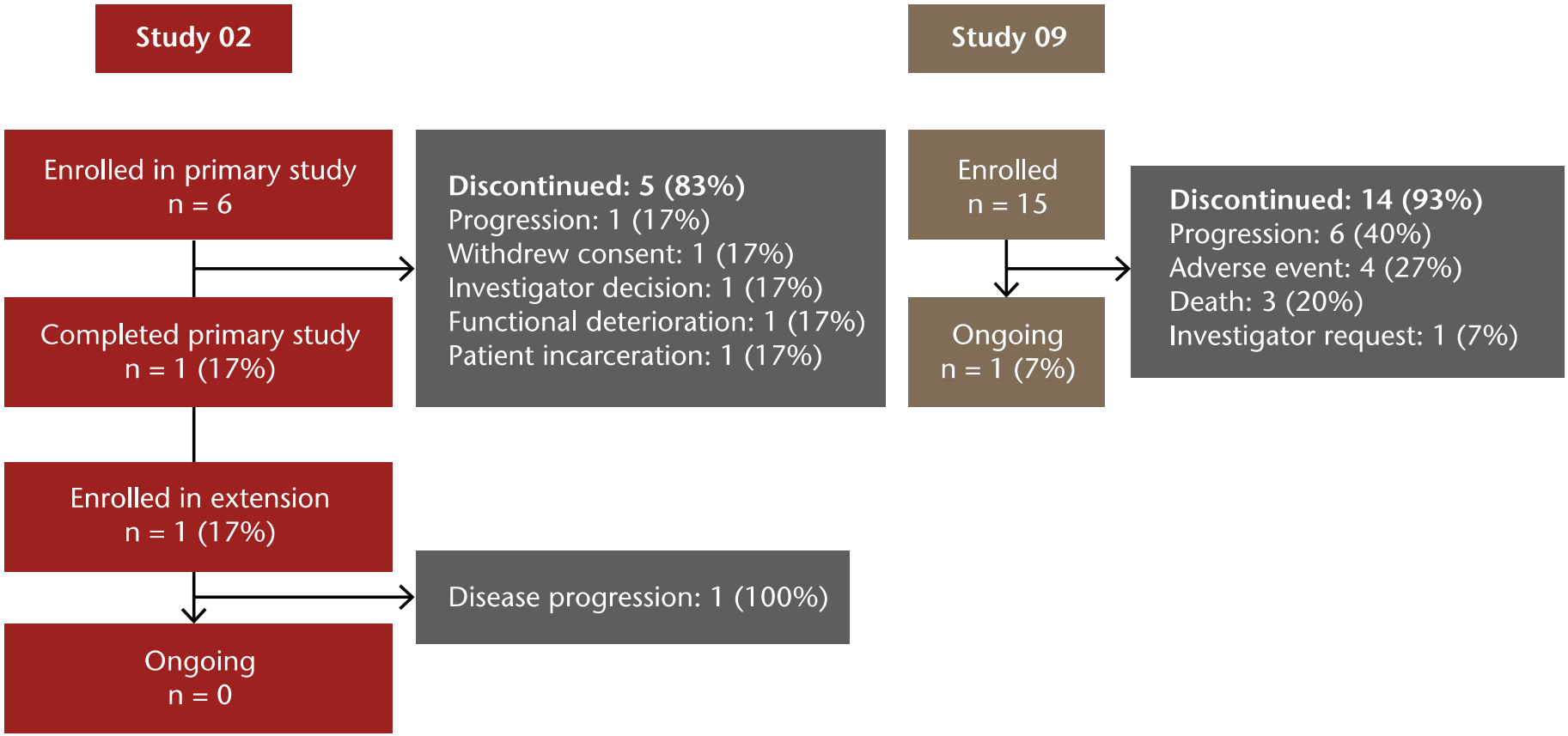
Baseline Characteristics

		Study 02 (n = 6)	Study 09 (n = 15)
Median age, years (range)		74 (62–91)	72 (50–87)
Male, n (%)		3 (50.0)	12 (80.0)
MZL subtype, n (%)	MALT NMZL SMZL	3 (50.0) 2 (33.3) 1 (16.7)	9 (60.0) 5 (33.3) 1 (6.7)
Ann Arbor stage IV, n (%)		6 (100.0)	13 (86.7)
Disease status, n (%)	Refractory* Relapsed	4 (66.7) 2 (33.3)	15 (100.0) N/A
Median number of prior regimens (range)		4.5 (1–10)	2.0 (2–9)
Idelalisib dose, n	150 mg bid × 28 days 150 mg bid × 21 days (21 days on, 7 days off) 200 mg bid × 28 days 350 mg bid × 28 days	— 3 1 2	15 — — —
Median idelalisib exposure, months (range)		5 (0.4–16.4)	6.4 (1.8–21.6)

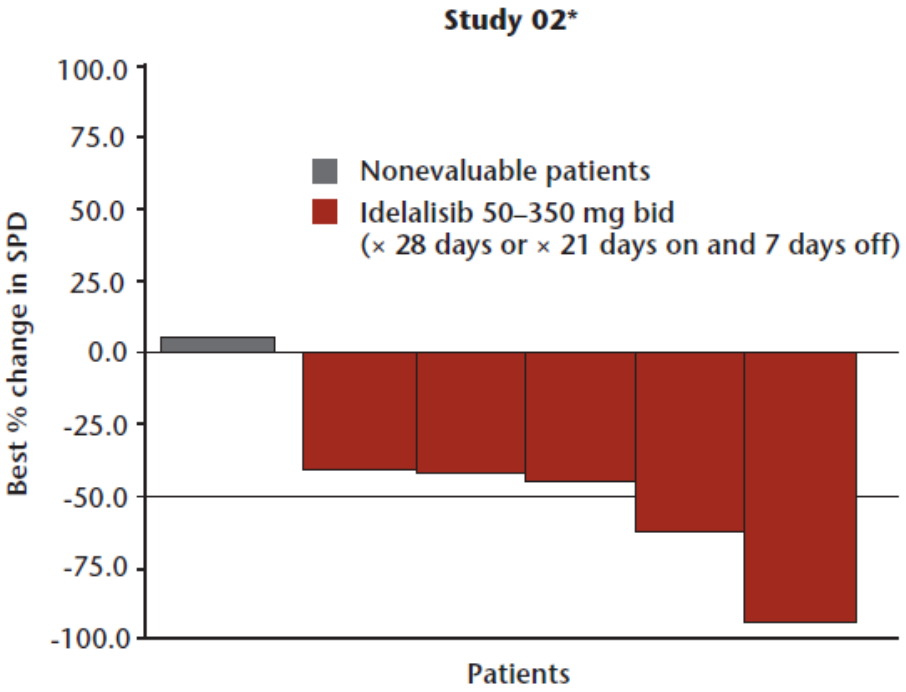
* All patients in Study 09 were double-refractory to rituximab and an alkylating agent.

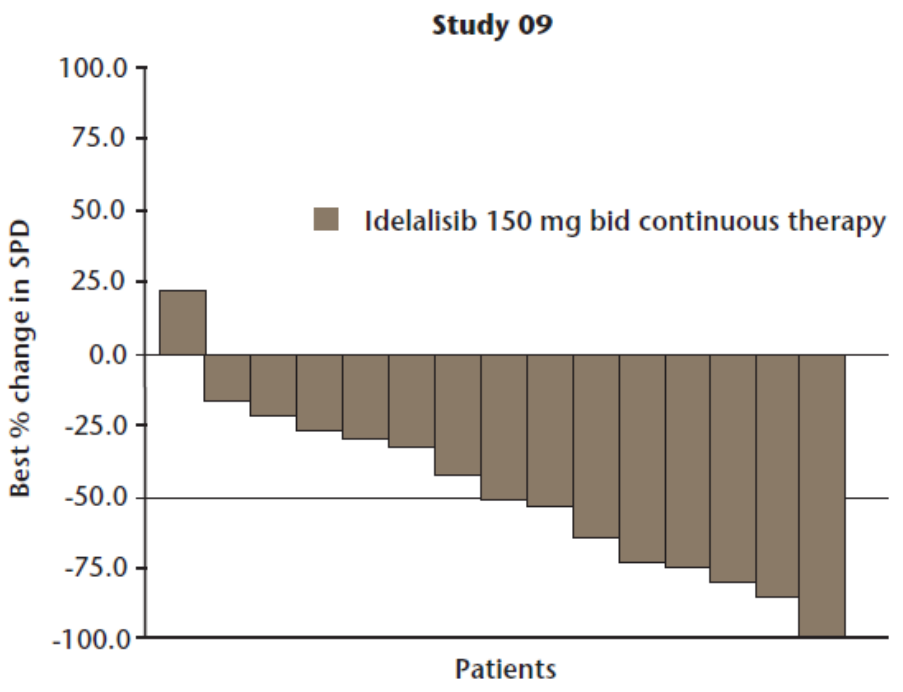
bid = twice a day; MALT = mucosa-associated lymphoid tissue; N/A = not available; NMZL = nodal marginal zone lymphoma; MZL = marginal zone lymphoma; SMZL = splenic marginal zone lymphoma

Patient Disposition



Nodal Response





bid = twice daily; SPD = sum of the products of the perpendicular diameters of measured lymph nodes
** Data available for core study only.*

Median follow-up was 3.1 months in Study 02 and 5.5 months in Study 09

Response Rates

ORR was 33% in Study 02 (2 PRs) and 47% in Study 09 (1 CR and 6 PRs)

- The disease control rate (CR/PR/SD) was 83% in Study 02 and 94% in Study 09
- One patient in each study had PD

In Study 02:

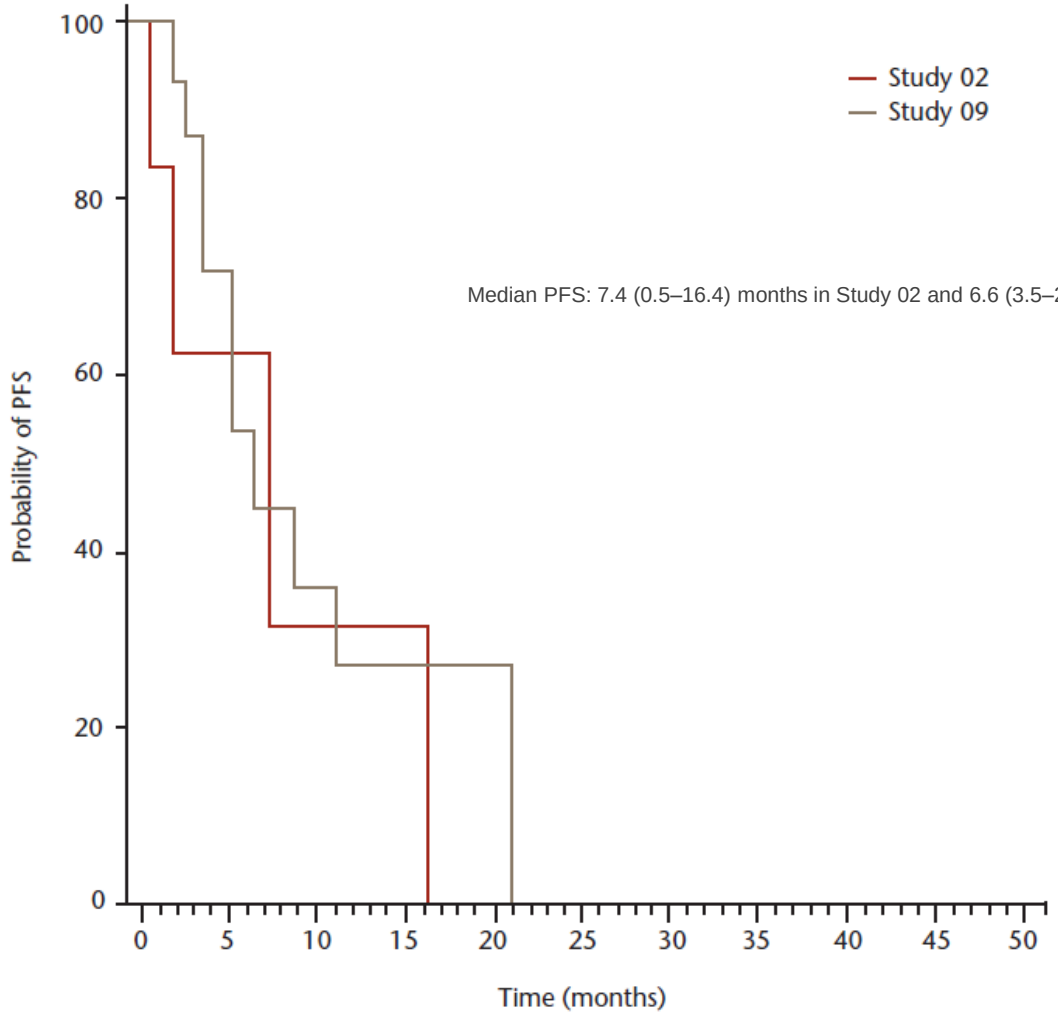
- One patient with NMZL and one with SMZL had a PR
  (both received idelalisib 350 mg bid)
- One patient with NMZL and two with MALT lymphoma had SD
  (2 patients received idelalisib 150 mg bid × 21 days on and 7 days off; one patient received idelalisib 200 mg bid)
- One patient with MALT lymphoma had PD
  (idelalisib 150 mg bid × 21 days on and 7 days off)

In Study 09:

- One patient with MALT lymphoma had a CR
- Four patients with MALT lymphoma, one with NMZL, and one with SMZL had a PR
- Four patients with MALT lymphoma and three with NMZL had SD
- One patient with NMZL had PD

bid = twice a day; CR = complete response; MALT = mucosa-associated lymphoid tissue; NMZL = nodal marginal zone lymphoma; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease; SMZL = splenic marginal zone lymphoma

PFS



Median PFS: 7.4 (0.5–16.4) months in Study 02 and 6.6 (3.5–22.1) months in Study 09

N at risk (events)

Study 02	6 (0)	2 (2)	1 (3)	1 (3)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)		
Study 09	15 (0)	13 (2)	6 (6)	5 (7)	3 (9)	2 (9)	2 (9)	1 (9)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)

PFS = progression-free survival

Efficacy

- Median time to response was one month in Study 02 and 3.5 (range: 1.8–5.5) months in Study 09
- Median (95% CI) DOR was 8.2 (1–15.4) months in Study 02 and 18.4 (3.6–18.4) months in Study 09
- Median OS was not reached in either study
  - In Study 02, OS was 100% at 1 year
  - In Study 09, median OS was 86.2% at 6 months, 79.0% at 9 months, and 71.8% at 1 year

CI = confidence interval; DOR = duration of response; OS = overall survival

Summary of AEs

n (%)	Study 02 (n = 6)		Study 09 (n = 15)	
	Any	Grade ≥3	Any	Grade ≥3
Any AE	6 (100)	6 (100)	15 (100)	12 (80.0)
Diarrhea	3 (50.0)	1 (16.7)	7 (46.7)	3 (20.0)
Chills	2 (33.3)	0	0	0
Fatigue	2 (33.3)	0	3 (20.0)	1 (6.7)
Pyrexia	2 (33.3)	0	1 (6.7)	0
Urinary tract infection	2 (33.3)	0	1 (6.7)	0
Dizziness	2 (33.3)	0	1 (6.7)	0
Decreased appetite	1 (16.7)	0	4 (26.7)	0
Nausea	1 (16.7)	0	4 (26.7)	0
Abdominal pain	1 (16.7)	0	3 (20.0)	0
Cough	0	0	3 (20.0)	0
Laboratory abnormality				
Anemia	2 (33.3)	2 (33.3)	3 (20.0)	1 (6.7)
Increased ALT	2 (33.3)	2 (33.3)	2 (13.3)	2 (13.3)
Increased AST	2 (33.3)	2 (33.3)	2 (13.3)	1 (6.7)
Neutropenia	2 (33.3)	2 (33.3)	6 (40.0)	3 (20.0)
Thrombocytopenia	4 (66.7)	4 (66.7)	3 (20.0)	2 (13.3)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase

Treatment Discontinuations and SAEs

- In Study 02, two patients (33.3%; n = 1, 150 mg bid × 21 days on 7 days off; n = 1, 350 mg bid × 28 days) discontinued because of AEs:
  - Thrombocytopenia (n = 2), hepatitis (n = 1), ALT elevation (n = 1) , and AST elevation (n = 1)
- In Study 09, seven patients (46.7%) discontinued because of AEs:
  - Diarrhea (n = 3), pneumonia (n = 2), ALT/AST elevation (n = 1), and septic shock (n = 1)
- There were three patients (50.0%) with SAEs in Study 02:
  - Thrombocytopenia (n = 2), anemia, asthenia, diarrhea, pneumonia, ALT/AST elevation, hematuria, renal failure (acute), and urinary retention (each n = 1)
- There were nine patients (60.0%) with SAEs in Study 09:
  - The most common SAEs were diarrhea (n = 3) and pneumonia (n = 2)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; bid = twice a day; SAE = serious adverse event

Summary and Conclusion

- Results of these post hoc analyses in small subgroups suggest that idelalisib monotherapy has clinical activity in patients with R/R MZL
  - Activity was apparent across the MALT, NMZL, and SMZL subgroups, with most patients able to achieve durable disease control
- Idelalisib was well tolerated
- No disease-specific safety signals were apparent
- Phase III trials of idelalisib combination therapy in patients with iNHL, including MZL, are currently underway (NCT01732913 and NCT01732926)

iNHL = indolent non-Hodgkin lymphoma; MALT = mucosa-associated lymphoid tissue; MZL = marginal zone lymphoma; NMZL = nodal marginal zone lymphoma; R/R = relapsed/refractory; SMZL = splenic marginal zone lymphoma