INTERIM UPDATE FROM A PHASE 2 MULTICENTER STUDY OF TAZEMETOSTAT, AN EZH2 INHIBITOR, IN PATIENTS WITH RELAPSED OR REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL) NHL-133

John Pagel¹, Franck Morschhauser², Hervé Tilly³, Aristeidis Chaidos⁴, Tycel Phillips⁵, Vincent Ribrag⁶, Phillip Campbell⁷, Christoph Fruchart⁸, Wojciech Jurczak⁹, Pamela McKay¹⁰, Stephen Opat¹¹, John Radford¹², Alice McDonald¹³, Haley Howell¹³, Kate Newberry¹³, Mark Woodruff¹³, Alicia Clawson¹³, John Larus¹³, Stephen Blakemore¹³, Harry Miao¹³, Gilles Salles¹⁴

¹Swedish Cancer Institute, Seattle, WA, USA, ²Centre Hospitalier Universitaire, Lille, France; ³Centre de Lutte Contre le Cancer Henri Becquerel, Rouen, France; ⁴Centre for Haematology, Department of Medicine, Imperial College London, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK; ⁵Division of Hematology and Oncology, University of Michigan, Ann Arbor, MI, USA; ⁶Gustave Roussy, Villejuif, France; ⁷Barwon Health, Geelong, VIC, Australia; ⁸Centre François Baclesse, Caen, France; ⁹UJCM, Krakow, Poland; ¹⁰Beatson West of Scotland Cancer Centre, Glasgow, Scotland, UK; ¹¹Monash University, Clayton, Australia; ¹²The University of Manchester, Manchester, UK; ¹³Epizyme, Cambridge, MA; ¹⁴Lyon-Sud Hospital Centre, Pierre-Bénite, France

OBJECTIVES

Tazemetostat for the Treatment of B-cell NHL

- EZH2 is an epigenetic regulator of gene expression and plays a critical role in multiple forms of cancer
 - Activating mutations of *EZH2* can act as an oncogenic driver, especially in FL and GCB-DLBCL, and is present in ~20% of patients
- Tazemetostat
 - First-in-class, potent, selective, reversible oral inhibitor of mutated and wild-type EZH2
 - Preclinical activity in DLBCL cell lines, with greater activity in EZH2 mutant models
 - Monotherapy activity and favorable safety in phase 1 studies in patients with relapsed or refractory NHL, as well as certain genetically defined solid tumors

Figure 1. Tazemetostat inhibits EZH2-mediated repression of transcription

METHODS

Tazemetostat Phase 2 NHL Study Design

- Global, multi-center, open-label study in 6 cohorts of patients with R/R FL or DLBCL
 - Patients prospectively assigned to cohorts according to *EZH2* mutational status
 - cobas® EZH2** Mutation Test (in development, Roche Molecular Systems)
 - ≥2 prior therapies
- Primary endpoint: overall response rate (ORR)
 - Secondary efficacy endpoints: progression-free survival (PFS) and duration of response (DOR)
 - Objective response assessed by IWG-NHL criteria (Cheson 2007)
 - Restaging every 8 weeks for 6 cycles, then every 12 weeks thereafter

Figure 2. Study design

RESULTS

Phase 2 NHL Study Progress; FL Cohorts

- Data cut-off:** May 1, 2018
- 82 patients enrolled into the FL cohorts
- Safety:** 82 patients
- Efficacy:**
 - FL wild-type *EZH2* – 54 evaluable for efficacy
 - Closed to accrual
 - FL mutated *EZH2* – 28 evaluable for efficacy
 - Open to accrual

Table 1. FL demographics and disease characteristics

Characteristic	EZH2 Status	
	Mutant (n=28)	Wild-type (n=54)
Age (years), median	61	61
Males, %	43	63
ECOG PS 0-1, %	96	93
B symptoms, n (%)	2 (7)	10 (19)
Median tumor burden ^a , mm ² (range)	2969 (162-16543)	2948 (128-29819)
Prior lines of therapy, n (%)		
1	1 (4)	0
2	12 (43)	17 (31)
3	6 (21)	10 (19)
4	3 (11)	11 (20)
≥ 5	5 (18)	16 (30)
median	3	4
Refractory to last regimen ^b , n (%)	10 (38)	22 (42)
Prior HSCT, %	11	39
Median time from initial diagnosis, years	5.1	6.4
Median time from last prior therapy, weeks	18.4	28.1

Data as of 01 May 2018. ^aSum of nodal plus extranodal; ^bRefractory to last regimen defined as SD or PD at best response to most recent prior therapy.

Table 2. Activity and durability observed across both cohorts

Best Response	FL EZH2 MT (n=28)	FL EZH2 WT (n=54)
Objective Response Rate (CR + PR), n (%)	20 (71)	18 (33)
95% CI ¹	51-87%	21-47%
Best response, n(%)		
Complete Response (CR)	3 (11)	3 (6)
Partial Response (PR)	17 (61)	15 (28)
Stable Disease (SD)	8 (29)	17 (31)
Study drug ongoing	6 (21)	1 (2)
Progressive Disease (PD)	0	17 (31)
No Data/Unknown (UNK)	0	2 (4)
Median Time to first Response, ^{2,3} weeks	11.9	15.9
Median Duration of response, ^{2,3} weeks	32.3+	76.0+
Patients with ongoing response, ^{3,4} n (%)	11 (55)	10 (56)
Median Progression-Free Survival, ^{3,4} weeks	48.6+	29.9
Median Progression-Free Survival (Responders), ^{3,4} weeks	48.6+	84.3+

Data as of 01 May 2018. Ongoing patients with Best Response of 'No Data, Unknown' are not included in this table. Patients who discontinued due to clinical or radiological progression without a valid response assessment are included in PD. ¹By Clopper-Pearson exact confidence interval. ²Calculated with Kaplan-Meier analysis. ³Not including time from Rollover study EZH-501. ⁴Includes discontinued patients with response ongoing at time of discontinuation. + Cohort median not yet reached.

Figure 3. Tumor change from baseline for mutated EZH2 FL patients

Data as of 01 May 2018. Plot does not include tumor measurements or status from Rollover study EZH-501. Per Cheson 2007, percent change of sum of target nodal lesion SPD and target extranodal lesion SPD.

Figure 4. Tumor response over time for mutated EZH2 patients

Data as of 01 May 2018. Plot does not include study days from Rollover study EZH-501.

Figure 5. Tumor change from baseline for wild-type EZH2 patients

Data as of 01 May 2018. Plot does not include tumor measurements or status from Rollover study EZH-501. Five wild-type FL EZH2 patients are not present as they do not have post-baseline scans. Per Cheson 2007, percent change of sum of target nodal lesion SPD and target extranodal lesion SPD.

Figure 6. Tumor response for wild-type EZH2 patients

Data as of 01 May 2018. Plot does not include study days from Rollover study EZH-501. Five wild-type FL EZH2 patients are not present as they do not have post-baseline scans.

Figure 7. Tumor change from baseline for FL patients

Data as of 01 May 2018. Plot does not include tumor measurements or status from Rollover study EZH-501. Five wild-type FL EZH2 patients are not present as they do not have post-baseline scans. Per Cheson 2007, percent change of sum of target nodal lesion SPD and target extranodal lesion SPD.

Table 3. Adverse events led to low rate of dose reductions and discontinuations in FL monotherapy

Patients, n(%) (N=82)	Treatment-Emergent Adverse Events (TEAEs) ¹	Treatment-related TEAEs
Adverse Event (AE), All grades	78 (95)	64 (78)
Grade ≥ 3	33 (40)	14 (17)
Serious AE	20 (24)	3 (4)
AE leading to dose interruption	24 (29)	15 (18)
AE leading to dose reduction	4 (5)	4 (5)
AE leading to drug discontinuation or study withdrawal	9 (11)	5 (6)

¹All treatment emergent adverse events that first appear during treatment, which were absent before or which worsened relative to the pre-treatment.

ACKNOWLEDGMENTS

We thank all of the physicians, study coordinators, site staff and most of all, the patients, caregivers, and families who have contributed to this study. We would also like to thank Drs. Barwick and Kanfer of Imperial College Healthcare NHS Trust for providing patient scans. Third-party writing assistance was provided by Ashfield Healthcare and funded by Epizyme, Inc.

Table 4. Few treatment-related grade ≥3 adverse events were observed

Adverse Event, n (%)	Patients (N=82)			
	Treatment Emergent Adverse Events (TEAEs) All Grades	Treatment Emergent Adverse Events (TEAEs) Grade ≥3	Treatment-Related TEAEs All Grades	Treatment-Related TEAEs Grade ≥3
Nausea	18 (22)	1 (1)	16 (20)	0
Fatigue	15 (18)	2 (2)	11 (13)	1 (1)
Anemia	14 (17)	5 (6)	11 (13)	3 (4)
Asthenia	12 (15)	3 (4)	8 (10)	1 (1)
Cough	12 (15)	0	1 (1)	0
Diarrhea	12 (15)	0	9 (11)	0
Upper respiratory tract infection	12 (15)	0	0	0
Alopecia	11 (13)	0	9 (11)	0
Back pain	10 (12)	0	0	0
Bronchitis	10 (12)	0	4 (5)	0
Headache	10 (12)	0	4 (5)	0
Thrombocytopenia	10 (12)	5 (6)	8 (10)	3 (4)
Abdominal pain	9 (11)	1 (1)	2 (2)	0
Muscle spasms	9 (11)	0	5 (6)	0
Pyrexia	9 (11)	0	1 (1)	0
Vomiting	9 (11)	1 (1)	4 (5)	0

Adverse events reported in ≥10% of patients. Data as of 01 May 2018.

Figure 8. Tumor response in a 62 year old female with EZH2 mutation

CONCLUSIONS

- Interim data from this phase 2 study of tazemetostat demonstrated clinical activity in heavily pretreated patients
 - ~71% ORR in patients with mutated EZH2
 - All patients showed a reduction in tumor volume
 - 35 patients (68%) enrolled as of June 8, 2018
 - ~33% ORR in patients with wild-type EZH2
 - Enrollment is complete
- Durable clinical responses and progression-free survival were observed in patients with or without an activating EZH2 mutation
- Tazemetostat was generally well tolerated
- Promising results from these interim data continue to support EZH2 as a potential novel and valid therapeutic target in relapsed/refractory follicular lymphoma

Copies of this poster obtained through QR (Quick Response) code are for personal use only and may not be reproduced without written permission from the author of this poster.