# Interim Update From a Phase 2 Multicenter Study of Tazemetostat, an EZH2 Inhibitor, in Patients With Relapsed or Refractory Follicular Lymphoma

Franck Morschhauser[1], Herve Tilly[2], Aristeidis Chaidos[3], Tycel Phillips[4], Vincent Ribrag[5], Phillip Campbell[6], Damaj Ghandi Laurent[7], Wojciech Jurczak[8], Pamela McKay[9], Stephen Opat[10], John Radford[11], Anand Rajarethinam[12], Jay Yang[12], Susan Navia[12], Kate J. Newberry[12], Deyaa Adib[12], Gilles Salles[13]

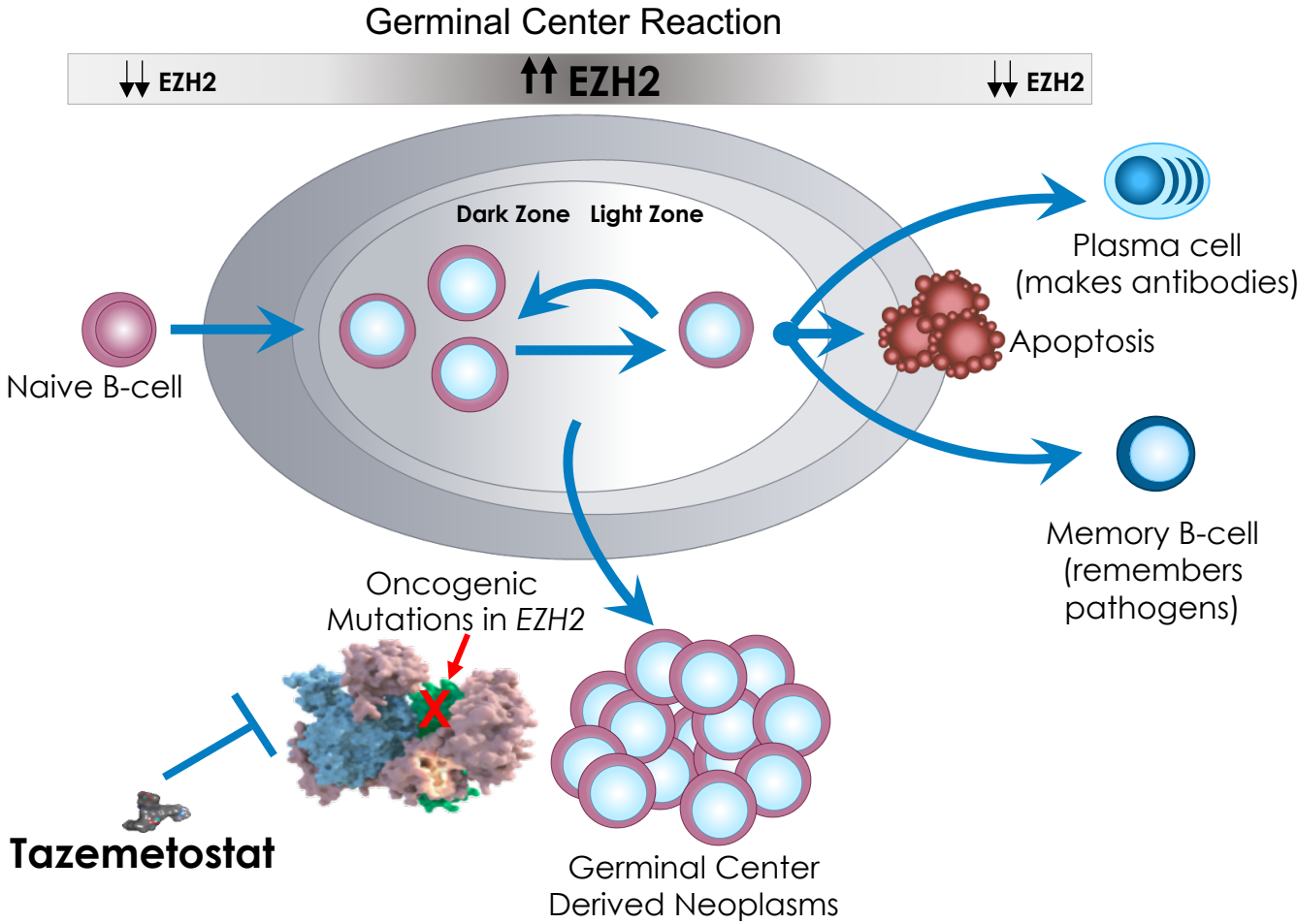
[1]Centre Hospitalier Universitaire, Lille, France; [2]Centre de Lutte Contre le Cancer Henri Becquerel, Rouen, France; [3]Centre for Haematology, Department of Medicine, Imperial College London, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK; [4]Division of Hematology and Oncology,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

# CONFLICT OF INTEREST DISCLOSURE

- Employment or leadership position: None
- Consultant or advisory role: Epizyme, Gilead, Servier, Roche/Genentech
- Stock ownership: None
- Honoraria: Celgene, BMS, Janssen
- Research funding: None
- Other remuneration: None

# FOLLICULAR LYMPHOMA (FL) AND EZH2

- *EZH2* is an epigenetic regulator of gene expression and cell fate decisions[1]
- *EZH2* is required for normal B-cell biology and germinal center formation[2]
  - Oncogenic mutations in *EZH2* suppress exit from germinal state and "lock" B cells in this state thereby transforming into a cancer[2]
- *EZH2* biology relevant in both mutant (MT) and wild-type (WT) *EZH2* FL
  - ~20% of patients with FL also have *EZH2* gain of function mutations[3]



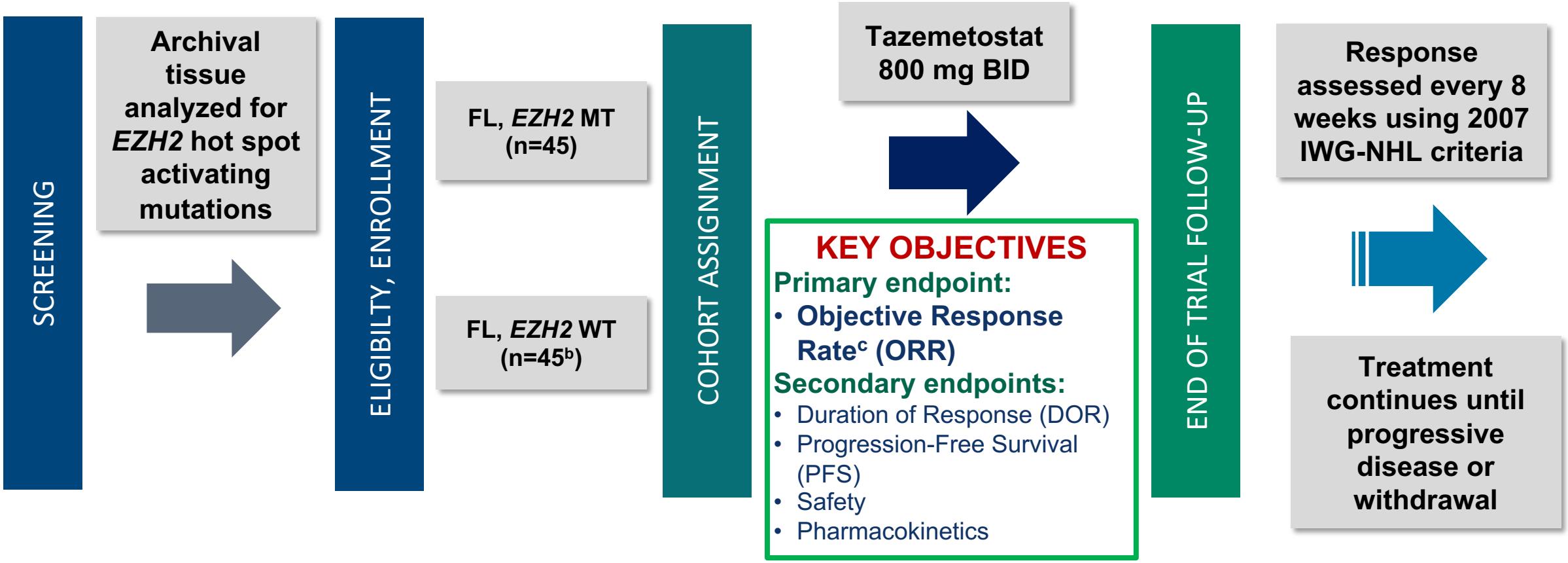

**Tazemetostat, an investigational, first-in-class, selective, oral inhibitor of EZH2 has shown antitumor activity in non-Hodgkin's lymphoma patients with either MT or WT EZH2[4,5]**




1. Gan L, et al. *Biomark Res*. 2018;6(1):10; 2. Béguelin W, et al. *Cancer Cell*. 2013;23(5)677-692. 3. Bödör C, et al. *Blood*. 2013;122:3165-3168. 4. Italiano A, et al. *Lancet Oncol*. 2018;19(5):649-59; 5. Morschhauser F, et al. *Hematol Oncol*. 2017 Jun;35:24-5.

# PHASE 2, OPEN-LABEL, MULTI-CENTER STUDY OF TAZEMETOSTAT

- Enrollment initiated July 2015 ; last data cut June 7, 2019[a]
- Conducted at 56 sites across North America, Europe, Asia, and Australia






[a] Ongoing study, preliminary datacut as of June 7, 2019. [b] Actual enrollment N=54. [c] ORR defined as the number of participants with a best overall response of complete response or partial response. BID, twice-daily; EOT, end of treatment; FL, follicular lymphoma; IWG-NHL, International, Working Group for non-Hodgkin's lymphoma; MT, mutant; WT, wild-type.

# KEY ELIGIBILITY CRITERIA[a]

| KEY ELIGIBILITY CRITERIA |
| --- |
| Age ≥18 years |
| Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 |
| Life expectancy ≥3 months |
| Histologically confirmed FL, all grades. Patients may have relapsed/refractory disease following ≥2 standard prior systemic treatment regimens where at least 1 anti-CD20-based regimen was used |
| Has measurable disease based on IWG-NHL[1] |



[a] For a full list of study eligibility criteria, please see Clinitcaltrials.gov. 1.Cheson, BD, et al. *J Clin Oncol*. 2007;25(5):579–586. FL, follicular lymphoma; IWG-NHL 2007, International Working Group criteria for non-Hodgkin's lymphoma.

# BASELINE DEMOGRAPHICS

## Intent-to-Treat Population

| Characteristic | MT *EZH2* n=45[a] | WT *EZH2* n=54[b] |
|---|---|---|
| Median age, years (range) | 62 (38–80) | 61 (36–87) |
| Males, n (%) | 19 (42) | 34 (63) |
| ECOG PS 0–1, n (%) | 45 (100) | 49 (91) |
| Prior lines of anticancer therapy[c], n (%) | | |
| 1 | 2 (4) | 0 (0) |
| 2 | 22 (49) | 18 (33) |
| 3 | 10 (22) | 11 (20) |
| 4 | 5 (11) | 9 (17) |
| ≥5 | 6 (13) | 16 (30) |
| Median (range) | 2 (1-11) | 3 (2–8) |

| Characteristic | MT *EZH2* n=45[a] | WT *EZH2* n=54[b] |
|---|---|---|
| Patients with transformed FL or Grade 3 B, n (%) | 3 (7) | 8 (15) |
| Refractory to rituximab containing regimen, n (%) | 18 (40) | 33 (61) |
| Refractory to last regimen[d], n (%) | 18 (40) | 20 (37) |
| Prior HSCT, n (%) | 4 (9) | 21 (39) |
| Double Refractory, n (%) | 10 (22) | 21 (39) |
| Median time from initial diagnosis, years | 4.7 | 6.5 |
| Median time from last exposure to last prior therapy, months | 4.2 | 6.8 |

[a] Two patients were not evaluable in MT due to unavailability of scan data in the database
[b] One patient not evaluable in WT as they withdrew consent before first scan



[c] Excludes maintenance, consolidation, adjuvant and neoadjuvant therapies when counted as their own line; [d] Denominator includes patients with response to last regimen of complete response, partial response, stable disease, or progressive disease; unknowns/missing patients are excluded. ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplantation; ITT, intent-to-treat; MT, mutant; PS performance status; WT, wild-type.

# ADVERSE EVENTS (AEs) IN ≥10% PATIENTS

| Category, n (%) | All Treatment-Emergent AEs (TEAEs) (N=99) | | Treatment-related AEs (N=99) | |
|---|---|---|---|---|
| | All Grades[a] | Grade ≥3[b] | All Grades[a] | Grade ≥3[b] |
| Nausea | 24 (24) | 0 (0) | 20 (20) | 0 (0) |
| Asthenia | 19 (19) | 4 (4) | 15 (15) | 2 (2) |
| Diarrhea | 18 (18) | 0 (0) | 12 (12) | 0 (0) |
| Fatigue | 17 (17) | 2 (2) | 12 (12) | 1 (1) |
| Alopecia | 17 (17) | 0 (0) | 14 (14) | 0 (0) |
| Cough | 16 (16) | 0 (0) | 2 (2) | 0 (0) |
| Upper respiratory tract infection | 15 (15) | 0 (0) | 1 (1) | 0 (0) |
| Bronchitis | 15 (15) | 0 (0) | 3 (3) | 0 (0) |
| Anemia | 14 (14) | 5 (5) | 9 (9) | 2 (2) |
| Abdominal pain | 12 (12) | 1 (1) | 2 (2) | 0 (0) |
| Headache | 12 (12) | 0 (0) | 5 (5) | 0 (0) |
| Vomiting | 12 (12) | 2 (2) | 6 (6) | 1 (1) |
| Back pain | 11 (11) | 0 (0) | 0 (0) | 0 (0) |
| Pyrexia | 10 (10) | 0 (0) | 2 (2) | 0 (0) |
| Thrombocytopenia | 10 (10) | 5 (5) | 8 (8) | 3 (3) |

- Treatment with tazemetostat was generally well tolerated
  - 5% patients discontinued treatment due to a treatment-related AE
  - 9% patients had a dose reduction due to a treatment-related AE
  - Low rate of grade ≥3 treatment related AEs
- There were no treatment-related deaths



[a] All grades TEAEs reported as occurring in ≥10% of patients; [b] Grade ≥3 TEAEs reported in ≥5% patients.

# CLINICALLY MEANINGFUL RESPONSE FOR BOTH MT AND WT *EZH2* FL PATIENTS

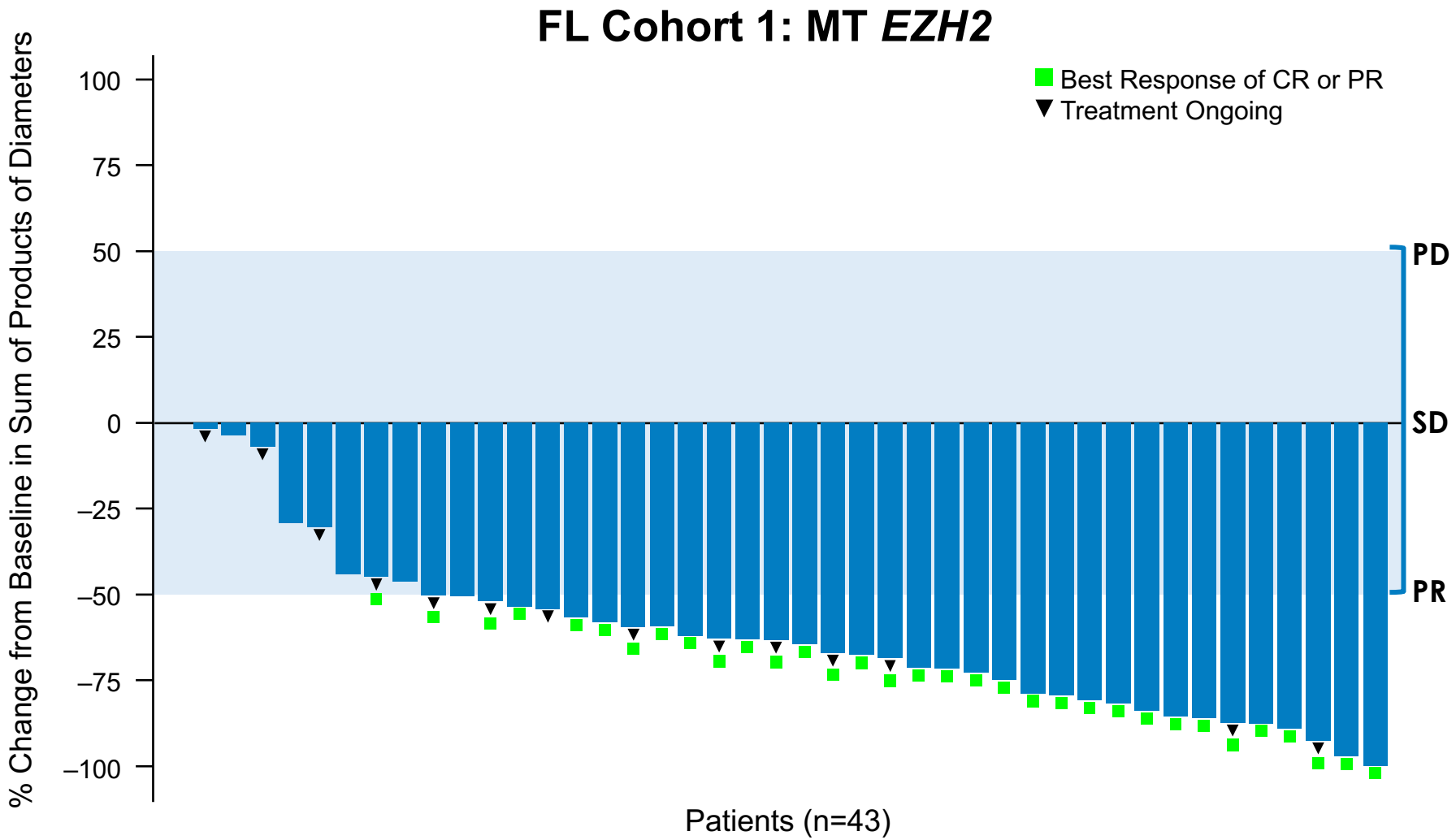
## Primary endpoint: ORR in Response Evaluable Population

| Endpoint<br>n (%) | MT *EZH2*<br>(n=43) | WT *EZH2*<br>(n=53) |
|---|---|---|
| ORR [CR+PR] | 33 (77%) | 18 (34%) |
| 95% CI[a] | (61.4–88.2) | (21.5–48.3) |
| CR | 3 (7%) | 3 (6%) |
| PR | 30 (70%) | 15 (28%) |
| SD | 10 (23%) | 16 (30%) |
| SD, treatment ongoing | 4 (9%) | 0 |
| DCR (CR+PR+SD) | 43 (100%) | 34 (64%) |
| PD | 0 | 19 (36%) |



Best overall response based on Cheson (2007) criteria for lymphomas. [a] By Brookmeyer and Crowley method. CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; MT, mutant; PD, progressive disease; PR, partial response; SD, stable disease; WT, wild-type.

# TUMOR CHANGE FROM BASELINE FOR MT *EZH2* FL PATIENTS

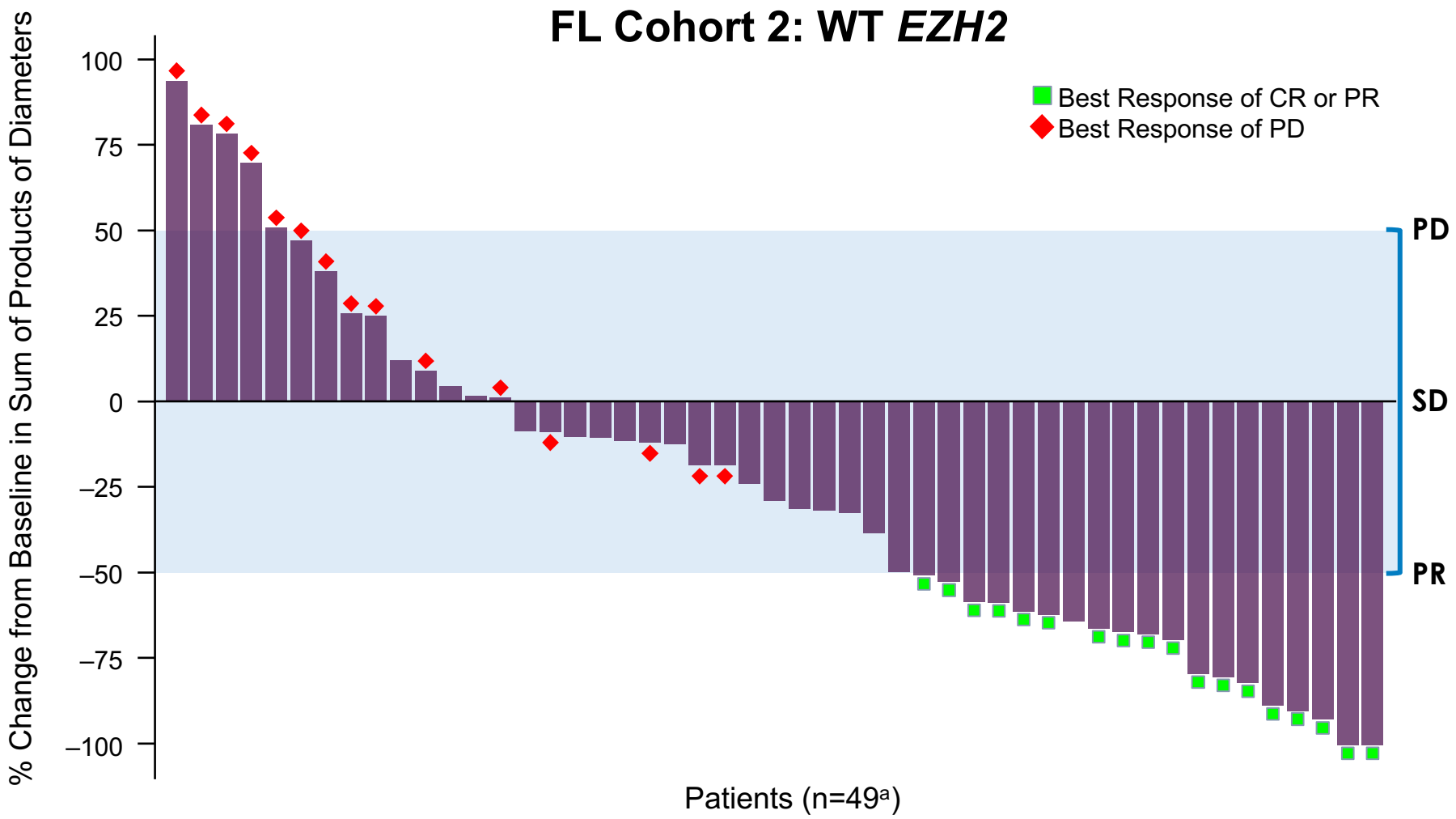



- **43 of 43 (100%) patients with evidence of tumor reduction**



CR, complete response; FL, follicular lymphoma; MT, mutant; PD, progressive disease; PR, partial response.

# TUMOR CHANGE FROM BASELINE FOR WT *EZH2* FL PATIENTS

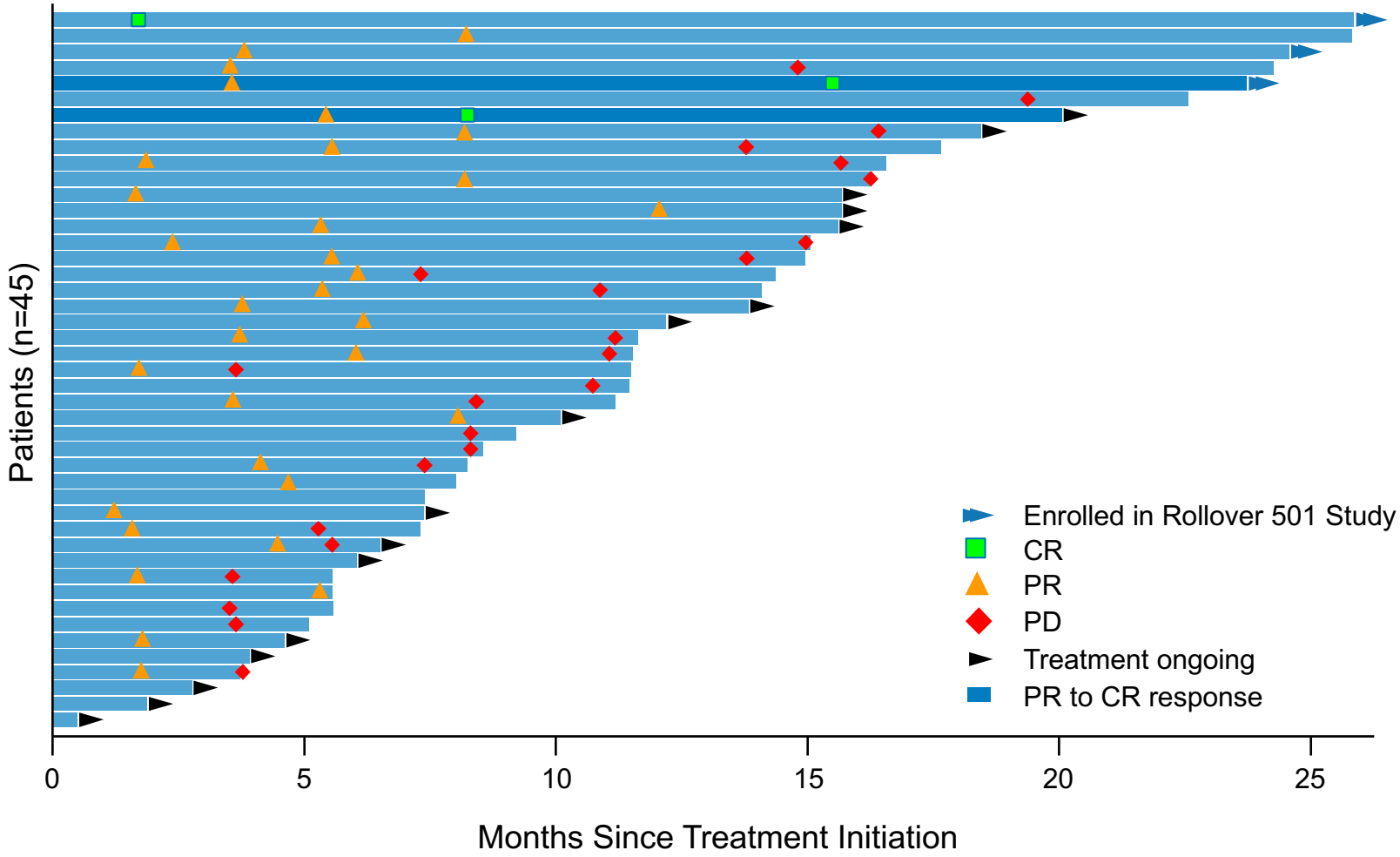



- **35 of 49 (71%) patients with evidence of tumor reduction**



[a] Of 53 evaluable patients. CR, complete response; FL, follicular lymphoma; PD, progressive disease; PR, partial response; WT, wild-type.

# TUMOR RESPONSE OVER TIME FOR MUTATED *EZH2* PATIENTS

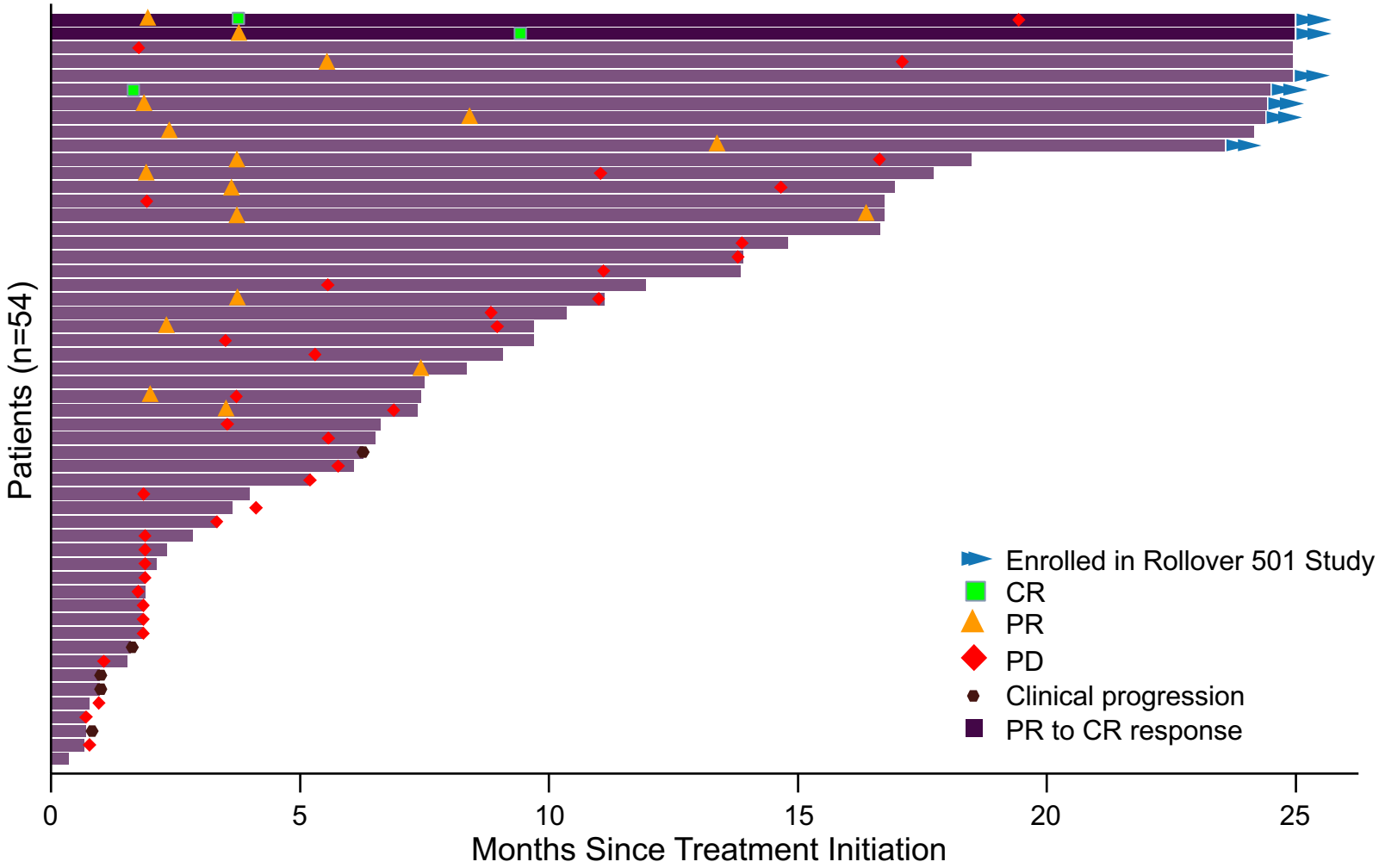



- **Median time to first response, 4.2 months**
- **Median follow-up of 15.9 months**
- **Median DOR not mature**
- **11 (24%) patients enrolled in the past 12 months**
- **17 (38%) patients ongoing**



CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response.

# TUMOR RESPONSE OVER TIME FOR WILD-TYPE *EZH2* PATIENTS




- **Median time to first response, 3.7 months**
- **Median follow-up of 24.9 months**
- **Median DOR, 13 months**



CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response.

# ACTIVITY AND DURABILITY OBSERVED ACROSS BOTH COHORTS

| Endpoint | Response Evaluable Population MT *EZH2* n=43 | WT *EZH2* n=53 |
|---|---|---|
| Median time to first response, months (range) | 4.2 (3.5–5.4) | 3.7 (2.1–3.8) |
| Median duration of response, months (95% CI) | 8.3[a] (4.0–12.7) | 13.0 (7.3–NE) |
| Median PFS, months (95% CI) | 11.1[a] (8.4–15.7) | 5.7 (3.5–11.1) |
| Median OS, months (95% CI) | Not reached (NR) (NE–NE) | 38.4 (25.0–NE) |
| Median follow-up, months (range) | 15.9 (0.4– 40.3) | 24.9 (0.3– 46.0) |

**Maximum DOR MT *EZH2*: 22.2 months; WT *EZH2* 22.6 months**

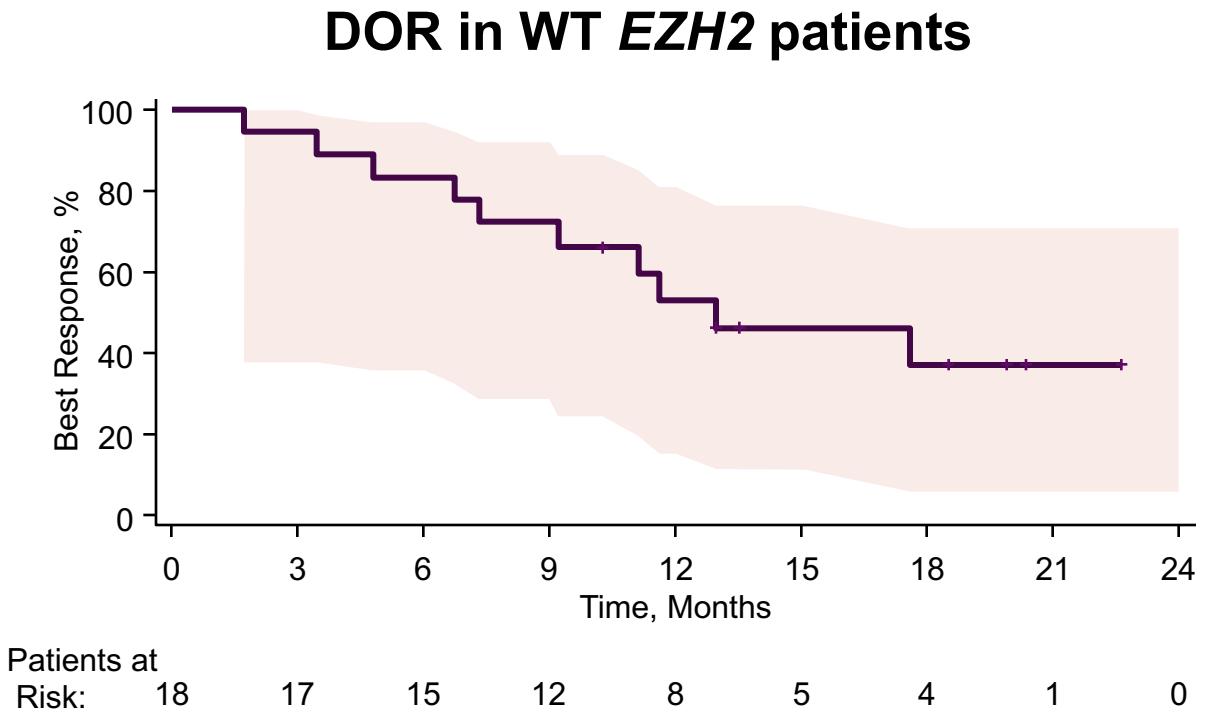
[a] Median DOR and PFS not mature for the MT cohort
11 (24%) patients enrolled in the past 12 months
17 (38%) patients ongoing



CI, confidence interval; DOR, duration of response MT, mutant; NE, not estimable; WT, wild-type.

# LANDMARK ANALYSIS FOR RESPONDERS IN WT *EZH2*

| Endpoint, n (%) | WT *EZH2* (n=18) |
|---|---|
| Patients with response ≥ 6 months | 15 (83) |
| Patients with response ≥ 12 months | 9 (50) |
| Patients with response ≥ 16 months | 6 (33) |



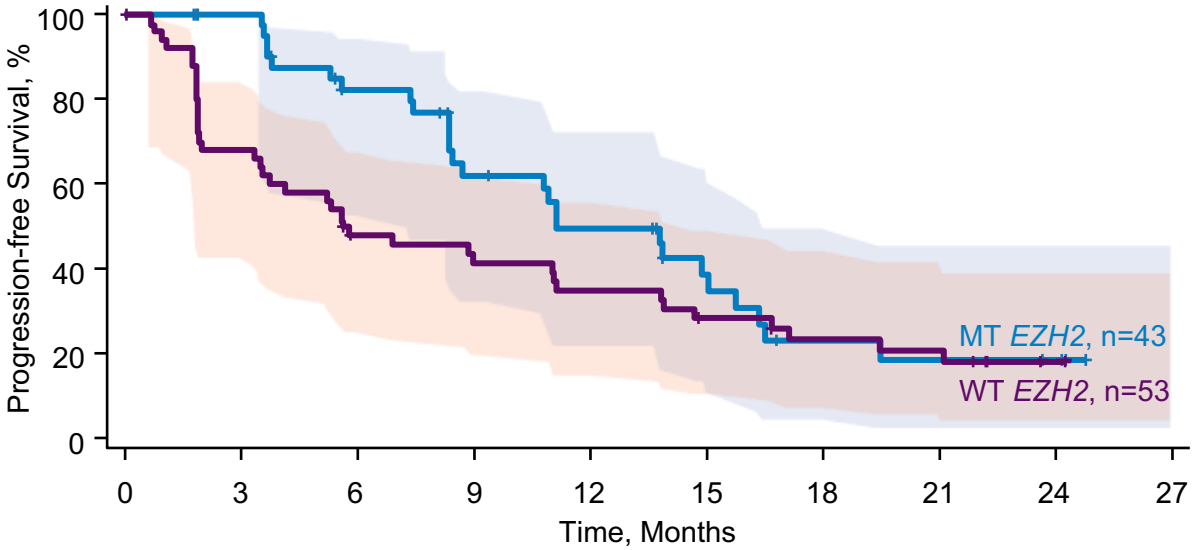



+, censored; DOR, duration of response; WT, wild-type.

# PROGRESSION-FREE AND OVERALL SURVIVAL

## Response Evaluable Population

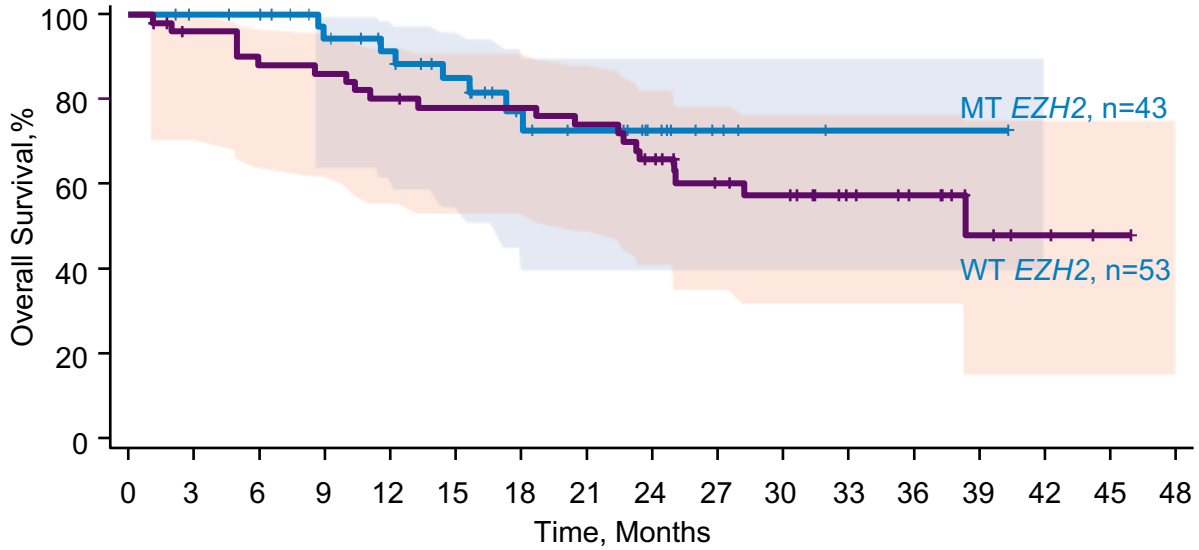
### PFS




Patients at Risk:

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| MT *EZH2* | 43 | 40 | 30 | 21 | 16 | 10 | 5 | 4 | 3 | 0 |
| WT *EZH2* | 53 | 34 | 22 | 19 | 16 | 12 | 9 | 8 | 1 | 0 |

### OS




Patients at Risk:

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MT *EZH2* | 43 | 41 | 40 | 34 | 30 | 25 | 17 | 14 | 9 | 4 | 2 | 1 | 1 | 1 | 0 | 0 | 0 |
| WT *EZH2* | 53 | 48 | 44 | 43 | 40 | 38 | 38 | 36 | 31 | 21 | 19 | 13 | 10 | 5 | 3 | 1 | 0 |

| Endpoint | Response Evaluable Population<br>MT *EZH2* (n=43) | <br>WT *EZH2* (n=53) |
|---|---|---|
| Median PFS, months (95% CI) | 11.1[a] (8.4–15.7) | 5.7 (3.5–11.1) |
| Median OS, months (95% CI) | Not reached (NR) (NE–NE) | 38.4 (25.0–NE) |



[a], Median PFS not mature for MT cohort; +, censored; CI, confidence interval; FL, follicular lymphoma; MT, mutant; NE, non-estimable; OS, overall survival; PFS, progression-free survival.

# SUMMARY

Tazemetostat, a first-in-class investigational EZH2 inhibitor, demonstrates durable, single agent, antitumor activity in difficult-to-treat patients with relapsed / refractory FL with

- An ORR of 77% and 34% in MT and WT *EZH2*, respectively
- All patients in the MT cohort and a majority of patients in WT cohort demonstrating a reduction in tumor volume
- Durable clinical activity across both MT and WT cohorts, with patients on therapy up to 23 months, and responses continuing to deepen over time.
- PFS of 11.1 and 5.7 months in MT and WT *EZH2*, respectively

Tazemetostat is well tolerated in FL patients, and is associated with a low frequency of drug-related AEs, including grade ≥3 TEAEs, and a low frequency of dose reduction or discontinuation due to AEs

Tazemetostat, if approved, represents a potential therapeutic option for patients with relapsed/refractory follicular lymphoma



AE, adverse event; FL, follicular lymphoma; MT, mutant; ORR, objective response rate; PFS, progression-free survival; TEAE, treatment emergent adverse event; WT, wild-type

## ACKNOWLEDGMENTS

Epizyme thanks all sites, study coordinators, and most of all, the patients, caregivers, and families that have contributed to the study