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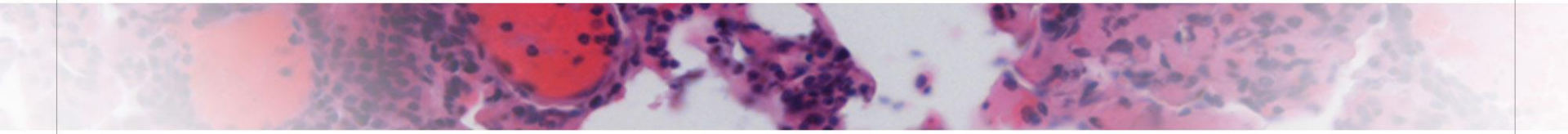

Analyzing Efficacy Outcomes From the Phase 2 Study of Single-Agent Tazemetostat as Third-Line Therapy in Patients With Relapsed or Refractory Follicular Lymphoma to Identify Predictors of Response

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Background

- Tazemetostat is a first-in-class, selective oral EZH2 inhibitor that was recently approved by the US FDA for treatment of patients with R/R FL[1] after demonstrating single-agent, antitumor activity in patients with WT or MT *EZH2*[2]
- POD24, exposure to multiple lines of prior therapy, and refractoriness to rituximab therapy can adversely affect the prognosis of patients receiving second- or third-line treatment regimens for R/R FL, including chemoimmunotherapy[3-5]

Objective

- Perform a post hoc exploratory analysis to better understand how these factors impact the outcomes in patients receiving tazemetostat, independently of *EZH2* mutation status

1. Tazverik [package insert]. Cambridge, MA: Epizyme, Inc.; 2020. **2.** Morschhauser F, et al. *Lancet Oncol*. 2020;21(11):1433-42. **3.** Juriovic V, et al. *Blood*. 2016;128(8):1112-20. **4.** Nastoupil LJ, et al. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):189-93. **5.** Li M, et al. *Medicine (Baltimore)*. 2017 Sep;96(35):e7988.

EZH2, enhancer of zeste homolog 2; FDA, Food and Drug Administration; FL, follicular lymphoma; MT, mutant; POD24, progression of disease within 24 months; R/R, relapsed/refractory; WT, wild type.

Model and Statistical Analysis

- Pooled patient data from the phase 2 open-label, multicenter study (NCT01897571) that evaluated tazemetostat 800 mg twice daily in patients with WT or MT *EZH2* R/R FL[1]
- Performed predictive modeling to identify variables predictive of response (ORR, DOR, and PFS by IRC assessment)
  - Stepwise logistic and Cox regression were used to determine possible predictors[b]
  - A final model was run using possible predictors identified from previous regressions
  - Contingency tables and K-M plots were used to examine significant variables ($P<0.05$)
- Initial exploratory statistical modeling using multiple demographic and baseline disease variables suggested that the number of prior therapies may be predictive of ORR and refractoriness to rituximab may be predictive of DOR, while both variables may be predictive of PFS
- We present here further exploratory analyses examining the relevant clinical variables potentially predictive for ORR, DOR, and PFS[a]

[a]95 observations were used.

[b]Inclusion at a specified step was based on $P\leq0.40$. Final model inclusion was based on $P\leq0.20$.

1. Morschhauser F, et al. *Lancet Oncol*. 2020;21(11):1433-42.

CR, complete response; DOR, duration of response; IRC, independent radiology committee; K-M, Kaplan-Meier; MT, mutant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; WT, wild type.

Phase 2 Efficacy Outcomes

Efficacy Outcome[a]	Combined WT and MT *EZH2* (N=99)	WT *EZH2* (n=54)[1]	MT *EZH2* (n=45)[1]
ORR, % (95% CI)	51 (40–61)	35 (23-49)	69 (53-82)
Median DOR, months (95% CI)	11 (7–19)	13 (6-NE)	11 (7-NE)
Median PFS, months (95% CI)	12 (8–15)	11 (4-15)	14 (11-22)
Median OS, months (95% CI)	NR (38–NE)	NR	NR

- The DOR was consistent between WT and MT *EZH2* groups[1]
- Consistent ORRs were also observed across high-risk subgroups, such as patients with POD24, double-refractory disease, and refractoriness to rituximab therapy, regardless of mutation status[1]

[a]ORR, DOR, and PFS are based on IRC assessments.

1. Morschhauser F, et al. *Lancet Oncology*; 2020;21(11):1433-42.

CI, confidence interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EZH2, enhancer of zeste homolog 2; IRC, independent radiology committee; MT, mutant; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; MT, mutant; NE, not evaluable; NR, not reached; PFS, progression-free survival; WT, wild type.

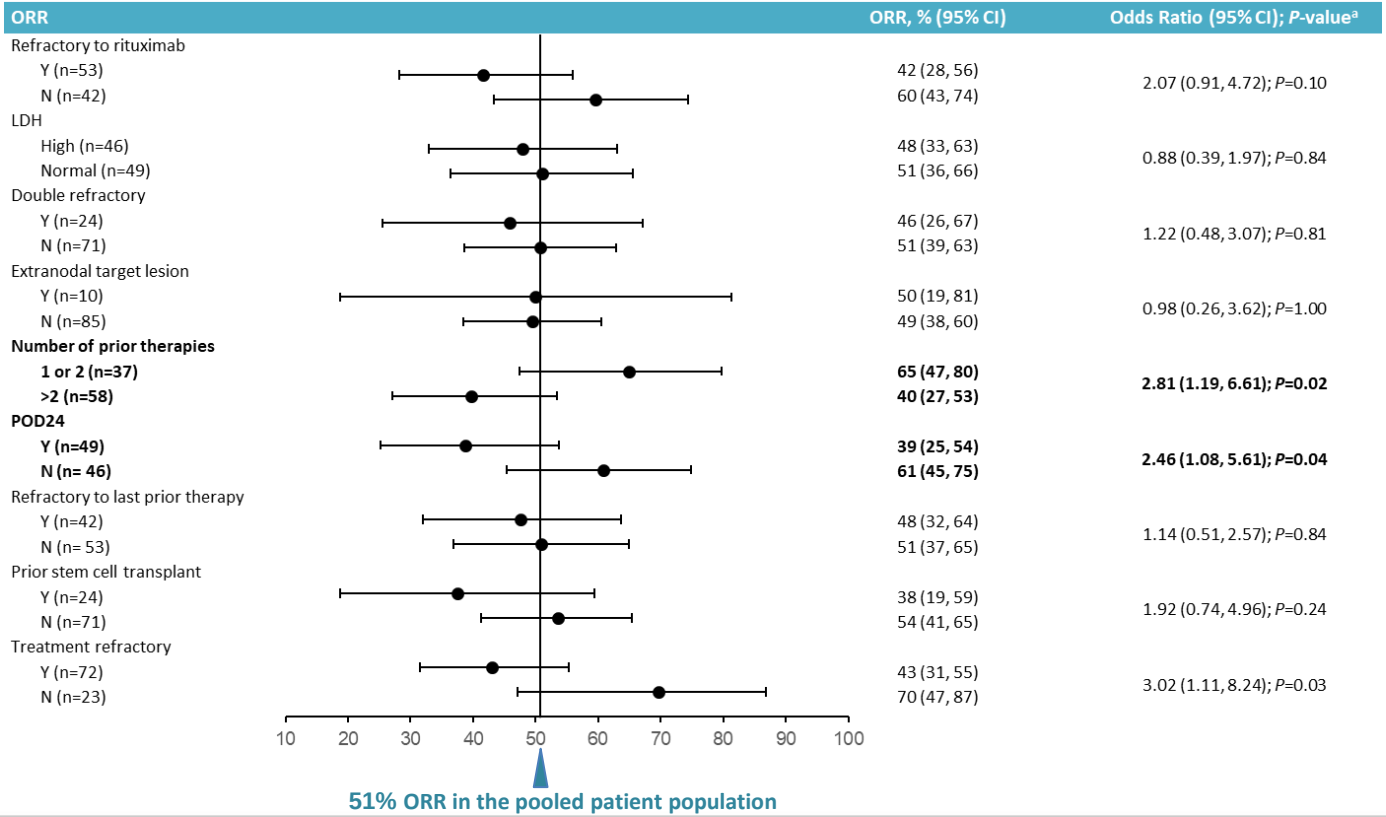
Exploratory Analysis in Subset of Disease Characteristics

Variables Examined

- LDH (high vs normal)
- Double refractory
- Extranodal target lesion (Y or N)
- Number of prior therapies (1 or 2 vs >2)
- POD24
- Refractory to last prior therapy
- Refractory to rituximab regimen
- Prior stem cell transplant

DOR, duration of response; LDH, lactate dehydrogenase; ORR, objective response rate; PFS, progression-free survival; POD24, progression of disease within 24 months.

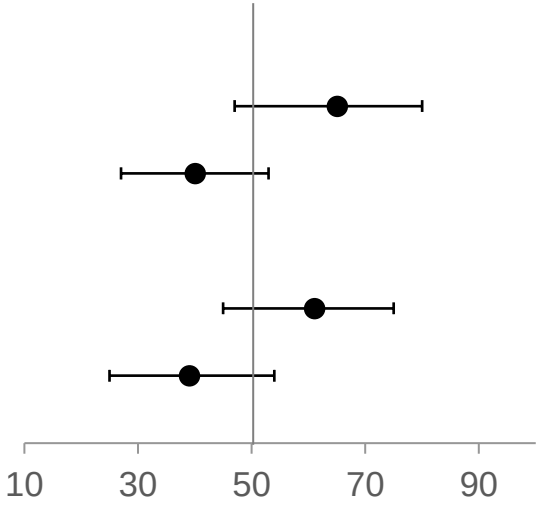
ORR for Clinical Variables



[a]*P*-values represent predictive variables identified in the regression analysis and do not represent significant differences between groups. CI, confidence interval; DOR, duration of response; LDH, lactate dehydrogenase; ORR, objective response rate; POD24, progression of disease within 24 months.

Variables Identified as Predictive of ORR

ORR	Rate, % (95% CI)	Odds Ratio (95% CI) P-value
Number of prior therapies		
1 or 2 (n=37)	65 (47, 80)	2.81 (1.19, 6.61) *P*=0.02
>2 (n=58)	40 (27, 53)	
POD24		
No (n=46)	61 (45, 75)	2.46 (1.08, 5.61) *P*=0.04
Yes (n=49)	39 (25, 54)	

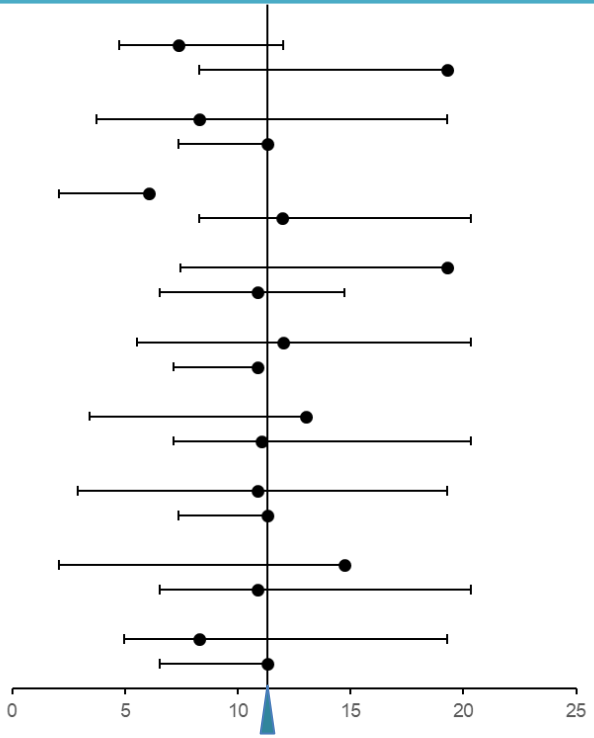


51% ORR in the pooled patient population

CI, confidence interval; DOR, duration of response; ORR, objective response rate; POD24, progression of disease within 24 months.

DOR for Clinical Variables[a]

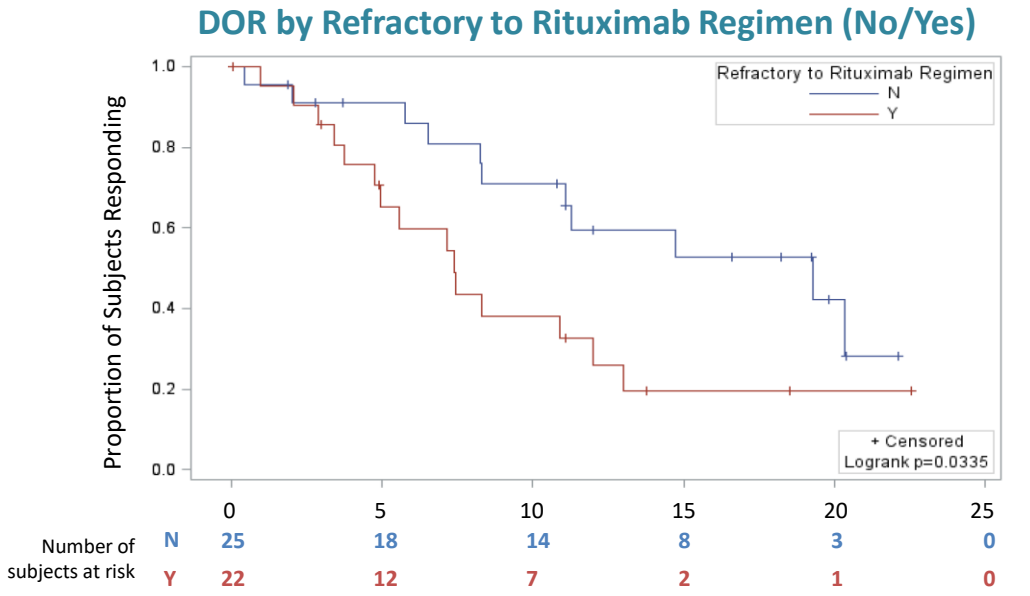
DOR	Median DOR, months (95% CI)	Hazard Ratio; *P*-value[b]
Refractory to rituximab		
Y (n=22)	**7 (5, 12)**	**0.43 (0.04)**
N (n=25)	**19 (8, NE)**	
LDH		
High (n=22)	8 (4, 19)	1.78 (0.15)
Normal (n=25)	11 (7, NE)	
Double refractory		
Y (n=11)	6 (2, NE)	0.51 (0.14)
N (n=36)	12 (8, 20)	
Extranodal target lesion		
Y (n=5)	19 (7, NE)	1.71 (0.39)
N (n=42)	11 (7, 15)	
Number of prior therapies		
1 or 2 (n=24)	12 (6, 20)	1.10 (0.80)
>2 (n=23)	11 (7, NE)	
POD24		
Y (n=19)	13 (3, NE)	1.06 (0.89)
N (n= 28)	11 (7, 20)	
Refractory to last prior therapy		
Y (n=20)	11 (3, 19)	0.63 (0.26)
N (n= 27)	11 (7, NE)	
Prior stem cell transplant		
Y (n=9)	15 (2, NE)	0.98 (0.96)
N (n=38)	11 (7, 20)	
Treatment refractory		
Y (n=31)	8 (5, 19)	0.75 (0.48)
N (n=16)	11 (7, NE)	



11-month median DOR in the pooled patient population

[a]Responders only (n=47); [b]*P*-values represent predictive variables identified in the regression analysis and do not represent significant differences between groups. CI, confidence interval; DOR, duration of response; LDH, lactate dehydrogenase; NE, not evaluable; ORR, objective response rate; POD24, progression of disease within 24 months.

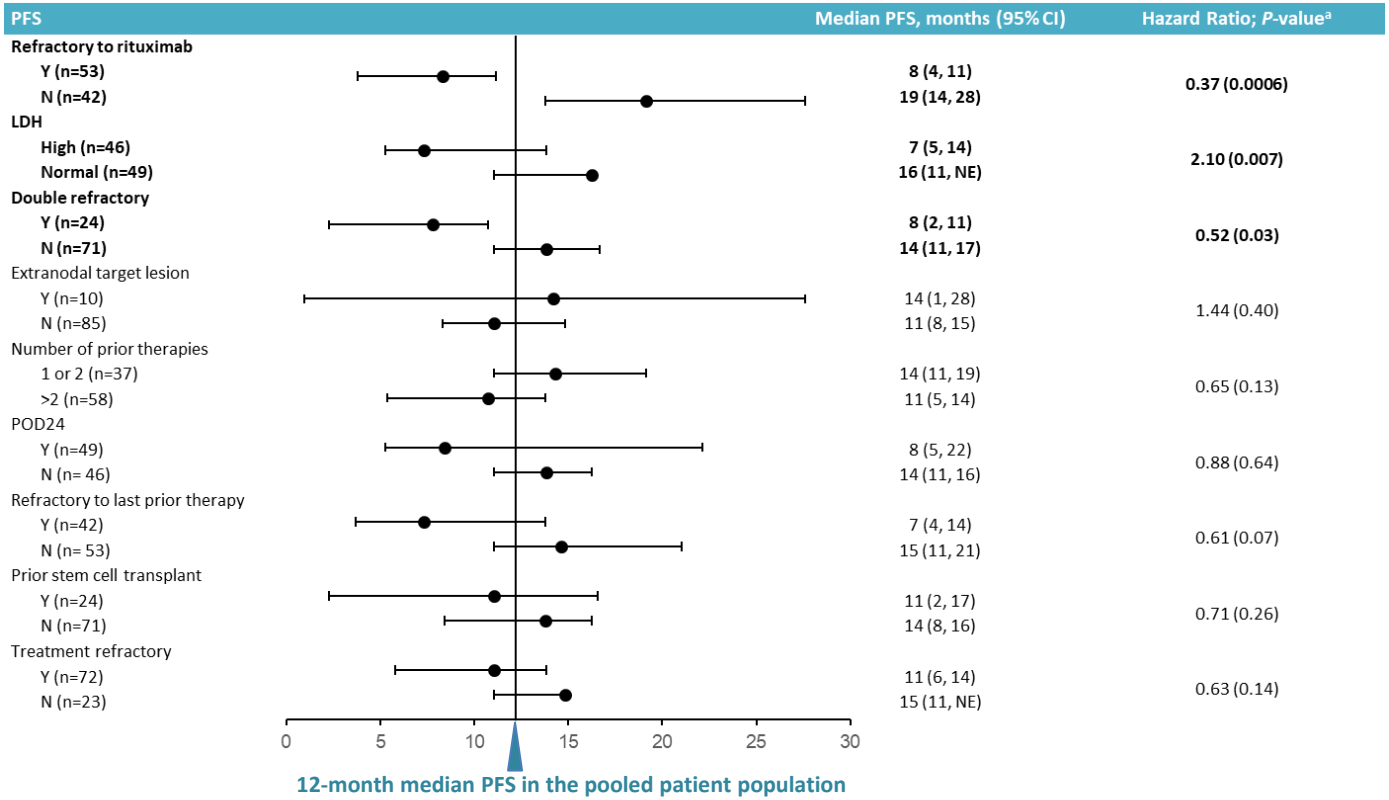
Variables Identified as Predictive of DOR



DOR	Median, mo (95% CI)	Hazard ratio (*P*-value)
No	19 (8, NE)	0.43 (0.04)
Yes	7 (5, 12)	

CI, confidence interval; DOR, duration of response.

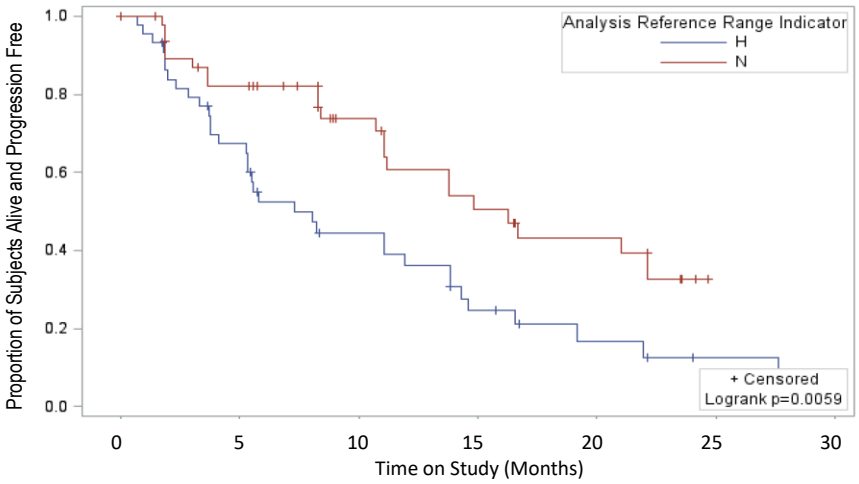
PFS for Clinical Variables



[a]*P*-values represent predictive variables identified in the regression analysis and do not represent significant differences between groups.
CI, confidence interval; DOR, duration of response; LDH, lactate dehydrogenase; NE, not evaluable; ORR, objective response rate; POD24, progression of disease within 24 months.

Variables Identified as Predictive of PFS

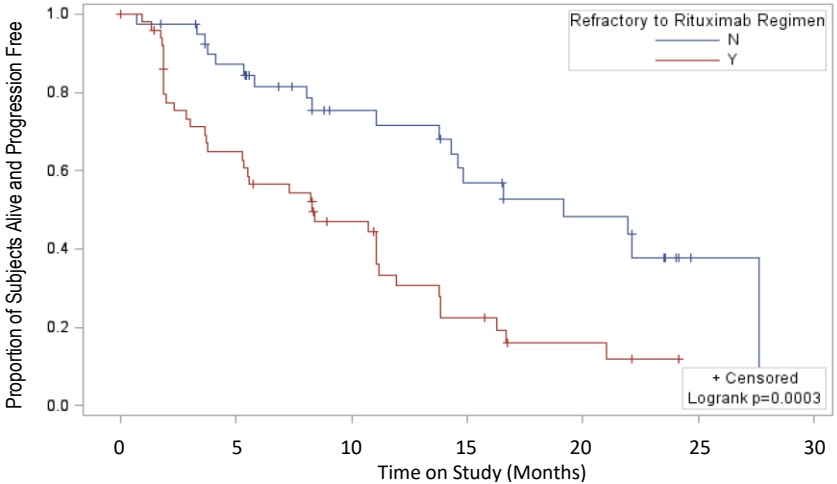
PFS by LDH Reference Range (H/N)



Number of subjects at risk							
H	46	28	16	8	4	1	0
N	49	36	23	15	11	0	

PFS - LDH	Median, mo (95% CI)	Hazard ratio (P-value)
High	7 (5, 14)	2.10 (0.0007)
Normal	16 (11, NE)	

PFS by Refractory to Rituximab Regimen (No/Yes)



Number of subjects at risk							
N	42	33	21	15	11	1	0
Y	53	31	18	8	4	0	

PFS – RR	Median, mo (95% CI)	Hazard ratio (P-value)
No	19 (14, 28)	0.37 (0.0006)
Yes	8 (4, 11)	

CI, confidence interval; H, high; LDH, lactate dehydrogenase; N, normal; NE, not evaluable; PFS, progression-free survival.

Conclusions

- Tazemetostat demonstrated single-agent, antitumor activity in heavily pretreated patients with R/R FL and at least 2 prior lines of therapy in a phase 2 study, with ORR in the WT and MT *EZH2* cohorts being 35% and 69%, median DOR being 13 months and 11 months, and median PFS being 11 months and 14 months, respectively[1]
  - Pooled WT and MT *EZH2* efficacy results: 51% ORR, 11-month median DOR, and 12-month median PFS
- Post hoc exploratory stepwise logistic and Cox regression analyses identified potential predictors of ORR, DOR, and PFS
  - Number of prior therapies (1 or 2 vs >2) and POD 24 were predictive for ORR
    - ORR was higher in patients with fewer lines of therapy
  - Refractoriness to rituximab was found to be predictive for DOR and PFS; LDH and double refractory also were predictive of PFS
- Clinical variables like prior stem cell transplant, refractory to last prior therapy, and extranodal target lesion had no effect on ORR, DOR, or PFS and tazemetostat activity showed consistent benefit in patients with across most variables
- No multiplicity adjustments were done, and prospective confirmatory studies are warranted to confirm these post hoc observations

1. Morschhauser F, et al. *Lancet Oncology*; 2020;21(11):1433-42.

DOR, duration of response; FL, follicular lymphoma; LDH, lactate dehydrogenase; MT, mutant; ORR, objective response rate; PFS, progression-free survival; POD24, progression of disease within 24 months; R/R, relapsed/refractory; WT, wild-type.

Conflict of Interest Disclosures

G. Salles has served as a consultant for or received honoraria from Abbvie, Autolus, Bristol Myers Squibb, Celgene, Debiopharm, Genmab, Gilead, F. Hoffmann-La Roche, Epizyme, Janssen, Karyopharm, Kite Pharma, and Takeda, and has participated in educational events for Abbie, Amgen, Celgene, Gilead, and Janssen. **H. Tilly** has received honoraria from Bristol Myers Squibb. **A. Chaidos** reports no conflicts. **P. McKay** has received fees for lectures from Gilead, Janssen, Roche, and Takeda; has received travel expenses and served on a speakers' bureau for Janssen and Takeda; and has served on a board of directors or advisory board for BeiGene, Celgene, Gilead, Janssen, Roche, and Takeda. **T. Phillips** has served as a consultant for AbbVie, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Cardinal Health, Incyte, Karyopharm, Pharmacyclics, and Seattle Genetics; received travel expenses from Incyte; and received research funding from AbbVie and Bayer. **S Assouline** has received research funding from BeiGene, F. Hoffmann-La Roche, and Takeda; has served on speakers' bureaus for AbbVie, AstraZeneca, and Janssen; and has served as a consultant for and received honoraria from AbbVie, AstraZeneca, BeiGene, F. Hoffmann-La Roche, Janssen, and Pfizer Inc. **C.L. Batlevi** has received research funding from Autolus, Bayer, Epizyme, Janssen, Novartis, Roche/Genentech, and Zynomics, and has served as a consultant for GLG Pharma, Juno/Celgene, Kite Pharma, Life Sciences, and Seattle Genetics. **P. Campbell** has served as a consultant for Amgen, AstraZeneca, CSL Behring, Janssen, Novartis, and Roche, and received research funding from Amgen, Celgene (BMS), Janssen, Novartis, and Roche. **V. Ribrag** has served as a consultant for Bristol Myers Squibb, Epizyme, Immune Design, Incyte, Infinity, MSD, Nanostring, Pharmamar, Roche/Genentech, and Servier; has served on advisory boards or board of directors for AstraZeneca, Bristol Myers Squibb, Epizyme, F. Hoffmann-La Roche, Gilead, Immune Design, Incyte, Infinity, MSD, Nanostring, Pharmamar, and Roche/Genentech; has received research funding from arGEN-X-BVBA, argenX, and Epizyme; holds equity in argenX and Epizyme, has received honoraria from AstraZeneca, AZD, Bristol Myers Squibb, Eisai, Epizyme, F. Hoffmann-La Roche, Gilead, Infinity, MSD, Nanostring, Pharmamar, and Servier; and holds patents and receives royalties for BAY1000394. **G. L. Damaj** has received honoraria from Accord, Roche, and Takeda; has served as a consultant for Accord, Iqone, Roche, and Takeda; and has received travel expenses from AbbVie, Pfizer, Roche, and Takeda. **M. Dickinson** has served as a consultant for Gilead, Janssen, Merck Sharp & Dohme, Novartis, and Roche; has received honoraria from and served on speakers' bureaus for board of directors for Gilead, Janssen, Novartis, and Roche; and has received research funding from Gilead and Novartis. **W. Jurczak** has served as a consultant for Acerta, Afimed, AstraZeneca, BeiGene, Epizyme, European Medicines Agency, Janssen, Sanofi-Novartis, and has received research funding from Acerta, Bayer, BeiGene, Celgene, Gilead, Janssen China, MEI Pharma, Merck, MorphoSys, Nordic Nanovecotr, Pharmacyclics, Roche, Servier, Takeda, and TG Therapeutics. **M. Kaźmierczak** has no conflicts to report. **S. Opat** has served as a consultant for AbbVie, CSL, F. Hoffman-La Roche, Gilead, Janssen, Merck, and Mundipharma; has received honoraria and/or served on an advisory board or board of directors for AbbVie, AstraZeneca, Celgene, CSL, Gilead, Janssen, Merck, Mundipharma, Roche, and Takeda. **J. Radford** has received honoraria from Bristol Myers Squibb, Novartis, and Seattle Genetics; has received research funding from ADCT, Pfizer, and Takeda; has served on a speakers' bureau or board of directors for ADCT, Bristol Myers Squibb, Seattle Genetics, and Takeda; has served as a consultant for Bristol Myers Squibb, Kite Pharma, Novartis, and Takeda; and holds equity in AstraZeneca and GlaxoSmithKline. **A. Schmitt** has received honoraria from Janssen and Roche and has served on an advisory board or board of directors for Celgene. **J. Whalen, A. Hamlett, B. Kamp,** and **D. Adib** are employees of Epizyme, Inc., and may own stock/options in the company. **F. Morschhauser** has served as a consultant for F. Hoffmann-La Roche, Genentech, and Servier; has received honoraria from Janssen; and has served on an advisory board or board of directors for AbbVie, Celgene, Epizyme, F. Hoffmann-La Roche, and Gilead.

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