REWRITING CANCER TREATMENT THROUGH EPIGENETIC MEDICINES

June 14, 2017

Non-Hodgkin Lymphoma Program Update

Epizyme™

FORWARD-LOOKING STATEMENTS

Any statements in this presentation about future expectations, plans and prospects for Epizyme, Inc. and other statements containing the words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: uncertainties inherent in the initiation of future clinical studies and in the availability and timing of data from ongoing clinical studies; whether results from preclinical studies or earlier clinical studies will be predictive of the results of future studies; whether interim data from clinical studies such as the data reported in this presentation will be indicative of the final results of the study; whether results from clinical studies will warrant meetings with regulatory authorities or submissions for regulatory approval; whether submissions for regulatory approval will be made when anticipated or at all and whether these submissions will be reviewed under the accelerated approval framework; whether the Company will receive will receive regulatory approvals to conduct trials or to market products; whether the Company's cash resources will be sufficient to fund the Company's foreseeable and unforeseeable operating expenses and capital expenditure requirements; other matters that could affect the availability or commercial potential of the Company's therapeutic candidates; and other factors discussed in the "Risk Factors" section of the Company's most recent Form 10-Q filed with the SEC and in the Company's other filings from time to time with the SEC. In addition, the forward-looking statements included in this press release represent the Company's views as of the date hereof and should not be relied upon as representing the Company's views as of any date subsequent to the date hereof. The Company anticipates that subsequent events and developments will cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so.

POSITIVE INTERIM DATA FROM PHASE 2 STUDY OF TAZEMETOSTAT IN RELAPSED OR REFRACTORY (R/R) PATIENTS WITH FOLLICULAR LYMPHOMA AND DIFFUSE LARGE B-CELL LYMPHOMA

CLINICALLY MEANINGFUL BENEFIT IN PATIENTS WITH FOLLICULAR LYMPHOMA

92% ORR in FL with EZH2 Mutations

ENHANCED ACTIVITY IN PATIENTS WITH EZH2 MUTATIONS

DURABLE RESPONSES OBSERVED IN FL AND DLBCL PATIENTS

FAVORABLE SAFETY PROFILE

MULTIPLE COMBINATION STUDIES UNDERWAY AND PLANNED

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Data as of 06/01/17

Data reported as from the Phase 2 portion of a Phase 1/2 study

81% OF ENROLLMENT COMPLETE; INCREASE IN EZH2 MT PATIENTS IN 1H 2017

Data cut-off: June 1, 2017

218 patients enrolled to date*

- FL with EZH2 mutation:19 patients to date; 13 evaluable for efficacy
- FL wild-type EZH2 completed enrollment with 54 patients; all evaluable for efficacy
- DLBCL with EZH2 mutations: 22 patients to date; 17 evaluable for efficacy
- DLBCL wild-type EZH2 (GCB & non-GCB) completed enrollment with 120 patients; 119 evaluable for efficacy

Evaluable population

- Safety: 210 patients
- Efficacy: 203 patients

Prevalence of EZH2 mutation patients enrolled is in-line with expectations

Increase in enrollment of EZH2 mutation patients began early 2017

FOLLICULAR LYMPHOMA: AN INCURABLE DISEASE TODAY[1]

~25,000 patients diagnosed in the U.S. and Europe annually[2]

15-20% of FL patients have EZH2 activating mutations

Treatment is most commonly multi-agent chemotherapy regimen, including rituximab-containing combinations

Majority of patients will relapse or become refractory to first-line treatment; limited benefit provided in R/R setting[3]

Tazemetostat could offer a meaningful new treatment option for these patients

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[1] Salles G: Current and future management of follicular lymphoma, 2012
[2] Decision Resources 2017
[3] Gopal, AK et al. 2014 NEJM 370:1008-1018

PHASE 2 R/R FOLLICULAR LYMPHOMA PATIENT DEMOGRAPHICS

Study enrollment requires all patients have had ≥ 2 prior treatments*

Median of 4 prior treatments

Approximately half of patients enrolled were refractory to last treatment

Characteristic		R/R Follicular Lymphoma	
EZH2 Status		**Mutant**	**Wild-type**
n		13	54
Age, median	years	62	61
Males		46%	63%
ECOG PS, median (range)		0 (0 - 2)	0 (0 - 2)
Prior lines of therapy, n (%)	1	1 (8%)	0
	2	2 (15%)	11 (20%)
	3	3 (23%)	9 (17%)
	4	1 (8%)	14 (26%)
	≥ 5	6 (46%)	20 (37%)
	median	4	4
Refractory to last regimen, n (%)		7 (54%)	26 (48%)
Prior HSCT		23%	41%
Median time from initial diagnosis	years	7.4	4.9
Median time from last prior therapy	weeks	13.0	41.3

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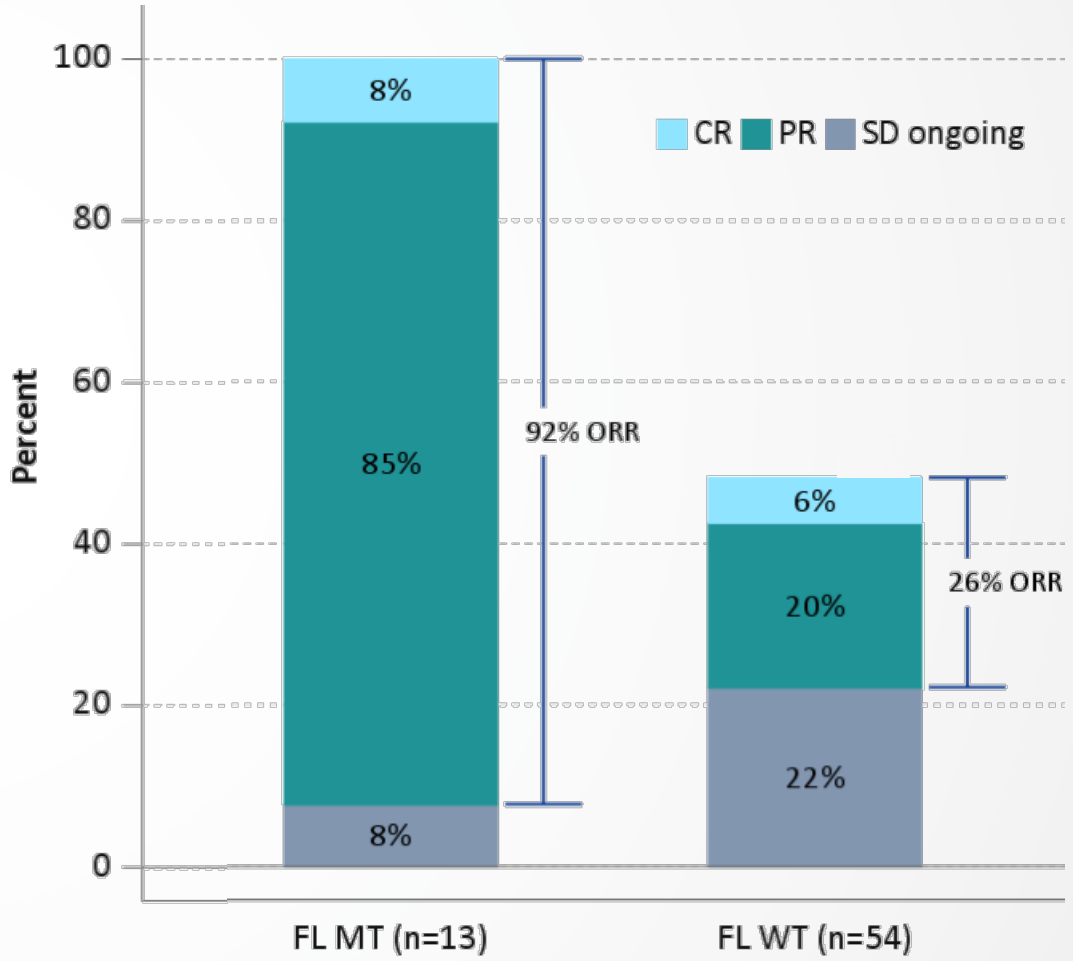
Data as of 06/01/17

Refractory to last regimen defined as SD or PD as best response to most recent prior therapy

POSITIVE INTERIM PHASE 2 EFFICACY RESULTS IN FOLLICULAR LYMPHOMA

Best Response	FL EZH2 MT (n=13)	FL EZH2 WT (n=54)
Objective Response Rate (CR + PR)	**12 (92%)**	**14 (26%)**
Complete Response (CR)	1 (8%)	3 (6%)
Partial Response (PR)	11 (85%)	11 (20%)
Stable Disease (SD)	1 (8%)	23 (43%)
SD study drug ongoing	1 (8%)	12 (22%)
Progressive Disease	0	13 (24%)
No Data, Unknown (UNK)	0	4 (7%)
Time to first Response (weeks) median (range)	11.9 (6.9 – 35.9)	15.2 (8.1 - 32.1)

Ongoing patients with Best Response of 'No Data, Unknown' are not included in the efficacy table. Patients who discontinued due to clinical or radiological progression without a valid response assessment are included in PD.



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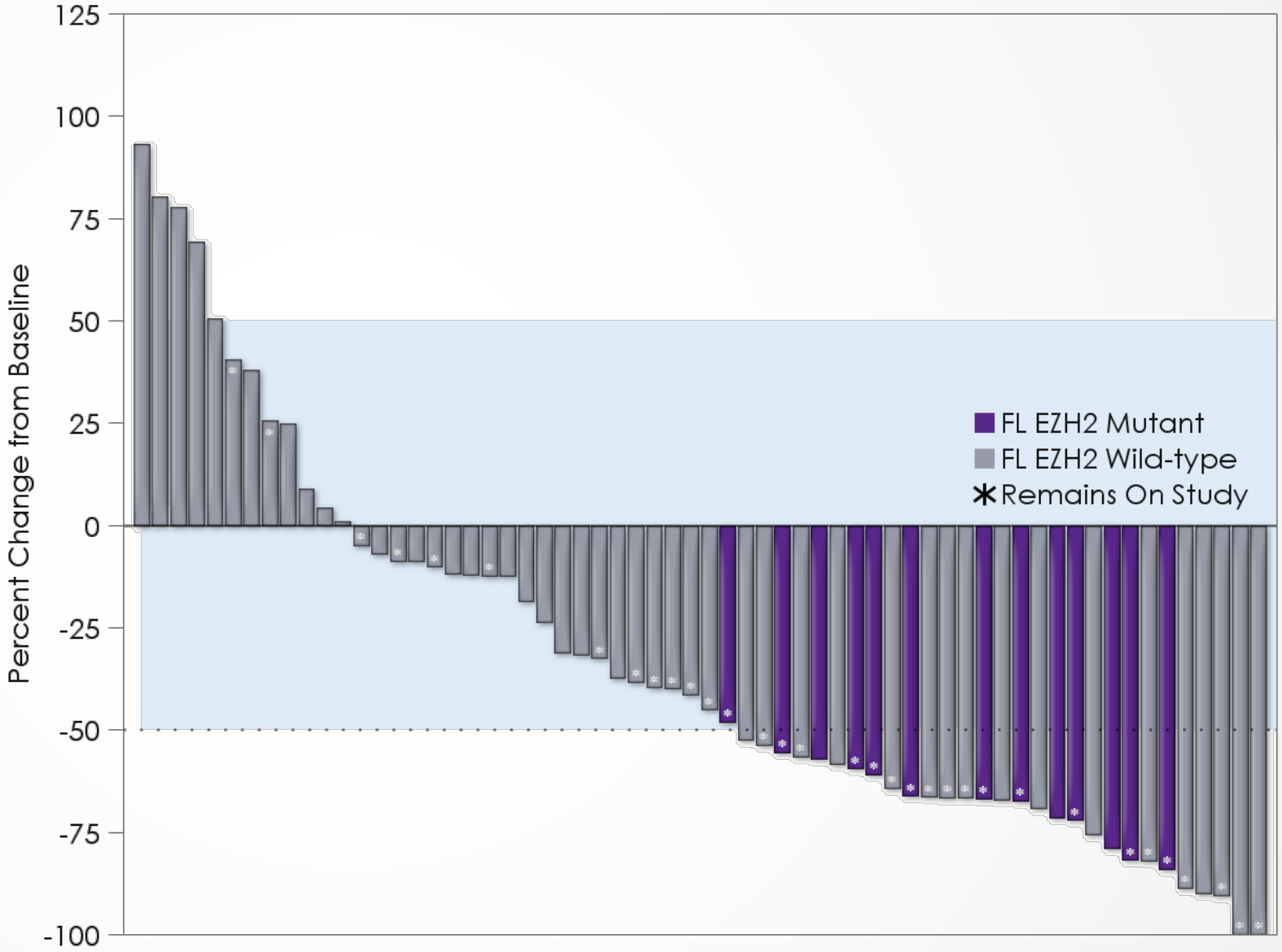
Data as of 06/01/17

*Percentages may not total to 100% due to rounding

MAJORITY OF FL PATIENTS EXPERIENCE TUMOR REDUCTION WITH TAZEMETOSTAT TREATMENT

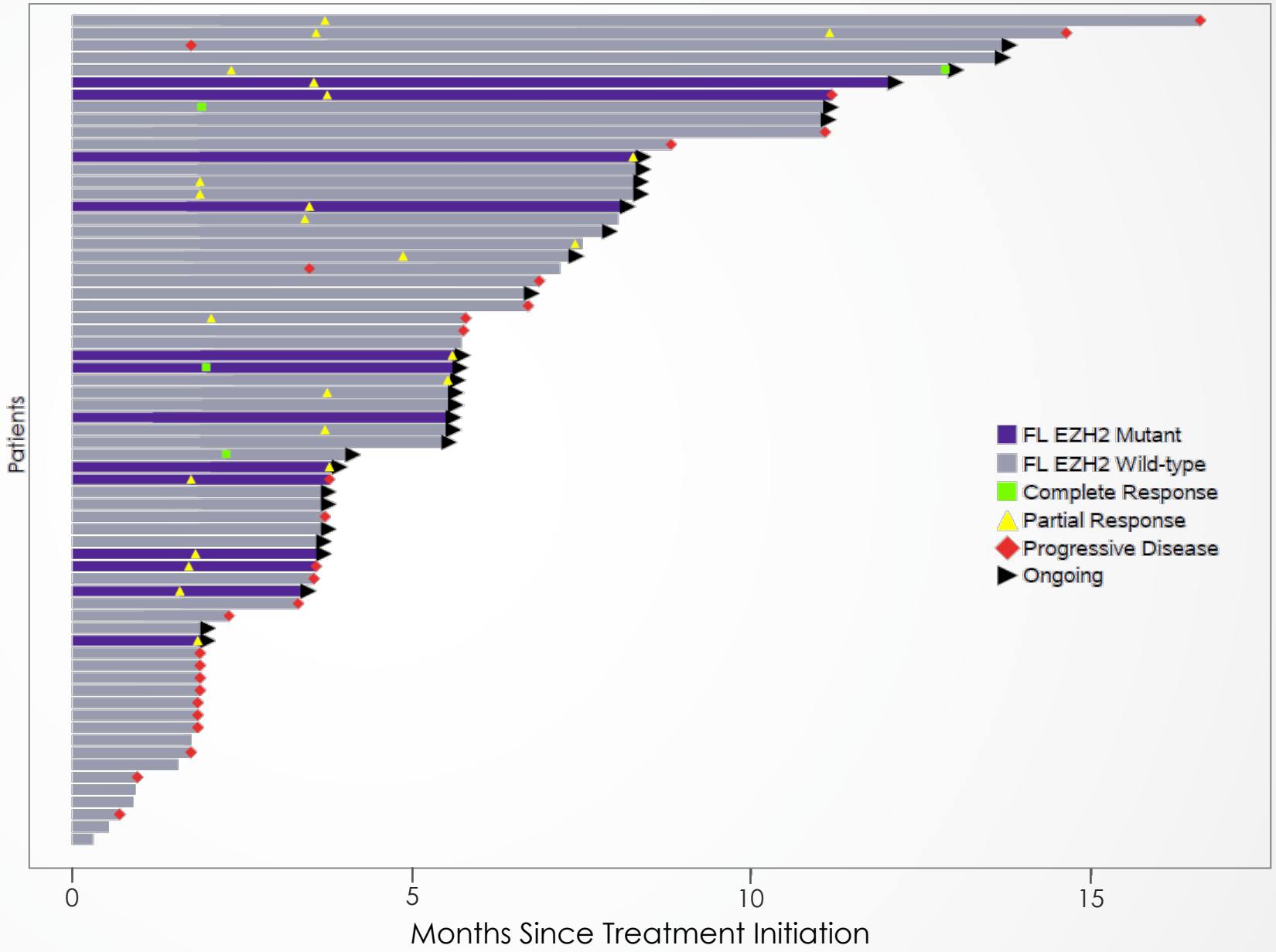
- 75% of patients experienced reduction in tumor burden
- 12 of 13 EZH2 mutant patients achieving an objective response (1 CR and 11 PRs)
- 13th patient with EZH2 mutation achieving >48% reduction in tumor volume; remains on study



Data as of 06/01/17

MEANINGFUL CLINICAL BENEFIT DEMONSTRATED IN FOLLICULAR LYMPHOMA

- Responses observed between 2 and 8 months
- Duration of responses observed out to 15 months
- 48% of patients still on treatment



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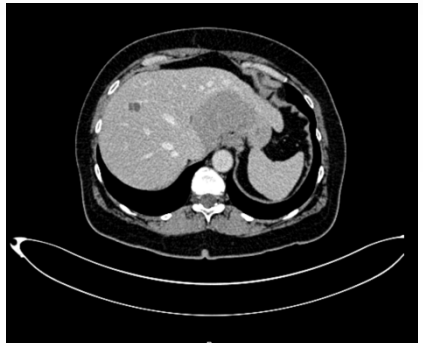
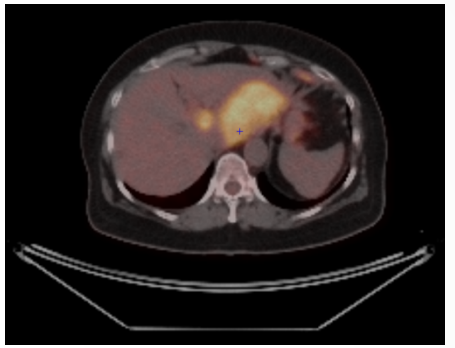
Data as of 06/01/17

PATIENT CASE STUDY: TUMOR RESPONSE IN FL WITH EZH2 MUTATION

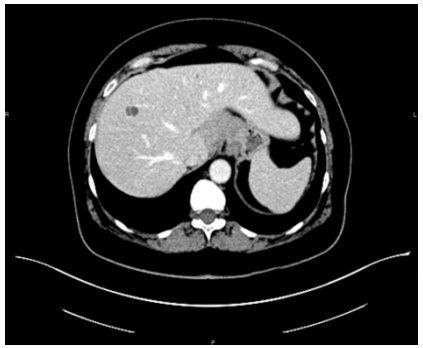
68 Y.O. FEMALE

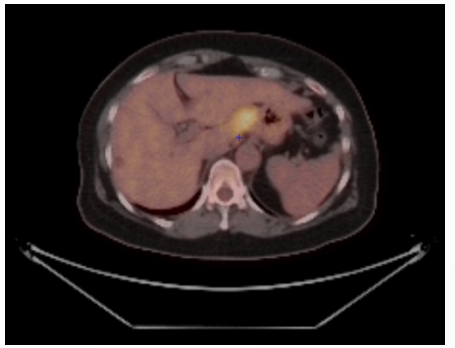
BASELINE

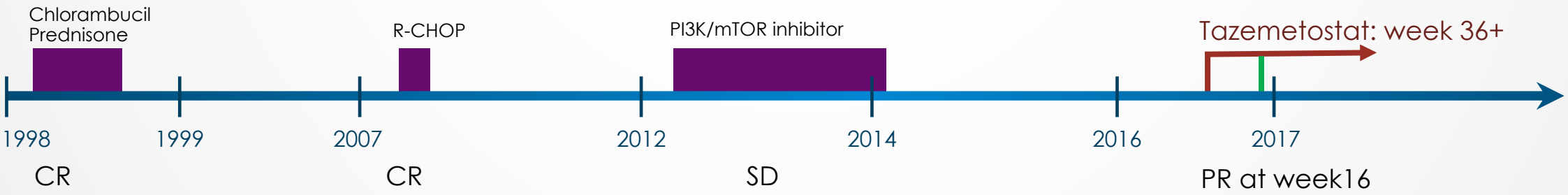




WEEK 24







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Data as of 06/01/17

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): AN AGGRESSIVE NHL

- Most common sub-type of NHL affecting ~45,000 new patients each year[1]
- 15-20% of GCB patients have EZH2 activating mutations
- 40-50% of all patients relapse or become refractory to standard-of-care[2]
- Upon relapse, salvage therapy options are limited and survival remains short
- Substantial need for new treatments for patients with R/R DLBCL

[1] Decision Resources 2017
[2] NCI November 2016

PHASE 2 DLBCL PATIENT DEMOGRAPHICS

- Study enrollment requires all patients have had ≥ 2 prior treatments
- Median of 3 prior treatments
- Highly refractory population: 82% of DLBCL EZH2 mutation and 63% of wild-type EZH2 patients refractory to last prior treatment regimen

Characteristic		R/R DLBCL	
EZH2 Status		**Mutant**	**Wild-type**
n		17	120
Age, median	years	61	69
Males		53%	58%
ECOG PS, median (range)		1 (0 - 2)	1 (0 - 2)
Prior lines of therapy, n (%)	1	0	3 (3%)
	2	4 (24%)	40 (33%)
	3	7 (41%)	28 (23%)
	4	3 (18%)	18 (15%)
	≥ 5	3 (18%)	31 (26%)
	median	3	3
Refractory to last regimen, n (%)		14 (82%)	75 (63%)
Prior HSCT		41%	24%
Median time from initial diagnosis	years	1.0	2.0
Median time from last prior therapy	weeks	8.6	11.6

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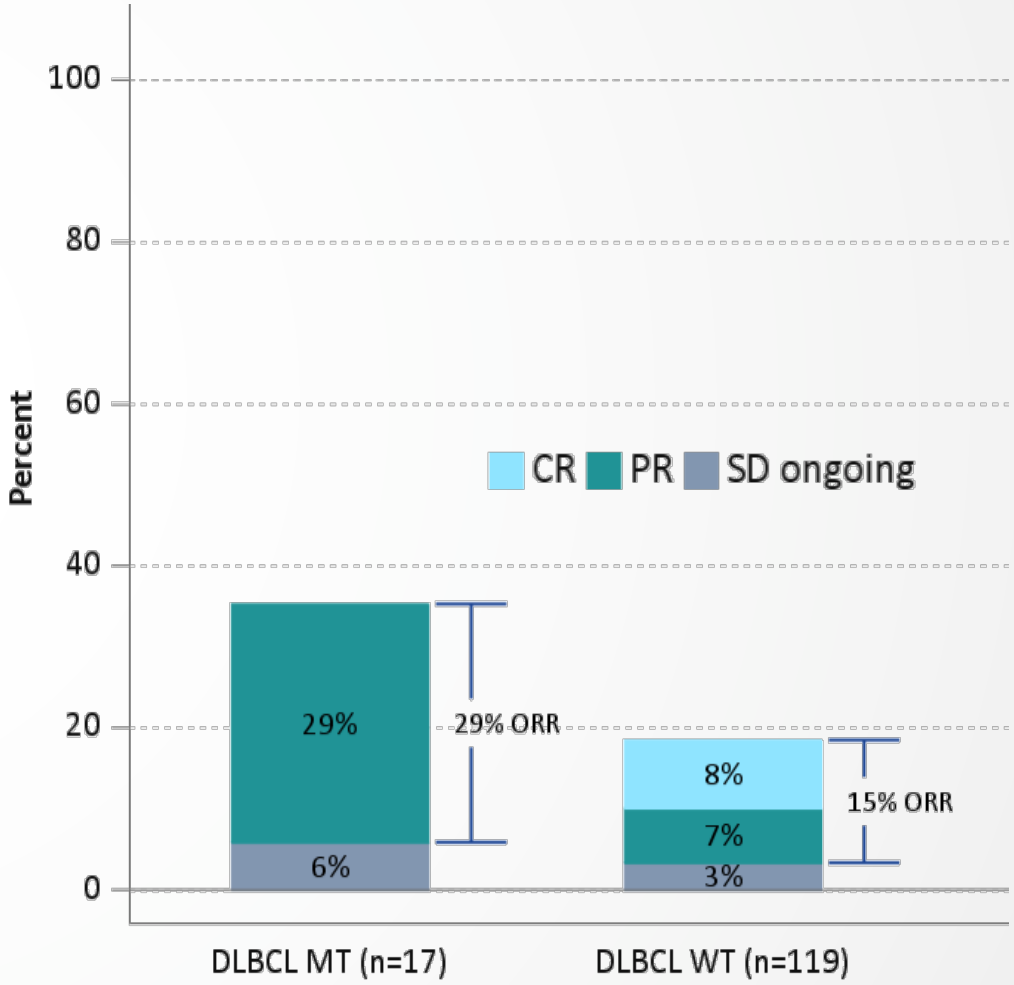
Data as of 06/01/17

Refractory to last regimen defined as SD or PD as best response to most recent prior therapy

POSITIVE INTERIM PHASE 2 EFFICACY RESULTS IN DLBCL PATIENTS WITH EZH2 MUTATIONS

Best Response	DLBCL EZH2 MT (n=17)	DLBCL EZH2 WT (n=119)
Objective Response Rate (CR + PR)	**5 (29%)**	**18 (15%)**
Complete Response (CR)	0	10 (8%)
Partial Response (PR)	5 (29%)	8 (7%)
Stable Disease (SD)	6 (35%)	22 (18%)
SD study drug ongoing	1 (6%)	4 (3%)
Progressive Disease	6 (35%)	60 (50%)
No Data, Unknown (UNK)	0	19 (16%)
Time to first Response (weeks) median (range)	8.3 (4.6 – 48.1)	8.5 (5.3 – 24.7)

Ongoing patients with Best Response of 'No Data, Unknown' are not included in this table. Patients that discontinued due to clinical or radiological progression without a valid response assessment are included in PD.



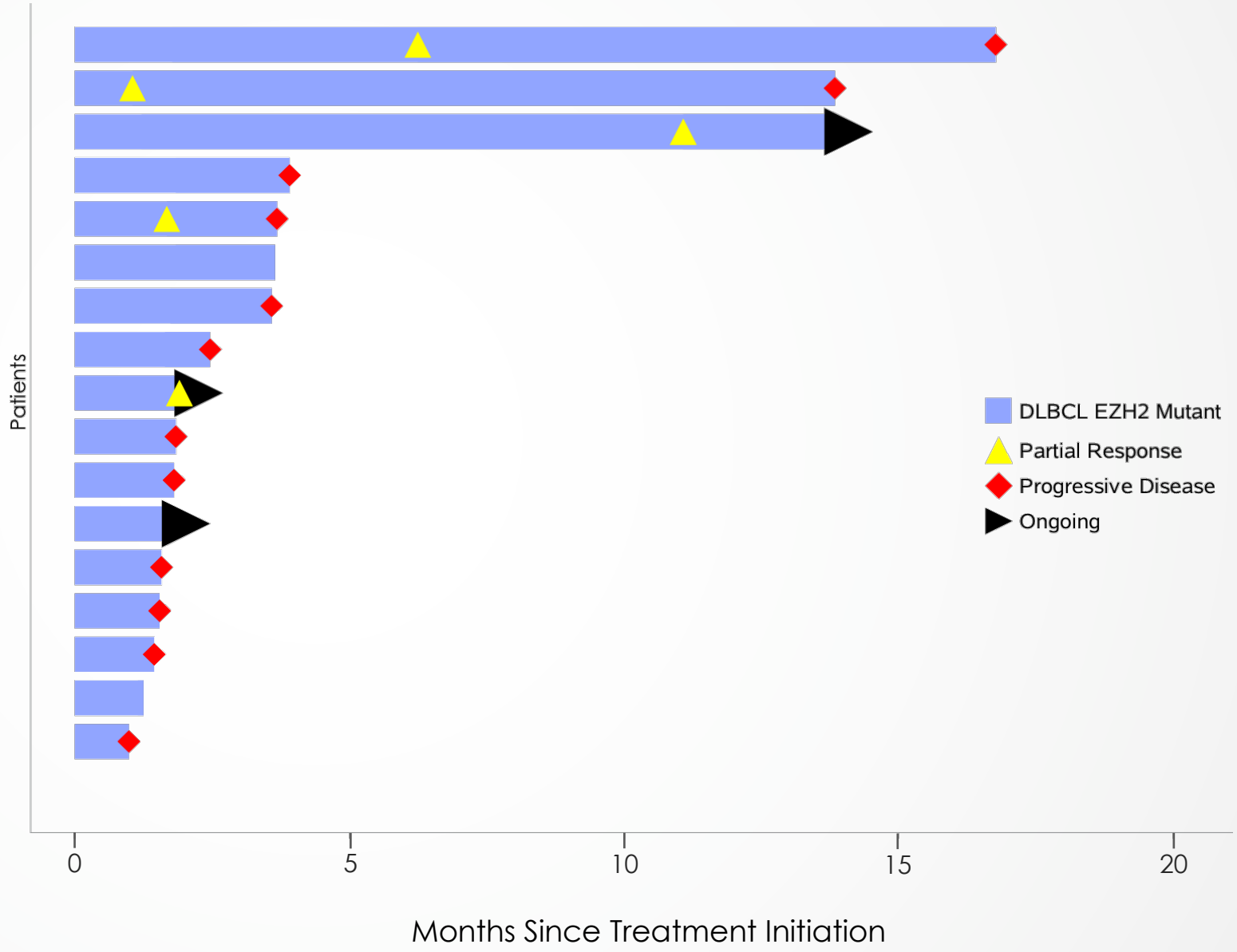
Data as of 06/01/17

PROMISING ACTIVITY IN DLBCL PATIENTS WITH EZH2 MUTATIONS

69% of patients experienced reduction in tumor burden

Responses observed between 1 and 12 months

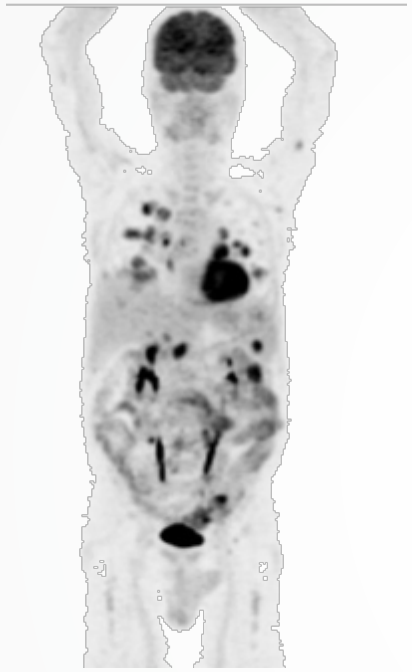
3 responders experienced clinical benefit for >1 year



Data as of 06/01/17

PATIENT CASE STUDY: TUMOR RESPONSE IN DLBCL WITH EZH2 MUTATION

61 Y.O. MALE



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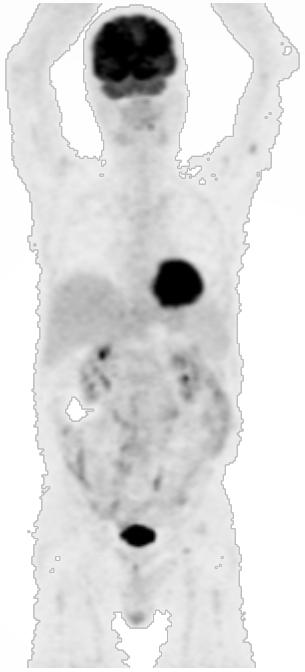
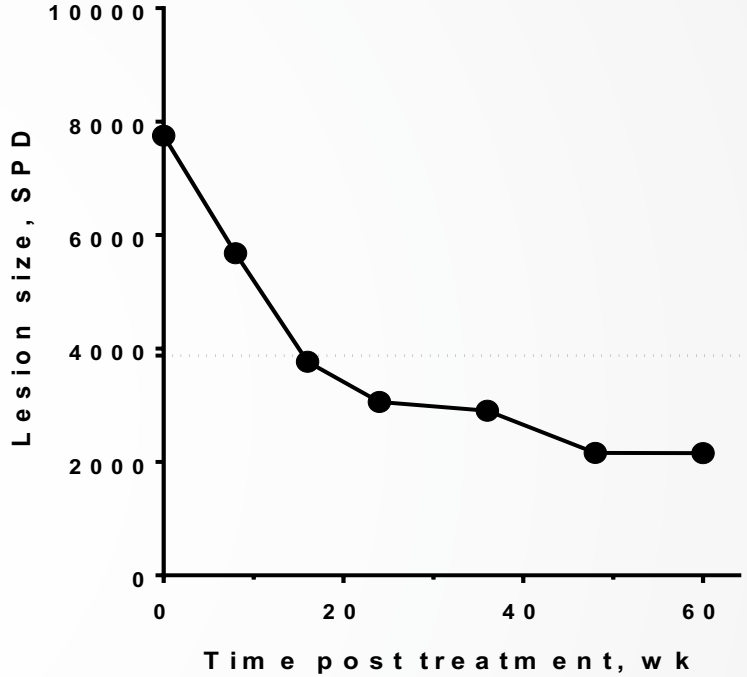
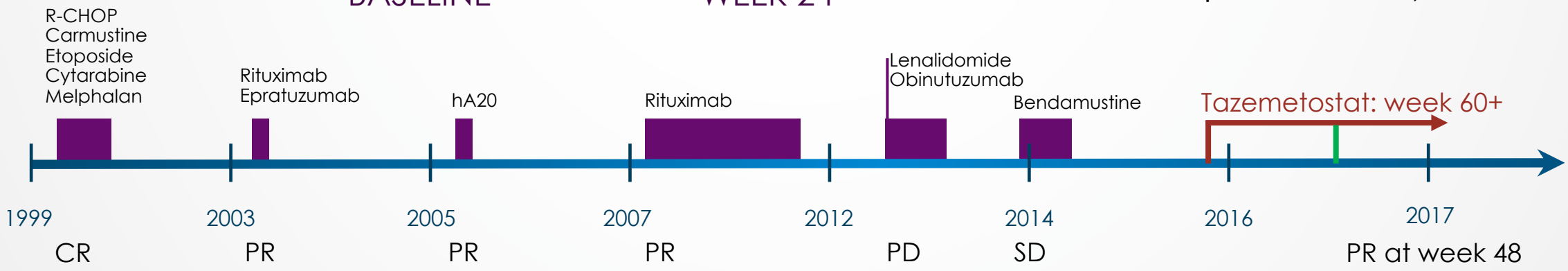


WEEK 24





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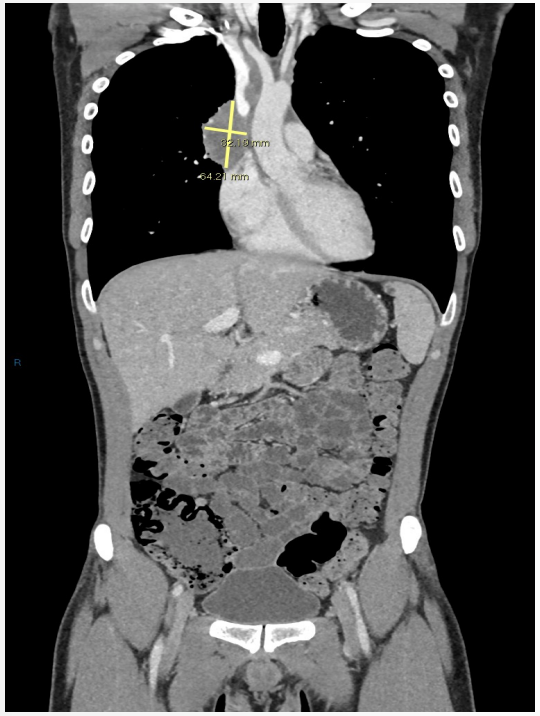
Data as of 06/01/17

TUMOR REDUCTION AFTER DISEASE PROGRESSION

36 Y.O. MALE



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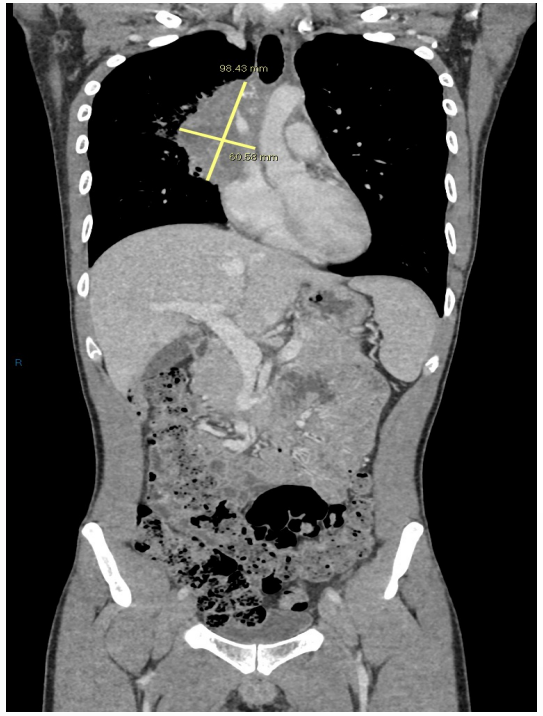
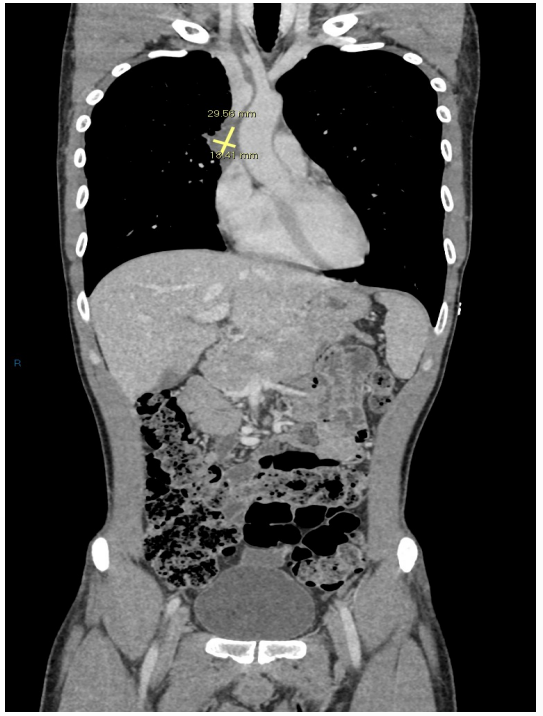
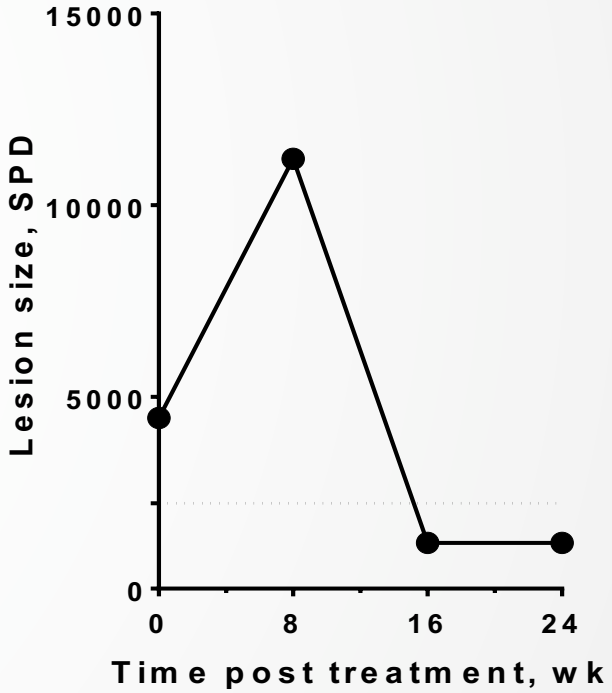


WEEK 8



WEEK 16



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Data as of 06/01/17

NO DIFFERENCES IN BEST RESPONSE WHEN COMPARING HANS VS NANOSTRING

Best Response	Hans Cell of Origin		nanoString Cell of Origin	
	DLBCL GCB EZH2 WT (n=45)	DLBCL non-GCB (n=47)	DLBCL GCB EZH2 WT (n=53)	DLBCL non-GCB (n=38)
Objective Response Rate (CR + PR)	**6 (13%)**	**10 (21%)**	**7 (13%)**	**8 (21%)**
Complete Response (CR)	3 (7%)	4 (9%)	4 (8%)	3 (8%)
Partial Response (PR)	3 (7%)	6 (13%)	3 (6%)	5 (13%)
Stable Disease (SD)	6 (13%)	9 (19%)	8 (15%)	7 (18%)
SD study drug ongoing	0	1 (2%)	1 (2%)	0
Progressive Disease	24 (53%)	22 (47%)	27 (51%)	19 (50%)
No Data, Unknown (UNK)	9 (20%)	6 (13%)	11 (21%)	4 (11%)

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Data as of 06/01/17

Ongoing patients with Best Response of 'No Data, Unknown' are not included in this table
Patients that discontinued due to clinical or radiological progression without a valid response assessment are included in PD

TAZEMETOSTAT DEMONSTRATES FAVORABLE SAFETY PROFILE

Low rates of grade 3 or higher treatment-related adverse events

Consistent safety across entire tazemetostat clinical program

Treatment-Emergent Adverse Event	Patients (n=210) with:			
	All TEAEs		Treatment-Related TEAEs	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Nausea	42 (20%)	1 (<1%)	29 (14%)	0
Thrombocytopenia	39 (19%)	19 (9%)	28 (13%)	12 (6%)
Anaemia	33 (16%)	16 (8%)	21 (10%)	9 (4%)
Cough	30 (14%)	1 (<1%)	4 (2%)	1 (<1%)
Fatigue	26 (12%)	5 (2%)	15 (7%)	2 (1%)
Diarrhoea	24 (11%)	1 (<1%)	17 (8%)	1 (<1%)
Asthenia	22 (10%)	3 (1%)	16 (8%)	1 (<1%)
Neutropenia[1]	21 (10%)	15 (7%)	19 (9%)	13 (6%)
Pyrexia	21 (10%)	1 (<1%)	2 (1%)	0
Vomiting	21 (10%)	2 (1%)	7 (3%)	1 (<1%)
Bronchitis	14 (7%)	0	2 (1%)	0
Constipation	13 (6%)	1 (<1%)	4 (2%)	1 (<1%)
Decreased appetite	13 (6%)	0	6 (3%)	0
Upper respiratory tract infection	13 (6%)	0	1 (<1%)	0
Abdominal pain	12 (6%)	3 (1%)	4 (2%)	0
Headache	12 (6%)	0	4 (2%)	0
Urinary tract infection	12 (6%)	0	4 (2%)	0
Back pain	11 (5%)	2 (1%)	1 (<1%)	0
Oedema peripheral	11 (5%)	2 (1%)	1 (<1%)	0
Dysgeusia	10 (5%)	0	7 (3%)	0
Rhinitis	10 (5%)	0	1 (<1%)	0

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Data as of 06/01/17

[1] One (1) TEAE of Febrile Neutropenia

Adverse events reported in ≥5% of patients

LOW RATE OF DOSE REDUCTIONS AND DISCONTINUATIONS DUE TO ADVERSE EVENTS

Patients (n=210)	Treatment-Emergent Adverse Events (TEAEs) *	Treatment-Related TEAEs
Adverse Event (any)	190 (90%)	123 (59%)
Grade ≥ 3	91 (43%)	38 (18%)
Serious AE	81 (39%)	20 (10%)
AE Leading to Dose Interruption	50 (24%)	31 (15%)
AE Leading to Dose Reduction	8 (4%)	7 (3%)
AE Leading to Drug Discontinuation or Study Withdrawal	26 (12%)	5 (2%)

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Data as of 06/01/17

MOLECULAR PROFILING IDENTIFIES TAZEMETOSTAT RESPONSE PREDICTORS

NGS analysis performed on archive tumor and circulating tumor DNA (ctDNA) for patient subset (n=92)

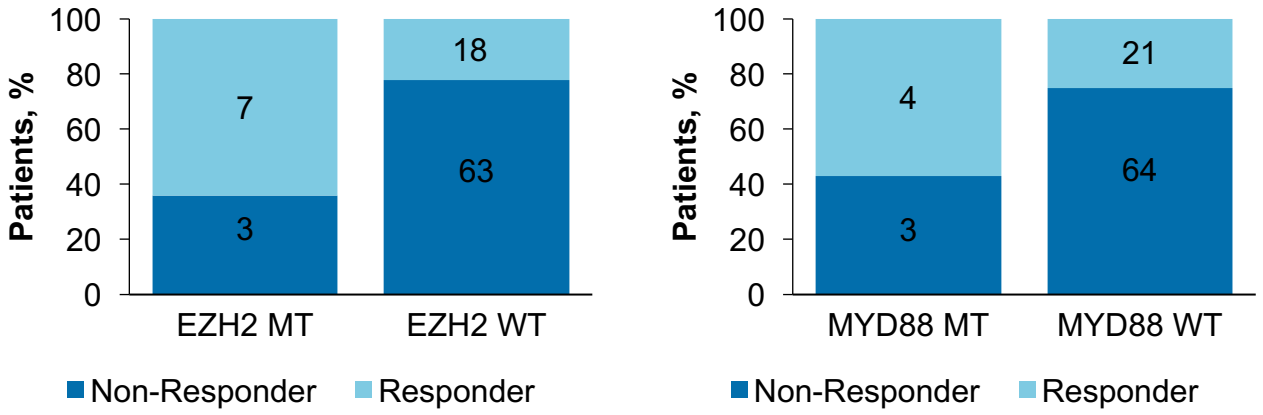
- Custom 62 gene panel includes common NHL somatic mutations
- Responder (CR+PR) vs. Non-Responder analyses
- Details presented in ICML Poster #154 (Blakemore et al.)

Positive and negative predictors for tazemetostat response (PR/CR) identified

- Positive predictors: **EZH2 & MYD88** activating mutations
- Negative predictors: **MYC, TP53** and **HIST1H1E**

- Detection of EZH2 mutations in ctDNA indicates potential for future use of plasma for patient identification

EZH2 and MYD88 mutually exclusive in patient subset
(i.e. potential for independent mechanism of sensitivity to tazemetostat in these patients)



POSITIVE INTERIM DATA TO SUPPORT REGULATORY ENGAGEMENT IN 2H17

INTERIM RESULTS CONSISTENT WITH SCIENTIFIC HYPOTHESIS

- Anti-tumor activity demonstrated across all subtypes of FL and DLBCL
  - 92% ORR in FL with EZH2 mutation
  - Encouraging activity in FL with wild-type EZH2
  - Encouraging ORR in DLBCL with EZH2 mutations
- Clinical activity characterized by durable objective responses in both FL and DLBCL
- Activity observed in EZH2 mutation patients exceeded that in wild-type EZH2 patients, consistent with tazemetostat MOA
- Favorable safety profile supporting use of tazemetostat as both monotherapy and combination agent

NEXT STEPS FOR PROGRAM ADVANCEMENT

- Continued enrollment of FL and DLBCL EZH2 mutation patients to assess total benefit
- Initiation of FL combination study with tazemetostat later this year
- Advancement of ongoing DLBCL combination studies
- Regulatory engagement in 2H17 to discuss registration pathways to bring tazemetostat to patients as quickly as possible

THANK YOU TO OUR:

Patients, along with their families and caregivers, who participate in our clinical trials

Physicians, nurses and medical staffs who champion tazemetostat

Employees, collaborators and advisors for their constant dedication to achieving our vision