



*Rewriting Treatments
for People with Cancer*

January 2022

Nasdaq: EPZM

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: whether commercial sales of TAZVERIK for epithelioid sarcoma and follicular lymphoma in the approved indications will be successful; whether the refinement of the company's commercial strategy and cost reductions will achieve the company's objectives; whether tazemetostat will receive marketing approval for epithelioid sarcoma or follicular lymphoma in other jurisdictions, full approval in the United States or approval in any other indication; 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 of the company's product candidates will be predictive of the results of future trials, such as the ongoing confirmatory trials of TAZVERIK; whether interim results of clinical studies will be predictive of the final results of the studies; whether results from clinical studies will warrant meetings with regulatory authorities, submissions for regulatory approval or review by governmental authorities under the accelerated approval process; whether the company will receive regulatory approvals, including accelerated approval, to conduct trials or to market products; whether the company's collaborations and licensing agreements with third parties will be successful; uncertainties as to the impact of the COVID-19 pandemic on the company's business, results of operations and financial condition; 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 success of tazemetostat; and other factors discussed in the “Risk Factors” section of the company's most recent Form 10-K or 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 presentation 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.

TAZVERIK® is a registered trademark of Epizyme, Inc.

EPIZYME

A FULLY INTEGRATED
COMMERCIAL PHARMACEUTICAL
COMPANY



FIRST-IN-CLASS EZH2 INHIBITOR APPROVED FOR 2 INDICATIONS

JANUARY 2020

Accelerated approval
granted in **epithelioid
sarcoma (ES)**

JUNE 2020

Accelerated approval
granted in **R/R follicular
lymphoma (FL)**

BILLION DOLLAR
PLUS

GLOBAL ONCOLOGY
MARKET OPPORTUNITY

LABEL EXPANSION
TRIALS REMAIN
ON TRACK

ENCOURAGING INITIAL
SAFETY RUN-IN RESULTS

PHASE 1A TRIAL OF
NOVEL SETD2
INHIBITOR,
EZM0414 OPEN

PATIENTS ACTIVELY
SCREENING FOR
ENROLLMENT

HIGH-VALUE
RESEARCH PIPELINE

ADVANCING
TOWARD CLINIC



TAZVERIKTM
(tazemetostat) tablets

**BROAD THERAPEUTIC POTENTIAL IN SOLID TUMORS
AND HEME MALIGNANCIES**

**NOVEL MECHANISM OF ACTION,
ORAL ADMINISTRATION**

ACTIVITY DEMONSTRATED IN MULTIPLE CANCERS

**GENERALLY WELL-TOLERATED;
LOW DISCONTINUATION RATES**

POTENTIAL FOR EXTENDED TREATMENT DURATION

**COMBINATION OPPORTUNITIES WITH SOC
AND NOVEL TREATMENTS**

Our Vision to Fuel Long-term Growth



1

MAXIMIZE COMMERCIAL EFFECTIVENESS

2

**BUILD ON TAVZERIK'S
PIPELINE-IN-A-DRUG POTENTIAL**

3

**EXPAND PIPELINE & PORTFOLIO TO
OVERCOME UNDRUGGABLE TARGETS**

4

**COLLABORATE TO EXPAND
PATIENT REACH & BUILD VALUE**

TAZVERIK[®]

Commercial Progress

TAZVERIK Adoption Trends Continue to Improve

Demand* †

- Continued quarter-over-quarter total demand growth for TAZVERIK throughout 2021
- Continued increase in new accounts prescribing TAZVERIK
 - Academic and Community accounts

Share^

- TAZVERIK market share continues to increase in both 2L and 3L treatment of FL
- TAZVERIK share in 3L estimated at ~14% overall, and at ~39% in EZH2 MT

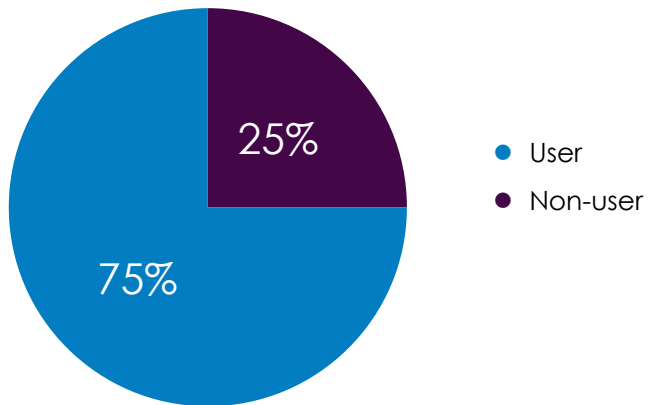
Intent to Prescribe^

- Physicians report that they intend to increase prescribing of TAZVERIK for R/R FL across all treatment lines
- Most physicians report a moderate to high rate of satisfaction with TAZVERIK in EZH2 MT, EZH2 WT and EZH2 Untested patients

Encouraging Progress on Important Commercial Metrics

TAZVERIK Adoption*

75% of FL Treaters Sampled Indicate They've Used TAZVERIK in Patients

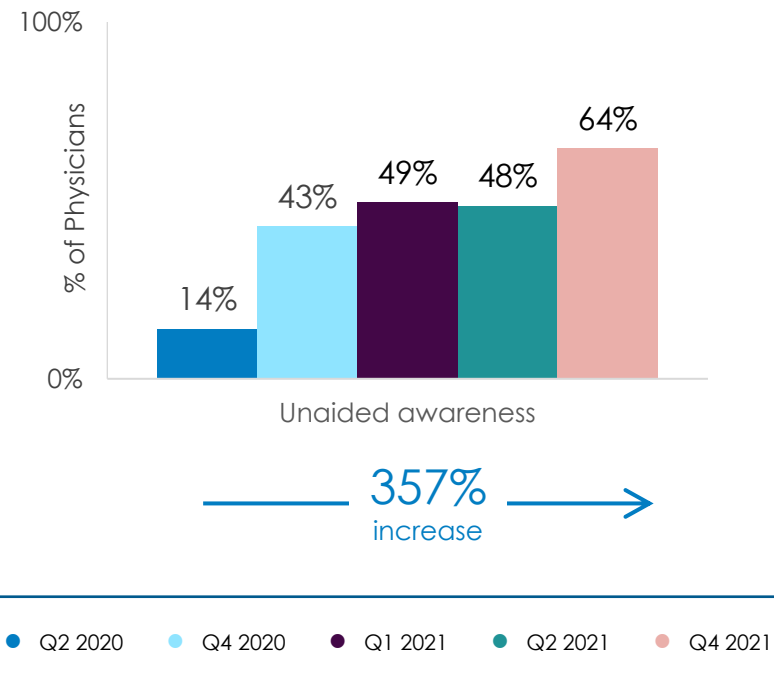


46% of physicians sampled practice in an **academic** setting

The percentage of physicians sampled prescribing TAZVERIK **has increased** in the past 12 months (**75%** in Q4 2021 vs. **56%** in Q4 2020)

Brand Awareness*

TAZVERIK Unaided Awareness Now Exceeds All Approved / Unapproved 3L+ FL Drugs



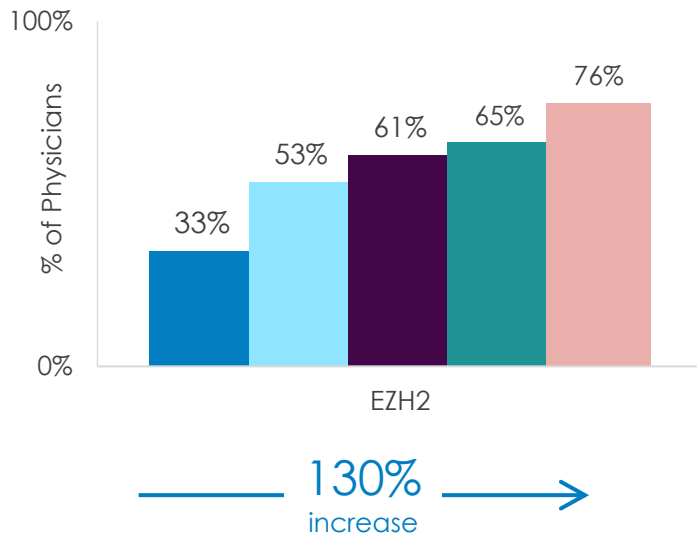
Customer Engagement^

Enhanced Salesforce Focus Gaining Traction with Physicians

- More Tier 1 and 2 accounts are now open for rep visits
 - ~45% of calls in-person in November 2021, up from ~31% in Q3 2021
- Success integrating TAZVERIK into important systems of care
- New field roles facilitating greater access and more in-depth discussions with key stakeholders

More HCPs Testing for EZH2 and Using Results in Treatment Choice*

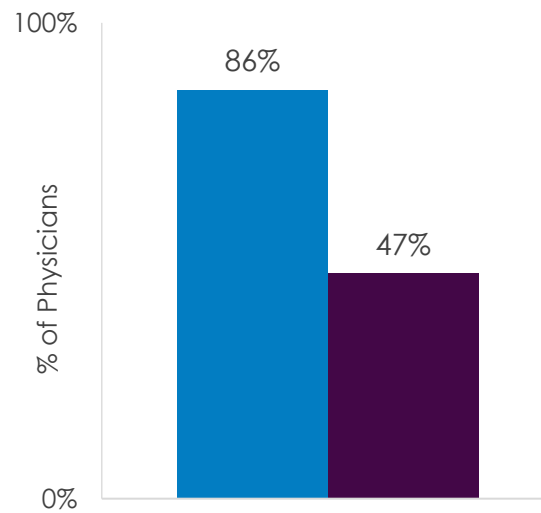
More Providers Now Testing for EZH2*



● Q2 2020 ● Q4 2020 ● Q1 2021 ● Q2 2021 ● Q4 2021

Physicians Who Test For EZH2 Have Significantly Higher Likelihood of Using TAZVERIK*

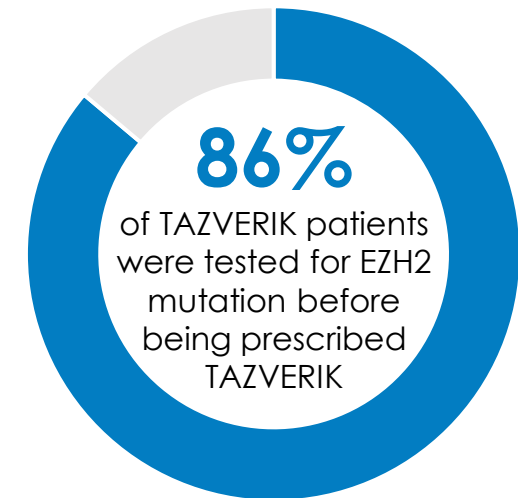
Physicians Testing for EZH2



● Users ● Non-users

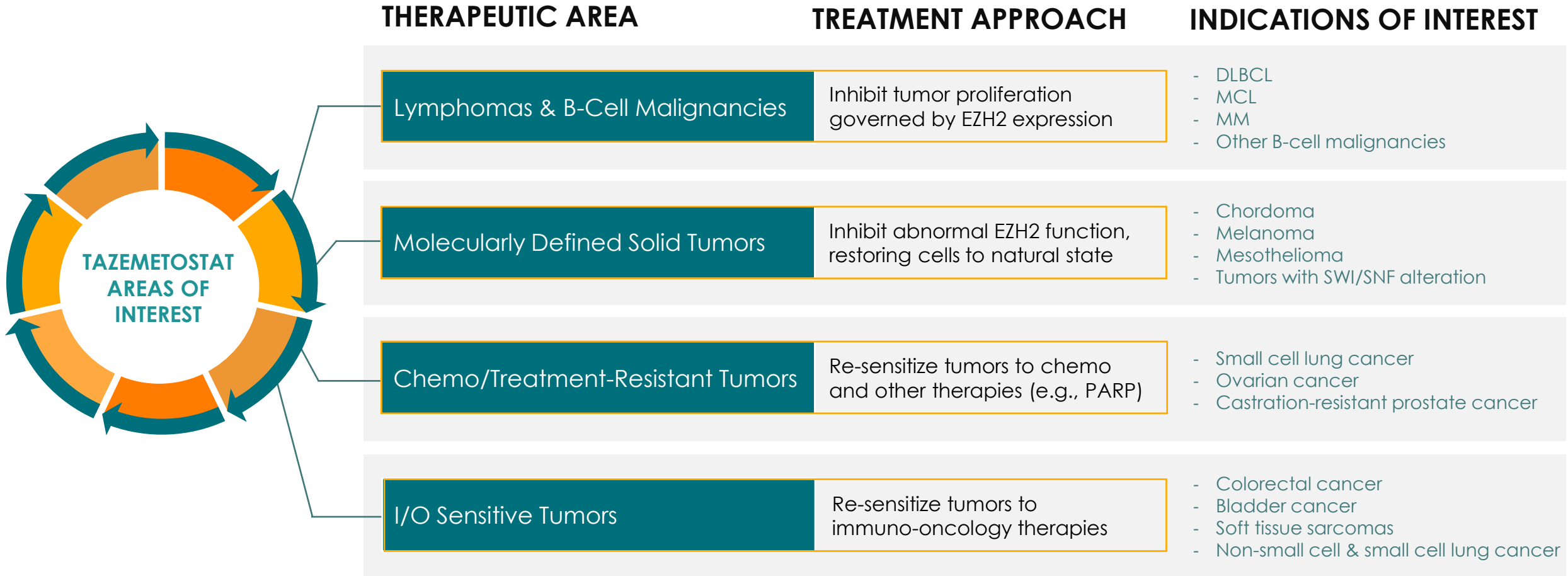
HCPs Choosing TAZVERIK Regardless of EZH2 Test Result*

Testing Leading To TAZVERIK Use in EZH2 WT and MT patients

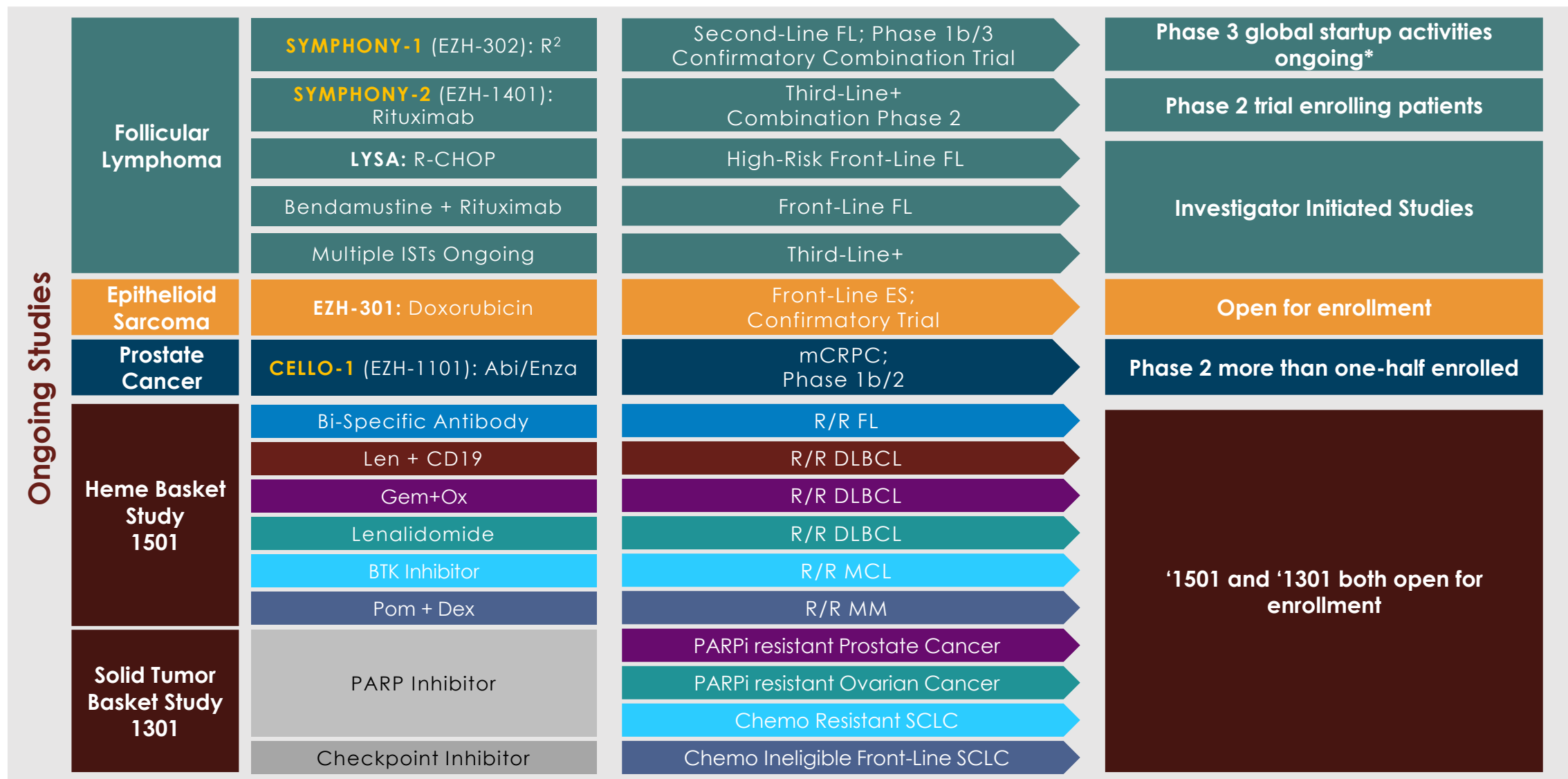


Tazemetostat Development Plans

Expansive Tazemetostat Development Program into Potential New Indications and Combinations

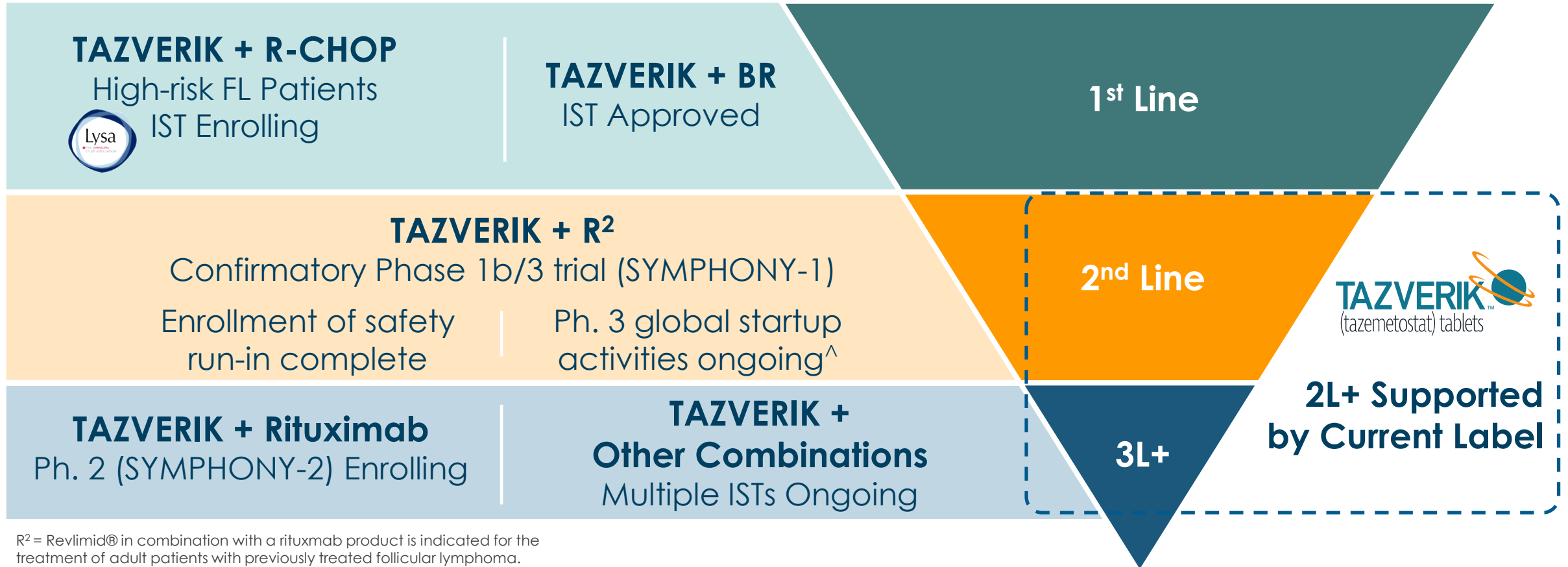


Multiple Ongoing Trials With Anticipated Steady Stream of Data



Developing TAZVERIK® to Become the Backbone of Therapy for Patients with Follicular Lymphoma

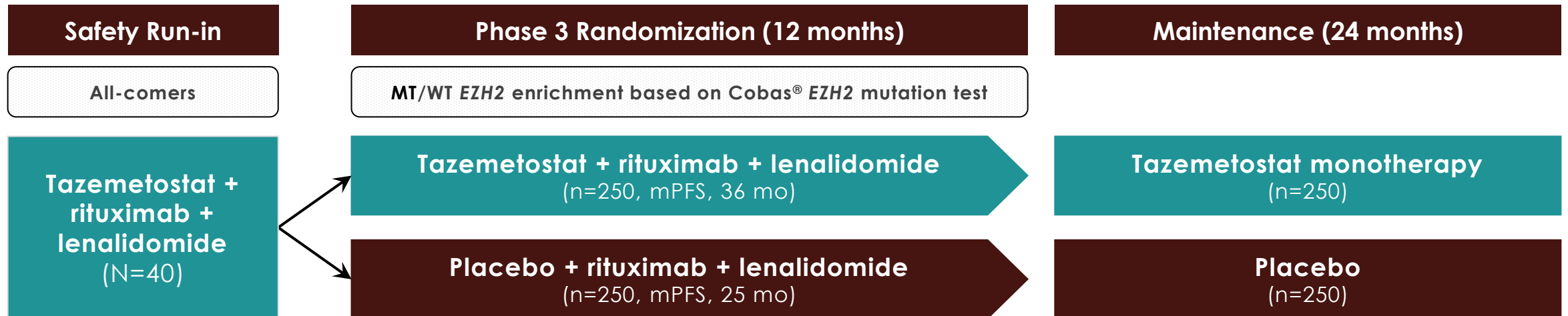
2021 Follicular Lymphoma Epidemiology
~13,700 Patients Diagnosed Annually*



R² = Revlimid® in combination with a rituxmab product is indicated for the treatment of adult patients with previously treated follicular lymphoma.

SYMPHONY-1: Phase 1b/3 Tazemetostat in Combination With R² in Patients With R/R FL

Population	Patients with relapsed / refractory FL who have been treated with at least 1 prior systemic therapy, including patients who are rituximab-refractory and/or POD24	
Key Objectives	Phase 1b (safety run-in) Safety, pharmacokinetics, antitumor activity, RP3D	Phase 3 (efficacy) Primary: PFS as determined by investigator; interim analyses for futility Secondary: PFS by IRC, response rate, duration of response, OS, QOL, safety



Stratification for randomized portion by EZH2 mutation status: treatment-sensitive vs refractory to prior rituximab-containing regimen, patients treated with 1 prior vs ≥2 prior systemic therapies

Celgene/BMS AUGMENT Clinical Trial Informed SYMPHONY-1 Trial Powering

AUGMENT Trial Overview

- Phase 3 clinical trial conducted by Celgene/BMS that led to the approval of R² in treating patients with R/R FL
 - Basis for powering SYMPHONY-1
- AUGMENT included 358 patients assigned to R² (N=178) or placebo plus rituximab (N=180)
- Patients previously treated with ≥ one prior systemic chemotherapy, immunotherapy or chemoimmunotherapy received ≥ 2 previous doses of rituximab
- Documented R/R or progressive disease after treatment with systemic therapy
- Patients must not be Rituximab-refractory

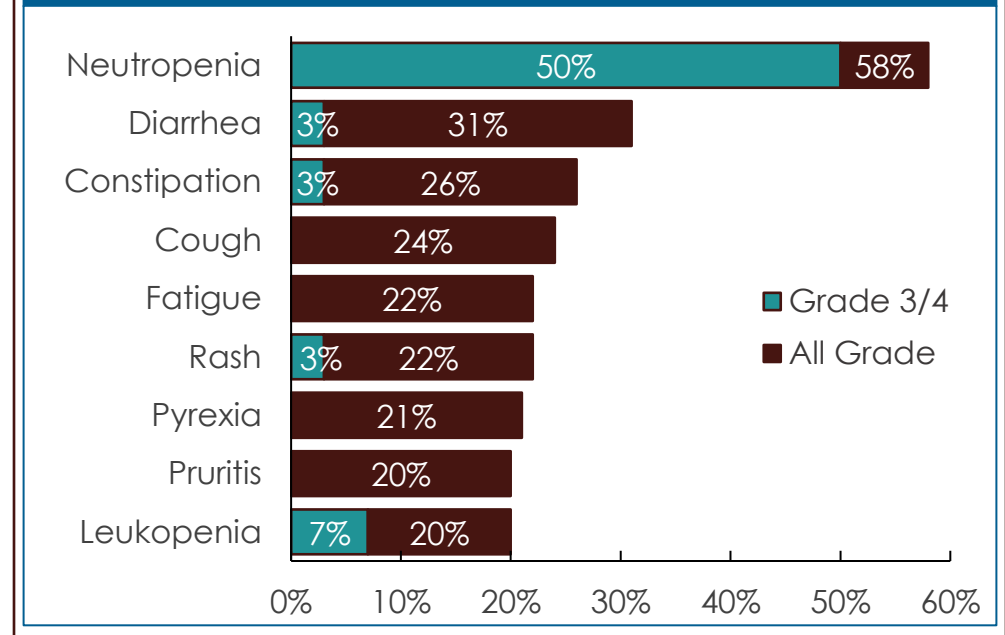
Key Safety Highlights

- Cumulatively, Grade 3-5 TEAEs were observed in 123 (70%) patients; SAEs in 45 (26%) patients
- AEs leading to any study drug modification, excluding interruptions in 112 (64%) patients
- AEs leading to dose modification interruptions in 125 (71%) patients

R² Safety and Efficacy Findings

Response	R ² in 2L+ (N=178)
ORR (CI)	78% (71, 83)
CR	35%
DOR (months)	36.6 (22.9-NR)
Median PFS (months)	25.3 (21.2, NR)

AEs Occurring ≥20% (N=176)



Source: AUGMENT study results. Leonard, et. Al, J Clin Oncol 37, no. 14 (May 10, 2019) 1188-1199.
 R², rituximab + lenalidomide; R/R, relapsed or refractory; CI, confidence interval; ORR, overall response rate; CR, complete response; DOR, duration of response; PFS, progression free survival;

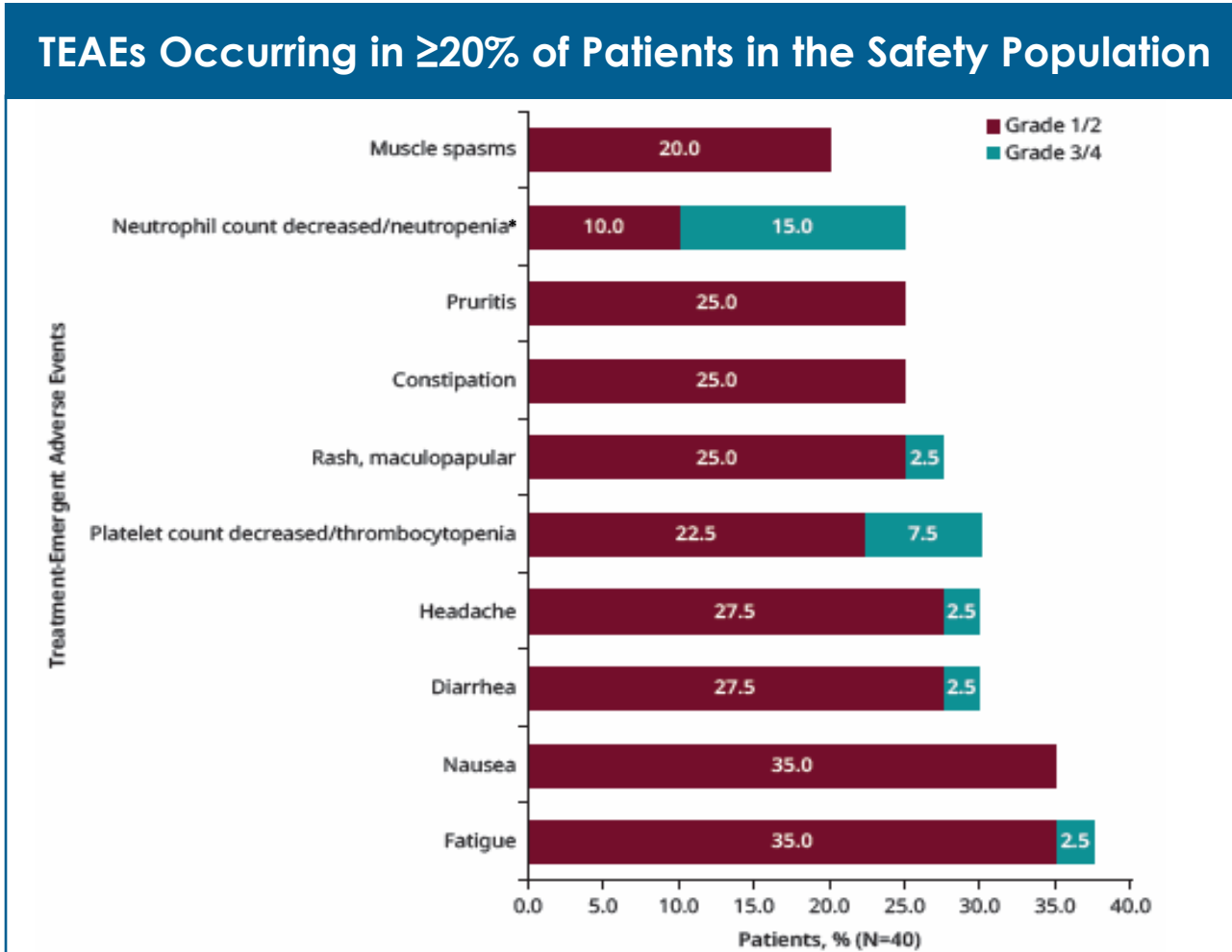
SYMPHONY-1 Interim Analysis: Safety Run-in Patient Background

Characteristic	Tazemetostat + R ² (n=40)
Median age in years (range)	67 (39–83)
Male, n (%)	24 (60.0)
Age ≥ 65 years, n (%)	24 (60.0)
ECOG PS, n (%)	
0	28 (70.0)
1	12 (30.0)
Prior lines of systemic anticancer therapy, n (%)	
1	19 (47.5)
2	13 (32.5)
≥3	8 (20.0)
Median prior lines of systemic anticancer therapy (range)	2 (1–4)
Prior classes of treatment, n (%)	
Prior anti-CD20 antibody + chemotherapy (R/G-bendamustine, R/G-CHOP-based therapy) n, (%)	30 (75.0)
Prior anti-CD20 antibody-only therapy, n (%)	10 (25.0)

- Robust number of patients (40) enrolled across the three tazemetostat dose groups: 400 mg (n=4), 600 mg (n=18) or 800 mg (n=18)
- Median age was 67 years (range, 39–83) and median number of prior therapies was 2 (range, 1–4)
- 75% of patients had prior anti-CD20 antibody + chemotherapy treatment

Note: Data cut off as of September 29, 2021.

SYMPHONY-1 Interim Analysis: Safety Run-in Adverse Events



- Cumulatively, Grade 3/4 TEAEs were observed in 17 (42.5%) patients
- The most common grade 3/4 TEAE ($\geq 10\%$) was neutrophil count decrease/neutropenia (15.0%)

Note: Data cut off as of September 29, 2021.

Safety profile of tazemetostat + R² consistent with safety information for the individual tazemetostat and R² package inserts

SYMPHONY-1 Interim Analysis: Safety Run-in Response Rates

Response, n (%)	Tazemetostat + R ² (n=35)
Overall Response Rate*	32 (91.4%)
Complete Response [^]	13 (37.1%)
Partial Response	19 (54.3%)
Stable Disease	3 (8.6%)
Progressive Disease	0

Note: Data cut off as of September 29, 2021.

- 35 of 40 patients treated with tazemetostat + R² were evaluable for tumor assessments; 32 patients responded to treatment
- Duration-of-response data were not mature because of short follow-up
- To date, no evaluable patient has exhibited Progressive Disease (PD) as best response

Impressive objective response rate (ORR) findings – patients being followed for durability (DOR). Data support expansion to randomized Phase 3 portion of the trial in 500 patients with R/R FL, including rituximab-refractory patients

*For best overall response, there were 27 PET-CT-based responses and 8 CT-based responses.

[^]For CR, 12 were PET-CT-based responses and 1 was a CT-based response.

CR, complete response; CT, computed tomography; PET, positron emission tomography; PD, progressive disease; PR, partial response; R², rituximab + lenalidomide; SD, stable disease.

SYMPHONY-1 Interim Analysis: Key Takeaways



Safety profile consistent with individual package inserts for R² and tazemetostat



Preliminary activity results are encouraging, with 13 complete responses, 19 partial responses and no patients with progressive disease as best response in the evaluable population of 35 patients



The randomized Phase 3 portion will further explore the efficacy and safety of tazemetostat + R² and tazemetostat maintenance in approximately 500 patients with R/R FL

Submitted protocol amendment to FDA with 800mg BID as RP3D; Phase 3 global startup activities underway

Tazemetostat Projected Publication & Data Dissemination 2021-2024

	December 2021	2022*	2023 – 2024*
Tazemetostat	<p>SYMPHONY-1 Interim Phase 1b</p>	<p>LYSA FL/DLBCL Interim Results</p> <p>Solid Tumor Basket Preliminary Data</p> <p>SYMPHONY-1 Updated Phase 1b</p> <p>SYMPHONY-2 Interim Analysis</p> <p>Heme Basket Preliminary Data</p> <p>CELLO-1 Phase 2 Updated Safety Run-in</p>	<p>CELLO-1 Phase 2 Study Results</p> <p>LYSA FL/DLBCL Study Results</p> <p>Solid Tumor Basket Final Phase 1b</p> <p>SYMPHONY-1 Phase 1b DOR/PFS</p> <p>SYMPHONY-2 Final Analysis</p> <p>Heme Basket Final Phase 1b</p> <p>Other Studies including ISTs and under collaborations</p>

Our Vision to Expand Tazemetostat's Utility

Monotherapy in R/R FL and ES

- Jan '20: Accelerated approval in ES
- Jun '20: Accelerated approval in R/R FL

Initial Combination Data

- Publication/presentation of multiple ongoing studies in FL exploring combinations with current standards-of-care across lines of therapy (SYMPHONY-1, SYMPHONY-2, LYSA)
- Initial data from ongoing heme and solid tumor basket trials

Potential Broad Combination Use in Solid Tumors and Heme Malignancies

- Backbone of therapy in FL in combination with multiple other active agents
- Combination with enzalutamide in mCRPC
- Combination opportunities in additional heme and solid tumors
 - DLBCL
 - MCL
 - MM
 - Ovarian Cancer
 - SCLC

Due to its unique mode of action and safety profile, we believe TAZVERIK is well-positioned to become a backbone of therapy in FL and utilized in combination with active agents in other hematological and solid tumors

Expanding Epizyme's Epigenetic Pipeline

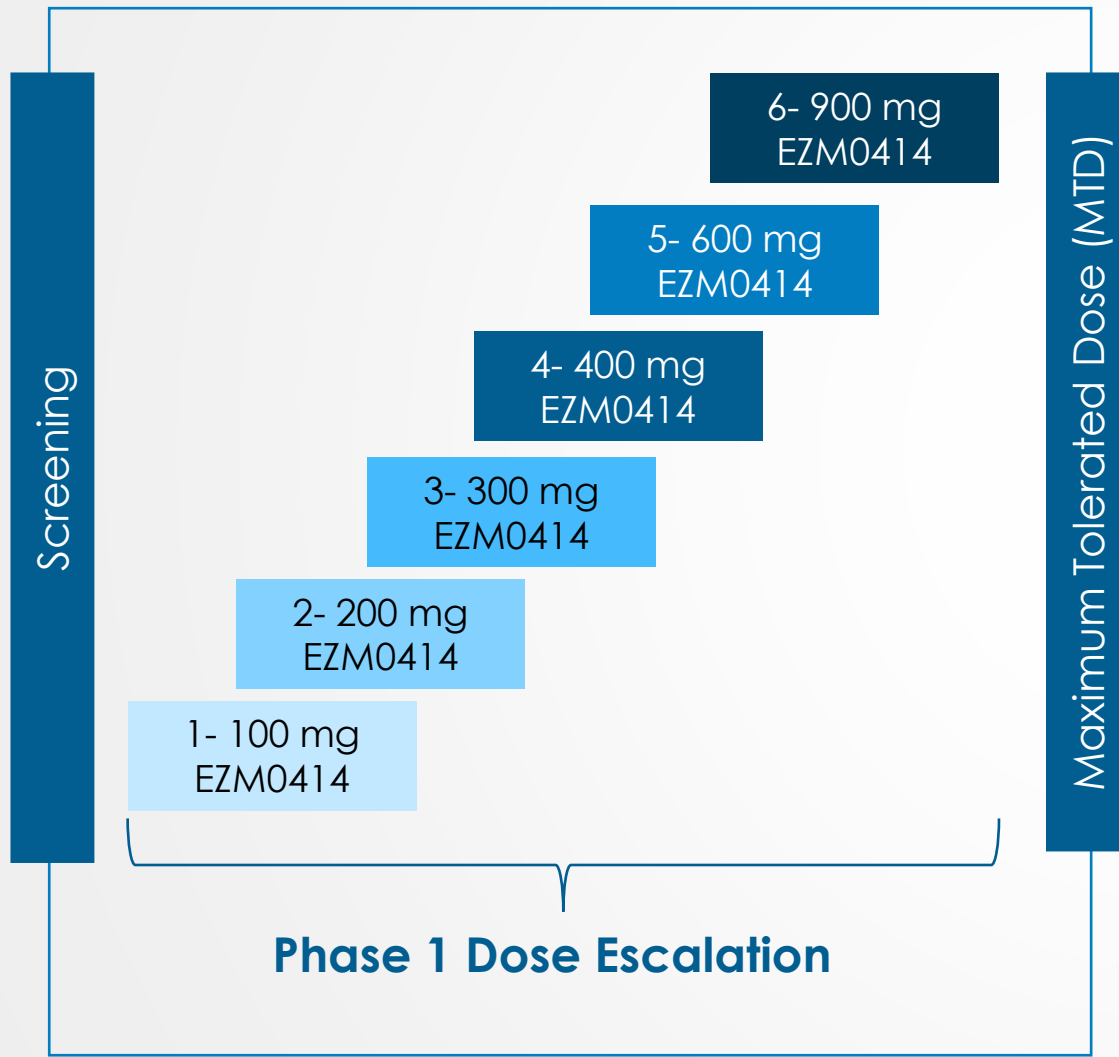
Robust Discovery Pipeline Across 3 Important Epigenetic Target Families

PROGRAM	POTENTIAL INDICATIONS	TARGET VALIDATION	LEAD DISCOVERY	LEAD OPTIMIZATION	DEVELOPMENT CANDIDATE	IND-ENABLING	PHASE 1
HMT INHIBITORS							
SETD2 (EZM0414)	Heme Malignancies	[Progress bar]					
HMT2	Heme & Solid Malignancies	[Progress bar]					
HMT3	Heme Malignancies	[Progress bar]					
HAT INHIBITORS							
HAT1	Heme & Solid Malignancies	[Progress bar]					
HAT2	Solid Malignancies	[Progress bar]					
HELICASE INHIBITORS							
HEL1	Solid Malignancies	[Progress bar]					
HEL2	Heme and Solid Malignancies	[Progress bar]					
HEL3	Solid Malignancies	[Progress bar]					
HEL4	Solid Malignancies	[Progress bar]					
HEL5	Solid Malignancies	[Progress bar]					
HEL6	Solid Malignancies	[Progress bar]					

Multiple Potential Opportunities for Epizyme's SETD2 Inhibitor Drug Candidate, EZM0414

<p>EZM0414 MM Monotherapy and synergy with MM therapies</p>	<ul style="list-style-type: none">• Specific therapy for EZM0414 MM• Explore monotherapy and combination with standard of care and/or emerging pipeline agents
<p>non – EZM0414 MM Synergy with MM therapies</p>	<ul style="list-style-type: none">• Therapy for non-EZM0414 MM• Explore combination with standard of care and/or emerging pipeline agents
<p>DLBCL Synergy with DLBCL therapies</p>	<ul style="list-style-type: none">• Explore combination with standard of care and/or emerging pipeline agents• Potential for biomarkers: e.g., mutant H1, SETD2, or MMSET
<p>Other Cancers (incl. Solid Tumors)</p>	<ul style="list-style-type: none">• Explore combination in other heme malignancies or cancers, including solids (e.g., lung)• Potential for biomarker: H3K36me2 overexpression or dysregulation

SET-101: Phase 1 Dose Escalation



SET-101 Phase 1 Dose Escalation Study Overview:

- SET-101 is a 3+3 dose escalation study
- Primary objective is safety
- EZM0414 is administered PO, with 6 dose levels planned from 100-900 mg QD
- Based upon nonclinical experiments, following monitoring and management proposed:
 - Serial ECGs, Serial vitals, Labs, including cardiac and hepatic safety, Observation during PK sampling timepoints
- ~30-36 relapsed/refractory patients will be enrolled in dose escalation (must enroll ~8 t(4;14) and ~8 non-t(4;14) MM, and ~8 R/R DLBCL, plus 10 additional patients of any type at MTD)
- SET-101 will then open to expansion cohorts of monotherapy for t4:14, non t4:14 and DLBCL (20 pts)

Collaborate To Expand Patient Reach And Build Value

Strategic Collaboration with HUTCHMED for Tazemetostat

Overview of Collaboration

Product: TAZVERIK[®] (tazemetostat)

Exclusive/co-exclusive License:

- Research & Development
- Manufacturing & Commercialization
- Territory: Greater China

R&D Synergies: investigate combos with HUTCHMED's novel oncology medicines portfolio

China Commercial: initially develop & seek approval in various hematological malignancies and solid tumors:

- Epithelioid sarcoma (ES)
- Follicular lymphoma (FL)
- Diffuse large b-cell lymphoma (DLBCL)

Ex-China impact: accelerate global development (HUTCHMED will contribute to global study/studies)

Key Financial Terms

Upfront: US\$25 million

Development & Regulatory Milestones: up to \$110 million, across up to 8 potential indications

Sales Milestones: up to \$175 million

Royalties: Tiered royalties of mid-teen to low-twenties % based on annual sales in Greater China

Warrant Rights:

- HUTCHMED has option to acquire shares of Epizyme common stock
- Term: 4 years
- Amount: up to \$65 million
- Exercise Price: \$11.50/share
- Shares: 5,653,000

Combination Potential For Tazemetostat With HUTCHMED'S Assets

	NEAR TERM		LONGER TERM	
SOLID TUMORS	+ FRUQUINTINIB (VEGFRI) <i>(China approved for CRC; Global Ph III ongoing)</i>	Lung	+ HMPL-295 (ERKi) <i>(China Ph I ongoing)</i>	K-Ras mutant tumors
		Ovarian		
SOLID TUMORS	+ SURUFATINIB (VEGFRI/FGFRI/CSF1RI) <i>(China approved for NET; U.S. NDA & EMA MAA submitted)</i>	Tumors w/ neuroendocrine differentiation (NED), e.g. NEPC	+ IMMUNOTHERAPIES, e.g. HMPL-A83 (CD47) <i>(IND-enabling stage)</i>	Macrophage-targeting such as breast cancer
		Sarcoma (<i>suru. in U.S. Ph Ib</i>)		
HEMATOLOGICAL MALIGNANCIES	+ HMPL-689 (PI3Kδi) <i>(China reg. Ph II initiated; U.S./E.U. Ph II ongoing)</i>	DLBCL	+ HMPL-760 (BTKi)	NHL
		TCL		
			+ HMPL-A83 (CD47)	
			+ Bi-specific Abs	1L NHL

Over The Next 5 Years Epizyme Aspires to:

MAXIMIZE COMMERCIAL EFFECTIVENESS

TAZVERIK adoption as backbone therapy for FL
TAZVERIK utilized in multiple combination regimens

BUILD ON TAZVERIK'S PIPELINE-IN-A-DRUG POTENTIAL

TAZVERIK approvals in additional heme and solid tumor indications
Robust flow of data read-outs

EXPAND PIPELINE & PORTFOLIO TO OVERCOME UNDRUGGABLE TARGETS

Progress new epigenetic programs into the clinic starting with novel SETD2 inhibitor, EZM0414
Robust flow of data read-outs

COLLABORATE TO EXPAND PATIENT REACH & BUILD VALUE

Partner TAZVERIK to reach ex-US markets
Multiple clinical and scientific collaborations

2022 Projected Milestones Driven by Multiple Ongoing Clinical Trials

SYMPHONY-1	Initiate enrollment in global Phase 3 trial in R/R FL patients; present additional follow-up data on 40 patients enrolled in Phase 1b safety run-in portion of study
CELLO-1	Complete enrollment in Phase 2 trial in mCRPC patients; present additional follow-up data on patients enrolled in Phase 1b
LYSA Study	Complete enrollment in Phase 2 trial in front-line, high-risk FL and DLBCL during 1Q 2022; expect interim results will be presented at a medical conference in 2022
EZH-1301 EZH-1501	Enroll patients in both solid tumor (EZH-1301) and hematological malignancy (EZH-1501) Phase 1/1b basket studies; provide updates as the studies reach key enrollment milestones along with preliminary data
SET-101	Enroll dose escalation portion of Phase 1/1b trial of EZM0414 and share preliminary safety data; prepare for expansion phase if MTD or MED is reached
Additional Activities	Continue to advance additional studies evaluating tazemetostat, including FDA post-marketing commitments; preclinical development on differentiated epigenetic assets to supplement pipeline

FDA-Approved For Treatment of Multiple Cancers

INDICATED FOR

- Adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection
- Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies
- Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options

TAZVERIK[™]
(tazemetostat) tablets



**FIRST AND ONLY APPROVED
EZH2 INHIBITOR**

**DURABLE RESPONSES
WITH POTENTIAL FOR EXTENDED
TREATMENT DURATION**

**WELL-TOLERATED WITH
NO BLACK BOX WARNINGS
OR CONTRAINDICATIONS;
NO REMS**

**ORAL, AT-HOME
ADMINISTRATION**

Safety Information Supports Low Rate of Treatment Discontinuations (6-8%)

MOST COMMON ADVERSE REACTION ($\geq 20\%$, ANY GRADE)

- ES: Pain, fatigue, nausea, decreased appetite, vomiting and constipation
- FL: Fatigue, upper respiratory infection, musculoskeletal pain, nausea and abdominal pain

WARNINGS & PRECAUTIONS

- Secondary malignancies: Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome or acute myeloid leukemia occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma.
- Embryo-fetal toxicity

DRUG INTERACTION

- Strong and Moderate Cytochrome P450 (CYP)3A Inhibitors: Avoid coadministration of strong and moderate CYP3A inhibitors with TAZVERIK. Reduce the dose of TAZVERIK if coadministration of moderate CYP3A inhibitors cannot be avoided
- Strong and Moderate CYP3A Inducers: Avoid coadministration with TAZVERIK