EZH2 Symposium
June 2014
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Today’s Objectives and Agenda

Today’s objective is to convey our growing understanding of EZH2’s important role in germinal center B-cell maturation and lymphomas and the corresponding expanding opportunities for EZH2 as a therapeutic target.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overview of Epizyme and HMTs</td>
<td>Robert Gould, Ph.D., Chief Executive Officer</td>
</tr>
<tr>
<td>EZH2 in B-Cell Biology and Pathobiology and Pre-clinical Characterization of EPZ-6438</td>
<td>Robert Copeland, Ph.D., Chief Scientific Officer</td>
</tr>
<tr>
<td>EPZ-6438 in Combination with Other Therapeutic modalities</td>
<td>Heike Keilhack, Ph.D., Director, Biological Sciences</td>
</tr>
<tr>
<td>Unmet Needs in Diffuse Large B-Cell Lymphoma and Follicular Lymphoma</td>
<td>Eric Hedrick, M.D., Chief Medical Officer</td>
</tr>
<tr>
<td>B-cell Lymphoma Patient Populations and Expanded Opportunity</td>
<td>Jason Rhodes, President and Chief Financial Officer</td>
</tr>
</tbody>
</table>
Biopharmaceutical company creating personalized therapeutics for patients with genetically defined cancers

- **First-in-class small molecule inhibitors** targeting histone methyltransferases (HMTs), a 96-member class of epigenetic enzymes that drive cancers & other diseases

- **Clinical programs for genetically defined cancers**
  - EPZ-5676 DOT1L inhibitor (demonstrated objective responses in adult Phase 1 dose escalation)
  - EPZ-6438 EZH2 inhibitor (Phase 1/2 ongoing)

- **Product platform** generating pipeline of novel personalized therapeutic programs

- **Intellectual property** with earliest composition of matter expected expirations in 2032

- **Rx collaborations** with Celgene, Eisai, and GSK and **CDx collaborations** with Abbott and Roche

- **$245 million cash and equivalents end of Q1 2014**
HMTome Target Class

- **HMTs** are part of regulatory system that **controls gene expression**, called **epigenetics**

- HMTs **regulate** gene expression by placing **methyl marks on histones**

- **Genetic alterations** can alter HMT activity making them **oncogenic** due to misregulated gene expression

- 96-member target class, **20 prioritized** based on oncogenic mechanism

Oncogenic HMT

Misregulated gene expression

Disease
HMTs – Equally Divided Between KMTs and RMTs

Lysine Methyl Transferases (KMTs)

Arginine Methyl Transferases (RMTs)
Genetically Altered HMTs as Drivers of Cancer

Lysine Methyl Transferases (KMTs)

Arginine Methyl Transferases (RMTs)

Copeland 2013 Clinical Cancer Research
HMTs as Drivers of Cancer

Lysine Methyl Transferases (KMTs)

- SMYD3: Breast, Liver, Colon, Gastric
- SMYD2: Esophageal Squamous
- EZH2: NHL, INI1, Breast, Prostate, Colon, Gastric, Bladder, Liver, Melanoma
- MLL4: Pancreatic, Glioblastoma
- SETDB1: Melanoma
- SETD2: Clear Cell Renal Carcinoma
- PRDM14: Breast
- SUV39H1: Colon
- NSD1: AML
- WHSC1L1: Lung, Breast
- WHSC1: Multiple Myeloma

Arginine Methyl Transferases (RMTs)

- SMYD3: Breast, Liver, Colon, Gastric
- PRMT: ALL, Glioblastoma, Ovarian
- EHM2: Lung, Prostate, HCC
- PRMT: Lymphoma
- CARM1: Breast, Prostate
- DOT1L: MLL-r AML, ALL
- NSUN2: Breast

Copeland 2013 Clinical Cancer Research
# A Spectrum of Genetic Alterations Confer Dependence on HMT Activity to Cancer Cells

<table>
<thead>
<tr>
<th>Genetic Alteration</th>
<th>Genetic Locus</th>
<th>HMT Affected</th>
<th>Effect</th>
<th>Clinical Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal Translocation</td>
<td>t(X;18)</td>
<td>EZH2</td>
<td>Altered methylation of H3K27</td>
<td>Synovial Sarcoma</td>
</tr>
<tr>
<td>(11q23)</td>
<td>DOT1L</td>
<td></td>
<td>Ectopic recruitment</td>
<td>MLL-r</td>
</tr>
<tr>
<td>t(5:11)</td>
<td>NSD1</td>
<td></td>
<td>Increased expression of HOX genes</td>
<td>AML</td>
</tr>
<tr>
<td>t(4:14)</td>
<td>NSD2</td>
<td></td>
<td>Overexpression</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>t(8:11)</td>
<td>NSD3</td>
<td></td>
<td>Novel fusion protein</td>
<td>AML</td>
</tr>
<tr>
<td>Point Mutations</td>
<td>EZH2</td>
<td>EZH2</td>
<td>Altered methylation of H3K27</td>
<td>Diffuse Large B-Cell Lymphoma (DLBCL) Follicular Lymphoma (FL)</td>
</tr>
<tr>
<td>MLL2</td>
<td>MLL2</td>
<td></td>
<td>Altered methylation of H3K4</td>
<td>Germinal Center-Derived B-cell Lymphoma</td>
</tr>
<tr>
<td>Chromosome Deletion</td>
<td>22q</td>
<td>EZH2</td>
<td>Altered methylation</td>
<td>Malignant Rhabdoid Tumor (MRT)</td>
</tr>
</tbody>
</table>

Copeland 2014 In Press
Expanded Opportunities for EZH2 Beyond Original Mutant NHL Hypothesis

• B-cell lymphomas of GC origin with mutated EZH2 remain an attractive target
  – Both DLBCL and FL are target patient populations
• B-cell lymphomas of GC origin with wild type EZH2 in both DLBCL and FL
• INI1-deficient tumors, such as synovial sarcoma and MRT
B-Cell Biology and Lymphomas
B-Cell Biology and Lymphomas

- B-cell differentiation/maturation in humoral immunity
- GC reaction: somatic hypermutation (SHM) and isotype switching
- EZH2 regulation critical for GC reaction and normal B-cell maturation
- SHM state favorable to lymphomagenic genetic alterations
- EZH2 activation commonly seen in all GC-derived lymphoma subtypes, mutant and wild type
Anatomy of the Lymph Node

- Capsule
- Subcapsular sinus
- Trabecula
- Afferent lymphatic vessels
- Efferent lymphatic vessels
- Hilus
- Medullary sinus
- Medullary cord
- Germinal center in follicle
- Cortex
- Follicle

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GC Reaction and EZH2

• GC reaction central to development of mature B-lymphocytes
  – Occurs in secondary lymphoid (e.g., spleen) follicles
  – During reaction B-cells undergo somatic hypermutation and isotype switching
  – Product of reaction is repertoire of B-cells with high affinity for specific antigens

• GC reaction requires attenuation of DNA damage response and replication checkpoints
  – Accomplished by developing transcriptionally repressed state
  – EZH2 and BCL6 are highly upregulated to suppress cell cycle checkpoints and proapoptotic responses
  – EZH2 regulates (silences) bivalent genes involved in B-cell differentiation and maturation (e.g., CDKN1A, PRDM1, IRF4)
  – Creates physiological state of high mutagenesis rate - can lead to aberrant mutations that favor lymphomagenesis

• Three main subtypes of GC-derived lymphoma are commonly seen:
  – Follicular Lymphoma (FL)
  – GCB Diffuse Large B-cell Lymphoma (GCB DLBCL)
  – Burkitt’s Lymphoma
  – Activation of EZH2, BCL6 and BCL2 seen in all of these GC-derived lymphoma subtypes
The Importance of Bivalent Histone Methylation in Stem and Progenitor Cells

- Many tumor suppressor and checkpoint regulator genes exist in bivalent state
  - Simultaneously H3K4me3 and H3K27me3
- These marks act in opposing manners:
  - H3K4me3 activates transcription
  - H3K27me3 suppresses transcription
- Bivalent genes poised for activation or suppression
  - Depends on relative abundance of each mark
  - Affected by changes in expression of EZH2 and H3K4 HMTs (e.g., MLL2) during normal B-cell maturation
  - Affected by genetic alterations in EZH2 and/or MLL2 activity in lymphoma
Gene Regulation in B-Cell Maturation and Lymphoma

Kuppers 2005 Nat Rev Cancer
Gene Regulation in B-Cell Maturation and Lymphoma

Genetic Alterations Affecting H3K27me3

- SET-domain mutations
- Overexpression of EZH2
- Overexpression of other PRC2 subunits
- LoF of HATs
- LoF of MLL2

Kuppers 2005 Nat Rev Cancer
EZH2 Alterations in B-Cell Lymphomas
Dysregulation of Epigenetic Pathways in GC-Derived Lymphomas

- **Point mutations in EZH2 SET domain**
- Overexpression of EZH2
- Overexpression of other PRC2 subunits
- LoF of HAT leading to reduced acetylation of histone lysines, including H3K27
- LoF of MLL2 resulting in disruption of balance for bivalent genes
- None seen in ABC subtype
EZH2 Mutations Identified in Non-Hodgkin Lymphomas

- EZH2 mutations identified in non-Hodgkin lymphomas (NHL)

- Summary of recent sequencing data suggests incidence of initial target population is ~12,000 NHL patients in major markets with EZH2 point mutations (22% DLBCL-GCB and FL)

- Y641 (equivalent to Y646, catalytic domain) is mutated and results in amino acid changes to F, N, H, S or C

- Mutations result in change of function that, in cooperation with wild type EZH2 result in hypertrimethylation of H3K27 that drives lymphomagenesis

Morin et al. 2010 Nature Genetics
Sneeringer et al. 2010 PNAS
Enzyme Kinetics Predict Increased Histone H3K27Me3 with Heterozygous WT/Y646 Mutant

Wild Type EZH2

Y646 Mutant EZH2

Heterozygous WT/Y646 Mutant EZH2

Wild Type Mutant

Mutant

Sneeringer et al. 2010 PNAS
## Summary of Published Findings of Lymphoma Cell Lines: Sensitivity to EZH2 Inhibition

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>EZH2 Mutant GCB</td>
<td>Consistent sensitivity to EZH2 inhibition shown by all investigators</td>
</tr>
<tr>
<td>EZH2 WT GCB</td>
<td>Sensitivity observed depending on drug concentration, timing of measurements and cell culture conditions</td>
</tr>
<tr>
<td>ABC</td>
<td>Consistent lack of sensitivity to EZH2 inhibition shown by all investigators</td>
</tr>
</tbody>
</table>

Knutson et al. 2012 *Nature Chem Biol*
McCabe et al. 2012 *Nature*
Beguelin et al. 2013 *Cancer Cell*
Knutson et al. 2014 *Mol Cancer Therapeut*
Pre-clinical Characterization of Single Agent Activity of EPZ-6438 (E7438), the First EZH2 Inhibitor to Enter Human Clinical Trials
• **Potent** against intended target in **wild type and mutant** form – 2.5 nM biochemical assay

• Highly **selective** vs. HMTs and other targets
  – Biochemical – >20,000-fold by $K_i$ (except EZH1)
  – Cellular – only inhibits target associated methyl mark

• **Orally bioavailable**

• **Target methyl mark inhibition** that leads to **specific killing** of **genetically defined cancer** cells **in vitro**

• **Combinations** with glucocorticoid receptor agonists or signaling pathway modulators **extends activity** to EZH2 wild type GC-derived NHL cells

• Profound and sustained **in vivo efficacy** in animal models following inhibition of target methyl mark

Knutson et al. 2013 *PNAS*
EPZ-6438 Specifically Inhibits Cellular H3K27 Methylation in a Time- and Dose-Dependent Manner

**WSU-DLCL2 cells (EZH2 Y646F) in vitro**

Methylation by ELISA

![Graph showing the effect of EPZ-6438 on H3K27 methylation in WSU-DLCL2 cells.](image)

**WSU-DLCL2 cells (EZH2 Y646F) in vitro**

Time Course at 1 µM

![Graph showing the time course of H3K27Me3 levels in WSU-DLCL2 cells.](image)

**OCI-LY19 cells (EZH2 WT) in vitro**

4-Day Treatment

![Images of EZH2 Products: H3K27Me1, H3K27Me2, H3K27Me3, H3K27acetyl, H3K4Me3, H3K9Me3, H3K36Me2, H3K79 Me2, Total H3.](image)

Knutson et al. 2014 MCT
EPZ-6438 Selectively Kills EZH2 Mutant Cells Despite Similar Target Inhibition in Both Mutant and WT Cells

**EZH2 Y646F Mutant**

*Day 11 IC$_{50}$ = 8.6 nM*

**EZH2 Y646 WT**

*Day 11 IC$_{50}$ = 6200 nM*

Knutson et al. 2014 *MCT*
KARPAS422 (EZH2 Y646N Mutant) Xenografts Are Highly Sensitive to Orally Dosed EPZ-6438

28-day Efficacy Study

- All doses were BID in efficacy study, no significant body weight loss during study
- In a 2nd study, mice were kept alive and remain tumor free 63 days after cessation of dosing

Knutson et al. 2014 MCT
EPZ-6438 Shows Strong Antitumor Activity in Multiple EZH2 Mutant Xenograft Models (NHL)

KARPAS-422 (Y646N)

No tumor re-growth for 63 days after dosing stop on Day 28 in two highest dose groups

WSU-DLCL2 (Y646F)

Pfeiffer (A682G)

Knutson et al. 2014 MCT
EPZ-6438: First EZH2 Inhibitor in Clinic

- EZH2 activity is critical for normal GC-reaction in B-cell maturation
- Multiple genetic alterations lead to elevated EZH2 activity in GC-derived lymphomas
- EPZ-6438 is a potent, selective inhibitor of wild type and lymphoma-associated mutants of EZH2
- EPZ-6438 displays robust and durable activity as a single agent in EZH2 mutant-bearing GC-derived lymphoma animal models
Synergy Between EZH2 Inhibition and Other Therapeutic Modalities
Strategies for Studying EPZ-6438 in Combinations in Pre-clinical Lymphoma Models

- EPZ-6438 showed promising single agent activity in pre-clinical models of DLBCL, especially EZH2 mutant models
- Drug combination studies were performed to further evaluate the potential of EPZ-6438, also in EZH2 inhibitor insensitive models (EZH2 mutant and WT)
- 3 categories of drugs were explored:
  - Standard of care reagents for B-NHL (i.e. R-CHOP)
  - Drugs addressing genetic alterations that co-occur with EZH2 mutations in B-NHL (i.e. BCL2/BCL6)
  - Novel reagents actively being investigated in B-NHL, for instance BCR pathway modulators (ibrutinib, idelalisib, etc.)
- Pre-clinical data demonstrate that several combinations amplify the anti-proliferative potency of EPZ-6438 and extend activity to GC-derived DLBCL cells
# EZH2 Inhibition Combination Benefit with CHOP Components Driven by GR Agonists in GCB Lymphoma

## 2013 Accomplishments

EZH2 Inhibition Combination Benefit with CHOP Components Driven by GR Agonists in GCB Lymphoma

<table>
<thead>
<tr>
<th>Standard of Care DLBCL</th>
<th>WSU-DLCL2 (EZH2 mutant GCB)</th>
<th>SU-DHL-10 (EZH2 mutant GCB)</th>
<th>Toledo (WT EZH2 ABC)</th>
<th>DOHH2 (WT EZH2 GCB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>Synergy</td>
<td>Additive</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Mafosfamide</td>
<td>Additive</td>
<td>Additive</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Additive</td>
<td>Additive</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Synergy</td>
<td>Synergy</td>
<td>No effect</td>
<td>Synergy</td>
</tr>
<tr>
<td>Other Therapies</td>
<td>Dexamethasone</td>
<td>Synergy</td>
<td>No effect</td>
<td>Synergy</td>
</tr>
</tbody>
</table>

### Potency shift EPZ-6438 + Prednisolone

**WSU-DLCL2 (Y646F)**

Max. 24-fold shift

### Activity of GRag combo in all GCB lymphoma lines

- **EPZ-6438**
- **EPZ-6438 + prednisolone**

Johnston, Knutson et al. 2013 *Blood (ASH Annual Meeting Abstracts)*

Epizyme
EPZ-6438 Synergizes with CHOP Chemotherapy \textit{in vivo}

**WSU-DLCL2 (Y646F)**

\textit{in vitro LCC: 170 nM}

**SUDHL6 (Y646N)**

\textit{in vitro LCC: 210 nM}

Johnston, Knutson et al. 2013 \textit{Blood} (ASH Annual Meeting Abstracts)
EPZ-6438 Synergizes with Drugs Targeting the BCR/PI3K Pathways *in vitro*

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug</th>
<th>Mutant EZH2 GCB</th>
<th>WT EZH2 GCB</th>
<th>WT EZH2 ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>WSU-DLCL2</td>
<td>SU-DHL-10</td>
<td>DOHH2</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>Prednisolone</td>
<td>Synergy</td>
<td>Synergy</td>
<td>Synergy</td>
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<tr>
<td></td>
<td>Dexamethasone</td>
<td>Synergy</td>
<td>Synergy</td>
<td>Synergy</td>
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<tr>
<td>BCL2</td>
<td>Navitoclax</td>
<td>Synergy</td>
<td>Synergy</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>Obatoclax</td>
<td>Additive</td>
<td>Additive</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>ABT-199</td>
<td>Synergy</td>
<td>Additive</td>
<td>No effect</td>
</tr>
<tr>
<td>B-cell Receptor Pathway</td>
<td>Everolimus</td>
<td>Synergy</td>
<td>Synergy</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>Trametinib</td>
<td>Synergy</td>
<td>Synergy</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>Bortezomib</td>
<td>Additive</td>
<td>Additive</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>MK-2206</td>
<td>Synergy</td>
<td>Synergy</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>Ibrutinib</td>
<td>Synergy</td>
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<td>No effect</td>
</tr>
<tr>
<td></td>
<td>Idelalisib</td>
<td>Synergy</td>
<td>Synergy</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>Tamatinib</td>
<td>Synergy</td>
<td>Synergy</td>
<td>No effect</td>
</tr>
</tbody>
</table>
EZH2 Inhibition Represents a Novel Therapeutic Approach for GCB Lymphomas

- Synergistic activity in GCB lymphoma cells with either wild type or mutant EZH2:
  - Modulators of B-cell receptor pathway
  - Inducers of apoptosis (BCL-2 family)
  - Glucocorticoid receptor agonists

- Clinically relevant combos with either SOC agents or novel active anti-lymphoma drugs
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  - Inducers of apoptosis (BCL-2 family)
  - Glucocorticoid receptor agonists
- Clinically relevant combos with either SOC agents or novel active anti-lymphoma drugs
Unmet Needs in Diffuse Large B-Cell Lymphoma and Follicular Lymphoma
EPZ-6438 Phase 1 Trial

- Development collaboration with Eisai, Inc.
- Design:
  - Part 1: Dose Escalation
    - 3+3 dose escalation design
    - Primary objective: Determine the maximum tolerated dose (MTD) or recommended Phase 2 dose RP2D
    - Secondary objectives: describe safety profile, pharmacokinetics, pharmacodynamics (H3K27 methylation)
    - Patient population: advanced solid tumors or hematologic malignancies (including B-cell NHL)
  - Part 2
    - Two-stage phase 2 design
    - Primary objective: evaluate the efficacy of EPZ-6438
    - Secondary objective: evaluate safety profile
    - Patient population: diffuse large B-cell lymphoma (DLBCL) with change-of-function EZH2 mutation
- Current Status:
  - Currently in dose-escalation phase
  - No DLT/ MTD encountered to date
  - Completion of dose escalation and initiation of phase 2 anticipated 2H 2014
DLBCL: Considerations for Development of Novel Agents

• Areas of progress:
  – First-line therapy in the rituximab era (R-CHOP) has improved outcomes in DLBCL; ~ 60% DLBCL patients cured with therapy

• Areas of Unmet Need:
  – Outcome with “standard” approach to salvage therapy (salvage chemoimmunotherapy followed by ASCT) for those not cured with R-CHOP appears worse in the rituximab era
    • Those failing R-CHOP within 12 months have a particularly dire outcome
    • Patients who fail ASCT have no curative option

• Regulatory landscape:
  – CHOP components approved for NHL
  – Rituximab the only agent specifically approved for DLBCL (in combination with CHOP)

• Current novel agent development landscape:
  – Multiple agents (bortezomib, lenalidomide, ibrutinib) appear to have selective activity in the ABC subtype of DLBCL and are in late-stage/ Phase 3 trials
  – No agents are currently in development specifically for GC origin DLBCL
DLBCL: Unmet Need Remains Despite R-CHOP

R-CHOP Does Not Result in a Cure for a Significant Proportion of DLBCL patients

Outcomes After Failure of R-CHOP Are Poor

Coiffier et al. 2010 Blood
Gisselbrecht et al. 2010 J Clin Oncol
FL: Considerations for Development of Novel Agents

- Areas of progress:
  - In the rituximab era, FL is considered a chronic yet incurable malignancy
    • 5-year survival approaching 90% overall

- Areas of Unmet Need:
  - Despite transformation of the treated natural history of FL, unmet need areas exist:
    • Active drugs which avoid the long-term consequences of current standard therapy (particularly prolonged myelosuppression and immunosuppression)
    • Early recurrence (<2 years) after R-CHOP or similar therapy, ~20% of FL

- Regulatory landscape:
  - CHOP components
  - Rituximab approved in untreated disease, relapsed disease, and maintenance settings
  - Alkylators (chlorambucil and bendamustine)
  - Idelalisib approval pending (NDA submission in patients who failed alkylator and rituximab-based therapy)

- Current novel agent development landscape:
  - BCR signaling antagonists and anti-CD20 therapies represent most of the ongoing late stage FL development efforts

Nastoupil, et al. 2014 Cancer
Casula, et al. 2013 Proc ASH
Early Failure After R-CHOP in FL is a Poor Prognostic Feature

Casula, et al. 2013 *Proc ASH*
Expanded Clinical Opportunity in Mutant and Wild Type GCB Lymphomas
B-Cell NHL Patient Populations in the Major Markets

**EZH2 Inhibitor Potential in Mutant EZH2 and Wild Type EZH2 B-Cell NHL, 2014**

Total Prevalent Treatment-Eligible Patients in Major Markets (US, EU28, Japan) - ~185,000

- **B-Cell NHL**
  - ~155k
  - ABC & non GC-Derived NHL, 82

- **GC-Derived B-Cell NHL**
  - ~72k
  - (12k mutant)
  - Burkitt’s, 3
  - PMLBCL, 4
  - mEZH2 FL, 6
  - mEZH2 GCB-DLBCL, 5.5
  - GCB-DLBCL, 24

- **On-Treatment Prevalence**
  - ~113k
  - (24k mutant)
  - mEZH2 FL (prev. dx), 22
  - FL (prev. dx), 80.5
  - mEZH2 GCB-DLBCL & PMLBCL (relapsed), 8.1

- **EZH2mut and EZH2wt Prevalent GC-Derived B-Cell NHL**
  - ~185k
  - (36k mutant)
  - mEZH2 FL, 28
  - PMLBCL, 5.5
  - mEZH2 GCB-DLBCL, 8
  - GCB-DLBCL, 30
  - FL, 110

**Note:** Values on graph are rounded; based on epidemiological calculations in Excel model (2Q2014). SS and MRT/Pediatric populations are excluded (no change in epidemiology).

**Sources:** Clarion analysis, incorporating SEER and GLOBOCAN epidemiology, and recent literature from ASH, NCI/NIH, and academic investigators.

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**Incidence**

**Prevalence**