Tazemetostat for the Treatment of Pediatric Patients with Malignant Rhabdoid Tumors and Other INI1-Negative Tumors

Presentation to the Pediatric Subcommittee of the
Oncology Drugs Advisory Committee

June 28, 2016

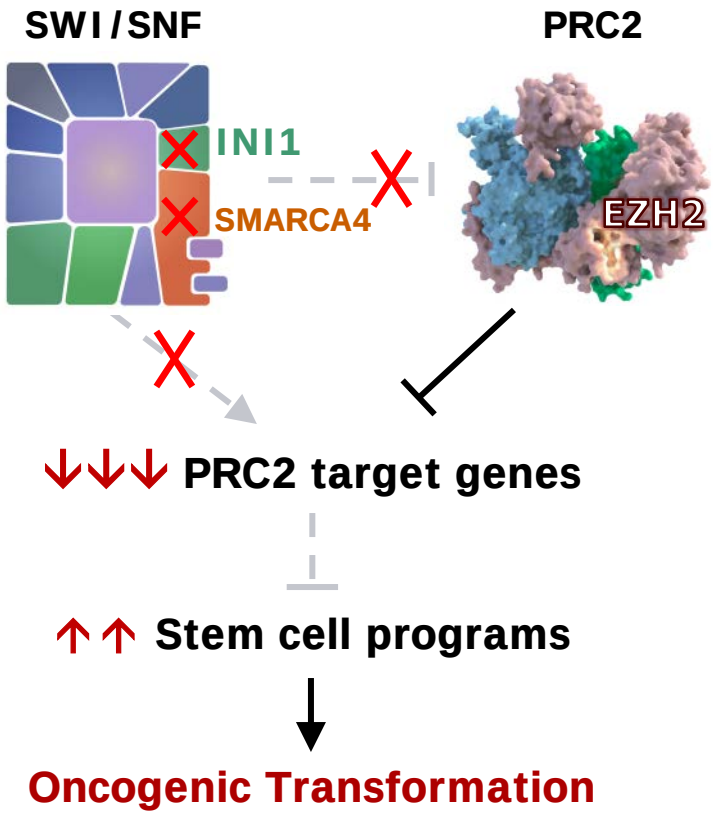
Epizyme

Agenda

- Tazemetostat background and preclinical data
- Relevance of EZH2 to childhood tumors
- Regulatory history
- Clinical trials experience in adults
- Pediatric phase 1 study and development program
- Challenges to development
- Summary

Antagonism of PRC2 and SWI/SNF-Dependent Chromatin Remodeling in Cancer

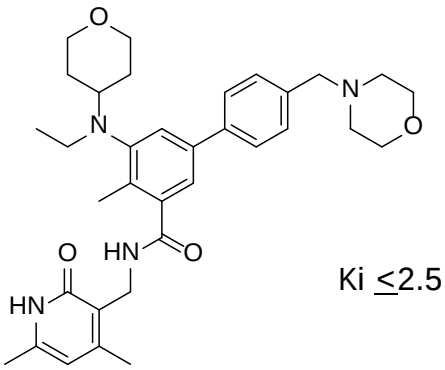
- SWI/SNF and PRC2 are chromatin remodeling complexes which promote or inhibit, respectively, gene transcription involved with cell cycle arrest and terminal differentiation
- Loss of SWI/SNF subunits INI1 or SMARCA4 in tumors upsets the balance between gene activation and repression, resulting in:
  - hyper-repression of PRC2 target genes
  - potentiation of stem cell programs
  - oncogenic transformation
- Tumors may be targeted by their oncogenic dependency on EZH2, the catalytic subunit of PRC2 that generates the transcriptionally repressive H3K27me1, H3K27me2, and H3K27me3 histone marks



Adapted from Wilson 2010

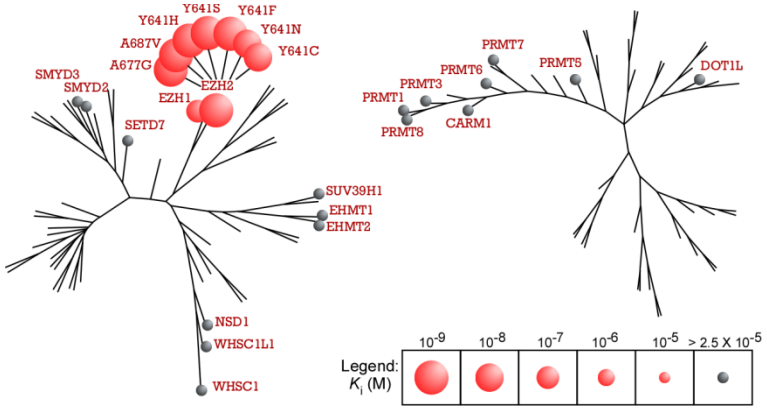
Tazemetostat (EPZ-6438): Potent and Highly Selective EZH2 Inhibitor

Potent Target Inhibition



Ki ≤2.5 nM

Selective for EZH2

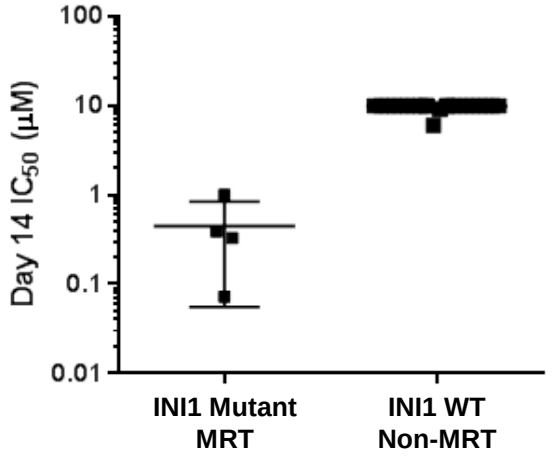


Selectivity >20,000-fold (100-fold for EZH1)

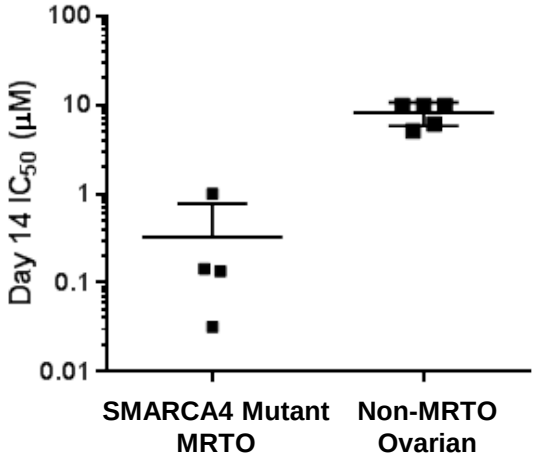
- Potent and selective SAM-competitive inhibitor of EZH2
- Elicits a time- and dose-dependent cellular reduction in H3K27me3 levels
- Orally bioavailable

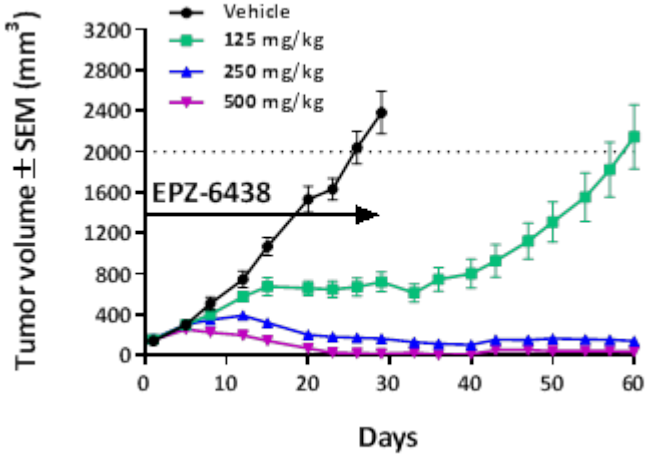
INI1- and SMARCA4-Negative Rhabdoid Tumor Models are Sensitive to Tazemetostat

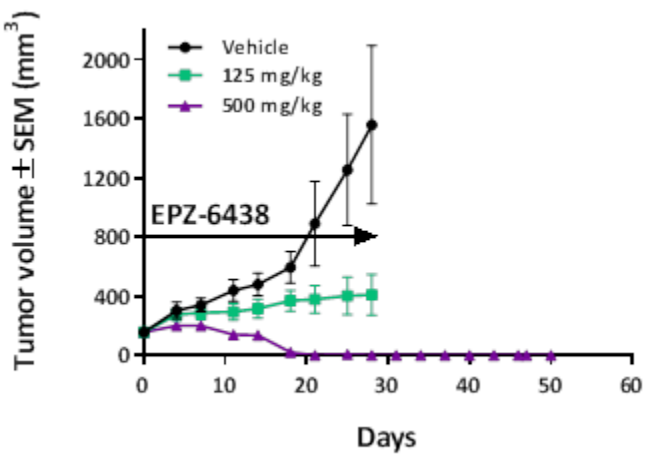
***In vitro and in vivo* cell killing of mutant *INI1* MRT cells**



***In vitro and in vivo* cell killing of mutant *SMARCA4* MRTO cells**







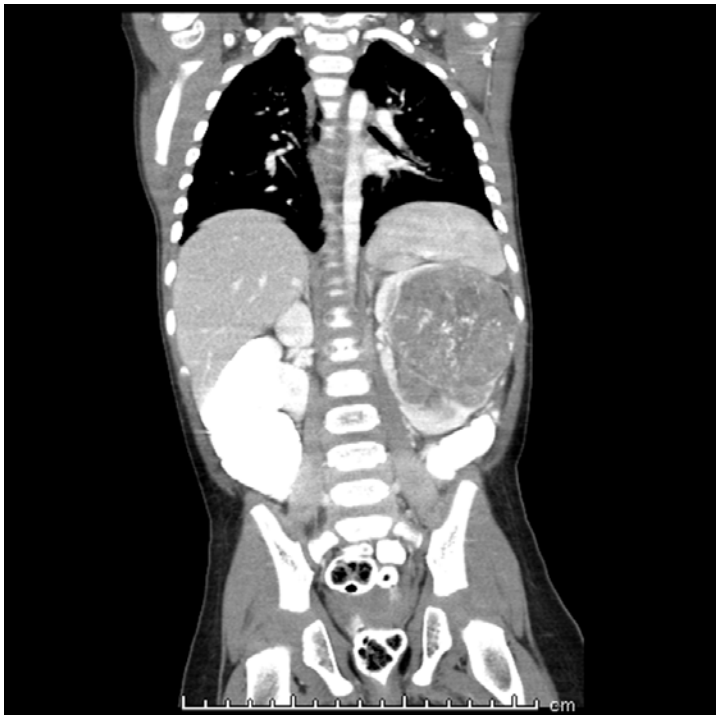
Knutson et al. PNAS , 2013
Penebre et al, EORTC, 2015

Malignant Rhabdoid Tumors (MRT)

- Genetic alteration in chromosome 22q11
  - Immunostaining for INI-1/Baf47 is diagnostic
- Genetic predisposition: monoallelic germline alteration in ~25% to 35% of pediatric patients
- Diverse anatomic locations
  - Kidney: Rhabdoid tumor of the kidney (RTK)
  - Central nervous system: Atypical teratoid rhabdoid tumor (ATRT)
  - Soft tissues, liver, neck, lungs, nerve plexus (MRT)
  - May have synchronous tumors in brain and ex-CNS

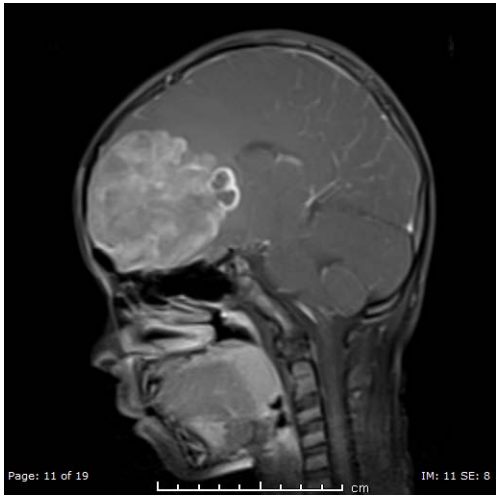
Rhabdoid Tumor of Kidney

- Historically included in National Wilms Tumor Study (NWTS) Group and Intergroup Rhabdomyosarcoma Study (IRS) protocols
- Represents <2% of childhood kidney tumors and <1% of all soft tissue tumors
- Median age = 10.6 months
- Survival <25%
  - Worse prognosis with younger age
    - <10% for infants <6 months
    - <20% for infants <12 months
  - Worse prognosis with higher stage
    - Metastases frequently seen



Atypical Teratoid Rhabdoid Tumor

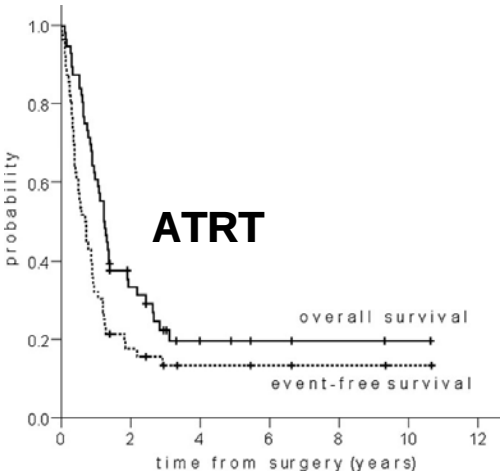
- Rare pediatric brain tumor
  - Approximately 1-2% of all pediatric brain tumors
- Historically misdiagnosed
  - Included within protocols for medulloblastoma and embryonal tumors
- Most often seen in infants
  - Median age <2 years
  - Occasionally in older children, rare in adults
- Anatomic location
  - ~60% in posterior fossa – predominantly in infants
  - Supratentorial – older child
  - Spinal – very rare
- 2-year survival <20% for children <3 years
- Molecular subgroups identified based on genomic profiling



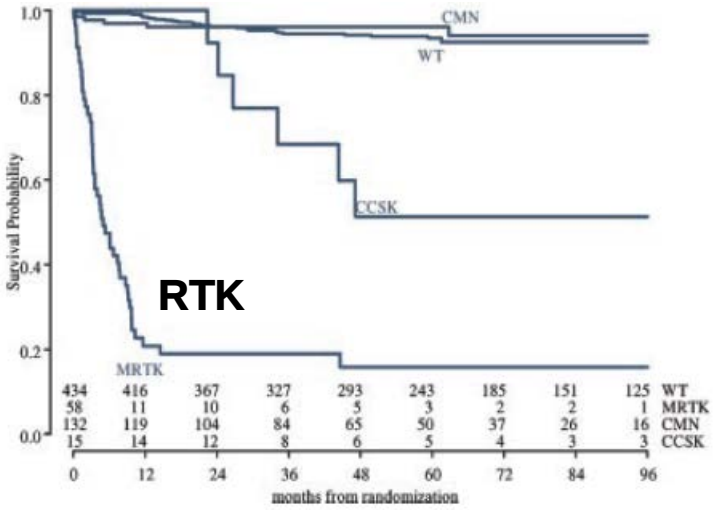
Current Therapies for Rhabdoid Tumors

- Maximal surgical resection
- Radiation therapy (RT)
  - *Limitations*
    - RTK: dose and field of RT may affect other surrounding normal organs (e.g. GI, liver, lungs)
    - ATRT: craniospinal RT for infants and high-dose RT required are prohibitive
    - Radiation recall reported
- Intensive multi-agent chemotherapy
  - Alkylators, platinum, anthracyclines, methotrexate (ATRT only)
  - Intrathecal chemotherapy for ATRT
  - *Limitations*
    - RTK: single kidney post-nephrectomy limits nephrotoxic agents such as platinum
    - ATRT: neurotoxicity of methotrexate and intrathecal chemotherapy
- High dose chemotherapy/autologous stem cell transplant
  - Published and anecdotal evidence of activity in ATRT without need for RT
  - Not considered standard of care for extra-cranial MRT

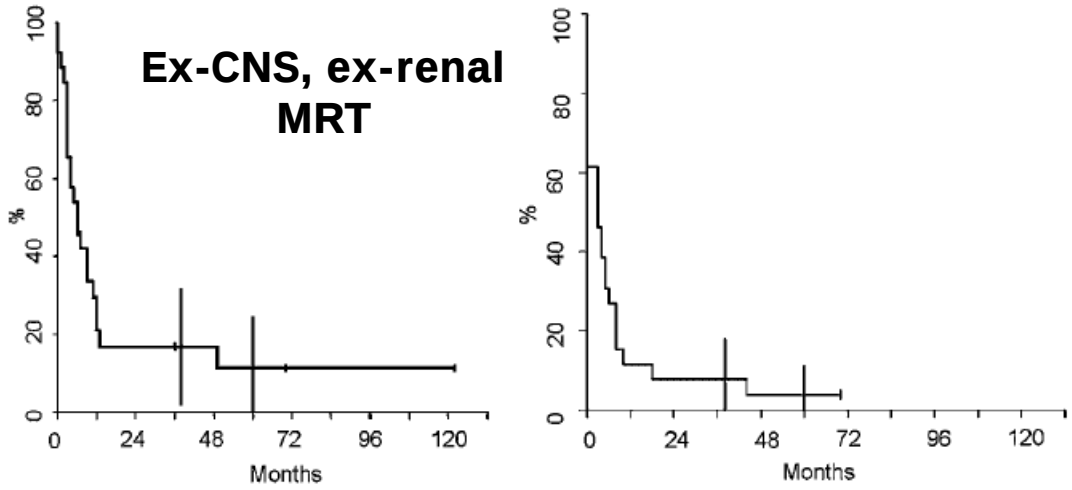
Survival Outcomes in Rhabdoid Tumors



Von Hoff, et al., PBC 2011



Van den Heuvel-Eibrink, et al. PBC 2008



Overall Survival **Relapse-Free Survival**

Bourdeaut, et al. PBC 2008

Regulatory History

- Non-Hodgkin lymphoma (E7438-G000-101)
  - 2013: ANSM (France) approved first-in-human, monotherapy, phase 1/2 study of tazemetostat in adult patients with advanced B cell lymphomas and solid tumors
  - 2015-16: IND/CTA/CTN acceptance in UK, Australia, Italy Canada, Germany and US for the phase 2 portion of this study
- Rhabdoid and non-rhabdoid INI1-negative or SMARCA4-negative tumors and synovial sarcoma
  - August 2015: IND accepted for INI1-negative solid tumors
  - December 2015: EZH-202 (phase 2 in adults) initiated in US
  - January 2016: EZH-102 (phase 1 in children) initiated in US
  - 2016: CTA/CTN acceptance of
    - EZH-102 – Canada, Australia, Denmark, UK, France and Germany
    - EZH-202 – Belgium, Italy, UK, France, Germany and Taiwan
  - February 2016: Orphan drug designation granted in US for the treatment of MRTs
- Mesothelioma (EZH-203)
  - May 2016: IND accepted for mesothelioma characterized by BAP1 loss-of-function
    - EU submissions in-progress

Clinical Trials Experience in Adults

- First-in-human
  - Phase 1 trial in France in patients with advanced solid tumors and B-cell non-Hodgkin lymphoma
    - Dose escalation, dose expansion, and clinical pharmacology cohorts
- Non-Hodgkin lymphoma
  - Global phase 2 trial for DLBCL and FL
    - Five cohorts – prospectively stratified according to cell-of-origin and EZH2 mutation status
- Rhabdoid tumors and other INI1-negative or SMARCA4-negative tumors
  - Global phase 2 trial
    - Five cohorts - 1) INI1- or SMARCA4-negative rhabdoid tumors, 2) relapsed/refractory synovial sarcoma, 3) other INI1 negative tumors, 4) renal medullary carcinoma and 5) epithelioid sarcoma

First-in-Human Phase 1 Trial E7438-G000-101

- Population: adult patients with relapsed or refractory B-cell lymphoma or solid tumors
- Age: ≥18 years
- Study design: 3+3 dose-escalation
  - Dose levels: 100, 200, 400, 800 and 1600 mg BID
  - Expansion cohorts: 800 mg and 1600 mg BID
  - Food effect sub-study: 200 mg ± food, then 400 mg BID
  - Drug-drug interaction sub-study: 800 mg BID
- Primary endpoint: determination of RP2D/MTD
- Secondary endpoints: safety, PK, PD and tumor response (every 8 weeks)

Patients – Solid Tumors

Relapsed or refractory solid tumor		**N=37**
INI1-negative (SMARCB1)*	Malignant rhabdoid tumor	5
	Epithelioid sarcoma	3
SMARCA4-negative*	Malignant rhabdoid tumor of ovary (SCCOHT)	2
	Thoracic sarcoma	1
Synovial sarcoma		4
GI malignancy		10
GU malignancy		2
GYN malignancy (non-SCCOHT)		5
CNS tumor/other sarcoma		5
Relapsed or refractory NHL		**N=21**

* INI1- or SMARCA4-negative by IHC

Data as of 07-Nov-2015
Source: Ribrag et al., ASH 2015

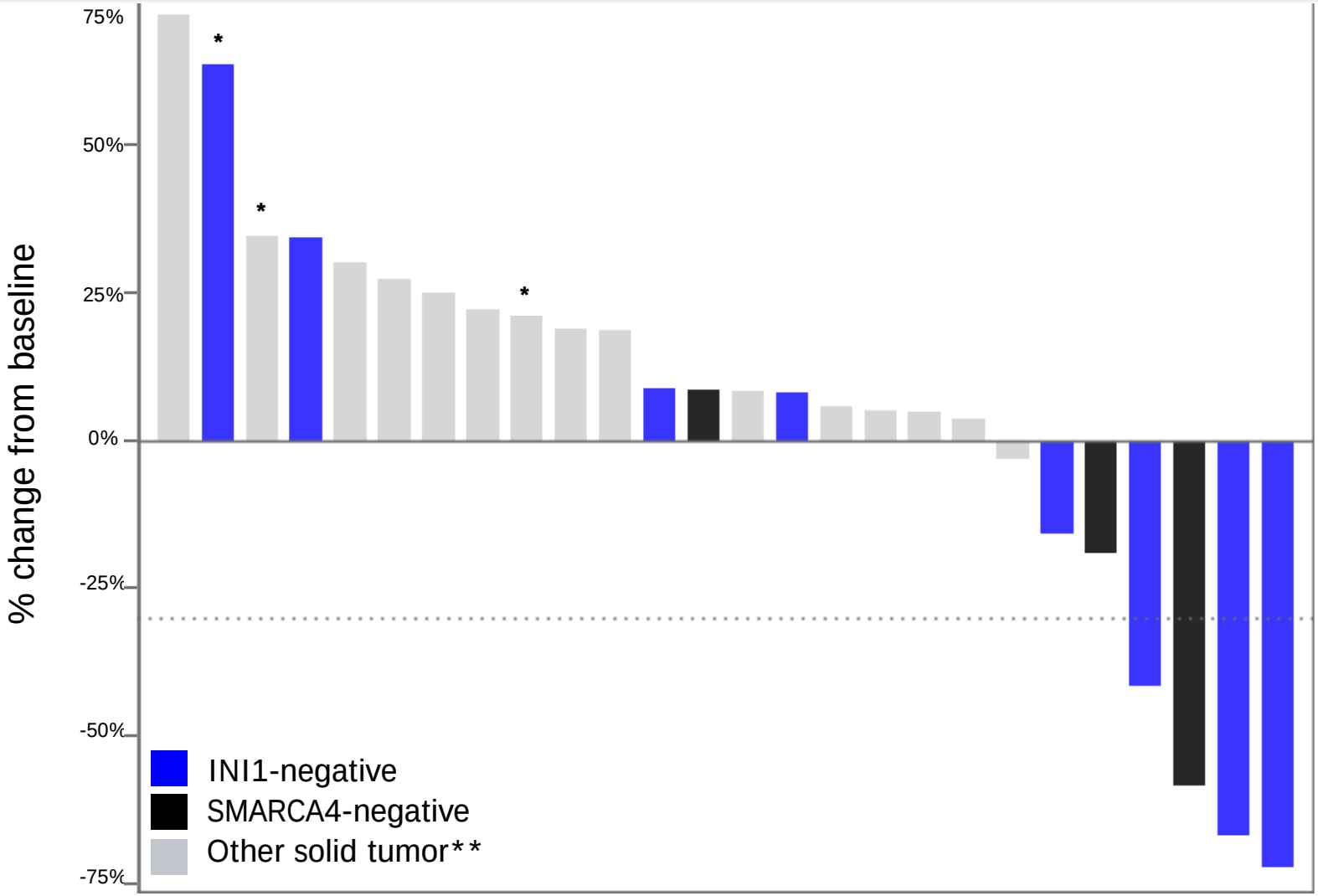
Treatment-Emergent Adverse Events Observed in ≥5% of 89 Patients [1]

Preferred Term	All Events n (%)		Treatment-Related Events n (%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Patients with at least 1 TEAE	78 (88)	22 (25)	51 (57)	7 (8)
Asthenia	31 (35)	0 (0)	19 (21)	0 (0)
Nausea	14 (16)	0 (0)	12 (14)	0 (0)
Thrombocytopenia	13 (15)	4 (5)	10 (11)	1 (1)
Decreased appetite	12 (14)	1 (1)	5 (6)	0 (0)
Anemia	11 (12)	3 (3)	7 (8)	0 (0)
Constipation	11 (12)	0 (0)	2 (2)	0 (0)
Dysgeusia	7 (8)	1 (1)	6 (7)	0 (0)
Vomiting	7 (8)	0 (0)	5 (6)	0 (0)
Diarrhea	6 (7)	0 (0)	5 (6)	0 (0)
Dry skin	6 (7)	0 (0)	5 (6)	0 (0)
Dyspnea	6 (7)	0 (0)	0 (0)	0 (0)
Muscle spasms	6 (7)	0 (0)	3 (3)	0 (0)
Abdominal pain	5 (6)	1 (1)	1 (1)	0 (0)
Neutropenia	5 (6)	2 (2)	5 (6)	2 (2)

Data as of 15-Jan-2016
Source: Investigators Brochure

[1] Phase 1 and Phase 2 studies combined

Best Response in Patients with Solid Tumors



* Patients censored at time of progression

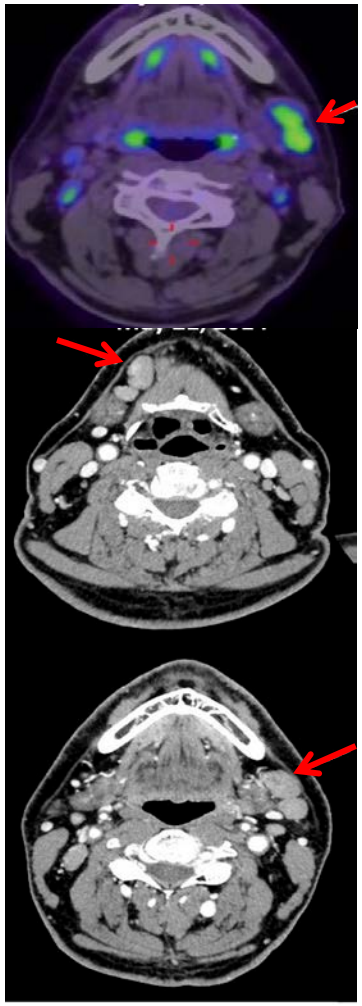
** Four additional other solid tumor patients with pending disease evaluation

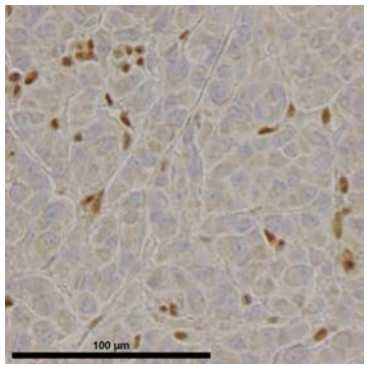
Data as of 31-Aug-2015

Source: Italiano et al., ECC 2015

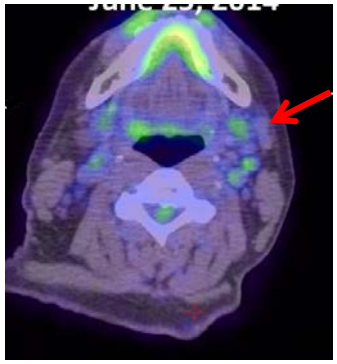
CR in Patient with INI1-Negative Malignant Rhabdoid Tumor

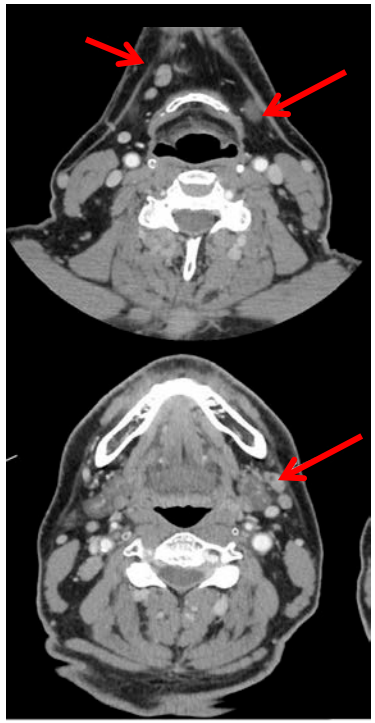
Baseline | **Week 4** | **Week 8: CR** | **Week 20**

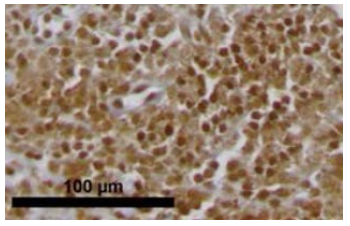


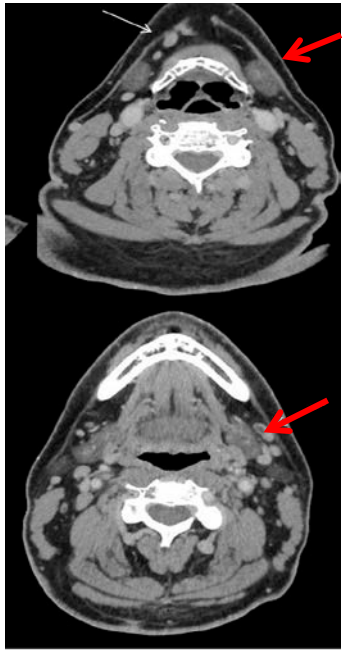


INI1 IHC

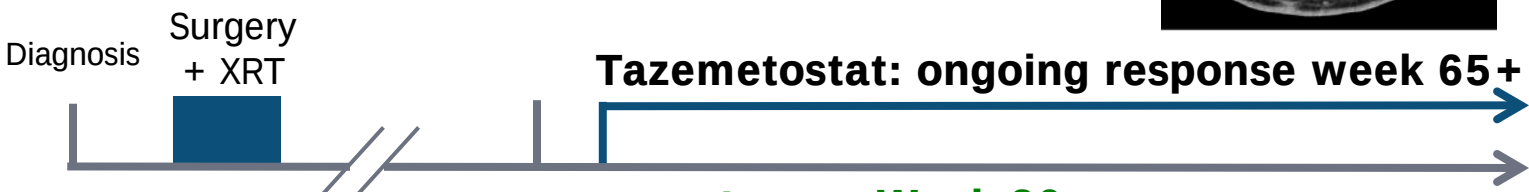








55 y.o. male
800 mg BID



Data as of 31-Aug-2015
Source: Italiano et al., ECC 2015

Phase 1 Summary in Adults

- Safety profile as monotherapy is favorable for development as both single agent and combination therapy
- Tazemetostat demonstrates clinical activity as monotherapy in patients with both B-cell NHL and solid tumors
  - Relapsed or refractory DLBCL (both GCB and non-GCB), FL and MZL
    - Objective responses include both CR and PR
    - Responses are durable – patients ongoing at 24+ to 30+ months
  - **Relapsed INI1- and SMARCA4-negative tumors**
    - **Malignant rhabdoid tumor, malignant rhabdoid tumor of ovary (SCCOHT), epithelioid sarcoma**
    - **Objective responses (CR and PR) observed**
    - **Additional patients with SD lasting ≥6 months observed**
- Pharmacodynamic inhibition of H3K27me3 demonstrated in tumor tissue and in surrogate tissue (skin)
- Pharmacokinetic results demonstrate that tazemetostat may be taken without regard to meals and is a weak inducer of CYP3A4/5
- RP2D dose of 800 mg BID supported by safety, efficacy, PK/PD

EZH-102: Pediatric Phase 1 Study
Overview and Design

- NCT02601937: "Phase 1 study of the EZH2 inhibitor tazemetostat in pediatric subjects with relapsed or refractory INI1-negative tumors or synovial sarcoma"
- Phase 1, open-label, multi-center dose escalation and dose expansion study of tazemetostat administered twice daily (BID) using an oral suspension formulation in pediatric subjects
- Enrollment based upon local pathology with central confirmation (IHC)
- Eligible malignancies include:
  - Rhabdoid tumors: (ATRT, MRT, RTK, selected tumors with rhabdoid features)
  - INI1-negative tumors: (epithelioid sarcoma, epithelioid malignant peripheral nerve sheath tumors, extraskeletal myxoid chondrosarcoma, myoepithelial carcinoma, renal medullary carcinoma, undifferentiated chordoma, other tumors with Sponsor approval)
  - Synovial sarcoma with SS18-SSX rearrangement

EZH-102: Pediatric Phase 1 Study
Overview and Design

- "Rolling 6" dose escalation design
  - Starting dose of 240 mg/m^2 BID derived from physiologically-based PK modeling of observed PK in adults
  - Subjects evaluated for dose limiting toxicities in Cycle 1
  - Dose levels:
    - 240 mg/m^2, 300 mg/m^2, 400 mg mg/m^2, and 520 mg/m^2 BID
- Following dose escalation, dose expansion cohorts will enroll up to 60 subjects (n=20 in each cohort)
  - Cohort 1: ATRT
  - Cohort 2: extra-CNS rhabdoid tumors (MRT, RTK)
  - Cohort 3: non-rhabdoid INI1-negative tumors

EZH-102: Study Endpoints

- Primary:
  - Dose Escalation: Identify dose-limiting toxicities and recommended phase 2 dose / maximum tolerated dose
  - Dose Expansion: Evaluate overall response rate (ORR)
- Secondary:
  - Dose Escalation: ORR and duration of response
  - Dose Expansion: Duration of response
  - Dose Escalation and Dose Expansion:
    - Progression-free survival and overall survival
    - Safety/tolerability
    - Pharmacokinetics
- Exploratory:
  - PK/PD, H3K27 methylation, tumor target gene expression and phenotypic markers, somatic mutation analysis of tumor tissue and blood derived from circulating DNA

EZH-102: Main Inclusion Criteria

- Age 6 months to 21 years
- Relapsed or refractory disease with no standard treatment options per local/regional standards of care and treating physician's discretion
- Local diagnostic pathology of original biopsy confirmed by CLIA/CAP certified laboratory documenting INI1 loss, SMARCA4 loss, or SS18-SSX rearrangement
- Measurable disease (dose expansion subjects only)
- For patients with CNS involvement, stable deficits at least 14 days prior to enrollment (seizures stable and controlled by anti-seizure medication at least 7 days)

EZH-102: Main Exclusion Criteria

- Received investigational drug within 30 days or five half-lives, whichever is longer, prior to the planned first dose of tazemetostat
- For patients with CNS involvement (primary tumor or metastatic disease): Have any active bleeding, or new intratumoral hemorrhage of more than punctate size on Screening MRI obtained within 14 days of starting study drug, or known bleeding diathesis or treatment with anti-platelet or anti-thrombotic agents
- Time from last prior anti-cancer therapy:
  - Investigational agent → 30 days or five half-lives
  - Cytotoxic chemotherapy → 21 days
  - Non-cytotoxic chemotherapy → 14 days
  - Immunotherapy (e.g. vaccine) → 6 weeks
  - Radiotherapy → 14 days (local); 21 days (stereotactic); 12 weeks (craniospinal, pelvic, total body irradiation)
  - Hematopoietic cell transplantation → 60 days
  - Hematopoietic growth factor → 14 days

Enrollment (as of June 15, 2016)

Dose Level	Age	Tumor Type
240 mg/m^2	2y 9m	MRT*
	1y 11m	ATRT*
	1y 7m	ATRT*
	7y 4m	ATRT
	2y 2m	ATRT
	1y 9m	ATRT
	2y 3m	ATRT
	1y 1m	ATRT
300 mg/m^2	14 y 10 m	Anaplastic chordoma
	1y 6 m	Myoepithelial carcinoma
	14 y	ATRT
	15 y 6 m	Epithelioid sarcoma
	12 y	ATRT
	13 y	MRT
400 mg/m^2	1 y 6 m	ATRT
	6 y 11 m	Malignant epithelioid neoplasm with rhabdoid features

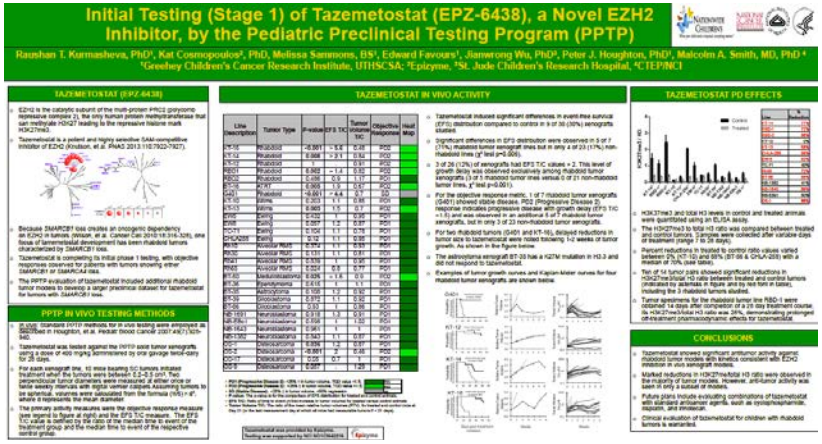
* Not DLT evaluable

Pediatric Formulation

- EZH-102 currently uses extemporaneously prepared suspension of 30 mg/mL of tazemetostat in Ora-Sweet® (flavored syrup vehicle) with no other excipients
  - Two-week supply prepared at investigational pharmacy
  - Stable under refrigeration for 21 days
  - Compatible with nasogastric and gastric tubes
- Commercial formulation under development
  - Powder for re-constitution in unit-dose packets
  - Composed of thickener, sweetener, flavor and other processing/suspension aids (no preservative needed)
  - Re-constituted with ~10 ml of water

Development Program in Pediatrics

- Pediatric Preclinical Testing Program
  - Tazemetostat supplied to PPTP to test preclinical activity in large panel of pediatric tumors including rhabdoid tumors, Ewing sarcoma, osteosarcoma, and pediatric brain tumors
  - Results presented at 2015 AACR-NCI-EORTC Conference



- Pediatric MATCH
  - Pediatric counterpart to the NCI-MATCH trial in adults
  - Led by the Children's Oncology Group
  - Will evaluate molecularly targeted therapies such as tazemetostat in children with advanced cancers who have few other treatment options
  - Tazemetostat proposed to be incorporated into Pediatric MATCH as one of the initial investigational agents to be tested

Challenges to Development

- ✓ Recruitment
  - Enrollment and US/EU/Australian site activations are on track and do not pose any major challenge to the pediatric clinical development
- ✓ Formulation
  - Proactively initiated development of a commercial formulation: powder for re-constitution in unit-dose packets to replace the extemporaneously prepared suspension prepared by the pharmacy and currently in use in clinical trials
- ❑ Rare disease
  - Evaluate clinical safety across multiple tumor types by enrolling up to 84 pediatric patients with genetically-defined INI1-negative and SMARCA4-negative tumors. Final sample size to be discussed with FDA
  - Safety profile of tazemetostat will be supplemented by the adult safety experience across all indications which currently include INI1-negative and SMARCA4-negative tumors, synovial sarcoma, B-cell NHL and mesothelioma
- ❑ High unmet medical need
  - Epizyme proposes to discuss with the Agency that this study be considered as adequate and well controlled in order to demonstrate efficacy and safety in this pediatric population
- ❑ Indication may be based on common genetics instead of histology
  - If supported by data, proposed labeled indication may include rhabdoid tumors with either loss of INI1 or of SMARCA4 and non-rhabdoid tumors with loss of INI1

Summary

- INI1-negative and SMARCA4-negative rhabdoid tumors are a Rare Disease with high unmet medical need
- Safety profile of tazemetostat as monotherapy is favorable for development as both single agent and combination therapy
- Tazemetostat demonstrates clinical activity as monotherapy in patients with both B-cell NHL and solid tumors
- Pediatric Study 102 may be considered for issuance of a Written Request

Tazemetostat for the Treatment of Pediatric Patients with Malignant Rhabdoid Tumors and Other INI1-Negative Tumors

Presentation to the Pediatric Subcommittee of the
Oncology Drugs Advisory Committee

June 28, 2016

Epizyme

Back-up Slides
Presented During Q&A

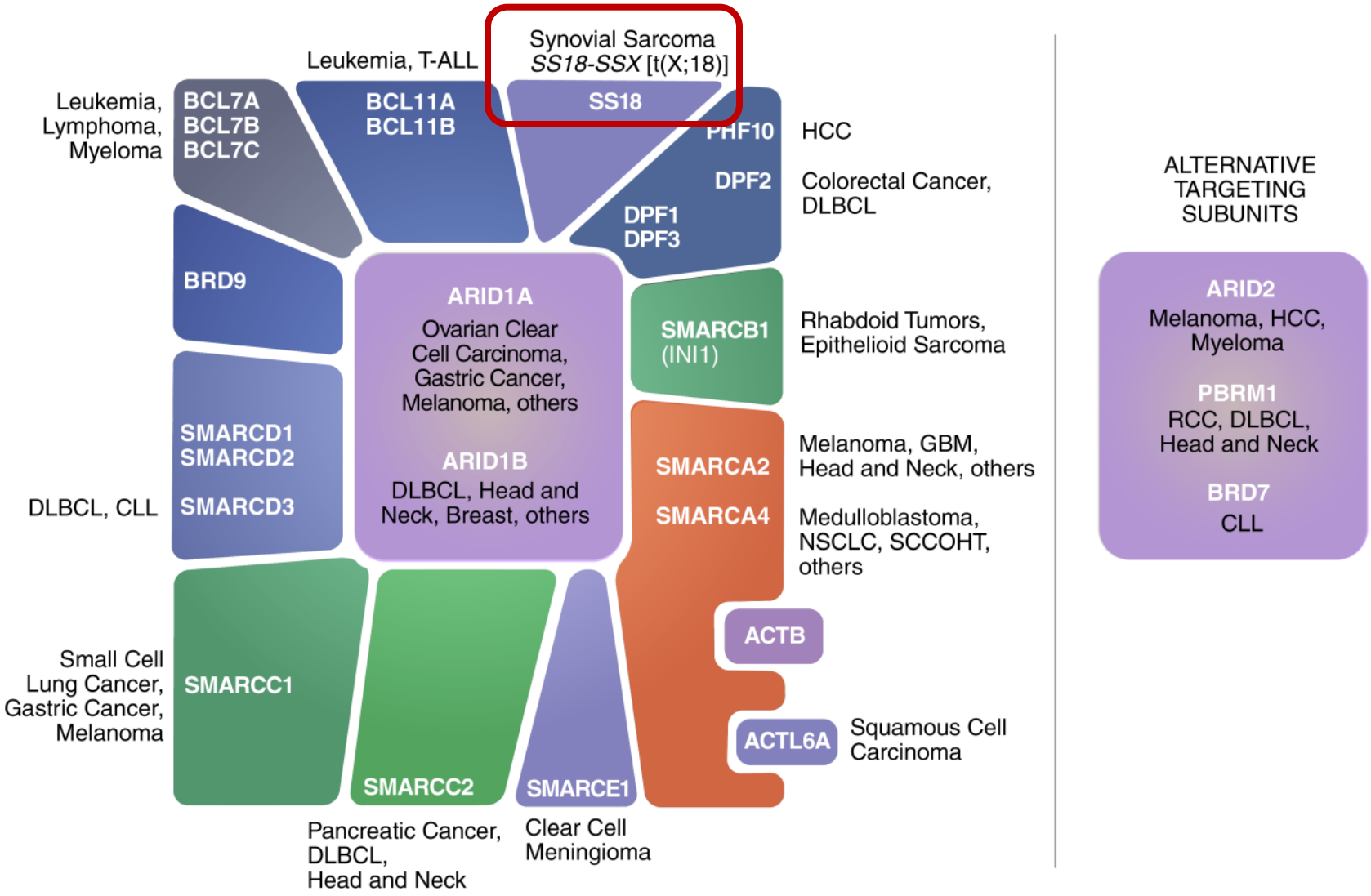
Thrombocytopenia and Neutropenia by Laboratory Results

Subjects (n=82) with:	
Thrombocytopenia *	9 (11%)
Grade 3	8 (10%)
Grade 4	1 (1%)
Neutropenia *	5 (6%)
Grade 3	2 (2%)
Grade 4	3 (4%)

* Determined by laboratory results, not by investigator assignment
Subjects are counted only once for their highest toxicity grade observed

Data as of 27-May-2016
Source: Morschhauser et al, ASH Lymphoma 2016

Synovial Sarcoma is a SWI/SNF Mutated Cancer

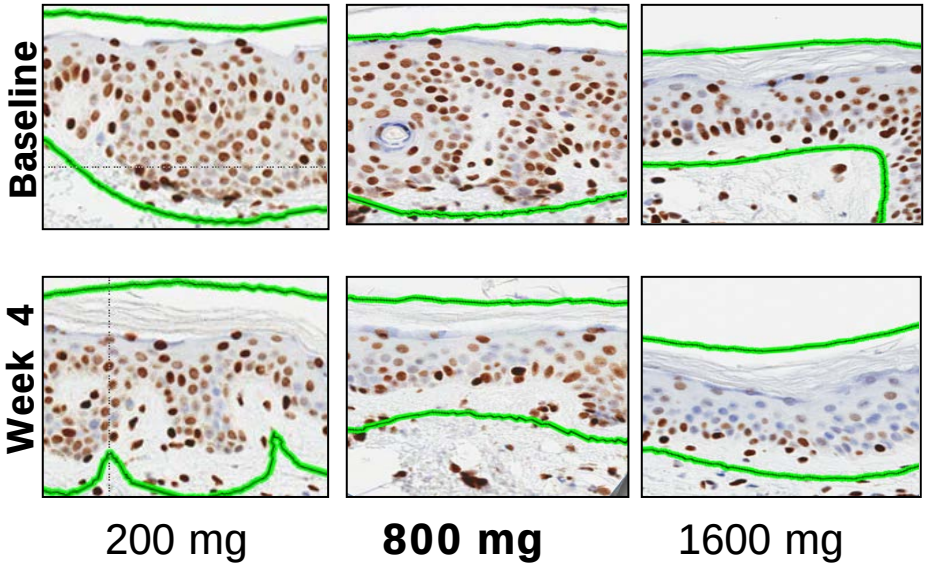


Adapted from Kadoch 2015

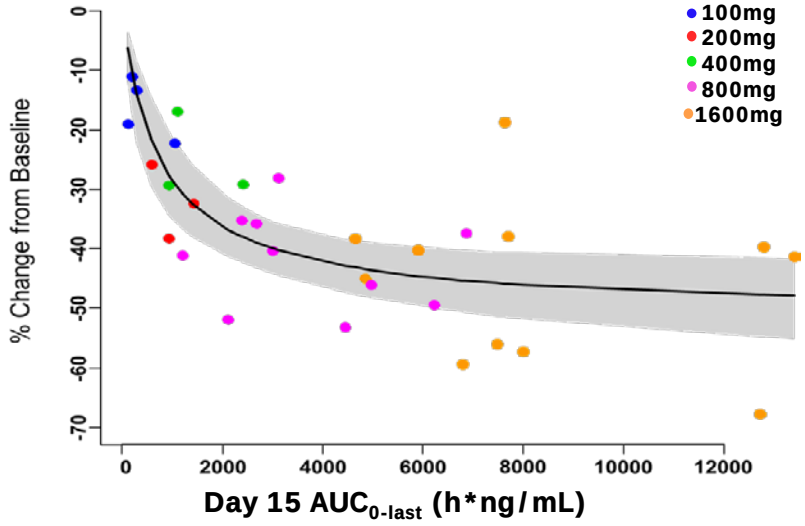
RP2D Selection Summary

Dose BID	Efficacy	Safety	PK/PD
	Response in NHL (%)	Grade ≥3 TEAE *	H3K27 Inhibition Emax **
<800 mg	2/9 (22%)	7/24 (29%)	-
800 mg	5/8 (62%)	3/19 (16%)	80%
1600 mg	2/4 (50%)	4/12 (33%	84%

****H3K27 me3 in Skin**



H3K27me3 vs. Exposure



* Treatment Emergent Adverse Events in all patients (n=55)

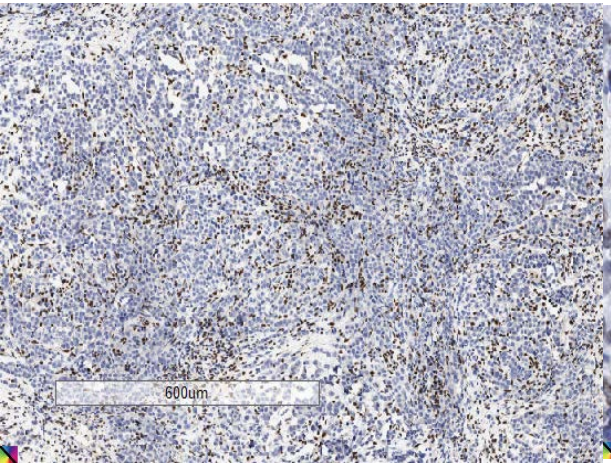
EZH2 Target Inhibition in Tumor Tissue

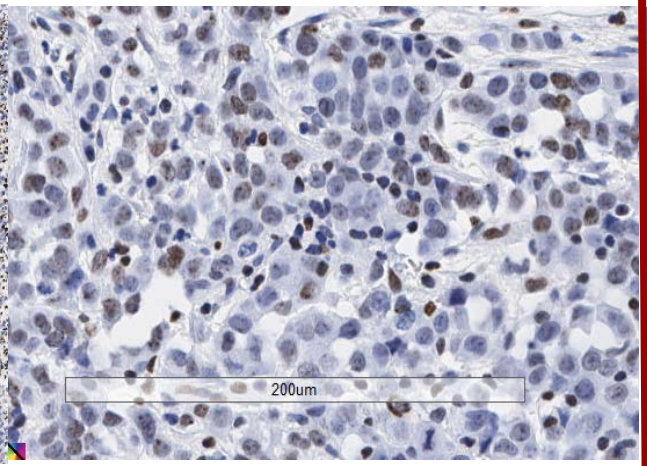
Pre-Dose

Post-Dose: Week 4

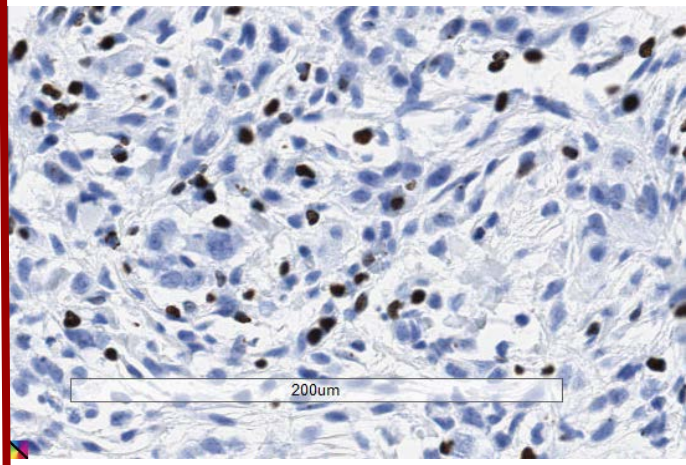
Rhabdoid Tumor of Kidney
INI1-negative

H3K27me3
Diffuse positive 1+: 100% tumor

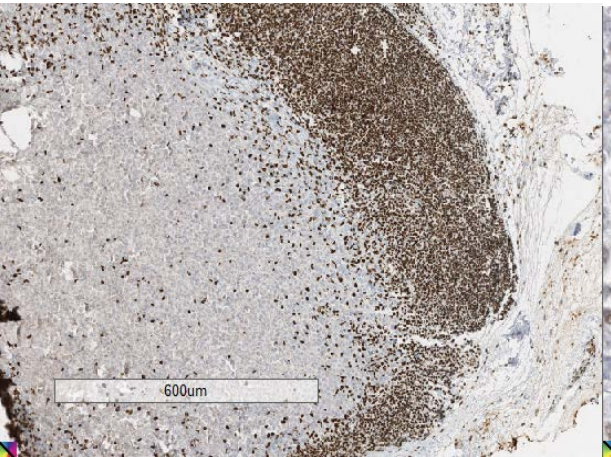




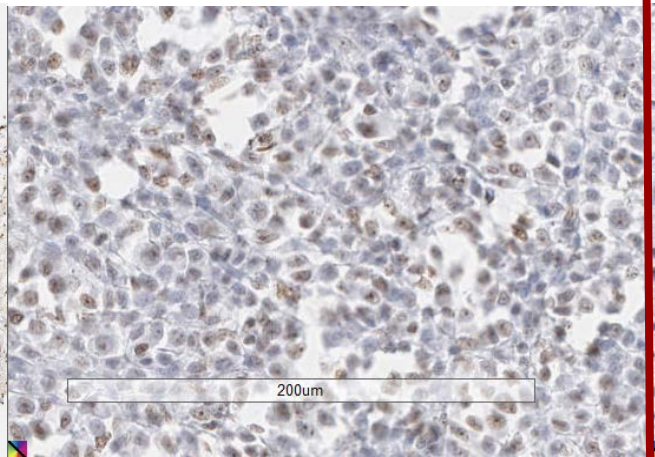
H3K27me3
Negative: 100% tumor



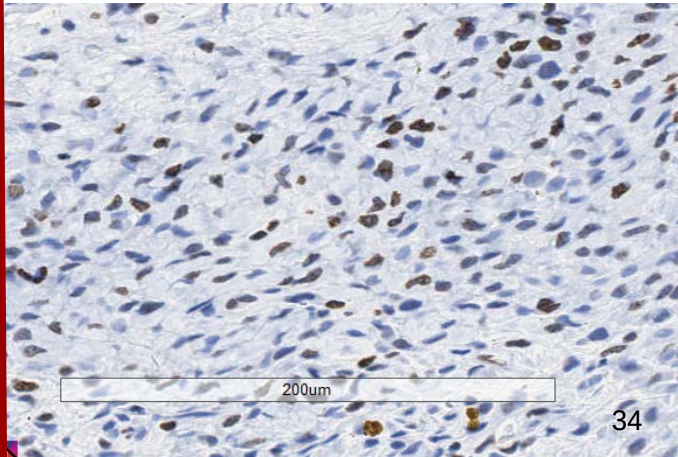
Epithelioid Sarcoma
INI1-negative



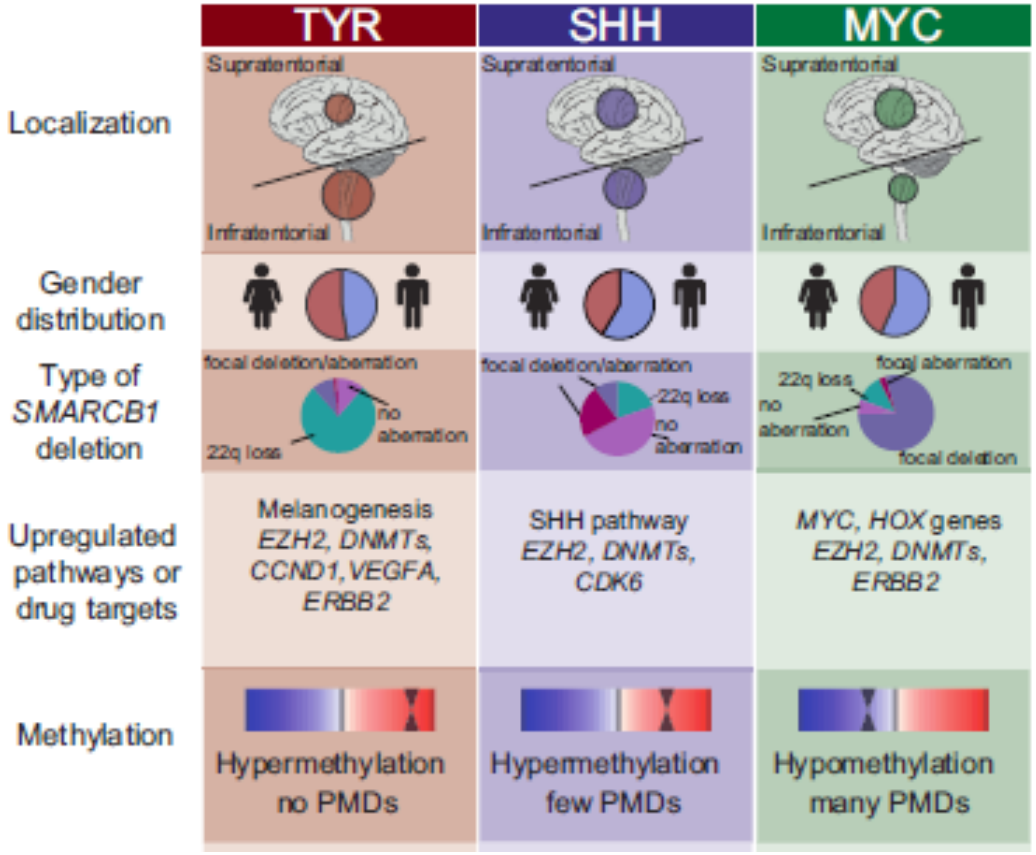
H3K27me3
Diffuse positive 1+: 100% tumor



H3K27me3
Negative: 50% tumor



INI1/SMARCB1 Loss is the Predominant Molecular Feature of ATRT



Johann et al. Cancer Cell, 2016