Marizomib

A Proteasome Inhibitor as a Potential Treatment for Pediatric Patients with HGG including GBM and DIPG

17 June 2020

Oncologic Drug Advisory Committee
Pediatric Subcommittee

Celgene | Bristol Myers Squibb™ Company

Agenda

Topic	Presenter
1. Introduction	Deborah Tady, PharmD, RAC Executive Director, Global Regulatory Strategy Celgene, a Bristol-Myers Squibb Company
2. Pediatric Research Commitment / Marizomib Development 3. Regulatory History & Key Activities for Pediatric Development	Sherry A. Leonard, BSc, RAC Director, Global Regulatory Strategy Celgene, a Bristol-Myers Squibb Company
4. Molecular Mechanism of Action 5. Clinical Trial Experience in Adults 6. Ongoing and Planned Clinical Trials in Pediatrics	Mark W. Kieran, MD, PhD Senior Director, Pediatric Oncology Bristol-Myers Squibb
7. Questions & Answers	Deborah Tady, PharmD, RAC (Moderator)

Commitment to Pediatric Research

- Our Commitment to Pediatric Cancer Research
  - Early evaluation of oncology pipeline using nonclinical models to inform on potential pediatric tumor types based on molecular targets
  - Early FDA discussions for alignment on pediatric development

- Goal is to improve treatment options for children with cancer by
  - Initiating pediatric studies earlier & decreasing lag time between adult studies
  - Submitting PPSRs earlier & enabling FDA to issue WRs earlier

Objectives for the Pediatric ODAC to Gain Advice

- Potential role of marizomib (MRZ) in pediatric cancers and hematologic disorders
- Optimal design of future pediatric studies that may serve as part of a Written Request

Today we present an overview of the MRZ program including development plans in pediatric HGG including GBM and DIPG

Marizomib (MRZ) Summary

- MRZ adult development focused on ndGBM
  - Irreversible proteasome inhibitor that crosses BBB
  - Dose-related, reversible CNS AEs (eg, ataxia and hallucinations) determined the benefit/risk was more favorable for patients with CNS vs non-CNS tumors
  - EORTC Phase 3 study in ndGBM adding MRZ to standard of care TMZ+RT → TMZ

- Overall MRZ pediatric strategy
  - Based on a molecular target of proteasome inhibition and CNS penetration, development focused on children with HGG including GBM and DIPG
  - Gain advice for a Written Request focused on HGG including GBM and DIPG

Regulatory History & Key Activities for Pediatric Development

Date	Description
Jan 2006	IND active for adults with advanced solid tumors, lymphoma & multiple myeloma
Jan 2015	IND active for adults with glioblastoma
Oct 2017	Pediatric expert advisory board convened by Celgene
Nov/Dec 2017	Regulatory pediatric advice from Germany BfArM, Spain AEMPS, Denmark DKMA
Apr 2019	FDA-EMA Cluster Meeting (Global pediatric development plan)
May 2019	Type C meeting to discuss iPSP
Dec 2019	Pediatric Investigation Plan (PIP) agreement with EMA
Mar 2020	Initial Pediatric Study Plan (iPSP) agreement with FDA

Marizomib is not currently approved for marketing in any country

Pediatric expert opinion and Health Authority advice guided the MRZ pediatric development plan

- Pediatric expert advisory board considered the activity of MRZ with PAN in DIPG cell lines and models[1] and recommended:
  - Initiating pediatric studies using a gated approach by starting with DIPG
  - If supported by nonclinical studies and the DIPG Phase 1 study, then consider midline glioma and other HGGs

- Scientific Advice from 3 EU National Health Authorities encouraged this approach

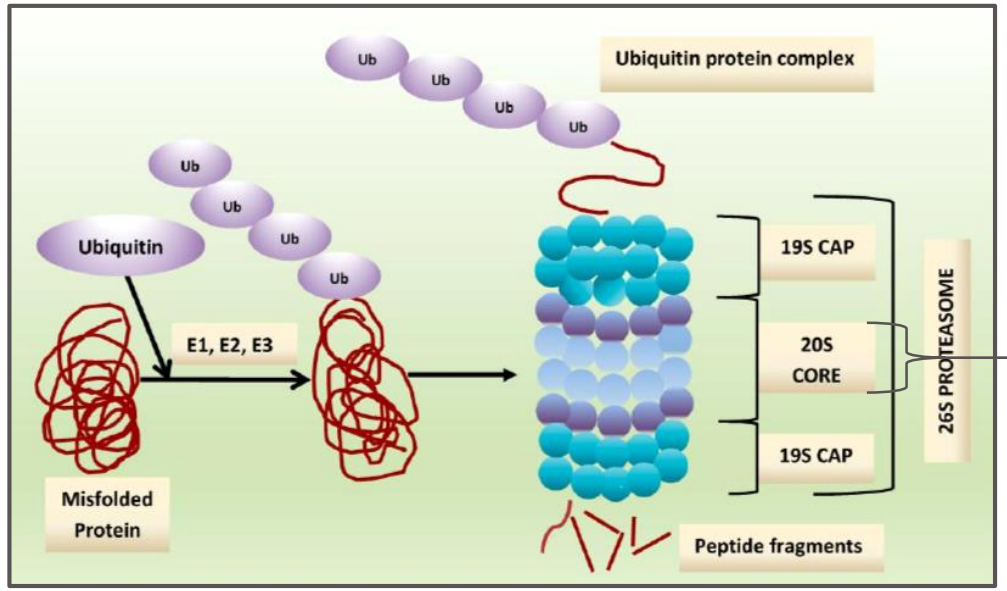
[1] CLin *et al*. Sci Transl Med. 2019;11(519)

Key Difference Between Agreed Pediatric Plans and Advice for a Written Request

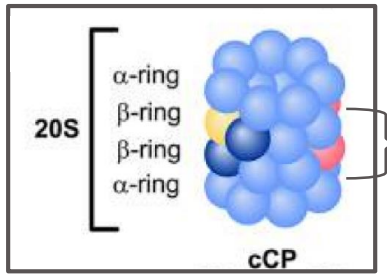
- FDA agreed iPSP includes indication of HGG, including GBM (adult indication)
- EMA agreed PIP for treatment of malignant glial tumors in children with DIPG or other HGGs

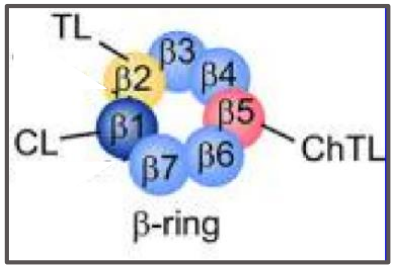
FDA encouraged seeking a Written Request for HGG, including GBM, and DIPG, and any other indications for which MRZ could offer a potential benefit to pediatric patients

Marizomib: Molecular Mechanism of Action

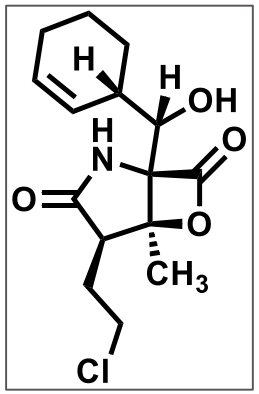


Marizomib binds irreversibly to β1, β2, β5 catalytic sites





Inhibition of the ubiquitin proteasome pathway may preserve key proteins that regulate cellular homeostasis and death



Lipophilic and non peptide structure of MRZ enhances CNS penetration

Chhabra Pharmaceuticals 2017;10(2)
Cromm & Crew ACS Cent Sci 2017;3:830-838
Groll *et al.* J Am Chem Soc 2006;128:5136-41

Non-GBM Adult AE Profile Supports MRZ Focus on GBM

Key findings from 5 non-GBM studies in patients (N=280) with advanced solid tumors, lymphoma and MM were consistent:

- Most common AEs: nausea, vomiting, fatigue and headaches
- MRZ caused dose-related CNS AEs (eg, gait disorders, hallucinations)
  - —generally reversible and resolved with dose delays/reductions
  - —Indirect clinical evidence that MRZ crosses the BBB

CNS penetrating qualities of MRZ make it ideally suited to primary CNS tumors

Several proteasome inhibitors are available for extra-CNS disease

Therefore, Phase 1/2 studies in GBM were initiated

MRZ GBM Studies in Adults (Celgene / BMS Sponsored)

Study Indication	Study Part / Treatment Arm	N	MRZ IV Dose Regimen	RP2D
MRZ-108 rGBM	Part 1: MRZ + BEV	36	0.55-0.8 mg/m^2 D1,8,15; Q4W	0.8 mg/m^2
	Part 2: MRZ alone	30	0.8 mg/m^2 D1,8,15; Q4W	0.8 mg/m^2
	Part 3: MRZ + BEV	41	0.8-1.0 mg/m^2 D1,8,15; Q4W intra-patient dose escalation	0.8 mg/m^2
	Total	**107**		
MRZ-112 ndGBM	Arm 1: Concomitant MRZ + TMZ/RT	35	0.55-1.0 mg/m^2 D1,8,15, 29, 36	0.8 mg/m^2
	Arm 2: Adjuvant MRZ + TMZ	18	0.55-1.0 mg/m^2 D1,8,15; Q4W	0.8 mg/m^2
	Optune: Adjuvant MRZ + TMZ + TTF	13	0.8 mg/m^2 D1,8,15; Q4W	0.8 mg/m^2
	Total	**66**		

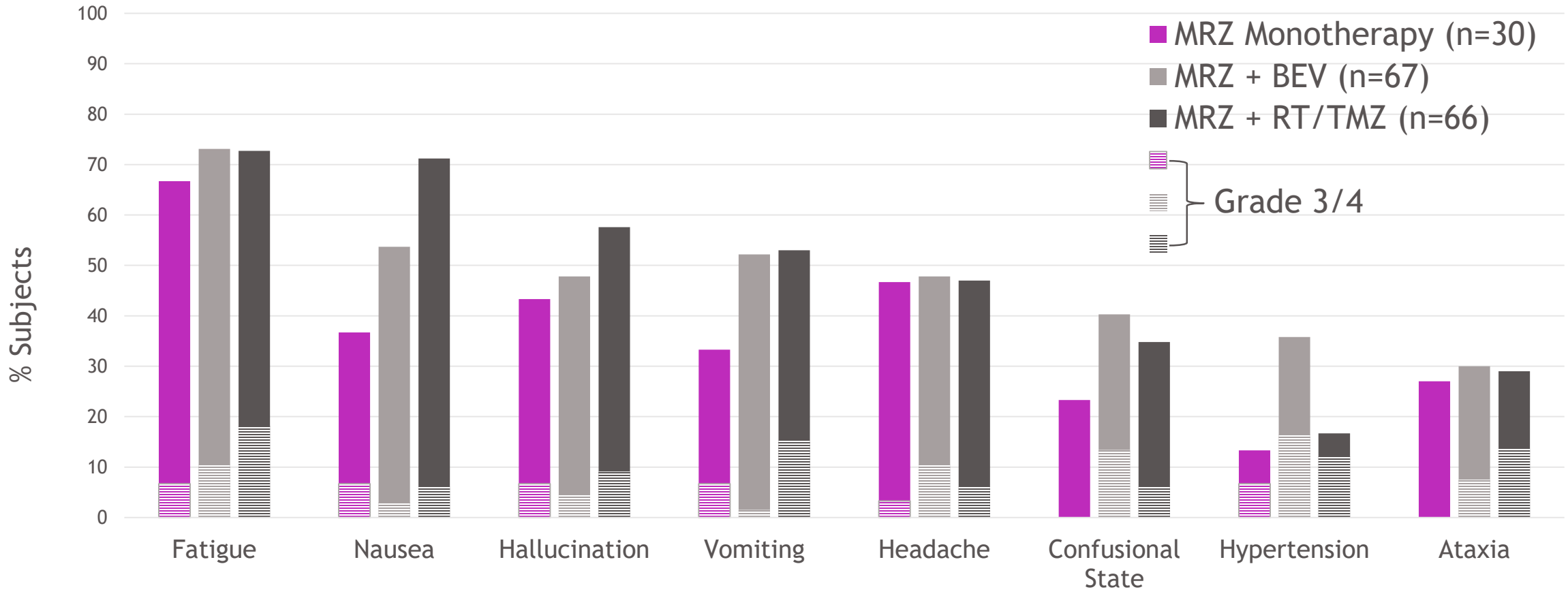
Benchmarking MRZ-108 rGBM Preliminary Activity

- Signals of clinical activity as single agent and improved ORR in combination
- In comparison to MRZ + BEV, the GLOBE BEV alone arm had ORR of 21.9% and DOR of 2.2 mo; no improvement for MRZ over BEV alone for mPFS or mOS[1]

Best Overall Response Assessed by RANO criteria	Part 2 MRZ 0.8 mg/m² N=30	Parts 1 + 3 MRZ 0.55-0.8 mg/m² + BEV N=67
Overall Response Rate (CR +PR) n (%)	1 (3.3)	23 (34.3)
Complete Response (CR) n (%)	0 (0.0)	2 (3.0)
Partial Response (PR) n (%)	1 (3.3)	21 (31.3)
Stable Disease n (%)	8 (26.7)	25 (37.3)
Progressive Disease n (%)	20 (66.7)	13 (19.4)
Duration of Response (DOR) mo (95% CI)	9.6 (NA, NA)	5.2 (3.68, 7.63)

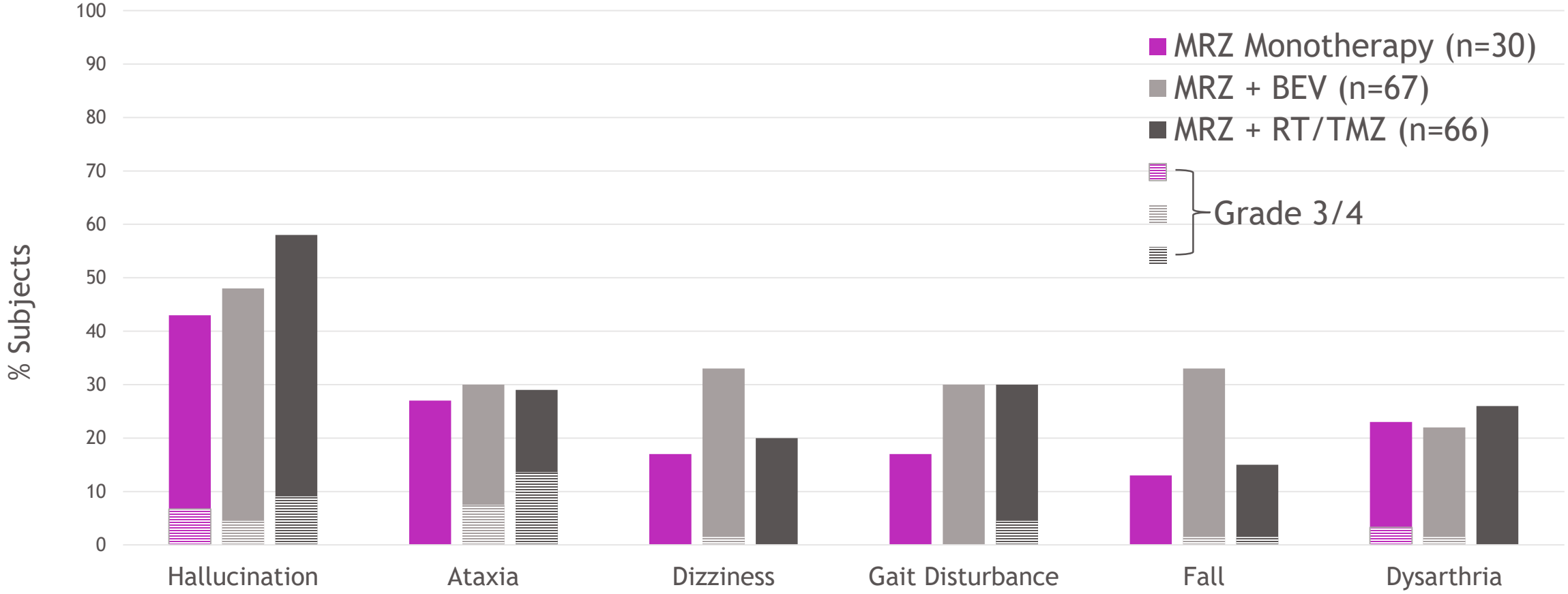
[1]Cloughesy, Neuro-Oncol. 2019;noz232

Most Common TEAEs in MRZ GBM Studies are Manageable Alone or in Combination with BEV or TMZ/RT & Majority were Grade 1 or 2



CNS AEs in MRZ GBM Studies are Manageable, Reversible & Majority were Grade 1 or 2

- Occur as early as first MRZ dose, usually late Cycle 1 or early Cycle 2
- Resolved by dose delays, reductions or occasional discontinuation & medical management



Conclusions for MRZ Studies in Adults

Overall, consistent results from MRZ Phase 1/2 studies (N=465, 185 in GBM):

- MRZ crosses the BBB (based on CNS AEs)
- Dose-related, reversible CNS AEs (eg, ataxia and hallucinations) determined the benefit/risk was more favorable for patients with CNS vs non-CNS tumors
- Safety profile in GBM patients was manageable as single agent and in combination; Majority of TEAEs and CNS AEs were Grade 1 or 2
- MRZ demonstrated preliminary activity in GBM as single agent and further efficacy potential when used in combination

These findings supported the ongoing EORTC Phase 3 study in patients with ndGBM for evaluating OS when MRZ added to standard TMZ + RT → TMZ

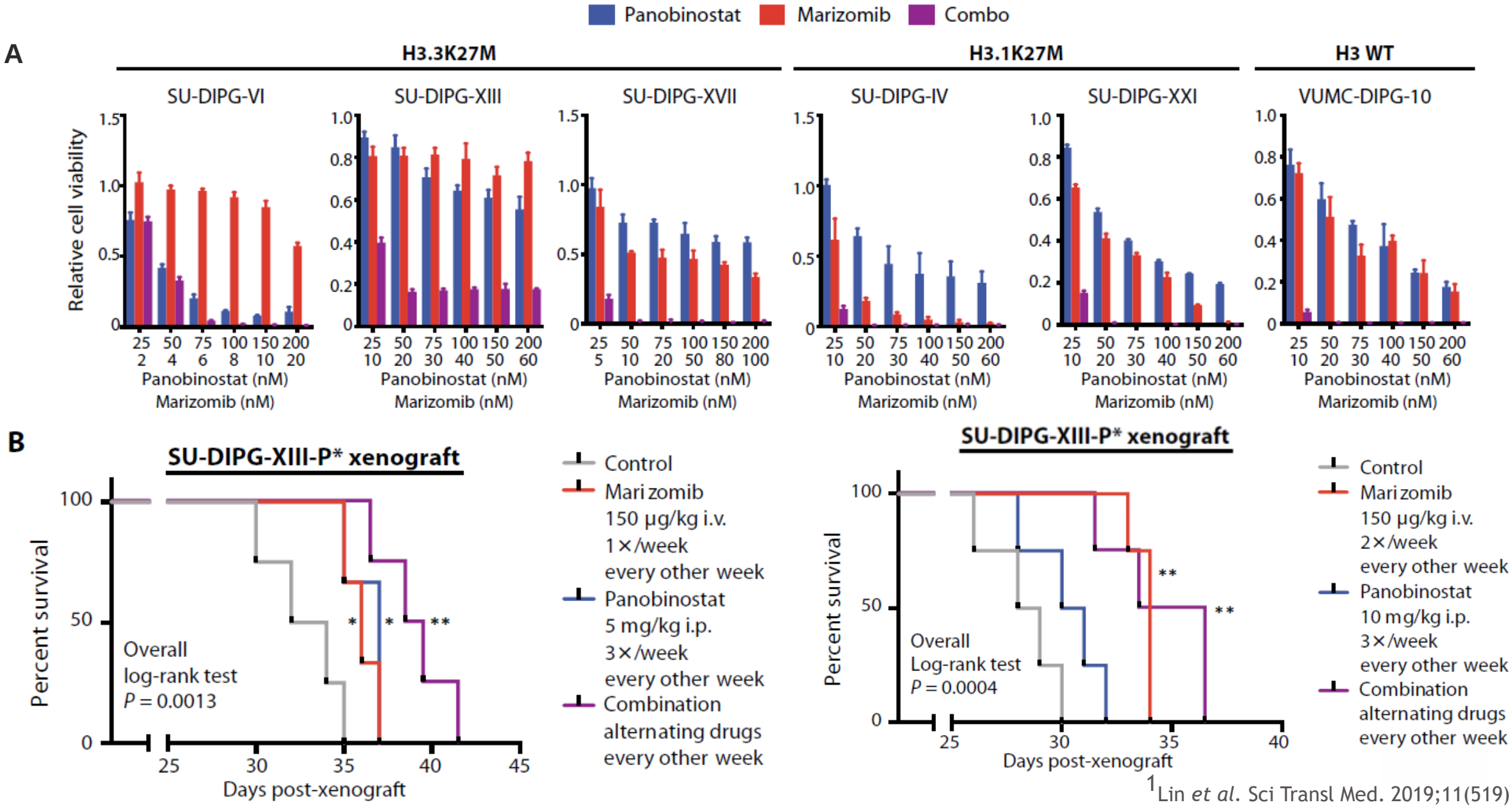
MRZ Global Pediatric Development Plan

- Based on a molecular target of proteasome inhibition and CNS penetration, development initiated in children with DIPG and work for HGG planned
  - Nonclinical findings with MRZ and PAN in DIPG cell lines and models supported initiation of a Phase 1 study of MRZ + PAN in DIPG
- These initial pediatric clinical and nonclinical data will help pave the way for further development

MRZ PIP Includes Additional Studies for DIPG

Area	Study	PIP	iPSP
Quality	Age appropriate dose content vial	✓	✓
Nonclinical	DIPG cell lines, antiproliferation ± other agents	✓	
	HGG cell lines, antiproliferation ± other agents	✓	✓
	DIPG models, antitumor effect ± PAN	✓	
	PK & safety nonhuman primates ± PAN	✓	✓
Clinical	Phase 1 safety, PK, preliminary effect MRZ alone then + PAN in DIPG	✓	
	Phase 2 safety & efficacy MRZ + PAN in DIPG	✓	
	Phase 1/2 safety, PK, preliminary effect MRZ + TBD in HGG	✓	✓

Nonclinical Activity Demonstrated by MRZ + PAN in DIPG[1]



[1]Lin *et al.* Sci Transl Med. 2019;11(519)

Ongoing: Phase 1 Trial in Children with DIPG

	IIT Phase 1 Study (NCT04341311)
Study design	Open-label trial to evaluate DLTs, PK, safety and activity of MRZ alone and in combination with PAN in children from birth to <22 years with DIPG who received prior RT
Number of participants	19 and up to 39 subjects evaluable for the primary analysis
Treatment regimen	MRZ alone for Cycle 1 administered on Days 1 and 15 of a 28-day cycle. Dosing frequency to be increased during escalation MRZ + PAN Cycle 2 and beyond; PAN administered PO 3x/week on a 1-week on/1-week off schedule
Primary endpoint(s)	Safety, tolerability and MTD/RP2D of MRZ as single agent and in combination with PAN PK parameters Preliminary efficacy
Main secondary endpoint(s)	Assessment of PFS and OS Safety and tolerability in relation to excipients (propylene glycol and ethanol)

Conclusion

- MRZ has a manageable safety profile in adults
- CNS penetrating qualities of MRZ make it ideally suited to primary CNS tumors
- Synergistic in vitro activity of MRZ with PAN supports rational for DIPG study

Based on a molecular target of proteasome inhibition and CNS penetration, development focused on children with HGG including GBM and DIPG

Gain advice for a Written Request focused on HGG including GBM and DIPG

Thank you

Questions & Answers

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