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SUPPLEMENTAL DATA

Preclinical systemic pharmacokinetics, dose-proportionality, and CNS distribution of the ATM inhibitor WSD0628, a novel radiosensitizer for the treatment of brain tumors

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Supplemental Figure S1

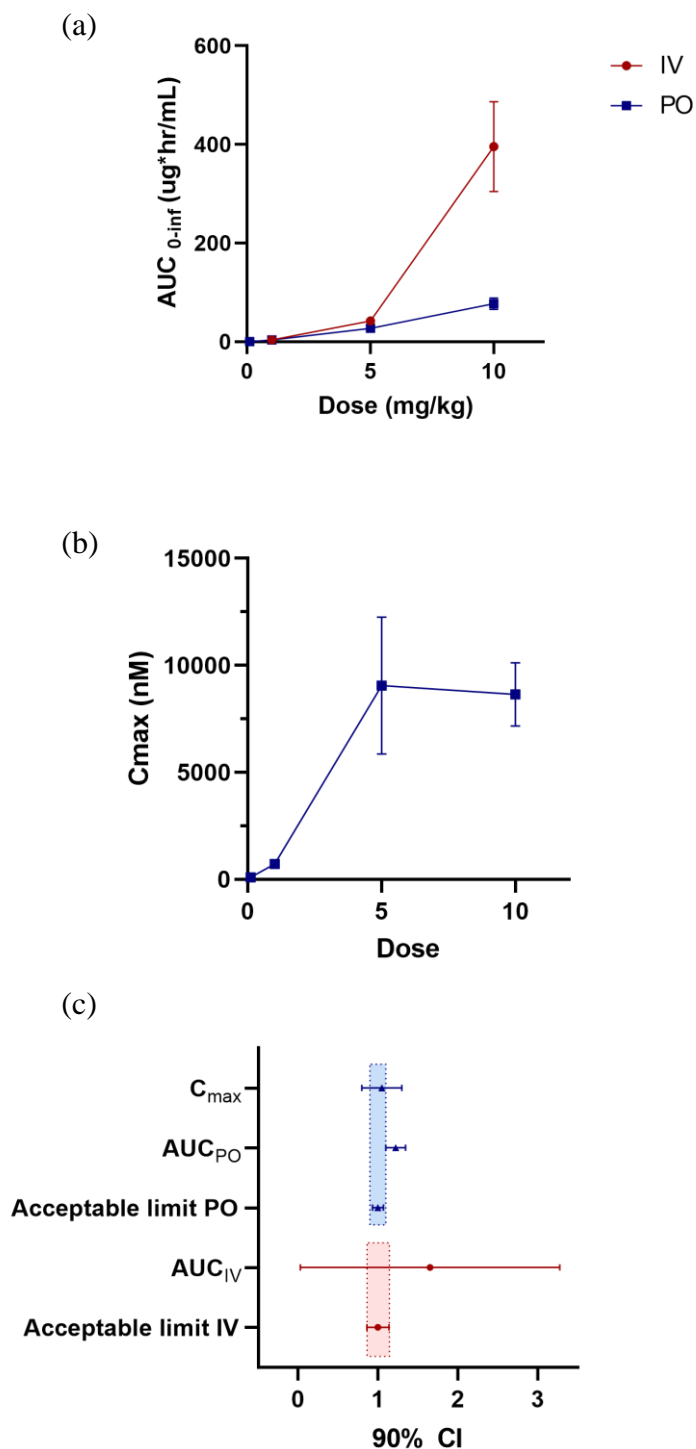


Figure S1: Evaluation of dose proportionality

(a) Plasma AUC_{0-inf} versus dose after intravenous or oral administration of 0.1 mg/kg (PO), 1 mg/kg, 5 mg/kg, and 10 mg/kg of WSD0628, error bars represent SEM

(b) Observed C_{max} versus dose in plasma after oral administration of 0.1 mg/kg, 1 mg/kg, 5 mg/kg and 10 mg/kg of WSD0628, Data represent mean \pm SD, n = 4

(c) 90% CI of the slope from linear regression of the log-transformed data vs log(Dose) compared to the acceptable 80-125% range in shaded box (IV in red, PO in blue) for dose proportionality

Supplemental Figure S2

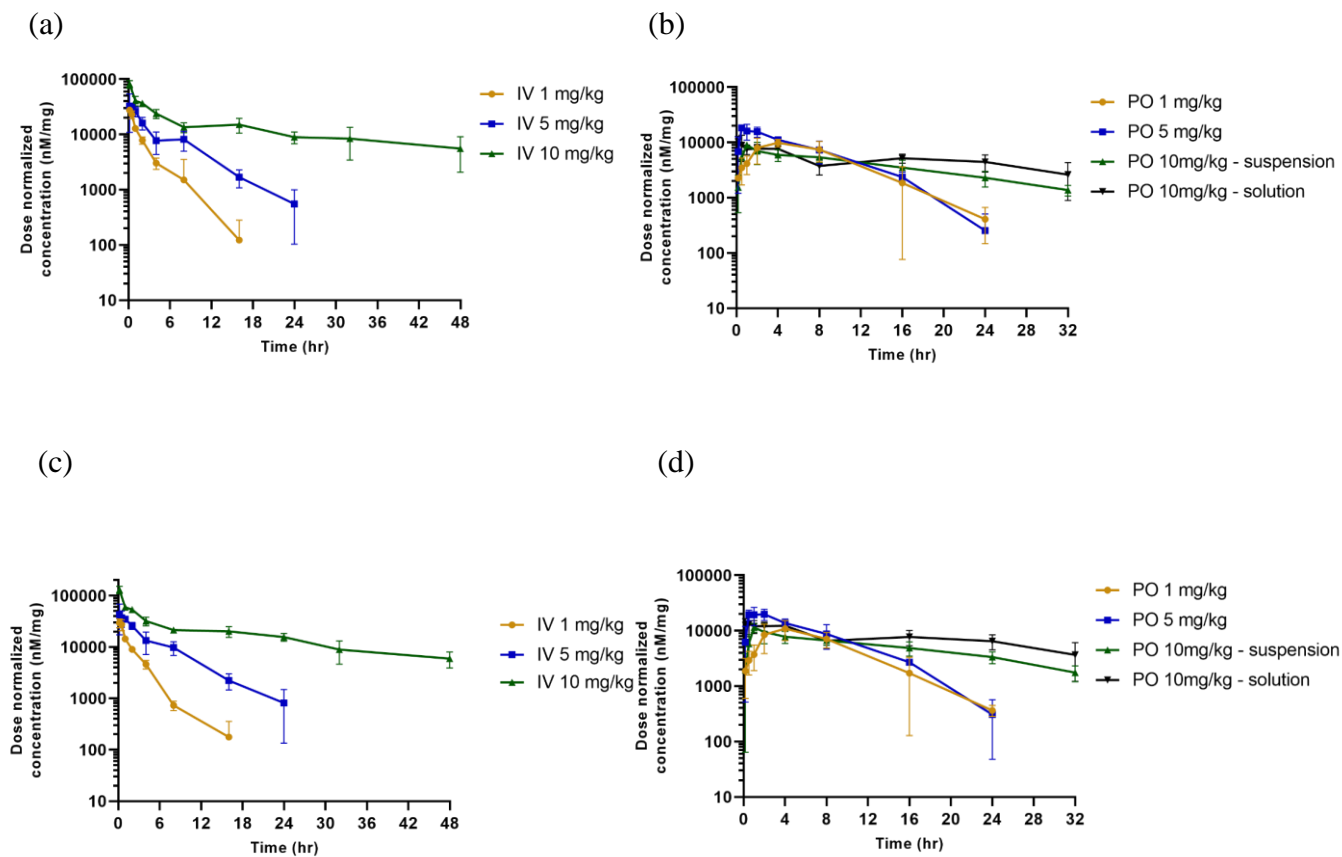


Figure S2:

Dose normalized concentration time profiles in brain after (a) intravenous and (b) oral administration; in spinal cord after (c) intravenous and (d) oral administration of WSD0628

Data represent mean \pm SD, n = 4

Supplemental Table 1: Tissue partition coefficients in different brain regions

Partition coefficient	2 hrs	8 hrs
Cortex	0.31 ± 0.03	0.32 ± 0.05
Thalamus and hypothalamus	0.33 ± 0.01	0.33 ± 0.05
Mid-brain	0.33 ± 0.05	0.32 ± 0.04
Pons	0.30 ± 0.01	0.34 ± 0.03
Cerebellum	0.31 ± 0.03	0.30 ± 0.01
Medulla*	0.26	0.27
Spinal cord	0.40 ± 0.05	0.42 ± 0.03

Data represent mean ± SD, n = 4

* Samples pooled from 4 mice

Supplemental Table 2: Tissue partition coefficients from steady-state tissue distribution study

Partition coefficient	Average \pm SD
Brain ^a	0.41 \pm 0.06
Spinal Cord	0.57 \pm 0.08
Esophagus* ^a	0.63
Spleen ^a	0.56 \pm 0.13
Tongue ^a	0.67 \pm 0.19
Heart ^a	0.84 \pm 0.11
Bone marrow	0.96 \pm 0.28
Sciatic nerve*	1.03
Lungs ^a	0.98 \pm 0.08
Small Intestine ^a	1.28 \pm 0.19
Optic nerve*	1.34
Kidneys ^a	1.36 \pm 0.19
Liver ^a	1.76 \pm 0.29

* Samples pooled from 6 mice

^a Concentrations corrected for residual blood in the tissue

Supplemental Table 3: Evaluation of drug distribution in tumor and regions of healthy brain tissue (normal brain) in mice bearing orthotopically implanted GBM43 PDX tumors

Tissue: Plasma concentration ratio	Average \pm SD (n = 5)
Normal brain	0.27 \pm 0.02
Tumor	0.32 \pm 0.03

Supplemental Table 4: PK model parameters determined from the simultaneous fitting of observed concentration time profiles at the studied dosing regimens

Parameter/ metric (units)	Value \pm SD
V_{max} ($\mu\text{g}/\text{kg}/\text{hr}$)	364.56 \pm 102.33
K_m ($\mu\text{g}/\text{mL}$)	1.07 \pm 0.563
k_{abs} (1/hr)	0.64 \pm 0.11
k_{1,2} (1/hr)	0.10 \pm 0.003
k_{2,1} (1/hr)	0.11 \pm 0.003
V_{central} (L/kg)	1.58 \pm 0.15

Supplemental Figure S3

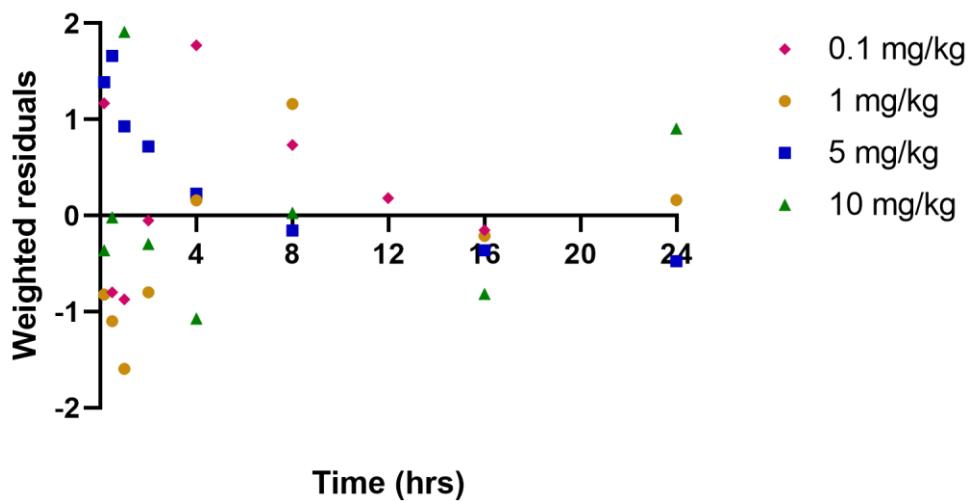


Figure S3: Model verification

Weighted residuals for plasma from observed versus predicted concentrations over time after an oral dose

Supplemental Table 5: Determination of CL_{Blood} and E_H

Parameter		Mean \pm SD	
Blood to plasma ratio (B:P)		0.88 \pm 0.14	
$AUC_{Blood} = B:P \text{ ratio} \times AUC_{Plasma}$ $CL_{Blood} = \frac{F \times Dose}{AUC_{Blood}}$ <i>Assuming total clearance is driven by hepatic mechanisms, $E_H = \frac{CL_H}{Q_H}$</i>			
Dose	AUC_{blood} ($\mu M \cdot hr$)	Cl_{blood} (L/hr/kg)	E_H
IV			
1	7.37	0.31	0.06
5	85.08	0.13	0.02
10	602.69	0.04	0.007
PO			
0.1	0.55	0.31	0.06
1	7.43	0.31	0.06
5	55.11	0.13	0.02
10	159.27	0.04	0.007
10	218.45	0.04	0.007