MPC-6827: An investigational anti-cancer drug with activity in a mouse orthotopic glioma model

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MPC-6827 overview

- Microtubule destabilizer
- Potent and rapidly acting VDA
- Not a substrate for MDR pumps
- Highly brain permeant
- Efficacious against a broad range of murine tumor models

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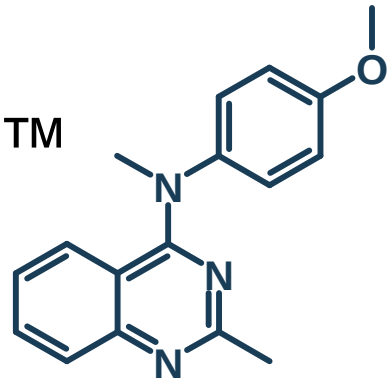
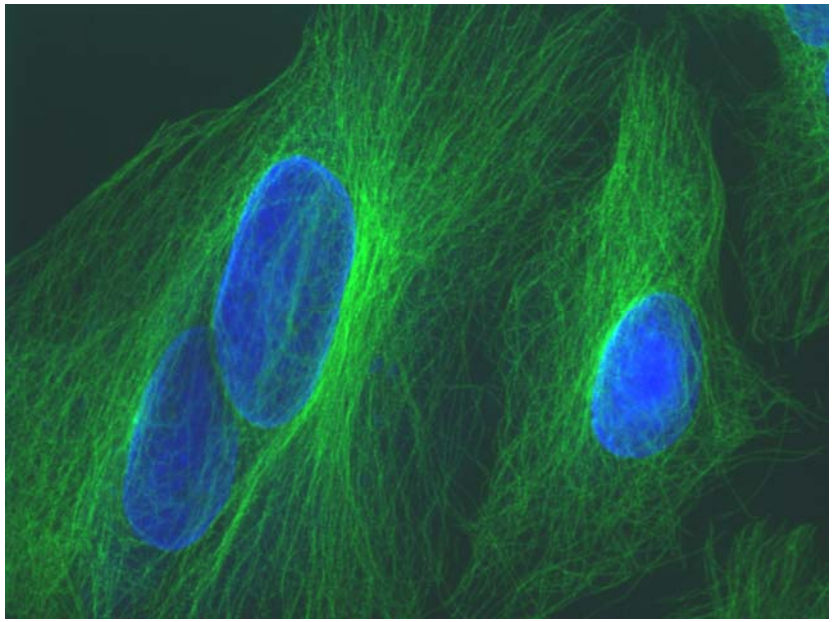
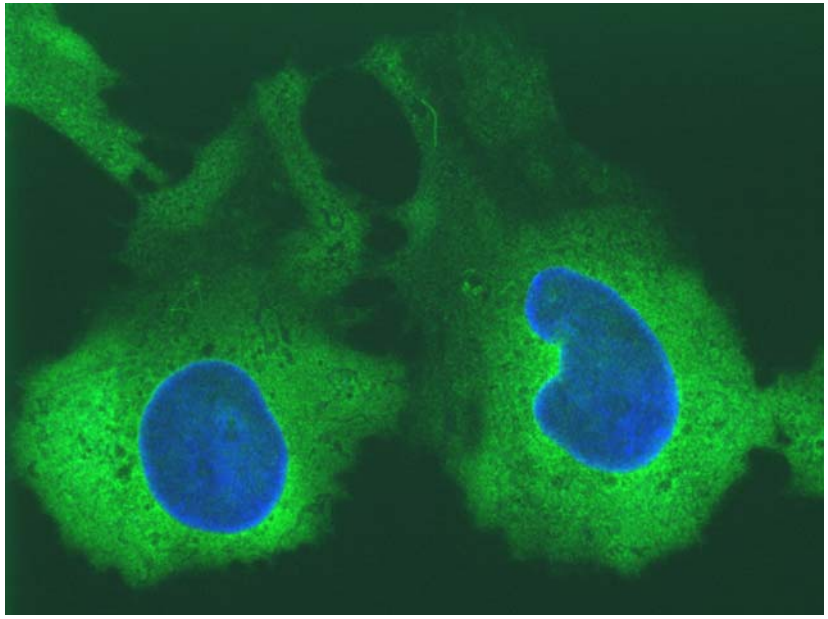


MPC-6827 is a potent cytotoxin that acts by microtubule destabilization

Vehicle



MPC-6827 (10 nM)



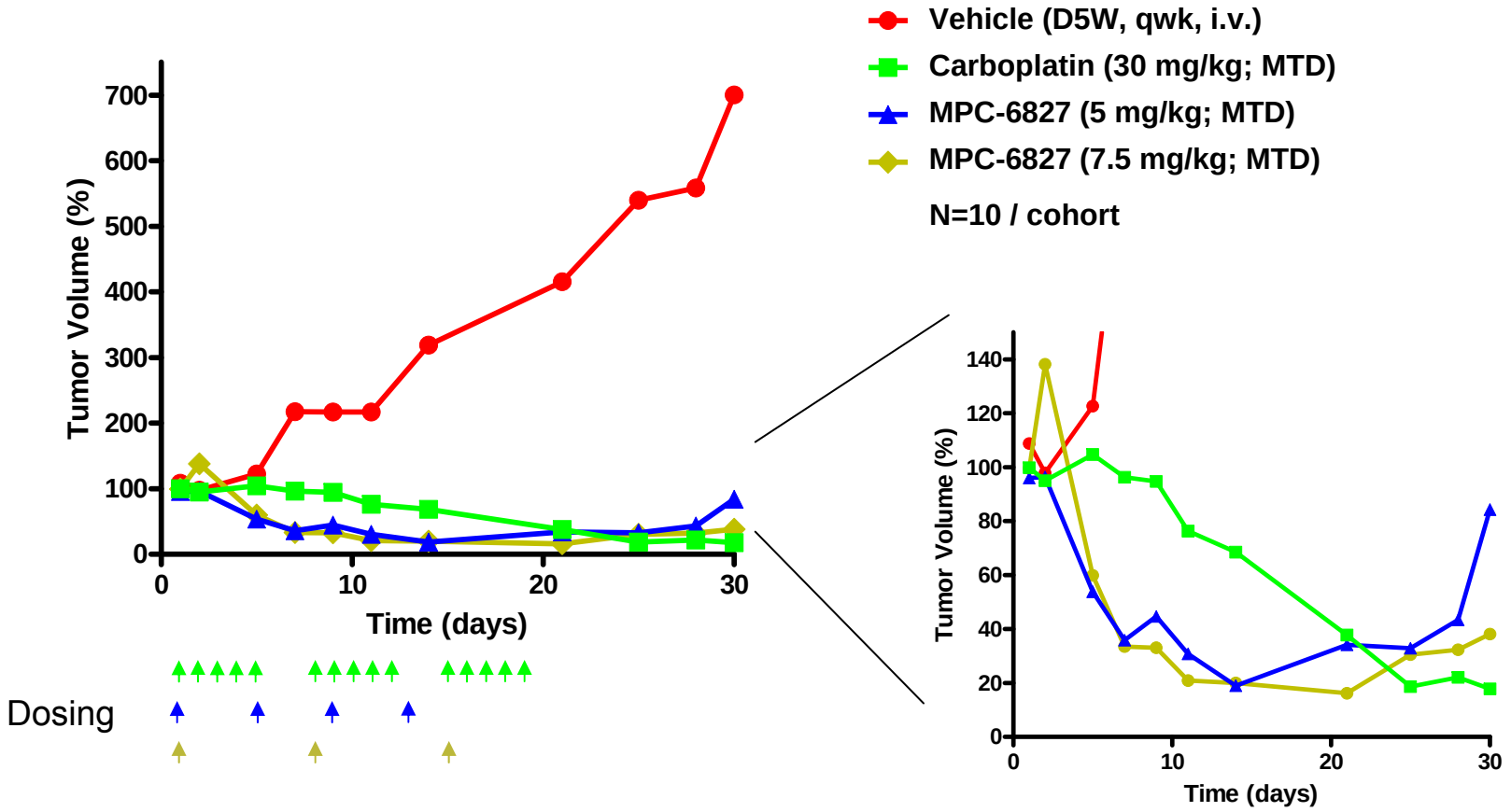
A549 Human NSCLC

Mean IC_{50} = 10 nM in over 90 cell lines, including MDR overexpressing cells and brain tumor derived cell lines

Kasibhatla et al., *Cancer Research*, **67**, 5865-5871 (2007)

MPC-6827 causes significant tumor regression

OVCAR-3 human ovarian xenograft



Pleiman et al., *AACR* (2007)

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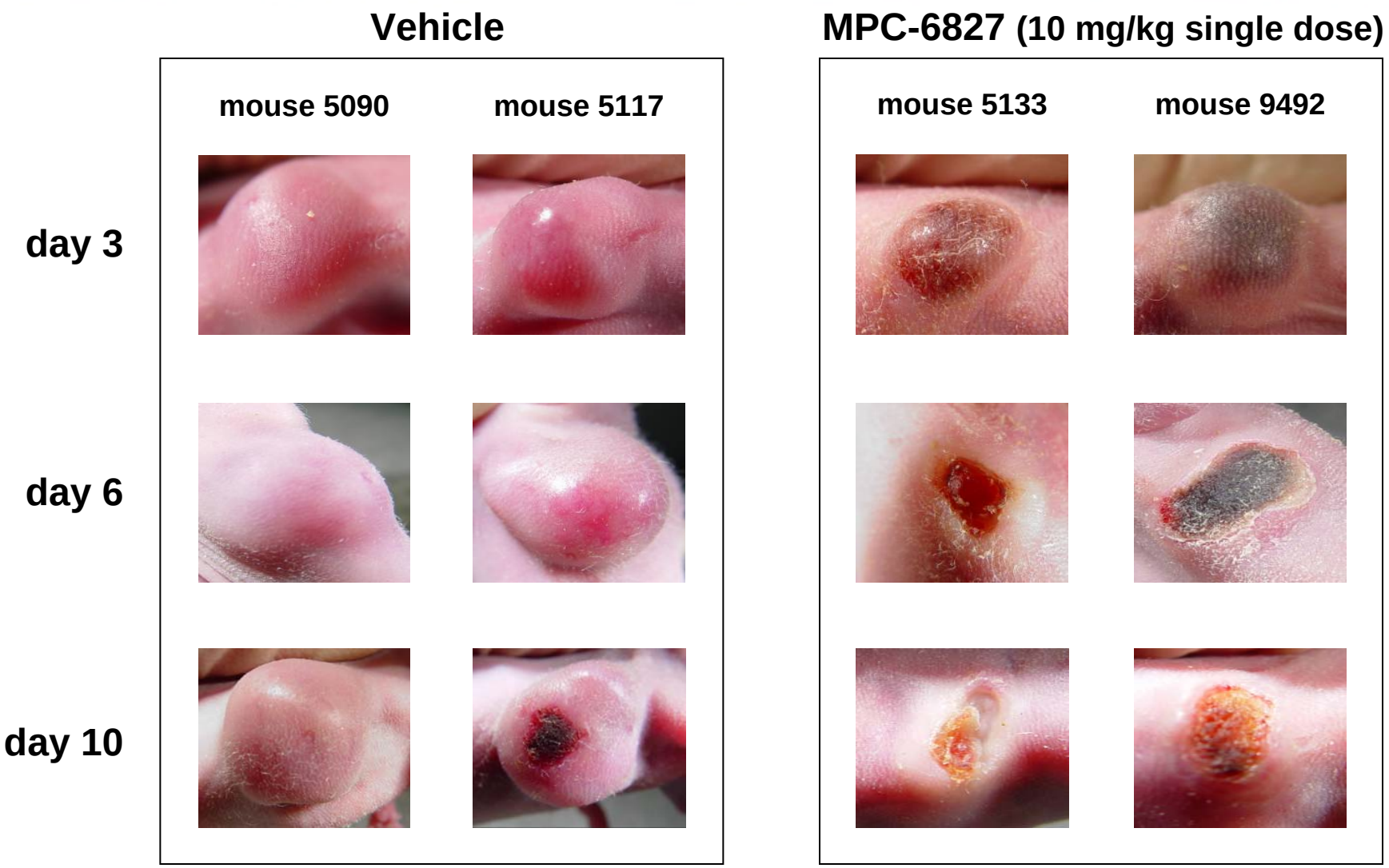
Evidence of VDA activity in MX-1 xenograft



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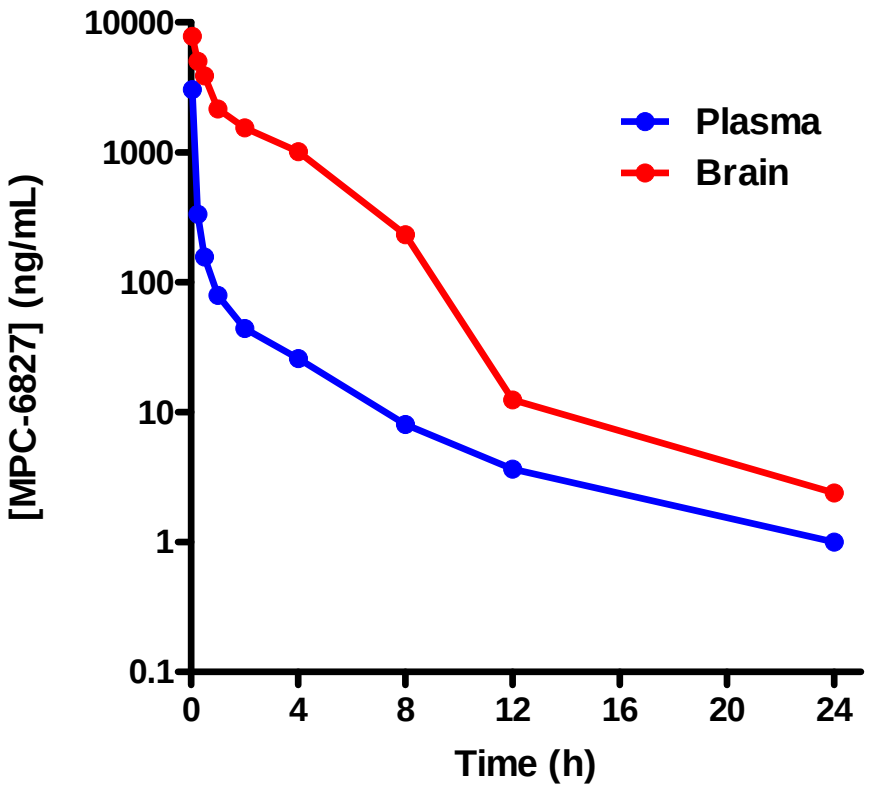
MPC-6827 concentrates in brain tissue



Nu/+ mice
2.5 mg/kg MPC-6827 IV

	Plasma	Brain
$t_{½}$ (h)	2.75	2.08
T_{max} (h)	0.05	0.05
C_{max} (ng/mL)	3,040	7,810
$AUC_{(0-\infty)}$ (h*ng/mL)	794	11,094

N = 5

⇨ brain/plasma AUC = 14

- Similar results observed in dogs
- In current study, brain and tumor concentrations were 12 and 4 times that of plasma

Jessing et al., *AACR* (2005)

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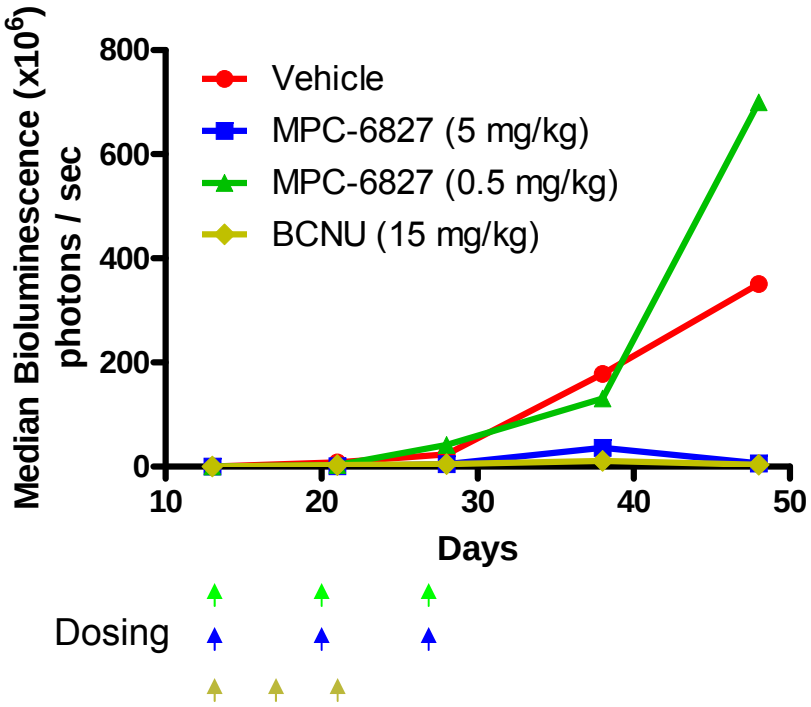
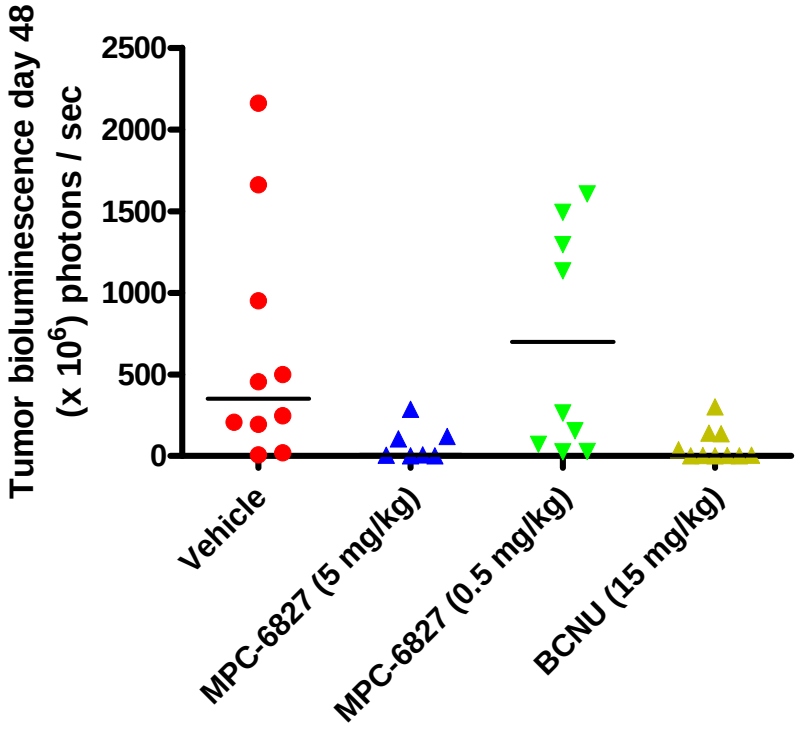
Orthotopic glioma model

- Nu/Nu mice intracranially implanted on day 0 with D54-MG human glioma cells overexpressing luciferase
- Tumor growth was quantified using the IVIS™ luminescence imaging system
  - Tumor take confirmed / drug dosing initiated on day 13
  - MPC-6827 dosed at 5 mg/kg and 0.5 mg/kg IV weekly for 3 weeks
  - BCNU dosed at 15 mg/kg IV every 4 days for 3 doses
- Survival endpoint
  - Animals sacrificed when body weight loss ≥ 20%

Tumor burden in treated animals





Treatment	Median bioluminescence (x10^6), day 48, Photons / second	N (day 48)	P-value vs vehicle day 48 (Mann-Whitney)
Vehicle	351.2	10	--
MPC-6827 (5 mg/kg)	6.4	7	0.0097
MPC-6827 (0.5 mg/kg)	699.6	10	.734
BCNU (15 mg/kg)	3.6	10	0.0021

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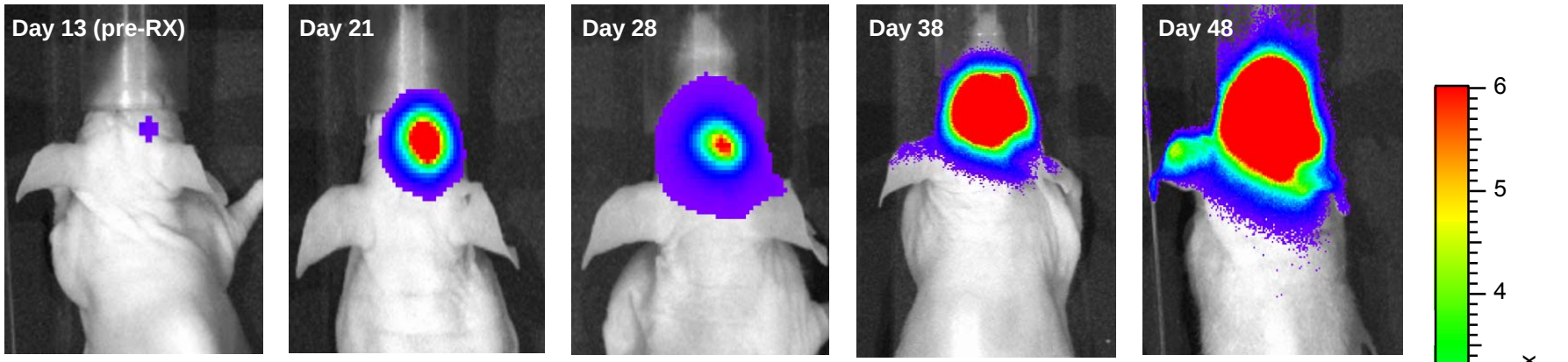
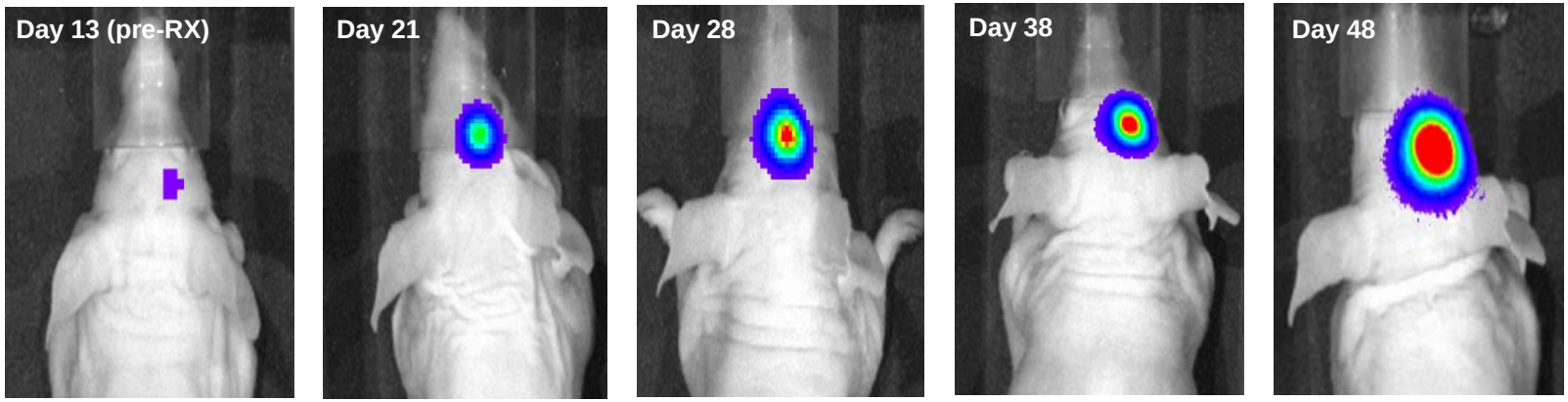
Monitoring tumor growth with luminescence

Vehicle Control – Group 1, Mouse 6 (IV; D13, 20, 27)



BCNU (15 mg/kg) – Group 4, Mouse 8 (IV; D13, 17, 21)



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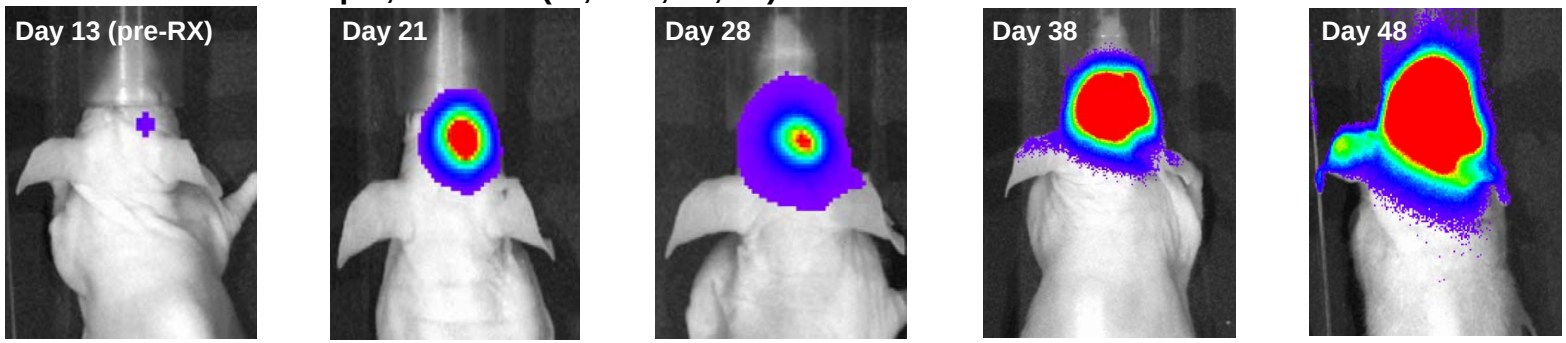
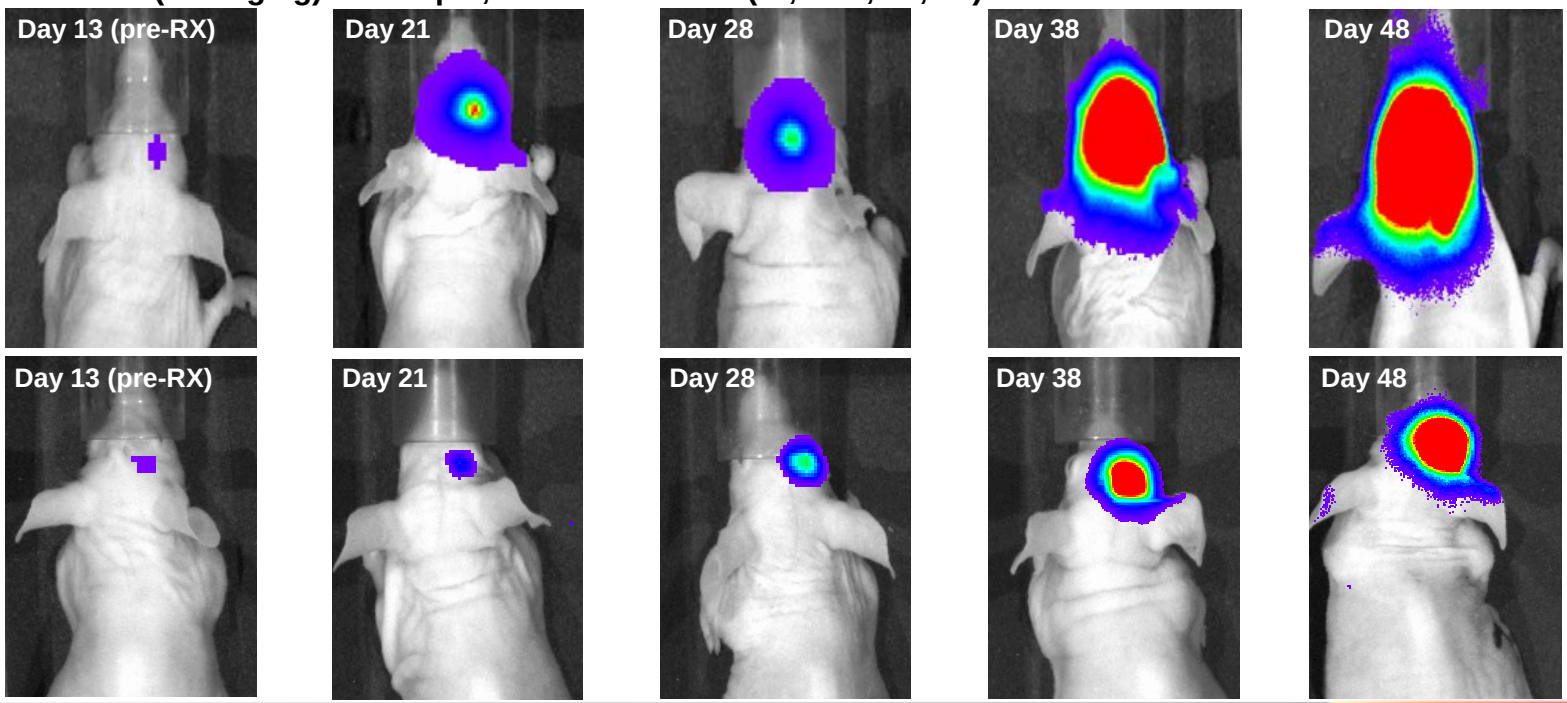
Mice treated with low dose MPC-6827 (0.5 mg/kg)

Vehicle Control – Group 1, Mouse 6 (IV; D13, 20, 27)



MPC-6827 (0.5 mg/kg) – Group 3, Mouse 3 and 10 (IV; D13, 20, 27)



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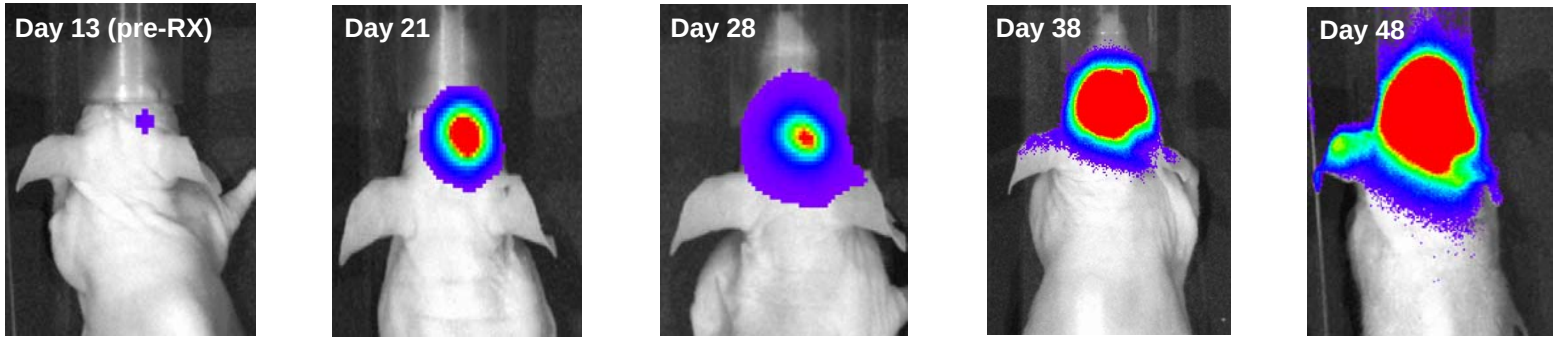
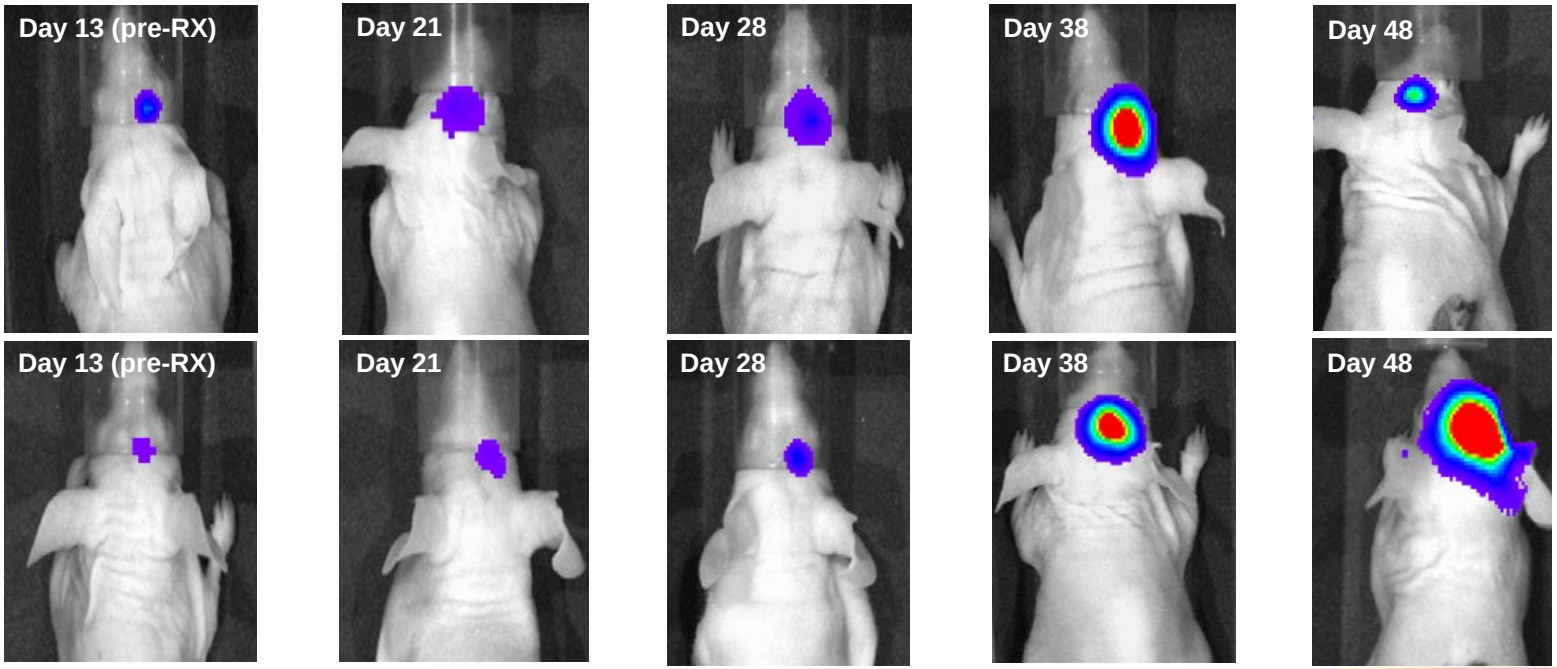
Treatment with high dose MPC-6827 (5 mg/kg) reduces tumor growth

Vehicle Control – Group 1, Mouse 6 (IV; D13, 20, 27)



MPC-6827 (5 mg/kg) – Group 2, Mouse 7 and 8 (IV; D13, 20, 27)



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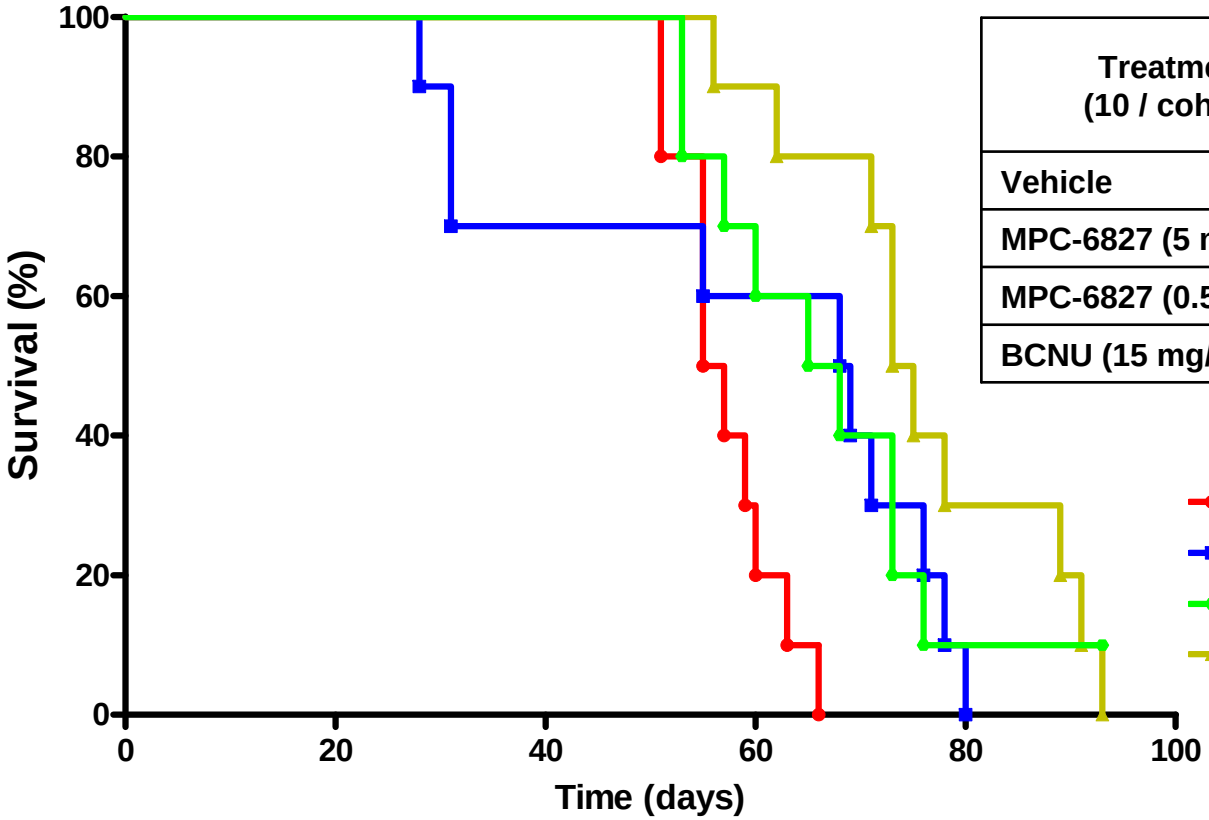
Survival of treated animals



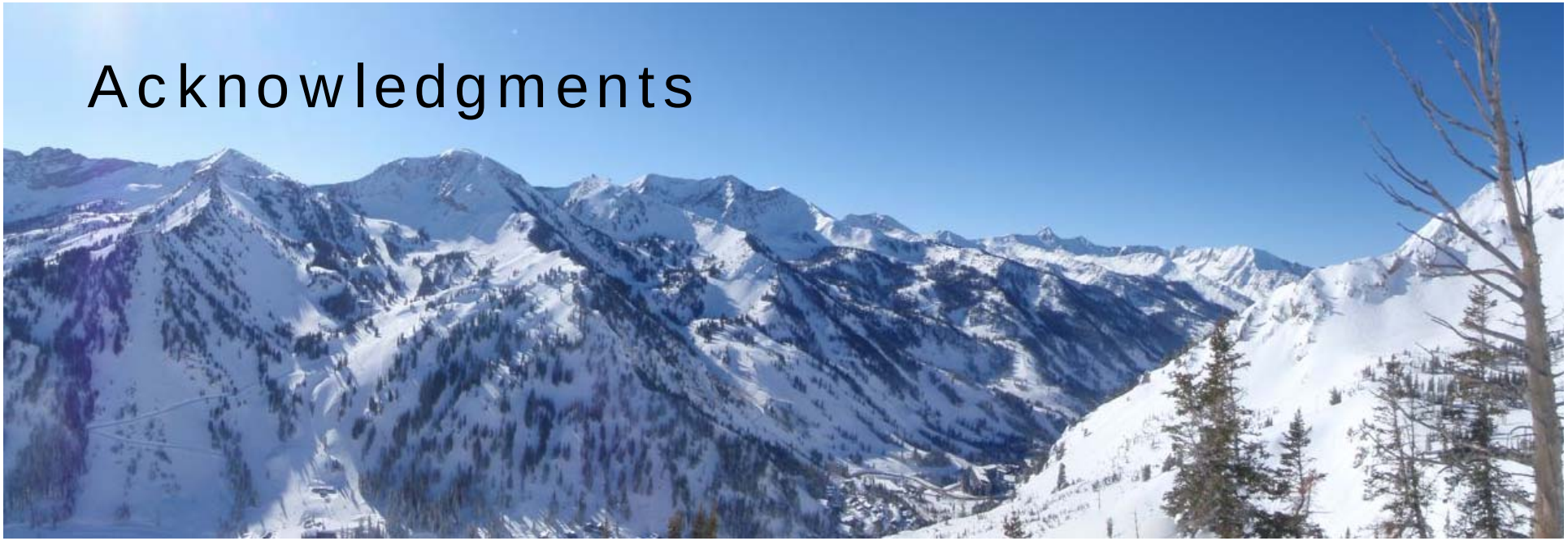
Treatment (10 / cohort)	Median Survival (days)	p-value vs vehicle (log-rank)
Vehicle	56	--
MPC-6827 (5 mg/kg)	69	0.039
MPC-6827 (0.5 mg/kg)	66	0.014
BCNU (15 mg/kg)	74	0.0001

- Animals were sacrificed when body weight loss ≥ 20%
- The Kaplan-Meier method was used to compute survival probabilities

Conclusions and development status

- MPC-6827 reduced the growth of an orthotopic glioma tumor
- MPC-6827 increased survival times over vehicle treated mice
- Clinical development status
  - Two phase 1 studies completed
  - Phase 2 in recurrent glioblastoma multiforme (GBM) with carboplatin ongoing
  - Phase 2 in metastatic melanoma with temozolomide ongoing
  - Phase 2 in grade 3 anaplastic glioma and GBM in first relapse, initiating

Acknowledgments



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