

# ORTHOTOPIC AND METASTATIC BRAIN TUMOR MODELS

Brain tumors are associated with significant morbidity and mortality and are often difficult to treat due to:

- Blood-brain barrier limits the entry of substances, including therapeutic agents
- Tumor location and invasiveness make complete surgical removal challenging
- Brain tumors can be genetically diverse, which can affect treatment response and contribute to resistance to therapies
- Some brain tumors, particularly glioblastomas, have a high resistance to standard treatments like radiation and chemotherapy
- The brain is a complex and delicate organ, and its treatment carries the risk of causing neurological damage

Preclinical brain tumor models have played a fundamental role in understanding tumor biology and developing anti-tumor strategies.

## Preclinical *In Vivo* Models

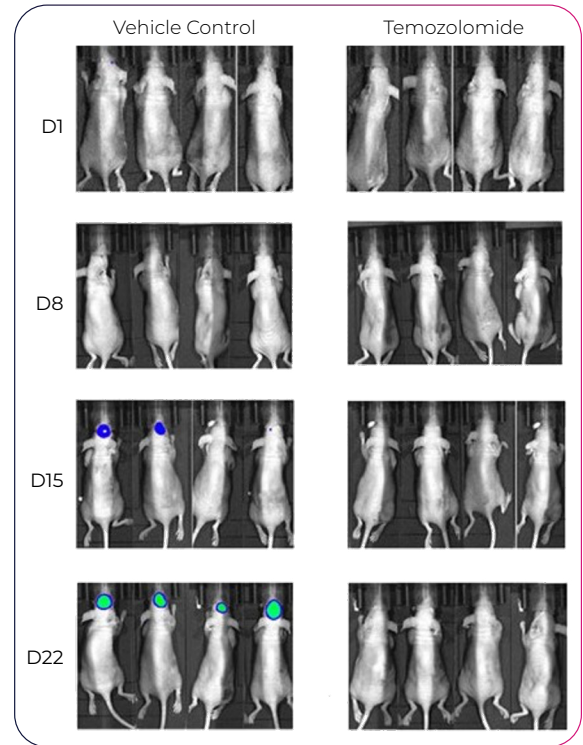
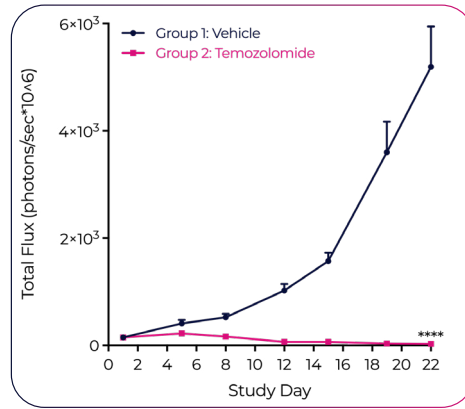
Tumor Type	Inoculation Route	Pros	Cons	Applications
Primary • CDX • PDX • Syngeneic	• Intracranial	• Clinically relevant location • Clinically relevant microenvironment	• Surgical procedure • Higher cost	• Targeted therapy • IO therapy • Combo therapy
	• Subcutaneous	• Lower cost	• Less relevant to clinical setting	• Targeted therapy
Metastatic • CDX • PDX • Syngeneic	• Intracarotid	• Clinically relevant • Intact BBB	• Technically challenging surgical procedure	• Targeted therapy • IO therapy • Combo therapy
	• Intracranial	• Clinically relevant • Mostly Intact BBB	• Surgical procedure	
	• Spontaneous met	• Clinically relevant • Intact BBB	• Not all models will develop brain met • Technically challenging • Require large N numbers	

## Validated Models

Intracranial		Intracranial Models	Intracarotid Models
Orthotopic	Metastatic	• NCI-H1975-Luc • A375-Luc • PC-9-Luc • NCI-H358-Luc	• A375-Luc • NCI-H358-Luc • PC-9-Luc
• U-87 MG-Luc2 • U251-Luc • AM-38-Luc • U-87 MG-EGFRvIII-Luc	• A375-Luc • NCI-H358-Luc • PC-9-Luc • NCI-H1975-Luc • NCI-H1299-Luc		

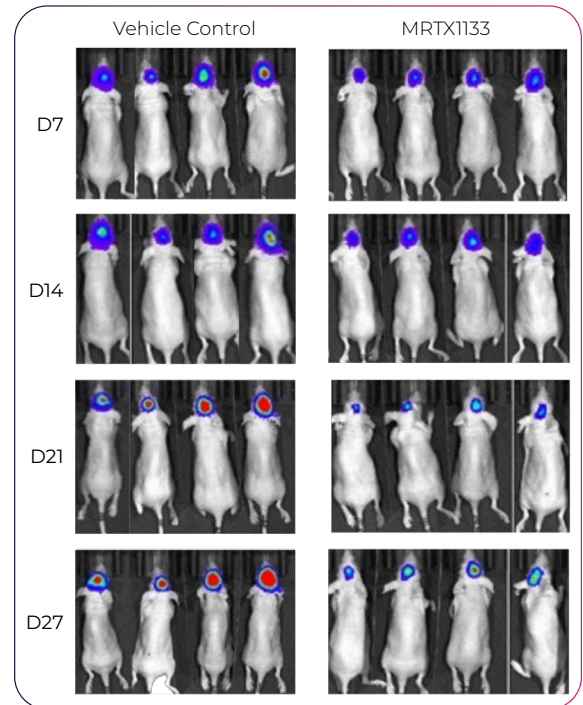
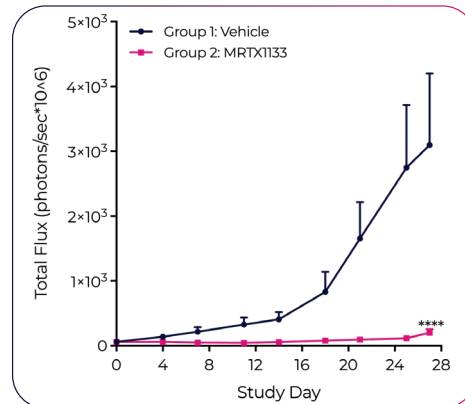
## U87 MG-Luc2 Intracranial Orthotopic Model

- Human glioblastoma cell line U-87 MG (ATCC) was transduced to express firefly luciferase (100% STR profile match).
- Brain tumors established by orthotopic cell implantation into the right hemisphere of nude mice.
- Treatment: Temozolomide showed a statistically significant reduction in tumor bioluminescence ( $n=8, p<0.0001$ ).



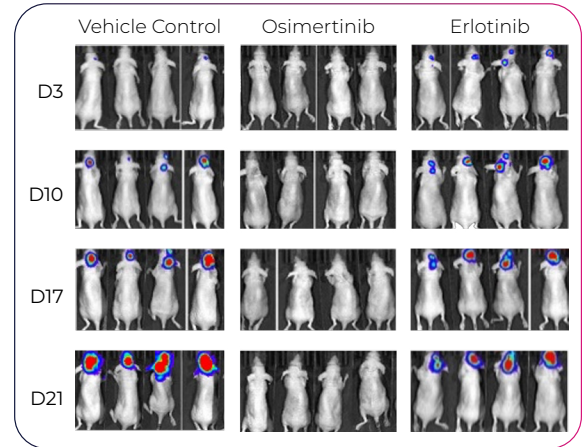
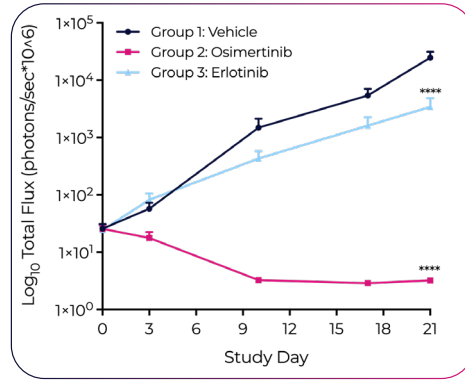
## GP2D-Luc Intracranial Metastatic Model

- Human colorectal cancer cell line GP2D sourced from ECACC, engineered to express firefly luciferase (100% STR profile match).
- Brain tumors established following intracranial implantation of tumor cells into the right hemisphere of nude mice.
- Treatment: MRTX1133 showed a statistically significant reduction in tumor bioluminescence ( $n=6, p<0.0001$ ).



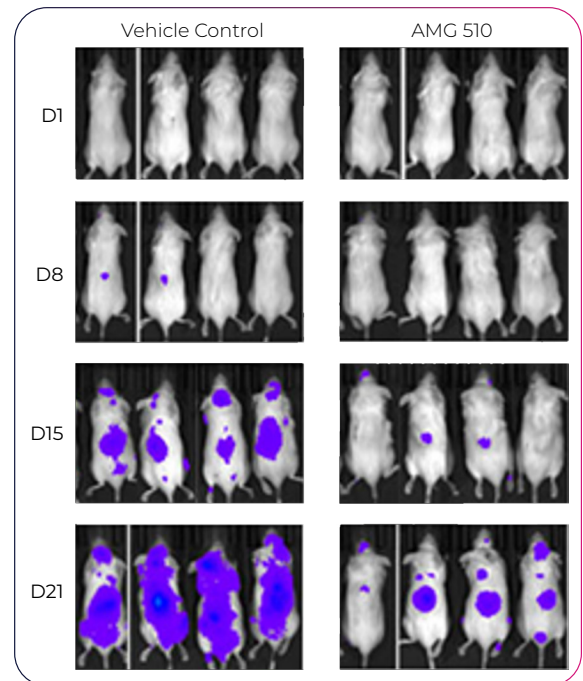
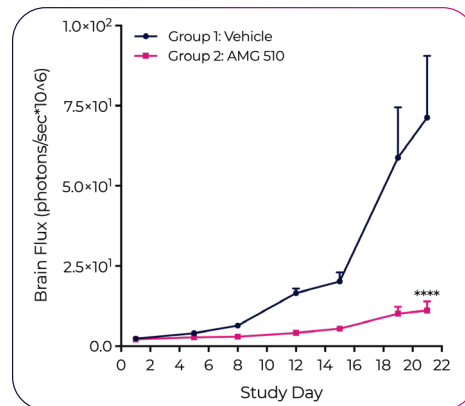
## PC-9-Luc Human Lung Cancer Intracarotid Metastatic Model

- PC-9 is a lung adenocarcinoma cell line with a deletion in exon 19 of the EGFR gene that exhibits high sensitivity to TKIs.
- Brain tumors developed following intracarotid injection of cells into nude mice.
- Treatment: Osimertinib and Erlotinib showed statistically significant reductions in tumor bioluminescence ( $n=10$ ,  $p<0.0001$ ).



## NCI-H358-Luc Intracardiac Metastatic Model

- Human non-small cell lung carcinoma cell line NCI-H358 sourced from ATCC, engineered to express firefly luciferase (100% STR profile match).
- Brain tumor and disseminated metastases established following intracardiac injection of cells into NCG mice.
- Treatment: AMG 510 showed a statistically significant reduction in tumor bioluminescence ( $n=6$ ,  $p<0.0001$ ).



## Summary

The utilization of *in vivo* orthotopic and metastatic models, including the intracranial, intracardiac and intracarotid models, represents a critical approach in advancing our knowledge of tumour biology and facilitating the development of novel therapeutic strategies for combating brain cancer.

The intracarotid model, in particular, offers a highly relevant and clinically translatable framework for studying brain metastases.

Our technical spotlight offers a comparative response to SoC treatment of NCI-H358-Luc tumors implanted via the intracranial, intracarotid and intracardiac routes.

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