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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

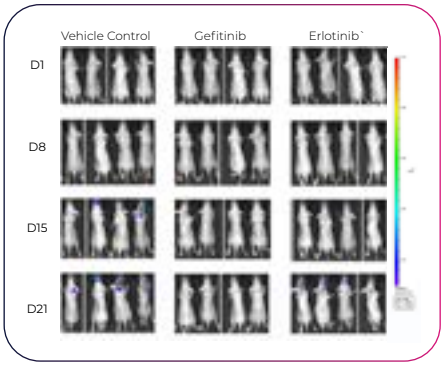
Tumor Type	Inoculation Route	Pros	Cons	Applications
Primary • CDX • PDX • Syngeneic	• Intracranial	• Clinically relevant location • Clinically relevant microenvironment	• Surgical procedure • Higher cost	• Targeted therapy • IO therapy • Combo therapy
	• Subcutaneous	• Lower cost	• Less relevant to clinical 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	

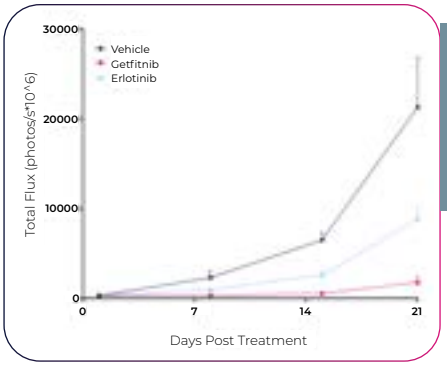
Validated Models

Intracranial Models		Intracarotid Models
• A375-Luc • NCI-H1299-Luc • H1975-Luc • H358-Luc	• PC-9-Luc • xBT474-Luc • X2MDA-MB-468-luc • XMDA-MB-231-luc	• A375-Luc • PC-9-Luc • xBT474-Luc • NCI-H1975-Luc

PC-9-Luc Human Lung Cancer Intracranial Metastatic Model

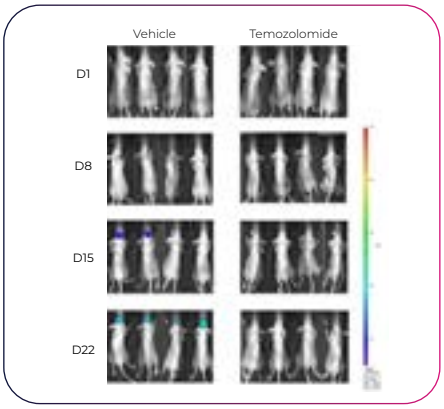
- PC-9 is a lung adenocarcinoma cell line with a deletion in exon 19 of the EGFR gene that exhibits high sensitivity to TKIs.
- Brain tumors established by intracranial implantation of cells into nude mice.
- Treatment: 6.25mg/kg Gef q.d. and 15mg/kg Erl showed statistically significantly reduced tumor growth (n=8, p<0.0001).

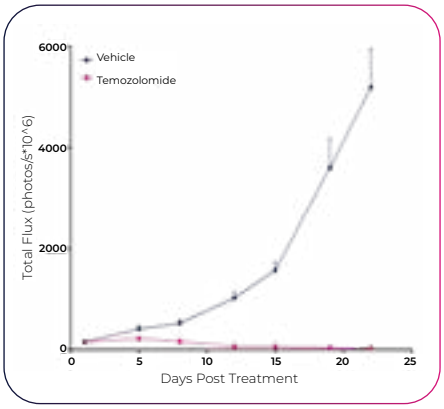




U87-MG-Luc2 Intracranial Orthotopic Model

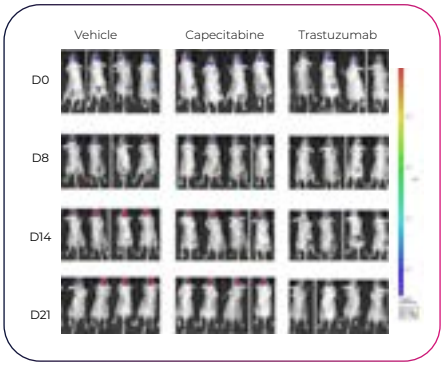
- Human glioblastoma cell line U-87MG was transduced to express firefly luciferase (100% STR profile match). Brain tumors established by intracranial cell implantation into nude mice.
- In-life growth assessed by bioluminescent imaging (BLI) using IVIS (PerkinElmer, US); mice were randomized to treatment groups based on their tumor-associated bioluminescence (TABL).
- Treatment: 45mg/kg TMZ q.d. showed statistically significantly reduced tumor growth (n=8, p<0.0001).

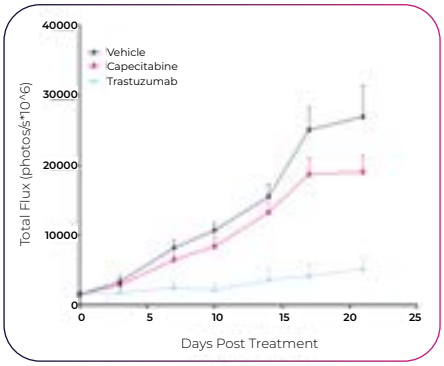




xBT-474-Luc Intracranial Metastases Model

- Human breast ductal carcinoma cell line BT474 sourced from ATCC, engineered to express firefly luciferase (BT474-luc, 100% STR profile match)
- Brain tumors established by intracranial implantation
- In-life growth and terminal ex vivo tumor burden assessed by bioluminescent imaging (BLI)





Summary

The utilization of *in vivo* orthotopic and metastatic models, including the intracranial 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.

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