NEO212: A NEW DRUG FOR TEMOZOLOMIDE RESISTANT MALIGNANT GLIOMAS

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Disclosure

I am the CEO and Chairman of NeOnc Technologies

Goals of Talk

1. Background
2. In-vitro Data: Functional Activity
3. Mechanism of Action
4. In-vivo Data
5. Pharmacokinetic Data
6. Toxicology Data
7. Upcoming Phase I/IIa Trial

BACKGROUND

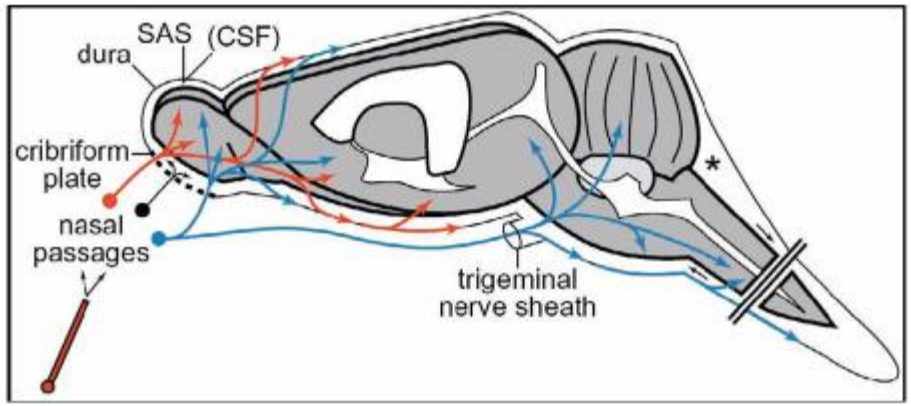
1. Perillyl Alcohol (POH) is a monoterpene that is found naturally in various fruits such as orange peel; it is a ras and cell cycle inhibitor

2. It has been used orally in clinical trials for metastatic cancer

3. More recently, it has been used intranasally for treatment of malignant gliomas

4. NeOnc is currently conducting a Phase I/IIa clinical trial using GMP quality POH (NEO100)

Intranasal brain delivery via Cranial Nerves I,V



Application of intranasal nebulizer

BACKGROUND (cont)

1. Temozolomide (TMZ) is the standard of care drug for gliomas

2. TMZ is a DNA alkylator whose efficacy is limited by MGMT (DNA repair enzyme), incomplete BBB penetrance, limited stability (prodrug)

3. POH is well tolerated, lipophilic, and induces ER stress

4. Hypothesis: Could TMZ be chemically conjugated to POH to produce a new drug that could have the following properties:

    a. Unique mechanism of action

    b. Effective in MGMT positive gliomas

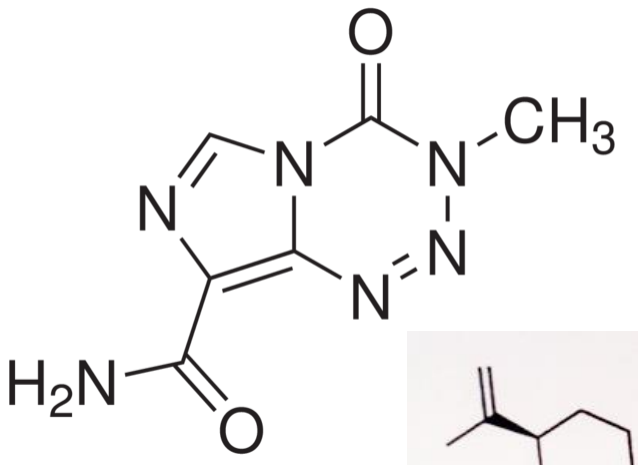
    c. Improved BBB penetrance

    d. Improved stability

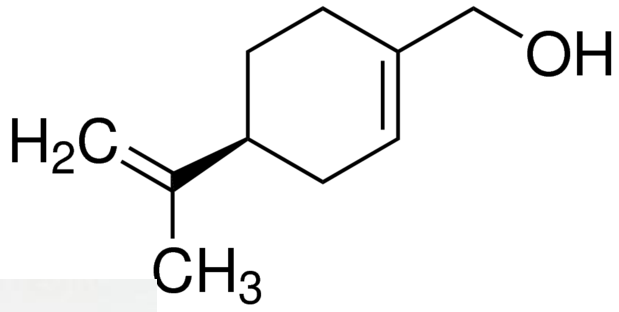
Temozolomide – Perillyl Alcohol (TMZ-POH; TP)

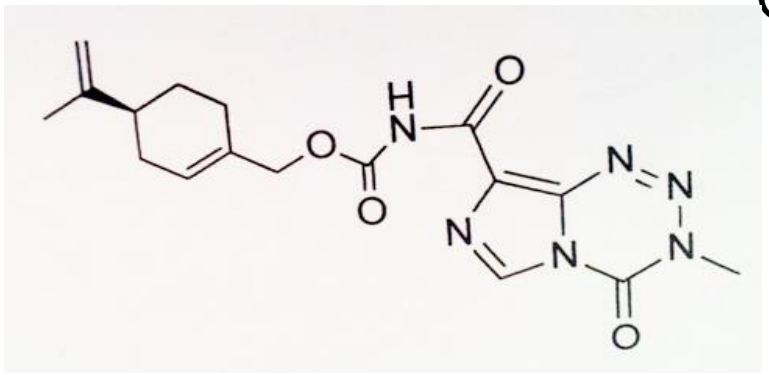
NEO 212

TMZ



POH



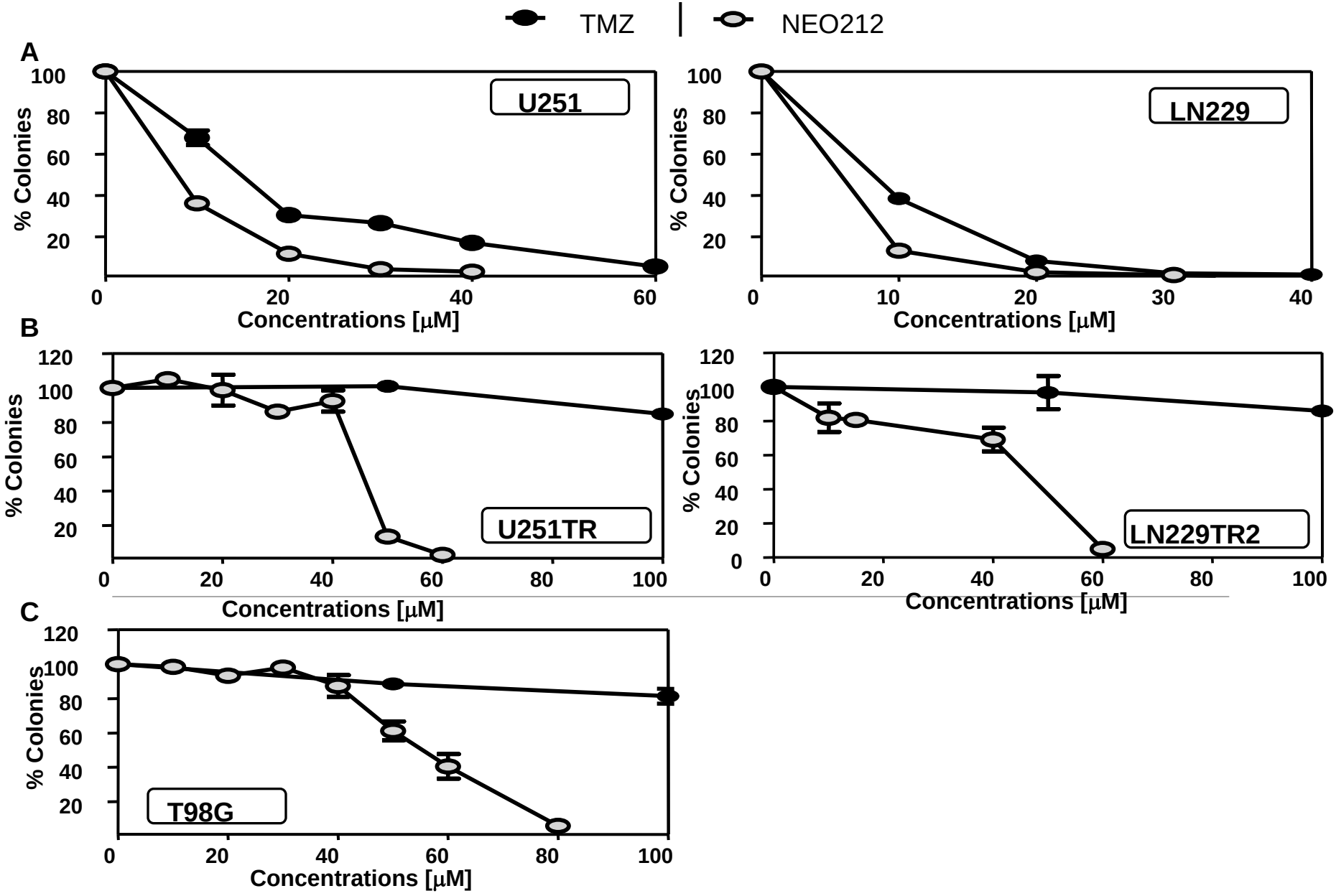


IN-VITRO DATA

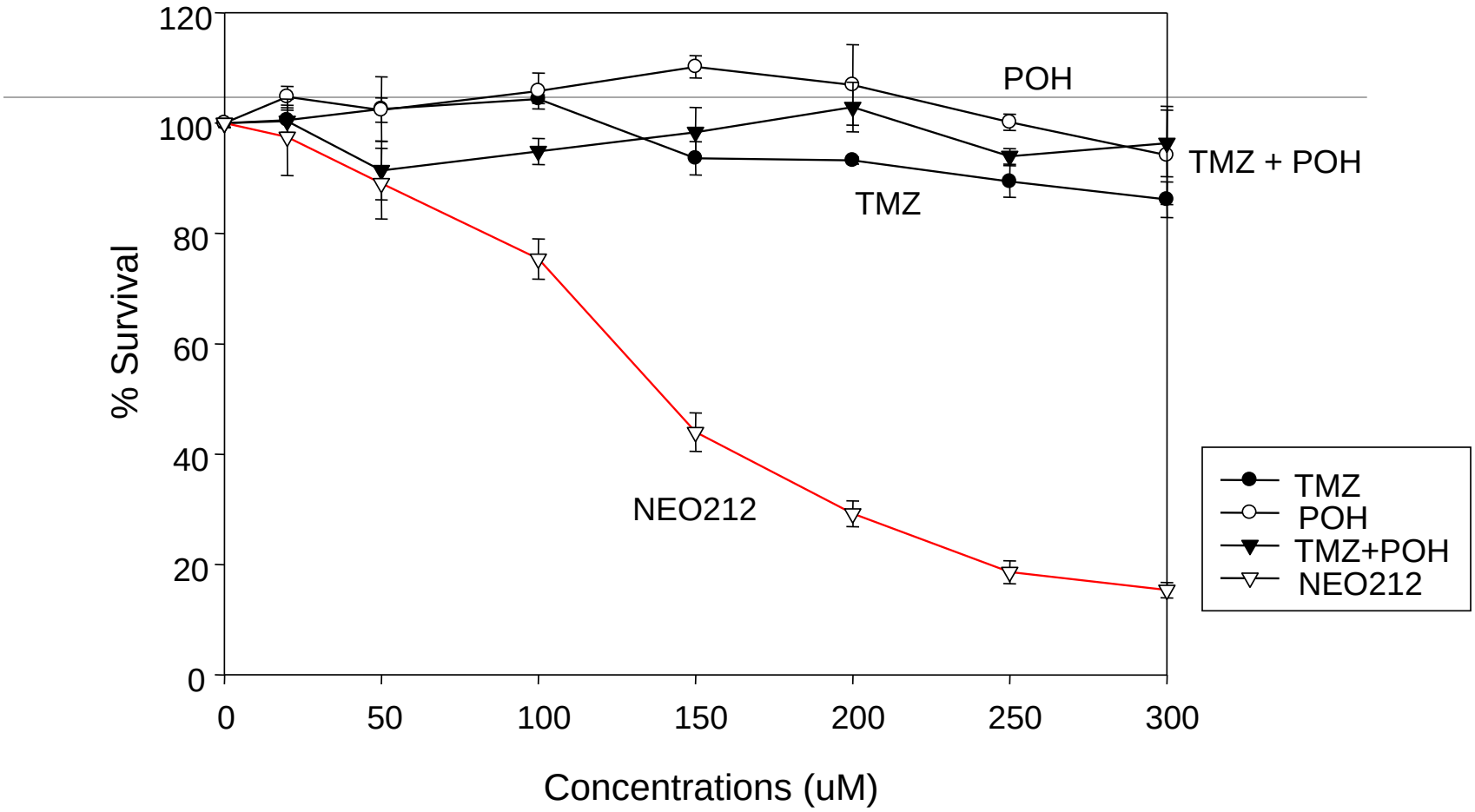
1. Does NEO212 have functional activity?

2. Is its activity similar to TMZ and POH together, or does it have different activity level?

3. Does it work on TMZ resistant cells?


TMZ
NEO212
A
U251
LN229
% Colonies
Concentrations [μM]
B
U251TR
LN229TR2
C
T98G

Comparison of Cytotoxicity Between NEO212 and Mixture of TMZ and POH Using T98G (MGMT+)



Conclusion: NEO212 is cytotoxic for T98G (MGMT+) glioma cells.

(O6-methylguanine-DNA methyltransferase)

MECHANISM OF ACTION

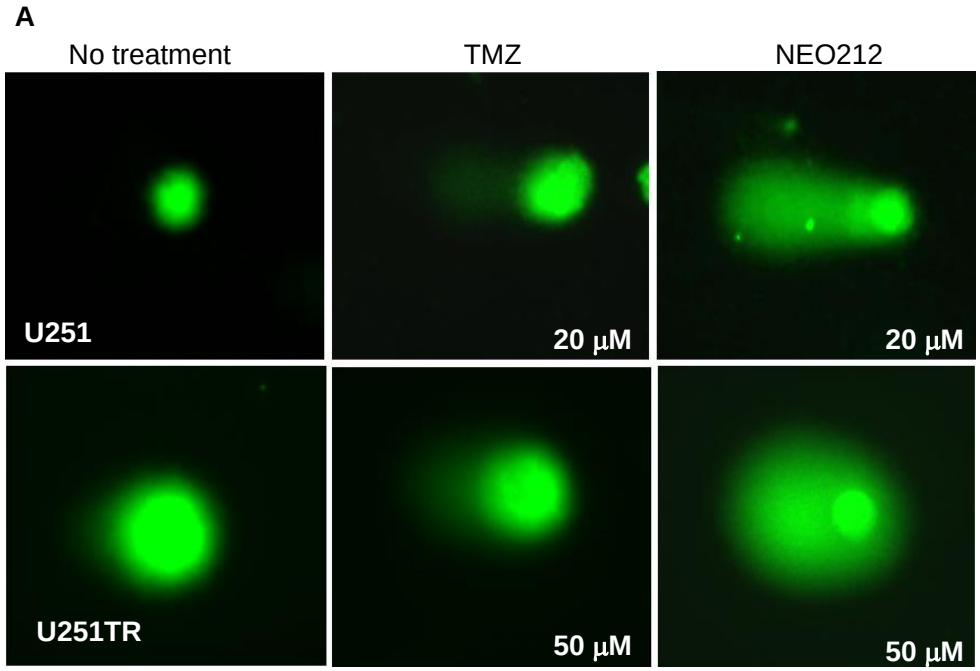
1. DNA alkylator-Induces DNA damage

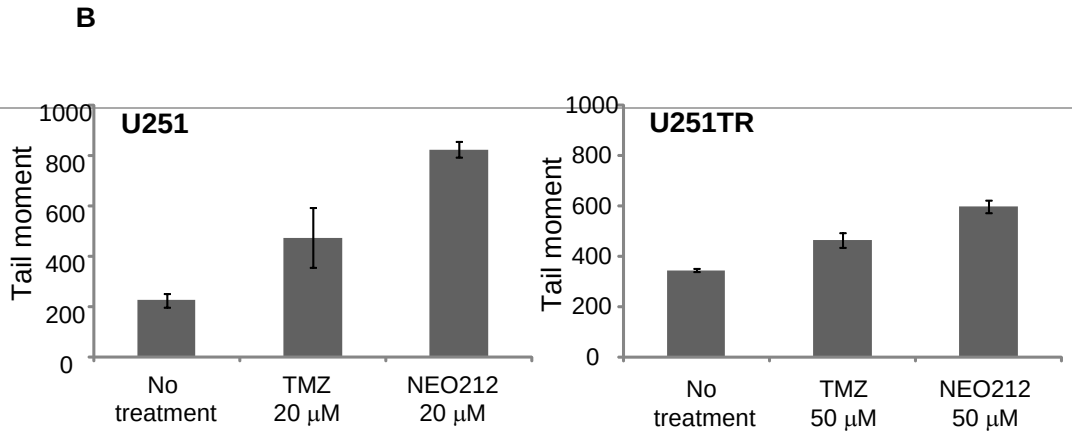
2. Inhibits DNA repair enzymes: MGMT (O^6 BG repair), base excision repair, mismatch repair

2. G2/M cell cycle inhibitor

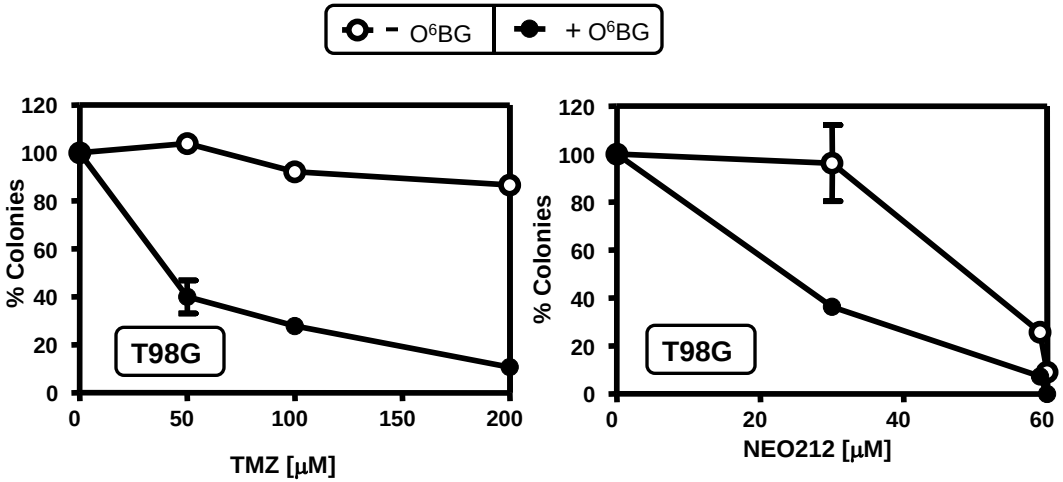
3. Induces endoplasmic reticulum stress (ER stress)

NEO 212 INDUCES DNA DAMAGE





NEO212 INHIBITS DNA REPAIR ENZYME MGMT



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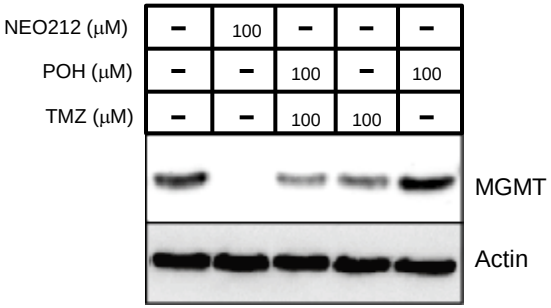
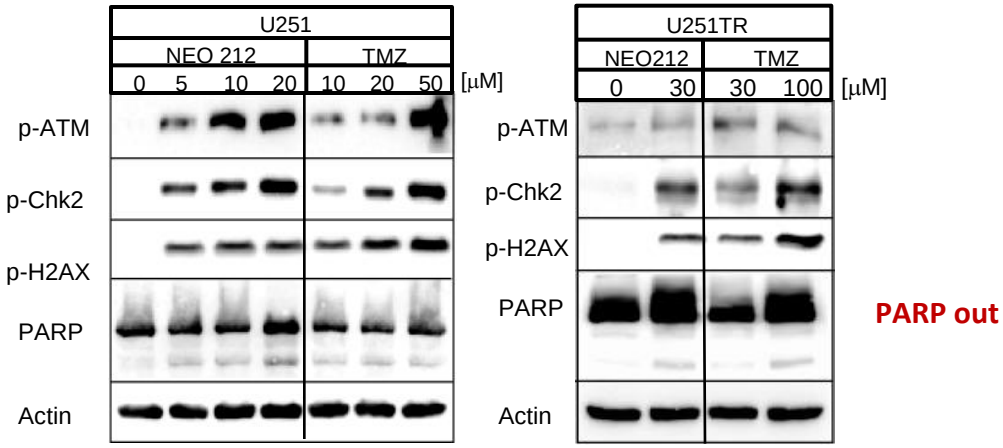


T98G

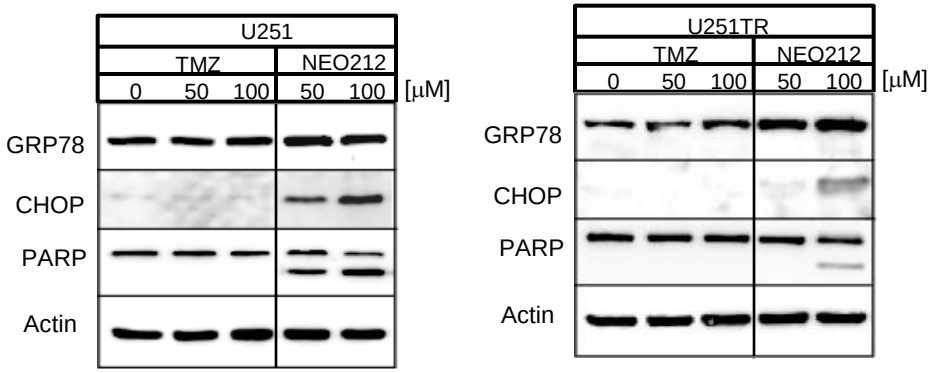
INDUCTION OF ER STRESS

C. DNA Damage

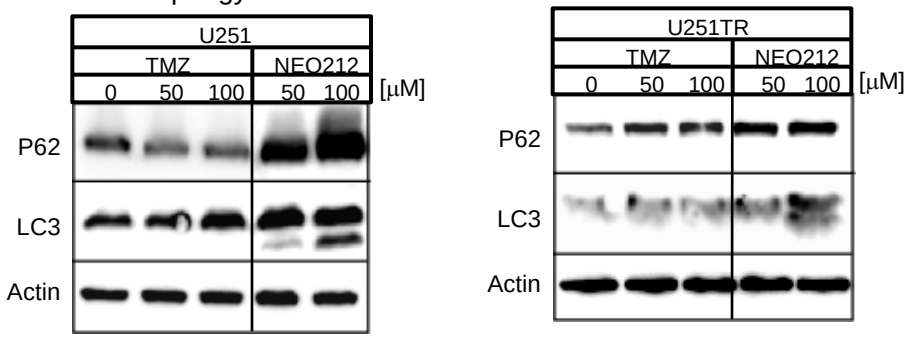


PARP out

D. ER Stress



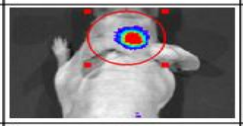
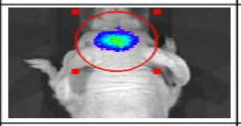
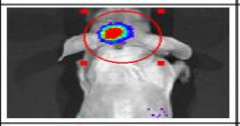
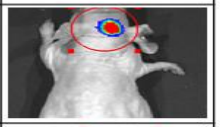
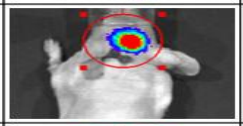
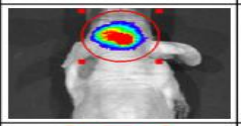
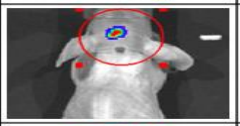
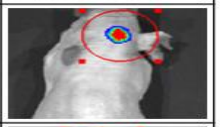
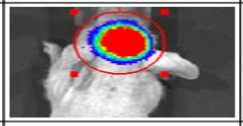
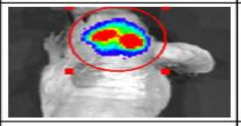
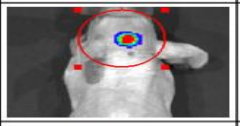
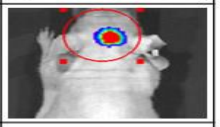
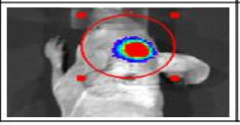
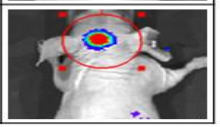
E. Autophagy



IN-VIVO DATA

NEO212 crosses the BBB and is effective on gliomas in vivo

A

Treatment / Post Implantation	Vehicle	TMZ (5 mg/kg)	TMZ-POH (5 mg/kg)	TMZ-POH (37.2 mg/kg)
Day 23				
Day 29				
Day 36				
Day 42	X Died	X Died		

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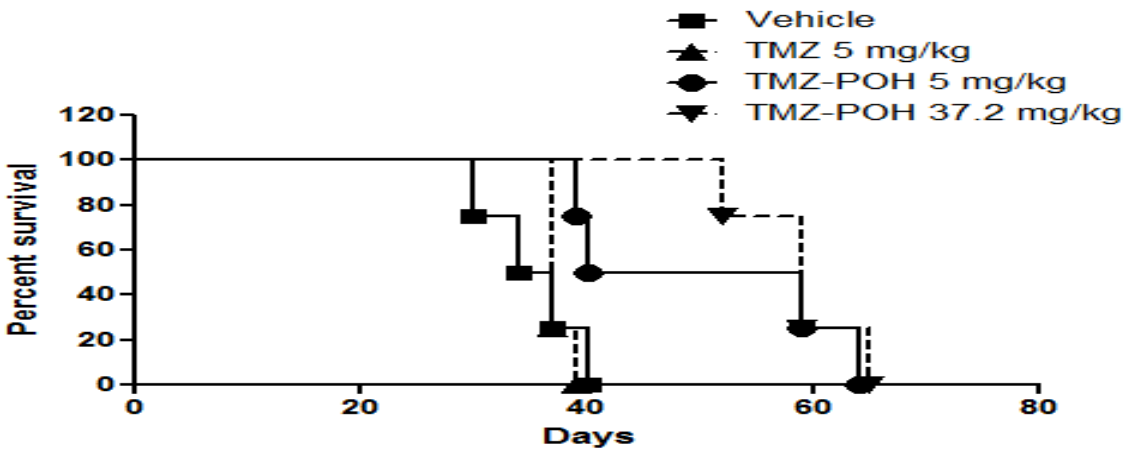
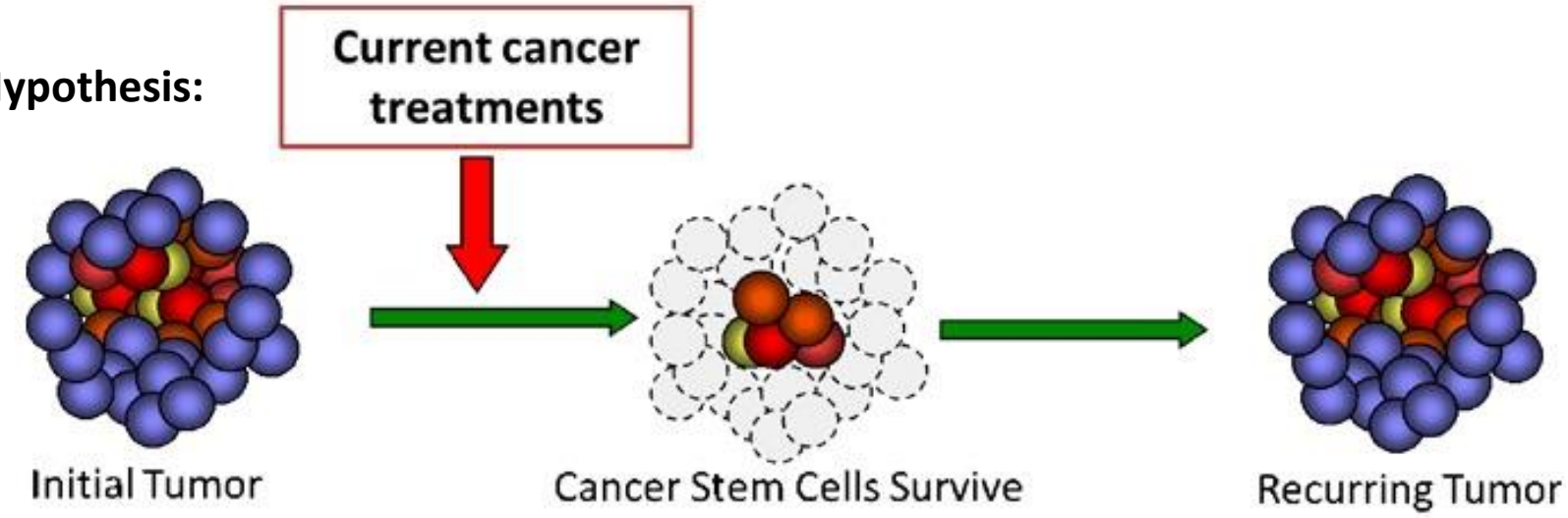


Current Hypothesis of Role of Cancer Stem Cells (CSC) In Tumor Recurrence

Hypothesis:



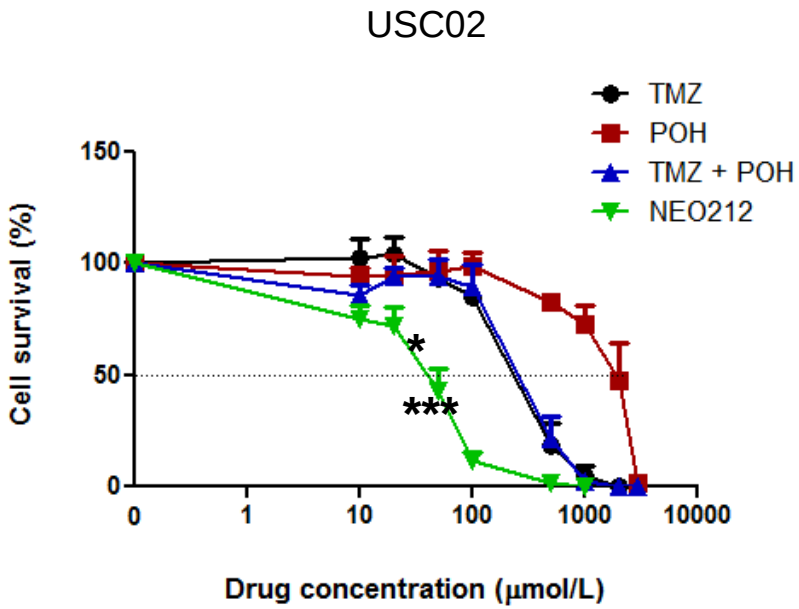
http://www.verastem.com/research/images/standard-approach.png

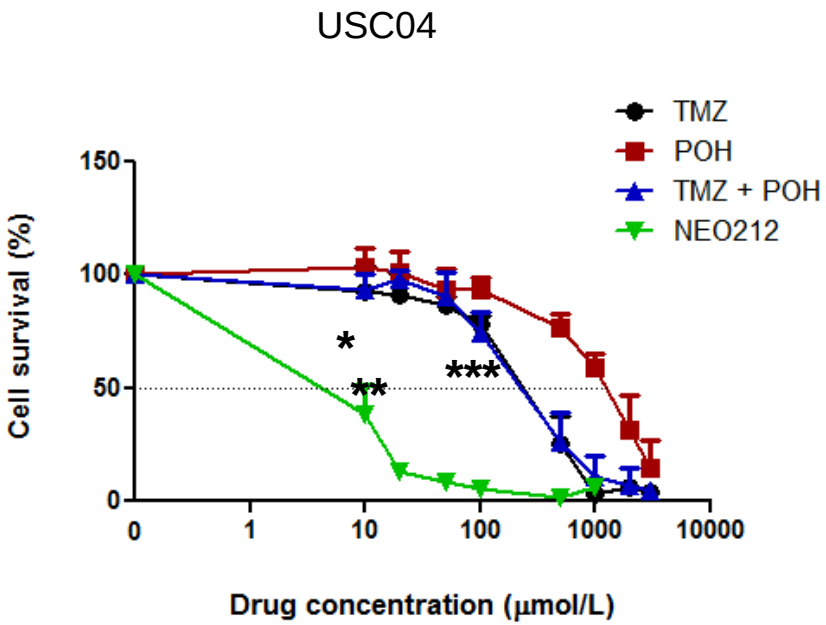
Summary – GSC Characteristics

	USC02	USC04
Self renewal in serum-free medium	✓	✓
Expression of stem cell markers	Sox 2 + Nestin + CD133 – c-Met +	Sox 2 – Nestin + CD133 + c-Met +
Resistance to Temozolomide	✓	✓
In vivo tumorigenicity	✓ 1000 cells	✓ 1000 cells
Gene signature	**Mesenchymal**	**Proneural**
mutation	**PTEN**	**p53**

Diverse GSC populations representing heterogeneity in human GBM tumors

NEO212 is a Novel Compound Withrespect to Cytotoxic activity

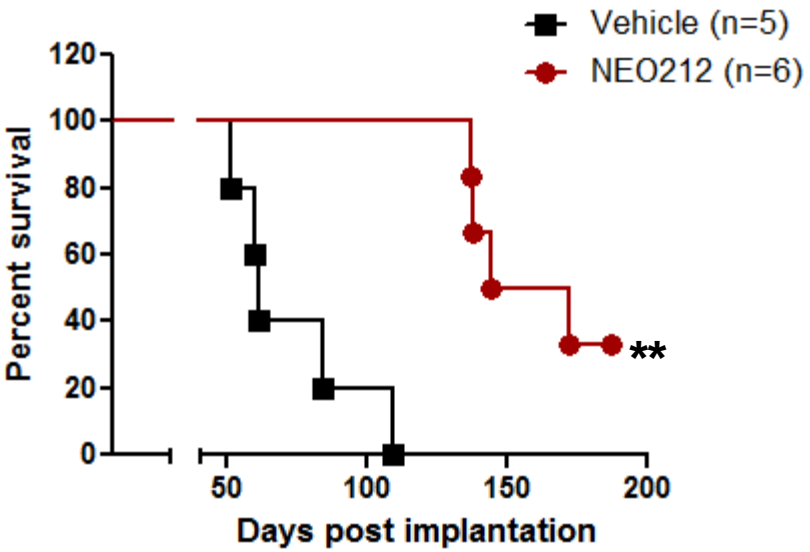




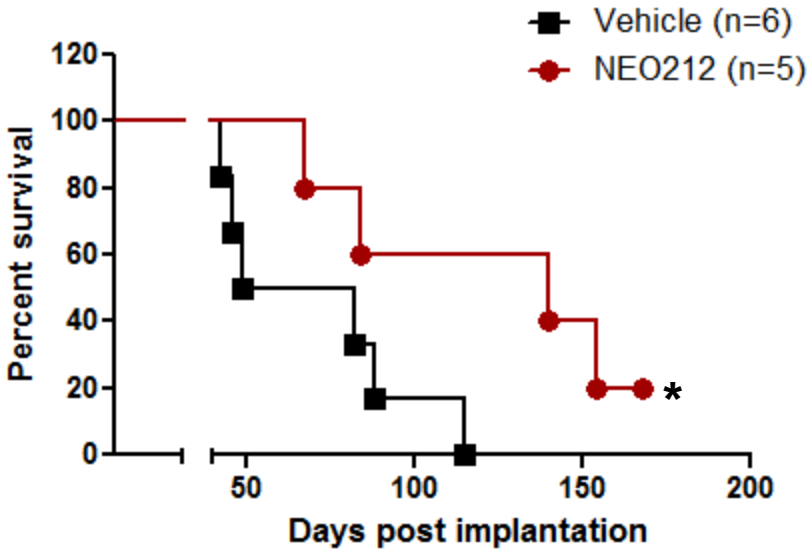
	IC50 (µmol/L)		Fold difference
	TMZ	NEO212	
USC02	317 ± 42	43 ± 9	7.4
USC04	323 ± 61	8 ± 2	40.4

A. **B.**

USC04 Proneural tumor



USC02 Mesenchymal tumor



Median survival: Vehicle – 61 days, NEO212 – 158 days

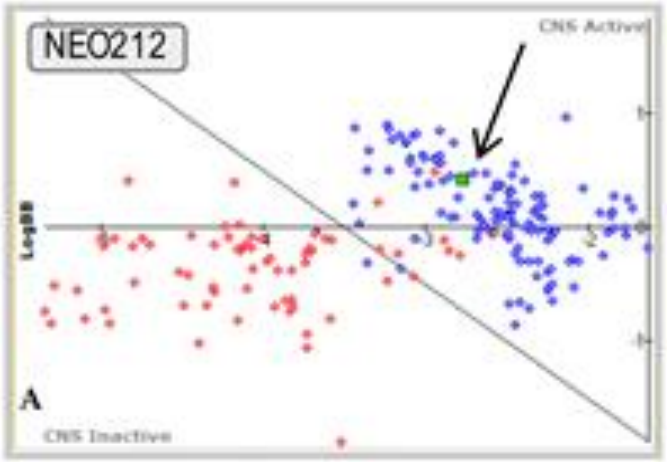
* 2/6 mice showed no signs of tumor growth at time of euthanization

Log Rank test, $p<0.005$

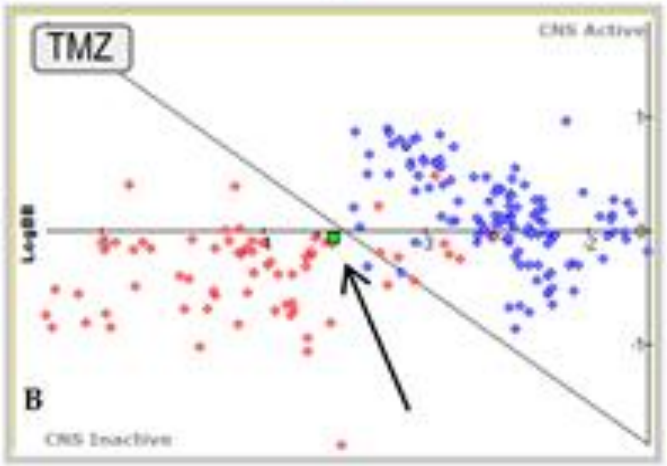
Pharmacokinetic Data

1. Crosses BBB better than TMZ
2. Better stability than TMZ

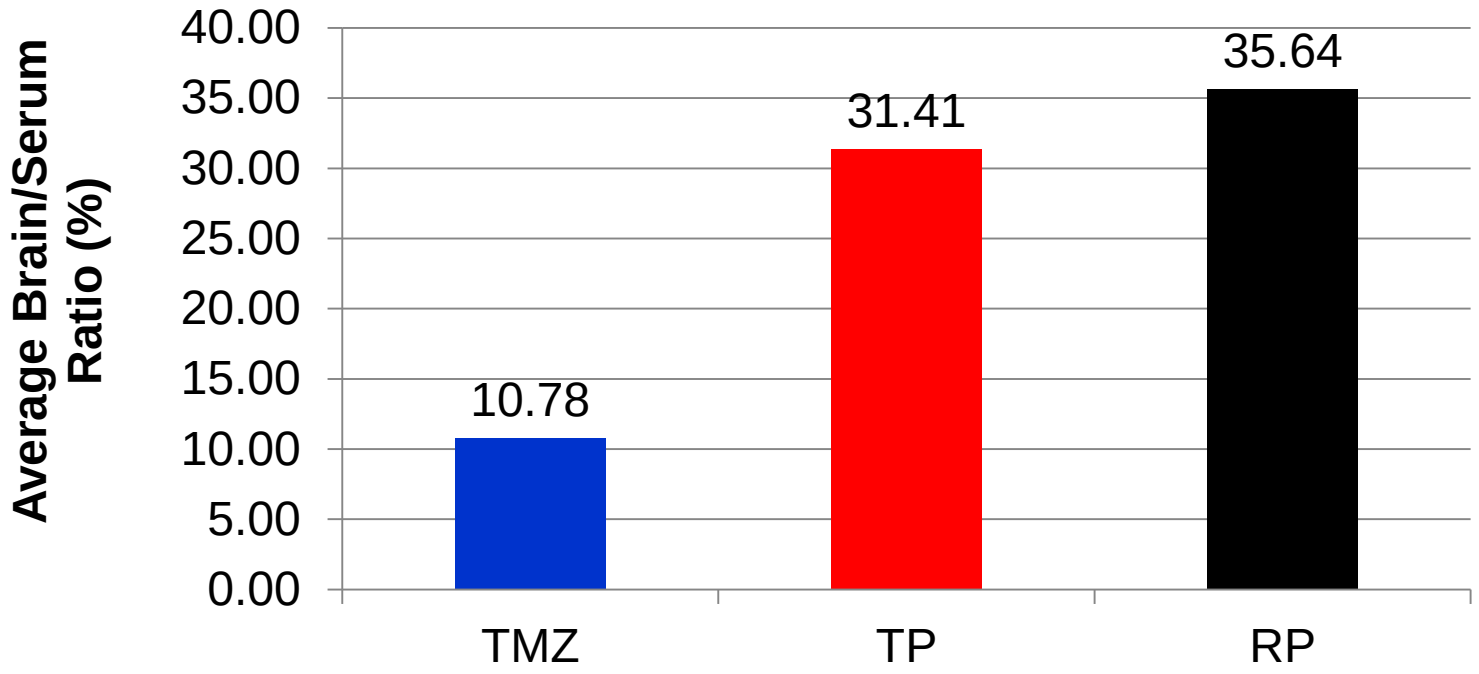
NEO 212 CROSSES BBB BETTER THAN TMZ



BBB transport parameters:
Rate of brain penetration:
LogPS: -2.0 more
Extent of brain penetration:
LogBB: 0.41 more
Brain/plasma equilibration rate:
Log(PS*fu, brain): -2.8
➔ Brain penetration sufficient for CNS activity.



BBB transport parameters:
Rate of brain penetration:
LogPS: -3.5 more
Extent of brain penetration:
LogBB: -0.07 more
Brain/plasma equilibration rate:
Log(PS*fu, brain): -3.6
➔ Probably low CNS activity due to low brain penetration.

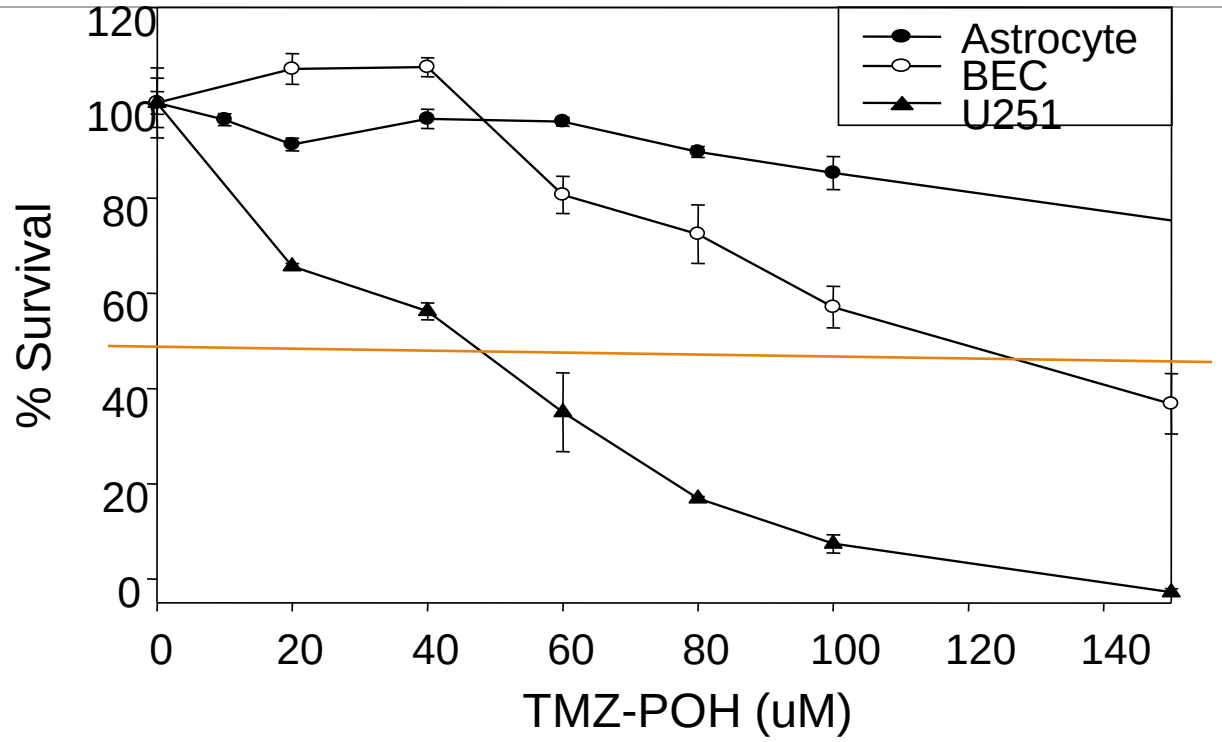


Summary: Conjugation of TMZ to POH enhances brain localization by ~3 fold

RP displays a similar level of brain to serum ratio indicating that RP is efficiently delivered to the brain

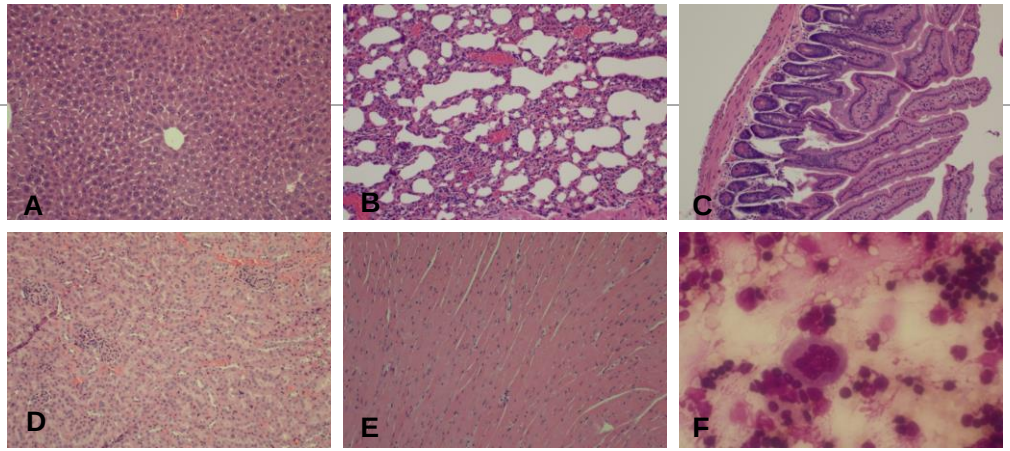
NEO212 TOXICITY DATA

Minimal Cytotoxic Effects of TMZ-POH on Astrocytes and Normal Brain Endothelial Cells (BEC)

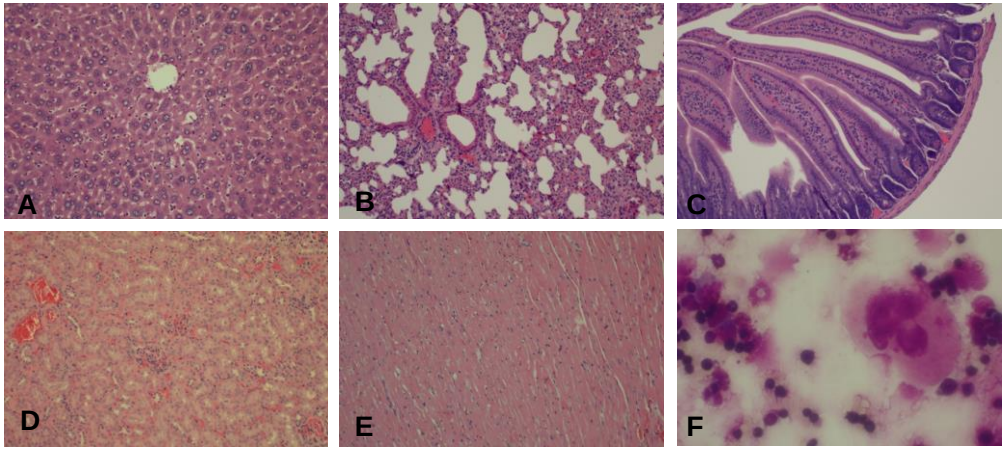


ORGAN TOXICITY

NEO212 Treated



Control



NEO212 Toxicity Studies

1. Charles Rivers-acute and chronic long term toxicity studies, large (beagles) and small animals (rats)

2. No acute toxicity on 5 day daily escalation up to 650 mg/kg.

3. Long term toxicity studies-5 day treatment period-MTD at 250 mg/kg-bone marrow toxicity. No significant chemistry or LFT changes.

4. In-vivo response at 25 mg/kg

UPCOMING NEO212 TRIAL

1. IND SUBMISSION
    a. GMP PRODUCTION CURRENTLY UNDERWAY
    b. TOXICITY STUDY-SMALL AND LARGE ANIMAL DONE
    c. CLINICAL TRIAL PROTOCOL for PHASE I/IIa to be written

SUMMARY

1. Background-creation of new drug from chemical conjugation of two old drugs

2. In-vitro Data: Functional Activity-NEO212 greater cytotoxicity greater TMZ or POH alone or in combination

3. Mechanism of Action: DNA damage, inhibition of DNA repair enzymes, ER stress

4. In-vivo Data: Better outcome data in small animal studies than TMZ

5. Pharmacokinetic Data: BBB penetrance improved; 3x higher concentration than TMZ

6. Toxicology Data: myelotoxicity at high concentrations (10x effective dose), safe on normal astrocytes, brain endothelial cells, other organs

7. Upcoming Phase I/IIa Trial-IND pending