A National Cancer Institute Designated Cancer Center

FRED & PAMELA BUFFETT CANCER CENTER

Repurposing FDA-Approved Drugs for Glioma Therapy

Nicole Shonka, MD
Professor
Division of Oncology & Hematology
nshonka@unmc.edu

Nebraska Medicine
BRAIN AND SPINE CANCER CENTER

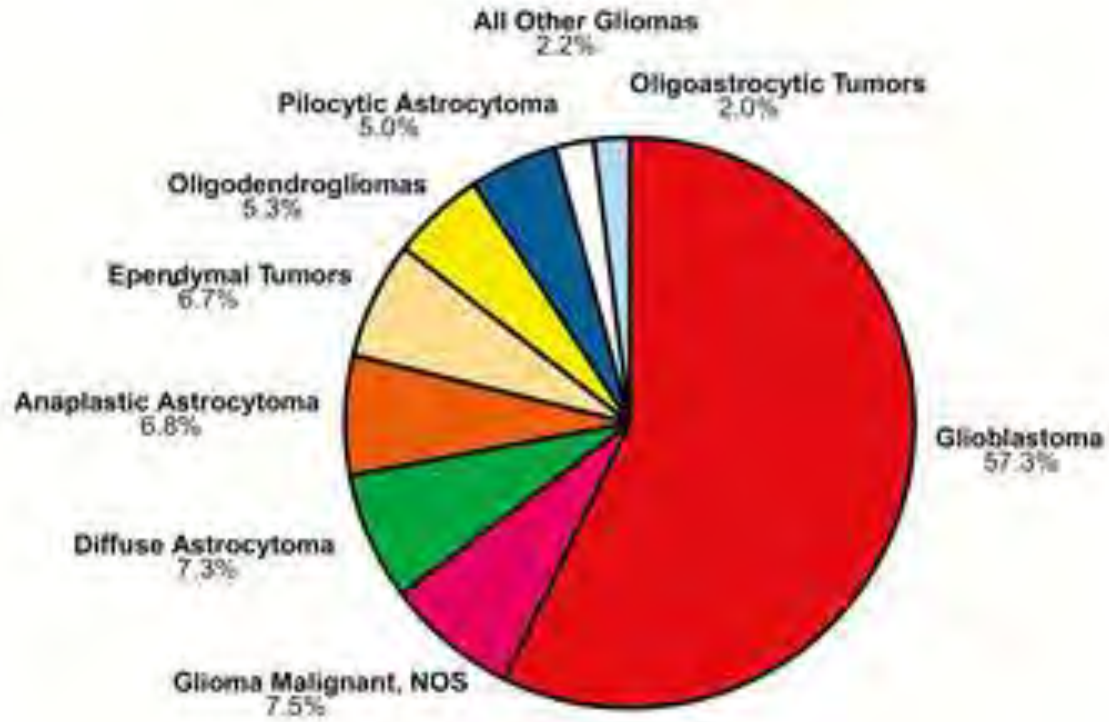
Disclosures

- Member, CNS tumors panel, National Comprehensive Cancer Network (NCCN)
- Consultant, GT Therapeutics

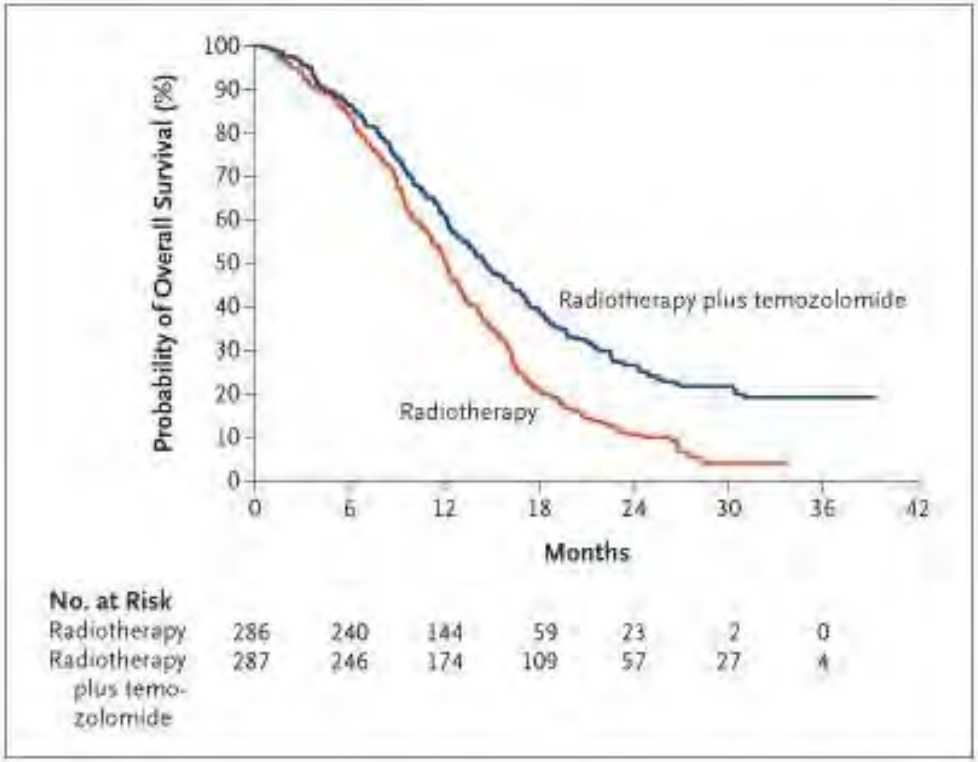
Outline

- Glioblastoma
- Connectivity Mapping
  - Abexinostat
  - Brompheniramine
  - Fedratinib

Glioblastoma is the most common malignant brain tumor in adults

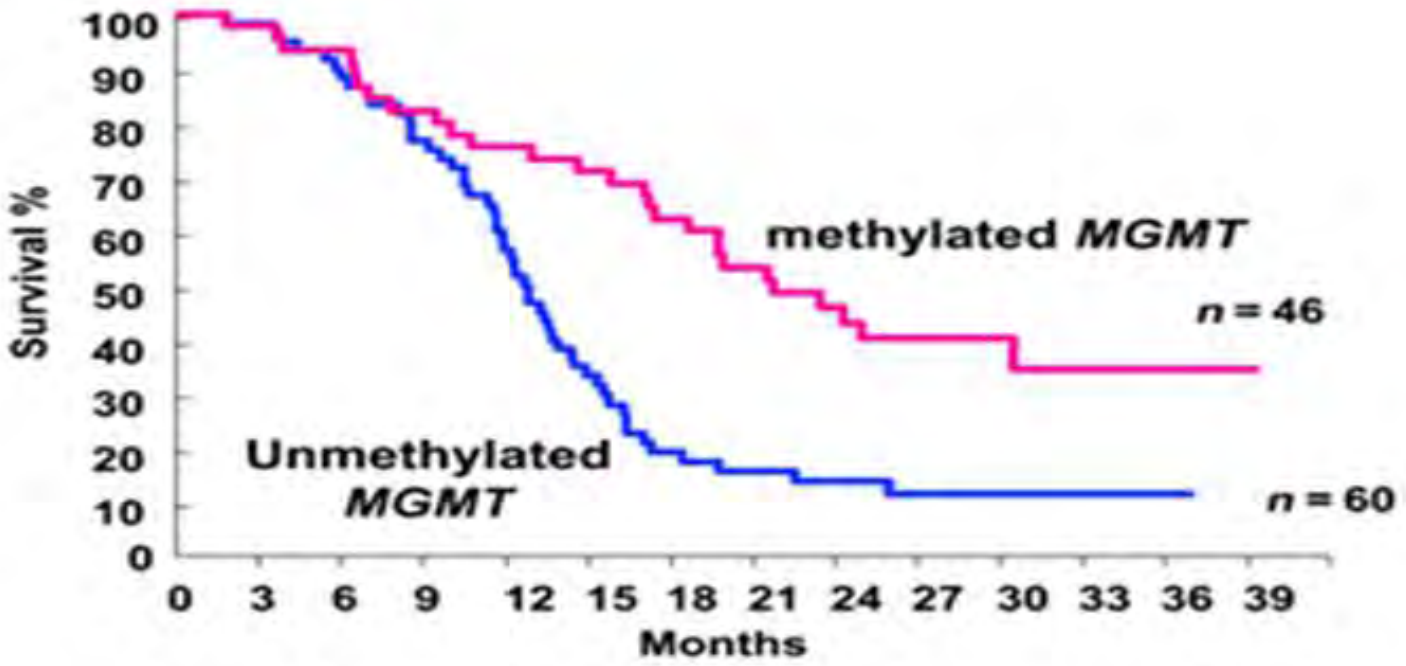


CBTRUS



Stupp R et al. N Engl J Med 2005;352:987-996

Glioblastoma and MGMT



NEJM 2005;352:997–1003

Options at progression

- Median 6-month PFS at progression is 15%

GLIOBLASTOMA

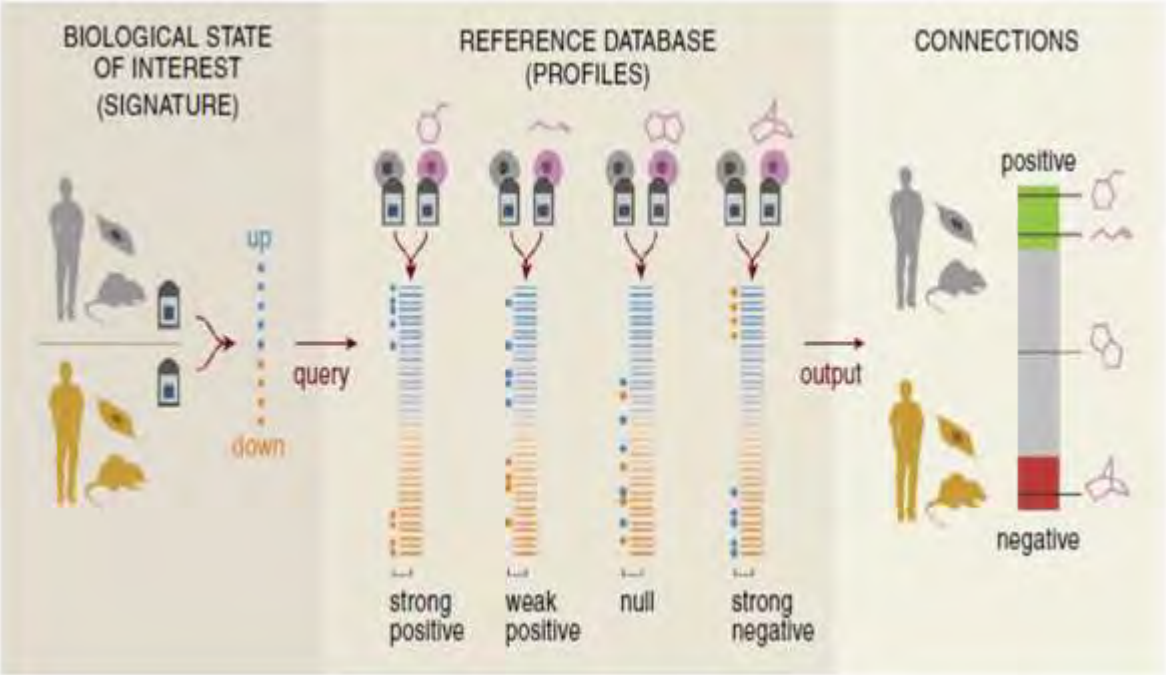
	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant Treatment	• RT with concurrent and adjuvant TMZ[43,44] ± TTF[45]	• None	• RT with concurrent and adjuvant TMZ (for patients age 70 or younger and KPS <60)[46] • TMZ (for patients with MGMT promoter-methylated tumors and KPS <60 or age >70 years and KPS ≥60)[43,47] • RT with concurrent and adjuvant lomustine and TMZ (for patients with MGMT promoter-methylated tumors, KPS ≥60, and age ≤70 years) (category 2B)[l,48]
Recurrence Therapy[h,m]	• Bevacizumab[i,k, 49-52] • TMZ[13,30,53,54] • Lomustine or carmustine[55-58] • PCV[a,59,60] • Regorafenib[61]	• Chemotherapy[j] + bevacizumab[i,k] ▸ Carmustine or lomustine + bevacizumab[i,k,62,63] ▸ TMZ + bevacizumab[i,k,64,65]	• If failure or intolerance to the preferred or other recommended regimens ▸ Etoposide (category 2B)[38] ▸ Platinum-based regimens[e, 40-42] (category 3) • *NTRK* gene fusion tumors ▸ Larotrectinib[18] ▸ Entrectinib[19] • *BRAF* V600E activation mutation ▸ BRAF/MEK inhibitors: ◊ Dabrafenib/trametinib[6,7] ◊ Vemurafenib/cobimetinib[8,9]

0.56-1.69%

https://www.nccn.org/professionals/physician_gls/pdf/cns_blocks.pdf

CONNECTIVITY MAPPING

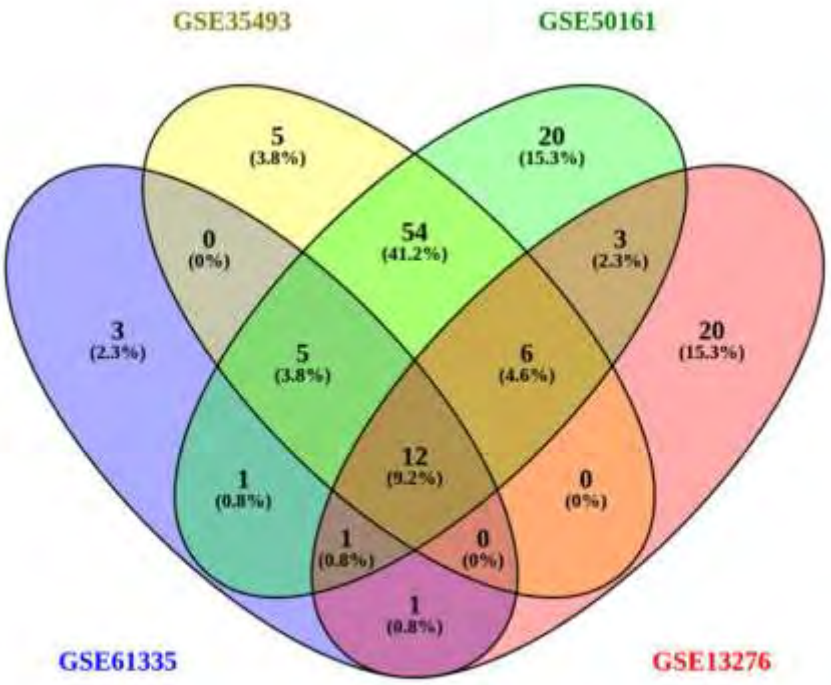
Connectivity Map (CMAP)



Lamb *et al*, 2006, Science **Pranitha**

CMAP Identified Top Candidates

Dataset code	Details		Platform
GSE61335	48	14	GPL570
GSE35493	12	8	GPL570
GSE50161	34	13	GPL570
GSE13276	5	3	GPL570
Total	99	38	



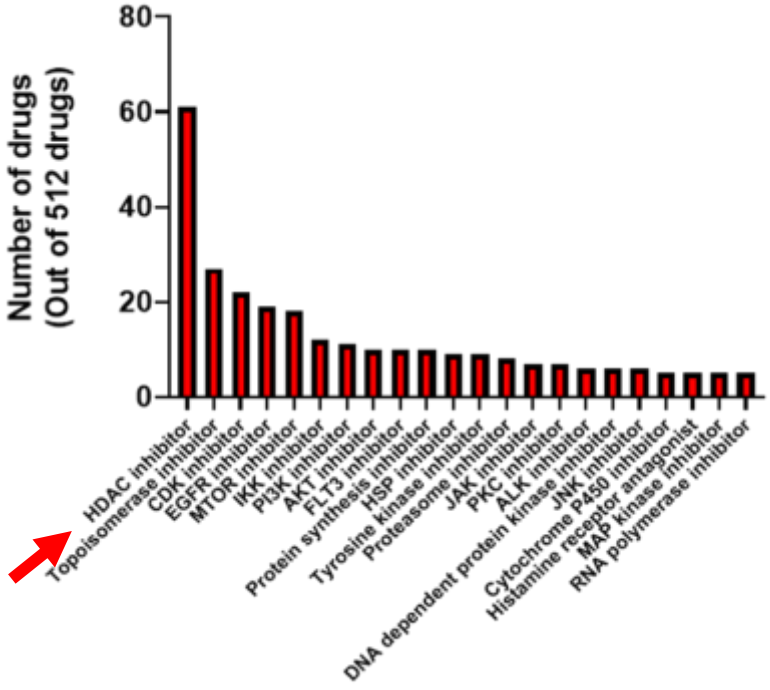
Drugs with -80 and above in each dataset were chosen and the 12 drugs common to each platform were selected

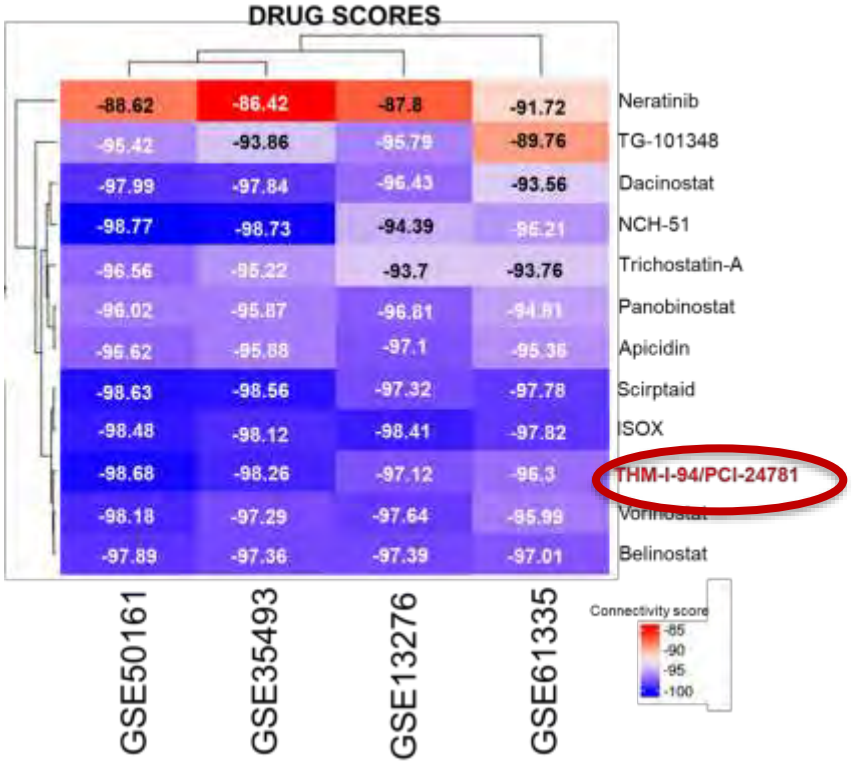
Pranitha

Nebraska Medicine
BRAIN AND SPINE CANCER CENTER

ABEXINOSTAT (PCI-24781)

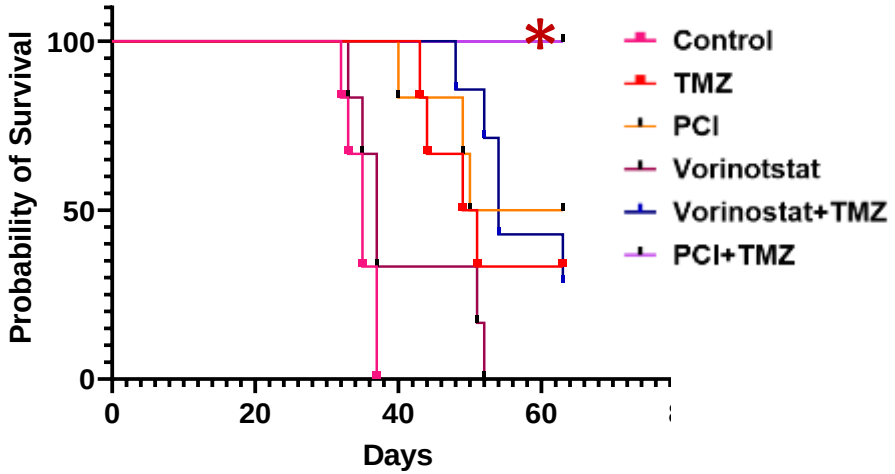
HDAC inhibitors



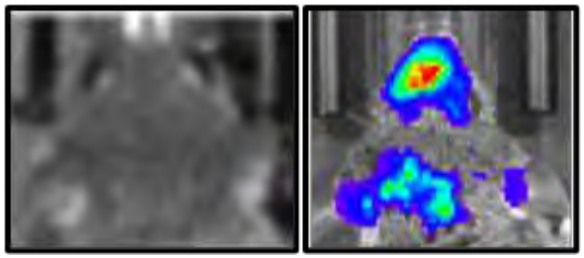


Abexinostat

- ✓ Specificity that matches GBM = HDACs 1 & 2, not HDAC11
- ✓ Induces cell death agnostic of p53, EGFRvIII and MGMT
- ✓ Decreases DNA repair machinery proteins Rad51, CHK1 and BRCA1
- ✓ Synergy with TMZ in p53 (mutated/wild type); MGMT (methylated/ un-methylated); GBM cells
- ✓ Increased OS in orthograft models (below)



Abexinostat decreases tumor burden in our GBM mouse model



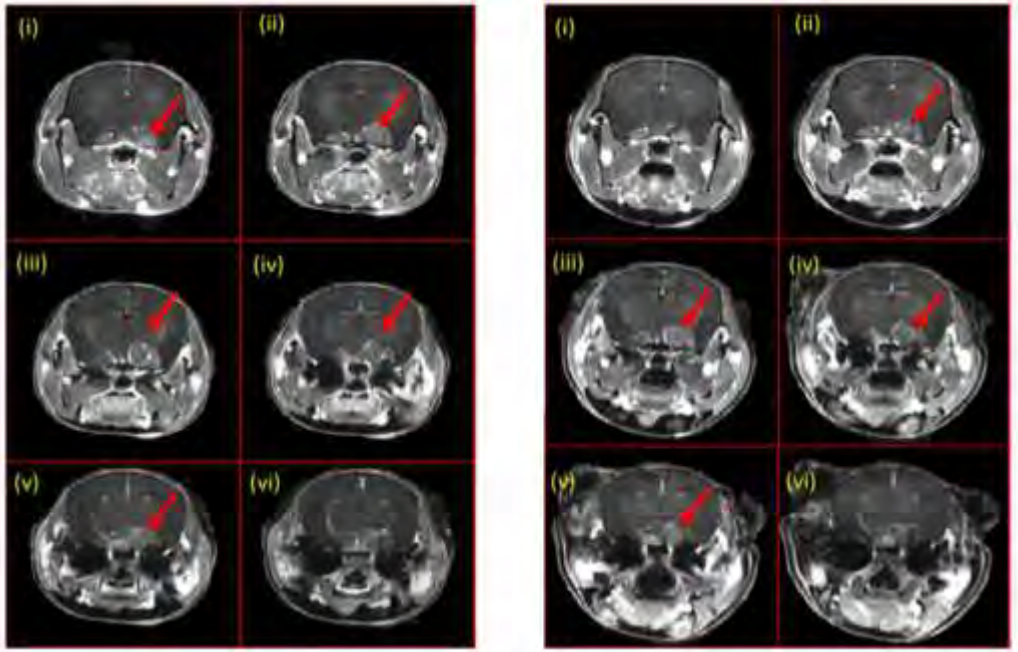
ROSA Luc & GFAP Cre

EGFRvIII; p16-/- ;ROSA Luc & GFAP Cre

Treatment

4 weeks of 5-days weekly PCI-24781 (12.5 mg/kg BW, BID, PO).

PTEN$^{+/-}$; EGFRvIII; p16$^{+/-}$ & GFAP Cre



Prior to treatment

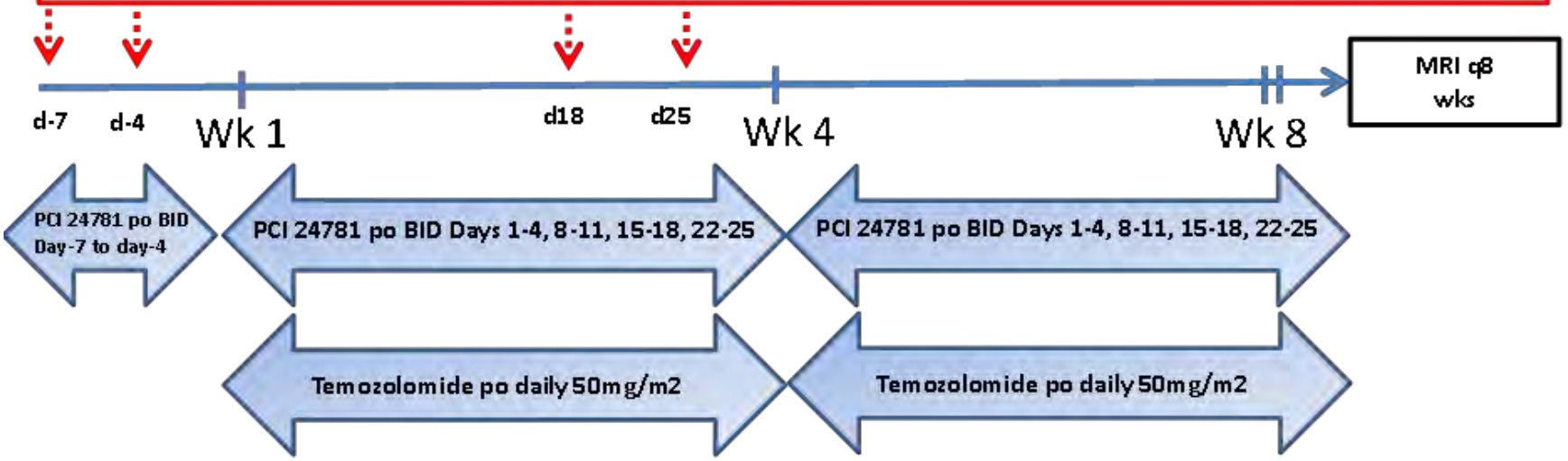
After 4 wks PCI-24781

Recurrent Grade 3 or 4 Glioma

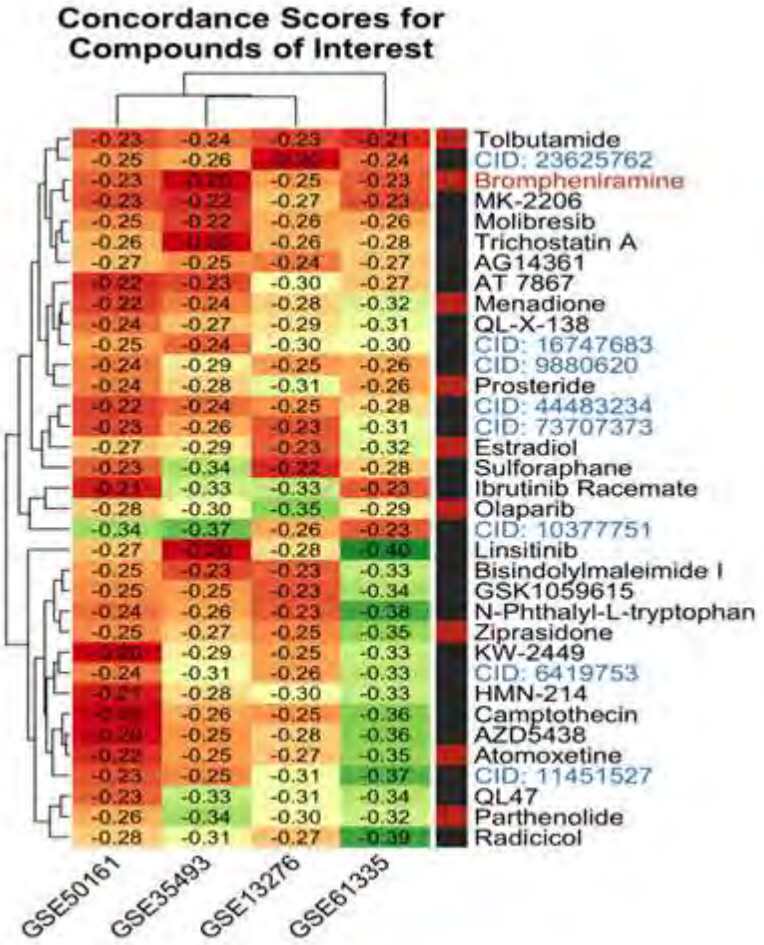
Schema

Subjects ≥19 y/o with recurrent (after RT and Temozolomide) grade III or IV glioma with ECOG of 0-2, excluding those on EIAEDs

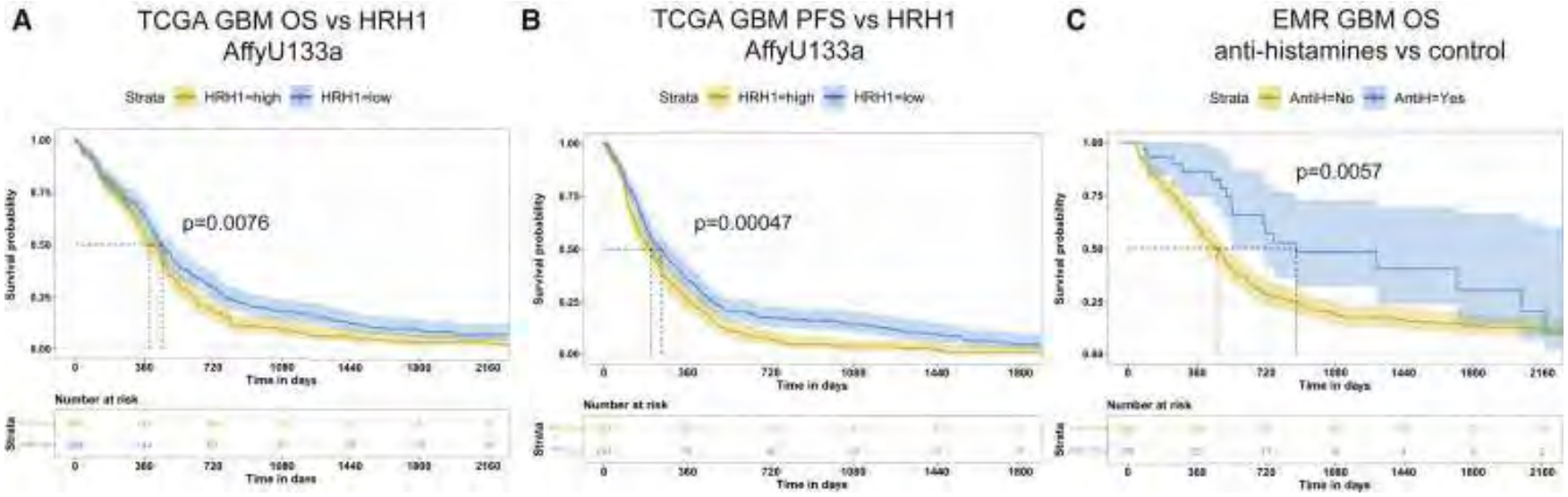
CBC, CMP, LDH, Mg, Phos Q2w
PBMCs at baseline (pre-dose day -7) and 4 hours after second dose on Cy 1 day 25 for acetylation of histones H3 and H4
Exosomes at baseline (pre-dose day -7)-and 4 hours after second dose on Cy 1 day 25 for acetylation of histones H3 and H4
PK samples on Day -7, Day -4 and Cy 1 Day 25: Predose, 0.5, 1, 2, and 4 hours after first dose and 0.5, 1, 2 and 4 hours after second dose



BROMPHENIRAMINE



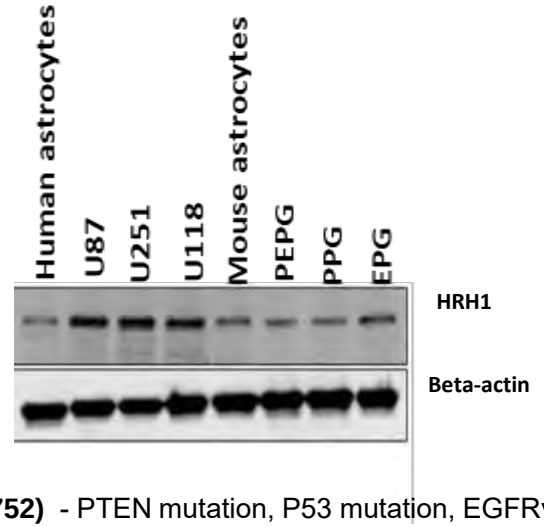
Antihistamine during treatment

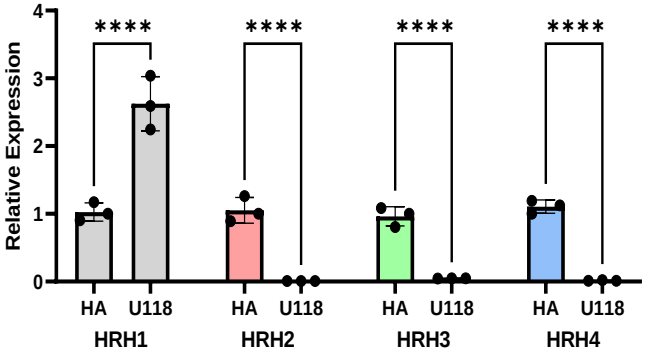


Improved PFS and OS

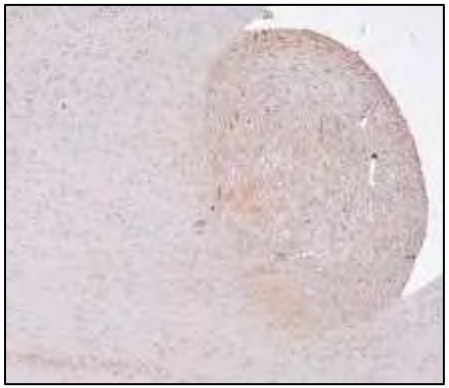
Chryplewicz et. al.,cancer cell, doi.org/10.1016/j.ccell.2022.08.014

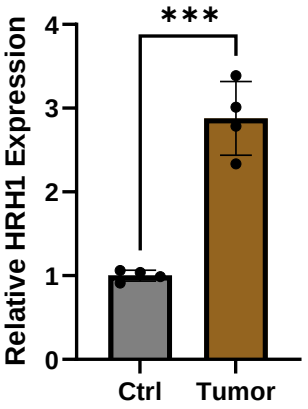
HRH1 is highly expressed on GBM compared to normal astrocytes



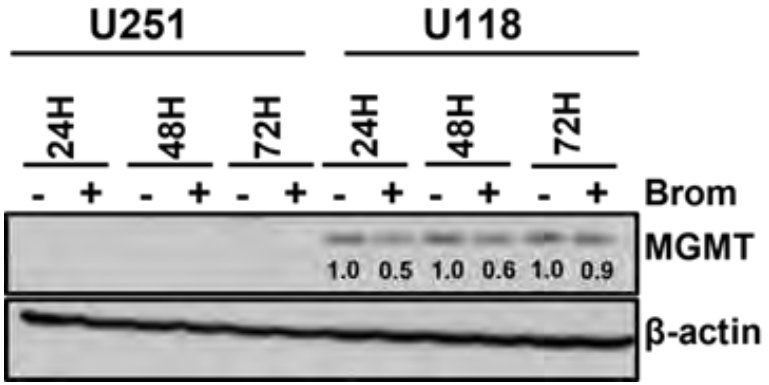


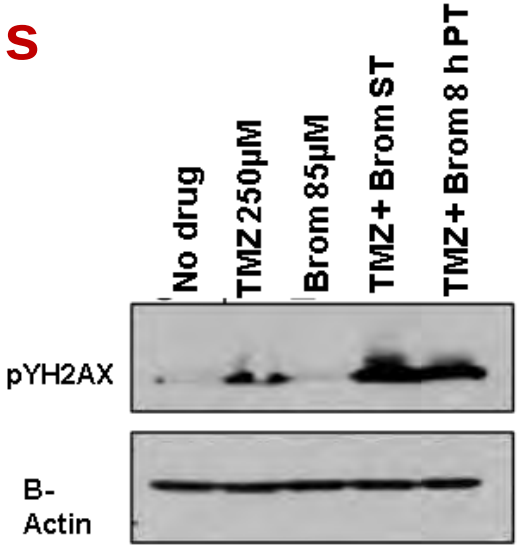
PEPG (752) - PTEN mutation, P53 mutation, EGFRvIII, GFAP-Cre
PPG (905) -PTEN mutation, P53 mutation, GFAP-Cre
EPG (146) - EGFRvIII, p16 deletion, GFAP-Cre

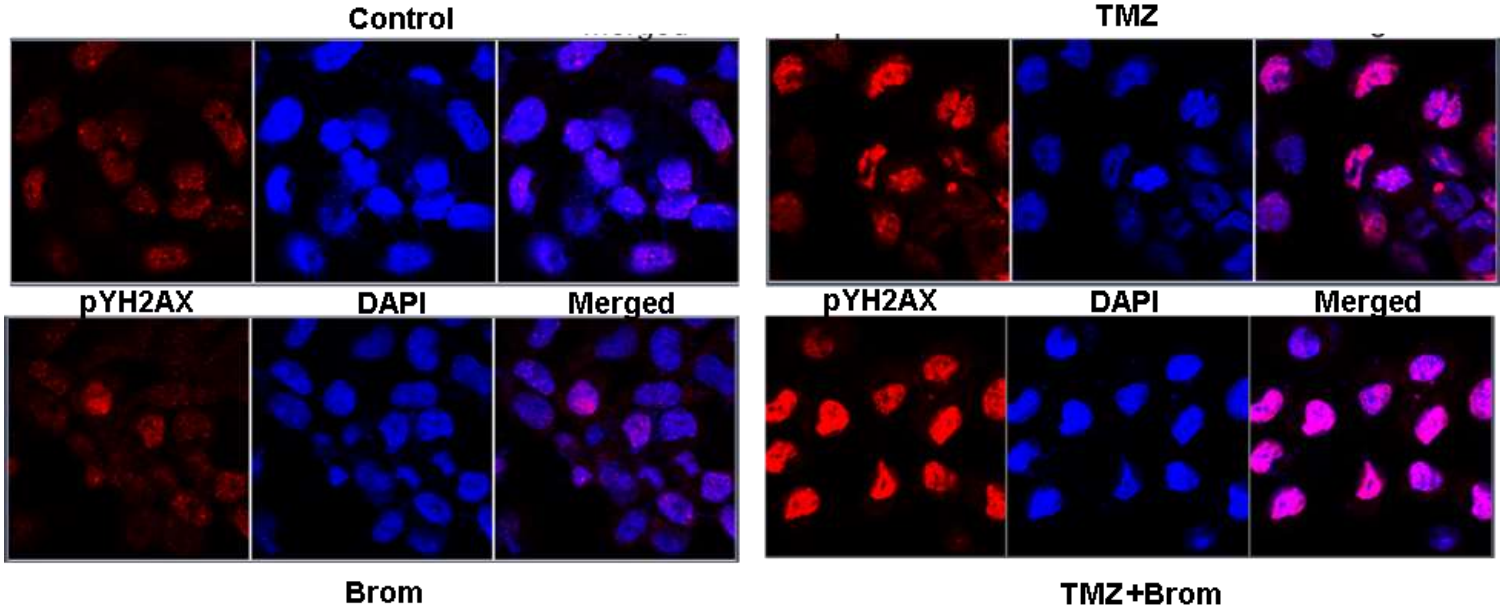




Combination treatment decreases MGMT expression and increases DNA damage in U118 cells

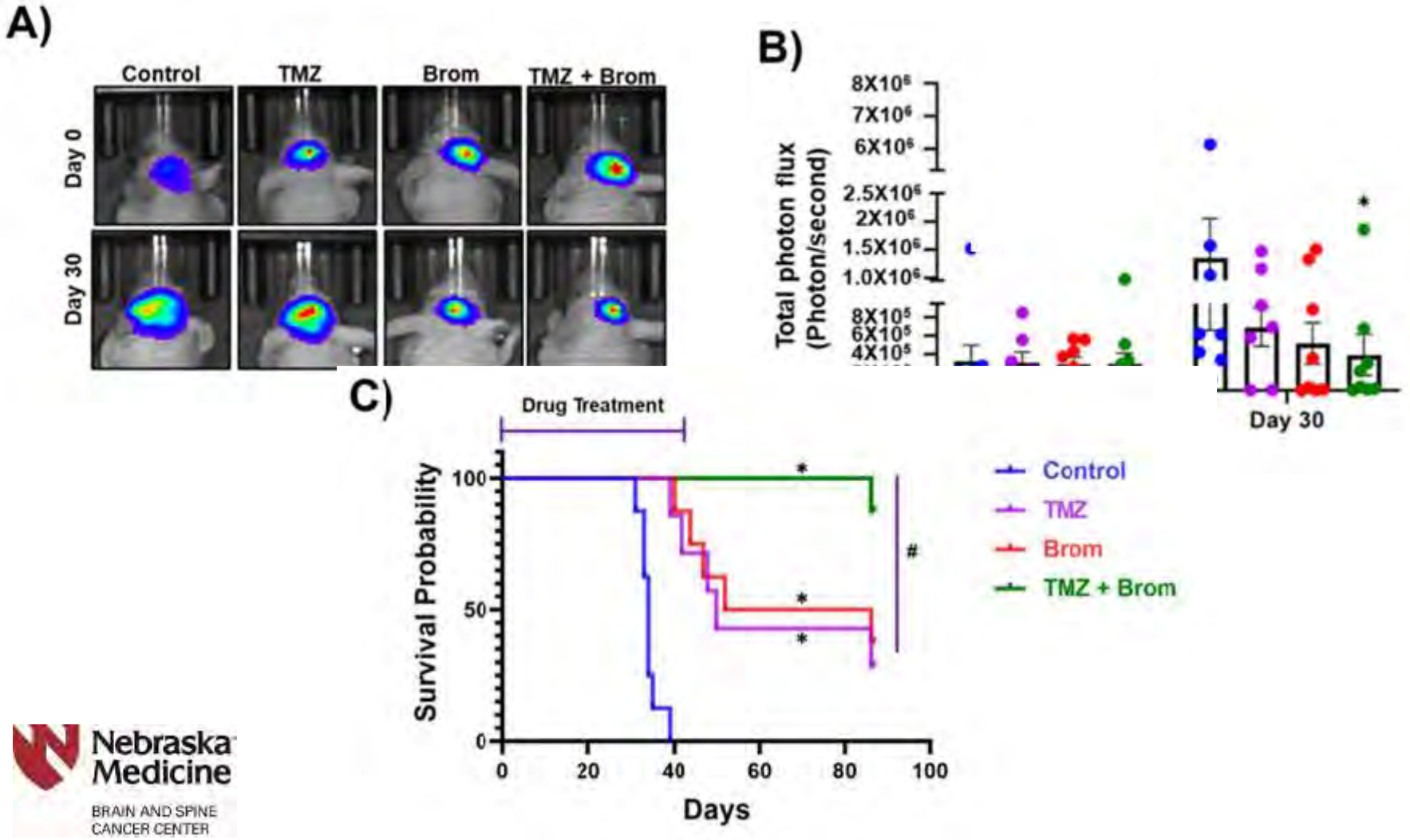




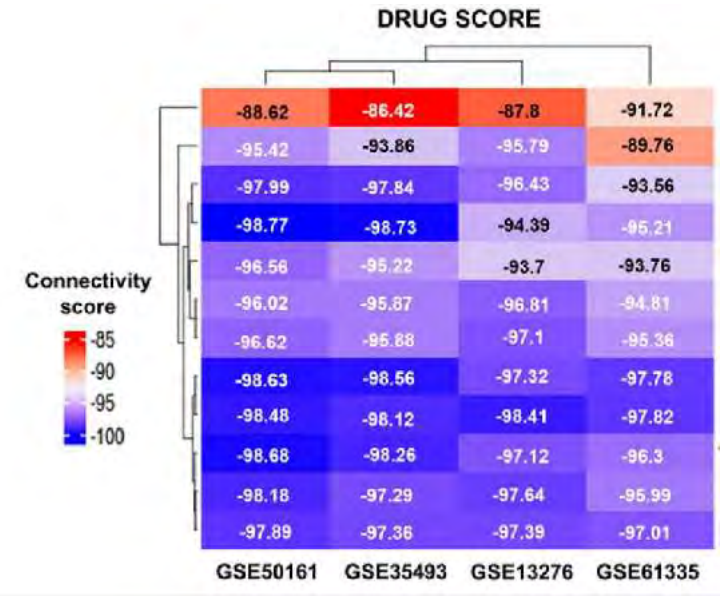


Nebraska Medicine
BRAIN AND SPINE CANCER CENTER

TMZ + Brom decreases tumor burden and significantly improves survival in vivo



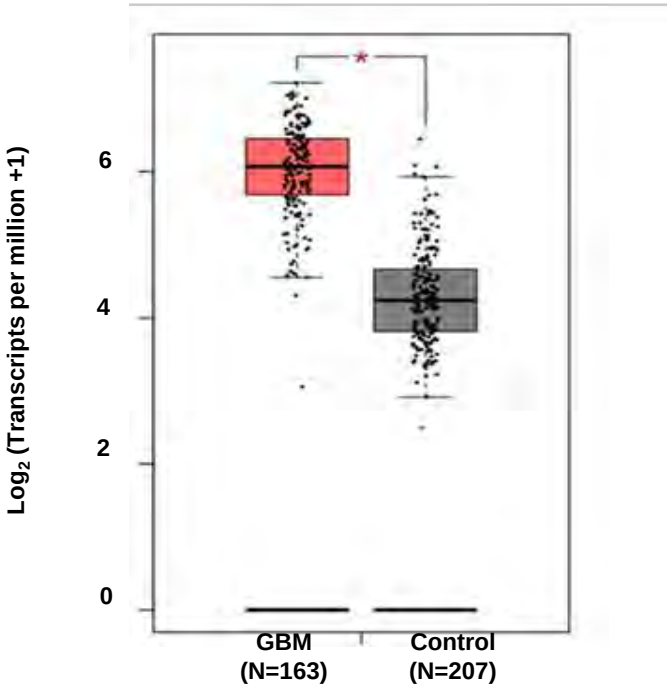
FEDRATINIB


DRUG SCORE
-88.62 -86.42 -87.8 -91.72
-95.42 -93.86 -95.79 -89.76
-97.99 -97.84 -96.43 -93.56
-98.77 -98.73 -94.39 -95.21
-96.56 -95.22 -93.7 -93.76
-96.02 -95.87 -96.81 -94.81
-96.62 -95.88 -97.1 -95.36
-98.63 -98.56 -97.32 -97.78
-98.48 -98.12 -98.41 -97.82
-98.68 -98.26 -97.12 -96.3
-98.18 -97.29 -97.64 -95.99
-97.89 -97.36 -97.39 -97.01
GSE50161 GSE35493 GSE13276 GSE61335
Connectivity score
-85
-90
-95
-100
Neratinib
TG-101348/Fedratinib
Dacinostat
NCH-51
Trichostatin-A
Panobinostat
Apicidin
Scirptaid
ISOX
THM-I-94/PCI-24781
Vorinostat
Bellinostat

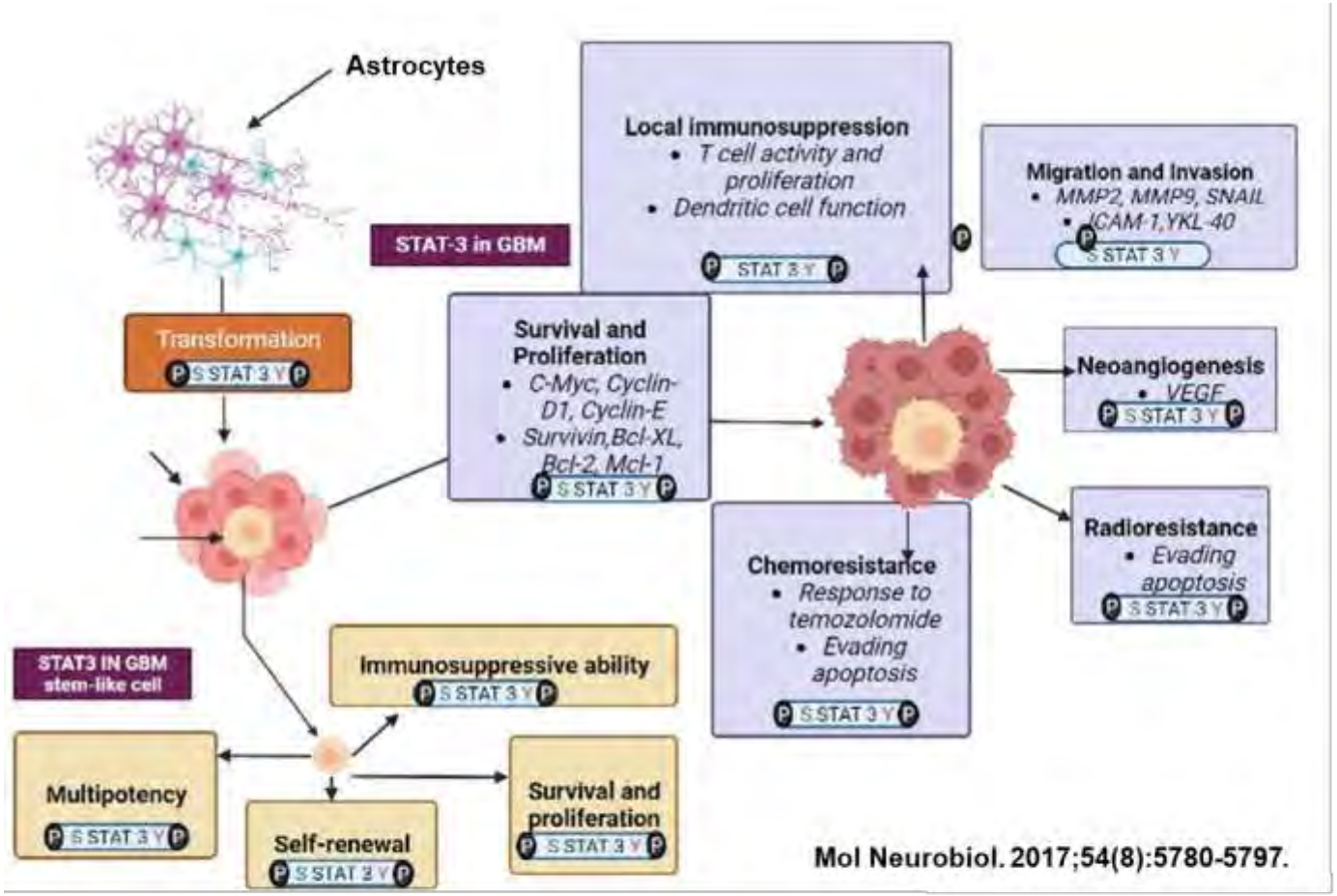
Role of JAK2/STAT3 in Glioblastoma

- JAK/ STAT pathway established in GBM

- STAT3 expression and p-STAT3 signaling highly activated in human GBM
- promotes aggressive phenotype and therapy resistance

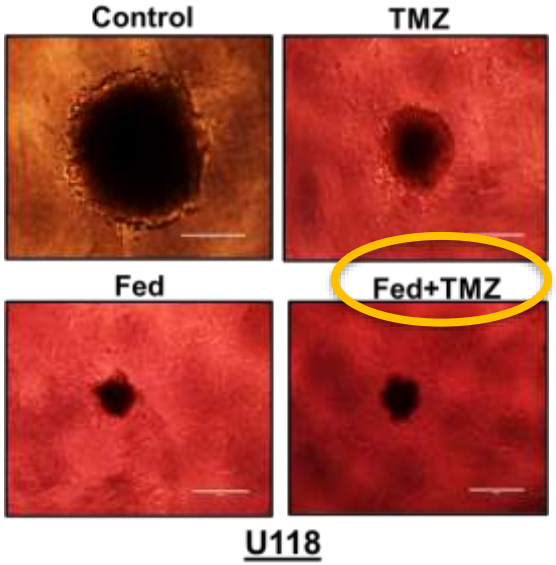


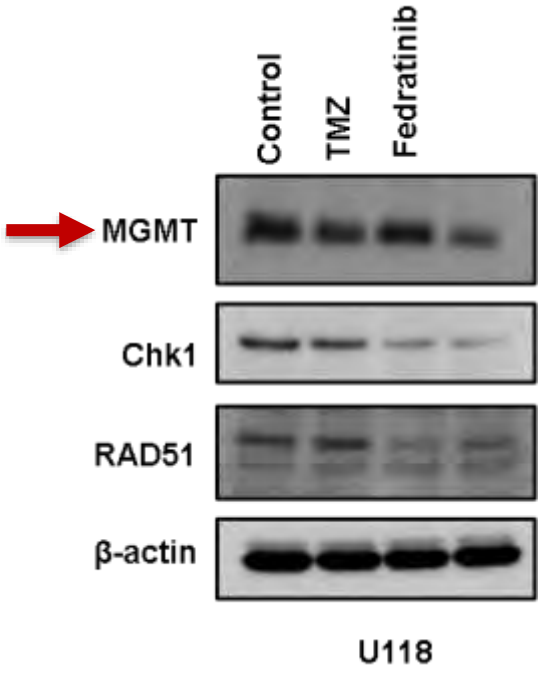
STAT3 pathway activation promotes GBM tumorigenesis



GBM cell line studies

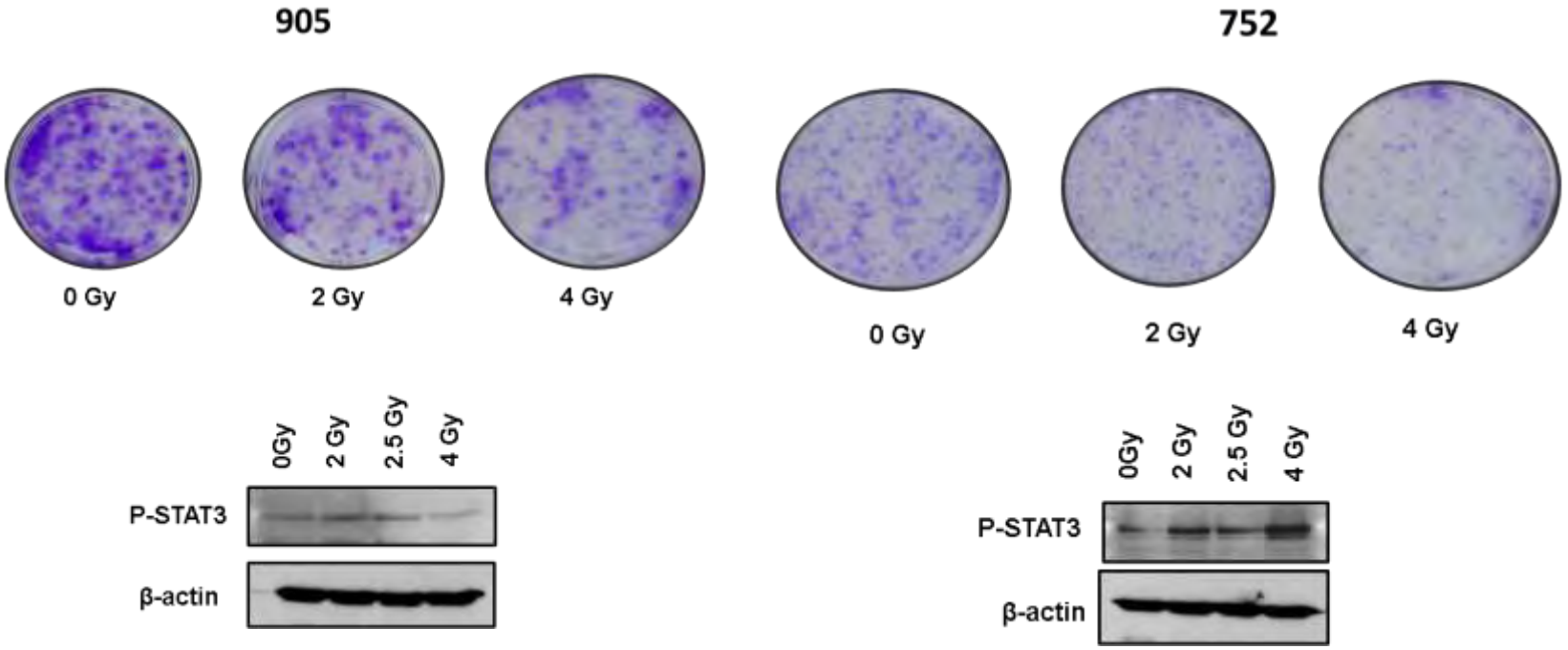
- Fed+TMZ decr proliferation in U251 and U118 GBM cells and increased apoptosis
- Fed+TMZ decreased STAT3 activation
- Fed+TMZ decreased spheroid forming invasive capacity of cell lines*
- Fed+TMZ decreased proliferation and stemness markers in mouse syngeneic cell lines
- Fed+TMZ decreased DNA repair enzymes*





Radiation increases STAT3 activation

- Syngeneic lines



Acknowledgements

Funding:

- **Nancy Langford and the William Langford Creative Mind Fund**
- **Department of Internal Medicine**
  Lynell Klassen & Debra Romberger
- **Nebraska Dept of Health & Human Services**
- **National Institute of Health** (1R01CA273319-01)

Direction and mentorship:

- **Surinder Batra**

Maneesh Jain
Apar Ganti
Raghupathy Vengoji
Moorthy Ponnusamy
Kavita Mallya
Pranita Atri
Poonam Yadav
Indumati Ramireddy
Zahraa Alsafwani
Caroline Davidson
Balaji Perumalsamy

<u>Animal imaging</u>
Yutong Li

<u>Brain & Spine Cancer Center</u>
Michele Aizenberg
Chi (Kevin) Zhang
Matthew White
Jie Chen
Sahara Cathcart
Nick Kavish

A National Cancer Institute Designated Cancer Center

FRED & PAMELA
BUFFETT CANCER CENTER

Nebraska Medicine

BRAIN AND SPINE CANCER CENTER