Novel Targets And Strategies in Glioblastomas

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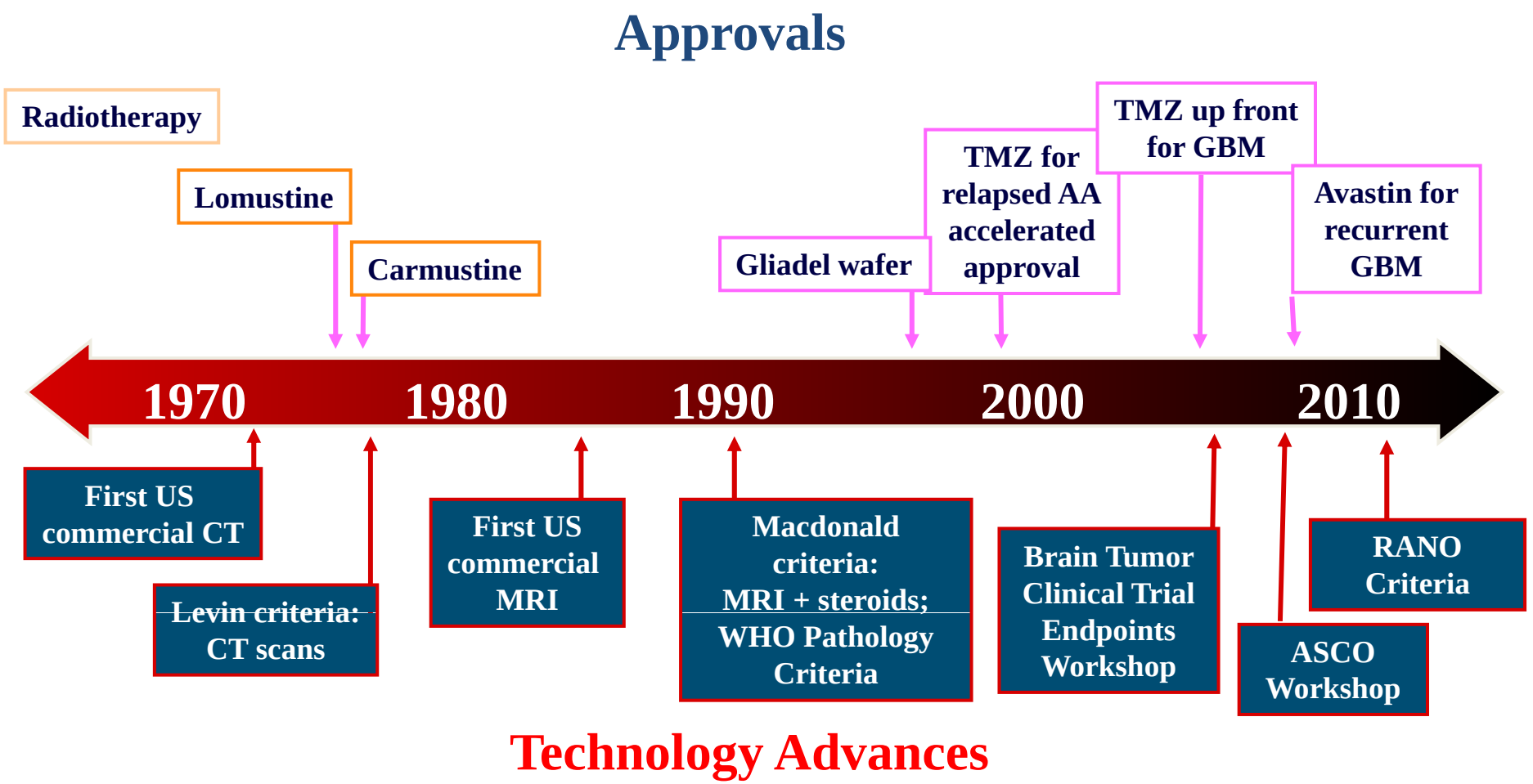
DISCLOSURES

- **Research Support**
  - Amgen
  - Astra Zeneca
  - Boehringer Ingelheim
  - Esai
  - Exelixis
  - Genentech/Roche
  - Geron
  - Medimmune
  - Merck
  - Novartis
  - Sanofi-Aventis
  - Vascular Biogenics
- **Advisory Board**
  - Merck
  - Novartis
  - Vascular Biogenic
  - NeOnc Inc
- **Speaker**
  - Merck
  - Genentech/Roche

Treatment of High-Grade Gliomas

Milestones in Neuro-Oncology



AA=anaplastic astrocytoma; CT=computed tomography; GBM=glioblastoma multiforme; MRI=magnetic resonance imaging; RANO=Response Assessment in Neuro-Oncology.

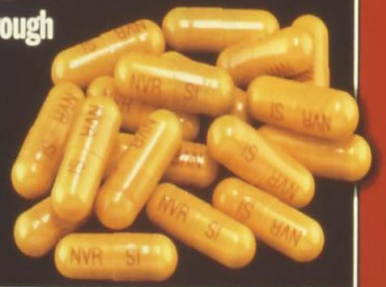
MAY 28, 2001

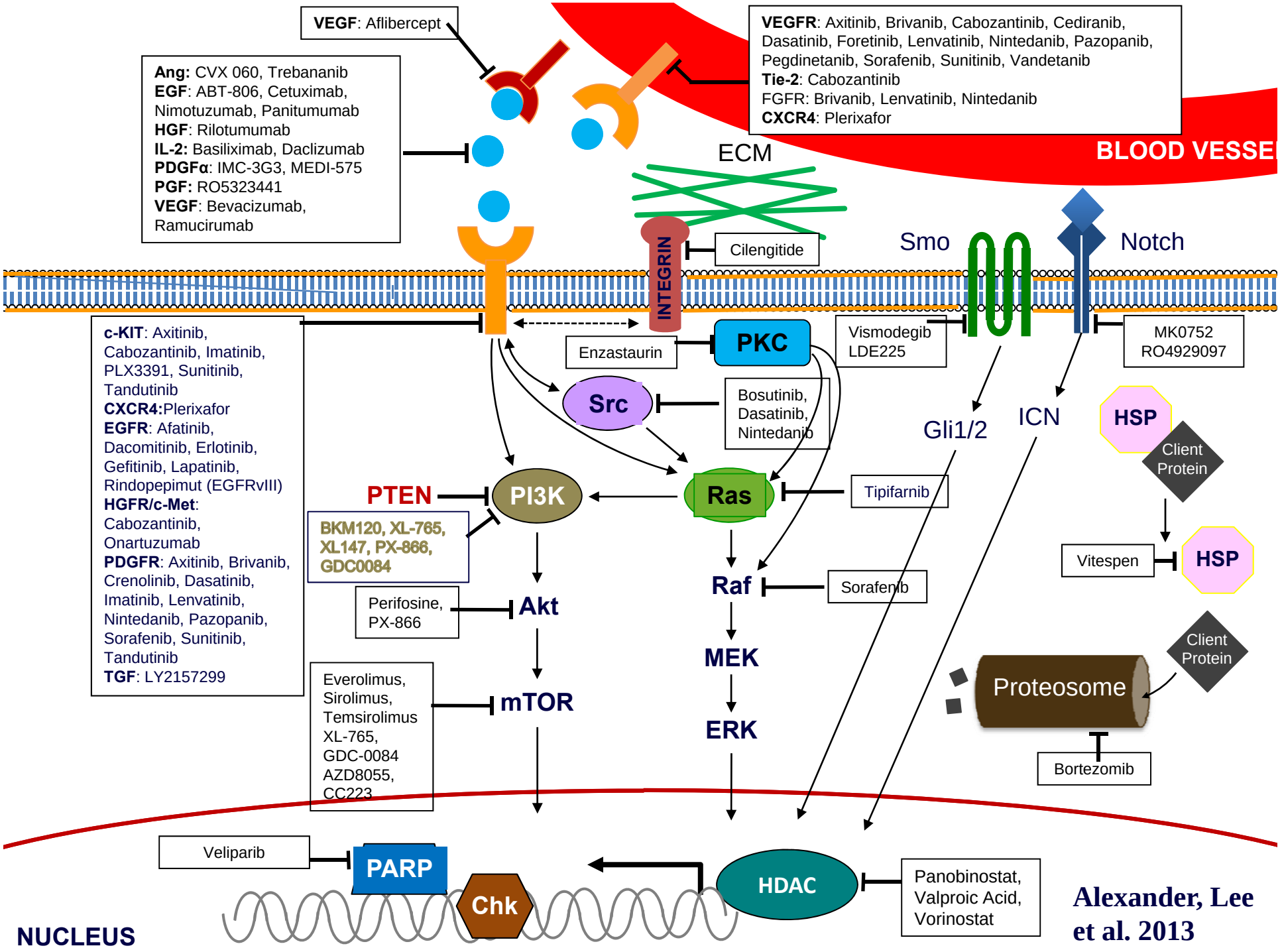
www.time.com AOL Keyword: TIME

TIME

THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?




VEGF: Aflibercept
Ang: CVX 060, Trebananib
EGF: ABT-806, Cetuximab, Nimotuzumab, Panitumumab
HGF: Rilotumumab
IL-2: Basiliximab, Daclizumab
PDGFα: IMC-3G3, MEDI-575
PGF: RO5323441
VEGF: Bevacizumab, Ramucirumab
VEGFR: Axitinib, Brivanib, Cabozantinib, Cediranib, Dasatinib, Foretinib, Lenvatinib, Nintedanib, Pazopanib, Pegdinetanib, Sorafenib, Sunitinib, Vandetanib
Tie-2: Cabozantinib
FGFR: Brivanib, Lenvatinib, Nintedanib
CXCR4: Plerixafor
BLOOD VESSE
ECM
INTEGRIN
Cilengitide
Smo
Notch
c-KIT: Axitinib, Cabozantinib, Imatinib, PLX3391, Sunitinib, Tandutinib
CXCR4:Plerixafor
EGFR: Afatinib, Dacomitinib, Erlotinib, Gefitinib, Lapatinib, Rindopepimut (EGFRvIII)
HGFR/c-Met: Cabozantinib, Onartuzumab
PDGFR: Axitinib, Brivanib, Crenolinib, Dasatinib, Imatinib, Lenvatinib, Nintedanib, Pazopanib, Sorafenib, Sunitinib, Tandutinib
TGF: LY2157299
Enzastaurin
PKC
Vismodegib
LDE225
MK0752
RO4929097
Src
Bosutinib, Dasatinib, Nintedanib
Gli1/2
ICN
HSP
Client Protein
PTEN
PI3K
Ras
Tipifarnib
BKM120, XL-765, XL147, PX-866, GDC0084
Raf
Sorafenib
Vitespen
HSP
Perifosine, PX-866
Akt
MEK
Client Protein
Everolimus, Sirolimus, Temsirolimus XL-765, GDC-0084 AZD8055, CC223
mTOR
ERK
Proteosome
Bortezomib
Veliparib
PARP
Chk
HDAC
Panobinostat, Valproic Acid, Vorinostat
NUCLEUS
Alexander, Lee et al. 2013

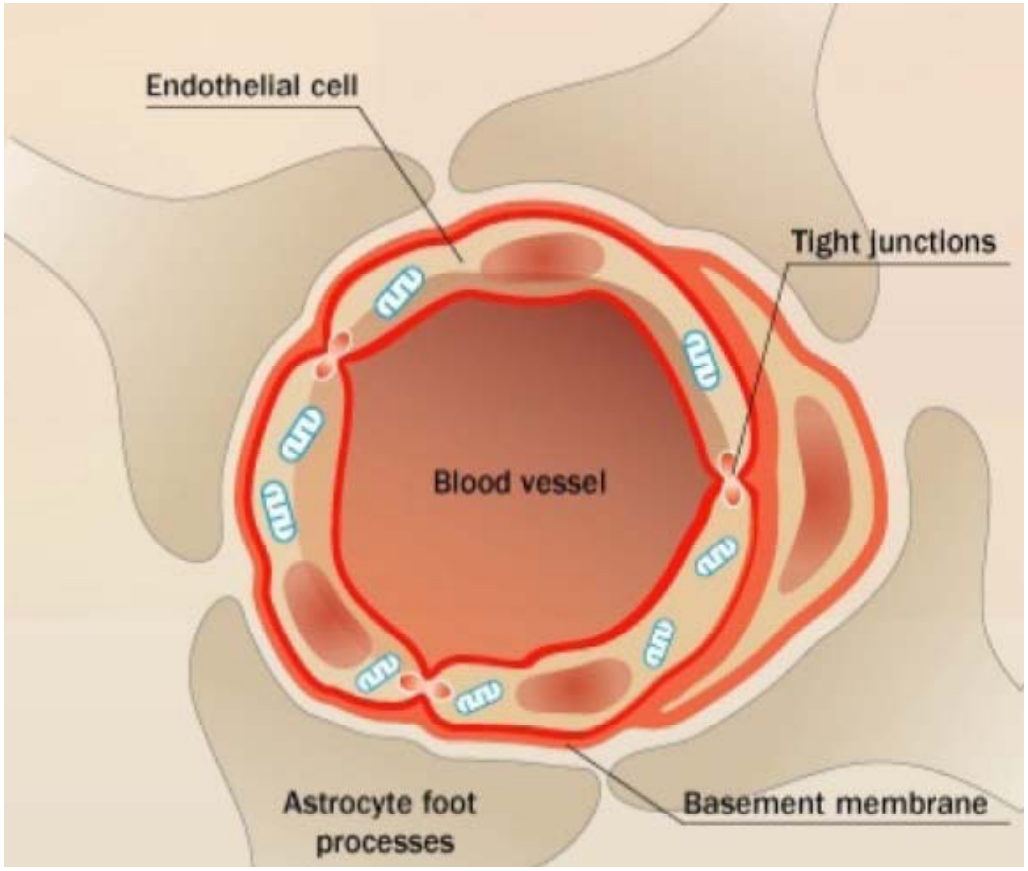
Outline

- Issues
- New therapies and targets
- New approaches to trial design

Reasons for Lack of Progress in Targeted Molecular Therapies in Glioblastomas

- Poor models
- Blood-brain barrier
- Co-activation of tyrosine kinases
- Redundant signaling pathways
- Spatial and temporal heterogeneity
- Failure to genetically enrich patient population
- Stem cells

Bypassing The Blood Brain Barrier



Endothelial cells forming the BBB:

- Express tight junctions
- Lack fenestra
- Lack transendothelial channels
- Lack pinocytic vesicles
- High levels of active efflux proteins, Pgp)

Benarroch **Neurology 2012;78:1268**

Figure 2 Transport mechanisms at the blood-brain barrier (BBB)

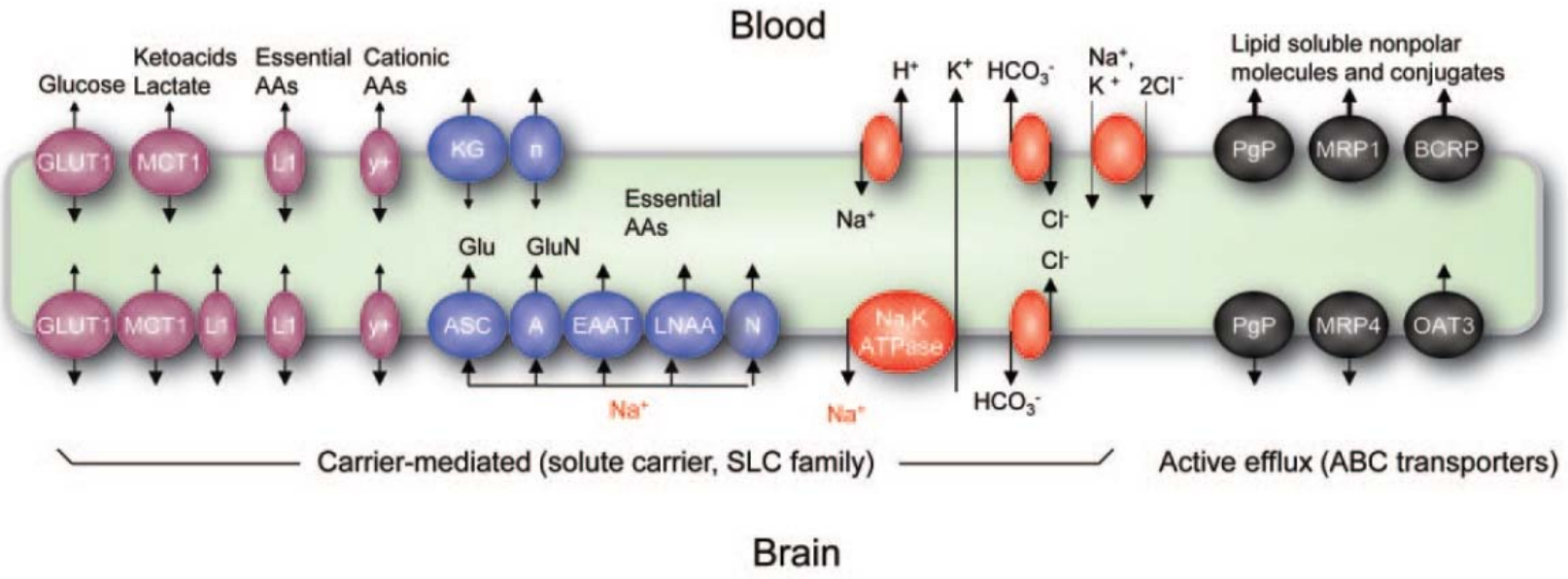
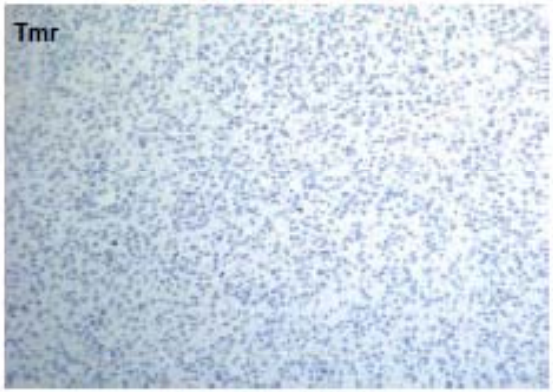


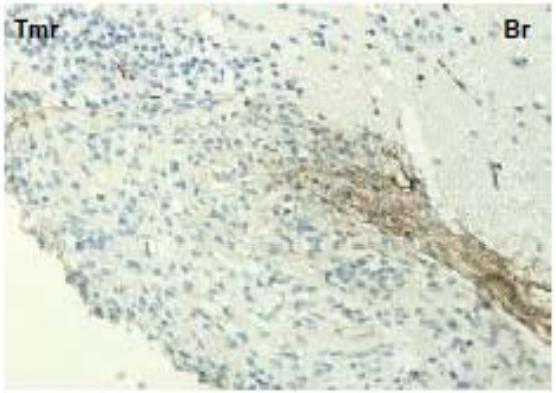
Figure 5. Inhibition of Ficlatuzumab Brain Tumor Penetration by Anti-VEGF Inhibitors in Orthotopic U87 Model

Human IgG-Treated Control

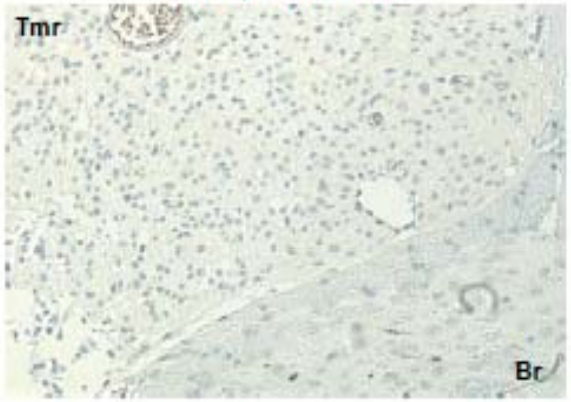


5 mpk Ficlatuzumab

5 mpk Ficlatuzumab +
5 mpk Bevacizumab



5 mpk Ficlatuzumab +
10 mpk Tivozanib



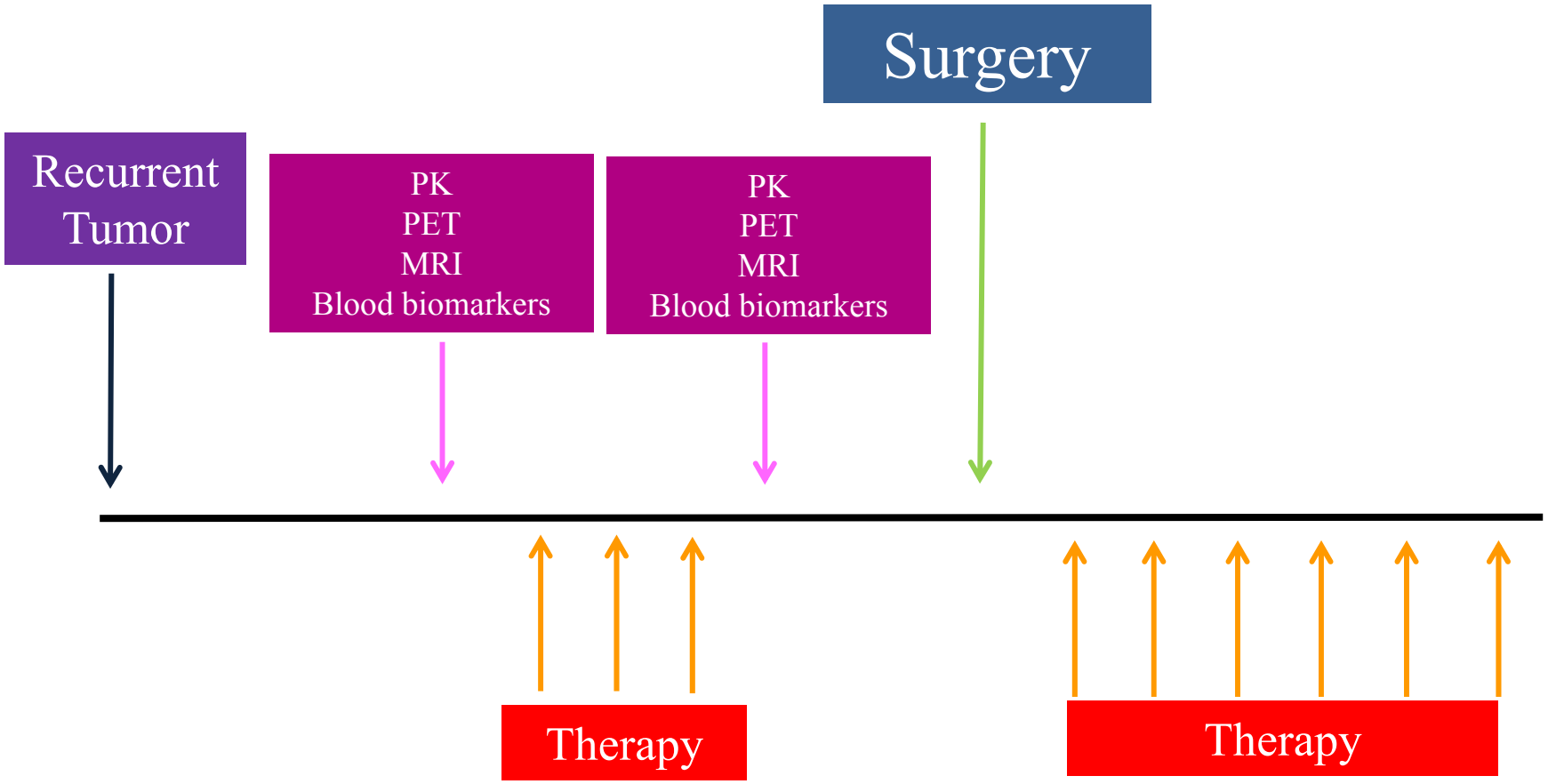
Group	Vehicle	5 mpk Ficlatuzumab	5 mpk Ficlatuzumab + 5 mpk Bevacizumab	5 mpk Ficlatuzumab + 10 mpk Tivozanib
Intensity	0	+ + +	+	0
Area of Tumor with Staining	0	+ +	+	0
Size of Tumor	+ + +	+ +	+ +	+

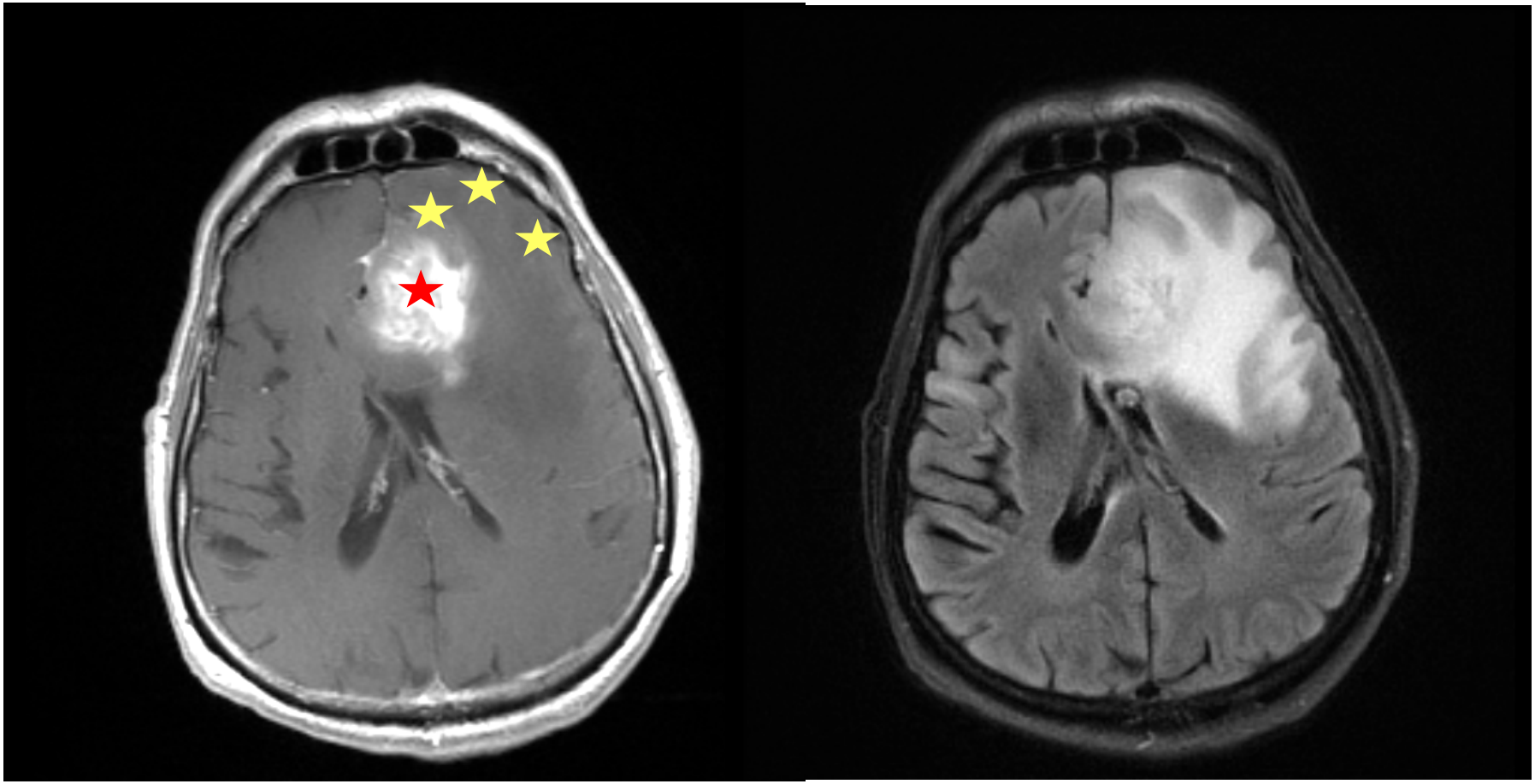
Analysis based on a 0-3 scale, 0 having no positive stain and 3 having 90% to 100% positive.
3 animals per group were analyzed and averaged when available.

Connolly et al, SNO 2012

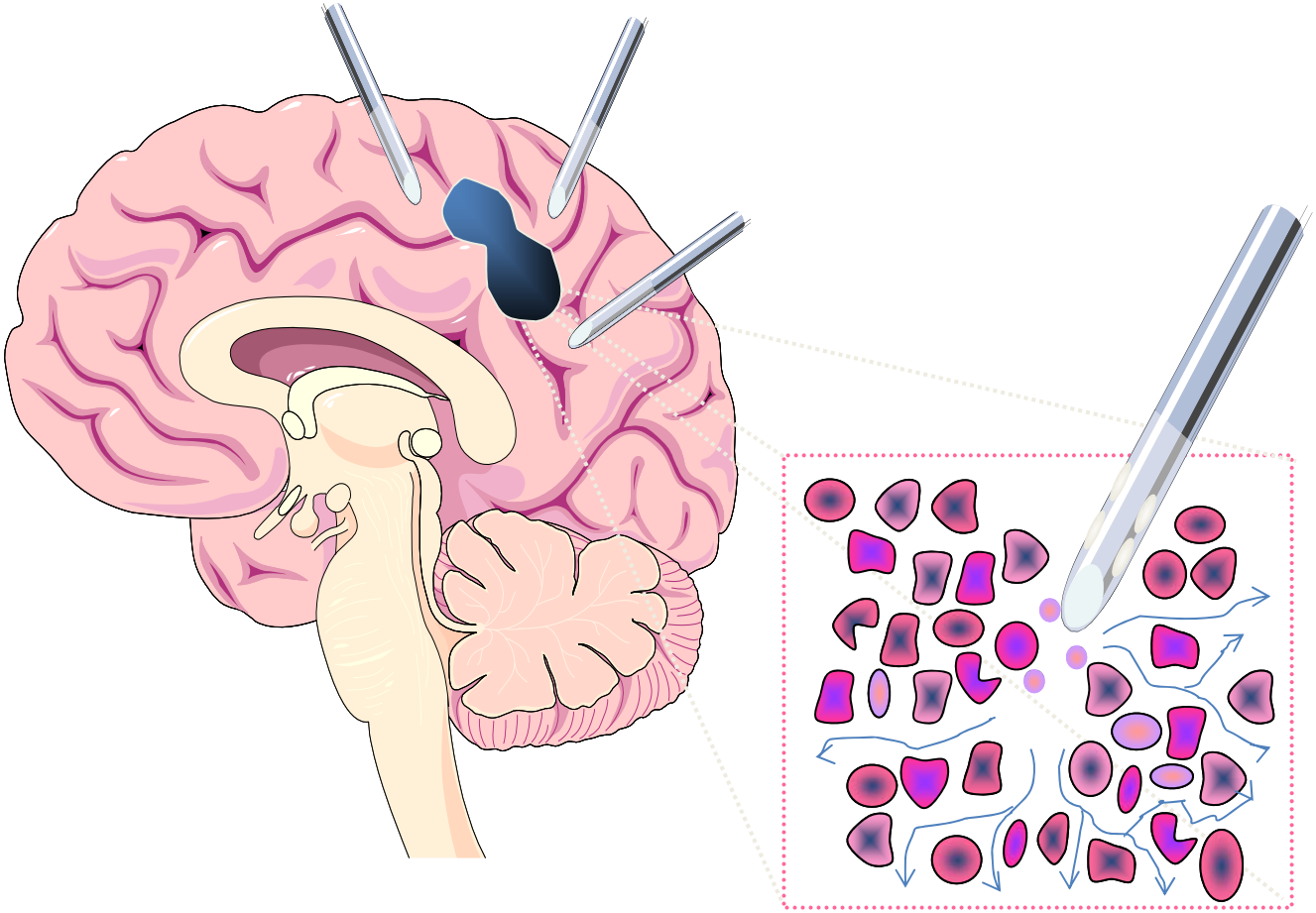
Slide courtesy of May Han, Aveo

Current Design

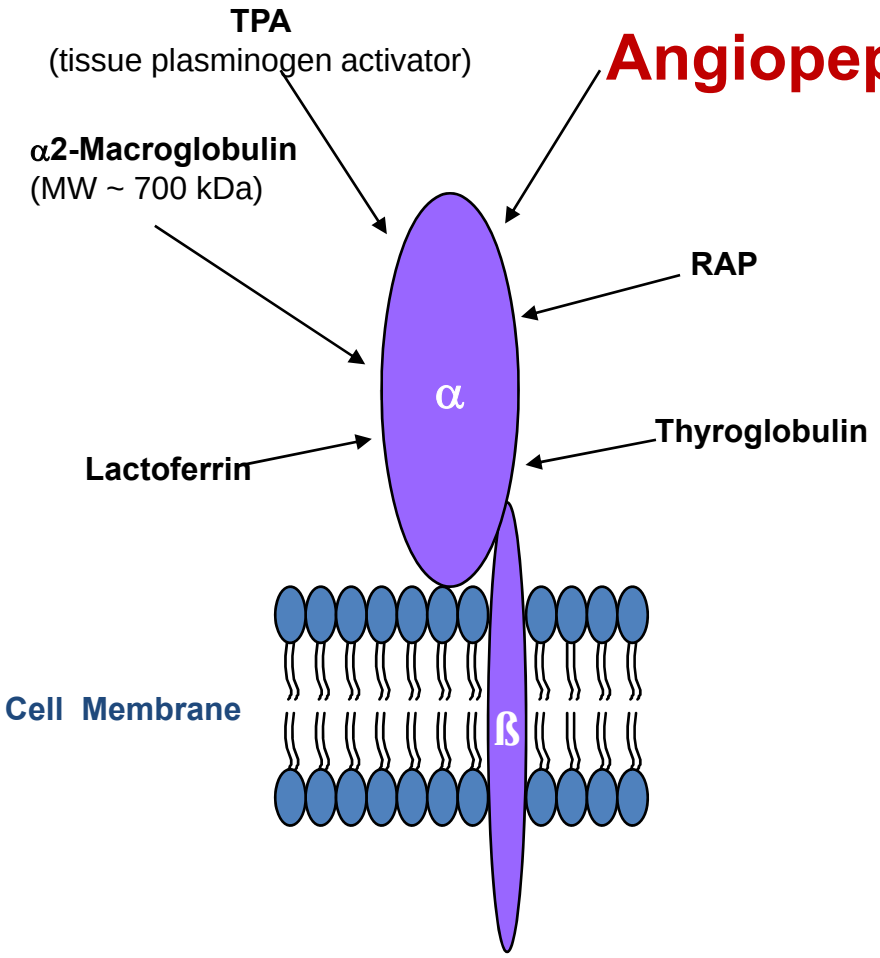




Convection-Enhanced Delivery



Low density Lipoprotein Receptor Related Protein (LRP-1)



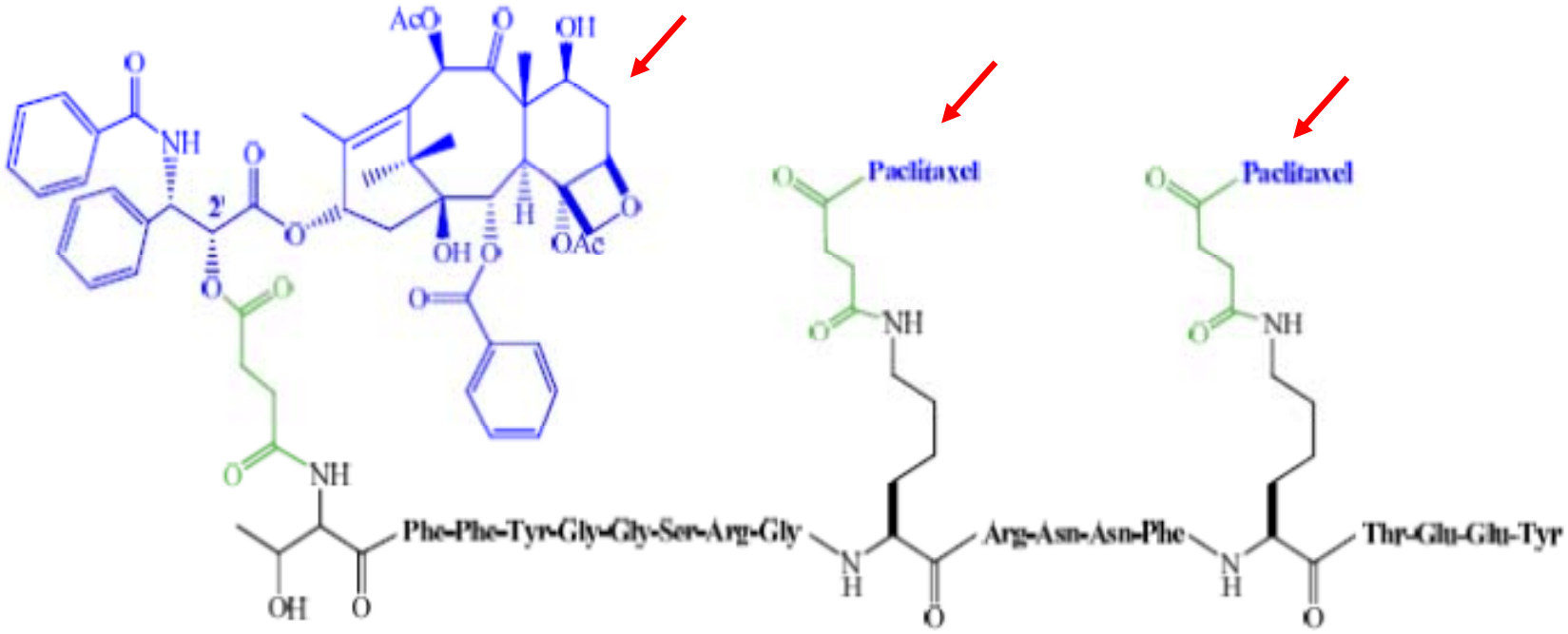
LRP-1: ~600kDa

(α:515, β: 85)

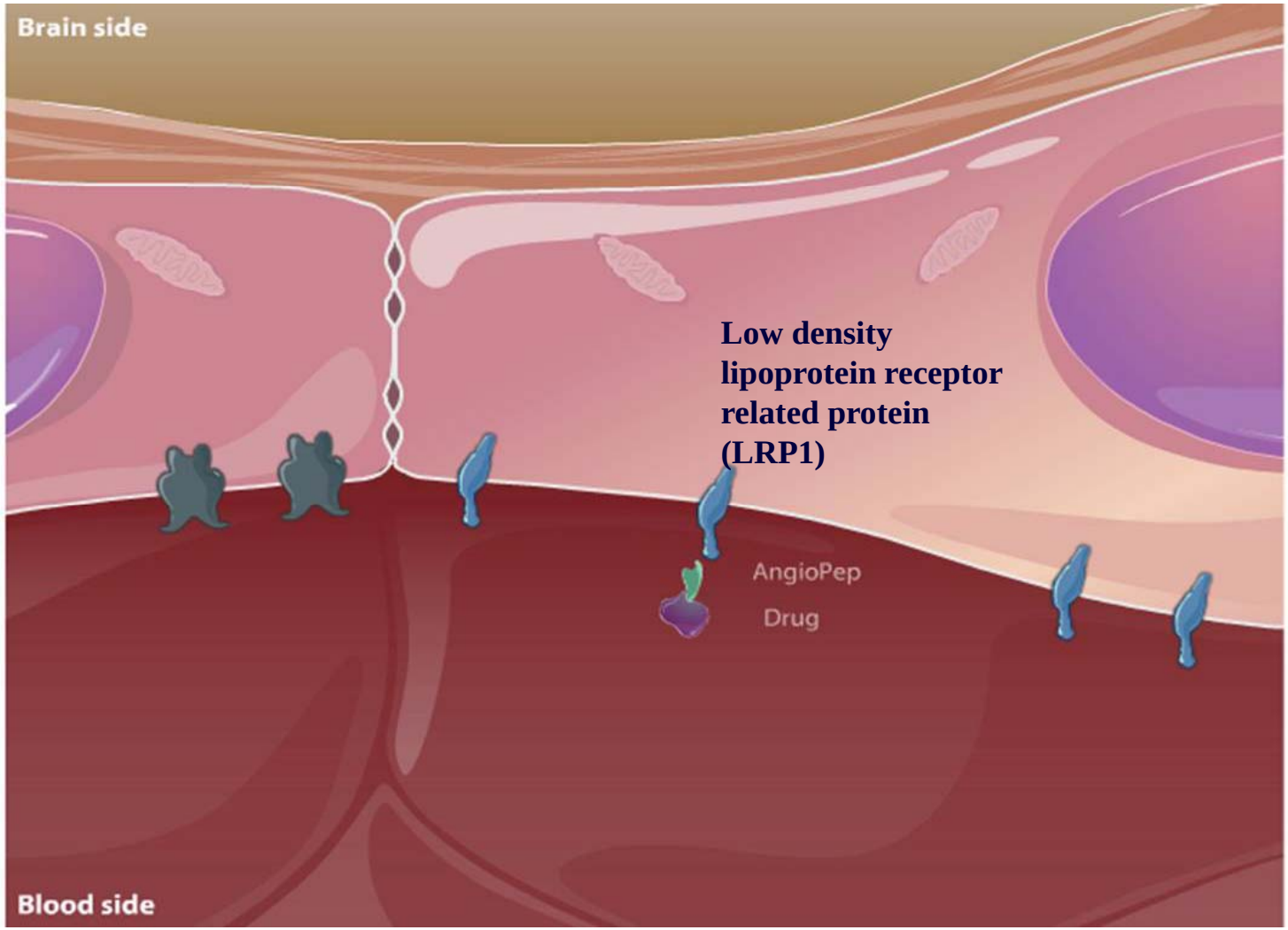
- Transports small and large molecules (> 40 ligands)
- One of the most expressed receptor at the surface of the BBB
- Expressed on cancer cells
- Expressed also in liver, lung and ovarian tissues

ANG1005

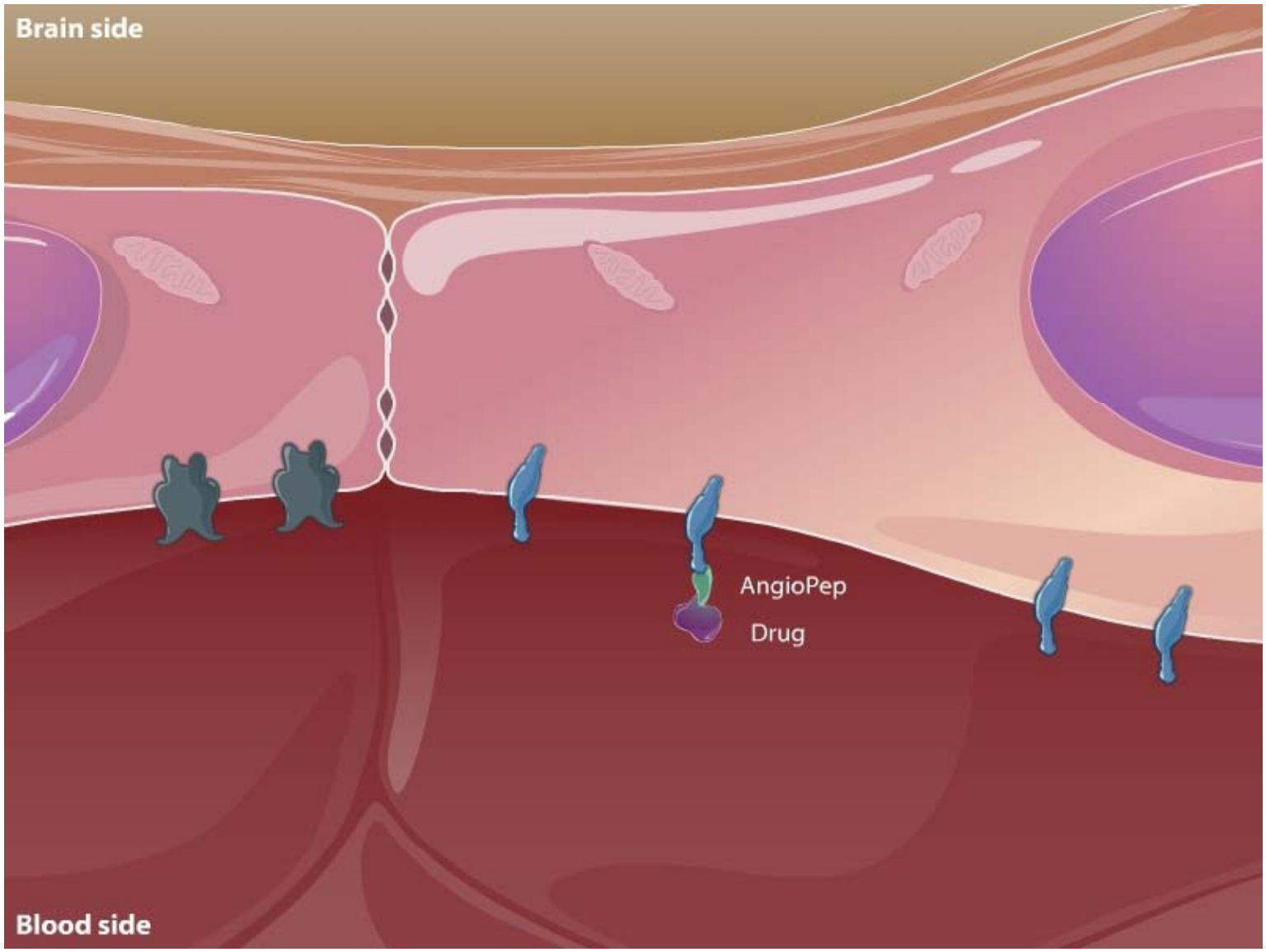
Figure 3.1-1 Schematic Representation of ANG1005 Composed of Three Molecules of Paclitaxel (in Blue) with its Succinyl Linker (in Green) Conjugated to Angiopep2 (in Black)



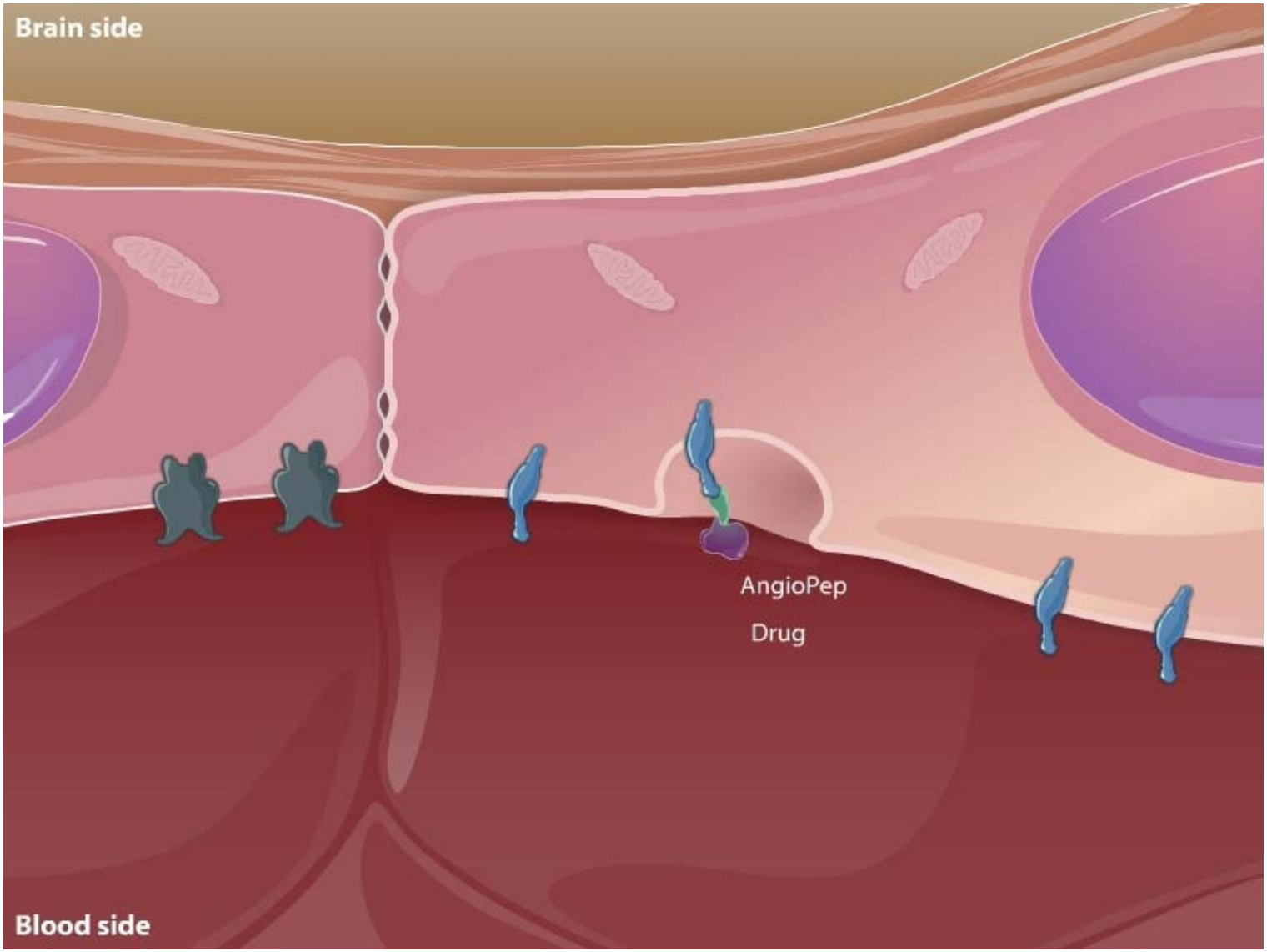
ANG1005


Brain side
Low density lipoprotein receptor related protein (LRP1)
AngioPep
Drug
Blood side

ANG1005



ANG1005



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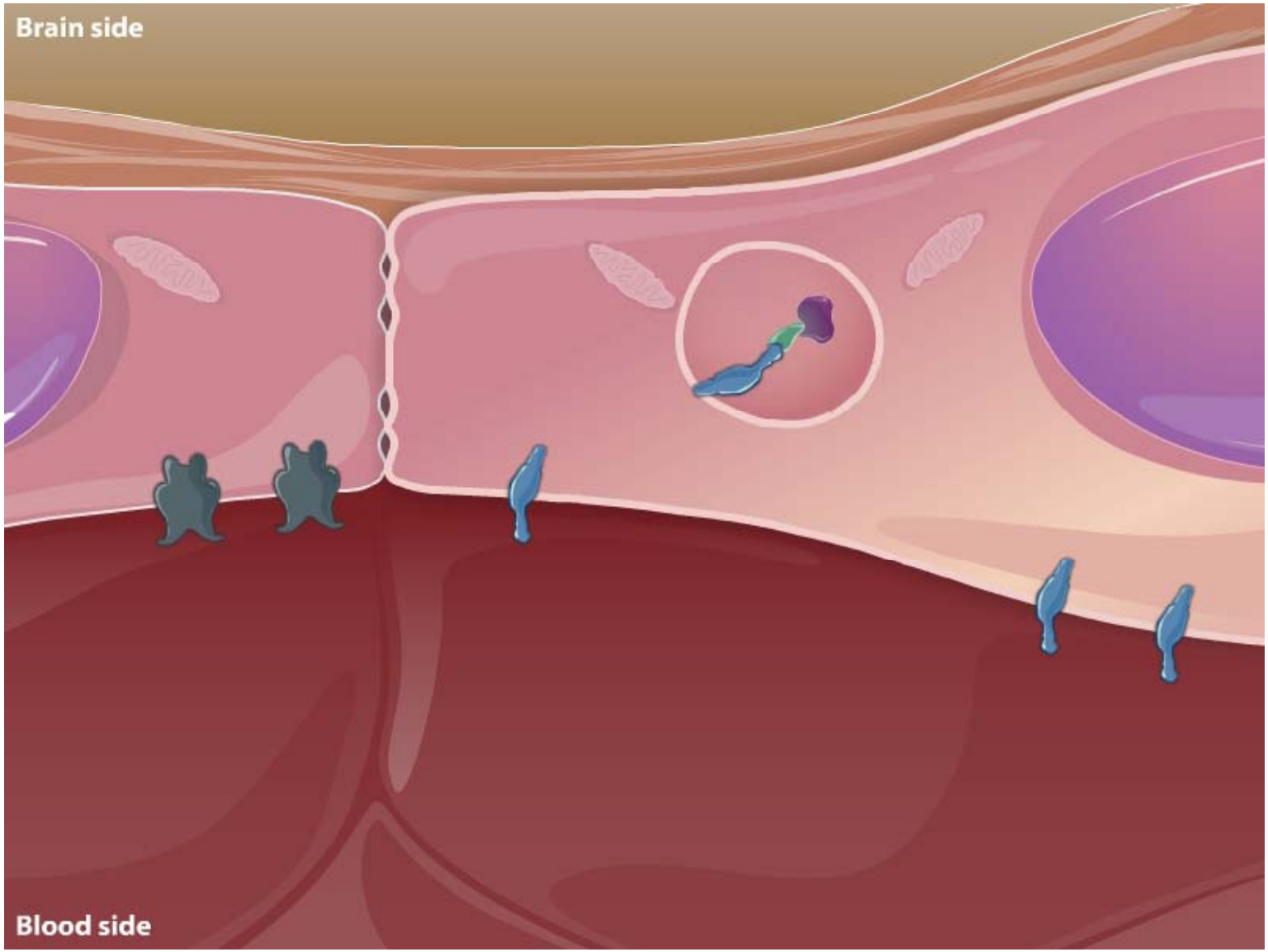

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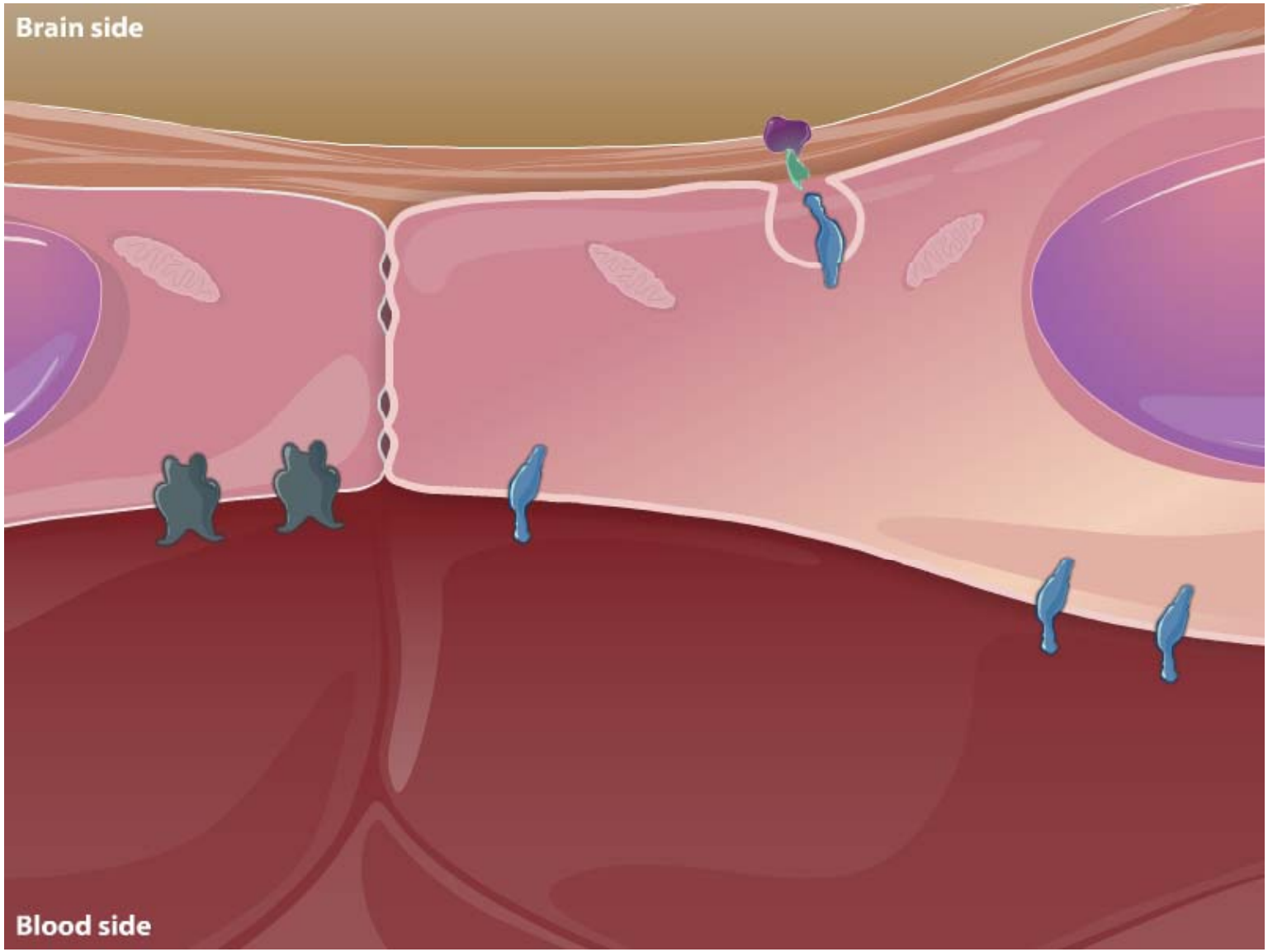

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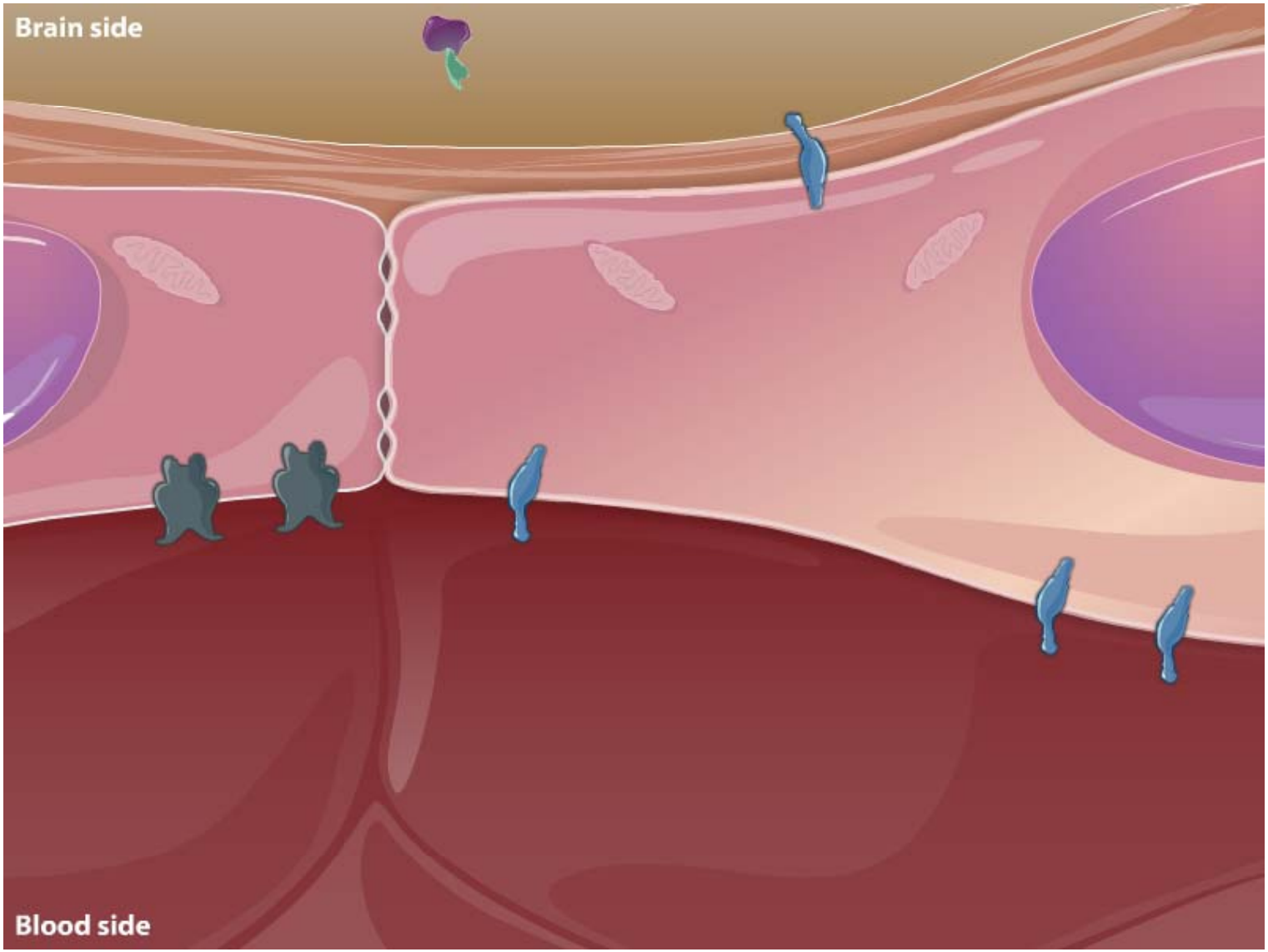
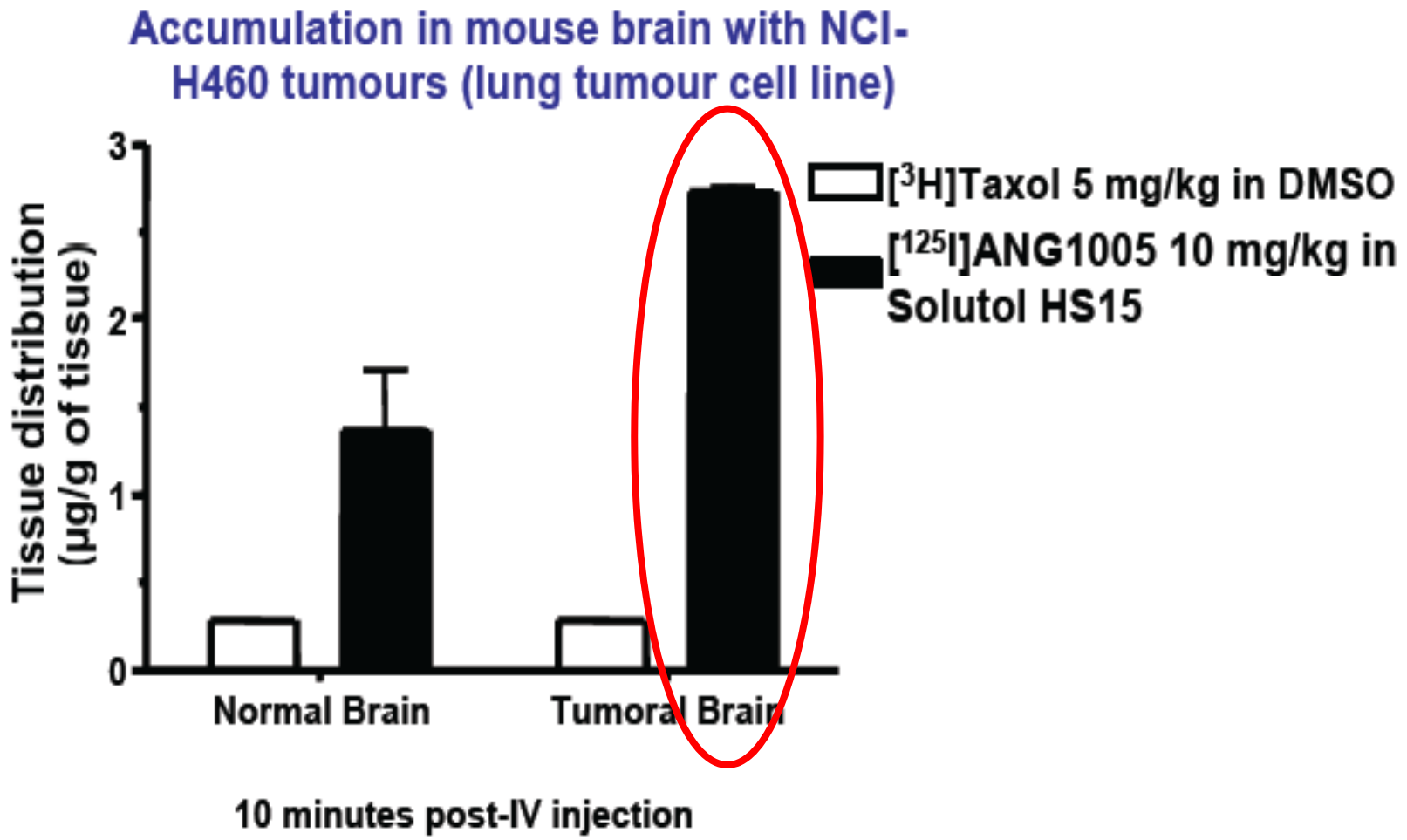


Accumulation of [^{3}H]Taxol and [^{125}I]ANG1005

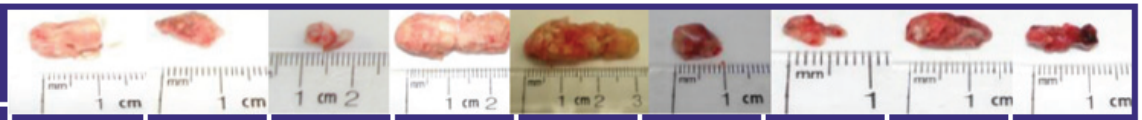


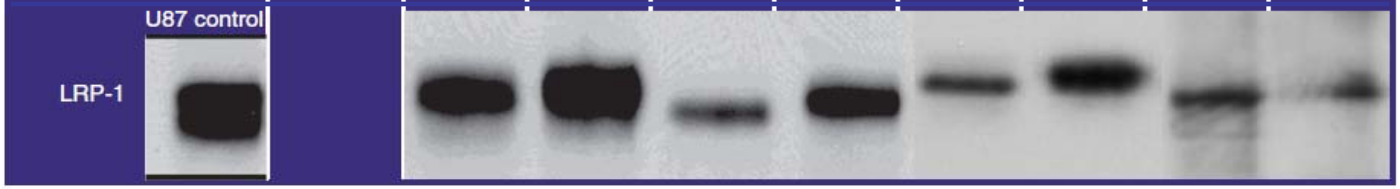
Clinical Cancer Research

2013; 19(6):1567-1576

Phase I Study of GRN1005 in Recurrent Malignant Glioma

Jan Drappatz[1,2,5,6], Andrew Brenner[7], Eric T. Wong[3,5], April Eichler[4,5], David Schiff[9], Morris D. Groves[8], Tom Mikkelsen[10], Steve Rosenfeld[11], John Sarantopoulos[7], Christina A. Meyers[8], Robert M. Fielding[12], Kelly Elian[13], Xiaolin Wang[14], Betty Lawrence[13], Mona Shing[14], Stephen Kelsey[14], Jean Paul Castaigne[13], and Patrick Y. Wen[1,2,5]

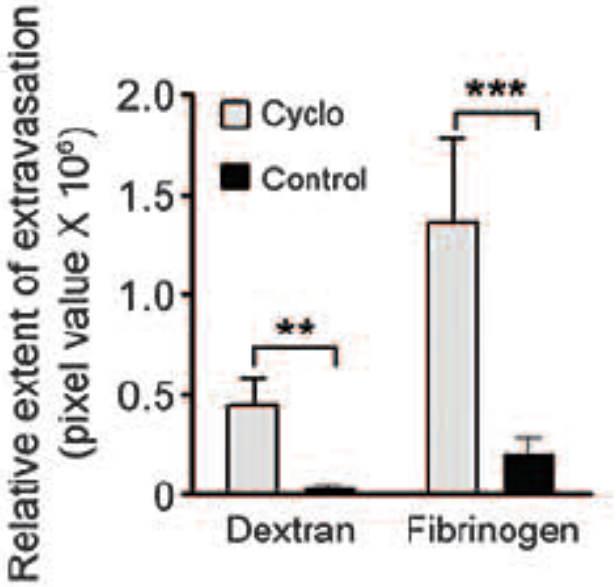
Tumor samples										
Patient		09-003-122[a]	09-005-129[a]	09-006-134[a]	09-008-139[a]	09-010-144[a]	09-011-146[a]	09-013-152[b]	02-028-162[c]	09-016-163[a]
Dose level		200 mg/m²	300 mg/m²	420 mg/m²	550 mg/m²	550 mg/m²	550 mg/m²	550 mg/m²	650mg/m²	550mg/m²
Extraction time		~ 4.0 h	~ 5.0 h	~ 4.0 h	~ 4.5 h	~ 6.0 h	~ 4.5 h	~ 6.0 h	~ 3.5 h	~ 5.5 h
PLASMA	GRN1005[d]	33.6 µmol/L	34.1 µmol/L	52.6 µmol/L	98.2 µmol/L	55.0 µmol/L	62.5 µmol/L	69.7 µmol/L	123.4 µmol/L	79.5 µmol/L
	Free paclitaxel	0.70 µmol/L	0.34 µmol/L	0.87 µmol/L	1.83 µmol/L	1.52 µmol/L	0.44 µmol/L	1.57 µmol/L	2.30 µmol/L	1.52 µmol/L
	% Free paclitaxel	2.0%	1.0%	1.6%	1.8%	2.7%	0.7%	2.2%	1.8%	1.9%
TUMOR[e]	GRN1005[d]	2.0 µmol/L	8.5 µmol/L	5.8 µmol/L	22.4 µmol/L	95.2 µmol/L	237.6 µmol/L	19.6 µmol/L	18.4 µmol/L	28.4 µmol/L
	Free paclitaxel	0.81 µmol/L	0.90 µmol/L	1.22 µmol/L	0.57 µmol/L	2.77 µmol/L	0.60 µmol/L	8.61 µmol/L	0.93 µmol/L	3.16 µmol/L
	% Free paclitaxel	28.7%	9.6%	17.3%	2.5%	2.8%	0.3%	30.5%	4.8%	10.0%
% Total Concentration in Tumor relative to Plasma		8.2%	27.3%	13.3%	23.0%	173%	379%	39.6%	15.4%	38.9%



Science 2011;344:1727

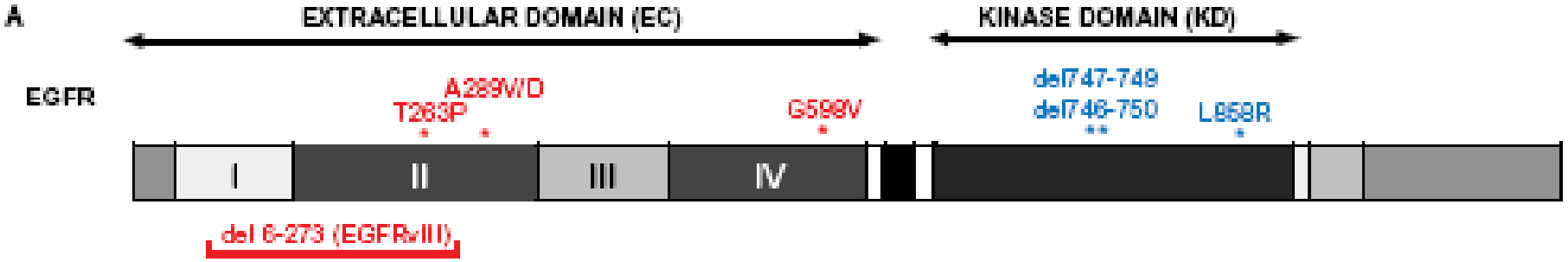
The Hedgehog Pathway Promotes Blood-Brain Barrier Integrity and CNS Immune Quiescence

Jorge Ivan Alvarez,[1*] Aurore Dodelet-Devillers,[1*] Hania Kebir,[1] Igal Ifergan,[1] Pierre J. Fabre,[2] Simone Terouz,[1] Mike Sabbagh,[1] Karolina Wosik,[1] Lyne Bourbonnière,[1] Monique Bernard,[1] Jack van Horssen,[3] Helga E. de Vries,[3] Frédéric Charron,[2] Alexandre Prat[1]†

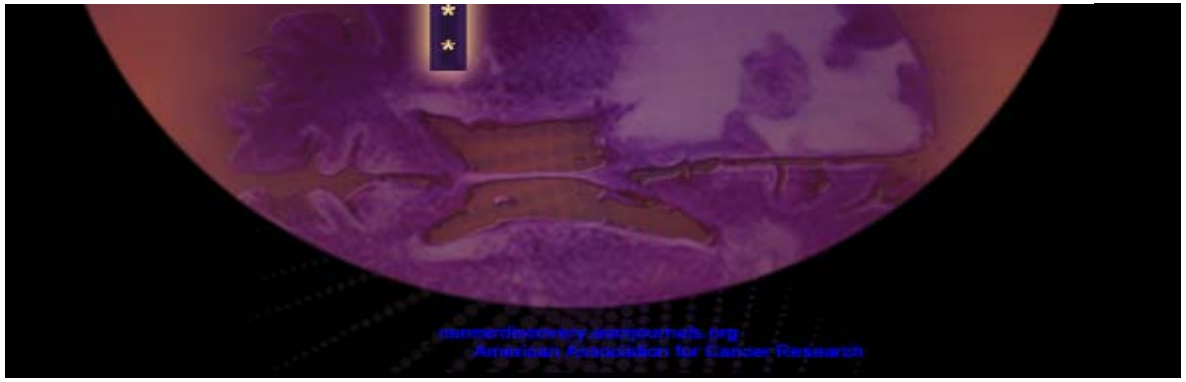


Pulse Dosing

Vivanco et al. Cancer Discovery 2012;2:458-71

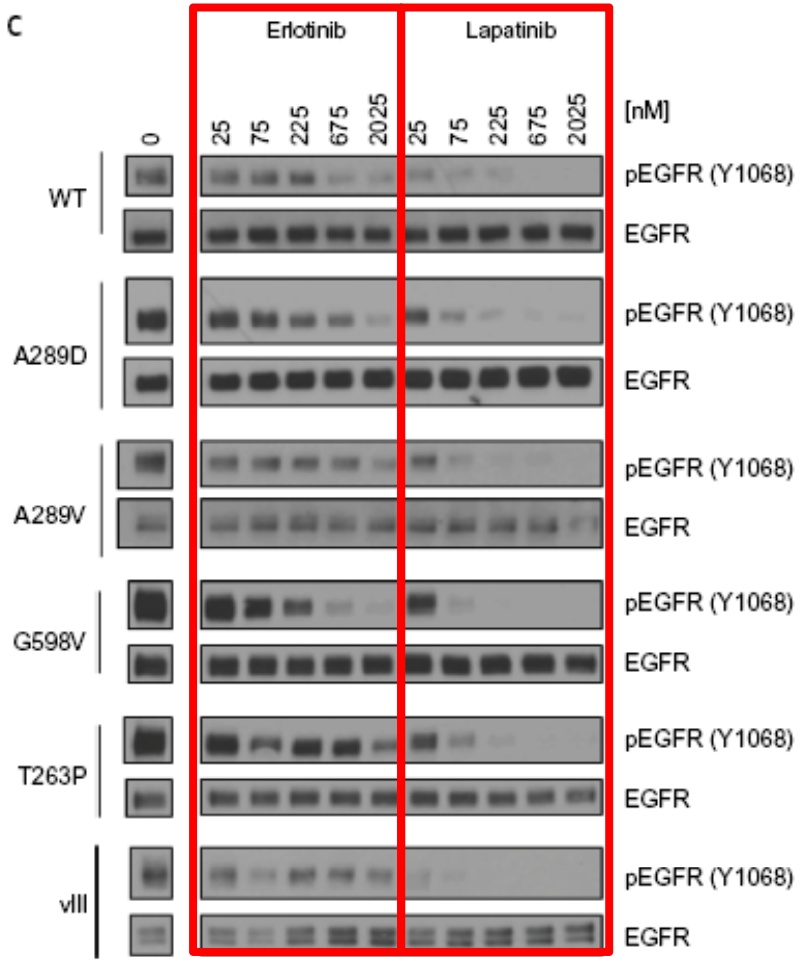


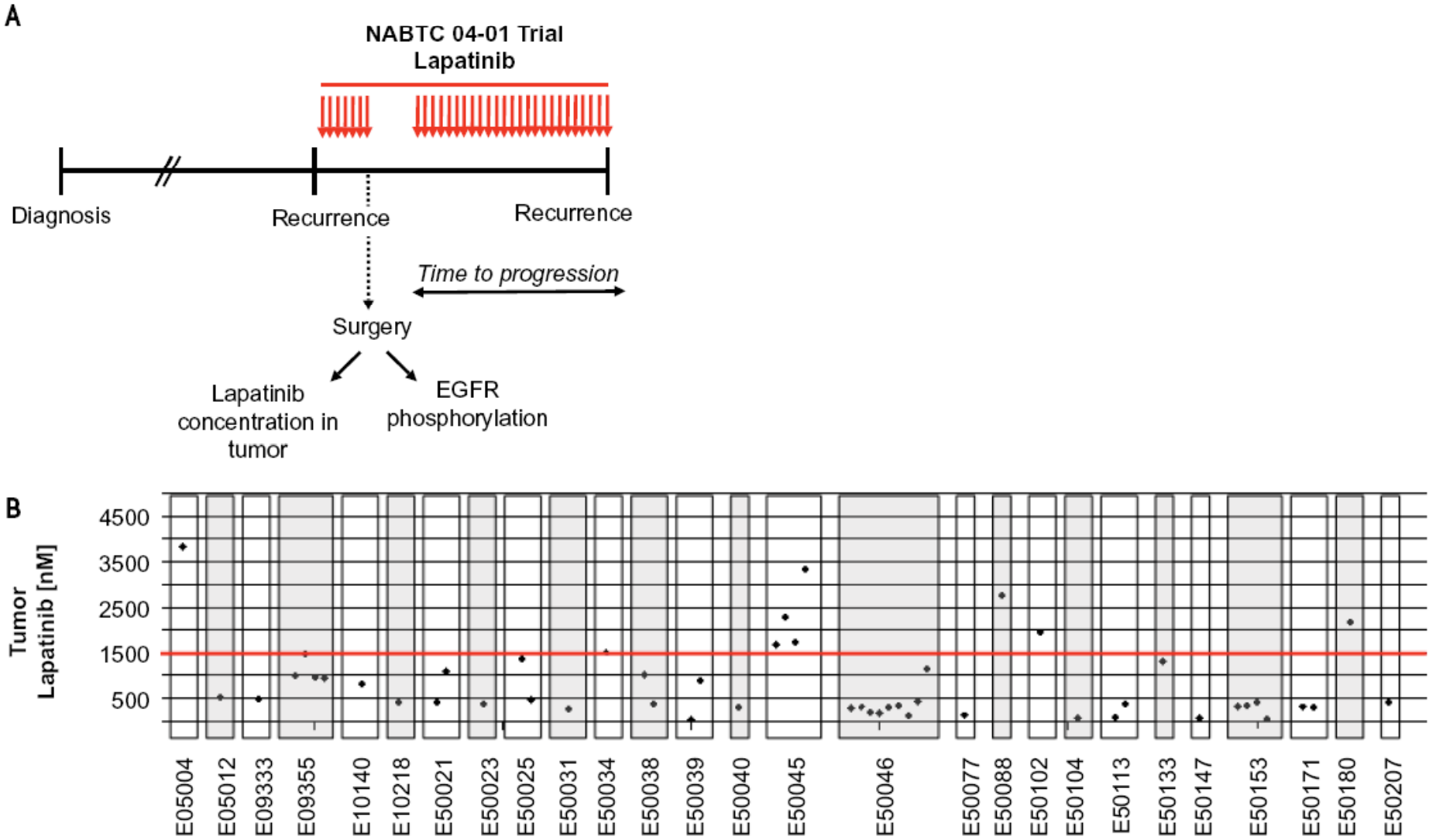
GBM **Lung Cancer**



Vivanco et al. Cancer Discovery 2012

EGFR TKI	KINASE BINDING
Lapatinib	Type II (inactive conformation)
Erlotinib	Type I (active conformation)

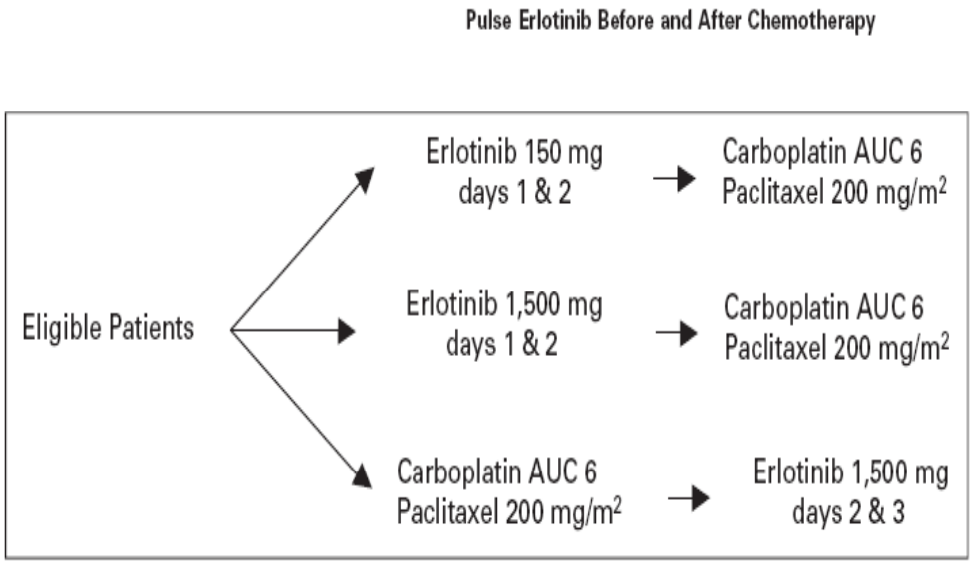


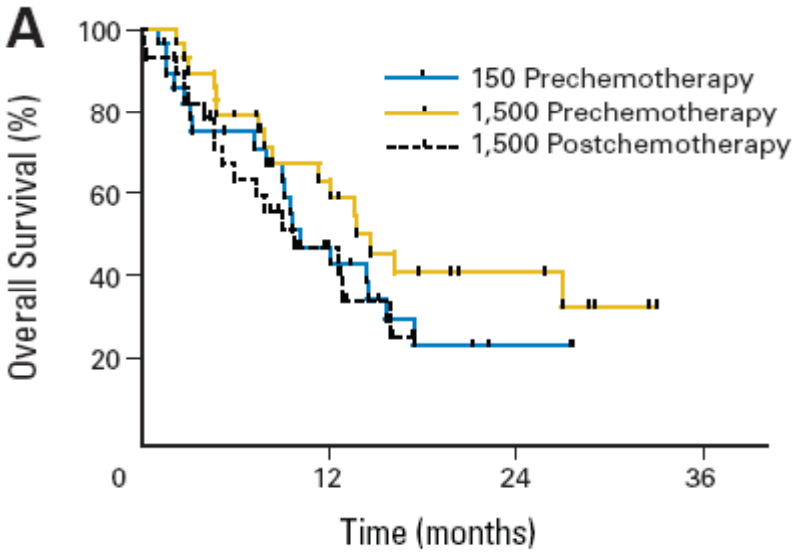


Vivanco et al. Cancer Discovery 2012

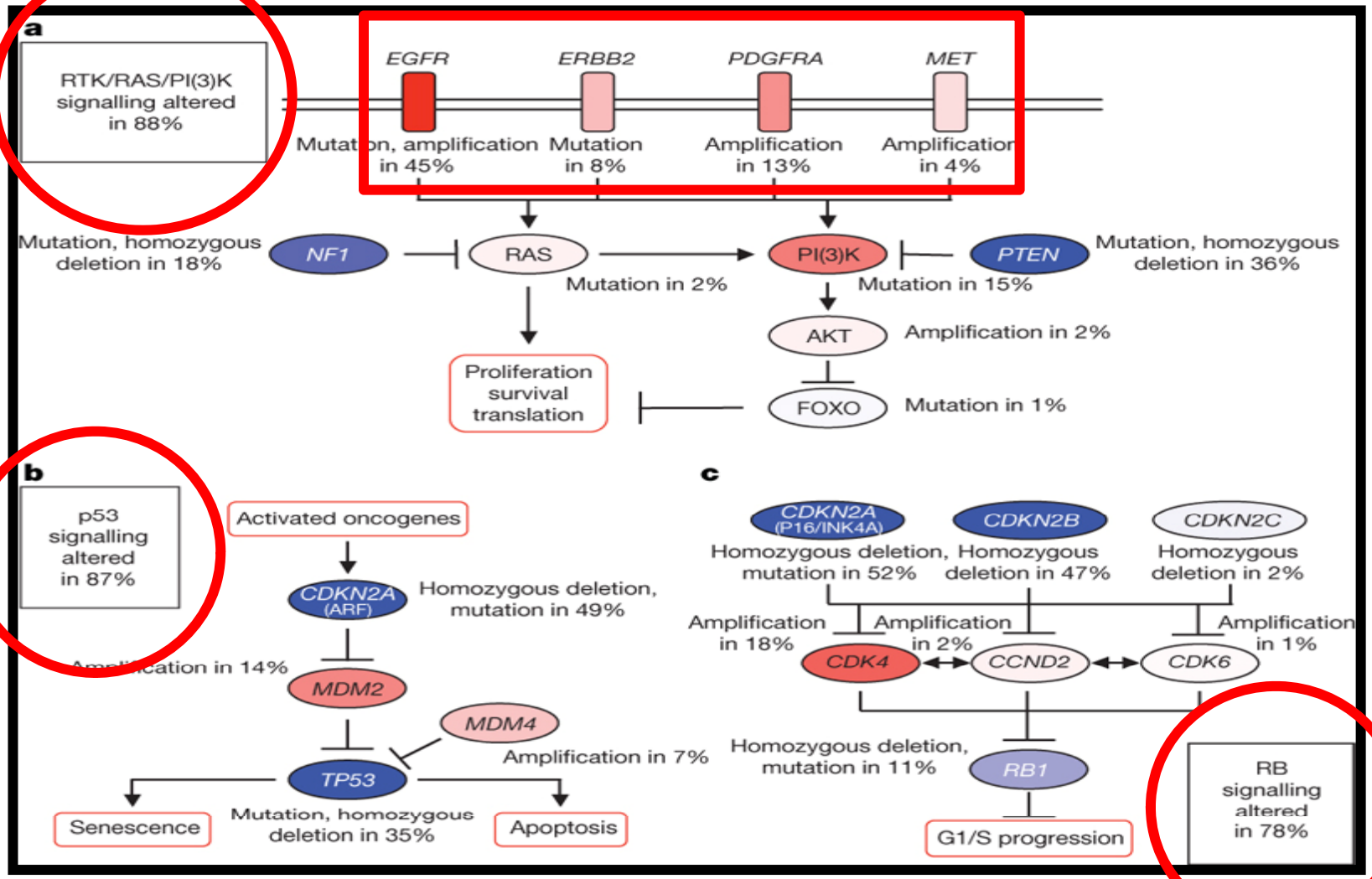
Are we delivering the drugs appropriately?

- Continuous dosing versus pulse dosing
- Administer targeted drug before or after chemotherapy
- NSCLC
  - Solit et al CCR 2005;11:1983
  - Riely JCO 2009:27;264

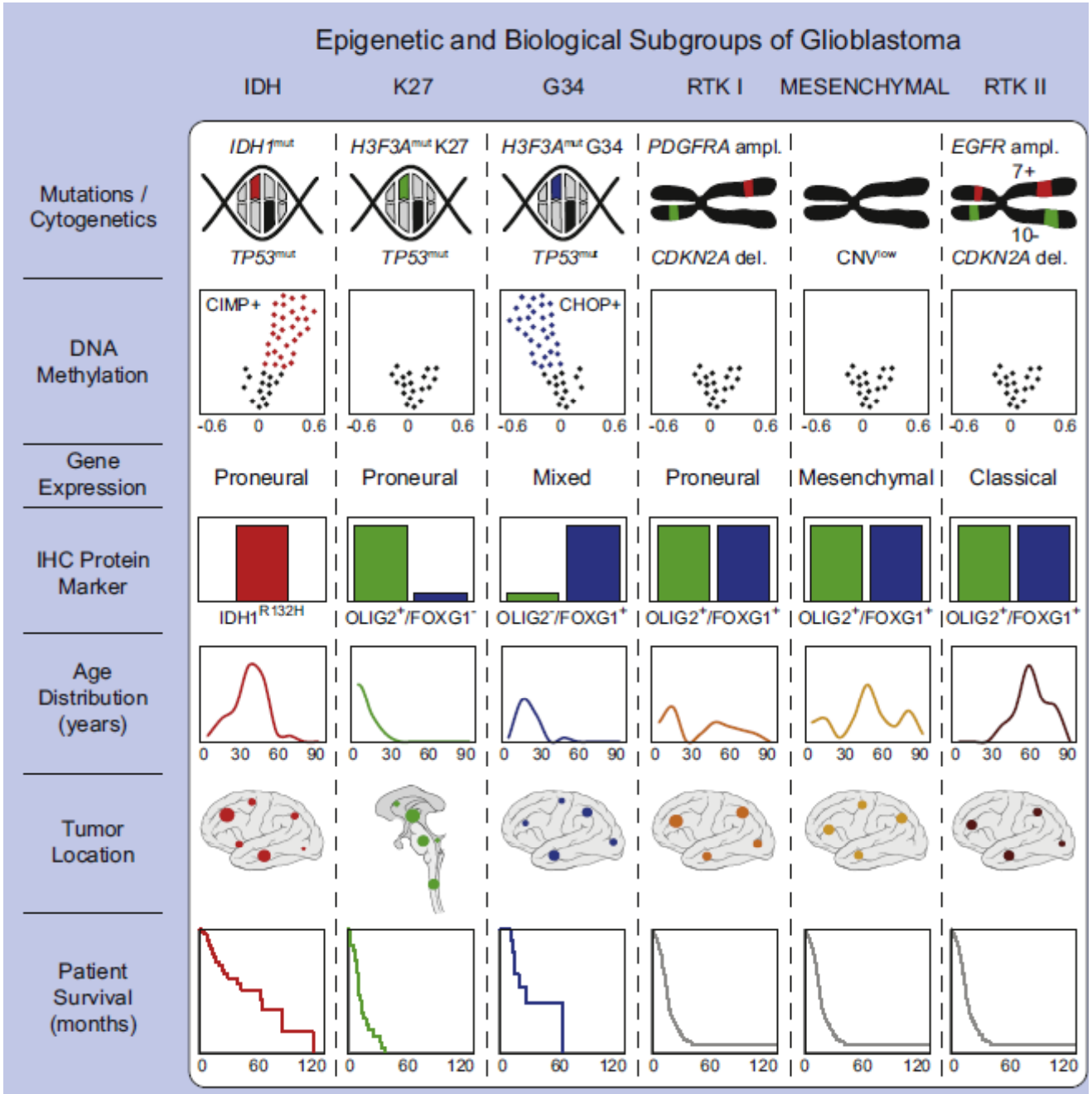




Targeted Molecular Therapies

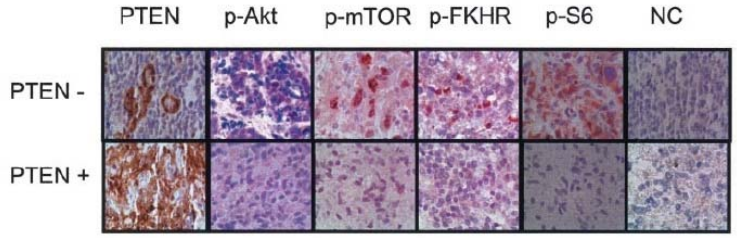


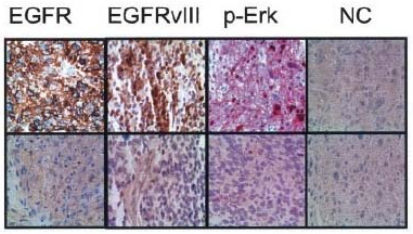
The Cancer Genome Atlas Research Network. *Nature*. 2008;455:1061-1068;

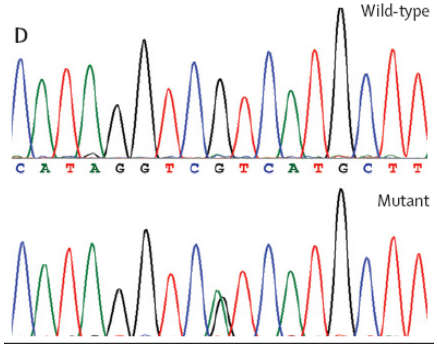


Stum et al.
Cancer Cell
2012;22:425-437

Failure To Genotype Patients

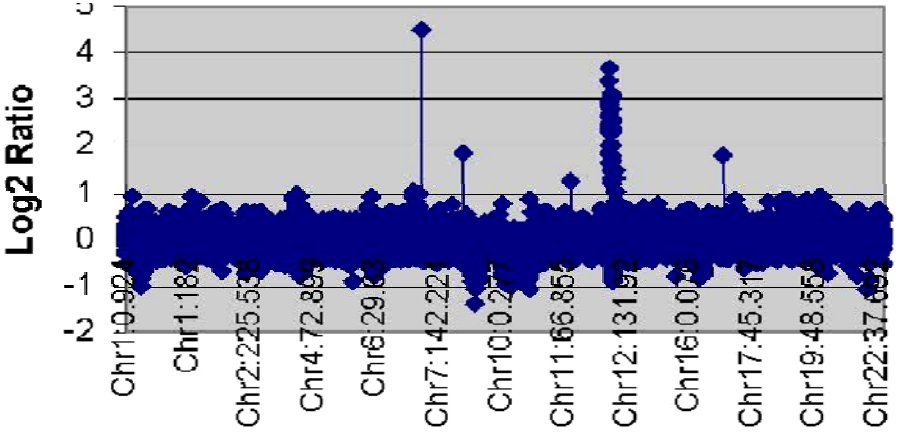


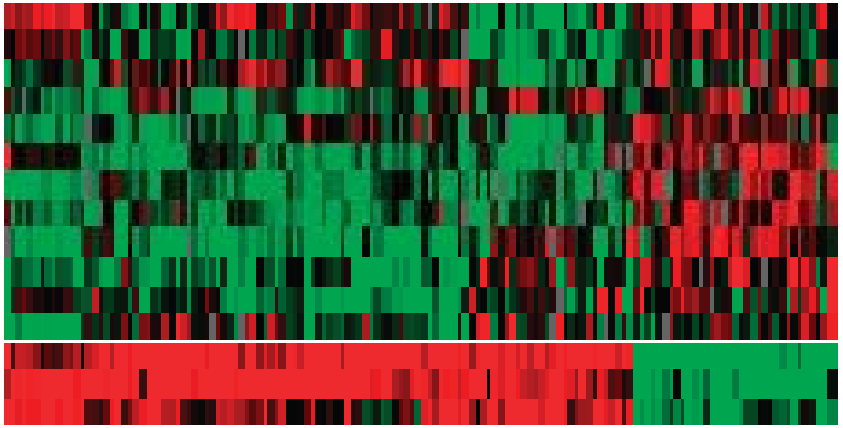




Sequencing

Epigenetic Analysis





Set of activated kinases and pathways

Combinations of appropriate drugs

Ivy Foundation Early Phase Clinical Trials Consortium

DF/HCC

MSKCC

UCLA

UCSF

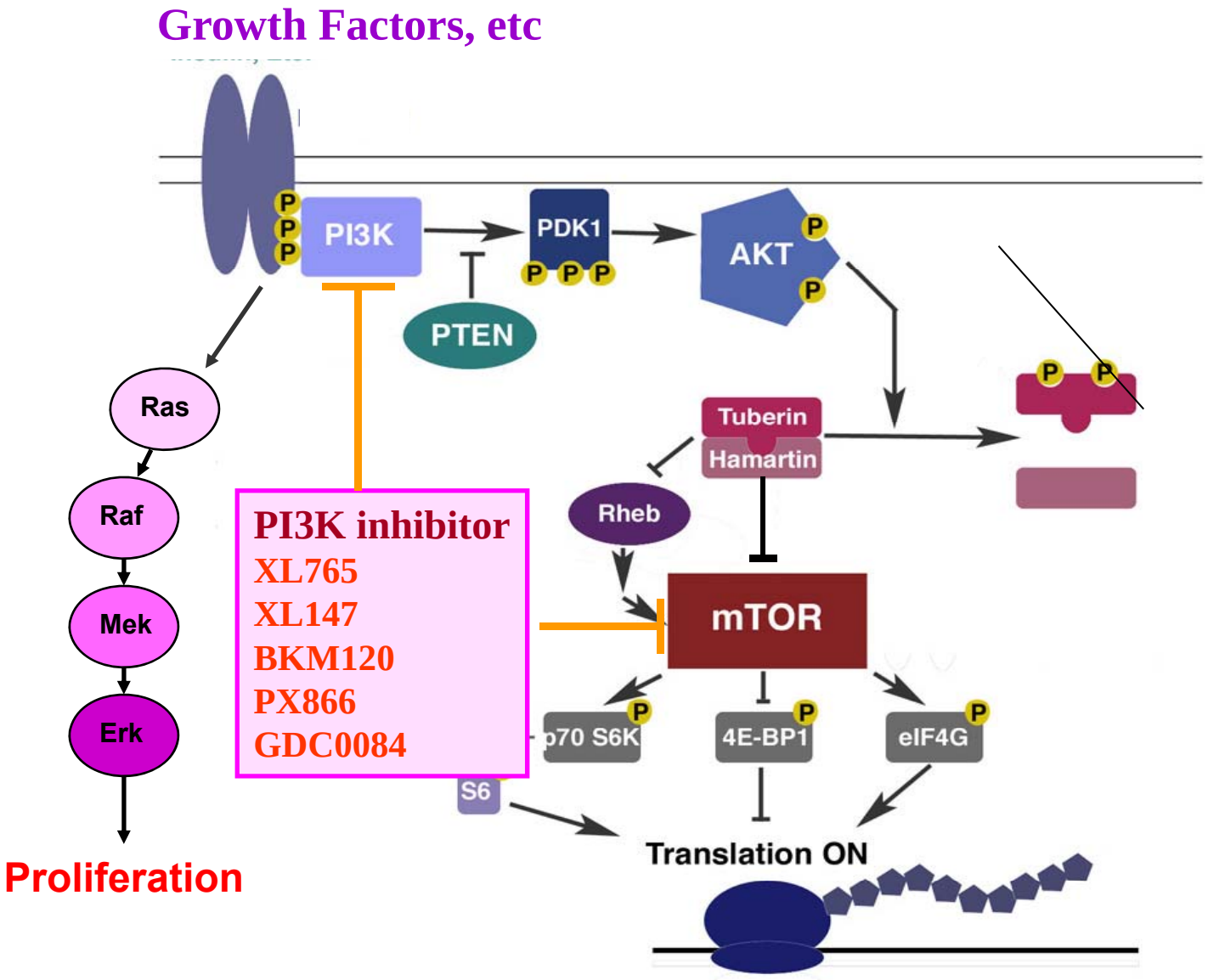
MDACC

U Utah

New Targets

- PI3K
- FGFR/TACC
- BRAF
- CDK4
- WeeI

PI3 Kinase Inhibitors



BKM120

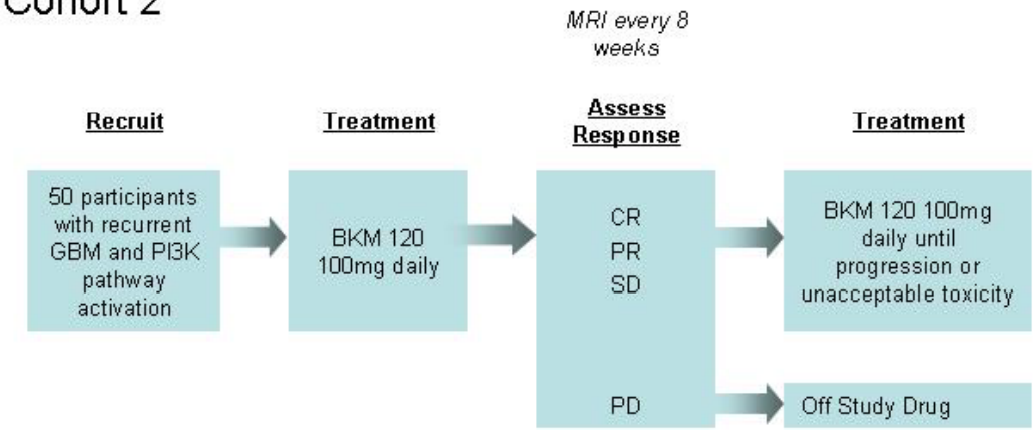
- Oral pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2,6-dimorpholino pyrimidine derivative family
- Inhibits p110α, p110β, p110δ and p110γ
- Cross the blood-brain barrier (brain/blood ratio 2)
- Taken orally once daily
- Inhibits the growth of U87MG and GBM explants in vivo

Ivy Foundation Early Phase Clinical Trials Consortium

A Phase II study of BKM120 for patients with recurrent glioblastoma and activated PI3K pathway

Cohort 1

Cohort 2



BKM 120 Trial

Patient Eligibility

- Activation of PI3K pathway:
  - PIK3CA/PIK3R1 mutation or
  - PTEN mutation, loss of PET by FISH, or PTEN IHC negative

Goal

- 30 PTEN loss
- 20 PIK3CA/PIK3R1 mutants

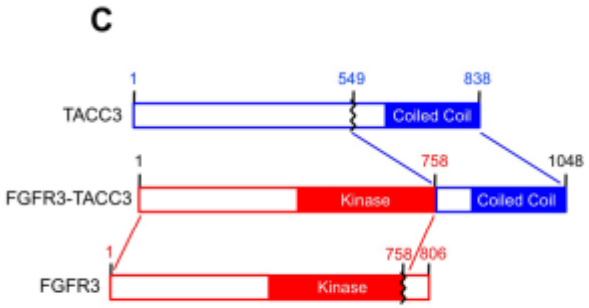
Next Steps

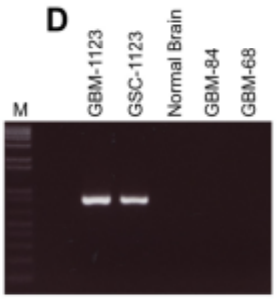
- Isoform specific Inhibitors
  - ? Beta specific isoforms better for PTEN loss
  - ? Alpha specific isoforms for PI3Ca mutants
- Combinations
  - BKM120 +RT+TMZ
  - BKM120 + LDE225 (SMO inhibitor)
  - BKM120 + INC 280 (MET inhibitor)

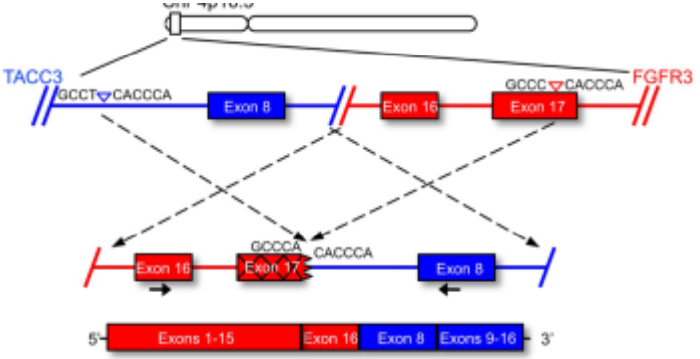
Transforming Fusions of *FGFR* and *TACC* Genes in Human Glioblastoma

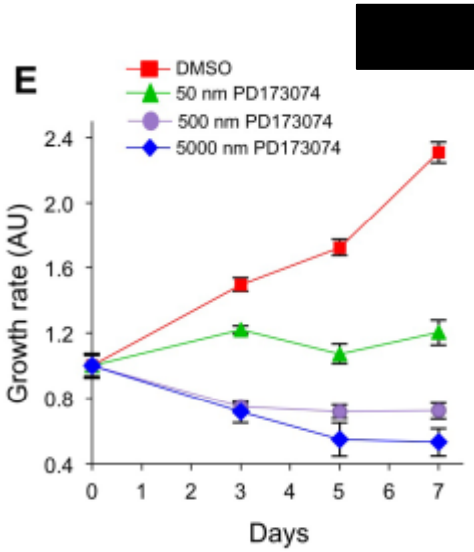
Science 2012

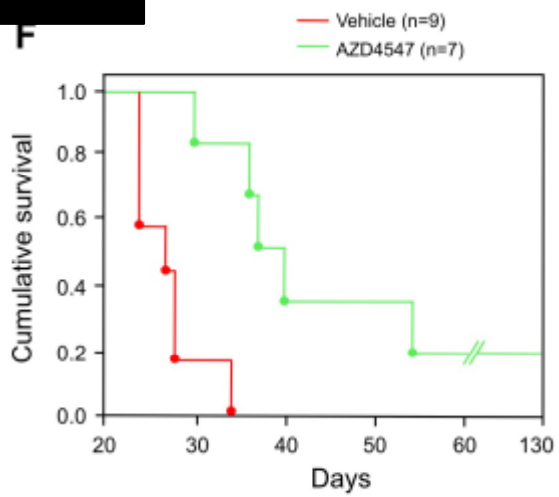
Devendra Singh,[1*] Joseph Minhow Chan,[2*] Pietro Zoppoli,[1*] Francesco Niola,[1*†] Ryan Sullivan,[1] Angelica Castano,[1] Eric Minwei Liu,[2] Jonathan Reichel,[2,3] Paola Porrati,[4] Serena Pellegatta,[4] Kunlong Qiu,[5] Zhibo Gao,[5] Michele Ceccarelli,[6] Riccardo Riccardi,[7] Daniel J. Brat,[8] Abhijit Guha,[9] Ken Aldape,[10] John G. Golfinos,[11] David Zagzag,[11,12] Tom Mikkelsen,[13] Gaetano Finocchiaro,[4] Anna Lasorella,[1,14,15]‡ Raul Rabadan,[2]‡ Antonio Iavarone,[1,15,16]‡



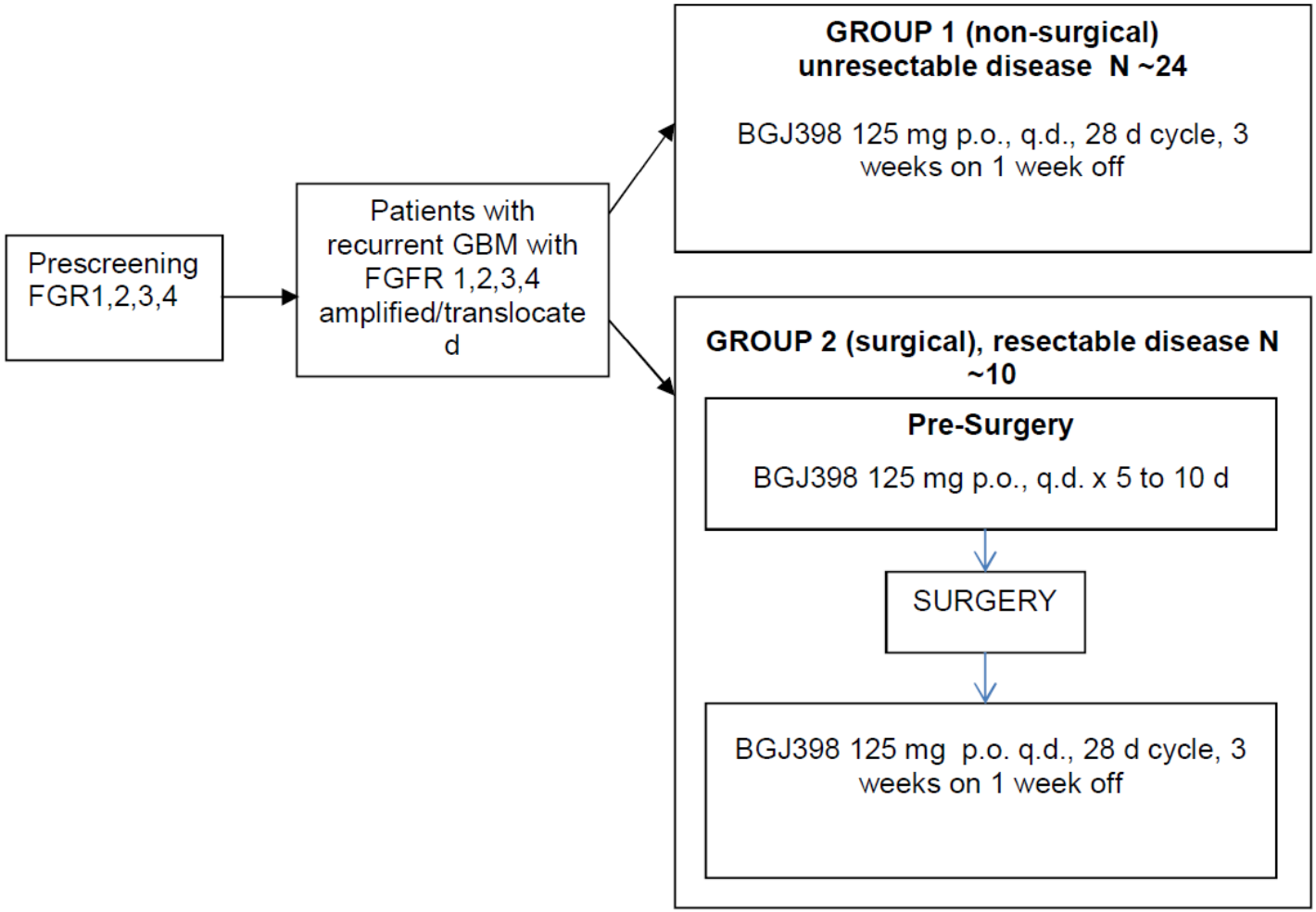




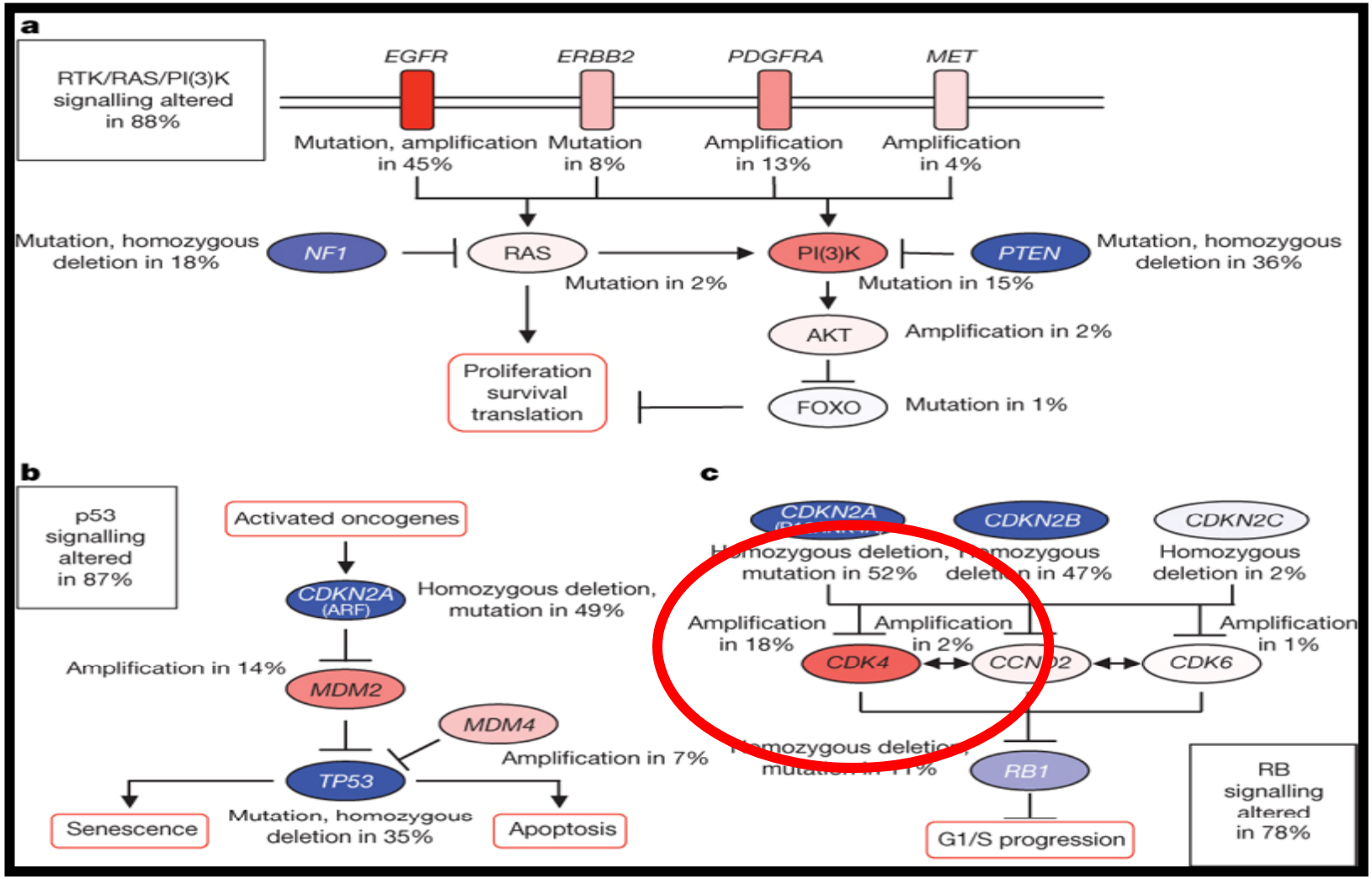




Phase II Trial of BGJ398 (FGFR inhibitor)

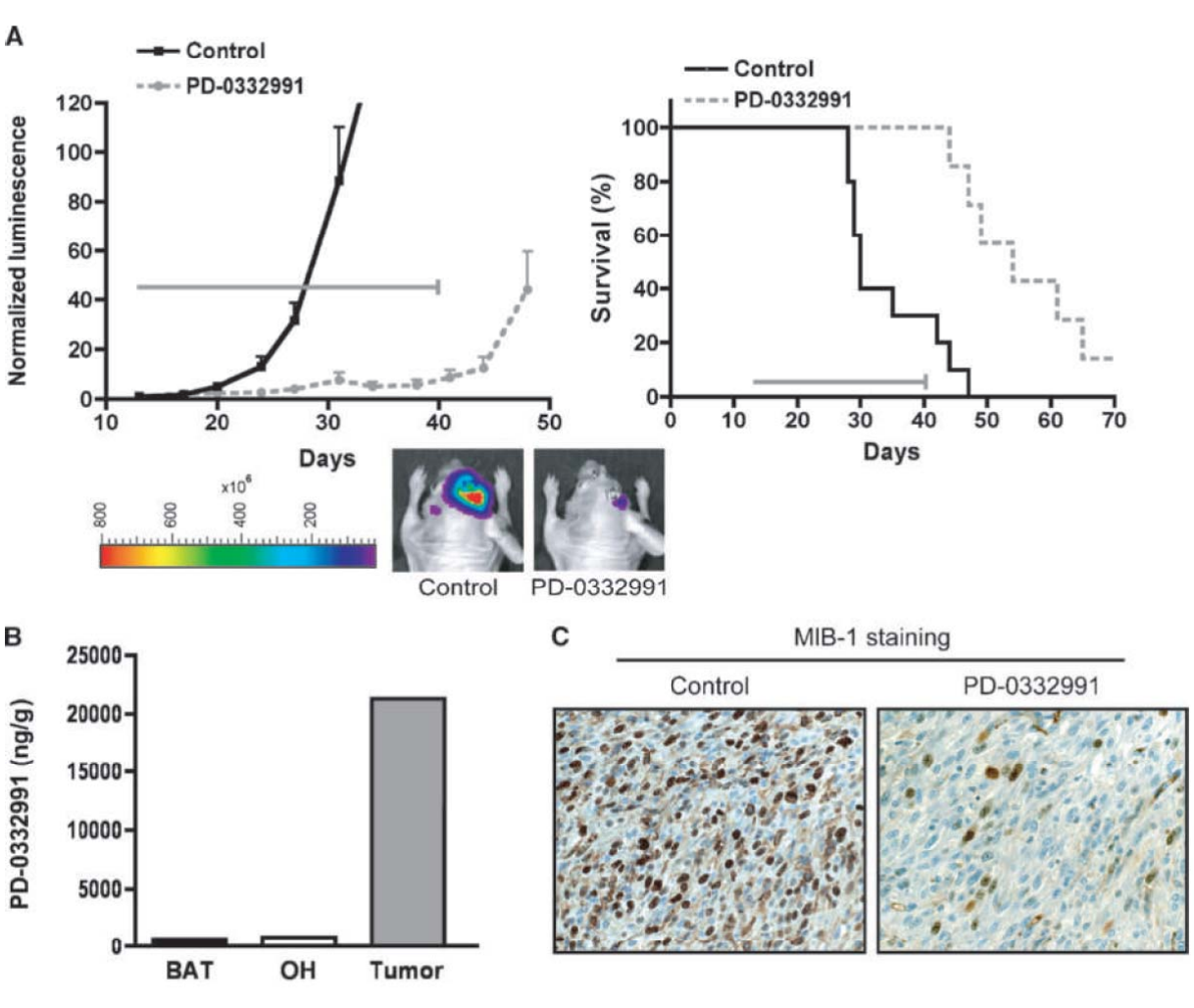


TCGA

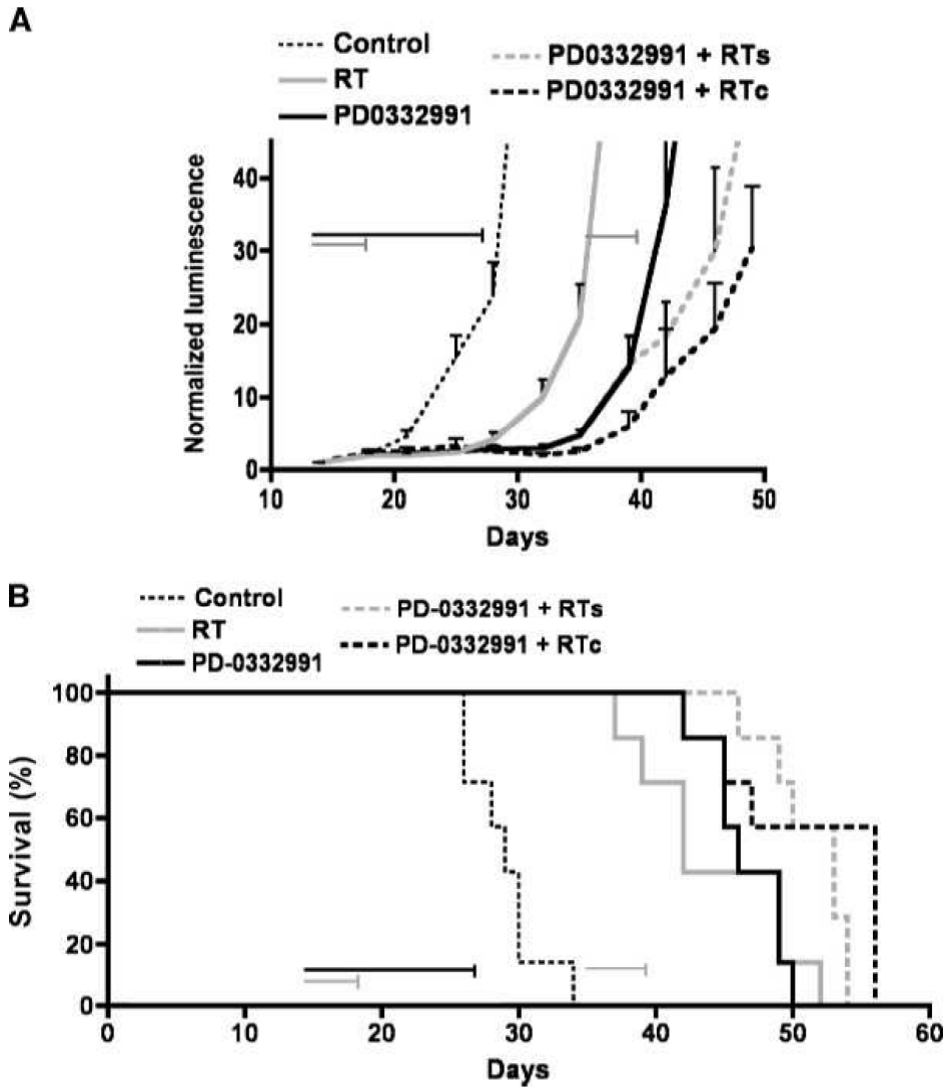


The Cancer Genome Atlas Research Network. *Nature*. 2008;455:1061-1068;

PD-0332991 (CDK 4/6 inhibitor)
Michaud et al: Cancer Res 2010;70:3228

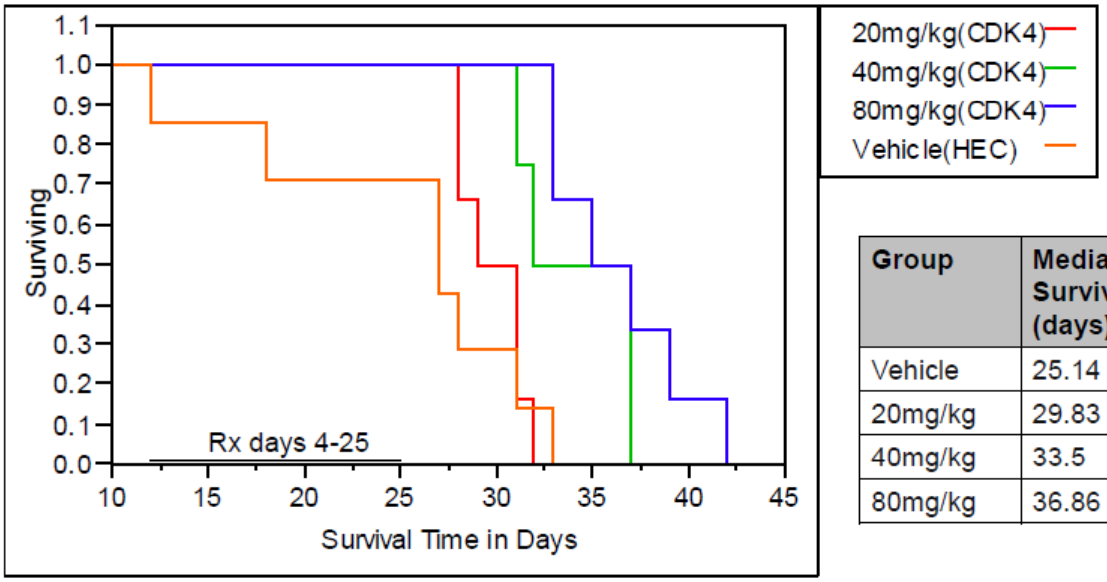


Michaud et al: Cancer Res 2010;70:3228

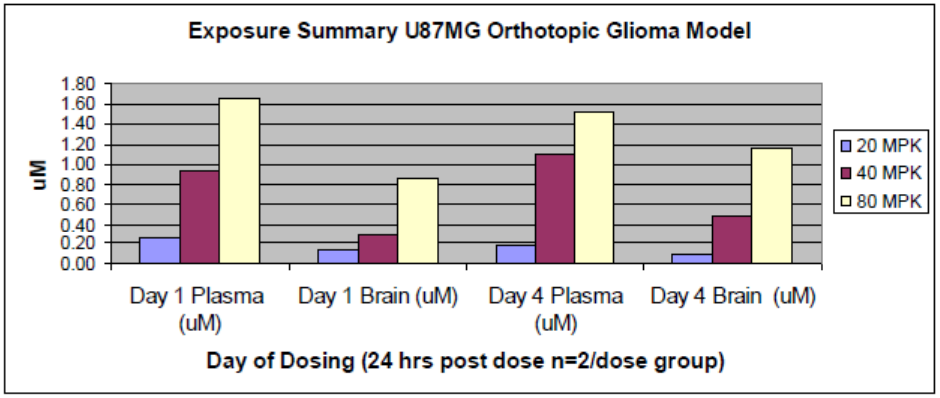


LY2835219 (CDK4/6 Inhibitor)
Sanchez Martinez et al

Dose-dependent efficacy of LY2835219-MsOH in a rat orthotopic glioma model

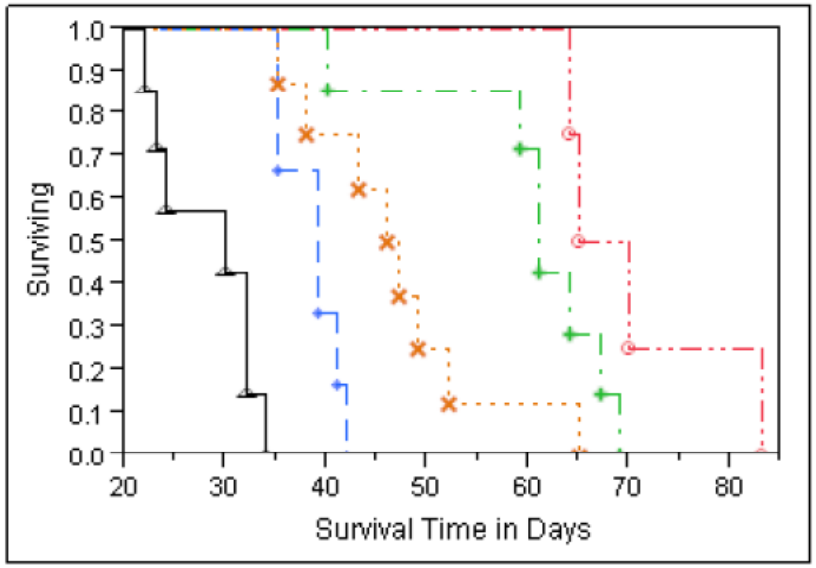


Group	Median Survival (days)	SE	P value Log-rank	p value Wilcoxon
Vehicle	25.14	2.82	-	-
20mg/kg	29.83	0.70	0.5	0.146
40mg/kg	33.5	1.32	0.0316	0.0333
80mg/kg	36.86	1.28	0.0006	0.0010



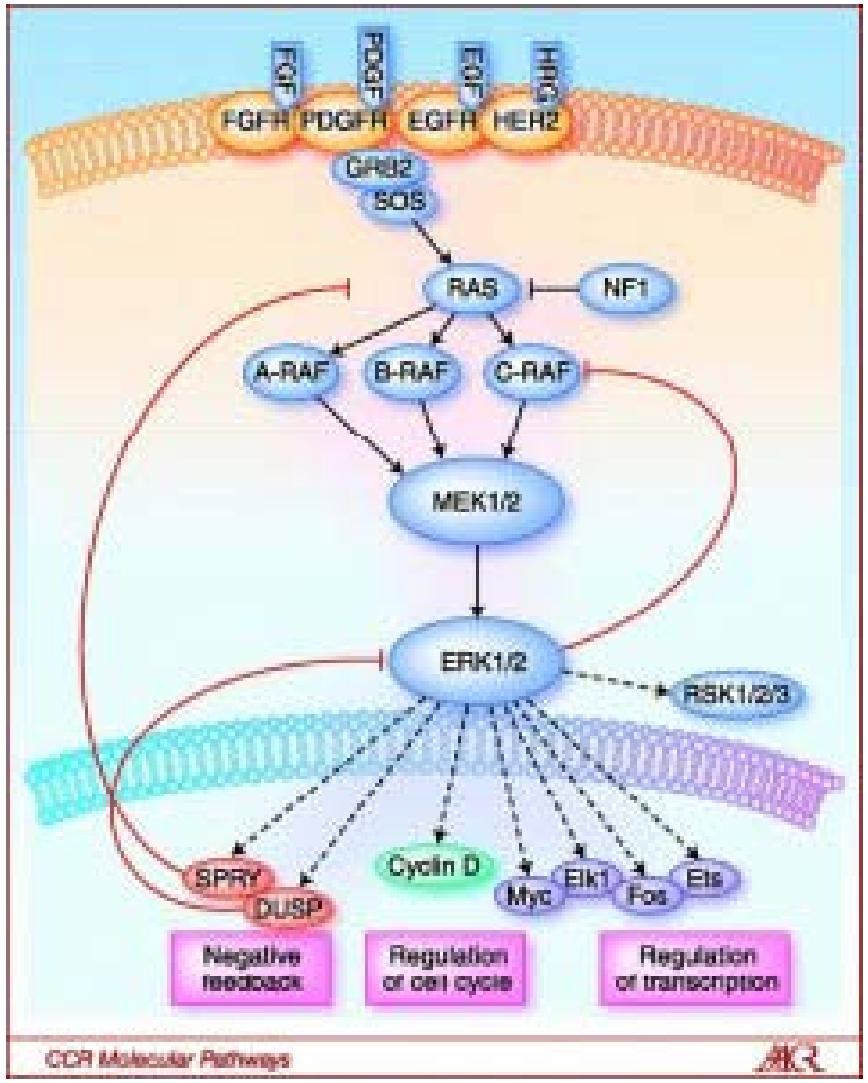
Sanchez-Martinez et al

Combinations of LY2835219-MsOH and temozolomide are additive in a rat orthotopic glioma model



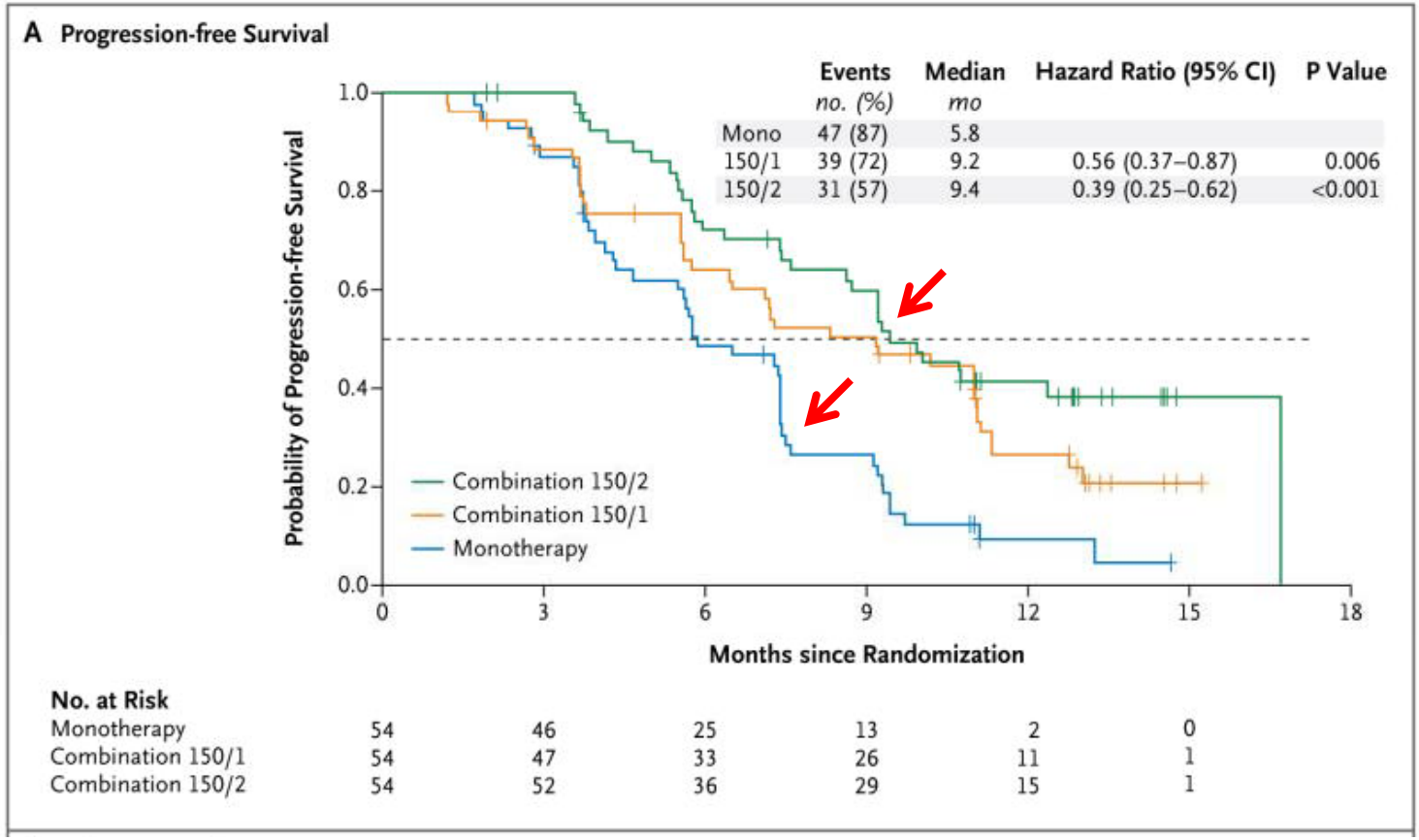
LY2835219-MsOH 40mg/kg q2dx10 & TMZ IP 3mg/kg(Days 6&13)
LY2835219-MsOH 40mg/kg qdx20 & TMZ IP 3mg/kg(Days 6 & 13)
LY2835219-MsOH PO 40mg/kg qdx20
TMZ IP 3mg/kg(Days 6 & 13)
Vehicle PO 1mL/kg qdx20

BRAF and/or MEK inhibitors for BRAFV600E mutated gliomas?

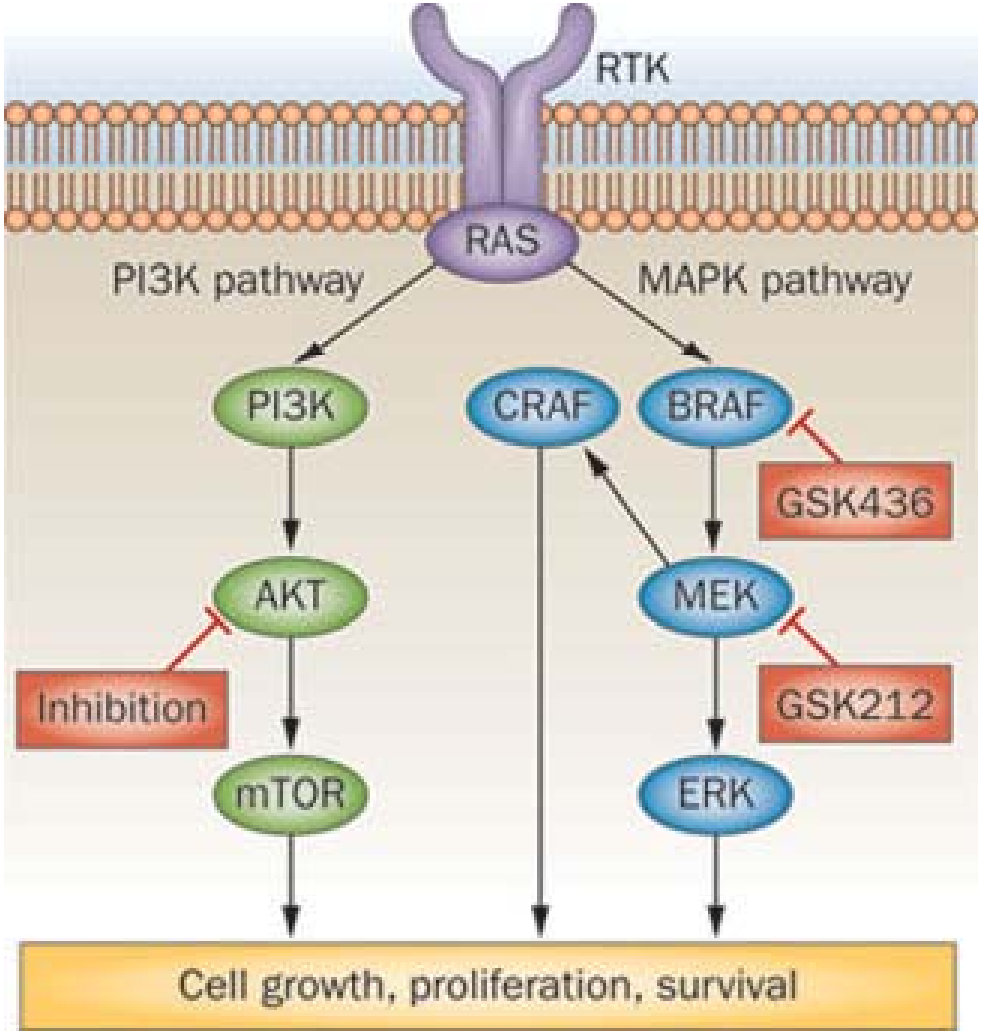


Flaherty et al. Combined BRAF and MEK Inhibition in Melanoma with BRAF V600E Mutations

NEJM 2012; 2012 Nov;367(18):1694-703



A Phase II, Open-label Study in Patients with BRAF V^{600E} Mutated Rare Cancers with Several Histologies to Investigate the Clinical Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib



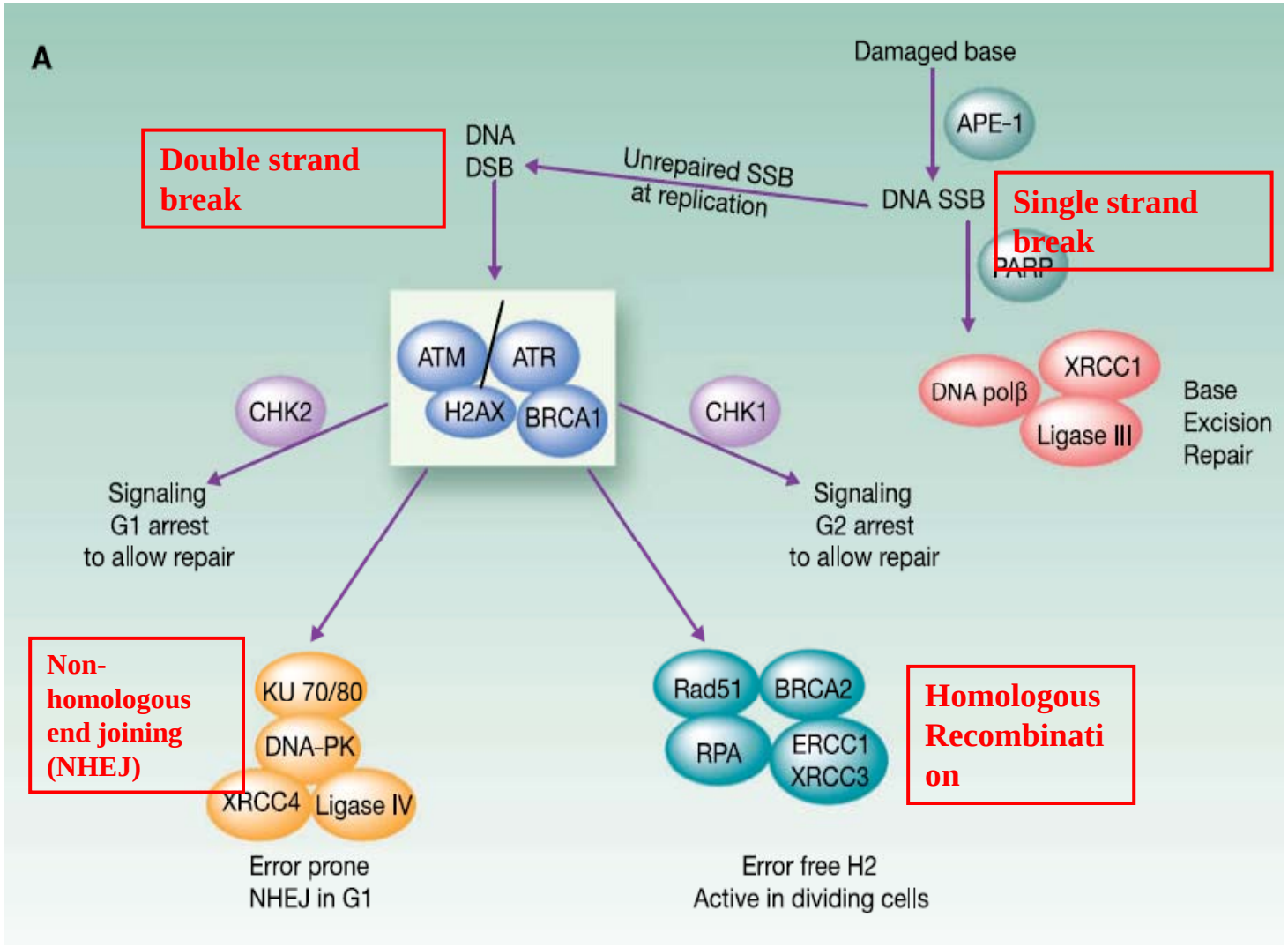
Dabrafenib

Trametanib

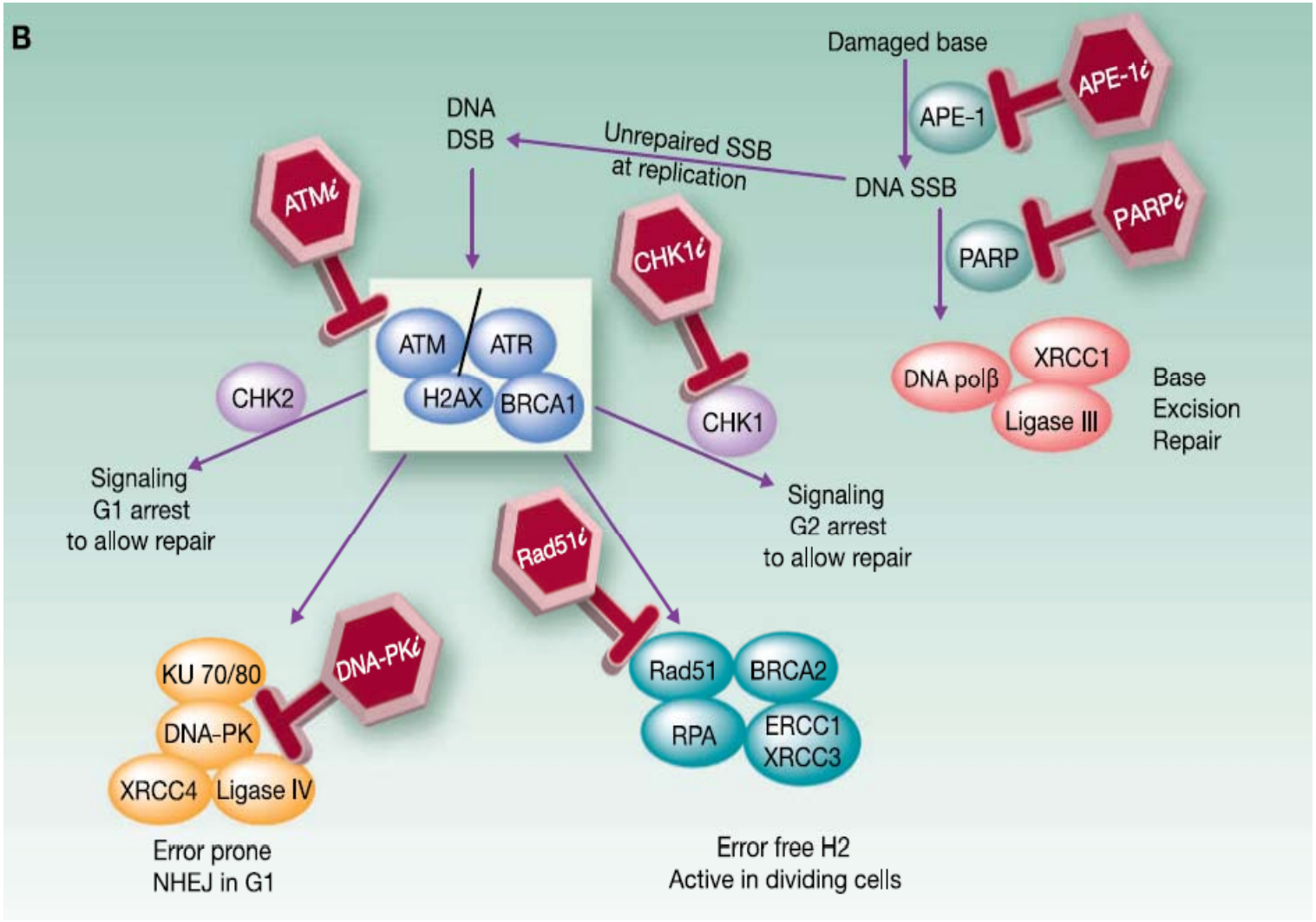
Histologies

- Anaplastic Thyroid Carcinoma
- Biliary Tract Cancer
- Diffuse Large B Cell Lymphoma
- GIST
- Hairy Cell Leukemia
- High Grade Glioma (GBM, Anaplastic PXA, Anaplastic ganglioglioma)
- Low-Grade Gliomas (PXA, Ganglioglioma, Pilocytic Astrocytoma)
- Multiple Myeloma
- NSGCT/NGGCT
- Small Intestine Adenocarcinoma

Plummer: Clin Cancer Res 2010;16(18); 4527–31



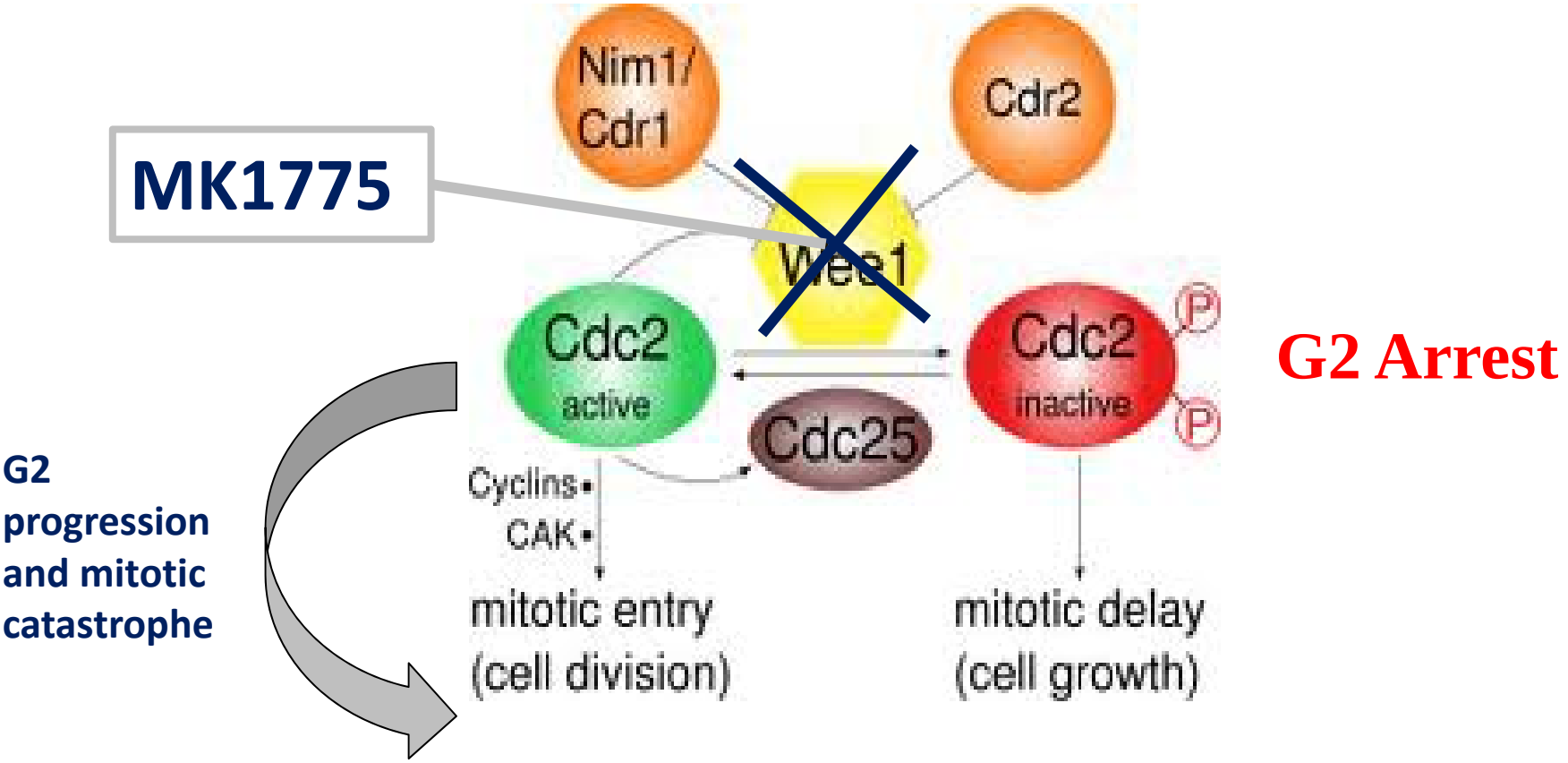
Plummer: Clin Cancer Res 2010;16(18); 4527–31



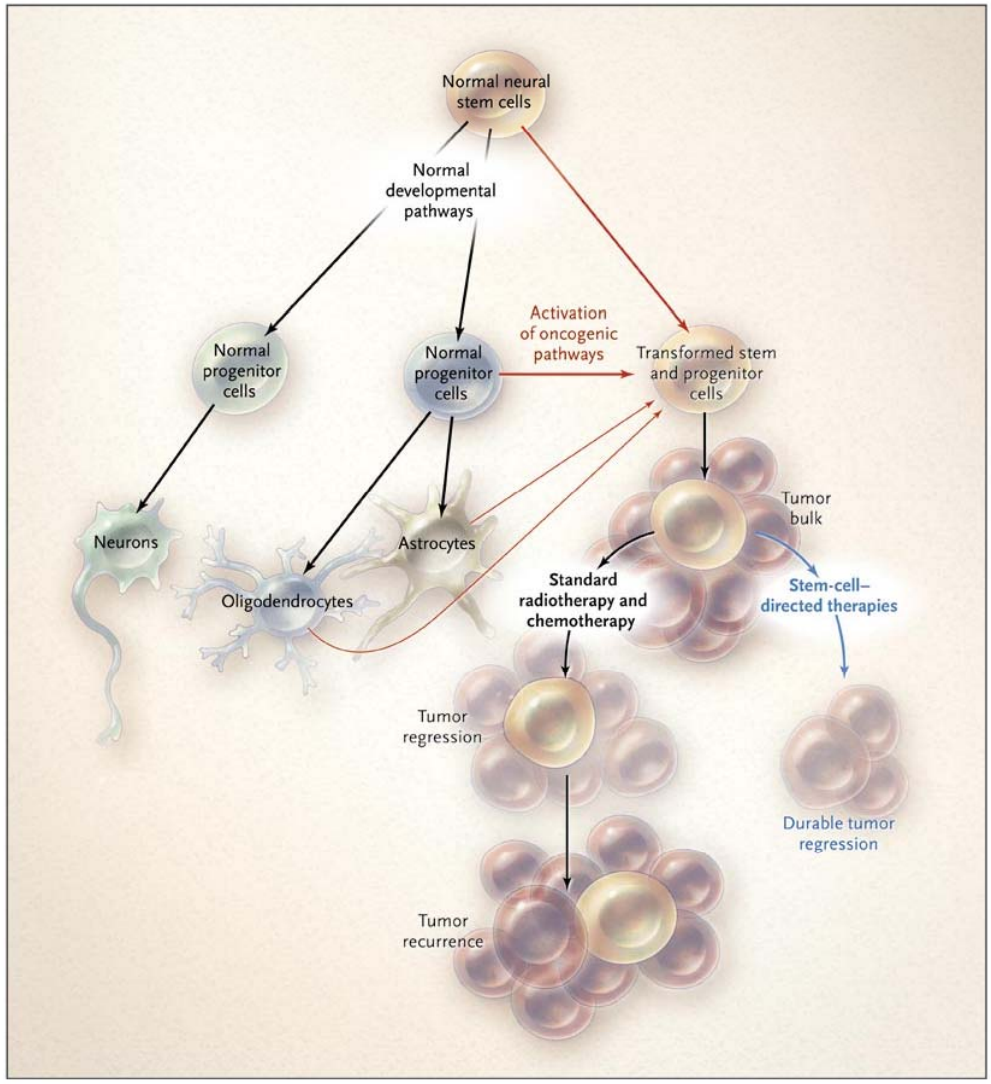
Increasing Cytotoxicity of TMZ and RT

- **PARP Inhibitors**
  - ABT 888 (ABTC; RTOG)
- **Wee1 Inhibitor**
  - MK1775

Wee1

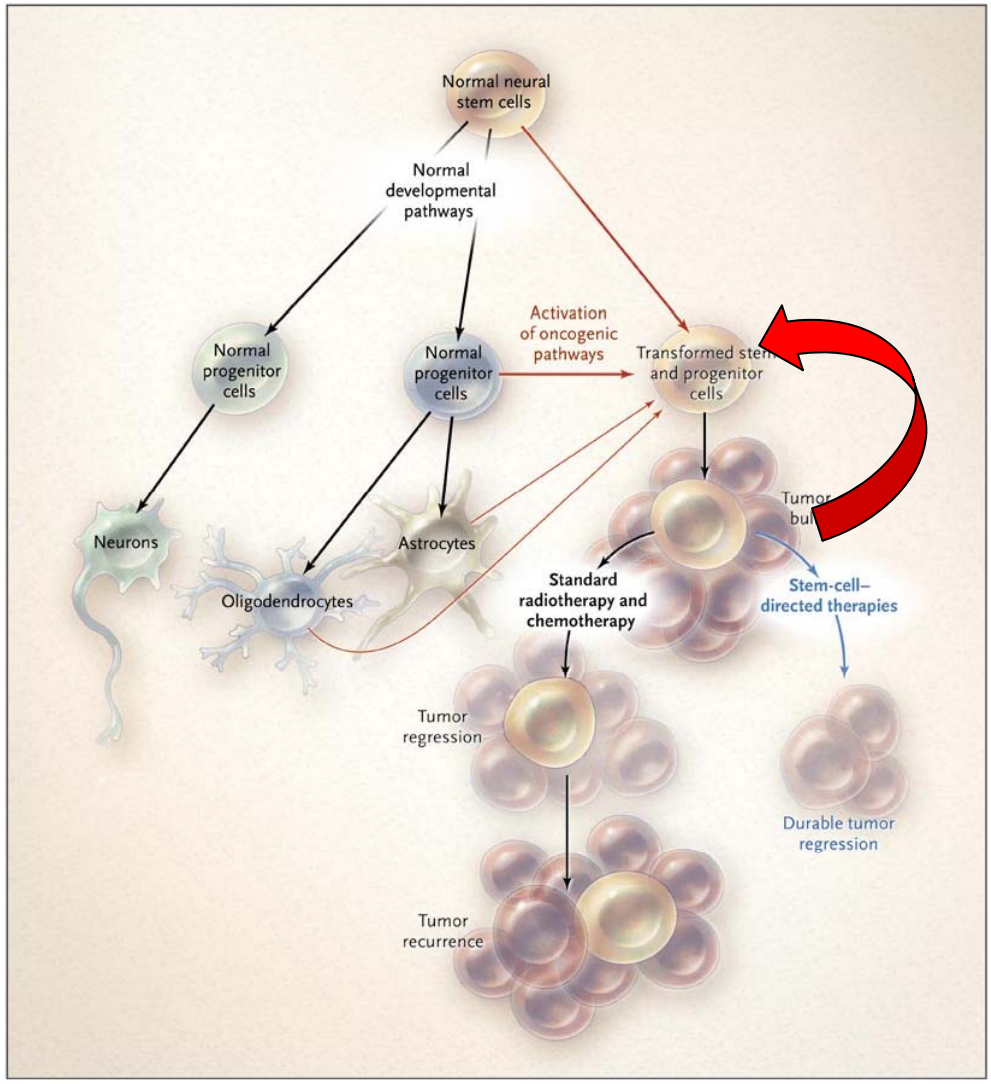

MK1775
Nim1/
Cdr1
Cdr2
Wee1
Cdc2
active
Cdc25
Cdc2
inactive
P
P
Cyclins
CAK
mitotic entry
(cell division)
mitotic delay
(cell growth)
G2 Arrest
G2
progression
and mitotic
catastrophe

Glioma Initiating Cells



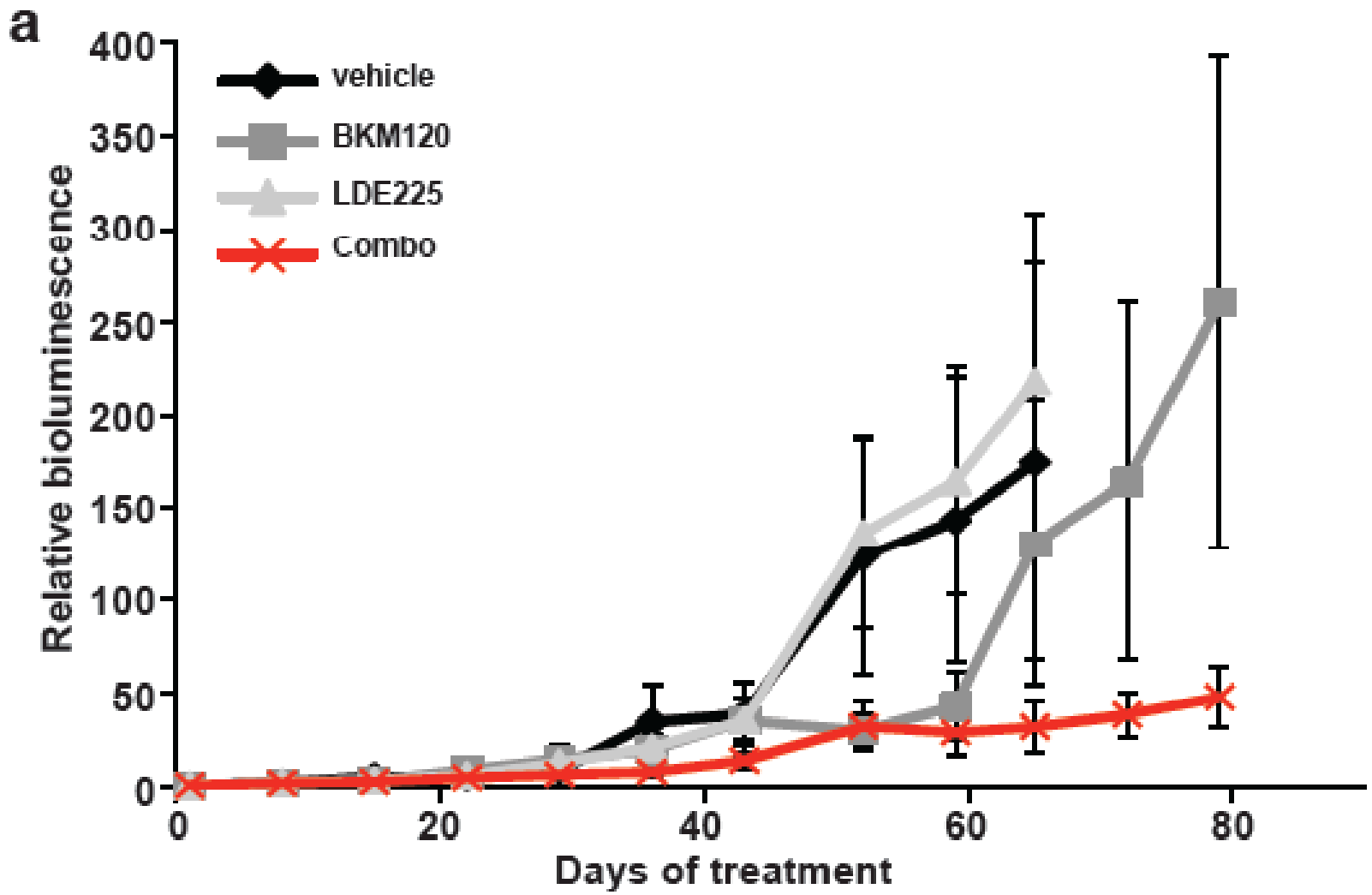
Wen PY, Kesari S. N Engl J Med 2008;359:492-507

Glioma Initiating Cells



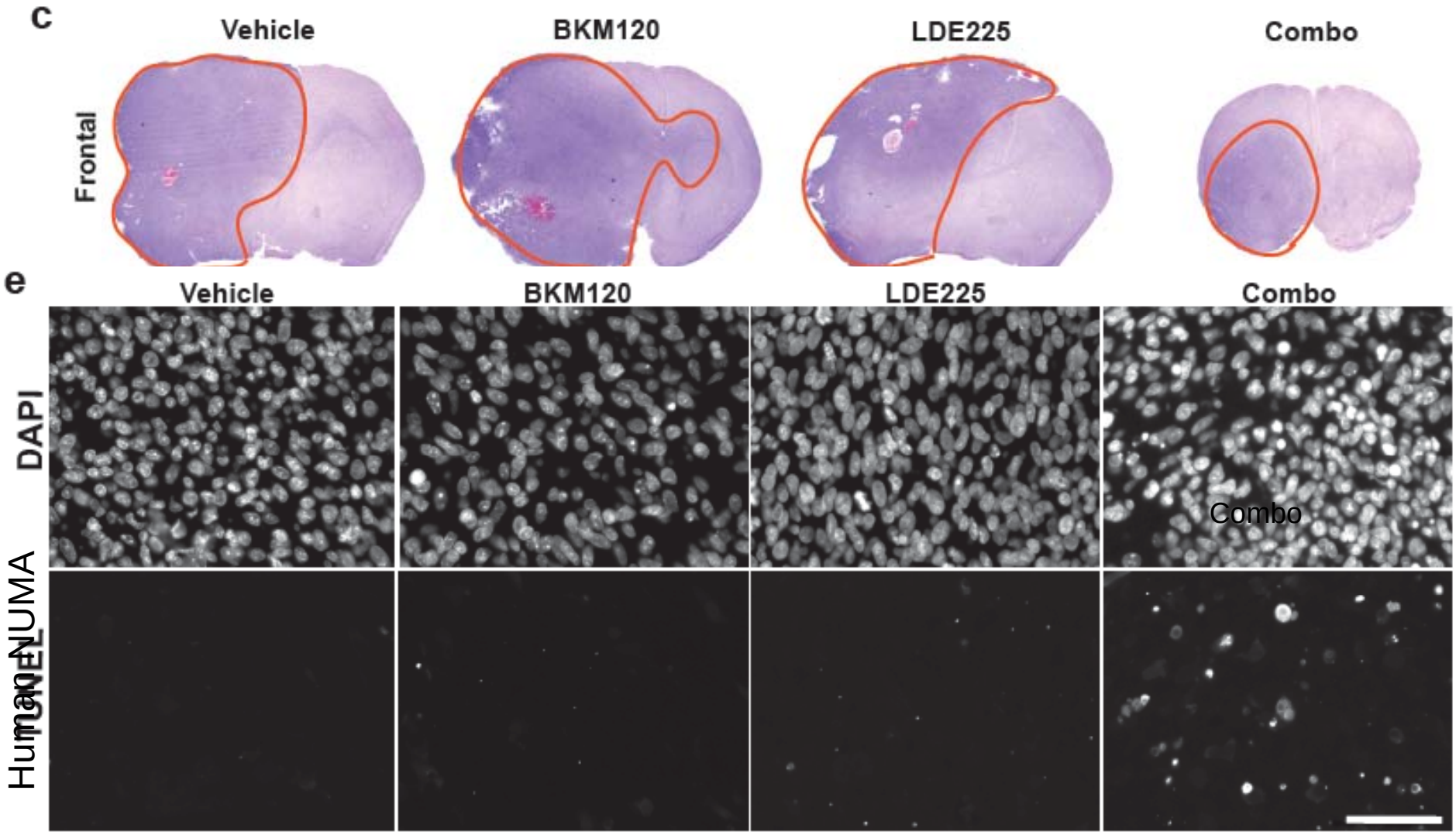
Wen PY, Kesari S. N Engl J Med 2008;359:492-507

BKM120+LDE225 In vivo data: orthotopic xenograft



Mariella Gruber-Olipitz et al. Nature Med. In Press

LDE225+BKM120



Many choices; limited resources

Challenges

- Phase II trials often not predictive of positive outcome in phase III studies
  - Imatinib mesylate and hydroxyurea
  - Enzastaurin
  - Cediranib
  - Cintredekin Besudotox *(IL13-PE38QQR)*
  - Cilengitide
- More drugs and more combinations
- Limited resources
- Need more efficient trial designs
- Need better response criteria, endpoints and more efficient trials and design

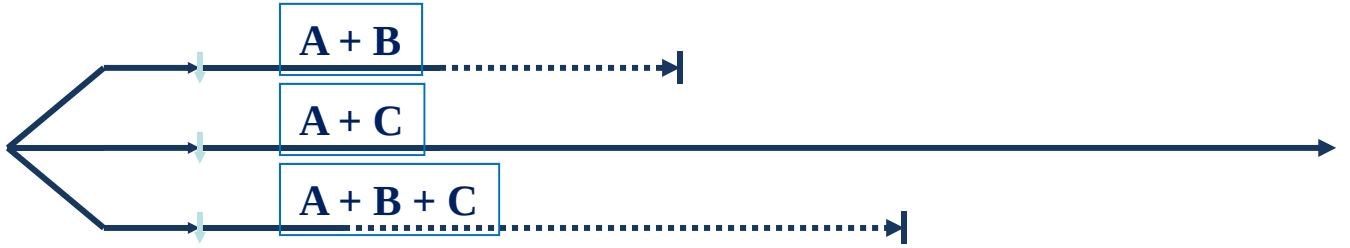
"I want you to find a bold and innovative way to do everything exactly the same way it's been done for 25 years."

New Clinical Trial Designs

- **Improve efficiency**
  - Rapid elimination of ineffective regimens
  - Test multiple combinations simultaneously
  - Shorter path to definitive testing
- **Designs**
  - "Pick the Winner"
  - Seamless integration of phase II/III trials
  - Sequential Accrual Design for Phase I/II studies
  - Factorial Design
  - Adaptive Randomization

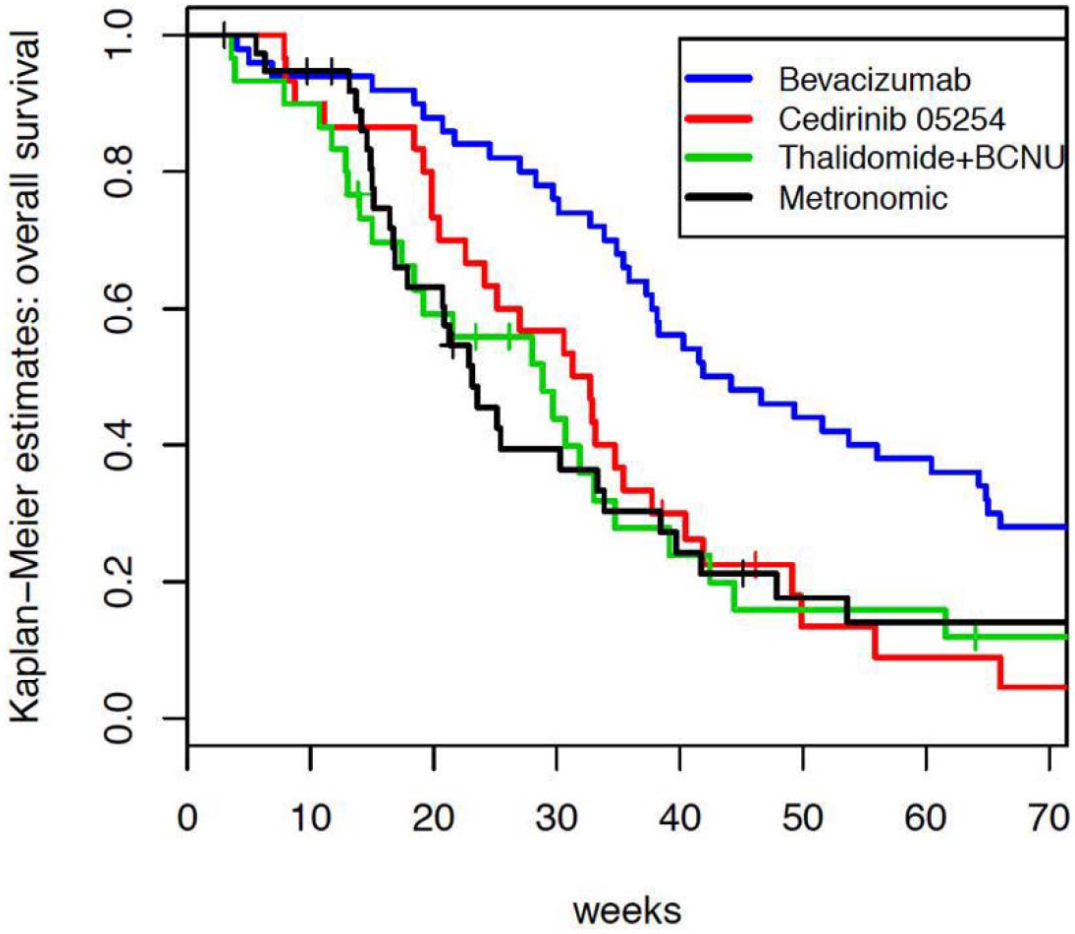
Adaptive Randomization Strategies

- Multiple arm study
- Allocation of patients based on Bayesian probability of treatment efficacy
- Treatment arms with success are more likely to accrue patients
- Treatment arms with poor results are dropped, alternative arms added, and accrual continues until clear evidence of superior treatment(s) emerge

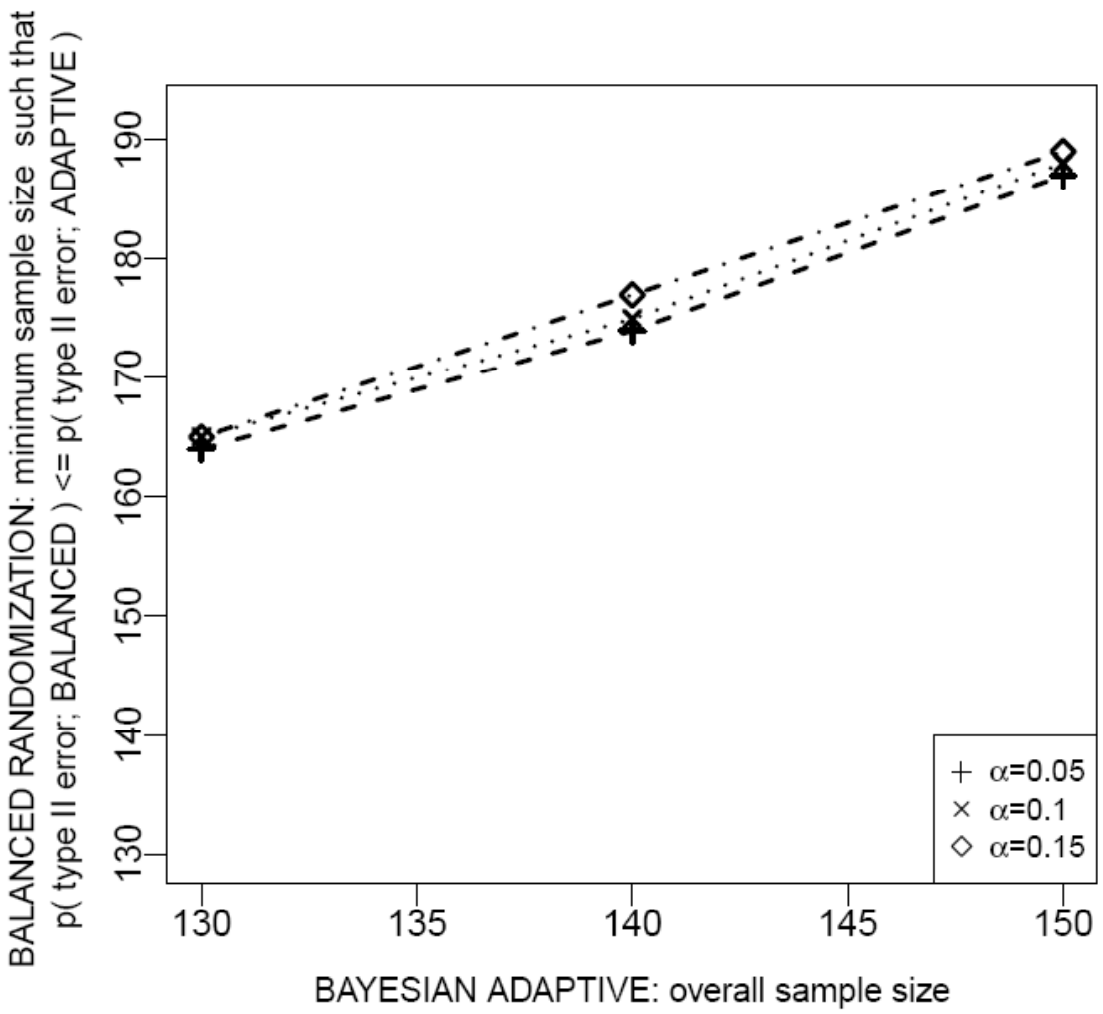


Adaptive Randomized "Bayesian" Design

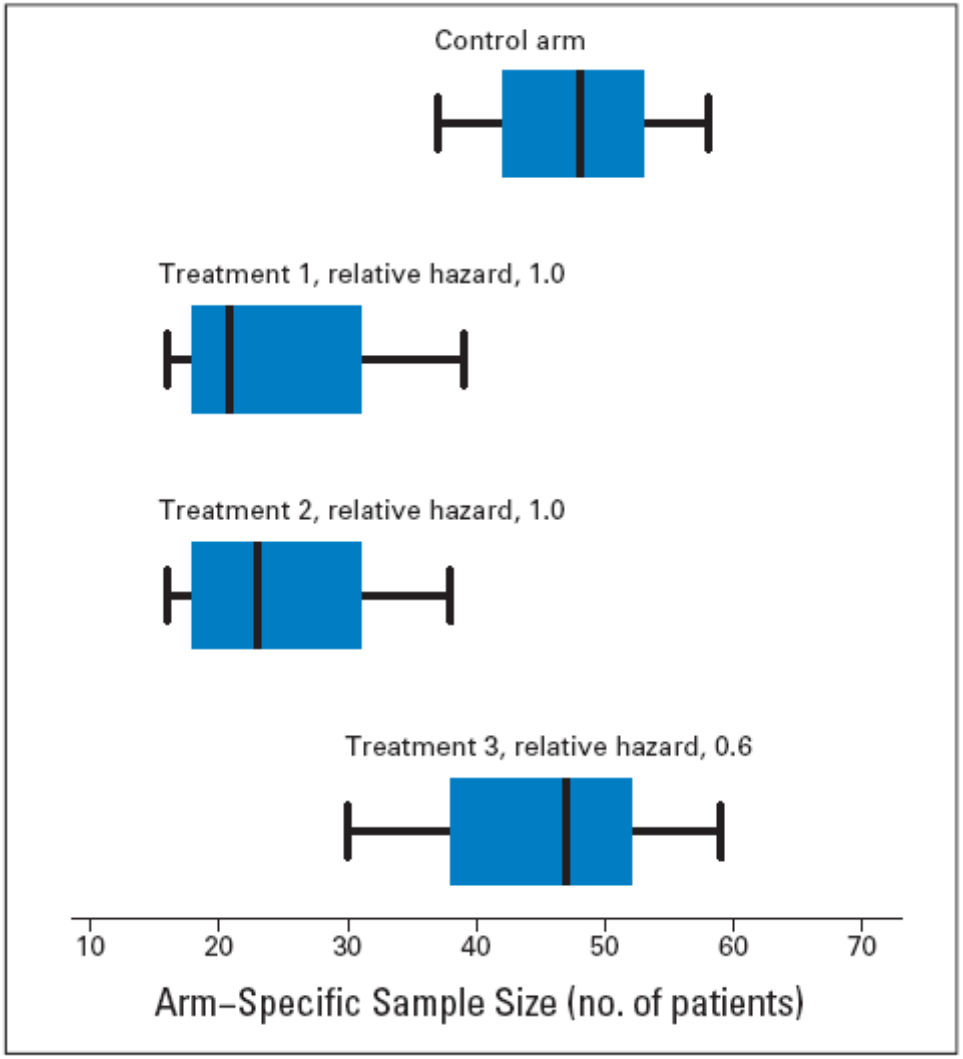
Trippa et al (JCO 2012; *30:3258-3263*)



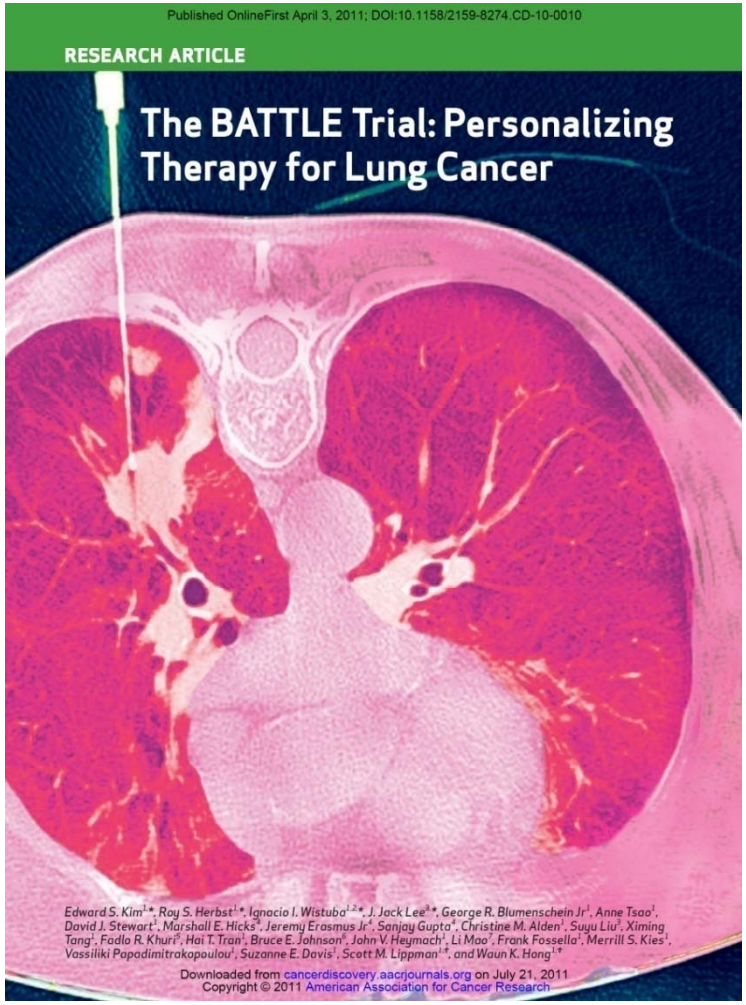
Trippa et al (JCO 2012;30:3258-3263)



Trippa et al (JCO 2012;30:3258-3263)



Ideally we can have trials that evaluate multiple drugs efficiently and identify predictive biomarkers


Published OnlineFirst April 3, 2011; DOI:10.1158/2159-8274.CD-10-0010
RESEARCH ARTICLE
The BATTLE Trial: Personalizing Therapy for Lung Cancer
Edward S. Kim[1,*], Roy S. Herbst[1,*], Ignacio I. Wistuba[1,2,*], J. Jack Lee[3,*], George R. Blumenschein Jr[1], Anne Tsao[1], David J. Stewart[1], Marshall E. Hicks[4], Jeremy Erasmus Jr[4], Sanjay Gupta[4], Christine M. Alden[1], Suyu Liu[3], Ximing Tang[2], Fadlo R. Khuri[5], Hai T. Tran[1], Bruce E. Johnson[6], John V. Heymach[1], Li Mao[7], Frank Fossella[1], Merrill S. Kies[1], Vassiliki Papadimitrakopoulou[1], Suzanne E. Davis[1], Scott M. Lippman[1,8], and Waun K. Hong[1,†]
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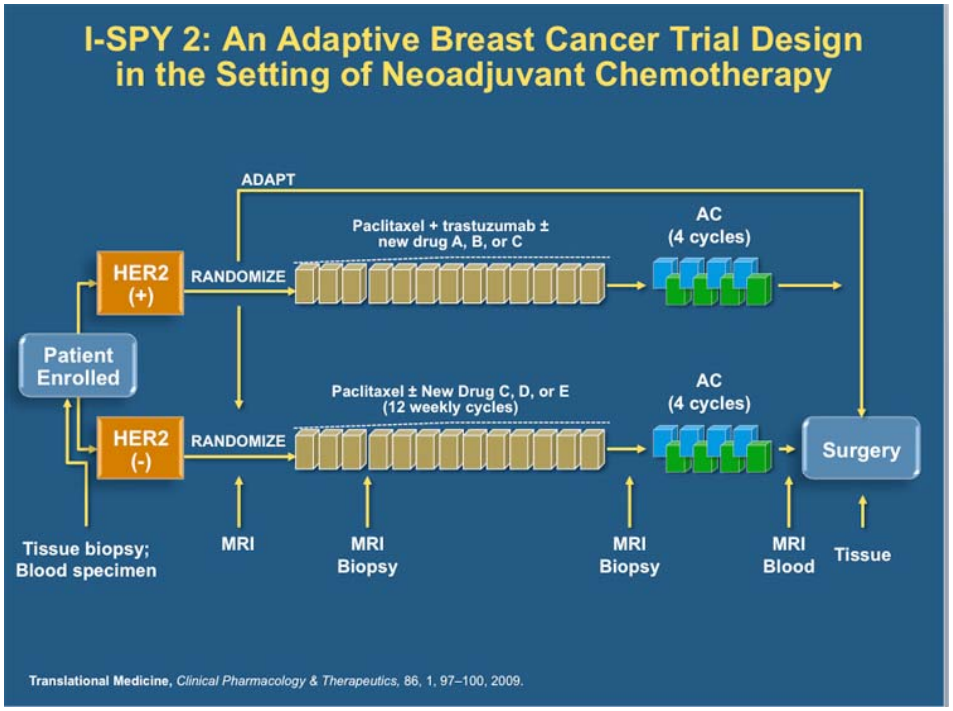
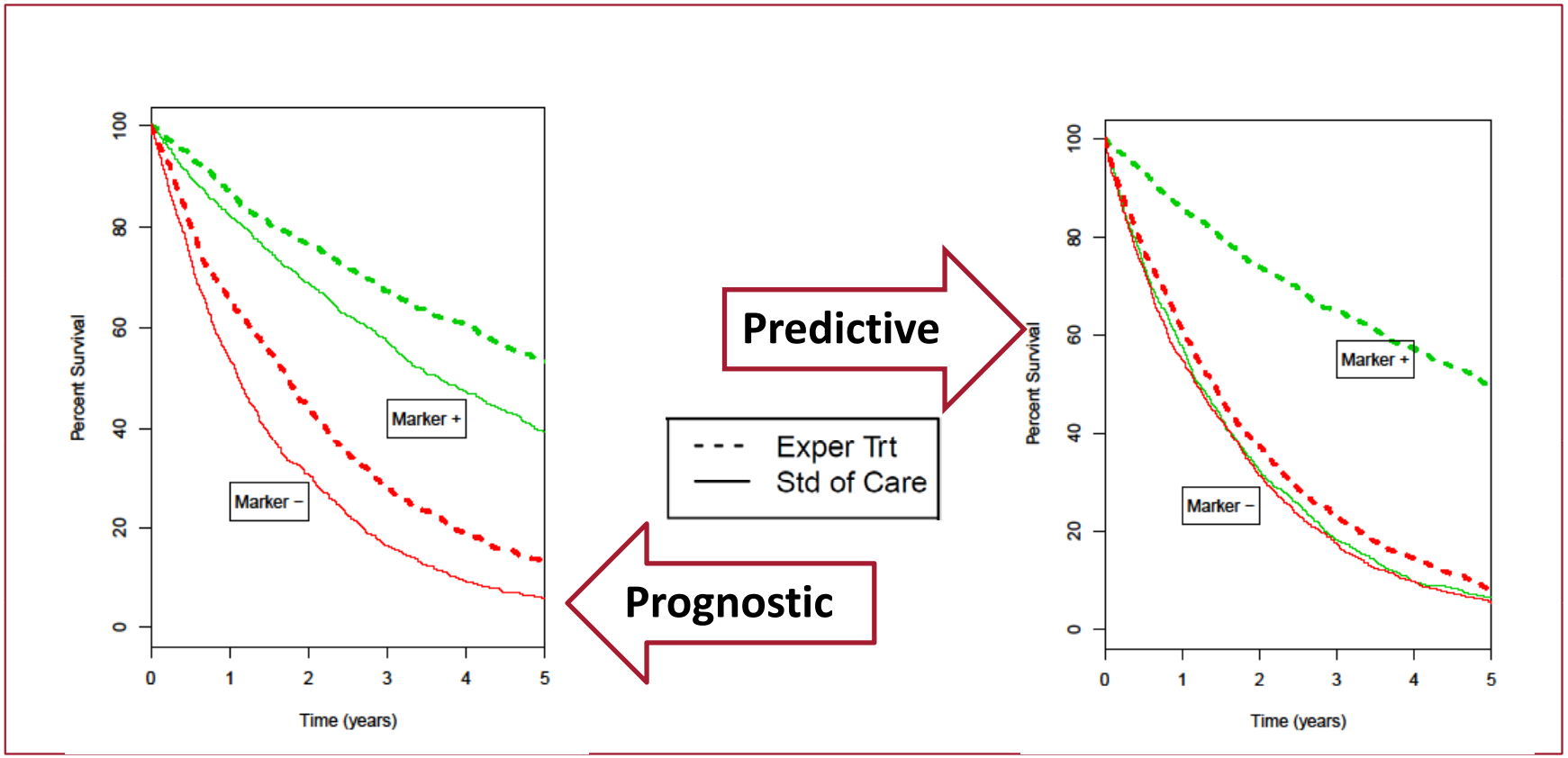
BREAST CANCER
I-SPY 2 TRIAL


I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy
ADAPT
Paclitaxel + trastuzumab ± new drug A, B, or C
AC (4 cycles)
HER2 (+)
RANDOMIZE
Patient Enrolled
Paclitaxel ± New Drug C, D, or E (12 weekly cycles)
AC (4 cycles)
HER2 (-)
RANDOMIZE
Surgery
Tissue biopsy; Blood specimen
MRI
MRI Biopsy
MRI Biopsy
MRI Blood
Tissue
Translational Medicine, Clinical Pharmacology & Therapeutics, 86, 1, 97–100, 2009.

What Molecular Subgroups?

- **EGFR amplification** (45%) or mutation (20%)
- **PTEN loss** (40%) / **PIK3Ca or PIK3R1 mutations** (15%)
- **CDK4/6 amp** (18%); **P16/15 loss (**50%)
- **MDM2 amplification** (15%) (with intact p53
- **PDGFRα amplification** (13%)
- Other less common subgroups

Predictive or Prognostic Biomarkers



EGFR	PI3K	MDM2	CDK4/6	n
+	+	+	+	1 (1%)
+	+	+	-	3 (3%)
+	+	-	+	3 (3%)
+	+	-	-	11 (12%)
+	-	+	+	4 (4%)
+	-	+	-	0 (0%)
+	-	-	+	1 (1%)
+	-	-	-	18 (20%)
-	+	+	+	2 (2%)
-	+	+	-	1 (1%)
-	+	-	+	0 (0%)
-	+	-	-	17 (19%)
-	-	+	+	1 (1%)
-	-	+	-	1 (1%)
-	-	-	+	4 (4%)
-	-	-	-	24 (26%)
41 (18)	38 (17)	13 (1)	16 (4)	91

TCGA (all)

Courtesy of
Brian Alexander

How to prioritize overlapping classification

- Adaptive design with equal or weighted randomization will allow each subgroup to be evaluated

Biomarkers

EGFR amplification/ mutation	Pik3Ca/PIK3R1 mutations/ PTEN loss	CDK4/6 amplification/P16 loss
+	+	+
+	+	0
+	0	+
+	0	0
0	0	+
0	+	0
0	+	+
0	0	0

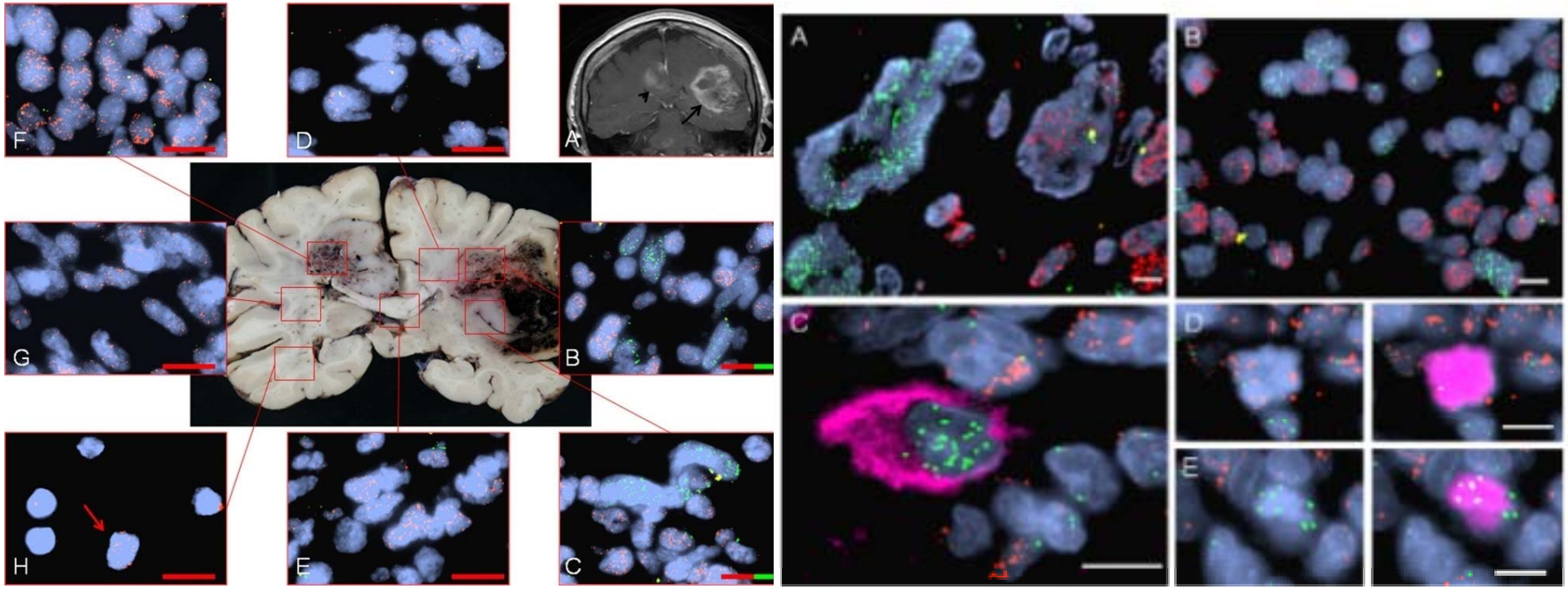
Recurrent GBM

Cancer Cell
Article

Mosaic Amplification of Multiple Receptor Tyrosine Kinase Genes in Glioblastoma

Matija Snuderl,[1,6] Ladan Fazlollahi,[1,6] Long P. Le,[1] Mai Nitta,[1] Boryana H. Zhelyazkova,[1] Christian J. Davidson,[1] Sara Akhavanfard,[1] Daniel P. Cahill,[2,4] Kenneth D. Aldape,[3,4] Rebecca A. Betensky,[5] David N. Louis,[1] and A. John Iafrate[1,*]

810 Cancer Cell 20, 810–817, December 13, 2011 ©2011 Elsevier Inc.

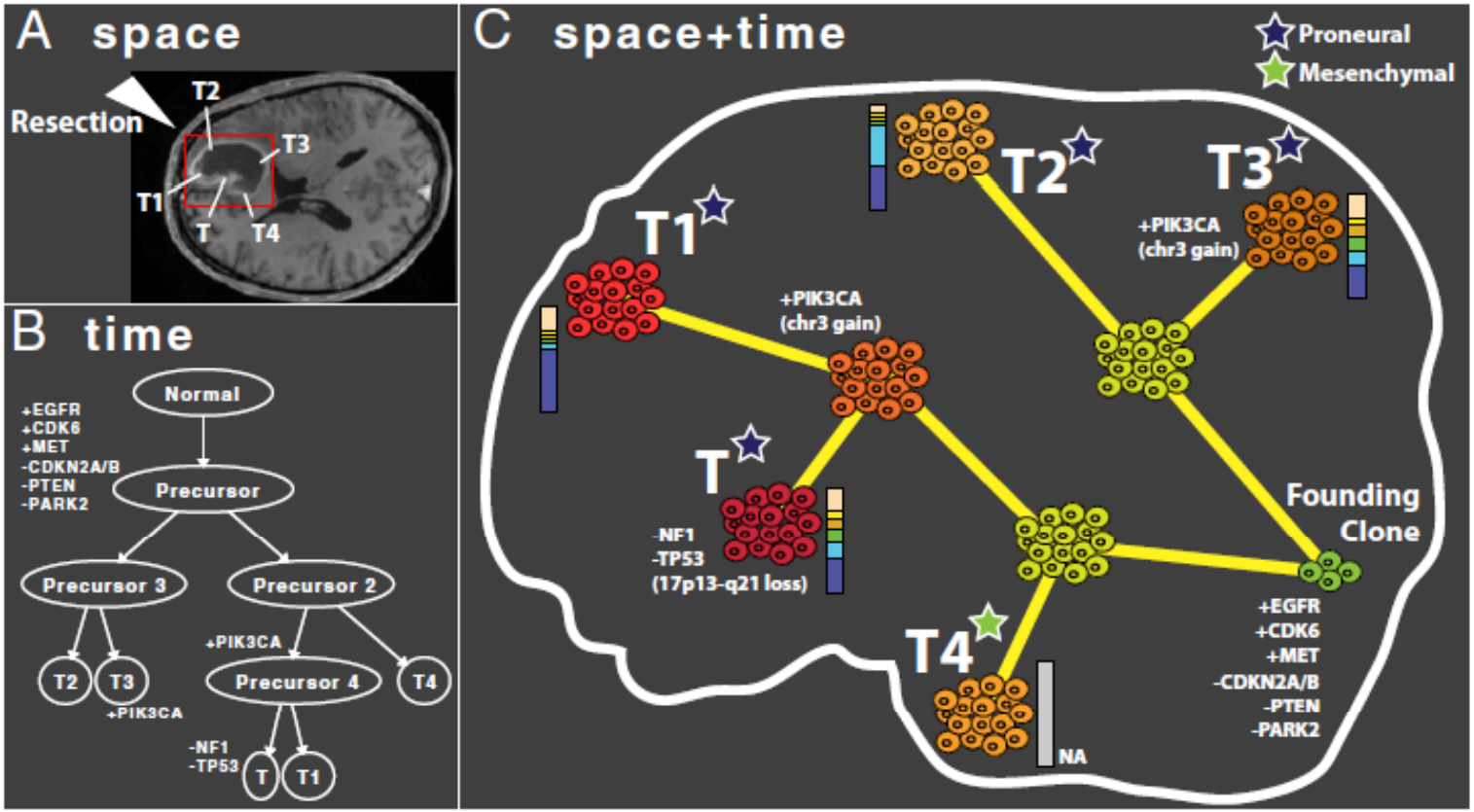


Red: EGFR Amplification
Green: PDGFRA Amplification

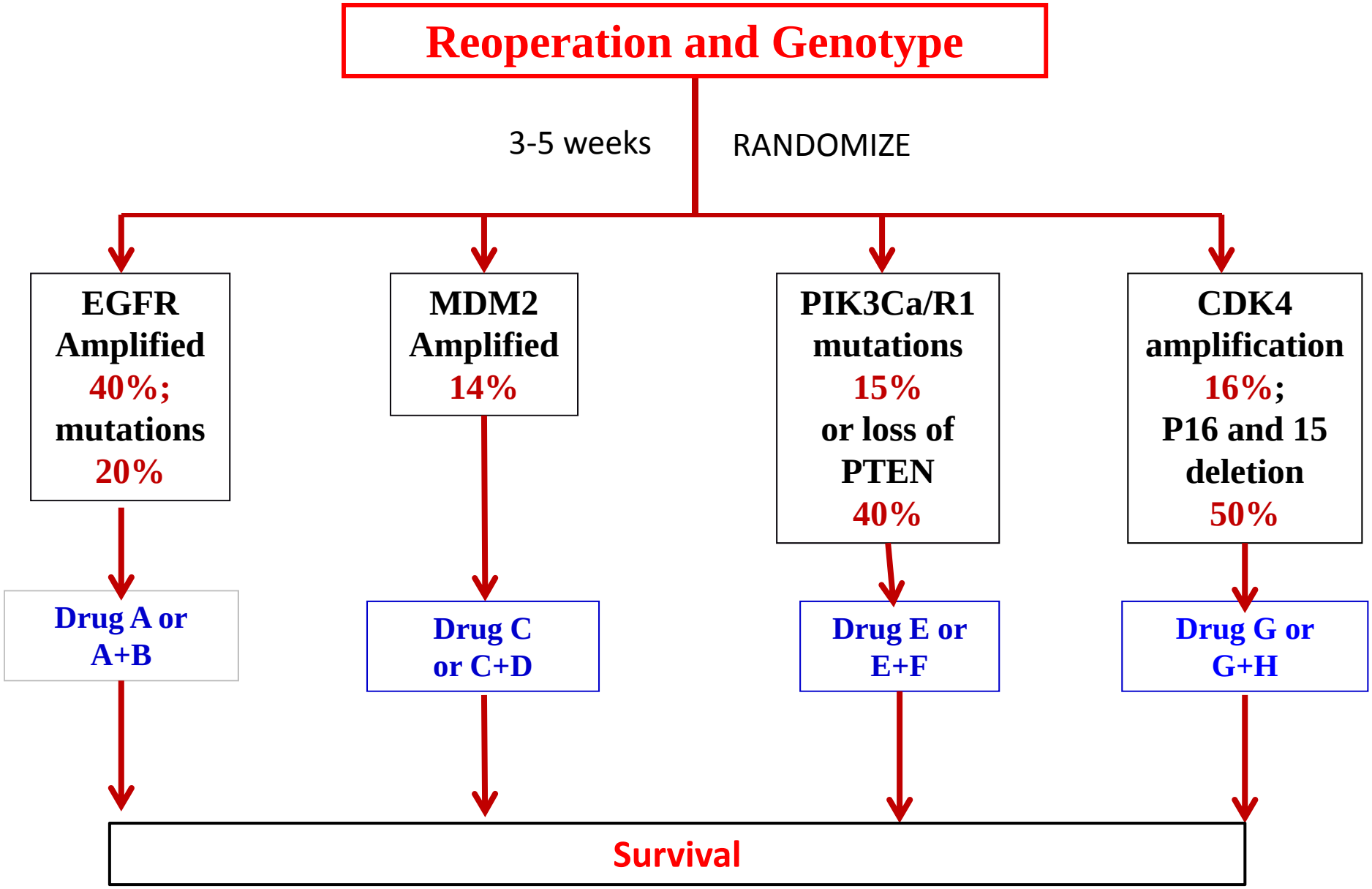
PNAS 2013;110:4013

Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics

Andrea Sottoriva[a,b,c,1], Inmaculada Spiteri[b,1], Sara G. M. Piccirillo[d], Anestis Touloumis[b,e], V. Peter Collins[f], John C. Marioni[e], Christina Curtis[c], Colin Watts[d,g,2], and Simon Tavaré[a,b,h,2]



Recurrent GBM



Surgical Study

Possible Studies

- PI3K + MEK
- EGFR/mTOR inhibitor + Arsenic Trioxide
- etc

PML mediates glioblastoma resistance to mammalian target of rapamycin (mTOR)-targeted therapies

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Iwanami et al:
Cell Cycle 2013:12:10, 1473–1474

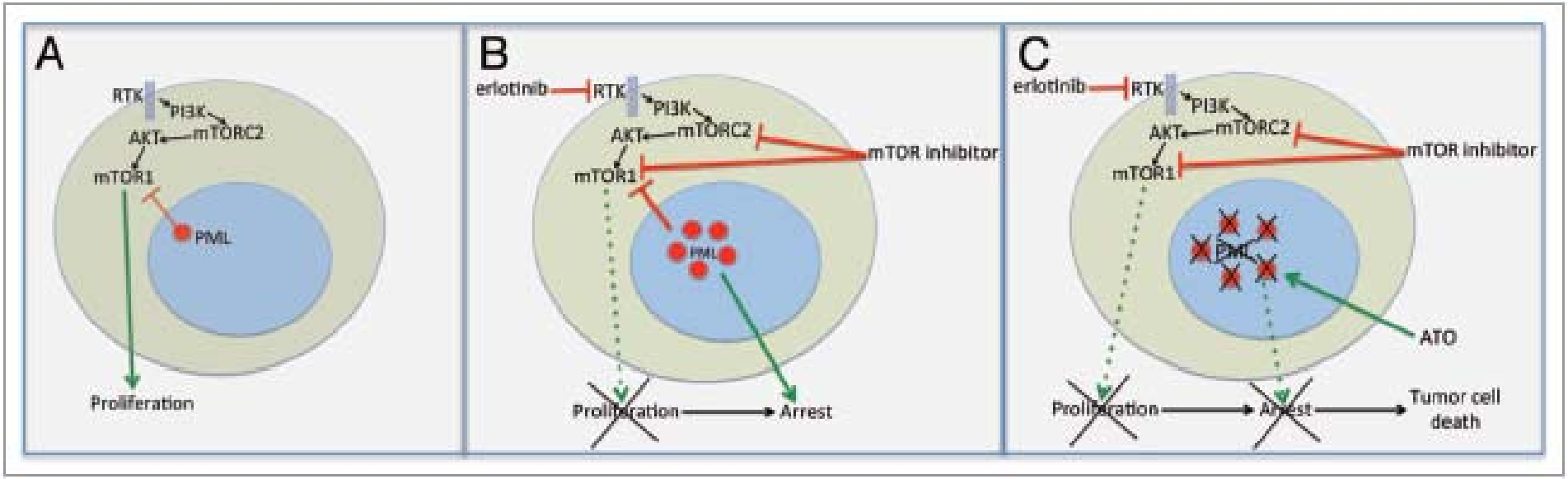
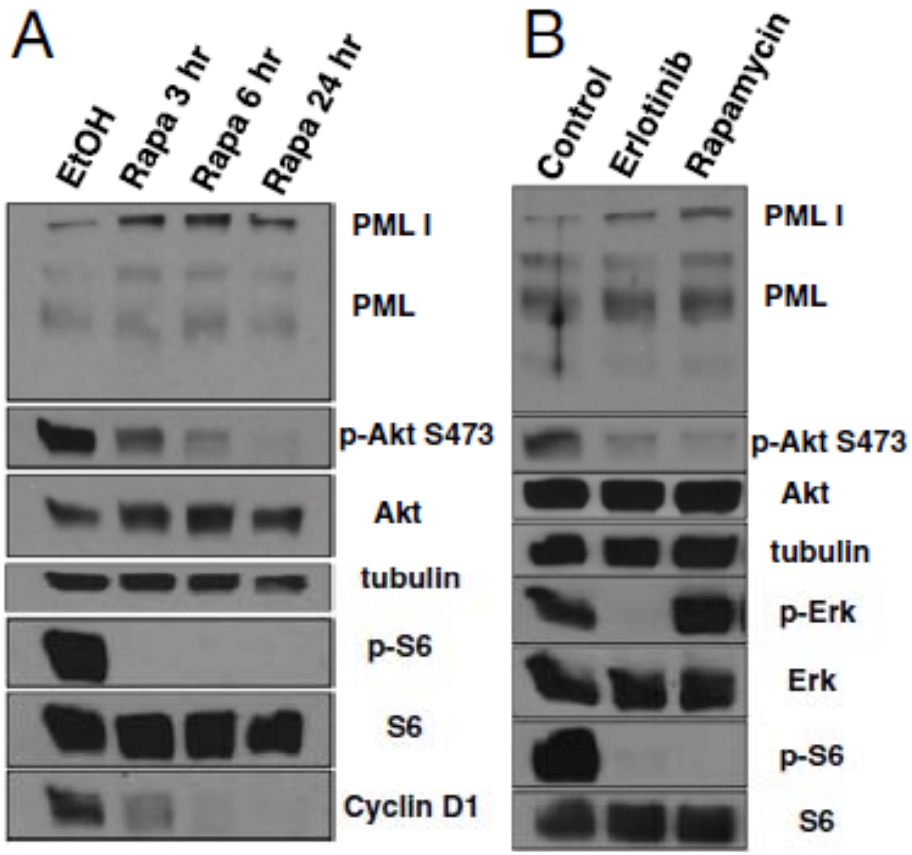
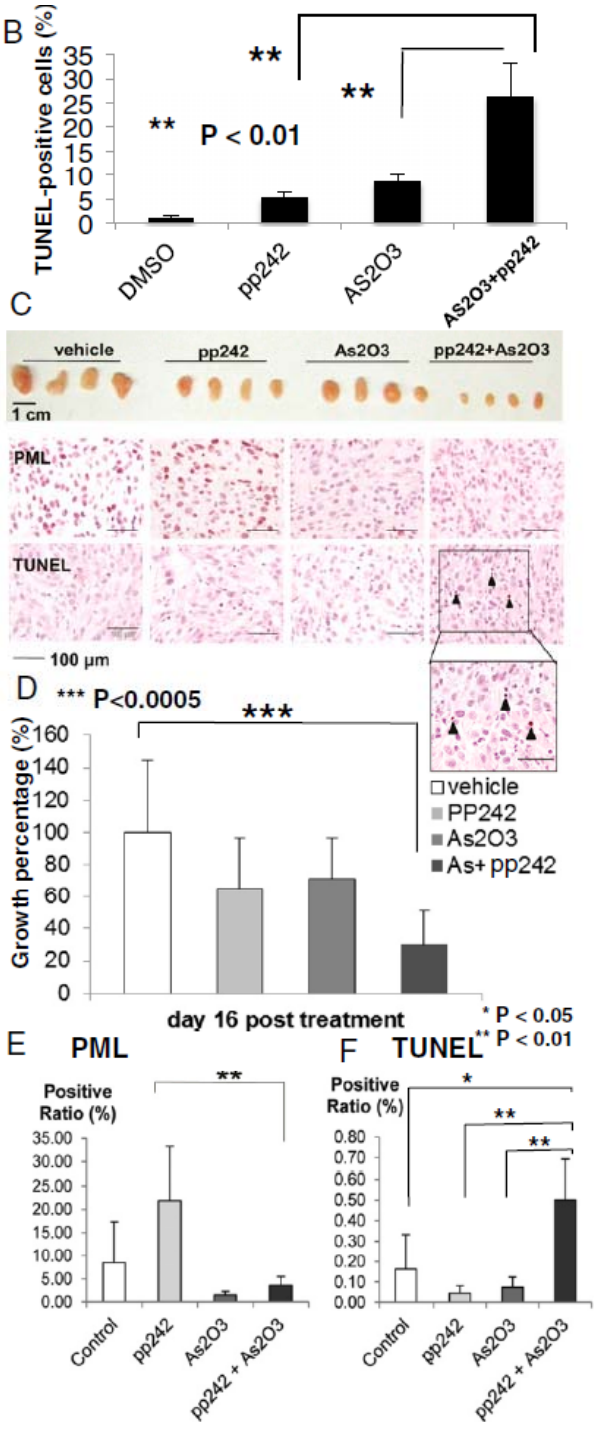


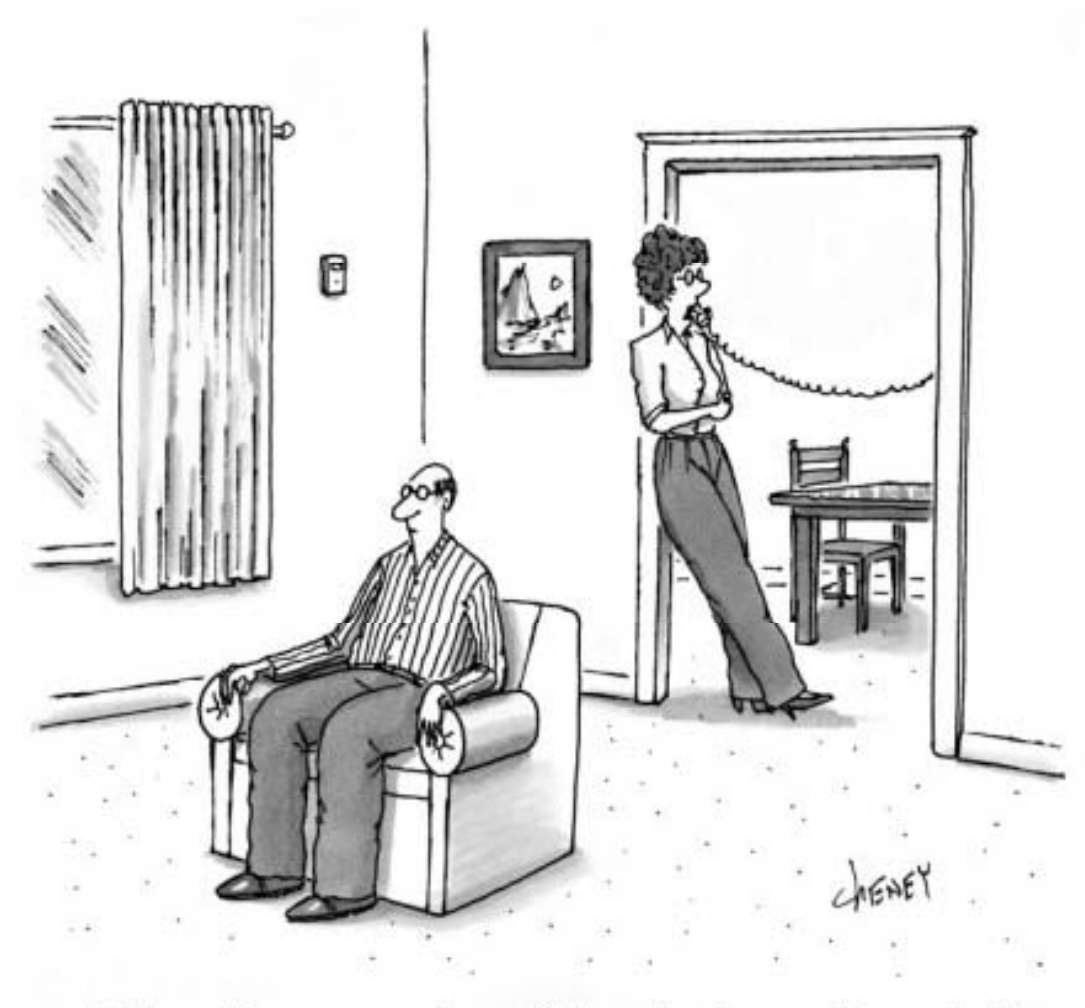
Figure 1. PML mediates resistance to mTOR targeted therapies in GBM, which is reversed by ATO. (**A**) Schematic diagram showing that persistent mTOR signaling promotes tumor cell proliferation, while PML opposes it. (**B**) In GBMs treated with mTOR inhibitors or EGFR inhibitors such as erlotinib that also block mTOR signaling, PML is upregulated, promoting tumor cell arrest. (**C**) ATO, which leads to degradation of PML protein, synergizes with mTOR inhibitors, potently causing tumor cell death.



U87 Human GBM



We are slowly making progress!



"We're making progress—he set off the motion detector this morning."


Patriots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Thank You!


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