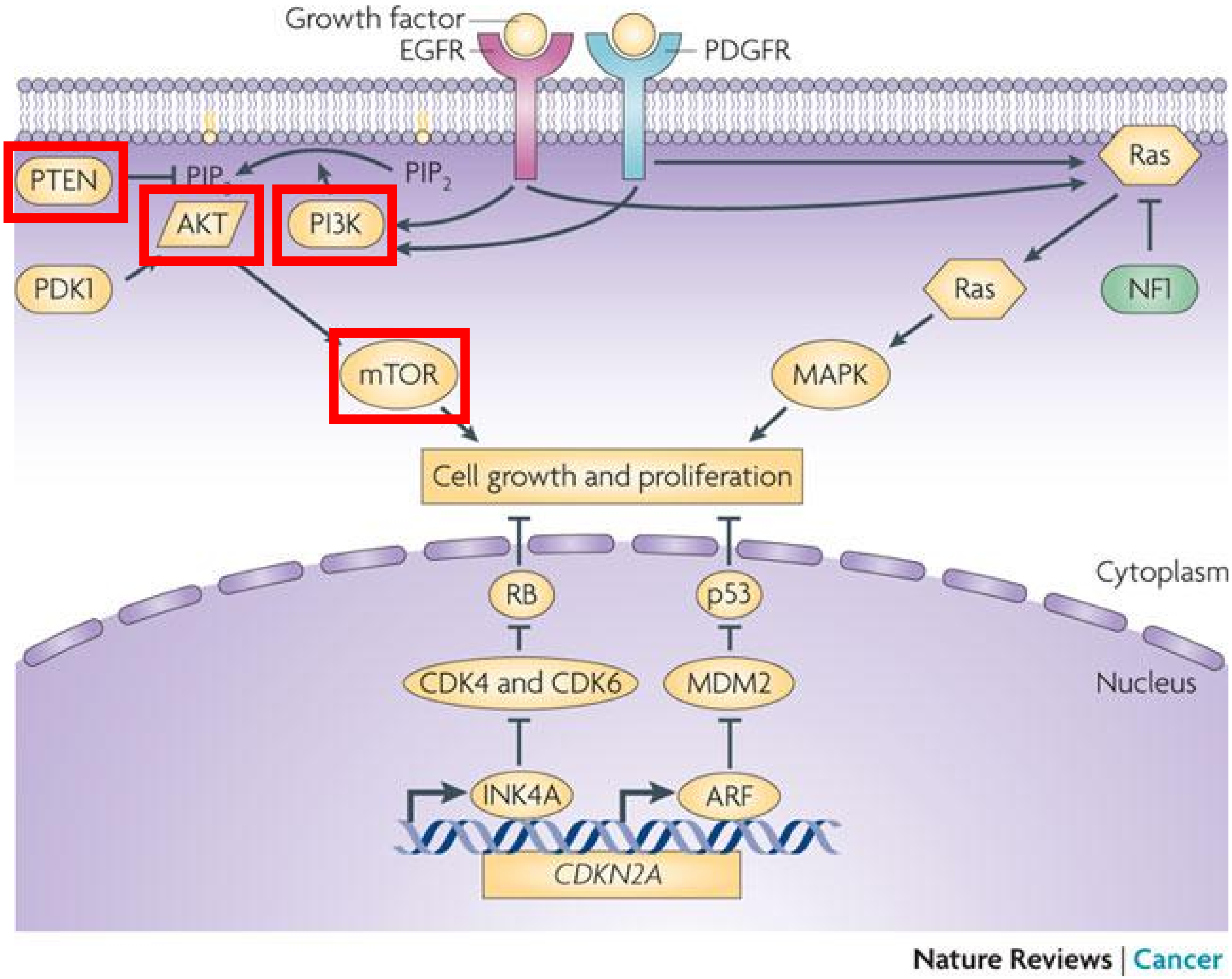
# PI3K-Akt-mTOR in gliomas

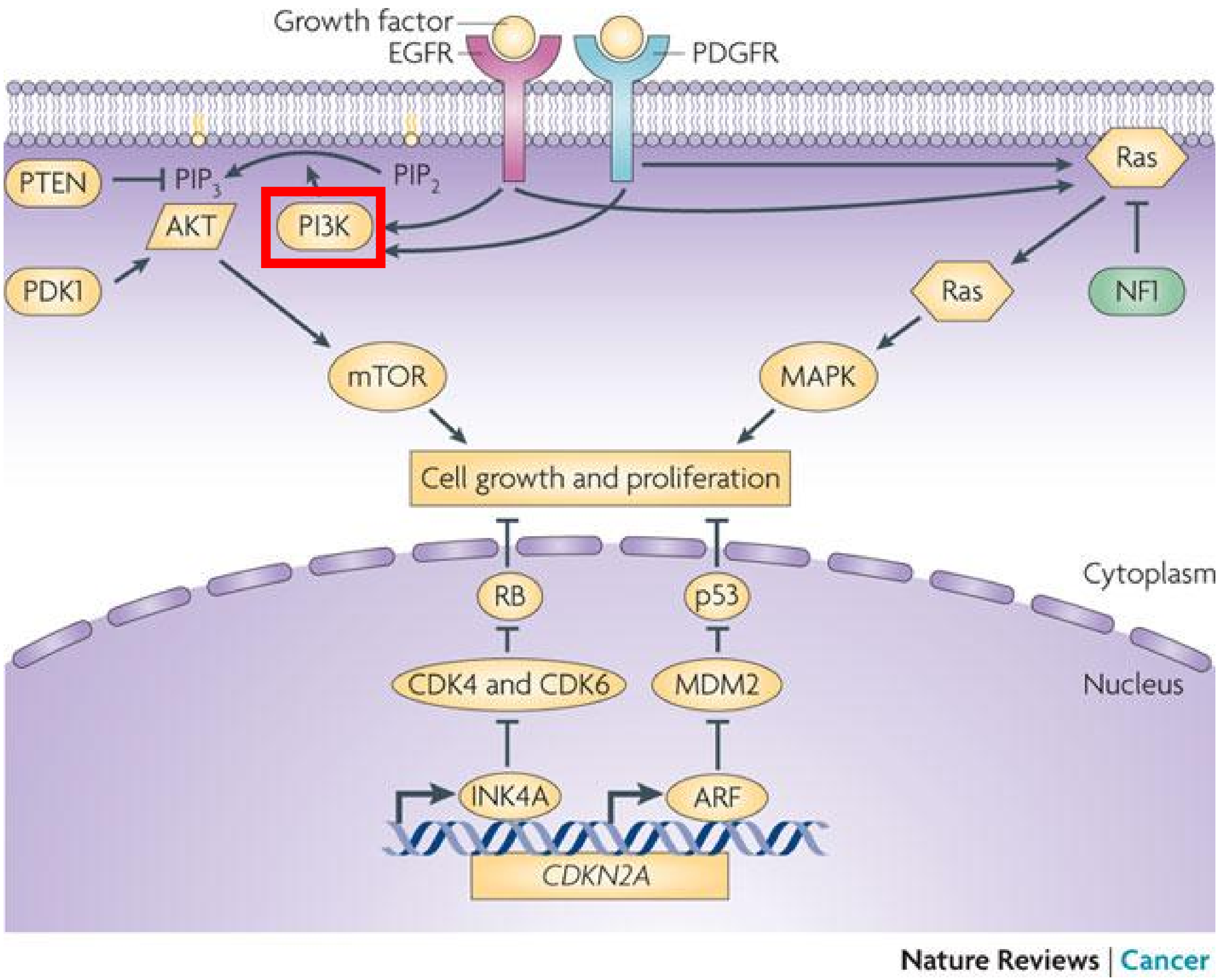
Craig Horbinski, M.D., Ph.D.
Associate Professor
Director of Molecular Anatomic Pathology
Director of Markey Biospecimen and Tissue Procurement Shared Resource Facility
University of Kentucky

# PI3K-Akt-mTOR pathway




Huse and Holland, Nature Reviews Cancer 10, 319-331 (May 2010)

# PI3K




Huse and Holland, Nature Reviews Cancer 10, 319-331 (May 2010)

*Proc. Natl. Acad. Sci. USA*
Vol. 81, pp. 2117–2121, April 1984
Cell Biology

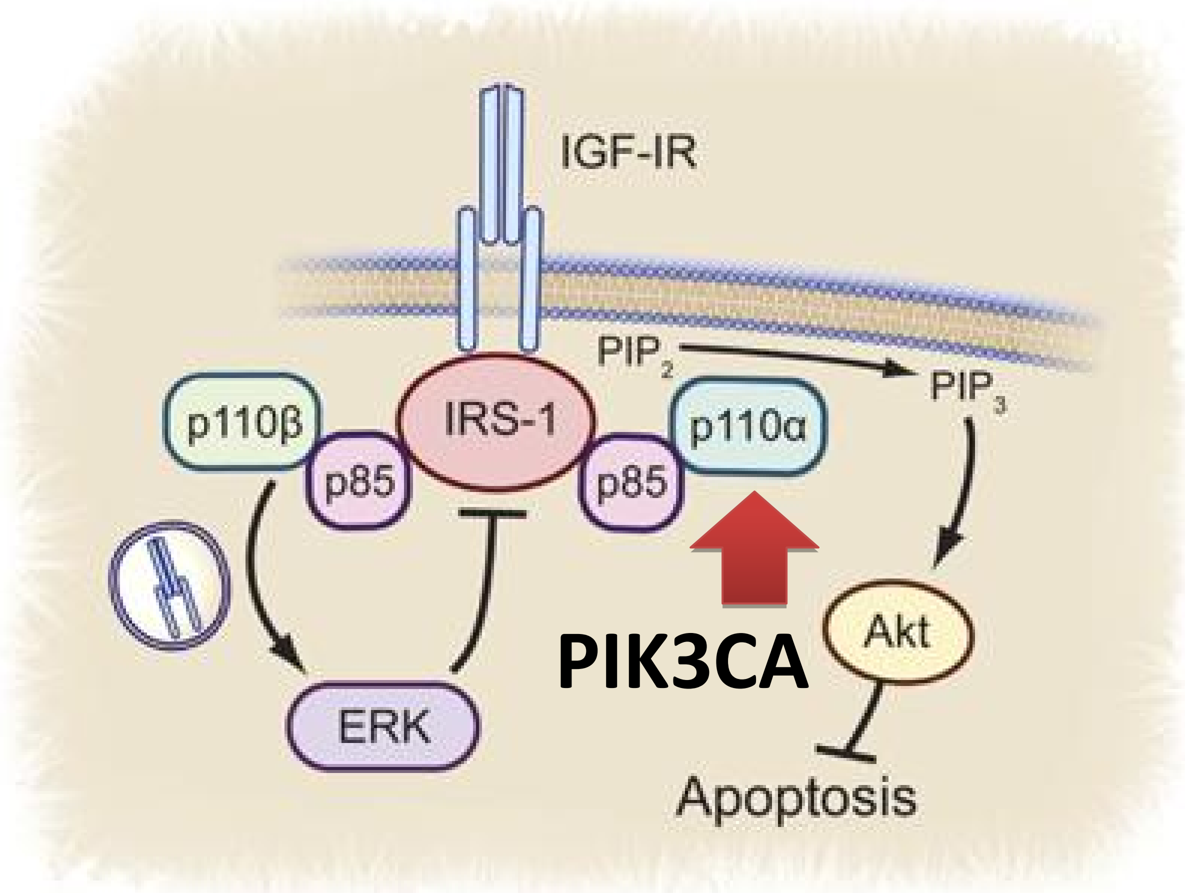
# Evidence that the Rous sarcoma virus transforming gene product phosphorylates phosphatidylinositol and diacylglycerol

(cell transformation/transforming gene function)

YOSHIKAZU SUGIMOTO*, MALCOLM WHITMAN†, LEWIS C. CANTLEY†, AND R. L. ERIKSON*

*Department of Cellular and Developmental Biology and †Department of Biochemistry and Molecular Biology, Harvard University, Cambridge, MA 02138

*Contributed by R. L. Erikson, December 30, 1983*




- p110α→ Akt activation
- P110β→ ERK activation

Matheny and Adamo, Cell Death and Differentiation (2010) 17, 677–688

# High Frequency of Mutations of the *PIK3CA* Gene in Human Cancers

Yardena Samuels,[1] Zhenghe Wang,[1] Alberto Bardelli,[1]
Natalie Silliman,[1] Janine Ptak,[1] Steve Szabo,[1] Hai Yan,[2]
Adi Gazdar,[3] Steven M. Powell,[4] Gregory J. Riggins,[1]
James K. V. Willson,[5] Sanford Markowitz,[5]
Kenneth W. Kinzler,[1] Bert Vogelstein,[1]
Victor E. Velculescu[1]*

| | Tumor type[#] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Colon | GBM | Gastric | Breast | Lung | Pancreas | Medullo-blastomas | Adenomas |
| Tumors with mutations | 74 | 4 | 3 | 1 | 1 | 0 | 0 | 2 |
| No. samples screened | 234 | 15 | 12 | 12 | 24 | 11 | 12 | 76 |
| Percent of tumors with mutations | 32% | 27% | 25% | 8% | 4% | 0% | 0% | 3% |

Science. 2004 Apr 23;304(5670):554.

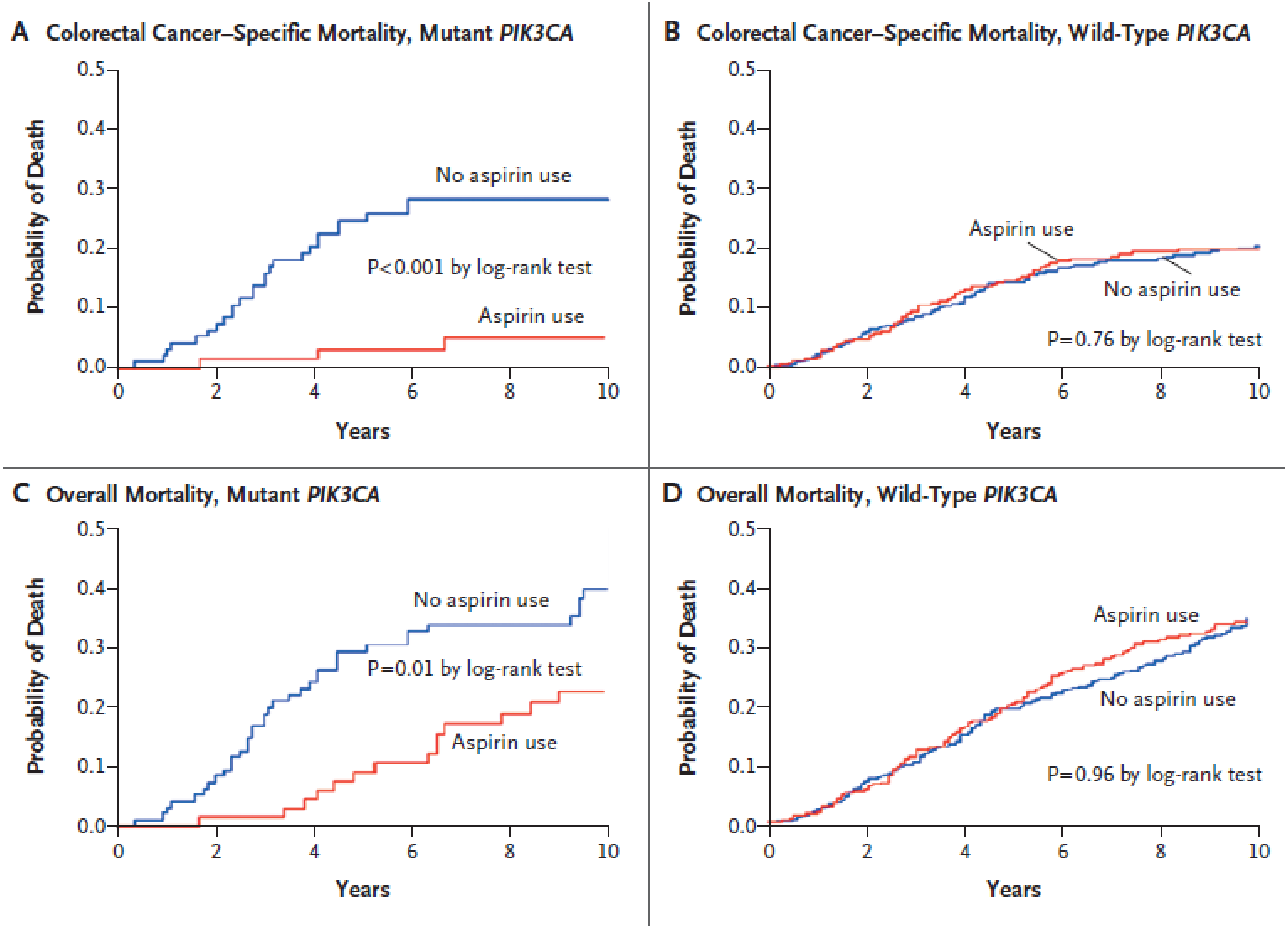
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Aspirin Use, Tumor *PIK3CA* Mutation, and Colorectal-Cancer Survival

Xiaoyun Liao, M.D., Ph.D., Paul Lochhead, M.B., Ch.B., Reiko Nishihara, Ph.D., Teppei Morikawa, M.D., Ph.D., Aya Kuchiba, Ph.D., Mai Yamauchi, Ph.D., Yu Imamura, M.D., Ph.D., Zhi Rong Qian, M.D., Ph.D., Yoshifumi Baba, M.D., Ph.D., Kaori Shima, D.D.S., Ph.D., Ruifang Sun, M.B., Katsuhiko Nosho, M.D., Ph.D., Jeffrey A. Meyerhardt, M.D., M.P.H., Edward Giovannucci, M.D., M.P.H., Sc.D., Charles S. Fuchs, M.D., M.P.H., Andrew T. Chan, M.D., M.P.H., and Shuji Ogino, M.D., Ph.D.

N Engl J Med. 2012 Oct 25;367(17):1596-606



A Colorectal Cancer–Specific Mortality, Mutant PIK3CA
Probability of Death
0.5
0.4
0.3
0.2
0.1
0.0
No aspirin use
P<0.001 by log-rank test
Aspirin use
0
2
4
6
8
10
Years
B Colorectal Cancer–Specific Mortality, Wild-Type PIK3CA
Probability of Death
Aspirin use
No aspirin use
P=0.76 by log-rank test
Years
C Overall Mortality, Mutant PIK3CA
Probability of Death
No aspirin use
P=0.01 by log-rank test
Aspirin use
Years
D Overall Mortality, Wild-Type PIK3CA
Probability of Death
Aspirin use
No aspirin use
P=0.96 by log-rank test
Years

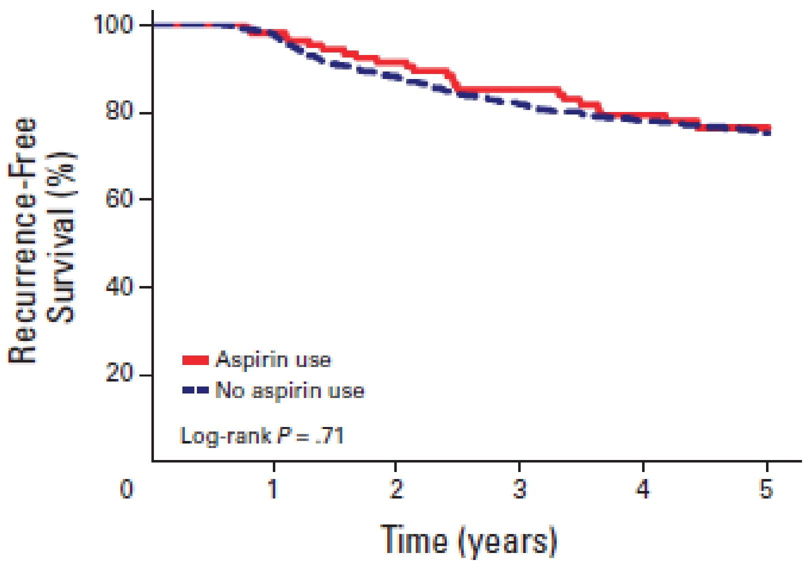
VOLUME 31 · NUMBER 34 · DECEMBER 1 2013

JOURNAL OF CLINICAL ONCOLOGY

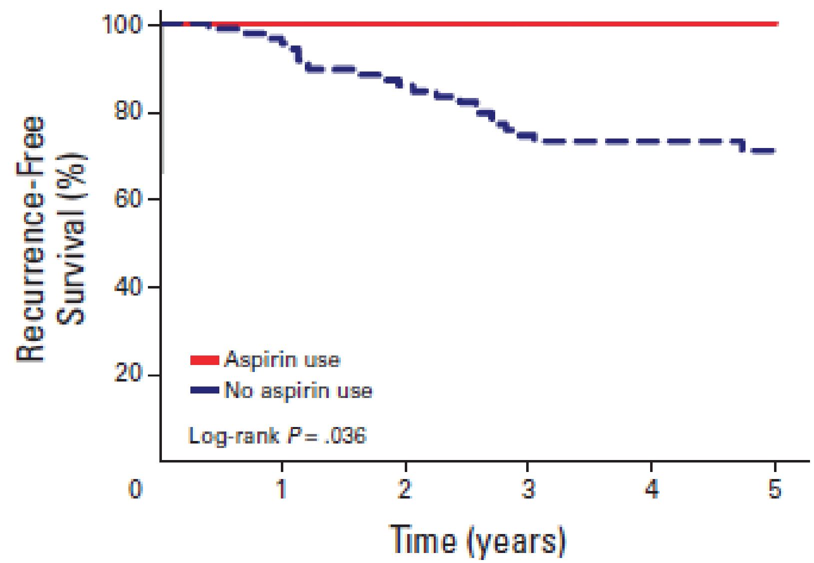
ORIGINAL REPORT

# Evaluation of *PIK3CA* Mutation As a Predictor of Benefit From Nonsteroidal Anti-Inflammatory Drug Therapy in Colorectal Cancer

*Enric Domingo, David N. Church, Oliver Sieber, Rajarajan Ramamoorthy, Yoko Yanagisawa, Elaine Johnstone, Brian Davidson, David J. Kerr, Ian P.M. Tomlinson, and Rachel Midgley*



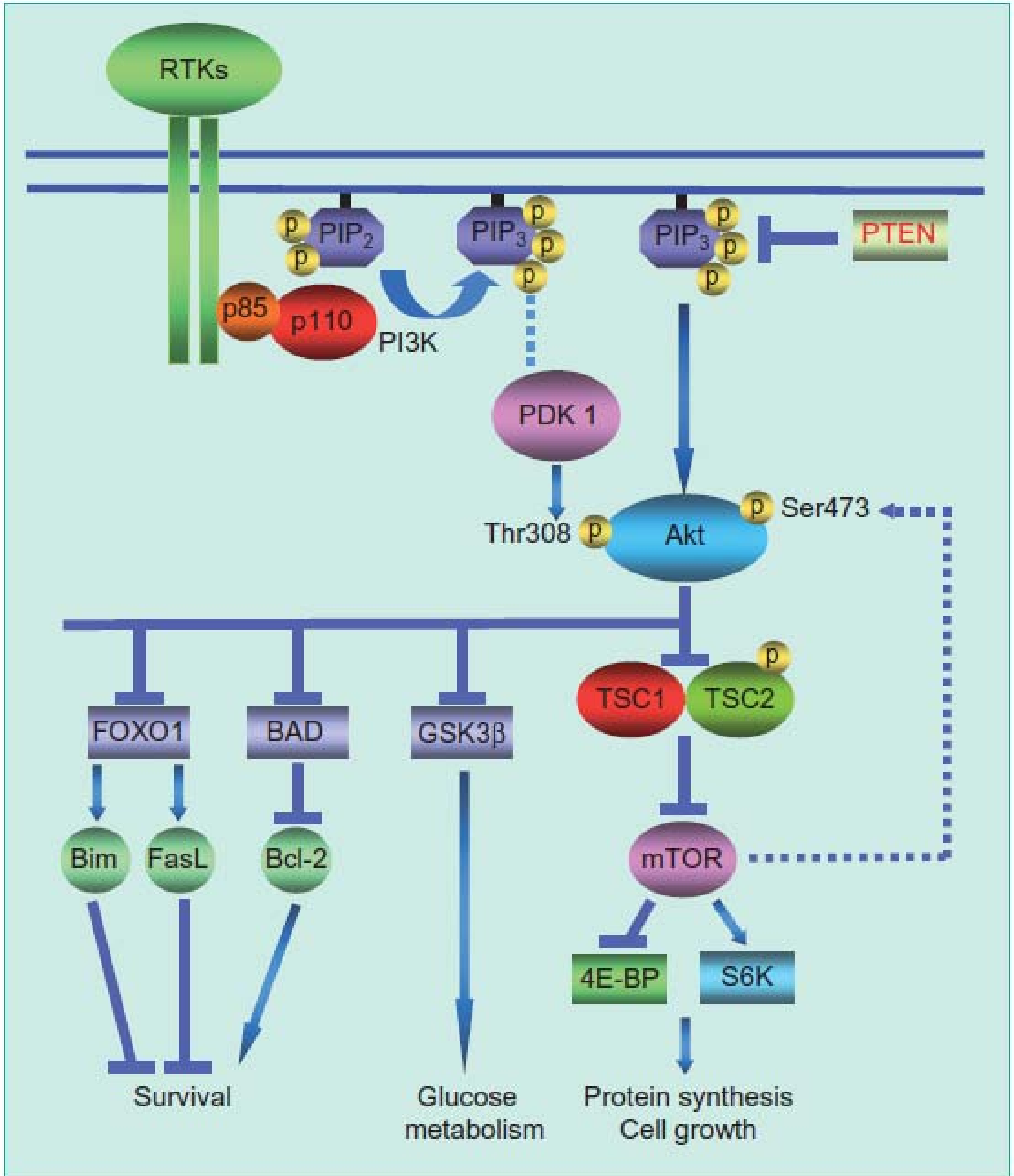

D



# take two aspirin for your GBM?

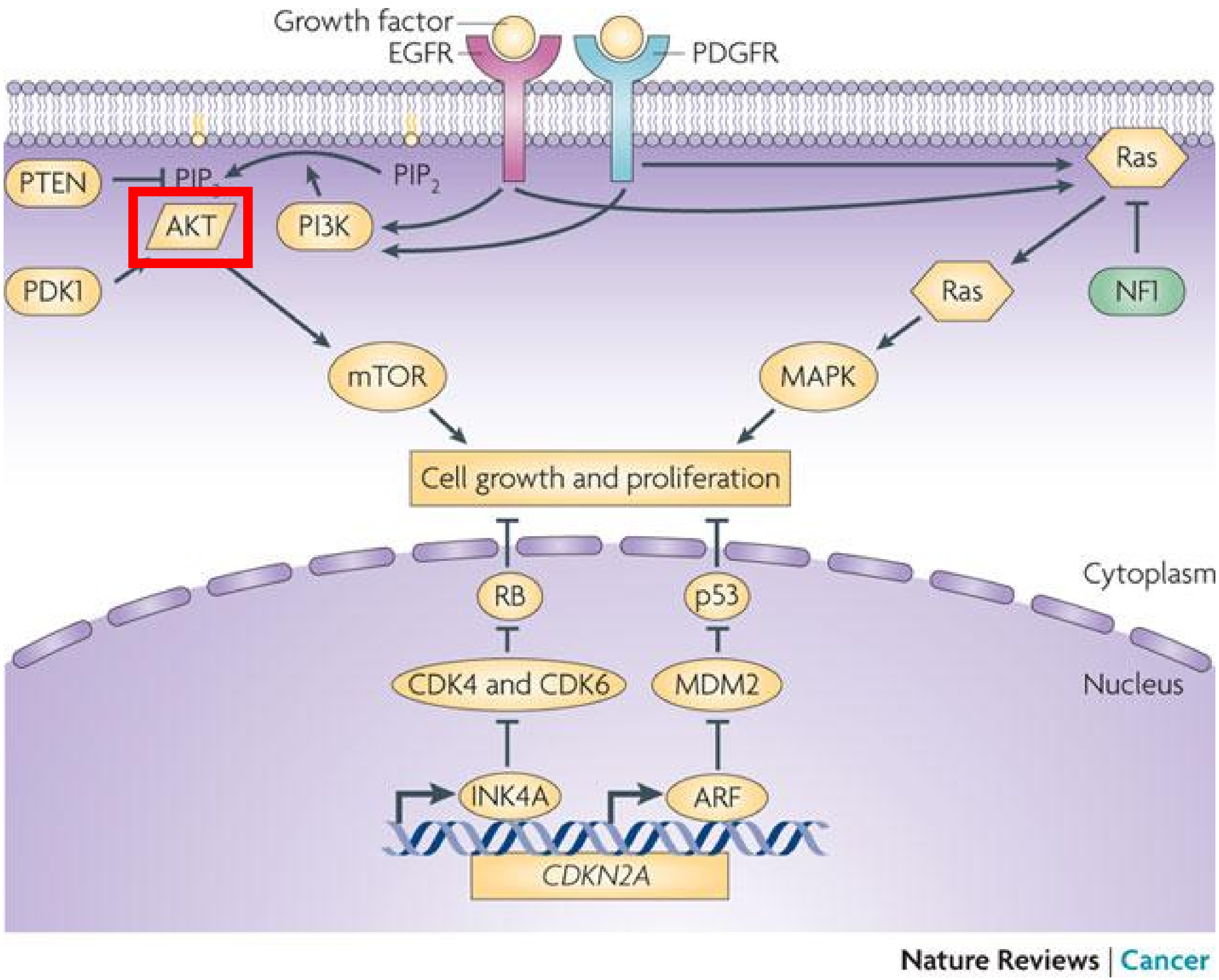
- activating mutations in the RTK–PI3K axis occur in over 80% of glioblastomas
- only about 5-10% of GBMs have PIK3CA mutations
- more in primary than secondary GBMs
- may be slightly higher in anaplastic oligodendrogliomas (~15%)

Hartmann et al. Acta Neuropathol. 2005 Jun;109(6):639-42
Gallia et al. Mol Cancer Res. 2006 Oct;4(10):709-14
Kita et al. Acta Neuropathol. 2007 Mar;113(3):295-302
Cheng et al., Brain Pathology 19 (2009) 112–120
Cancer Res. 2004 Aug 1;64(15):5048-50




Cheng et al., Brain Pathology 19 (2009) 112–120

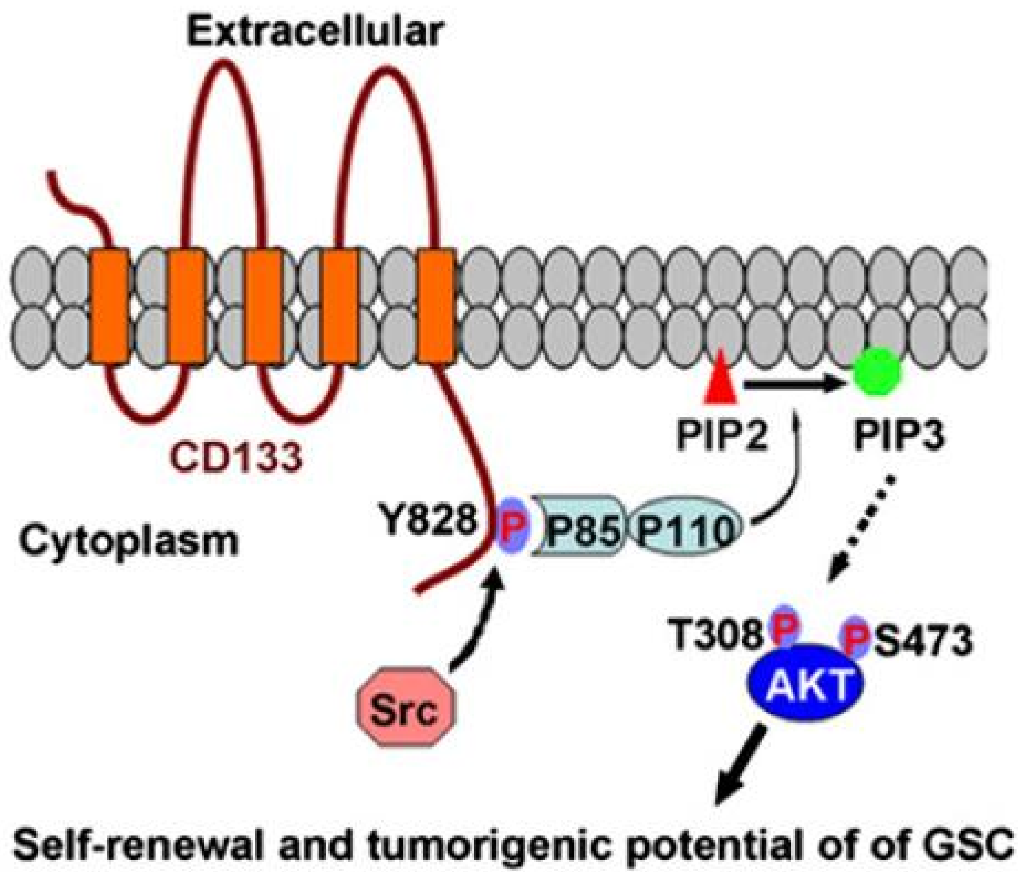
# Akt



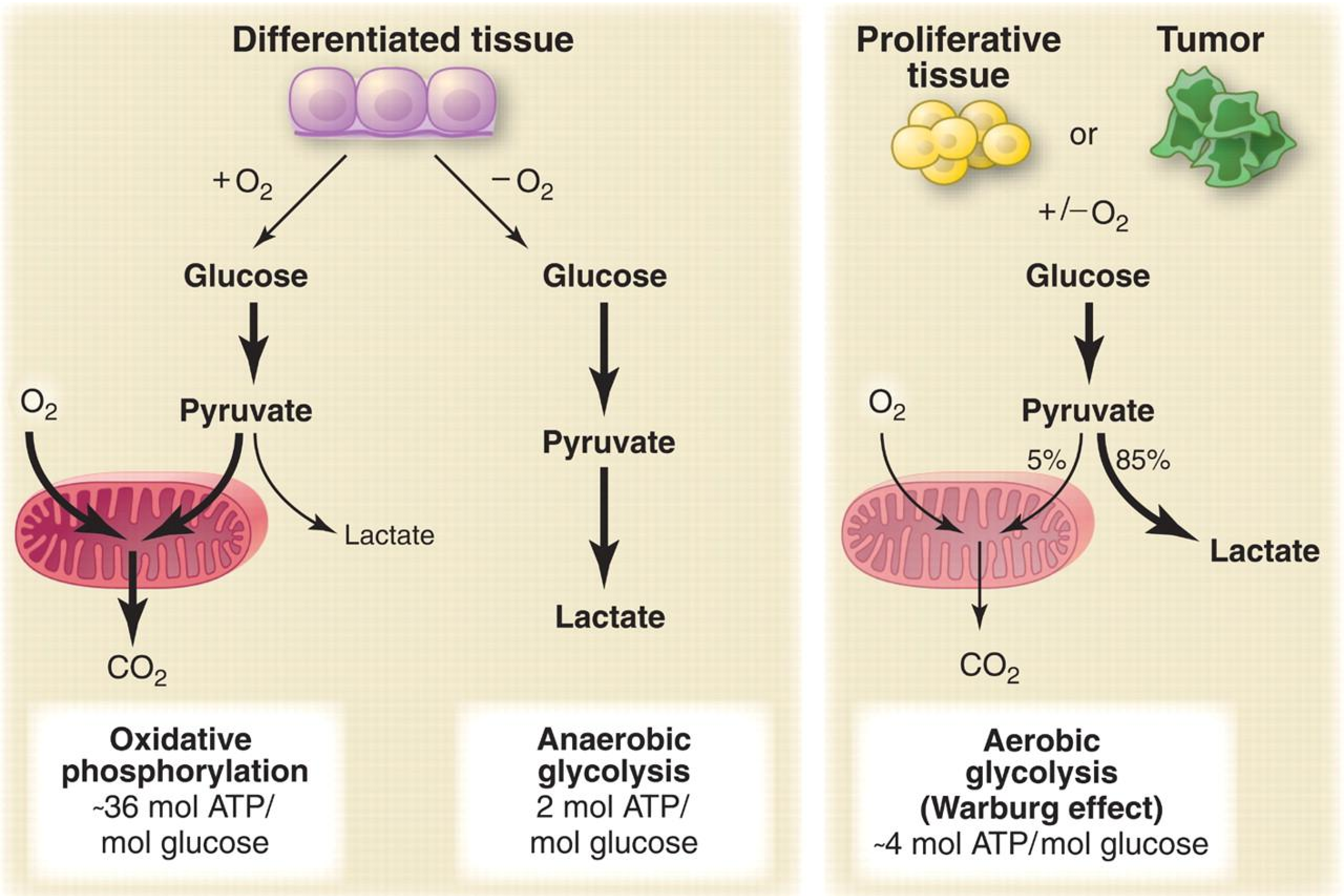

Huse and Holland, Nature Reviews Cancer 10, 319-331 (May 2010)

# Activation of PI3K/Akt pathway by CD133-p85 interaction promotes tumorigenic capacity of glioma stem cells

Yuanyan Wei[a,1], Yizhou Jiang[a,1], Fei Zou[a,1], Yingchao Liu[b,1], Shanshan Wang[a], Nuo Xu[a], Wenlong Xu[c], Chunhong Cui[a], Yang Xing[a], Ying Liu[a], Benjin Cao[a], Chanjuan Liu[a], Guoqiang Wu[a], Hong Ao[d], Xiaobiao Zhang[c], and Jianhai Jiang[a,2]




Proc Natl Acad Sci U S A. 2013 Apr 23;110(17):6829-34




Vander Heiden et al. Science. 2009 May 22;324(5930):1029-33

[CANCER RESEARCH 64, 3892–3899, June 1, 2004]

# Akt Stimulates Aerobic Glycolysis in Cancer Cells

**Rebecca L. Elstrom,[1] Daniel E. Bauer,[1] Monica Buzzai,[1] Robyn Karnauskas,[3] Marian H. Harris,[1] David R. Plas,[1] Hongming Zhuang,[2] Ryan M. Cinalli,[1] Abass Alavi,[2] Charles M. Rudin,[4] and Craig B. Thompson[1]**

*[1]Abramson Family Cancer Research Institute, Department of Cancer Biology, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [2]Division of Nuclear Medicine, Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania; [3]Department of Medicine, University of Chicago, Chicago, Illinois; and [4]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, Maryland*

- Akt activation→ Glut1 goes to cell membrane & hexokinase is turned on→ glycolysis
- High Akt activation inhibits glioma cells from using non-glucose substrates

J Neuropathol Exp Neurol

Vol. 65, No. 12
December 2006
pp. 1181–1188

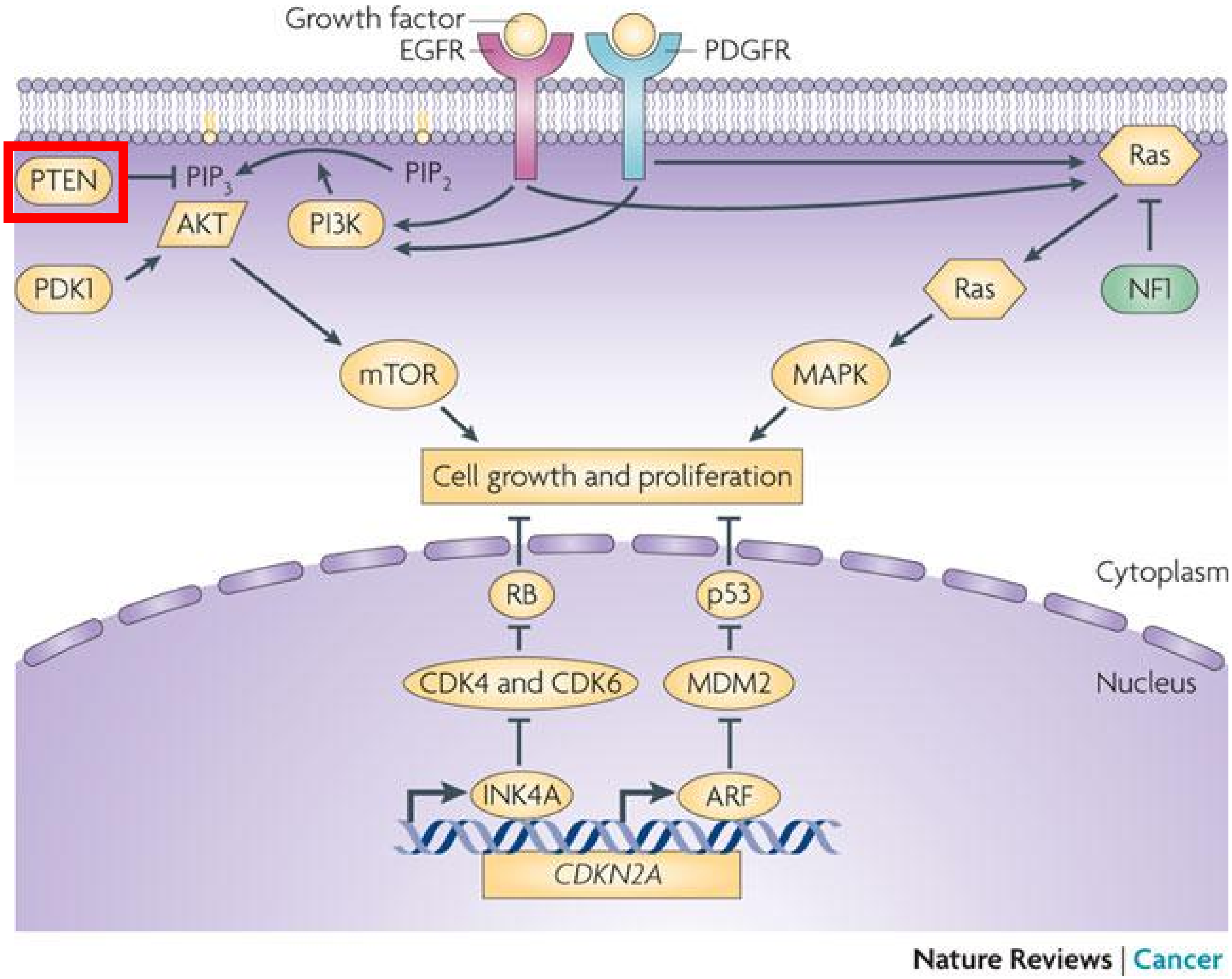
ORIGINAL ARTICLE

# Activation of STAT3, MAPK, and AKT in Malignant Astrocytic Gliomas: Correlation With EGFR Status, Tumor Grade, and Survival

Masahiro Mizoguchi MD, Rebecca A. Betensky, PhD, Tracy T. Batchelor, MD, Derek C. Bernay, BS, David N. Louis, MD, and Catherine L. Nutt, PhD

- High EGFR expression correlates with pAkt
- pAkt higher in GBM vs AA
- Weakly correlates with worse survival

# PTEN




Huse and Holland, Nature Reviews Cancer 10, 319-331 (May 2010)

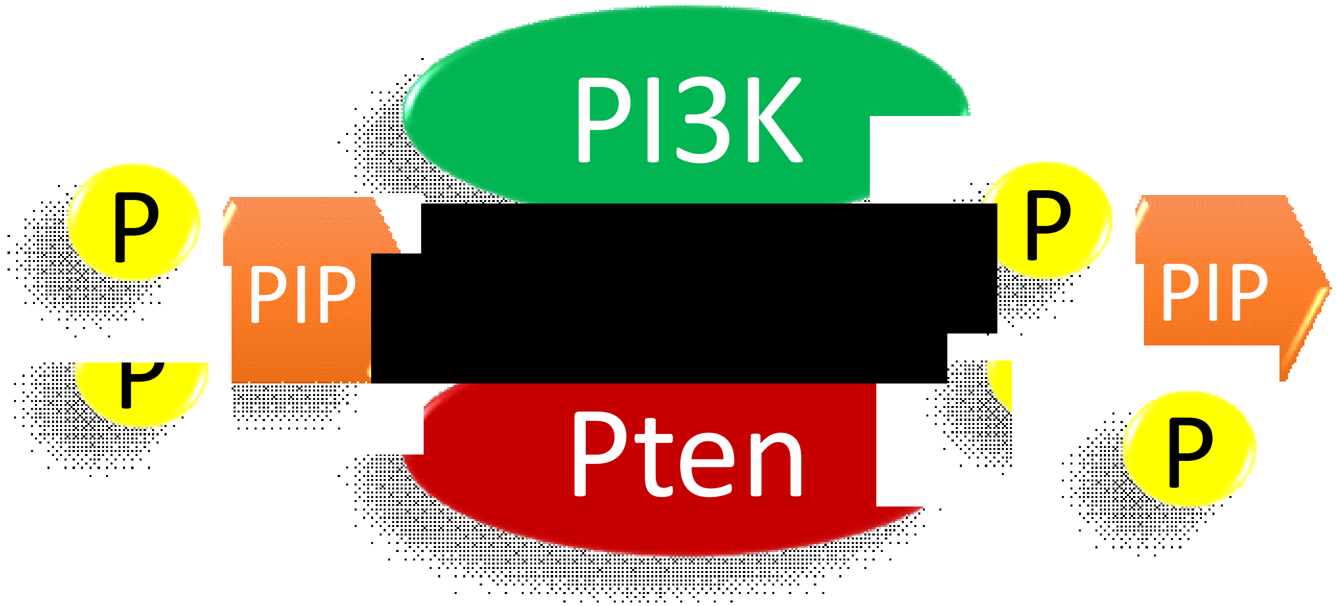
# *PTEN*, a Putative Protein Tyrosine Phosphatase Gene Mutated in Human Brain, Breast, and Prostate Cancer

Jing Li,* Clifford Yen,* Danny Liaw,* Katrina Podsypanina,* Shikha Bose, Steven I. Wang, Janusz Puc, Christa Miliaresis, Linda Rodgers, Richard McCombie, Sandra H. Bigner, Beppino C. Giovanella, Michael Ittmann, Ben Tycko, Hanina Hibshoosh, Michael H. Wigler, Ramon Parsons†

SCIENCE • VOL. 275 • 28 MARCH 1997

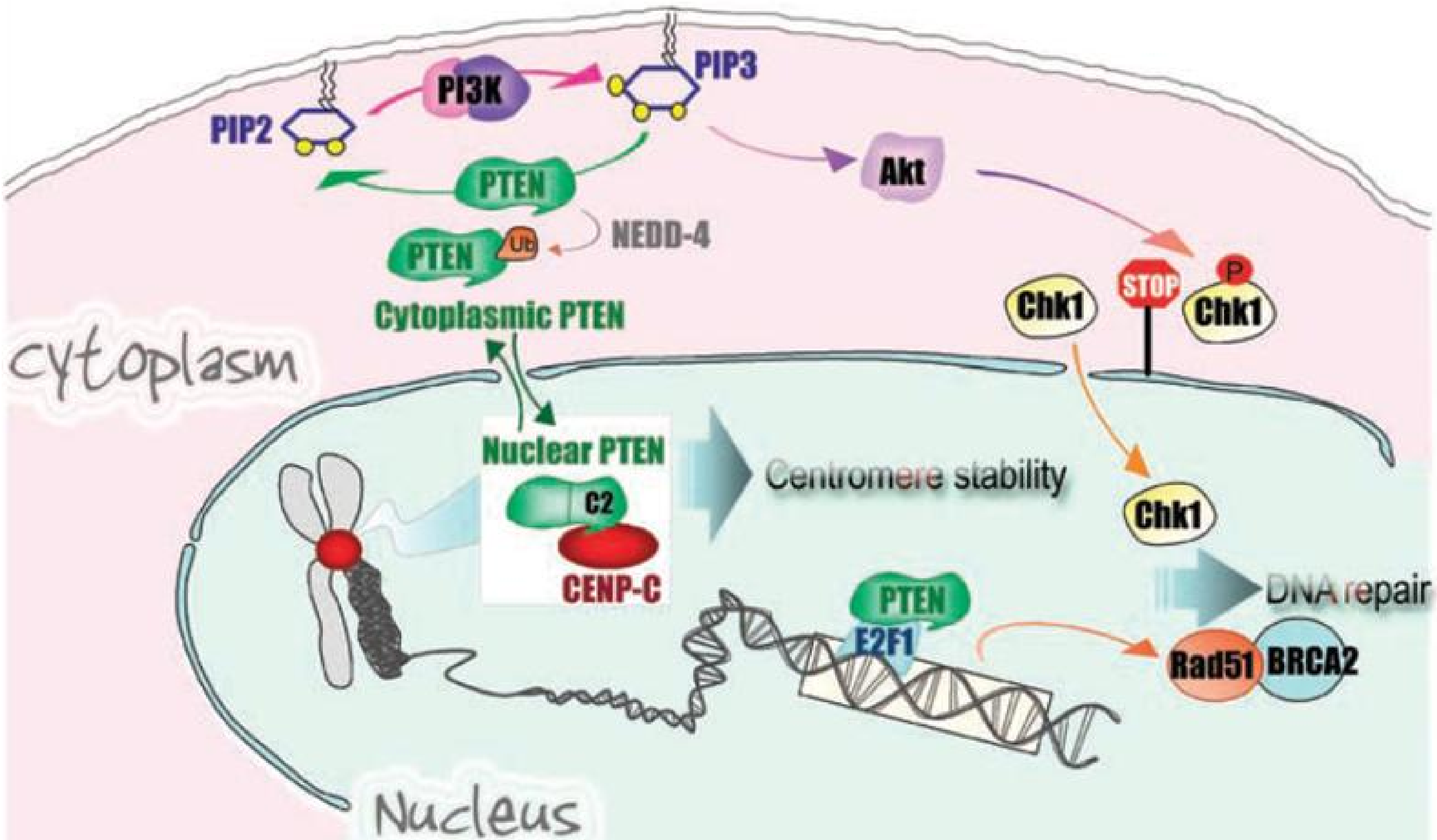
# PTEN

- **p**hosphatase and **ten**sin homolog




- converts PIP-3 back to PIP-2

# another guardian of the genome




Oncogene. 2008 Sep 18;27(41):5443-53

# PTEN in cancer

- majority of infiltrative gliomas have some sort of PTEN inactivation
  - point mutation
  - deletion
  - promoter methylation
  - polyubiquitination

| Histology | Number Methylated (%) | Number Not Methylated (%) |
|---|---|---|
| Nontumor brain ($n = 13$) | 0 (0) | 13 (100) |
| Grade II oligoastrocytomas ($n = 15$) | 10 (67) | 5 (33) |
| Grade II astrocytomas ($n = 14$) | 6 (43) | 8 (57) |
| Grade II oligodendrogliomas ($n = 8$) | 4 (50) | 4 (50) |
| Grade III astrocytomas ($n = 19$) | 13 (68) | 6 (32) |
| De novo GBM ($n = 23$) | 2 (9) | 21 (91) |
| Secondary GBM ($n = 11$) | 9 (82) | 2 (18) |

Comparisons of methylation status yielded the following $p$-values (based on Fisher's exact test or its extension [Fisher-Freeman-Halton]): all seven tissue categories, $p < 0.001$; the six tumor types, $p < 0.001$; de novo GBM samples versus grade II tumors, $p < 0.001$; the four tumor types that were initially low-grade tumors (low-grade plus secondary GBM), $p = 0.22$; de novo GBMs versus secondary GBMs, $p < 0.001$.

Wiencke et al. Neuro Oncol. 2007 Jul;9(3):271-9

Wang et al. Cancer Res. 1997 Oct 1;57(19):4183-6

# Ubiquitination Regulates PTEN Nuclear Import and Tumor Suppression

Lloyd C. Trotman,[1,2,11] Xinjiang Wang,[3] Andrea Alimonti,[1,2] Zhenbang Chen,[1,2] Julie Teruya-Feldstein,[2] Haijuan Yang,[4] Nikola P. Pavletich,[4,5] Brett S. Carver,[6] Carlos Cordon-Cardo,[2] Hediye Erdjument-Bromage,[7] Paul Tempst,[7] Sung-Gil Chi,[8] Hyo-Jong Kim,[9] Tom Misteli,[10] Xuejun Jiang,[3] and Pier Paolo Pandolfi[1,2,*]

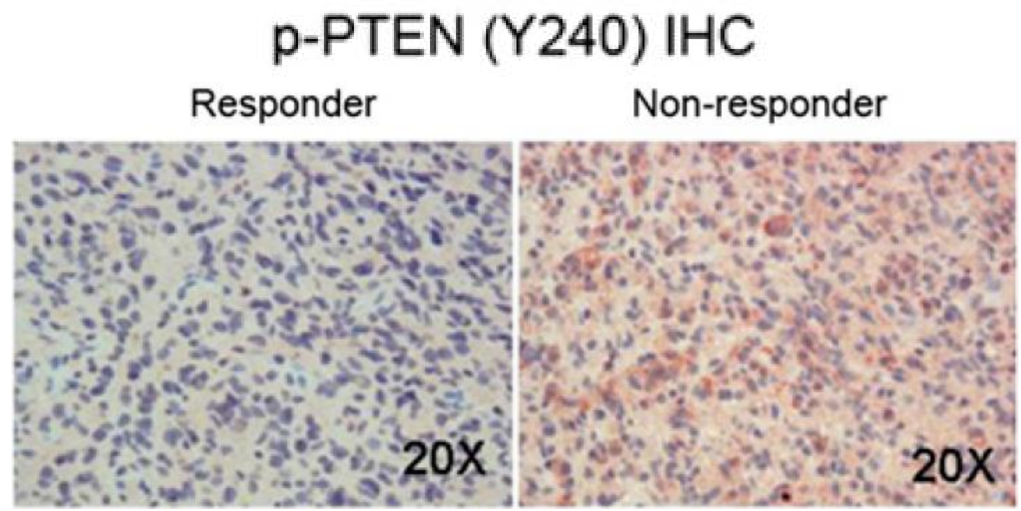
- monoubiquitination at K13 and K289 → nuclear localization
  - still antagonizes Akt
  - enhances p53 DNA binding
  - p53-independent apoptosis
  - blocks MAPK pathway
  - prevents DNA breaks
  - cell cycle arrest
- polyubiquitination→ proteasomal degradation

Cell. 2007 Jan 12;128(1):141-56
Oncogene. 2008 Sep 18;27(41):5387-97
Oncogene. 2008 Sep 18;27(41):5416-30
Oncogene. 2008 Sep 18;27(41):5443-53

# Resistance to EGF receptor inhibitors in glioblastoma mediated by phosphorylation of the PTEN tumor suppressor at tyrosine 240

Tim R. Fenton[a,1], David Nathanson[b], Claudio Ponte de Albuquerque[a], Daisuke Kuga[c], Akio Iwanami[c], Julie Dang[c], Huijun Yang[c], Kazuhiro Tanaka[c], Sueli Mieko Oba-Shinjo[d], Miyuki Uno[d], Maria del Mar Inda[a], Jill Wykosky[a], Robert M. Bachoo[e], C. David James[f], Ronald A. DePinho[g], Scott R. Vandenberg[h,i,j], Huilin Zhou[a,k], Suely K. N. Marie[d], Paul S. Mischel[b,c], Webster K. Cavenee[a,h,i,2], and Frank B. Furnari[a,h,i,j,2]

- FGFR or SFKs→ phosphorylation of tyrosine 240 (p-Y240) on Pten→ resistance to EGFR inhibitor erlotinib




- occurs in 75% of GBMs
- Y240 phosphorylation does NOT inhibit Pten's ability to convert PIP-3 back to PIP-2

Proc Natl Acad Sci U S A. 2012 Aug 28;109(35):14164-9

*Neuro-Oncology* 14(9):1146–1152, 2012.
doi:10.1093/neuonc/nos140
Advance Access publication June 29, 2012

NEURO-ONCOLOGY

# PTEN promoter methylation and activation of the PI3K/Akt/mTOR pathway in pediatric gliomas and influence on clinical outcome

Sabine Mueller, Joanna Phillips, Arzu Onar-Thomas, Eloy Romero, Shichun Zheng, John K. Wiencke, Sean M. McBride, Cynthia Cowdrey, Michael D. Prados, William A. Weiss, Mitchel S. Berger, Nalin Gupta, and Daphne A. Haas-Kogan

- PI3K/Akt/mTOR activation
  - ~80% of peds HGG
  - ~40% of peds LGG

| Molecular Marker | Grade I | Grade II | Grade III | Grade IV |
|---|---|---|---|---|
| | Number positive/total number (%) | | | |
| PTEN promoter methylation | 6/17 (35) | 6/7 (86) | 2/6 (33) | 3/9 (33) |
| PTEN expression by IHC | 19/25 (76) | 4/7 (57) | 3/7 (43) | 2/8 (25) |
| Phospho-S6 expression | 11/25 (44) | 3/7 (43) | 5/7 (71) | 7/8 (88) |
| Phospho-PRAS40 | 5/25 (20) | 1/7 (14) | 2/7 (28) | 4/4 (100) |
| Phospho-4EBP1 | 12/25 (48) | 4/7 (57) | 4/7 (57) | 8/8 (100) |

OPEN ACCESS Freely available online

PLoS one

# Loss of PTEN Is Not Associated with Poor Survival in Newly Diagnosed Glioblastoma Patients of the Temozolomide Era

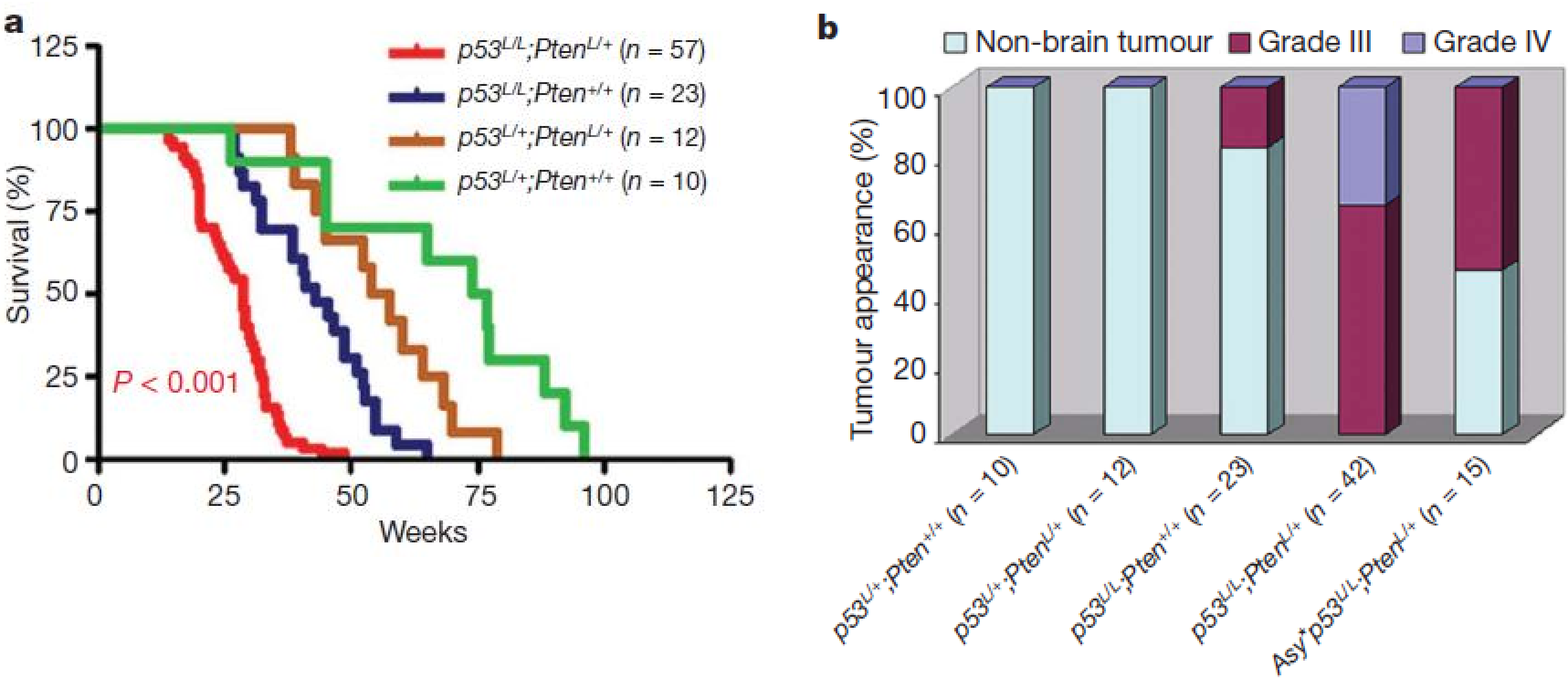
Christine Carico[1], Miriam Nuño[1], Debraj Mukherjee[1], Adam Elramsisy[1], Jocelynn Dantis[1], Jethro Hu[1], Jeremy Rudnick[1], John S. Yu[1], Keith L. Black[1], Serguei I. Bannykh[2], Chirag G. Patil[1*]

- 155 GBMs
- by IHC 54% had no PTEN expression
- no difference in survival

PLoS One. 2012;7(3):e33684

# p53 and Pten control neural and glioma stem/progenitor cell renewal and differentiation

Hongwu Zheng[1]*, Haoqiang Ying[1]*, Haiyan Yan[1], Alec C. Kimmelman[1,4], David J. Hiller[8], An-Jou Chen[1], Samuel R. Perry[1,2], Giovanni Tonon[1], Gerald C. Chu[1,2,5], Zhihu Ding[1], Jayne M. Stommel[1], Katherine L. Dunn[1], Ruprecht Wiedemeyer[1], Mingjian J. You[1], Cameron Brennan[9,10], Y. Alan Wang[1,2], Keith L. Ligon[1,3,5,6], Wing H. Wong[8], Lynda Chin[1,2,7] & Ronald A. DePinho[1,2,11]

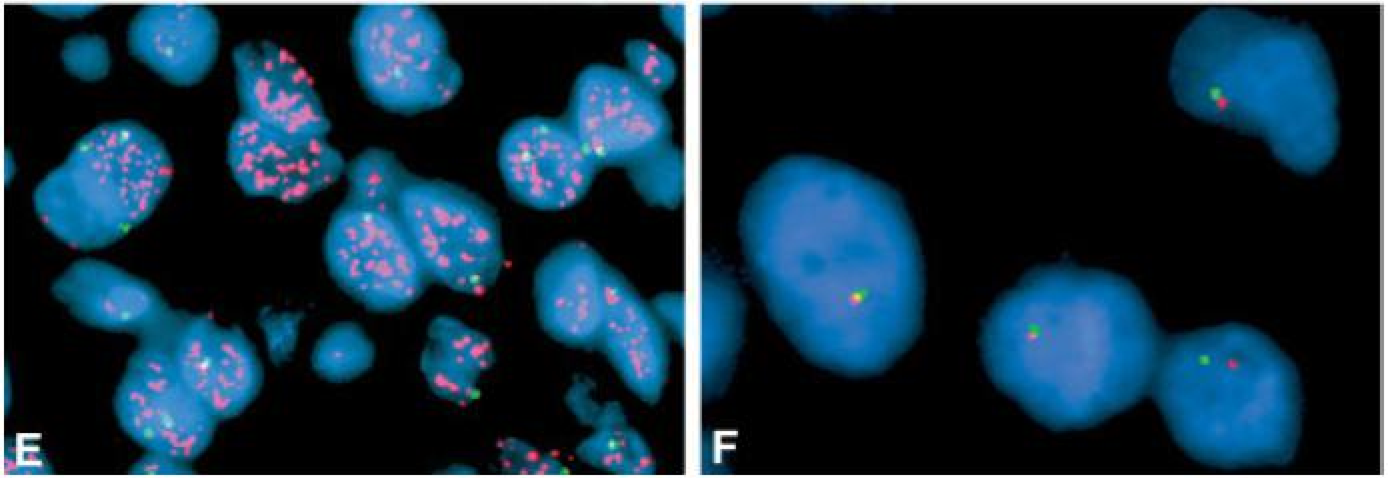



Nature. 2008 Oct 23;455(7216):1129-33

# Small Cell Astrocytoma: An Aggressive Variant That Is Clinicopathologically and Genetically Distinct from Anaplastic Oligodendroglioma

Features that Favor Small Cell Astrocytoma Diagnoses or Anaplastic Oligodendroglioma Diagnoses

| Feature | Small cell astrocytoma | Anaplastic oligodendroglioma |
| --- | --- | --- |
| Radiologic | Ring enhancement; lack of enhancement despite high-grade histology | Patchy or nodular enhancement |
| Histologic | Oval rather than round nuclei; bland cytology despite markedly elevated mitotic/proliferative index; pseudopalisading necrosis | Uniformly round nuclei; epithelioid cells with clear-to-amphophilic cytoplasm, vesicular nuclei, and nucleoli; mucin-rich microcystic spaces; minigemistocytes |
| Immunohistochemical | GFAP-positive cytoplasmic processes; EGFR-vIII immunoreactivity | GFAP-negative or GFAP-positive minigemistocytes and gliofibrillary oligodendrocytes |
| Genetic | *EGFR* gene amplification; chromosome 10q deletion | 1p/19q codeletions |




Perry et al., Cancer. 2004 Nov 15;101(10):2318-26.

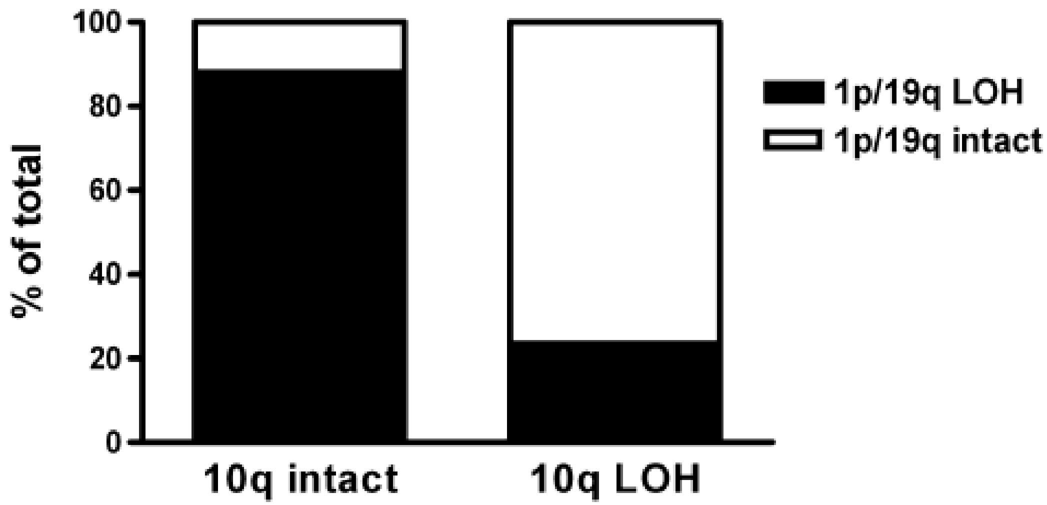
J Neuropathol Exp Neurol

Vol. 71, No. 1
January 2012
pp. 73–82

ORIGINAL ARTICLE

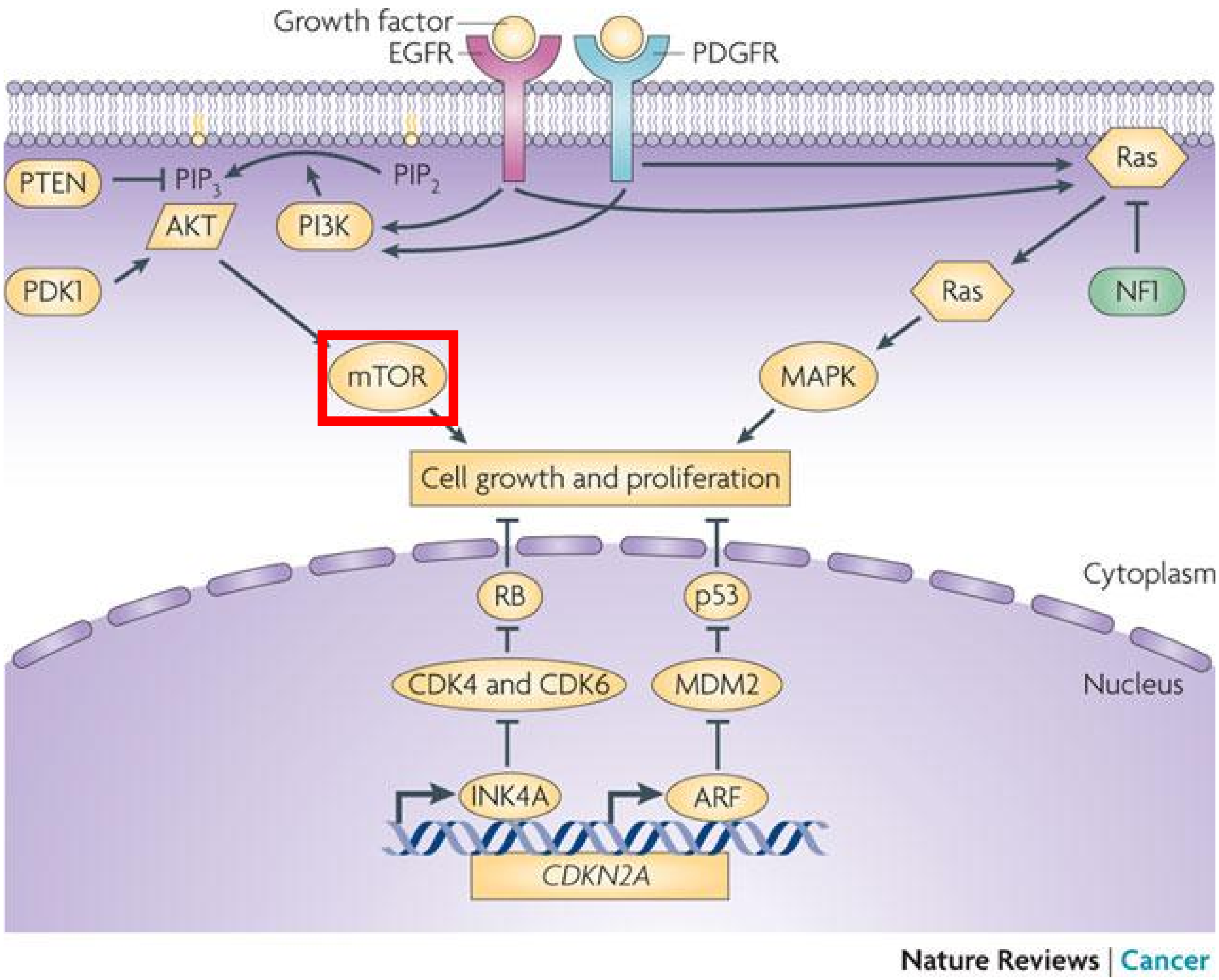
# The Importance of 10q Status in an Outcomes-Based Comparison Between 1p/19q Fluorescence In Situ Hybridization and Polymerase Chain Reaction–Based Microsatellite Loss of Heterozygosity Analysis of Oligodendrogliomas

Craig Horbinski, MD, PhD, Marina N. Nikiforova, MD, Jonathan Hobbs, BS, Stephanie Bortoluzzi, BS, Kathleen Cieply, MLS, Sanja Dacic, MD, PhD, and Ronald L. Hamilton, MD




- when FISH calls a glioma codeleted, it is most likely to be a false-positive result if 10q is also deleted

# mTOR

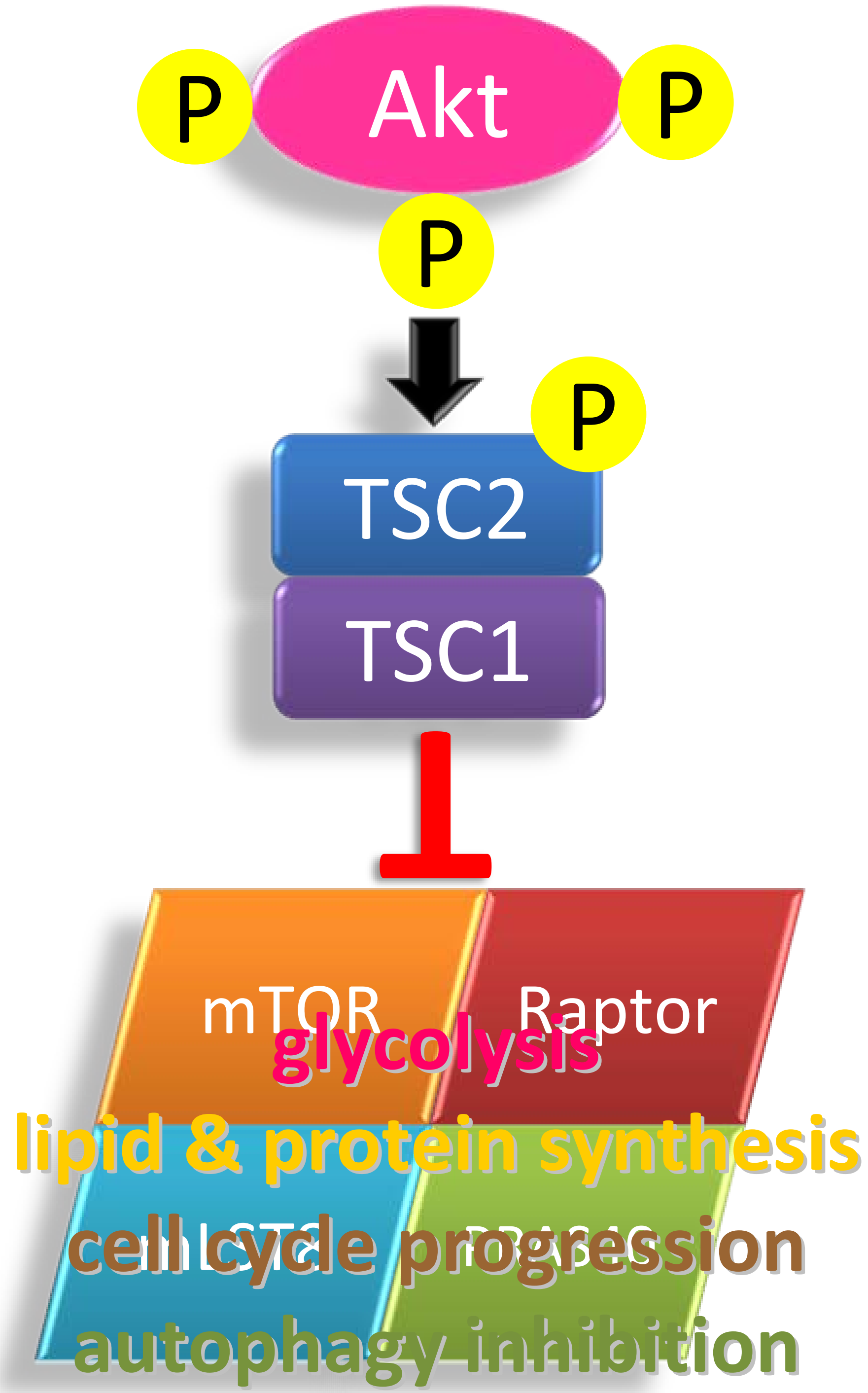



Huse and Holland, Nature Reviews Cancer 10, 319-331 (May 2010)

# mTOR

- mammalian target of **rapamycin**
  - antifungal discovered on Easter Island in 1975
- forms complexes with other proteins
  - mTORC1: mTOR/mLST8/**Raptor**
  - mTORC2: mTOR/mLST8/**Rictor**

Takei and Nawa, Front Mol Neurosci. 2014 Apr 23;7:28


P
Akt
P
P
P
TSC2
TSC1
mTOR
Raptor
glycolysis
lipid & protein synthesis
cell cycle progression
autophagy inhibition

**Pediatric glioma-associated *KIAA1549:BRAF* expression regulates neuroglial cell growth in a cell type-specific and mTOR-dependent manner**

Aparna Kaul,[1,3] Yi-Hsien Chen,[1,3] Ryan J. Emnett,[1] Sonika Dahiya,[2] and David H. Gutmann[1,4]

J Neurooncol (2011) 103:453–458
DOI 10.1007/s11060-010-0424-1

LABORATORY INVESTIGATION - HUMAN/ANIMAL TISSUE

*Neuro-Oncology* 15(12):1604–1614, 2013.
doi:10.1093/neuonc/not132

NEURO-ONCOLOGY

**Activation of mTORC1/mTORC2 signaling in pediatric low-grade glioma and pilocytic astrocytoma reveals mTOR as a therapeutic target**

Marianne Hütt-Cabezas, Matthias A. Karajannis, David Zagzag, Smit Shah, Iren Horkayne-Szakaly, Elisabeth J. Rushing, J. Douglas Cameron, Deepali Jain, Charles G. Eberhart, Eric H. Raabe, and Fausto J. Rodriguez

**Association between AKT/mTOR signalling pathway and malignancy grade of human gliomas**

Xue-yuan Li · Lian-qun Zhang · Xue-guang Zhang · Xin Li · Yu-bo Ren · Xiang-yu Ma · Xin-gang Li · Le-xin Wang

www.impactjournals.com/oncotarget/ Oncotarget, April, Vol.4, No 4

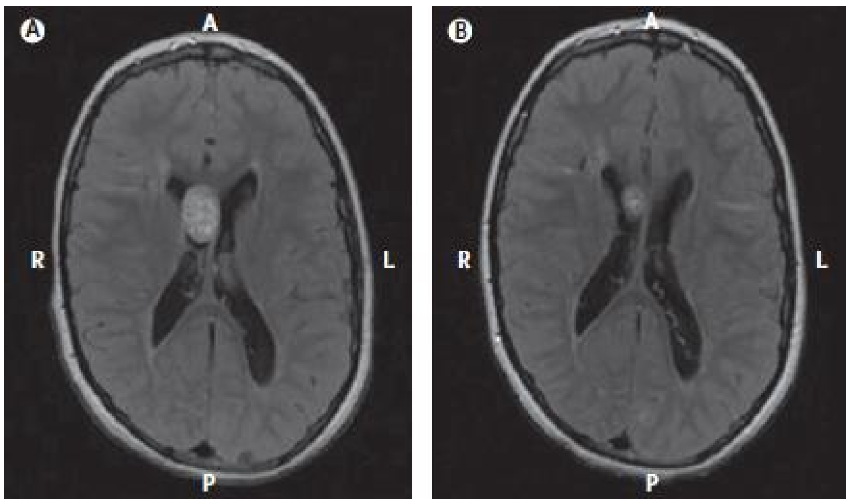
**Exomic Sequencing of Four Rare Central Nervous System Tumor Types**

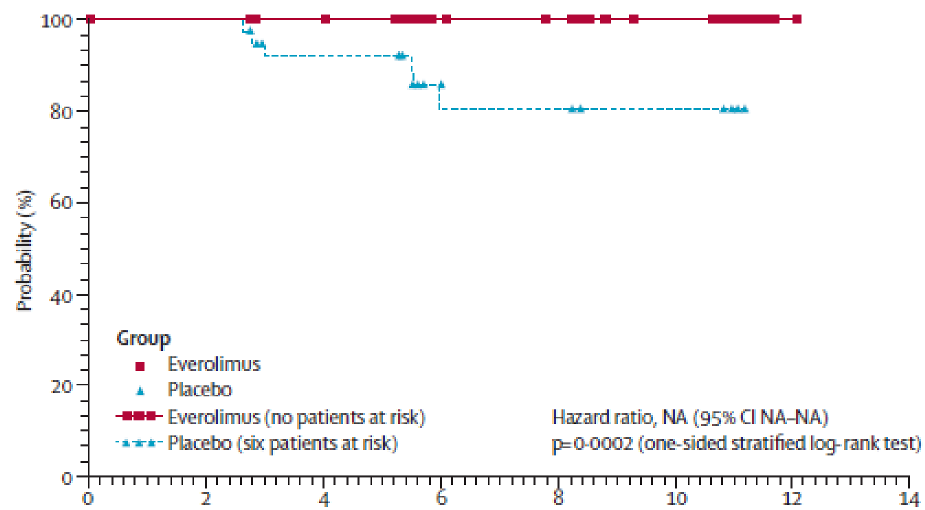
Chetan Bettegowda[1,2,*], Nishant Agrawal[2,3,*], Yuchen Jiao[2,*], Yuxuan Wang[2], Laura D. Wood[4], Fausto J. Rodriguez[4], Ralph H. Hruban[4], Gary L. Gallia[1], Zev A. Binder[1], Callen J. Riggins[1], Vafi Salmasi[5], Gregory J. Riggins[1], Zachary J. Reitman[6], Ahmed Rasheed[6], Stephen Keir[6], Sueli Shinjo[7], Suely Marie[7], Roger McLendon[6], George Jallo[1], Bert Vogelstein[2], Darell Bigner[6], Hai Yan[6], Kenneth W. Kinzler[2] and Nickolas Papadopoulos[2]

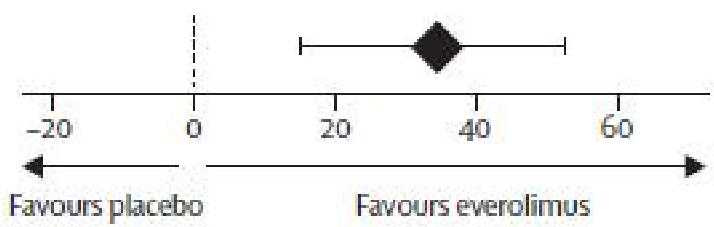
- mTOR activation seen in all grades of gliomas
- both kids and adults
- stronger with increasing grade

# Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial

David Neal Franz, Elena Belousova, Steven Sparagana, E Martina Bebin, Michael Frost, Rachel Kuperman, Olaf Witt, Michael H Kohrman, J Robert Flamini, Joyce Y Wu, Paolo Curatolo, Petrus J de Vries, Vicky H Whittemore, Elizabeth A Thiele, James P Ford, Gaurav Shah, Helene Cauwel, David Lebwohl, Tarek Sahmoud, Sergiusz Jozwiak



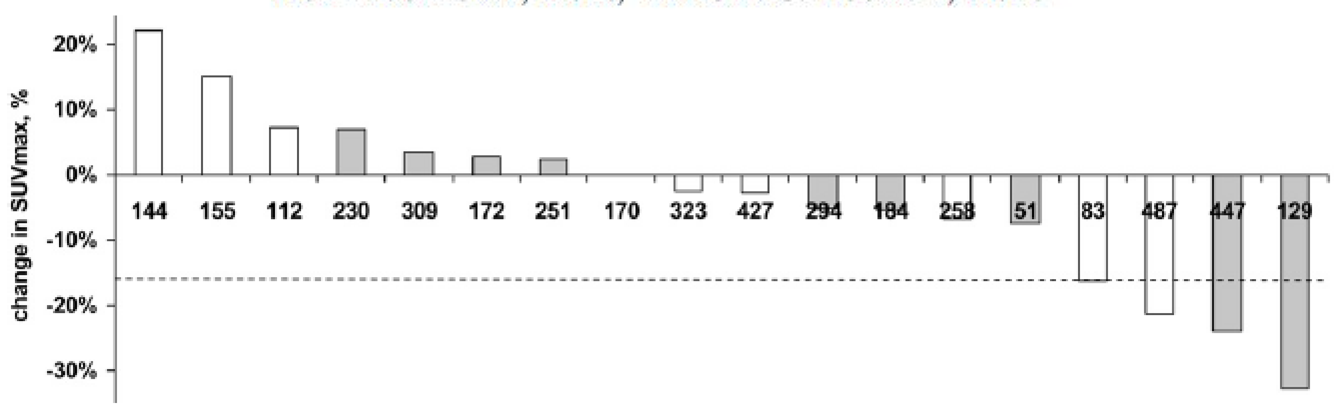

Lancet. 2013 Jan 12;381(9861):125-32

# RTOG 0913: A Phase 1 Study of Daily Everolimus (RAD001) in Combination With Radiation Therapy and Temozolomide in Patients With Newly Diagnosed Glioblastoma

Prakash Chinnaiyan, MD,* Minhee Won, MA,† Patrick Y. Wen, MD,‡
Amyn M. Rojiani, MD, PhD,§ Merideth Wendland, MD,|| Thomas A. Dipetrillo, MD,¶
Benjamin W. Corn, MD,# and Minesh P. Mehta, MD, FASTRO**

# NORTH CENTRAL CANCER TREATMENT GROUP PHASE I TRIAL N057K OF EVEROLIMUS (RAD001) AND TEMOZOLOMIDE IN COMBINATION WITH RADIATION THERAPY IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME

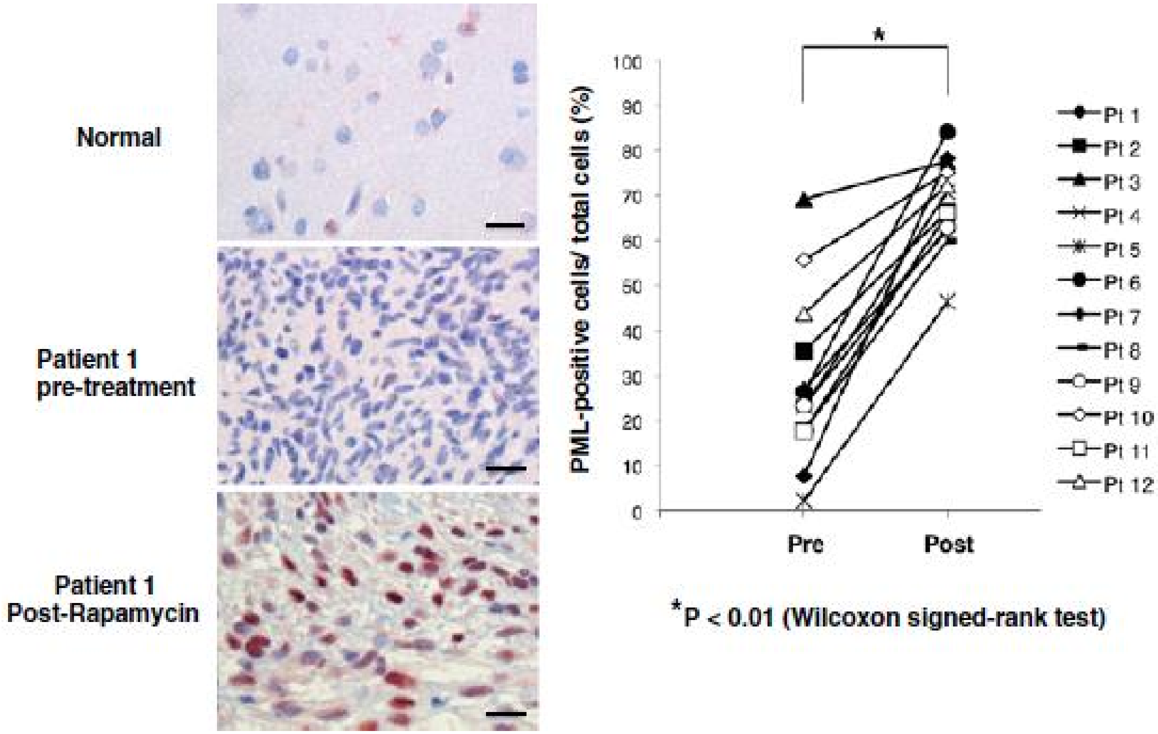
Jann N. Sarkaria, M.D.,* Evanthia Galanis, M.D.,* Wenting Wu, Ph.D.,* Patrick J. Peller, M.D.,*
Caterina Giannini, M.D.,* Paul D. Brown, M.D.,* Joon H. Uhm, M.D.,* Steven McGraw, M.D.,†
Kurt A. Jaeckle, M.D.,‡ and Jan C. Buckner, M.D.*




Int J Radiat Oncol Biol Phys. 2013 Aug 1;86(5):880-4
Int J Radiat Oncol Biol Phys. 2011 Oct 1;81(2):468-75

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

Akio Iwanami[a], Beatrice Gini[b,c,1], Ciro Zanca[b,1], Tomoo Matsutani[b], Alvaro Assuncao[d], Ali Nael[e], Julie Dang[f], Huijun Yang[b], Shaojun Zhu[g], Jun Kohyama[g], Issay Kitabayashi[h], Webster K. Cavenee[b,i], Timothy F. Cloughesy[j], Frank B. Furnari[b,i,k], Masaya Nakamura[a], Yoshiaki Toyama[a], Hideyuki Okano[l], and Paul S. Mischel[b,i,k,2]




- rapamycin→ upregulation of PML→ inhibition of cell death
- treatment with **arsenic trioxide** prevents PML upregulation→ restores sensitivity to rapamycin

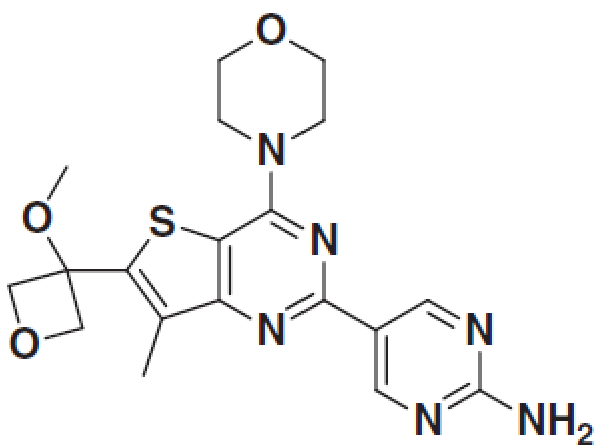
Proc Natl Acad Sci U S A. 2013 Mar 12;110(11):4339-44

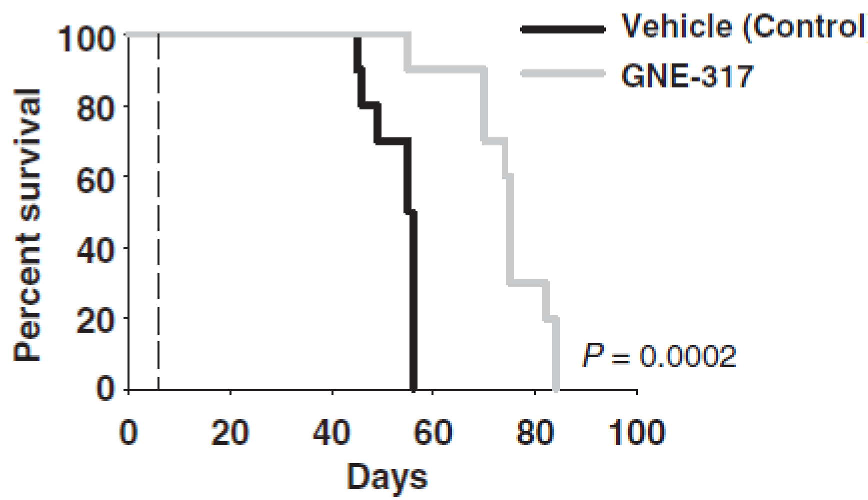
Cancer Therapy: Preclinical

Clinical Cancer Research

# Targeting the PI3K Pathway in the Brain—Efficacy of a PI3K Inhibitor Optimized to Cross the Blood–Brain Barrier

Laurent Salphati[1], Timothy P. Heffron[2], Bruno Alicke[3], Merry Nishimura[3], Kai Barck[4], Richard A. Carano[4], Jonathan Cheong[1], Kyle A. Edgar[3], Joan Greve[4], Samir Kharbanda[3], Hartmut Koeppen[5], Shari Lau[5], Leslie B. Lee[3], Jodie Pang[1], Emile G. Plise[1], Jenny L. Pokorny[6], Hani Bou Reslan[4], Jann N. Sarkaria[6], Jeffrey J. Wallin[3], Xiaolin Zhang[1], Stephen E. Gould[3], Alan G. Olivero[2], and Heidi S. Phillips[3]



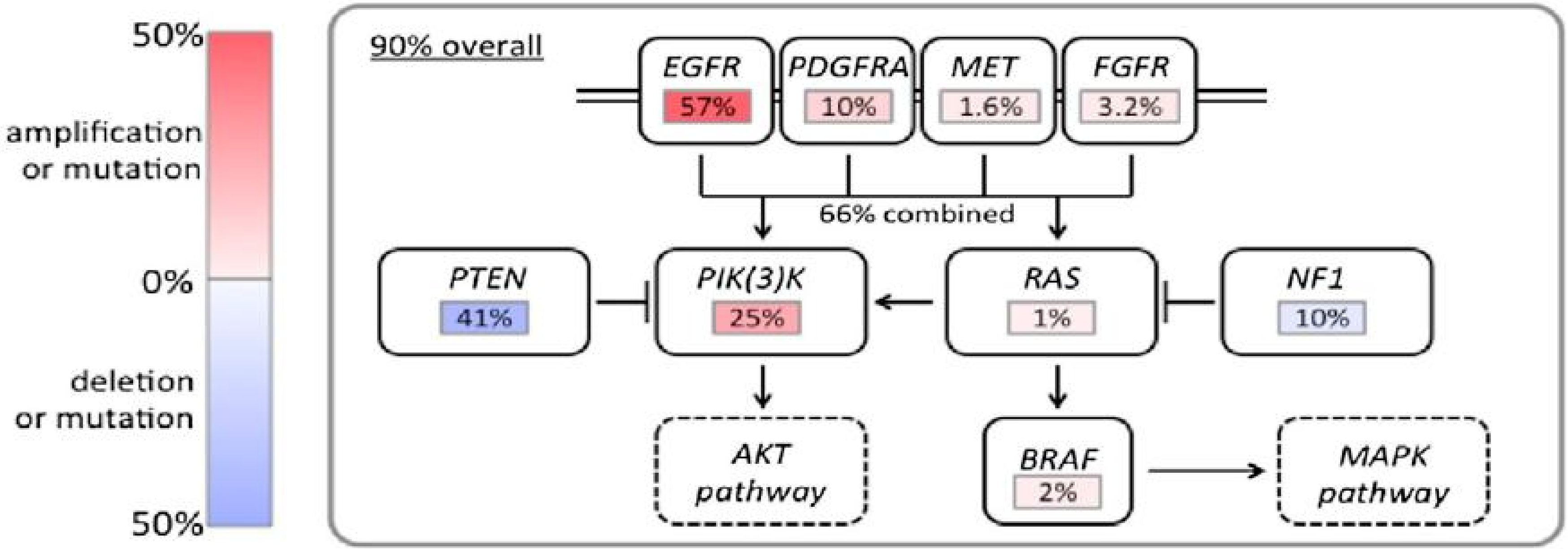

GNE-317

dual PI3K-mTOR inhibitor

Clin Cancer Res. 2012 Nov 15;18(22):6239-48

# The Somatic Genomic Landscape of Glioblastoma

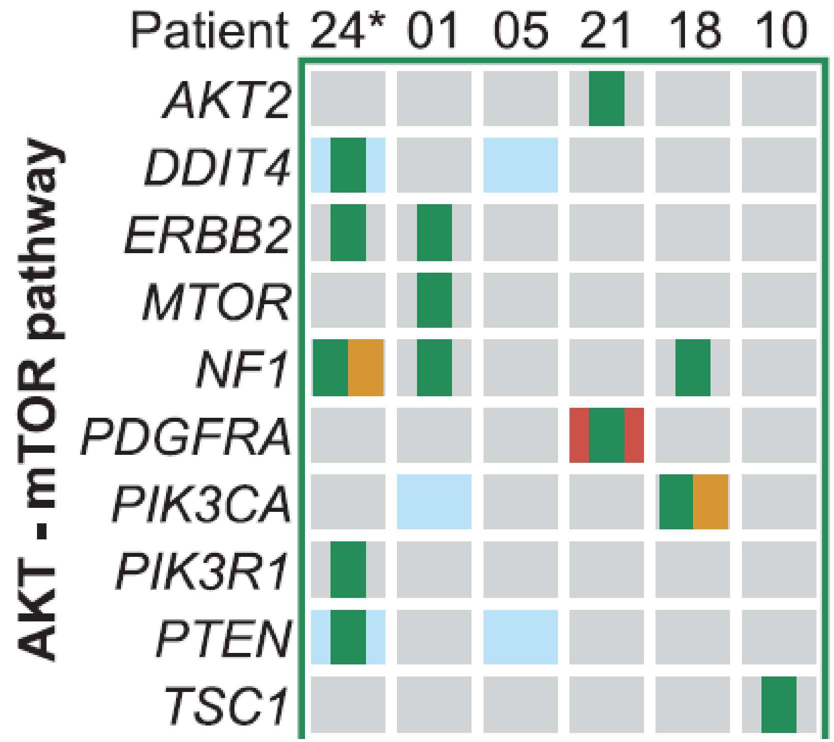
Cameron W. Brennan,[1,2,40,*] Roel G.W. Verhaak,[3,11,40] Aaron McKenna,[4,40] Benito Campos,[5,6] Houtan Noushmehr,[7,8] Sofie R. Salama,[9] Siyuan Zheng,[3] Debyani Chakravarty,[1] J. Zachary Sanborn,[9] Samuel H. Berman,[1] Rameen Beroukhim,[4,5] Brady Bernard,[10] Chang-Jiun Wu,[11] Giannicola Genovese,[11] Ilya Shmulevich,[10] Jill Barnholtz-Sloan,[12] Lihua Zou,[4] Rahulsimham Vegesna,[3] Sachet A. Shukla,[5] Giovanni Ciriello,[13] W.K. Yung,[14] Wei Zhang,[15] Carrie Sougnez,[4] Tom Mikkelsen,[16] Kenneth Aldape,[15] Darell D. Bigner,[17] Erwin G. Van Meir,[18] Michael Prados,[19] Andrew Sloan,[20] Keith L. Black,[21] Jennifer Eschbacher,[22] Gaetano Finocchiaro,[23] William Friedman,[24] David W. Andrews,[25] Abhijit Guha,[26] Mary Iacocca,[27] Brian P. O'Neill,[28] Greg Foltz,[29] Jerome Myers,[30] Daniel J. Weisenberger,[7] Robert Penny,[31] Raju Kucherlapati,[32] Charles M. Perou,[33] D. Neil Hayes,[33] Richard Gibbs,[34] Marco Marra,[35] Gordon B. Mills,[36] Eric Lander,[4] Paul Spellman,[37] Richard Wilson,[38] Chris Sander,[13] John Weinstein,[3] Matthew Meyerson,[4,5] Stacey Gabriel,[4] Peter W. Laird,[7] David Haussler,[9,39] Gad Getz,[4] Lynda Chin,[4,11,*] and TCGA Research Network




Cell. 2013 Oct 10;155(2):462-77

# Mutational Analysis Reveals the Origin and Therapy-Driven Evolution of Recurrent Glioma

Brett E. Johnson,[1*] Tali Mazor,[1*] Chibo Hong,[1] Michael Barnes,[2] Koki Aihara,[3,4] Cory Y. McLean,[1†] Shaun D. Fouse,[1] Shogo Yamamoto,[3] Hiroki Ueda,[3] Kenji Tatsuno,[3] Saurabh Asthana,[5,6] Llewellyn E. Jalbert,[7] Sarah J. Nelson,[7,8] Andrew W. Bollen,[2] W. Clay Gustafson,[9] Elise Charron,[10] William A. Weiss,[1,9,10] Ivan V. Smirnov,[1] Jun S. Song,[11,12] Adam B. Olshen,[6,11] Soonmee Cha,[1] Yongjun Zhao,[13] Richard A. Moore,[13] Andrew J. Mungall,[13] Steven J. M. Jones,[13] Martin Hirst,[13] Marco A. Marra,[13] Nobuhito Saito,[4] Hiroyuki Aburatani,[3] Akitake Mukasa,[4] Mitchel S. Berger,[1] Susan M. Chang,[1] Barry S. Taylor,[5,6,11‡] Joseph F. Costello[1‡]




Science. 2014 Jan 10;343(6167):189-93

# take-home points

- PI3K-Akt-mTOR pathway is active in all grades of glioma
- other than PTEN, none of the components are routinely used in surgical neuropathology
- drugs targeting PI3K and mTOR are already being tested and/or used
- resistance is tricky, especially in higher grades