Targeting the IGF Pathway in Pediatric Sarcomas-Lessons Learned and Questions Raised

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Role of IGF Signaling- Previous Studies

- IGFII is an autocrine growth and motility factor in rhabdomyosarcoma (El-Badry et al. Cell Growth and Diff 1990)
- Loss of Imprinting (LOI) of IGFII in Rhabdomyosarcomas (Zhan S, Shapiro DN, and Helman LJ JCI 1994)
- LOI of IGFII in Ewing's Sarcoma (Zhan S, Shapiro DN, and Helman LJ Oncogene 1995)
- IGFIR is required for EWS-FLI-1 transformation of fibroblastsl (Toretsky J. et al. JBC 1997)

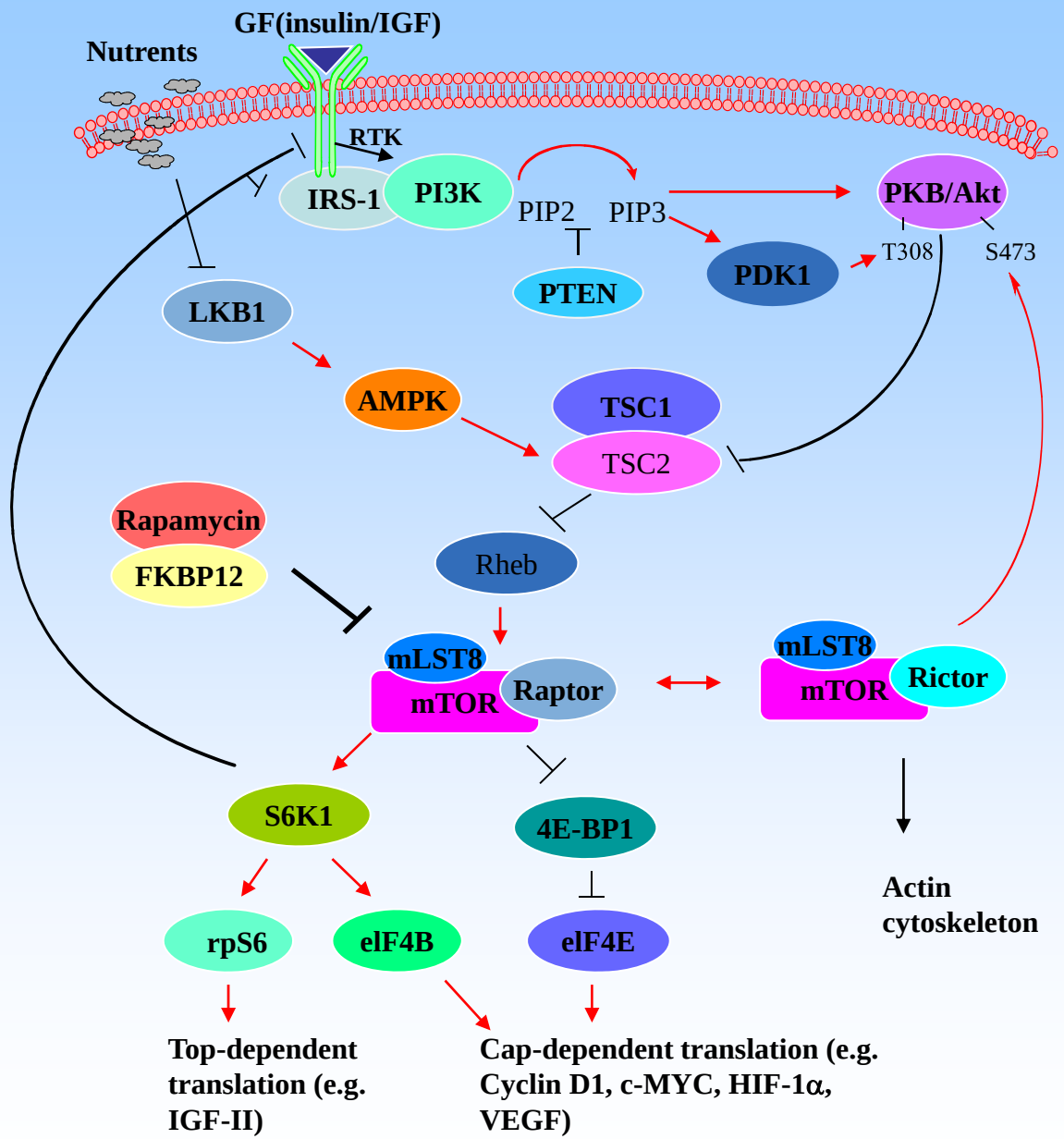
Previous Studies

- IGF-II overexpression in C2 myoblasts led to diminished G1 checkpoint (Zhang et al. JBC 1999)

- Resistance to apoptosis most directly correlated with phosphorylation of p70S6 kinase and 4E-BP-1. Resistance to apoptosis in IGF-II overexpressing cells was reversed by rapamycin (Wan and Helman Neoplasia 2002)

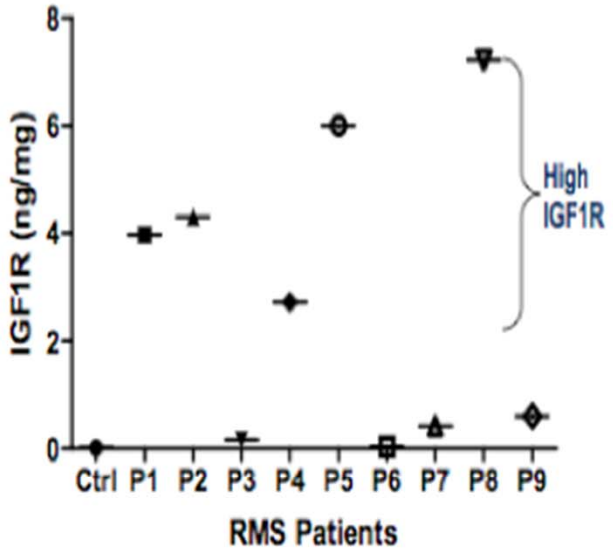
Rapalogs and IGF Signaling

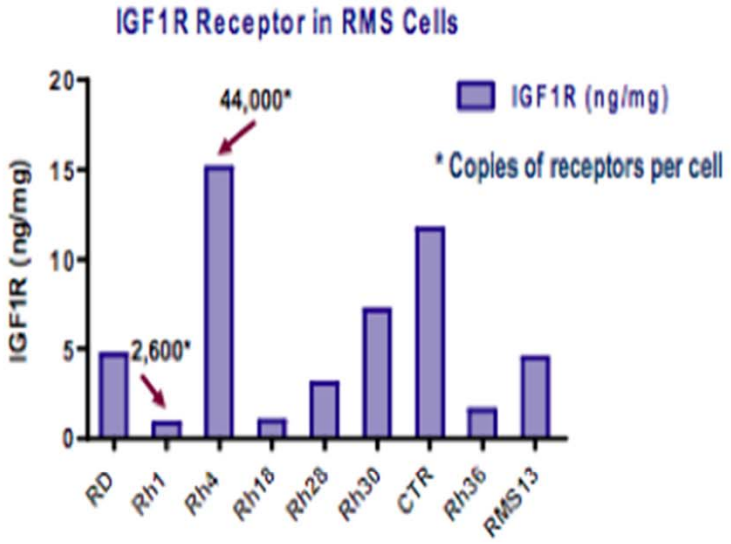
- Demonstrated that rapalog treatment of RMS leads to activation of Akt *in vivo*
- Demonstrated that this activation is IGF dependent and can be blocked with IGFIR blockade (Wan et al. Oncogene 2006)
- Proteomic analysis of Dx tumor biopsies in Stage III RMS demonstrated activation of mTOR pathway proteins predicted poor DFS in both ERMS and ARMS (Petricoin EF et al. Ca Res 2007)


GF(insulin/IGF)
Nutrents
RTK
IRS-1
PI3K
PIP2
PIP3
PKB/Akt
T308
S473
PDK1
PTEN
LKB1
AMPK
TSC1
TSC2
Rapamycin
FKBP12
Rheb
mLST8
mTOR
Raptor
mLST8
mTOR
Rictor
S6K1
4E-BP1
Actin
cytoskeleton
rpS6
elF4B
elF4E
Top-dependent translation (e.g. IGF-II)
Cap-dependent translation (e.g. Cyclin D1, c-MYC, HIF-1α, VEGF)

Preclinical Studies with human IGFIR Ab

Variable levels of IGFIR in RMS tumors and cell lines



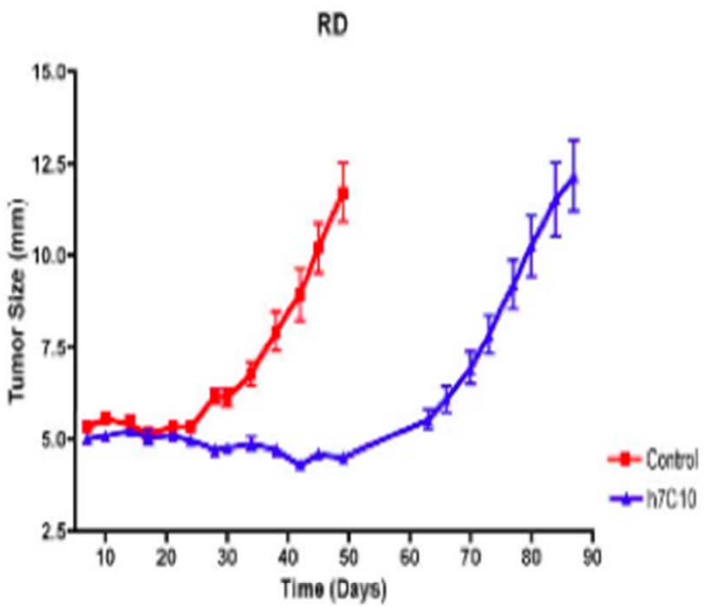


A. Variable levels of IGF1R in RMS tumors
- Ctrl = normal skeletal muscle
- P = patients' tumor

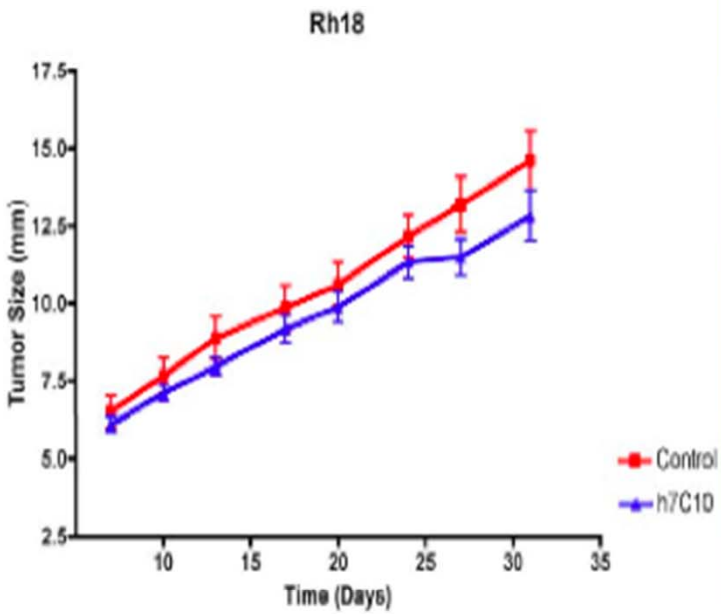
B. Similar degree of variation of IGF1R in RMS lines

Cao, L,,et al. Ca Res 2008

In vivo Correlation of IGF1R and anti-IGF1R Response



IGF1R (R/cell): 13,800

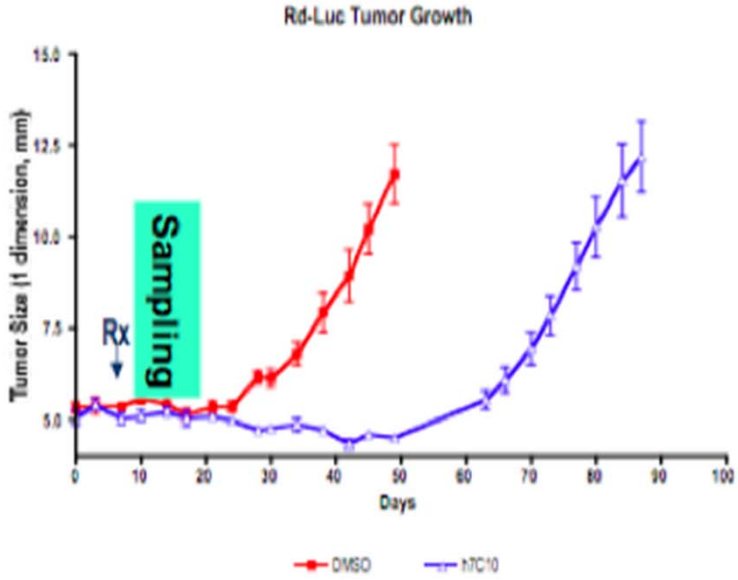


IGF1R (R/cell): 2,900

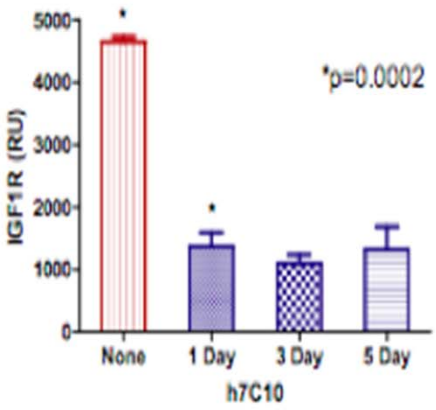
Results represent largest diameter shown at Mean±SEM (n=10)

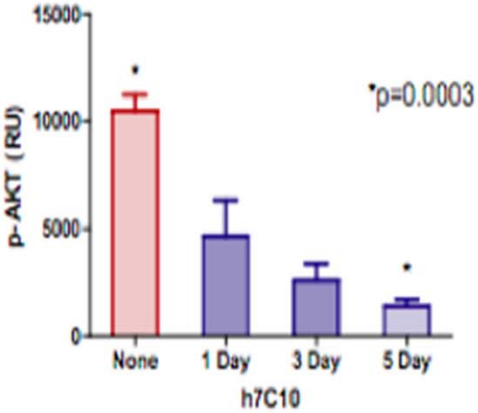
Anti-tumor Effects of h7C10 Associated with Initial Inhibition of IGF1R and p-AKT

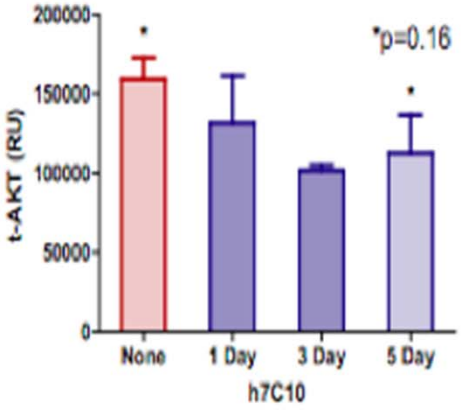
A. Drug effects on tumor growth



B. h7C10 initially inhibits both IGF1R and p-AKT in vivo

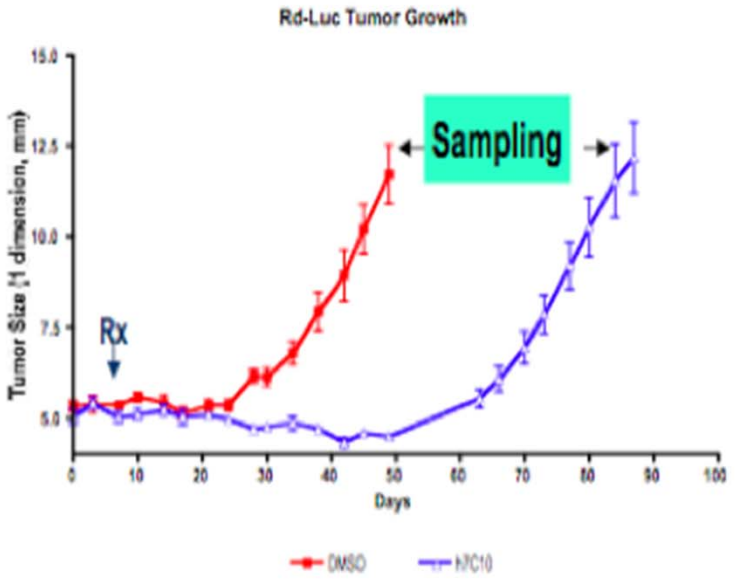




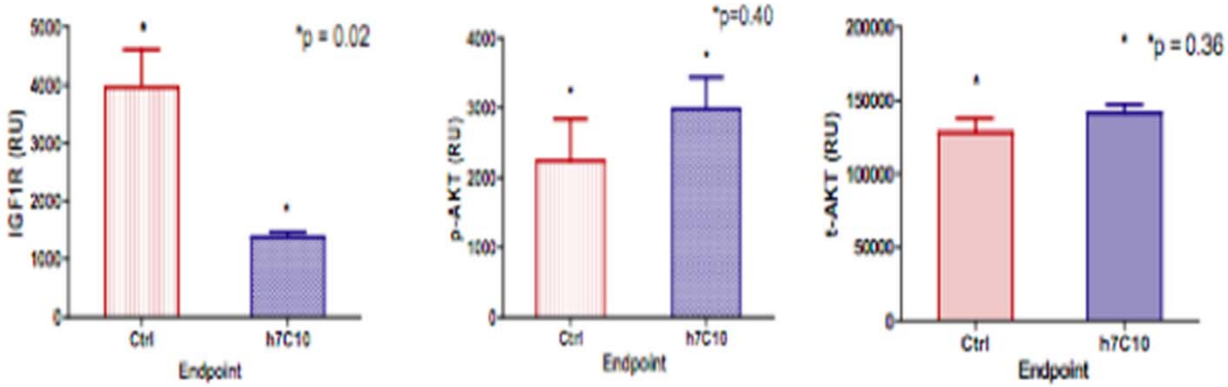


Resistance to h7C10 is Associated with Reactivated AKT Signaling

A. Drug effects on tumor growth

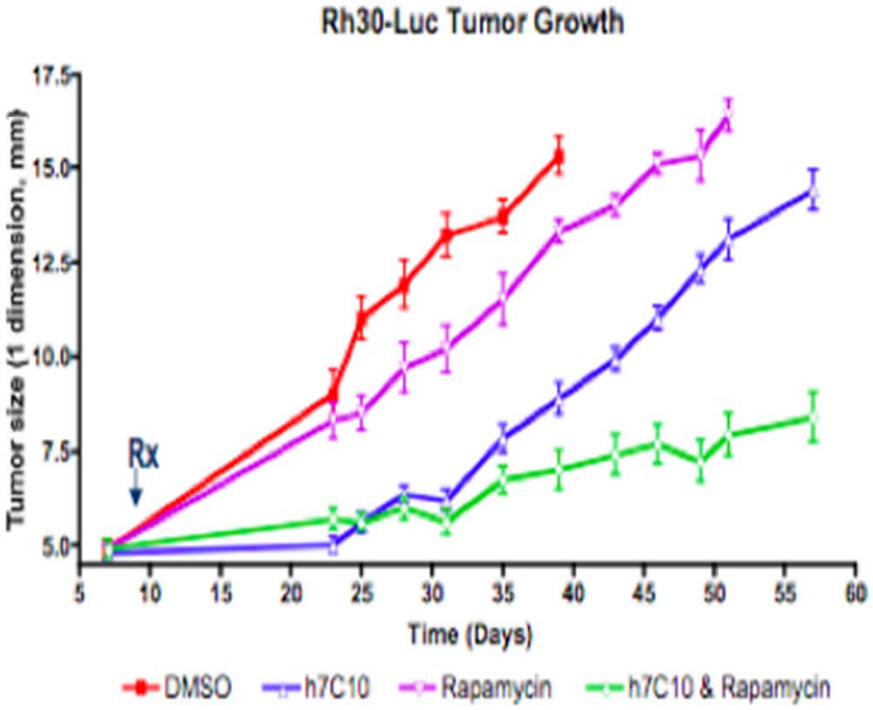


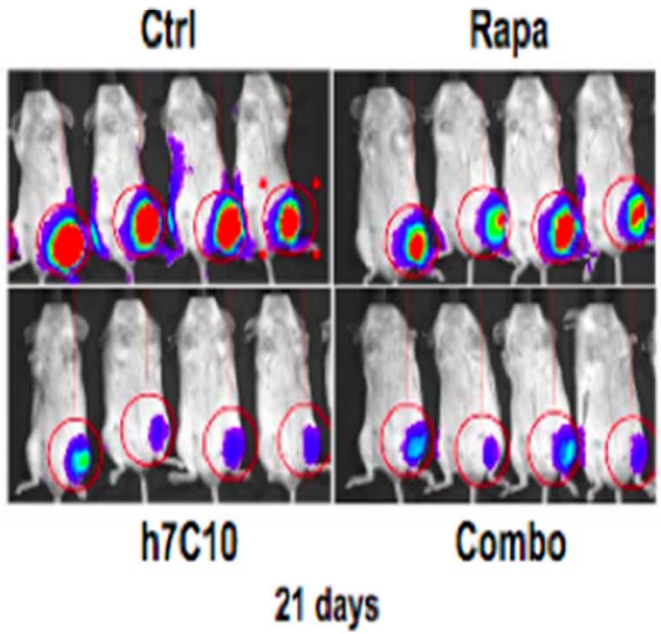
B. Resistance associated with reactivated p-AKT



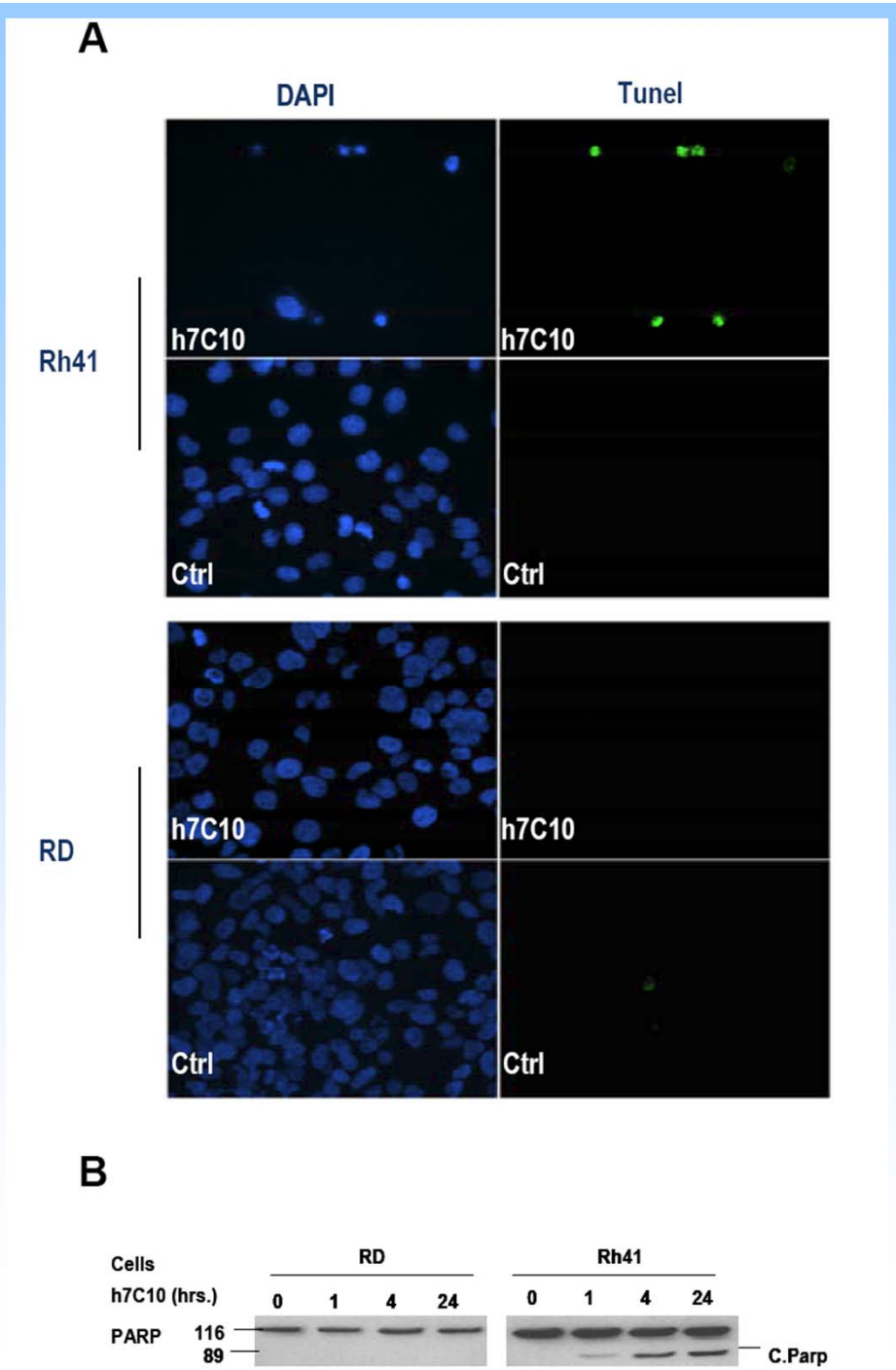
Synergistic Inhibition between IGF1R antibody and Rapamycin

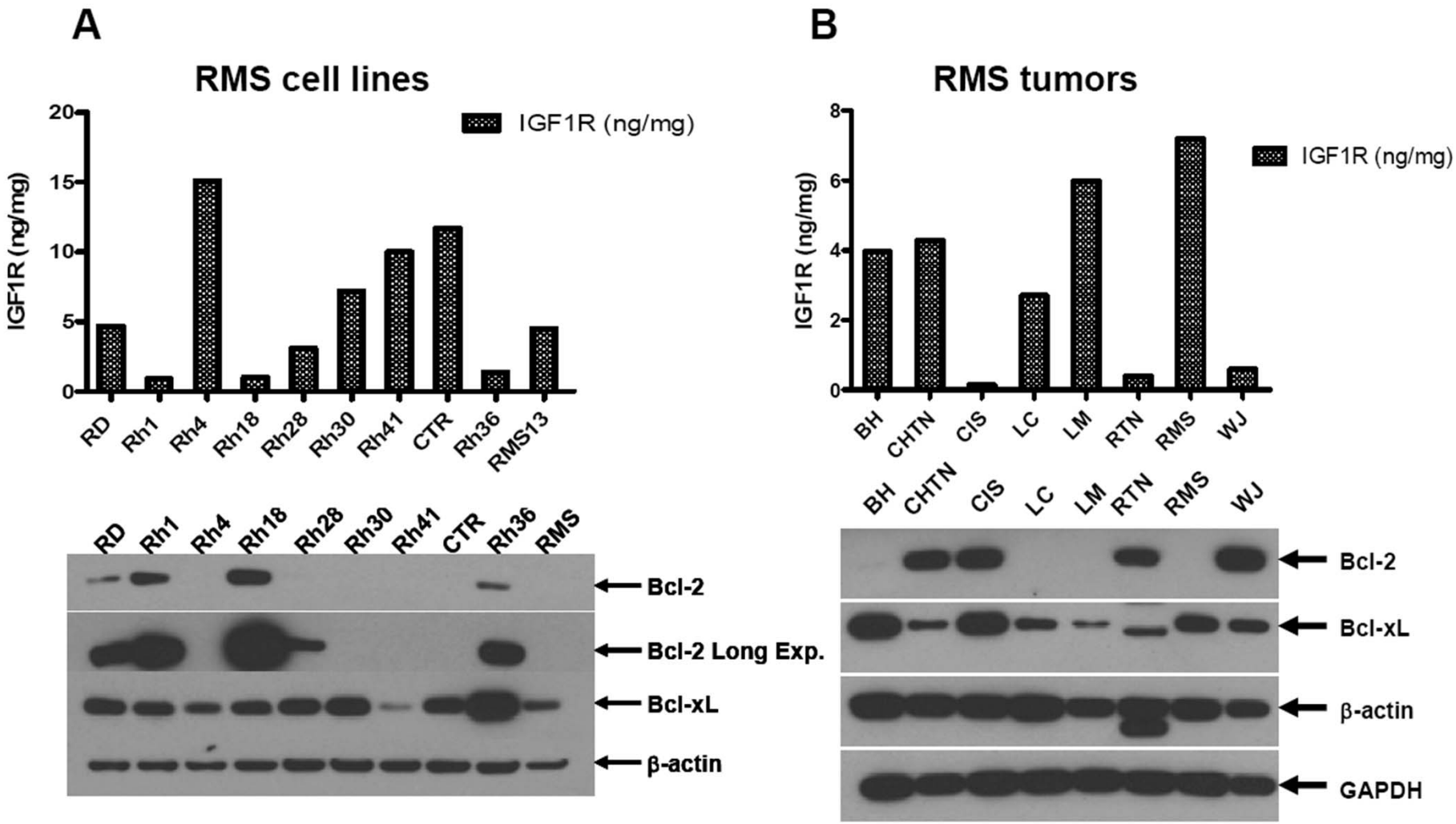
A

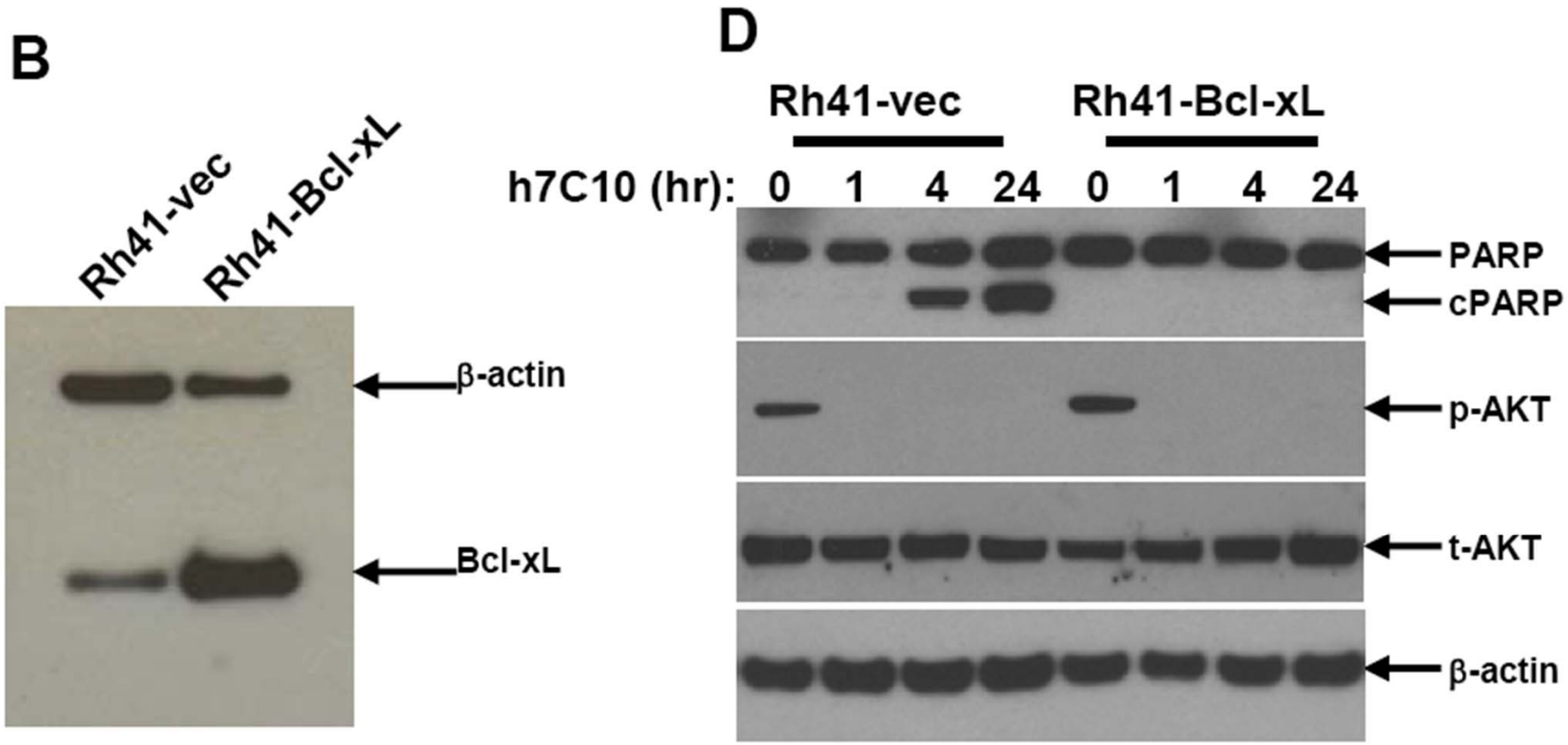


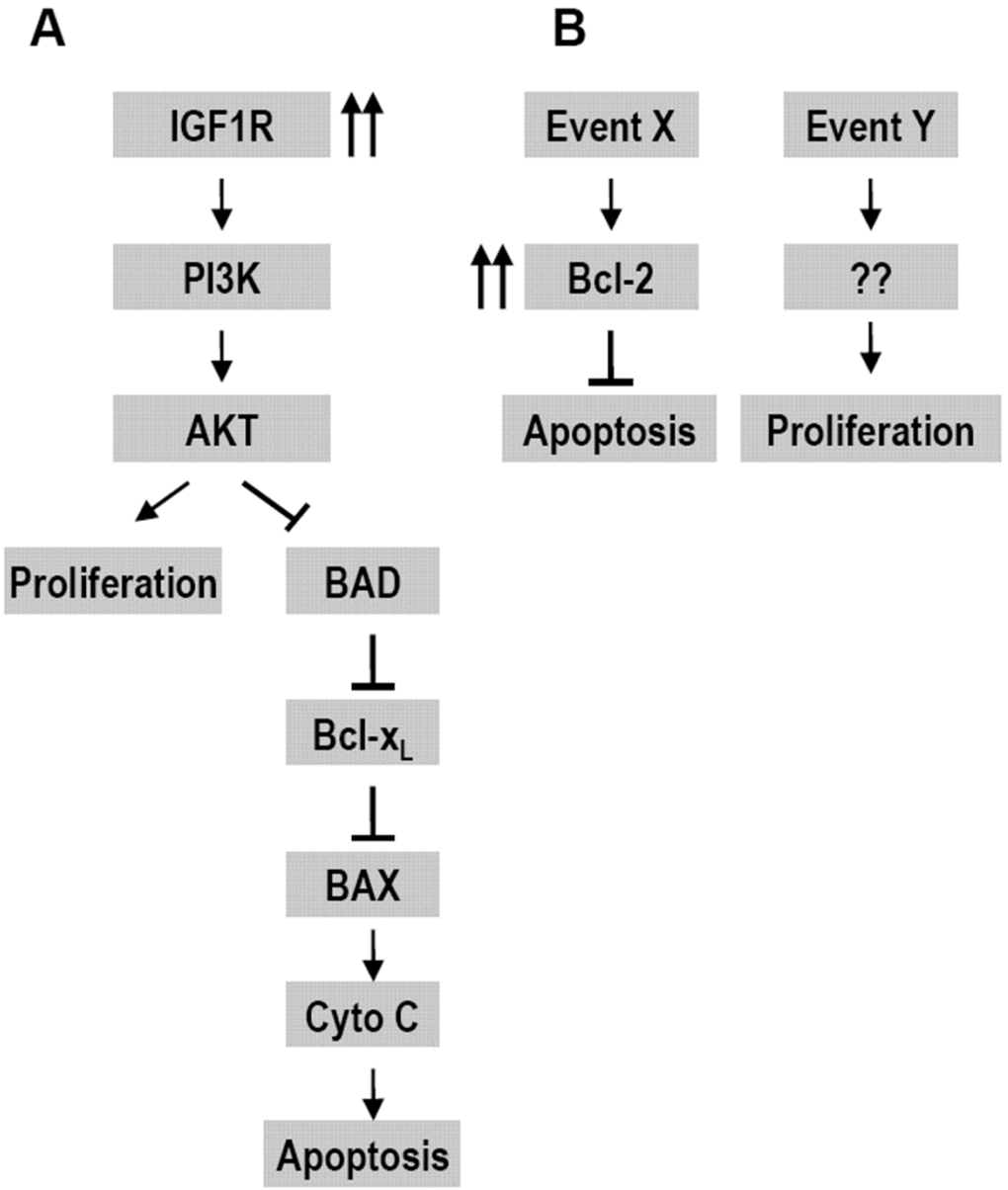


Combination effect of h7C10 and Rapa


A
DAPI
Tunel
Rh41
h7C10
h7C10
Ctrl
Ctrl
RD
h7C10
h7C10
Ctrl
Ctrl
B
Cells
RD
Rh41
h7C10 (hrs.)
0
1
4
24
0
1
4
24
PARP
116
89
C.Parp

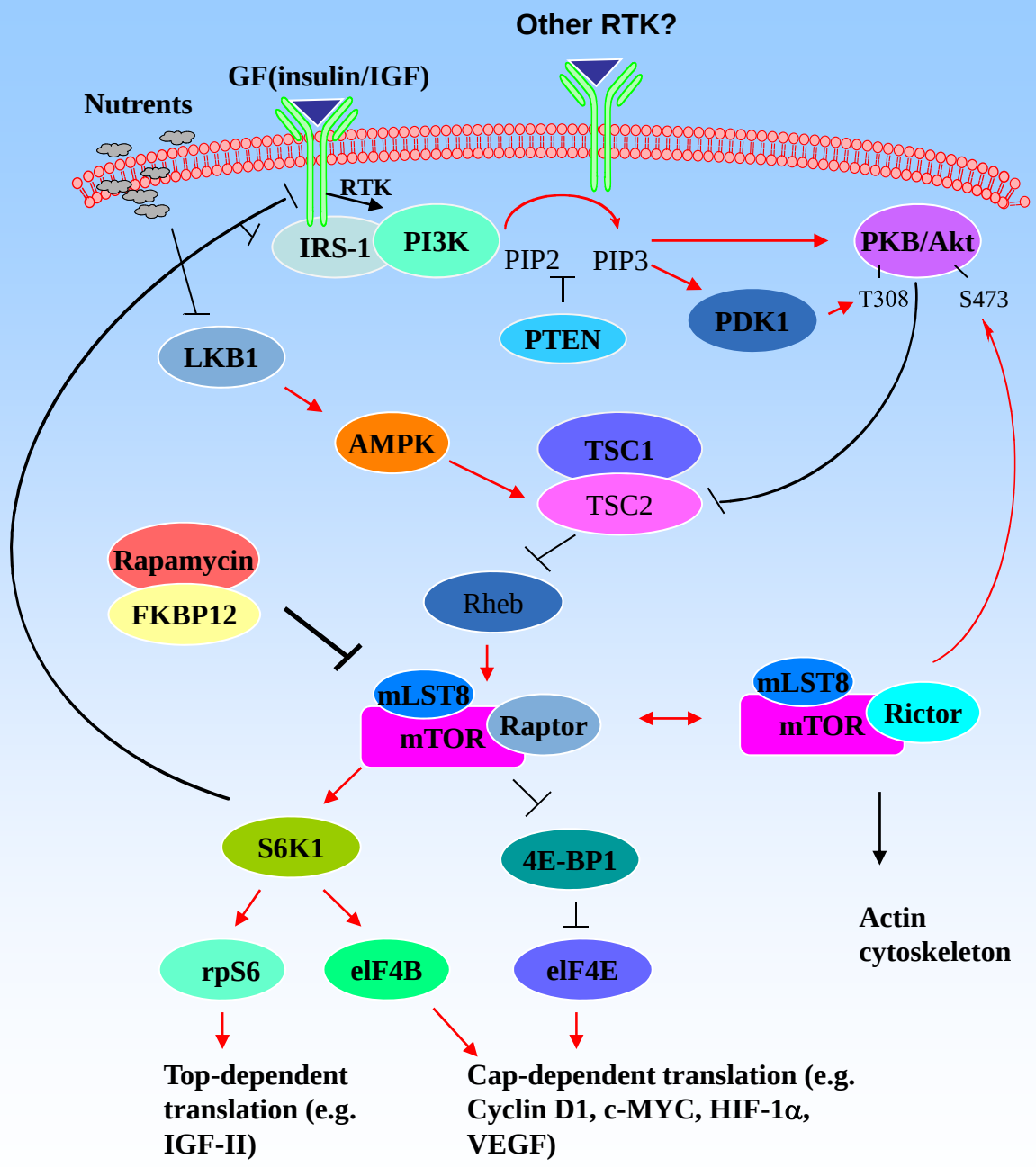

A
RMS cell lines
IGF1R (ng/mg)
IGF1R (ng/mg)
20
15
10
5
0
RD
Rh1
Rh4
Rh18
Rh28
Rh30
Rh41
CTR
Rh36
RMS13
RD
Rh1
Rh4
Rh18
Rh28
Rh30
Rh41
CTR
Rh36
RMS
Bcl-2
Bcl-2 Long Exp.
Bcl-xL
β-actin
B
RMS tumors
IGF1R (ng/mg)
IGF1R (ng/mg)
8
6
4
2
0
BH
CHTN
CIS
LC
LM
RTN
RMS
WJ
BH
CHTN
CIS
LC
LM
RTN
RMS
WJ
Bcl-2
Bcl-xL
β-actin
GAPDH


B
Rh41-vec
Rh41-Bcl-xL
β-actin
Bcl-xL
D
Rh41-vec
Rh41-Bcl-xL
h7C10 (hr): 0 1 4 24 0 1 4 24
PARP
cPARP
p-AKT
t-AKT
β-actin


A
IGF1R
PI3K
AKT
Proliferation
BAD
Bcl-xL
BAX
Cyto C
Apoptosis
B
Event X
Bcl-2
Apoptosis
Event Y
??
Proliferation

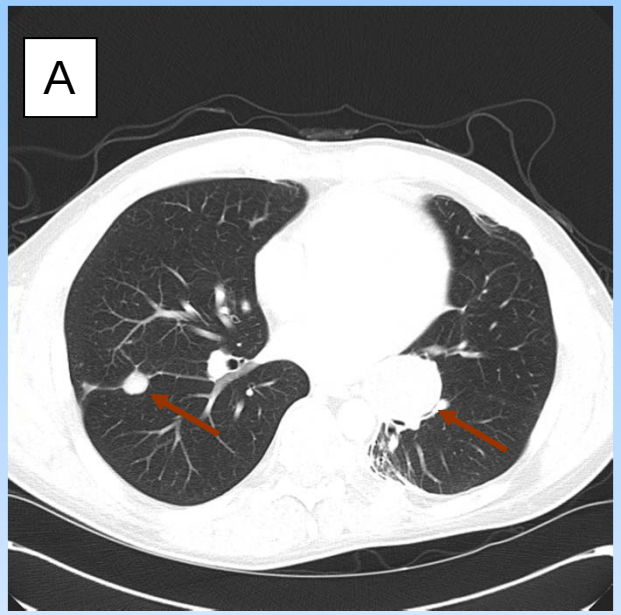
Conclusions

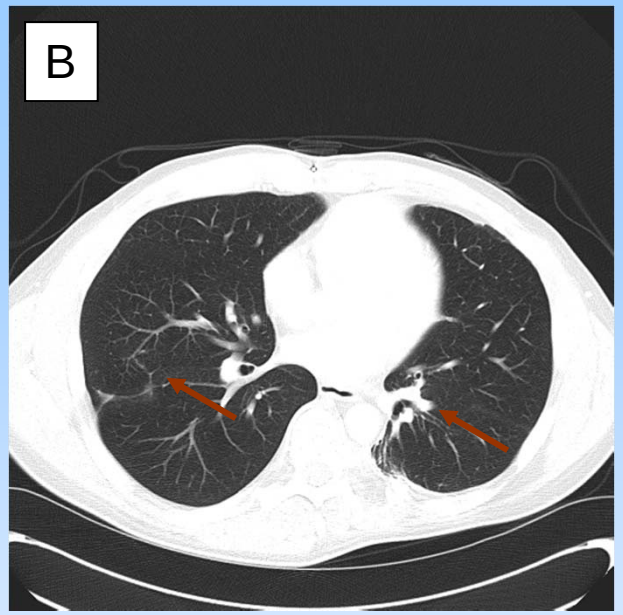
- Early evidence to suggest beneficial combination of mTOR inhibition combined with IGFIR inhibition
- Effect of IGFIR inhibition correlates with IGFIR levels
- Effect of IGFIR blockade on decrease in pAkt is lost in long-term xenografts, and this "tachphylaxis" is abrogated with mTOR inhibtion
- Raises question of whether Ab should be stopped in patients who respond and then progress

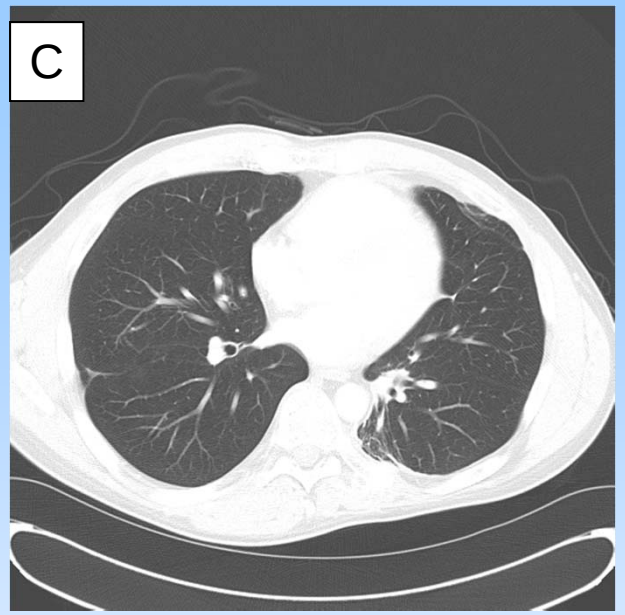

Other RTK?
GF(insulin/IGF)
Nutrents
RTK
IRS-1
PI3K
PIP2
PIP3
PKB/Akt
T308
S473
PDK1
PTEN
LKB1
AMPK
TSC1
TSC2
Rapamycin
FKBP12
Rheb
mLST8
mTOR
Raptor
mLST8
mTOR
Rictor
S6K1
4E-BP1
rpS6
elF4B
elF4E
Actin
cytoskeleton
Top-dependent translation (e.g. IGF-II)
Cap-dependent translation (e.g. Cyclin D1, c-MYC, HIF-1α, VEGF)

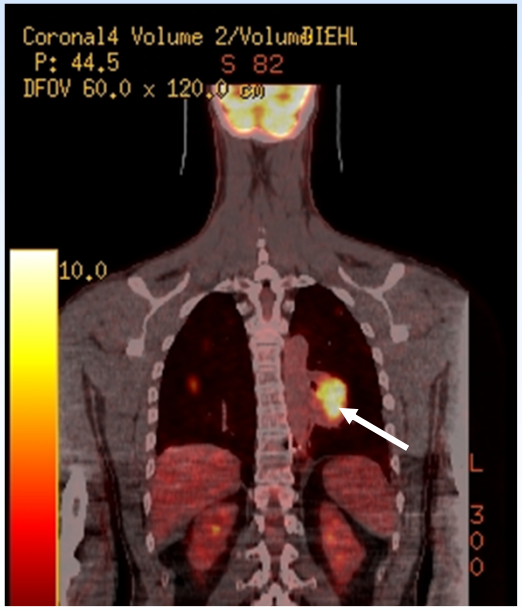
Clinical Studies in Ewing's and other Sarcomas

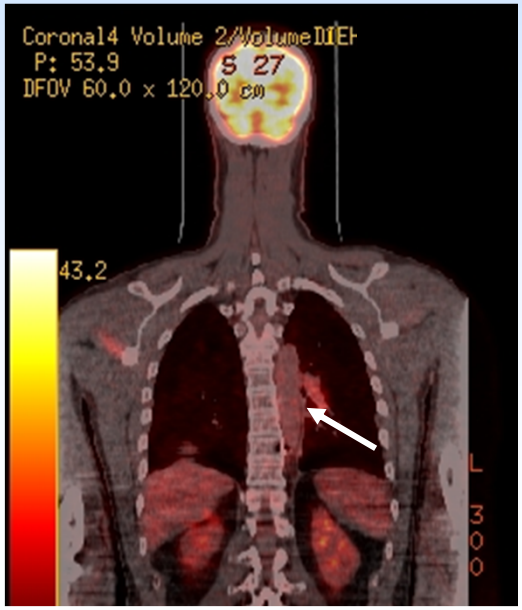
44 year old US farmer with third systemic relapse of Ewing's sarcoma

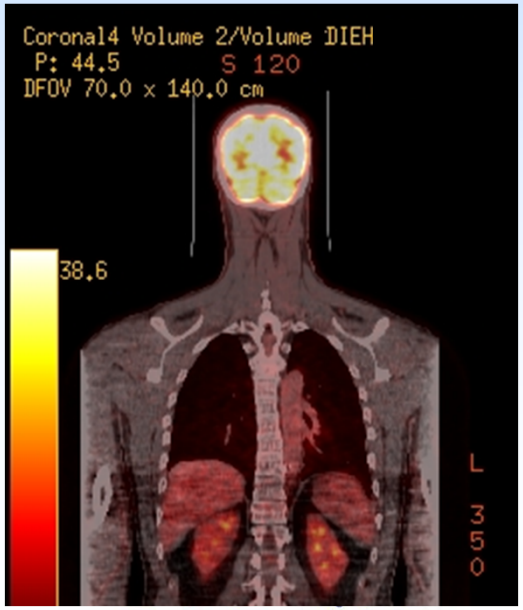












SARC Protocol #: SARC 011
Hoffmann-La Roche Protocol #: N021157

TITLE: SARC Global Collaboration*: A Phase II Trial of R1507, a Recombinant Human Monoclonal Antibody to the Insulin-Like Growth Factor-1 Receptor for the treatment of patients with recurrent or refractory Ewing's sarcoma, osteosarcoma, synovial sarcoma, rhabdomyosarcoma and other sarcomas

*SARC Global Collaboration represents collaboration among the Innovative Therapies for Children with Cancer (ITCC), Istituti Ortopedici Rizzoli, European Organization for Research (EORTC/STBG), Cooperative Osteosarcoma Study Group (COSS), EuroEwings, Euramos

Sponsor: F. Hoffmann-LaRoche

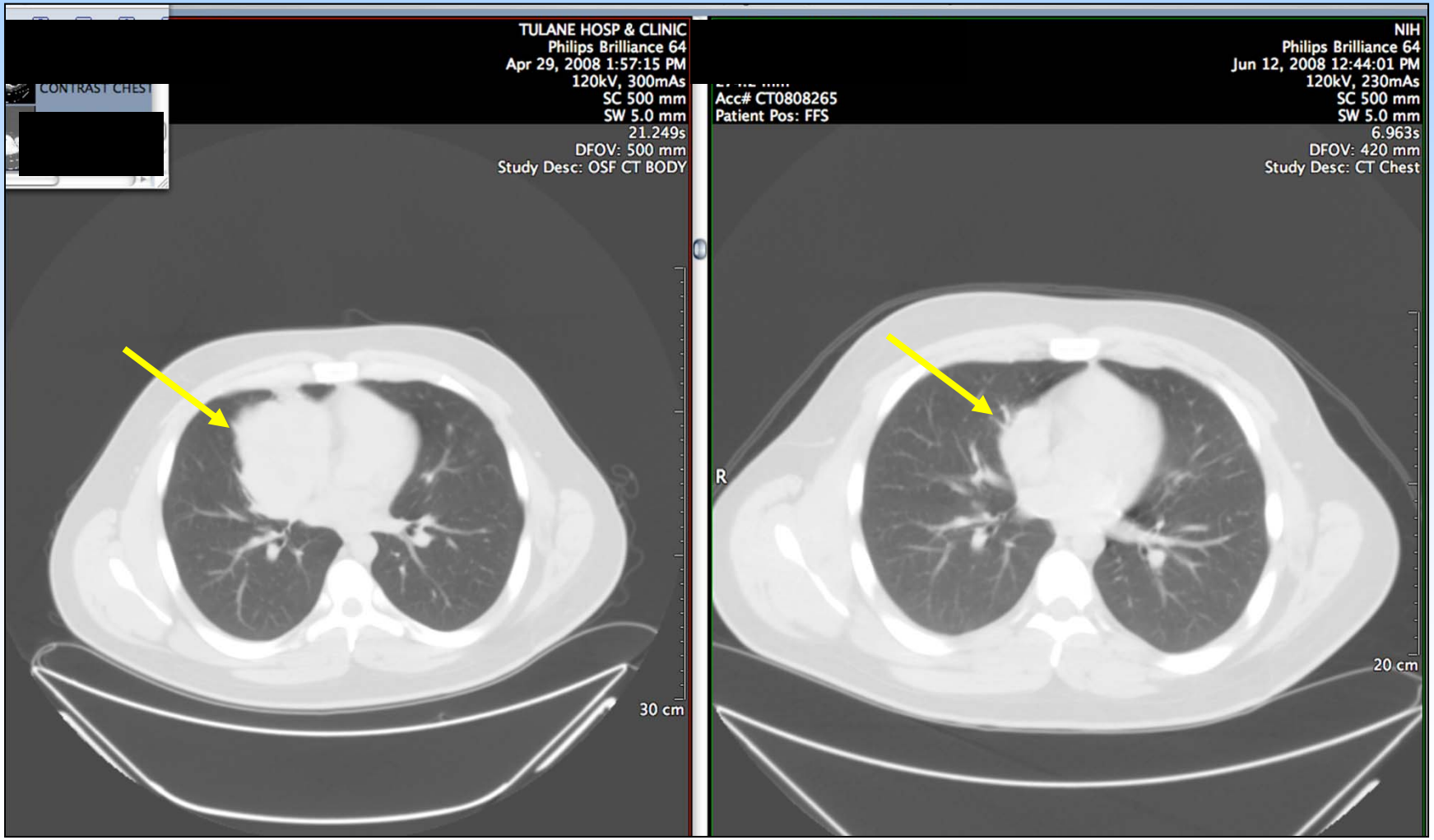
Coordinating Center: SARC (Sarcoma Alliance for Research through Collaboration)

SARC Sarcoma Alliance for Research through Collaboration
Collaborating for a Cure.

17 yo boy with multiply recurrent Ewing's sarcoma

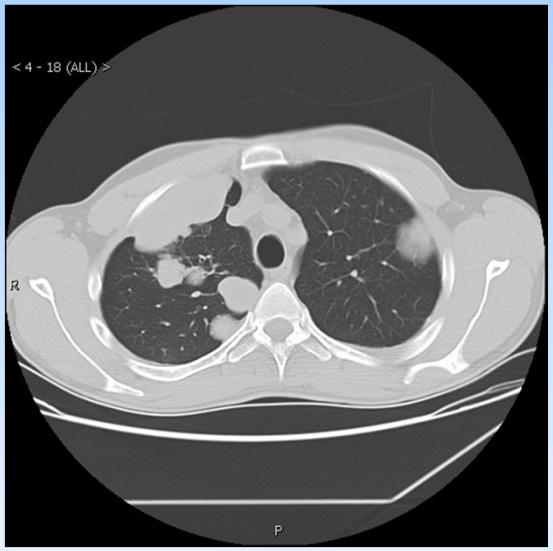
Baseline CT Chest

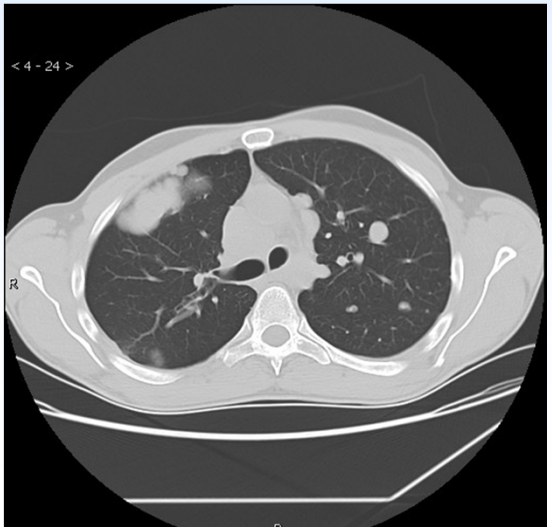
Week 6 CT Chest



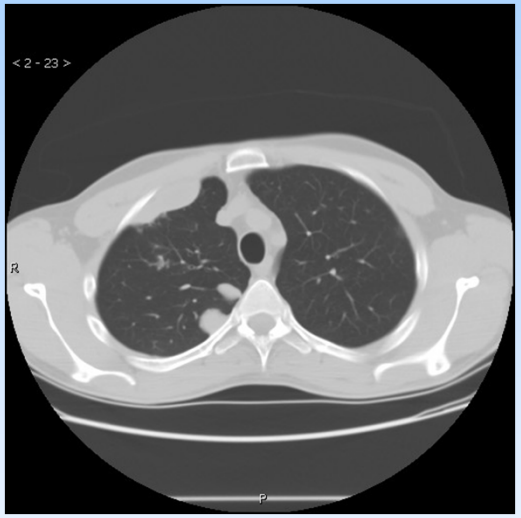
Refractory 25yo with EWS and Retinal Metastasis Rx with R1507

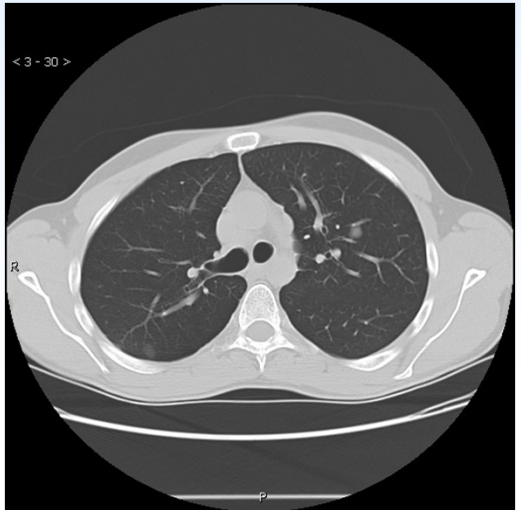
Baseline



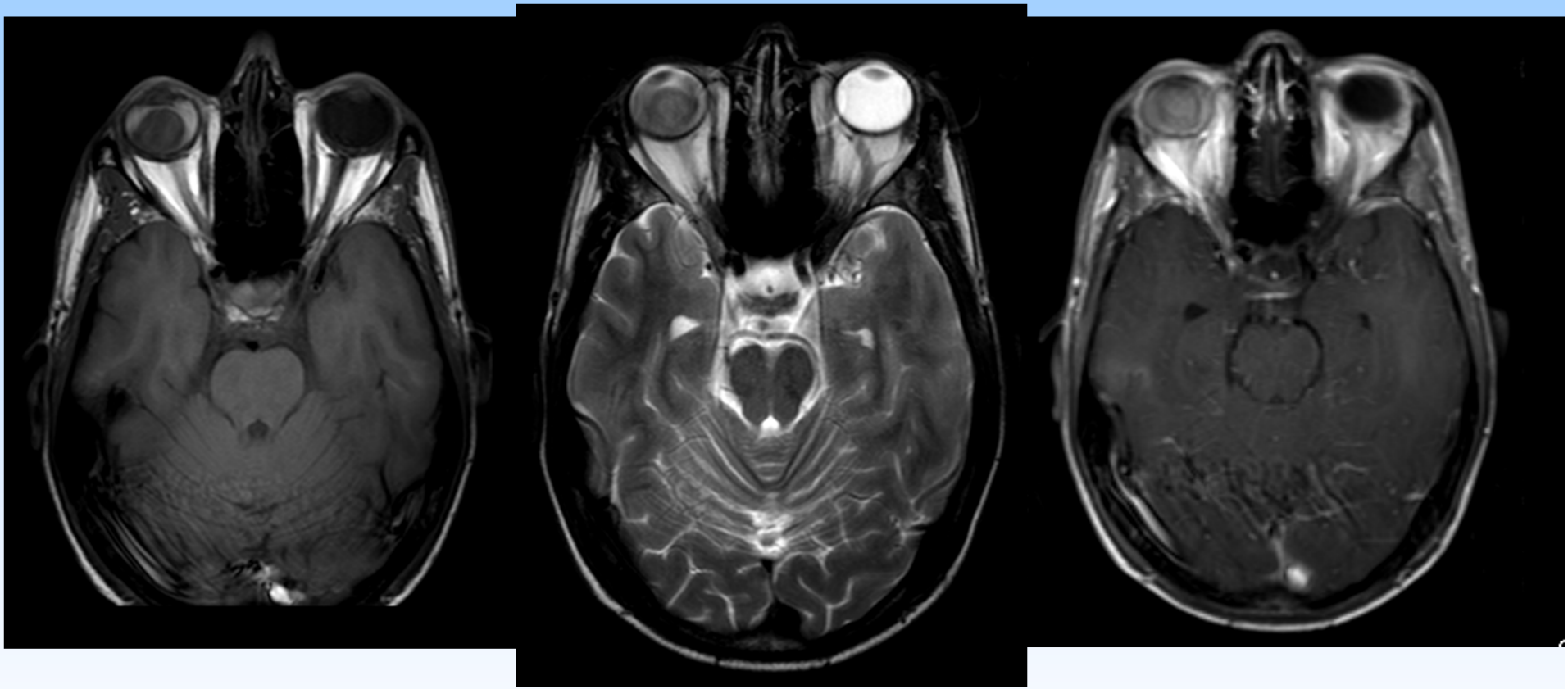


Week 6





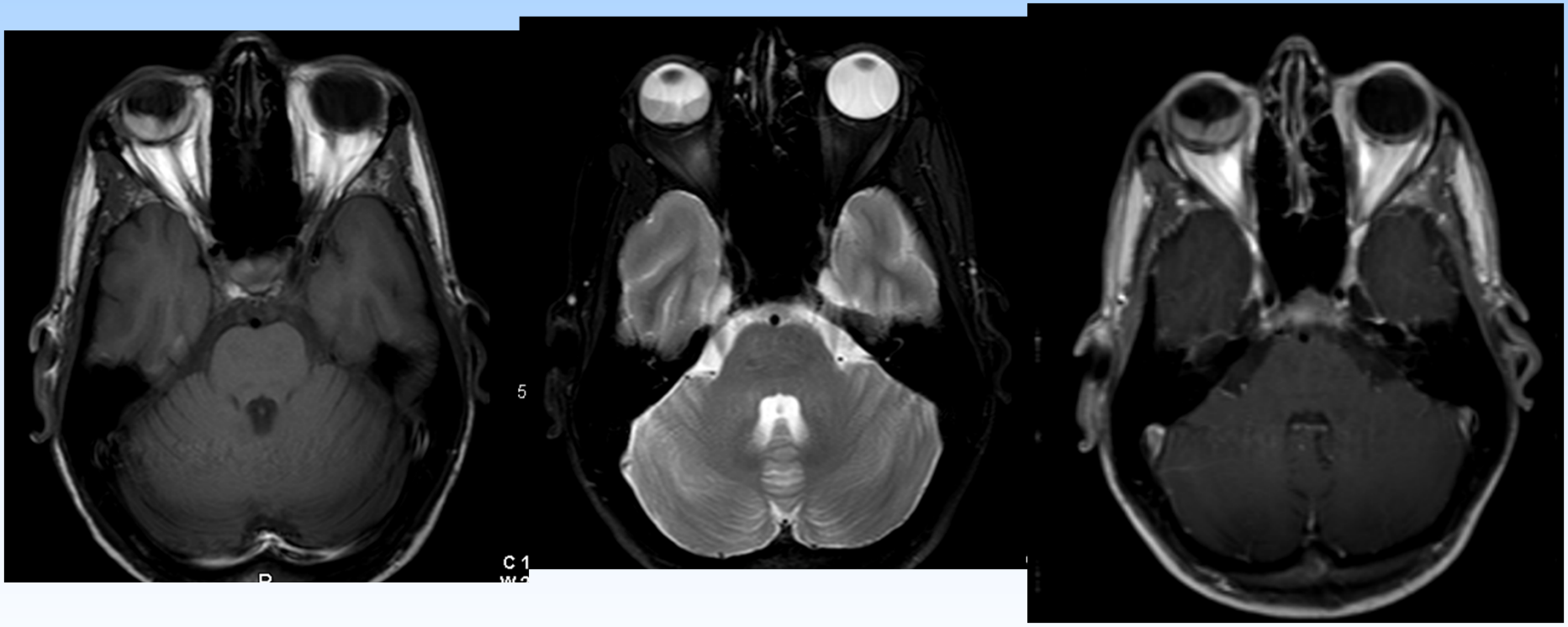
9/9/08 NIH MRI



1.6 X 1.4 X 1.6 CM

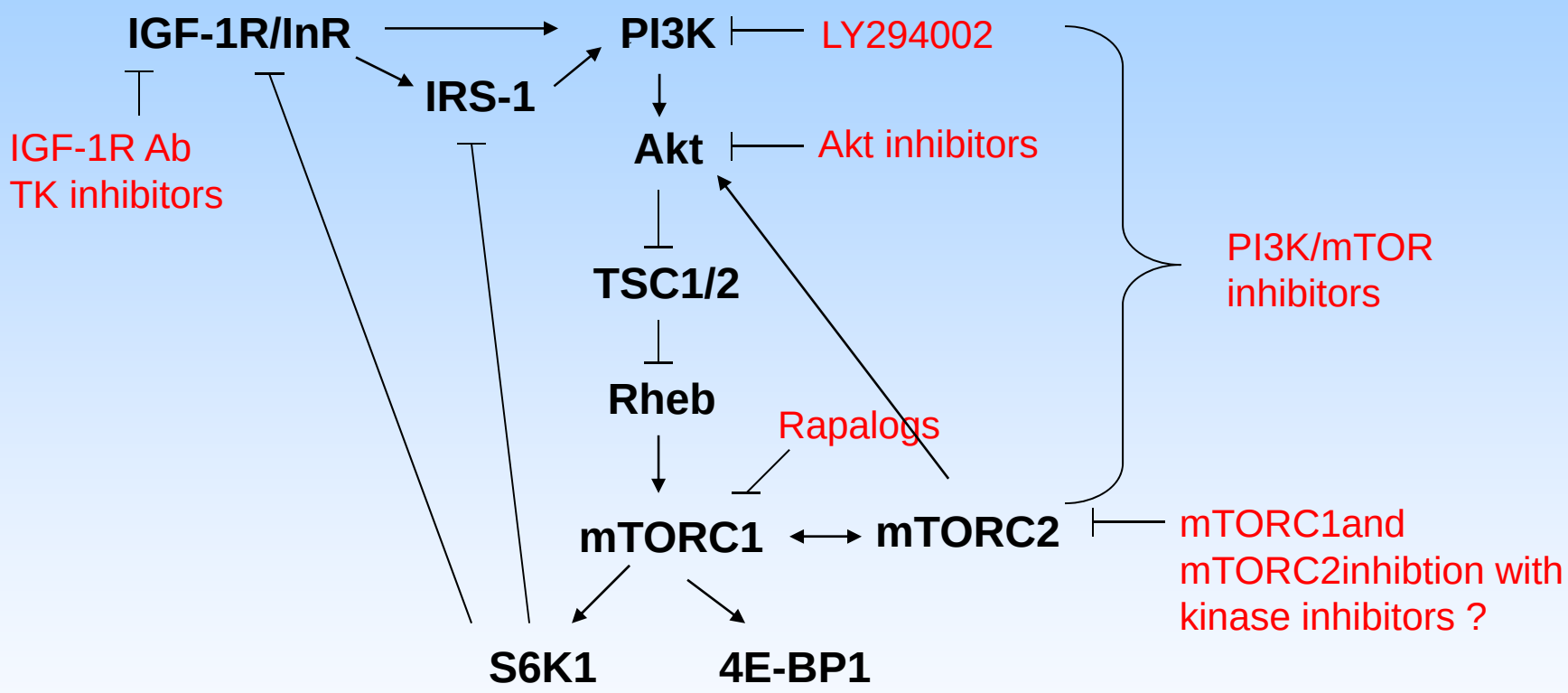
9/9/08 NIH PET CT: Right orbital mass SUV 4.7

10/14/08 NIH MRI



Conclusions

- IGFIRAb 1507 has good clinical activity in EWS and perhaps RMS
  - No mutations found in pathway to date
- Preclinical models did not accurately predict dramatic tumor shrinkage, but did predict activity
- Response rates less than 50%, so challenge is to identify factors that predict good response
- Must find ways to combine with other targeted Rx and or ChemoRx


IGF-1R/InR
PI3K
LY294002
IRS-1
IGF-1R Ab
TK inhibitors
Akt
Akt inhibitors
TSC1/2
PI3K/mTOR
inhibitors
Rheb
Rapalogs
mTORC1
mTORC2
mTORC1and
mTORC2inhibtion with
kinase inhibitors ?
S6K1
4E-BP1

Liang Cao (not shown) Lee Helman

Chand Khanna Choh Yeung Issac Darko(not shown)

Sung-Hyeok Hong

Xiaolin Wan Patrick Grohar

Duane Currier (not shown)