Why were IGF-1R inhibitors disappointing?

Can we improve our results by patient selection or use of combinations?

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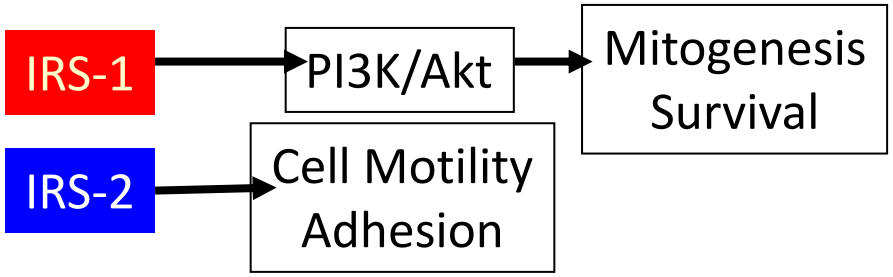
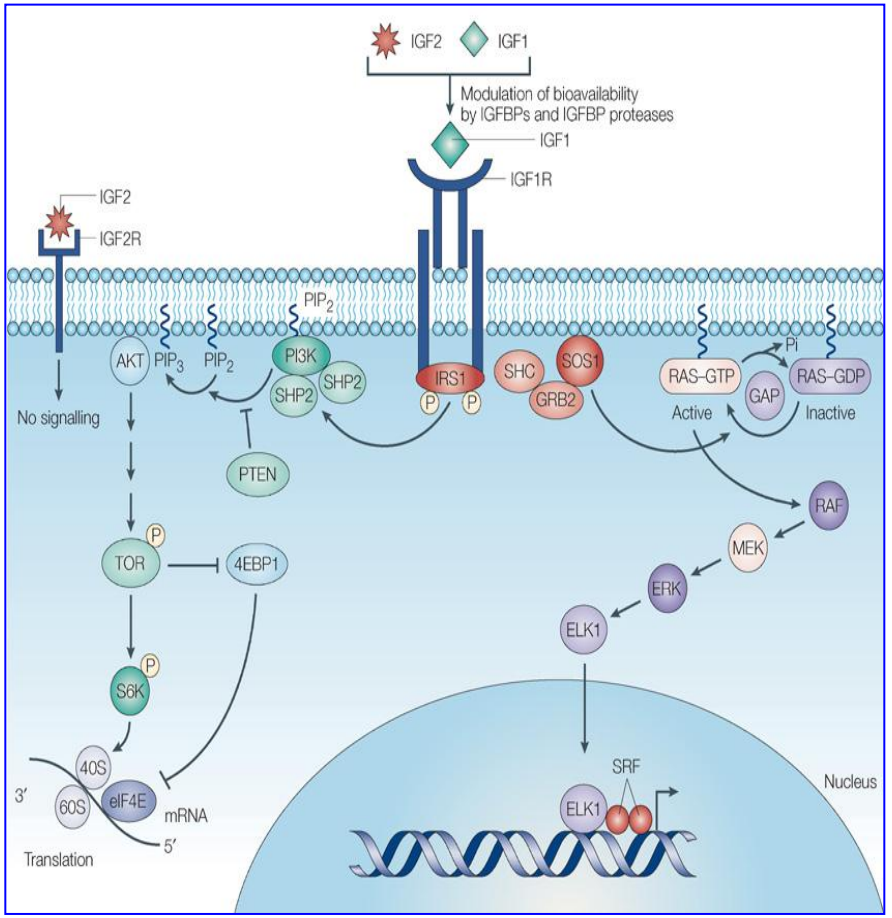
Disclosures

- I do not have any disclosure to discuss

Introduction (I)

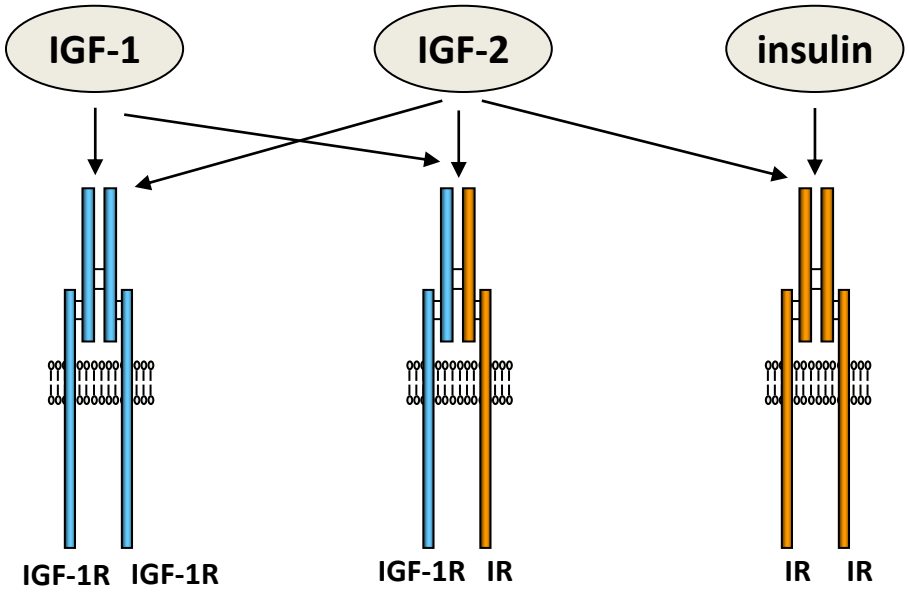
The insulin-like growth factor I receptor (IGF-IR) is a receptor tyrosine kinase that regulates various biological processes, including cell growth, proliferation, and inhibition of apoptosis





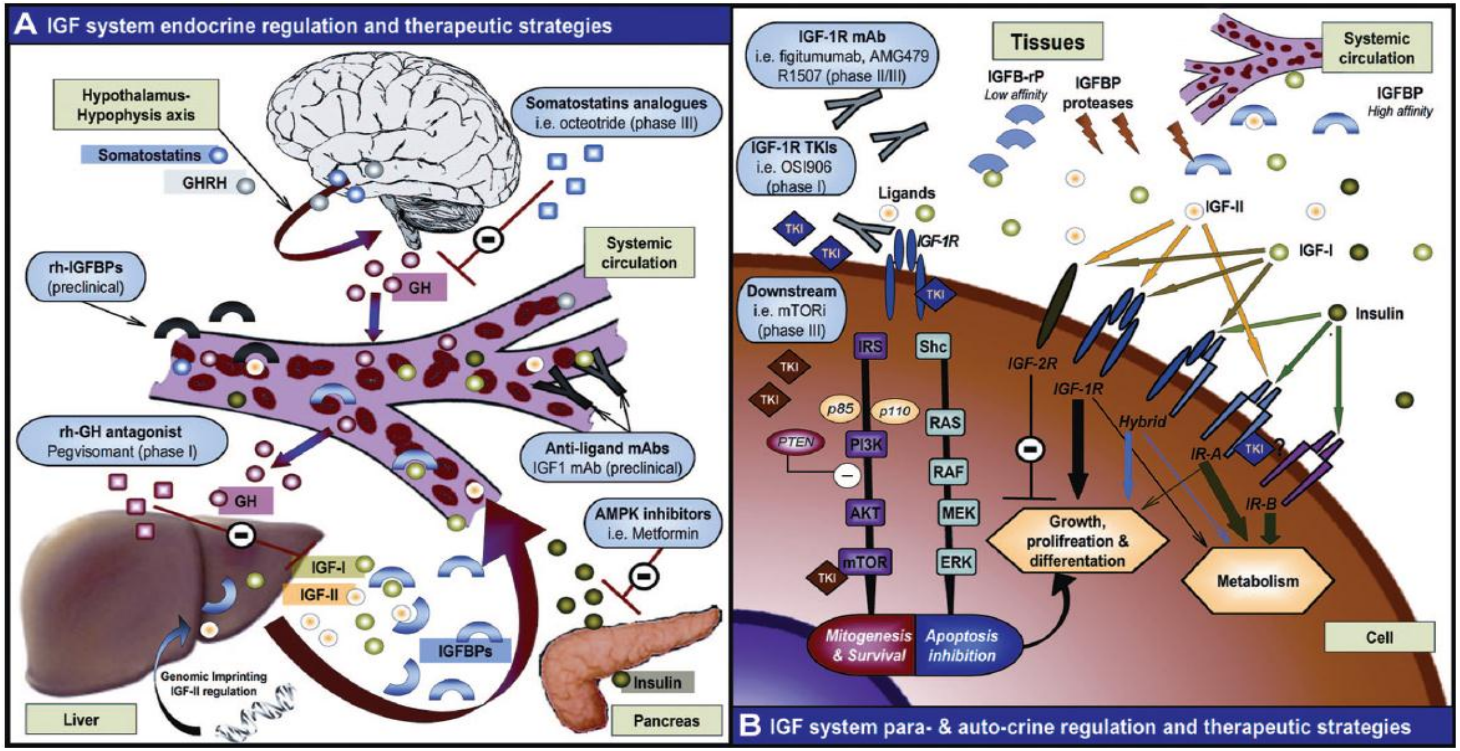
M. Pollak et al Nature Reviews Cancer

Introduction (II)



- Ligands: IGF1, IGF2 & Insulin
- Receptors: IGF-1R, IGF-2R, IR-A, IR-B and heterodimers

Introduction (III)



- Complex system with endocrine, paracrine and autocrine levels of regulation (& genetic regulation):
  - In addition to different ligands and receptors have several **Binding proteins** and **binding proteins proteases**

Olmos et al. Cancer J. 2010

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A long journey from the bench to the bedside

1990

IGF-1R pathway is implicated for 1st time in the pathogenesis of sarcoma

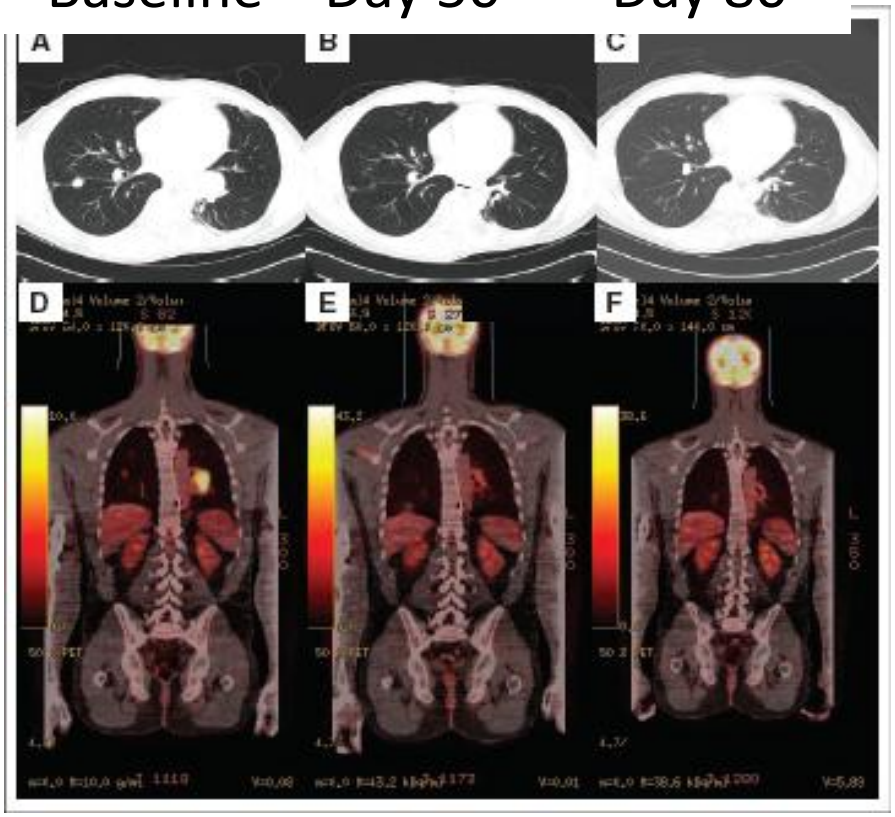
2007

1st sign of antitumor activity in a sarcoma patient is reported

Yee et al. J Clin Invest 1990
El-Badry et al. Cell Growth Differ 1990
Tolcher et al. ASCO 2007

First responses to IGF-1R in Ewing sarcoma

Baseline Day 50 Day 80

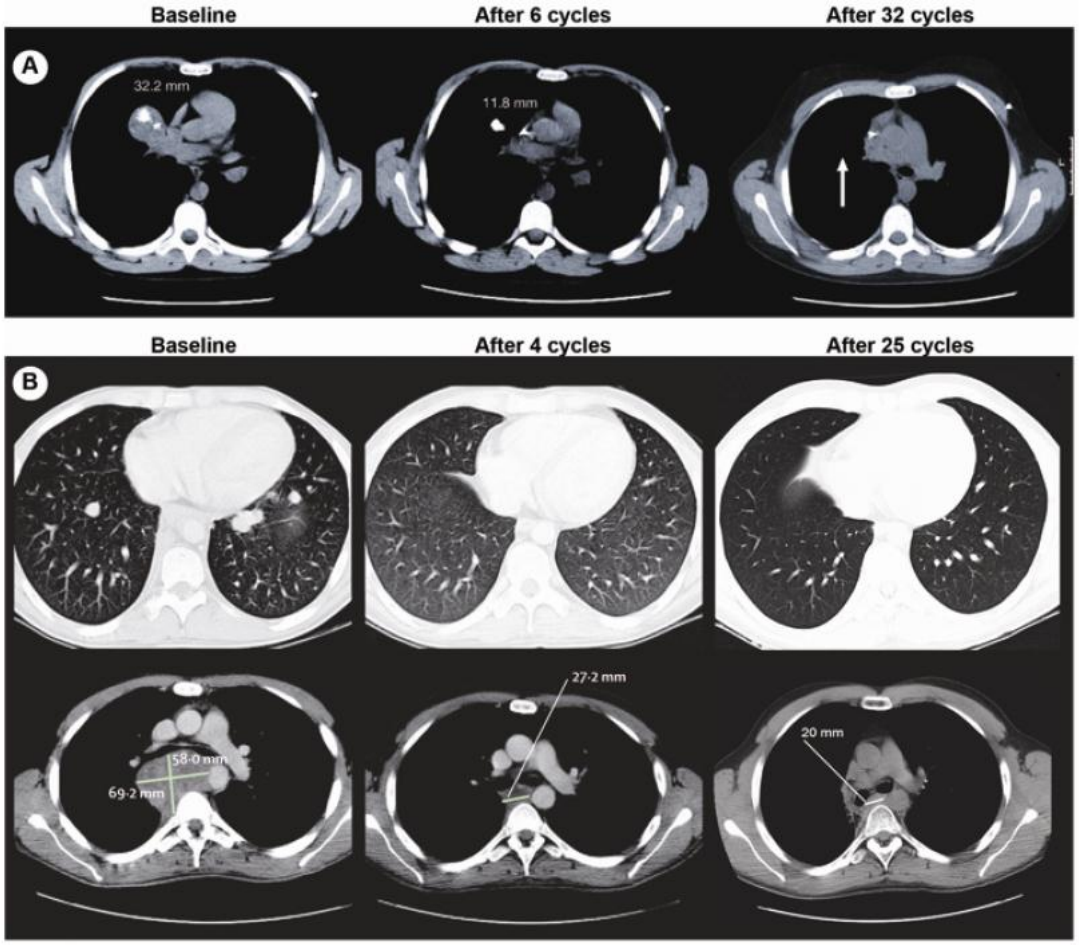


Baseline Day 8 Day 50

AMG-479 (Ganitumumab) 20 mg/kg every 2 weeks

Tolcher et al. J Clin Oncol 2009
1st reported At ASCO 2007

First responses to IGF-1R in Ewing sarcoma



Figitumumab 20 mg/kg every 4 weeks

Olmos et al. ASCO 2008
Olmos et al. Lancet Oncol 2010
Olmos et al. Cancer J. 2010

Anti-IGF-1R mAb in Ewing sarcoma

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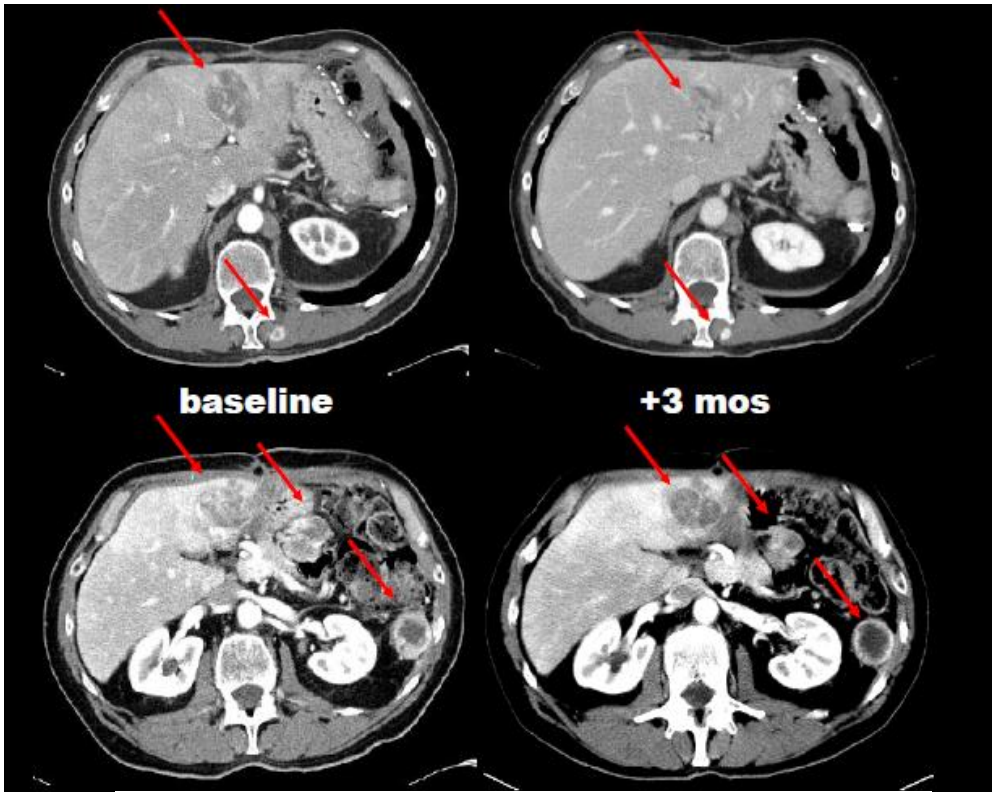
Drug	Trial	PR/CR	Source
Figitumumab CP-751,871	Ph. I-expansion	1 CR, 1 PR	Olmos et al. Lancet Oncol 2010
Ganitumumab AMG-479	Ph .I-expansion	1 CR, 1 PR	Tolcher et al. J Clin Oncol 2009
Robatumumab R1507	Ph. I-expansion	2 PR	Kurzrock et al. Clin Cancer Res 2010
SCH-717454	Ph. I/II	3 PR	Anderson et al. CTOS 2008 (abs.)
Cixutumumab IMC-A12	Ph. I/II paediatric	3 PR	Malempati S et al. J Clin Oncol 2012

IGF-1R mAb activity in other subtypes?

Solitary Fibrous Tumour



Figitumumab 20 mg/kg every 4 weeks

Stacchiotti et al. Mol Cancer Ther 2010

Sporadic radiological responses in:

- RMS (R1507)
- Osteosarcoma (R1507)
- ASPS (R1507)

Sporadic SD>3 m

- Leiomyosarcoma (R1507)
- Fibrosarcoma (CP-751,871)
- DSRCT (AMG-479)
- Synovial sarcoma (CP-751,871)
- Liposarcoma (IMC-A12)

Single agent Phase II with mAb

- **SARC-011 study with R1507**
  - **Five arms: Ewing sarcoma, Osteosarcoma, Rhabdomyosarcoma, Synovial sarcoma and other sarcomas. Recommended dose 9mg/kg weekly 100-500 patients**
- **Pfizer study 4021020 with Figitumumab**
  - **Ewing only, recommended dose, two phase 20 + 20 patients – target minimum 3 objective responses in first 20 patients**
- **Phase 2 Study of AMG 479**
  - **Ewing sarcoma and DSCRT, 38 patients**
- **Phase 2 Study to Determine the Activity of SCH 717454**
  - **Relapsing Osteosarcoma (proliferation rate) and Ewing's sarcoma (OS), 190 patients**
- **A Five-Tier, Phase 2 Open-Label Study of IMC-A12**
  - **Ewing Sarcoma, rhabdomyosarcoma, Leiomyosarcoma, adipocitic sarcomas, and synovial sarcoma. 85 patients (17pts per tier)**

Anti-IGF-1R mAb Phase II in EWS

Study	N	CR	PR	Median PFS
Figitumumab Phase II (20 mg/kg q4w)	106	0	15 (14%)	1.9 months
SARC-011: R-1507* (9 mg/kg q1w)	111	1 (1%)	7 (6%)	29 weeks
AMG-479 Phase II* (20 mg/kg q2w)	19	0	1 (5%)	7.9 months*

*** In the DSRCT arm PFS was 19 months.**

Juergens et al. J Clin Oncol 2012
Pappo et al. J Clin Oncol 2011
Tap et al. J Clin Oncol 2012

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Were these results disappointing?

or a promising beginning?

In a global drug development context

Study	N	ORR	Median duration CB	Median PFS
Figitumumab Phase II (20 mg/kg q4w)	106	14%	4.7 m	1.9 m
Trastuzumab single agent 1st line HER2+ Breast Ca	222	15%	8 m	3.4 m
Cetuximab single agent EGFR+ CRC	57	9%	4.2 m	1.4 m

Juergens et al. J Clin Oncol 2012
Vogel et al. Eur J Cancer 2001
Saltz et al. J Clin Oncol 2004

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What has happened to IGF-1R mAb strategies?

Basu & Olmos. Br J Cancer 2011

IGF1R: Why is it important?

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BUT the activation of IGF-1R

- **It is the key receptor in the IGF pathway**
- **Its activation stops sarcomas cells from going to apoptosis**
- **Abrogates the need for any other growth factor signals in cancer cells**
- **Has been linked to treatment resistance:**
  - **To conventional chemotherapy**
  - **To radiotherapy**
  - **To other targeted treatments**

Pollak et al. Nat Rev Cancer 2008
Olmos et al. Cancer J. 2010

IGF-1R: is it the most appropriate therapeutic target : One size may not fit all!!

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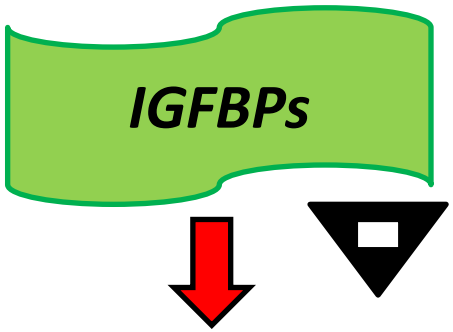
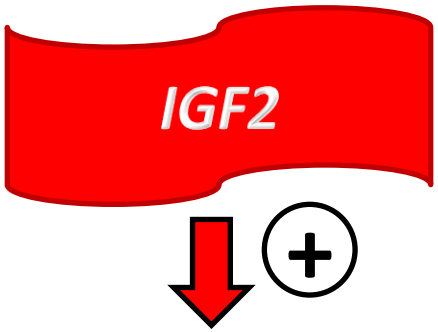


Ewing Sarcoma
•*EWS-FLI1* ↓expression

Osteosarcoma
• *P53* mutant ↓expression



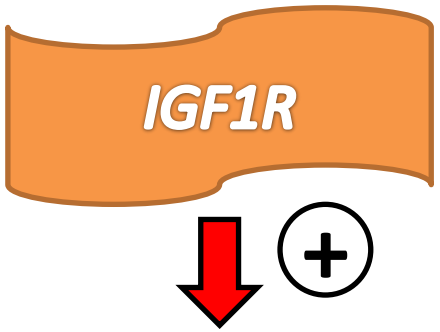
Embryonal RMS
• LOH *IGF-II* ↑expression

Alveolar RMS
• *PAX3/FOXO* ↑expression

Synovial Sarcoma
• *SS18-SSX ~LOI* ↑expression

Solitary Fibrous Tumours
• LOI *IGF-II* ↑expression

Leiomyosarcoma
• LOI *IGF-II* ↑expression



DSRCT
• *EWS-WT1* ↑expression

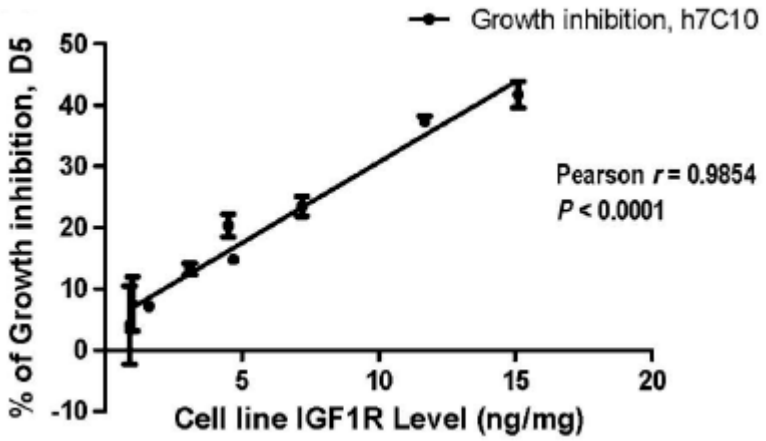
***KIT*^{WT} GIST childhood/juvenile**
•IGF1R gene amplification

Olmos et al. Cancer J. 2010
Rikhof et al. J Pathol 2009

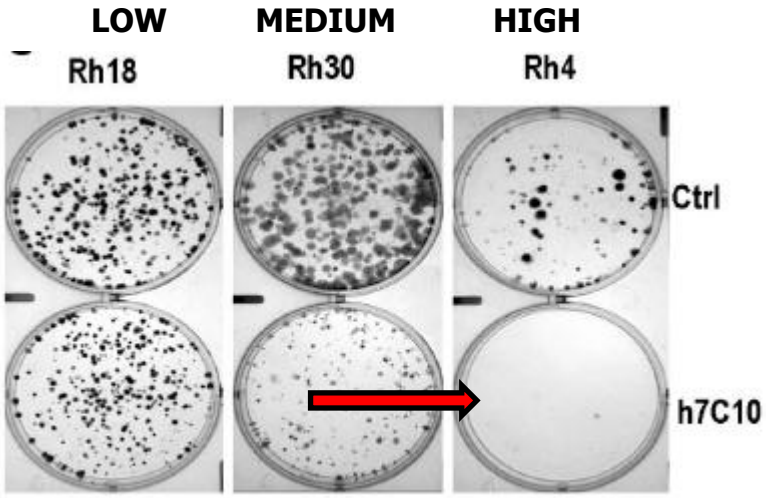
VIENNA 2012 ESMO congress

www.esmo2012.org

Potential biomarker
IGF-1R: a relation density/response?



IGF-1R expression



AMG-479 in EWS and DSRCT

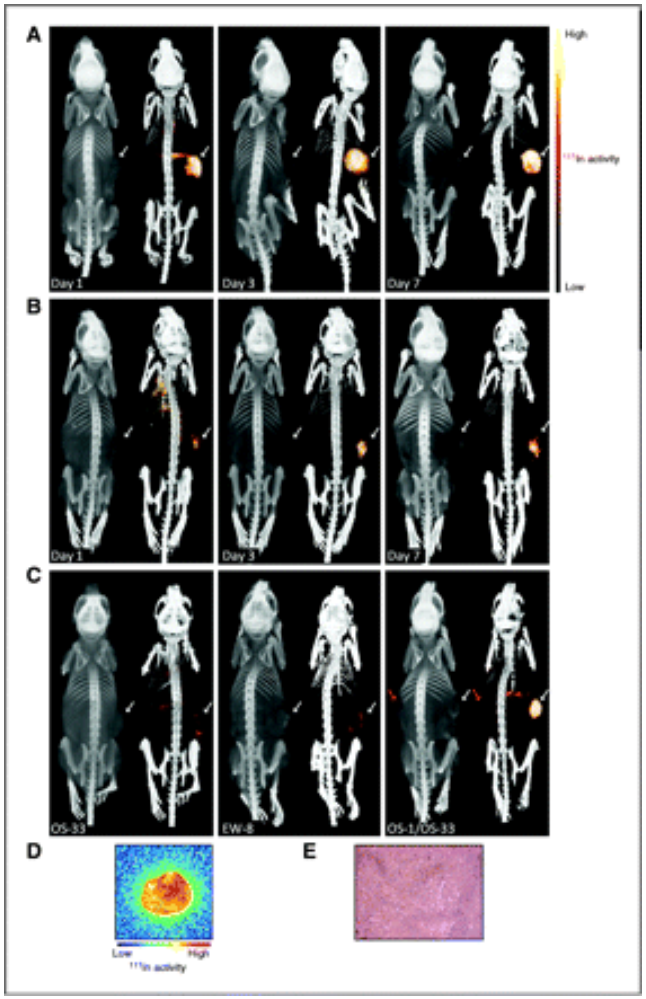
	EFT	DSCRT
CR	0	0
PR	1 (5%)	1 (6%)
SD	7 (37%)	10 (63%)
SD > 24 weeks	1 (5%)	3 (18%)
CB (CR+ PR + SD > 24 weeks)	2 (11%)	4 (25%)
PD	10 (53%)	4 (25%)
Not Evaluable	1 (5%)	1 (6%)

- **EWS-WT1 increases IGF-1R**
- **EWS/FLI-1 does not**

Cao et al. Cancer Res 2008
Tap et al. ASCO 2010

www.esmo2012.org

Can we measure IGF-1R density in vivo

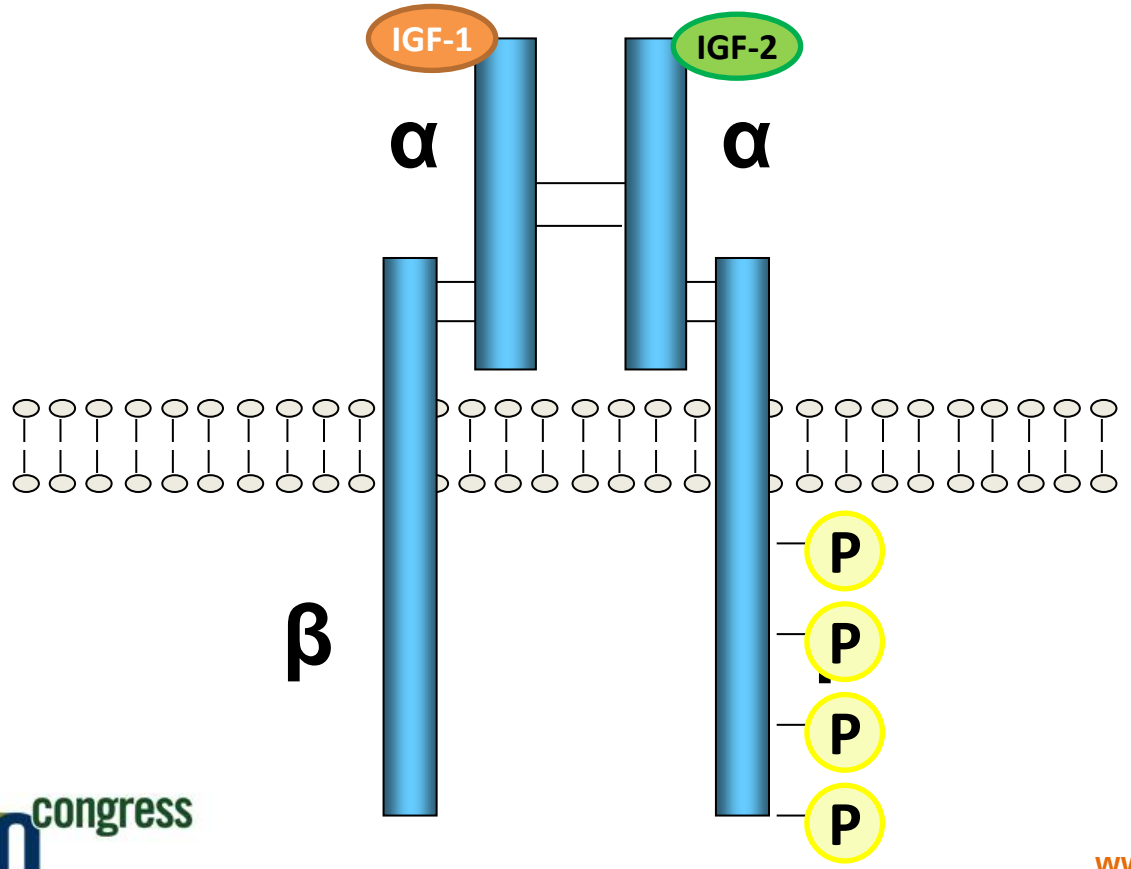


Immuno-SPECT Imaging with In-111-R1507

- Osteosarcoma & EWS xenograft.
- Good correlation with IHC, but IGF-1R expression can vary between different areas of the tumour.
- Good correlation to response to R1507 in this models
- Could this be applied to select patients? or to different mAb?

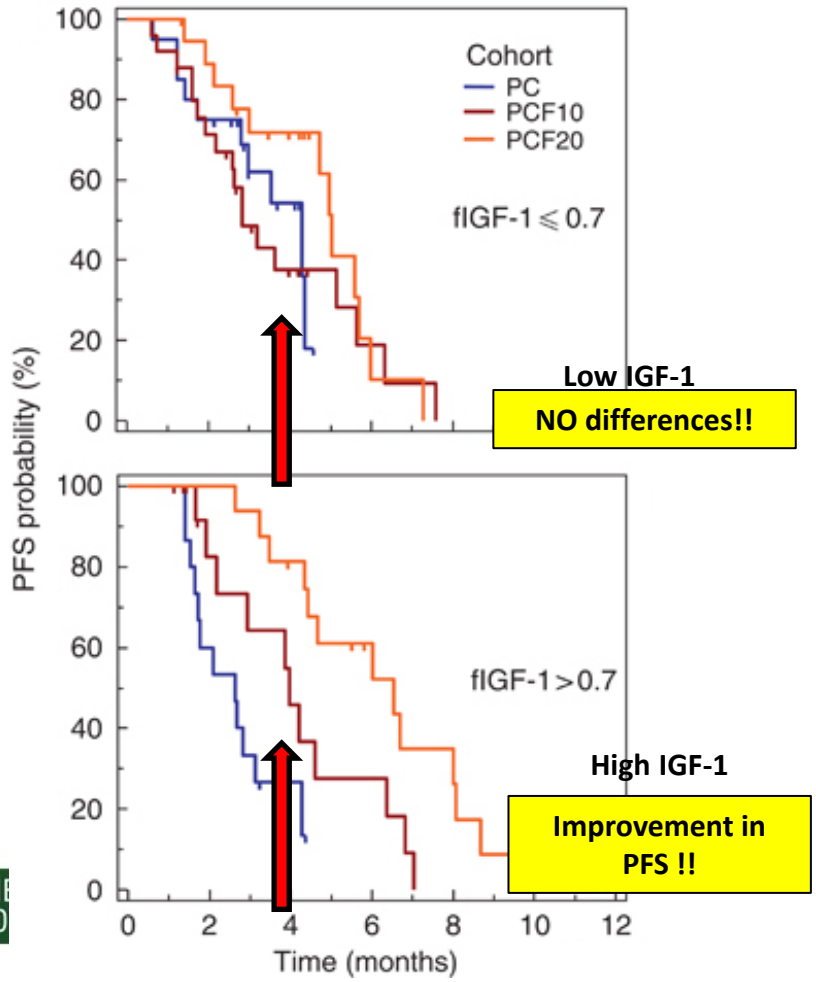
Fleurent et al. Clin Cancer Res 2011

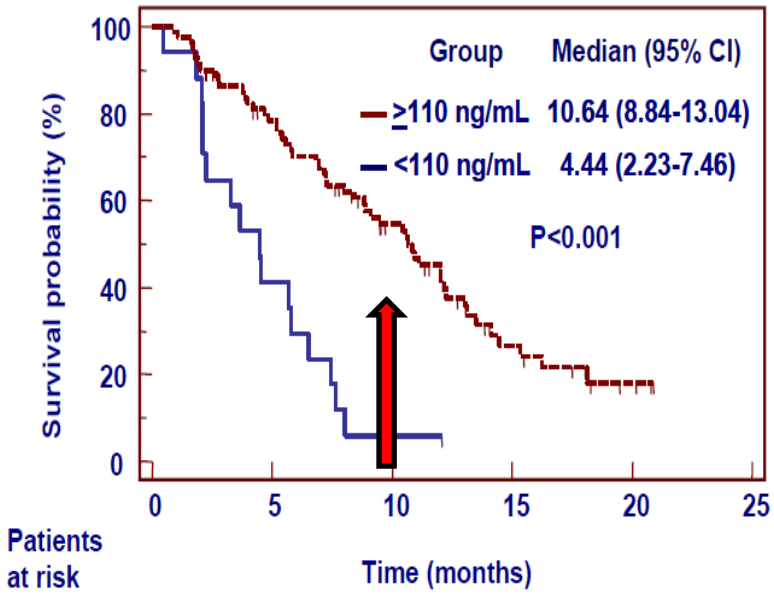
Two different ligands can activate IGF-1R



Potential biomarker: Levels of IGF-I

Lung Cancer: Figitumumab plus Carbo/Taxol



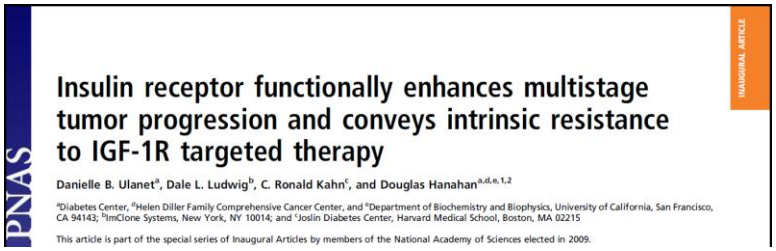


Just prognostic or maybe predictive too?

Gualberto et al. Br J Cancer 2011
Juergens et al. ESMO 2010

www.esmo2012.org

IGF-II & IR-A loop activation confers resistance to IGF-1R inhibition



PNAS

INAUGURAL ARTICLE

Insulin receptor functionally enhances multistage tumor progression and conveys intrinsic resistance to IGF-1R targeted therapy

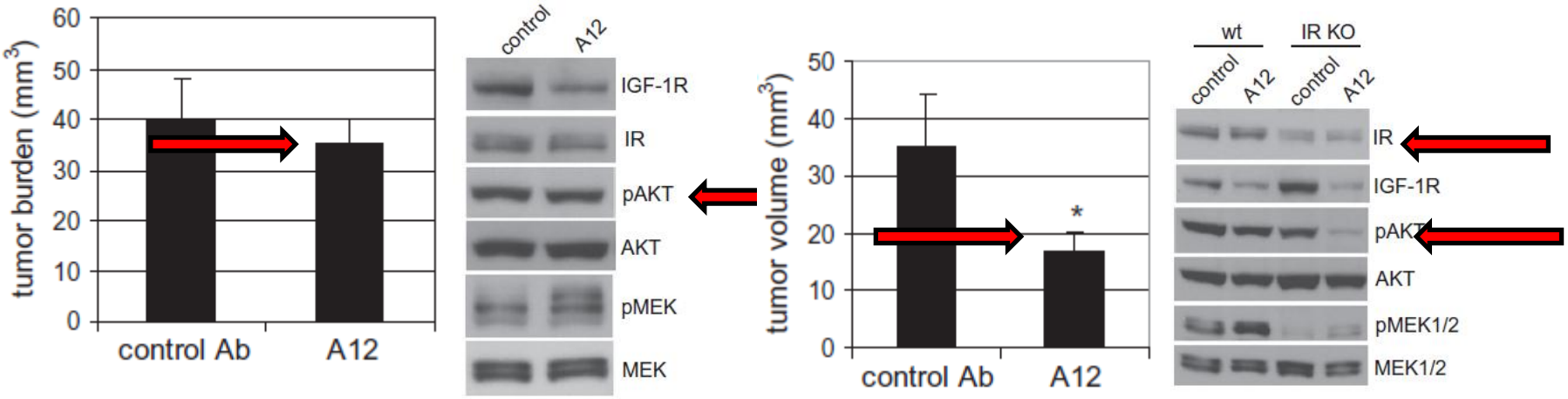
Danielle B. Ulanet[a], Dale L. Ludwig[b], C. Ronald Kahn[c], and Douglas Hanahan[a,d,e,1,2]

[a]Diabetes Center, [d]Helen Diller Family Comprehensive Cancer Center, and [e]Department of Biochemistry and Biophysics, University of California, San Francisco, CA 94143; [b]ImClone Systems, New York, NY 10014; and [c]Joslin Diabetes Center, Harvard Medical School, Boston, MA 02215

This article is part of the special series of Inaugural Articles by members of the National Academy of Sciences elected in 2009.

In Ewing sarcoma: IGF1R resistant cells are able to switch from IGF-1/IGF-1R to IGF-2/IR-A

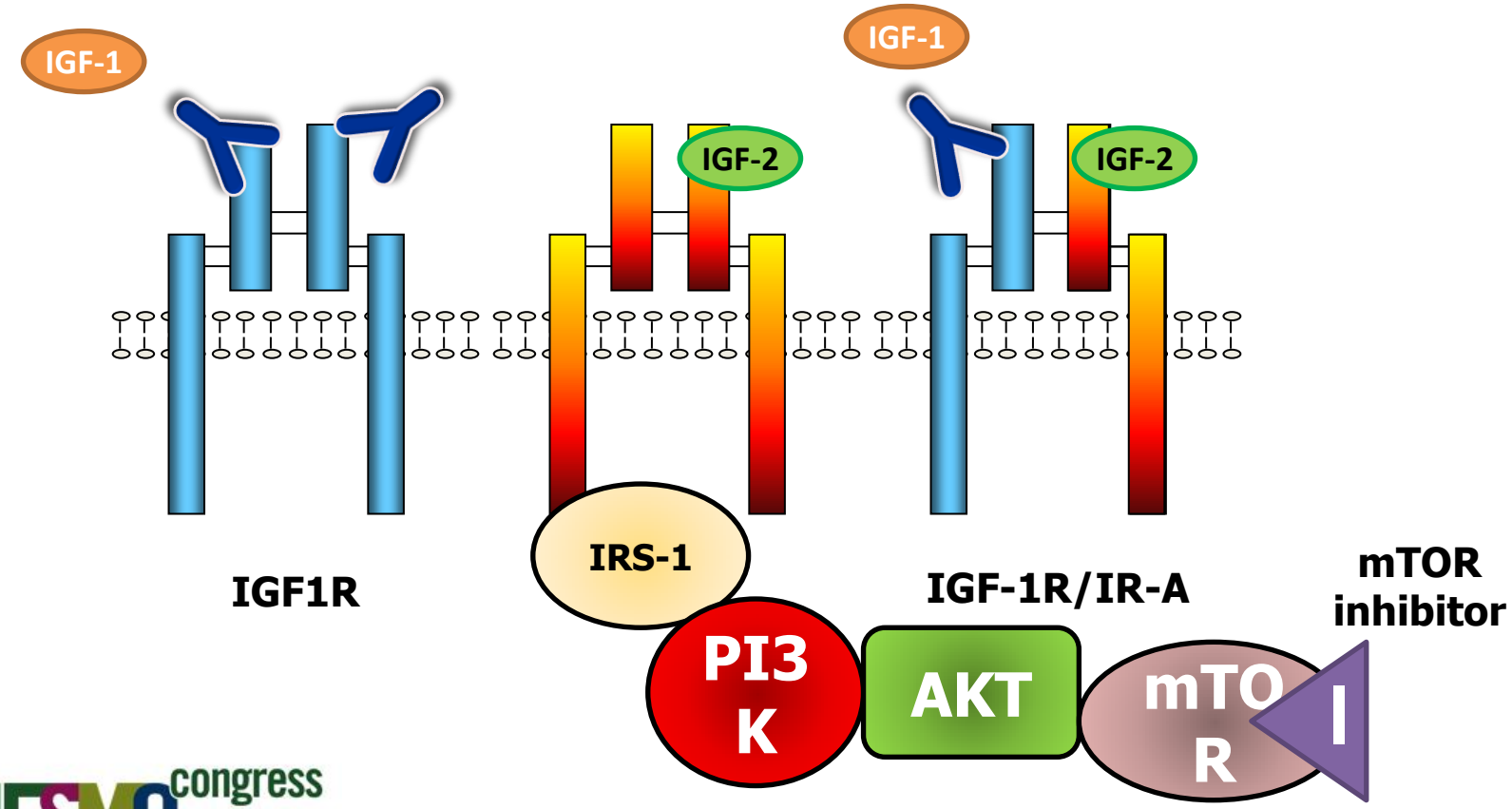
Garofalo et al. Oncogene. 2011
Garofalo et al. Mol Endrocr. 2012



RIP-1 = Neuroendocrine pancreatic tumour model

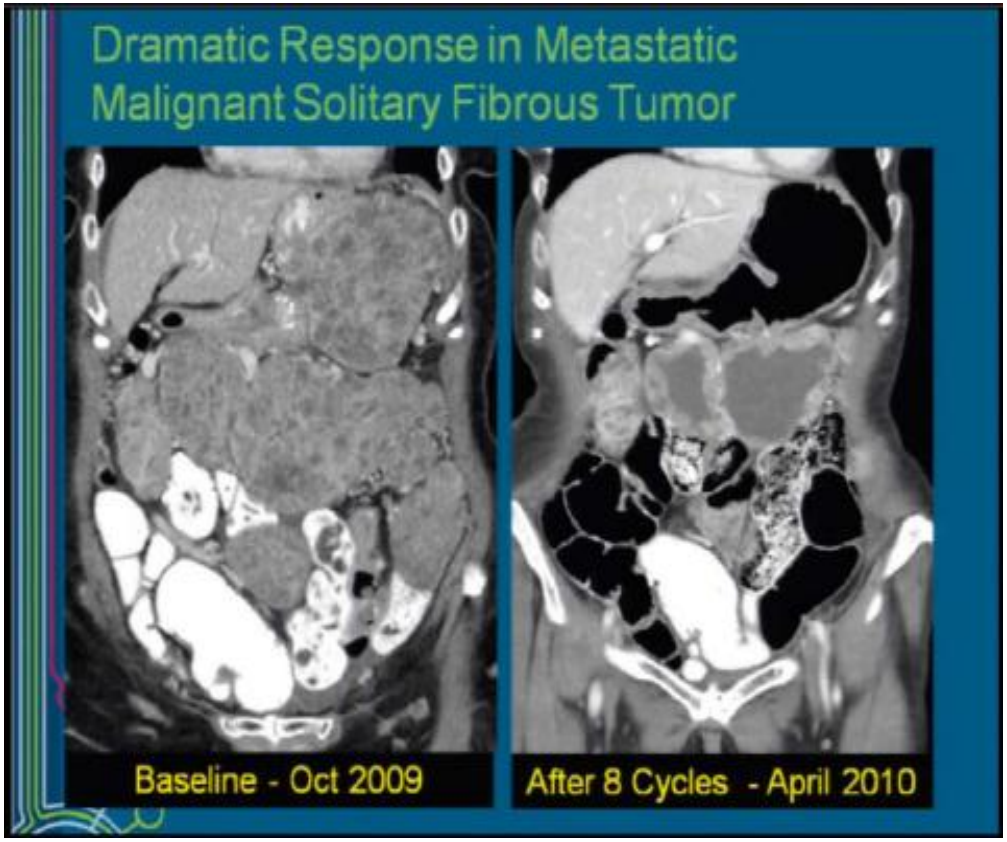
Ulanet et al. Proc Natl Acad Sci. 2010

Potential strategy: Combination of IGF1R with mTOR



Combination of IGF1R with mTOR

Figitumumab plus everolimus



Quek et al. ASCO 2010
Quek et al. Clin Cancer Res 2011

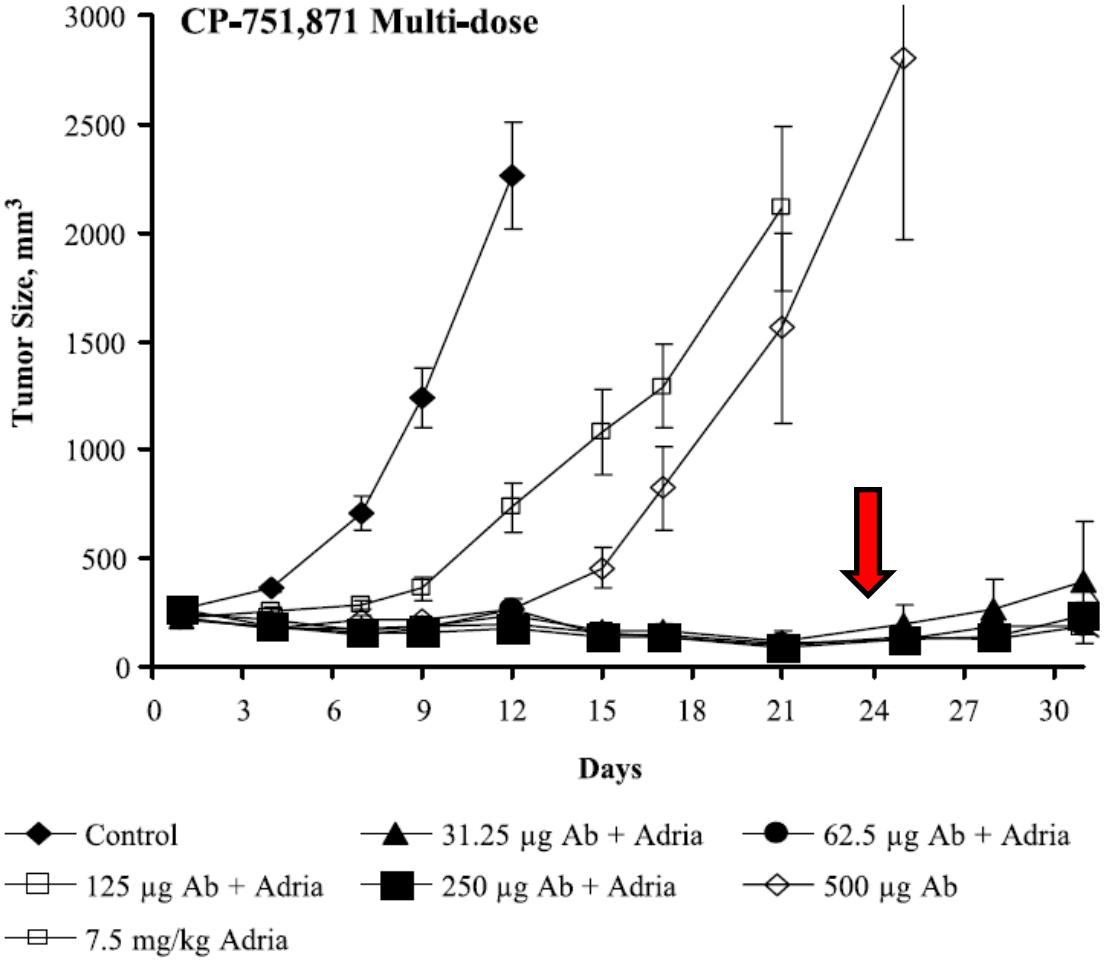
SFT:
Associated with
IGF-2
upregulation

Cixutumumab + Temsirolimus

- Phase I trial: 20 pts
- 2 CR, 1 of them in a patient previously refractory to single agent IGF-1R antibody.

Naing et al. Clin Cancer Res 2011

Classical strategy: combining IGF1R targeting with chemotherapy



IGF-1R mAb

+

Chemotherapy

Athymic mice bearing 3T3/IGF-1R tumors were significantly smaller when treated with Figitumumab and Adriamycin in combination.

B.D. Cohen et al. Clin Cancer Res 2006

Clinical trials: IGF1R mAb + chemotherapy

- **NCT00720174**: **Phase I/II**

  "IMC-A12 and Doxorubicin Hydrochloride in Treating Patients With Unresectable, Locally Advanced, or Metastatic Soft Tissue Sarcoma"

  - Chugh et al ASCO 2012: 4/22 pts with PR: Angiosarcoma, Myxoid LPS, LMS, HGUPS. 6-months PFS (23% previous chemotherapy)

Ongoing Trials

- **NCT01055314**: **Phase I**

  "Temozolomide, Cixutumumab, and Combination Chemotherapy in Treating Patients With Metastatic Rhabdomyosarcoma"

- **NCT0096006**: **Phase I**

  "A Study of SCH 717454 in Combination With Different Treatment Regimens in Pediatric Subjects With Advanced Solid Tumors"

Source: Clinicaltrials.gov

Conclusions

- **IGF-1R targeting agents are active in a broad range of sarcomas...**
  ... but long-term benefit is limited to a few patients
- **Optimal therapeutic approaches to improve current results:**
  - **Biomarkers (Tissue and blood): IGF-1R expression, IGF-1 and IGF-2 levels monitoring, IR-A/IGF-1R expression rate. Nuclear in vivo imaging?**
  - **Combinations:**
    - **A) Chemotherapy**
    - **B) mTOR inhibitors**
    - **C) other targeted combinations according to IGF pathway biology in each patient**

Acknowledgments

- To Prof. Ian Judson (who could not give this talk today)
- To all our patients and their families
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- To the Clinical Research Programme at the Spanish National Cancer Research Centre (CNIO)
- **Funding:**