

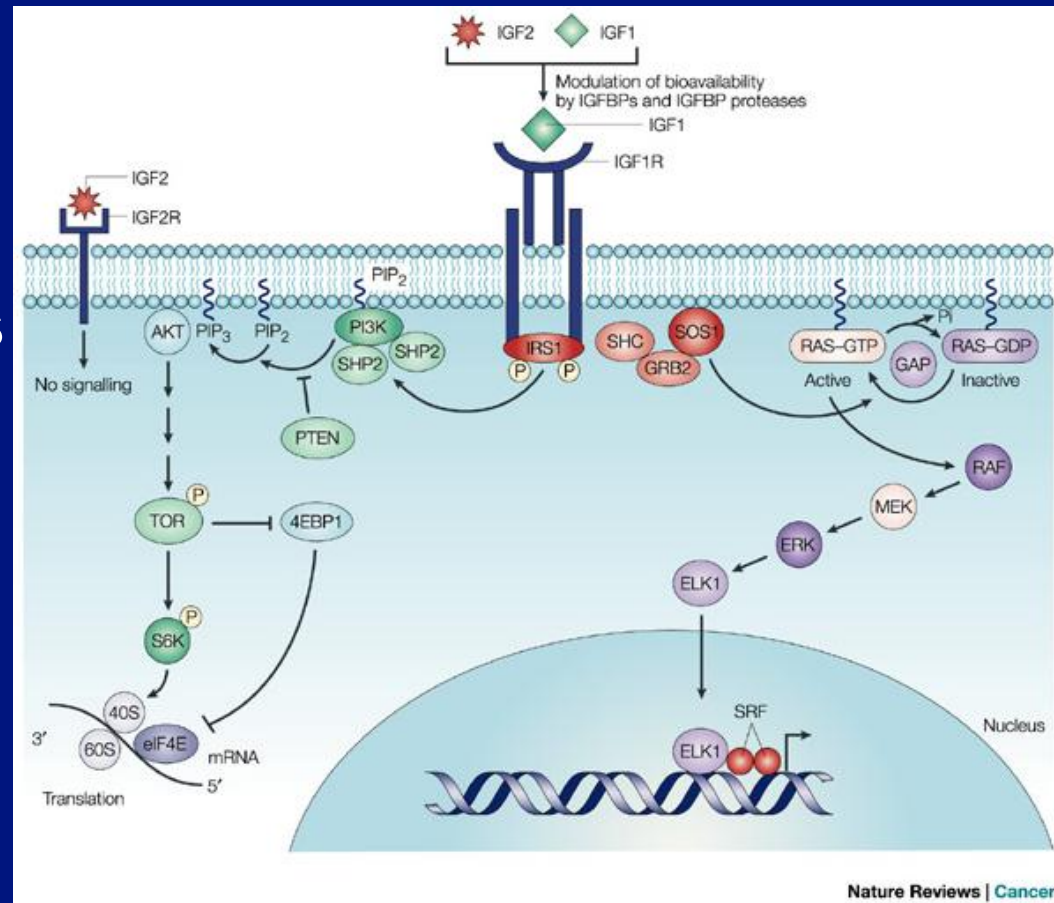
IGF-1R Inhibitors



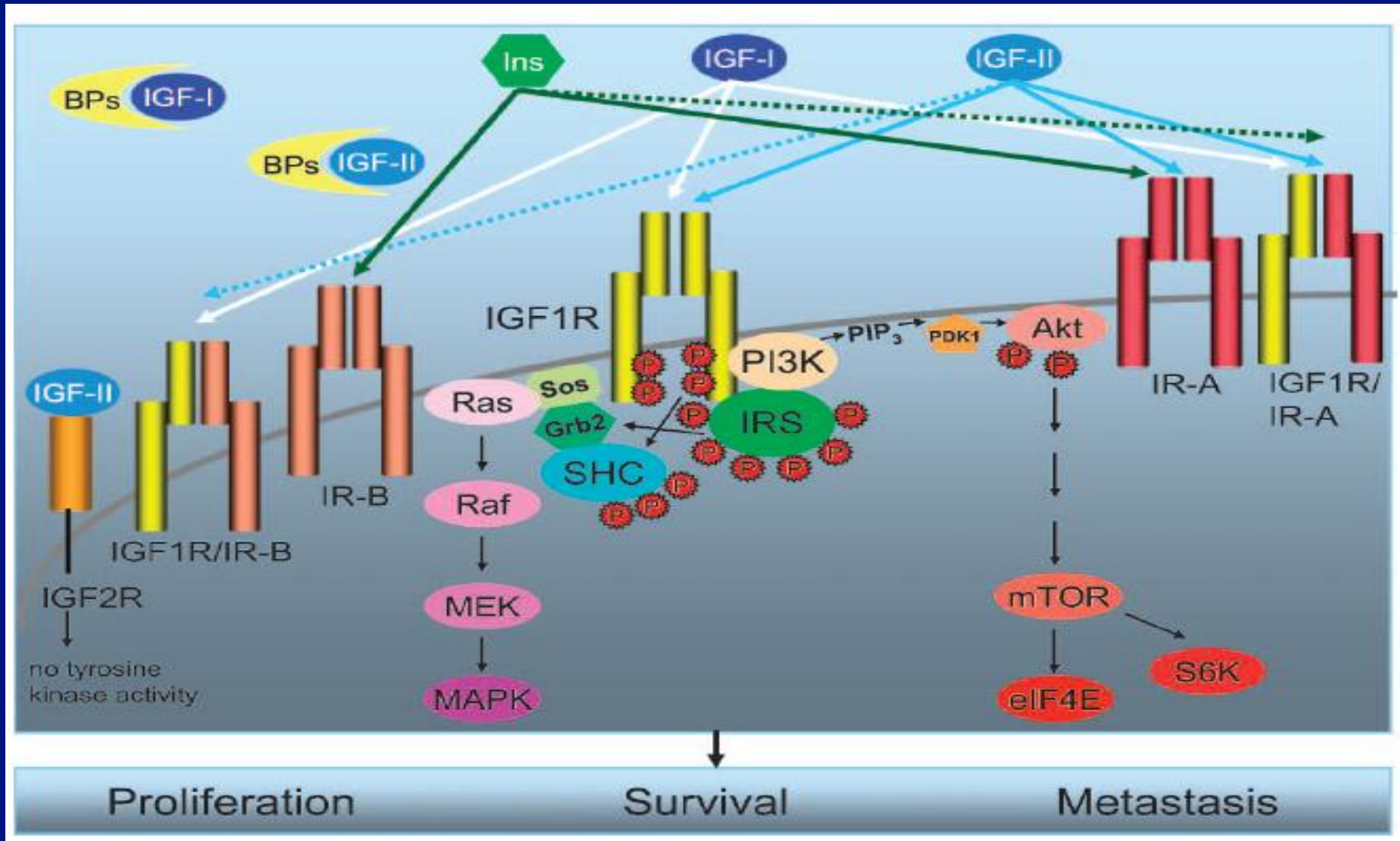
Luis Paz-Ares
Hospital Universitario
Virgen del Rocío
Seville, Spain

Insulin-like Growth Factor 1 Receptor (IGF-1R)

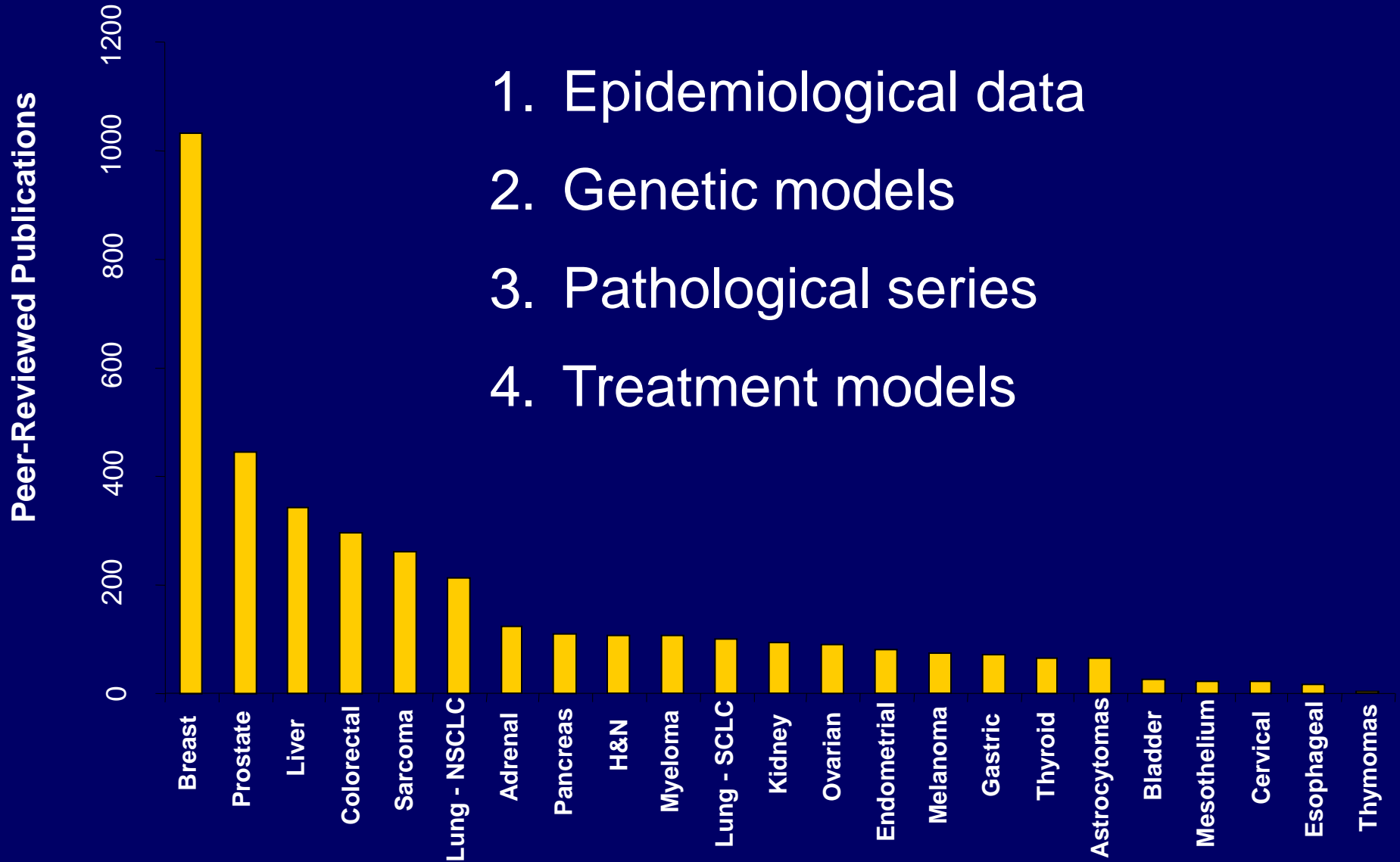
- Transmembrane tyrosine kinase receptor, with structural homology to insulin receptor
- Widely expressed across many cell types
- Activated by growth factors IGF-1 and IGF-2
- Activation of IGF-1R triggers multiple signaling pathways
 - Inhibition of apoptosis, cell proliferation, differentiation



Insulin-like Growth Factor 1 Receptor (IGF-1R)



Insulin-like Growth Factor Receptor Axis in Human Cancer



Relation of IGF-I levels to risk of prostate cancer

Meta-analysis

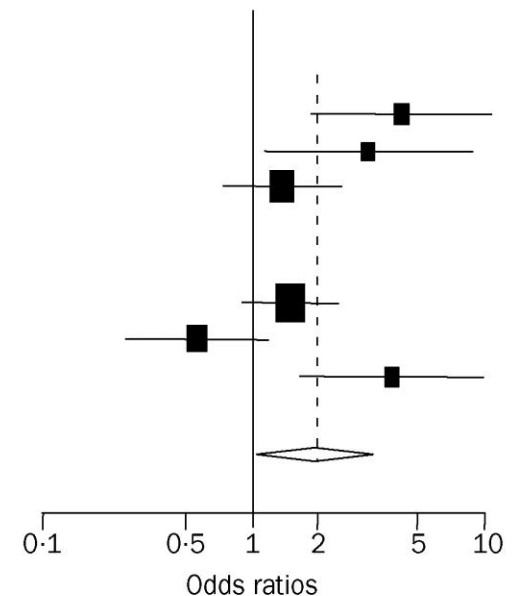
(a) Prostate cancer

Cohort studies

Chan 1998 ⁵	152/152	Quartiles	4.32 (1.76–10.6)
Harman 2000 ²⁴	72/203	Tertiles	3.11 (1.11–8.74)
Stattin 2000 ²⁵	149/298	Quartiles	1.32 (0.73–2.39)
All cohort studies			2.43 (1.11–5.32)

Case-control studies

Wolk 1998 ²²	224/224	Quartiles	1.43 (0.88–2.33)
Finne 2000 ²³	179/486	Quartiles	0.57 (0.28–1.16)
Chokkalingam 2001 ²⁶	128/306	Quartiles	3.92 (1.58–9.70)
All case-control studies			1.42 (0.56–3.60)
All studies			1.83 (1.03–3.26)

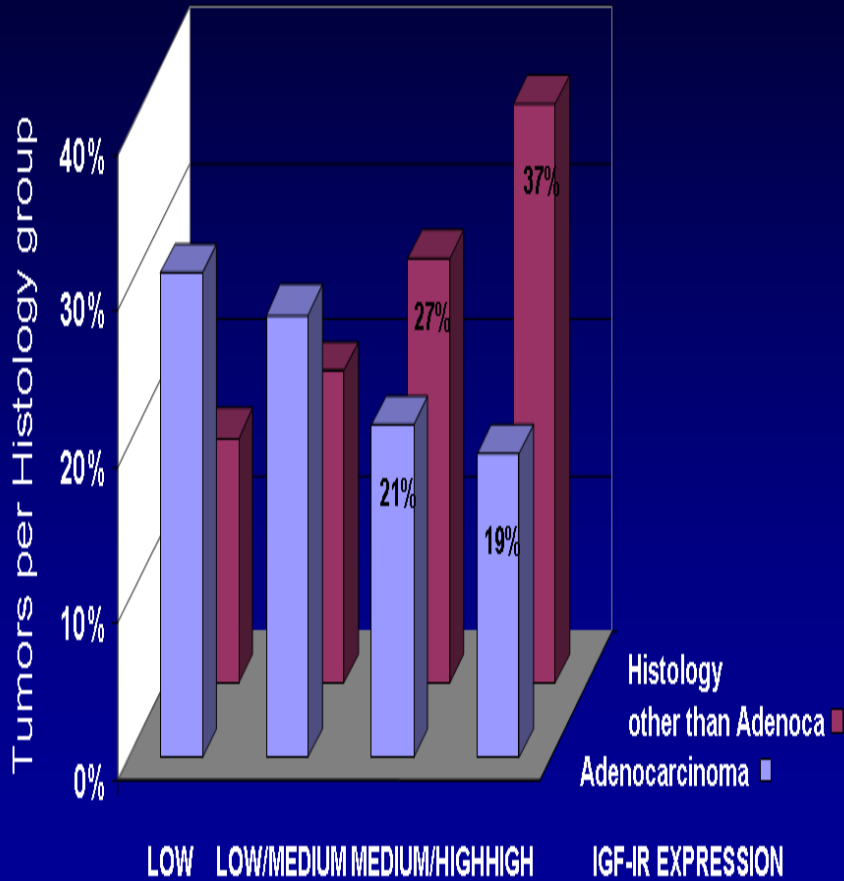


The IGF Axis in NSCLC

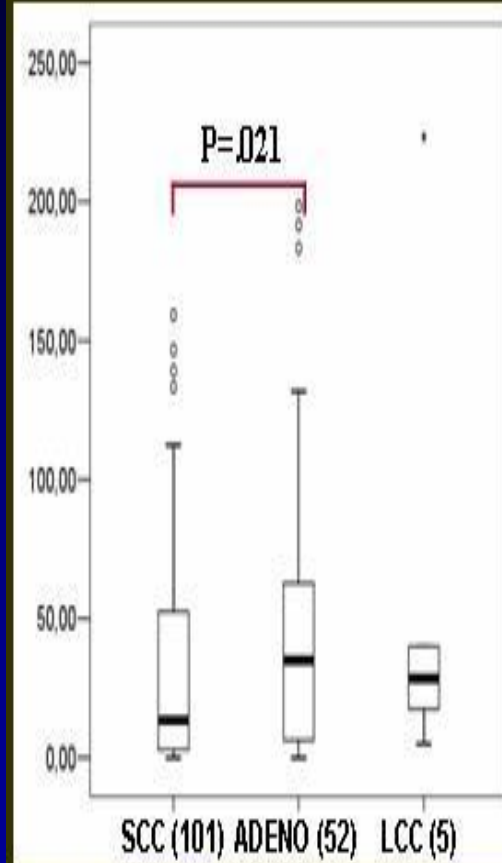
- Increased IGF-1, Decreased IGFBP-3 assoc. with increased cancer risk in humans ¹
 - Transgenic over-expression of IGF-1 induces spontaneous lung tumors in mice. ²
 - Highest IGF-IR in squamous subtype (AQUA IHC technology) ³
 - H-Y Lee Lab, MDACC:
 - Decreased IGFBP3 expression assoc. with poor prognosis in Stage I resected NSCLC. ⁴
 - IGF-IR activation in human NSCLC
1. Yu et al. JNCI 1999
 2. Frankel SK et al. Am J Phys Lung Cell Mol Phys. 2005
 3. Unpublished data. Pfizer Global R&D, New London, CT.
 4. Chang YS et al. CCR 2002 (a), CCR 2002 (b), Oncogene 2004
 5. Morgillo F et al. CCR 2006, Cancer Res. 2006

IGF-IR Expression by Histology

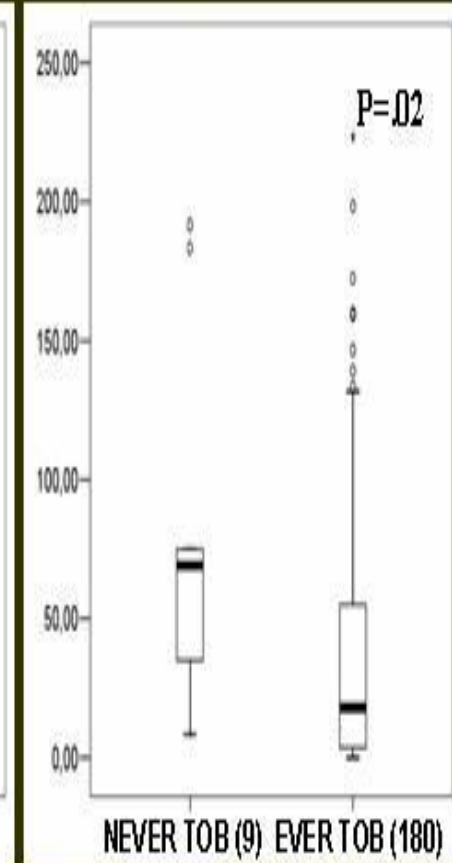
The majority of specimens from NSCLC histology other than adenocarcinoma express medium-high levels of IGF-IR



Median IGF1R H-scores by histology or tobacco history



Median IGF1R H-score is higher in adenocarcinoma than in squamous cell carcinoma (n).

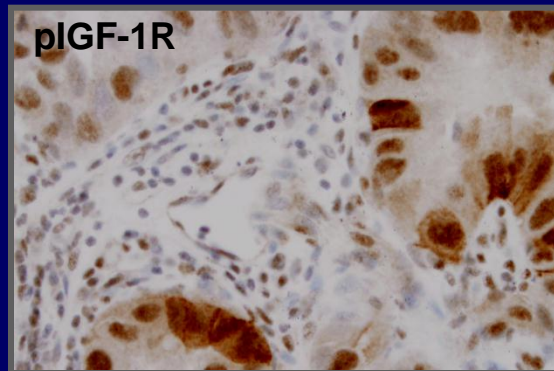
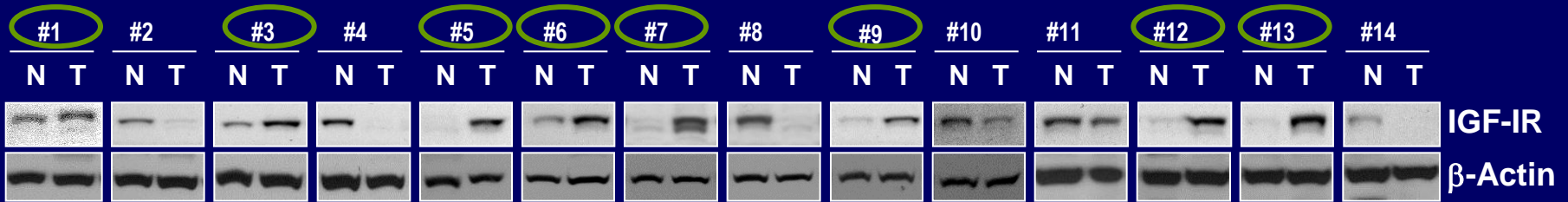


Median IGF1R H-score is higher in never smokers (NEVER TOB) than in ever smokers (EVER TOB) (n).

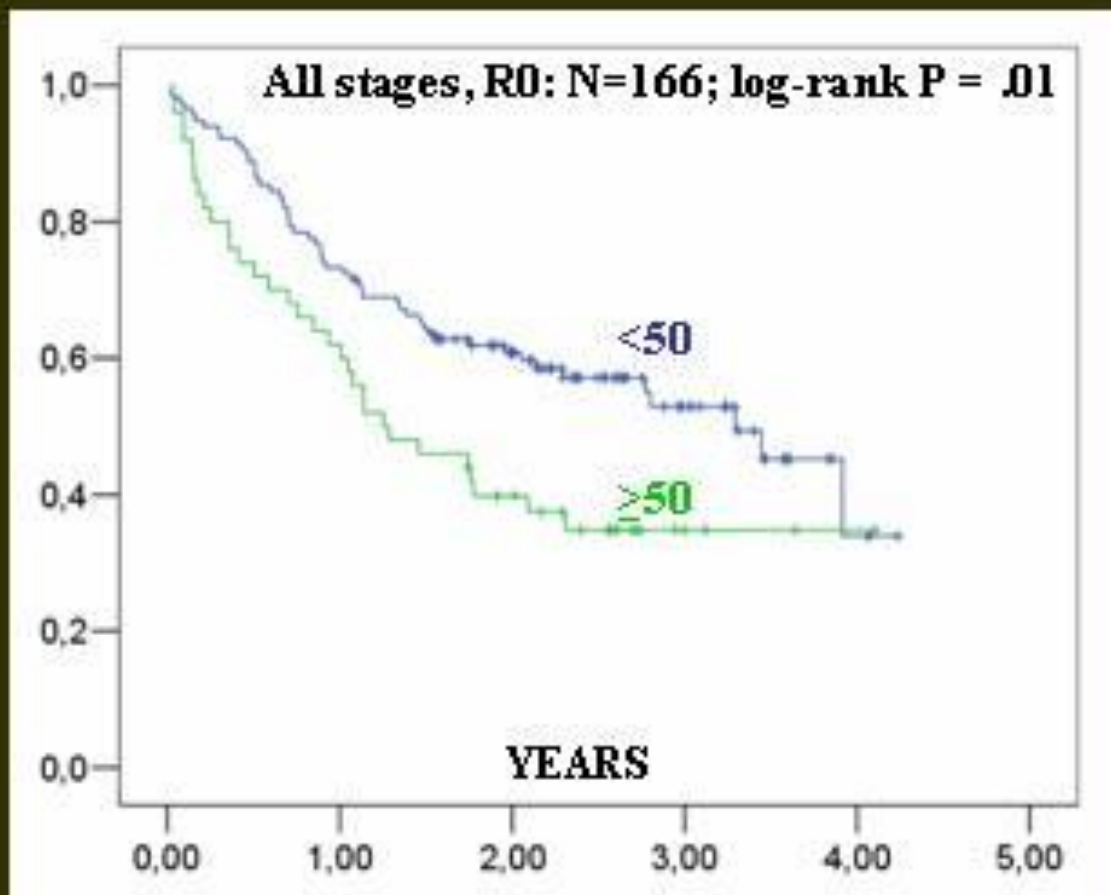
The IGF Axis in NSCLC

- Increased IGF-1, Decreased IGFBP-3 assoc. with increased cancer risk in humans ¹
 - Transgenic over-expression of IGF-1 induces spontaneous lung tumors in mice. ²
 - Highest IGF-IR in squamous subtype (AQUA IHC technology) ³
 - H-Y Lee Lab, MDACC:
 - Decreased IGFBP3 expression assoc. with poor prognosis in Stage I resected NSCLC. ⁴
 - IGF-IR activation in human NSCLC
1. Yu et al. JNCI 1999
 2. Frankel SK et al. Am J Phys Lung Cell Mol Phys. 2005
 3. Unpublished data. Pfizer Global R&D, New London, CT.
 4. Chang YS et al. CCR 2002 (a), CCR 2002 (b), Oncogene 2004
 5. Morgillo F et al. CCR 2006, Cancer Res. 2006

IGF-IR is Activated in Human NSCLC












Results – IGF1R score and survival (1)



Statistically significant association between high IGF1R expression and decreased survival in completely resected patients

IGF1R Inhibitors - Mabs

Drug	Company	Class	Status					Notes
			PRE	IND	I	II	III	
Monoclonal antibodies								
CP-751,871	Pfizer	Fully human IgG2 mab						Ongoing trials: phase I/II for pediatric patients with Ewing's sarcoma family of tumors. Phase Ib with docetaxel in HRPC. Phase II with exemestane in breast cancer, with Carbo/Taxol in NSCLC, with docetaxel/prednisone in HRPC. Phase II single agent in metastatic CRC.
IMC-A12	Imclone	Fully human IgG1 mab						Development with NCI-CTEP. Ongoing trials: phase I/II. Phase II single agent in HRPC and in Ewing's sarcoma family of tumors, in combination with cetuximab for CRC and H&N cancer.
R1507	Roche	Fully human IgG1 mab						Previously known as RO4858696. Ongoing trials: phase I in pediatric patients. Phase II single agent in sarcomas.
AMG-479	Amgen	Fully human mab						Phase II single agent in Ewing's sarcoma family of tumors and in combination with gemcitabine for pancreatic cancer.
SCH-717454	Schering-Plough	Fully human mab						Previously known as 19D12 (Medarex). Phase I trial done in healthy volunteers. Phase II single agent for CRC
AVE-1642	Sanofi-Aventis	Humanized mab						Previously known as EM164 (ImmunoGen)
MK-0646	Merk/Pierre Fabre	Humanized mab						Previously known as A2CHM, F50035, 7C10, or 7H2HM. Ongoing trials: phase II in combination with irinotecan/cetuximab in CRC.
BIIB022	Biogen Idec	Fully human nonglycosylated IgG4.P antibody						Devoid of Fc-effector function to eliminate potential Fc mediated toxicity to the normal vital organs.
Tyrosine kinase inhibitors								
INSM-18	Insmad and UCSF	Reversible ATP-competitive						Ongoing phase I/II. Inhibits IGF-IR and HER2, and it could act as an inhibitor of transcription (blocking also cdc2, survivin, and VEGF). Initially developed by Erimos Pharmaceuticals (EM-1421 or Terameprocol).

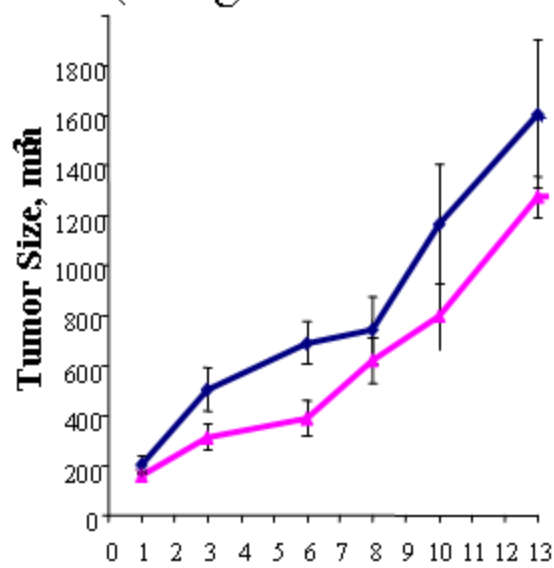
IGF1R Inhibitors - TKIs

Drug	Company	Class	Status					Notes
			PRE	IND	I	II	III	
OSI-906	OSI Pharmaceuticals	Oral small molecule. Reversible ATP-competitive						Derived from compound-1, also known as PQIP.
XL-228	Exelixis	Oral small molecule						Inhibits bcr-abl, scr and IGF-IR. Ongoing phase I for CML and ALL. Also known as XL-2280
NVP-ADW742	Novartis	Reversible ATP-competitive						
NVP-AEW541	Novartis	Reversible ATP-competitive						
AG-1024	Merk	Non-ATP-competitive						
BMS-536924	Bristol-Myers Squibb							
BMS-554417	Bristol-Myers Squibb	Oral small molecule. Reversible ATP-competitive						
BVP-51004	Biovitrum	Oral small molecule. Non-ATP-competitive						Also known as Cycloignan PPP. Causes IGF-IR down-regulation, probably through the induction of ubiquitination.
Other								
ATL-1101	Antisense therapeutics	Topical Antisense oligonucleotide						Developed for the treatment of psoriasis.
ANT-429	Antyra	HotSpot pharmaphores						

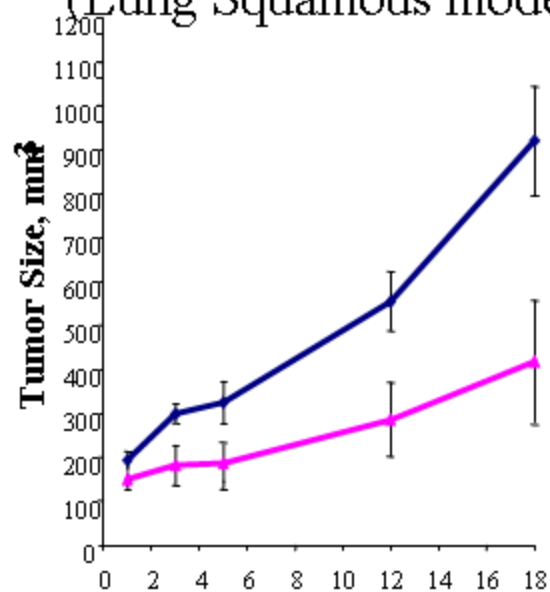
Mouse Xenograph Models

- No or marginal single agent activity in adenocarcinoma models of lung, breast, colon and prostate cancer
- Single agent activity in Squamous, fibroblast and sarcoma models

H460
(Lung adenoca model)



EBC-1
(Lung Squamous model)



Time, days

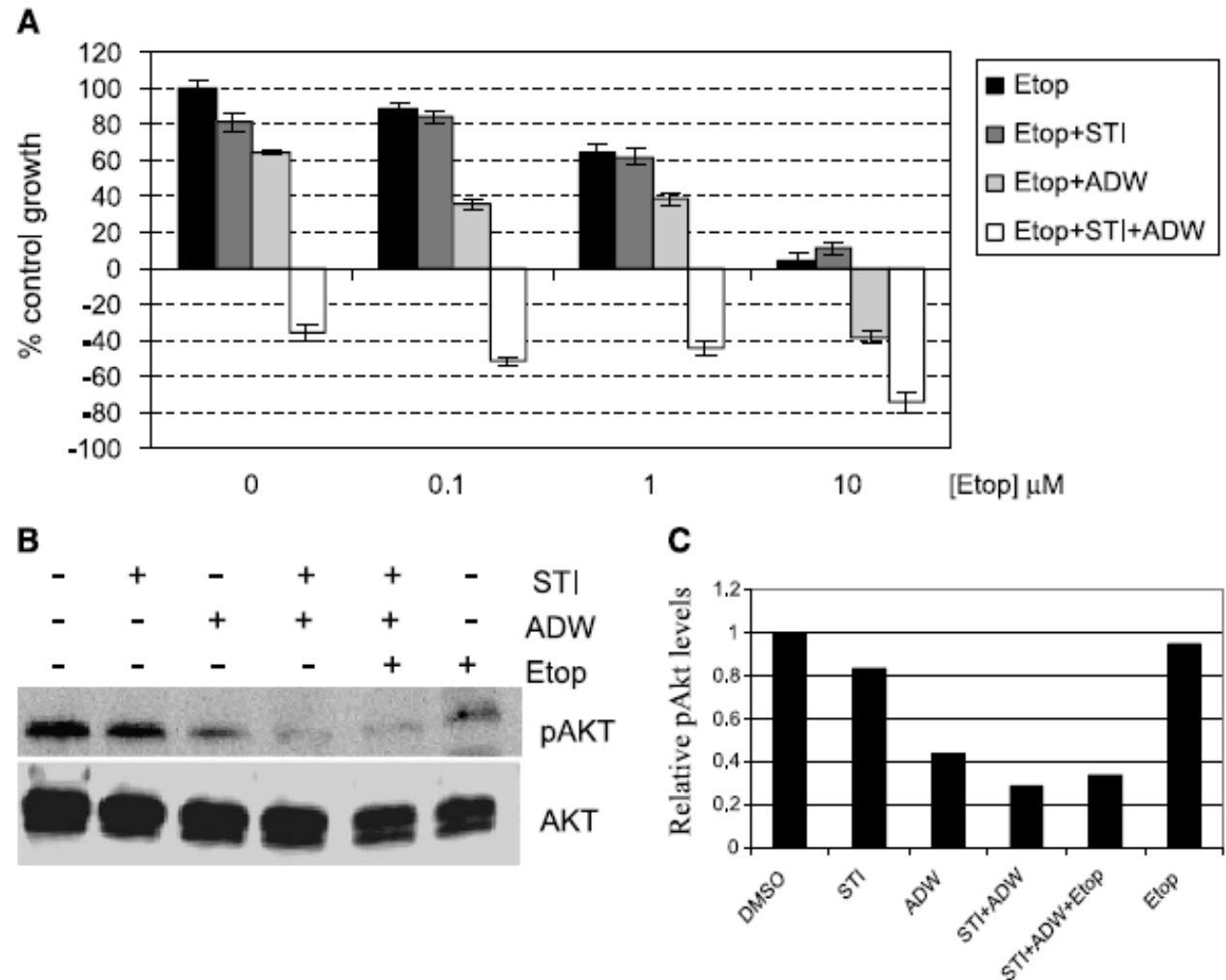
Control

500 µg CP-751,871

Time, days

Chemo + Anti IGF1R Combos

Fig. 4 Suppression of Akt activity by the combination of NVP-ADW742 and imatinib results in enhanced sensitivity of WBA cells to etoposide. **A**, an MTT assay was performed over 72 hours with the WBA SCLC cell line in complete medium containing 5 $\mu\text{mol/L}$ NVP-ADW742 (*ADW*), 5 $\mu\text{mol/L}$ imatinib (*STI*), and increasing concentrations of etoposide (*Etop*). Data is displayed as a percentage of control growth, with a negative value indicating net cytotoxicity (representative of at least three individual experiments); columns, mean of eight replicate wells; bars, $\pm\text{SE}$; **B**, representative Western blot illustrating the proportionate decrease in Akt reactive with anti-pAkt (Ser⁴⁷³) in the presence of both NVP-ADW742 and imatinib; **C**, quantitative analysis of the reduction in pAkt levels corrected for the amount of total Akt in the illustrated Western blot.



IGF-IR/EGFR Crosstalk

- IGF-IR is required for EGFR-mediated mitogenesis and transformation in mouse embryo cells¹
- Resistance to EGFR tyrosine kinase inhibitors (cetuximab, gefitinib, erlotinib) is associated to enhanced dependency on IGF-IR signaling²⁻⁶
- Activated EGFR protects IGF-IR from ubiquitin-mediated proteasomal degradation⁷
- Co-targeting the EGFR and the IGF-IR results in synergistic or supra-additive anti-tumor effects⁸⁻¹¹

1. Coppola D et al 1994; Mol Cell Biol 14; 4588–95.

2. Jones HE et al 2004 Endocrine-Related Cancer 11:1–22

3. Jones HE et al 2006 Endocr. Relat. Cancer. 2006;13:S45-51.

4. Chakravati A et al 2002 Cancer Res 62:200–207

5. Liu B et al 2001 Oncogene 20:1913–22

6. Morgillo et al 2006 Cancer Res 66, 10100-11

7. Riedemann J and Macaulay VM 2006 Endocr Relat Cancer. 13:S33-43

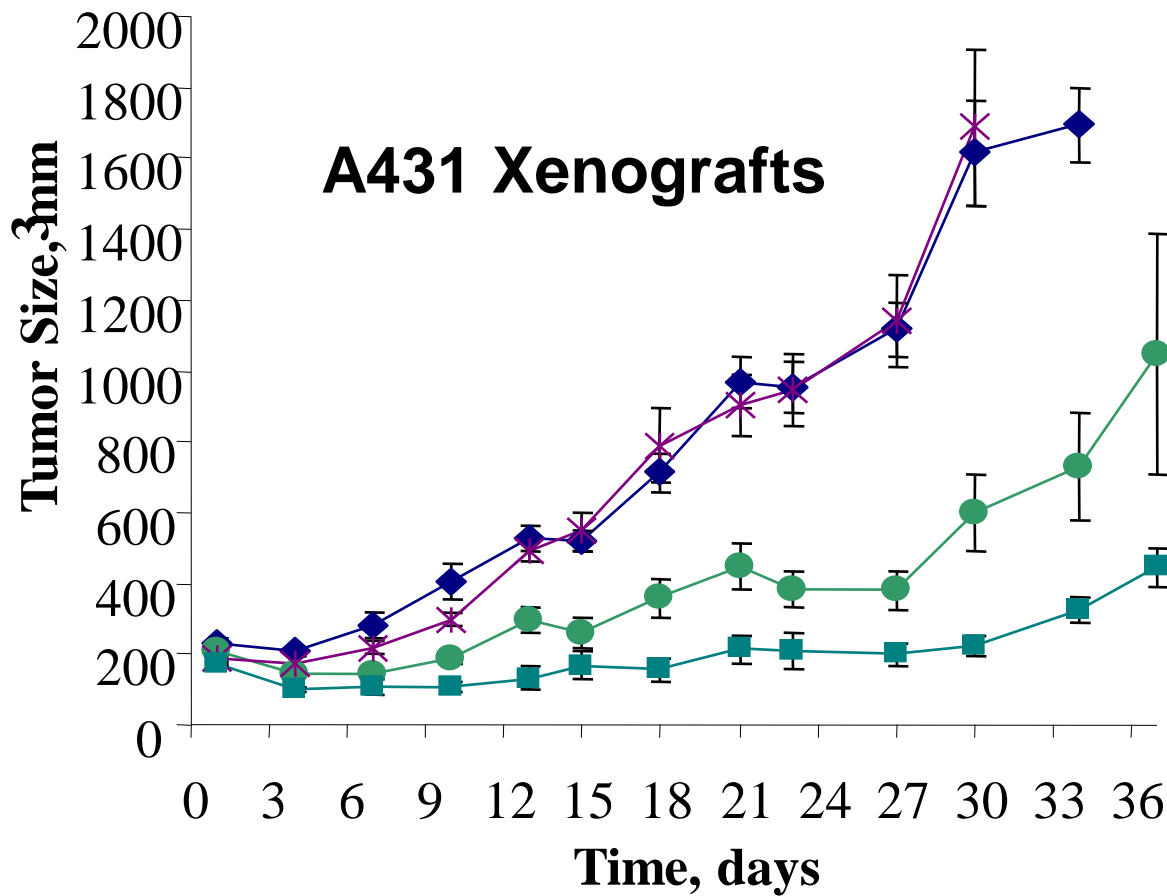
8. Camirand A 2005 Breast Cancer Res 7 R570–R579

9. Lu D et al 2005 J Biol Chem 280 19665–19672

10. Steinbach JP et al 2004 Biochem Biophys Res Com 321:524–530.

11. Goetsch L et al 2005 Inter J Cancer 113:316–328

IGF-IR/EGFR Crosstalk Tumor Models



◆ Control

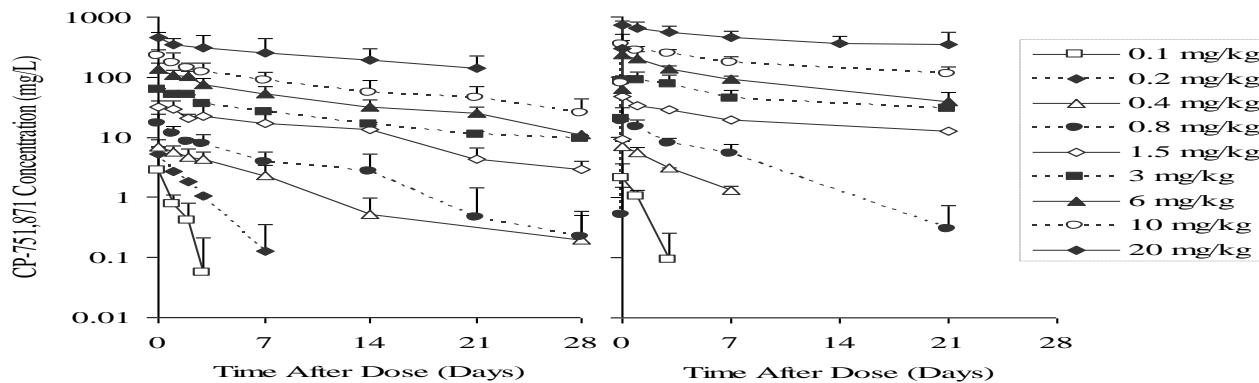
✱ 500 µg CP-751,871

● 10 mg/kg Erlotinib

■ 10 mg/kg Erlotinib
+ CP-751,871

Phase I Trials

Agent	Doses	Schedule	DLT	t 1/2
Pfizer CP-751,871	10-20 mg/kg	Q 3 Weeks	No	14-21 days
Amgen AMG 479	20 mg/Kg	Q 2 Weeks	No	7-11 days ¹
ImClone A12	6-10 mg/Kg	Q 1 Weeks	No	8-9 days ²
Roche R1507	16 mg/Kg	Q 3 Weeks	No	~8 days ³



1. Tolcher et al. 2007
ASCO
Ab No. 3002
2. Higano et al. 2007
ASCO
Ab No. 3505
3. Rodon et al. 2007
ASCO Ab
No. 3590

Hyperglycemia – anti IGF-1R

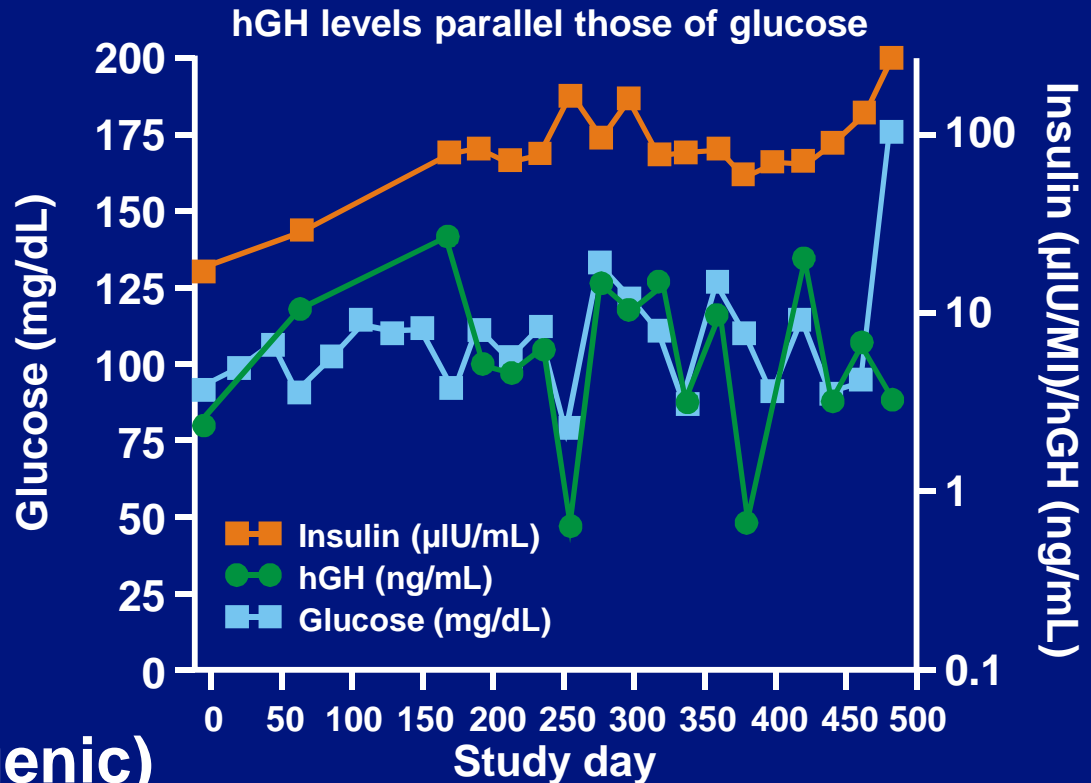
Class Effect

Mechanisms:

- Diabetes
- Steroid use
- MoA-related

↓ Hypoglycemic effect of IGF-1

↑ hGH (neoglycogenic)



↑ hGH

↑ Insulin

= Glucose

↑ hGH

~~↑ Insulin~~

↑ Glucose

AMG 479 Phase I Trial Activity

AMG 479 ¹⁸F-DG-PET/CT: Best Response



- 17/26 patients had some decrease in metabolic activity
- All PET/CT scans were analyzed by a central reader (including metabolic CR⁷)

Phase II of CP-751,871 with paclitaxel, carboplatin in first-line advanced NSCLC

Study 1002

150 patients

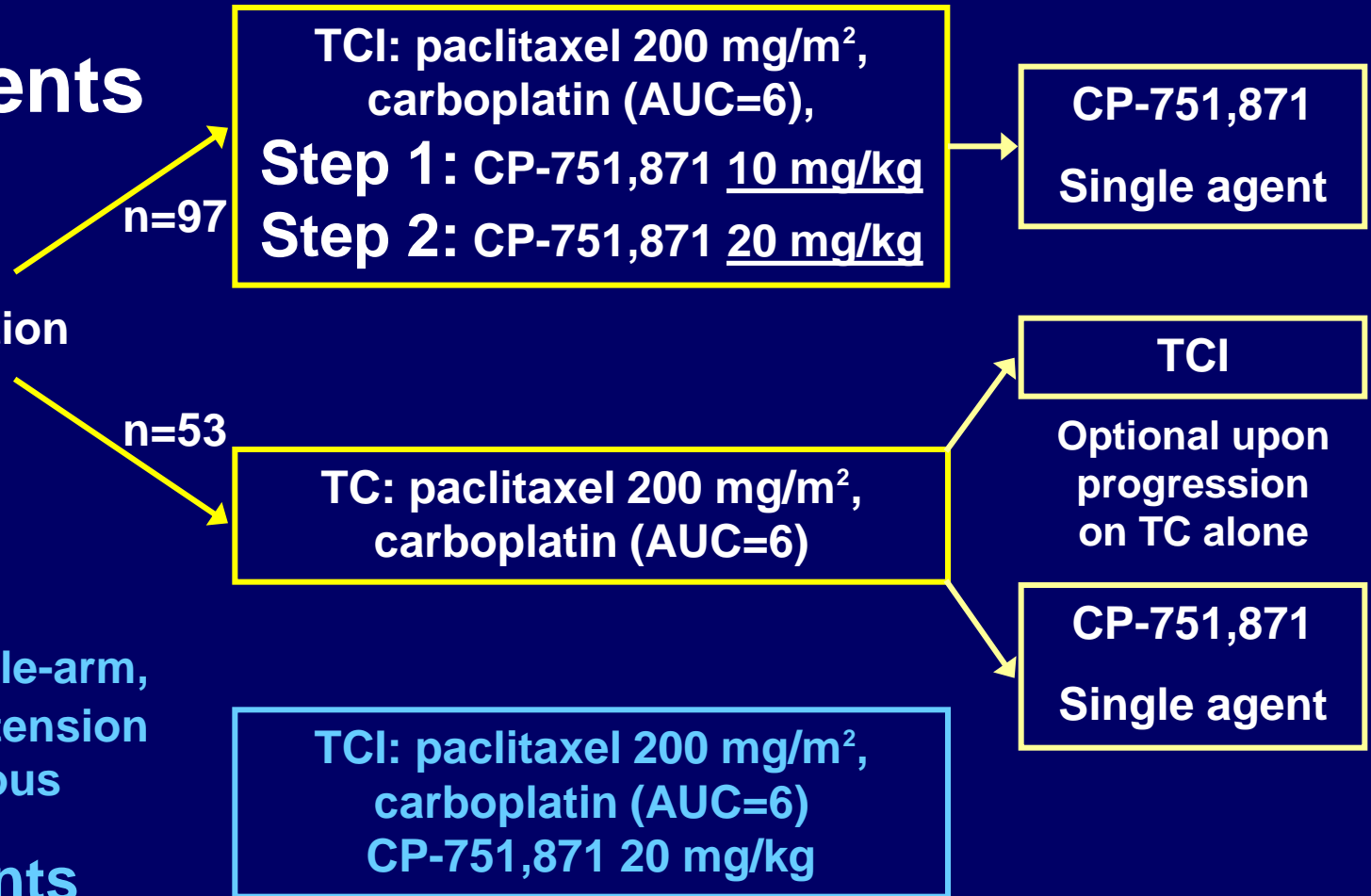
H0: 28%

HA: 40%

2:1 randomization

Step 3: single-arm,
post-study extension
in squamous

30 patients
(14 evaluable)



TCI versus TC adverse events: hyperglycemia/neutropenia

Adverse event (%)	Grade 3		Grade 4	
	TCI	TC	TCI	TC
Neutropenia	18	11	12	5
Hyperglycemia*	15	8	5	0
Fatigue	10	8	0	0
Anorexia	7	4	0	0
Thrombocytopenia	6	6	1	1
Diarrhea	6	4	0	0
Neuropathy	5	9	1	0
Pain	5	8	0	0
Dyspnea	5	9	0	0
Nausea	4	2	0	0
Dehydration	3	4	0	0
Confusion	3	0	0	0
Cough	3	4	0	0
Infection	3	2	1	1

*Glucose levels in grade 3 hyperglycemia: 251–500 mg/dL; grade 4 >500 mg/dL

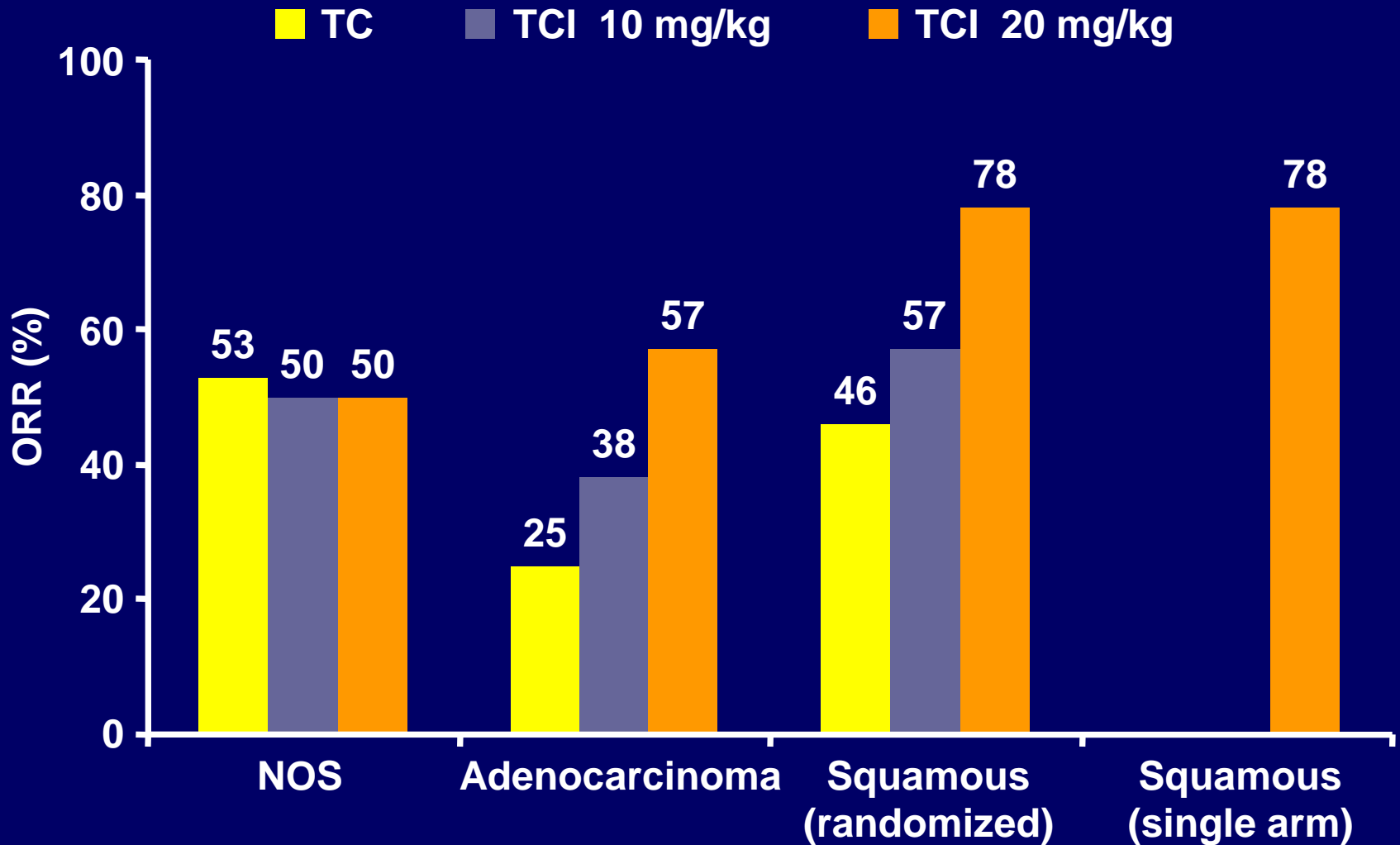
Objective Response Rate

	Objective responses	ORR
TCI	52/97	54%
TC	22/53	41%

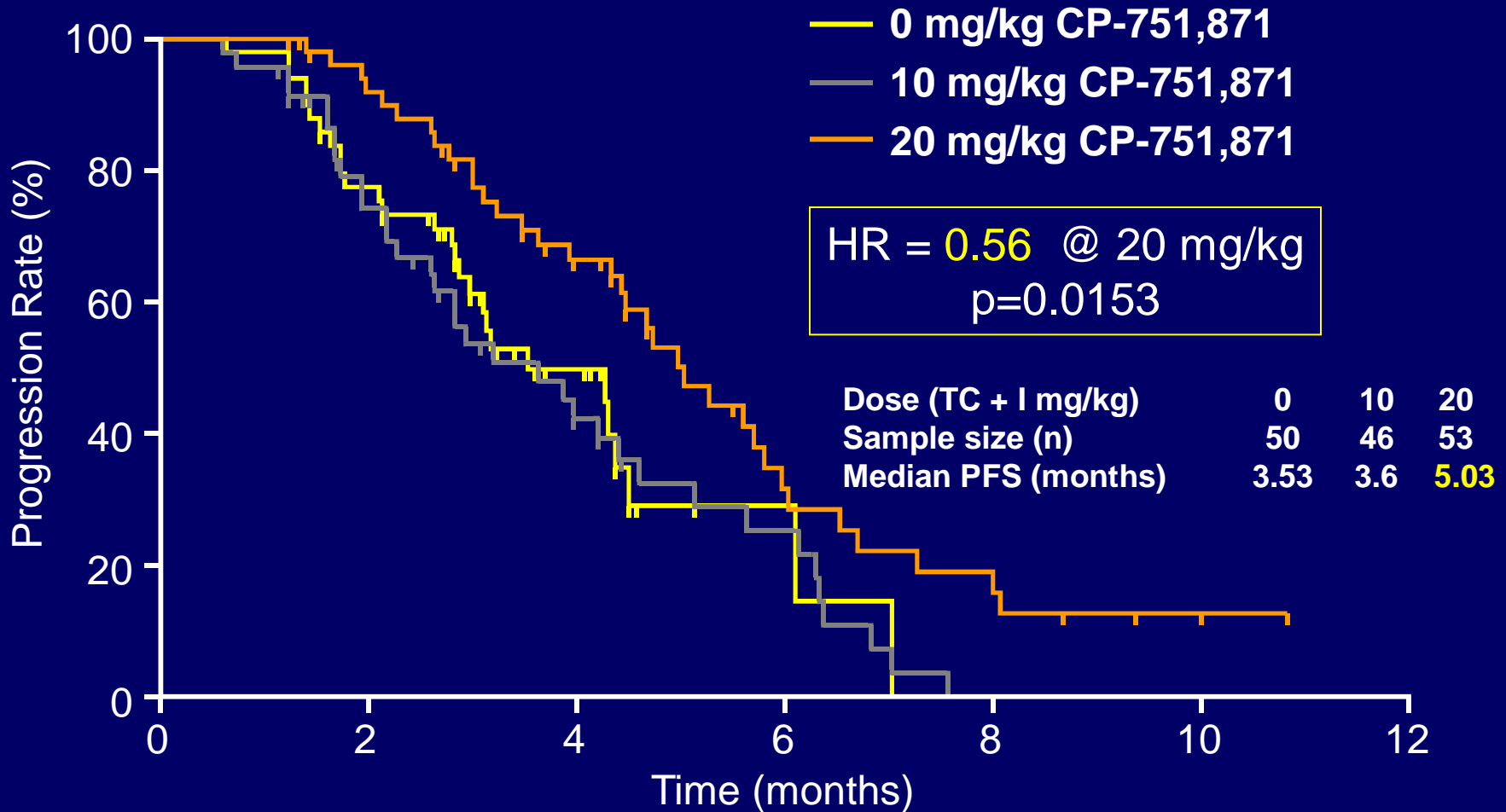
TCI ORR = 54% (95% CI 43-64%)

Response probability > 28% (null hypothesis) $p < 0.00001$

Objective Response Rate by Dose and Histology



PFS by Dose

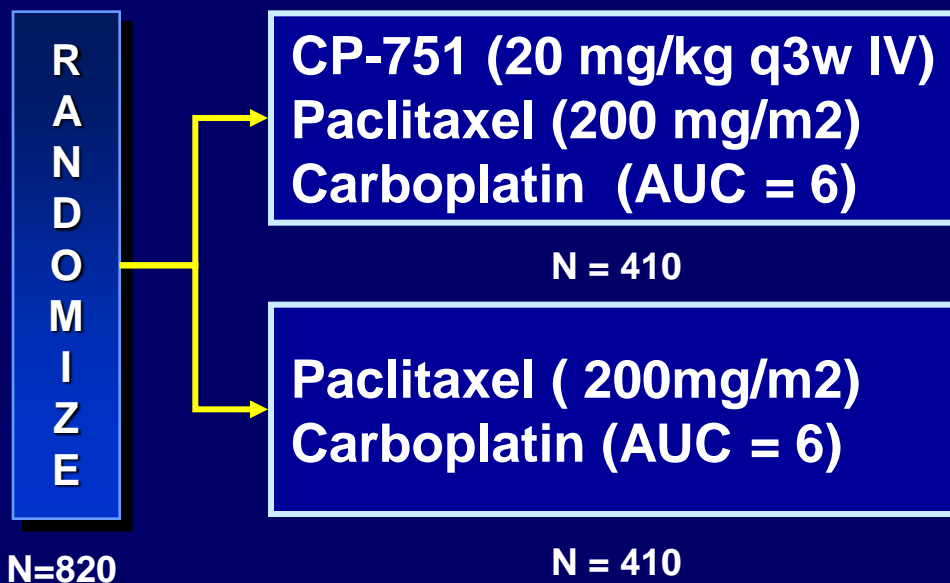


Study A1016: Phase 3 Study of Carbo/Pac +/- CP-751 in 1st Line Non-Adenoca NSCLC

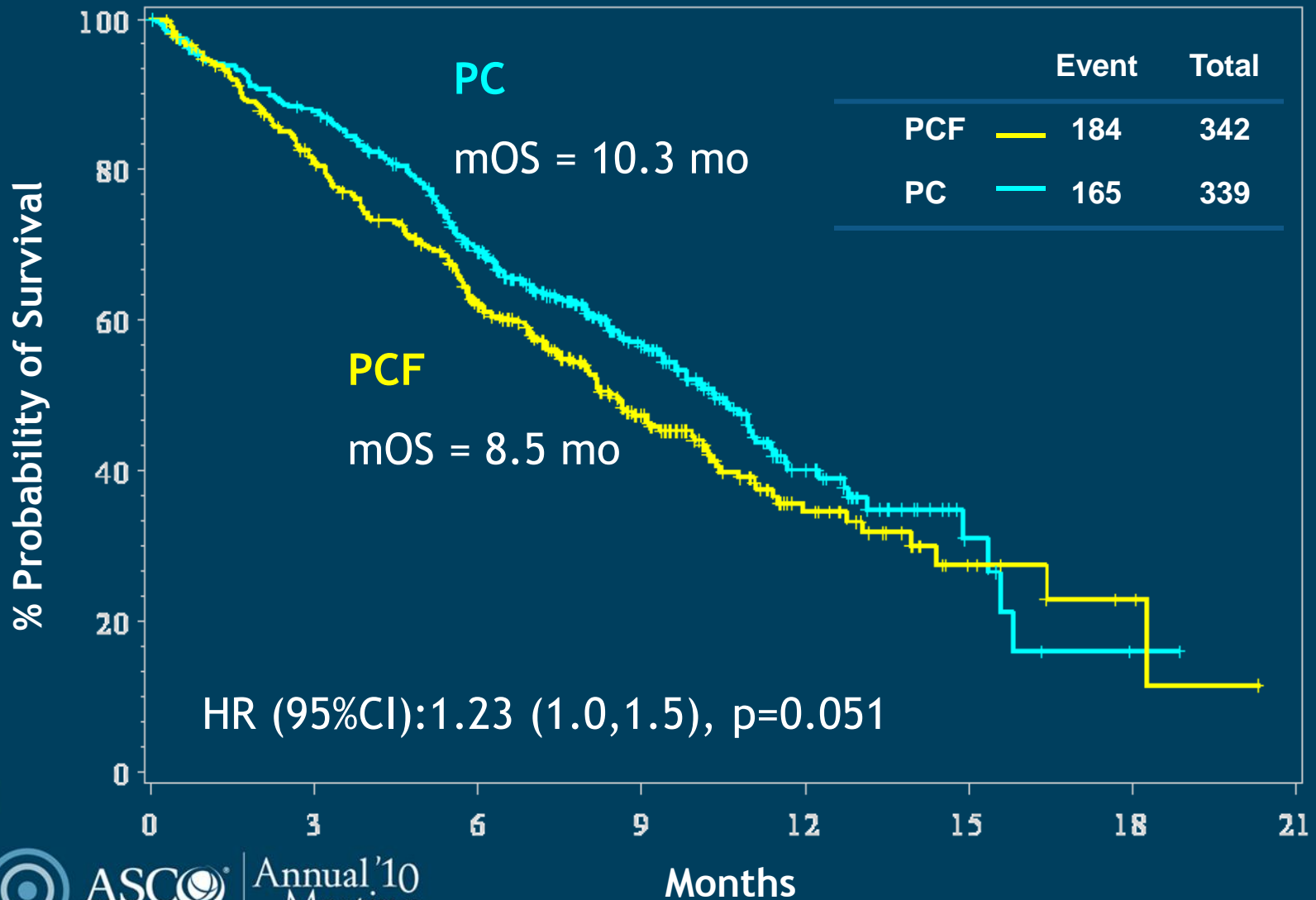
<i>Trial Design</i>	<i>Endpoints</i>	<i>Stratification</i>	<i>Study Sites</i>	<i>FSFV</i>
Multi-center, randomized, open-label	Primary: OS Secondary: PFS, ORR, Safety, QoL, biomarkers, pharm-economics	Region Stage (IIIB vs. IV) Adjuvant Rx (Y/N)	Global	2Q08

Key Entry Criteria

- Other than Adenoca
- Brain mets allowed
- Adjuvant > 12 month prior

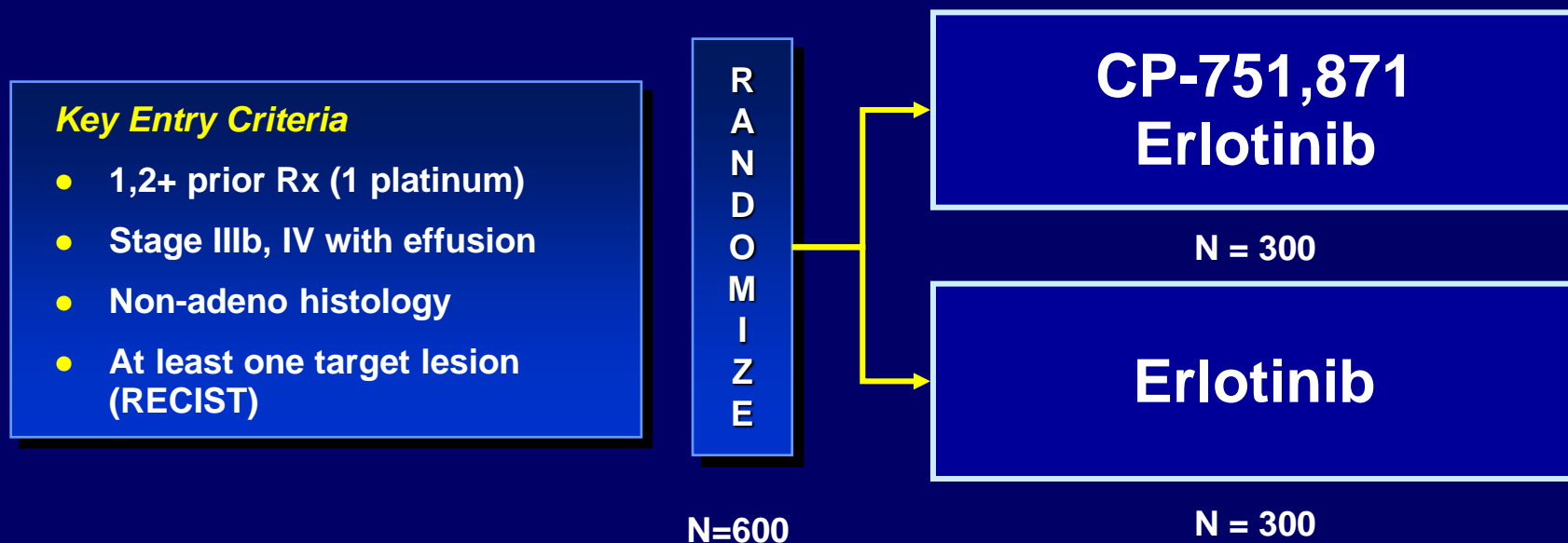


Overall Survival



Study A1018: Phase III Study of Erlotinib +/- CP-751,871 in Non-Adenoca NSCLC

<i>Trial Design</i>	<i>Study Objectives</i>	<i>Stratification</i>	<i>Study Sites</i>	<i>FSFV</i>
Multi-center, randomized, open-label	Primary: OS Secondary: <u>PFS</u> ORR, Safety, QoL, biomarkers	Gender Region PS	WW	2Q08



Consequences of effect of blockade of host (not tumor) IGF-IRs

- Neuroendocrine axis perceives IGF-I deficiency
- GH increases in attempt to compensate
- IGF-I increases
- GH induces insulin resistance in muscle
- Glucose increases
- Insulin increases

Consequences of effect of blockade of host (not tumor) IGF-IRs

- Neuroendocrine axis perceives IGF-I deficiency
- GH increases in attempt to compensate
- IGF-I increases
- GH induces insulin resistance in muscle
- **Glucose increases**
- **Insulin increases**

Are there subsets of patients who cannot tolerate?

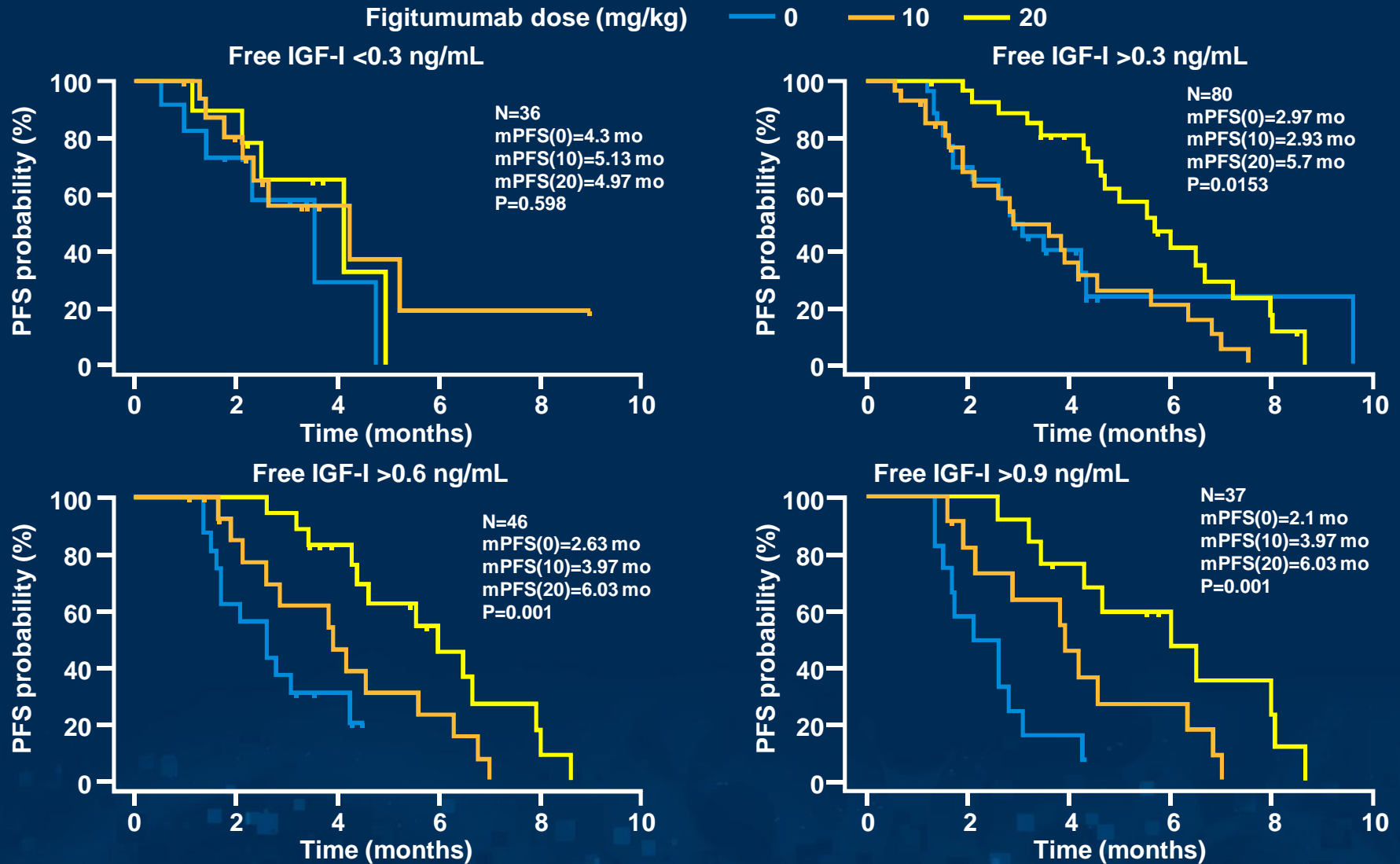
Consequences of effect of blockade of host (not tumor) IGF-IRs

- Neuroendocrine axis perceives IGF-I deficiency
- GH increases in attempt to compensate
- IGF-I increases
- GH induces insulin resistance in muscle
- **Glucose increases**
- **Insulin increases**

Are there subsets of patients who cannot tolerate?

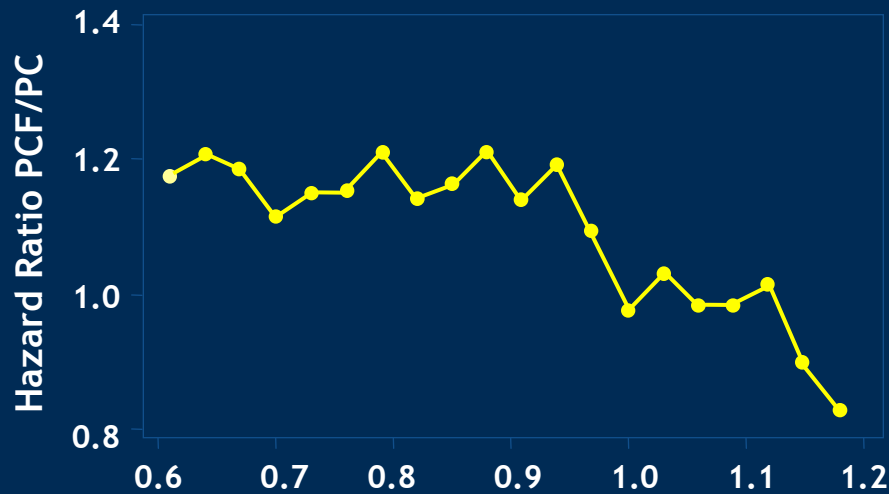
Are there subsets of tumors that exhibit insulin mediated resistance to IGF-IR blockade?

PFS analysis using free IGF-I criteria



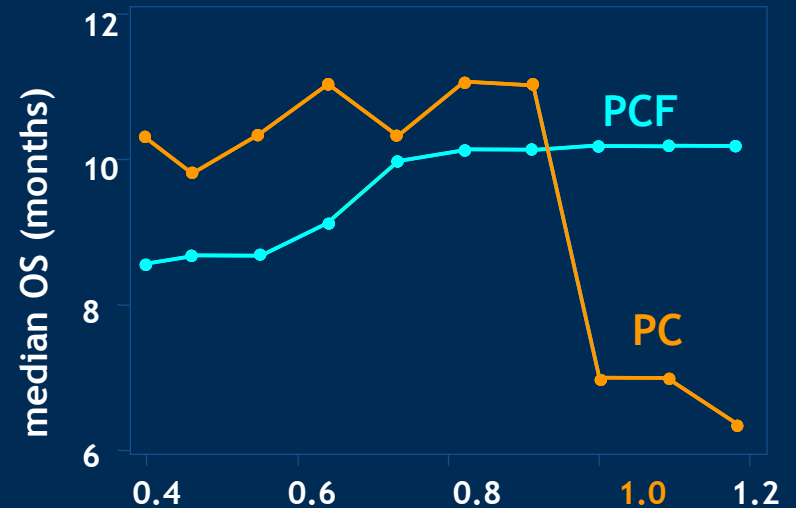
A fIGF-1/Treatment Interaction also Observed in Phase III (Study 1016, PC +/- Figitumumab)

Hazard Ratio above Free IGF-1 Criterion



Free IGF-1 Criterion (ng/mL) (pre-treatment)

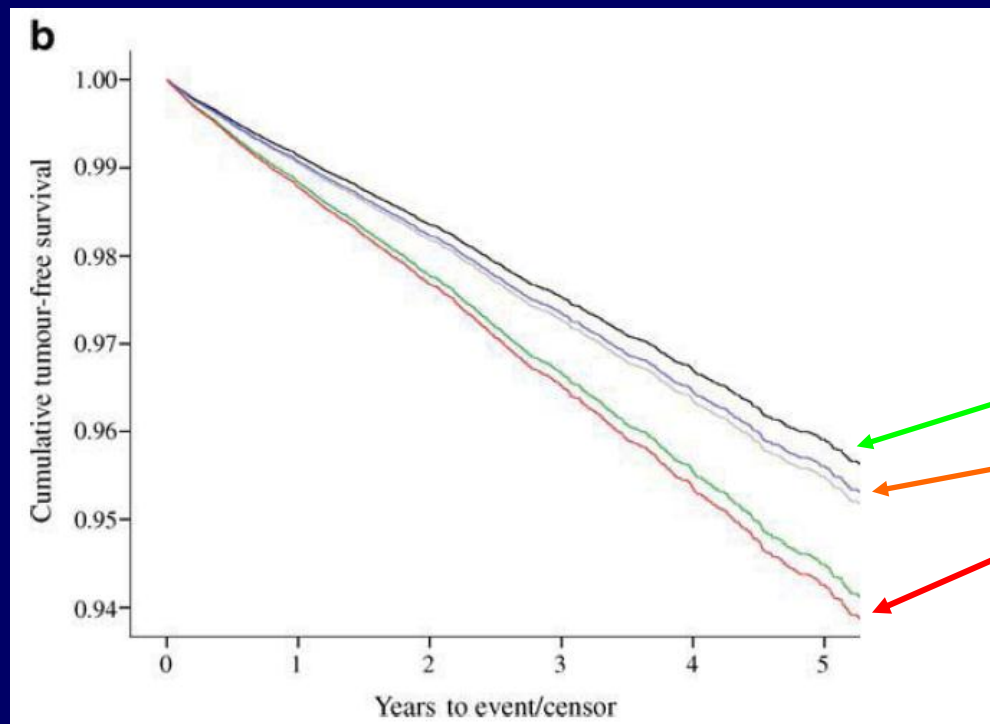
Median OS above Free IGF-1 Criterion



Free IGF-1 Criterion (ng/mL) (pre-treatment)

The influence of glucose-lowering therapies on cancer risk in type 2 diabetes

C. J. Currie • C. D. Poole • E. A. M. Gale



Metformin

No diabetes

insulin

Next steps regarding efficacy

- Co-administration of pegvisomant or metformin
- Exploring both host and tumor characteristics predictive of benefit to select patients -- a very well travelled road for “targeted therapies”
- Targeting method: anti-receptor, anti-ligand vs. TKI
- Rational combinations

Conclusions

- The IGF /IGF-1R signalling axis is relevant in the biology of many tumor types, and its therapeutic interference is of potential interest
- Anti IGF-1R mAbs and TKIs have proven preclinical activity and are in early clinical development
- Need for tumor & host markers of efficacy/safety for anti IGF-1R drugs (alone or in combination)
- Routine use of Metformin??
- Further study is warranted in many diseases, including SCLC