Milano, 20 giugno 2008

I NETs: a che punto siamo?

I nuovi farmaci: associazione o superamento del trattamento con analoghi

Nicola Fazio

Istituto Europeo di Oncologia

NET: possible targets for novel drugs

Angiogenesis

VEGF, EGF, IGF, PDGF, HGF, TGF-α

VEGFR, EGFR, IGFR, PDGFR

PI3K→Akt→mTOR

Ras→Raf→MAP-K

Proteasoma

Aurora kinase

HADC

Rationale for Evaluating Novel Therapies in Clinical Trials in Patients with pancreatic NETs

Molecular Target	Expression in animal model	Expression in human tissue	Activation/ mutations in human tissue	Efficacy of inhibitors in animal model	Efficacy of inhibitors in cell lines	Ongoing Clinical Trials
VEGF	+ [13]*	+ [18,19,20] - [21,22]	Not evaluated	+ [98]	Not evaluated	+
EGFR	Not evaluated	+[42,43,47,48,52] - [49]	+ [48,52]	Not evaluated	+ [51]	-
c-Kit	Not evaluated	+[44,57] - [45,56,58]	Not evaluated	+ [17]	+ [60]	-
IGF-1	Not evaluated	+ [83,84,99]	Not evaluated	Not evaluated	+ [85]	-
mTOR	Not evaluated	+ [78]	+ [78]	Not evaluated	+ [73]	+

From Capurso et al., Recent Patents on Endocrine, Metabolic & Immune Drug Discovery 2007

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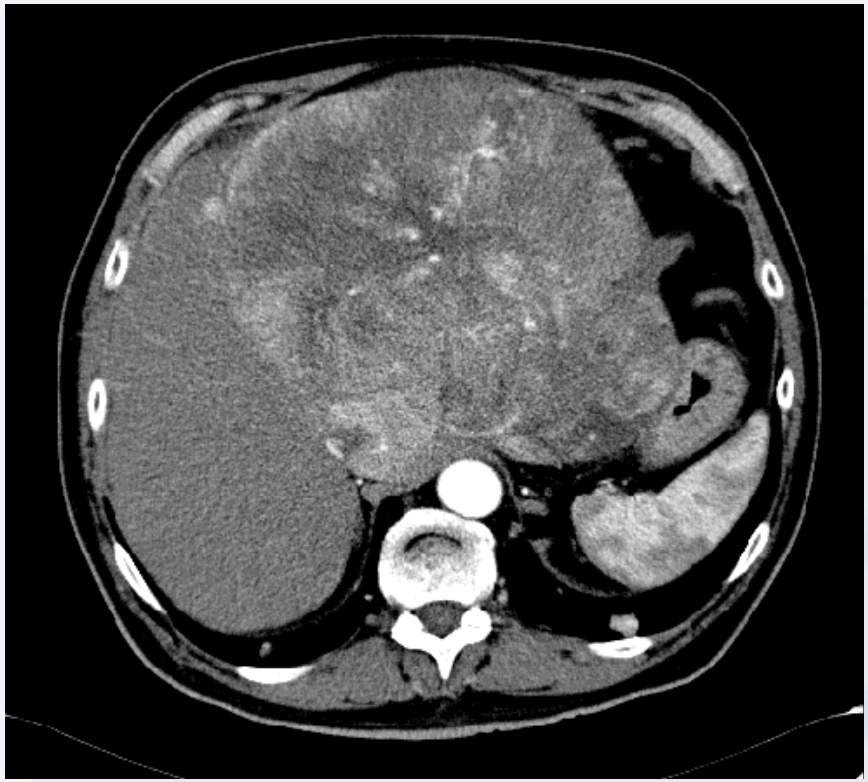
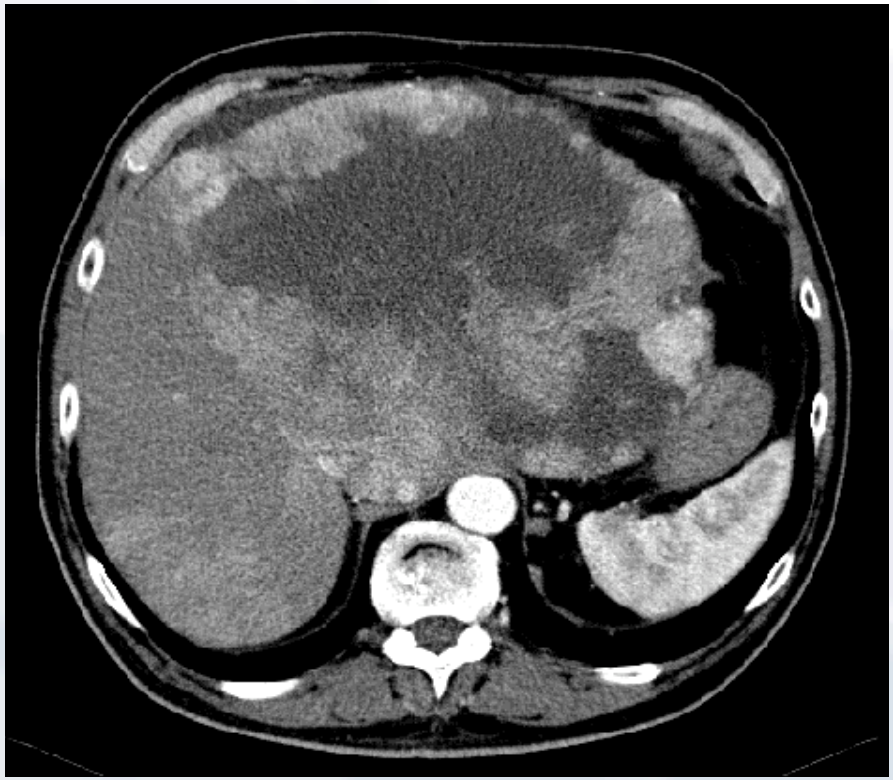
Agent	Study Design	Tumour type	Disease Stage	Histology	Behaviour before entry	TX duration (median)	Imaging Evaluation	Efficacy (Tumour type subanalysis)
Bevacizumab	PII RT + OCT BVZ vs IFN	40 CT	Metastatic Unresectable	NR	NR	18 weeks	CT RECIST	BVZ : 15%PR 80%SD 5%PD IFN: 0%PR 75%SD 25%PD
Bevacizumab	P II +Temozolomide	18 PET 16 CT	Metastatic	27 WDEC 7 PDEC	NR	22 weeks	CT RECIST	14% PR, 79% SD, 7% PD PET better
Sunitinib	P II OCT allowed	52 PET 41 CT	Advanced Unresectable	NR	NR	204 days (26-543)	CT RECIST	9% PR, 83% SD, 8% PD PET better
Thalidomide	P II +Temozolomide	11 PET 15 CT, 3 PC	Metastatic	28 WDEC 1 PDEC	NR	7.3 months (1-23)	CT RECIST	25% PR, 68% SD, 7% PD PET better
Endostatin	P II OCT allowed	20 PET 22 CT	Metastatic	38 WDEC 4 PDEC	PD 11/23 evaluated	6.4 months (10-45)	CT or MRI WHO	80% SD, 20% PD
Gefitinib	P II OCT allowed	39 PET 57 CT	Metastatic	NR	PD	NR	CT RECIST	4% PR, 69% SD, 27% PD CT better
Imatinib	P II OCT allowed	27 CT	Metastatic	27 G1/G2	PD 14/24 evaluated	NR	CT or MRI RECIST	3% PR, 62% SD, 33% PD SD in 7 of 14 with PD at entry
Everolimus	P II + OCT	13 PET 18 CT	Advanced	"low grade"	PD in 21	NR	NR RECIST	12% PR, 61% SD, 27% PD PR or SD in 61% PD at entry
Temsirolimus	P II Single agent	15 PET 21 CT	Metastatic	NR	PD	16 weeks (1-21)	CT RECIST	6% PR, 55% SD, 29% PD PET better

Sorafenib in HCC
"Tissue response" rather than tumor shrinkage



Pre-treatment



4 months later

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The Oncologist®

HAESUN CHOI *The Oncologist* 2008;13(suppl 2):4–7

Response Evaluation of Gastrointestinal Stromal Tumors

Size and density at CT-scan vs SUV at PET-scan

Good correlation

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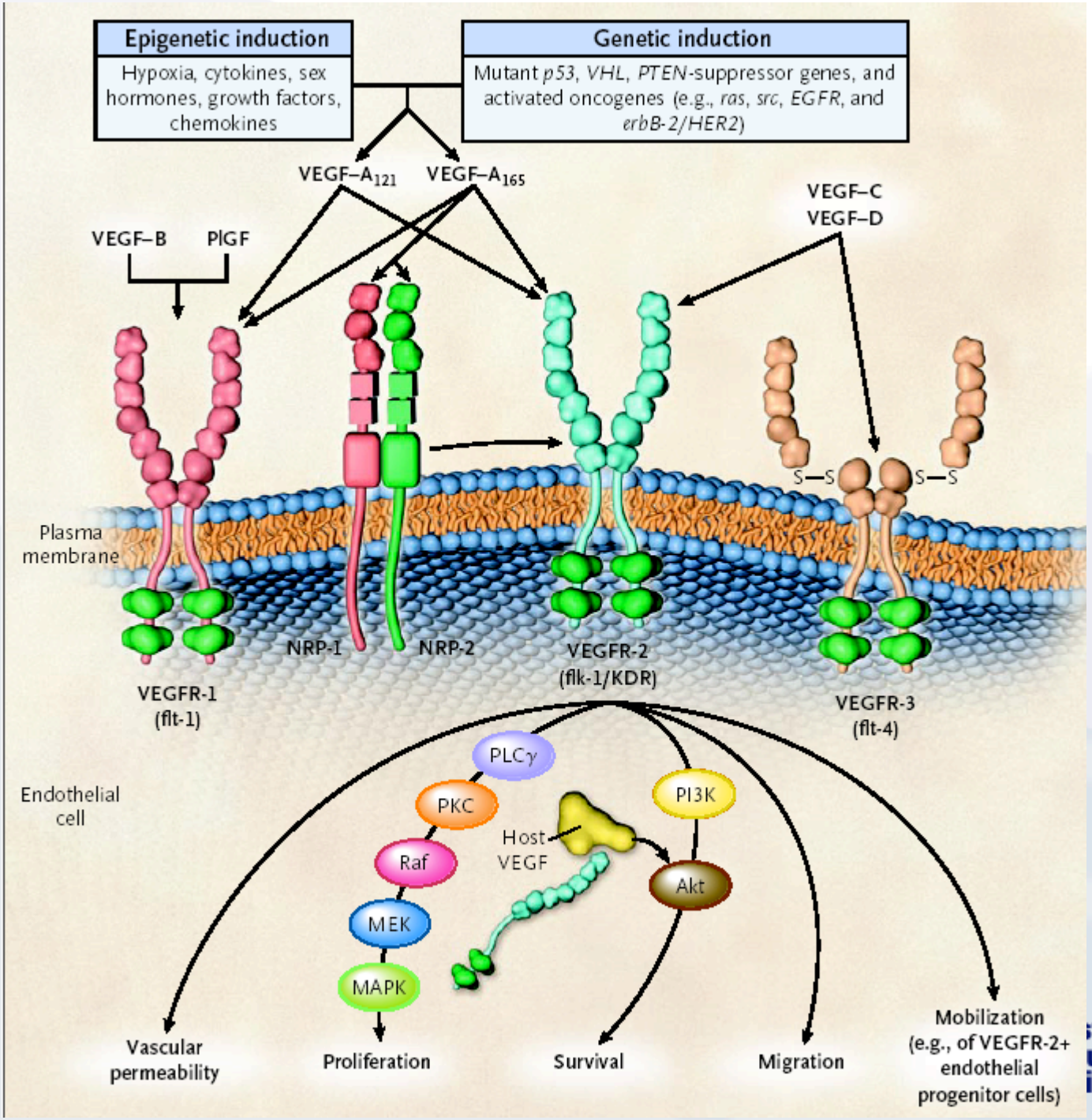

Hypervascularized GEP-NET overexpress VEGF and VEGFR-1,2 in tumor cells and surrounding vasculature

Wiedenmann et al., Neuroendocrinology 2004

	VEGF	VEGFR
Carcinoids	100 %	70 %
Pancreatic	85 %	75 %

Kulke, ASCO 2006

High VEGF expression correlates with increased angiogenesis and decreased PFS in low-grade NET

Zhang et al., Cancer 2007

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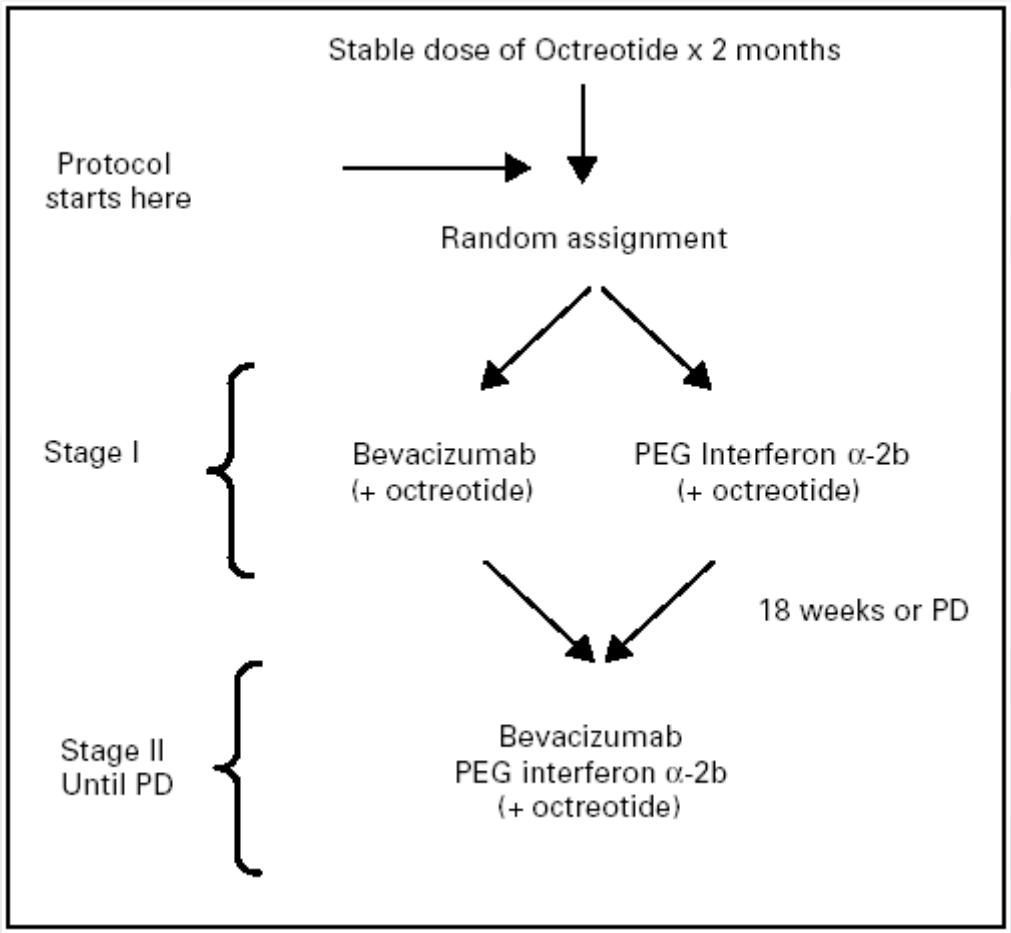
Targeting Vascular Endothelial Growth Factor in Advanced Carcinoid Tumor: A Random Assignment Phase II Study of Depot Octreotide With Bevacizumab and Pegylated Interferon Alfa-2b

Yao et al., J Clin Oncol 26:1316-1323. © 2008



Octreotide LAR not more than 30 mg q3w

BV 15 mg/Kg q3w

PEG-IFN 0.5 mcg/Kg/w

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Characteristic	Overall	
	No.	%
Disease at entry		
PD	23	52.3
SD	18	40.9
Unknown	3	6.8
Primary site		
Foregut	6	13.6
Gastric	1	2.3
Lung	4	9.1
Thymus	1	2.3
Midgut	24	54.5
Ileum	11	25.0
Small intestine	12	27.3
Caecum	1	2.3
Hindgut	4	9.1
Rectum	4	9.1
Unknown	10	22.7

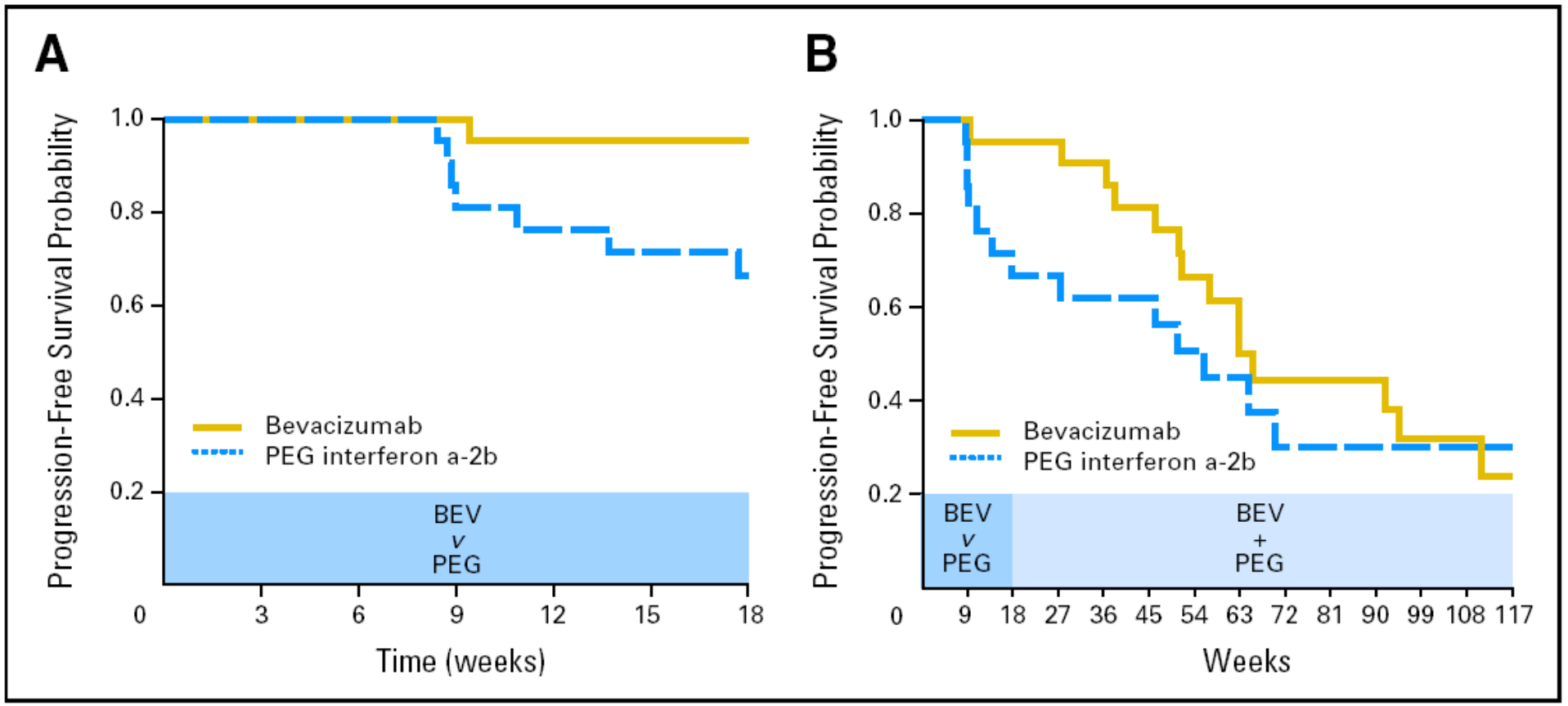
Yao et al., J Clin Oncol 26:1316-1323. © 2008

PFS at 18 w = **95%** BV v **68%** PEG-INF; p = 0.02

Overall PFS for 44 pts = **63 w** (95%CI: 51-75)

PFS **66 w** BV v **56 w** PEG-IFN; p = 0.34

PFS shorter for pts with PD at study entry; p= 0.005



Yao et al., J Clin Oncol 26:1316-1323. © 2008

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		Activity		
Arm	pts	PR	SD	PD
BV	22	18%	77%	5%
IFN	22	0	68%	27%

7 pts with PD during PEG-IFN

with combination → PR 1

SD 5

1 pt with PD during BV

with combination → PD

Yao et al., J Clin Oncol 26:1316-1323. © 2008

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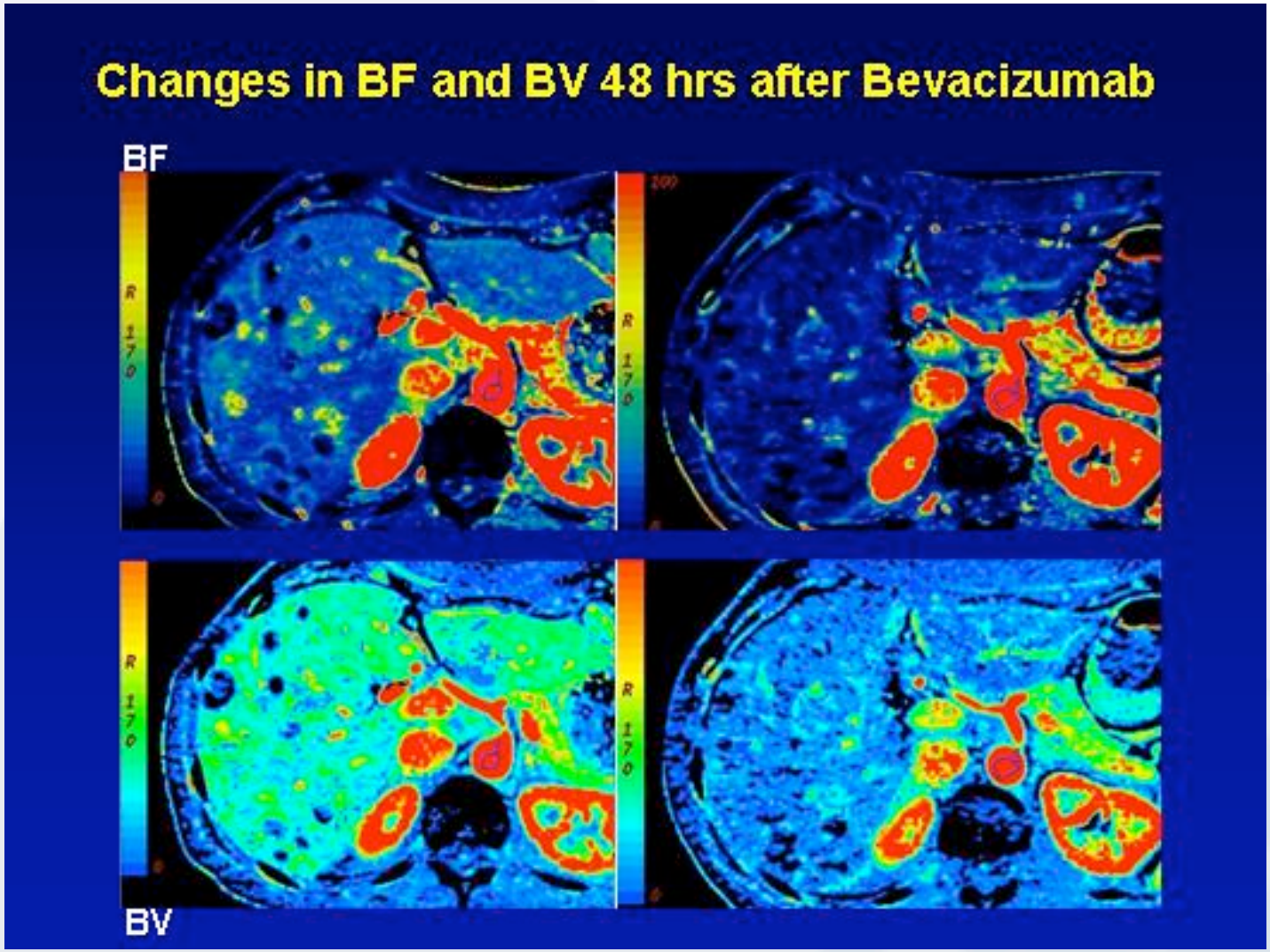
Table 3. Selected Grade 3/4 Events During Stage I Monotherapy (first 18 weeks) by Treatment Arm According to Common Toxicity Criteria (version 2)

	Bevacizumab		PEG Interferon		
Toxicity	No. of Patients	%	No. of Patients	%	*P*
Granulocytopenia	0	0	6	27	.02
Hypertension	8	36	0	0	.01
Nausea	0	0	2	9	.48
Fatigue	4	18	5	23	.99
Vomiting	1	5	1	5	.99
Myalgia	2	9	2	9	.99
Headache	1	5	0	0	.99
Anxiety	0	0	1	5	.99
AlkPhos Inc	0	0	1	5	.99

Abbreviation: PEG, pegylated.

Yao et al., J Clin Oncol 26:1316-1323. © 2008



Yao et al., J Clin Oncol 26:1316-1323. © 2008

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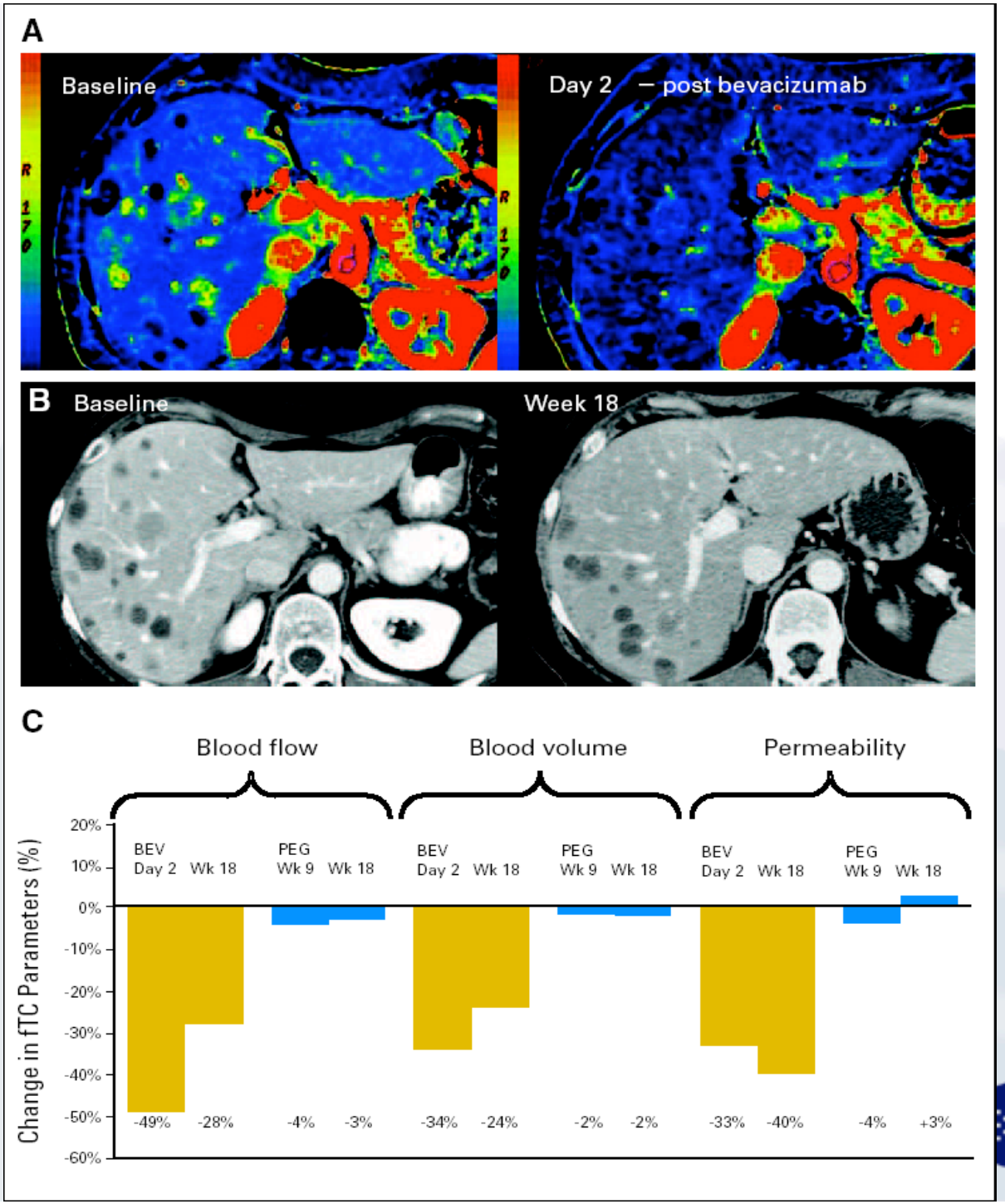

Yao et al., J Clin Oncol 26:1316-1323. © 2008

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Functional CT = 24 pts

Only 2 responders had fCT

lower day 2 BV = longer PFS (predictive?)

PEG-IFN → reduction bFGF, increase IL-18

Yao et al., J Clin Oncol 26:1316-1323. © 2008

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SWOG phase III trial (study S0518)
OCT + IFNα vs OCT + BV

ongoing

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Bevacizumab: ongoing studies in NET

NCI phase I-II trial with FOLFOX plus BV in refractory carcinoids and pancreatic endocrine tumors	*Ongoing (102 pts from Jun '05)*
BV + RAD001 in Advanced Low or Intermediate Grade Neuroendocrine Carcinoma	*Ongoing from Jan '08*
XELBEVOCT: Xeloda 2000 mg/sm/day continuously + BV 5 mg/Kg/q2w + OCT LAR	*Torino-Bologna-S.Giov Rot – 15 pts*
Xeloda + BV + TMZ	*Uppsala*
XELOX + BV Temozolomide + BV Panzem + BV	

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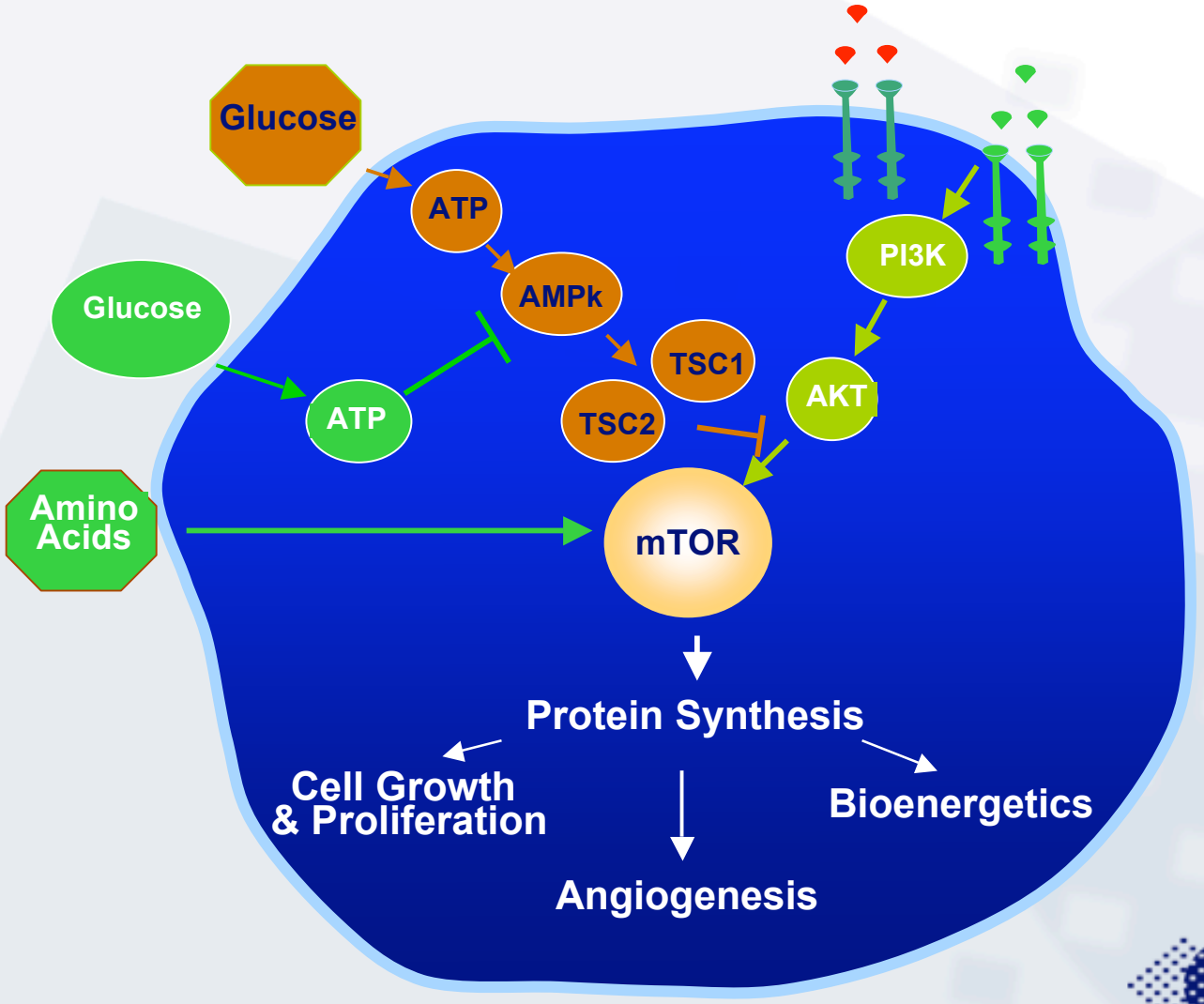
Types of stimuli that modulate mTOR:
Growth Factors, hypoxia, amino acids, intracellular ATP concentrations



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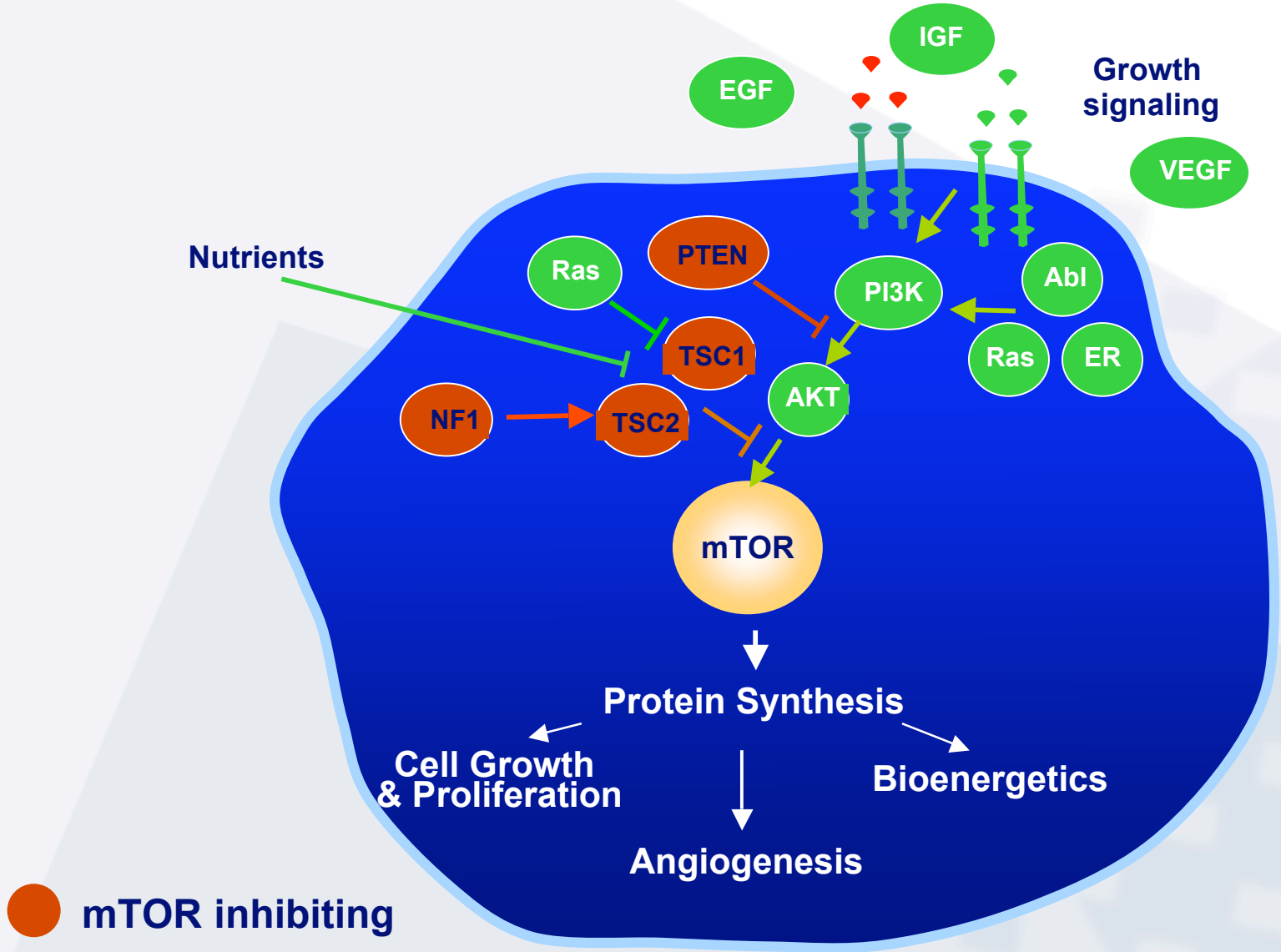
mTOR pathway is deregulated by mutations in cancer



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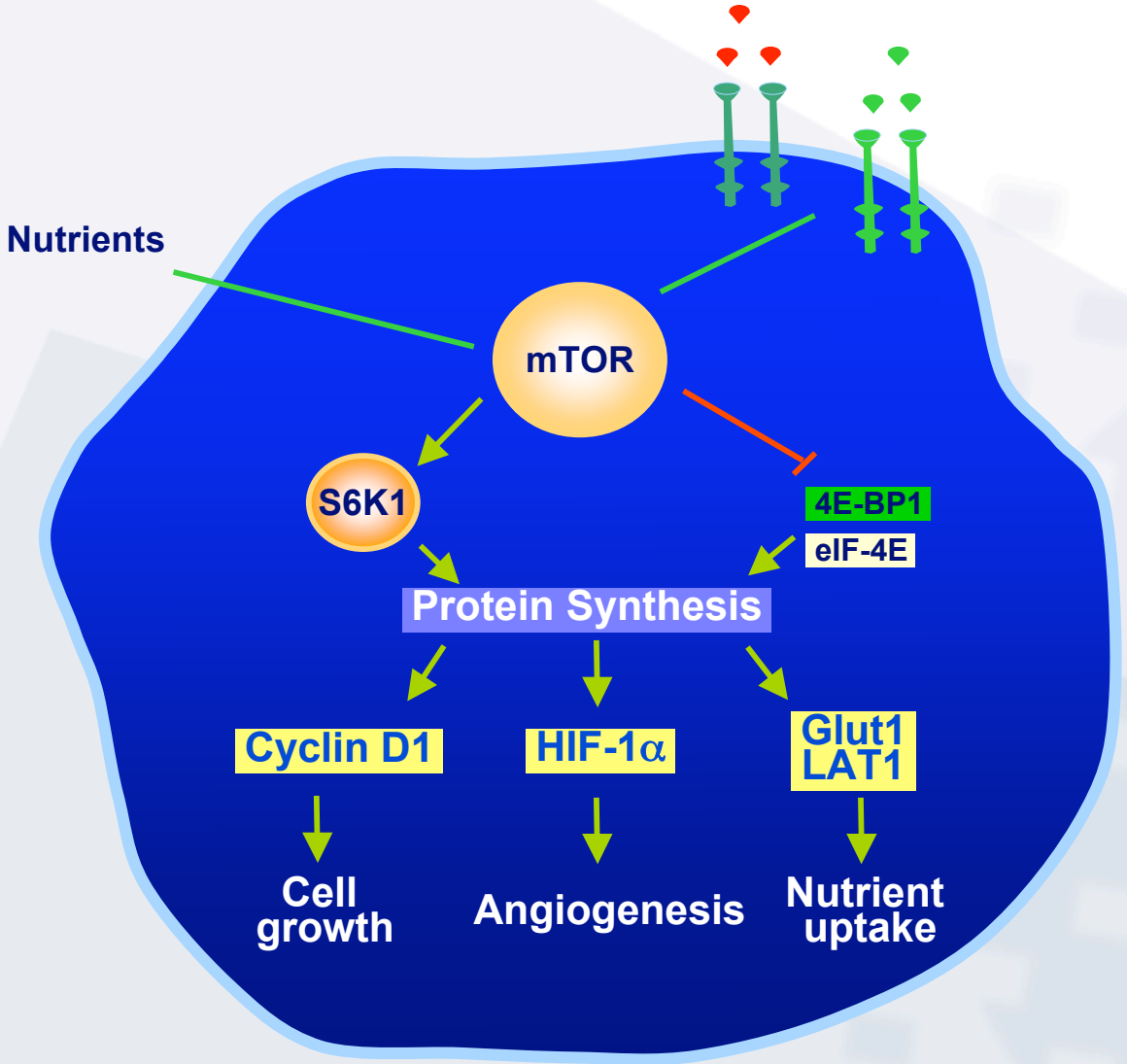
mTOR activation supports cancer cell growth



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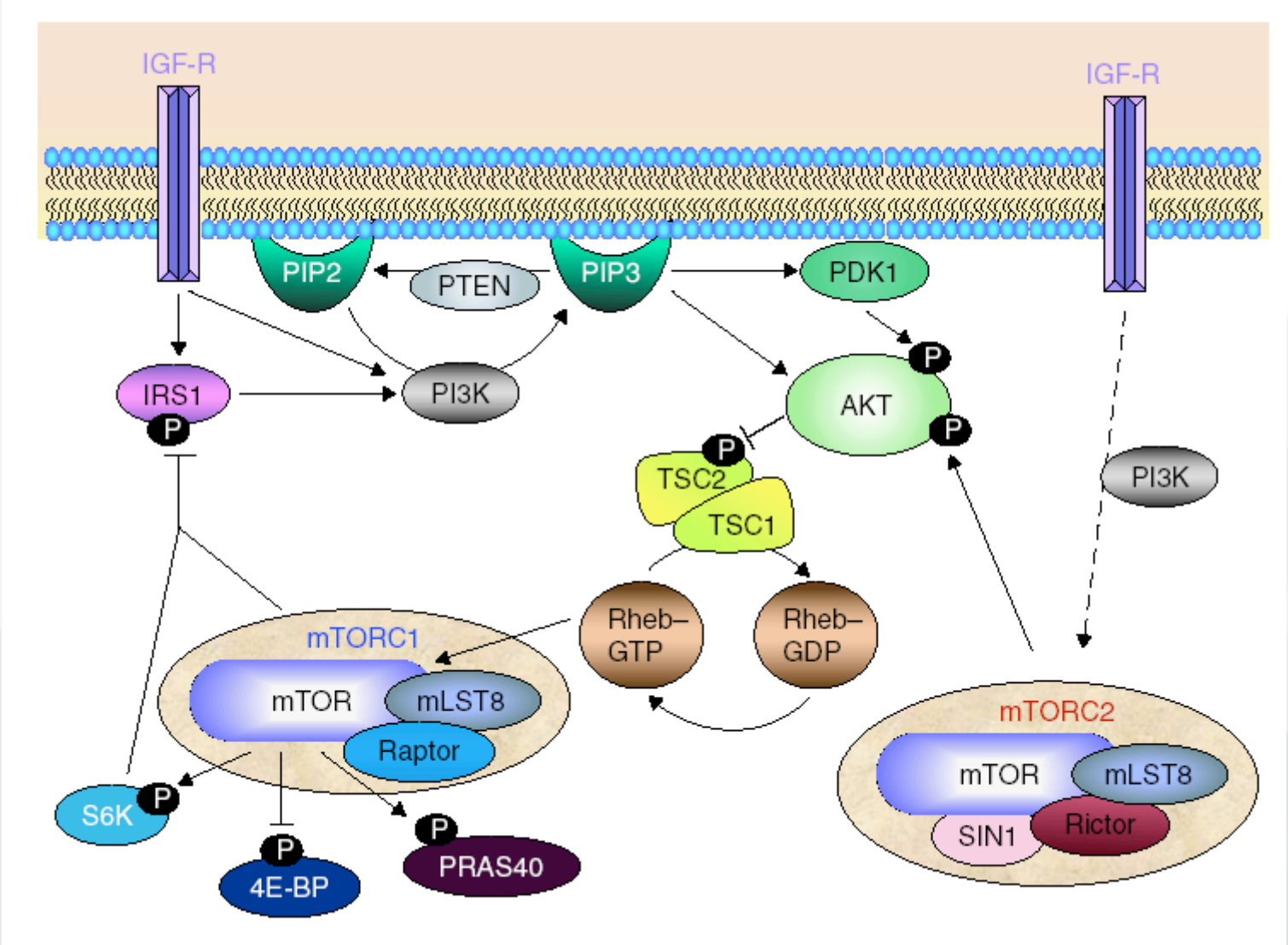

From Abraham, Expert Opin Ther Targets 2008

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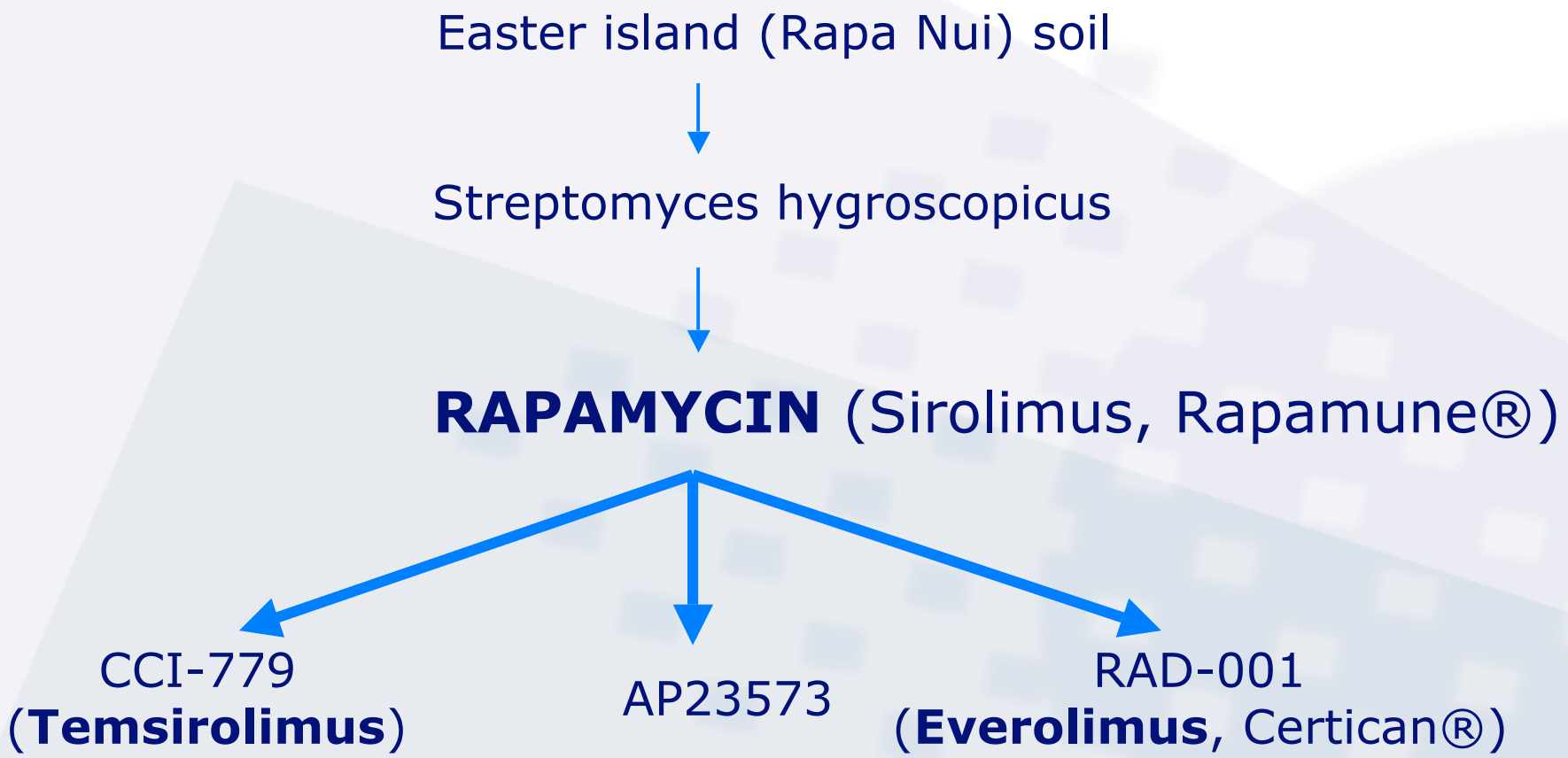
mTOR inhibitors



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Phase II study of Temsirolimus in advanced neuroendocrine carcinoma

37 progressive pts

Efficacy

PR	5.6% (95% CI 0.6-18.7%)
TTP	6 months
1-y OS	71.5%

Toxicity all grades

Fatigue	78%
Hyperglycemia	69%
Rash/desquamation	64%

Duran et al., Br J Cancer 2006

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Phase II study of Temsirolimus in advanced neuroendocrine carcinoma

Temsirolimus effectively inhibited the **phosphorylation of S6** (*P*=0.02).

Higher baseline levels of **pmTOR** (*P*=0.01) predicted for a better response.

Increases in **pAKT** (*P*=0.041) and decreases in pmTOR (*P*=0.048) after treatment were associated with an increased TTP

Duran et al., Br J Cancer 2006

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Expression and activation of mTOR in neuroendocrine tumors. Effects of mTOR inhibition by RAD001 upon growth, cell cycle regulation and signalling in neuroendocrine cell lines

D. Hörsch, et al. ASCO 2007

mTOR is expressed and activated in different NET and inhibition of mTOR by RAD001 induces growth inhibition, cell cycle arrest and decreased signaling by mTOR and ERK1/2 in neuroendcrine cell lines INS-1 and BON.

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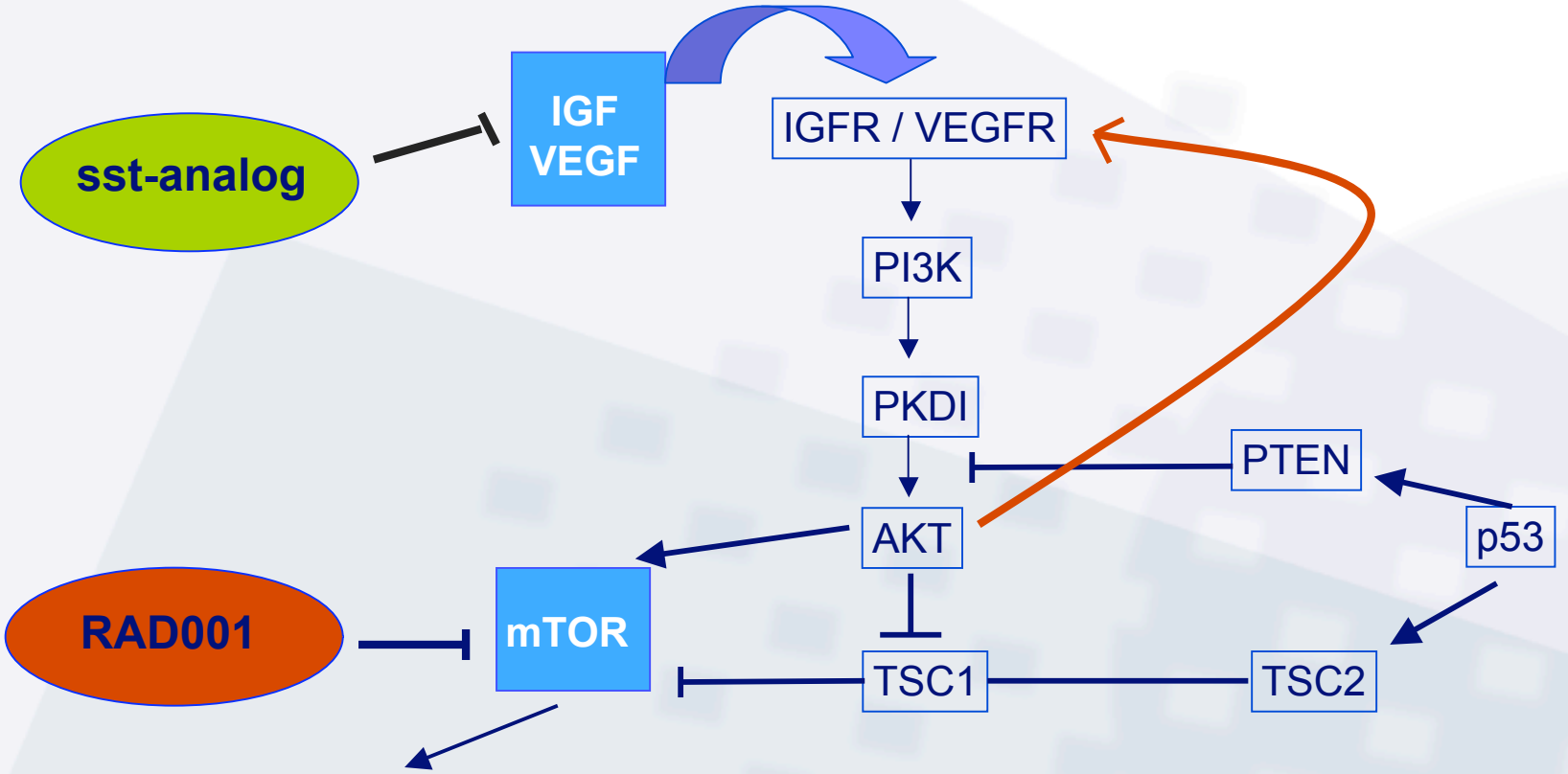
mTOR- inhibitor + IGFR-inhibitor



O'Reilly et al., Cancer Res 2006

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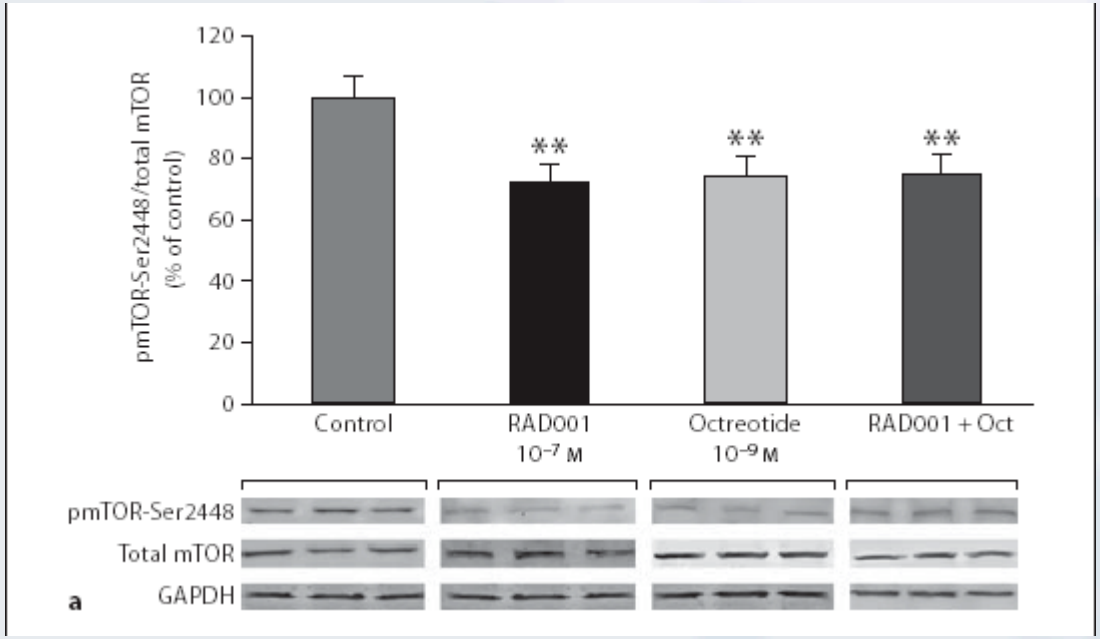
Octreotide and the mTOR Inhibitor RAD001 (Everolimus) Block Proliferation and Interact with the Akt-mTOR-p70S6K Pathway in a Neuro-Endocrine Tumour Cell Line

Simona Grozinsky-Glasberg

Neuroendocrinology 2008;87:168–181

Octreotide and RAD001 share common endpoints

No additive effect when used together



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Phase II study of RAD001 plus Octreotide LAR

Metastatic WD NET

Single-arm

Cohort 1 → 30 pts (RAD 5 mg/day)

Cohort 2 → 30 pts (RAD 10 mg/day)

Octreotide LAR 30 mg I.M. q 4 w

Yao et al., ASCO 2007

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Phase II study of RAD001 plus Octreotide LAR

Baseline PD	65%
Baseline SD	27%
Most pre-treated	
Pancreatic	29 (48%)
Midgut	16 (27%)
Liver mets	95%

Yao et al., ASCO 2007

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Phase II study of RAD001 plus Octreotide LAR

G3-4 non-hematological toxicity

	5 mg	10 mg
Mucositis	6%	9%
Fatigue	15%	6%
Diarrhea	9%	13%
Skin rash	6%	3%
Pneumonitis	0	3%

Yao et al., ASCO 2007

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Phase II study of RAD001 plus Octreotide LAR

G3-4 hematological toxicity

	5 mg	10 mg
Thrombocytopenia	3%	6%
Anemia	3%	3%
Leukopenia	3%	6%
Hyperglicemia	3%	13%
Hypoglicemia	6%	0
Hypertrigliceridemia	0	6%
Hypophosphatemia	6%	16%
Hypokaliemia	3%	3%
Elevated AST	3%	3%
Elevated ALT	0	6%
Hyperbilirubinemia	0	3%

Yao et al., ASCO 2007

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Phase II study of RAD001 plus Octreotide LAR

Efficacy by dose level

	Overall n=60	5 mg n=30	10 mg n=30
PR	12 (20%)	4 (13%)	8 (**27%**)
SD	43 (72%)	22 (73%)	21 (70%)
PD	5 (8%)	4 (13%)	1 (3%)
PFS	59 w	50 w	62 w

Yao et al., ASCO 2007

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Phase II study of RAD001 plus Octreotide LAR

PFS in pts with PD at study entry = 50 w (95% CI 34-66)

PFS in pts with SD at study entry = **73 w** (95% CI 65-80)

MOS not reached

2-year survival rate 78%

Yao et al., ASCO 2007

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Phase II study of RAD001 plus Octreotide LAR

IHC on 25 samples

Pre- and on-treatment = 19 pts

PTEN expression, pAkt, pmTOR, p4EBP1, pS6

All tumors expressed pmTOR and almost all PTEN

Carcinoids more pAkt than pancreatic

Increase in pAkt not associated with PD

Meric-Bernstam et al., AACR 2008

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RAD001 In Advanced Neuroendocrine Tumors
RADIANT

RADIANT-1: Phase 2 open label study of RAD001 in advanced pancreatic neuroendocrine tumors after failure of chemotherapy (2239) - CLOSED

RADIANT-2: Phase 3 double-blind placebo-controlled study of RAD001 in pts receiving Octreotide LAR for advanced carcinoid tumors (2325) - CLOSED

RADIANT-3: Phase 3 double-blind placebo-controlled study of RAD001 in advanced pancreatic tumors (2324)- ONGOING

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mTOR-I — Anti-EGFR

Inhibition of mTOR pathway by everolimus cooperates with EGFR inhibitors in human tumours sensitive and resistant to anti-EGFR drugs

R Bianco[1] **British Journal of Cancer (2008) 98,** 923–930

Targeting mTOR pathway with everolimus
overcomes resistance to EGFR inhibitors
and
produces a cooperative effect with EGFR inhibitors

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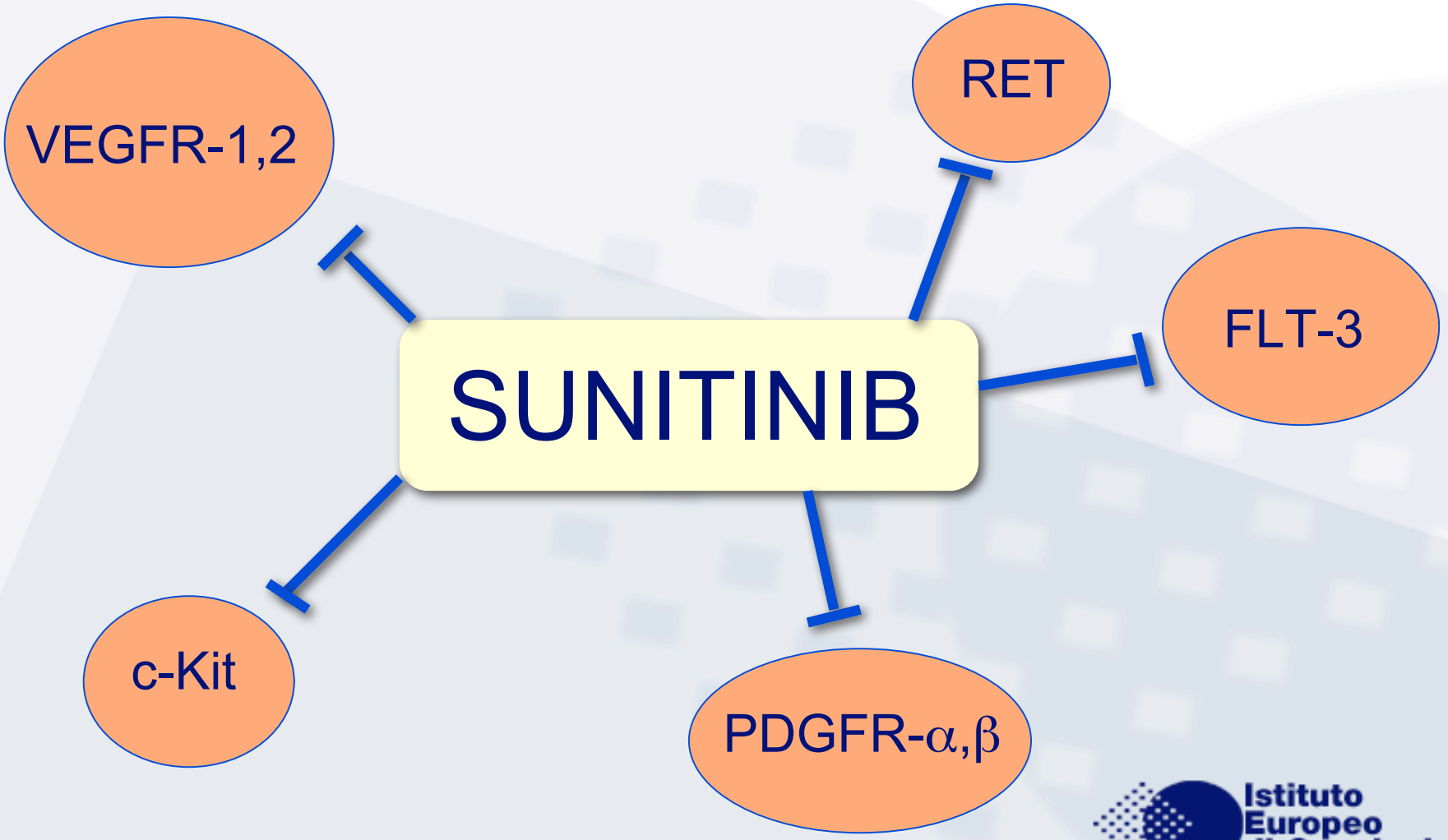
SUNITINIB MALATE (SU11248, SUTENT)



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Phase I study of Sunitinib (SU11248, Sutent) in advanced carcinomas

28 pts → 4 pts with NET (1 PR e 1 MR)

Faivre et al., JCO 2006

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Phase II study of Sunitinib (SU11248, Sutent) in advanced carcinoid tumors

106 pretreated pts: pancreatic/carcinoid balanced

Sunitinib 50 mg/d po on schedule 4/2

15% PR and 75% SD in pancreatic
2% PR and 93% SD in carcinoids

Low rate of G3-4 toxicity: diarrhea, fatigue, hypertension, myelotox

Kulke et al., ASCO 2005

sVEGFR-3 as novel biomarker for the biological activity of sunitinib
IL-8 potential predictor of response

Bello, ASCO 2006

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Sunitinib trials ongoing in NET

A phase III randomized, double-blind study of SUNITINIB (SU011248,SUTENT®) vs placebo in pts with progressive advanced WD pancreatic islet cell tumors

Sunitinib 37.5 mg daily starting dose, continuous daily regimen

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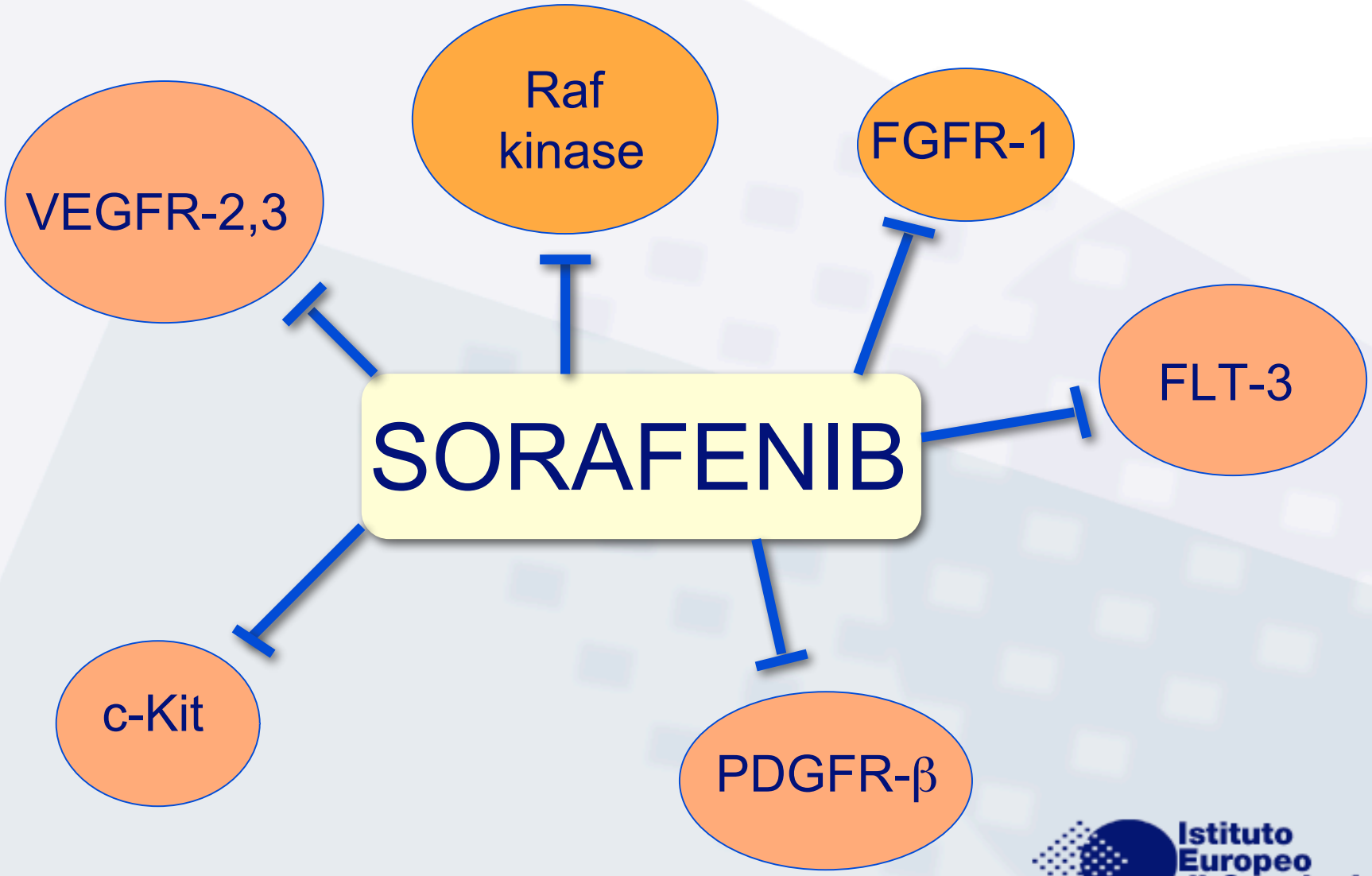
SORAFENIB (BAY 43-9006)



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MC044h, a phase II trial of sorafenib in patients (pts) with metastatic neuroendocrine tumors (NET): A Phase II Consortium (P2C) study

90 pts (50 intestinal, 43 pancreatic)

Sorafenib 400 mg po BID

10% PR in intestinal and 10% in islet cell
6m PFS in 8/20 intestinal and 14/23 islet cell

Grade 3-4 toxicity 43% of pts
- skin 20%
- GI 7%
- fatigue 9%

Hobday et al., ASCO 2007

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Sorafenib trials ongoing in NET

An international multicenter phase II study of Sorafenib in pts with progressive metastatic neuroendocrine tumors (Mayo Clinic)

Ongoing: Jun ’05 – 90 pts

Oral sorafenib twice daily on days 1-28

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Phase II trial of **temozolomide** plus thalidomide in NET

TMZ 150 mg/m2/day po 1 week on 1 week off + THAL 200 mg/day po

29 pts 28 WD e 1 PD

13 pretreated with chemo

RR 25% (pancreas 45%, pheocrom 33%, carcinoids 7%)

SD 68%

Response duration 13 m (2-31 m) – **PFS e OS not yet reached**

2-y surv 60%

Tox: 60% G3-4 lymphopenia (3 cases of opportunistic infections)

55% pts withdrew due to toxicity within an average of 8 months

Kulke et al. JCO Jan 2006

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Temozolomide as Monotherapy Is Effective in Treatment of Advanced Malignant Neuroendocrine Tumors

Sara Ekeblad, Clin Cancer Res 2007;13(10) May 15, 2007

36 pts with advanced NET (1 gastric, 7 thymic and 13 bronchial,12 pancreatic,1 paraganglioma, 1 foregut, and 1 cecal)

Temozolomide (200 mg/m2) for 5 days every 4 weeks

PR 14% SD 53%

Low MGMT = better response rate

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Temozolomide: metronomic?

The resistance to TMZ may be partially overcome by changing conventional to metronomic schedule

Temozolomide 50 mg/m2/d continuously

Verhoeff et al., AACR 2008

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Novel drugs in NET: open questions

- ✓Homogeneous populations
- ✓Status of disease at study entry
- ✓RECIST
- ✓PET with 5-HTTP or L-DOPA
- ✓Surrogate biomarkers
- ✓Combination of different biological agents
- ✓SS analogs as control arm (?)
- ✓Subgroup identification based on predictive factors
- ✓TNM classification

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