

# A Phase II Study of the Insulin-Like Growth Factor-1 Receptor (IGF-1R) Inhibitor, MK-0646, in Patients with Metastatic Well Differentiated Neuroendocrine Tumors



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## Background

Well-differentiated neuroendocrine tumors frequently express both IGFs and their receptors (IGFR), and, as such, are potentially dependent of autocrine stimulation by this pathway for growth and survival.<sup>1,2</sup>

Preclinical studies have implicated the IGF-1 receptor in the pathogenesis of neuroendocrine tumors.<sup>3</sup>

Therapy directed at the IGFR mediated signaling pathways has potential for conferring enhanced anti-tumor activity.

We evaluated the safety and efficacy of MK-0646, a fully human monoclonal antibody (mab) that blocks the insulin-like growth factor-1 receptor (IGF-1R), as monotherapy in patients with metastatic well differentiated neuroendocrine tumors.

## Methods

### Hypothesis:

A phase II study was performed in which patients received MK-0646 at a dose of 10 mg/kg i.v. over 1 hour every week. Archived pretreatment tumor tissue was obtained when possible for immunohistochemistry for IGF-1R, PTEN as well as beta-catenin

## Patient Characteristics

Patient Characteristics	Carcinoid (15)	Pancreatic NET (10)
Male	8 (53%)	7 (70%)
Female	7 (47%)	3 (30%)
Median Age, Years	64	59
Age Range, Years	83-37	70-48
ECOG PS		
0	4	4
1	11	6
Radiographic POD prior to disease entry	14	8
Time since initial diagnosis (in months)	132 (6-138)	49 (1-50)
Primary diagnosis		
Foregut: lungs, stomach	6	Gastrinoma 1
Midgut: small bowel, appendix	5	Insulinoma 1
Hindgut: colon, rectum	3	VIPoma 0
Unknown	1	Glucagonoma 1
Functioning	3	Other 0
Nonfunctioning	12	Nonfunctioning 7
Prior Therapies		
Prior Octreotide*	9 (60%)	9 (90%)
Prior Systemic Chemotherapy	6(40%)	4(40%)
Prior Surgery	11(73%)	3(30%)

\* 6 patients who were not on octreotide had somatostatin scintigraphy negative tumors

## Results: Efficacy

Parameter	Carcinoid Tumor (n = 15)		Pancreatic Tumor (n = 10)	
	No. of Patients	%	No. of Patients	%
Partial response	0	0	0	0
Progression Free Survival (in months)	2.7 (2-3)		4.2 (0.7-6.7)	
Median Overall Survival (in months)	10.5 (5.6-*)		*	
Stable disease	2	15%	5	50%
Progressive disease	11	85%	5	50%

\*too few events to calculate

## Results: Toxicity Thought to be Possibly Related to MK-0646

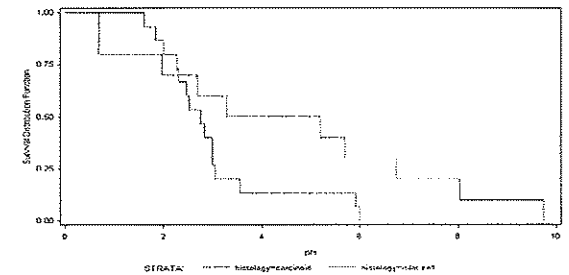
Toxicity Attributed to MK-0646	Incidence
Gr 1 Fatigue	3
Gr 2 Fatigue	2
Gr 2 Hypersensitivity Reaction	1
Gr 1 Skin Rash	1
Gr 1 Polyuria	1
Gr 1 Metallic Taste	1
Gr 3 Lipase	1
Gr 1 Muscle ache	1
Gr 1 Diarrhea	1

## Hyperglycemia Thought to be Possibly Related to MK-0646

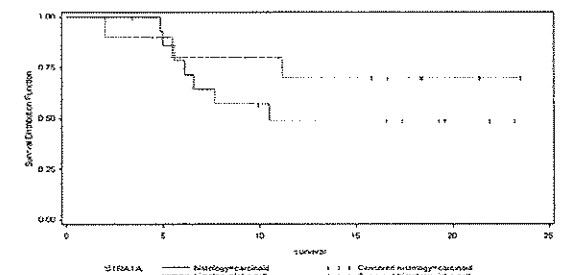
Hyperglycemia	Incidence n=25
Grade 1	24 (15/24 had Gr 1 at baseline)
Grade 2	17 (2/17 had Gr 2 at baseline)
Grade 3	7
Grade 4	1

References: von Wichert G, Jehle P, Hoefflich A, et al. Insulin-like Growth Factor-I Is an Autocrine Regulator of Chromogranin A Secretion and Growth in Human Neuroendocrine Tumor Cells. *Cancer Research* 2000;60:4573-81.; 2. Hopfner M, Baradari V, Heuther A, et al. Insulin-like growth factor receptor 1 is a promising target for novel treatment approaches in neuroendocrine gastrointestinal tumours. *Endocrine Related Cancer* 2006;13:135-49.; 3. Margier S, Strauss O, Strowski ea. Insulin-like growth factor-1 increases intracellular calcium concentration in human primary neuroendocrine pancreatic tumor cells and a pancreatic neuroendocrine tumor cell line (BON-1) via R-type Ca<sup>2+</sup> channels and regulates chromogranin a secretion in BON-1 cells. *Neuroendocrinology*.

## Progression free survival



## Survival



		IGF-1a membrane/cytoplasmic staining intensity	Beta-catenin
1	carcinoid	1	normal
2	PNET	0	didn't work
3	carcinoid	0	normal
4	carcinoid	1	normal
5	carcinoid	0	normal
6	carcinoid	0	normal
7	carcinoid	0	normal
8	carcinoid	0	normal
9	carcinoid	0	normal
10	PNET	1	normal
11	PNET	0	normal
12	PNET	0	normal
13	carcinoid	1	normal

\*PTEN stains failed; attempt at repeat is ongoing

## Conclusions

MK-0646 alone was well tolerated with the exception of hyperglycemia that was manageable with antihyperglycemic medications,

No meaningful activity was seen. No further single agent studies are planned.