

SUTENT[®] (sunitinib malate) Capsules

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Oncologic Drugs Advisory Committee Meeting

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FDA White Oak Campus
Silver Spring, MD

Proposed Indication

- SUTENT[®] is indicated for the treatment of unresectable pancreatic neuroendocrine tumors (pNET)

Topics for Today's Discussion

Mace Rothenberg, MD

Head of Clinical Development & Medical Affairs
Pfizer Oncology
New York, NY

- Introduction and Background
- Evaluation of SUTENT® in Pancreatic NET

Matthew Kulke, MD

Director, Carcinoid & Neuroendocrine Tumor Program
Dana-Farber/Brigham and Women's Cancer Center
Boston, MA

- Clinical Aspects of Pancreatic NET
- Perspectives on Treatment Options

Additional Experts

Eric Raymond, MD, PhD

Chef de Service, Hôpital Beaujon, Clichy France

- Phase 3 Study Principal Investigator

Robert Maki, MD, PhD

Senior Faculty in Medicine, Mount Sinai Medical Center, New York, NY

- Phase 3 Independent DMC Chair

Gary Koch, PhD

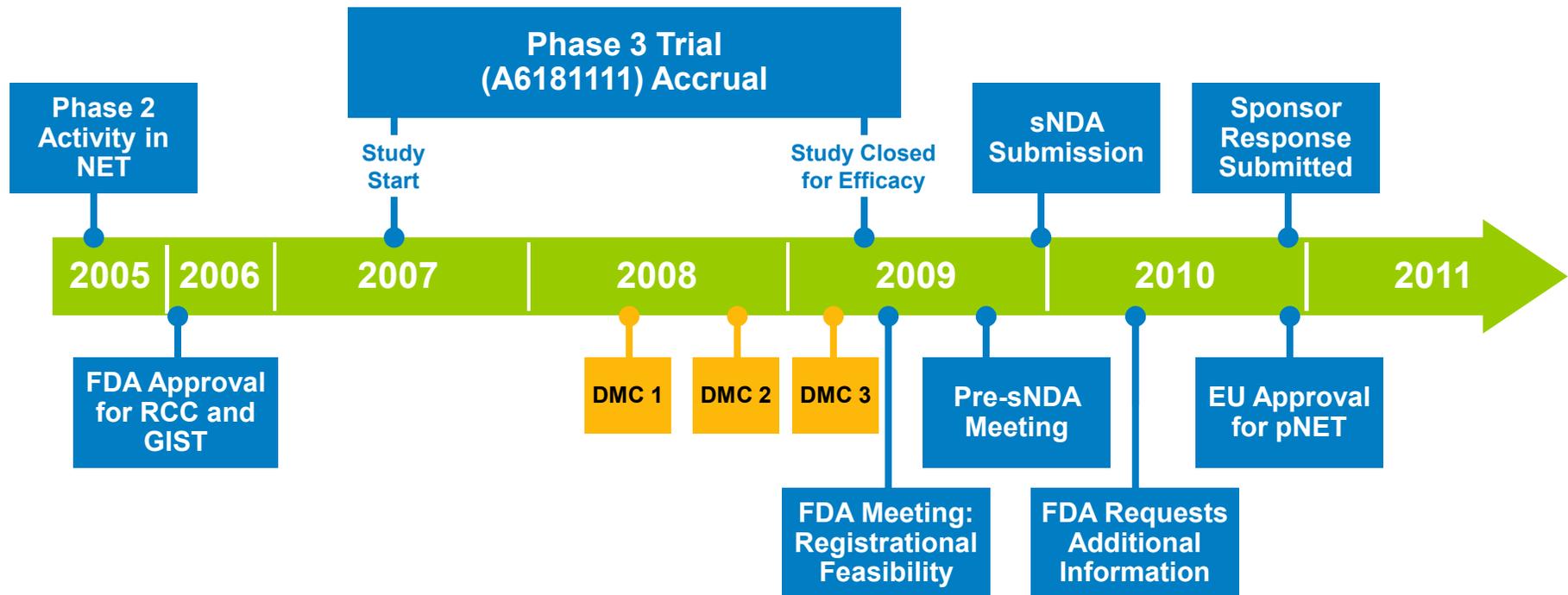
Professor of Biostatistics, University of North Carolina, Chapel Hill, NC

- Statistical Consultant

History

- SUTENT[®] (sunitinib malate) was approved in 2006 for the treatment of:
 - Advanced renal cell carcinoma (RCC)
 - Gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate
- Over 100,000 patients have been treated globally

Development Timeline



Basis for sNDA

- Favorable Benefit/Risk profile
- ~6-month improvement in median PFS vs. placebo
- OS and ORR also favored sunitinib
- No new or unexpected adverse events

Pancreatic Neuroendocrine Tumors

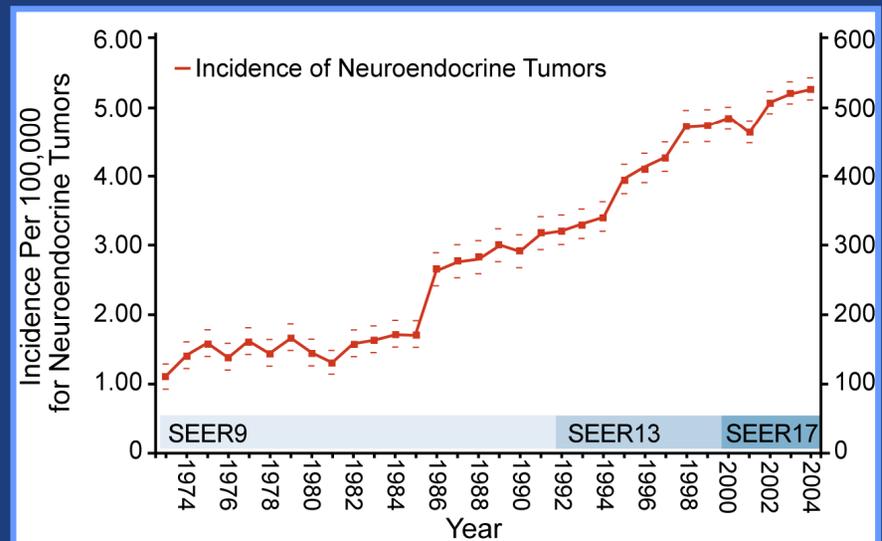
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Neuroendocrine Tumors: Incidence and Prevalence

- Early estimates of incidence 1–2 per 100,000 population¹
- Diagnosed incidence increasing, likely due to improved awareness, classification, and diagnostic modalities²
- Prevalence estimated to be >100,000 in United States

Incidence per 100,000 for Neuroendocrine Tumors



1. Modlin et al. *Cancer* 2003; 97: 934-59

2. Yao JC et al. *J Clin Oncol.* 2008;26:3063-3072

Cases selected from SEER database (1973 to 2004) using International Classification of Disease for Oncology histology codes 8150 to 8157, 8240 to 8246, and 8249

Neuroendocrine Tumors: Histologic Classification

Differentiation	Grade	Mitotic Count	KI-67 index	ENETS, WHO
Well Differentiated *	Low (G1)	< 2 per 10 HPF	≤ 2%	Neuroendocrine Tumor, Grade 1
	Intermediate (G2)	2–20 per 10 HPF	3–20%	Neuroendocrine Tumor, Grade 2
Poorly Differentiated	High (G3)	>20 per 10 HPF	>20%	Neuroendocrine Carcinoma, Grade 3, Small Cell
				Neuroendocrine Carcinoma Grade 3, Large Cell

* This includes moderately differentiated

Neuroendocrine Tumors

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graph TD; NET[Neuroendocrine Tumors] --> PN[Pancreatic Neuroendocrine Tumors (Islet cell tumors)]; NET --> CT[Carcinoid Tumors];
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Pancreatic Neuroendocrine Tumors (Islet cell tumors)

- 6% of all NET (SEER)¹
- 22–28% of all NET (Institutional Databases)^{2,3}

Carcinoid Tumors

1. Yao JC et al. *J Clin Oncol*. 2008;26:3063-3072
2. Pape UF et al. *Endocrine-Related Cancer* 2008; 15: 1083-97
3. Ter-Minassian et al. Proc ASCO 2010

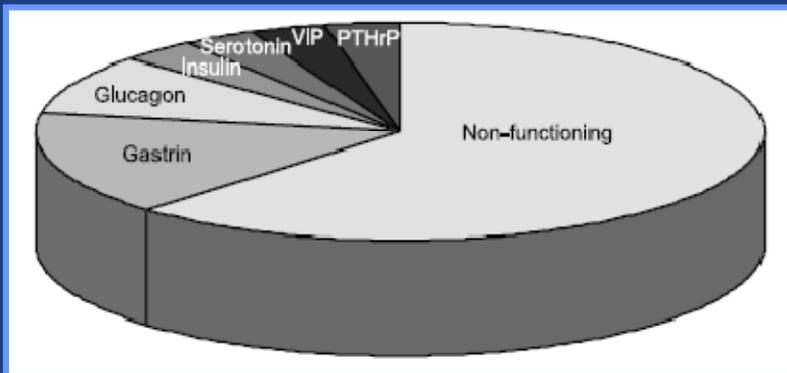
Pancreatic NET: Classification by Hormone Secretion

- 30–40% associated with symptoms of hormone hypersecretion
- 60–70% “Non-functioning”

Necrolytic Migratory Erythema
Associated with Glucagonoma



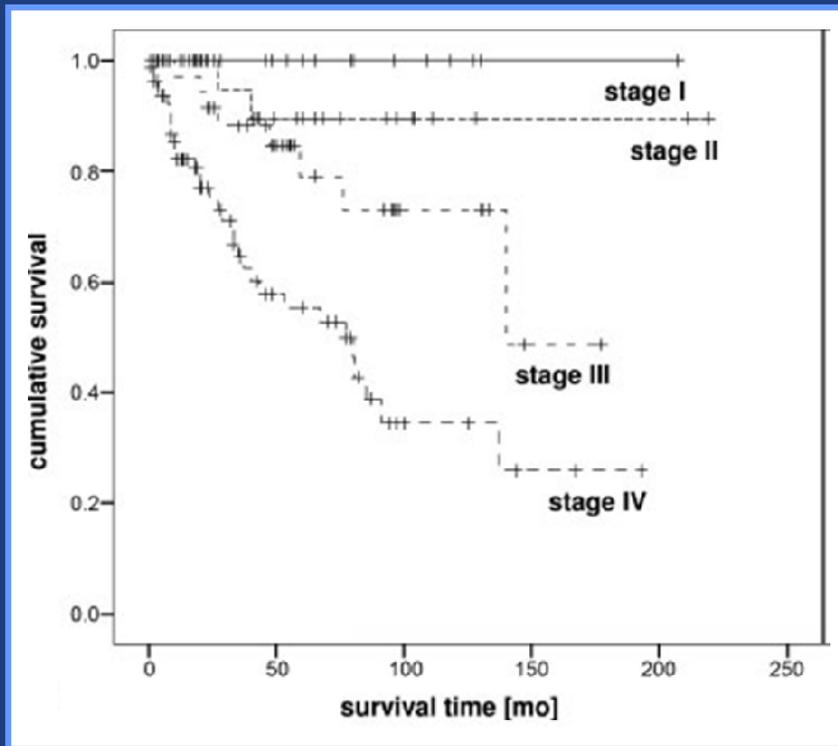
Tumor Subtypes



Management of Localized Disease: Surgical Resection

- Enucleation or distal pancreatectomy rather than Whipple resection may be possible depending on tumor size/location
- Prognosis good when complete resection performed

Neuroendocrine Tumors: Survival by Stage



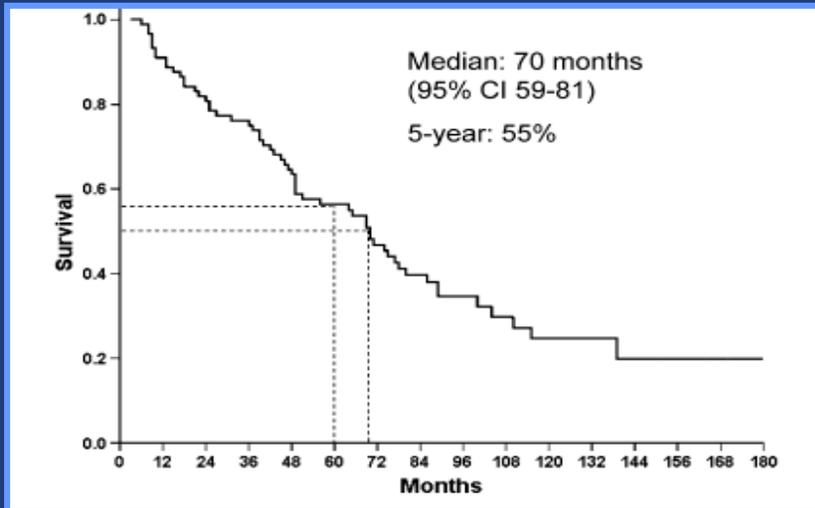
- Survival shown from institutional series of pancreatic (n=131), duodenal (n=23) and gastric (n=48) NET

- Proportion alive at 10 years:

- Stage I: 100%
- Stage II: 89%
- Stage III: 73%
- Stage IV: 34%

Metastatic Pancreatic NET: Overall Survival

Median Survival in Single-institution
Database (n=90): 5.8 Years



Kaplan-Meier Curve of Overall Survival
From Diagnosis of Metastases¹

1. Strosberg et al. *Pancreas* 2009; 38: 255-58

2. Yao et al. *J Clin Oncol* 2008; 26: 3063-72

Median Survival in SEER: 2 Years

Median Survival (months)²

Site	Localized	Regional	Distant
Appendix	>360	>360	27
Cecum	135	107	41
Colon	261	36	5
Duodenum	107	101	57
Gastric	154	71	13
Liver	50	14	12
Lung	227	154	16
Pancreas	136	77	24
Rectum	290	90	22
Small bowel	111	105	56
Thymus	110	68	40

Metastatic and/or Unresectable Pancreatic NET: Current Treatment Options

- Somatostatin analogs
- Hepatic-directed therapies
- Cytotoxic chemotherapy

Somatostatin Analogs in Pancreatic NET

- Effective in treating symptoms of hormone hypersecretion:
 - Indicated for treatment of VIPoma
 - Commonly used for symptoms of glucagonoma, gastrinoma
- PROMID study showed improved TTP associated with octreotide in midgut carcinoid tumors but did not include pancreatic NET¹
- Antiproliferative effect of somatostatin analogs in pancreatic NET has not, to date, been demonstrated

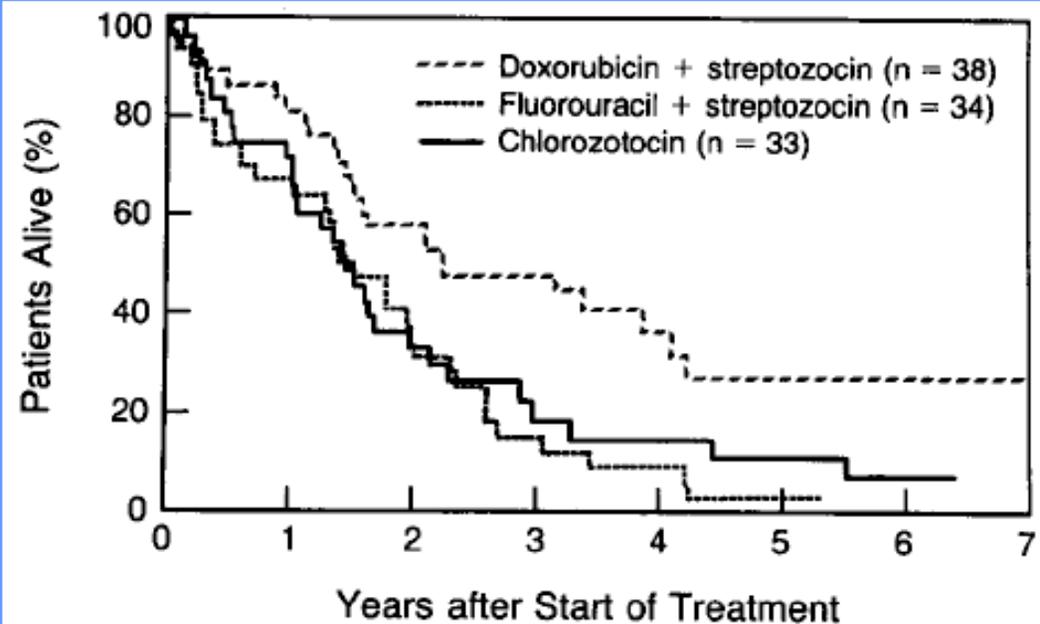
Hepatic-directed Therapy

- Hepatic-directed approaches used in patients with liver metastases and limited extra-hepatic disease
 - Hepatic resection for patients with limited number of liver metastases
 - Embolization, chemoembolization, or radioembolization for unresectable liver metastases
 - Transplant (rare)
- Little randomized data evaluating effect of hepatic-directed therapy on PFS or OS

Streptozocin-based Therapy for Pancreatic NET

- Approved by FDA for advanced pancreatic NET (1982)
- Streptozocin/Doxorubicin associated with response rate of 69% and survival benefit in randomized study (1992)¹
- Many physicians are nevertheless reluctant to use streptozocin-based therapies

Median Survival 2.2 years (STZ/Dox)
vs. 1.5 yrs (STZ/5FU)



1. Moertel et al. *N Engl J Med* 1992; 326: 519-23

Streptozocin-based Therapy: Challenges

- Response rates in pancreatic NET tumors not as high as initially reported: overall tumor response rate 6–39% in retrospective series¹⁻³
- Cumbersome 5-day infusion schedule
- Toxicity: renal, hematologic, nausea/vomiting

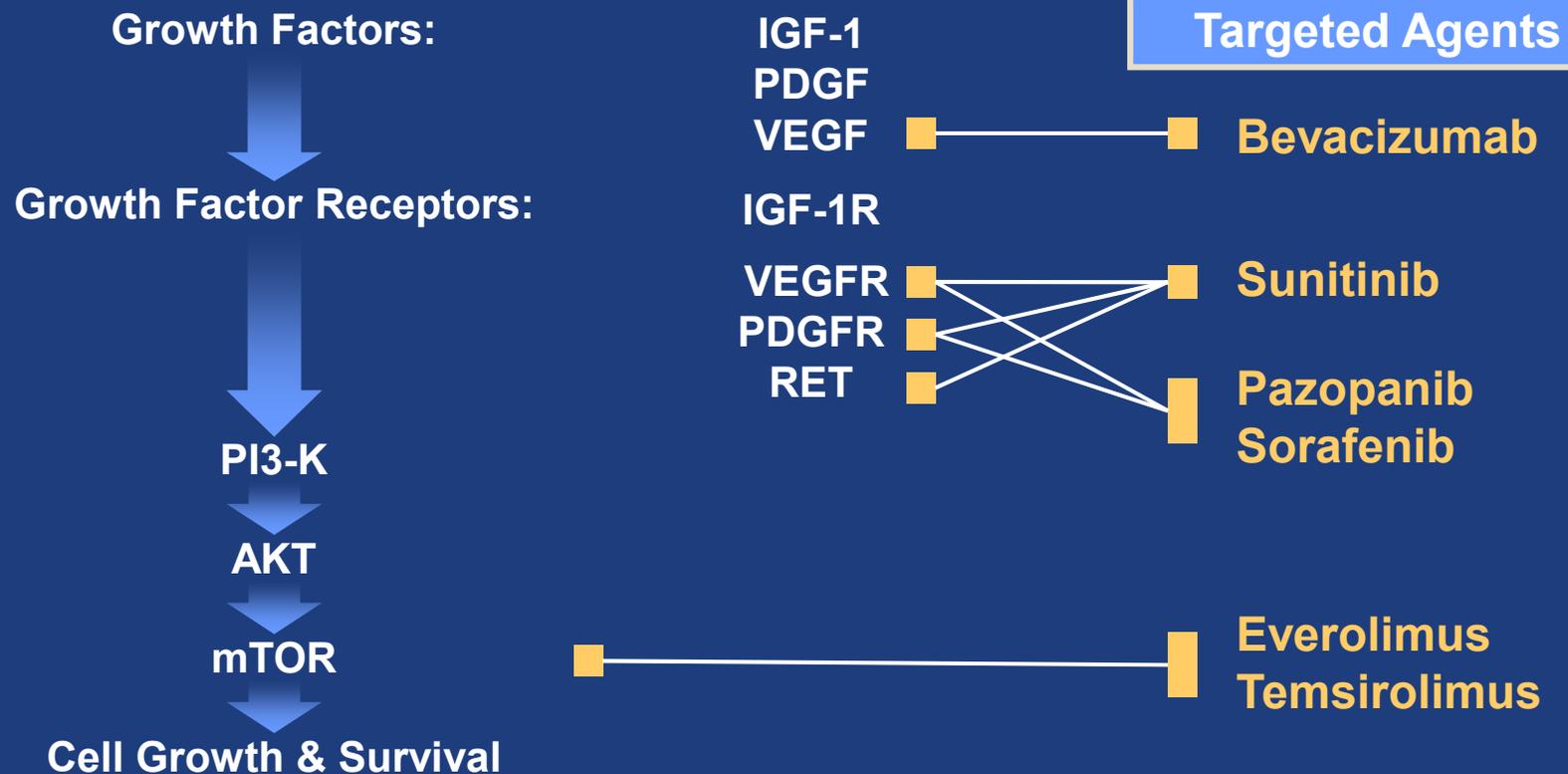
AE ¹	Streptozocin + 5-FU (%)		Streptozocin + Doxorubicin (%)	
	Any	Severe	Any	Severe
Creatinine elevation³	29	7	44	2
Chronic renal insuff.	7		4	
Leukopenia²	56	25	57	5
Vomiting	81	41	80	20

1. Cheng et al. *Cancer* 1999; 86: 944-8; 2. McCollum et al. *Am J Clin Oncol* 2004; 27: 485-8; 3. Kouvaraki et al. *J Clin Oncol* 2004; 22: 4762-71; 4. For vomiting and leukopenia the results are for the first course of therapy only. The values for creatinine elevation are for all courses. Only the patients who had toxic reactions are included; 5. Leukopenia: any = $<4 \times 10^9$ cells/liter, severe = $<2 \times 10^9$ cells/liter; 6. Creatine elevation: any >0.03 mg/dl, severe >1.0 mg/dl. Adapted from Moertel 1992.

Available Treatment Options

- Somatostatin analogs for symptoms of hormone hypersecretion; effect on tumor proliferation not demonstrated
- Hepatic-directed therapy may be helpful, but is limited to patients with hepatic-predominant disease
- Cytotoxic chemotherapy used in selected patients due to side effect profile
- *Clear need for new treatment options for patients with advanced pancreatic NET*

Novel Therapies: Targeting the RTK/PI3-K/AKT/mTOR Pathway in NET



NCI Neuroendocrine Tumor Task Force Clinical Trials Planning Meeting Recommendations

- Biologically targeted therapies in NET associated with modest RECIST-defined response rates but high rates of disease stabilization
- Overall survival may not be a practical primary endpoint for advanced NET due to the variability of survival durations and likelihood of multiple post-study therapies
- Progression-free survival recommended as the primary endpoint for phase III studies in NET

Conclusions

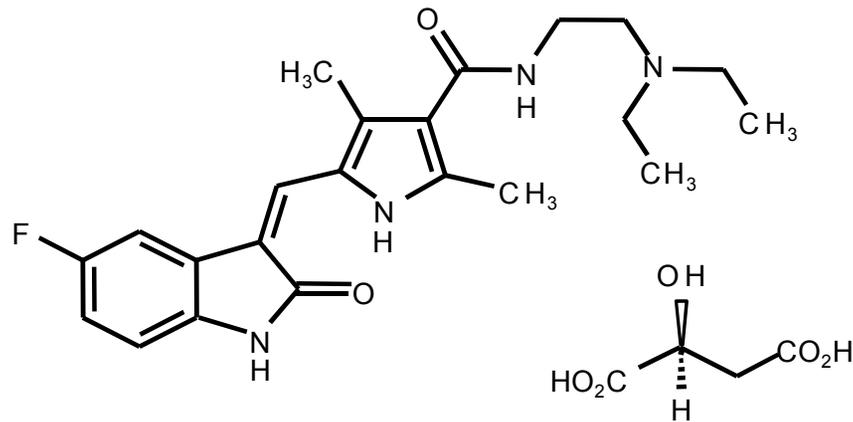
- Clear need for new therapeutic options for patients with advanced pancreatic NET
- For biologically targeted agents, PFS is an appropriate endpoint in trials for NET
- Targeted therapies attractive because:
 - Favorable safety profile, especially compared to current treatment
 - Availability of randomized data supporting their use

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Sunitinib Malate

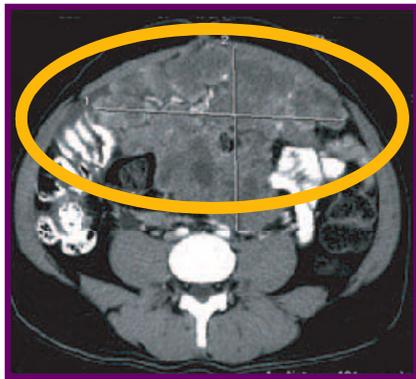


- Sunitinib is a receptor tyrosine kinase inhibitor of VEGFR2, VEGFR3, VEGFR1, PDGFR α , PDGFR β , KIT, FLT-3, CSF-1R, and RET¹
- Anti-angiogenic and anti-tumor agent

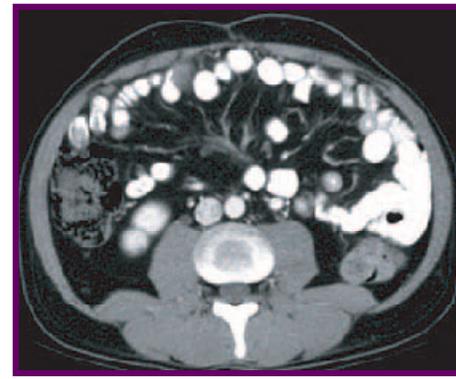
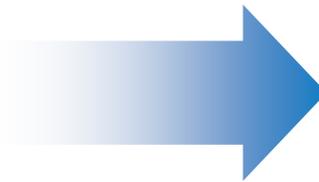
1. Mendel DB, et al. *Clin Cancer Res* 2003;9:327–37

Early Signals of Sunitinib Activity in NET

- Preclinical activity in RIP1-Tag2 transgenic model of pancreatic NET¹
- Phase 1 clinical activity in patients with NET²
 - One PR confirmed in rectal NET
 - One minor response/stable disease was observed in NET of mediastinum



Baseline



12 Weeks

1. Bergers et al. *Science* 1999; 284: 808-11
2. Faivre S, et al. *J Clin Oncol.* 2006;24(1):25-35

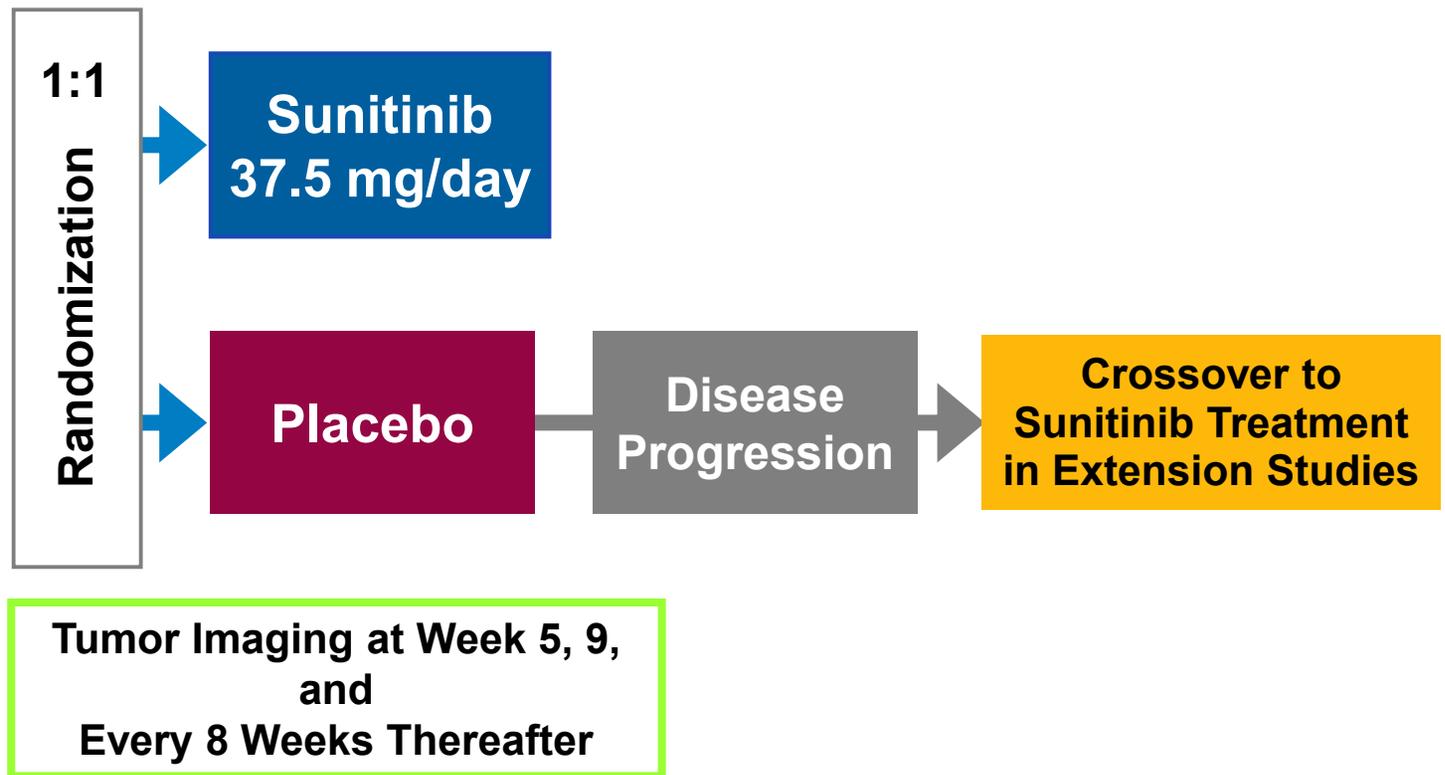
Phase 2 Experience with Sunitinib in NET

	N (%)	
Pancreatic NET Cohort	N=66	95% CI
Best objective response		
PR	11 (16.7%)	
SD ≥6 months	37 (56.1%)	
Overall objective response rate (RECIST) %	16.7%	(8.6 – 27.9)
Median OS	Not Reached	
Median follow-up for OS	12.5 months	(12.0, 15.5)

Phase 3 Study Design

**N = 340 patients
(Planned)**

- Unresectable pancreatic NET
- Well-differentiated
- Pre-study progression by RECIST



Major Entry Criteria

■ Inclusion Criteria

- Well-differentiated pancreatic islet cell tumor (histologically or cytologically proven)
- Documented, RECIST-defined disease progression within the past 12 months
- Not amenable to treatment with curative intent (surgery, radiation or combined modality)
- ECOG performance status 0 or 1

■ Exclusion Criteria

- Current anticancer treatment, other than somatostatin analogs
- Prior treatment with a tyrosine kinase inhibitor or an anti-VEGF angiogenesis inhibitor

Study Objectives

- Primary endpoint
 - Progression-Free Survival (PFS)
- Secondary endpoints
 - Overall survival (OS)
 - Objective response rate (ORR)
 - ◆ Duration of response (DR)
 - ◆ Time to tumor response (TTR)
 - Patient-reported outcomes (PROs)
- Safety and tolerability

Statistical Design

- Sample size assumptions
 - Hypothesis to test $\geq 50\%$ improvement ($HR \leq 0.67$) in median PFS
 - 340 patients required to observe 260 PFS events with 90% power
 - Two-sided, unstratified log-rank test at a significance level of 0.049
- Analysis of primary endpoint (PFS) based on
 - Intent-to-treat (ITT) population
 - Investigator overall tumor assessment
- Planned analyses
 - Interim analysis at 130 events for safety, futility and efficacy (stop for $p < 0.0031$)
 - Final analysis at 260 events

Third DMC Meeting – February 2009

- Data reviewed on 154 patients (73 PFS events)
 - 49 PFS events on placebo
 - 24 PFS events on sunitinib
- Observed HR for PFS was 0.397 (95% CI: 0.243 – 0.649)
 - Conditional probability to stop with $p < 0.0031$ after 130 events was 99.9% based on HR=0.397
 - Conditional probability to stop with $p < 0.0031$ after 130 events was 91% based on HR=0.649
- 15 deaths on placebo and 5 deaths on sunitinib
- 28 SAEs on placebo and 20 SAEs on sunitinib

Outcome: Study Closure

- DMC recommended that the study be closed based upon the differences in PFS, deaths and SAEs
- DMC recommendation accepted by Sponsor
- Study was closed in April 2009

Evolution of Data: Number of PFS Events Over Time

PFS Events				
	DMC1			
Sunitinib	5			
Placebo	15			

Evolution of Data: Number of PFS Events Over Time

PFS Events				
	DMC1	DMC2		
Sunitinib	5	16		
Placebo	15	34		

Evolution of Data: Number of PFS Events Over Time

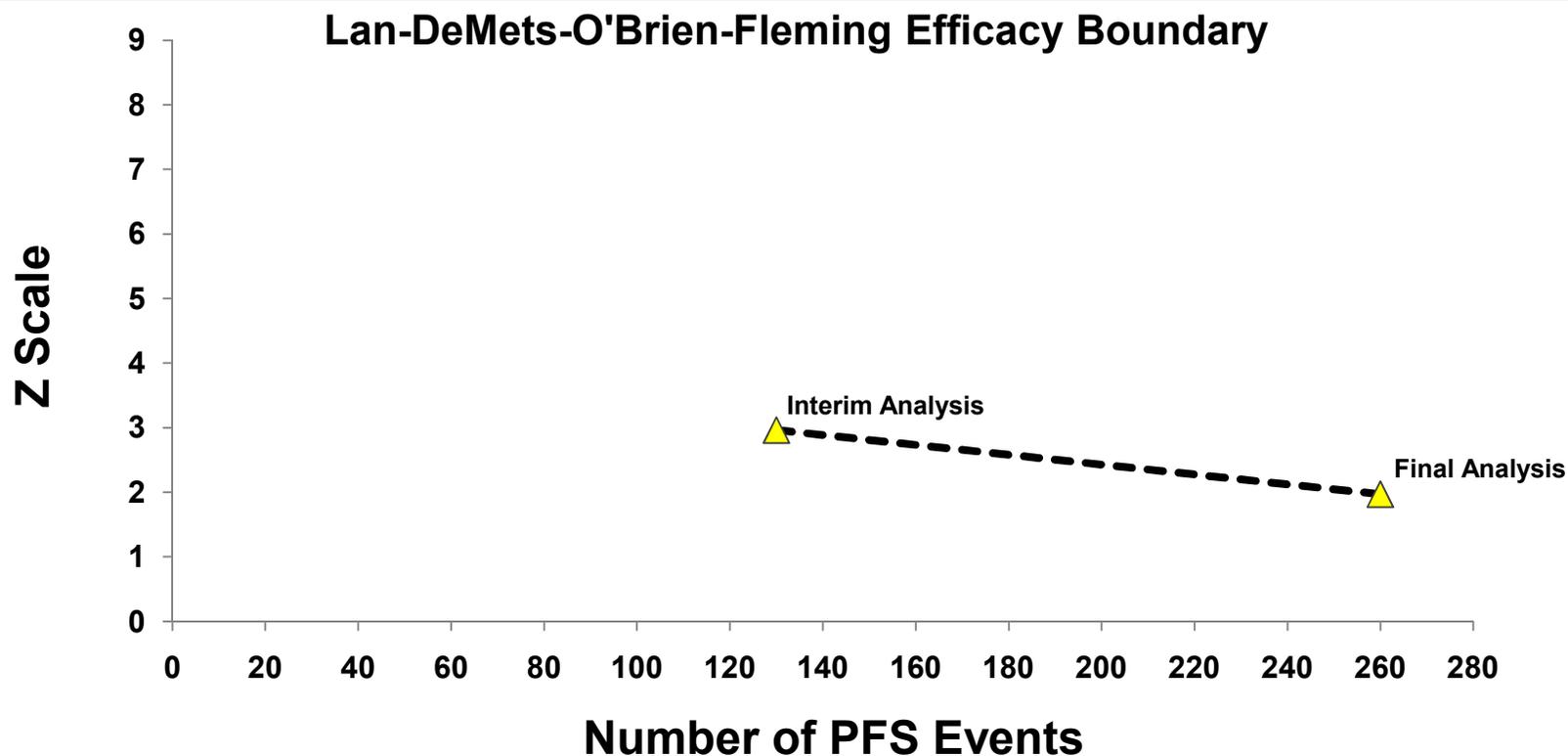
PFS Events				
	DMC1	DMC2	DMC3	
Sunitinib	5	16	24	
Placebo	15	34	49	

Evolution of Data: Number of PFS Events Over Time

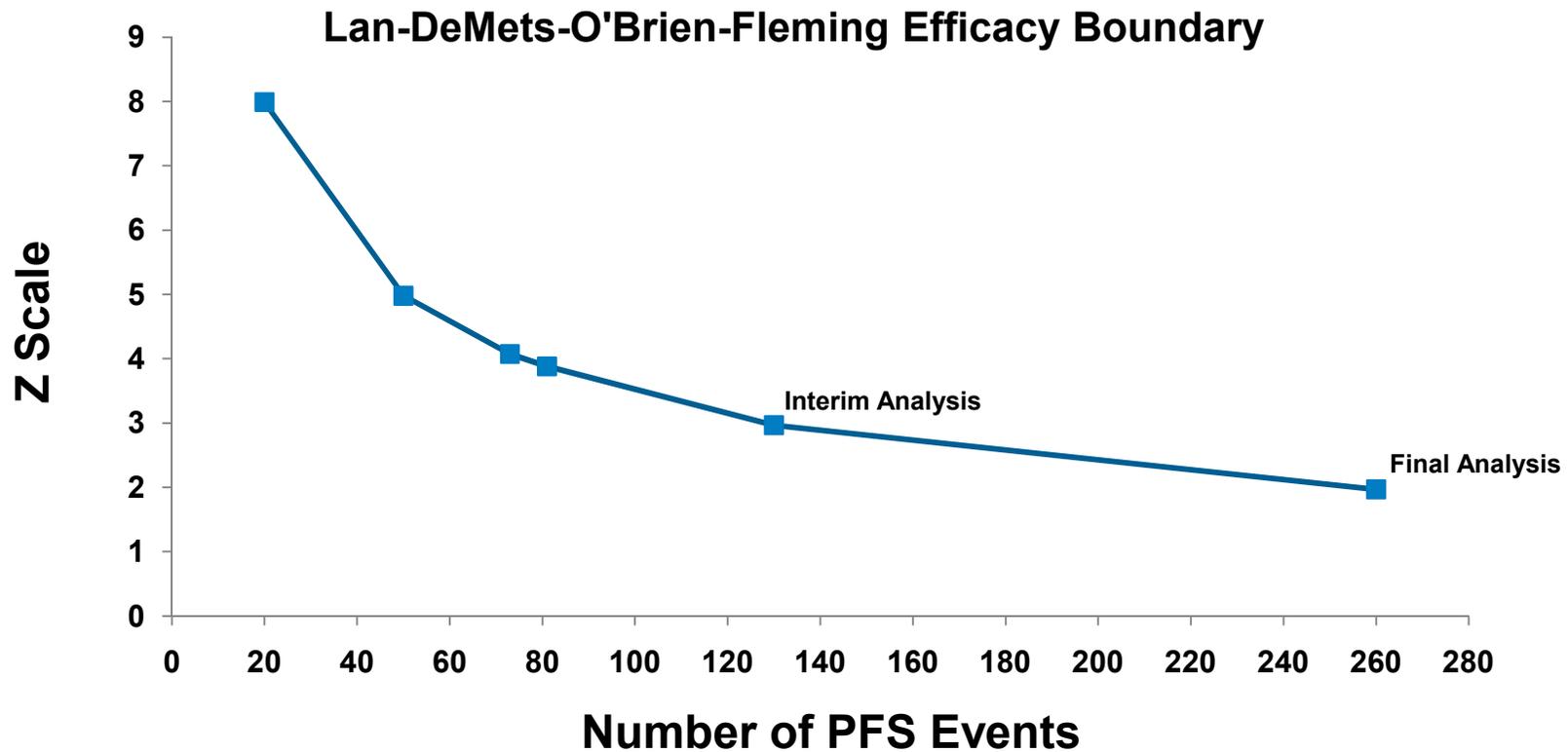
PFS Events				
	DMC1	DMC2	DMC3	Final
Sunitinib	5	16	24	30
Placebo	15	34	49	51

Between the data cutoff for the DMC and study closure, 17 patients were randomized

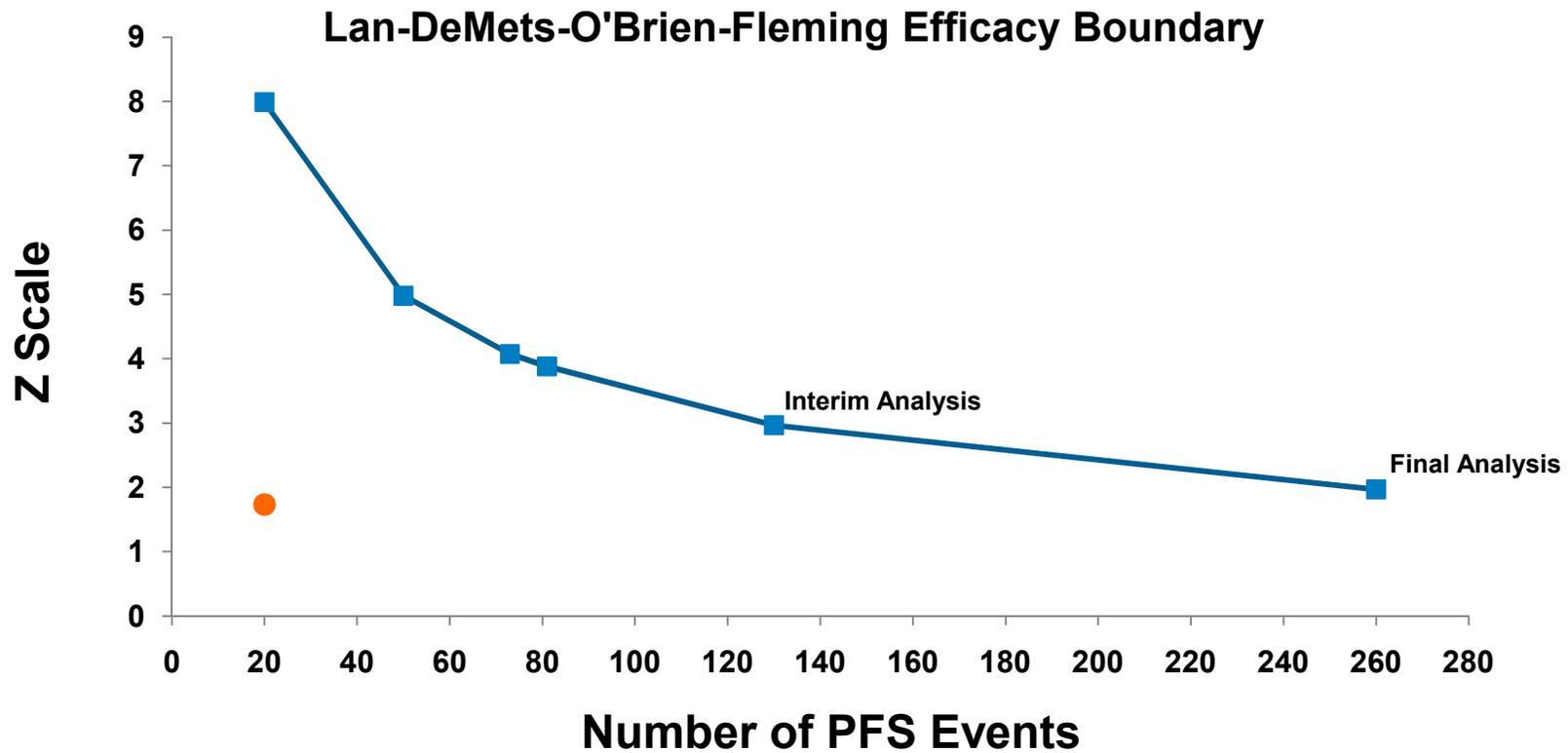
Evolution of Data: Relationship to Early Stopping Boundary



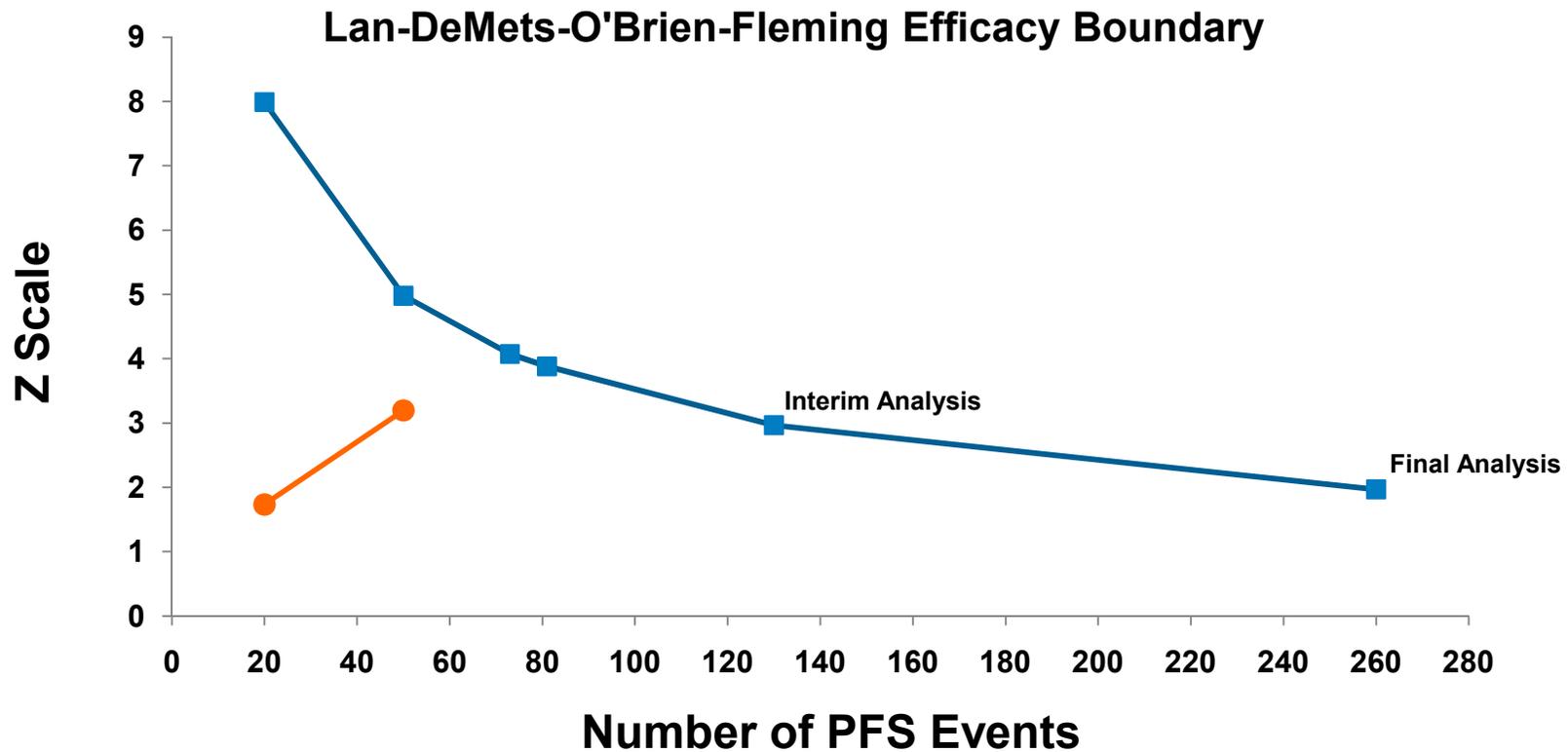
Evolution of Data: Relationship to Early Stopping Boundary



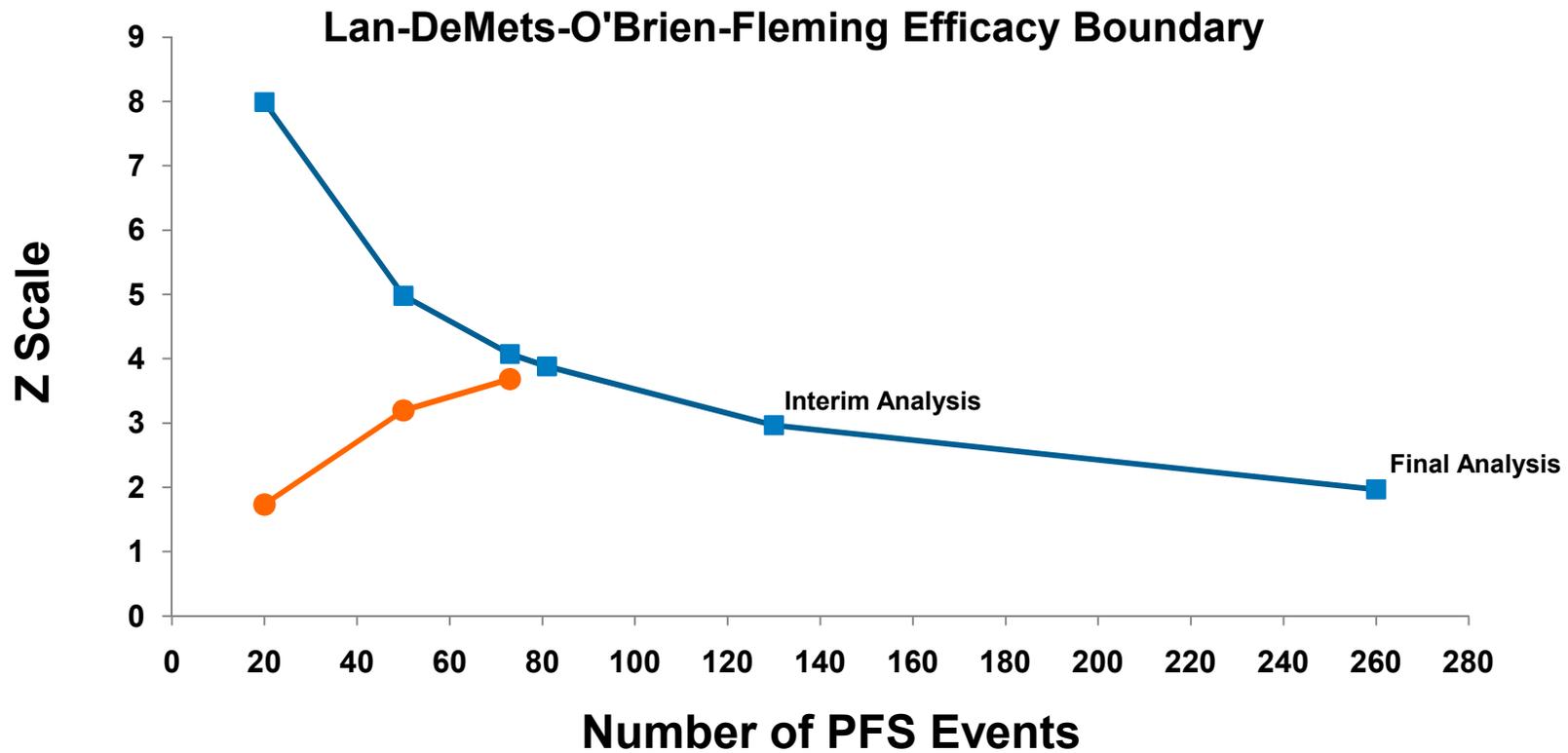
Evolution of Data: Relationship to Early Stopping Boundary



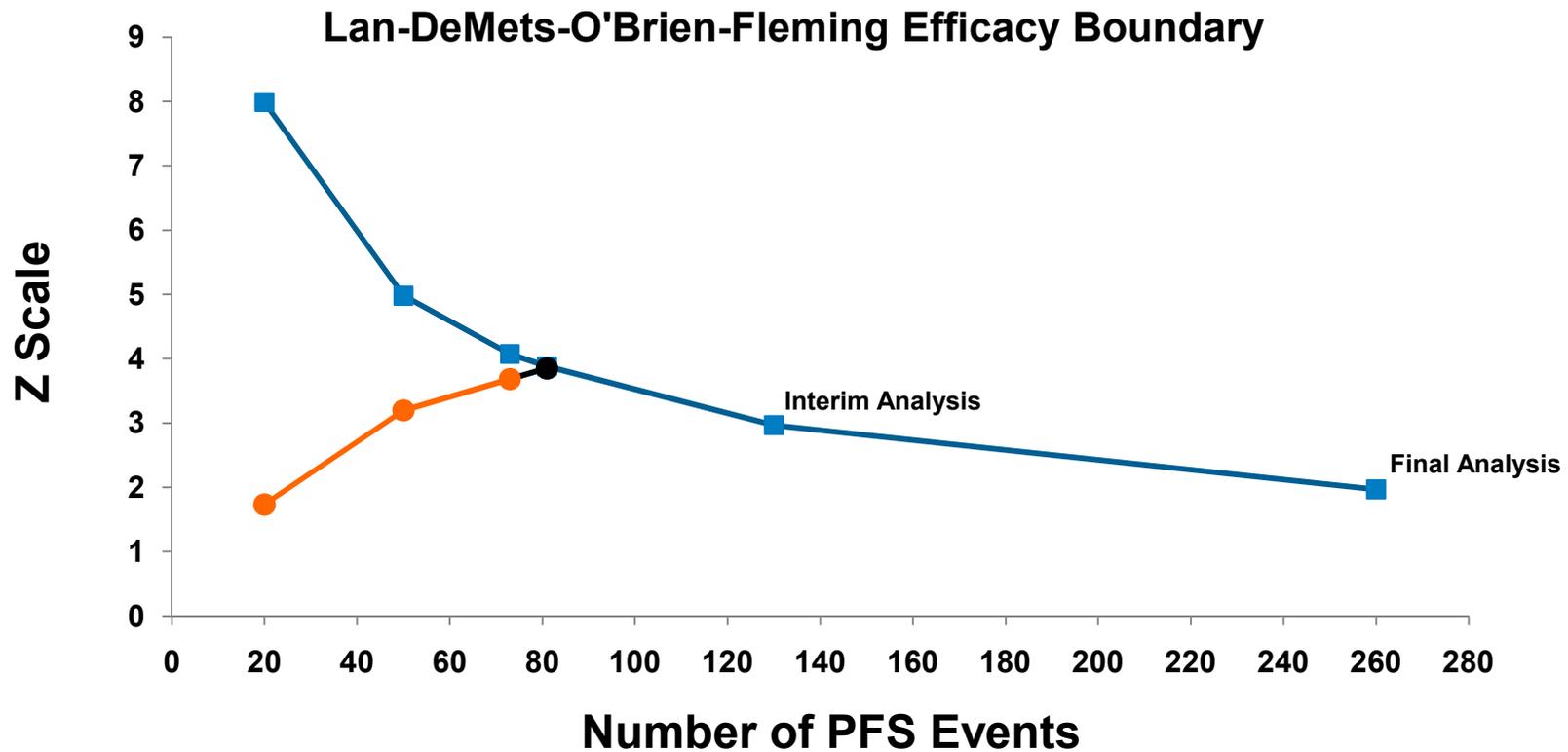
Evolution of Data: Relationship to Early Stopping Boundary



Evolution of Data: Relationship to Early Stopping Boundary

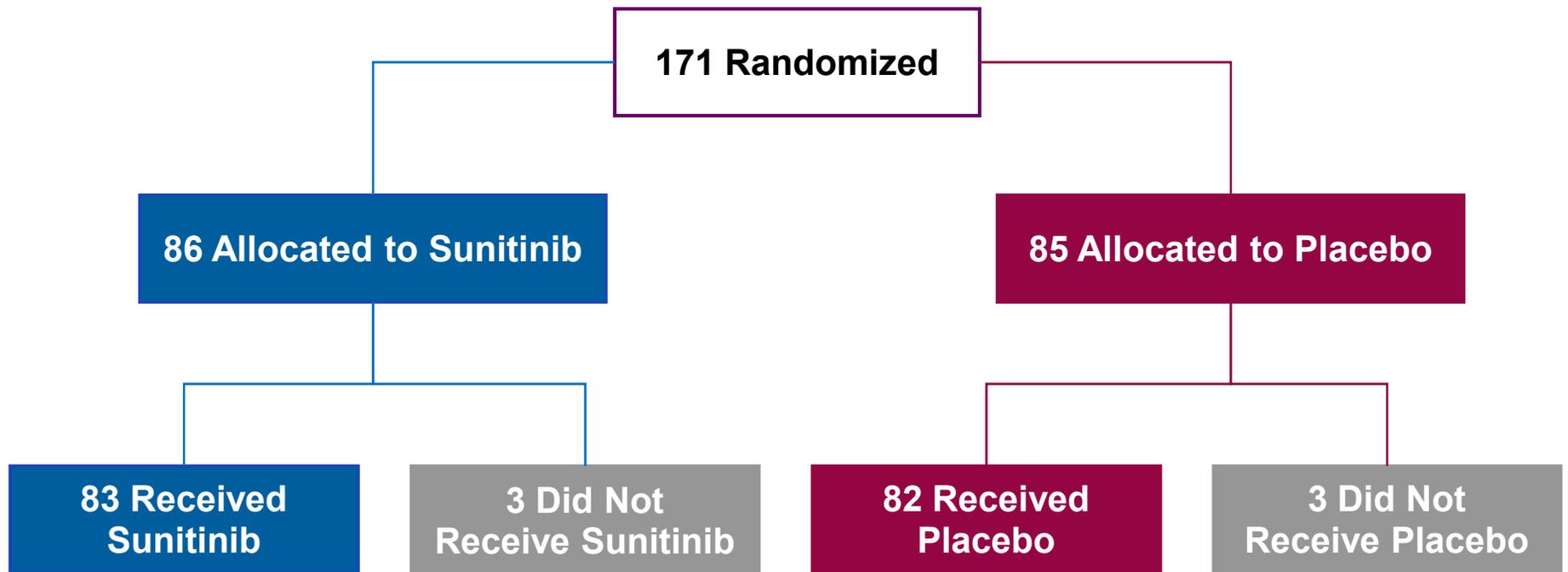


Evolution of Data: Relationship to Early Stopping Boundary



Between the data cutoff for the DMC and study closure, 17 patients were randomized for a total of 171 patients

Patient Enrollment and Allocation



Demographic and Baseline Characteristics

N (%)	Sunitinib N=86	Placebo N=85
Median (range) age, years	56 (25–84)	57 (26–78)
≥65 years	22 (25.6%)	23 (27.1%)
Sex		
Male	42 (48.8%)	40 (47.1%)
Female	44 (51.2%)	45 (52.9%)
ECOG performance status		
0	53 (61.6%)	41 (48.2%)
1	33 (38.4%)	43 (50.6%)
2	0	1 (1.2%)
Race		
White	48 (55.8%)	53 (62.4%)
Asian	13 (15.1%)	10 (11.8%)
Other/unspecified*	25 (29.1%)	22 (25.9%)
Prior systemic treatments	57 (66.3%)	61 (71.8%)

*Per local regulations, ethnicity data were not routinely collected in France

Tumor and Disease Characteristics at Baseline

N (%)	Sunitinib N=86	Placebo N=85
Presence of distant metastases	82 (95.3%)	80 (94.1%)
Non-functioning	42 (48.8%)	44 (51.8%)
Functioning	25 (29.1%)	21 (24.7%)
Gastrinoma	9 (10.5%)	10 (11.8%)
Glucagonoma	3 (3.5%)	2 (2.4%)
Insulinoma	2 (2.3%)	2 (2.4%)
VIPoma	0	2 (2.4%)
Somatostatinoma	1 (1.2%)	0
Other/multi-secretory/unknown	10 (11.6%)	5 (5.9%)
Not specified	19 (22.1%)	20 (23.5%)
Median (range) time since diagnosis, years	2.4 (0.1–25.6)	3.2 (0.1–21.3)

Analysis of PFS

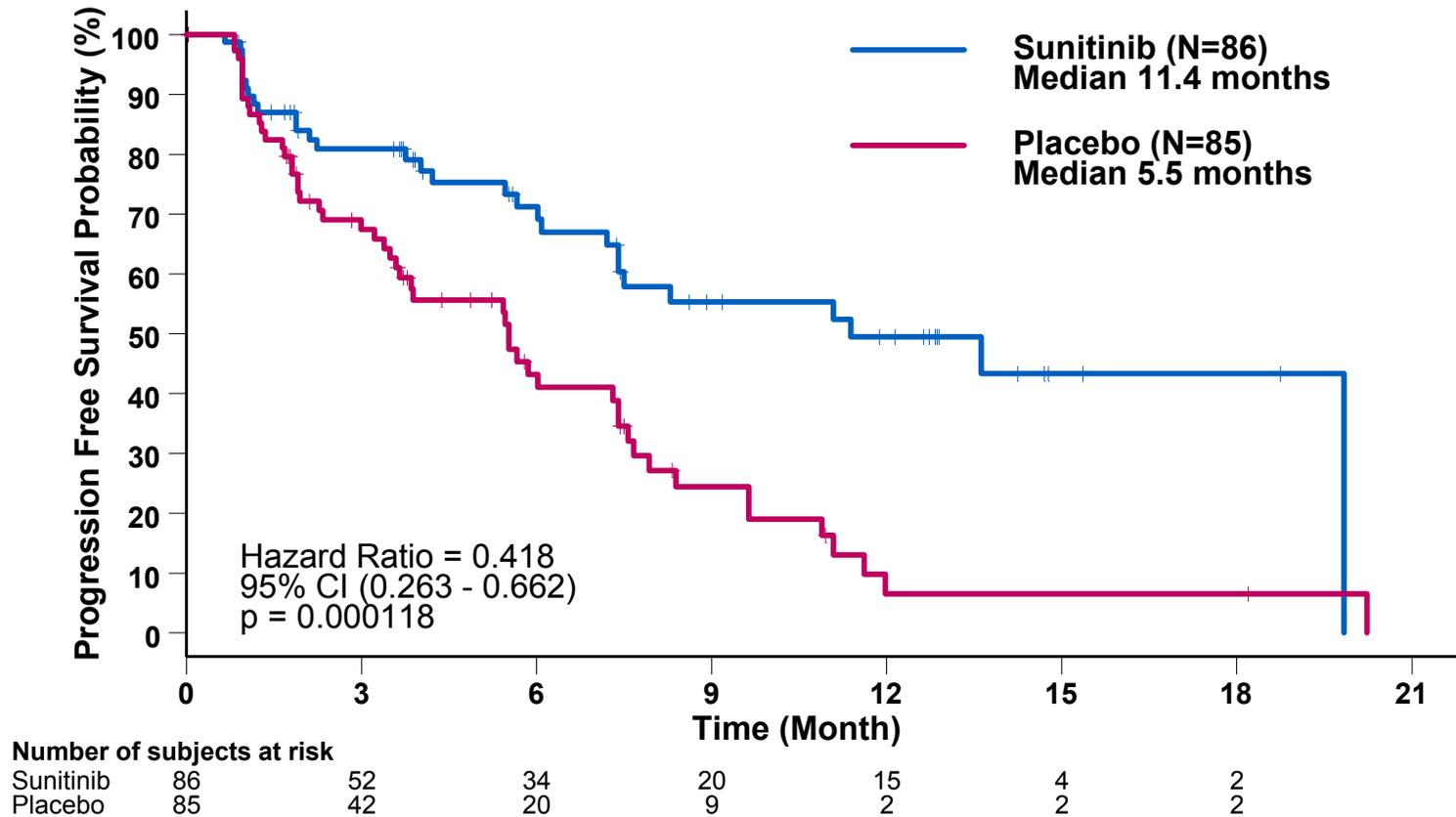
PFS Was Calculated Using 3 Different Methods to Determine Disease Progression Using RECIST and Identical Censoring Rules

Analysis Method	Determination of Progression	Reason for Analysis
1. Investigator Overall Tumor Assessment	■ Investigators' assessment of tumor measurements	Study specified
2. Algorithmic Assessment	■ Sponsor's analysis of investigators' tumor measurements	FDA request
3. Blinded, Independent Central Review	■ Central radiological review of CT/MRI scans	FDA request

Progression-Free Survival (Investigator Overall Tumor Assessment)

N (%)	Sunitinib N=86	Placebo N=85
Number with PFS event	30 (34.9%)	51 (60.0%)
Type of event		
Disease progression	27 (31.4%)	48 (56.5%)
Death without progression	3 (3.5%)	3 (3.5%)
Kaplan-Meier estimate of median PFS (95% CI)	11.4 months (7.4, 19.8)	5.5 months (3.6, 7.4)
Hazard ratio (95% CI)	0.418 (0.263, 0.662)	
p-value	0.000118	
Number censored	56 (65.1%)	34 (40.0%)

Progression-Free Survival (IOTA)



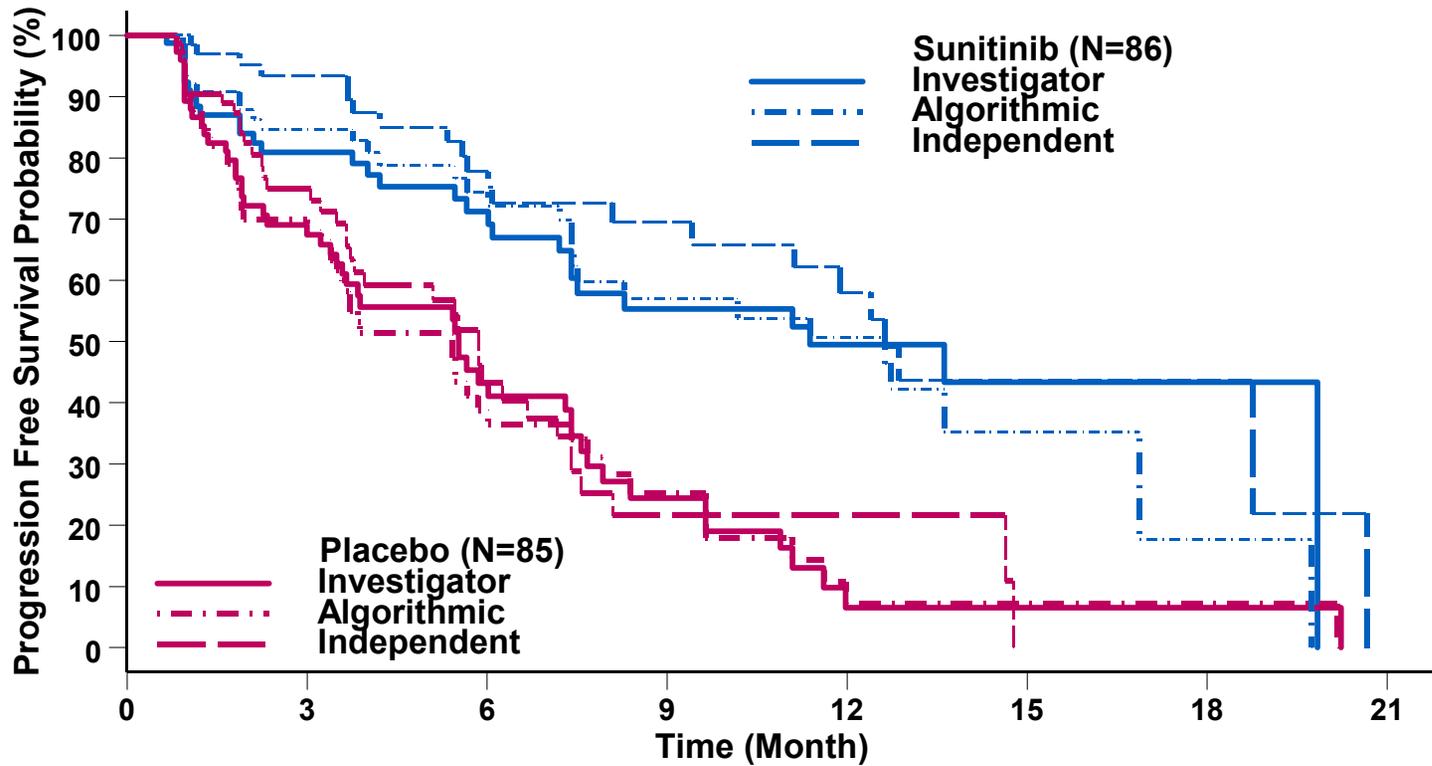
Progression-Free Survival (Algorithmic Assessment)

N (%)	Sunitinib N=86	Placebo N=85
Number with PFS event	30 (34.9%)	49 (57.6%)
Type of event		
Disease progression	27 (31.4%)	46 (54.1%)
Death without progression	3 (3.5%)	3 (3.5%)
Kaplan-Meier estimate of median PFS (95% CI)	12.6 months (7.4, 16.9)	5.4 months (3.5, 6.0)
Hazard ratio (95% CI)	0.401 (0.252, 0.640)	
p-value	0.000066	
Number censored	56 (65.1%)	36 (42.4%)

Progression-Free Survival (Blinded Independent Central Review)

N (%)	Sunitinib N=86	Placebo N=85
Number with PFS event	22 (25.6%)	39 (45.9%)
Type of event		
Disease progression	19 (22.1%)	34 (40.0%)
Death without progression	3 (3.5%)	5 (5.9%)
Kaplan-Meier estimate of median PFS (95% CI)	12.6 months (11.1, 20.6)	5.8 months (3.8, 7.2)
Hazard ratio (95% CI)	0.315 (0.181, 0.546)	
p-value	0.000015	
Number censored	64 (74.4%)	46 (54.1%)

Progression-Free Survival (Comparison of Estimates)

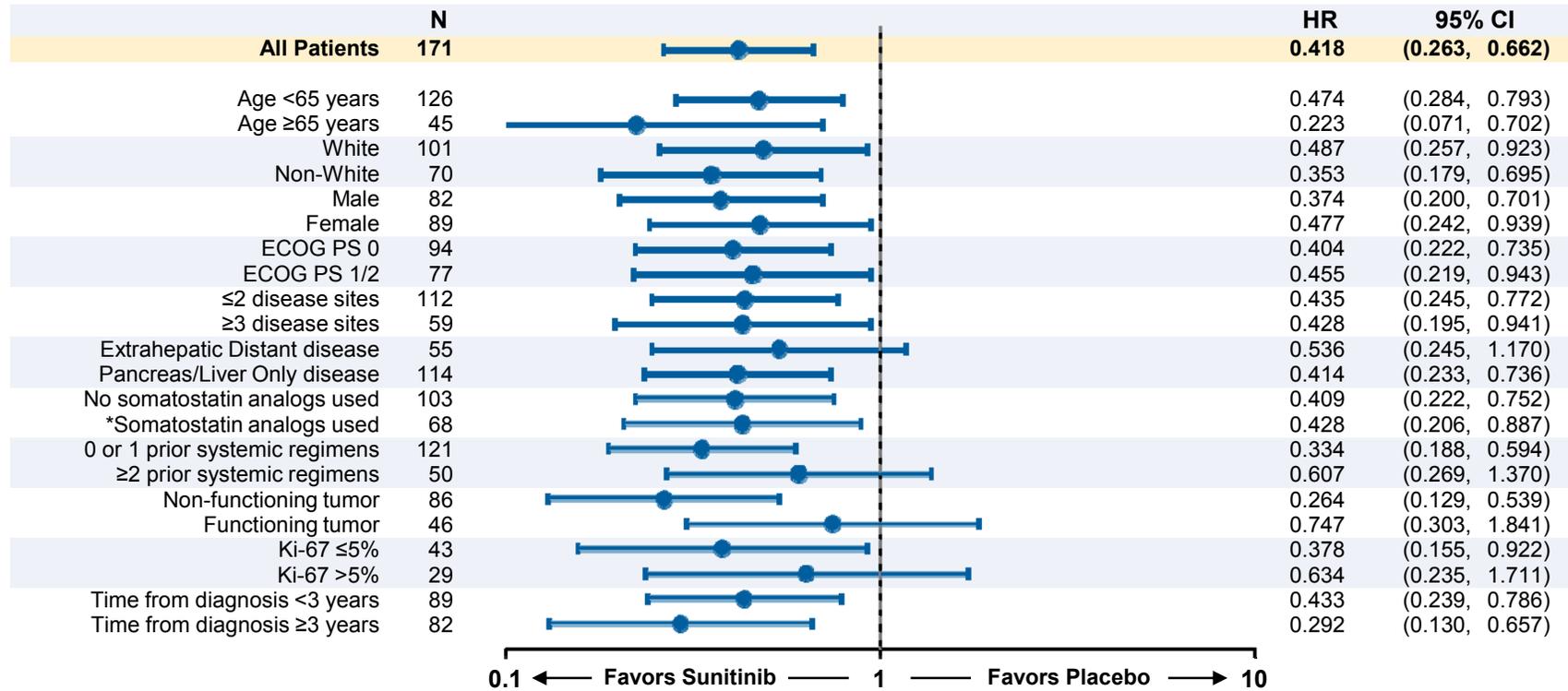


Confidence Intervals for HR of PFS

Hazard Ratio	Confidence Level	LCL, UCL
0.418 (IOTA)	95.0%	0.263, 0.662
	99.7%	0.208, 0.839
0.401 (Algorithmic)	95.0%	0.252, 0.640
	99.7%	0.198, 0.813
0.315 (BICR)	95.0%	0.181, 0.546
	99.7%	0.136, 0.722

LCL – lower confidence limit; UCL – upper confidence limit

Subgroup Analysis



* Includes all patients receiving somatostatin analogs at any time before and/or concomitant with study treatment.
 ECOG PS, Eastern Cooperative Oncology Group Performance Score

Multivariate Analysis Adjusting for Selected Baseline Factors

Factors Included in Model

- + Time From Diagnosis (≥ 3 vs. < 3 years)
- + ECOG (0 vs. 1/2)
- + Number of Disease Sites (< 3 vs. ≥ 3)
- + Liver-Directed Therapy (no vs. yes)
- + Disease Extent (Pancreas/Liver Only vs. Extrahepatic Distant Mets)

Multivariate Cox Model	Hazard Ratio	95% CI	P value [†]
Treatment Effect (sunitinib vs. placebo)	0.400	0.248, 0.647	0.000185

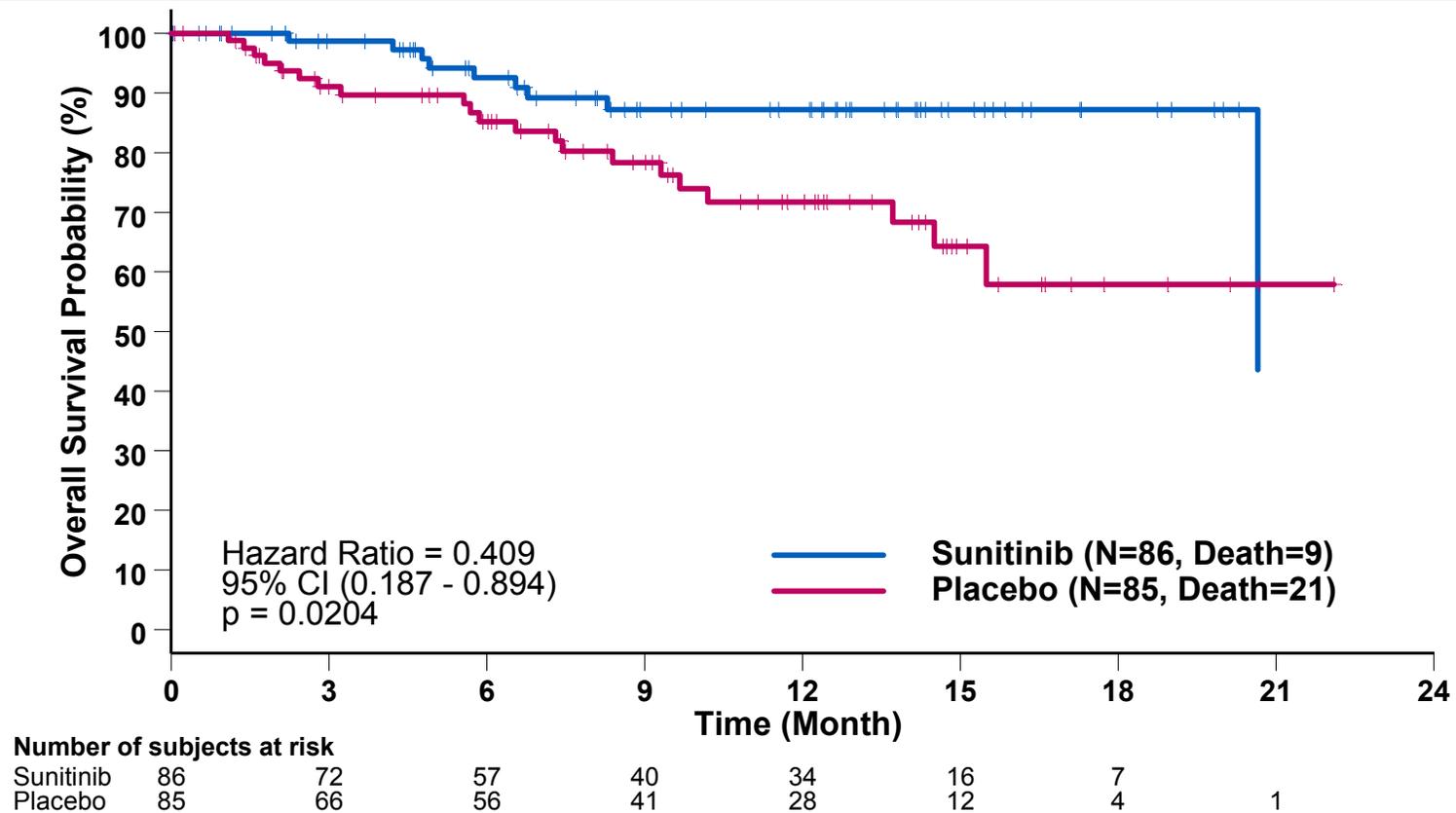
[†] Wald Chi-Square test

All baseline factors, including age, race, gender, ECOG PS, no. of disease sites, distant metastases, SSA use, no. of prior systemic therapies, tumor function status and time from diagnosis were used in multivariate analyses

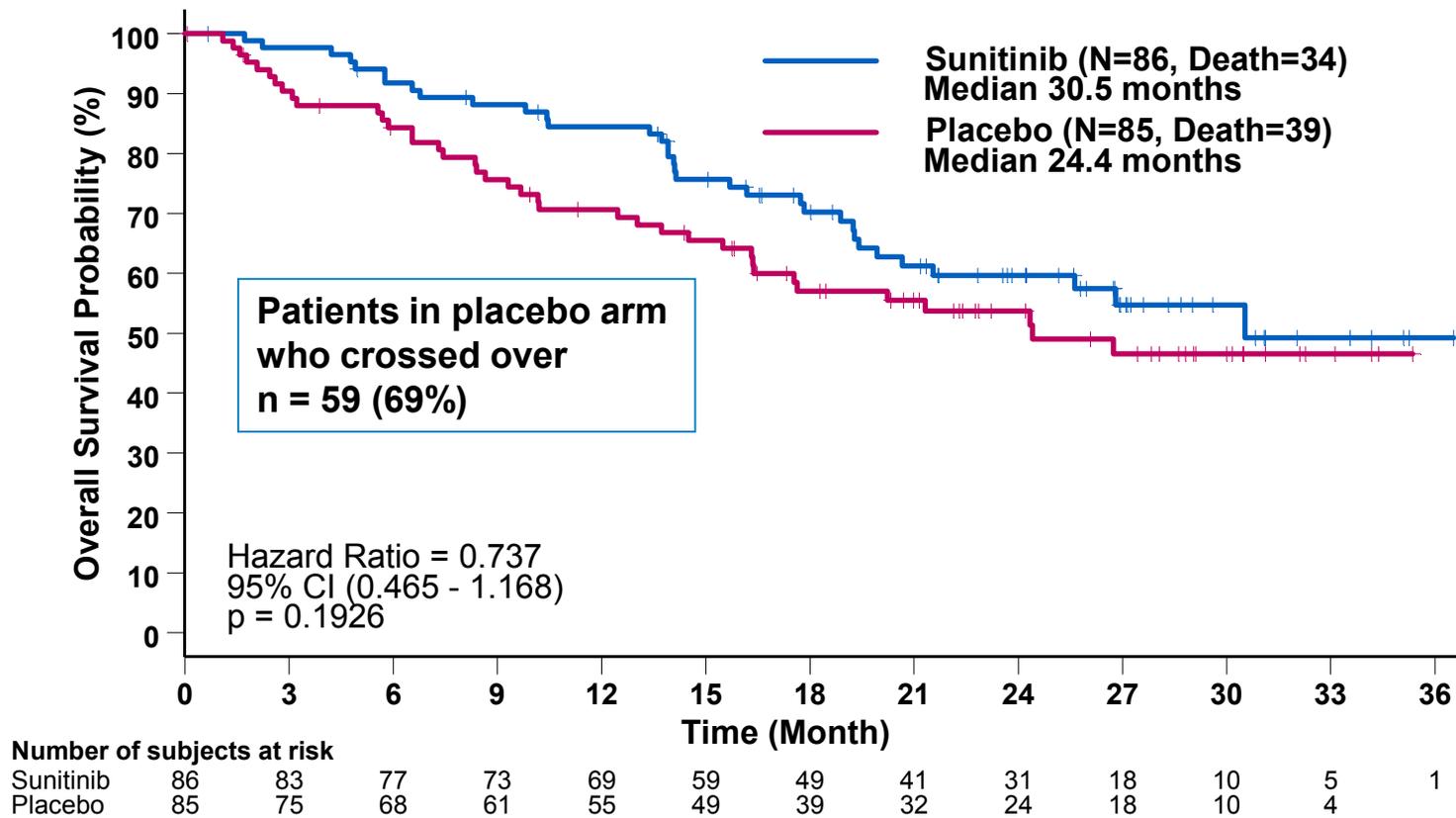
Overall Survival (April 2009)

N (%)	Sunitinib N=86	Placebo N=85
Number of deaths	9 (10.5%)	21 (24.7%)
Patients censored	77 (89.5%)	64 (75.3%)
Reason for censoring		
Alive and in follow-up at data cutoff	75 (87.2%)	61 (71.8%)
Withdrew consent for additional follow-up	2 (2.3%)	1 (1.2%)
Lost to follow-up	0	2 (2.4%)
Survival probability at 6 months (95% CI)	92.6% (86.3, 98.9)	85.2% (77.1, 93.3)
Hazard ratio (95% CI)	0.409 (0.187, 0.894)	
p-value	0.0204	

Overall Survival (April 2009)



Overall Survival (June 2010)



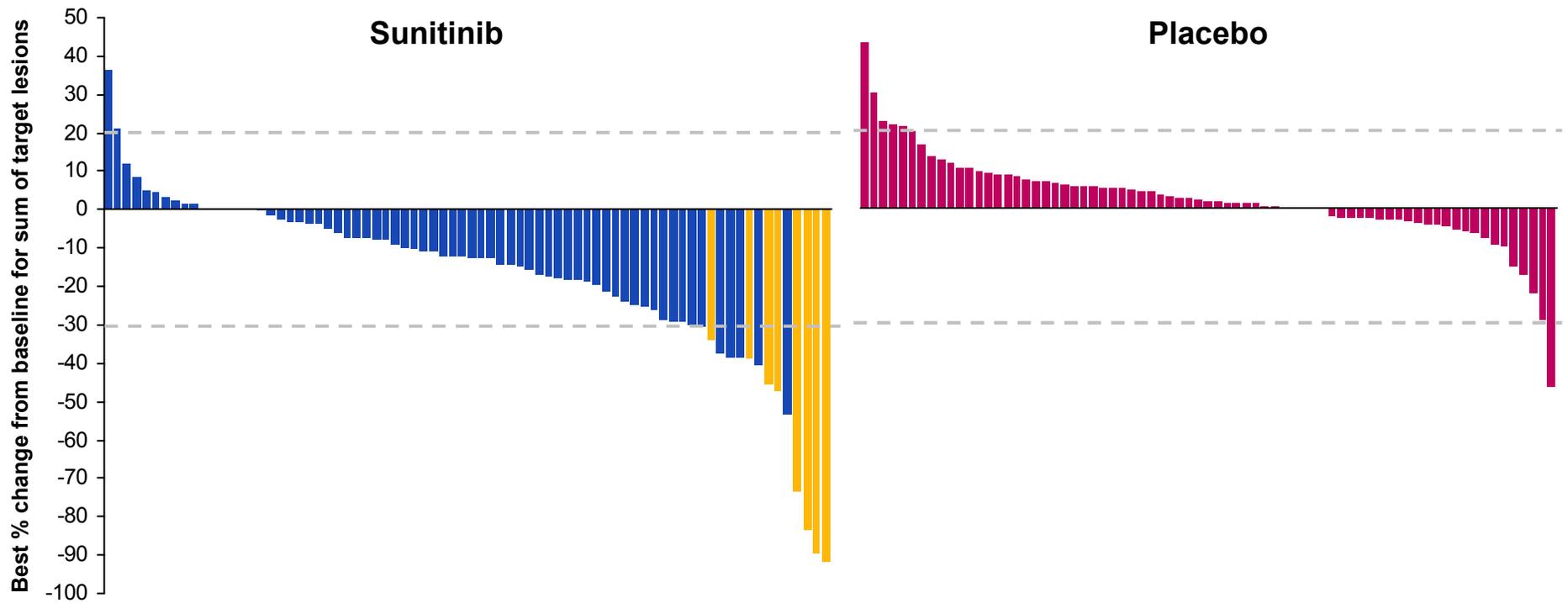
Objective Response Rate

N (%)	Sunitinib N=86	Placebo N=85
Best observed RECIST response		
Complete response	2 (2.3%)	0
Partial response	6 (7.0%)	0
Stable disease/no response	54 (62.8%)	51 (60.0%)
Objective progression	12 (14.0%)	23 (27.1%)
Not evaluable	12 (14.0%)	11 (12.9%)
Objective response rate (95% CI)	9.3% (3.2, 15.4)	0
p-value	0.0066	
Median time to response (range)	3.1 months	NA
Median response duration (range)	8.1+ months	NA

NA, not applicable

ORR using IOTA

Tumor Shrinkage in Patients Receiving Sunitinib



Confirmed Response
Confirmed responses were those that persisted on repeat imaging ≥ 4 weeks after initial documentation

Sunitinib Safety Profile in Pancreatic NET

- All Causality Adverse Events (AEs)
- Grade 3/4 all Causality AEs
- Serious Adverse Events (SAEs)
- Other SAEs of Interest
- Deaths
- Safety Conclusions

All Causality Adverse Events (All Grades)

All Grade Adverse Events (≥20% in Either Arm), N (%)	Sunitinib N=83	Placebo N=82
Total	82 (98.8%)	78 (95.1%)
Diarrhea	49 (59.0%)	32 (39.0%)
Nausea	37 (44.6%)	24 (29.3%)
Asthenia	28 (33.7%)	22 (26.8%)
Vomiting	28 (33.7%)	25 (30.5%)
Fatigue	27 (32.5%)	22 (26.8%)
Hair color changes	24 (28.9%)	1 (1.2%)
Neutropenia	24 (28.9%)	3 (3.7%)
Abdominal pain	23 (27.7%)	26 (31.7%)
Hypertension	22 (26.5%)	4 (4.9%)
Hand-foot syndrome	19 (22.9%)	2 (2.4%)
Anorexia	18 (21.7%)	17 (20.7%)
Stomatitis	18 (21.7%)	2 (2.4%)
Dysgeusia	17 (20.5%)	4 (4.9%)
Epistaxis	17 (20.5%)	4 (4.9%)

All Causality Grade 3/4 Adverse Events

N (%), of Patients (≥4 pts in Either Arm)	Sunitinib N=83	Placebo N=82
Total	41 (49.4%)	36 (43.9%)
Neutropenia	10 (12.0%)	0
Hypertension	8 (9.6%)	1 (1.2%)
Hand-foot syndrome	5 (6.0%)	0
Leukopenia	5 (6.0%)	0
Diarrhea	4 (4.8%)	2 (2.4%)
Asthenia	4 (4.8%)	3 (3.7%)
Fatigue	4 (4.8%)	7 (8.5%)
Abdominal pain	4 (4.8%)	8 (9.8%)
Hypoglycemia	4 (4.8%)	1 (1.2%)
Back pain	0	4 (4.9%)

All Causality Serious Adverse Events in 2 or More Patients in Either Arm

N (%)	Sunitinib N=83	Placebo N=82
Total	22 (26.5%)	34 (41.5%)
Disease progression	3 (3.6%)	2 (2.4%)
Cardiac failure	2 (2.4%)	0
Abdominal pain	2 (2.4%)	4 (4.9%)
Abdominal pain upper	2 (2.4%)	0
Nausea	2 (2.4%)	1 (1.2%)
Vomiting	2 (2.4%)	3 (3.7%)
Renal failure / Renal failure acute	2 (2.4%)	1 (1.2%)
General physical health deterioration	1 (1.2%)	2 (2.4%)
Hepatic pain	1 (1.2%)	2 (2.4%)
Pyrexia	1 (1.2%)	2 (2.4%)
Back pain	0	2 (2.4%)
Hematemesis	0	2 (2.4%)
Hepatic failure	0	2 (2.4%)
Hypoglycemia	0	2 (2.4%)
Hypotension	0	2 (2.4%)
Melena	0	2 (2.4%)
Pulmonary Embolism	0	2 (2.4%)

Other Serious Adverse Events of Interest

N (%)	Sunitinib N=83	Placebo N=82
Hepatic encephalopathy	1 (1.2%)	1 (1.2%)
Pancreatitis / Pancreatitis acute	1 (1.2%)	1 (1.2%)
Cerebral hematoma	1 (1.2%)	0
Hepatic dysfunction	1 (1.2%)	0
Leukoencephalopathy	1 (1.2%)	0
Ventricular arrhythmia	1 (1.2%)	0

Other Serious Adverse Events of Interest

N (%)	Sunitinib N=83	Placebo N=82
Hepatic encephalopathy	1 (1.2%)	1 (1.2%)
Pancreatitis / Pancreatitis acute	1 (1.2%)	1 (1.2%)
Cerebral hematoma	1 (1.2%)	0
Hepatic dysfunction	1 (1.2%)	0
Leukoencephalopathy	1 (1.2%)	0
Ventricular arrhythmia	1 (1.2%)	0
Acidosis	0	1 (1.2%)
Cerebrovascular Accident	0	1 (1.2%)
Cholangitis	0	1 (1.2%)
Duodenal Ulcer Perforation	0	1 (1.2%)
Deep vein thrombosis	0	1 (1.2%)
Multi-Organ Failure	0	1 (1.2%)

Summary of Deaths

N (%) of Patients	Sunitinib N=83	Placebo N=82
Deaths	9 (10.8%)	21 (25.6%)
Patients who Died While On Study^a	5 (6.0%)	9 (11.0%)
Disease under study	4 (4.8%)	7 (8.5%)
Cardiac Failure	1 (1.2%)	0
Dehydration	0	1 (1.2%)
Hepatic Failure	0	1 (1.2%)
Patients who Died During Follow-up^b	4 (4.8%)	12 (14.6%)
Disease under study	3 (3.6%)	12 (14.6%)
Cardiac Failure	1 (1.2%)	0

Deaths of patients in extension studies are included

N = number of patients

^a On study deaths are those that occurred after the first dose of study drug and within 28 days of last dose of study medication

^b Follow-up deaths are those that occurred more than 28 days after last dose of study medication

Based on April 2009 analysis

Safety Conclusions

- The most common sunitinib-related AEs were generally consistent with the known safety profiles of sunitinib and pancreatic NET
- AEs were manageable through the use of dose modifications and/or standard medical therapy
- No new or unexpected AEs
- Safety profile is well characterized in >10,000 patients in clinical trials across multiple tumor types

Patient-reported Outcomes Assessment

- PROs were measured using the validated, self-administered EORTC QLQ-C30*^{1, 2} which includes:
 - Global HRQoL
 - Functional scales
 - ◆ Cognitive, emotional, physical, role and social functioning
 - Symptom items/scales
 - ◆ Appetite loss, constipation, diarrhea, dyspnea, fatigue, insomnia, nausea and vomiting, pain

- Patients completed questionnaire at baseline (Cycle 1, Day 1), Day 1 of every cycle thereafter (treatment cycle = 28 days), and at end of treatment or withdrawal

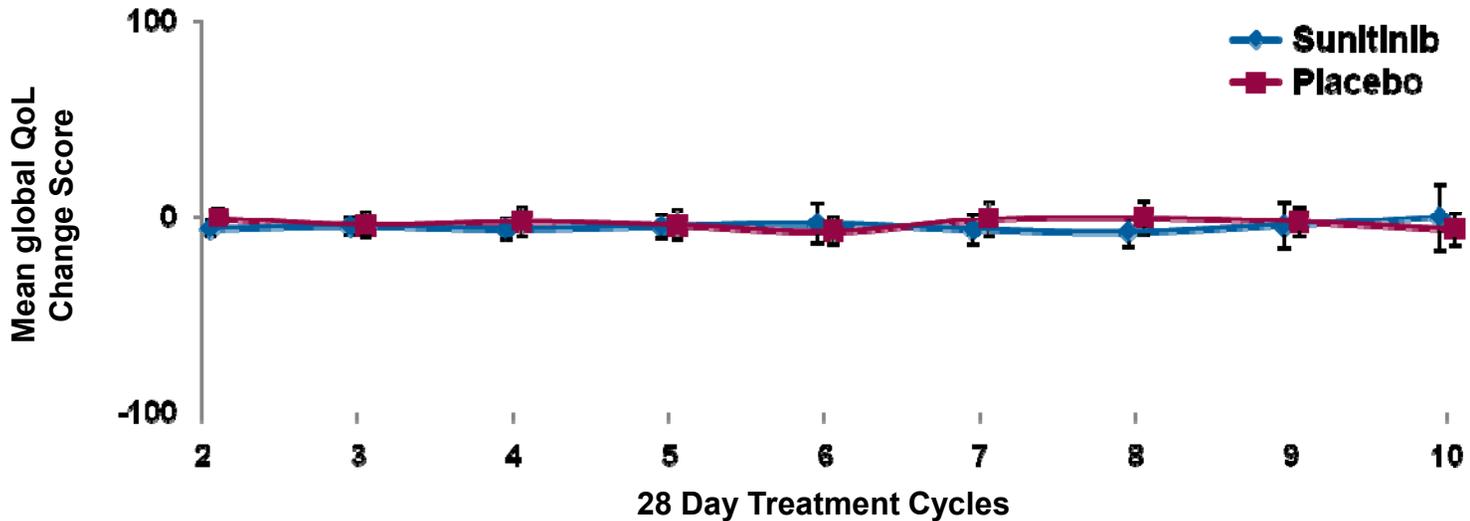
* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (version 3.0)

1. Fayers PM, et al. EORTC QLQ-C30 Scoring Manual, 2001

2. Aaronson NJ, et al. J Natl Cancer Inst 1993;85:365–76

EORTC QLQ-C30: Global HRQoL Change from Baseline Over Time

No Statistically or Clinically Significant Difference or Change Was Observed Within as Well as Between Treatment Arms in Global HRQoL



N	2	3	4	5	6	7	8	9	10
Sunitinib	61	54	50	45	38	33	29	31	25
Placebo	61	52	39	37	27	25	21	18	14

* Between-treatment differences in mean change from baseline were neither clinically (≥ 10 points) nor statistically (95% CI) significant at all time points through 10 cycles

Summary

- Sunitinib provides a clinically meaningful, ~6 month improvement in PFS while maintaining Global HRQoL in patients with pancreatic NET
- The improvement in PFS is consistent across all analyses, confirming the robust treatment effect of sunitinib
- Sunitinib favorably impacts overall survival (HR = 0.409)
- Sunitinib results in objective tumor shrinkage (RR = 9.3% in sunitinib vs. 0% in placebo)
- Adverse events are consistent with the known safety profile of sunitinib and/or the signs and symptoms of pancreatic NET

*These data demonstrate a favorable benefit/risk profile for sunitinib
in patients with unresectable pancreatic NET*

Clinical Perspective



Matthew Kulke, MD

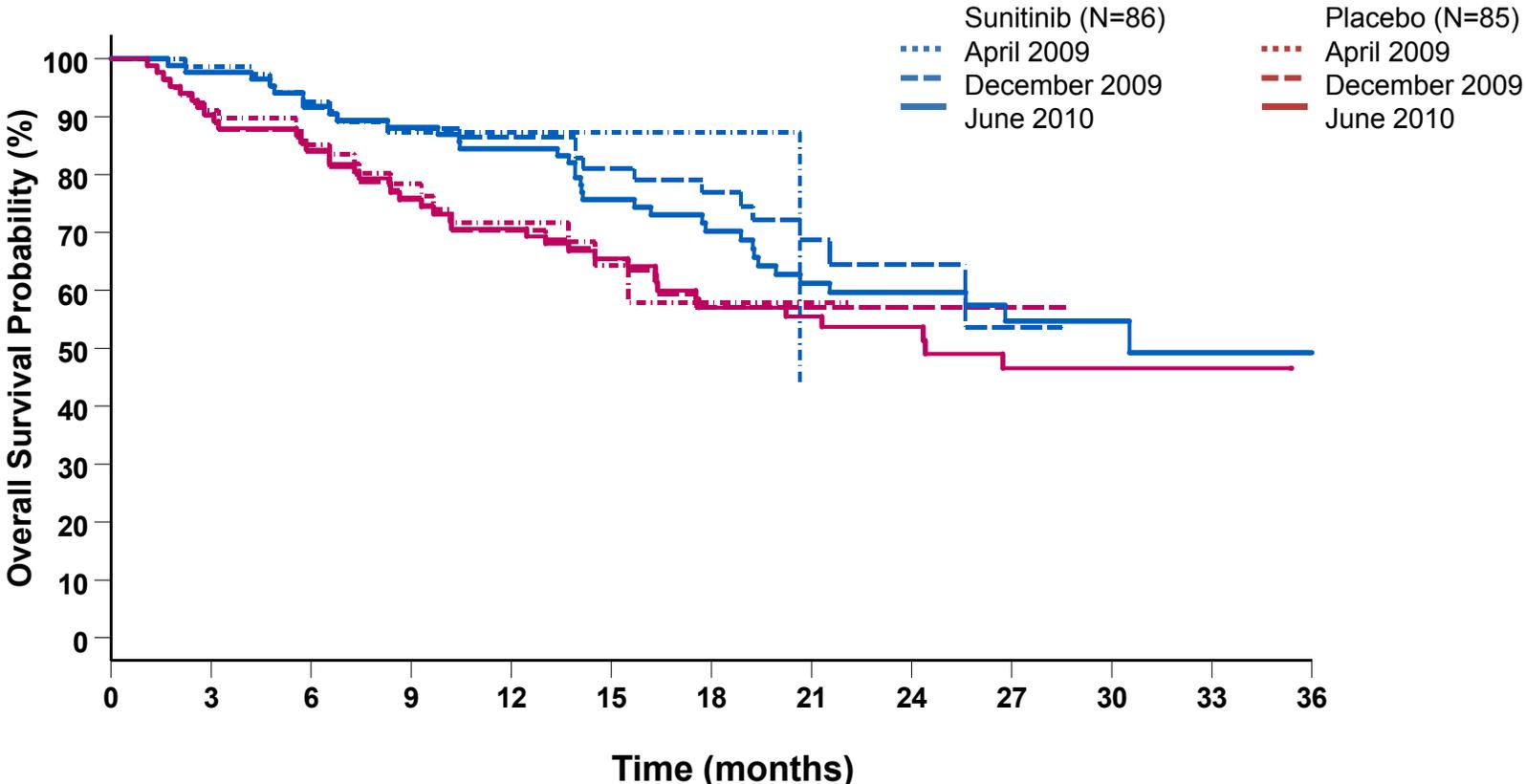
Director, Carcinoid and Neuroendocrine Tumor Program
Dana-Farber/Brigham and Women's Cancer Center
Boston, MA

OS Analyses Adjusting for Crossover

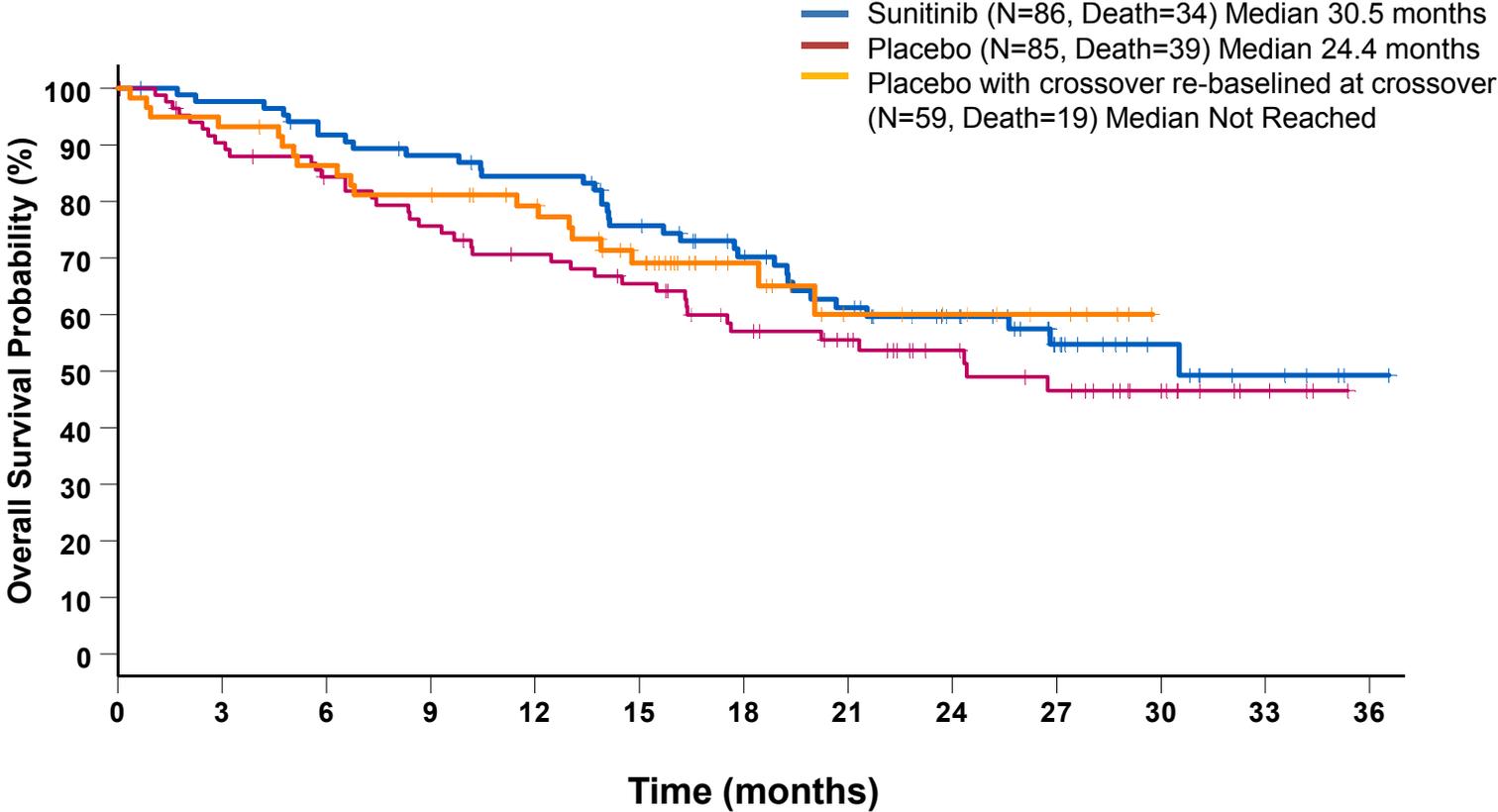
Approach	HR (95% CI)
ITT Analysis (June 2010)	0.737 (0.465, 1.168)
Censor at Crossover Analysis	0.416 (0.230, 0.752)
Time Dependent Treatment Analysis	0.468 (0.268, 0.818)
RPSFT * Analysis	0.499 (0.351, 0.947)

*Rank Preserving Structural Failure Time

Overall Survival All Three Analyses – Phase 3



Overall Survival (June 2010) Placebo Re-baseline at Crossover – Phase 3



Treatment Effect Adjusted for Baseline Factors: Univariate Analysis (IOTA)

	HR	95% CI
All Patients	0.418	(0.263, 0.662)
Age (≥ 65 vs. Age < 65)	0.408	(0.257, 0.648)
Race (Non-White vs. White)	0.414	(0.260, 0.659)
Gender (Female vs. Male)	0.416	(0.262, 0.659)
ECOG Score (0 vs. 1/2)	0.420	(0.264, 0.667)
Number of Disease sites (≤ 2 vs. ≥ 3)	0.426	(0.268, 0.678)
Disease Extent (Pancreas/Liver vs. Extrahepatic Distant)	0.446	(0.279, 0.713)
Somatostatin Analogs* Used? (Yes vs. No)	0.422	(0.265, 0.672)
Number of Prior Systemic Regimens (≥ 2 vs. 0/1)	0.418	(0.263, 0.662)
Histology (Non-Functioning vs. Other)	0.426	(0.269, 0.676)
Time from Diagnosis (≥ 3 Years vs. < 3 Years)	0.374	(0.234, 0.599)



* Includes all patients receiving somatostatin analogs at any time before and/or concomitant with study treatment.

Discordance Rate of PFS Event

	BICR PD Inv. no PD	BICR no PD Inv. PD	Ratio	Total Event discordance	%
Sunitinib (n=81)	6	13	2.2	19	23%
Placebo (n=82)	10	18	1.8	28	34%
Total* (n=163)	16	31	1.9	47	29%

* Excluding 8 subjects who did not have BICR evaluation due to missing scans

Note: Algorithmic vs BICR

Conditional Power of Stopping the Study

- ◆ **The probability that the study would be stopped at the planned interim analysis at 130 events**
 - If the true HR is 0.397 (same as the observed HR at DMC review in Feb 2009), the conditional power was estimated to be 99.9%
 - Conservatively assuming that the true HR is 0.649 (same as the upper bound 95% CI of observed HR), the conditional power was estimated to be 91%
 - **If the true HR is 0.509 (the observed HR + 1 standard error), the conditional power was estimated to be 98.8%**

Analyses of PFS (DMC) and OS (April 2009) as Multiple Events Based on Three Marginal Models

	Hazard Ratio	95% CI		P-value (Sandwich)	P-value (Model-based)
WLW	0.398	0.250	0.634	0.0001	<0.0001
Andersen-Gill	0.467	0.316	0.690	0.0001	0.0004
Conditional	0.433	0.286	0.654	<0.0001	0.0001

Conditional Power for the Final Analysis

Hypothetical Hazard Ratios for Remainder of Study	Conditional Power
0.40	1.0
0.50	0.99999
0.60	0.99982
0.67	0.99797
0.70	0.99472
0.80	0.95356
0.90	0.81791
1.00	0.58551

DMC Membership

- ◆ **Robert G. Maki, MD, PhD** **Chair**
 - Memorial Sloan Kettering Cancer Center
- ◆ **Alan Astrow, MD** **Clinician**
 - Maimonides Cancer Center
- ◆ **David Oakes, PhD** **Statistician**
 - University of Rochester

DMC Chartering Meeting

- ◆ **March 13, 2008**
- ◆ **Open session only; no blinded data**
- ◆ **Protocol reviewed**
- ◆ **Tables requested for review:**
 - Demographics
 - Baseline characteristics
 - Enrollment by site
 - Histology of enrolling patients
 - Toxicity by arm overall and since last meeting
 - Progression by arm and by site, overall and since last visit
 - RECIST lesion data if available
 - PFS curve
 - Violations by arm
 - SAEs by arm
 - Any summary QOL data

Exposure to Treatment - Average Weekly Dose, Relative Dose Intensity - Phase 2 vs Phase 3

	Phase 3		Phase 2 ^e
	Sunitinib N=86	Placebo N=85	Pancreatic NET N=66
Total number of cycles started, median (range)	5 (1-20)	4 (1-22)	5 (1-11)
Average weekly dose administered ^c (mg)			
Mean (SD)	239.5 (38.7)	264.0 (34.0)	211.9 (29.4)
Median (Range)	262.1 (145.1-330.0)	262.5 (184.9-381.8)	231.5 (132.1-272.1)
Relative dose intensity (mg) ^d			
Mean (SD)	91.3 (14.7)	100.6 (13.0)	91.0 (117.7)
Median (Range)	99.8 (55.3-125.7)	100.0 (70.4-145.5)	94.4 (34.7-100.0)

^a Total number of days on which study drug was actually administered.

^b A6181111: last dose date – first dose date + 1; RTKC-0511-015: number of days from first dose to termination or 14 days after last dose.

^c Average weekly dose administered = [(total dose administered)/(total number of weeks drug administered)].

^d Relative dose intensity = [(total dose administered)/(total dose assigned/intended)] x100. In Study A6181111, dose assigned was 37.5 mg/day. In Study RTKC-0511-015, dose assigned was the dose assigned for each cycle (e.g., if a subject had a dose reduction to 37.5 mg/day for Cycle 2, the subject could still have been counted as having had 100% dose intensity for the cycle by completing 28 days at 37.5 mg).

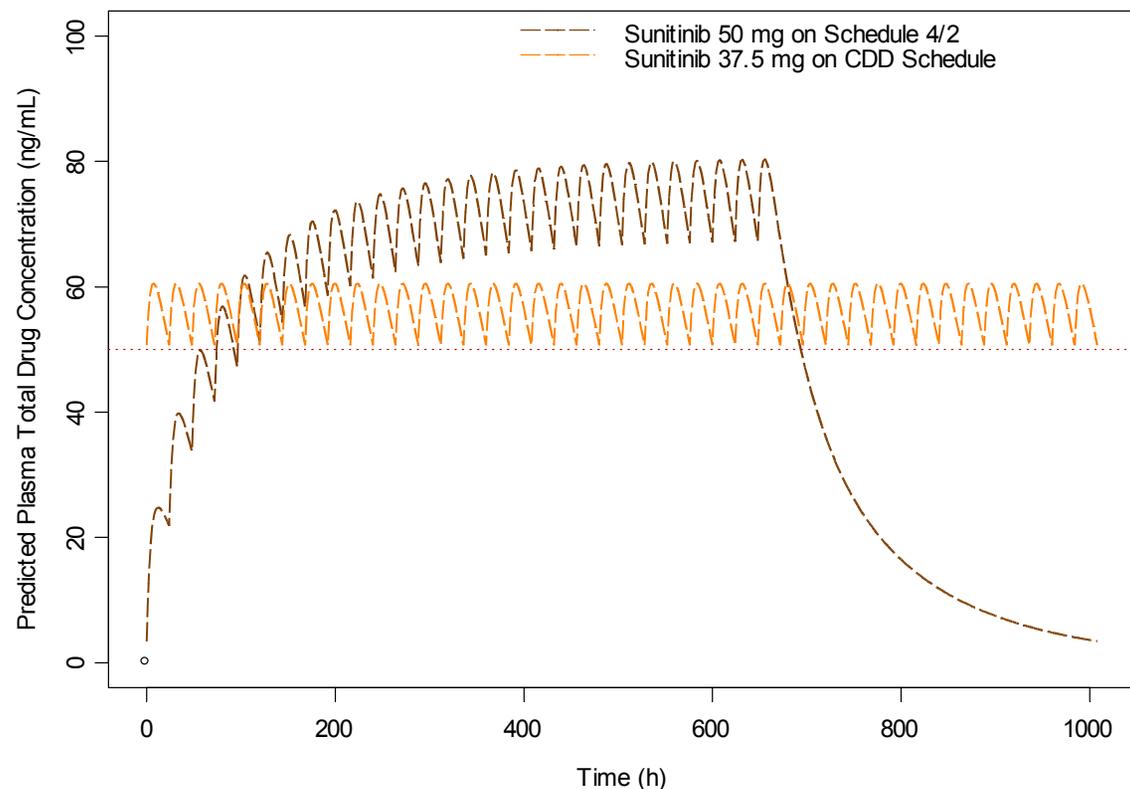
^eSubjects in Study RTKC-0511-015 completing a protocol specified number of treatment cycles were transferred to an extension study.

N = number of subjects included in the population, n = number of subjects; NET = neuroendocrine tumors; SD = standard deviation.

Phase 3 Study and Dosing Schedule Rationale

- ◆ **Activity of sunitinib in pancreatic NET on 50 mg Schedule 4/2 observed in Phase 2 study**
- ◆ **The 37.5 mg continuous daily dosing schedule selected over 50 mg 4/2 based on:**
 - Potential for continuous anti-tumor activity
 - Potential for improved tolerability due to lower peak plasma concentrations
 - Similar systemic clearance and average weekly dose
 - Similar overall total plasma exposure per 6-week period

Simulated Plasma Profiles Comparing Sunitinib 37.5 mg on CDD Schedule vs Sunitinib 50 mg on 4/2 Schedule



Based on population pharmacokinetic parameter estimates from Houk et al [*Clin Cancer Res* 15(7) 2009] for a male non-Asian patient with solid tumors, ECOG PS of zero, weighing 77 kg.

Number of Subjects by Treatment Group and by Ki-67 - Index Range

