AFINITOR® (everolimus)

United States Food and Drug Administration Oncologic Drugs Advisory Committee

April 12, 2011

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AFINITOR® (everolimus) Introduction

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Afinitor (everolimus)

- mTOR inhibitor
- Approved in the US in
  - Advanced renal cell carcinoma (2009)
  - Subependymal giant cell astrocytoma (SEGA) (2010)
- 3400-patient years exposure in RCC

Neuroendocrine Tumors (NET)

- Rare cancers
  - Different biology and treatment options
  - Orphan designation
- Two distinct tumor types studied
  - Pancreatic neuroendocrine tumors
    - Pivotal Phase III study (Study 24)
    - Supportive Phase II study (Study 39)
  - Carcinoid tumors (GI or lung origin)
    - Pivotal Phase III study (Study 25)

Proposed Indication

- ***Treatment of patients with advanced neuroendocrine tumors of <u>pancreatic origin</u>***

- **Not seeking indication of advanced neuroendocrine tumors of gastrointestinal or lung origin (carcinoid tumors) today**
  - **Based on FDA briefing document feedback**
  - **Challenges interpreting carcinoid data**

Key Regulatory Interactions

- Jan 2006: FDA guidance
  - Conduct separate trials (pancreatic NET, carcinoid tumors) as natural histories and chemosensitivities are different
- Key Phase III design elements agreed upon with FDA
  - Primary endpoint: PFS
  - Patient population, size of study, and comparator
- pNET protocol amended → SPA no longer in effect
  - PFS based on central revised to investigator review
  - PFS by central review became secondary endpoint

Overview of sNDA

- sNDA filed (Nov 2010)
- Pancreatic NET: Phase III and supportive Phase II trial
  - Pivotal Phase III trial met primary PFS endpoint
    - Results consistent across all 3 measures: investigator, central, and adjudicated review
    - Greater than 2-fold improvement in median PFS
- Carcinoid: Phase III trial
  - Results indicate evidence of benefit
- Priority review granted

Summary

- Everolimus has demonstrated clinical benefit in pancreatic NET
  - Primary endpoint met; robust results
- Safety profile in pancreatic NET and carcinoid studies
  - Consistent with the approved label
- Everolimus fulfills an unmet need in patients with advanced pancreatic NET

Outline of Today's Presentation

Pancreatic Neuroendocrine Tumors: Disease Background	Larry K. Kvols, MD Professor of Medicine Department of GI Oncology H. Lee Moffitt Cancer Center and Research Institute
Everolimus Efficacy and Safety	David Lebwohl, MD Global Program Head, Afinitor Novartis Oncology
Management of Pancreatic Neuroendocrine Tumors: A Clinician's Perspective	James Yao, MD Deputy Chair Department of GI Medical Oncology University of Texas M.D. Anderson Cancer Center

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Pancreatic Neuroendocrine Tumors: Disease Background

Larry K. Kvols, MD

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MOFFITT CANCER CENTER

Pancreatic Neuroendocrine Tumors: Burden of Disease

- Rare tumors
  - Annual incidence ~ 3/1,000,000
- Disease-related symptoms: abdominal and back pain, early satiety, obstruction, etc.
- Functional tumors produce hormones that cause symptom complexes
  - Gastrin → reflux, ulcers, diarrhea
  - Glucagon → anorexia, weight loss, glucose intolerance, rash
  - VIP → severe watery diarrhea, hypokalemia
  - Insulin → hypoglycemia

Pancreatic Neuroendocrine Tumors: Survival by Stage

Stage	N	Median OS, months (95% CI)
Overall[a]	1483	28 (25, 32)
Localized	164	100 (68, 148)
Regionally advanced	307	69 (52, 86)
Metastatic	893	17 (14, 19)

[a] Includes 119 unstaged patients.
Adapted from Halfdanarson TR, et al. *Ann Oncol.* 2008;19:1727-1733.

Single Approved Therapy for Oncologic Control of Advanced Pancreatic NET

- Streptozocin (approved 1982) is the current backbone for treatment of advanced pNET despite limitations[a,b]
  - PFS and OS benefits are not well established
  - Toxicity limits use
  - Availability is sporadic

[a] Halfdanarson TR, et al. *Ann Oncol*. 2008;19:1727-1733.
[b] Yao JC, et al. *J Clin Oncol*. 2008;26:3063-3072.

Carcinoid Tumors Are Distinct From Pancreatic Neuroendocrine Tumors

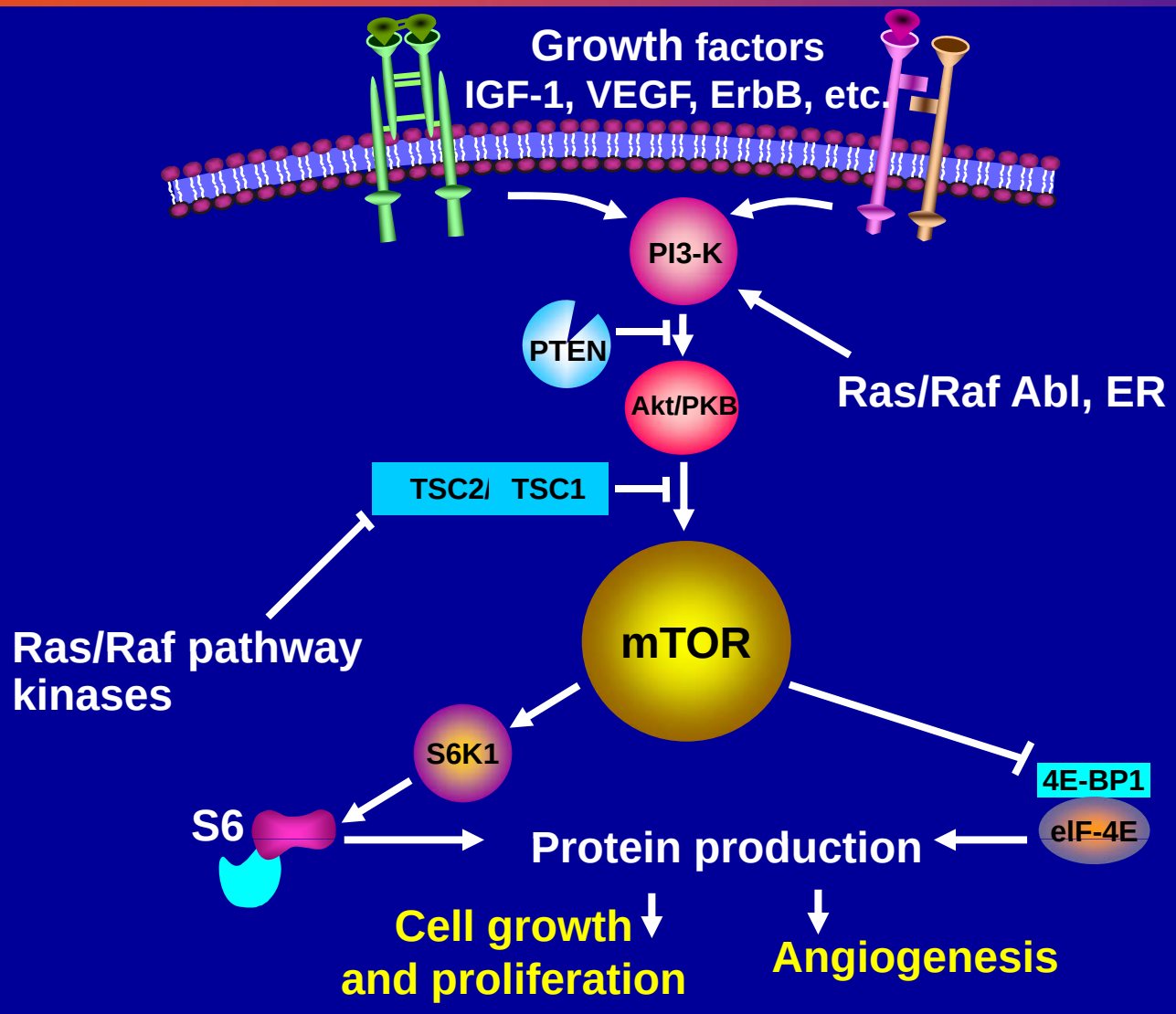
- Biologically and genetically different from pNET
  - Functional tumors (serotonin → 5-HIAA)[a]
  - Flushing, diarrhea, wheezing, cardiac complications
- Resistant to most cytotoxic chemotherapy
- Overall survival for advanced disease is short (15 - 24 months)[b]
- No approved agents for tumor control

[a] Vinik AI, et al. *Pancreas.* 2010;39:713-734.
[b] Sun W, et al. *J Clin Oncol*. 2005;23(22):4897-4904.

Pancreatic Neuroendocrine Tumors: Summary

- pNET is a rare disease
- Survival is short for patients with metastatic disease
- Few therapeutic options are available
  - Streptozocin has limited use
- Effective new therapies are needed
- Strong scientific rationale for use of mTOR inhibitor

Scientific Rationale for mTOR Inhibition



AFINITOR® (everolimus) Efficacy and Safety in Pancreatic NET

David Lebwohl, MD

Global Program Head, Afinitor
Oncology Global Development
Novartis Pharmaceuticals Corporation

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Program in Pancreatic NET (N = 570)

Study	Study design/objectives	Patients, n
24	Double-blind, randomized, placebo-controlled Phase III Efficacy and safety	410 Everolimus: 207 Placebo: 203
39	Open-label, Phase II Efficacy and safety after failure of cytotoxic chemotherapy	160 Everolimus: 115 Everolimus + octreotide: 45

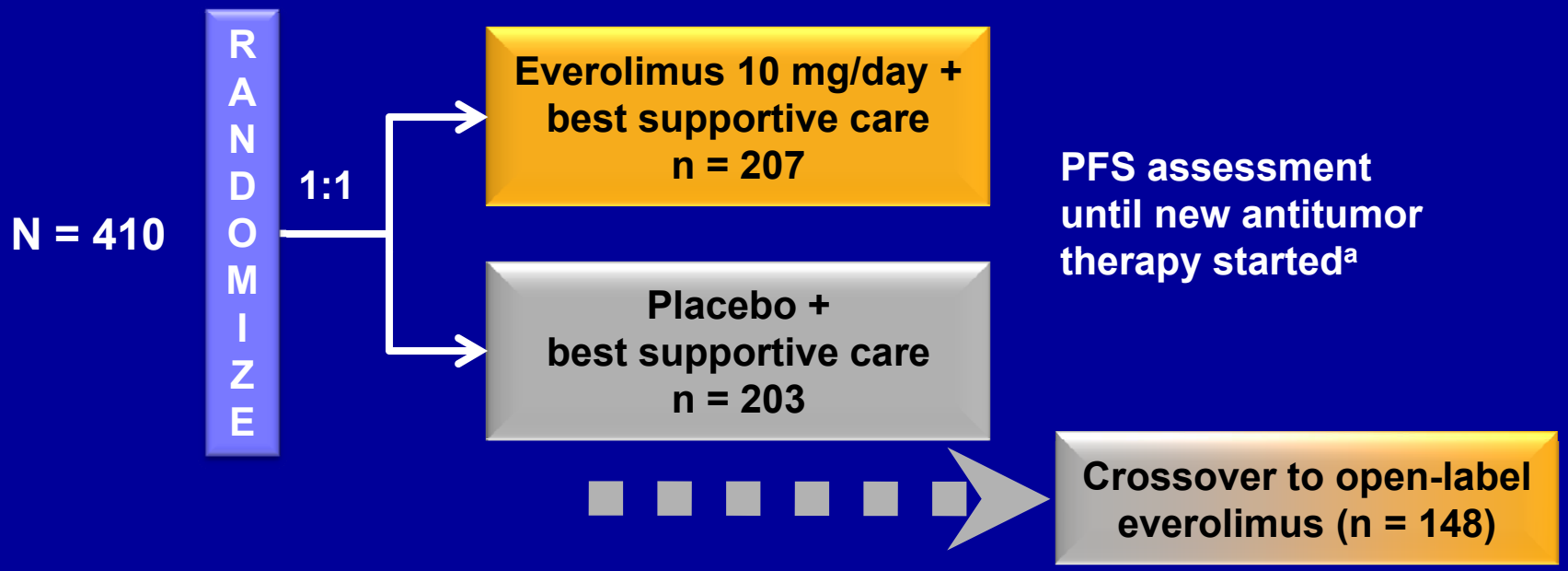
Patients With Advanced Pancreatic NET

Phase III Study 24

Study Design
Pancreatic NET

- Patient population
  - Advanced low- or intermediate-grade pancreatic NET
  - Radiologic disease progression within 12 months
- Stratification by WHO PS and prior chemotherapy
- Double-blind, placebo-controlled, randomized, crossover
- PFS (RECIST 1.0) primary endpoint
  - Assessed every 12 weeks by multiphasic CT or MRI
- Secondary endpoints
  - ORR, OS, biomarkers, safety, PK
- Oversight by IDMC and Steering Committee

Study Conduct
Pancreatic NET



- Primary analysis of PFS amended from central review to investigator assessment based on concerns of informative censoring

[a] As per protocol, patients who were discontinued for reasons other than PD were followed until PD.

Baseline Characteristics
Pancreatic NET

	Everolimus N = 207	Placebo N = 203
Median age, yr (range)	58 (23 - 87)	57 (20 - 82)
Male, %	53	58
WHO performance status, %		
0	67	66
1 - 2	33	34
Median time since diagnosis, mo	30	35
Median time from progression to randomization, mo	1.7	1.7
Distant organ involvement, %		
Liver	92	92
Lung	14	15
Bone	6	14

Prior Therapy
Pancreatic NET

	Patients, %	
	Everolimus N = 207	Placebo N = 203
Any TAE/TACE[a]	23	22
Somatostatin analogue	49	50
Prior systemic therapy	58	58
Chemotherapy	50	50
Doxorubicin/epirubicin	25	32
Streptozocin	21	23
Fluorouracil	20	19
Platinum compound	16	22
Capecitabine	6	9
Dacarbazine	5	5
Sunitinib malate	4	3
Interferon	4	5
Mitomycin	3	5

[a] Values derived from manual review of data.

Treatment Disposition
Pancreatic NET

Disposition, %	Everolimus N = 207	Placebo N = 203
Ongoing	32	13
Discontinued	68	87
Reason for discontinuation		
Disease progression	44	80[a]
Adverse event(s)	17	3
Consent withdrawn	2	2
Death	2	2
Protocol deviation	2	0
Lost to follow-up	1	0
Exposure (median), wks	38	16

[a] 148 crossed over out of 163 patients who discontinued for disease progression.

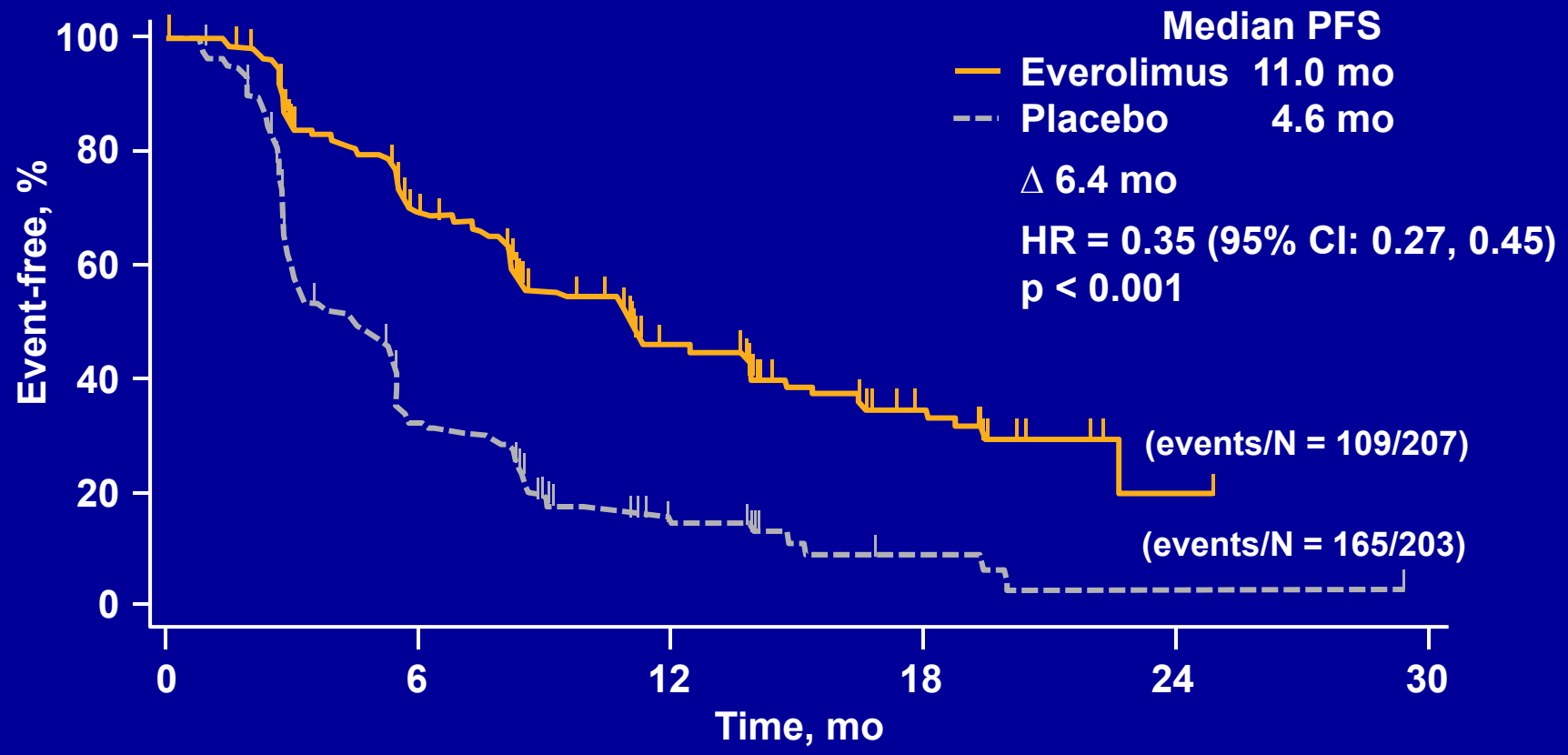
PFS—Consistent Results
Pancreatic NET

Analyses	HR (95% CI)	p value	Median PFS, mo (95% CI)		Δ
			Everolimus	Placebo	
Original primary					
IRC = Central	0.38 (0.28, 0.51)	< 0.001	13.7 (11.2, 18.8)	5.7 (5.4, 8.3)	8.0
Amended primary					
INV = Investigator	0.35 (0.27, 0.45)	< 0.001	11.0 (8.4, 13.9)	4.6 (3.1, 5.4)	6.4
Supportive					
IAC = Adjudicated	0.34 (0.26, 0.44)	< 0.001	11.4 (10.8, 14.8)	5.4 (4.3, 5.6)	6.0

p value obtained from stratified one-sided log-rank test.
Hazard ratio obtained from stratified unadjusted Cox model.

PFS—65% Risk Reduction

Pancreatic NET—Investigator Assessment

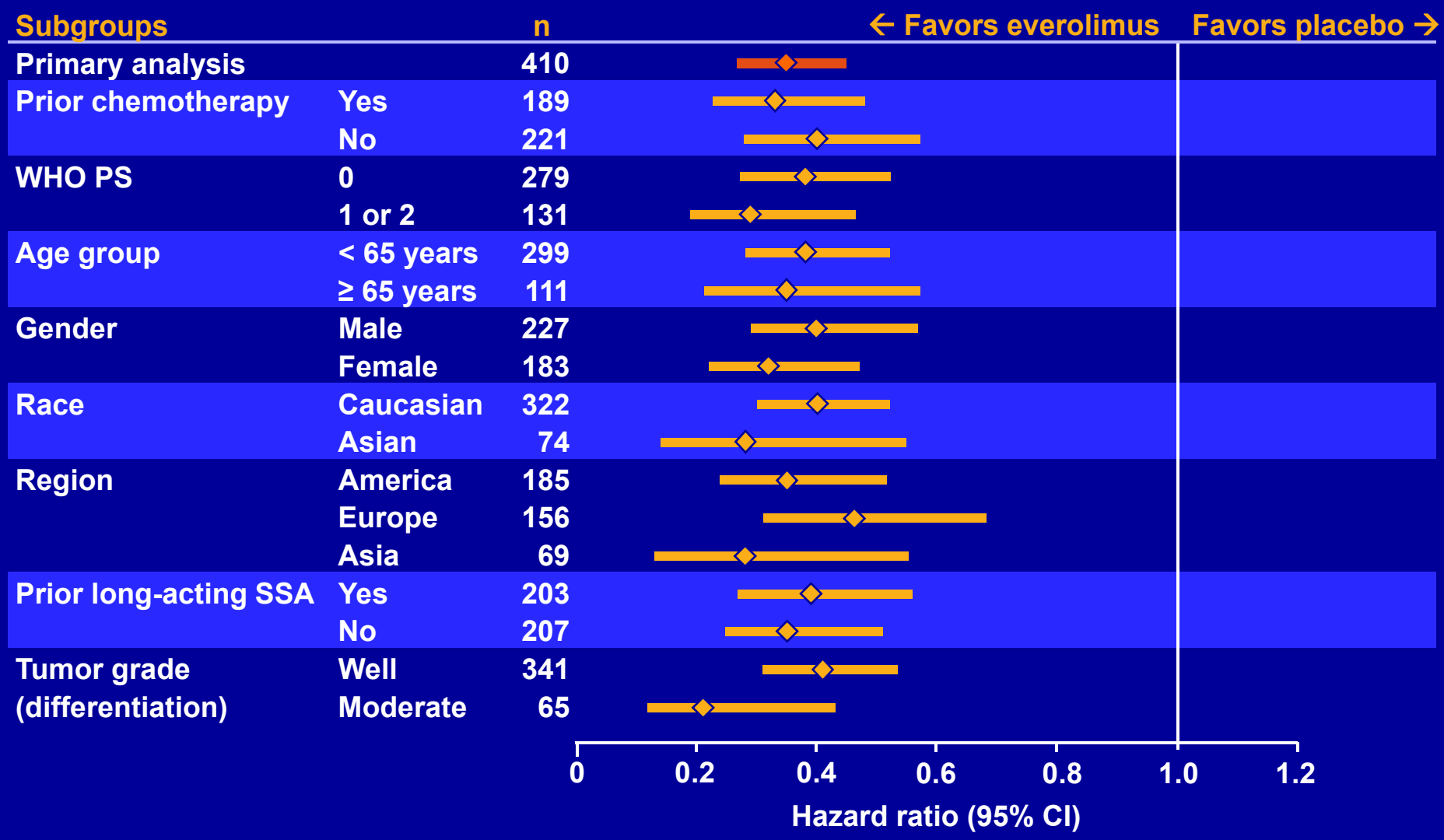


Patients at risk, n

Everolimus	207	189	153	126	114	80	49	36	28	21	10	6	2	0	0	0
Placebo	203	177	98	59	52	24	16	7	4	3	2	1	1	1	1	0

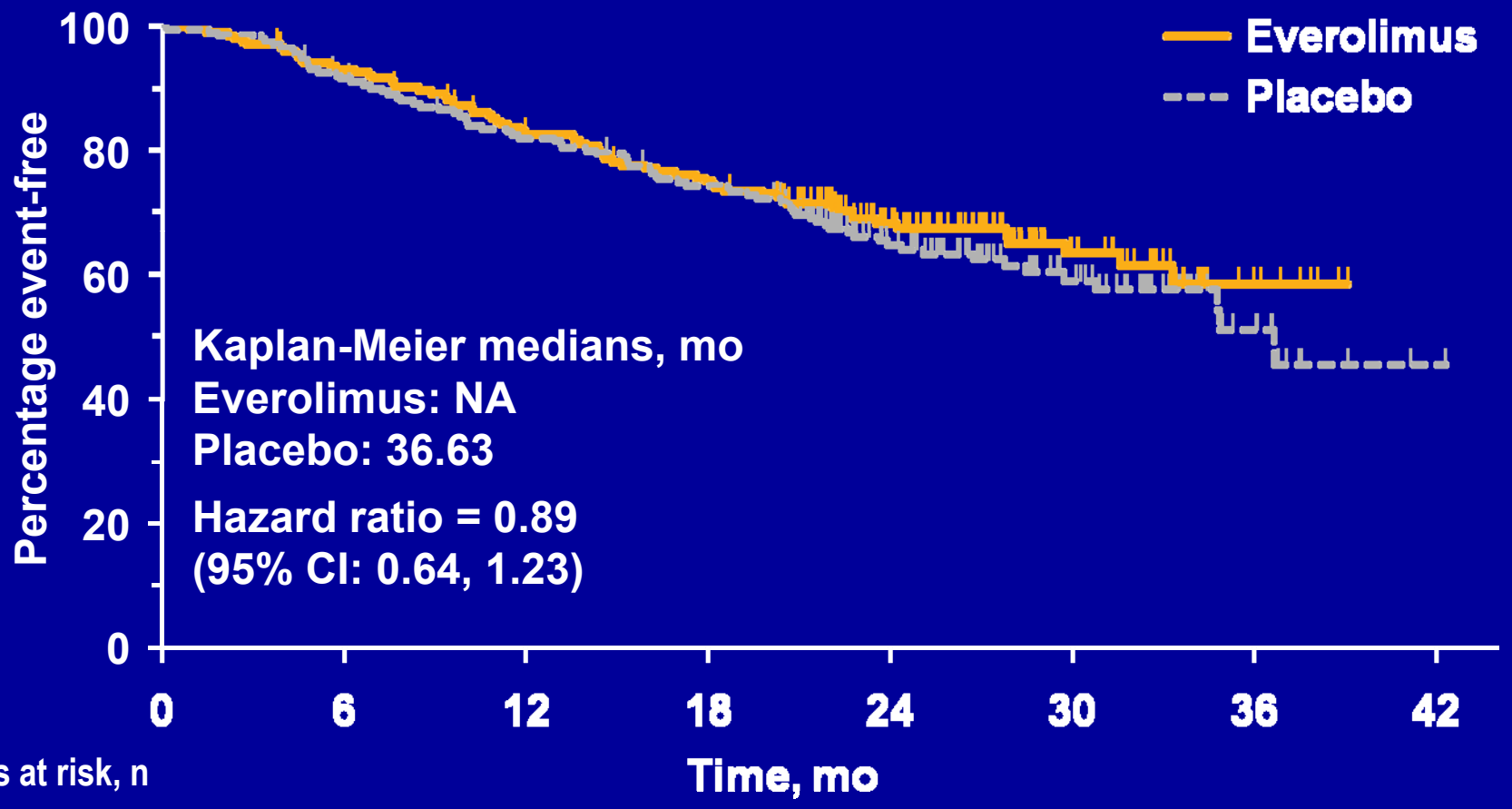
PFS Subgroup Analysis—Consistent Treatment Effect

Pancreatic NET—Investigator Assessment



Overall Survival—Cutoff Feb 23, 2011

Pancreatic NET

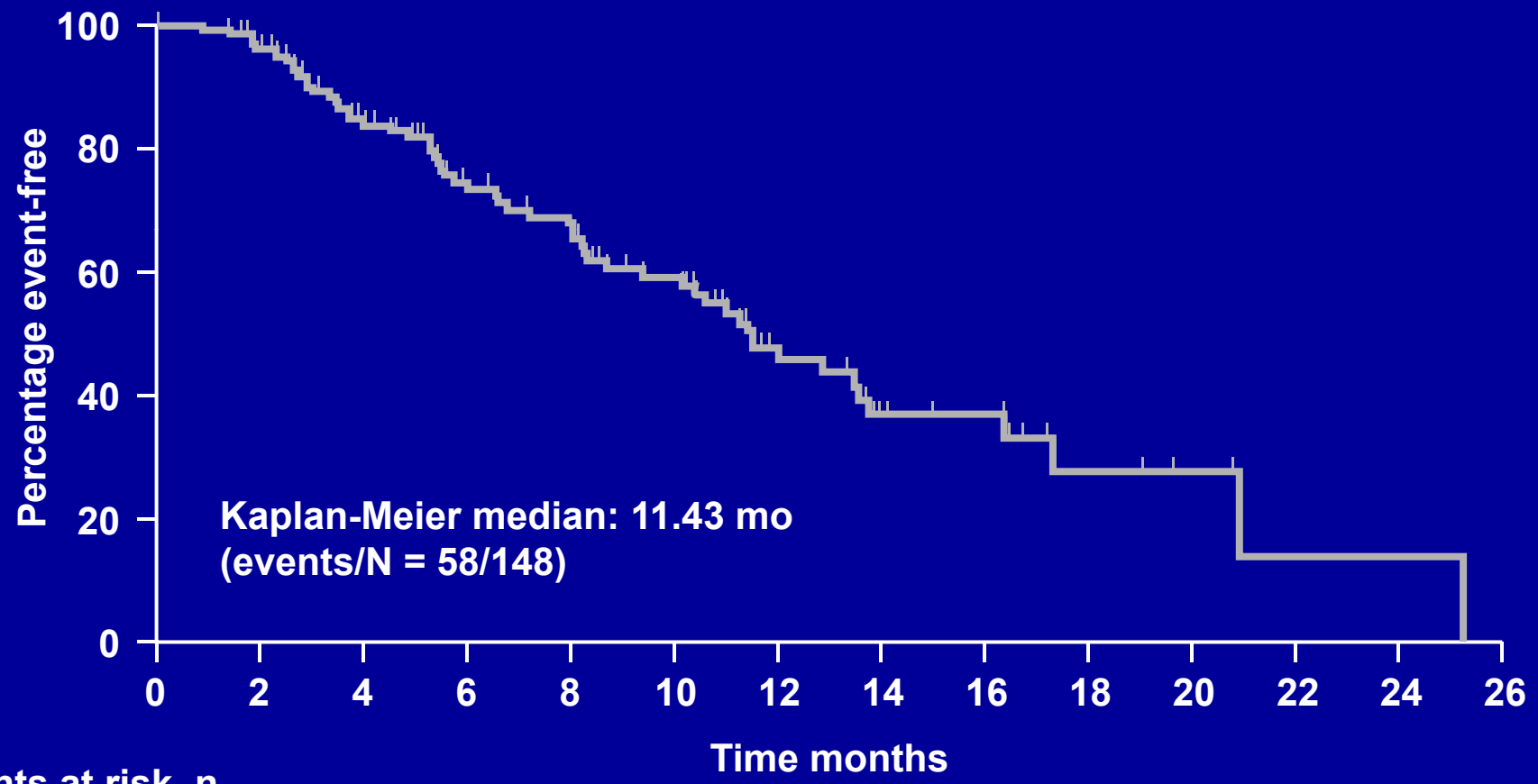


Patients at risk, n

Everolimus	207	203	195	189	182	174	163	159	151	147	142	119	91	70	53	39	27	16	7	3	0	0	0
Placebo	203	199	195	183	175	168	162	157	150	144	140	118	93	77	59	44	31	20	13	3	2	1	0

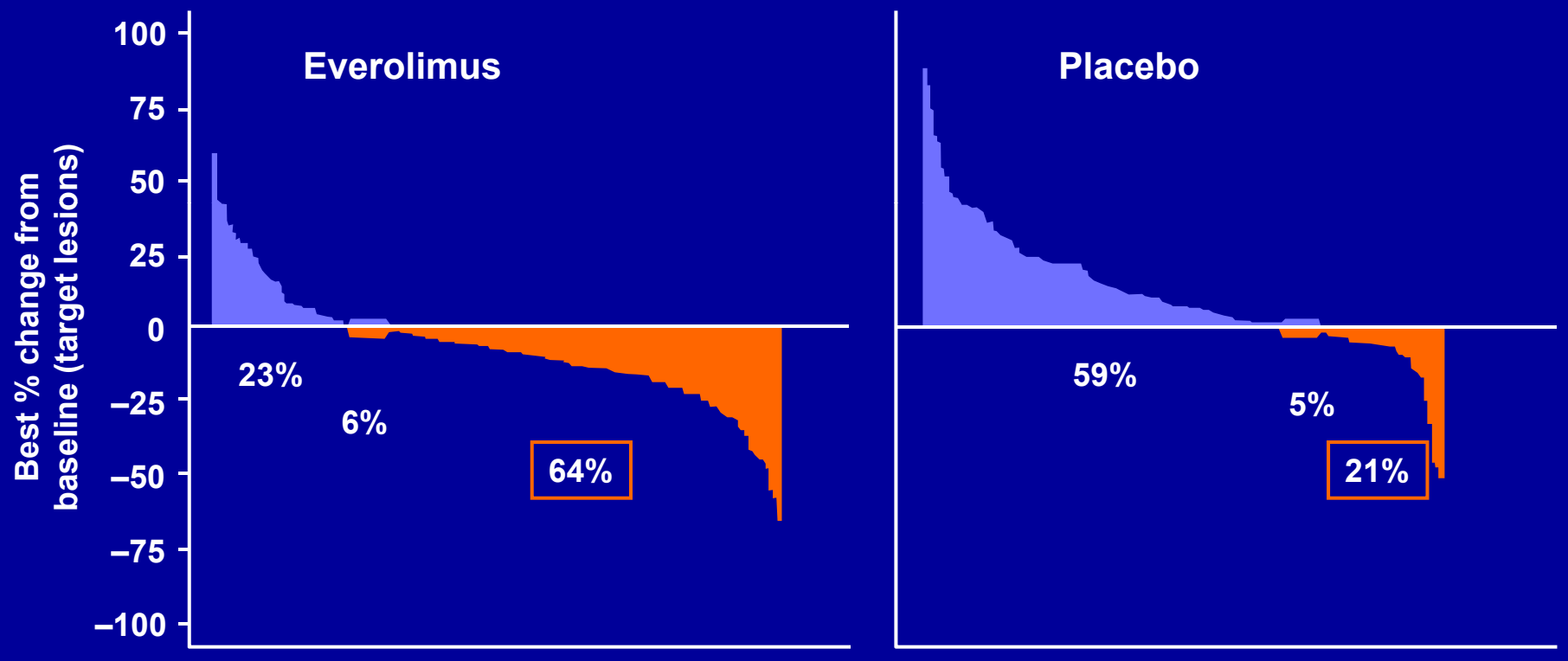
PFS Post-crossover

Pancreatic NET—Open-label Everolimus



Patients at risk, n														
Open-label	148	125	91	67	59	42	23	13	11	5	3	1	1	0

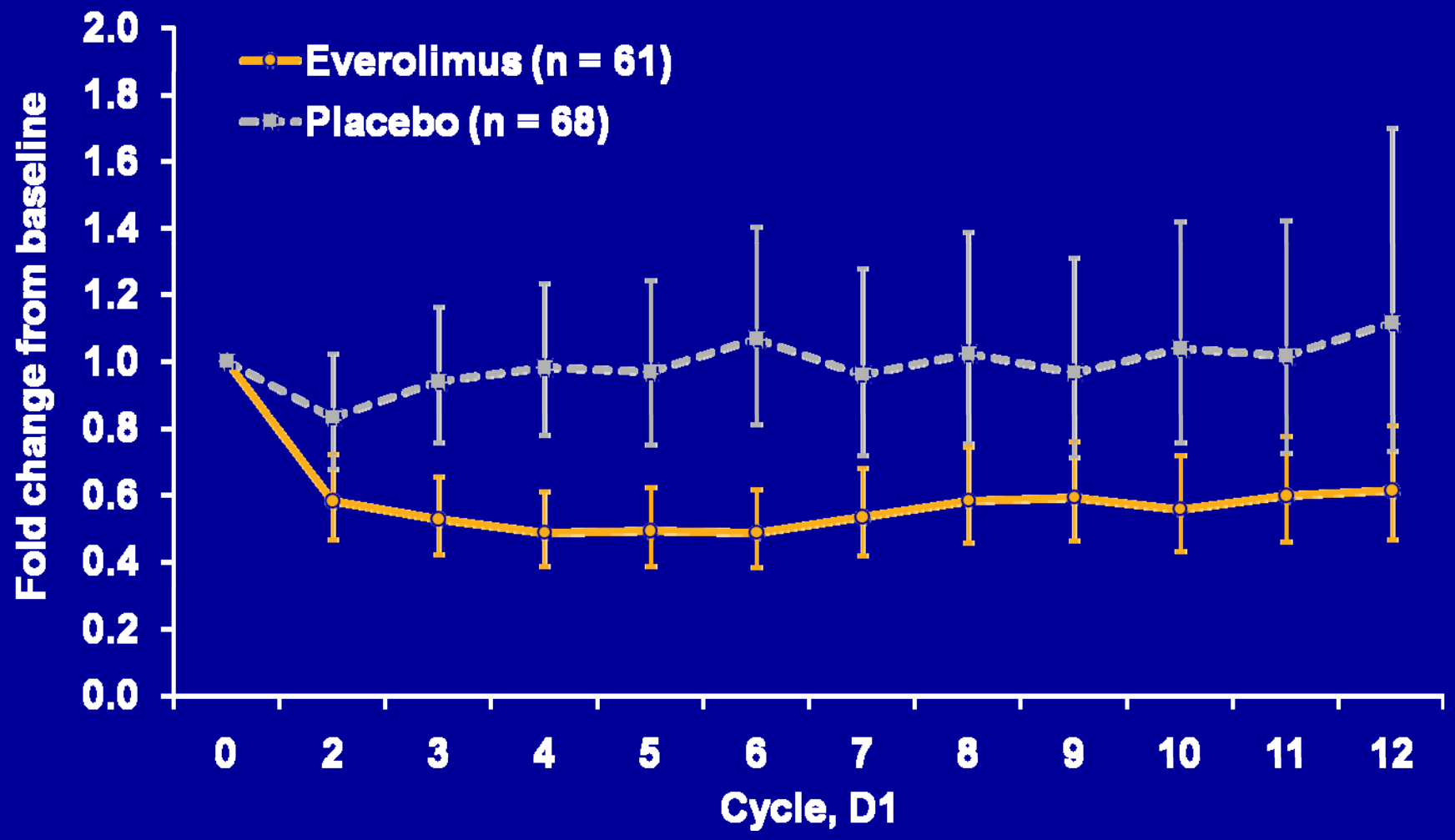
Waterfall Plot by INV
Pancreatic NET



ORR = 5% 2%

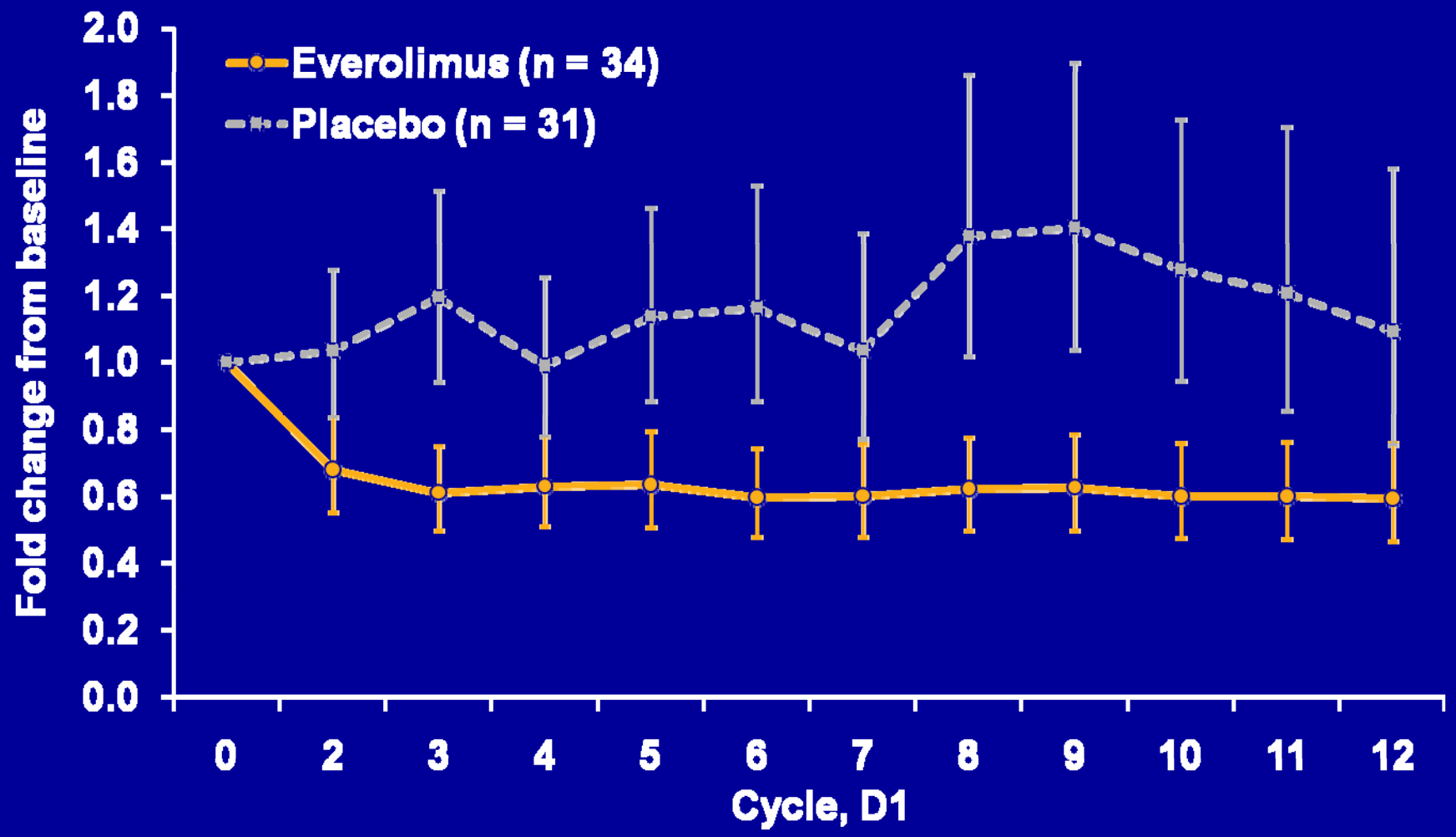
Best % change in target lesions when available.
Target lesions available but contradicted: 7% in everolimus arm and 15% in placebo arm.

Change in Gastrin
Pancreatic NET



Mean fold change and 95% CI obtained using a mixed model. Only patients with elevated level at baseline (> ULN) are summarized.

Change in Glucagon
Pancreatic NET



Mean fold change and 95% CI obtained using a mixed model. Only patients with elevated level at baseline (> ULN) are summarized.

Most Common Adverse Events
Pancreatic NET

	Patients, %			
	Everolimus (N = 204)		Placebo (N = 203)	
	All grades	Grade 3/4	All grades	Grade 3/4
Stomatitis[a]	68	7	18	0
Infections[a]	56	7	34	2
Rash	52	< 1	16	0
Diarrhea	47	5	24	2
Fatigue	44	3	27	2
Peripheral edema	36	< 1	12	< 1
Nausea	32	2	33	2
Headache	30	< 1	15	< 1
Pyrexia	29	< 1	12	< 1
Decreased appetite	29	1	18	1
Vomiting	28	< 1	21	2
Weight decreased	28	< 1	11	0
Abdominal pain	24	3	24	6
Pulmonary events[a]	19	3	0	0

Median duration of exposure was 38 weeks in everolimus arm and 16 weeks in placebo arm.
[a] Related toxicities grouped for calculation.

Dose Modifications
Pancreatic NET

	Everolimus N = 204	Placebo N = 203
Patients requiring dose modification, n (%)	59	28
Patients requiring dose interruption	57	26
Patients requiring dose reduction	30	8
Planned dose, mg/day	10	10
Dose intensity, mg/day[a]		
Mean (standard deviation)	8.6 (2.0)	9.7 (0.8)
Median	9.8	10
Range	2.4 - 10.0	5.0 - 10.0

[a] Dose intensity = cumulative dose/duration of exposure

Deaths—Up to 28 Days After Discontinuation

Pancreatic NET

	Patients, n (%)	
	Everolimus N = 204	Placebo N = 203
On-treatment deaths	12 (6)	4[b] (2)
Death due to disease progression	5 (3)	3 (2)
AE as primary cause of death	7[a] (3)	1 (0.5)

Median duration of exposure was 38 weeks in everolimus arm and 16 weeks in placebo arm.
[a] 1 case of death is suspected to be drug related. [b] An additional patient died 1st day after crossover

Deaths—Up to 28 Days After Discontinuation (2)

Pancreatic NET

Time to death, days	Everolimus N = 204 n, cause of death	Placebo N = 203 n, cause of death
1 to < 30	1 acute renal failure	1 pulmonary embolism
30 to < 60	1 unknown[a]	2 PD
60 to < 90	1 infection; 3 PD	
90 to < 180	1 hepatic failure[a]; 1 PD	
180 to < 270	1 cardiac arrest[a]	1 PD
270 to < 360	1 ARDS[b]; 1 pneumonia; 1 PD	

Median duration of exposure was 38 weeks in everolimus arm and 16 weeks in placebo arm.

[a] Disease progression also indicated as a cause of death.

[b] 1 case of death is suspected to be drug related.

Patients With Advanced Pancreatic NET

Phase II Study 39

Study Conduct
Phase II Pancreatic NET

Open-label, non-randomized

Patients with advanced pNET progressing during or after chemotherapy

N = 160

Stratum 1
n = 115 →

Everolimus 10 mg/d
(No octreotide LAR ≤ 60 d prior to enrollment)

→ Stratum 2[a]
n = 45

Everolimus 10 mg/d + octreotide LAR ≤ 30 mg, q 28 d
(Octreotide LAR ≥ 3 mo prior to enrollment)

- Primary endpoint: ORR with everolimus monotherapy (Stratum 1)
- Secondary endpoints: ORR with combination therapy (Stratum 2), PFS, response duration, OS, safety and PK in both strata

[a] Patients required to progress on SSA as well.

Yao JC, et al. *J Clin Oncol*. 2010;28(1):69-76.

Baseline Characteristics
Phase II Pancreatic NET

	Stratum 1 Everolimus N = 115	Stratum 2 Everolimus + octreotide N = 45
Median age, yr (range)	55 (23 - 79)	55 (21 - 77)
Male, %	57	53
WHO performance status, %		
0	58	71
1	33	20
2	8	7
Missing	1	2
Median time since initial diagnosis, mo	43	53
Organ type involved, %		
Liver	95	93
Lung	17	18
Lymph nodes	48	38
Bone	15	13
Pancreas	46	29

Treatment Disposition
Phase II Pancreatic NET

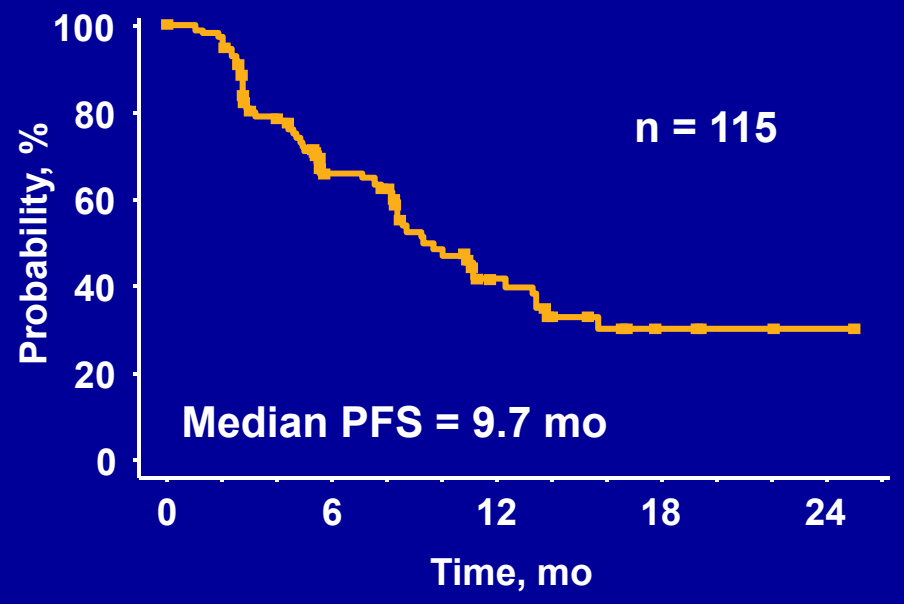
	Stratum 1 Everolimus N = 115	Stratum 2 Everolimus + octreotide N = 45
Ongoing, %	21	24
Discontinued, %	79	76
Reason for discontinuation, %		
Disease progression	54	33
Adverse event(s)	13	24
Consent withdrawn	7	4
Death	4	4
New cancer therapy	1	0
Protocol violation	0	4
Lost to follow-up	0	2
Abnormal laboratory value	0	2
Exposure (median), wks	36	44

Efficacy Results

Phase II Pancreatic NET—Central Review

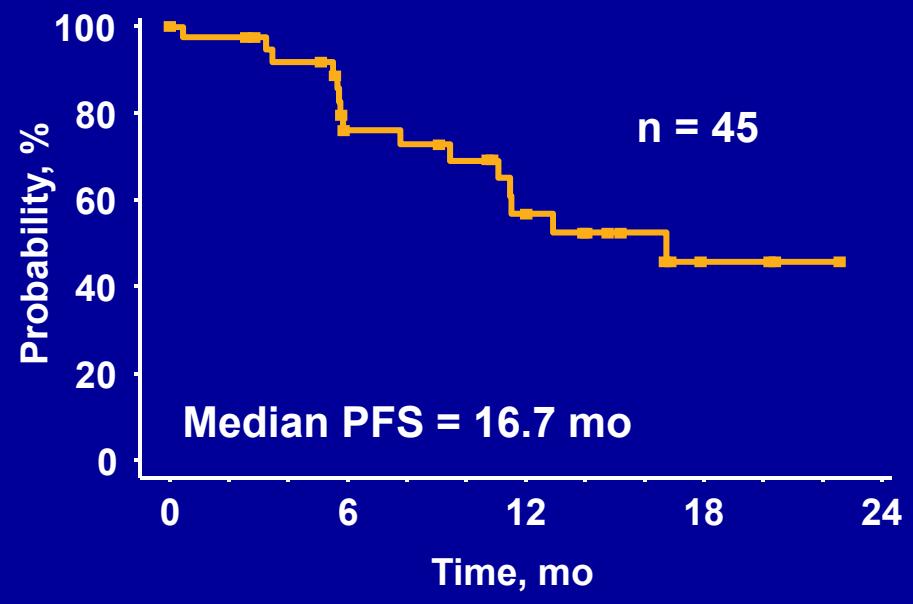
Stratum 1: Everolimus

ORR = 10%



Stratum 2: Everolimus + Octreotide LAR

ORR = 4%



Yao JC, et al. *J Clin Oncol*. 2010;28(1):69-76.

Most Common Grade 3/4 AEs Suspected to be Study Drug Related

Phase II Pancreatic NET

Grade 3/4 AE	Patients, %	
	Stratum 1 Everolimus N = 115	Stratum 2 Everolimus + octreotide N = 45
Asthenia	5	2
Anemia	4	4
Hyperglycemia	4	4
Fatigue	4	2
Stomatitis	4	2
Neutropenia	4	0
Diarrhea	3	0
Thrombocytopenia	3	9
Dyspnea	2	2
Anorexia	1	4
Nausea	1	0

Yao JC, et al. *J Clin Oncol*. 2010;28(1):69-76.

Summary
Pancreatic NET

- Everolimus reduces risk of disease progression by 65% relative to placebo (HR = 0.35, $p < 0.001$)
  - 6.4-month improvement in median PFS (INV)
  - Consistent results across PFS analyses
  - Similar PFS benefit across all subgroups
- No difference in OS between arms (HR = 0.89)
- Tumor shrinkage in 64% of everolimus-treated patients
- Biomarker response supports efficacy of everolimus
- Phase II data support results from pivotal study
- Safety profile is consistent with previous clinical experience

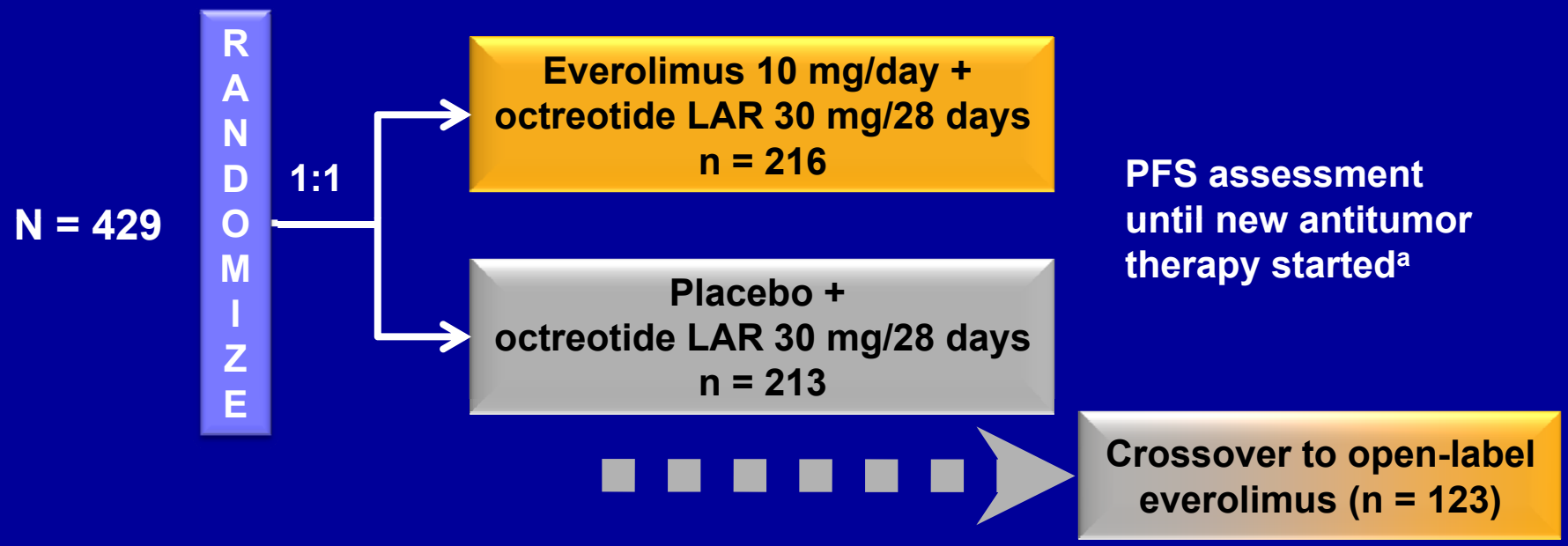
Patients With Advanced Carcinoid Tumors

Study 25

Study Design
Carcinoid Tumors

- Patient population
  - Advanced low- or intermediate-grade carcinoid tumor
  - History of flushing and/or diarrhea related to carcinoid
  - Radiologic disease progression within 12 months
- No stratification
- Double-blind, placebo-controlled, randomized, crossover
- PFS (RECIST 1.0) primary endpoint
  - Assessed every 12 weeks by multiphasic CT or MRI
- Secondary endpoints
  - ORR, OS, biomarkers, safety, PK
- Oversight by IDMC and Steering Committee

Study Conduct
Carcinoid Tumors



- 2 interim analyses performed
- Primary PFS analysis amended from central to IAC after second interim analysis

[a] As per protocol, patients who were discontinued for reasons other than PD were followed until PD.

Baseline Characteristics
Carcinoid Tumors

	Everolimus + octreotide N = 216	Placebo + octreotide N = 213
Median age, years (range)	60 (22 - 83)	60 (27 - 81)
Male, %	45	58
WHO performance status, %[a]		
0	55	66
1 - 2	45	34
Well-differentiated	77	82
Median time from progression to randomization, mo	1.7	1.6
Primary site, %[b]		
Small intestine	51	53
Lung	15	5
Colon	6	7
Prior systemic therapy, %	46	38
Chemotherapy	35	26
Somatostatin analogue	80	78

[a] One missing PS in placebo arm; [b] Other sites of origin were balanced.

Treatment Disposition
Carcinoid Tumors

Disposition	Everolimus + octreotide N = 216	Placebo + octreotide N = 213
Ongoing, %	17	16
Discontinued, %	83	84
Reason for discontinuation, %		
Disease progression	44	69[a]
Adverse event(s)	26	7
Consent withdrawn	8	5
Death	3	1
Protocol violation	1	2
New cancer therapy	1	1
Lost to follow-up	0	1
Exposure (median), wks	37	37

[a] 123 crossed over out of 146 patients discontinued for disease progression.

Actions After Discrepant PFS at Interim
Carcinoid Tumors

	PFS events, n	Hazard ratio (95% CI)	p value	Median PFS, months		
				Everolimus + octreotide	Placebo + octreotide	Δ
IRC	174	0.90 (0.66, 1.21)	0.233	13.0	11.1	1.9
INV	220	0.69 (0.53, 0.91)	0.003	11.7	8.6	3.1

- Discrepant treatment effect estimates by IRC and INV
  - NET experts adjudicate discrepant cases
- Loss of events in IRC indicates informative censoring
  - Determine impact of informative censoring using IPCW

INV = Investigator; IPCW = Inverse probability of censoring weights; IRC = Independent Review Committee.

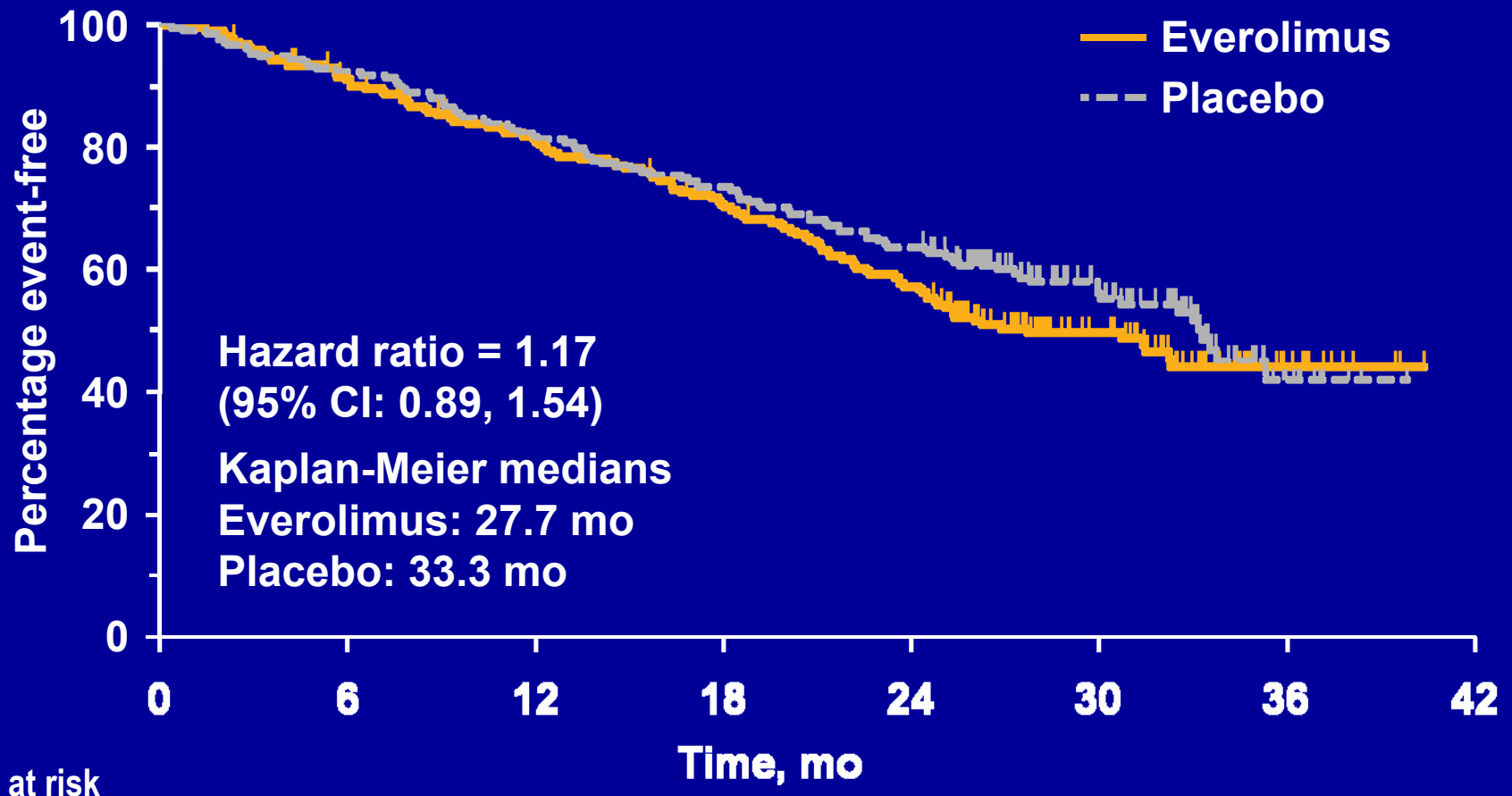
Final PFS Results
Carcinoid Tumors

	HR (95% CI)	p value	Median PFS, mo (95% CI)		
			Everolimus + octreotide	Placebo + octreotide	Δ
Original primary					
IRC	0.93 (0.71, 1.22)	0.298	14.9 (12.2, 19.4)	13.9 (9.7, 19.1)	1.0
Amended primary					
IAC	0.77 (0.59, 1.00)	0.026[a]	16.4 (13.7, 21.2)	11.3 (8.4, 14.6)	5.1
Supportive					
INV	0.78 (0.62, 0.98)	0.018	12.0 (10.6, 16.1)	8.6 (8.1, 11.1)	3.4

IAC = Independent Adjudication Committee; INV = Investigator; IRC = Independent Review Committee.
[a] Threshold for statistical significance was 0.0246.

Overall Survival—90-Day Update

Carcinoid Tumors

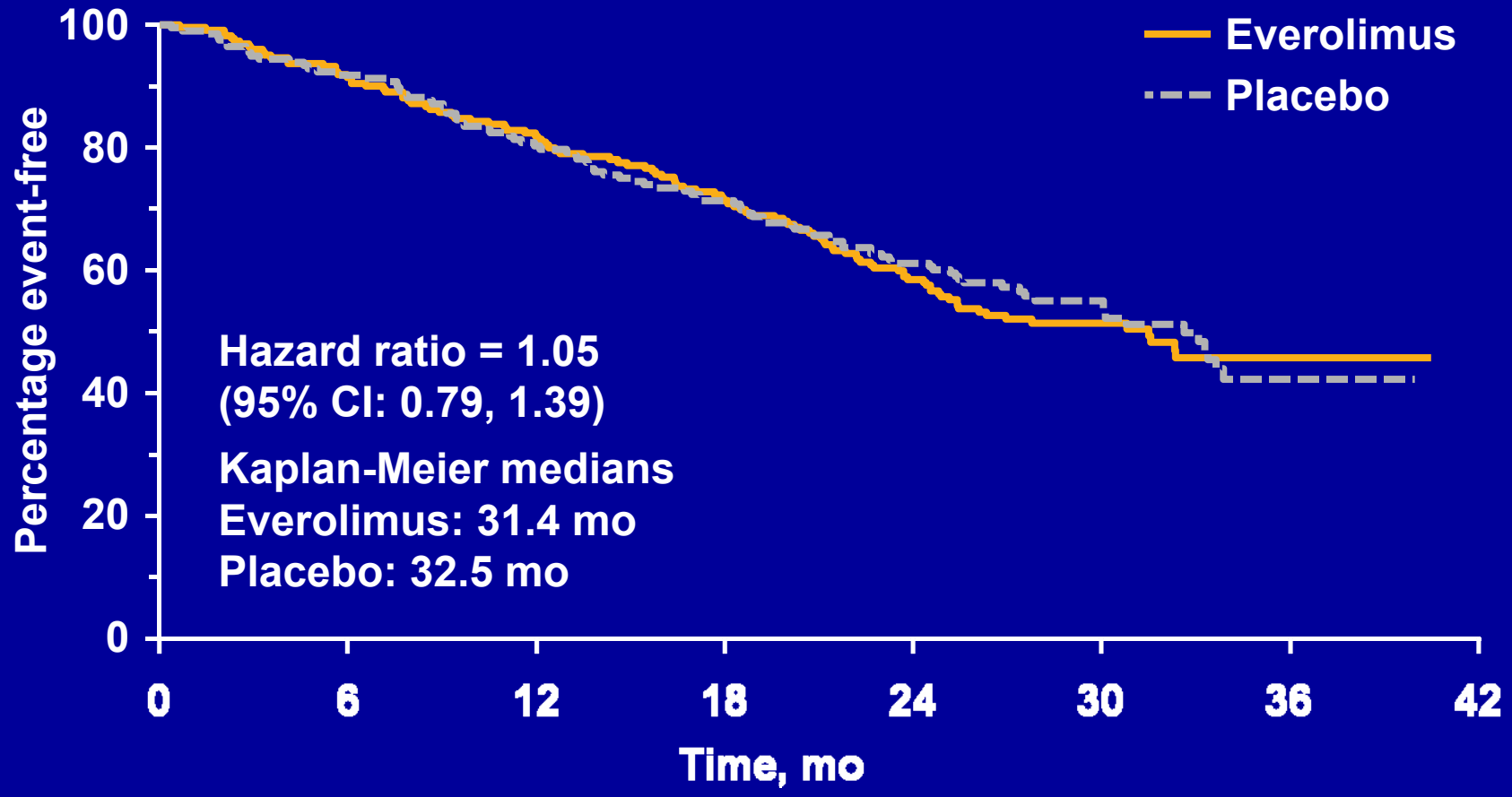


Patients at risk

Everolimus	216	213	202	191	180	172	166	160	152	143	134	124	115	91	70	54	40	24	13	4	1	0
Placebo	213	205	199	193	185	175	168	160	155	151	143	135	128	108	80	63	48	24	9	2	0	0

Overall Survival—90-Day Update (Adjusted[a])

Carcinoid Tumors



[a] Prespecified covariates (WHO, age, gender, ethnicity, prior somatostatin analogue use).

Most Common Adverse Events
Carcinoid Tumors

	Patients, %			
	Everolimus + O (N = 215)		Placebo + O (N = 211)	
	All grades	Grade 3/4	All grades	Grade 3/4
Stomatitis[a]	65	7	15	0
Infections[a]	65	14	45	5
Diarrhea	53	13	36	8
Fatigue	48	11	43	3
Peripheral edema	42	2	22	2
Nausea	42	4	30	2
Rash	41	1	18	0
Vomiting	33	4	20	2
Abdominal pain	32	9	34	10
Headache	30	0	23	1
Decreased appetite	30	2	18	< 1
Dyspnea	29	6	9	0
Cough	28	1	15	0
Weight decreased	27	2	14	< 1
Asthenia	24	5	15	4
Pulmonary events[a]	12	3	< 1	0

[a] Related toxicities grouped for calculation.

Deaths—Up to 28 Days After Discontinuation

Carcinoid Tumors

	Patients, n (%)	
	Everolimus + octreotide N = 215	Placebo + octreotide N = 211
On-treatment deaths	18 (8)	11 (5)
Death due to disease progression	6 (3)	6 (3)
AE as primary cause of death	12 (6)	5 (2)

Summary
Carcinoid Tumors

- The primary PFS endpoint by IRC was not met (HR = 0.93, p = 0.298, Δ median PFS 1.0 mo)
  - Informative censoring affected this analysis
- PFS by investigator showed evidence of benefit
  - INV: HR = 0.78, p = 0.018, Δ median PFS 3.4 mo
  - IAC: HR = 0.77, p = 0.026, Δ median PFS 5.1 mo
- No benefit observed in OS
- Safety profile was consistent with previous clinical experience with everolimus

Next Steps— Carcinoid Tumors

- Novartis is committed to investigating therapies for patients with carcinoid tumors
- Future Phase III studies
  - Real-time central review
  - Stratification by important baseline factors

Management of Pancreatic Neuroendocrine Tumors: A Clinician's Perspective

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Scientific Rationale for mTOR Inhibition

CB-2

- mTOR activating genetic cancer syndromes associated with development of pancreatic NET
  - Tuberous Sclerosis,[1] Neurofibromatosis[1,2]
- Somatic mutations in mTOR pathway identified in pancreatic NET[3]
  - TSC2, PTEN, PIK3CA, NF1, IRS1
- Low protein expression of TSC2 and PTEN associated with short PFS and OS in pancreatic NET[4]

1. Yao JC, et al. in DeVita VT: Cancer: Principles & practice of oncology (ed 8th)., 2008;1702-1721.
2. Johannessen CM, et al. *Proc Natl Acad Sci USA*. 2005;102:8573-2578.
3. Jiao Y, et al. *Science*. 2011;331:1199-1203.
4. Missiaglia E, et al. *J Clin Oncol*. 2010;28:245-255.

Goals of Therapy in Pancreatic NET

CB-3

- Control tumor growth
  - Only streptozocin approved
- Minimize disease symptoms
  - Octreotide approved in VIPoma
  - Everolimus in malignant insulinoma[1]
- Prolong overall survival
  - No treatment option approved

1. Kulke MH et al. *N Engl J Med*. 2009;360:195-197.

Everolimus Clinical Study in Pancreatic NET

CB-4

- Largest well-controlled clinical trial in this setting
  - Conducted at major NET centers of excellence
- Well-defined patient population
- Rigorous application of RECIST, including central radiology
  - Consistent results in sensitivity analyses and with supportive studies[1,2]

1. Yao JC, et al. *J Clin Oncol*. 2008; 26:3063-3072.
2. Yao JC, et al. *J Clin Oncol*. 2010;28(1):69-76.

What Do the Data Mean for Patients?

CB-5

- Clinically meaningful improvement in PFS
  - 6.4-month prolongation
  - Consistent benefit across all subgroups
- Tumor shrinkage in majority of patients
- Decrease in tumor-secreted hormones associated with disease-related symptoms
- Acceptable safety profile
  - Adverse events generally manageable and reversible

Everolimus Benefit/Risk Assessment

CB-6

- Unmet need in advanced pNET
  - Rare disease
  - Limited evidence-based treatments available
  - Paucity of well-controlled contemporary clinical trials
- Everolimus led to statistically significant and clinically relevant improvement in PFS
- Everolimus represents an effective new therapeutic option where there have been few alternatives

Supportive Slides

Subgroup Analysis of PFS per INV—Somatostatin Analogue Use

Pancreatic NET

Subgroup	N	Hazard ratio (95% CI)	Median PFS, mo E	Median PFS, mo P
All patients	(410)	0.35 (0.27, 0.45)	11.0	4.6
Without concomitant SSA	(247)	0.34 (0.25, 0.46)	10.8	4.5
With concomitant SSA	(163)	0.43 (0.29, 0.64)	13.7	5.1
Without prior SSA	(207)	0.36 (0.25, 0.51)	10.8	4.9
With prior SSA	(203)	0.40 (0.28, 0.57)	11.2	3.7

Hazard ratio (95% CI)

← Favors Everolimus Favors Placebo →

E = Everolimus; P = Placebo.

DV Study 24 CSR Tables 11-7, 14.2-1.3, 14.2-1.26

Baseline Characteristics
Pancreatic NET

	Patients, n (%)	
	Everolimus N = 207	Placebo N = 203
Time since initial diagnosis		
Median (range), months	30 (0.8 - 297.2)	35 (0.5 - 216.2)
≤ 2 years	89 (43.0)	76 (37.5)
> 2 years to ≤ 5 years	54 (26.1)	81 (39.9)
> 5 years	64 (30.9)	46 (22.7)
Time from progression to randomization		
Median (range), months	1.7 (0.03 - 80.1)	1.7 (0.03 - 12.0)
≤ 3 months	146 (70.6)	143 (70.4)
> 3 month to ≤ 12 months	58 (28.0)	54 (26.6)
> 12 months	3 (1.4)	1 (0.5)
Missing	0	5 (2.5)

DV Study 24 CSR Table 11-4; Study 24 CSR 14.1-3.2

Tumor-Specific Characteristics at Baseline

Pancreatic NET

	Patients, n (%)	
	Everolimus N = 207	Placebo N = 203
Number of organs involved[a]		
1	51 (24.6)	62 (30.5)
2	85 (41.1)	64 (31.5)
≥ 3	70 (33.8)	77 (37.9)
Organ type involved[a]		
Liver	190 (91.8)	187 (92.1)
Pancreas	92 (44.4)	84 (41.4)
Lymph nodes	68 (32.9)	73 (36.0)
Other	53 (25.6)	56 (27.6)
Lung	28 (13.5)	30 (14.8)
Bone	13 (6.3)	29 (14.3)
Types of lesions[b]		
Target only	62 (30.0)	59 (29.1)
Target and non-target	144 (69.6)	144 (70.9)

[a] Organs as per target and non-target lesion locations observed at baseline by investigator.
[b] Types of lesions observed at baseline by investigator.

DV Study 24 CSR Table 11-5

Randomized Patients by Region and Country

Pancreatic NET

Region	Country	Number of sites	Randomized patients, n
America	Brazil	1	1
	Canada	5	19
	United States	24	165
EU	Belgium	3	15
	France	13	52
	Germany	5	18
	Greece	1	3
	Italy	7	30
	Spain	2	16
	Sweden	1	1
	Netherlands	1	7
	United Kingdom	4	9
ROW	Japan	3	40
	Slovakia	1	3
	South Korea	4	9
	Switzerland	1	2
	Taiwan	4	18
	Thailand	2	2
Total		82	410

Discordance in PFS Events Between Local (INV) and Central (IRC)

Pancreatic NET

Treatment group	Local investigator (INV)	Independent central radiology review (IRC)		
		Death	PD	Censor
Everolimus (N = 207)		n = 11	n = 76	n = 120
Death	n = 14	10	4	0
PD	n = 95	1	59	35
Censor	n = 98	0	13	85
Placebo (N = 203)		n = 10	n = 102	n = 91
Death	n = 7	6	1	0
PD	n = 158	4	93	61
Censor	n = 38	0	8	30

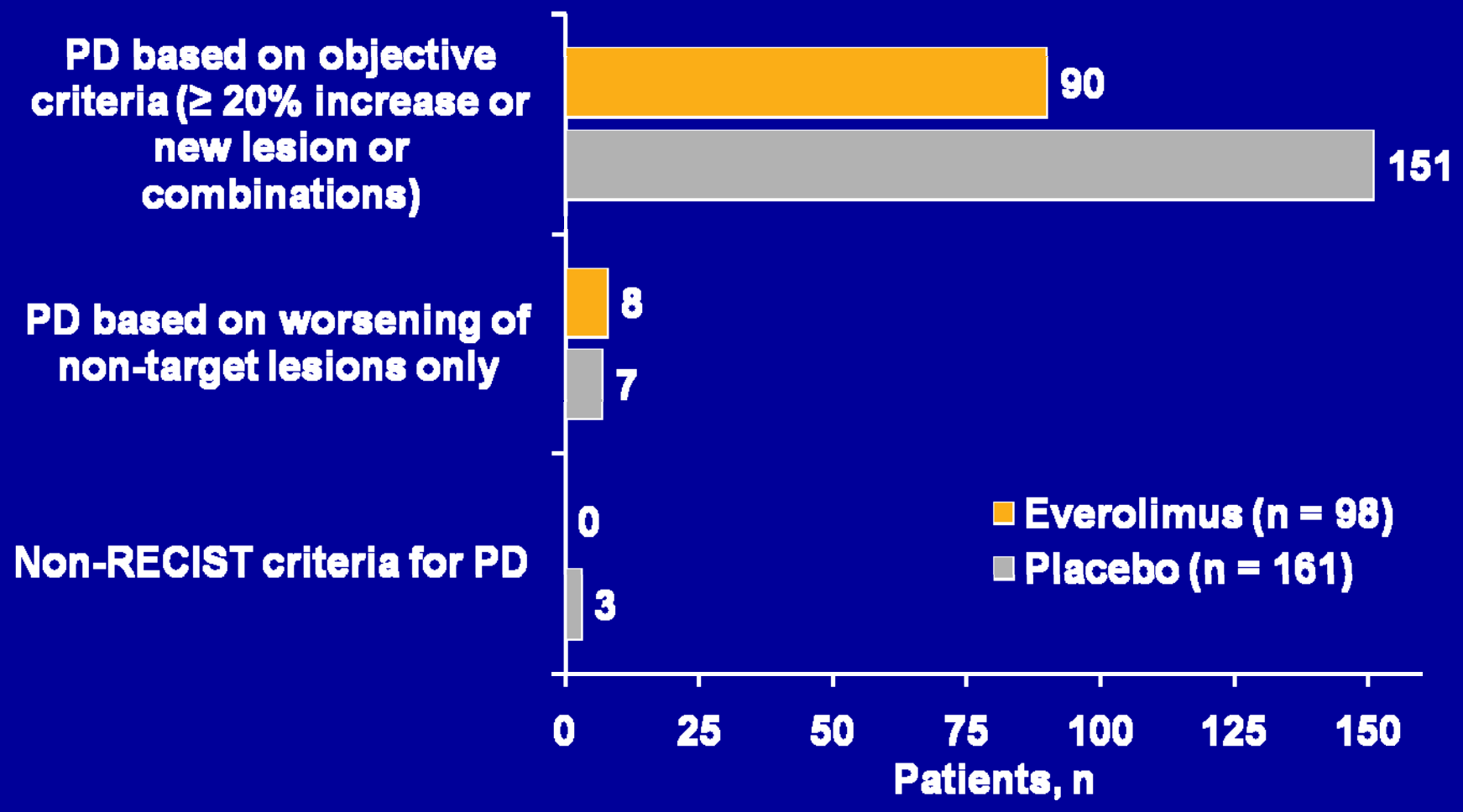
Discordance rates	
Everolimus	23%
Placebo	34%
Overall	29%

PD = Progressive disease.

Pancreatic NET CSR Table 14.2-1.10b, Table 11-10

RECIST Criteria Leading to Progression—INV by Category

Pancreatic NET



DV Study 24 CSR Table 14.2-1.18

PFS: Sensitivity Analyses
Carcinoid Tumors

	Median PFS, mo (95% CI)		
	Everolimus + octreotide n = 216	Placebo + octreotide N = 213	Hazard ratio (95% CI)
IRC			
Original primary	14.88 (12.22, 19.38)	13.90 (9.66, 19.09)	0.93 (0.71, 1.22)
IPCW			0.64 (0.45, 0.90)
IAC			
Amended primary	16.43 (13.67, 21.19)	11.33 (8.44, 14.59)	0.77 (0.59, 1.00)
Pre-specified adjusted model	16.43 (13.67, 21.19)	11.33 (8.44, 14.59)	0.76 (0.58, 1.00)
Per-protocol	16.62 (13.77, 21.75)	11.33 (8.44, 14.38)	0.75 (0.57, 0.98)
Actual event	16.36 (13.67, 19.48)	11.96 (8.71, 14.59)	0.80 (0.62, 1.02)
Backdating	13.77 (11.10, 16.62)	11.04 (8.31, 13.90)	0.84 (0.65, 1.07)
Combining INV & IRC	11.07 (8.80, 13.60)	8.15 (5.91, 8.61)	0.81 (0.65, 1.01)
INV	11.99 (10.61, 16.13)	8.61 (8.08, 11.14)	0.78 (0.62, 0.98)

DV Study 25 CSR Table 11-9, 11-10, 11-13, Table 14.2-14a, Table 14.2-14b, Table 14.2-1.4c, Table 14.2-1.11, Table 14.2-1.10, table 14.2-1.7b

Comparison of PFS by Baseline CgA Level— INV

Pancreatic NET—Full Analysis Set

	CgA ≤ 2 × ULN N = 218	CgA > 2 × ULN N = 187
Everolimus		
Patients, n	121	84
Events, n	63	45
Median PFS, months (95% CI)	11.17 (8.54, 16.49)	8.54 (7.69, 13.80)
Placebo		
Patients, n	97	103
Events, n	75	88
Median PFS, months (95% CI)	4.90 (2.99, 5.55)	4.34 (2.86, 5.39)
Stratified Cox model hazard ratio[a] (95% CI)[b]	0.38 (0.27, 0.53)	0.31 (0.21, 0.46)
Log-rank test[c] p value	< 0.001	< 0.001

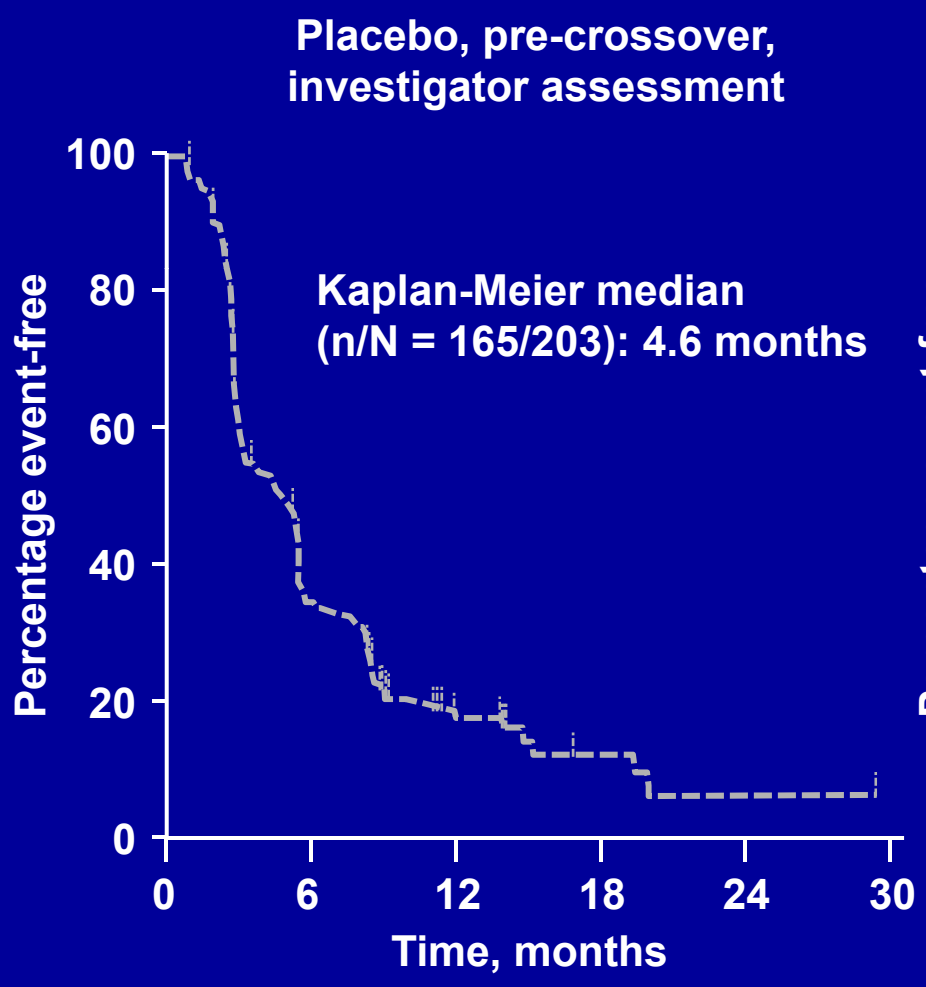
[a] Stratification factors are: prior cytotoxic chemotherapy (yes/no) and WHO performance status at baseline (0 vs 1-2).
[b] Hazard ratio < 1 implies lower risk of progression for patients in Everolimus 10 mg.
[c] p value obtained from one-sided stratified log-rank test adjusting for above stratification factors.

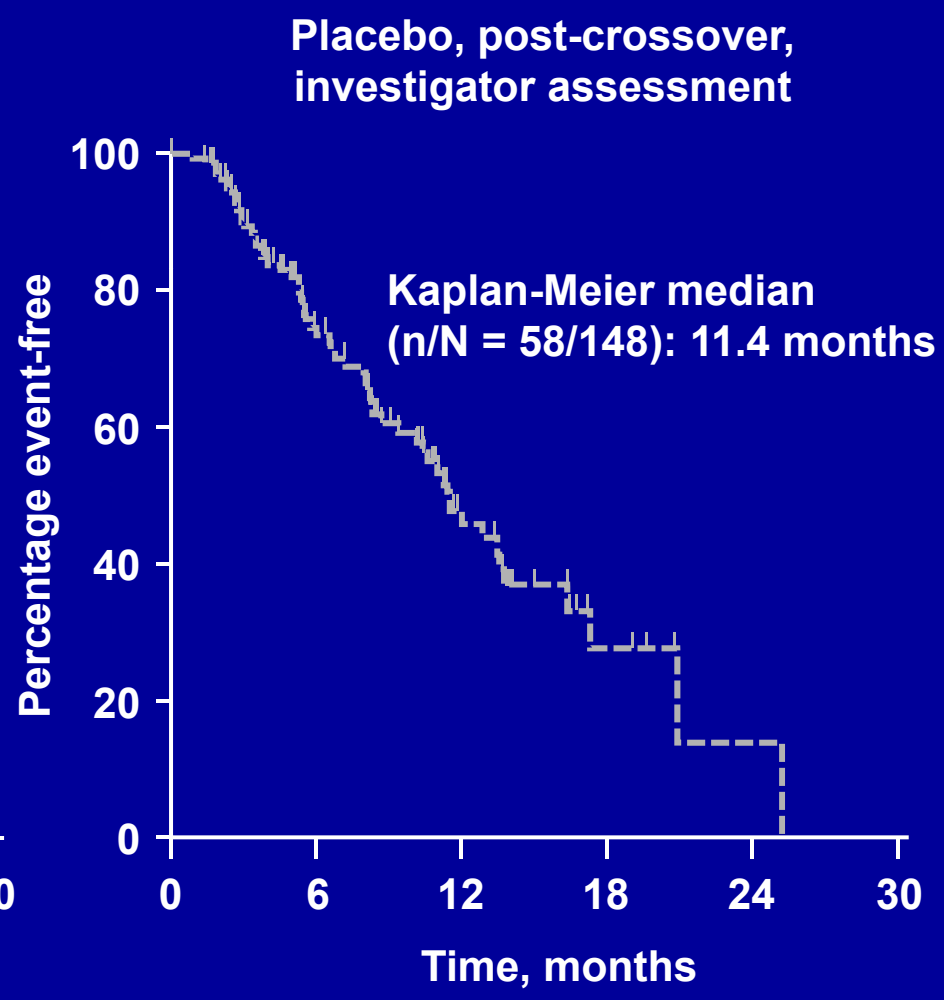
DV Study 24 CSR Table 14.2-6.4a

Subgroup Analysis of PFS by Prior Octreotide
Carcinoid Tumors

Data source for PFS/subgroups	N	HR (95% CI)	Median PFS, mo (95% CI)	
			Everolimus + Octreotide	Placebo + Octreotide
IRC	429			
Prior octreotide	321	0.98 (0.71 , 1.35)	14.23	13.90
Octreotide naive	108	0.82 (0.48 , 1.41)	16.43	13.04
IAC	429			
Prior octreotide	321	0.83 (0.61 , 1.12)	14.29	11.10
Octreotide naive	108	0.61 (0.36 , 1.04)	25.17	11.33
INV	429			
Prior octreotide	321	0.78 (0.60 , 1.01)	11.43	8.44
Octreotide naive	108	0.70 (0.42 , 1.17)	19.32	11.14

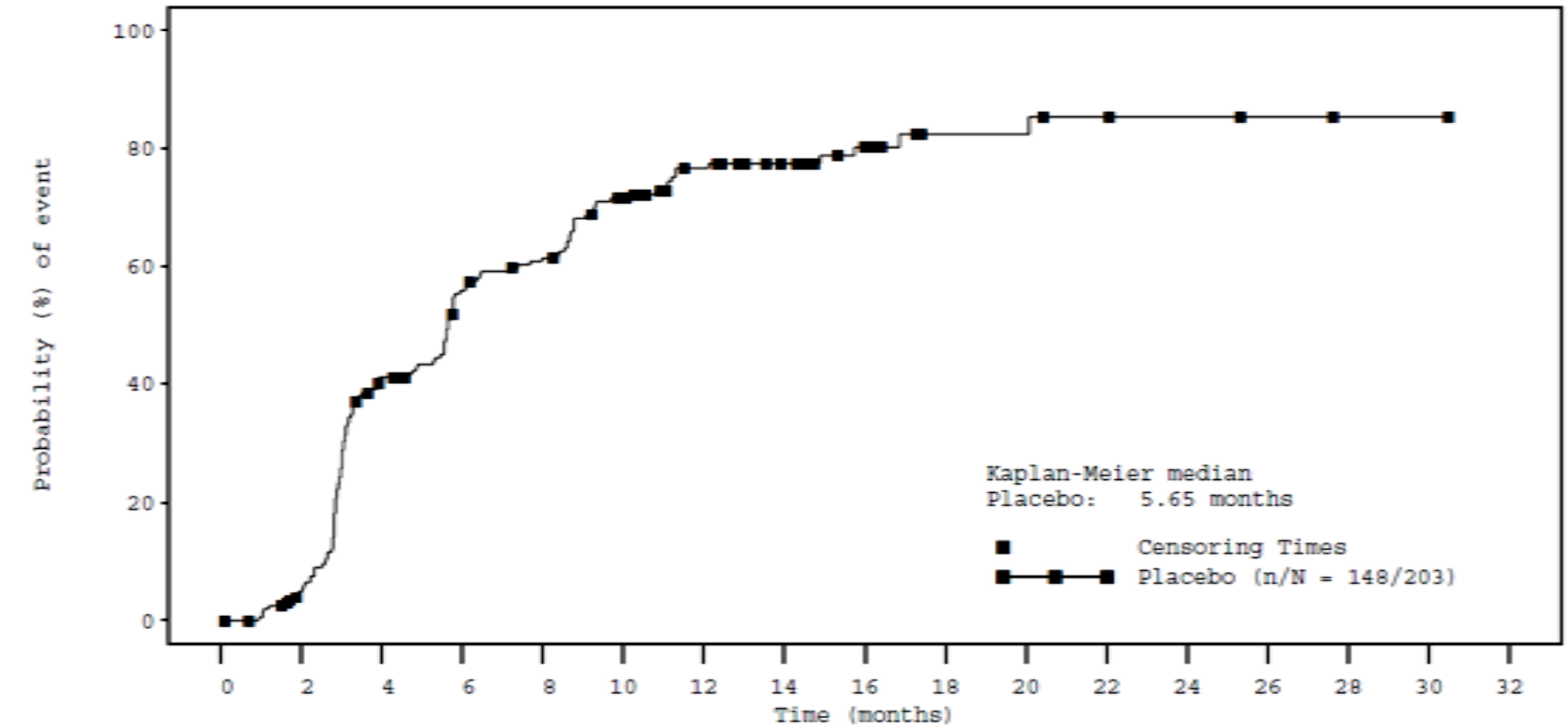
PFS Pre- and Post-crossover
Pancreatic NET





Time From Randomization to Crossover to Open-label Everolimus—Placebo Group

Pancreatic NET

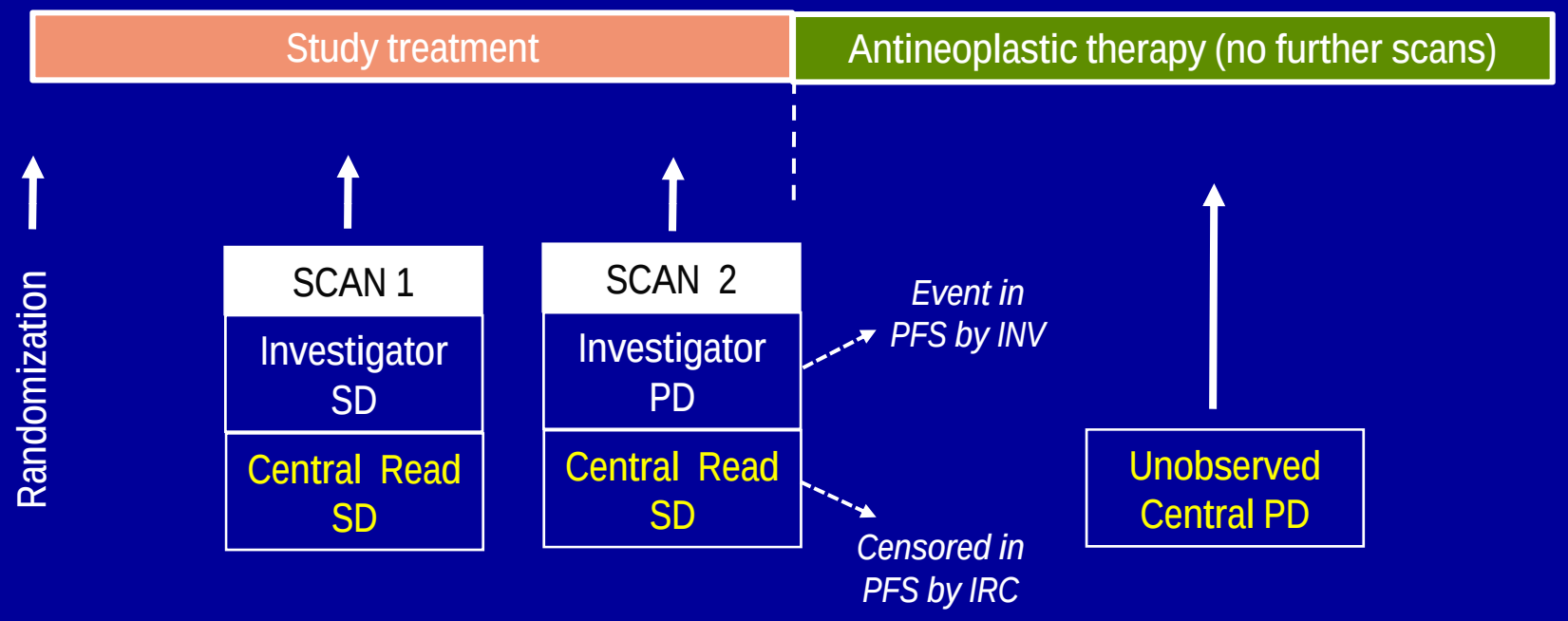


No. of patients still at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
Placebo	203	187	113	81	69	47	30	22	12	6	6	4	3	2	1	1	0

- n represents the number of patients in the placebo arm who received open-label Everolimus

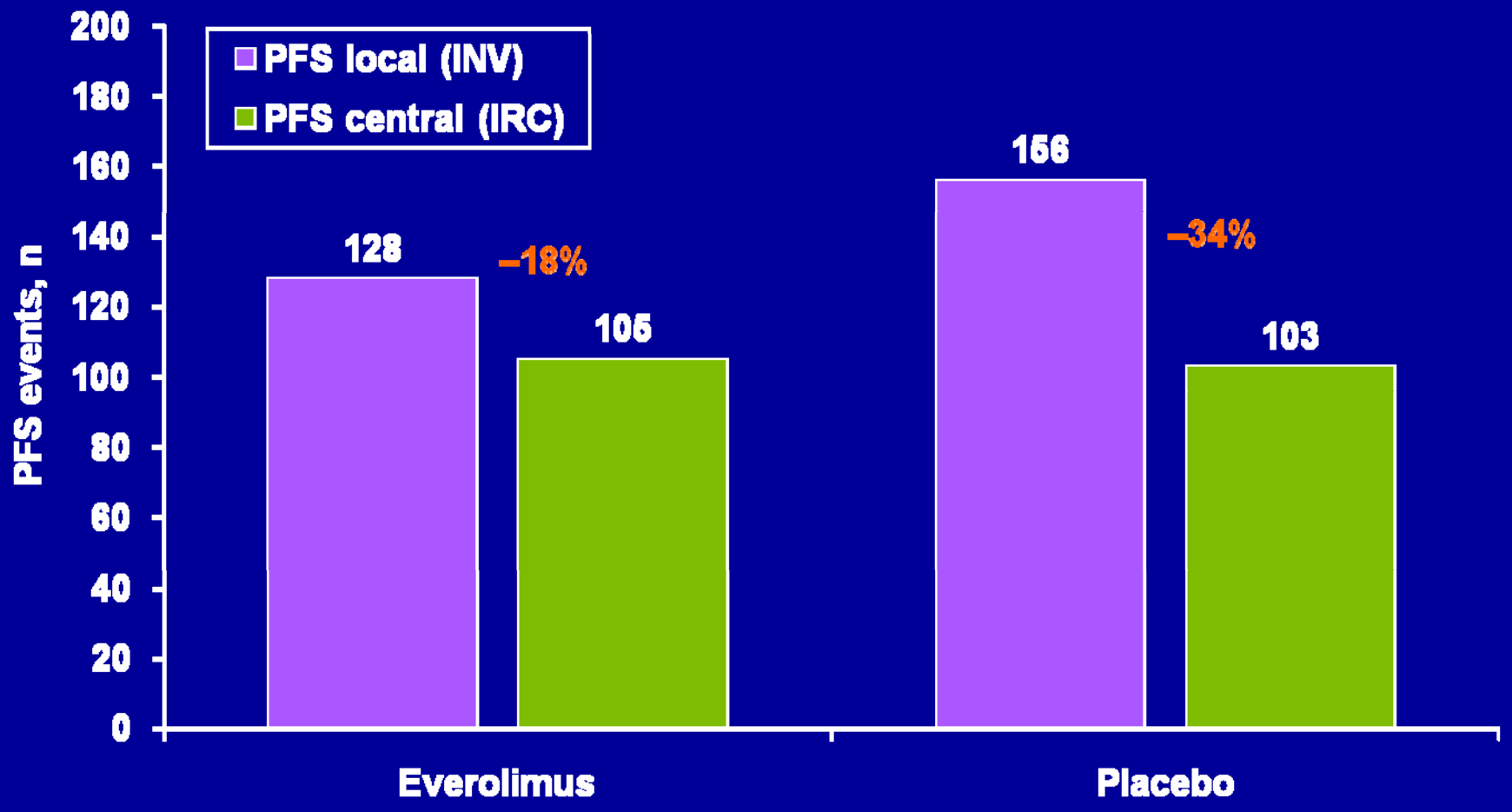
Informative Censoring in PFS by Central Radiology Review



- **May occur differentially in the two study arms leading to a confounded treatment effect estimate**

Number of PFS Events by Treatment Arm

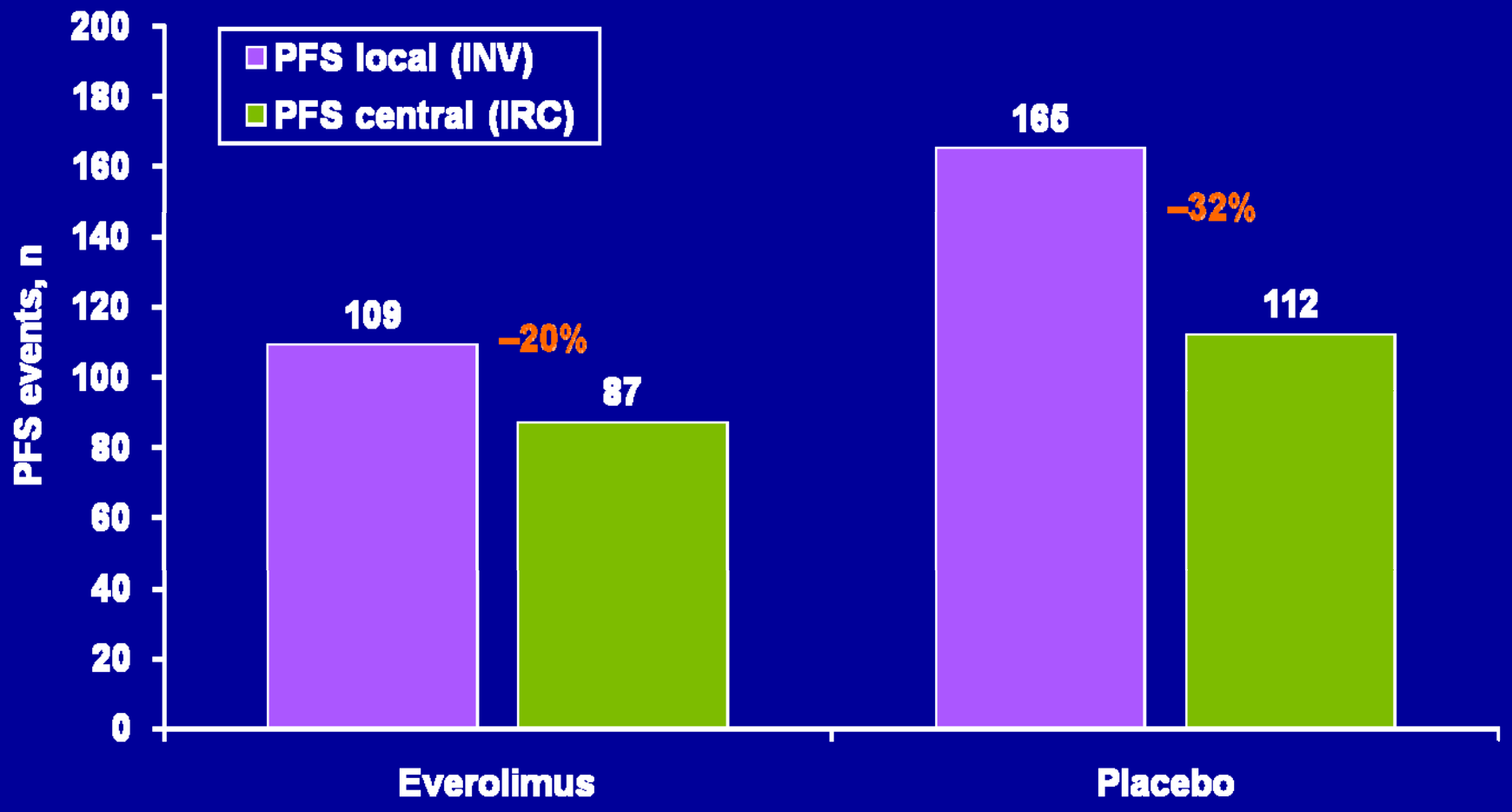
Carcinoid Tumors



Carcinoid Tumors CSR Tables 11-9 and 11-10

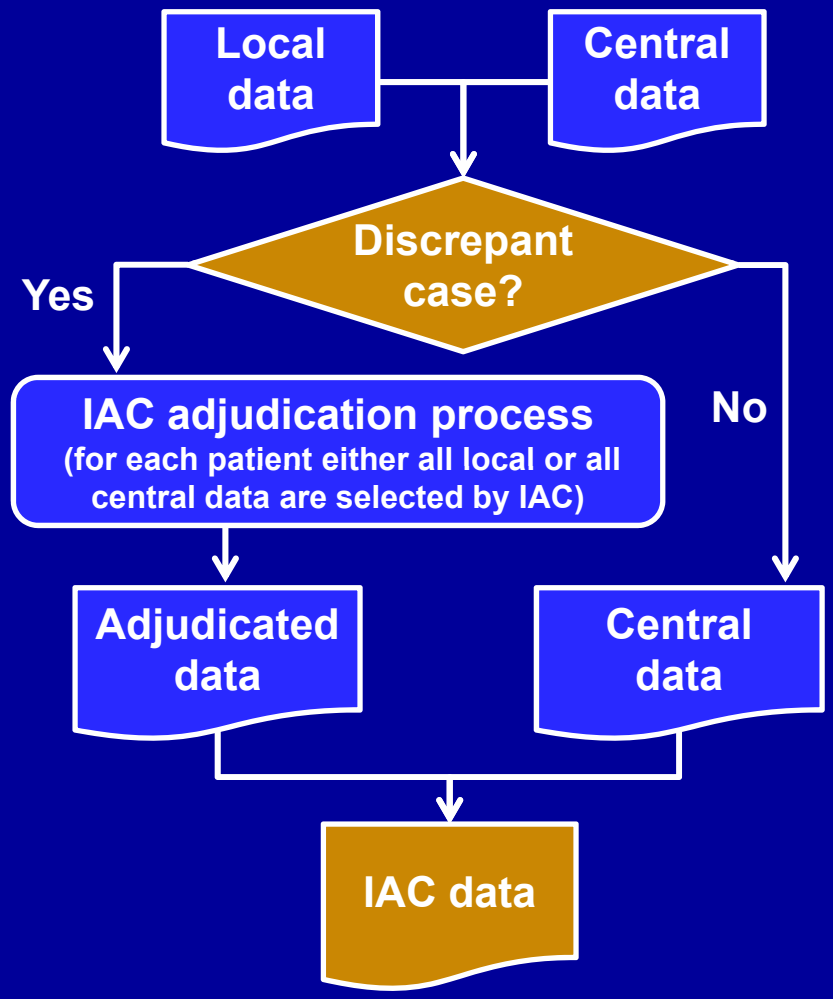
Number of PFS Events by Treatment Arm

Pancreatic NET



Pancreatic NET CSR Tables 11-7 and 11-9

Adjudication Process



IRC Confirmation of INV PD
Pancreatic NET

	Everolimus N = 207	Placebo N = 203
INV PDs[a]	95	158
Proportion of INV PDs confirmed by IRC	62%	59%

[a] Counted as PFS events

Pancreatic NET CSR Table 14.2-1.10b, Table 11-10.

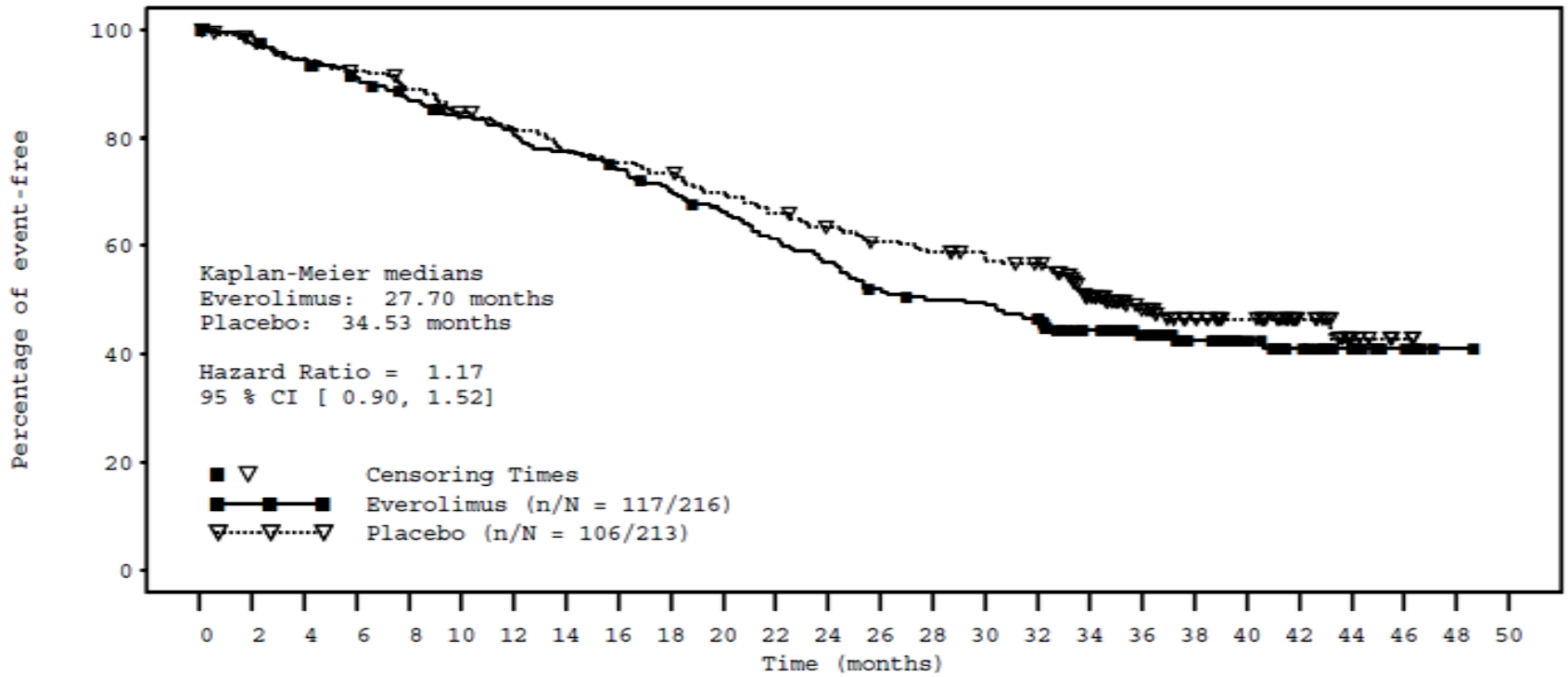
Overall Survival
Pancreatic NET

	Everolimus N = 207	Placebo N = 203
Analysis in CSR (Data cutoff Feb 28, 2010)	HR = 1.05 (95% CI: 0.71, 1.55) p = 0.594	
Events, n	51	50
Censored, n	156	153
90-day Safety Update (Data cutoff Jun 03, 2010)	HR = 0.99 (95% CI: 0.68, 1.43)	
Events, n	55	58
Censored, n	152	145
Data cutoff Feb 23, 2011	HR = 0.89 (95% CI: 0.64, 1.23)	
Events, n	68	78
Censored, n	139	125

Hazard ratio obtained from unadjusted stratified Cox model.
p value obtained from stratified one-sided log rank test.

DV Study 24 CSR Figure 14.2-2.1a; HEOF Figure 14.2.2.2a; 90-Day Safety Update Figure 5-1

Overall Survival—Cutoff March 10, 2011
Carcinoid Tumors



No. of patients still at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Everolimus	216	213	202	192	181	173	166	160	152	143	134	124	115	104	99	97	91	73	55	40	30	21	13	5	1	0
Placebo	213	205	199	193	185	175	168	160	155	151	143	135	128	121	117	112	108	82	59	43	35	18	6	2	0	0

- Hazard ratio is obtained from unstratified unadjusted Cox Model.

PFS Censoring Patterns
Local (INV) and Central (IRC) Assessment
Pancreatic NET

	Patients, n (%)			
	Local investigator (INV)		Central radiology (IRC)	
Reasons for censoring	Everolimus 10 mg N = 207	Placebo N = 203	Everolimus 10 mg N = 207	Placebo N = 203
Total censored patients	98 (47.3)	38 (18.7)	120 (58.0)	91 (44.8)
Ongoing without event	68 (69.4)	27 (71.1)	67 (55.8)	23 (25.3)
Lost to follow-up	1 (1.0)	0	1 (0.8)	0
Withdrew consent	2 (2.0)	3 (7.9)	1 (0.8)	3 (3.3)
Adequate assessment no longer available	9 (9.2)	1 (2.6)	13 (10.8)	0
New cancer therapy added	11 (11.2)	4 (10.5)	33 (27.5)	65 (71.4)
Event documented after ≥ 2 missing tumor assessments	7 (7.1)	3 (7.9)	5 (4.2)	0

Pancreatic NET CSR Table 14.2-1.7a, Table 14.2-1.7d

PFS: Sensitivity Analysis on IRC/IAC Censoring Patterns

Pancreatic NET

Conservative sensitivity analysis:

1. Everolimus patients censored for :
   - ‘lost-to-follow up’
   - ‘adequate assessment no longer available’
   - ‘event documented after 2 or more missing assessments’

   => event imputed at date of censoring
2. Patients in both arms censored for
   - ‘new cancer therapy’

   => event imputed at a simulated time based on the pooled distribution of the other patients

=> PFS by IAC: HR=0.50 (0.45; 0.56)
PFS by IRC: HR=0.58 (0.50; 0.66)

PFS—Sensitivity Analysis Combining IRC and INV

Pancreatic NET

Median PFS, mo (95% CI)		Comparison	
Everolimus n = 207	Placebo N = 203	p value	Hazard ratio (95% CI)
8.74 (8.31, 11.20)	4.57 (3.02, 5.39)	< 0.001	0.37 (0.29, 0.48)

Comparison of PFS by Ki 67 Level—INV

Pancreatic NET—Full Analysis Set

	Ki 67 ≤ 2% N = 24	2% < Ki 67 ≤ 5% N = 37	Ki 67 > 5% N = 42
Everolimus			
Patients, n	7	24	20
Events, n	5	13	13
Median PFS, months (95% CI)	12.52 (3.42, 14.75)	10.94 (5.55, 16.59)	7.69 (5.59, NA)
Placebo			
Patients, n	17	13	22
Events, n	12	11	17
Median PFS, months (95% CI)	3.68 (2.86, 5.52)	8.48 (3.78, 13.83)	3.15 (2.79, 5.55)
Stratified Cox model hazard ratio[a] (95% CI)[b]	0.36 (0.10, 1.33)	0.59 (0.24, 1.44)	0.36 (0.16, 0.82)
Log-rank test[c] p value	0.0564	0.1224	0.0055

[a] Stratification factors are: prior cytotoxic chemotherapy (yes/no) and WHO performance status at baseline (0 vs 1-2).
[b] Hazard ratio < 1 implies lower risk of progression for patients in Everolimus 10 mg.
[c] p value obtained from one-sided stratified log-rank test adjusting for above stratification factors.

DV Study 24 CSR Table 14.2-6.8a

Summary of AE Categories Adjusted for Exposure

Pancreatic NET—Safety Set

	Adjusted rate	
	Everolimus N = 204	Placebo N = 203
Adverse events (AEs)	126.3	200.8
Suspected to be drug related	122.0	153.1
Grade 3/4 AEs	76.3	80.1
Suspected to be drug related	57.5	28.4
Clinically notable AEs	120.7	146.0
Suspected to be drug related	115.7	86.2

% of patients adjusted for patient year exposure.

Subgroup Analysis of PFS by INV—Time From Prior Disease Progression to Randomization

Pancreatic NET

	Local (INV)	
	Everolimus N = 207	Placebo N = 203
≤ 3 months from prior PD to randomization		
Patients, n	148	146
PFS events, n (%)	84 (56.8)	120 (82.2)
Median PFS, mo	10.84	3.91
Improvement in median PFS, mo	6.93	
Hazard ratio (95% CI)	0.38 (0.29, 0.51)	
> 3 months from prior PD to randomization		
Patients, n	59	52
PFS events, n (%)	25 (42.4)	40 (76.9)
Median PFS, mo	14.00	5.72
Improvement in median PFS, mo	8.28	
Hazard ratio (95% CI)	0.36 (0.22, 0.61)	

DV Additional Efficacy Analysis Table 3-2