Everolimus

April 12, 2011

Kristen Snyder, MD, Efficacy
Gwynn Ison, MD, Safety

Review Team

Discipline	Reviewer	Team Leader
Clinical	Kristen Snyder (efficacy) Gwynn Ison (safety)	Ellen Maher
Pharm/Tox	Luan Lee	Haleh Saber
CMC	Jean Tang	Hari Sarker Sarah Pope
Clin Pharm	Sarah Schrieber Justin Earp	Qi Liu Christine Garnett
Biometrics	Kiki Ko	Shenghui Tang
Project Mgmt	Christy Cottrell	Alice Kacuba

Indications

- **Initial Proposed Indication**
  - Everolimus in the treatment of patients with advanced neuroendocrine tumors of gastrointestinal, lung, or pancreatic origin
- **Revised Proposed Indication**
  - Everolimus in the treatment of patients with advanced neuroendocrine tumors of pancreatic origin

Background Neuroendocrine Neoplasms

- Originate from neuroendocrine cells with various biologically active hormones
- Annual incidence 5.25 cases per 100,000
- Functional (insulinoma, gastrinoma, VIPoma, glucagonoma) vs Non-functional
- Occur as part of familial cancer predisposition syndromes: MEN1, VHL, NF1, TSC2
- Slow growing with low mitotic activity

Background
Neuroendocrine Carcinoma Survival

	Median OS (mo)	5 year OS	10 year OS
PNET (1988-2004)			
Regional	111	62%	46%
Metastatic	27	27%	11%
Carcinoid (1973-2004)			
Regional	111	68%	48%
Metastatic	33	35%	17%

Products Indicated for Neuroendocrine Tumors

- **Streptozocin**
  - Treatment of metastatic islet cell carcinoma of the pancreas
  - Limited to patients with symptomatic or progressive metastatic disease

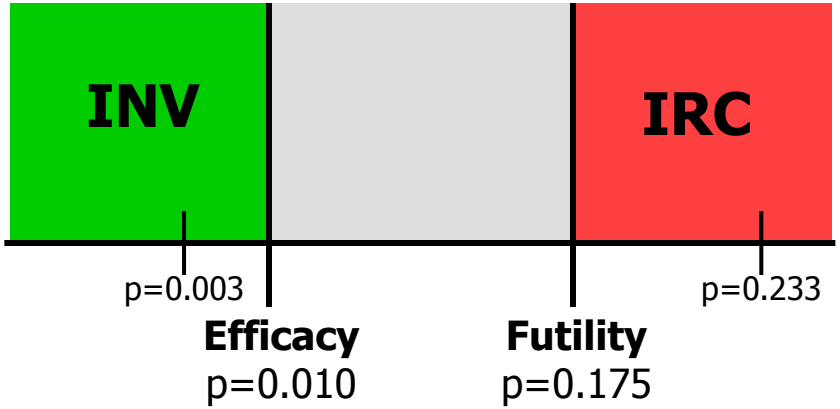
- **Octreotide acetate**
  - Symptomatic treatment of metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.

Regulatory History

January 2006	EOP2 meeting: Agreed two Phase 3 trials in the treatment of neuroendocrine tumors with 1° EP PFS by **IRC** would be submitted for SPAs
August - September 2007	SPA agreement reached for both Phase 3 trials **PNET:** PFS determined by **IRC** **Carcinoid:** PFS determined by **IRC**
February 2008	Orphan drug designation for treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NET) (September 2010 amended NET only)

Discordant Results

Carcinoid Trial (C2325) 2nd interim analysis demonstrated discordance of PFS between INV and IRC



- **IRC** PFS (p=0.233) crossed the **Futility Boundary** (p = 0.175)
- **INV** PFS (p=0.003) crossed the **Efficacy Boundary** (p = 0.010)

Discordant Results

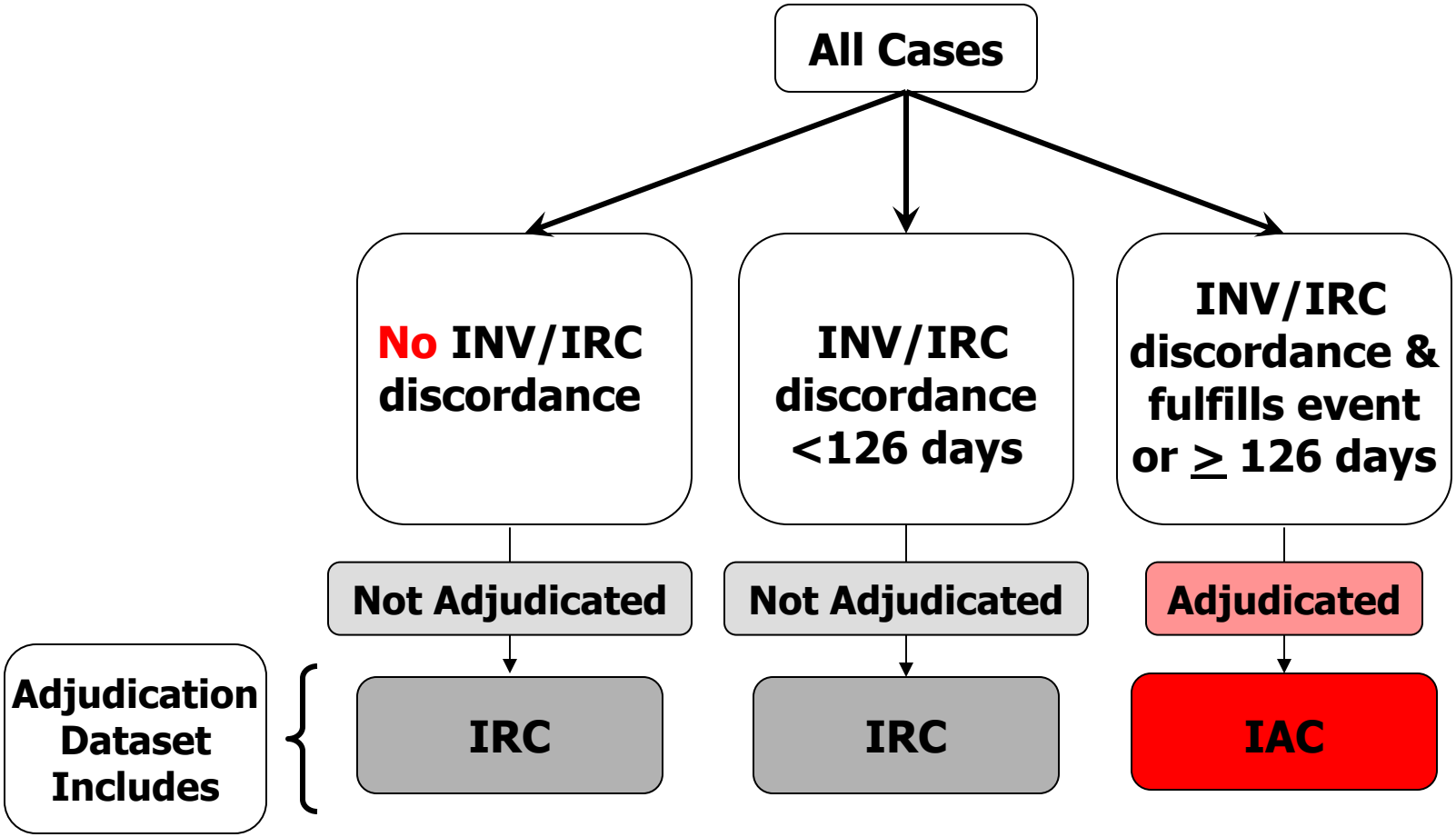
Applicant's amendments invalidating SPAs

- C2324 (PNET): PFS determined by **INV**
- C2325 (Carcinoid): PFS determined by **IAC** and final analysis cutoff changed from 287 PFS events to calendar date

Discordance Between INV and IRC

- **Timing of Event**
  - Date of Event
- **Type of Event**
  - PFS vs. Censored

Adjudication Analysis Dataset



Main Issues

1. C2324 (PNET) Trial
   - High discordance between INV and IRC reviews
   - Benefit-risk ratio

2. C2325 (Carcinoid) Trial
   - Primary endpoint did not reach statistical significance
   - High rate of discordance
   - Overall Survival at interim analysis favors placebo
   - Benefit-risk ratio

Study Design C2324 (PNET)

Patients w/ unresectable or metastatic, biopsy-proven pancreatic NET

Stratified by: Prior chemotherapy and WHO PS

Randomize 1:1

Everolimus 10 mg po daily + BSC

N = 207

Placebo po daily + BSC

N = 203

Assessments q12 wks ±1 week until progression as determined by local investigator using RECIST guidelines

Optional crossover to open-label Everolimus after documented PD
72.9% Crossover

Endpoints

1°: PFS by **IRC**; amended to **INV**

2°: OS, RR, duration of response

Final Analysis 282 PFS Events

C2324 (PNET)

Key Eligibility Criteria
1. Unresectable or metastatic PNET 2. Low or intermediate-grade neuroendocrine carcinoma 3. Disease progression $\leq$ 12 mo prior to entry 4. Measurable disease per RECIST 5. No hepatic embolization $\leq$ 6 mo prior to entry; unless other sites of measurable disease 6. No cryoablation/radiofrequency ablation $\leq$ 4 wks prior to entry 7. Performance status 0-2

C2324 (PNET) Results

C2324 (PNET) Baseline Demographics

	PNET	
	Everolimus N=207	**Placebo N=203**
Mean age (standard deviation)	57 (± 12.2)	56.2 (±11.4)
Sex		
Male	110	117
Female	97	86
Race		
Caucasian	158	166
Hispanic	7	11
Black	9	2
Asian	40	34
Native American	0	0
Other	0	1
Performance Status		
0	140	131
1	61	63
2	6	9

C2324 (PNET) Prior Therapies

	PNET	
	Everolimus N=207	**Placebo N=203**
Median Time Since Diagnosis (Range)	2.5 years (0.07 – 24.7)	2.9 years (0.04 - 18)
Prior Therapy		
Surgery (including biopsy)	207	207
Radiation Therapy	47	40
Chemotherapy	119	118
Octreotide	101	102
Embolization	43	42

C2324 (PNET) Disease Characteristics

	PNET	
	Everolimus N=207	Placebo N=203
Primary Site		
Pancreas	97.1%	98.5%
Unknown	1.9%	1.0%
Other	1.0%	0.5%
Histological Grade		
Well Differentiated	82.1%	84.2%
Moderately Differentiated	16.9%	14.8%
Poorly Differentiated	0	0
Unknown	1.0%	1.0%
Sites of Target/Non-Target Lesions		
Liver	92.2 %	92.1%
Pancreas	44.4%	41.4%
Lymph Node/Spleen	33.8%	36.5%
Lung/Pleura	15.5%	16.7%
Bone	6.3%	14.3%

C2324 (PNET) Disposition at Data Cut-off

	PNET Cut-off Date (2-28-10)	
	Everolimus	**Placebo**
Randomized	207	203
Treated	204	203
Ongoing	66	26
Discontinued	141	177
Progressive Disease	92	163
Death due to Disease	1	2
Adverse Event	36	7
Death due to Adverse Event	3	1
Patient Decision	4	4
Lost to Follow Up	1	0
Protocol Violation	4	0
New Cancer Therapy	0	0

[1] One cause of death listed as unknown. Review of the narrative suggests progressive disease.

C2324 (PNET) 1° Endpoint: PFS

	PNET					
	INV		IRC		Adjudication	
	Everolimus	Placebo	Everolimus	Placebo	Everolimus	Placebo
# PFS Events	109	165	87	112	95	142
# Censored Events	98	38	120	91	112	61
Median PFS (mo)	11.0	4.6	13.7	5.7	11.4	5.4
Hazard Ratio[1]	0.35		0.38		0.34	
p-value[2]	< 0.001		< 0.001		< 0.001	

[1] Stratified (prior cytotoxic chemotherapy and performance status), unadjusted Cox proportional hazards model
[2] Stratified logrank test

C2324 (PNET)
Discordant and Adjudicated Cases

	Everolimus N=207	**Placebo N=203**	Total N=410
INV/IRC Discordant Cases	78 (37.7%)	90 (44.3%)	168 (41.0%)
Adjudicated Cases	58 (28.0%)	75 (36.9%)	133 (32.4%)

C2324 (PNET)
Discordant and Adjudicated Cases

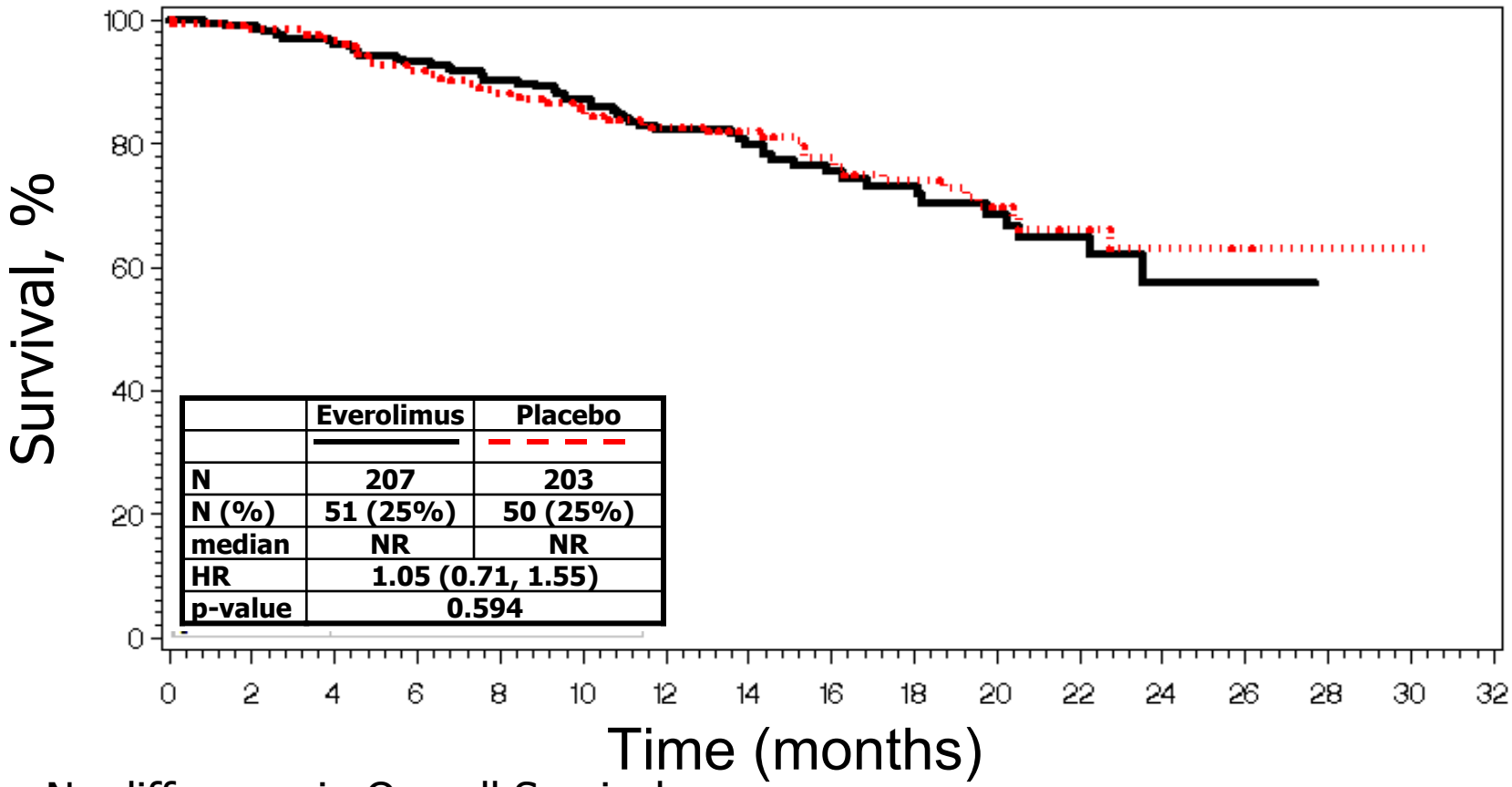
Discordance Between INV and IRC Assessment of PFS Events (Cut-off Dates 2-10)						
	Everolimus			**Placebo**		
	Type	Timing	Total	Type	Timing	Total
PNET N=168	25.6%	12.1%	37.7%	36.4%	7.9%	44.3%

C2324 (PNET)
2° Endpoint: Response Rate (INV)

	PNET					
	INV		IRC		Adjudication	
Best Overall Response	Everolimus N= 207	Placebo N=203	Everolimus N= 207	Placebo N=203	Everolimus N= 207	Placebo N=203
Objective response rate (ORR[CR or PR])	4.8%	2.0%	2.4%	0.5%	2.9%	0.5%
95% CI for ORR[1]	(2.3, 8.7)	(0.5, 5.0)	(0.8, 5.5)	(0.0, 2.7)	(1.1, 6.2)	(0.0, 2.7)

[1] Confidence interval (CI) based on the exact binomial CI.

C2324 (PNET)
2° Endpoint: OS



	Everolimus	Placebo
	———	- - - -
N	207	203
N (%)	51 (25%)	50 (25%)
median	NR	NR
HR	1.05 (0.71, 1.55)	
p-value	0.594	

- No difference in Overall Survival
- Response rate < 5%

C2325 Carcinoid Trial

C2325 (Carcinoid) Study Design

Patients w/ unresectable or metastatic, biopsy-proven carcinoid tumor w/ measurable disease and history of carcinoid syndrome

Randomize 1:1

Everolimus 10 mg po daily + Octreotide IM q 28 days

N = 216

Assessments q12 wks ±1 week until progression as determined by local investigator using RECIST guidelines

Placebo po daily + Octreotide IM q 28 days

N = 213

Optional crossover to open-label Everolimus after documented PD
58.2% Crossover

Endpoints

1°: PFS by **IRC** amended post-hoc to **IAC**;

2°: ORR, duration of response, OS, 5-HIAA and CgA levels

C2325 (Carcinoid)

Key Eligibility Criteria
1. Unresectable or metastatic carcinoid tumor 2. Low or intermediate-grade neuroendocrine carcinoma 3. Disease progression ≤ 12 mo prior to entry 4. Measurable disease per RECIST 5. No hepatic embolization ≤ 6 mo prior to entry; unless other sites of measurable disease 6. No cryoablation/radiofrequency ablation ≤ 4 wks prior to entry 7. Performance status 0-2 8. History of diarrhea/flushing or both, symptoms not required at entry

C2325 (Carcinoid) Statistical Analysis Plan

- Sample size determination
  - Planned: 287 PFS events to detect HR=0.67
  - Two interim analyses planned at 20% and 60%
  - Final analysis amended to calendar date cut-off
- Censoring rules for PFS
  - PD/death after ≥2 missing assessments (~6 months) censor at last adequate assessment
- Sensitivity analyses
  - IPCW (inverse probability censoring weights)
  - Actual Event
  - Backdating

C2325 (Carcinoid) Results

C2325 (Carcinoid) Baseline Demographics

	Everolimus N=216	Placebo N=213
Mean age (std dev)	60.1 (± 10.7)	59.4 (±11.1)
Sex		
Male	97	124
Female	119	89
Race		
Caucasian	207	200
Hispanic	3	1
Black	5	7
Asian	1	1
Native American	1	0
Other	2	5
Performance Status		
0	118	140
1	84	62
2	14	10
Unknown	0	1

C2325 (Carcinoid) Baseline Demographics

	Everolimus N=216	Placebo N=213
Median Time Since Diagnosis (Range in years)	3.6 years (0.04 – 38.4)	3.5 years (0.08 – 34.2)
Prior Therapy		
Surgery	216	212
Radiation Therapy	52	58
Chemotherapy	101	84
Embolization	31	30
History of Flushing and/or Diarrhea	206	205
Flushing and/or Diarrhea at Entry	170	172
Somatostatin Use at Entry	173	165

C2325 (Carcinoid) Disease Characteristics

	Everolimus N=216	Placebo N=213
Primary Site		
Small Intestine	111	113
Lung	33	11
Unknown/Other	26	27
Colon	14	14
Pancreas	11	15
Other	21	33
Histological Grade		
Well Differentiated	166	175
Moderately Differentiated	38	30
Poorly Differentiated	1	1
Unknown	11	7
Sites of Target/Non-Target Lesions	215	212
Liver	199	200
Lymph Node/Spleen	89	91
Lung/Pleura/Mediastinum	79	61
Bone	40	27
Number of Organs Involved		
1-3	165	183
$\geq$ 4*	50	30

* This imbalance is not present in the IRC review

C2325 (Carcinoid) Disposition at Data Cut-off

	Carcinoid (Cut-off Date 4-2-10)	
	Everolimus	**Placebo**
Randomized	216	213
Treated	215	211
Ongoing	37	34
Discontinued	179	179
Progressive Disease	95	146
Death due to Disease	1	0
Adverse Event	57	14
Death due to Adverse Event	5[1]	2
Patient Decision	17	11
Lost to Follow Up	0	1
Protocol Violation	3	4
New Cancer Therapy	1	1

[1] One cause of death listed as unknown. Review of the narrative suggests progressive disease.

Efficacy Results of Study C2325

C2325 (Carcinoid) Discordant and Adjudicated Cases

	Everolimus N=216	Placebo N=213	Total N=429
INV/IRC Discordant Cases	105 (48.6%)	118 (55.4%)	223 (52.0%)
Adjudicated Cases	77 (35.6%)	92 (43.1%)	169 (39.4%)

C2325 (Carcinoid) Discordant Cases

Discordance Between INV and IRC Assessment of PFS Events in (Cut-off Dates 2-10)						
	Everolimus			Placebo		
	Type	Timing	Total	Type	Timing	Total
Carcinoid N=169	32.4%	16.2%	48.6%	40.8%	14.4%	55.4%

C2325 (Carcinoid) Trial Discordance in Individual PFS Events

Carcinoid-Discordances in Individual PFS Events (Cut-off Date 4-2-10)						
	Everolimus			**Placebo**		
	INV-Death	INV-PD	INV-Censored	INV-Death	**INV-PD**	INV-Censored
IRC-Death	0	10	1	0	1	0
IRC-PD	3	26	16	5	28	14
IRC-Censored	0	40	9	0	67	3
Total	3	76	26	5	96	17

C2325 (Carcinoid) Discordant Cases

Carcinoid-Discordances in Individual PFS Events (Cut-off Date 4-2-10)						
	Everolimus			**Placebo**		
	INV-Death	**INV-PD**	INV-Censored	INV-Death	**INV-PD**	INV-Censored
IRC-Death	0	10	1	0	1	0
IRC-PD	3	26	16	5	28	14
IRC-Censored	0	40	9	0	67	3

C2325 (Carcinoid) 1° Endpoint: PFS

	INV		IRC		Adjudication	
	Everolimus N=216	Placebo N=213	Everolimus N=216	Placebo N=213	Everolimus N=216	Placebo N=213
# PFS Events	128	156	105	103	103	120
# Censored Events	88	57	111	110	113	93
Median PFS	12.0	8.6	14.9	13.9	16.4	11.3
Δ PFS (months)	7.6		1		5.1	
Hazard Ratio[1]	0.78		0.93		0.77	
p-value[2]	0.018		0.298		0.026	

[1] Unstratified, unadjusted Cox proportional hazards model
[2] Unstratified logrank test

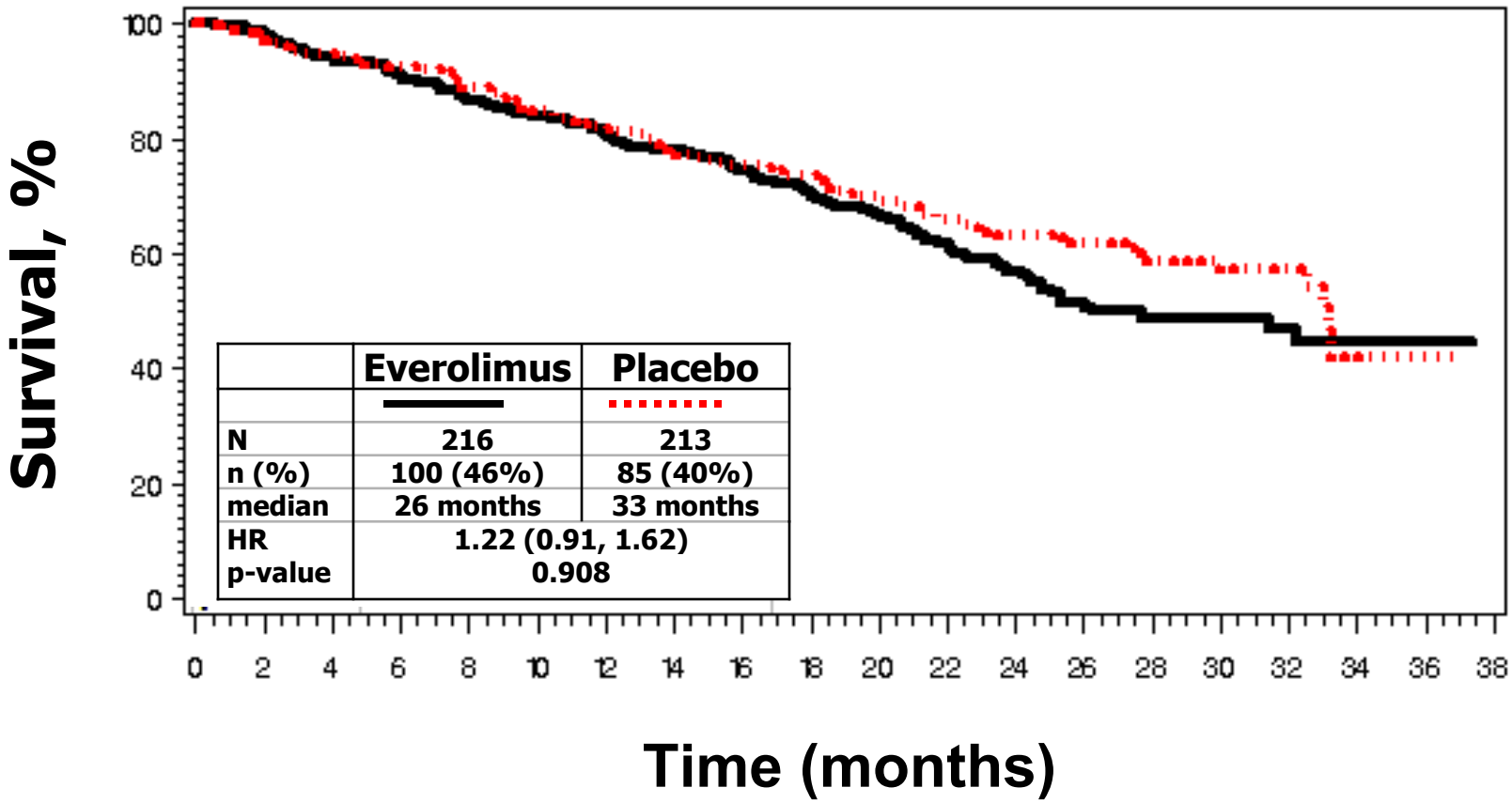
- Prespecified α for final analysis 0.024
- Agency: p = 0.298
- Applicant: p = 0.026

C2325 (Carcinoid)
2° Endpoint: Response Rate (IAC)

	INV		IRC		Adjudication	
Best Overall Response	Everolimus N=216	Placebo N=213	Everolimus N=216	Placebo N=213	Everolimus N=216	Placebo N=213
Objective response rate (ORR[CR or PR])	3.2%	2.4%	1.9%	1.4%	2.3%	1.9%
95% CI for ORR[1]	(1.3, 6.6)	(0.8, 5.4)	(0.5, 4.7)	(0.3, 4.1)	(0.8, 5.3)	(0.5, 4.7)

[1]Confidence interval (CI) based on the exact binomial CI.

C2325 (Carcinoid) 2° Endpoint: OS



	Everolimus	Placebo
	———	·····
N	216	213
n (%)	100 (46%)	85 (40%)
median	26 months	33 months
HR	1.22 (0.91, 1.62)	
p-value	0.908	

Safety Results

Safety Summary

Study	Design/Population	No. patients receiving 10 mg dose
PNET (C2324)	Double-blind, randomized placebo-controlled, Phase 3 + open-label extension/ Adv. PNET	**204 + 153** (open-label following placebo cross-over)
Carcinoid (C2325)	Double-blind, randomized placebo-controlled, Phase 3 + open-label extension/ Adv. Carcinoid Tumor	**215 + 128** (open-label following placebo cross-over)
PNET (2239)	Open-label stratified Phase 2/ Adv. PNET after chemotherapy	Stratum 1: **115** Stratum 2: **45**
Total		**858**

Exposure

	PNET		Carcinoid	
	E n=204	**P** N= 203	**E** N=215	**P** N= 211
Median in wks (Range)	37.3 (1.1-129.9)	16.1 (0.4-146.0)	37.0 (0.6-175.6)	36.6 (0.4-165.1)

Exposure

	PNET		Carcinoid	
	E N=204	**P** N=203	**E** N=215	**P** N=211
Delay and/or Reduction	61.3%	29.1%	67.0%	37.0%
1 Delay/ Reduction	15.2%	14.3%	15.3%	20.9%
≥2 Delays/ Reductions	45.1%	14.8%	51.6%	16.6%

Safety Overview

	PNET		Carcinoid	
	E n= 204	P n=203	E+O n=215	P+O n=211
All Deaths	5.9%	2.5%	8.8%	5.7%
Discontinuations	20.1%	5.9%	28.3%	20.9%
SAE	40.7%	25.6%	58.6%	34.6%
G 3-4 AE	61.8%	40.4%	74.9%	51.7%
G 1-4 AE	99.5%	97.5%	100%	96.2%

PNET Study
Safety

PNET (Double-Blind) Deaths/Discontinuations due to AEs

	Everolimus N= 204	**Placebo** N= 203
All deaths during double-blind therapy	**12**	**5**
Deaths due to AE	7	1
Deaths due to PD	5	4
Discontinuation due to AE	41	12

PNET DB- Cause of Death

Adverse Event	E N= 204	P N=203
Acute renal failure	1	0
ARDS	1	0
Cardiac arrest	1	0
Death NOS	1	0
Hepatic failure	1	0
Pneumonia	1	0
Pulmonary Embolus	0	1
Sepsis	1	0
Total	**7**	**1***

*There were 2 additional deaths in placebo patients who crossed to everolimus during open-label: 1 sudden death, 1 hypoglycemia.

PNET DB- G3-4 AEs ≥ 5%

Preferred Term	E N= 204 %	P N= 203 %
Any	61.8	40.4
Anemia	12.7	2.0
Hyperglycemia	10.3	3.9
Stomatitis	6.9	0
Hypophosphatemia	6.4	0.5
Fatigue/ Malaise	5.4	5.4
Diarrhea	5.4	2.5
Abdominal pain	3.9	7.4

PNET DB- G1-4 AEs ≥ 30%

Preferred term	E N=204 %	P N= 203 %
Any	99.5	97.5
Stomatitis	69.6	19.7
Rash	59.3	18.7
Diarrhea	49.5	9.9
Fatigue/ Malaise	44.6	27.1
Edema	39.2	11.8
Abdominal Pain	36.3	31.9
Nausea	31.9	32.5
Pyrexia	30.9	12.8
Headache/ Migraine	30.4	14.8

Carcinoid Study Safety

Octreotide Adverse Events

- Cardiac conduction abnormalities
- Hyper or hypoglycemia
- Gallstone formation
- Liver dysfunction (mostly cholestatic) and pancreatitis
- Hypothyroidism
- ↓ Vitamin B12 Level
- Headache, dizziness

Carcinoid (Double-Blind) Deaths/Discontinuations due to AEs

	E + O N= 215	P + O N= 211
All deaths during double blind	**19**	**12**
Deaths due to AE	12	5
Deaths due to PD	7	7
Discontinuation due to AE	61	44*

*Compared with 12 AE-related discons on placebo arm in the PNET trial.

Carcinoid DB- Cause of Death

Adverse Event	E+O N= 216	P+O N= 213
Acute respiratory failure	1	0
Cardiopulmonary failure/ CHF	2	1
Cardiac arrest/ sudden death	2	1
Hepatic failure	2	3
Pneumonia	1	0
Pulmonary embolism	2	0
Sepsis	1	0
Death NOS	1	0
Total	**12**	**5**

Carcinoid DB- G3-4 AEs >5%

Preferred Term	E + O N= 216	P + O N= 213
Any	74.5%	51.2%
Diarrhea	15.3	8.0
Hypokalemia	12.5	1.4
Fatigue/ Malaise	11.1	3.8
Abdominal pain	10.6	12.2
Hyperglycemia	6.9	0.9
Anemia	6.0	1.9
Cardiac valve disease	5.6	1.9
Pneumonia	5.6	0.9
Stomatitis	5.9	0.5
Dyspnea	5.6	0.5
Tachycardia	5.6	0

Carcinoid DB- G1-4 AEs ≥ 30%

Preferred term	E +O N=215	P +O N= 213
Any	100%	95.3%
Stomatitis	66.0	16.1
Diarrhea	54.4	38.9
Fatigue/ Malaise	49.3	45.5
Rash	43.7	18.3
Edema	43.3	23.0
Nausea	42.8	30.0
Abdominal Pain	39.5	44.1
Vomiting	33.0	20.2
Dyspnea	32.1	13.6
Headache	31.6	23.9
Cough	30.7	16.0
Anemia	30.2	12.3

Adverse Events of Interest

- Pneumonitis
- Opportunistic infections
- Renal failure

Pneumonitis

- Adverse event reports
- Chest CT evaluated for evidence of pneumonitis q 12 wks
- Information captured on bronchoscopies

Pneumonitis Adverse Events

Incidence by AE report	N= 858 (%)
Grade 4	1 (0.1)
Grade 3	14 (1.6)
Grade 2	46 (5.4)
Grade 1	32 (3.7)
Total	**93 (10.8)**

Pneumonitis

- Median onset- 169 days
- Median duration- 59.5 days
- Median age for pneumonitis patients- 61 y
- Caucasian (80%), Asian (14%)
- Males = Females
- 58/93 patients on 10 mg everolimus at onset

Pneumonitis by Imaging

- 5.9% at baseline
- 14.2% placebo
- 135 (35.4%) everolimus
- Of the 135 patients, the adverse event pneumonitis was reported in 39 patients

Opportunistic Infections

- **Hepatitis B-** 1 case reactivation of prior infection in everolimus patient in PNET study resulted in hepatic failure and death
- **Mycobacterial-** 3 cases identified in PNET study, all in everolimus patients
- **Invasive fungal (aspergillus)-** 1 PNET patient on everolimus, 1 carcinoid patient on everolimus

Renal Failure

	PNET		Carcinoid	
# cases	**E**	**P**	**E+O**	**P+O**
G 3-4	6	3	8	1

Conclusion – PNET Trial

- Improvement in median PFS ranged from 6 to 8 months, with consistent HR (0.34 - 0.38) using various assessments of PFS
- No difference in OS between the two arms (20% event rate, 73% crossover)
- Safety profile consistent with the known toxicities of everolimus
- 7 deaths attributable to AE in the everolimus arm, compared with 1 on the placebo arm
- Benefit-risk analysis should be considered in light of the natural history of this disease

Conclusion – Carcinoid Trial

- Does not lend support to the PNET indication, a related neuroendocrine tumor
- Trend in OS favors placebo
- Adverse events reported more frequently in the Carcinoid than in the PNET trial
- 12 deaths attributable to AE on the everolimus arm of this trial, compared with 5 on the placebo arm