X Seminario I.T.M.O.

Neoplasie a bassa incidenza

07 maggio 2012

Nuove approvazioni da EMA per i NETs

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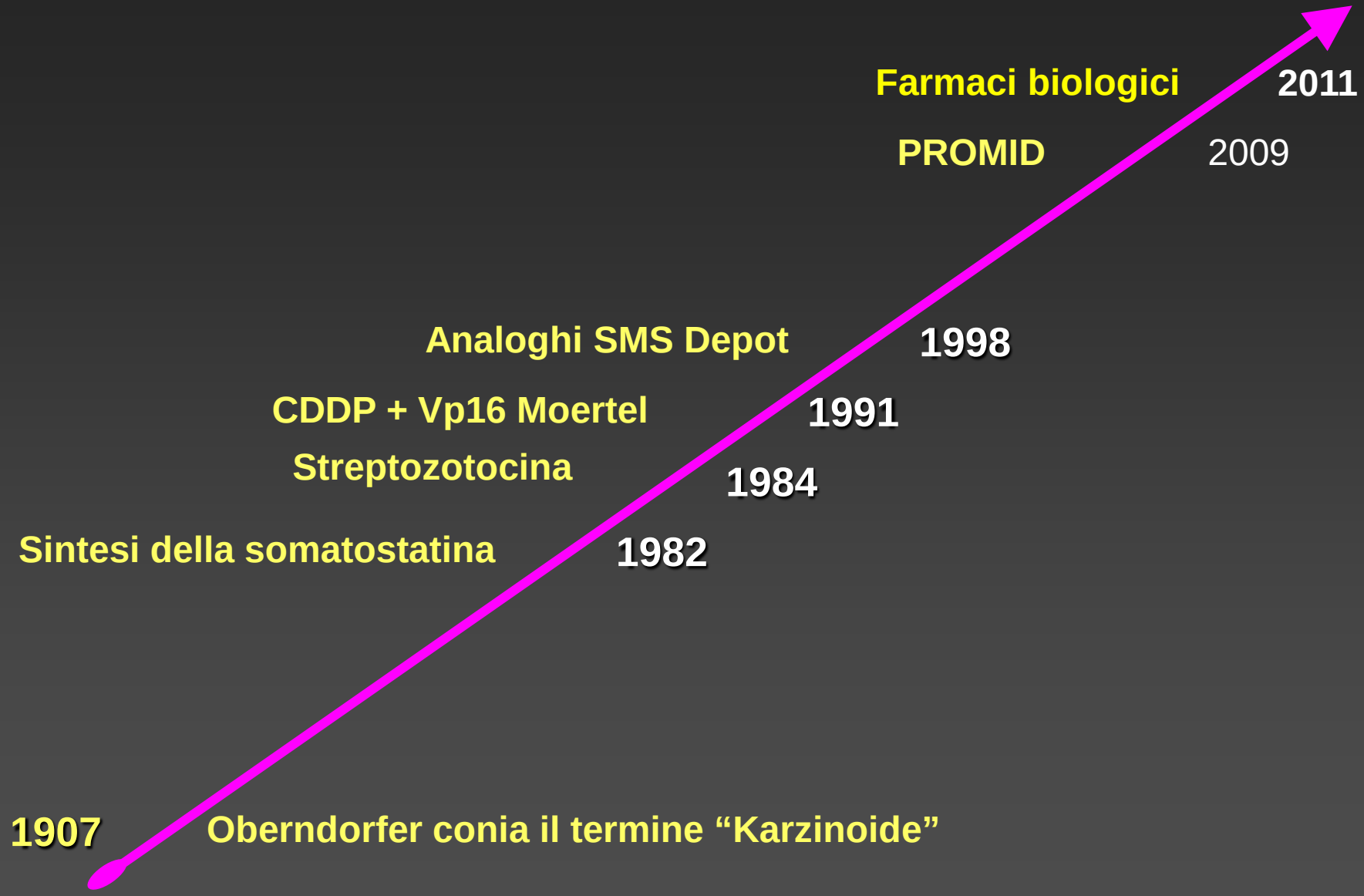

Farmaci biologici
2011
PROMID
2009
Analoghi SMS Depot
1998
CDDP + Vp16 Moertel
1991
Streptozotocina
1984
Sintesi della somatostatina
1982
1907
Oberndorfer conia il termine “Karzinoide”

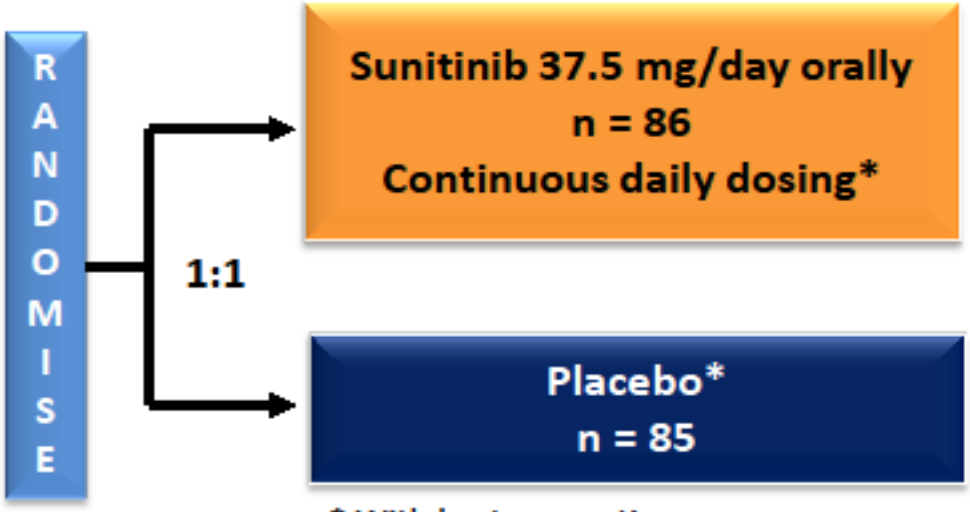
Sunitinib vs Placebo in Advanced pNET

Phase III, Randomised, Placebo-Controlled, Double-Blind Trial

- Trial terminated early due to significant treatment effect

Eligibility Criteria

- Well differentiated malignant pNET
- Disease progression in past 12 mos
- Not amenable to curative treatment
- 340 patients planned
- 171 patients enrolled



* With best supportive care
Somatostatin analogues were permitted

Primary Endpoint: PFS

Secondary Endpoints: OS, overall response rate (ORR), time to recurrence, duration of response, safety, and patient-reported outcomes

pNET = pancreatic neuroendocrine tumour

Raymond E, Dahan L, Raoul J, et al. *NEJM*. 2011;364:501-13.

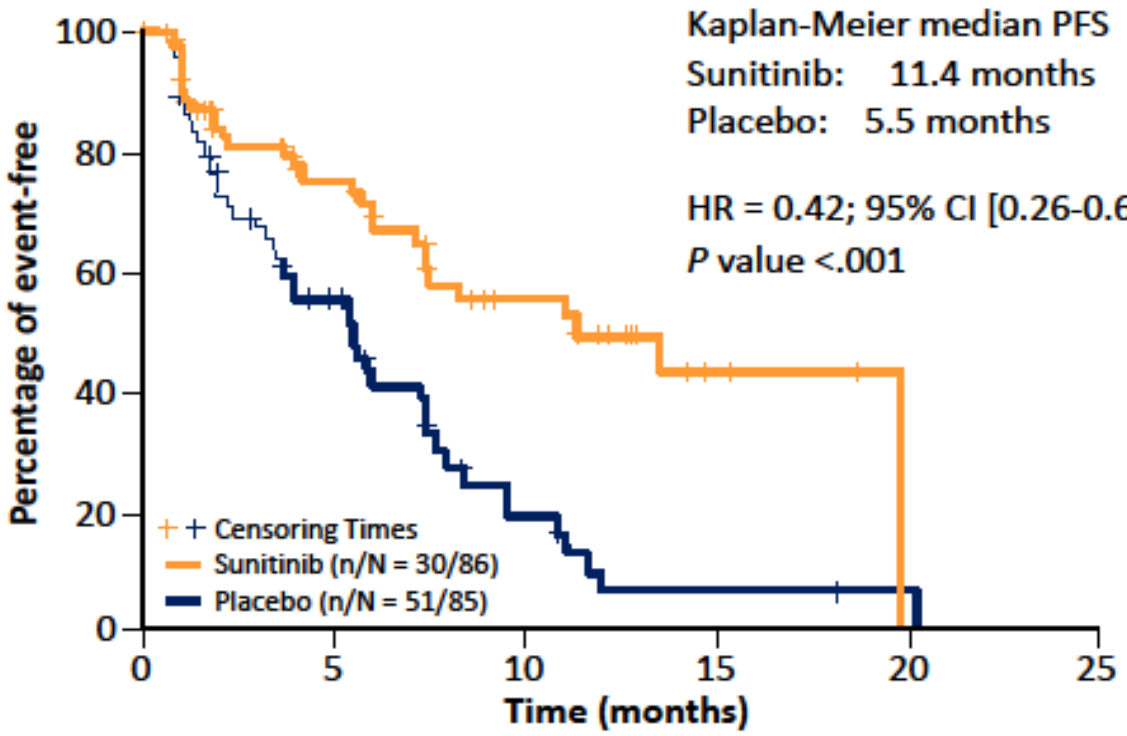
Sunitinib: Baseline Characteristics

	Sunitinib (n = 86)	Placebo (n = 85)
Median age, years (range)	56 (25-84)	57 (26-78)
Male : Female (%)	49:51	47:53
ECOG PS (%)		
0/ 1/ 2[1]	62/ 38/ 0	48/ 51/ 1
Number of disease sites (%)		
1	35	27
2	36	31
>3	28	41
Not reported	1	1
Previous somatostatin analogues (%)	35	38
Previous systemic chemotherapy (%)		
Any	66	72
Streptozocin	28	33
Anthracyclines	31	41
Fluoropyrimidines	23	29

[1]Enrollment of this patient was a protocol deviation

Raymond E, Dahan L, Raoul J, et al. *N Engl J Med*. 2011;364:501-513.

Sunitinib: Progression-Free Survival



No. at risk						
Sunitinib	86	39	19	4	0	0
Placebo	85	28	7	2	1	0

Unplanned early analysis,
Raymond E, Dahan L, Raoul J, et al. *N Engl J Med.* 2011;364:501-513.

Sunitinib: Treatment-Related Adverse Events

- Sunitinib toxicities were similar to those seen in other tumour types
- Most frequently reported all-grade AEs with sunitinib were diarrhea (59%), nausea (45%), asthenia (34%), vomiting (34%), and fatigue (33%)
- Grade 3/4 AEs (≥5%) in the sunitinib arm included neutropenia (12%), hypertension (10%), palmar–plantar erythrodysesthesia (6%), diarrhea (5%), asthenia (5%), fatigue (5%) and abdominal pain (5%)

Raymond E, Dahan L, Raoul J-L, et al. *N Engl J Med*. 2011;364:501-513.

Sunitinib: Summary

- In patients with advanced pNET, sunitinib 37.5 mg/day resulted in a clinically meaningful improvement in PFS compared with placebo
- Continuous daily dosing with sunitinib was well tolerated in patients with advanced pNET

APPROVED

RADIANT-3: Study Design

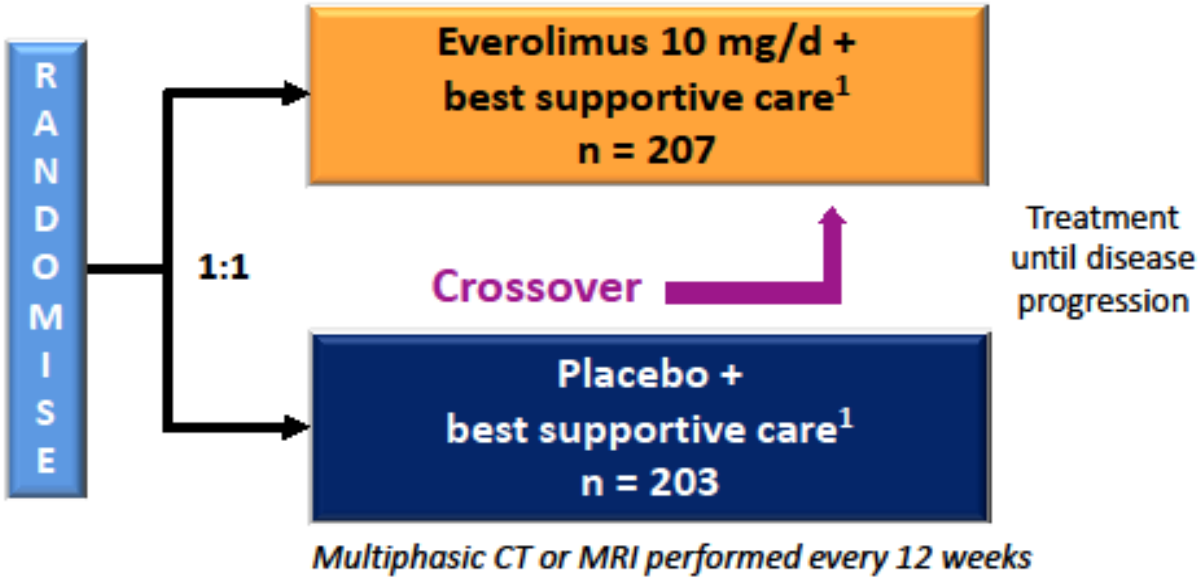
Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced pNET,

N = 410

Stratified by:

- WHO PS
- Prior chemotherapy



Primary Endpoint: PFS

Secondary Endpoints: OS, ORR, biomarkers, safety, pharmacokinetics (PK)

1. Concurrent somatostatin analogues allowed

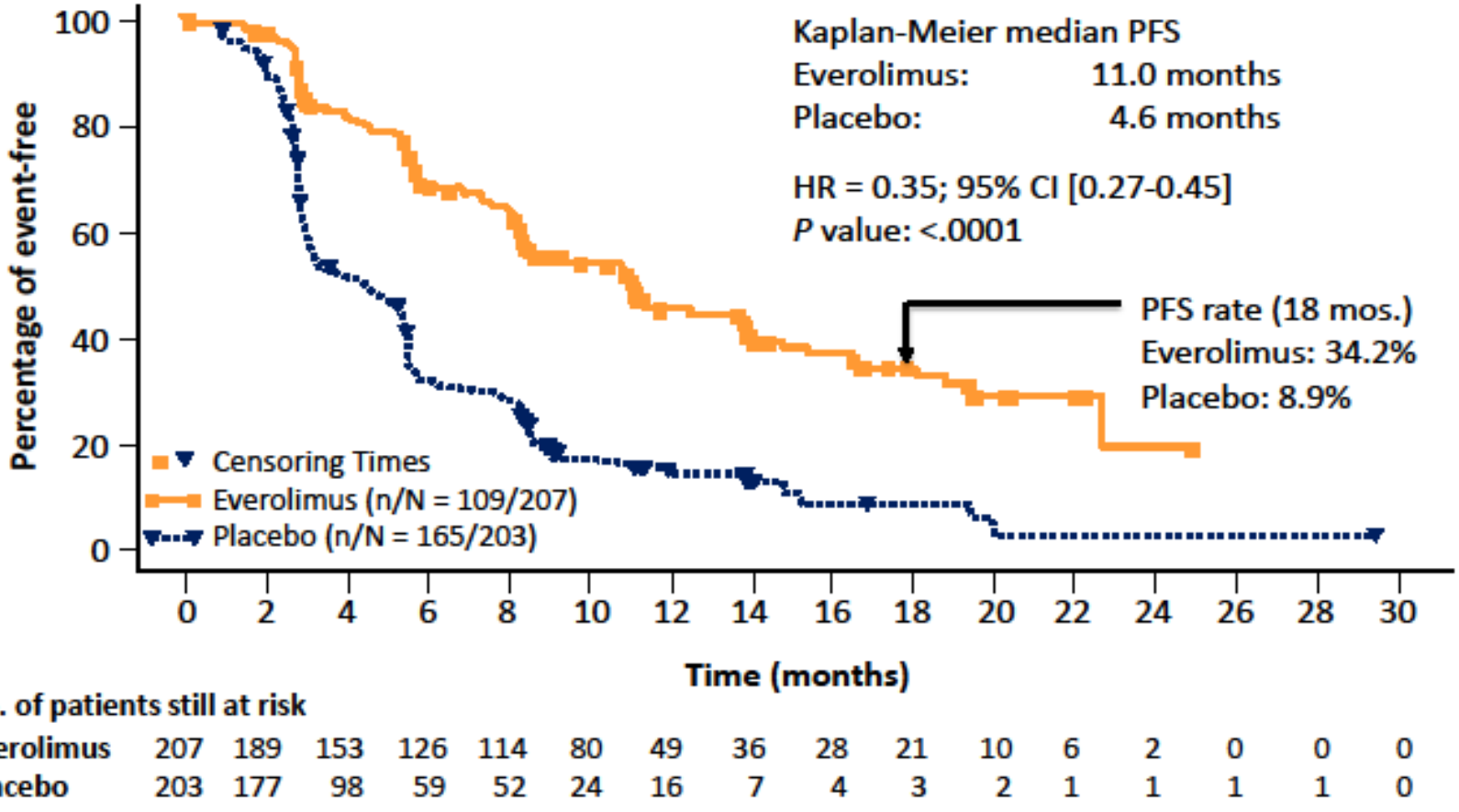
Yao J, Shah M, Ito T, et al. *N Engl J Med*. 2011;364:514-523.

RADIANT-3: Baseline Characteristics

	Everolimus (n = 207)	Placebo (n = 203)
Median age, years (range)	58 (23-87)	57 (20-82)
Male : Female (%)	53 : 47	58 : 42
WHO PS (%)		
0 / 1 / 2	67 / 30 / 3	66 / 32 / 3
No. of disease sites(%)		
1	25	31
2	41	32
≥3	34	38
Histologic Grade (%)		
Well differentiated	82	84
Moderately differentiated	17	15
Unknown	1	1
Prior Treatment (%)		
Somtatostatin analogues	49	50
Chemotherapy	50	50
Radiotherapy	23	20

Yao J, Shah M, Ito T, et al. *N Engl J Med*. 2011;364:514-523.

RADIANT-3: PFS by Investigator Review



No. of patients still at risk

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

P-value obtained from stratified one-sided log-rank test
Hazard ratio is obtained from stratified unadjusted Cox model
Yao J, Shah M, Ito T, et al. *N Engl J Med*. 2011;364:514-523.

RADIANT-3: Treatment-Related Adverse Events

- Everolimus toxicities were similar to those seen in other tumour types
- Most frequently reported all-grade treatment-related AEs with everolimus were stomatitis (64%), rash (49%), diarrhea (34%), fatigue (31%), and infections (23%)
- Grade 3/4 AEs (≥5%) in the everolimus arm included stomatitis (7%), anemia (6%), and hyperglycemia (5%)

Yao JC, Shah MH, Ito T, et al. *N Engl J Med*. 2011;364:514-523.

RADIANT-3: Summary

- Everolimus therapy resulted in a statistically and clinically significant 6.4-month increase in median PFS (4.6 months to 11.0 months)
- Everolimus provided a 65% reduction in risk for progression compared to placebo (HR = 0.35, *P*<.0001)
  - PFS rate at 18 months: 34% everolimus versus 9% placebo demonstrates that everolimus provides a durable benefit
- Everolimus has an acceptable safety profile in patients with advanced pNET

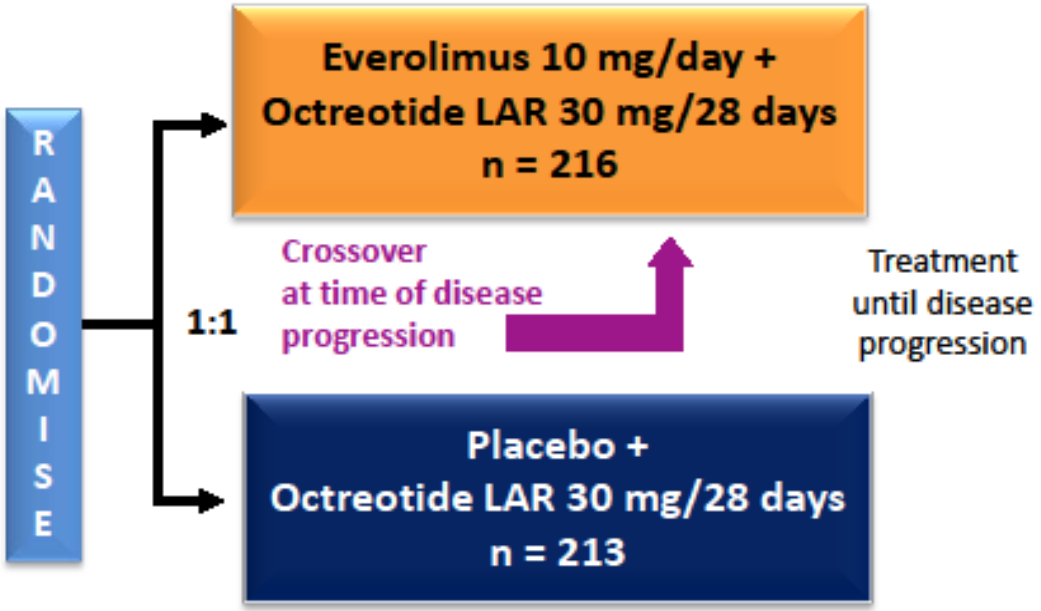
APPROVED

RADIANT-2: Study Design

Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicenter Trial

Patients with advanced NET and a history of flushing and/or diarrhea (N = 429)

- Advanced low- or intermediate-grade NET
- Radiologic progression ≤12 months
- Prior antitumour therapy allowed
- WHO PS ≤2

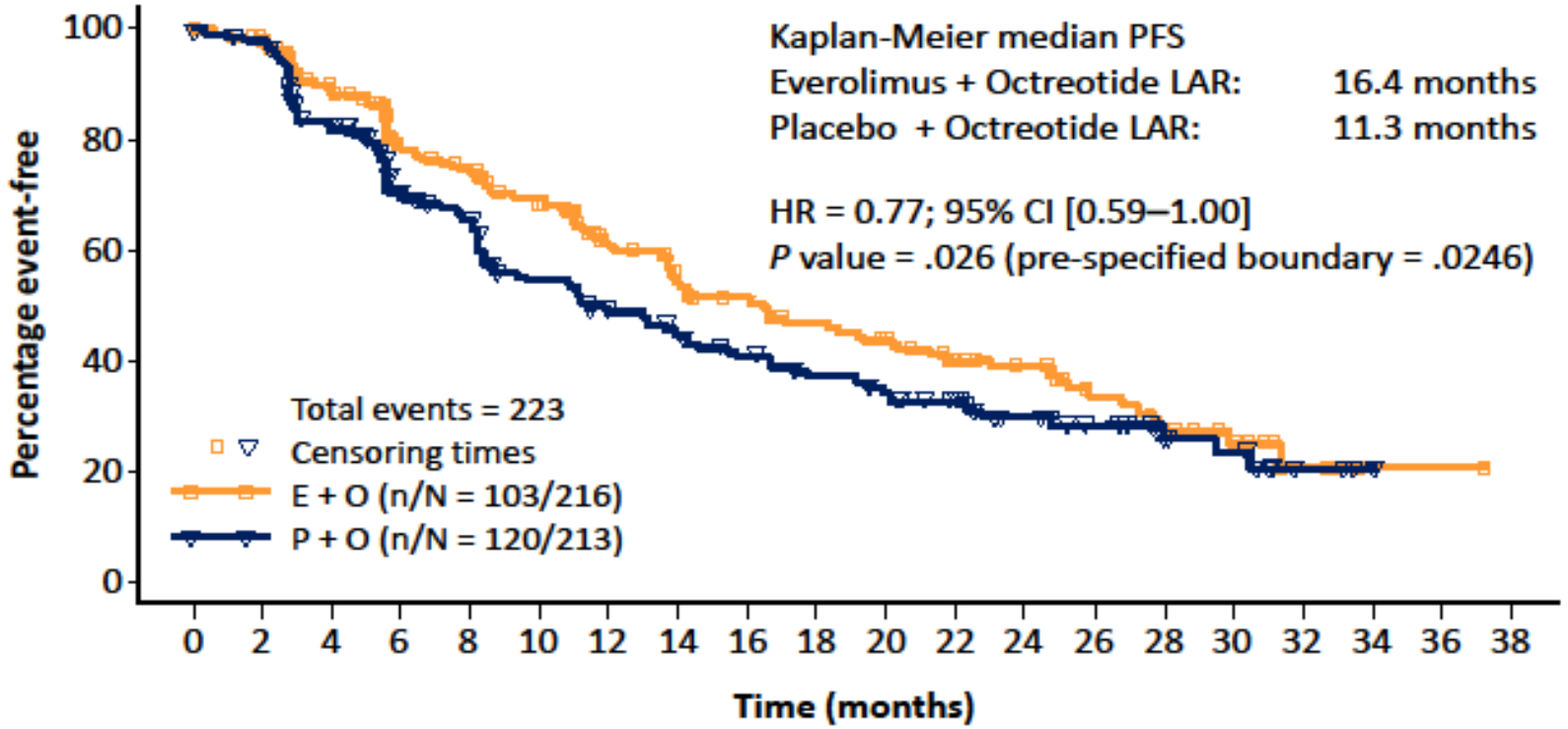


Primary Endpoint: PFS by central adjudicated review

Secondary Endpoints: OS, ORR, biomarkers, safety, PKs

Pavel ME et al, Lancet 2011, dec 10; 378: 2005-12

RADIANT-2: PFS by Central Review*



No. of patients still at risk

E + O	216	202	167	129	120	102	81	69	63	56	50	42	33	22	17	11	4	1	1	0
P + O	213	202	155	117	106	84	72	65	57	50	42	35	24	18	11	9	3	1	0	0

* Independent adjudicated central review committee
P-value is obtained from the one-sided log-rank test
HR is obtained from unadjusted Cox model

E + O = Everolimus + Octreotide LAR
P + O = Placebo + Octreotide LAR

Clinical Trial Advances in NET Summary

- Quality randomized phase III trials will transform the treatment landscape for patients with advanced NET
- Control of tumour progression in patients with advanced NET has been demonstrated in pivotal phase III clinical trials
  - PROMID: Octreotide LAR 30 mg provided a significant 8.3 month improvement in TTP compared to placebo; HR = 0.34, *P*=.000072
  - Sunitinib 37.5 mg provided a clinically meaningful 5.9 month improvement in PFS compared to placebo; HR = 0.42, *P*<.001 in pNET
  - RADIANT-3: Everolimus 10 mg provided a statistically and clinically significant 6.4 month improvement in PFS compared to placebo; HR = 0.35, *P*<.001 in pNET
  - RADIANT-2: Everolimus 10mg + octreotide LAR 30 mg provided a clinically meaningful 5.1 month improvement in PFS compared to placebo; HR = 0.77, *P*=.026 in NET of different origin

pNETs

Studio	n° pz	RR	PFS	OS
RADIANT-3	410	4.8	11.0 *vs* 4.6	nr
Sunitinib vs placebo	171	9.3	11.4 *vs* 5.5	30.5 vs 24.4 (P:ns)

pNETs: analisi costo-efficacia
RADIANT-3 vs A6181111

- Coorte simulata di pNETs
- Costo dei farmaci e di tutte le altre terapie
- Costo terapie post-PD
- Costo medici, servizi, ospedalizzazione
- Valutazione degli AEs in rapporto alle SD

- Everolimus è associato ad un aumento dei costi
- Everolimus è associato ad un aumento degli anni di vita aggiustati x la qualità (QALYs)
- Ratio 41,702 dollari

Casciano et al JCO 2012, 30 (Supp 4): Abst 226

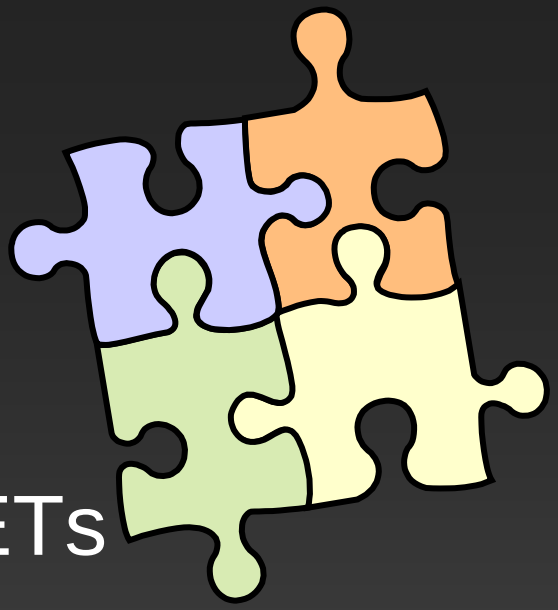
OS: post-hoc analysis

- Confronto tra dati relativi a RADIANT-3 e A6181111 aggiustati per caratteristiche basali e criteri di inclusione.

- Trattamento con everolimus associato ad un incremento della OS confrontato con sunitinib. (P=0.04)

Signorovitch et Al, JCO 2012: Abs 237

Conclusioni



- Sequenza terapeutica nei pNETs
- Indicazione nei NETs non pancreatici
- Combinazioni con analoghi della SMS