



**18:00-19:00h** **THE RELEVANCE OF SUBGROUPS IN NEUROENDOCRINE TUMORS / LA RELEVANCIA DE LOS ANÁLISIS DE SUBGRUPOS EN TUMORES NEUROENDOCRINO**

**18:00 -18:10h** **Anatomopathologic subgroups: clinical effects based on pathology**  
*Los subgrupos anatomopatológicos: repercusión clínica basada en la patología*  
Dr. Ángel Castaño. Servicio de Anatomía Patológica. Hospital Universitario de Fuenlabrada, Madrid

**18.10-18:20h** **Clinical subgroups: focus on hormone liberation**  
*Los subgrupos clínicos: foco en la liberación hormonal*  
Dr. Guillermo Crespo. Servicio de Oncología Médica. Hospital Universitario de Burgos

**18:20 -18:30h** **Subgroups analysis on clinical trials: effects on clinical practice**  
*Análisis de subgrupos en los estudios clínicos: repercusión en la práctica clínica*  
Dra. Paula Jiménez-Fonseca. Servicio de Oncología médica. Hospital Universitario Central de Asturias, Oviedo

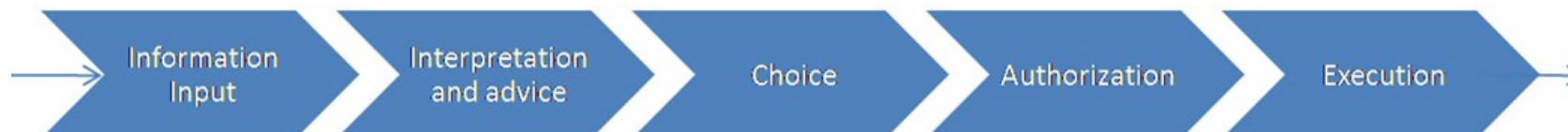
**18:30-19:00h** **Discussion / Discusión**

# Index

1. Keys in decision-making
2. Therapeutic algorithm according with NET subtypes
3. GETNE clinical trials in NET subtypes
4. Phase III study: RADIANT-4

# Index

- 1. Keys in decision-making**
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# Keys in decision making: patients



1. Age
2. Performance status
3. Comorbidities
4. Preferences

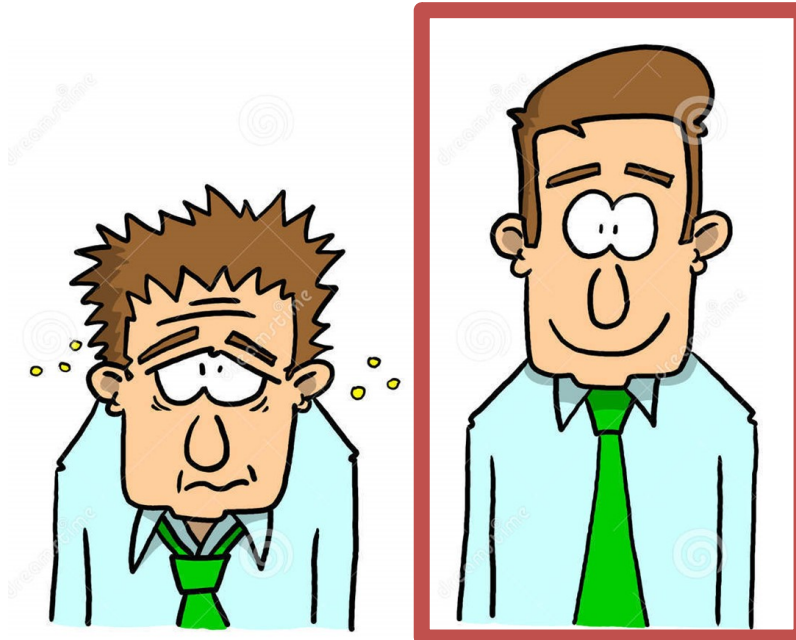
# Keys in decision making: patients



1. Age
2. Performance status
3. Comorbidities
4. Preferences



Less important due to:  
**Young**  
**Good performance status**



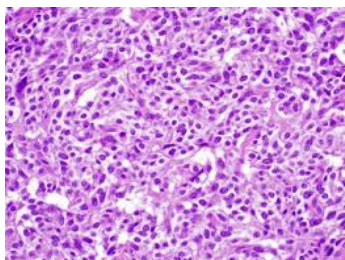
# Keys in decision making: tumor



1. Age
2. Performance status
3. Comorbidities
4. Preferences



Less important due to:  
**Young**  
**Good functionality**



1. **Origin**
2. **Tumor Burden**
3. **Progression**
4. Histology, SSTR
5. Functionality
6. Resectability

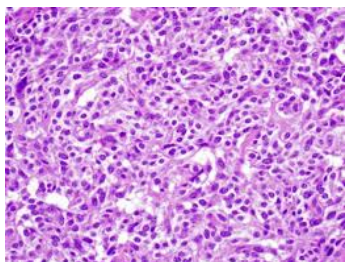
# Keys in decision making: tumor



1. Age
2. Performance status
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Less important due to:  
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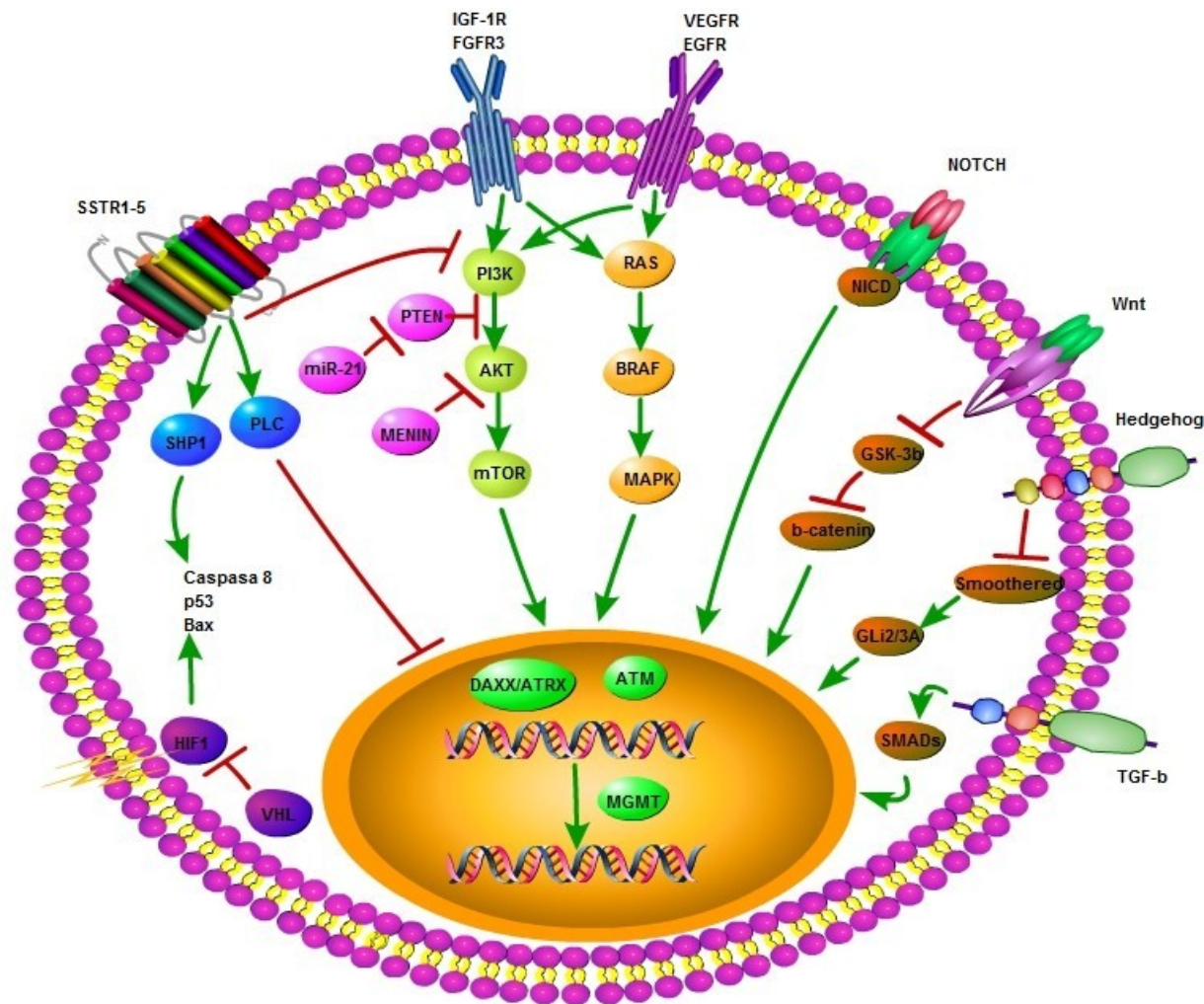


1. **Origin**
2. **Tumor Burden**
3. **Progression**
4. Histology, SSTR
5. Functionality
6. Resectability



Location or **molecular targets?**  
Histology, burden or **evolution?**

# Biomarkers predictors of response, better approach than **the origin?**



# Progression free survival after systemic treatment, better approach than **the histology?**

**Ki 67**

**Drug:**

- SSA
- Everolimus
- Sunitinib
- Chemotherapy

**PFS:**

< vs. > 11-12 months

## High t. burden, fast PD, SSTR-: **SSA, PRRT?** Bone metastases, non midgut-NET: **PRRT?**

1. **PROMID**: octreotide → **liver burden >10%**: poor PFS

Factor	Bivariate Analysis			Multivariate Analysis		
	<i>P</i>	HR	95% CI	<i>P</i>	HR	95% CI
Octreotide LAR v placebo*				< .0001	0.27	0.14 to 0.49
Liver involvement > v ≤ 10%	.0009	2.81	1.53 to 5.18	.0023	2.63	1.41 to 4.90

2. **CLARINET**: lanreotide → **96% stable disease**

3. **NETTER-1**: PRRT →  
**PROGRESSION**: during **36 months previous**  
**Krenning index**: 3 or > (STTR+++)  
**Midgut**

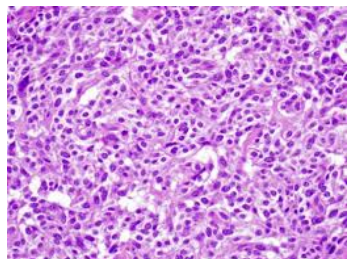
# Keys in decision making: physician



1. Age
2. Performance status
3. Comorbidities
4. Preferences



Less important due to:  
Young  
Good functionality



1. **Origin**
2. **Tumor Burden**
3. **Progression**
4. Histology, SST
5. Functionality
6. Resectability



Location or molecular targets?  
Histology, burden or evolution?



1. Multidisciplinary team
2. Clinical trials
3. Diagnostic tools
4. Therapeutic tools

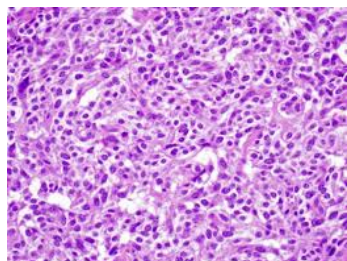
# Keys in decision making: physician



1. Age
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Less important due to:  
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1. **Origin**
2. Histology
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Location or molecular  
targets?  
Histology or evolution?



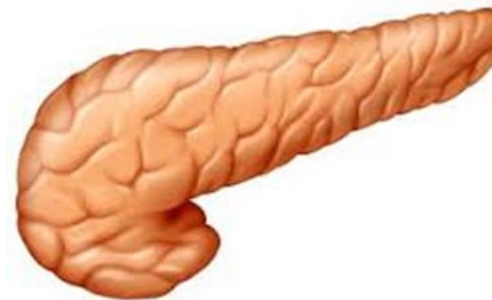
1. Multidisciplinary team
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3. Diagnostic tools
4. Therapeutic tools



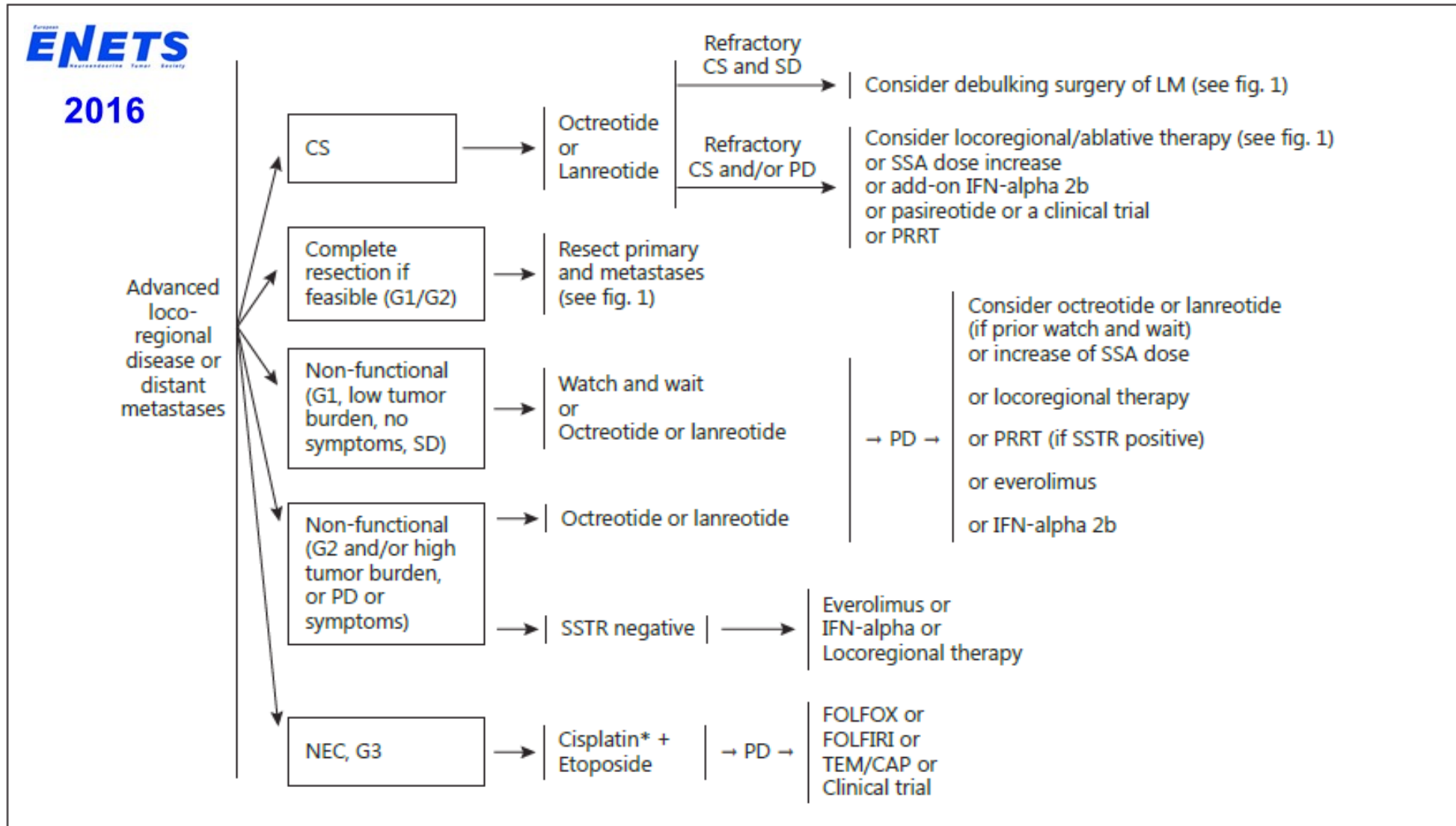
Reference centres  
Experts

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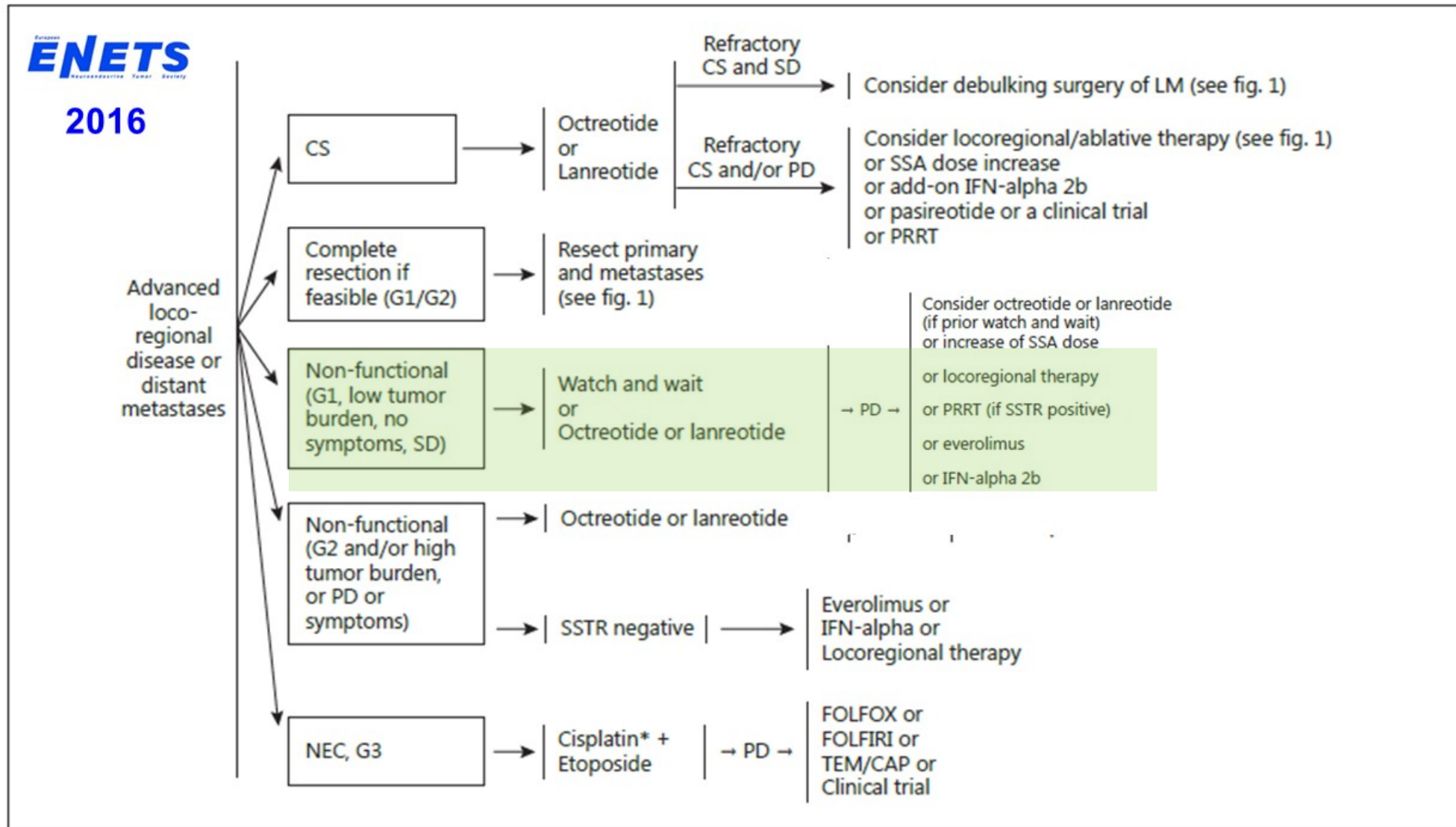
1. Keys in decision-making
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3. GETNE clinical trials in NET subtypes
4. Phase III study: RADIANT-4



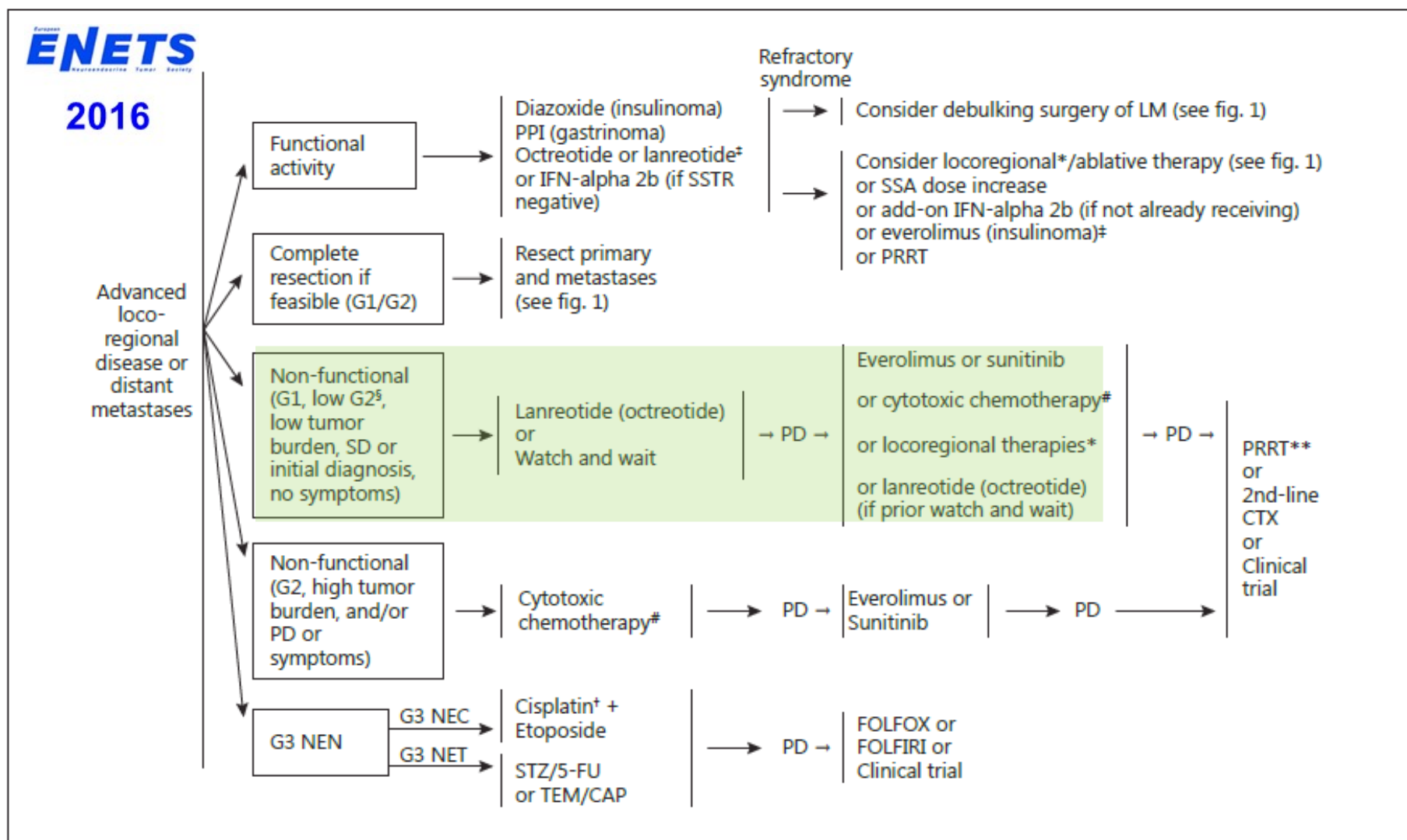
# Intestinal-advanced NET



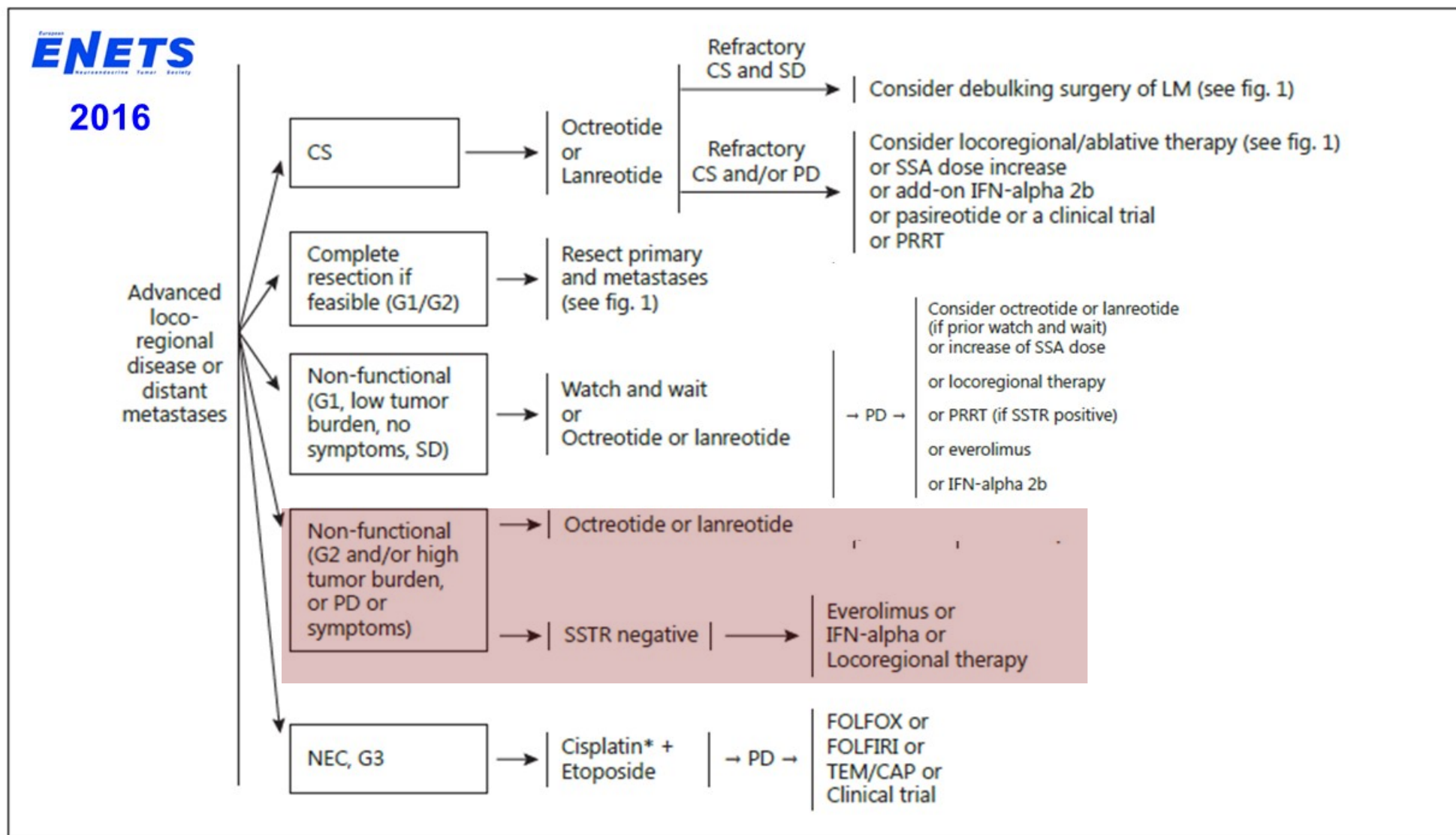
# Intestinal-advanced NET



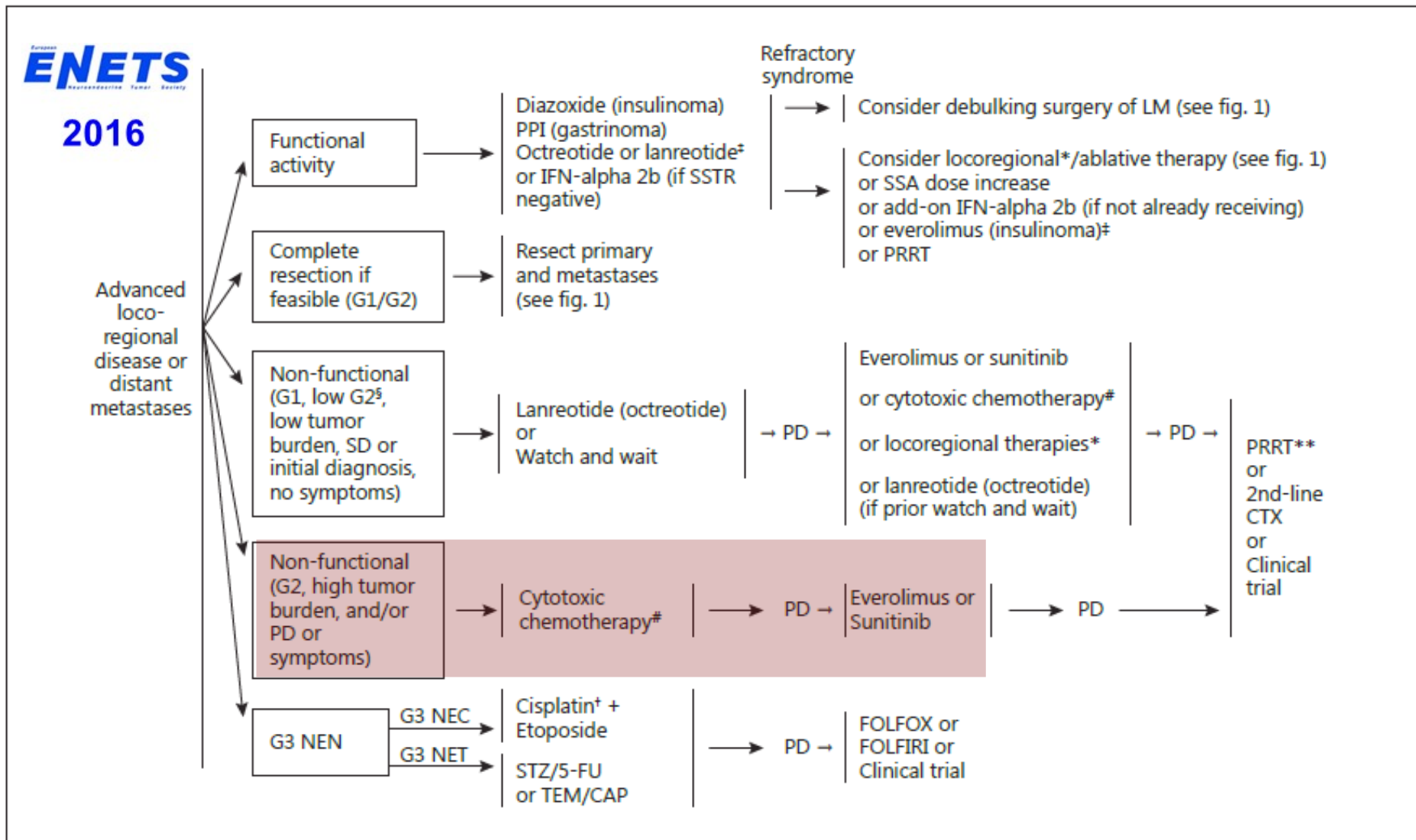
# Pancreatic-advanced NET



# Intestinal-advanced NET



# Pancreatic-advanced NET



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Grupo Español de Tumores  
Neuroendocrinos

# GETNE: clinical trials

1. **PNET- SEQTOR, phase III**: sequence  
**CT (Stz + FU) → Everolimus vs Everolimus → CT**
2. **PNET-RESUNET**: rescue **sunitinib** after progression
3. **GINET- AXI-IIG-02, phase III**: 2nd line  
**SSA +- axitinib**
4. **NET- TALENT**: 2nd line  
**lenvatinib**
5. **NET- DUNE**: refractarios  
**durvalumab (MEDI4736) + tremelimumab**

# GETNE: observational trials

## 1. PNET- CRIPNET: CHOI vs RECIST

**Sunitinib**

2. **NET-TRASGU**: nomogram predictor of benefit with  
SSA in first line

**Octreotide/lanreotide**

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## RADIANT-4: study design

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin

(N = 302)

- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Enrolled within 6 months from radiologic progression

R  
A  
N  
D  
O  
M  
I  
Z  
E

2:1

Everolimus 10 mg/day  
N = 205

Placebo  
N = 97

Treated until PD,  
intolerable AE,  
consent withdrawal

### Endpoints:

- **Primary: PFS (central)**
- **Key Secondary: OS**
- **Secondary: ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK**

### Stratified by:

- **Prior SSA treatment (yes vs. no)**
- **Tumor origin (stratum A vs. B)\***
- **WHO PS (0 vs. 1)**

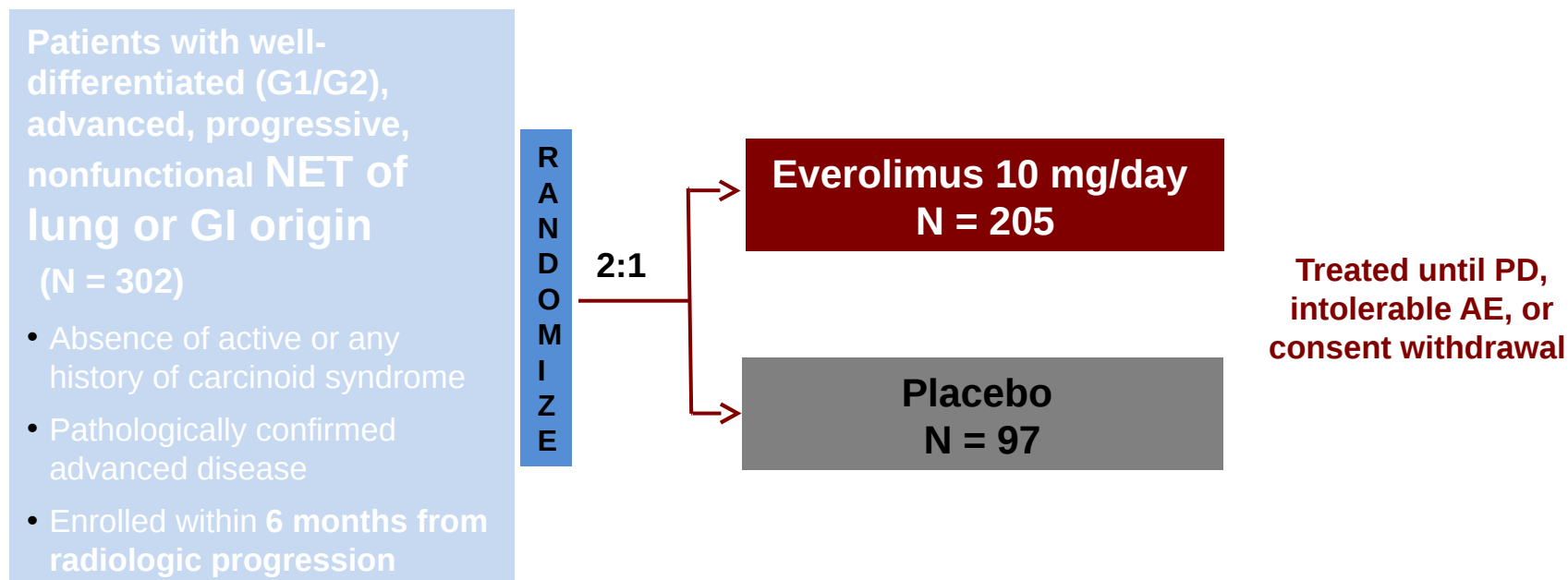
\*Based on prognostic level, grouped as:

**Stratum A (better prognosis)** - appendix, caecum, jejunum, ileum, duodenum, and unknown primary.

**Stratum B (worse prognosis)** - lung, stomach, rectum, and colon except caecum.

Crossover to open label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

## RADIANT-4: assumptions and sample size



### Assumptions

Median PFS in placebo arm: **5 months**, based on historical data

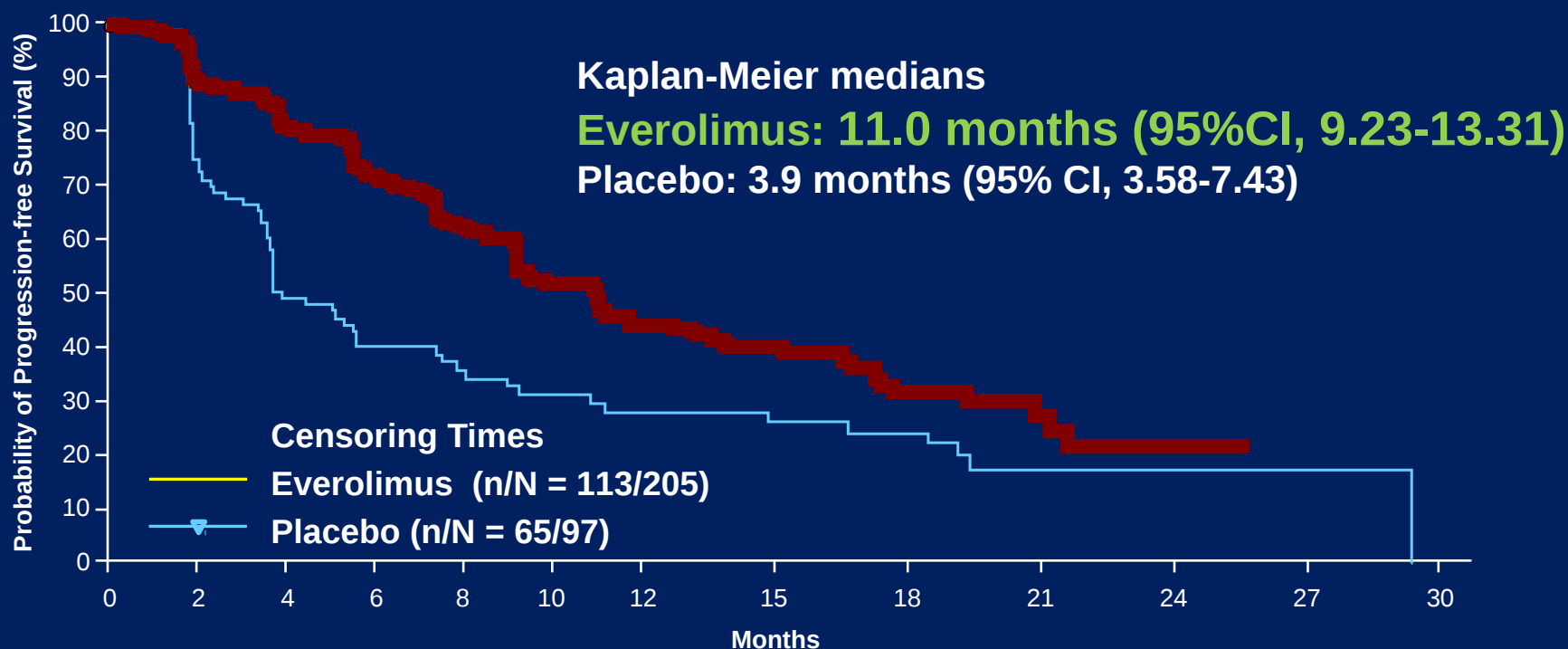
Median PFS in everolimus arm: **8.5 months**, to achieve clinically meaningful benefit of a 41% reduction in the risk of disease progression/death (target **HR = 0.59**)

Required events: 176 to detect a HR of 0.59

## RADIANT-4: baseline characteristics

Characteristic	Everolimus N = 205	Placebo N = 97
<b>Tumor grade</b>		
Grade 1 / grade 2	63% / 37%	67% / 33%
<b>Metastatic extent of disease<sup>†</sup></b>		
Liver	80%	78%
<b>Median time from PD until enrolment, months (range)</b>	1.68 (0.0-7.8)	1.45 (0.2-11.8)
<b>Prior treatments</b>		
Somatostatin analogues <sup>§</sup>	53%	56%
Surgery	59%	72%
Chemotherapy	26%	24%
Radiotherapy including PRRT	22%	20%
Locoregional and ablative therapies	11%	10%
<b>Primary tumor site</b>		
Lung	31%	28%
Ileum	23%	25%
Rectum	12%	16%
Jejunum	8%	6%
Stomach	3%	4%
Duodenum	4%	2%
Colon	2%	3%
NET of unknown primary	11%	13%

**52% reduction in the relative risk of progression or death with everolimus vs placebo**  
**HR = 0.48 (95% CI, 0.35-0.67); P < 0.00001**

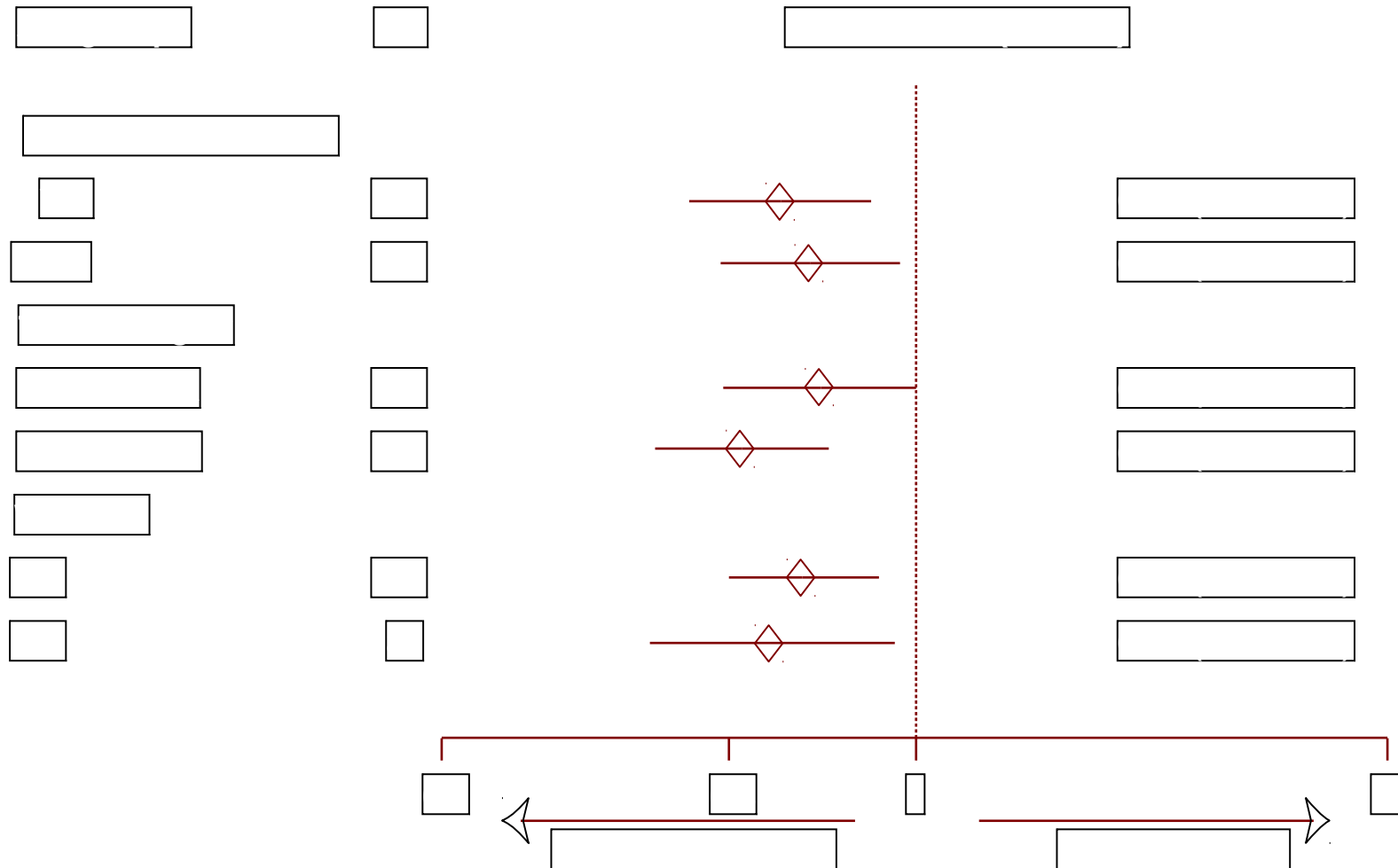


No. of patients still at risk

Everolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

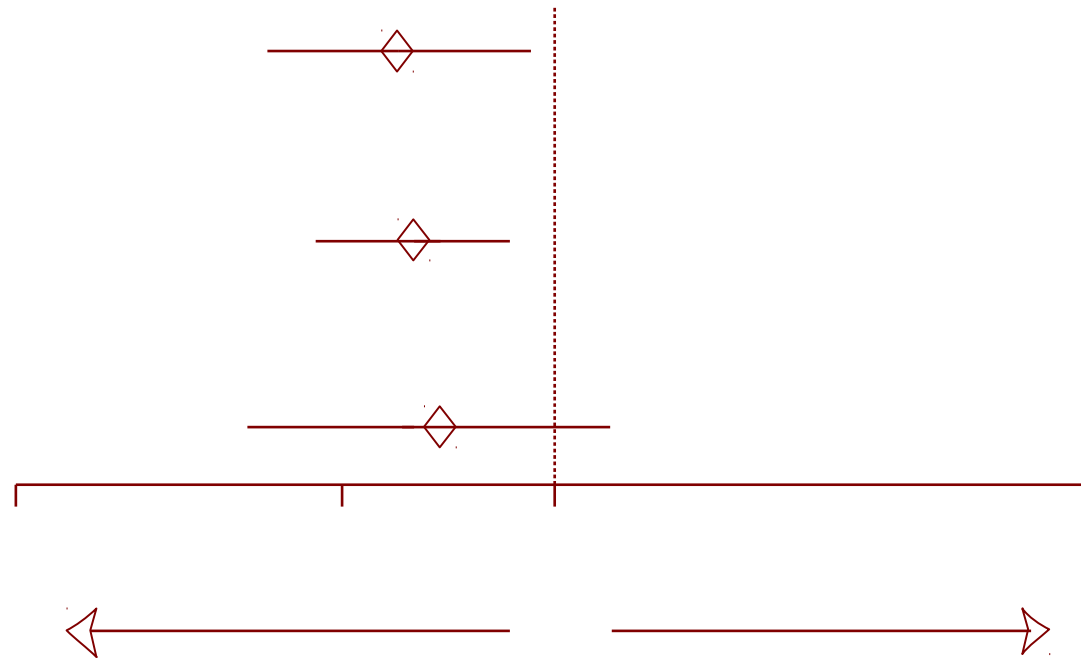
P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.

# RADIANT-4: PFS HR by Stratification Factors



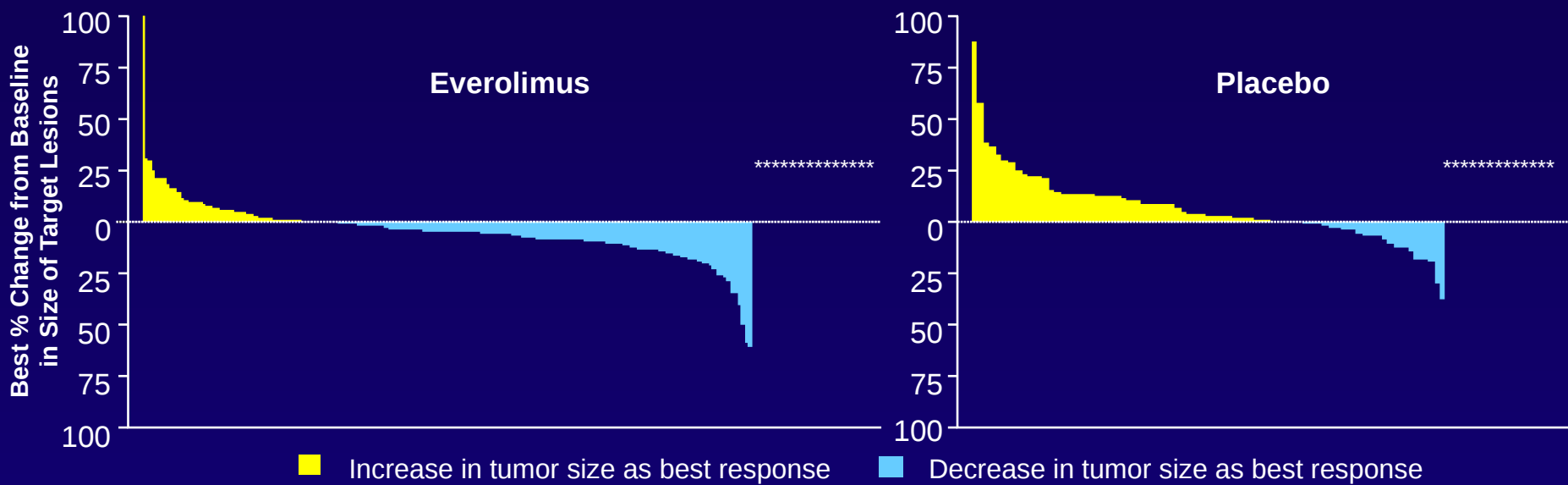
# RADIANT-4: PFS HR by Primary Origin

## – Retrospective Analysis



**64%: any degree of tumor shrinkage**

Best Overall Response	Everolimus N = 205, n (%)	Placebo N = 97, n (%)
ORR (CR + PR)	4 (2.0)	1 (1.0)
DCR (CR + PR + SD)	169 (82.4)	63 (64.9)
PD	19 (9.3)	26 (26.8)
Unknown	17 (8.3)	8 (8.2)



\*Fourteen patients (7.6%) in the everolimus arm and 13 patients (15.3%) in the placebo arm showed a change in the available target lesion that contradicted the overall response.

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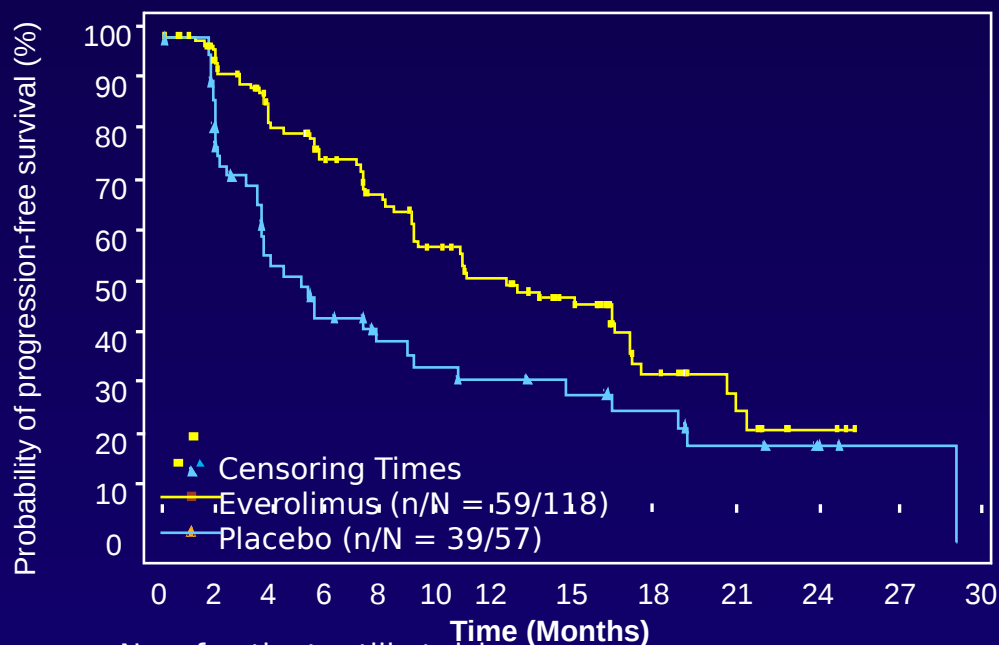
## GI Subgroup

### Kaplan-Meier medians

Everolimus: 13.1 m (95% CI, 9.2-17.3)

Placebo: 5.4 m (95% CI, 3.6-9.3)

HR: 0.56 (95% CI, 0.37; 0.84)<sup>1</sup>



No. of patients still at risk

Everolimus	118	99	82	71	60	49	41	33	16	8	3	0
Placebo	57	40	27	21	16	14	12	10	8	5	4	1

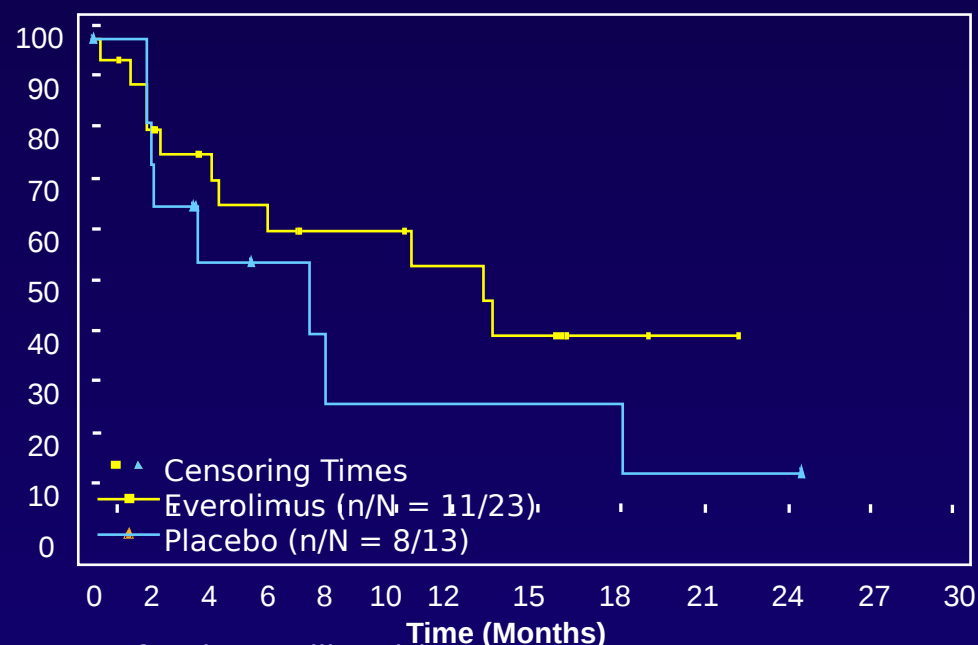
## Unknown Primary

### Kaplan-Meier medians

Everolimus: 13.6 mo (95% CI, 4.1-NA)

Placebo: 7.5 mo (95% CI, 1.9-18.5)

HR: 0.60 (95% CI, 0.24; 1.51)<sup>1</sup>



No. of patients still at risk

Everolimus	23	18	15	13	10	10	8	6	2	1	0	0	0
Placebo	13	10	5	4	3	2	2	2	2	1	1	0	0

**Midgut**

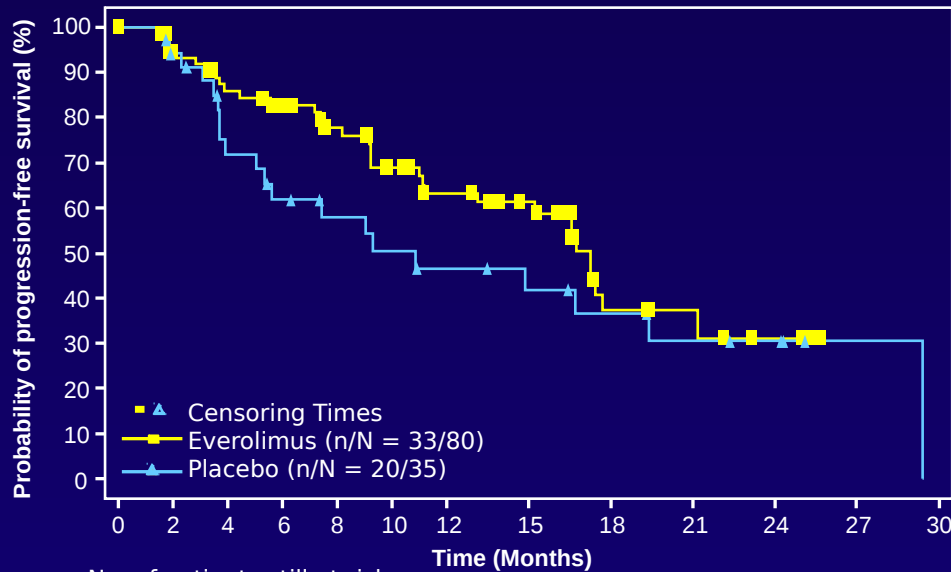
29% reduction in RR of progression  
median PFS Δ6.4 m

**Kaplan-Meier medians**

**Everolimus: 17.3 mo (95% CI, 11.2-21.9)**

**Placebo: 10.9 mo (95% CI, 5.1-19.4)**

**HR: 0.71 (95% CI, 0.40-1.26)**



	0	2	4	6	8	10	12	15	18	21	24	27	30
Everolimus	80	66	58	52	45	38	32	27	11	6	3	0	0
Placebo	35	31	22	18	15	13	11	9	7	5	4	1	0

**Non-midgut**

**(stomach, colon, and rectum)**

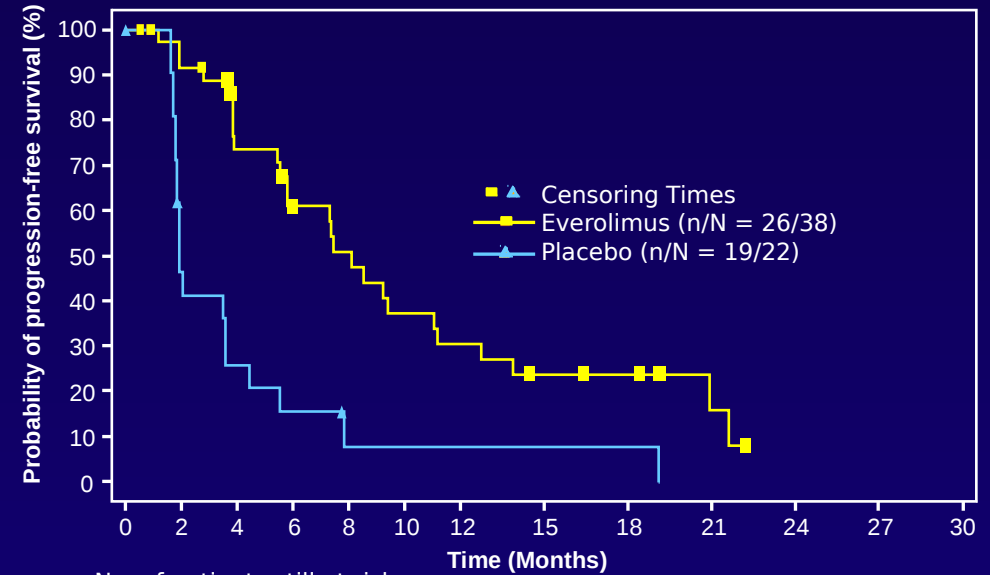
73% reduction in RR of PE  
median PFS Δ6.2 months

**Kaplan-Meier medians**

**Everolimus: 8.1 mo (95% CI, 5.5-11.2)**

**Placebo: 1.9 mo (95% CI, 1.8-3.6)**

**HR: 0.27 (95% CI, 0.15-0.51)**



	0	2	4	6	8	10	12	15	18	21	24	27	30
Everolimus	38	33	24	19	15	11	9	6	5	2	0	0	0
Placebo	22	9	5	3	1	1	1	1	1	0	0	0	0

**50% reduction in risk of progression; HR = 0.50 (95% CI, 0.28-0.88)**

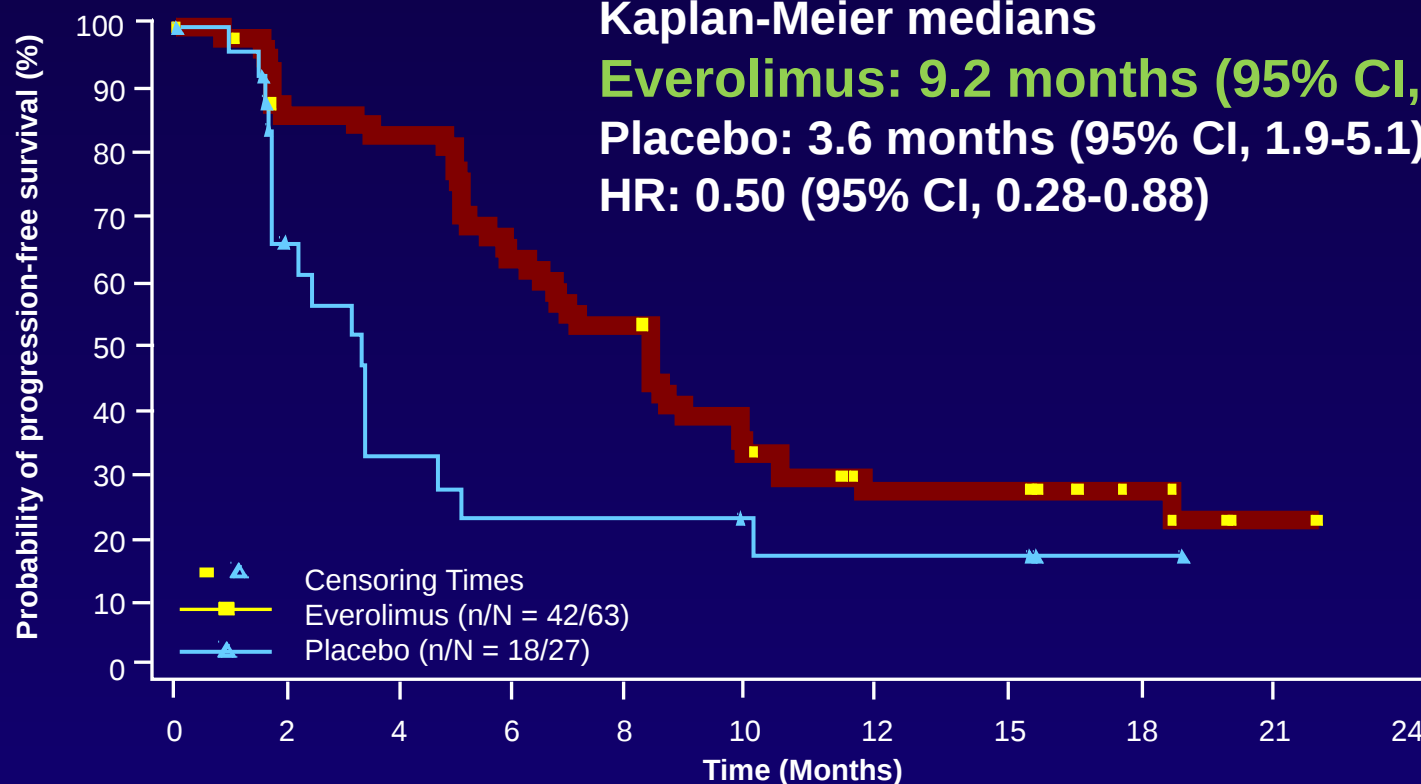
## LUNG NET

Kaplan-Meier medians

**Everolimus: 9.2 months (95% CI, 6.8-10.9)**

**Placebo: 3.6 months (95% CI, 1.9-5.1)**

**HR: 0.50 (95% CI, 0.28-0.88)**



	No. of patients still at risk										
	0	2	4	6	8	10	12	15	18	21	24
Everolimus	63	51	48	40	31	22	16	13	8	1	0
Placebo	27	15	7	5	5	5	3	3	1	0	0

## RADIANT-4: message to take home

1. **Everolimus** is the first targeted agent to show **robust antitumor activity** across a broad spectrum of NET: pancreas, lung, and GI tract.
2. **Everolimus** presents a **new standard treatment option** in **advanced, progressive, well-differentiated, nonfunctional NET**.

### PNET

- SSA
- Everolimus
- Sunitinib
- Chemotherapy

### GI NET

- SSA
- Everolimus
- PRRT
- Chemotherapy ¿?

### Lung

- Everolimus
- Chemotherapy
- SSA ¿?

## INFORME SEOM DE EVALUACIÓN DE FÁRMACOS

**Everolimus (Afinitor®) para tumores neuroendocrinos grado 1/2 de la OMS, no funcionantes, irresecables o metastásicos, en progresión, de origen gastrointestinal y broncopulmonar**

### 6. RECOMENDACIONES FINALES

Siguiendo las recomendaciones y aprobaciones de las distintas autoridades regulatorias en base a los resultados del estudio fase III prospectivo y aleatorizado RADIANT-4, everolimus se debe recomendar para el tratamiento de pacientes afectos de TNEs avanzados o irresecables de origen broncopulmonar y gastrointestinal, bien-moderadamente diferenciados, grados 1/2 de la OMS, no funcionantes y con progresión documentada por criterios RECIST en los últimos 6 meses de seguimiento.

Le llaman suerte, pero es  
constancia. Le llaman  
casualidad, pero es  
disciplina. Le llaman  
genética, pero es sacrificio.  
Ellos hablan, tú entrena.

Accid  
poñt

