Avances en el Tratamiento de los Tumores Neuroendocrinos

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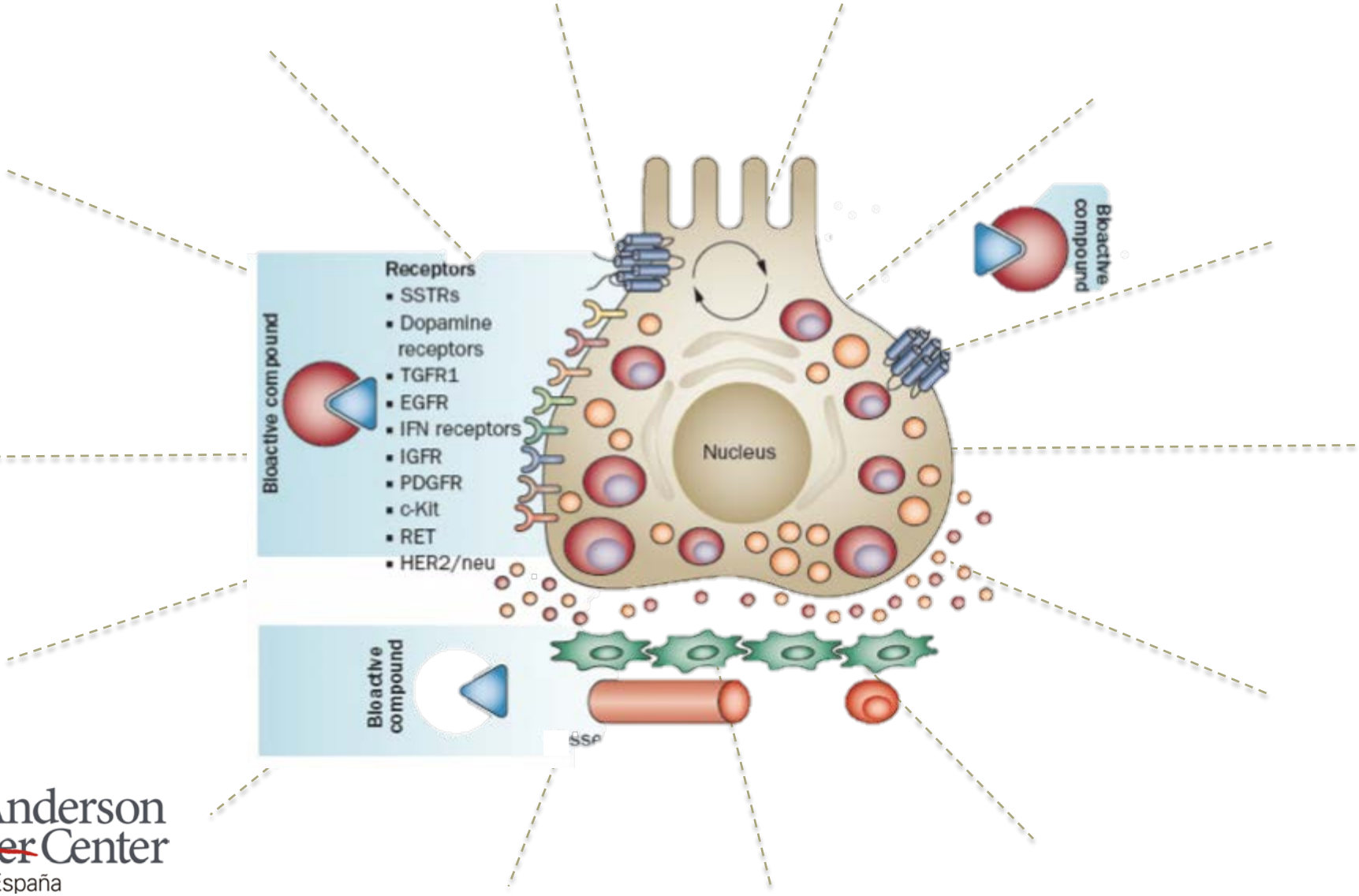
Conflictos de Interés

- Honoraria for ad boards and/or lectures:
  - Pfizer, BMS, IPSEN, Roche, Eisai, Eusa Pharma, MSD, Sanofi-Genzyme, Adacap, Novartis, Pierre Fabre, Lexicon, Celgene
- Research Grants:
  - Pfizer, Astra Zeneca, MTEM/Threshold, Roche, IPSEN, Lexicon
- Leadership roles in medical societies:
  - ENETS, GETNE and GETHI
- Stocks or ownership interest:
  - None

El Reto de los Tumores Neuroendocrinos



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El Reto de los Tumores Neuroendocrinos

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Ki67/
Grado de
Diferenciación

Funcionante vs
No funcionante

Octreoscan
Positivo o
Negativo

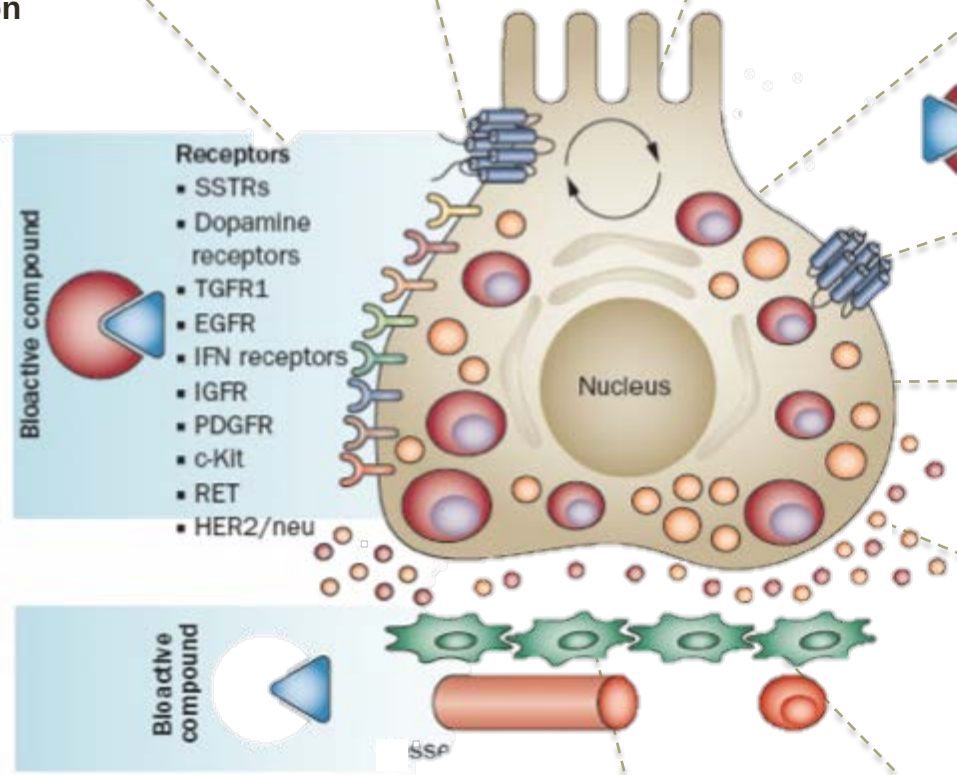
En progresión vs
No progresión

Carga
Tumoral

Origen del
Tumor Primario

Baja
Incidencia

Multidisciplinaridad



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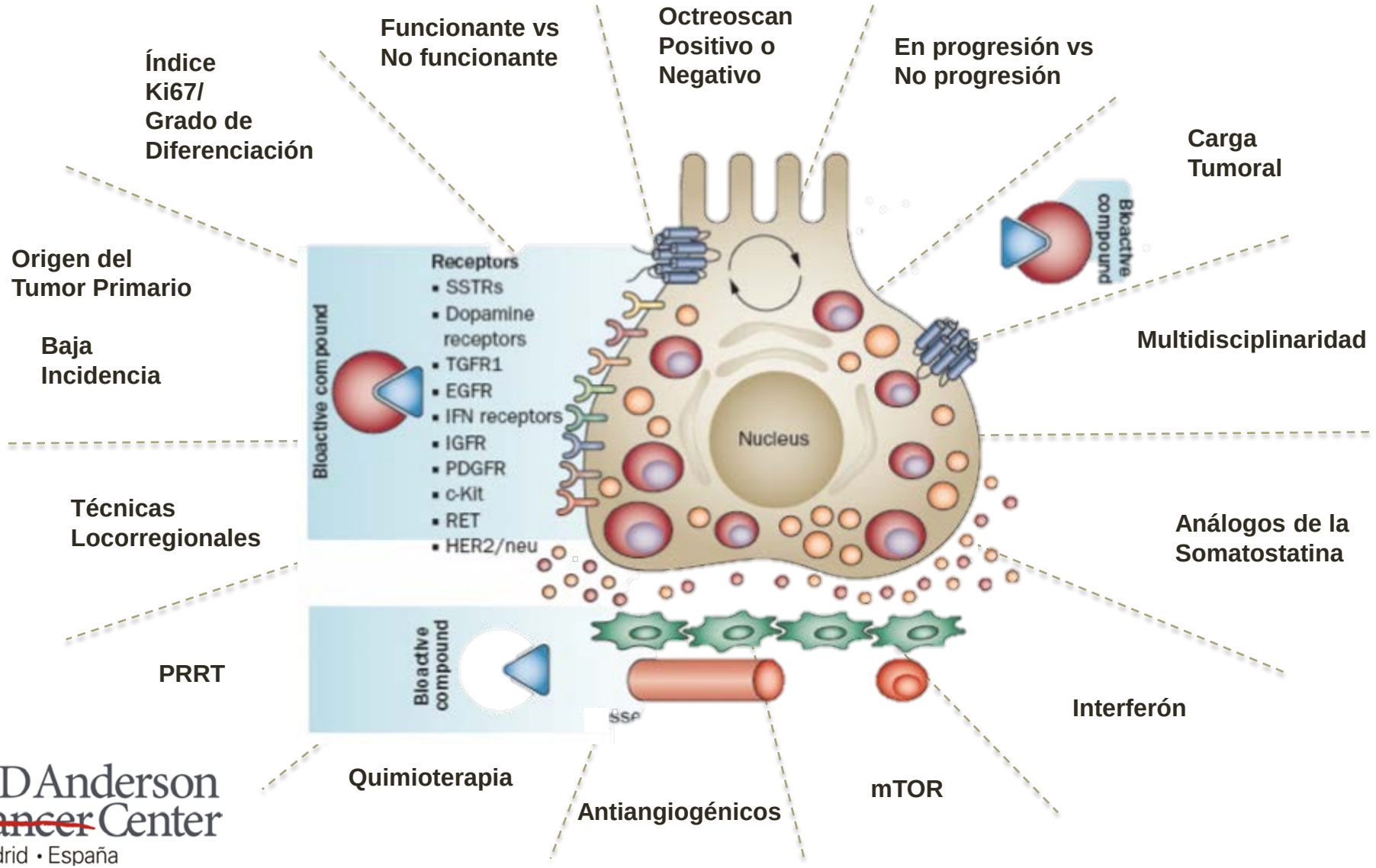
El Reto de los Tumores Neuroendocrinos



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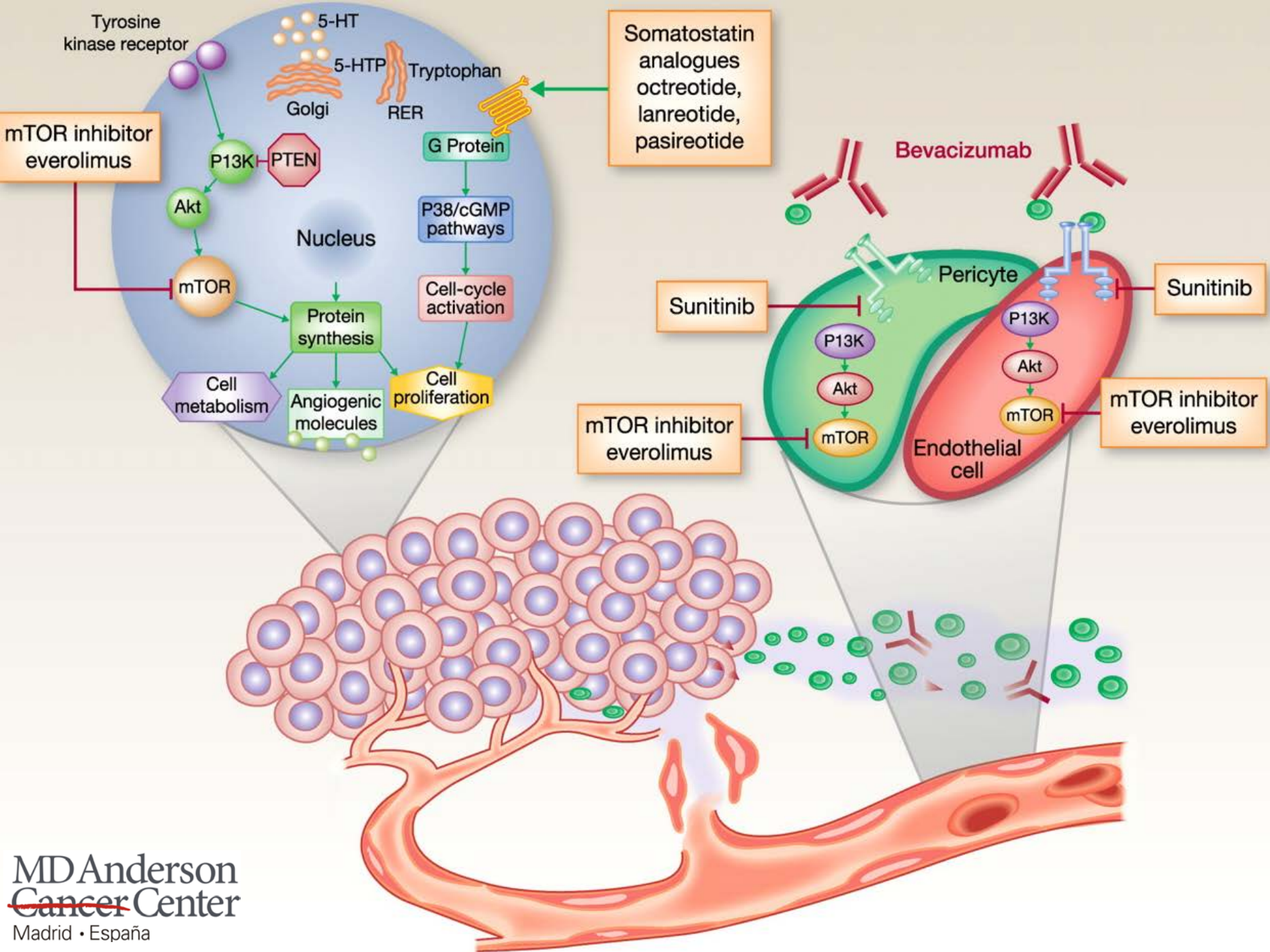

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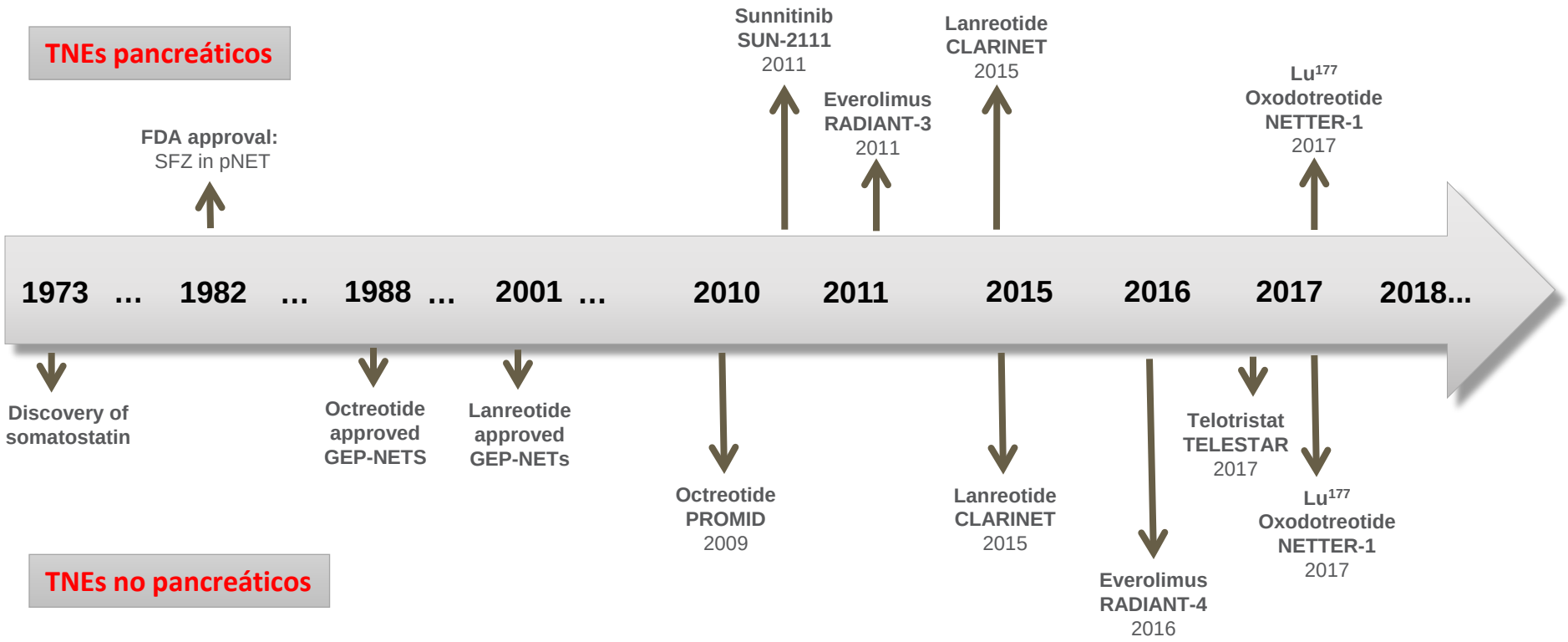
Aprobaciones de fármacos en Tumores Neuroendocrinos



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Adapted from Pavel M, et al. Neuroendocrinol 2017

Estrategias actuales de tratamiento en los TNEs

- Análogos de la Somatostatina
- Quimioterapia
- Terapias Dirigidas
- Inmunoterapia

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Estrategias actuales de tratamiento en los TNEs

- **Análogos de la Somatostatina**
- Quimioterapia
- Terapias Dirigidas
- Inmunoterapia

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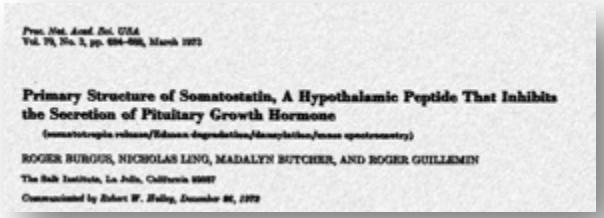
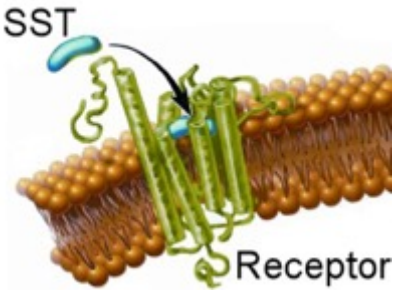
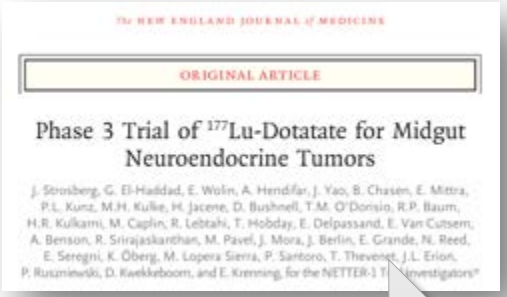
La Somatostatina como ejemplo de Medicina de Precisión en Cáncer



Primary Structure of Somatostatin, A Hypothalamic Peptide That Inhibits the Secretion of Pituitary Growth Hormone

ROGER BURGUS, NICHOLAS LING, MADALYN BUTCHER, AND ROGER GUILLEMIN





ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

1973 **2017**

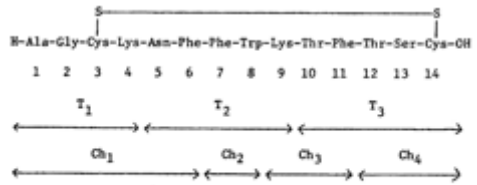
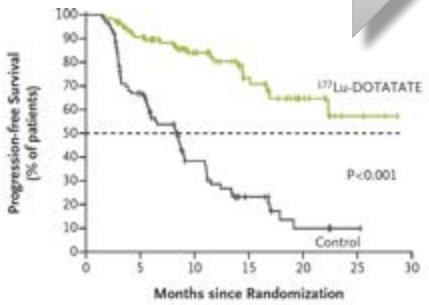


FIG. 1. Peptide fragments observed after treatment of ovine somatostatin with trypsin (T_1–T_3) or chymotrypsin (Ch_1–Ch_4).



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Burgus R, et al. Proc. Nat. Acad. Sci. USA 1973
Strosberg J, et al. N Engl J Med 2017

COMPETE Study: Efficacy and Safety of ^{177}Lu-edotreotide PRRT (Solucin®) in GEP-NET Patients

- **Well-differentiated NETs of non-functional gastroenteric origin (GE-NET) or both functional or non-functional pancreatic origin (P-NET)**
- **SSTR+ disease**
- Progressive disease per RECIST 1.1. criteria

N = 300 pts

R

^{177}Lu-edotreotide
3-monthly up to 4 cycles

Everolimus 10 mg/day
Until progression

Primary endpoint: Progression Free Survival
Estimated Primary Completion Date: Dec 2020

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ITM Solucin GmbH. NCT03049189

Estrategias actuales de tratamiento en los TNEs

- Análogos de la Somatostatina
- **Quimioterapia**
- Terapias Dirigidas
- Inmunoterapia

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SEQTOR Trial: Efficacy and Safety of Everolimus and STZ-5FU Given One Upfront the Other Upon Progression in Advanced pNET

- Advanced **pancreatic NETs**
- **G1 or G2**
- Progressive disease documented by radiology 12 months prior to study inclusion
- Previous treatment with somatostatin (SS) analogues is allowed

N = 180 pts

R

Everolimus 10 mg/day → **STZ-5FU** every 6 or 3 weeks

STZ-5FU every 6 or 3 weeks → **Everolimus 10 mg/day**

Primary endpoint: Second Progression Free Survival
Estimated Primary Completion Date: March 2020

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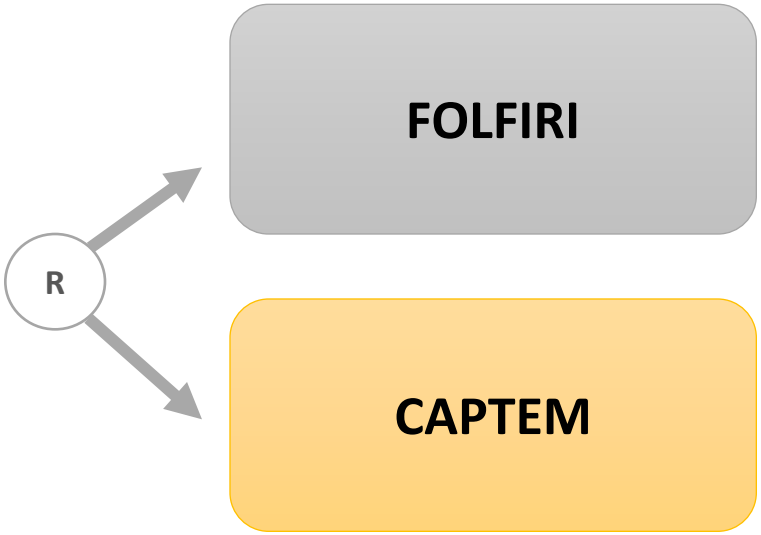
PI: Dr. Ramón Salazar. NCT02246127

SENECA Trial: CAPTEM or FOLFIRI as SEcond-line Therapy in NEuroendocrine CArcinomas

- **Neuroendocrine carcinomas (GEP NEC and lung NEC), G3 with ki67 > 20%**
- **Failure to prior first line treatment for metastatic disease with platinum** compound-based regimen chemotherapy
- ECOG 0-2
- Life expectancy > 3 months

N = 112 pts



Primary endpoint: Clinical Benefit Rate at 12 weeks
Estimated Primary Completion Date: Jan 2021

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PI Dr. Toni Ibrahim. Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST). NCT03387592

Estudios en marcha de fase II con quimioterapia en TNEs

Regimen	Population	Sample Size	Primary endpoint	Completion Date	Identifier
Lanreotide Autogel + Temozolomide	G1/G2 Lung or Thymus	40	ORR	March 2019	NCT02698410
Temozolomida + Capecitabine	NEC GI or pancreas	31	ORR	May 2019	NCT03079440
Temozolomide + pazopanib	Pancreatic NET	39	ORR	Aug 2019	NCT01465659
Temozolomide + TAS 102	G1/G2 NET any origin	33	ORR	Aug 2019	NCT02943733
LV5FU2 + Streptozocin + Bev vs TEM + CAP + Bev	G1/G2 pancreatic NET	140	PFS	Dec 2020	NCT03351296
Temozolomide + everolimus	NEC with a Ki67 of 20-55%	40	PFS at 6 months	Dec 2018	NCT02248012
FOLFIRI + Bevacizumab	NEC GI or pancreas	124	OS at 6 months	Sept 2020	NCT02820857
Cisplatin + etoposide vs Cisplatin + Irinotecan	NEC G3(Ki67>20%)	144	ORR	May 2019	NCT03168594

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https://clinicaltrials.gov

SUNEVO Trial: A Study to Assess the Safety and the Efficacy of the Combination of Evofosfamide (TH-302) and Sunitinib in Pancreatic Neuroendocrine Tumours

- Advanced **pancreatic NETs**
- **G1 or G2**
- Progressive disease documented by radiology **12 months** prior to study inclusion
- Patients may be treated with somatostatin analogues prior or during the trial

N = 43 pts

Evofosfamide 340 mg/m2 IV on days 8, 15 and 22 of each 28 day cycle

+

Sunitinib 37,5 mg/day orally everyday of each cycle

Primary endpoint: Objective Response Rate
Estimated Primary Completion Date: May 2018

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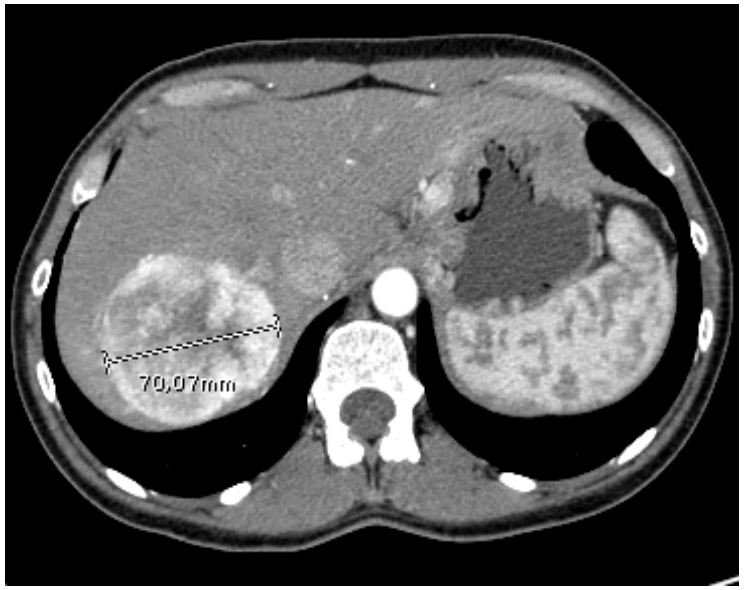
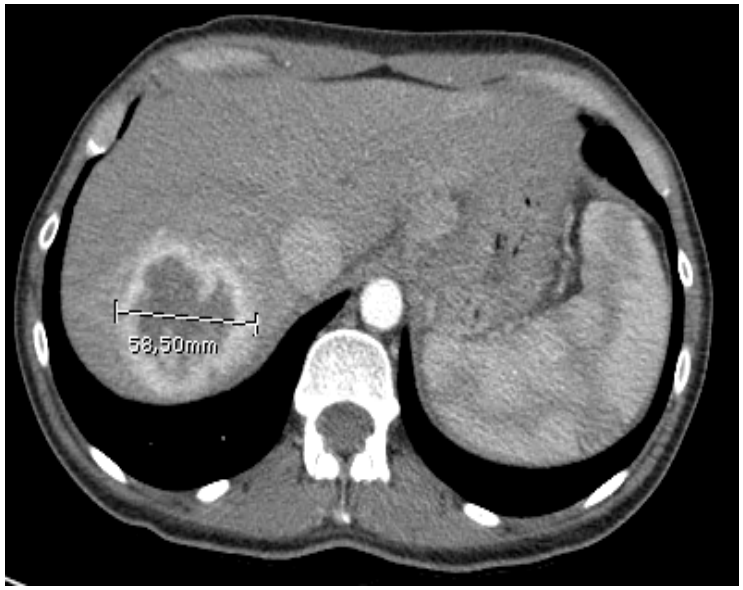
PI: Dr. Enrique Grande. NCT02402062

SUNEVO Trial: A Study to Assess the Safety and the Efficacy of the Combination of Evofosfamida (TH-302) and Sunitinib in Pancreatic Neuroendocrine Tumours



Baseline



8 weeks

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PI: Dr. Enrique Grande. NCT02402062

Estrategias actuales de tratamiento en los TNEs

- Análogos de la Somatostatina
- Quimioterapia
- **Terapias Dirigidas**
- Inmunoterapia

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AXINET Trial: Sandostatin LAR and Axitinib vs Placebo in Patients With Advanced Well differentiated in Non-pancreatic NETs

- **G1-G2 neuroendocrine tumor** of histologically confirmed **non-pancreatic origin**
- **Functioning and non-functioning**
- **Clinical and/or radiological disease progression** documented in the **12 months prior** to study entry
- Prior treatment is allowed with **up to 2 antineoplastic systemic treatment lines different from SAs or IFN**
- **Prior treatment** with targeted therapy against **VEGF or VEGFR is not allowed**

R

Axitinib 5 mg BID + **Sandostatin LAR** 30mg/28 days

Placebo BID + **Sandostatin LAR** 30mg/28 days

N = 253 pts

Primary endpoint: Progression Free Survival
Estimated Primary Completion Date: Nov 2019

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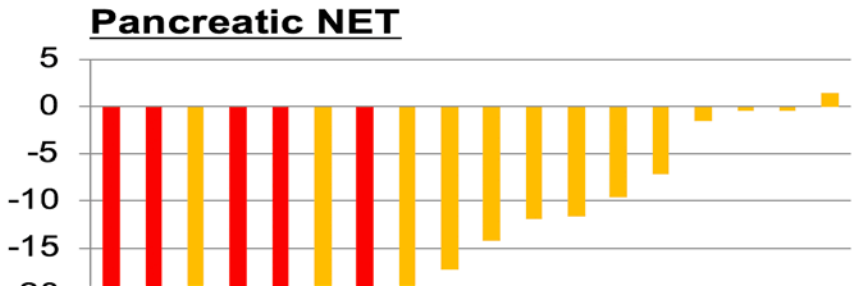
PI: Dr. Rocío García Carbonero. NCT01744249

Estudio Fase II de cabozantinib en pacientes con TNEs

% (95% CI)
5% (5-36%)
5% (53-89%)



Response	N=20	
PR	3	1
SD	15	75
Unknown*	2	1

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Chan JA, et al. Presented at ASCO GI 2017

Estudio Fase II de cabozantinib en pacientes con TNEs

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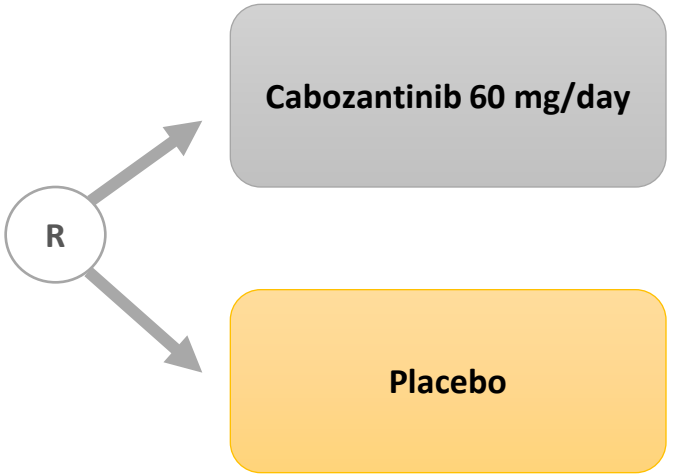
Chan JA, et al. Presented at ASCO GI 2017

CABINET Trial: Double-Blinded Phase III Study of Cabozantinib Versus Placebo in Patients With Advanced NETs After Progression on Everolimus

- **Well- or moderately-differentiated neuroendocrine tumors or pancreatic and non-pancreatic origin**
- Target lesions must have shown disease progression within **6 months**
- Patient must have failed **at least one prior systemic therapy that included everolimus**



N = 395 pts

Primary endpoint: Progression Free Survival by ICR
Estimated Primary Completion Date: Jan 2021

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PI Dr. Jennifer Chan. National Cancer Institute. NCT03375320

Estudios de Fase II en marcha con terapias dirigidas en TNEs

Regimen	Mode of action	Population	Sample Size	Primary endpoint	Completion Date	Identifier
Sapanisertib	TORC1 and 2	G1/G2 pancreatic NET refractory to mTOR	40	ORR	Aug 2019	NCT02893930
LEE011 (ribociclib) + everolimus	CDK4/6 + mTOR	WDNETs of foregut origin	42	PFS	Feb 2019	NCT03070301
Regorafenib	BRAF, VEGFR, KIT, TIE-2	G1/G2 GEP NETs	48	PFS	Aug 2019	NCT02259725
Fosbretabulin + everolimus	Disrupting vascular agent + mTOR	G1-3 NETs	30	Safety	Aug 2018	NCT03014297
Ibrutinib	Bruton's tyrosine kinase	G1/G2 GEP NETs	51	ORR	Dec 2018	NCT02575300
Ramucirumab	VEGFR2	G1/G2 GEP NETs	43	PFS	Dec 2019	NCT02795858
Nintedanib	VEGFR, PDGFR, FGFR	Non pancreatic G1/G2 NET	30	PFS	Mar 2018	NCT02399215
Famitinib	VEGFR, PDGFR, KIT	G1/G2 GEP NETs	63	ORR	Nov 2017	NCT01994213

TALENT Trial: A phase II trial to Assess the efficacy of LENvatinib in metastatic neuroendocrine Tumors

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

Lenvatinib 24 mg/day

N = 110 pts

Cohort A

Patients with advanced/metastatic G1/G2 **neuroendocrine tumors of the pancreas** after progression to a previous targeted agent

Cohort B

Patients with advanced/metastatic G1/G2 **neuroendocrine tumors of the gastrointestinal tract** after progression to somatostatin analogues

Primary endpoint: Overall response rate (ORR) by RECIST v 1.1 upon central radiologic assessment
Estimated Primary Completion Date: Completed

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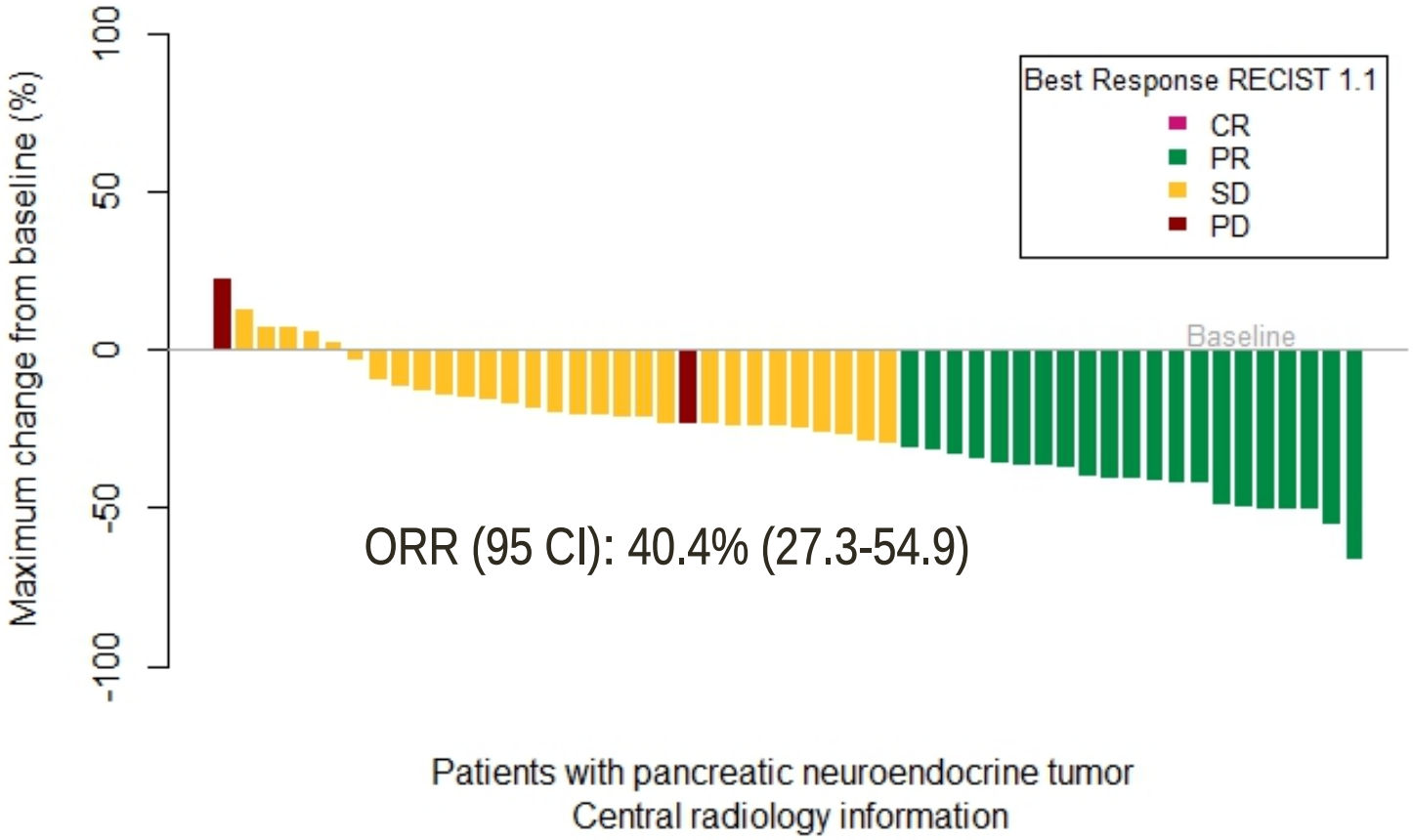
PI: Dr. Jaume Capdevila. NCT02678780

TALENT Trial: A phase II trial to Assess the efficacy of LENvatinib in metastatic neuroendocrine Tumors



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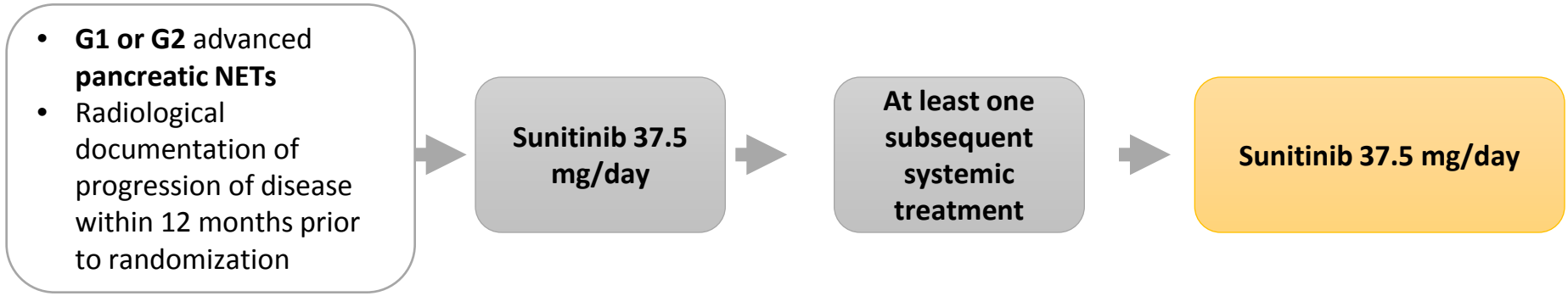
RESUNET Trial: A phase II trial to assess the efficacy of REchallenge with SUNitinib in metastatic pancreatic NEuroendocrine Tumor previously failed to sunitinib



N = 36 pts

Primary endpoint: Progression Free Survival rate at 6 months
Estimated Primary Completion Date: April 2019

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PI: Dr. Enrique Grande. NCT02713763

Estrategias actuales de tratamiento en los TNEs

- Análogos de la Somatostatina
- Quimioterapia
- Terapias Dirigidas
- **Inmunoterapia**

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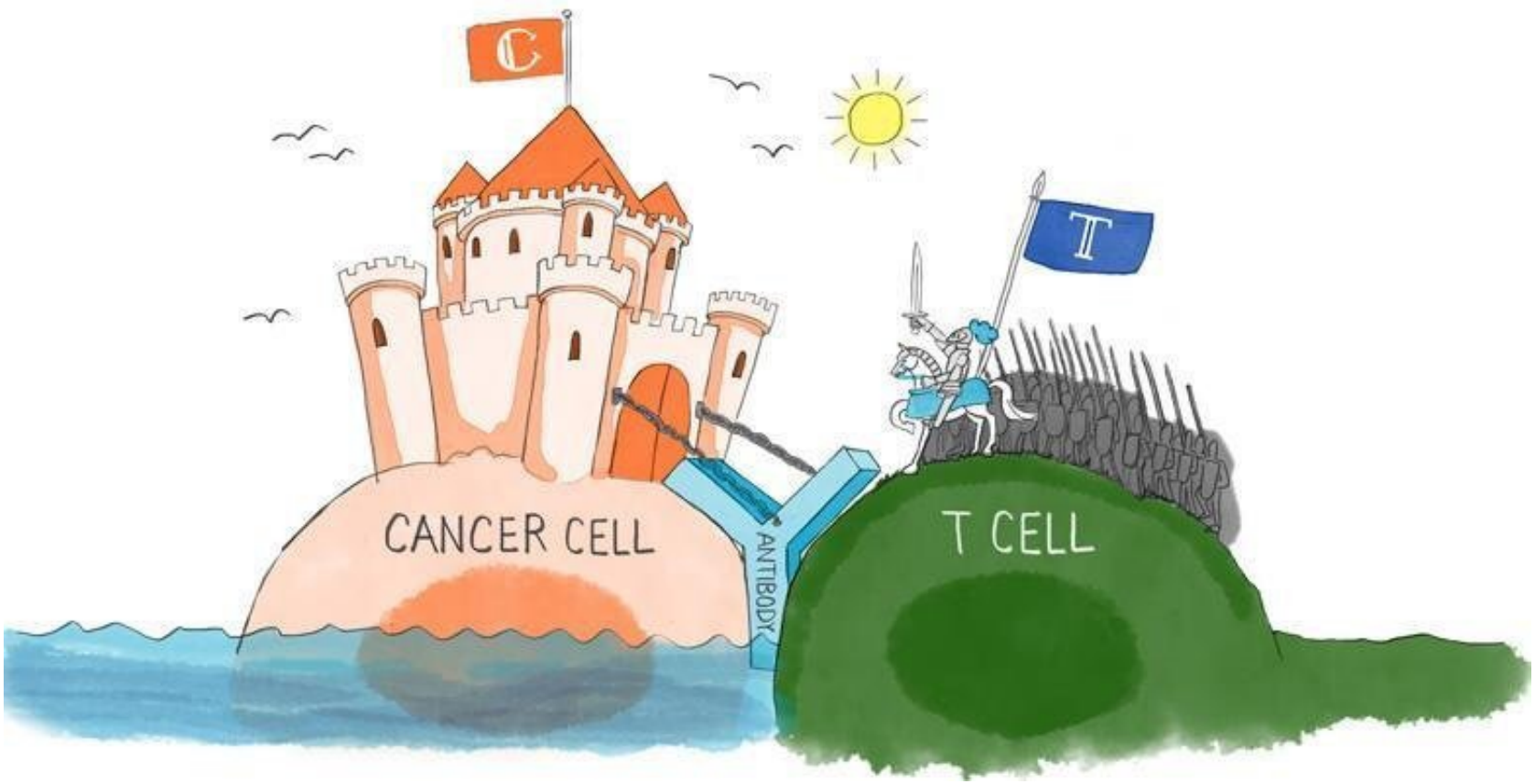
Inmunoterapia y Cáncer



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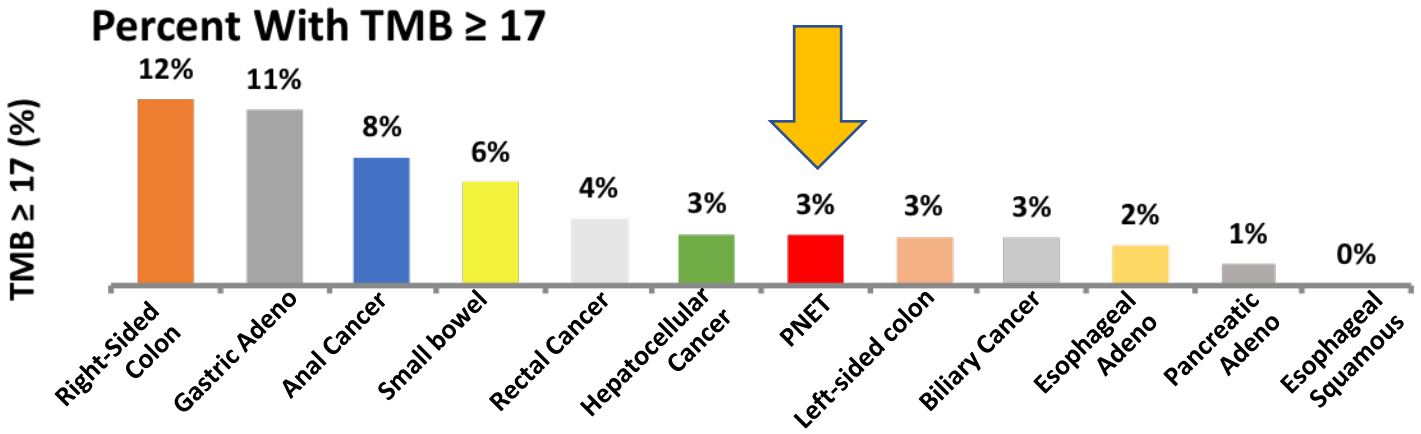
Carga mutacional en los pacientes con tumores digestivos



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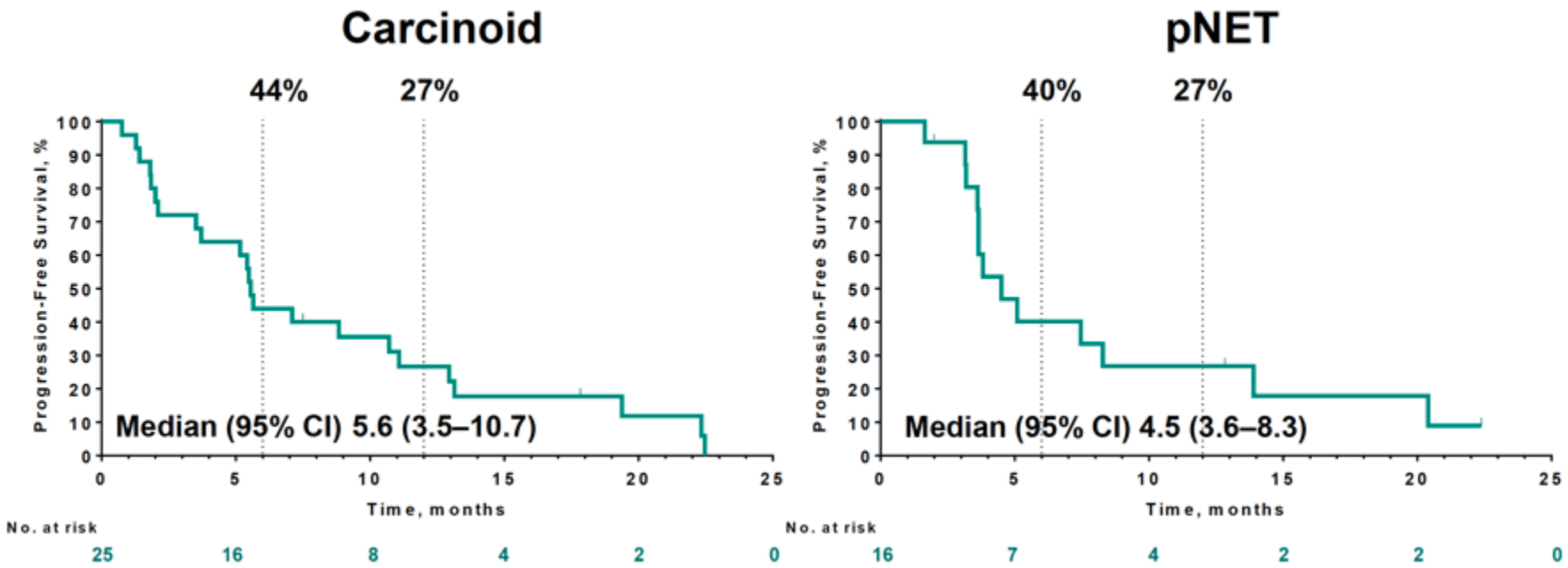
Salem ME, et al. ASCO GI 2017. Abstract 530

KEYNOTE-028: Pembrolizumab for patients with PD-L1 positive carcinoid or pancreatic NETs



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Mehnert JM; et al. Oral presentation at ESMO 2017. Madrid, Spain

Estudios de Fase II en marcha con inmunoterapia en TNEs

Trial Name / Location	Regimen	Population	Sample Size	Primary endpoint	Completion Date	Identifier
Fox Chase	Pembrolizumab	G3 NETs (Ki67 >20%)	21	ORR	Aug 2018	NCT02939651
CPDR001 E2201	Spartalizumab (PDR001)	G1/G2 GEP and Lung NET & GEP NEC	110	ORR	Dec 2019	NCT02955069
NET-002	Avelumab	G2/G3 GEP NET or Lung	36	ORR	Sept 2020	NCT03278379
NET-001	Avelumab	NEC GEP or lung	10	ORR	Set 2019	NCT03278405
Sidney Kimmel CC	Nivolumab + Ipilimumab	G1/G2 GEP NET or Lung	64	ORR	Jan 2023	NCT03420521
Uppsala	Recombinant Adenovirus AdVince	GI, pancreas or lung NEC	35	Safety	Aug 2019	NCT02749331
PLANET	Pembrolizumab + Lanreotide	G1/G2 GEP NET	26	ORR	Jun 2020	NCT03043664
Shanghai Junshi Bioscience	JS001	Refractory NET and NECs	40	ORR	Apr 2018	NCT03167853

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https://clinicaltrials.gov

DUNE Trial: A phase II study of durvalumab plus tremelimumab for the treatment of patients with advanced neuroendocrine neoplasms of gastroenteropancreatic or lung origin

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

Durvalumab 1500 mg
Q4W for 12 months
+
Tremelimumab 75 mg
Q4W for up to 4 doses/cycles

N = 126 pts

Cohort 1	Well-moderately differentiated neuroendocrine tumors of the **lung**
Cohort 2	Well-moderately differentiated **GI NETs** after progression to SSA and one targeted therapy (mTOR or TKI)
Cohort 3	Well-moderately differentiated **G1/G2 pancreatic NETs** after progression to standard therapies (at least 2)
Cohort 4	**Neuroendocrine neoplasms (WHO grade 3)** of gastroenteropancreatic origin of unknown primary site (excluding lung primary tumors) after progression to first-line chemotherapy with a platinum based regimen

Primary endpoint: Clinical benefit rate at 9 months
Estimated Primary Completion Date: May 2019

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PI: Dr. Jaume Capdevila. NCT03095274

Exploratory basket trial of CABozantinib plus ATezolizumab in advanced and progressive neoplasms of the ENdocrine system – The CABATEN study

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

Cabozantinib 60 mg PO
+
Atezolizumab 1200 mg Q3W

Cohort 1	**Well differentiated thyroid cancer**, including papillary, follicular, and poorly differentiated thyroid cancers	N = 9 + 15 pts
Cohort 2	**Anaplastic thyroid cancer**	N = 9 + 15 pts
Cohort 3	**Adrenocortical carcinoma**	N = 9 + 15 pts
Cohort 4	**Pheochromocytoma and paraganglioma**	N = 9 + 15 pts
Cohort 5	**Well-differentiated neuroendocrine tumors of gastroenteropancreatic and lung origin** (WHO grade 1 and 2) origin	N = 9 + 15 pts
Cohort 6	**Poorly differentiated neuroendocrine tumors** (WHO grade 3), excluding small cell lung cancer	N = 9 + 15 pts

Primary endpoint: Overall Objective Response Rate
Estimated Primary Completion Date: June 2020

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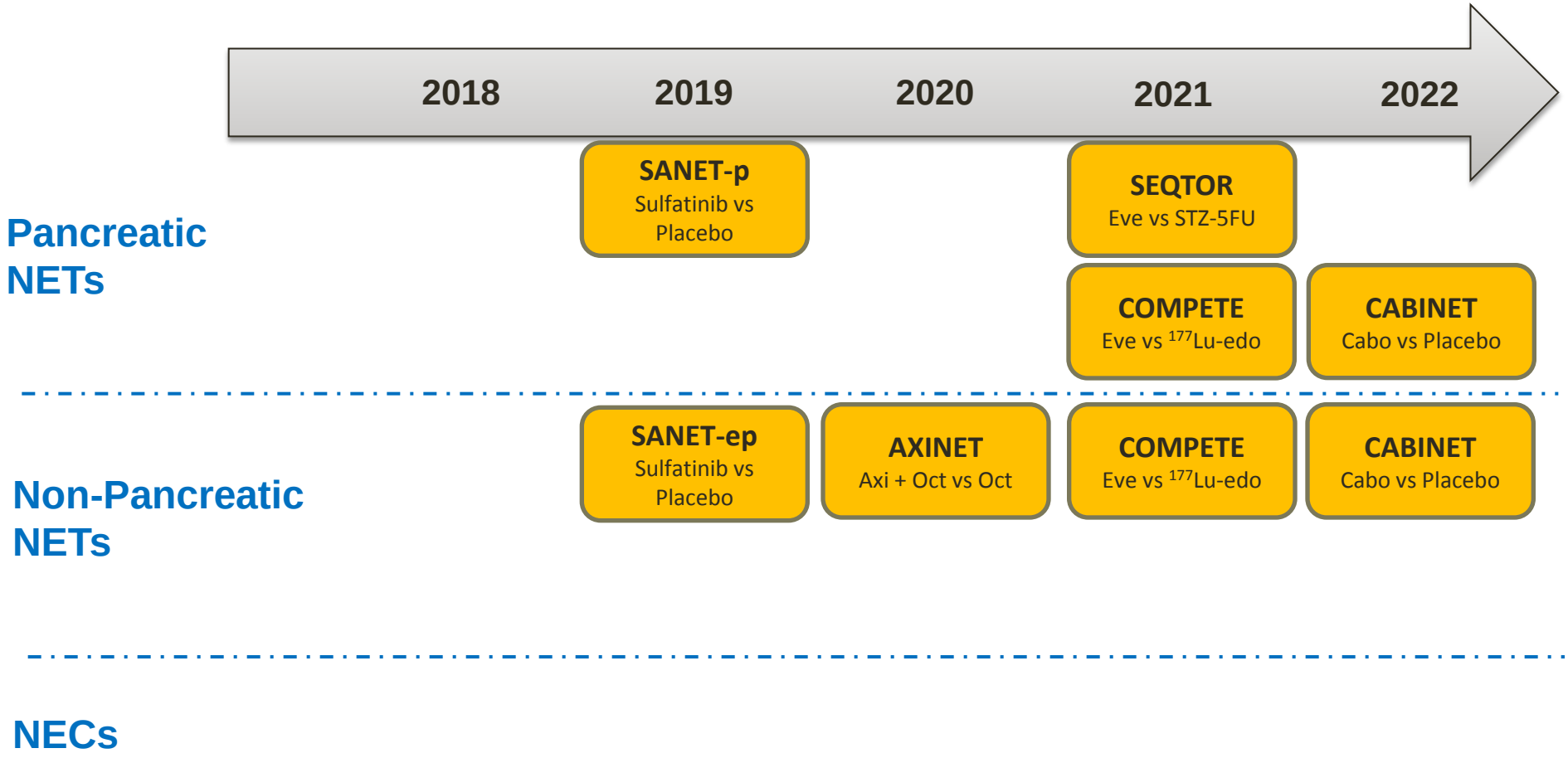
PI: Dr. Jaume Capdevila
Dr. Enrique Grande

Qué nos espera en los próximos años en TNEs?



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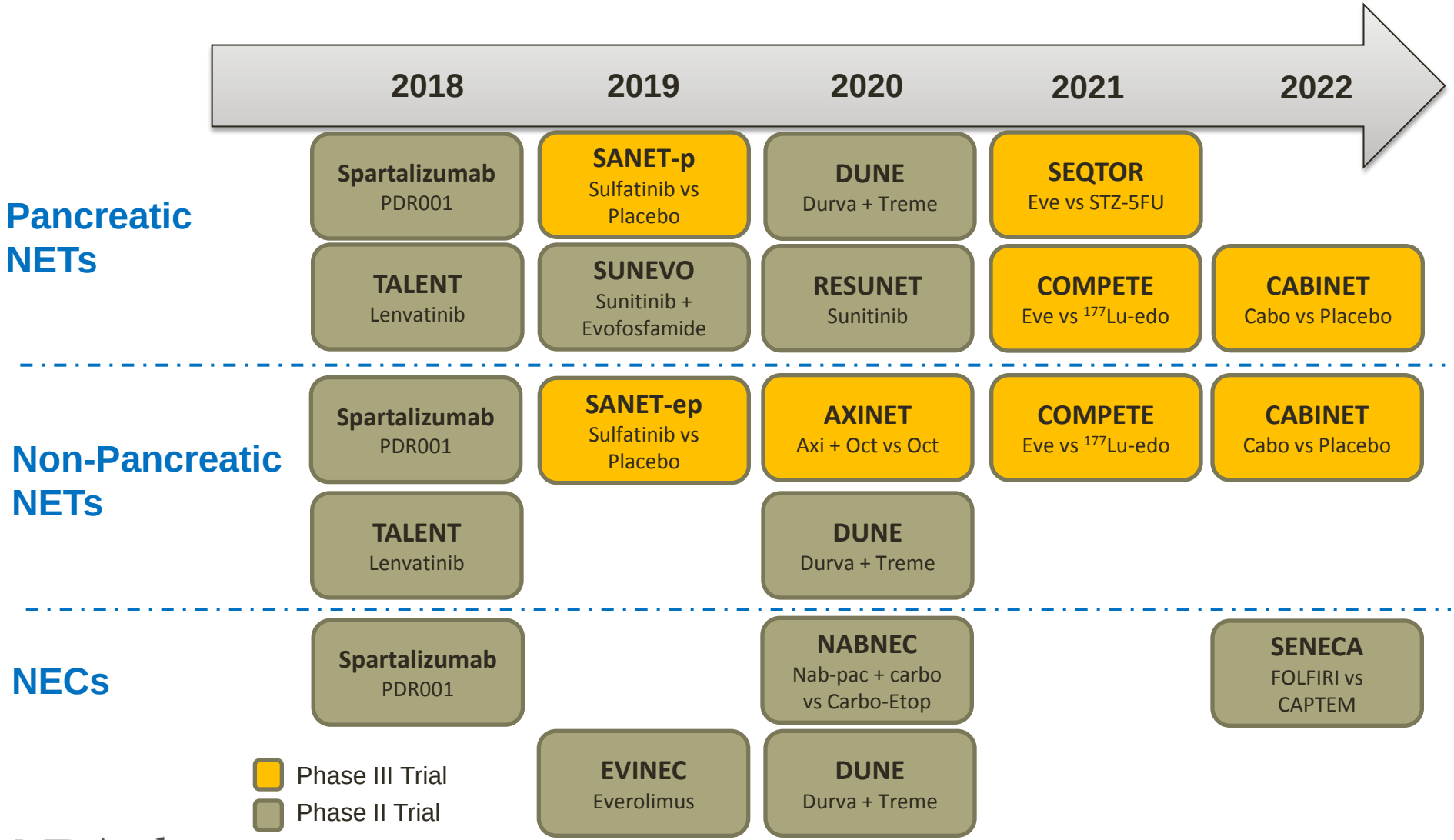
www.clinicaltrialsgov.com

Qué nos espera en los próximos años en TNEs?



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Retos que quedan aún pendientes en los TNEs

- Estudios de adyuvancia para pacientes con alta posibilidad de recaída tras cirugía?
- Estudios de neoadyuvancia para pacientes con tumores localmente avanzados?
- Estudios en tumores G3 bien diferenciados?
- Biomarcadores?

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Biomarcadores en Cáncer

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Curaremos el cáncer algún día?

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