¿TIENE FUTURO LA INMUNOTERAPIA EN TNE?

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HOSPITAL CLÍNICO UNIVERSITARIO DE VALLADOLID

12 – DICIEMBRE – 2017 **II ACLO-TNE**

¿TIENE FUTURO LA INMUNOTERAPIA EN TNE?

1 – INTRODUCCIÓN-INMUNOTERAPIA

2 - PRECLÍNICA

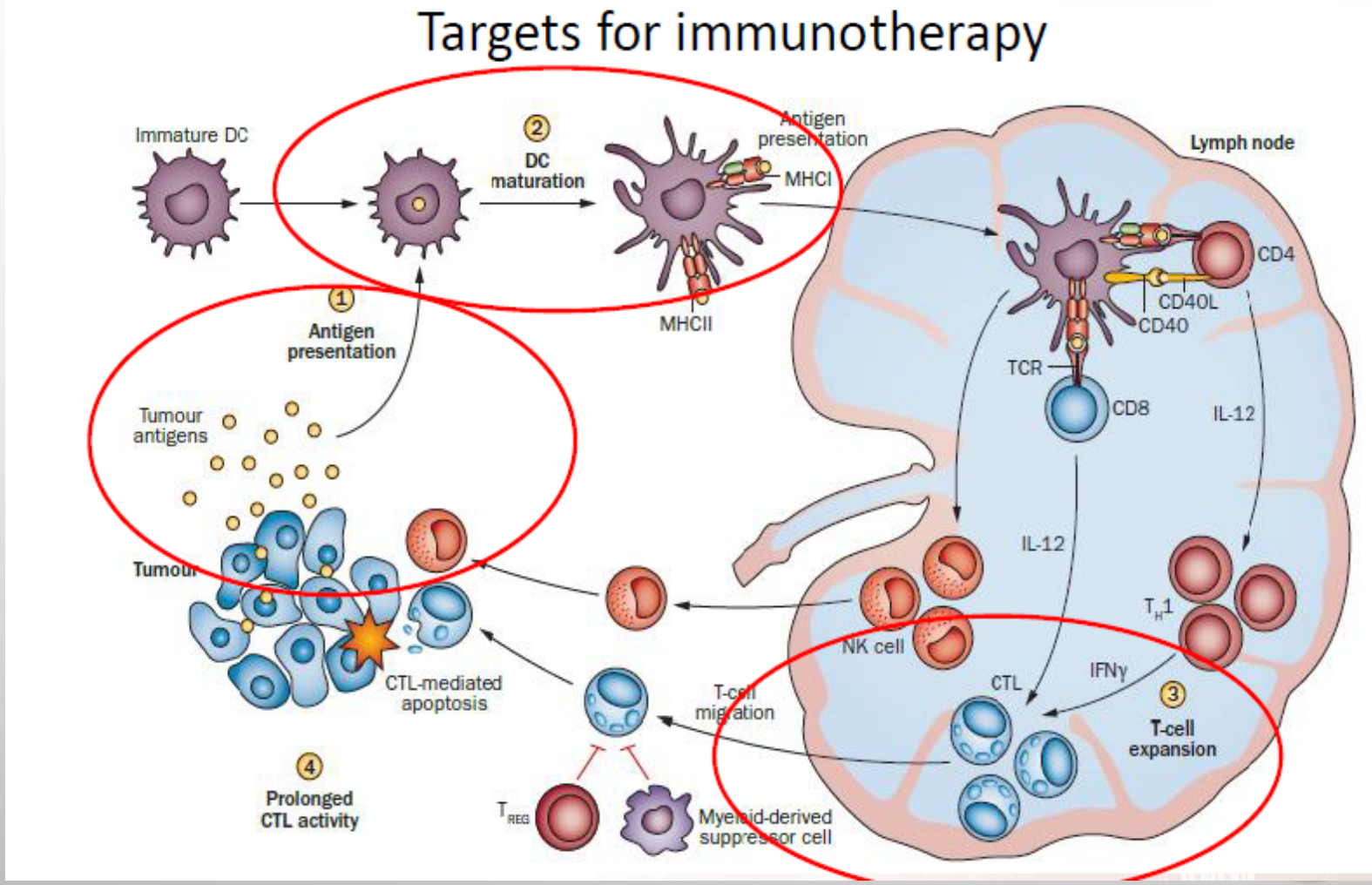
3 – ESTUDIOS EN MARCHA EN LA ACTUALIDAD

- **KEYNOTE-028 IB (PEMBROLIZUMAB)**
- **MK 3475-158 (PEMBROLIZUMAB) // PDR001**
- **DUNE (DURVALUMAB + TREMELIMUMAB)**

4- APROBACIONES : **AVELUMAB -MERKEL**

5- CONCLUSIONES

INMUNOTERAPIA



Melero I. Nat Rev 2014

NEN:

-Grupo heterogéneo

-Grupo minoritario

-Resistencia citostáticos clásicos

-G1-2: Estabilizaciones prolongadas

-G3:

¿ Mayor carga mutacional ?

¿ Mayor escape inmune ?

INMUNOTERAPIA

"PUNTOS DE CONTROL INMUNITARIOS" → INMUNE CHECKPOINTS

Vía de escape tumoral (EVASIÓN INMUNE)

FUNCIÓN: bloquear estas vías con Ac específicos denominados "inhibidores de los puntos de control inmunitarios"

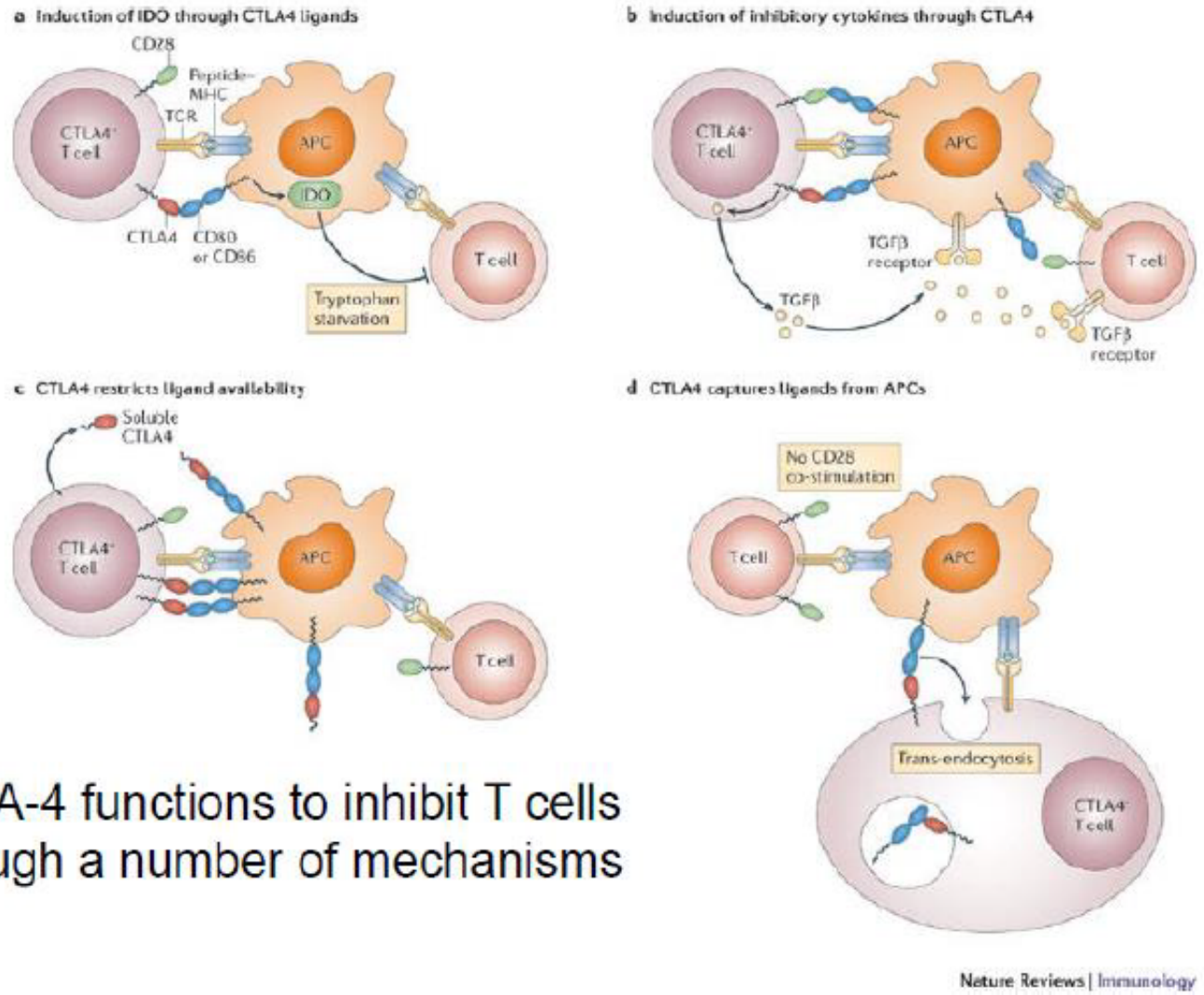
NIVEL: célula principal sistema inmunitario→ LINFOCITO T

Varias moléculas expresadas por los linfocitos T que tienen función de checkpoints inmunes: CTLA-4, PD1, TCR, LAG-3, TIM-3, CEACAM-1, CD200R O TIGIT

MAYOR RELEVANCIA CLÍNICA

- **CTLA-4** (cytotoxic t-lymphocyte-associated protein 4)
- **PD1** (programmed cell death 1)

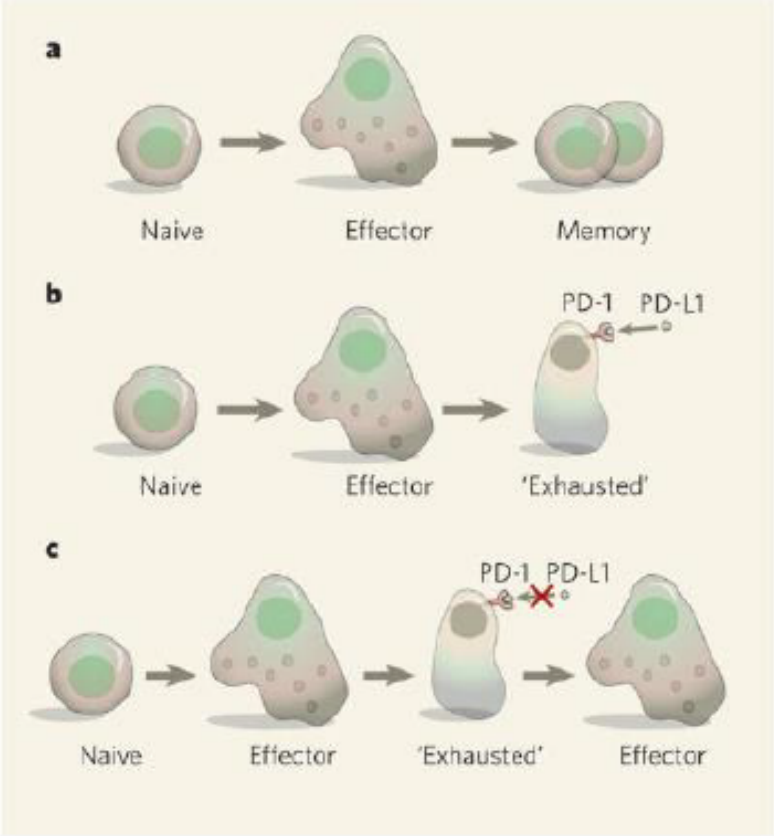
INMUNOTERAPIA



CTLA-4 functions to inhibit T cells through a number of mechanisms

INMUNOTERAPIA

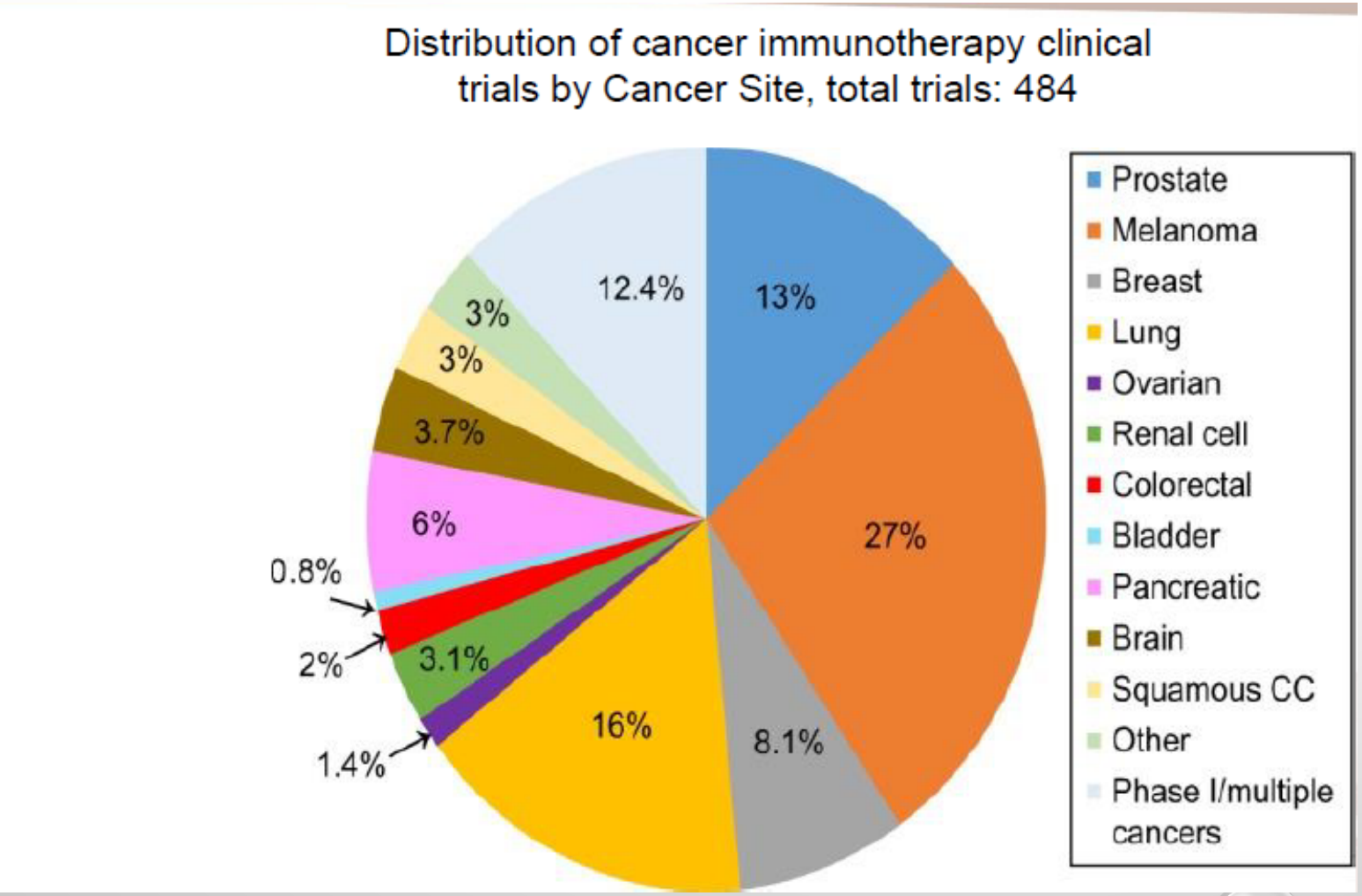
PD-1 is another negative regulator of T cell activity



Chronic LCMV infection with clone 13 which persists

(PD-1 blockade as a potential therapeutic for chronic viral infections

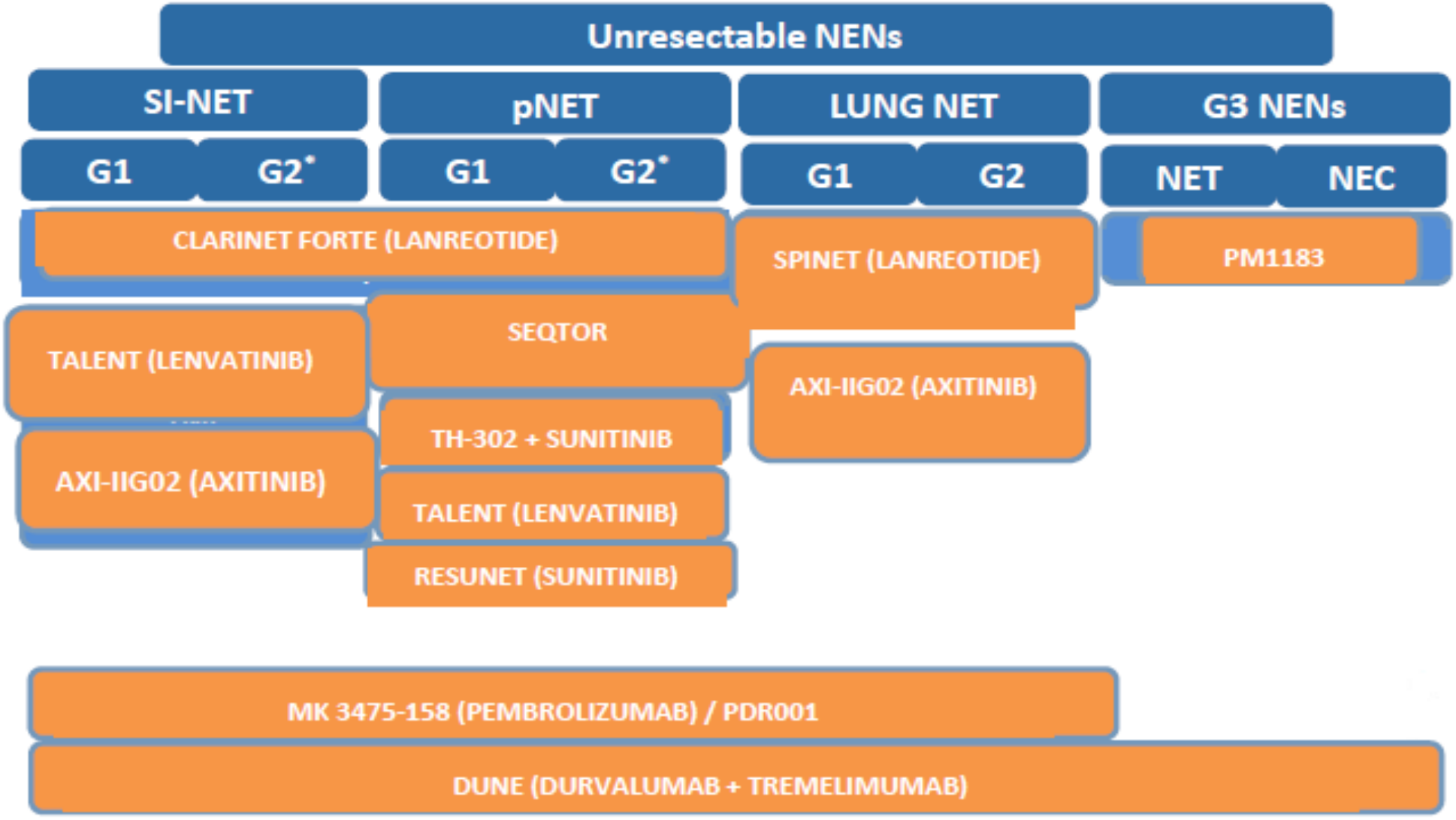
INMUNOTERAPIA



OTROS 3% ??

FASES I 12%??

Juergens RA. Biomark Cancer. 2016;8(Suppl 2):1-13


Unresectable NENs
SI-NET
pNET
LUNG NET
G3 NENs
G1
G2*
G1
G2*
G1
G2
NET
NEC
CLARINET FORTE (LANREOTIDE)
SPINET (LANREOTIDE)
PM1183
SEQTOR
TALENT (LENVATINIB)
AXI-IIG02 (AXITINIB)
TH-302 + SUNITINIB
AXI-IIG02 (AXITINIB)
TALENT (LENVATINIB)
RESUNET (SUNITINIB)
MK 3475-158 (PEMBROLIZUMAB) / PDR001
DUNE (DURVALUMAB + TREMELIMUMAB)

PRE-CLÍNICA

EXPRESSION OF PD-1 AND PD-L1 IN POORLY DIFFERENTIATED NEUROENDOCRINE CARCINOMAS OF THE DIGESTIVE SYSTEM: A POTENTIAL TARGET FOR ANTI-PD-1/PD-L1 THERAPY

Roberts, Jordan A; Gonzalez, Raul S; Das, Satya; Berlin, Jordan; Shi, Chanjuan (Human Pathology)

N: 37 (Vanvderbilt University Medical Center 1997-2016)

IHQ PD-1 y PD-L1 **células tumorales** (32% c.pequeña, 68% c.grande; WHO 2010) y **células inmunes asociadas a tumor** (infiltrado linfocitario-TILs, macrófagos, células plasmáticas)

Expresión de PD-L1 biomarcador de respuesta

Sobreexpresión de PD-1 marcador de posible agresividad tumoral

Expresión en membrana 0-1-2-3 (**IHQ**-DAKO)

-Células tumorales <1%, 1-10%, 11-50%, >50%

-Células Inmunes <1%, 1-5%, 5-10%, >10%

PRE-CLÍNICA

* Todas las células tumorales que presentaban PD-1 +, también presentaban PD-1+ en células inmunes asociadas.

* Hubo PD-L1 + coincidente en células tumorales e inmunes en un 32%

* PD-L1 + fue más frecuente en células peritumorales que tumorales

* Expresión de PDL-1, puede ser marcador predictivo de respuesta??

* No hubo diferente expresión en células pequeñas y grandes

In conclusión, PD-1/PD-L1 expression is a frequent occurrence in poorly-differentiated neuroendocrine carcinomas of the digestive system. Checkpoint blockade targeting the PD-1/PD-L1 pathway may have a potential role in treating patients with this disease

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KEYNOTE-028 → MADRID 2017 ESMO congress

Pembrolizumab for Patients With PD-L1–Positive Advanced Carcinoid or Pancreatic Neuroendocrine Tumors: Results From the KEYNOTE-028 Study

Janice M. Mehnert,[1] Emily Bergsland,[2] Bert H. O'Neil,[3] Armando Santoro,[4] Jan H. M. Schellens,[5] Roger B. Cohen,[6] Toshihiko Doi,[7] Patrick A. Ott,[8] Michael J. Pishvaian,[9] Igor Puzanov,[10] Kyaw L. Aung,[11] Chiun Hsu,[12] Christophe Le Tourneau,[13] Jean-Charles Soria,[14] Elena Élez,[15] Kenji Tamura,[16] Marlena Gould,[17] Guoqing Zhao,[17] Karen Stein,[17] Sarina A. Piha-Paul[18]

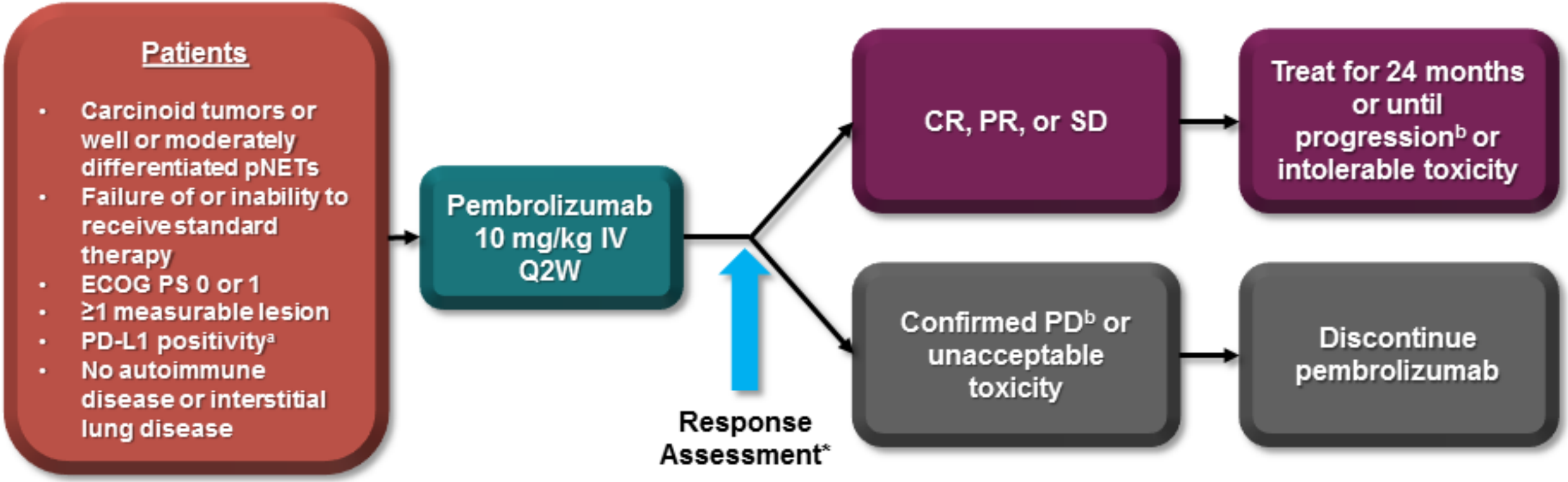
- Multicohort phase 1b study evaluating safety and antitumor activity of pembrolizumab in a variety of PD-L1–positive advanced solid tumors
- This is the first report from the carcinoid and pNET cohorts of KEYNOTE-028

Rationale for Pembrolizumab in Carcinoids and Pancreatic Neuroendocrine Tumors (pNETs)

- Systemic therapies are available for patients with advanced or metastatic carcinoids/pNETs[1-3]
  - Dependent on tumor type, systemic therapy may include
    - Somatostatin analogues, cytotoxic chemotherapy, everolimus, interferon-2α, cisplatin/carboplatin plus etoposide, sunitinib, peptide receptor radionuclide therapy
- Many patients experience treatment failure or are unable to receive standard therapy[4]
- Prolonged survival with pembrolizumab in melanoma,[5] non–small-cell lung cancer,[6,7] and urothelial cancer[8] suggested potential antitumor activity in other solid tumors

1. National Comprehensive Cancer Network (NCCN). Neuroendocrine tumors, V3.2017. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf.
2. Öberg K, et al. *Ann Oncol*. 2012;23(Suppl 7):vii120-vii123.
3. Öberg K, et al. *Ann Oncol*. 2012;23(Suppl 7):vii124-vii130.
4. Kunz, P. *J Clin Oncol*. 2015;33(16):1855-1863.
5. Robert C, et al. *Lancet*. 2014;384(9948):1109-1117.
6. Garon EB, et al. *N Engl J Med*. 2015;372(21):2018-2028.
7. Herbst R, et al. *Lancet*. 2016;387(10027):1540-1550.
8. Bellmunt J, et al. *N Engl J Med*. 2017;376:1015-1026.

KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors



***Response assessment**: Every 8 weeks for first 6 months; every 12 weeks thereafter

Primary endpoints: ORR per RECIST v1.1 (investigator review)

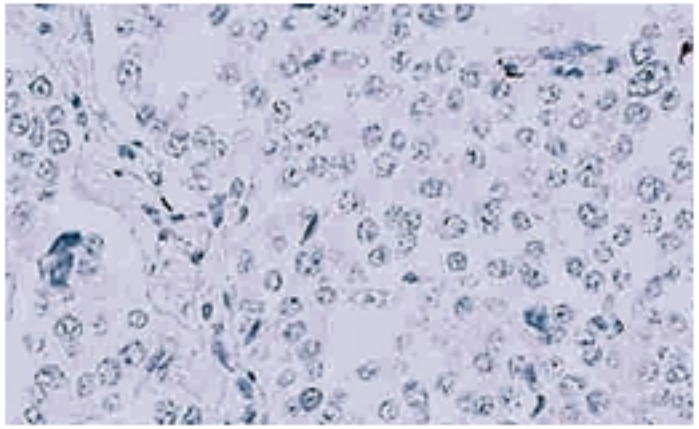
Secondary endpoints: PFS, OS, duration of response, and safety

[a]At least 1% modified proportion score or interface pattern (QualTek IHC using 22C3 antibody clone).
[b]If SD or better when pembrolizumab discontinued and subsequently have PD, patients may be eligible to resume pembrolizumab for ≤1 year.
[c]If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later.

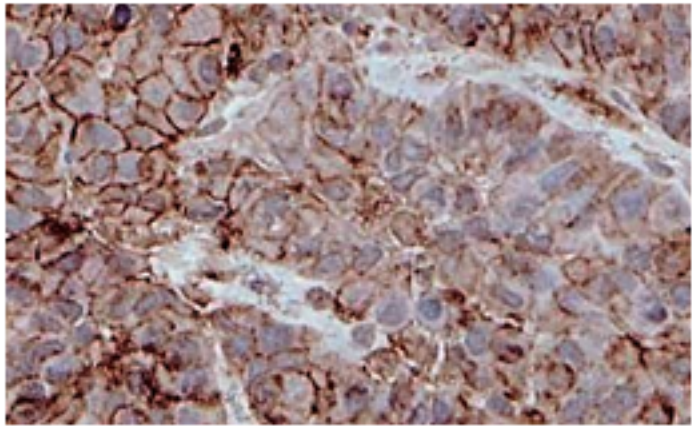
Analysis of PD-L1 Expression

- Tumor samples: archival or newly obtained core or excisional biopsy of a nonirradiated lesion
- Immunohistochemistry: assessed at central laboratory using QualTek assay and 22C3 antibody clone (Merck & Co., Inc., Kenilworth, NJ)
- Positivity: membranous PD-L1 expression in ≥1% of cells in tumor nests or positive bands in stroma

Examples of PD-L1 Staining in Neuroendocrine Tumor Specimens From KEYNOTE-028

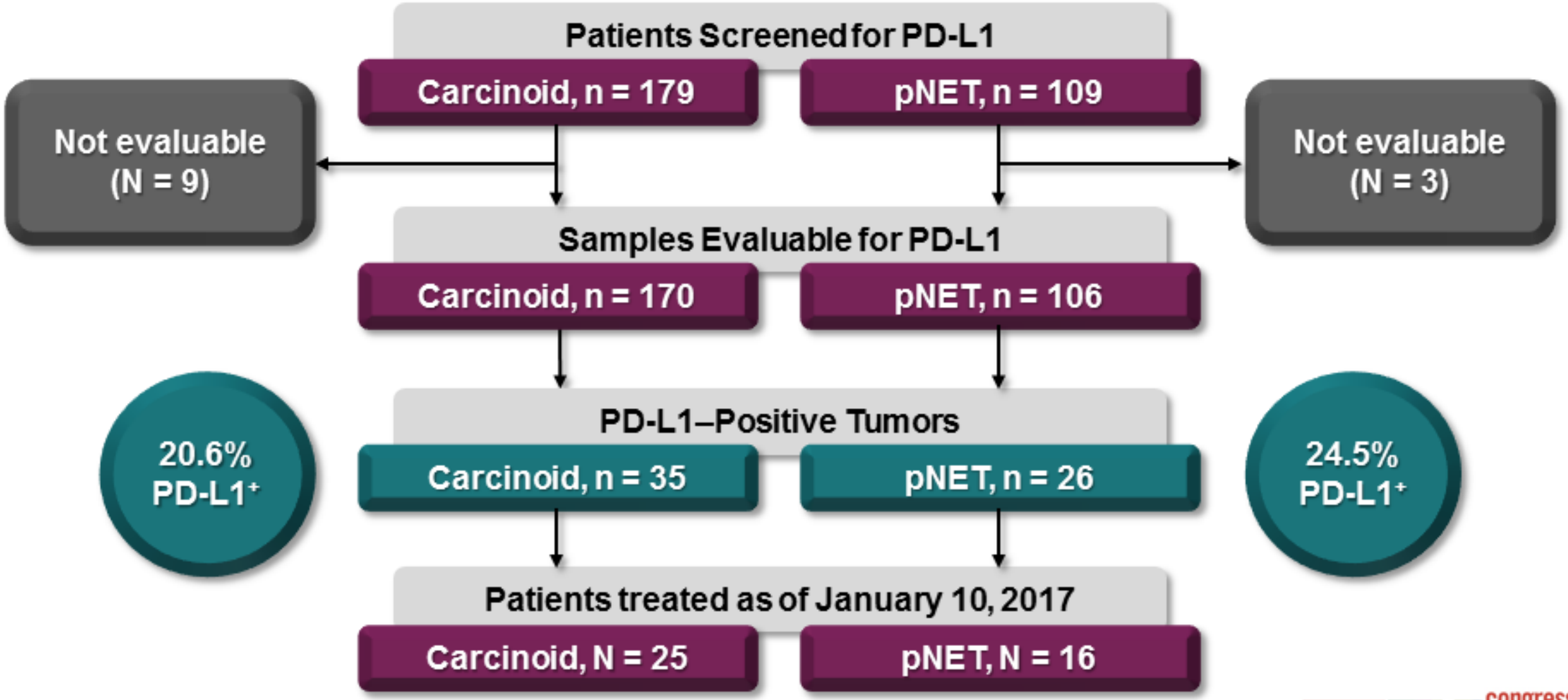


PD-L1 Negative



PD-L1 Positive

PD-L1 Screening: Carcinoid/pNET Cohorts



[a]Patients with CNS metastases that were stable for ≥4 weeks could enroll.

Baseline Characteristics

Characteristic	Carcinoid N = 25	pNET N = 16
Median age, years (range)	63.0 (43–81)	61.0 (35–80)
Male, n (%)	8 (32)	5 (31)
Race, n (%)		
White	15 (60)	9 (56)
Asian	5 (20)	2 (13)
Black or African American	3 (12)	3 (19)
Other/not specified	2 (8)	2 (13)
ECOG PS, n (%)		
0	6 (24)	10 (63)
1	19 (76)	6 (38)
Metastatic staging		
MX	2 (8)	1 (6)
M0	0	2 (13)
M1	21 (84)	11 (69)
Unknown/missing	2 (8)	2 (13)

Characteristic, n (%)	Carcinoid N = 25	pNET N = 16
Stable brain metastases, n (%)	1 (4)	0
Site of disease, n (%)		
Lung	9 (36)	–
Gut	7 (28)	–
Other	9 (36)	–
Prior therapies for recurrent/ metastatic disease, n (%)		
0	3 (12)	1 (6)
1	5 (20)	5 (31)
≥2	11 (44)	8 (50)
Unknown	6 (24)	2 (13)
Select prior therapies,[a] n (%)		
Chemotherapy	18 (72)	9 (56)
Somatostatin analogues	6 (24)	6 (38)
Everolimus	3 (12)	10 (63)
Sunitinib	0	4 (25)
Investigational therapy	3 (12)	1 (6)

[a]Patients could have received ≥1 type of prior therapy.
Data cutoff date: February 20, 2017.

Treatment-Related AEs: Carcinoid

Occurring in ≥10% Patients	n (%)
Any	17 (68)
Diarrhea	7 (28)
Fatigue	6 (24)
Hypothyroidism	4 (16)
Pyrexia	3 (12)
Weight decreased	3 (12)
Decreased appetite	3 (12)
AST increase	3 (12)
ALT increase	3 (12)

- Median follow-up: 20.2 months (range, 2.0–34.7)
- No grade 4 or 5 events occurred

Grade 3	n (%)
Any	8 (32)
Diarrhea	3 (12)
ALT increase	2 (8)
AST increase	2 (8)
Feces discolored	1 (4)
Fatigue	1 (4)
Decreased appetite	1 (4)
Hyperglycemia	1 (4)
Hypovolemia	1 (4)
Arthralgia	1 (4)
Dyspnea	1 (4)
Pneumonitis	1 (4)
Dermatitis	1 (4)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Data cutoff date: February 20, 2017.

Treatment-Related AEs: pNET

Occurring in ≥10% Patients	n (%)
Any	11 (69)
Fatigue	6 (38)
Diarrhea	4 (25)
Pruritus	3 (19)
Hypothyroidism	2 (13)
Myalgia	2 (13)
Rash	2 (13)

Grade 3	n (%)
Any	1 (6)
Fatigue	1 (6)

- No grade 4 or 5 events occurred

- Median follow-up duration: 20.7 months (range, 4.5–31.7)

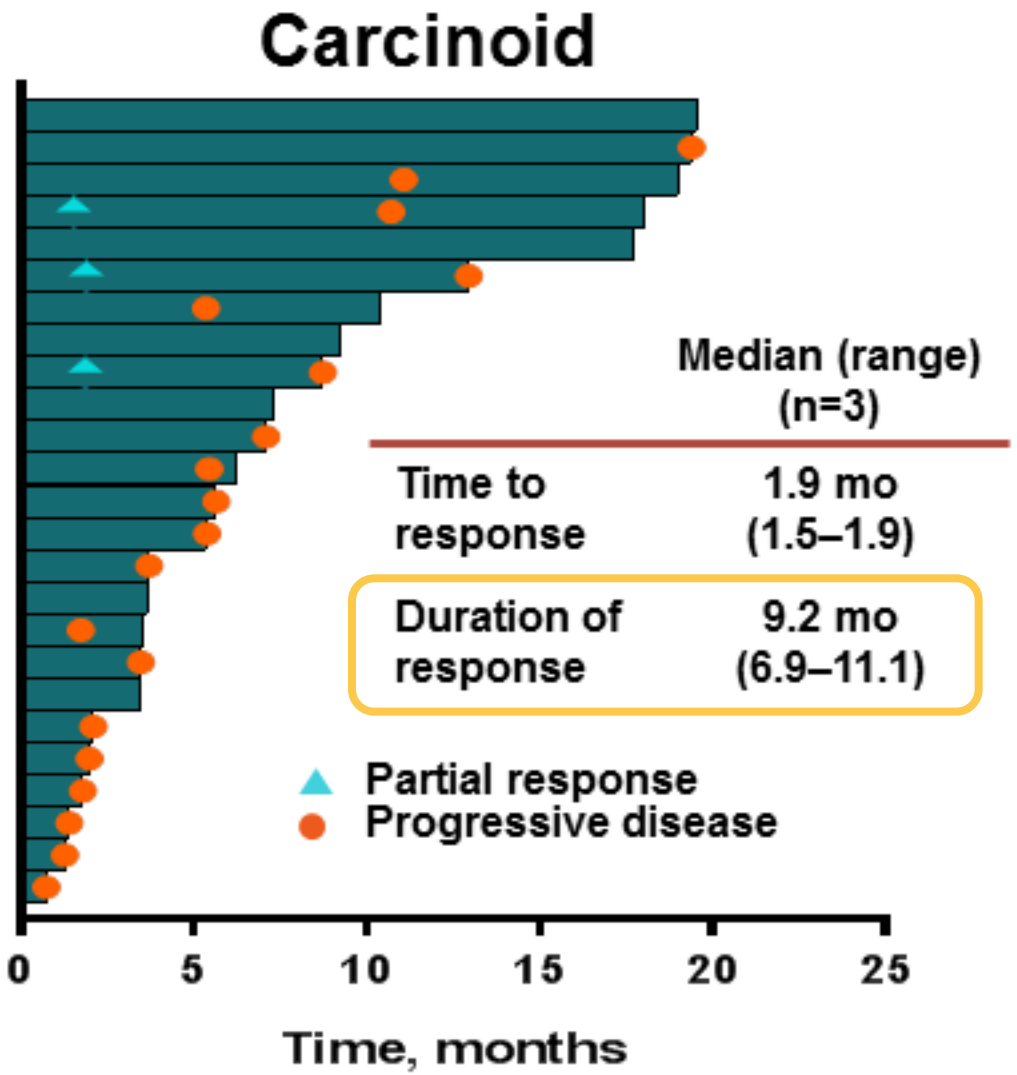
Data cutoff date: February 20, 2017.

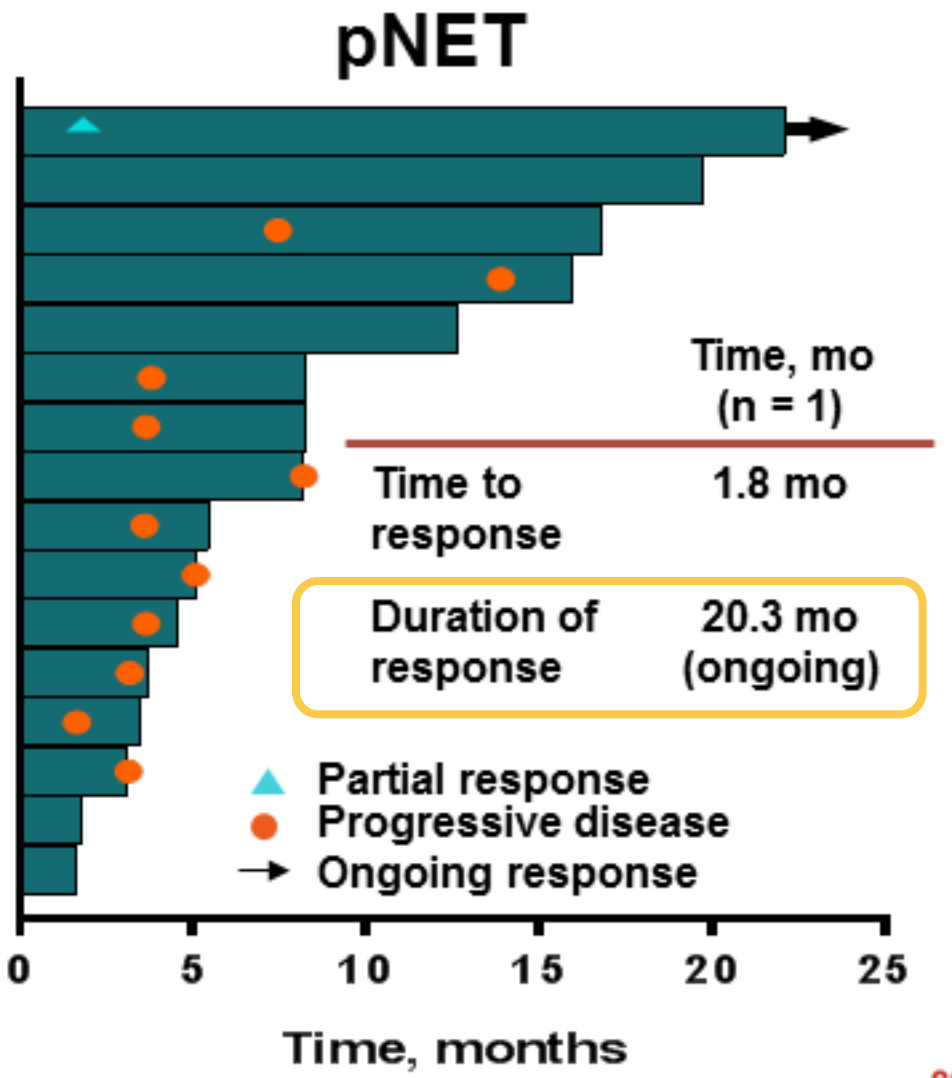
Antitumor Activity
(RECIST v1.1, Investigator Review[a])

	Carcinoid (N = 25)	pNET (N = 16)
Objective Response Rate, % (95% CI)	12% (3–31)	6% (0.2–30)
Best overall response, n (%)		
Complete response	0	0
Partial response	3 (12%)	1 (6%)
Stable disease	15 (60%)	14 (88%)
≥6 months	8 (32%)	5 (31%)
Progressive disease	7 (28%)	1 (6%)

[a]Only confirmed responses are included.
Data cutoff date: February 20, 2017.

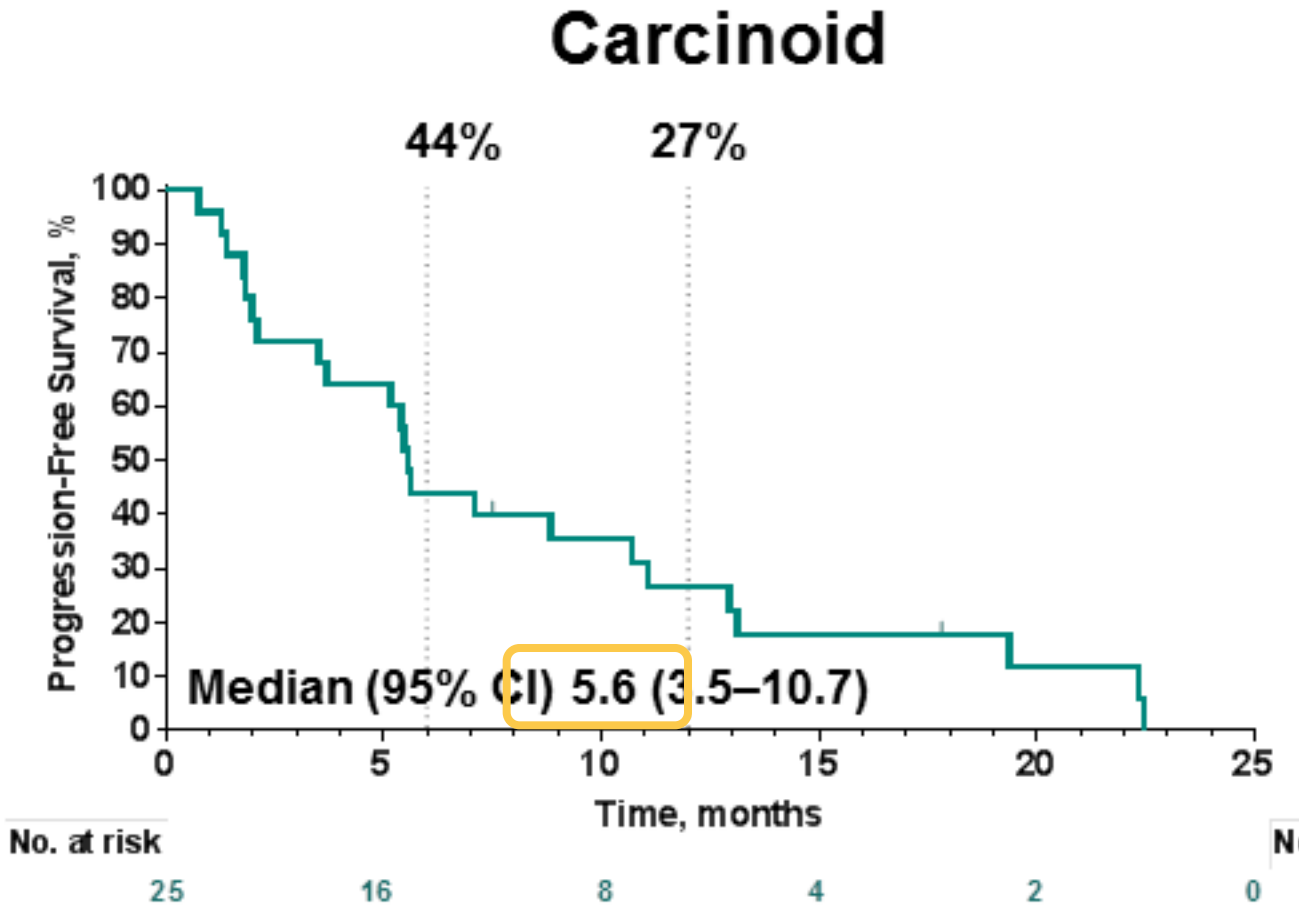
Treatment Exposure and Response Duration (RECIST v1.1, Investigator Review)

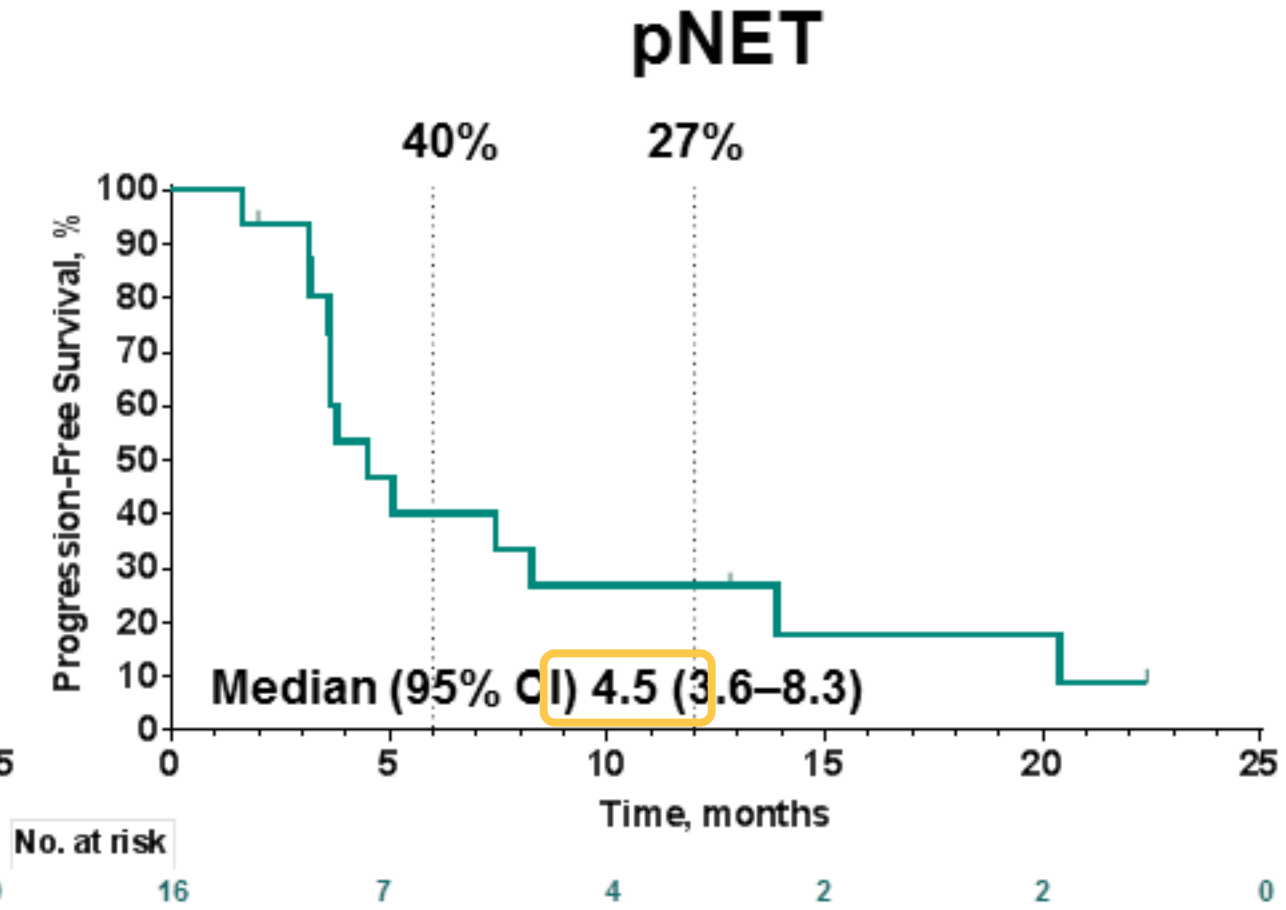




Bar length is equivalent to the time to the last imaging assessment.
Data cutoff date: February 20, 2017.

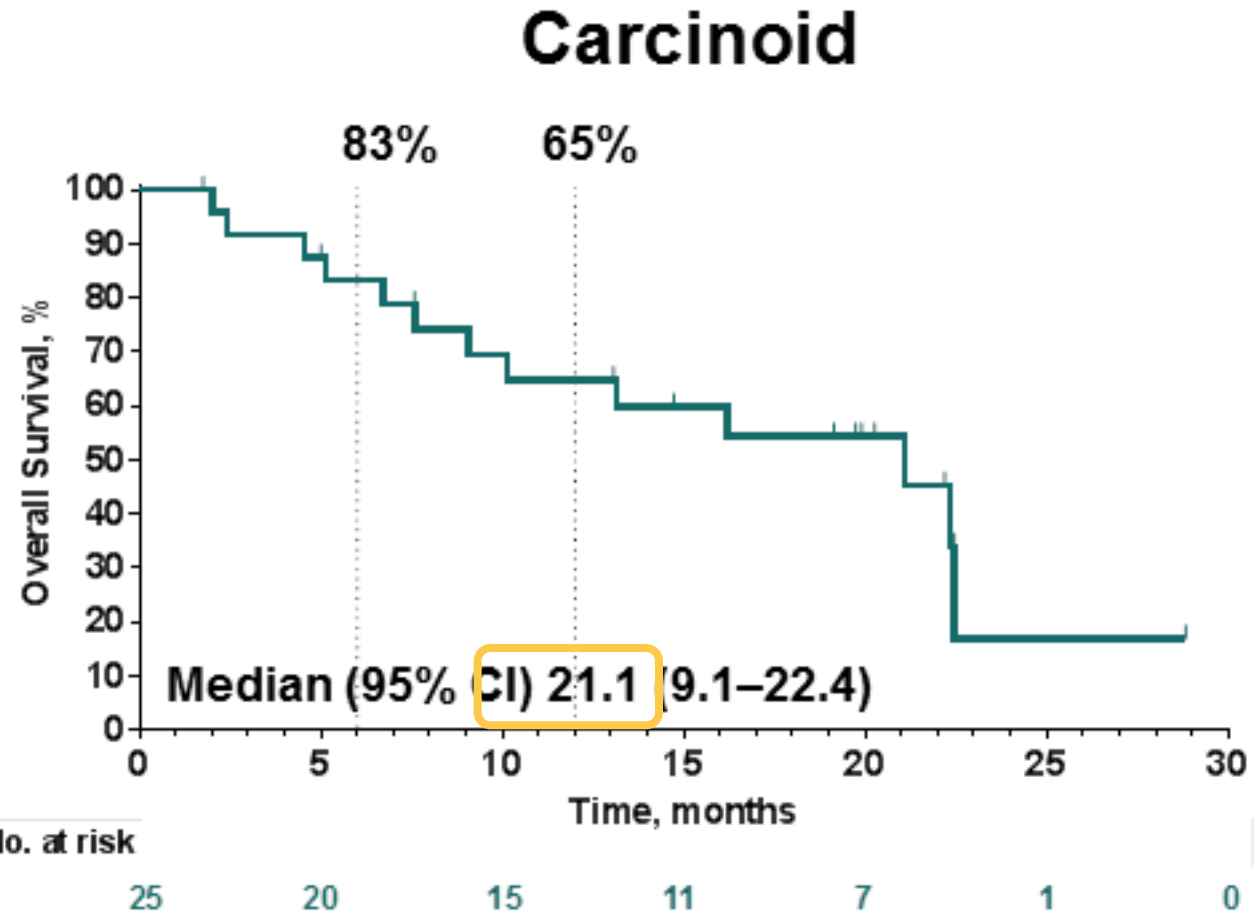
Progression-Free Survival
(RECIST v1.1, Investigator Review)

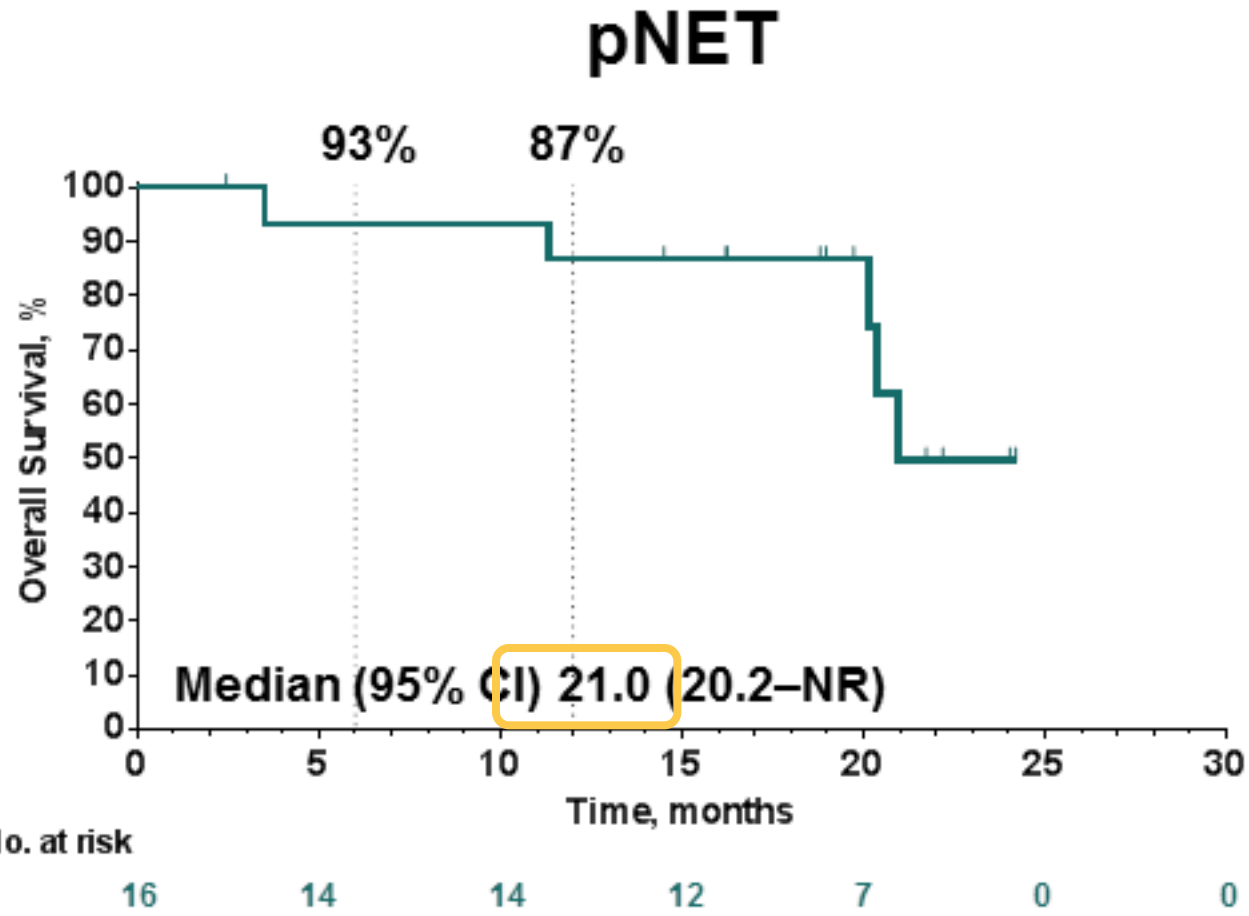




Data cutoff date: February 20, 2017.

Overall Survival





Data cutoff date: February 20, 2017.

Conclusions

- Pembrolizumab was generally well-tolerated in both study cohorts
  - Safety profile was consistent with previous experience for pembrolizumab monotherapy in other tumor types
- Pembrolizumab provided an ORR of 12% in patients with carcinoid tumors and 6% in patients with pNETs
  - Responses were durable, with all lasting ≥6 months
  - Median time to response was <2 months in both cohorts
- Given the heavily pretreated patient populations, the 12-month PFS and OS rates were encouraging
- Further evaluation of pembrolizumab in carcinoids and pNETs is warranted
  - KEYNOTE-158 is evaluating pembrolizumab in larger cohorts of patients with advanced solid tumors, including neuroendocrine tumors, with additional biomarker evaluation[1]

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02628067.

DUNE (DURVALUMAB + TREMELIMUMAB)

ESTUDIO CLÍNICO DE FASE II DE DURVALUMAB (MEDI4736) MÁS TREMELIMUMAB PARA EL TRATAMIENTO DE PACIENTES CON TUMORES NEUROENDOCRINOS AVANZADOS DE ORIGEN GASTROENTEROPANCREÁTICOS O PULMONARES

PROMOTOR: GETNE (Grupo Español de Tumores Neuroendocrinos)

COORDINADORES: Dr. Jaume Capdevila / Dr. Ignacio Matos
LABORATORIO (PARTNER): AstraZeneca

Periodo de reclutamiento estimado: 24 meses (Enero 2017 a Enero 2019)

- Informe final del estudio: Mayo 2020
- Periodo de seguimiento estimado: 3 años

DUNE (DURVALUMAB + TREMELIMUMAB)

RACIONAL <=> JUSTIFICACIÓN:
Alternativa para pacientes que han empeorado durante el tratamiento con ASS es el interferón alfa-2b. El mecanismo antitumoral **podría estar relacionado con la estimulación de las células T**

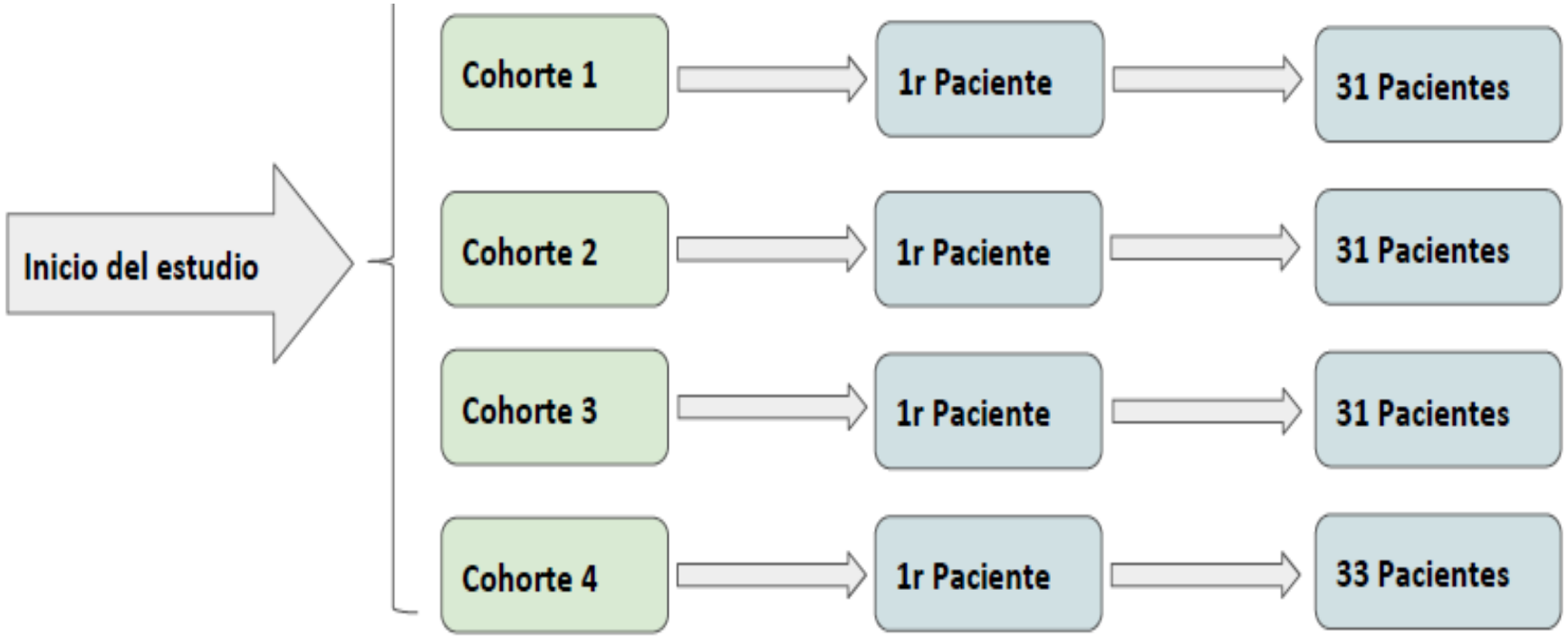
Estudio dirigido a **estimular los linfocitos T con Durvalumab** (Ac monoclonal anti-PDL-1, **y Tremelimumab** (Ac monoclonal anti CTLA-4)

4 Cohortes paralelas e independientes.
4 Ciclos de tratamiento con Durvalumab y Tremelimumab, cada ciclo de 28 días
Posteriormente monoterapia con Durvalumab hasta completar 13 ciclos (cada 28 días)

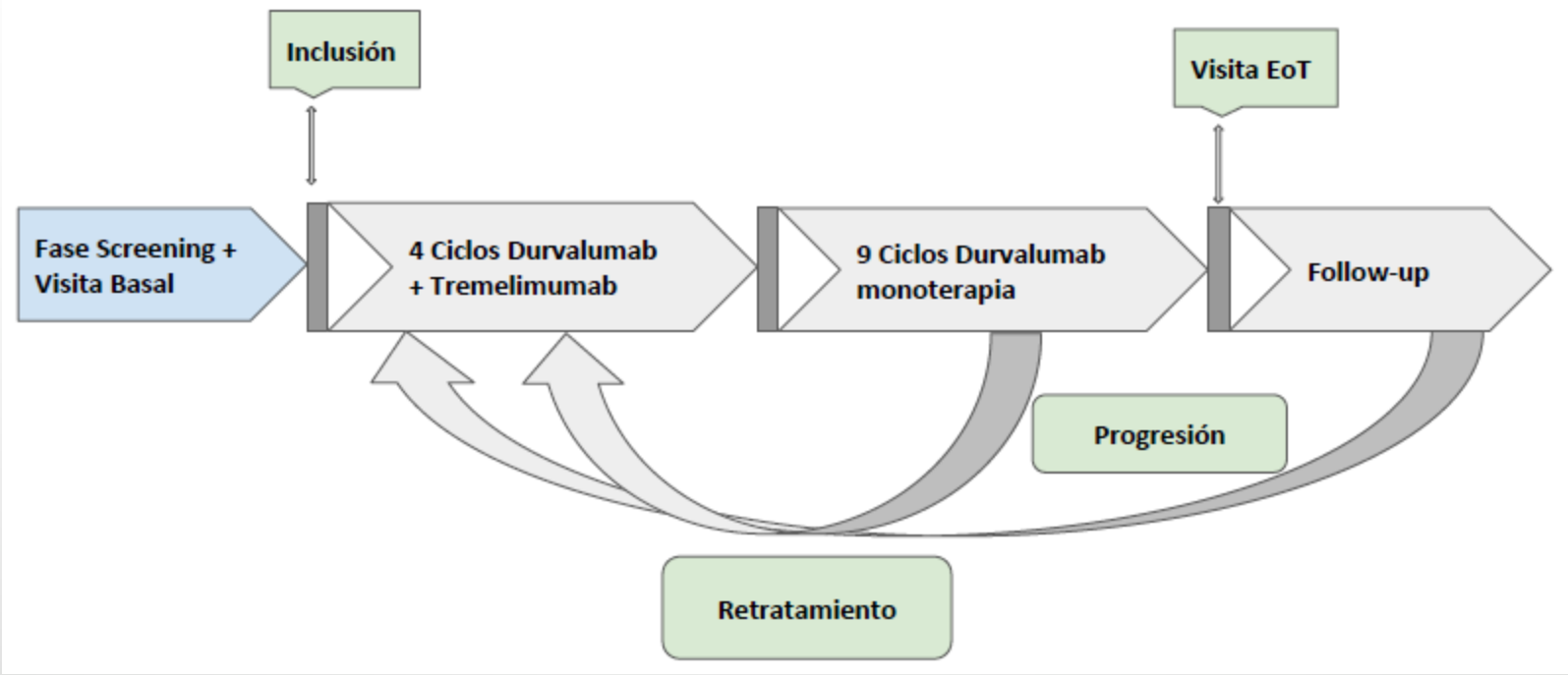
DUNE (DURVALUMAB + TREMELIMUMAB)

Cohortes:

- **Cohorte 1:** Tumores neuroendocrinos pulmonares bien-moderadamente diferenciados
- **Cohorte 2:** Tumores neuroendocrinos gastrointestinales G1/G2 (OMS grado 1 y 2)



DUNE (DURVALUMAB + TREMELIMUMAB)



DUNE (DURVALUMAB + TREMELIMUMAB)

El retratamiento está permitido (solo una vez). Se administrará la misma dosis, con la misma frecuencia y el mismo calendario de procedimientos. **Se permite el retratamiento en los siguientes casos una vez se presente PE confirmada o no**:

- Pacientes que hayan obtenido y mantenido **un control de la enfermedad (RC, RP y EE)**. Cuando estos pacientes finalicen los 12 meses de tratamiento.

- Pacientes que hayan **completado los 4 ciclos** de la combinación (con un beneficio clínico a juicio investigador-consultar con promotor).

No se permite a aquellos pacientes que hayan obtenido una progresión confirmada durante la terapia en combinación con durvalumab + tremelimumab (4 primeros ciclos).

DUNE (DURVALUMAB + TREMELIMUMAB)

OBJETIVO PRINCIPAL:

Variable principal para las cohortes 1, 2 y 3:

- **Tasa de beneficio clínico** (TBC) a **9 meses**, valorado por (**irRECIST**), que se define como el porcentaje de pacientes que alcanzaron **respuesta completa (RC), respuesta parcial (RP) o enfermedad estable (EE).**

Variable principal de la cohorte 4:

- **Tasa de supervivencia global a 9 meses**.

DUNE (DURVALUMAB + TREMELIMUMAB)

OBJETIVOS SECUNDARIOS:

- **Tasa de respuesta global** (TRG) por irRECIST
- Duración de la respuesta por irRECIST
- Mediana de **SLP** por irRECIST.
- Perfil de **seguridad**
- Mediana de **SG**
- Respuesta a 6 y 12 meses por irRECIST

OBJETIVOS EXPLORATORIOS

- **Respuesta bioquímica** (niveles de CGA y NSE) y su asociación TRO y SLP
- **Biomarcadores predictivos** de respuesta (tumor y sangre)
- **Biomarcadores** y su relación con la **eficacia y/o toxicidad**

DUNE (DURVALUMAB + TREMELIMUMAB)

Exclusion Criteria:

- WHO G3 neuroendocrine neoplasms of lung origin (oat cell/large cell)
- Prior treatment with anti-PDL-1/anti-PD-1 or anti-CTL-4 therapy
- Current or prior use of immunosuppressive medication within 28 days before the first dose.
- Active or prior documented autoimmune disease within the past 2 years
- History of allogeneic organ transplant.
- Subjects having a diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 28 days prior to the first dose of trial treatment.
- Knowledge of active central nervous system (CNS) metastases and/or carcinomatous meningitis.
- Receipt of live attenuated vaccination within 30 days prior to study entry

DUNE (DURVALUMAB + TREMELIMUMAB)

Evaluación del tumor cada 12 semanas mediante criterios RECIST 1.1 e irRECIST hasta progresión

MUESTRAS PARA EL ANÁLISIS FARMACOGENÓMICO

MUESTRAS PARA EL ANÁLISIS DE BIOMARCADORES DE PROTEÍNAS

OBJETIVOS EXPLORATORIOS

- **Respuesta bioquímica** (niveles de CGA y NSE) y su asociación TRO y SLP
- **Biomarcadores predictivos** de respuesta (tumor y sangre)
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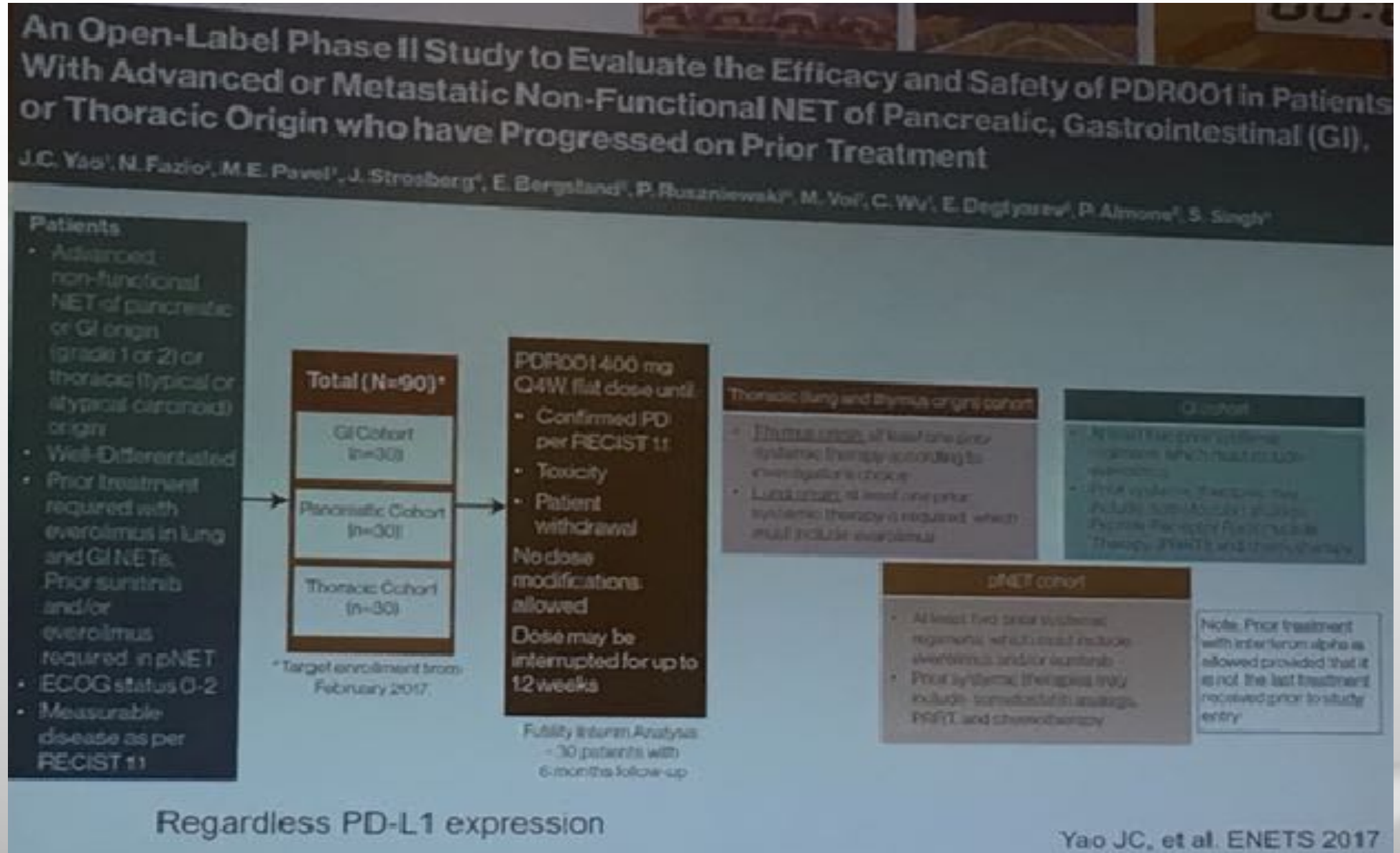
MK 3475-158 (PEMBROLIZUMAB) / PDR001

PDR001


An Open-Label Phase II Study to Evaluate the Efficacy and Safety of PDR001 in Patients With Advanced or Metastatic Non-Functional NET of Pancreatic, Gastrointestinal (GI), or Thoracic Origin who have Progressed on Prior Treatment
J.C. Yao, N. Fazio, M.E. Pavel, J. Strosberg, E. Bergstand, P. Ruszniewski, M. Voi, C. Wu, E. Degtyarev, P. Almone, S. Singh
Patients
Advanced non-functional NET of pancreatic or GI origin (grade 1 or 2) or thoracic (typical or atypical carcinoid) origin
Well-Differentiated
Prior treatment required with everolimus in lung and GI NETs. Prior sunitinib and/or everolimus required in pNET
ECOG status 0-2
Measurable disease as per RECIST 1.1
Total (N=90)*
GI Cohort (n=30)
Pancreatic Cohort (n=30)
Thoracic Cohort (n=30)
* Target enrollment from February 2017
PDR001 400 mg Q4W flat dose until
Confirmed PD per RECIST 1.1
Toxicity
Patient withdrawal
No dose modifications allowed
Dose may be interrupted for up to 12 weeks
Futility Interim Analysis - 30 patients with 6-months follow-up
Thoracic lung and thymus origin cohort
Thymus origin: at least one prior systemic therapy according to investigator's choice
Lung origin: at least one prior systemic therapy is required, which must include everolimus
GI cohort
pNET cohort
At least two prior systemic regimens, which must include everolimus and/or sunitinib
Prior systemic therapies may include somatostatin analogs, PRRT, and chemotherapy
Note: Prior treatment with interferon alpha is allowed provided that it is not the last treatment received prior to study entry
Regardless PD-L1 expression
Yao JC, et al. ENETS 2017

PDR001→ NCT02955069 STUDY→ elevatION NET 201

- www.clinicaltrials.gov/ct2/show/NCT02955069?term=NCT02955069&rank=1
- 1. Yao JC et al. ElevatION NET 201:Ph II Study of PDR001 in Metastatic, Well Differentiated NET of Pancreatic/ GI/Thoracic Origin or Poorly Differentiated GEP NEC

Journal of Thoracic Oncology Vol 12S1556-0864(17)30808-0

- 2. Yao JC et al. ElevatION NET-201: An Open-Label Phase II Study to Evaluate the Efficacy and Safety of PDR001 in Patients With Advanced or Metastatic, Well-Differentiated, Non-Functional NET of Pancreatic, Gastrointestinal (GI), or Thoracic Origin or Poorly-Differentiated Gastroenteropancreatic Neuroendocrine Carcinoma (GEP-NEC) Who Have Progressed on Prior Treatment.

Poster NANETS 2017 (242)

PDR001 → NCT02955069 STUDY → elevatION NET 201

levatION NET-201: An Open-Label Phase II Study to Evaluate the Efficacy and Safety of PDR001 in Patients With Advanced or Metastatic, Well-Differentiated, Non-Functio astrointestinal (GI), or Thoracic Origin or Poorly-Differentiated Gastroenteropancreatic Neuroendocrine Carcinoma (GEP-NEC) Who Have Progressed on Prior Treatment

C. Yao[1], N. Fazio[2], M.E. Pavel[3], J. Strosberg[4], E. Bergsland[5], P. Ruszniewski[6], M. Voi[7], C. Wu[7], E. Degtyarev[8], P. Aimone[8], S. Singh[9]

iversity of Texas/MD Anderson Cancer Center, Houston, Texas, USA; [2]European Institute of Oncology, Milan, Italy; [3]Dept. of Medicine 1, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany; [4]Department of Medicine, Moffitt Cancer Center, Tampa, Florida, USA; [5]UCSF Helen Diller Family Comprehensive Can astroenterology and Pancreatology Department, Beaujon Hospital, Clichy, France; [7]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [8]Novartis Pharma AG, Basel, Switzerland; [9]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

troduction

Monoclonal antibody (mAb) inhibitors of immune-checkpoints, including anti-programmed cell death protein-1 (PD-1) and its ligands PD-L1/2, have become established treatment options in various solid tumors.[1]

Although many advances with checkpoint inhibitors have been made in other tumor types, the data generated in neuroendocrine tumors (NETs) are limited.

PD-1 is a receptor, expressed on activated T cells and other lymphocytes, which negatively regulates T-cell function.[2]

- Binding of PD-1 by PD-L1 or PD-L2 results in the inhibition of T-cell function, and the protection of tumor cells from attack by cytotoxic T cells[3]
- Tumors can evade the immune system by upregulating expression of PD-L1[4]

PD-L1 overexpression has been associated with poorer prognosis in some tumor types.[5,6]

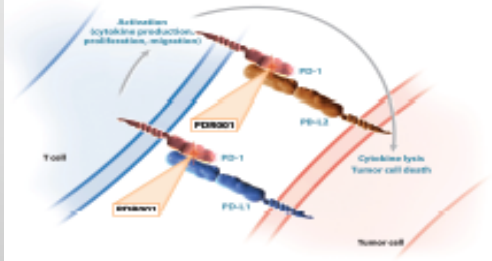
In GEP-NET tumors PD-L1 expression was found to be significantly associated with high grade tumors (Grade 3)[7]

In preclinical models, PD-1 blockade has been shown to restore effector T-cell function, leading to T-cell proliferation, interferon-γ secretion, and increased cytolytic function.[8,9]

PDR001 is a high-affinity, humanized IgG4 antibody directed against PD-1 that blocks the binding of PD-L1 and PD-L2 to PD-1[10,11] (Figure 1).

In a phase I trial of PDR001 (mAb checkpoint inhibitor targeting PD-1) conducted in patients with multiple solid tumor types, a patient with histologically confirmed metastatic atypical pulmonary carcinoid demonstrated a partial response with (according to RECIST v1.1) resolution of liver and pleural metastases.[10]

gure 1. Mechanism of Action of PDR001



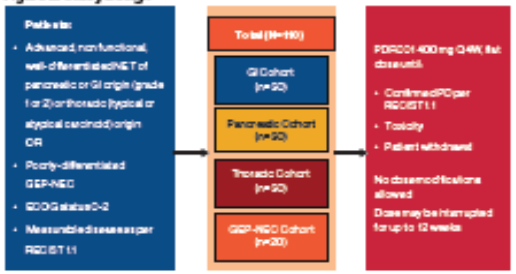
ethods

udy Design

This is a phase II (NCT02955069), single-arm, open-label, multicenter study in patients with advanced or metastatic, well-differentiated, non-functional, NET of pancreatic, gastrointestinal (GI) or thoracic origin or poorly-differentiated gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC) who have progressed on or after their last treatment (Figure 2).

Patients will receive PDR001 (400 mg, once every 4 weeks) administered via intravenous (IV) infusion over 30 minutes until disease progression, unacceptable toxicity, or patient withdrawal.

Figure 2. Study Design



ECOG, eastern cooperative oncology group; GEP-NEC, gastroenteropancreatic neuroendocrine carcinoma; GI, gastrointestinal; NET, neuroendocrine tumor; PD, progressive disease; PDR, programmed cell death receptor; Q4W, every 4 weeks; RECIST, response evaluation criteria in solid tumors.

Study Endpoints

Primary endpoint

- Overall Response Rate (ORR) per RECIST 1.1 and Blinded Independent Review Committee (BIRC)

Key secondary endpoint

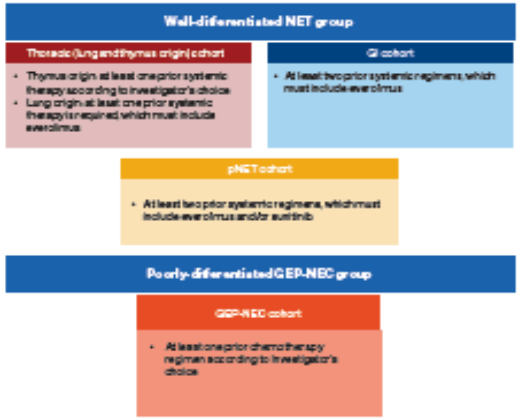
- Duration of Response (DOR) per RECIST 1.1 and BIRC

Additional secondary endpoints

- Disease Control Rate (DCR) per RECIST 1.1 and BIRC
- Time to Response (TTR) per RECIST 1.1 and BIRC
- Progression-free Survival (PFS) per RECIST 1.1 and BIRC
- 1-year and 2-year overall survival rates
- Efficacy endpoints based on immune response criteria per immune-related RECIST and BIRC (irORR, irDCR, irDOR, irTTR, irPFS)
- Changes from baseline in chromogranin A and neuron-specific enolase
- Pharmacokinetic (PK) parameters
- Global health status/Quality of Life (QoL) score of the EORTC QLQ-C30 and the index score of the EQ-5D-5L
- Anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment
- Frequency and severity of adverse events (AEs)

Key Inclusion Criteria

- Pathologically confirmed, advanced (unresectable or metastatic):
  - Well-differentiated (Grade 1 or Grade 2) based on local pathology report, non-functional NET of GI or pancreatic origin or thoracic (including lung and thymus) origin (typical or atypical carcinoid)
  - Poorly-differentiated GEP-NEC based on local pathology report
- No active symptoms related to carcinoid syndrome during the last 3 months prior to start of study treatment.
- Patients must have received prior treatment for advanced disease.
- Tumor biopsy material must be provided for all patients for the purpose of biomarkers analysis.
  - Well-differentiated NET: Biopsy material must be provided following the diagnosis of metastatic disease. The tumor sample must be collected from a metastatic site not previously irradiated and should preferably be taken within 6 months but not more than 24 months prior to start of study treatment.
  - Poorly-differentiated GEP-NEC: Biopsy material must be collected from the primary tumor or from a metastatic site not previously irradiated, taken not more than 24 months prior to start of study treatment.

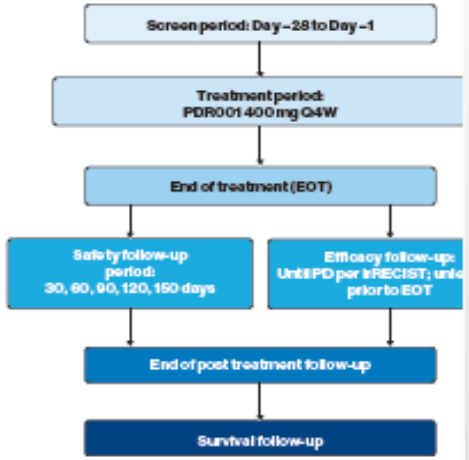


- Radiological documentation of disease progression:
  - Well-differentiated NET: disease progression while on/or after the last treatment; progression must have been observed within 6 months prior to start of study treatment (i.e. maximum of 24 weeks from documentation of progression until study entry). Disease must show evidence of progression based on scans performed not more than one year apart.
  - Poorly-differentiated GEP-NEC: disease progression while on/or after prior treatment
- At least one measurable lesion assessed by CT and/or MRI according to RECIST 1.1.

Key Exclusion Criteria

- Well-differentiated, Grade-3 neuroendocrine tumors; poorly-differentiated neuroendocrine carcinomas of any origin (other than GEP-NEC) (including NEC of unknown origin, adenocarcinoid, and goblet cell carcinoid)
- Pretreatment with interferon-α as last treatment prior to start of study treatment
- Prior treatment for study indication with:
  - Antibodies or immunotherapy within 6 weeks before the first dose of study treatment
  - PRRT administered within 6 months of the first dose
  - Systemic antineoplastic therapy (including cytotoxic chemotherapy, radiotoxin immune-conjugates) or any experimental therapy within 14 days or 5 half-lives
  - Tyrosine kinase inhibitors within 14 days or 5 half-lives, before the first dose of study treatment
  - Prior PD-1- or PD-L1-directed therapy
  - Cryoablation, radiofrequency ablation, or transarterial embolization of hepatic metastases within 2 months before the first dose of study treatment
- History of severe hypersensitivity reactions to other mAb which in the opinion of the investigator may pose an increased risk of a serious infusion reaction
- Known history or current interstitial lung disease or non-infectious pneumonitis
- Use of somatostatin analogs or any other medications administered to control active symptoms related to carcinoid syndrome during the last 3 months prior to start of study treatment

Study Flow



Statistical Analysis

The primary efficacy variable of the study is ORR, defined as the proportion of patients w best overall response (BOR) of complete response (CR) or partial response (PR), as per independent central review. ORR will be evaluated according to RECIST 1.1. ORR will be c separately within well-differentiated NET and poorly-differentiated GEP-NEC groups. N hypothesis testing will be conducted.

The response rate within each group with 95% two-sided confidence interval (exact met be computed.

Study Enrollment

PDR001 → NCT02955069 STUDY → elevatION NET 201

Patients:

- Advanced, non functional, well-differentiated NET of pancreatic or GI origin (grade 1 or 2) or thoracic (typical or atypical carcinoid) origin

OR

- Poorly-differentiated GEP-NEC
- ECOG status 0-2
- Measurable disease as per RECIST 1.1

→

Total (N=110)

- GI Cohort (n=30)
- Pancreatic Cohort (n=30)
- Thoracic Cohort (n=30)
- GEP-NEC Cohort (n=20)

→

PDR001 400 mg Q4W, flat dose until:

- Confirmed PD per RECIST 1.1
- Toxicity
- Patient withdrawal

No dose modifications allowed

Dose may be interrupted for up to 12 weeks

PDR001: mAb checkpoint inhibitor targeting PD-1

PDR001→elevatION NET 201

Study Endpoints

Primary endpoint

- Overall Response Rate (ORR) per RECIST 1.1 and Blinded Independent Review Committee (BIRC)

Key secondary endpoint

- Duration of Response (DOR) per RECIST 1.1 and BIRC

Additional secondary endpoints

- Disease Control Rate (DCR) per RECIST 1.1 and BIRC
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- Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment
- Frequency and severity of adverse events (AEs)

PDR001 → elevatION NET 201

Well-differentiated NET group

Thoracic (lung and thymus origin) cohort

- Thymus origin: at least one prior systemic therapy according to investigator's choice
- Lung origin: at least one prior systemic therapy is required, which must include everolimus

GI cohort

- At least two prior systemic regimens, which must include everolimus

pNET cohort

- At least two prior systemic regimens, which must include everolimus and/or sunitinib.

Poorly-differentiated GEP-NEC group

GEP-NEC cohort

- At least one prior chemotherapy regimen according to Investigator's choice

PDR001 → elevatION NET 201

Statistical Analysis

The primary efficacy variable of the study is ORR, defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR), as per blinded independent central review. ORR will be evaluated according to RECIST 1.1. ORR will be calculated separately within well-differentiated NET and poorly-differentiated GEP-NEC groups. No formal hypothesis testing will be conducted.

The response rate within each group with 95% two-sided confidence interval (exact method) will be computed.

Study Enrollment

CARCINOMA DE MERKEL

- Enfermedad **RARA**: 0,2-0,8 casos/100,000 habitantes
- Enfermedad **AGRESIVA**: 33% mortalidad (melanoma x3)
- Descripción relativamente reciente→ TRABECULAR CARCINOMA OF THE SKIN (arch dermatol 1972)
- **NO fases III**: aceptado clásicamente su tratamiento con platino
- Se prevée **AUMENTO DE INCIDENCIA**: envejecimiento poblacional (>65 años), mayor exposición solar, mayor supervivencia de inmunodeprimidos y mayor conocimiento de la propia enfermedad

CARCINOMA DE MERKEL

- **CIRUGÍA** PRIMARIO **+/-RDT** único tratamiento curativo (margen 1-2cm)
- GANGLIO CENTINELA en ganglios clínica y radiológicamente negativos
- **LINFADENECTOMÍA** en ganglios positivos clínicos o tras bsgc positiva

- **RADIOTERAPIA** ADYUVANTE: en estadio I/II, aumenta supervivencia
- **QT** ADYUVANTE: **NO** hay indicación estandar

CARCINOMA DE MERKEL

ESTADIO IV:

– 1ªL REGÍMENES BASADOS EN PLATINO/ETOPÓSIDO, alquilantes, taxanos…

(NO estudios aleatorizados)

– 2°L = ??

RACIONAL PARA INMUNOTERAPIA:

–mayor frecuencia en inmunodeprimidos

–casos de regression espontánea

–infiltración linfocitaria = mejor pronóstico

Schadendorf 2017 EJC

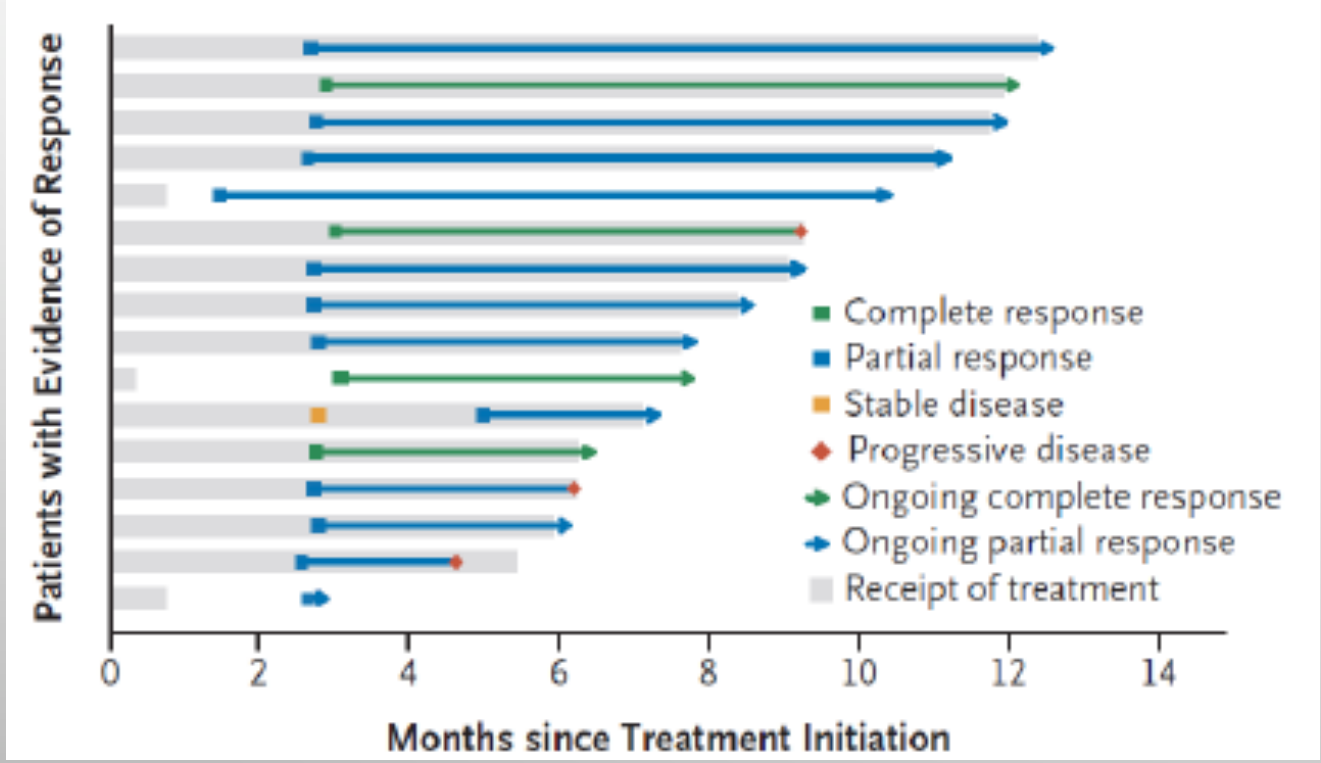
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma

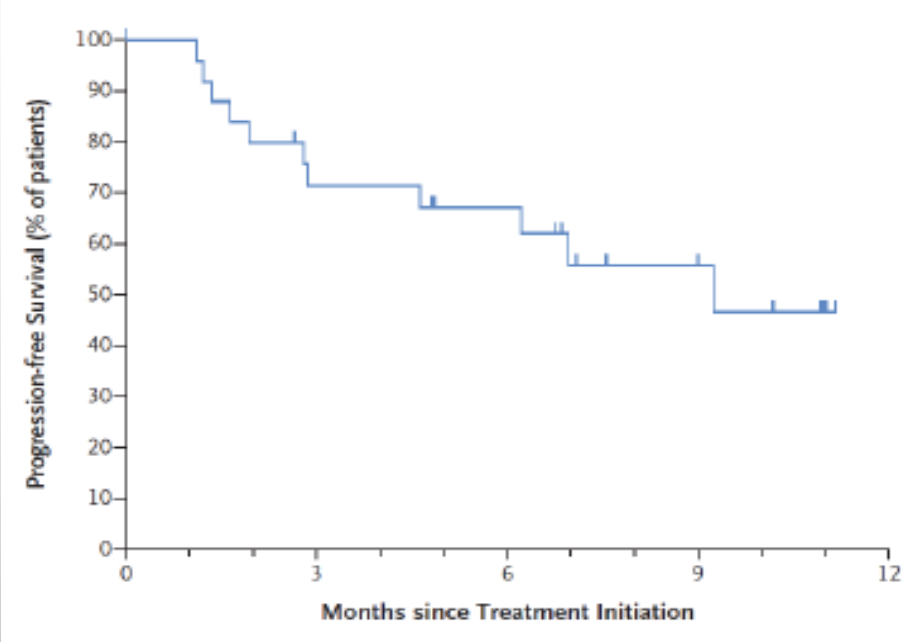
Paul T. Nghiem, M.D., Ph.D., Shailender Bhatia, M.D., Evan J. Lipson, M.D., Rapini R. Kudchadkar, M.D., Natalie J. Miller, B.A.,

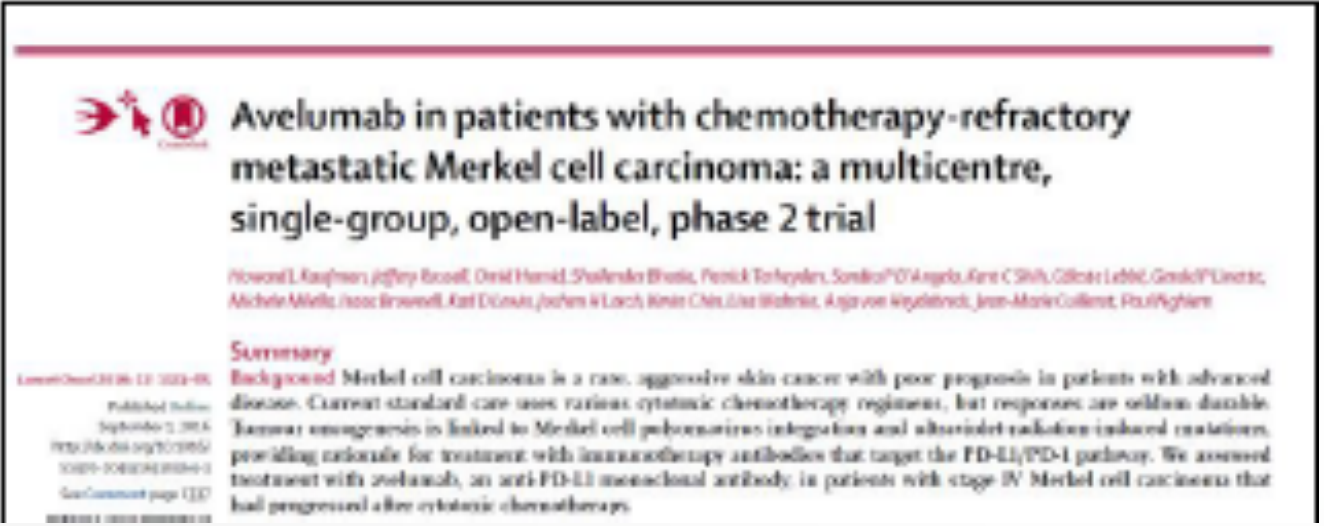
NGHIEM 2016 NEJM



Fase II: 26 pac con CM recurrente o enfermedad metastásica **sin tto sistémico previo** (1°Linea)
(92% estadio IV, 68 años de media)

9 meses PFS
67% libres de progresión a los 6m





Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial

Summary

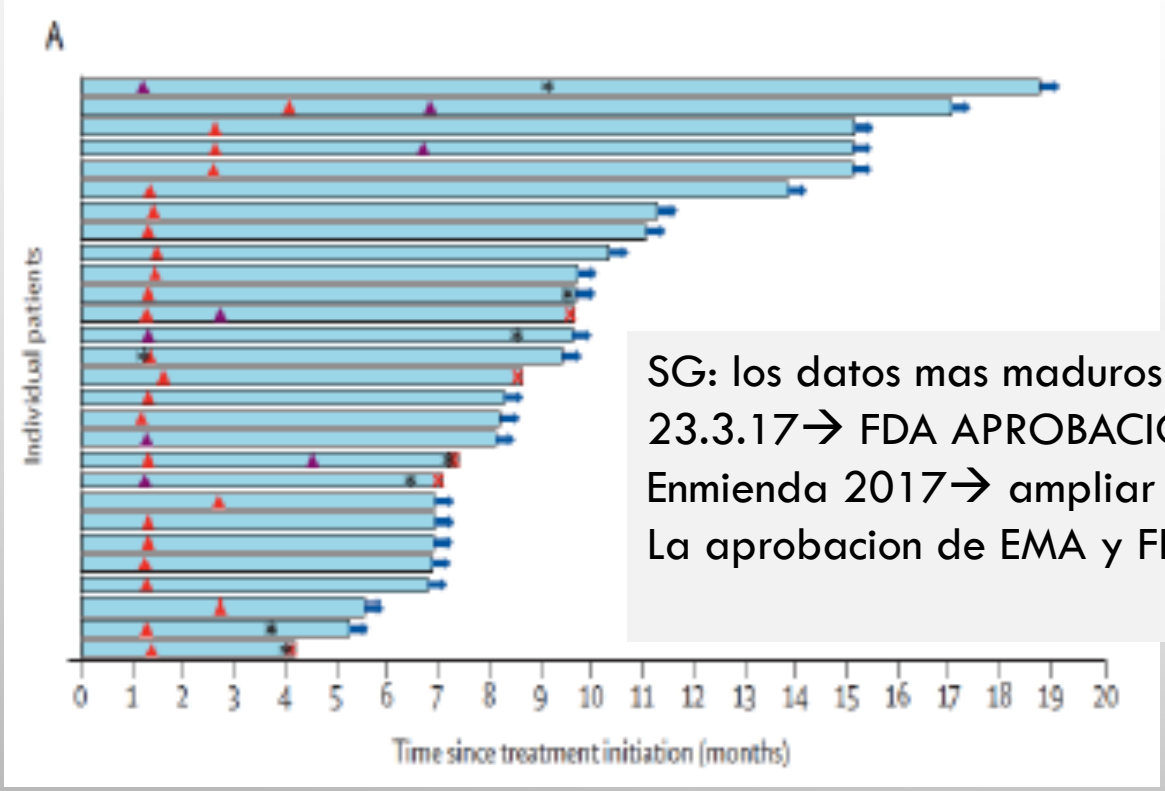
Background Merkel cell carcinoma is a rare, aggressive skin cancer with poor prognosis in patients with advanced disease. Current standard care uses various cytotoxic chemotherapy regimens, but responses are seldom durable. Tumour oncogenesis is linked to Merkel cell polyomavirus integration and ultraviolet radiation-induced mutations, providing rationale for treatment with immunotherapy antibodies that target the PD-L1/PD-1 pathway. We assessed treatment with avelumab, an anti-PD-L1 monoclonal antibody, in patients with stage IV Merkel cell carcinoma that had progressed after cytotoxic chemotherapy.

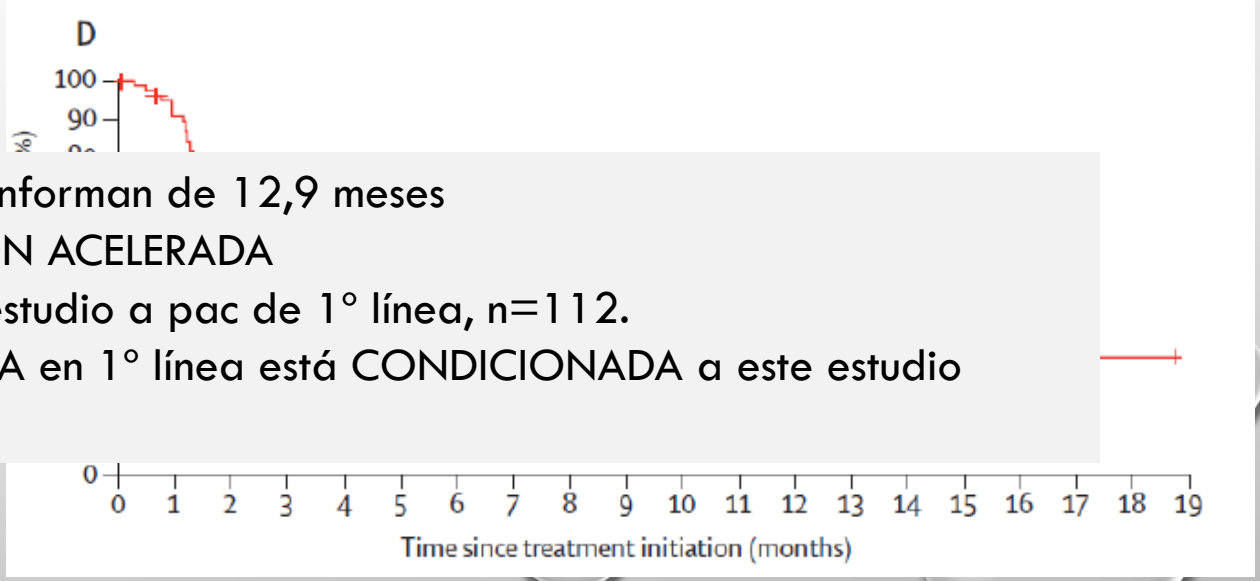
Kaufman 2016 Lancet Oncol

Fase II (JAVELIN) no aleatorizado
n88 pac con CM IV refractario
al menos a una dosis de QT
•O1°: tasa de respuestas

(75% >65 años; 41% > 1L)

2,7 meses PFS
40% libres de progresión a los 6 meses
52% vivos a 1 año





SG: los datos mas maduros informan de 12,9 meses
23.3.17→ FDA APROBACION ACELERADA
Enmienda 2017→ ampliar estudio a pac de 1° línea, n=112.
La aprobacion de EMA y FDA en 1° línea está CONDICIONADA a este estudio

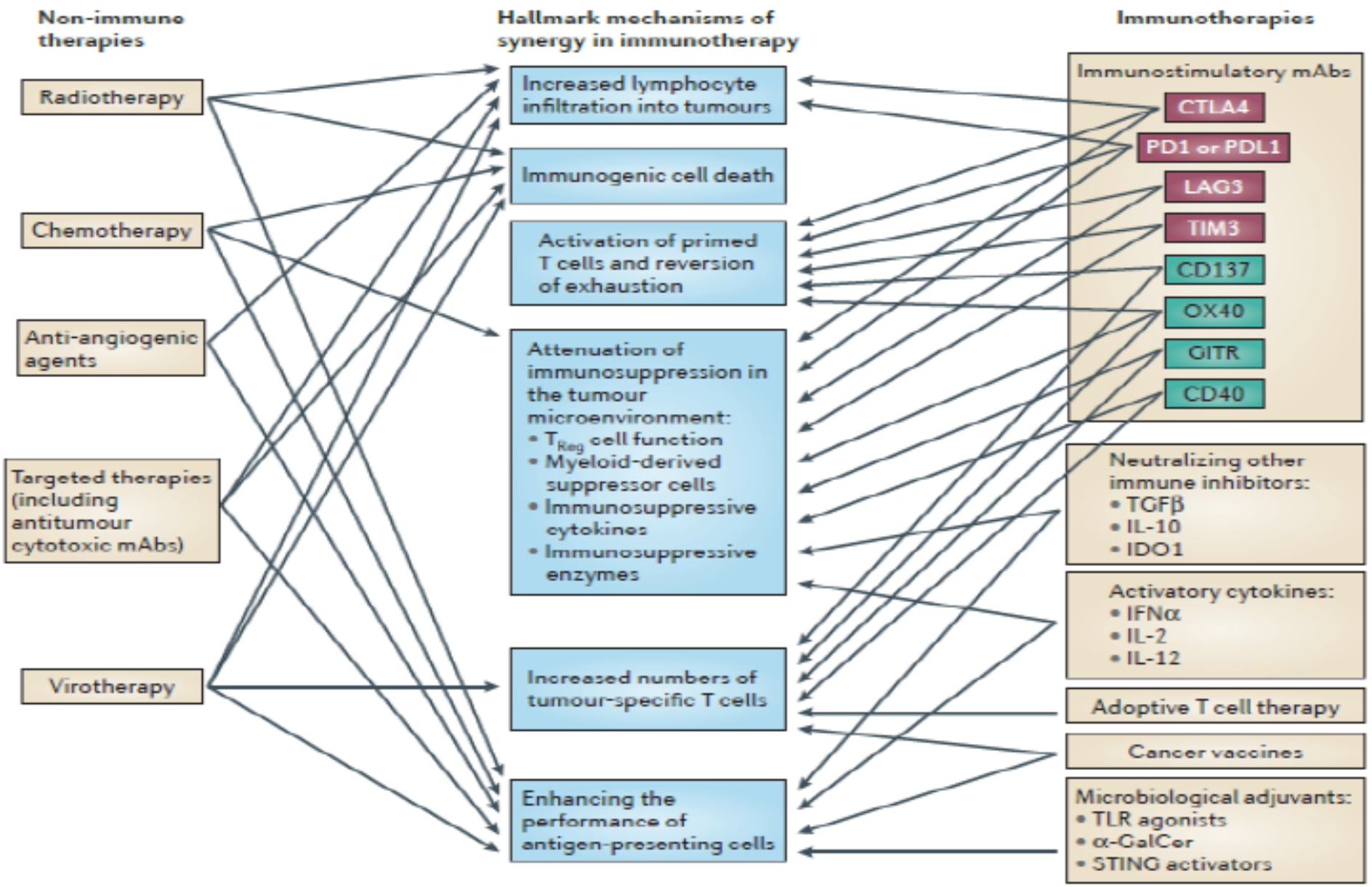
CARCINOMA DE MERKEL

Nombre	Fármaco en evaluación	Fármaco 2	Fármaco 3
	Avelumab[5,6]	Pembrolizumab[8]	Nivolumab [9]
Presentación	IV	IV	IV
Posología	CADA DOS SEMANAS	CADA 3 SEMANAS	Cada 2 semanas
Características diferenciales positivas	BAJA TASA DE TOXICIDAD Cuenta con aprobación regulatoria para este uso N=88 en pretratados, 29 de momento en no pre-tratados	BAJA TASA DE TOXICIDAD Menos frecuencia de tratamientos, al ser tres semanas	BAJA TASA DE TOXICIDAD
Características diferenciales negativas	No existencia de marcador Reacciones infusionales que implican premedicación	No existencia de marcador No aprobado para este uso	No existencia de marcador No aprobado para este uso
TASA DE RESPUESTAS (%) PRIMERA LÍNEA	62.5%	56%	73%
TASA DE RESPUESTAS (%) SEGUNDA LÍNEA	33%		

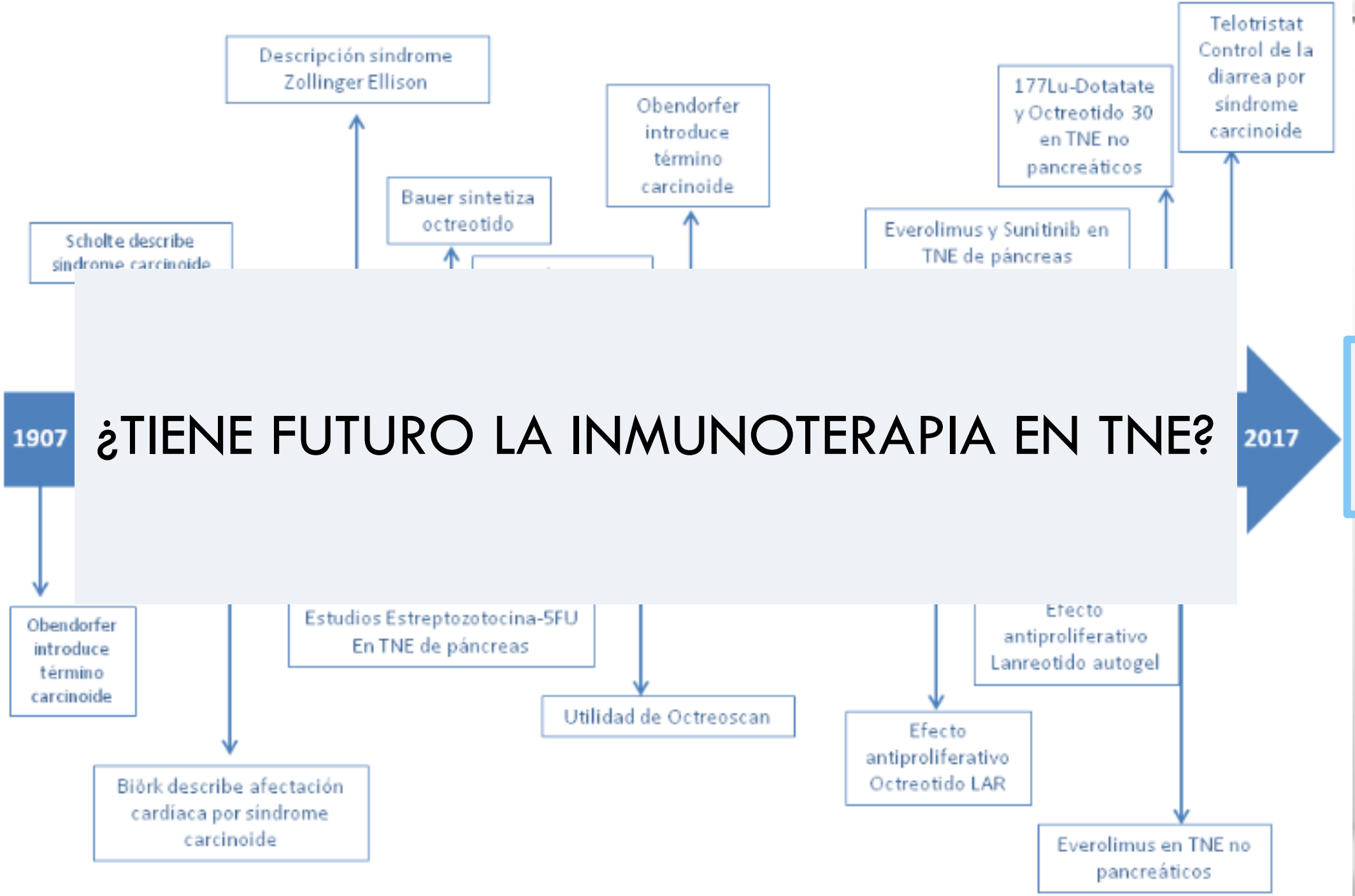
Topalian SL et al. En: AACR 2017. Non-comparative, Open-label, Multiple Cohort, Phase 1/2 Study to Evaluate Nivolumab in Patients With Virus-associated Tumors (CheckMate 358)

CONCLUSIONES:

Melero Nature Rev Cancer 2015



¿TIENE FUTURO LA INMUNOTERAPIA EN TNE?



SEOM:

AVANCES EN TNE, 7.12.17

CONCLUSIONES:

- APERTURA DE NUEVO HORIZONTE ESPERANZADOR
- MUCHOS INDICIOS, POCAS CONCLUSIONES
- POCA APLICABILIDAD REAL (“GENERAL-GLOBAL”) EN LA ACTUALIDAD
- TRABAJO MULTIDISCIPLINAR Y CENTROS DE REFERENCIA

¡ MUCHAS GRACIAS !