New opportunities of molecular targeted therapies and combined role with immunotherapy

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Molecular targeted therapy in NEN

Main areas

- mTOR pathway
- TKIs
- Specific settings

RTK

PIK3R1 (p85) activating mutation

PIK3CA (p110α) mutation

PI3K

Loss of PTEN

PTEN

TSC-2

NF1

TSC-1

Akt

Everolimus

mTORC1

mTORC2

4E-BP1

p70S6K

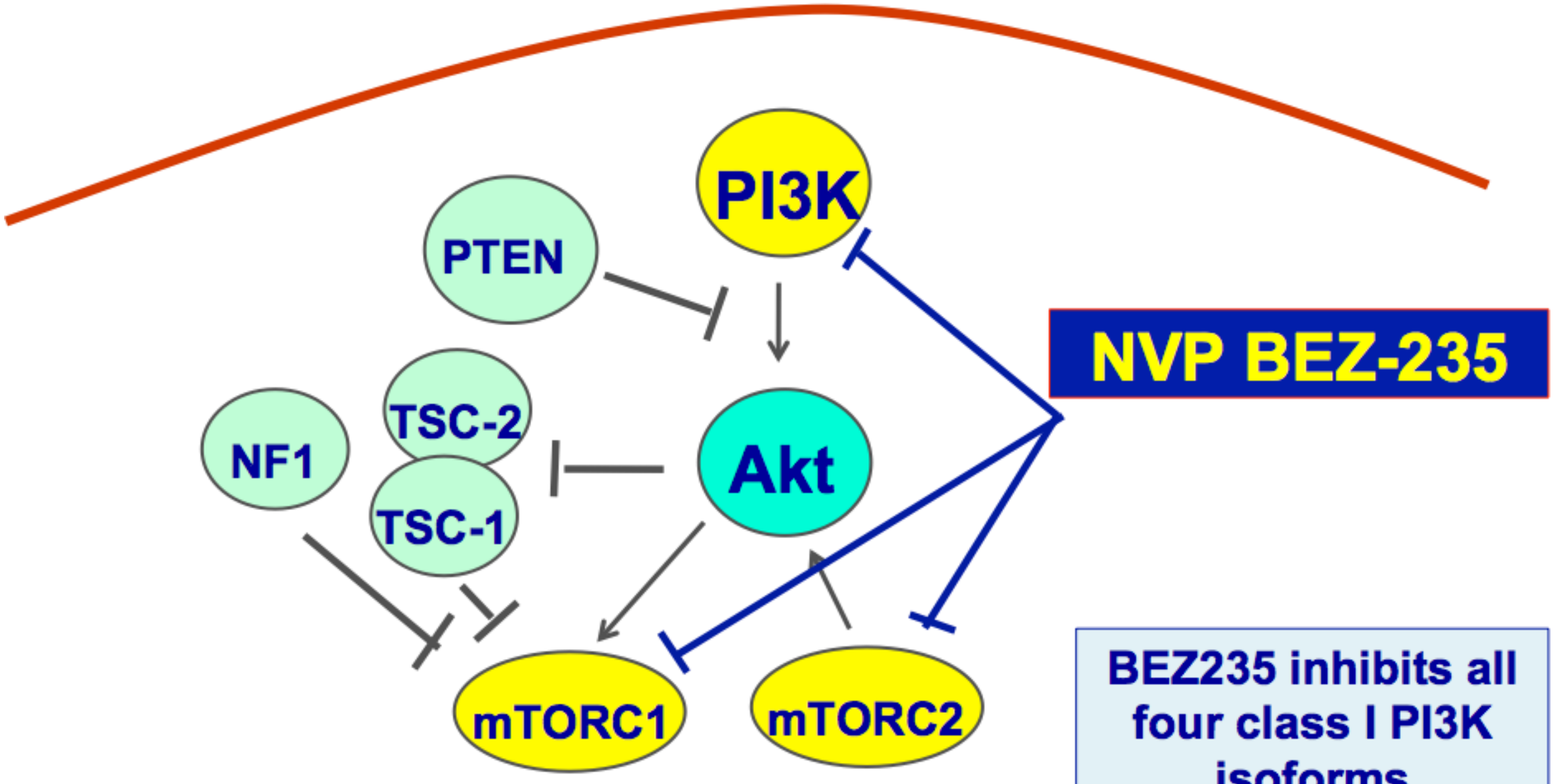
BLOCK OF APOPTOSIS

PROLIFERATION

GROWTH

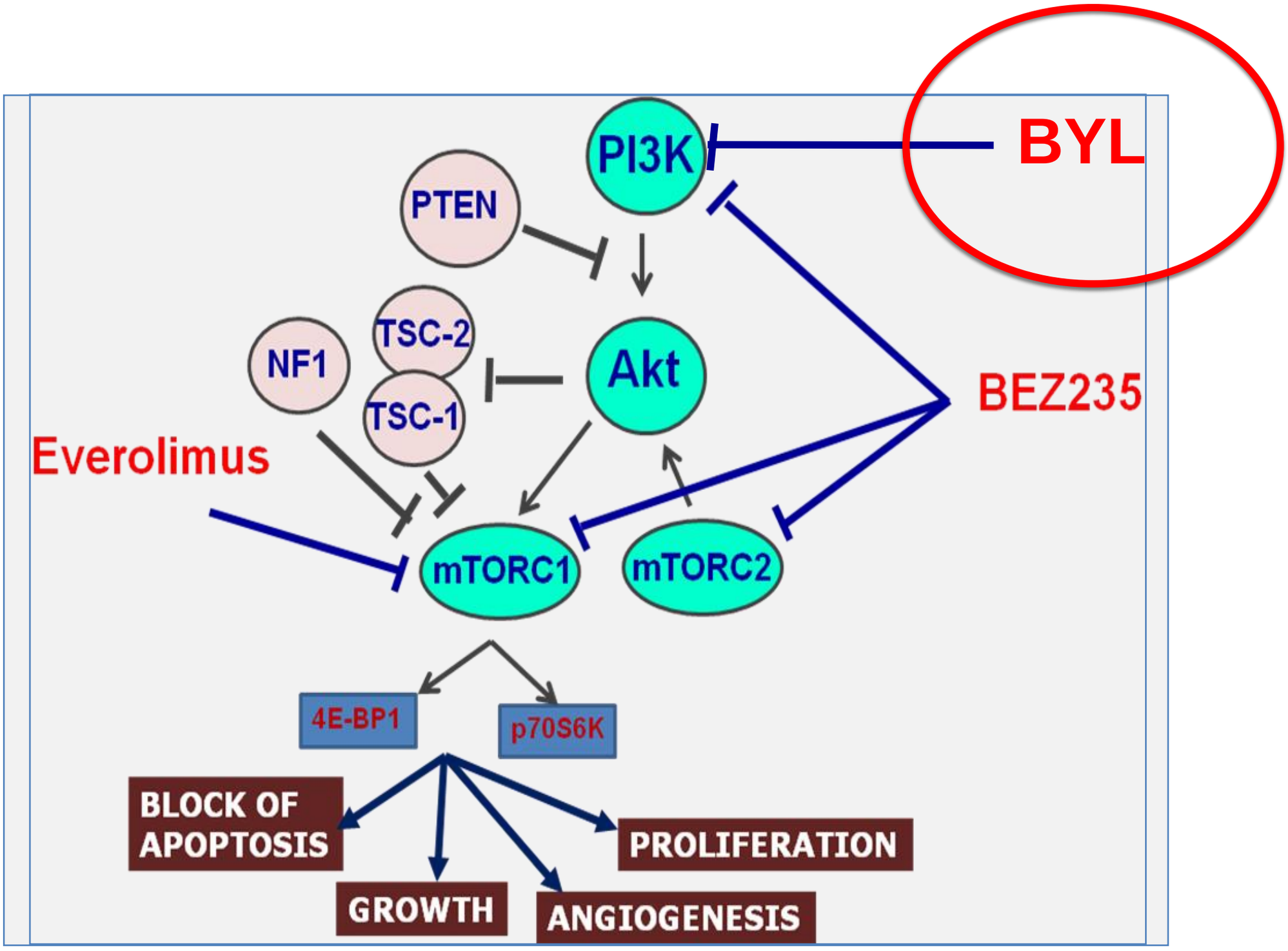
ANGIOGENESIS

The most effective therapeutic approach depends on the particular mechanism of PI3K–Akt activation



BEZ235 inhibits all four class I PI3K isoforms + mTORC1/2

BYL-719:
PI3Kα-inhibitor



Novel TKIs in GEP NETs

Compound	VEGFR			PDGFR		FGFR	CSF1R	KIT	FLT-3	RET	MET	
	1	2	3	α	β							
Sunitinib		✔	✔	✔	✔			✔	✔	✔		> Phase III
Pazopanib	✔	✔	✔	✔	✔			✔				
Cabozantinib	✔	✔	✔						✔	✔	✔	> Phase III
Lenvatinib	✔	✔	✔	✔		✔		✔		✔		
Axitinib	✔	✔	✔		✔			✔				> Phase III
Sulfatinib	✔	✔	✔			✔	✔		✔			> Phase III
Nintedanib	✔	✔	✔	✔	✔	✔						

Targ Oncol
DOI 10.1007/s11523-017-0506-5

REVIEW ARTICLE

Predictive Markers of Response to Everolimus and Sunitinib in Neuroendocrine Tumors

Diana Martins[1] &Francesca Spada[1] &Ioana Lambrescu[1] &Manila Rubino[1] &
Chiara Cella[1] &Bianca Gibelli[2] &Chiara Grana[3] &Dario Ribero[4] &Emilio Bertani[4] &
Davide Ravizza[5] &Guido Bonomo[6] &Luigi Funicelli[7] &Eleonora Pisa[8] &Dario Zerini[9] &
Nicola Fazio[1] &IEO ENETS Center of Excellence for GEP NETs

No validate predictive biomarker for sunitinib and everolimus so far

Martins et al., Targeted Oncol 2017

Human Pathology (2016) 49, 124–134

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

In this issue

Colorectal poorly differentiated neuroendocrine carcinomas frequently exhibit BRAF mutations and are associated with poor overall survival☆

Dane C. Olevian MD[a], Marina N. Nikiforova MD[a], Simon Chiosea MD[a], Weijing Sun MD[b], Nathan Bahary MD, PhD[b], Shih-Fan Kuan MD, PhD[a], Reetesh K. Pai MD[a,□]

[a]Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA 15213
[b]Department of Internal Medicine, Division of Medical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA 15213

2006→2014: 4453 resected CRC (32 NECs)

BRAF mutations were identified in 59% of NECs and in only 5% of poorly differentiated conventional adenocarcinoma (15/17 V600E)

Olevian et al., Hum Pathol 2016

B-RAF mutation = 9% of 108 colorectal NEC cases (80% V600E)

A dramatic tumor response to **BRAF-MEK inhibitors** has been reported in two cases of high grade B-RAF mutated rectal NEC refractory to standard chemotherapy.

Klempner et al. Cancer Discov 2016

FDA Approves Dabrafenib/Trametinib Combination for *BRAF*-Positive Anaplastic Thyroid Cancer

By The ASCO Post

In NEN

More prognostic than predictive biomarkers

NGS in panNET

80 pts, 96 tumor samples

All pts metastatic and pre-treated

Somatic alterations in 95 % of cases

Most common alterated genes (*MSK-IMPACT 486 genes*):

- MEN-1 56 %
- DAXX 40 %
- ATRX 25 %
- TSC-2 25%

Raj N et al., JCO Precision Oncology 2018

ASCO 2018 Poster session: *Puccini et al.*

Comprehensive genomic profiling of 724 GEP-NETs

Methods: NGS (MiSeq on 47 genes, NextSeq on 592 genes), IHC and ISH

Low grade	ATRX	(13%)	Low grade	TML	(1%)
	MEN1	(10%)		MSI	(0%)
				PD-L1	(1%)
High grade	TP53	(51%)			
	KRAS	(30%)	High grade	TML	(7%)
	RB1	(11%)		MSI	(4%)
				PD-L1	(6%)

In HG → higher TML, B-RAFm, KRASm, PIK3CAm

Immune checkpoint inhibitor therapy in NETs:

Debated points

- What predictive factors ?
- What clinical setting ?
- What combinations ?

Immune checkpoint inhibitor therapy in NETs:

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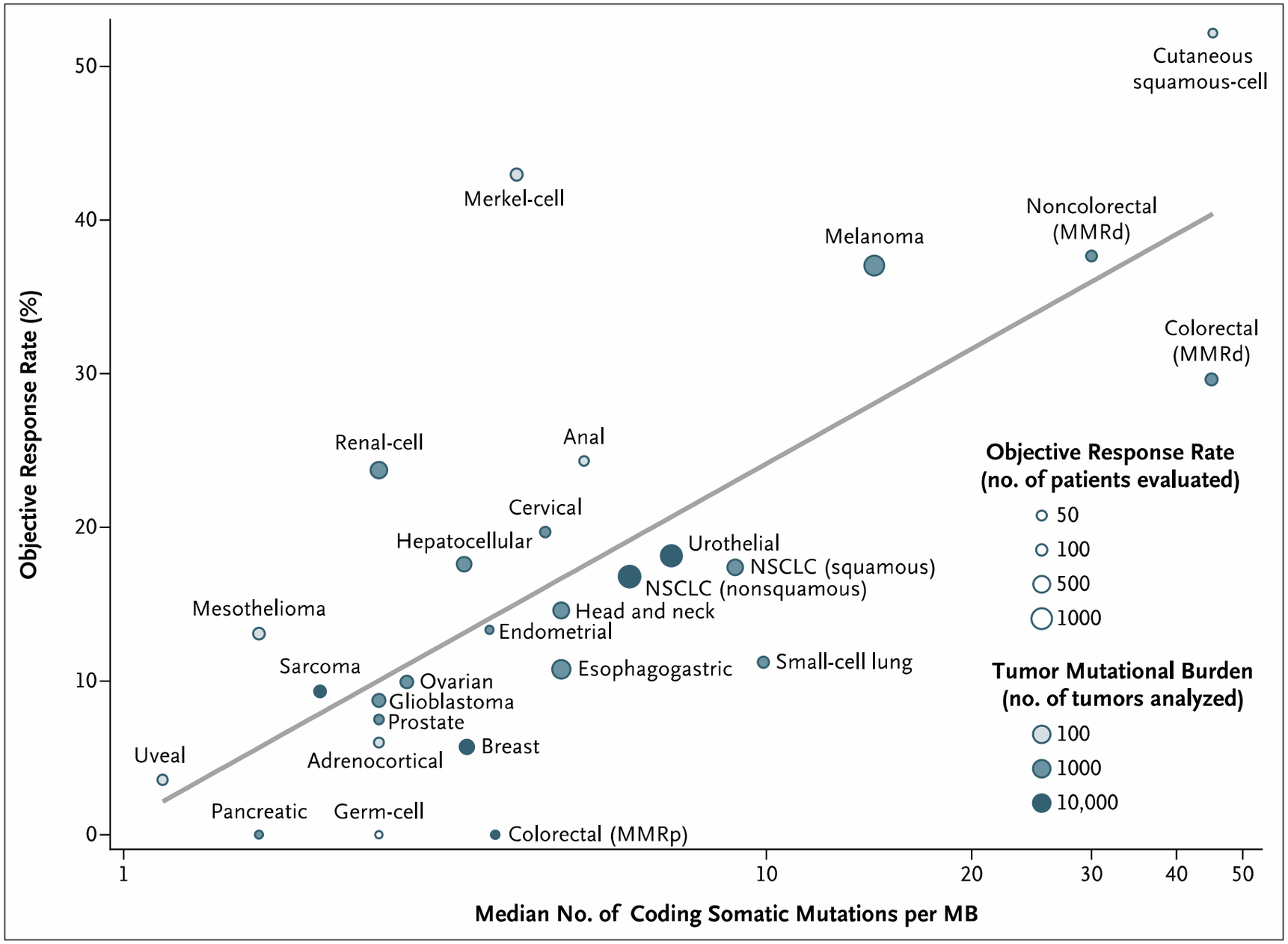
Tumor Mutational Burden and Response Rate to PD-1 Inhibition

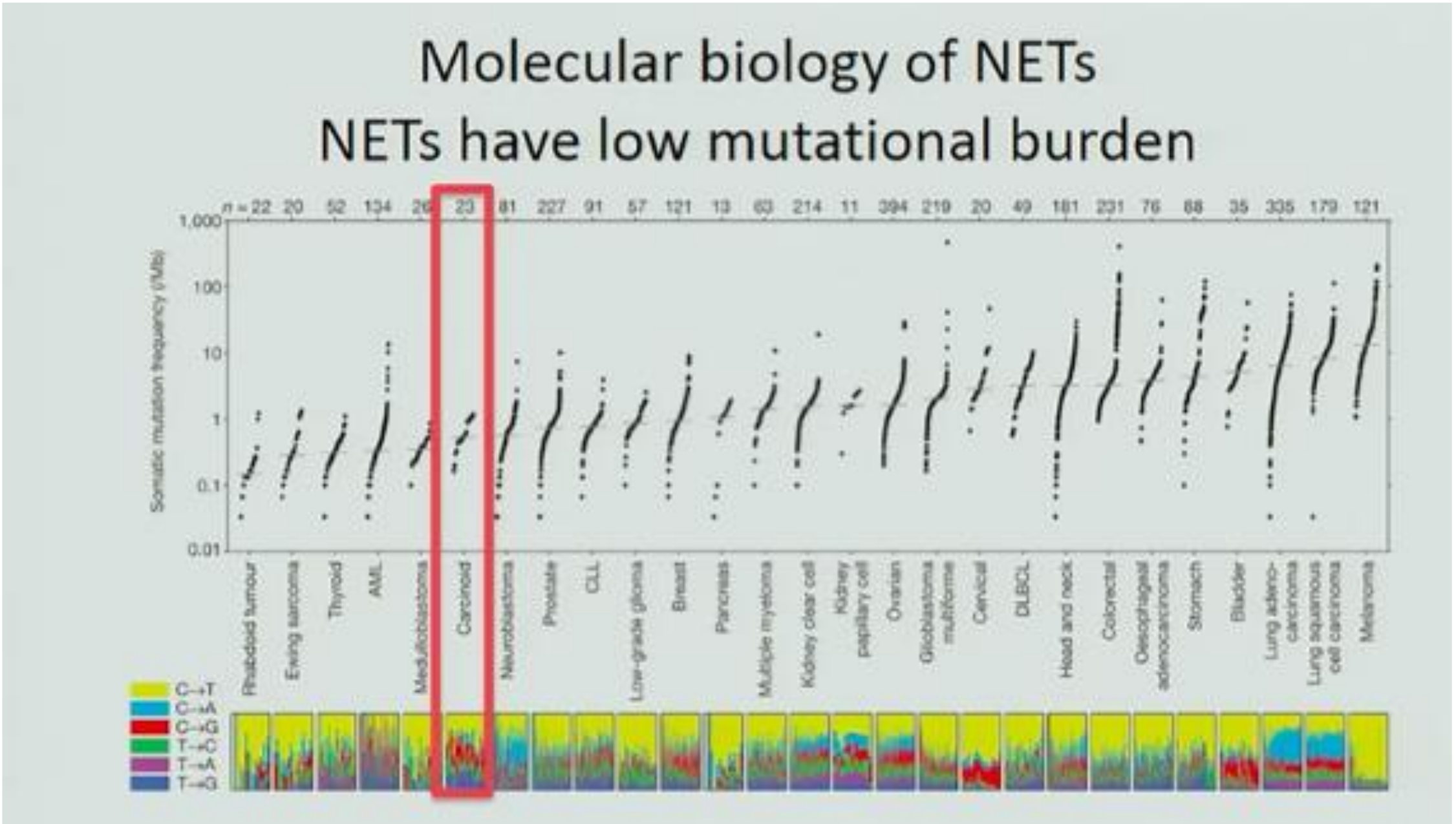


We anticipate a low objective response rate (<5%) for several other cancers (e.g., pilocytic astrocytoma and small-intestine carcinoid).[4] A limita-

Yarchoan et al., NEJM Dec 2017

Molecular biology of NETs

NETs have low mutational burden



Yao, ENETS 2017, Oral presentations

Immune checkpoint inhibitors predictive factor: Mutational burden or Immunogenicity ?

“…….mutational burden increases the likelihood that a tumour is immunogenic, but that it may not be an absolute requirement for checkpoint blockade response.”

Cogdill et al., Br J Cancer 2017

Tumor response **better** than predicted by the TMB

→ Merkel Cell Carcinoma

Tumor response **worse** than predicted by the TMB

→ MSI-H Colorectal carcinoma

Limitations :

- **Low number**
- **Mixed population**
- **Method**

Message → PD-L1 expression was associated with high grade

Small bowel NET can be target for immune checkpoint inhibitor therapy other than panNET and NEC

PD-1, PD-L1, PD-L2, TILs: which is the right predictive biomarker?

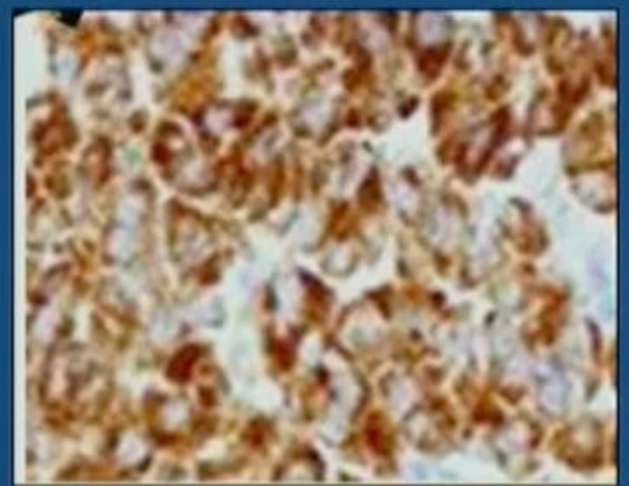
62 Well differentiated small bowel NETs

63 PD-1, PD-L1, PD-L2 and TILs

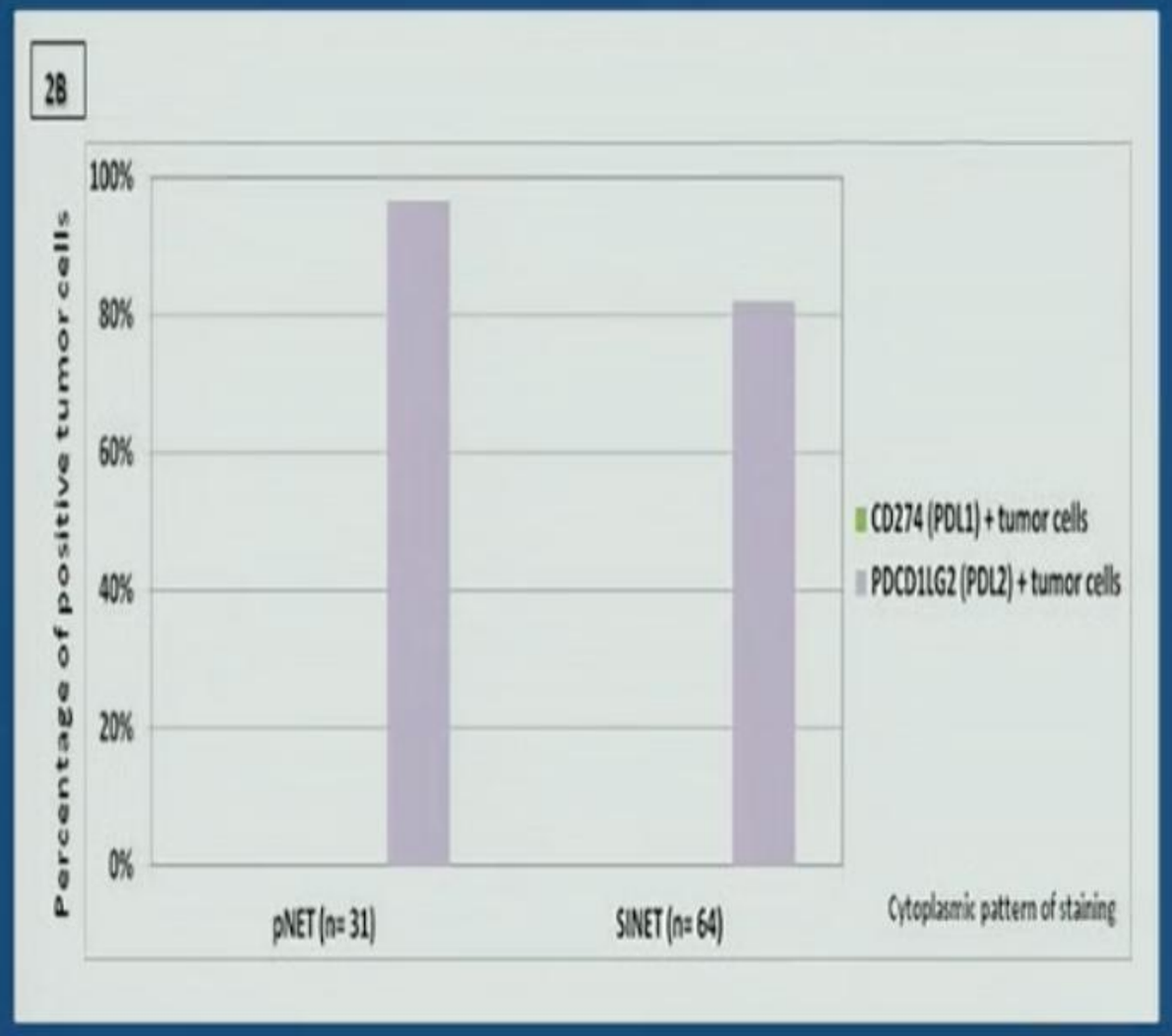
- 30% of WD small bowel NET expressed PD-L1 within tumor cells and/or TILs.
- No PD-L2 IHC expression
- TILs were in a significat amount within WD small bowel NET
- RT-PCR confirmed the IHC results

Lamarca A. et al., Oncotarget Feb 2018

Cytoplasmic tumoral expression of PD-L2 in pNET and SINET



Cytoplasmic expression of PD-L2 in pNET



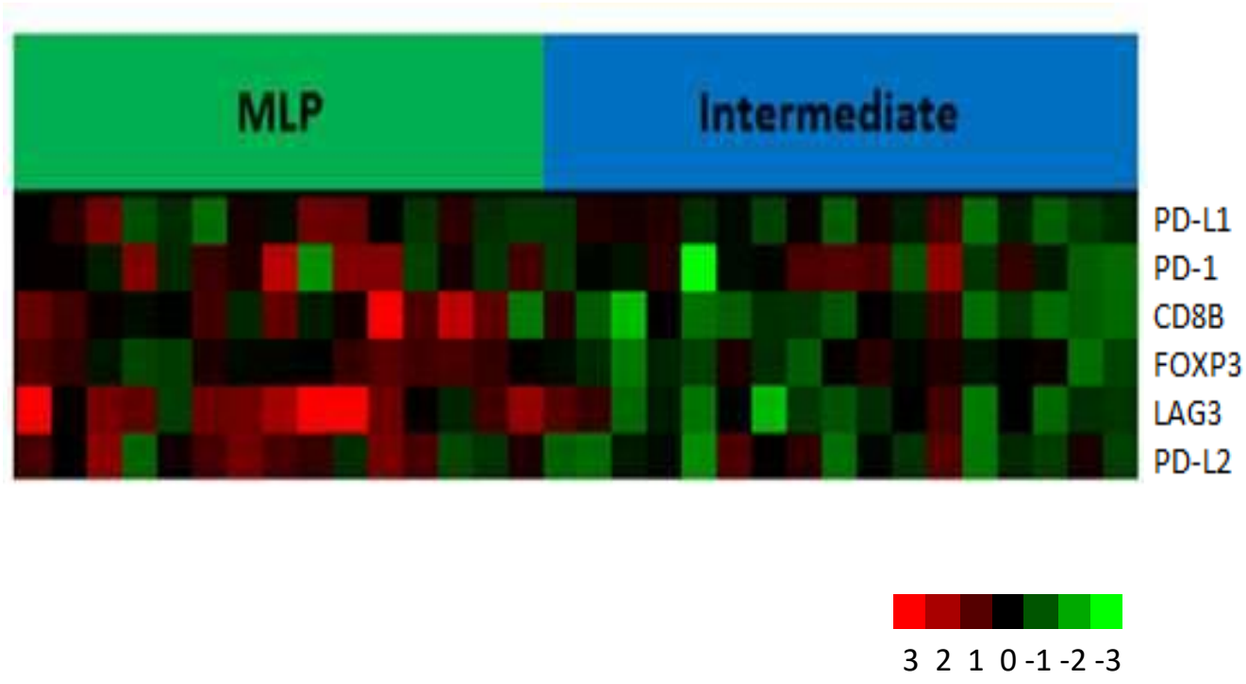
Da Silva et al, NANETS 2016 Annual Symposium

Kulke M.,
Neuroendocrine Tumors: Immune environment and tumor heterogeneity
ENETS 2017

Expression of Other Key Immune Genes

CD8B, FOXP3 and LAG3 more highly expressed in MLP subtype

More heterogeneous expression of PD-L1, PD-L2 and PD-1

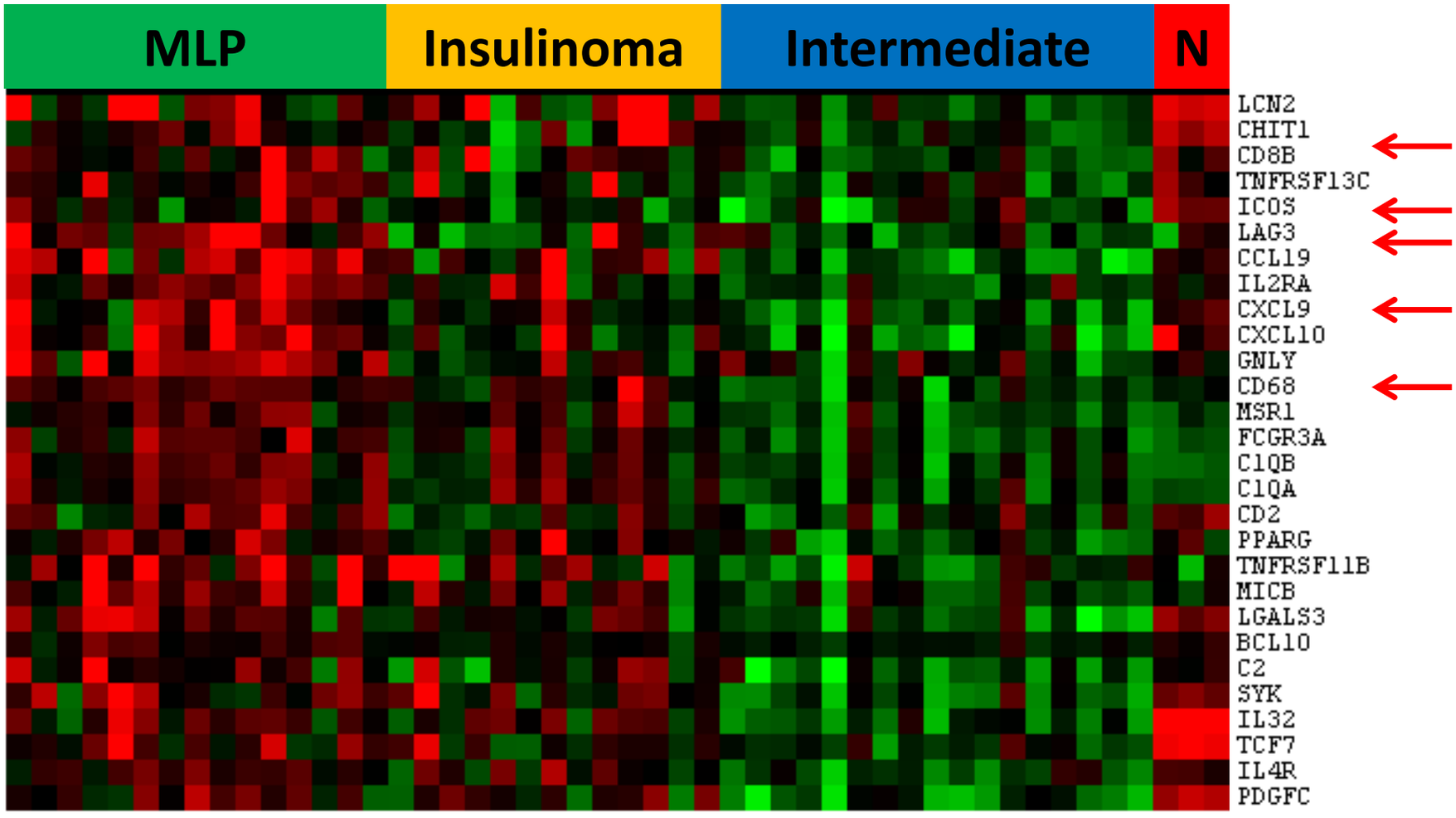


Young K, ESMO 2017

Immune genes enriched in MLP subtype

40% immune genes differentially expressed in MLP and Intermediate subtypes

All had a higher expression in MLP and a lower expression in Intermediate Subtype



MLP subtype = immune high phenotype

Young K, ESMO 2017

Immune checkpoint inhibitor therapy in NETs:

Debated points

- What predictive factors ?
- What clinical setting ?
- What combinations ?

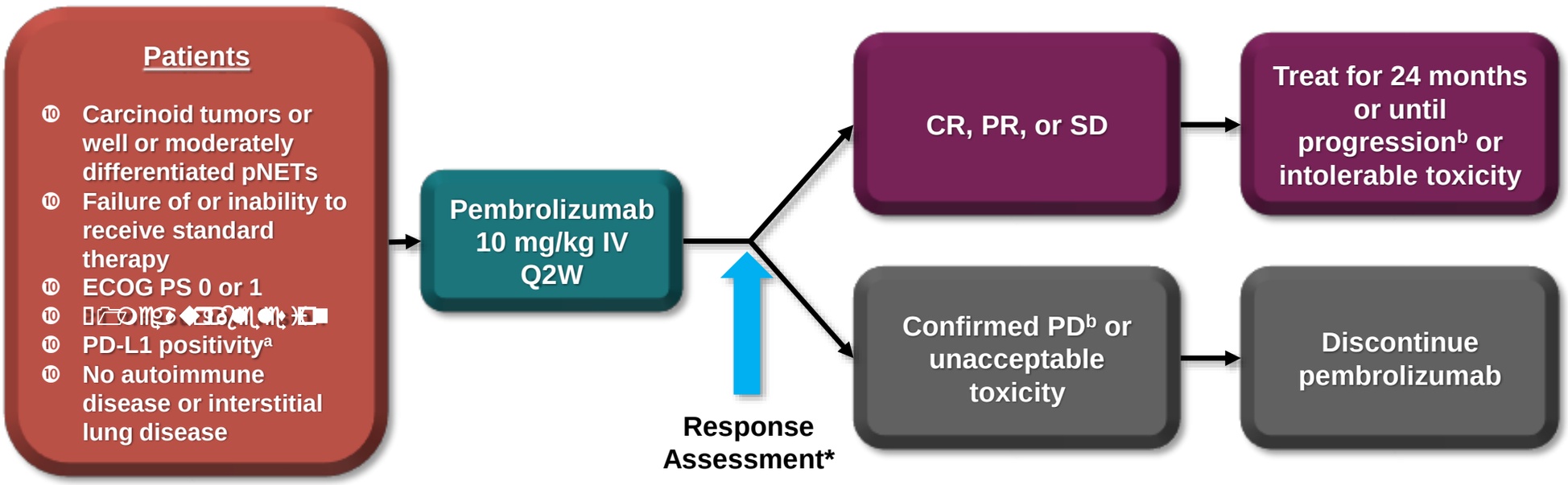
MADRID 2017 ESMO congress

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]

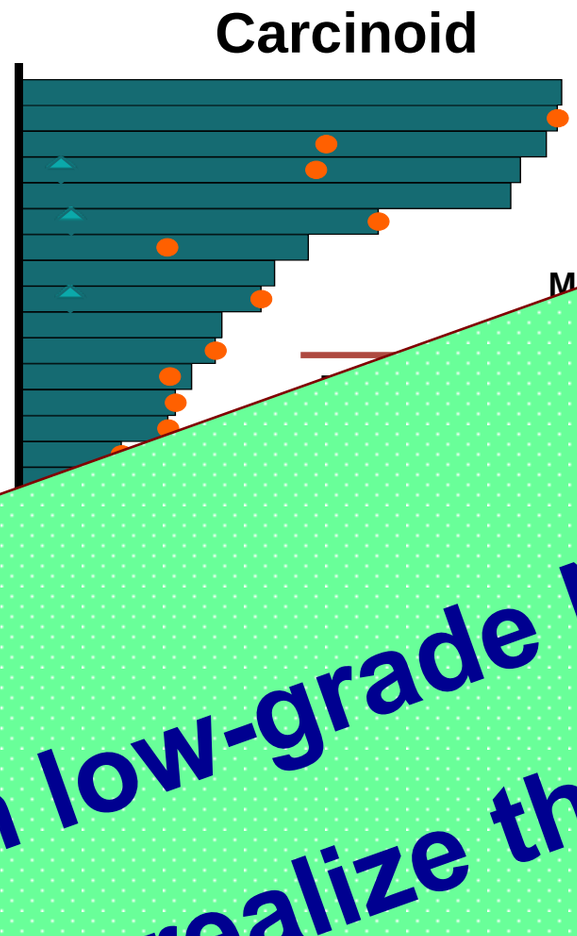
Well differentiated PD-L1+ NETs

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



Mehnert J, ESMO 2017

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



In low-grade NET can be more difficult to realize the benefit of a long-lasting tumor response

-
- **…tion of response especially in pNET**

Mehnert J, ESMO 2017

Toxicity comparable with what already known

Treatment-Related AEs: Carcinoid

Occurring	n (%)	Grade 3
Any	17 (68)	
Diarrhea	7 (28)	
Fatigue		
Hypothyroidism		
Pyrexia		
Weight		
		(4)
		1 (4)
		1 (4)
		1 (4)
…atitis		1 (4)

AL
Data

Toxicity impact of immune checkpoint inhibitors therapy may be an issue in patients with slow-growing NETs

MADRID 2017 ESMO congress

Mehnert J, ESMO 2017

Wang *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:75
DOI 10.1186/s40425-017-0281-y

Journal for ImmunoTherapy of Cancer

CASE REPORT Open Access

Checkpoint inhibitor is active against large cell neuroendocrine carcinoma with high tumor mutation burden

Victoria E. Wang[1*], Anatoly Urisman[2], Lee Albacker[3], Siraj Ali[3], Vincent Miller[3], Rahul Aggarwal[1] and D

Case report → signific

The benefit of immunotherapy can be clearer in poor prognosis NECs

plification **and tumor**

mutations/megabases)

Preliminary studies suggest immune checkpoint inhibitor therapy has activity in SCLC

- Keynote 028 (Pembrolizumab*), Ott et al., JCO 2017*

- Checkmate 032 (Nivolumab, Ipilimumab)*, Antonia et al. Lancet Oncol 2016*

ASCO Annual Meeting 2016

Abstract 4020 (166618): Genomic profiling to distinguish poorly differentiated neuroendocrine carcinomas arising in different sites. Bergsland et al.

- **Retrospective search of Foundation Medicine Genomic Data set to include 368 GEP-NEC and 608 SCLC.**

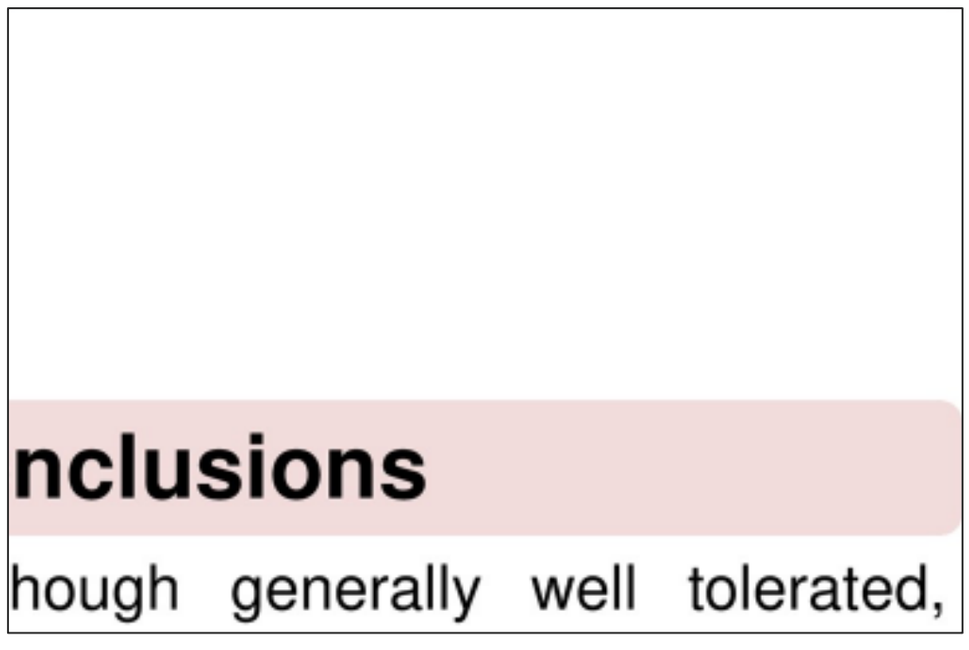
SCLC is different from extra-lung SCC

	SCLC	Pancreas		Colorectal		Other GI*
Group (N)	(593)	1 (123)	2(91)	1 (92)	2(51)	1(59)
Gene						
TP53	90%	18% SCO	15% SC	59% SP	67%SP	49% SP
RB1	67%	10% SC	11% SC	34% SP	47%P	29% S
APC	2%	3% C	2% C	47% SPO	45%SP	8% C
CDKN2A	3%	21% SC	22% SC	5% PO	2%P	25% SC
KRAS	4%	7% C	7% C	37% SPO	39%SP	3% C
MEN1	1%	33% SCO	29% SC	3% P	0%P	2% P
CDKN2B	1%	16% SC	18% S	1% PO	2%	19% SC
CCNE1	4%	2% O	2%	1% O	2%	17% SPC
DAXX	0%	20% SCO	14%S	0% P	0%	0% P
FBXW7	3%	1%C	0%C	14%SP	16% SP	5%

Hidalgo, Discussant ASCO 2016

ASCO 2018 Poster session: *Vijayvergia et al.*

Pembrolizumab monotherapy in patients with previously treated metastatic high grade neuroendocrine neoplasms

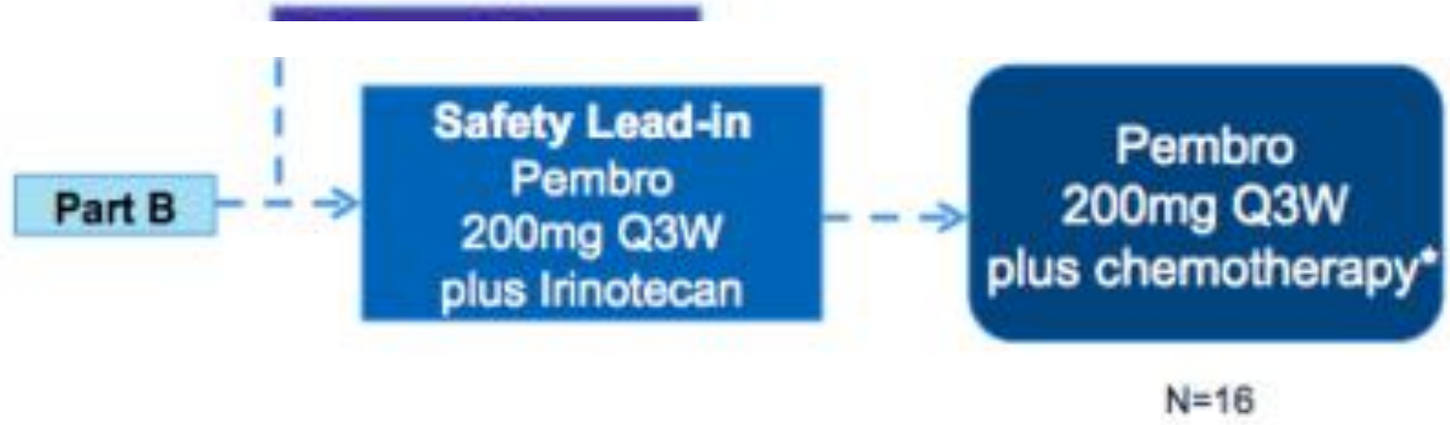


ASCO 2018 Poster session: *Hooker et al.*

A pilot study of pembrolizumab-based therapy in previosly treated extrapulmonary poorly differentiated neuroendocrine carcinoma

(Part A) and PEM plus che
(IRI) or paclitaxel (P); physicia

Figure 2



*Physician's choice: Paclitaxel or weekly Irinotecan

Imaging Q9W x 6 months, then Q12W

ility:

SION CRITERIA	KEY EXCLUSION CRITERIA
ly confirmed locally	Merkel cell carcinoma

Analysis plan:

- If >2 responses out of.14 pts by week 18 (1 part A), then 21 additional patients (pt enroll in stage 2 (Part A), corresponding 10% vs. H1 26% at type I error of 0.0 power 80%.

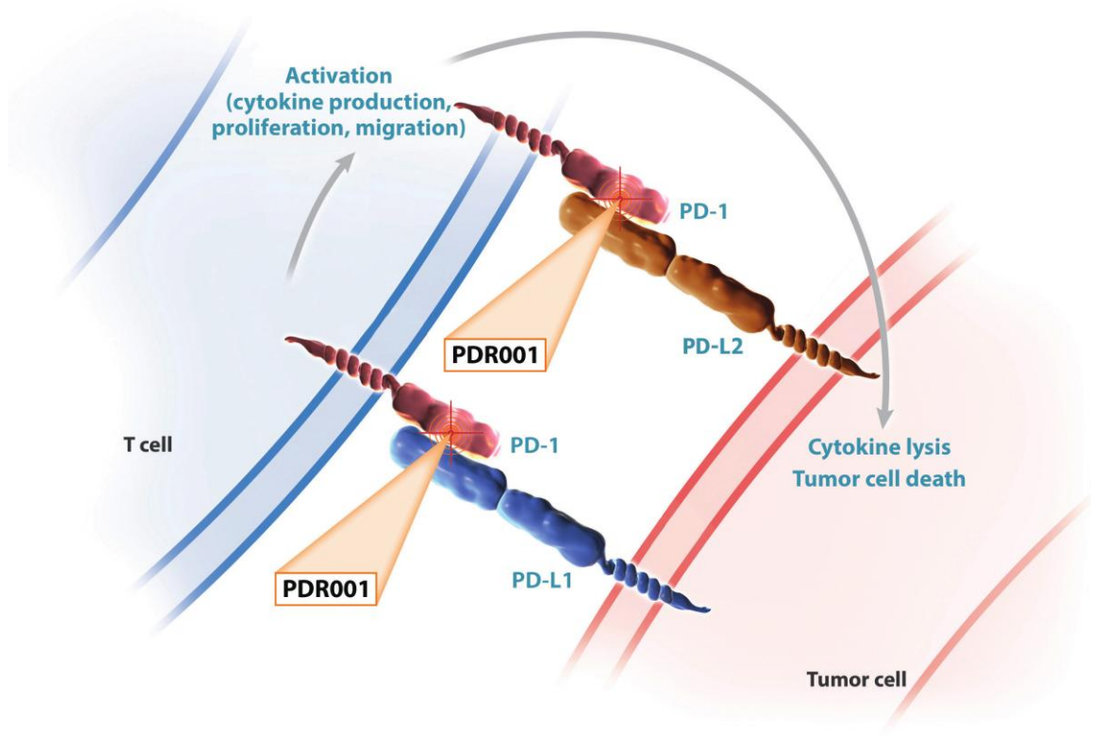
Analysis plan:

- If >2 responses out of 1

PDR001 in GEP and Lung NET/NEC

Phase II multi-cohort international study

PDR001 binds to PD-1 so blocking both PD-L1 and PD-L2



- Well differentiated:
  - GI cohort (n=2
  - Pancrea
  - Th
- P differentiated:
  - GEP cohort (n=20)

Results at ESMO 2018

A multicohort phase II study of **durvalumab plus tremelimumab** for the treatment of patients (PTS) with advanced neuroendocrine neoplasms (NENs) of gastroenteropancreatic (GEP) or lung origin (the DUNE trial-GETNE1601-).

Single-arm Phase II
126 pts

- Well differentiated:
  - GI cohort (n=30)
  - Pancreatic co
  - Thoraci =30)
- Poorly differentiated:
  - GEP cohort (n=20)

Ongoing

Durvalumab
(anti-PD-L1)

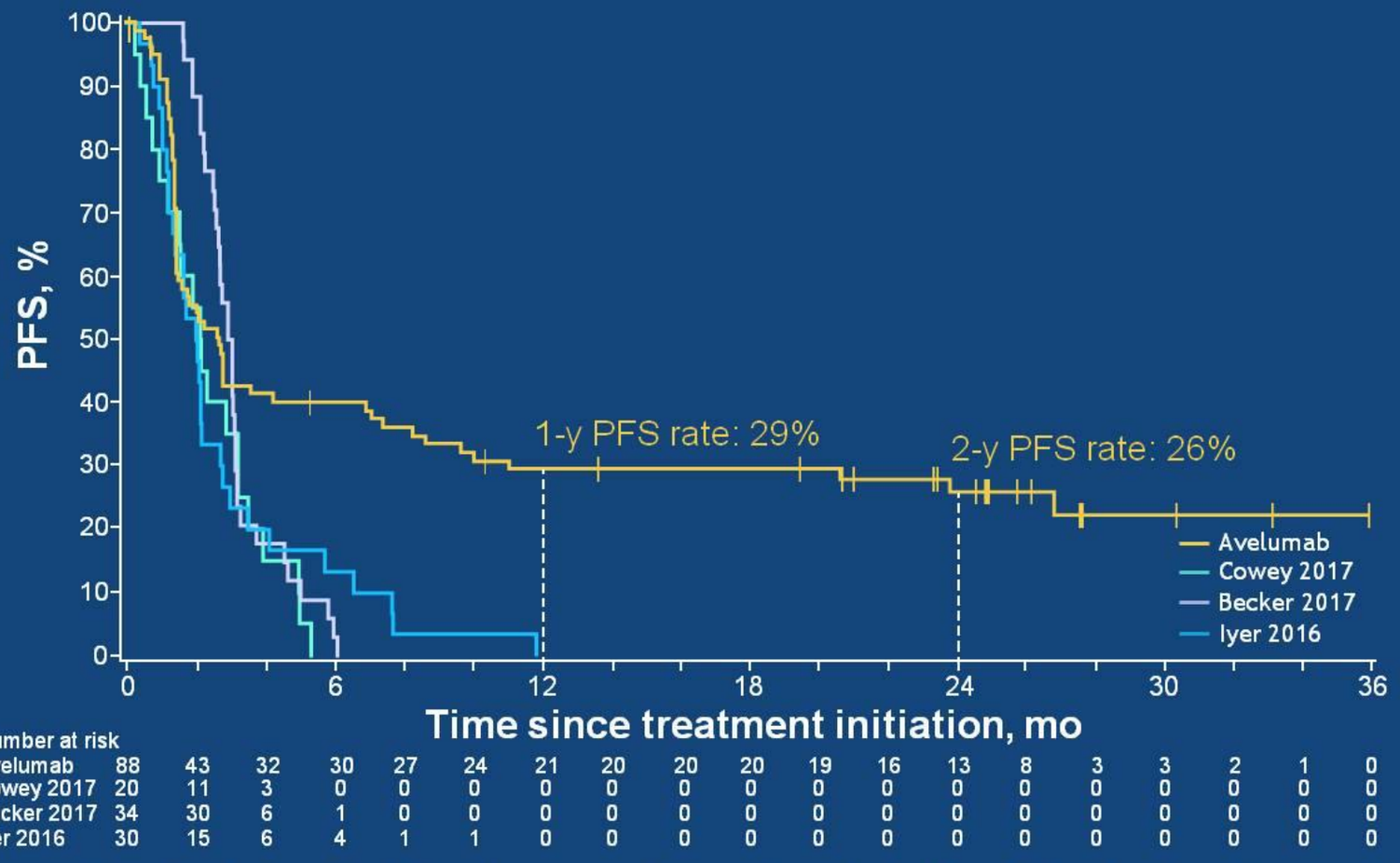
+

Tremelimumab
(anti-CTLA-4)

Merkel Cell Carcinoma

ASCO 2018 Second-line Avelumab in MCC: an update
Nghiem P

Progression-free survival with avelumab and retrospective chemotherapy data[1-3,*]



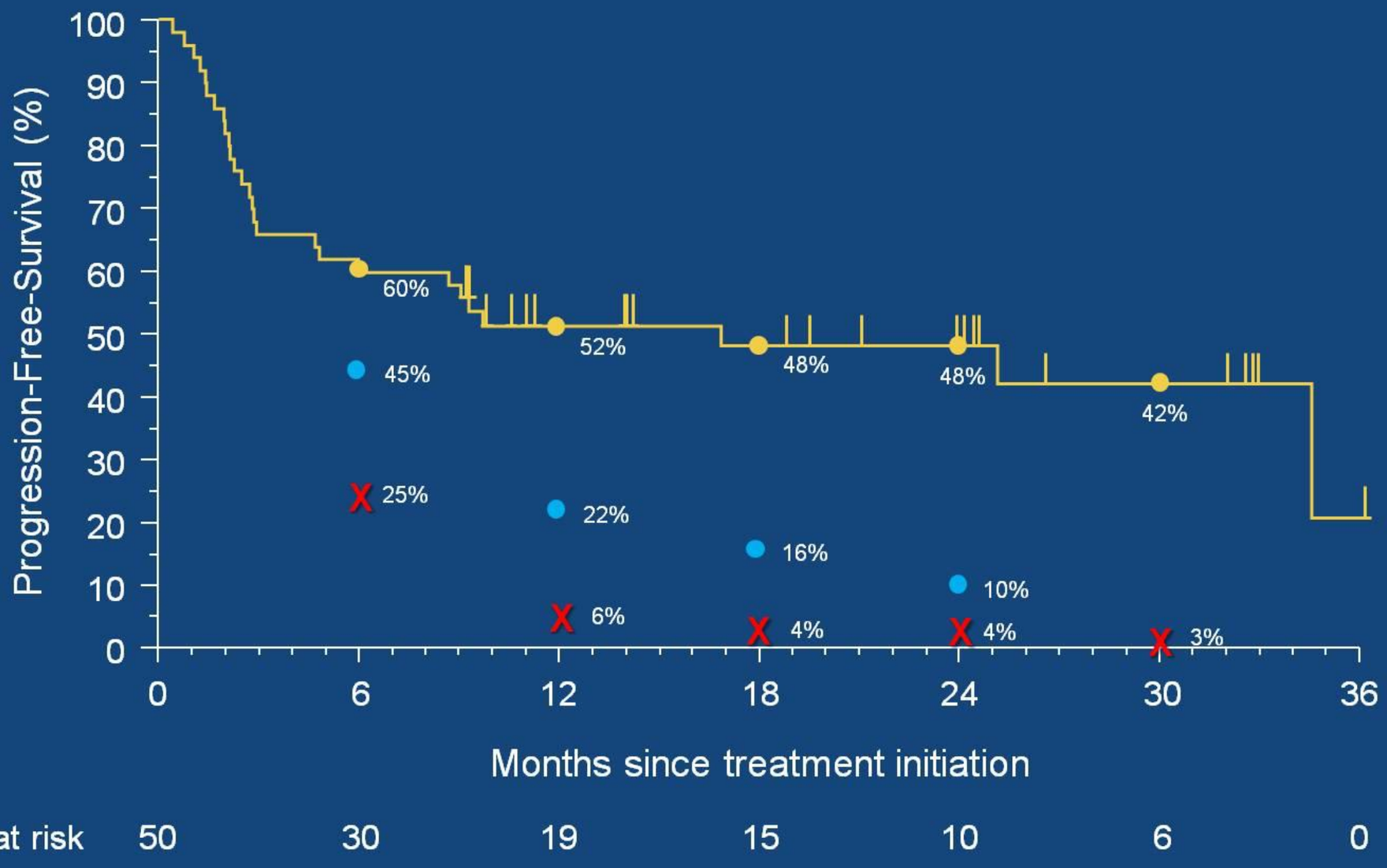
Number at risk

Avelumab	88	43	32	30	27	24	21	20	20	20	19	16	13	8	3	3	2	1	0
Cowey 2017	20	11	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Becker 2017	34	30	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Iyer 2016	30	15	6	4	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0

* This figure is for illustrative purposes only and is not a direct head-to-head comparison; it incorporates multiple different data sets and is not from a randomized clinical trial

1. Cowey CL, et al. *Future Oncol*. 2017;13(19):1699-1710. 2. Becker J, et al. *Oncotarget*. 2017;8(45):79731-41. 3. Iyer JG, et al. *Cancer Med*. 2016;5(9):2294-301.

Progression-free survival with pembrolizumab for MCC



Pembrolizumab 1st line (N= 50)

X 1st line chemotherapy historical data (N= 62) Iyer, et al (Cancer Medicine, 2016)

● 1st line chemotherapy historical data (N=67) Cowey, et al (Future Oncology, 2017)

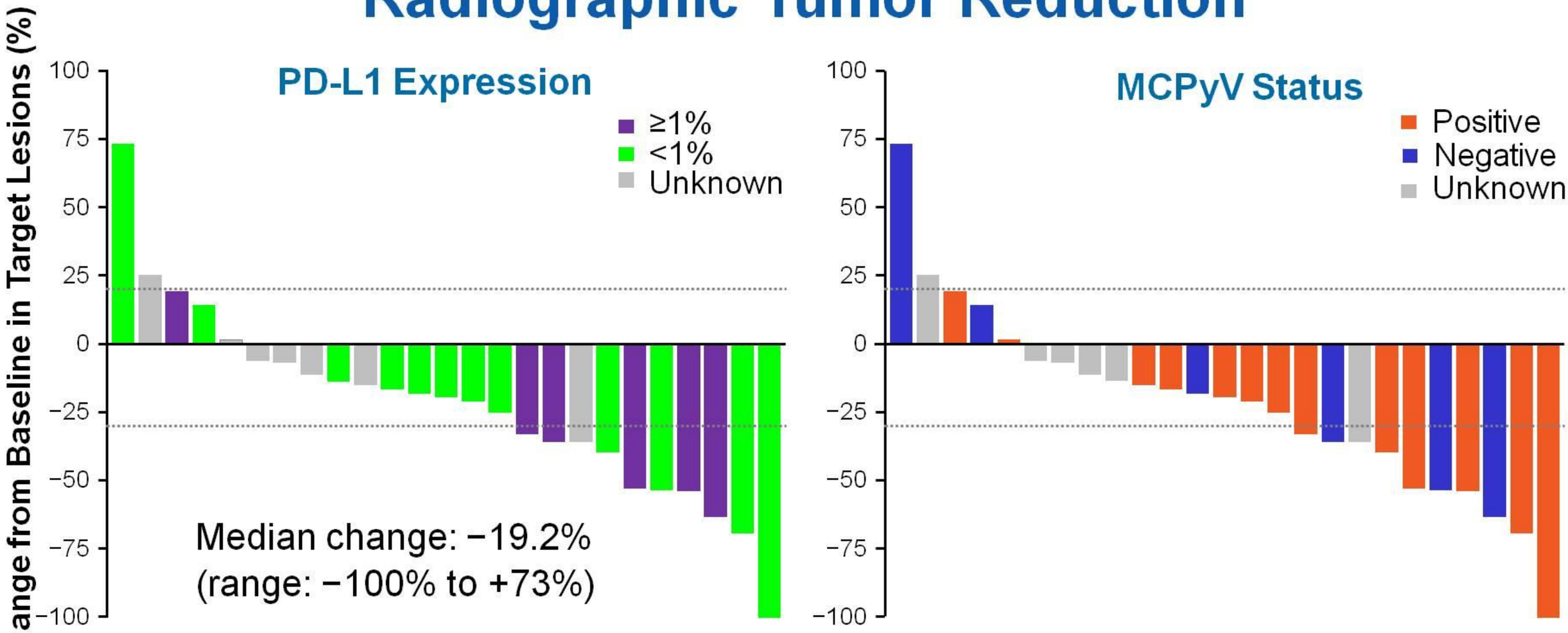
Median PFS (months)	
Pembrolizumab	16.8 [95% CI 4.6,.]
Chemo (Iyer)	3.1 [0.4-33, range]
Chemo (Cowey)	4.6 [95% CI 3.0-7.0]

Database Cutoff Date : 06Feb2018

ASCO 2018 Nivolumab as neoadjuvant therapy in MCC
Topalian S

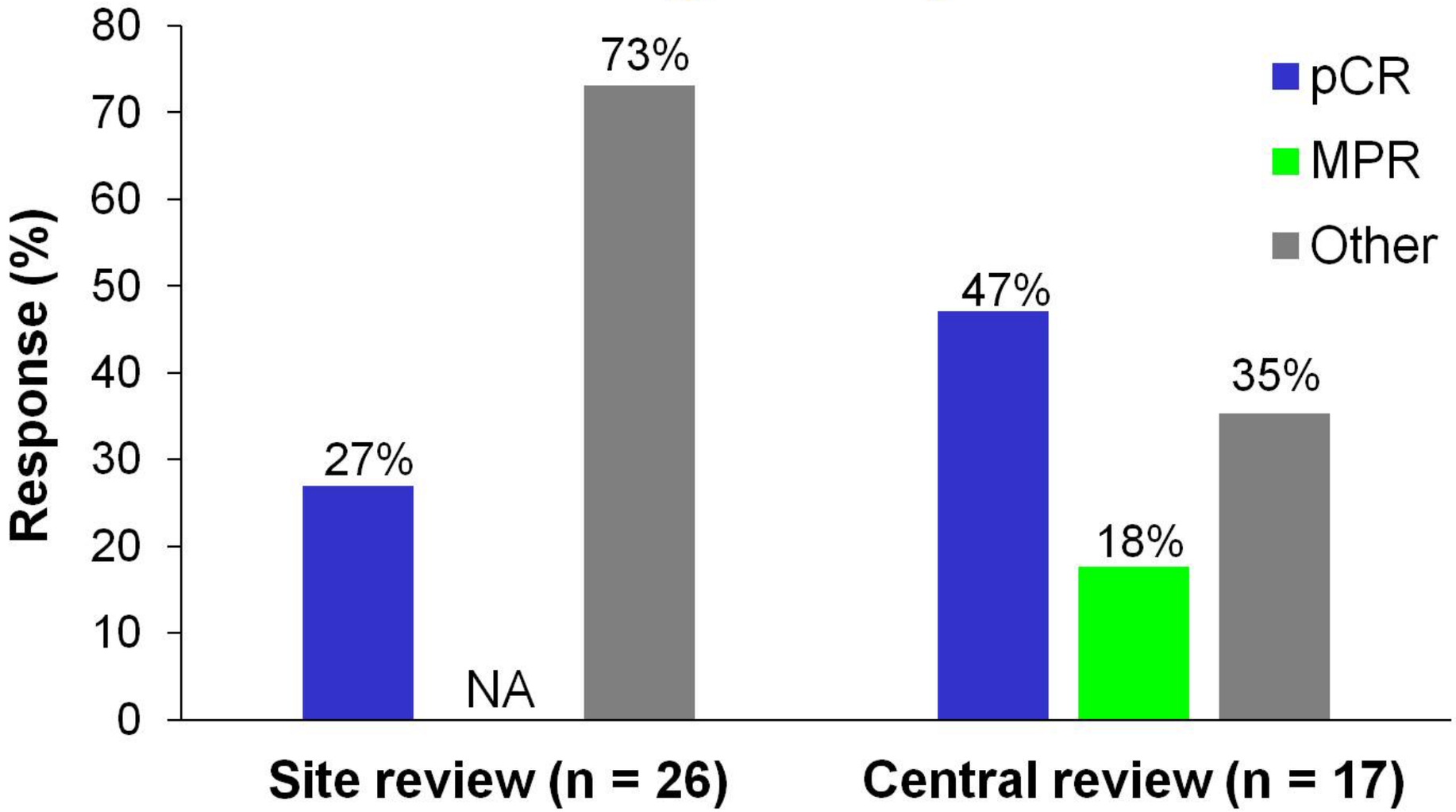
CheckMate 358

Radiographic Tumor Reduction



- 40% of 25 CT-evaluable patients had target lesion reductions >30%.
- Radiographic response and tumor MCPyV status were investigator-assessed.

Pathologic Response



pCR = pathologic complete response; MPR = major pathologic response (≤10% residual viable tumor); NA = not assessed.

Immune checkpoint inhibitor therapy in NETs:

Debated points

- What predictive factors ?
- What clinical setting ?
- What combinations ?

Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth

Acquired resistance to Temozolomide in CRC

→ Increased tumor mutational burden

→ Improved immunosurveillance

MSH-6: normal pre-TMZ, mutated post-TMZ

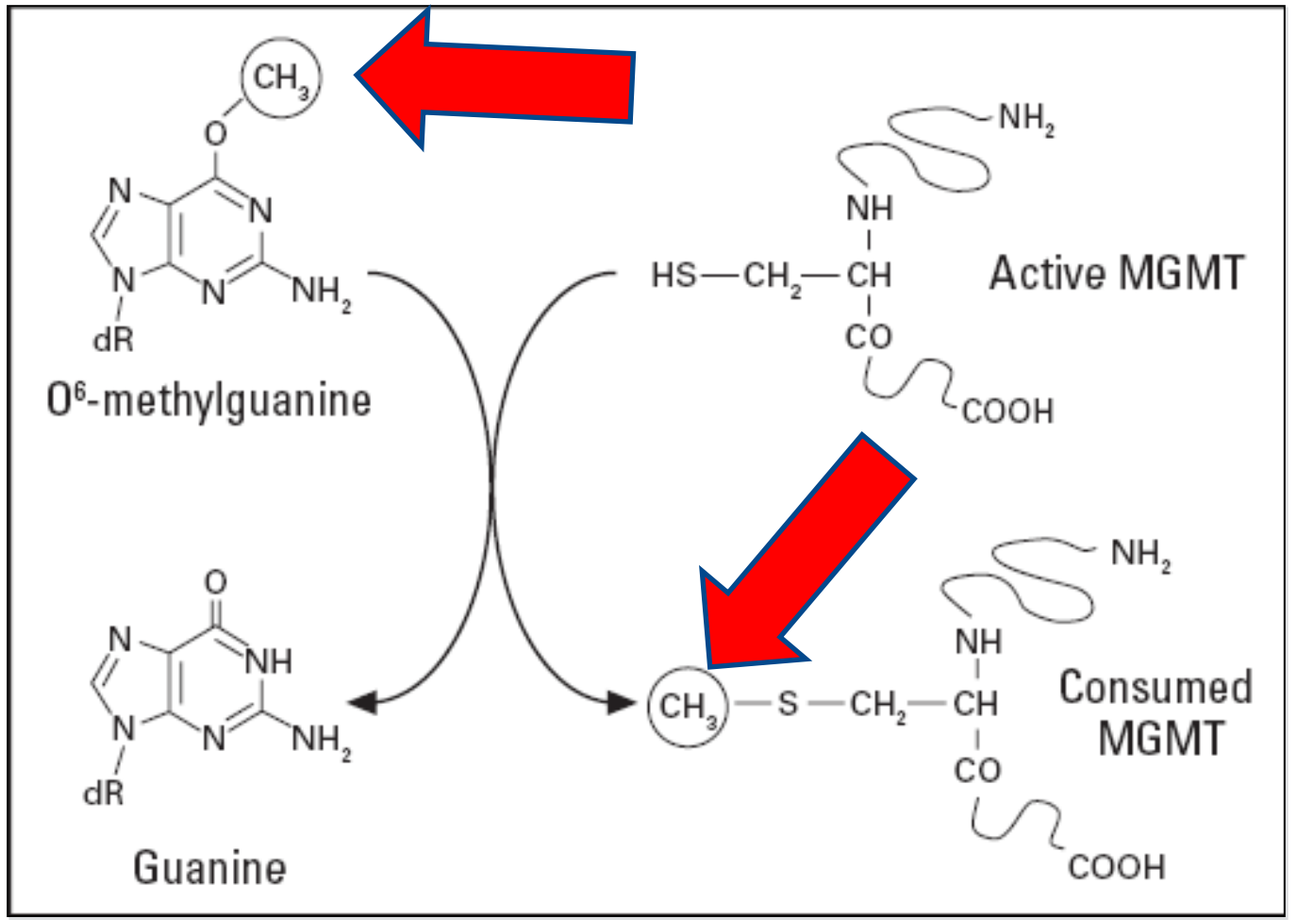
This is a "proof of concept that it is possible to inactivate DNA repair in vivo to improve immune surveillance and responses to immune-checkpoint blockade."

Germano G et al., Nature Dec 2017

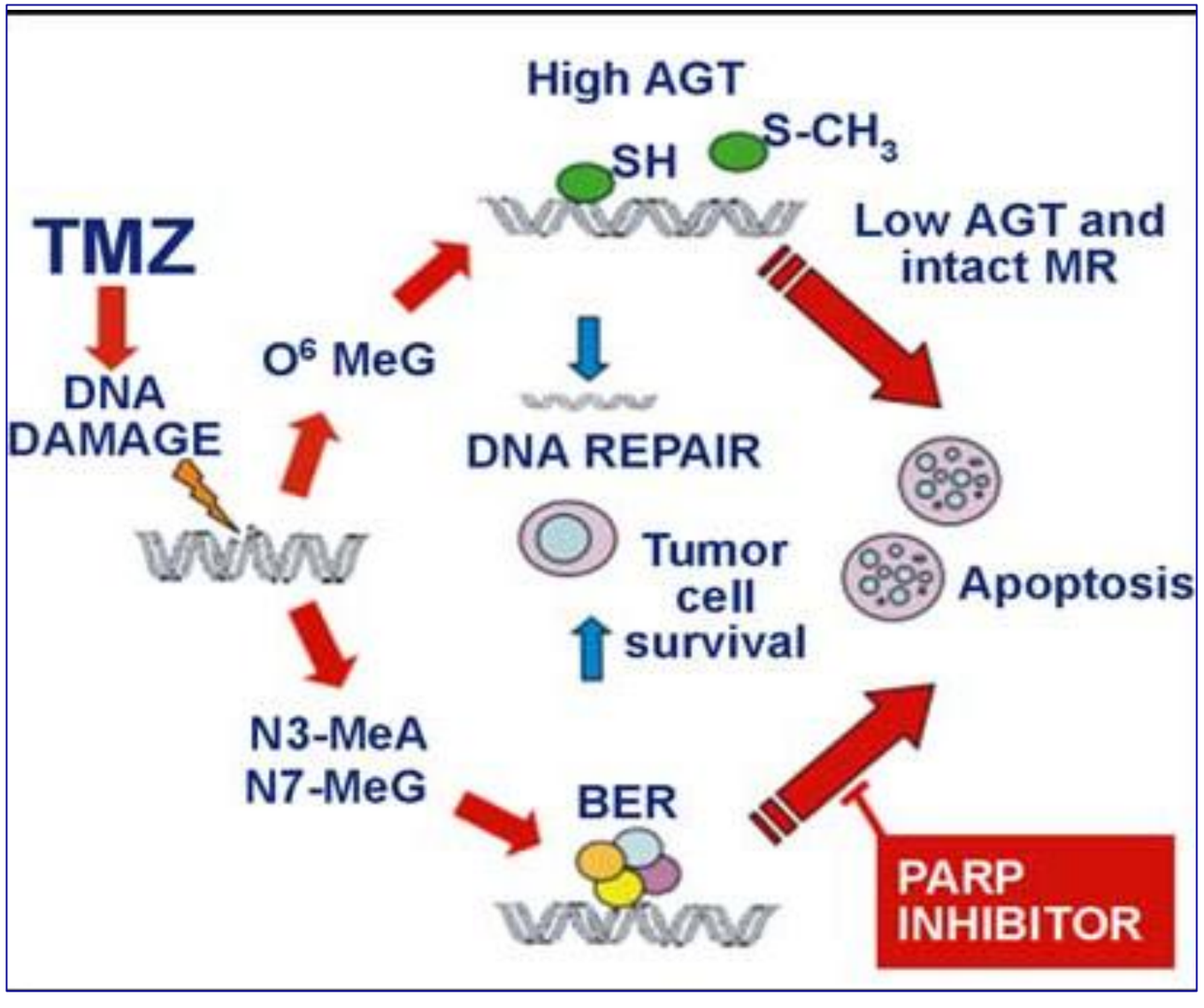
Temozolomide in Advanced Neuroendocrine Neoplasms: Pharmacological and Clinical Aspects

Koumarianou A, Kaltsas G, Kulke MH, Oberg J, Strosberg J, Spada F, Galdy S, Barberis M, Fumagalli C, Berruti A, and Fazio N

Neuroendocrinology, June 2015



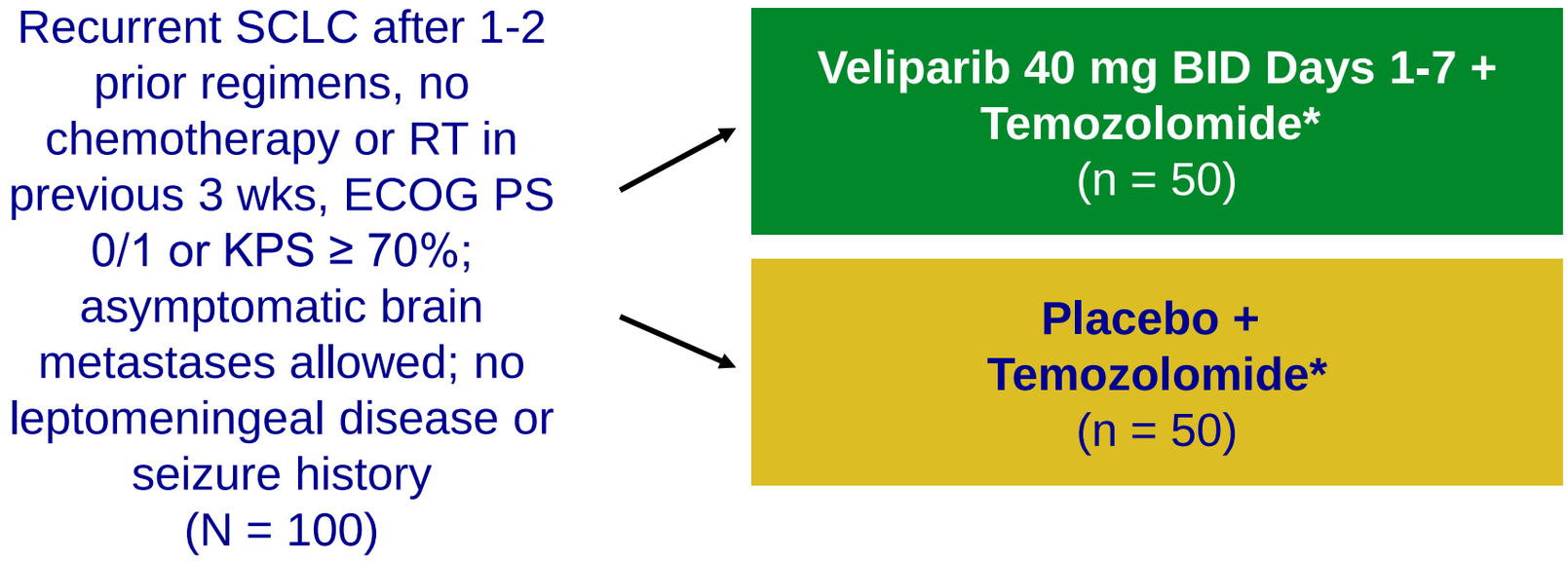
PARP-I + TMZ



Inhibition of PARP avoids recruitments of base excision repair (BER) components involved in the repair process of *N*-methylpurines; this results in generation of strand breaks and induction of apoptosis

Veliparib + Temozolomide for Treatment of Recurrent ES-SCLC

- Double-blind, randomized, placebo-controlled phase II trial



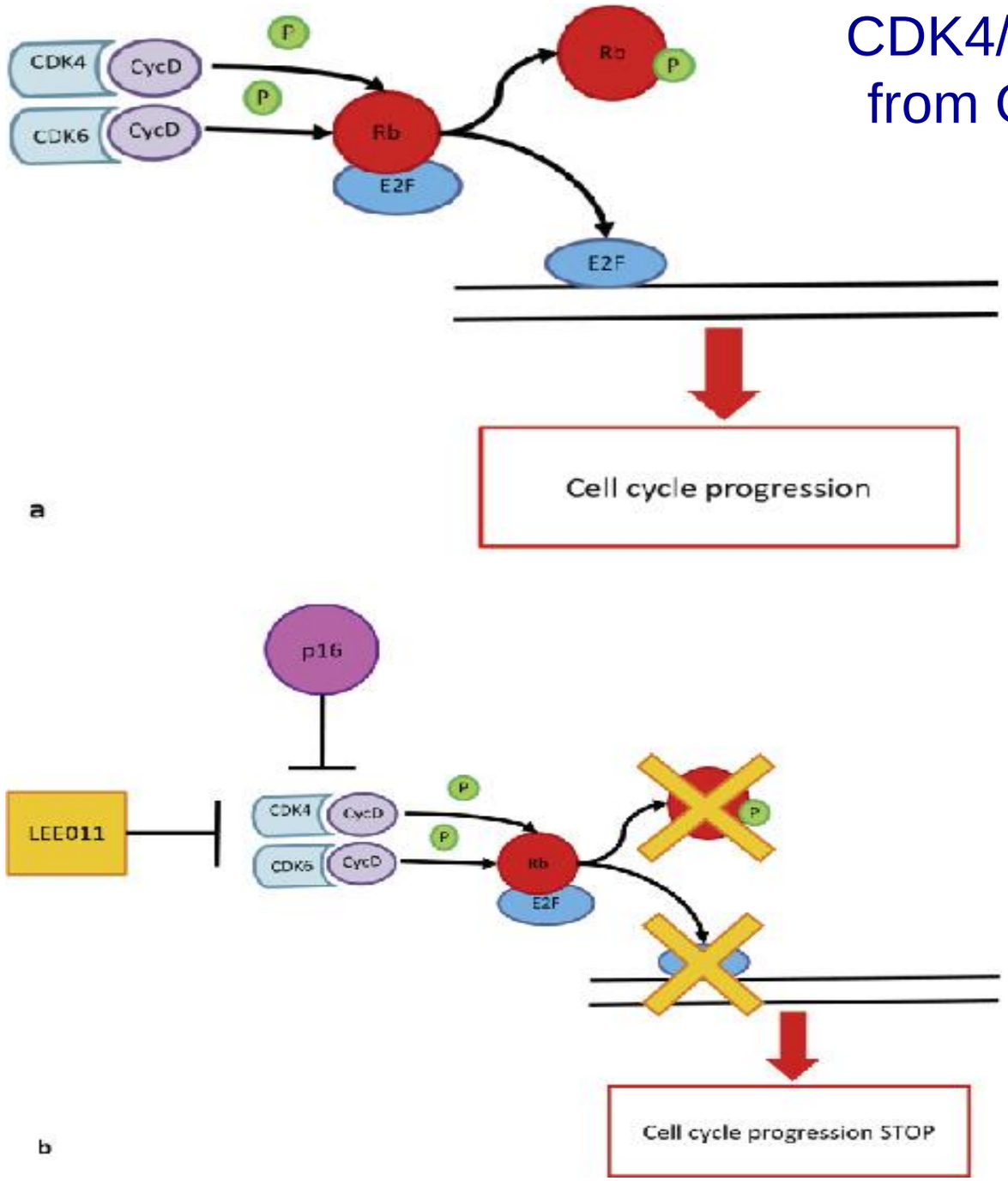
- Primary endpoint: 4-mo PFS

- Secondary endpoints: ORR (RECIST v1.1), OS, safety/toxicity, biomarkers

Pietanza MC, et al. ASCO 2016. Abstract 8512.

CDK 4/6 inhibitors → immune checkpoint inhibitors

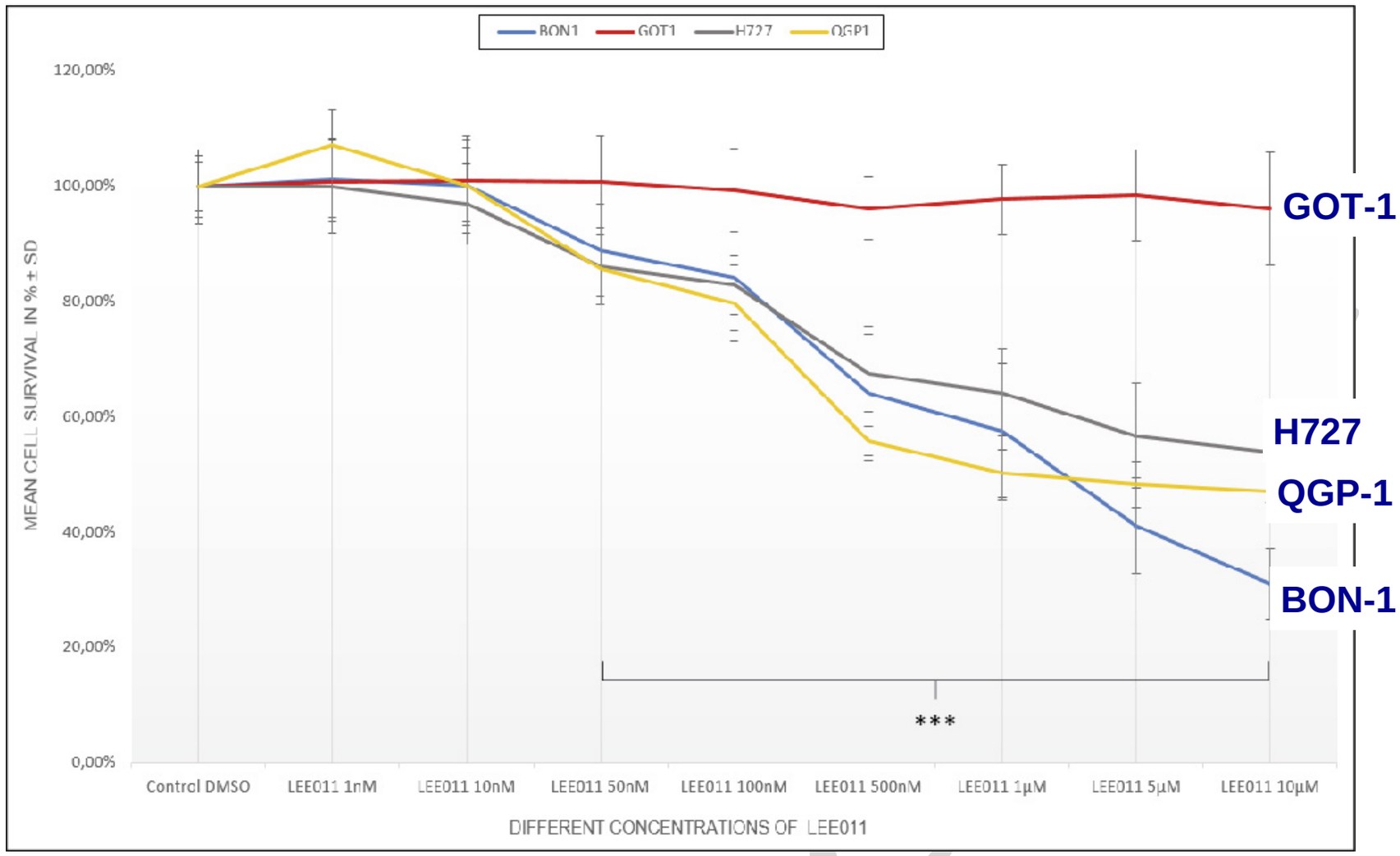
CDK 4/6 inhibition in NET: preclinical studies with **ribociclib** and **palbociclib**



CDK4/6 controls cell cycle progression from G1 to S phase by regulating the activity of Rb

Prada et al, Neuroendocrinology 2016
Tang L. et al., Clin Cancer Res 2012

Ribociclib-based therapy in NET: a preclinical study



Ribociclib sensitivity was associated with high expression of cyclin-1 and Rb

Ribociclib/Everolimus or 5-FU combinations were superior to the single-agent therapies, by downregulating mTOR and MEK pathways

Prada et al, Neuroendocrinology 2016

Abstract 429O

A phase II trial of palbociclib in metastatic grade 1/2 pancreatic neuroendocrine tumors: the PALBONET study on behalf of the Spanish Taskforce Group of Neuroendocrine Tumors (GETNE)

Enrique Grande[1], Alexandre Teulé[2], Teresa Alonso-Gordoa[1], Paula Jiménez-Fonseca[3], Marta Benavent[4], Jaume Capdevila[5], Ana Custodio[6], Ruth Vera[7], Javier Munárriz[8], Adelaida La Casta-Muñoa[9], Rocío García-Carbonero[10]

Patients treated	21

	N	%
Partial response (PR)	0	0
Stable disease (SD)	11	55
Progression disease (PD)	9	45

mPFS: 2.6 months (95% CI 0–14.4)

A Phase II Study of LEE011 (Ribociclib) in Patients with Advanced Neuroendocrine Tumors of Foregut Origin (CLEE011 XUS02T)

US only

CDK4/6 inhibition triggers anti-tumour immunity

CDK4/6 inhibitors not only induce tumour cell cycle arrest, but also promote anti-tumour immunity

→ *Stimulation of type III IFNs* → *enhancement of tumor antigen presentation*

→ *Suppression of T-Reg*

Goel S et al, Nature 2017

Cancer Letters xxx (2017) 1–11

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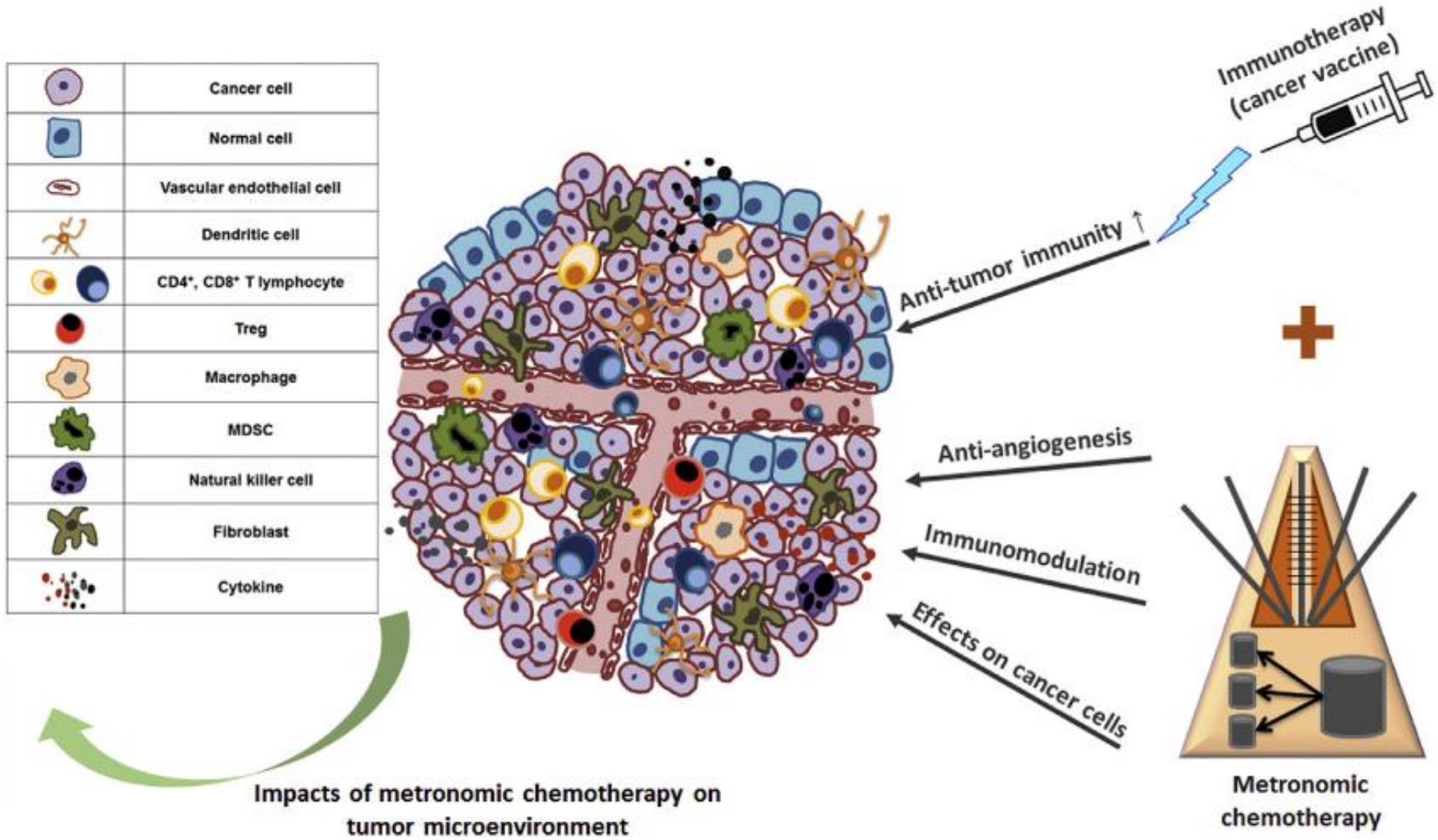
journal homepage: www.elsevier.com/locate/canlet

Mini-review

Metronomic chemotherapy and immunotherapy in cancer treatment

Yu-Li Chen [a, b, c], Ming-Cheng Chang [c], Wen-Fang Cheng [c, d, e, *]



Chen Y-L et al., Cancer Letters 2017

Small cell lung cancer – ES : Phase I-II clinical trial NCT03325816

Maintenance setting after first-line chemotherapy

PRRT
(^{177}Lu-DOTATATE)

+

Nivolumab

European Institute of Oncology, IEO, Milan, Italy

ENETS Center of Excellence for GEP NETs

IEO NET MDT

Istituto Europeo di Oncologia

Thanks !