



Change in grade and differentiation: What do we learn for patient management?

Thursday, 27 March 2025, 18:00 – 19:10 CET

Disclosure Statement

Margot TESSELAAR (Moderator) has the following potential conflicts of interest to disclose:

- **Receipt of grants/research support:** Merck BV

The Aim and Concept:

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- ✓ Webinars are free of charge and can be accessed by all.
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- ✓ **This webinar is intended for HCPs qualified by law to prescribe medicine.**

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Live poll question: Getting to know the audience

In which medical discipline are you trained or currently working?

Tonight's faculty



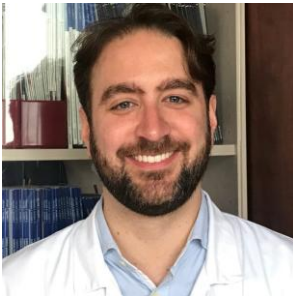
Margot TESSELAAR

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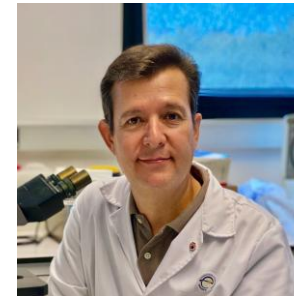
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Louis DE MESTIER

Beaujon Hospital, Université Paris-Cité
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Gastroenterology



Justo CASTAÑO

IMIBIC-Maimónides Institute for
Biomedical Research of Córdoba-
University of Cordoba, Spain
Molecular Biology

Tonight's agenda

Moderator: Margot TESSELAAR, (NED)

- | | |
|---------------|---|
| 18:00 – 18:05 | Opening comments – Margot TESSELAAR (NED) |
| 18:05 – 18:20 | Does NET/NEC transformation exist? – Halfdan SORBYE (NOR) |
| 18:20 – 18:35 | Increased grading over time (justify re-biopsy) – Louis DE MESTIER (FRA) |
| 18:35 – 18:50 | Role of therapeutic pressure – Justo CASTAÑO (ESP) |
| 18:50 – 19:05 | Panel discussion |
| 19:05 – 19:10 | Closing comments – Margot TESSELAAR (NED) |

Does NET/NEC transformation exist?

Halfdan Sorbye

Medical Oncologist, Professor
Cancer Clinic, Bergen, Norway

DISCLOSURE INFORMATION

Receipt of honoraria or consultation fees:

- Ipsen
- Advanced Accelerator
- BMS
- Pierre Fabre
- SAM Nordic
- Hutchinson
- Daiichi Sankyo

NET and NEC

NET and NEC are distinct tumours with different genetic profiles.

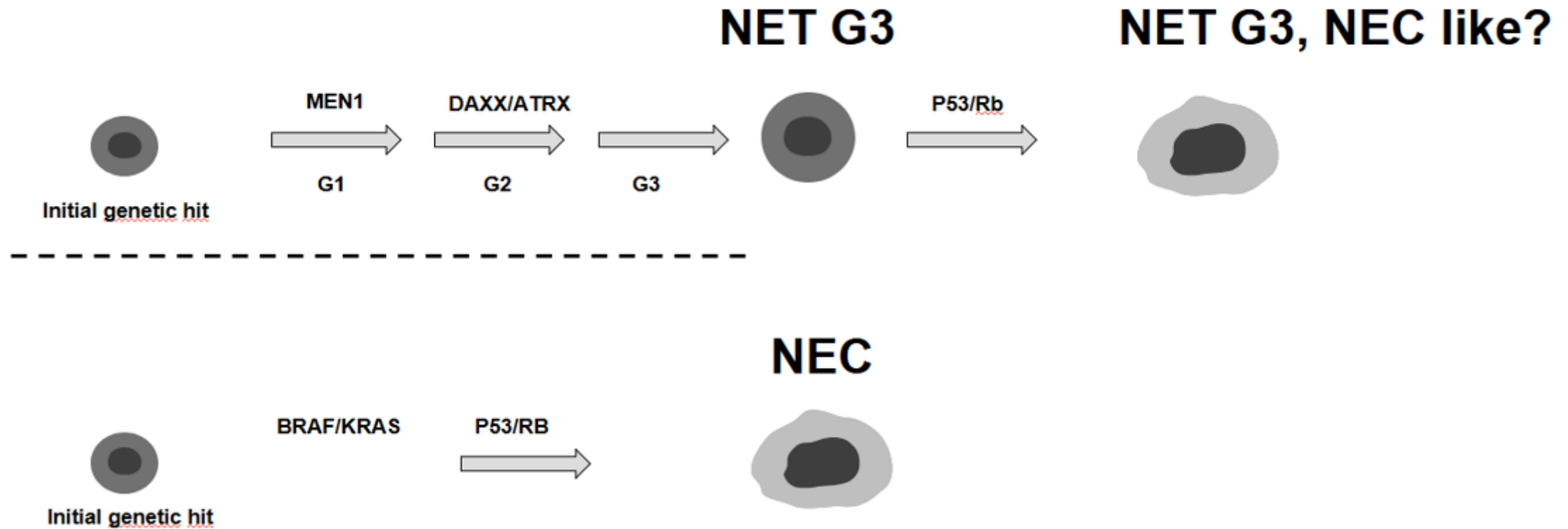
NEC: driver mutations of adenocarcinomas and co-alteration of *TP53* and *RB1*.

NET genetics are site-dependent, alterations in *MEN1*, *ATRX*, *DAXX*, and *TSC1/2* in pancreatic NET.

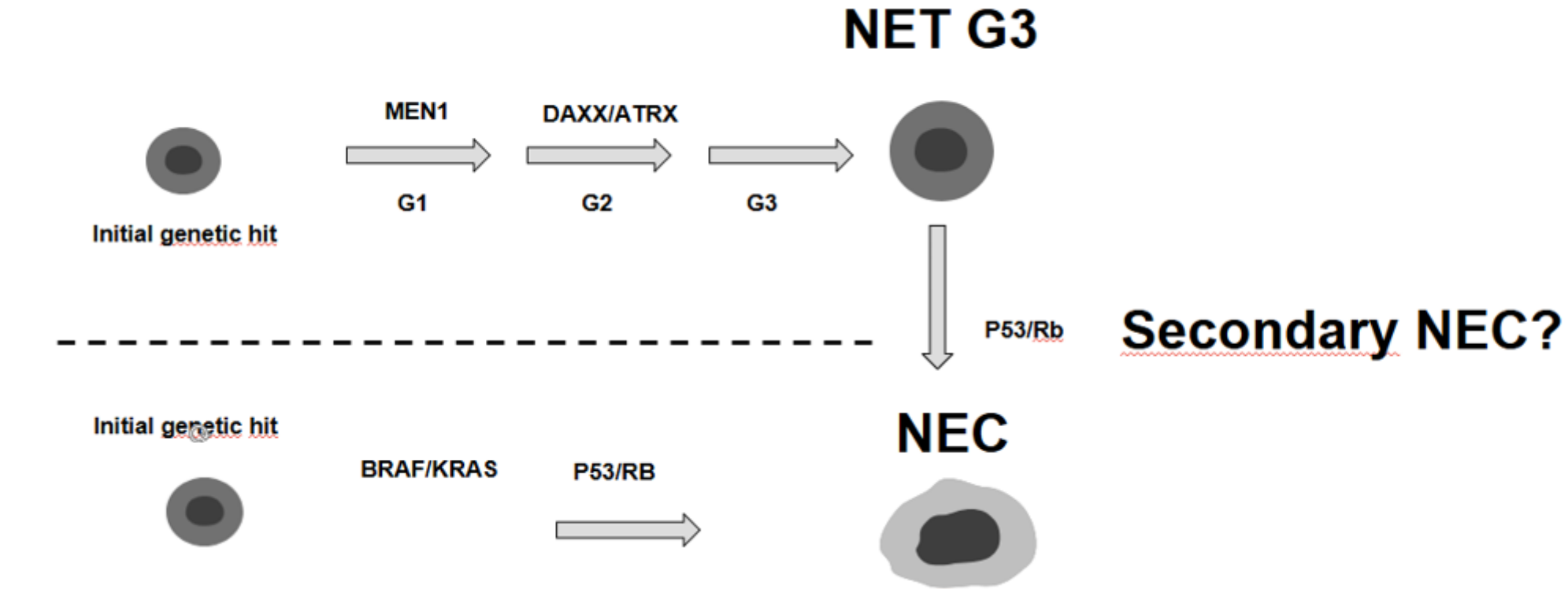
TP53 and *RB1* alterations rare in NET, however up to 35% of NET G3.

Progression from NET to NEC is debated and is not well described.

Concept of NEN G3, based on cell of origin



Integrative concept for NEN G3, gray zone



Nomenclature NET to NEC

Transformed NEC

Secondary NEC

NET with NEC-like features

NET G3 with TP53 mutations

NET with NEC-like transformation

Well-Differentiated Neuroendocrine Tumors with a Morphologically Apparent High-Grade Component: A Pathway Distinct from Poorly Differentiated Neuroendocrine Carcinomas ✓

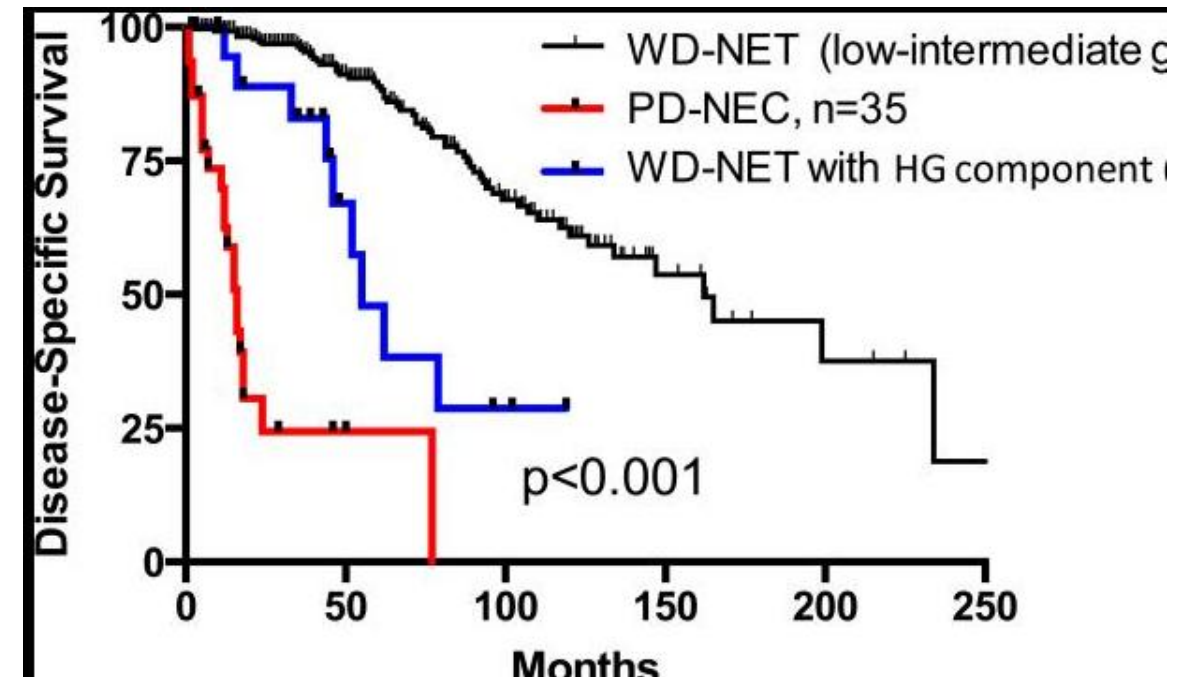
Laura H. Tang ✉; Brian R. Untch; Diane L. Reidy; Eileen O'Reilly; Deepti Dhall; Lily Jih; Olca Basturk; Peter J. Allen;

Controversial in 2016: The primary can consist of both a NET and a NEC like part. Most NEC come from a NET?

31 NET component of high-grade NEC

The high-grade component had sometimes histologic overlaps with large-cell NEC.
No TP53 alterations

The prognosis remained good, closer to NET, far better than purely high-grade NEC.



Tang LH, Clin Cancer Res 2016, 22:1011–7.

22 year. Resected 2009 panNET Ki-67 10%, liver metastases
TEMCAP in 2010 with PR. SSA maintenance. SRI neg
2015 suddenly single liver progression; LC-NEC Ki-67 80%, MI 20

Initial liver metastasis: MSS without gene alterations

New metastasis: MSI+ many mutations e.g MEN1, TP53. Temozolomide induced?

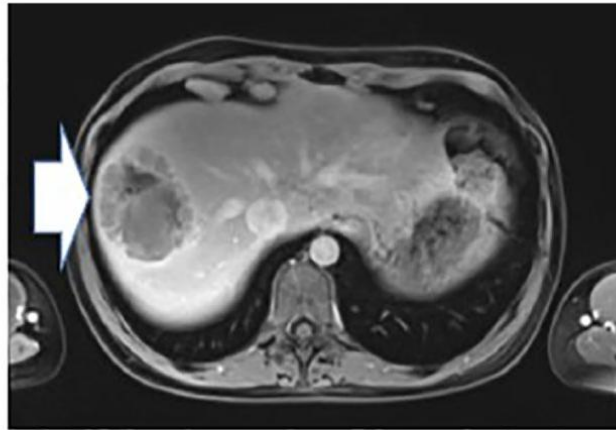
Liver surgery – no recurrence after 45 m.

A



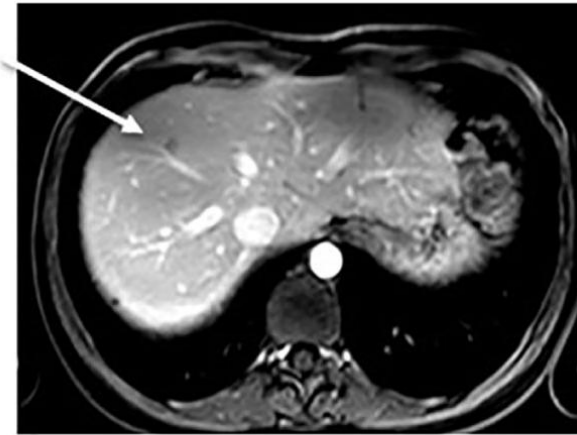
November 2010

B



March 2016

C

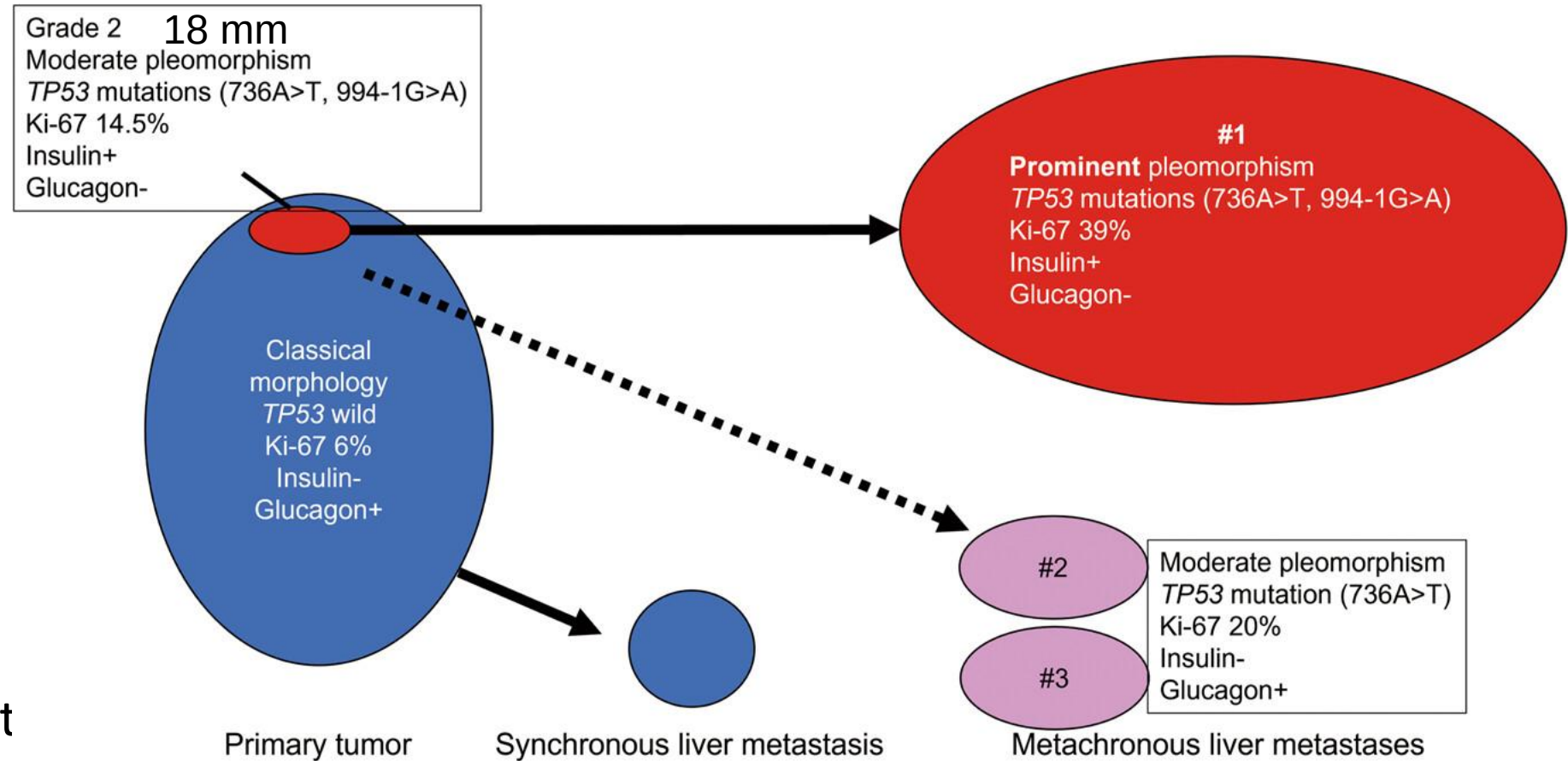


18FDG-PET

Raoul JL: Front Oncol 2021: 11:646992

High-grade transformation of pancreatic neuroendocrine tumor associated with *TP53* mutations: A diagnostic pitfall mimicking neuroendocrine carcinoma

52-year man
Surgery of panNET + liver met.
2 y liver recurrence
NET like morphology
ATX mutations
NET G3 with Tp53mut



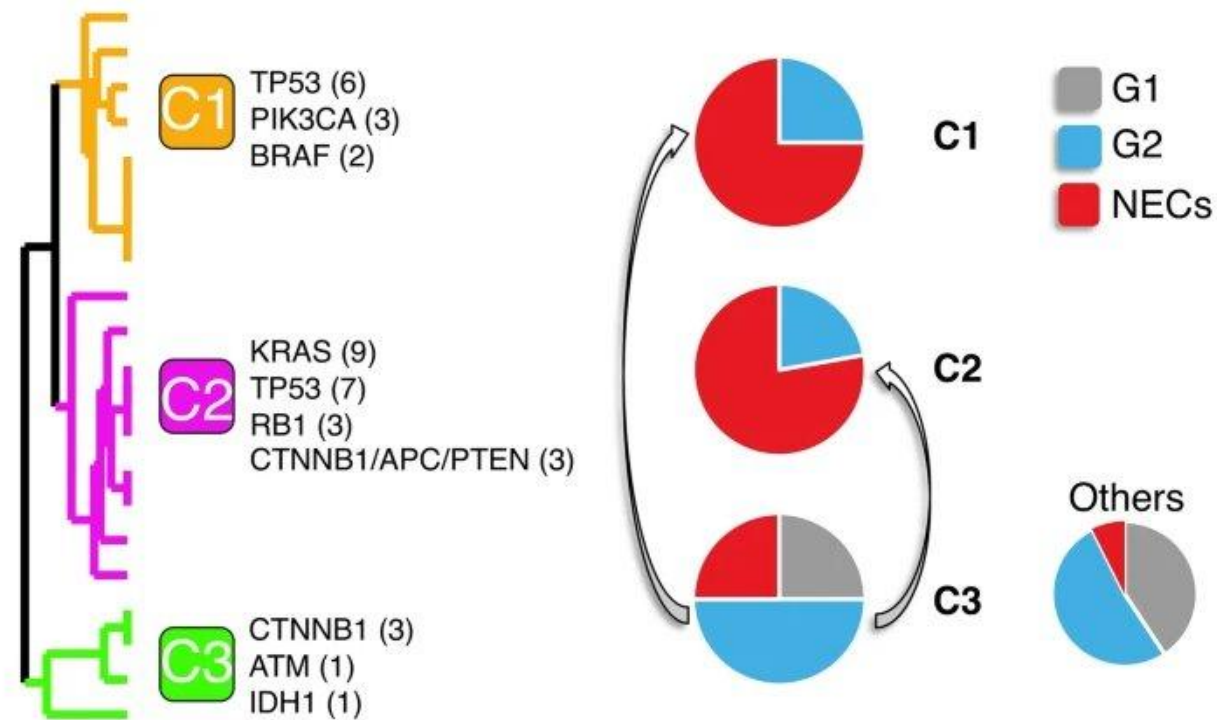
Tanaka M: Pathology Int 2021; 1-8

A Subset of Large Cell Neuroendocrine Carcinomas in the Gastroenteropancreatic Tract May Evolve from Pre-existing Well-Differentiated Neuroendocrine Tumors

Giuseppe Pelosi ^{# 1 2}, Fabrizio Bianchi ^{# 3}, Elisa Dama ³, Jasna Metovic ⁴, Marco Barella ⁵, Angelica Sonzogni ⁶, Adriana Albini ⁷, Mauro Papotti ⁴, Yulan Gong ⁸, Namrata Vijayvergia ⁹

48 GEP-NEN cases, 13 pancreatic.

Fig. 3



Relationship between clusters and tumor composition (C1→C3). Pie charts indicate the distribution of different tumor types in the clusters, which are positioned according to the clustering tree shown on the left of picture with the corresponding gene alterations (the numbers in brackets correspond to mutation burden). APC (APC regulator of WNT signaling

Transformation of G1-G2 neuroendocrine tumors to neuroendocrine carcinomas following peptide receptor radionuclide therapy

Igryl S Cordero-Hernandez ¹, Alicia C Ross ¹, Arvind Dasari ¹, Daniel M Halperin ¹, Beth Chasen ², James C Yao ¹

We have all seen NET patients with rapid disease progression some time after PRRT.

152 NET G1-2 treated with PRRT.

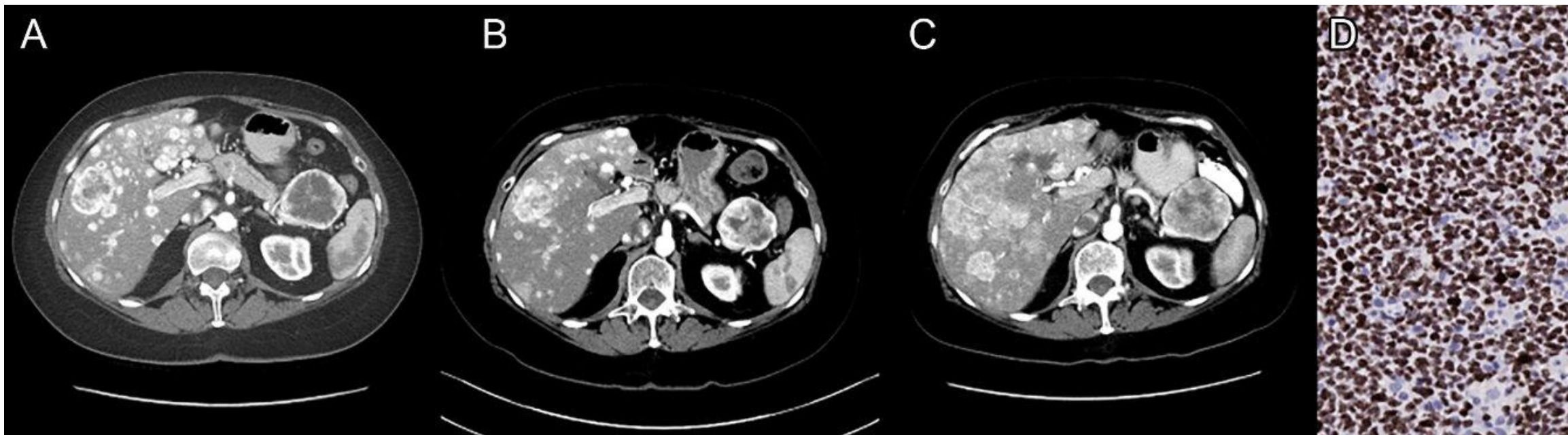
7 cases transformed from NET to NEC, all poorly differentiated. One small-cell case

Median time from start of PRRT to transformation 8 m.

All pancreatic tail cases and all prior Temozolomide treatment.

OS from transformation only 3.3 months (6 given platinum/eto, usually 10-11 months).

NGS: TP53 and/or ATM mutations. Two with ATRX mutations



(A) CT prior to PRRT

(B) CT at completion of PRRT

(C) Repeat CT abdomen 5 months after PRRT

(D) Liver biopsy confirmed poorly differentiated neuroendocrine carcinoma with high Ki-67

Progression of Low-Grade Neuroendocrine Tumors (NET) to High-Grade Neoplasms Harboring the NEC-Like Co-alteration of RB1 and TP53

Nancy M Joseph ¹, Sarah E Umetsu ², Grace E Kim ², Merryl Terry ², Arie Perry ², Emily Bergsland ³, Sanjay Kakar ²

Five low-grade NET progressed to high-grade NEN with co-alteration RB1 and TP53.

Remained well-differentiated in some cases despite RB1/TP53 co-alteration.

Some cases had NEC-like features.

OS 41 m from first metastatic disease and 12 m from acquisition of RB1/TP53 co-alteration.

Low-grade NET can progress via acquisition of TP53 and RB1 alteration, similar to NEC. Whether this represents a transformation from NET to NEC remains unclear.

Rapid Evolution of Metastases in Patients with Treated G3 Neuroendocrine Tumors Associated with NEC-Like Transformation and TP53 Mutation

Atsuko Kasajima ¹, Nicole Pfarr ², Eva-Maria Mayr ², Ayako Ura ², Elisa Moser ²,
Alexander von Werder ³, Abbas Agaimy ^{4 5}, Marianne Pavel ^{6 5}, Günter Klöppel ²

Longitudinal study of 40 metastasised and treated NET G3.

High-grade transformation with NEC-like histology in nine 9 (22%) cases (seven pancreatic).

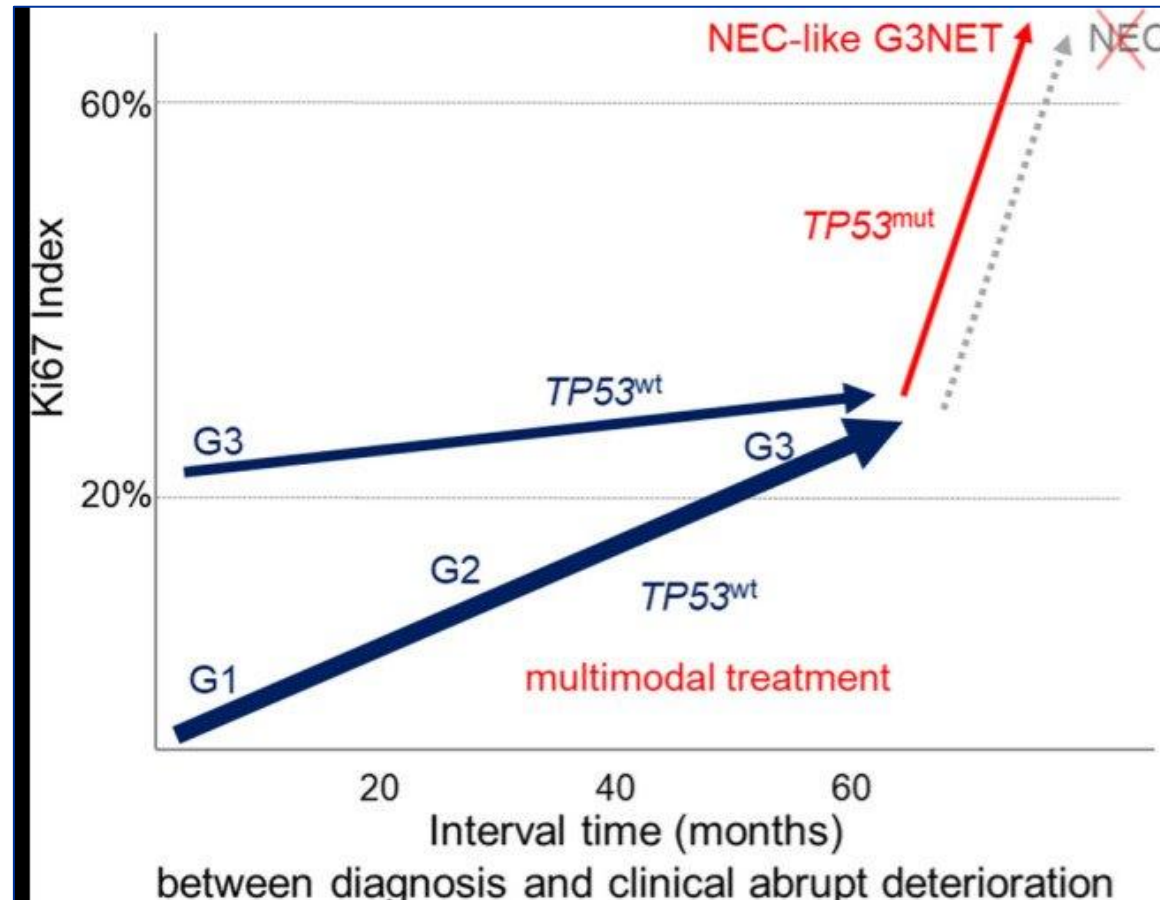
Eight large-cell, one small-cell like histology.

All nine had TP53 (100%), no RB1 mutations.

All retained NET-typical mutations such as MEN1 or DAXX (five of the pancreatic NET).

Last treatments prior to NEC-like transformation PRRT (n = 3), alkylating agents (n = 2).

None cases exhibited a complete transformation to a typical NEC,
tumours retained partial histological and genetic features of NET.



Majority of NET G3 (70%) evolved from NET G1-2, only 30% were primary G3NET (blue). Nine (22%) exhibited abrupt deterioration after a median interval time of 60 months, accompanied by NEC-like transformation and TP53 mutation (red trajectories).

Nomenclature in the upcoming new WHO classification

NET with NEC-like features

Does exist – depends on your re-biopsy strategy.

Due to tumour heterogeneity (present initially) or true transformation? – likely both?

Mainly large-cell morphology

Future research:

Risk factors for transformation?

Primary tumour site relevance

Treatment consequences?

Delay treatment with alkylating chemotherapy and PRRT (NETTER-3)?

Prognosis – subgroups – treatment of transformed cases?

Increased grading over time (justify re-biopsy)

Pr Louis de Mestier, MD PhD

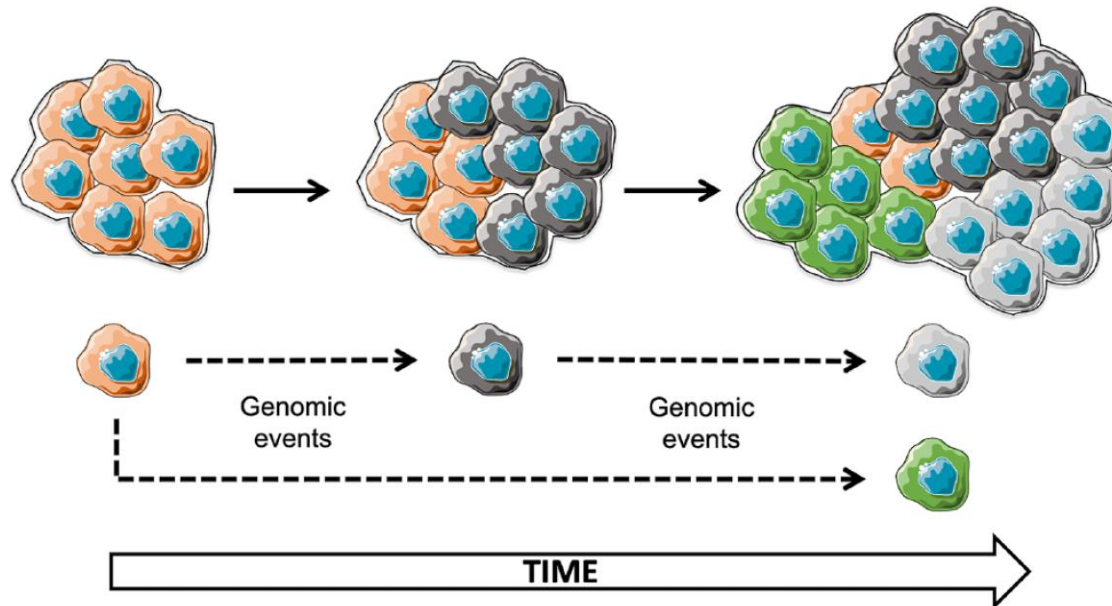
Beaujon Hospital, Université Paris-Cité, France

DISCLOSURE SLIDE

- **Consultancy:** AAA/Novartis, Boehringer-Ingelheim, Esteve, Ipsen, Mayoly, Viatrix
- **Research funding:** Boehringer-Ingelheim, Esteve, Ipsen

Spatial and temporal heterogeneity of NENs

- ✓ NENs are initially monoclonal → progressively polyclonal
- ✓ Different genotypic/phenotypic characteristics → biological and clinical variation over time
- ✓ Ki-67 index, cell morphology, hormone secretion, sensitivity to treatments...

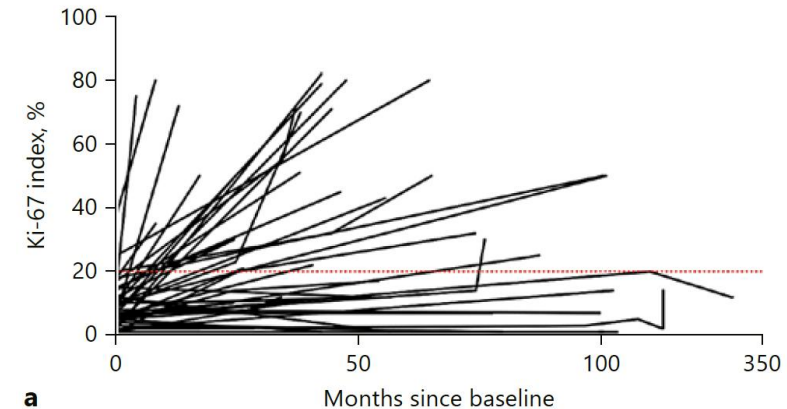


de Mestier et al. Ann Int Med 2015; Crona et al., J Clin Endoc Metabol 2016; Bourdeleau et al., Ther Adv Med Oncol 2023

Increased grading over time is frequent

- ✓ More frequent in PanNETs than other primary NETs
- ✓ More frequent when second sample in a context of clinical progression

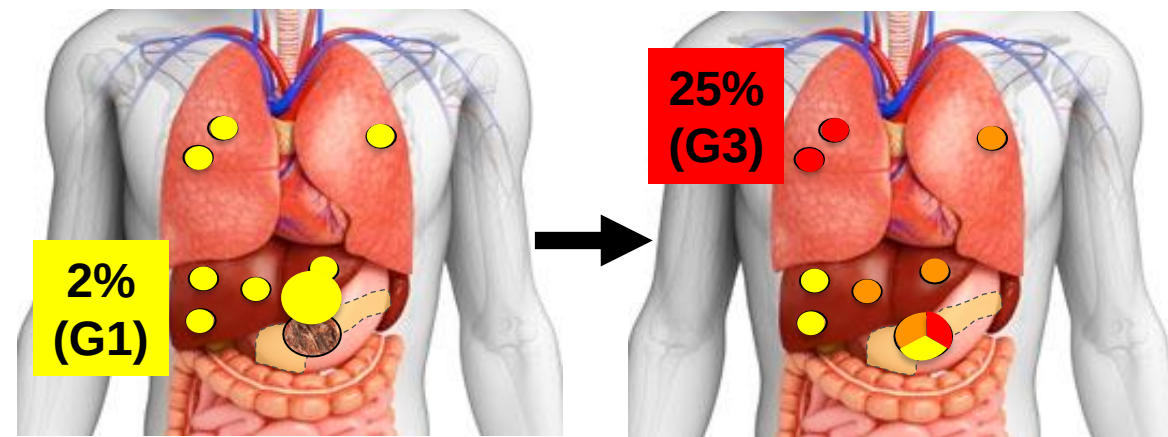
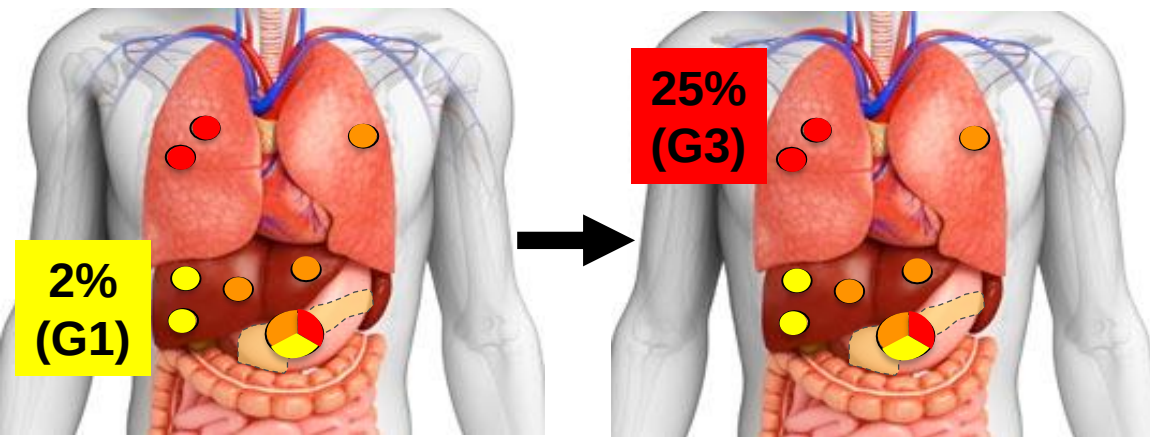
	n	% PanNETs	Time elapsed (y)	Ki-67 increase	Grade increase
Panzuto 2017	43	56%	4.7	65%	33%
Botling 2020	46	100%	3.7	-	58%
Merola 2022	47	43%	3.3	66%	34%
Kasajima 2024	40	55%	2.4	-	65%
Bourdeleau 2025	109	100%	4.1	61%	36%



Panzuto et al., PLoS One 2017; Botling et al., Neuroendocrinology 2020; Merola et al., J Neuroendocrinology 2022; Kasajima et al., Endocrine Pathol 2024; Bourdeleau et al., Endoc Rel Cancer 2025

Why does grading increase over time?

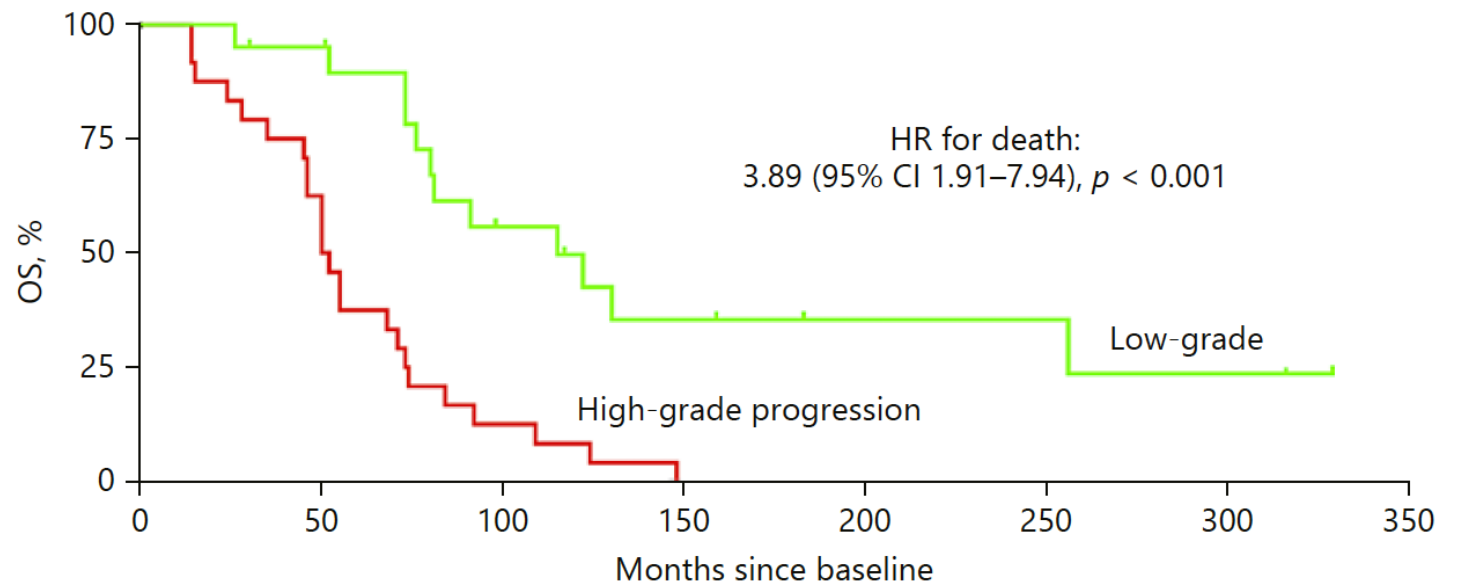
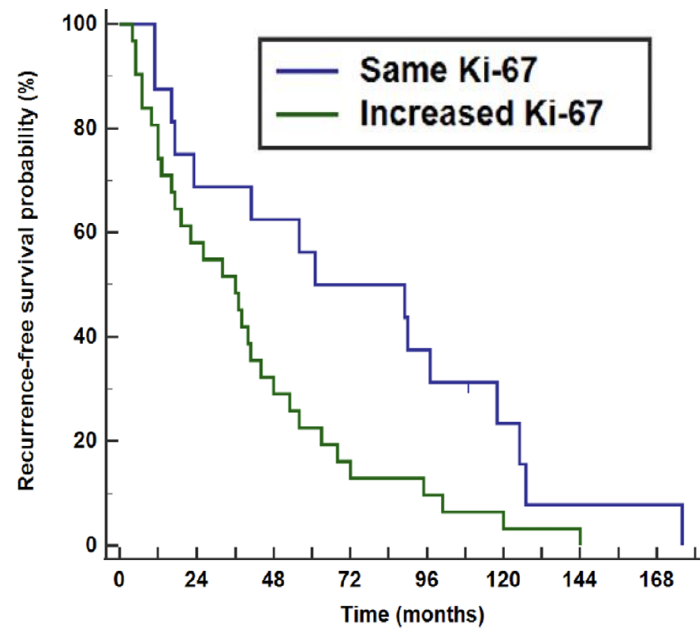
- ✓ **Two main hypotheses (non mutually exclusive):**
 - ✓ Spatial heterogeneity is the main explanation (sampling bias)
 - ✓ Temporal evolution is the main explanation
- ✓ Hard to dissociate as one lesion is resected only once and is rarely biopsied repeatedly



Bourdeleau et al., Ther Adv Med Oncol 2023

Increased grading over time impacts prognosis

- ✓ Both heterogeneities coexist, but temporal evolution might be the main driver
 - ✓ Increased Ki-67 and/or grade has prognostic impact
 - ✓ Tumour grading is prognostic at any time → high-grade (G3) progression strongly impacts prognosis



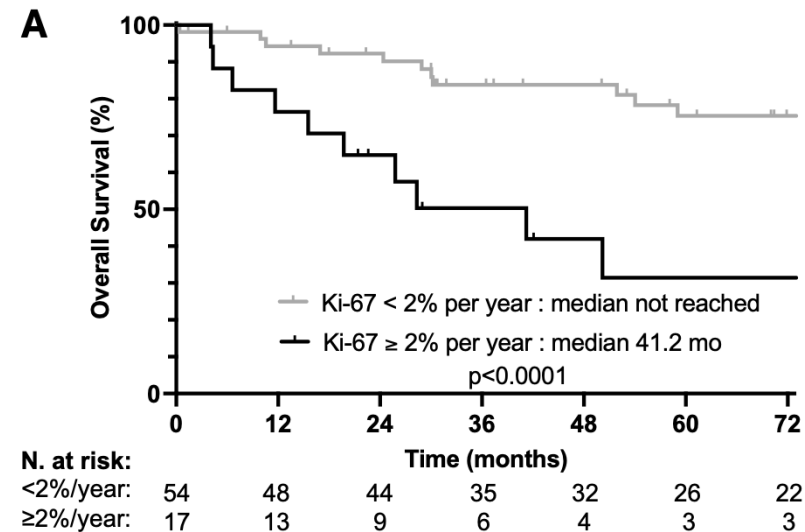
Botling et al., Neuroendocrinology 2020; Merola et al., J Neuroendocrinology 2022; Bourdeleau et al., Endoc Rel Cancer 2025

Increased grading over time impacts prognosis

- ✓ Grade increase is more frequent in case of progression, but both have independent prognostic impact

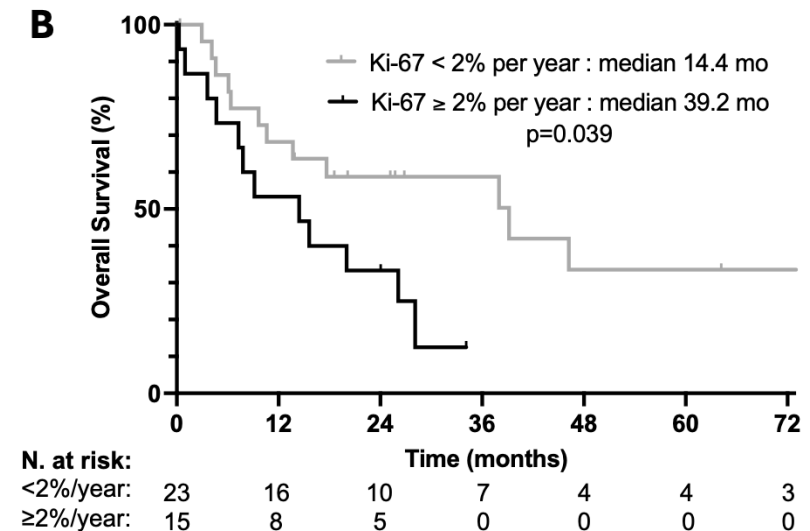
If last sample is a surgical sample

Median delta Ki-67 +1%



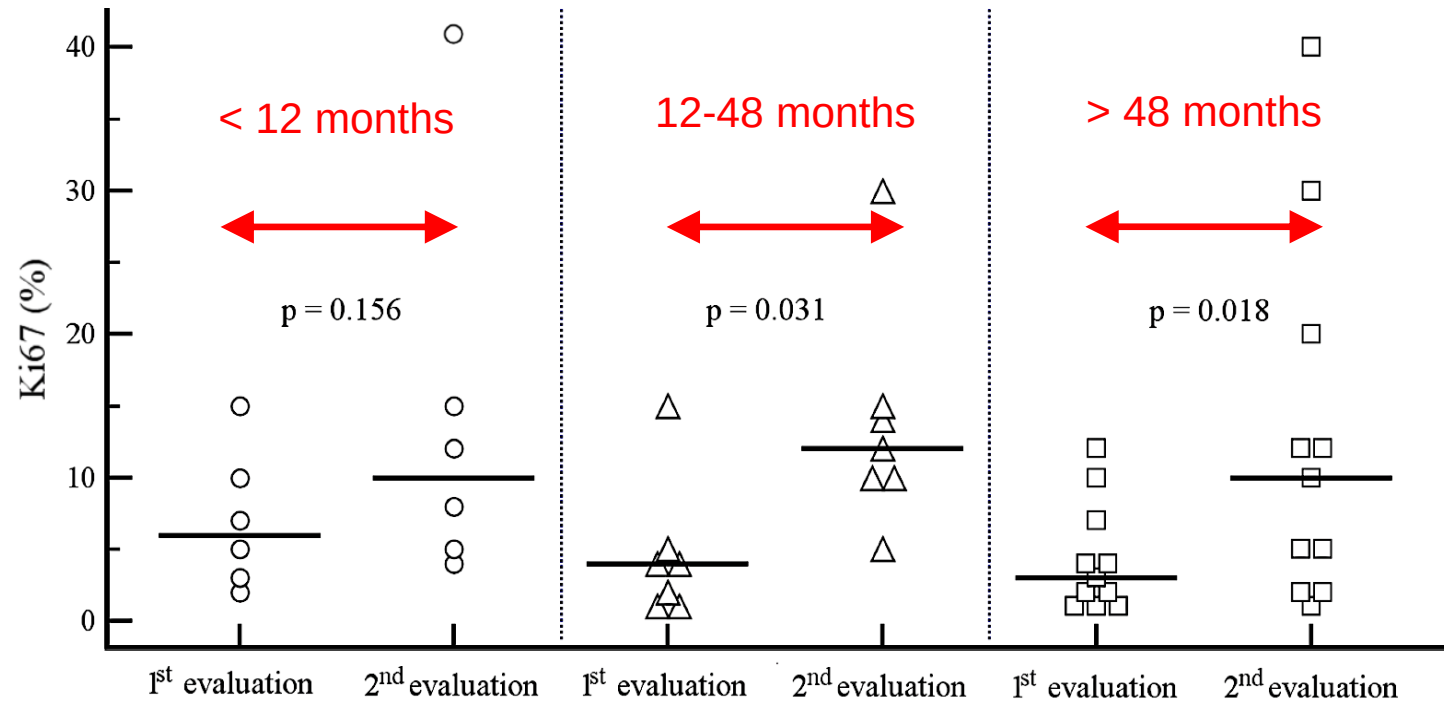
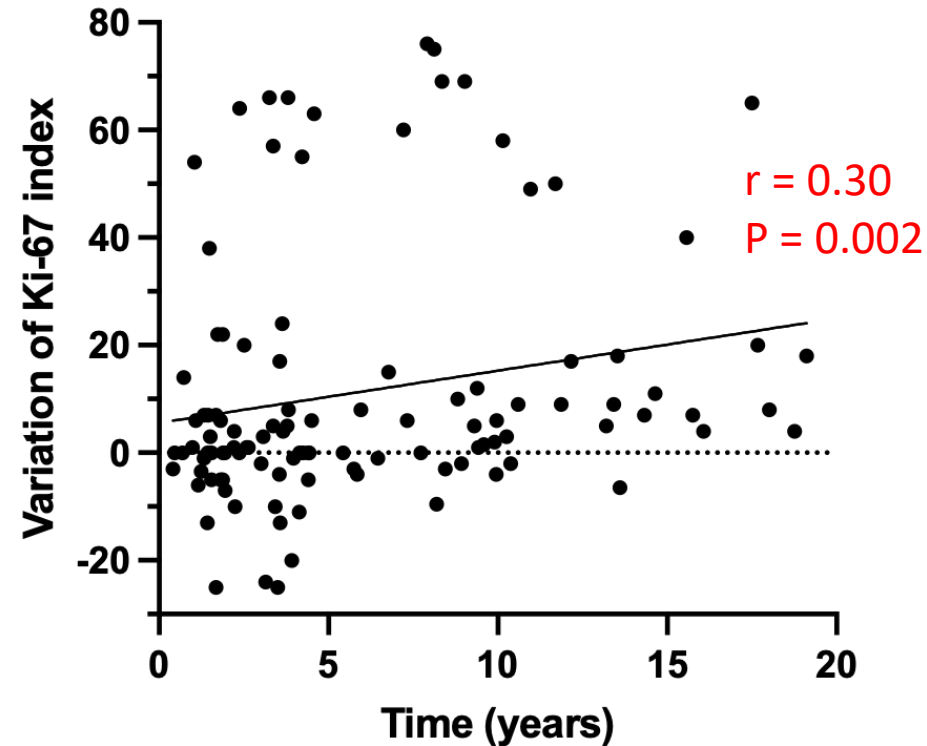
If last sample is a biopsy in context of progression)

Median delta Ki-67 +7.5%



Bourdeleau et al., Endoc Rel Cancer 2025

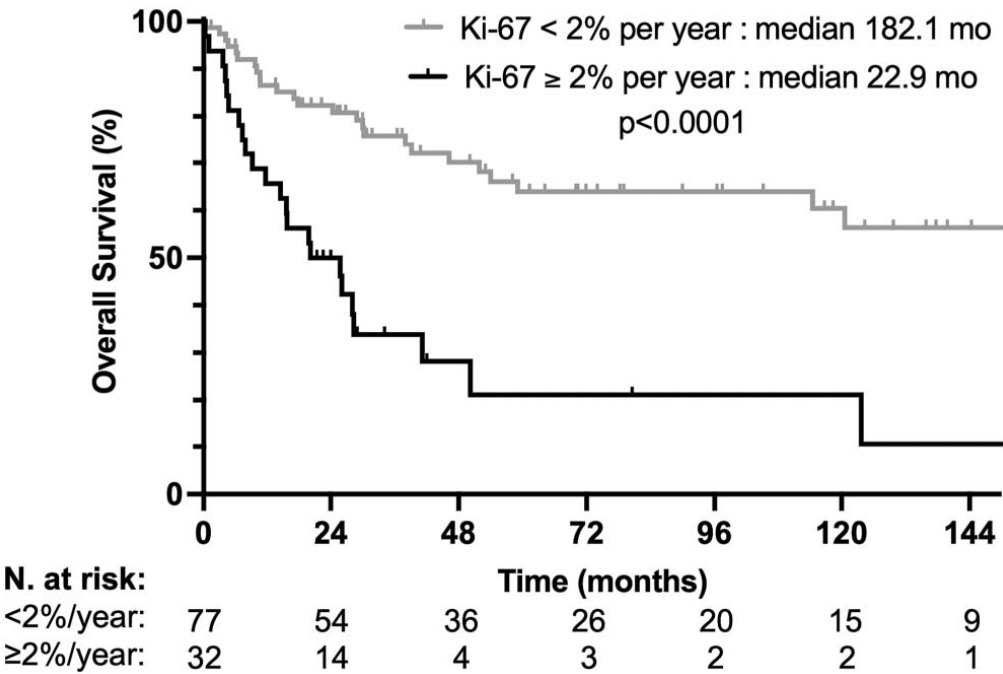
Increased grading over time is time-dependent



✓ Hence, the impact of temporal heterogeneity might be > spatial heterogeneity

Panzuto et al., PLoS One 2017; Kasajima et al., Endocrine Pathol 2024; Bourdeleau et al., Endoc Rel Cancer 2025

Variation of proliferation: acceleration > increase



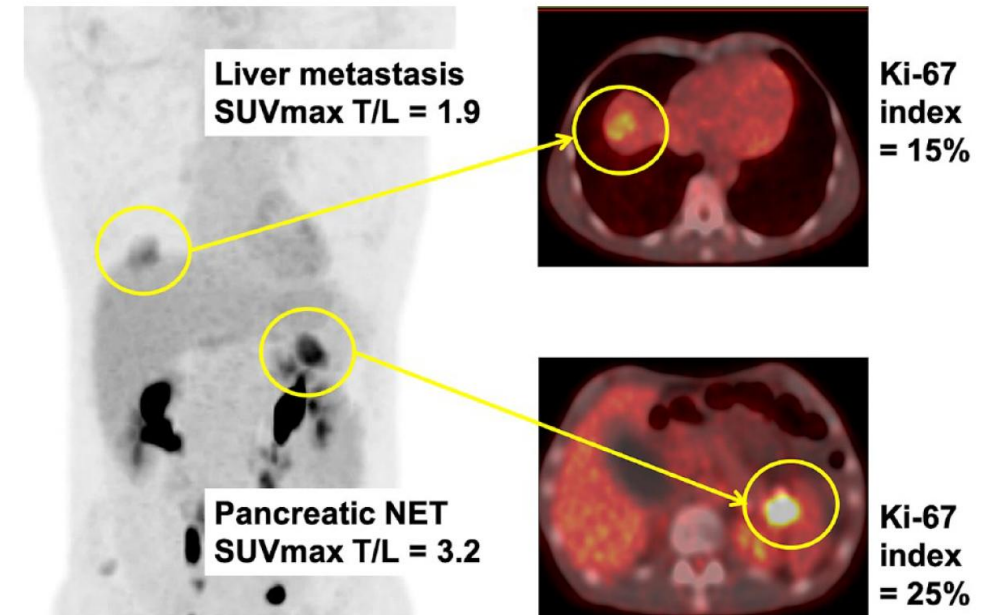
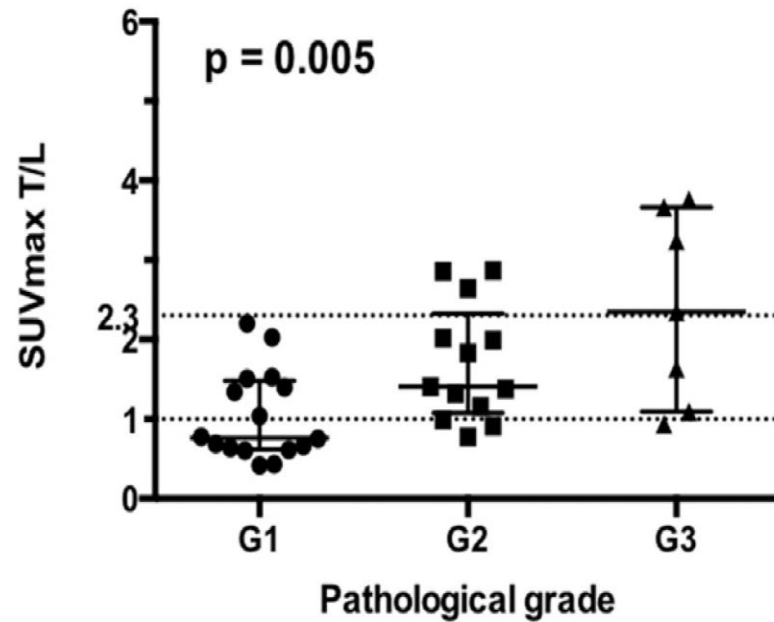
Multivariable Cox (n=97)	HR	95% CI	p-value
Female sex	0.51	0.27 – 0.95	0.034
Worsening of PS	4.58	2.30 – 9.09	<0.001
Liver involvement > 25% at Smax	3.68	1.81 – 7.66	<0.001
Variation of Ki-67 ≥ 2%/year	1.95	1.02 – 3.72	0.042

✓ Again, the impact of temporal heterogeneity may be > spatial heterogeneity

Bourdeleau et al., Endoc Rel Cancer 2025

What lesion to rebiopsy?

- ✓ Usually, most easily accessible or sometimes guided by morpho. progression
- ✓ ^{18}F FDG-PET is a whole-body exam → can show spatial heterogeneity
- ✓ ^{18}F FDG uptake on PET/CT is correlated with Ki-67 ($r=0.55$, $p<0.001$)
- ✓ Hence ^{18}F FDG-PET can be relevant at guiding biopsies



de Mestier et al., Dig Liv Dis 2019; Bourdeleau et al., Ther Adv Med Oncol 2023

Why does grading increases over time?

✓ Impact of treatments received between the two samples

- 1 treatment: OR = 2.3 (p=0.41)
- 2 treatments: OR = 7 (p=0.099)
- 3 treatments: OR = 14 (p=0.055)



✓ Impact of specific treatments

- Alkylating agents: yes +++
- SST analogues: no (slow evolution and prolonged PFS → biological stability?)
- Other chemo: maybe
- PRRT: maybe

Table 4 Multivariable logistic regression model of factors associated with Ki-67 increase $\geq 2\%$ /year between S0 and Smax. Area under the ROC curve: 0.78 (95% CI, 0.68–0.88), $P < 0.0001$.

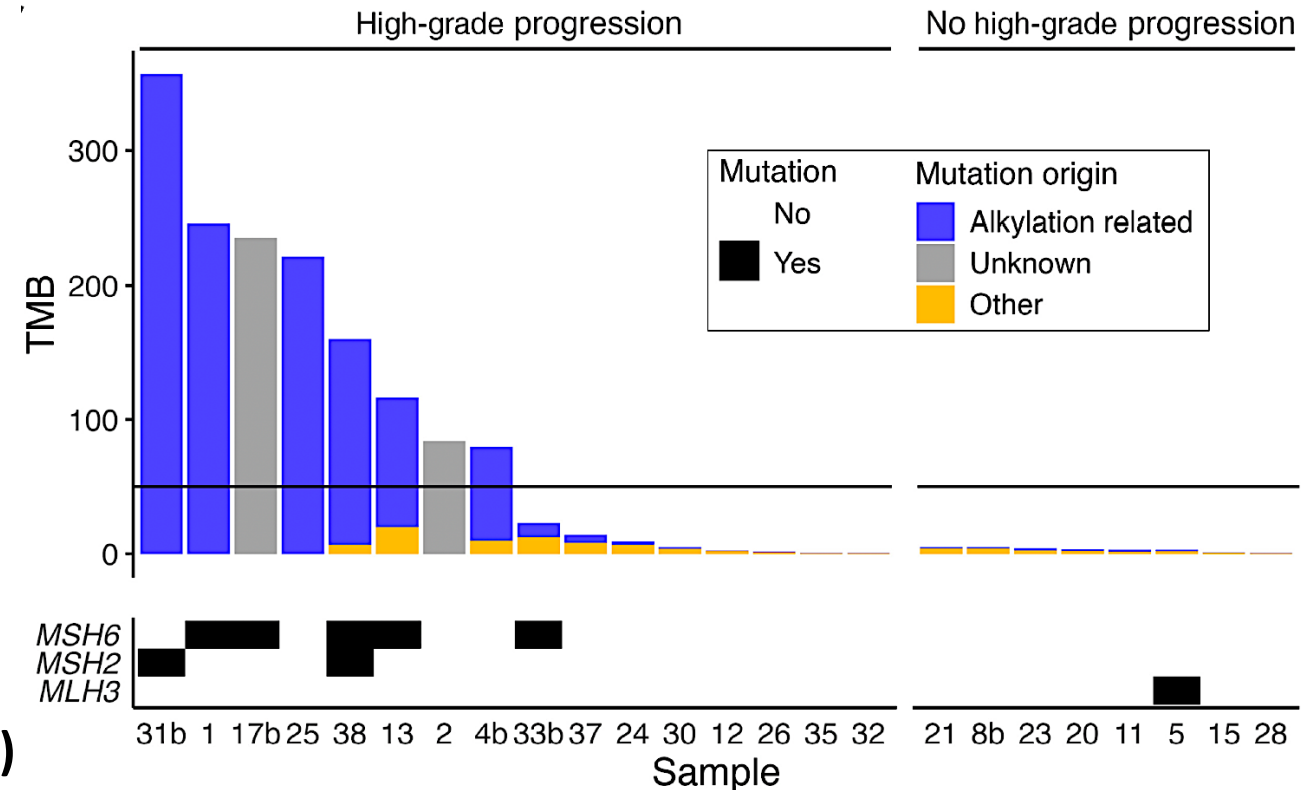
<i>n</i> = 93	OR	95% CI	<i>P</i> -value
Worsening of performance status*	1.17	0.33–3.98	0.80
Metastatic stage at S0	3.25	0.93–13.28	0.079
Increasing liver metastatic involvement*	3.92	1.28–13.18	0.021
Tumour control under SST analogues	0.27	0.08–0.82	0.027
Alkylating agents	4.47	1.48–15.38	0.011

*Variations between S0 and Smax.

Botling et al., Neuroendocrinology 2020; Bourdeleau et al., Endoc Rel Cancer 2025

Alkylating agents promote grade progression

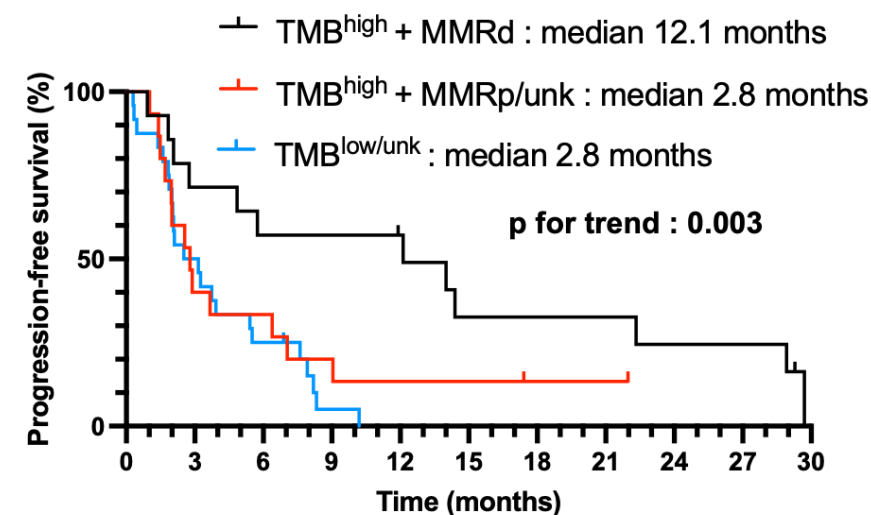
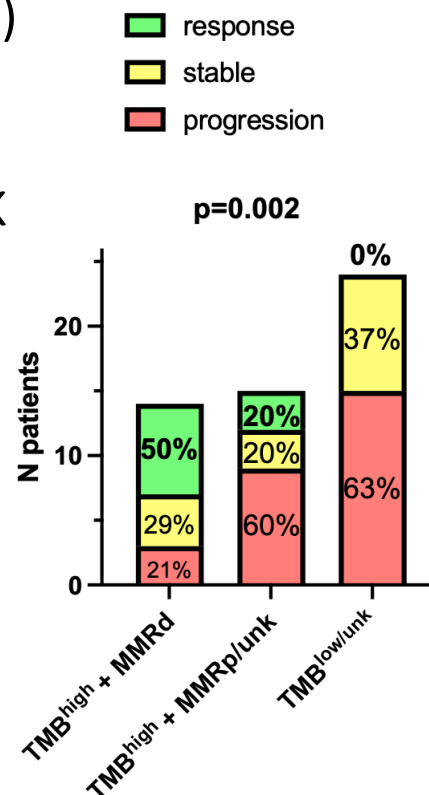
- Acquisition of a hypermutator phenotype (increase in TMB)
- Increase in the SBS11 (C>T) signature
- Frequent alterations of the MMR genes, but without MSI phenotype
- Through chemo-induced mutagenicity and/or clonal selection
- **Candidate for ICI ? (suggested in colon cancer)**



de Mestier et al., ENETS 2024; Backman et al., J Pathol 2024

Application: efficacy of immunotherapy in patients with PanNETs and post-alkylating MMR deficiency

- Retrospective international study (n=53 pts)
 - Pretreated metastatic wd-PanNETs
 - 4 previous lines (incl. 13 cycles of ALK)
 - 28% G3 at before ALK → 51% after ALK
- ICI : mostly ipilimumab + nivolumab (64%)
 - Median 5 cycles, well tolerated
 - Median PFS was 3.3 months
 - ORR was 19%
- Impact of TMB high (>10 mut/Mb)
- Higher impact of MMRd (NGS/IHC)



de Mestier et al., ENETS 2025

Key messages

- Frequent (PanNETs+++): $\approx 40\%$ after 4-5 years of follow-up
- Happens during clinical progression... but not only !!
- Prognostic impact (high-grade progression and/or Ki-67 $\geq +2\%/year$)
- Why? Mostly explained by temporal evolution $\pm$ spatial heterogeneity
- Promoted by alkylating agents: relative risk $\approx 4-9$

For clinical practice

- Rebiopsy often, do not take decisions on “old” pathological data
- FDG-PET-guided biopsies may be preferred than most accessible lesion
- Up-to-date prognostic evaluation
- Chance to identify targetable molecular abnormality (e.g., post-ALK TMBhigh + MMRd)

Main perspective

- Liquid biopsy ++++++

Change in grade and differentiation: what do we learn for patient management?

ROLE OF THERAPEUTIC PRESSURE

Justo P. Castaño

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University of Córdoba

Reina Sofía University Hospital

CiberObn

Córdoba. Spain



ciberobn



DISCLOSURE INFORMATION

Type of affiliation / financial interest

Name of commercial company

Receipt of grants/research supports:

IPSEN

Receipt of honoraria or consultation fees:

Endocrine Oncology Editor in Chief (Bioscientifica)

Speaker fees or travel support:

IPSEN, ADACAP (Novartis), Medscape (prIME Oncology)

Outline

- The question: does therapeutic pressure *drive* NEN progression?
- Early evidence and profound experience in other cancers: lung and prostate
- **The Context: Is there any support for a role of treatment in NEN progression?**
- Scant evidence for mixed NET-NEC phenotypes
- Limited support for treatment-induced progression or NET-NEC lineage plasticity
- **Recent evidence of chemotherapy inducing dMMR, hypermutation, and NET progression**
- Conclusions

The question: does treatment drive progression?

- Evidence: Obviously, progression occurs in the absence of treatment
- Incomplete knowledge → NENs natural history, tumour biology & evolution
NETs <-> NECs; cell(s) of origin; mechanisms of progression
- Emerging evidence → (certain) treatments can influence tumour progression through a selective pressure of therapies: *Trigger? Facilitate? Catalyse? Accelerate?*
- Let's refine the question:
 - Does treatment cause NET progression G1->G2->G3?
 - Does treatment cause histology transformation NET → NEC ?
- This problem → still poorly known in NETs
- BUT: compelling evidence + large experience in *lung and prostate* cancers

Early evidence and experience in other cancers: *lung and prostate*



Original evidence ~ 2006 NEJM SCLC

EGFR Mutations in Small-Cell Lung Cancers in Patients Who Have Never Smoked

Maureen F. Zakowski, M.D.
Marc Ladanyi, M.D.
Mark G. Kris, M.D.

Published July 13, 2006 | N Engl J Med 2006;355:213-215 | DOI: 10.1056/NEJM

unclear whether our patient originally had a combination of non-small-cell lung cancer and small-cell lung cancer or whether the non-small-cell lung cancer transdifferentiated to small-cell lung cancer after prolonged treatment with erlotinib. Nevertheless, the combined data suggest that EGFR mutations are a recurrent alteration in small-cell lung cancer that arises in patients who have never smoked; the prevalence of the mutations warrants further study.

Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors

Lecia V. Sequist *et al.*
Sci Transl Med 3, 75ra26 (2011)

A

Histology	Adeno	Adeno	Adeno
Genotype	L858R TP53	L858R TP53 T790M	L858R TP53
EGFR TKI status	Sensitive	Resistant	Sensitive
Tumor burden			
Treatment	Chemo	Erlotinib	Chemo
Timeline	2007	2008	2009

B

Histology	Adeno	SCLC	Adeno	SCLC
Genotype	L858R	L858R PIK3CA	L858R	L858R PIK3CA
EGFR TKI status	Sensitive	Resistant	Sensitive	Resistant
Tumor burden				
Treatment	Erlotinib	C+RT	Erlotinib	C+RT
Timeline	2008	2009	2010	

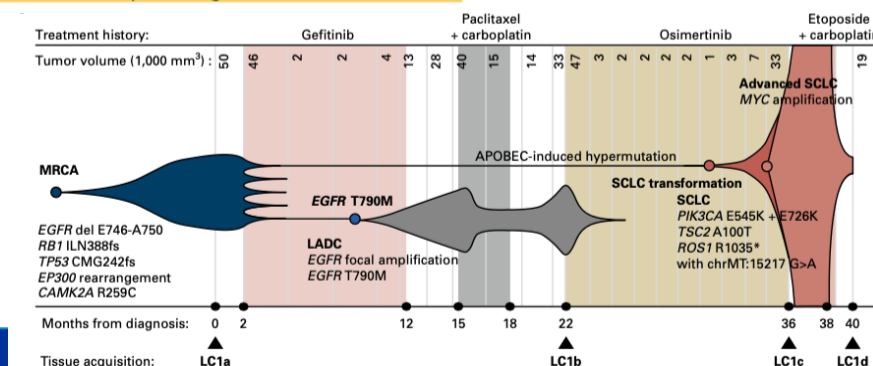
Clonal History and Genetic Predictors of Transformation Into Small-Cell Carcinomas From Lung Adenocarcinomas

June-Koo Lee, Junehawk Lee, Sehui Kim, Soyeon Kim, Jeonghwan Youk, Seongyeol Park, Yohan An, Bhumsuk Keam, Dong-Wan Kim, Dae Seog Heo, Young Tae Kim, Jin-Soo Kim, Se Hyun Kim, Jong Seok Lee, Se-Hoon Lee, Keunchil Park, Ja-Lok Ku, Yoon Kyung Jeon, Doo Hyun Chung, Peter J. Park, Joon Kim, Tae Min Kim, and Young Seok Ju

J Clin Oncol 35. © 2017

Conclusion

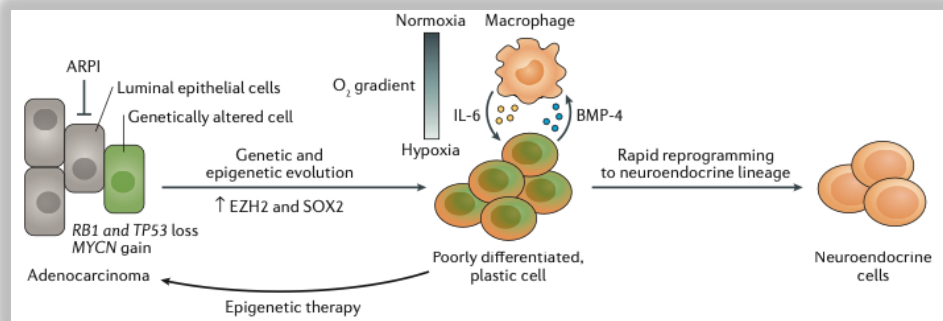
EGFR TKI-resistant SCLCs are branched out early from the LADC clones that harbor completely inactivated *RB1* and *TP53*. The evaluation of *RB1* and *TP53* status in EGFR TKI-treated LADCs is informative in predicting small-cell transformation.



Cellular plasticity and the neuroendocrine phenotype in prostate cancer

NATURE REVIEWS | UROLOGY

Alastair H. Davies^{1,2}, Himisha Beltran³ and Amina Zoubeidi^{1,2}



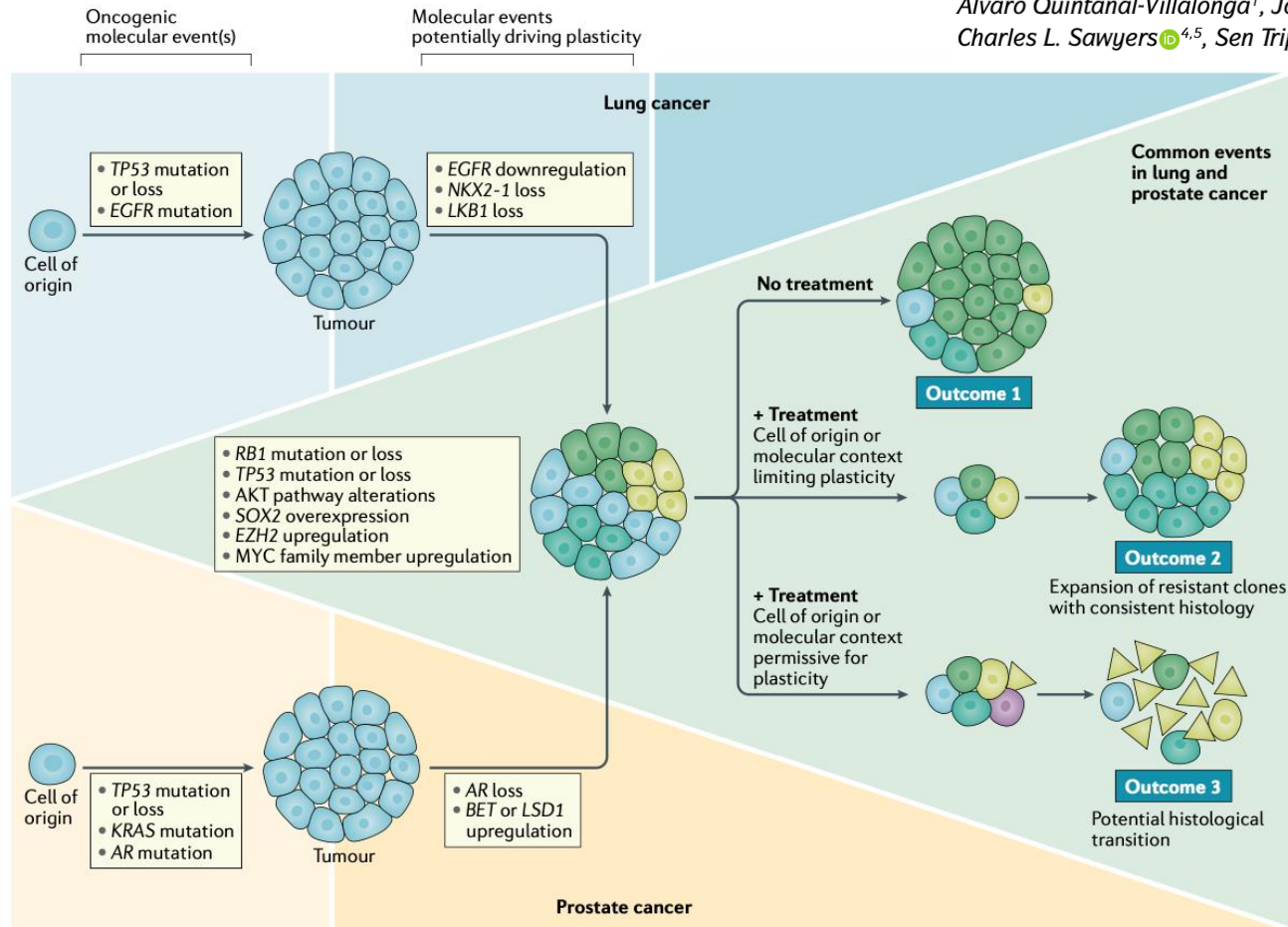
Compelling evidence and large experience in other cancers: *lung and prostate*

Lineage plasticity in cancer: a shared pathway of therapeutic resistance

NATURE REVIEWS | CLINICAL ONCOLOGY

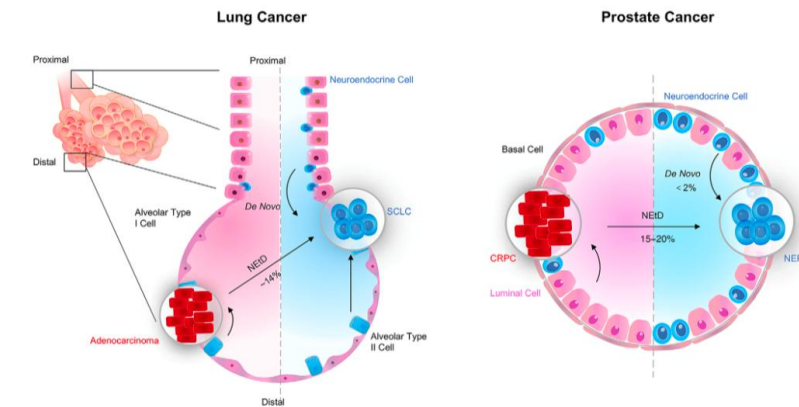
Álvaro Quintanal-Villalonga¹, Joseph M. Chan^{1,2,3}, Helena A. Yu¹, Dana Pe'er^{2,3}, Charles L. Sawyers^{4,5}, Sen Tripathy¹ and Charles M. Rudin¹

MedComm
Open Access



Neuroendocrine transdifferentiation in human cancer: molecular mechanisms and therapeutic targets

Jun Jiang^{1,2,#} | Donghui Han^{1,#} | Jiawei Wang³ | Weihong Wen^{4,*} | Rui Zhang^{5,*} | Weijun Qin^{1,*}



Revealing neuroendocrine transformation in gynecological cancers through genomic analysis

npj | precision oncology

Check for updates

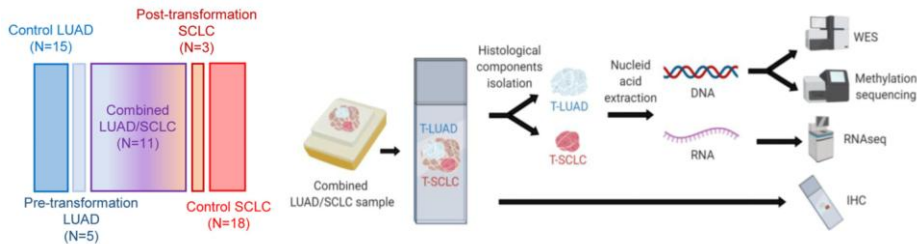
Ann Oluloro¹, David L. Wells², Charles K. Childers², Tiffany Luu¹, Keith D. Eaton^{3,4}, Renata R. Urban¹, Eric Q. Konnick², Vera A. Paulson² & Kalyan Banda^{3,4}

Compelling evidence and large experience in other cancers: *lung and prostate*

Multi-omic analysis of lung tumors defines pathways activated in neuroendocrine transformation

Cancer Discov. 2021

Alvaro Quintanal-Villalonga^{1,*}, Hirokazu Taniguchi¹, Yingqian A. Zhan², Maysun M. Hasan³,

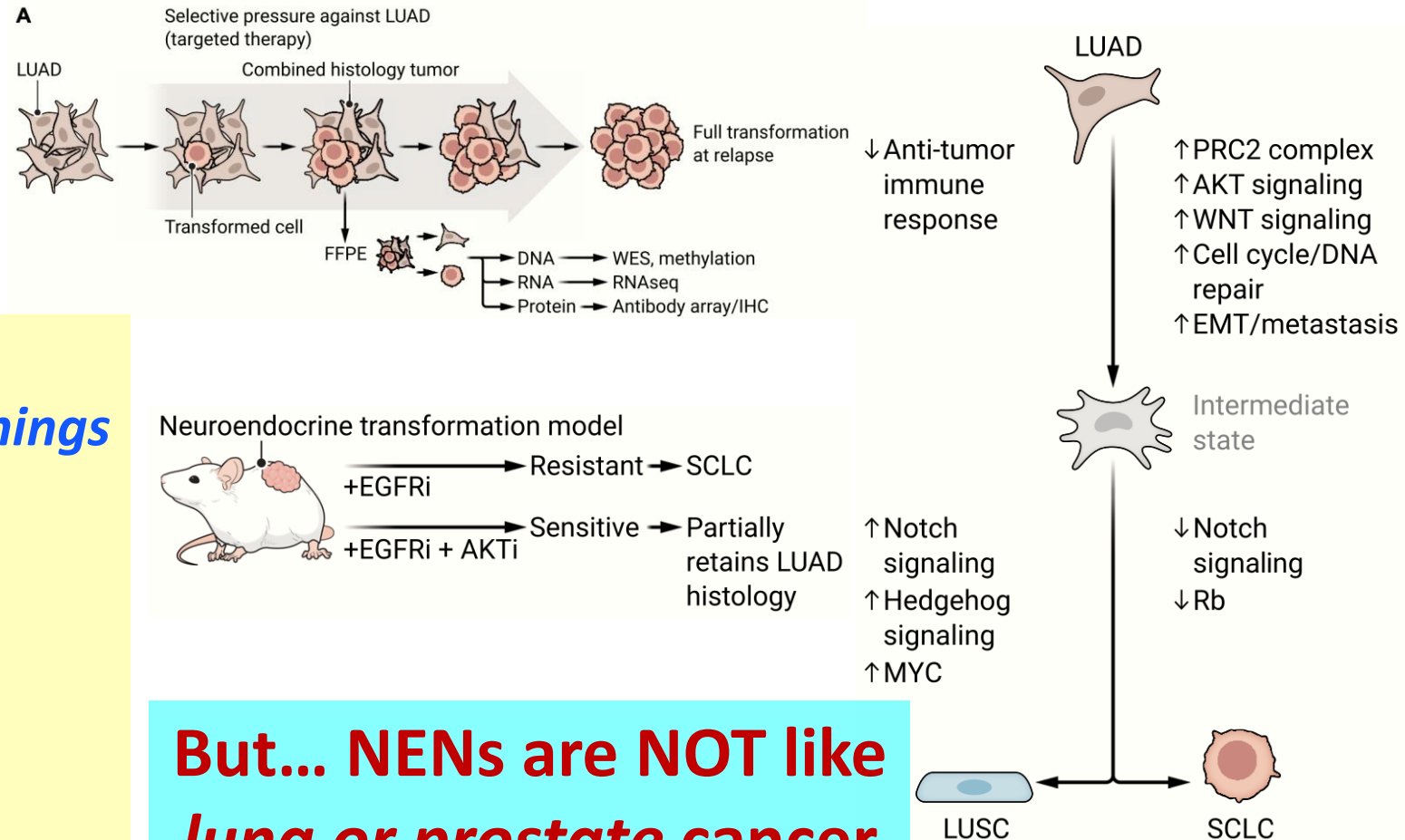


Define:

- **Molecular underpinnings**
- **Signalling pathways**
- **Cell types involved**
- **Mechanisms**
- **Lineage plasticity**
- **Transdifferentiation**
- **Tumour behaviour**

An identity crisis for lung cancer cells

Álvaro Quintanal-Villalonga* SCIENCE TRANSLATIONAL MEDICINE



**But... NENs are NOT like
lung or prostate cancer**

Let's refine the question:

Does therapeutic pressure cause NET progression G1-G2-G3?

Does treatment cause histology transformation NET→NEC?

The Context

- Genomic, epigenomic and transcriptomic landscapes of NETs and NECs differ between them and are substantially distinct from other cancers
- Types of therapeutic approaches also differ (SSA, PRRT, mTOR inhibitors) while other are common (alkylating agents, TKI)

What is the evidence?

- Cases described of histological transformation/plasticity
- Investigative (particularly rebiopsy) studies tracing tumour evolution

Scant evidence for treatment-induced changes in NENs

Description of limited cases BUT → AFTER TREATMENT?

- Changes in grade G1-G2 → G3 or histology NETG3 → NEC
- Tumours showing mixed NET/NEC histology and/or molecular profile

Progression of Low-Grade Neuroendocrine Tumors (NET) to High-Grade Neoplasms Harboring the NEC-Like Co-alteration of *RB1* and *TP53*

Endocrine Pathology (2024) 35:325–337

Nancy M. Joseph¹ · Sarah E. Umetsu¹ · Grace E. Kim¹ · Merryl Terry¹ · Arie Perry¹ · Emily Bergsland² · Sanjay Kakar¹

a series of five patients

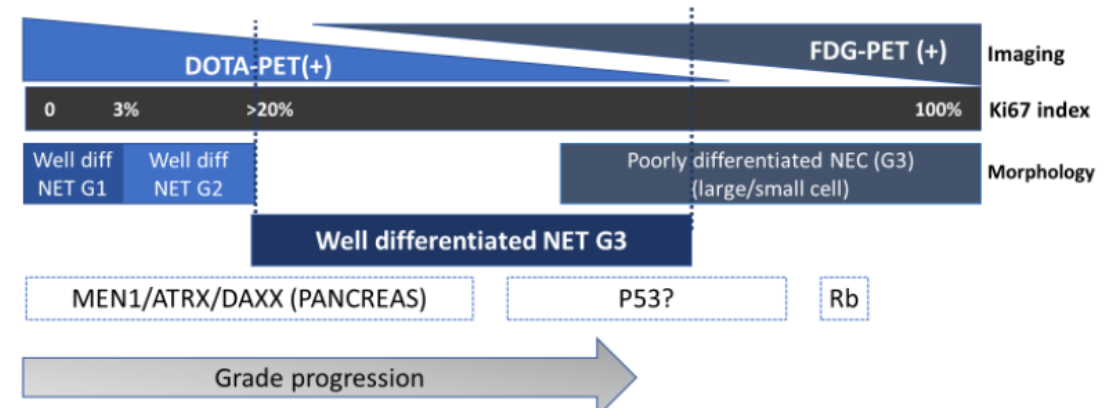
acquisition of *RB1/TP53* co-alteration. Our data demonstrate that low-grade NET can progress via the acquisition of both *TP53* and *RB1* alteration, similar to NEC, but whether this represents a transformation from NET to NEC remains unclear.

Grade Progression and Intrapatient Tumor Heterogeneity as Potential Contributors to Resistance in Gastroenteropancreatic Neuroendocrine Tumors

Cancers 2023, 15, 3712.

Diana Grace Varghese¹, Jaydira Del Rivero^{1,†} and Emily Bergsland^{2,*,†}

5.5. Treatment-Related Changes in High-Grade Tumors



Role of TREATMENT? → Inconclusive

Real-Time Genomic Characterization of Metastatic Pancreatic Neuroendocrine Tumors Has Prognostic Implications and Identifies Potential Germline Actionability

JCO Precis Oncol. © 2018

Twelve patients underwent NGS of tumor collected before and after treatment.

Conclusion A clinical NGS platform reveals perturbations of biologic pathways in metastatic panNETs that may inform prognosis and direct therapies. Repeat sequencing at disease progression reveals increasing tumor grade and genetic evolution, demonstrating that panNETs adopt a more aggressive behavior through time and therapies. In

Scant evidence for treatment-induced changes in NENs

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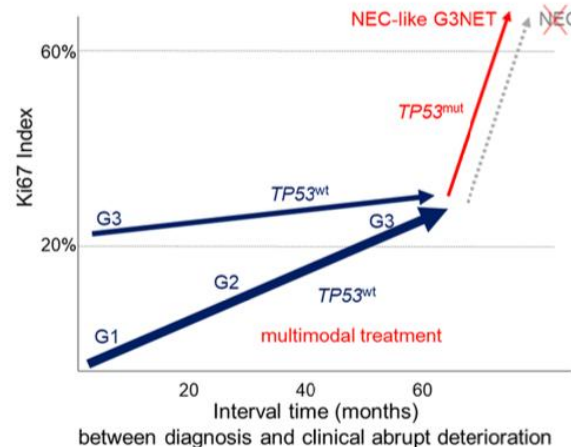
Rapid Evolution of Metastases in Patients with Treated G3 Neuroendocrine Tumors Associated with NEC-Like Transformation and TP53 Mutation

Endocrine Pathology (2024) 35:313–324

Atsuko Kasajima¹ · Nicole Pfarr¹ · Eva-Maria Mayr¹ · Ayako Ura¹ · Elisa Moser¹ · Alexander von Werder² · Abbas Agaimy^{3,5} · Marianne Pavel^{4,5} · Günter Klöppel¹

DAXX. This observation lends support to the hypothesis that no morphomolecular transformation into a typical NEC had occurred. Future studies with spatial transcriptomics may be

Treatment of NET G3 Patients Prior to NEC-Like Transformation



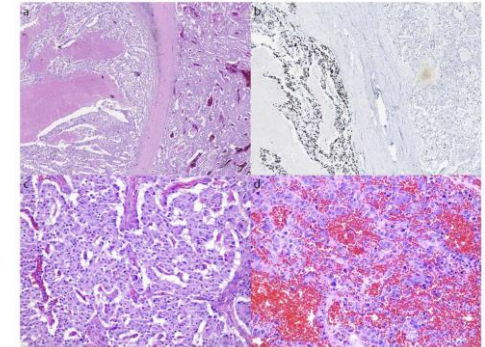
Case Report *Journal of Surgical Case Reports*, 2024, 12, rjae746

The first case of combined pancreatic neuroendocrine tumour and neuroendocrine carcinoma

Tegan Lun^{1,*}, Christophe Rosty^{2,3}, Pranavan Palamuthusingam^{4,5}

CHEMOTHERAPY (2 cycles):

- 1.- capecitabine/temozolomide
- 2.- carboplatin/etoposide



Integrated Genomic and Clinicopathologic Approach Distinguishes Pancreatic Grade 3 Neuroendocrine Tumor From Neuroendocrine Carcinoma and Identifies a Subset With Molecular Overlap

Sarah E. Umetsu^a, Sanjay Kakar^a, Olca Basturk^b, Grace E. Kim^a, Deyali Chatterjee^c, Kwun Wah Wen^a, Gillian Hale^d, Nafis Shafizadeh^e, Soo-Jin Cho^a, Julia Whitman^f, Ryan M. Gill^a, Kirk D. Jones^a, Pooja Navale^f, Emily Bergsland^g, David Klimstra^{b,h}, Nancy M. Joseph^{a,*}

Mod Pathol 36 (2023)

MODERN PATHOLOGY

in Supplementary Tables S5 and S6, respectively. Both cases 5 and 11 had prior treatment with temozolomide, which is known to result in hypermutation in a subset of tumors following therapy.^{48,49}

Recent evidence for treatment-induced changes in NENs

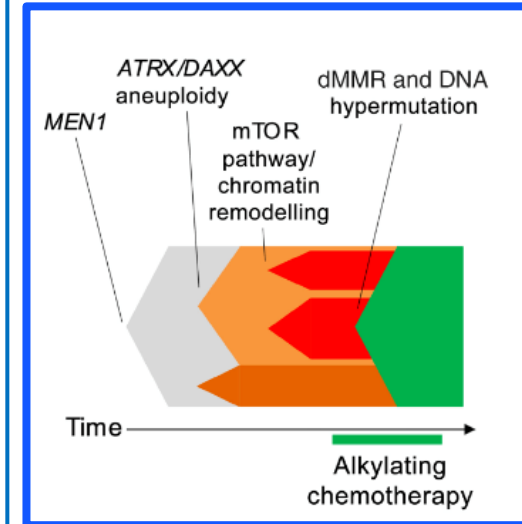
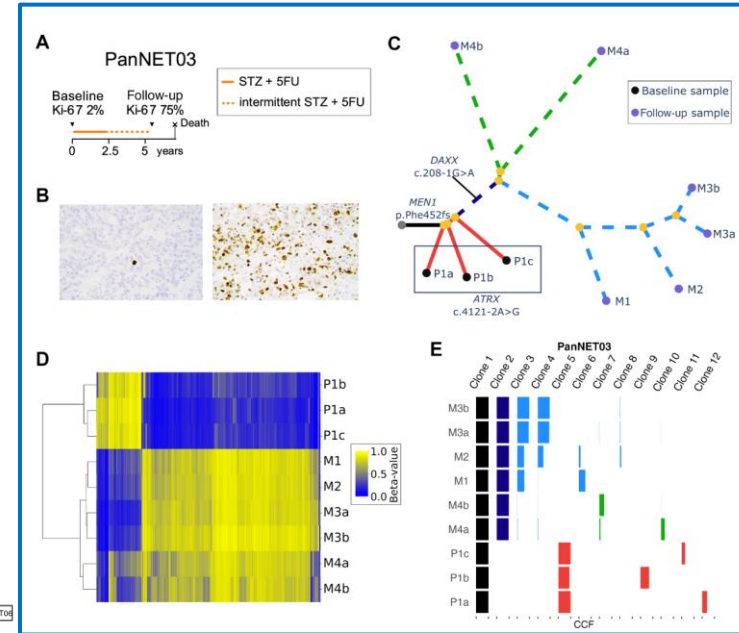
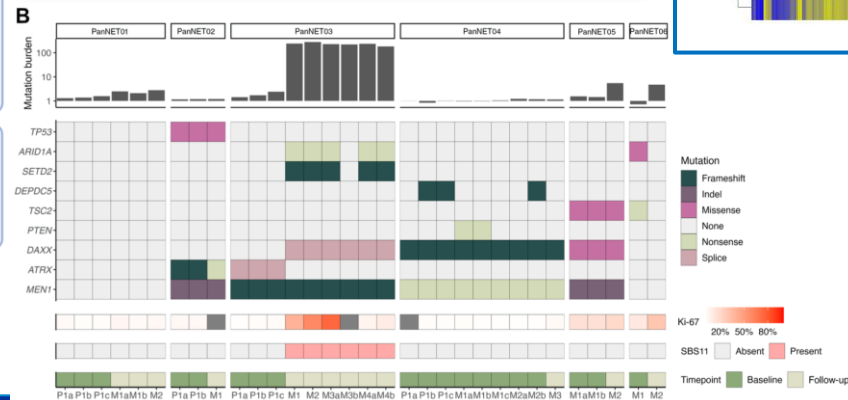
Investigative studies tracing tumour evolution

The evolutionary history of metastatic pancreatic neuroendocrine tumours reveals a therapy driven route to high-grade transformation

Journal of Pathology
J Pathol December 2024; 264: 357–370

Samuel Backman¹, Johan Botling^{2,3}, Helena Nord², Suman Ghosal⁴, Peter Stålberg¹, C. Christofer Juhlin⁵, Jonas Almlöf², Anders Sundin⁶, Liang Zhang⁷, Lotte Moens², Barbro Eriksson⁷, Staffan Welin⁷, Per Hellman¹, Britt Skogseid⁷, Karel Pacak⁴, Kazhan Mollazadegan⁷, Tobias Åkerström¹ and Joakim Crona^{7*}

32 longitudinal samples from 6 patients with metastatic low/ intermediate grade PanNETs



Systemic therapy may lead to potential negative consequences for patients with PanNET, with alkylating chemotherapy resulting in acquired mismatch repair deficiency, DNA hypermutation, and high-grade progression

Take home messages

There is ample evidence that targeted therapies can exert a selective pressure causing neuroendocrine differentiation in various cancers

Despite limited evidence, there seems to be common agreement that treatments can contribute to G1-G3 progression in NETs

The potential contribution of selective pressure by therapy to lineage plasticity in NENs, and more precisely to NET → NEC transdifferentiation is still controversial, especially in PanNETs

The effects of treatments on NEN progression and lineage plasticity are likely dependent on the specific type of tumour and therapy. Elucidating this question requires new models and further studies



**THANK YOU VERY MUCH!
¡MUCHAS GRACIAS!**



ENDOCRINE ONCOLOGY



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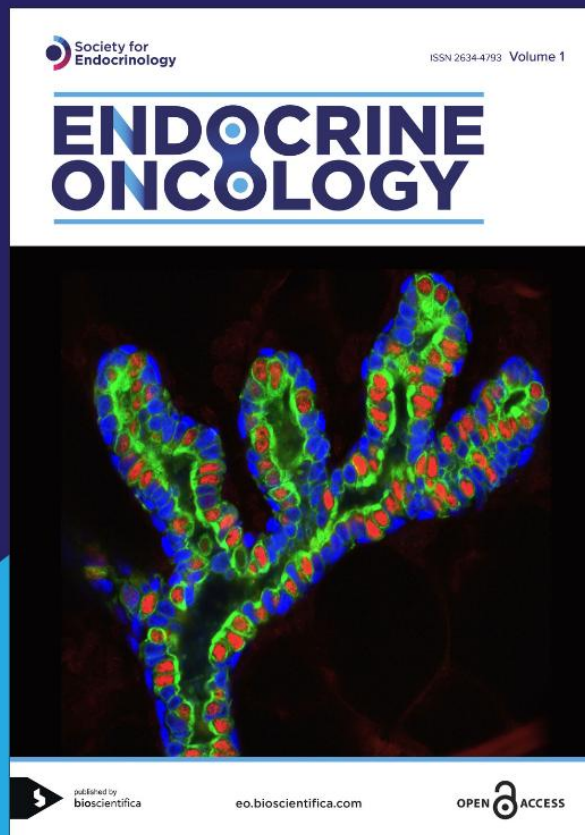
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Discussion



Closing comments

Take-home messages

- ✓ Increased grading happens over time: G1 to G2 to G3 or NET with NEC like features
- ✓ Mostly due to evolution and heterogeneity of the tumour
- ✓ More often after alkylating agents and in pNETs
- ✓ Rebiopsy often especially in case of change of clinical behaviour
- ✓ But new models and further studies are needed

A BIG "Thank You" to:

- ✓ Our speakers and moderators
- ✓ The ENETS Office team: Leah MATTHEWS, Ulrike KNELL, and Martina FLESCHEN
- ✓ The ENETS Education Group
- ✓ YOU, our valued participants

The ENETS Education Group

- Eric BAUDIN | Endocrinology | France
- Emanuel CHRIST | Endocrinology | Switzerland
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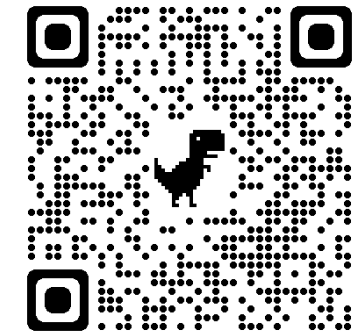
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- ✓ 68 Centers of Excellence worldwide as of 2025



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