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MEETING SUMMARY
ENETS 2020
VIRTUAL MEETING

Dr. Mauro Cives

Assistant Professor
University of Bari, Italy

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DISCLOSURES DR. CIVES

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**PRESIDENTIAL ABSTRACT
BASIC SCIENCE:**

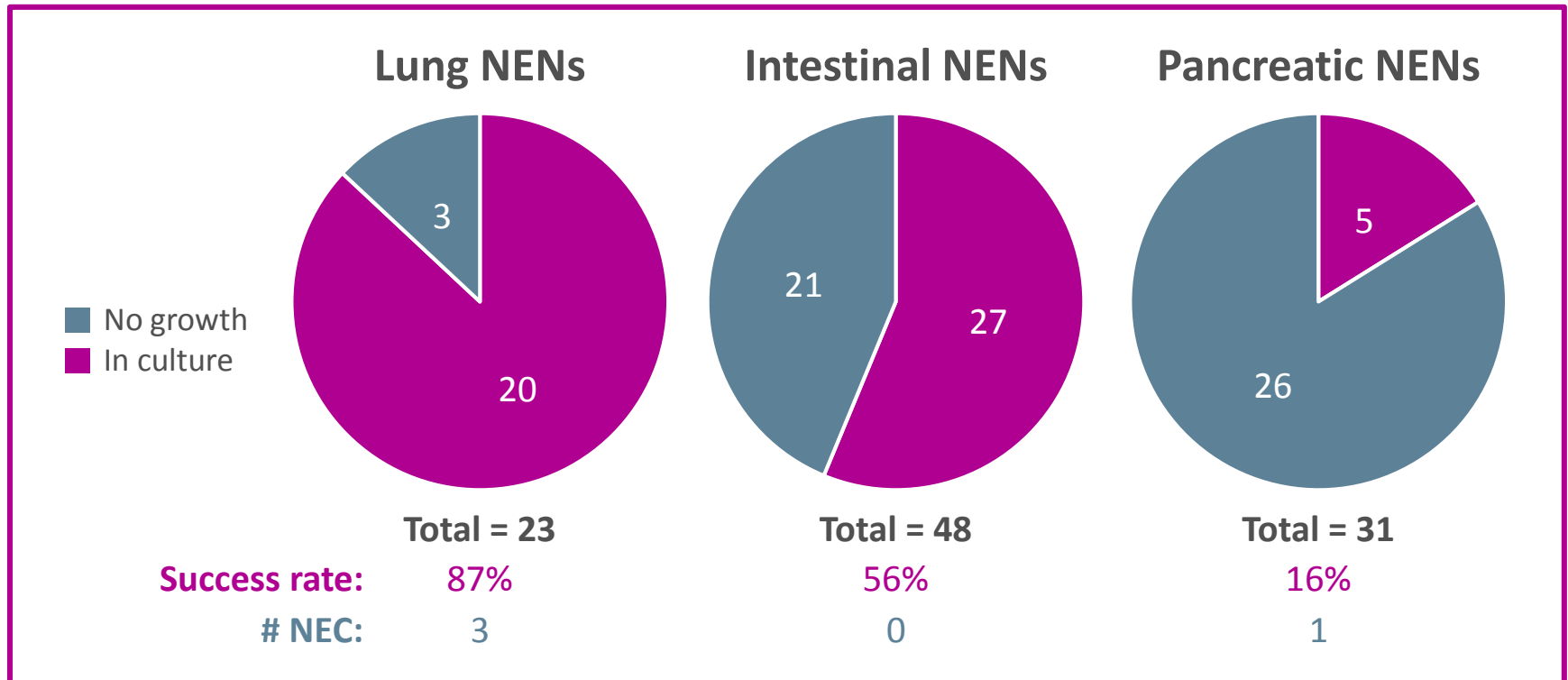
**ORGANOID MODELS OF
NEUROENDOCRINE CELL GROWTH
AND TUMORIGENESIS**

Dayton T, et al. ENETS 2020. Abstract #B01

- **There are few models** that can be used **for mechanistic and drug response studies for neuroendocrine neoplasms (NENs)**
- Advantages of organoids:
 - Defined in vitro system
 - Can be grown from both healthy and diseased tissues
 - Recapitulate stem cell differentiation dynamics
- **This research aimed to build a NEN biobank of pancreatic, intestinal and lung NECs and NETs**
 - To be used to study normal neuroendocrine cells and model their transformation to NENs
 - Generating pulmonary neuroendocrine cell enriched human airway organoids for characterization and modelling of lung NENs

KEY RESULTS

SUCCESS RATE IN GENERATING ORGANOIDS

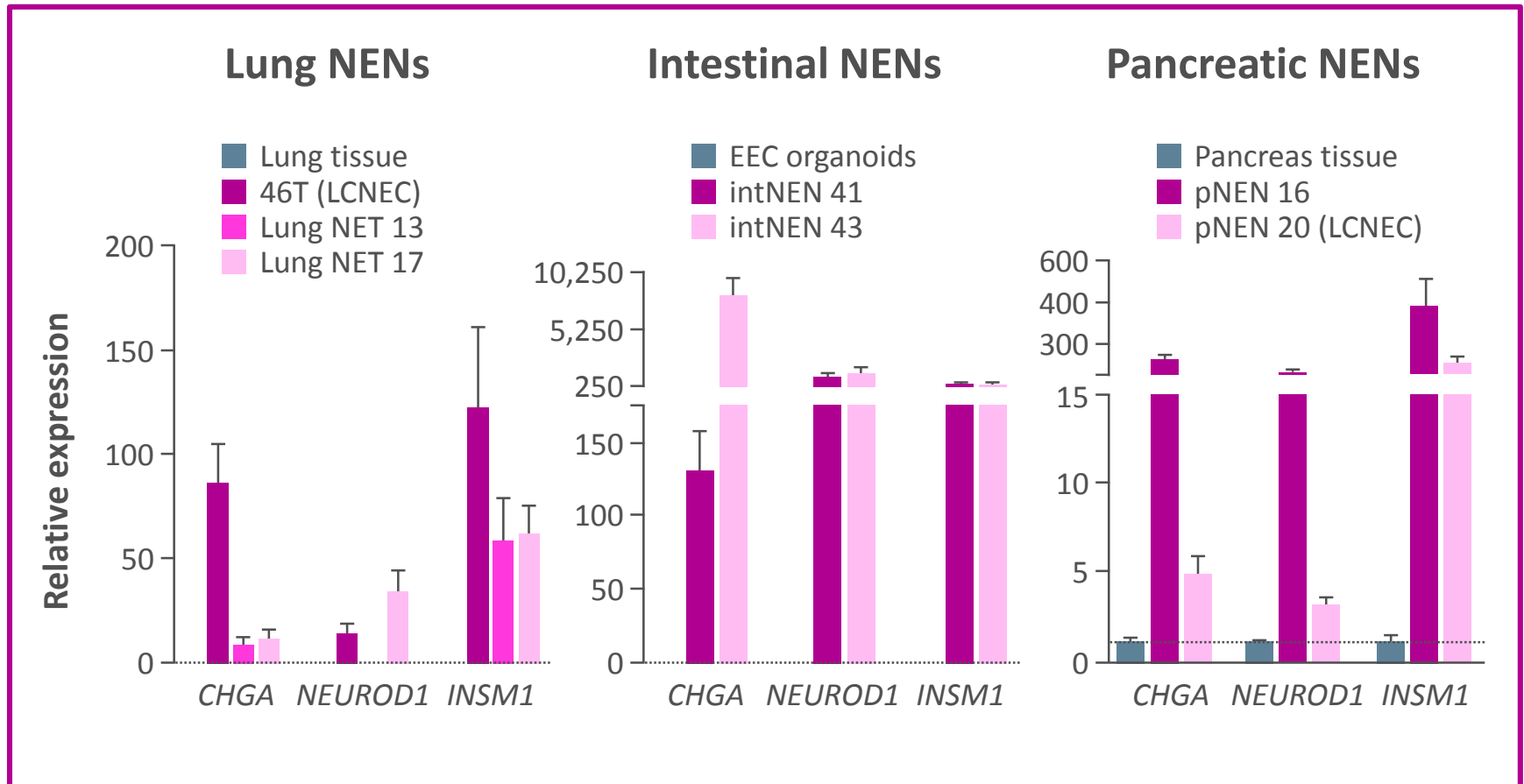


- Success rate in generating organoids higher in lung NENs (87%) as compared with intestinal (56%) or pancreatic NENs (16%)

IntNENs, intestinal neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; PaNENs, pancreatic neuroendocrine neoplasm

KEY RESULTS

NEN ORGANOIDS EXPRESS NE MARKERS



CHGA, chromogranin A; EEC, enteroendocrine cell; INSM1, insulinoma-associated 1; IntNENs, intestinal neuroendocrine neoplasm; LCNEC, large cell neuroendocrine carcinoma; NE, neuroendocrine; NEN, neuroendocrine neoplasm; NEUROD1; neurogenic differentiation factor 1; NET, neuroendocrine tumours; PaNEN (pNEN), pancreatic neuroendocrine neoplasm

KEY RESULTS

- **Media components critically influence NEN organoid growth**
 - Suggests potential therapeutic vulnerabilities
- NEN organoids **maintain expression of neuroendocrine markers across multiple passages**
- NEN organoids **maintain the intratumour heterogeneity** of the primary tumour
- NEN organoids **allow phylogenetic dissection of tumour sub-clones**
- Pulmonary neuroendocrine cell differentiation can be achieved in organoids

SUMMARY

- **NEN organoids** and PNEC-enriched fetal AOs **are novel preclinical in vitro models for the study of NE biology and disease**
- A collection of organoid cultures from NEN primary tumours and matched normal tissue has been established
- The expression of NE markers and the presence of the same genetic alterations identified in the primary tumour suggest that **organoids may serve as a bona fide model of NENs**
- PNECs are maintained long term over multiple passages and high numbers of differentiated PNEC can be achieved
- PNEC differentiation can be promoted by using a specific cocktail of small molecules

**MUTATIONAL LANDSCAPE OF
109 HIGH-GRADE
GASTROENTEROPANCREATIC
NEUROENDOCRINE NEOPLASMS G3**

Venizelos AA, et al. ENETS 2020. Abstract #C20

- **Gastroenteropancreatic (GEP) G3 NENs are rare with a poor outcome**
- The genetic background of G3 NENs (NETs + NECs) has been **poorly investigated to date**
- **The aim of this research was to gain tools for better prediction and to aid treatment decisions to improve survival in this patient population**
- The genetic landscape of **109 high-grade GEP NEN patients (16 NET G3 and 93 NEC)** was assessed from the **Nordic Prospective Registry** between 2013–2017
- DNA from FFPE samples and matched blood samples was analysed
 - All cases were re-assessed by a pathology expert
- NGS targeted sequencing using a pan-cancer panel was used

KEY RESULTS

NEC	
Frequently mutated genes	
TP53	59%
APC	31%
BRAF	24%
KRAS	24%
Stratified by tumour site	
Colon (n=31)	
TP53	68%
BRAF	52%
APC	42%
Rectal (n=24)	
TP53	50%
APC	50%
KRAS	25%

NET G3	
Frequently mutated genes	
ATRX	19%
SF3B1	19%
MEN1	12%

- In remaining tumours (pancreatic, oesophageal, gastric) TP53 was mutated >50%
 - Less frequently mutated genes included DICER, EGFR, FOXO1 and SOX9

SUMMARY

- **NEC are altered in 87.1% of cases**
 - Most common mutations include TP53, APC, BRAF, and KRAS
 - MSI detected in 9% of cases
 - Colon NEC are enriched in mutations of BRAF
- **NET G3 are altered in 68.75% of cases**
 - Most common mutations include ATRX, SFB1, MEN1
- **NET G3 and NEC have distinct genetic features**
- **This may pave the way to more personalized treatments** in the future

**INTERIM ANALYSIS OF PROSPECTIVE
EVALUATION OF THE MANAGEMENT
OF SPORADIC NON-FUNCTIONING
ASYMPTOMATIC PANCREATIC
NEUROENDOCRINE NEOPLASMS
≤2 CM (ASPEN STUDY)**

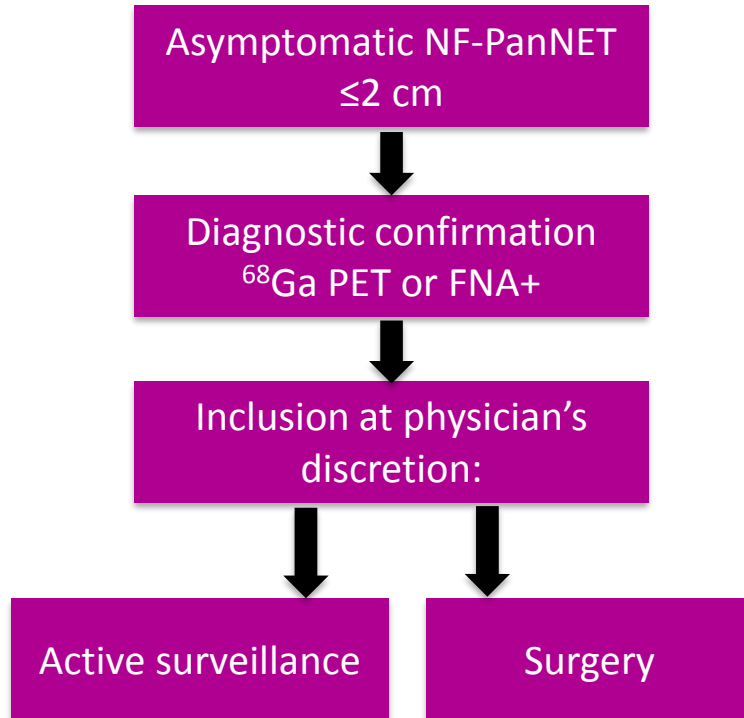
Partelli S, et al. ENETS 2020. Abstract #D40

BACKGROUND

- **In the last decade a dramatic increase in diagnosis of small, incidentally discovered, NF-PanNENs was observed**
- **A relationship between the tumour diameter and low risk of malignancy and systemic progression has been noted**
 - a tumour size ≤ 2 cm seems to be associated with a negligible risk of disease recurrence and with a very low incidence of aggressive features such as lymph node involvement
- **Guidance regarding most appropriate management of sporadic asymptomatic NF-PanNETs varies in current guidelines:**
 - **ENETS:** ‘In patients with... p-NETs ≤ 2 cm or with NF-pNETs on imaging studies, routine surgical exploration continues not to be generally recommended. In patients with p-NETs > 2 cm, enucleation at surgery remains the generally recommended surgical procedure’
 - **NANETS:** ‘...initial observation is an acceptable treatment strategy for asymptomatic patients with PanNET < 1 cm (...) it is recommended that decision to observe or resect an asymptomatic PanNET 1 to 2 cm in size be individualized’
- **Available data are based on retrospective studies** with a significant heterogeneity of inclusion criteria and different tumour diameter cut-off and the appropriate management. **The ASPEN study investigated most appropriate management prospectively**

ENETS, European Neuroendocrine Tumour Society; NANETS, North America Neuroendocrine Tumour Society; NF, non-functioning; PanNET, pancreatic neuroendocrine tumour

STUDY FLOW CHART



Prospective international multicenter cohort study

Target enrolment: 1000 patients

Study duration: 6 years (2017-2023)

43 centres involved, including 20 ENETS CoE

Primary objectives:

- To evaluate the most appropriate management (active surveillance versus surgery) of sporadic asymptomatic NF-PanNET ≤ 2 cm

Secondary objectives:

- To estimate the frequency of asymptomatic sporadic NF-PanNET ≤ 2 cm among overall sporadic NF-PanNET
- To observe NF-PanNET evolution (development of symptoms, tumour growth, development of distant metastases)
- To evaluate the perceived burden of surveillance or follow-up after surgery for participants

KEY RESULTS

RESULTS

	Surveillance n=310 n (%)	Surgery n=76 n (%)	P
Age, median (IQR)	65 (56-72)	58 (51-68)	<0.01
Diameter, mean (SD)	12.9 (3.9)	14.5 (4.4)	<0.01
Site lesion			
Head	83 (26.8)	15 (19.7)	0.08
Uncinate process	36 (11.6)	7 (9.2)	
Body	107 (34.5)	22 (28.9)	
Tail	84 (27.1)	32 (42.2)	
MPD (mm), mean (SD)	2.4 (3.0)	4.3 (3.8)	<0.01
ECOG			
0	268 (86.5)	71 (93.4)	0.45
1	34 (11.0)	5 (6.6)	
≥2	7 (2.5)	0 (0.0)	
Liver metastases			
Yes	0	2 (0.2)	1
Ki67 mean (SD)	1.4	2.4	0.01

- Indications for surgery:
 - Patient's preference: 46%
 - Physician's preference: 35%
 - Presence of dilation of the main pancreatic duct: 13%
 - Increase in tumour size: 4%
 - Presence of distant metastases: 3%

SURGICAL OUTCOMES

Variable	N (%)
Resection type	
Pancreaticoduodenectomy	15 (19.7)
Central pancreatectomy	2 (2.6)
Distal pancreatectomy	39 (51.3)
Enucleation	13 (17.1)
Other	7 (9.2)
Surgical approach	
Minimally invasive	46 (60.5)
Laparotomy	30 (39.5)
Complication grade	
No complication	52 (68.4)
I	8 (10.5)
II	7 (9.2)
III	5 (6.6)
IV	4 (5.3)

SUMMARY

- **A large majority of patients with asymptomatic NF-PanNET ≤ 2 cm undergo active surveillance** but a fraction undergo surgery despite guideline recommendations
- The **risk of malignant behaviour** for asymptomatic NF-PanNET ≤ 2 cm **exists although very low**
- The **main indication for surgery is still related to patient's preference** who cannot cope with a surveillance strategy
- **Tumour size and patient's age influence physician's strategy**
- We await the full results of the ASPEN trial

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Email
antoine.lacombe@cor2ed.com



NET CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com

