

Wenzel M. Hackeng (1), Lodewijk A.A. Brosens (1), Joo Young Kim (2), Roderick J. O'Sullivan (3), You-Na Sung (4), Ta-Chiang Liu (5), Dengfeng Cao (5), Michelle Heayn (6), Jacqueline Brosnan-Cashman (7), Soyeon An (8), Folkert H.M. Morsink (1), Charlotte M. Heidsma (9), Gerlof D. Valk (10), Menno R. Vriens (11), Els J.M. Nieveen van Dijkum (9), G. Johan A. Offerhaus (1), Koen M.A. Dreijerink (1,12), Herbert J. Zeh (13), Amer H. Zureikat (14), Melissa E. Hogg (15), Kenneth Lee (14), David Geller (14), J. Wallis Marsh (16), Alessandro Paniccia (14), Melanie C. Ongchin (14), James F. Pingpank (14), Nathan Bahary (17), Muaz Aijazi (17), Randall E. Brand (17), Jennifer S. Chennat (17), Rohit Das (17), Kenneth E. Fasanella (17), Asif Khalid (17), Kevin McGrath (17), Savreet Sarkaria (17), Harkirat Singh (17), Adam Slivka (17), Michael A. Nalesnik (6), Xiaoli Han (6), Marina N. Nikiforova (6), Rita T. Lawlor (18), Andrea Mafficini (18), Borislav Rusev (18), Vincenzo Corbo (18,19), Claudio Luchini (19,20), Samantha Bersani (19), Antonio Pea (21), Sara Cingarlini (17,20), Luca Landoni (20,21), Roberto Salvia (20,21), Massimo Milione (23), Michele Milella (20,22), Aldo Scarpa (18,19,20), Seung-Mo Hong (4), Christopher M. Heaphy (7,24) and Aatur D. Singhi (6)

Most pancreatic neuroendocrine tumors (PanNETs) are clinically indolent, although a subset may behave aggressively and metastasize.

Several promising prognostic biomarkers have been described, including ATRX/DAXX loss, alternative lengthening of telomeres (ALT)<sup>1</sup>, and ARX/PDX1 transcription factor subtypes<sup>2</sup>.

Studies reporting prognostic biomarkers have mostly been limited to single center studies, limited in size and with diverse patient populations (including hereditary and functional tumors, often with synchronous metastases)

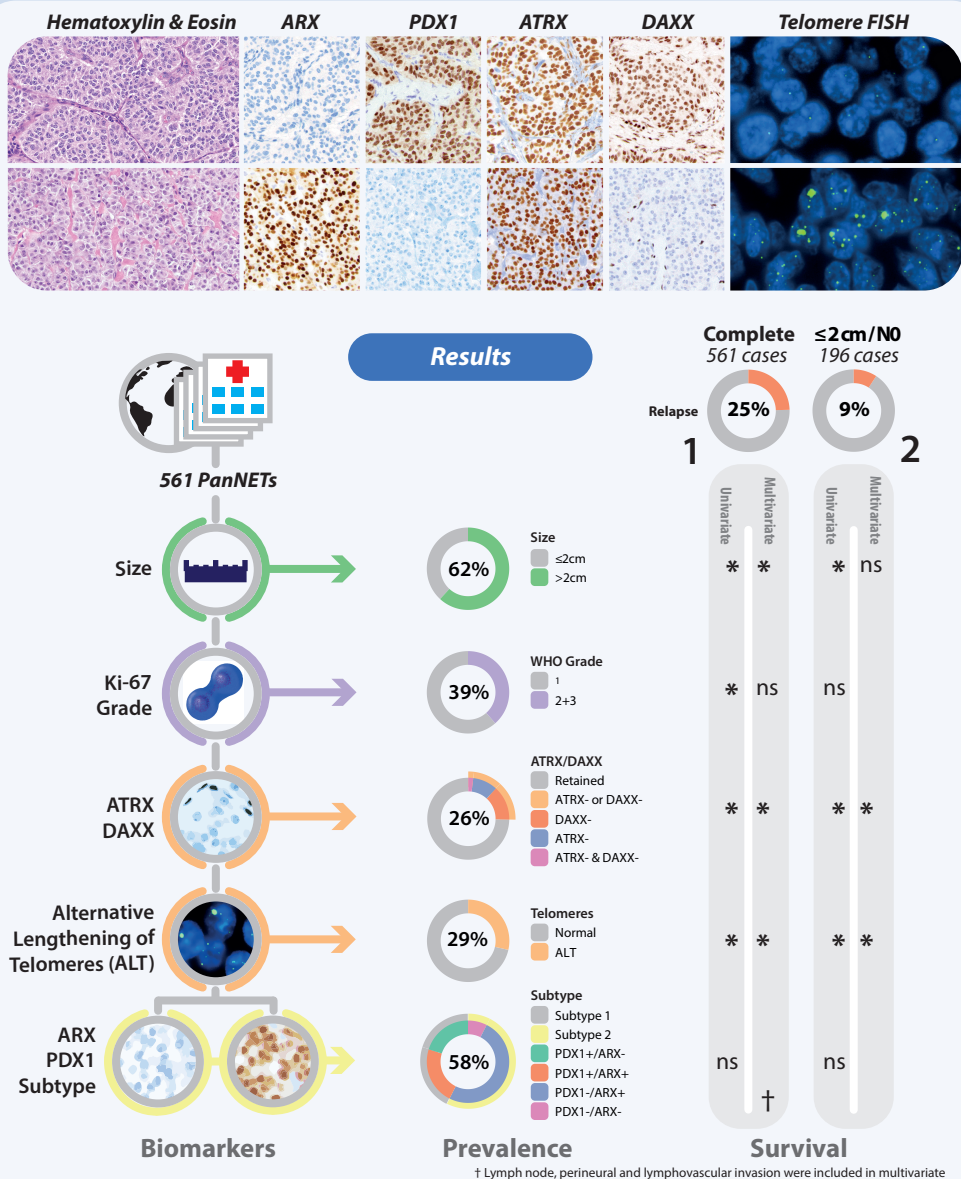
Determine the prognostic value of biomarkers of metastatic PanNET behaviour in an international multicentric study for highly selected clinically relevant subgroups of NET:

1. Sporadic non-functional PanNET, without synchronous metastases at surgery. n = 561
2. Sporadic non-functional PanNET  $\leq 2\text{cm}$ , without synchronous metastases or tumor positive lymph nodes at surgery. n = 196
3. Metastatic PanNET and non-pancreatic NETs (not discussed here) n = 680

## Multicentric international collaboration



- Sufficient material (whole slides or TMA)
- ATRX/DAXX status, Ki67 (grade), ARX/PDX1 subtype immunohistochemistry
- Telomere fluorescence in situ hybridisation
- Selection of complete cases for biomarkers
- Cox regression analysis for Relapse Free Survival (RFS)



### ***Sporadic NF-PanNETs pM0***

- Shorter RFS independently** associated with PanNETs >2cm or continuous size.
- Shorter RFS** associated with WHO grade >1, not independent of other variables
- Shorter RFS independently** associated with either ALT or ATRX/DAXX loss of protein expression.
- Combinations, subtypes or single markers did not correlate with RFS. ARX expression was associated with ALT
- Shorter RFS independently** associated with tumor positive lymph nodes

**Sporadic NF-PanNETs  $\leq 2\text{cm}$  pN0 pM0**

- **Shorter RFS independently** associated with ALT or ATRX/DAXX loss in relation to tumor size (continuous or >1.6cm)
- **Shorter RFS** associated with tumor size (continuous or >1.6cm), but not independent of ALT or ATRX/DAXX

1. Heaphy, Christopher M., et al. "Altered telomeres in tumors with ATRX and DAXX mutations." *Science* 333.6041 (2011): 425-425.
2. Cejas, Paloma, et al. "Enhancer signatures stratify and predict outcomes of non-functional pancreatic neuroendocrine tumors." *Nature medicine* 25.8 (2019): 1260-1265.

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