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The Evolutionary History of Metastatic Pancreatic Neuroendocrine Tumours Reveals a Therapy Driven Route to High-Grade Transformation

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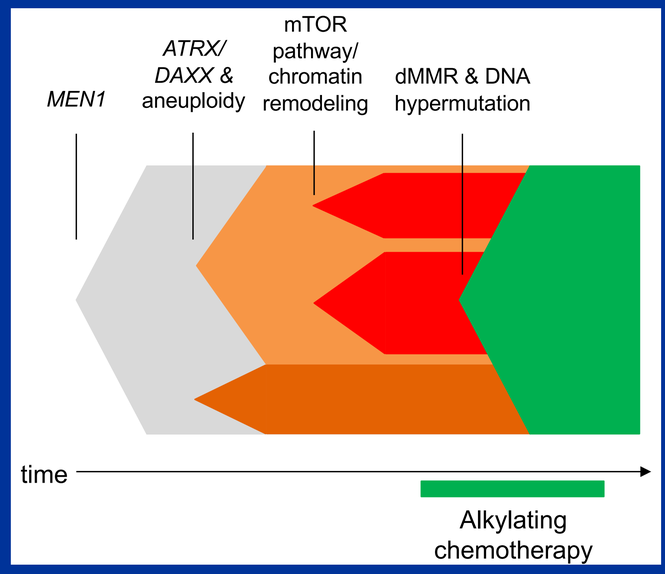
Background:

- Tumour evolution with acquisition of more aggressive disease characteristics is a hallmark of metastatic cancers.
- Metastatic pancreatic neuroendocrine tumours (PanNETs), show frequent progression from a low/intermediate to a high-grade disease.
- We aimed to understand the molecular mechanisms underlying metastatic progression as well as transformation from a low/intermediate to a high-grade PanNET.

Methods:

- Paired metachronous tumor samples were subjected to Whole Genome Sequencing, RNA-Seq and methylation array analysis (surgical specimens, n=27 from four patients) or Exome sequencing (core needle biopsies, n=5 from two patients)
- Findings were validated in 24 post-treatment samples using targeted NGS

Therapy-driven disease evolution is a hallmark of metastatic PanNET



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Results:

- Early *MEN1*-inactivation
- Parallell and convergent evolution involving *ATRX*/*DAXX* and mTOR pathways
- Following alkylating chemotherapy, some patients develop mismatch repair deficiency and acquire a hypermutation phenotype