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A Phase II Trial of **N**iraparib and **E**verolimus in ARID1A-**M**utated or **N**euro**E**ndocrine GYN Cancer

GYN Neuroendocrine Tumours (NET)

- Significant clinical challenge:
  - poor survival, eg 38% 3 years stage III/IV small cell cervix
  - limited standard treatment options extrapolated from lung cancer paradigms
  - no molecular guided therapy or selection markers

- Heterogeneous
  - well differentiated (typical and atypical carcinoid)
  - poorly differentiated (small cell/large cell)

- Rare
  - Cervix: 2% small cell, 0.5% large cell
  - Ovarian: 0.1% small cell (hypercalcaemic, pulmonary)
  - Endometrium, vagina, vulva – very few published reports

NET and BRCA

- Very little known in GYN NET
  - No systematic evaluation published
  - One conference case report (Giovannoni et al ESGO 2015) - olaparib

- Of 6 known cases at UCLH (ovary and cervix)
  - 4/4 tested have BRCA mutation or VUS
  - 2 not yet tested (in process)
  - 2 treated with PARP inhibitor, 1 treated with mtori on progression
  - Investigating further with FM panels in a cohort of patients UCLH/Leeds

- 1/11 patients with pancreatic NET had *BRCA2* mutn (Lucas et al CCR 2013)

- Pancreatic NET whole genome landscape (Scarpa et al, Nature 2017)
  - DNA damage repair, mainly BRCA2
  - Mtor signalling

NET and mTOR inhibition

- Data derived from GI NET
- PI3K pathway mutation drives pathogenesis and progression of NETs (Pusceddu 2017)
- RADIANT3 Phase III (Yao et al 2012)
  - Everolimus monotherapy vs placebo in pancreatic NET
  - 34% progression free at 18/12 (all subgp) vs 9% placebo
- Everolimus is a standard of care in GI NET

Dual PARP and PI3K pathway inhibition

- CompAKT trial
  - AKT inhibitor and olaparib (PARPi)
- BKM120 or BYL719 and olaparib
  - PI3K inhibitor or PI3Kalpha inhibitor and PARPi
- Niraparib and everolimus
  - Mtor inhibitor and PARPi
  - Currently undergoing dose/safety evaluation Phase Ib

- Tolerable
- Observed efficacy in PARPi monotherapy resistant patients
- Efficacy in endometrial and ovarian GYN cancers

ARID1A mutation

- Strongly linked with PI3K pathway mutation
- Strongly linked with DNA repair pathway perturbation: BRCAm and ATRm
- Relatively common (~30%) in clear cell and endometrioid ovarian and endometrial ca

- Unmet targeted need
- Different drug targets from other planned trials in clear cell eg PEACCOC - immunotherapy

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- Tesaro have approved the concept as an IIS
  - Awaiting full submission
  - Phase IB dose finding/safety already underway

- Proposed population:
  - Advanced, metastatic disease
  - First (if mutation) or subsequent line treatment
  - Any neuroendocrine GYN cancer
  - Any GYN cancer with ARID1A mutation
  - Prior PARPi or ATRi allowed
  - Stratify for well differentiated versus poorly differentiated
  - TR to evaluate DNA repair, TMB and PI3K/mtor pathways
  - FM panel inclusion

- Stats TBD
  - Primary endpoint PFS; OS secondary?