Current trials in Neuroendocrine Tumours: A systematic review

DRAFT

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Introduction/background

Trials in neuroendocrine tumours (NETs) have increased markedly in number over the last 10 years.

- No comprehensive registry of NET trials exists; researchers do not have ready access to a summary of open trials to identify research gaps.
- We aimed to systematically identify currently open, registered trials in NET
  - To describe the current research landscape and
  - To direct future trials

Methods

- Databases identified and searched for NET trials.
- 9 databases (clinicaltrials.gov, ISRCTN, clinicaltrialsregister.eu, ANZCTR, Canadiancancertrials.ca, 3CTN, UK clinical trials gateway, National Cancer Institute, NCIC), as well as conference abstracts (ENETs, ASCO, ASCO GI) searched.

Inclusion criteria:

- Prospective trials open/recently closed (<6 months) to accrual
- Involving neuroendocrine tumours (Phase I trials for multiple solid tumour sites excluded)
- Classified into RCTs and single-arm trials by investigational agent's mode of action

Sample search strategies:

Clinicaltrials.gov – "neuroendocrine", "carcinoid" – restricted to open trials

Other websites – "neuroendocrine"

- Open NET trials were included and classified into randomised trials (RCTs), single-arm interventional trials and non-interventional trials. Unreported trials recently closed to accrual were also identified.

Results

Fig.1: Trial Flow Diagram

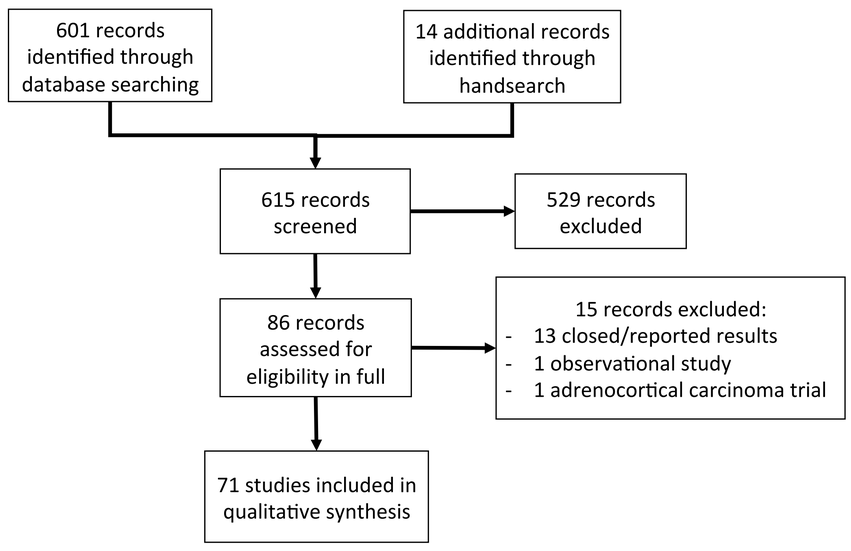

Table 1: Summary of search results

	RCT	Single-arm	Total
Somatostatin analogues	2	2	4
PRRT	3	2	5
Antiangiogenic agents	3	14	17
mTOR inhibitors	3	3	6
Novel drugs/combinations	5	28	33
Other	1	5	6
Total	**17**	**54**	**71**

- NB 8 trials (1 RCT, 7 single-arm) were excluded from time of abstract submission as they have reported results/closed to accrual.
- The RCTs identified are described in Figure 2.

Table 2: Identified Randomized Controlled Trials

Treatment	ID No. (Study Name)	Phase/ patients	Intervention	Comparator	Population	Study Start
PRRT	NCT02358356 (CONTROL NETS)	II/165	Lutate + CAPTEM	Comparator 1: Lutate. Comparator 2: CAPTEM	Unresectable, progressive, pNET/midgut NET, SSR +ve	Jul-15
	NCT01860742	III/66	Lutate	IFN-alfa 2B	Non-pancreatic, GIT NET	Mar-15
	NCT02230176 (OCLURANDOM)	II/80	Lutate	Sunitinib	pNET	Feb-15
Anti-angiogenic	NCT01841736	II/165	Pazopanib Hydrochloride	Placebo	Advanced NET	Jun-13
	NCT01731925 (SUNLAND)	2II/104	Lanreotide + Sunitinib	Lanreotide + Placebo	Advanced mNET	Dec-12
	NCT01803503	II/80	Sunitinib + docetaxel	Docetaxel	Solid tumours including NET	May-13
mTOR	NCT02031536	II/150	Everolimus	Placebo	Pancreatic NET – after resected liver metastases	Jan-14
	NCT02246127	III/180	Everolimus	STZ-5FU	Pancreatic NET	Oct-14
	2014-003951-72	II/30	Maintenance everolimus	Observation	GEP/lung NEC, Ki67<55%, SD+ on 6 cycles of platinum/etoposide	Mar-15
Novel drugs/ combinations	2013-000043-78	II/222	Ipilimumab	Observation	Resected merkel cell carcinoma	Apr-14
	2012-004018-33/ NCT02054884	II/90	Paclitaxel+-F16IL2 (IL2 antibody)	Paclitaxel	Merkel	Oct-13
	NCT01824875	II/145	Temozolomide + Capecitabine	Tem	pNET	May-13
	2013-000726-66 (SEQTOR)	III/180	Everolimus ->STZ5FU	STZ5FU-> Everolimus	Advanced PNET	Jun-14
	NCT02595424	II/126	Cisplatin/ etoposide	CAPTEM	G3 GEPNEC – non-small-cell	Jan-16
SSA	2013-004069-14	II-III/222	Lanreotide maint	Observation	GEPNET, Ki67<20%, at least SD on first-line (everolimus, sunitinib, chemo)	Jan-15
	NCT02288377 (REMINET)	II-III/222	Lanreotide	Placebo	Non-resectable, progressive pNET	Sep-14
Others	2011-006097-76	III/140	Octreotide+TAE	Octreotide	NET with hepatic mets	Mar-12

Lutate: ^{177}Lu-based peptide receptor radionuclide therapy, TAE: Trans-arterial embolization, mNET: midgut NET, pNET: pancreatic NET, SD: Stable disease, NEC: Neuroendocrine carcinoma, CAPTEM: Capecitabine + temozolomide, STZ-5FU: Streptozocin/5-fluorouracil

- 44 trials (19 RCTs, 25 single-arm) recently closed to accrual, awaiting full results
- 169 further observational trials were identified.
- Only 5 trials (2 RCT, 3 single-arm) investigated grade 3 NECs.
- Most trials either included all NETs or restricted to GEPNETs, midgut or pancreatic primaries; only two studies investigated Merkel cell tumours, and none specifically enrolled for rarer primaries (eg lung, thymus).
- Only three trials investigated liver-directed therapies (one RCT, two single-arm trials).
- No currently open trials investigated surgical therapies, nor used symptom control or quality of life as primary endpoints (although we note TELESTAR and TELECAST which recently completed accrual).

Discussion

- This is the first systematic review of open trials in NET.
- Few current randomized trials investigate
  - Treatment of Grade 3 NEC
  - Surgical/locoregional therapies
- Several trials have recently investigated symptom control as a primary endpoint. Given the considerable impact of NETs on patients, ongoing research in this area is of high priority[1].
- The ongoing challenges of disease heterogeneity and patient accrual may argue for novel trial designs going forward.

Conclusions

- **A wide range of systemic therapies are currently being investigated in treatment of NETs.**
- **Ongoing trials and randomized data, particularly in areas such as symptom control and locoregional therapies, are needed to improve the patient journey in NETs.**

References:

1. Leyden J., Sissons M., Goldstein G., Kolarova T., Bouvier C., The Neuroendocrine Tumor (NET) Patient (pt) Perspective: Results from the First Global NET Pt Survey – A Collaboration between the International Neuroendocrine Cancer Alliance (INCA) and Novartis Pharmaceuticals, Neuroendocrinology 2015;102:77–168, Abstract #R3