Australasian Gastrointestinal Trials Group (AGITG) CONTROL NET Study: Phase II studies of receptor radionuclide therapy (LuTate PRRT) +/- capecitabine, temozolomide (CAPTEM) or CAPTEM alone for neuroendocrine tumours (NETs (Nuclear Medicine - Imaging and Therapy (PRRT))

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Introduction: Chemotherapy is often combined with PRRT to treat NETs of pancreatic or midgut origin (pNET/mNET) based on the principle of radiosensitization.

Aims: To determine the relative activity of CAPTEM/PRRT in G1-2, unresectable, metastatic mNET and pNET.

Materials and methods: mNET: Phase II 2:1 randomisation PRRT /CAPTEM vs. PRRT (control); pNET: 2:1 randomisation to PRRT /CAPTEM vs CAPTEM (control). PRRT /CAPTEM: 7.8GBq LuTate day(D) 10, 8 weekly x 4, with b.i.d. oral CAP 750mg/m^2 D1-14 & TEM 75mg/m^2 D10-14, 8 weekly x 4, vs. PRRT 8 weekly x 4, or CAPTEM 4 weekly x 8. Primary endpoint: Progression free survival (PFS) (15 months (m) mNETs/12m pNETs). Secondary endpoints: objective tumour response rate (OTRR), clinical benefit rate (CBR), toxicity, QOL.

Results: 75 patients (pts) enrolled: mNET 33 PRRT/CAPTEM & 14 PRRT; pNET 9 CAPTEM & 19 PRRT/CAPTEM. Prior to treatment 3 withdrew. Characteristics were balanced except mNET gender (female 58% vs.14%). Two mNET & 3 pNET pts received 2 prior systemic regimens. mNET: After median follow-up of 32m, 15m PFS is 90% (95%CI: 73-97%) v 92% (95%CI: 57-99%); OTRR 25% vs 15%; PRRT/CAPTEM v PRRT respectively. pNET efficacy data awaited. mNET treatment related adverse events (AEs): 22/32 PRRT/CAPTEM had one Grade(G)3 event (69%) vs 5/13 (38%, PRRT); 4/32 pts had one G4 event (13%) v 1/13 (8%) respectively. One pt failed to complete therapy due to PRRT/CAPTEM toxicity. pNET AEs: 5/18 PRRT/CAPTEM pts had one G3 event (28%) vs 2/9 (22%, CAPTEM); 3/18 had one G4 event (17%) v 1/9 (11%) respectively; 3 failed to complete therapy due to toxicity, 2 CAPTEM, 1 PRRT/CAPTEM.

Conclusion: At initial analysis 15 m PFS is similarly high in mNETs with CAPTEM/PRRT relative to PRRT. OTRR is higher but at the cost of more toxicity. pNET AE rate was similar.

Background:

Several positive international randomised clinical trials (RCTs) of targeted therapy in gastrointestinal (GI) NETs have been completed.

- PROMID demonstrated improved median time to tumour progression with monthly Sandostatin LAR® 30 mg in well-differentiated midgut NETs.[1]
- RADIANT-3 demonstrated prolonged PFS with everolimus (10 mg daily), in patients with progressive low or intermediate Grade pancreatic NETs.[2]
- CLARINET demonstrated prolonged PFS with monthly Lanreotide Autogel 120 mg in treatment naïve patients with well-differentiated metastatic GEPNETs.[3]
- NETTER-1 demonstrated 177Lu-DOTA0-Tyr3-Octreotate (Lutathera®) to be superior to 60 mg Octreotide LAR in progressive midgut NET patients by prolonging PFS, HR 0.21 [95% CI: 0.13-0.33] p < 0.0001, median PFS not reached for Lutathera and 8.4 mo. with Octreotide LAR [95% CI: 5.8-11.0 months]. Patients were selected by Octreoscan.[4]

A single centre Australian Phase II study of capecitabine with LuTate in progressive GEPNETs demonstrated stabilization of tumours in 94% of patients.[5] A subsequent phase I/II study, of capecitabine and temozolomide (CAPTEM) and LuTate in progressive GEPNETs, achieved an ORR of 57% and stable disease in 37%. Median PFS was 31 months.[6]

These Australian studies indicated promising activity of CAPTEM in combination with LuTate, supporting the hypothesis that the combination may be better than either treatment alone.

CONTROL NETS was developed to further explore if CAPTEM/LuTate combined following progression on SSAs was sufficiently active to evaluate further in a Phase III trial.

CONTROL NETS will assess the (relative) activity of CAPTEM chemotherapy and PRRT combined in midgut (m)NETS and pancreatic (p)NETS.

Given the long and unpredictable natural history of NETs, a contemporary non-comparative control group is included in each study arm (CAPTEM for pNETS, PRRT alone for mNETS).

Study Design: Non-comparative, parallel group, phase II randomised, open label trial with two cohorts.

Cohort A – low to intermediate grade pancreatic NETs (pNETs) - [PRRT + CAPTEM] vs CAPTEM (control)

Cohort B – low to intermediate grade midgut NETs (mNETs) - [PRRT + CAPTEM] vs PRRT (control)

Demographics

Characteristic		Cohort A - pNETS		Cohort B - mNETS	
		CAPTEM (n=9)	PRRT/CAPTEM (n=19)	PRRT (n=14)	PRRT/CAPTEM (n=33)
Age	years	66.3 (9.93)	57.8 (10.4)	64.5 (11.2)	63.3 (7.36)
Gender	Female	2 (22%)	7 (37%)	2 (14%)	19 (58%)
	Male	7 (78%)	12 (63%)	12 (86%)	14 (42%)
WHO Tumour grade	G1 Low	5 (56%)	7 (37%)	8 (57%)	20 (61%)
	G2 Intermediate	4 (44%)	12 (63%)	6 (43%)	13 (39%)
Previous system therapy regimens	≤1	9 (100%)	16 (84%)	14 (100%)	31 (94%)
	2	0 (0%)	3 (16%)	0 (0%)	2 (6%)
ECOG Status (0 v 1)	0	7 (78%)	13 (68%)	11 (79%)	29 (88%)

Grade 3+ Adverse Events pNETS and mNETs

#Number (proportion) patients with at least one Grade 3+ AE or SAE: any or related	Cohort A - pNETS		Cohort B - mNETS	
	CAPTEM (n=9)	PRRT/CAPTEM (n=18)	PRRT (n=13)	PRRT/CAPTEM (n=32)
Any Grade 3+ AE	4 (44%)	8 (44%)	6 (46%)	28 (88%)
Any treatment-related Grade 3+ AE	3 (33%)	8 (44%)	6 (46%)	26 (81%)
Any SAE	0	5 (28%)	1 (8%)	10 (31%)
Any treatment-related SAE	0	4 (22%)	1 (8%)	7 (22%)

Progression Free Survival (PFS) mNETS

PFS proportion at 15 months	PRRT/CAPTEM (n=32)	PRRT (n=13)	Difference in proportions (95% CI)
	90.2% (72.7 to 96.8)	92.3% (56.6 to 98.9)	2.1% (-15.8 to 19.9)

Clinical Benefit Rate mNETS

	PRRT/CAPTEM (n=32)	PRRT (n=13)	Difference in proportions (95% CI)
Clinical Benefit Rate (CR/PR/SD)			
ITT population	31 (96.9%)	12 (92.3%)	4.6% (-11%, 20.3%)
Excluding unknown/early withdrawals*	31 (100%)	12 (92.3%)	7.7% (-6.8%, 22.2%)

**Early treatment withdrawal due to toxicity, drug intolerance or treatment-related death*

Objective Tumour Response Rate mNETS

	PRRT/CAPTEM (n=32)	PRRT (n=13)	Difference in proportions (95% CI)
Best Overall Response			
CR - Complete Response	0	0	
PR - Partial Response	8 (25%)	2 (15%)	
SD - Stable Disease	23 (72%)	10 (77%)	
PD - Progressive Disease	0	1 (8%)	
Early withdrawal	1 (3%)	0	
Objective Tumour Response Rate (CR/PR)			
ITT population	8 (25.0%)	2 (15.4%)	9.6% (-15%, 34.3%)
Excluding unknown/early withdrawals*	8 (25.8%)	2 (15.4%)	10.4% (-15%, 35.4%)

**Early treatment withdrawal due to toxicity, drug intolerance or treatment-related death*

Adverse Events pNETS and mNETs

Pancreas NETs patients	PRRT/CAPTEM (n = 18)		CAPTEM (n = 9)		P Value* Any Grade Adverse Event
Adverse Event^	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	**
Any adverse event	18 (100%)	8 (44%)	9 (100%)	4 (44%)	
Gastrointestinal Disorders					
Diarrhoea	7 (39%)	0 (0%)	8 (89%)	1 (11%)	0.02
Mucositis oral	3 (17%)	0 (0%)	3 (33%)	0 (0%)	0.37
Vomiting	8 (44%)	0 (0%)	6 (67%)	0 (0%)	0.42
Gastroesophageal reflux disease	2 (11%)	0 (0%)	2 (22%)	0 (0%)	0.58
Nausea	14 (78%)	0 (0%)	8 (89%)	0 (0%)	0.64
Constipation	9 (50%)	0 (0%)	3 (33%)	0 (0%)	0.68
Abdominal pain	5 (28%)	0 (0%)	2 (22%)	0 (0%)	>0.95
Haematological Disorders					
Platelet count decreased	8 (44%)	0 (0%)	1 (11%)	0 (0%)	0.19
Anaemia	5 (28%)	1 (6%)	1 (11%)	0 (0%)	0.63
White blood cell decreased	7 (39%)	3 (17%)	2 (22%)	0 (0%)	0.67
Neutrophil count decreased	10 (56%)	3 (17%)	4 (44%)	1 (11%)	0.69
Lymphocyte count decreased	7 (39%)	5 (28%)	3 (33%)	1 (11%)	>0.95
General Disorders					
Fatigue	16 (89%)	0 (0%)	8 (89%)	0 (0%)	>0.95
Insomnia	3 (17%)	0 (0%)	1 (11%)	0 (0%)	>0.95
Nervous System Disorders					
Headache	4 (22%)	0 (0%)	0 (0%)	0 (0%)	0.27
Dysgeusia	2 (11%)	0 (0%)	2 (22%)	0 (0%)	0.58
Dermatological Disorders					
Palmar-plantar erythrodysesthesia syndrome	5 (28%)	1 (6%)	6 (67%)	0 (0%)	0.10
Dry skin	2 (11%)	0 (0%)	3 (33%)	0 (0%)	0.29
Flushing	2 (11%)	0 (0%)	3 (33%)	0 (0%)	0.29
Alopecia	5 (28%)	0 (0%)	1 (11%)	0 (0%)	0.63
Rash maculo-papular	3 (17%)	0 (0%)	1 (11%)	0 (0%)	>0.95
Hepatic Disorders					
Alanine aminotransferase increased	4 (22%)	1 (6%)	1 (11%)	0 (0%)	0.64
Vascular Disorders					
Flushing	2 (11%)	0 (0%)	3 (33%)	0 (0%)	0.29

Midgut NETs Patients	PRRT/CAPTEM (n = 32)		PRRT (n = 13)		P Value* Any Grade Adverse Event
Adverse Event^	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	**
Any adverse event	32 (100%)	28 (88%)	13 (100%)	6 (46%)	
Gastrointestinal Disorders					
Vomiting	13 (41%)	1 (3%)	0 (0%)	0 (0%)	0.009
Stomach pain	2 (6%)	0 (0%)	4 (31%)	0 (0%)	0.05
Nausea	26 (81%)	0 (0%)	7 (54%)	0 (0%)	0.08
Abdominal pain	13 (41%)	1 (3%)	3 (23%)	0 (0%)	0.32
Diarrhoea	24 (75%)	0 (0%)	9 (69%)	0 (0%)	0.72
Constipation	9 (28%)	0 (0%)	3 (23%)	0 (0%)	>0.95
Haematological Disorders					
Neutrophil count decreased	20 (63%)	6 (19%)	1 (8%)	0 (0%)	<0.001
Anaemia	17 (53%)	1 (3%)	2 (15%)	0 (0%)	0.02
Platelet count decreased	24 (75%)	8 (25%)	6 (46%)	1 (8%)	0.09
White blood cell decreased	17 (53%)	5 (16%)	5 (38%)	0 (0%)	0.51
Lymphocyte count decreased	20 (63%)	18 (56%)	7 (54%)	4 (31%)	0.74
General Disorders					
Fatigue	25 (78%)	0 (0%)	11 (85%)	0 (0%)	>0.95
Nervous System Disorders					
Dizziness	9 (28%)	0 (0%)	0 (0%)	0 (0%)	0.04
Headache	7 (22%)	0 (0%)	0 (0%)	0 (0%)	0.09
Dermatological Disorders					
Palmar-plantar erythrodysesthesia syndrome	6 (19%)	0 (0%)	0 (0%)	0 (0%)	0.16
Rash maculo-papular	6 (19%)	0 (0%)	1 (8%)	0 (0%)	0.65
Alopecia	7 (22%)	0 (0%)	2 (15%)	0 (0%)	>0.95
Hepatic Disorders					
Alanine aminotransferase increased	8 (25%)	1 (3%)	1 (8%)	1 (8%)	0.25
GGT increased	4 (13%)	0 (0%)	3 (23%)	1 (8%)	0.39
Aspartate aminotransferase increased	5 (16%)	1 (3%)	2 (15%)	1 (8%)	>0.95
Alkaline phosphatase increased	4 (13%)	0 (0%)	2 (15%)	1 (8%)	>0.95
Respiratory Disorders					
Upper respiratory infection	3 (9%)	0 (0%)	2 (15%)	0 (0%)	0.62
Vascular Disorders					
Flushing	13 (41%)	0 (0%)	4 (31%)	0 (0%)	0.74
Musculoskeletal Disorders					
Arthralgia	4 (13%)	0 (0%)	1 (8%)	0 (0%)	>0.95

***p-value** based on a Fisher's exact test for any grade adverse event (AE) between two treatment groups.
^Adverse events which were reported by at least 10% of patients.
**** no p-value** to compare any AE between the two treatments as all patients experienced at least one AE of any grade.

Eligibility Criteria

Adults ≥ 18 years old with histologically proven, moderate to well-differentiated, unresectable G1/2 pancreatic or midgut NETs with Ki-67 < 20%;

Presence of somatostatin receptor avidity suitable for PRRT demonstrated on 68Ga-octreotate PET scan;

Advanced/metastatic disease that has progressed during or after ≤ 2 prior systemic therapies; OR previously untreated advanced/metastatic disease with high symptomatic burden and non-functional tumours for which other therapy is not indicated or appropriate;

ECOG performance status 0-2; Adequate renal, bone marrow and liver function; Life expectancy of at least 9 months;

No primary NETs other than small bowel (midgut) or pancreatic NETs; No cytotoxic chemotherapy, targeted therapy, or biotherapy within the last four weeks; No prior intrahepatic 90Y microspheres, such as SIR-Spheres in the past six months;

No prior Peptide Receptor Radionuclide Therapy; No uncontrolled metastatic disease to the central nervous system. No active infections

Recruitment

Midgut NETs: December 2015 February 2018
Pancreatic NETs: December 2015 to November 2018

Patient follow up mNETS and pNETs

	Cohort A pNETS	Cohort B mNETS
Median follow-up time:	33.8 months	34.7 months
Minimum follow-up time:	11.4 months	9.6 months
Maximum follow-up time:	42.0 months	45.1 months

Conclusion. This initial planned analysis of **midgut NET patients** demonstrates **similarly high 15 month PFS for CAPTEM/PRRT relative to PRRT alone.**
PFS in both arms is **superior to** what was expected from initial estimates (15 month PFS with Lutathera in NETTER1 was ~ 73%).
Objective Tumour Response Rate is numerically **higher** for **combined therapy** but at the **cost** of **greater G3/4 toxicity, mainly haematologic.**
Pancreas NET patients adverse event profile is similar to mNETs patients.
Longer follow up to 36 months is planned to see if PFS with CAPTEM/PRRT is sufficient to warrant Phase III evaluation.

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