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PReCedeNT Trial: Phase III Randomised Controlled Trial of PRRT with Lutetium – 177 DOTATATE Plus Chemotherapy Versus PRRT Alone in FDG-avid, Well-Differentiated Gastro-Entero-Pancreatic Neuroendocrine Tumors

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BACKGROUND

Well-differentiated GEP NETs show positive uptake on Ga-68-DOTATOC PET/CT, a somatostatin-receptor (SSTR)-specific imaging tracer. 18F-FDG PET/CT is preferred for aggressive, high-grade NETs as GLUT (glucose-transporter) receptor expression entails poorer prognosis. Grade 2 NET may demonstrate heterogenous uptake of both tracers; suggestive of tumor heterogeneity. PRRT is widely available at reasonable cost since Lu-177-DOTATATE is manufactured indegenously, and is recommended in all International Guidelines. CAPTEM (Capecitabine-Temozolamide) regimen is equally cost-effective; hence combination treatment would be reasonable. We propose to prospectively study combination of PRRT and chemotherapy versus PRRT alone in FDG-positive well-differentiated NETs, to generate robust evidence to address tumor heterogeneity.

METHODS

This is a 2-arm, parallel design, open label, superiority, phase 3 randomized controlled trial, with 1:1 randomisation. Arm A being PRRT with Lu-177-DOTATATE, 180-200 mCi administered intravenously for 4 cycles, at interval duration of 8-12 weeks and Arm B being PRRT with Lu-177-DOTATATE, 180-200 mCi administered intravenously for 4 cycles, at interval duration of 6-8 weeks plus CAP-TEM Protocol: Day 1: Oral Capecitabine 1500 mg/m2, per oral, twice daily within 15 min of food for 14 days, followed by 2 week rest period. One week before every cycle - Hematological, liver function, renal function and quality of life parameters shall be assessed. Immediately after PRRT and on day 15, hematological, liver function parameters will be assessed. At each visit history, physical examination and adverse events (CTCAE version 4.03) would be noted. Primary End-points of the study are Progression-free survival and Objective Response Rate on RECIST 1.1 and EORTC criteria. Secondary End-points being Quality of Life parameters and Overall Survival.

RESULTS

Based on the NETTER-1 trial, we assumed that PRRT will give a 2 year PFS of 60%, the experimental arm will improve the 2 year PFS by an absolute value of 15%. With a type 1 error (one-sided) of 5% and Type 2 error of 20 %, with 10% lost to follow up, with study duration of 8 years, sample size of 162 patients, with 95 events required for analysis. For any statistical test performed, significance level will be set to 5%. The study period is 6 years and follow-up period is 2 years.

CONCLUSIONS

Based on the hypothesis, that combination therapy is more efficacious than PRRT alone, this study shall provide a reliable conclusion with regards to the superiority between both the arms.

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