RENET: A randomized phase III trial comparing REgorafenib to placebo in patients with advanced, progressive, well-differentiated NEuroendocrine Tumors (NETs).

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Statistician: Dr Isabelle Borget, Gustave Roussy, Villejuif, France

Sponsor: UNICANCER

Groups: UNICANCER, FFCD, GERCOR (PRODIGE), GTE, CommNETS

Countries: France, Europe, Canada, Australia…

Antiangiogenics are effective treatments in NETs

Study	Phase	Study drug	Patients (pNETs)	ORR (%)	PFS (months)	OS (months)
(Raymond et al., 2011)	III (vs. placebo)	Sunitinib	171 (171)	9	11.4 vs 5.5 (p<0.001)	38.6 vs 29.1 (p=0.094)
(Grande et al., 2015)	II	Pazopanib	44 (18)	9	12.8	24.1
(Phan et al., 2015)	II	Pazopanib + octreotide LAR	32 (32)	22	14.4	25
(Phan et al., 2015)	II	Pazopanib + octreotide LAR	20 (-)	0 (tumor shrinkage, 58)	12.2	18.5
(Ahn et al., 2013)	II	Pazopanib	37 (12)	19	9.1	NR
(Strosberg et al., 2016)	II	Axitinib	30 (-)	3 (tumor shrinkage, 68)	26.7	45.3
(Chan et al., 2017)	II	Cabozantinib	61 (20)	15	31.4 (carcinoids) 21.8 (pNET)	NR
(Xu et al., 2017)	II	Sulfatinib	81 (41)	15 (carcinoids) 17 (pNETs)	13.4 (carcinoids) 19.4 (pNETs)	NR
Capdevilla et al	II	Lenvatinib	110 (55)	40,4 (pNET); 18,5 (GI)	14,2 (pNETs) 17,6 (GI-NETs)	NR

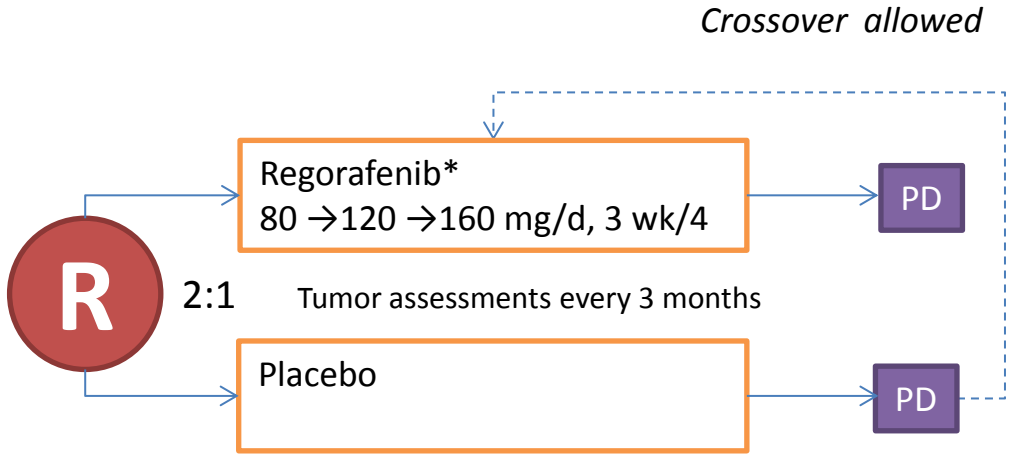
MAIN INCLUSION CRITERIA

- Well- or moderately-differentiated, grade 1-2 & G3 (with Ki67<60% or MI <20) NETs or typical/atypical carcinoids (review by expert pathologist is encouraged)
- Any primary (pancreas, GI, thoracic, unknown, etc.)
- Locally advanced (unresectable) or metastatic disease not amenable to surgery or locoregional therapies
- Disease progression in the previous 12 months (RECIST)
- Failed available, validated systemic Tx:
  - **Pancreatic NETs**: everolimus and/or sunitinib, at least one line of cytotoxic chemotherapy (if available and patient eligible), and PRRT (if available and patient eligible)
  - **Digestive NETs**: everolimus and PRRT (if available and patient eligible)
  - **Other NETS**: everolimus
- Prior somatostatin analog (SSA) treatment allowed
- Concomitant SSA for functional NET-related symptoms allowed
- No contraindication to antiangiogenics
- ECOG PS 0 or 1, age ≥18 yrs, life expectancy >3 months
- Adequate bone marrow, liver and renal function

MAIN EXCLUSION CRITERIA

- Poorly differentiated Grade 3 NEC
- Pheochromocytoma
- Prior treatment with regorafenib
- Congestive heart failure ≥ class 2, unstable angina, cardiac arythmia, uncontrolled arterial hypertension despite optimal management
- Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery)
- Clinically significant Grade 3 bleeding within 30 days before randomization
- Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding within 6 months of randomization
- History of gastrointestinal perforation or fistula
- Previously untreated or concurrent cancer except cervical cancer in-situ, treated basal cell carcinoma, or superficial bladder tumor; subjects surviving a cancer that was curatively treated and without evidence of disease for more than 5 years before randomization are eligible
- Arterial or venous thrombotic or embolic events within 6 months before study entry

Design: phase III randomized trial



Stratification:

1. Primary (pancreas vs other)
2. ECOG PS 0 vs 1
3. Prior anti angio: no vs yes
4. Grade G1 vs G2 –G3

* REDOS regimen: weekly dose escalation according to observed toxicity during cycle 1; optimal dose will be used for subsequent cycles

Bekaii-Saab TS et al. Regorafenib dose optimization study (ReDOS): Randomized phase II trial to evaluate dosing strategies for regorafenib in refractory metastatic colorectal cancer (mCRC): An ACCRU Network study. J Clin Oncol 2018;36(suppl):611

Endpoints

- Primary: Progression-free survival (PFS) (RECIST 1.1, investigator-assessed)
- Secondary
  - Objective response rate (RECIST 1.1)
  - Overall survival
  - Clinical response of carcinoid syndrome
  - Safety (NCI CTC v 5.0
  - Quality of life (QLQ-C30, QLQ-GI.NET21 [NET-specific questionnaires from EORTC])

Statistics

Study objective: to increase PFS from 8 (H0) to 12 (H1) months (HR=0.67)
Power=90%, unilateral alpha=0.025: 318 pts needed

HR=0.50 (PFS 6 vs 12 months): 109 pts needed

HR=0.60 (PFS 7 vs 12 months): 200 pts needed

HR=0.75: 633 pts needed

1) EARLY SAFETY STOPPING RULE

This rule will be based on the percentage of patients who will not begin Cycle 4 because of toxicity (Cycle 4 in case of RECIST evaluation every 3 months)

→ If > 25% of the first XXX patients have to stop regorafenib because of toxicity during the first 3 cycles, the trial will be stopped.

Note:

- *13-17% of pts stopped everolimus or sunitinib for toxicity in the phase III pNET studies.*
- *In the REDOS randomized Phase II study in mCRC, <10% of pts stopped regorafenib (administered with the study toxicity-driven dose escalation regimen) for toxicity during the first two cycles (~ 50% stopped for disease progression).*

2) **INTERIM ANALYSIS**

This interim analysis will be performed in order to stop the trial in case of futility, efficacy or lack of efficacy, after Y events have occurred and Z patients enrolled.

Feasibility - Funding

- France: PRODIGE (UNICANCER + FFCD + GERCOR) + GTE
- Canada, Australia: will be discussed at CommNETs meeting (07-dec-2018)
- Funding: Bayer (global internal review: go signal)

Competitive trials

- Cabozantinib (phIII, CABINET, USA, NCT03375320)
- Axitinib (PhII/III, Germany, Spain, Italy, UK, NCT01744249)
- Sulfatinib (phIII, China, NCT02588170)
- Lenvatinib? (after ph II results at ESMO 2018)

Discussion