Discordance between central versus local response assessments in neuroendocrine tumor (NET) patients (pts) enrolled in A021202

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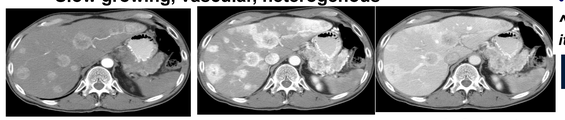
BACKGROUND

- Limited treatment options for progressive well differentiated neuroendocrine tumors *NET) arising outside the pancreas (aka carcinoids, CARC)
- FDA-approved therapies include lanreotide[1], everolimus[2], and Lu177 dotatate [3]
- Eventual resistance is the rule
- Sunitinib improves PFS in pancreatic NETs (FDA-approved)[4]
- Randomized studies suggest TKIs (including pazopanib, surufatinib) have activity in carcinoid (stability>> shrinkage)[5,6]
- Well diff NET can be difficult to assess radiographically
  - Slow growing, vascular, heterogenous [7,8]



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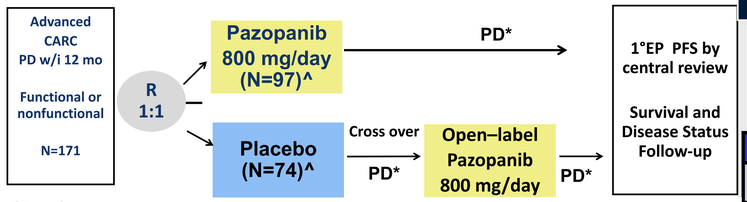
- RADIANT-2 trial confounded by loss of 21% events and informativ censoring (leading to loss of power) due to discordance between local /central review (e.g. when local site calls PD prematurely, and central review is not real-time) [9]
- RECIST1.1 has no ability to subclassify patients with stable diseas
  - No ability to predict who will do well long term
- A021202 was a positive randomized phase II study of pazopanib v placebo in progressive CARC (ASCO 2019[5])- primary EP -PFS by (real time) central review

  (ClinicalTrials.gov Id: NCT01841736)
- A021202 included serial blood samples & centrally banked images

GOAL OF OUR NETRF PROJECT

Accelerate drug discovery in NETs by incorporating superior endpoints for quantifying and tracking response to therapy, improved stratification of patients, and novel clinical trial designs requiring fewer patients

SCHEMA-A021202



Stratified by:
- Site of origin (SB v other)
- Concurrent somatostatin analog

*RECIST 1.1 by central review (at the time of PD by local review)

^*Randomization imbalance due to an error in the computer randomization algorithm made it slightly more likely to be assigned to pazopanib (1.3:1)*

RESULTS-A021202

Median PFS 11.6 mo (PZ) v 8.5 mo (PL)-CENTRAL READ[5]
HR 0.53; P=0.0005; Adj HR 0.57, p=0.002 (gender, functional status, site or primary, concurrent SSA)

Median PFS 11.6 mo (PZ) v 8.6 mo (PL) – LOCAL READ[5]
HR 0.61, p= .0042; Adj HR 0.64, p=0.0143

- No overall survival benefit
- Mostly radiographically stable disease
- PZ associated with increased (all grades) fatigue, nausea, HTN, AST/ALT increase, diarrhea
- PZ associated with increased Gr 3 and higher HTN, AST/ALT

AIMS-NETRF GRANT

Aim 1: To characterize the nature of radiologic progression in patients enrolled in A021202

a. **Characterize the discordance between local and central radiology assessment of progression (ASCO GI, 2021)**

b. Characterize the type and rate of progression in carcinoid tumors from A021202 patients (Including tumor growth rate)[14]

c. Evaluate tumor volume for assessing solid tumor burden in original CT images [15]

Aim 2: To assess the angiome in patients enrolled on A021202 and associate with clinical outcomes

Aim 3: To develop new trial designs for testing the next generation of carcinoid therapeutics

Discordances between central vs. local review of response and progressive disease status

SCAN LEVEL: discordances in 724 single evaluations across all pts (***scan-specific, not patient-specific***)

Central vs Local Review Outcomes - Initial Treatment

Local response classification	Central review classification PR (N=22)	SD (N=534)	PD (N=175)
PR	10 (45.5%)	16 (3.0%)	1 (0.6%)
SD	10 (45.5%)	479 (90.0%)	82 (46.9%)
PD	2 (9.1%)	32 (6.0%)	92 (52.6%)

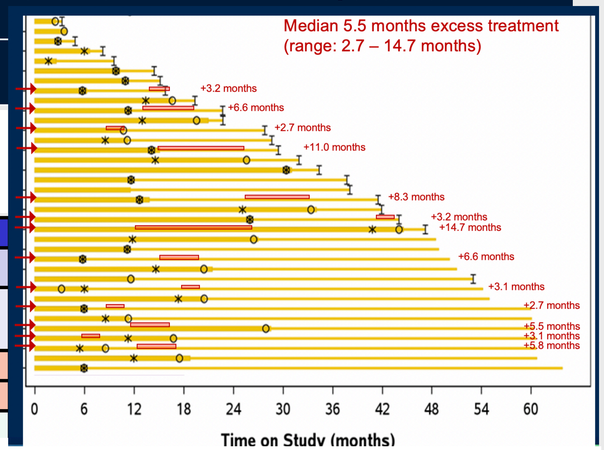
Cohen's kappa statistic indicated only moderate concordance across all scans: K = 0.48. 95% CI: 0.42 – 0.55

PATIENT LEVEL: 78 of 151 pts (52%) with local and central review had discordances between the local vs. central review classifications of response
- 45/82=55% Pazopanib and 33/69=48% Placebo pts with at least one discordance
- 7 pts had two types of discordances, 1 had three types of discordances

Central vs Local Review Outcomes - Initial Treatment- PATIENT LEVEL

Local response classification	Central review classification PR	SD	PD
PR	2	9	**1**
SD	3	121	**44**
PD	1	29	92

Cohen's kappa statistic again indicated only moderate concordance: K = 0.41; 95% CI: 0.32 – 0.50



swimmers plots for ***pazopanib pts*** off treatment due to PD; timeframe of extended therapy ------ due to discordances between local review (O) vs. central review (*); thick line indicates duration of active treatment

CONCLUSIONS

- Potential benefit of pazopanib needs to be considered in the context of the risk of toxicity; strategies for selecting pts most likely to benefit needed
- RECIST criteria may not be best response criteria for NET pts
- **Discordances in scan classifications observed in both directions in A021202 (50 treatment sites)**
  - **52% with discordance in one direction or another**
  - **Risk of over-treatment in 29%**
  - **More pts classified with earlier PD by central review than with later PD in relation to local review**
  - **Neither disease nor clinical factors appeared to influence ability to have full concordance in scan classifications**

  -Research exploring new models of carcinoid growth and response assessment is ongoing

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