New strategies to improve drug development in carcinoid tumors (Alliance A021202)

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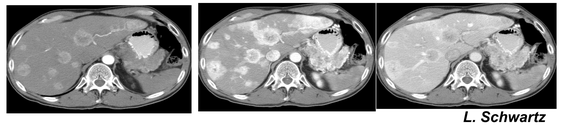
BACKGROUND

- Limited treatment options for progressive well differentiated neuroendocrine tumors arising outside the pancreas (aka carcinoids)
- FDA-approved therapies include lanreotide[1], everolimus[2], and Lu177 dotatate [3]
- Eventual resistance is the rule
- VEGF and its receptors expressed in GI/pancreas NETs [4-6]
- Sunitinib improves PFS in pancreatic NETs (FDA-approved)[7]
- Phase II studies suggest small molecule TKIs (including pazopanib) have activity in carcinoid (stability>> shrinkage)[8,9]
- Well diff NET can be difficult to assess radiographically
  - Slow growing, vascular, heterogenous [10,11]



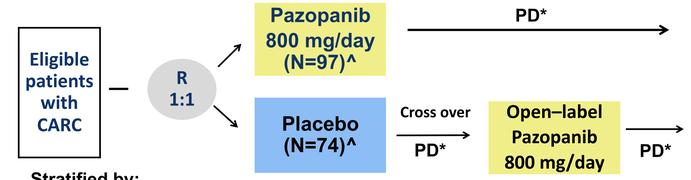
L. Schwartz

- RADIANT-2 trial confounded by loss of 21% events and informative 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) [12]
- RECIST1.1 has no ability to subclassify patients with stable disease
  - No ability to predict who will do well long term
- A021202 was a positive randomized phase II study of pazopanib v placebo in progressive carcinoid tumors (see ASCO 2019[13])- primary EP was 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



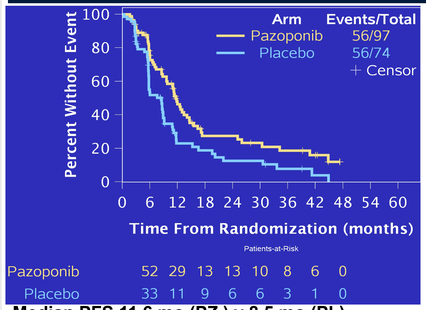
- Locally advanced or metastatic low- or intermediate-grade NET (carcinoid tumor) arising in the foregut, midgut or hindgut (or other nonpancreatic site)
- Functional or nonfunctional tumor
- Measurable disease by RECIST
- Radiological evidence for PD within 12 mo
- No prior VEGF inhibitors (prior everolimus OK)
- Prior SSA required for patients with documented SB1° Concurrent SSA OK if SSA started >2mo prior to registration and PD on SSA documented radiographically

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



- 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

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

AIMS-NETRF GRANT

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

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

Aim 1: To characterize the nature of radiologic progression in patients enrolled in A021202 (L. Schwartz, Columbia)

a. Characterize the discordance between local and central radiology assessment of progression

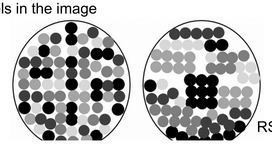
b. Characterize the type and rate of progression in carcinoid tumors from A021202 patients (Including tumor growth rate)[14]

c. Evaluate tumor volume for assessing solid tumor burden in original CT images [15]
e.g. semi-automated volume of liver metastases

RADIOMICS-use of computer algorithms to extract quantitative features, not obvious to the unaided human eye, from routine radiologic imaging to identify tumor phenotypes, and information beyond tumor size or burden [16]

Texture analysis provides an objective, quantitative assessment of tumor heterogeneity by analyzing the distribution and relationship of pixel or voxel gray levels in the image

Can potentially be used to noninvasively assess:
- Benign v malignant
- Grade
- Mutation status
- Histologic subtype
- Predict for response to therapy



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Aim 2: To assess the angiome in patients enrolled on A021202 and associate with clinical outcomes (A. Nixon- Duke Cancer Duke University, Durham, NC)

a. Determine whether IL-6 or VEGF-D are predictive of benefit for pazopanib [17,18]
b. Determine whether other plasma angiome components are predictive of benefit for pazopanib
c. Evaluate the changes in the plasma angiome after treatment with or without pazopanib

Aim 3: To develop new trial designs for testing the next generation of carcinoid therapeutics (M. Maitland-Inova Schar Cancer Institute, Fairfax, VA)

a. To develop a new computational model of carcinoid growth based on CT imaging metrics [19]
b. To incorporate known elements of pazopanib pharmacodynamics and plasma biomarker changes into the new computational model of carcinoid growth and assess treatment effects in A021202

CONCLUSIONS

- Pazopanib improves PFS (central review) in progressive carcinoid tumors
- No improvement in OS (cross-over is likely confounder)
- Expected AE profile (although relatively high rate of grade 3 HTN); overall increase in grade ≥ 3 AEs
- VEGF pathway is a valid target for therapy in carcinoid; potential benefit of pazopanib needs to be considered in the context of the risk of toxicity
- Need to identify strategies for mitigating toxicity and/or selecting patients most likely to benefit
- Predictive biomarker analyses pending
- NETRF funded work is ongoing and aims to identify superior endpoints for tracking response to therapy and improved stratification of patients

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