Clinical Trials in Neuroendocrine Tumors

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Disclosures

- Novartis—Advisory Board
- Pfizer—Honoraria for educational lecture on NET
- Lexicon—Consulting
- Bristol Myers Squibb—spouse is an employee and receives salary and benefits
Well Differentiated Neuroendocrine Tumors
Management of Well-Differentiated NETs

- Localized disease → surgical resection
- Limited metastatic disease → surgical debulking
- Liver dominant disease → liver directed therapy

- Metastatic disease
  - Somatostatin analogues
  - Targeted therapy (mTOR or VEGF inhibitors) if not seeking response
  - Chemotherapy if seeking tumor response
  - PRRT for somatostatin avid disease (if available)
Liver Directed Therapy

- NCCN, NANETS and ENETS all recommend embolization therapy for progressive or symptomatic liver dominant disease

- General Approaches
  - Chemoembolization
  - Radioembolization
  - Bland Embolization
  - Drug-eluting Beads
RETNET Trial

- Randomized Embolization Trial for NeuroEndocrine Tumor Metastases to the Liver
- (ClinicalTrials.gov Identifier NCT02724540)

180 subjects randomized to bland, TACE, or DEB-TACE
- Is one more or less effective?
- Is one more or less toxic?
- Does one provide better or worse QOL?
Four out of 10 patients in the drug-eluting bead arm experienced major complications
  • DEB arm was closed due to toxicity
  • This is the second trial demonstrating this

NCCN guidelines changing as a result!
Integration with Systemic Therapies—CapTemY90

- Grade 2 NETs have an intermediate proliferative rate and progress more aggressively than low-grade NETs

- Temozolomide and capecitabine chemotherapy results in a 30% response rate

- Temozolomide and capecitabine are synergistic with radiation and often used concurrently in other malignancies

- Safety study recently conducted
  - CapTem during first two of four weeks while Y90 was planned
  - Radioembolization treatments done on day 7 of subsequent CapTem cycles

Kunz et al., ASCO 2018
Soulen et al., Pancreas 2018
Integration with Systemic Therapies—CapTemY90

RESULTS

Median CGA reduction of 87%

ORR of 74% with 3 CRs

Starting a 50 patient, 3 institution study

Soulen et al., Pancreas 2018
Management of Well-Differentiated NETs

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Somatostatin Receptor

• Expressed in 80-100% of PNETs and carcinoids

• Five types of SSTRs
  • Higher and more diverse levels of expression in well differentiated tumors

• High levels of SSTR expression usually results in a positive octreotide scan or gallium PET scan

• Serve both diagnostic and therapeutic purposes

Oberg KE et al, Gastroenterology 2010
Gallium-68 DOTATATE Imaging

- Has largely replaced the octreotide scan

- Indications to obtain
  - Evaluate for PRRT candidacy
  - Aid in distinguishing between more and less aggressive tumors
  - More refined detail regarding disease status
  - Identification of an unknown primary
  - Aid in diagnosing a neuroendocrine tumor (e.g. elevated chromogranin)
177Lu-Dotatate is a radiolabeled derivative of octreotide that binds to somatostatin receptors

Extensive experience in Europe in both carcinoid and PNETs
- Rotterdam study of 310 patients showing a PFS of 33 months and an OS of 46 months

Requires patient to have a positive octreotide scan or gallium DOTATATE PET scan

Kwekkeboom DJ et al, JCO 2008
### Metastatic G1/G2 midgut carcinoid with progression on SSA and somatostatin receptor positive disease (n=230)

<table>
<thead>
<tr>
<th>RANDOMIZE</th>
<th>Octreotide LAR (high dose – 60mg every 4 weeks)</th>
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<td>7.4 GBq of $^{177}$Lu-Dotatate every 8 weeks x 4 + SSAs for symptom control</td>
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#### Progression free survival:
- 8.4 months vs. not reached (HR 0.21, p<0.0001)
- Estimated PFS in $^{177}$Lu-Dotatate arm: 40 months
- Response Rate: 3% vs. 19%

Strosberg J et al, NEJM 2017
Xencor

- Phase I trial of a SSTR2/CD3 bispecific antibody (antibodies bind to two things) that draws immune cells to neuroendocrine tumors expressing the somatostatin receptor, triggering an immune attack on the cancer cells

http://www.genscript.com/bispecific-antibody.html
Xencor—Treatment Plan

Grade 1 or 2 NET of the pancreas, GI tract or lung who have progressed on an SSA and one other targeted agent

XmAb18087 intravenously on days 1, 8, 15 and 22 of a 28 day cycle for 3 cycles

CT Chest, Abdomen and Pelvis to assess response

• Study Objectives
  • Primary
    • Assess safety and toxicity, determine best treatment dose
  • Secondary
    • Response rate, duration of response, progression free survival
  • Exploratory
    • Laboratory studies (pharmacokinetics, immune markers)
Phase I trial of a SSTR2 receptor ligand linked to DM1 that delivers DM1 (a kind of chemotherapy) directly to neuroendocrine tumors
  • For carcinoid tumors that are somatostatin receptor positive

Utilizes a pentarin molecule

**Primary Objective:** safety, toxicity, recommended phase II dose

**Secondary Objectives:** efficacy, biologic correlative studies
Trials in Development at Penn

- Phase I CAR-T trial in pancreatic neuroendocrine tumors and neuroendocrine tumors of the GI tract

- Phase II trial of PARP inhibition and immunotherapy in combination with temozolomide and capecitabine in pancreatic neuroendocrine tumors
Temozolomide Induced DNA Damage

O\textsuperscript{6}-methylguanine (O\textsuperscript{6}-mG) Direct DNA repair with MGMT

N\textsuperscript{7}-methylguanine (N\textsuperscript{7}-mG) and N\textsuperscript{3}-methyladenine (N\textsuperscript{3}-mA) Base Excision Repair
Telomere Maintenance

- Normal cells have a gradual degeneration of their telomeres

- Telomerase maintains telomeres allowing cells to live longer than planned
  - 85-90% of cancer cells express greater than normal levels of telomerase

- Remaining 10-15% of cancer cells maintain telomeres via another mechanism

Weinberg RA, The Biology of Cancer
www.optimalhealthspecturms.com
Alternative Lengthening of Telomeres

- Telomeres maintained independently of telomerase

- Present in 10-15% of cancers

- Unclear how ALT becomes activated

- Mutations seen in many pancreatic neuroendocrine tumors are required for this mechanism to be activated

- Dependent on homologous recombination (HR) and show molecular characteristics of hyperactive HR

Lovejoy et al., PLoS Genetics 2012
DNA Repair Mechanisms

- Direct Repair
- Base Excision Repair
- Nucleotide Excision Repair
- Mismatch Repair
- Homologous Recombination
- Non-homologous End Joining
- Inter-strand Crosslink Repair
- Concerted DNA repair
Trials in Development at Penn

- Phase I CAR-T trial in pancreatic neuroendocrine tumors and neuroendocrine tumors of the GI tract

- Phase II trial of PARP inhibition and immunotherapy in combination with temozolomide and capecitabine in pancreatic
  - Determine if this combination of medicines can be given safely and with minimal side effects
  - Take an early look at if this might be more efficacious than CapTem alone
  - Learn more about the scientific mechanisms that drive these tumors
High Grade Neuroendocrine Carcinomas
Current Standard Therapy

- Very limited clinical trial data specific to G3 tumors with most data extrapolated from small cell lung cancer literature

- Multiple small cell lung cancer studies showing platinum and etoposide to be the “best” treatment option
  - Response rate: 44-86%
  - Median overall survival: 8-11.4 months

- No recent prospective data that has parsed treatment data out taking into consideration well-differentiated G3 vs. poorly differentiated G3

Ihde DC et al, J Clin Oncol 1994
Noda K et al, N Engl J Med 2002
Hanna N et al, J Clin Oncol 2006
Lee SM et al, Thorax 2009
Lara PN Jr et al, J Clin Oncol 2009
High grade GI NECs of GI origin with Ki-67 20-100% OR mitotic rate >10/10 HPF

**Randomize**

Carboplatin AUC 5 IV on day 1 OR Cisplatin 25 mg/m2 IV daily days 1-3 AND Etoposide 100 mg/m2 IV daily days 1-3 Repeat every 21 days (N=63)

Capecitabine 750 mg/m2 orally twice daily on days 1-14 Temozolomide 200 mg/m2 orally daily on days 10-14 Repeat every 28 days (N=63)

Primary Endpoint: PFS (improvement from 6 months to 10 months) Secondary Endpoints: RR, OS, laboratory and imaging correlates
CABINET: Randomized phase II trial of cabozantinib vs placebo in patients with GI and pancreatic neuroendocrine tumors whom have progressed on prior therapy

Randomized phase II trial of PRRT vs everolimus in neuroendocrine tumors of the lung

Phase II trial of temozolomide based therapy in pheochromocytoma and paraganglioma

PRRT in pheochromocytoma and paraganglioma
Thank You!

Questions?