Clinical Trials in Neuroendocrine Tumors

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Penn Medicine

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

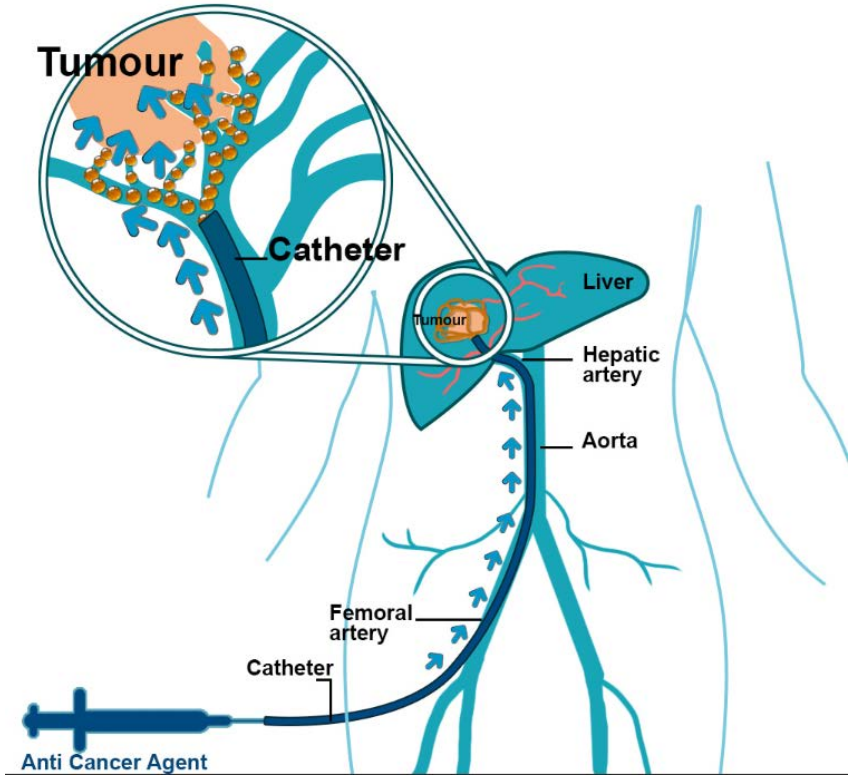
Management of Well-Differentiated NETs

- **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**

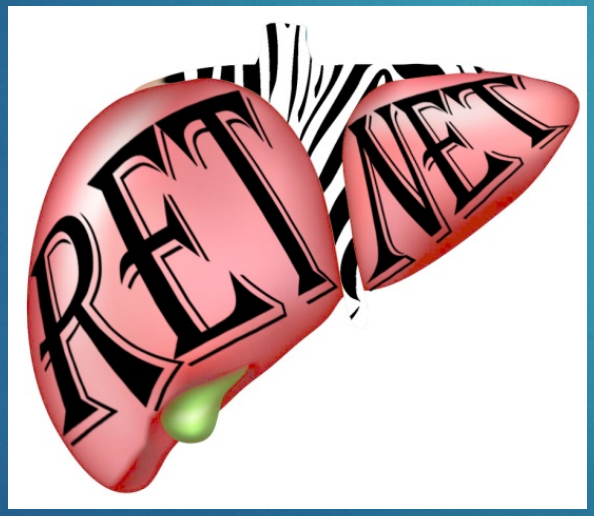
- **General Approaches**
  - Chemoembolization
  - Radioembolization
  - Bland Embolization
  - Drug-eluting Beads



deliver.iut-auvergne.com

RETNET Trial

- **R**andomized **E**mbolization **T**rial for **N**euro**E**ndocrine **T**umor 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?

RETNET-First Safety Analysis

- **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!**

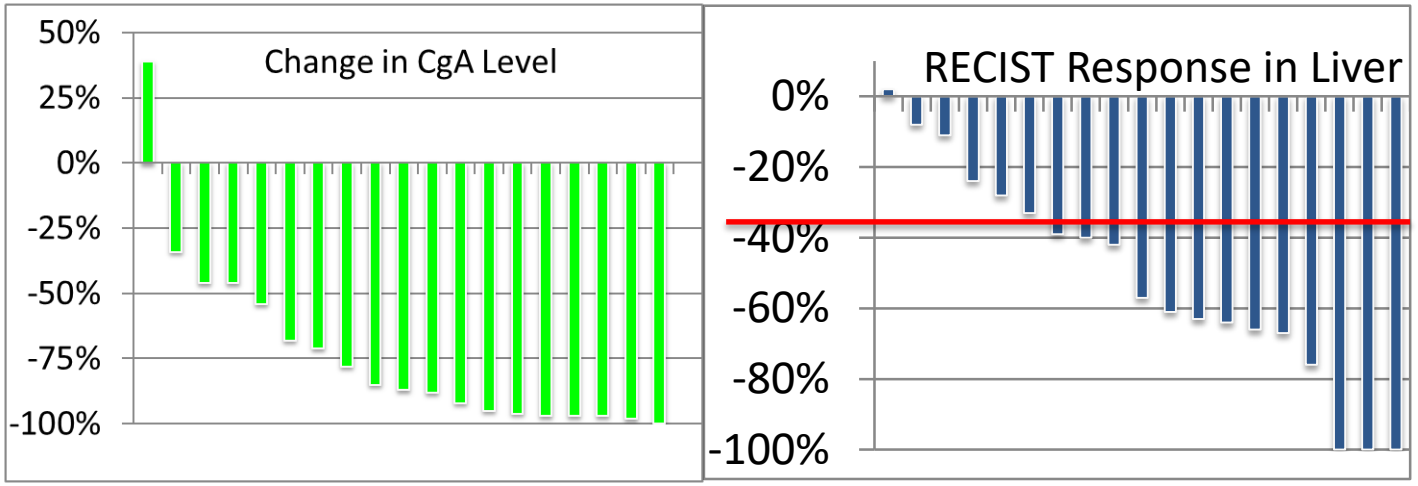
Integration with Systemic Therapies—CapTemY90

- 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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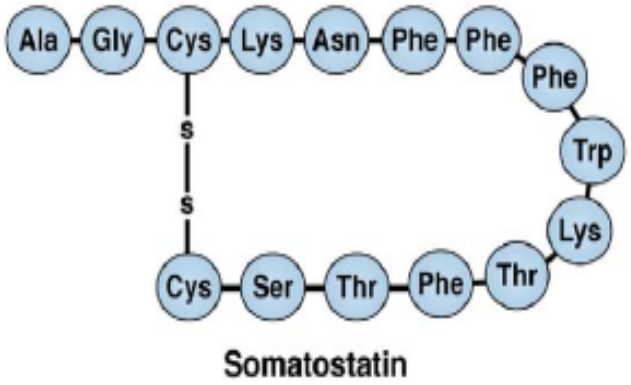
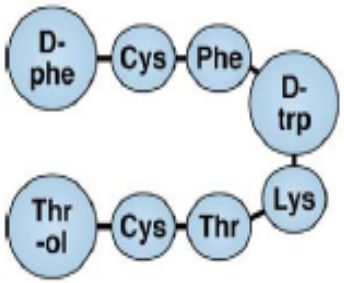
Somatostatin Receptor

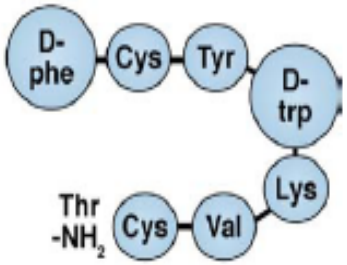
- **Expressed in 80-100% of PNETs and carcinoids**
- **Five types of SSTRs**
  - Higher and more diverse levels of expression in well differentiated tumors
- **High levels of SSTR expression usually results in a positive octreotide scan or gallium PET scan**
- **Serve both diagnostic and therapeutic purposes**



Somatostatin



Octreotide acetate



Lanreotide

Oberg KE et al, Gastroenterology 2010

Gallium-68 DOTATATE Imaging

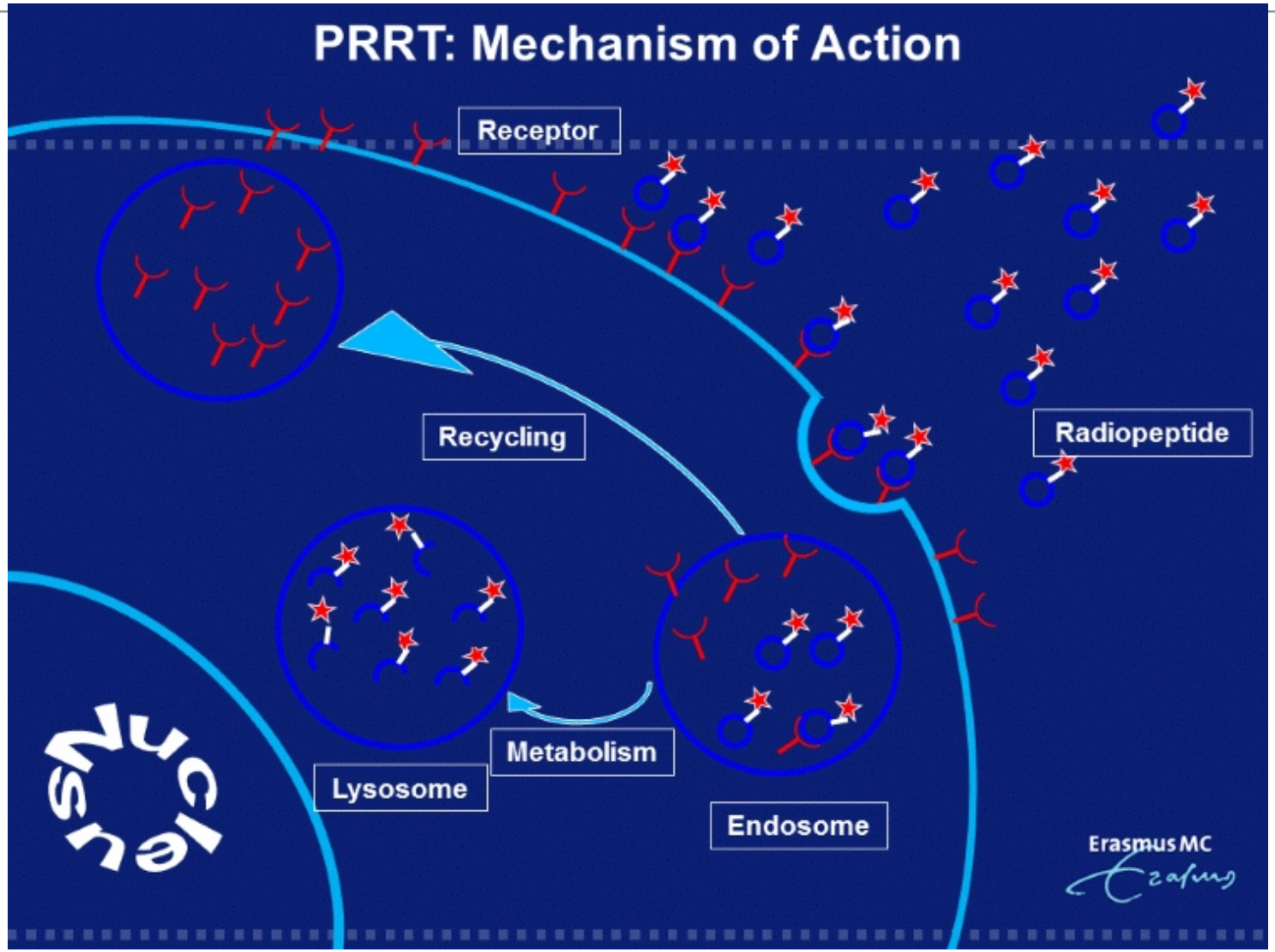
- **Has largely replaced the octreotide scan**

- **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)

Peptide Receptor Radionuclide Therapy

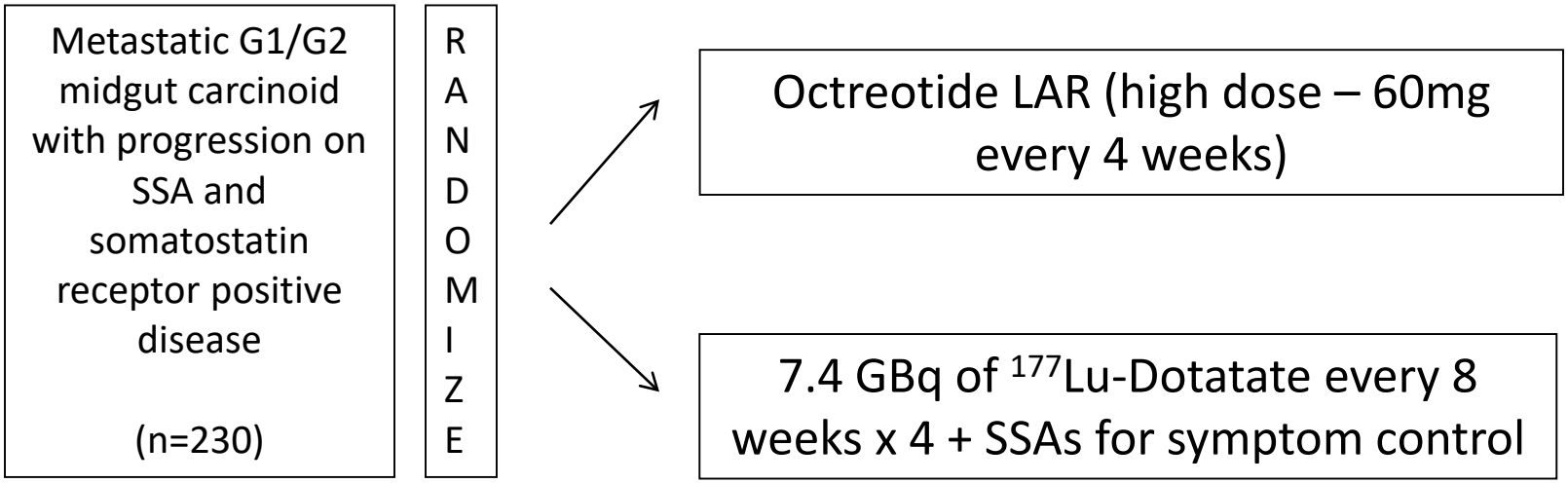
- ^{177}Lu-Dotatate is a radiolabeled derivative of octreotide that binds to somatostatin receptors
- Extensive experience in Europe in both carcinoid and PNETs
  - Rotterdam study of 310 patients showing a PFS of 33 months and an OS of 46 months
- Requires patient to have a positive octreotide scan or gallium DOTATATE PET scan

Kwekkeboom DJ et al, JCO 2008



Breeman WAP and de Blois E, University Medical Center Rotterdam

NETTER-1



Progression free survival: 8.4 months vs. not reached (HR 0.21, p<0.0001)

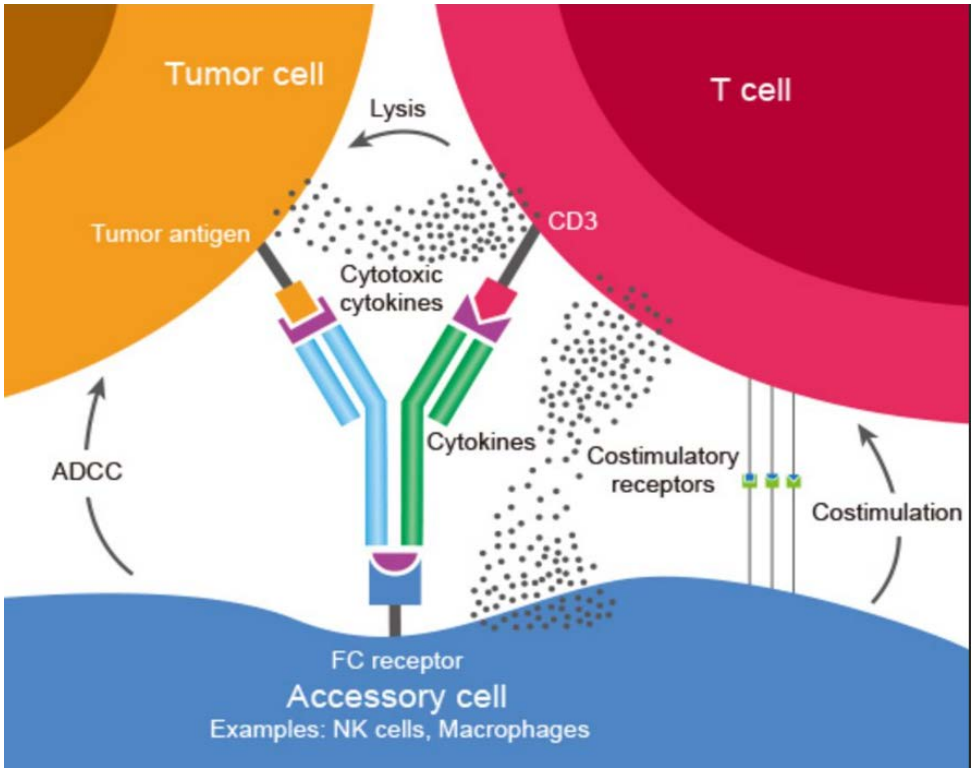
Estimated PFS in ^{177}Lu-Dotatate arm: 40 months

Response Rate: 3% vs. 19%

Strosberg J et al, NEJM 2017

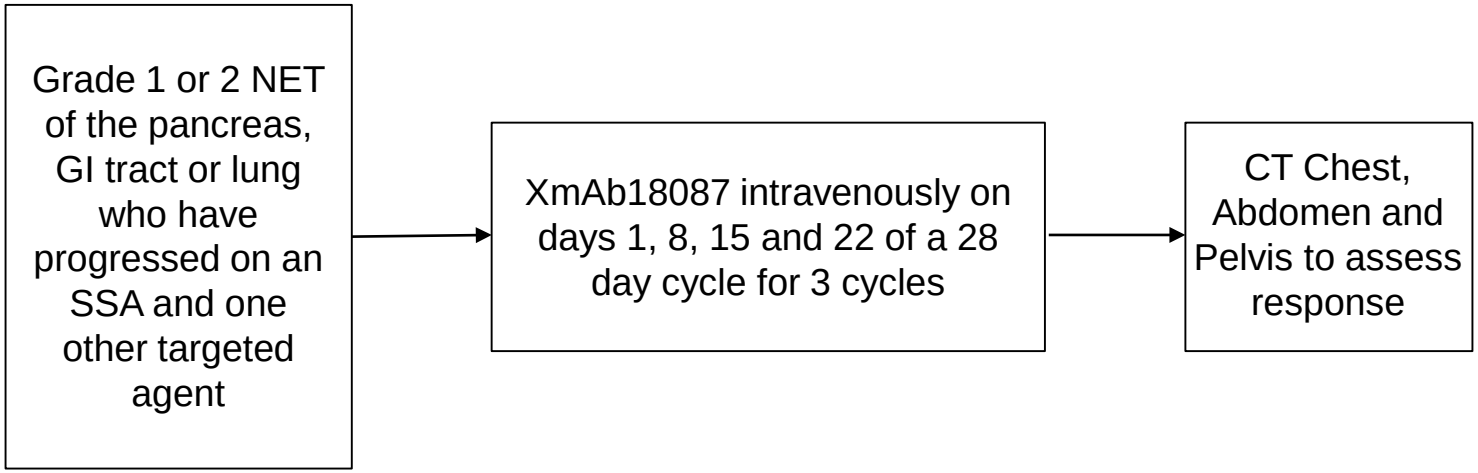
Xencor

- 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

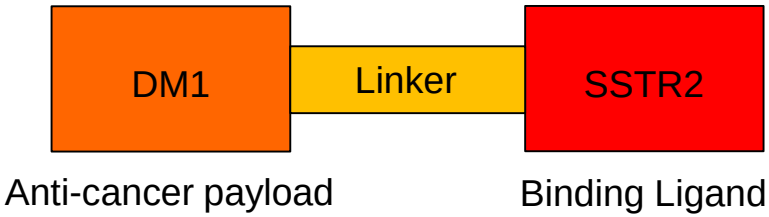
Xencor—Treatment Plan

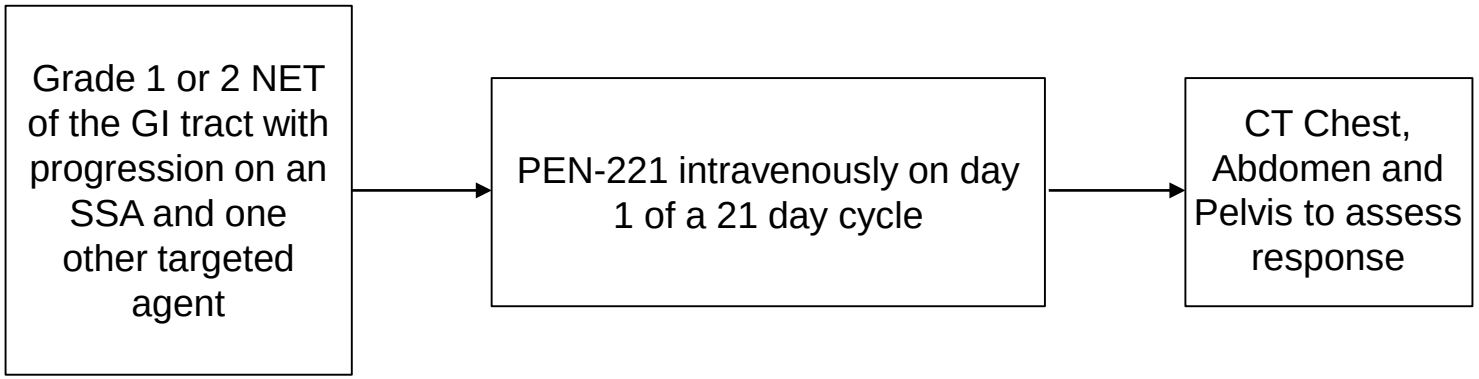


- Study Objectives
  - Primary
    - Assess safety and toxicity, determine best treatment dose
  - Secondary
    - Response rate, duration of response, progression free survival
  - Exploratory
    - Laboratory studies (pharmacokinetics, immune markers)

Tarveda

- 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





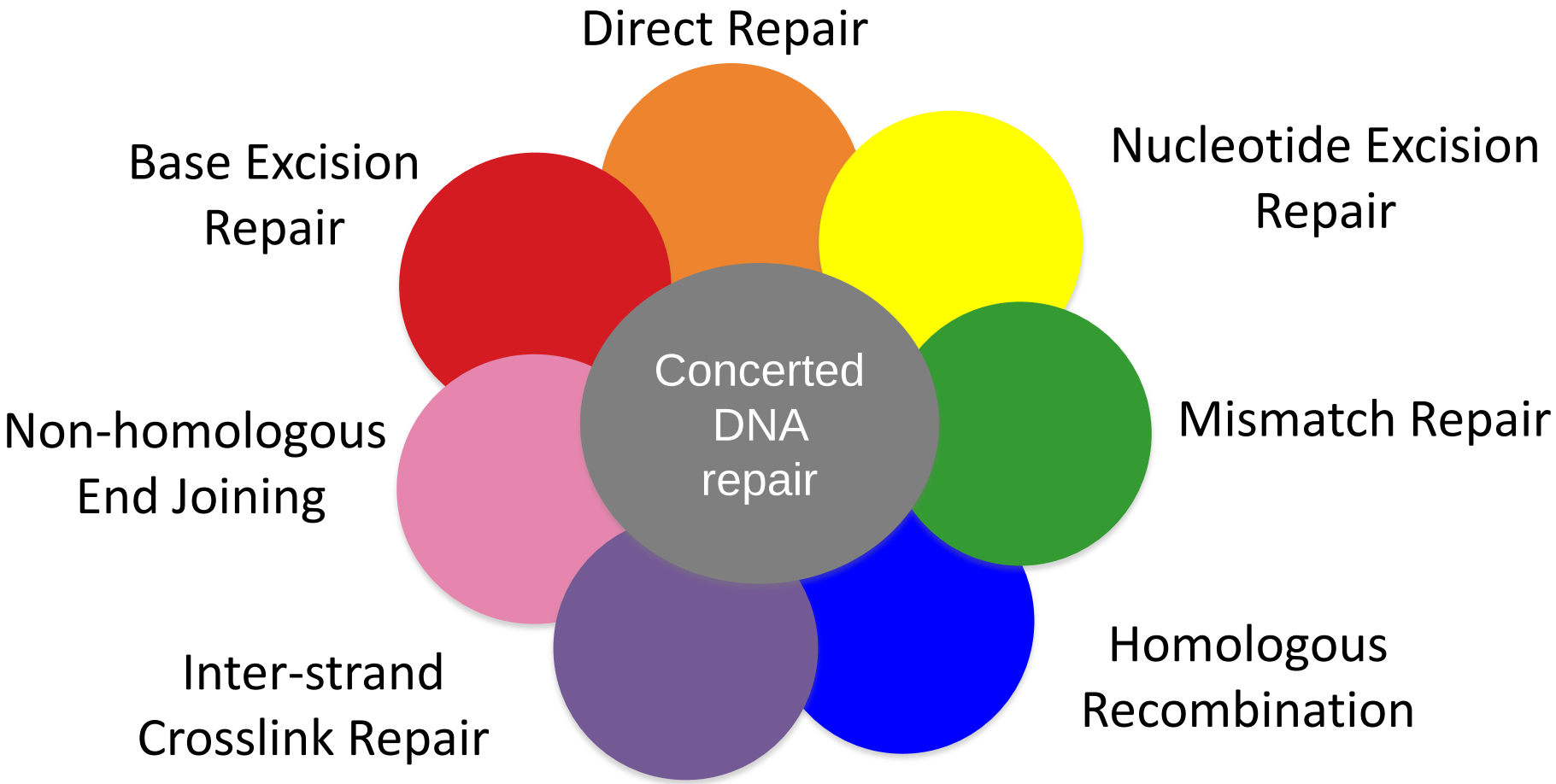
Primary Objective: safety, toxicity, recommended phase II dose
Secondary Objectives: efficacy, biologic correlative studies

Trials in Development at Penn

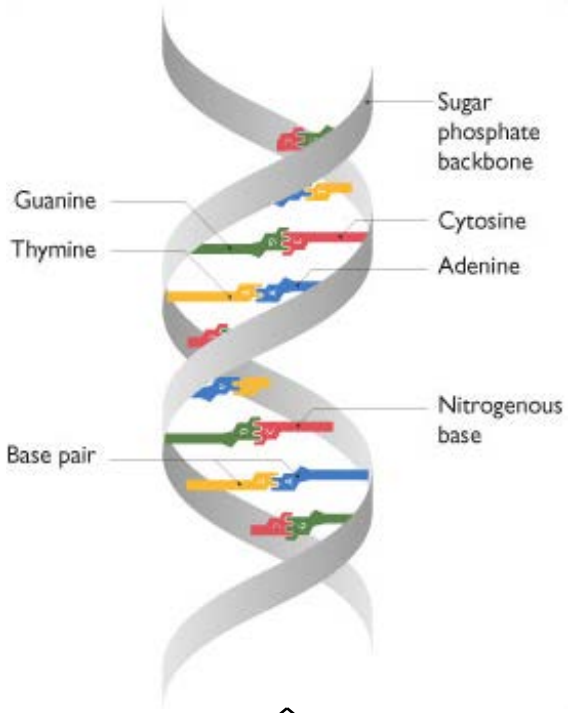
- **Phase I CAR-T trial in pancreatic neuroendocrine tumors and neuroendocrine tumors of the GI tract**

- **Phase II trial of PARP inhibition and immunotherapy in combination with temozolomide and capecitabine in pancreatic neuroendocrine tumors**

DNA Repair Mechanisms



Temozolomide Induced DNA Damage



Temozolomide

O^6-methylguanine (O^6-mG)
Direct DNA repair with MGMT

N^7-methylguanine (N^7-mG) and N^3-methyladenine (N^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**

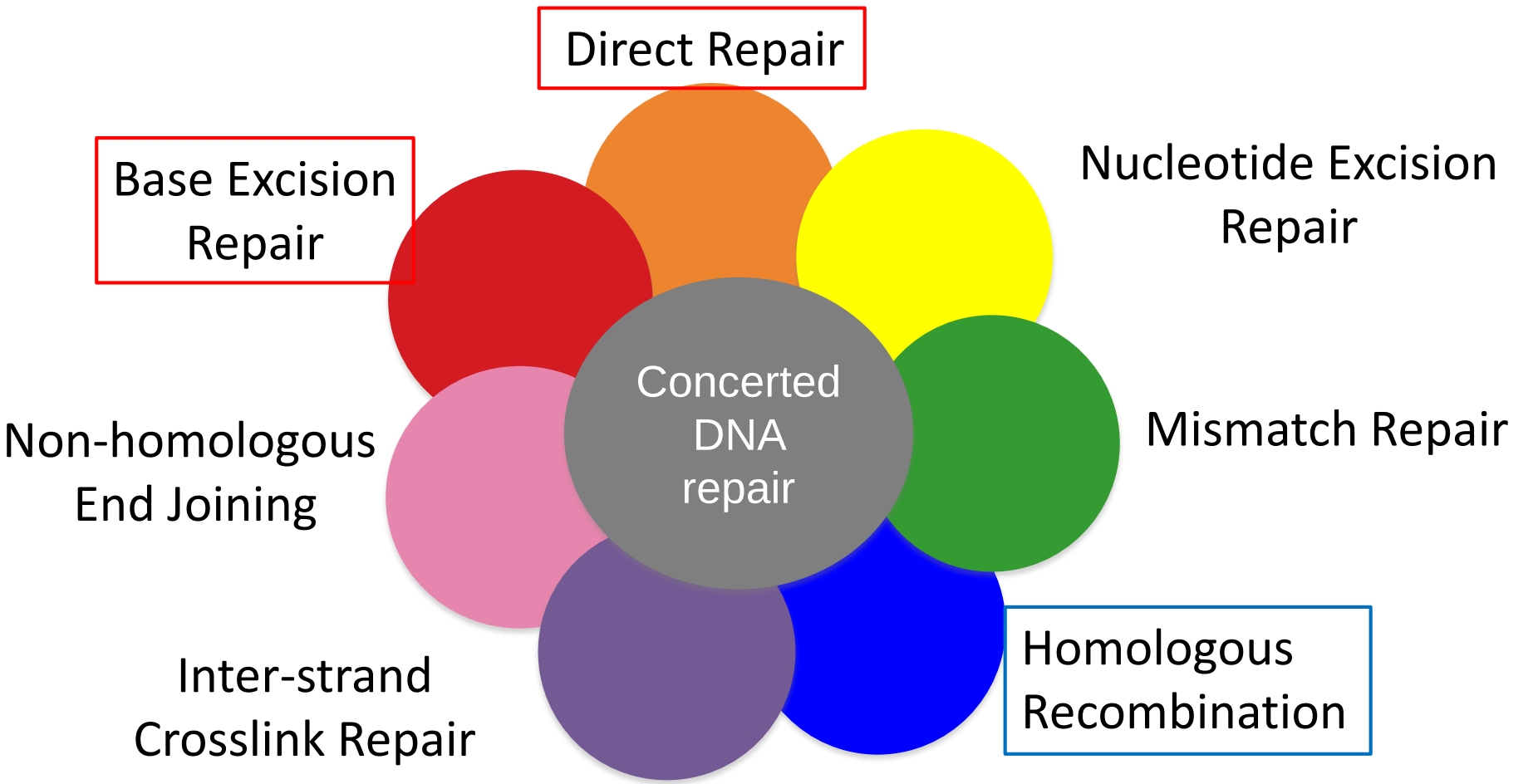
Weinberg RA, The Biology of Cancer
www.optimalhealthspecturms.com

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



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

EA2142

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

National Trial Activity—Active and in Development

- **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?