Wake Forest™
School of Medicine

Charles L. Spurr Piedmont Oncology Spring Symposium

March 1, 2019

Bridger Field House
Winston-Salem, North Carolina

Planning Committee

Bayard Powell, MD
Glenn Lesser, MD
Susan Poindexter, RN, BSN
Debbie Olson

This activity is sponsored by Wake Forest University School of Medicine.

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March 1, 2019

Dear Participant:

We are delighted you have chosen to attend the **Charles L. Spurr Piedmont Oncology Symposium**. An outstanding continuing medical education (CME) activity has been planned for you today. We hope you will enjoy this educational experience.

Agenda/Faculty/Commercial Supporters:
The conference agenda, list of participating faculty, and commercial supporters are enclosed for your review.

Disclosure Statement:
As an accredited CME provider, Wake Forest University Health Sciences/Wake Forest School of Medicine requires that everyone involved with a CME activity comply with the *2004 Updated Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support: Standards to Ensure the Independence of CME Activities*. All planning committee members, staff, and speakers have disclosed any financial interests or relationships they have with the manufacturer(s) of any commercial products/services. Their responses are enclosed for your review.

Attendance/Credit Certificates/Evaluation:
Please be sure to sign in at the registration desk. Sign in sheets will be available through the afternoon break.
Your Certificate of Completion will be available online within 10 business days. To receive your continuing education certificate, you must complete the online program evaluation for this activity. You will be emailed the link to the online evaluation within 10 business days. We will need your current email address to send you instructions for obtaining your certificate. **Evaluations and certificates will be available online for 2 weeks after evaluation link is received.**

Once again, we hope you find this course helpful. If there is anything we can do for you while you are here, please do not hesitate to ask any of the faculty or our staff at the registration table. If you have any questions once you leave, please call us using our direct number (336-713-7700). Thank you for coming.

Credit:
Credit Statement

The Wake Forest School of Medicine designates this live activity for a maximum of **5.0** ***AMA PRA Category 1 Credits*™**. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Accreditation Statement:
The Wake Forest School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

5.0 Continuing Nursing Education (CNE) Contact Hours

Northwest Area Health Education Center (NWAHEC) is an approved provider of continuing nursing education by the North Carolina Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

(#AP006-190301)

Participants must attend the entire activity in order to earn contact hour credit. No partial credit will be awarded. Verification of participation will be noted by learner-signature on the roster and completion of the online evaluation.

5.0 Contact Hours from Northwest AHEC

0.50 CEUs from Wake Forest School of Medicine

Learning Objectives:

- Describe the clinical presentation of neuroendocrine tumors and therapeutic treatment options.
- Examine recent changes to diagnostic and therapeutic approaches to HER2-positive breast cancer.
- Identify appropriate management steps for immune mediated adverse events.
- Discuss important prognostic and predictive factors in the treatment of colorectal cancer.
- Examine the impact of anti-CD19 CAR-T therapy on the prognosis of patients with relapsed or refractory large B-cell lymphoma.

Wake Forest® School of Medicine

OFFICE OF CONTINUING MEDICAL EDUCATION

LEARNER BILL OF RIGHTS

Wake Forest School of Medicine (WFSM) recognizes that you are a lifelong learner who has chosen to engage in continuing medical education (CME) to identify or fill a gap in knowledge, skill, or performance. As part of WFSM's duty to you as a learner, you have the right that your CME experience with us includes:

- Content that:
  - Promotes improvements or quality of health care;
  - Is valid, reliable, and accurate;
  - Offers balanced presentations that are free of commercial bias for or against a product/service;
  - Is vetted through a process that resolves any conflicts of interest of planners, teachers, or authors;
  - Is driven and based on learning need, not commercial interests;
  - Addresses the stated objectives or purpose; and
  - Is evaluated for its effectiveness in meeting the identified educational needs.

- A learning environment that:
  - Supports learners' ability to meet their individual needs;
  - Respects and attends to any special needs of the learners;
  - Respects the diversity of groups of learners; and
  - Is free of promotional, commercial, and/or sales activities.

- Disclosure of:
  - Relevant, financial relationships planners, teachers, and authors have with commercial interests related to the content of the activity; and
  - Commercial support (funding or in-kind resources) of the activity.

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Charles L. Spurr Piedmont Oncology Spring Symposium

Planning Committee, Faculty, & Staff Disclosure

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- *Dr. Eric Liu serves as a consultant for Curium. He is a speaker for Novartis, Lexicon, Ipsen, and Advanced Accerlerator Applications.*

- *Dr. John Marshall receives grant/research support from Genentech, Amgen, Bayer, Merck, Celgene, Taiho, and Caris. He serves as a consultant for Genentech, Amgen, Bayer, Merck, Celgene, Taiho, and Caris. He is a speaker for Genentech, Amgen, Bayer, Merck, Celgene, Taiho, and Caris.*

- *Dr. Alexandra Thomas receives grant/research support from Syndax. She serves as an advisor for BeyondSpring Pharmaceuticals. She owns stock in Johnson & Johnson and Gilead Sciences. She has received other support from Genentech. Her husband receives royalties from Up-to-Date.*

Speakers Dr. Elizabeth Hexner and Dr. Pierre Triozzi have nothing to disclose related to this educational activity. Planning committee members Dr. Bayard Powell, Dr. Glenn Lesser, Susan Poindexter, and Debbie Olson have nothing to disclose related to this educational activity.

Printed 2/20/19. Any additional disclosures received after this date will be announced.

Charles L. Spurr Piedmont Oncology Symposium
Spring Symposium

8:00-8:50 am	**Registration, Continental Breakfast, and Exhibits**
8:50-9:00 am	**Welcome & Remarks** Bayard Powell, MD
9:00-10:00 am	**Neuroendocrine Tumors Clinical Update** Eric H. Liu, MD, FACS Co-Founder and Director of Surgical Services, The Neuroendocrine Institute Rocky Mountain Cancer Centers
10:00-11:00 am	**Using Genetically Modified T Cells to Treat Cancer** Elizabeth Hexner, MD, MTR Medical Director, Center for Cellular Immunotherapies Division of Hematology and Oncology Abramson Cancer Center University of Pennsylvania
11:00-12:00 pm	**Potpourri of CRC: Adjuvant Therapy, The Wild West of Rectal Cancer, Immune therapy** John L. Marshall, MD Director, Ruesch Center for the Cure of GI Cancers Chief, Hematology and Oncology Georgetown University School of Medicine
12:00-1:30 pm	**Lunch and Exhibits**
1:30-2:30 pm	**Management of Autoimmune Phenomena and Disease in Patients Treated with Immune Checkpoint Inhibitors** Pierre L. Triozzi, MD Professor of Medicine Section on Hematology and Oncology Wake Forest School of Medicine
2:30-3:30 pm	**HER2-Positive Breast Cancer: A Long and Winding Road** Alexandra Thomas, MD Director, Breast Cancer Program Professor of Medicine Section on Hematology and Oncology Wake Forest School of Medicine
3:30 pm	**Adjourn**

Neuroendocrine Tumors Clinical Update
Eric H. Liu, MD, FACS
Co-Founder and Director of Surgical Services, The Neuroendocrine Institute
Rocky Mountain Cancer Centers

Neuroendocrine Tumors
Clinical Update

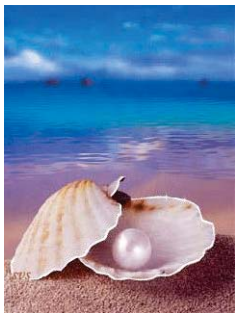
Eric H. Liu, M.D.
Co-Founder, Director of Surgical Services
The Neuroendocrine Institute
Rocky Mountain Cancer Centers
Presbyterian-St. Luke's Medical Center
Denver, CO, USA
Chief Medical Advisor, The Healing NET Foundation

Disclosures

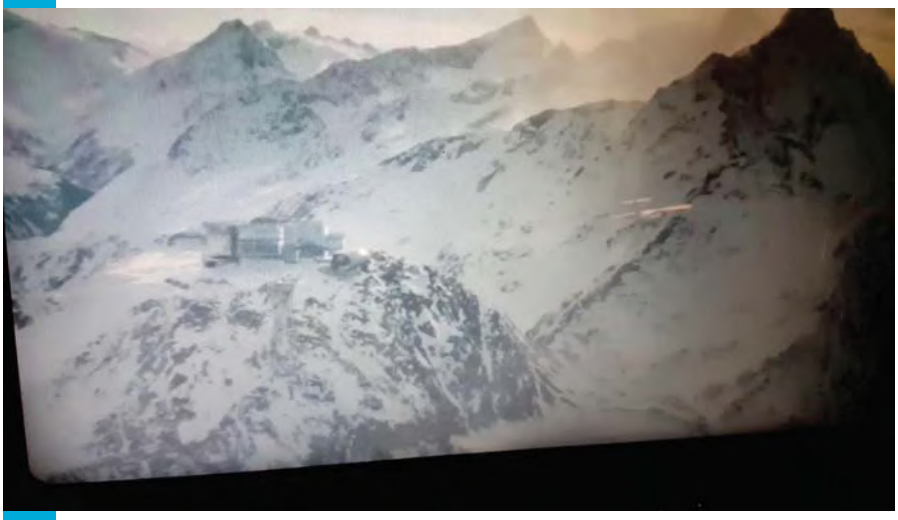
- Novartis – speaker bureau, education/training
- Ipsen – speaker bureau, education/training
- Lexicon – speaker bureau, education/training
- AAA – speaker bureau, education/training
- Curium – education/training

Goals Of Today's Presentation

- Quick Basics of Neuroendocine (epidemiology, diagnosis)
- Diagnosis
- Pathology
- Therapies

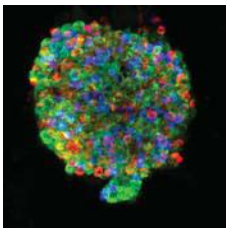


My Clinic



Basics of Neuroendocrine Cells

- Found in bronchial, gastroenteropancreatic tract
- Secrete hormones
  - Serotonin
  - Insulin
  - Gastrin
  - Glucagon
  - VIP
  - Somatostatin
  - Histamine
- Express SOMATOSTATIN RECEPTORS

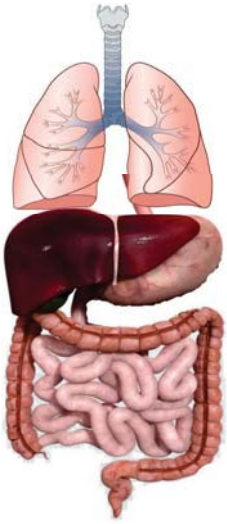


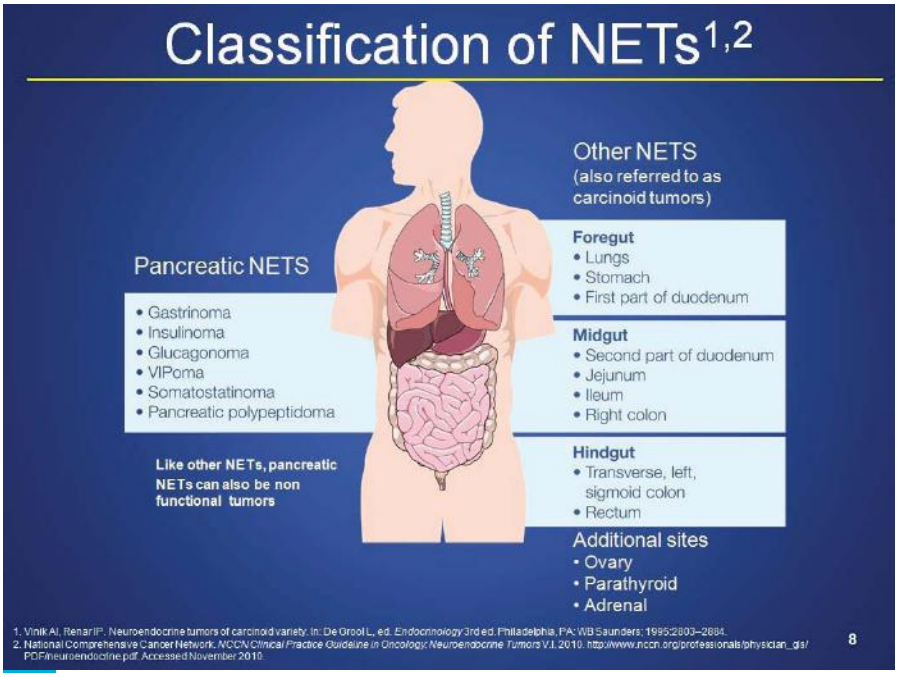
Liu and Oberg, Endo Meta Clin N Am, 39(4):697-71, 2010

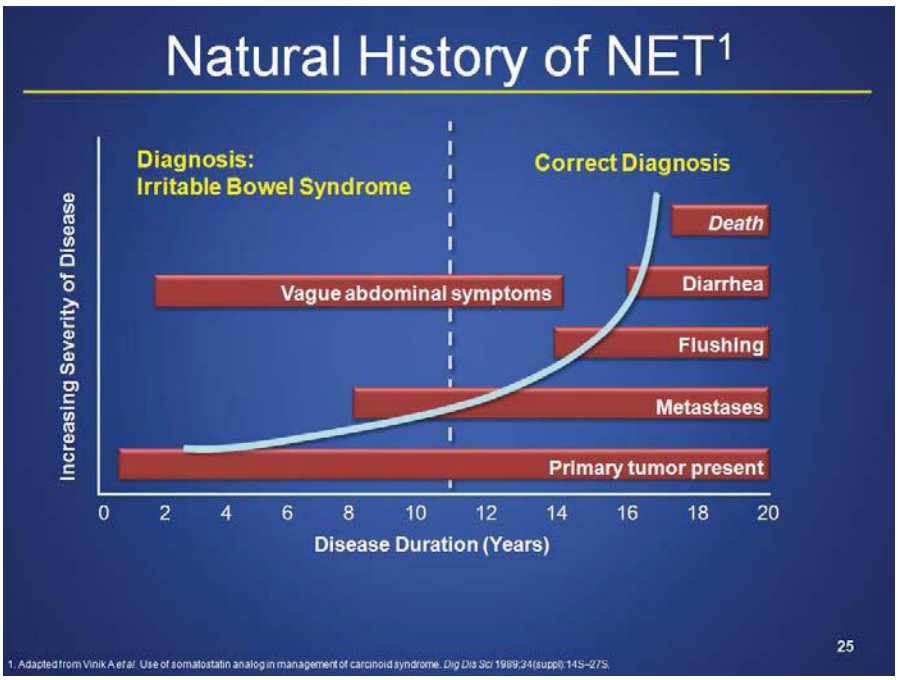
Definitions

<u>Neuroendocrine Tumors</u>
tumors derived from diffuse endocrine cells that can secrete many hormones

<u>Carcinoid</u>
slow growing tumor of the GI and bronchial tracts that derives from enterochromaffin cells that frequently secrete serotonin







NET Patient Complications

- Hormone Excess – Symptoms
- Mechanical Complications
- Nutrition
- Cardiac
- Anesthesia

EPIDEMIOLOGY

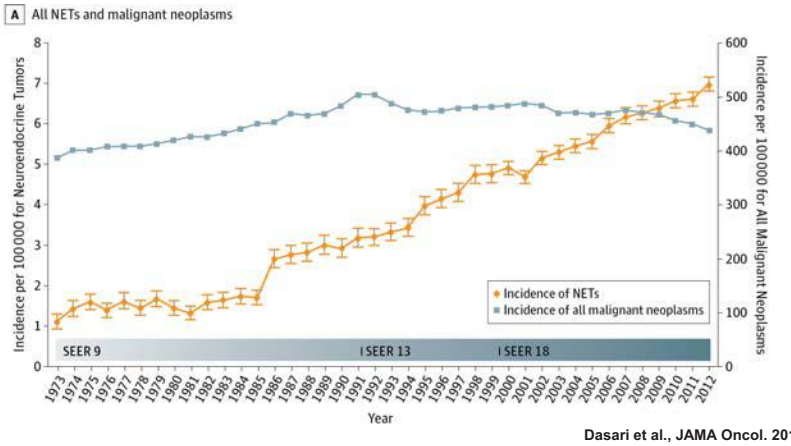
Incidence of neuroendocrine tumors

1.09-6.98/100,000 inhabitants

Dasari et al., JAMA Oncol. 2017

Incidence of neuroendocrine tumors

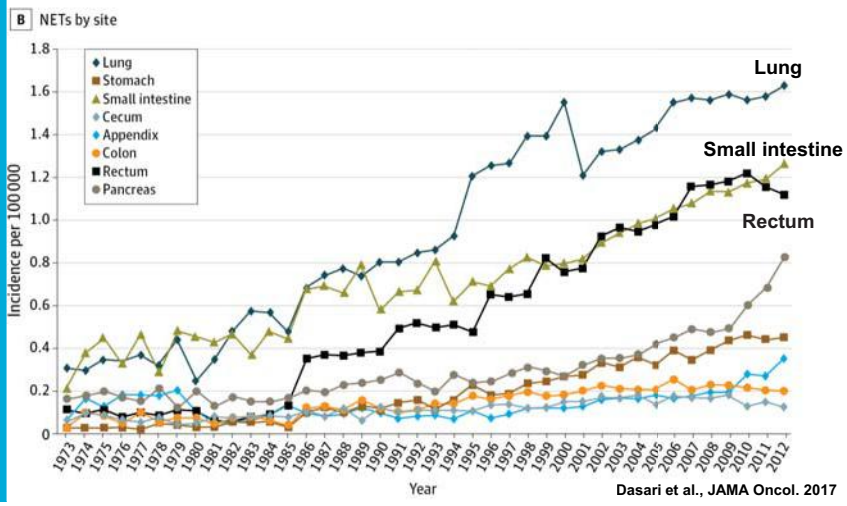
1.09-6.98/100000 inhabitants



Dasari et al., JAMA Oncol. 2017

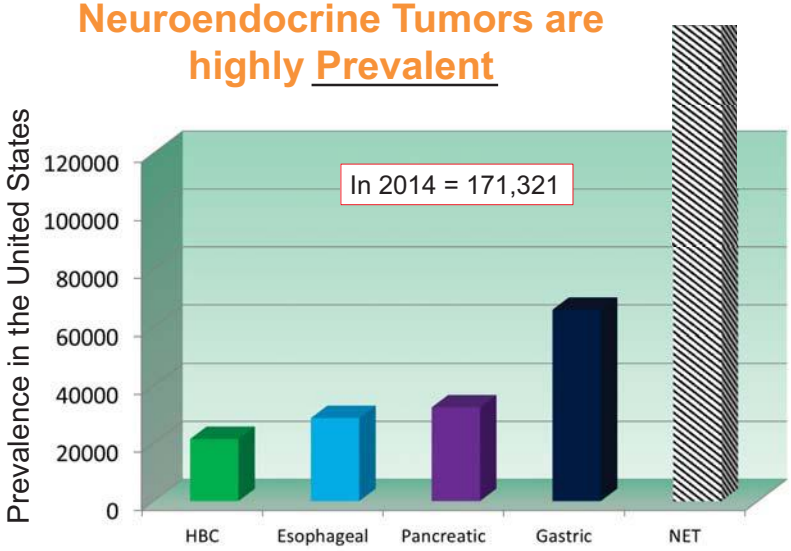
Incidence of neuroendocrine tumors

Surveillance, Epidemiology and End Results (SEER), US population 1974-2012



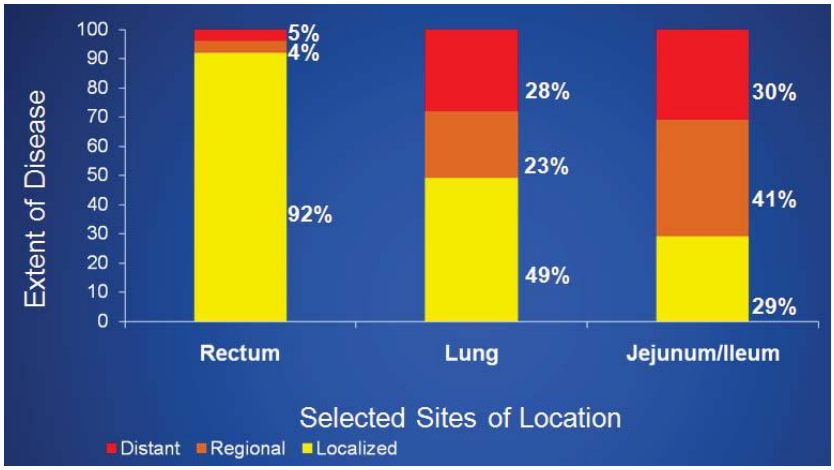
Dasari et al., JAMA Oncol. 2017

Neuroendocrine Tumors are highly Prevalent



Modlin et al., Lancet Oncol. 2008; Dasari et al. JAMA Onc, 2017

Metastatic Rates by Primary Site



Modlin et al., Lancet Oncol. 2008

DIAGNOSTICS

DIAGNOSTICS

- Office Visit
- Labs
- Imaging
- Nuclear Imaging
- Endoscopy
- Biopsy-Pathology

Symptoms

Diarrhea	Abdominal swelling
Jaundice	Abdominal pain
Heart disease	Intestinal obstructions
Blood sugar problems	Bleeding
Rashes	Anger
Flushing	Loss of consciousness
Wheezing	Gallstones
Ulcers	Blood clots

Symptoms

Diarrhea	Abdominal swelling
Jaundice	Abdominal pain
Heart disease	Intestinal obstructions
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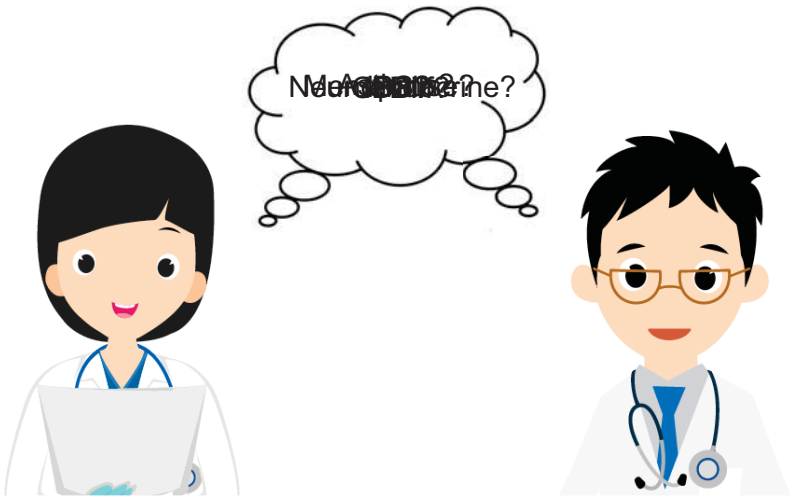
Ulcers	Blood clots

70% NETs have NO SYNDROME

SOMEONE TO THINK ABOUT NETs



Biochemical Testing

- Hormone levels (serum and urine)
  - 5-HIAA
  - Gastrin
  - Insulin/C-peptide/Proinsulin
  - Glucagon
  - VIP
  - Serotonin
  - And others…

Biochemical Testing

- Biomarkers
  - Chromogranin A
  - Chromogranin B
  - Pancreastatin
  - Neuron specific enolase
  - Ghrelin
  - Pancreatic Polypeptide
  - Substance P
  - And more…

Chromogranin A (CgA)

Establish diagnosis[1]

- Despite certain limitations, considered the best general marker for NETs

Has prognostic significance[2]

- Shown to reflect tumor mass and
- Increases in level are associated with progressive disease

Monitor for disease progression and therapy response

- Levels start to increase earlier than changes in tumor size can be seen on CT or magnetic resonance imaging[2]
- Increased levels may also be caused by other factors[3]
  - Renal failure
  - Chronic atrophic gastritis
  - Proton pump inhibitors

1. Ardill JE, Erikkson B. The importance of the measurement of circulating markers in patients with neuroendocrine tumours of the pancreas and gut. *Endocr Relat Cancer* 2003;10:459–462.
2. Öberg K. Gastrointestinal neuroendocrine tumors. *Ann Oncol* 2010;21:vii72–vii80.
3. Modlin IM *et al*. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 2008;9:61–72.

5-Hydroxyindoleacetic Acid (5-HIAA)

- Metabolite of serotonin measured in a 24-hour urine specimen[1]
- Serotonin-rich foods may alter 5-HIAA levels, resulting in false positives[1]

Bananas  Chocolate  Walnuts 

Examples of serotonin-rich foods

- Some medications can affect 5-HIAA levels: Phenacetin, cough and cold remedies, muscle relaxants, phenothiazines, chlorpromazine, prochlorperazine, promethazine, methanamines[2]
- The test is widely available with a specificity of approximately 88%; however, it is cumbersome and time consuming[1]
- Used to estimate extent of disease and survival[3]
- Correlates with extent of cardiac valve disease[1]

1. Modlin IM *et al*. Current status of gastrointestinal carcinoids. *Gastroenterology* 2005;128:1717–1751.
2. Boudreaux JP *et al*. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: Well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. *Pancreas* 2010;39:753–766.
3. Formica V *et al*. The prognostic role of WHO classification, urinary 5-hydroxyindoleacetic acid and liver function tests in metastatic neuroendocrine carcinomas of the gastroenteropancreatic tract. *Br J Cancer* 2007;96:1178–1182.

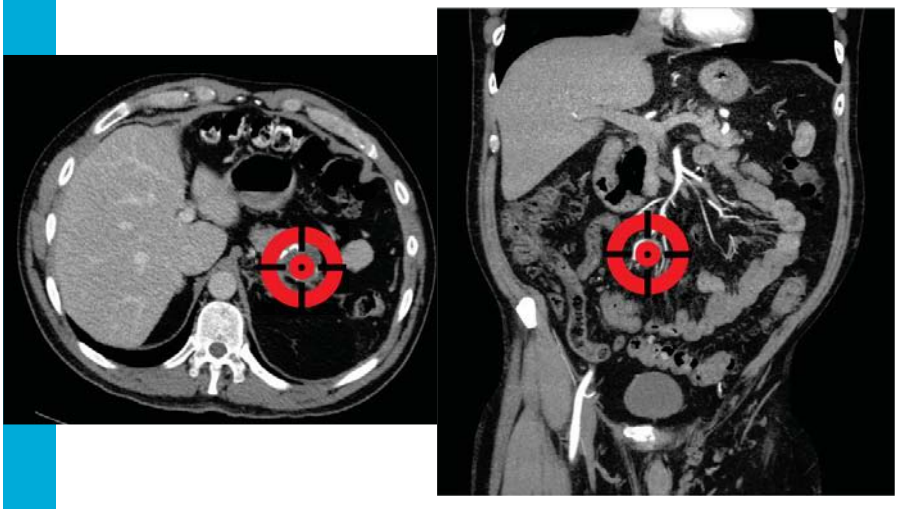
The Ideal Imaging Modality

The Ideal Imaging Modality

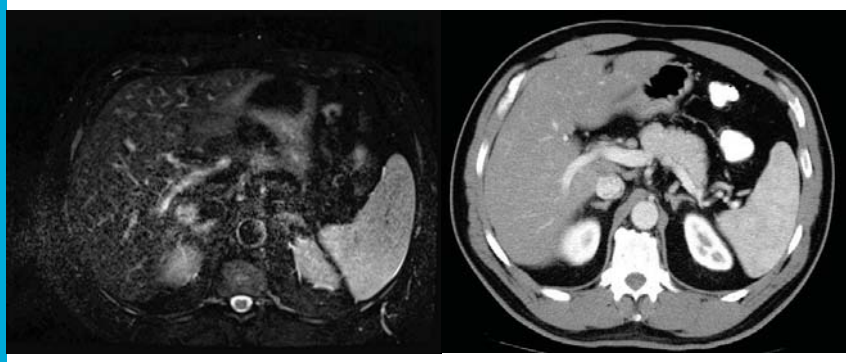
Imaging

- CT
- MRI
- Ultrasound
- Octreoscan (SPECT)
- 68-Gallium DOTA-SSA PET/CT

Finding NETs Usually Isn't Hard



CT vs. MRI

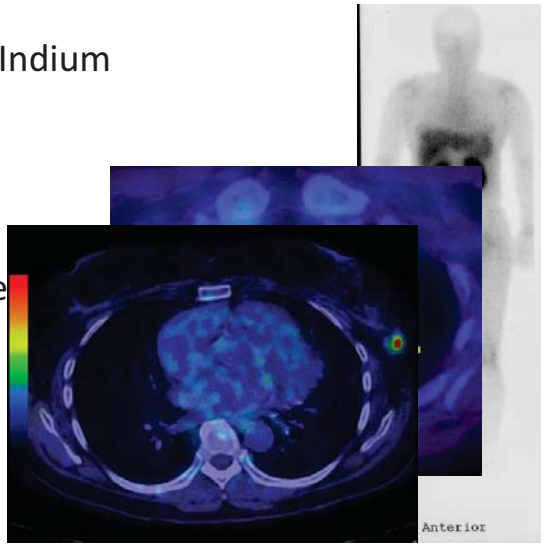


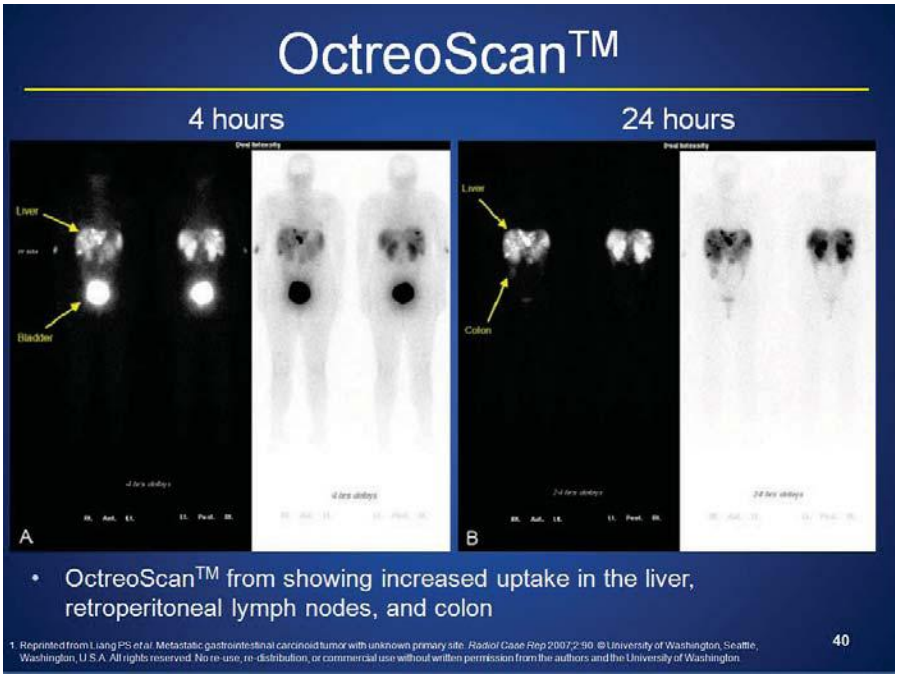
MRI may pick up ~ 20% more lesions

Giesel et al, 2011, Dromain, et al, 2005

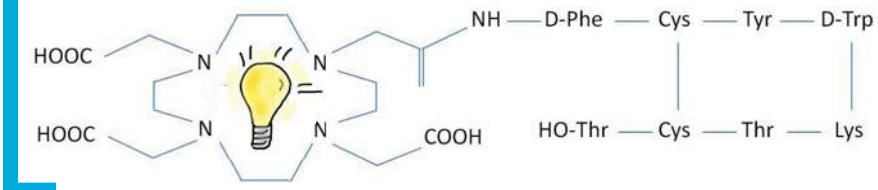
Nuclear Imaging

- Octreoscan: ^{111}Indium
- FDG
- ^{11}C-HTP
- ^{18}F-DOPA
- ^{68}Ga-octreotate





68Ga-DOTATATE PET/CT (NETSPOT)



PET Imaging Technology for NETs

Octreoscan

68Ga-PET/CT

PATHOLOGY

Pathological Classification

- NETs are classified by grade and by differentiation[1]

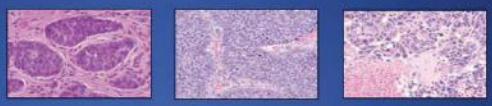
	Grading Systems for NETs[1]	
	Grade	WHO[2]
Well differentiated	Low (Typical)	<2 mitoses/10 HPF
	Intermediate (Atypical)	2 to 20 mitoses/10 HPF
Poorly differentiated	High	>20 mitoses/10 HPF

- Grade will determine tumor aggressiveness and management plan

HPF, high-power field; WHO, World Health Organization.

1. Klimstra DS *et al.* The pathological classification of neuroendocrine tumors. *Pancreas* 2010;39:707–712.
2. Bosman MB *et al.* *WHO Classification of Tumours of the Digestive System* 2010. IARC Press.

Pathological Classification of NETs



Histological classification	Well-differentiated	Moderately differentiated*	Poorly differentiated
Appearance	Monomorphic population of small, round cells		Cellular pleomorphism
Prognosis	Prolonged survival	Intermediate	Poor
Mitotic rate (mitoses/10 HPF)	<2		>10
Ki-67 (MIB-1) index	<2%		>10%
Necrosis	Absent		Present

Images courtesy of Nasir Aejaz, MD, Department of Pathology, H. Lee Moffitt Cancer Center and Research Institute, Tampa. Reproduced with permission from Strosberg J *et al.* *Gastrointest Cancer Res* 2:113–125. © 2008 by International Society of Gastrointestinal Oncology.

*Not well defined in the medical literature.

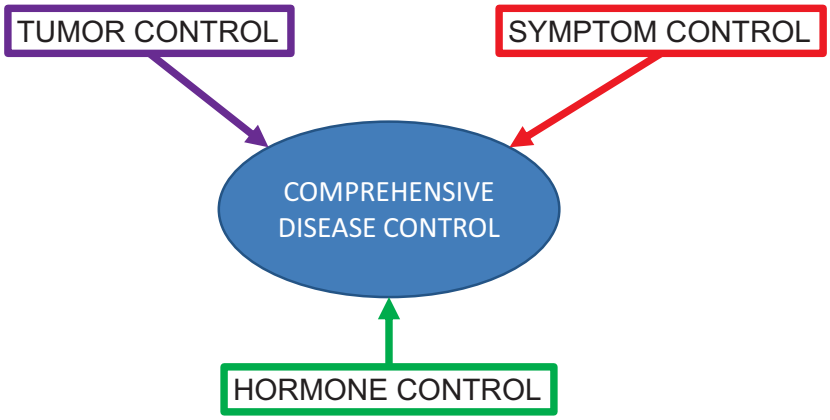
1. Reproduced from Strosberg JR *et al.* Biology and treatment of metastatic gastrointestinal neuroendocrine tumors. *Gastrointest Cancer Res* 2008;2:113–125.

THERAPIES

Therapies

- Surgery (Locoregional)
- Suppressive Hormone (Systemic)
- Hormone Synthesis Blockade (Systemic)
- Molecularly Targeted Therapies (Systemic)
- Chemotherapy (Systemic)
- Hepatic Embolization (Regional)
- Peptide Receptor Radionuclide Therapy (Systemic)

Think of NETs Differently



CUT IT OUT

CUT IT OUT

CUT IT OUT

Surgical Treatment of Neuroendocrine Metastases to the Liver: A Plea for Resection to Increase Survival

Juan M Sarmiento, MD, Glenroy Heywood, MD, Joseph Rubin, MD, Duane M Ilstrup, MS, David M Nagorney, MD, FACS, Florencia G Que, MD, FACS

Surgical Treatment of Advanced-Stage Carcinoid Tumors

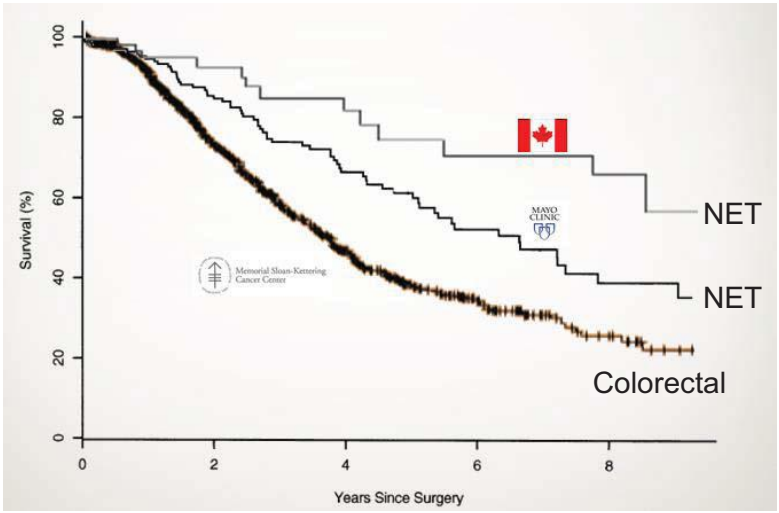
Lessons Learned

J. Philip Boudreaux, MD, Bradley Putty, MD,† Daniel J. Frey, MD,* Eugene Woltering, MD,* Lowell Anthony, MD,‡ Ivonne Daly, MD,* Thiagarajan Ramcharan, MD,* Jorge Lopera, MD,§ and Wilfrido Castaneda, MD§*

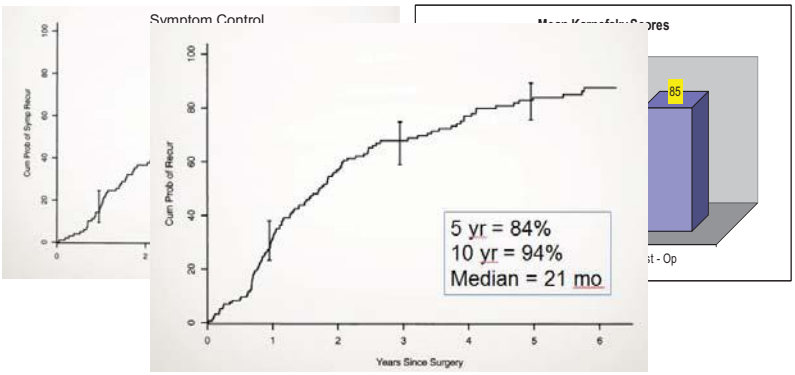
The palliative benefit of aggressive surgical intervention for both hepatic and mesenteric metastases from neuroendocrine tumors

Anthony J. Chambers, MS, FRACS,[a,b,c] Janice L. Pasieka, MD, FRCSC, FACS,[a,b,d] Elijah Dixon, MD, MSc(Epi), FRCSC, FACS,[a,b] and Otto Rorstad, MD, PhD,[a,d] *Calgary, Alberta, Canada*

Neuroendocrine Surgery is Different from Adenocarcinoma



Debulking Helps a Lot

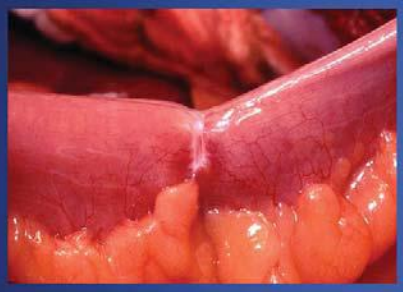


But Expect Disease Recurrence

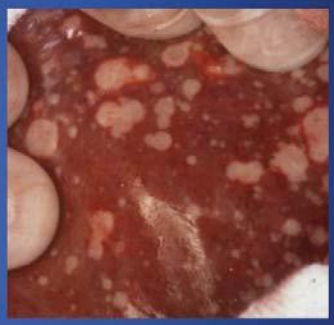
Sarmiento et al, JACS, 2003

Boudreaux et al, Ann Surg, 2005

Gross Morphology

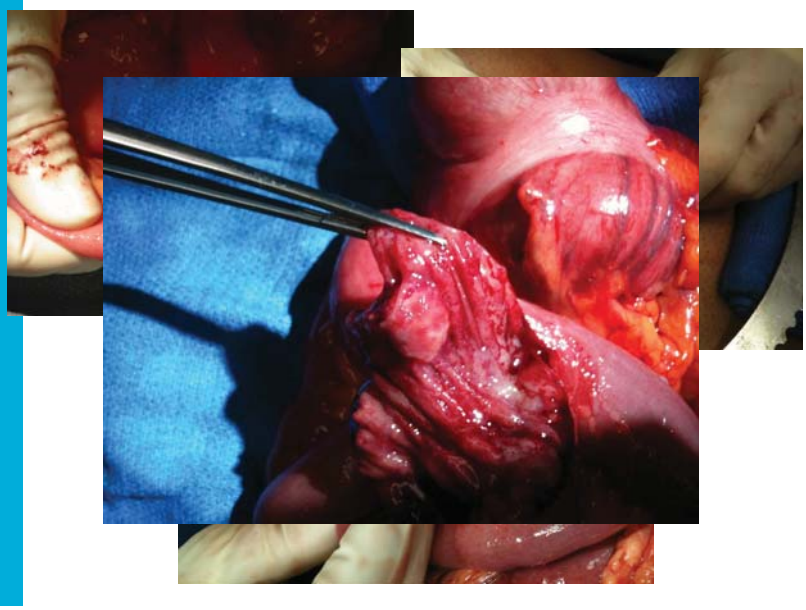


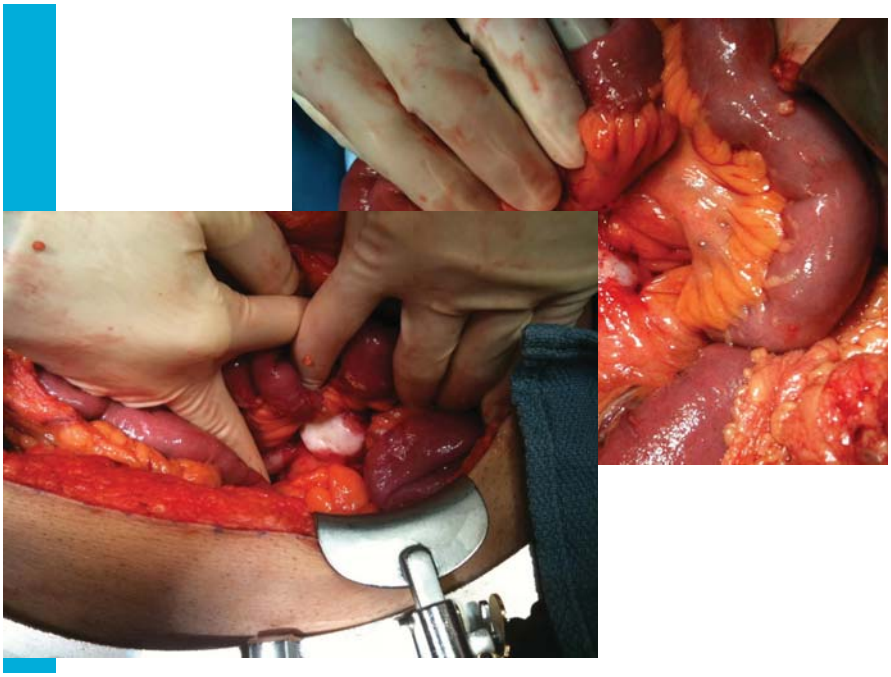
Primary Tumor

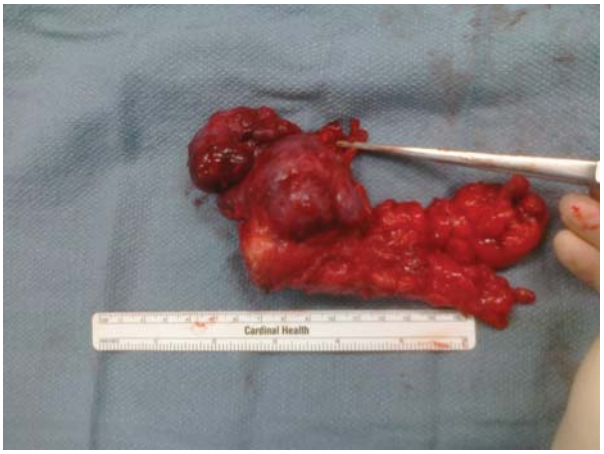


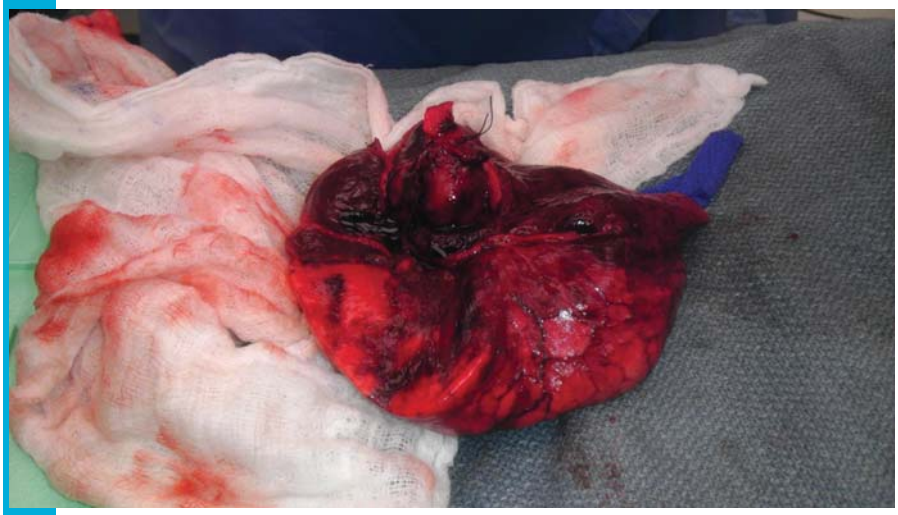
Liver Metastases

Images courtesy of Dr. Rodney Pommier

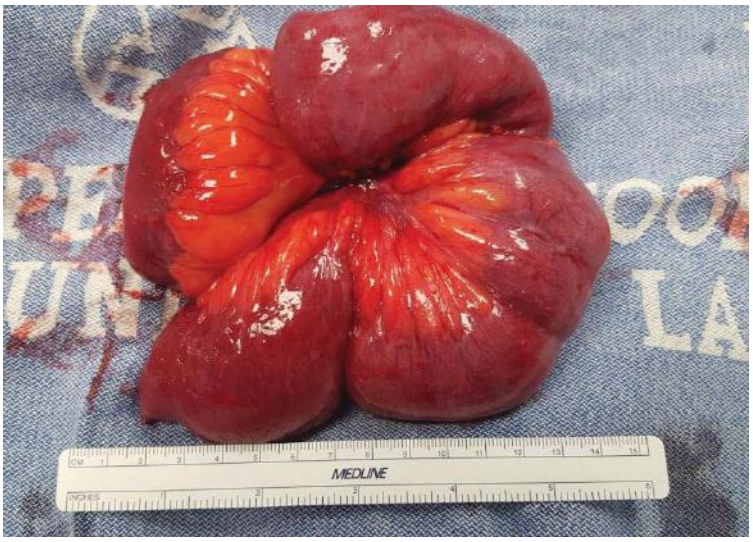








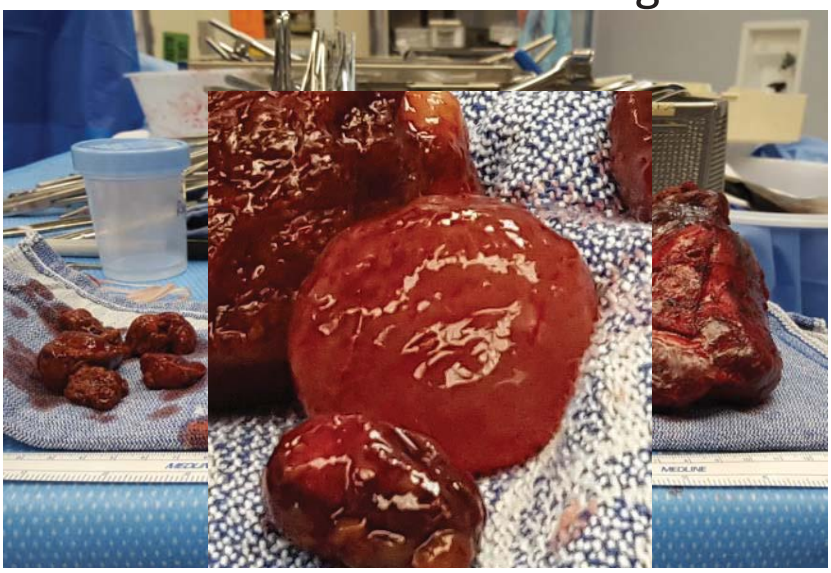
Chronic Small Bowel Obstruction



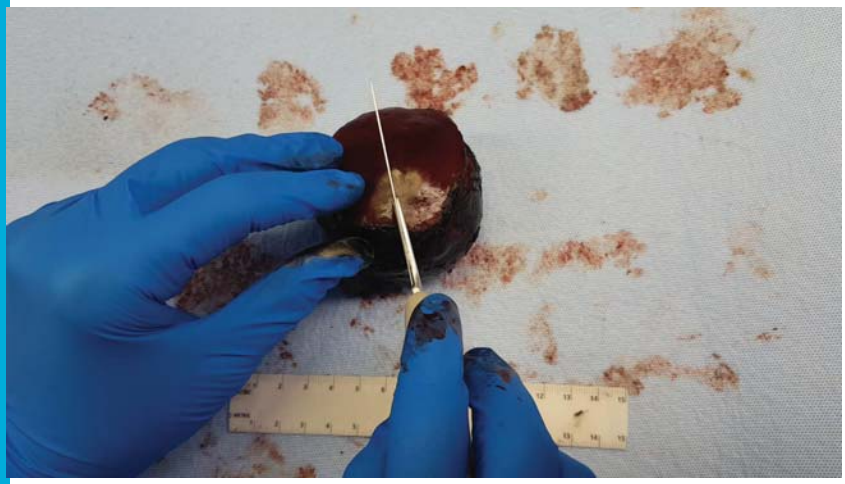
Multiple Liver Tumors DEBULKING

COMPLETE RESPONSE!

Liver Tumor Debulking

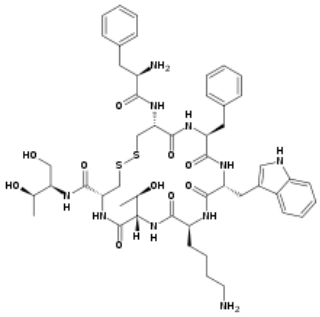


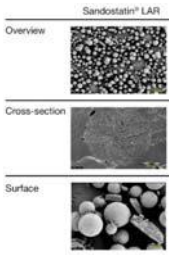
Not all the TUMORS are the same



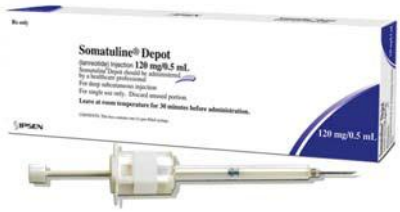
Medicines for Tumor Control

- Somatostatin Analogues (Fast Acting vs. Depot)
- Interferon

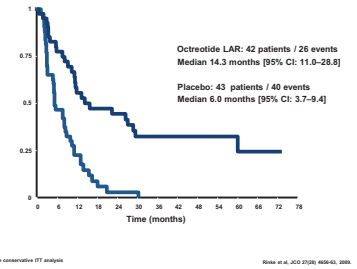




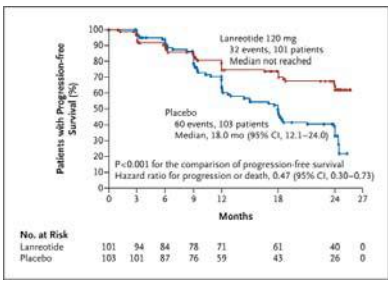
Many Amazing Medicines



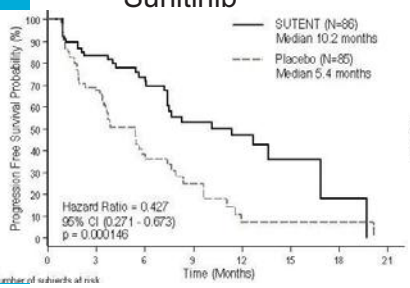
Octreotide



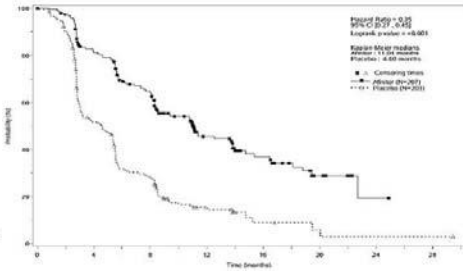
Lanreotide



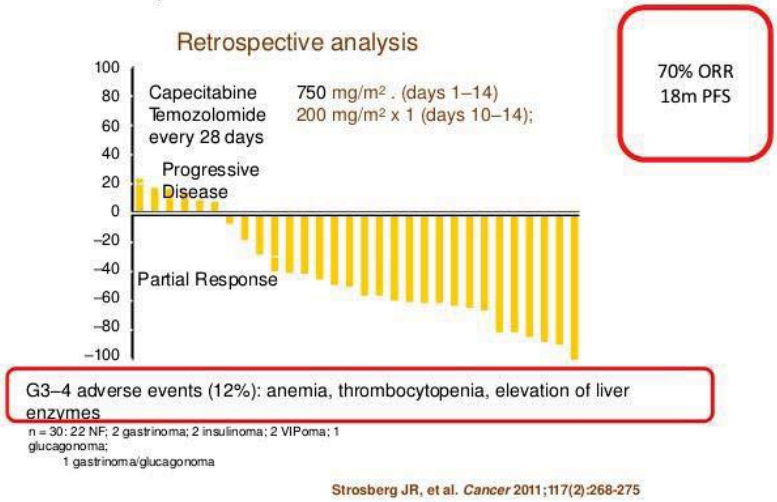
Sunitinib



Everolimus

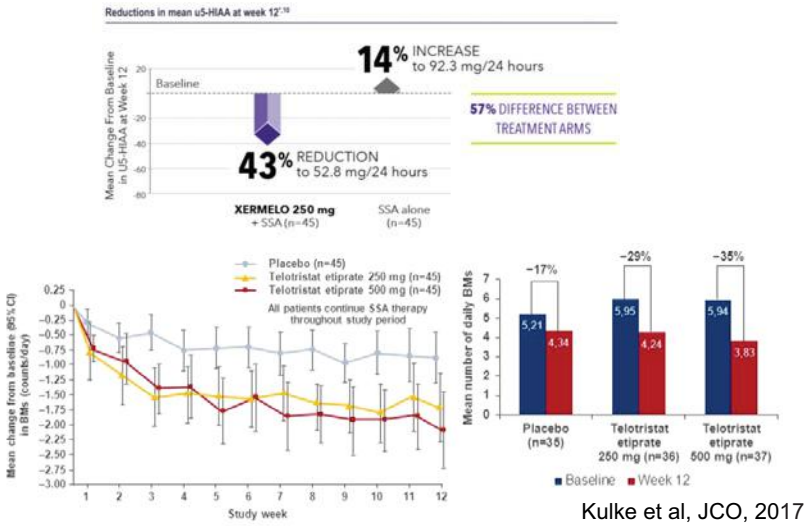


Capecitabine-Temozolomide in NET



Strosberg JR, et al. *Cancer* 2011;117(2):268-275

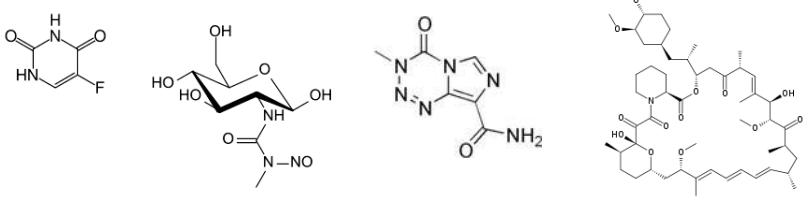
Telotristat Blocks Serotonin Synthesis and Reduces Bowel Movements



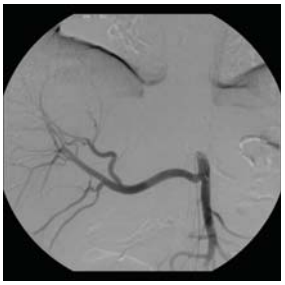
Kulke et al, JCO, 2017

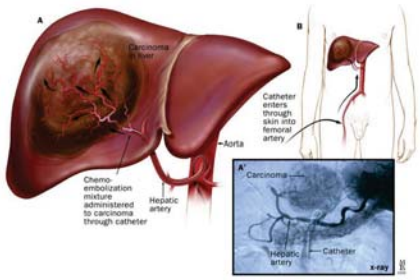
Chemotherapy

- 5-FU
- Streptozotocin
- Temozolomide
- Everolimus
- Bevacizumab
- Sunitinib
- Etoposide
- Doxorubicin
- Platinum
- Dacarbazine
- Taxotere



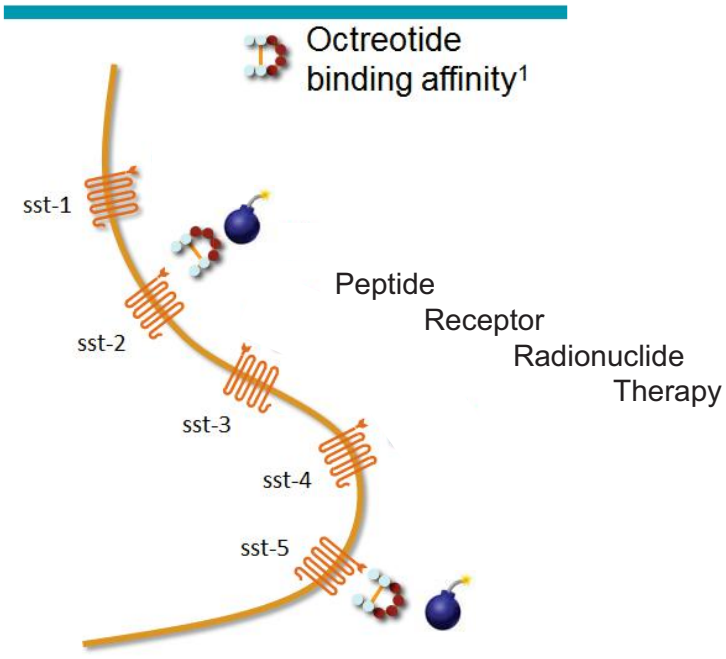
Interventional Radiology: Embolization



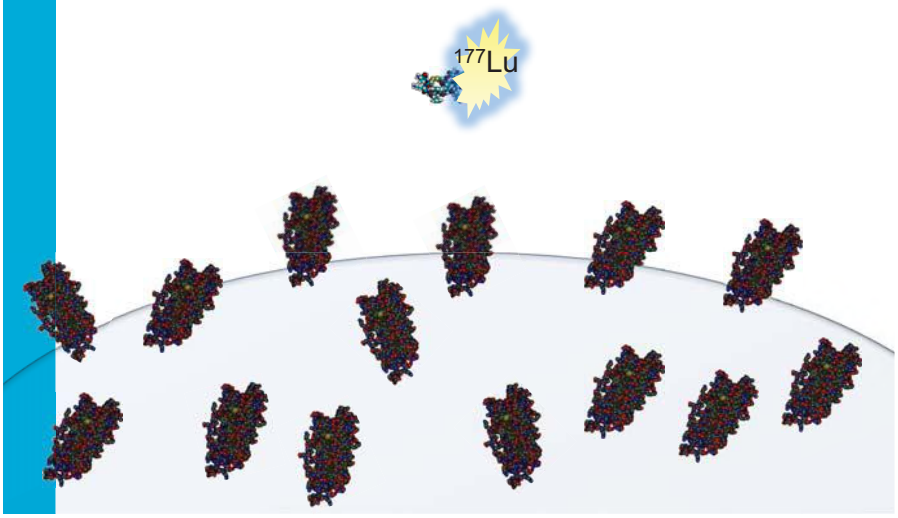


- Bland embolization
- Chemoembolization
- Radioembolization
  - 85% responded

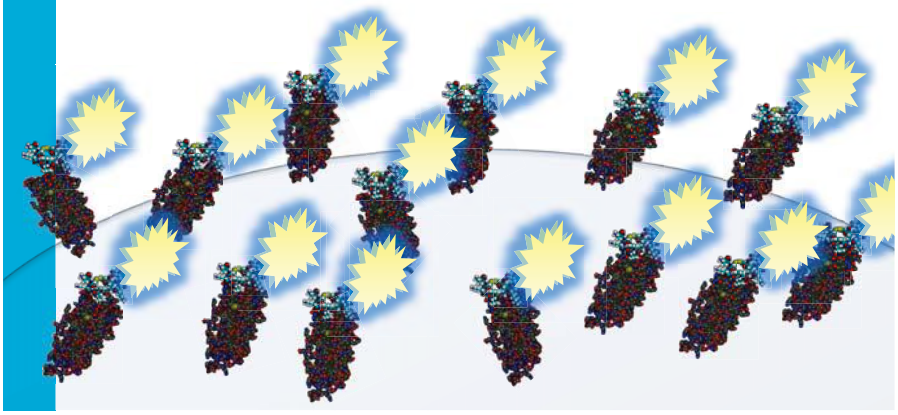
NUCLEAR MEDICINE IN NETS



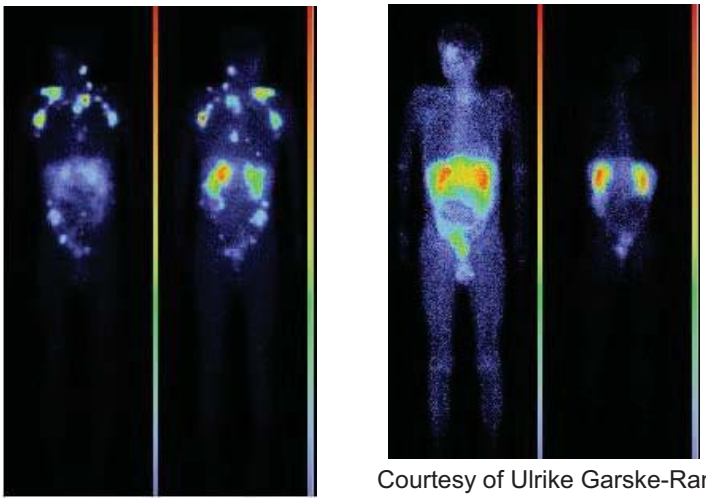
Radiopeptide Therapy



Radiopeptide Therapy

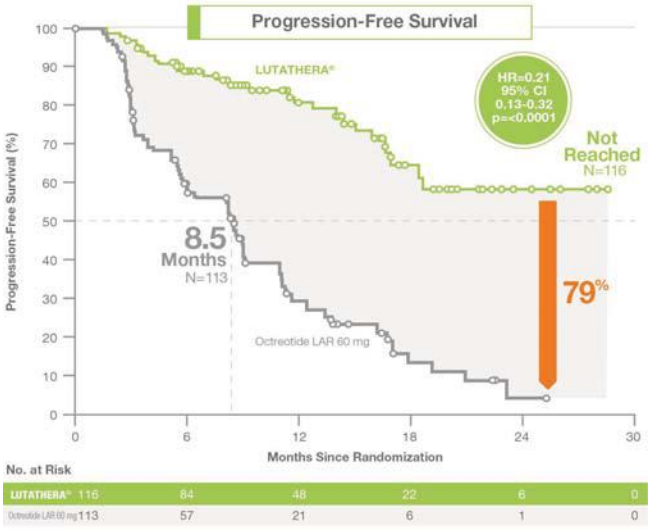


Metastatic Insulinoma Treated with ^{177}Lu-DOTA-Octreotate



Courtesy of Ulrike Garske-Ramon

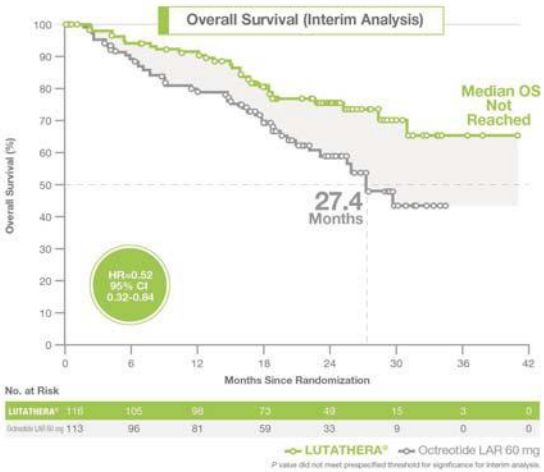
NETTER-1 TRIAL



Strosberg, et al, NEJM 2016

Preliminary evidence suggests an overall survival (OS) benefit[1]

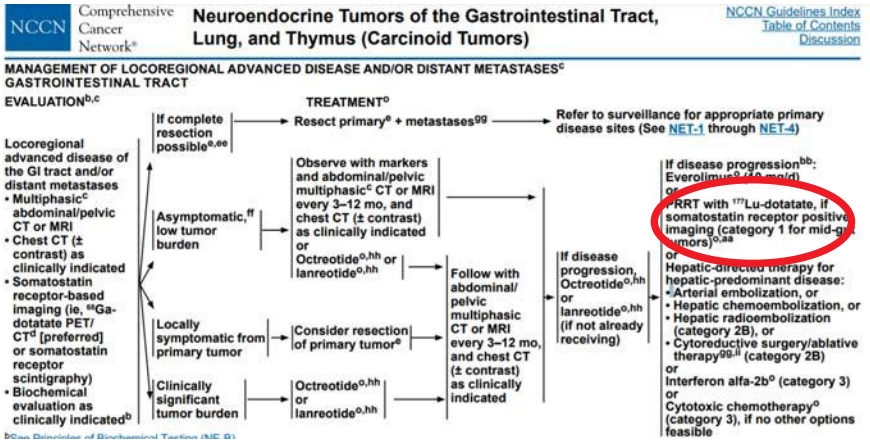
- Updated 2016 interim overall survival analysis suggests longer overall survival with LUTATHERA® (lutetium lu 177 dotatate) vs long-acting octreotide 60 mg
- 48% reduction in estimated risk of death (HR 0.52; 95% CI, 0.32, 0.84)[1]
  - LUTATHERA® = 27 deaths
  - Long-acting octreotide 60 mg = 43 deaths
- The final analysis of OS is planned after 158 cumulative deaths or 5 years from last patient randomization[2]



"The art of Neuroendocrine is not WHAT to do, it's WHEN to do it"

-Ancient Chinese NET specialist

NCCN Guidelines



NCCN Comprehensive Cancer Network®

Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

NCCN Guidelines Index
Table of Contents
Discussion

MANAGEMENT OF LOCOREGIONAL ADVANCED DISEASE AND/OR DISTANT METASTASES[c]
GASTROINTESTINAL TRACT

EVALUATION[b,c]

Locoregional advanced disease of the GI tract and/or distant metastases
- Multiphasic[c] abdominal/pelvic CT or MRI
- Chest CT (± contrast) as clinically indicated
- Somatostatin receptor-based imaging (ie, ^{68}Ga-dotatate PET/CT[d] [preferred] or somatostatin receptor scintigraphy)
- Biochemical evaluation as clinically indicated[b]

TREATMENT[O]

If complete resection possible[e,ee] → Resect primary[e] + metastases[gg] → Refer to surveillance for appropriate primary disease sites (See NET-1 through NET-4)

Asymptomatic,[ff] low tumor burden → Observe with markers and abdominal/pelvic multiphasic[c] CT or MRI every 3–12 mo, and chest CT (± contrast) as clinically indicated
or
Octreotide[o,hh] or lanreotide[o,hh]

Locally symptomatic from primary tumor → Consider resection of primary tumor[e]

Clinically significant tumor burden → Octreotide[o,hh] or lanreotide[o,hh]

Follow with abdominal/pelvic multiphasic CT or MRI every 3–12 mo, and chest CT (± contrast) as clinically indicated

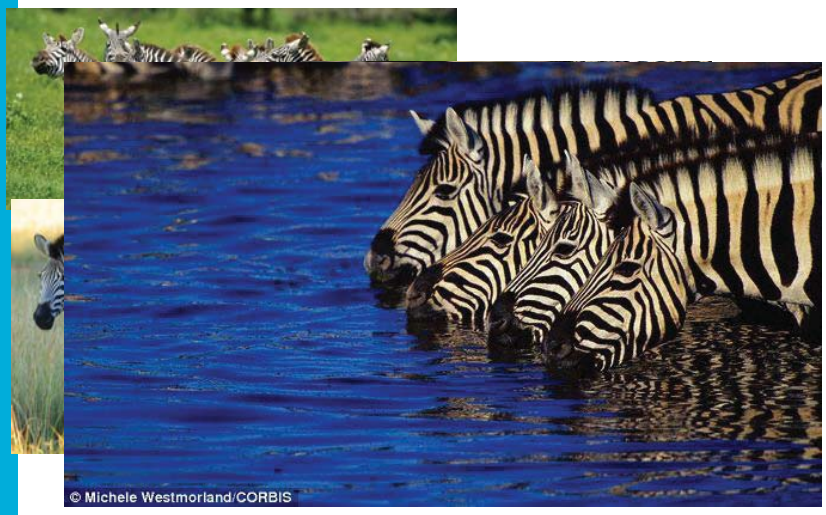
If disease progression, Octreotide[o,hh] or lanreotide[o,hh] (if not already receiving)

If disease progression[bb]:
Everolimus[o] (10 mg/d)
or
PRRT with ^{177}Lu-dotatate, if somatostatin receptor positive imaging (category 1 for mid-gut tumors)[o,aa]
or
Hepatic-directed therapy for hepatic-predominant disease:
- Arterial embolization, or
- Hepatic chemoembolization, or
- Hepatic radioembolization (category 2B), or
- Cytoreductive surgery/ablative therapy[gg,ii] (category 2B)

or
Interferon alfa-2b[o] (category 3)
or
Cytotoxic chemotherapy[o] (category 3), if no other options feasible

[b]See Principles of Biochemical Testing (NE-B)

Each Individual is Different



The Healing NET Foundation

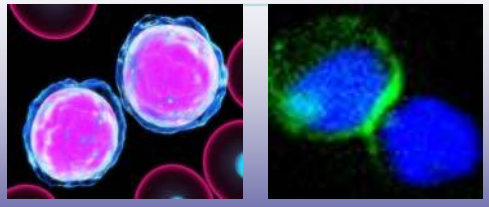
Thehealingnet.org

Thank You

Using Genetically Modified T Cells to Treat Cancer

Elizabeth Hexner, MD, MTR
Medical Director, Center for Cellular Immunotherapies Division of Hematology and Oncology
Abramson Cancer Center
University of Pennsylvania

Using genetically modified T cells to treat cancer

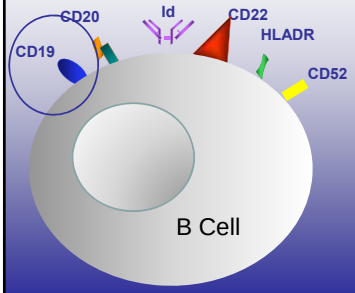


Elizabeth Hexner. MD MTR
March 1, 2019
Charles L. Spurr Oncology Symposium
Wake Forest, NC

Learning objectives and outline

- Describe genetically modified T cells
- Recognize principles of selecting tumor targets
- Understand CD19 as the most developed target of genetically modified T cells
  - Chronic lymphocytic leukemia
  - Acute lymphoblastic leukemia (pediatric and adult)
  - Non Hodgkin's lymphoma, multiple myeloma
- Recognize common toxicities: cytokine release syndrome; neurotoxicity
- Predict the future: other tumor targets and potential role in non-malignant disease

Cell-Surface Proteins are Targets for New Therapies

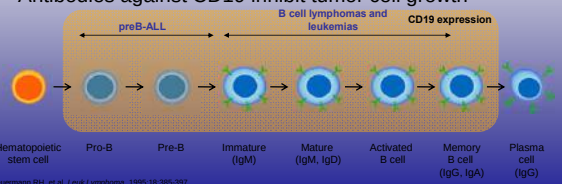


- Many cancer cells have well characterized surface proteins
- These proteins can be targeted to kill the cell with:
  - Monoclonal antibody
  - Engineered antibody
  - Immune (T) cells

Adapted from Press O, et al. *Cancer J Sci Am*. 1998;4(suppl 2):s18–s26.

CD19: An Ideal Tumor Target in B-Cell Malignancies

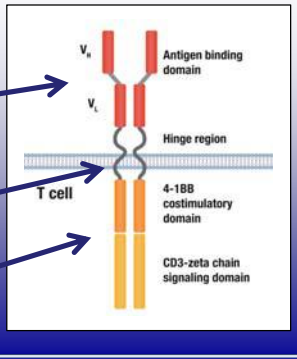
- CD19 is expressed by most B-cell malignancies[1]
- Normal CD19 expression is restricted to B cells and B cell precursors[1]
  - Spares hematopoietic stem cells[1]
  - Dispensible
    - Patients can live relatively normally without CD19+ B cells
- Antibodies against CD19 inhibit tumor cell growth



1. Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397.
Image adapted from Janeway CA, Travers P, Walport M, et al. *Immunobiology*. 5th ed. New York, NY: Garland Science; 2001:221-293; Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397; and Feldman M, Marini JC. Cell cooperation in the antibody response. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. Maryland Heights, Missouri: Mosby;2001:131-146.

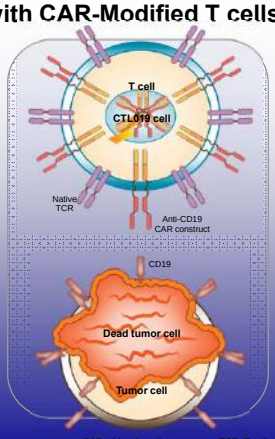
Targeting with Chimeric Antigen Receptors

- Antibody to target a specific protein on cancer cell (scFv fragment).
- Sequences bring and keep protein on the surface of T cell
- Signals for T cell activation (killing), growth, and survival



Targeting CD19+ CLL with CAR-Modified T cells

- CARs combine an antigen recognition domain of antibody with intracellular signaling domains into a single chimeric protein
- Gene transfer (lentiviral vector) to stably express CAR on T cells confers novel antigen specificity



CAR, chimeric antigen receptor; TCR, T-cell receptor.

Rationale for Targeted Cellular Therapy with CAR T Cells

- Ultimately, targeted cellular immunotherapy could overcome many limitations of conventional chemotherapy and other forms of adoptive immunotherapy
- Genetically modified, immune (T) cells with redirected specificity to tumor antigens may combine advantages of:
  - Antibody therapy (specificity)
  - Cellular therapy (amplified response)
  - Vaccine therapy (memory activity)

CARs Meet Hematologic Malignancies

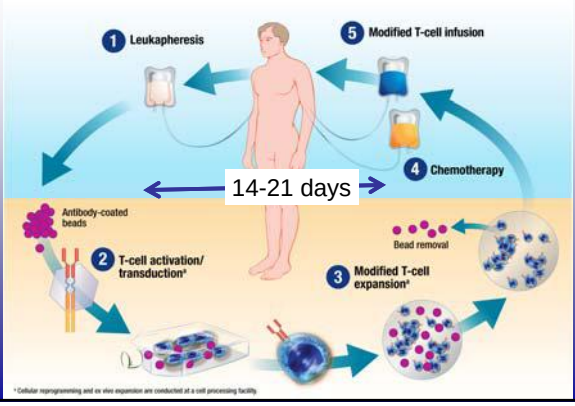
300+ CART19 subjects

- CLL
- ALL
  - Pediatrics
  - Adults
- NHL
- MM

CARs Meet other Malignancies

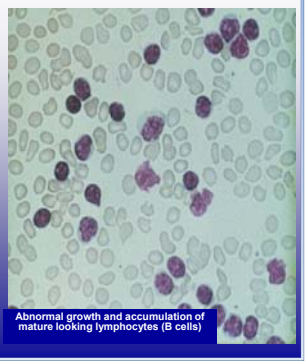
- Multiple myeloma
  - Target: BCMA
- Glioblastoma multiforme:
  - Target: EGFrviii
- Adenocarcinoma prostate
  - Target: PSMA
- Lung, ovarian (*pancreatic*)
  - Target: mesothelin

Overview of CART19 Therapy

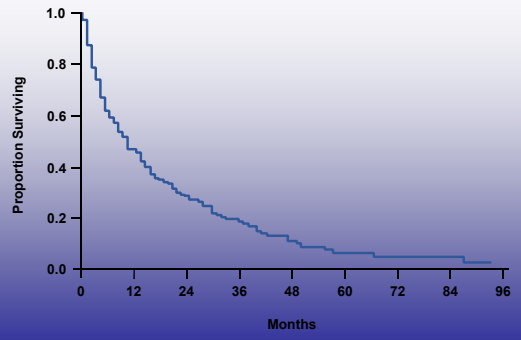


Chronic Lymphocytic Leukemia

- CLL is a cancer of B lymphocytes
- Usually "chronic" or slow growing; can be aggressive and deadly
- Results in accumulation of the malignant B cells.
- Incurable with conventional therapies


Abnormal growth and accumulation of mature looking lymphocytes (B cells)

Median OS of fludarabine-refractory CLL is 10 months



Brown J R Hematology 2011;2011:110-118, from Keating et al. 2002 Leuk Lymphoma 43:1755-1763 ©2011 by American Society of Hematology

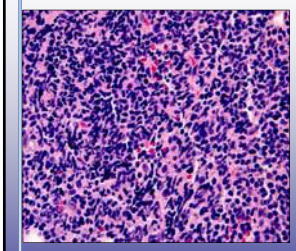
CART19 Pt 01, Aug 2010

- 59M, stage IV CLL, 46 XY
- 7 prior therapies, chemotherapy resistant
- No standard options available
- Received lymphodepleting chemotherapy fludarabine/cyclophosphamide.
- Treated with CART19 8/3/10.
- Course complicated beginning 10 day after infusion by high fevers (pneumonia?), hypoxia, hypotension.
- Critically ill requiring ICU care.
- Symptoms lasted ~14 days.

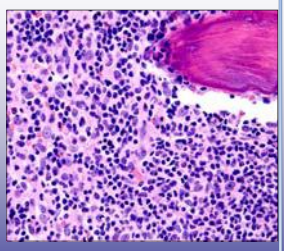
CART19 Therapy: Pt 01

- Normalization of blood counts
- Bone marrow without leukemia
  - including flow cytometry and negative IgH PCR
- CT scans with resolution of enlarged lymph nodes.
- Achieved COMPLETE REMISSION by day 31
- CART19 cells expanded 1000-10,000x
- CART19 cell detectable at >60 mo.
- CR sustained > 6 years

CLL Marrow Response by Day 31



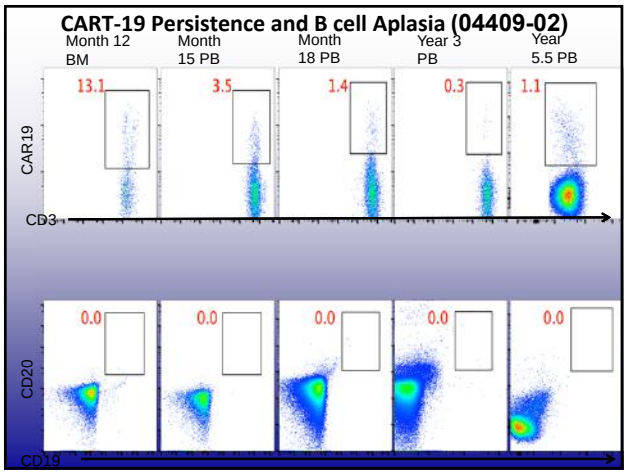
Pre-infusions marrow: >50% involved by CLL (40x)



Day 31
No evidence CLL and negative by flow cytometry, cytogenetics, FISH or deep sequencing

Porter et al. NEJM, 2011

CART-19 Persistence and B cell Aplasia (04409-02)

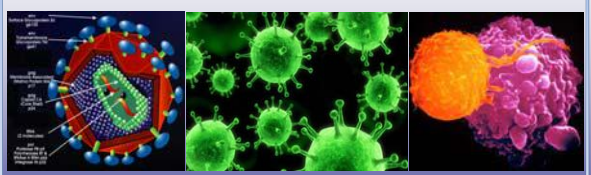


Clinical Responses:
Bulky Tumor Eradicated Following CART19 Infusion

Patient	Total Baseline Tumor Burden		Response
	# cells	tumor mass (pounds)	
UPN 01	2.51E+12	5.52	CR (+24 months)
UPN 02	3.48E+12	7.67	PR (4 months)
UPN 03	1.32E+12	2.90	CR (+24 months)

Porter et al. NEJM, 2011
Kalos et al. Sci Trans Med 2011

CART19 For Relapsed, Refractory ALL



Structure of a Lenti-virus

Lenti-viruses used for T-cell transduction

Transduced T-cell attacks a tumor cell

CART 19: potent activity in relapsed and refractory ALL

Study	Construct	N	CR
Seattle (Turtle, 102)	CD3z 4-1BB	34	94%
Penn (Frey 7002)	CD3z 4-1BB	30	72%
MSK (Park, 7003)	CD3z CD28	46	78%
Seattle Children's (Gardner, 3048)	CD3z 4-1BB	36	91%
Penn (Maude 3011)	CD3z 4-1BB	59	93%

Patients treated at UPENN with CART19

"First generation" trials, through 12/2016

Disease	Transduced cell dose (fractions)	N (infused)	Overall Response*	Relapse free survival (1y)
CLL	1 - 5 x 10^7 (1) 1 - 5 x 10^8 (1) 1 - 5 x 10^8 (3)	14 14 10	37%	66% (6m)
ALL(peds)	0.15 - 50 x 10^8 (3)	62	92%	63%
ALL (adult)	0.1 - 5 x 10^8 (3)	29	62%	39%
NHL	1-5 x 10^8 (1)	48	56%	81%

* Overall response = complete response + partial response

Represents aggregate data of UPCC 03712, 13413, 21413, CHP959

From proof of concept to FDA approval


F.D.A. Approves First Gene-Altering Leukemia Treatment, Costing $475,000

Setting the Body's 'Serial Killers' Loose on Cancer

Immune System, Loaded With Remade T-cells, Vanquishes Cancer

A Breakthrough Against Leukemia Using Altered T-Cells

F.D.A. Panel Recommends Approval for Gene-Altering Leukemia Treatment

Companies Rush to Develop 'Utterly

From proof of concept to FDA approval

"We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer."

–FDA Commissioner Scott Gottlieb, M.D.

Genetically modified T cells: The Now and the Future

The Now

- B cell malignancies
  - Chronic lymphocytic leukemia
  - Acute lymphoblastic leukemia
  - Non-Hodgkin's lymphoma
  - Multiple myeloma

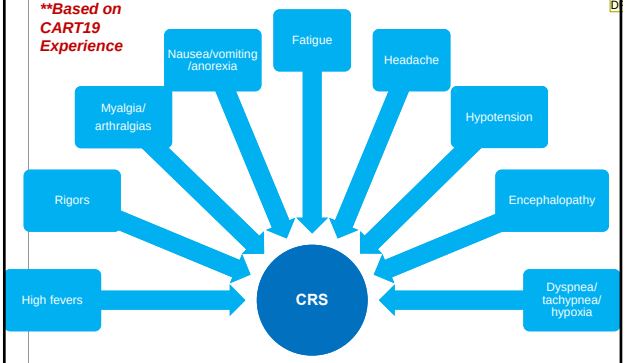
The Future

- Solid tumor targets?
- Overcoming the tumor microenvironment
- Non malignant diseases? *Can we use genetically modified T cells to treat autoimmune diseases?*
- Universal CAR T cells

CRS Toxicity Management

CRS- Common Symptoms

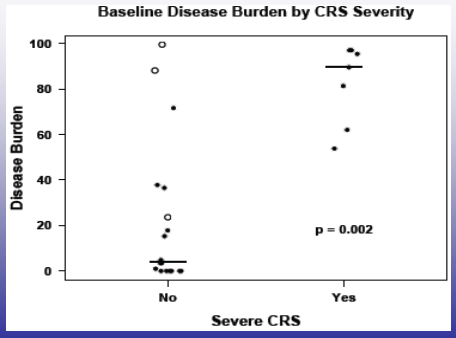
***Based on CART19 Experience**



Diagnosis based on clinical symptoms and events

25

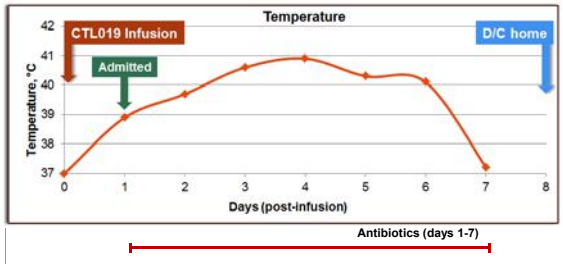
Severity of CRS correlates with disease burden



Maude SL, Frey NO, et al. N Engl J Med 2014;371:1507-1517.

The NEW ENGLAND JOURNAL of MEDICINE

Mild/moderate CRS: Typical Patient Case

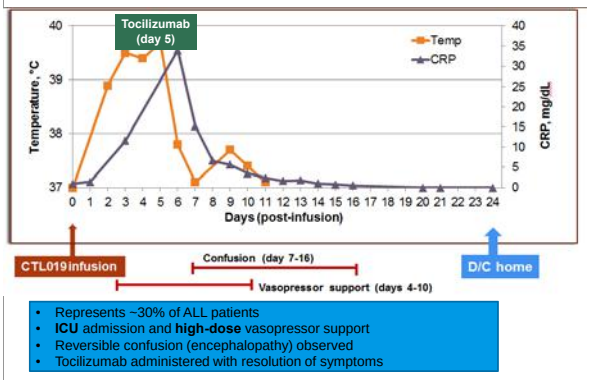


- Represents the majority of patients
- **Fevers** and/or **myalgia** are typically the first clinical manifestations
- No need for tocilizumab or ICU admission
- **Antibiotics** administered in setting of neutropenia per local guidelines.

Penn Medicine

27

Severe CRS: Typical Patient Case



- Represents ~30% of ALL patients
- **ICU** admission and **high-dose** vasopressor support
- Reversible confusion (encephalopathy) observed
- Tocilizumab administered with resolution of symptoms

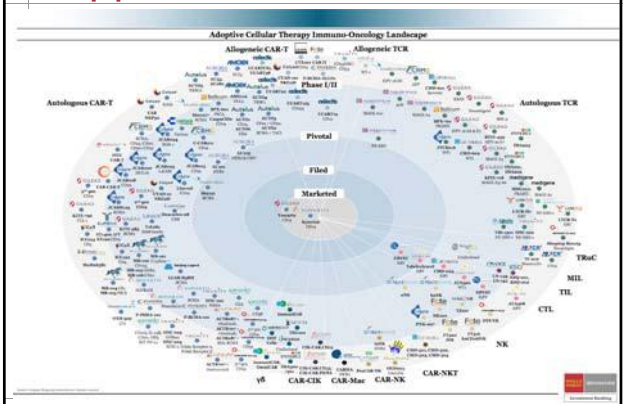
Summary: CART19 for B cell malignancies

- Promising! *CLL, ALL, NHL, MM*
- Massive CART19 expansion (1000 – 10,000 fold *in vivo*)
- Eradication of large tumor (2.5-7 lbs)
- CART19 cells can persist for >60 months after a single treatment
  - Persisting cells remain functional: *Living drugs*
- Many potential severe side effects; generally manageable with careful supportive care
- CAR T cells are both "personalized" and "precise"

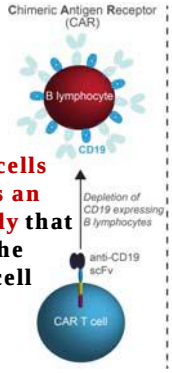
The future: other tumors, targets, and more.

- **Glioblastoma: EGFrViii**
- **PSMA, TGF-β "DNR"**
- **Gene editing**
  - Acknowledges role of tumor microenvironment
- **non-malignant diseases?**
  - Chimeric **AutoAntibody** Receptor (CAAR) T cells
  - Atherosclerotic disease?!
    - *Work of Robbie Schwab, MD,MTR candidate*

The pipeline….

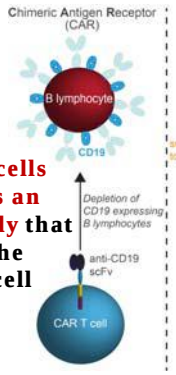


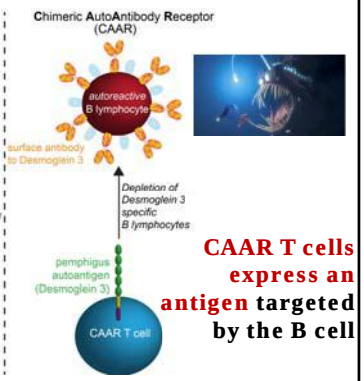
CAR-T versus CAAR-T



CAR T cells express an antibody that binds the target cell

CAR-T versus CAAR-T





CAR T cells express an antibody that binds the target cell

CAAR T cells express an antigen targeted by the B cell

Colleagues and Collaborators (too many to list)

CCI and ACC

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Novartis

CTL019
Development Team

Study Participants

DSMC Members

LEUKEMIA & LYMPHOMA SOCIETY
fighting blood cancers

Adaptive TcR, Inc

Novartis

Potpourri of CRC: Adjuvant Therapy, The Wild West of Rectal Cancer, Immune therapy

John L. Marshall, MD
Director, Ruesch Center for the Cure of GI Cancers
Chief, Hematology and Oncology
Georgetown University School of Medicine

Potpourri of CRC: Adjuvant Therapy, The Wild West of Rectal Cancer, Immune therapy

John L Marshall, MD
Director, Ruesch Center for the Cure of GI Cancers
Georgetown University
Washington DC

Disclosures

- Genentech
- Amgen
- Bayer
- Taiho
- Celgene
- Merck
- Caris
- Indivumed

RUESCH CENTER: Vision & Mission

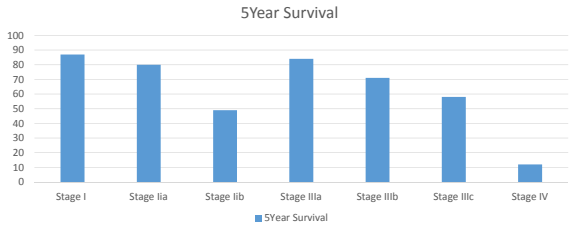
VISION
Cure every person with gastrointestinal cancer

MISSION
Integrate scientific discoveries with a patient-centered philosophy to transform the standard of care

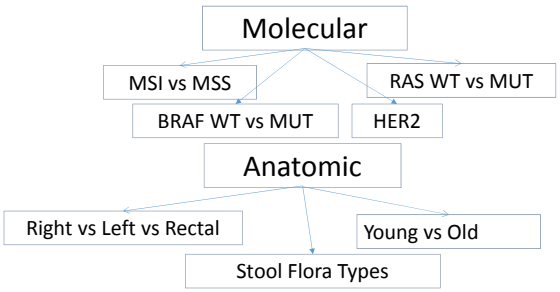
Our Primary Goals

- Cure the patient
- Preserve organ function
- Minimize chronic toxicity

Rectal Cancer 5 Year Survival by Stage ACS/SEER 2004-10



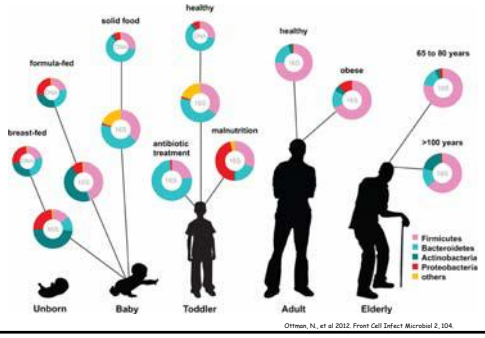
Colon Cancer: More than One Disease



CRC Screening

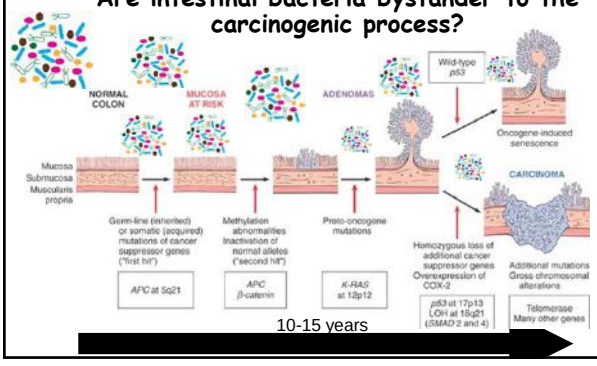
- Underutilized
- Expensive, Invasive
- Recent widening to 45 and 80 y/o
- Not all colon cancer starts as a benign polyp

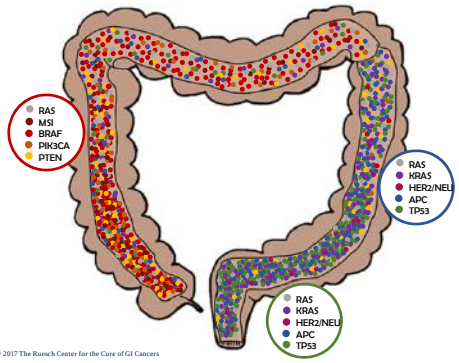
Microbial colonization through life



Ottman, N., et al. 2012. Front Cell Infect Microbiol 2, 104.

Are intestinal bacteria bystander to the carcinogenic process?





Testing Today

- RAS Generally reserved for met CRC
  - BRAF sometimes done if RAS WT
- HER2?
- MSI/MSS
  - IHC for MLH1, MSH2, MSH6 and PMS2 proteins
    - If MLH1 and PMS2 are absent, the patient likely has acquired methylation of the MLH1
    - If MSH2 and MSH6 are absent, the patient likely has LS.
    - If only MSH6 or PMS2 is absent, the patient may have LS.
    - Up to 15% are still missed, family history still critical
  - PCR for MSI-H
- Gene profiling
  - Adjuvant- Oncotype, Coloprint
  - Metastatic- Caris, Foundation, other

Prevention

- ASA
- Vit D
- Exercise
- Tree nuts

Adjuvant by Stage

- Stage 1- none
- Stage 2- long talk, no oxali
- Stage 3- fu + oxali
- Over 70- No oxali

- We treat them all the same
  - Rt/Lt
  - RAS/RAF/MSI/HER2

QUASAR Study

- Study of chemo (n, 1622) vs no chemo (n,1617)
  - 92% were stage II
  - 29% were rectal cancer
  - Multiple options for therapy
    - High and low dose leucovorin allowed
    - Levamisole was included for some
    - Q 4 week or weekly regimens

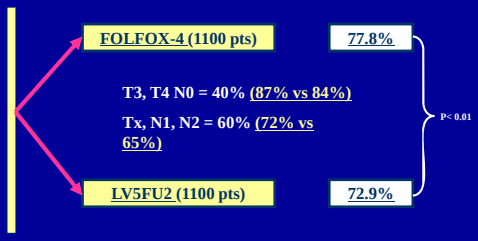
Gray RG, et al, for the QUASAR Collaborative Group. *J Clin Oncol.* 2004;22(14S):Abstract 3501.

QUASAR Study

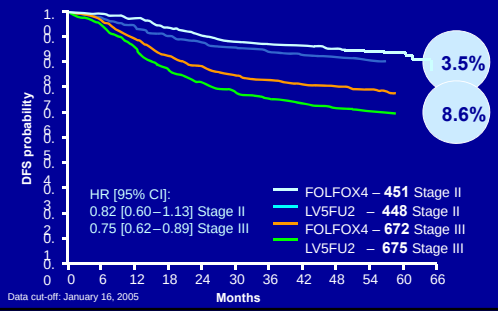
- 5-year survival
  - 80.3% vs 77.4%, p = 0.02 favoring chemo
- Other facts
  - High and low dose leucovorin therapy appears equivalent
  - Levamisole did not contribute to positive outcome
  - Q 4week schedule is equivalent to weekly

Gray RG, et al, for the QUASAR Collaborative Group. *J Clin Oncol.* 2004;22(14S):Abstract 3501.

Adjuvant Oxaliplatin: Mosaic Trial (3 year data)

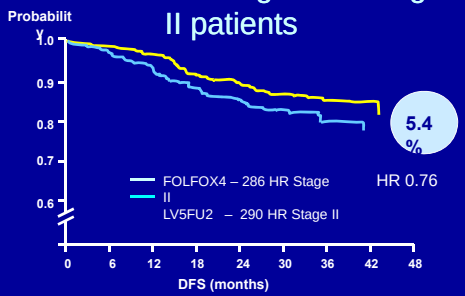


Disease-free Survival (ITT) Stage II and Stage III Patients



Data cut-off: January 16, 2005

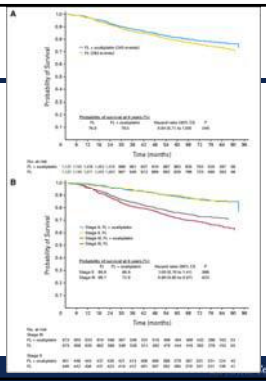
DFS curves for high-risk* stage II patients



**T4 and/or bowel obstruction and/or tumor perforation and/or poorly differentiated tumor and/or venous invasion and/or <10 examined lymph nodes*

Data cut-off: January 16, 2005

Mosaic Final

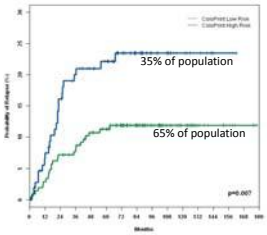


Stage 2/3 Colon CA: Need A Sorting Hat

- Cured by Surgery
- Not cured by surgery and chemo will not cure you
- Not cured by surgery but 5FU will cure you
- Not cured by surgery but 5FU and Oxali will cure you

Coloprint:

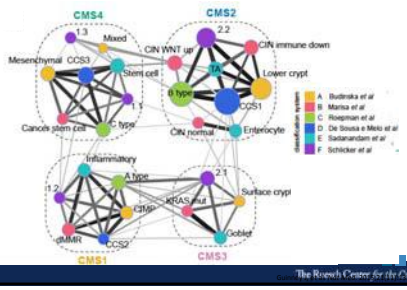
Probability of Relapse



ColoPrint High Risk patients have a 1 in 5 risk of relapse within 3 yrs.

ColoPrint Low Risk patients have a 1 in 13 risk of relapse within 3 yrs.

The Colorectal Cancer Consortium
Consensus for Molecular Subtypes (n >4500)



The Rogwch Center for the Cure of Gastrointestinal Cancers

Prospective Pooled Analysis of Six Phase III Trials Investigating Duration of Adjuvant Oxaliplatin-based therapy (3 vs. 6 months) for Patients with Stage III Colon Cancer: The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration

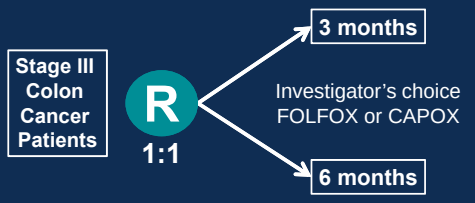
Qian Shi, Alberto F. Sobrero, Anthony F. Shields, Takayuki Yoshino, James Paul, Julien Taieb, Ioannis Souglakos, Rachel Kerr, Roberto Labianca, Jeffrey A. Meyerhardt, Franck Bonnetain, Toshiaki Watanabe, Ioannis Boukovinas, Lindsay A. Renfro, Axel Grothey, Donna Niedzwiecki, Valter Torri, Thierry Andre, Daniel J. Sargent, Timothy Iveson

Study Overview

- **Objective**
  To evaluate the ***non-inferiority (NI)*** of 3m compared with 6m of adjuvant oxaliplatin-based treatment in stage III colon cancer
- **Approach**
  Prospectively-designed, pooled analysis of individual patient data from six concurrently conducted phase III randomized trials

Study Schema

Total planned accrual ≥ 10,500



FOLFOX: 5FU/LV + Oxaliplatin CAPOX: Capecitabine + Oxaliplatin

IDEA Trials Summary

Trial	Regimen(s)	Stage III Colon Cancer Patients*	Enrolling Country
TOSCA	CAPOX or FOLFOX4	2402	Italy
SCOT	CAPOX or mFOLFOX6	3983	UK, Denmark, Spain, Australia, Sweden, New Zealand
IDEA France	CAPOX or mFOLFOX6	2010	France
C80702	mFOLFOX6	2440	US, Canada
HORG	CAPOX or FOLFOX4	708	Greece
ACHIEVE	CAPOX or mFOLFOX6	1291	Japan

*Only stage III colon cancer patients were included in the pooled primary analysis

Statistical Design

- **Primary Endpoint: Disease-free survival (DFS)**
  - Time from date of randomization (enrollment) to the earliest date of relapse, secondary colorectal primary tumor, or death due to all causes
- **Primary Analysis Population: Modified Intent-To-Treat**
  - Randomized and received any dose of treatment
  - Analysis according to patients' original randomization assignment
- DFS Hazard ratio (HR; 3m vs. 6m) and two-sided 95% confidence interval (CI) were estimated by Cox model **stratified by study**
- **Pre-planned Subgroup Analyses: By regimen and T/N stage**

Rationale for Non-inferiority Margin

Historical Data from MOSAIC

5FU/LV + Oxaliplatin vs. 5FU/LV

24% relative risk reduction

IDEA Consensus (Oncologists and Patient Advocates)

Oxaliplatin-based Treatment: **3m vs. 6m**

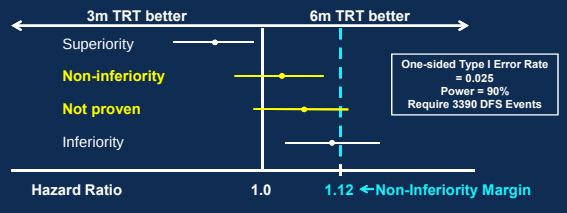
12% relative risk increase (upper 95% CI)

→ NI Margin: DFS HR = 1.12

Andre et al. N Engl J Med 2004; Andre et al. Curr Colorectal Cancer Rep 2013

Non-inferiority Hypothesis Testing

Statistical Conclusions Under Different Scenarios



TRT: treatment

Piaggio et al. JAMA 2012;308(24):2594-2604

Results: mITT Population

N patients	**12,834**
Total DFS events	**3,263 (96% of planned)**
ECOG PS 0 / 1	**79% / 21%**
N1 / N2	**72% / 28%**
T1-2	**13%**
T3	**66%**
T4	**21%**
FOLFOX / CAPOX	**60% / 40%**

Data frozen on Feb 1st, 2017

Patient Characteristics by Study

Patient Characteristics	TOSCA (N=2402)	SCOT (N=3983)	IDEA France (N=2010)	C80702 (N=2440)	HORG (N=708)	ACHIEVE (N=1291)
Median Age, years	64	65	64	61	67	66
ECOG PS*						
0	95%	71%	74%	71%	82%	96%
1	5%	29%	25%	28%	18%	4%
T Stage						
T1-2	13%	12%	12%	18%	8%	15%
T3	75%	59%	70%	67%	78%	57%
T4	12%	29%	18%	15%	14%	28%
N Stage						
N1	73%	69%	75%	73%	67%	74%
N2	27%	31%	25%	27%	33%	26%
Chemotherapy						
CAPOX	35%	67%	10%	0%	58%	75%
FOLFOX	65%	33%	90%	100%	42%	25%
Median follow-up time, m	62	37	51	35	48	37

*1% of PS 2 in IDEA France and C80702 trials

Patient Characteristics by Duration and Regimen

Patient characteristics	FOLFOX		CAPOX	
	3m Arm (N=3870)	6m Arm (N=3893)	3m Arm (N=2554)	6m Arm (N=2517)
Median Age, years	64	64	65	65
ECOG PS*				
0	77%	77%	82%	81%
1	22%	22%	18%	19%
T Stage				
T1-2	13%	14%	13%	12%
T3	68%	67%	63%	63%
T4	19%	19%	24%	25%
N Stage				
N1	72%	73%	71%	71%
N2	28%	27%	29%	29%

*1% of PS 2 in FOLFOX treated patients

Treatment Compliance

Treatment Compliance	FOLFOX		CAPOX	
	3m Arm	6m Arm	3m Arm	6m Arm
Total no. weeks received treatment Median (Q1-Q3)	12 (12-12)	24 (20-24)	12 (12-12)	24 (18-24)
Reached the planned last cycle[1]	90%	71%	86%	65%
% of dose actually delivered, Mean (Standard Deviation)				
5FU[2]	92.4 (22.7)	81.6 (26.6)	---	---
Capecitabine	---	---	91.2 (23.5)	78.0 (29.4)
Oxaliplatin	91.4 (19.9)	72.8 (25.6)	89.8 (21.7)	69.3 (28.3)

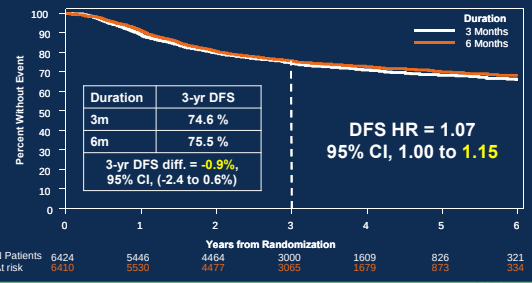
[1] 1% of patients assigned to 3m treatment (both FOLFOX and CAPOX) received > 3m of treatment; [2] combining infusion and bolus

Adverse Events

Adverse Events	FOLFOX			CAPOX		
	3m Arm	6m Arm	p-value[1]	3m Arm	6m Arm	p-value[1]
Overall						
G2	32%	32%	<.0001	41%	48%	<.0001
G3-4	38%	57%		24%	37%	
Neurotoxicity						
G2	14%	32%	<.0001	12%	36%	<.0001
G3-4	3%	16%		3%	9%	
Diarrhea						
G2	11%	13%	<.0001	10%	13%	0.0117
G3-4	5%	7%		7%	9%	

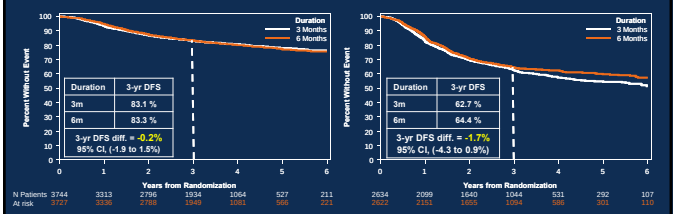
[1]Chi-squared test for trend; Total of 19 grade 5 events; Adverse events only collected on first 617 patients enrolled to SCOT trial

Primary DFS Analysis (mITT)



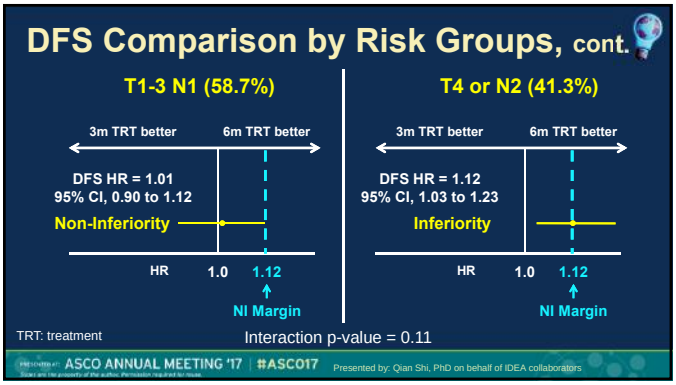
DFS Comparison by Risk Groups

T1-3 N1 (58.7%) **T4 or N2 (41.3%)**



Interaction p-value = 0.11

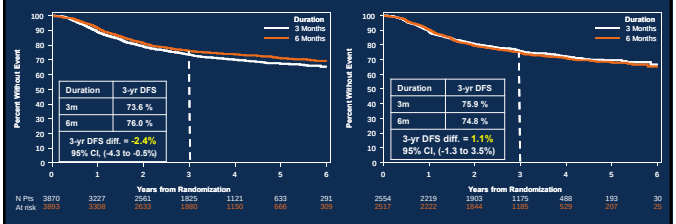
DFS Comparison by Risk Groups, cont.



TRT: treatment

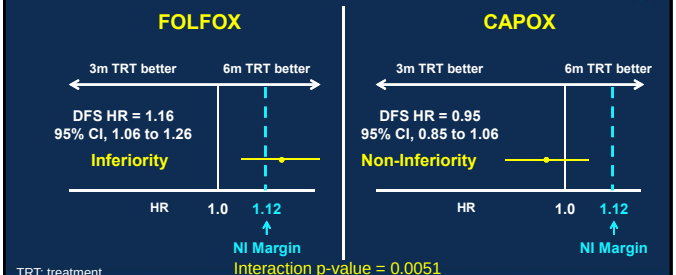
Interaction p-value = 0.11

DFS Comparison by Regimen



Interaction p-value = 0.0051

DFS Comparison by Regimen, cont.



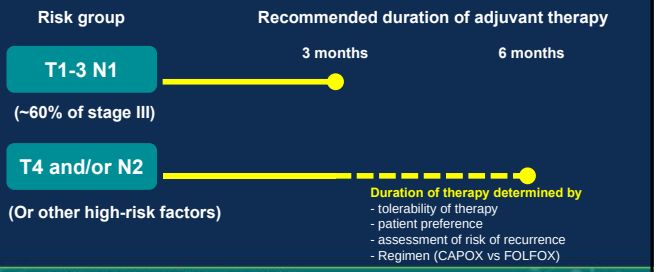
TRT: treatment

Interaction p-value = 0.0051

Summary

- 3m (vs. 6m) treatment: higher treatment compliance
- 3m (vs. 6m) treatment: substantially lower (G2+) neurotoxicity
  - FOLFOX: 17% (3m) vs. 48% (6m)
  - CAPOX: 15% (3m) vs. 45% (6m)
- The DFS non-inferiority of 3m oxaliplatin-based adjuvant therapy was not established in overall stage III colon cancer
- However, results comparing DFS between 3m and 6m treatment depend on risk group and regimen

IDEA Clinical Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer



The Impact of 3 vs 6 mo in adjuvant CRC

- Does this change everything?
  - Should colon results be applied to rectal cancer
  - Stage 2 patients?
  - Stage 4 NED patients?
  - Do ongoing trials need to be modified?
  - What to do in your next patient?

Let's do some math- for every 100 patients

- Assume a 25% absolute increase in DFS with FU + Oxaliplatin
  - 20% from FU – treatment fails 75% of the time
  - 5% from oxaliplatin – treatment fails 95% of the time
- T3 N1
  - 50% reduction in cost
  - 30% less grade 2/3 neurotoxicity
  - Same 3 year DFS 83%, 17 people relapse
- T4 N2
  - 50% reduction in cost
  - 30% less grade 2/3 neurotoxicity
  - 64.4% vs 62.7% = 1.7 patients, 36 vs 38 people relapse

6 vs 3, Cape vs 5Fu

- What is the target cell?
  - Is prolonged exposure somehow more effective?
  - Does initial oxaliplatin dose intensity matter?
  - Why did bevacizumab and cetuximab and irinotecan all fail
- If you did not kill it by 3 mo, why would 6 mo?
  - Should we extend further than 6 in high risk?
    - Maintenance therapy
    - Role of NSAIDs, exercise, tree nuts, vitamin D
    - HIPEC?
- Should we do a trial of Cape vs CapeOx?

Rectal Basics

- We regularly up-stage and over-treat
- Our treatments have a major negative impact on QOL
- Outcomes depend on experience, access to robots, high end imaging
- We do not have consistent guidelines or recommendations
- We will do almost anything to avoid local relapse

Location yields three different strategies

High
- Surgery first?
- Avoid radiation

Middle
- Chemo vs Chemo RT first
- Pre-treatment staging critical

Low
- Local, transanal surgery, no surgery?
- Unsure about the nodes

Case Study

- 65 y/o female, single, lives alone, works full time
- Moderately obese
- Rectal exam: mass palpable at finger tip
- CT CAP negative except for rectal lesion and one enlarged peri-rectal node
- Colonoscopy: Non-obstructing mass, friable, 8 cm from anal verge
- MRI: T3N1

Stage 2/3 Rectal CA: Need A Sorting Hat, Maybe Two?

Cured by Surgery

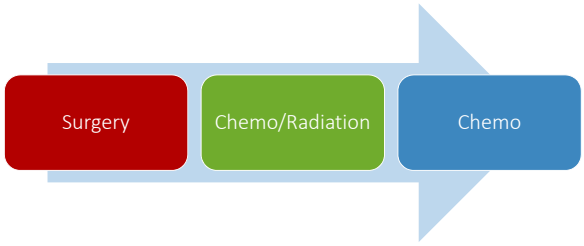
Not cured by surgery or chemo but radiation will cure you

Not cured by surgery but 5FU will cure you

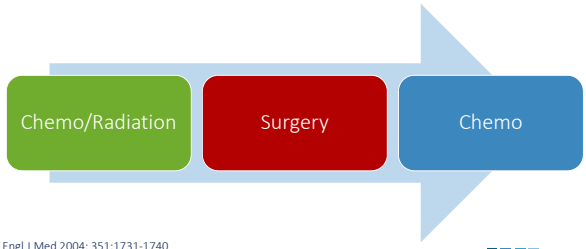
Not cured by surgery but 5FU and Oxali will cure you

Not cured by surgery, chemo or radiation will not cure you

The Original

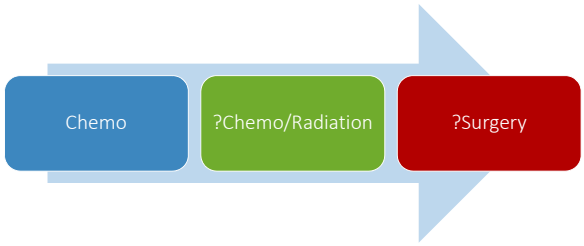


Post Sauer Study



N Engl J Med 2004; 351:1731-1740

The Current Research/Fashion



Location yields three different strategies

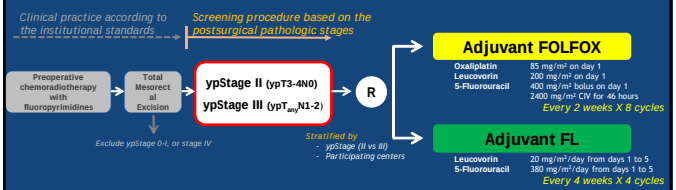
High
- Surgery first?
- Avoid radiation

Middle
- Chemo vs Chemo RT first
- Pre-treatment staging critical

Low
- Local, transanal surgery, no surgery?
- Unsure about the nodes

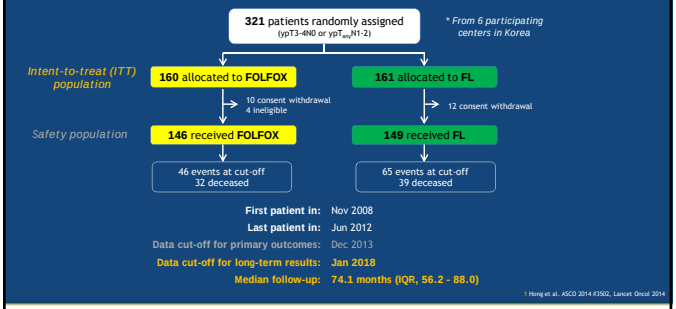
The Ruesch Center for the Cure of Gastrointestinal Cancers

Study design and Rationale



Key inclusion criteria
- Preoperative chemoradiotherapy with fluoropyrimidines alone; *oxaliplatin or other combined regimens were not allowed.*
- Total mesorectal excision (TME) was mandatory.
- Curative surgery (no microscopic residual tumor), ≤ 8 weeks prior to randomization.

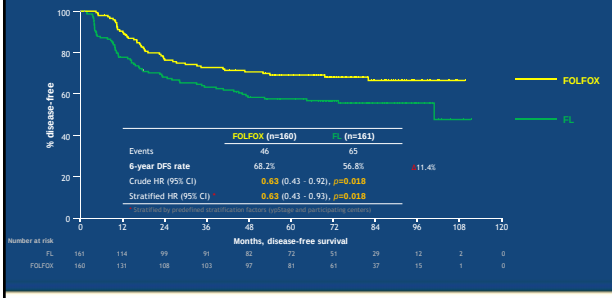
Patient Disposition



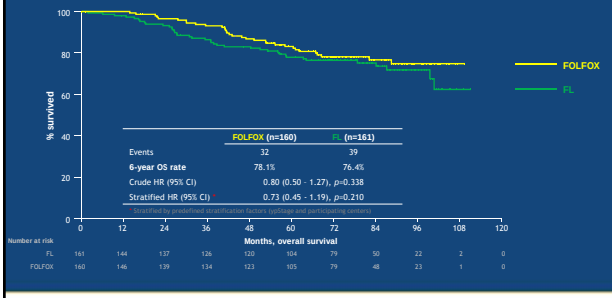
First patient in: Nov 2008
Last patient in: Jun 2012
Data cut-off for primary outcomes: Dec 2013
Data cut-off for long-term results: Jan 2018
Median follow-up: 74.1 months (IQR, 56.2 – 88.0)

† Hong et al. ASCO 2014 #3502, Lancet Oncol 2014

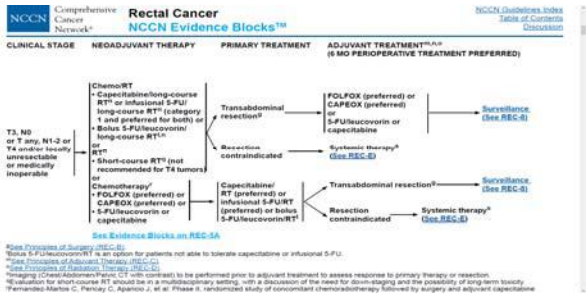
Disease-free survival, ITT population



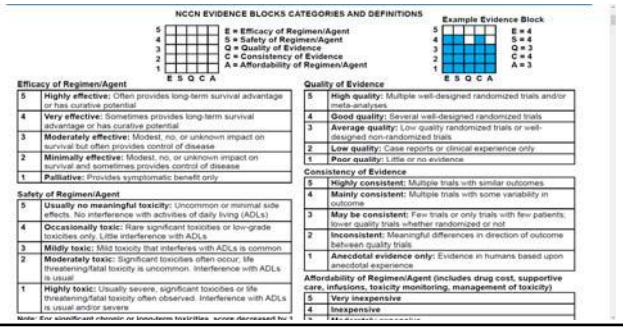
Overall survival, ITT population



Permission to follow many different paths



NCCN Evidence Blocks



NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS

E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

E S Q C A

Example Evidence Block

E = 4
S = 4
Q = 3
C = 4
A = 3

E S Q C A

Efficacy of Regimen/Agent

5	**Highly effective:** Often provides long-term survival advantage or has curative potential
4	**Very effective:** Sometimes provides long-term survival advantage or has curative potential
3	**Moderately effective:** Modest, no, or unknown impact on survival but often provides control of disease
2	**Minimally effective:** Modest, no, or unknown impact on survival and sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal side effects. No interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only. Little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs is common
2	**Moderately toxic:** Significant toxicities often occur; life threatening/fatal toxicity is uncommon. Interference with ADLs is usual
1	**Highly toxic:** Usually severe, significant toxicities or life threatening/fatal toxicity often observed. Interference with ADLs is usual and/or severe

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** Several well-designed randomized trials
3	**Average quality:** Low quality randomized trials or well-designed non-randomized trials
2	**Low quality:** Case reports or clinical experience only
1	**Poor quality:** Little or no evidence

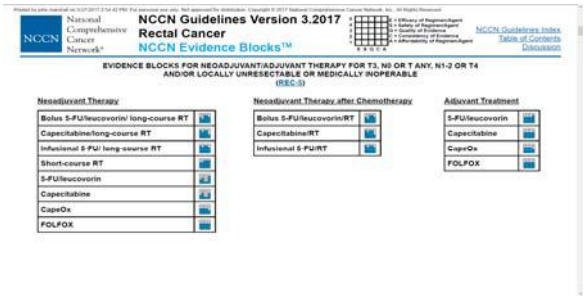
Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients; lower quality trials whether randomized or not
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**

What is our Evidence?



NCCN National Comprehensive Cancer Network

NCCN Guidelines Version 3.2017
Rectal Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

EVIDENCE BLOCKS FOR NEOADJUVANT/ADJUVANT THERAPY FOR T3, N0 OR T ANY, N1-2 OR T4 AND/OR LOCALLY UNRESECTABLE OR MEDICALLY INOPERABLE (REC-3)

Neoadjuvant Therapy

Bolus 5-FU/leucovorin/ long-course RT
Capecitabine/long-course RT
Infusional 5-FU/ long-course RT
Short-course RT
5-FU/leucovorin
Capecitabine
CapeOx
FOLFOX

Neoadjuvant Therapy after Chemotherapy

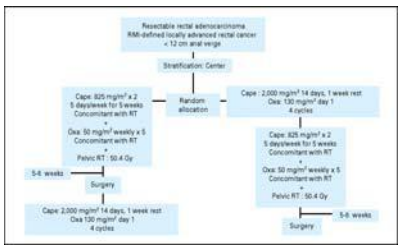
Bolus 5-FU/leucovorin/RT
Capecitabine/RT
Infusional 5-FU/RT

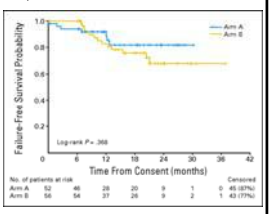
Adjuvant Treatment

5-FU/leucovorin
Capecitabine
CapeOx
FOLFOX

Phase II, Randomized Study of Concomitant Chemoradiotherapy Followed by Surgery and Adjuvant Capecitabine Plus Oxaliplatin (CAPOX) Compared With Induction CAPOX Followed by Concomitant Chemoradiotherapy and Surgery…

Fernandez-Martos et al: J Clin Oncol 28:859-65, 2010





PROSPECT

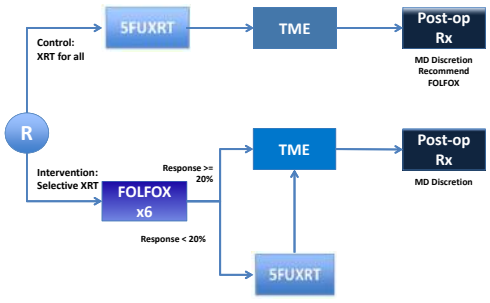
Preoperative Radiation Or Selective Preoperative radiation and Evaluation before Chemotherapy and TME (N1048)

An NCI-NCIC-SAKK National Clinical Trials Network (NCTN) Phase II/III Trial
Study Chair: Deb Schrag
Radiation Oncology Chair: Harvey Mamon
Surgery Chairs: Martin Weiser and Alessandro Fichera
Medical Oncology Chairs: L. Saltz and R. McWilliams
Radiology: Marc Golub
Pathology: Wendy Frankel
Correlative Sciences: David Solit
Biostatistics: Dan Sargent and Qian Shi

PROSPECT: Protocol Summary

- Objective:
  - To determine if selective use of 5FUXRT is a reasonable alternative strategy to universal use of preoperative 5FUXRT for management of locally advanced rectal cancer that is amenable to sphincter sparing TME.
- Hypothesis:
  - Treatment with neoadjuvant FOLFOX followed by selective use of neoadjuvant 5FUXRT for patients with locally advanced rectal cancer who are candidates for curative intent sphincter sparing surgery with TME is not inferior to the standard approach to treatment with neoadjuvant 5FUXRT followed by surgery.

Protocol Schema for PROSPECT N1048



Total Neoadjuvant Therapy (TNT) for Locally Advanced Rectal Cancer

- MSKCC Retrospective Review
- Conclusions:
  - The data add weight to current NCCN guidelines
  - TNT facilitates delivery of systemic chemotherapy
  - TNT leads to high pCR and cCR rates and be beneficial as part of a non-operative management strategy

	ChemoRT	TNT
628 pts 2009-15	320	308
% 5FU/Oxali	88/73	96/90
%pCR	16	19
%Complete Clinical Response	7.5	24
Median FU mo	42	25

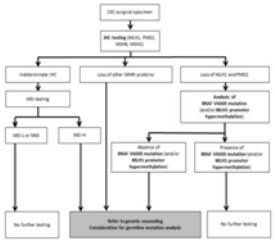
Cercek A, Roxburgh CS, Weiser M.; **ASCO 2017 Abstract 3519**

MSI-H in stage 2 and 3

- Good prognosis stage 2, ?stage 3
- Impact of chemo- maybe negative

Measuring MSI is Confusing

- IHC test for the presence 4 proteins
  - MLH1, MLH6, PMS2, MSH2
  - Present = Normal
  - Missing- reflex to gene test
- Gene sequencing
  - Length of microsatellites compared to normal
  - Can be done by NexGen
  - Need normal tissue
- Germ Line vs Somatic



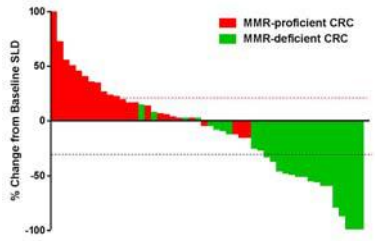
Tough case: What would you do?

- 74 y/o with CAD, diagnosed with stage 3 (T3N1) sigmoid cancer
  - IHC on biopsy showed absent MLH1/PMS2= dMMR
  - NEXGEN confirms MSI-H, TMB 25
- Common wisdom
  - Oxali does not work or 70 y/o
  - 5FU might make outcomes worse in MSI
- Is MSI predictive and/or prognostic?
- Are we pushing the curve up or down?
- No prospective studies: all small, retrospective studies

Immune Therapy for CRC

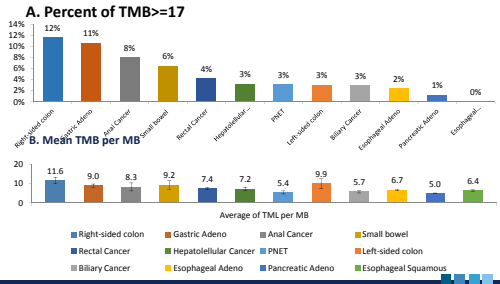
- Pembro approved for MSI-H cancers
  - Le et al: Updated ASCO 2018
- Nivo approved for MSI-H CRC
- Ipi + Nivo approved for MSI-H CRC
  - Andre et al: ASCO 2018
  - FDA approval 7/2018

Pembrolizumab in MMR-Deficient CRC: Change in Target Lesions

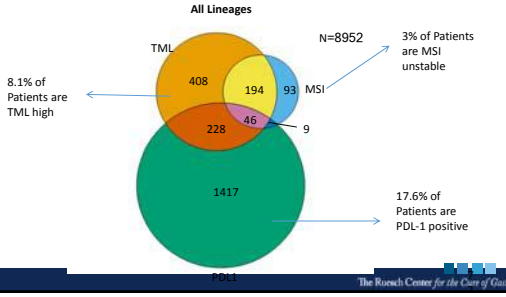


Le DT, et al. ASCO 2016. Abstract 103.

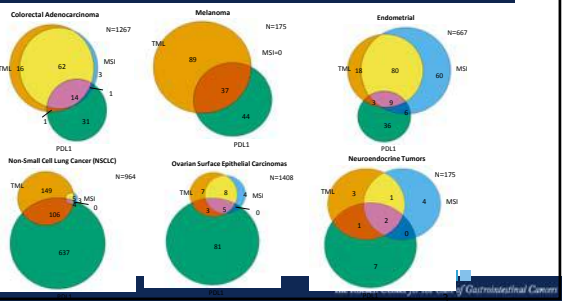
Percent of cases carrying a TMB of >=17 and (B) Mean TMB per megabase (MB) in the 12 cancer types. Error bars on (B) are standard errors.



Relationship between MSI, TML, PDL-1



MSI, TML, and PDL-1 by lineage



Management of Autoimmune Phenomena and Disease in Patients Treated with Immune Checkpoint Inhibitors

Pierre L. Triozzi, MD
Professor of Medicine
Section on Hematology and Oncology
Wake Forest School of Medicine

Wake Forest School of Medicine

Management of autoimmune phenomena and disease in patients treated with immune checkpoint inhibitors

Pierre L. Triozzi, MD
Section of Hematology-Oncology

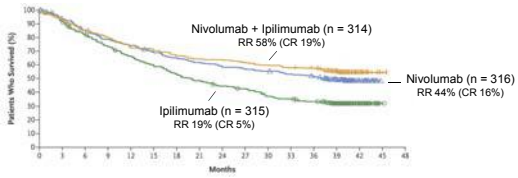
IMMUNE CHECKPOINT INHIBITORS

Target	CTLA-4	PD-1			PD-L1		
Drug	*Ipilimumab (Yervoy)*	*Nivolumab (Opdivo)*	*Pembrolizumab (Keytruda)*	*Cemiplimab (Libtayo)*	*Atezolizumab (Tecentriq)*	*Avelumab (Bavencio)*	*Durvalumab (Imfinzi)*
Indication	Melanoma	Melanoma	Melanoma				
		NSCLC	NSCLC		NSCLC		
		Urothelial	Urothelial		Urothelial	Urothelial	Urothelial
	RCC	RCC					
		HNSCC	HNSCC				HNSCC
		MSI-High	MSI-High				
		Hodgkin's	Hodgkin's				
		HCC	HCC				
			Gastric				
			Cervical				
		SCLC					
						Merkel CC	
			PMBCL				
				CuSCC			

Merkel cell

NIVOLUMAB + IPILIMUMAB *v*. NIVOLUMAB *v*. IPILIMUMAB

Melanoma



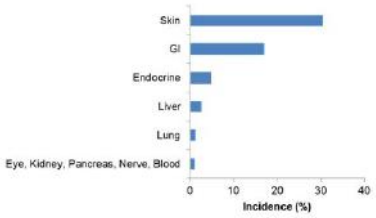
	Nivolumab + Ipilimumab	Nivolumab	Ipilimumab
Grade 3/4 AE	59%	21%	28%
Discontinuation	39%	12%	16%

Wolchok et al. N Engl J Med 2017

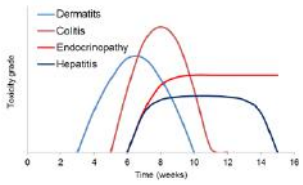
•Management of patients who develop autoimmune toxicities

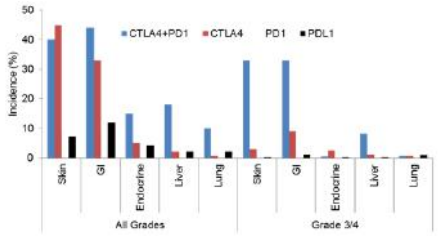
•Management of patients with per-existent autoimmune disease

CHECKPOINT BLOCKADE
Immune Related Adverse Events (irAE)



CHECKPOINT BLOCKADE
Time Course of irAEs





Xu et al BMJ 2018

IMMUNE CHECKPOINT INHIBITORS
Comparative Safety

	Any grade	*Grade 3/4*	*Comment*
Ipilimumab (CTLA4)	87	29	dermatologic, GI, renal
Pembrolizumab (PD1)	75	20	arthralgia, pneumonitis, hepatic
Nivolumab (PD1)	72	14	endocrine
Atezolizumab (PDL1)	49	15	hypothyroidism, N/V

36 head-to-head phase II and III randomized trials (n=15,370)

Xu et al. BMJ 2018

irAEs
Mechanisms

Mechanism	*Reference*
Increased eosinophils	Schindler et al. ASOC 2014
Increased circulating IL-17	Tarhini et al. I Immunother Cancer 2017
Diversification of T-cell repertoire	Oh et al. Cancer Res 2017
Specific inflammatory gene activation (cytokine, chemokine, COX2)	Shahabi et al J Transl Med 2013 Friedlander et al. J Immunother Cancer 2018
Pre-existing autoantibody	Gowen et al. J Transl Med 2018

irAEs
Clinical Predictors

- Baseline sarcopenia and low muscle attenuation
- Concomitant use of medicines with autoimmune toxicities (e.g. anti-arrhythmics, antibiotics, anticonvulsants, antipsychotics)
- Previous viral infections (e.g. HIV or hepatitis)
- Personal or family history of autoimmune disease

Daly et al. Br J Cancer 2017; Champiat et al. Ann Oncol 2016

TOXICITY BIOMARKERS

+	-
Early recognition → more effective management	Most patients are monitored closely Most toxicities can be managed effectively (severe disability or death 0.4-1.2%)

irAE
Management

Mild (Grade 1)	• Manage symptomatically • Continue treatment
Moderate (Grade 2)	• Hold treatment • PO corticosteroids (0.5-1.0 mg/kg/d prednisone) • Taper corticosteroids over 4-6 weeks • Resume treatment when resolved or improved to mild on <7.5 mg/d prednisone
Severe (Grade 3) Life threatening (Grade 4)	• Suspend treatment • IV corticosteroids (1-2 mg/kg/d "prednisone") • If no improvement with IV corticosteroids after 2-3 days, infliximab • Taper corticosteroids over 4-6 weeks

DERMATOLOGIC

Presentation	• Rash and/or pruritus • Reticular, maculopapular, erythematous rash trunk or extremities • Vitiligo • Stevens-Johnson / toxic epidermal necrolysis (rare) • Alopecia (rare)
Rule out	• Non-inflammatory causes (other medications, photosensitivity, etc.)

DERMATOLOGIC
Management

Mild Localized	• Topical corticosteroids • Oral antipruritics (hydroxyzine, diphenhydramine)
Moderate Diffuse <50% skin surface	• Hold treatment • Topical corticosteroids and oral antipruritics • Oral corticosteroids (0.5 mg/kg/d "prednisone") • Resume treatment when resolved or improved to mild on <7.5 mg/d prednisone
Severe – Life threatening Stevens-Johnson TEN Full thickness ulceration Necrosis Bullous Hemorrhagic	• Permanently discontinue treatment • Blistering should be evaluated by a dermatologist and biopsy considered • Corticosteroids (1-2 mg/kg/d "prednisone") • When controlled, taper corticosteroids over 1 month

DIARRHEA/COLITIS

- Diarrhea (increase in stool frequency)
- Colitis (abdominal pain, radiographic or endoscopic findings of colonic inflammation)

Presentation	• Diarrhea • Abdominal pain / cramping • Blood or mucus in stool • Fever • Peritoneal signs (bowel perforation) • Ileus
Rule out	• C. difficile • Other bacterial/viral pathogens

DIARRHEA/COLITIS

KUB	Colon edema
CT	Colon edema
Rectosigmoid-/colon-oscopy	Mucosal erythema and ulcerations, bleeding
Biopsy	Neutrophilic, lymphocytic, or mixed neutrophilic-lymphocytic infiltrates

DIARRHEA/COLITIS
Management

Mild <4 stools/d over baseline	• Anti-motility drugs (loperamide or diphenoxylate-atropine) • Budensonide if symptoms persist but do not escalate after 2-3 days • ADA colitis diet
Moderate 4-6 stools/d over baseline	• Withhold treatment • Manage symptomatically • Consider CT or rectosigmoid-/colon-oscopy • Corticosteroid PO (0.5 mg/kg/d "prednisone") − Persists >1 week − Colitis on CT or colonoscopy • Resume treatment when resolved or improved to mild on <7.5 mg/d "prednisone"
Severe – Life threatening >7 stools/d over baseline or other complications	• Permanently discontinue treatment. • Corticosteroids IV (1-2 mg/kg/d "prednisone") • If no improvement with corticosteroids IV after 2-3 days, infliximab • Mycophenolate mofetil if refractory

DIARRHEA/COLITIS
Colonoscopy

- Lower endoscopy is advised for patients with grade 3 or 4 symptoms of diarrhea, but no recommendations are provided on differential treatment based on endoscopic findings.
- Patients with ulcers or higher endoscopy severity scores (e.g., van der Heide or Mayo scores) required infliximab.
- No correlation between the grade of diarrhea and ulcers / endoscopic severity.
- No correlation between the presence of abdominal pain and ulcers / endoscopic severity.
- Ascending colon > descending colon in 23%.
  - Severity would have been underestimated by sigmoidoscopy only
- Histopathology confirms diagnosis. It does not guide therapy beyond what is found endoscopically.

Geukes Foppen MH, et al. ESMO Open. 2018

DIARRHEA/COLITIS
Prevention

	n	*Grade ≥2 diarrhea*
ipilimumab (10 mg/kg q 3 w X4) + budesonide	58	33%
ipilimumab (10 mg/kg q 3 w X4) + placebo	57	35%

Weber et al. Clin Cancer Res 2009

PROBIOTICS

- A more diverse array of microbes in the gut is associated with better response to ICI
- Certain types of bacteria, such as *Faecalibacterium*, were linked to better outcomes.
- 312 melanoma patients who were starting checkpoint inhibitor therapy, >40% used of probiotics
  - Less diverse microbiome.
  - Lower odds for responding.

Gopalakrishnan et al. Science 2018; Gopalakrishnan et al SITC 2018 (abstract)

ENDOCRINOPATHY
Thyroiditis

Presentation	• Nonspecific symptoms such as fatigue. • Thyroid function is monitored prior to each dosing. • Hypothyroidism / destructive thyroiditis (most common) • Hyperthyroidism associated with Graves' disease • Transient hyperthyroidism followed by hypothyroidism
Rule out	• Hypophysitis

ENDOCRINOPATHY
Hypophysitis

Presentation	• Fatigue and headache. • ACTH is monitored prior to each dosing • Decreased TSH and ACTH − Decreased LH and prolactin. • CT/MRI - enhancement / swelling of pituitary
Rule out	• Thyroiditis • Adrenal insufficiency

ENDOCRINOPATHY
Management

Mild Asymptomatic	• Continue treatment • Hormone replacement therapy
Moderate Symptomatic Not interfering with ADL	• Continue / withhold treatment • Hormone replacement therapy • Corticosteroids PO (1-2 mg/kg/d "prednisone") • If improved, taper steroids over at least 4 weeks • Resume treatment when asymptomatic on <7.5 mg/d "prednisone"
Severe – Life threatening Symptomatic Interfering with ADL Hypotension	• Withhold / discontinue treatment • Adrenal crisis – R/O sepsis, BP support • Corticosteroids IV (1-2 mg/kg/d "prednisone") • Stress doses of mineralocorticosteroid

ENDOCRINOPATHY
Infertility/Sexual Health

- No study has specifically commented on infertility or sexual side effects.
- Biochemical profiling in 2 studies suggests <1% develop hypogonadism.

Pregnancy with successful foetal and maternal outcome in a melanoma patient treated with nivolumab in the first trimester: case report and review of the literature.

Xu W, Moor RJ, Walpole ET, Atkinson VG

Melanoma Res. 2019 Feb 5. doi: 10.1097/CMR.0000000000000586. [Epub ahead of print]

Sood et al. Current Urology Reports 2018

HEPATITIS

Presentation	Most episodes are asymptomatic Fever (occasional)
Rule out	Infection Alcohol Hepatotoxic medications Biliary disease/obstruction Progressing cancer

HEPATITIS

Labs	LFTS predominantly hepatocellular ± cholestatic
CT	Mild hepatomegaly, periportal edema, or periportal lymphadenopathy
Biopsy	Severe panlobular hepatitis with prominent perivenular infiltrate with endothelialitis

HEPATITIS
Management

Mild AST/ALT <2.5X ULN Bilirubin <1.5X ULN	• Continue treatment
Moderate AST/ALT 2.5-5X ULN Bilirubin >1.5-3X ULN	• Withhold treatment • Corticosteroids 1-2 mg/kg/d prednisone – taper over >4 weeks • Resume treatment when AST/ALT <2.5X ULN and bilirubin <1.5X ULN on <7.5 mg/d prednisone
Severe – Life threatening AST/ ALT >5X ULN Bilirubin >3X ULN	• Permanently discontinue treatment • Corticosteroids 1-2 mg/kg/d prednisone – taper over >4 weeks • Vedolizumab or mycophenolate mofetil if refractory

PNEUMONITIS

Presentation	• Cough and dyspnea
Rule out	• Pulmonary embolism • Cardiac causes • Infections • COPD

PNEUMONITIS
Risk Factors

	Cancer	*No of patients*	*All grades*		*Grade ≥ 3*	
			N	*%*	*N*	*%*
Monotherapy	Lung	1159	45	4	20	2
	Renal cell	607	35	4	6	1
	Melanoma	2155	35	2	5	0.2
Combination therapy	Melanoma	575	38	7	9	1

Nishino et al. JCO Precision Oncology 2017

Deaths have been rarely reported;
most have been in patients with NSCLC
(Ma et al. Front Pharmacol 2018)

PNEUMONITIS
Risk Factors

Characteristic	*P*
Age	NS
Sex	NS
Race	NS
Smoking	NS
ECOG ≥ 2	NS
COPD	NS
Histology	NS
Initial cancer stage	NS
Treatment line	NS
PD-L1 expression	NS
Prior chemotherapy	NS
Prior EGFR-TKI	NS
Prior thoracic radiotherapy	NS
Prior surgery	NS
ICI agent	NS
Combination therapy	NS

Kunger et al. Chest 2017; Suresh et al. J Thorac Oncol 2018; Cho et al. Lung Cancer 2018

PNEUMONITIS
CT Findings

Specific findings	Ground glass opacities Reticular opacities Consolidations
Patterns	Cryptogenic organizing pneumonia (COP) > Non-specific interstitial pneumonia (NSIP) > Hypersensitivity pneumonitis (HP) > Acute interstitial pneumonia/acute respiratory distress syndrome (AIP/ARDS)
Involvement	Lower > middle > upper lungs
Distribution	Mixed and multifocal > peripheral and lower and diffuse

Widmann et al. Current Radiology Reports 2017

PNEUMONITIS
Management

Mild Radiographic changes only	• Delay treatment • Repeat imaging every 3 weeks
Moderate Cough and dyspnea	• Delay treatment • Consider admission to hospital • Methylprednisolone IV 0.5–1.0 mg/kg/d • Taper steroids over 1 month • Repeat imaging in days to weeks
Severe - Life threatening Hypoxia	• Permanently discontinue treatment • Admit to hospital or ICU • Methylprednisolone IV 2–4 mg/kg/d • Infliximab ± cyclophosphamide, mycophenolate mofetil at 48 hours if no improvement • Taper steroids over 6 weeks • Repeat imaging in days to weeks

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NEUROLOGIC
Suspend ICI

	Grade 1	*Grade 2*	*Grade 3*	*Grade 4*
Guillain Barre	X	X	X	X
Myasthenia Gravis			X	X
Transverse myelitis	X	X	X	X
Aseptic meningitis			X	X
Encephalitis		X	X	X
Peripheral neuropathy			X	X

RENAL

- AKI that mimics other drug-induced interstitial nephritis
- median time of onset - 13 weeks
- Renal function usually restored after corticosteroids
- Dialysis may be required for some patients.

OCULAR

- Episcleritis, conjunctivitis, and uveitis
- Topical corticosteroid drops are sufficient to treat most
- Systemic immunosuppression required only for more severe

HEMATOLOGIC

- Autoimmune anemia, neutropenia, thrombocytopenia or acquired hemophilia A
- Supportive treatment and corticosteroids

PANCREATITIS

- Although amylase/lipase levels may be increased in ICI-treated patients, they are often asymptomatic and do not require serial monitoring.

	Without pancreatitis (n=18)	*With pancreatitis (n=3)*
Lipase UI/L, mean (range)	247 (116-2389)	1029 (770-1099)
Typical epigastric pain	0	2
CT findings	0	2

- Lipase increase in an asymptomatic patient without radiographic abnormalities of pancreas can be regarded as not clinically significant, allowing the continuation of the ICI

Michot et al. J Immunother 2018

MONOCLONAL ANTIBODIES
Elimination Half Life

	$T_{1/2}$ (days)
Ipilimumab	16
Nivolumab	12-20
Pembrolizumab	14–22
Atezolizumab	21

Pharmacodynamics

Months to years?

irAE - EFFICACY RELATIONSHIP

Drug	Cancer	n	Result	Reference
Ipilimumab	Melanoma	139	Early AE → ↑response	Downey et al. Clin Cancer Res 2007
Ipilimumab	Melanoma	855	No association with OS	DiGiacomo et al. ASCO 2013
Ipilimumab	Melanoma	298	No association with OS	Horvat et al. J Clin Oncol 2015
Nivolumab	Melanoma	576	Any-grade AE → ↑response	Weber et al. J Clin Oncol 2017
Nivolumab	Melanoma	148	Rash, vitiligo, any-grade AE → ↑OS	Freeman-Keller et al. Clin Cancer Res 2016
Pembrolizumab	Melanoma	67	Vitiligo→↑response	Hua et al. JAMA Dermatol 2016
Immunotherapy	Melanoma	322	Vitiligo-like depigmentation → ↑OS	Teuling et al. J Clin Oncol 2015

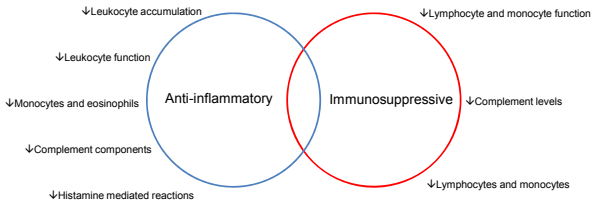
irAE - EFFICACY RELATIONSHIP

Drug	Cancer	n	Result	Reference
Nivolumab	NSCLC	70	RR, DCR, and PFS better in irAE vs non irAE patients Pre-existing anti-thyroid antibody associated with response	Toi et al. The Oncologist 2018

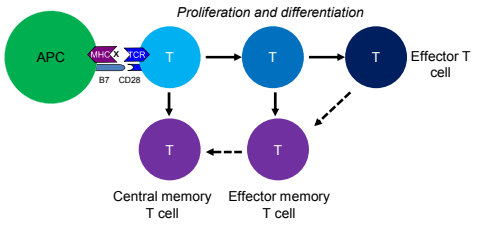
Response → more treatment → more toxicity?

IMMUNITY	*INFLAMMATION*
Recognize foreign/antigen	Isolate damage
Eliminate foreign/antigen	Attract immune mediators
Remember foreign/antigen	Repair damage

CORTICOSTEROIDS



T CELL RESPONSE



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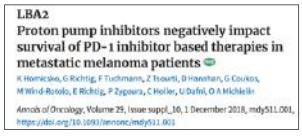
CORTICOSTEROIDS

- Baseline corticosteroid use of ≥ 10 mg of prednisone equivalent was associated with poorer outcome in patients with NSCLC treated with PD-(L)1.
- Prudent use of corticosteroids at the time of initiating PD-(L)1 blockade is recommended.
- In the absence of specific indications such as prior infusion reaction or concurrent chemotherapy, routine premedication with corticosteroids is not

Arbour et al. J Clin Oncol. 2018

CORTICOSTEROIDS
Ulcer Prophylaxis?



LBA2

Proton pump inhibitors negatively impact survival of PD-1 inhibitor based therapies in metastatic melanoma patients

K Homicsko, G Richtig, F Tuchmann, Z Tsourti, D Hanrahan, G Coukos, M Wind-Rotolo, E Richtig, P Zagoura, C Heller, U Dafni, O A Michielin

Annals of Oncology, Volume 29, Issue suppl_10, 1 December 2018, mdy511.001, https://doi.org/10.1093/annonc/mdy511.001

Retrospective analysis ≈230 melanoma patients treated with ICI mono- and combination therapy
PPI at treatment initiation decreased response rates by ≈50%
Reduced PFS and OS of ipilimumab + nivolumab but not ipilimumab alone.
PPIs might produce a unique anti-inflammatory immune status

Avoid PPIs?

Homicsko et al. ESMO 2018 (abstract)

CORTICOSTEROIDS
Infection Prophylaxis?

Infections in patients with melanoma (n=740) treated with ICI

Infection Type	No. of cases (%)
Bacterial	46 (6%)
Pneumonia	13
Bacteremia	13
C. difficile	10
Intra-abdominal	7
Craniofacial	3
Fungal	6 (1%)
Pneumocystis	3
Aspergillosis	2
Candidemia	1
Viral	5 (1%)
H. zoster	3
CMV	1
EBV	1
Total	58 (7%)

Del Castillo et al. Clin Infect Dis. 2016

Factors associated with infection
- Corticosteroids (OR 7.71)
- Infliximab (OR 4.74)
- Ipilimumab + nivolumab (OR 3.26)

- Nivolumab (OR .29)
- Pembrolizumab (OR 0)

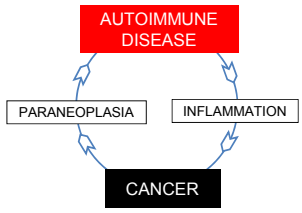
PCP prophylaxis (e.g.TMP-SMX) if >3 weeks of 30 mg prednisone or equivalent anticipated

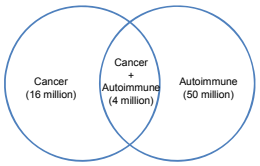
Fungal prophylaxis (fluconozole) if >6-8 weeks of 20 mg prednisone or equivalent anticipated

RADIATION + ICI

Radiation Toxicity	*ICI Toxicity*
Dermatitis	Dermatitis
Mucositis	Mucositis
Colitis	Colitis
Esophagitis	Esophagitis
Pneumonitis	Pneumonitis

- No difference in adverse effects were noted among patients in most studies of combination therapy compared to either modality alone
- Increase in brain mass edema and hemorrhage in patients (50%) treated with radiation during or before ipilimumab, but in patients treated with radiation after ipilimumab





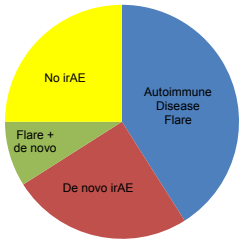
IMMUNE CHECKPOINT INHIBITORS

Pre-existing Autoimmunity

Study	*ICI*	*n*	*AID Flare*	*De novo*	*Comment*	*Response Rate*
Johnson et al. JAMA Oncol 2016	CTLA4	30	27%	33%	1 death	20% (melanoma)
Menzies et al. Ann Oncol 2017	PD1	52	38%	29%	8% d/c 0 deaths	33% (melanoma)
Gutzmer et al. Eur J Cancer 2017	PD1	19	42%	16%	0 d/c 0 deaths	32% (melanoma)
Danlos et al. Eur J Cancer 2018	PD1	45	55%	22%	11% d/c 0 deaths	38%(melanoma, NSCLC)
Tison et al. Ann Rheum Dis 2018	PD1/PDL1	112	42%	38%	1 death	48% (melanoma) 54% NSCLC
Kahler et al. Cancer Immunol Immunother 2018	CTLA4	41	29%	29%	2% d/c	12% (melanoma)
Abdel-Wahab et al. Ann Intern Med 2018	PD1, CTLA4, PD1+CTLA4	123	45%	29%	21% d/c 3 deaths	25/50 (50%) with irAE responded 5/14 (36%) without irAE responded

IMMUNE CHECKPOINT INHIBITORS

Pre-existing Autoimmunity



Abdel-Wahab N, et al. Ann Intern Med 2018

IMMUNE CHECKPOINT INHIBITORS

Pre-existing Autoimmunity

	Patients, n	*Any irAE*	*Disease Flare*	*De Novo irAE*
AID status at CPI start				
Active	49	67%	47%	33%
Inactive	57	75%	50%	25%
Any therapy at CPI start				
Yes	44	59%	39%	23%
No	57	83%	58%	35%
Immunosuppressive therapy at CPI start				
Yes	27	67%	48%	19%
No	74	74%	50%	34%
CPI				
Ipilimumab	55	66% (n=36)	36%	42%
Anti-PD1/PDl1	65	82% (n=53)	62%	26%
Combination ipi/nivo	3	100% (n=3)	33%	67%

Abdel-Wahab N, et al. Ann Intern Med 2018

IMMUNE CHECKPOINT INHIBITORS
Pre-existing Autoimmune Disease

	No. of patients	*No. with irAE (%)*	*AID flare*	*De novo irAE*	*Flare + de novo*	*Discontinued*	*Deaths*
Psoriasis and/or Psoriatic Arthritis	28	25 (89%)	18	3 (colitis, hypophysitis, lichenoid reaction)	4 (colitis, pneumonitis, hepatitis, ITP)	6	2 (colitis, unknown)
Rheumatoid arthritis	20	15 (75%)	3	5 (colitis, thyroiditis, myasthenia gravis)	3 (colitis, hypophysitis)	7	
Inflammatory bowel	13	8 (62%)	5	2 (Crohn's → UC)	1 (TEN)	3	1 (TEN)
Thyroid	11	5 (45%)	2	3 (hypophysitis, hyperthyroidism, type 1 diabetes)		2	
Multiple sclerosis	6	2 (33%)	2				
Myasthenia gravis	4	4 (100%)	3	1 (sarcoid-like reaction)			

Abdel-Wahab N, et al. Ann Intern Med 2018

IMMUNE CHECKPOINT INHIBITORS
Pre-existing Autoimmune Disease

- The risk in patients with preexisting autoimmune disease relates to flares and worsening disease status and not necessarily to an increase in de novo irAEs
- No differences in frequency of adverse events in patients with active versus inactive preexisting autoimmune disease
- Patients receiving immunosuppressive therapy at initiation of CPI therapy seemed to have fewer adverse events than those not receiving therapy.
- Ipilimumab was associated with more de novo irAEs, anti–PD-1/PD-L1 agents with more disease flares
- Although the frequency of de novo irAEs may be similar in patients with or without autoimmune disease, they might be more severe in patients with

IMMUNE CHECKPOINT INHIBITORS
Autoimmune Disease

.

Most adverse events were managed with corticosteroids, and 16% required other immunosuppressive therapies.

Adverse events improved in more than half of cases without the need to discontinue CPI therapy.

Data are too scarce to infer whether maintenance immune suppressive therapy might have a protective effect on exacerbations

Death from a serious adverse event was reported in 2% of patients.

IMMUNE CHECKPOINT INHIBITORS
Autoimmune Disease

Higher proportion of patients who experienced irAEs had a favorable tumor response compared with those not having irAEs.

AUTOIMMUNE DISEASE
ICI Contraindication?

- Life-threatening disorders
- Neurologic autoimmune disorders
- Autoimmune disease inadequately controlled with immunosuppressives
- Patients requiring high doses of immunosuppressive agents
  Goal is prednisone <10 mg qd (or equivalent) prior to initiating ICI)

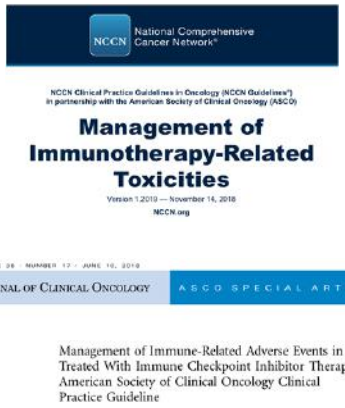
AUTOIMMUNE DISEASE
Immune Checkpoint Inhibitors

What do we do with patients require ongoing immunosuppressive therapy? What agents and doses?

Will concomitant immunosuppressive therapies for preexisting or flaring autoimmune diseases blunt the ICI antitumor response?

Can patients who flare or develop a de novo irAE that leads to treatment suspension be retreated?

Should patients who flare or develop a de novo irAE that leads to treatment suspension be switched to another ICI?



AUTOIMMUNE DISEASE
Immune Checkpoint Inhibitors

Most have flares

Most are manageable

Monitor closely

RISK : BENEFIT

HER2-Positive Breast Cancer: A Long and Winding Road

Alexandra Thomas, MD
Director, Breast Cancer Program
Professor of Medicine
Section on Hematology and Oncology
Wake Forest School of Medicine

HER2-positive Breast Cancer
A Long and Winding Road

Alexandra Thomas MD, FACP
March 1, 2019

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Disclosures

- Genentech – meals (<$200 value) to discuss future support of a grant submitted to NCI
- Beyond Spring Pharmaceuticals – DSMB
- Syndax – research support (to the institution)
- Johnson and Johnson – stock ownership
- Gilead Science – stock ownership
- Up-to-Date – royalties (husband)

HER2-positive Breast Cancer Overview

- Background
  - 2018 Guidelines
  - AJCC Staging 8th Edition
- HER2-targeting therapy
- Current issues in HER2-positive breast cancer
- Wake Forest studies in HER2-positive breast cancer

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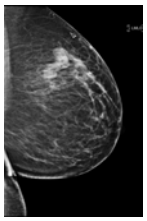
Patient Case



39 yo African American woman

- HPI:
  - presented January 2018
  - cT3N1 ER/PR-negative, HER2-positive (IHC 2+ FISH Amplified)
- PMH:
  - G4P2
  - HTN
- Social History:
  - Married
  - No tobacco, no alcohol
  - Teaching assistant
- Family History:
  - No malignancy
- Clinical course
  - Received neoadjuvant TCH+P
  - Excellent clinical response by Cycle #2
  - Anemia required dose-delays and required transfusion
  - HTN required Cardiology consultation

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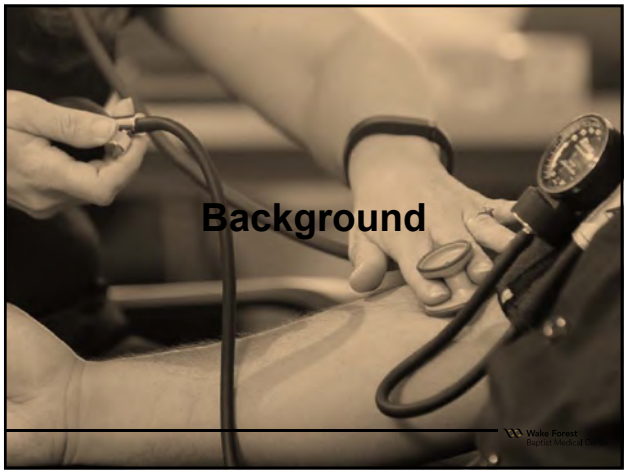

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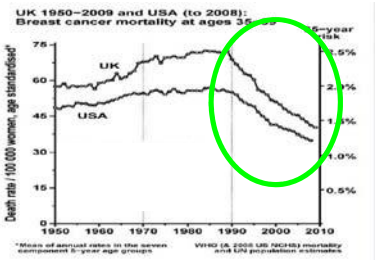
Breast Cancer Mortality



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Early Breast Cancer Trialists' Collaborative Group (*EBCTCG*) *Lancet*. 2011

HER-2 positive breast cancer

- ~ 15 % of breast cancer tumors overexpress HER-2
- HER2 overexpression ***had*** *been* associated with an aggressive clinical phenotype:
  - High-grade and proliferative tumors
  - Early metastatic disease
  - Decreased rates of disease-free and overall survival

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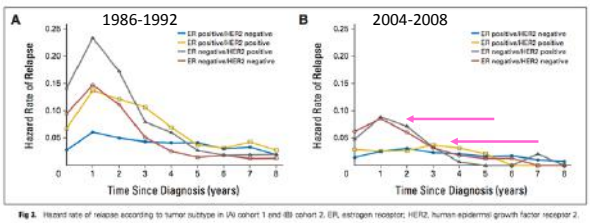
Breast Cancer Outcomes by Subtype



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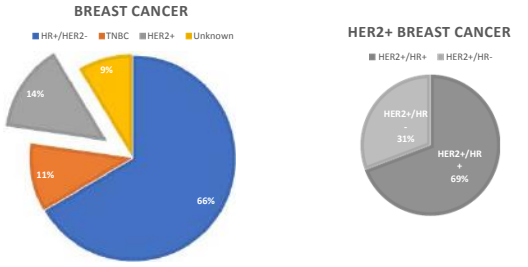
Cossetti, J., et al, *JCO*, 2015

Subtypes of HER2-positive Breast Cancer



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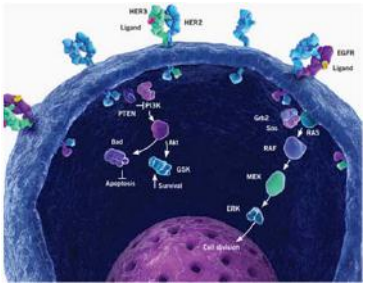
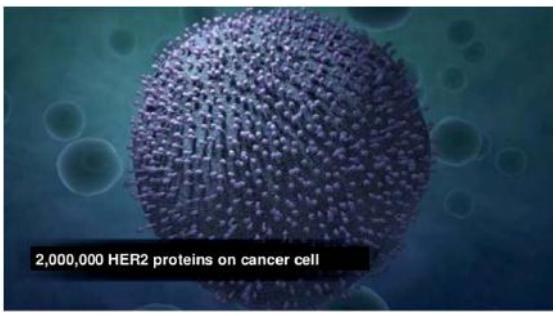
Howlander, N., et al. *Cancer, Epidemiology, Biomarkers and Prevention*, 2018



HER-2 Pathway

- HER proteins are cell membrane receptors
- HER2 dimerizes with HER2 or other HER proteins
- Normal function promotes cell growth and division

HER2 Protein Overexpression



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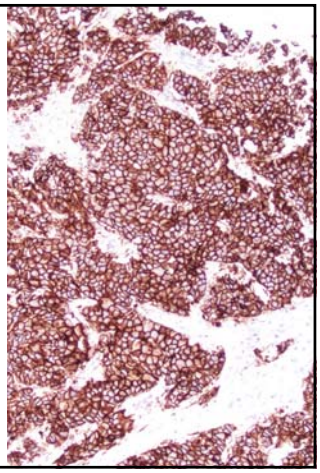
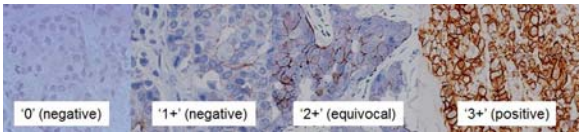
HER2 protein Overexpression

- Marked over expression of the HER2 protein
- IHC 3+ staining
- Therefore an attractive therapeutic target

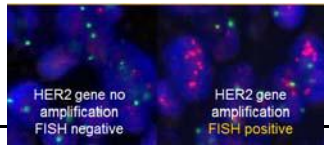


Current assays for HER2

Immunohistochemistry



Fluorescence In Situ Hybridization (FISH)



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Murthy SS, et al. *Indian J Pathol Microbiol.* 2011;54(3):532-538

Which tumors are HER2-positive in 2019?

it's Complicated

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2018 HER2 Testing Guidelines Key points

Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update

- IHC 2+ means "weak to moderate membrane staining observed in >10% of cells"
- New HER2 test *may* be ordered for reasons including that initial test was negative and tumor is Grade 3.
- Further refinement of complex ISH test results

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Focus of ASCO-CAP HER2 Guidelines

Year	Guideline Focus	IHC 3+	FISH +
2007	Avoid false positives	>30%	Ratio >2.2 (dual) ≥6 HER copies (single)
2013	Avoid false negatives	>10%	Ratio >2.0 (dual) ≥6 HER copies (single)
2018	Clarify less common FISH patterns	>10%	Creates 5 groups

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2018: Interpreting ISH testing

		2013	2018
Positive	HER2/CEP17 HER2 copy number	≥2.0 and ≥4.0-signals/cell or	Group 1
	HER2/CEP17 HER2 copy number	≥2.0 and <4.0-signals/cell or	Group 2
	HER2/CEP17 HER2 copy number	<2.0 and ≥ 6.0-signals/cell	Group 3
Equivocal	HER2/CEP17 HER2 copy number	<2.0 and ≥ 4.0-<6.0 signals/cell	Group 4
Negative	HER2/CEP17 HER2 copy number	<2.0 and <4.0 signals/cell	Group 5

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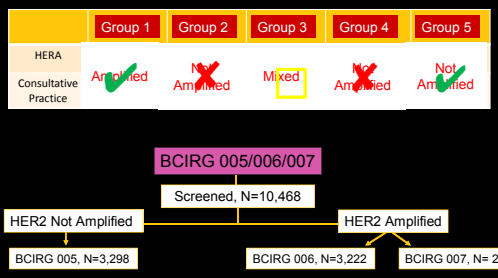
2018: Interpreting ISH testing



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BCIRG 005/006/007: HER2 FISH Ratio and Copy Number Compared with IHC Score by ASCO/CAP groups

HER2: CEP17 ratio	Average HER2 copy #/cell	N	%	P-value (* with IHC 0/1+, # with IHC 3+)	2013 ASCO/CAP group	2013 ASCO/CAP ISH- category
≥2.0	≥4.0	4,269	40.8%	<0.0001#	Group 1	ISH-positive
	<4.0	71	0.7%	0.0007*	Group 2	ISH-positive
<2.0	≥6.0	55	0.5%	0.3881*	Group 3	ISH-positive
	≥4.0-<6.0	432	4.1%	<0.0001*	Group 4	ISH-equivocal
	<4.0	5641	53.9%	<0.0001*	Group 5	ISH-negative

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HER2 Testing and Outcomes in BCIRG 005 and BCIRG 006

BCIRG 005 – TAC v AC+T

	ASCO/CAP 2013 Ratio	Copy#	Interpretation	IHC-expression	DFS/OS Outcome
Group 4	<2.0	≥ 4.0-<6.0	ISH equivocal	Low, p<0.0001	Not worse than group 5
Group 5	<2.0	<4.0	ISH negative	Low, p<0.0001	

BCIRG 006 – AC+T vs AC+TH vs TCH

	ASCO/CAP 2013 Ratio	Copy#	Interpretation	IHC-expression	Benefit from Trastuzumab
Group 1	≥2.0	≥4.0	ISH positive	High, p<0.0001	DFS, hazard ratio=0.71, 95% CI 0.60-0.83 OS, hazard ratio= 0.69, 95% CI 0.55-0.85
Group 2	≥2.0	<4.0	ISH positive	Low, p<0.0007	No benefit
Group 3	<2.0	≥6.0	ISH positive	Mixed	Indeterminate

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2018 ISH Interpretation

HER2: CEP17 ratio	Average HER2 copy #/cell	2013 ASCO/CAP group	2013 ASCO/CAP ISH- category	2018 ASCO/CAP ISH- category
≥2.0	≥4.0	Group 1	ISH-positive	ISH-positive
	<4.0	Group 2	ISH-positive	ISH-negative*
<2.0	≥6.0	Group 3	ISH-positive	ISH-positive*
	≥4.0-<6.0	Group 4	ISH-equivocal	ISH-negative*
	<4.0	Group 5	ISH-negative	ISH-negative

* Negative/Positive with comment

Another way of looking at it:

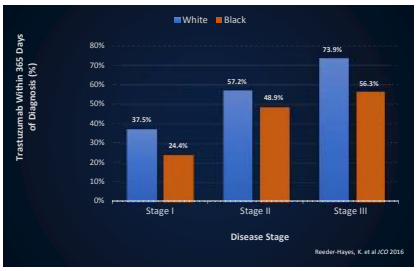
Summary of HER2 ISH Diagnostic Criteria

HER2 Positive	HER2 Negative
Dual Probe Assay	
Group 1	Group 2 AND concurrent IHC 0-1+ or 2+
Group 2 AND concurrent IHC 3+	Group 3 AND concurrent IHC 0-1+
Group 3 AND concurrent IHC 2+ or 3+	Group 4 AND concurrent IHC 0-1+ or 2+
Group 4 AND concurrent IHC 3+	Group 5

it's SUPER Complicated

Is the question less which tumors are HER2+, but more which ones respond to HER2-targeted therapy?

Delivery of HER2-directed therapy: SEER-Medicare 2010-2011



AJCC 8th Edition and HER2-positive Breast Cancer

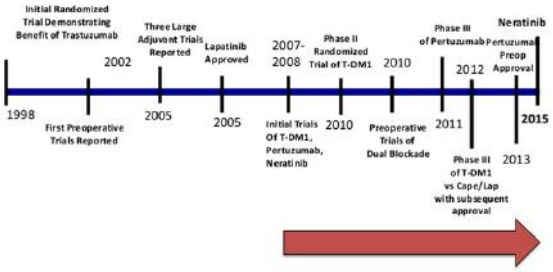
- Many patients with HER2+/ER+/PR+ breast cancer will be *down-staged* reflecting the improved prognosis of this group in the HER2-targeted therapy era

HER2-targeted Therapies

- Development timeline
- Adjuvant therapy
- Neo-adjuvant therapy
- Therapy for metastatic disease
- Future directions

1998

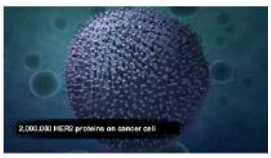
HER2 Amplified Breast Cancer Major Therapeutic Advances

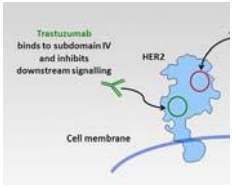


Courtesy Eric P. Winer MD, Dana Farber CC

What is trastuzumab?

- Immunoglobulin G monoclonal antibody directed against HER2

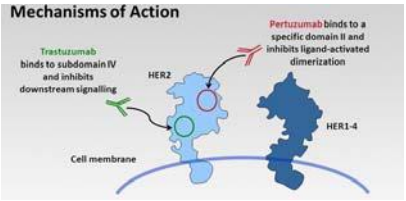




Franklin, MC. Et al. Cancer Cell. 2004

What is pertuzumab?

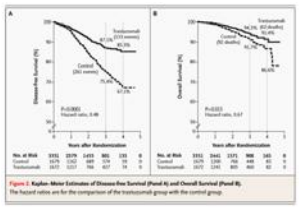
- Monoclonal antibody targeting both HER2 and HER3



Franklin, MC. Et al. Cancer Cell. 2004

Adjuvant therapy

- NSABP B-31 and NCCTG 9831
- Chemotherapy +/- trastuzumab
- There was a 48% relative improvement in disease free survival and a 39% relative reduction in mortality.



Romond. E et al, *NEJM* 2005

Treatment order

Neoadjuvant (Preoperative) therapy

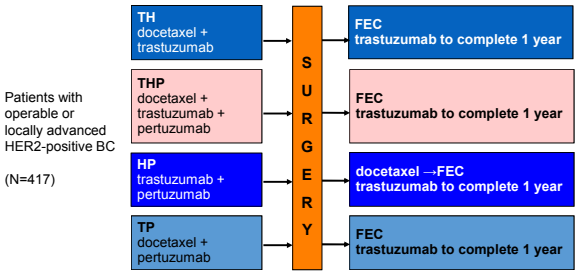
- When to consider:
  - T2N0 or N1 tumors or greater
  - Meet criteria for breast conserving therapy except for tumor size
  - Node positive disease likely to become node negative
- Need core biopsy of breast with placement of image-detectable marker and axillary imaging with US or MRI with biopsy of suspicious nodes
- Must complete up to one year of HER2 targeted therapy with trastuzumab +/- pertuzumab

QUESTION

Neo-adjuvant trial landscape

- NOAH established the benefit of trastuzumab in the neoadjuvant setting with current chemotherapeutic options
- Neo-Allto – benefit to *dual HER2 blockade* with lapatinib and trastuzumab, not seen in Allto
- Neo-Sphere, Tryphena added pertuzumab

NEOSPHERE: Study Design



Study dosing: q3w x 4

Gianni L, et al. *Lancet Oncology* 2012

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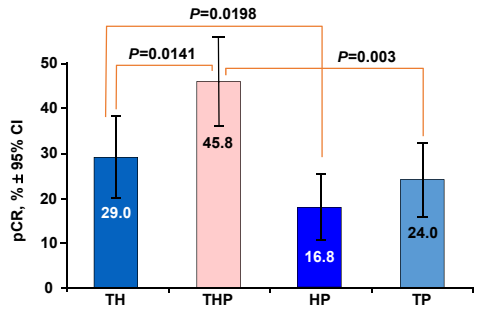
NEOSPHERE: pCR Rates



H, trastuzumab; P, pertuzumab; T, docetaxel

Gianni L, et al. *Lancet Oncology* 2012

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TRYPHAENA

- Neo-adjuvant trial looking at cardiotoxicity
- The combination of pertuzumab with trastuzumab and standard chemotherapy resulted in low rates of symptomatic LVSD
- ≅60% of patients achieved a pathological complete response with pertuzumab and trastuzumab in combination chemotherapy

Schneeweiss, A. et al *Ann Oncol*. 2013 Sep;24(9):2278-84.

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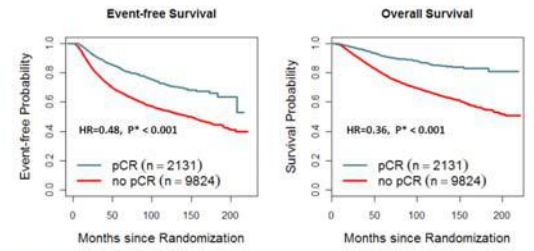
PCR and Survival in Breast Cancer



pCR=ypT0/is ypN0 * Nominal p-value

Cortazar, P., et al, *Lancet*, 2014

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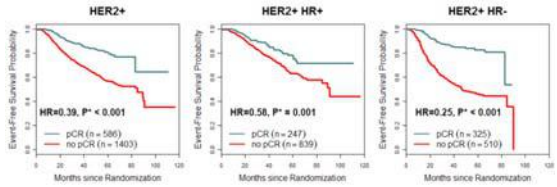
PCR by HER2 subtype



pCR=ypT0/is ypN0 * Nominal p-value

Cortazar, P., et al, *Lancet*, 2014

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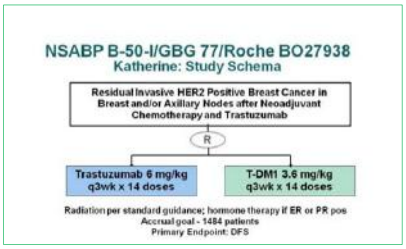
Neoadjuvant vs adjuvant?

2019 rationale for neoadjuvant:

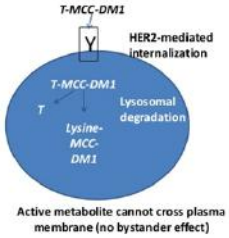
- Can escalate care and improve outcomes in the higher risk setting of residual disease post neoadjuvant therapy

KATHERINE
San Antonio Breast Cancer Symposium 2018



TDM1 – trastuzumab emtansine

- Maytansine analogue DM1 (antitubule akin to vincas) conjugated to trastuzumab – similar to gemtuzumab (Myelotarg)



Beeram et al. *J Clin Oncol* 2008.

Rationale for KATHERINE Study Design

- HER2-positive early breast cancer patients with residual invasive disease following neoadjuvant chemotherapy combined with HER2-targeted therapy have an increased risk of recurrence and death
- T-DM1 is active in HER2-positive metastatic breast cancer following prior exposure to taxanes and HER2-targeted therapy
- KATHERINE investigated whether substituting adjuvant T-DM1 for trastuzumab would improve outcomes for patients with residual invasive cancer following neoadjuvant therapy

Slide courtesy of Charles E. Geyer Jr.

KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

R 1:1

N=1486

T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles

Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative

Slide courtesy of Charles E. Geyer Jr.

San Antonio Breast Cancer Symposium December 4–8, 2018

Statistical Considerations

Primary Endpoint: IDFS

IDFS analyses

Final IDFS
- Adjuvant trastuzumab assumed to provide 3-year IDFS of 70% and improvement with T-DM1 to 76.5% (HR=0.75) would be clinically meaningful
- To provide 80% power with 2-sided alpha 5%, 384 events required

Single Pre-specified Interim Analysis of IDFS
- When 67% of events (~257) occurred
- Early reporting boundary:
  - HR < 0.732 or
  - *P* < 0.0124

First Interim OS analysis
- Performed at time of interim IDFS analysis IF boundary is crossed
- The overall type I error controlled at 0.05 using the Lan−DeMets alpha spending function with O'Brien−Fleming boundary

Slide courtesy of Charles E. Geyer Jr.

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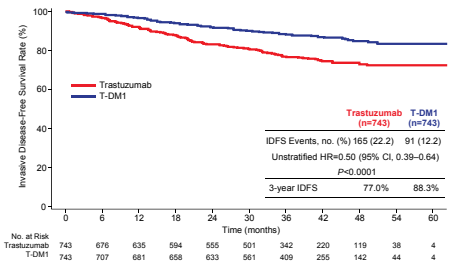
Invasive Disease-Free Survival

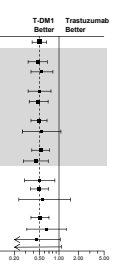


	Trastuzumab (n=743)	T-DM1 (n=743)
IDFS Events, no. (%)	165 (22.2)	91 (12.2)
Unstratified HR=0.50 (95% CI, 0.39–0.64)		
P<0.0001		
3-year IDFS	77.0%	88.3%

Slide courtesy of Charles E. Geyer Jr.

IDFS Subgroup Analysis

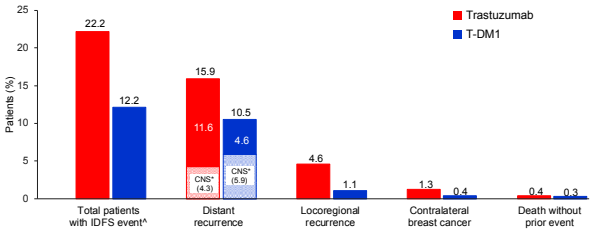
Group	Total N	Trastuzumab (n=743) 3-Year IDFS	T-DM1 (n=743) 3-Year IDFS	Hazard Ratio	95% CI
All	1486	77.0	88.3	0.50	(0.39–0.64)
Clinical stage at presentation					
Operable	1111	82.8	92.3	0.47	(0.33–0.66)
Inoperable	375	60.2	76.0	0.54	(0.37–0.80)
Hormone receptor status					
Negative (ER negative and PgR negative/unknown)	412	66.6	82.1	0.50	(0.33–0.74)
Positive (ER and/or PgR positive)	1074	80.7	90.7	0.48	(0.35–0.67)
Preoperative HER2-directed therapy					
Trastuzumab alone	1196	75.9	87.7	0.49	(0.37–0.65)
Trastuzumab plus additional HER2-directed agent(s)	290	81.8	90.9	0.54	(0.27–1.06)
Pathological nodal status after preoperative therapy					
Node positive	689	67.7	83.0	0.52	(0.38–0.71)
Node negative/not done	797	84.6	92.8	0.44	(0.28–0.68)
Age group (years)					
<40	296	74.9	86.5	0.50	(0.29–0.86)
40–64	1064	77.1	88.8	0.49	(0.36–0.67)
≥65	126	81.1	87.4	0.55	(0.22–1.34)
Race*					
White	1082	79.1	88.8	0.51	(0.37–0.69)
Asian	129	71.9	82.5	0.65	(0.32–1.32)
American Indian or Alaska Native	86	60.3	81.8	0.44	(0.18–1.03)
Black or African American	40	66.0	94.7	0.13	(0.02–1.10)



*149 were of multiple races or unknown race.

Slide courtesy of Charles E. Geyer Jr.

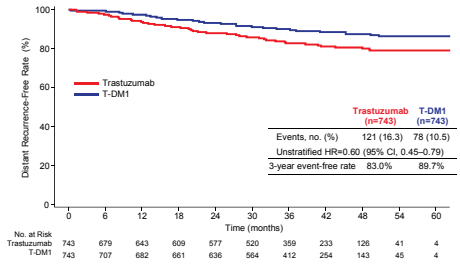
First IDFS Events



^Patients who experience additional IDFS event(s) within 61 days of their first IDFS event are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Death without prior event.
*CNS metastases as component of distant recurrence (isolated or with other sites). Trastuzumab T-DM1

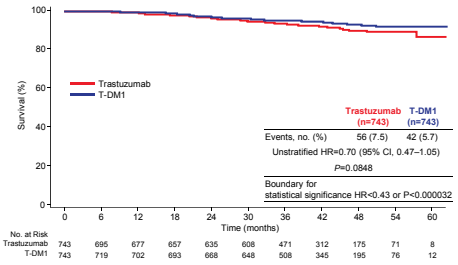
Slide courtesy of Charles E. Geyer Jr.

Distant Recurrence



Slide courtesy of Charles E. Geyer Jr.

Overall Survival



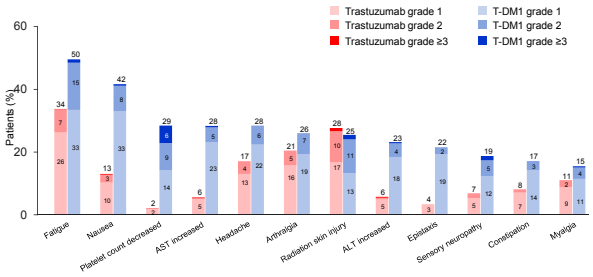
Slide courtesy of Charles E. Geyer Jr.

AEs Leading to Treatment Discontinuation (≥1% Incidence Either Arm)

	Trastuzumab n=720	T-DM1 n=740
Patients discontinuing due to adverse events	15 (2.1%)	133 (18.0%)
Platelet count decreased	0	31 (4.2%)
Blood bilirubin increased	0	19 (2.6%)
Aspartate aminotransferase (AST) increased	0	12 (1.6%)
Alanine aminotransferase (ALT) increased	0	11 (1.5%)
Peripheral sensory neuropathy	0	11 (1.5%)
Ejection fraction decreased	10 (1.4%)	9 (1.2%)

Slide courtesy of Charles E. Geyer Jr.

All Grade AEs ≥15% Incidence in Either Arm



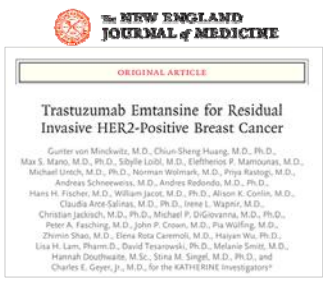
Slide courtesy of Charles E. Geyer Jr.

KATHERINE Summary and Conclusions

- Adjuvant T-DM1 demonstrated both a statistically significant and clinically meaningful improvement in IDFS compared with trastuzumab
  - Unstratified HR=0.50; 95% CI 0.39–0.64; *P*<0.0001
  - 3-year IDFS rate improved from 77.0% to 88.3% (difference=11.3%)
- Benefit of T-DM1 was consistent across all key subgroups including HR status, extent of residual invasive disease, and single or dual HER2-targeted neoadjuvant therapy
- The safety data were consistent with the known manageable toxicities of T-DM1, with expected increases in AEs associated with T-DM1 compared to trastuzumab
- Additional follow-up will be necessary to evaluate the effect of T-DM1 on OS
- The KATHERINE data will likely form the foundation of a new standard of care in this population and increase the use of neoadjuvant therapy in HER2-positive EBC

Slide courtesy of Charles E. Geyer Jr.

San Antonio Breast Cancer Symposium December 4–8, 2018


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

Gunter von Minckwitz, M.D., Chiun-Sheng Huang, M.D., Ph.D., Max S. Mano, M.D., Ph.D., Sibylle Loibl, M.D., Eleftherios P. Mamounas, M.D., Michael Untch, M.D., Ph.D., Norman Wolmark, M.D., Priya Rastogi, M.D., Andreas Schneeweiss, M.D., Andres Redondo, M.D., Ph.D., Hans H. Fischer, M.D., William Jacot, M.D., Ph.D., Alison K. Conlin, M.D., Claudia Arce-Salinas, M.D., Ph.D., Irene L. Wapnir, M.D., Christian Jackisch, M.D., Ph.D., Michael P. DiGiovanna, M.D., Ph.D., Peter A. Fasching, M.D., John P. Crown, M.D., Pia Wülfing, M.D., Zhimin Shao, M.D., Elena Rota Caremoli, M.D., Haiyan Wu, Ph.D., Lisa H. Lam, Pharm.D., David Tesarowski, Ph.D., Melanie Smitt, M.D., Hannah Douthwaite, M.Sc., Stina M. Singel, M.D., Ph.D., and Charles E. Geyer, Jr., M.D., for the KATHERINE Investigators*

Slide courtesy of Charles E. Geyer Jr.

On-going Trials in the Residual Disease Space

Hormone receptor- positive breast cancer

Triple negative breast cancer

SWOG S1418/NRG BR006
RPhIII Pembrolizumab for Residual TNBC post NAC

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QUESTION

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What about very small tumors?

Adjuvant trials of chemotherapy plus anti-HER2 treatment for node-negative patients have included few subjects with tumors measuring < 2 cm and virtually none with tumors ≤ 1 cm

Yet these patients have been shown to be at high risk of recurrence

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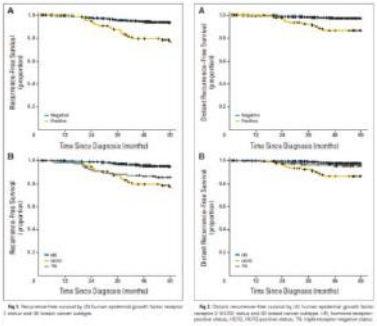
Disease free survival in T1a and T1b HER2-positive tumors



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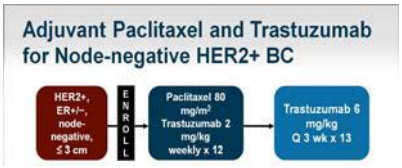
Gonzales-Angulo, A.M. et al. *JCO* 2009

Dana-Farber Study

N = 406 pts



- Non-randomized, prospective trial
- Patients have generally done well
- NCCN endorsed

Tolaney, S., et al *NEJM* 2015; 372:134-141

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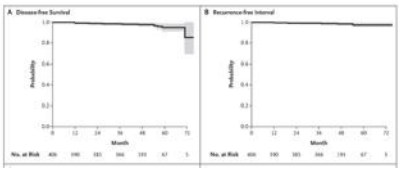
Adjuvant therapy in early stage HER2 positive cancer

- Adjuvant chemotherapy with weekly paclitaxel and trastuzumab can be considered for T1, N0, M0, HER2 positive cancers, particularly if the primary cancer is ER negative



Tolaney NEJM 2015

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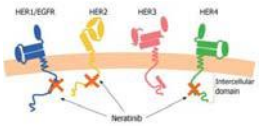
Extended adjuvant therapy

- Neratinib
- Irreversible tyrosine kinase inhibitor of HER1, HER2, and HER4 and EGFR
- Per NCCN- consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with **HR positive, HER2 positive** disease with a perceived **high risk of recurrence**



http://www.bocsci.com/blog/wp-content/uploads/2017/09/neratinib.png

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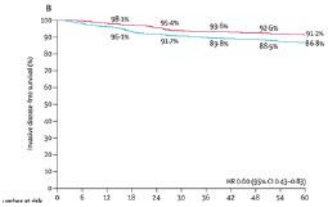
Neratinib

- For use in year after completion of trastuzumab
- DIARRHEA – 40% with grade 3-4 vs 2% in the placebo group
- Pre-medications:
  - Can try very specific anti-diarrheal regimen
- Approved in US, not in Europe

ExteNET Trial



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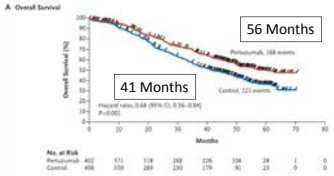
Martin, M et al, Lancet 2017; 18, 1688-1700

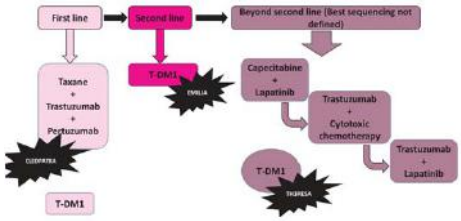
First-Line: Pertuzumab

- THP (docetaxol, trastuzumab, pertuzumab) = 56.5 months of median overall survival
- Tail of curve phenomenon



Swain. NEJM. 2015

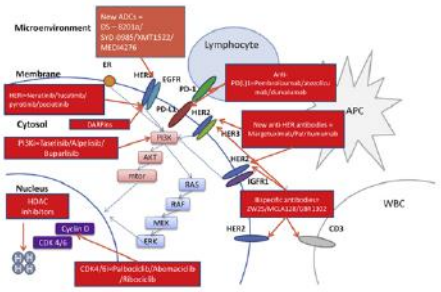
Later Lines of Therapy
HER2-positive Metastatic Breast Cancer



Current treatment of metastatic HER2-positive breast cancer

Ponde, Cancer Treatment Reviews 2018

HER2-targeted therapy: New Drugs and New Combination Strategies



Ponde, *Cancer Treatment Reviews* 2018

Current issues in HER2 amplified breast cancer

Current Issues in HER2+ Breast Cancer

- Brain Metastases *Tucatinib ?*
- Complex assay results *Do 2018 guidelines help?*
- Disparities in delivery of targeted therapy
- Chemotherapy-free regimens
  - De-escalation of therapy
- Cost of therapy
- Extended NED

De-escalation: Can some patients avoid chemotherapy?

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Proposed de-escalation trials HER2+ ER+ breast cancer

Biomarker	Strategy (neo-adjuvant)	
	Low tumor burden and PAM 50 HER2e	High tumor burden and PAM 50 HER2e
Most attractive: PAM50 HER2 enriched	Dual HER2 blockade + endocrine therapy	TDM-1 → endocrine rx or Paclitaxel+tras+pert
Other options: Ki… tumor infiltrating lymphocytes ?Reproducible	In case of pCR *NO CHEMOTHERAPY*	

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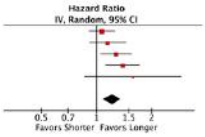
Adapted from M. Piccart, ASCO 2018

Persephone Trial

- ASCO 2018
- 6 MO of trastuzumab vs 12 MO
- 6 MO non-inferior to 12 MO
- Large British Health Services study

Why stay at 12 months for now?
Meta-analysis of shorter duration trastuzumab

Trial	N	Trastuzumab duration	Observed DFS HR
Persephone	4089	6M vs 12M	1.05 (0.88 -1.25)
Short-HER	1253	9W vs 12M	1.13 (0.89-1.42)
PHARE	3384	6M vs 12M	1.28 (1.05-1.56)
SOLD	2176	9W vs 12M	1.39 (1.12-1.72)
HORG	481	6M vs 12M	1.57 (0.86-2.10)
TOTAL			**1.21 (1.09- 1.36)**
		Node Positive	1.37 (1.17- 1.60)
		ER-negative	1.33 (1.15- 1.54)



Cardiac events increase with longer duration OR: 2.48 (1.94-3.17)

Niraula, S. et al, *BCRT*, 2018

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Why stay at 12 months of trastuzumab? …for now

There are likely subgroups for whom 12 months might be superior:

- ER-
- Taxane only
- Neo-adjuvant chemotherapy

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COSTS

- Significant amount of cost data missing on patient questionnaires (60%)
- Analysis therefore relied on case report forms
  - Includes trastuzumab and administration cost
  - Cardiac assessment and treatment
  - Endocrine therapies
  - In-patient stays
  - Surgical procedures

	6 Months (95% CI)	12 Months (95% CI)	Cost Saving (95% CI)
Average per Patient Cost	£2,538 (£2,383 - £2,700)	£12,333 (£12,098 - £12,562)	£9,793 (£9,515 - £10,071)

Hall, P, et al, ESMO 2018

Current Issues in HER2+ Breast Cancer

- Brain Metastases Tucatinib ?
- Complex assay results Do 2018 guidelines help?
- Disparities in delivery of targeted therapy
- Chemotherapy-free regimens
  - De-escalation of therapy
- Cost of therapy
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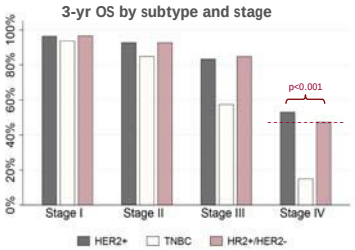
Survival in Stage IV HER2-positive Breast Cancer



- Survival for women with HER2+ breast cancer now exceeds that of women with advanced breast cancer of other subtypes
- Survival gains continued to increase from 2010 to 2013

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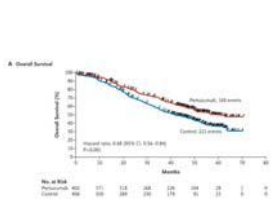
Tail of the Curve Phenomena



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Holding HER2-Targeted Therapy in Metastatic HER2+ breast cancer

Study	N	Stopping Criteria	Outcome (After holding HER2-targeted Rx)
M.D. Anderson, 2015	9	Not reported	6 remain in remission, 3 relapses
France, 2014	2	Patient decision	Remain in remission
Ontario, 2016	2	Durable CR after 5 years on trastuzumab	Remain in remission with 1 year follow-up
Italy/Ireland, 2012	11	Durable CR after 2-5 years on trastuzumab	8 remain in remission, 3 relapsed at 4, 8, 21 MO after cessation

Bishop, AJ et al *Cancer* 2015
Viel, E et al *BMC Cancer* 2014
Haq, R, *Current Oncology* 2016
Gullo, G et al *Annals of Oncology* 2012

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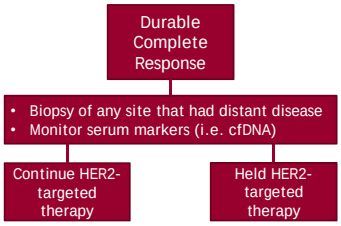
Possible Registry Schema



Outcomes: Overall survival
Breast cancer-free survival
Heart failure events
QoL
Value analysis

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Questions which could be addressed

- Disease burden
  - *How long of a prolonged remission is needed?*
  - *NED? Role of biopsy in assessing NED*
  - *Does local therapy for oligometastatic disease impact outcome?*
- Disease subtype
  - *Molecular signatures of subset with durable complete remission*
- Disease sensitivity
  - *Will disease respond to re-challenge if progression occurs?*

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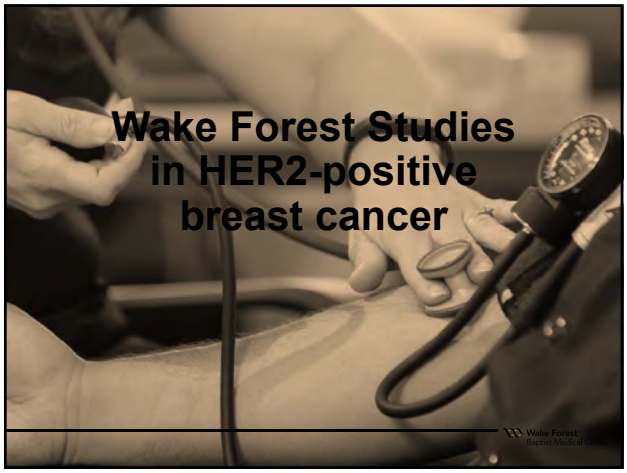

QUESTION

CLINICAL TRIALS IN HER2 SPACE

Treatment Space	Trial	Agents
Neo-Adjuvant	ISPY	Tucatinib
Metastatic	SOPHIA	Margetuximab

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Recent Publications:

Carpenter, R. L., Paw, I, Dewhirst, M.W. and **Lo, H.-W.** Akt phosphorylates and activates HSF-1 independent of heat shock, leading to Slug overexpression and epithelial-mesenchymal transition (EMT) of HER2-overexpressing breast cancer cells. **Oncogene** 34:546–557, 2015.

Carpenter RL, Sirkisoon S., Zhu D., Tadas Rimkus, Harrison A., Anderson A., Paw I., Qasem, S., Xing F., Liu Y., Chan M., Metheny-Barlow, L., Pasche, B., Debinski, D., Watabe, K., **Lo, H-W.** Combined inhibition of AKT and HSF1 suppresses breast cancer stem cells and tumor growth. **OncoTarget** 8(43):73947-73963, 2017.

Sirkisoon, SR., Carpenter, RL., Rimkus T., Anderson, A., Harrison, A., Lange, AM., Jin, G., Watabe, W., & **Lo, H.W.** Interaction between STAT3 and GLI1/tGLI1 oncogenic transcription factors promotes the aggressiveness of Triple-negative and HER2-enriched breast cancers. **Oncogene** 37(19):2502-2514, 2018.

Active Grants:

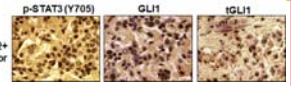
BC160850 Lo (PI) 3/1/17 - 2/29/20
Breast Cancer Research Program - Breakthrough Award Level 2
Department of Defense
Synergistic targeting of the JAK2-STAT3 and SMO-GLI1 pathways in triple-negative and HER2-enriched breast cancers

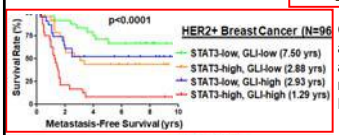
BC180389 Lo (PI) 4/1/19 - 3/31/22
Breast Cancer Research Program - Breakthrough Award Level 2
Department of Defense
Targeting Triple-negative and HER2-positive Breast Cancers through Combined Inhibition of TrkA and JAK2

Synergistic targeting of the JAK2-STAT3 and SMO-GLI1 pathways in HER2+ breast cancer using FDA-approved drugs

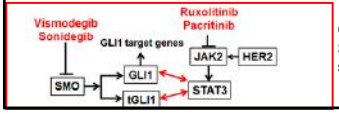
JAK2-STAT3 and SMO-GLI1 pathways are co-activated in the majority of HER2+ breast cancers

	Triple-negative	HER2-enriched	Luminal
p-STAT3+	100% (11/11)	89% (17/19)	47% (14/17)
GLI1+	73% (8/11)	84% (16/19)	82% (8/17)
tGLI1+	91% (10/11)	84% (16/19)	65% (11/17)
p-STAT3+GLI1+tGLI1+	64% (7/11)*	68% (13/19)**	41% (7/17)*,**





Co-activation of the JAK2-STAT3 and SMO-GLI1 pathways are associated with shortened metastasis-free survival in HER2+ breast cancers



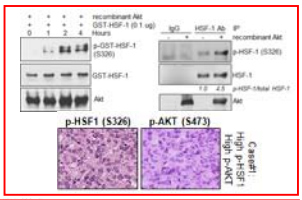
Combined inhibition of JAK2 and SMO leads to synergistic suppression of metastasis

Oncogene 37(19):2502-2514, 2018

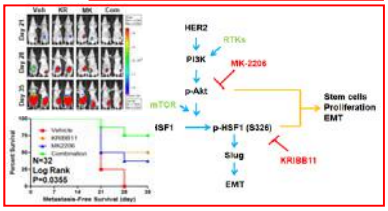
Combined targeting of the AKT and HSF1 pathways in HER2+ breast cancer

HER2 promotes breast cancer progression by activating AKT-mediated HSF1 phosphorylation

AKT and HSF1 are highly co-activated in HER2+ breast cancer

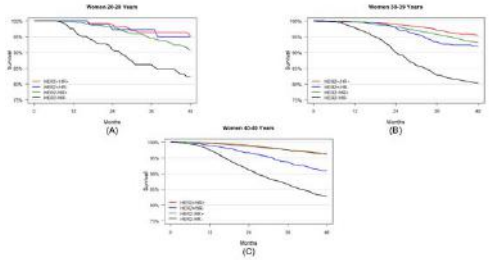


Combined targeting of AKT and HSF1 significantly suppresses tumor growth and metastasis



Oncogene 34:546–557, 2015
OncoTarget 8(43):73947-73963, 2017

HER2-positive Breast Cancer Premenopausal women: SEER18



- Incidence of HER+/HR+ Breast Cancer is increasing
- For youngest women, early out comes for are superior for HER2-positive subtype

Thomas et al, SABCS 2018

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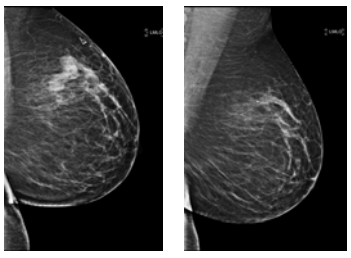
Patient Case

39 yo woman

- Treatment:
  - Excellent clinical response **by Cycle #2** to trastuzumab, pertuzumab, docetaxol and carboplatin
  - Anemia required dose-delays and transfusion
  - HTN required Cardiology consultation
- Surgery:
  - Complete pathologic response
- Adjuvant Treatment:
  - Completing a year of trastuzumab

December 2017 May 2018



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State of the Art Imaging to Assess Response to Neo-adjuvant Therapy

MSOT

- Multispectral Optoacoustic Tomography
  - Light in – Sound out
- Clinic room tool to assess response before each cycle
- Highly accurate assessment of on-treatment response
- Measures objects down to the width of an eyelash

MSOT IN THE CLINIC

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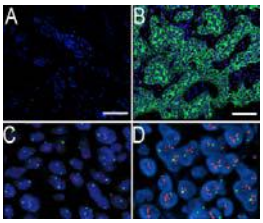
Trastuzumab-based dye to enhace imaging in HER2-positive breast cancer

- Binding of T-800 (trastuzumab linked to IR700 dye) in human breast cancer tissue
- A microscope with an infrared fluorescent camera was utilized to identify T-800 binding (pseudo green) to breast cancer patient tissues
  - Patient (**A**) HER2- (1+)
  - Patient (**B**) HER2+ (3+).
  - (**C**) and (**D**) Confirmation FISH testing



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What next?

Thank You!