Banner MD Anderson Cancer Center
Making Cancer History®

ESOPHAGEAL & GASTRIC CANCER

Madappa N. Kundranda. MD. PhD.

Director, Gastrointestinal Oncology Program

March 14th 2017

ID Anderson
ancer Center
cing Cancer History®

DISCLOSURES

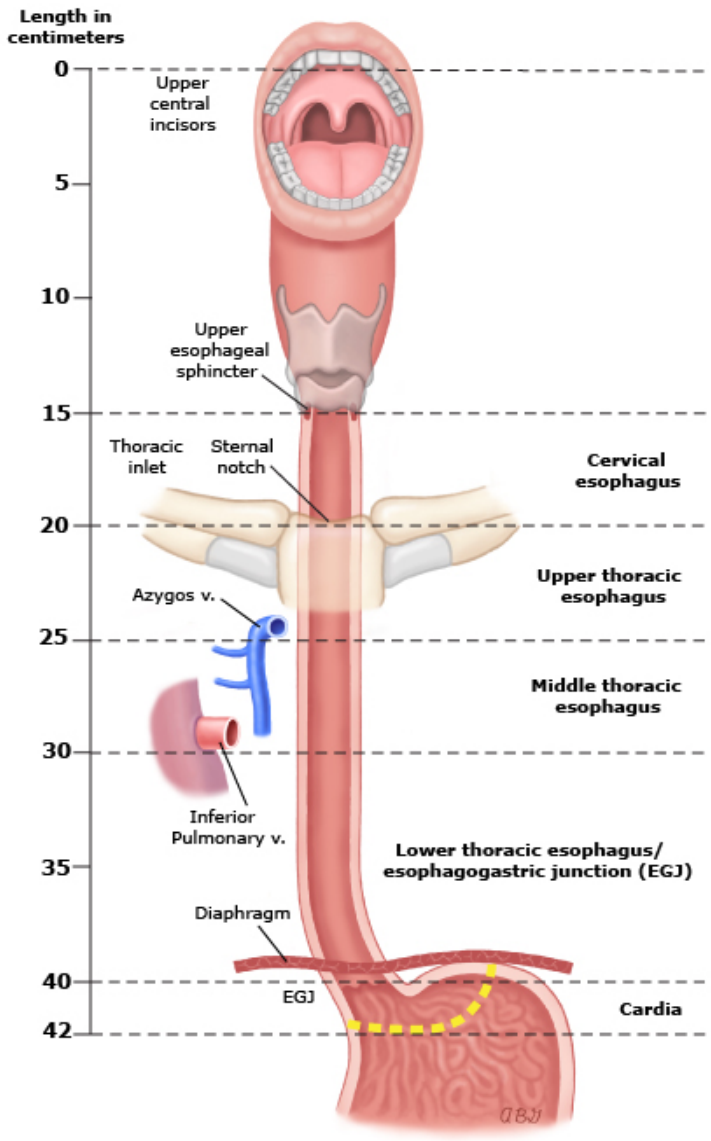
- No Relevant Financial Disclosures
- Will Discuss Investigational Techniques/Off Label use

Banner MD Anderson Cancer Center
Making Cancer History®

Objectives

- Understand the pathophysiology of esophageal and gastric cancer
- Evaluate common presentations of esophageal and gastric cancer
- Management of esophageal and gastric cancer

Banner MD Anderson Cancer Center
Making Cancer History®



Banner MD Anderson Cancer Center
Making Cancer History®

Epidemiology

- 1960s:
  - Squamous cell carcinoma (SCC) >90%
- 2000's:
  - Adenocarcinoma >60 (US)
- Worldwide: SCC still predominates

Banner MD Anderson Cancer Center
Making Cancer History®

Risk Factors

- SCC:
  - Smoking
  - Alcohol
- Adenocarcinomas:
  - Barrett's esophagus with specialized intestinal metaplasia (GERD)
  - Obesity
  - Smoking
  - GERD

Banner MD Anderson Cancer Center
Making Cancer History®

Clinical Vignette

- 75 yo male with h/o smoking and ETOH use presents with progressive dysphagia and odynophagia.

Next step?

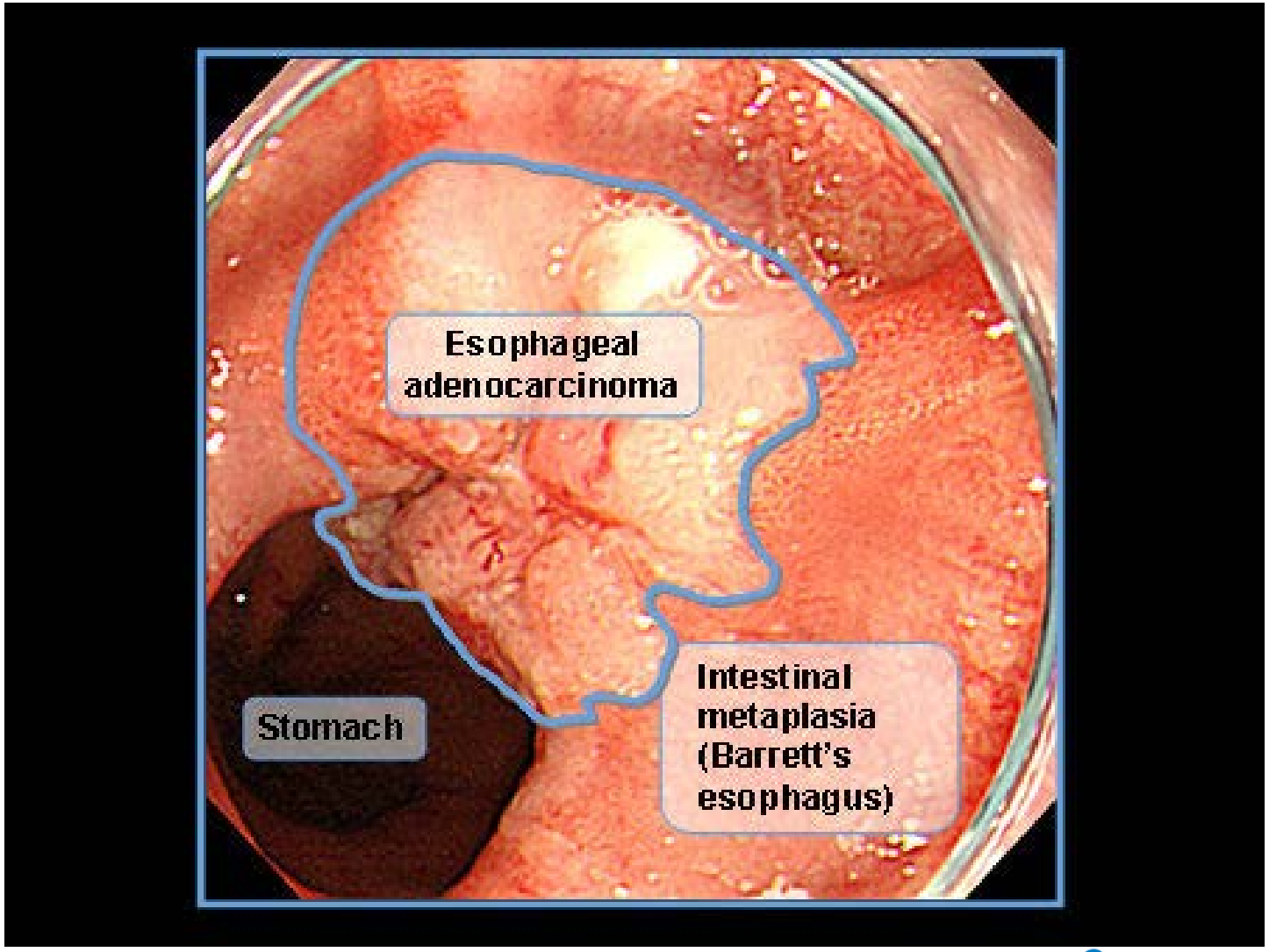
EUS

EGD

Cross sectional imaging

Surgery

Banner MD Anderson Cancer Center
Making Cancer History®



Banner MD Anderson Cancer Center
Making Cancer History®

Clinical Vignette (cont..)

- 75 yo male with h/o smoking and ETOH use presents with progressive dysphagia and odynophagia. EGD demonstrates a 4 cm partially obstructing tumor at the GEJ. Bx: moderately differentiated adenocarcinoma

Next step?

EUS

Her2Neu testing

Cross sectional imaging

Surgery

Banner MD Anderson Cancer Center
Making Cancer History®

Clinical Vignette (cont..)

EUS demonstrates a T3 lesion and PET/CT shows uptake in the 2 para esophageal lymphnodes and no evidence of metastatic disease.

Next step?

- Her2Neu testing
- Neoadjuvant chemoradiation
- Surgery

Banner MD Anderson Cancer Center
Making Cancer History®

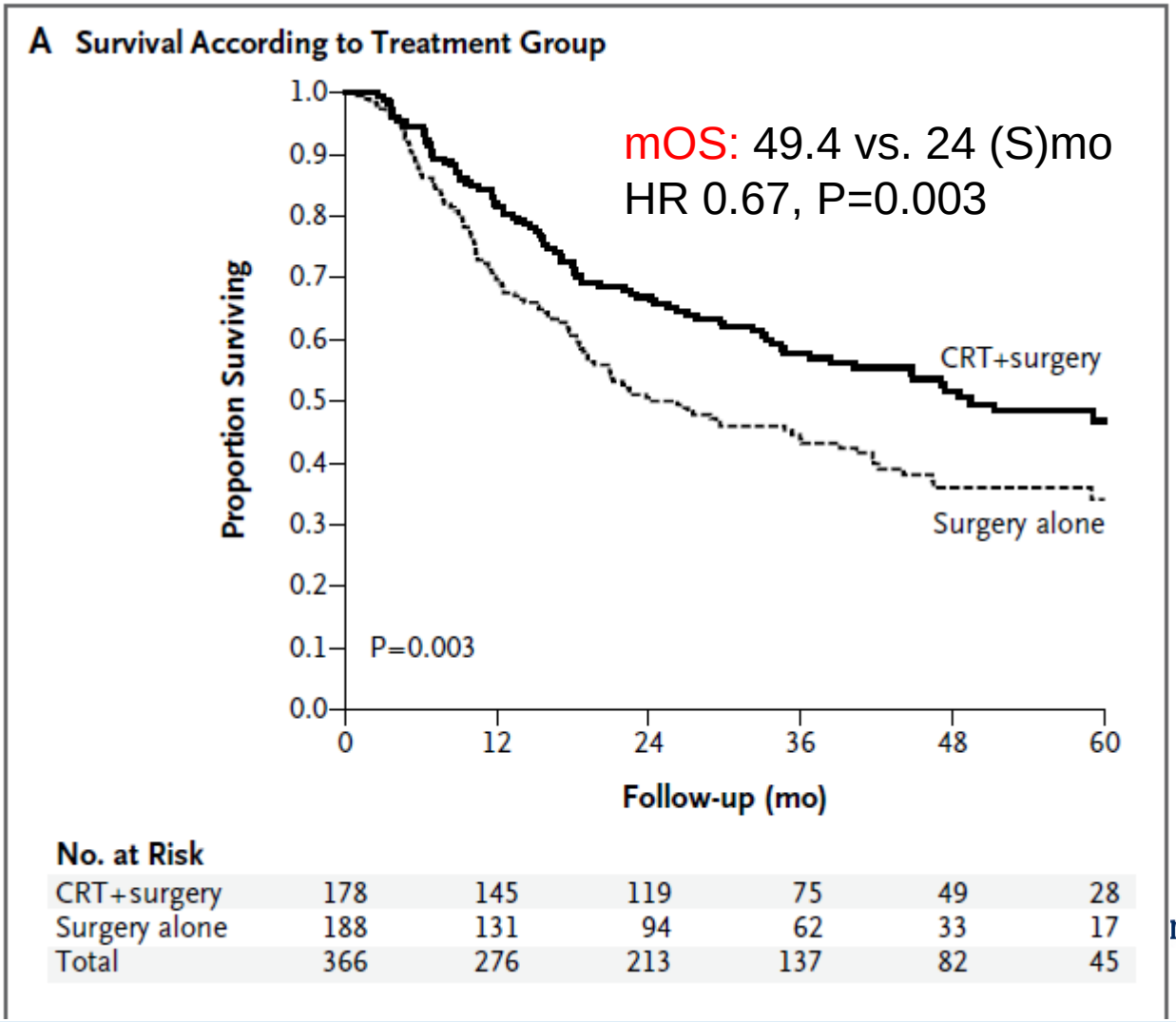
Adenocarcinoma carcinoma

Stage	T	N	M
0	Tis (HGD)	N0	M0
IA	T1	N0	M0
IB	T1	N0	M0
	T2	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
	T1-2	N1	M0
IIIA	T1-2	N2	M0
	T3	N1	M0
	T4a	N0	M0
IIIB	T3	N2	M0
IIIC	T4a	N1-2	M0
	T4b	Any	M0
	Any	N3	M0
IV	Any	Any	M1

Squamous cell carcinoma◇

Stage	T	N	M	Grade	Tumor location §
0	Tis (HGD)	N0	M0	1, X	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1, X	Lower, X
IIA	T2-3	N0	M0	1, X	Upper, middle
	T2-3	N0	M0	2-3	Lower, X
IIB	T2-3	N0	M0	2-3	Upper, middle
	T1-2	N1	M0	Any	Any
IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

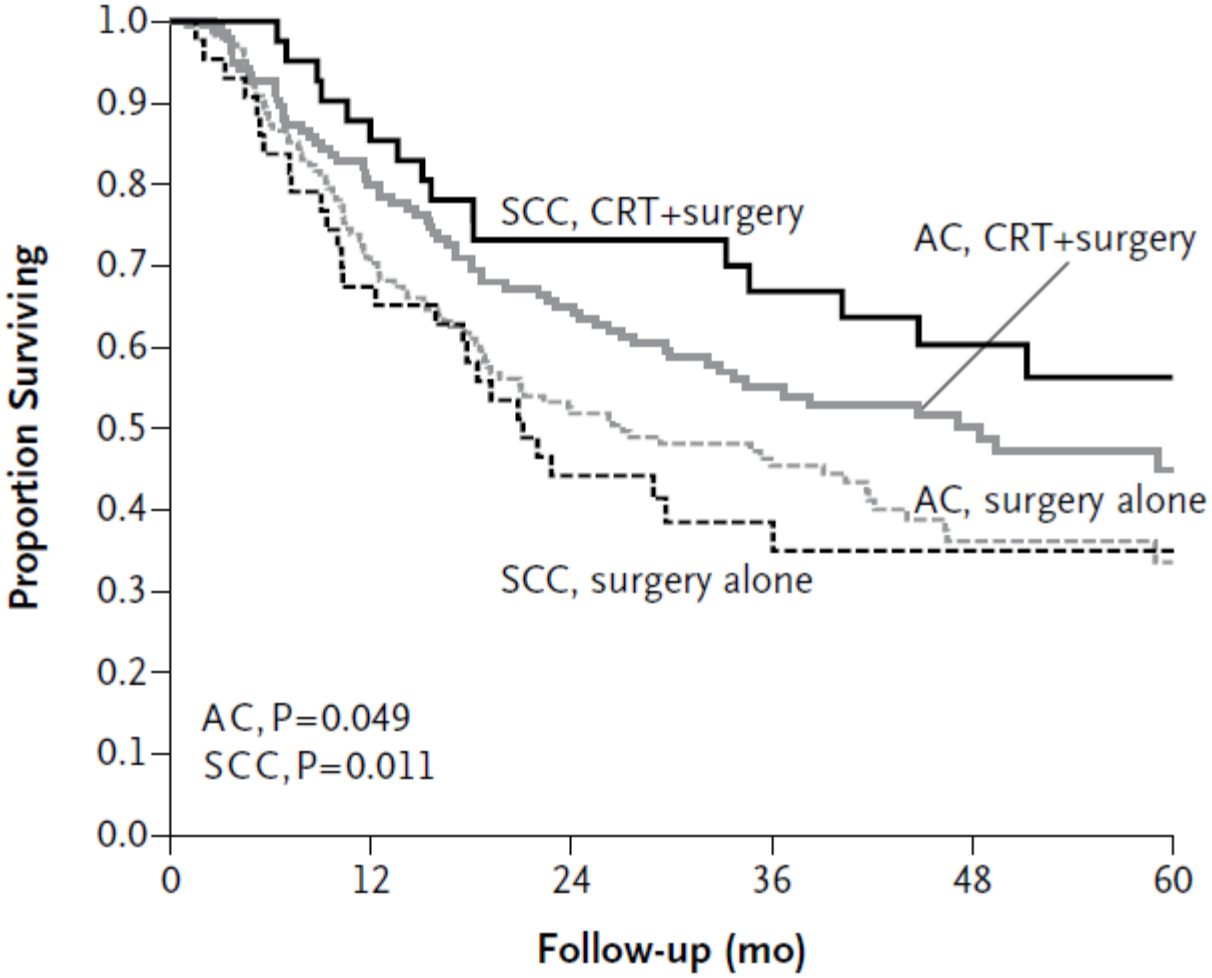
Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer - CROSS TRIAL



Van Hagen et al; N Engl J Med 2012;366:2074-84

MD Anderson Cancer Center
Making Cancer History®

B Survival According to Tumor Type and Treatment Group



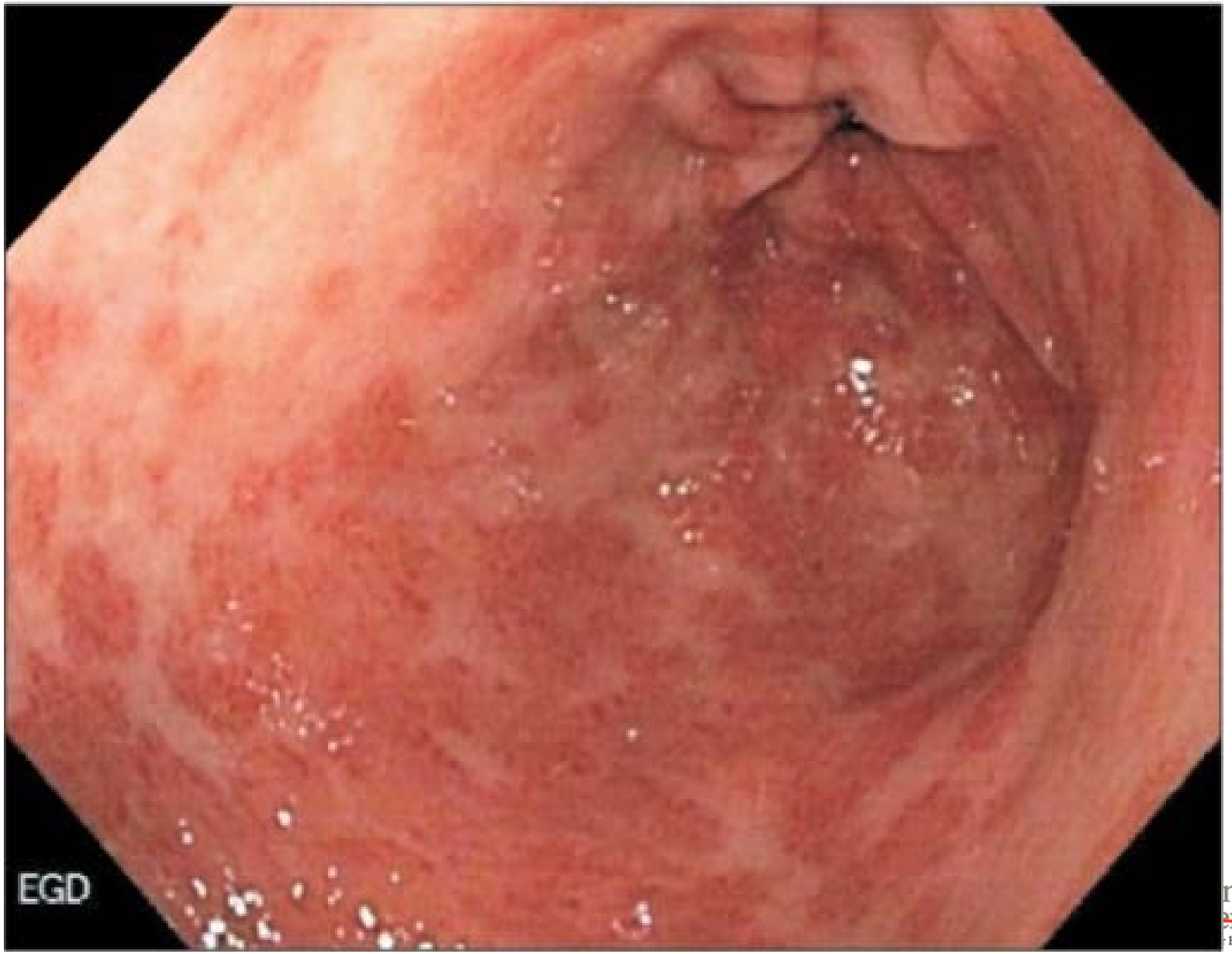
No. at Risk

AC, CRT+surgery	134	107	87	53	34	18
AC, surgery alone	141	99	73	50	25	10
SCC, CRT+surgery	41	35	30	21	15	8
SCC, surgery alone	43	29	19	11	8	4
Total	359	270	209	135	82	40

Management

- Early stage: ESD/EMR (T1a)
- T2N0: Esophagectomy
- Node positive/advanced: Chemo RT – Sx
- Metastatic: Palliative chemotherapy
  - Fluropyrimidine plus platinum
  - Her2Neu testing

Banner MD Anderson Cancer Center
Making Cancer History®


EGD

Epidemiology

- Risk factors
  - H.Pylori
  - Refrigeration
  - Geographic variation
  - Migration patterns

Banner MD Anderson Cancer Center
Making Cancer History®

Histology

- Intestinal gastric cancer is more common in males and older age groups. It is more prevalent in high-risk areas and is likely linked to environmental factors

- Diffuse or infiltrative type, is equally frequent in both sexes, is more common in younger age groups, and has a worse prognosis than the intestinal type

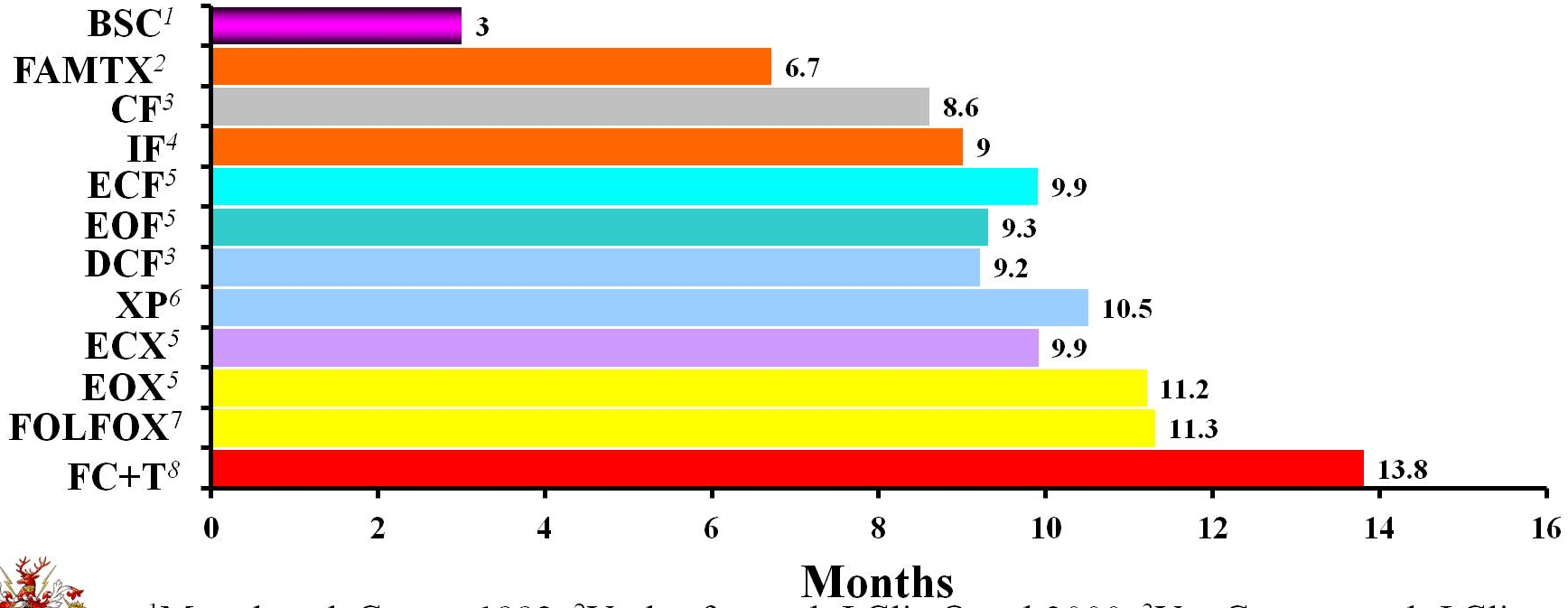
Banner MD Anderson Cancer Center
Making Cancer History®

Clinical Vignette

- 48 yo male with abdominal discomfort eval by endoscopy noted to have a distal stomach mass; poorly differentiated adenocarcinoma. EUS and imaging dem T3N1 disease with no distant metastasis.
- What is NOT a SOC option
  - Radiation and chemo followed by Sx
  - Gastrectomy followed by adj ChemoRT
  - Perioperative chemotherapy
  - Gastrectomy followed by chemotherapy

Banner MD Anderson Cancer Center
Making Cancer History®

Overall survival with chemotherapy in advanced OG cancer



[1]Murad et al. Cancer 1993; [2]Vanhoefer et al. J Clin Oncol 2000; [3]Van Cutsem et al. J Clin Oncol 2006; [4]Dank et al. Ann Oncol 2008; [5]Cunningham et al. N Engl J Med 2008; [6]Kang et al. Ann Oncol 2009; [7]Shah et al JAMA Oncol 2016; [8]Bang et al. Lancet 2010

THE ROYAL MARSDEN

Banner MD Anderson Cancer Center
Making Cancer History®

COLORECTAL CANCER

Banner MD Anderson Cancer Center
Making Cancer History®

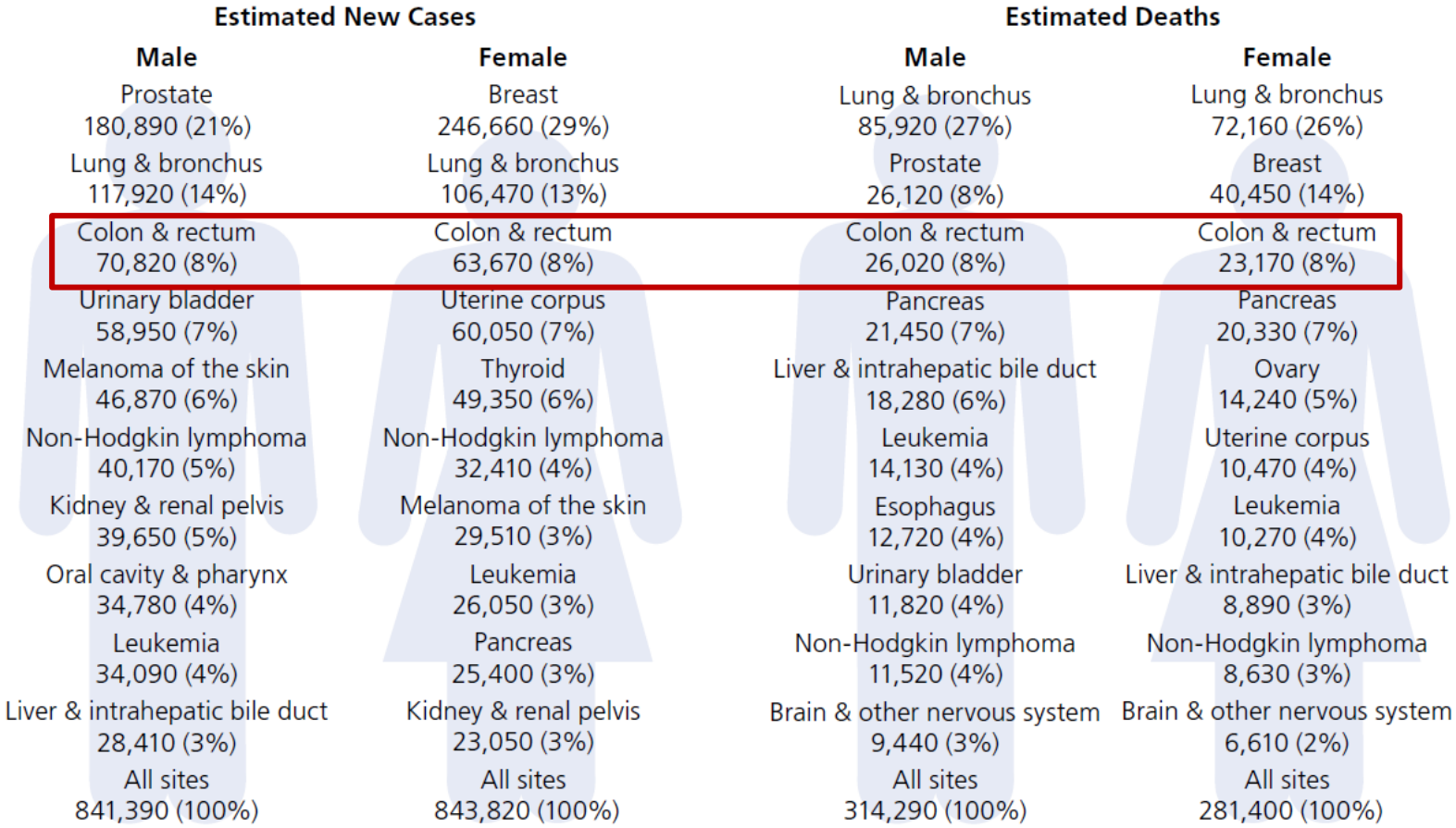
Objectives

- Understand the pathophysiology of CRC
- Evaluate common presentations of suspected CRC
- Management of CRC

Banner MD Anderson Cancer Center
Making Cancer History®

The Problem

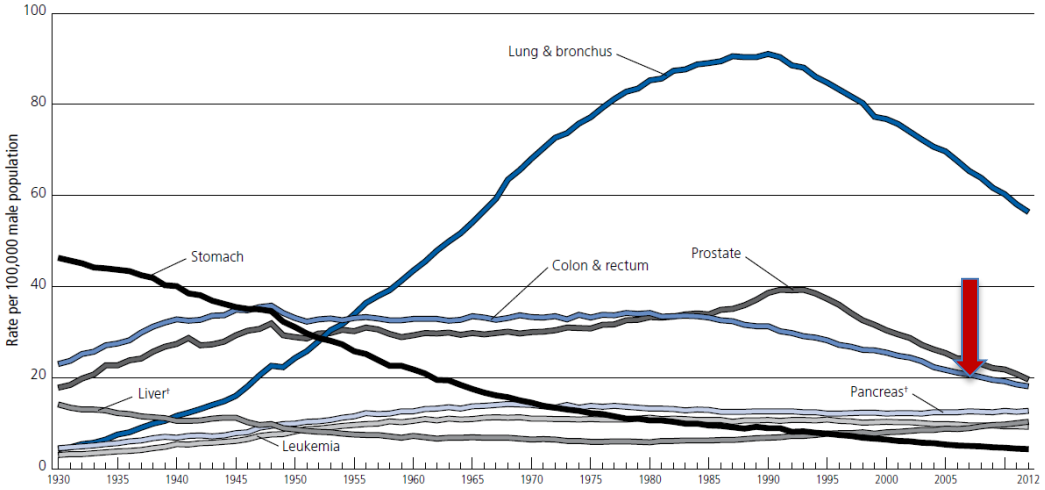
Figure 3. Leading Sites of New Cancer Cases and Deaths – 2016 Estimates



Estimated New Cases		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 180,890 (21%)	Breast 246,660 (29%)	Lung & bronchus 85,920 (27%)	Lung & bronchus 72,160 (26%)
Lung & bronchus 117,920 (14%)	Lung & bronchus 106,470 (13%)	Prostate 26,120 (8%)	Breast 40,450 (14%)
Colon & rectum 70,820 (8%)	Colon & rectum 63,670 (8%)	Colon & rectum 26,020 (8%)	Colon & rectum 23,170 (8%)
Urinary bladder 58,950 (7%)	Uterine corpus 60,050 (7%)	Pancreas 21,450 (7%)	Pancreas 20,330 (7%)
Melanoma of the skin 46,870 (6%)	Thyroid 49,350 (6%)	Liver & intrahepatic bile duct 18,280 (6%)	Ovary 14,240 (5%)
Non-Hodgkin lymphoma 40,170 (5%)	Non-Hodgkin lymphoma 32,410 (4%)	Leukemia 14,130 (4%)	Uterine corpus 10,470 (4%)
Kidney & renal pelvis 39,650 (5%)	Melanoma of the skin 29,510 (3%)	Esophagus 12,720 (4%)	Leukemia 10,270 (4%)
Oral cavity & pharynx 34,780 (4%)	Leukemia 26,050 (3%)	Urinary bladder 11,820 (4%)	Liver & intrahepatic bile duct 8,890 (3%)
Leukemia 34,090 (4%)	Pancreas 25,400 (3%)	Non-Hodgkin lymphoma 11,520 (4%)	Non-Hodgkin lymphoma 8,630 (3%)
Liver & intrahepatic bile duct 28,410 (3%)	Kidney & renal pelvis 23,050 (3%)	Brain & other nervous system 9,440 (3%)	Brain & other nervous system 6,610 (2%)
All sites 841,390 (100%)	All sites 843,820 (100%)	All sites 314,290 (100%)	All sites 281,400 (100%)

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Figure 1. Trends in Age-adjusted Cancer Death Rates* by Site, Males, US, 1930-2012

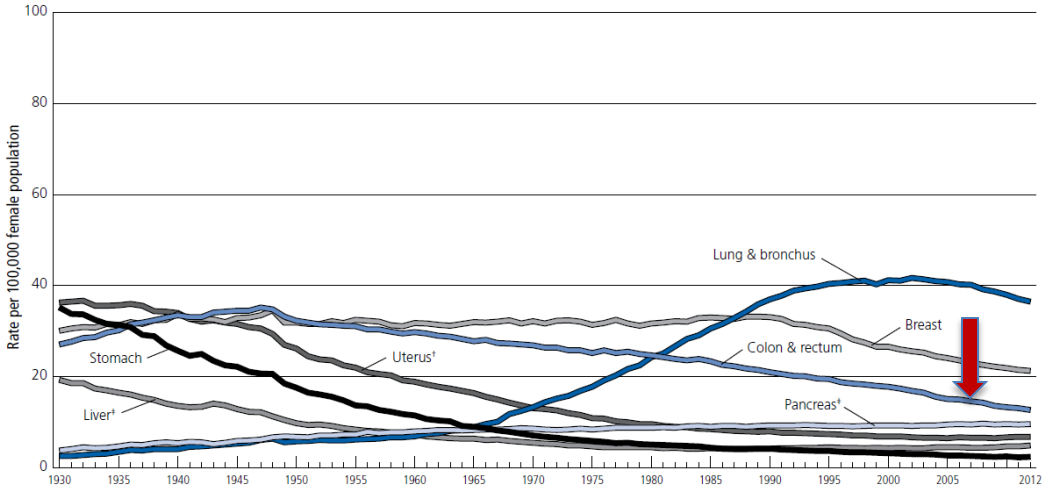


*Per 100,000, age adjusted to the 2000 US standard population. †Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959 and US Mortality Data 1960 to 2012, National Center for Health Statistics, Centers for Disease Control and Prevention.

Figure 2. Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930-2012

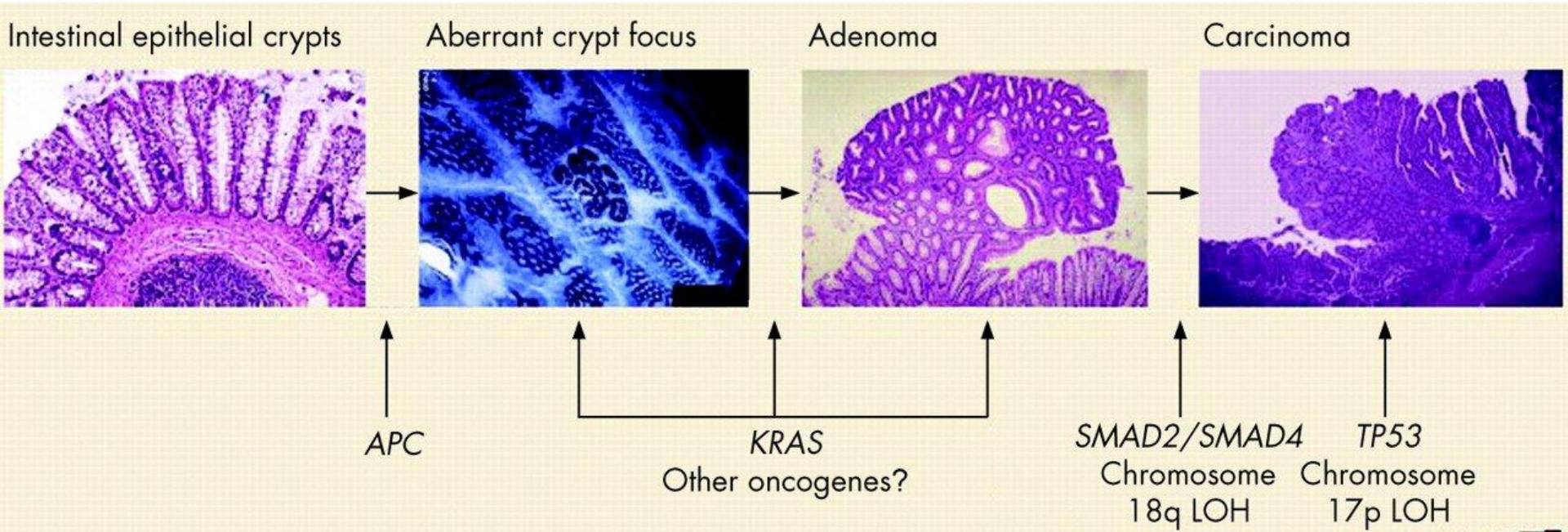


*Per 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined. ‡Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2012, National Center for Health Statistics, Centers for Disease Control and Prevention.

The ‘Suspected’ Cause - Pathogenesis

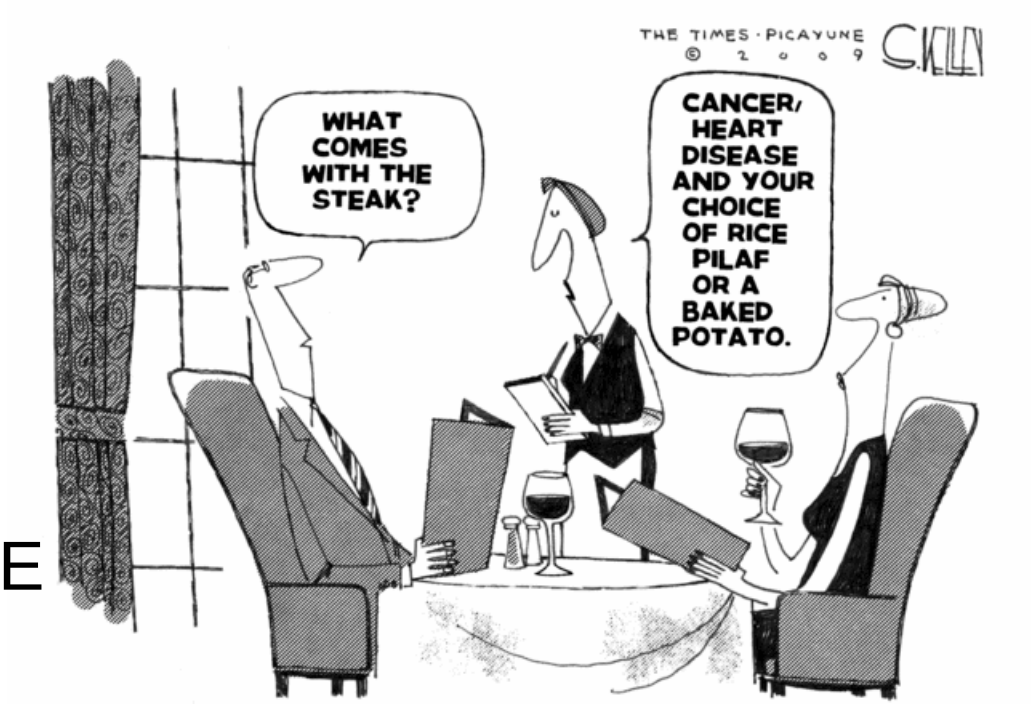


- **Chromosomal instability**
- ***Microsatellite instability pathway***
  - inactivation of DNA mismatch repair proteins
- ***CpG island methylator pathway (CIMP)***
  - underlies MSI associated with MLH1 hypermethylation

Banner MD Anderson Cancer Center
Making Cancer History®

Potential Risk Reduction Strategies

- Less Red



- Regular PE
- BMI
- Avoidance of ETOH
- 5-7 servings of fresh fruits and vegetables

NONE OF THESE HAVE SHOWN TO BE AS EFFECTIVE AS SCREENING

Banner MD Anderson Cancer Center
Making Cancer History®

Staging

TNM staging for colorectal cancer, 7th edition

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria*
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum ¶
T4b	Tumor directly invades or is adherent to other organs or structures ¶ Δ
Regional lymph node (N) ◇	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (eg, liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

MD Anderson Cancer Center
Making Cancer History®

Clinical Vignette

- 45 yo female undergoes a Rt hemicolectomy for a largeT3 poorly differentiated tumor. 0/35 LN. Here to discuss adjuvant therapy:

Which statement is accurate

  - RAS mutation Analysis can guide adjuvant therapy decision
  - Stage II MSI high tumors have an excellent prognosis and don't req adjuvant Rx
  - Most cases of MSI-H tumors occur as a manifestation of Lynch syndrome

Banner MD Anderson Cancer Center
Making Cancer History®

Management

- Stage I: surgery alone
- Stage II:
  - low risk vs. high risk

  Surgery +/- Adjuvant chemo
- Stage III: Surgery plus adjuvant chemotherapy
- Stage IV: Palliative Chemotherapy

Banner MD Anderson Cancer Center
Making Cancer History®

Stage II

- High Risk:
  - T4 primary
  - Inadequately sampled lymph nodes (less than 13 in the surgical specimen)
  - Bowel obstruction or perforation
  - High-grade/poorly differentiated histology
  - Lymphovascular invasion (LVI)
  - Perineural invasion (PNI)
  - Close, indeterminate, or positive margins
  - High preoperative serum carcinoembryonic antigen (CEA) level

What about MSI and Stage II

- MSI-H:
  - Hypermutability that occurs due to a deficiency in the DNA MMR
  - DNA Replication with accumulated errors
  - Microsatellites aka repeated sequences of DNA
  - MSI can be
    - Sporadic-15%; due to hypermethylation of the MLH1 gene promoter
    - Genetic-Lynch syndrome; germline mutation in MLH1, MSH2, MSH6, PMS2

Banner MD Anderson Cancer Center
Making Cancer History®

- MSI-H (IHC or PCR) portends to a better prognosis and don't respond to 5-FU based regimens*
- Popat et al# in a systematic review of 32 studies of CRC demonstrated that MSI-H pts derived no benefit from adjuvant FU-containing chemotherapy
- Sargent et al^ demonstrated that MSI-H pts treated with chemotherapy was associated with a reduced OS

*Ribic CM, NEJM,2003; #Popat S, JCO,2005;^Sargent DJ, JCO 2010

Banner MD Anderson Cancer Center
Making Cancer History®

Stage IV

- Palliative intent

- 5FU (or capecitabine) and Oxaliplatin
- 5FU (or capecitabine) and Irinotecan
- YES-BEVACIZUMAB, CETUXIMAB, PANITUMUMAB, ziv-AFLIBERCEPT, RAMUCIRUMAB
- NO Radiation

Banner MD Anderson Cancer Center
Making Cancer History®

Adjuvant therapy

- 5FU (or capecitabine) and Oxaliplatin
- **NO** BEVACIZUMAB, CETUXIMAB, PANITUMUMAB, ziv-AFLIBERCEPT, RAMUCIRUMAB
- **NO** Radiation unless its rectal cancer

Banner MD Anderson Cancer Center
Making Cancer History®

What about CEA?

- Causes for elevated CEA in an individual without cancer
  - Biliary disease
  - Hepatic injury
  - Pulmonary infections
  - Smokers
  - Bowel disease

Banner MD Anderson Cancer Center
Making Cancer History®

Newer biomarkers

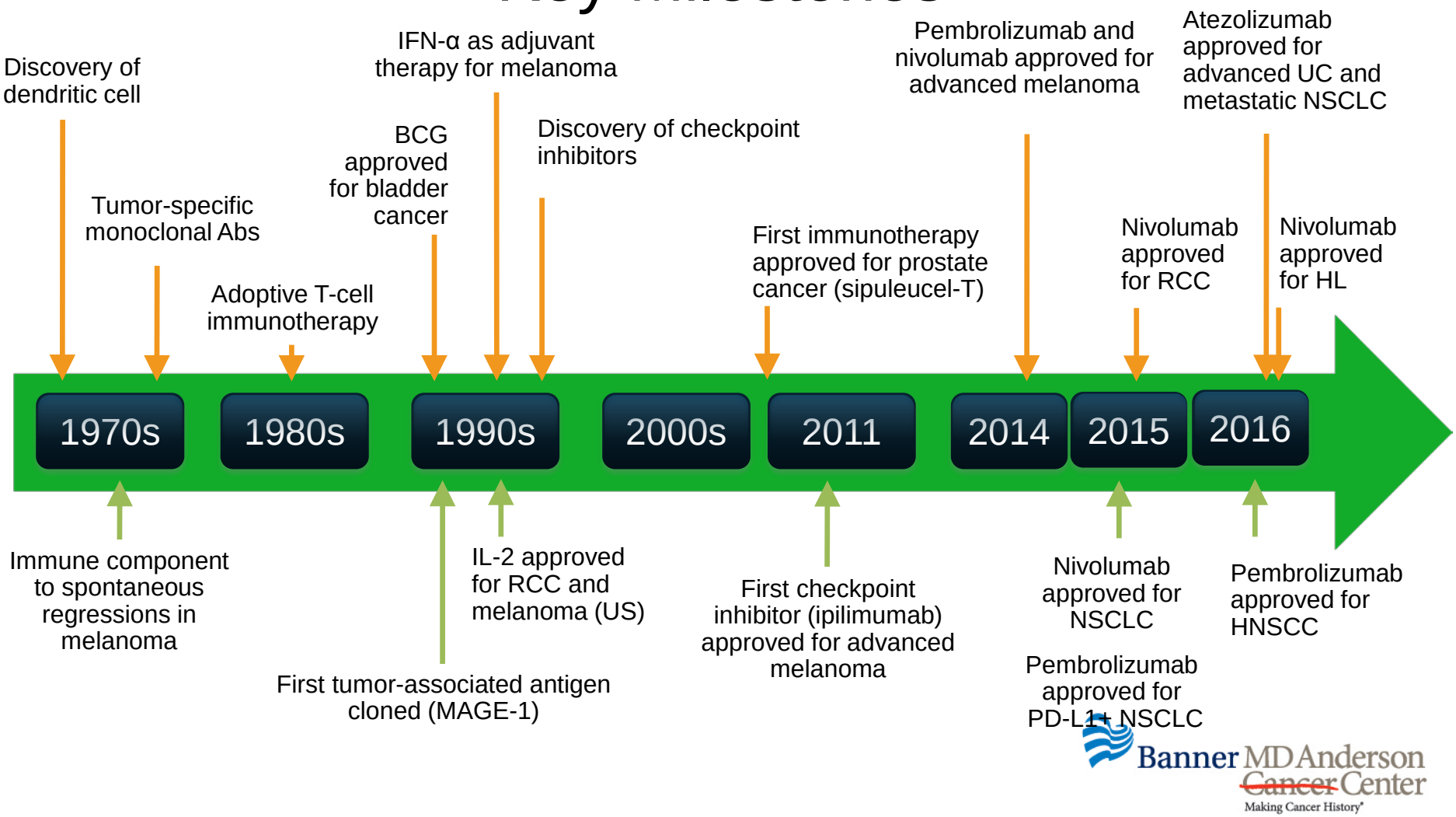
- Holy grail of onco-monitoring
- Several modalities of testing incl:
  - Quantitatively or structurally-altered proteins
  - Cancer-associated autoantibodies
  - Cell-free nucleic acids (cfNAs)
  - Circulating tumor cells (CTCs)
  - Cancer derived extracellular vesicles (EVs)

Banner MD Anderson Cancer Center
Making Cancer History®

IMMUNOTHERAPY IN ONCOLOGY

Banner MD Anderson Cancer Center
Making Cancer History®

History of Cancer Immunotherapy: Key Milestones



Banner MD Anderson Cancer Center
Making Cancer History®

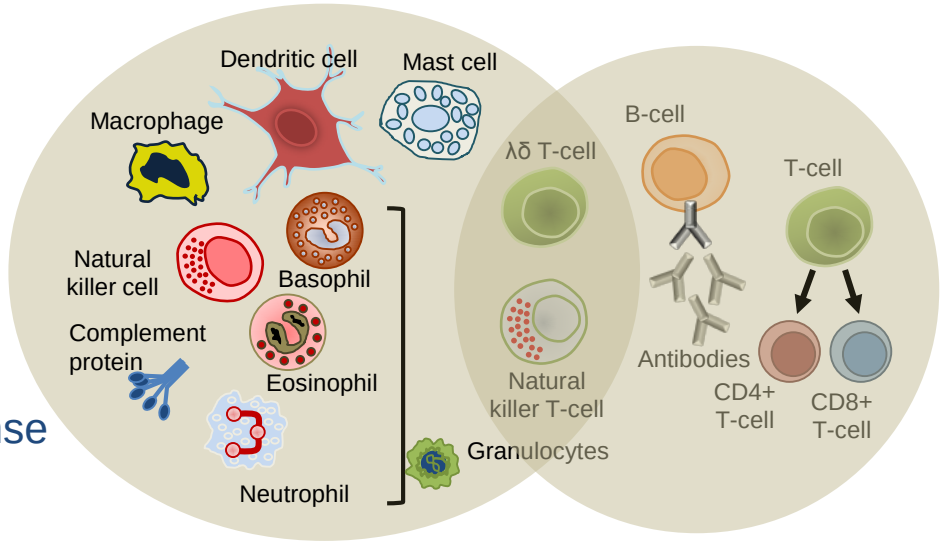
References in slidenotes.

Immune System Function and Immune Response

Identify and destroy foreign or abnormal cells in the body

Innate Immunity

- Nonspecific
- First line of defense
- WBCs (natural killer cells, neutrophils)
- Activation of adaptive response



Adaptive Immunity

- Specific
- Adapts specifically to diverse stimuli
- B-cell antibody production
- T-cell stimulation
- Memory functions

Immune surveillance:

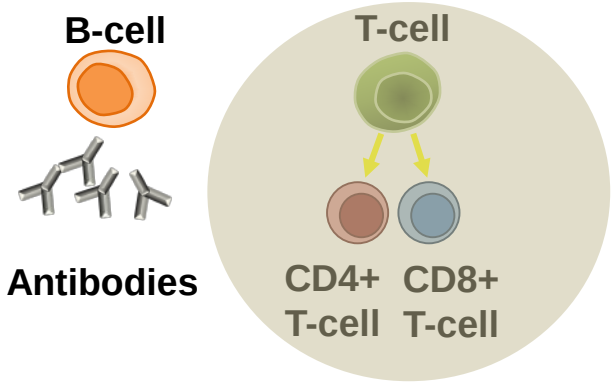
- Involves both innate and adaptive immune mechanisms
- Goal of immunotherapy for cancer: to "educate and liberate" underlying anticancer immune responses

Banner MD Anderson Cancer Center
Making Cancer History®

Janeway CA Jr, et al. Immunobiology: the immune system in health and disease. 2001.

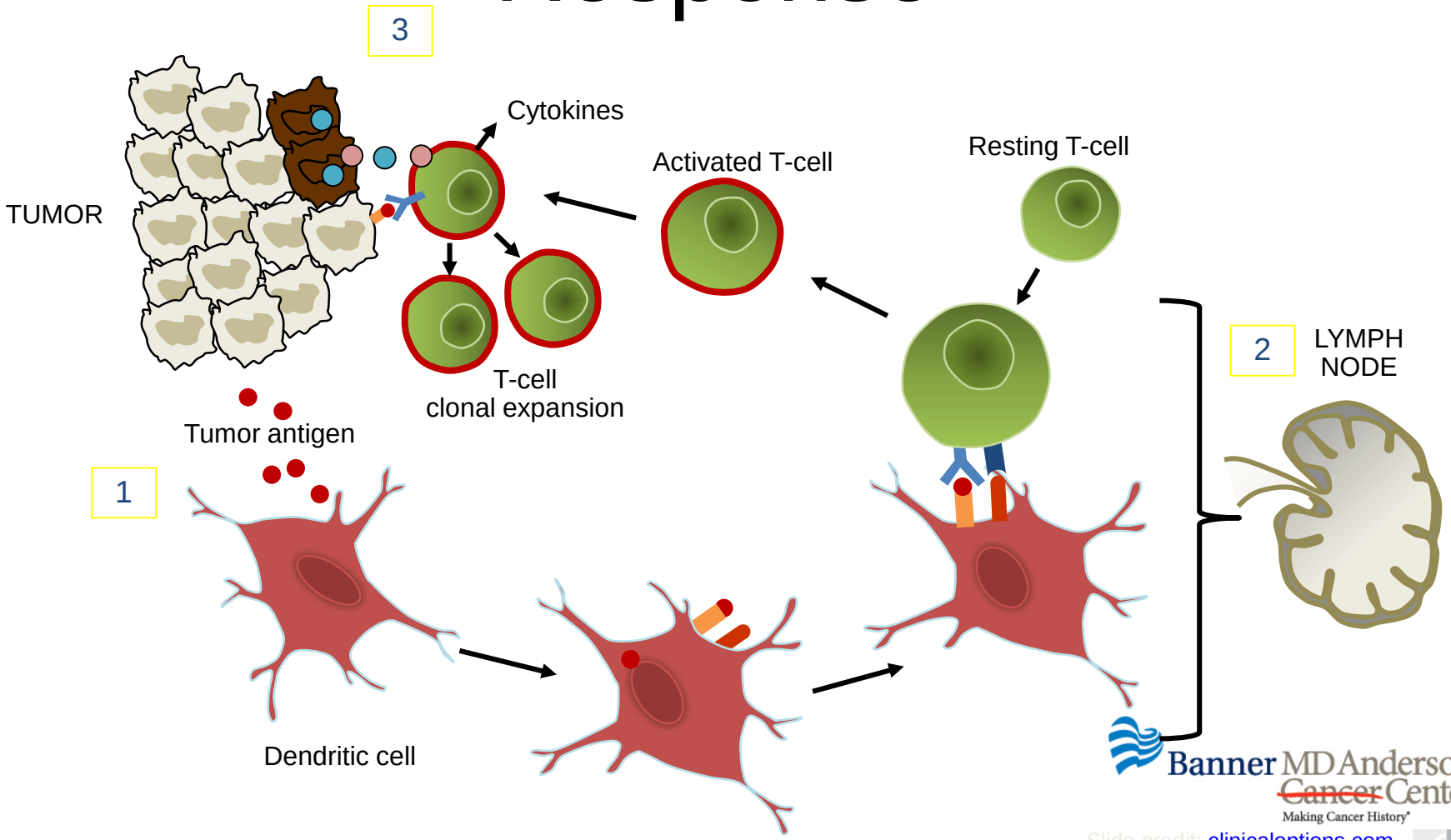
Adaptive Immune System: T-Cells

- 4 main types of T-cells
  - Helper T-cells (CD4+)
  - Cytotoxic T-cells (CD8+)
  - Suppressor T-cells (CD4+ Foxp3+ CD25+ Tregs)
  - Memory T-cells (CD4+ or CD8+ CCR7+ CD45RO)



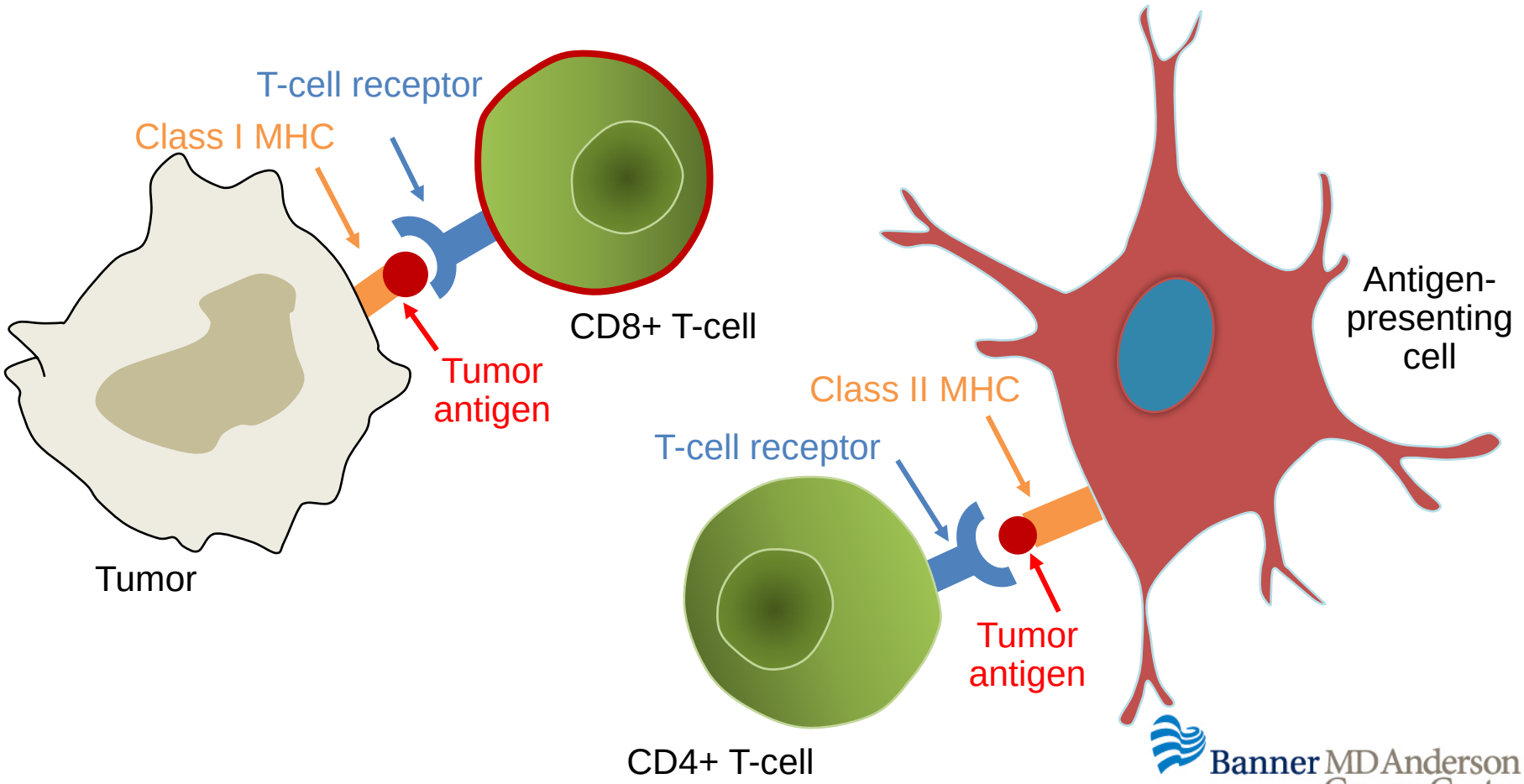
Slide credit: clinicaloptions.com

Tumor Specific Immune Response



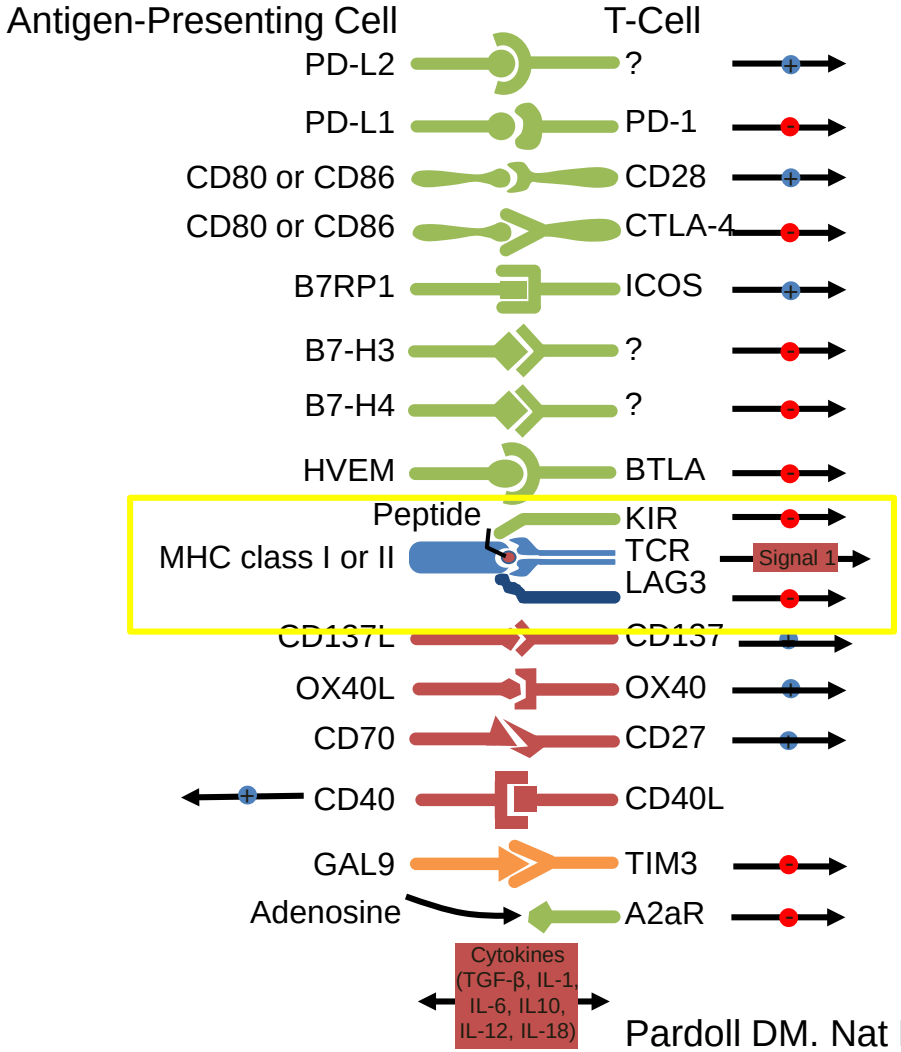
Slide credit: clinicaloptions.com

T-Cell Response: First Signal



Adapted from: Snyder A, et al. Curr Opin Genet Dev. 2015;30:7-16.

T-Cell Regulation via Multiple Costimulatory and Inhibitory Interactions

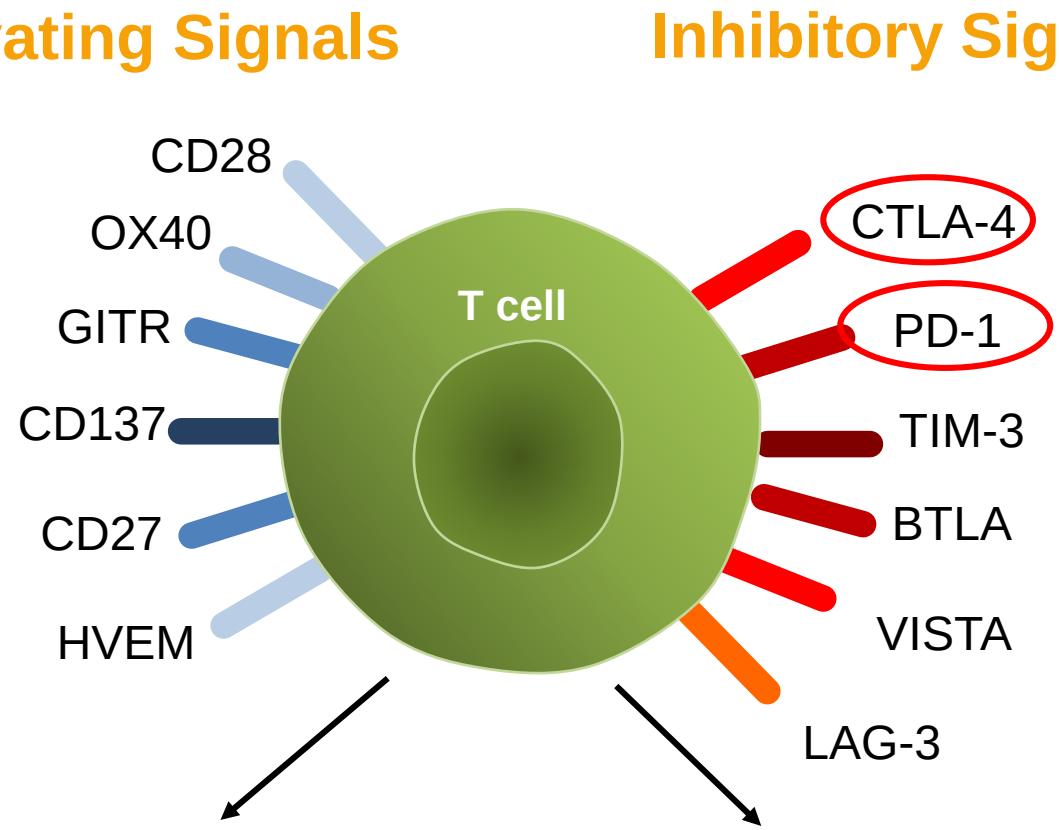


- T-cell response to antigen is mediated by peptide-MHCs recognized specifically by TCR (first signal)
- B7 family of membrane-bound ligands binds both activating and inhibitory receptors (second costimulatory signal)
- Targeting CTLA-4 and PD-1 inhibitory receptors has been a major clinical focus

Pardoll DM. Nat Rev Cancer. 2012;12:252-264

Banner MD Anderson Cancer Center
Making Cancer History®

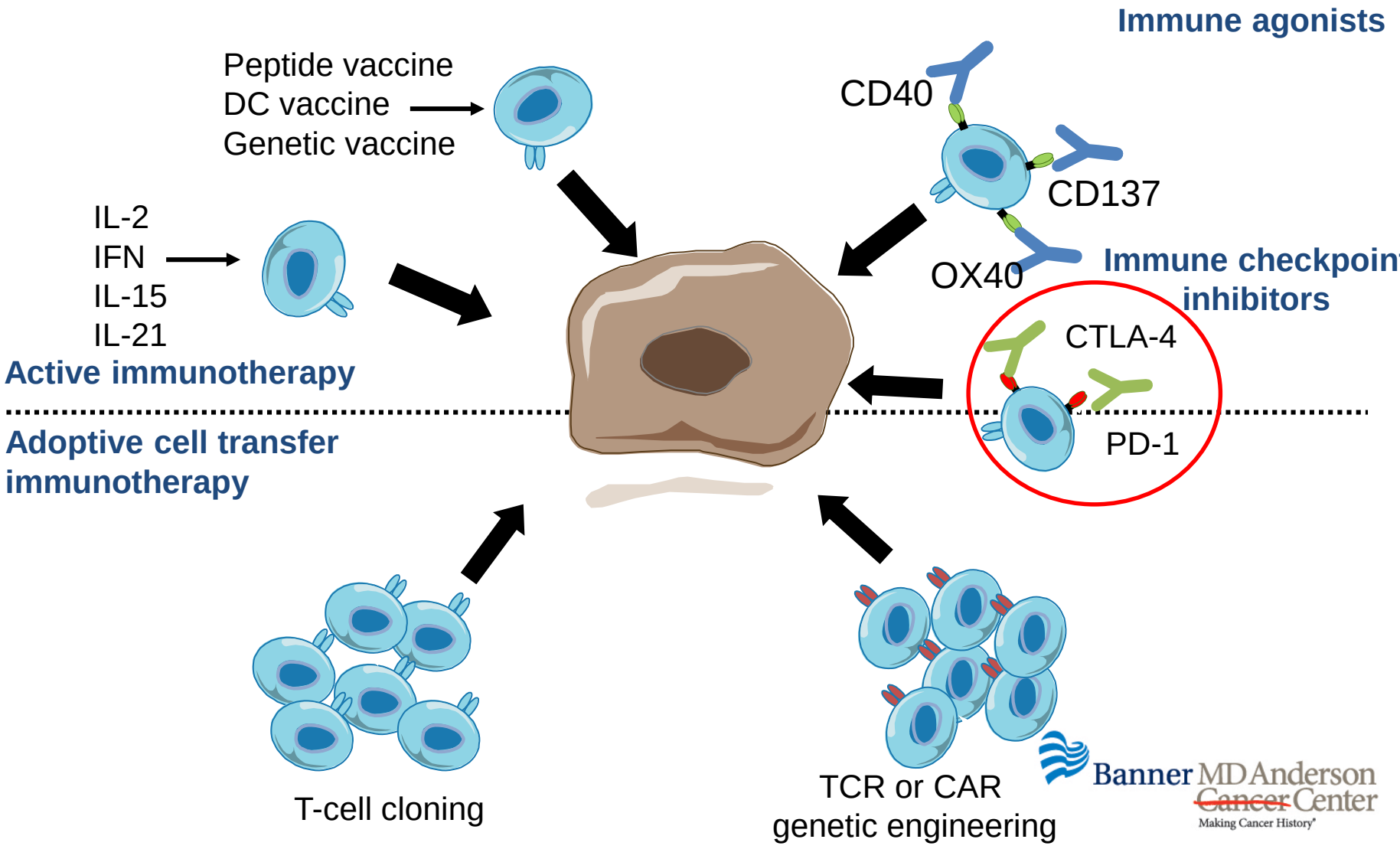
T-Cell Response: Accelerate or Brake?



Mellman I, et al. Nature. 2011;480:480-489.

Banner MD Anderson Cancer Center
Making Cancer History®

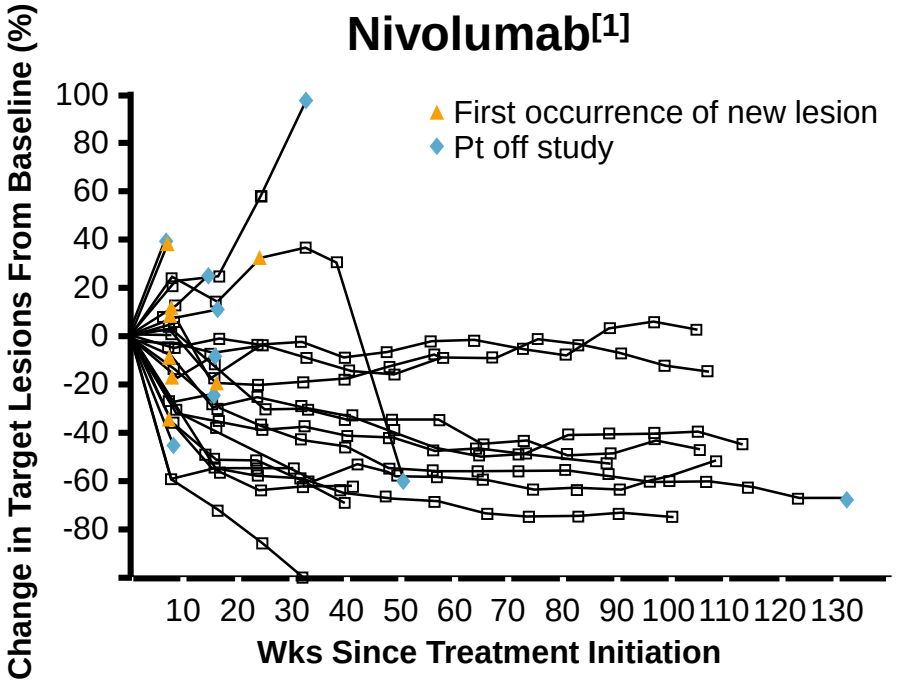
Targeting Cancer with Immunotherapy



Banner MD Anderson Cancer Center
Making Cancer History®

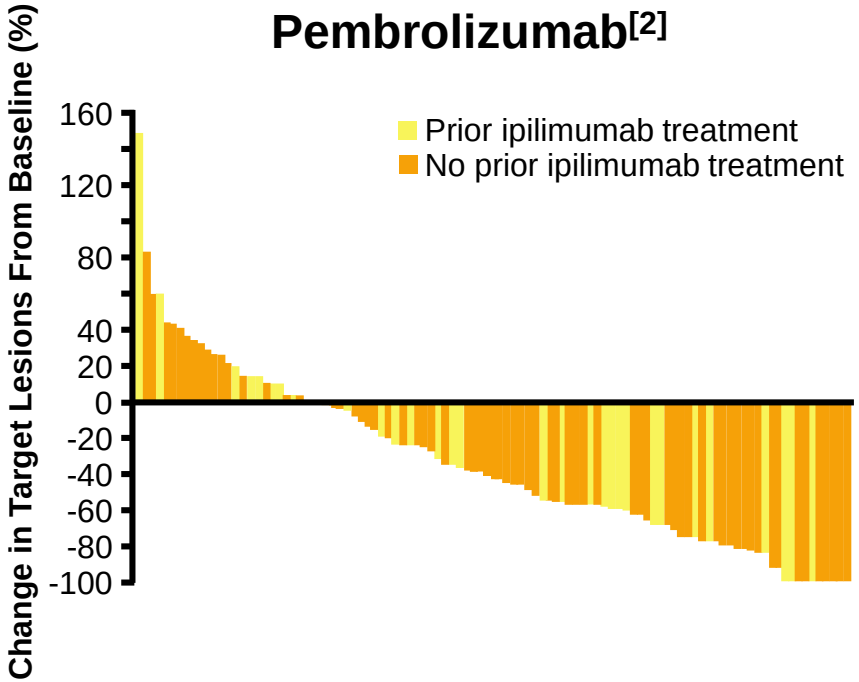
Response Rates With Anti–PD-1 Antibodies

Nivolumab[1]



- ORR
  - Melanoma: 28%
  - NSCLC: 18%
  - Renal cell cancer: 27%

Pembrolizumab[2]



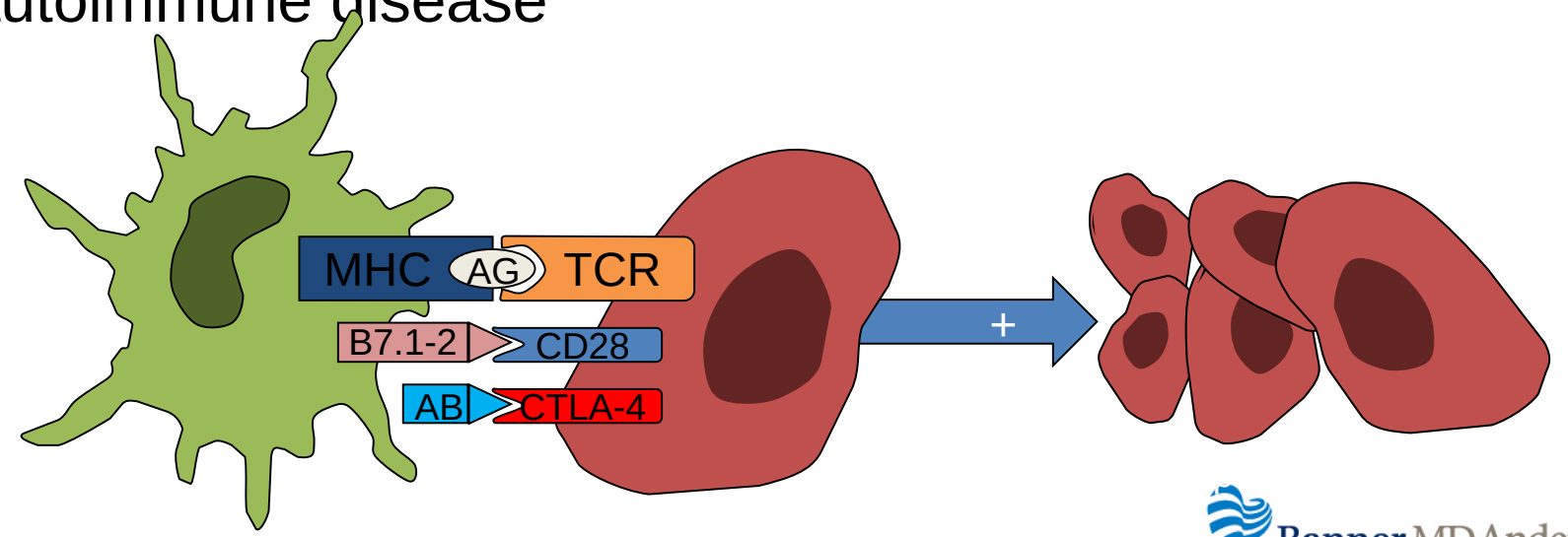
- Confirmed ORR
  - Melanoma: 38% (comparable ± previous ipilimumab)

1. Topalian SL, et al. N Engl J Med. 2012;366:2443-2454.
2. Hamid O, et al. N Engl J Med. 2013;369:134-144.

Banner MD Anderson Cancer Center
Making Cancer History®

Immune-Related Adverse Events: Mechanism of Action

- “Achilles heel” of checkpoint inhibitors: autoimmunity via irAEs
- Dysregulation of host immune system leads to unique toxicities of immune checkpoint inhibitors, similar to autoimmune disease



Banner MD Anderson Cancer Center
Making Cancer History®

Dillard T, et al. Pituitary. 2010;13:29-38.
Kim KW, et al. Invest New Drugs. 2013;31:1071.

Immune-Related AEs With Immunotherapy

Skin
- Dermatitis exfoliative
- Erythema multiforme
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Vitiligo
- Alopecia

Eye
- Uveitis
- Iritis

Endocrine
- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Hypophysitis

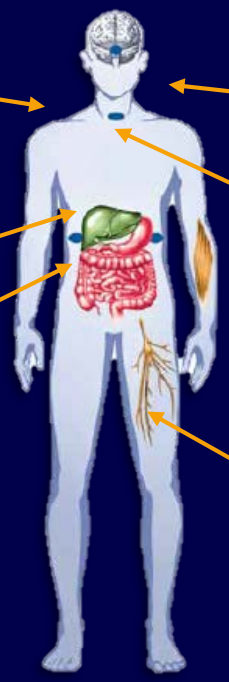
Hepatic
- Hepatitis, autoimmune

Pulmonary
- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

Gastrointestinal
- Colitis
- Enterocolitis
- Necrotizing colitis
- GI perforation

Neurologic
- Autoimmune neuropathy
- Demyelinating polyneuropathy
- Guillain-Barré
- Myasthenia gravis–like syndrome

Renal
- Nephritis, autoimmune
- Renal failure



If not vigilant, may result in more serious immune-related AEs

Slide credit: clinicaloptions.com

Ipilimumab (Anti–CTLA-4): Suspected irAEs in Pts With Melanoma

irAE, %	All Grades	Grade 3	Grade 4
Dermatologic	43.5	1.5	0
▪ Pruritus	24.4	0	0
▪ Rash	19.1	0.8	0
▪ Vitiligo	2.3	0	0
Gastrointestinal	29.0	7.6	0
▪ Diarrhea	27.5	4.6	0
▪ Colitis	7.6	5.3	0
Endocrine	7.6	2.3	1.5
▪ Hypothyroidism	1.5	0	0
▪ Hypopituitarism	2.3	0.8	0.8
▪ Hypophysitis	1.5	1.5	0
▪ Adrenal insufficiency	1.5	0	0
Hepatic	3.8	0	0
▪ Increase in ALT	1.5	0	0
▪ Hepatitis	0.8	0	0

Hodi FS, et al. N Engl J Med. 2010;363:711-723.

Nivolumab (Anti–PD-1): Suspected irAEs in Pts with Melanoma

- n = 206 pts with malignant melanoma

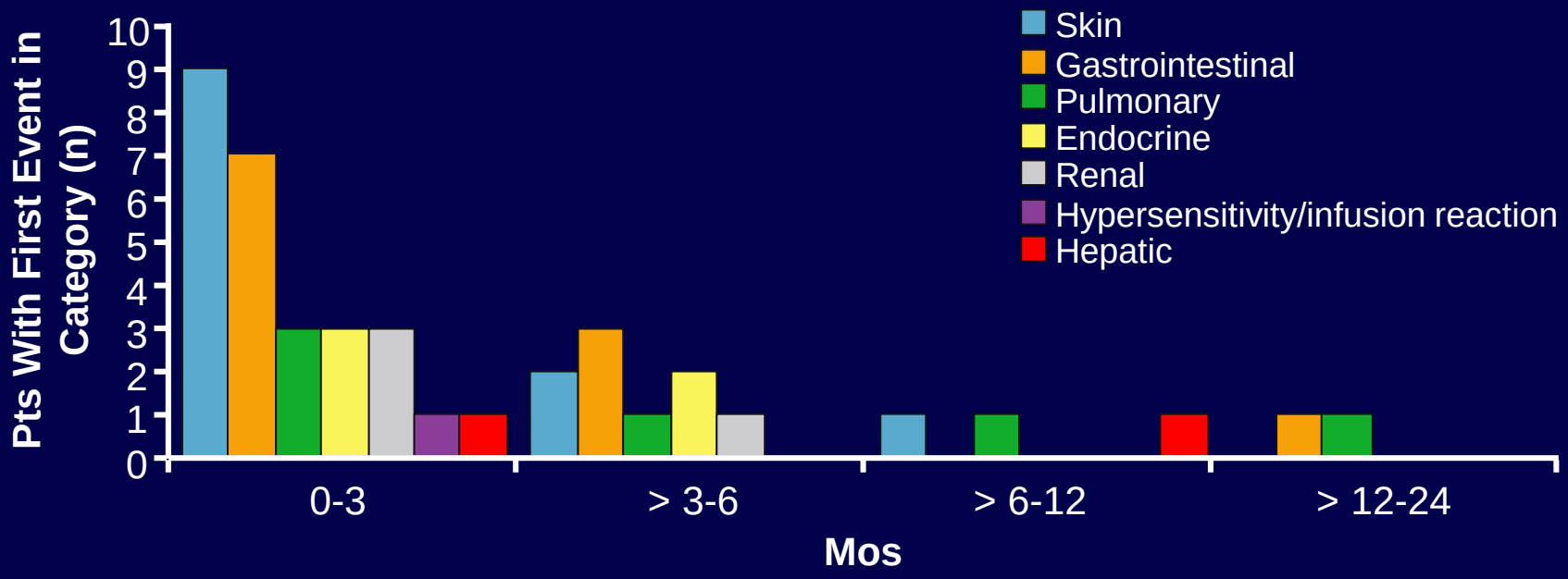
Suspected irAE, %	All Grades	Grade 3/4
Dermatologic	37.4	1.5
Pruritus	17	0.5
Rash	15	0.5
Vitiligo	10.7	0
Gastrointestinal	17	1.5
Diarrhea	16	1
Colitis	1	0.5
Endocrine	7.3	1
Hypothyroidism	4.4	0
Hyperthyroidism	3.4	0
Diabetes mellitus	0.5	0
Hypophysitis	0.5	0.5

Suspected irAE, %	All Grades	Grade 3/4
Hepatic	3.4	1.5
ALT increase	1.5	1
Bilirubin increase	1	0
Other		
Renal	1.9	0.5
Pulmonary	1.5	0

Robert C, et al. N Engl J Med. 2015;372:320-330.

Time to Onset of Select First Treatment-Related AE With Nivolumab (Any Grade)

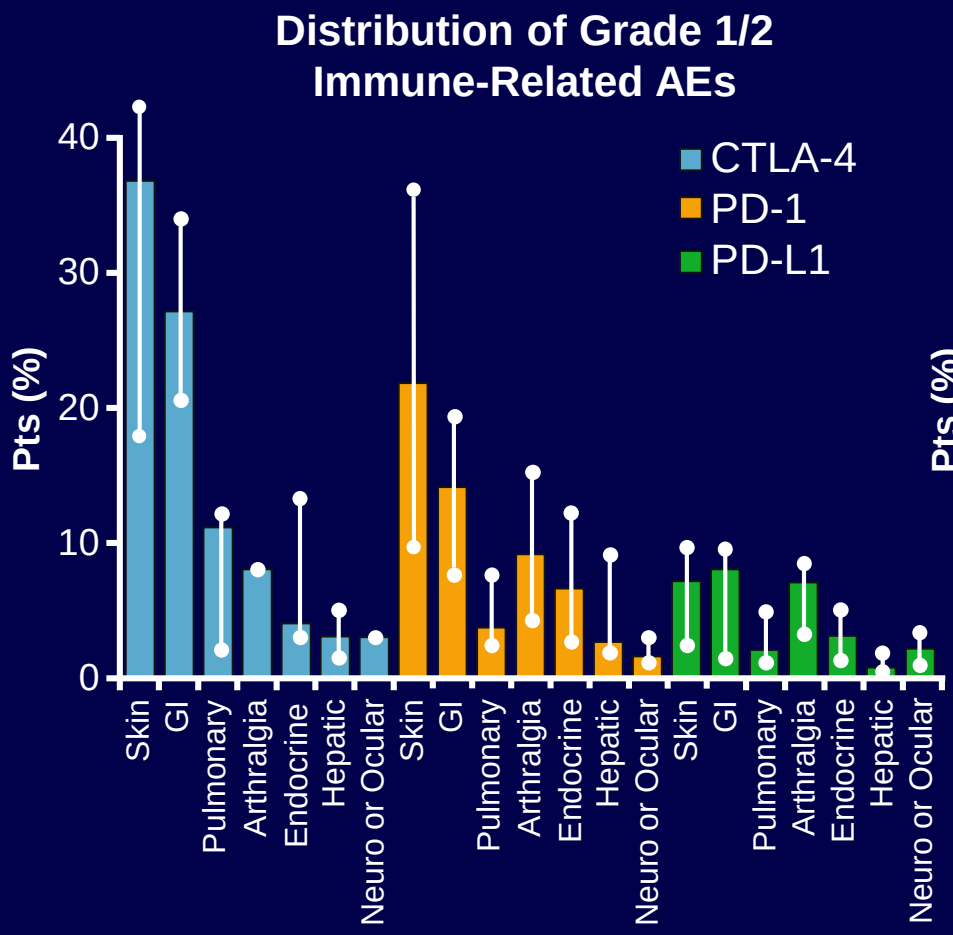
- Majority of treatment-related AEs occurred within first 3 mos of treatment

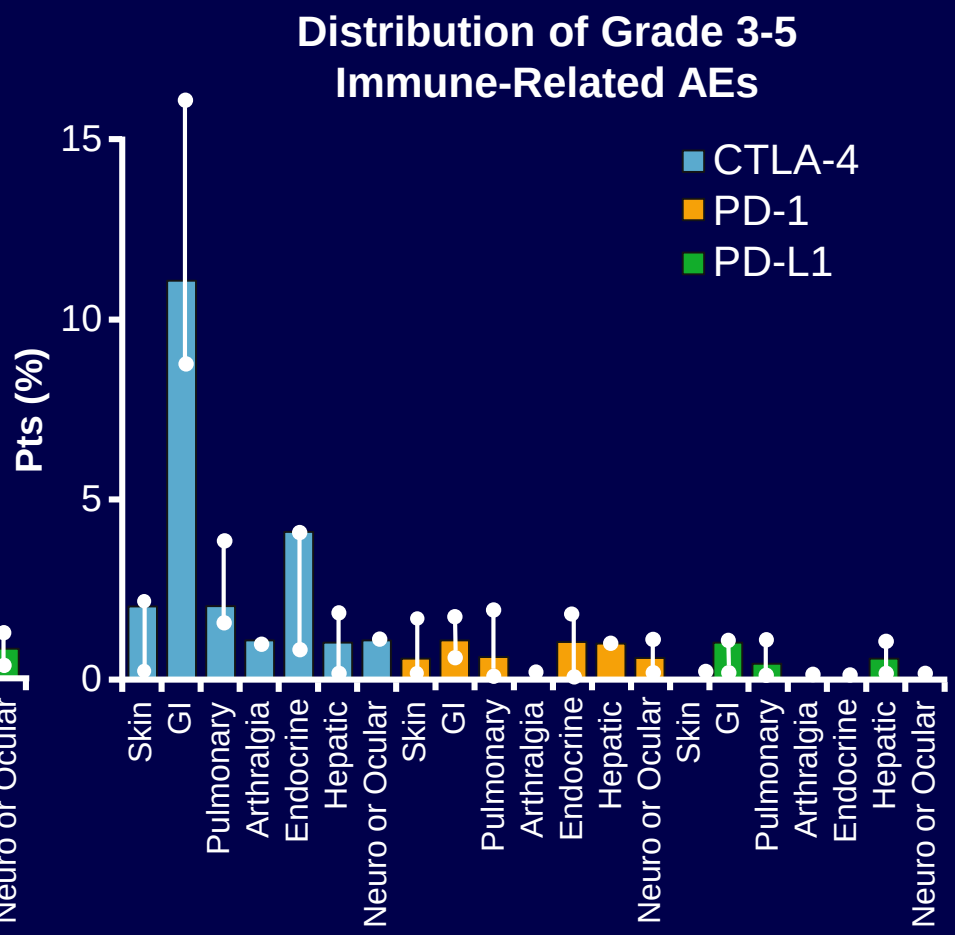


Pts still on study, n	131	112	85	52
Pts still on treatment, n	131	73	51	25
Total pts with first event, n	24	6	2	1

Reckamp K, et al. WCLC 2015. ORAL02.01.

Distribution of Immune-Related AEs With CTLA-4, PD-1, and PD-L1 Inhibition





Michot JM, et al. Eur J Cancer. 2016;54:139-148.

Clinical Vignette

- A 72-yr-old male is treated with nivolumab on a clinical trial for metastatic HCC
- After his third cycle of treatment, he develops diarrhea, 3 times/day, treated with loperamide
- Despite conservative management, his diarrhea increases to 8 times/day

Banner MD Anderson Cancer Center
Making Cancer History®

In addition to discontinuing nivolumab, which other step would you take?

A. IV hydration
B. Methylprednisolone (or equivalent)
C. Infliximab
D. Methylprednisolone (or equivalent) and infliximab

Banner MD Anderson Cancer Center
Making Cancer History®

Conclusions

- Immunotherapy has emerged as an exciting therapeutic strategy
- We need to enrich the clinical experience of checkpoint inhibitors in treating malignancies
- Assessing the molecular biomarkers that are important in predicting treatment response, resistance, and treatment-related AEs
- Combination strategies to improve the efficacy of checkpoint inhibitors under investigation
- Clinicians should be vigilant in monitoring the unique AE profiles of immunotherapy
  - Close monitoring and timely management of irAEs critical

Banner MD Anderson Cancer Center
Making Cancer History®

Questions?

Banner MD Anderson Cancer Center
Making Cancer History®