MEDICAL ONCOLOGY UPDATE 2019

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I HAVE NO CONFLICTS OF INTEREST WITH THIS PRESENTATION AND WILL NOT DISCUSS OFF LABEL DRUG USAGE

GOALS OF PRESENTATION

- Provide an understanding of the present state of medical oncology care in the US.
- Briefly familiarize you with the science of new treatment modalities:
  - So that you might be effective within the team of decision makers for your patients
- Bullet point standard of care for four major malignancies
- Minimally discuss surgery, radiation and cancer screening

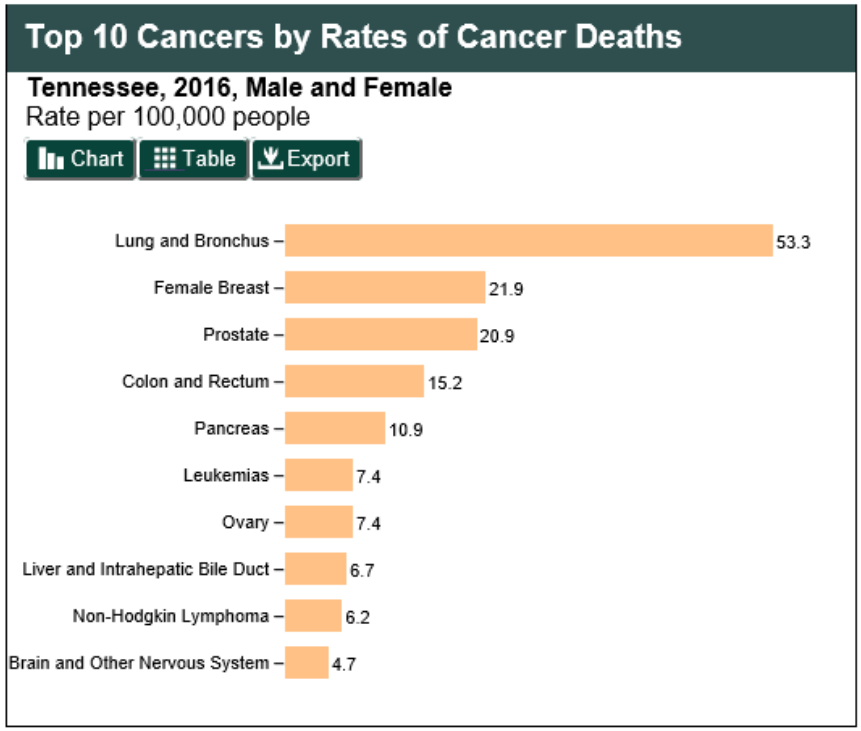
CDC USCS DATA VISUALIZATION

Cancer burden: Tennessee

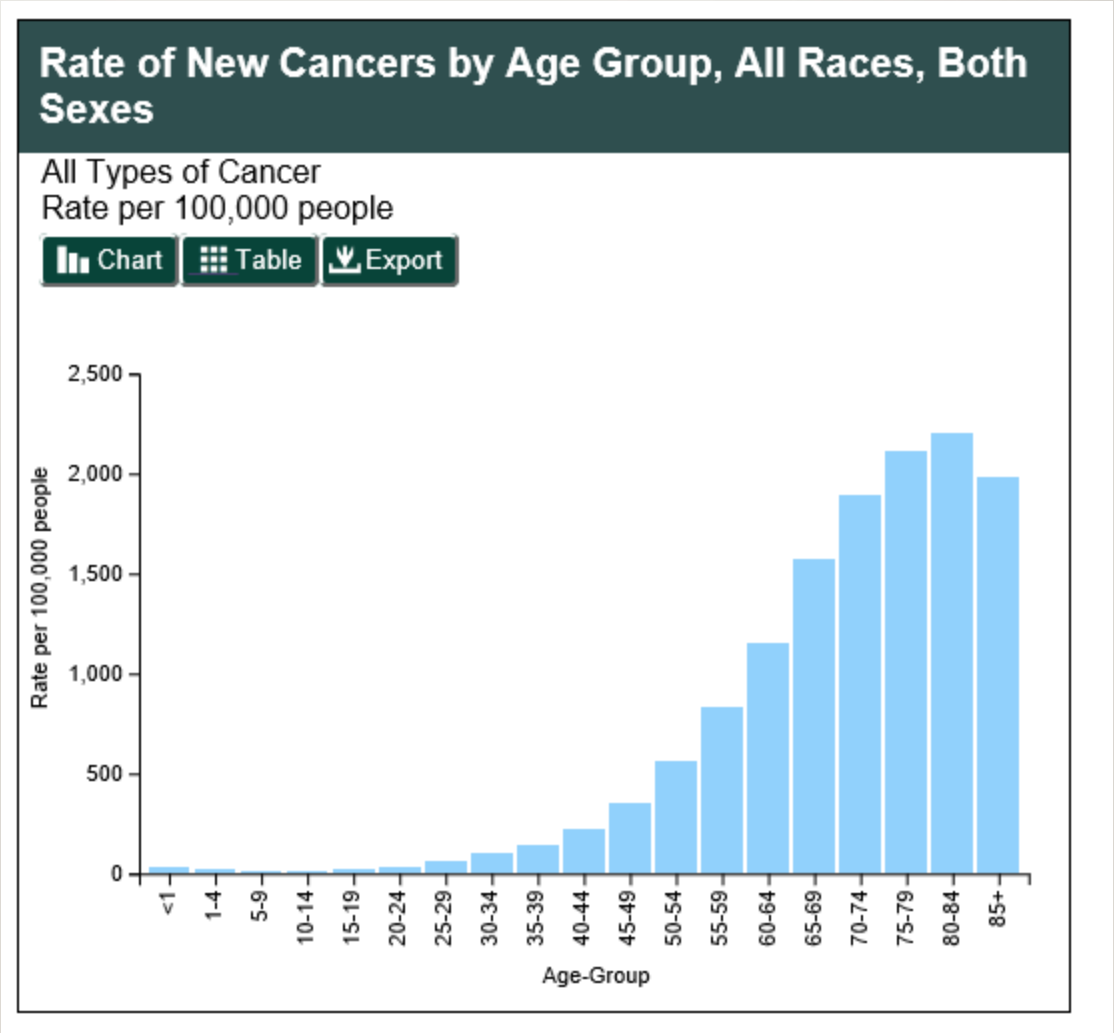
All Types of Cancer, 2016

In **Tennessee** in **2016**, there were **36,598 new cases of cancer**. For every 100,000 people, **456 cancer cases were reported.**

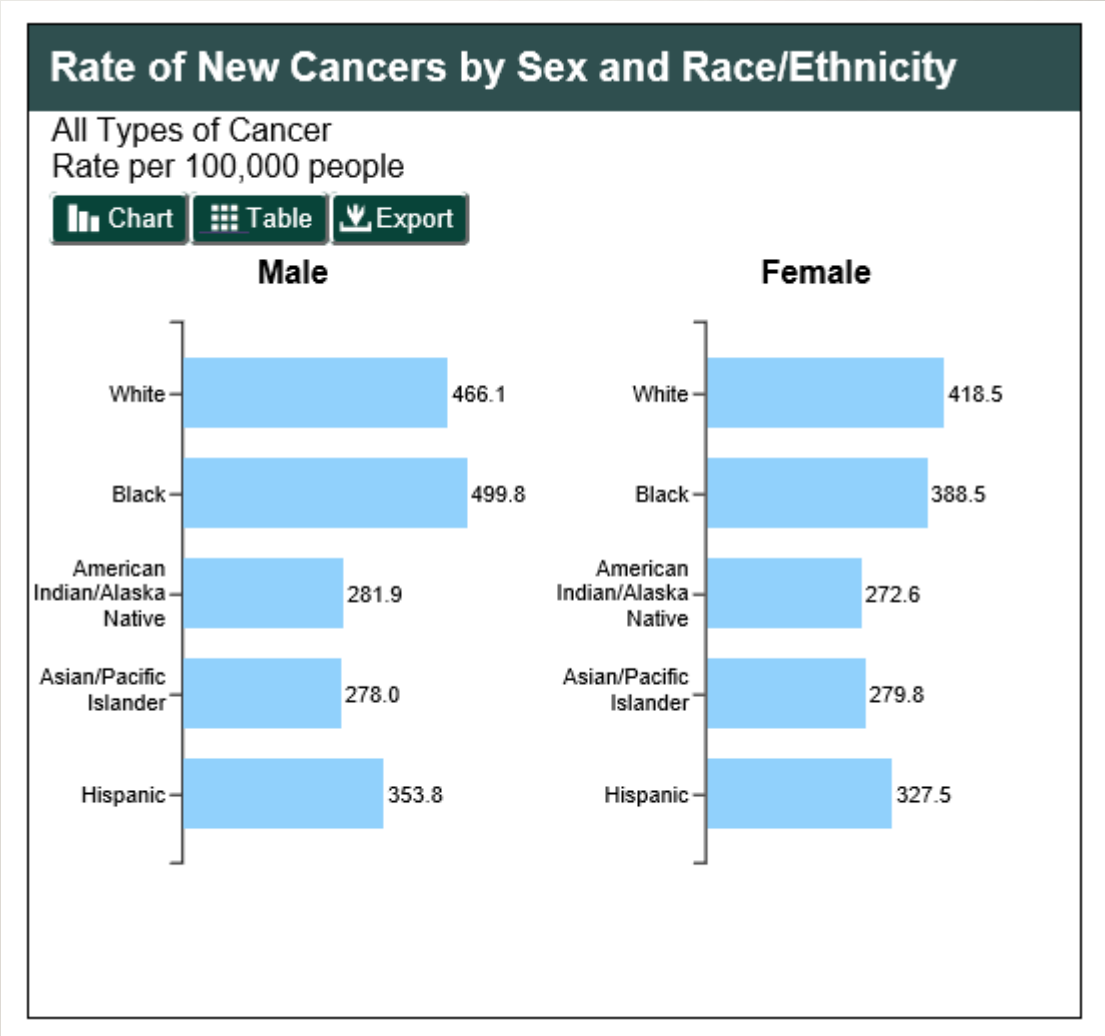
The same year, there were **14,450 people who died of cancer.** For every 100,000 people in **Tennessee, 181 died of cancer.**



CDC 2016


Rate of New Cancers by Age Group, All Races, Both Sexes
All Types of Cancer
Rate per 100,000 people
Chart
Table
Export
2,500
2,000
1,500
1,000
500
0
Rate per 100,000 people
<1
1-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85+
Age-Group

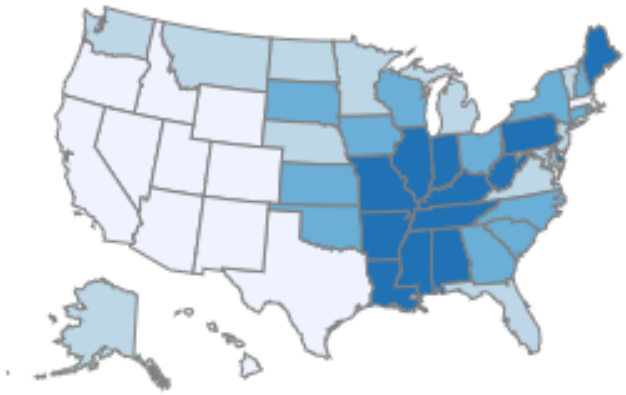
CDC 2016


Rate of New Cancers by Sex and Race/Ethnicity
All Types of Cancer
Rate per 100,000 people
Chart
Table
Export
Male
White
466.1
Black
499.8
American Indian/Alaska Native
281.9
Asian/Pacific Islander
278.0
Hispanic
353.8
Female
White
418.5
Black
388.5
American Indian/Alaska Native
272.6
Asian/Pacific Islander
279.8
Hispanic
327.5

Rate of New Tobacco-associated Cancers by State

All Tobacco-associated Cancers, Male and Female, United States, 2016
Rate per 100,000 people

Map | Table | Export



NH
VT
MA
RI
CT
NJ
DE
MD
DC

Rate per 100,000 people

122.8 - 172.8	175.3 - 186.1	186.7 - 196.4	199.4 - 235.8

PREVENTION

- 1. Stop smoking
- 2. Stay thin
- 3. Choose your relatives
- 4. Consider sun screen
- 5. Treat underlying infections
  - a. H pylori
  - b. HIV
  - c. Hep B and C
- 6. Tamoxifen or aromatase inhibitor
- 7. Vaccinate HPV

PREVENTION

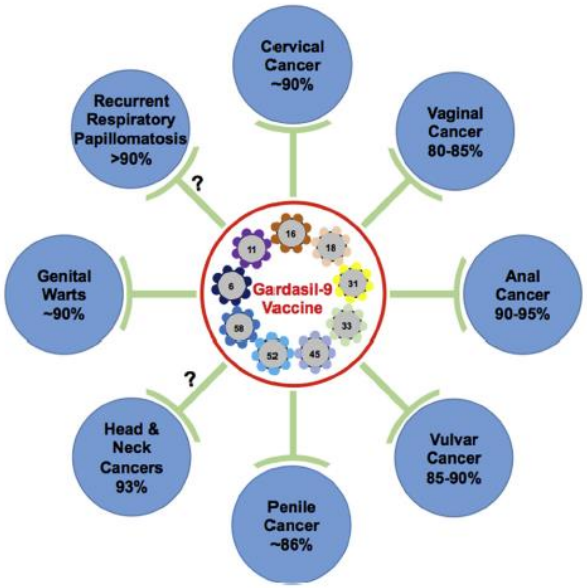


Fig. 2. Worldwide estimated percentages of HPV-associated cancers, HPV-associated warts, and papillomatosis to be protected by Gardasil-9. Estimates are based on the prevalence and the sum of percent contributions of vaccine HPV types to different HPV-associated (cervical, vaginal, anal, vulvar, penile, head and neck) cancers, genital warts including recurrent respiratory papillomatosis. For example, 90% protection against cervical cancer is base on the fact that HPV16 is associated with (~55.4%), HPV18 (16.1%), HPV45 (4.7%), HPV31 (3.8%), HPV33 (4.1%), HPV52 (2.8%), and HPV58 (3.0%) of cervical cancer cases worldwide.

LUNG CANCER SCREENING

Table Harms Vs Benefits

The table below shows the trade-offs of low-radiation-dose CT screening for lung cancer:

Potential Benefits	Potential Harms
Mortality benefits • 20% relative decrease in lung cancer death (from 1.66% to 1.33%, or 3 fewer deaths per 1,000 screened) • 7% relative reduction in all-cause mortality	Harms related to test characteristics • Radiation exposure from screening CT • False reassurance (aggressive cancers may develop in intervals between screening examinations) • Overdiagnosis of clinically insignificant cancers (15% to 20% of tumors detected)
Psychosocial benefits and behavioral changes • Reassurance if normal CT • Teachable moment for smoking cessation	Harms related to findings of test • False positives and other incidental findings • Potential harms from downstream evaluation of findings

Source: Adapted from: Wiener R, et al. *Am J Resp Crit Care Med.* 2015;192:881-891

MODALITIES OF TREATMENT

1. Surgery
2. Radiation
3. Cytotoxic chemotherapy
    1. Immuno-chemotherapies
4. Targeted therapies
5. Immunotherapies
    1. Checkpoint inhibitors
    2. CAR-T
    3. Allogeneic bone marrow transplant

- Immune Therapy

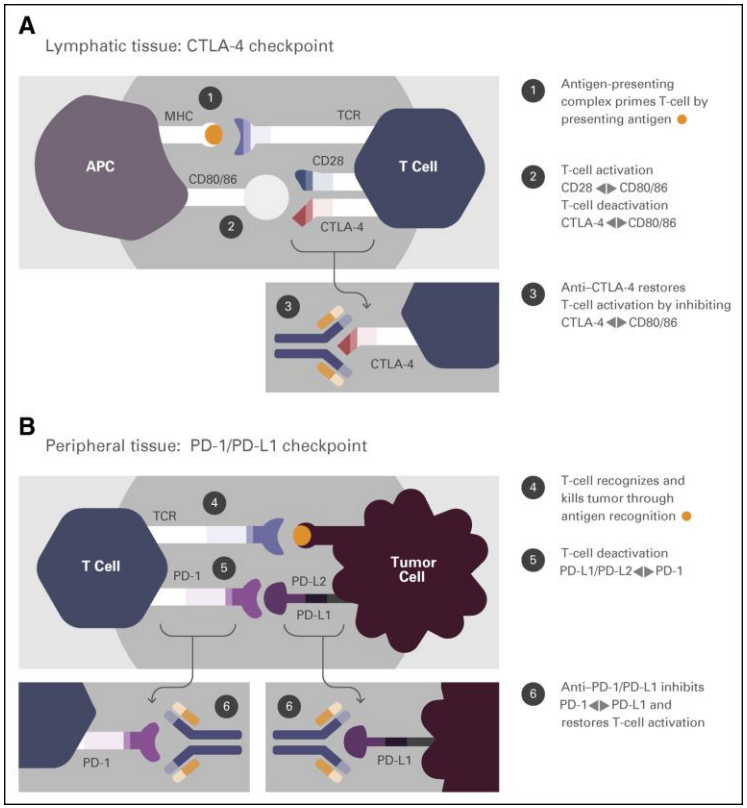


Fig 1. Immune system activation and regulation in the antitumor response. APC, antigen-presenting cell; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1/2, programmed death ligand 1/2; TCR, T-cell receptor.

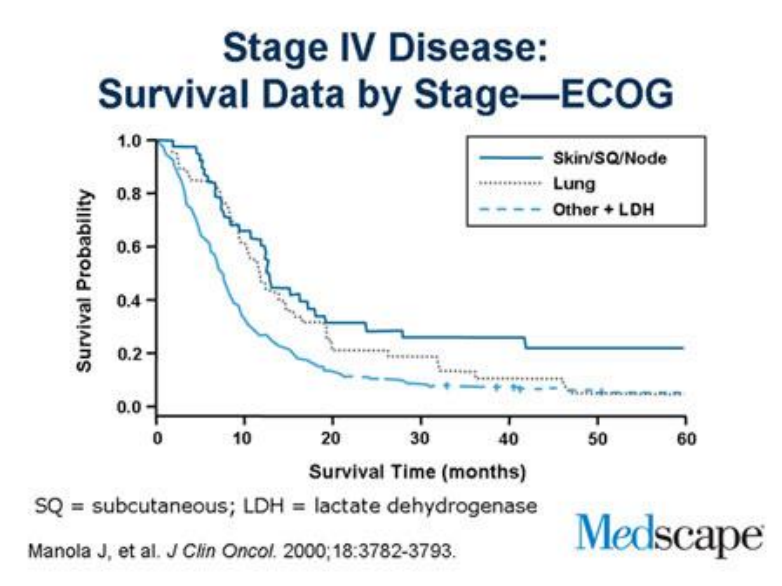
Published in: Barbara Melosky; Quincy Chu; Rosalyn Juergens; Natasha Leighl; Deanna McLeod; Vera Hirsh; *Journal of Clinical Oncology* 2016 341676-1688.
DOI: 10.1200/JCO.2015.63.8049

IMMUNE RESPONSIVE TUMORS

- Melanoma
- Non Small Cell Lung Cancer
- Renal Cell
- Hodgkin's Lymphoma
- Urothelial Cancer
- Head and Neck cancer
- Hepatocellular Cancer

MELANOMA 2000-MELANOMA NOW

J Clin Oncol 37:867-875. © 2019 by American Society of Clinical Oncology



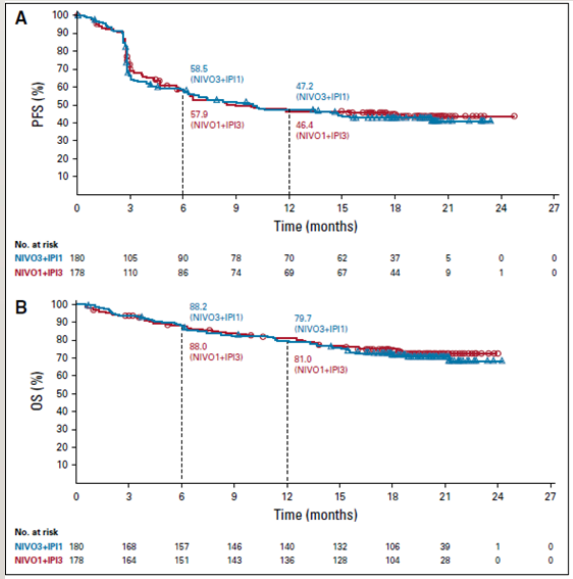
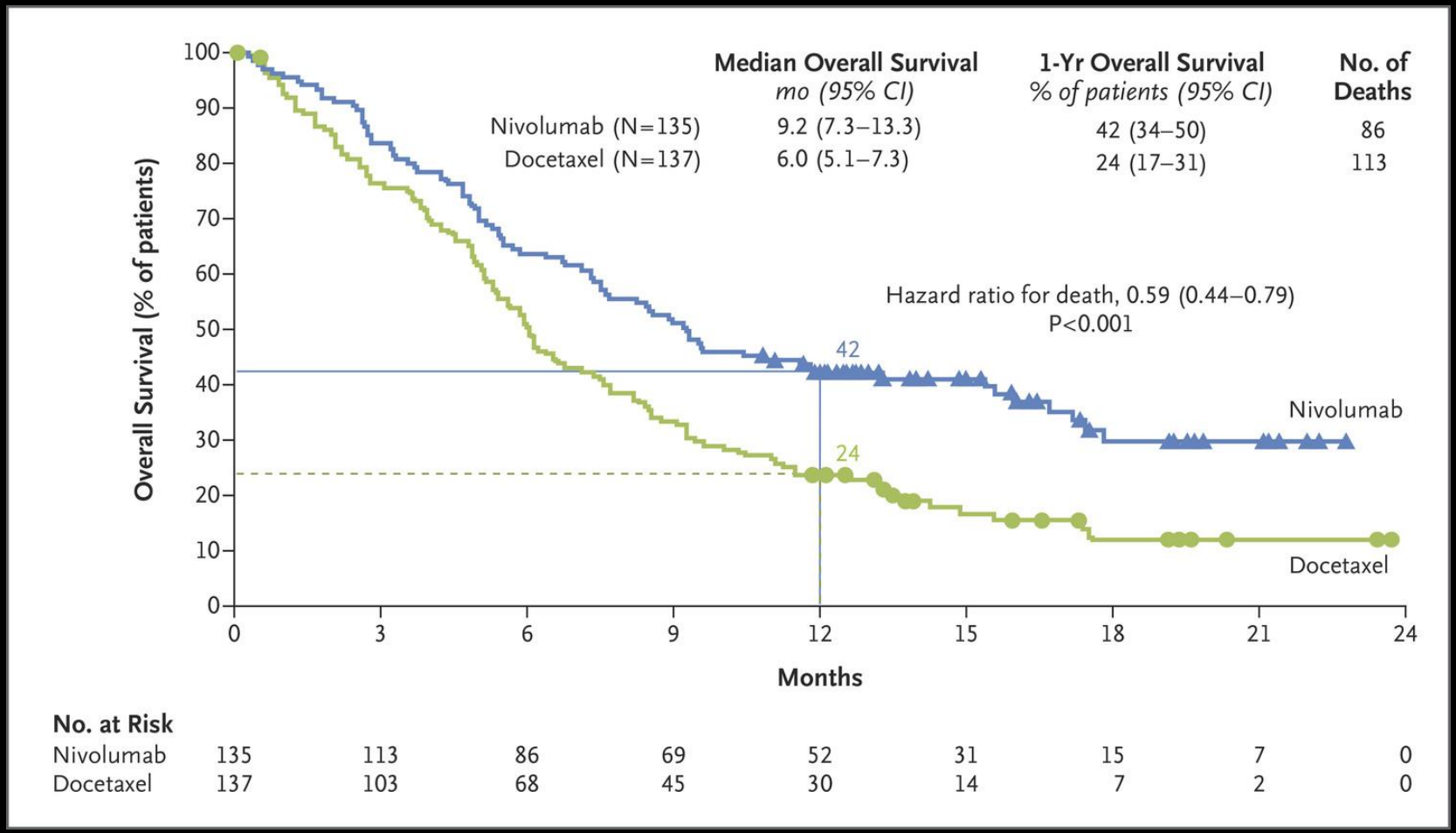


FIG 2. Kaplan-Meier plot of (A) progression-free survival (PFS) and (B) overall survival (OS) in patients who received NIVO3+IPI1 (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg) or NIVO1+IPI3 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg). Symbols indicate censored observations. Median PFS was 9.92 months in the NIVO3+IPI1 group and 8.94 months in the NIVO1+IPI3 group (hazard ratio, 1.06; 95% CI, 0.79 to 1.42). Median OS was not reached in either group (hazard ratio, 1.09; 95% CI, 0.73 to 1.62).

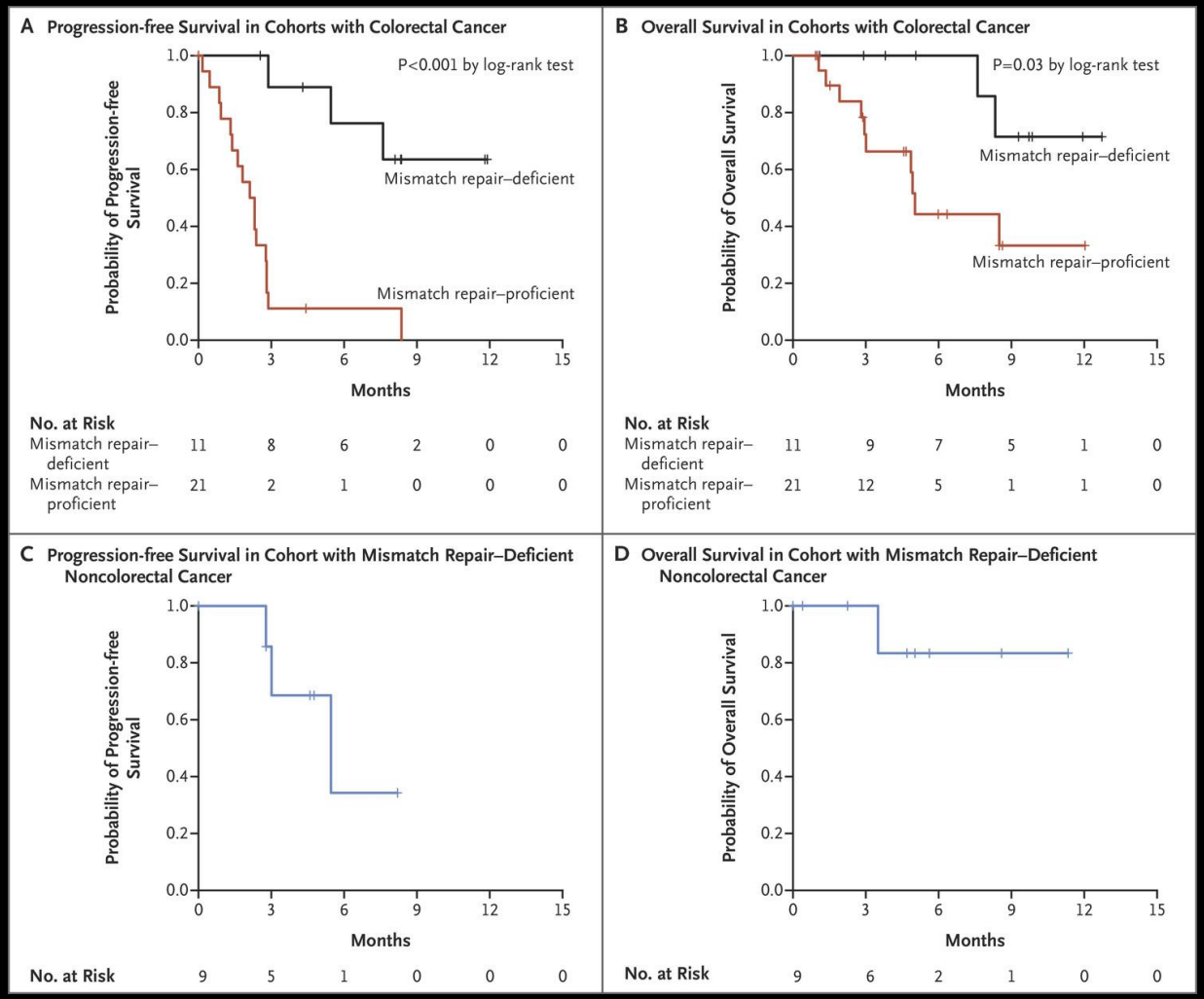
Kaplan–Meier Curves for Overall Survival.



Brahmer J et al. N Engl J Med 2015;373:123-135.

The NEW ENGLAND JOURNAL of MEDICINE

Clinical Benefit of Pembrolizumab Treatment According to Mismatch-Repair Status.



Le DT et al. N Engl J Med 2015;372:2509-2520.

The NEW ENGLAND JOURNAL of MEDICINE

INITIAL IMMUNE THERAPY VS CHEMOTHERAPY NSCLC

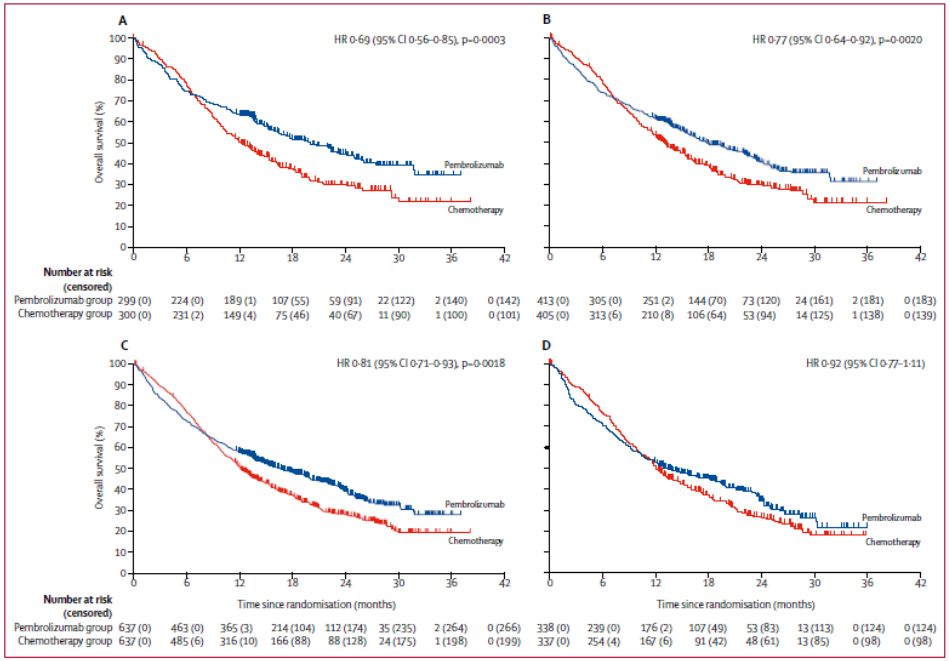


Figure 2: **Kaplan-Meier estimates of overall survival**
(A) PD-L1 TPS 50% or greater population. (B) PD-L1 TPS 20% or greater population. (C) PD-L1 TPS 1% or greater population. (D) PD-L1 TPS 1–49% population (exploratory analysis). Tick marks indicate censoring of the data at the last time the patient was known to be alive. HR=hazard ratio. PD-L1=programmed death ligand 1. TPS=tumour proportion score.

MOK, ET AL. WWW.THELANCET.COM PUBLISHED ONLINE APRIL 4, 2019 HTTP://DX.DOI.ORG/10.1016/S0140-6736(18)32409-7

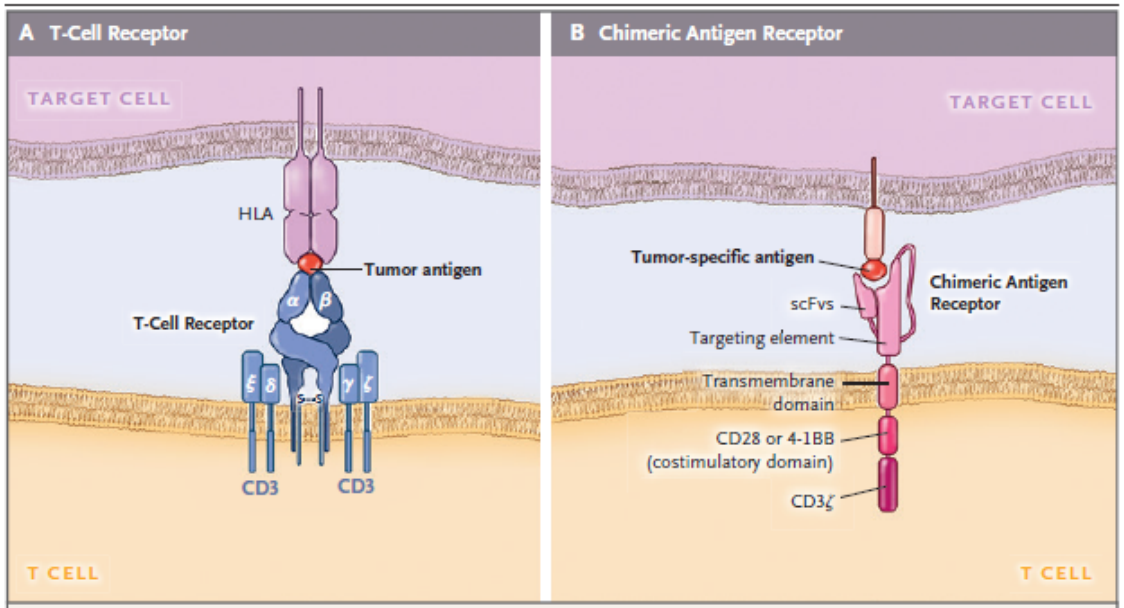


Figure 2. Structure of CARs and T-Cell Receptors.

Panel A shows the structure of a T-cell receptor, which consists of heterodimeric and antigen-specific α and β chains that closely associate with the invariant ε, δ, γ, and ζ chains of the CD3 complex. The T-cell receptor binds to the HLA allele that has a bound peptide derived from a tumor antigen on the target cell. Panel B shows the CAR, which includes the single-chain variable fragment (scFv) that binds to tumor antigens, fused to a spacer and transmembrane domain. The intracellular domain contains costimulatory domains, such as CD28 and 4-1BB and the CD3ζ chain, which drive signal activation and amplification of CAR T cells. S–S denotes disulfide bond.

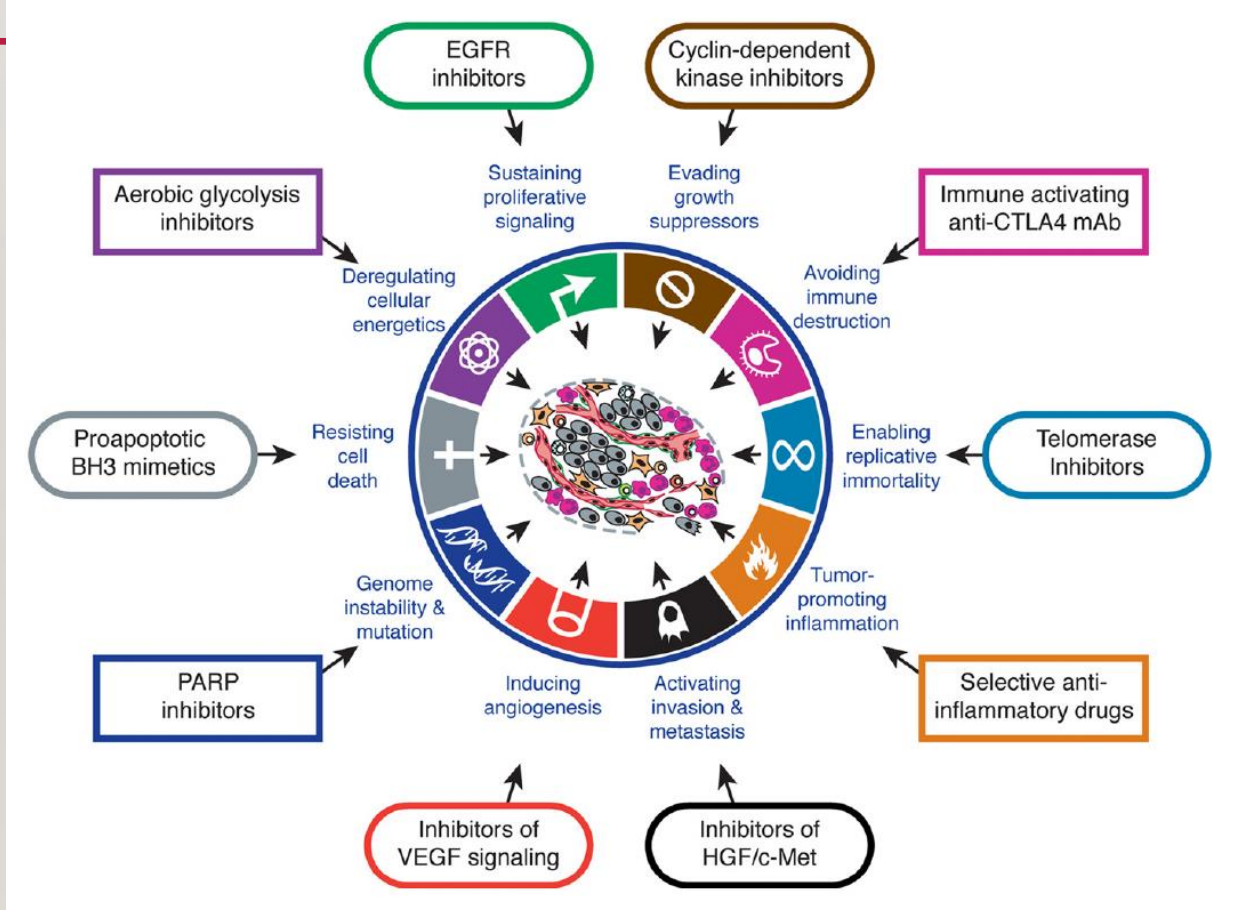
CAR-T

N ENG J MED 2018;379:64-73.
DOI: 10.1056/NEJMRA1706169

- Targeted Therapy

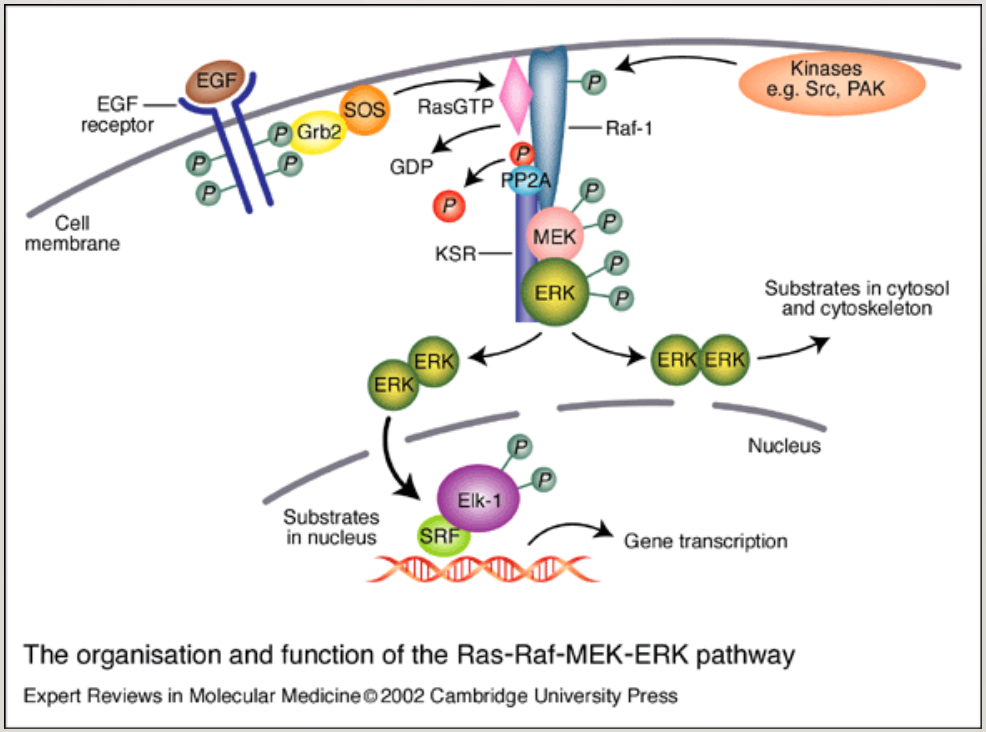
Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland
[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
*Correspondence: dh@epfl.ch (D.H.), weinberg@wi.mit.edu (R.A.W.)
DOI 10.1016/j.cell.2011.02.013



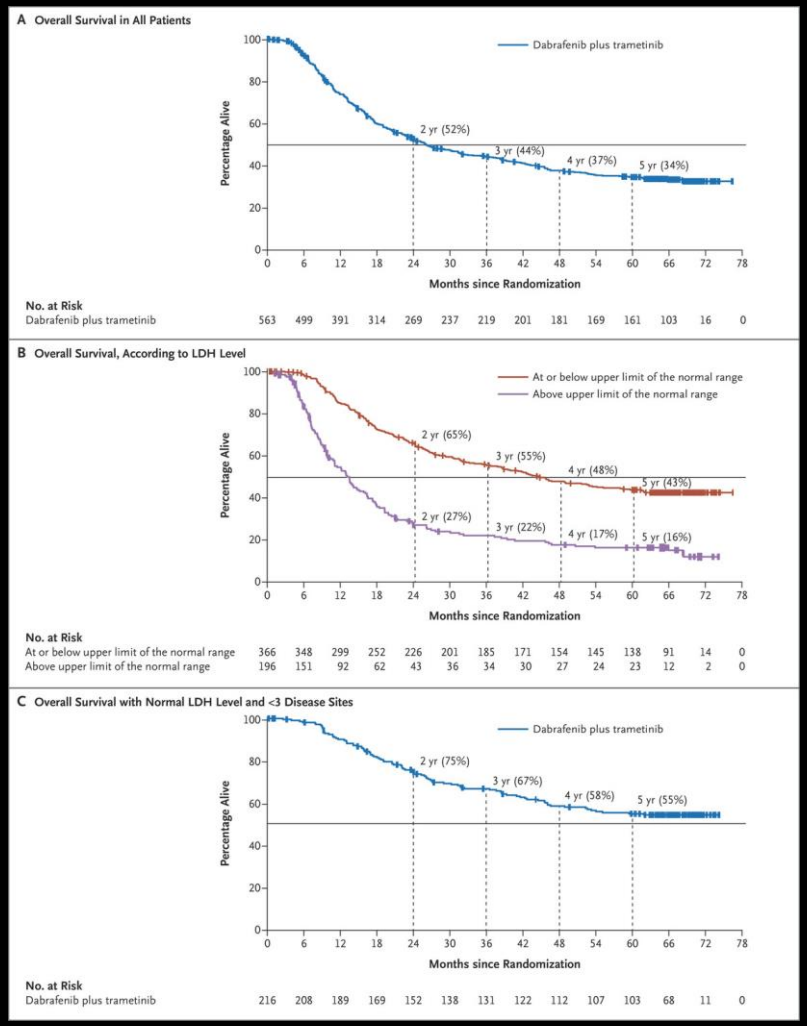
Hanahan & Weinberg, Cell, 2011

RAS PATHWAY



The organisation and function of the Ras-Raf-MEK-ERK pathway

Overall Survival.



C Robert et al. N Engl J Med 2019;381:626-636.

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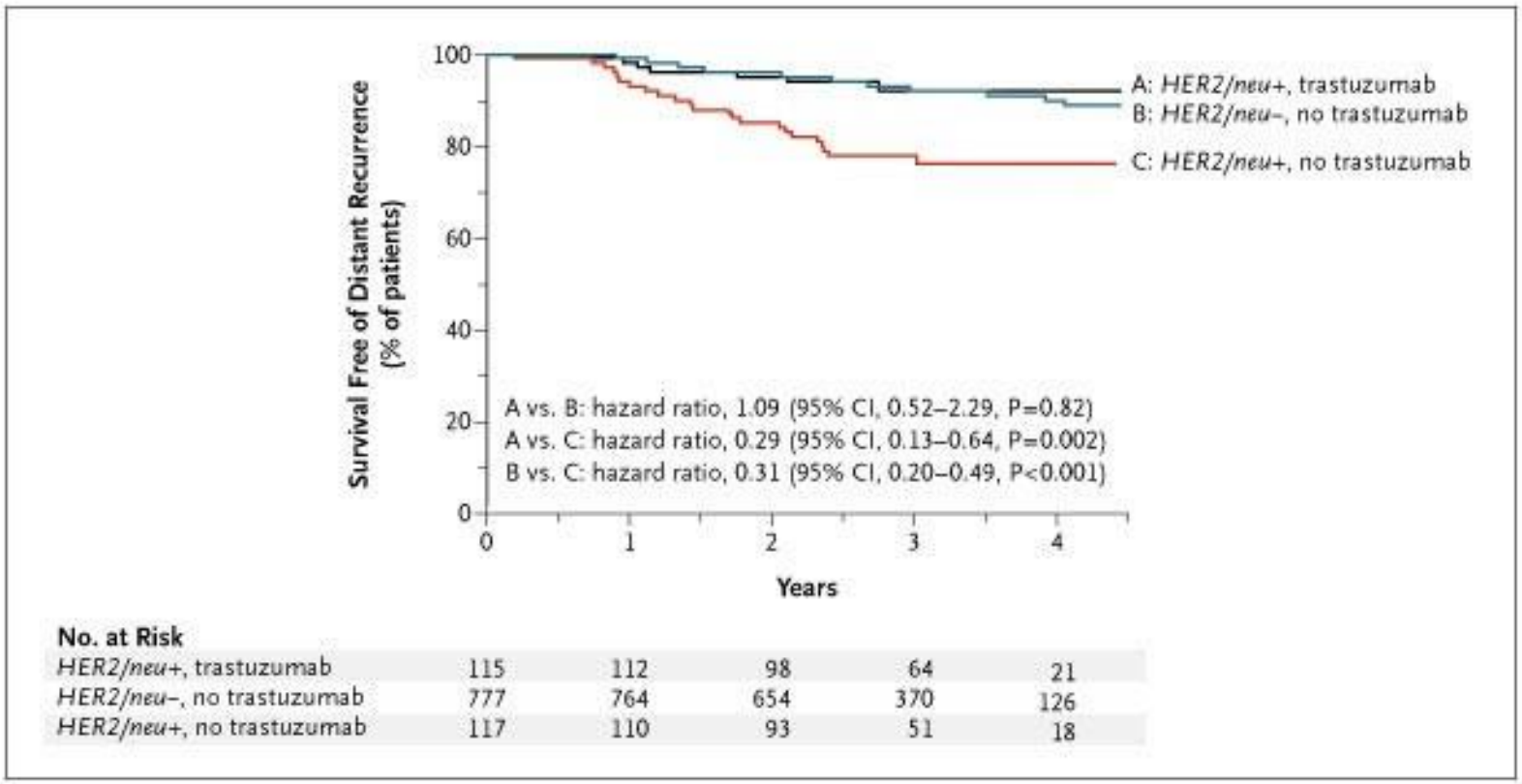
Effect of *HER2/neu* Amplification and Trastuzumab on the Kaplan–Meier Estimates of Survival Free of a First Distant Recurrence of Breast Cancer.



No. at Risk					
HER2/neu+, trastuzumab	115	112	98	64	21
HER2/neu–, no trastuzumab	777	764	654	370	126
HER2/neu+, no trastuzumab	117	110	93	51	18

Joensuu H et al. N Engl J Med 2006;354:809-820.

The NEW ENGLAND JOURNAL of MEDICINE

High Response Rates for the Seven NCCN Targets in Lung Adenocarcinoma

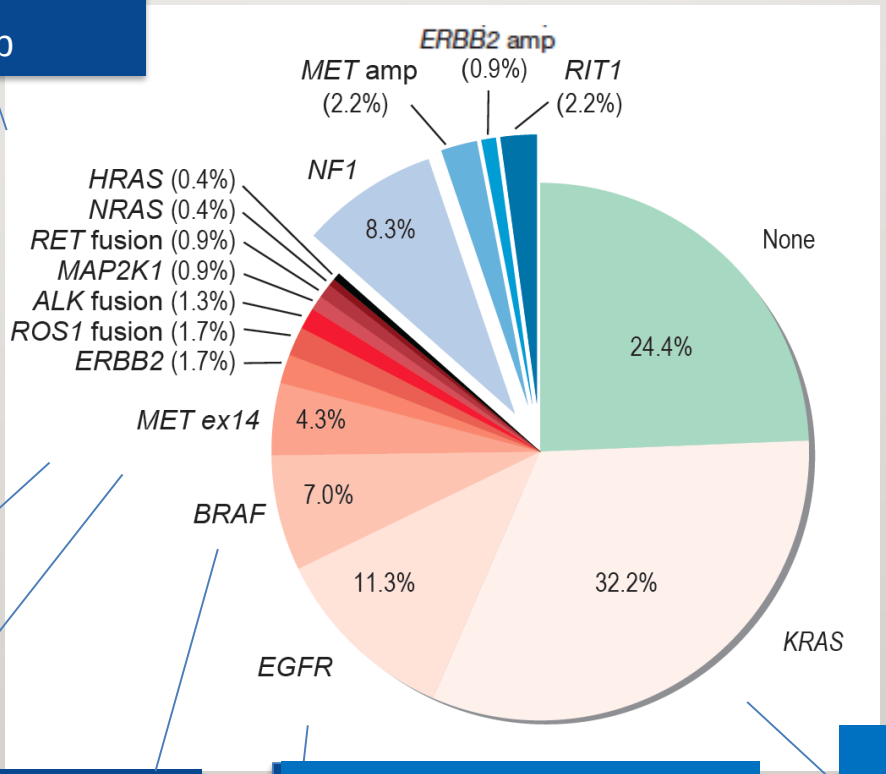
RET: 40% RR to Cabozantinib

ALK: 65% RR to Crizotinib; ~70% RR to 2° Gen TKI Ceritinib in resistant cancers

ROS1: 70% RR to Crizotinib

HER2 (*ERBB2*) mutation: >50% RR to Afatinib; ~20% RR to Dacomitinib

MET exon 14: >50% RR to Crizotinib



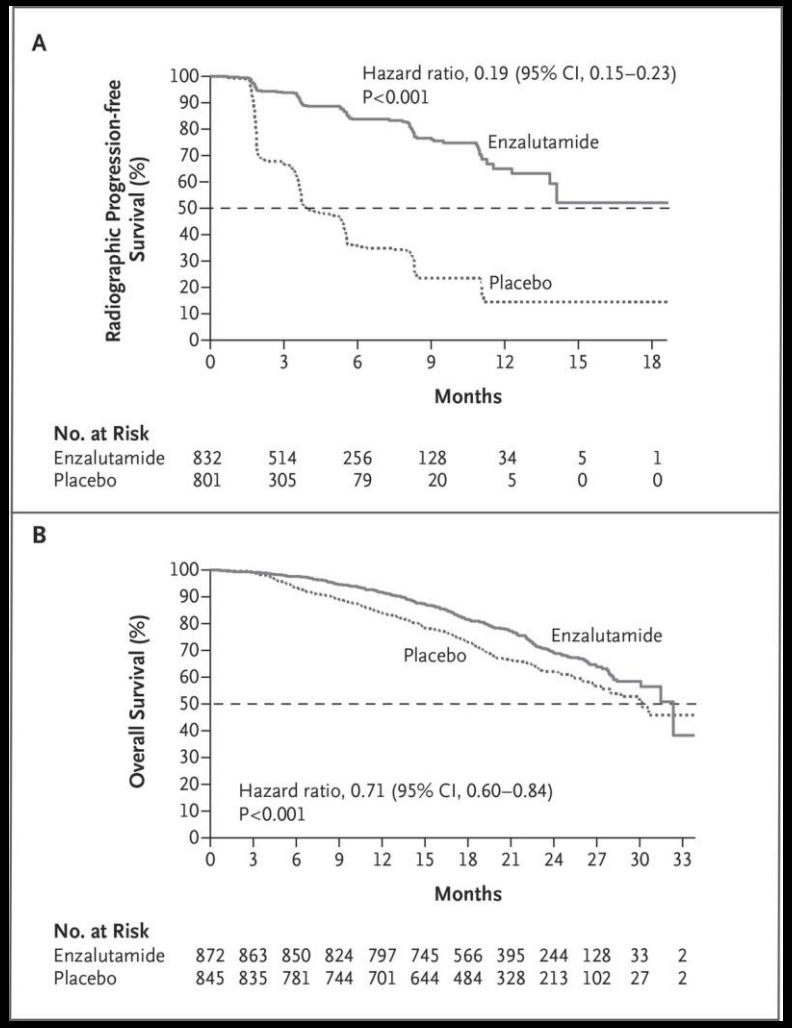
BRAF (V600E): >60% RR to *BRAF* + *MEK* inhibitor combo

EGFR: >70% RR to 1°-2° Gen TKIs; ~60% RR to 3° Gen TKIs in resistant cancers

KRAS: 35% RR to *MEK* inhibitors + Chemotherapy

TCGA 2014 *Nature*

Kaplan–Meier Estimates of Radiographic Progression-free Survival and Overall Survival.



Beer TM et al. N Engl J Med 2014;371:424-433.

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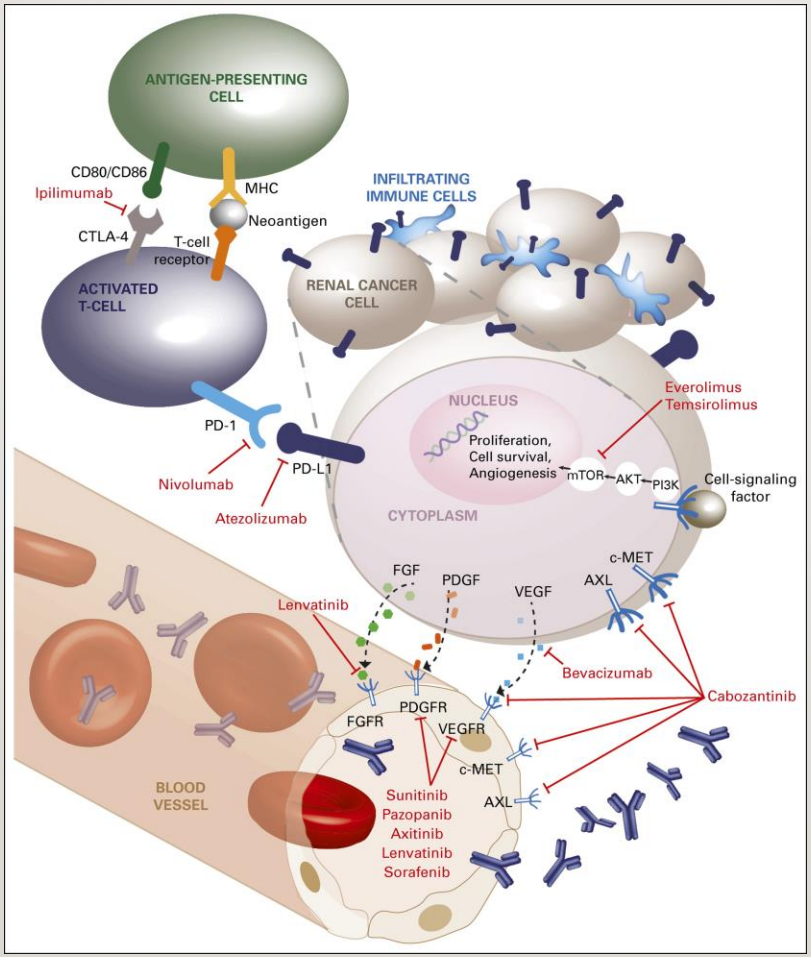
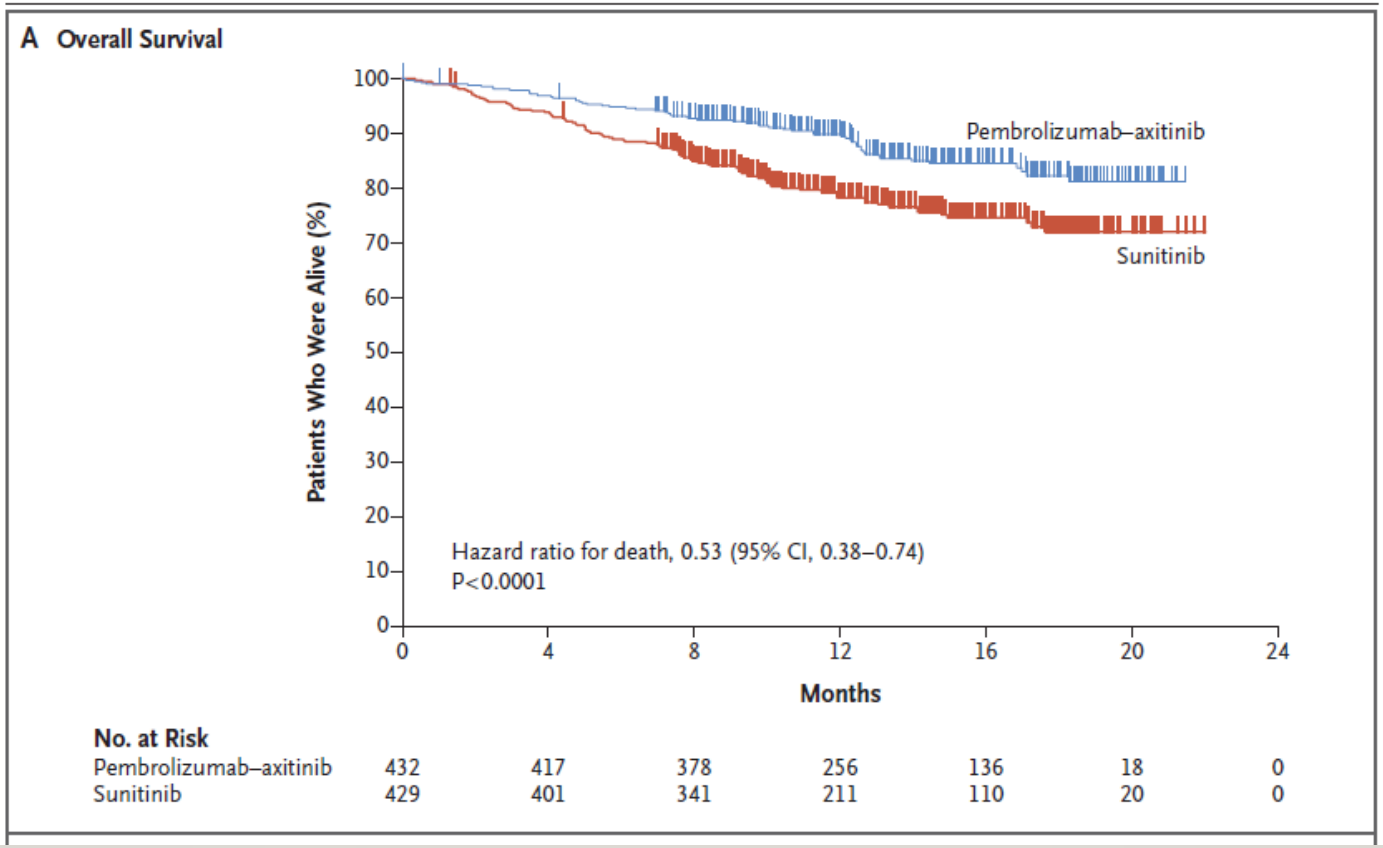


Fig 1. Mechanism of actions of active drugs for advanced and metastatic renal cell carcinoma.

Published in: Rana R. McKay; Dominick Bossé; Toni K. Choueiri; *Journal of Clinical Oncology* 2018 363615-3623.
DOI: 10.1200/JCO.2018.79.0253

PEMBROLIZUMAB PLUS AXITINIB FOR RENAL-CELL CARCINOMA



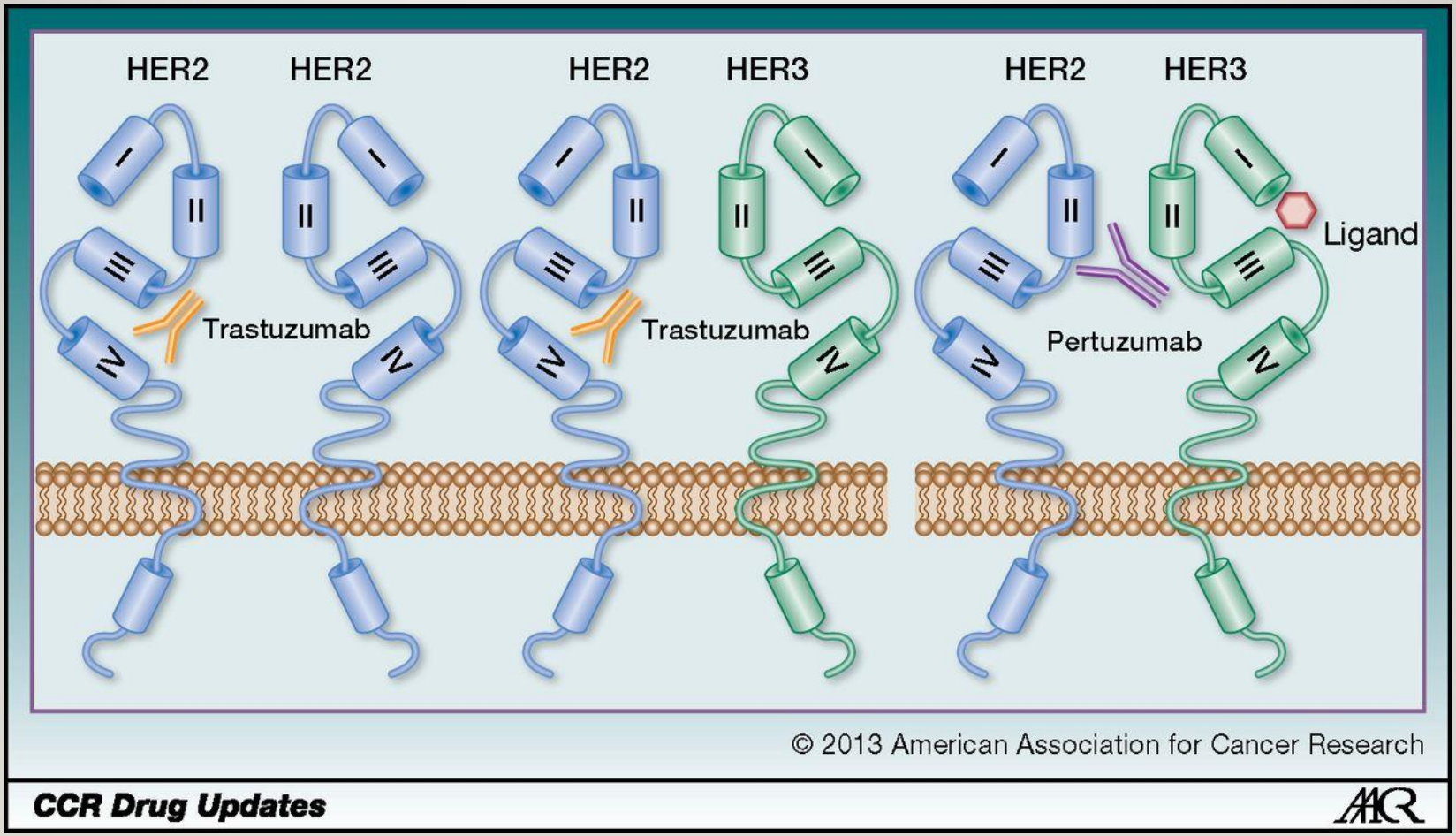
NEW ENGLAND J MED 2019;380:1116-27.
DOI: 10.1056/NEJMOA1816714

- Silver Bullets

TARGETED CHEMOTHERAPY THE SILVER BULLET

- Immuno-Chemotherapy
  - Breast Cancer
  - Diffuse Large cell Lymphoma
  - Hodgkin's lymphoma
  - T cell lymphoma
- Immuno-radiotherapy lymphoma

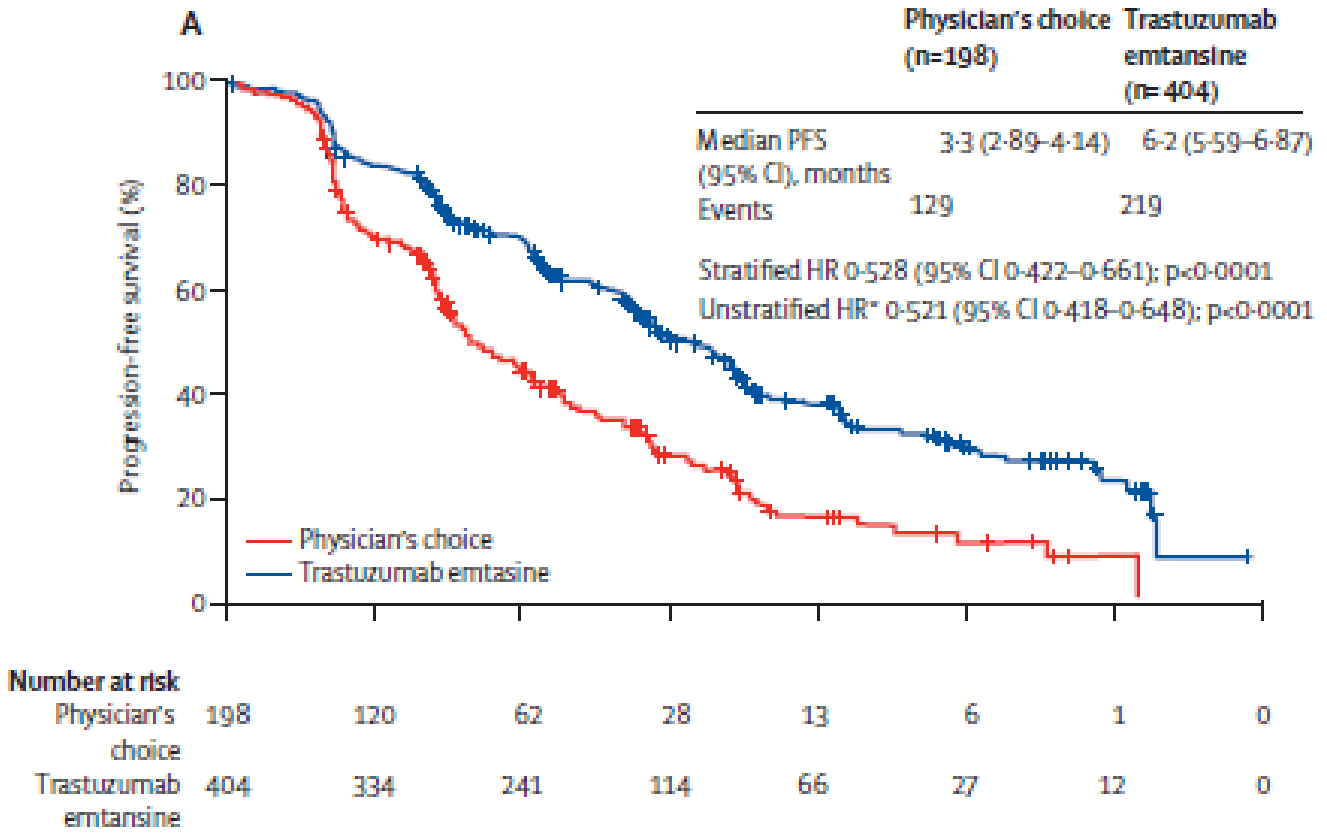
The mechanism of action of pertuzumab and trastuzumab.



Otto Metzger-Filho et al. Clin Cancer Res 2013;19:5552-5556

TDM-1 BREAST CANCER

KROP, ET AL. LANCET ONCOL 2014;15:689-699



TOXICITIES

IMMUNOTHERAPIES

1. Colitis
2. Pneumonitis
3. Nephritis
4. Endocrine
5. Cutaneous

TARGETED THERAPIES

1. Cutaneous
2. GI
3. Hand-Foot
4. Fatigue
5. Hypertension
6. Renal

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion

GASTROINTESTINAL ADVERSE EVENT(S)

- Diarrhea
- Colitis[a]

ASSESSMENT/GRADING

Mild (G1)[b] → **MANAGEMENT[f]**
- Consider holding immunotherapy[g]
- Loperamide or diphenoxylate/atropine
- Hydration
- Close monitoring[h]

Moderate (G2)[c] or Severe (G3–4)[d]
- Stool evaluation to rule out infectious etiology[e]
  - Nucleic acid amplification tests (NAATs) for GI pathogens/bacterial culture
  - C. difficile
  - Ova & parasites; molecular testing for *Giardia* and *Cryptosporidium* spp and *E. histolytica*; consider microsporidia, *Cyclosporal/isospora* spp
  - Viral pathogens testing when available
  - Based on institutional availability, consider lactoferrin/calprotectin
- Consider abdominal/pelvic CT with contrast
- Consider GI consultation
  - Colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy (EGD) with biopsy

MANAGEMENT[f]

Moderate (G2)[c]
- Hold immunotherapy[g]
- Prednisone/methylprednisolone[i] 1 mg/kg/day[j]
- No response in 2–3 days:
  - Increase dose to 2 mg/kg/day[j]
  - Consider adding infliximab[k]

Severe (G3–4)[d]
- G3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity[g]
- G4: Permanently discontinue immunotherapy agent responsible for toxicity[g]
- Consider inpatient care for provision of supportive care
- Intravenous (IV) methylprednisolone[i] (2 mg/kg/day)[j]
  - No response in 2 days:
    - ◊ Continue steroids, consider adding infliximab[k]
    - ◊ If infliximab-refractory, consider vedolizumab

[a] Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever. Blood in the stools and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including peptic ulcer disease (PUD) and malignant bleeding.

[b] Fewer than 4 bowel movements above baseline per day and no colitis symptoms.

[c] 4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.

[d] More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (eg, ischemic bowel, perforation, toxic mega-colon).

[e] It is not necessary to wait for test results before providing therapy to manage immune-related adverse events (irAEs).

[f] See Principles of Immunosuppression (IMMUNO-A).

[g] See Principles of Immunotherapy Rechallenge (IMMUNO-C).

[h] If progressive, consider stool evaluation to rule out infectious etiology.

[i] Convert to prednisone when appropriate.

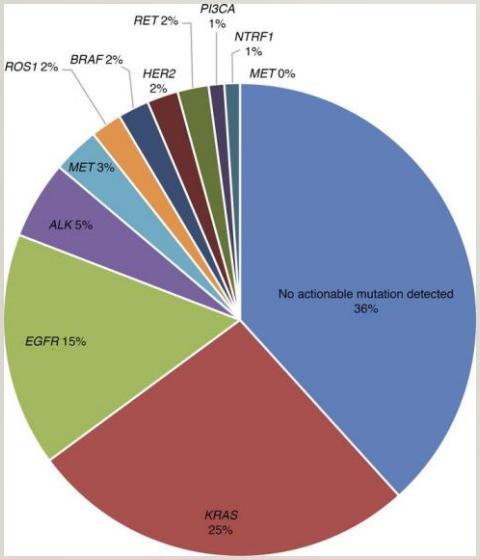
[j] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

[k] Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers is not clearly defined, but is usually a single dose. Repeat endoscopy may be helpful, but optional for the guidance of treatment. (See Principles of Immunosuppression [IMMUNO-A] regarding TB testing.)

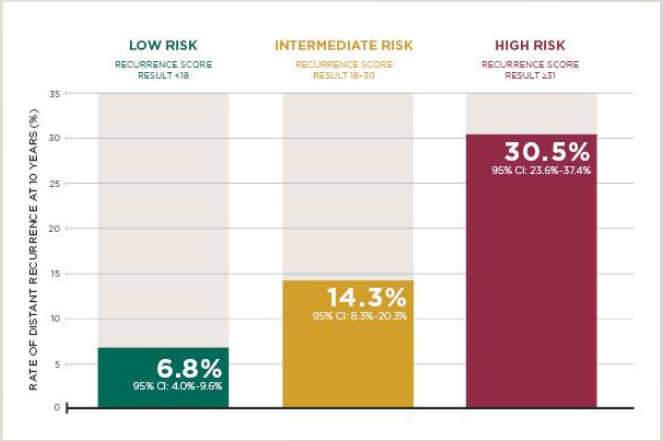
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

DIAGNOSTICS

NEXT GEN SEQUENCING

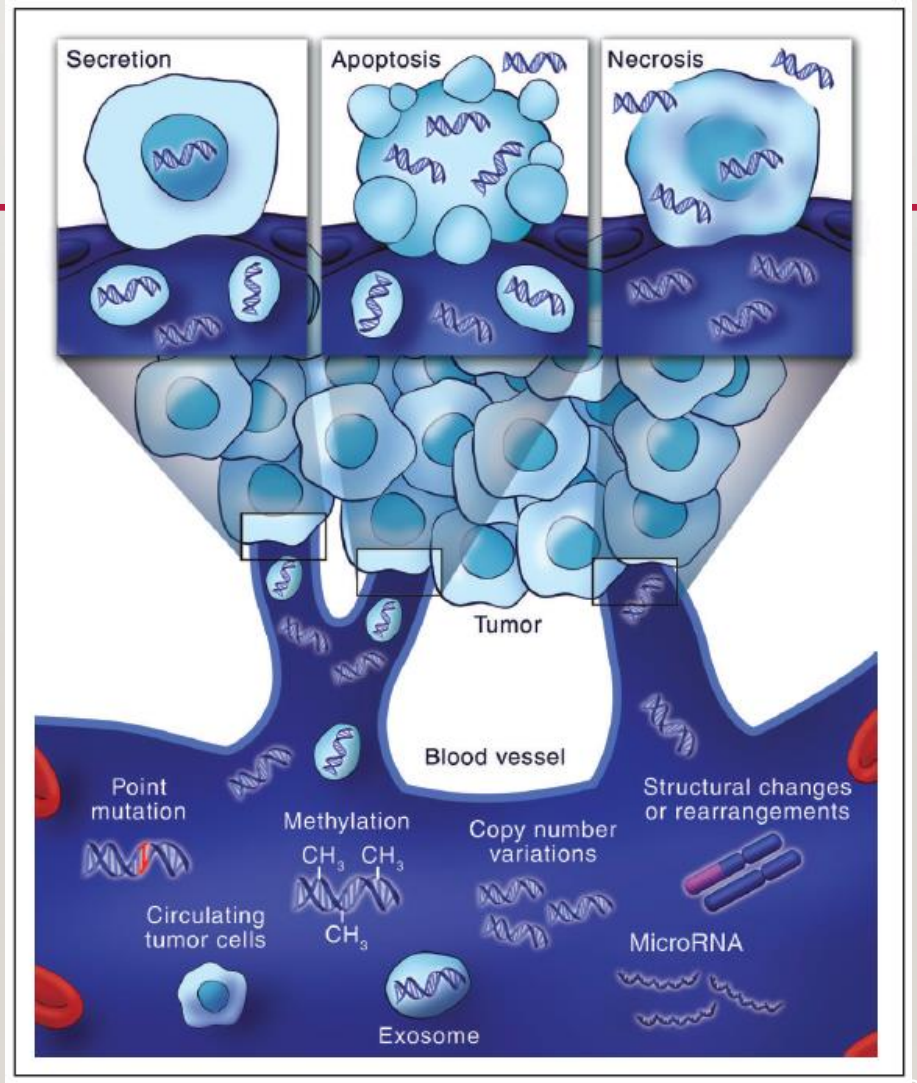


ONCOTYPE DX



PROBING THE BLOOD FOR TUMOR MATERIAL

CTCs
ctDNA
miRNA
Exosomes
Methylation
Proteins

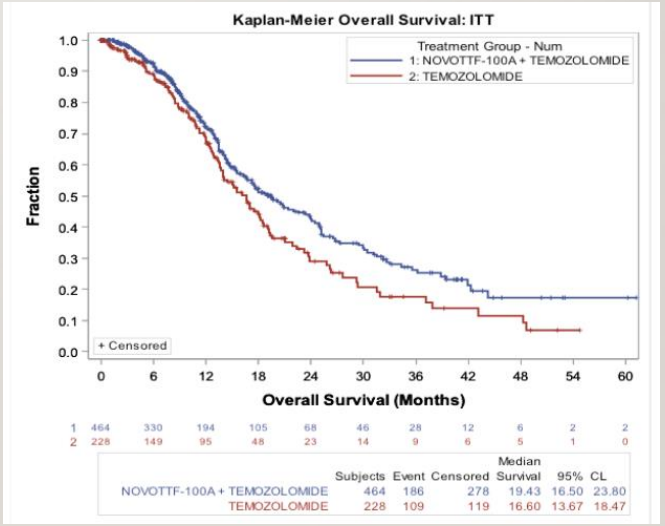


source: Diaz, JCO; 2014

GLIOBLASTOMA

TUMOR TREATING FIELDS (TTFIELDS): A NOVEL TREATMENT MODALITY ADDED TO STANDARD CHEMO AND RADIOTHERAPY IN NEWLY DIAGNOSED GLIOBLASTOMA—FIRST REPORT OF THE FULL DATASET OF THE EF14 RANDOMIZED PHASE III TRIAL. ASCO 2015 ABSTRACT #2000

24 MONTH OS 43% VS 29%,

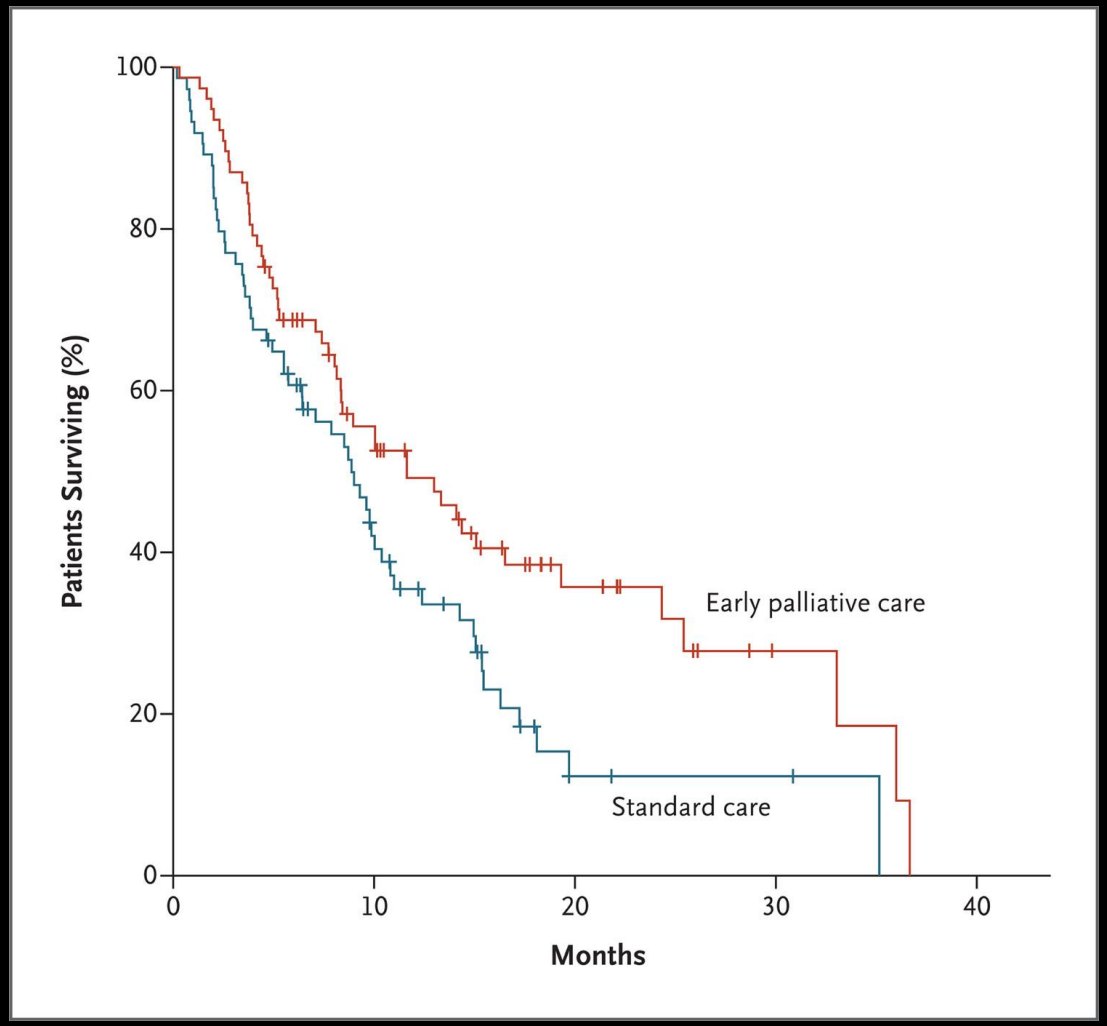


AVOID SURGERY?

Organ Preservation in Responders With Rectal Cancer

- A retrospective review of patients at Memorial Sloan Kettering Cancer Center showed that patients with stage I to III rectal cancer who achieved a clinical complete response to neoadjuvant therapy can often forego resection.
- Cohorts with clinical complete responses and those with pathologic complete responses who underwent surgery had similar disease-free survival and overall survival.
- Of the nonoperatively managed patients, 77% had rectal preservation.
- The local recurrence rate was 26%; all but one patient was successfully salvaged.

Kaplan–Meier Estimates of Survival According to Study Group.



Temel JS et al. N Engl J Med 2010;363:733-742.

The NEW ENGLAND JOURNAL of MEDICINE

NON SMALL CELL LUNG CANCER

1. Resection alone if node negative and < 4 cm
2. Resection with adjuvant chemotherapy if > 4 cm or node positive
3. Chemotherapy and radiation followed by checkpoint inhibition if mediastinal nodes involved
4. Resection with stereotactic radiation for cure if solitary brain met
5. Checkpoint inhibition and chemotherapy if advanced disease
6. Checkpoint inhibition only if PD L1 > 50%
7. Stereotactic radiation ablation of oligo-metastasis

BREAST CANCER

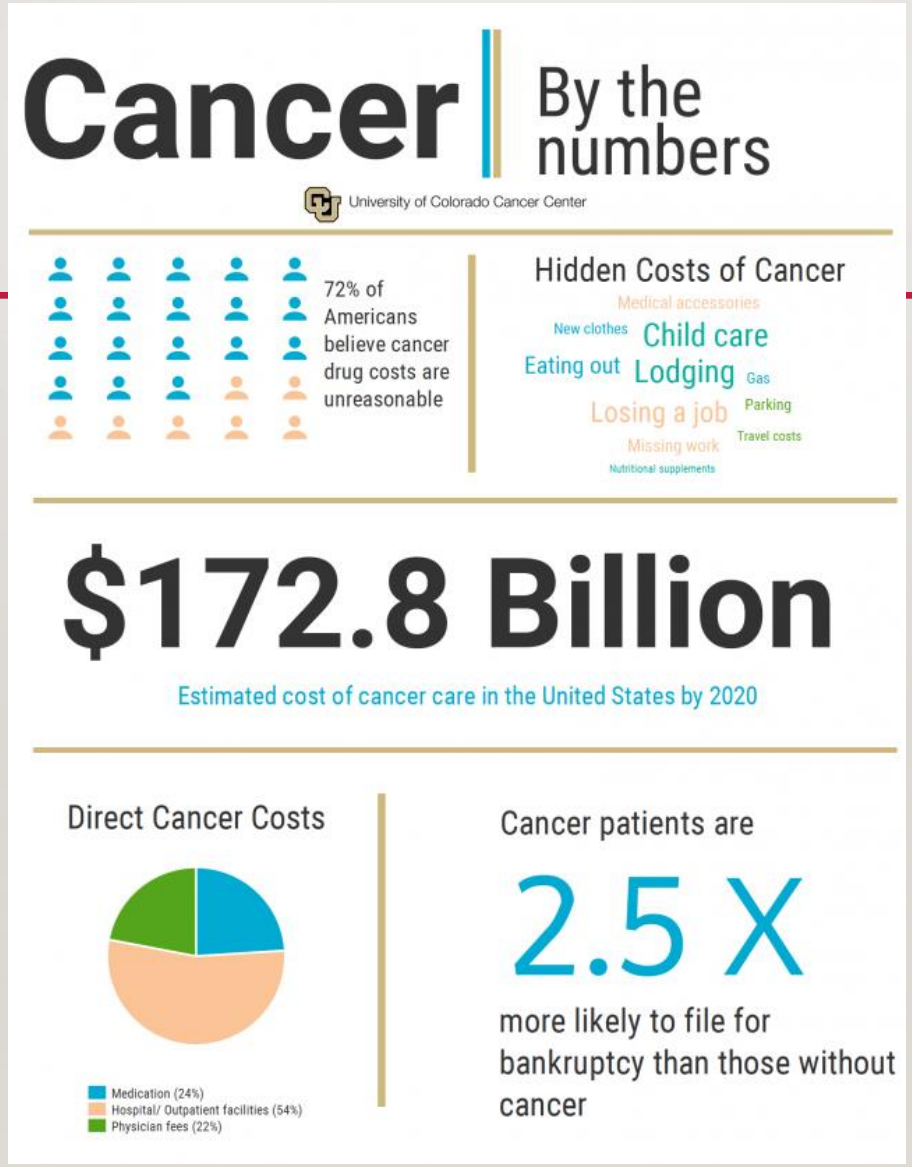
1. Resection with no adjuvant chemotherapy for most tumors < 1 cm
2. Lumpectomy plus radiation equivalent to mastectomy when possible
3. Axillary lymph node dissection not necessary if no clinically positive nodes and positive sentinel nodes < 3.
4. Adjuvant hormonal therapy for all hormone receptor positive
5. Adjuvant chemotherapy for most patients with lymph node positive, guided by Oncotype DX
6. Adjuvant chemotherapy for all hormone receptor negative cancers > 1 cm
7. Trastuzumab adjuvant therapy for all Her 2 positive patients > .5 cm
8. Hormonal therapy for all metastatic hormone sensitive patients with or without CDK4/6 inhibitors as first line
9. Her 2 therapies for Her 2 positive metastatic disease
10. Chemotherapy eventually for most metastatic cancer

PROSTATE CANCER

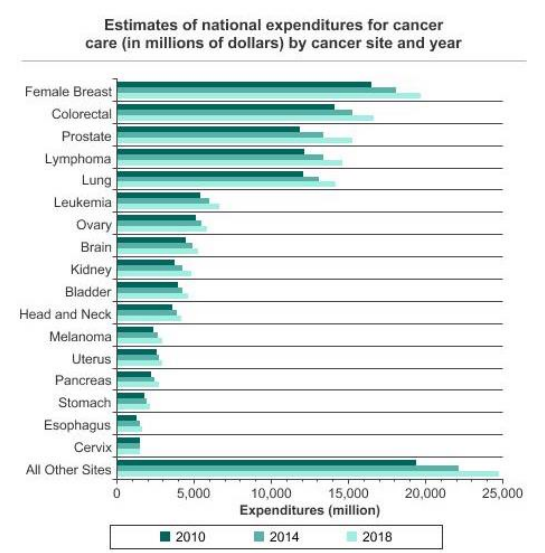
1. Screening with PSA reasonable after discussions
2. Resection or radiation if localized and likely to affect mortality
3. Active surveillance if not likely to affect mortality
4. Observation or hormonal therapy if biochemical relapse without metastases
5. Hormone reduction therapy if hormone sensitive metastatic disease with addition of either short course chemotherapy, androgen blockade or testosterone production inhibitor (abiraterone)
6. Consideration of second generation androgen blocker for castrate resistant biochemical-only relapse
7. Chemotherapy, abiraterone, second generation androgen blocker for metastatic castrate resistant disease
8. Bisphosphonates or Rank ligand inhibitor for bone disease
9. Radiation if needed for painful metastases
10. Checkpoint inhibitors or PARP inhibitors for certain molecular types

COLORECTAL CANCER

1. Resection only of most tumors with negative nodes for colon lesions; for rectal cancer, same if tumor does not invade through bowel wall and nodes negative
2. Adjuvant chemotherapy if node positive or high risk node negative: 3-6 months depending on number of nodes
3. Adjuvant chemotherapy and radiation for rectal cancers through bowel wall or node positive: preop, postop or total neoadjuvant
4. Resection for cure with solitary or oligo metastases to liver, lung or brain
5. Chemotherapy with anti EGFR therapy for metastatic disease from left sided colon lesions if mutations negative
6. Chemotherapy +/- bevacizumab if right sided or mutation positive
7. Targeted therapies for specific mutations
8. Checkpoint inhibition for MSI high, mismatch repair gene mutations.


Cancer
By the numbers
University of Colorado Cancer Center
72% of Americans believe cancer drug costs are unreasonable
Hidden Costs of Cancer
Medical accessories
New clothes
Child care
Eating out
Lodging
Gas
Parking
Losing a job
Travel costs
Missing work
Nutritional supplements
$172.8 Billion
Estimated cost of cancer care in the United States by 2020
Direct Cancer Costs
Medication (24%)
Hospital/ Outpatient facilities (54%)
Physician fees (22%)
Cancer patients are
2.5 X
more likely to file for bankruptcy than those without cancer

137.4 BILLION DOLLARS 2010



Source: Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the U.S.: 2010-2020. J Natl Cancer Inst 2011; 103(2):117-28.
Cancer Prevalence and Cost of Care Projections: http://costprojections.cancer.gov/
Cost estimates expressed in 2010 dollars using CMS cost adjusters and adjusted for out-of- pocket expenditures, including co-payments and deductibles
Estimates for the population younger than 65 were developed using ratios of cost in the younger than 65 and older 65 populations from studies conducted in managed care populations.

JAMA Internal Medicine | Original Investigation

Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval

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Table 2. Recent Cancer Drug Indications That Received Accelerated Approval From US Food and Drug Administration Without Overall Survival Changes in the Postapproval Trial

Drug	Indication	Basis for Accelerated Approval	Primary End Point for Confirmatory RCTs	Results of Confirmatory RCTs	Current FDA Status
Bevacizumab	Glioblastoma	RR in phase 2	OS	OS HR, 0.95 (95% CI, 0.74-1.21); $P = .65$ PFS improved[25]	Converted to regular approval
Nivolumab	Melanoma after ipilimumab/ BRAF-inhibitor	RR in phase 3	OS	OS HR, 0.95 (95.54% CI, 0.73-1.24) PFS not improved[26]	Submitted/undecided (April 2019 status: delayed)
Atezolizumab	Urothelial	RR in phase 2	OS	OS HR, 0.87 (95% CI, 0.63-1.21); $P = .41$ PFS not improved[27]	Submitted/undecided (April 2019 status: submitted)
Pembrolizumab	Head and neck cancer	RR in phase 2	OS	OS HR, 0.82 (95% CI, 0.67-1.01) in 2018 OS HR, 0.80 (95% CI, 0.65-0.98) PFS not improved[24]	Submitted/undecided[a] (April 2019 status: delayed)

Abbreviations: FDA, US Food and Drug Administration; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized clinical trial; RR, response rate.

[a] This trial was considered as "confirmation of benefit" for our analysis.

UNDERSTAND LEGITIMATE GOALS OF CARE VS SURROGATE GOALS OF CARE

LEGITIMATE

- Cure
- Prolong survival
- Improve quality of life
- Prevent impending disaster

SURROGATE

- Response rate
- Time to progression
- Progression free survival
- Metastasis free survival
- Phase II trials