Cancer Biology Course

Tuesdays, 12 noon,

All students, postdocs, faculty, staff welcome

Schedule for 2016 Course

1/12	Cancer Biology Pathway Luncheon	
1/19	Lee Ratner, MD, PhD	Introduction of Oncology, chapter 2
1/26	Jason Weber PhD	Cell Cycle Regulation, chapter 8
2/2	Ron Bose, MD, PhD ^	Cytoplasmic Signaling, chapter 6
2/9	Amy Barone, MD *	Perspective on New Challenges in Oncology Drug Regulation in the Era of Genomics, chapter 16
2/16	Luis Batista, PhD	Immortalization and Cancer, chapter 10
2/23	Vivek Arora, MD, PhD	Nuclear Receptors in Prostate Cancer, chapter 5
3/1	Blair Madison, PhD	Multistep Colon Carcinogenesis, chapter 11
3/8	Terrence Wong, MD, PhD	p53 and Cancer, chapter 9
3/15	Chris Maher, PhD	Long Non-Coding RNAs in Cancer,
3/22	Mark Krasnow *	Lung Development and Cancer, chapter 13
3/29	Saima Waqar, MD, and Len Maggi, PhD	Genomics of Lung Cancer, Chapters 4 and 7
4/5	Jian Campian, MD, PhD and Milan Chheda, MD	Neural Stem Cells and Cancer, chapter 12
4/12	Jackie Payton, MD, PhD	Epigenomic Regulation of Cancer, chapter 1
4/19	Student Selected Speaker	TBD
4/26	Student Selected Speaker	TBD

Attendance of all sessions & **active** discussion esp during presentation classic paper

Introduction

- Nature of Cancer
- Advance in Cancer Research 2015

See Weinberg, Chap 2, Nature of Cancer

JCO Mar 2015, Clinical Cancer Advances

deVita NEJM 2012 History of Cancer

Hanahan & Weinberg Cell, 2011

Cancer – Historical Perspective

1600 BC Egyptian physician record 1st description of breast cancer

460 BC Hippocrates uses “carcinos” to describe tumors (Greek – crab)

129 AD Galen attributed cancer to black bile

1660 Mastectomy for breast cancer

1713 Ramazzini noted lack of cervical ca but increased breast ca in nuns

1775 Pott described scrotal cancer in chimney sweeps

1838 Muller described cancer as abnormalities of cells

Table 1. Singular Discoveries and Major Events in the Cancer Field and Changing Relative Survival Rates for Patients with Cancer in the United States, 1863–2006.*

Year	Discovery or Event	Relative Survival Rate
1863	Cellular origin of cancer (Virchow)	
1889	Seed-and-soil hypothesis (Paget)	
1914	Chromosomal mutations in cancer (Boveri)	
1937	Founding of NCI	
1944	Transmission of cellular information by DNA (Avery)	
1950	Availability of cancer drugs through Cancer Chemotherapy National Service Center	
1953	Report on structure of DNA	35%
1961	Breaking of the genetic code	
1970	Reverse transcriptase	
1971	Restriction enzymes Passage of National Cancer Act	
1975	Hybridomas and monoclonal antibodies Tracking of cancer statistics by SEER program	50%
1976	Cellular origin of retroviral oncogenes	
1979	Epidermal growth factor and receptor	
1981	Suppression of tumor growth by p53	
1984	G proteins and cell signaling	
1986	Retinoblastoma gene	
1990	First decrease in cancer incidence and mortality	
1991	Association between mutation in APC gene and colorectal cancer	
1994	Genetic cancer syndromes Association between *BRCA1* and breast cancer	
2000	Sequencing of the human genome	
2002	Epigenetics in cancer MicroRNAs in cancer	
2005	First decrease in total number of deaths from cancer	68%
2006	Tumor stromal interaction	

Cancer in the US

1.6 million new cases this year

21% decrease in cancer-related deaths in men vs 1990s

12% decline in women

13 million cancer survivors alive in US

Cancer-related death rates decline 1.5%/yr

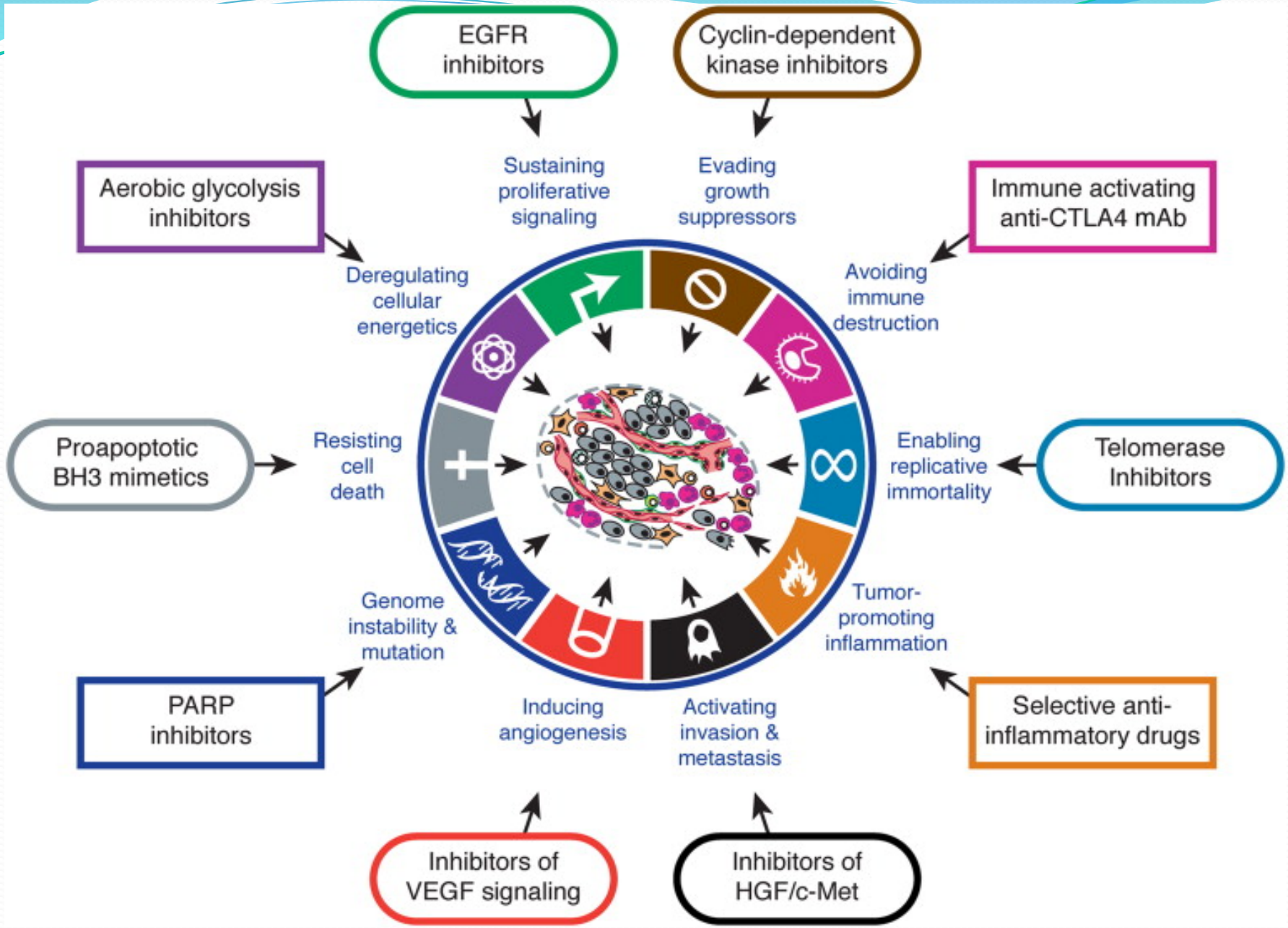
580,000 Americans died of cancer in 2013

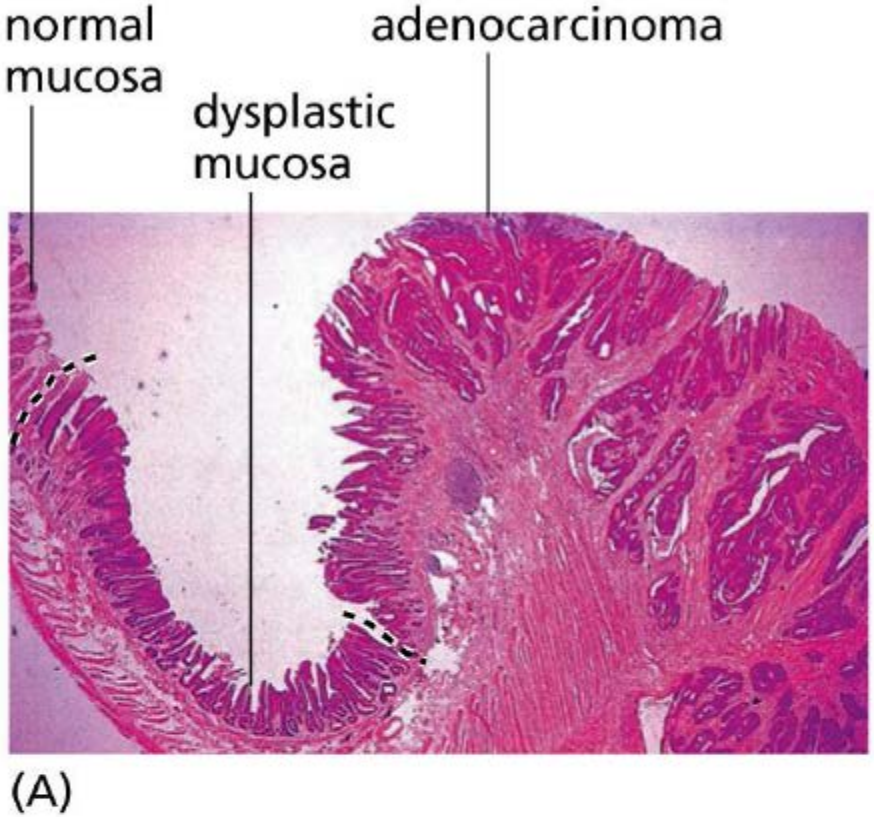
Leading New Cancer Cases and Deaths – 2014 Estimates

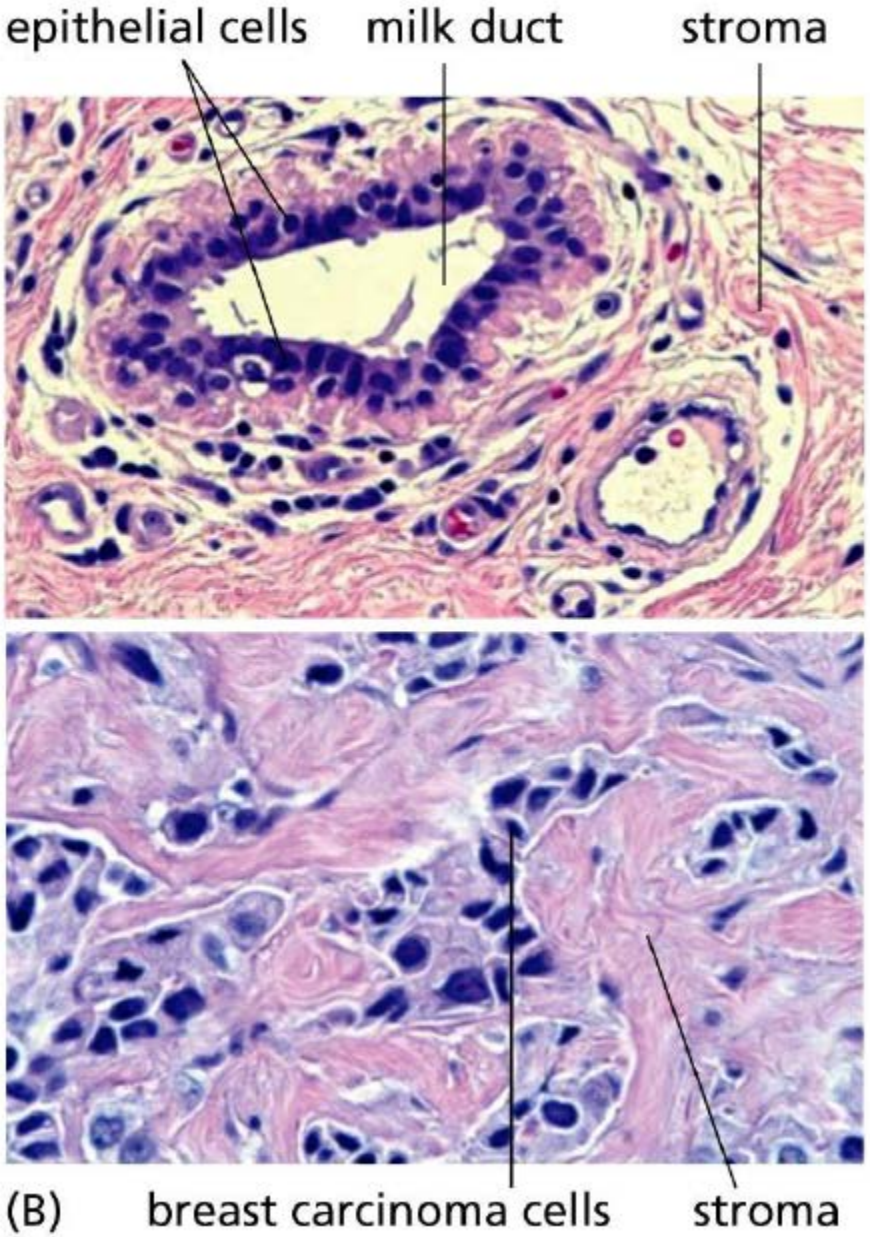
Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 233,000 (27%)	Breast 232,670 (29%)	Lung & bronchus 86,930 (28%)	Lung & bronchus 72,330 (26%)
Lung & bronchus 116,000 (14%)	Lung & bronchus 108,210 (13%)	Prostate 29,480 (10%)	Breast 40,000 (15%)
Colon & rectum 71,830 (8%)	Colon & rectum 65,000 (8%)	Colon & rectum 26,270 (8%)	Colon & rectum 24,040 (9%)
Urinary bladder 56,390 (7%)	Uterine corpus 52,630 (6%)	Pancreas 20,170 (7%)	Pancreas 19,420 (7%)
Melanoma of the skin 43,890 (5%)	Thyroid 47,790 (6%)	Liver & intrahepatic bile duct 15,870 (5%)	Ovary 14,270 (5%)
Kidney & renal pelvis 39,140 (5%)	Non-Hodgkin lymphoma 32,530 (4%)	Leukemia 14,040 (5%)	Leukemia 10,050 (4%)
Non-Hodgkin lymphoma 38,270 (4%)	Melanoma of the skin 32,210 (4%)	Esophagus 12,450 (4%)	Uterine corpus 8,590 (3%)
Oral cavity & pharynx 30,220 (4%)	Kidney & renal pelvis 24,780 (3%)	Urinary bladder 11,170 (4%)	Non-Hodgkin lymphoma 8,520 (3%)
Leukemia 30,100 (4%)	Pancreas 22,890 (3%)	Non-Hodgkin lymphoma 10,470 (3%)	Liver & intrahepatic bile duct 7,130 (3%)
Liver & intrahepatic bile duct 24,600 (3%)	Leukemia 22,280 (3%)	Kidney & renal pelvis 8,900 (3%)	Brain & other nervous system 6,230 (2%)
All sites 855,220 (100%)	All sites 810,320 (100%)	All sites 310,010 (100%)	All sites 275,710 (100%)

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Therapeutic Targeting of the Hallmarks of Cancer







Normal vs Neoplastic Tissue

What are characteristic pathologic features of cancer?

Tumor classification hierarchy

I - Differentiation state
1 - Epithelial
2 - Nonepithelial
3 - Mixed

II - Embryonic origin
1 - Ectoderm
2 - Endoderm
3 - Mesoderm

III - Biological behavior
1 - Benign
2 - Malignant

Differentiation state - I
EPITHELIAL

Embryonic derivation Ectoderm

Bilayer epithelium

Cell type
breast
sweat glands
salivary glands

Benign
adenoma
Malignant
adenocarcinoma

Multi-layer epithelium

Cell Type:
skin
keratinocytes

Benign:
papilloma
Malignant:
squamous
cell carcinoma

Embryonic derivation Endoderm

Single-layer epithelium

Cell type
thyroid
lung
stomach
liver
pancreas
small intestine
colon
prostate

Benign
adenoma
Malignant
adenocarcinoma

Multi-layer epithelium

Cell Type
bladder

Benign
papilloma
Malignant
transitional cell
carcinoma

Embryonic derivation Mesoderm

Single-layer epithelium

Cell type
kidney
testis
endometrium

Benign
adenoma
Malignant
adenocarcinoma

Differentiation state - III
MIXED multilineage

Cell type: germ cell
Benign: dermoid cyst
Malignant: embryonal carcinoma, teratoma

Cell Type: somatic cell
Benign: hamartoma, adenomyoma, mixed tumor of salivary glands
Malignant: Wilms tumor, mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma

Differentiation state - II
NONEPITHELIAL

Embryonic derivation Mesoderm

Stromal (mesenchymal)

Cell type	*Tumor name* *Benign*	*Malignant*
fibroblasts	fibroma	fibrosarcoma
fat cells	lipoma	liposarcoma
bone	osteoma	osteosarcoma
cartilage	chondroma	chondrosarcoma
smooth muscle	leiomyoma	leiomyosarcoma
endothelial cell	hemangioma	hemangiosarcoma

Hematopoietic

Cell type	*Tumor name*
lymphocyte	lymphoma
leukocyte	leukemia

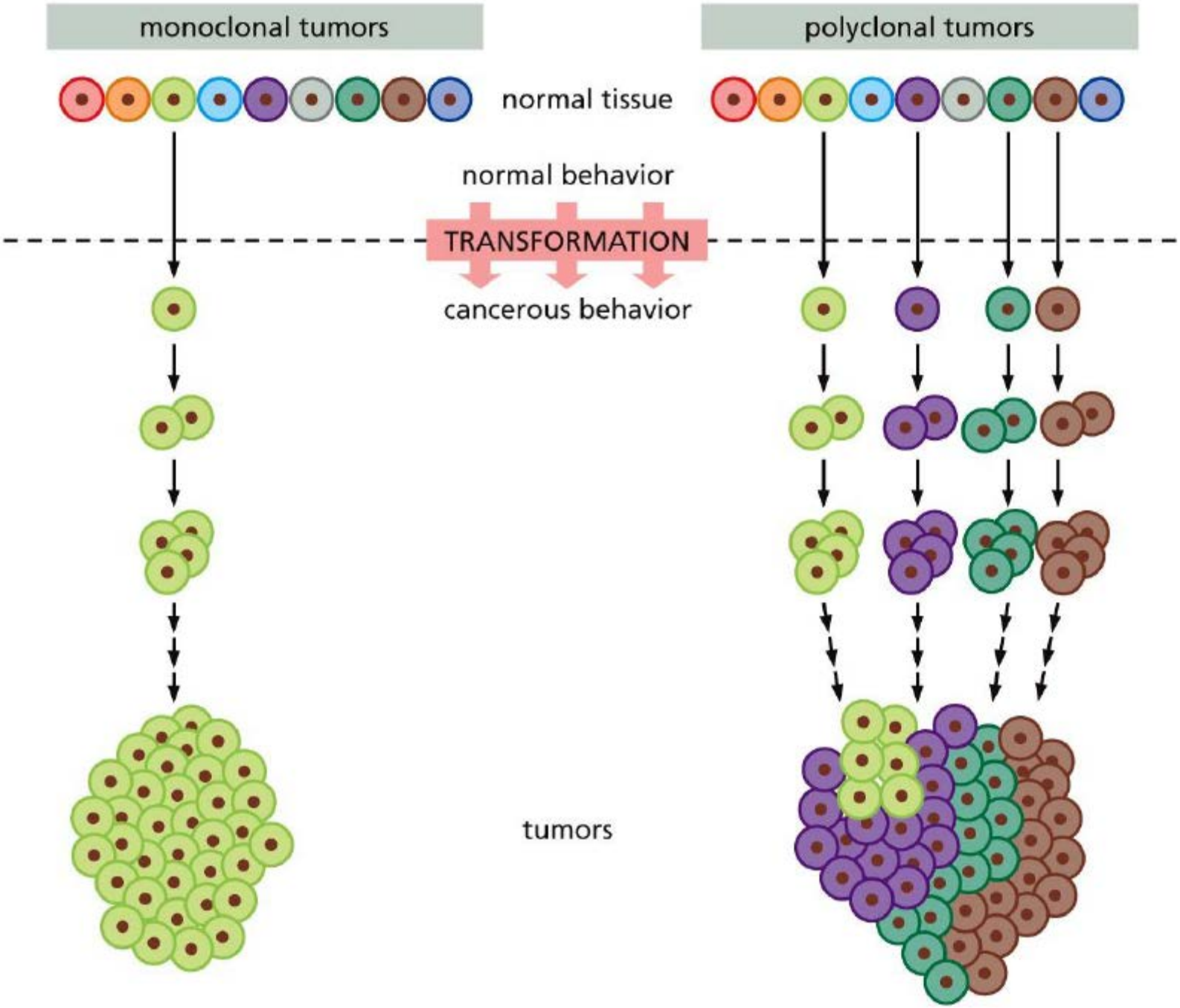
Embryonic derivation Neuro-ectoderm

Nervous system

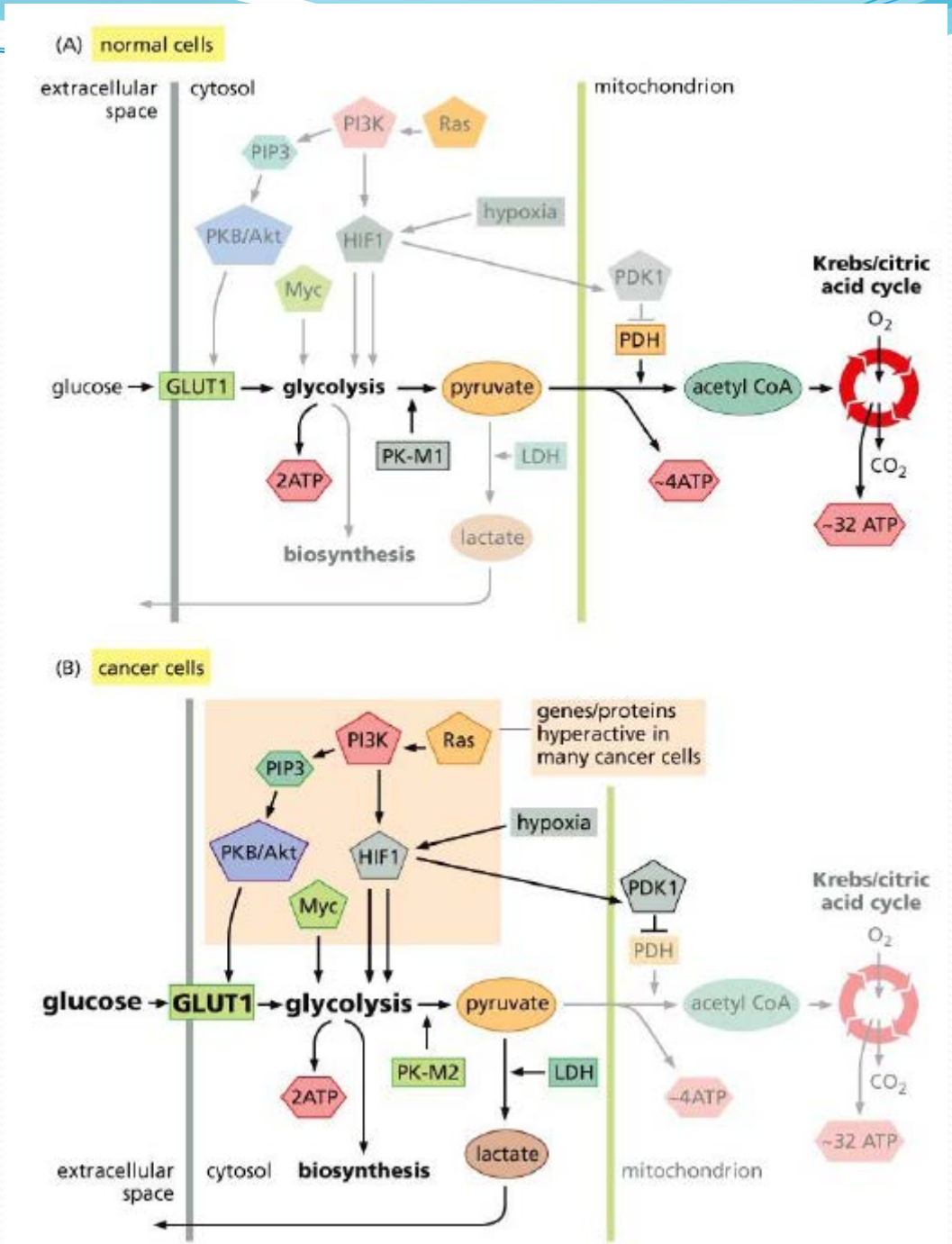
Cell type	*Tumor name*
astrocyte	astrocytoma
retina	retinoblastoma
oligodendrocyte	oligodendroglioma
schwann	schwannoma

Other

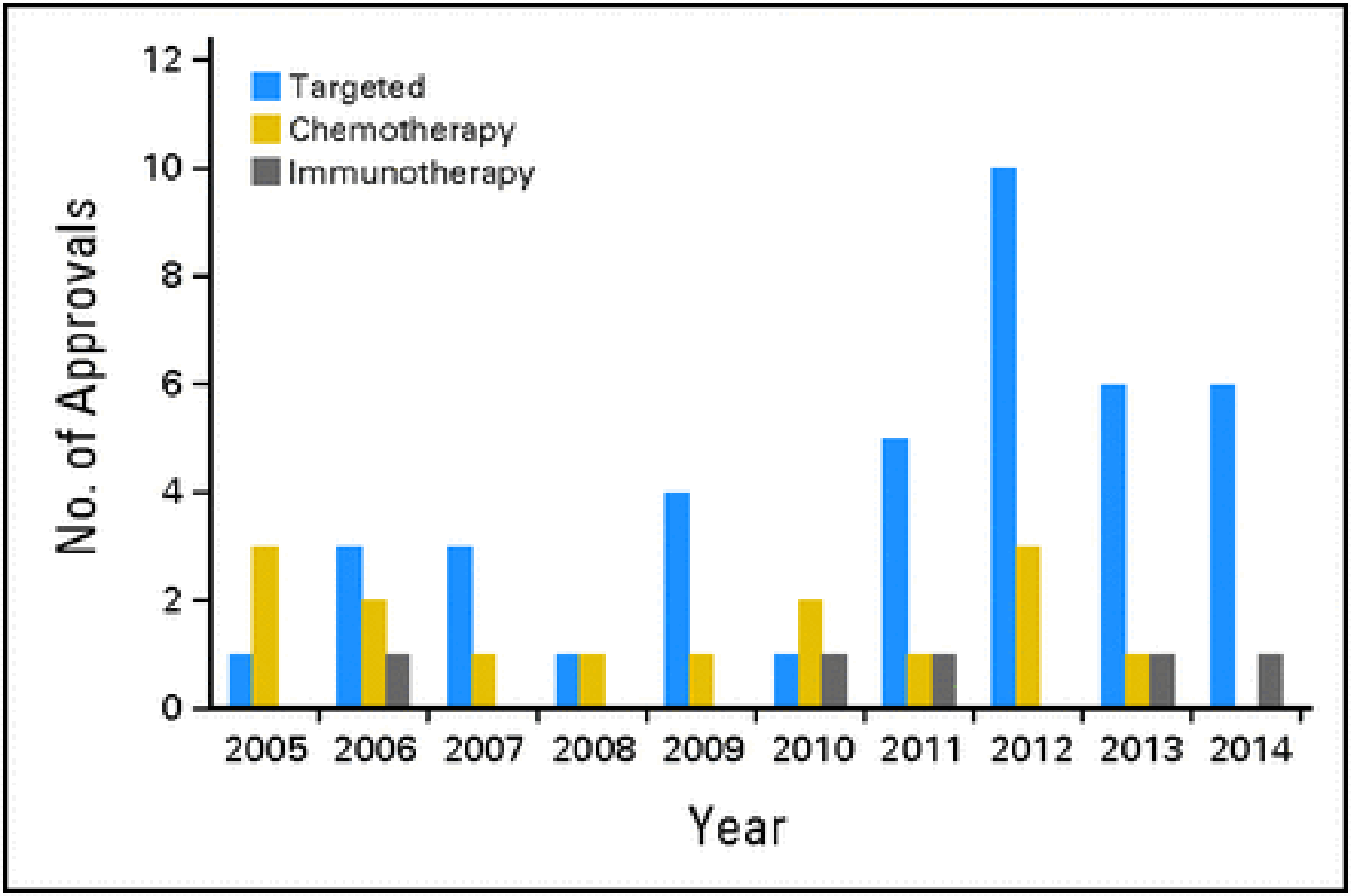
melanocyte	melanoma


monoclonal tumors
polyclonal tumors
normal tissue
normal behavior
TRANSFORMATION
cancerous behavior
tumors

Abnormal Metabolism in Cancer



New Drug Approvals 2014



2015 Cancer Drug Approvals

Alecensa (alectinib); Roche; For the treatment of ALK-positive, metastatic non-small cell lung cancer , Approved December 2015

Cotellic (cobimetinib) ; Genentech; For the treatment of BRAF V600E or V600K melanoma, Approved November 2015

Darzalex (daratumumab); (anti-CD38) Janssen Biotech; For the treatment of multiple myeloma, Approved Nov

Empliciti (elotuzumab); (anti-SLAMF7) Bristol-Myers Squibb; For the treatment of patients with multiple myeloma who have received prior therapies, Approved November 2015

Farydak (panobinostat); Novartis; For the treatment of multiple myeloma, Approved February 2015

Ibrance (palbociclib); Pfizer; For the treatment of ER-positive, HER2-negative breast cancer, Approved February 2015

Imlygic (talimogene laherparepvec) ; (HSV) Amgen; For the treatment of unresectable recurrent melanoma, Approved October 2015

Lenvima (lenvatinib); Eisai; For the treatment of thyroid cancer, Approved February 2015

Lonsurf (trifluridine and tipiracil); Taiho Oncology; For the treatment of metastatic colorectal cancer , Approved September 2015

Ninlaro (ixazomib); Millennium Pharmaceuticals; For the treatment of multiple myeloma, Approved November 2015

Odomzo (sonidegib); Novartis; For the treatment of locally advanced basal cell carcinoma, July 2015

Onivyde (irinotecan liposome injection); Merrimack; For the treatment of metastatic pancreatic cancer following gemcitabine-based therapy, Approved October 2015

Opdivo (nivolumab); Bristol-Myers Squibb; For the treatment of metastatic squamous non-small cell lung cancer, Approved March 2015

Portrazza (necitumumab) (anti-EGFR) ; Eli Lilly; For the treatment of metastatic squamous non-small cell lung cancer, Approved November 2015

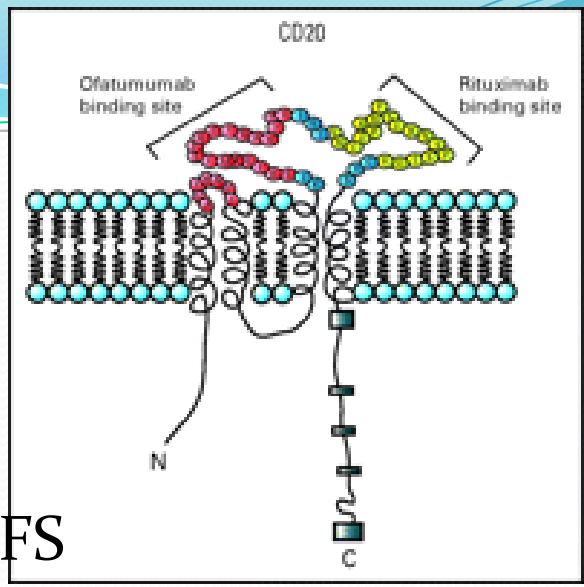
Tagrisso (osimertinib); AstraZeneca; For the treatment of EGFR T790M mutation positive non-small cell lung cancer , Approved November 2015

Unituxin (dinutuximab); United Therapeutics; For the treatment of pediatrics with high-risk neuroblastoma, Approved March 2015

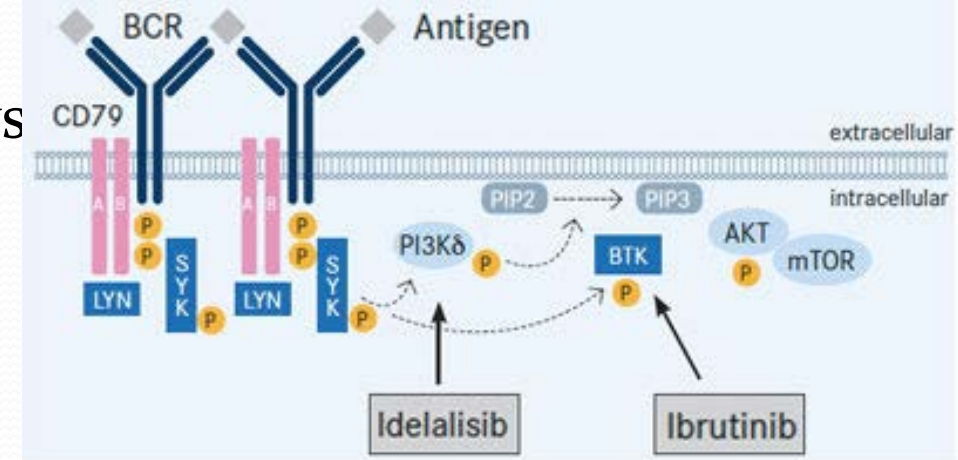
Varubi (rolapitant); Tesaro; For the prevention of delayed nausea and vomiting associated with chemotherapy, Approved September 2015

Yondelis (trabectedin); Janssen; For the treatment of liposarcoma or leiomyosarcoma, Approved October 2015

Advance of the Year – CLL - 2014

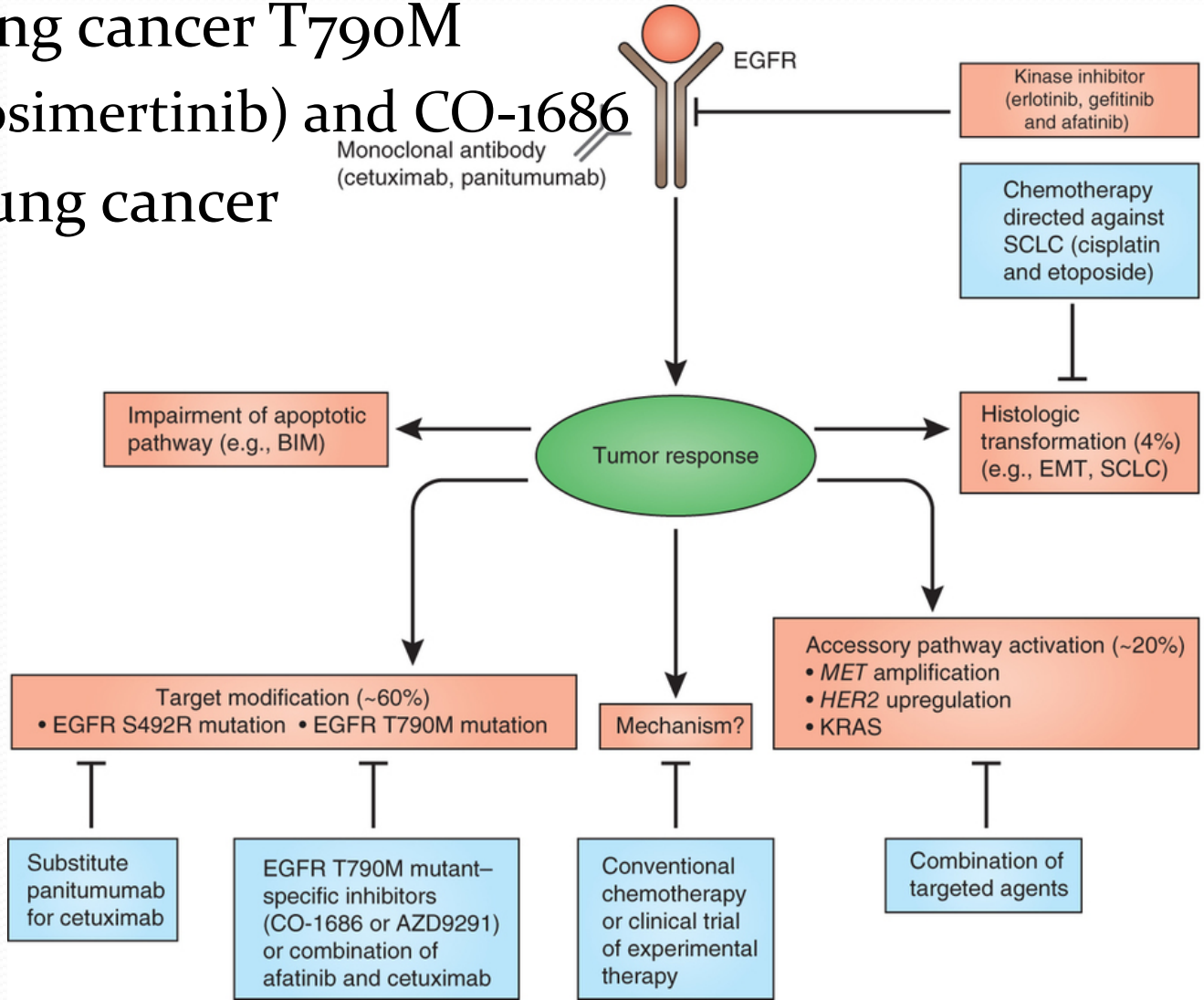


- Newly Diagnosed CLL
  - Obinutuzumab (obinut-chlorambucil vs rituimxab-chlorambucil 23 vs 11 m DFS
  - Ofatumumab (ofat-chlorambucil vs chlorambucil 22.4 vs 13.1 m DFS)
- Relapsed CLL
  - Ibrutinib (Ibrutinib vs Ofatumumab 90% vs 81% 12 m OS)
  - Idelalisib (Idelalisib-Rit vs Rit 10.7 vs 5.5 m DFS)



Overcoming Treatment Resistance

- EGFR mut lung cancer T790M
  - AZD9291 (osimertinib) and CO-1686
- EML4-ALK lung cancer
  - Ceritinib



Therapy-Resistant Gastric Cancer

- Ramucirumab (5.2 vs 3.8 mo OS)

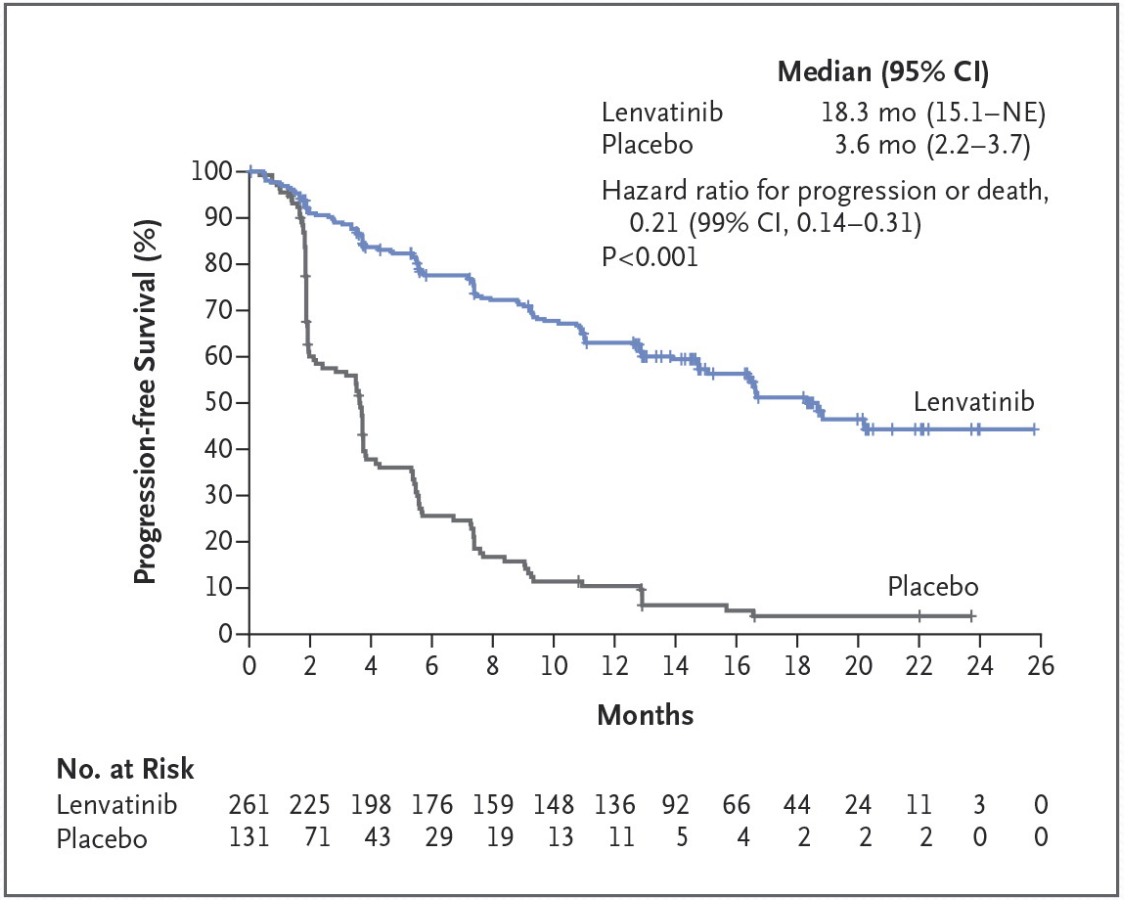
Agents Targeting VEGF Receptors

Class	Examples	Targets	Stage of Development
Tyrosine kinase inhibitors[a]	Sunitinib	VEGFR-2, PDGFR, c-Kit	Approved RCC and GIST
	Sorafenib	VEGFR-2, Raf, VEGFR-1	Approved RCC and HCC
	Pazopanib	VEGFR-2, PDGFR, c-Kit	Approved RCC
	Axitinib	VEGFR-1/2, c-Kit, PDGFR	Approved RCC
	Tivozanib	VEGFR-1, -2, -3	Phase 3
Antibodies[b]	Ramucirumab (IMC 1121B)	VEGFR-2	Phase 2

[a] Eliceiri BP, Cheresh DA. *Cancer J.* 2000;6:S245-S249; Nelson AR, et al. *J Clin Oncol.* 2000;18:1135-1149; Hasan J, Jayson GC. *Expert Opin Biol Ther.* 2001;1:703-718; Hennequin LF, et al. *J Med Chem.* 2002;45:1300-1312. [b] Spratlin JL. *J Clin Oncol.* 2010;28:780-787.

RAI-Resistant Thyroid Cancer

- Lenvatinib – (NEJM Feb 2015) – blocks VEGFR2 and 3



Geographic Variation in Cancer Incidence & Death Rates

Countries showing highest and lowest incidence of specific types of cancer[a]			
Cancer site	Country of highest risk	Country of lowest risk	Relative risk H/L[b]
Skin (melanoma)	Australia (Queensland)	Japan	155
Lip	Canada (Newfoundland)	Japan	151
Nasopharynx	Hong Kong	United Kingdom	100
Prostate	U.S. (African American)	China	70
Liver	China (Shanghai)	Canada (Nova Scotia)	49
Penis	Brazil	Israel (Ashkenazic)	42
Cervix (uterus)	Brazil	Israel (non-Jews)	28
Stomach	Japan	Kuwait	22
Lung	U.S. (Louisiana, African American)	India (Madras)	19
Pancreas	U.S. (Los Angeles, Korean American)	India	11
Ovary	New Zealand (Polynesian)	Kuwait	8
Geographic areas showing highest and lowest death rates from specific types of cancer[c]			
Cancer site	Area of highest risk	Area of lowest risk	Relative risk H/L[b]
Lung, male	Eastern Europe	West Africa	33
Esophagus	Southern Africa	West Africa	16
Colon, male	Australia, New Zealand	Middle Africa	15
Breast, female	Northern Europe	China	6

Environmental and lifestyle factors known or suspected to be etiologic for human cancers in the United States[a]	
Type	**% of total cases[b]**
Cancers due to occupational exposures	1–2
Lifestyle cancers	
Tobacco-related (sites: e.g., lung, bladder, kidney)	34
Diet (low in vegetables, high in nitrates, salt) (sites: e.g., stomach, esophagus)	5
Diet (high fat, low fiber, broiled/fried foods) (sites: e.g., bowel, pancreas, prostate, breast)	37
Tobacco plus alcohol (sites: mouth, throat)	2

Specific carcinogenic agents implicated in the causation of certain cancers[c]	
Cancer	**Exposure**
Scrotal carcinomas	chimney smoke condensates
Liver angiosarcoma	vinyl chloride
Acute leukemias	benzene
Nasal adenocarcinoma	hardwood dust
Osteosarcoma	radium
Skin carcinoma	arsenic
Mesothelioma	asbestos
Vaginal carcinoma	diethylstilbestrol
Oral carcinoma	snuff
ER+ breast cancer[d]	hormone replacement therapy (E + P)[e]

Advances in Prevention & Screening

- Obesity – 84,000 cancers/yr – esophagus, pancreas, colon, breast, endometrium, kidney, thyroid, gall bladder
- HPV screening with Pap q 3 yrs
- Breast Cancer
  - Anastrazole decreased risk of breast cancer 50% in high risk women (similar or greater than tamoxifen, raloxifene, exemestane)
- Lung Cancer
  - Low dose CT screening for age 55-80 with >30 pack-yr smoking and have quit <15 yo ago
  - miRNA profiling may decrease false-positive 5-fold

Low-Dose CT Screening for Lung Cancer (NEJM 2013)

- A total of 53,439 eligible participants were randomly assigned to a study group (26,715 to low-dose CT and 26,724 to chest radiography)
- Lung cancer was diagnosed in 292 participants (1.1%) in the low-dose CT group versus 190 (0.7%) in the radiography group (stage 1 in 158 vs. 70 participants)
- Sensitivity and specificity were 73.4% and 93.8% for low-dose CT and 73.5% and 91.3% for chest radiography, respectively.

CANCER RESEARCH PROGRESS THREATENED

Cancer touches us all. The need for continued progress is urgent and growing.

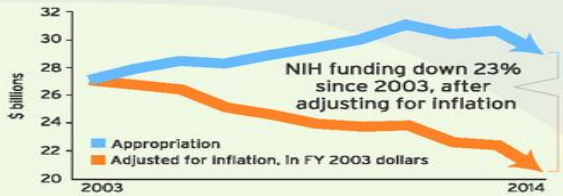
Nearly **1** in every **4** deaths in the U.S. is caused by cancer[1]

Over **1.6 MILLION AMERICANS** received a new cancer diagnosis in the past year. By 2030, this number will increase **45%**[1,2]

Yet federal funding for cancer research is at the **lowest point in decades...**

...Putting U.S. scientific leadership **in jeopardy**

National Institutes of Health Budget FY2003-2013[3]



Russia increasing basic research funding 65%[4]

Europe increasing research spending 40% over seven years

China announced a 26% boost in basic research funding in 2012

NIH research funding cuts harm us all

FEWER CLINICAL TRIAL OPTIONS FOR CANCER PATIENTS

Patient Enrollment in NIH's Clinical Trials Network[5]

29,000 PATIENTS IN 2009

20,000 PATIENTS in 2013

NEW TREATMENTS DELAYED

U.S. oncologists report:[6]

- **75%** Current funding situation is directly impacting their ability to conduct cancer research
- **38%** Reduced time spent on research
- **26%** Delayed launching a clinical trial

HARM TO LOCAL ECONOMIES

$1 = $2.21

For **every one NIH grant dollar cut, $2.21 will be lost** in local economies through lost business activity, jobs and wages[7]

IT'S TIME TO RE-IGNITE OUR NATION'S COMMITMENT TO CANCER RESEARCH.

ASCO is calling on Congress to provide a **strong investment for NIH in 2016** to sustain the search for cures.

Sources:
1. American Cancer Society. Cancer Facts & Figures 2014. Atlanta: American Cancer Society; 2014.
2. Smith B, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol* 27:2758-2765, 2009.
3. One Voice Against Cancer. *Impact of Sequestration Cancer Research* [Fact Sheet]. Published June 2013.
4. NIH Director: Impending NIH Budget Cut Would Be 'Devastating' [ASCO in Action News Brief]. Published March 27, 2012.
5. Comis R: Implementing a National Cancer Clinical Trials System for the 21st Century: Workshop #2. Presented at the National Cancer Policy Forum Workshop, Washington, DC, February 11, 2013.
6. American Society of Clinical Oncology. Impact Survey: Federal Funding Cuts to Cancer Research [Press Release]. Published September 16, 2013.
7. Families USA's Global Health Initiative. *In Your Own Backyard: How NIH Funding Help's Your State's Economy*. Published June 2008.

For more information, go to: www.CancerProgress.Net ASCO

Gregory A. Masters et al. JCO
doi:10.1200/JCO.2014.59.9746