The evolution of cancer therapy

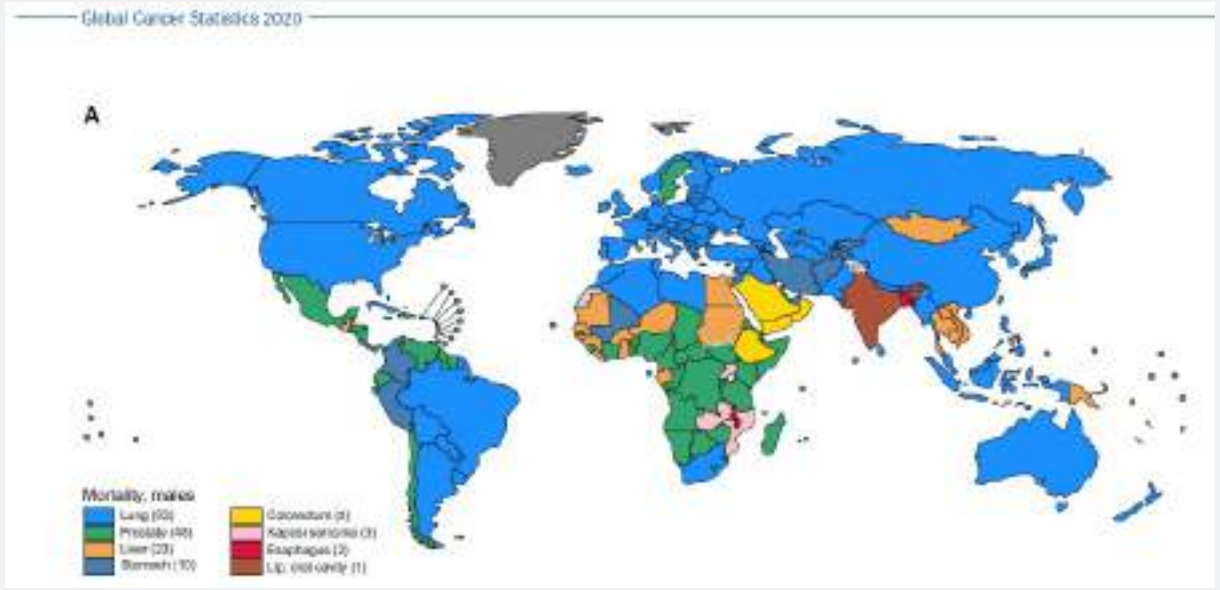
Alessandro Comandone

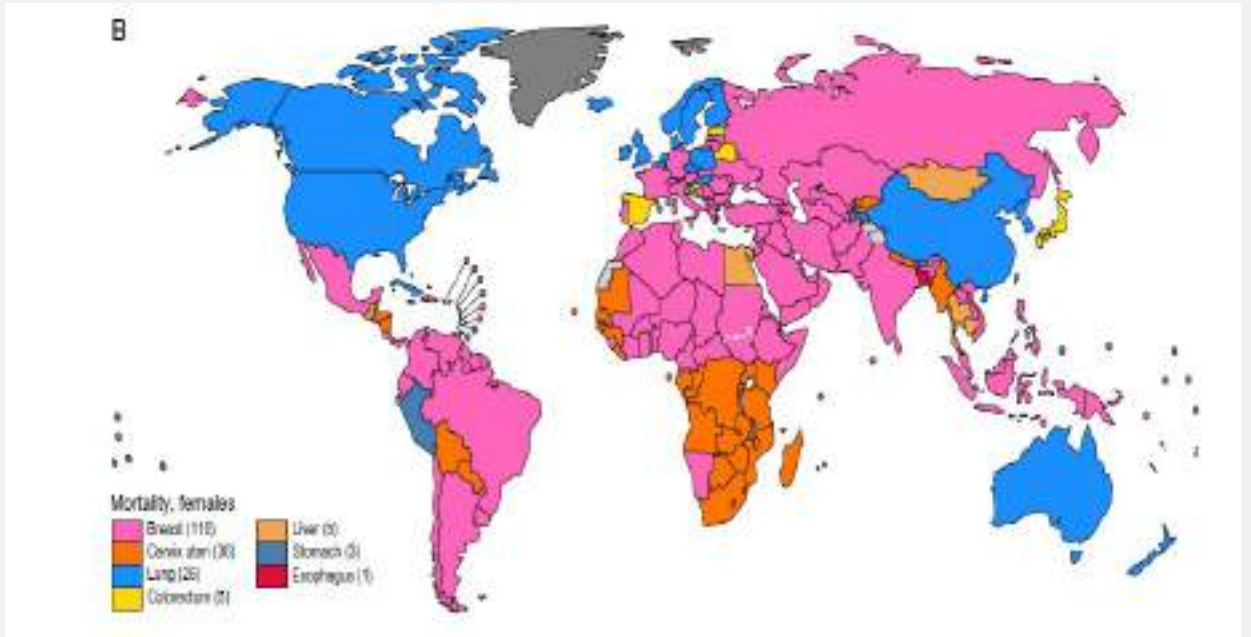
SC ONCOLOGIA ASL CITTA' DI TORINO

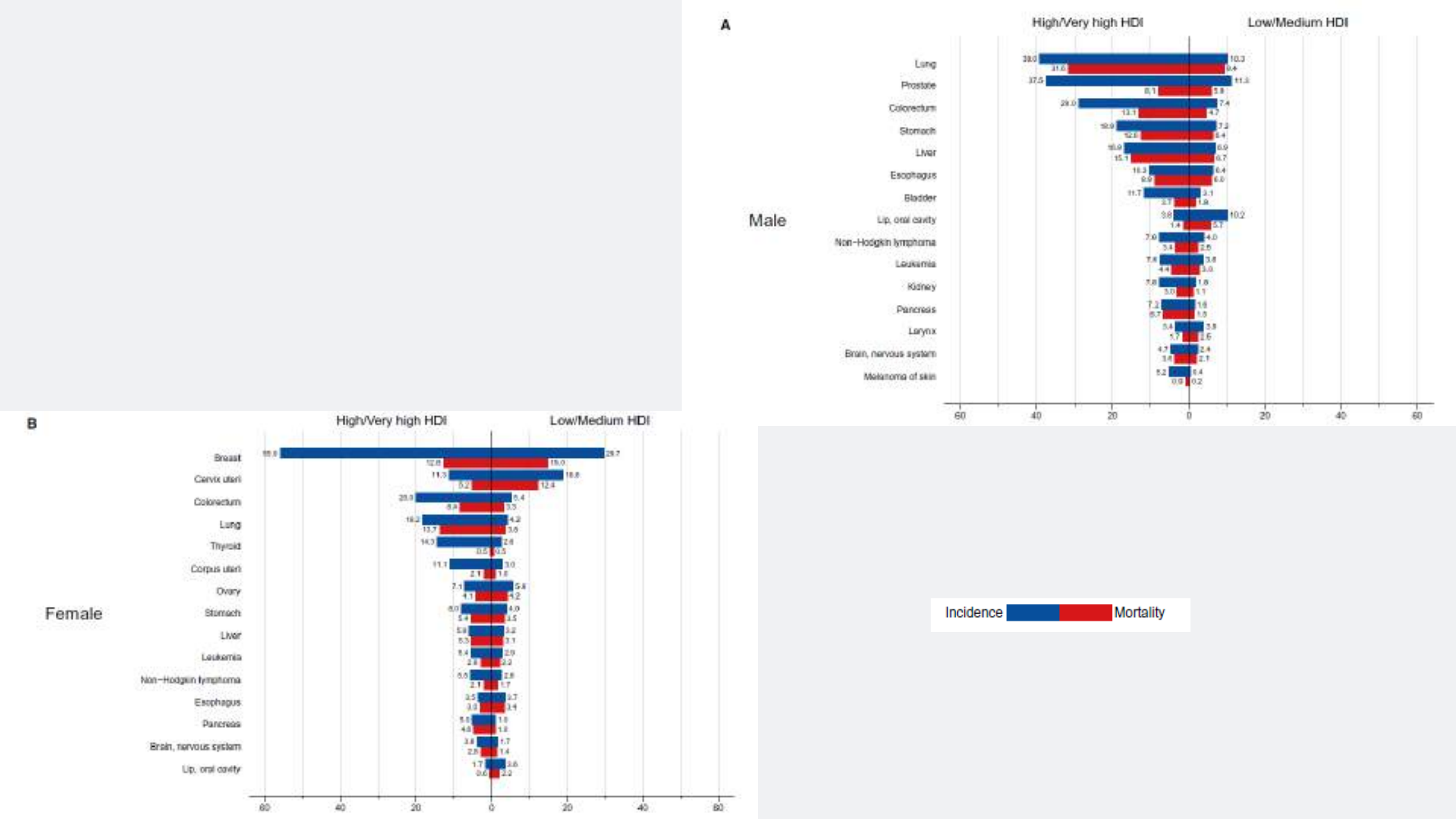
CA CANCER J CLIN 2021;71:209-249

Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries

Hyuna Sung, PhD [1]; Jacques Ferlay, MSc, ME[2]; Rebecca L. Siegel, MPH [1]; Mathieu Laversanne, MSc[2]; Isabelle Soerjomataram, MD, MSc, PhD[2]; Ahmedin Jemal, DMV, PhD[1]; Freddie Bray, BSc, MSc, PhD[2]



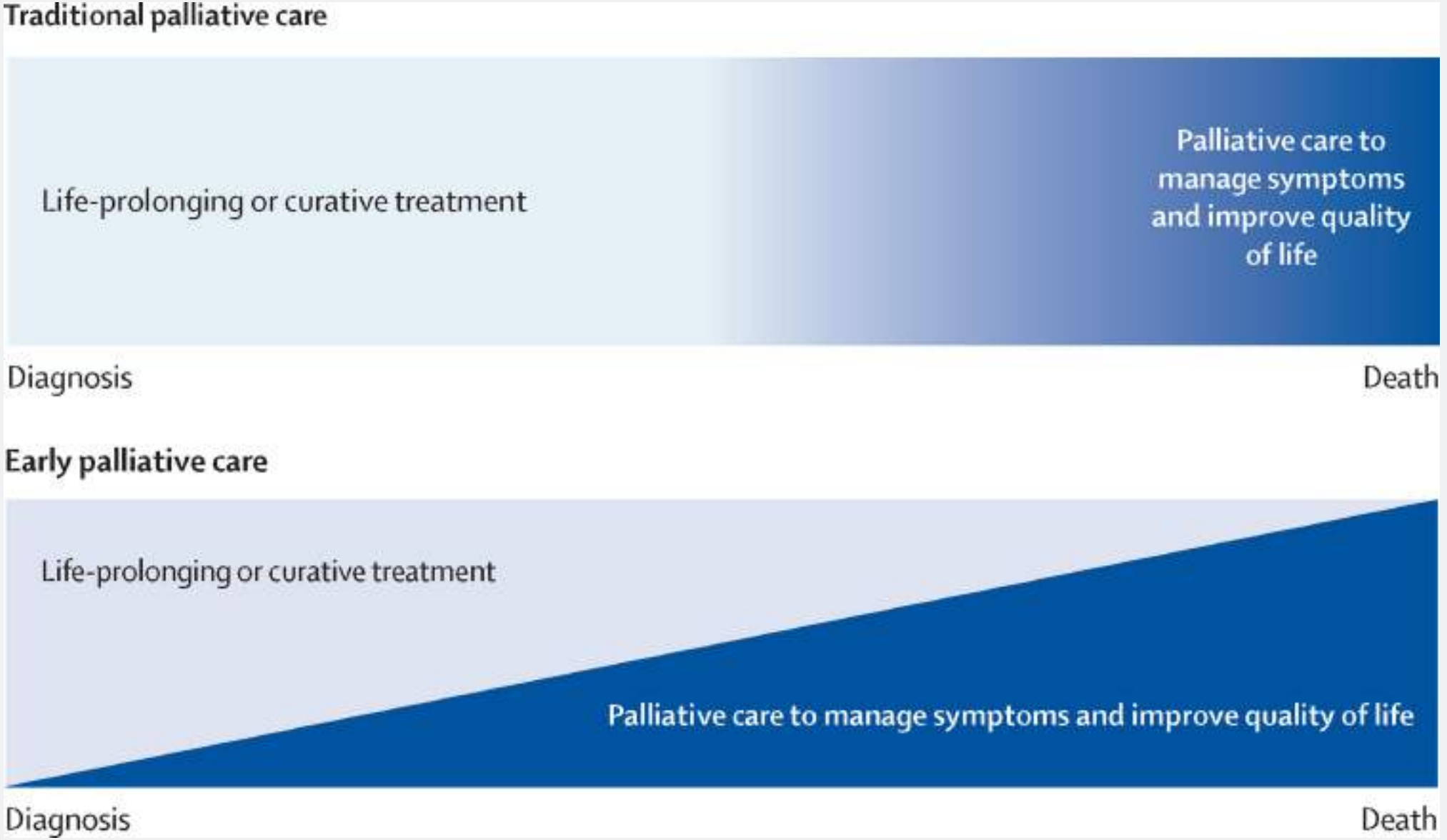



A
High/Very high HDI
Low/Medium HDI
Male
Lung
Prostate
Colorectum
Stomach
Liver
Esophagus
Bladder
Lip, oral cavity
Non−Hodgkin lymphoma
Leukemia
Kidney
Pancreas
Larynx
Brain, nervous system
Melanoma of skin
60
40
20
0
20
40
60
B
High/Very high HDI
Low/Medium HDI
Female
Breast
Cervix uteri
Colorectum
Lung
Thyroid
Corpus uteri
Ovary
Stomach
Liver
Leukemia
Non−Hodgkin lymphoma
Esophagus
Pancreas
Brain, nervous system
Lip, oral cavity
60
40
20
0
20
40
60
Incidence
Mortality

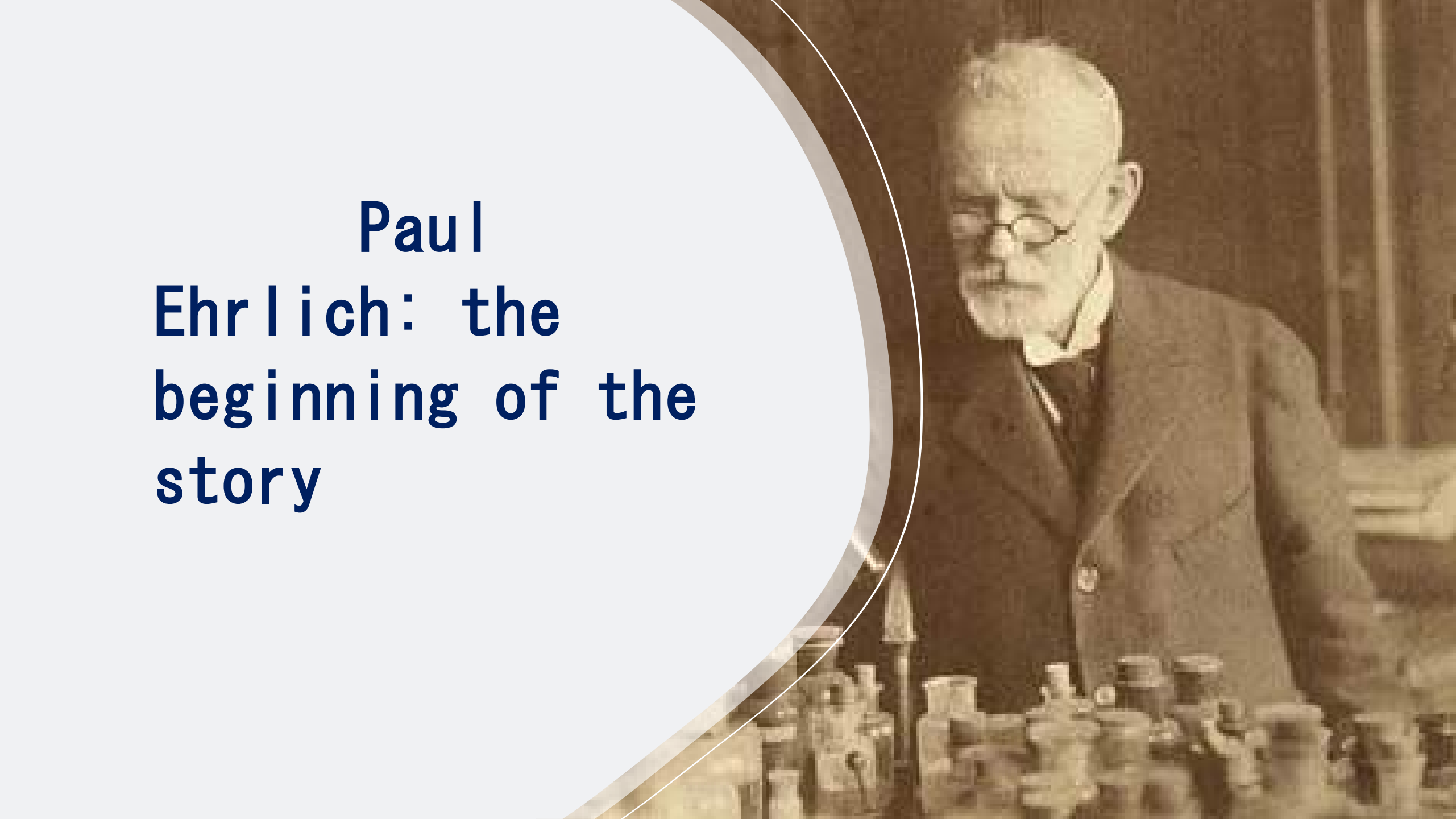
The cancer journey

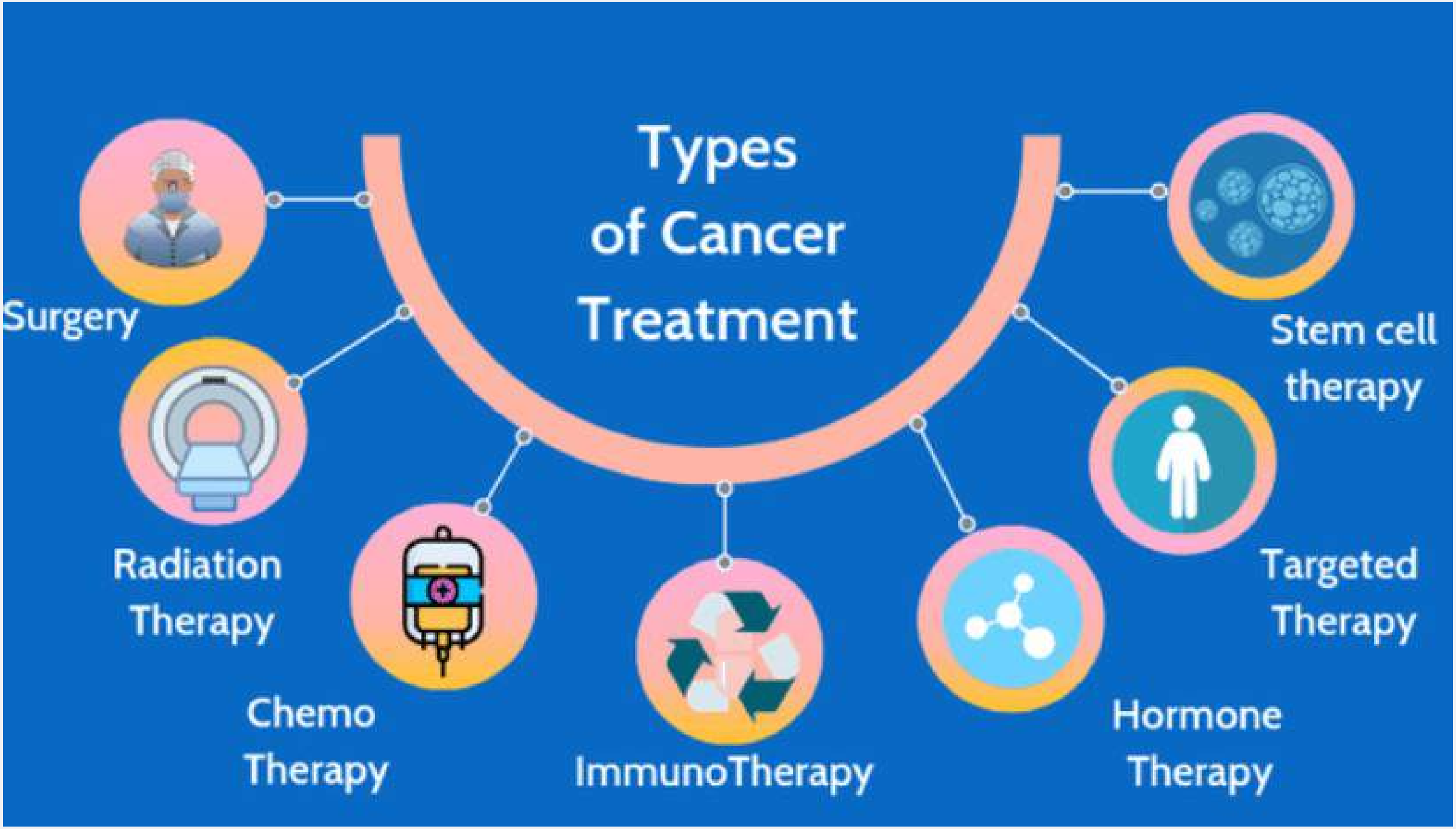
Better cancer services every step of the way

Six areas of cancer care

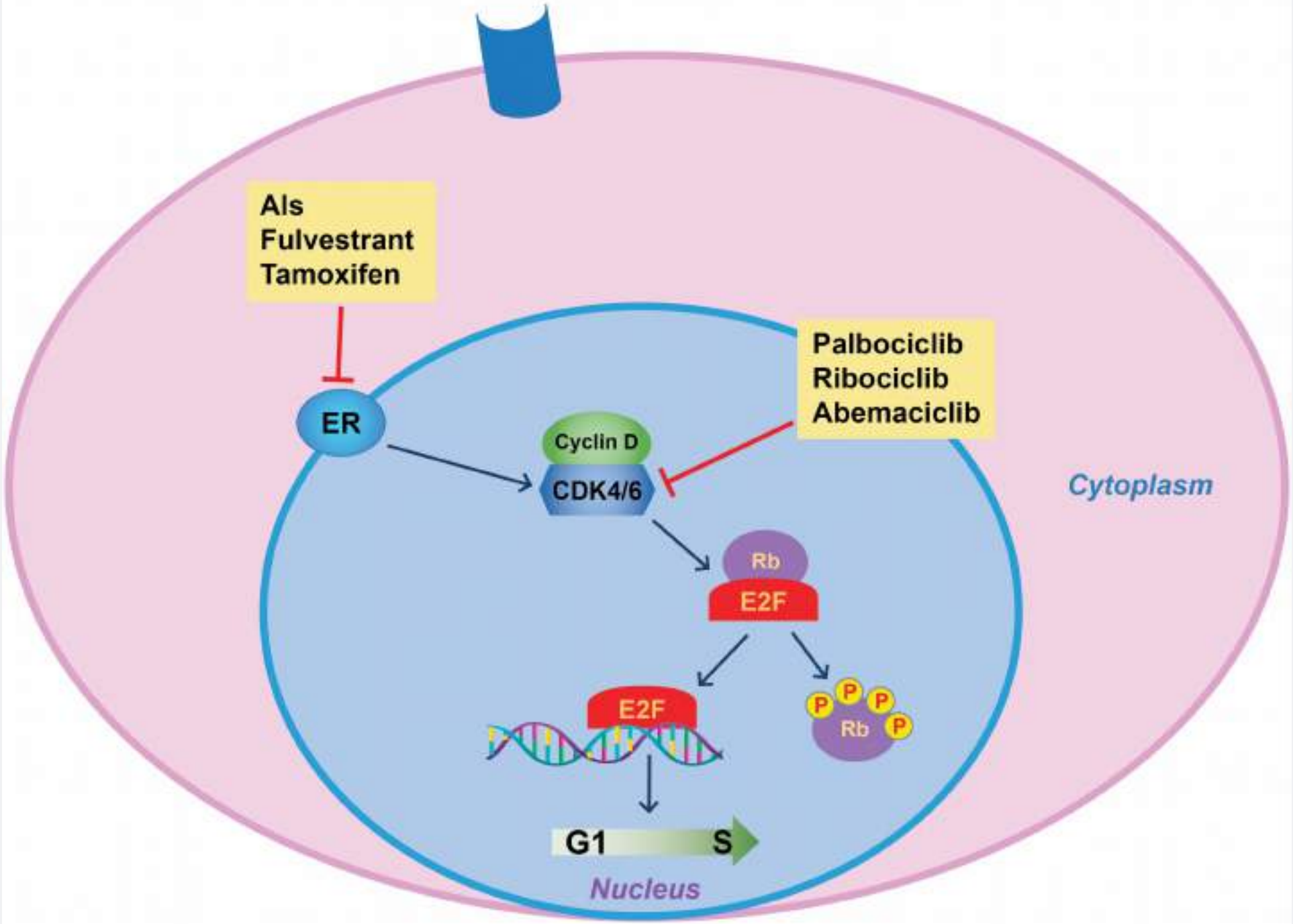

Traditional palliative care
Life-prolonging or curative treatment
Palliative care to manage symptoms and improve quality of life
Diagnosis
Death
Early palliative care
Life-prolonging or curative treatment
Palliative care to manage symptoms and improve quality of life
Diagnosis
Death

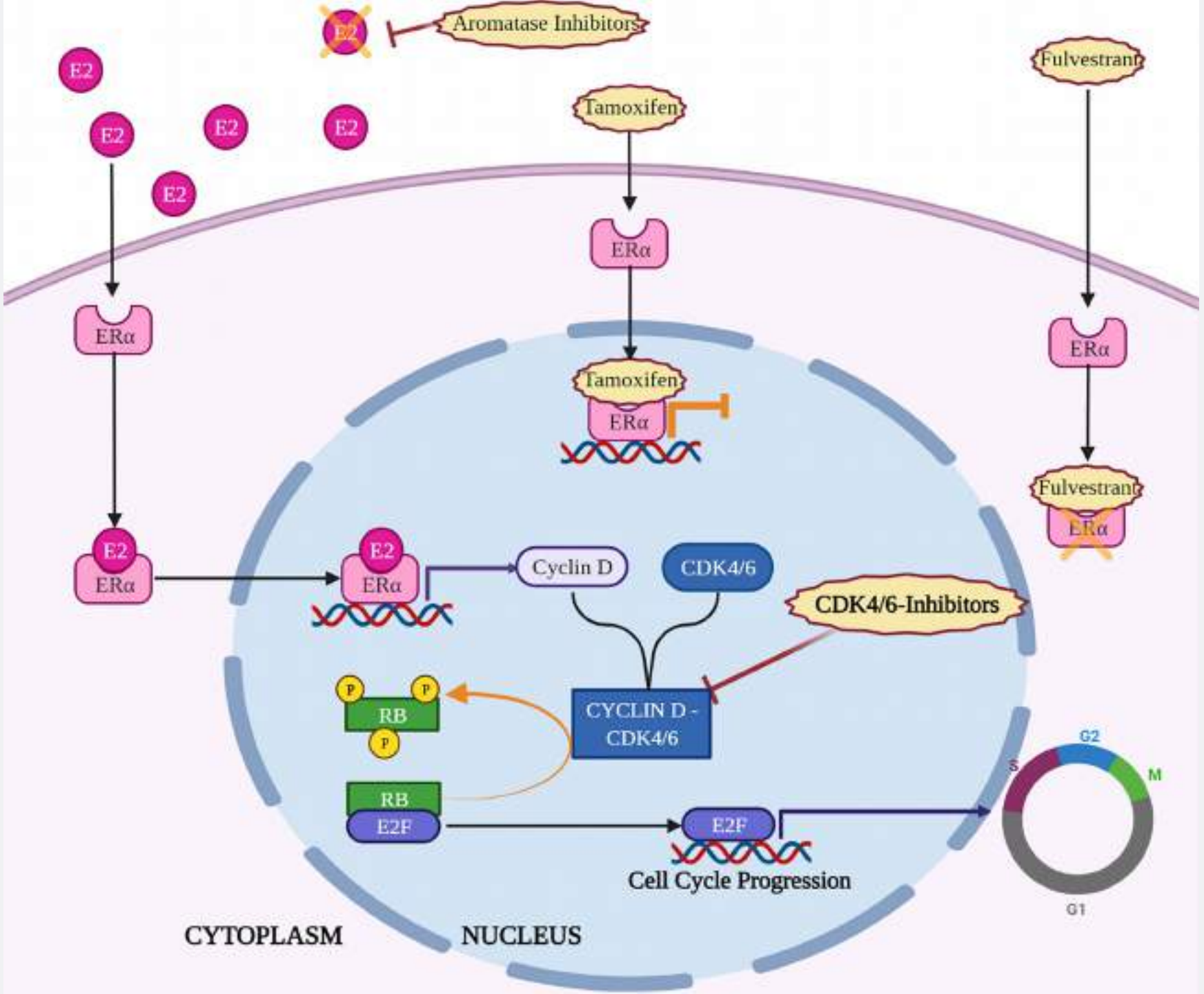
Paul Ehrlich: the beginning of the story

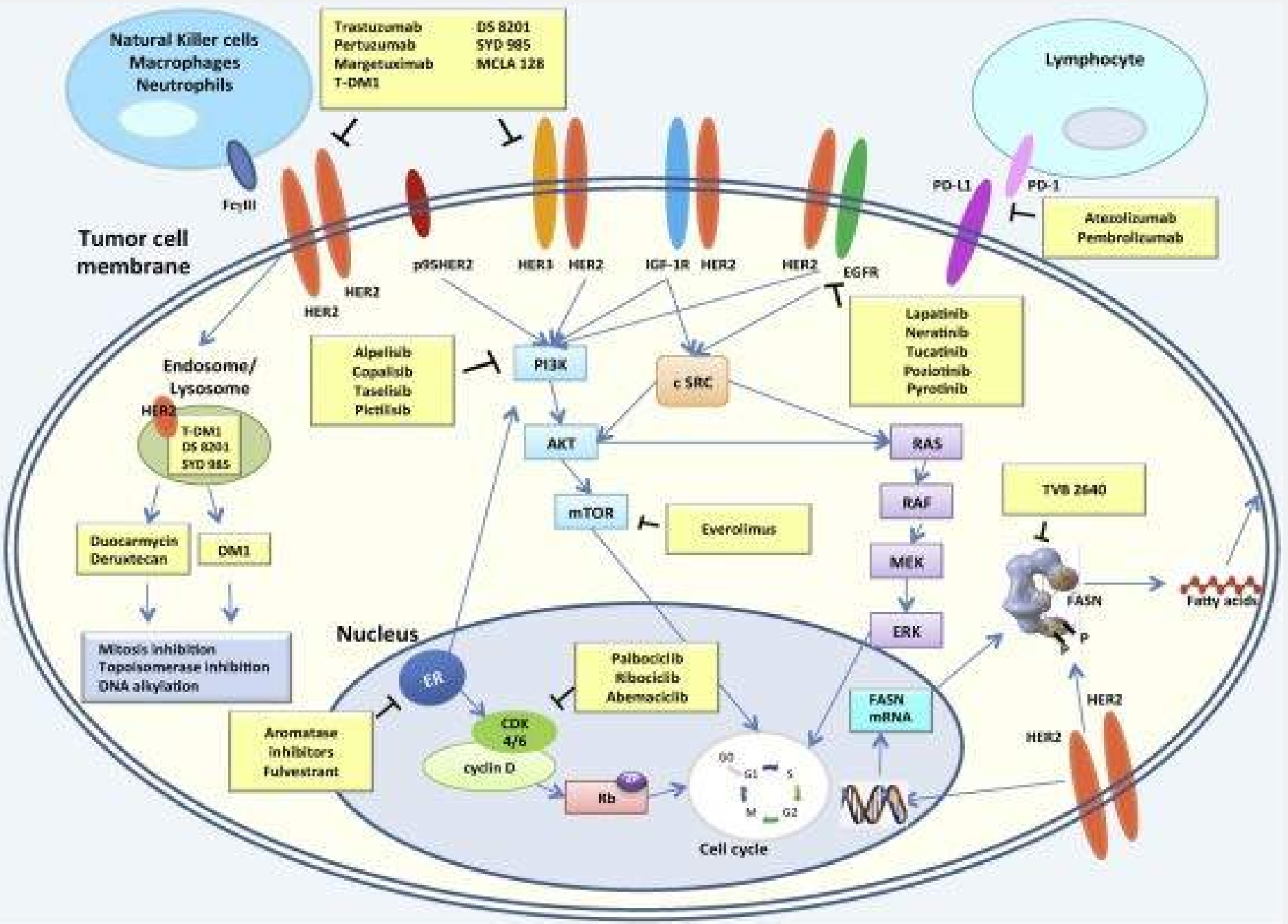



Types
of Cancer
Treatment
Surgery
Radiation
Therapy
Chemo
Therapy
ImmunoTherapy
Hormone
Therapy
Targeted
Therapy
Stem cell
therapy


Hormonal
Therapy

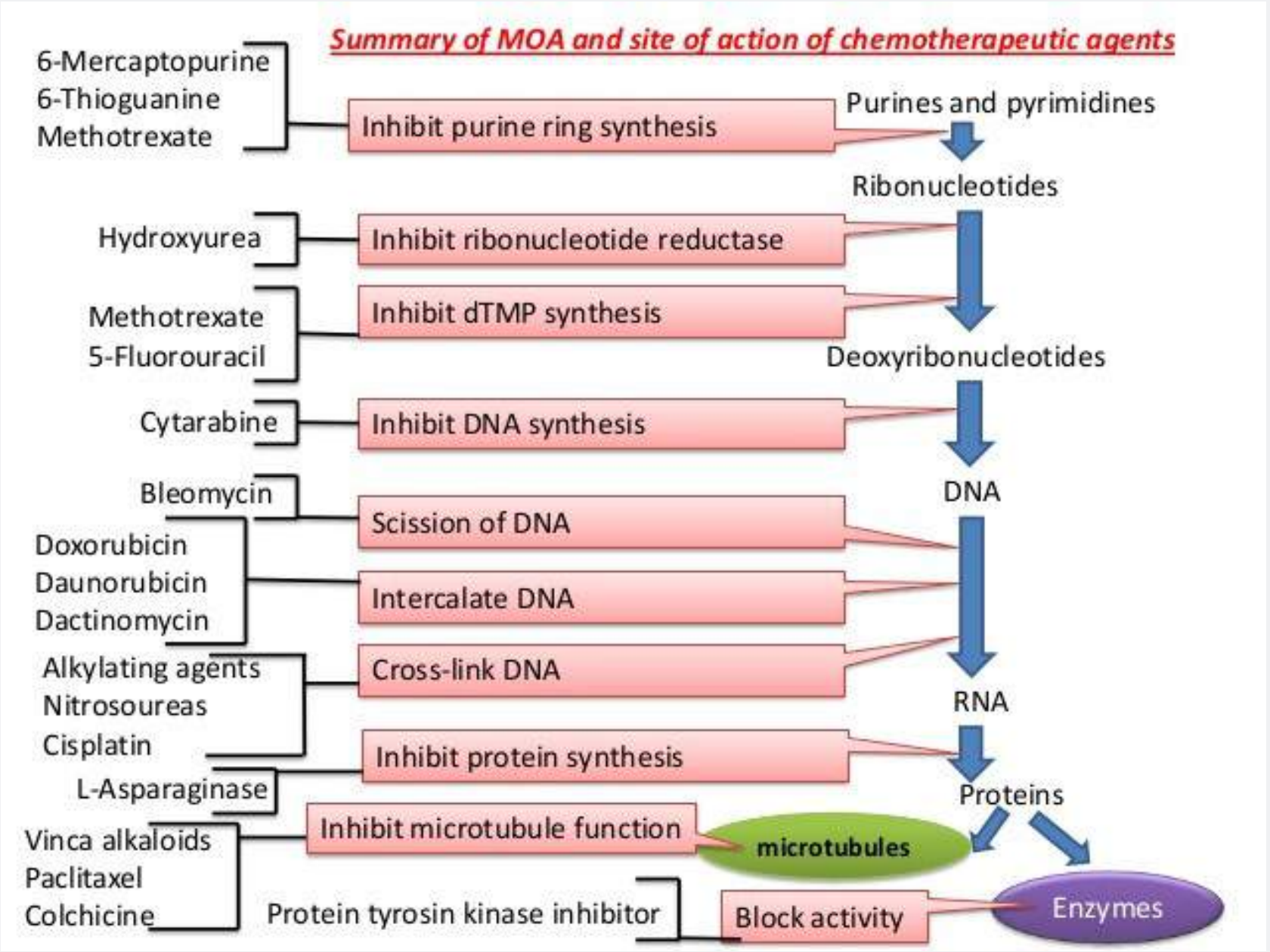

AIs
Fulvestrant
Tamoxifen
ER
Palbociclib
Ribociclib
Abemaciclib
Cyclin D
CDK4/6
Cytoplasm
Rb
E2F
E2F
P
P
P
Rb
P
G1
S
Nucleus


Aromatase Inhibitors
E2
E2
E2
E2
E2
Tamoxifen
Fulvestrant
ERα
ERα
ERα
Tamoxifen
ERα
ERα
Fulvestrant
ERα
E2
ERα
E2
ERα
Cyclin D
CDK4/6
CDK4/6-Inhibitors
P
P
RB
P
CYCLIN D -
CDK4/6
RB
E2F
E2F
Cell Cycle Progression
G2
S
M
G1
CYTOPLASM
NUCLEUS


Natural Killer cells
Macrophages
Neutrophils
Trastuzumab
Pertuzumab
Margetuximab
T-DM1
DS 8201
SYD 985
MCLA 128
Lymphocyte
FcγIII
PD-L1
PD-1
Atezolizumab
Pembrolizumab
Tumor cell membrane
HER2
HER2
p95HER2
HER3
HER2
IGF-1R
HER2
HER2
EGFR
Lapatinib
Neratinib
Tucatinib
Poziotinib
Pyrotinib
Endosome/
Lysosome
HER2
T-DM1
DS 8201
SYD 985
Alpelisib
Copalisib
Taselisib
Pictilisib
PI3K
c SRC
AKT
RAS
RAF
MEK
ERK
mTOR
Everolimus
TVB 2640
FASN
P
Fatty acids
Duocarmycin
Deruxtecan
DM1
Mitosis inhibition
Topoisomerase inhibition
DNA alkylation
Nucleus
ER
Palbociclib
Ribociclib
Abemaciclib
Aromatase
inhibitors
Fulvestrant
CDK
4/6
cyclin D
Rb
P
FASN
mRNA
HER2
HER2
G0
G1
S
M
G2
Cell cycle

New Drugs in Cancer Chemotherapy

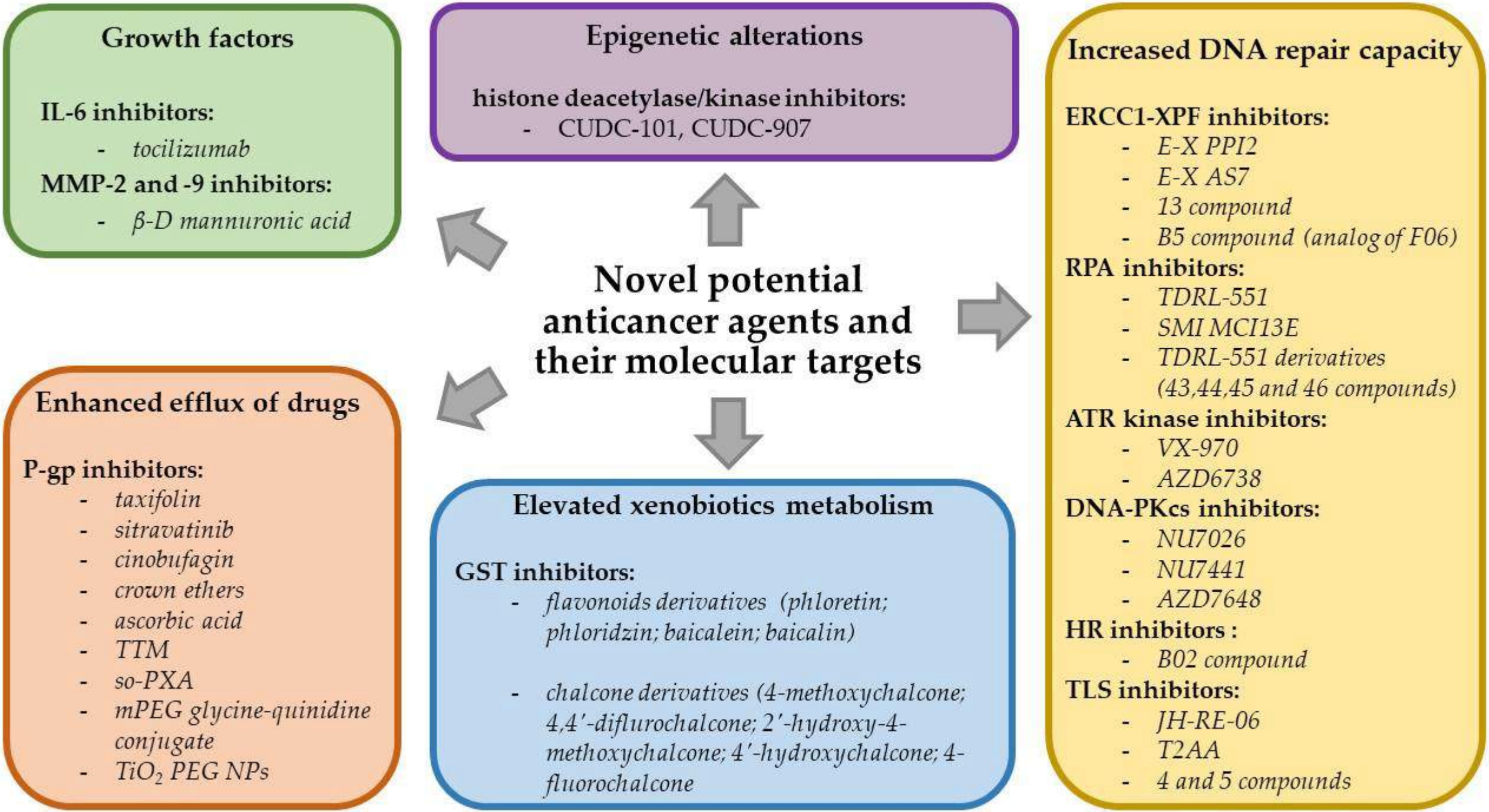
Edited by
S. K. Carter Y. Sakurai H. Umezawa


Summary of MOA and site of action of chemotherapeutic agents
6-Mercaptopurine
6-Thioguanine
Methotrexate
Inhibit purine ring synthesis
Purines and pyrimidines
Ribonucleotides
Hydroxyurea
Inhibit ribonucleotide reductase
Methotrexate
5-Fluorouracil
Inhibit dTMP synthesis
Deoxyribonucleotides
Cytarabine
Inhibit DNA synthesis
DNA
Bleomycin
Scission of DNA
Doxorubicin
Daunorubicin
Dactinomycin
Intercalate DNA
Alkylating agents
Nitrosoureas
Cisplatin
Cross-link DNA
RNA
L-Asparaginase
Inhibit protein synthesis
Proteins
Vinca alkaloids
Paclitaxel
Colchicine
Inhibit microtubule function
microtubules
Protein tyrosin kinase inhibitor
Block activity
Enzymes

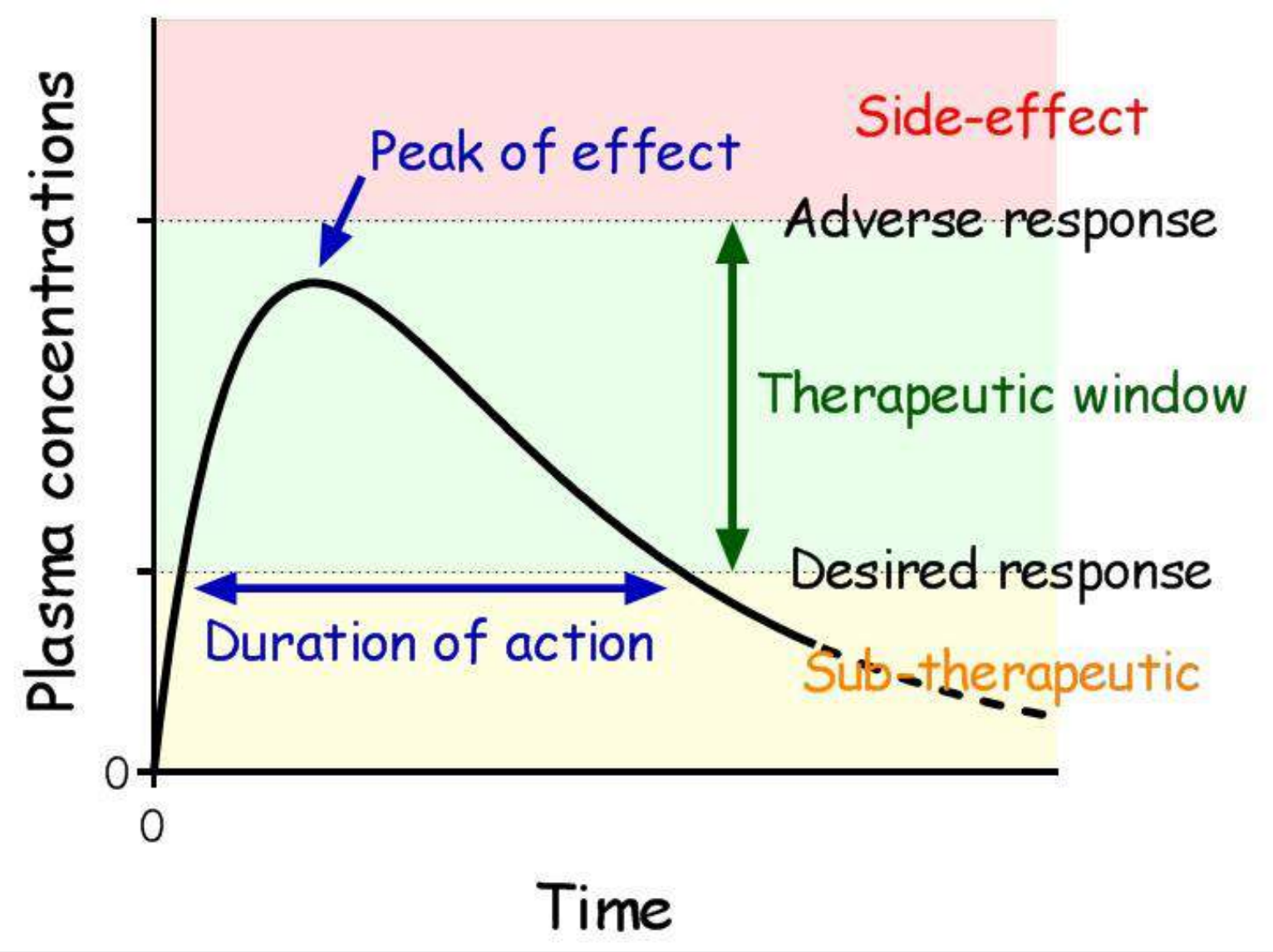
Chemotherapic agents

- Chemotherapy from natural agents
- Doxorubicin
- Vinca alcaloids
- Taxans
- Camptotheca derived agents
- Trabectedine
- Eribuline

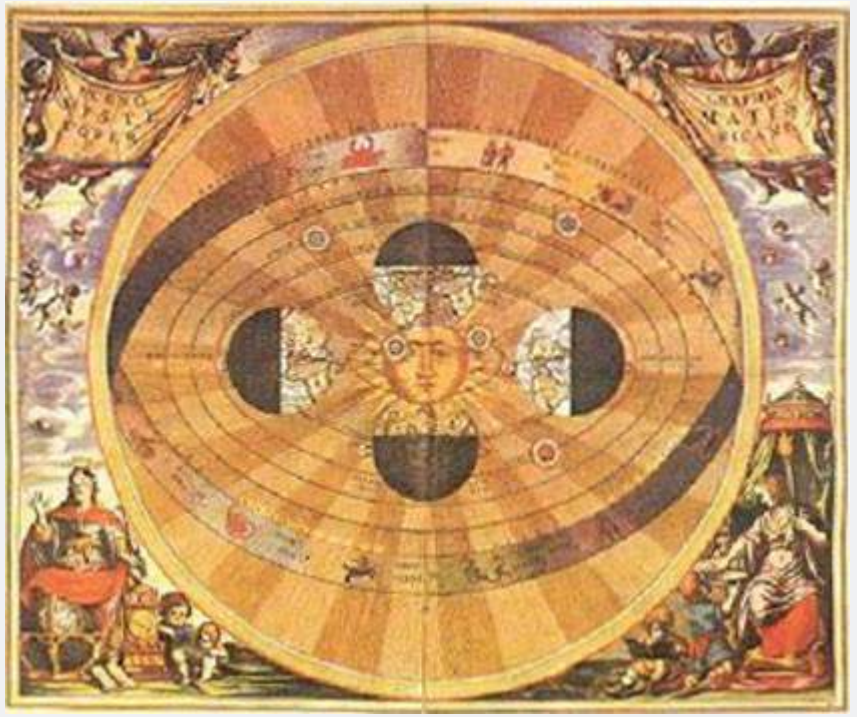
- Synthetic drugs
- Mecloretamine
- Cyclofosfamide
- Busulfan
- Methotrexate
- 5 fluorouracil
- Platinum analogs
- Dacarbazine


Growth factors
IL-6 inhibitors:
- tocilizumab
MMP-2 and -9 inhibitors:
- β-D mannuronic acid
Epigenetic alterations
histone deacetylase/kinase inhibitors:
- CUDC-101, CUDC-907
Increased DNA repair capacity
ERCC1-XPF inhibitors:
- E-X PPI2
- E-X AS7
- 13 compound
- B5 compound (analog of F06)
RPA inhibitors:
- TDRL-551
- SMI MCI13E
- TDRL-551 derivatives (43,44,45 and 46 compounds)
ATR kinase inhibitors:
- VX-970
- AZD6738
DNA-PKcs inhibitors:
- NU7026
- NU7441
- AZD7648
HR inhibitors :
- B02 compound
TLS inhibitors:
- JH-RE-06
- T2AA
- 4 and 5 compounds
Novel potential anticancer agents and their molecular targets
Enhanced efflux of drugs
P-gp inhibitors:
- taxifolin
- sitravatinib
- cinobufagin
- crown ethers
- ascorbic acid
- TTM
- so-PXA
- mPEG glycine-quinidine conjugate
- TiO_2 PEG NPs
Elevated xenobiotics metabolism
GST inhibitors:
- flavonoids derivatives (phloretin; phloridzin; baicalein; baicalin)
- chalcone derivatives (4-methoxychalcone; 4,4′-difluorochalcone; 2′-hydroxy-4-methoxychalcone; 4′-hydroxychalcone; 4-fluorochalcone

Therapeutic window



The Copernican revolution in Pharmacology



Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
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DOI 10.1016/j.cell.2011.02.013

REVIEW

Hallmarks of Cancer: New Dimensions

Douglas Hanahan

AACR American Association for Cancer Research

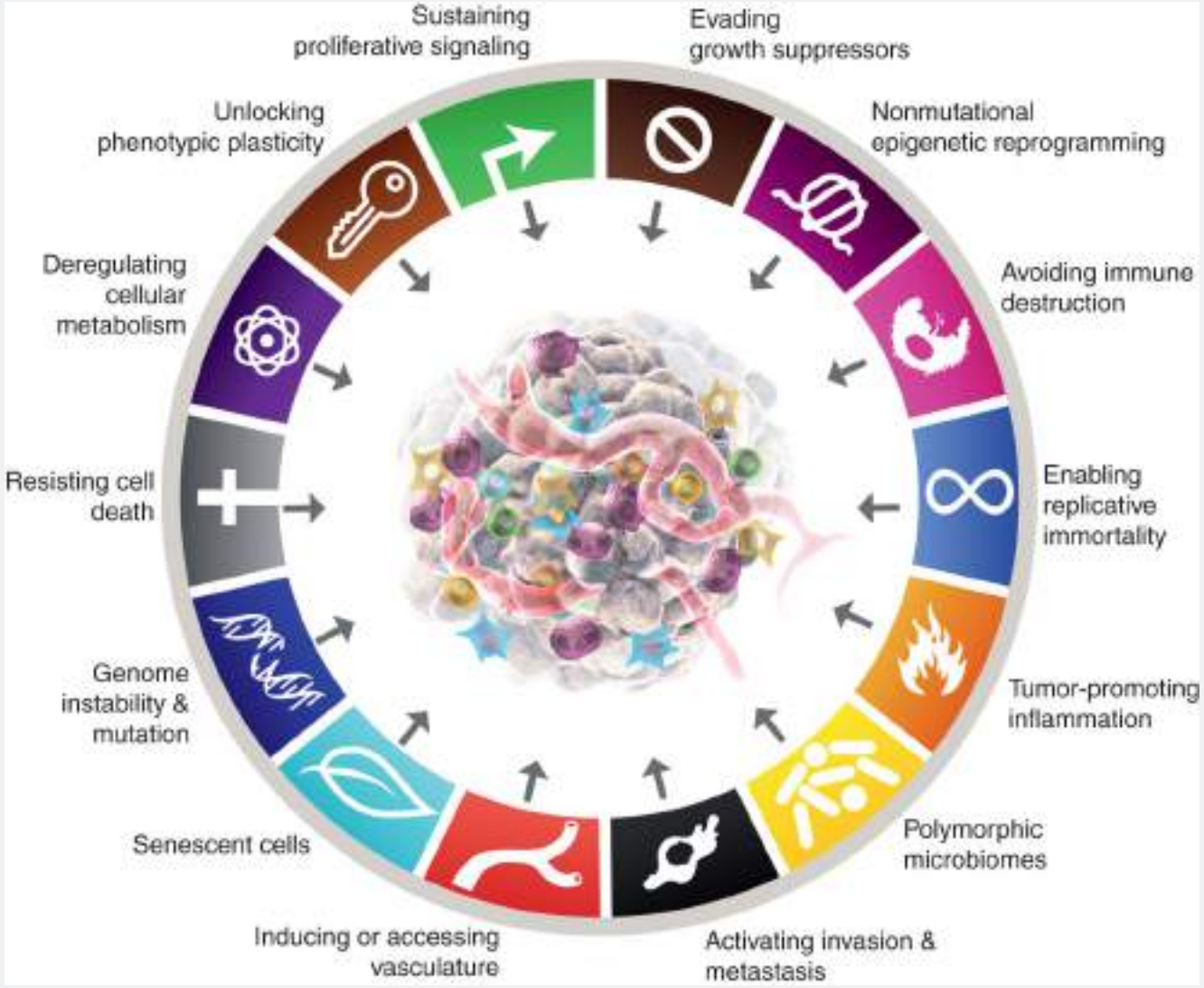
JANUARY 2022 CANCER DISCOVERY | 31

ABSTRACT The hallmarks of cancer conceptualization is a heuristic tool for distilling the vast complexity of cancer phenotypes and genotypes into a provisional set of underlying principles. As knowledge of cancer mechanisms has progressed, other facets of the disease have emerged as potential refinements. Herein, the prospect is raised that phenotypic plasticity and disrupted differentiation is a discrete hallmark capability, and that nonmutational epigenetic reprogramming and polymorphic microbiomes both constitute distinctive enabling characteristics that facilitate the acquisition of hallmark capabilities. Additionally, senescent cells, of varying origins, may be added to the roster of functionally important cell types in the tumor microenvironment.

Significance: Cancer is daunting in the breadth and scope of its diversity, spanning genetics, cell and tissue biology, pathology, and response to therapy. Ever more powerful experimental and computational tools and technologies are providing an avalanche of "big data" about the myriad manifestations of the diseases that cancer encompasses. The integrative concept embodied in the hallmarks of cancer is helping to distill this complexity into an increasingly logical science, and the provisional new dimensions presented in this perspective may add value to that endeavor, to more fully understand mechanisms of cancer development and malignant progression, and apply that knowledge to cancer medicine.

From: **Hallmarks of Cancer: New Dimensions**

Cancer Discov. 2022;12(1):31-46. doi:10.1158/2159-8290.CD-21-1059



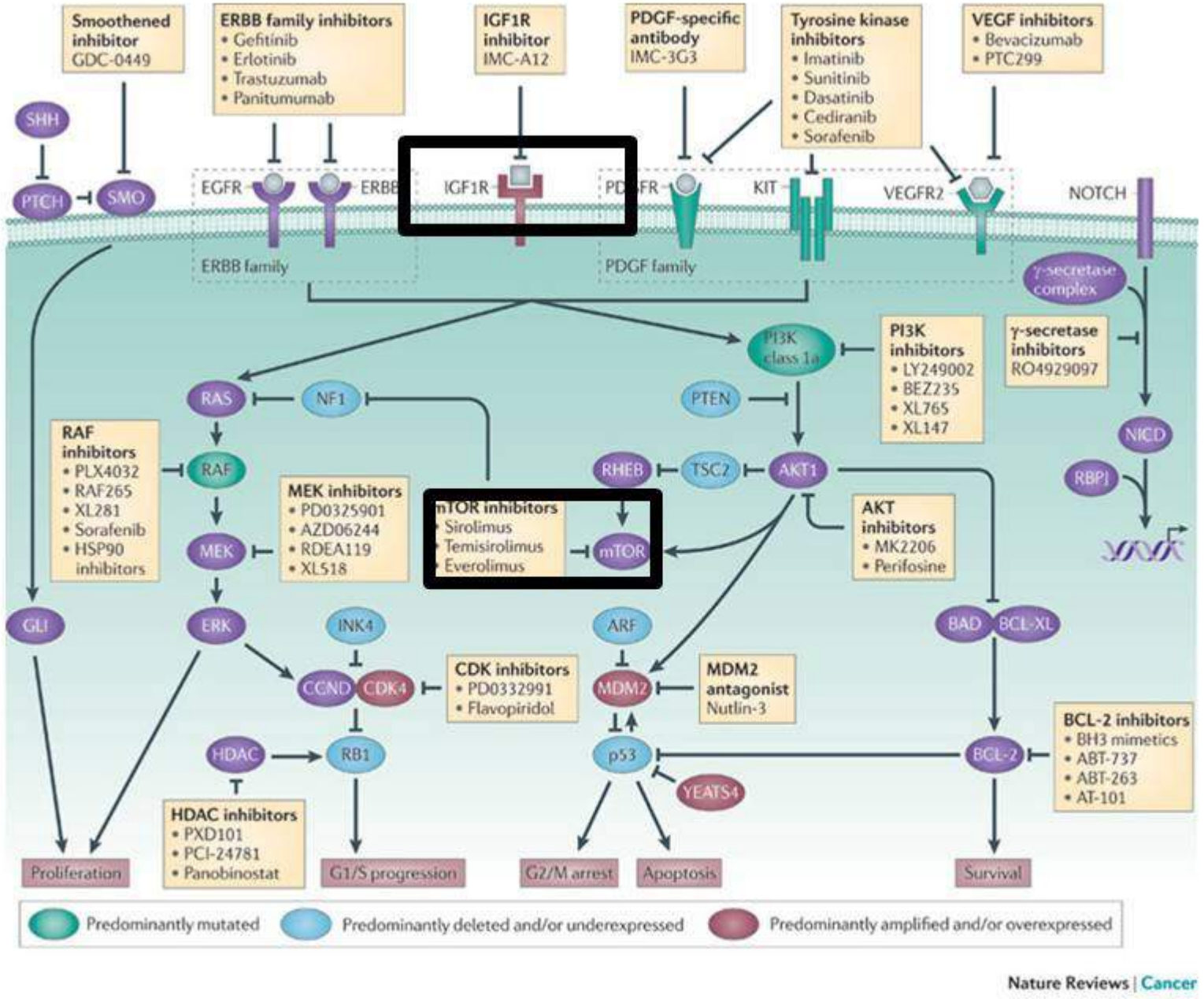
CANCER CELLS CHARACTERISTICS

- PROLIFERATION
- ADHESION
- INVASION & MIGRATION
- METASTASIS
- NEOANGIOGENESIS
- APOPTOSIS INHIBITION

HANAHAN & WEINBERG 2000

- IMMORTALIZATION
- UNCONTROLLED GROWTH
- DIFFERENT METABOLISM

HANAHAN & WEINBERG 2011



Taylor, BS, Barretina J, Maki RG et al. NRC 2011

Combinatorial chemistry

Is a new method to reduce time and costs to produce new drugs

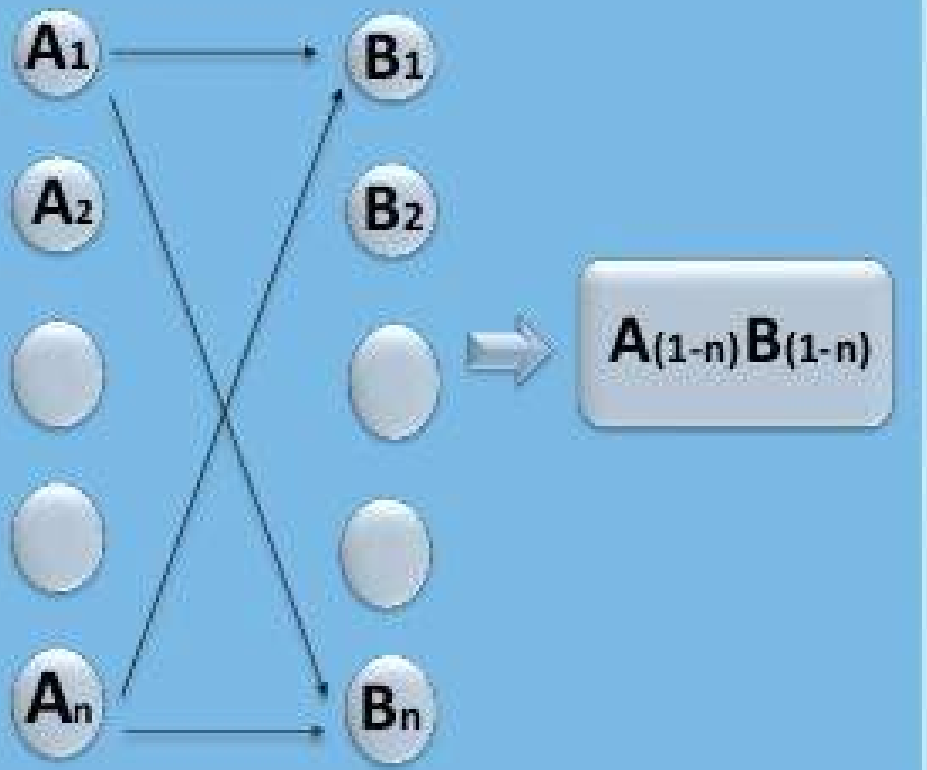
A large number of molecules can be produced contemporary

It is applied in Human Pharmacology

Biotechnology and Agro industry

Traditional synthesis

Combinatorial synthesis



NOBELPRISET I KEMI 2022
THE NOBEL PRIZE IN CHEMISTRY 2022

KUNGL. VETENSKAPS-AKADEMIEN
THE ROYAL SWEDISH ACADEMY OF SCIENCES

Photo: Grace Science Foundation

Carolyn R. Bertozzi
Stanford University
USA

Photo: University of Copenhagen

Morten Meldal
University of Copenhagen
Denmark

Photo: Scripps Research

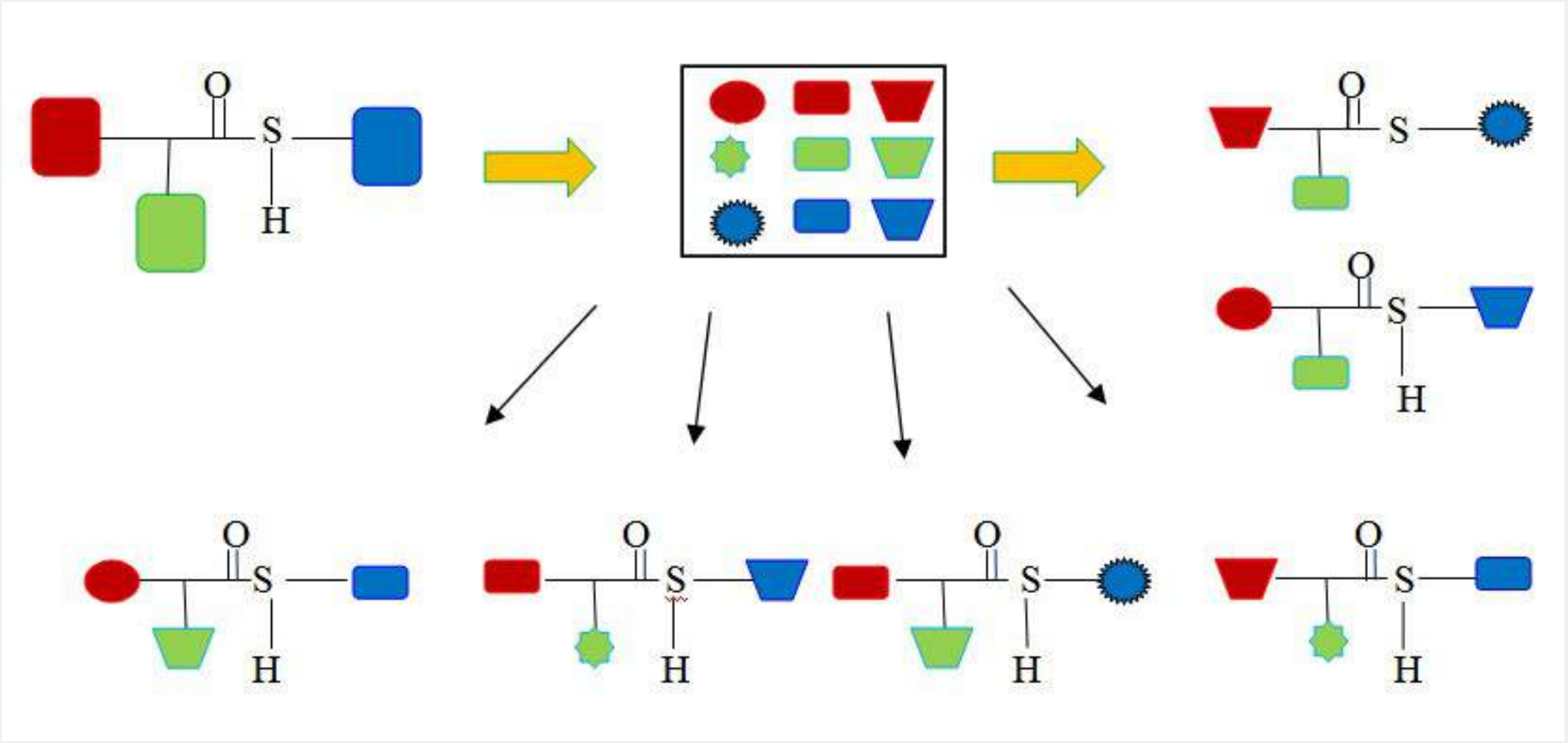
K. Barry Sharpless
Scripps Research
USA

”för utveckling av klickkemi och bioortogonal kemi”

“for the development of click chemistry and bioorthogonal chemistry”

#nobelprize

THE NOBEL PRIZE


O
S
H
O
S
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O
S
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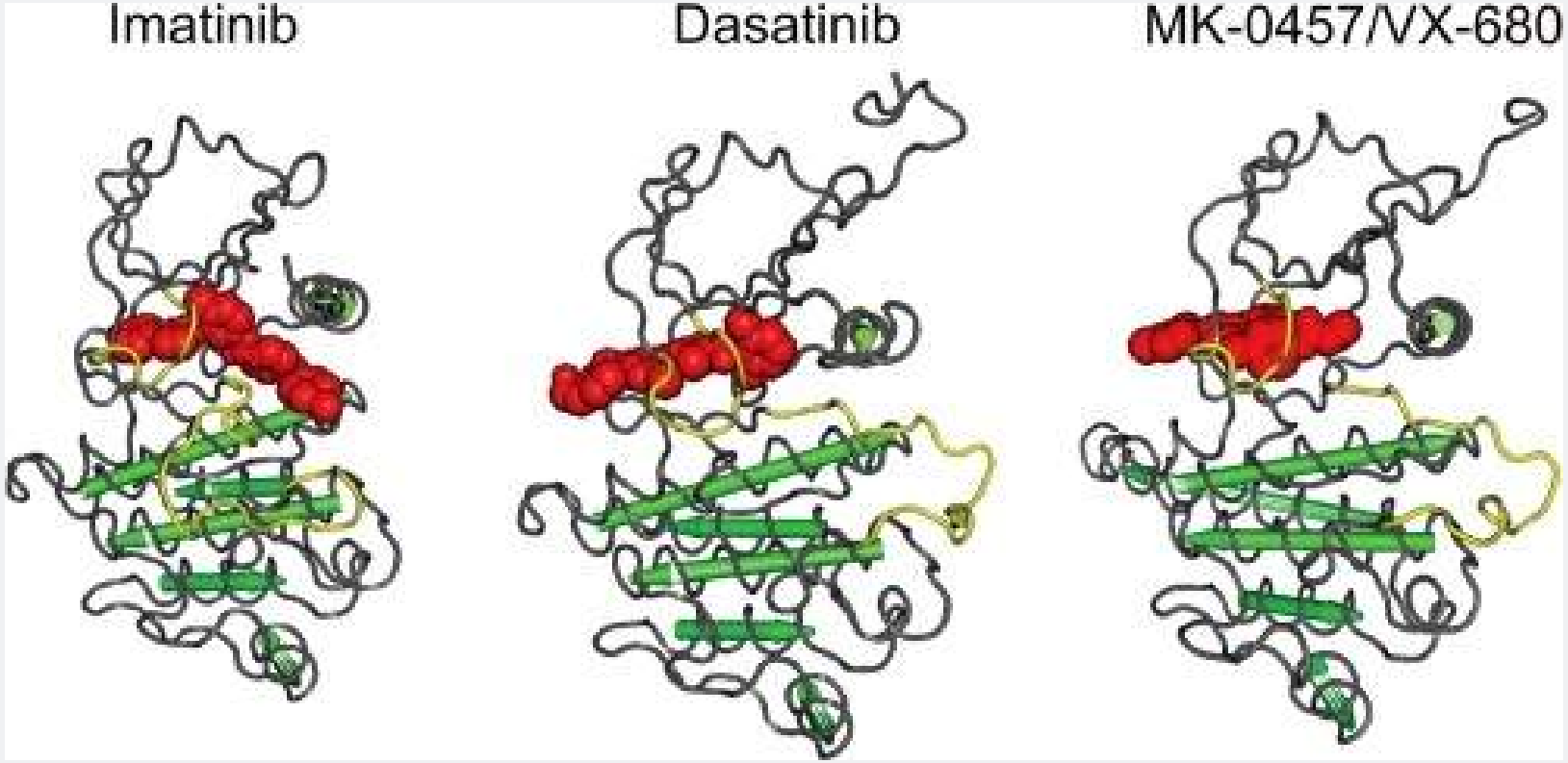
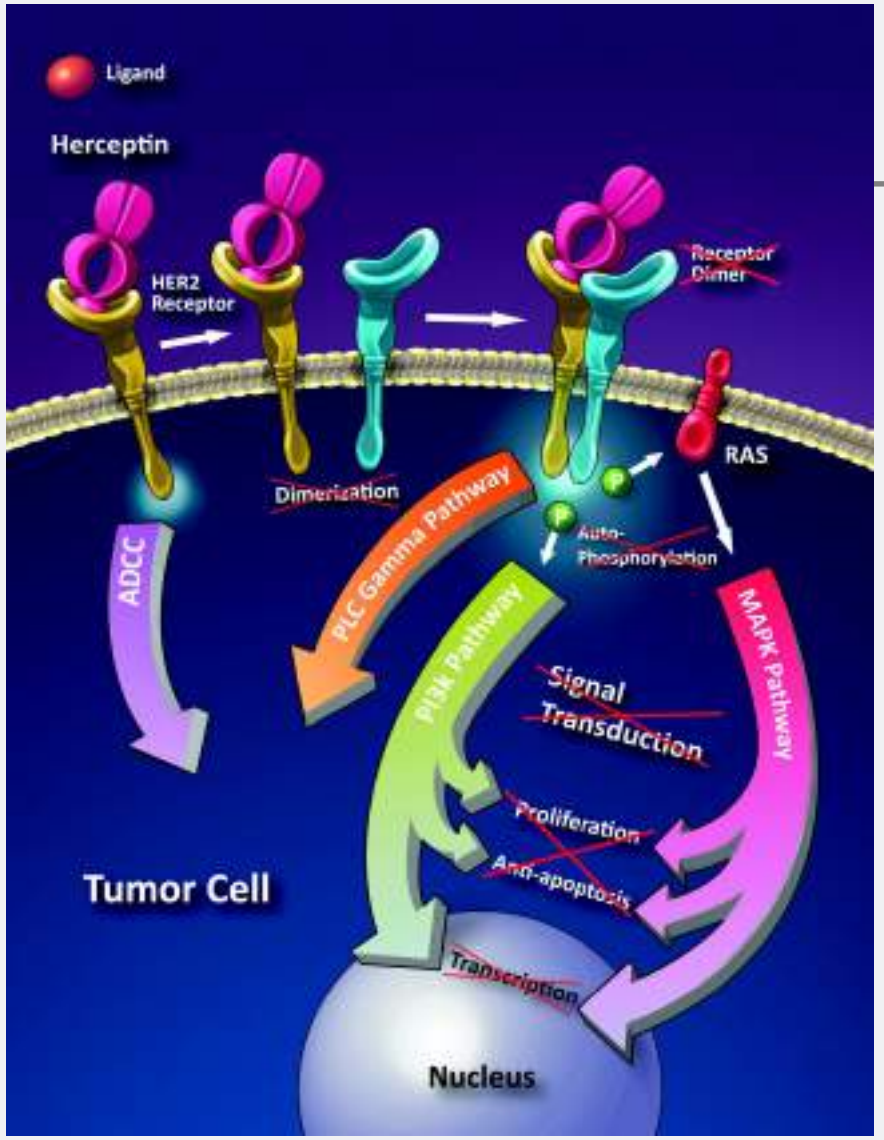
O
S
H
O
S
H

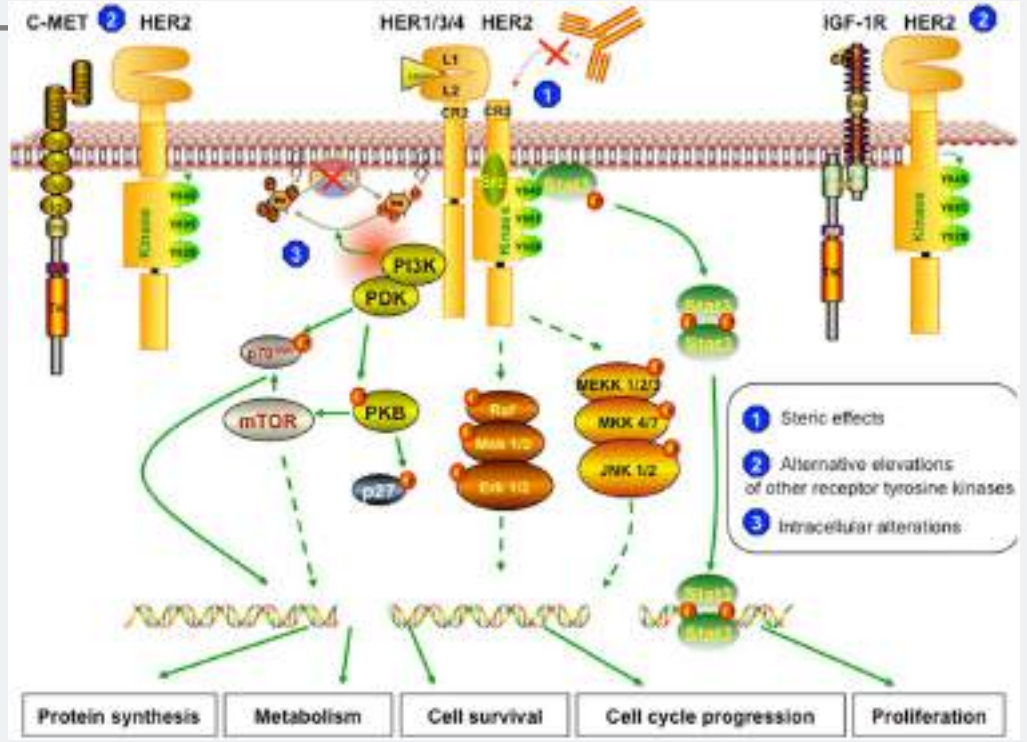
Silico

Modeling

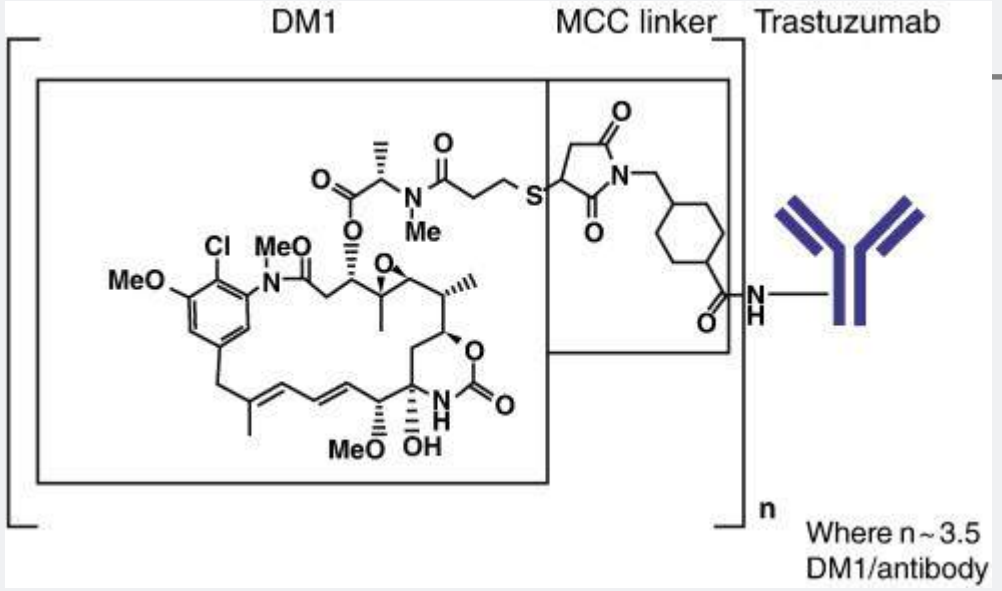


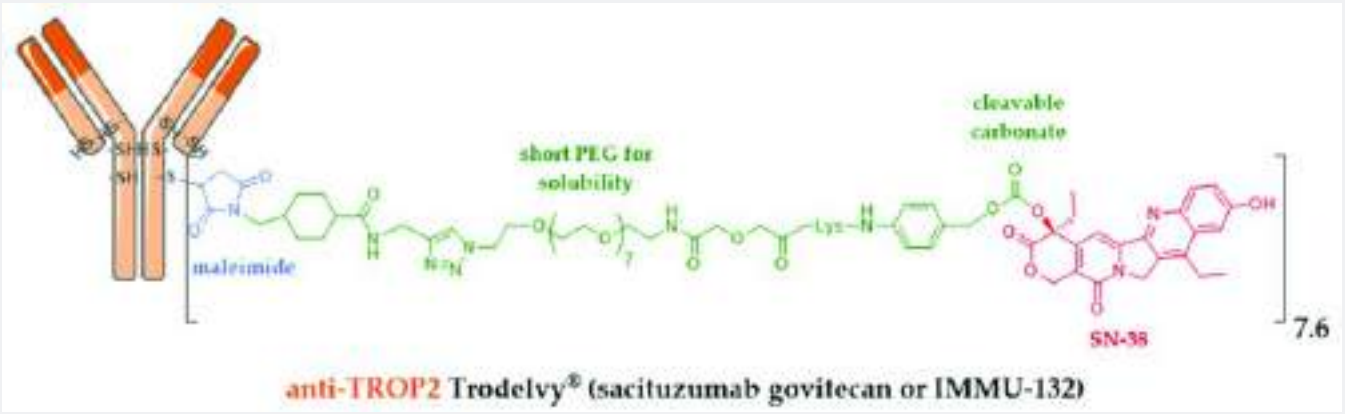
Monoclonal antibodies. Trastuzumab





Antibody Drugs conjugated (ADC)





anti-TROP2 Trodelvy® (sacituzumab govitecan or IMMU-132)

Approved Antibody Drug Conjugated

ADC	Antigen Target	Drug	Drug Mechanism	Indication
Brentuximab vedotin [11]	CD30	Auristatin	Microtubule disruptor	Hodgkin lymphoma
Gemtuzumab ozogamicin [12]	CD33	Calicheamicin	DNA damage	Acute myeloid leukemia
Inotuzumab ozogamicin [13]	CD22	Calicheamicin	DNA damage	Acute lymphoblastic leukemia
Moxetumomab pasudotox [14]	CD22	PE38	Apoptosis induction	Hairy cell leukemia
Polatuzumab vedotin [15]	CD79b	Auristatin	Microtubule disruptor	B-cell lymphoma
Enfortumab vedotin [16]	Nectin-4	Auristatin	Microtubule disruptor	Bladder Cancer
Trastuzumab deruxtecan [4]	HER2	Deruxtecan	Topoisomerase I inhibitor	HER2 positive breast cancer
Trastuzumab emtansine [3]	HER2	Maytansine	Microtubule disruptor	HER2 positive breast cancer
Sacituzumab govitecan [17]	Trop-2	SN38	Topoisomerase inhibitor	Triple-negative breast cancer

IMMUNOTHERAPY

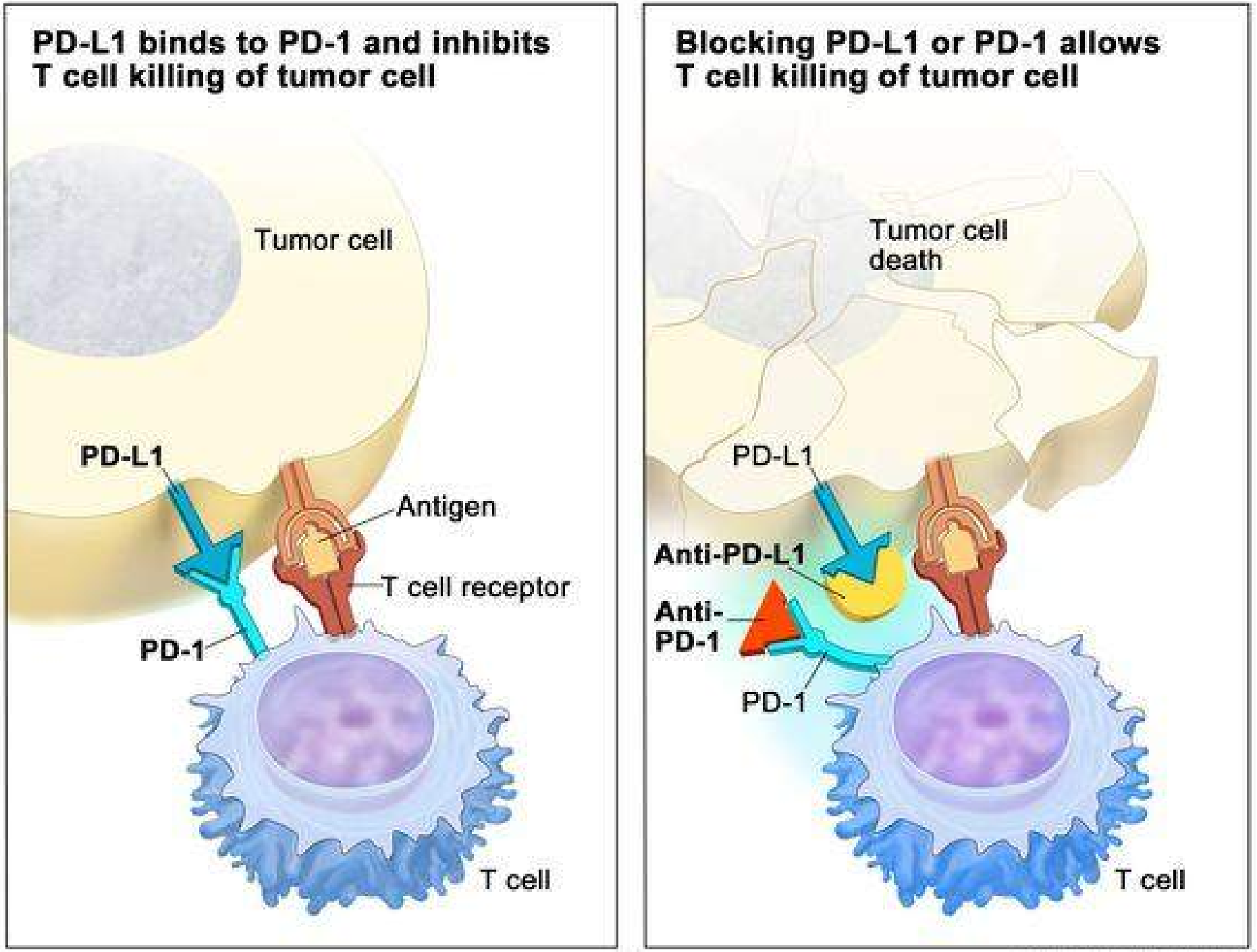
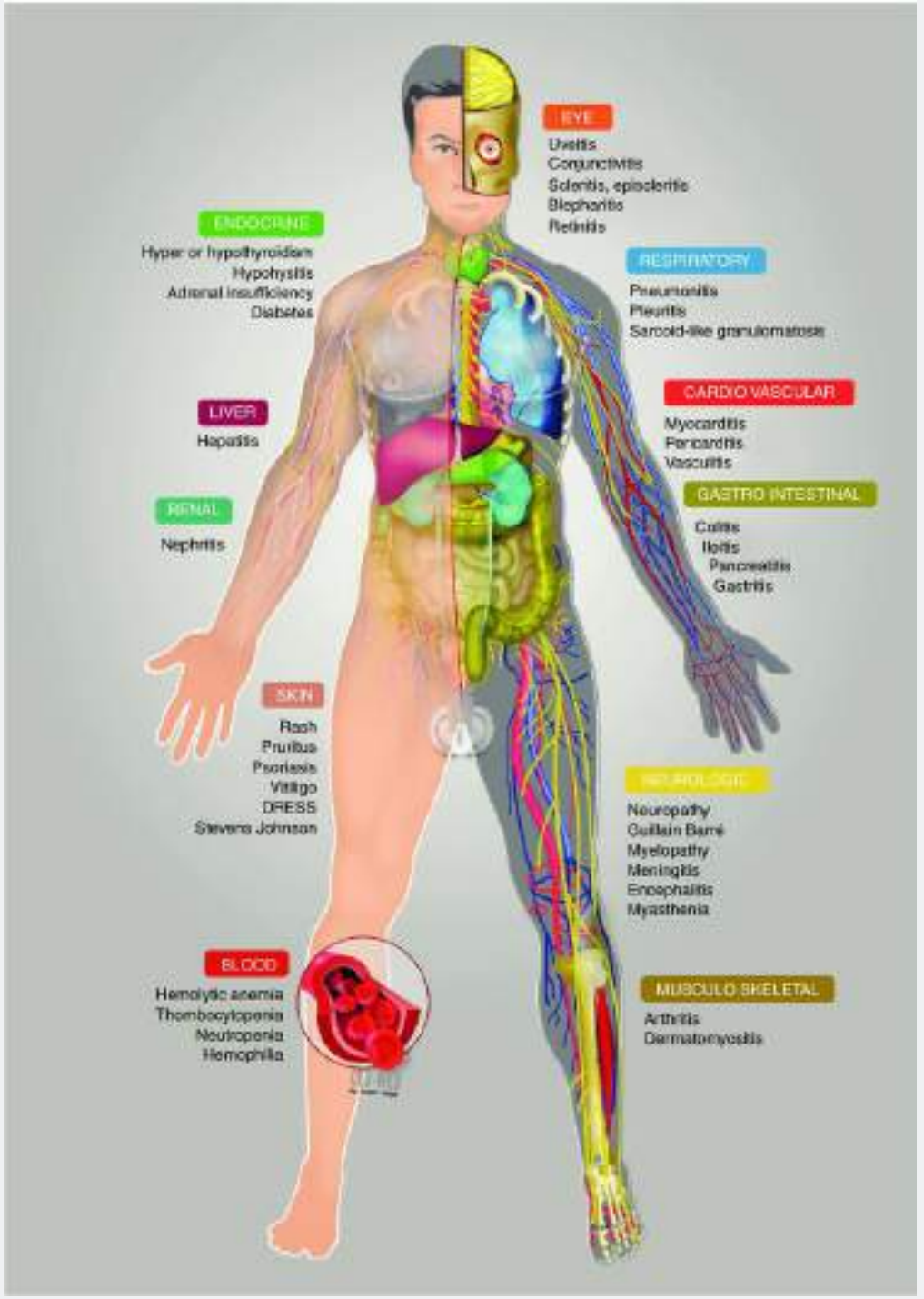
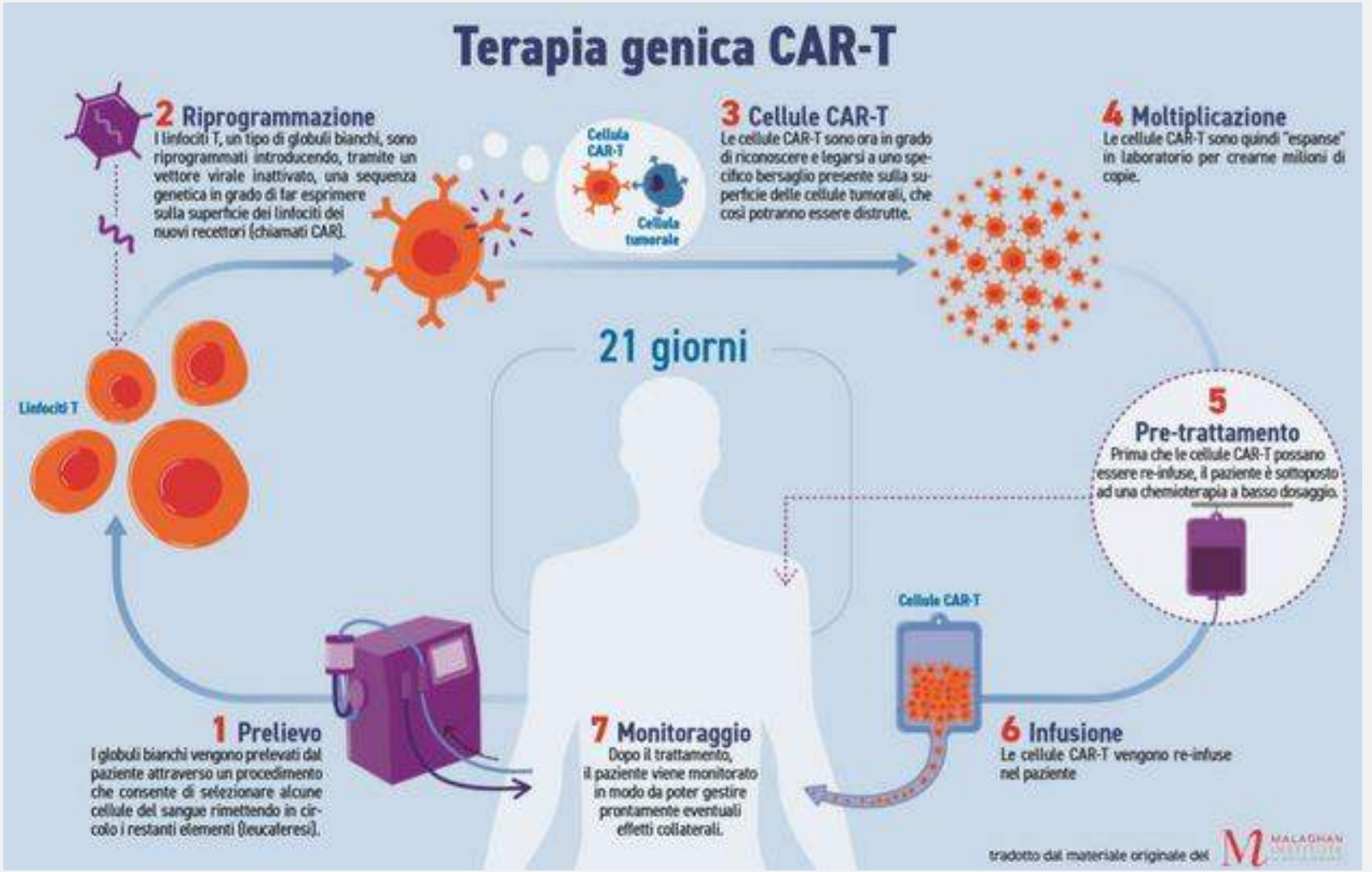

PD-L1 binds to PD-1 and inhibits T cell killing of tumor cell
Tumor cell
PD-L1
Antigen
T cell receptor
PD-1
T cell
Blocking PD-L1 or PD-1 allows T cell killing of tumor cell
Tumor cell death
PD-L1
Anti-PD-L1
Anti-PD-1
PD-1
T cell

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.


EYE
Uveitis
Conjunctivitis
Sclentis, episcleritis
Blepharitis
Retinitis
ENDOCRINE
Hyper or hypothyroidism
Hypophysitis
Adrenal insufficiency
Diabetes
RESPIRATORY
Pneumonitis
Pleuritis
Sarcoid-like granulomatose
CARDIO VASCULAR
Myocarditis
Pericarditis
Vasculitis
LIVER
Hapatitis
GASTRO INTESTINAL
Colitis
Ileitis
Pancreatitis
Gastritis
RENAL
Nephritis
SKIN
Rash
Pruritus
Psoriasis
Vitiligo
DRESS
Stevens Johnson
Neuropathy
Guillain Barré
Myelopathy
Meningitis
Encephalitis
Myasthenia
BLOOD
Hemolytic anemia
Thombocytopenia
Neutropenia
Hemophilia
MUSCULO SKELETAL
Arthritis
Dermatomyositis


Terapia genica CAR-T
2 Riprogrammazione
I linfociti T, un tipo di globuli bianchi, sono riprogrammati introducendo, tramite un vettore virale inattivato, una sequenza genetica in grado di far esprimere sulla superficie dei linfociti dei nuovi recettori (chiamati CAR).
Cellula CAR-T
Cellula tumorale
3 Cellule CAR-T
Le cellule CAR-T sono ora in grado di riconoscere e legarsi a uno specifico bersaglio presente sulla superficie delle cellule tumorali, che così potranno essere distrutte.
4 Moltiplicazione
Le cellule CAR-T sono quindi "espanse" in laboratorio per crearne milioni di copie.
21 giorni
Linfociti T
5
Pre-trattamento
Prima che le cellule CAR-T possano essere re-infuse, il paziente è sottoposto ad una chemioterapia a basso dosaggio.
Cellule CAR-T
1 Prelievo
I globuli bianchi vengono prelevati dal paziente attraverso un procedimento che consente di selezionare alcune cellule del sangue rimettendo in circolo i restanti elementi (leucaferesi).
7 Monitoraggio
Dopo il trattamento, il paziente viene monitorato in modo da poter gestire prontamente eventuali effetti collaterali.
6 Infusione
Le cellule CAR-T vengono re-infuse nel paziente
tradotto dal materiale originale del

THE 5 MAJOR KINDS OF CANCER IMMUNOTHERAPY

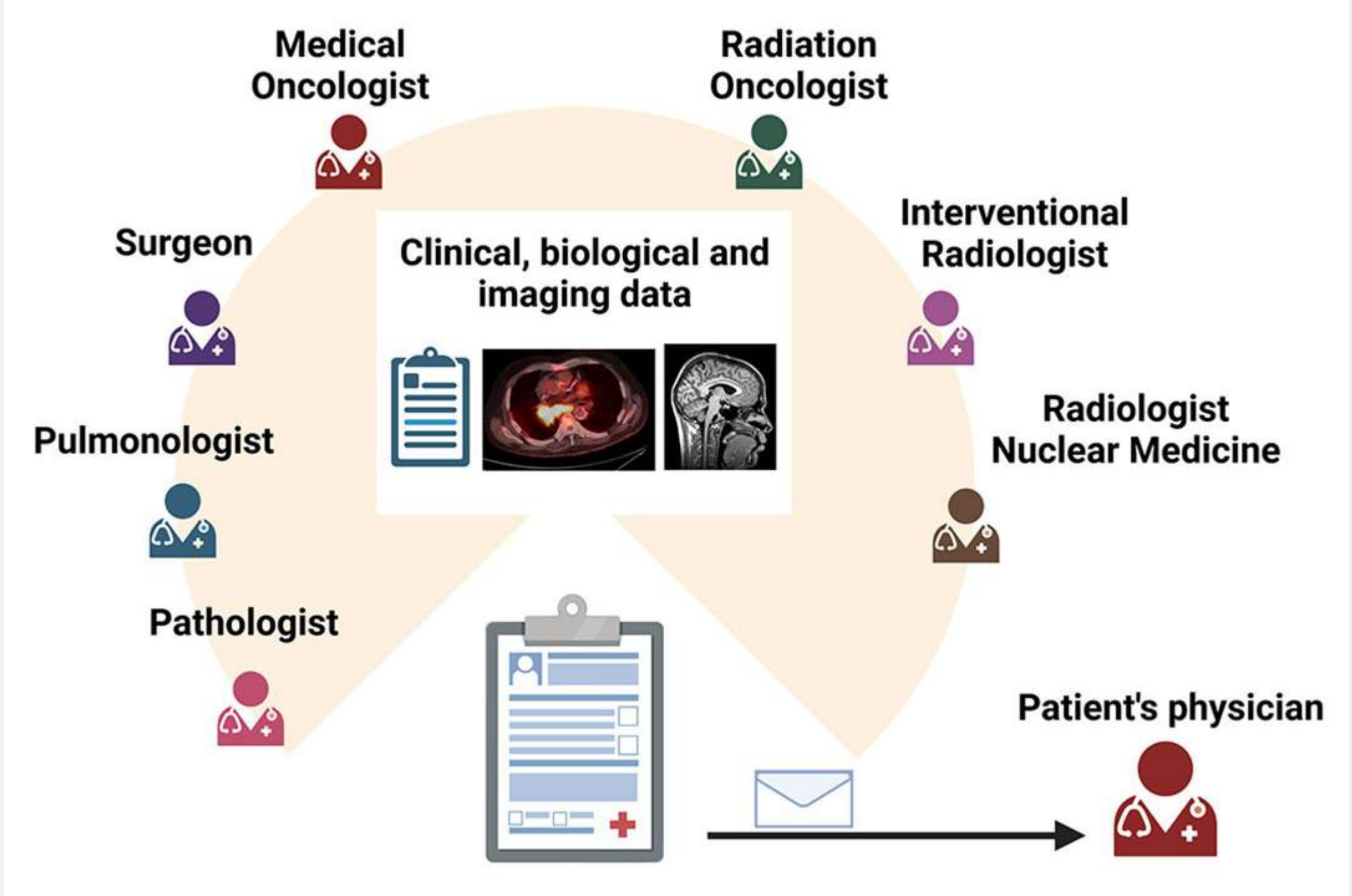
New treatments become available all the time so this may not be a complete list. This list does not include clinical trials. **These are the immunotherapies that are available as of November 2020.** For the latest information go to **CancerSupportCommunity.org** and search for your tumor type to find out if new immunotherapy drugs have been approved.

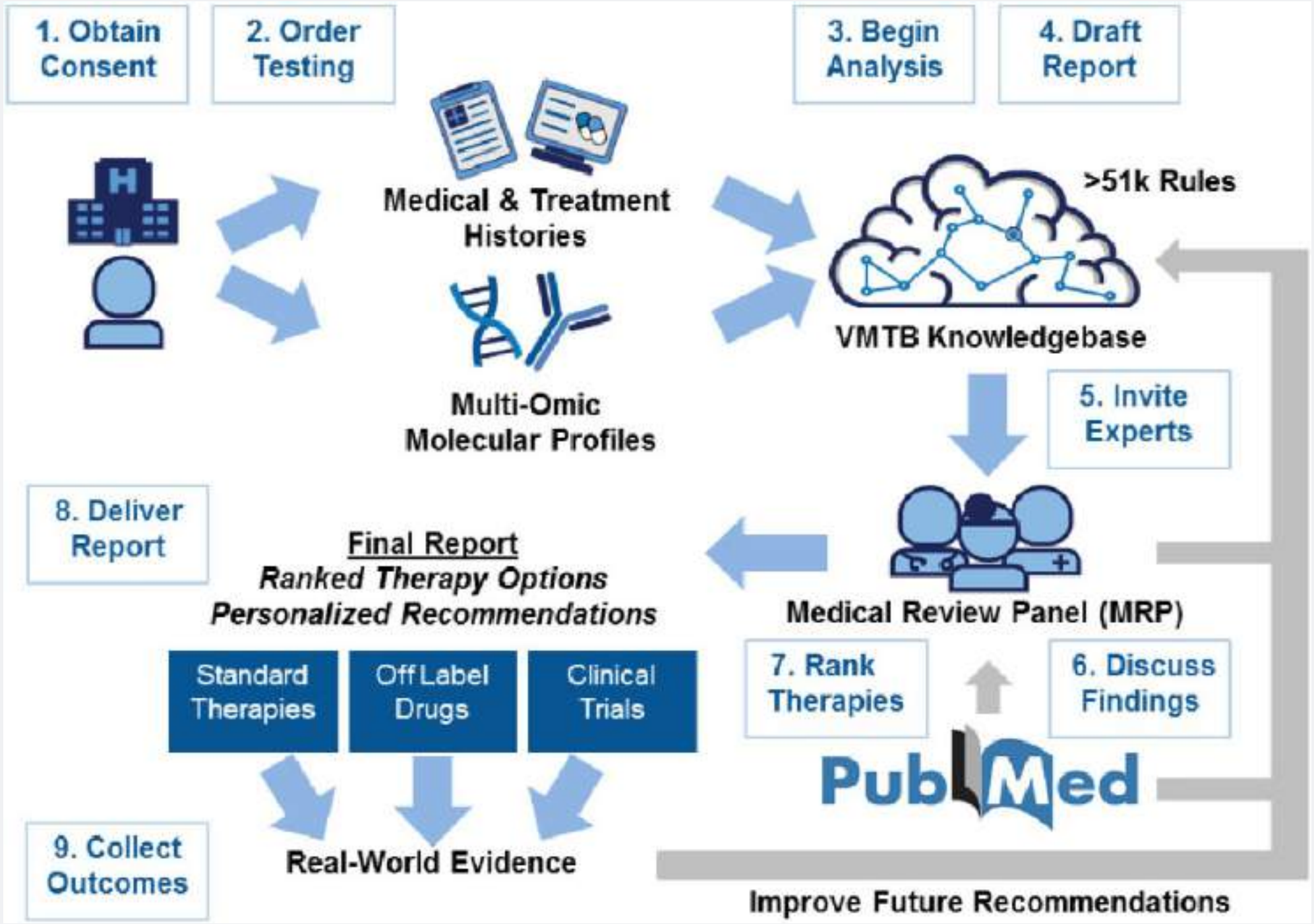
CANCER IMMUNOTHERAPY	DESCRIPTION	GIVEN BY	APPROVED TO TREAT
CHECKPOINT INHIBITORS	Prevents tumor from turning off cancer-fighting cells	IV	Melanoma, Hodgkin lymphoma, Merkel cell and cutaneous squamous cell carcinoma, head and neck cancer, triple negative breast cancer, and lung, colorectal, kidney, bladder, cervical, endometrial, liver, and stomach cancers, as well as any non-blood cancers that test positive for the biomarkers MSI-high/dMMR
CELL THERAPY	Modifies the body's own immune cells to become a cancer treatment drug	IV	CAR T therapy for leukemia and lymphoma
CYTOKINES	Boosts the body's immune system generally	IV	Advanced melanomas and kidney cancers
TREATMENT VACCINES	Teaches the body's immune cells to find cancer cells	IV	Prostate cancer
ONCOLYTIC VIRUS THERAPY	Uses viruses to fight cancer cells	IV	Advanced melanoma

ALLEANZA
CONTRO
IL CANCRO

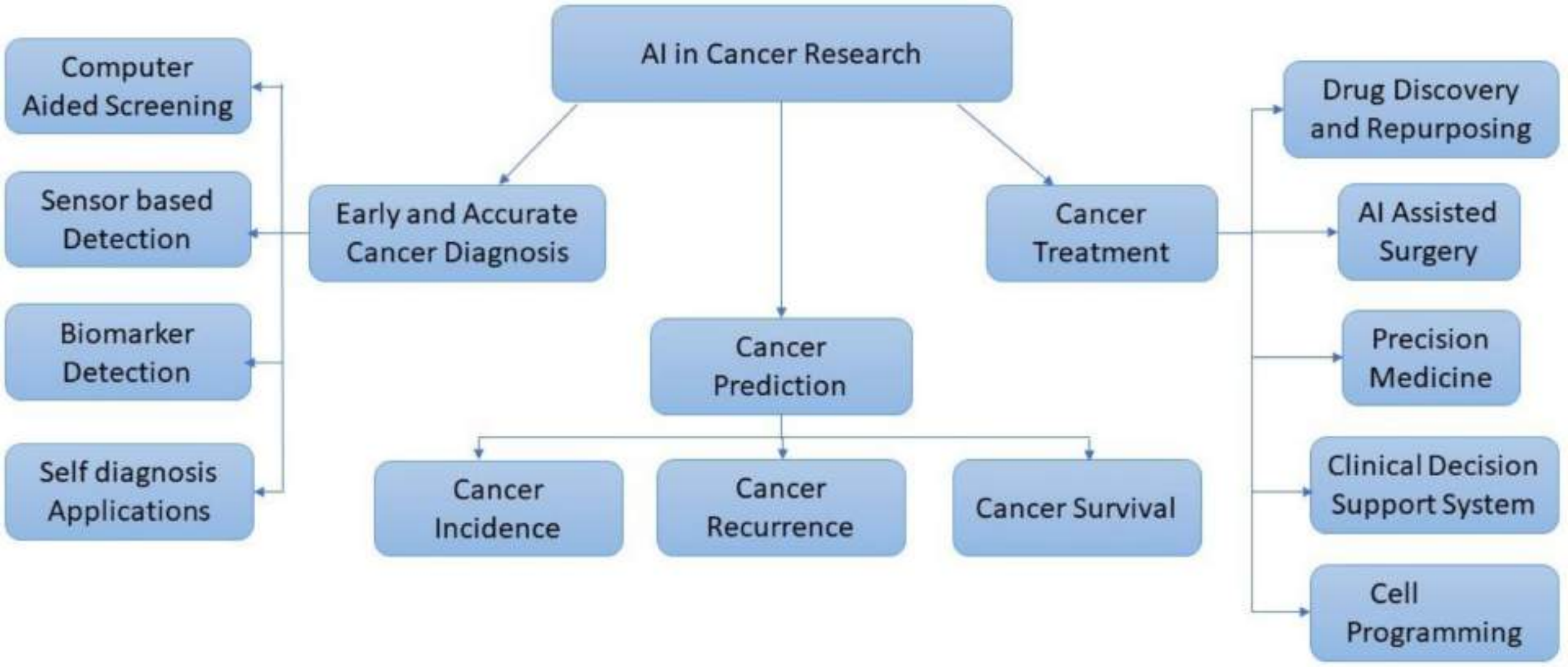
MTB

MOLECULAR TUMOR BOARD


Medical Oncologist
Radiation Oncologist
Surgeon
Clinical, biological and imaging data
Interventional Radiologist
Pulmonologist
Radiologist Nuclear Medicine
Pathologist
Patient's physician


1. Obtain Consent
2. Order Testing
3. Begin Analysis
4. Draft Report
Medical & Treatment Histories
Multi-Omic Molecular Profiles
>51k Rules
VMTB Knowledgebase
5. Invite Experts
Medical Review Panel (MRP)
7. Rank Therapies
6. Discuss Findings
PubMed
8. Deliver Report
Final Report
Ranked Therapy Options
Personalized Recommendations
Standard Therapies
Off Label Drugs
Clinical Trials
Real-World Evidence
9. Collect Outcomes
Improve Future Recommendations

The future in cancer research



New perspectives in cancer researches

- Microenvironment
- Immunology
- Interfering on biological pathways
- Gene therapy
- Liquid biopsy to monitor cancer in every moment
- Big Data
- Artificial intelligence
- Cancer prevention
- Social changes

Cancer as Chronic Disease

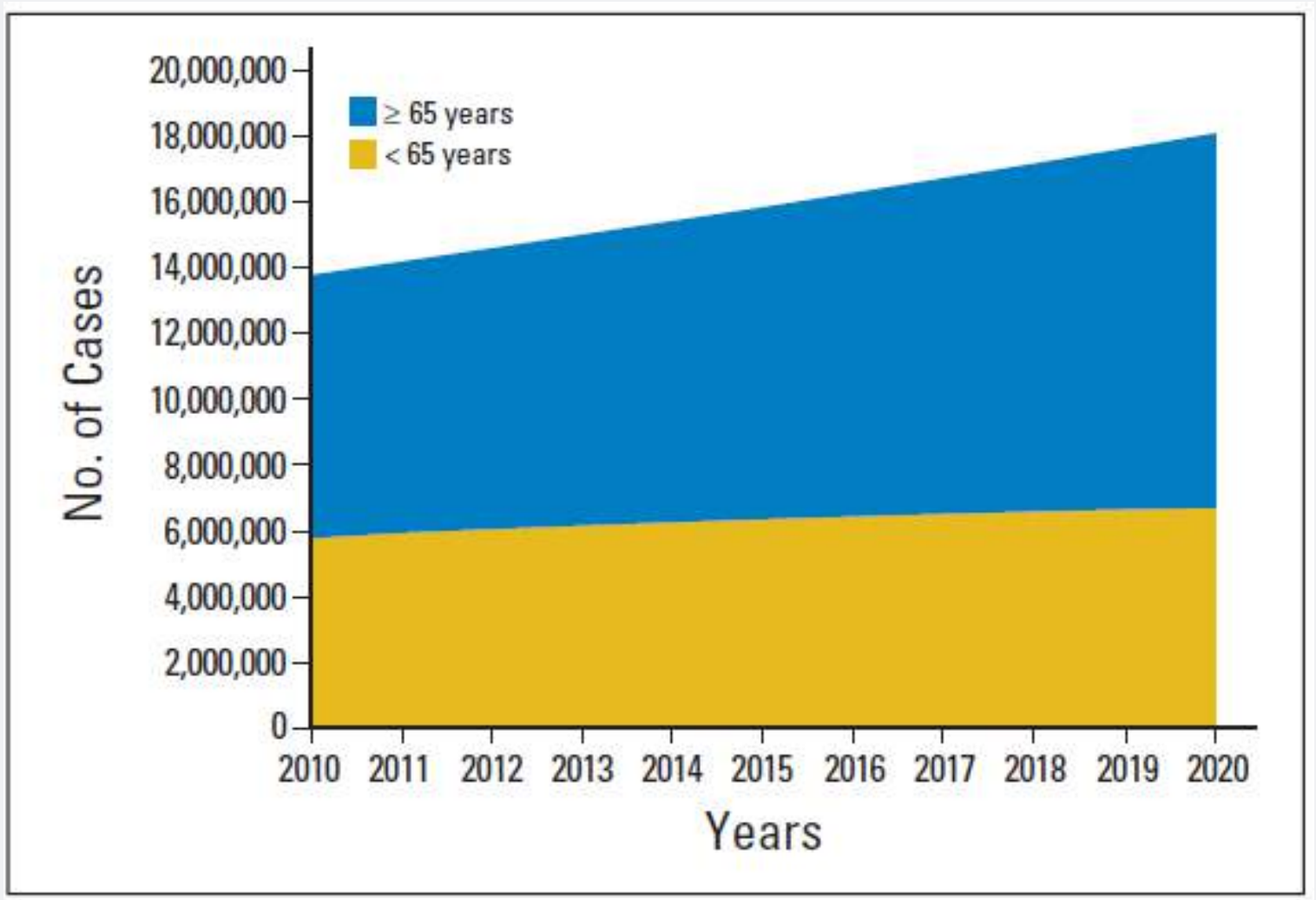
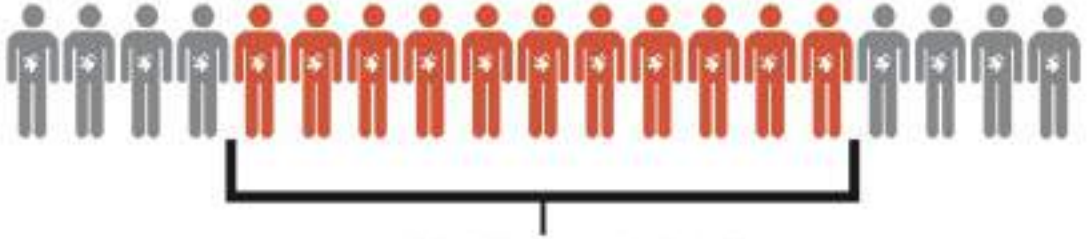


Fig 1. Estimated number of persons with history of cancer from 1971 to 2008, by age group, projected through the year 2030. Data adapted.[1]

Persone in Italia che vivono avendo avuto una diagnosi di tumore

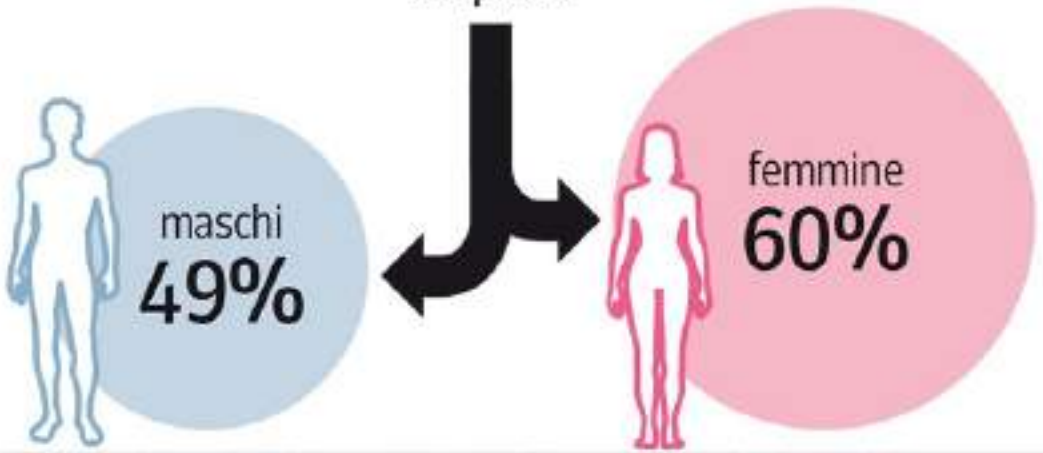
2.250.000



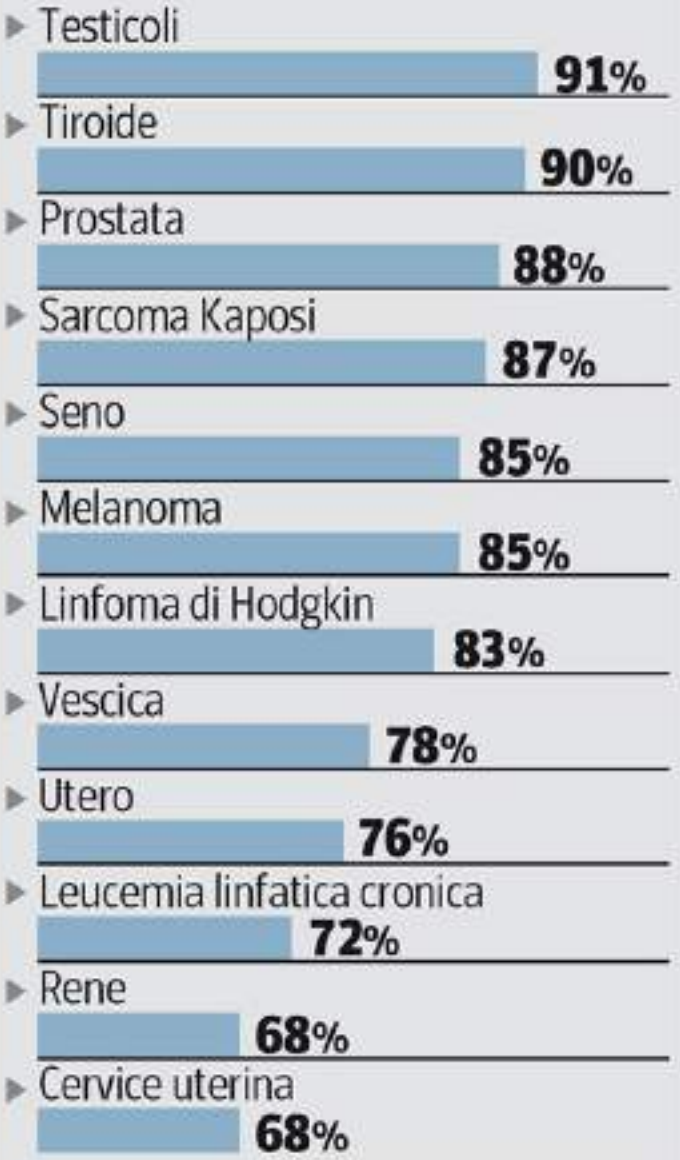
1.300.000

sono i cosiddetti lungo-sopravviventi
(cioè hanno avuto la diagnosi almeno 5 anni prima)

Di questi



Forme per cui il tasso di sopravvivenza dopo 5 anni è maggiore



Fonte: **Rapporto 2011 Airtum, La sopravvivenza dei pazienti oncologici in Italia**

CORRIERE DELLA SERA

SPECIAL ARTICLE

Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus

G. Curigliano[1*], S. Banerjee[2], A. Cervantes[3,4], M. C. Garassino[5], P. Garrido[6], N. Girard[7,8], J. Haanen[9], K. Jordan[10],

Family caregivers (FCGs) play a vital role in the direct care and support of patients with cancer. The importance of FCGs is significantly increasing given the shift to outpatient and home-based care, the increasing age of the population, the increase of median survival of the patients and social and economical changes. COVID 19 Pandemics has increased the hardship.

FINANCIAL TOXICITY

What is Financial Toxicity in Cancer ?

Know more about Financial Distress or Financial Burden of Cancer, its Impact, Factors That Contribute to toxicity & Ways To Reduce cancer related financial toxicity.

TRIDGE CANCER