Evoluzione della farmacologia oncologica

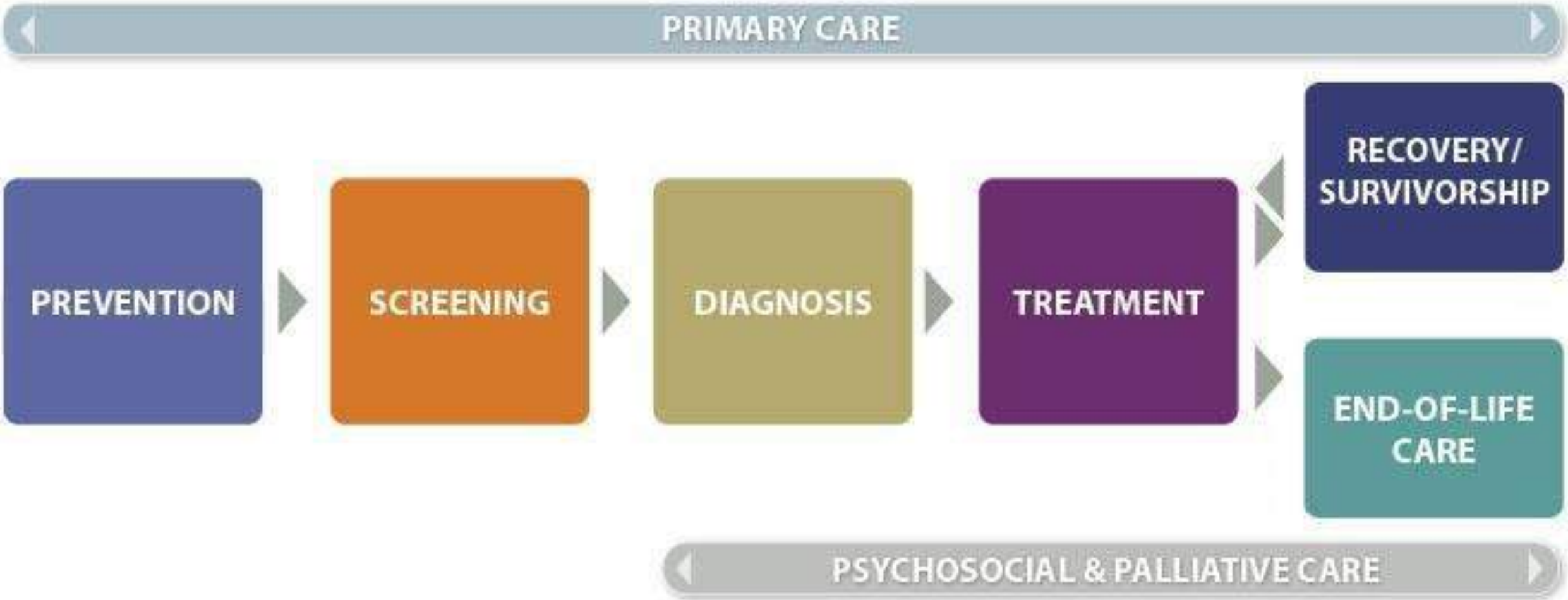
Alessandro Comandone

Rete Oncologica Piemonte e Valle d'Aosta

SC Oncologia ASL Città di Torino

The cancer journey

Better cancer services every step of the way



Traditional palliative care

Early palliative care

Types of Cancer Treatment

Surgery

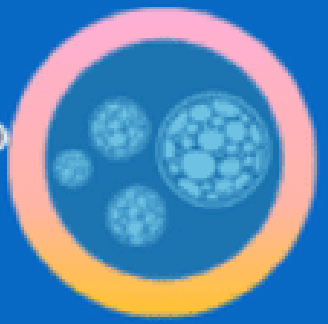
Radiation Therapy

Chemo Therapy

ImmunoTherapy

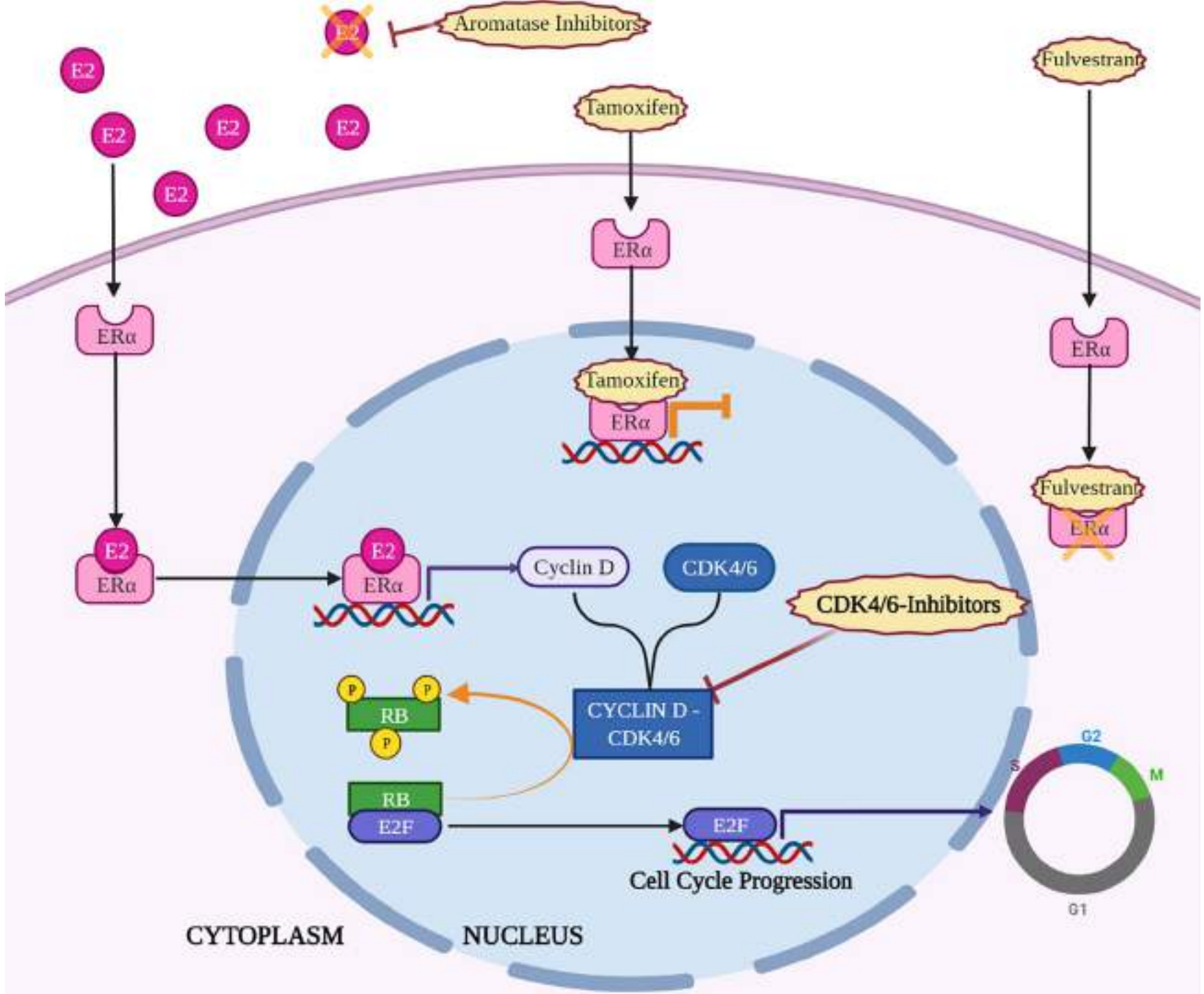
Hormone Therapy

Targeted Therapy



Stem cell therapy


Hormonal
Therapy


Aromatase Inhibitors
E2
E2
E2
E2
E2
Tamoxifen
Fulvestrant
ERα
ERα
ERα
Tamoxifen
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

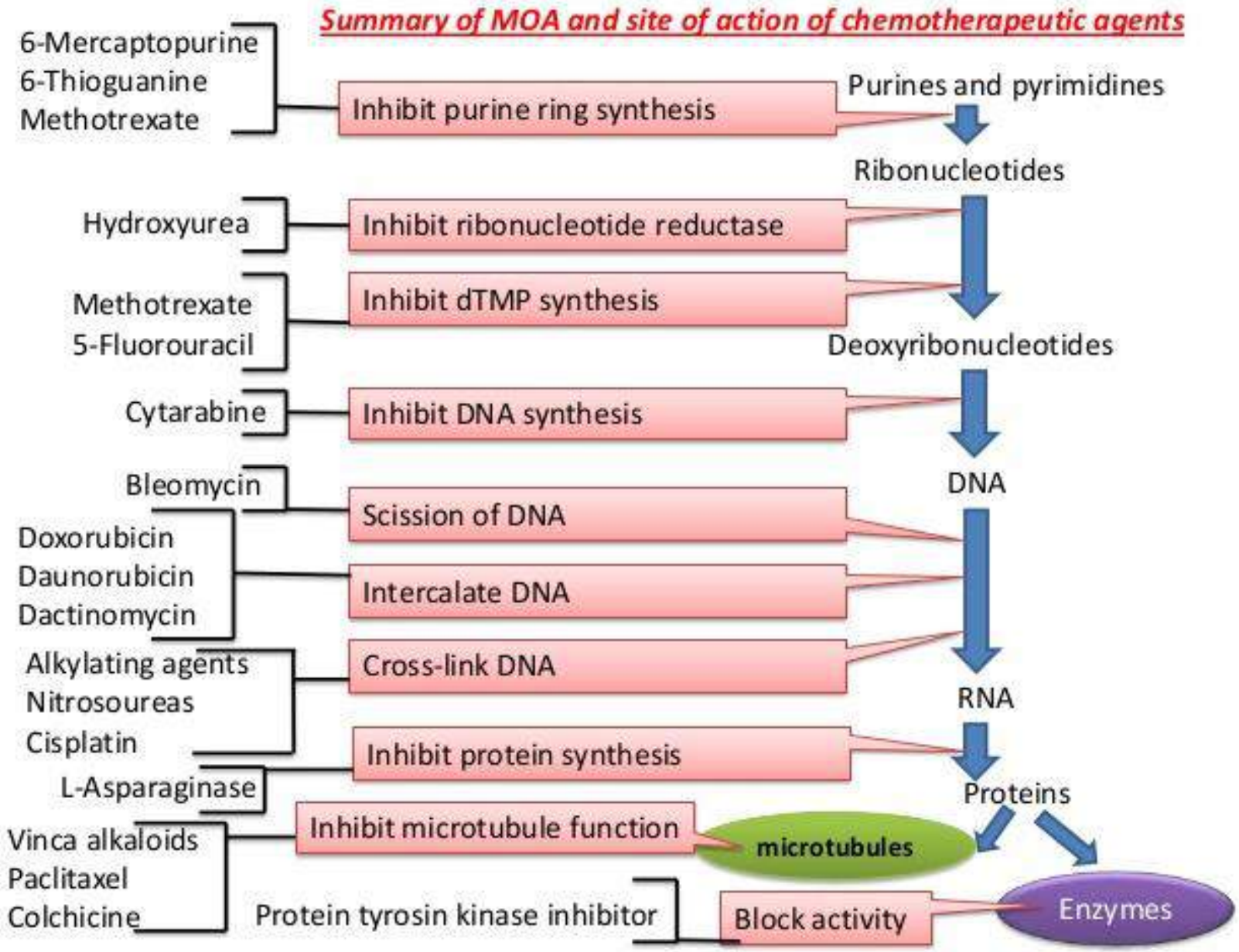
New Drugs in Cancer Chemotherapy

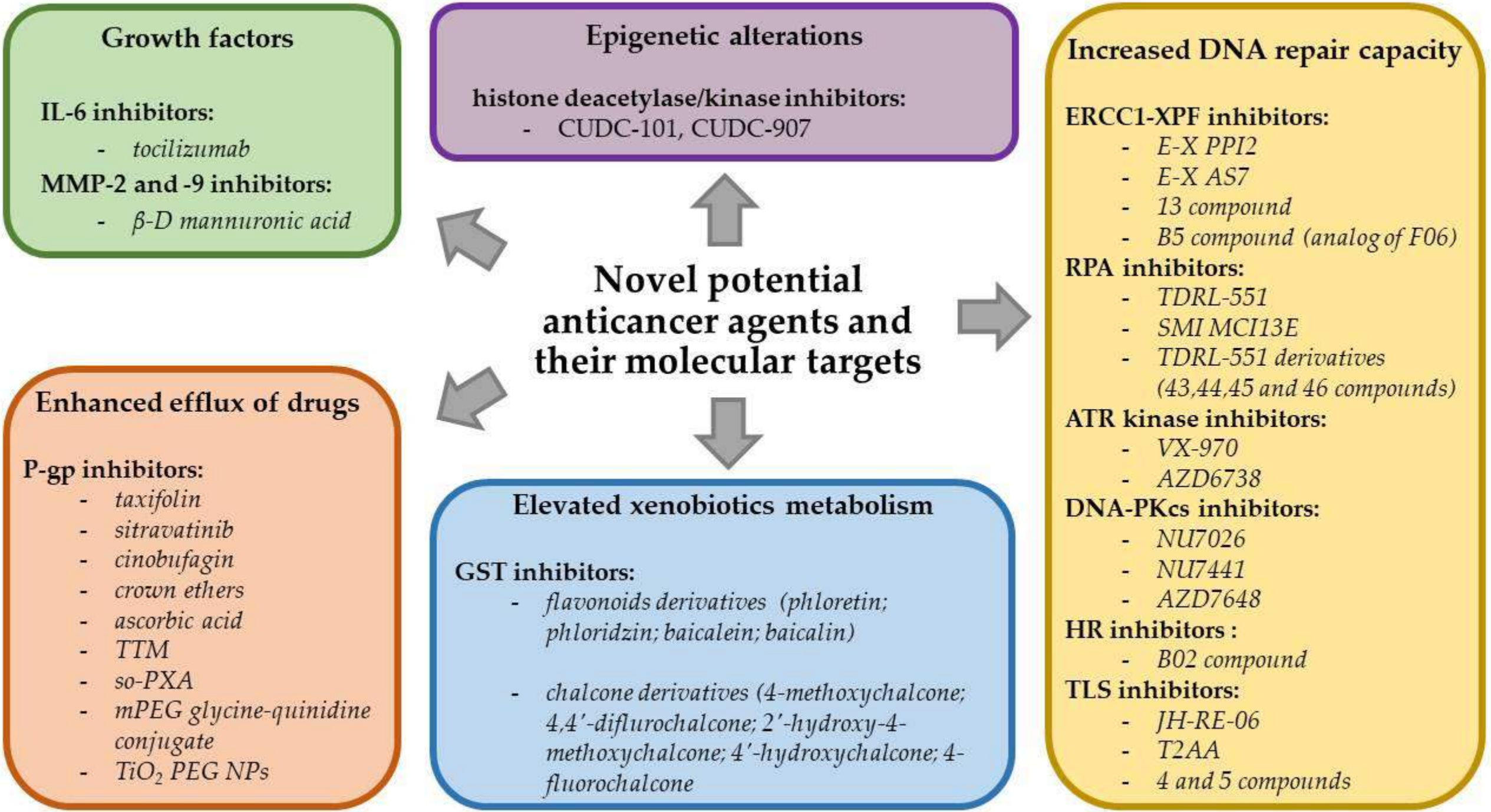
Edited by
S.K.Carter Y. Sakurai H.Umezawa

Chemotherapic agents

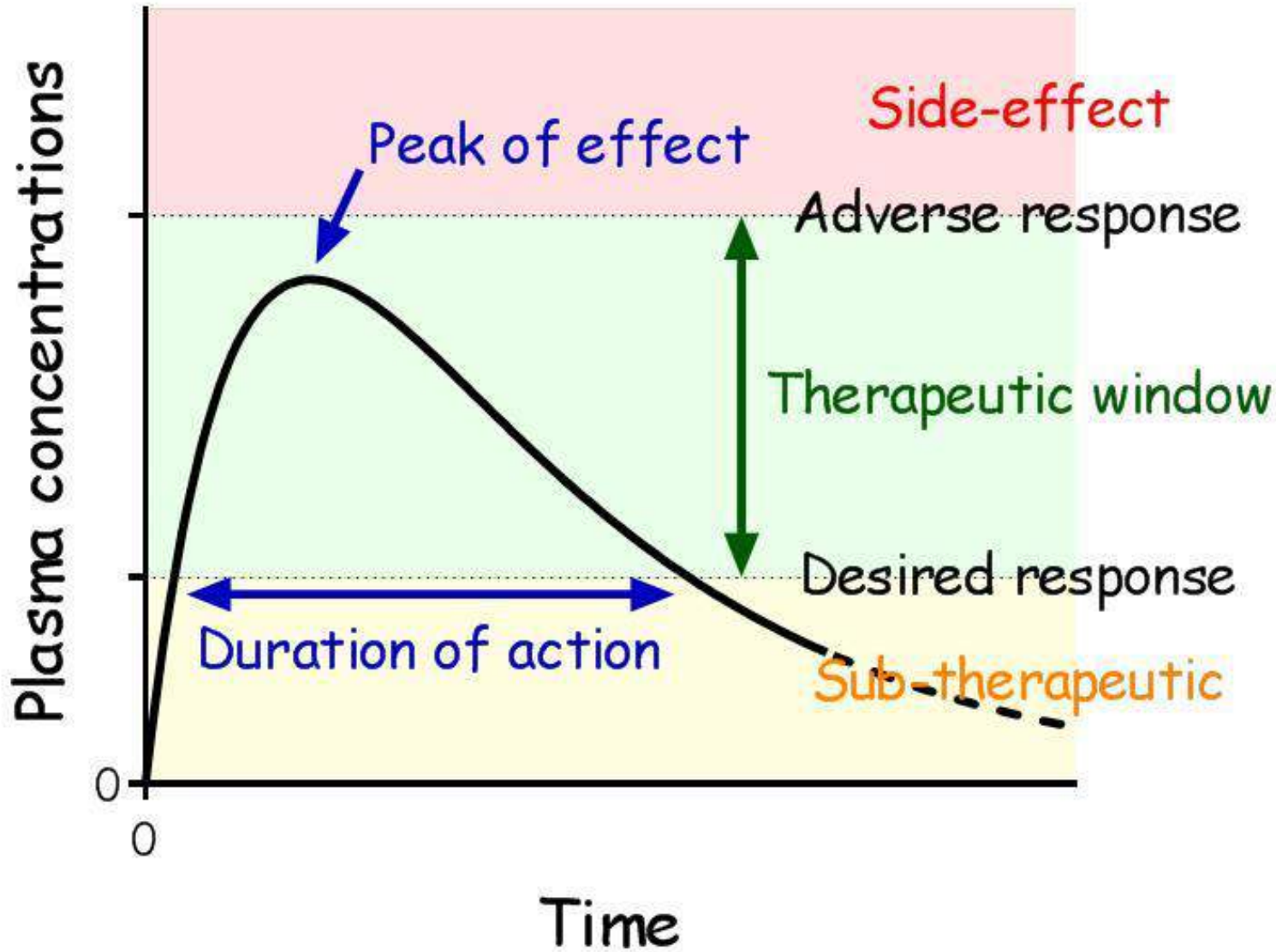
- Chemotherapy from natural agents
- Doxorubicin
- Vinca alcaloids
- Taxans
- Camptotheca derived agents
- Trabectedine
- Eribuline

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

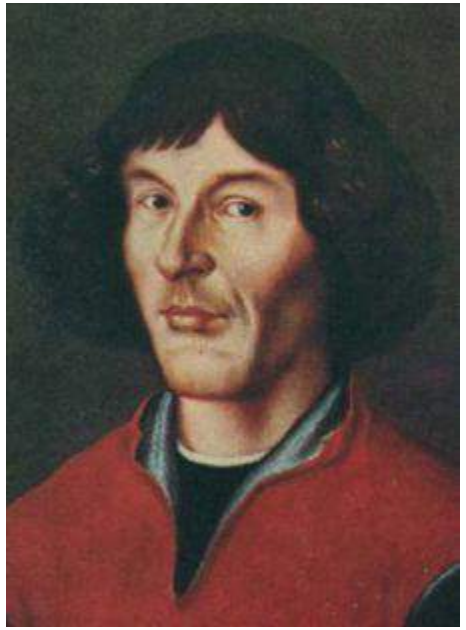

Summary of MOA and site of action of chemotherapeutic agents
6-Mercaptopurine
6-Thioguanine
Methotrexate
Inhibit purine ring synthesis
Purines and pyrimidines
Ribonucleotides
Hydroxyurea
Inhibit ribonucleotide reductase
Methotrexate
5-Fluorouracil
Inhibit dTMP synthesis
Deoxyribonucleotides
Cytarabine
Inhibit DNA synthesis
DNA
Bleomycin
Doxorubicin
Daunorubicin
Dactinomycin
Scission of DNA
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

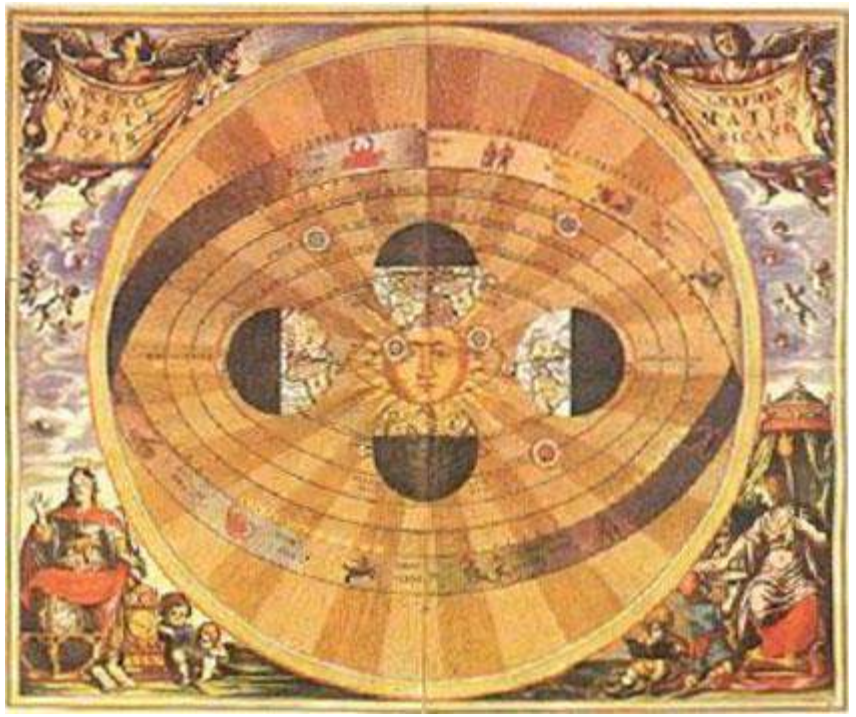

Growth factors
IL-6 inhibitors:
- tocilizumab
MMP-2 and -9 inhibitors:
- β-D mannuronic acid
Epigenetic alterations
histone deacetylase/kinase inhibitors:
- CUDC-101, CUDC-907
Increased DNA repair capacity
ERCC1-XPF inhibitors:
- E-X PPI2
- E-X AS7
- 13 compound
- B5 compound (analog of F06)
RPA inhibitors:
- 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

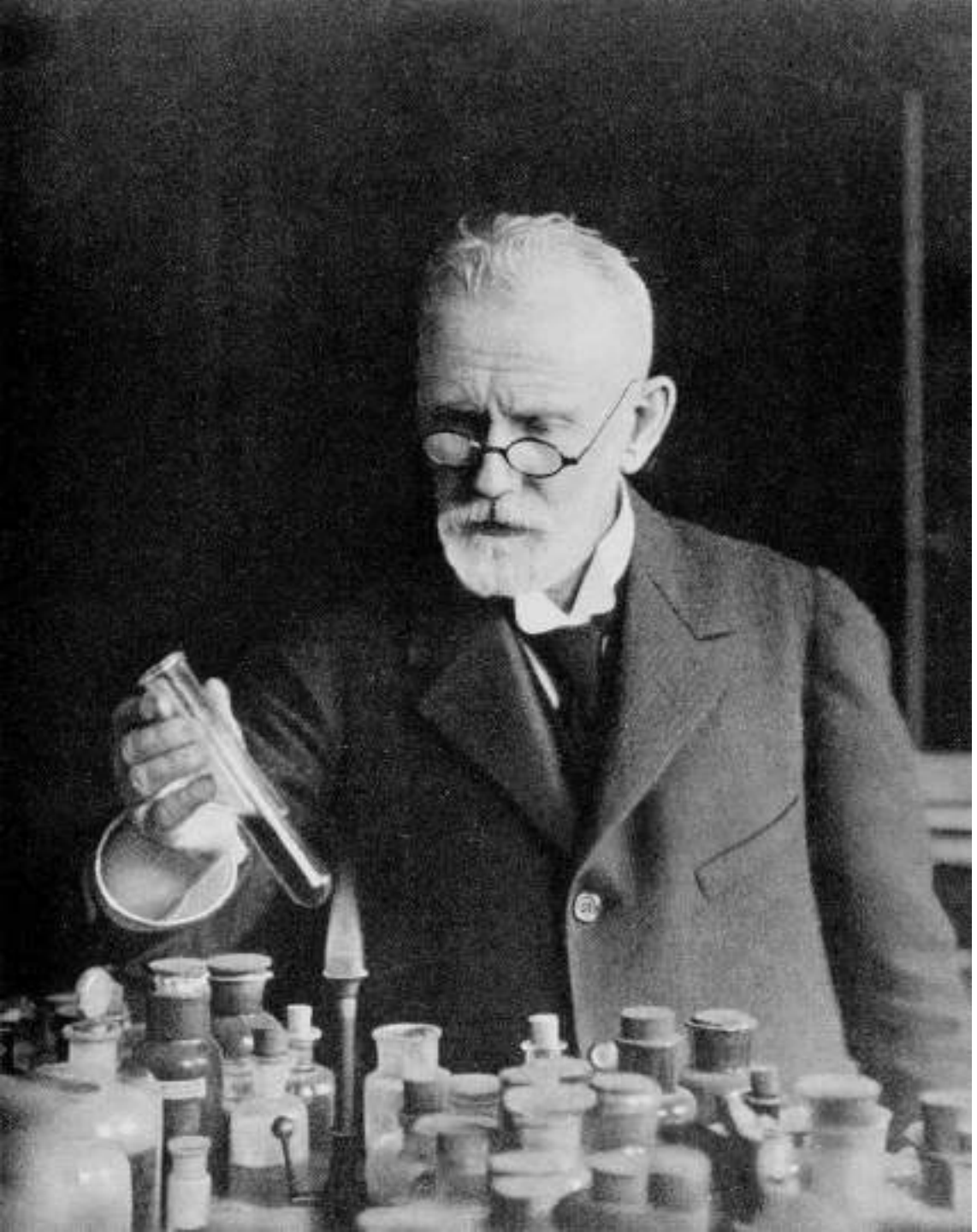
Therapeutic window



The Copernican revolution in Pharmacology







- PAUL EHRLICH
- MAGIC BULLET
- CHEMOTHERAPY

- “ Improving the therapeutic window and reducing side effects”

(Ziwen Fu 2022)

Cell

Leading Edge
Review

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

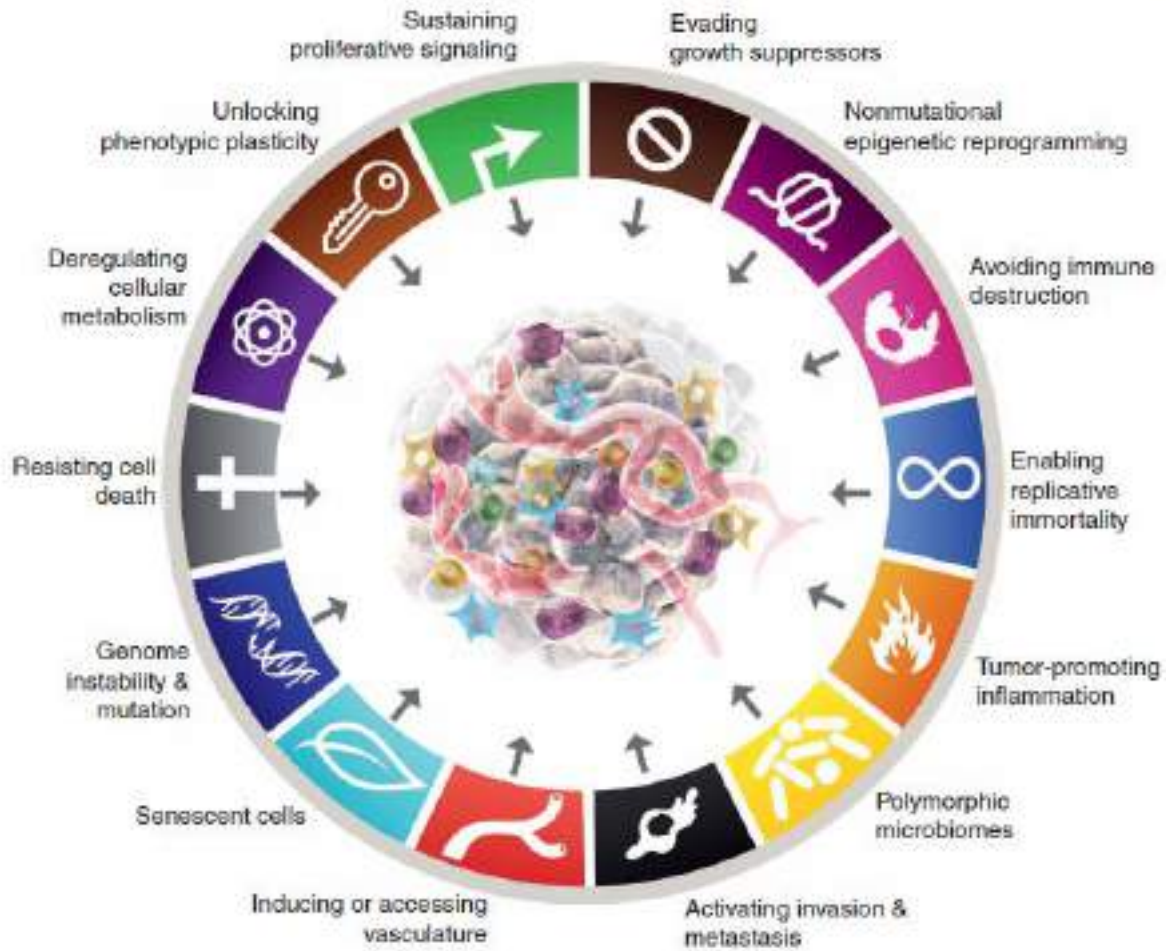


Figure 6. Hallmarks of Cancer—new additions. Depicted are the canonical and prospective new additions to the "Hallmarks of Cancer." This treatise raises the possibility, aiming to stimulate debate, discussion, and experimental elaboration, that some or all of the four new parameters will come to be appreciated as generic to multiple forms of human cancer and hence appropriate to incorporate into the core conceptualization of the hallmarks of cancer. The hallmarks of cancer graphic has been adapted from Hanahan and Weinberg (2).

CANCER CELLS CHARACTERISTICS

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

HANAHAN & WEINBERG 2000

- IMMORTALIZATION
- UNCONTROLLED GROWTH
- DIFFERENT METABOLISM

HANAHAN & WEINBERG 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
-

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

Introduction:

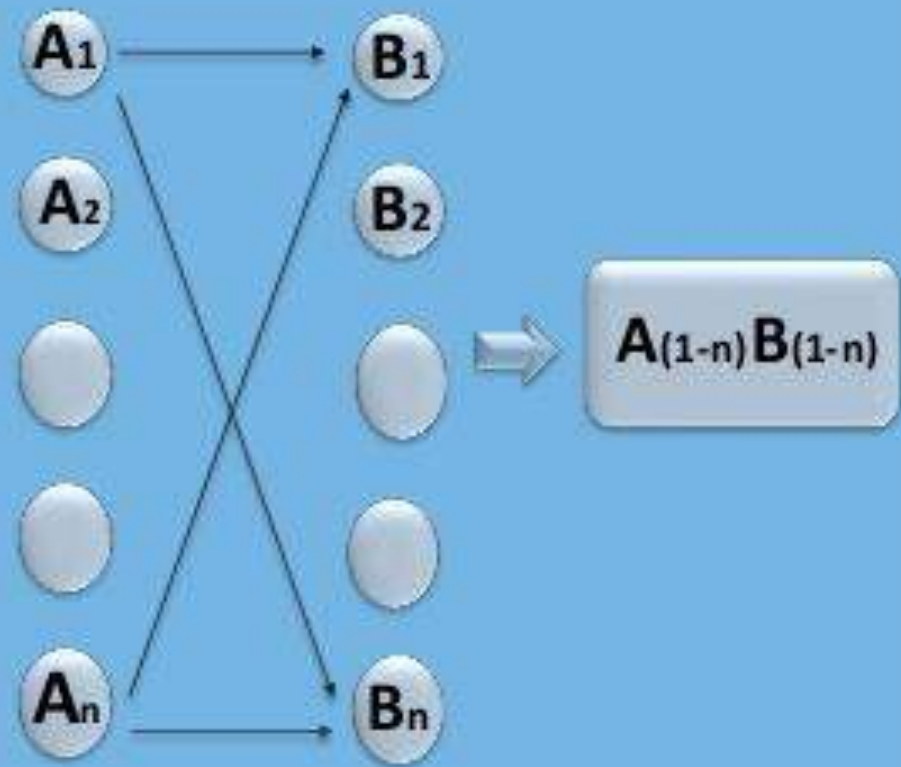
•Combinatorial Chemistry is a new method developed by academics and researchers to reduce the time and cost of producing effective, marketable and competitive new drugs.

• Scientists use Combinatorial Chemistry to create large numbers of molecules that can be detected efficiently.

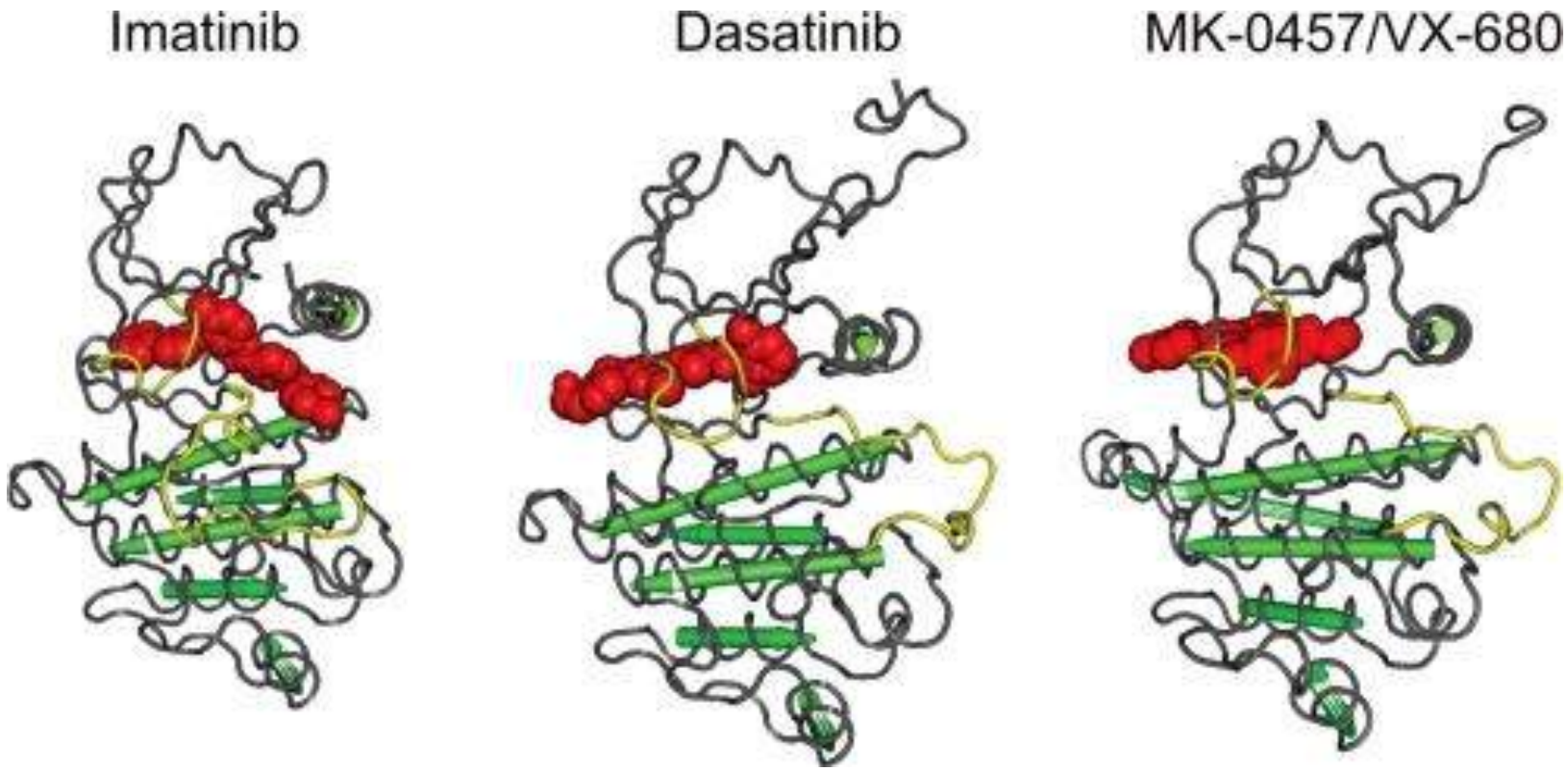
•This technique has captured the attention of many areas such as Pharmaceutical chemistry, Biotechnology and Agro chemistry.

Traditional synthesis

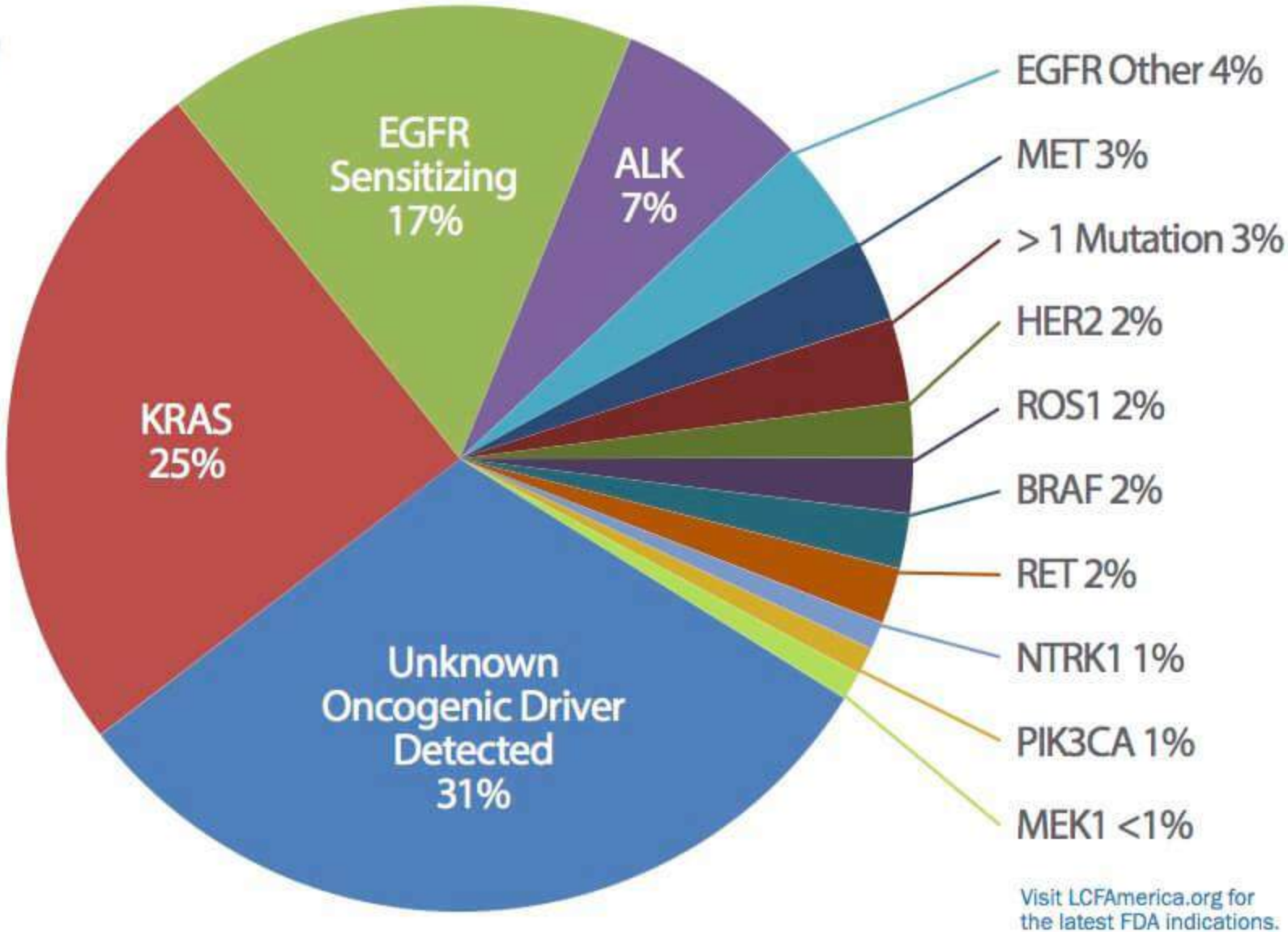
Combinatorial synthesis

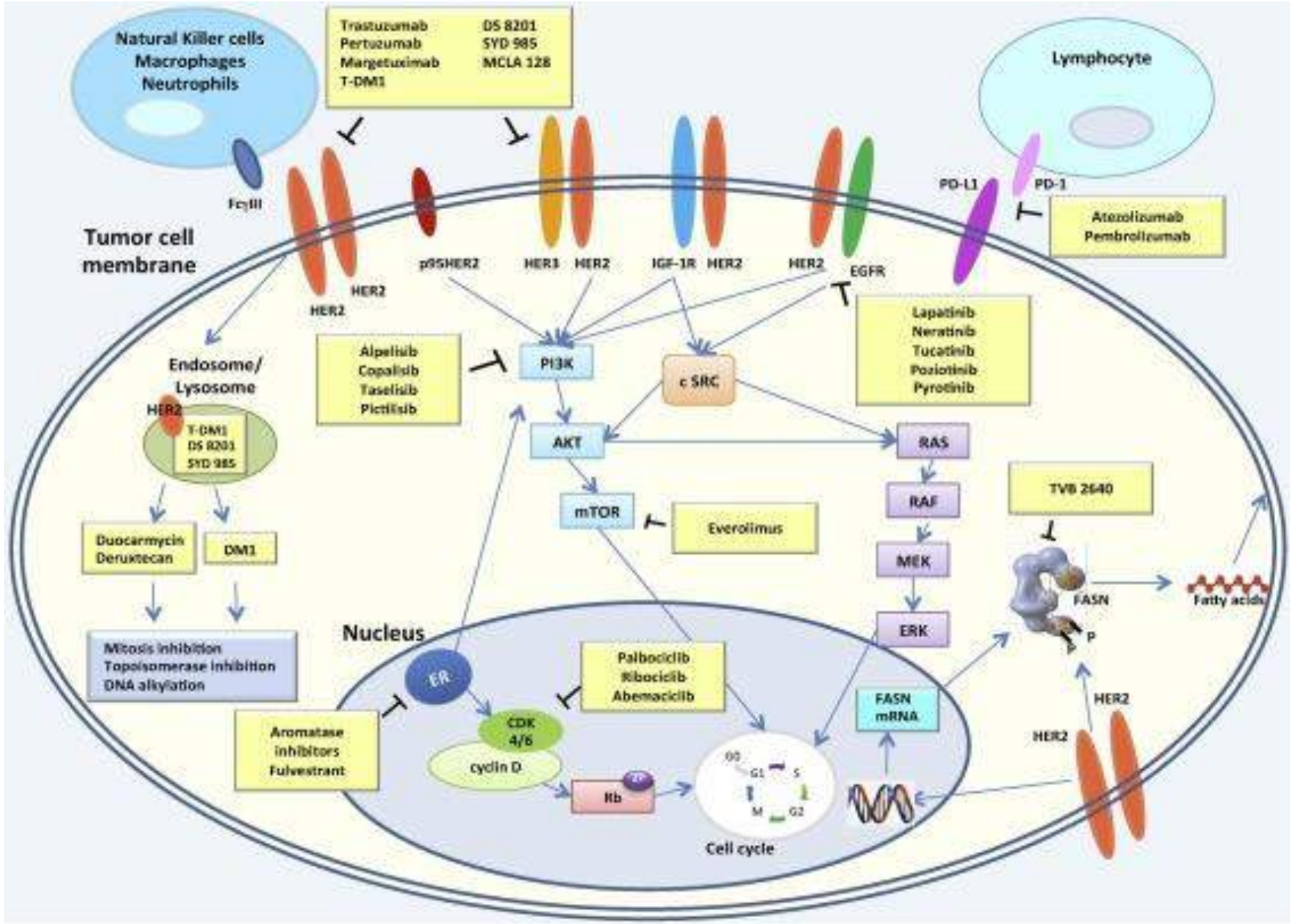


Silico Modeling



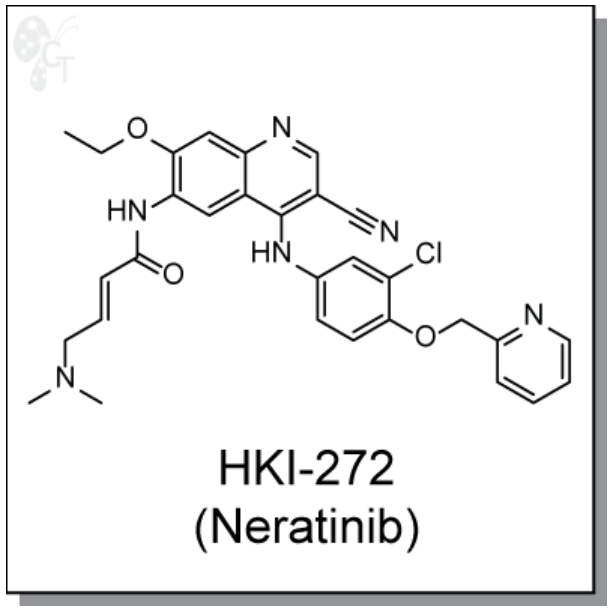
NSCLC ONCOGENE ADDICTION

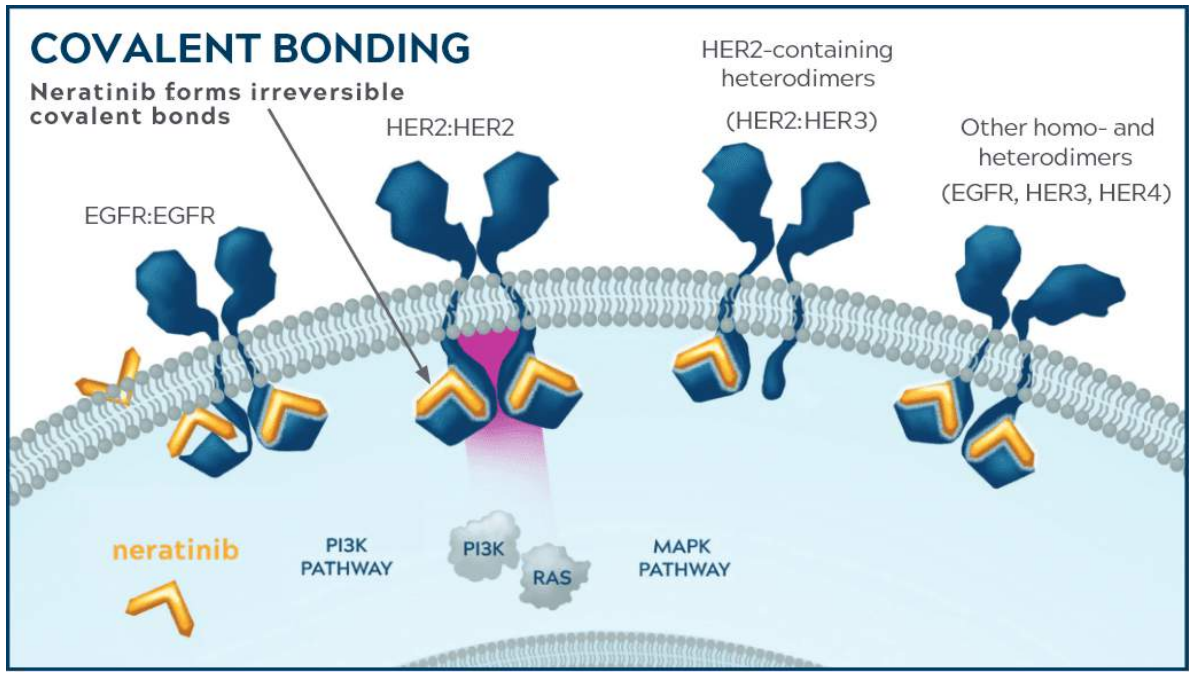



Natural Killer cells
Macrophages
Neutrophils
Trastuzumab
Pertuzumab
Margetuximab
T-DM1
DS 8201
SYD 985
MCLA 128
Lymphocyte
FcγIII
PD-L1
PD-1
Atezolizumab
Pembrolizumab
Tumor cell membrane
HER2
HER2
p95HER2
HER3
HER2
IGF-1R
HER2
HER2
EGFR
Lapatinib
Neratinib
Tucatinib
Poziotinib
Pyrotinib
Endosome/
Lysosome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

NERATINIB

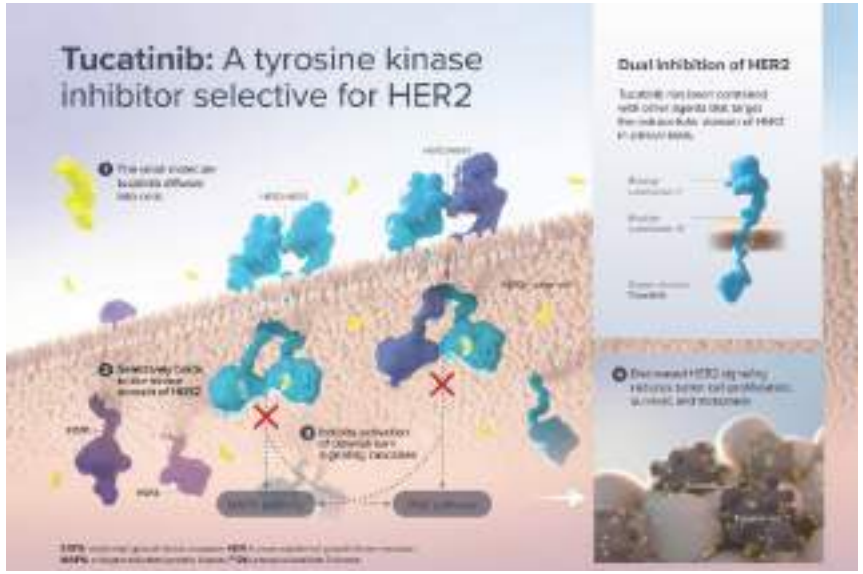
Indicazioni terapeutiche Nerlynx è indicato nel trattamento adiuvante esteso di pazienti adulti con carcinoma mammario in fase iniziale positivo al recettore ormonale con iperespressione/amplificazione di HER2 che hanno completato la terapia adiuvante a base di trastuzumab da meno di un anno.

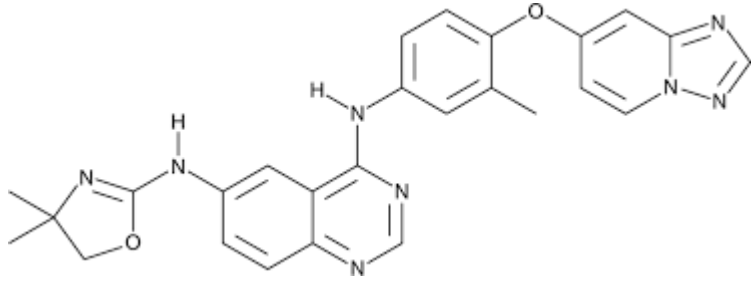




Tucatinib

- Indicazione: TUCATINIB è indicato in associazione a trastuzumab e capecitabina per il trattamento di pazienti adulti affetti da cancro della mammella localmente avanzato o metastatico HER2-positivo che abbiano ricevuto almeno 2 precedenti regimi di trattamento anti-HER2



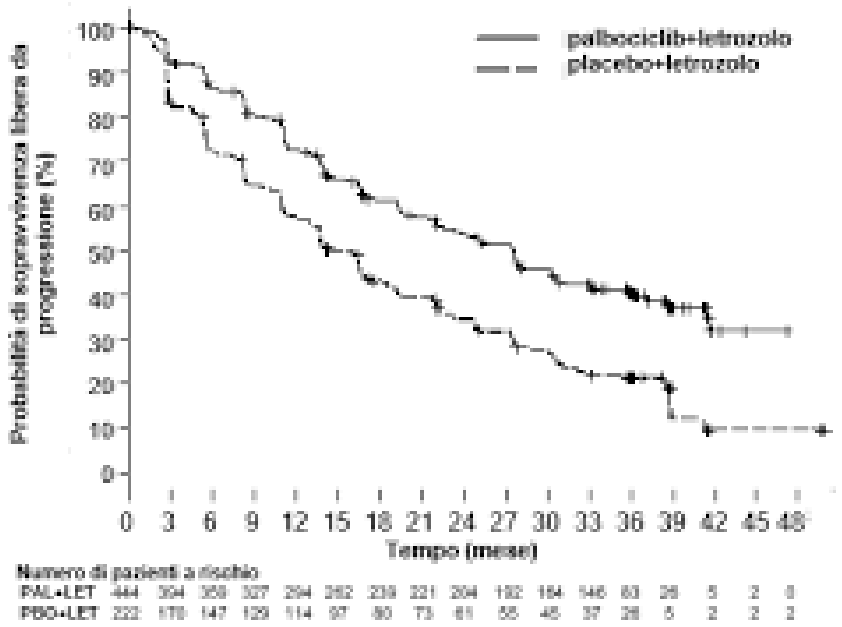


Cyclin Dependent Kinase 4-6 Inhibitors

- PALBOCICLIB (PALOMA STUDY)
- RIBOCICLIB (MONALEESA 2)
- ABEMACICLIB (MONARCH 2 & 3)

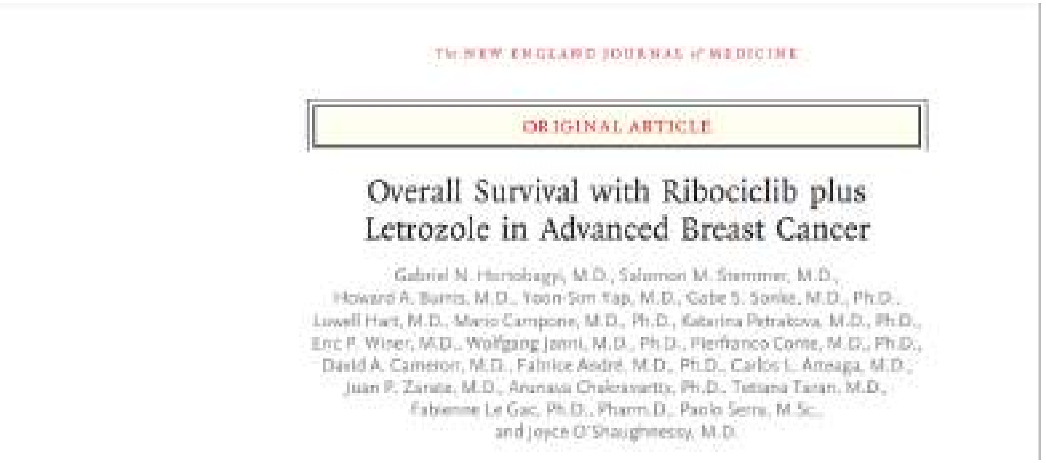
PALBOCICLIB

IBRANCE è indicato per il trattamento del carcinoma mammario localmente avanzato o metastatico positivo ai recettori
ormonali e negativo al recettore del fattore di crescita epidermico umano 2 (HER2):
- in associazione ad un inibitore dell'aromatasi;
- in associazione a fulvestrant in donne che hanno ricevuto una terapia endocrina precedente.
In donne in pre- o perimenopausa, la terapia endocrina deve essere associata ad un agonista dell'ormone di rilascio
dell'ormone luteinizzante (LHRH).



RIBOCICLIB

Indicazioni terapeutiche Kisqali, in associazione a un inibitore dell’aromatasi o a fulvestrant, è indicato nelle donne con cancro della mammella in stadio localmente avanzato o metastatico positivo per il recettore ormonale (HR) e negativo per il recettore 2 per il fattore di crescita epidermico umano (HER2), come terapia iniziale a base endocrina o in donne che hanno in precedenza ricevuto una terapia endocrina. In donne in pre- o perimenopausa, la terapia endocrina deve essere associata ad un agonista dell’ormone di rilascio dell’ormone luteinizzante (LHRH).


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer

Gabriel N. Hortobagyi, M.D., Salomon M. Stemmer, M.D., Howard A. Burris, M.D., Yoon-Sim Yap, M.D., Gabe S. Sonke, M.D., Ph.D., Lowell Hart, M.D., Mario Campone, M.D., Ph.D., Katarina Petrakova, M.D., Ph.D., Eric P. Winer, M.D., Wolfgang Janni, M.D., Ph.D., Pierfranco Conte, M.D., Ph.D., David A. Cameron, M.D., Fabrice André, M.D., Ph.D., Carlos L. Arteaga, M.D., Juan P. Zarate, M.D., Arunava Chakravartty, Ph.D., Tetiana Taran, M.D., Fabienne Le Gac, Ph.D., Pharm.D., Paolo Serra, M.Sc., and Joyce O’Shaughnessy, M.D.

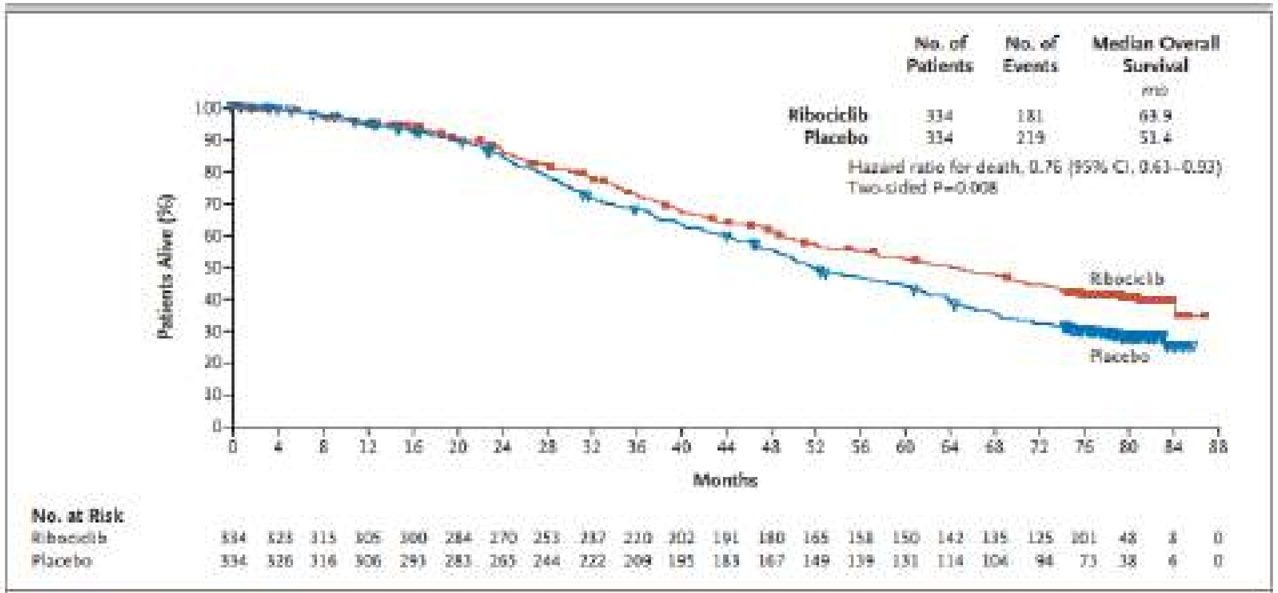


Figure 1. Overall Survival.
Patients in both groups also received letrozole. Squares (ribociclib group) and triangles (placebo group) indicate censored data.

ABEMACICLIB

Verzenios in associazione alla terapia endocrina è indicato endocrina con inibitore dell'aromatasi deve essere associata a un agonista dell'ormone di rilascio dell'ormone luteinizzante (LHRH). per il trattamento adiuvante di pazienti adulti con carcinoma mammario in fase iniziale, positivo al recettore ormonale (HR), negativo al recettore del fattore di crescita umano epidermico di tipo 2 (HER2), linfonodo-positivo, ad alto rischio di recidiva *(vedere paragrafo 5.1).Nelle donne in pre- o perimenopausa, la terapia

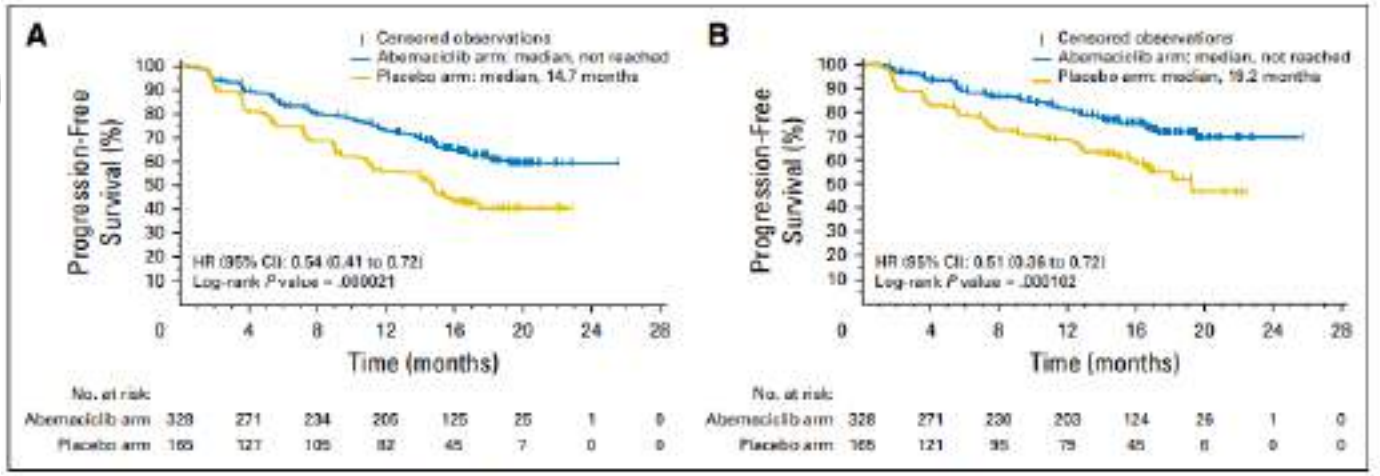
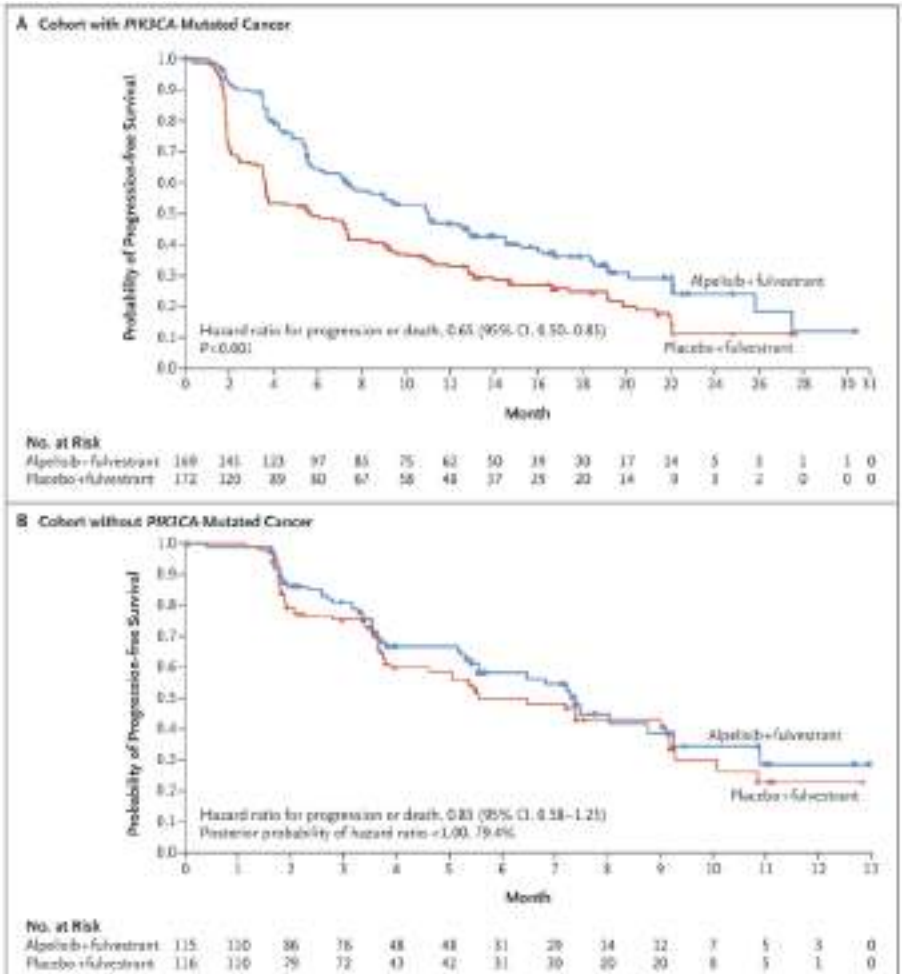
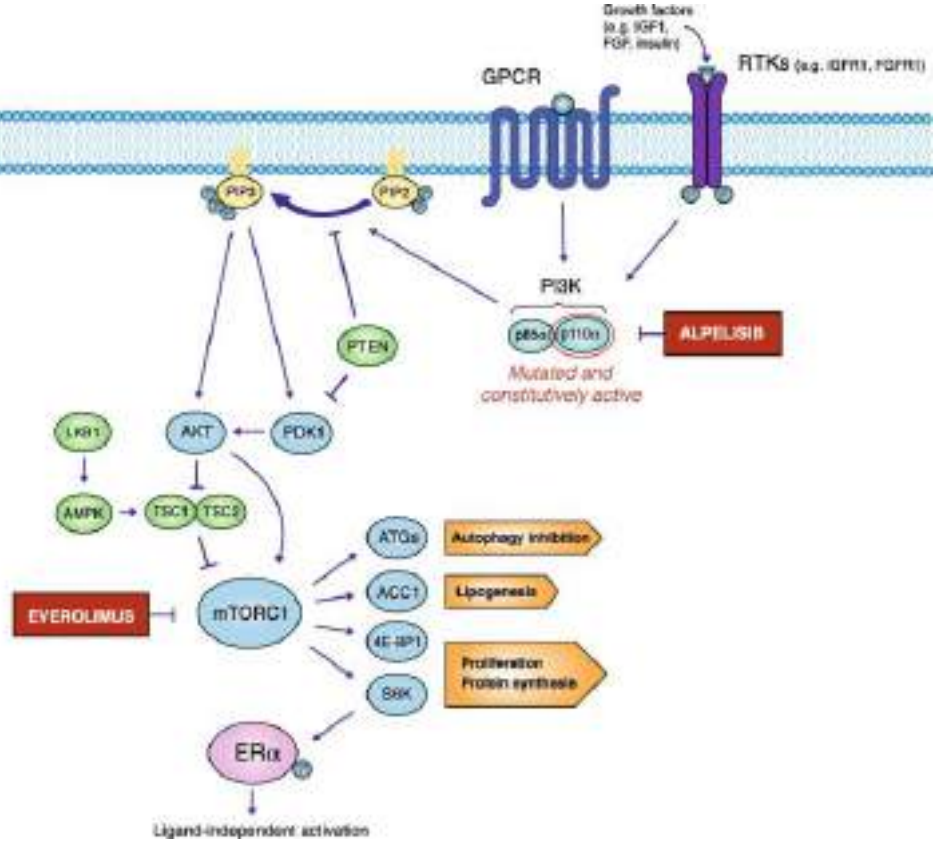


Fig 2. Progression-free survival. (A) Investigator-assessed progression-free survival in the intent-to-treat population. (B) Progression-free survival in the intent-to-treat population as evaluated by a blinded, independent central review. Abbreviations: HR, hazard ratio.

ALPELISIB

ALPELISIB è indicato in associazione a fulvestrant per il trattamento delle donne in post-menopausa, e degli uomini, affetti da carcinoma mammario localmente avanzato o metastatico positivo ai recettori ormonali (HR), negativo al recettore del fattore umano di crescita epidermico di tipo 2 (HER2),con mutazione di PIK3CA, dopo progressione di malattia successiva a terapia endocrina come monoterapia .





PARP INIBITORI

Section Editors: Christopher J. Campen and Beth Eaby-Sandy

Olaparib: A Novel Therapy for Metastatic Breast Cancer in Patients With a *BRCA1/2* Mutation

SARAH E. CAULFIELD, PharmD, BCOP, CHRISTINE C. DAVIS, PharmD, and KRISTINA F. BYERS, PharmD, BCOP

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer

A.N.J. Tutt, J.E. Garber, B. Kaufman, G. Viale, D. Fumagalli, P. Rastogi, R.D. Gelber, E. de Azambuja, A. Fielding, J. Balmaña, S.M. Domchek, K.A. Gelmon, S.J. Hollingsworth, L.A. Korde, B. Linderholm, H. Bandos, E. Senkus, I.M. Suga, Z. Shao, A.W. Pippas, Z. Nowecki, T. Huzarski, P.A. Ganz,

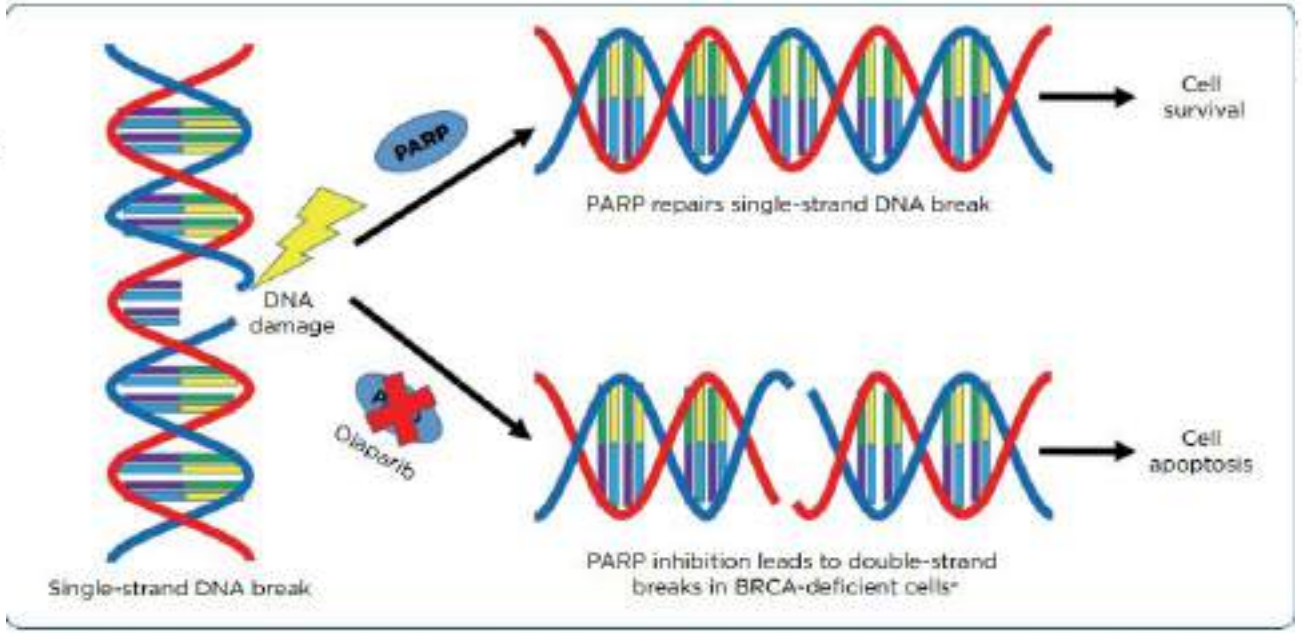
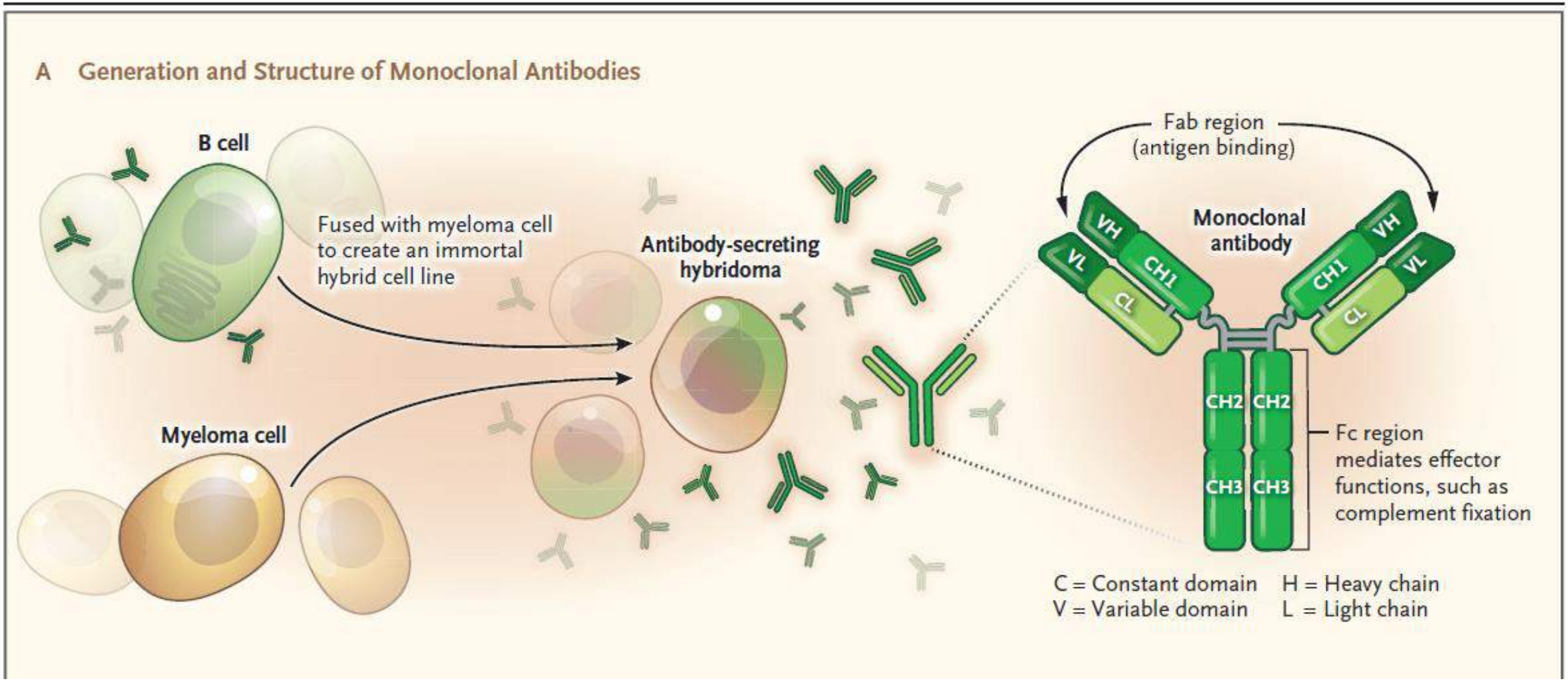
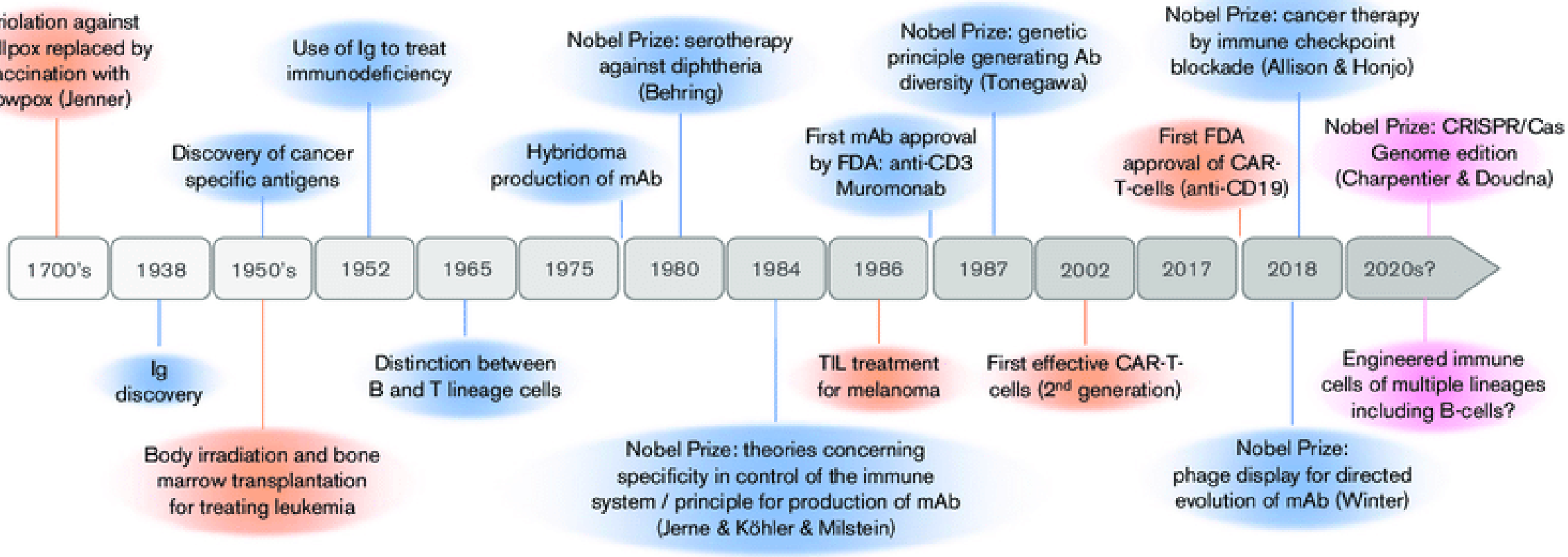
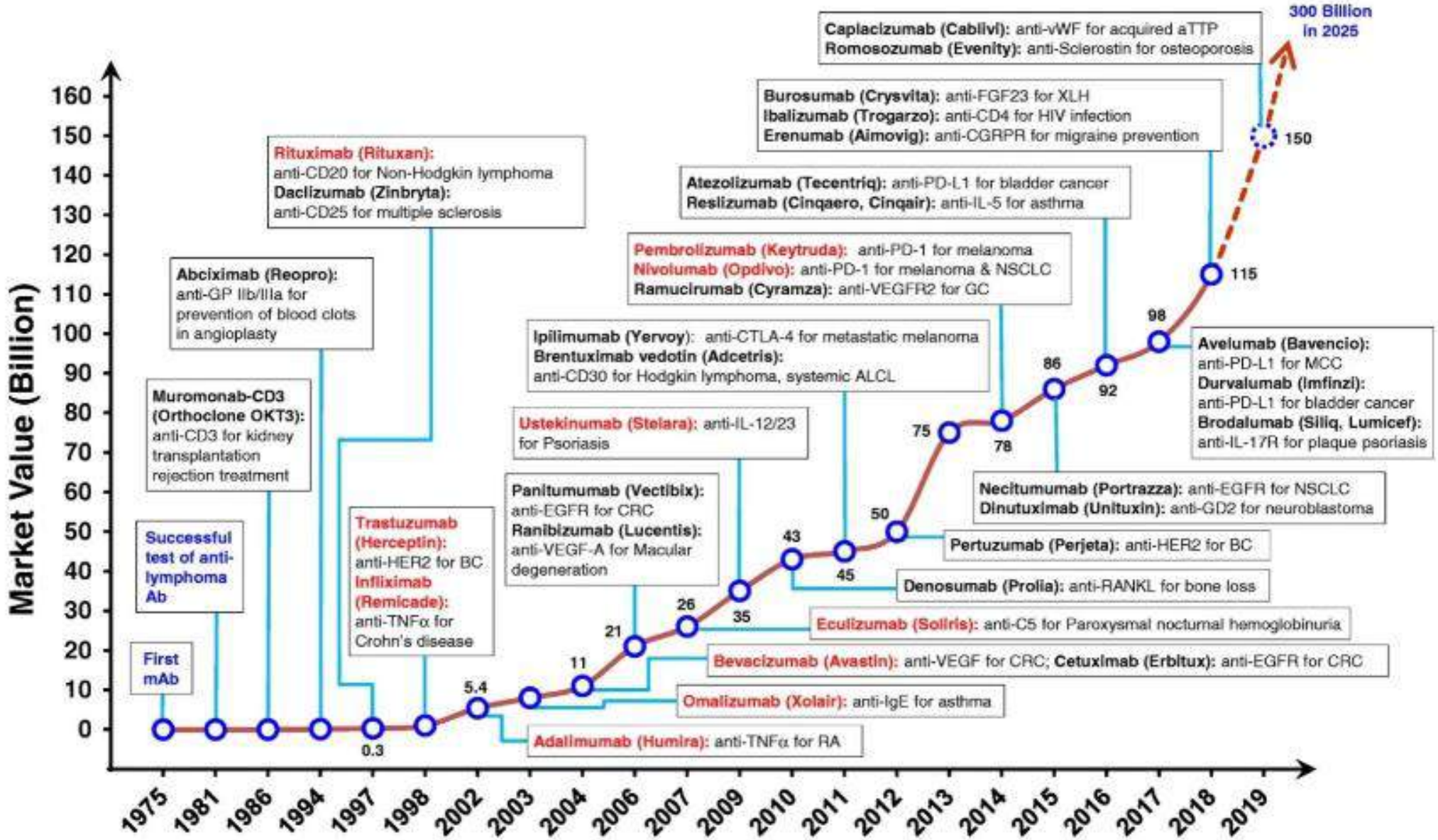


Figure 1. Olaparib mechanism, specifically in BRCA-deficient cells compared to normal cells. PARP = poly (ADP-ribose) polymerase; BRCA = breast cancer gene 1.
*BRCA-proficient cells can repair double-strand breaks, resulting in cell survival.

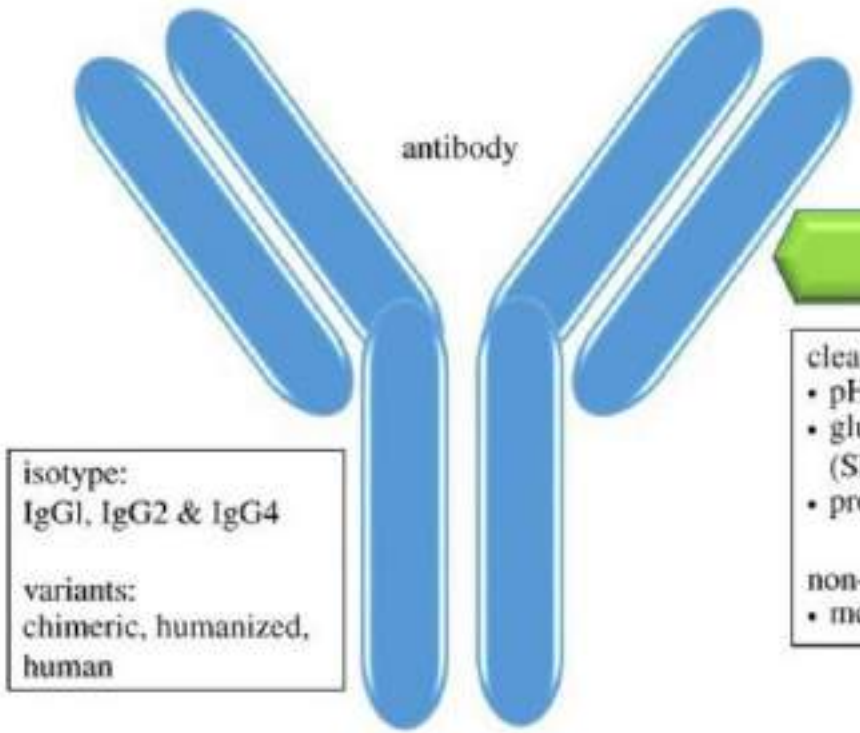

A Generation and Structure of Monoclonal Antibodies
B cell
Myeloma cell
Fused with myeloma cell to create an immortal hybrid cell line
Antibody-secreting hybridoma
Fab region (antigen binding)
Monoclonal antibody
VH
VL
CH1
CL
CH2
CH3
Fc region mediates effector functions, such as complement fixation
C = Constant domain
V = Variable domain
H = Heavy chain
L = Light chain

Immunotherapy progresses through the ages




Market Value (Billion)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
1975
1981
1986
1994
1997
1998
2002
2003
2004
2006
2007
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
First mAb
Successful test of anti-lymphoma Ab
Muromonab-CD3 (Orthoclone OKT3): anti-CD3 for kidney transplantation rejection treatment
Abciximab (Reopro): anti-GP IIb/IIIa for prevention of blood clots in angioplasty
Rituximab (Rituxan): anti-CD20 for Non-Hodgkin lymphoma
Daclizumab (Zinbryta): anti-CD25 for multiple sclerosis
Trastuzumab (Herceptin): anti-HER2 for BC
Infliximab (Remicade): anti-TNFα for Crohn's disease
Panitumumab (Vectibix): anti-EGFR for CRC
Ranibizumab (Lucentis): anti-VEGF-A for Macular degeneration
Ustekinumab (Stelara): anti-IL-12/23 for Psoriasis
Ipilimumab (Yervoy): anti-CTLA-4 for metastatic melanoma
Brentuximab vedotin (Adcetris): anti-CD30 for Hodgkin lymphoma, systemic ALCL
Pembrolizumab (Keytruda): anti-PD-1 for melanoma
Nivolumab (Opdivo): anti-PD-1 for melanoma & NSCLC
Ramucirumab (Cyramza): anti-VEGFR2 for GC
Atezolizumab (Tecentriq): anti-PD-L1 for bladder cancer
Reslizumab (Cinqaero, Cinqair): anti-IL-5 for asthma
Burosumab (Crysvita): anti-FGF23 for XLH
Ibalizumab (Trogarzo): anti-CD4 for HIV infection
Erenumab (Aimovig): anti-CGRPR for migraine prevention
Caplacizumab (Cablivi): anti-vWF for acquired aTTP
Romosozumab (Evenity): anti-Sclerostin for osteoporosis
300 Billion in 2025
Avelumab (Bavencio): anti-PD-L1 for MCC
Durvalumab (Imfinzi): anti-PD-L1 for bladder cancer
Brodalumab (Siliq, Lumicef): anti-IL-17R for plaque psoriasis
Necitumumab (Portrazza): anti-EGFR for NSCLC
Dinutuximab (Unituxin): anti-GD2 for neuroblastoma
Pertuzumab (Perjeta): anti-HER2 for BC
Denosumab (Prolia): anti-RANKL for bone loss
Eculizumab (Soliris): anti-C5 for Paroxysmal nocturnal hemoglobinuria
Bevacizumab (Avastin): anti-VEGF for CRC; Cetuximab (Erbitux): anti-EGFR for CRC
Omalizumab (Xolair): anti-IgE for asthma
Adalimumab (Humira): anti-TNFα for RA
0.3
5.4
11
21
26
35
43
45
50
75
78
86
92
98
115
150

Characteristics of the linker



isotype:
IgG1, IgG2 & IgG4

variants:
chimeric, humanized, human

linker

cleavable linkers:
- pH-sensitive: hydrazone
- glutathione-sensitive: SPDB, (SPP)
- protease-sensitive: vc, va

non-cleavable linkers:
- mcc, mc

payload

DNA intercalators:
calicheamicin, duocarmycin
daunomycin, PBD dimers

microtubule destabilizers
auristatins: MMAE, MMAF
maytanisoids: DM1, DM4

https://royalsocietypublishing.org/
https://www.biochempeg.com/article/87.html

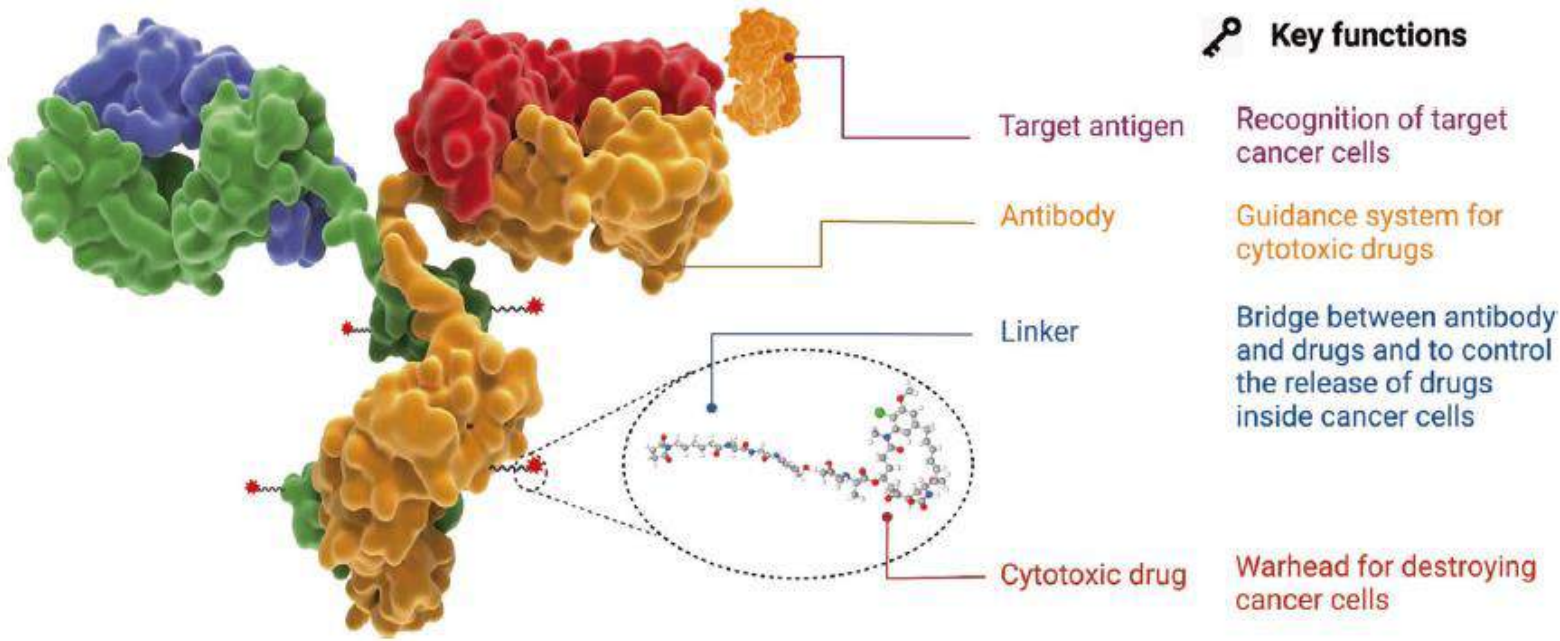
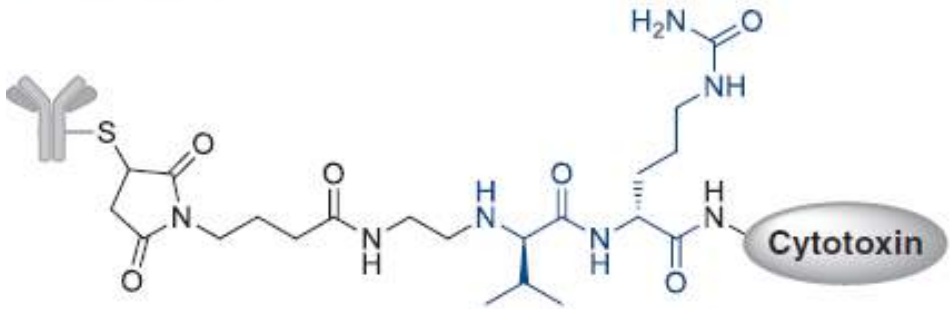


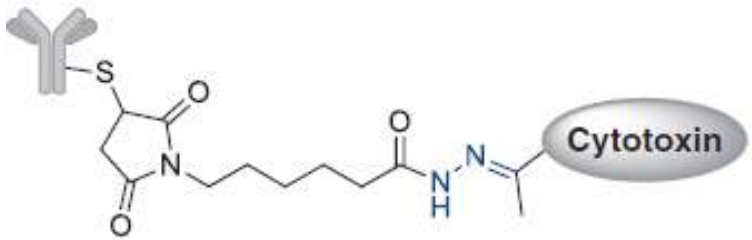
Fig. 2 The structure and characteristic of an ADC drug. The core components including target antigen, antibody, linker, cytotoxic drug along with their key functions are demonstrated.

Examples of ADC drug linkers

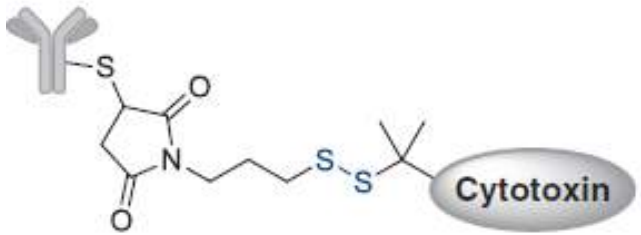
Cleavable linkers



Valine-Citrulline (protease sensitive)

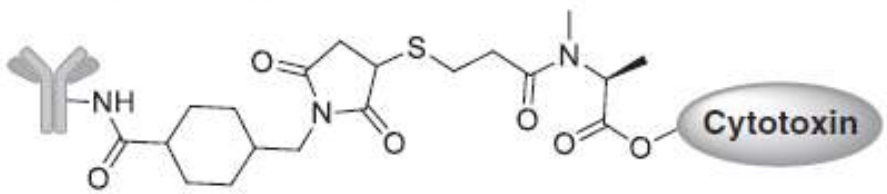


Hydrazone (acid-sensitive)

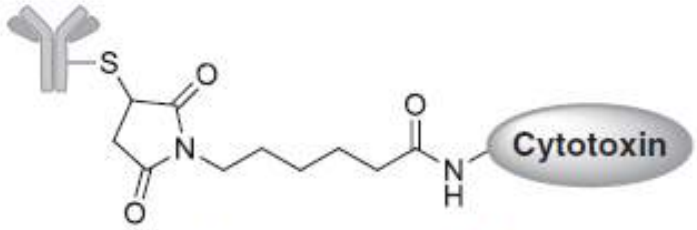


Disulfide (glutathione-sensitive)

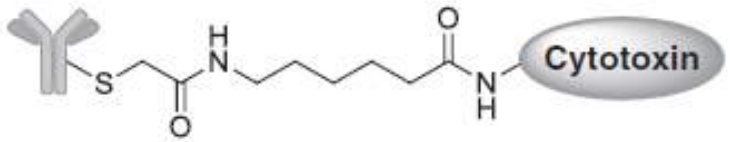
Noncleavable linkers



N-Maleimidomethylcyclohexane-1-carboxylate (MCC)

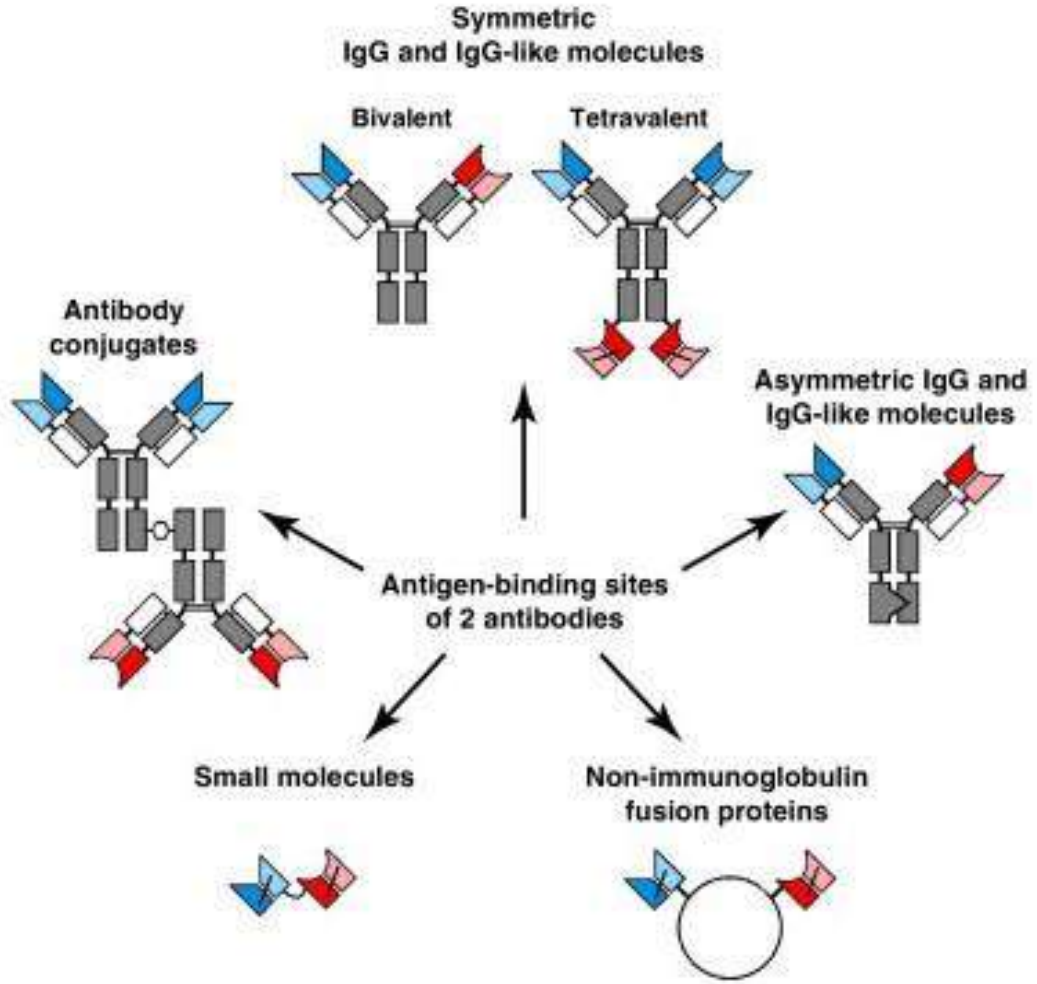


Maleimidocaproyl



Mercaptoacetamidocaproyl

Bifunctional antibodies

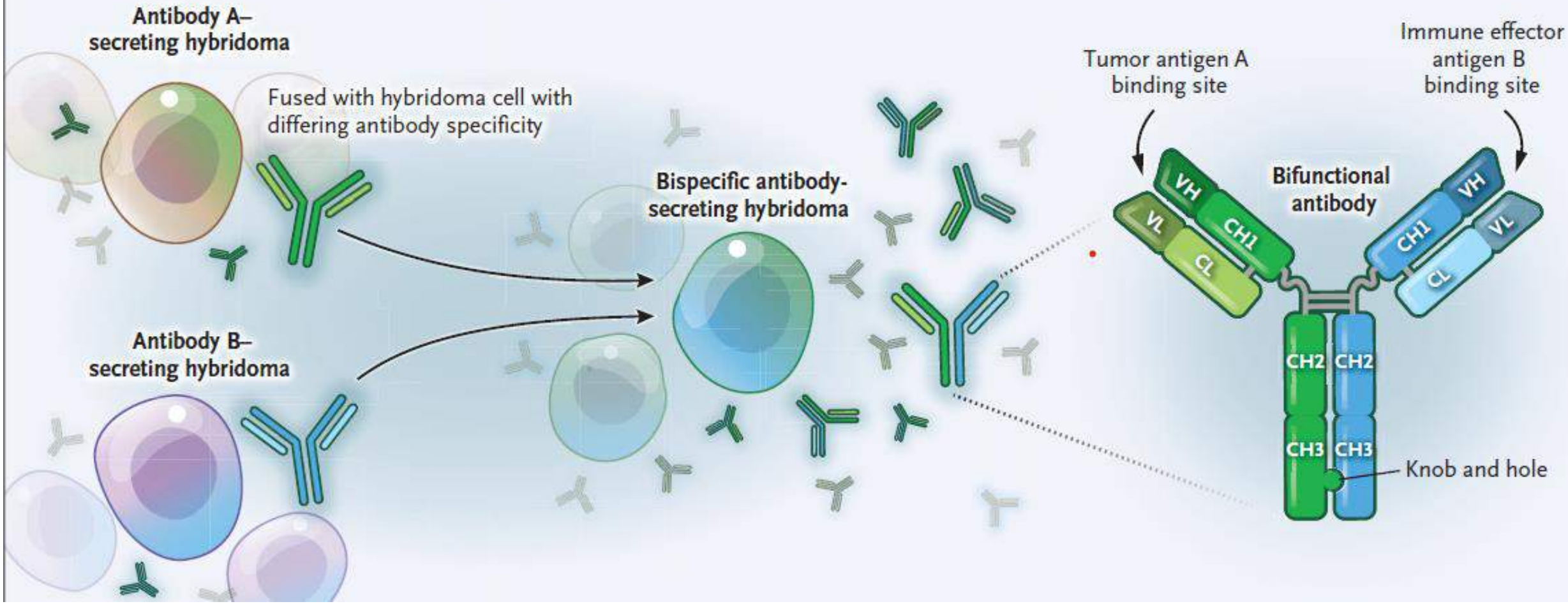


SCIENCE BEHIND THE STUDY
Elizabeth G. Phimister, Ph.D., *Editor*

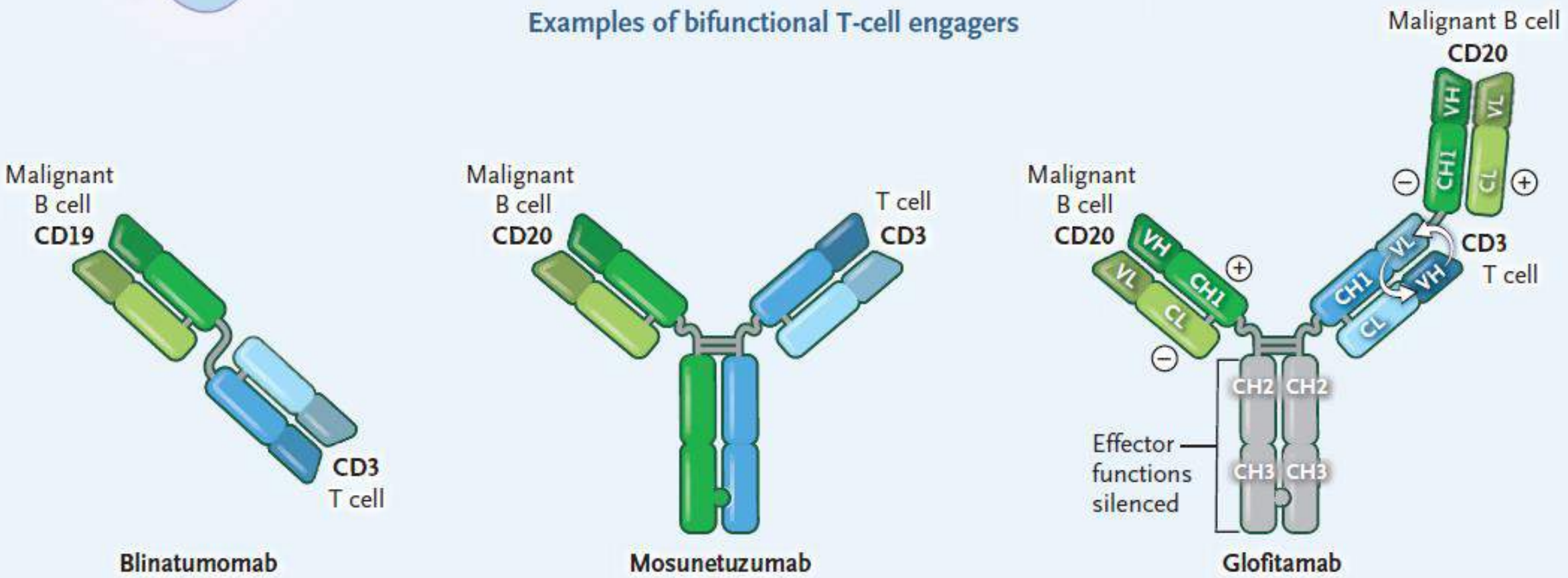
The Expanding Clinical Role of Bifunctional Antibodies

Dan L. Longo, M.D.

B Generation and Structure of Bifunctional Antibodies



Examples of bifunctional T-cell engagers



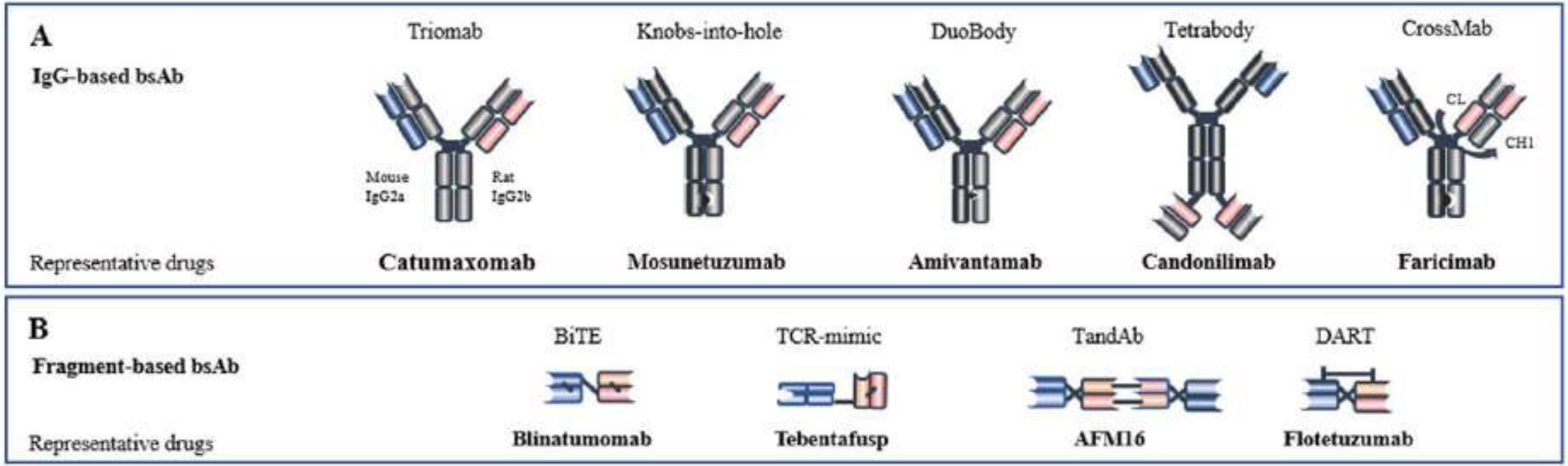
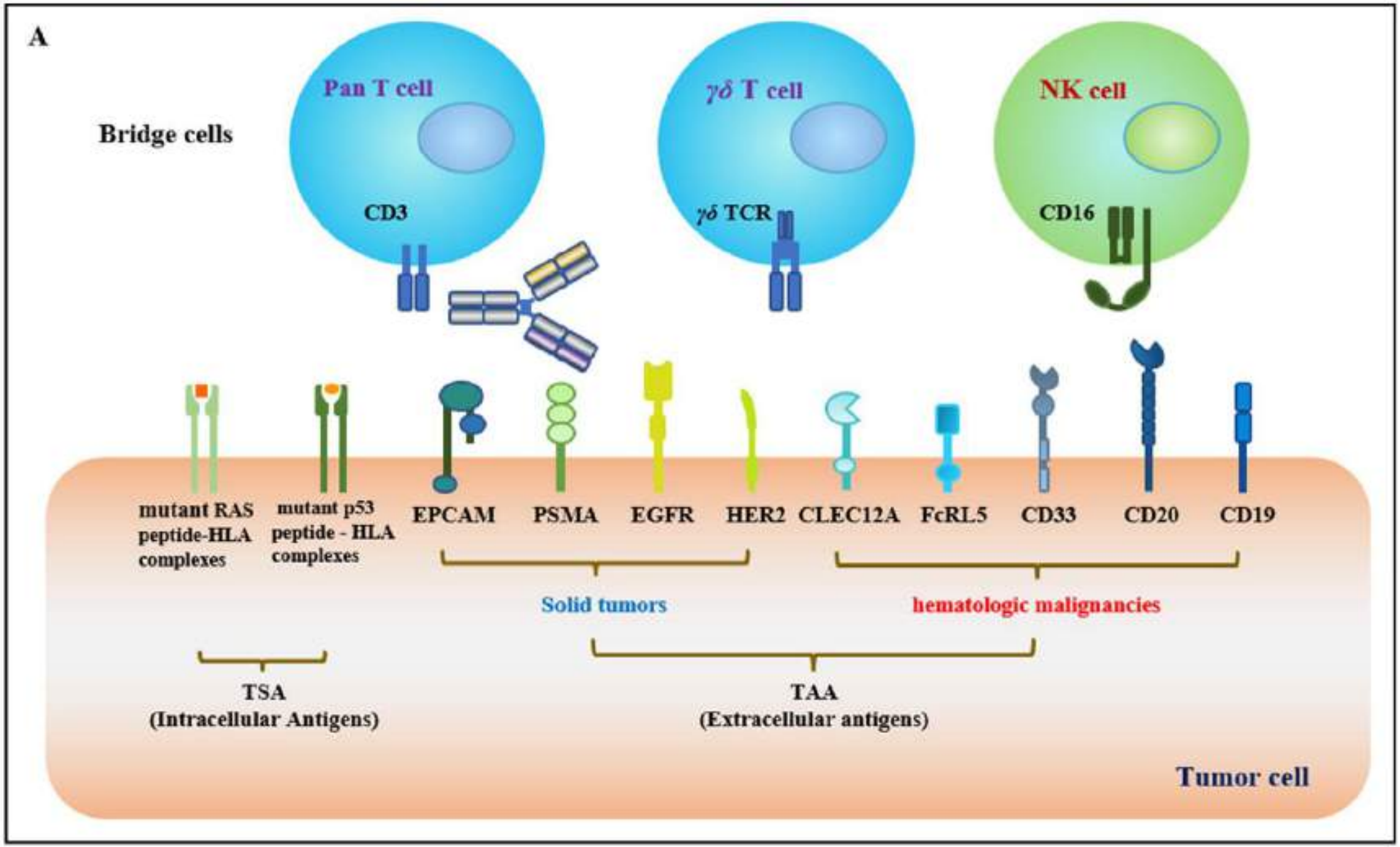
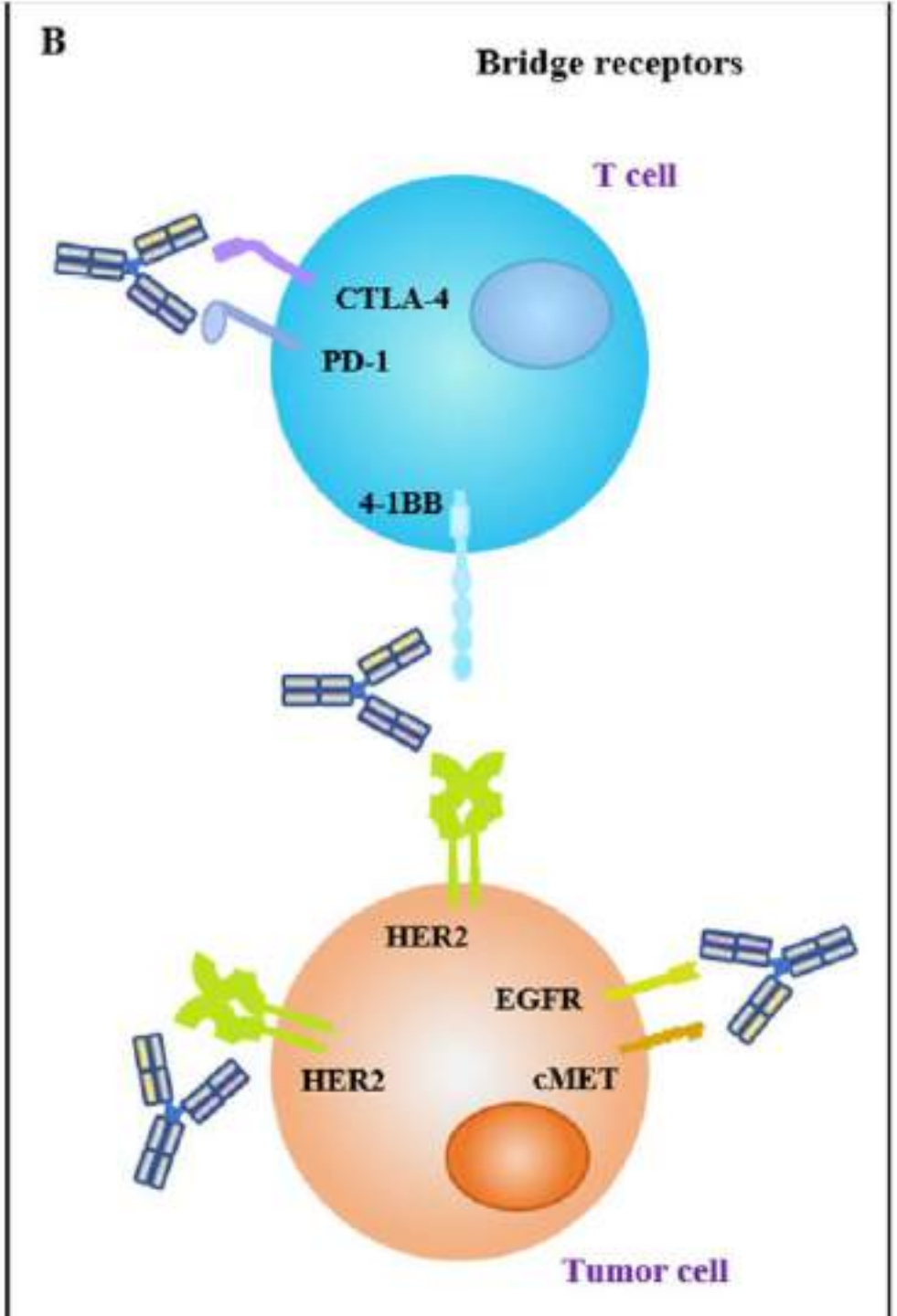


Figure 2 Representative bispecific antibodies and their format. According to the existence of the Fc region, bispecific antibodies can be divided into two categories: (A) IgG-based bsAbs and (B) Fragment-based bsAbs. BiTE, bispecific T-cell engager; TandAb, tandem diabody; DART, dual affinity retargeting.

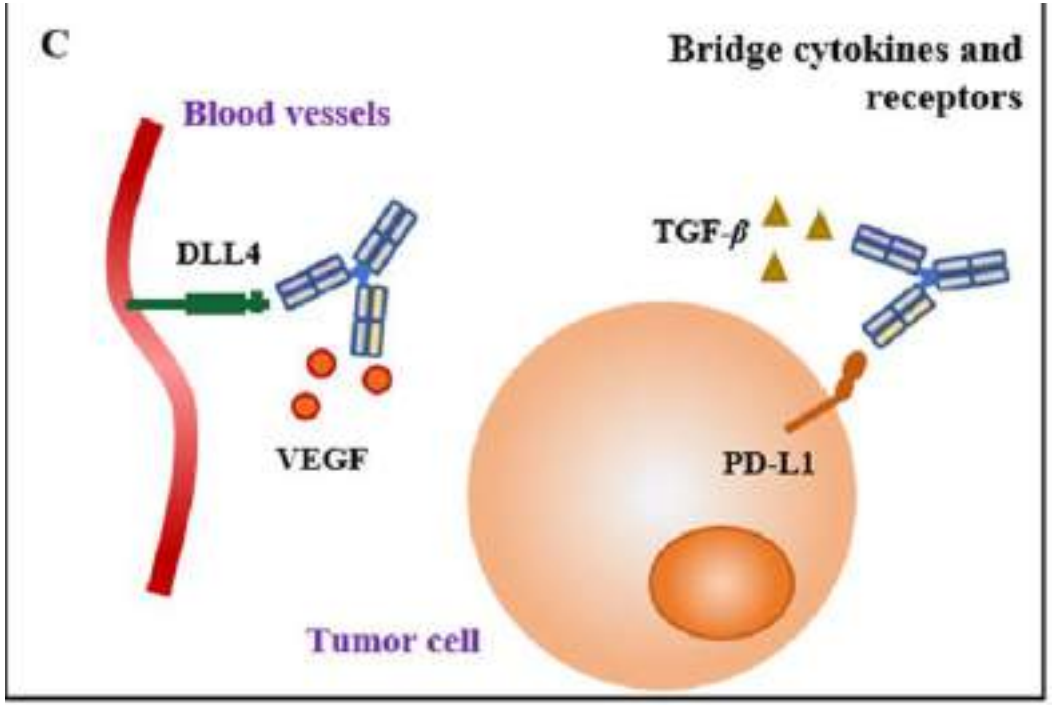
How can act bifunctional Monoclonal Antibodies

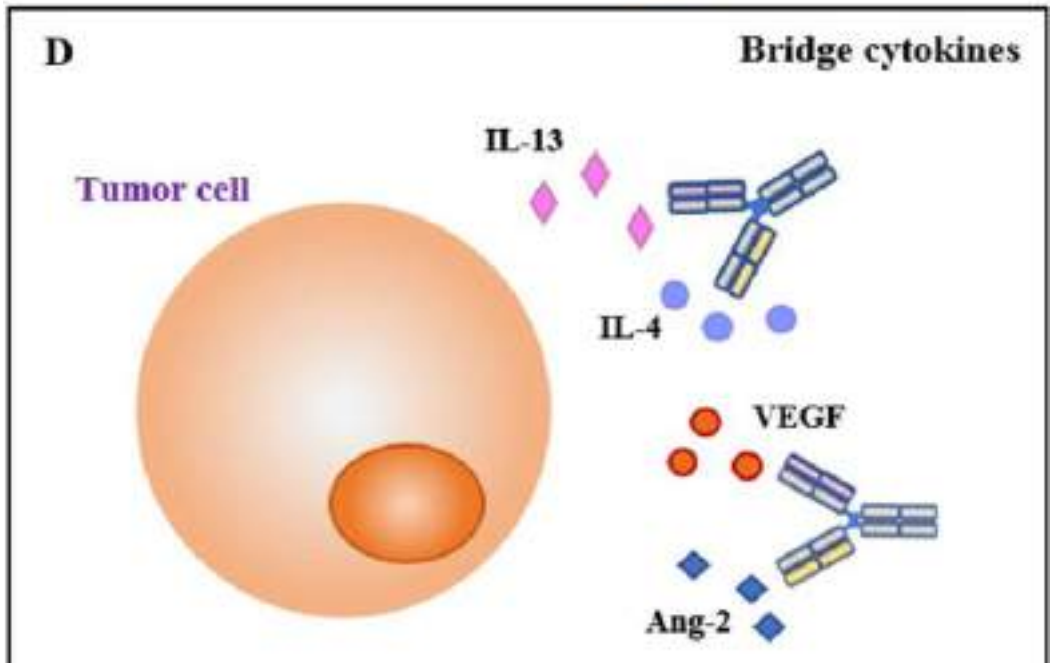

A
Bridge cells
Pan T cell
CD3
γδ T cell
γδ TCR
NK cell
CD16
mutant RAS peptide-HLA complexes
mutant p53 peptide - HLA complexes
EPCAM
PSMA
EGFR
HER2
CLEC12A
FcRL5
CD33
CD20
CD19
Solid tumors
hematologic malignancies
TSA
(Intracellular Antigens)
TAA
(Extracellular antigens)
Tumor cell



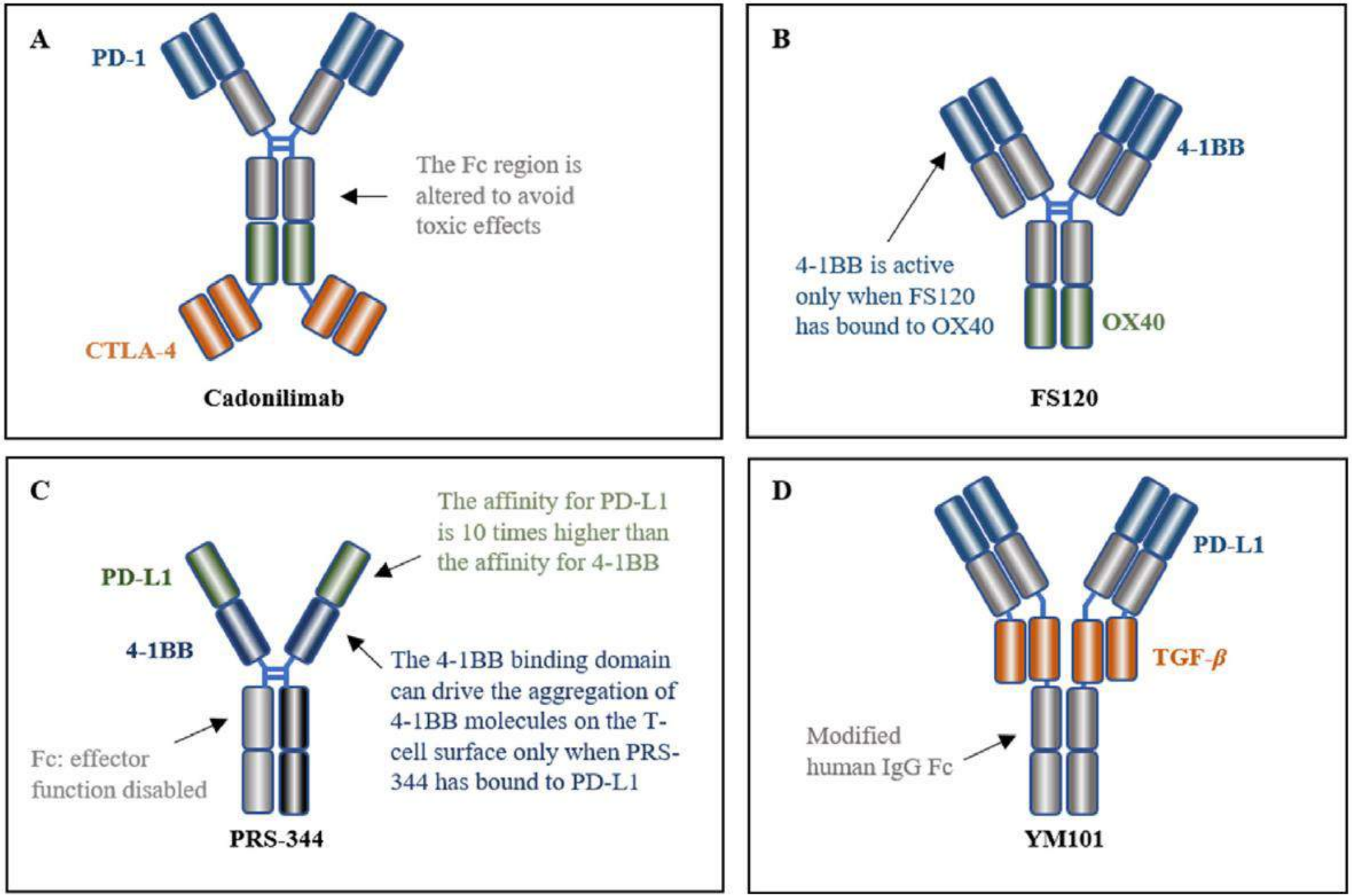
Until now we succeed to hit two different receptors using a mixture of two Mo Ab

i.e. Trastuzumab + Pertuzumab in HER2 + Breast cancer





Circulating Antigens are a true problem in Clinical Oncology:
they prevent the cellular receptor / Mo Ab link and can fill the Fab variable portion of the MoAb hampering its immunological function.
Bifunctional Mo Ab can overcome this problem


A
PD-1
The Fc region is altered to avoid toxic effects
CTLA-4
Cadonilimab
B
4-1BB
4-1BB is active only when FS120 has bound to OX40
OX40
FS120
C
The affinity for PD-L1 is 10 times higher than the affinity for 4-1BB
PD-L1
4-1BB
The 4-1BB binding domain can drive the aggregation of 4-1BB molecules on the T-cell surface only when PRS-344 has bound to PD-L1
Fc: effector function disabled
PRS-344
D
PD-L1
TGF-β
Modified human IgG Fc
YM101

Take home messages

- La farmacologia oncologica ha registrato negli ultimi 25 anni enormi progressi derivanti dalle conoscenze in biologia molecolare e in chimica organica.
- Pochissime neoplasie sono rimaste escluse da questa rivoluzione: tumori cerebrali, carcinoma del pancreas, la maggior parte dei sarcomi.
- La complessità delle terapie richiede sempre di più una expertise pluridisciplinare che include Farmacologi, Farmacisti, Ematologi, Oncologi, Infermieri
- Si profilano due problemi: le disparità di cura e la sostenibilità economica.