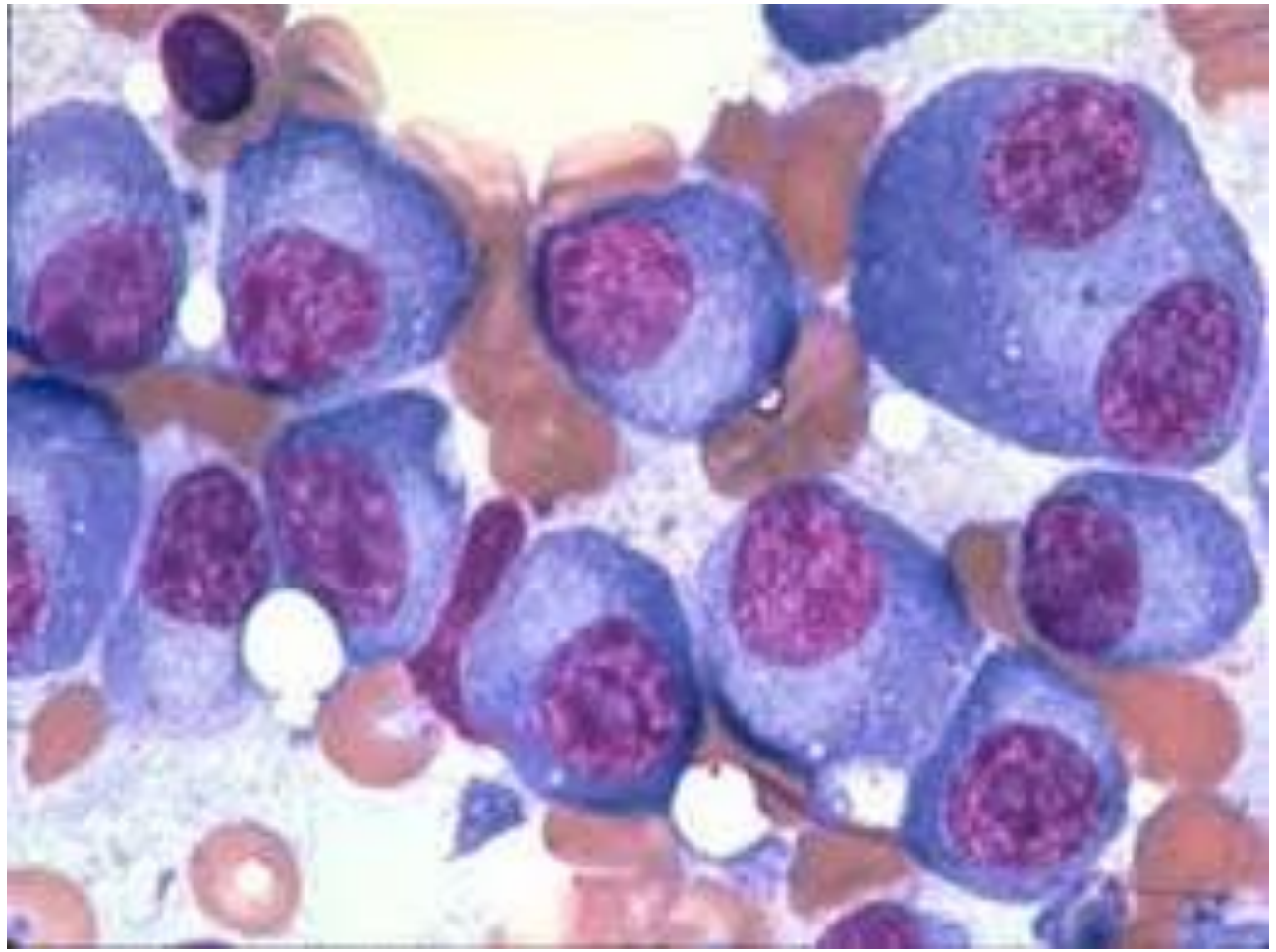


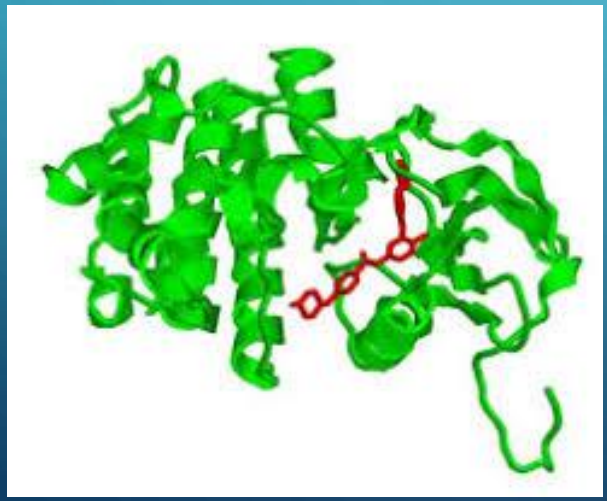
«CHEMO-FREE» TREATMENT IN MULTIPLE MYELOMA

OUTLINE

- The «magic» bullet
- The cure of cancer with «biological agents»
- The «biological» treatment of myeloma

THE MAGIC BULLET

- 2000, Imatinib approved for CML
- «biological agent»
- Tyrosine Kinase Inhibitor

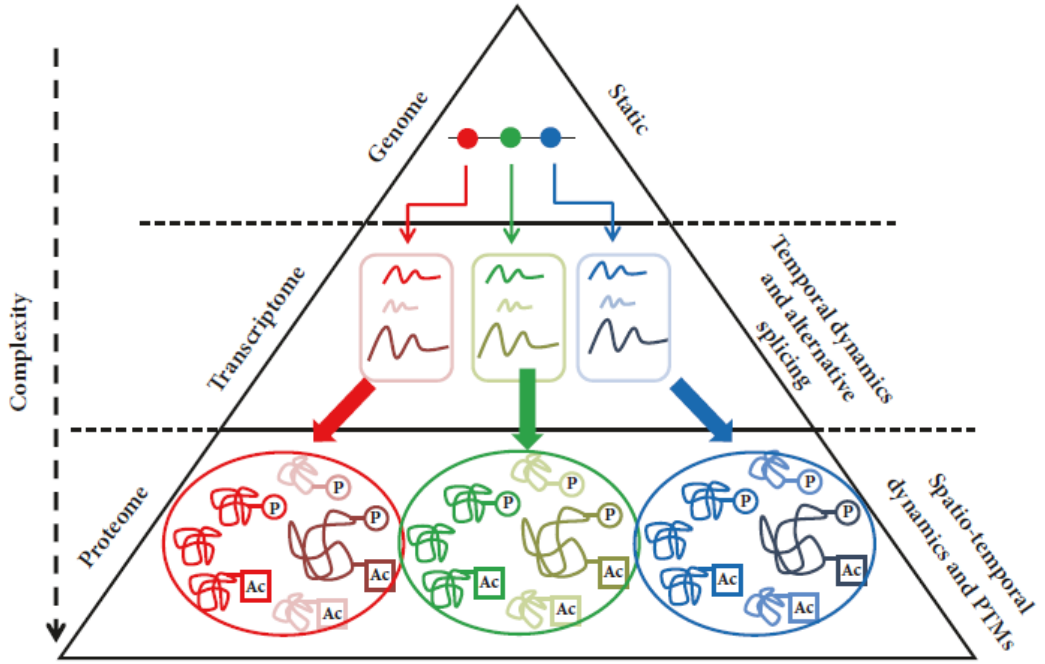


28, may 2001

Different layers of research

- Exposomic
- Genomic
- Transcriptomic
- Epigenomic
- Proteomic
- Metabolomic
- Microbiomic
- Radiomic
- «Psycho-socialomic»…

Yoo 2017



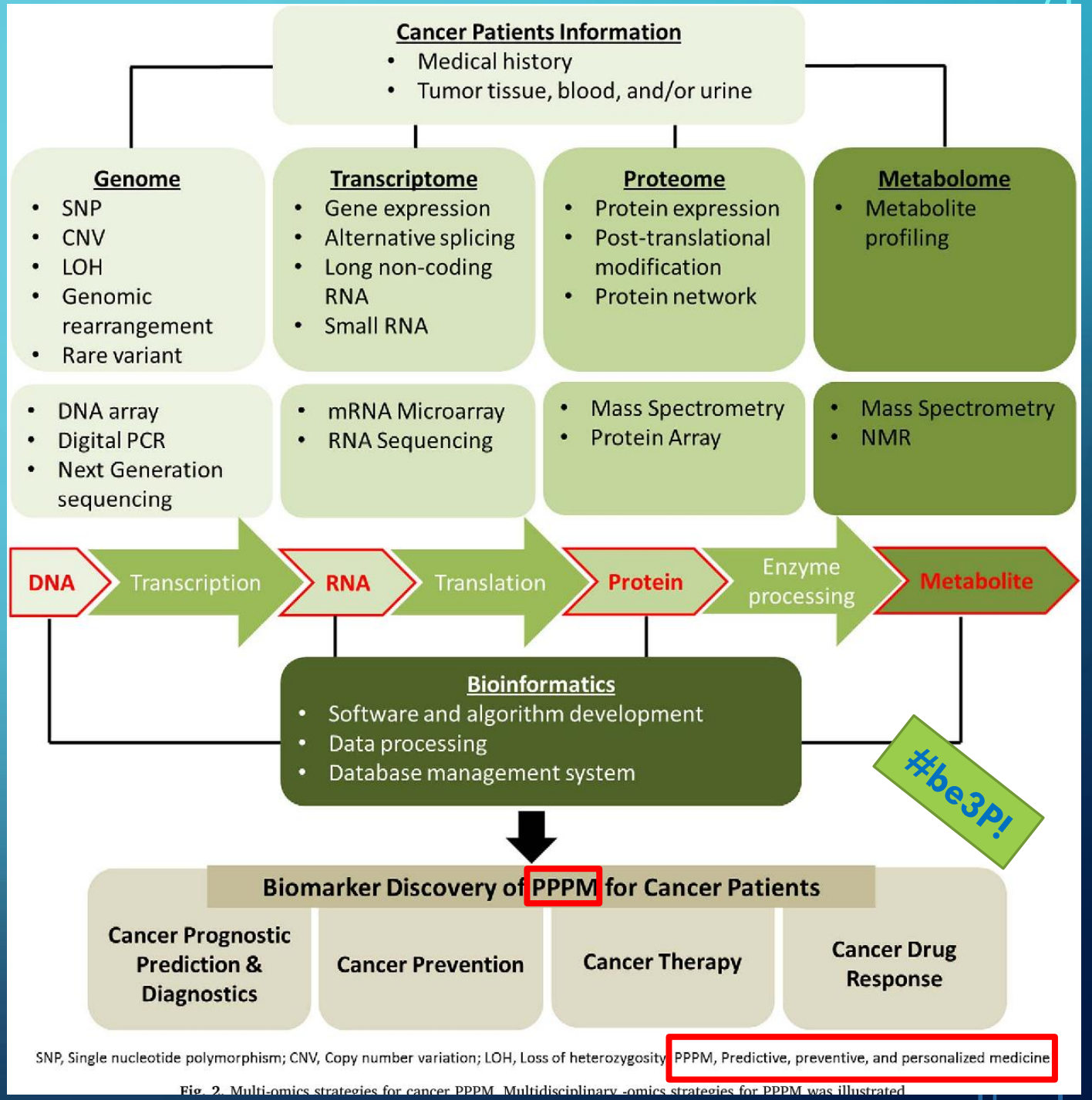
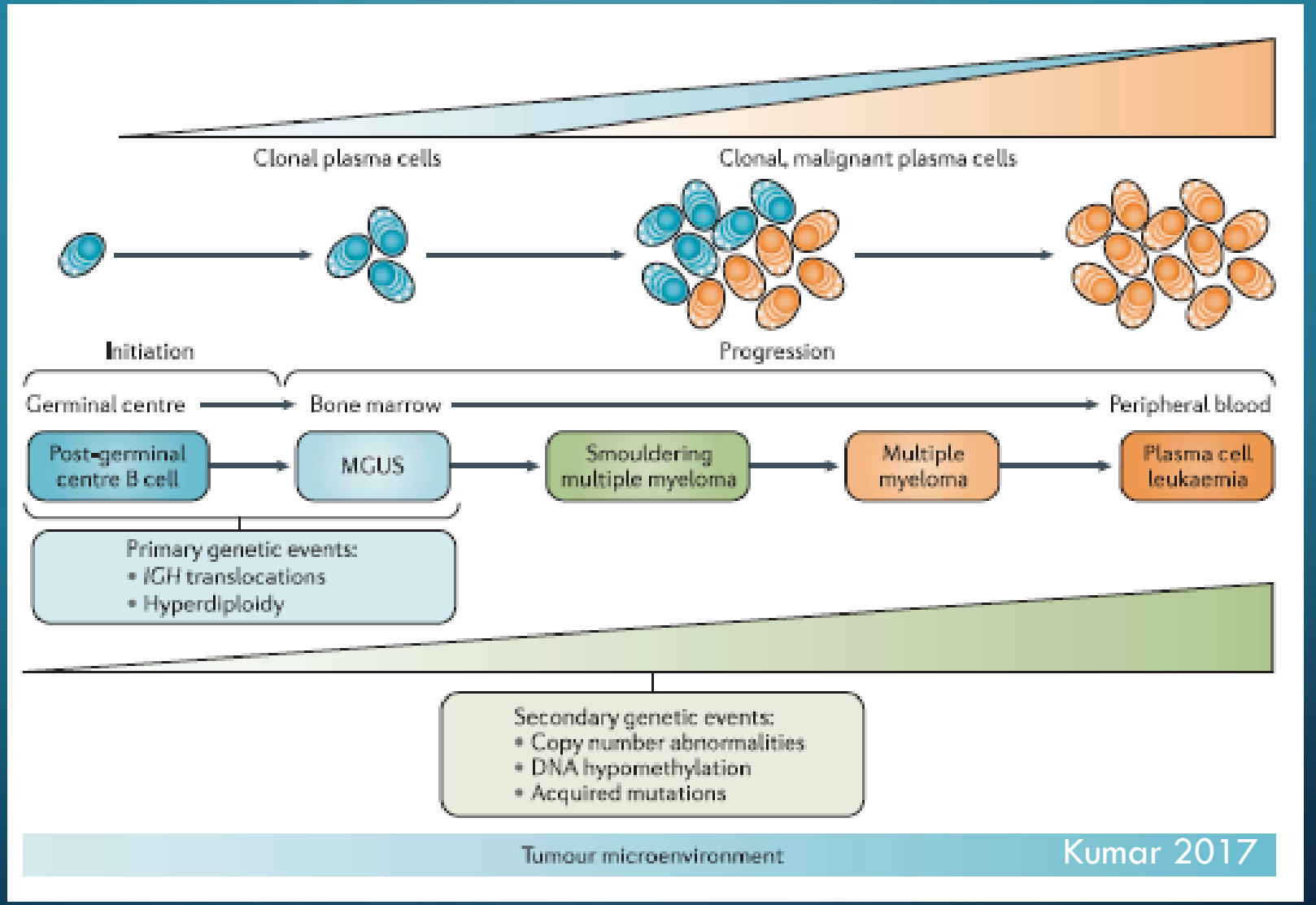


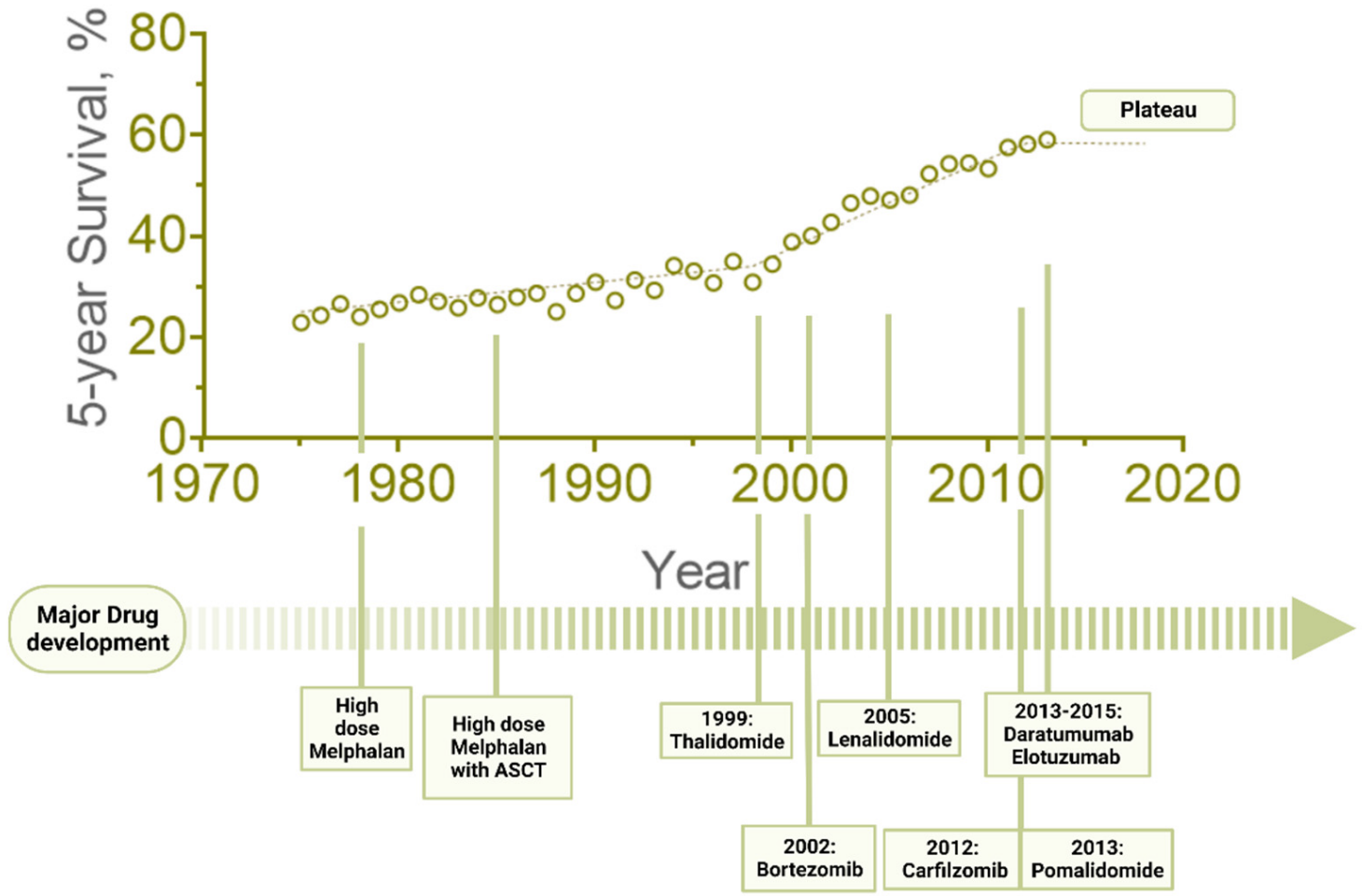
Fig. 2. Multi-omics strategies for cancer PPPM. Multidisciplinary -omics strategies for PPPM was illustrated

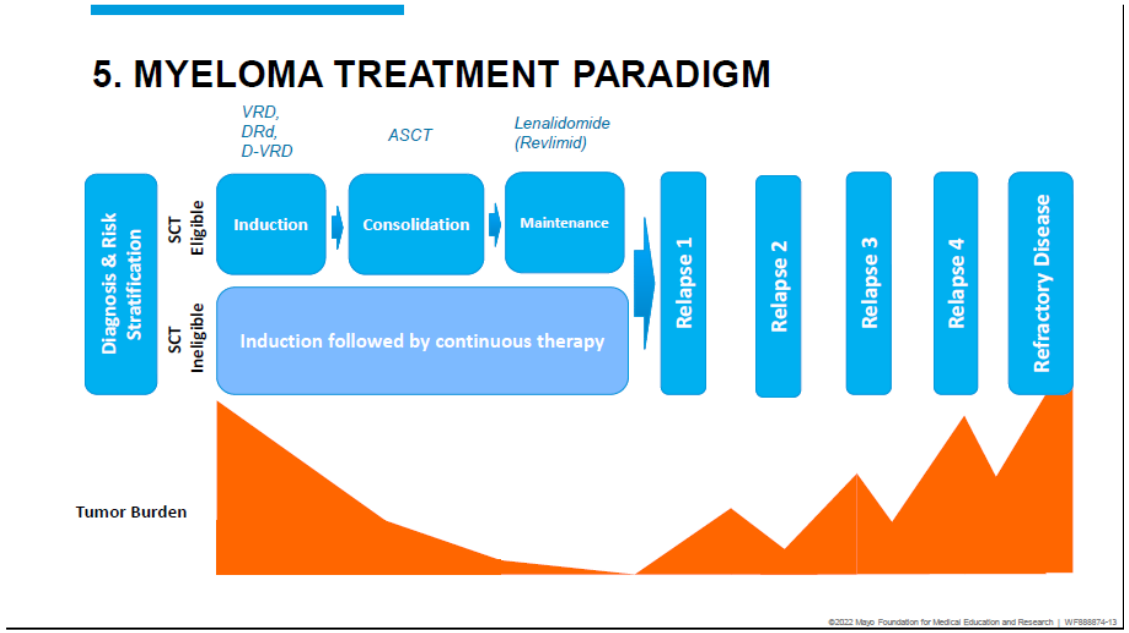
BIOLOGICAL TREATMENT OF CANCER

- Adoptive cell transfer
- Angiogenesis inhibitors
- Bacillus Calmette-Guerin therapy
- Biochemotherapy
- Cancer vaccines
- Chimeric antigen receptor (CAR) T-cell therapy
- Cytokine therapy
- Gene therapy
- Immune checkpoint modulators
- Immunoconjugates
- Monoclonal antibodies
- Oncolytic virus therapy
- Targeted drug therapy



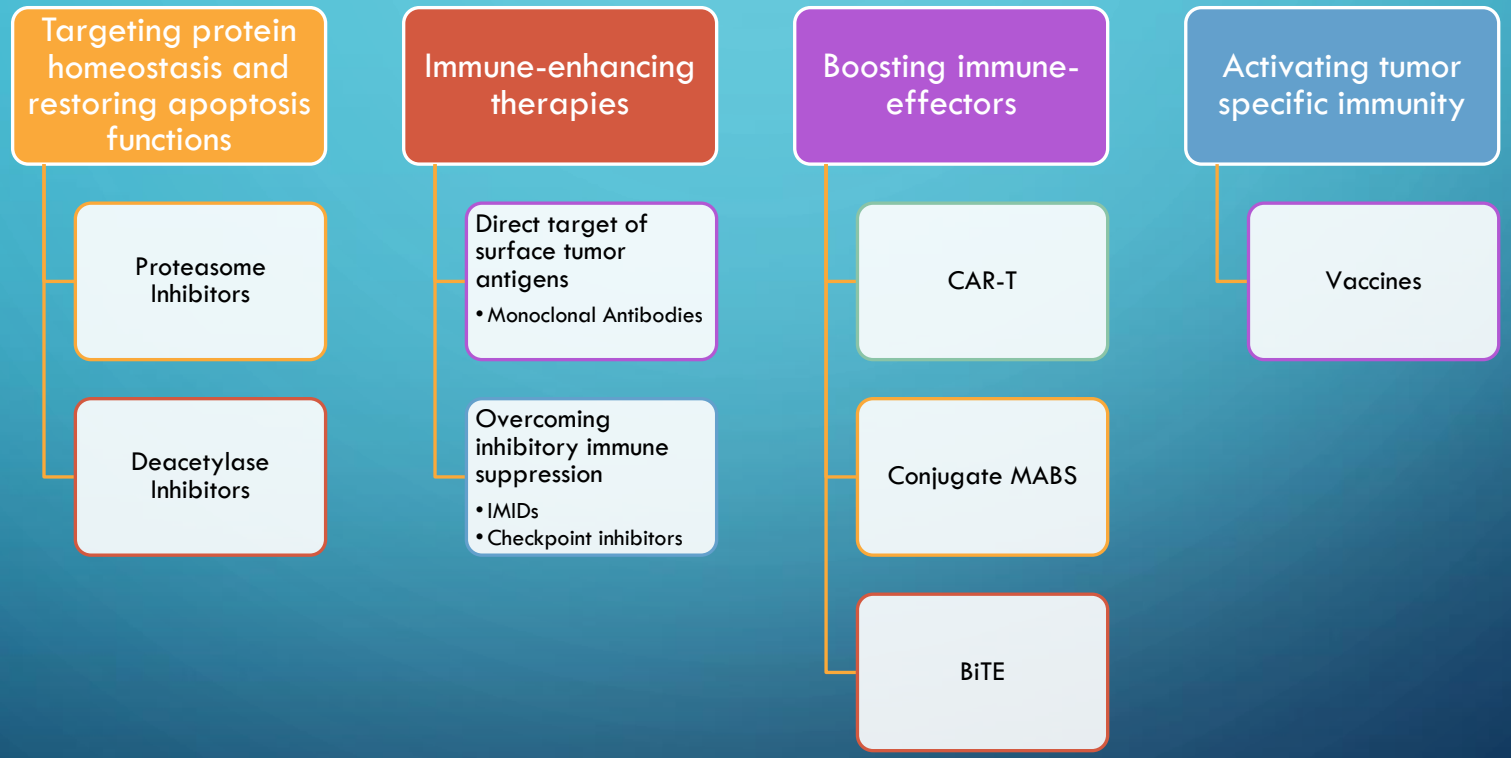
PATHOGENESIS


5-year Survival, %
80
60
40
20
0
1970
1980
1990
2000
2010
2020
Year
Plateau
Major Drug development
High dose Melphalan
High dose Melphalan with ASCT
1999: Thalidomide
2002: Bortezomib
2005: Lenalidomide
2012: Carfilzomib
2013-2015: Daratumumab Elotuzumab
2013: Pomalidomide



EXPANDING TREATMENT OPTIONS FOR MULTIPLE MYELOMA: MIBS, MIDS AND MABS

NEW DRUGS FOR MYELOMA: CLASSIFICATION



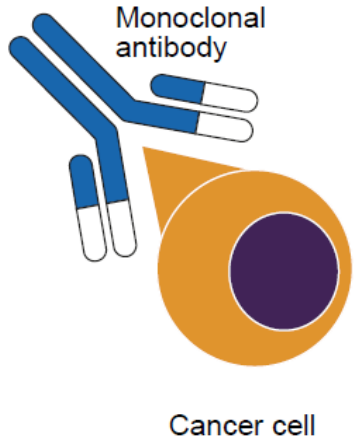
MABS, MIBS, NIBS, MIDS

MABS (Monoclonal Antibodies):	First segment: decision of the drug developer Second segment: Target or Disease Class Third segment: Source Fourth segment: -MAB
MIBS (single small molecules): suffix «zomib» is the designation for protease or proteasome inhibitors	Bortezomib, Carfilzomib, Ixazomib
NIBS: suffix «nib» indicates a small-molecule inhibitor	«tinib» Tyrosin-kinase Inhibitor «anib» Angiogenesis inhibitor
iMIDS: Immunomodulatory Drugs	ThalidoMIDe LenalidoMIDe

https://www.medscape.com/viewarticle/867446_1

MABS

NAKED ANTIBODIES



MONOCLONAL ANTIBODIES

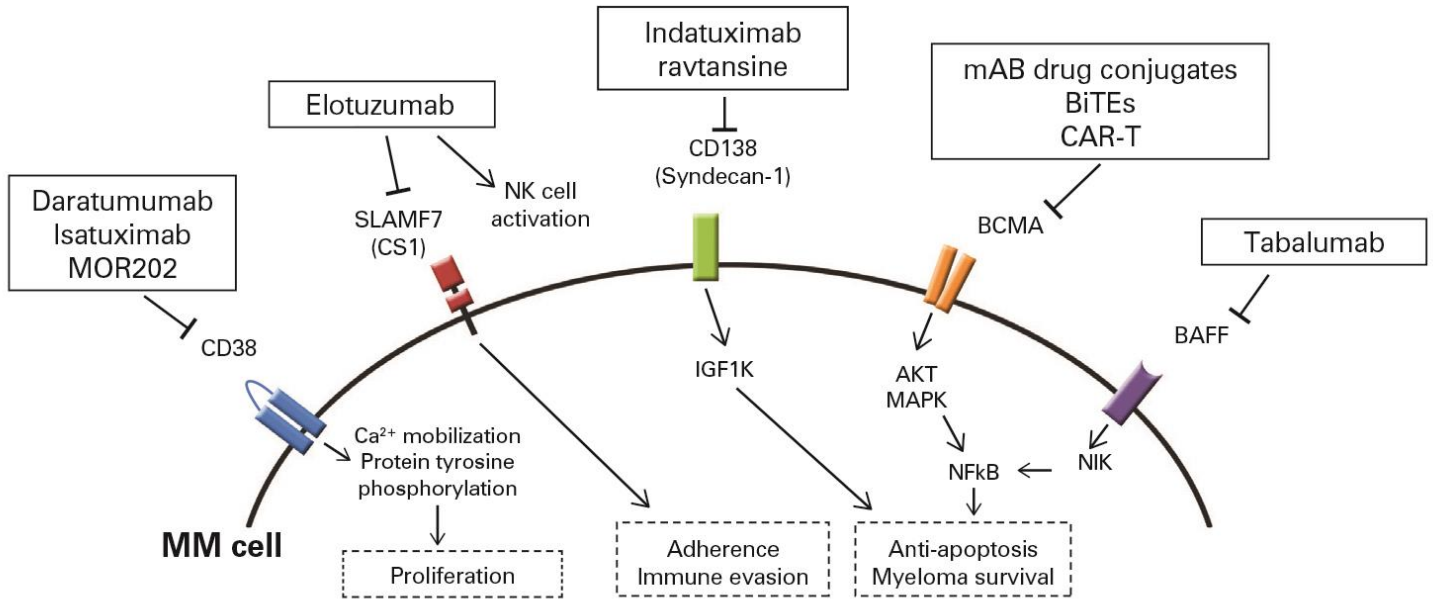
Anti CD38

- Daratumumab
- Isatuximab

Anti SLAM7

- Elotuzumab

Figure. Current and Investigational Targets of mAb Therapies in MM



Abbreviations: BiTEs, bi-specific T-cell engagers; CAR-T, chimeric antigen receptor T cells; mAb, monoclonal antibody; MM, multiple myeloma; NK, natural killer.

https://dailynews.ascopubs.org/do/10.1200/ADN.19.190275/full/

DARATUMUMAB

Combined action

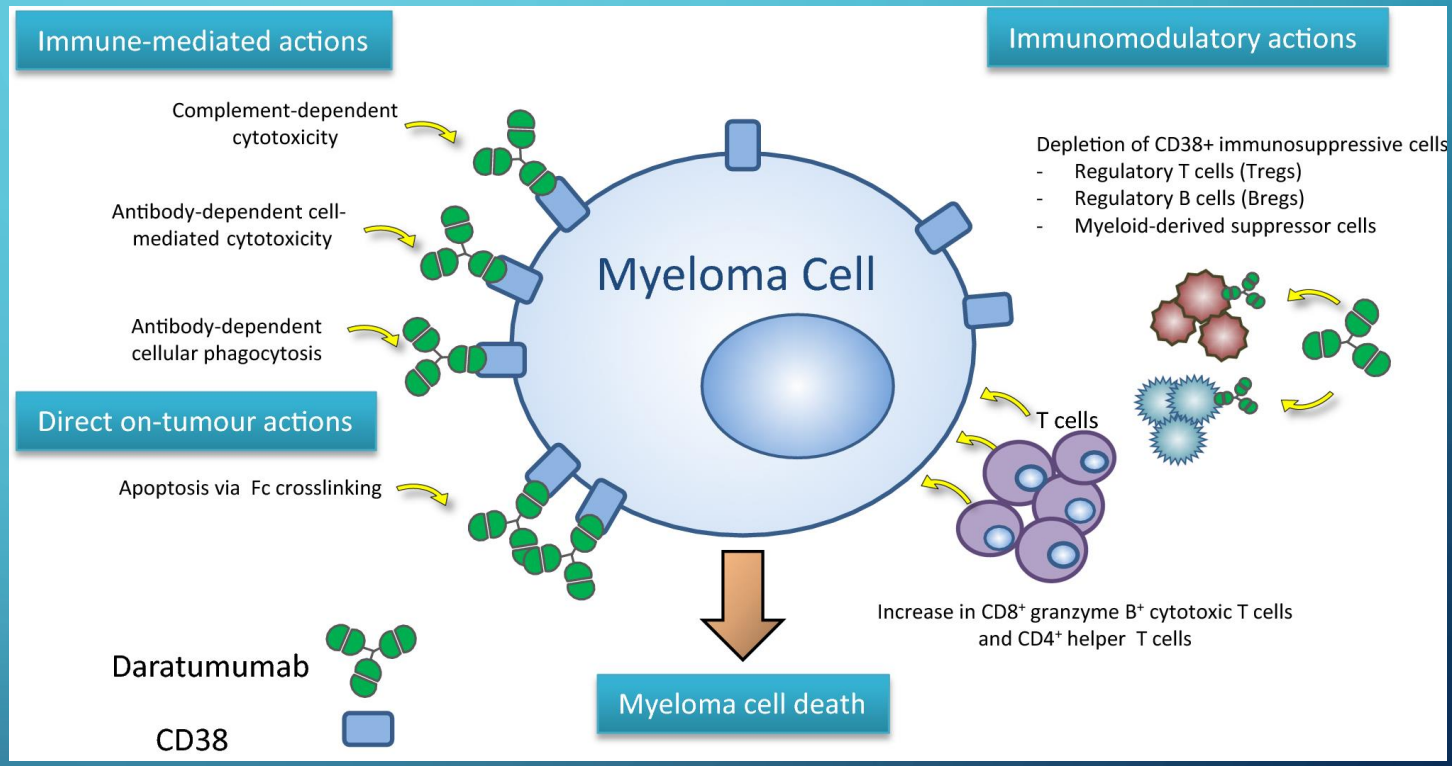
- Immune mediated
- Direct on-tumor
- Immunomodulatory
- Myeloma Cell Death

IV route

In combination or alone

Adverse events

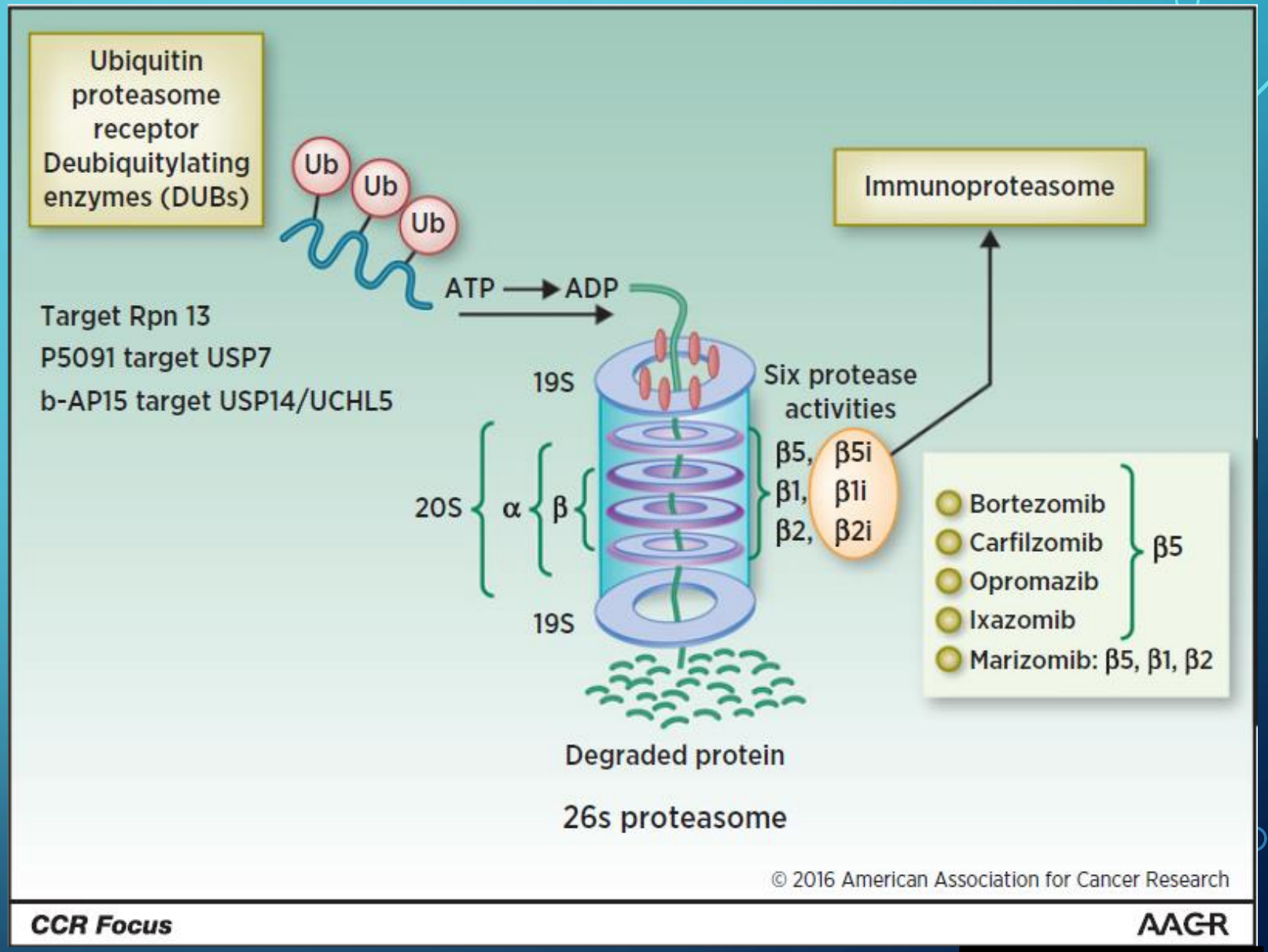
- Infusional reactions
- Coombs Test alterations



McKeage 2016

MIBS

- First class of new target therapies
- PROTEASOME highly active in MM Cells
- Blocking proteasome → ER stress → apoptosis
- NFkB inhibitors
- Multiple activities:
  - Plasma cells apoptosis
  - Osteoclasts inhibition
  - Angiogenesis inhibition
- Adverse events
  - Neuropathy (Bortezomib, Ixazomib)
  - Cardiovascular, Pulmonary HT (Carfilzomib)
  - Hematological toxicity
  - Gastrointestinal toxicity



Anderson 2016

Targeting protein homeostasis and restoring apoptosis functions

Proteasome Inhibitors

- Bortezomib
- Carfilzomib
- Ixazomib

Immune-enhancing therapies

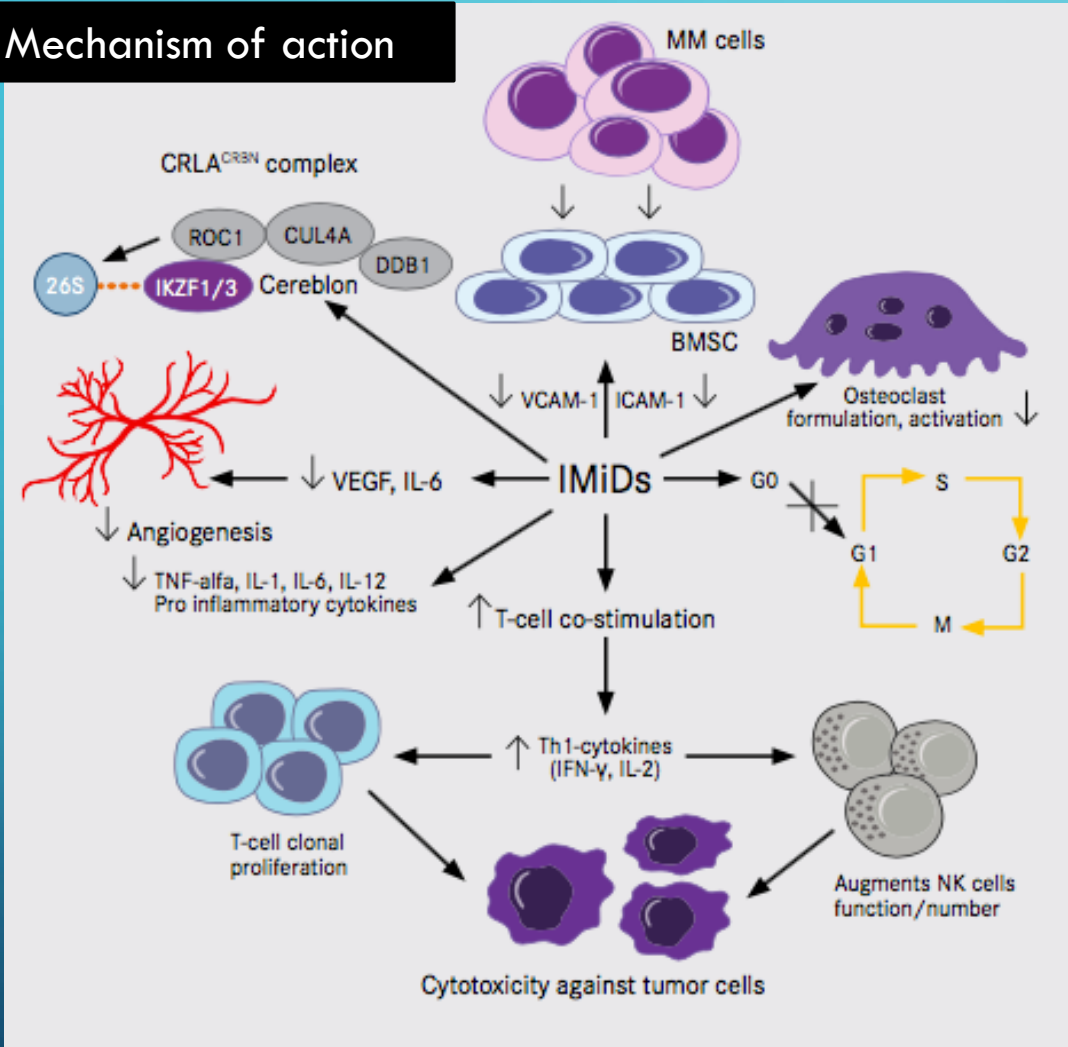
Overcoming inhibitory immune suppression

IMIDs

Checkpoint inhibitors

IMIDS

IMIDS Mechanism of action



Thalidomide, Lenalidomide, Pomalidomide

Oral route

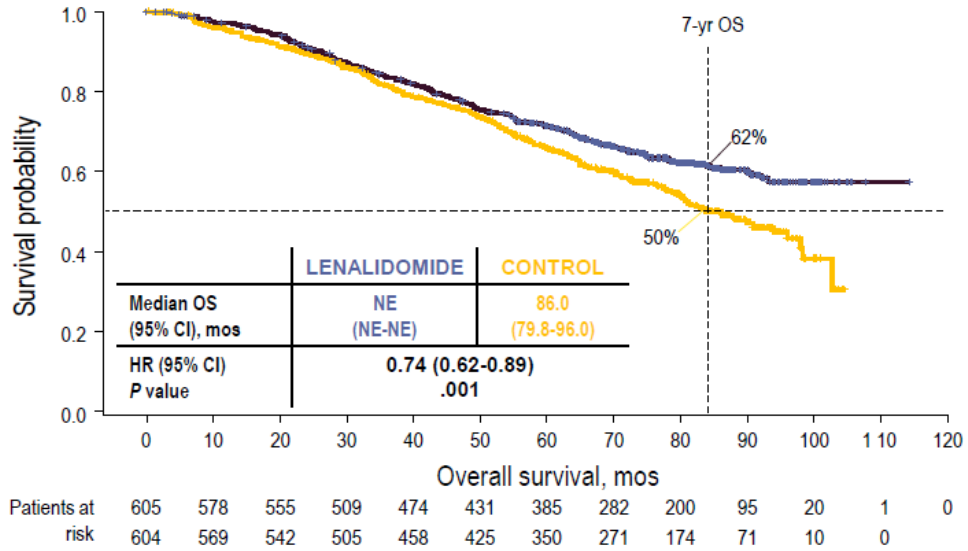
Active in combination or alone in maintainance

Adverse events:

- Fatigue, Neuropathy
- Hematologic toxicity
- Thrombosis

Neri 2016

There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival*



Attal 2016

LENALIDOMIDE MAINTENANCE

Immune-enhancing therapies

Overcoming inhibitory immune suppression

IMIDs

Checkpoint inhibitors

PD1/PD-1L INHIBITORS

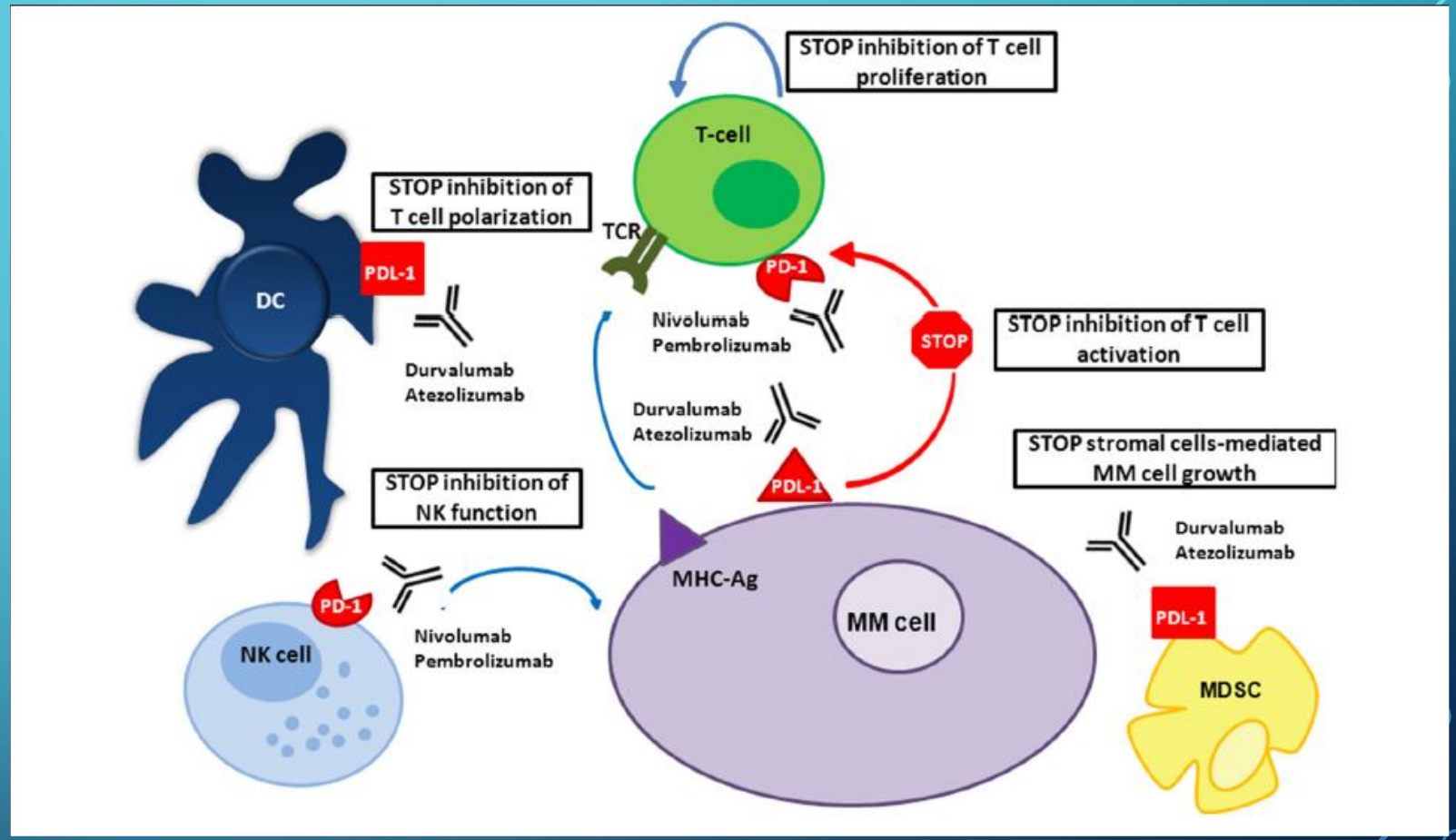
Pemrolizumab, Nivolumab, Durvalumab

PD1/2L expressed on APC and tumor cells → PD1/2 inhibition of T cell activation (immune escape)

Unsatisfactory results alone

Toxicity with IMIDS

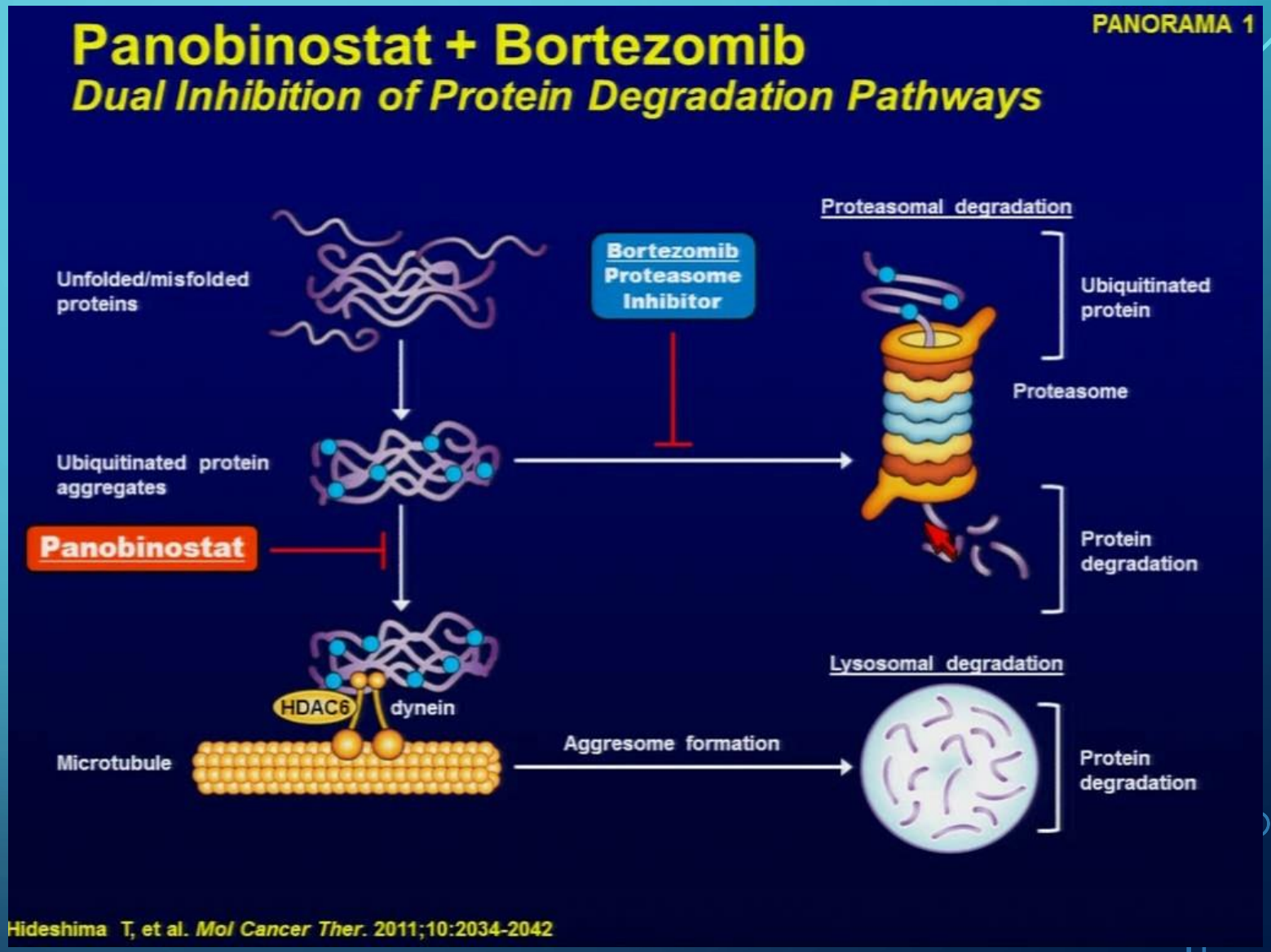
To date no evidence of clinical result in RRMM (Relapsed/Refractory MM)



Oliva 2018

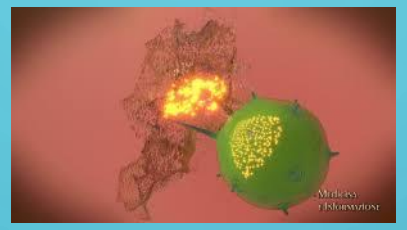
DEACETYLASE INHIBITORS

- Used in combination with PIs
- Overcome PIs resistance
- Oral route
- Adverse events
  - Gastrointestinal/pulmonary hemorrage
  - Hepatotoxicity
  - Gastrointestinal
  - Hypophosphatemia
  - Nephrotoxicity
- Limited use

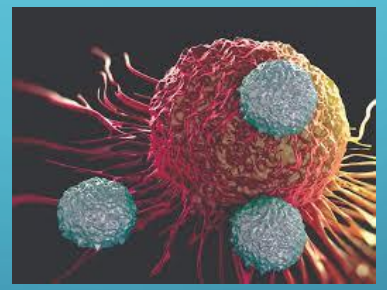


Boosting immune-effectors

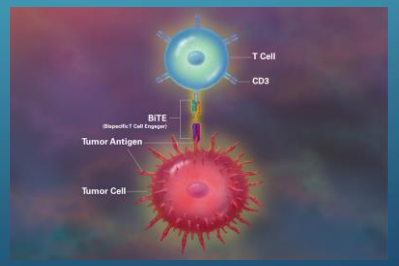
- Conjugate MABS



- CAR-T

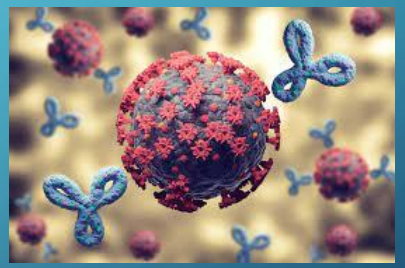


- BiTE



Activating tumor specific immunity

- Vaccines



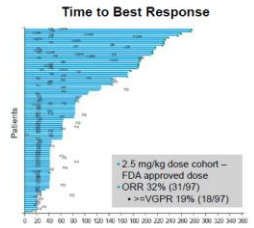
MABS-CONJUGATE

ANTIBODY DRUG CONJUGATE (ADC)

Benefits	Risk
• Targeted release of chemotherapy/ immunotoxin/ immunotherapy	• Still not 100% specific for myeloma cells and can cause tissue specific toxicity
• Attracts immune cells that clear cancer even if the treatment does not	
• Dead cancer cells attract even more immune effector cells enhancing its potential response	

BELANTAMAB

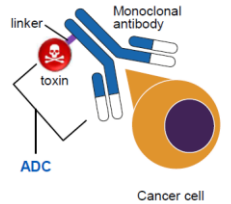
- BCMA ADC
  - Humanized IgG1 anti-BCMA monoclonal antibody & monomyethyl auristatin F (toxin)
  - IV infusion over 3 minutes every 3 weeks
- Progression free survival 2.8 months
- Continued response can be seen in patients with ADC on hold



Redrawn from: Lonial et al. Lancet Oncol 2020; 21: 207

CAVE: ocular toxicity

ANTIBODY DRUG CONJUGATE

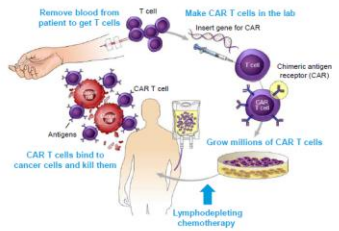


CAR-T

CAR T-CELL THERAPY

Benefits

- High response rates (~ 75% of patients)
- No maintenance
- No steroids
- Effective even in heavily pretreated or previously refractory patients



WHY DOES CAR T NOT ALWAYS WORK ?

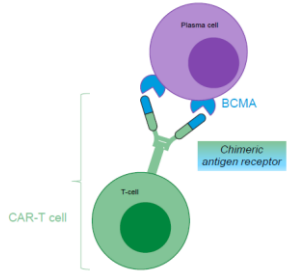
MM is too aggressive (progresses before infusion)

Patient T cells are less effective

Do not persist long enough

Loss of target by MM cell

CAR-T CELLS



BITE

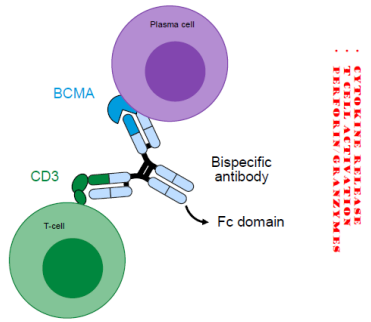
OVERVIEW OF BISPECIFIC ANTIBODIES

- Several targeting BCMA in clinical trials
- Non-BCMA directed antibodies are encouraging
- CRS and neurotoxicity less grade 3, than CAR T cells
- Maximum response and duration of response yet to be determined
- More likely to be an option to combine with other agents

BISPECIFIC ANTIBODIES

- Novel immune therapy approach designed to bind antigens on MM cells and cytotoxic T cells
- Early phase clinical trials targeting BCMA, GPRC5D, and FcRH5 have shown favorable safety profiles
- Most are IV or subcutaneous injections weekly or every other week
- Therapy is ongoing until progression
- Unknown sequence of therapy if benefit after CAR T

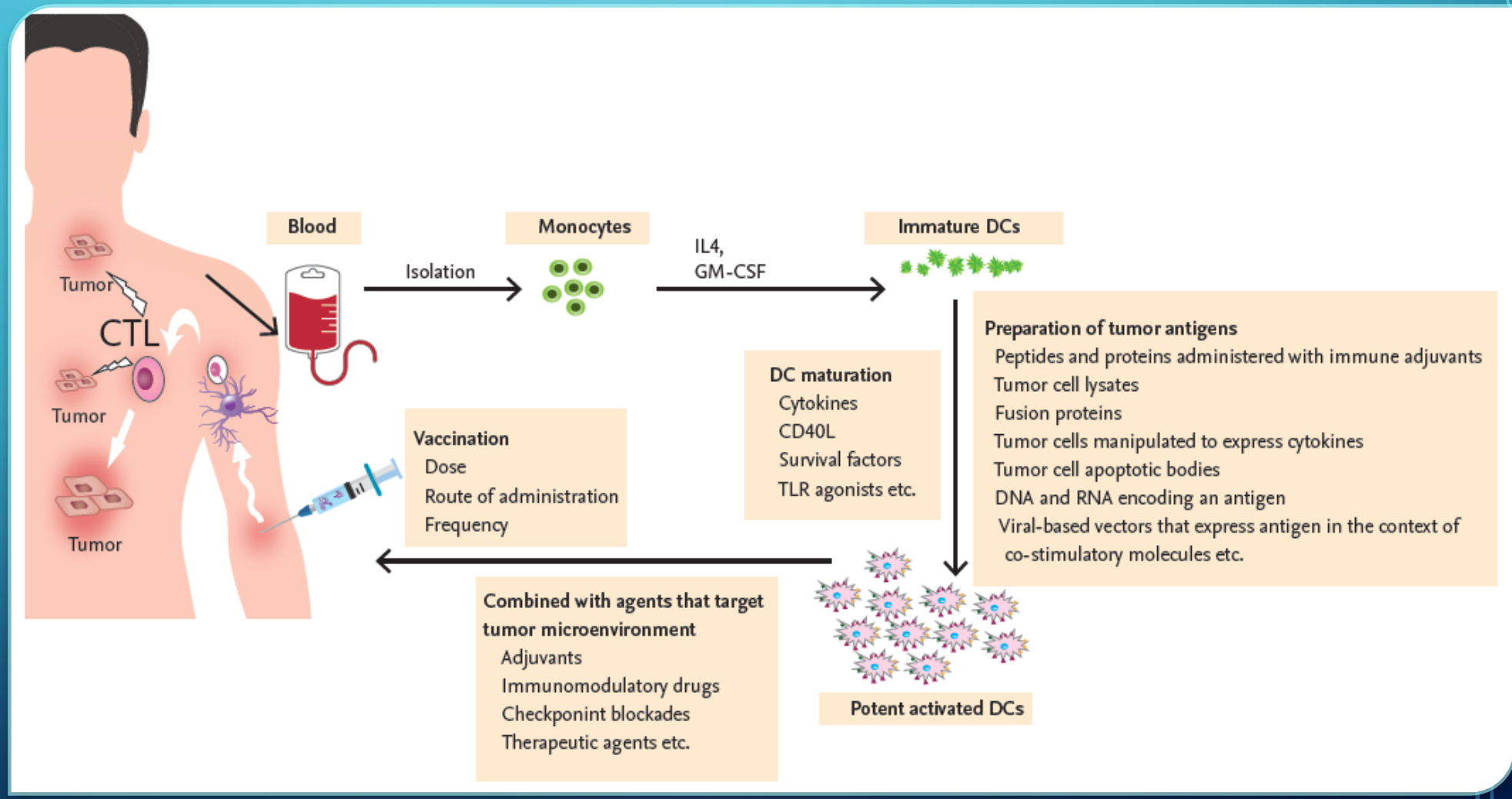
BISPECIFIC ANTIBODY



Proc. Nat. Acad. Sci. USA
Vol. 68, No. 9, pp. 2078–2082, September 1971

Preparation of a "Chemical Vaccine" Against Tumor Progression

VACCINES ?



Vo 2019

COSTS OF NEW DRUGS

Regimen	Approximate annual cost
VRd	$294,000
KRd (27 mg/m2 dose of K)	$397,000
KRd (56 mg/m2 dose of K)	$573,000
DRd**	$400,000
Dara-VRd**	$486,000
Dara-KRd**(27 mg/m2 dose of K)	$589,000
Dara-KRd**(56 mg/m2 dose of K)	$765,000
CAR-T	$230,000 to $465,000*

*Depends on whether estimated PFS is one year vs 2 years
** SQ Dara

https://www.goodrx.com/thalidomides
https://www.drugs.com/price-guide/
All accessed April 20, 2022

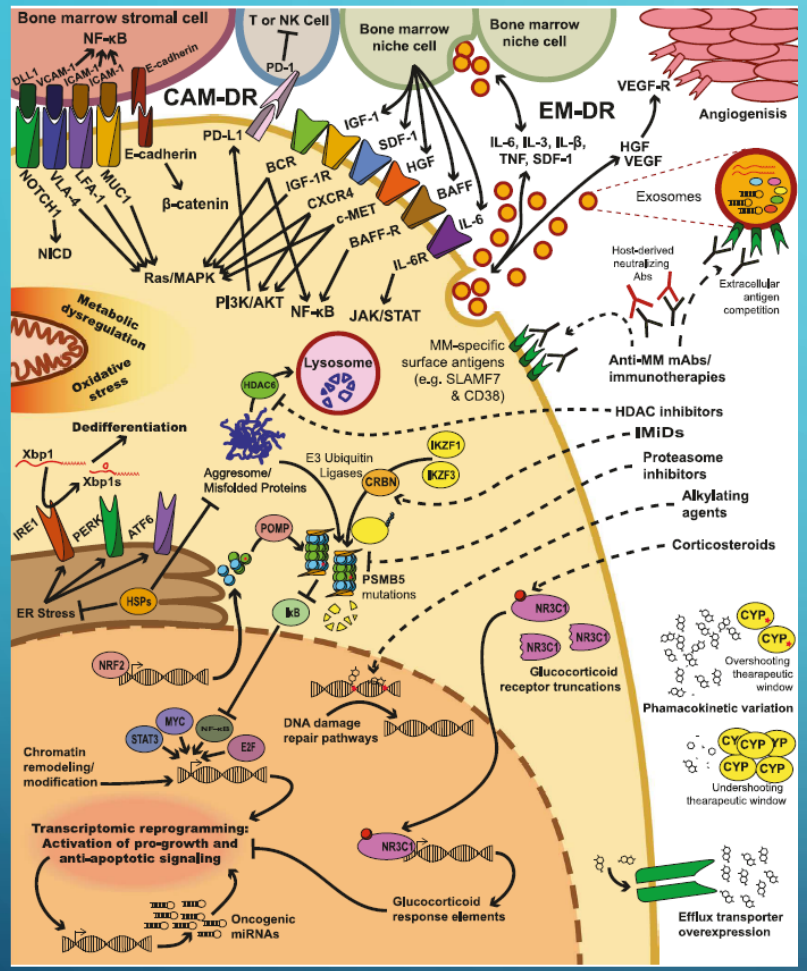
Rajkumar SV. 2022

Costo di un trapianto autologo: $ 10000
Rimborso regionale Euro 30000

Rajkumar 2022

Doctors have no interest in health. Disease is their passion. No disease, no doctors. Billions saved.

Richard Smith, @Richard56 14.07.2015



I think the extreme complexity of medicine has become more than an individual clinician can handle. But not more than teams of clinicians can handle.

Atul Gawande

enrico.morello@unibs.it