Living Well with Myeloma:

Novel Agents & Clinical Trials 2017

International Myeloma Foundation

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Disclosures

Craig Cole,MD has no relevant financial interests to disclose

What We Will Discuss Today

- **Definitions**
  - **What is a response with myeloma treatment?**
- **Novel Agents**
  - **BCL-2 and BCL-2 inhibitors**
  - **Check-point inhibitors**
- **Clinical Trials**
  - **Facts and Myths**

What are we talking about? Definitions in Myeloma Treatment….

Did it work?:

International Myeloma Working Group Response Criteria

- **Complete response (CR)**
  - Treatment where there are ≤5% plasma cells in the bone marrow and/or **no evidence of laboratory myeloma proteins in the serum or urine.**
- **Very good partial response (VGPR)**
  - Treatment outcome where there is a greater than 90% decrease in M protein
- **Partial response (PR)**
  - Treatment outcome where there is a greater than 50% decrease in M protein
- **Stable disease (SD)**
  - Treatment outcome where the disease has not responded to therapy (no change in M-protein) but has not progressed.

What are we talking about? Definitions in Myeloma Treatment….

Did it work?

- **Overall response rate (ORR)**
  Percentage of patients who respond in a clinical trial with a partial response (>50% reduction) or better.
- **Clinical Benefit Rate (CBR)**
  Percentage of patients who respond in a clinical trial with STABLE DISEASE or better (anything other than progressive disease).

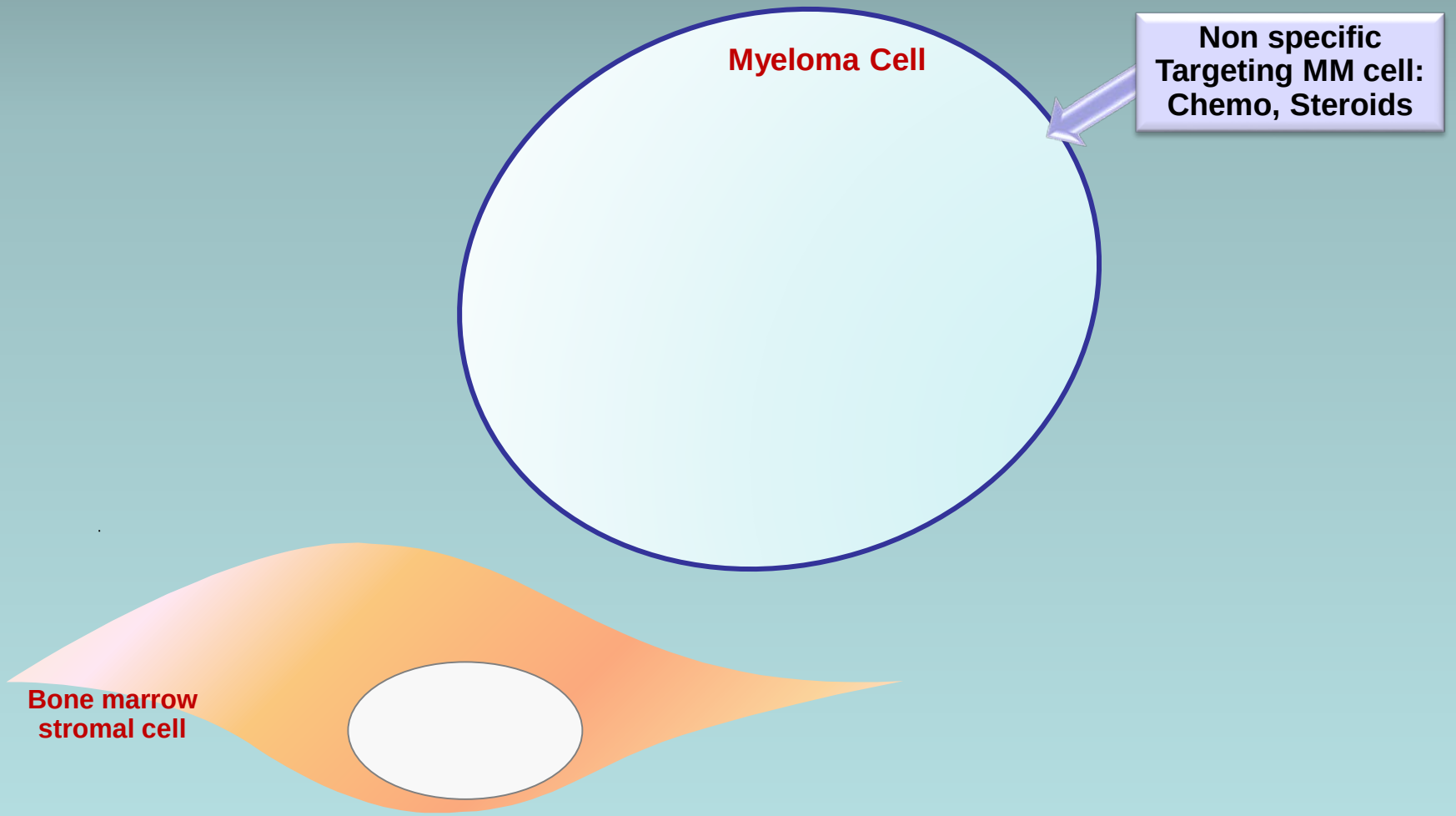
How long did it work/ what are the side effects?

OS: Overall Survival

PFS: Progression-Free Survival (from start of new treatment until it's failure)

AE: Adverse Events- Bad side effects

Old Therapies for Myeloma



Hideshima T, Anderson KC. *Nature Rev Cancer*. 2002;2:927.
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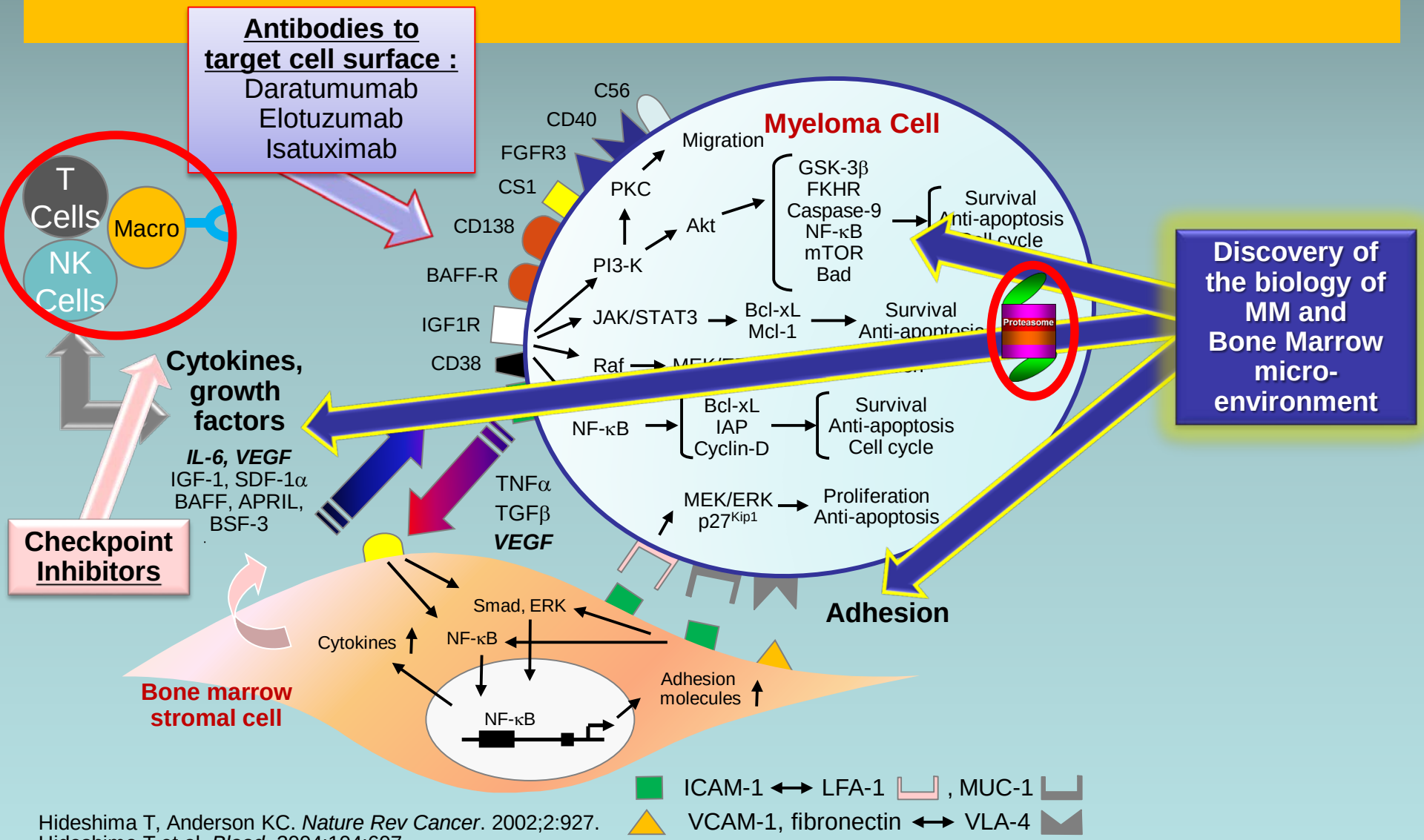
Currently Available Therapies Targeting Myeloma Cells in the Bone Marrow Microenvironment



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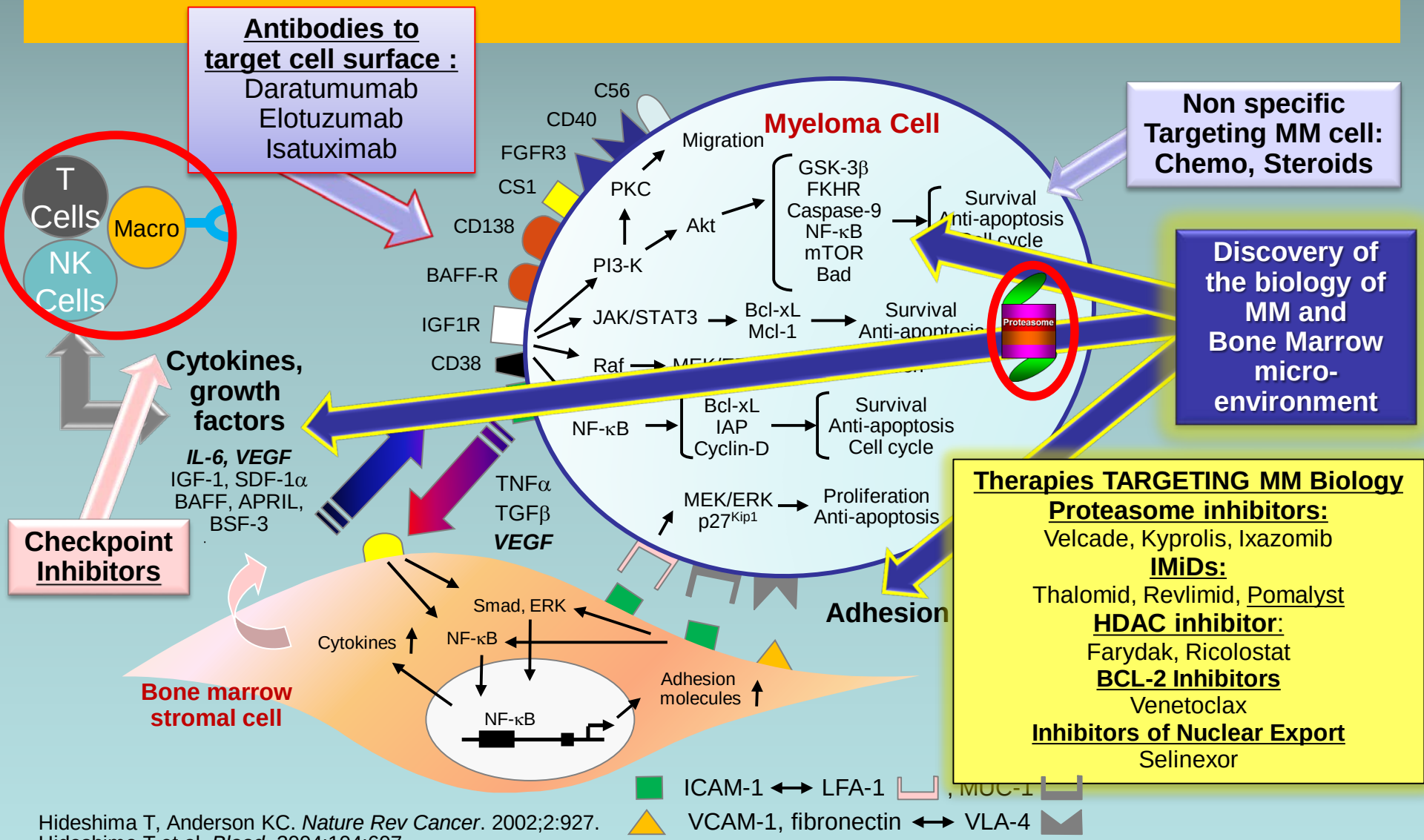

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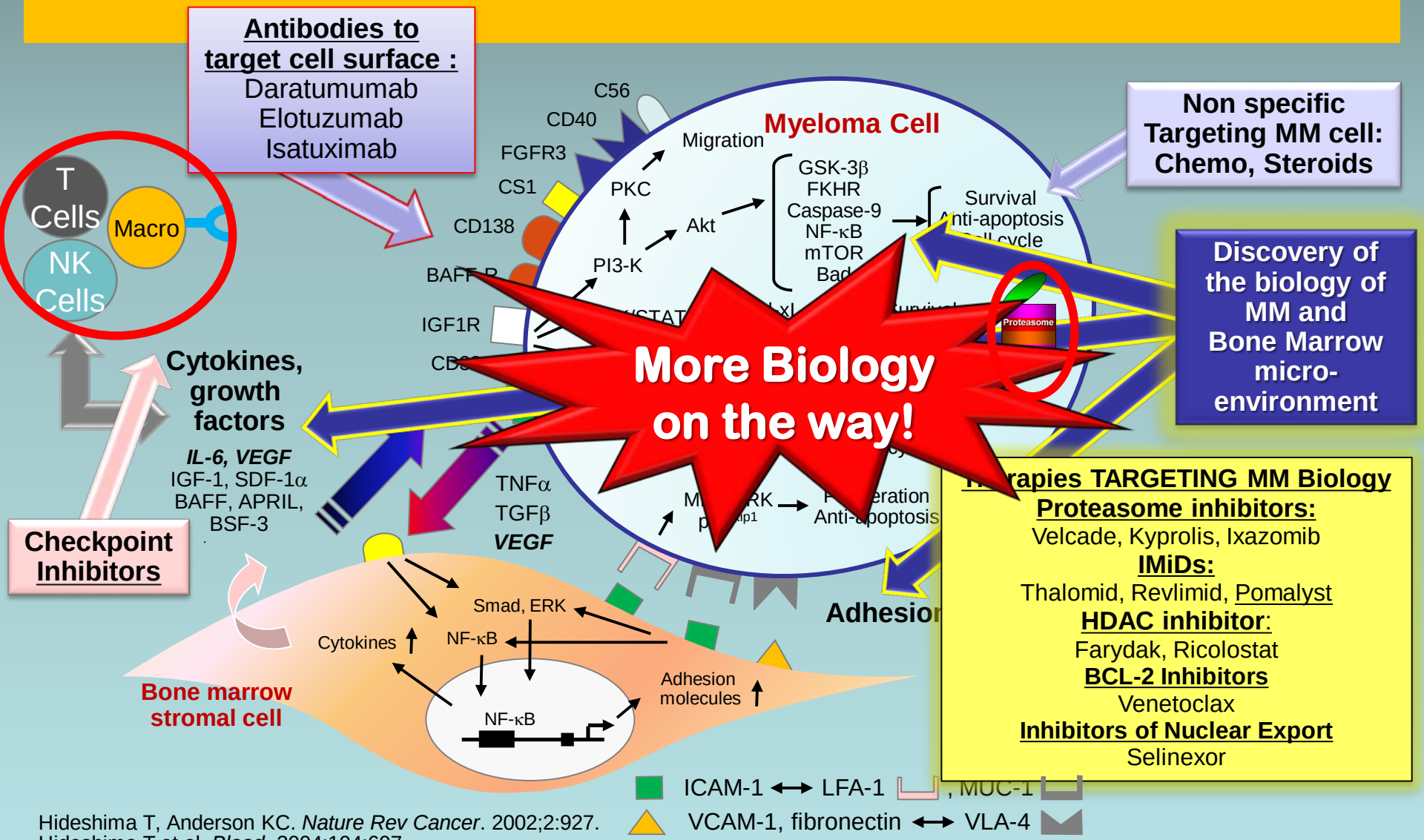

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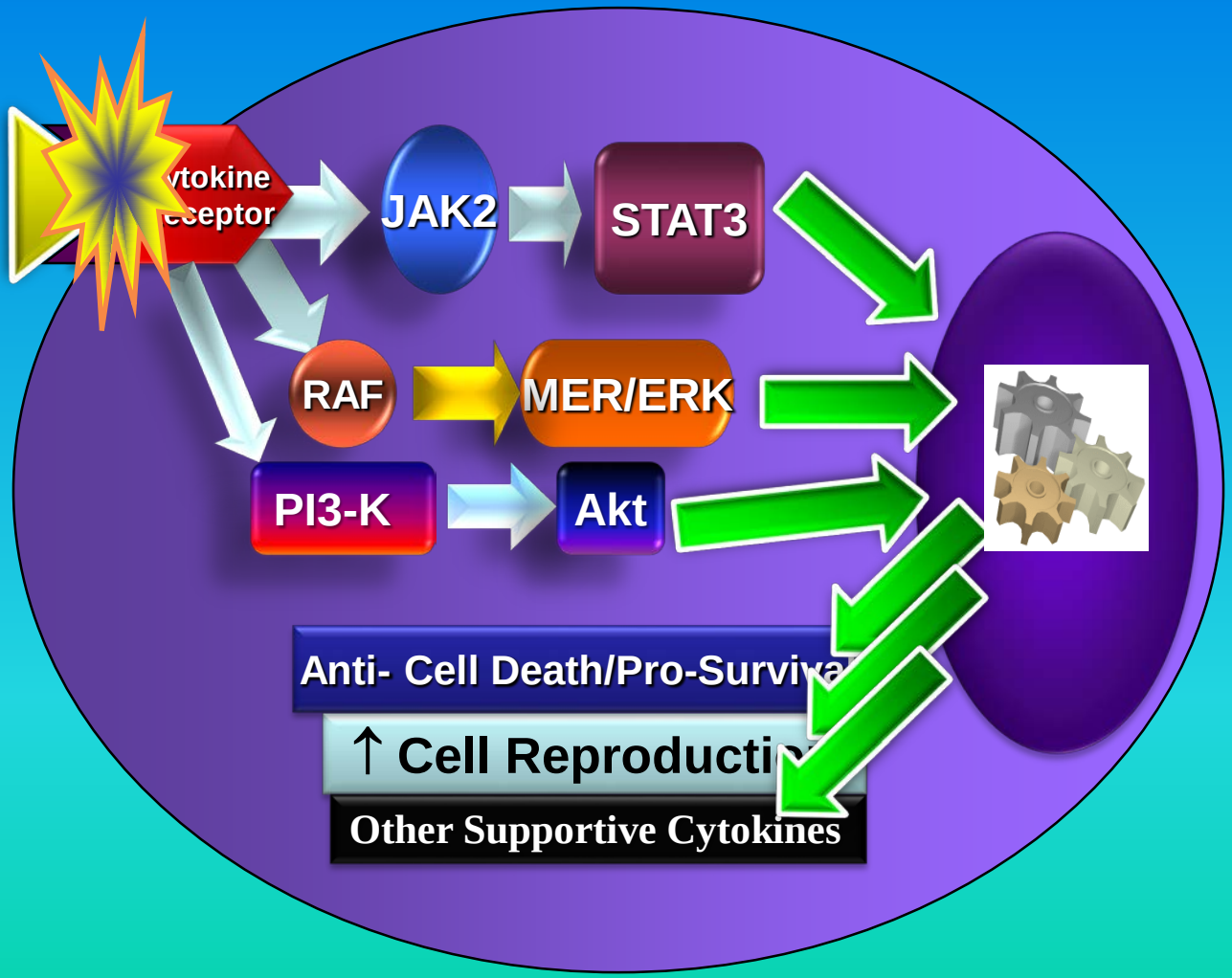
Hideshima T, Anderson KC. *Nat Rev Cancer*. 2007;7:585.

Applying the Science:
Novel Agents in Myeloma

Application of Science: BCL-2 and Chromosome 11 and 14

Cytokines
Signal for MM growth



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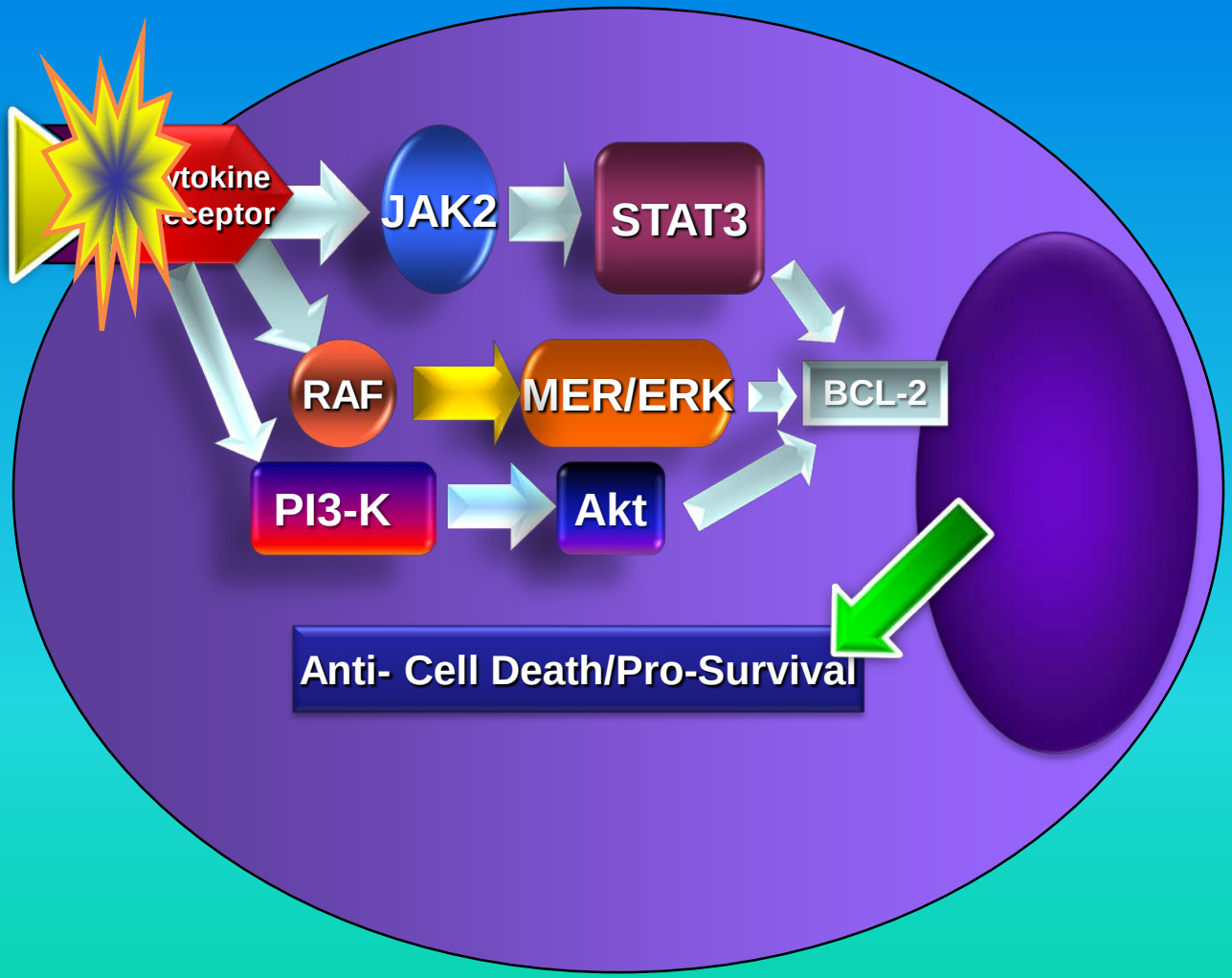
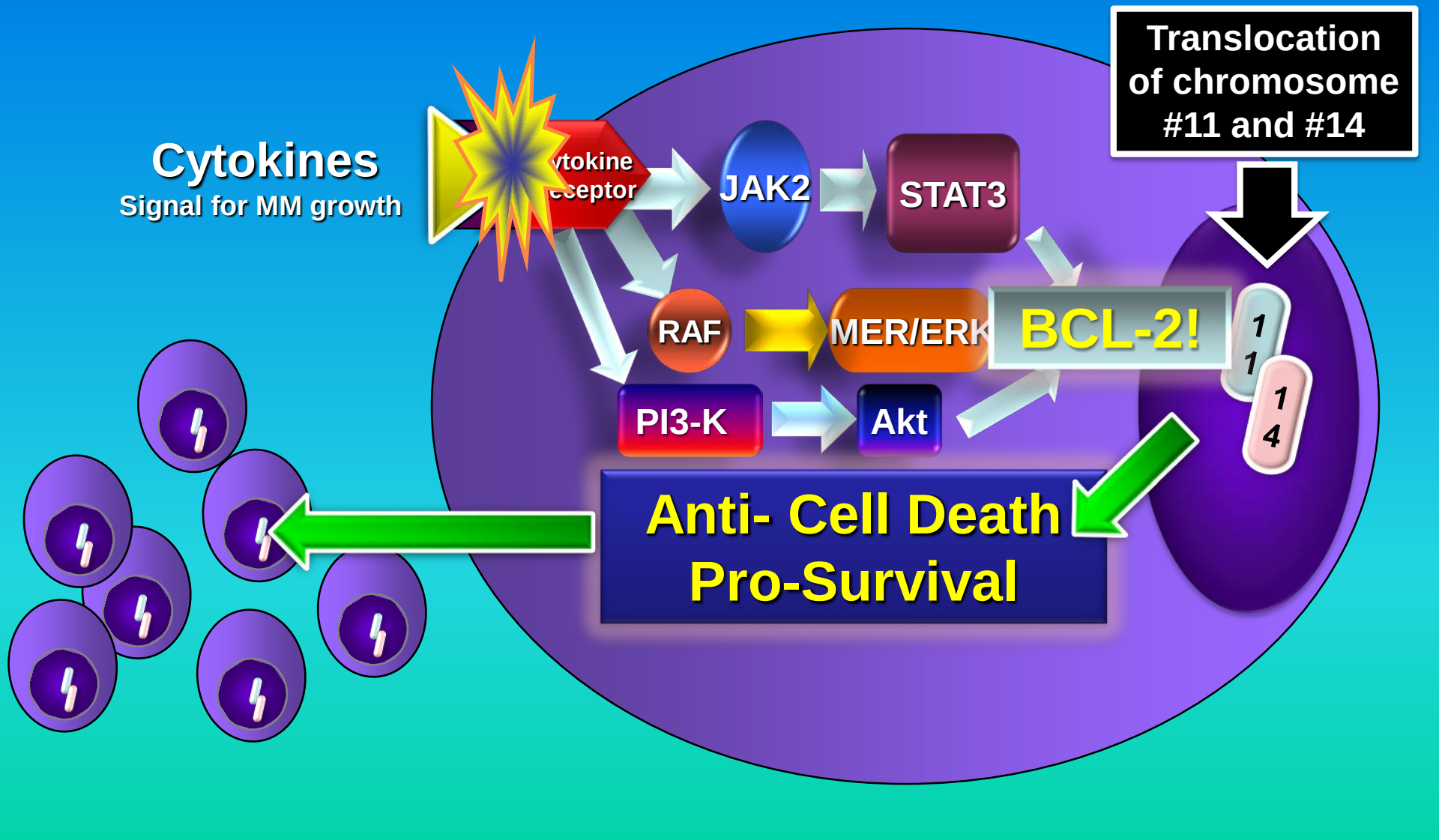
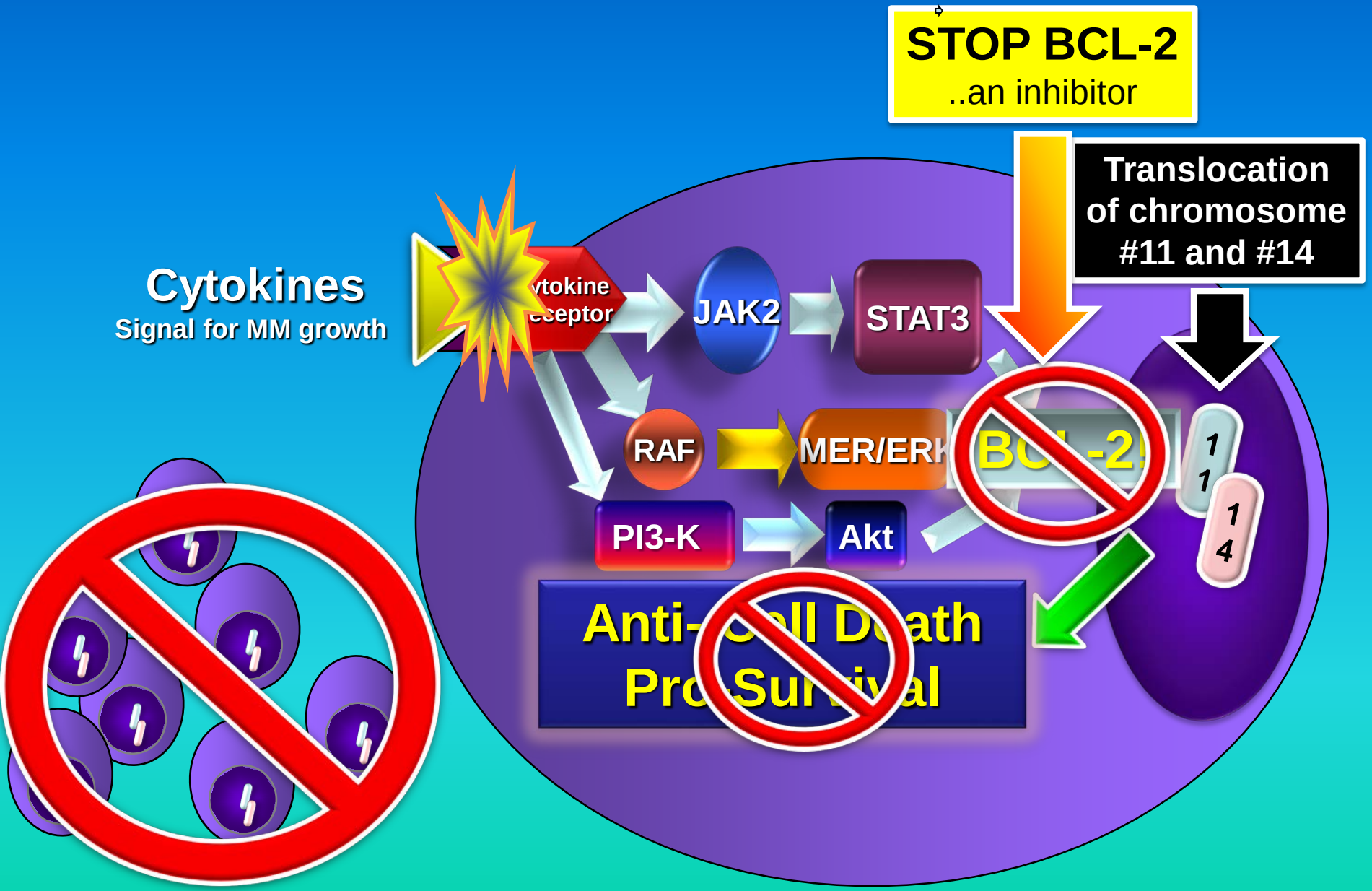


Application of Science: BCL-2 and Chromosome 11 and 14




STOP BCL-2
..an inhibitor
Translocation of chromosome #11 and #14
Cytokines
Signal for MM growth
JAK2
STAT3
RAF
PI3-K
Akt
11
14


YEAH BOSS...
CLEAR AS MUD
memegenerator.net

Venetoclax for Relapsed/ Refractory MM: Background

- Survival of cancer cells is promoted by proteins BCL-2 and which allow cells to survive and proliferate.
  - Overexpression of Bcl-2 in some cancers has sometimes shown to be linked with increased resistance to chemotherapy.
- **Venetoclax (Venclexta) is a oral (*pill*) Bcl-2 inhibitor.**
  - It blocks (Bcl-2) protein leading to programmed cell death of cancer cells.
- FDA approval for high risk types of chronic lymphocytic leukemia (CLL) in 2015.
- In CLL the common side effects were low white blood cell count, nausea, anemia, diarrhea, upper respiratory tract infection, fatigue.
  - Major side effect in CLL was ***Tumor Lysis Syndrome*** (sudden cancer cell death with unstable electrolytes).

Touzeau C, et al. Leukemia. 2014;28:210-214. Punnouse EA, et al. Mol Cancer Ther. 2016;15:1132-1144. Kumar S, et al. ASH 2016. Abstract 488.

Venetoclax Monotherapy for Relapsed/ Refractory MM: Background

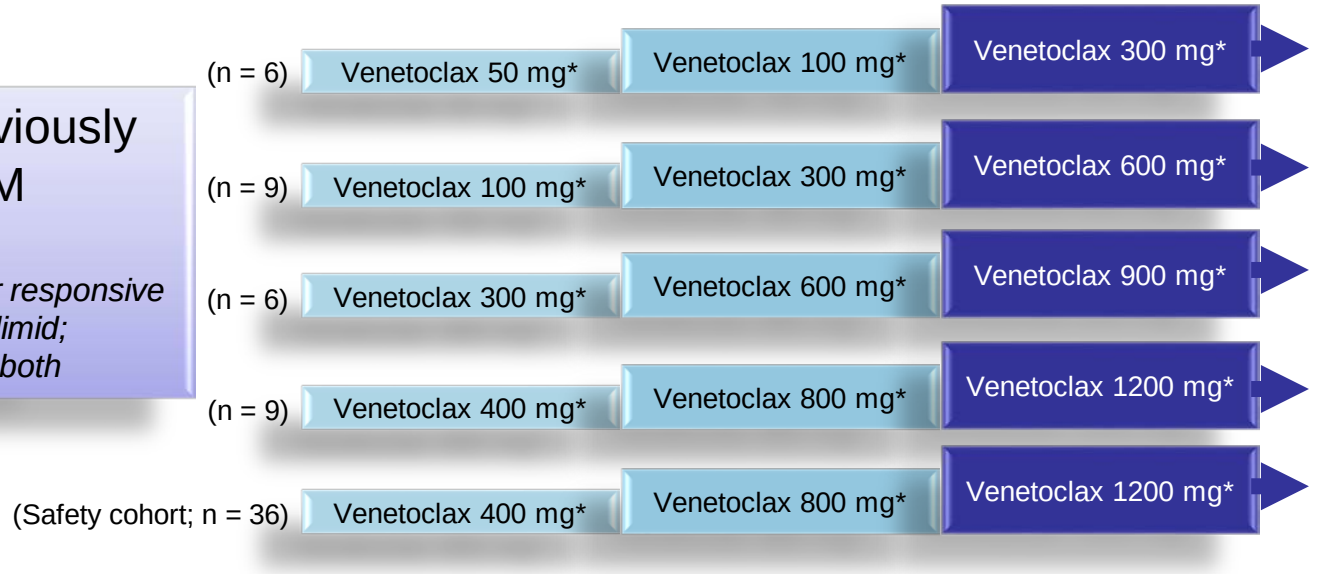
- **Laboratory studies show venetoclax induces Myeloma cell death in cell line samples**.
  - Cells positive for translocation 11 and14 (t11;14) are particularly susceptible.
  - t11;14 correlated with higher ratios of *BCL2/MCL1* genes and *BCL2/BCL2L1* (BCL-X_L) mRNA.
- **This exploratory (Phase-1) study evaluated safety and tolerability of venetoclax solo-therapy in pts with previously treated MM.**

Touzeau C, et al. Leukemia. 2014;28:210-214. Punnouse EA, et al. Mol Cancer Ther. 2016;15:1132-1144. Kumar S, et al. ASH 2016. Abstract 488.

Venetoclax Monotherapy for Relapsed/ Refractory MM: Phase I Study Design

66 Pts with previously treated MM

More than 70% no longer responsive to Velcade or Revlimid; 61% refractory to both



*Pts who progressed on venetoclax could add dexamethasone and continue on study.

Kumar S, et al. ASH 2016. Abstract 488.

Venetoclax Monotherapy for Relapsed/ Refractory MM: Overall Response Rate

Outcome, %	Overall Population (N = 66)	Pts With t(11;14) (n = 30)	Pts Without t(11;14) (n = 36)	Pts With High *BCL2/BCL2L1* (n = 9)	Pts With Low *BCL2/BCL2L1* (n = 15)
Overall RR	21	**40**	6	**88**	**20**
sCR	3	**4**	3	**11**	**0**
CR	4	**10**	0	**33**	**0**
VGPR	8	**13**	3	**11**	**13**
Partial R	6	**13**	0	**33**	**7**

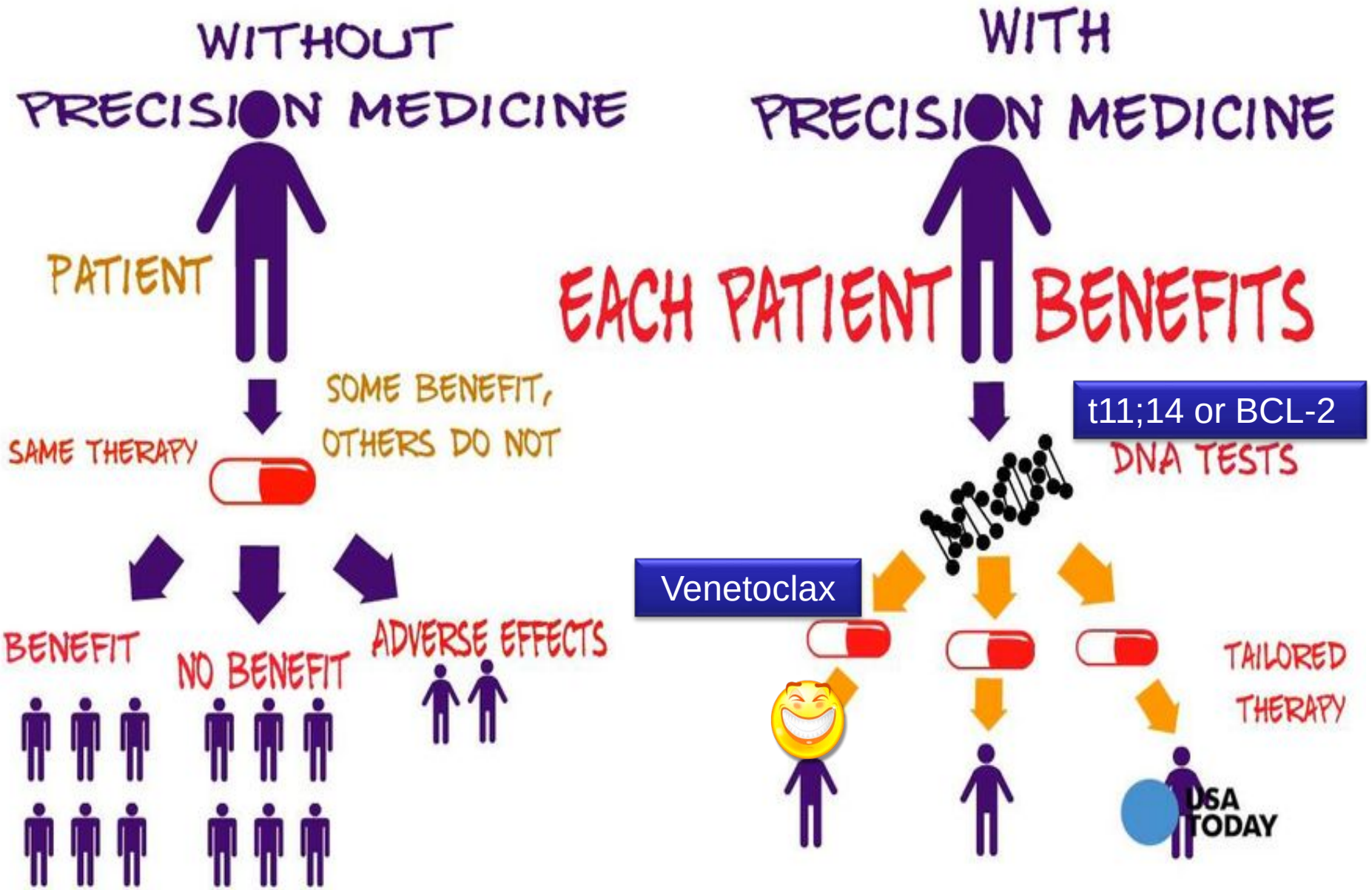
Kumar S, et al. ASH 2016. Abstract 488.

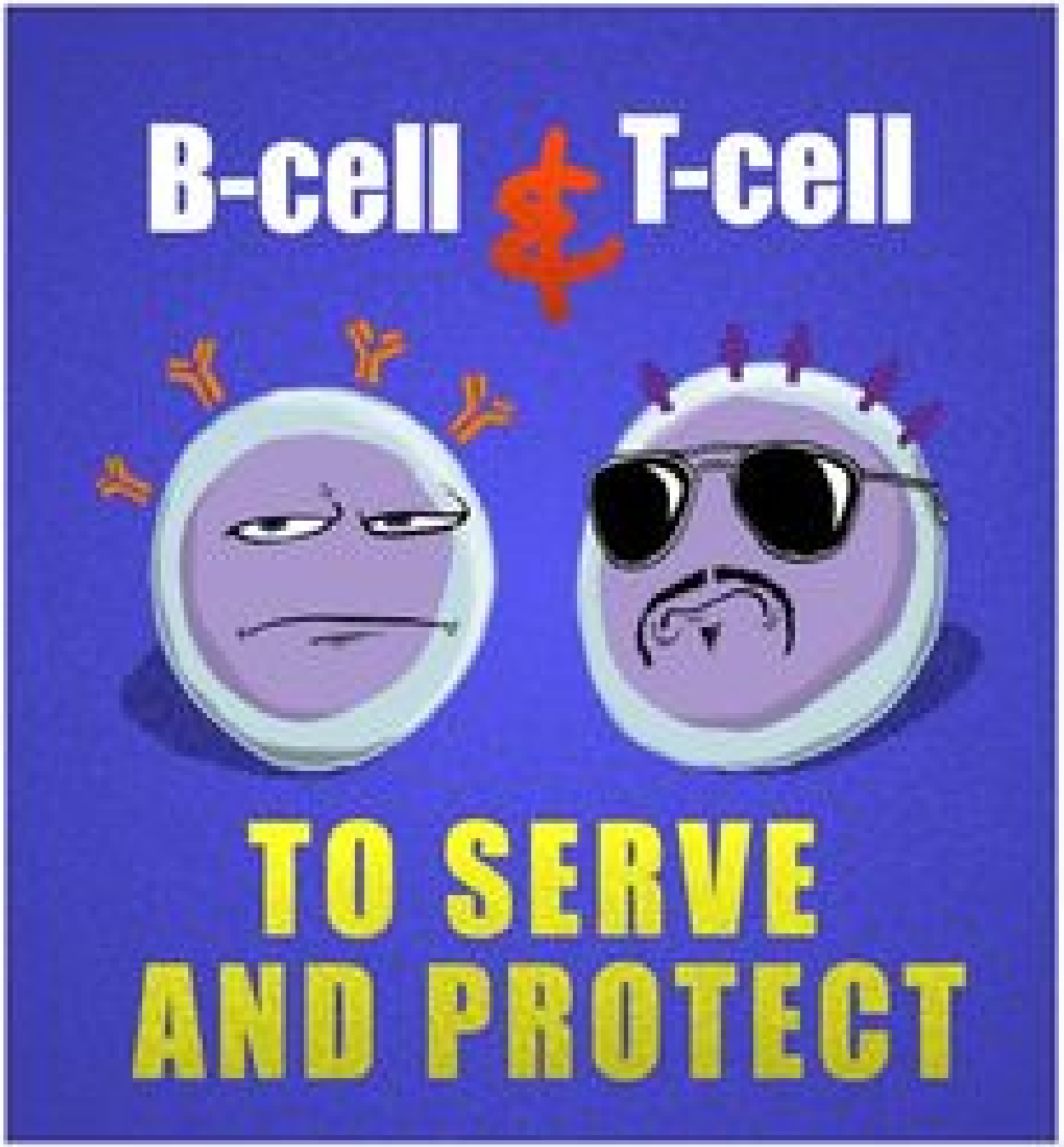
Venetoclax Monotherapy for Relapsed/ Refractory MM: Conclusions

- In pts with previously treated MM, BCL-2 inhibitor venetoclax solo-therapy was safe and tolerable.
  - Dose-limiting toxicity at 600 mg was abdominal pain, nausea (n = 2).
  - Tumor lysis syndrome (sudden cancer cell death with unstable electrolytes) was NOT documented.
- Overall Response Rate: 21% for total population
- **Overall Response Rate in t(11;14) patients :40%**
  - Higher Overall Response Rates, deeper responses, and greater time to progression in patients with t(11;14)
  - **Venetoclax activity independent of previous treatment history in pts with t(11;14)**
  - Higher ORR also seen in pts with high vs low *BCL2/BCL2L1* ratio
- **This is Precision Therapy in Myeloma!**

Kumar S, et al. ASH 2016. Abstract 488.

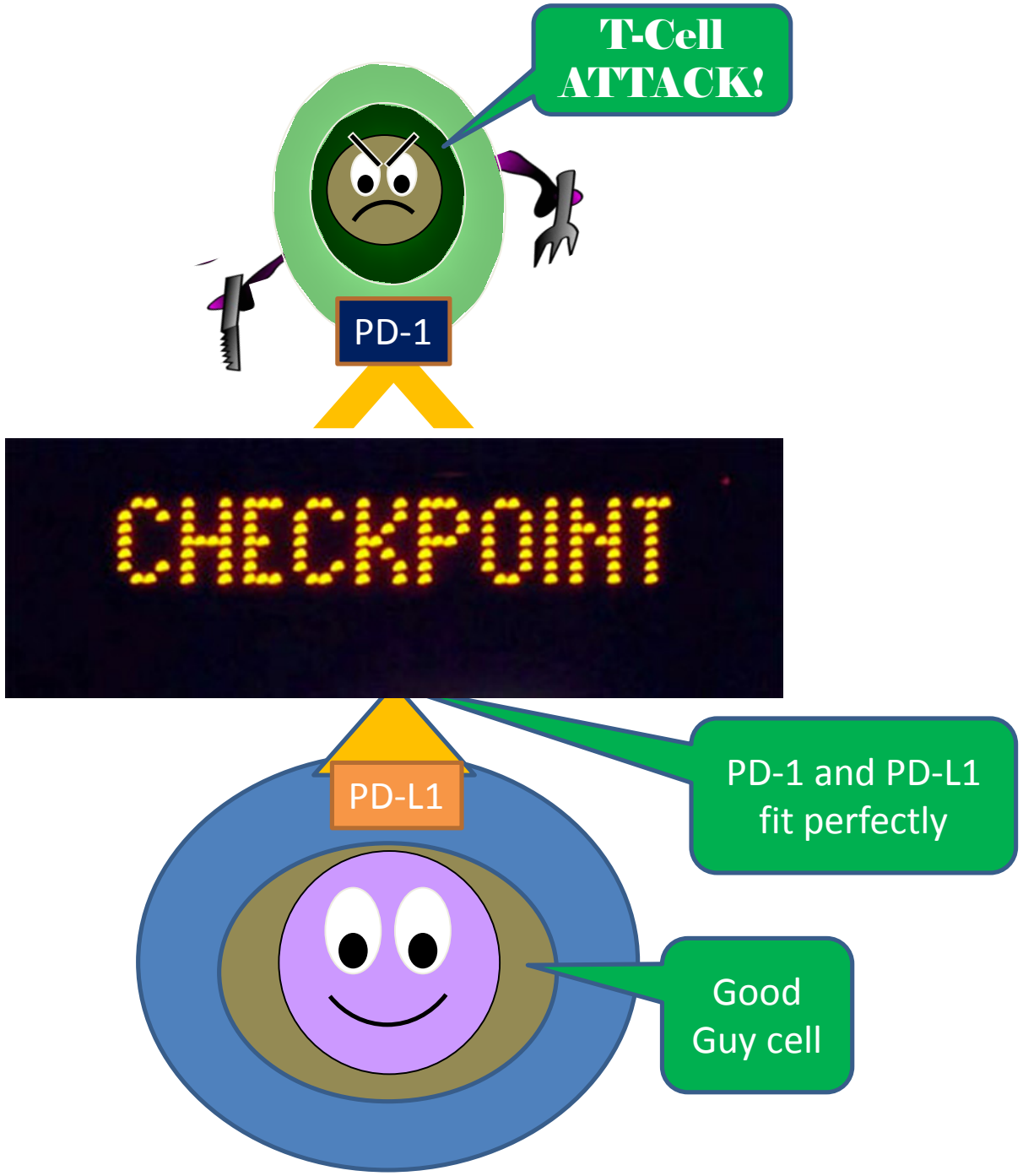
What is Precision Medicine?

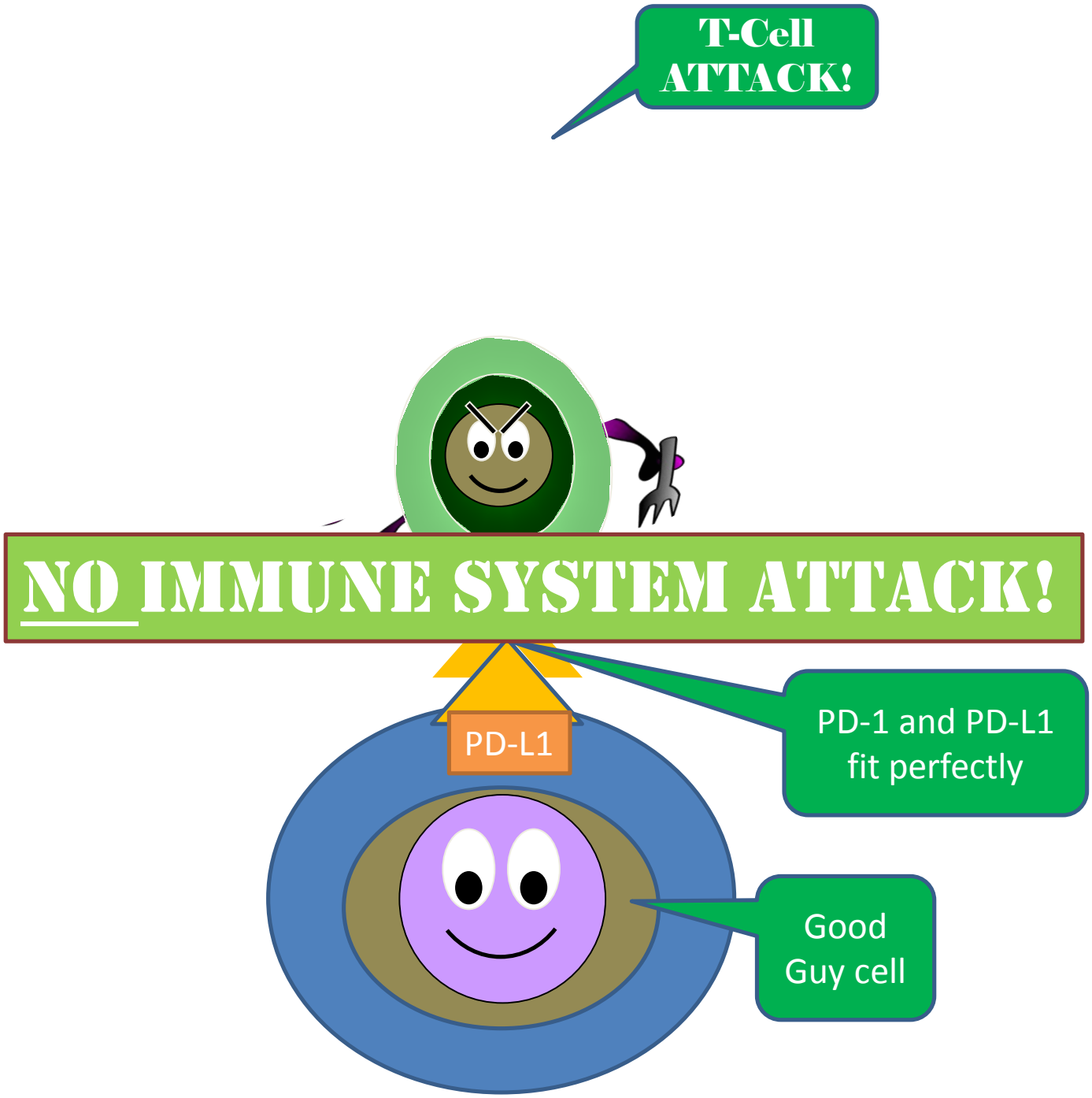


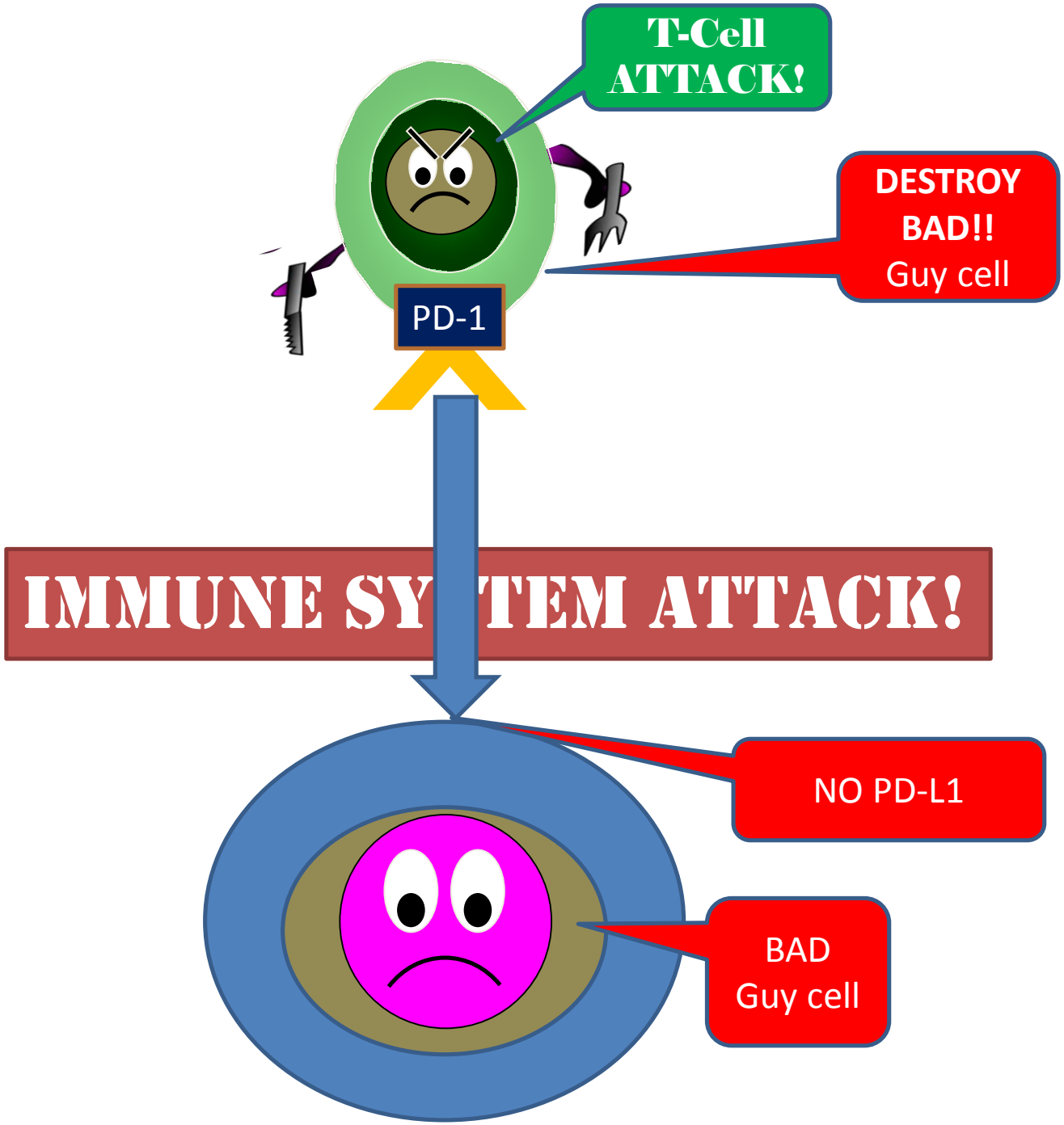

B-cell & T-cell
TO SERVE
AND PROTECT

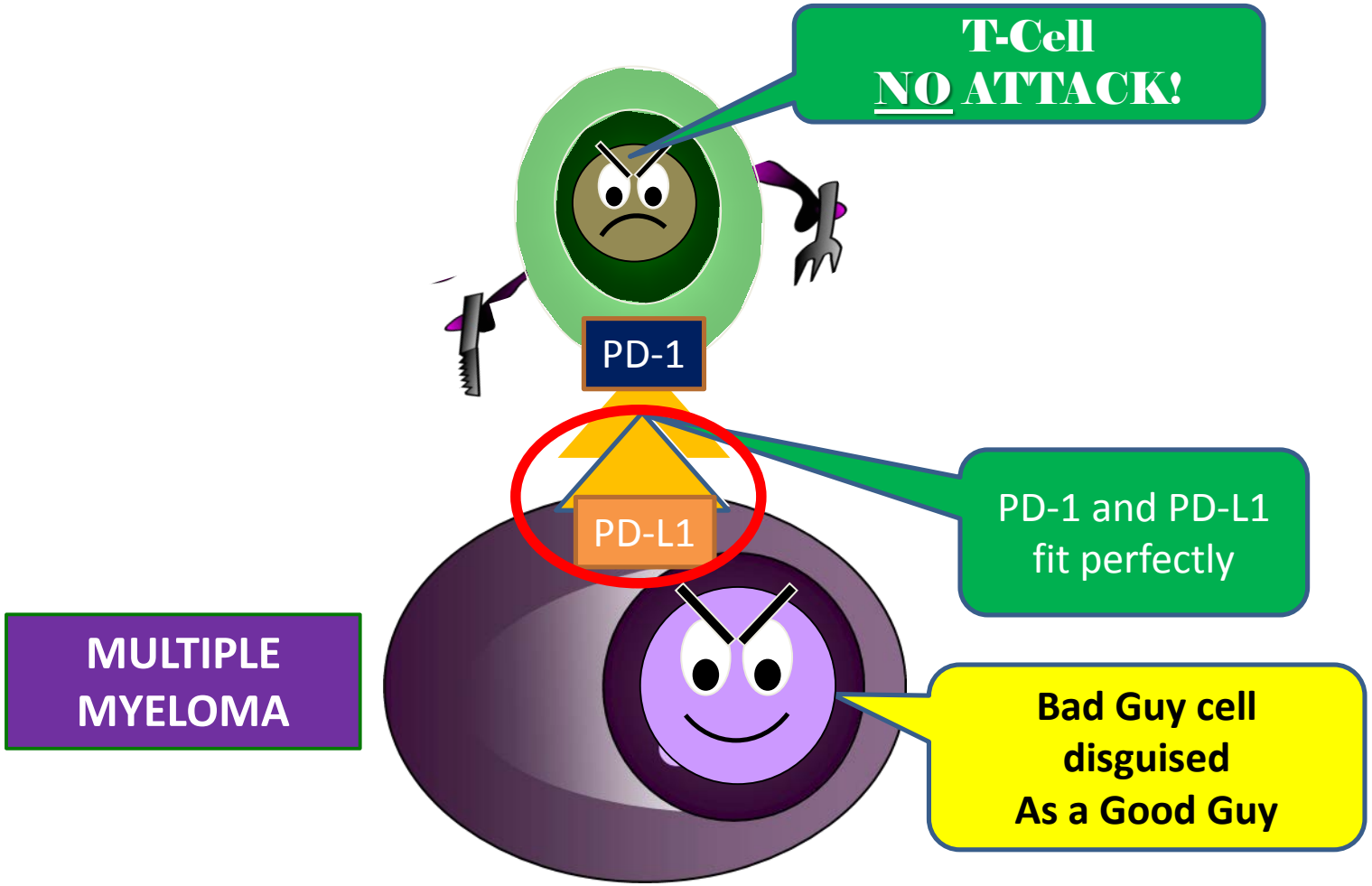
Immune checkpoint inhibitors to treat cancer

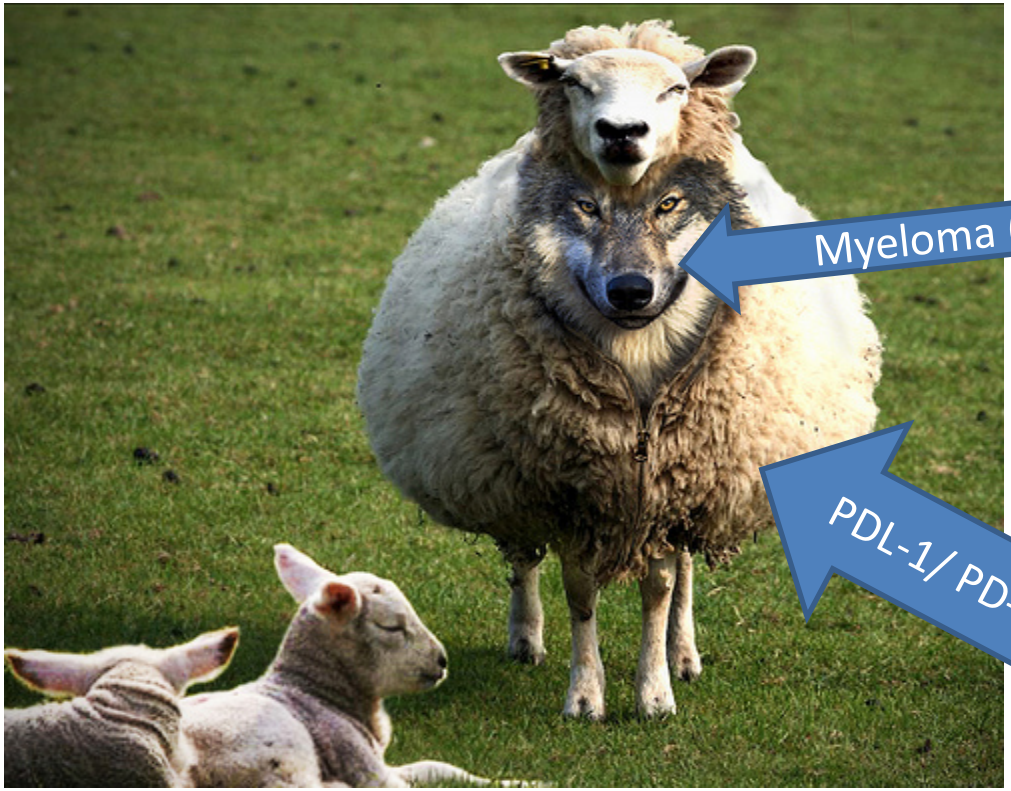
- The Immune system has the ability to tell between **normal cells** from **abnormal cells**.
  - This lets the immune system attack the bad cells while leaving the normal cells alone.
- **The immune system uses "checkpoints" – molecules on certain immune cells to attack abnormal cells or leave normal cells alone.**
- Cancer cells sometimes find ways to use these checkpoints **to avoid being attacked** by the immune system.


T-Cell ATTACK!
PD-1
CHECKPOINT
PD-L1
PD-1 and PD-L1 fit perfectly
Good Guy cell

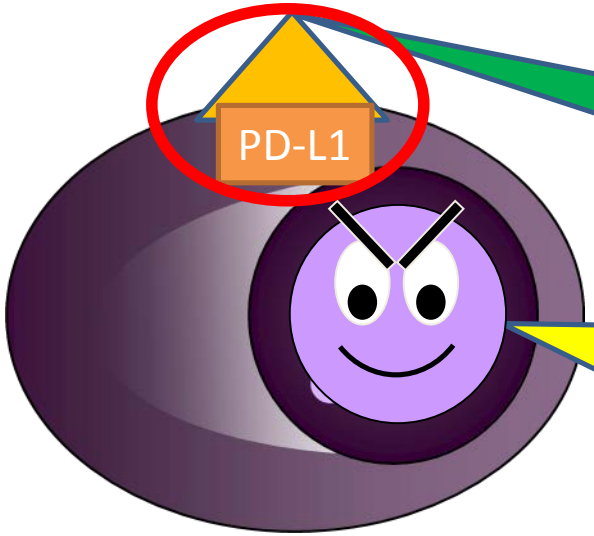

T-Cell
ATTACK!
NO IMMUNE SYSTEM ATTACK!
PD-L1
PD-1 and PD-L1
fit perfectly
Good
Guy cell


T-Cell
ATTACK!
DESTROY
BAD!!
Guy cell
PD-1
IMMUNE SY TEM ATTACK!
NO PD-L1
BAD
Guy cell


T-Cell
NO ATTACK!
PD-1
PD-L1
PD-1 and PD-L1
fit perfectly
MULTIPLE
MYELOMA
Bad Guy cell
disguised
As a Good Guy

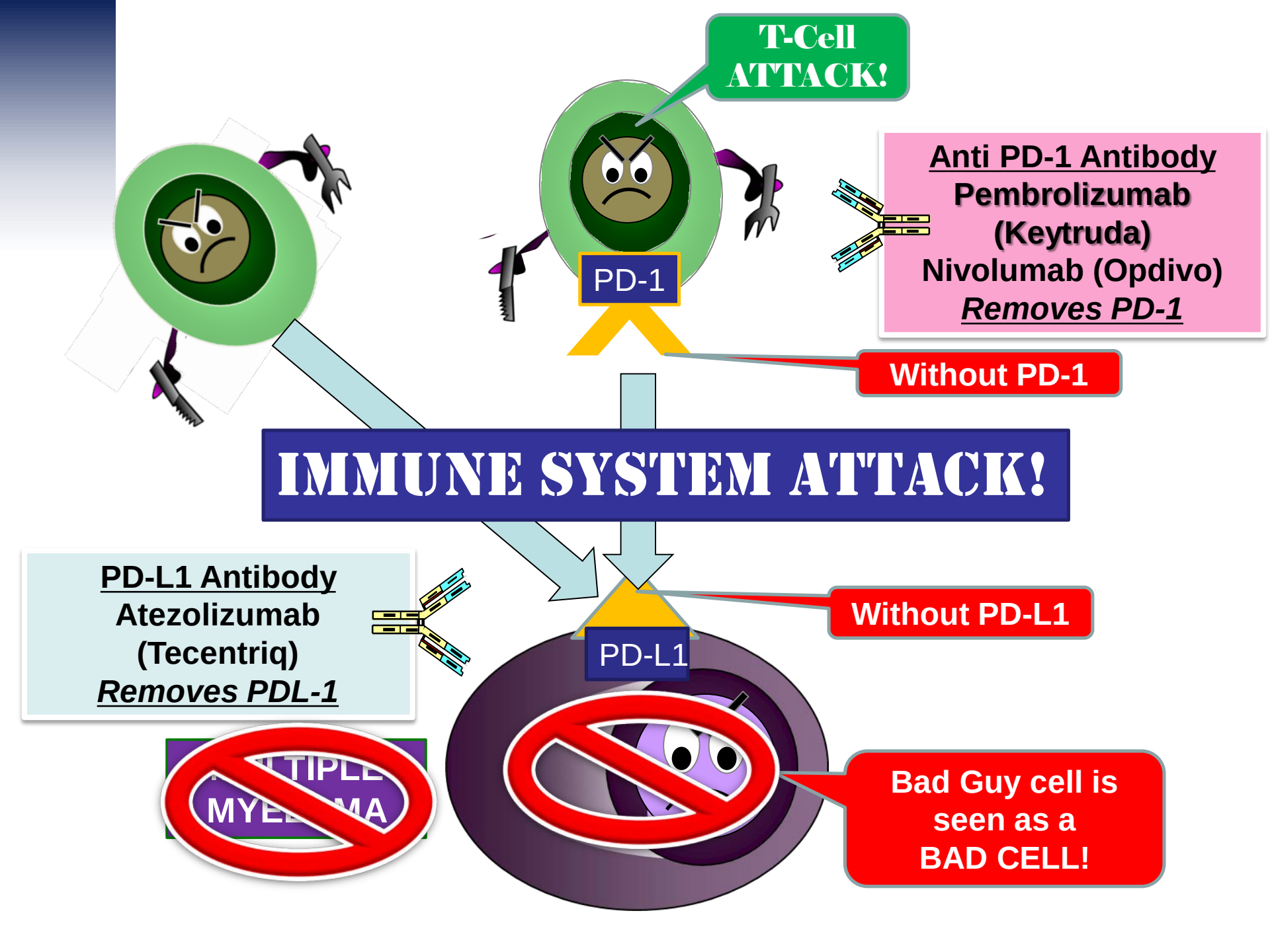


MULTIPLE MYELOMA



PD-1 and PD-L1 fit perfectly

Bad Guy cell disguised As a Good Guy

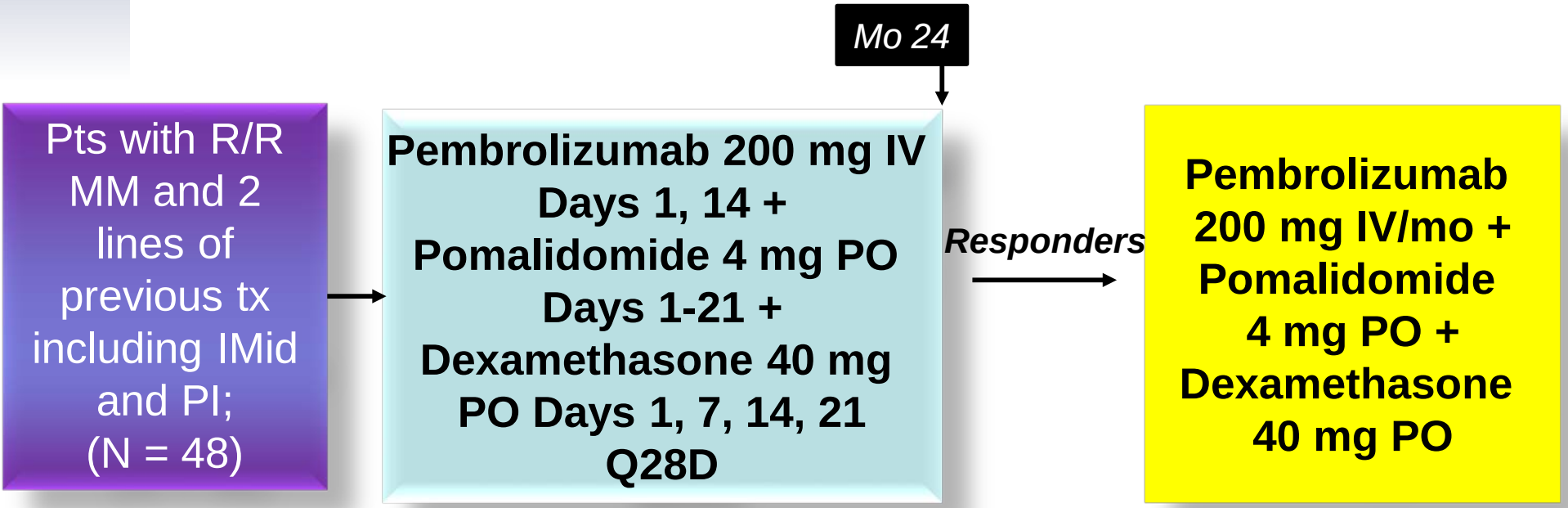

T-Cell ATTACK!
PD-1
Anti PD-1 Antibody
Pembrolizumab (Keytruda)
Nivolumab (Opdivo)
Removes PD-1
Without PD-1
IMMUNE SYSTEM ATTACK!
PD-L1 Antibody
Atezolizumab (Tecentriq)
Removes PDL-1
Without PD-L1
PD-L1
Bad Guy cell is seen as a BAD CELL!

Check-point inhibitor studies

- Anti PD-L1 antibodies FDA approved:
  - **Atezolizumab** approved for bladder cancer treatment.
- Anti PD-1 antibodies FDA approved:
  - **Nivolumab** is approved to treat melanoma, lung cancer, kidney cancer and Hodgkin's lymphoma.
  - **Pembrolizumab** is approved for is approved to treat melanoma and lung cancer.
- At the ASCO 2016 the first Check-point inhibitor study was presented.
  - KEYNOTE-023: phase I study evaluating pembrolizumab 200mg + Revlimid 25mg + Dexamethasone 40mg in pts with Relapsed/Refractory MM with more than 3 prior therapies.
  - Overall Response rate: 50%
  - **Revlimid failure (refractory) response rate: 38%**
  - **88% of pts showed some decrease in M protein or free light chains from baseline**

Mateos MV, et al. ASCO 2016. Abstract 8010.

Pembrolizumab, Pomalidomide, Dexamethasone for Relapsed Refractory MM



Characteristic	Pts (N = 48)
Median lines of earlier therapy (range)	3 (2-5)
Refractory, %	
▪ Proteasome inhibitors (Velcade/Kyprolis)	79
▪ Revlimid	90
▪ IMiDs + proteasome inhibitors	73

Badros AZ, et al. ASH 2016. Abstract 490.

Pembrolizumab, Pomalidomide, Dexamethasone for R/R MM: Adverse Events

Adverse Events	All Severities		High Severity Grade > 3	
In > 30% of pts	Fatigue Neutropenia Hyperglycemia Thrombocytopenia Anemia	Dizziness Constipation infection Short of breath Edema	Neutropenia	
In > 20% to 30% of pts	Lymphopenia Muscle spams Rash Diarrhea	Infection Pneumonia Nausea	Anemia Hyperglycemia	
In ≥ 10% to 20% of pts	Hypotension Peripheral neuropathy Arrhythmia		Pneumonia Fatigue Lymphopenia	Low Platelets
Immune Reaction AEs in any pt	**Pneumonitis (12%)** **Hypothyroidism (10%)**	**Adrenal** **Hepatitis** **Vitiligo**	**Hypothyroidism** **Pneumonitis**	**Adrenal** **Hepatitis**

Badros AZ, et al. ASH 2016. Abstract 490.

Pembrolizumab, Pomalidomide, Dexamethasone for R/R MM:
How well does it work?

Response, %	Full Population (N = 45)	Refractory to 2 Classes (n = 32)	High-Risk Cytogenetics (n = 27)
Overall Response Rate	**65**	**68**	**56**
Clinical benefit	**72**	**69**	**60**
Best response			
▪ sCR	7	3	7
▪ CR	2	3	4
▪ VGPR	20	18	4
▪ **PR**	**36**	**44**	**41**
▪ MR	7	3	4
▪ **SD**	**23**	**22**	**31**
▪ PD	5	4	7
sCR + CR+ VGPR, %	**29**	**24**	**15**

Badros AZ, et al. ASH 2016. Abstract 490.

Pembrolizumab, Pomalidomide, Dexamethasone for R/R MM: Duration of Response and Survival

Outcome in months	Full Efficacy Population (N = 45)
Median duration of response	16.3 (9.9-19.1)
Median Progression Free Surv	17.4 (11.7-18.8)
Median Overall Survival	Not reached (18.8-not reached)

- PFS significantly longer in low-risk vs high-risk subgroups.
- Side effects occurred in ~ 50% of the study population
  - Discontinuation in only10%; most side effects were manageable.
  - Most dose reductions were due to Pomalyst

Badros AZ, et al. ASH 2016. Abstract 490.

Clinical Trials

The Original Standard for Multiple Myeloma: Urethane Therapy

- Urethane was first prepared in the nineteenth century.
  - Was known to inhibit plant root growth and a chemical weapon.
- 1947-report that urethane produced a significant response in ***two patients*** with myeloma.
- For almost **20 years**, urethane was the standard treatment for multiple myeloma.
- **1966 - Randomized clinical trial between urethane and cola in myeloma.**

No difference in survival!

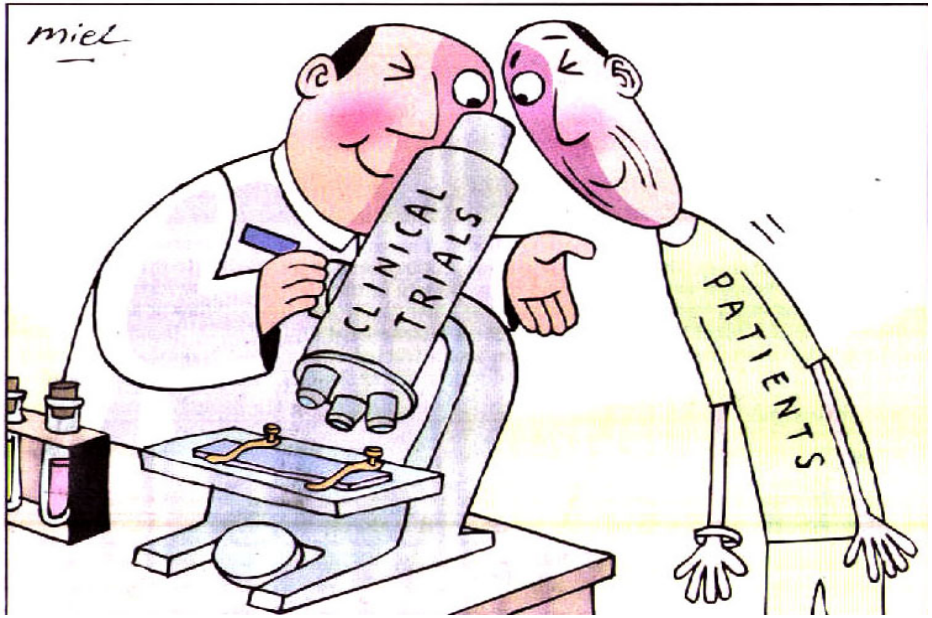
Kyle RA;www.hememalignancies.com

Lancet.1947 Sep 13;2(6472):388. Acta Medica Scandinavica.1951Vol.139;69-72. Blood. 1966;27:328-342.

How Medical Care Advances:

Where does the standard of care come from?

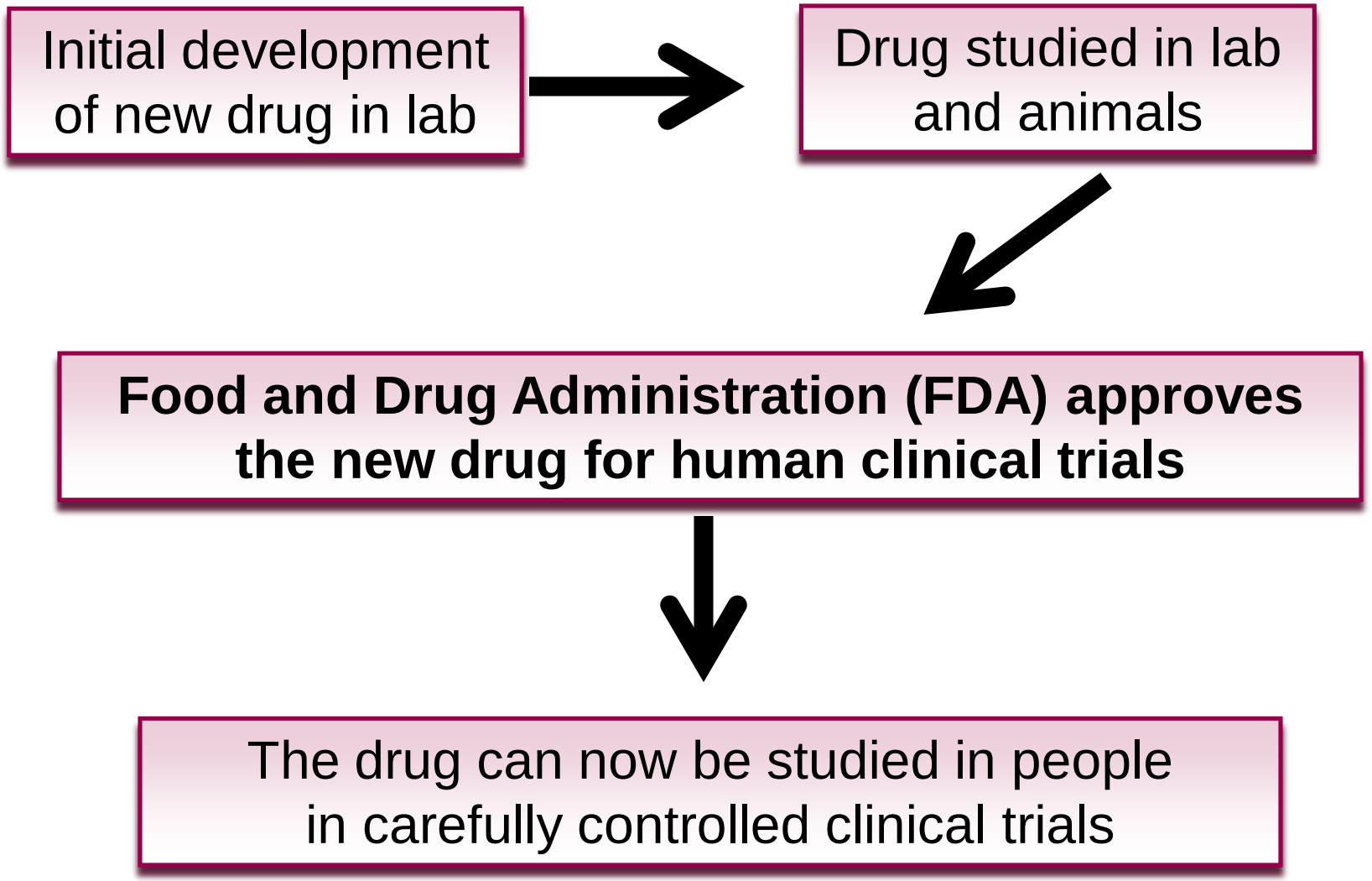
Clinical Trials!



What are Clinical Trials?

- Cancer clinical trials are:
  - Carefully controlled research studies
  - Conducted by doctors to improve the care and treatment of cancer patients
- The aim of a clinical trial is to:
  - Study a new therapy or a new use for an already approved therapy
- Compare a new treatment with a standard treatment to find out which one works better and/or has fewer side effects
- Each cancer clinical trial has a written detailed study design called a ***written protocol.***
  - What drug or drug(s) are being tested.
  - Safety measures throughout the clinical trial program.
  - Who is eligible for the clinical trial.

Clinical trials:
A key step in drug development



Types of Clinical Trials

Phase 1: **investigates for *safety and side effects*, as well as dosage and best way to give treatment.**

- **Includes 20 or more people**

Phase 2: **determines *how well does it work* and safety.**

- **Includes 50 to 300 people**

Phase 3: **looks at effectiveness, side effects and safety *in comparison with other standard treatments***

- **Includes 100s to 1000s of people**

Drug receives FDA approval, it's available to everyone, and it might become standard practice!

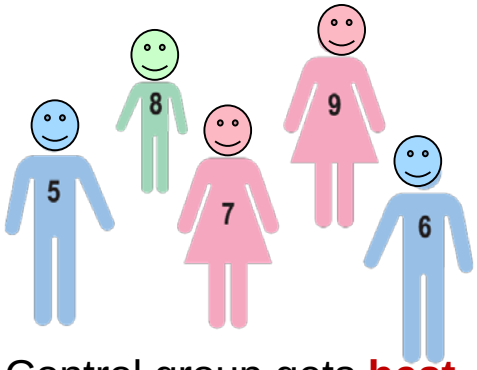
Phase 4: **gathers more information after FDA approval**

Randomized clinical trials (Phase 3): Getting assigned to a group

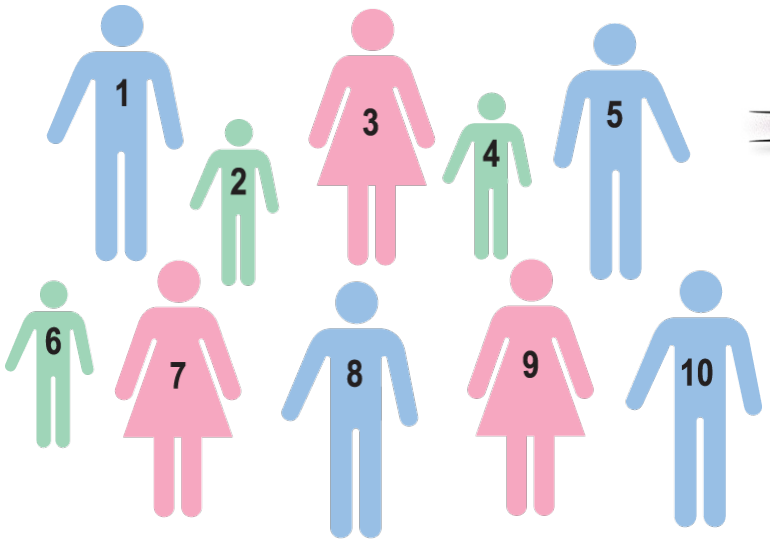
Many cancer clinical trials are “randomized” to enable doctors to compare **new treatments** with **standard treatments**.

Patients are divided into different groups at random:

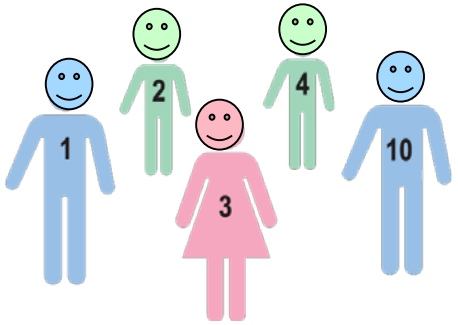
- “**Control group” receives the best standard treatment available**
- **“Treatment group” receives the treatment under study**



Control group gets **best available treatment**



Randomization



Investigational or study group gets **study drug**


FACT
OR
MYTH
?

What do you think?

If I enter a clinical trial, there's a good chance that I could receive a placebo

Fact or Myth

Fact: Placebos are rarely used in cancer clinical trials

What do you think?

A clinical trial is a treatment of last resort

Fact or Myth

Fact: There are clinical trials for people at every stage of disease

What do you think?

Clinical trials are riskier than FDA-approved drugs

Fact or Myth

Fact: Treatment on a clinical trial has as good a chance for success as standard treatment

What do you think?

If my doctor doesn't mention clinical trials, it must not be right for me.

Fact or Myth

Fact: Your doctor may not be aware or remember that there is clinical trial for you.

What do you think?

The trial is more important than the patient.

Fact or Myth

Fact: Never! You can stop your participation on a clinical trial at **ANY TIME** and for **ANY** reason.

What do you think?

If I enter a clinical trial,
I'll be a "guinea pig"

Fact or Myth

Fact: Clinical trials provide patients either the best treatment currently available, or a new and possibly more effective therapy

Clinical trial protocols ensure that patients are closely monitored

- Patients get a lot of attention and support!
- Patients are watched closely by their doctor, as well as other members of their medical team and research team to ensure their safety.

Safety in clinical trials

- **Sponsor asks outside experts to review merit of study.**
- **Many centers have a protocol review committee and a safety board to review the trial before its approved.**
- **Institutional Review Board (committee of experts):**
  - Looks at trial's scientific, legal and ethical merit.
  - Are risks minimized and reasonable vs. anticipated benefits?
  - Is informed consent process in place and documented? (no coercion or "undue" influence to participate).
  - Does data monitoring include patient safety data?
  - Is there a process to protect privacy of patients?

Process of informed consent

- Your doctor must give you an **informed consent document** before you enroll in a clinical trial.
  - Must be in a language you understand.
  - Ask for a language interpreter if needed.

- **Bring an advocate!**
- **Ask your doctor to explain anything you don't understand.**

Take your time in reading and signing the informed consent form. You may take back your consent to participate at any time.

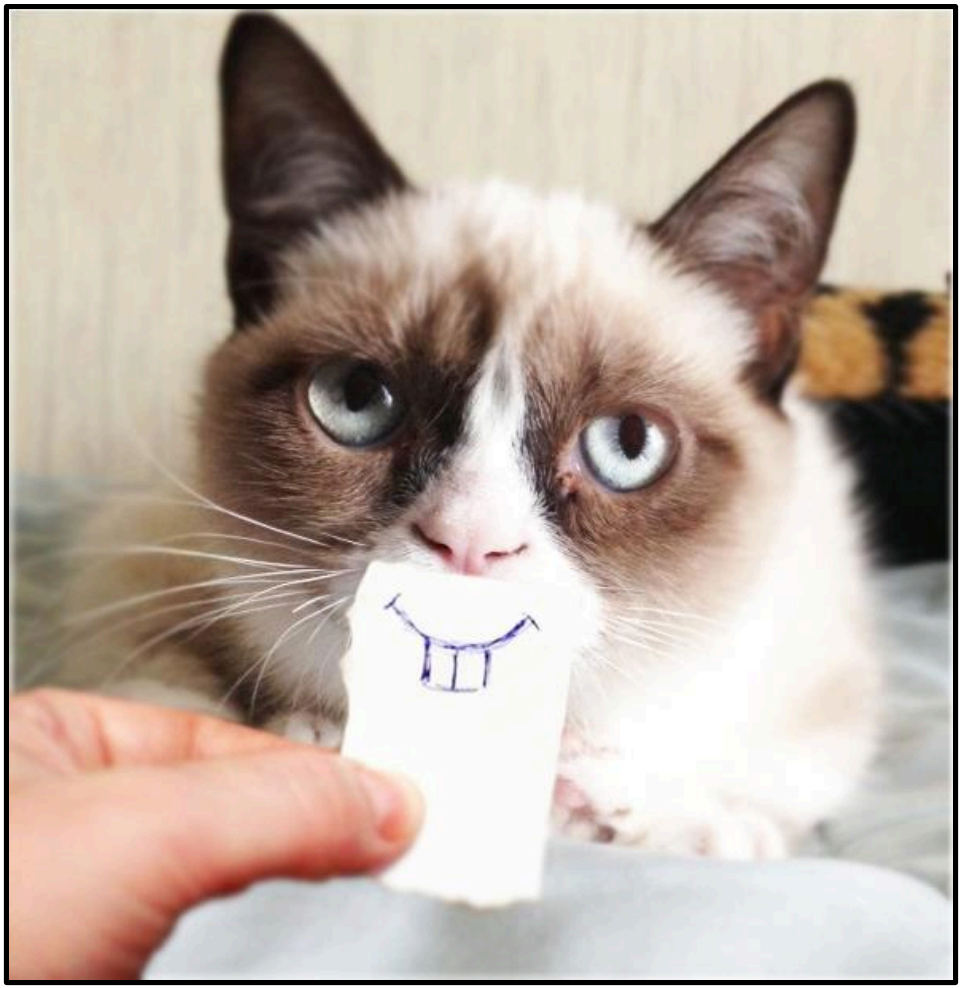
Selected Novel Drugs Being Explored in Clinical Trials

Third/ Fourth-generation agents	Proteasome inhibitors	marizomib, oprozomib, ixazomib
	IMIDs	CC-220
Novel classes of Therapy	Monoclonal antibodies	anti-CD38, anti–CD-138 conjugate, anti-BCMA conjugate, antiSLAM7-conjugate
	Check Point Inhibitors	Durvalumab, Atezolizumab, Pembrolizumab Nivolumab
	BTKi	Ibrutinib, AVL-292
	HDAC inhibitors	panobinostat,* romidepsin, ricolinostat
	Pleiotropic Pathway Modifier	CC:122
	Kinesin Spindle Inh	ARRY
	CDK	PD0332991, SCH727965, AT7519
	BCL antagonist	ABT263
	HSP90	Ganetespib (STA-9090)
	SINE XPO antagonist	KPT-330 (Selinexor)
	FGFR3	TKI258, MFGR1877S
	17p mutated	Idasanutlin

Clinical trials…

- **Clinical Trials** are an important **option** for **everyone!**
- **Clinical Trials** can be for newly diagnosed, with limited disease, or advanced disease.
- **Clinical Trials** are appropriate and safe for people of different ages, genders, and races.
- **Clinical Trials** that include people of ethnicity are critical to knowing if a treatment really works!
- **Clinical Trials take into account all the above factors as well as stage of disease, other treatments used, and presence of any other medical conditions to assure safety.**

Remember…communication with your healthcare team is important in making treatment decisions about standard treatment or clinical trial treatment!



Thank You!

For Your Time and Attention