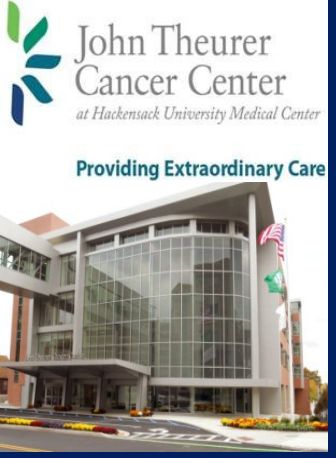

Multiple Myeloma: Relapsed and Refractory

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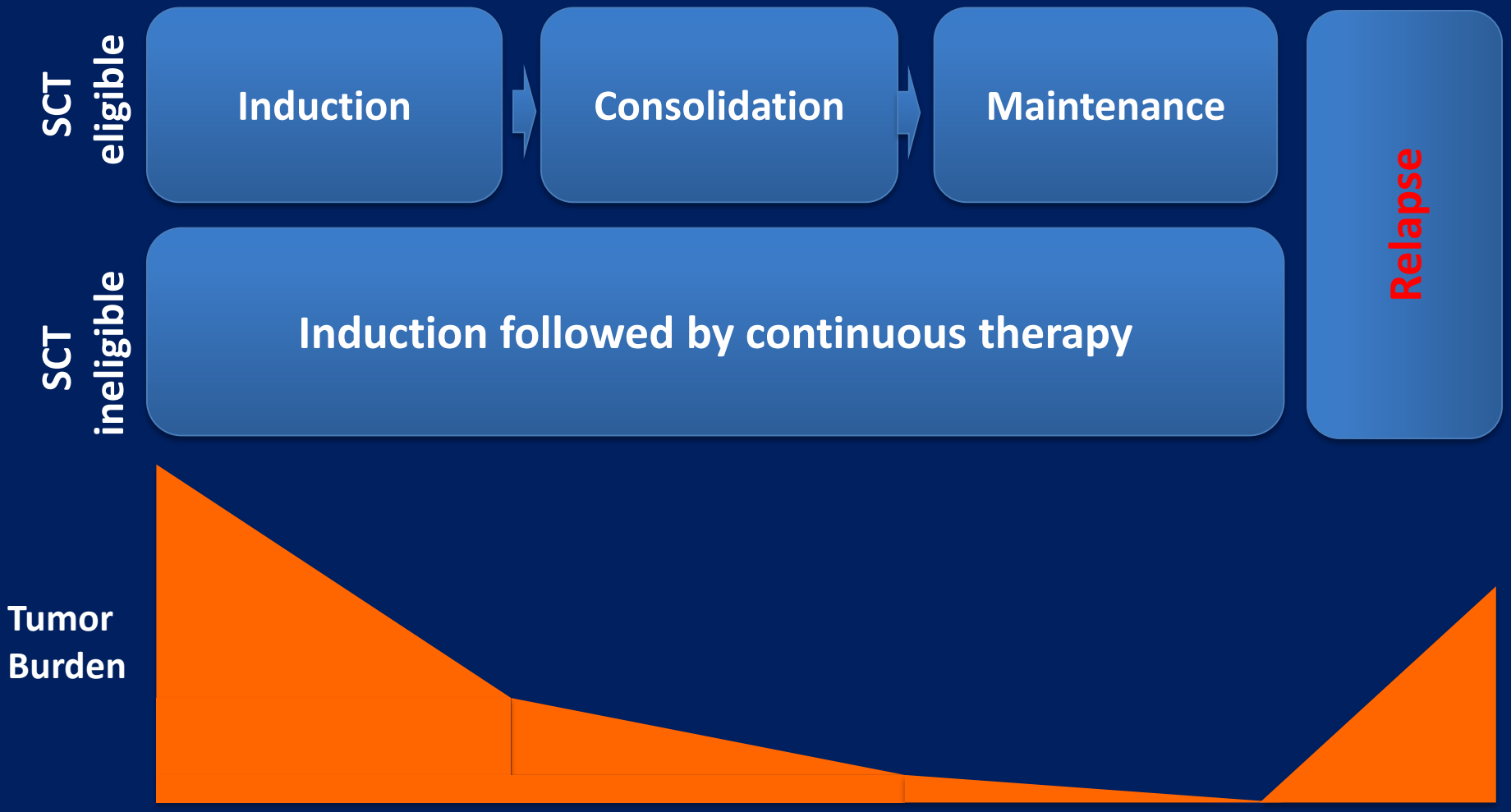
Myeloma treatment paradigm



Case 1

- A 65-yr-old male with ISS stage 1, standard risk MM received Velcade, Revlimid, dexamethasone induction therapy for 4 cycles followed by transplant. He declined lenalidomide maintenance treatment and was in CR for 2 yrs
- He now presents with M protein of 0.6 g/dL and no anemia or other abnormalities on skeletal survey
- Hb is 14 g/dL, UPEP is negative, serum free light chain ratio is 2:1, and creatinine and calcium levels are normal
- 3 mos later, repeat testing shows M protein of 0.8 g/dL
- 6 mos later, M protein is 0.9 g/dL with no changes in the other laboratory values

What would you do now?

A. Re-treat the patient
B. Observe the patient
C. I don’t know

When to Consider Retreatment

- Differences between biochemical relapse and symptomatic relapse need to be considered
- Patients with asymptomatic rise in M protein can be observed to determine the rate of rise and nature of the relapse

  Caveat: patients with known aggressive or high-risk disease should be considered for salvage even in the setting of biochemical relapse
- CRAB criteria are still listed as the indication to treat in the relapse setting

  C: Calcium elevation (> 11.5 mg/L or ULN)
  R: Renal dysfunction (serum creatinine > 2 mg/dL)
  A: Anemia (Hb < 10 g/dL or 2 g < normal)
  B: Bone disease (lytic lesions or osteoporosis)

Case 2

- A 65-yr-old female presents with ISS stage 2 MM. She is treated with RVD (Revlimid, Velcade, Dex) followed by autologous transplant. Posttransplantation, she achieves a VGPR and is started on Revlimid maintenance therapy
- After 2 yrs, she progresses on Revlimid maintenance therapy. She has no neuropathy
- M protein is 1.2 g/dL, Hb is 9.3 g/dL, calcium is normal, serum free light chain ratio is 6:1, and IgG is 2900 mg/dL
- Skeletal survey shows new lytic disease. UPEP is negative, bone marrow shows 10% to 20% plasma cells with normal cytogenetics

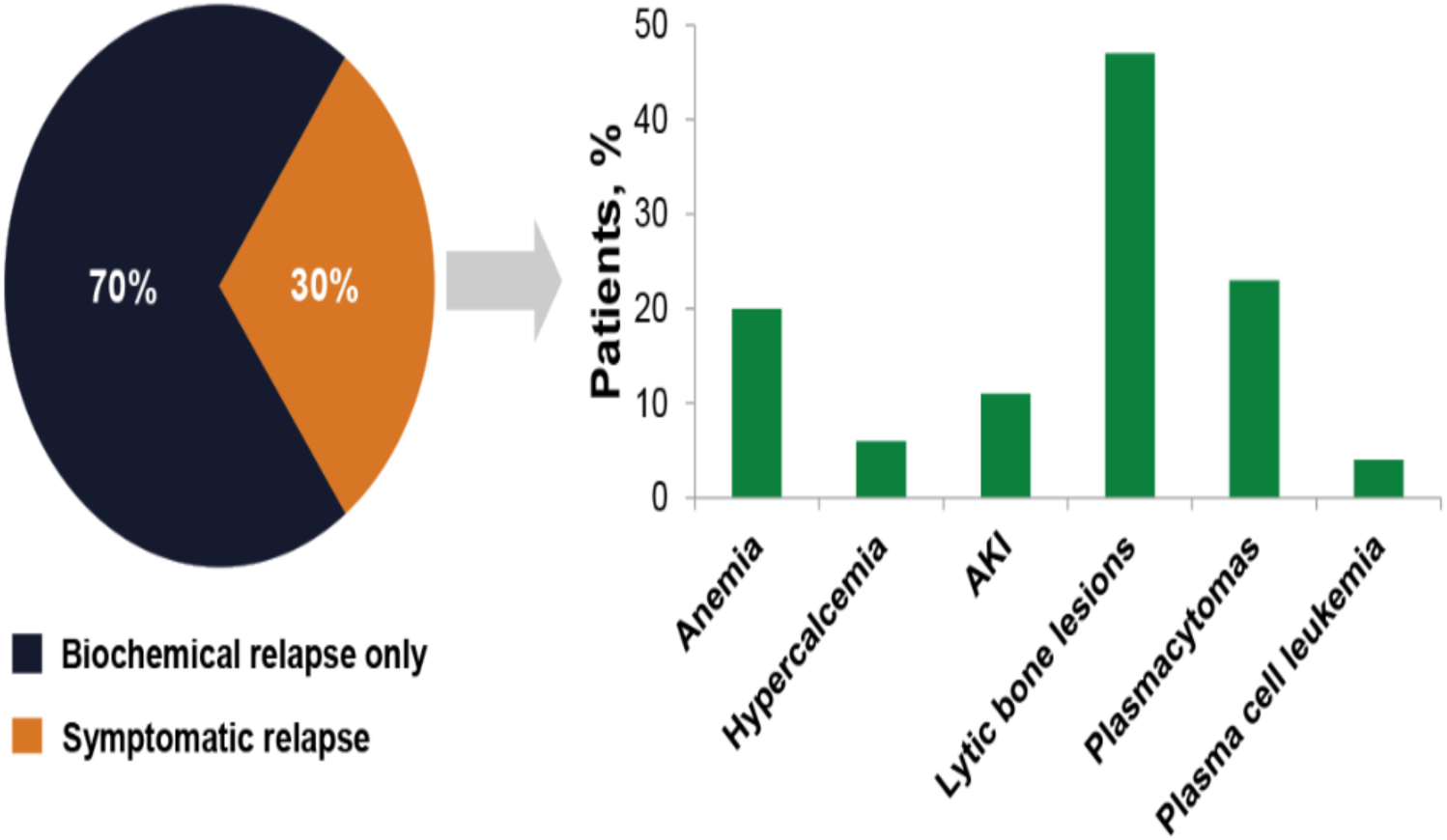
What would you do now?

A. Re-treat the patient
B. Observe the patient
C. I don’t know

What treatment would you choose?

A. Revlimid-based
B. Velcade-based
C. Velcade/Revlimid/dexamethasone (VRD)
D. Darzalex-based
E. Kyprolis-based
F. Empliciti-based

Post-HCT: Patterns of Relapse[1]



1. Gonsalves WI et al. *Bone Marrow Transplant*. 2016;51:1156-1158.

PeerView.com

What is relapsed/refractory disease?

- ***Relapsed:*** recurrence after a response to therapy
- ***Refractory:*** progression despite ongoing therapy

Restarting Therapy and Prognostic Factors in Relapsed Myeloma[1-3]

- No prospective studies; patients can have an indolent course

Indications to start therapy

- CRAB features
- Rapid rise in M protein
- High levels of free light chain w/renal presentation
- High-risk cytogenetics with biochemical progression

Prognostic factors

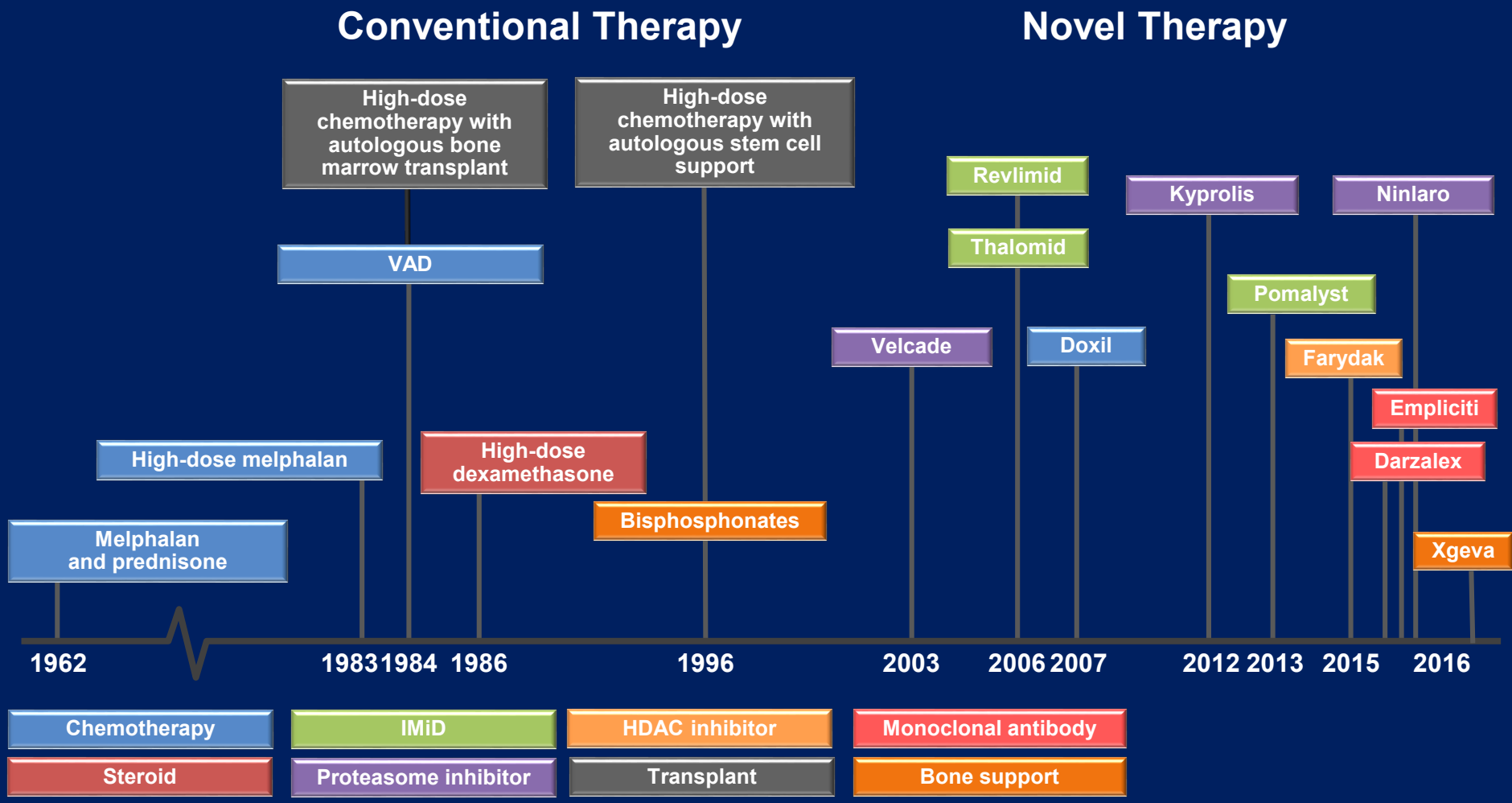
- Duration of initial response
- Acquisition of new abnormalities (1qamp, del17p)
- ISS/RISS
- Performance status
- Presence of EMD
- Circulating plasma cells

1. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. V.3.2018. https://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf. Accessed February 21, 2018.
2. Sonneveld P, Broijl A. *Haematologica*. 2016;101:396-406. 3. Original slide courtesy of Shaji Kumar, MD.

Choosing Therapy for Relapsed/Refractory Myeloma

- **What do we know about the patient's myeloma?**
  - What prior therapy has been used?
  - How well did it work?
  - Did the myeloma progress on active therapy?
  - High-risk cytogenetics/FISH/GEP?
- **What do we know about the patient?**
  - Age
  - Other medical problems
    - Diabetes
    - Blood clots
  - Lasting side effects from past therapies
    - Peripheral neuropathy
  - Personal preferences and values

Evolution of Multiple Myeloma Treatment: 11 New Drugs Approved in ≤15 Years



VAD, vincristine, doxorubicin, dexamethasone; IMiD, immunomodulatory drug; HDAC, histone deacetylase.

Factors to Consider in Treatment Selection

DISEASE-RELATED

- DOR to initial therapy
- FISH/cytogenetics/genomics profile

PRIOR TREATMENT–RELATED

- Prior drug exposure
- Toxicity of regimen
- Mode of administration
- Previous SCT

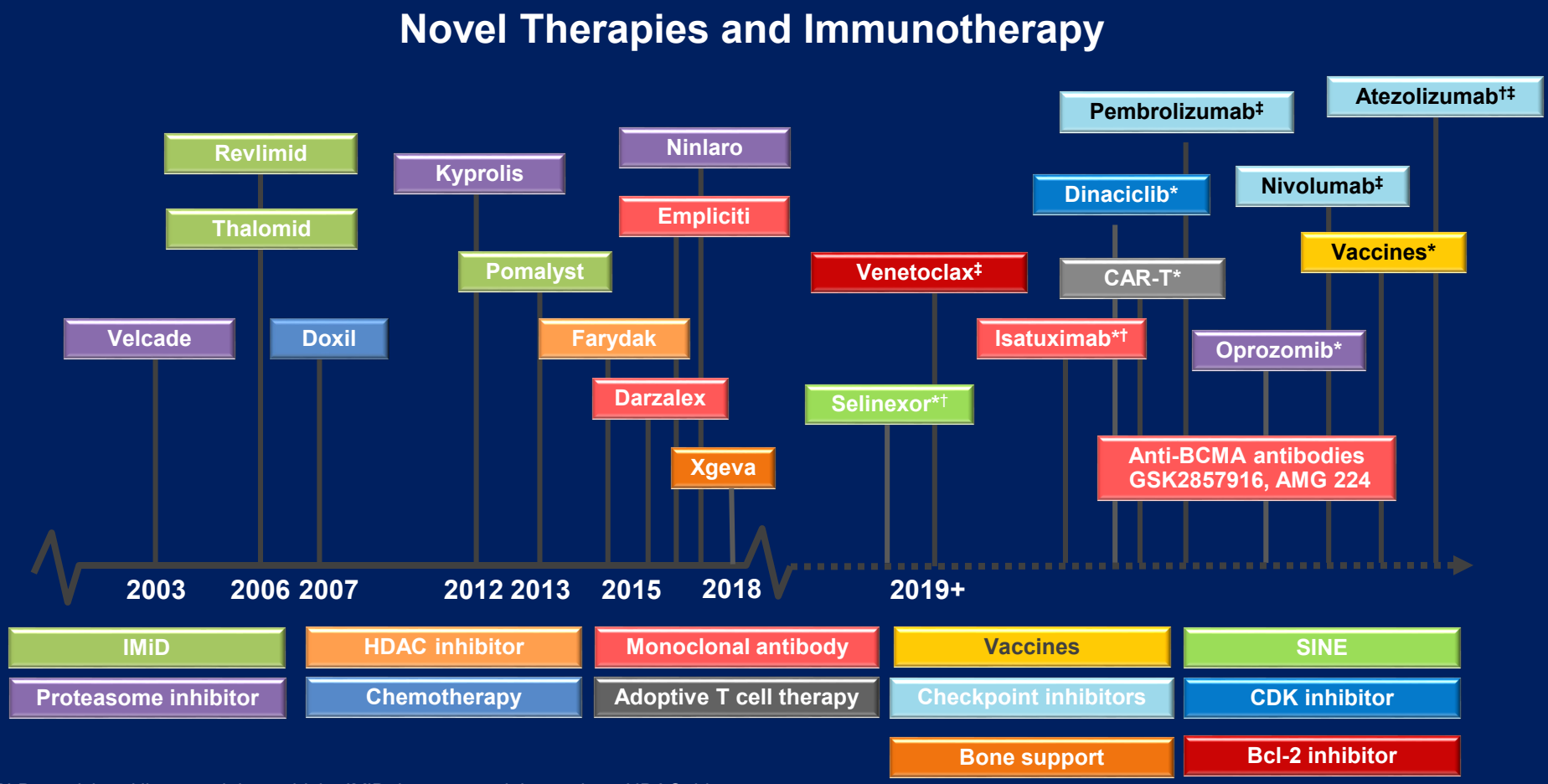
PATIENT-RELATED

- Pre-existing toxicity
- Presence of other conditions
- Age
- General health
- Personal lifestyle and preferences

DOR, duration of response; FISH, fluorescence in situ hybridization; SCT, stem cell transplant

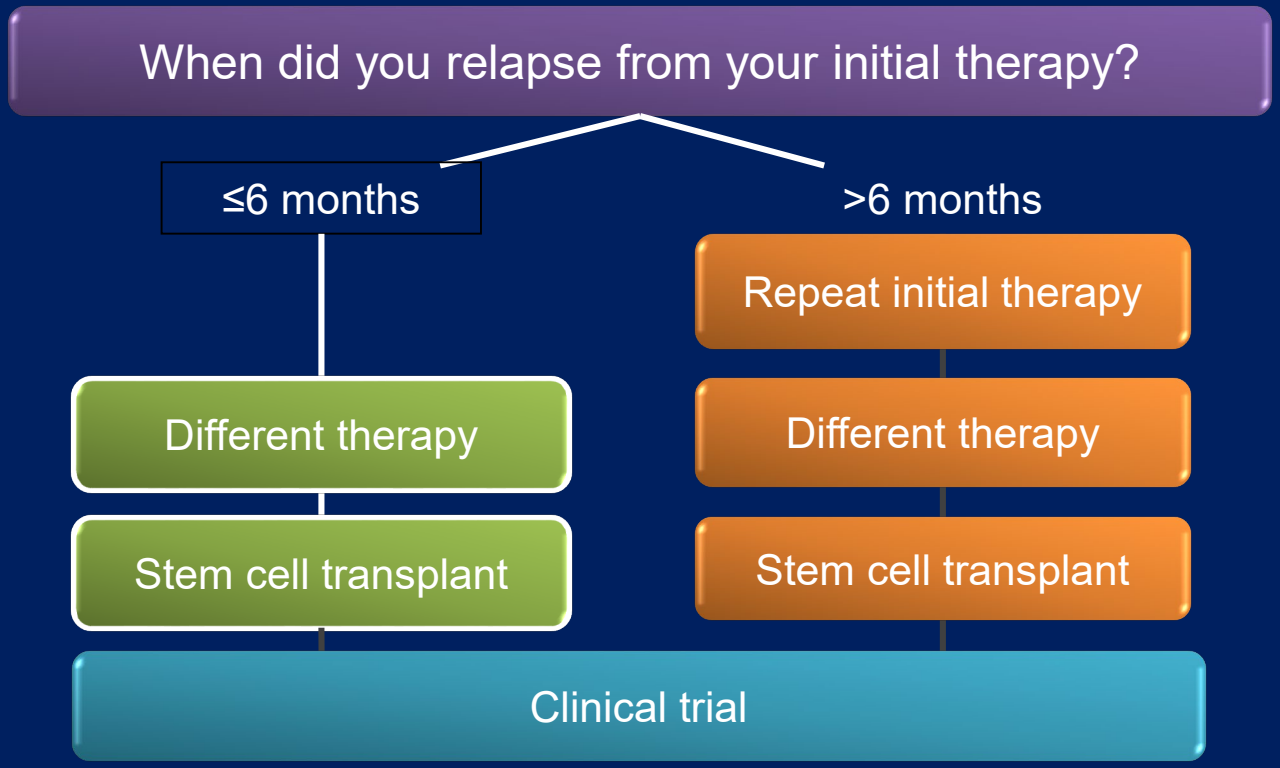
Lonial S. *Hematology Am Soc Hematol Educ Program*. 2010;303.

Continuing Evolution of Multiple Myeloma Treatment: New Classes and Targets

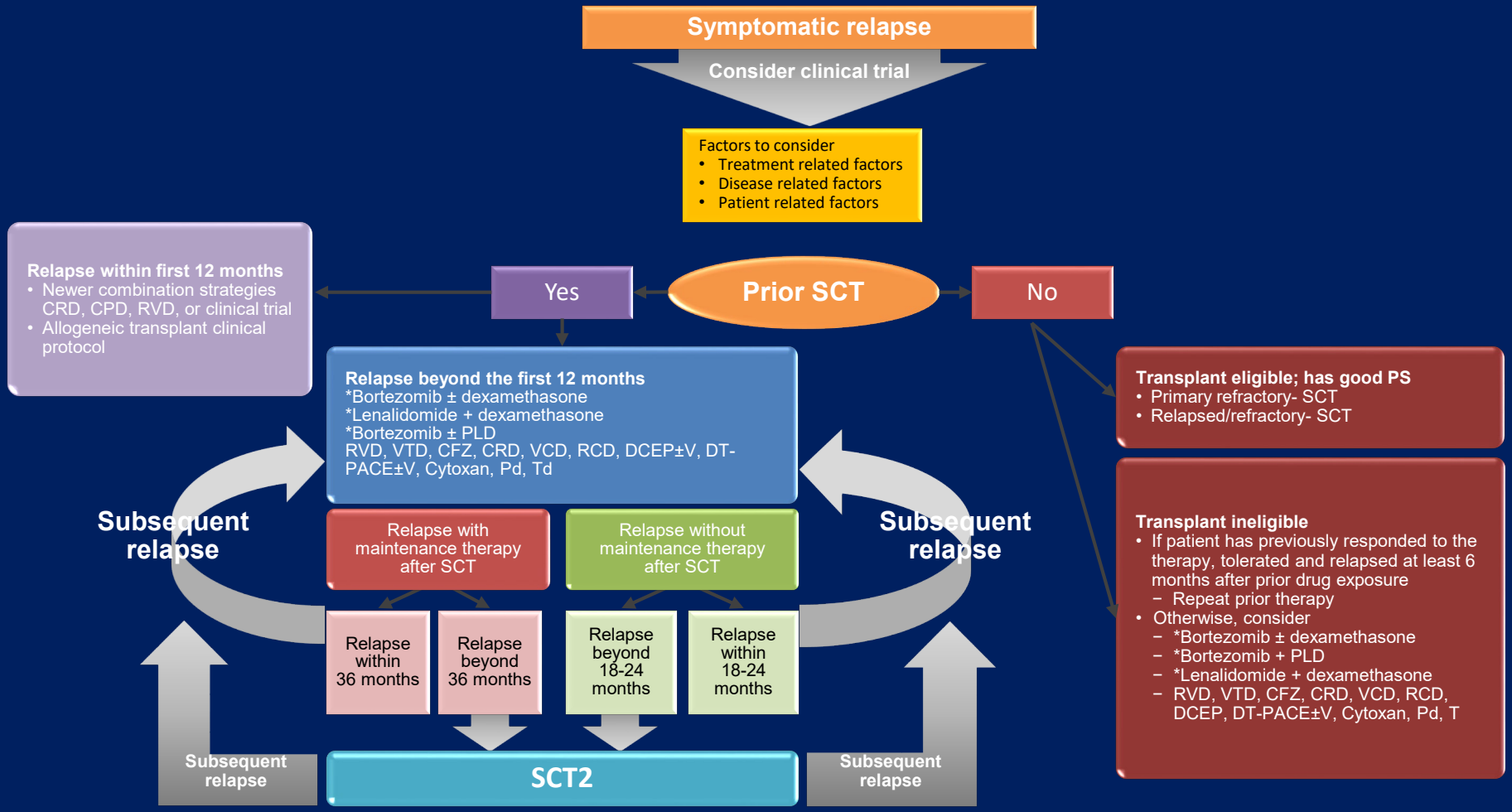


PLD, peglylated liposomal doxorubicin; IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export
*Not yet FDA-approved; only available in clinical trials
†Treatments studied in MMRC trials
‡FDA-approved for a non-MM indication

Options for Relapsed/Refractory Disease Continue to Increase



How to Choose From Treatment Options for Relapsed and Refractory Myeloma



*NCCN category 1 recommendations

Nooka AK et al. *Blood*. 2015;125:3085.

Available Anti-Myeloma Agents: So Many Choices!

IMiDs	Proteasome Inhibitors	Chemotherapy Anthracyclines	Chemotherapy Alkylators	Steroids	HDAC Inhibitors	mAbs
Thalomid (thalidomide)	Velcade (bortezomib)	Adriamycin	Cytoxan (cyclophosphamide)	Dexa-methasone	Farydak (panobinostat)	Empliciti (elotuzumab)
Revlimid (lenalidomide)	Kyprolis (carfilzomib)	Doxil (liposomal doxorubicin)	Bendamustine	Prednisone	Zolinza (vorinostat)	Darzalex (daratumumab)
Pomalyst (pomalidomide)	Ninlaro (ixazomib)		Melphalan			

New formulations, new dosing, and new combinations, too!

IMiD, immunomodulatory drug; HDAC, histone deacetylase; mAb, monoclonal antibody.

Possible Anti-Myeloma Regimens: So Many Choices!

Pomalyst (pomalidomide)	Kyprolis (carfilzomib)	Darzalex (daratumumab)	Empliciti (elotuzumab)	Ninlaro (ixazomib)	Farydak (panobinostat)
Dara Pom D	KD	Dara	Elo RD	Ixa	Pano VD
Car Pom D	KRD	Dara Pom	Elo PomD	Ixa Dex	Car Pano Dex
Ixa Pom Dex	K Cy Dex	Dara Len	Elo BortD	IRD	Len Pano
Bort Pom Dex	K Dara Dex	Dara Bort		Ixa Pom Dex	
Elo Pom Dex	Car Pano	Dara Carfil			
Pom Cy Dex					

Dara, Darzalex (daratumumab); Pom, Pomalyst (pomalidomide); Car/K/Carfil, Kyprolis (carfilzomib); Ixa/I, Ninlaro (ixazomib); Bort/V, Velcade (bortezomib); Elo, Empliciti (elotuzumab); Dex/D, dexamethasone; R/Len, Revlimide (lenalidomide); Cy, cyclophosphamide; Pano, Farydak (panobinostat).

Therapy for relapsed disease

MYELOMA THERAPY[1-4,12]

Therapy for Previously Treated Multiple Myeloma (assess for response after each cycle)

Preferred Regimens

- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib (twice weekly)[8]/dexamethasone (category 1)[9]
- Carfilzomib[8]/lenalidomide/dexamethasone (category 1)[13]
- Daratumumab[14]/bortezomib/dexamethasone (category 1)
- Daratumumab[14]/lenalidomide/dexamethasone (category 1)
- Elotuzumab[15]/lenalidomide/dexamethasone (category 1)[13]
- Ixazomib[17]/lenalidomide/dexamethasone (category 1)[13]

Other Recommended Regimens

- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib[8]/cyclophosphamide/dexamethasone
- Carfilzomib (weekly)[8]/dexamethasone[9]
- Cyclophosphamide/lenalidomide/dexamethasone
- Bortezomib/dexamethasone (category 1)[9]
- Daratumumab[14,16]
- Daratumumab[14]/pomalidomide[20]/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Ixazomib[17]/dexamethasone[9]
- Ixazomib/pomalidomide[20]/dexamethasone
- Lenalidomide/dexamethasone[18] (category 1)[9]
- Panobinostat[19]/bortezomib/dexamethasone (category 1)
- Panobinostat[19]/carfilzomib[8,9]
- Panobinostat[19]/lenalidomide/dexamethasone
- Pomalidomide[20]/cyclophosphamide/dexamethasone
- Pomalidomide[20]/dexamethasone[18] (category 1)[9]
- Pomalidomide[20]/bortezomib/dexamethasone
- Pomalidomide[20]/carfilzomib[8]/dexamethasone

Useful In Certain Circumstances

- Bendamustine
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[21]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[21] ± bortezomib (VTD-PACE)[21]
- High-dose cyclophosphamide

[1]Selected, but not inclusive of all regimens.
[2]Herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.
[3]Subcutaneous bortezomib is the preferred method of administration.
[4]Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
[8]Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[9]Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.
[12]Consideration for appropriate regimen is based on the context of clinical relapse.
[13]Clinical trials with these regimens primarily included patients who were lenalidomide-naive or with lenalidomide-sensitive multiple myeloma.
[14]May interfere with serological testing and cause false-positive indirect Coombs test. (See MYEL-E)
[15]Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.
[16]Indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.
[17]Indicated for the treatment of patients who have received at least one prior therapy.
[18]Consider single-agent lenalidomide or pomalidomide for steroid-intolerant individuals.
[19]Indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.
[20]Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy.
[21]Generally reserved for the treatment of aggressive multiple myeloma.

MYEL-D
(3 OF 3)

MAYO CLINIC

First Relapse Off-Study

Relapsing after Auto Transplant		Relapsing after Non-Transplant Therapy		
On Maintenance	Off-therapy/ Unmaintained	On Therapy/ Maintenance		Off-therapy/ Unmaintained
CyBorD if Rev maintenance*; Rd, or KRd if Vel maintenance*	Rd or CyBorD if standard-risk*; CyBorD or VRd if high risk*	Not Eligible for ASCT → CyBorD if Rev maintenance; Rd, or KRd if Vel maintenance	Transplant Eligible → Auto SCT	Not Eligible for ASCT → Repeat first-line Rx if remission off therapy is >12months; If not, CyBorD if relapsing after ImiD based Rx; otherwise Pom/dex or KRd

*Consider 2nd auto if eligible and >18 months unmaintained or >36 months maintained response to first auto

v3 //last reviewed Mar 2015

MAYO CLINIC

Second or later Relapse* Off-Study

Not Plasma Cell Leukemia (PCL) or Similar extramedullary disease (EMD)

Dual-Refractory (Bortezomib and Lenalidomide)**	Triple-Refractory (Bortezomib, Lenalidomide and Carfilzomib)**	Triple-Refractory (Bortezomib, Len, and Pomalidomide)**
KRd or Pom/dex to maximum response or 18 months, then Rd	PCD, PVD or Car-Pom-Dex to maximum response or 18 months, then Pom/dex	KRd or Car-Pom-Dex to maximum response or 18 months, then Rd or Pom/dex

* If single refractory, refer to First Relapse algorithm; **Auto transplant is an option, if transplant candidate and feasible; Doublets such as Cylco-Pred, Pd or Kd could be considered in patients with indolent disease

v3 //last reviewed Mar 2015

Clinical Trials

How do clinical trials work?

Phase I investigates for safety and side effects, dosage and best way to give treatment–includes 20 or more people

Phase II determines effectiveness and safety–typically includes fewer than 100 (may include up to 300) people

Phase III looks at effectiveness, side effects and safety in comparison with other treatments–includes 100s to 1000s of people

Phase IV gathers more information after FDA approval & drug is on market

Placebos are rarely used in cancer clinical trials and only in the context of another active drug

Clinical trials

- Are an important option for everyone
- Can be for people newly diagnosed, with limited disease or advanced disease
- Are appropriate for people of different age, gender, and race, depending on the purpose and phase of the study
- Take into account all the above factors as well as stage of disease, other treatments used and presence of any other illness

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

Why Do So Few Cancer Patients Participate in Clinical Trials?

Patients may:

- Be unaware of clinical trials
- Lack access to trials
- Fear, distrust, or be suspicious of research
- Have practical or personal obstacles
- Face insurance or cost problems
- Be unwilling to go against their physicians' wishes

Benefits of Clinical Trials

- You will have normal standard of care in terms of office visits, lab work, etc
- You may even have additional care and investigation as a part of the clinical trial
- You will generally see your health care providers and will also have a research coordinator involved in your care
- You will likely even have a higher standard of care than normal!

Questions That Can be Addressed by Conducting Clinical Trials

- Should patients with smoldering multiple myeloma be treated?
- What is the best treatment for newly diagnosed (untreated) multiple myeloma?
- What are the best drugs and combinations of drugs for relapsed/ refractory multiple myeloma?
- How can treatments be matched to patients' subtypes/genomics (personalized medicine)?

Impact of Clinical Trials in Myeloma: Dramatic Improvements in Survival in <10 Years

- Survival rates have nearly doubled; further improvements expected in near future.
- 11 new drugs approved since 2003.
- Many new drugs being studied in clinical trials.
- Understanding of the biology of myeloma improving, with the eventual goal of personalized medicine.

How do I find a clinical trial?

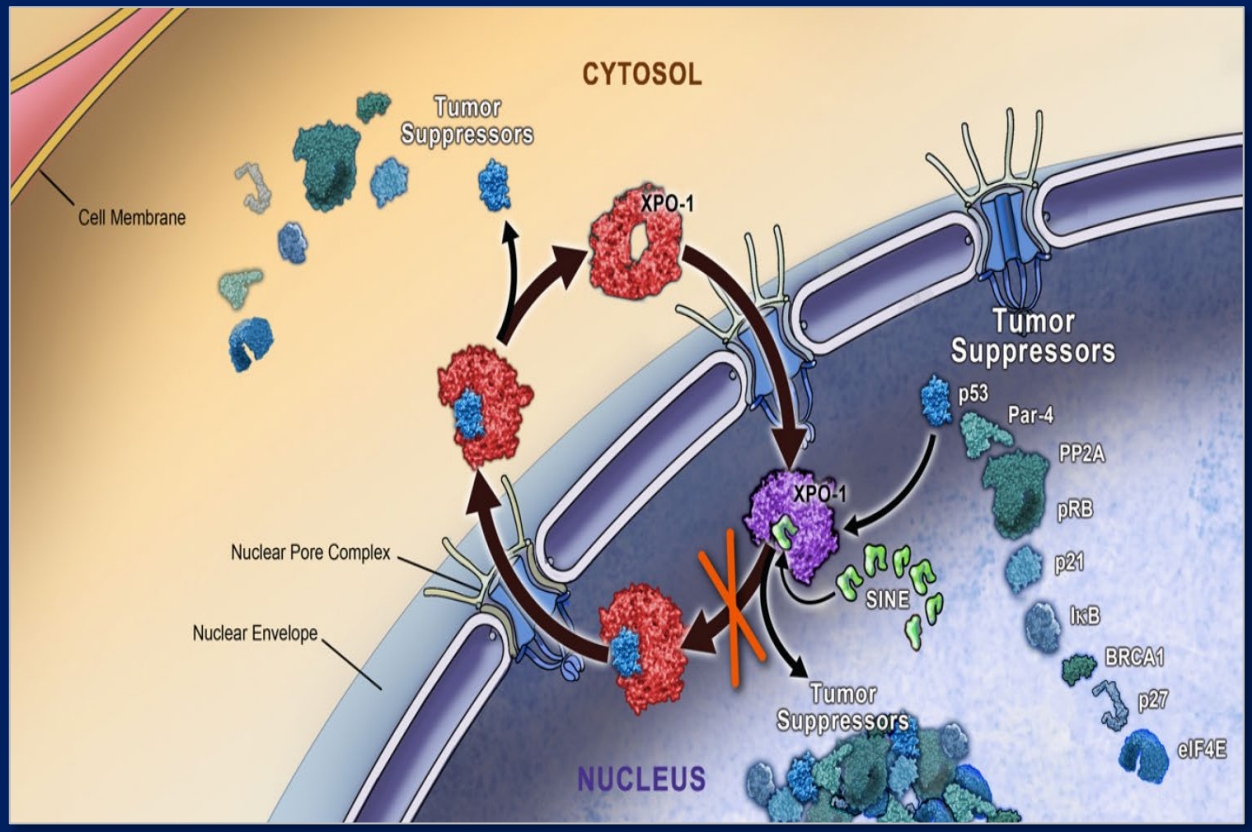
1. Ask your treating hematologist/oncologist about any available trials
2. Check with any academic medical centers close to your home
3. The National Cancer Institute (www.cancer.gov)
4. The IMF/MMRF/LLS

New Agents in Myeloma Therapy

New IMiDs	Oral proteasomes	Kinase inhibitors	Novel MOA	HDAC inhibitors	Immuno-therapies
• Lenalidomide • Pomalidomide • CC-122 • CC-220	• Bortezomib • Carfilzomib • Ixazomib • Oprozomib • Marizomib	• Vemurafenib • Afuresertib • Dinaciclib • Ibrutinib • Trametinib • Dabrafenib • JNJ-42756493 • Sotatercept • CB-5083	• Venetoclax • Selinexor • Filanesib • Idasanutlin	• Panobinostat • Ricolinostat	• Monoclonal antibodies – Daratumumab – Elotuzumab – **Isatuximab** • **Antibody-drug conjugates** • **Immune cell therapy** – **CAR T** – **BiTEs** – **Vaccines** • Immune checkpoint inhibitors – Durvalumab

IMiD, immunomodulatory drug; HDAC, histone deacetylase inhibitor, MOA mechanism of action, BiTE, bispecific T-cell engager; CAR-T, chimeric antigen receptor (CAR) T cells

New Drug in a New Class: Selinexor



- Exportin 1 (XPO1) is the nuclear exporter for the majority of tumor suppressor proteins (and also steroid receptor) that put the brakes on MM growth
- Selinexor* is a first-in-class XPO1 inhibitor

*Investigational agent; not yet approved by the FDA

Efficacy of Selinexor in Relapsed/Refractory Myeloma: Selinexor + Dexamethasone

- 48 pts refractory to REV, POM, V, K (**Quad**)
- 31 pts refractory to above + anti-CD38 mAbs (**Penta**)

Efficacy	All	Quad	Penta
ORR	21%	21%	20%

Efficacy	ORR, n (%)
Standard risk	4 (17)
High risk*	6 (35)

*Includes patients with: del(17p), t(14;16), or t(4;14)

Safety, n (%) Gr 3/4 (≥10%)	All patients
Thrombocytopenia	58
Neutropenia	21
Anemia	25
Fatigue	14
Hyponatremia	20

The combination of selinexor and dexamethasone has an overall response rate of 21% in patients with heavily pretreated, refractory myeloma with limited therapeutic options.

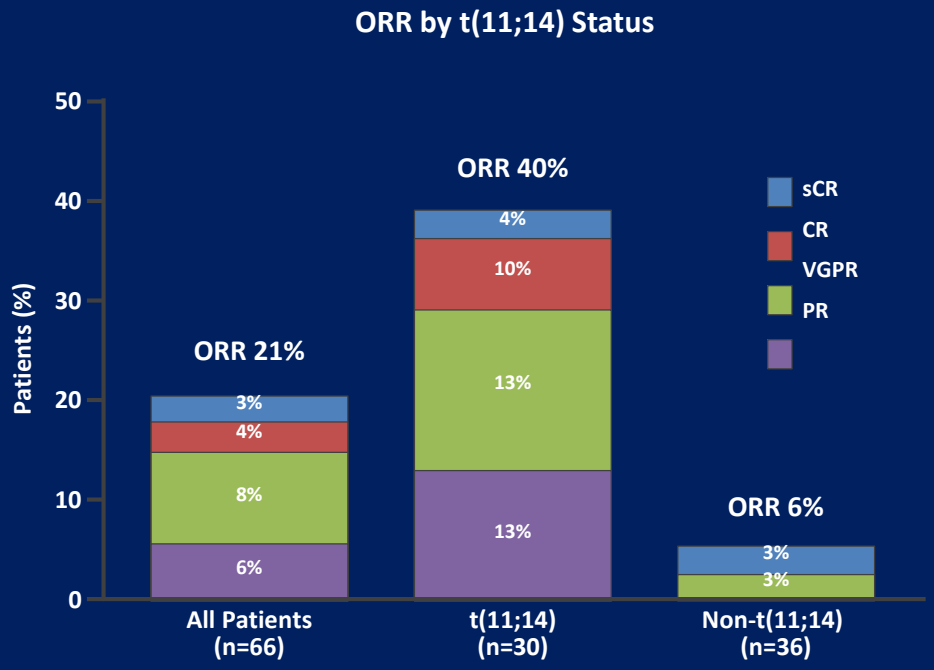
STORM Trial
Vogl DT et al. *J Clin Oncol*. 2018;36:859.

New Drug in a New Class: Venetoclax

- Bcl-2 inhibitor; targets myeloma growth and proliferation
- Approximately 15% of myeloma patients have t(11;14) which is the primary target of the Bcl-2 inhibitor

*Approved for a non-MM indication

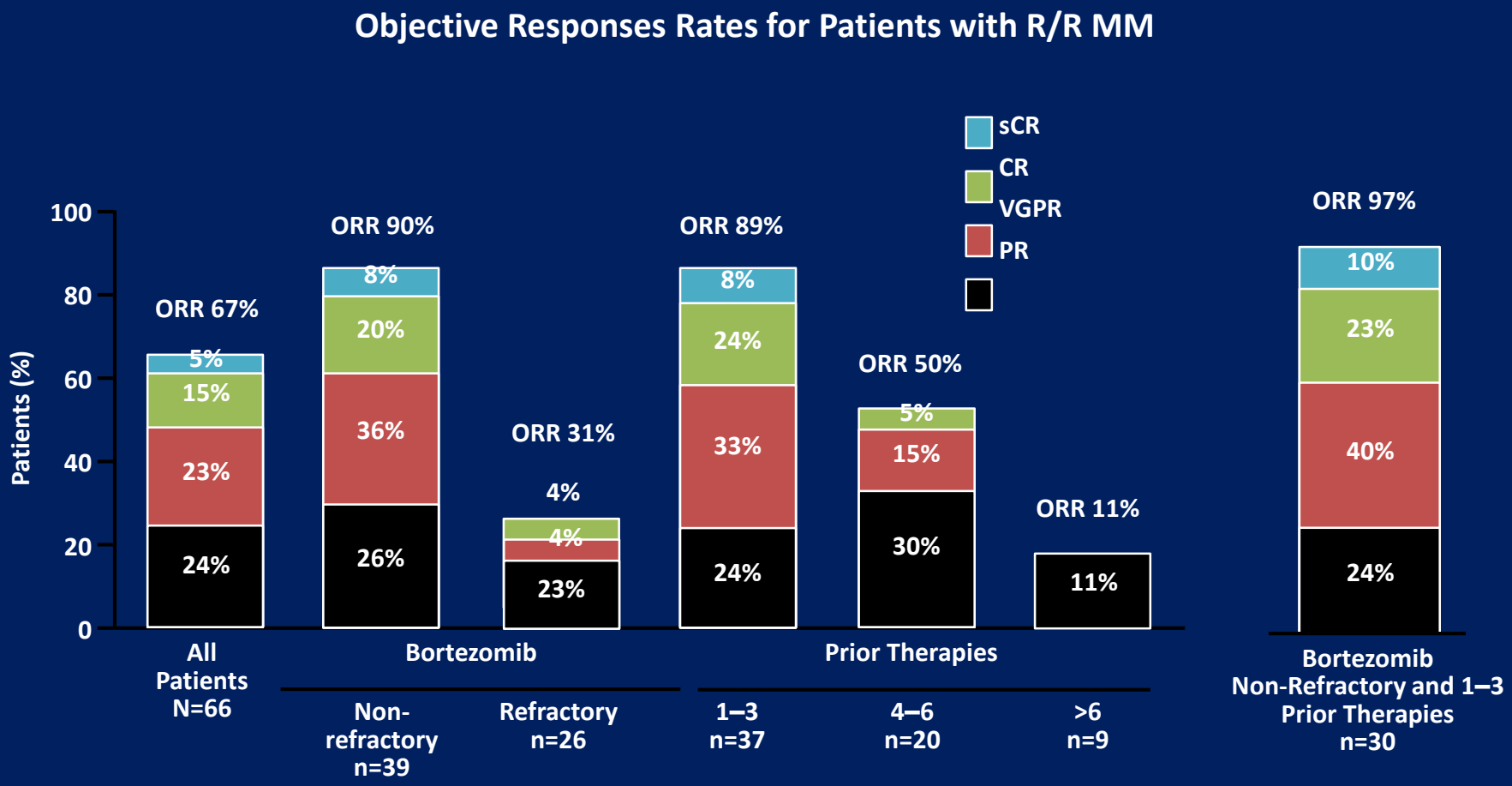
Efficacy of Venetoclax in Relapsed/Refractory Myeloma: Venetoclax Monotherapy



Median TTP: t(11;14) 6.6 mos vs 1.9 mos without t(11;14)

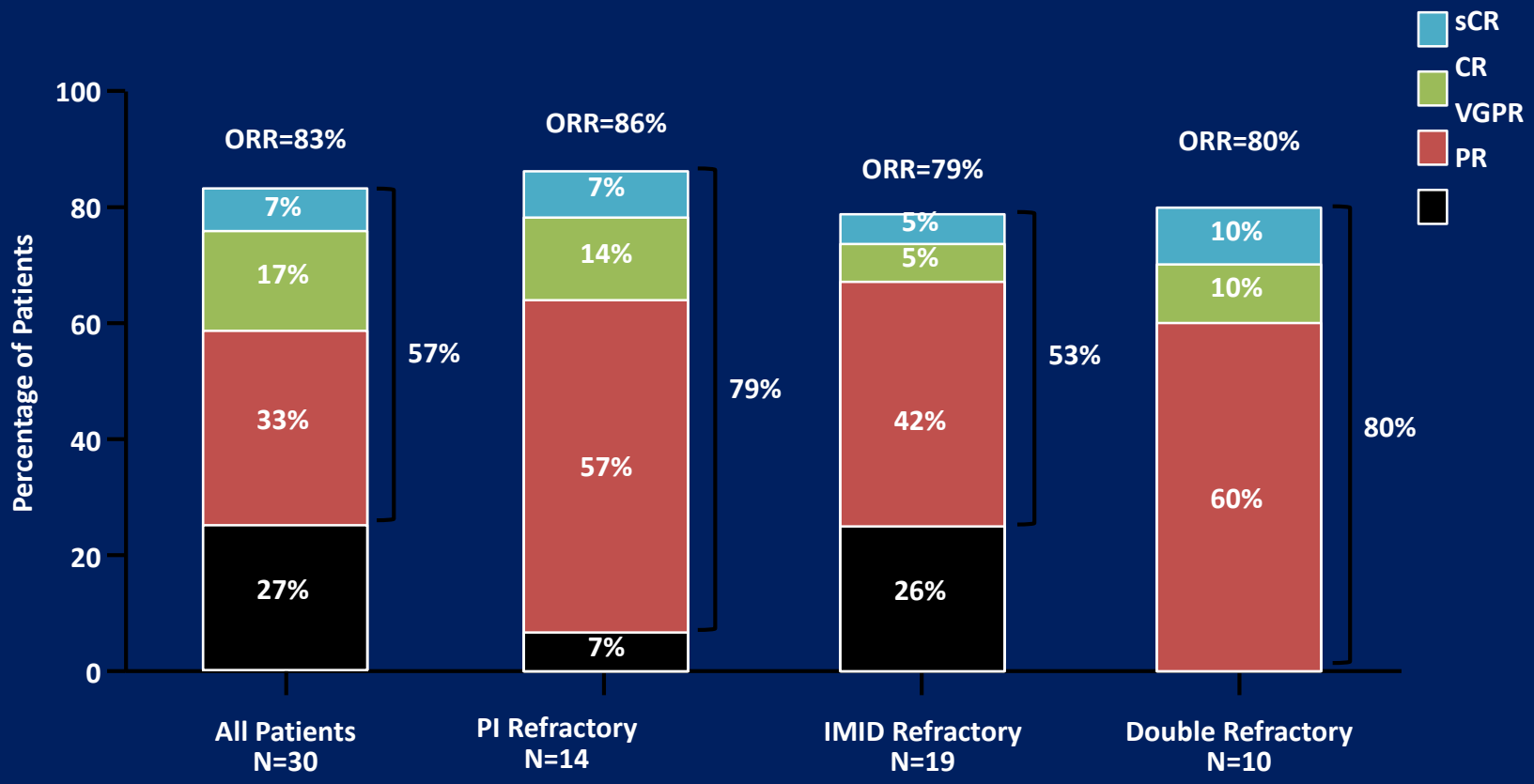
Kumar S et al. *Blood*. 2017;130:2401.

Efficacy of Venetoclax in Relapsed/Refractory Myeloma: Venetoclax + Velcade + Dexamethasone



Moreau P et al. *Blood.* 2017;130:2392.

Efficacy of Venetoclax in Relapsed/Refractory Myeloma: Carfilzomib + Venetoclax



Costa LJ et al. *J Clin Oncol*. 2018;36: Abstract 8004.
1 PR was unconfirmed as of 18 Apr 2018.

Drugs in Development: Phase 1–2 Trials

Small-Molecule Inhibitors

- AT7519M
- BMS 833923
- **CB-5083**
- CC-220
- **Dabrafenib**
- Dinaciclib
- Filanesib
- Ganetespib
- **Ibrutinib**
- **Idasanutlin**
- **JNJ-42756493**
- KPT-8602
- KW-2478
- Linsitinib
- Marizomib
- Nelfinavir
- Oprozomib
- Quisinostat
- Ricolinostat
- **Ruxolitinib**
- **Selinexor**
- Selumetinib
- Sonidegib
- **Sotatercept**
- TH-302
- Tivantinib
- **Trametinib**
- Veliparib
- VLX1570

Monoclonal Antibodies

- ABBV-838
- Atezolizumab
- DFRF4539A
- Durvalumab
- Indatuximab
- Lorvotuzumab mertansine
- Milatuzumab
- MOR03087
- Tabalumab
- Ulocuplumab

Bold = treatments studied in MMRC trials

Main Targets for Immunotherapy

Rodriguez-Otero P et al. *Haematologica*. 2017;102:423

Monoclonal Antibody: Darzalex (daratumumab)

Current Indications

- For newly diagnosed myeloma patients who are ineligible for autologous stem cell transplant (ASCT), in combination with Velcade, melphalan, and prednisone
- For relapsed/refractory myeloma alone or in combination with Revlimid and dexamethasone, or Velcade and dexamethasone, or Pomalyst and dexamethasone

How is Darzalex administered?

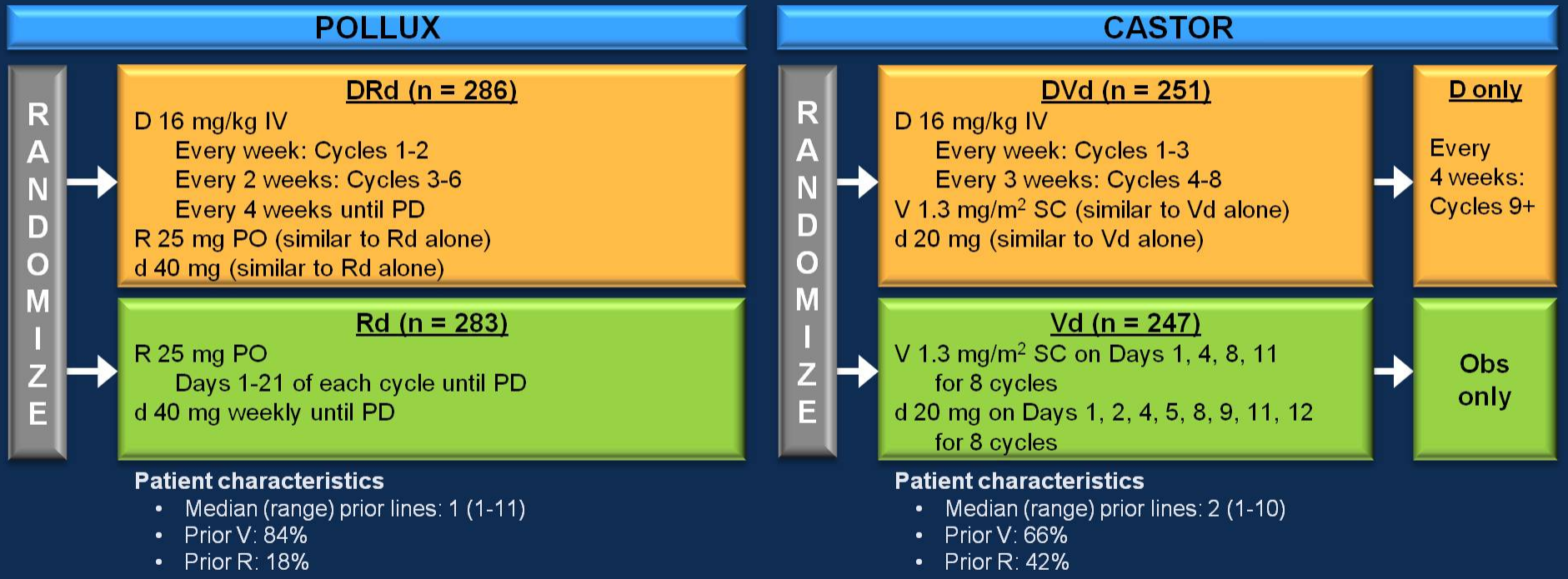
- Intravenously
- Once a week for the first 8 weeks then every 2 weeks for 4 months then monthly
- Pre- and post-medication for infusion reactions
- Future SC administration may decrease infusion reactions and infusion time

What are the possible side effects?

- Infusion reactions 40%
- Fatigue
- Upper respiratory tract infection

POLLUX and CASTOR Study Designs[1,2]

Open-label, multicenter, randomized (1:1), active-controlled, phase 3 studies in RRMM patients with ≥1 prior line of therapy

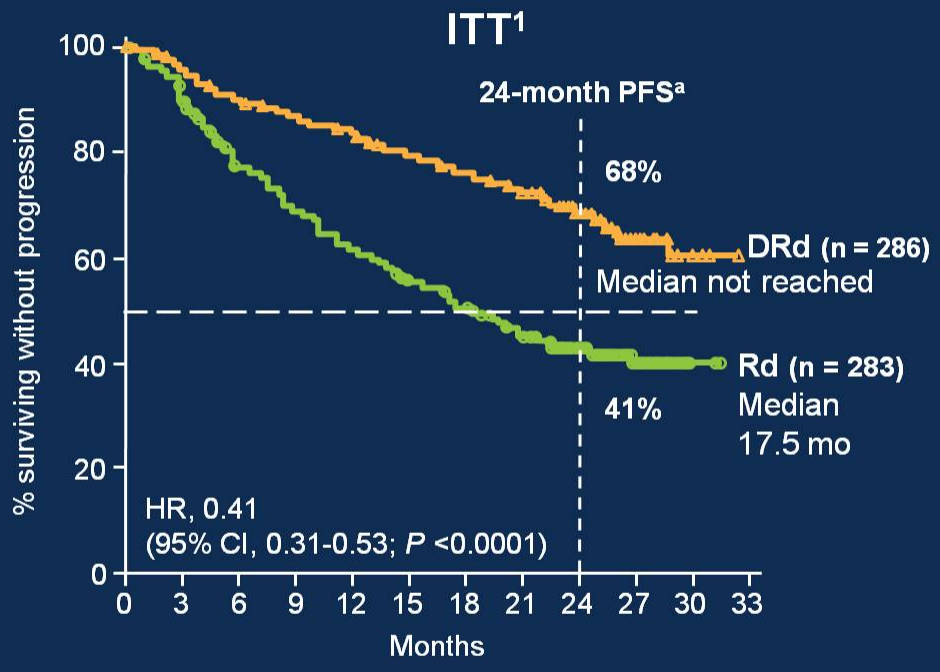


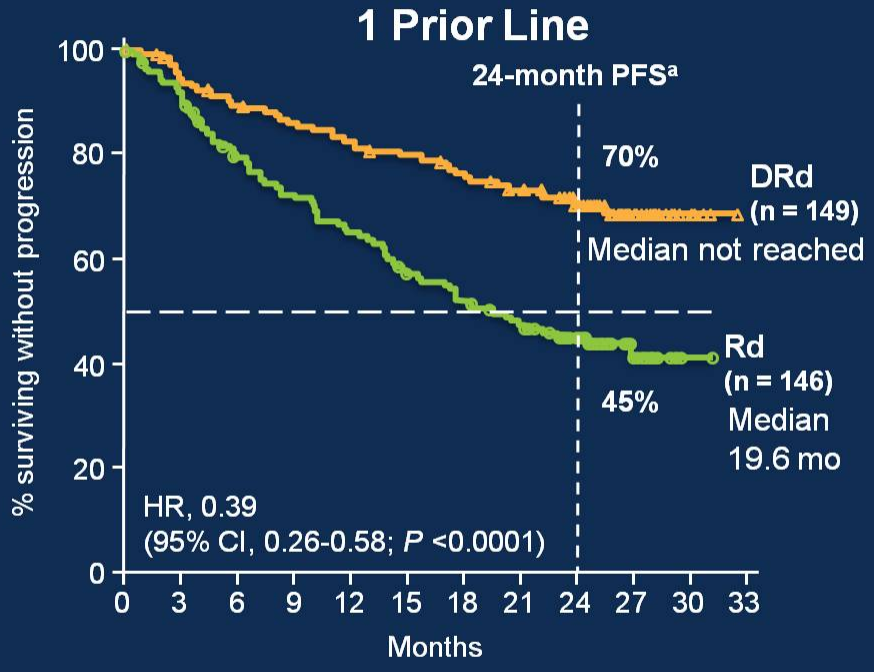
RRMM, relapsed or refractory multiple myeloma; DRd, daratumumab, lenalidomide, and dexamethasone; D, daratumumab; IV, intravenous; PD, progressive disease; R, lenalidomide; PO, orally; Rd, lenalidomide and dexamethasone; d, dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; V, bortezomib; SC, subcutaneous; Vd, bortezomib and dexamethasone; Obs, observation.

1. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331. 2. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.

POLLUX: 1-Year Update[a]

- Median follow-up of 25.4 months

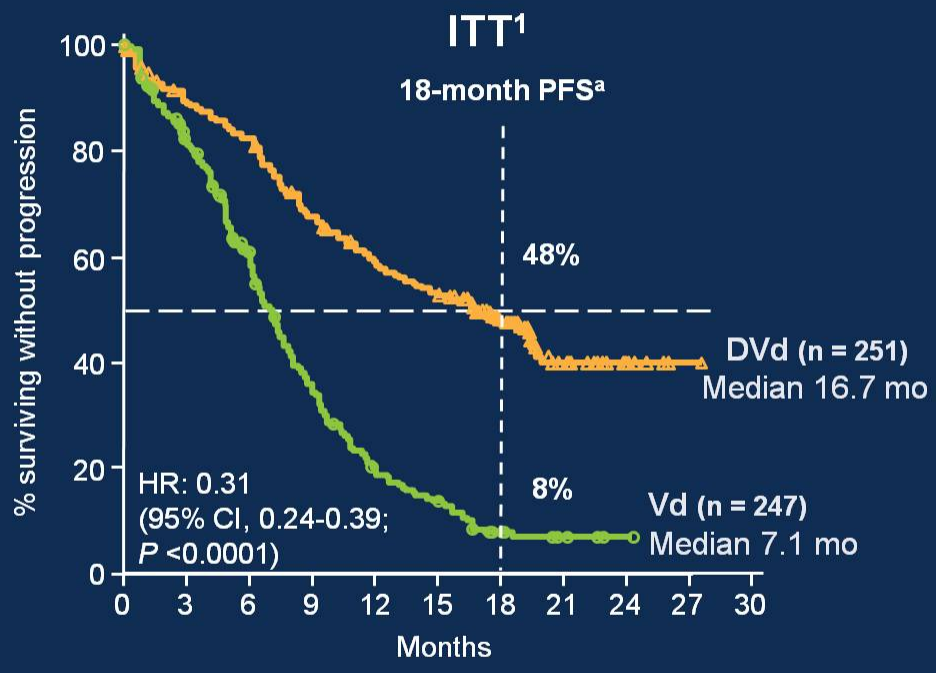


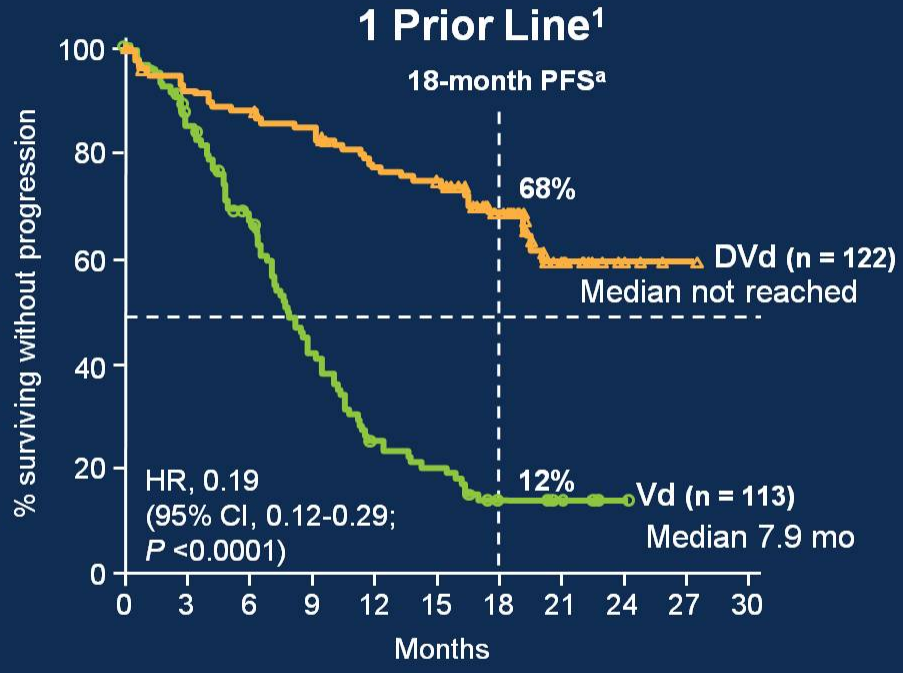


ITT, intent-to-treat; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimates; exploratory analyses based on 1-year update: clinical cut-off date of March 7, 2017.
1. Bahlis NZ, et al. Poster presentation at ASCO 2017. Abstract 8025.

CASTOR: 1-Year Update[a]

- Median follow-up of 19.4 months





Adding daratumumab to SOC regimens significantly prolongs PFS

SOC, standard of care.
[a]Kaplan-Meier estimates; exploratory analyses based on 1-year update: clinical cut-off date of January 11, 2017. 1. Lentzsch S, et al. Poster presentation at ASCO 2017. Abstract 8036.

Monoclonal Antibody: Empliciti (elotuzumab)

Current Indications

- For relapsed/refractory myeloma in combination with Revlimid or Pomalyst and dexamethasone

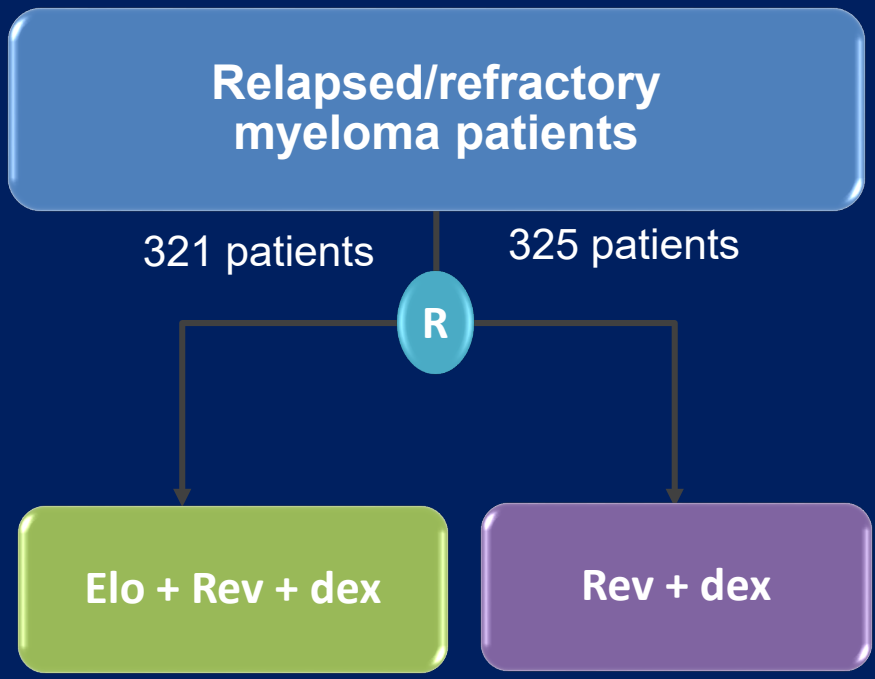
How is Empliciti administered?

- Intravenously
- Once a week for the first 8 weeks then every 2 or 4 weeks
- Premedication in anticipation of infusion reactions

What are the possible side effects?

- Fatigue
- Diarrhea
- Fever
- Constipation
- Cough
- Peripheral neuropathy
- Infusion reactions
- Nasopharyngitis
- Upper respiratory tract infection
- Decreased appetite
- Pneumonia
- Small chance of second new cancer

Efficacy of Empliciti in Relapsed/Refractory Myeloma: Empliciti + Revlimid + Dexamethasone



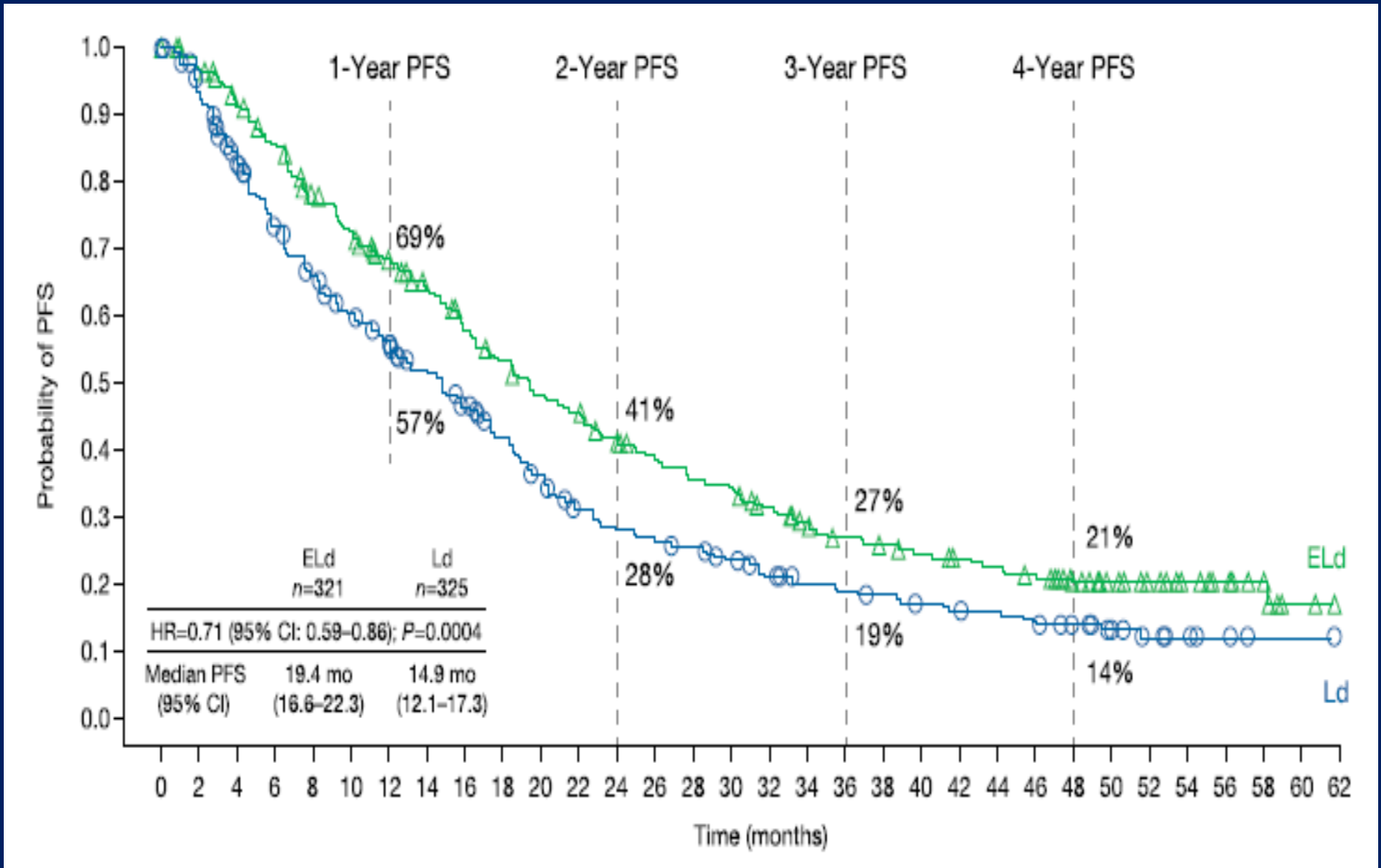
PFS benefit seen with elotuzumab in all predefined subgroups

- Compared to Revlimid and dexamethasone alone, the addition of elotuzumab significantly increased
  - Progression-free survival
  - Overall response rates
- The triple combination resulted in a 30% reduction in the risk of disease progression or death
- Another phase 3 trial comparing the same combinations is under way in patients with newly diagnosed disease

ELOQUENT-2 Trial
Lonial S et al. *N Engl J Med*. 2015;373:621.

Efficacy of Empliciti in Relapsed/Refractory Myeloma: Empliciti + Revlimid + Dexamethasone

Extended Four-Year Follow-Up Data

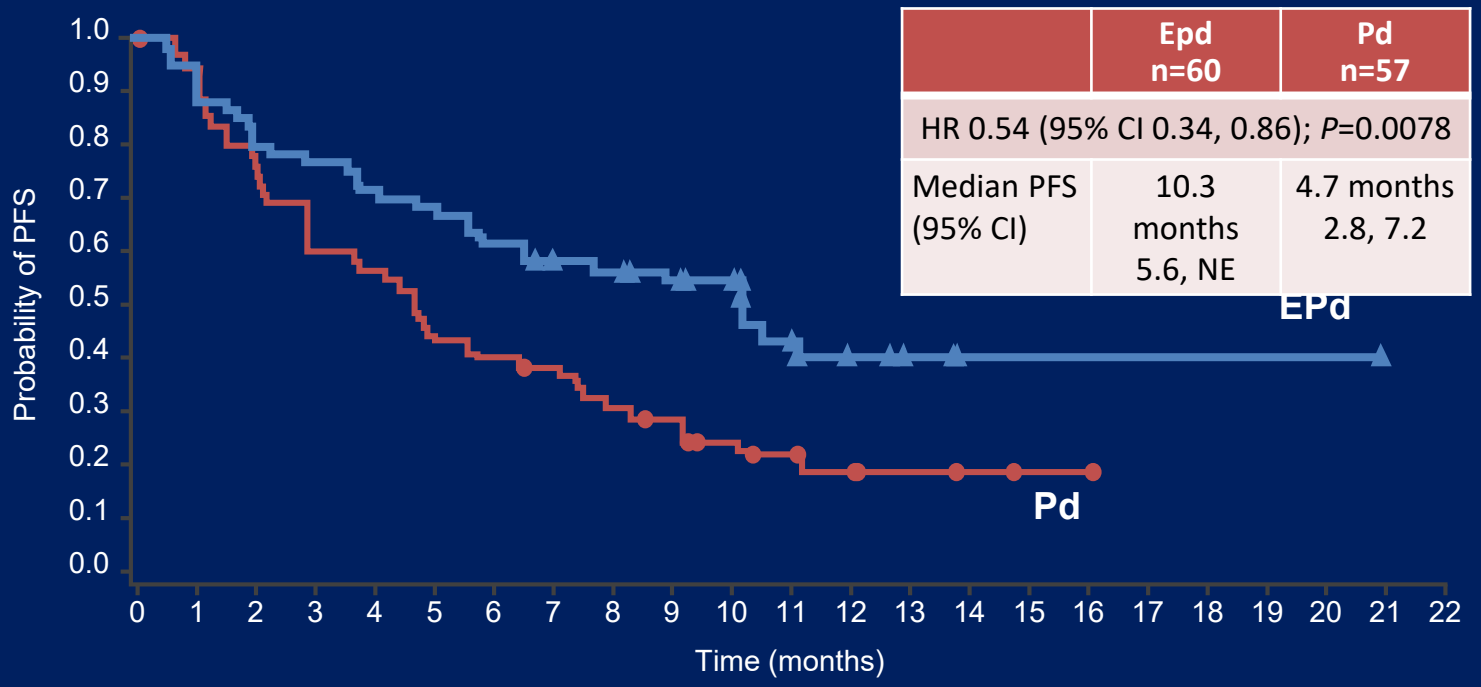


HR, hazard ratio

ELOQUENT-2 Trial

Dimopoulos MA et al. *Cancer*. 2018;124:4032.

Efficacy of Empliciti in Relapsed/Refractory Myeloma: Empliciti + Pomalyst + Dexamethasone



	Epd n=60	Pd n=57
HR 0.54 (95% CI 0.34, 0.86); *P*=0.0078		
Median PFS (95% CI)	10.3 months 5.6, NE	4.7 months 2.8, 7.2

- 46% reduction in the risk of progression or death with EPd
- Median PFS was more than twice as long with EPd vs Pd

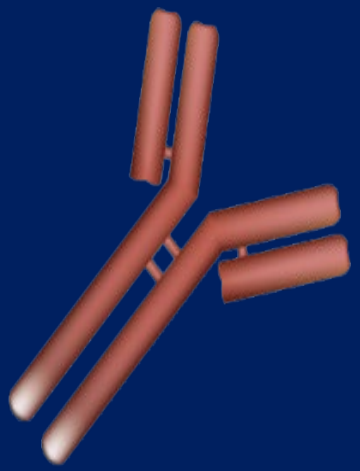
ITT, intent-to-treat; NE, not estimable

ELOQUENT-3

Dimopoulos MA et al. *N Engl J Med*. 2018;379:1811

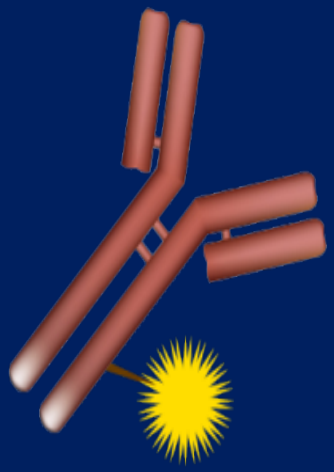
Types of Monoclonal Antibodies

Naked



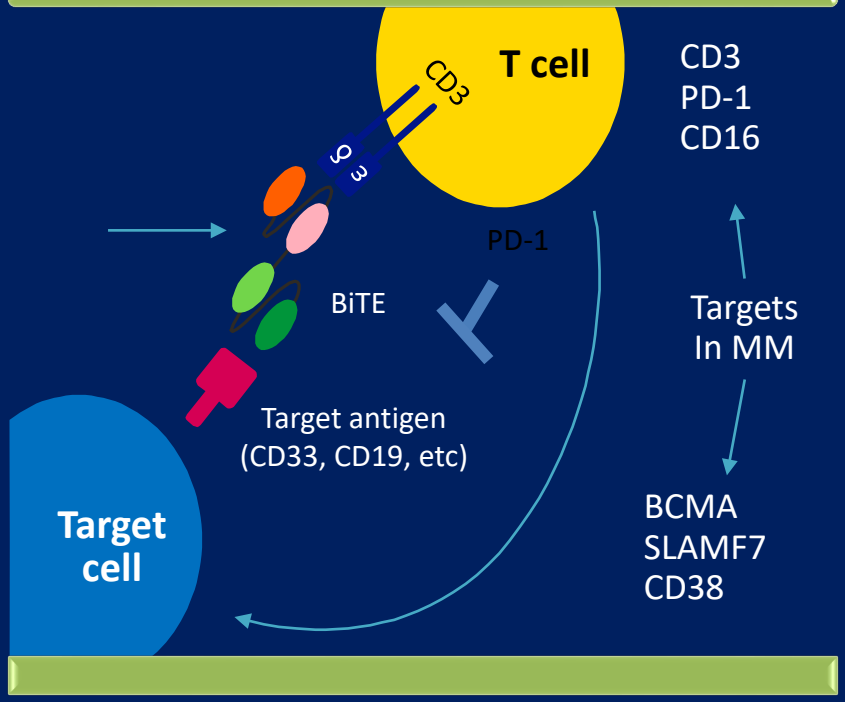
- Nothing is attached

Drug conjugates

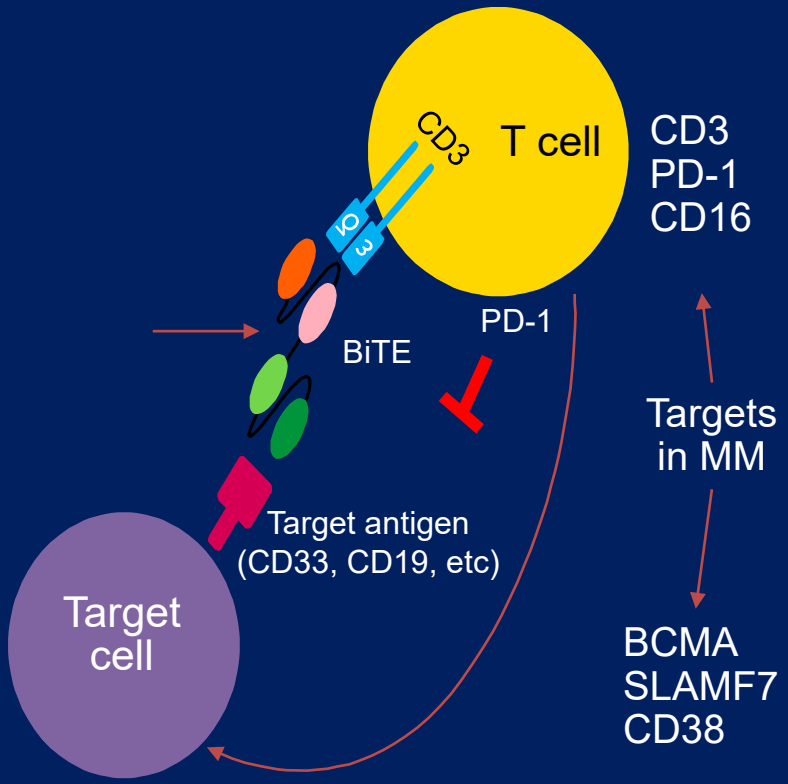


- A toxin or radioactive isotope is attached

Bispecific



Bispecific Antibodies



- Clinical trials
- Several ongoing trials
- Too early for data results
- Some of the molecules and targets
  - GBR1342-101 (CD38 × CD3)[1]
  - PF-06863135 (BCMA × CD3)[2]
  - JNJ-64407564 (GPRC5D × CD3)[3]
  - GO39775 (FcRH5 × CD3)[4]
  - JNJ-644007957 (BCMA × CD3)[5]
  - CC-93269 (BCMA × CD3)[6]

BiTE, bispecific T-cell engager

1. https://clinicaltrials.gov/ct2/show/NCT03309111.
2. https://clinicaltrials.gov/ct2/show/NCT03269136.
3. https://clinicaltrials.gov/ct2/show/NCT03399799.
4. https://clinicaltrials.gov/ct2/show/NCT03275103.
5. https://clinicaltrials.gov/ct2/show/NCT03145181.
6. https://clinicaltrials.gov/ct2/show/NCT03486067.

BiTEs to Watch

AMG 420[1]*

- Binds to the CD3 molecule on T cells and the BCMA molecule on myeloma cells
- Phase 1 clinical trial results
  - 42 relapsed myeloma patients
  - 70% of patients responded
  - Therapy was associated with infections
- This drug will continue its clinical development in 2019

AMG 701[2]*

- Similar to AMG 420 but has an extended half-life (longer time in the bloodstream)
- Preclinical analysis
  - Kills MM cells (and is enhanced by Revlimid)
  - Promotes the activation of T cells

Others

BCMA targets

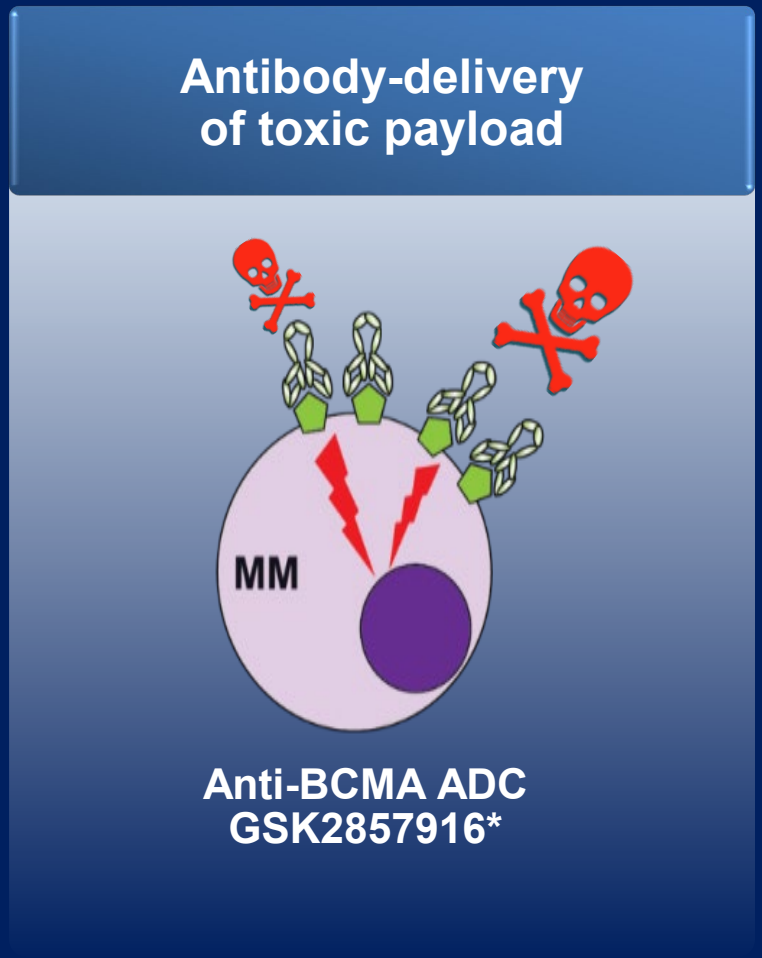
- BI 836909†
- PF-06863135‡
- CC-93269¶

Other targets

- Blinatumomab (CD19)*
- GBR1342-101 (CD38)§
- JNJ-64407564 (GPRC5D)**
- BFCR4350A (FcRH5)††

1. Topp M et al. *Blood*. 2018;132: Abstract 1010; 2. Cho S-F et al. *Blood*. 2018;132: Abstract 592.
*Amgen; †Boehringer Ingelheim; ‡Pfizer; ¶Celgene;§Glenmark Pharmaceuticals; **Janssen; ††Genentech

New Monoclonal Antibody: Antibody-Drug Conjugate (ADC)

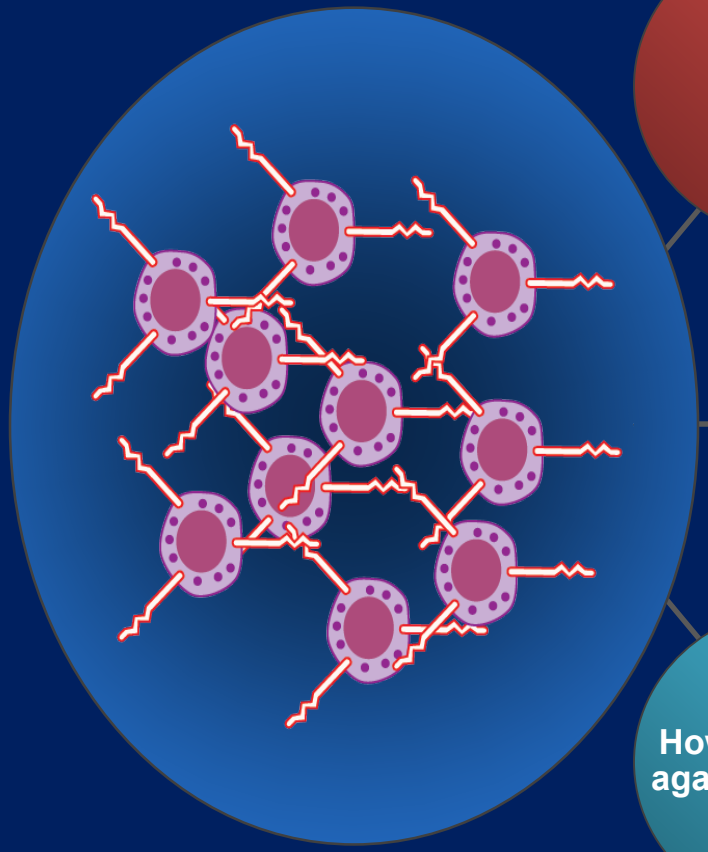


- 35 patients with relapsed/ refractory MM (many who had previously received more than 5 different regimens) were treated with GSK2857916 via an intravenous (IV) infusion
- Results from the trial revealed that 60% of patients had a response
- The most commonly occurring side effects were corneal events (such as blurred vision, dry eye) and low platelet counts

*Investigational agent; not yet approved by the FDA

Trudel S et al. *Lancet Oncol*. 2018;19:1641.

Immune Cell Therapy



What is it?

- It is an infusion of autologous *myeloma-directed* T cells

How are the T cells directed to myeloma cells?

In two main ways

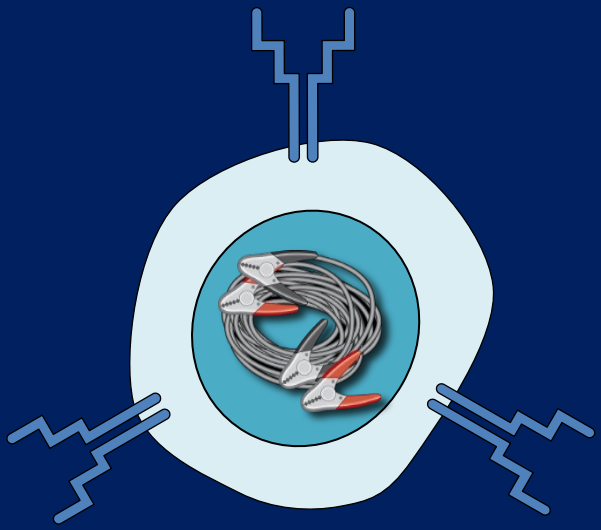
1. Patient's T cells are harvested and then engineered in a lab to be able to identify specific surface markers on myeloma cells
2. These engineered T cells are then stimulated in a lab to make them more active and to proliferate and grow

How does it work against myeloma?

- Infused, myeloma-directed T cells directly kill myeloma cells and stimulate T-cell immunity

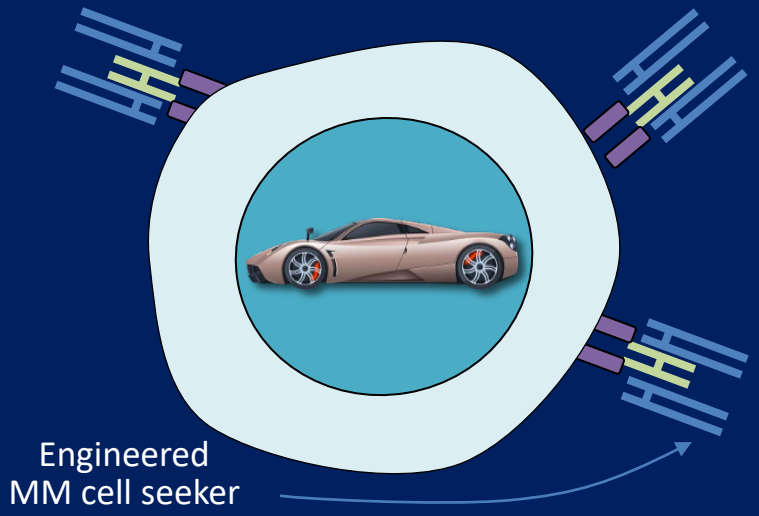
Normal T Cells vs CAR T Cells

Natural T cell with T cell receptor (TCR)



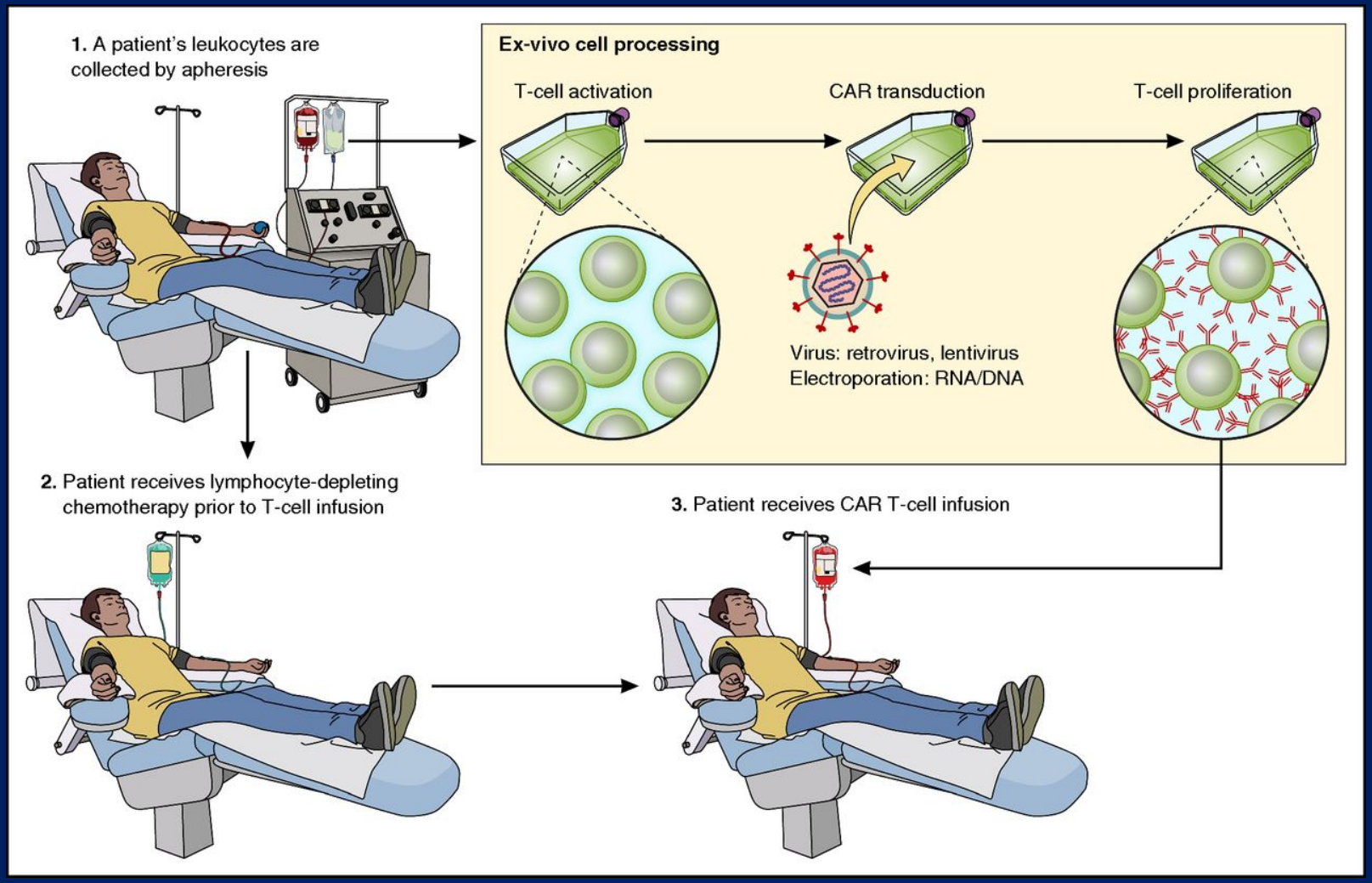
- Needs a jump start to target and kill myeloma cells

Engineered T cell with chimeric antigen receptor (CAR)



- Homing beacon built in to target and kill myeloma cells

The CAR-T therapy Process

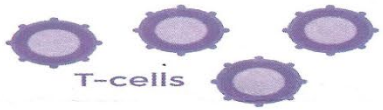


Lekha Mikkilineni, and James N. Kochenderfer Blood 2017;130:2594-2602

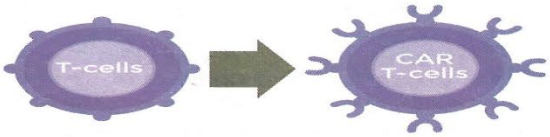
BOOSTING OUR OWN CANCER-KILLING CELLS

White blood cells known as T-cells protect the body from disease and infection. CAR T-cell therapy gives T-cells the power to fight cancer.

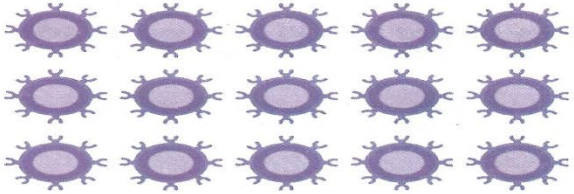
1 Collection
T-cells are collected from patient's blood and sent to the lab. This is the same basic process as when a person donates blood.

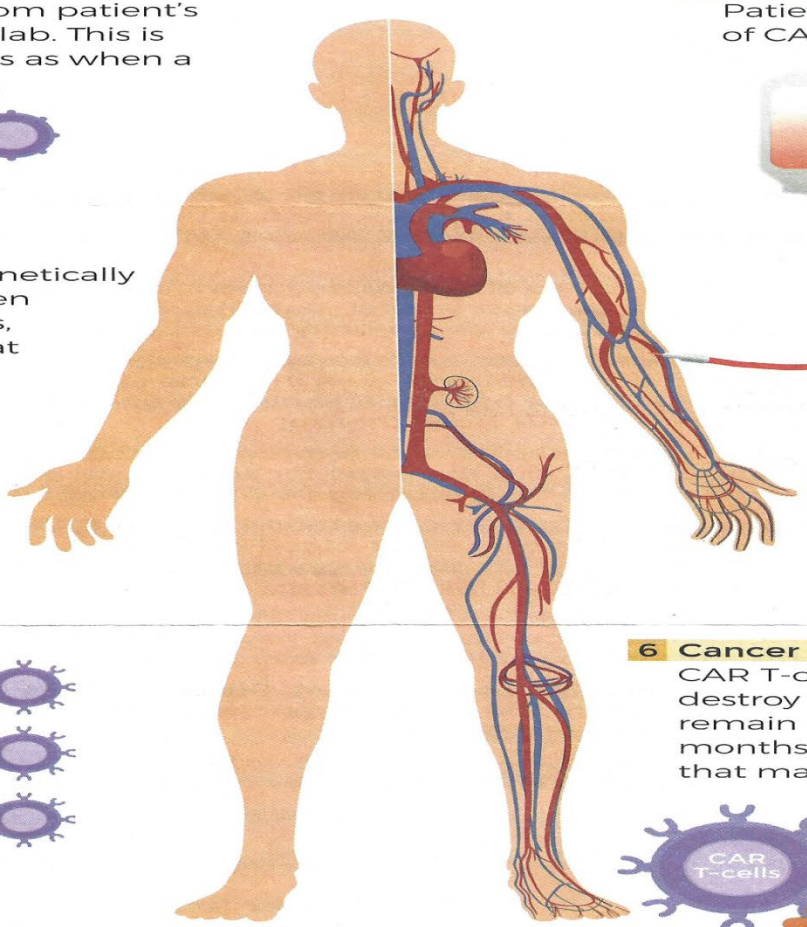


2 Conversion
In the lab, T-cells are changed genetically so that they grow chimeric antigen receptors (CARs) on their surfaces, turning them into CAR T-cells that can find and kill cancer cells.



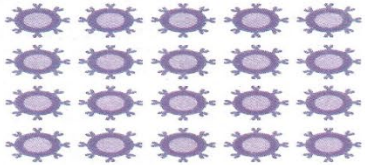
3 Replication
CAR T-cells are expanded in the lab.





4 Infusion
Patient receives infusion of CAR T-cells.

5 Expansion
The number of CAR T-cells continues to expand in the patient as they seek out and contact their target cancer cells.



6 Cancer cells destroyed
CAR T-cells in the patient destroy the cancer cells, and remain on alert for many months for any cancer cells that may have initially escaped.

BCMA-Directed CAR T Cells in Multiple Myeloma

	NCI[1]	PENN[2]	BB2121 BLUEBIRD[3]	LCAR-B38M LEGEND[4]	MCARH171 MSK/JUNO[5]
Population	26 (16*)	24 (19*)	21 (18*)	35 (30*)	6
# Prior Tx	10	7	7	3–4	7.5
Efficacy					
ORR	81%*	53%*	94%*	100%	NR
CR	18%		56%	63% (sCR)	NR
Toxicity					
CRS	81%	83%	71%	83%	50%
CRS (Gr 3/4)	37%	33%	10%	5.7%	None
Neurotoxicity (all grades)	19%	25%	24%	None	None

*Responses at therapeutic CAR T dose levels

1. Ali et al. *Blood*. 2016;128:1688. 2. Cohen AD et al. *Blood*. 2017;130: Abstract 505. 3. Berdeja JG et al. 2017;130: Abstract 740.
4. Zhang W et al. *Haematologica*. 2017;102: Abstract S103.5. Smith EL et al. *Blood.* 2017;130: Abstract 742.

CAR T-Cell Therapy Future Directions

Race to FDA approval

- Global pivotal phase 2 trial (KarMMa) is open for enrollment
  - bb2121 dose range: 150–450 × 10^6 CAR+ T cells
  - 9 sites in US and 10 in Europe
- Legend/Janssen soon to start pivotal trial of LCAR-B38M
- Others not far behind

Improving efficacy

- Understand why CAR T cells fail or stop working
- Next-generation or “armored” CAR T cells

Improving safety

- Identify correlates to predict and reduce rates of cytokine release syndrome and neurotoxicity
- Safety switches to induce suicide or eliminate CAR T cells

Improving access

- Allogeneic off-the-shelf CAR T cells
- CAR T-cell therapy for other stages of disease, new disease targets

Key Points

- Everyone is excited about CAR T, but this is a strategy that is still very toxic and of very limited availability.
- We still don't know the long-term outcome for CAR T.
- What are the best targets? How do we identify them?
- Antibody drug conjugates are very exciting; a number are already in clinical trials.