



Welcome & Introductions

Dr. Anderson's slides are available for download at

www.LLS.org/programs



Emerging Therapies for Multiple Myeloma



Larry D. Anderson, Jr, MD, PhD
*Associate Professor of Internal Medicine
Director of Myeloma, Waldenström's, and
Amyloidosis Program
Attending, Hematologic Malignancies/Blood
and Marrow Transplantation Program
UT Southwestern Medical Center
Simmons Comprehensive Cancer Center
Dallas, TX*



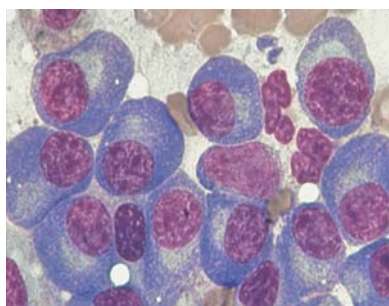
Disclosures

Speaker Bureau for Celgene, Amgen, and Takeda

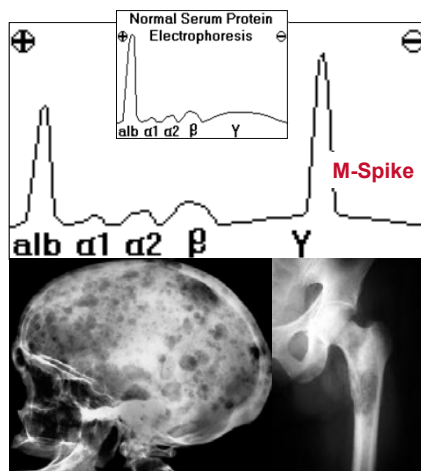
Will discuss off-label use of therapies



Multiple Myeloma Classic Triad



>10% Clonal Plasma Cells
In Bone Marrow



Lytic Bone Lesions



Multiple Myeloma Facts



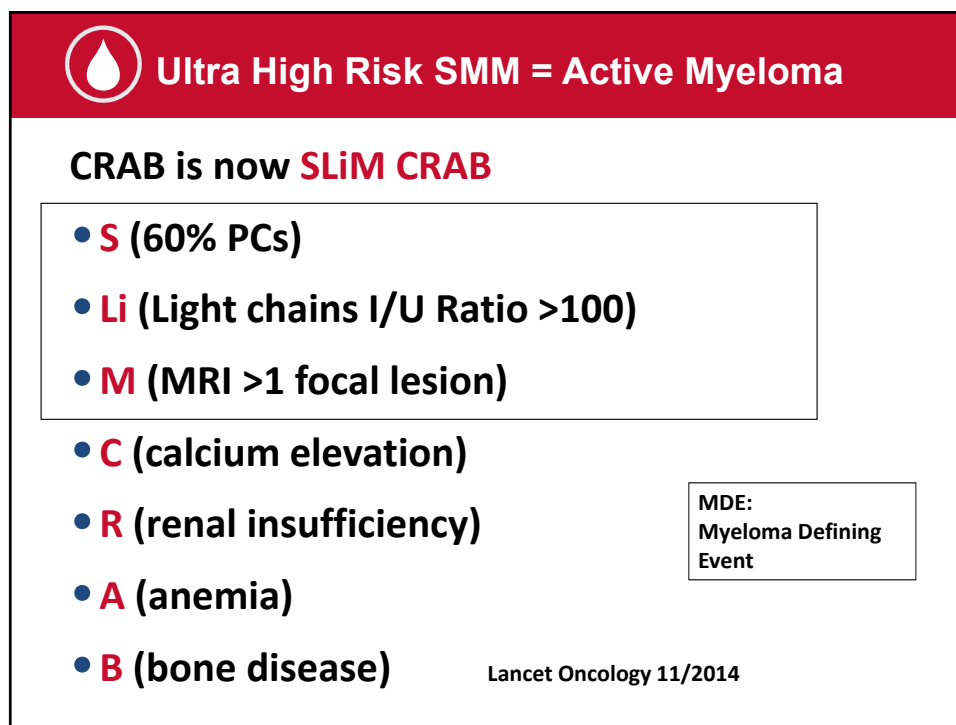
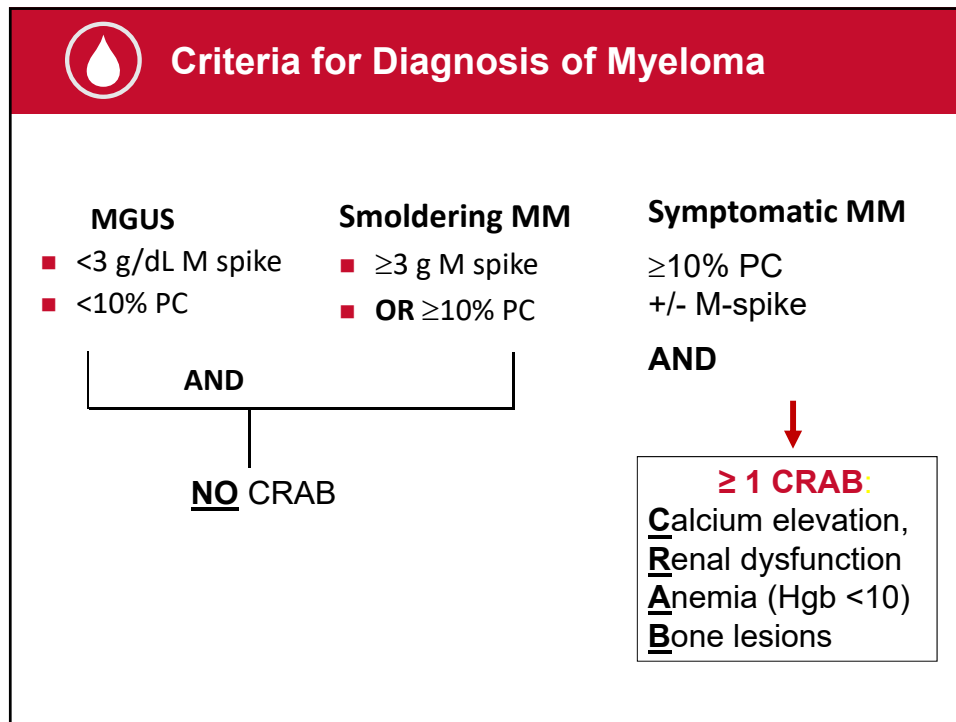
- **2nd most common Hematologic Malignancy**
- **~30,280 people Dx with MM in 2017 in US**
- **103,463 people in the US living with MM**
- **12,650 MM patients die each year in US**
- **Median age at Dx ~67 years (only 4% <45)**
- **Incidence twice as high in African Americans**



Multiple Myeloma Facts (cont.)

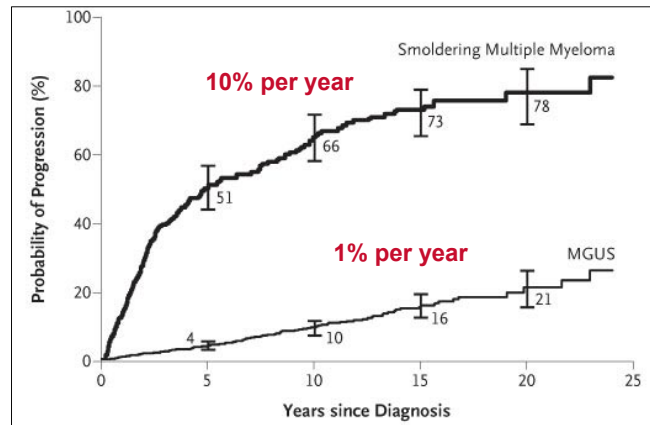


- **More frequent in men (1.3:1)**
- **bone/back pain, fatigue/anemia or infections**
- **This disease remains incurable in most patients**
- **Median survival with older therapies 3yrs, with transplant 5-7 years, and with novel therapies + transplant probably 8-10 years (still improving)**
- **M protein seen in 99% of cases in serum and/or urine, IgG > 50%, IgA 20-25%, IgE/IgD 1-3%, IgM 1%, light chain only 5-10%, Nonsecretory 1%**





Probability of Progression to Active/Symptomatic MM in pts with Smoldering MM or MGUS



These patients DO NOT require treatment!!
 (unless on a Clinical Trial).
Many NEVER require treatment!

Kyle RA et al. N Engl J Med 2007;356:2582-2590



REVISED INTERNATIONAL STAGING SYSTEM (R-ISS)



Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2 -microglobulin < 3.5 mg/L, serum albumin \geq 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2 -microglobulin \geq 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.



Management of Active/Symptomatic MM

- Those patients with SLIM-CRAB (Stage II or III Disease) need treatment
- Even Active MM outcomes can vary widely, and there are many treatment options
 - Need to stratify prognosis based on risk factors and whether or not the pt is a stem cell transplant candidate
 - mSmart System



Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART.org)



mSMART 3.0: Classification of Active MM

High-Risk

- FISH^{a,b}
 - Del 17p
 - t(4;14)
 - 1q gain
 - t(14;16)
 - t(14;20)
- RISS Stage 3
- High Plasma Cell S-phase^c
- GEP: High risk signature

Standard-Risk^a

- All others including:
- Trisomies
 - t(11;14)^d
 - t(6;14)

**As of 5/2018 NO more
"Intermediate Risk" Group**

^aTrisomies may ameliorate



Polling Question #1

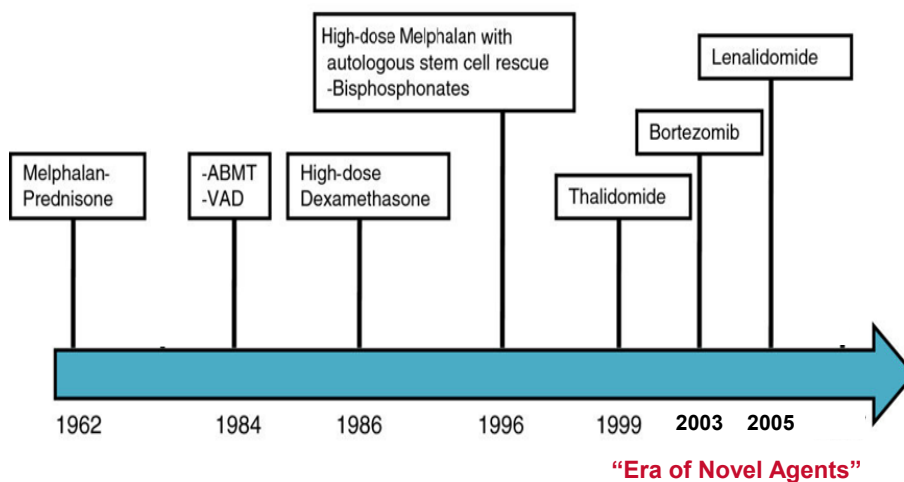


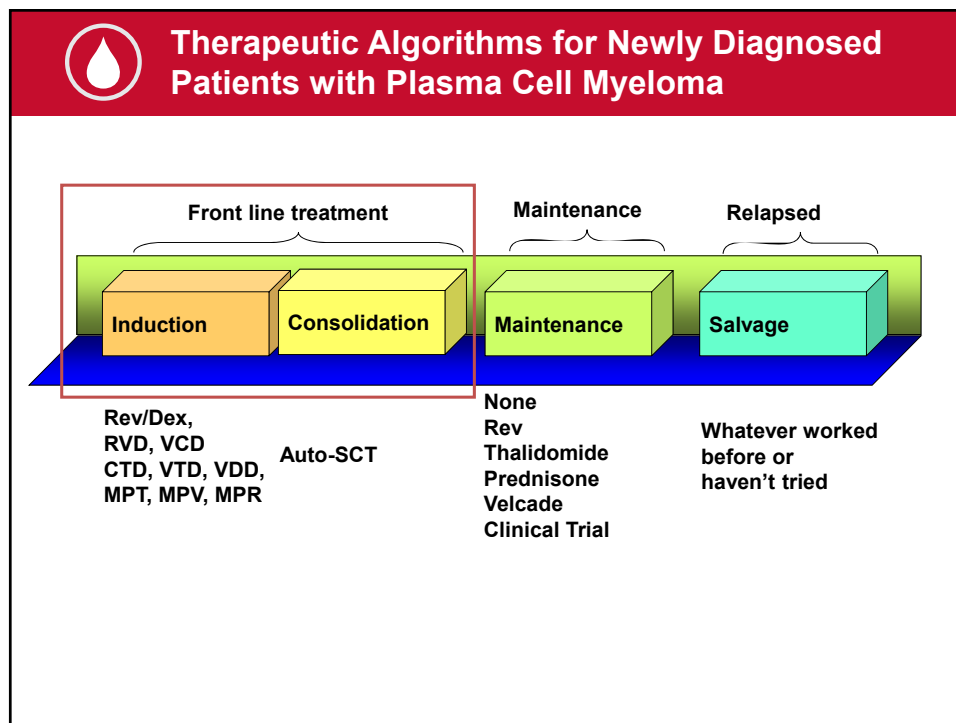
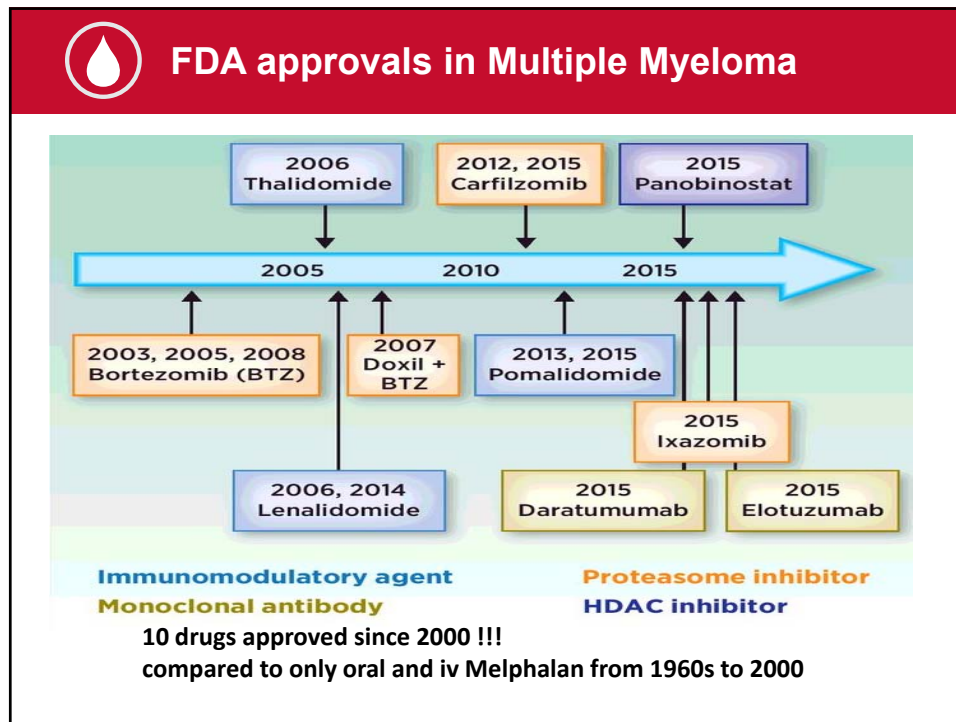
How many of you are the following:

- A. Myeloma patient on or after treatment
- B. MGUS or Smoldering Myeloma patients not needing treatment yet
- C. Caregiver or Family of Myeloma patient
- D. Healthcare worker (RN, MD, RD, etc)
- E. Just interested in Health topics



Major Milestones in Myeloma Therapy







International Myeloma Working Group Uniform Response Criteria

PR: $\geq 50\%$ reduction in serum M-protein

VGPR: $> 90\%$ reduction in M-protein

Near CR: Negative SPEP/UPEP but **POSITIVE Immunofixation**
(Faint monoclonal band but too small to quantitate)

CR: Negative SPEP AND **Negative Immunofixation (serum and urine)**

Stringent CR: CR + Normalization of free light chain ratio,
absence of aberrant cells on flow cytometry

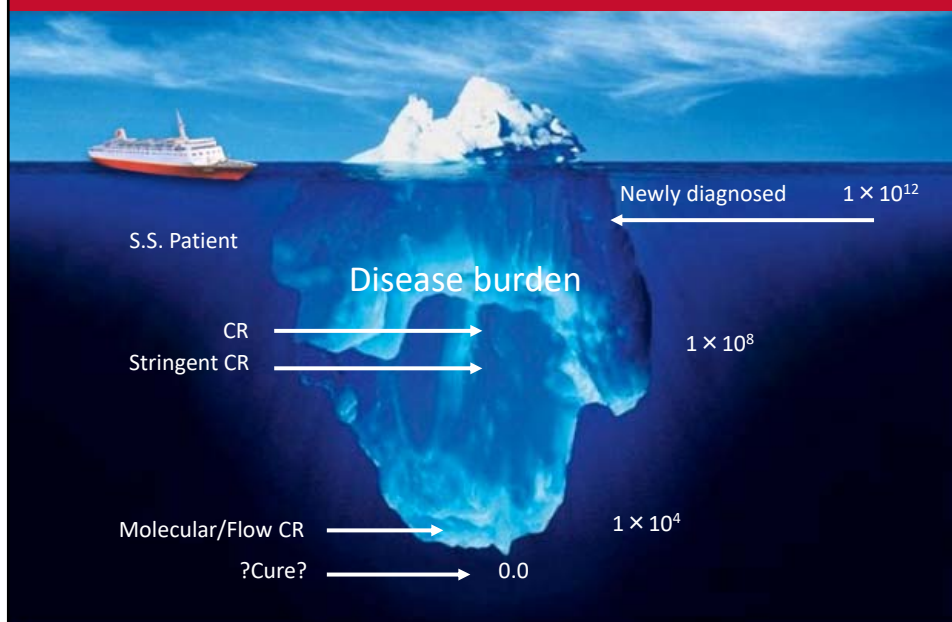
MRD Negative (Molecular Remission): Using either PCR or
high throughput multicolor flow cytometry to find MM in 1 in
 1×10^6 marrow cells

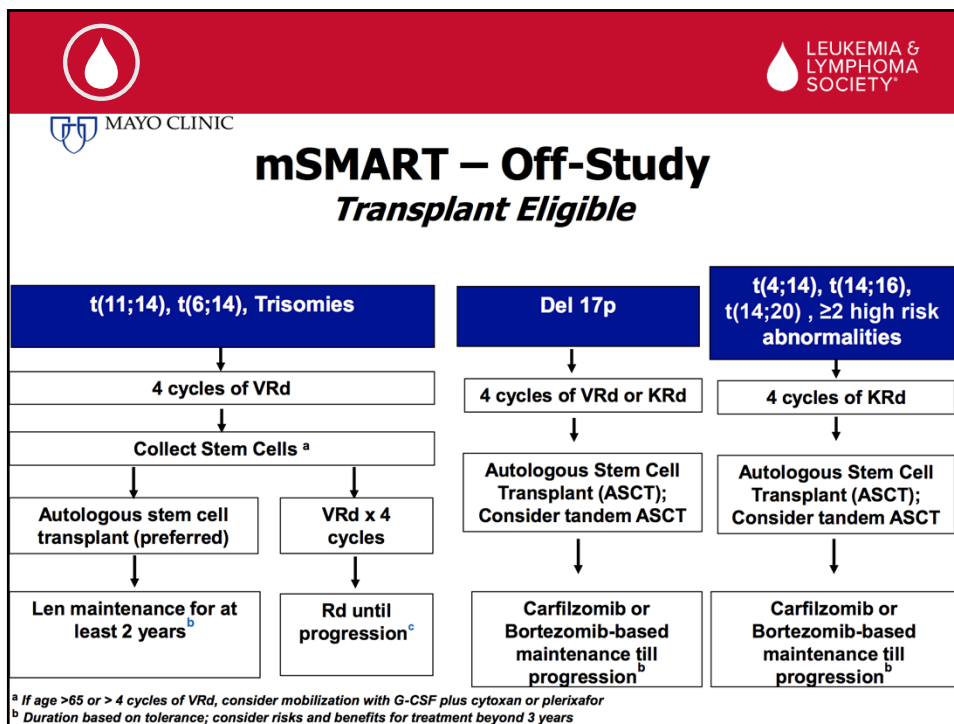
Anything VGPR or better considered a “Deep Remission”

Durie BGM, et al. Leukemia. 2006;20:1467-1473.



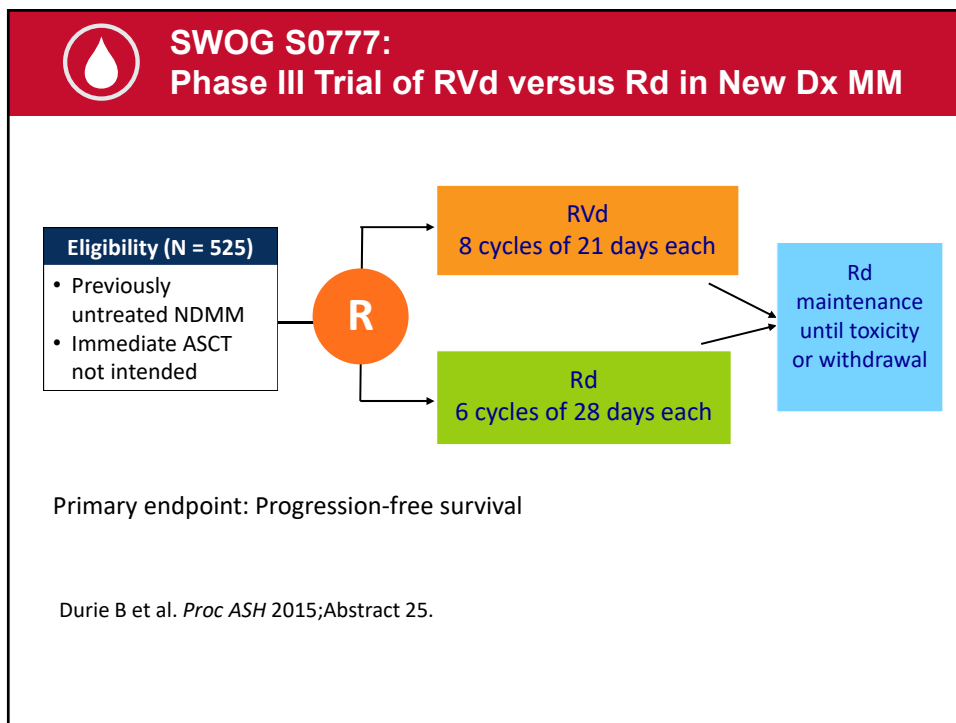
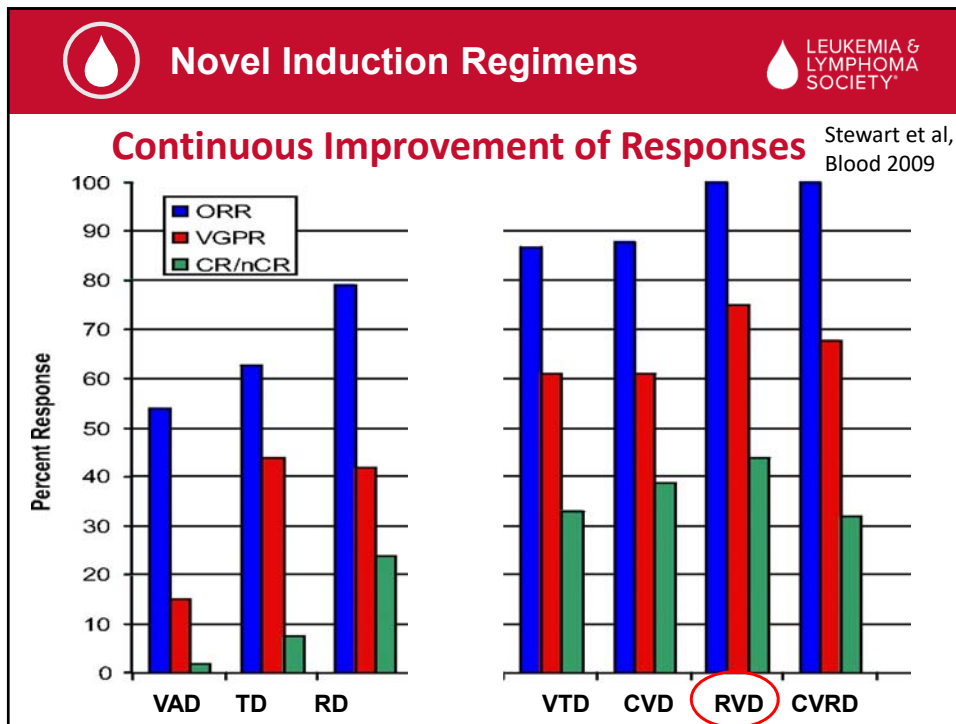
Getting to Minimal Residual Disease (MRD)

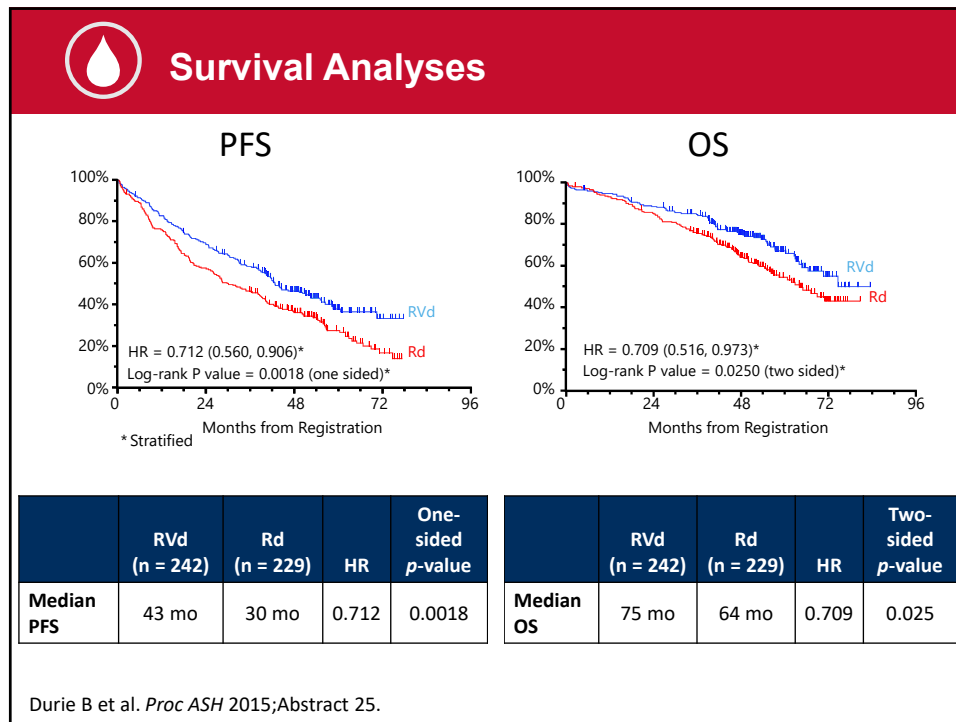




Novel Therapies

- Anti-cancer therapy but NOT traditional chemotherapy (which kills both cancer and healthy cells by attacking cell division)
- These drugs target the cancer cells by attacking other pathways besides cell division and are more cancer specific, often less toxic

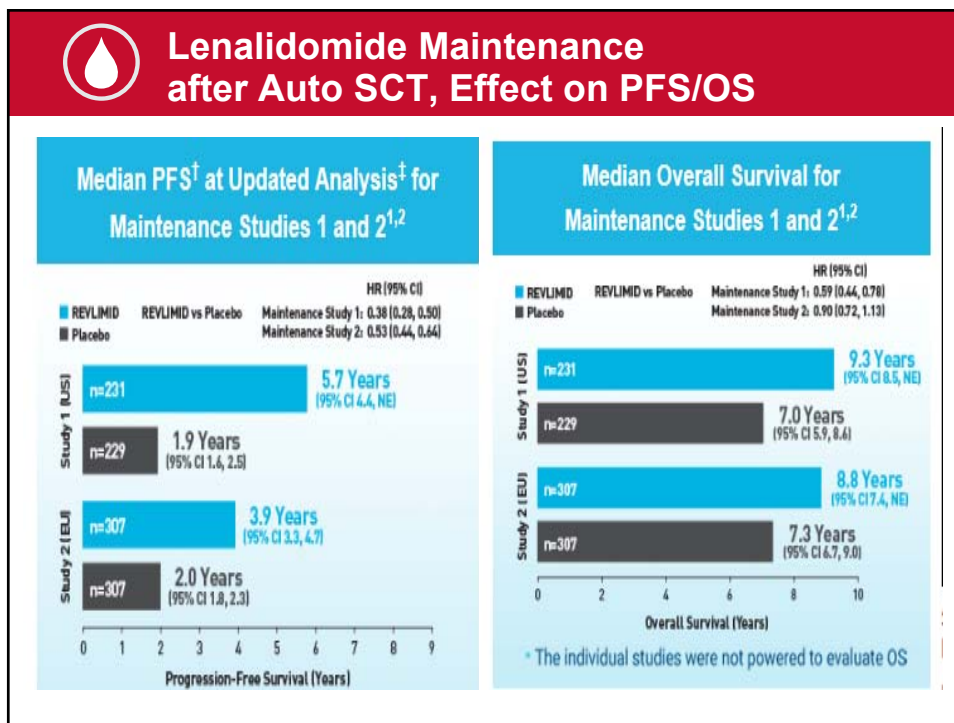
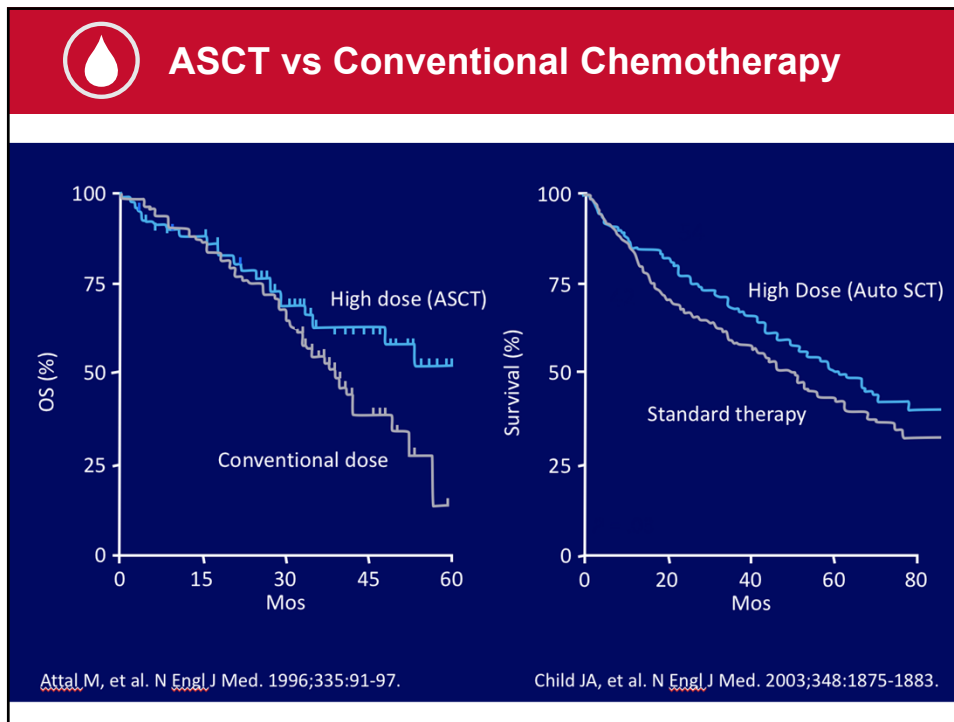


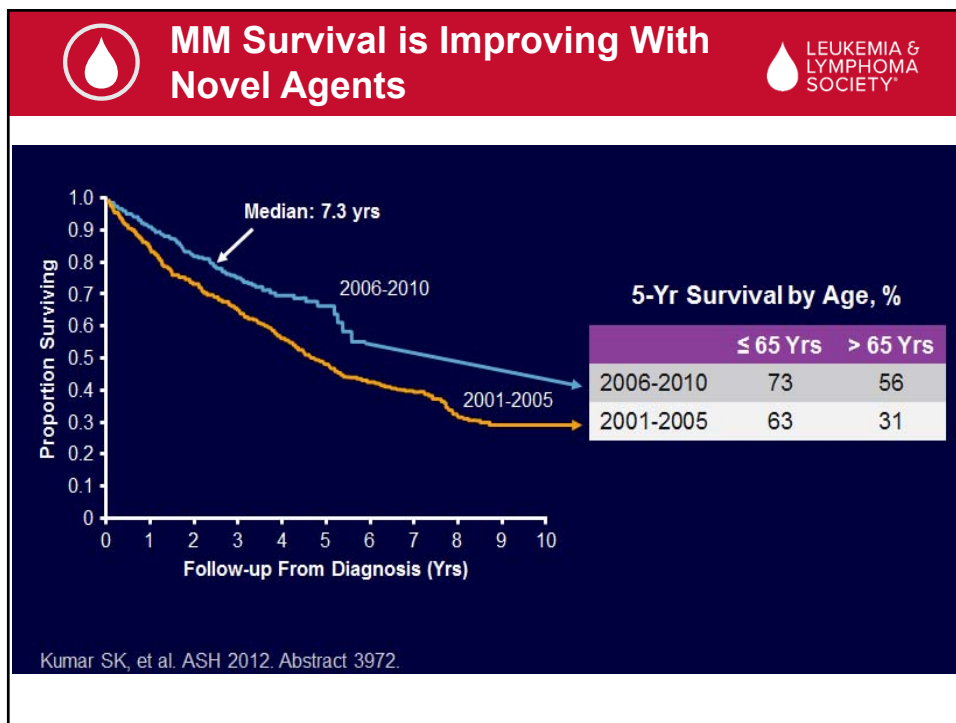
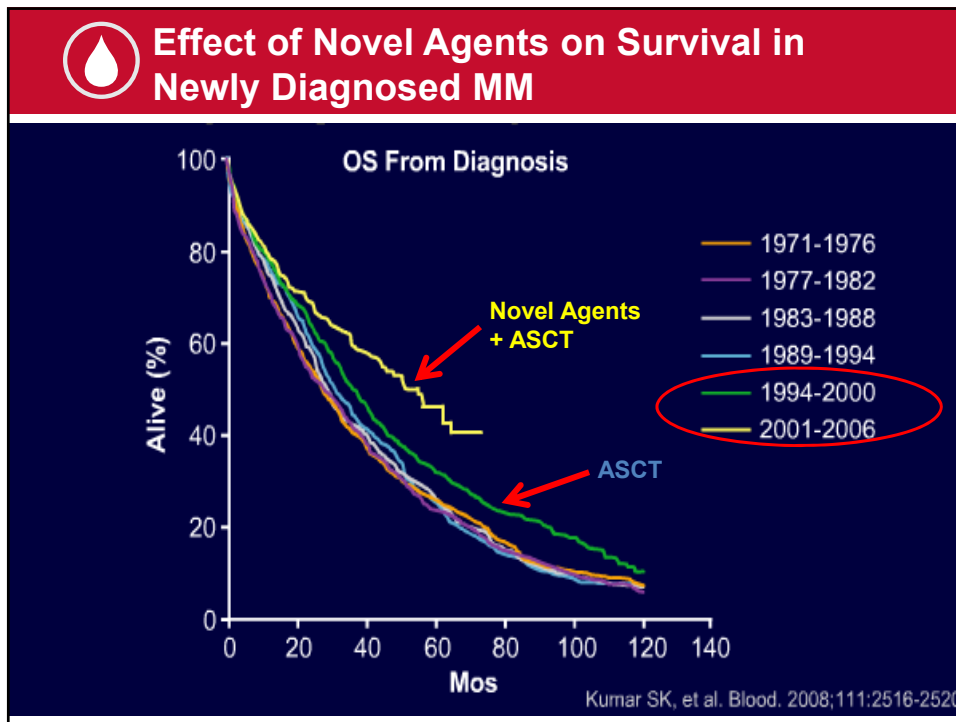


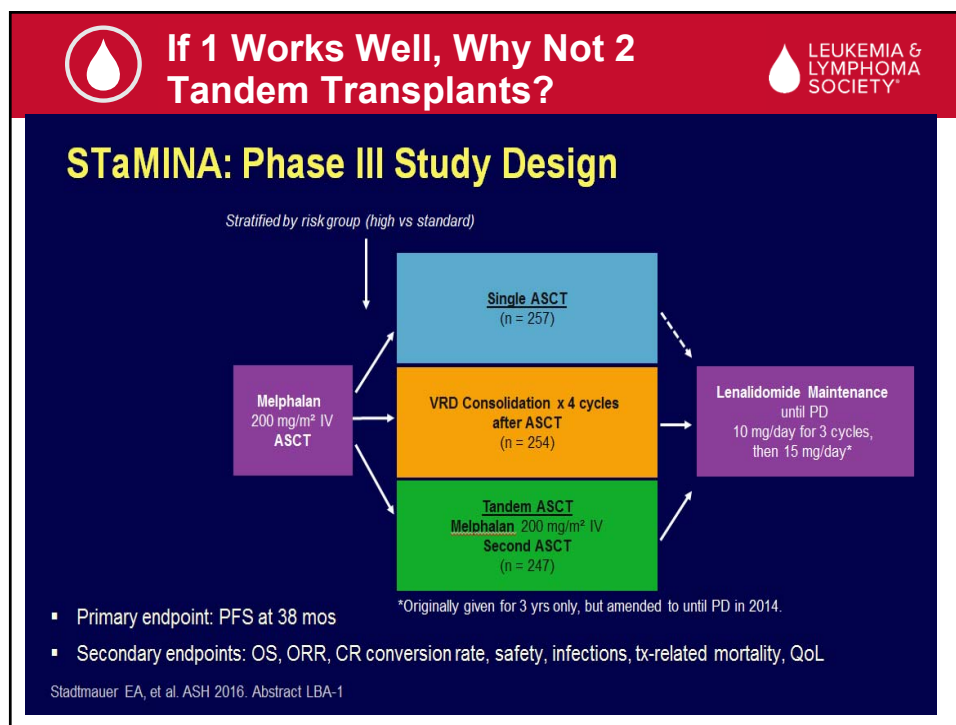
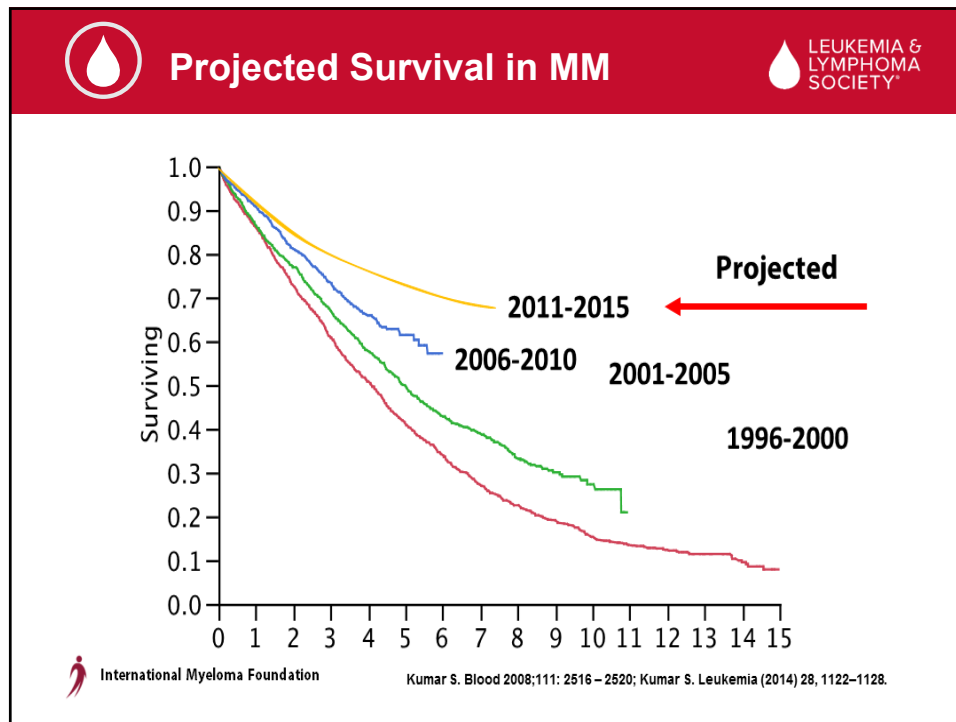
High-Dose Chemotherapy With Autologous Stem Cell Transplantation (ASCT)

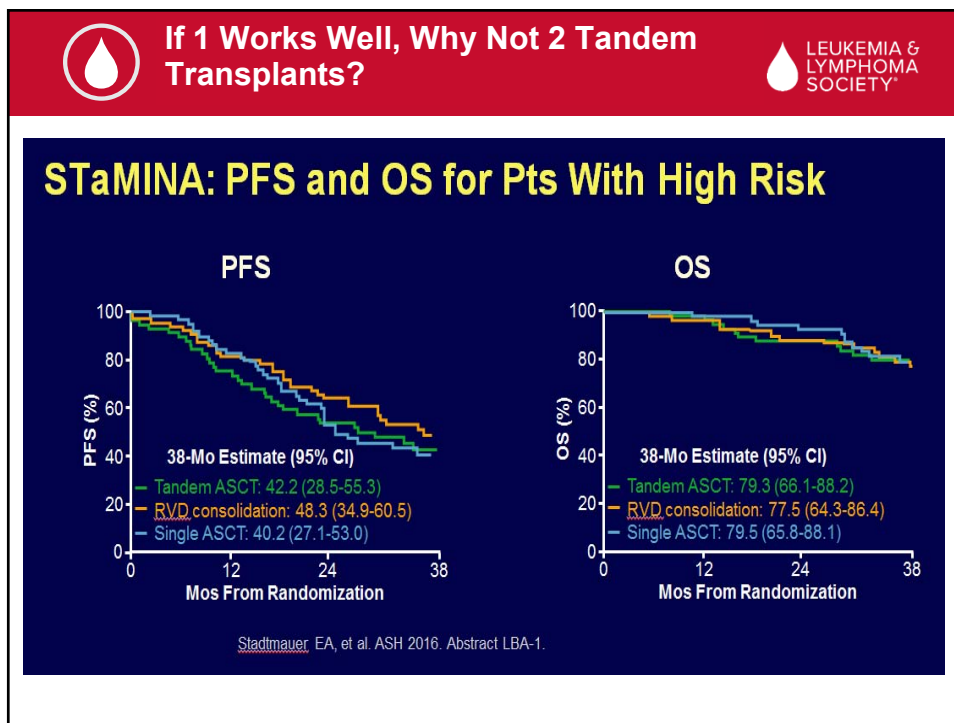
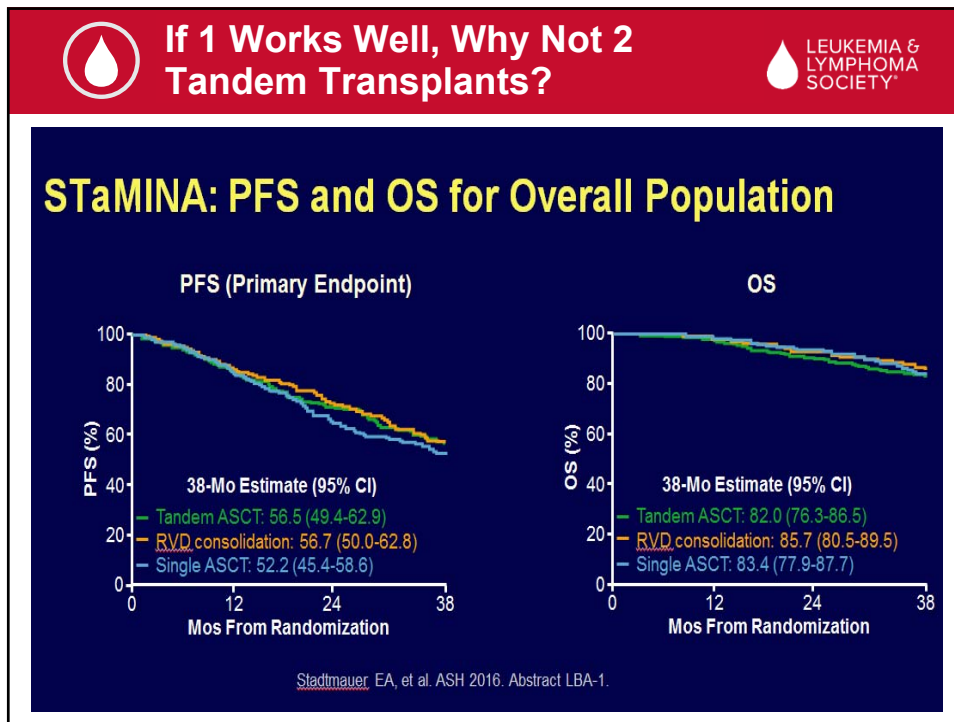
- Autologous peripheral blood stem cells collected by apheresis, frozen, later used as a “rescue” from marrow ablative effect of high dose chemo
- Introduced in the 1980’s, several randomized trials in the 1990’s and early 2000’s using high dose melphalan and ASCT showed improved PFS and Overall Survival
- Generally see 1-2 year survival increase compared to conventional chemotherapy
- SOC since the 1990’s and remains today (up to age 75)


Attal M, et al. *N Engl J Med* 1996;335:91-7. Child JA, et al. *N Engl J Med* 2003;1875-83.








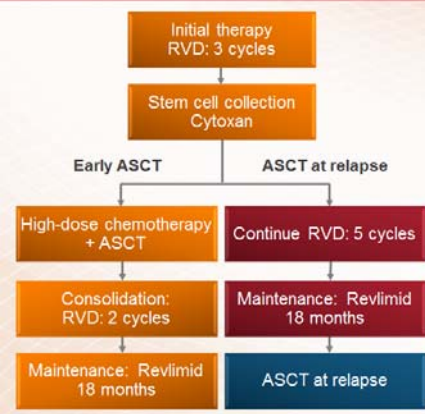




Early vs Delayed Auto SCT



Should I get a transplant after induction therapy or should I wait until after I relapse? *Ongoing Clinical Trial (IFM/DFCI)*




```


graph TD
    A[Initial therapy RVD: 3 cycles] --> B[Stem cell collection Cytoxan]
    B --> C[Early ASCT]
    B --> D[ASCT at relapse]
    C --> E[High-dose chemotherapy + ASCT]
    D --> F[Continue RVD: 5 cycles]
    E --> G[Consolidation: RVD: 2 cycles]
    F --> H[Maintenance: Revlimid 18 months]
    G --> I[Maintenance: Revlimid 18 months]
    H --> J[ASCT at relapse]
    
```

- Better/deeper response rates with early transplant
- Longer remissions when transplant done early (43 months vs 34 months)
- Overall survival at 4 years was not significantly different so delaying doesn't compromise long-term outcome
- Continuous therapy with maintenance until progression to be addressed by US study*

RVD, Revlimid, Velcade, dexamethasone; Cytoxan, cyclophosphamide
 Attal M et al. *Blood*. 2015;126: Abstract 391.
 Avez-Lopes H et al. *Blood*. 2015;126: Abstract 191.



Early vs Delayed Auto SCT?

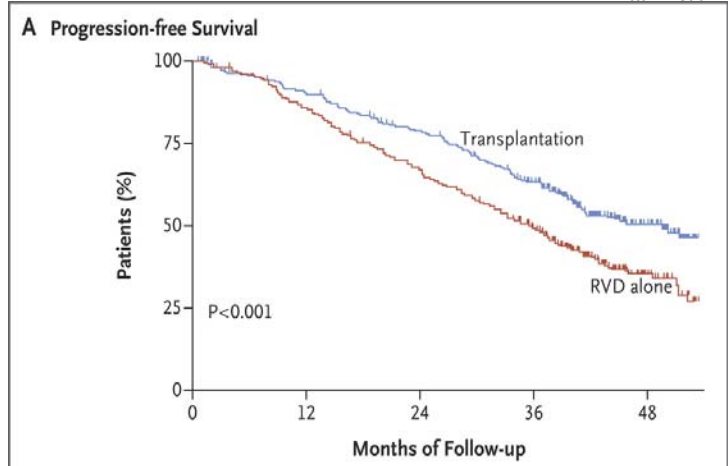


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 6, 2017 VOL. 376 NO. 14

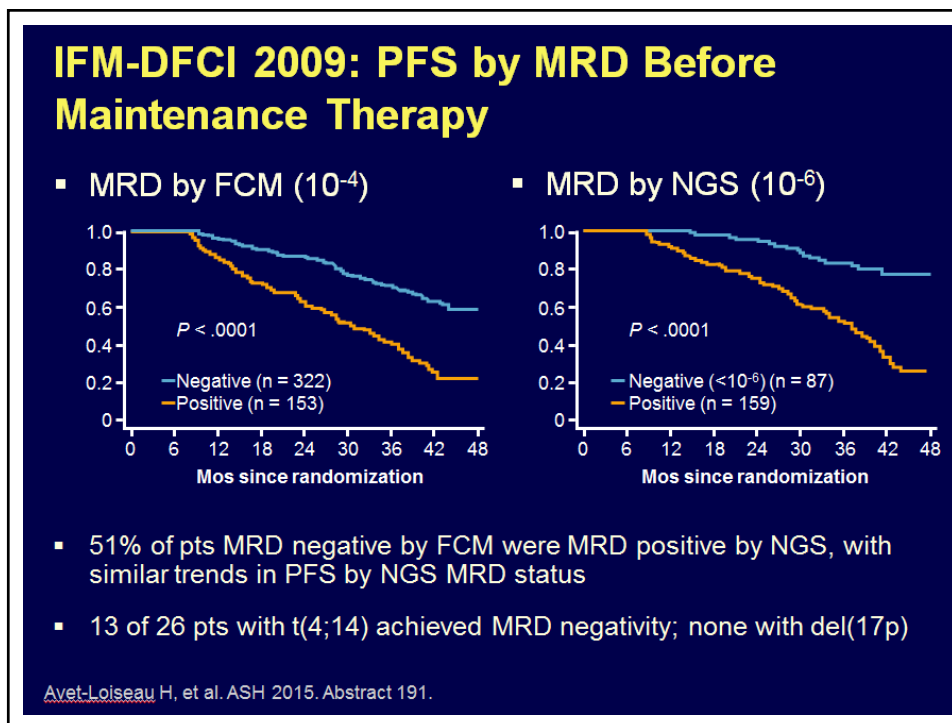
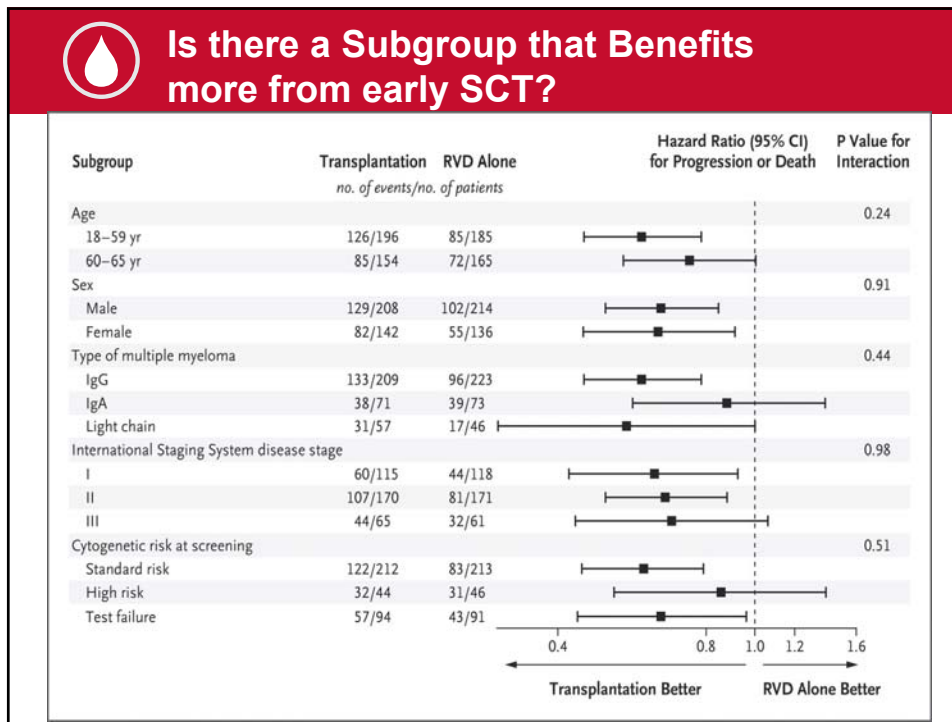
Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma Attal M et al

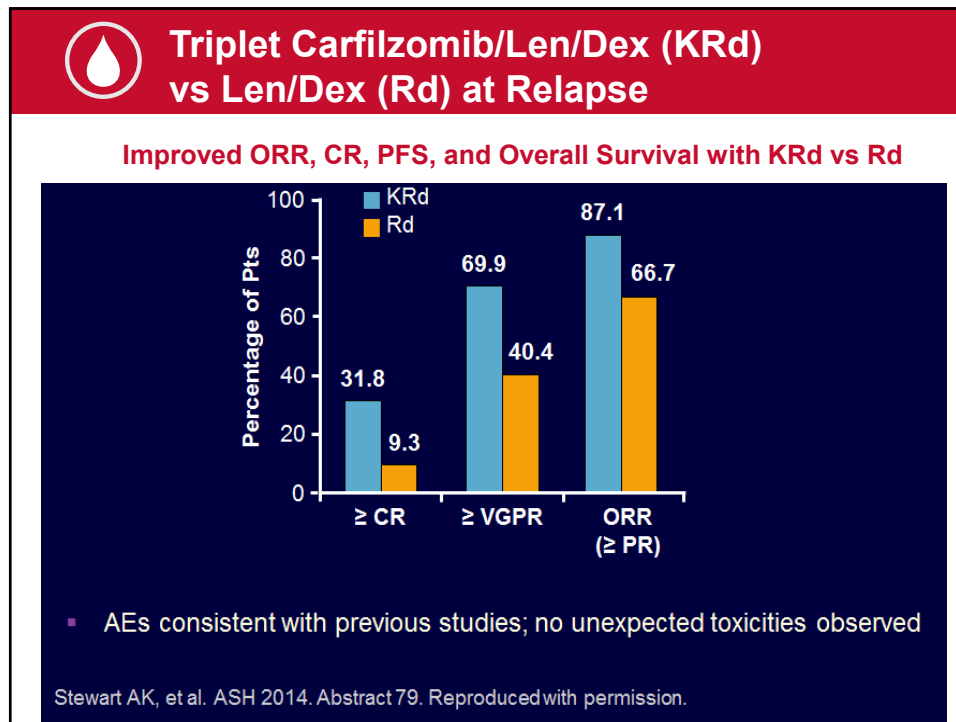
A Progression-free Survival



The graph shows progression-free survival over 48 months. The 'Transplantation' group (blue line) maintains a higher percentage of patients in remission compared to the 'RVD alone' group (red line). A p-value of <math>P < 0.001</math> is indicated.

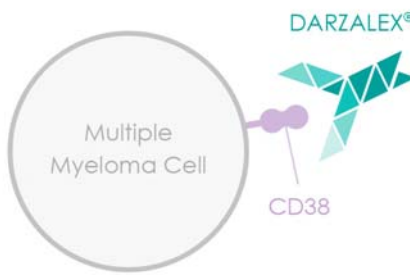
Months of Follow-up	Transplantation (%)	RVD alone (%)
0	100	100
12	~95	~85
24	~80	~65
36	~65	~45
48	~50	~30





- 4 Recently Approved Therapies**
- New Proteasome Inhibitors (ORAL)
 - Ixazomib (Ninlaro) – weekly pill combined with Rev/Dex in relapsed pts (**Triple Oral Therapy with less PN!!!**)
 - New IMiDs (Oral, More potent, less toxic)
 - Pomalidomide - 30% Response in Rev and Vel-Refractory pts (FDA approved 2/2013)
 - Monoclonal Antibodies targeting PCs
 - Daratumumab (mAb targeting CD38), single agent responses 29%, combined with Imid OR Velcade 83-93% (initially 4th line but now 2nd line therapy as triple Rx!)
 - Elotuzumab (Anti-CS1/SLAMF7) ~ 80% Response in Relapsed pts combined with Rev/dex but not alone (activates NK cells)

Monoclonal Antibodies for MM
LEUKEMIA & LYMPHOMA SOCIETY™



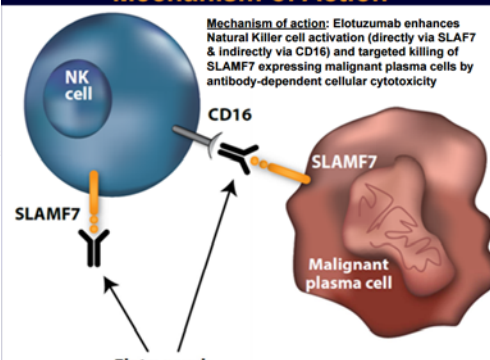
Multiple Myeloma Cell

DARZALEX®

CD38

Monoclonal Antibody therapy for relapsed Myeloma
Combinations can induce deep molecular remissions

Elotuzumab in MM Mechanism of Action



Mechanism of action: Elotuzumab enhances Natural Killer cell activation (directly via SLAF7 & indirectly via CD16) and targeted killing of SLAMF7 expressing malignant plasma cells by antibody-dependent cellular cytotoxicity

POLLUX Extended Follow-up: Study Design. (DRd vs Rd at Relapse)

- Multicenter, open-label, randomized phase III trial

Stratified by number of previous lines of therapy, ISS stage at entry, previous lenalidomide use

R/R MM pts with previous use of ≥ 1 line of therapy* and CrCl ≥ 30 mL/min (N = 569)

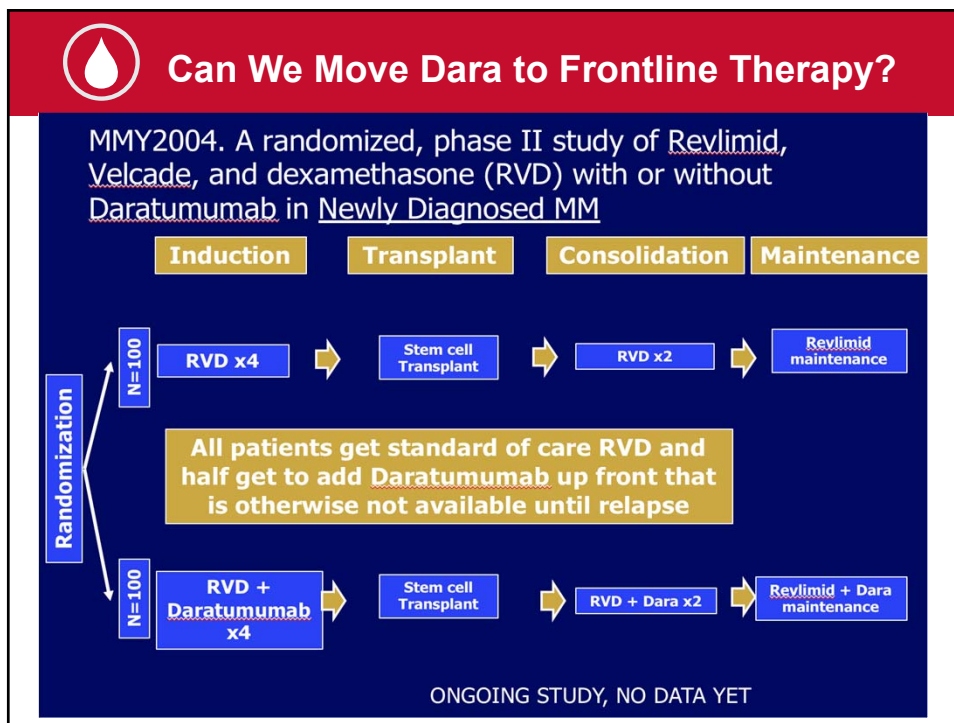
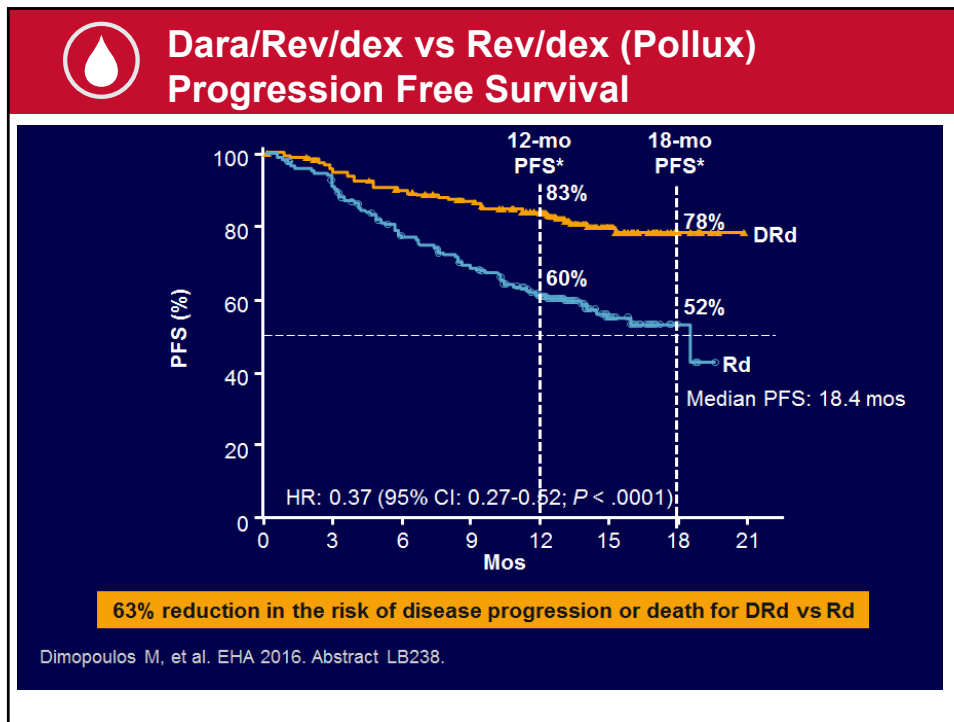
Daratumumab + Lenalidomide + Dexamethasone (DRd)
(n = 286)

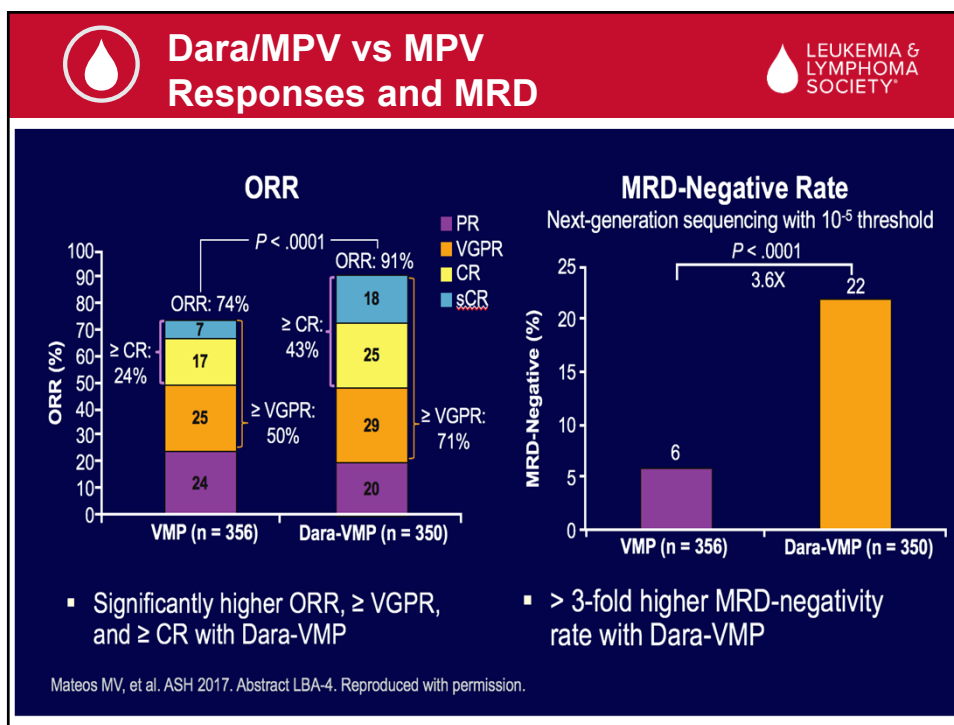
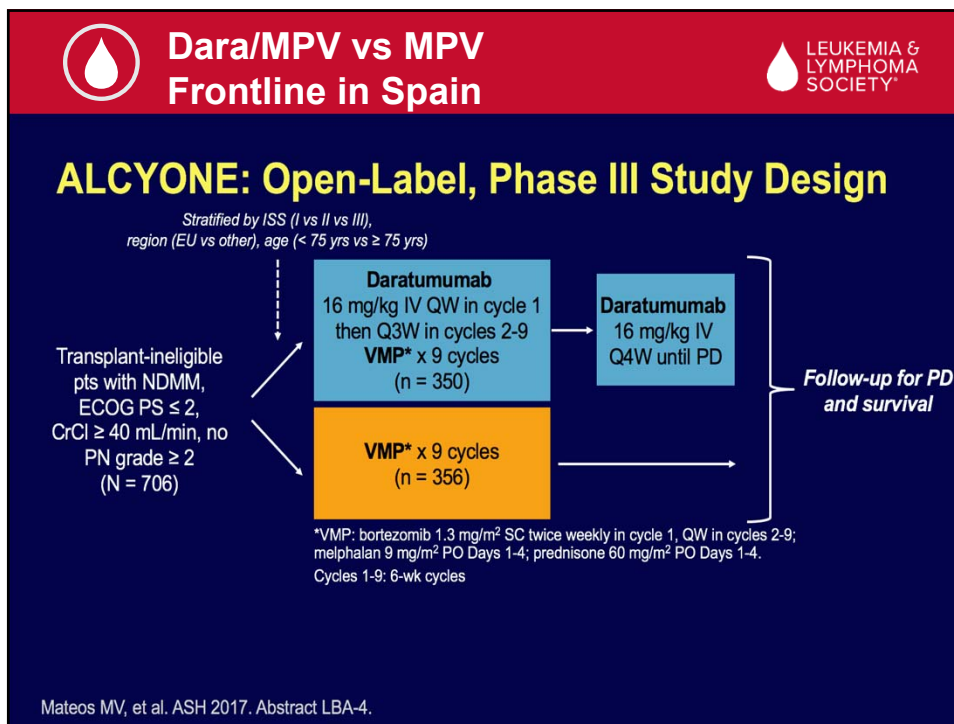
Lenalidomide + Dexamethasone (Rd)
(n = 283)

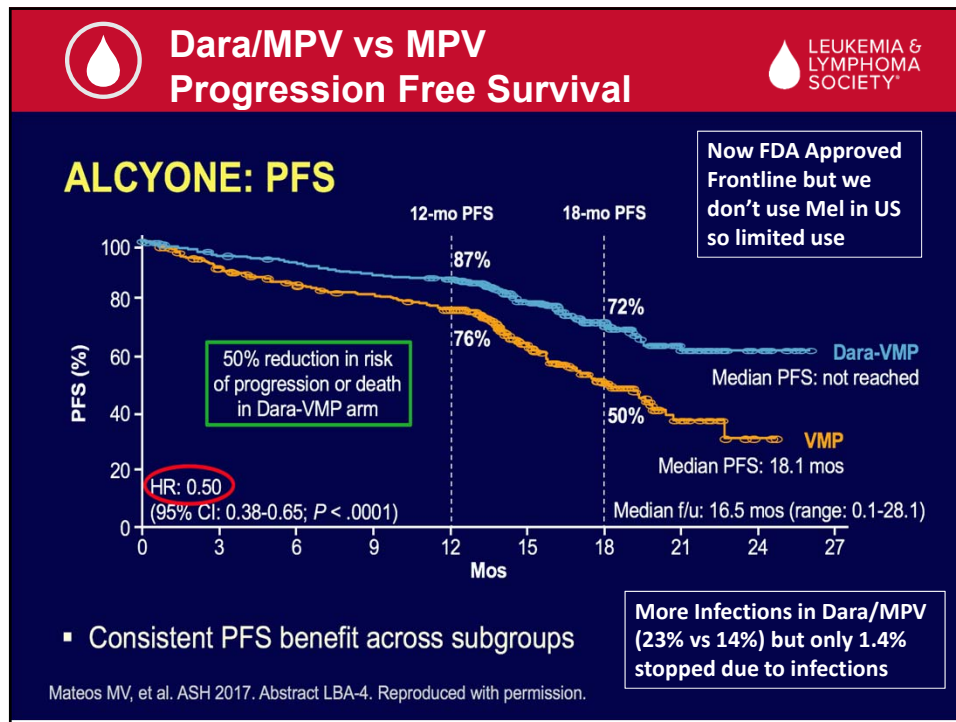
Pts treated until PD

*Pts eligible if lenalidomide experienced but not lenalidomide refractory.
 Dosing (28-day cycles): daratumumab 16 mg/kg IV QW in cycles 1-2, Q2W in cycles 3-6, and then every 4 wks;
 lenalidomide 25 mg PO on Days 1-21; dexamethasone 40 mg PO QW.

Dimopoulos MA, et al. ASH 2017. Abstract 739.







FDA Approved CAR-T Therapies A New Era of Immunotherapy

LEUKEMIA & LYMPHOMA SOCIETY

Tisagenlecleucel (Kymriah; Novartis)

- Acute Lymphoblastic Leukemia (< 25 yrs of age)
- Price: \$475,000

Axicabagene ciloleucel (Yescarta; Kite Pharma)

- Non-Hodgkins Lymphoma
- Price: \$373,000

⦿

What are CAR T Cells?

Chimeric Antigen Receptor T Cells

LEUKEMIA & LYMPHOMA SOCIETY

Chimeric – Chimera – Greek Mythology = Monster with Lion’s head Part Antibody, Part T Cell Receptor Signaling domains

Antigen – Protein target on cancer cells that T cells are engineered to recognize

Receptor – CAR – Engineered Receptor Added to surface of T cells Recognizes specific target antigen on cancer cells

T-Cells – Re-engineered T cells are forced to recognize the cancer cells and kill them

⦿

CAR Design: Critical Elements of T-Cell Activation and Function in a Single Molecule

CAR T cells are genetically altered to express CAR on the cell surface.

T Cell Receptor

Chimeric Antigen Receptor

scFv: recognize tumor surface proteins

Costimulatory Signal 2: CD28 or 4-1BB or OX40

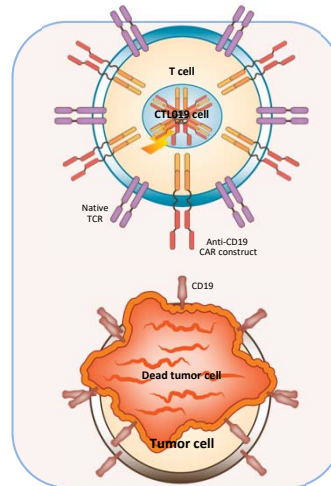
Essential Signal 1: CD3ζ

Activation Independent of MHC
Limited to cell surface proteins



Redirecting T-Cell Specificity with Chimeric Antigen Receptor (CAR) T-Cell Therapy

- Gene transfer technology stably expresses CARs on T cells^{1,2}
- Takes advantage of the cytotoxic potential of T cells, killing tumor cells in an *antigen-dependent* manner^{1,3}
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells³
- **T cells are *non-cross resistant* to chemotherapy**



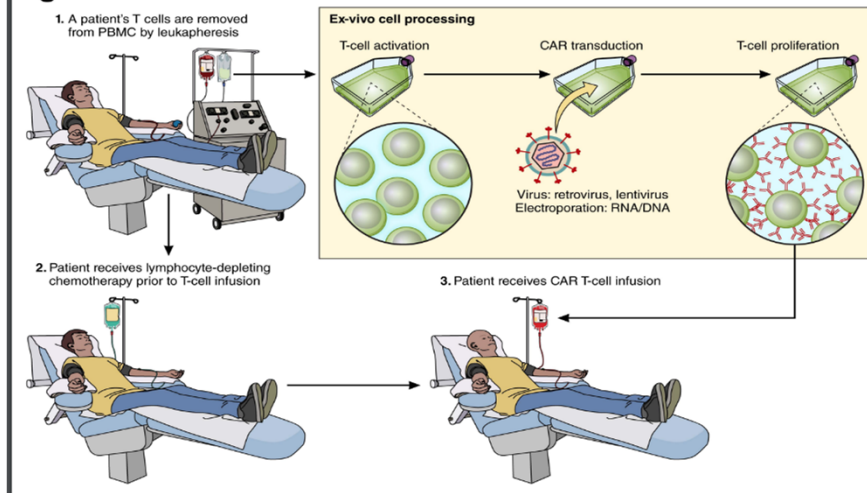
1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464.
 2. Hollyman D, et al. *J Immunother.* 2009;32:169-180.
 3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.



Overview of CAR T-Cell Process



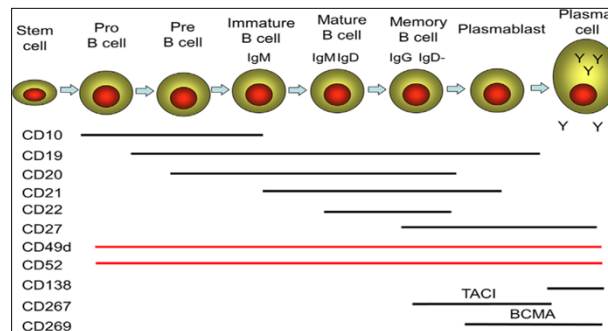
Figure 2





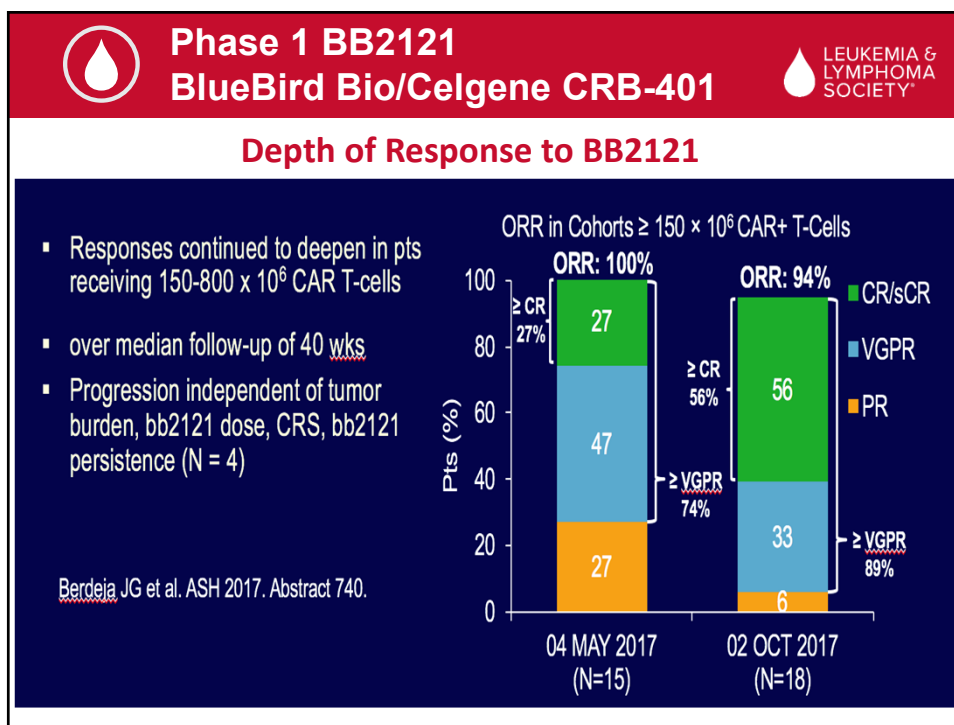
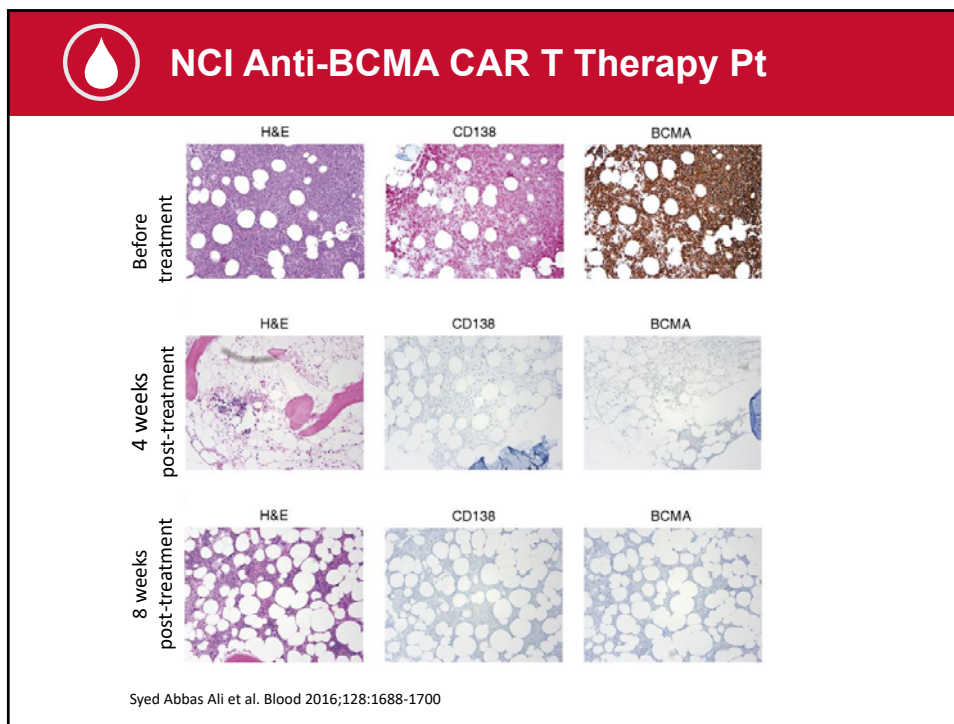
BCMA as a Target for Myeloma CAR T-Cell Therapy

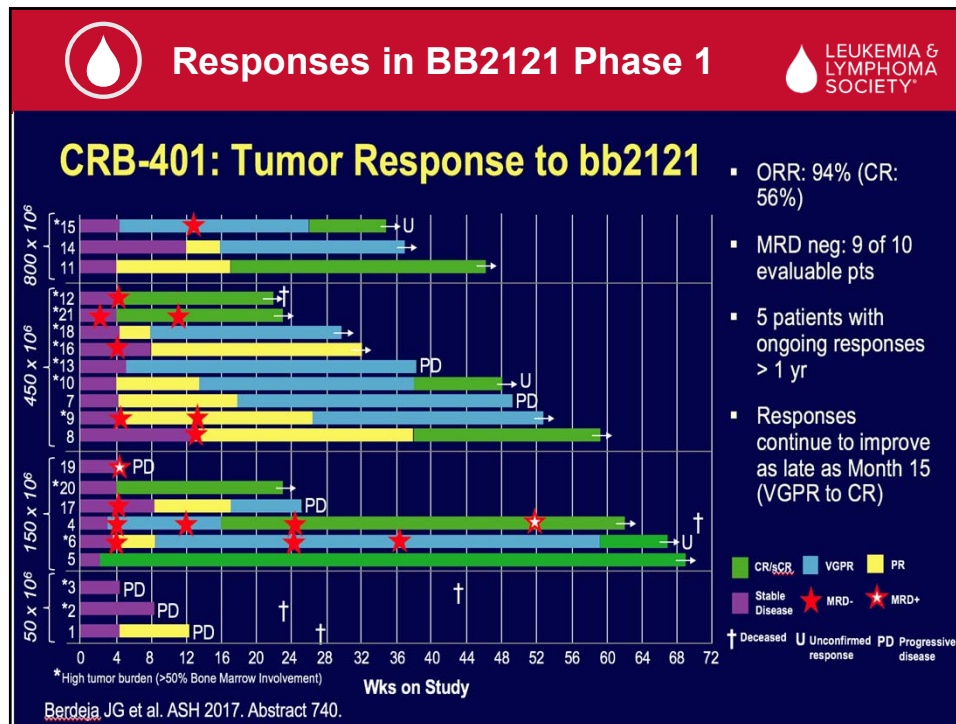
- **BCMA:** B Cell Maturation Antigen
- Receptor expressed on Myeloma tumor cells, nonmalignant plasma cells, and some late stage mature B-cells
- Cell lineage specific so avoids off target toxicity



CAR T-Cell BCMA Phase 1 Studies in Myeloma

- 4 Phase 1 Studies presented: NIH, U Penn, Chinese, and Bluebird Bio
- LBA3001 ASCO 2017, Fan et al: 100% ORR, 33/35 patients in remission at 2 mo
- U Penn also promising with high ORR, Cohen et al, ASH '16
6 out of 9 responses in U Penn
My pt WW is pt #1, in CR at 29 months
- NCI CART-BCMA, Ali et al, Blood 2016, 3 out of 6 at higher dose levels had either VGPR or CR
- BlueBird Bio (Celgene) BB2121 ASH '17, Berdeja et al 94% ORR, 56% CR. (out of 12 pts with over 150×10^6)
- FDA Breakthrough Designation for BlueBird Bio CAR T on 11/17/17
- **UTSW participating in Phase 2 KarMMa Study (1 out of 9 sites in US and only site in Tx, 1st infusion 3/19/18, 7 infused and 9 enrolled already)**





BB2121 Phase 1 Conclusions

LEUKEMIA & LYMPHOMA SOCIETY

- Investigators conclude that bb2121 confers deep, durable responses at active doses (150-800 x 10⁶ CAR T cells) in heavily pretreated pts with R/R MM
 - ORR: 94%, ≥ VGPR: 89%, CR: 56%
 - 90% of evaluable pts MRD negative at 40 wks of follow-up
- Safety profile of bb2121 manageable up to 800 x 10⁶ CAR T-cell dose
 - 2 cases of grade 3 CRS during dose escalation; resolved within 24 hours
 - 1 case of delayed, reversible grade 4 neurotoxicity during dose expansion associated with TLS and CRS in patient with highest tumor burden
- Global phase II KarMMa trial evaluating bb2121 at doses of 150-300 x 10⁶ CAR T-cells open for enrollment (NCT03361748)

Berdeja JG et al. ASH 2017. Abstract 740.



CAR T Future Directions



- This is a new Era of exciting treatment options for Hematologic Malignancies. Some diseases that never had an option for a cure may now have that option (Myeloma, FL, Chemo-refractory ALL/DLBCL)
- Solid Tumor CARs are on the horizon (prostate, etc)
- Antigen Escape:
 - Infusion of 2 different CAR T products (CD19 and CD22, etc)
 - Tandem CAR that recognizes 2 different targets from same CAR
- Lack of persistence of CAR T-Cells:
 - Reinfusion after loss
 - Isolation of Central Memory T-Cells with self renewal capacity
- Lack of Efficacy:
 - TRUCKs (T-cells redirected for universal cytokine-mediated killing) (IL-12)
 - **Earlier** therapy (after induction, after SCT, ? Instead of SCT)
- Cost and Availability: Off the shelf CAR T-Cells
- Insertional mutagenesis: Working on CRISPR instead of viral gene insertion
- Toxicity of CRS: Pre-emptive anti-IL-6 mAb infusion with rise of CRP or ferritin?



Venetoclax/Carfilzomib/Dex in R/R MM

A Phase II Trial of Venetoclax, Carfilzomib, and Dexamethasone for Relapsed/Refractory Myeloma

- **VenKd** associated with no new safety signals in patients with R/R MM^[1]
- Investigators selected carfilzomib at 70 mg/m² once weekly for combo
- Preliminary data suggest VenKd active in R/R MM (ORR: 83%)^[1]
 - **Highest ORR observed in subgroup with t(11;14)**
 - ORR similar for patients with high-risk vs standard-risk cytogenetics
- Investigators concluded that interim results suggest VenKd well tolerated and with promising efficacy, justifying ongoing study in R/R MM^[1]

1. Costa LJ, et al. ASCO 2018. Abstract 8004. 2. Berenson JR, et al. Blood. 2016;127:3360-3368. 3. Moreau P, et al. Blood. 2017;130:2392-2400.



Conclusions



- **No new MM drugs approved for 4 decades from the 60's until 2000s but 10 approved since then**
- **Survival is Improving in Myeloma with combinations of Novel Agents (triple therapy), Auto SCT, and maintenance therapy over the past decade**
- **Adding Antibodies may allow deeper responses up front without much added toxicity of 4 drug regimens**
- **Although we have effective therapies, all MM pts relapse and become refractory to all therapies, so we need more**
- **Combinations of these new drugs can often make Myeloma a controllable chronic disease but ongoing studies using immunotherapy (Up front Darzalex and CAR-T) may be approaching a cure**



Polling question #2



I find that these Webinars are:

- A. Helpful to stay up to date on Emerging Treatment Options
- B. Too complicated to be useful



Questions?



We have seen many changes in therapy of Myeloma over the past few years and many more are expected to come!



#WeightWatchers, Walking, and jogging
#73 pounds down so far



Emerging Therapies for Multiple Myeloma



Q&A Session

Ask a question by phone:

- Press star (*) then the number 1 on your keypad.

Ask a question by web:

- Click green "Q&A" box in lower left corner
- Type your question
- Click "Submit"

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.



The Leukemia & Lymphoma Society Offers:

- **Information Specialists:** Master's level oncology professionals available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.

➤ **TOLL-FREE PHONE:** 1-800-955-4572

➤ **EMAIL:** infocenter@LLS.org



- **Free Education Booklets:**

➤ www.LLS.org/booklets

- **Free Telephone/Web Programs:**

➤ www.LLS.org/programs

- **Live, weekly Online Chats:**

➤ www.LLS.org/chat



The Leukemia & Lymphoma Society Offers:

- **LLS Podcast, *The Bloodline with LLS*:** Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.LLS.org/thebloodline

- **Education Video:** Free education videos about survivorship, treatment, disease updates and other topics: www.LLS.org/educationvideos

- **Information on myeloma:** For information about myeloma, visit www.LLS.org/myeloma

- **Patti Robinson Kaufmann First Connection Program:** Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection

- **Free Nutrition Consults:** Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition

- **What to ask:** Questions to ask your treatment team: www.LLS.org/whattoask

- **Support Resources:** LLS Community, blogs, support groups, financial assistance and more: www.LLS.org/support





**THANK
YOU FOR
PARTICIPATING!**

We have one goal:
**A world without
blood cancers**



LEUKEMIA &
LYMPHOMA
SOCIETY