# IMMUNOTHERAPEUTIC INTERVENTION INTO MYELOMA THERAPY

**Yi Lin, MD, PhD**
*Consultant*, Department of Internal Medicine
*Consultant*, Department of Laboratory Medicine and Pathology
*Associate Professor*, Medicine
Mayo Clinic Division of Hematology, Rochester, MN
*Chair*, Cell Therapy Cross-Disciplinary Group
Mayo Clinic Cancer Center

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# Disclosures

**Yi Lin, MD, PhD,** has affiliations with BlueBird Bio, Celgene, Kite/Gilead, Merck, Takeda (*Principle Investigator of Clinical Trials*); Janssen (*Laboratory Research*); Sorrento (*DSMB Member*); Celgene, JUNO, Kite/Gilead, Novartis (*Advisory Board*).

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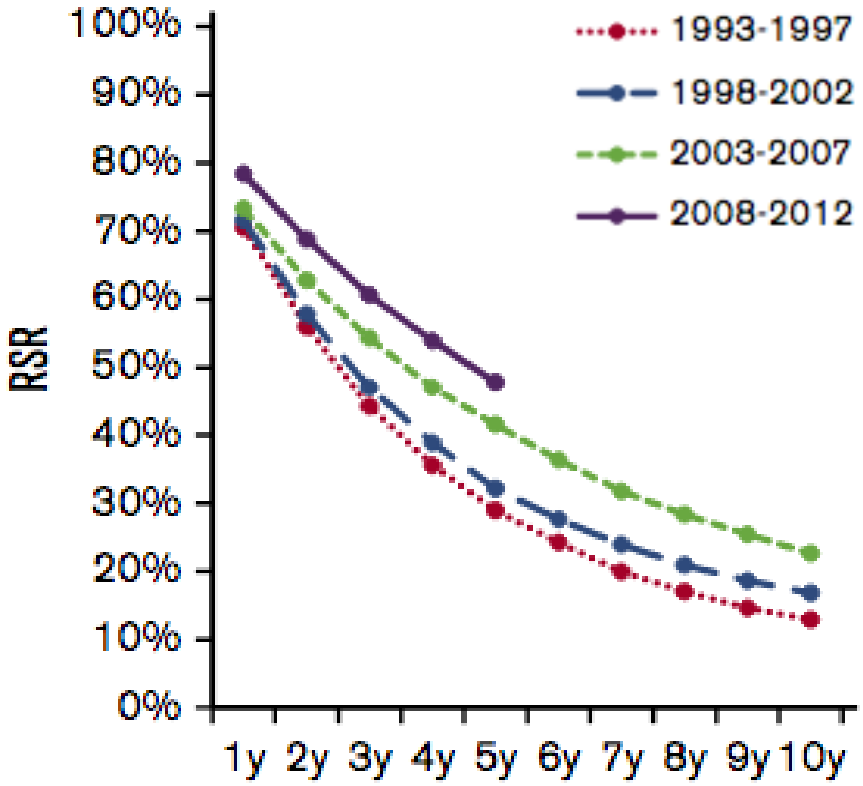
# Multiple Myeloma

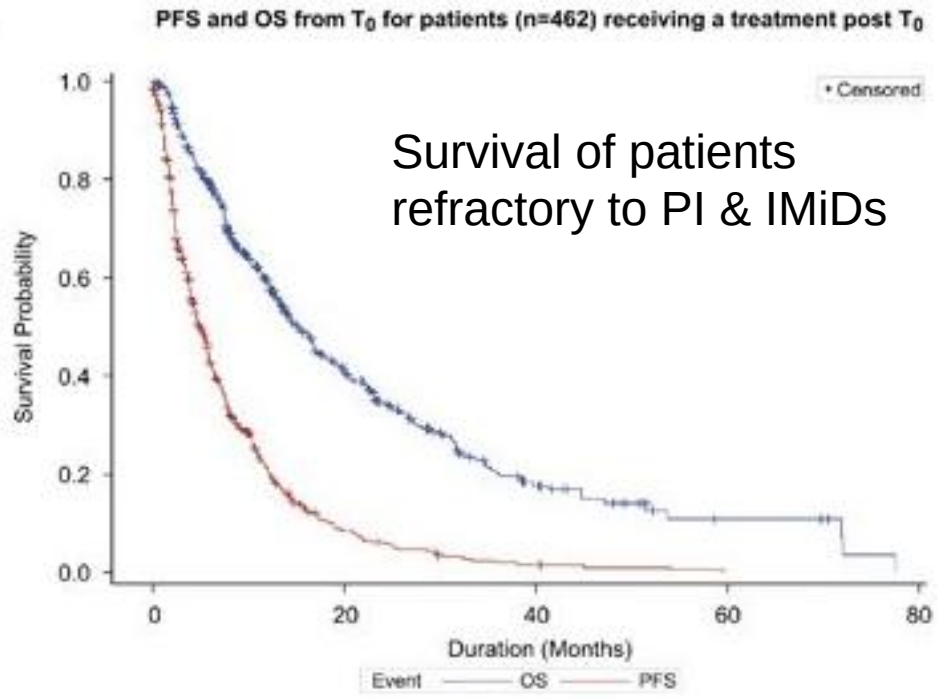
- Cancer of the plasma cells
- Major advances in treatments and improved survival but no cure




RSR = relative survival rate

Costa LJ, et al. *Blood Adv*. 2017;1(4):282-287.

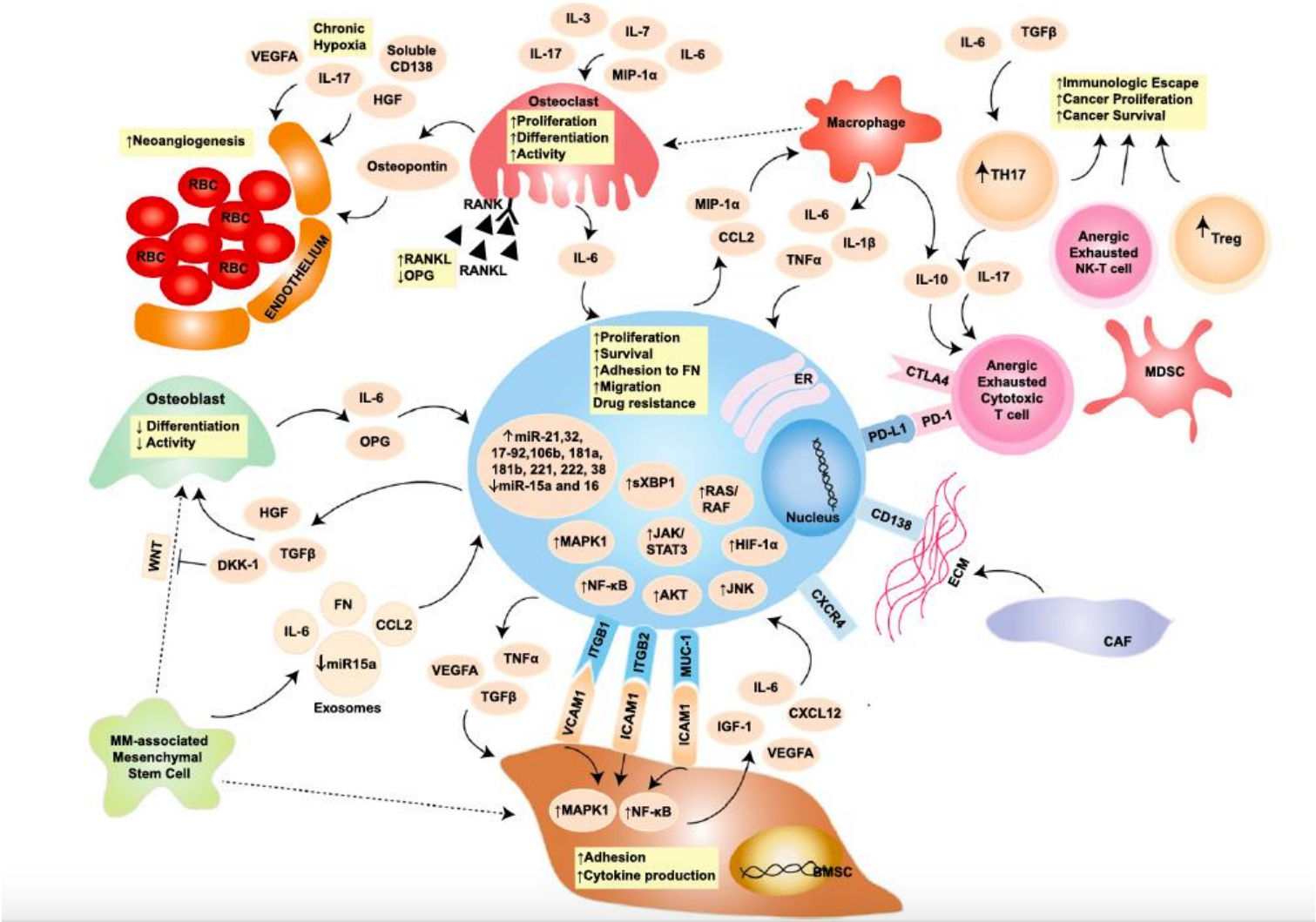
- Backbones of current therapy
  - Proteasome inhibitors (PI), IMiDs, and mAbs
- Survival remains poor for:
  - Disease with high-risk cytogenetics
  - Multi-drug refractory disease




Survival of patients refractory to PI & IMiDs

Kumar SK, et al. *Leukemia*. 2017;31(11):2443-2448.

# Myeloma Immune Landscape




Bianchi G, et al. *Blood.* 2015;125(20):3049-3058.

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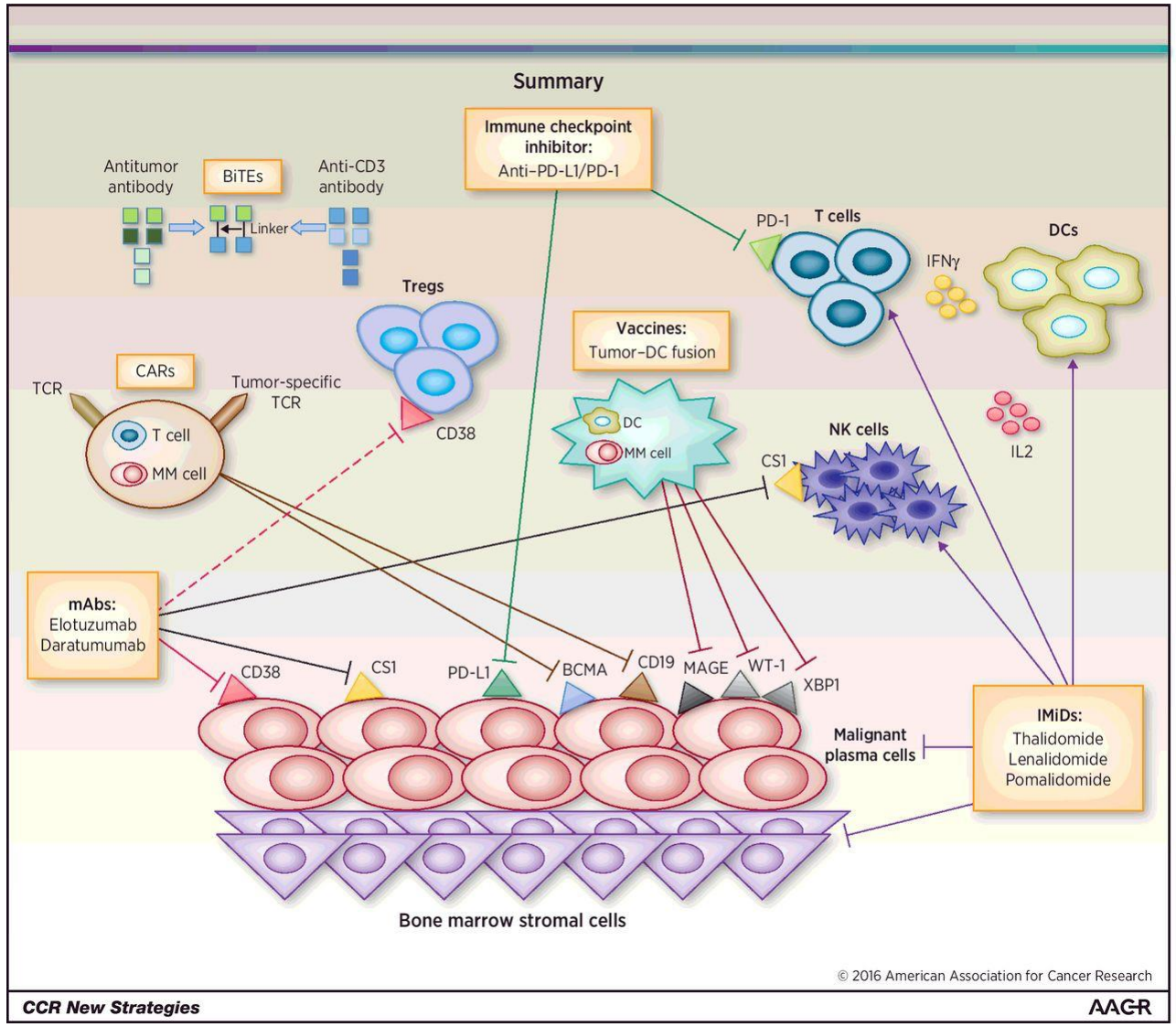
# Immune Therapy Strategies in Myeloma




| Reverses Immune Paralysis | Targets Malignant Clones | Activates Immune Cells |
|---|---|---|
| IMiDs | Monoclonal Antibodies (mAb) | Bispecific Antibodies |
| Immune Checkpoint Inhibitors | Antibody Drug Conjugates (ADC) | Cellular Therapies |

Neri P, et al. *Clin Cancer Res*. 2016;22(24):5959-5965.

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# Monoclonal Antibodies for Myeloma

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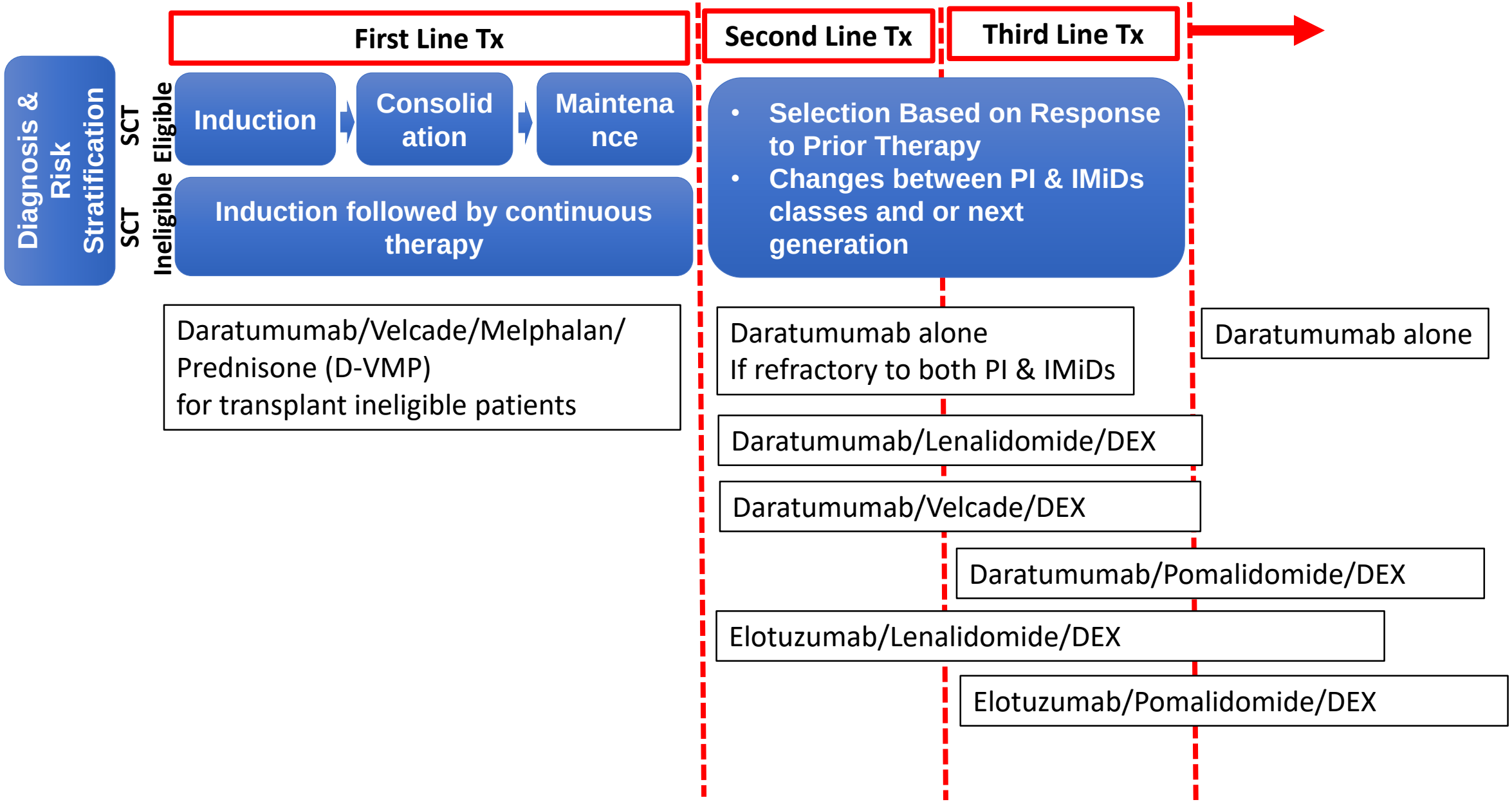
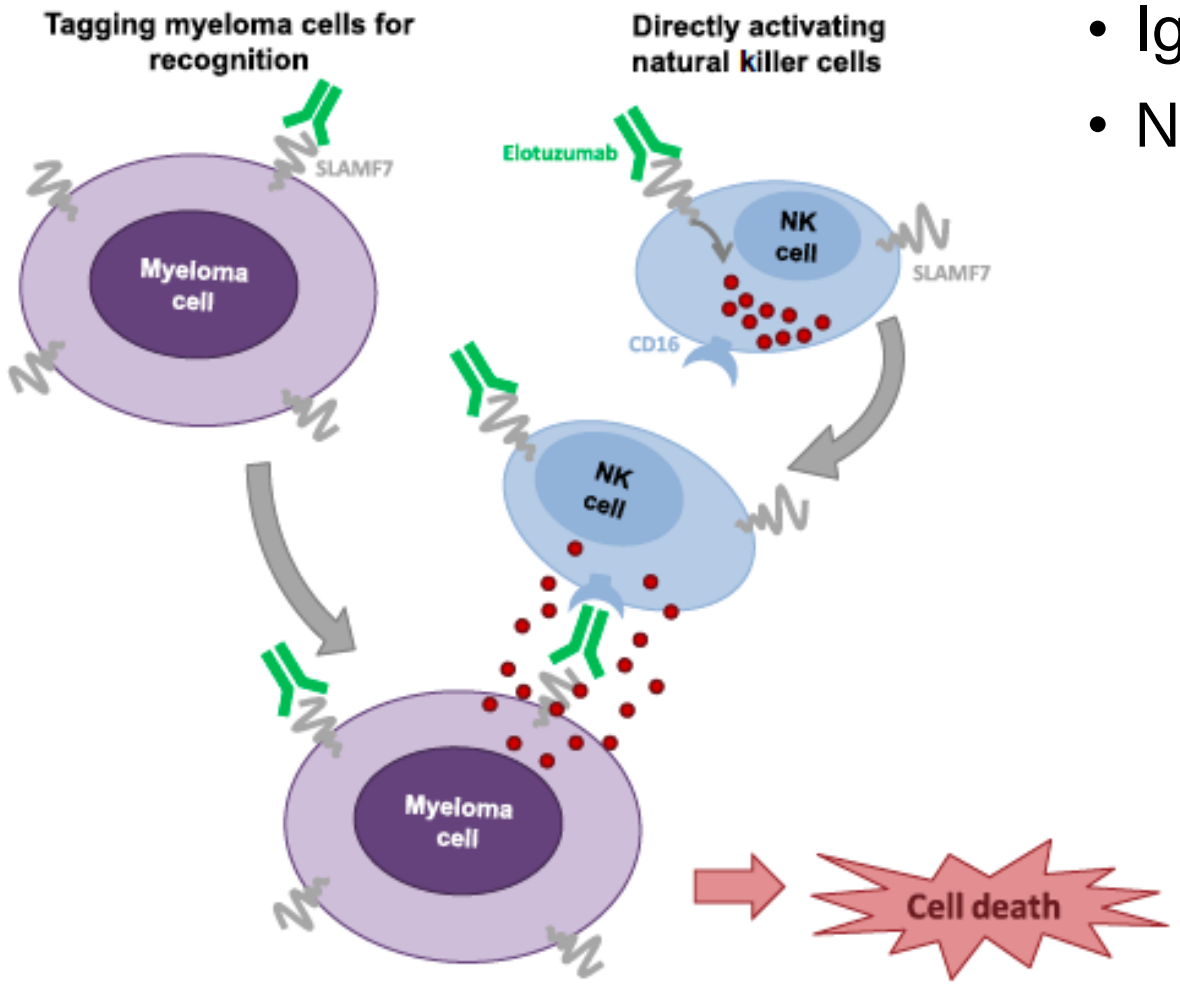
# Current Treatment Paradigm



# Elotuzumab: Mechanism of Action




- IgG1κ mAb against CS-1/SLAMF7
- No activity as a single agent[1]


1. Zonder JA, et al. *Blood*. 2012;120(3):552-559.
2. Verga C, et al. *Br J Haematol*. 2018;181(4):447-459.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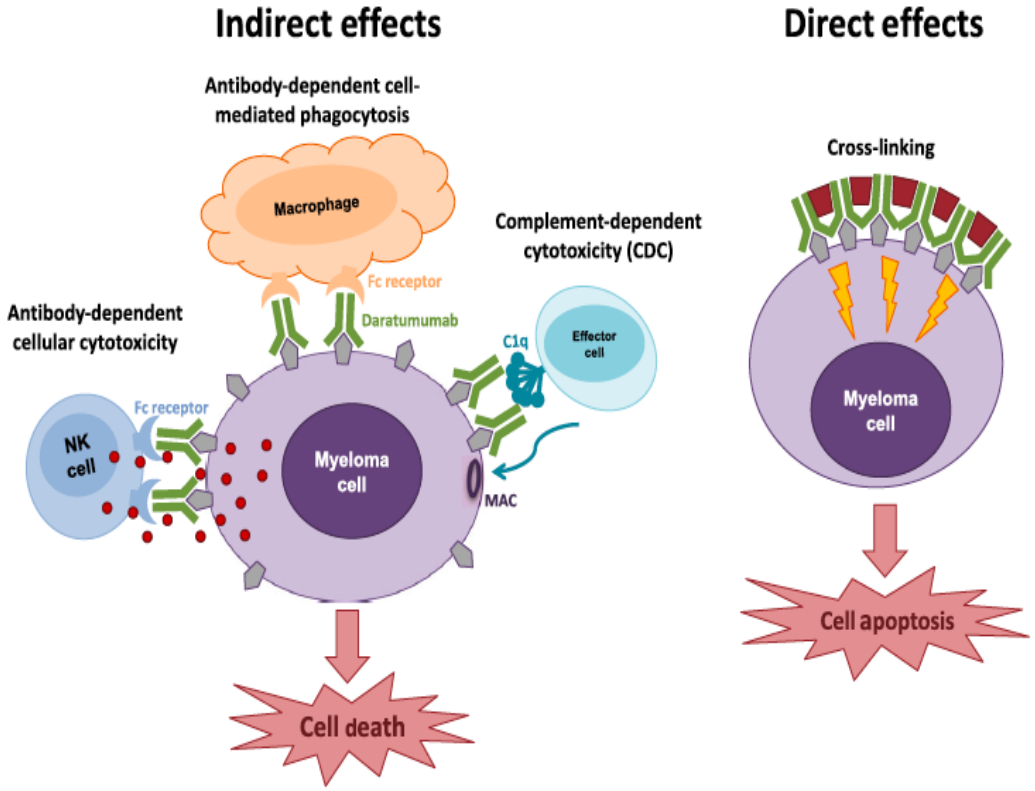
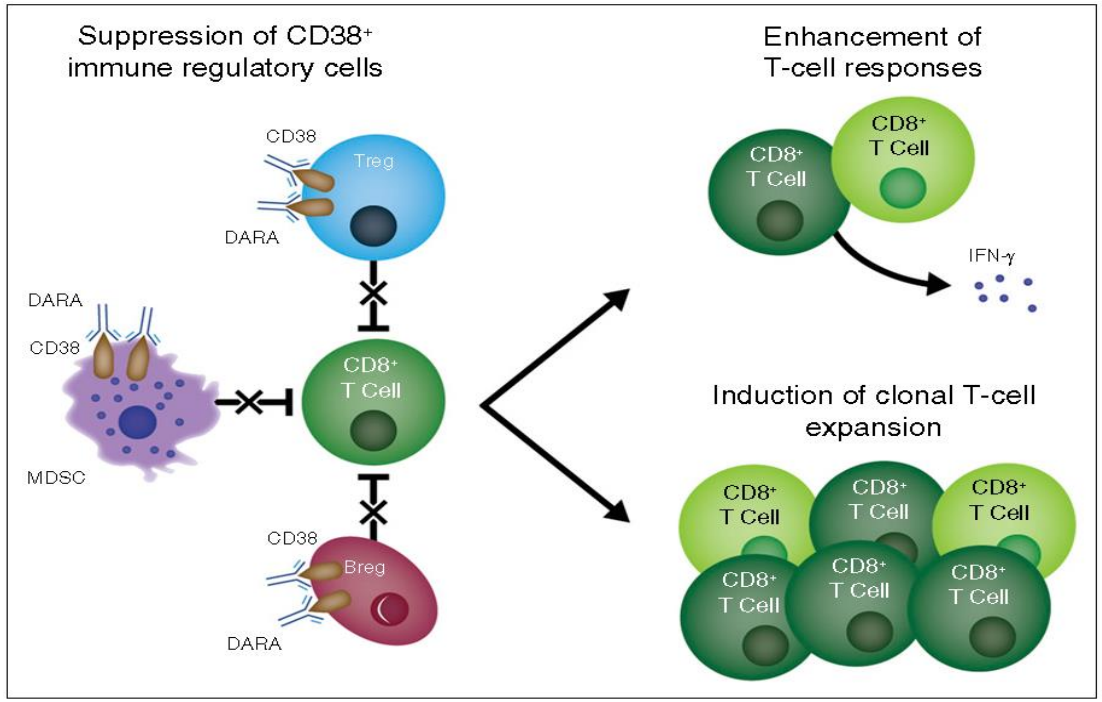
# Daratumumab: Mechanism of Action

- IgG1κ mAb against CD38; Direct & indirect effects of plasma cells
- Depletes CD-38+ immunosuppressive cells (T-regs, B-regs, and myeloid derived suppressor cells)
- Promotes T-cell expansion and activation
- Suppress monocytes conversion to osteoclasts

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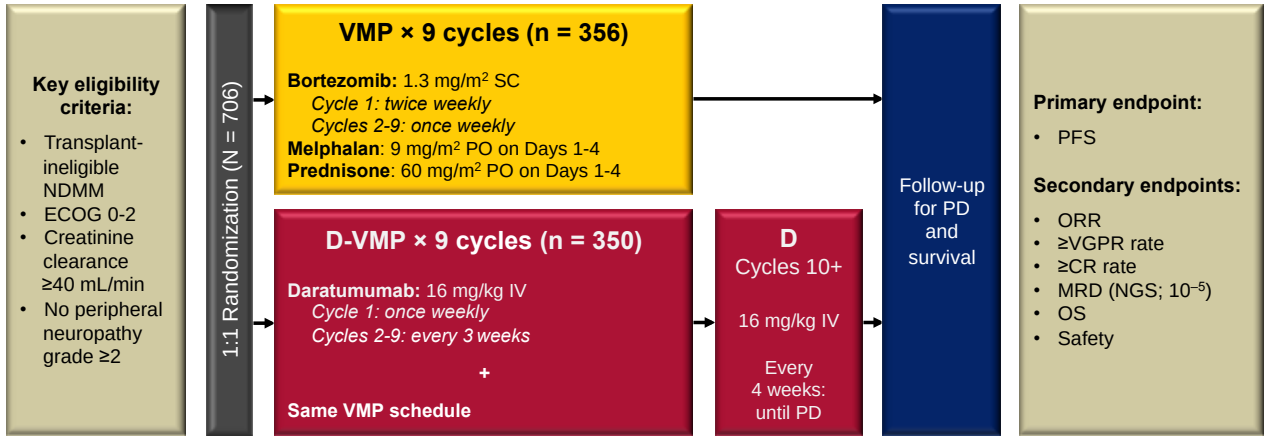
Verga C, et al. *Br J Haematol*. 2018;181(4):447-459; Krejcik J, et al. *Blood*. 2016;128(3):384-394; Costa F, et al. *Oncotarget*. 2017;8(34):56598-56611.

# FDA Approved Indication for mAb in Newly Diagnosed Myeloma



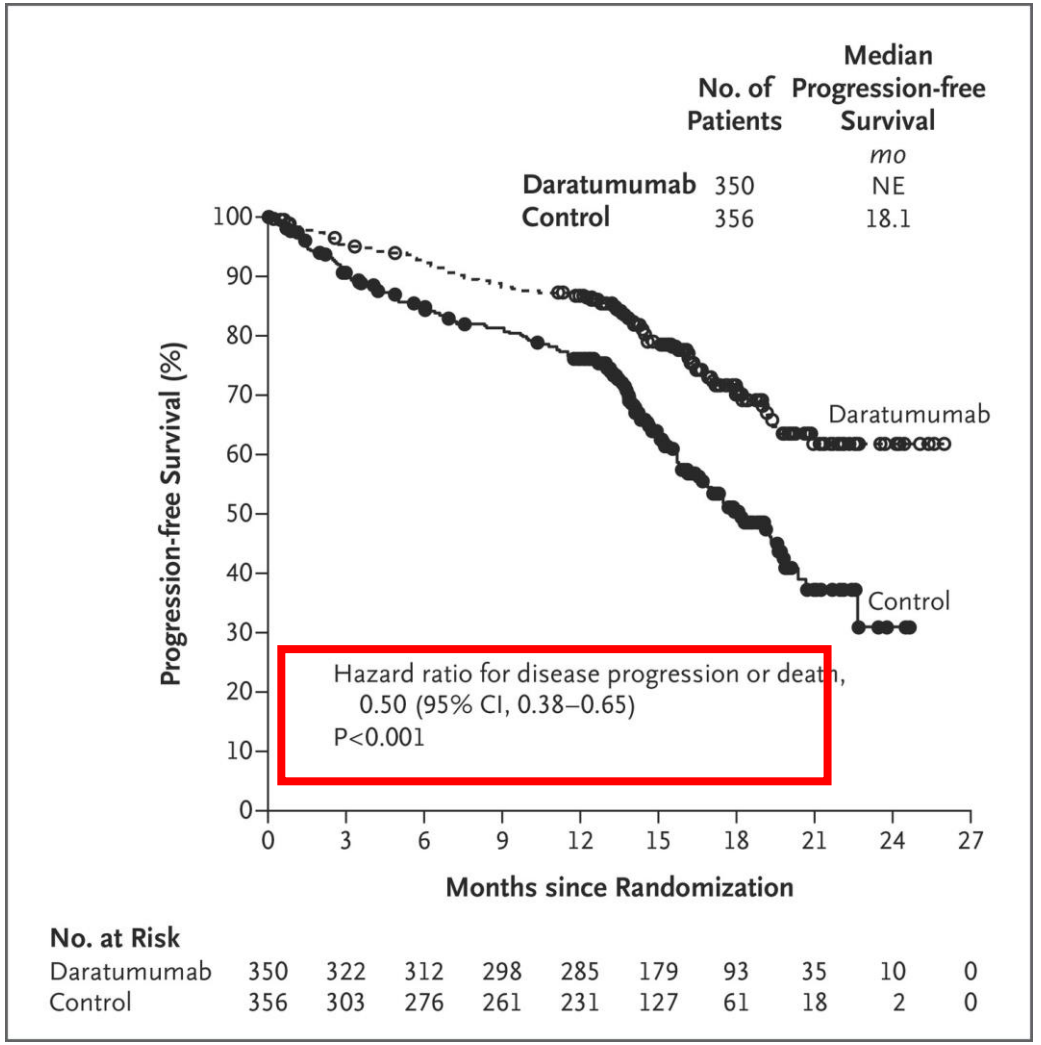

**Stratification factors**
- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

**Statistical analyses**
- 360 PFS events: 85% power for 8-month PFS improvement[a]
- Interim analysis: ~216 PFS events

Mateos et al. ASH 2017.

| | Dara – VMP (n=350) | VMP (n=356) | *P* value |
|---|---|---|---|
| **ORR** No, % (95% CI) | 318, 90.9% (87.3 to 93.7) | 263, 73.9% (69 to 78.4) | <.001 |
| **sCR/CR** No, % | 149 (42.6%) | 87 (24.4%) | <.001 |
| **VGPR or better** No, % | 249 (71.1%) | 177 (49.7%) | <.001 |




Mateos MV, et al. *N Engl J Med.* 2018;378(6):518-528.

# FDA Approved mAb Indications

| | Elo-Rd[1] | Elo-Pd[2] | Dara[3,4] | DRd[5, 6] | DVd[7, 8] | DPd[9] |
|---|---|---|---|---|---|---|
| FDA Indications | 1-3 prior therapies | ≥ 2 prior therapies | ≥3 therapies or double refractory | ≥1 line of therapy | ≥1 line of therapy | ≥2 line of therapy |
| Study populations | Len-sensitive or naïve population | Len/PI relapsed/refractory Pom naive | Exposure to multiple IMiDs/PI | Len sensitive | Vel sensitive | Dara/Pom naive |
| Response Rate | ORR 79% (vs 66% Rd) ≥CR 4% (vs 7% Rd) | ORR 53.3% (vs 26.3% Pd) | ORR 31% | ORR 93% (vs 76% Rd) ≥CR 55% (vs 23% Rd) | ORR 83% (vs 63% Vd) ≥CR 19% (vs 9% Vd) | ORR 66% ≥CR 22% |
| PFS HR (95% CI) | 0.71 (0.59 – 0.86) | 0.54 (0.34 – 0.86) | | 0.51 (0.38 – 0.67) | 0.47 (0.36 – 0.63) | mPFS 9.9 mo (5.4 – 15.4 mo) |
| Cost* | Elo alone $142,080 YR1 $123,136 >YR1 | | Dara alone $117,000 YR1 $70,200 >YR1 | | | |

*** Estimated cost based on wholesale drug cost for an average weight person.**


1. Lonial S et al. N Engl J Med 2015;373:621. 2. Dimopoulos et al. EHA 2018, Abstr LB2606. 3. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219. 4. Lonial S, et al. *Lancet*. 2016; 387:1551-1560. 5. Dimopoulos MA et al. NEJM 2016; 375:1319-31. 6. Dimopoulos MA, et al. ASH 2017. Abstract 739. 7. Palumbo A et al. N Engl J Med 2016;375:754-766. 8. Lentzsch et al. ASH 2017. Abstract 1852. 9. Fancon T et al. Blood 2017. Abstr 1824.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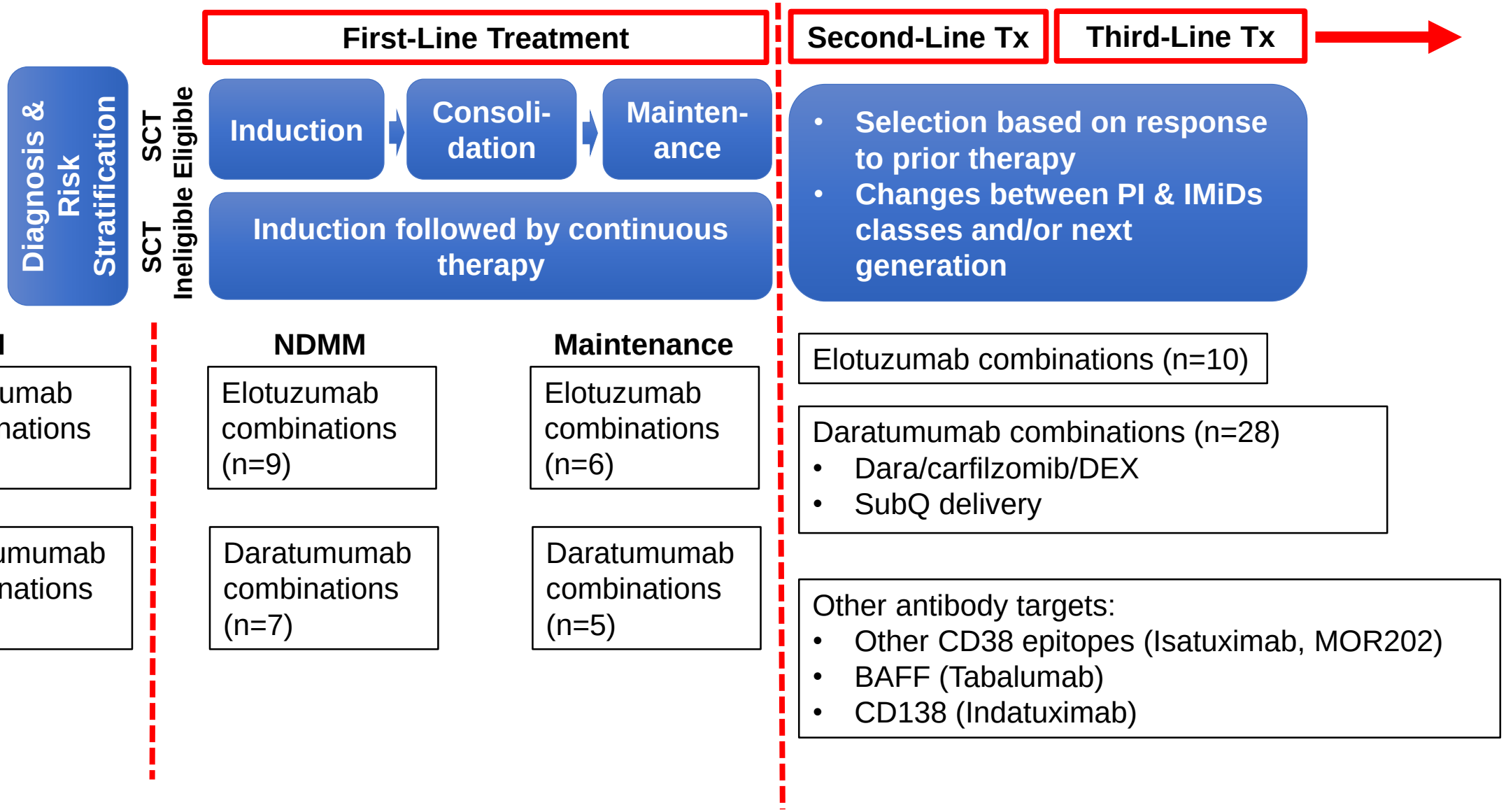
# mAb Ongoing Investigations

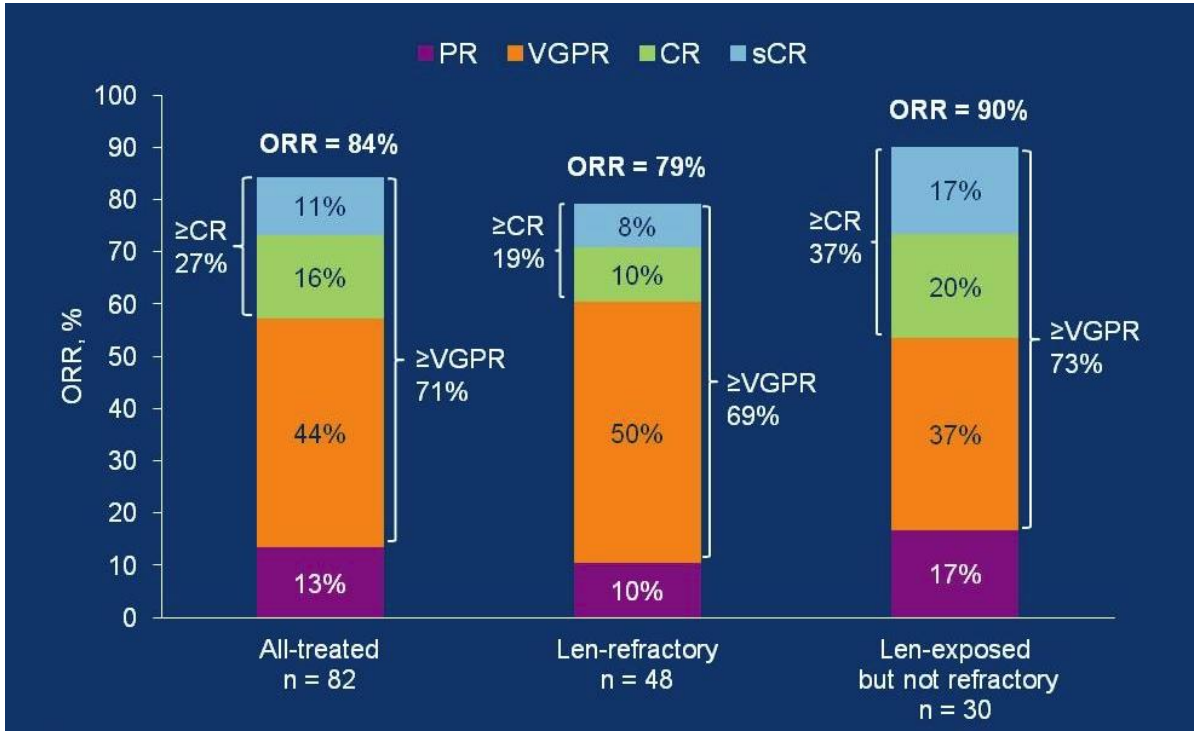


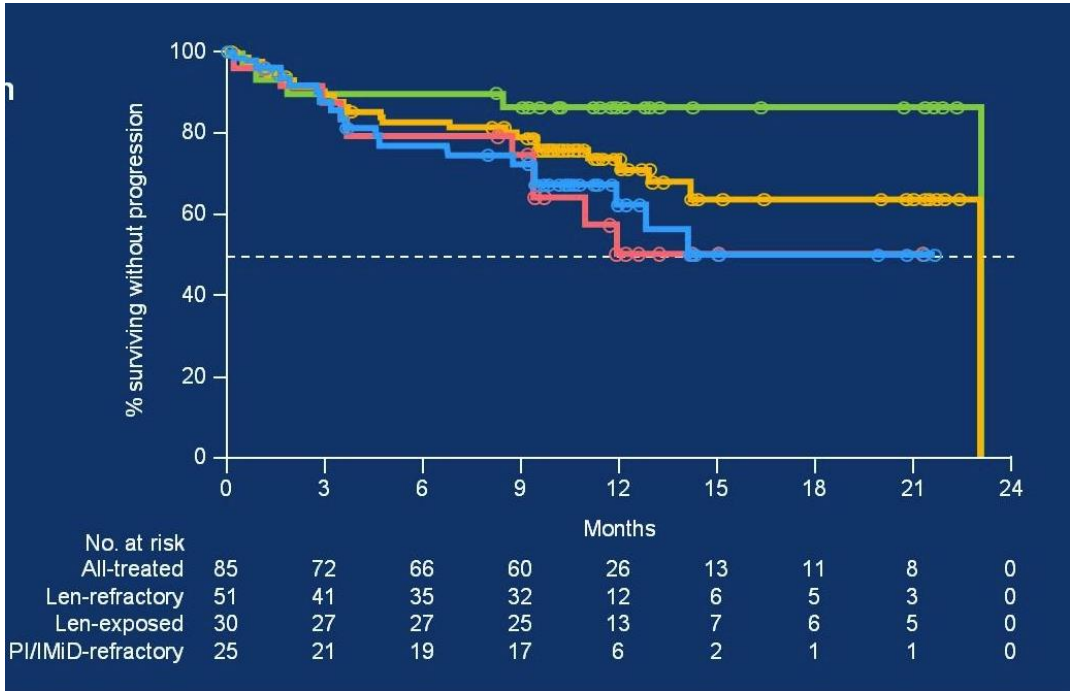
# Dara – Carfilzomib/DEX

- Prior 1 to 3 lines of therapy
- Lenalidomide refractory allowed
- Carfilzomib naïve

- Median follow-up: 12.0 months

| | Median PFS, mo | 12-month PFS, % |
|---|---|---|
| All-treated | NE | 71% |
| Len-exposed but not refractory | NE | 87% |
| Len-refractory | 14.1 (95% CI, 12.0-NE) | 62% |
| PI/IMiD-refractory | NE (95% CI, 9.4-NE) | 51% |




Chari A, et al. Presented at ASCO 2018. Hematologic Malignancies – Plasma Cell Dyscrasia [abstract 8002].

# mAb Landscape

- Clear clinical activities
- Being tested more prevalently across spectrum of early-to-late disease state
- Advances in administration and monitoring of this therapy modality
- Monitor for long-term outcome
  - Immune suppression related toxicities
  - Secondary malignancies
- Unanswered questions
  - Role for sequencing same Ab targets with different epitopes & different mAbs
  - Optimal mAb combination with other myeloma drugs

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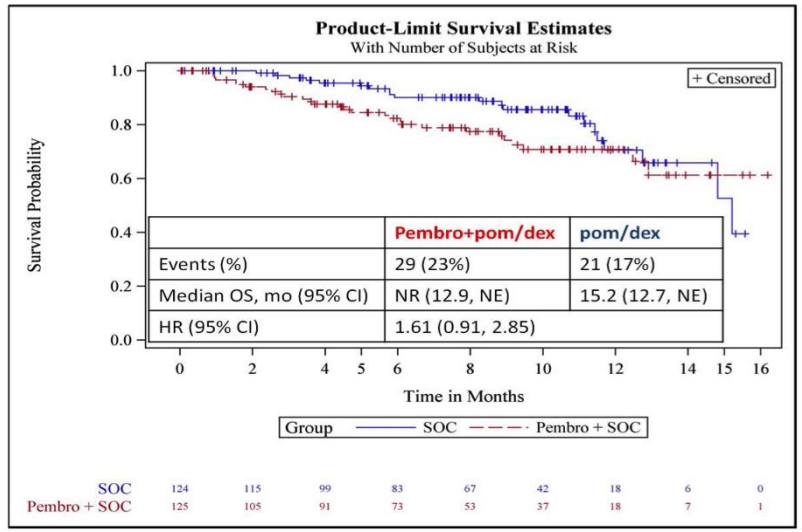
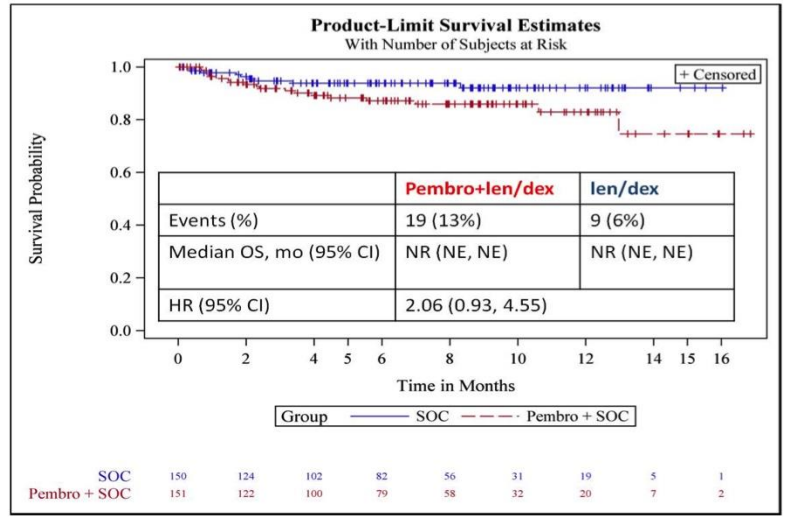
# Checkpoint Inhibitors in Myeloma

- No activities as a single agent (Nivolumab)[1]
- Combinations showing more clinical response
  - Pembro-Rd[2] & Pembro-Pd[3]
- July – Sep 2017: FDA stopped Pembro & Nivo based combination trials in RRMM due to increased risk of deaths
- Cautious restart of Nivo-based combos in Dec 2017
  - Checkmate-309: Nivo + Dara ± Pom/DEX
  - CA204142: Elo/Pom vs Elo/Nivo
- Other approaches
  - CD47/SIRP1-a
  - Lirilumab





1. Lesokhin AM, et al. *J Clin Oncol*. 2016;34(23):2698-2704.
2. San Miguel J, et al. Presented at the 57th American Society of Hematology Annual Meeting; December 5-8, 2015. Orlando, FL; Abstract 505.
3. Badros A, et al. *Blood*. 2017;130(10):1189-1197.
4. Krauss. Presented at ASCO 2018.

# Cell Therapy Approaches in Myeloma

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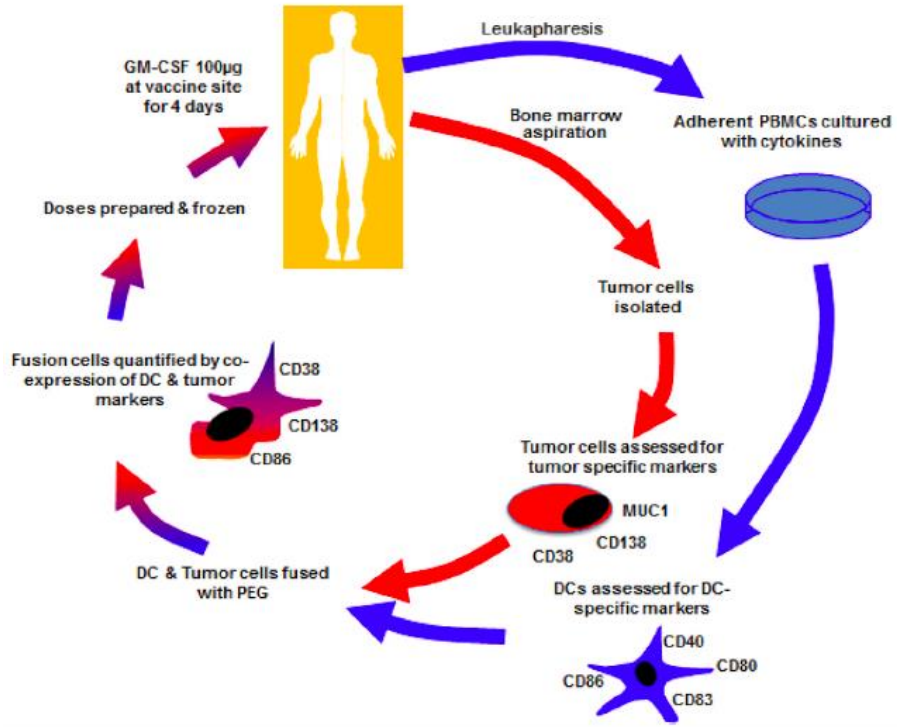
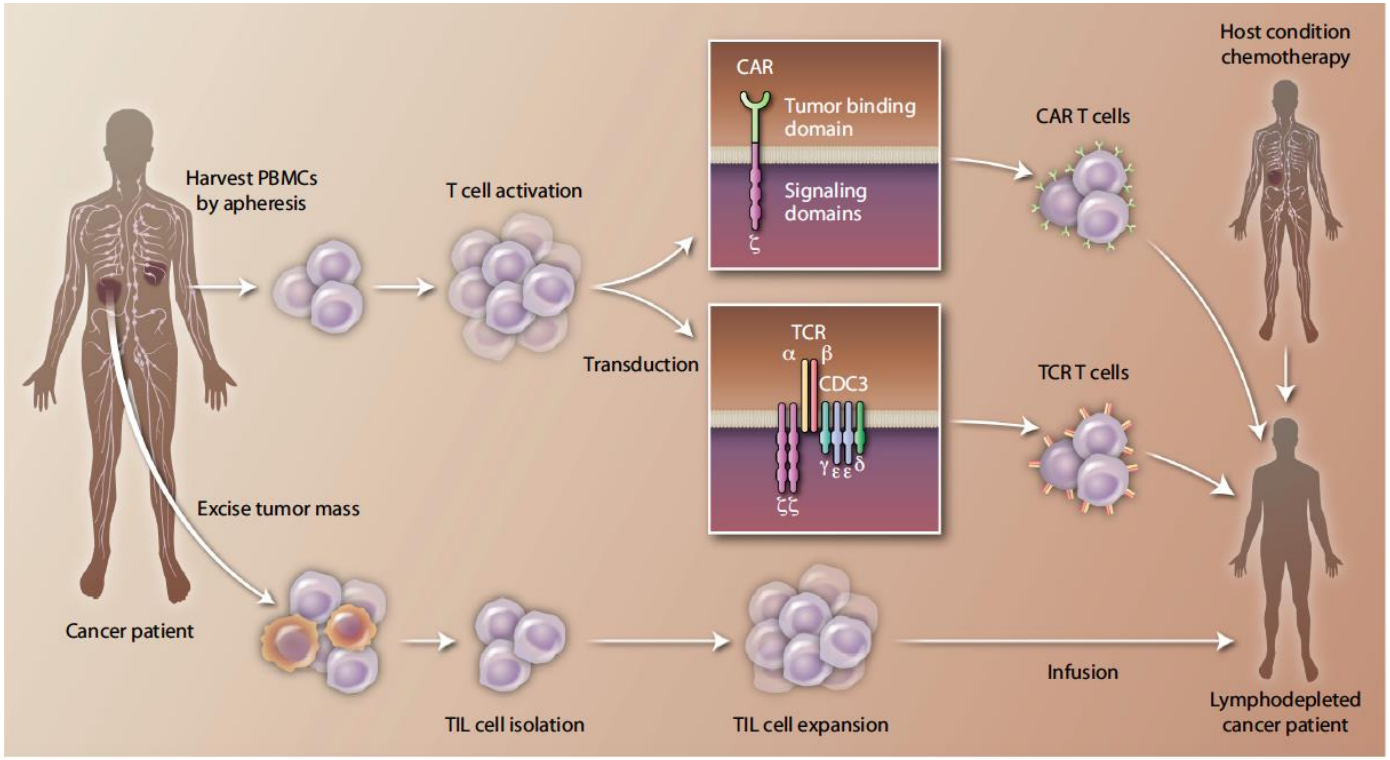
# Individualized Cellular Manufacturing

## Dendritic Vaccine




## Adoptive Cell Therapy

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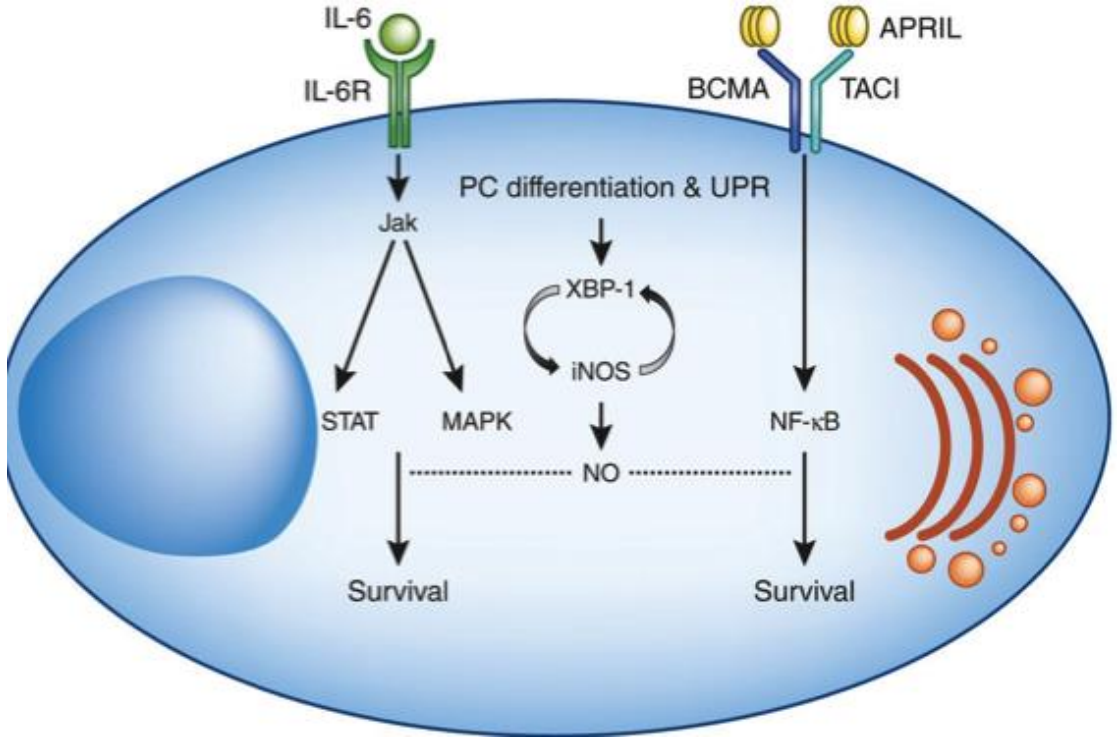
Weinstock M, et al. *Mol Ther Methods Clin Dev*. 2017;5:66-75; June CH, et al. *Sci Transl Med*. 2015;7(280):280ps7.

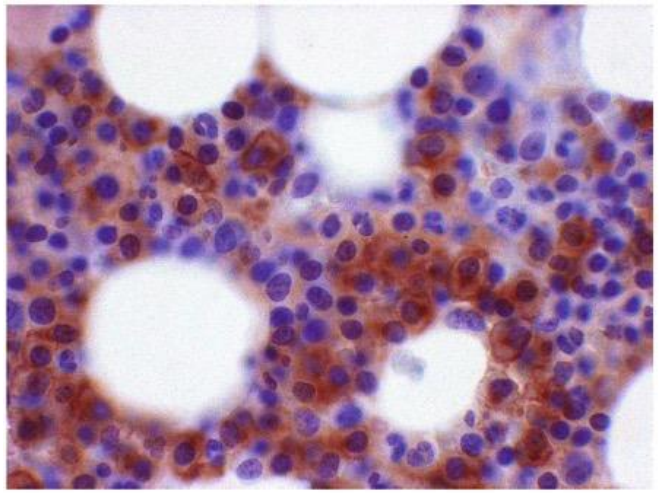
| Approach | Type of Therapy | Tumor Target | Cell Source | Activities | Ref |
|---|---|---|---|---|---|
| Vaccine | Dendritic Cells | Idiotype; mRNA; Fused myeloma cells | Auto | • N=131 across 6 trials<br>• IV/SQ administration<br>• SD to 47% CR/nCR | Reviewed in Weinstock M, et al. *Mol Ther Methods Clin Dev*. 2017;5: 66-75. |
| Adoptive Cell Therapy | Marrow Infiltrating Lymphocytes (MIL) | Endogenous | Auto | • N=22<br>• IV post autologous SCT<br>• ORR 54% (27% CR; 27% PR)<br>• Median PFS 18 mo | Noonan KA, et al. *Sci Transl Med*. 2015; 7(288):288ra78. |
| | Natural Killer Cells (NK) | Allo/CAR | Haploidentical/ Cord Blood | • N=33, cord blood source<br>• IV pre-autologous SCT<br>• ≥VGPR 79%; CR/nCR 64%; est 3yr PFS 52% | Shah N, et al. Presented at ASCO 2018 [abstract 8006] |
| | TCR T Cells | Surface & Intracellular Antigen/Neo-Antigen | Auto<br>Need to be HLA-matched | • N=20; NY-ESO1 TCR for HLA-A0201<br>• IV post autologous SCT<br>• ORR 80% (70% CR; 10% VGPR)<br>• Median PFS 19 mo | Rapoport AP, et al. *Nat Med*. 2015;21(8):914-921. |
| | CAR-T Cells | Surface Antigen CAR | Auto | • K FLC: N=7, no activities.[1]<br>• CD19: 1 case report; ongoing study.[2,3]<br>• BCMA: Most activities. | 1. Ramos CA, et al. *J Clin Invest*. 2016; 126(7):2588-2596.<br>2. Garfall AL, et al. *N Engl J Med*. 2015; 373:1040-1047.<br>3. Garfall Al, et al. *Blood*. 2016;128:974. |

# BCMA is a Promising Target

B-cell maturation antigen (BCMA) is member of the TNF receptor superfamily

- Expressed nearly universally on multiple myeloma cells
- Expression largely restricted to plasma cells and some mature B cells
- Plays critical role in plasma cell survival



BCMA Expression on myeloma cells
(brown color = BCMA protein)

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Njau MN, et al. *Nat Immunol*. 2014;15(3):219-221.

# BCMA CAR-T Trial Treatments

| | NCI | UPenn | bb2121 (BlueBird Bio/Celgene) | LCAR-B38M (Nanjing Legend) |
|---|---|---|---|---|
| NCT # | Phase I<br>NCT02215967 | Phase I<br>NCT02546167 | Phase I<br>NCT02658929 | Phase I/II<br>NCT03090659 |
| CAR construct | mBCMA scFv<br>CD28 | hBCMA scFv<br>41BB | mBCMA scFv<br>41BB | VHH-bi-epitope<br>BCMA<br>41BB |
| Myeloma BCMA expression | Positive | Any | ≥50% (dose esc.)<br>Any (expansion) | ≥50% |
| Lympho-depletion chemo | Fludarabine/Cytoxan<br>Day -5, -4, -3 | None (Cohort 1)<br>Cytoxan (Cohort 2, 3) | Fludarabine/Cytoxan<br>Day -5, -4, -3 | Cytoxan<br>Day -5, -4, -3 |
| Dosing schedule | Day 0 | Day 0, 1, 2 | Day 0 | Day 0, 2, 6 |
| CAR-T doses | 0.3 – 9x10^6 /kg | 10 – 500 x 10^6 fixed dose | 50 – 800 x 10^6 fixed dose | 1.5 – 7 x 10^6 /kg |

# BCMA CAR-T Trial Demographics

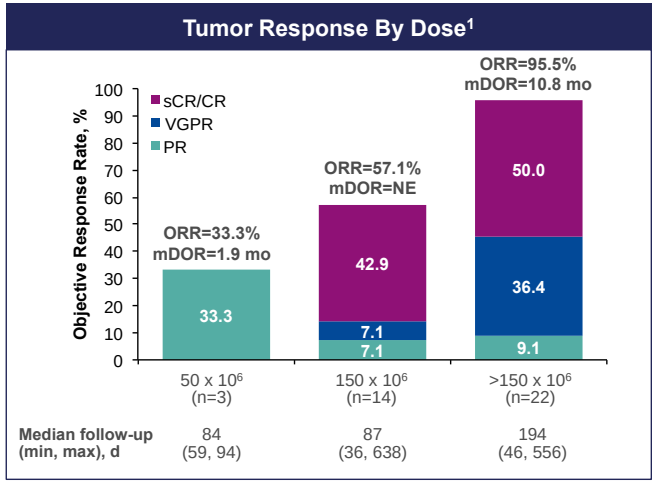
| | NCI | UPenn | bb2121 ASCO 2018 | LCAR-B38M EHA 2017 |
|---|---|---|---|---|
| Patient dosed | 16 expansion cohort at 9 x 10^6/kg (24 total) | 24 | 43 | 40 |
| Age | | 58 (44 to 75) | 58 (37 to 74) | 55 (43 to 72) |
| Male | | 16 (67%) | 26 (62%) | 19 (54%) |
| High-risk cytogenetics | 11 (69%) | 23 (96%) | 17 (40%) | 2 of 8 tested has 17p del |
| Prior lines of therapy | 9.5 (3 to 19) | 7 (3 to 13) | 7 (3 to 14) | 3 to 4 (86%); ≥5 (14%) |
| Prior ASCT | | 22 (92%) | 43 (100%) | 4 (11%) |
| Dual/Penta refractory (%) | | 96/42 | 65/30 | |

# BCMA CAR-T Trial Results

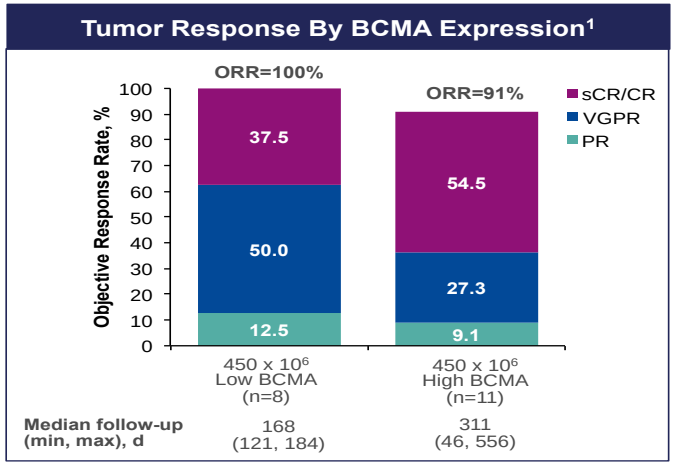
| | NCI | UPenn | bb2121 (BlueBird Bio/Celgene) | LCAR-B38M (Nanjing Legend) |
|---|---|---|---|---|
| Source | Brudno JN, et al. *J Clin Oncol*. 2018;36(22):2267-2280. | Phase I Interim Analysis ASH 2017 | Phase 1 Interim Analysis ASCO 2018 | China Immuno-Oncology Conference June 2018 |
| Enrollment | 16 highest dose | 28 (24 evaluable) | 43 (39 evaluable) | 74 (40 evaluable) |
| Efficacy | **ORR 13 (81%)**<br>sCR 2, VGPR 9<br>Median EFS 31 weeks | **ORR 11 (46%)**<br>CR/sCR 2, VGPR 3 | **ORR 30 (77%)**<br>CR/scR 17, VGPR 9<br>**Median PFS 11.8 mo** | **ORR 37 (92.5%)**<br>CR/sCR 23, VGPR 12<br>3 of 4 pts > 2 yrs post Tx remains in response |
| Safety | • Any CRS: 15 (94%)<br>• ≥Gr 3 CRS: 6 (38%)<br>Adjusted enrollment criteria for BM PC<30% due to CRS | • Any CRS: 20 (83%)<br>• ≥Gr 3 CRS: 8 (33%)<br>• ≥Gr 3 NE: 3 (12.5%)<br>2 DLT: PRES, Pleural hemorrhage | • Any CRS: 27 (63%)<br>• ≥Gr 3 CRS: 2 (5%)<br>• ≥Gr 3 NE: 1 | • Any CRS:37 (91.9%)<br>• ≥Gr 3 CRS: 3 (7.5%) 1 death<br>• ≥Gr 3 NE: 0 |
| Intervention | • Toci: 5<br>• Steroid: 4 | • Toci/Silt: 6 | • Toci: 9<br>• Steroid: 4 | |

# BCMA CAR-T Clinical Activities (bb2121)

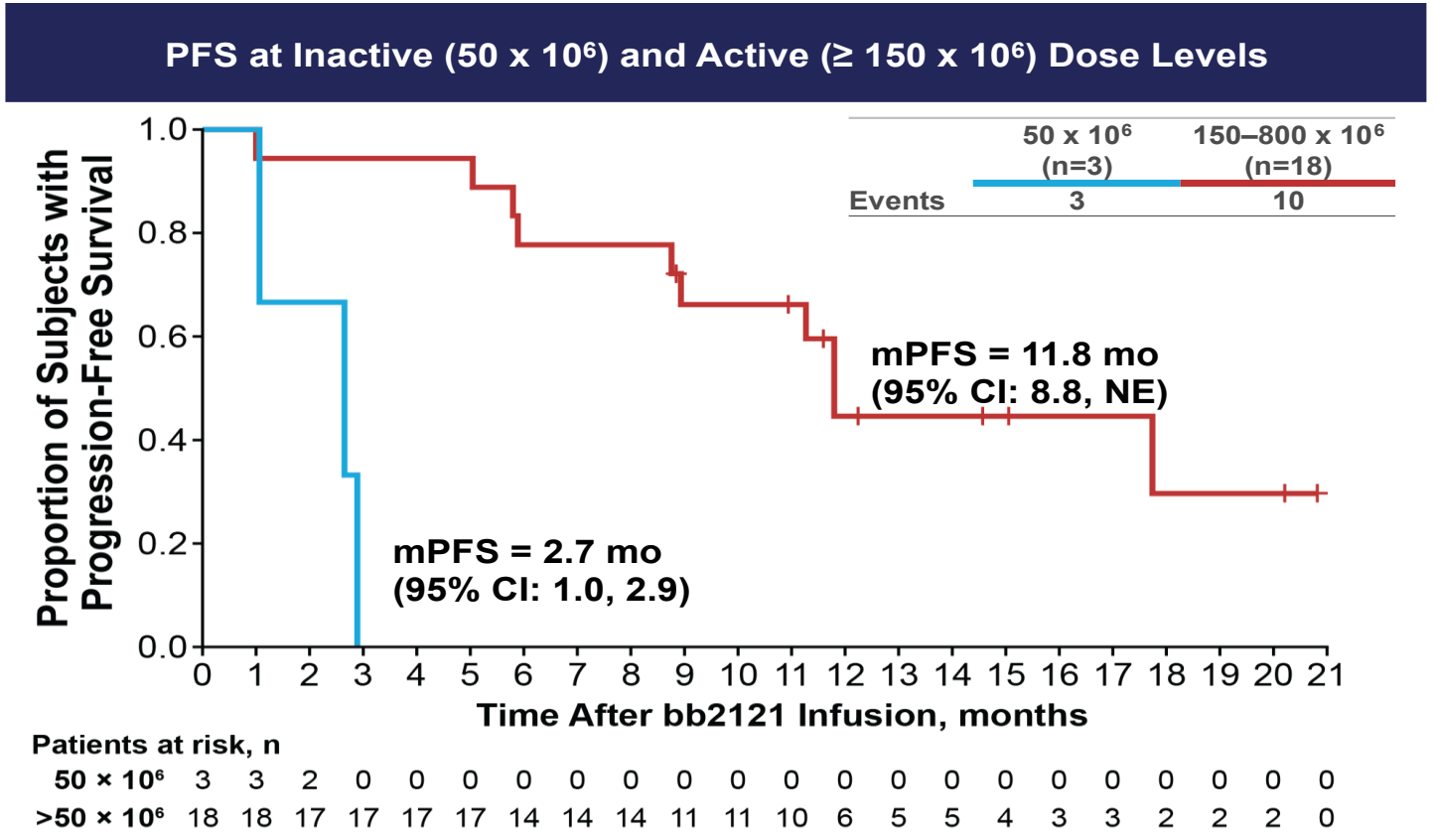
## Dose-Dependent Response




Response independent of BCMA expression at higher CAR-T Dose.




## Long-time disease control can be achieved in heavily pretreated patients.




Median and 95% CI from Kaplan-Meier estimate. NE, not estimable; mPFS, median progression free survival.

mPFS 17.7 months for patients who had at least 1 bone marrow MRDneg by NGS ($10^{-6}$, n=16).

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Raje NS, et al. Presented at ASCO 2018 [abstract 8007].

# CAR-T Ongoing Activities

- Bb2121 registration trial, KarMMa (US & Europe, Celgene, NCT03361748)
- Janssen JNJ-68284528 (Nanjing Legend CART), now open in US (NCT03548207)

- **CAR-T Composition Strategies**
  - More memory like T cell functions (bb21217, BlueBird, NCT0327419)
  - Defined CD4/CD8 ratio (Fred Hutch & JACR125, JUNO, NCT03338972, NCT03430011)
  - CD8 only (Cartesian Therapeutics, NCT03448978)
- **CAR-T Constructs**
  - CARTyrin, transposon (Poseida, NCT03288493)
  - CD28 (Kite, NCT03318861)
  - APRIL CAR (Autolus, NCT03287804)
  - BCMA mAb + Fc CART (Unum Therapeutics, NCT03266692 )
  - Numerous studies in China
- **CAR-T Combinations**
  - CART + lenalidomide (MSK, NCT03070327)

- Next generation CAR-T
  - Example: autologous CAR-T express CS1-NKG2D-DAP10[1]
- Allogeneic/Universal CAR Approaches
  - NK Cells
    - CS1-CD28 CAR expressing NK cells[2]
    - CS1-IL15-iCasp9 CAR in cord blood NK cells[3]
  - Gene-editing of CART
    - TALEN to knock out TCRa and endogenous CS1 expression on T cells transduced to expressed CS1-41BB CAR (UCARTCS1)[4]


1.Nikiforow S, et al. *Blood*. 2016;128(22):4052.
2.Chu J, et al. *Leukemia*. 2014;28(4):917-927.
3.Li L, et al. *Blood*. 2017;4454.
4.Mathur R, et al. *Blood*. 2017;130(Suppl 1):502.


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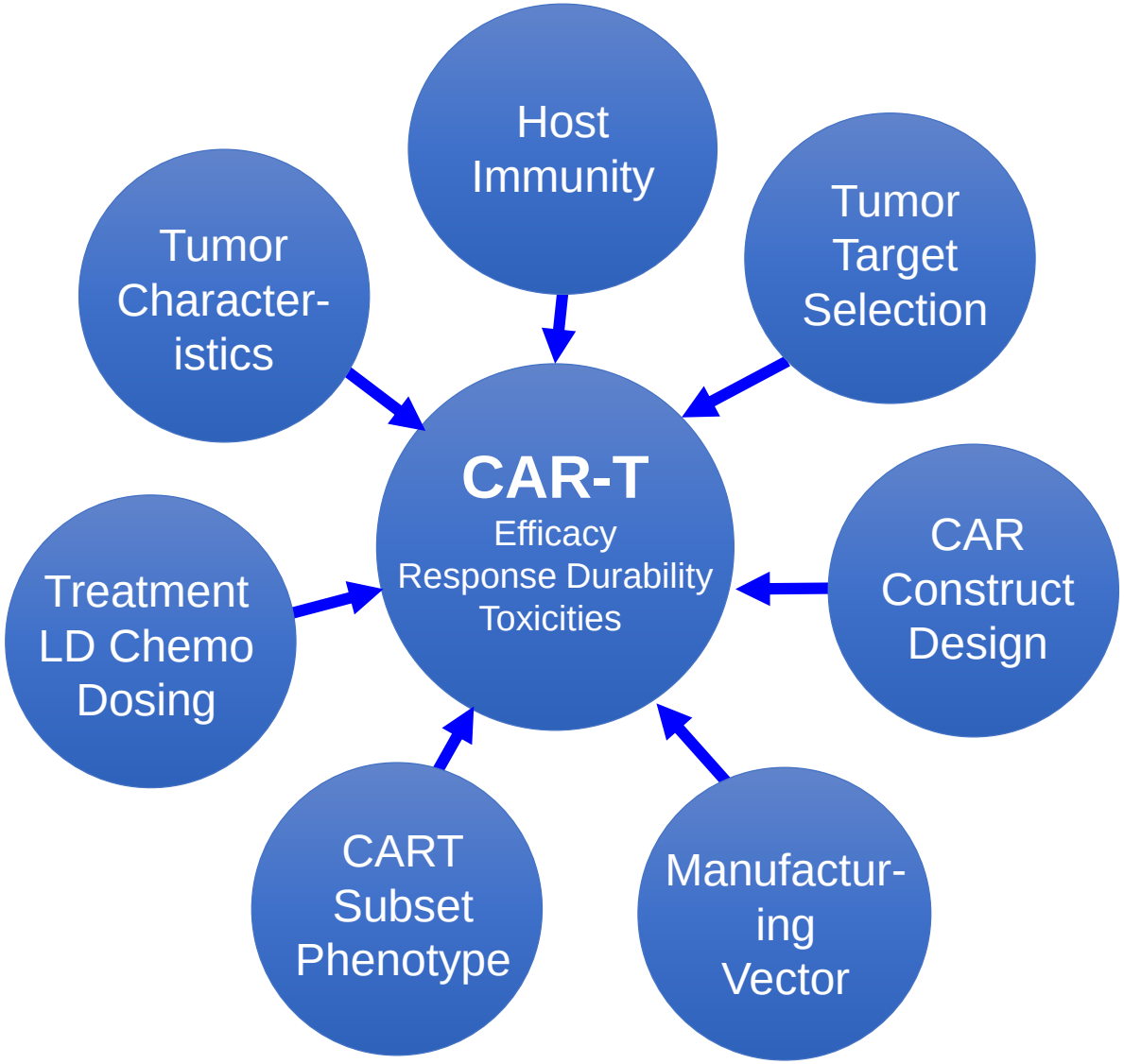
# CAR-T Future Directions




- Multi-center access is feasible
- Manufacturing feasible in heavily pretreated patients
- Clinical response exciting but varied across trial
- Unanswered questions
  - Predictors of response & toxicities
  - Optimal sequence among therapies
  - Mechanism of relapse

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# Other BCMA Targeting Approach

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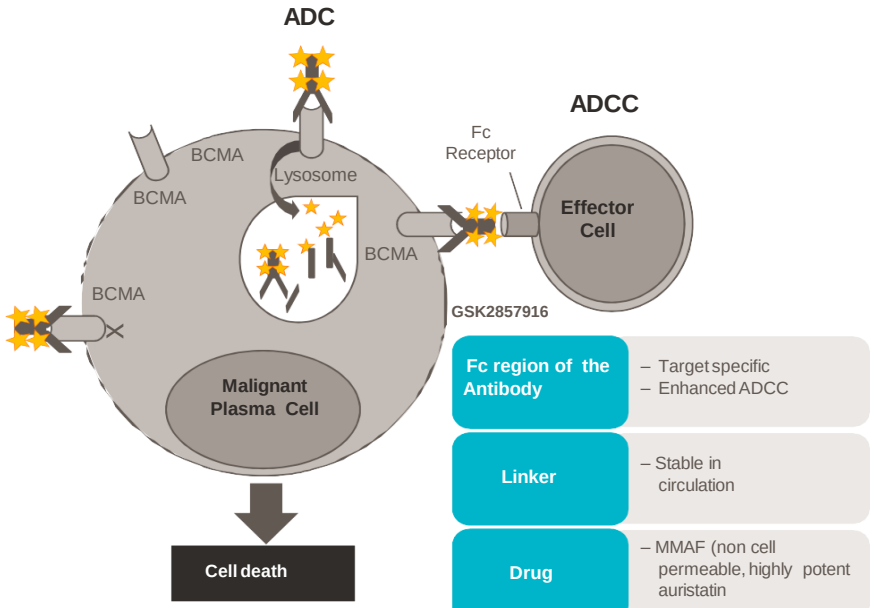
# BCMA Antibody Drug Conjugate (ADC)

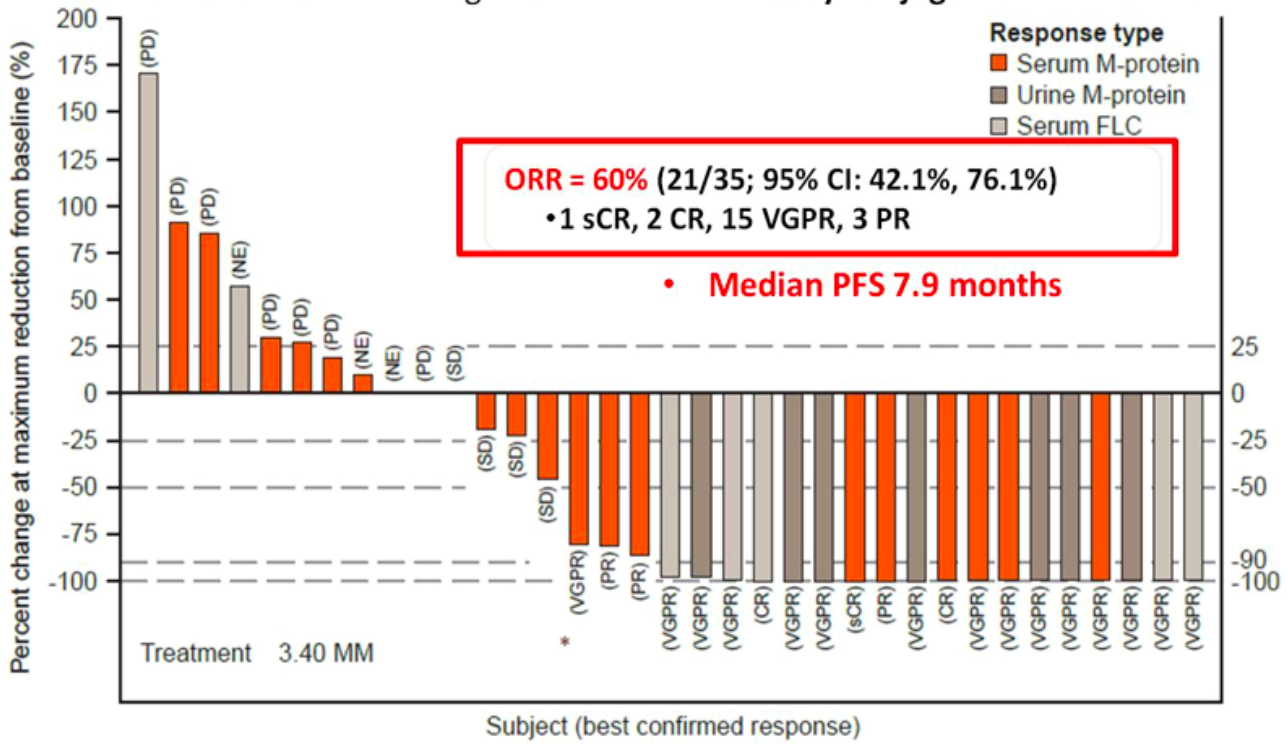



| | |
|---|---|
| **Fc region of the Antibody** | – Target specific<br>– Enhanced ADCC |
| **Linker** | – Stable in circulation |
| **Drug** | – MMAF (non cell permeable, highly potent auristatin |

**Mechanisms of Action:**

1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death
4. BCMA receptor signalling inhibition

▪**GSK2857916:** humanized IgG1 **anti-BCMA antibody conjugated with Auristatin**




*One patient with a VGPR had a <90% reduction in serum M-protein due to missing laboratory data, which was confirmed by investigators as too small to quantify after the data cut-off

CI, confidence interval; CR, complete response; FLC, free light chain; M-protein, myeloma protein; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response

Tai YT, et al. *Blood*. 2014;123(20):3128-3138; Trudel S, et al. Presented at ASH 2017 [abstract 741].

# Bispecific Antibodies

| | IgG Like | Non-IgG Like |
|---|---|---|
| Advantages | • Longer serum half-life<br>• Retained Fc function | • Better tissue penetration<br>• Better access to epitopes |
| Example | Removab (Epcam x CD3)<br>• Approved in Europe<br>• Treats malignant ascites in epcam+ carcinomas | Blinatumomab (BiTE, scFv CD19 x CD3)<br>• Approved in US and Europe<br>• Treats B-ALL |
| BCMA bispecific antibodies in myeloma | • PF-06863115 (Pfizer, NCT03269136)[1]<br>• JNJ-64007957 (DuoBody/GenMab Janssen, NCT03145181)[2]<br>• EM901 (EngMab/Celgene)[3]<br>• Bi-Fab[4] | • BI 836909 (AMG420, Amgen, NCT0251439)[5]<br>• AMG 701 (NCT03287908) |


1. Panowski SH, et al. *Blood*. 2016;128:383.
2. Pillarisetti K, et al. *Blood*. 2016;128:2116.
3. Moreno L, et al. *Blood*. 2016;128:2096.
4. Ramadoss NS, et al. *J Am Chem Soc*. 2015;137(16):5288-5291.
5. Hipp S, et al. *Leukemia*. 2017;311(8):1743-1751.

# Immunotherapy Considerations

| | Accessibility | Treatment | Toxicities |
|---|---|---|---|
| mAb | Off-the-shelf | Repeated dosing until progression | • Infusion related reactions<br>• Infections |
| ADC | Off-the-shelf | Repeated dosing until progression | • Ocular |
| BiSpecific | Off-the-shelf | Repeated dosing until progression | • Cytokine release syndrome<br>• Neurotoxicities |
| CAR-T | Individual manufacturing | Single Dose | • Cytokine release syndrome<br>• Neurotoxicities |

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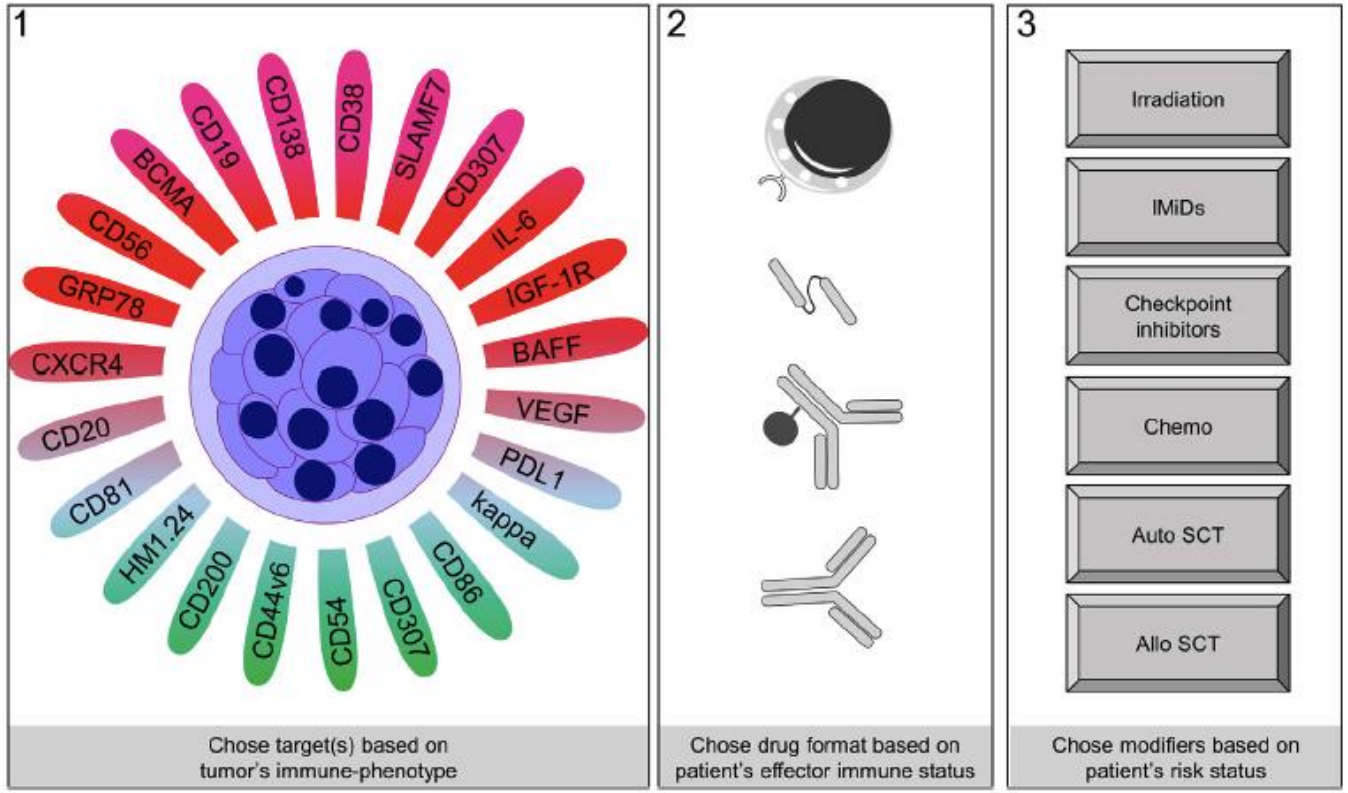
# Towards Individualized Immunotherapy in Myeloma

## Opportunities & Challenges

- High-risk cytogenetics disease
- Rational combinations
- Rational sequencing of therapies
- Predictive biomarkers for immunotherapy

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Rasche L, et al. *Cancer Treat Rev*. 2017;55:190-199.