Please note, these are the actual video-recorded proceedings from the live CME event and may include the use of trade names and other raw, unedited content.

Novel Strategies Under Investigation for the Treatment of MM

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Disclosures

Consulting Agreements	Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Janssen Biotech Inc, Merck, Takeda Oncology

Questions regarding novel investigational strategies for the treatment of MM

Dr Johl

Dr Kumar

Dr Bessnow

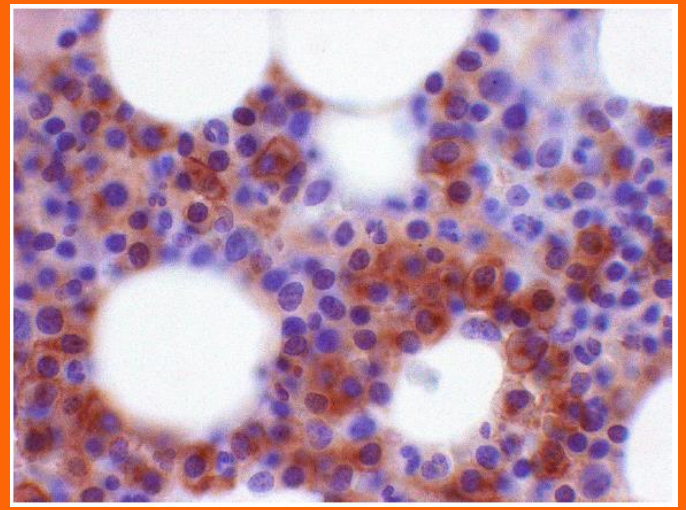
Overview

- Biologic rationale for targeting B-cell maturation antigen (BCMA) in MM
- Similarities and differences between various BCMA-targeted chimeric antigen receptor (CAR) T-cell therapy platforms under investigation
- Early efficacy and safety results with BCMA-targeted CAR T-cell therapy in MM
- Ongoing investigation of venetoclax and potential clinical role, particularly in patients with t(11;14)
- Other promising agents and strategies under investigation

BCMA: A promising target in MM

B-cell maturation antigen (BCMA)

- A member of the TNF receptor superfamily
- Expression is largely restricted to plasma cells and mature B cells
- Not detectable in any other normal tissues
- Expressed nearly universally on multiple myeloma cells
- Anti-MM efficacy validated in initial studies



Multiple myeloma cells expressing BCMA

(brown color = BCMA protein)

BCMA Directed Strategies

- BCMA Antibodies
- BCMA Bispecific monoclonal antibodies
- BCMA CAR-T cells

What are chimeric antigen receptors (CAR) and CAR-T cells?

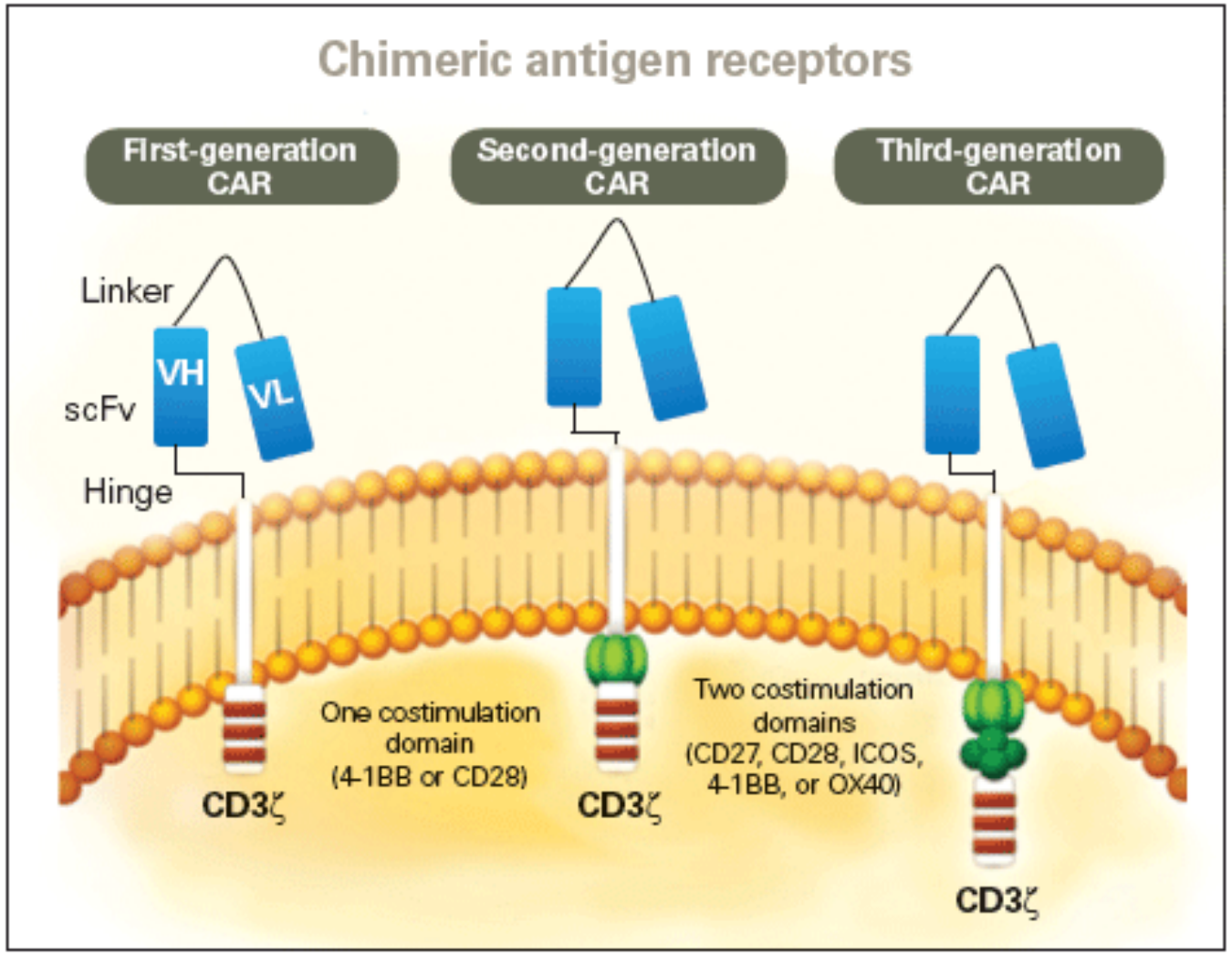
CAR = transmembrane receptor that contains:

1. Extracellular domain: Antibody domain (scFv) against a tumor antigen
2. Transmembrane domain
3. Intracellular domain:

   First generation CARs: CD3ζ (T-cell coreceptor necessary for T-cell activation)

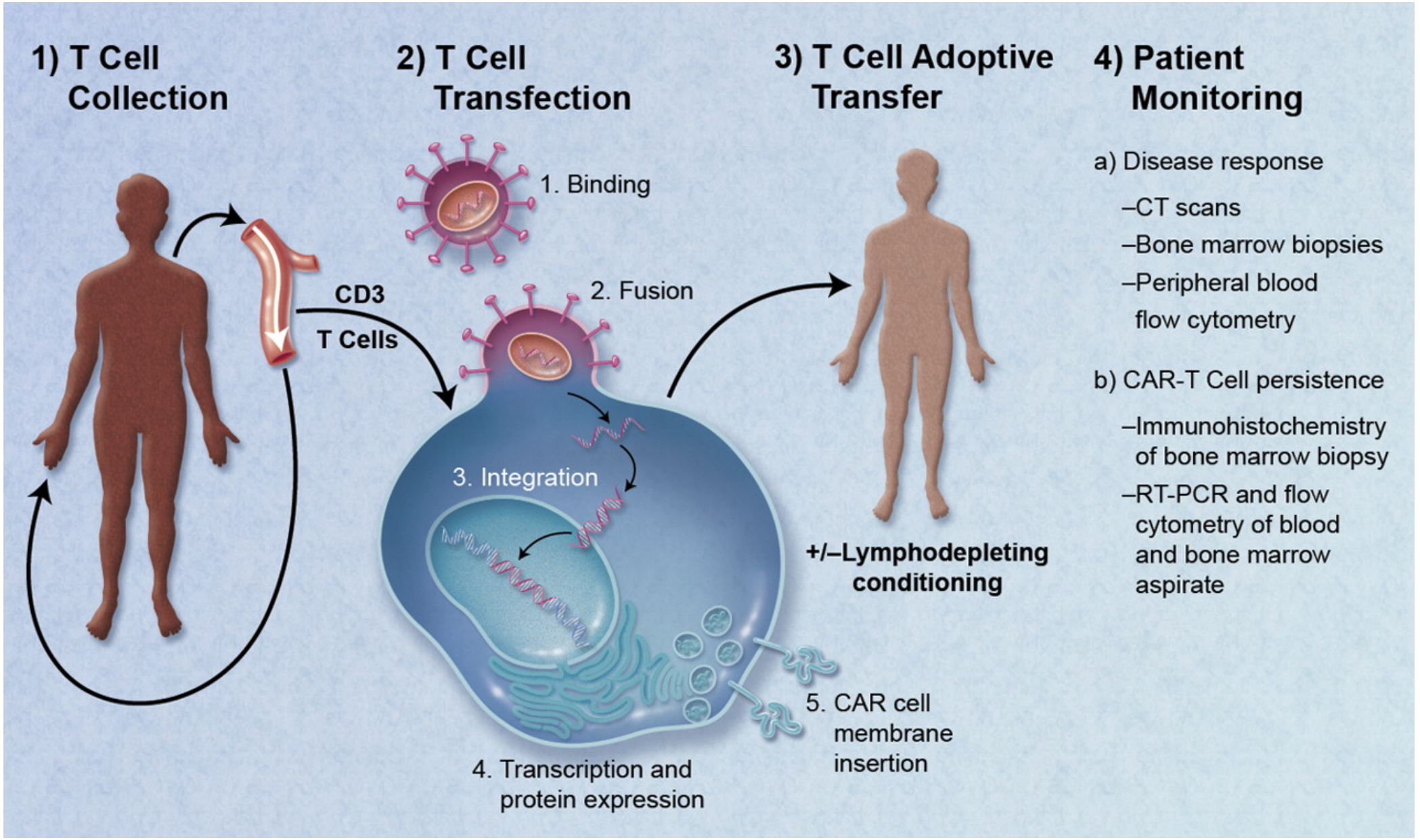
   Second generation CARs: CD3ζ + either CD28 or 4-1BB (costimulatory domain)

   Third generation CARs to come: CD3ζ + two costimulatory domains (CD28, 4-1BB, OX40, ICOS, CD27)



CAR-T cells = T cells transfected with DNA encoding a CAR, so the CAR is expressed on the T-cell surface

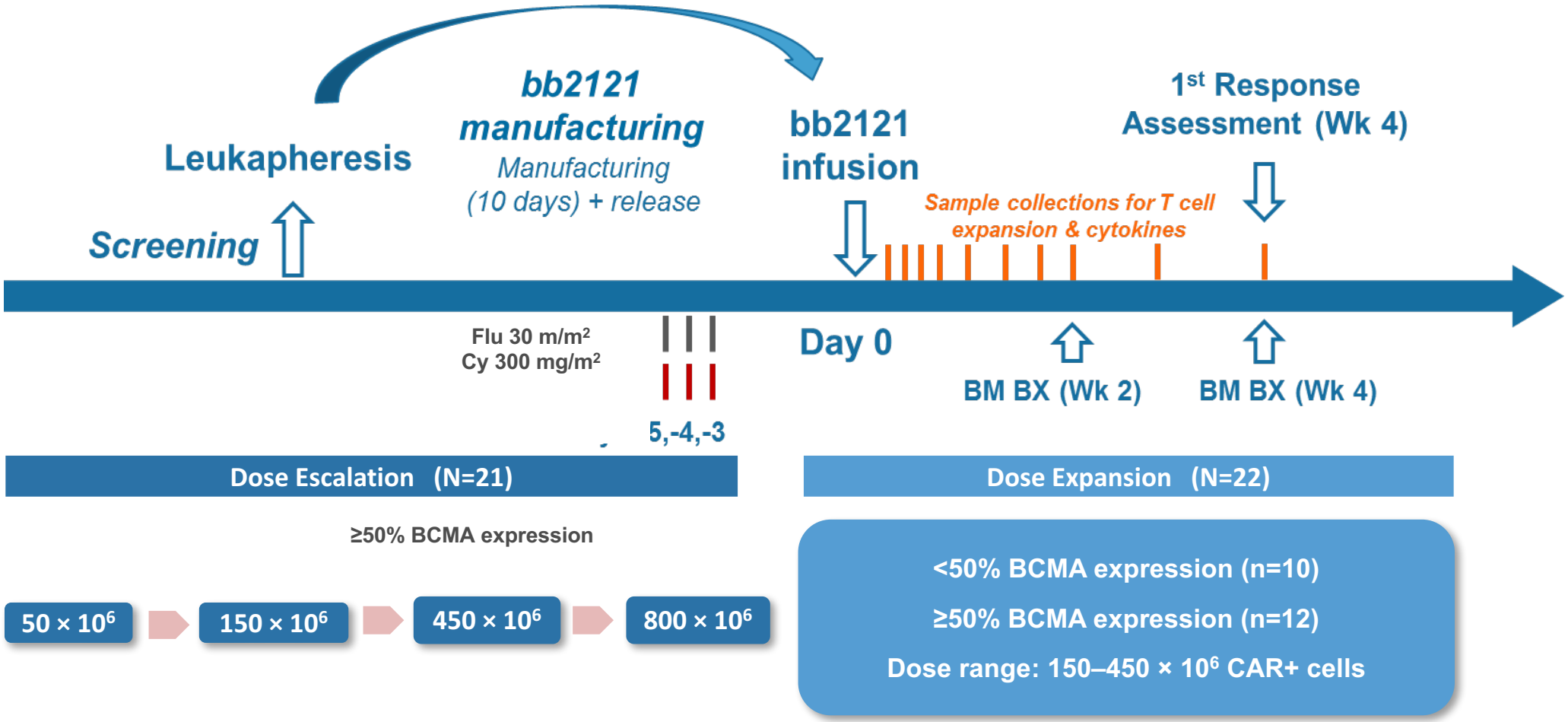
Manufacturing of CAR-T cells



Summary of ongoing BCMA CAR-T trials for MM

Name	Anti-BCMA CAR	Bb2121	LCAR-B38M	CART-BCMA
Binder/co-stimulatory signal	Murine/CD3ζ, CD28	Murine/CD3ζ, 4-1BB	Murine/CD3ζ, 4-1BB	Fully human/CD3ζ, 4-1BB
Transfection	γ-retroviral	Lentiviral	Lentiviral	Lentiviral
BCMA expression required?	Yes	Yes	Yes	No

CRB-401 PHASE 1 STUDY DESIGN



Manufacturing success rate of 100%

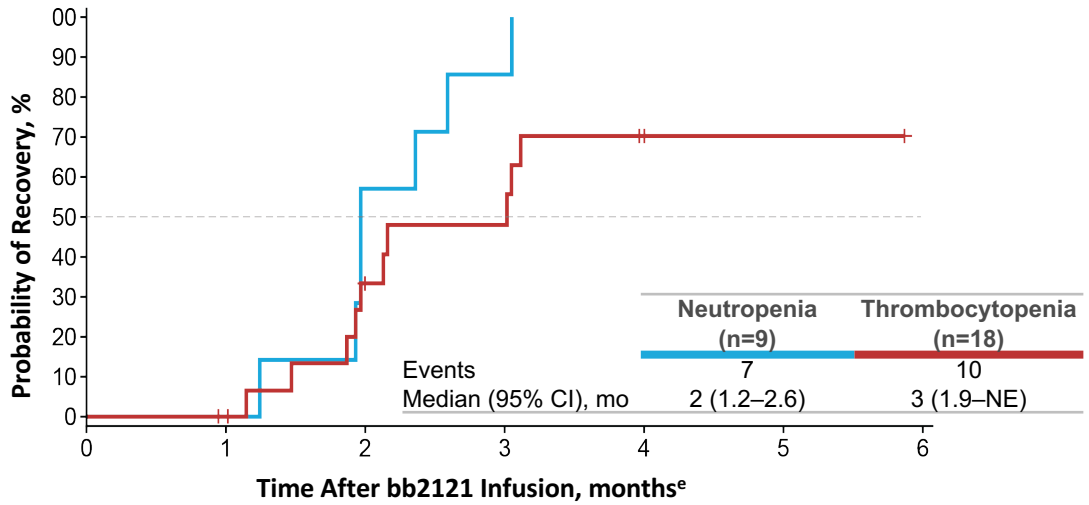
Raje N et al, *ASCO* 2018

ADVERSE EVENTS OF SPECIAL INTEREST

CAR T Treatment-Emergent Adverse Events
All Infused Patients (N=43)

TEAE, n (%)	Overall	Grade ≥3
Cytokine release syndrome[a]	27 (63)	2 (5)
Neurotoxicity[b]	14 (33)	1 (2)
Neutropenia	35 (81)	34 (79)
Thrombocytopenia	26 (61)	22 (51)
Anemia	24 (56)	19 (44)
Infection[c]		
Overall	26 (61)	9 (21)
First Month	10 (23)	2 (5)

Time to Recovery of Grade 3/4 Cytopenias in Patients Without Recovery by Month 1[d]



- No grade 4 CRS events
- No fatal CRS or neurotoxicity events

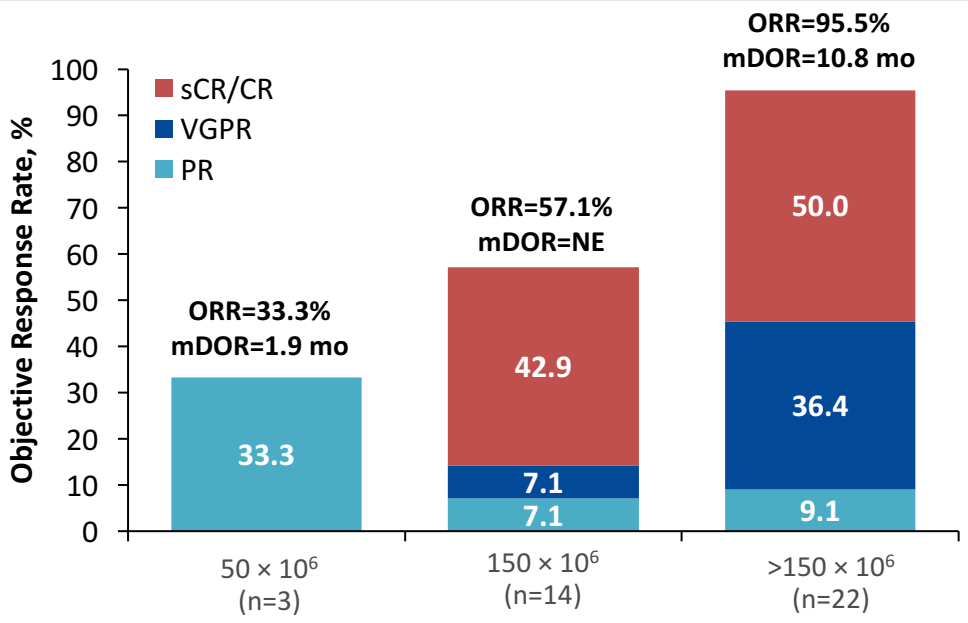
- 31/40 (78%) recovered ANC to ≥1000/μL by Day 32
- 22/40 (55%) recovered PLT to ≥50,000/μL by Day 32

Data cutoff: March 29, 2018. NE, not estimable. [a]CRS uniformly graded per Lee DW, et al. *Blood.* 2014;124(2):188-195. [b]Events occurring in first 28 d and including dizziness, bradyphrenia, somnolence, confusional state, nystagmus, insomnia, memory impairment, depressed level of consciousness, neurotoxicity, lethargy, tremor and hallucination. [c]Includes the SOC Infections and Infestations. Events observed in >10% include upper respiratory tract infection and pneumonia. [d]Includes patients treated with active doses (150–800 × 10^6 CAR+ T cells; N=40). Median and 95% CI from Kaplan-Meier estimate. [e]Time from first bb2121 infusion to the first grade ≤2 event after day 32.

Raje N et al, *ASCO* 2018

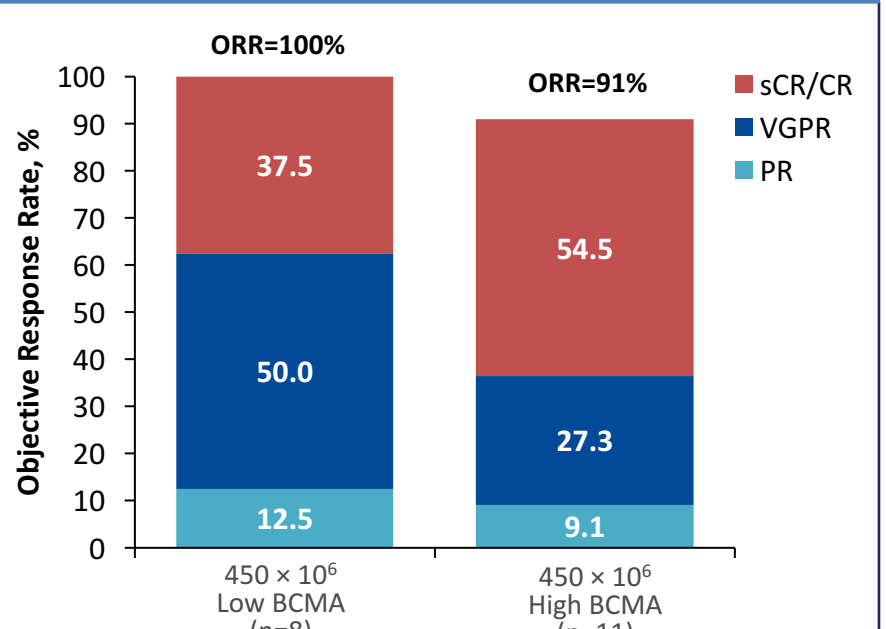
TUMOR RESPONSE: DOSE-RELATED; INDEPENDENT OF TUMOR BCMA EXPRESSION

Tumor Response By Dose[a]



Median follow-up (min, max), d	84 (59, 94)	87 (36, 638)	194 (46, 556)

Tumor Response By BCMA Expression[a]



Median follow-up (min, max), d	168 (121, 184)	311 (46, 556)

Data cutoff: March 29, 2018. CR, complete response; mDOR, median duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; VGPR, very good partial response. [a]Patients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Low BCMA is <50% bone marrow plasma cells expression of BCMA; high BCMA is defined as ≥50%.

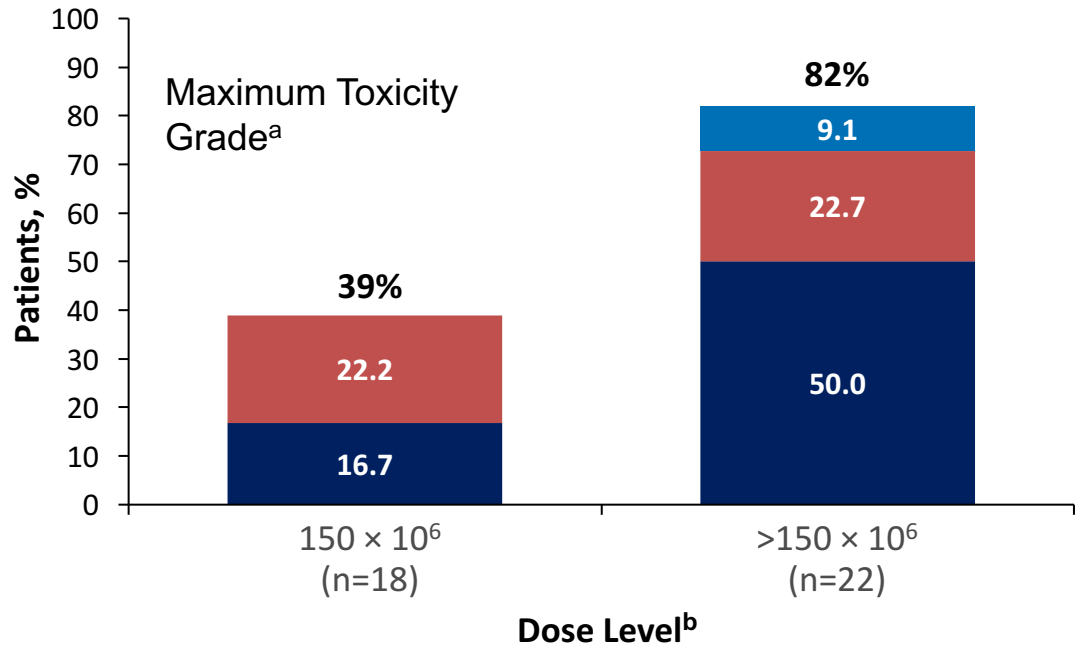
Raje N et al, *ASCO* 2018

CYTOKINE RELEASE SYNDROME: MOSTLY LOW GRADE AND MANAGEABLE

Cytokine Release Syndrome Parameters

Parameter	Dosed Patients (N=43)
Patients with a CRS event, n (%)	27 (63)
Maximum CRS grade[a]	
None	16 (37)
1	16 (37)
2	9 (21)
3	2 (5)
4	0
Median (min, max) time to onset, d	2 (1, 25)
Median (min, max) duration, d	6 (1, 32)
Tocilizumab use, n (%)	9 (21)
Corticosteroid use, n (%)	4 (9)

Cytokine Release Syndrome By Dose Level

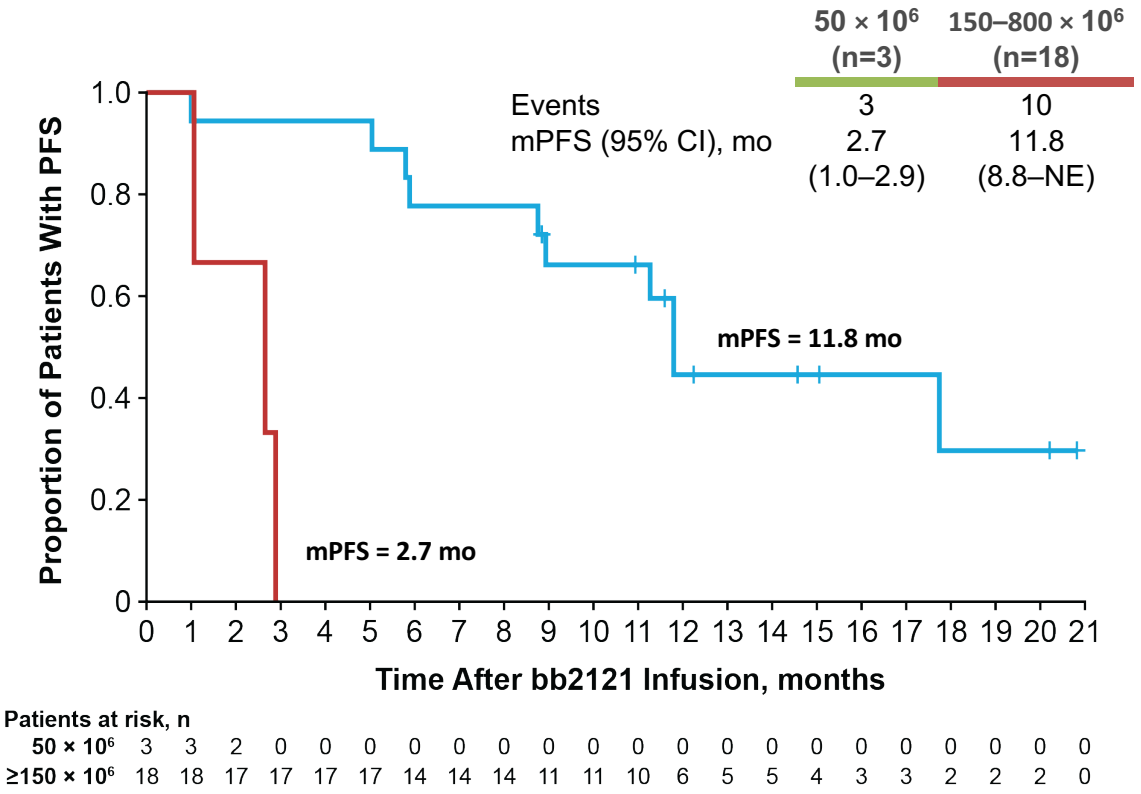


Data cutoff: March 29, 2018. [a]CRS uniformly graded according to Lee DW, et al. *Blood.* 2014;124(2):188-195. [b]3 patients were treated at the 50 x 10^6 dose level for a total of 43 patients.

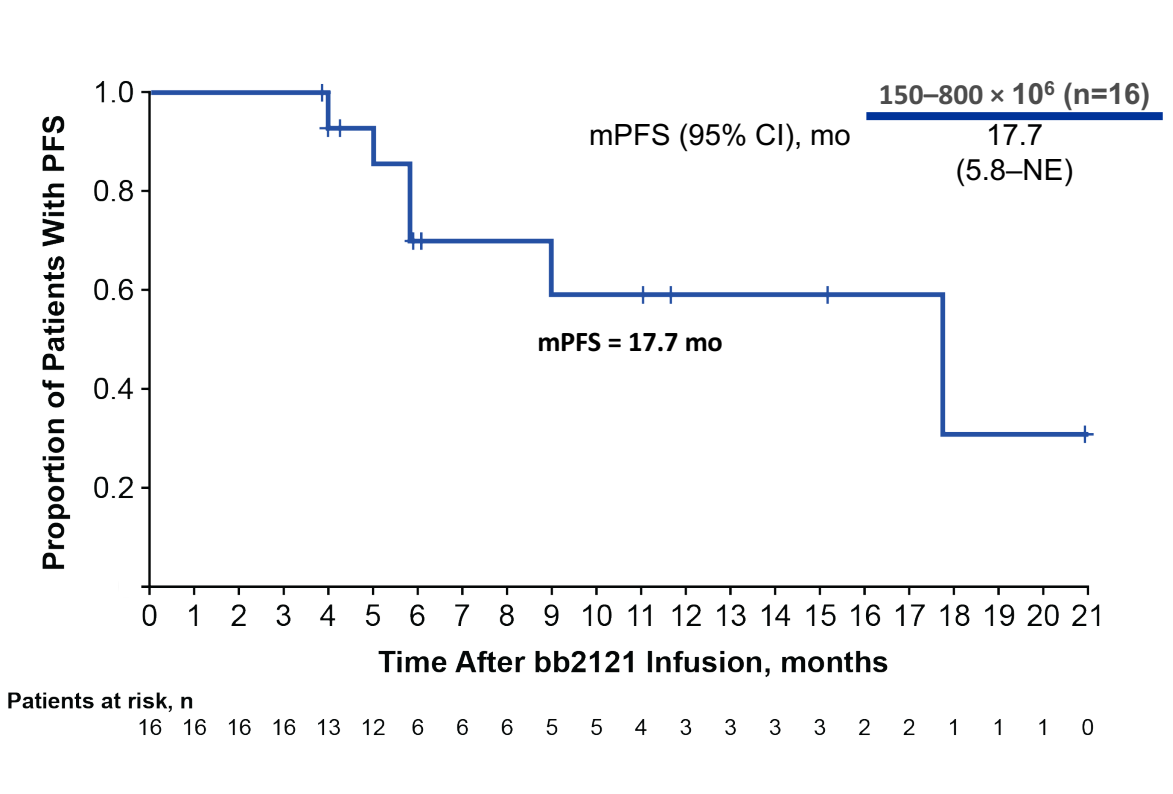
PROGRESSION-FREE SURVIVAL

- mPFS of 11.8 months at active doses (≥150 × 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

PFS at Inactive (50 × 10^6) and Active (150–800 × 10^6) Dose Levels[a]



PFS in MRD-Negative Patients



Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. [a]PFS in dose escalation cohort.

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Transfection	γ-retroviral	Lentiviral	Lentiviral	Lentiviral
BCMA expression required?	Yes	Yes	Yes	No
Median prior lines of tx	7, 11	7	3	9
Efficacy	1 sCR (relapsed), 1 VGPR, 2 PR, 8 SD Responses in highest cell dose; **9/11 in top dose**	10 CRs, 6 VGPR, 1 PRs (4 eventual PD), n=18 at >5 e7 : **94% RR** 9 MRD neg	**33 CR or VGPR,** n=35, 1 relapse; 5 MRD neg > 1 yr	**6/9, 2/5, 5/6** responses in 3 cohorts
Safety	Toxicity substantial (Gr3-4CRS) but reversible esp in highest doses (9 e6/kg); protocol modified to pts with lower tumor burden	CRS in 71%; transient Gr3 10%; 5 deaths (cardio-pulm arrest, unrelated, 1 MDS, 3 PD at lowest dose) Early report of 1 Gr 4 neurotoxicity	Transient CRS 29/35, no neurotox	CRS in 17/21 pts (6 with Gr2), with neurotox in 3 pts 1 death – candidemia/PD

Challenges in CAR-T therapy for MM

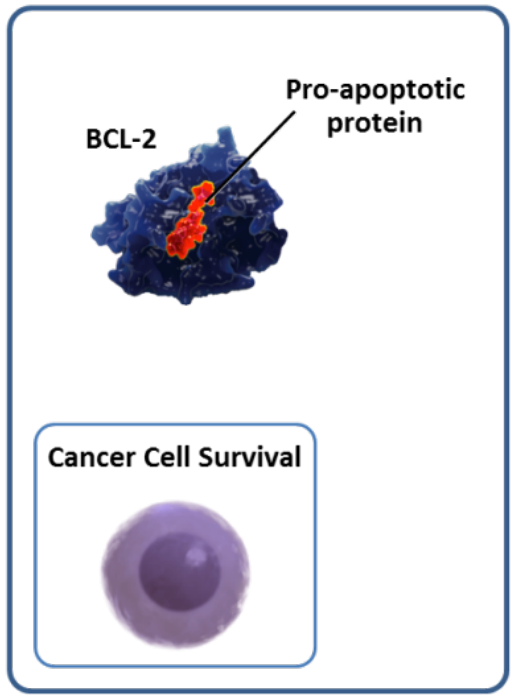
- CRS (hopefully not as much of an issue as with ALL)
- Persistence
  - Lymphodepletion
  - Cytokine-based T-reg elimination
  - Virus-specific T cells as primary CAR-T population
- Optimizing co-stimulatory signaling
  - 41BB>CD28
- Nature of MM is waxing and waning, should the cells be that way as well?
  - “ON-switch” CARs
  - Targeting multiple antigens
  - T cells redirected for universal cytokine-mediated killing (TRUCKs)

But where are we really going…?

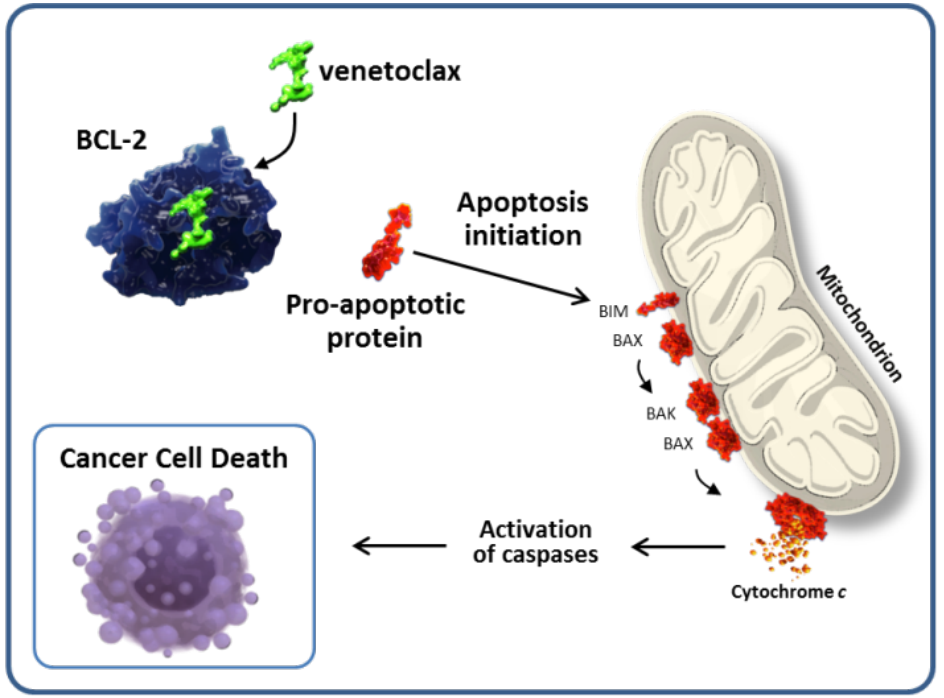
- Timing of CAR-T
- Disease burden
- Position relative to autologous transplant
- Cost
- Time and financial cost of proving superiority
  - Clinical trial design
  - MRD as endpoint

Venetoclax Background

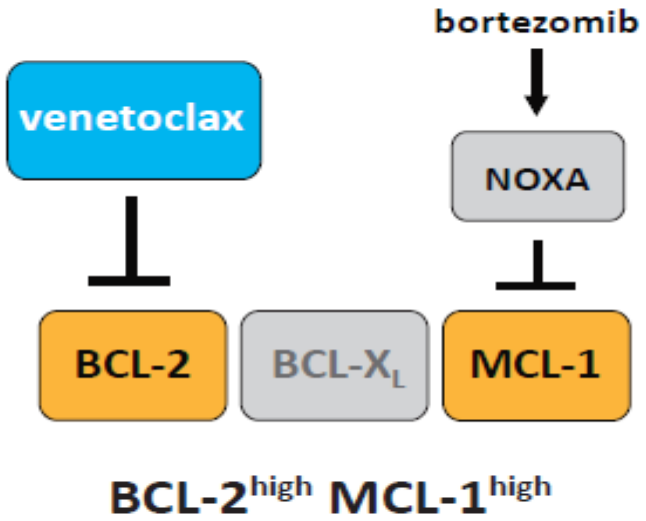
- BCL-2 and MCL-1 promote multiple myeloma (MM) cell survival
- Venetoclax is a selective, orally available small molecule BCL-2 inhibitor,[1] and bortezomib can indirectly inhibit MCL-1
- Venetoclax enhanced bortezomib activity in vitro and in vivo[2]



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]



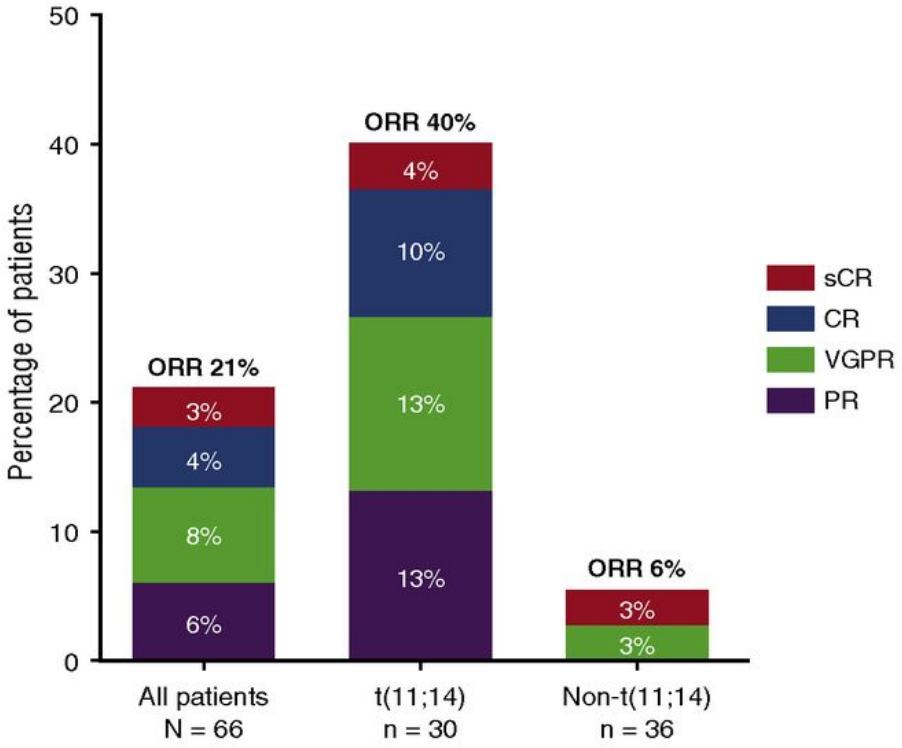
Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).[4-6]

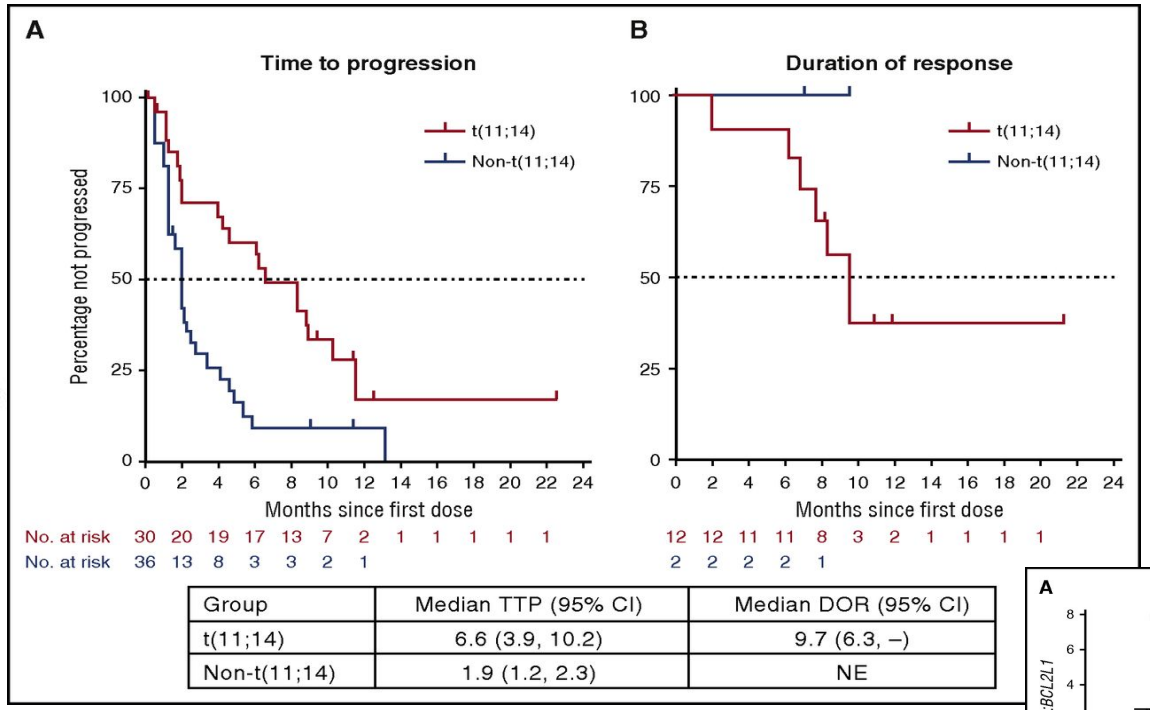


1. Roberts AW et al. NEJM 2015
2. Punnoose E et al. Mol Cancer Ther 2016

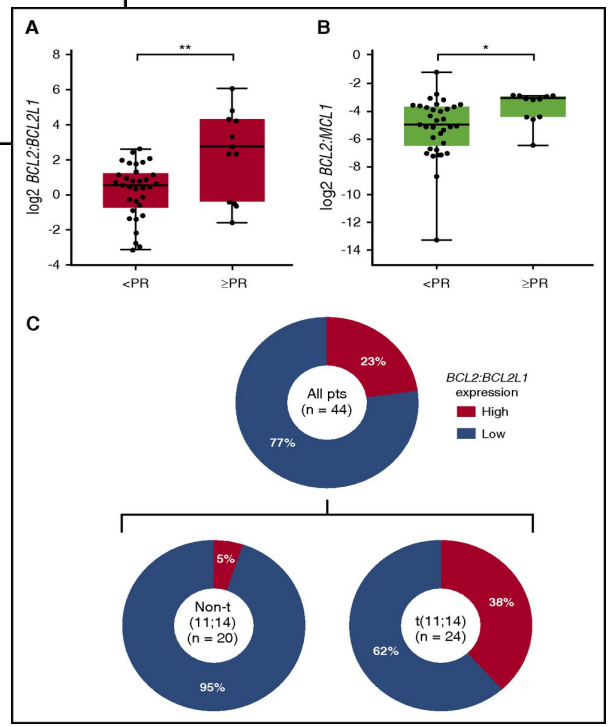
1. Leverson JD, et al. *Sci Transl Med* 2015; 7:279ra40. 2. Czabotar, et al. *Nature Reviews* 2014;15:49-63. 3. Plati J, Bucur O, Khosravi-Far R. *Integr Biol (Camb)* 2011;3:279–296.
4. Certo M, et al. *Cancer Cell*. 2006;9(5):351-65. 5. Souers AJ, et al. *Nat Med*. 2013;19(2):202-8. 6. Del Gaizo Moore V et al. *J Clin Invest*. 2007;117(1):112-21.

Venetoclax in Myeloma





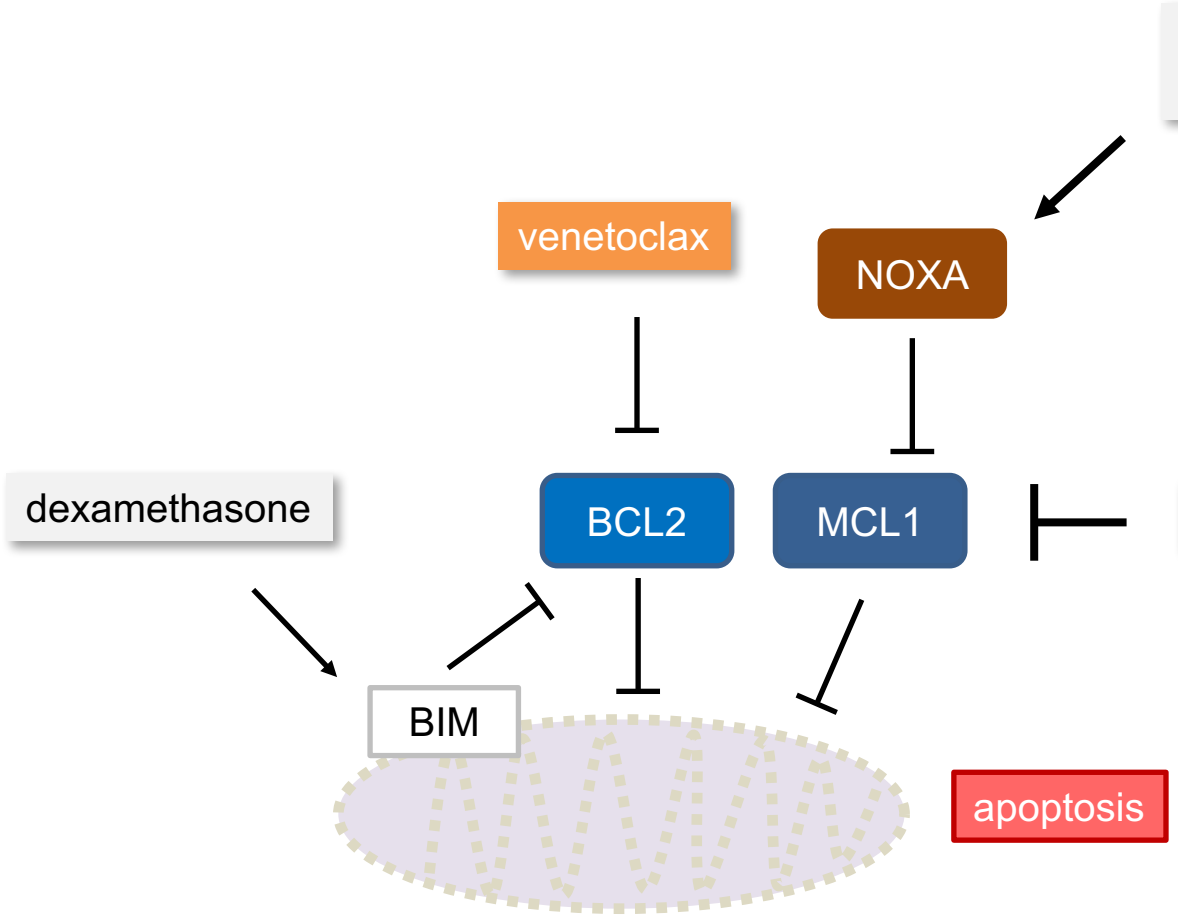
Group	Median TTP (95% CI)	Median DOR (95% CI)
t(11;14)	6.6 (3.9, 10.2)	9.7 (6.3, –)
Non-t(11;14)	1.9 (1.2, 2.3)	NE



No tumor lysis syndrome
AEs mild to moderate GI toxicities
Grade 3-4 hematologic toxicities
AEs did not lead to study drug discontinuation

Kumar S et al, *Blood* 2017

Enhancing activity of venetoclax



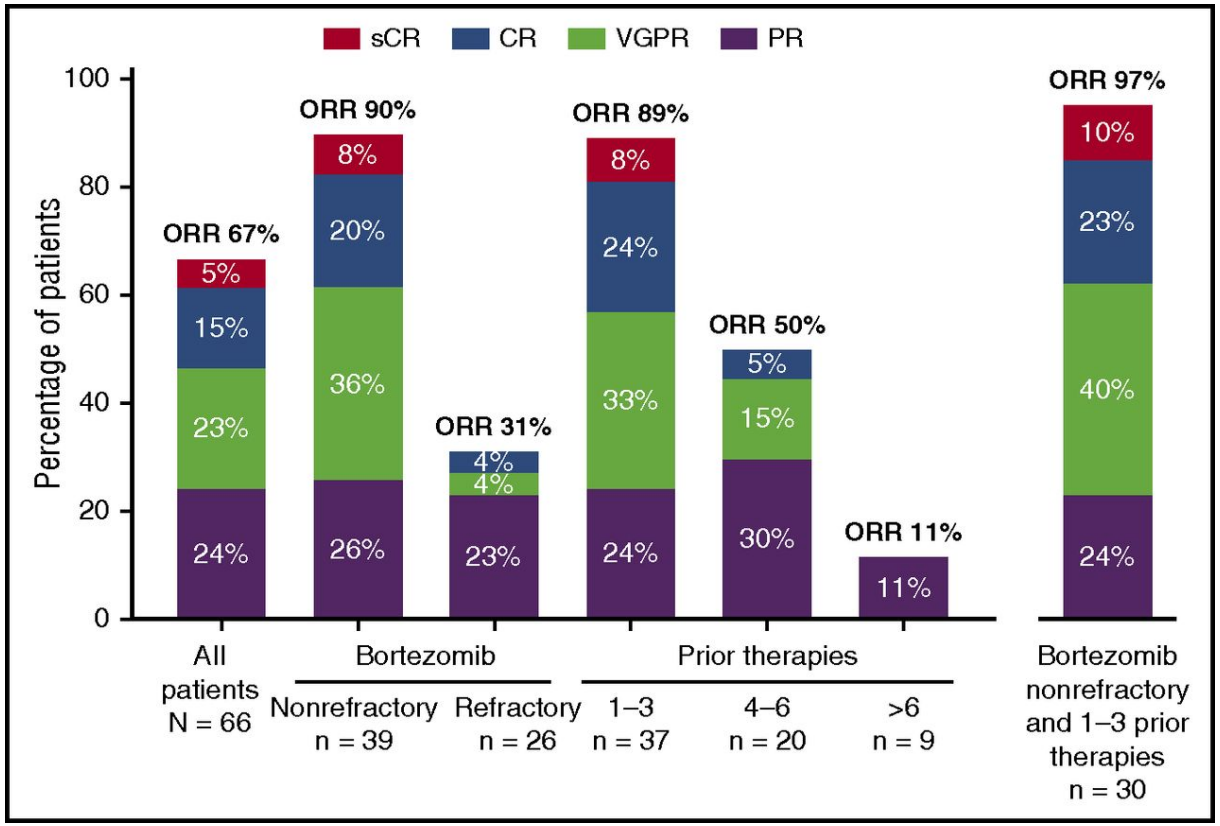
- Bortezomib upregulates NOXA
- NOXA leads to degradation of MCL1 (a prosurvival protein)

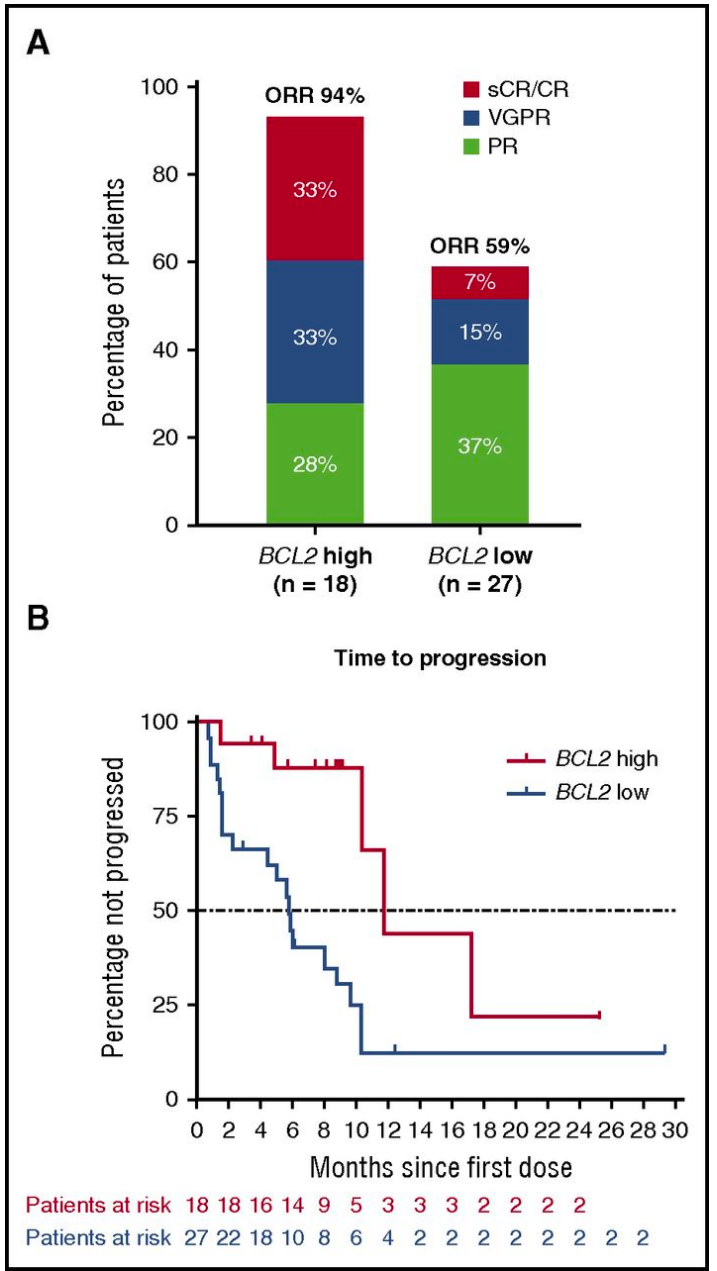
AMG 176 (NCT02675452)

- Dexamethasone upregulates expression of proapoptotic activator protein BIM and shifts its binding to BCL2.
- Dexamethasone increases sensitivity to venetoclax.

Matulis SM et al, *Leukemia* 2016
Punnoose EA et al, *Mol Cancer Ther* 2016

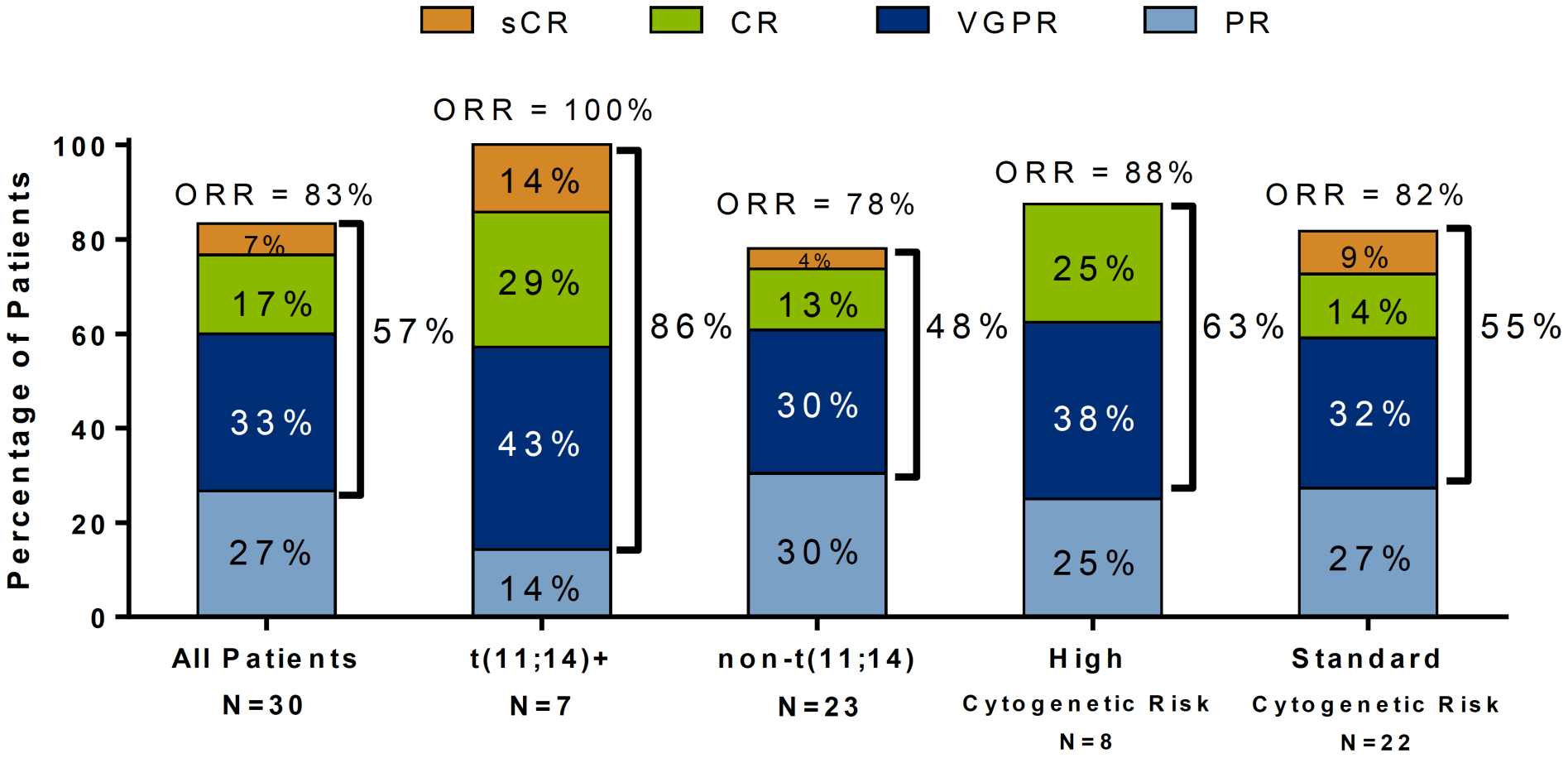
Venetoclax + BzB in Myeloma





- Reponses seen *regardless* of t(11;14) status
- **t(11;14), ORR 78%**
- **Non-t(11;14), ORR 65%**
- Mild gastrointestinal toxicities were the most common AEs reported (5% grade 3-4 nausea, 6% grade 3-4 diarrhea), and cytopenias were the most common grade 3/4 AEs; these were manageable and did not lead to study discontinuation
- Recommended phase II dose, 800 mg

Phase I trial of venetoclax, carfilzomib, and dexamethasone



Study continues with 42 patients
Expansion cohort: carfilzomib 70 mg/m^2 weekly with venetoclax 800 mg daily

Costa LJ et al, ASCO 2018

Other targets of interest

- *MCL inhibitors*
- *Selinexor*
- *CELMoDs*
- *Mutation specific targeted agents: BRAF/MEK*

Acknowledgements

Our Patients

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HARVARD MEDICAL SCHOOL

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