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Novel Strategies Under Investigation for the Treatment of Multiple Myeloma

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Disclosures

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Contracted Research	Acetylon Pharmaceuticals Inc, Lilly

Case presentation 7: Dr Brenner

78-year-old woman; refractory multiple myeloma, has been treated for the past 6 years

- Currently receiving pomalidomide- and daratumumab-based regimen
  - Stable disease
  - No remaining standard treatment options
- Referred for evaluation of potential for CAR T-cell therapy

Case presentation 8: Dr Morganstein

78-year-old woman

- 2013: MM with t(11;14)
- Received bortezomib, lenalidomide, pomalidomide, ixazomib
- 2017: Very heavily transfusion-dependent after multiple regimens, most recently daratumumab and bortezomib with slowly decreasing M spike and significant anemia

What we will cover

- CAR T Cells
- Venetoclax and other late stage compounds
- Denosumab

What are Chimeric Antigen Receptors (CAR) and CAR T cells?

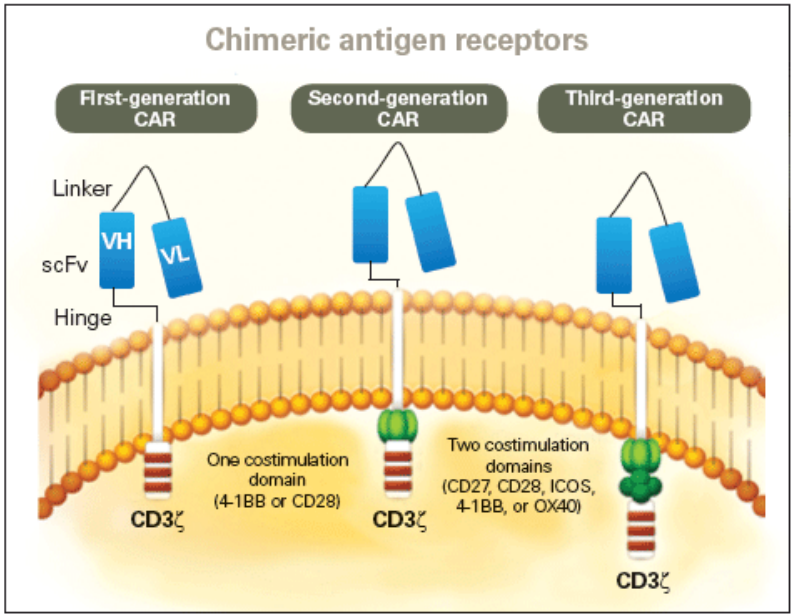
CAR = transmembrane receptor that contains:

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)

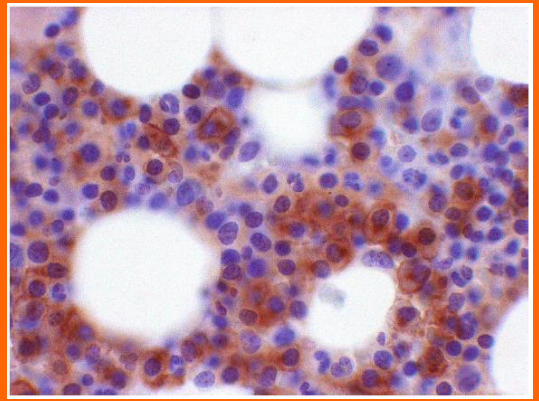


CAR T cells = T cells transfected with DNA encoding a CAR, so the CAR is expressed on the T-cell surface

BCMA: A Promising Target in Multiple Myeloma (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



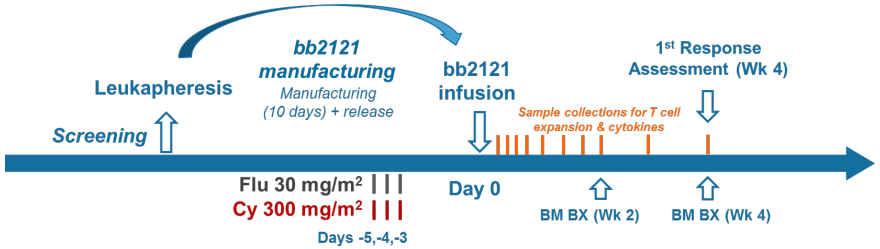
Multiple myeloma cells expressing BCMA

(brown color = BCMA protein)

BCMA directed Strategies

- BCMA Antibodies
- BCMA BITES
- BCMA CAR T cells

CRB-401 Open-label Phase 1 Clinical Study of bb2121



3 + 3 Dose Escalation of CAR + T Cells

50×10^6 → 150×10^6 → 450×10^6 → 800×10^6 → $1200 \times 10^{6*}$

- CRB-401 is a phase 1 dose-escalation and dose response study in relapsed / refractory MM
- Objectives: Determine preliminary safety and efficacy and recommended phase 2 dose
- 50 patients planned, standard 3 + 3 dose escalation followed by expansion cohort
- Key eligibility criteria
  - Relapsed / refractory MM with ≥ 3 prior lines of therapy (including PI and IMiD), or double refractory
  - Measurable disease
  - ≥ 50% BCMA expression by IHC
  - Adequate bone marrow (ANC ≥1,000, platelet count ≥50,000), adequate renal and hepatic function

Study Status

Consented N=35

Cells Collected N=24

Clinical deterioration prior to infusion N=3

Dosed N=21

1 Month Response Evaluation N=18

** bb2121 Successfully manufactured for all patients collected*

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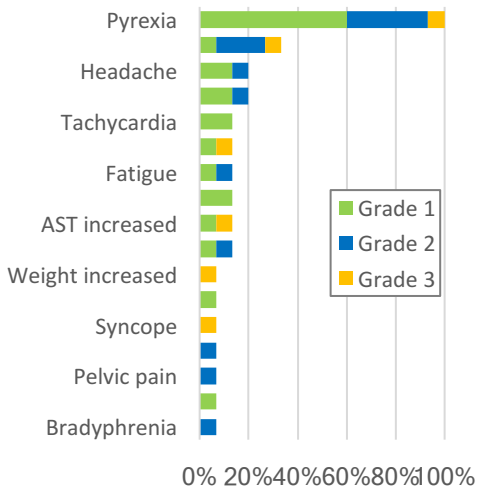
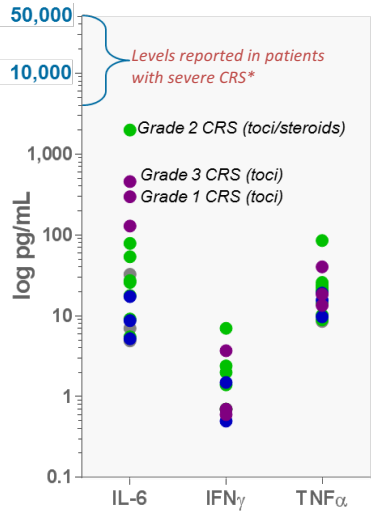
Cytokine Release Syndrome Readily Manageable

Reported CRS-Related Symptoms
In 15/21 treated patients with CRS



- **15/21 (71%) with cytokine release syndrome (CRS)**
  - 2 patients with Grade 3 CRS that resolved in 24 hours
  - 4 patients received tocilizumab, 1 (Grade 2 CRS) with steroids
  - CRS grade does not appear related to tumor burden
- **CRS-related symptoms mostly Grade 1-2**
- **No Grade 3/4 neurotoxicity**

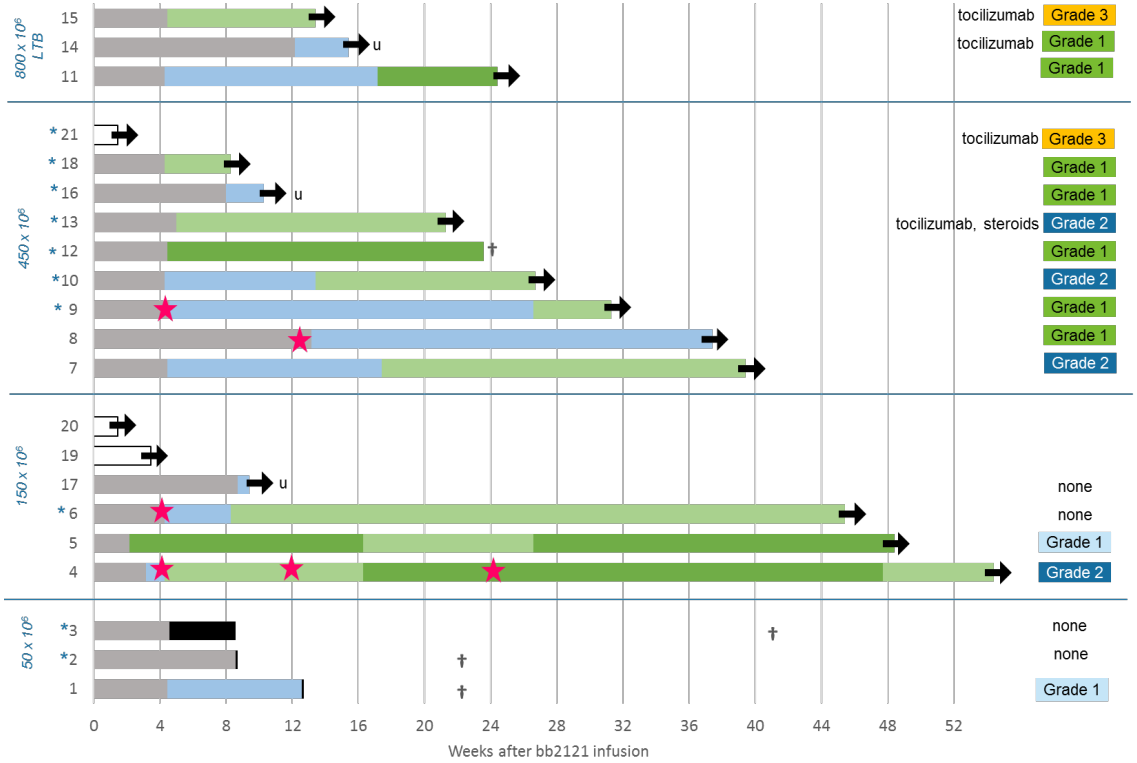
Peak Cytokine Levels



**In anti-BCMA and anti-CD19 CAR T studies. Ali et al., Blood 2016 128: 1688. Maude et al., NEJM 2014*

Berdeja et al, ASCO 2017

All Patients in Active Dose Cohorts Achieved an Objective Response, Duration up to 54 Weeks



Stable Disease PR

VGPR CR/sCR PD

MRD- † deceased

u = unconfirmed response

*High tumor burden (>50% bone marrow involvement)

Includes unscheduled assessments.

Berdeja et al, ASCO 2017

Clinical Response: Time to Response and MRD

Response Rates and Timing

Efficacy Parameter	% (95% CI)
ORR all doses	89% (65-99)
ORR (> 50 x 10^6 CAR+ cells)	100% (78.2-100)
≥VGPR (> 50 x 10^6 CAR+ cells)	73%
CR rate (> 50 x 10^6 CAR+ cells)	27%
	Median (range)
Time to First Response (days)	31 (15-92)
Time to Best Response (days)	59.5 (15-186)
Duration of Response (days, as of data cut-off)	134+ (7-361)

ORR: overall response rate among patients evaluable for clinical response

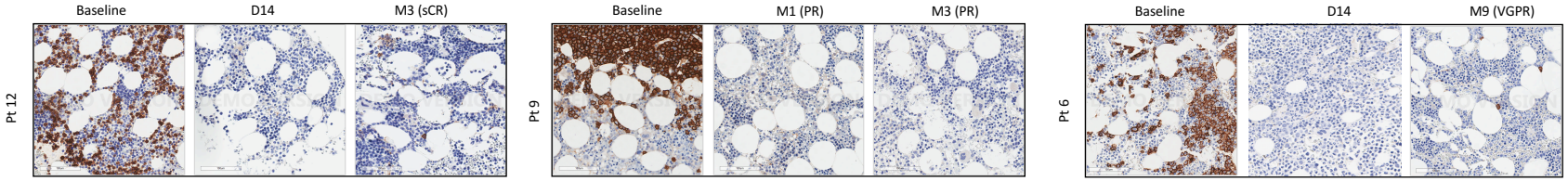
Assessment of Minimal Residual Disease (MRD)†

Patient ID	Month 1	Month 3	Month 6
4	**Negative 10^{-5}**	**Negative 10^{-4}** (10^{-5} undetermined) (10^{-6} undetermined)	**Negative 10^{-4} & 10^{-5}** Positive 10^{-6}
6	**Negative 10^{-5}**	*failed QC*	N/A
8	N/A	**Negative 10^{-4} and 10^{-5}** (10^{-6} undetermined)	N/A
9	**Negative 10^{-4} & 10^{-5}** (10^{-6} undetermined)	**Negative at 10^{-4} & 10^{-5}** (10^{-6} undetermined)	N/A

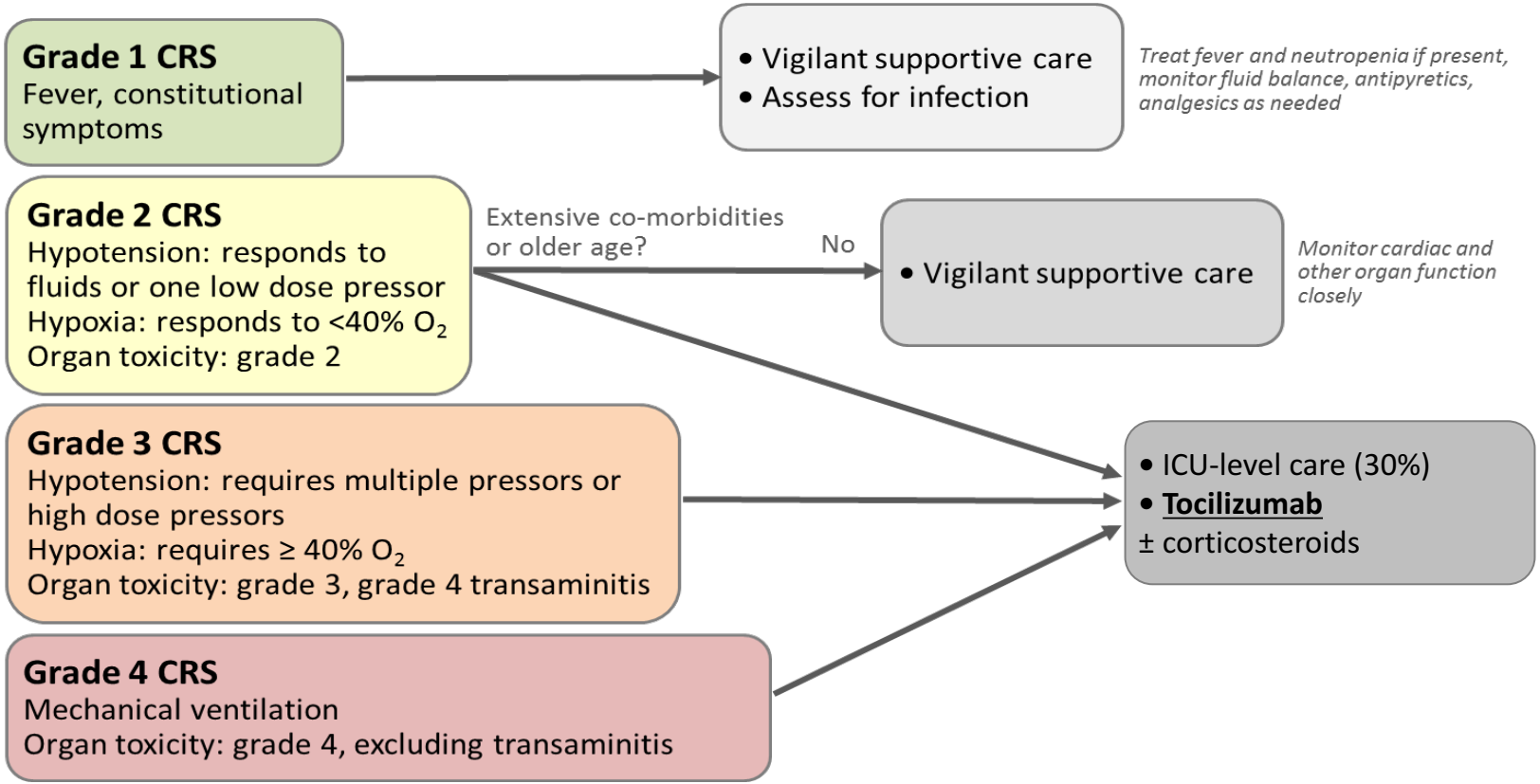
*Pt 5 and Pt 7 had no clone identified at baseline; Pt 10 Month 1 failed QC

† MRD assessed using next-gen sequencing immunoSEQ, Adaptive, Inc.

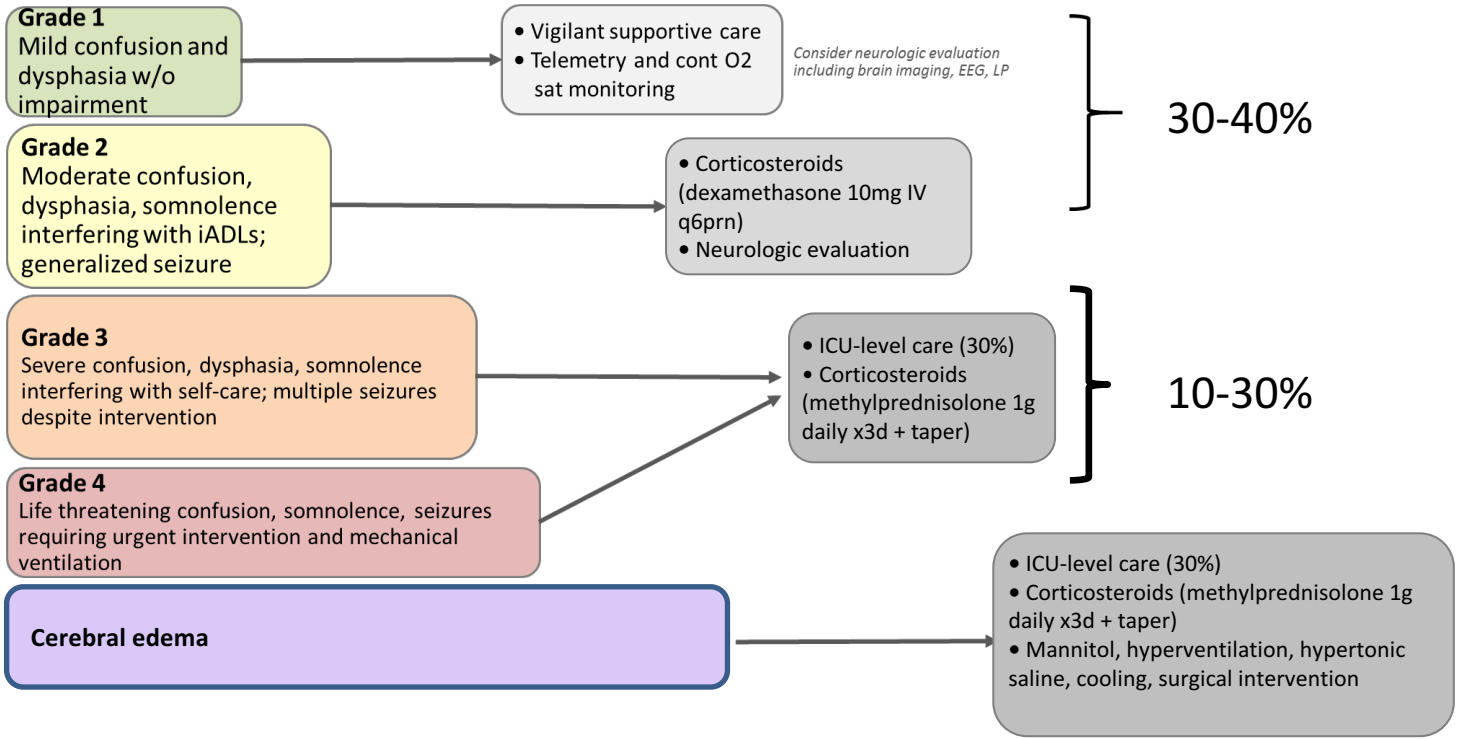
- Durable responses in all evaluable subjects at doses > 50 x 10^6 CAR+ cells
- 4 of 4 evaluable patients are MRD negative at 10^{-5} sensitivity level



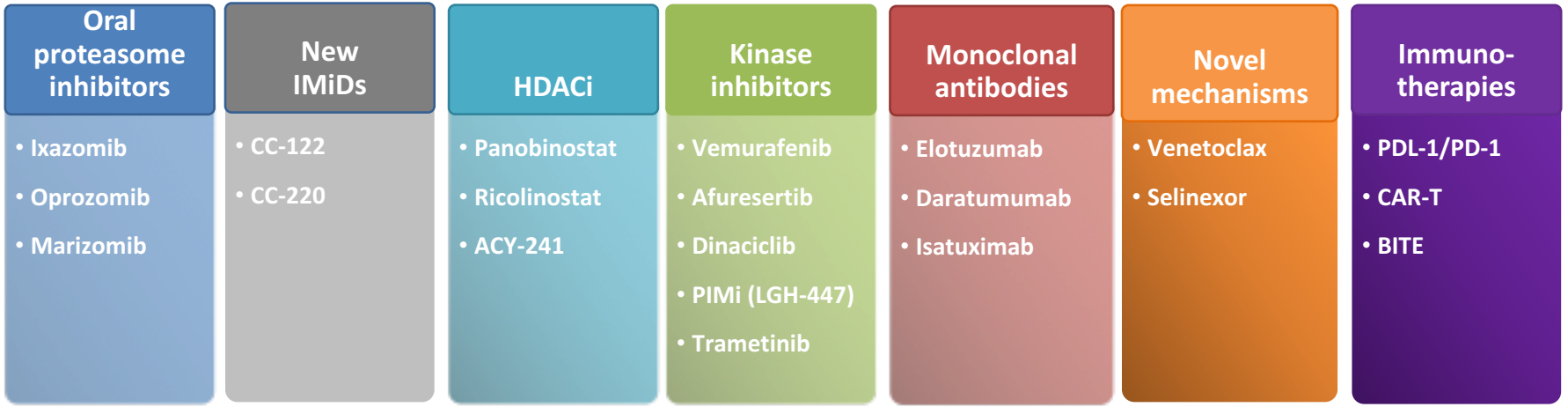
CAR T-cell Toxicity: Cytokine Release Syndrome



CAR T-cell Toxicity: Neurotoxicity



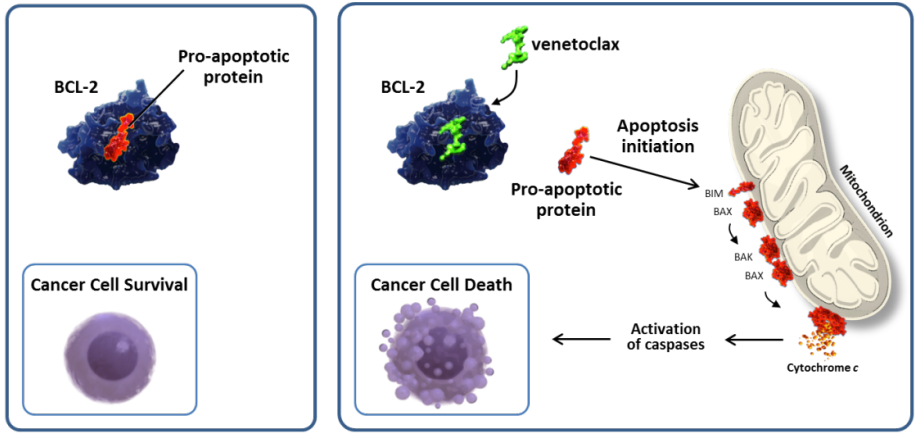
What Else Is New in MM?



HDACi, histone deacetylase inhibitor; PIMi, PIM kinase inhibitor

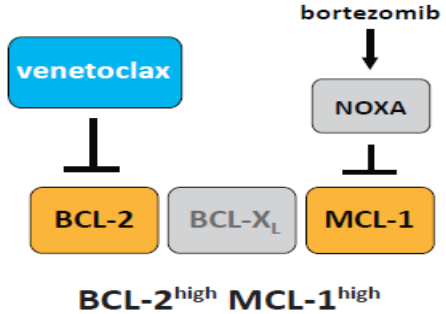
Venetoclax Background

- 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]

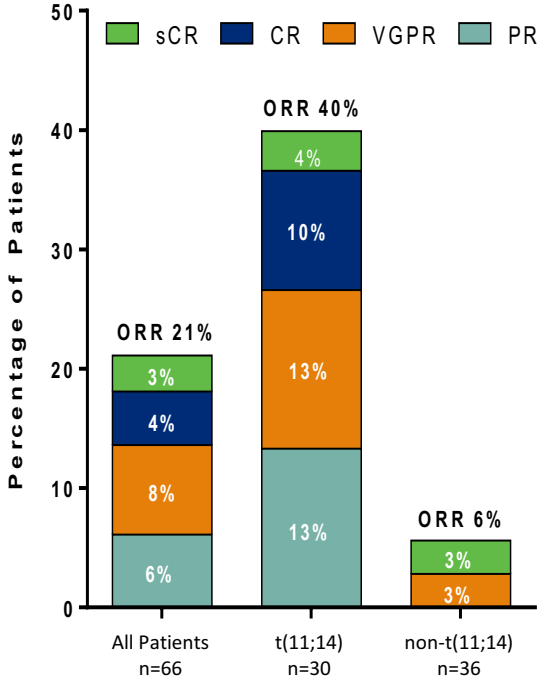


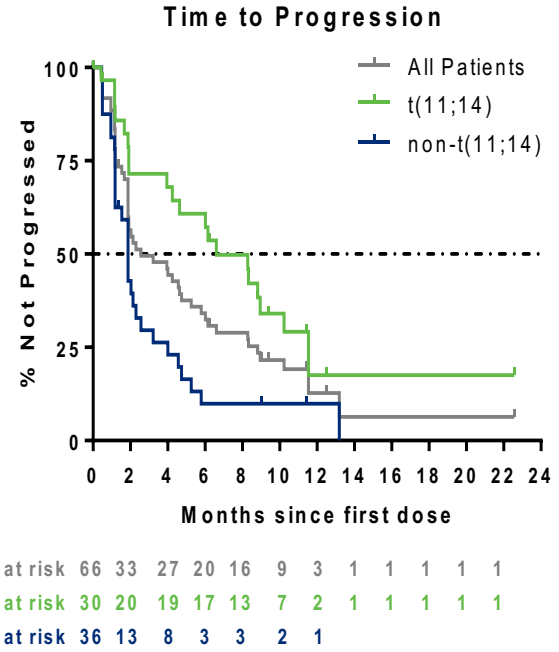
1. Roberts AW et al. NEJM 2015
2. Punnoose E et al. Mol Cancer Ther 2016

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.

Moreau P et al ASH 2016

Phase 1 Venetoclax for RRMM: response and TTP in all patients and by t(11;14) status

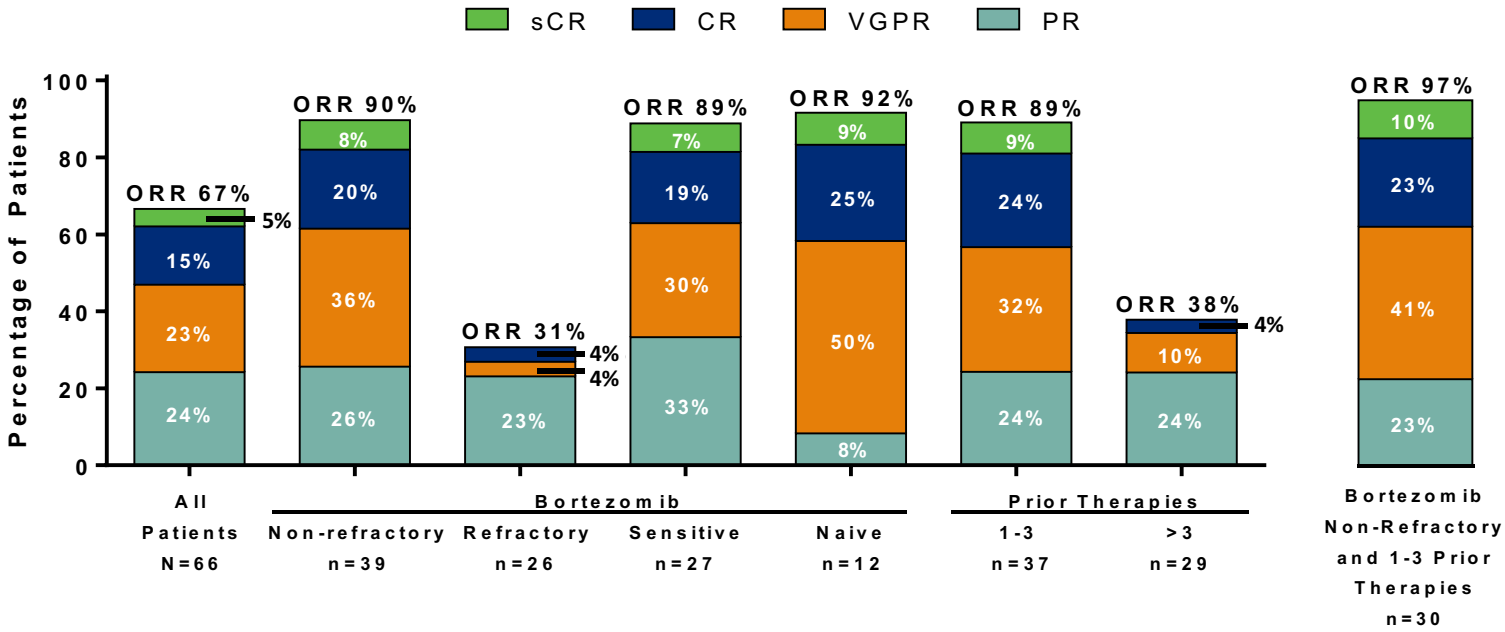




Data cutoff of 19 Aug 2016

Kumar ASH 2016 Abstract 488

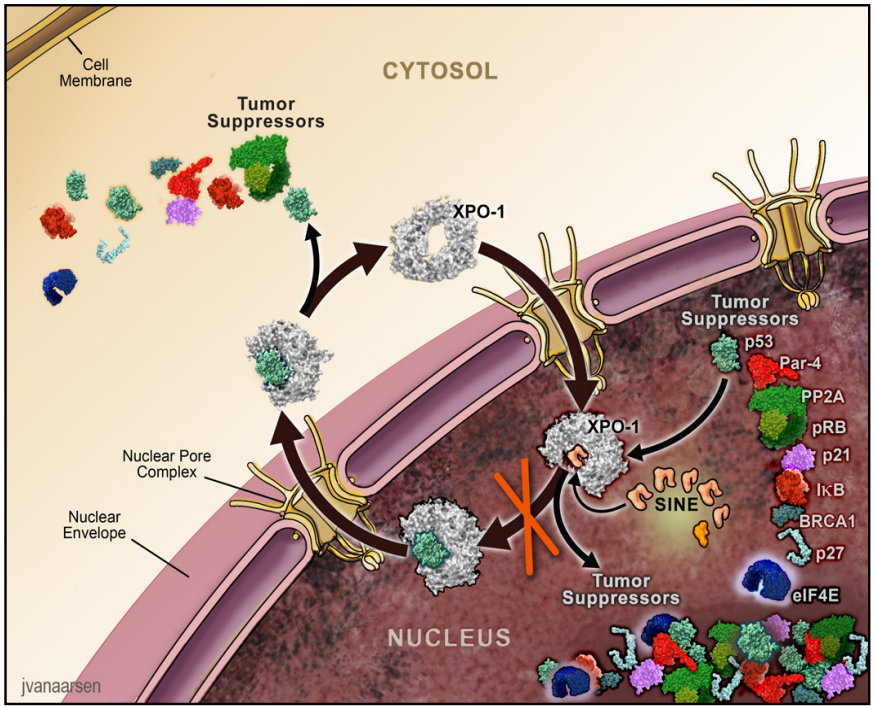
Objective Responses



ORR=PR or better; numbers are based on evaluable patients per subgroups.

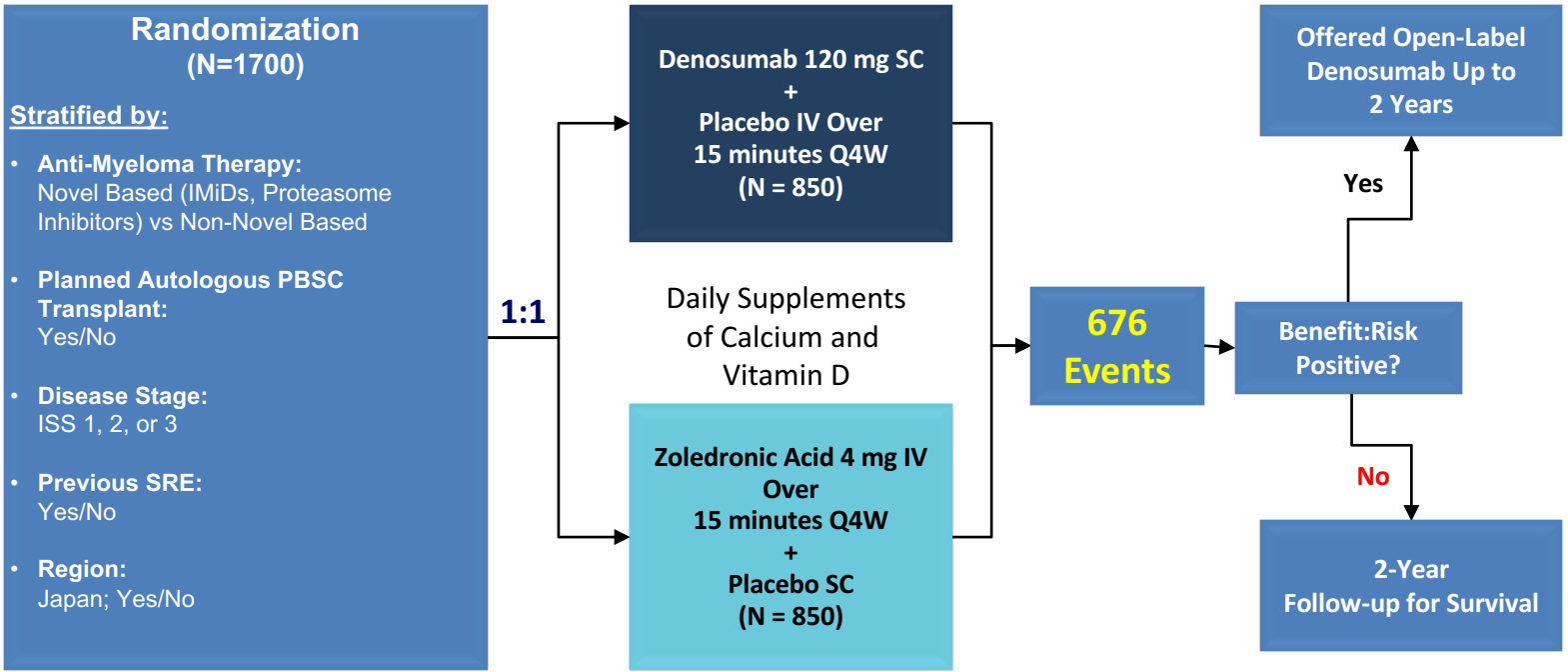
As of 19 Aug 2016

Selinexor Mechanism of Action



- Exportin 1 (XPO1) is the only nuclear exporter for the majority of tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs
- Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression

An International, Randomized, Double Blind Phase III Trial Comparing Denosumab With Zoledronic Acid for the Treatment of Bone Disease in Patients With Newly Diagnosed Multiple Myeloma



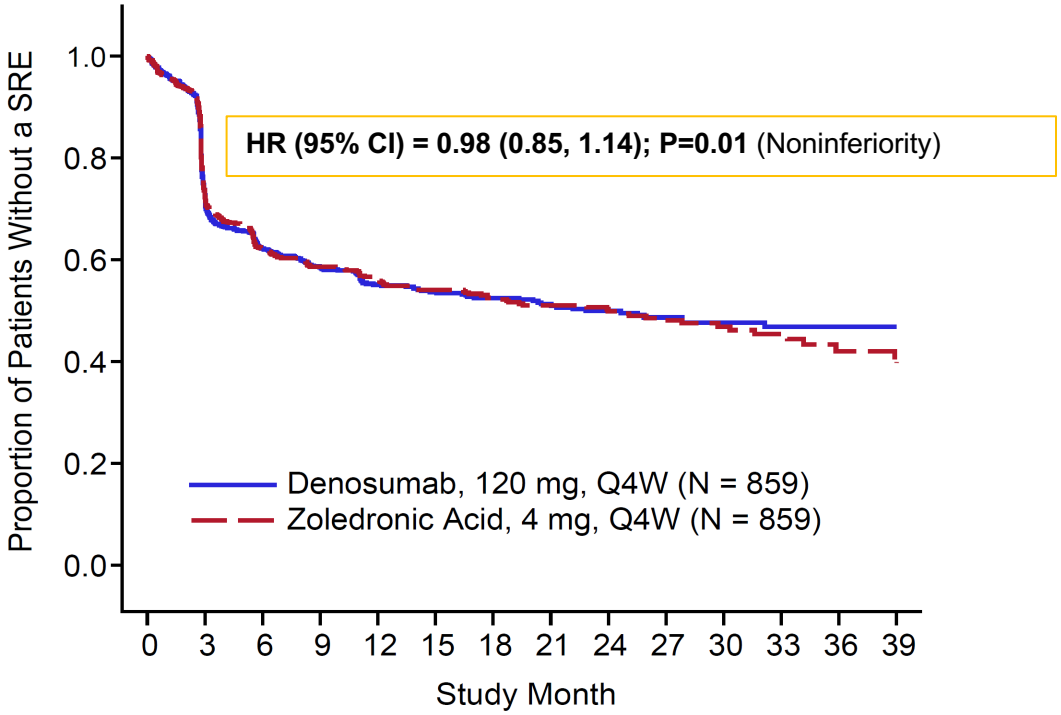
Per protocol and zoledronic acid label, IV product was dose adjusted for baseline creatinine clearance and subsequent dose intervals were determined by serum creatinine levels. No SC dose adjustments were required.

Raje et al ASCO 2017. Abstract 8005

Results

Primary Endpoint Met:

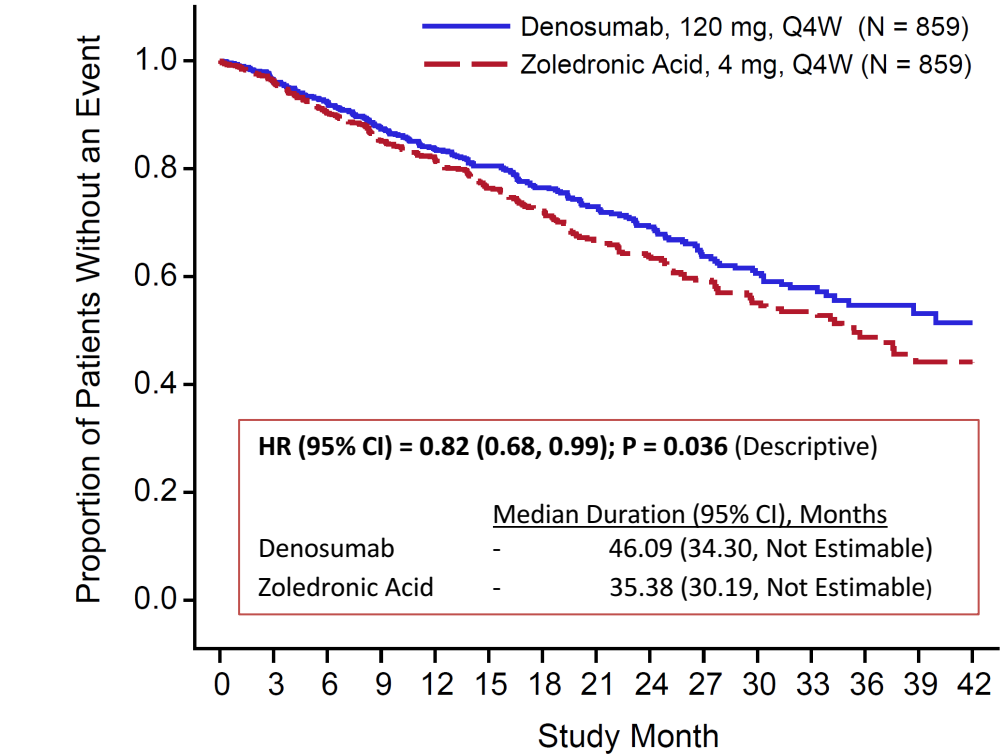
Noninferiority for Time to First On-Study Skeletal-Related Event



Raje et al ASCO 2017

Results

Exploratory Endpoint: Progression-Free Survival



Raje et al ASCO 2017

Results: Much Better Tolerated with Respect to Renal Toxicity

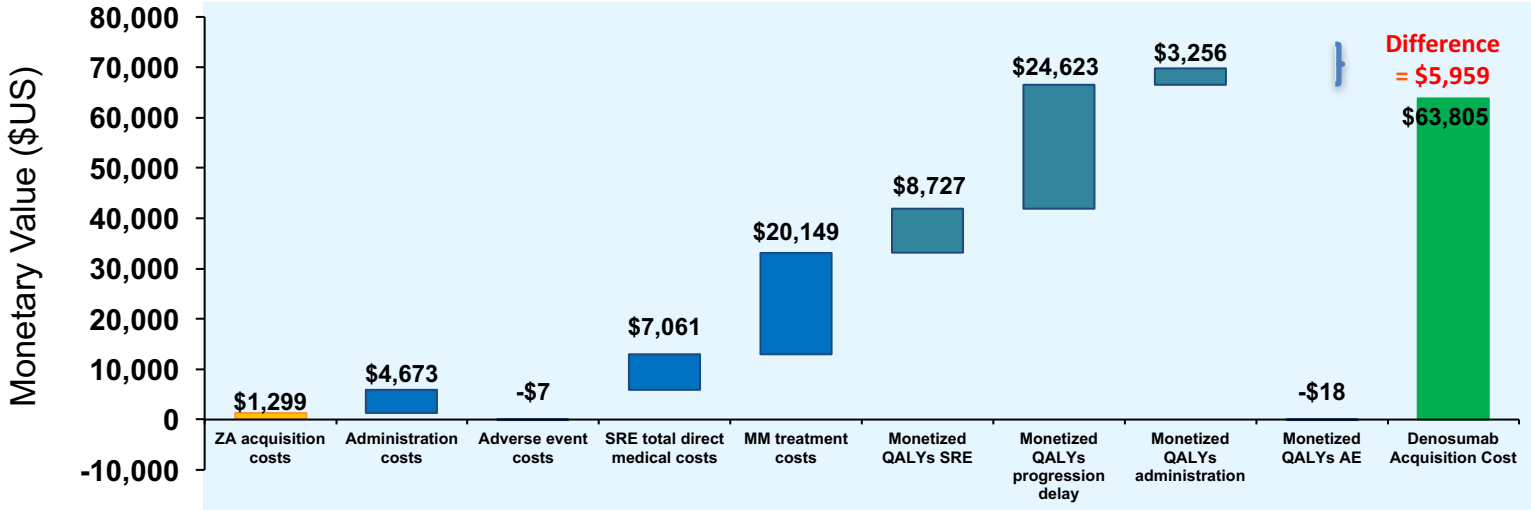
- There were significantly lower incidences of adverse events potentially related to renal toxicity with denosumab therapy compared to zoledronic acid, particularly in those patients with baseline CrCl ≤60mL/minute.
- The incidence of hypocalcemia, with the majority of events either grade 1 or 2, was greater for denosumab compared to zoledronic acid; there were no grade 5 events.

	All Patients			Patients With Baseline CrCl ≤60mL/minute		
	Denosumab N = 850		Zoledronic Acid N = 852	Denosumab N = 233		Zoledronic Acid N = 220
Renal Toxicity TEAEs, n (%)	85 (10.0)	P<0.001	146 (17.1)	30 (12.9)	P<0.001	58 (26.4)
Creatinine >2mg/dL; n/N1 (%)	31/824 (3.8)	P=0.010	54/823 (6.6)	20/216 (9.3)	P=0.054	32/203 (15.8)
Creatinine Doubled From Baseline; n/N2 (%)	28/841 (3.3)	P=0.002	55/840 (6.5)	6/233 (2.6)	P=0.027	16/220 (7.3)
Hypocalcemia TEAEs, n (%)	144 (16.9)	P=0.009	106 (12.4)	46 (19.7)	P=0.056	28 (12.7)
Osteonecrosis of the Jaw, Positively Adjudicated; n (%)	35 (4.1)	P=0.147	24 (2.8)	10 (4.3)	P=0.175	4 (1.8)

CrCl = Creatinine clearance; N = Number of patients who received ≥1 active dose of investigational product; N1 = Number of patients with baseline serum creatinine ≤2 mg/dL; N2 = Number of patients with non-missing baseline value of serum creatinine; TEAE = Treatment-emergent adverse event. Descriptive P's based on Fisher's exact test.

Results: The Value of Denosumab: Payer Perspective

The NMB of denosumab vs. zoledronic acid is $5,959[a].



Cost per QALY (incremental cost-effectiveness ratio): $52,524[a] - $125,568[b]

Payer perspective includes: SRE Direct costs (hospital, outpatient, long-term care & hospice, strong opioid) + QALY monetization. Assumes only 50% MM treatment cost offsets. Drug costs are ASP.

[a]Based on zoledronic acid ASP; [b]based on zoledronic acid WAC.

AE Adverse event; ASP Average sales price; MM Multiple myeloma; QALY Quality-adjusted life years; SRE Skeletal-related events; WAC Wholesale acquisition cost; ZA Zoledronic acid.