ANCO: ASCO Highlights 2018 Hematologic Malignancies

Brian A. Jonas, M.D., Ph.D.
UC Davis Comprehensive Cancer Center
August 25, 2018

UCDAVIS COMPREHENSIVE CANCER CENTER

Brian Jonas, MD, PhD

ANCO: ASCO Highlights 2018

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Consulting: AbbVie, Amgen, Tolero
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ASCO 2018 Annual Meeting Heme Abstracts

Devel Thera n=255 | Leuk, MDS, Allo n=83 | Plasma Cell n=60 | Lymphoma and CLL n=89

→ Abstracts Covered n=5

- **Abstract 7000**: Ivosidenib in mutant IDH1 relapsed/refractory acute myeloid leukemia: Results of a Phase 1 study.
- **Abstract 7010**: Durable response with venetoclax in combination with decitabine or azacitidine in elderly patients with acute myeloid leukemia.
- **Abstract 7502**: Phase 2 CAPTIVATE results of ibrutinib plus venetoclax in first-line CLL.
- **Abstract 8000**: Once-weekly vs twice-weekly carfilzomib dosing plus dexamethasone in patients with relapsed and refractory multiple myeloma: Results of the randomized phase 3 study A.R.R.O.W.
- **Abstract 8007**: bb2121 anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: Updated results from a multicenter phase I study.

Abstract 7000

7000

Ivosidenib (IVO; AG-120) in mutant IDH1 relapsed/refractory acute myeloid leukemia (R/R AML): Results of a phase 1 study

Daniel A Pollyea[1], Courtney D DiNardo[2], Stéphane de Botton[3], Eytan M Stein[4], Gail J Roboz[5], Alice S Mims[6], Ronan T Swords[7], Jessica K Altman[8], Robert H Collins[9], Gabriel N Mannis[10], Geoffrey L Uy[11], Will Donnellan[12], Arnaud Pigneux[13], Amir T Fathi[14], Hua Liu[15], Bin Wu[15], Eyal C Attar[15], Martin S Tallman[4], Richard M Stone,[16] Hagop M Kantarjian[2]

[1]University of Colorado School of Medicine, Aurora, CO; [2]University of Texas MD Anderson Cancer Center, Houston, TX; [3]Institut Gustave Roussy, Villejuif, France; [4]Memorial Sloan Kettering Cancer Center, New York, NY; [5]Weill Cornell Medical College, New York, NY; [6]Ohio State University Wexner Medical Center, Columbus, OH; [7]Sylvester Comprehensive Cancer Center, Miami, FL; [8]Northwestern University, Chicago, IL; [9]UT Southwestern Medical Center, Dallas, TX; [10]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; [11]Washington University School of Medicine, St Louis, MO; [12]Sarah Cannon Research Institute, Nashville, TN; [13]CHU Bordeaux, Bordeaux, France; [14]Massachusetts General Hospital Cancer Center, Boston, MA; [15]Agios Pharmaceuticals, Inc., Cambridge, MA; [16]Dana-Farber Cancer Institute, Boston, MA

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, June 1–5, 2018, Chicago, IL, USA 1

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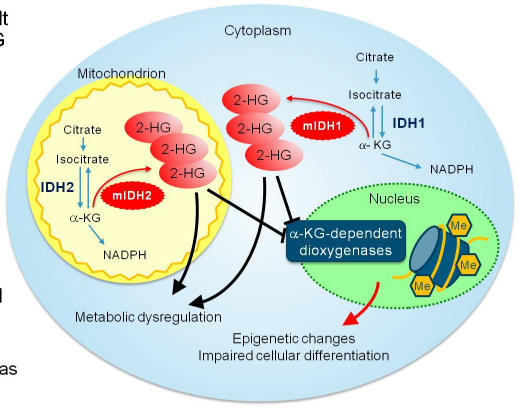
Isocitrate Dehydrogenase (IDH) Mutations as a Target in AML

- Somatic IDH1 and IDH2 mutations result in accumulation of oncometabolite 2-HG
  - → epigenetic changes, impaired cellular differentiation
- mIDH identified in multiple solid and hematologic tumors

	mIDH1	mIDH2
% of AML patients	~6–10%	~9–13%

- **Ivosidenib (AG-120):** an investigational first-in-class, oral, potent, reversible, targeted inhibitor of mIDH1 enzyme
  - under evaluation in multiple clinical trials as a single agent and in combinations



2-HG, 2-hydroxyglutarate; mIDH, mutant IDH

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IDH1 R132

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Study Design and Objectives

Single-arm, open-label, phase 1, multicenter trial

Dose escalation (n=78)
Enrollment complete

Patients with mIDH1+ advanced hematologic malignancies

Oral ivosidenib daily in continuous 28-day cycles

Doses included 100 mg BID, 300, 500, 800, 1200 mg QD

Dose expansion (n=180)
Enrollment complete: 500 mg QD in continuous 28-day cycles

1. R/R AML in 2nd+ relapse, relapse after SCT, refractory to induction or reinduction, or relapse within 1 year, **n=126**
2. Untreated AML not eligible for SOC, **n=25**
3. Other non-AML mIDH1 R/R advanced hematologic malignancies, **n=11**
4. Other R/R AML not eligible for Arm 1, **n=18**

Study objectives

Primary	Safety and tolerability, MTD and/or RP2D, clinical activity in mIDH1 R/R AML enrolled in expansion Arm 1
Secondary	DLTs, pharmacokinetics and pharmacodynamics (including 2-HG), preliminary clinical activity in advanced hematologic malignancies
Exploratory	Determination of comutations and mIDH1 variant allele frequency (VAF)

ClinicalTrials.gov NCT02074839. DLTs, dose limiting toxicities; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose

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Data reported on R/R AML 500mg (n=179) from escalation and Arm 1

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AEs of Interest: R/R AML 500 mg (n=179)

- **Leukocytosis[a]**
  - Grade ≥ 3 leukocytosis reported in 14/179 patients (8%)
  - Managed with hydroxyurea
  - None were fatal
- **ECG QT prolongation**
  - Grade ≥ 3 QT prolongation reported in 18/179 patients (10%)
  - Study drug was reduced in 2 patients and held in 13 patients (all grades)
  - None were fatal
  - QT prolonging medications such as antifungals and fluoroquinolone anti-infectives were allowed on study with monitoring
- **IDH differentiation syndrome (IDH-DS)**
  - All grade reported in 19/179 patients (10.6%)
  - Resolved in 17 patients, ongoing in 2 patients at data cut
  - Grade ≥ 3 IDH-DS in 9 (5.0%)
  - 7/19 IDH-DS patients had co-occurring leukocytosis
  - Study drug held in 6 patients (3.4%)
  - No instances of IDH-DS led to dose reduction, permanent treatment discontinuation, or death
  - Managed with corticosteroids and diuretics, and hydroxyurea if accompanied by leukocytosis
  - Best response for the 19 patients with IDH-DS:

Best Response	CR	CRh	CRi/CRp	MLFS	SD	NE
n=19	5	0	3	2	8	1

These events were managed using standard of care treatments and ivosidenib dose modifications as required

[a]Grade 3 = WBC > 100,000/mm^3; Grade 4 = clinical manifestations of leukostasis, urgent intervention indicated

Data cutoff: 10Nov2017 CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; NE, not evaluable; SD, stable disease

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Other G3+ TEAE in >1 patient – febrile neutropenia (29.1%), anemia (20.1%), diarrhea (2.2%), fatigue (1.7%), dyspnea (3.9%), pyrexia 1.1%)

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Response in R/R AML 500 mg (n=179)

	R/R AML 500 mg (n=179)
CR+CRh rate, n (%) [95% CI]	**57 (31.8) [25.1, 39.2]**
Time to CR/CRh, median (range) months	2.0 (0.9, 5.6)
Duration of CR/CRh, median [95% CI] months	8.2 [5.6, 12.0]
CR rate, n (%) [95% CI]	43 (24.0) [18.0, 31.0]
Time to CR, median (range) months	2.8 (0.9, 8.3)
Duration of CR, median [95% CI] months	10.1 [6.5, 22.2]
CRh rate, n (%)	14 (7.8)
Duration of CRh, median [95% CI] months	3.6 [1.0, 5.5]

	R/R AML 500 mg (n=179)
Overall Response Rate, n (%) [95% CI]	**75 (41.9) [34.6, 49.5]**
Time to first response, median (range) months	1.9 (0.8, 4.7)
Duration of response, median [95% CI] months	6.5 [5.5, 10.1]
Best response, n (%)	
CR	43 (24.0)
CRi or CRp	21 (11.7)
MLFS	11 (6.1)
SD	68 (38.0)
PD	15 (8.4)
NA	21 (11.7)

CRh = 9 patients with investigator-assessed responses of CRi/CRp and 5 with MLFS

Among the 179 patients with R/R AML, 5 from dose escalation and 1 from dose expansion were not positive for mIDH1 by the companion diagnostic test and none of these 6 patients achieved a CR or CRh
CR+CRh was consistent across baseline age groups, including patients who were > 65 years of age
Overall response rate includes CR, CRi/CRp, MLFS and PR

Data cutoff: 10Nov2017. PD, progressive disease; PR, partial response

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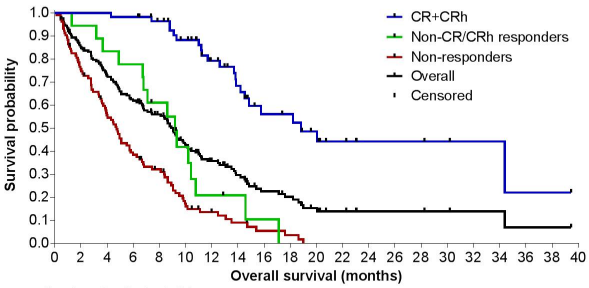
Overall Survival by Best Response in R/R AML 500 mg (n=179)



	Months
Overall survival, median [95% CI]	
CR+CRh	18.8 [14.2, NE]
Non-CR/CRh responders	9.2 [6.7, 10.8]
Non-responders	4.7 [3.7, 5.7]
All	9.0 [7.1, 10.0]
Overall follow-up, median (range)	15.3 (0.2–39.5)

Number of patients at risk:

CR+CRh	57	57	57	56	50	43	32	25	16	15	11	7	4	4	4	3	2	2	1	1
Non-CR/CRh responders	18	17	15	14	10	6	3	2	1	0										
Non-responders	104	77	55	38	29	15	9	6	3	2	0									

Non-CR/CRh responders include CRi, CRp, and MLFS who are not CRh
Non-responders = all others including those with best responses of SD, PD, or not evaluable

Data cutoff: 10Nov2017 NE, not estimable 13

Overall transfusion independence: Platelet 38.5%, RBC 42.3%

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Abstract 7000 Conclusions

- Ivosidenib is an oral IDH1 inhibitor that is well tolerated and induces durable responses in patients with R/R IDH1-mutated AML
  - Non-CR/CRh responders also had favorable OS
  - 23% of CR/CRh responders cleared IDH1 mutation
- Need to be aware of IDH-DS
- Study impact:
  - Results published in NEJM 2018; 378(25): 2386-98
  - Ivosidenib (Tibsovo) FDA approved on 7/20/18
  - New standard of care for R/R mIDH1 AML

Abstract 7010

Durable Response with Venetoclax in Combination with Decitabine or Azacitidine in Elderly Patients with Acute Myeloid Leukemia

Courtney D. DiNardo[1], Keith Pratz[2], Jalaja Potluri[3], Vinod Pullarkat[4], Brian A. Jonas[5], Andrew H. Wei[6], Pamela S. Becker[7], Olga Frankfurt[8], Martha Arellano[9] Tu Xu[3], Wan-Jen Hong[10], Brenda Chyla[3], Daniel A. Pollyea[11], Anthony Letai[12]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; [3]AbbVie Inc., North Chicago, IL, USA; [4]Department of Hematology and Hematopoietic Cell Transplantation and Gehr Family Center for Leukemia Research, City of Hope National Medical Center, Duarte, CA, USA; [5]University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA; [6]The Alfred Hospital and Monash University, Melbourne, Australia; [7]Clinical Research Division, Fred Hutchinson Cancer Research Center and Division of Hematology, Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA; [8]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [9]Department of Hematology and Oncology, Emory University School of Medicine, Atlanta, GA, USA; [10]Genentech, Inc., South San Francisco, CA, USA; [11]University of Colorado School of Medicine, Aurora, CO, USA; [12]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

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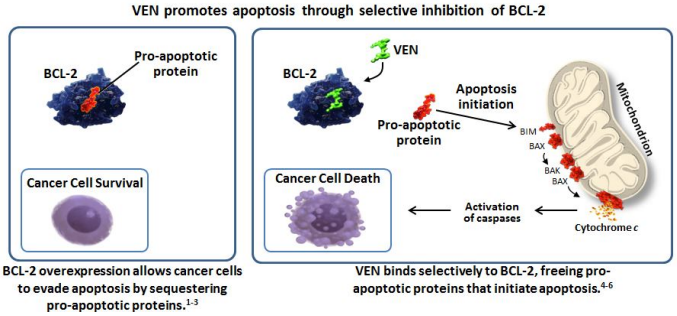
Venetoclax and AML



- AML – median age at diagnosis 68 and pts are often ineligible for or refractory to intense chemotherapy
- BCL-2 is highly expressed in AML and is associated with poor outcomes
- Ven is an oral BCL-2 inhibitor with activity in AML

Pratz et al, BSH, #BSH18-OR-007.
Mihalyova et al, Exp Hematol 2018.

Study Design and Objectives

- **Design:** Phase 1b, open label, multicenter dose escalation and expansion
- **Endpoints:** Safety, Rates of CR/CRi, Overall Survival (OS), and Duration of Response (DOR)

PRIMARY OBJECTIVE

To assess the safety of venetoclax in combination with decitabine or azacitidine in patients ≥65 years of age with untreated AML who are ineligible for standard induction chemotherapy

SECONDARY OBJECTIVE

To assess CR, CRi, DOR, and OS

EXPLORATORY OBJECTIVE

To assess the impact of venetoclax on minimal residual disease (MRD)

***Venetoclax dose ramped up from 100mg to 400mg or 800mg over 3-4 days**

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Treatment Emergent Adverse Events (AE)

AEs in ≥25% of patients	Any grade	Grade 3/4
Any event, n (%)	145 (100)	141 (97)
Nausea	88 (61)	2 (1)
Diarrhea	76 (52)	7 (5)
Constipation	70 (48)	2 (1)
Febrile neutropenia	63 (43)	63 (43)
Fatigue	54 (37)	8 (6)
Hypokalemia	49 (34)	15 (10)
Decreased appetite	48 (33)	3 (2)
Decreased WBC count	45 (31)	45 (31)
Vomiting	44 (30)	0
Platelet count decreased	42 (30)	35 (24)
Anemia	40 (28)	36 (25)
Cough	41 (28)	0
Peripheral edema	41 (28)	0

Serious AEs in ≥3% of patients	N = 145
Any event, n (%)	102 (70)
Febrile neutropenia	46 (32)
Pneumonia	17 (12)
Bacterial Infection	9 (6)
Lung Infection	7 (5)
Sepsis	6 (4)
Hypotension	5 (3)
Mental Status Changes	4 (3)
Gastrointestinal Hemorrhage	4 (3)
Mucosal Inflammation	4 (3)

Patient Disposition	N=145
Deaths, n (%)	
≤30 days after Ven start	5 (3)
≤60 days after Ven start	11 (8)

- Rates of AEs between patients treated with Dec or Aza were similar at respective Ven doses
- No events of laboratory or clinical tumor lysis syndrome (TLS) were observed

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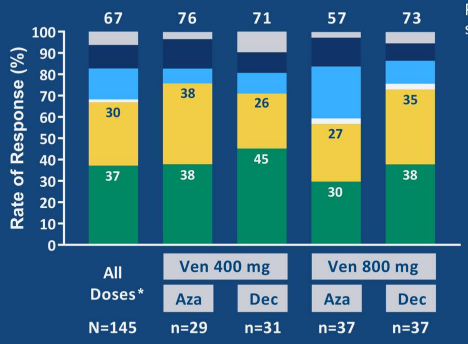
Response Rates by Treatment



Patients (%) with CR/CRi shown at the top of each bar

Other
RD
MLFS
PR
CRi
CR

CR/CRi and MRD Negative: 29% overall 45% Aza 400

* All doses includes 11 patients that received 1200 mg venetoclax

Abbreviations: CR, complete remission; CRi, CR with incomplete blood count recovery; PR, partial remission; MLFS, morphogenic leukemia free state; RD, resistant disease.

Other, disease progression, or discontinued prior to assessment

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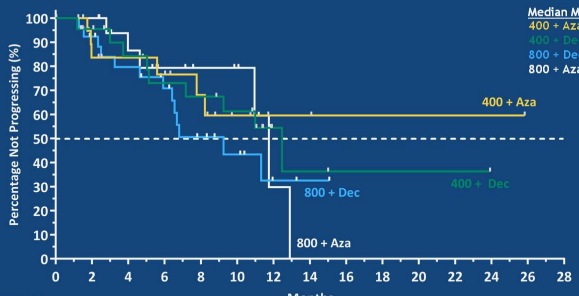
Duration of Response after CR/CRi



Median Months of Response (95% CI)

400 + Aza	NR (5.6 – NR)
400 + Dec	12.5 (5.1 – NR)
800 + Dec	9.2 (5.9 – NR)
800 + Aza	11.7 (4.6 – 12.9)

Patients at Risk

400 + Dec	22	19	15	13	12	10	3	2	1	1	1	1	
400 + Aza	22	15	13	11	8	4	2	2	1	1	1	1	1
800 + Dec	27	23	19	15	9	6	2	1					
800 + Aza	21	18	12	8	6	5	1						

Abbreviations:
400, 400 mg venetoclax;
800, 800 mg venetoclax
NR, not reached
NA, not available

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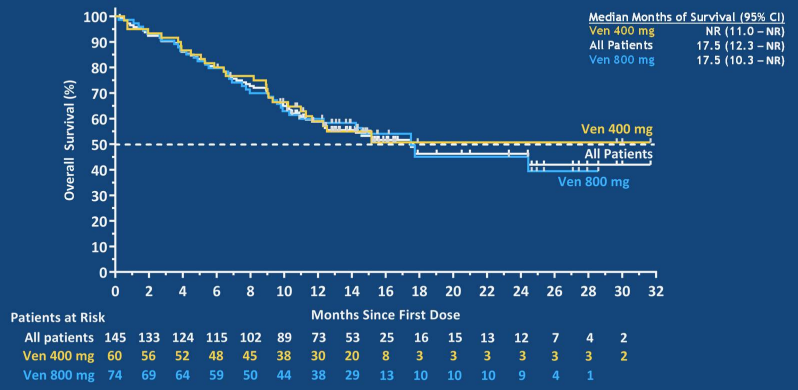
Overall Survival



Patients at Risk

All patients	145	133	124	115	102	89	73	53	25	16	15	13	12	7	4	2
Ven 400 mg	60	56	52	48	45	38	30	20	8	3	3	3	3	3	3	2
Ven 800 mg	74	69	64	59	50	44	38	29	13	10	10	10	9	4	1	

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PRESENTED BY: Courtney D. DiNardo, MD, MSCE

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Abstract 7010 Conclusions

- The combination of Ven + HMA has significant activity in elderly and high risk AML, including high CR/CRi rates, MRD negativity, DoR and OS
- Regimen is tolerable but management is very different from typical HMA monotherapy
- Study impact:
  - Results published in Lancet Oncology 2018; 19: 216-28
  - FDA breakthrough designation for AML 1/2016
  - Regimen is already being used off-label by many groups
  - May become the standard of care for elderly AML - P3 RDBPC trial of Aza+Ven vs Aza+Placebo is ongoing

Abstract 7502

Phase 2 CAPTIVATE Results of Ibrutinib Plus Venetoclax in First-line Chronic Lymphocytic Leukemia (CLL)

William G. Wierda, MD, PhD,[1] Tanya Siddiqi, MD,[2] Ian W. Flinn, MD, PhD,[3] Xavier C. Badoux, MBBS, FRACP, FRCPA,[4] Thomas J. Kipps, MD, PhD,[5] John N. Allan, MD,[6] Alessandra Tedeschi, MD,[7] John M. Pagel, MD, PhD,[8] Bryone J. Kuss, MBBS, PhD, FRACP, FRCPA,[9] Eva Gonzalez-Barca, MD, PhD,[10] Paolo Ghia, MD, PhD,[11] Karl Eckert, BA,[12] Kristin Russell, BS,[12] Cathy Zhou, MS,[12] Joi Ninomoto, PharmD,[12] James P. Dean, MD, PhD,[12] Danelle F. James, MD, MAS,[12] Constantine S. Tam, MBBS[13]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]City of Hope National Medical Center, Duarte, CA, USA; [3]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [4]St George Hospital, Sydney, NSW, Australia; [5]University of California San Diego, Moores Cancer Center, San Diego, CA, USA; [6]Weill Cornell Medicine, New York, NY, USA; [7]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [8]Swedish Cancer Institute, Seattle, WA, USA; [9]Flinders Medical Centre, Adelaide, SA, Australia; [10]Institut Català d'Oncologia L'Hospitalet, IDIBELL, Barcelona, Spain; [11]Università Vita-Salute San Raffaele and IRCCS Istituto Scientifico San Raffaele, Milano, Italy; [12]Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA, USA; [13]Peter MacCallum Cancer Centre and St. Vincent's Hospital, Melbourne, VIC, Australia

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Introduction

- Ibrutinib: first-in-class, once-daily oral BTK inhibitor
  - High single-agent efficacy in CLL but undetectable MRD is rare[1-3]
- Venetoclax: oral BCL-2 inhibitor with high activity in CLL
- Rationale for ibrutinib + venetoclax (I+V)
  - Synergy and complementary clinical activities with combination in preclinical and ongoing clinical studies[4-6]
  - Potential for deeper remissions and ibrutinib treatment holidays with all-oral combination
  - Potential to lower tumor lysis syndrome (TLS) risk with ibrutinib lead-in[7-9]
- Phase 2 CAPTIVATE study (PCYC-1142): I+V in first-line CLL
  - Primary objectives (MRD Cohort):
    - Pre-randomization phase: undetectable MRD ($<10^{-4}$) clinical response rate with I+V
    - Randomization phase: 1-year disease-free survival (DFS)* to evaluate if ibrutinib discontinuation in the setting of confirmed undetectable MRD with I+V allows for treatment holiday

*Defined as continued undetectable MRD response without progression or death at least 1 year after randomization.

1. Burger JA, et al. N Engl J Med. 2015;373(25):2425-37; 2. Byrd JC, et al. N Engl J Med. 2013;369(1):32-42; 3. Byrd JC, et al. Blood. 2015;125(16):2497-506; 4. Cervantes-Gomez F, et al. Clin Cancer Res. 2015;21(16):3705-15; 5. Deng J, et al. Leukemia. 2017;31(10):2075-84; 6. Tam CS, et al. N Engl J Med. 2018;378(13):1211-23; 7. Olin JL, et al. J Oncol Pharm Pract. 2017; Jan 1 [Epub ahead of print]; 8. VENCLEXTA™ (venetoclax) prescribing information. North Chicago, IL: AbbVie, Inc. 2017; 9. Wierda WG, et al. iwCLL 2017. Abstract 106.

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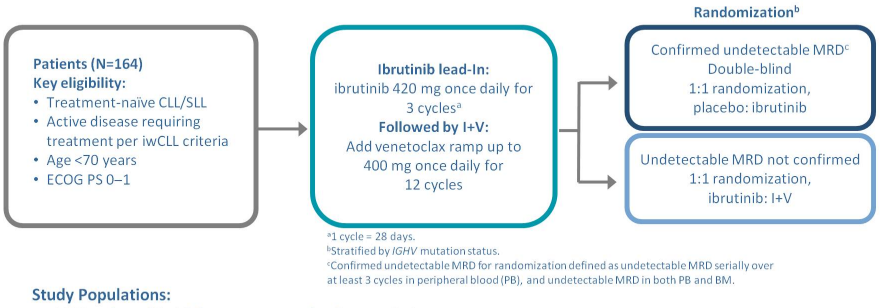
Phase 2 CAPTIVATE Study Design (NCT02910583)



[a]1 cycle = 28 days.
[b]Stratified by *IGHV* mutation status.
[c]Confirmed undetectable MRD for randomization defined as undetectable MRD serially over at least 3 cycles in peripheral blood (PB), and undetectable MRD in both PB and BM.

Study Populations:

- MRD cohort (N=164): exposure and safety analysis
  - Safety Run-in: first 14 patients completed C15 treatment (12 cycles of I+V); no dose-limiting toxicities (DLT) or clinical TLS during first 6 weeks of I+V combination
  - Prespecified analysis of the first 30 patients who completed C9 treatment (6 cycles of I+V) for MRD evaluation
- Fixed Duration cohort (N=159): separate cohort; analysis not shown

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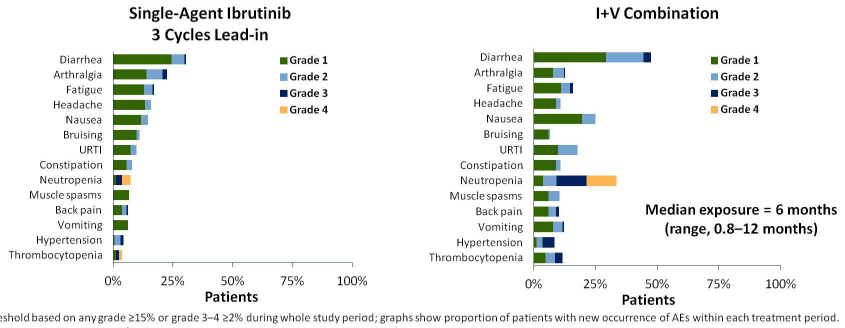
Most Common Adverse Events* by Time of Onset in All Treated Population (N=164)



*Threshold based on any grade ≥15% or grade 3–4 ≥2% during whole study period; graphs show proportion of patients with new occurrence of AEs within each treatment period.
URTI, upper respiratory tract infection.

- Atrial fibrillation: 5 patients (3.0%; grade 3 in 1.2%) during ibrutinib lead-in; 7 patients (4.3%; grade 3 in 0.6%) during I+V combination; no grade 4 events
- Grade 3 infections: 4 patients (2.4%) during ibrutinib lead-in; 4 patients (2.4%) during I+V combination; no grade 4 infections

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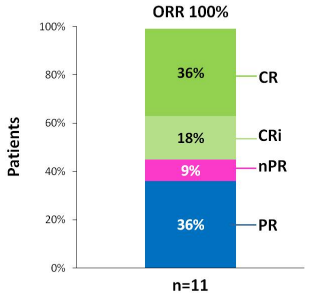
Deep Responses Achieved With 12 Cycles I+V With Undetectable MRD in PB and BM



MRD and Full ORR Assessments to Date (n=11)	CR/CRi (n=6)	PR/nPR (n=5)[a]
Confirmed undetectable MRD (n=9)	6/6[b]	3/5
Detectable MRD (n=2)[c]	0/6	2/5

[a]4/5 patients had LN 1.6 to 2.5 cm.
[b]Includes 1 patient with variant CLL.
[c]CLL cells <1% in these 2 patients.

- Clinical response assessment in 11/14 patients who completed 12 cycles of I+V
  - 6/11 (55%) CR/CRi and 5/11 (45%) nPR/PR
- Confirmed undetectable MRD ($<10^{-4}$) in all patients with CR/CRi
- CR/CRi in 2/2 patients with del17p and 4/9 patients without del17p

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Undetectable MRD is <1 CLL cell per 10,000 leukocytes ($<10^{-4}$) by 8-color flow

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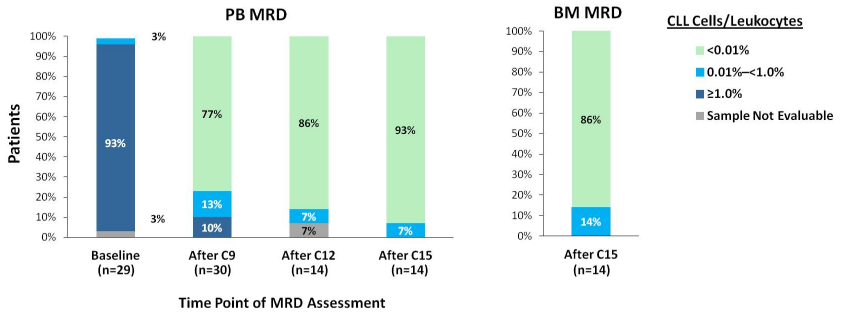
Early Undetectable MRD Responses Sustained Over Time



- High rates of undetectable MRD (77%) in PB after 6 cycles of I+V
- Confirmed undetectable MRD* in 11 of 14 patients (79%) after 12 cycles of I+V

*Confirmed undetectable MRD defined as undetectable MRD serially over at least 3 cycles in PB, and undetectable MRD in both PB and BM. BM MRD was assessed per protocol after C15 for all patients who reached this time point as of the data extract.

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ASCO 2018, 1142 Wierda et al.

Presented By William Wierda at 2018 ASCO Annual Meeting

Abstract 7502 Conclusions

- The combination of ibrutinib and venetoclax induces high rates of response and MRD negative response in untreated CLL, including del(17p).
- Tumor debulking with ibrutinib lead-in phase decreased risk of TLS with venetoclax
- Study impact:
  - Both ibrutinib and venetoclax (after 1 prior Rx) are approved in CLL
  - Promising combination that merits further study
  - P3 trial evaluating I+V fixed duration in 1st line CLL

Abstract 8000

Once-weekly Versus Twice-weekly Carfilzomib Dosing in Patients with Relapsed and Refractory Multiple Myeloma: Results of the Randomized Phase 3 Study A.R.R.O.W.

María-Victoria Mateos,[1] Philippe Moreau,[2] James R. Berenson,[3] Katja Weisel,[4] Antonio Lazzaro,[5] Kevin Song,[6] Meletios A. Dimopoulos,[7] Mei Huang,[8] Anita Zahlten-Kumeli,[8] and A. Keith Stewart[9]

[1]Hematology, Hospital Clinico Universitario de Salamanca-IBSAL, Salamanca, Spain; [2]Hematology Department, University of Nantes, Nantes, France; [3]Institute for Myeloma and Bone Cancer Research, West Hollywood, CA, USA; [4]Universitatsklinikum Tubingen, Tubingen, Germany; [5]Department of Clinical Oncology and Hematology, Division of Hematology and Bone Marrow Transplant Center, Hospital Gulielmo da Saliceto, Piacenza, Italy; [6]Leukemia/Bone Marrow Transplant Program of British Columbia, Vancouver, British Columbia, Canada; [7]National and Kapodistrian University of Athens, Athens, Greece; [8]Amgen Inc., Thousand Oaks, CA, USA; [9]Division of Hematology/Oncology, Mayo Clinic, Scottsdale, AZ, USA

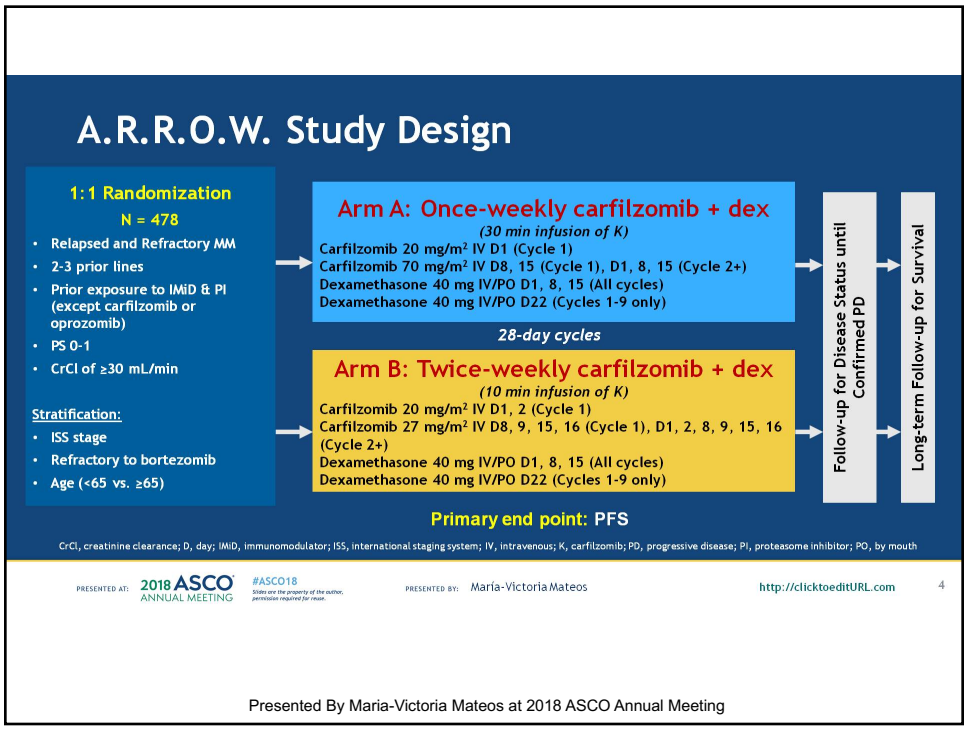
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: María-Victoria Mateos

Presented By Maria-Victoria Mateos at 2018 ASCO Annual Meeting

A.R.R.O.W. Study Background

- Carfilzomib approved for RRMM
  - Single agent: 20/27mg/m2 days 1, 2, 8, 9, 15 and 16 on a 28d schedule
  - Kd: 20/56mg/m2 days 1, 2, 8, 9, 15 and 16 on a 28d schedule with Dex (ENDEAVOR)
  - KRd: 20/27mg/m2 days 1, 2, 8, 9, 15 and 16 on a 28d schedule with Len and Dex (ASPIRE)
- CHAMPION-1 study in RRMM established MTD for weekly Carfilzomib at 70mg/m2



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Hematologic and Nonhematologic Adverse Events

Hematologic TEAE %, preferred term	Once-weekly Kd (n=238)		Twice-weekly Kd (n=235)	
	All grades	Grade ≥3	All grades	Grade ≥3
Anemia	26	18	32	18
Thrombocytopenia	13	7	9	7
Neutropenia	9	6	8	7
Nonhematologic TEAE % (≥20% in either arm), preferred term				
Pyrexia	23	1	16	2
Hypertension	21	6	20	5
Fatigue	20	5	20	2
Diarrhea	19	1	20	1
Insomnia	15	1	20	0

TEAE, treatment-emergent adverse event.

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Safety findings consistent with known safety profile of carfilzomib, including risks of neuropathy, renal failure, cardiac failure, ischemic heart disease and pulm HTN.

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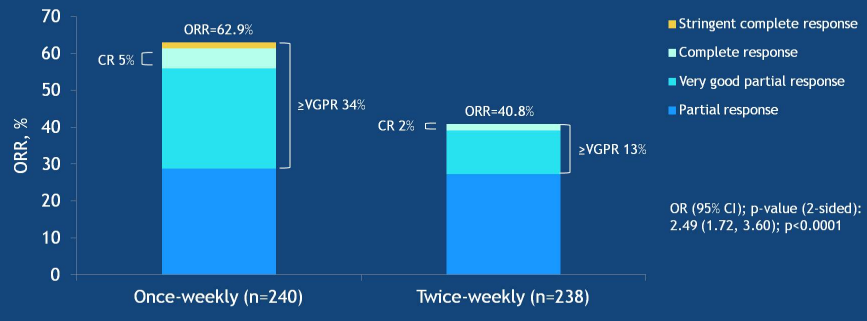
Overall Response Rates



CI, confidence interval; CR, complete response; OR, odds ratio; VGPR, very good partial response.

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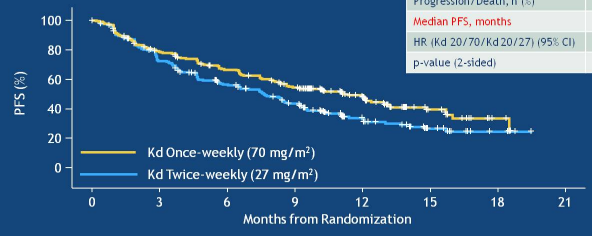
Primary Endpoint: PFS

	Once-weekly Kd 20/70 mg/m² (n=240)	Twice-weekly Kd 20/27 mg/m² (n=238)
Progression/Death, n (%)	126 (53%)	148 (62%)
Median PFS, months	11.2	7.6
HR (Kd 20/70/Kd 20/27) (95% CI)	0.693 (0.544, 0.883)	
p-value (2-sided)	0.0029	



Number of Patients at Risk:

Kd 20/70	240	178	145	114	69	24	5	0
Kd 20/27	238	164	119	86	41	15	4	0

Data cutoff date: June 15, 2017; Median follow-up: 12.6 (once-weekly) and 12.0 (twice-weekly) months

CI, confidence interval; HR, hazard ratio

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http://clicktoeditURL.com 7

No significant difference in OS (median NR for both arms)

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Abstract 8000 Conclusions

- Once-weekly Kd at 70mg/m2 improved PFS and ORR compared to twice-weekly Kd at 27mg/m2
- Overall safety profile was comparable
- Study impact:
  - Results published in Lancet Oncology 2018; 19(7): 953-64
  - A new convenient treatment option in RRMM that appears to be safe and effective
  - Overall, however, the optimal schedule and dose of carfilzomib remains unclear (e.g. 1 vs 2 times weekly, 27mg/m2 vs 56mg/m2 vs 70 mg/m2)

Abstract 8007

ABSTRACT 8007

bb2121 Anti-BCMA CAR T Cell Therapy in Patients With Relapsed/Refractory Multiple Myeloma: Updated Results From a Multicenter Phase I Study

Noopur Raje, MD,[1] Jesus Berdeja, MD,[2] Yi Lin, MD, PhD,[3] Nikhil Munshi, MD,[4] David Siegel, MD, PhD,[5] Michaela Liedtke, MD,[6] Sundar Jagannath, MD,[7] Deepu Madduri, MD,[7] Jacalyn Rosenblatt, MD,[8] Marcela Maus, MD, PhD,[1] Ashley Turka,[9] Lyh Ping Lam, PharmD,[9] Richard A. Morgan, PhD,[9] M. Travis Quigley,[9] Monica Massaro, MPH,[9] Kristen Hege, MD,[10] Fabio Petrocca, MD,[9] and James N. Kochenderfer, MD[11]

[1]*Massachusetts General Hospital Cancer Center, Boston, MA;* [2]*Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN;* [3]*Mayo Clinic, Rochester, MN;* [4]*Dana-Farber Cancer Institute, Boston, MA;* [5]*Hackensack University Medical Center, Hackensack, NJ;* [6]*Stanford University Medical Center, Palo Alto, CA;* [7]*Mount Sinai Medical Center, New York, NY;* [8]*Beth Israel Deaconess Medical Center, Boston, MA;* [9]*bluebird bio, Inc, Cambridge, MA;* [10]*Celgene Corporation, San Francisco, CA;* [11]*Experimental Transplantation and Immunology Branch, National Cancer Institute/National Institutes of Health, Bethesda, MD*

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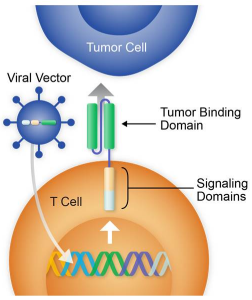
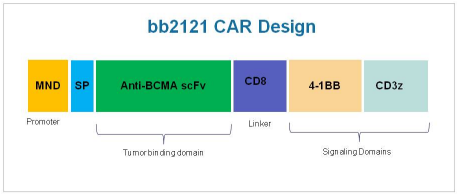
bb2121: AN OPTIMAL BCMA CAR T CELL DESIGN





- Autologous T cells transduced with a lentiviral vector encoding a CAR specific for human BCMA
- State of the art lentiviral vector system
- Optimal 4-1BB costimulatory signaling domain: associated with less acute toxicity and more durable CAR T cell persistence than CD28 costimulatory domain[1]

1. Ali SI, et al. *Blood*. 2016;128(13):1688-700.

BCMA (B-cell maturation antigen) is highly expressed in MM and is not expressed in normal human tissues except for plasma cells.

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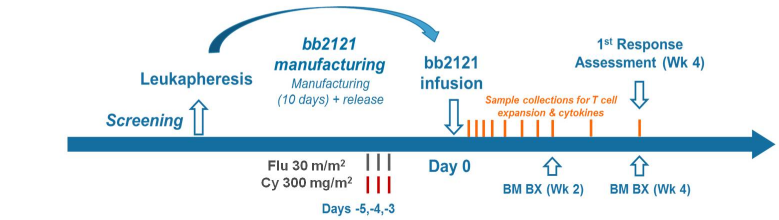
CRB-401 PHASE 1 STUDY DESIGN



Dose Escalation (N=21)

≥50% BCMA expression

50 × 10⁶ → 150 × 10⁶ → 450 × 10⁶ → 800 × 10⁶

Dose Expansion (N=22)

<50% BCMA expression (n=10)

≥50% BCMA expression (n=12)

Dose range: 150–450 × 10⁶ CAR+ cells

Manufacturing success rate of 100%

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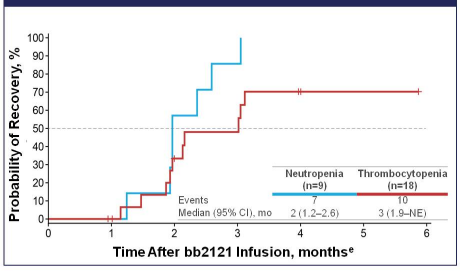
ADVERSE EVENTS OF SPECIAL INTEREST

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 × 10⁶ 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.

CRS – 39% (no G3) at 150 x10^6 cells and 82% (no G4, 9% G3) at >150 x10^6 cells
Median time to onset 2d (1-25)

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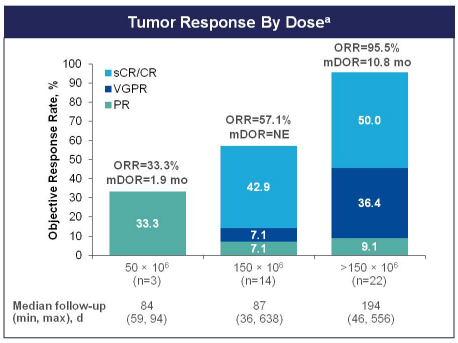
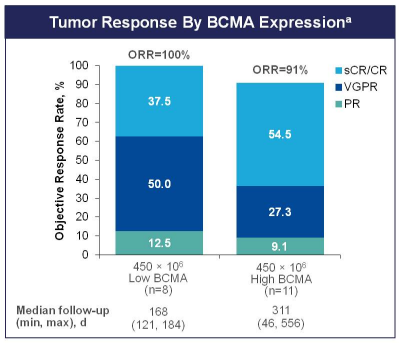
TUMOR RESPONSE: DOSE-RELATED; INDEPENDENT OF TUMOR BCMA EXPRESSION





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%.

MRD-evaluable responders (n=16) – 100% were MRD-neg (< 1 x 10^{-4} by NGS)

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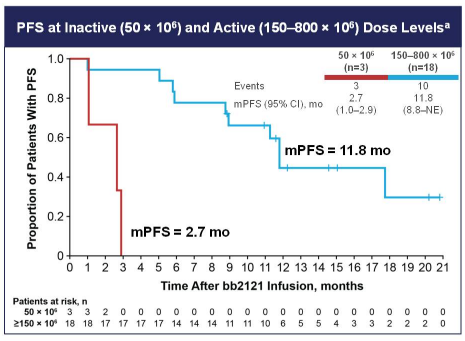
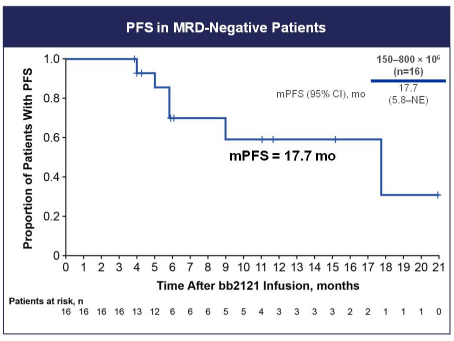
PROGRESSION-FREE SURVIVAL

- 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





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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Abstract 8007 Conclusions

- bb2121 at active doses (≥150 x 10^6 CAR T-cells) induces deep and durable responses in heavily pretreated RRMM
- Tolerable safety profile with mostly G1/2 CRS and infrequent tocilizumab and steroid use
- Study impact:
  - FDA breakthrough designation for RRMM 11/2017
  - Anti-CD19 CAR T-cells are approved for R/R aggressive B-cell NHL and R/R B-ALL, and this study shows that a CAR T-cell platform for MM is also feasible and effective

Summary and Take Home Points

- Ivosidenib is an oral mIDH1 inhibitor and is a new standard of care for R/R IDH1-mutated AML. IDH-DS is a possible dangerous side effect.
- Venetoclax plus HMA has significant activity in elderly AML and may ultimately become the standard of care for older unfit AML. Management is very different from standard HMA monotherapy.
- The combination of ibrutinib plus venetoclax is highly active and induces a high rate of MRD negative responses in 1st line CLL. The regimen has potential to become a standard regimen for CLL.
- Convenient once weekly carfilzomib 70mg/m2 dosing plus dex appears safe and effective in RRMM and represents a new treatment option. The optimal dose and schedule of carfilzomib remains unclear.
- Anti-BCMA CAR T-cell therapy has a tolerable safety profile and is effective in RRMM, and may ultimately join the list of approved CAR T-cell therapies.

Questions?

bajonas@ucdavis.edu

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Other Abstracts of Potential Interest

- **Abstract 7001**: Early HMA for low risk MDS
- **Abstract 7002**: Bosutinib vs imatinib first line for CML
- **Abstract 7003**: Long-term TFR after second-line nilotinib discontinuation
- **Abstract 7004**: moxetumomab pasudotox for R/R hairy cell leukemia
- **Abstract 8003**: ibrutinib/rituximab vs placebo/rituximab in R/R WM
- **Abstracts 8015, 8017, 8022 and 8032**: carfilzomib schedule and dosing
- **Abstract 8025**: autotransplant in MM feasible in ages 75+
- **Abstract 7500:** lenaidomide plus rituximab vs chemo plus rituximab followed by rituximab maintenance for untreated follicular lymphoma
- **Abstract 7501**: acalabrutinib for untreated and R/R WM
- **Abstract 7504**: anti-CD47 plus rituximab for R/R NHL
- **Abstract 7508**: High rates and durability of MRD- with venetoclax plus rituximab in R/R CLL
- **Abstract 7515**: Rituximab maintenance after BR in MZL