Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

September 11 , 2021

ANCO

Educating and Empowering the
Northern California Cancer Community

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Association of Northern California Oncologists (ANCO)

presents

Hematologic Malignancies Updates: Leukemias, Lymphomas. & Myeloma 2021

Virtual

Agenda & Schedule for September 11, 2021

9:00AM Welcome & Introductions
Courtney Flookes, ANCO Executive Director

9:05AM Myeloma U*pdate 2021*
Nina Shah, MD, University of California, San Francisco

9:50 AM Lymphoma Update 2021
Joseph Tuscano, MD, University of California, Davis

10:35AM Stretch Break and Faculty Meet and Greet

11:00 AM Leukemia U*pdate 2021*
Gabriel Mannis, MD, Stanford University

11:45AM Case Presentations Leukemias, Lymphomas. & Myeloma
Tamer Adel Othman, MD, Fellow, University of California, Davis

12:30PM ADJOURN

Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Program Faculty

Gabriel N. Mannis, **MD**
Assistant Professor of Medicine, Stanford University

Joseph M. Tuscano, **MD**
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Professor of Clinical Medicine, University of California, San Francisco

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UC Davis Comprehensive
Cancer Center

Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Disclosure of Relevant Financial Relationships

The *Faculty* members have disclosed the following actual or potential conflicts of interest in regard to this program:

Gabriel N. Mannis, MD*,* disclosed that he is a consultant for AbbVie, Agios, Macrogenics, Pfizer; He serves on the advisory board for AbbVie, Agios, Astellas, BMS/Celegene, Genentech, and Stemline and has received grant/research support from Glycomimetics, Forty Seven/Gilead, and Jazz Pharmaceuticals.

Joseph M. Tuscano, MD has disclosed that he has received grant/research support from Achrotech, BMS,Genentech, and Pharmacyclics.

Nina Shah, MD, disclosed that she has received grant/research support from Celgene/BMS, Janssen, Bluebird Bio, Sutro Biopharma, Teneobio, Poseida, Nektar, and Precision Bioscience; she is a consultant for GSK, Amgen, Indapta Therapeutics, Sanofi, CareDx, Kite, Karyopharm, Oncopeptides, and CSL Behring

Tamer Adel Othman, MD*,* disclosed that he does not have any relevant financial relationships with any commercial interests.

Acknowledgement of Financial Support

This activity is supported by:

AbbVie

AstraZeneca

Bristol Myers Squibb

GSK

Morphosys US

Pharmacyclics

Takeda Oncology

Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Confessions of a #Myelennial: Multiple myeloma as we know it in 2021

Nina Shah, MD
Professor of Clinical Medicine
Multiple Myeloma Translational Initiative
Division of Hematology-Oncology
University of California San Francisco

Topics we can all disagree on

- Choice of induction regimen
  - Transplant eligible
    - Transplant optional
  - Transplant ineligible
- To transplant or not to transplant
- What to do at 1st relapse
- How to treat RRMM

VRD =

Is K the new V ??

- *KRD vs VRD…*

ECOG-ACRIN cancer research group
Reshaping the future of patient care

Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma: results of ENDURANCE (E1A11) phase 3 trial

Shaji K. Kumar, Susanna J. Jacobus, Adam D. Cohen, Matthias Weiss, Natalie Scott Callander, Avina A. Singh, Terri L. Parker, Alexander Menter, Alex Yang, Benjamin Marshall Parsons, Pankaj Kumar, Prashant Kapoor, Aaron Seth Rosenberg, Jeffrey A. Zonder, Edward Anthony Faber, Sagar Lonial, Paul G. Richardson, Robert Z. Orlowski, Lynne I. Wagner, S. Vincent Rajkumar

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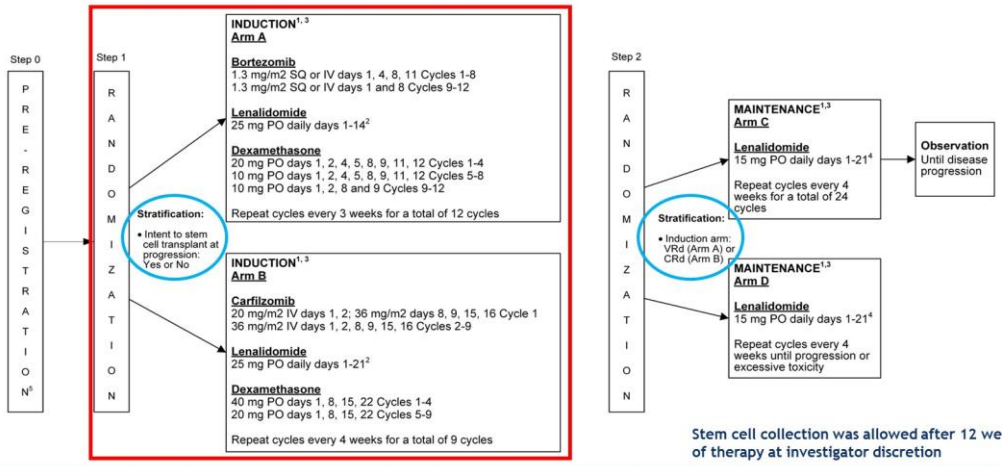
Presented By Shaji Kumar at ASCO 2020

Patient Randomization and Treatment Schedule



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Induction Treatment Status

N=1053 starting assigned treatment

	VRd (n=527)	KRd (n=526)	Total (n=1053)
Reason	**N (%)**	**N (%)**	**N (%)**
Treatment Completed	228 (43.3)	324 (61.6)	552 (52.4)
Disease Progression	33 (6.3)	19 (3.6)	52 (4.9)
Adverse Events/ Complications	91 (17.3)	52 (9.9)	143 (13.6)
Death	6 (1.1)	15 (2.9)	21 (2.0)
Patient Withdrawal/ Refusal	39 (7.4)	22 (4.2)	61 (5.8)
Alternative Therapy	93 (17.7)	72 (13.7)	165 (15.7)
Other Complicating Disease	13 (2.5)	5 (1.0)	18 (1.7)
Non-Compliance	7 (1.3)	3 (0.6)	10 (1.0)
MD Decision	8 (1.5)	4 (0.8)	12 (1.1)
Other	9 (1.7)	10 (1.9)	19 (1.8)

	VRd (n=542)	KRd (n=545)	Total (n=1087)
	N (%)	N (%)	N (%)
Received SCT	152 (28.0)	146 (26.8)	298 (27.4)
Median (range); months	6.5 (3.5-36.6)	8.9 (3.7-56.9)	
IQR	4.8-10.4	6.0-15.1	

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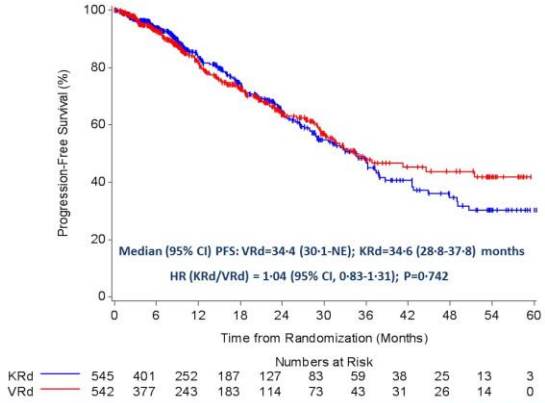
Progression Free Survival from Induction Randomization



- 2nd interim analysis of PFS (Jan 2020): 298 PFS events (75% of 399 planned)
- Median (95% CI) estimated follow up of 15 (13-18) months
- For patients >/= 70 years, median PFS(95% CI) for VRd = 37 (29-NE) and KRd = 28 (24-36) months
- With censoring at SCT or alternative therapy: Median PFS (95% CI) for VRd = 31·7 (28·5-44·6) and KRd = 32·8 (27·2-37·5) months

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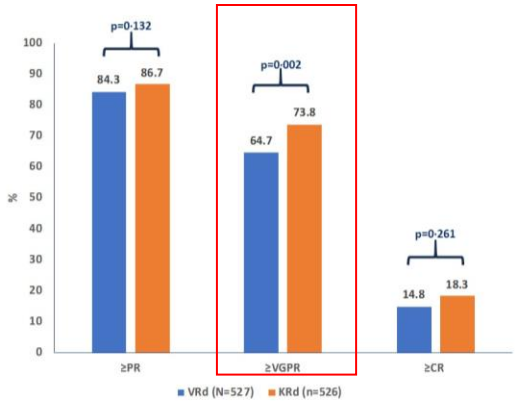
Response To Induction

	VRd (n=527)	KRd (n=526)	Total (n=1053)
Category	N (%)	N (%)	N (%)
Stringent Complete Response	21 (4.0)	31 (5.9)	52 (4.9)
Complete Response	57 (10.8)	65 (12.4)	122 (11.6)
Very Good Partial Response	263 (49.9)	292 (55.5)	555 (52.7)
Partial Response	103 (19.5)	68 (12.9)	171 (16.2)
Stable Disease	40 (7.6)	34 (6.5)	74 (7.0)
Progressive Disease	1 (0.2)	0 (0.0)	1 (0.1)
Unevaluable/Insufficient	42 (8.0)	36 (6.8)	78 (7.4)



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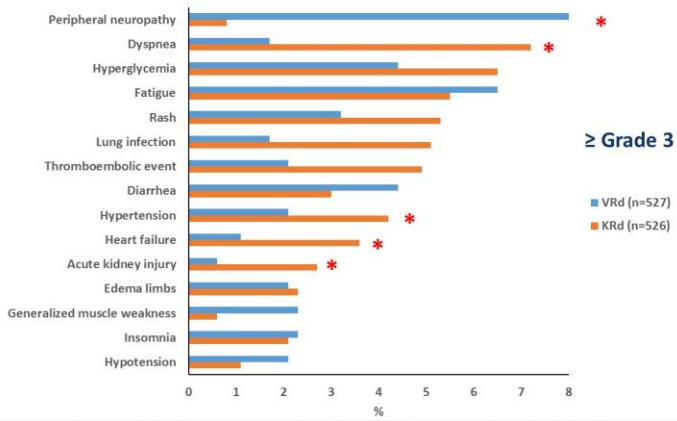
Non-hematologic: Treatment-Related AEs (≥2%)



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My take on ENDURANCE

- No transplant so hard to interpret for that population
- If your pt has neuropathy→ don't give VRD
- If your pt has CHF→ don't give KRD
- Don't tweet about it unless you have time!!!

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Tweet

sergio giralt @sgiraltbmtdoc

Power of randomized trials no benefit of KRD over RVD in NDMM and more cardiopulmonary events. Confession this was not what I expected and makes me think that the results in high risk disease may not be better congrats to Shaji and team

7:37 AM · May 29, 2020 · Twitter for iPhone

20 Retweets 4 Quote Tweets 101 Likes

Shaji Kumar @myelomaMD · Jun 1, 2020
Replying to @sgiraltbmtdoc
Thanks Sergio

Ola Landgren, M.D. @DrOlaLandgren · May 29, 2020
Replying to @sgiraltbmtdoc
Amigo, Majorly flawed study design! Study did not compare VRd vs KRd. Transplant was "optional". As expected higher rates of early transplant on RVd arm; also permitted "alternative therapy" (dara?) =should be censored! Actual arms: RVd+early transplant+alternative therapy vs KRd

Jonathan Kaufman, MD @kaufman_MMdoc · May 29, 2020
Where is that data? It's not in the abstract.

Phari @Phari · May 29, 2020
Replying to @sgiraltbmtdoc
was an important qn to ask and like the CHOP qn in NHL. SOC for TE pt is RVD plus Tx and Len maintenance as STaMINA long term shows. wait for results of Griffin and others. @myelomaMD @mtmdphd @bhemato @BldCancerDoc

Vincent Rajkumar @VincentRK · May 31, 2020
#ASCO20 Plenary presentation today. ENDURANCE randomized trial shows no benefit of KRd over VRd in newly diagnosed myeloma. Toxicity increased with KRd. VRd remains standard of care. @eaonc @myelomaMD @szusmani @SagarLonialMD @mtmdphd #ASCO20 #ASCO20VR meetinglibrary.asco.org/record/186906/...

	VRd	KRd
Median induction duration (mos)	5.9	8.2
Reason off study		
Disease progression	6%	4%
Adverse events	17%	9%
Alternative therapy	18%	14%
Patient withdrawal	7%	4%

6 54 81

Ola Landgren, M.D. @DrOlaLandgren · May 31, 2020
As stated by @akeithstewart : abstract shows VRd not better than KRd and twice as many stop VRd due to AEs. Be honest Bro @VincentRK and show PFS for VRd vs KRd & VRd-early transplant vs KRd-early transplant separately; reversible vs chronic toxicities; alternative therapy=censor

1 7 15

Phari @Phari · May 31, 2020
.. also means despite more early stoppage in VRD and K 36/m2 KRD not meaningfully better. Let's move off in class PI vs. PI to better quadruplets on VRD backbone

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Since 40 is the new 30…

Is 4 the new 3 ??

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Daratumumab (DARA) Plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients with Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of GRIFFIN after 12 Months of Maintenance Therapy*

Jonathan L. Kaufman,[1] Jacob Laubach,[2] Douglas W. Sborov,[3] Brandi Reeves,[4] Cesar Rodriguez,[5] Ajai Chari,[6] Rebecca Silbermann,[7] Luciano J. Costa,[8] Larry D. Anderson Jr,[9] Nitya Nathwani,[10] Nina Shah,[11] Yvonne A. Efebera,[12] Sarah A. Holstein,[13] Caitlin Costello,[14] Andrzej Jakubowiak,[15] Tanya M. Wildes,[16] Robert Z. Orlowski,[17] Kenneth H. Shain,[18] Andrew J. Cowan,[19] Yana Lutska,[20] Padma Bobba,[20] Huiling Pei,[21] Jon Ukropec,[22,†] Jessica Vermeulen,[23] Thomas S. Lin,[20] Paul G. Richardson,[2] Peter M. Voorhees[24]

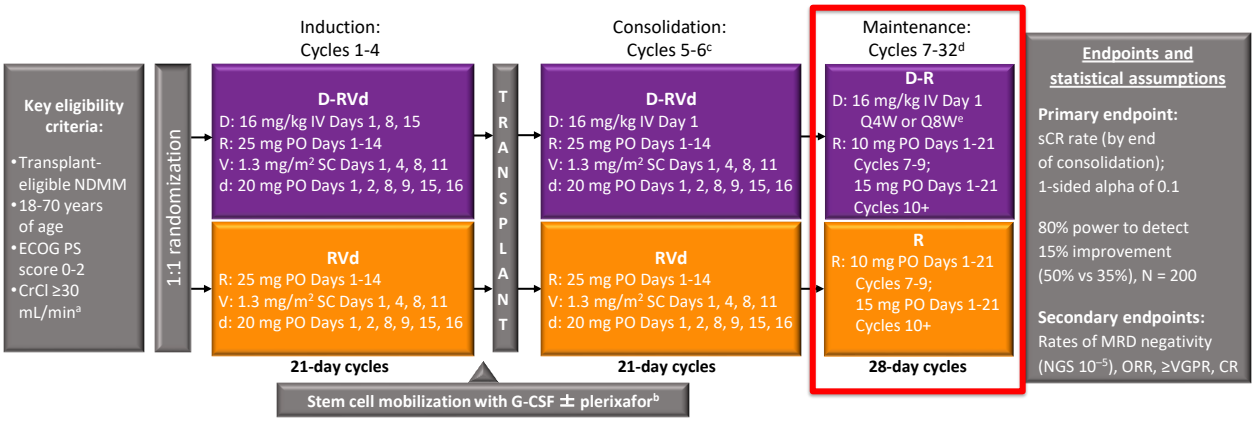
[1]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA; [4]University of North Carolina – Chapel Hill, Chapel Hill, NC, USA; [5]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [6]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [7]Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; [8]University of Alabama at Birmingham, Birmingham, AL, USA; [9]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [10]Judy and Bernard Briskin Center for Multiple Myeloma Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [11]Department of Medicine, University of California San Francisco, San Francisco, CA, USA; [12]The Ohio State University Comprehensive Cancer Center; Columbus OH, USA; [13]Division of Oncology & Hematology, University of Nebraska Medical Center, Omaha, NE, USA; [14]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA; [15]University of Chicago Medical Center, Chicago, IL, USA; [16]Division of Oncology, Section Medical Oncology, Washington University School of Medicine, St. Louis, MO, USA; [17]Department of Lymphoma–Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [18]Department of Malignant Hematology, H. Lee Moffitt Cancer Center, Tampa, FL, USA; [19]Division of Medical Oncology, University of Washington, Seattle, WA, USA; [20]Janssen Scientific Affairs, LLC, Horsham, PA, USA; [21]Janssen Research & Development, LLC, Titusville, NJ, USA; [22]Janssen Global Medical Affairs, Horsham, PA, USA; [23]Janssen Research & Development, LLC, Leiden, The Netherlands; [24]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA. ([†] At the time of study)

*ClinicalTrials.gov Identifier: NCT02874742.

Additional information can be viewed by scanning the QR code or accessing this link: https://epg-digital.com/u/ASH2020-Kaufman. The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

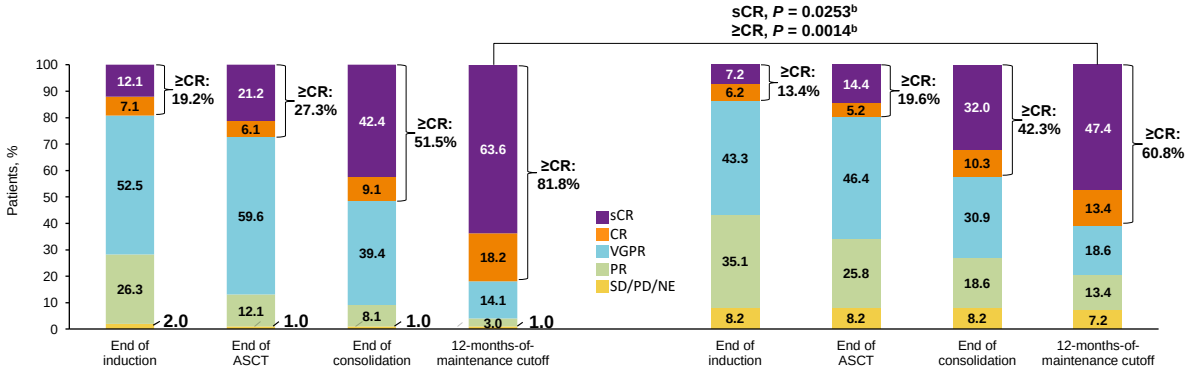
GRIFFIN: Randomized Phase

- Phase 2 study of D-RVd versus RVd in transplant-eligible NDMM, 35 sites in the United States with enrollment between December 2016 and April 2018



ECOG PS, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; IV, intravenous; PO, oral; G-CSF, granulocyte colony-stimulating factor; Q4W, every 4 weeks; Q8W, every 8 weeks; NGS, next-generation sequencing; ORR, overall response rate; VGPR, very good partial response; CR, complete response. [a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60 to 100 days post transplant. [d]Patients who complete maintenance cycles 7 to 32 may continue single-agent lenalidomide thereafter. [e]Protocol Amendment 2 allowed for the option to dose daratumumab Q4W, based on pharmacokinetic results from study SMM2001 (NCT02316106).

Responses Deepened over Time[a]

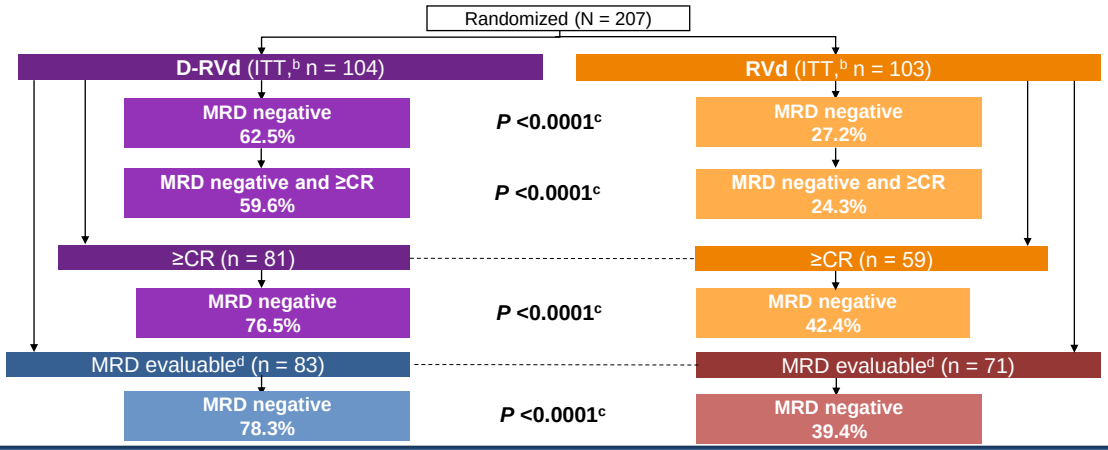


- *Results for end of induction, ASCT, and consolidation are based on a median follow up of 13.5 months at the primary analysis*
- *Median follow up at 12-months-of-maintenance therapy cutoff was 27.4 months*

Response rates and depths were greater for D-RVd at all time points

PR, partial response. SD/PD/NE, stable disease/progressive disease/not evaluable. [a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran–Mantel–Haenszel chi-square test.

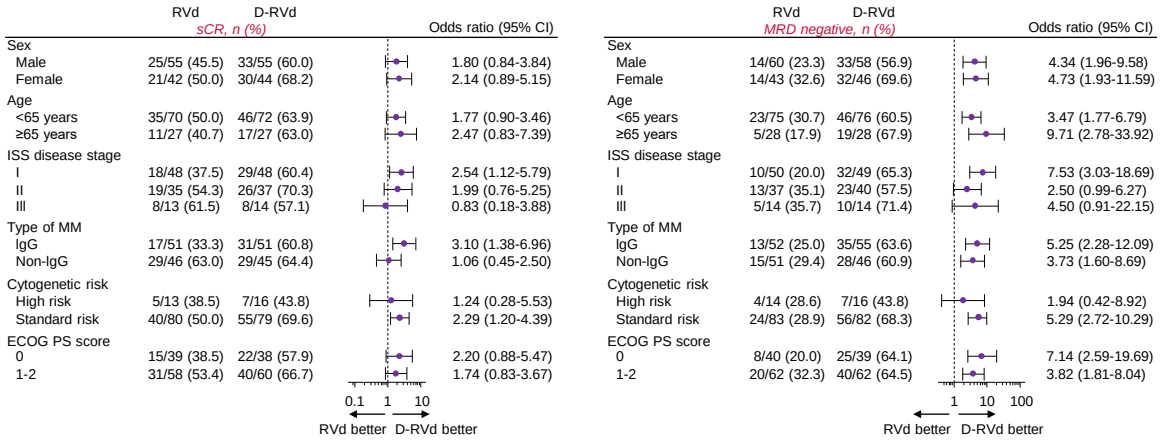
MRD (10^{-5}) Negativity[a] at the 12-Months-of-Maintenance Therapy Cutoff



D-RVd improved MRD-negativity rates versus RVd

[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on the assessment of bone marrow aspirates by NGS in accordance with International Myeloma Working Group criteria. Median follow-up was 27.4 months. [b]For the ITT population, patients with a missing or inconclusive assessment were considered MRD positive. [c]*P* values were calculated using the Fisher's exact test. [d]The MRD-evaluable population includes patients who had both baseline (with clone identified/calibrated) and post-baseline MRD (with negative, positive, or indeterminate result) samples taken.

Subgroup Analysis of sCR and MRD Negativity[a] by the 12-Months-of-Maintenance Therapy Cutoff



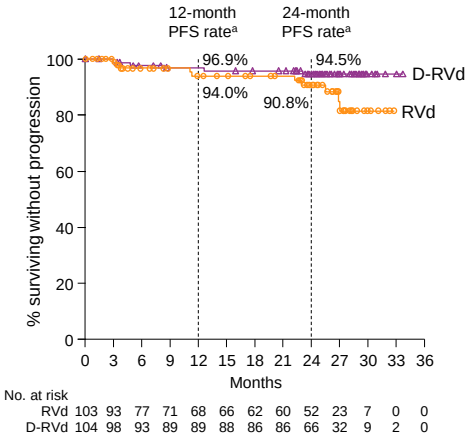
D-RVd improved sCR and MRD-negativity rates across most subgroups

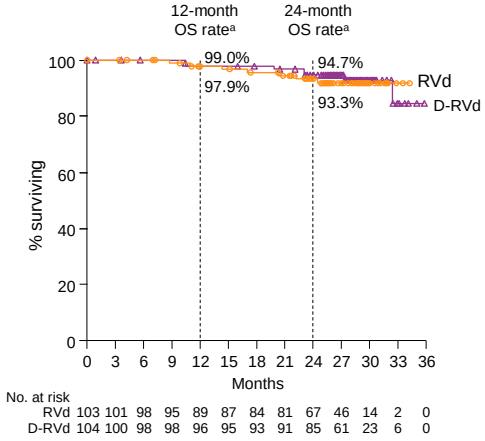
CI, confidence interval. [a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on the assessment of bone marrow aspirates by NGS in accordance with International Myeloma Working Group criteria. Median follow-up was 27.4 months.

Presented By Jonathan Kaufman at ASH 2020

PFS and OS in the ITT Population

- Median follow-up = 27.4 months





Median PFS and OS were not reached for D-RVd and RVd

OS, overall survival. [a]Kaplan–Meier estimate.

Presented By Jonathan Kaufman at ASH 2020

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Ongoing phase 3 PERSEUS study is evaluating DARA SC plus RVd in ASCT-eligible MM

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NCCN Guidelines for ASCT-Eligible MM (Updated in 2021)

Primary Therapy[1]

Preferred

- Bortezomib/lenalidomide/dex (category 1)
- Bortezomib/cyclophosphamide/dex

Other Recommended

- Carfilzomib/lenalidomide/dex
- Daratumumab/lenalidomide/bortezomib/dex
- Ixazomib/lenalidomide/dex (category 2B)

Useful in Certain Circumstances

- Bortezomib/doxorubicin/dex
- Carfilzomib/cyclophosphamide/dex
- Ixazomib/cyclophosphamide/dex
- Cyclophosphamide/lenalidomide/dex
- Daratumumab/bortezomib/thalidomide/dex
- Daratumumab/cyclophosphamide/bortezomib/dex
- Bortezomib/thalidomide/dex (category 1)
- VTd-PACE

1. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version.4.2021.

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My take on GRIFFIN

- Dara makes most things better
- Real data = Perseus
  - (but #myelennials are impatient, as is NCCN apparently…)
- Real meat is in the PFS; GRIFFIN plan is long haul
- Since VRD=KRD → can you say D-VRD>KRD….??
  - BUT NO TRANSPLANT IN ENDURANCE!

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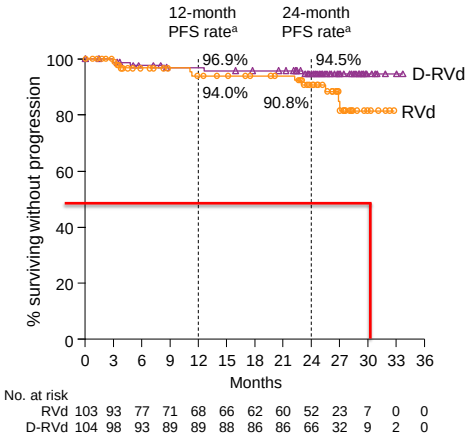
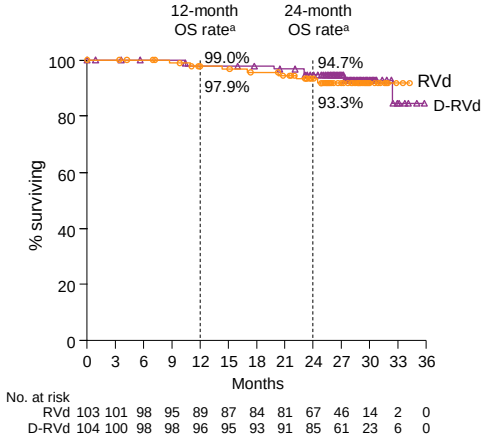
PFS and OS in the ITT Population

- Median follow-up = 27.4 months





Median PFS and OS were not reached for D-RVd and RVd

OS, overall survival. [a]Kaplan–Meier estimate.

Role of transplant

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Autologous stem cell transplant in newly diagnosed multiple myeloma: long-term follow-up analysis of the IFM 2009 trial

Aurore Perrot[1], Valérie Lauwers-Cances[2], Titouan Cazaubiel[3], Thierry Facon[4], Denis Caillot[5], Lauriane Clément-Filliatre[6], Margaret Macro[7], Olivier Decaux[8], Karim Belhadj[9], Mohamad Mohty[10], Lionel Karlin[11], Jean Claude Eisenmann[12], Mourad Tiab[13], Frédérique Orsini[14], Cyrille Touzeau[15], Xavier Leleu[16], Hervé Avet-Loiseau[17], Nikhil C. Munshi[18], Kenneth Anderson[19], Paul G. Richardson[20], Philippe Moreau[21], Michel Attal[22].

[1]CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France; [2]USMR, service d'Epidémiologie, CHU Toulouse, Toulouse, France; [3]CHU de Bordeaux, Service d'Hématologie et de Thérapie Cellulaire, Bordeaux, France; [4]Centre Hospitalier Universitaire (CHU) Lille, Service des Maladies du Sang, University of Lille, Lille, France; [5]CHU de Dijon, Service d'Hématologie, Dijon, France; [6]CHU de Nancy, Service d'Hématologie, Nancy, France; [7]Service d'Hématologie, CHU de Caen, Caen, France; [8]Service d'Hématologie, CHU de Rennes, Rennes, France; [9]Lymphoid Malignancies, Centre Hospitalier Universitaire Henri Mondor, Créteil, France; [10]Hôpital Saint Antoine, Service d'Hématologie et Thérapie Cellulaire, Paris, Paris, France; [11]Hématologie, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Pierre-Bénite, France; [12]Centre Hospitalier de Mulhouse, MULHOUSE, FRA; [13]CH la Roche Sur Yon, La Roche Sur Yon Cedex 9, France; [14]Service Hématologie, CH Annecy, ANNECY, France; [15]Hématologie, CHU de Nantes, Nantes, France; [16]CHU de Poitiers - Hôpital La Milétrie, Service d'Hématologie et Thérapie Cellulaire, Pôle Régional de Cancérologie, POITIERS, France; [17]Unite de Génomique du Myélome, IUC-T Oncopole, Toulouse, France; [18]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [19]Jerome Lipper Multiple Myeloma Center, LeBow Institute for Myeloma Therapeutics, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [20]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [21]Department of Hematology, University Hospital of Nantes, Nantes, France; [22]Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France

IFM 2009 Study design

700 patients randomized stratified on ISS and FISH

Arm A – RVD alone	Arm B - Transplantation
3 RVD	3 RVD
PBSC collection (cyclophosphamide 3g/m² and GCSF 10 µg/kg/d)	
5 RVD	HD Melphalan 200 mg/m² + ASCT
	2 RVD
Lenalidomide maintenance 13 cycles (10-15 mg/d)	

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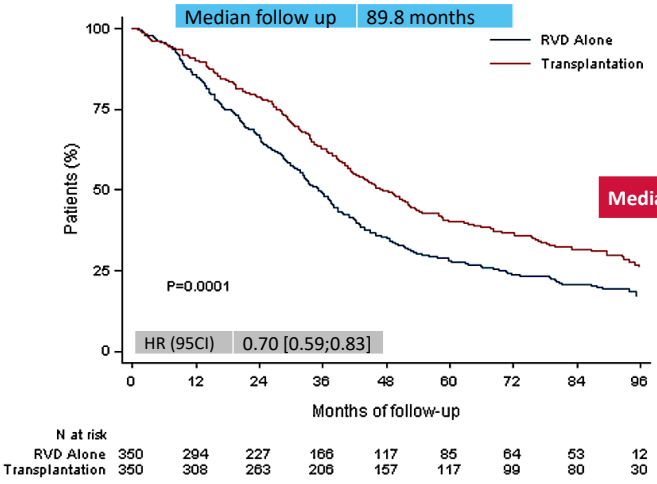
RVd 21d cycles
. Lenalidomide 25 mg/d: D1-D14
. Bortezomib 1.3 mg/m² D1, D4, D8, D11
. Dexamethasone 20 mg/d: D1, D2, D4, D5, D8, D9, D11, D12

Primary endpoint = PFS

Secondary endpoints
. ORR, MRD
. TTP
. OS
. Toxicity

M Attal et al, N Engl J Med 2017

Updated PFS (primary endpoint)



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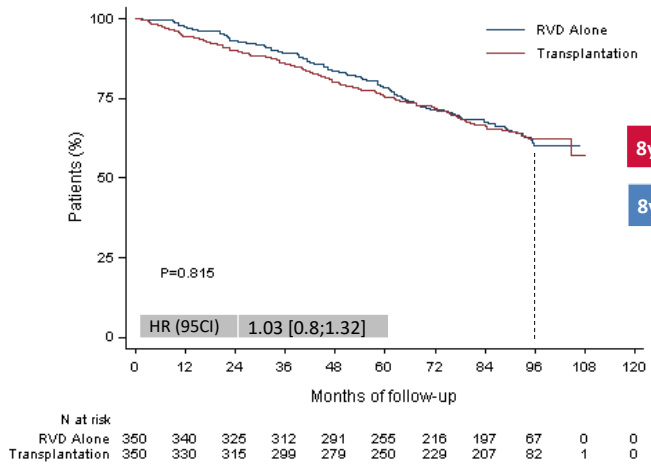
Median PFS 47.3 months (Transplantation, arm B)

Median PFS 35 months (RVD alone, arm A)

30% reduction in the risk of progression or death in patients receiving transplant

OS

Median follow up | 89.8 months



Place video here

8y-OS 62.2% (Transplantation, arm B)

8y-OS 60.2% (RVD alone, arm A)

More than 60% of the patients in the two arms are alive after 8 years of follow-up

American Society of Hematology

Presented By Aurore Perrot at ASH 2020

My comments

- This is a study of upfront versus delayed transplant (not transplant vs no transplant)
- Upfront transplant is better than delayed (I still try to take pts to transplant in 1st consolidation)
  - The patient is youngest at the day you first meet him/her
- No data on high risk pts
- Unclear if change in induction regimen (KRD or Dara-VRD) would change results

62nd ASH Annual Meeting, December 5-8, 2020
Abstract #141

Survival Analysis of Newly Diagnosed Transplant-Eligible Multiple Myeloma Patients in the Randomized FORTE Trial

Francesca Gay[1]*, Pellegrino Musto[1], Delia Rota-Scalabrini[1], Monica Galli[1], Angelo Belotti[1], Elena Zamagni[1], Luca Bertamini[1], Renato Zambello[1], Micol Quaresima[1], Giovanni De Sabbata[1], Giuseppe Pietrantuono[1], Mattia D'Agostino[1], Daniela Oddolo[1], Andrea Capra[1], Anna Marina Liberati[1], Salvatore Palmieri[1], Franco Narni[1], Massimo Offidani[1], Michele Cavo[1], Mario Boccadoro.[1]

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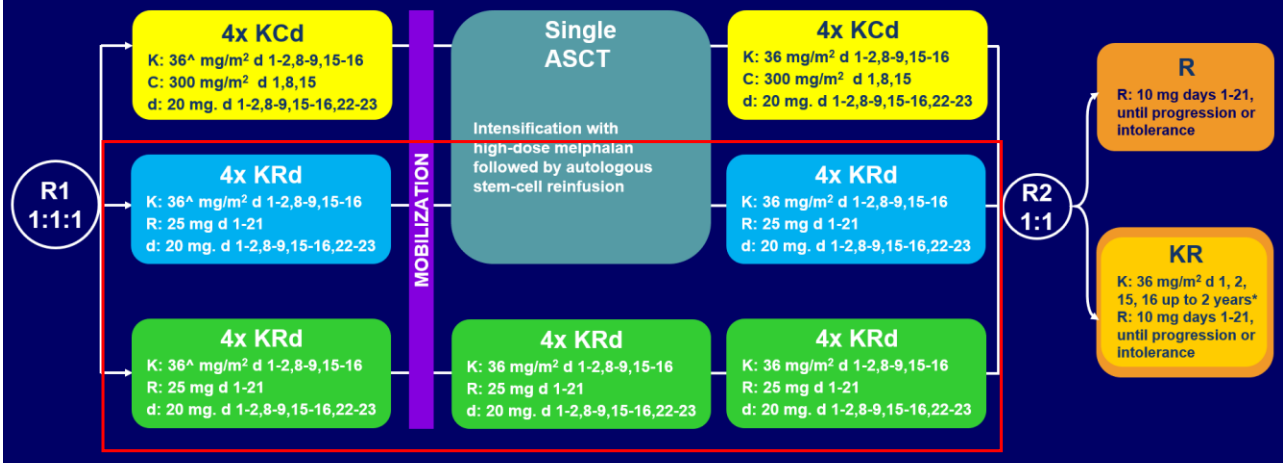
1. GIMEMA / European Myeloma Network, Italy

Trial design

474 NDMM patients, transplant-eligible and younger than 65 years

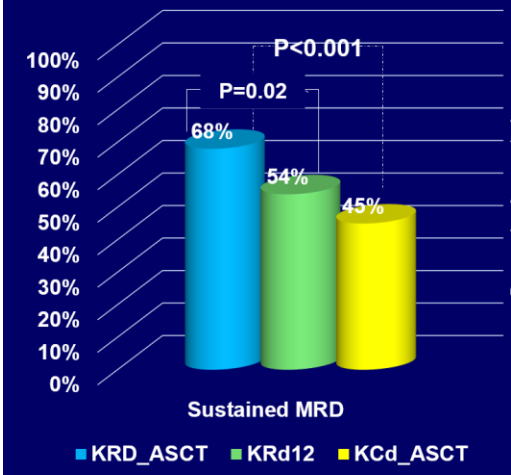


^20 mg/m² on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards.

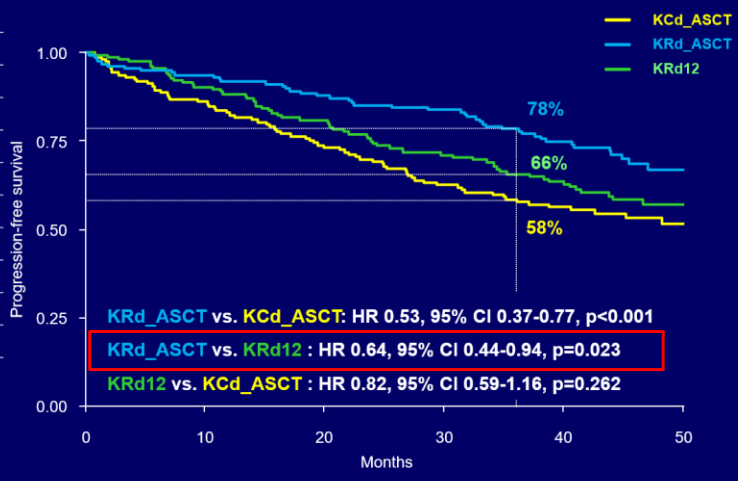
Progression-free survival: Random 1

Median follow-up from Random 1: 45 months (40-49 months)

Rate of sustained MRD MCF 10^{-5}



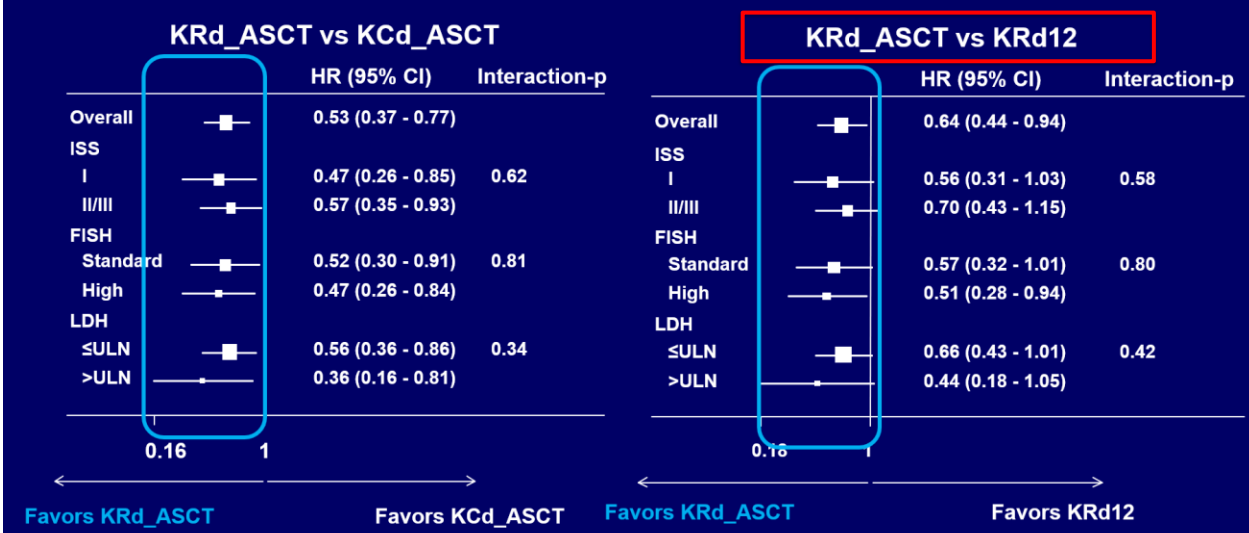
Progression-free survival



Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; p, p-value; HR, hazard ratio; CI, confidence interval; MRD, minimal residual disease; MFC, multiparameter flow cytometry; 3-year PFS reported in the figure.

Progression-free survival: Random 1

Subgroup Analyses



SIMILAR HR IN STANDARD AND HIGH RISK PATIENTS TREATED WITH KRD_ASCT

PFS, progression-free survival; Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; HR, hazard ratio; CI, confidence interval; p, p-value; ISS, International Staging System stage; FISH, fluorescence *in situ* hybridization; LDH, lactate dehydrogenase; ULN, upper limit of normal.

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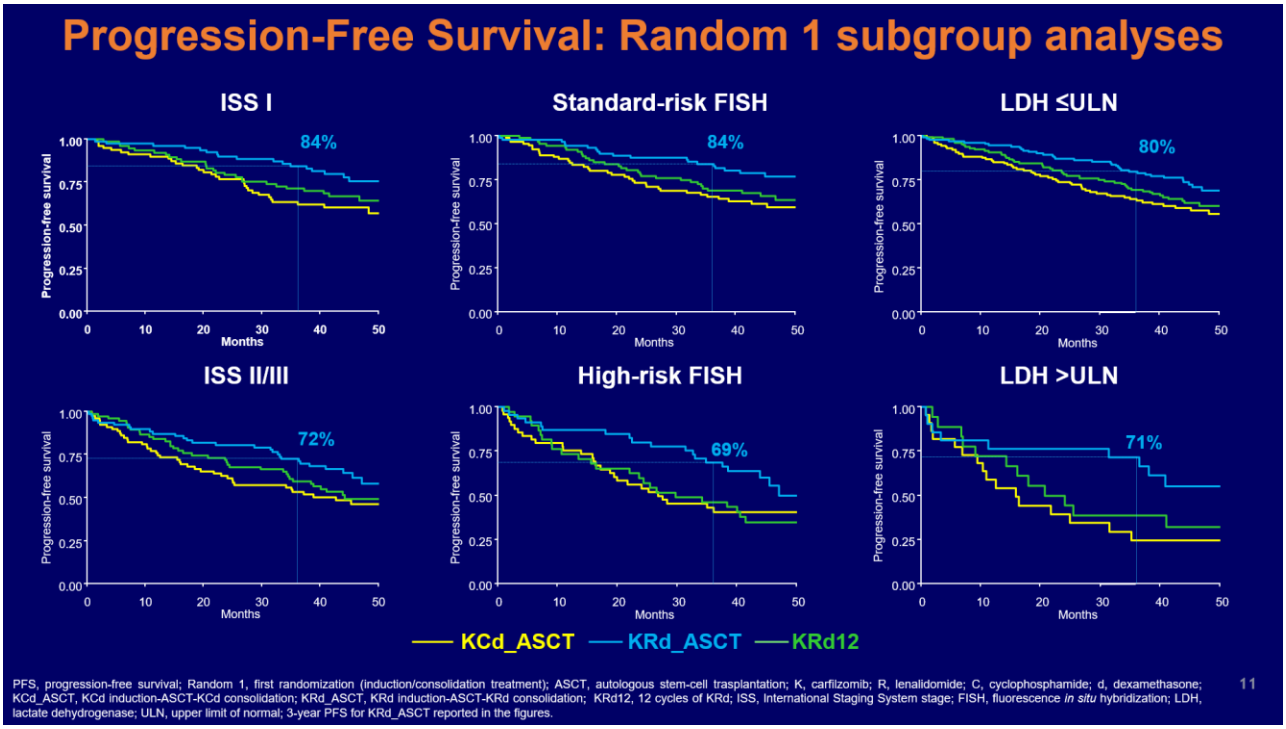

My comments

- This is a study of transplant vs no transplant
- Upfront transplant is better than no transplant (I still try to take pts to transplant in 1st consolidation)
- Subgroup data suggests benefit is across the board (high risk pts too)
- This is using a novel induction regimen (KRD)

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Induction therapy for transplant-ineligibile patients

UCSF

NCCN Regimens for Non-Transplant Candidates

Primary Therapy for Non-Transplant Candidates
Preferred Regimens • VRd (category 1) • Dara-Rd (category 1) • Rd (category 1) • VCd
Other Recommended Regimens • KRd • Ixazomib-Rd • Dara-VMP (category 1)
Useful in Certain Circumstances • Vd • CRd • KCd

VMP, bortezomib, melphalan, and prednisone.

NCCN Guidelines Version 4.2020.

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UCSF

OVERALL SURVIVAL RESULTS WITH DARATUMUMAB, LENALIDOMIDE, AND DEXAMETHASONE VERSUS LENALIDOMIDE AND DEXAMETHASONE IN TRANSPLANT-INELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA: PHASE 3 MAIA STUDY

Thierry Facon,[1,*] Shaji K. Kumar,[2] Torben Plesner,[3] Robert Z. Orlowski,[4] Philippe Moreau,[5] Nizar Bahlis,[6] Supratik Basu,[7] Hareth Nahi,[8] Cyrille Hulin,[9] Hang Quach,[10] Hartmut Goldschmidt,[11] Michael O'Dwyer,[12] Aurore Perrot,[13] Christopher P. Venner,[14] Katja Weisel,[15] Joseph R. Mace,[16] Noopur Raje,[17] Mourad Tiab,[18] Margaret Macro,[19] Laurent Frenzel,[20] Xavier Leleu,[21] Tahamtan Ahmadi,[22] Jianping Wang,[23] Rian Van Rampelbergh,[24] Clarissa M. Uhlar,[25] Brenda Tromp,[26] Maria Delioukina,[25] Jessica Vermeulen,[26] Saad Z. Usmani[27]

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*Presenting author.

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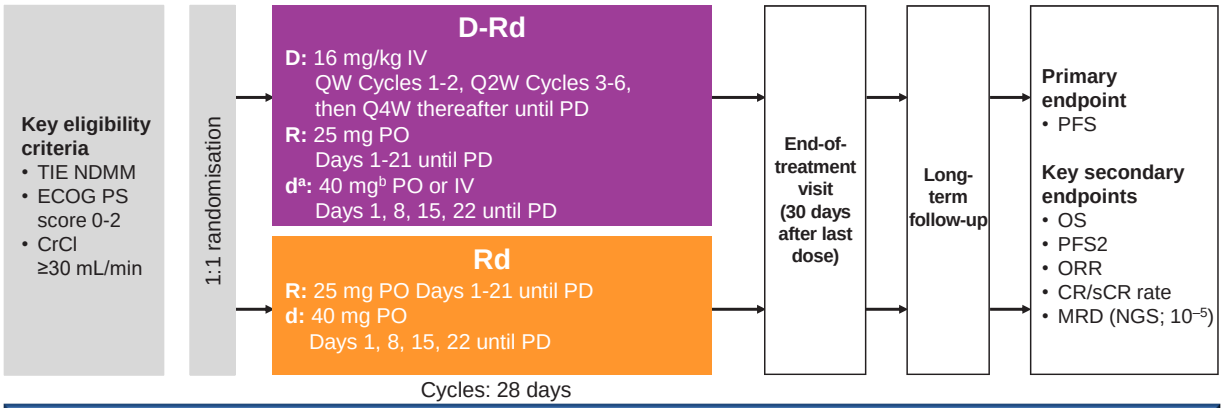
EHA2021 VIRTUAL

Study Design

- Patients were enrolled in MAIA from March 2015 through January 2017

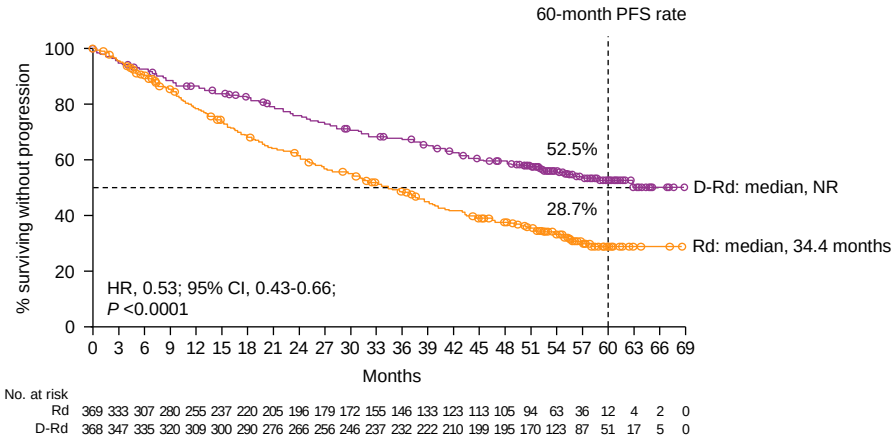


MAIA is a multicentre, randomised, open-label, active-controlled, phase 3 study of D-Rd versus Rd alone in patients with NDMM who are transplant ineligible

TIE, transplant-ineligible; ECOG PS, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; IV, intravenous; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; PD, progressive disease; PO, oral; ORR, overall response rate; CR, complete response; sCR, stringent complete response; MRD, minimal residual disease; NGS, next-generation sequencing; BMI, body mass index.
[a]On days when DARA is administered, dexamethasone will be administered to patients in the D-Rd arm and will serve as the treatment dose of steroid for that day, as well as the required pre-infusion medication. [b]For patients >75 years of age or with BMI <18.5 kg/m^2, dexamethasone was administered at a dose of 20 mg QW.

EHA2021 VIRTUAL

Updated PFS

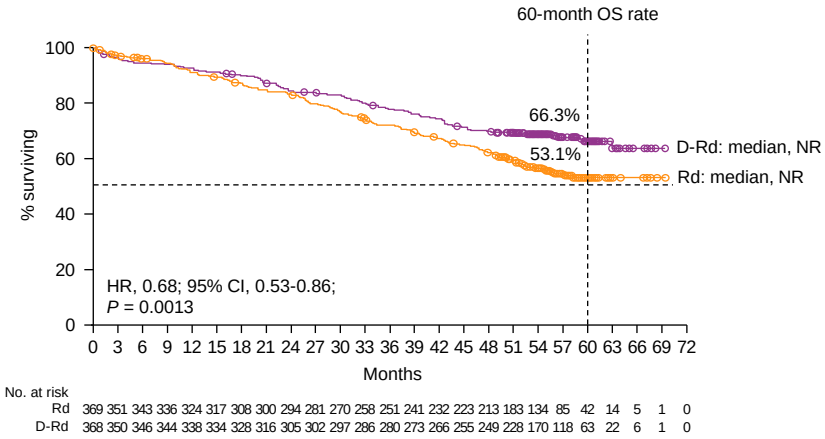


- D-Rd continued to demonstrate a significant PFS benefit, with median PFS not reached with D-Rd
- These data provide a new PFS benchmark in patients with NDMM who are transplant ineligible

NR, not reached; CI, confidence interval.

EHA2021 VIRTUAL

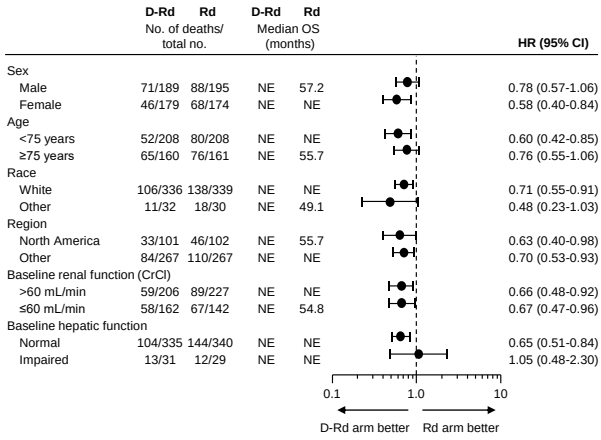
OS

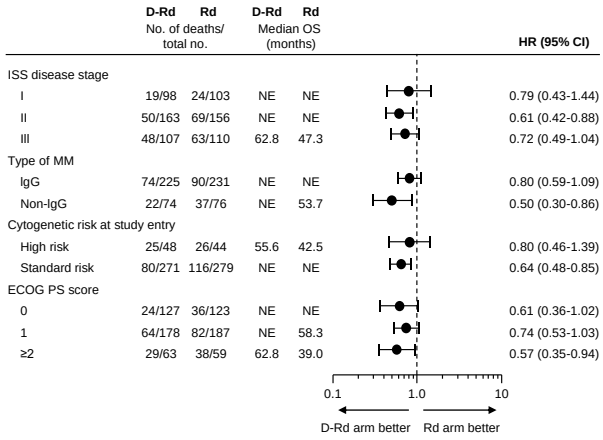


D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible

EHA2021 VIRTUAL

Subgroup Analysis of OS





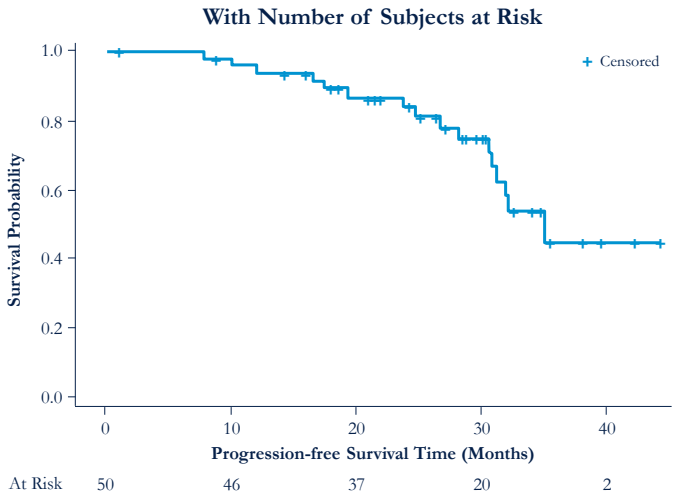
OS benefit with D-Rd was generally consistent across patient subgroups

NE, not estimable; CrCl, creatinine clearance.

EHA2021 VIRTUAL

RVd-Lite

- Regimen (N=53)
  - Lenalidomide: 15 mg po days 1 to 21
  - Bortezomib: 1.3 mg/m2 SC 1× weekly on days 1, 8, 15, 22
  - Dexamethasone
    - If ≤75 years, 20 mg 2× weekly
    - If >75 years, 20 mg 1× weekly
- Results
  - 86% ORR
  - 66% ≥VGPR
  - Median PFS: 35.1 months
  - Median OS: NR
  - Median follow-up: 30 months
  - Median age: 73 years (range: 65-91)
  - PN: 62%
  - Only 1 patient had grade 3 symptoms



46 PN, peripheral neuropathy.
O'Donnell et al. *Br J Haematol*. 2018;182:222-230.

Some unanswered questions

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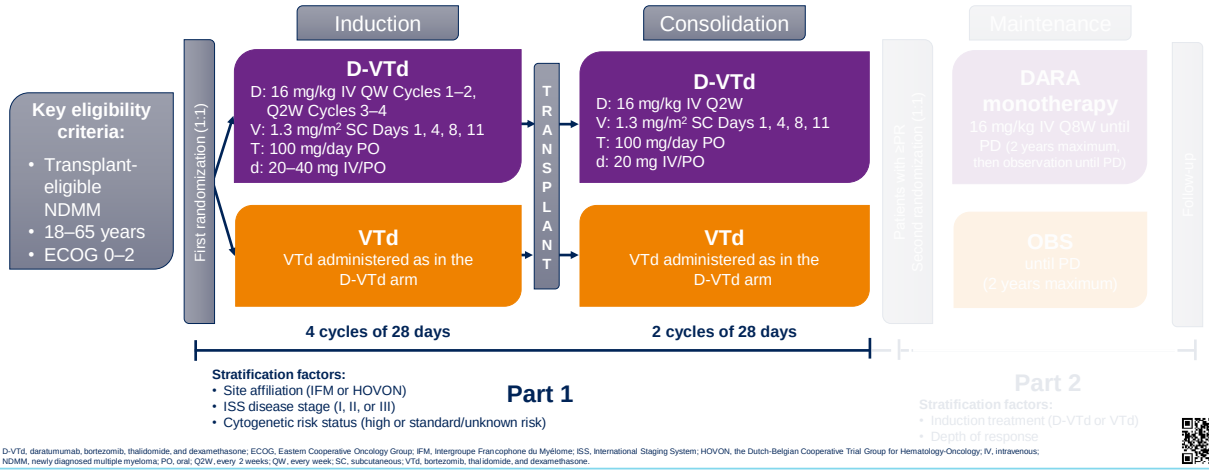
CASSIOPEIA Part 1 Study Design

- Part 1 compared D-VTd vs VTd as induction/consolidation



D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; ECOG, Eastern Cooperative Oncology Group; IFM, Intergroupe Francophone du Myélome; ISS, International Staging System; HOVON, the Dutch-Belgian Cooperative Trial Group for Hematology-Oncology; IV, intravenous; NDMM, newly diagnosed multiple myeloma; PO, oral; Q2W, every 2 weeks; QW, every week; SC, subcutaneous; VTd, bortezomib, thalidomide, and dexamethasone.

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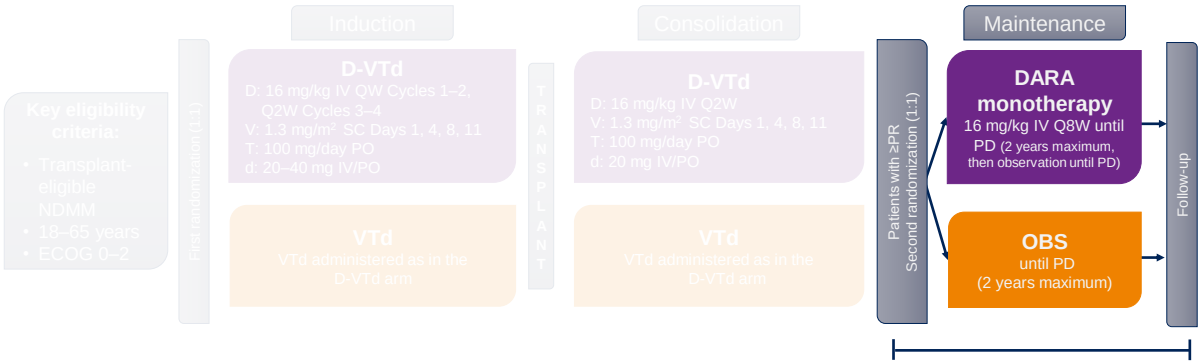
CASSIOPEIA Part 2 Study Design

- Patients who completed consolidation and achieved ≥PR were re-randomized 1:1 to DARA 16 mg/kg IV every 8 weeks or OBS (no maintenance) for 2 years



≥PR, partial response or better; DARA, daratumumab; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; IV, intravenous; OBS, observation; PD, progressive disease; Q8W, every 8 weeks; VTd, bortezomib, thalidomide, and dexamethasone.

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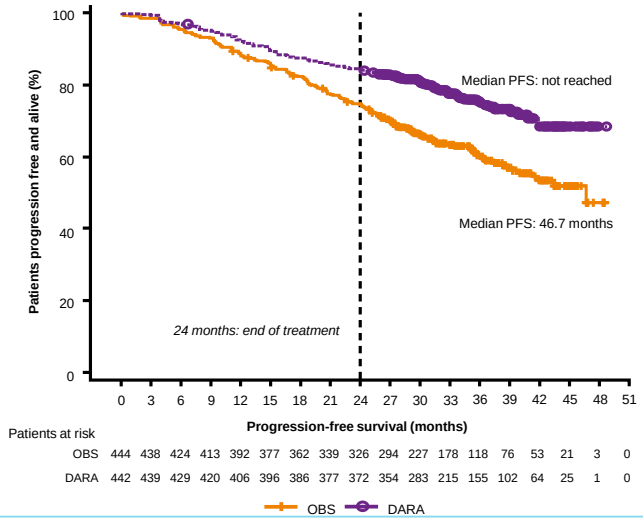
DARA Significantly Improved PFS From Second Randomization vs OBS

Median follow-up: 35.4 months from second randomization



HR 0.53 (95% CI 0.42–0.68) *P*<0.0001

CI, confidence interval; DARA, daratumumab; HR, hazard ratio; OBS, observation; PFS, progression-free survival.

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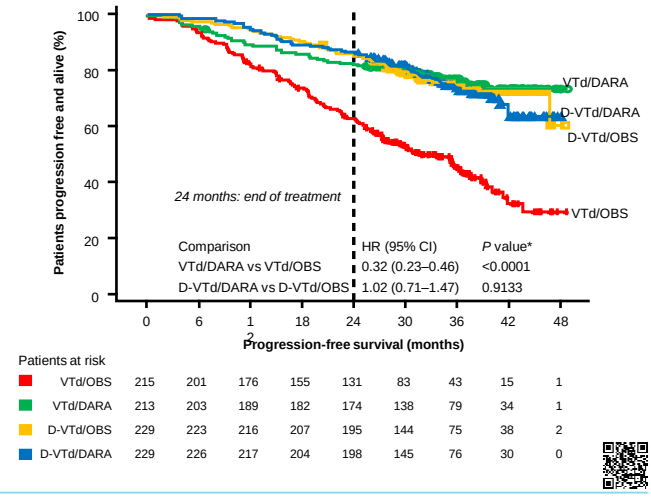
DARA Significantly Improved PFS vs OBS in Patients Treated With VTd Induction/Consolidation

- **A prespecified analysis showed significant interaction between maintenance and induction/consolidation therapy**
- **A PFS benefit was observed for VTd/DARA vs VTd/OBS**
- **PFS was not different for D-VTd/DARA vs D-VTd/OBS**



*Nominal *P* value.
CI, confidence interval; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; DARA, daratumumab; HR, hazard ratio; OBS, observation; PFS, progression-free survival; VTd, bortezomib, thalidomide, and dexamethasone.

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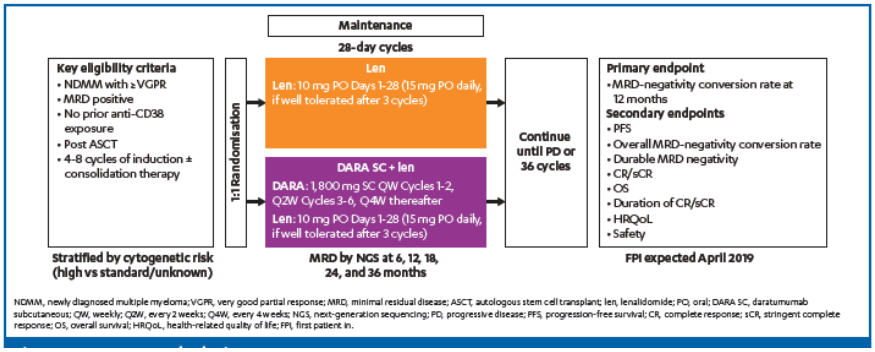
Conclusions

- **Reduced-frequency DARA maintenance (every 8 weeks) significantly improved post-ASCT outcomes in patients with NDMM who received VTd induction/consolidation**
- **Longer follow-up is needed to assess potential PFS2 or OS benefit in patients who received D-VTd induction/consolidation**
- **Updated results from Part 1 support the early use of DARA-containing regimens as induction/consolidation**
  - These findings are further supported by higher rates of dropout in the VTd group compared with the D-VTd group
- **Ongoing studies such as GRIFFIN, PERSEUS, and AURIGA will shed light on optimal maintenance strategies using DARA plus lenalidomide**

ASCT, autologous stem cell transplant; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; DARA, daratumumab; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS2, progression-free survival after next line of therapy; VTd, bortezomib, thalidomide, and dexamethasone.

Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma (NDMM) After Frontline Transplant: A Multicentre, Randomised, Phase 3 Study (AURIGA)



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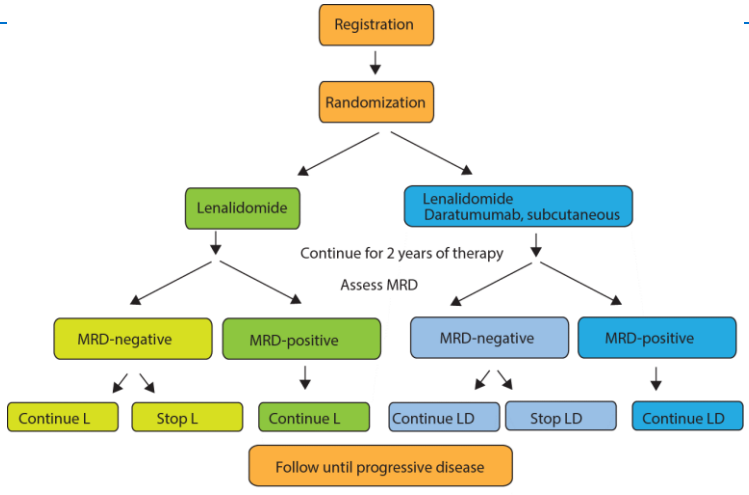

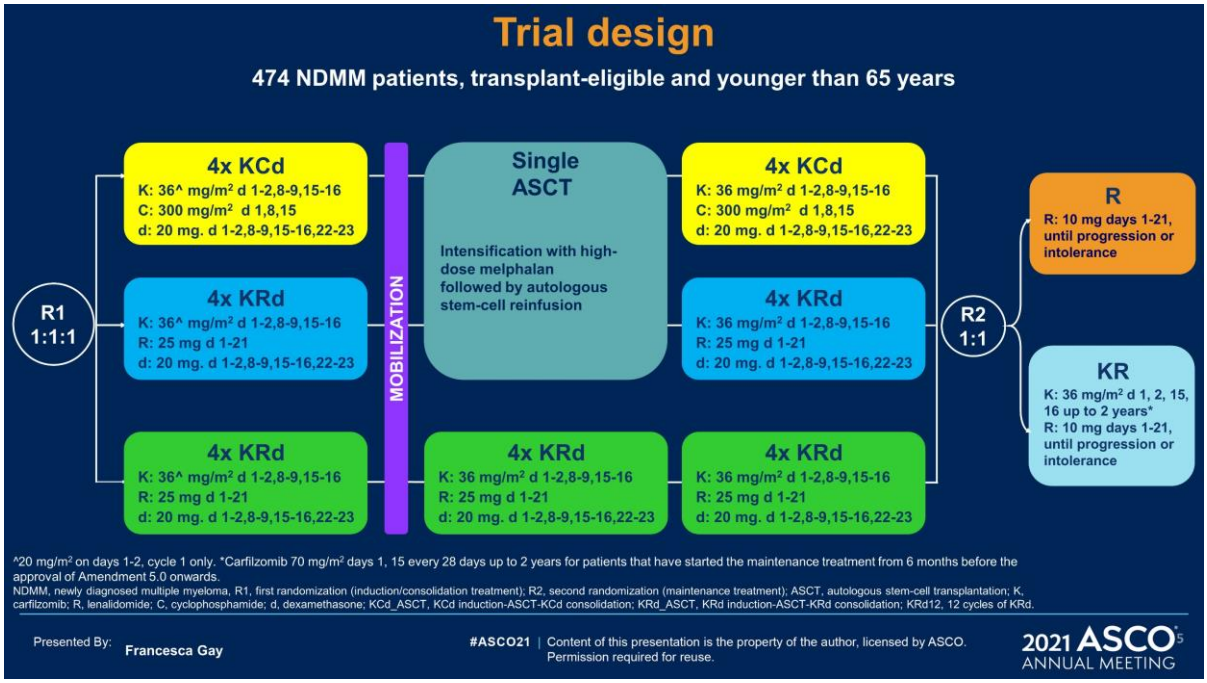

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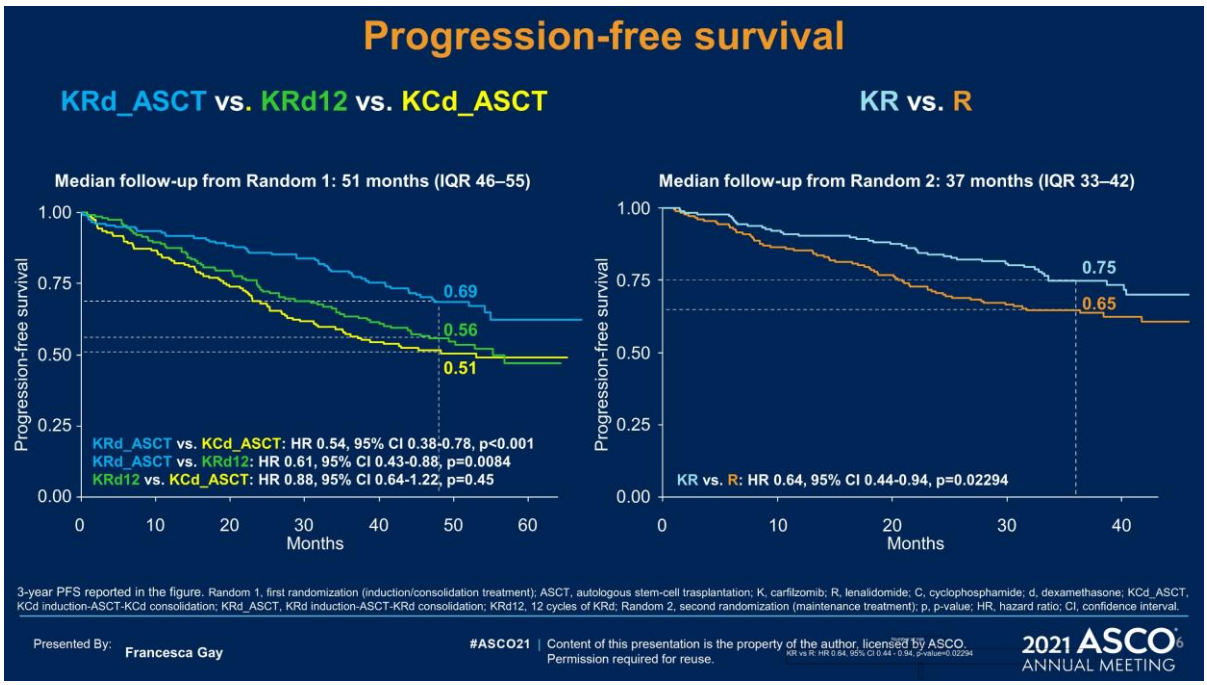

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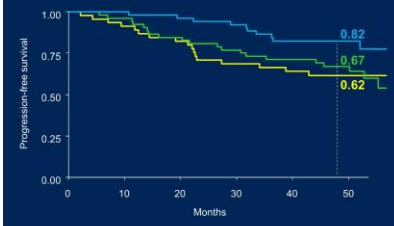
Progression-free survival: Random 1

KRd_ASCT vs. KRd12 vs. KCd_ASCT

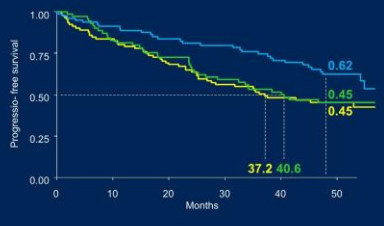
Median follow-up from Random 1: 51 months (IQR 46-55)

Standard risk (N=153)



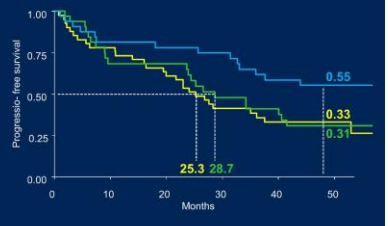
KRd_ASCT vs. KCd_ASCT: HR 0.44, p=0.04
KRd_ASCT vs. KRd12: HR 0.46, p=0.04
KRd12 vs. KCd_ASCT : HR 0.96, p=0.9

High risk (N=243)



KRd_ASCT vs. KCd_ASCT: HR 0.57, p=0.01
KRd_ASCT vs. KRd12: HR 0.6, p=0.04
KRd12 vs. KCd_ASCT: HR 0.95, p=0.8

Double hit (N=105)



KRd_ASCT vs. KCd_ASCT: HR 0.49, p=0.03
KRd_ASCT vs. KRd12: HR 0.53, p=0.07
KRd12 vs. KCd_ASCT: HR 0.91, p=0.75

Random 1, first randomization (induction/consolidation treatment): ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; HR, hazard ratio; CI, confidence interval; p, p-value; iQR, interquartile range.

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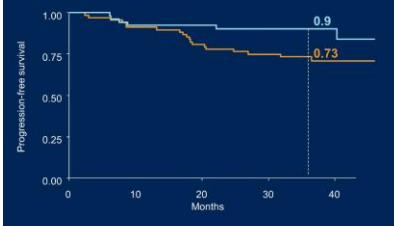
Progression-free survival: Random 2

KR vs. R

3-year progression-free survival

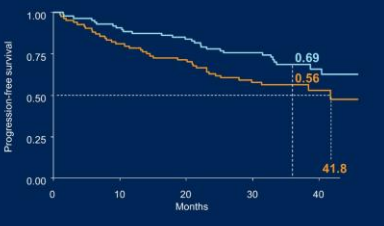
Median follow-up from Random 2: 37 months (IQR 33-42)

Standard risk (N=120)



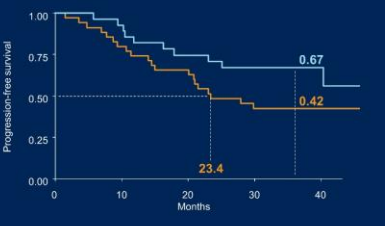
KR vs. R: HR 0.4, p=0.05

High risk (N=172)



KR vs. R: HR 0.6, p=0.04

Double hit (N=105)



KR vs. R: HR 0.53, p=0.1

Random 2, second randomization (maintenance treatment); IQR, interquartile range; K, carfilzomib; R, lenalidomide; HR, hazard ratio; CI, confidence interval; p, p-value.

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Conclusions

- **KRd_ASCT** significantly prolonged PFS vs. KRd12 in:
  - SR patients: 4-year PFS → **82%** vs. 67%
  - HiR patients: 4-year PFS → **62%** vs. 45%
  - DH patients: 4-year PFS → **55%** vs. 33%
- **KRd_ASCT** increased the rate of 1-year sustained MRD negativity vs. Krd12 in patients with both HiR (50% vs 39%) and DH (47% vs 25%) MM.
- **KR** significantly prolonged PFS from start of maintenance vs. R alone
  - SR patients: 3-year PFS → **90%** vs. 73%
  - HiR patients: 3-year PFS → **69%** vs. 59%
  - DH patients: 3-year PFS → **67%** vs. 42%
- The benefit of **KRd_ASCT** vs. KRd12 and **KR** vs R was observed in all subgroups: del(17p), gain(1q), del(1p), and t(4;14), **except** amp(1q).

PFS, progression-free survival; ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; SR, standard risk; HiR, high risk; DH, double hit; MRD, minimal reisudal disease.

Presented By: Francesca Gay

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2021 ASCO ANNUAL MEETING

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My comments

- Lenalidomide is still the GOAT of maintenance…
- But it's still worth it to find out if we can do better
  - AURIGA, SWOG, a phase III of KR vs R
- High risk pts are still an unmet need
- Generally: combo therapy for longer = better for high risk

Relapsed/Refractory Myeloma 1-3 prior lines

UCSF

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

APOLLO: Phase 3 Randomized Study of Subcutaneous Daratumumab Plus Pomalidomide and Dexamethasone (D-Pd) Versus Pomalidomide and Dexamethasone (Pd) Alone in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM)*

Meletios A. Dimopoulos,[1] Evangelos Terpos,[1] Mario Boccadoro,[2] Sosana Delimpasi,[3] Meral Beksac,[4] Eirini Katodritou,[5] Philippe Moreau,[6] Luca Baldini,[7] Argiris Symeonidis,[8] Jelena Bila,[9] Albert Oriol,[10] Maria-Victoria Mateos,[11] Hermann Einsele,[12] Ioannis Orfanidis,[13] Tahamtan Ahmadi,[14] Jon Ukropec,[15,†] Tobias Kampfenkel,[16] Jordan M. Schecter,[17] Yanping Qiu,[18] Himal Amin,[17] Jessica Vermeulen,[16] Robin Carson,[19] Pieter Sonneveld[20]

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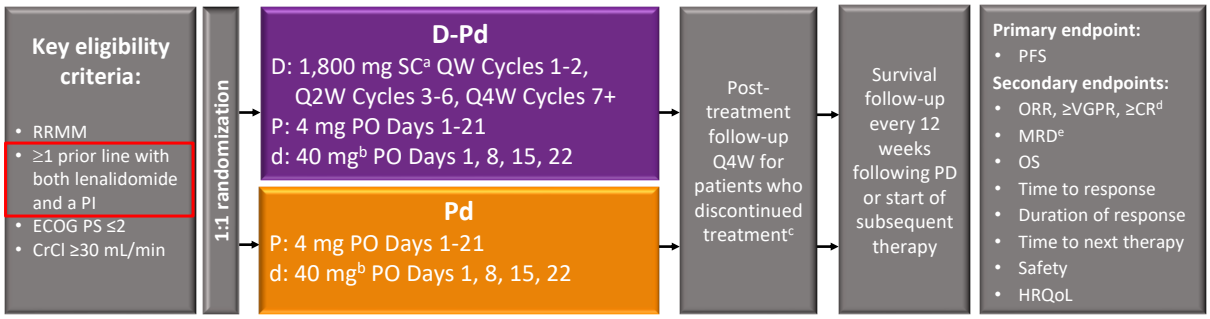
[20]Erasmus University Medical Center Cancer Institute, Rotterdam, The Netherlands. ([†]At the time of study)

*ClinicalTrials.gov Identifier: NCT03180736.

Additional information can be viewed by scanning the QR code or accessing this link: https://epg-digital.com/u/ASH2020-Dimopoulos. The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Study Design

- Phase 3 study of D-Pd versus Pd in RRMM conducted in collaboration between EMN and Janssen

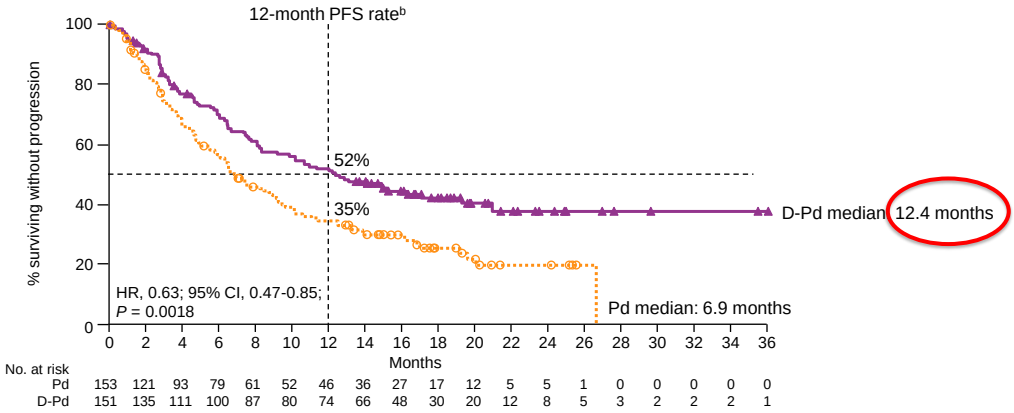


Stratification factors
- Number of lines of prior therapy (1 vs 2-3 vs ≥4)
- ISS disease stage (I vs II vs III)

Cycle duration: 28 days
Treatment until PD or unacceptable toxicity

EMN, European Myeloma Network; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CrCl, creatinine clearance; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; PO, oral; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response, MRD, minimal residual disease, OS, overall survival; HRQoL, health-related quality of life; ISS, International Staging System; SC, subcutaneous; sCR, stringent complete response. [a]Patients initially were given DARA 16 mg/kg IV; following Protocol Amendment 1, new patients in the D-Pd arm received DARA SC. Patients who had already received DARA IV prior to this amendment may switch to DARA SC on Day 1 of any cycle from Cycle 3+. [b]Patients aged ≥75 years received 20 mg weekly. [c]Follow-up is for patients who discontinued treatment for reasons other than PD, death, lost to follow-up, or withdrawal of consent. [d]Disease assessments were collected every cycle for the first 14 months and every other month thereafter by a central laboratory. [e]MRD was assessed by next-generation sequencing using bone marrow aspirate samples obtained at screening, at the time of suspected CR or sCR, and at 6, 12, 18, 24, and every 12 months after achieving CR or sCR, until disease progression.

PFS at a Median Follow-up of 16.9 Months[a]

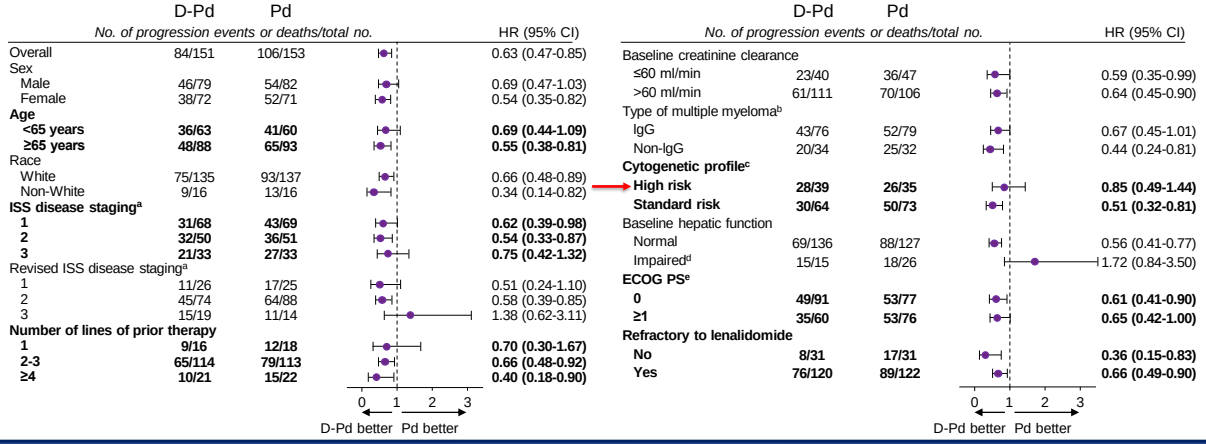


- Median PFS among patients refractory to lenalidomide was 9.9 months for D-Pd and 6.5 months for Pd

Addition of DARA SC to Pd improved PFS, with a 37% reduction in the risk of progression or death

HR, hazard ratio; CI, confidence interval. [a]Intent-to-treat population. [b]Kaplan–Meier estimate.

PFS in Pre-specified Subgroups



Observed treatment effect was generally consistent across subgroups

[a]Derived based on the combination of serum β2-microglobulin and albumin levels, with higher stages indicating more advanced disease. [b]Performed on data from patients who had measurable disease in serum. [c]Defined by detection of del17p, t(14;16), and/or t(4;14) on fluorescence in situ hybridization. [d]Includes mild impairment (total bilirubin level ≤ the ULN and aspartate aminotransferase level > the ULN, or total bilirubin level > the ULN and ≤1.5 times the ULN), moderate impairment (total bilirubin level >1.5 times and ≤3 times the ULN), and severe impairment (total bilirubin level >3 times the ULN). [e]Scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.

Most Common TEAEs[a]

Most common TEAEs, n (%)	D-Pd (n = 149)		Pd (n = 150)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic				
Neutropenia	105 (70)	101 (68)	80 (53)	76 (51)
Anemia	55 (37)	25 (17)	66 (44)	32 (21)
Thrombocytopenia	48 (32)	26 (17)	50 (33)	27 (18)
Leukopenia	39 (26)	25 (17)	18 (12)	7 (5)
Lymphopenia	22 (15)	18 (12)	12 (8)	5 (3)
Febrile neutropenia	13 (9)	13 (9)	4 (3)	4 (3)
Nonhematologic				
Infections	105 (70)	42 (28)	83 (55)	34 (23)
Upper respiratory tract infection	34 (23)	0	24 (16)	3 (2)
Pneumonia	30 (20)	20 (13)	19 (13)	10 (7)
Lower respiratory tract infection	29 (19)	17 (11)	24 (16)	14 (9)
Fatigue	38 (26)	12 (8)	38 (25)	7 (5)
Asthenia	33 (22)	8 (5)	24 (16)	1 (1)
Diarrhea	33 (22)	8 (5)	21 (14)	1 (1)
Pyrexia	29 (19)	0	21 (14)	0
Hyperglycemia	15 (10)	8 (5)	19 (13)	7 (5)

Safety profile of D-Pd is consistent with the known profiles of DARA SC and Pd

TEAE, treatment-emergent adverse event. [a]All patients who received ≥1 dose of treatment were included in the safety population. TEAEs of any grade that were reported in ≥15% of patients in either group or grade 3/4 TEAEs that were reported in ≥5% of patients in either group are listed (TEAEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03; terms were coded using MedDRA dictionary version 23.0).

Session Name: 653. Myeloma: Therapy, excluding Transplantation: Poster II
Date: Sunday, December 6, 2020
Abstract #2325

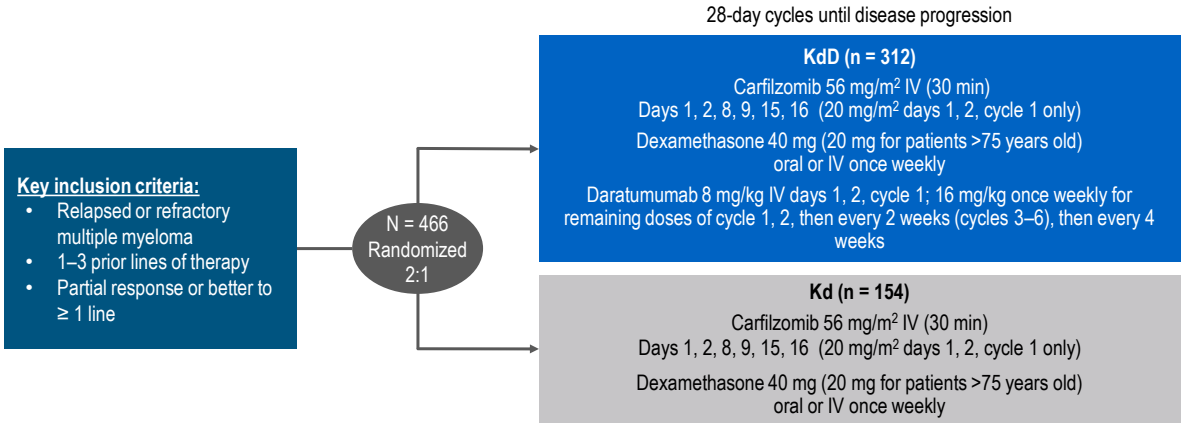
Carfilzomib, Dexamethasone, and Daratumumab Versus Carfilzomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Efficacy and Safety Results of the Phase 3 CANDOR Study

Meletios Dimopoulos,[1] Hang Quach,[2] Maria-Victoria Mateos,[3] Ola Landgren,[4] Xavier Leleu,[5] David Siegel,[6] Katja Weisel,[7] Maria Gavriatopoulou,[8] Albert Oriol,[9] Neil Rabin,[10] Ajay Nooka,[11] Ming Qi,[12] Bifeng Ding,[13] Anita Zahlten-Kumeli,[13] Saad Z Usmani[14]

[1]National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; [2]University of Melbourne, St Vincent's Hospital, Melbourne, Victoria, Australia; [3]University Hospital Salamanca/ISAL, Salamanca, Spain; [4]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA: [5]CHU de Poitiers – La Miletrie/INSERM CIC 1402, Poitiers, France; [6]John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ, USA: [7]Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [8]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; [9]Hematology Department, Insitut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Barcelona, Spain; [10]Department of Hematology, University College London Hospitals NHS Foundation Trusts, London, UK; [11]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [12]Janssen Research & Development, Spring House, PA, USA; [13]Amgen Inc., Thousand Oaks, CA, USA; [14]Atrium Health, Charlotte, NC, USA

62nd American Society of Hematology Annual Meeting and Exposition, Virtual Meeting; December 5–8, 2020

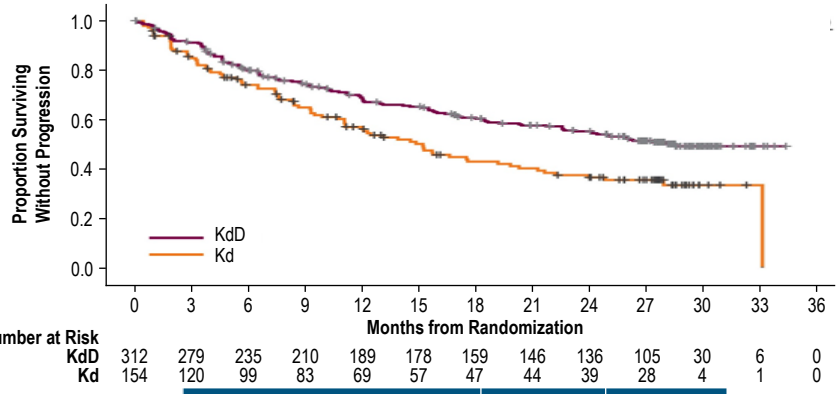
Study design for CANDOR



Primary endpoint: PFS
Key secondary endpoints: OS, ORR, safety

CR, complete response; IV, intravenous; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

41% reduction in the risk of progression/death and a 13.4-month improvement in median PFS with KdD versus Kd

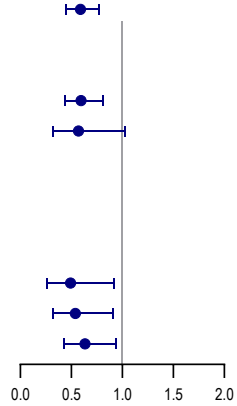


	KdD (n = 312)	Kd (n = 154)
Median treatment duration, months	18.3	9.3
Median PFS follow-up, months	27.8	27.0
Median PFS by ORCA, months	**28.6**	**15.2**
HR (KdD/Kd) (95% CI)	**0.59 (0.45–0.78)**	

CI, confidence interval; HR, hazard ratio; ORCA, Onyx Response Computer Algorithm; OS, overall survival; PFS, progression-free survival.

Generally consistent PFS benefit for KdD versus Kd across subgroups

Subgroup	KdD (n = 312) Events/ Patients	KdD (n = 312) Median PFS, months	Kd (n = 154) Events/ Patients	Kd (n = 154) Median PFS, months	Hazard ratio for KdD vs Kd (95% CI)
All randomized subjects	140/312	28.6	85/154	15.2	0.59 (0.45, 0.78)
ISS stage per IXRS at screening					
1 or 2	101/252	NE	68/127	15.8	0.60 (0.44, 0.81)
3	39/60	13.0	17/27	7.4	0.57 (0.32, 1.03)
Age at baseline (years)					
≤65					0.51 (0.35, 0.73)
>65					0.73 (0.48, 1.12)
Cytogenetic risk group					
High risk	30/48	15.6	18/26	5.6	0.49 (0.26, 0.92)
Standard risk	39/107	NE	26/56	16.6	0.54 (0.32, 0.91)
Unknown	71/157	28.1	41/72	15.7	0.64 (0.43, 0.94)



CI, confidence interval; ISS, International Staging System; IXRS, interactive voice/web response system; NE, not estimable; PFS, progression-free survival.

Updated safety analysis

	KdD (n = 308)	Kd (n = 153)
Adverse events, %		
Grade ≥3	87.0	75.8
Fatal*†	8.8	4.6
Leading to carfilzomib treatment discontinuation	26.0	22.2
Exposure-adjusted AE rates per 100 patient years		
Grade ≥3	171.2	151.9
Fatal	6.9	5.6

AE, adverse event
*Excludes patients whose death was listed as disease progression
†One fatal AE in the KdD arm (due to arrhythmia) and one fatal AE in the Kd arm (due to COVID-19 pneumonia) had occurred since the primary analysis.

IKEMA Depth of Response and Response Kinetics of Isatuximab plus Carfilzomib and Dexamethasone in Relapsed Multiple Myeloma: IKEMA Interim Analysis

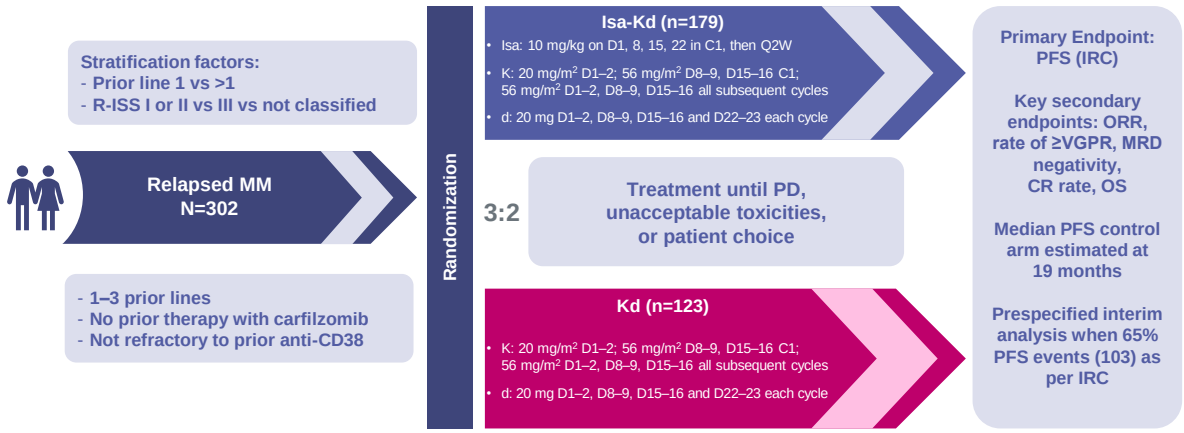
Thomas Martin,[1] Joseph Mikhael,[2] Roman Hajek,[3] Kihyun Kim,[4] Kenshi Suzuki,[5] Cyrille Hulin,[6] Mamta Garg,[7] Hang Quach,[8] Hanlon Sia,[9] Anup George,[10] Tatiana Konstantinova,[11] Marie-Laure Risse,[12] Gaelle Asset,[13] Sandrine Macé,[12] Helgi van de Velde,[14] Philippe Moreau[15]

[1]Department of Medicine, University of California, San Francisco, CA, USA; [2]Translational Genomics Research Institute, City of Hope Cancer Center, Phoenix, AZ, USA; [3]Faculty of Medicine, University Hospital Ostrava, Ostrava, Czech Republic; [4]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [5]Department of Hematology, Japanese Red Cross Medical Center, Tokyo, Japan; [6]Department of Hematology, University Hospital Bordeaux, Bordeaux, France; [7]Department of Haematology, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [8]Faculty of Medicine, University of Melbourne and St Vincent's Hospital, Victoria, Australia; [9]Cancer Care & Haematology Unit, The Tweed Hospital, Tweed Heads, NSW, Australia; [10]Wellington Blood and Cancer Center, Wellington, New Zealand; [11]Hematology Department, Regional Hospital #1, Ekaterinburg, Russia; [12]Sanofi Research and Development, Vitry-Sur-Seine, France; [13]Sanofi Research and Development, Chilly-Mazarin, France; [14]Sanofi, Cambridge, MA; [15]Department of Hematology, University Hospital of Nantes, Nantes, France

Presentation at the 62nd American Society of Hematology (ASH) Virtual Scientific Meeting, December 5–8, 2020

Presentation Code: 414

IKEMA
Study design: Isa-Kd vs Kd in relapsed multiple myeloma

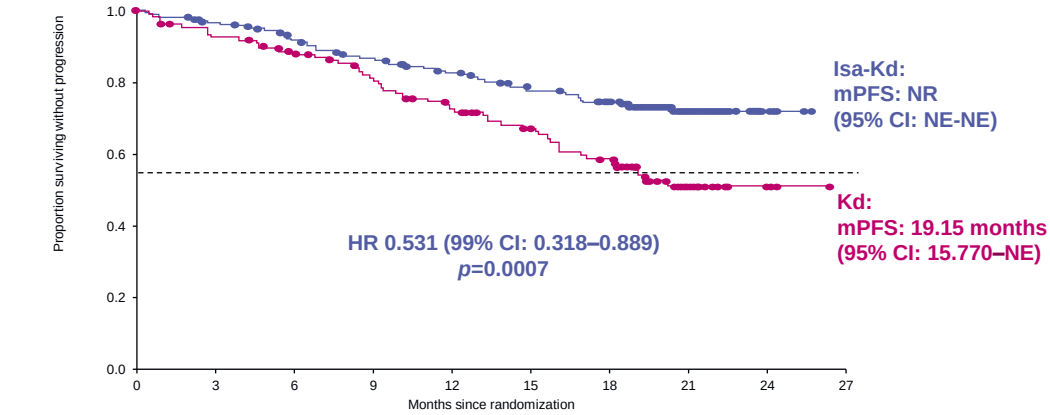


Sample size calculation: ~300 patients and 159 PFS events to detect 41% risk reduction in hazard rate for PFS with 90% power and one-sided 0.025 significance level

Moreau P, et al. Future Oncol. 2020;16:4347–4358.

IKEMA study: NCT03275285
C, cycle; CD, cluster of differentiation; CR, complete response; D, day; d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q2W, once every 2 weeks; R-ISS, Revised International Staging System; VGPR, very good partial response.

IKEMA
Interim PFS analysis – IRC assessment in ITT population (primary endpoint)



One-sided *p* value, level of significance <0.005

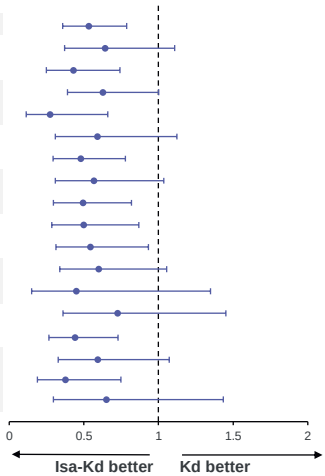
Isa-Kd showed improvement in PFS with 47% reduction of risk of progression or death vs Kd

Presented By Philippe Moureau at EHA 2020

CI, confidence interval; d, dexamethasone; HR, hazard ratio; IRC, Independent Review Committee; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; m, median; NE, not estimable; NR, not reached; PFS, progression-free survival

IKEMA
PFS subgroup analyses

Subgroup		Isa-Kd No. of events/total no.	Kd No. of events/total no.	Hazard ratio (95% CI)
All patients		48/179	55/123	0.531 (0.359–0.786)
Age	<65 years	25/88	26/66	0.640 (0.370–1.109)
	≥65 years	23/91	29/57	0.429 (0.248–0.742)
Baseline eGFR (MDRD)	≥60 mL/min/1.73 m²	32/122	38/93	0.625 (0.391–1.001)
	<60 mL/min/1.73 m²	10/43	10/18	0.273 (0.113–0.660)
Number of prior lines of therapy	1	18/80	19/55	0.589 (0.309–1.123)
	>1	30/99	36/68	0.479 (0.294–0.778)
Prior PI treatment*	Yes	22/81	20/47	0.565 (0.308–1.036)
	No	26/98	35/76	0.493 (0.296–0.819)
Prior IMiD treatment*	Yes	22/81	29/62	0.498 (0.286–0.869)
	No	26/98	26/61	0.542 (0.314–0.933)
Refractory to Len	Yes	23/57	25/42	0.598 (0.339–1.055)
	No	5/15	9/17	0.448 (0.149–1.349)
High-risk cytogenetic status	Yes	17/42	15/31	0.724 (0.361–1.451)
	No	27/114	35/77	0.440 (0.266–0.728)
ISS staging at study entry	I	20/89	24/71	0.592 (0.327–1.071)
	II	17/63	16/31	0.375 (0.188–0.748)
	III	11/26	14/20	0.650 (0.295–1.434)



Consistent treatment effect was seen for Isa-Kd across subgroups

*Prior treatment at last line

CI, confidence interval; d, dexamethasone; eGFR, estimated glomerular filtration rate; IMiD, immunomodulatory drug; Isa, isatuximab; K, carfilzomib; Len, lenalidomide; MDRD, modified of diet in renal disease; PFS, progression-free survival; PI, proteasome inhibitor; ISS, International Staging System

Presented By Philippe Moureau at EHA 2020

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My comments: RRMM, 1-3 prior lines

Trial	Arms	PFS triplet (mo)	PFS doublet (mo)	HR	P value
Apollo	DPd vs Pd	12.4	6.9	0.63	0.0018
CANDOR	KdD vs Kd	28.6	15.2	0.59	NA
IKEMA	IKd vs Kd	NR	19.15	0.531	0.0007

- Targeting CD38 = Peloton; everyone is doing it
- Combo with carfilzomib = very effective
- ….but what if you used Dara in the 1st line??

UCSF

HOSPITAL UNIVERSITARIO DE SALAMANCA

IBSAL Instituto de Investigación Biomédica de Salamanca

University of Salamanca

Randomized phase 2 study of weekly Carfilzomib 70 mg/m² and dexamethasone with or without cyclophosphamide in Relapsed and/or Refractory Multiple (MM) patients (GEM-KyCyDex)

María-Victoria Mateos[1], Enrique M. Ocio[2], Anna Sureda[3], Albert Oriol[4], Mª Esther González[5], Mª José Moreno[6], Miguel Granell[7], Fernando Escalante[8], Verónica González-Calle[1], Laura Rosiñol[9], Estrella Carrillo[10], Otro del 12 de Octubre[11], Victoria Dourdil[12], Sonia González[13], Jaime Pérez-de-Oteyza[14], Felipe de Arriba[15], Miguel T. Hernández[16], Mª Aránzazu García-Mateo[17], Ana Pilar González-Rodríguez[18], Rafael Ríos[19], Mª Carmen Cabrera[20], Joan Bargay[21], Paula Rodríguez-Otero[22], Luis Felipe Casado[23], María Casanova[24], Mª Jesús Blanchard[25], Joan Bladé[9], Juan J. Lahuerta[11], Jesús F. San Miguel[22]

On Behalf of the Spanish Myeloma Group, GEM/Pethema

GEM-KyCydex: Study Design

Multicenter, open-label, randomized phase II trial

Randomization 1:1

N=198

- RRMM patients after 1-3 prior lines of therapy
- Prior therapy with PIs was allowed
- Patients refractory to PIs were not allowed
- CrCl >30 mlx minute
- LVEF > 50%

KyCydex (n=97)

- Carfilzomib 70 mg/m² IV
  Days 1, 8 and 15 (20 mg/m² day 1 cycle 1 only)
  Infusion duration: 30 minutes for all doses
- Dexamethasone 40 mg weekly: 20 mg the day of Ky and 20 mg the day after.
- Cyclophosphamide 300 mg/m² IV
  Days 1, 8 and 15

28-day cycles until PD or unacceptable toxicity

Kydex (n=101)

- Carfilzomib 70 mg/m² IV
  Days 1, 8 and 15 (20 mg/m² day 1 cycle 1 only)
  Infusion duration: 30 minutes for all doses
- Dexamethasone 40 mg weekly: 20 mg the day of Ky and 20 mg the day after.
- 28-day cycles until PD or unacceptable toxicity

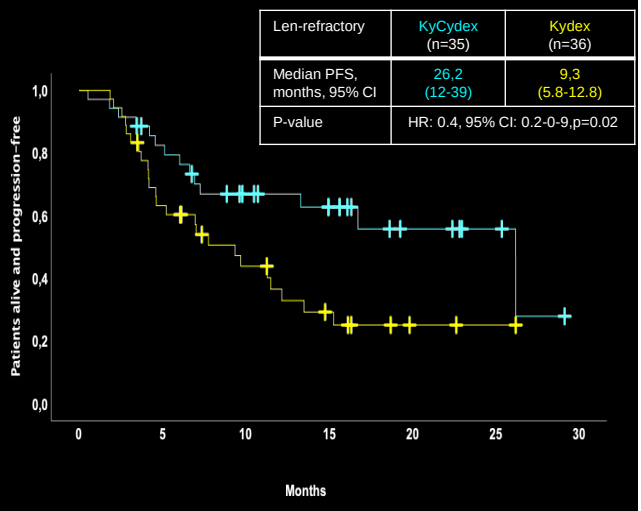
Dex 20 mg weekly for pts older than 75

Ky and Cyclo only on days 1 and 15 since cycle 12

GEM-KyCydex
PFS in len-exposed and refractory patients

Median follow-up: 15.6 (1.3-29)

PFS by subgroup	KyCydex (n=97)	Kydex (n=101)
Len-refractory after last line of therapy	32 (33%)	36 (36%)
Median PFS, months, 95% CI	26,2 (12-39)	9,3 (5.8-12.8)
P-value	0.02	
- After 1PL (n=11 and 10)	NR	9.7
- After 2PL (n=12 and 17)	NR	9.3
- After 3PL (n=9 and 9)	26	9.0



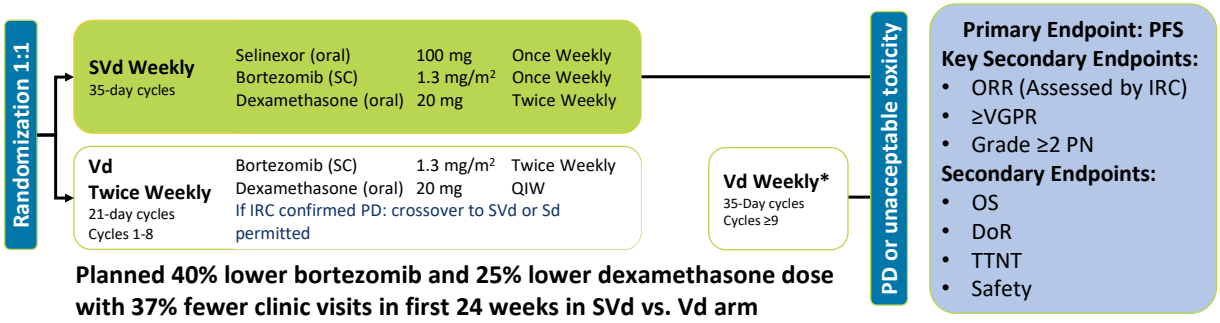
Effect of Prior Treatment with Proteasome Inhibitors on the Efficacy and Safety of Once-Weekly Selinexor, Bortezomib, and Dexamethasone in Comparison with Twice-Weekly Bortezomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma: Subgroup Analysis from the BOSTON Study

Maria V Mateos[1], Maria Gavriatopoulou[2], Thierry Facon[3], Holger Auner[4], Xavier Leleu[5], Roman Hájek[6], Meletios A. Dimopoulos[7], Sosana Delimpasi[8], Maryana Simonova[9], Ivan Špička[10], Luděk Pour[11], Iryna Kriachok[12], Halyna Pylypenko[13], Vadim Doronin[14], Ganna Usenko[15], Reuben Benjamin[16], Tuphan K Dolai[17], Dinesh K Sinha[18], Christopher Venner[19], Mamta Garg[20], Don A Stevens[21], Hang Quach[22], Sundar Jagannath[23], Philippe Moreau[24], Moshe Levy[25], Ashraf Z. Badros[26], Larry A. Anderson[27], Nizar J Bahlis[28], Dr Michele Cavo[29], Yi Chai[30], Melina Arazy[30], Jatin Shah[30], Sharon Shacham[30], Michael G Kauffman[30], Paul G Richardson[31], Sebastian Grosicki[32]

[1]Hospital Universitario de Salamanca, Salamanca, Spain; [2]Alexandra Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [3]CHU Lille Service des Maladies du Sang F-59000, Lille, France; [4]Imperial College London, London, UK; [5]Department of Hematology, CHU la Miletrie and Inserm CIC 1402, Poitiers, France; [6]University Hospital Ostrava, Department of Hematooncology, Ostrava Czech Republic; [7]National and Kapodistrian University of Athens, Athens Greece; [8]General Hospital Evangelismos, Athens Greece; [9]Institute of Blood Pathology and Transfusion Medicine of NAMS of Ukraine, Lviv Ukraine; [10]Charles University and General Hospital, Prague, Czech Republic; [11]University Hospital Brno, Brno, Czech Republic; [12]National Cancer Institute, Kiev, Ukraine; [13]Cherkassy Regional Oncological Center, Cherkassy, Ukraine; [14]City Clinical Hospital #40, Moscow, Russian Federation; [15]City Clinical Hospital No.4 of Dnipro City Council, Dnipro Ukraine; [16]Kings College Hospital NHS Foundation Trust, London, UK; [17]Nil Ratan Sircar Medical College and Hospital, Kolkata, India; [18]State Cancer Institute, Indira Gandhi Institute of Medical Sciences, Patna, India; [19]Cross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada; [20]University Hospitals of Leicester NHS Trust, Leicester UK; [21]Norton Cancer Institute, St. Matthews Campus, Louisville, KY; [22]University of Melbourne, St Vincent's Hospital, Melbourne, Victoria Australia; [23]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [24]University Hospital, Hotel-Dieu, Nantes, France; [25]Baylor University Medical Center, Dallas, TX; [26]University of Maryland, Greenebaum Comprehensive Cancer Center, Baltimore, MD; [27]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; [28]University of Calgary, Charbonneau Cancer Research Institute, Calgary, AB; [29]Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; [30] Karyopharm Therapeutics Inc, Newton, MA; [31]Dana Farber Cancer Institute, Boston, MA; [32]Medical University of Silesian, Katowice, Poland

BOSTON Study Trial Design

BOSTON Trial: Phase 3, Global, Randomized, Open Label, Controlled Study in Patients with MM who had Received 1–3 Prior Therapies



Planned 40% lower bortezomib and 25% lower dexamethasone dose with 37% fewer clinic visits in first 24 weeks in SVd vs. Vd arm

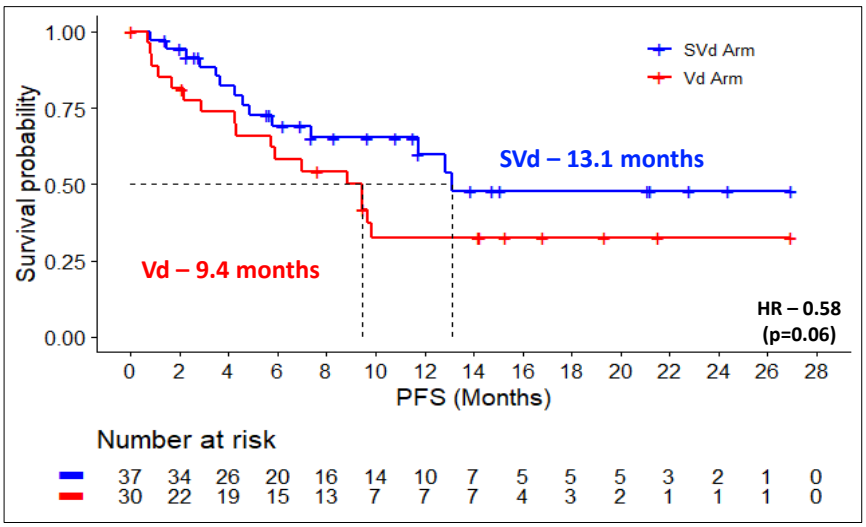
Stratifications:

Prior PI therapies (Yes vs No); Number of prior anti-MM regimens (1 vs >1); R-ISS stage at study entry (Stage III vs Stage I/II)
5HT-3 prophylactic recommended in SVd arm

CR= complete response, DoR = duration of response, IMWG = International Myeloma Working Group, IRC = Independent Review Committee, OS = overall survival, PD = progressive disease, PFS = progression free survival, PR = partial response, PN = peripheral neuropathy, sCR = stringent complete response, TTNT = time to next therapy, VGPR = very good partial response. PFS defined as: Time from date of randomization until the first date of progressive disease, per IMWG response criteria, or death due to any cause, whichever occurred first, as assessed by IRC. ORR: Any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to IMWG response criteria (Kumar et al. Lancet oncology 2016). All changes in MM disease assessments were based on baseline MM disease assessments. *Vd weekly dosing and schedule for cycles≥ 9 as per SVd arm description.

SVd is Effective Among Patients that Received Bortezomib Prior to ASCT as Induction Therapy – PFS, ORR

PFS for Bort-Treated Prior to ASCT



My comments: RRMM, 1-3 prior lines

Trial	Arms	PFS triplet (mo)	PFS doublet (mo)	HR	P value	Notes
APOLLO	DPd vs Pd	12.4	6.9	0.63	0.0018	Duh!
CANDOR	KdD vs Kd	28.6	15.2	0.59	NA	Good for high risk
IKEMA	IKd vs Kd	NR	19.15	0.53	0.0007	Hope it's cheaper!
GEM-KyCyDex	KCd vs Kd	20.7	15.2	1.2	0.24	Good for lenalidomide refractory
BOSTON	SVd vs Vd	13.93	9.46	0.70	0.0075	OK for prior bortezomib in 1st line

UCSF

Relapsed/Refractory Myeloma >3 prior lines

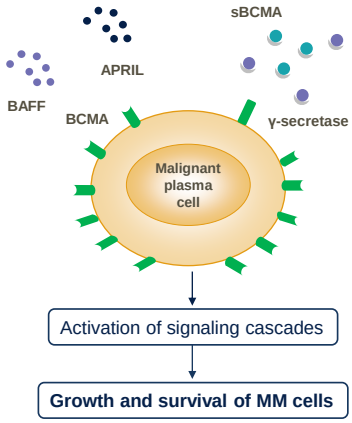
UCSF

Let's start with the CARs

UCSF

Rationale for Targeting BCMA

- BCMA is a cell surface protein expressed on late-stage B cells and plasma cells but virtually absent on naïve and memory B cells[1-3]
- BCMA is highly expressed on malignant plasma cells in all patients with MM[3-5]
  - BCMA ligands, BAFF and APRIL, are detected in increased levels in the circulation of patients with MM[3,5]
- BCMA is essential for the proliferation and survival of malignant plasma cells[3]



APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; sBCMA, serum BCMA.

1. Tai YT, et al. *Immunotherapy*. 2015;7(11):1187-1199. 2. Ryan MC, et al. *Mol Cancer Ther*. 2007;6(11):3009-3018. 3. Cho S-F, et al. *Front Immunol*. 2018;9:1821. doi:10.3389/fimmu.2018.01821.
4. Novak AJ, et al. *Blood*. 2004;103(2):689-694. 5. Tai YT, et al. *Blood*. 2014;123(20):3128-3138.

UCSF

Video

Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy, in patients with relapsed and refractory multiple myeloma: updated results from phase 1 CRB-401 study

Yi Lin,[1] Noopur S. Raje,[2] Jesús G. Berdeja,[3] David S. Siegel,[4] Sundar Jagannath,[5] Deepu Madduri,[5] Michaela Liedtke,[6] Jacalyn Rosenblatt,[7] Marcela V. Maus,[2] Monica Massaro,[8] Fabio Petrocca,[8] Andrea Caia,[9] Zhihong Yang,[9] Timothy B. Campbell,[9] Kristen Hege,[9] Nikhil C. Munshi,[10] and James N. Kochenderfer[11]

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

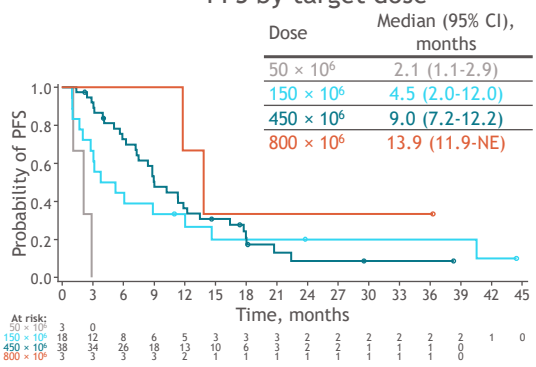
ASH 2020, Presentation 131

CRB-401

PFS and OS

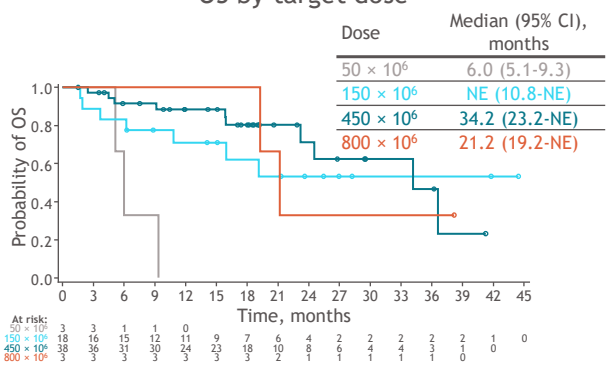
Video

PFS by target dose



Median PFS 8.8 months
(95% CI, 5.9-11.9 months) across all treated patients

OS by target dose



Median OS 34.2 months
(95% CI, 19.2-NE months) across all treated patients

Median and 95% CI from Kaplan-Meier estimate. NE, not estimable.

Lin Y, et al. ASH 2020. Abstract 131.

2020 ASCO ANNUAL MEETING

KarMMa™

Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-targeted CAR T cell therapy, in patients with relapsed and refractory multiple myeloma (RRMM): initial KarMMa results

Nikhil C. Munshi, MD[1]; Larry D. Anderson, Jr, MD, PhD[2]; Nina Shah, MD[3]; Sundar Jagannath, MD[4]; Jesus Berdeja, MD[5]; Sagar Lonial, MD[6]; Noopur Raje, MD[7]; David S. Siegel, MD, PhD[8]; Yi Lin, MD, PhD[9]; Albert Oriol, MD[10]; Philippe Moreau, MD[11]; Ibrahim Yakoub-Agha, MD, PhD[12]; Michel Delforge, MD[13]; Fabio Petrocca, MD[14]; Jamie N. Connarn, PhD[15]; Payal Patel[15]; Liping Huang, PhD[15]; Timothy B. Campbell, MD, PhD[15]; Kristen Hege, MD[15]; and Jesus San Miguel, MD, PhD[16] *on behalf of the KarMMa study investigators*

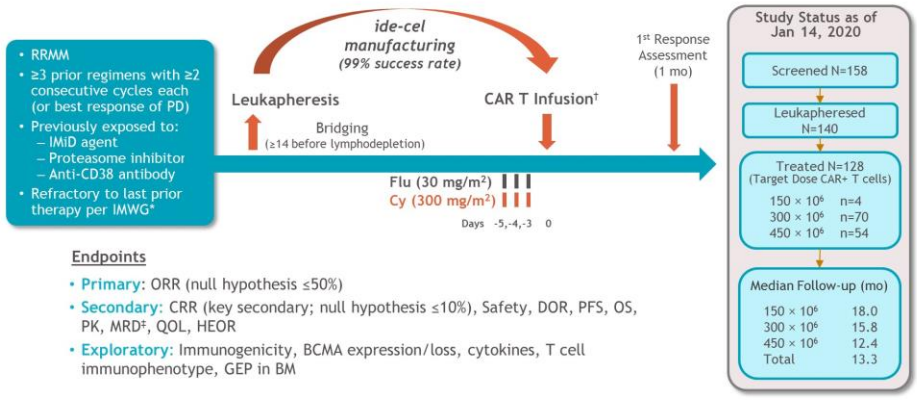
[1]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [3]University of California San Francisco, San Francisco, CA, USA; [4]Mount Sinai Hospital, New York, NY, USA; [5]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [6]Emory School of Medicine, Atlanta, GA, USA; [7]Massachusetts General Hospital, Boston, MA, USA; [8]Hackensack University Medical Center, Hackensack, NJ, USA; [9]Mayo Clinic, Rochester, MN, USA; [10]Institut Josep Carreras and Institut Catala d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain; [11]Centre Hospitalier Universitaire de Nantes, Nantes, France; [12]Centre Hospitalier Regional Universitaire de Lille, Lille, France; [13]University Hospital Leuven, Leuven, Belgium; [14]bluebird bio, Cambridge, MA, USA; [15]Bristol Myers Squibb, Princeton, NJ, USA; and [16]Clinical Universidad de Navarra, Navarra, Spain

Presentation Number 8503

Presented By Nikhil Munshi at ASCO 2020

Phase II Pivotal KarMMa Study

KarMMa™



Endpoints

- **Primary:** ORR (null hypothesis ≤50%)
- **Secondary:** CRR (key secondary; null hypothesis ≤10%), Safety, DOR, PFS, OS, PK, MRD‡, QOL, HEOR
- **Exploratory:** Immunogenicity, BCMA expression/loss, cytokines, T cell immunophenotype, GEP in BM

CRR, complete response rate; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP in BM, gene expression profile in bone marrow; HEOR, health economics and outcomes research; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.
*Defined as documented disease progression during or within 60 d from last dose of prior antimyeloma regimen. †Patients were required to be hospitalized for 14 d post-infusion. Ide-cel retreatment was allowed at disease progression for best response of at least stable disease. ‡By next-generation sequencing.

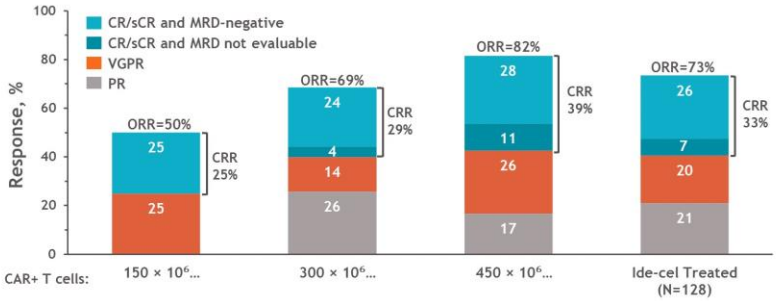
EudraCT: 2017-002245-29
ClinicalTrials.gov: NCT03361748

Presented By Nikhil Munshi at TBD

Median # prior regimens: 6

CRS: 84%
Neurotox: 18%

Best Overall Response



- Primary (ORR >50%) and key secondary (CRR >10%) endpoints met in the ide-cel treated population
  - *ORR of 73% (95% CI, 65.8–81.1; P<0.0001*)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7–40.9; P<0.0001)*
- Median time to first response of 1.0 mo (range, 0.5–8.8); median time to CR of 2.8 mo (range, 1.0–11.8)
- Median follow-up of 13.3 mo across target dose levels

Data cutoff: 14 Jan 2020. MRD-negative defined as <10⁻⁵ nucleated cells by next generation sequencing. Only MRD values within 3 mo of achieving CR/sCR until progression/death (exclusive) were considered.
Values may not add up due to rounding.
CR/sCR, complete response/stringent CR; CRR, CR rate; MRD, minimal residual disease; ORR, overall response rate (≥PR); PR, partial response; VGPR, very good PR. *P value at the primary data cutoff with same ORR and 95% CI.

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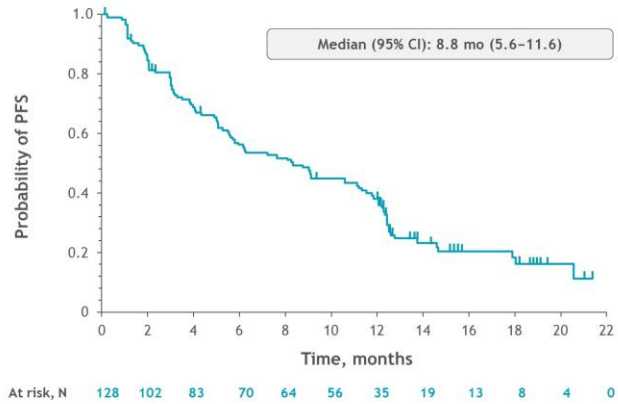
Munshi et al, ASCO 2020

Progression-Free Survival



Data cutoff: 14 Jan 2020. PFS, progression-free survival.

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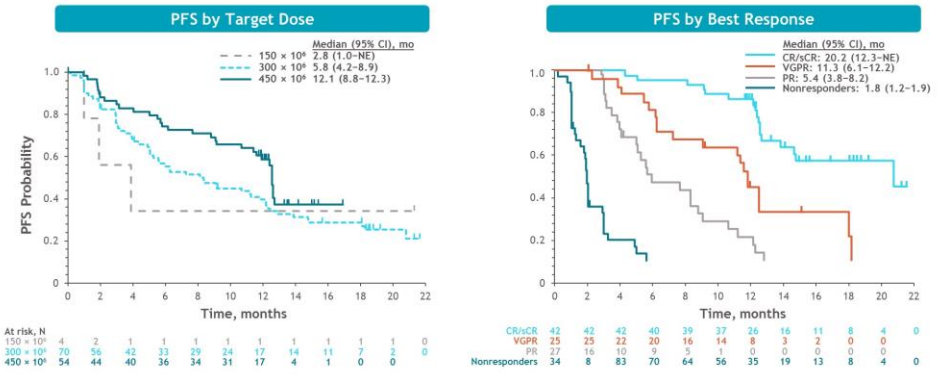
Munshi et al, ASCO 2020

Progression-Free Survival

KarMMa™



- PFS increased with higher target dose; median PFS was 12 mo at 450 × 10^6 CAR+ T cells
- PFS increased by depth of response; median PFS was 20 mo in patients with CR/sCR

Data cutoff: 14 Jan 2020. NE, not estimable; PFS, progression-free survival.

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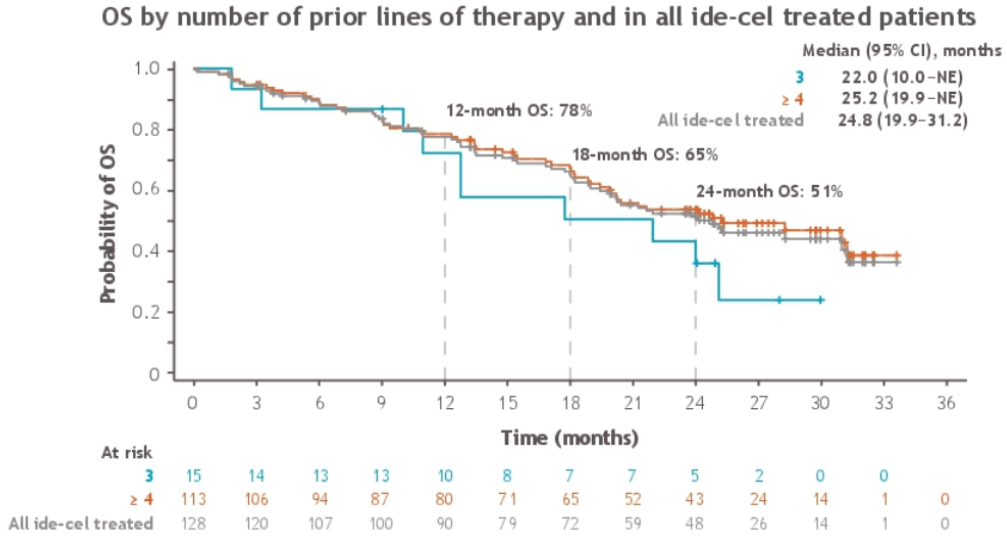
Munshi et al, ASCO 2020

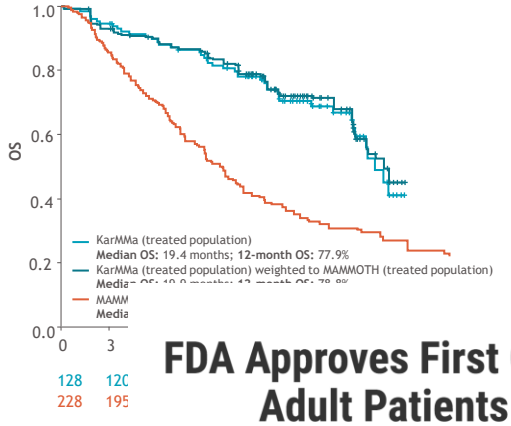
KarMMa: Updated OS[1]



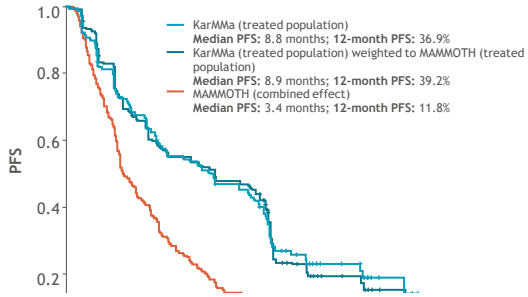
1. Anderson LD, et al. ASCO 2021. Abstract 8016.

OS and PFS: ide-cel versus conventional care

OS: Ide-cel (KarMMa treated population) versus conventional care (MAMMOTH treated population)



PFS: Ide-cel (KarMMa treated population) versus conventional care (MAMMOTH treated population)



FDA NEWS RELEASE

FDA Approves First Cell-Based Gene Therapy for Adult Patients with Multiple Myeloma

- Median O… and median PFS were significantly longer for the ide-cel treated population (weight matched) compared with the conventional care population in MAMMOTH in the base case

OS, overall survival; PFS, progression-free survival.

Shah N, et al. ASH 2020 [abstract #1653]

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2021 ASCO ANNUAL MEETING

CILTACABTAGENE AUTOLEUCEL, A B-CELL MATURATION ANTIGEN–DIRECTED CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY, IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: UPDATED RESULTS FROM CARTITUDE-1

Saad Z Usmani[1], Jesus G Berdeja[2], Deepu Madduri[3], Andrzej Jakubowiak[4], Mounzer Agha[5], Adam D Cohen[6], Parameswaran Hari[7], Tzu-Min Yeh[8], Yunsi Olyslager[9], Arnob Banerjee[10], Carolyn C Jackson[8], Alicia Allred[10], Enrique Zudaire[10], William Deraedt[9], Xiaoling Wu[11], Marlene J Carrasco-Alfonso[11], Muhammad Akram[11], Yi Lin[12], Thomas Martin[13], Sundar Jagannath[3]

[1]Levine Cancer Institute-Atrium Health, Charlotte, NC, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]Mount Sinai Medical Center, New York, NY, USA; [4]University of Chicago, Chicago, IL, USA; [5]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [6]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [7]Medical College of Wisconsin, Milwaukee, WI, USA; [8]Janssen R&D, Raritan, NJ, USA; [9]Janssen R&D, Beerse, Belgium; [10]Janssen R&D, Spring House, PA, USA; [11]Legend Biotech USA, Inc, Piscataway, NJ, USA; [12]Mayo Clinic, Rochester, MN, USA; [13]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

June 8, 2021

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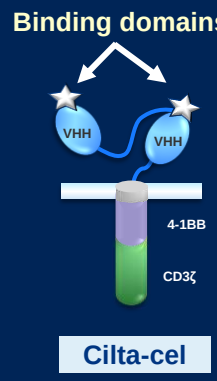
CARTITUDE-1: Introduction

- CARTITUDE-1 (NCT03548207) is a phase 1b/2 study evaluating cilta-cel, a CAR T-cell therapy with two BCMA–targeting single-domain antibodies, in patients with R/R MM who have been heavily pretreated[1]
  - At a median follow-up of 12.4 months after cilta-cel treatment, the overall response rate was 97% with an sCR rate of 67%; overall 12-month PFS and OS rates were 77% and 89%, respectively
- Here, we present updated results from CARTITUDE-1 in patients with a longer follow-up (median: 18 months)



BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; OS, overall survival; PFS, progression-free survival; R/R MM, relapsed refractory multiple myeloma; sCR, stringent complete response; VHH, variable heavy chain.
1. Madduri D, et al. *Blood* 2020;136(Suppl 1):22–25.

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CARTITUDE-1: Baseline Characteristics

Characteristic	
Age, median (range) years	61.0 (43–78)
Male, n (%)	57 (58.8)
Black/African American, n (%)	17 (17.5)
All plasmacytomas,[a] n (%)	19 (19.6)
Extramedullary plasmacytomas, n (%)	13 (13.4)
Bone-based plasmacytomas, n (%)	6 (6.2)
Bone-marrow plasma cells ≥60%, n (%)	21 (21.9)
Years since diagnosis, median (range)	5.9 (1.6–18.2)
High-risk cytogenetic profile, n (%)	23 (23.7)
del17p	19 (19.6)
t(14;16)	2 (2.1)
t(4;14)	3 (3.1)
Tumor BCMA expression ≥50%, n (%)	57 (91.9)[b]

Characteristic	
Prior lines of therapy, median (range)	6.0 (3–18)
Prior lines of therapy, n (%)	
3	17 (17.5)
4	16 (16.5)
≥5	64 (66.0)
Previous stem-cell transplantation, n (%)	
Autologous	87 (89.7)
Allogeneic	8 (8.2)
Triple-class exposed,[c] n (%)	97 (100)
Penta-drug exposed,[d] n (%)	81 (83.5)
Triple-class refractory[c]	85 (87.6)
Penta-drug refractory[d]	41 (42.3)
Refractory status, n (%)	
Carfilzomib	63 (64.9)
Pomalidomide	81 (83.5)
Anti-CD38 antibody	96 (99.0)
Refractory to last line of therapy, n (%)	96 (99.0)

BCMA, B-cell maturation antigen; IMiD, immunomodulatory drug; PI, proteasome inhibitor.
[a]All plasmacytomas include extramedullary and bone-based plasmacytomas. [b]Denominator n=62, the number of evaluable samples; BCMA expression detected in all evaluable samples. [c]At least 1 PI, at least 1 IMiD, and 1 anti-CD38 antibody. [d]At least 2 PIs, at least 2 IMiDs, and 1 anti-CD38 antibody.

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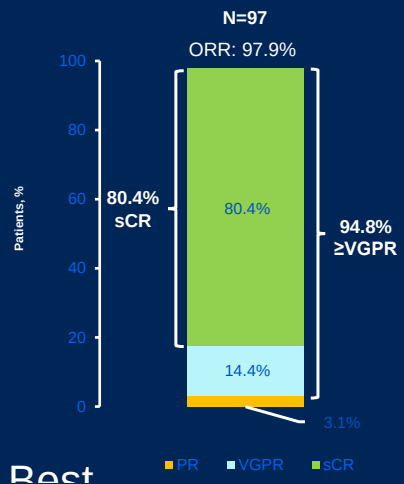
CARTITUDE-1: Overall Response Rate



With longer follow-up, responses deepened with increasing rate of sCR

- Median time to first response: 1 month (range, 0.9–10.7)
- Median time to best response: 2.6 months (range, 0.9–15.2)
- Median time to ≥CR: 2.6 months (range, 0.9–15.2)
- Median duration of response: 21.8 months (95% CI, 21.8–NE)
  - Estimated 73% of responders have not progressed or died at 12 months
  - Median duration of response not reached in patients with sCR
- Response rates were comparable (range, 95–100%) across different subgroups (eg, number of prior lines of therapy, refractoriness, extramedullary plasmacytomas, and cytogenetic risk)[a]

CR, complete response; ORR, overall response rate; sCR, stringent complete response; VGPR, very good partial response. ORR assessed by independent review committee. [a]Subgroups by number of prior lines of therapy (≤4, >4), refractoriness (triple-class, penta-drug), cytogenetic risk (high risk, standard risk), baseline bone marrow plasma cells (≤30%, >30 to <60%, ≥60%), baseline tumor BCMA expression (≥median, <median), and baseline plasmacytomas (including extramedullary and bone-based).

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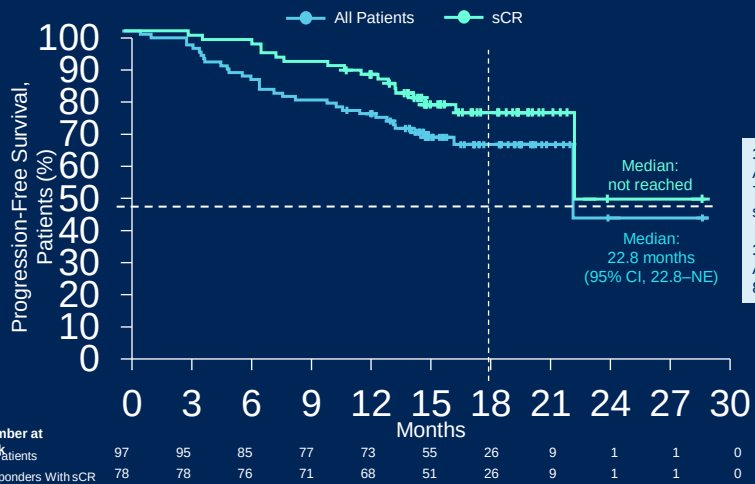
CARTITUDE-1: Progression-Free Survival



18-month PFS
All Patients: 66.0% (95% CI, 54.9–75.0)
sCR: 75.9% (95% CI, 63.6–84.5)

18-month OS
All patients: 80.9% (95% CI, 71.4–87.6)

NE, not estimable; PFS, progression-free survival; OS, overall survival; sCR, stringent complete response.

Median duration of follow-up: 18 months (range, 1.5–30.5)

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CARTITUDE-1: Safety

No new safety signals with longer follow-up

	N=97	
	Any grade	Grade 3/4
Hematologic AEs ≥25%, n (%)		
Neutropenia	93 (95.9)	92 (94.8)
Anemia	79 (81.4)	66 (68.0)
Thrombocytopenia	77 (79.4)	58 (59.8)
Leukopenia	60 (61.9)	59 (60.8)
Lymphopenia	51 (52.6)	48 (49.5)
Nonhematologic AEs ≥25%, n (%)		
Metabolism and nutrition disorders		
Hypocalcemia	31 (32.0)	3 (3.1)
Hypophosphatemia	30 (30.9)	7 (7.2)
Decreased appetite	28 (28.9)	1 (1.0)
Hypoalbuminemia	27 (27.8)	1 (1.0)
Gastrointestinal		
Diarrhea	29 (29.9)	1 (1.0)
Nausea	27 (27.8)	1 (1.0)
Other		
Fatigue	36 (37.1)	5 (5.2)
Cough	34 (35.1)	0
AST increased	28 (28.9)	5 (5.2)
ALT increased	24 (24.7)	3 (3.1)

CRS	N=97
Patients with a CRS event,[a] n (%)	92 (94.8)
Time to onset, median (range) days	7 (1–12)
Duration, median (range) days	4 (1–97)[b]

Of 92 patients with CRS, majority (94.6%) were grades 1/2
CRS resolved in 91 (98.9%) patients within 14 days of onset

	N=97
Total CAR T-cell neurotoxicities, n (%)	
Any Grade	20 (20.6)
Grade ≥3	10 (10.3)
ICANS, n (%)	
Any Grade	16 (16.5)
Grade ≥3	2 (2.1)
Other neurotoxicities,[c] n (%)	
Any Grade	12 (12.4)
Grade ≥3	9 (9.3)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis.
[a]CRS was graded using Lee et al. (*Blood* 2014) in the phase 1b portion of the study and ASTCT in phase 2; in this combined analysis, Lee et al. criteria were mapped to ASTCT criteria for patients in the phase 1b portion.
[b]The patient with 97-day duration died due to CRS/HLH. [c]Events not reported as ICANS (ie, onset after a period of recovery from CRS and/or ICANS).

Presented By: **Saad Z Usmani**

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2021 ASCO ANNUAL MEETING

House of CARs

Trial	Company	CAR T product	Med prior lines	Special Sauce	ORR	CRS %	Neurotox %	Survival data	Notes
Karmma-1 (phase II, n=128)	Celgene/ BMS	Bb2121 (Ide-cel)	6		73% (82% @450 dose)	84%	18%	mPFS 8.8mo, 12.1 mo @450 dose OS 24.8	CAR-T Par-T in 2021!!
CARTITUDE-1 (phase Ib/II, n-97)	Janssen	JNJ-4528 (Ciltacel)	6	Bi-epitope binding to BCMA	97%	92%	20.1% (16.5% ICANS)	@ 18 mo: 66% prog-free; DOR 21.8 m	Google to the yahoo?
LUMMICAR-2 (phase Ib/II, n=18-20)	CARSgen	CT053	5	Fully human	94% (n=18)	77-83%	15-17%	NA	
PRIME (phase I/II, n=55)	Poseida	P-BCMA-101	8	Piggy-bac system, centyrin technology	67% w/ nanoplasmid (n=6); 44-75% w/OG mfg (n=30)	17%	3.8%	NA	
CRB-402 (phase I, n-69)	Bluebird	bb21217	6	PI3Ki culture to increase Tscm cells	68% (73% at 450 dose, 84% w/ new mfg)	70%	16%	mDOR 17 mo (all doses)	Memory cell phenptype in DP may correlate w/ response
UNIVERSAL (phase I, n=26-31)	Allogene	Allo-715	5	Allo CART	60-67% at 320 dose	45%	0	NA	Variability in LD, tx within 5 days of enrollment!! No GVH
FasT CART	Gracell	GCO12F	5	CD19 BCMA dual CAR T, ON manufact	95%	95%	0	NA	

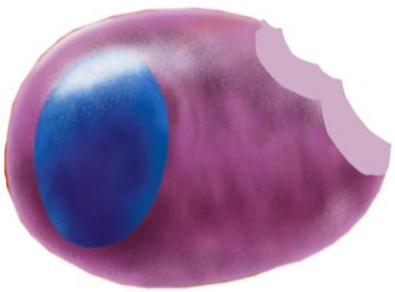
Ide-cel has arrived…now what??

- Label: 4 lines of treatment
- Our patients
  1. VRD→ ASCT→ len maintenance
  2. DPD
  3. KCD
- But what about the #myelennial patients??
- KRD, D-VRD may make this a little more challenging
- → but no one ever said single agent dex couldn't be a line…

UCSF

Myeloma 2021 Homecoming Queen

=



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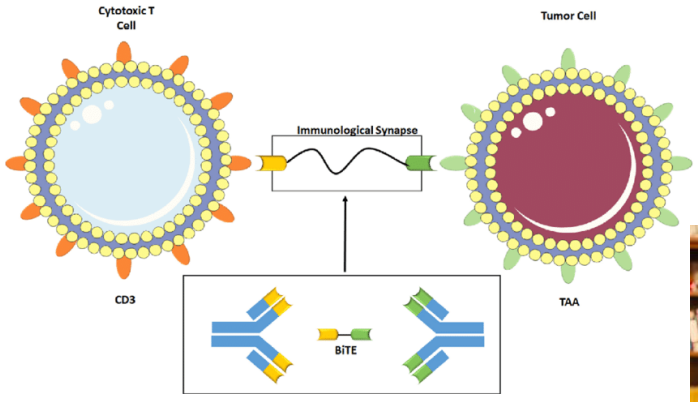
Bispecific T cell engagers



"Hello, I am Sima from Mumbai…"

UCSF

2021 ASCO ANNUAL MEETING

UPDATED PHASE 1 RESULTS OF TECLISTAMAB, A B-CELL MATURATION ANTIGEN × CD3 BISPECIFIC ANTIBODY, IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

Amrita Krishnan[1], Alfred L Garfall[2], María-Victoria Mateos[3], Niels WCJ van de Donk[4], Hareth Nahi[5], Jesús F San-Miguel[6], Albert Oriol[7], Laura Rosinol[8], Ajai Chari[9], Manisha Bhutani[10], Lionel Karlin[11], Lotfi Benboubker[12], Lixia Pei[13], Raluca Verona[13], Suzette Girgis[13], Tara Stephenson[13], Jenna D Goldberg[14], Arnob Banerjee[13], Saad Z Usmani[10]

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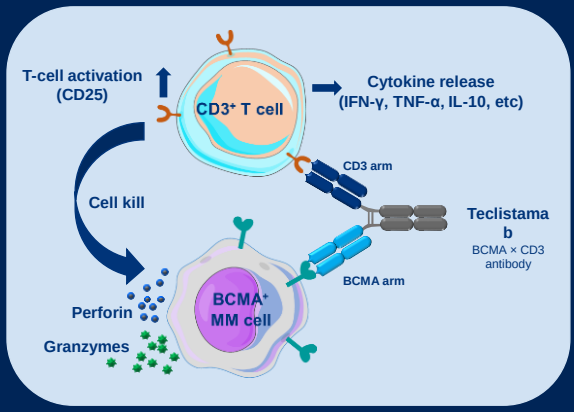
TECLISTAMAB

BCMA × CD3 Bispecific Antibody

- Standard treatments and newly approved therapies for RRMM have limitations[1–3]
- Agents with new MOAs, including BCMA-targeted immunotherapies, offer considerable promise for RRMM
- Teclistamab (JNJ-64007957) is an off-the-shelf, full-size, BCMA × CD3, T-cell redirecting, bispecific antibody
- In the phase 1, first-in-human study in patients with RRMM (MajesTEC-1; NCT03145181), teclistamab was administered IV or SC in different dosing cohorts[4]
  - The RP2D was identified as a QW SC dose of teclistamab 1500 µg/kg with step-up doses of 60 µg/kg and 300 µg/kg
  - We present updated RP2D results with additional patients and longer follow-up



BCMA=B-cell maturation antigen; IFN=interferon; IL=interleukin; MM=multiple myeloma; MOA=mechanism of action; QW=once weekly; RP2D=recommended phase 2 dose; RRMM=relapsed/refractory multiple myeloma; SC=subcutaneous; TNF=tumor necrosis factor.

1. Chari A, et al. *N Engl J Med* 2019;381:727-38. 2. Lonial S, et al. *Lancet Oncol* 2020;21:207-21. 3. Munshi NC, et al. *N Engl J Med* 2021; 384: 705-16. 4. Garfall AL, et al. ASH 2020. Abstract 180.

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TECLISTAMAB

MajesTEC-1 Study Design

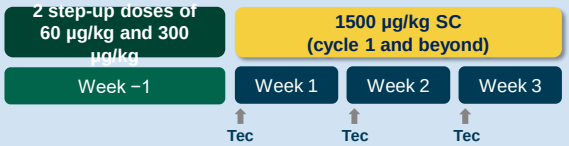
Key Objectives

- Part 1: Identify RP2D
- Part 2: Safety and tolerability at RP2D
- Antitumor activity, pharmacokinetics, pharmacodynamics

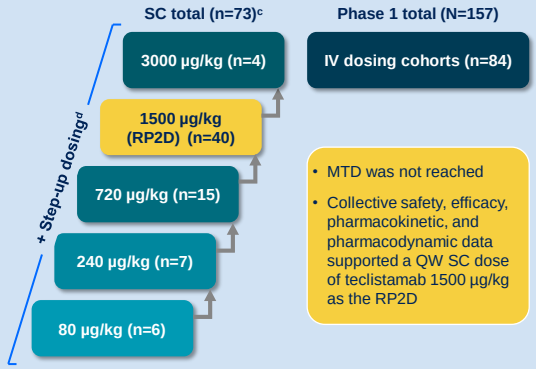
Key Eligibility Criteria

- Adults with measurable MM
- RR or intolerant to established MM therapies
- Hemoglobin ≥8 g/dL, platelets ≥75×10⁹/L,[a] ANC ≥1.0×10⁹/L
- No prior BCMA-targeted therapy

Dosing Schedule at RP2D



- Premedications[b] were limited to step-up doses and first full dose
  - No steroid requirement after first full dose



- MTD was not reached
- Collective safety, efficacy, pharmacokinetic, and pharmacodynamic data supported a QW SC dose of teclistamab 1500 µg/kg as the RP2D

- The data cut-off date for these analyses was March 29, 2021

ANC=absolute neutrophil count; BCMA=B-cell maturation antigen; IV=intravenous; MM=multiple myeloma; MTD=maximum tolerated dose; QW=once weekly; Q2W=every 2 weeks; RP2D=recommended phase 2 dose; RR=relapsed/refractory; SC=subcutaneous; Tec=teclistamab. [a]≥50×109/L for patients with ≥50% bone marrow plasma cells. [b]Glucocorticoid, antihistamine, and antipyretic. [c]1 patient had received step-up doses but not the first full dose as of the data cutoff date. [d]1-3 step-up doses given within 1 week before a full dose.

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TECLISTAMAB

Patient Demographics and Disease Characteristics

Characteristic	SC total n=73	RP2D (1500 µg/kg SC QW)[a] n=40
Age, years, median (range)	64.0 (39–84)	62.5 (39–84)
Aged ≥70 years, n (%)	18 (25)	9 (23)
Sex, n (%)		
Male	43 (59)	26 (65)
Female	30 (41)	14 (35)
Time since diagnosis, years, median (range)	5.9 (0.8–23.5)	5.7 (0.8–17.4)
Extramedullary soft tissue plasmacytomas ≥1, n (%)[b]	11 (15)	8 (20)
Bone marrow plasma cells ≥60%, n (%)[c]	12 (18)	3 (8)
High-risk cytogenetics, n (%)[d]	16 (30)	10 (37)
ISS stage, n (%)[e]		
I	36 (50)	24 (62)
II	25 (35)	11 (28)
III	11 (15)	4 (10)

Characteristic	SC total n=73	RP2D (1500 µg/kg SC QW)[a] n=40
Prior number of lines of therapy, median (range)	5.0 (2–14)	5.0 (2–11)
Prior transplantation, n (%)	63 (86)	34 (85)
Exposure status, n (%)		
Triple-class[f]	71 (97)	40 (100)
Penta-drug[g]	50 (68)	26 (65)
Refractory status, n (%)		
PI[h]	65 (89)	35 (88)
Carfilzomib	49 (67)	27 (68)
IMiD[i]	70 (96)	38 (95)
Pomalidomide	55 (75)	28 (70)
Anti-CD38 mAb[j]	68 (93)	39 (98)
Triple-class[f]	58 (79)	33 (83)
Penta-drug[g]	28 (38)	15 (38)
Refractory to last line of therapy	64 (88)	33 (83)

IMiD=immunomodulatory drug; ISS=International Staging System; mAb=monoclonal antibody; PI=proteasome inhibitor; QW=once weekly; RP2D=recommended phase 2 dose; SC=subcutaneous
[a]Step-up doses of 60 µg/kg and 300 µg/kg. [b]Soft-tissue component of a bone-based plasmacytoma not included. [c]Percentages calculated from n=66 for SC total and n=36 at RP2D. [d]del(17p), t(4;14), and/or t(14;16); percentages calculated from n=53 for SC total and n=27 at RP2D.
[e]At baseline; percentages calculated from n=72 for SC total and n=39 at RP2D. [f]≥1 PI, ≥1 IMiD, and 1 anti-CD38 mAb. [g]≥2 PI, ≥2 IMiD, and 1 anti-CD38 mAb. [h]Bortezomib, carfilzomib, and/or ixazomib. [i]Thalidomide, lenalidomide, and/or pomalidomide. [j]Daratumumab and/or isatuximab.

TECLISTAMAB

Safety Profile

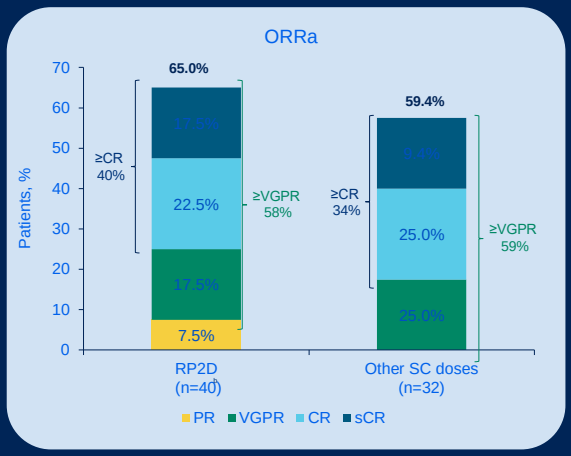
AE (≥20% of total SC), n (%)	SC total n=73		RP2D (1500 µg/kg SC QW)[a] n=40	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic				
Neutropenia	46 (63)	32 (44)	26 (65)	16 (40)
Anemia	37 (51)	19 (26)	20 (50)	11 (28)
Thrombocytopenia	30 (41)	15 (21)	18 (45)	8 (20)
Leukopenia	19 (26)	9 (12)	13 (33)	7 (18)
Nonhematologic				
CRS	44 (60)	0	28 (70)	0
Pyrexia	15 (21)	0	5 (13)	0
Diarrhea	17 (23)	2 (3)	9 (23)	2 (5)
Fatigue	21 (29)	1 (1)	15 (38)	1 (3)
Injection site erythema	20 (27)	0	13 (33)	0
Nausea	23 (32)	0	13 (33)	0
Headache	18 (25)	0	8 (20)	0
Cough	15 (21)	1 (1)	4 (10)	0

AE=adverse event; CRS=cytokine release syndrome; QW=once weekly; RP2D=recommended phase 2 dose; SC=subcutaneous.
[a]Step-up doses of 60 µg/kg and 300 µg/kg.

- First onset of grade 3/4 cytopenias generally confined to step-up dosing and cycles 1 and 2
- Infections reported in 51% of SC-treated patients (grade 3/4: 21%); 45% at RP2D (grade 3/4: 23%)
- Neurotoxicity occurred in 1 (1%) SC-treated patient
  - Patient treated at RP2D and remains on therapy
  - Event was grade 1 and resolved without intervention
- Injection-site reactions reported in 42% of SC-treated patients (50% at RP2D)
  - Events were mild (all grade 1/2) and manageable
- 2 deaths due to AEs across SC cohorts (none at RP2D) were unrelated to teclistamab
  - General health deterioration (n=1)
  - Sepsis (n=1)

TECLISTAMAB

Overall Response Rate



- The RP2D of 1500 µg/kg SC QW has been administered to 40 patients with a median duration of follow-up of 6.1 months (range: 1.2–12.2)
  - ORR was 65%, with 58% of patients achieving ≥VGPR and 40% achieving ≥CR
  - Median time to first confirmed response was 1.0 month (range: 0.2–3.1)
  - ORR in 33 triple-class refractory patients was 61%
- 6/6 evaluable patients in RP2D cohorts achieved MRD-negative CR/sCR at 10^{-6} (n=5) or 10^{-5} (n=1)
  - Across IV and SC cohorts, 18/26 evaluable patients (69%) had MRD-negative CR/sCR at 10^{-6} (n=16) or 10^{-5} (n=2)
  - MRD negativity was sustained >12 months after CR in 2 evaluable patients

CR=complete response; MRD=minimal residual disease; ORR=overall response rate; PR=partial response; QW=once weekly; RP2D=recommended phase 2 dose; SC=subcutaneous; sCR=stringent complete response; VGPR=very good partial response.
[a]Investigator assessment of evaluable patients who had ≥1 dose of teclistamab and ≥1 postbaseline disease evaluation per 2011 International Myeloma Working Group response criteria; includes unconfirmed response. [b]1500 µg/kg SC QW, with step-up doses of 60 and 300 µg/kg.

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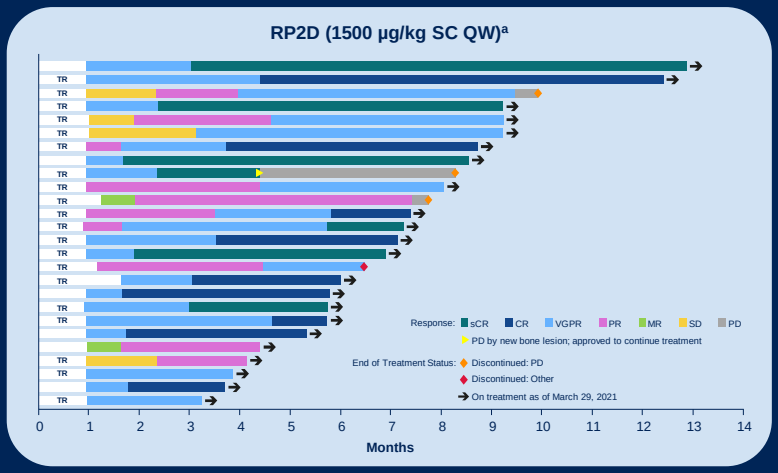
TECLISTAMAB

Duration of Response at RP2D



- At the RP2D of 1500 µg/kg SC QW:
  - Responses were durable and deepened over time
  - Median duration of response was not reached
  - 22/26 responders (85%), after median follow-up of 7.1 months (range: 3.0–12.2), were alive and continuing on treatment
- Across SC cohorts 36/45 responders (80%), after median follow-up of 9.3 months (range: 3.0–19.4), were alive and continuing on treatment
- Across IV cohorts 19/32 responders (59%), after median follow-up of 15.6 months (range: 5.4–29.6), were alive and continuing on treatment
  - 6 (19%) had ≥18 months of follow-up

CR=complete response; MR=minimal response; PD=progressive disease; PR=partial response; QW=once weekly; RP2D=recommended phase 2 dose; SC=subcutaneous; sCR=stringent complete response; SD=stable disease; TR=triple-class refractory; VGPR=very good partial response. [a]Step-up doses of 60 µg/kg and 300 µg/kg.

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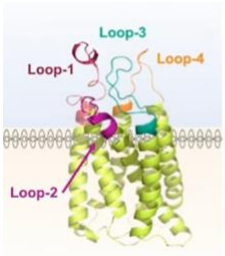
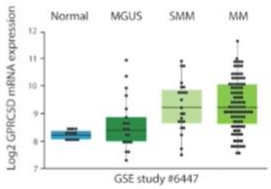
Bispecifics

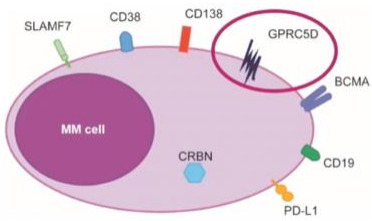
Drug	Target	Med prior lines	Dosing	ORR	CRS %	Neurotox %	Notes
Teclistamab (n=68)	**BCMA**	**6 (5@RP2D)**	**SC weekly for RP2D**	**65% @RP2D)**	**60 (70%)**	**5% (1%)**	**SC dosing!**
Teneobio TNB-383B (n=58, 15)	**BCMA**	**6**	**Q3 weeks**	**80% @higher doses, n=15**	**45%**	**0**	**Q 3 week, allowed for CrCl 30**
REGN-5458 (n=49, 8)	**BCMA**	**5**	**Q2 week**	**63% @highest does, n=8**	**39%**	**12%**	
AMG-701 (n=85, 6)	**BCMA**	**6**	**weekly**	**83% @highest does, n=6**	**64% (9% G3)**	**3.8%**	
Ernlantamab (n=30)	**BCMA**	**8**	**SC weeekly**	**70 @≥215 ug/kg dose**	**73%**	**20%**	**23% with prior BMCA tx! Some PN in phase 2 (back up running)**
Talquetamab (SC cohort n=82, 30 in RP2D	GPRC5D	6	SC weekly; 405 ug/kg = RP2D	66% @ higher doses (n=50), 69% @ RP2D (n=13)	67% (73% @RP2D)	5%, (7% @RP2D)	16% in RP2D with prior BCMA tx SC dosing! some G3 skin rash, oral toxicity, back pain
Cevostamab (n=53, 34)	FcRH5	6	Q3 weeks	53% in higher doses, 61% @ top dose (n=18); 63% in prior BCMA (n=8)	76% (2% G3	28%	21% with prior BCMA tx

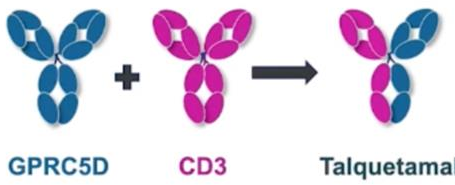
Talquetamab: GPRC5D x CD3 Bispecific

- GPRC5D x CD3 Bispecific Antibody
  - Orphan GPCR of unknown function with limited expression in healthy human tissue; primarily plasma cells and hair follicles
  - Highly expressed in myeloma cells and associated with poor prognostic features in myeloma
  - No known extracellular shedding









Chari A et al. ASH 2020: Abstract 290.

UCSF

TALQUETAMAB

Safety Profile

AE (≥20% of total SC), n (%)	SC Total n=82		RP2D (405 µg/kg SC QW)[a] n=30	
	Any grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic				
Neutropenia	47 (57)	40 (49)	20 (67)	18 (60)
Anemia	37 (45)	23 (28)	17 (57)	8 (27)
Thrombocytopenia	23 (28)	15 (18)	10 (33)	6 (20)
Leukopenia	21 (26)	16 (20)	11 (37)	8 (27)
Lymphopenia	19 (23)	19 (23)	9 (30)	9 (30)
Nonhematologic				
CRS	55 (67)	1 (1)	22 (73)	1 (2)
Dysgeusia	38 (46)	NA	18 (60)	NA
Fatigue	26 (32)	0	9 (30)	0
Pyrexia	23 (28)	1 (1)	7 (23)	1 (2)
Dry mouth	22 (27)	0	8 (27)	0
Dysphagia	21 (26)	0	11 (37)	0
Headache	19 (23)	1 (1)	7 (23)	0
Diarrhea	18 (22)	0	7 (23)	0
Nausea	18 (22)	0	7 (23)	0

AE, adverse event, CRS, cytokine release syndrome; DLT, dose-limiting toxicity; NA, not applicable; RP2D, recommended phase 2 dose; SC, subcutaneous.

- Talquetamab has a tolerable safety profile at the RP2D of 405 µg/kg SC
  - No DLTs at the RP2D
  - Cytopenias mostly confined to step-up doses and cycles 1/2
  - Neutropenias generally resolved within a week and were limited to cycles 1/2
- Infections in 37% of SC and RP2D patients (grade 3/4: 9% for SC total, 3% for RP2D)
- Neurotoxicities (all grade 1/2) in 4 patients with SC dosing; 2 patients (7%) at RP2D
- Injection-site reactions in 17% of SC patients (including RP2D) were mild and manageable (all grade 1/2)
- Skin-related AEs[b] in 67% of SC patients; 77% at RP2D (majority grade 1/2)
  - Nail disorders[c] in 21% of patients; 27% at RP2D
- No deaths due to AEs at the RP2D

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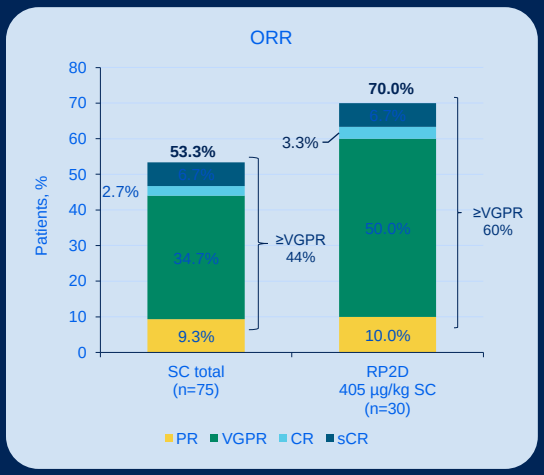
TALQUETAMAB

Overall Response Rate



- The RP2D of 405 µg/kg SC QW has been administered to 30 patients with a median follow-up of 6.3 months (range: 1.4–12.0) for responders
- At the RP2D:
  - 70.0% ORR (21/30)
  - Median time to first confirmed response was 1 month (range: 0.2–3.8)
  - 65.2% (15/23) of triple-refractory patients responded
  - 83.3% (5/6) of penta-refractory patients responded
- Of 6 evaluable patients across IV and SC cohorts, 4 had MRD-negative CR/sCR at 10^{-6}, including 1 patient in RP2D cohort
  - MRD negativity was sustained 7 months post CR in 1 evaluable patient

[a]Investigator assessment of evaluable patients who had ≥1 dose of talquetamab and ≥1 postbaseline disease evaluation per 2011 International Myeloma Working Group response criteria; includes unconfirmed response.
CR, complete response; IV, intravenous; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

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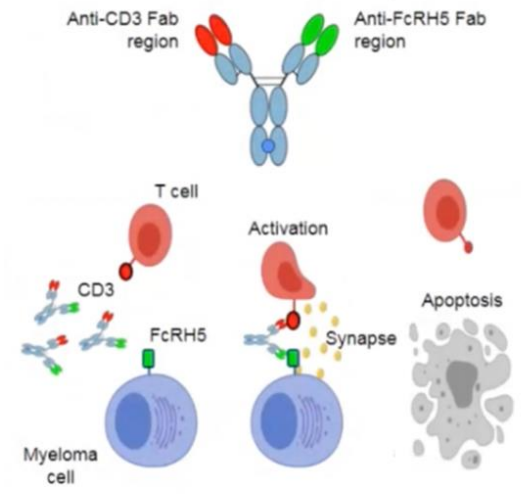
Cevostamab: FcRH5 x CD3 Bispecific

- Fc receptor-homolog 5 (FcRH5)
  - Expressed on myeloma cells with near 100% prevalence
  - Also expressed on normal B-cells, but higher in myeloma and plasma cells
  - Gene located on chromosome 1
- Cevostamab BFCR4350A:
  - Humanized IgG based FcRH5 x CD3 Bispecific Antibody



Cohen A et al. ASH 2020: Abstract 291.

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Drug	Target	Med prior lines	Dosing	ORR	CRS %	Neurotox %	Notes
Teclistamab (n=68)	BCMA	6 (5@RP2D)	SC weekly for RP2D	65% @RP2D)	60 (70%)	5% (1%)	SC dosing!
Teneobio TNB-383B (n=58, 15)	BCMA	6	Q3 weeks	80% @higher doses, n=15	45%	0	Q 3 week, allowed for CrCl 30
REGN-5458 (n=49, 8)	BCMA	5	Q2 week	63% @highest does, n=8	39%	12%	
AMG-701 (n=85, 6)	BCMA	6	weekly	83% @highest does, n=6	64% (9% G3)	3.8%	
Ernlantamab (n=30)	BCMA	8	SC weeekly	70 @≥215 ug/kg dose	73%	20%	23% with prior BMCA tx! Some PN in phase 2 (back up running)
Talquetamab (SC cohort n=82, 30 in RP2D	**GPRC5D**	**6**	**SC weekly; 405 ug/kg = RP2D**	**66% @ higher doses (n=50), 70% @ RP2D (n=13)**	**67% (73% @RP2D)**	**5%, (7% @RP2D)**	**16% in RP2D with prior BCMA tx SC dosing! some G3 skin rash, oral toxicity, back pain**
Cevostamab (n=53, 34)	**FcRH5**	**6**	**Q3 weeks**	**53% in higher doses, 61% @ top dose (n=18); 63% in prior BCMA (n=8)**	**76% (2% G3**	**28%**	**21% with prior BCMA tx**

Comparing options

	CAR T	Bispecifics	ADCs
Treatment logistics	Specialized center, need to wait for production	TBA, likely community-friendly, off-the shelf Need for long-acting	community-friendly, off-the shelf
Length of treatment	~2 months	??	Possibly limited cycles
Toxicities	CRS, neurotoxicity, cytopenias	CRS, pneumonia	Corneal, thrombocytopenia
Cost	? $400K	? But have to consider length of treatment	$24K/month

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Conclusions

- It's your patient – do what you want: VRD, KRD, D-VRD
- Don't delete your favorite transplanter's contact info just yet…
  - I'm still a transplant #fangirl
- If you didn't use daratumumab 1st line, you have to do it in 2nd line
  - Or you will be uncool
- CAR-T coming to a peer-to-peer near you
- The future is BCMA bright
  - I suspect 2nd line by 2023
  - No worries – always room for new CELMoDs, alkylating agents and Selinexor, new immunotherapy targets
- 60 is the new 30!!

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THANK YOU!

@ninashah33

#myelennial

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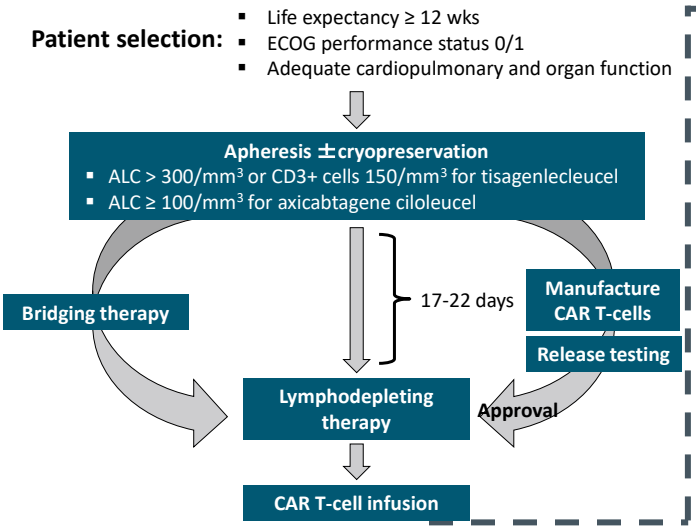
Overview

- Seven new agents FDA approved for R/R DLBCL within the last few years
- 3 different CAR T cell therapeutics and 4 new targeted agents
- How can these be integrated into the treatment of R/R DLBCL
- Is there a role allogeneic transplantation ?
- Bispecific antibodies for the treatment of R/R DLBCL

The CAR T-Cell Therapy Process



Potential Unique Adverse Events

- Class effects

1. **Cytokine Release Syndrome (CRS)**
2. **Neurotoxicity**
   aka, immune effector cell–associated neurotoxicity syndrome (ICANS)
3. **Prolonged Cytopenias**
4. **"B-Cell Aplasia"/ Hypogammaglobulinemia**

FDA-Approved CD19-Targeted CAR T-Cell Therapies

Therapy	Indications
Axicabtagene ciloleucel	▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy,** including DLBCL NOS, DLBCL arising from follicular lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma
Brexucabtagene autoleucel	▪ **Adults with R/R MCL**
Lisocabtagene maraleucel	▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy**, including DLBCL NOS (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B
Tisagenlecleucel	▪ **Patients aged up to 25 yrs with B-cell precursor ALL that is refractory or in second or later relapse** ▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy**, including DLBCL NOS, DLBCL arising from follicular lymphoma, high-grade B-cell lymphoma

1. Axicabtagene ciloleucel PI. 2. Tisagenlecleucel PI. 3. Brexucabtagene autoleucel PI.

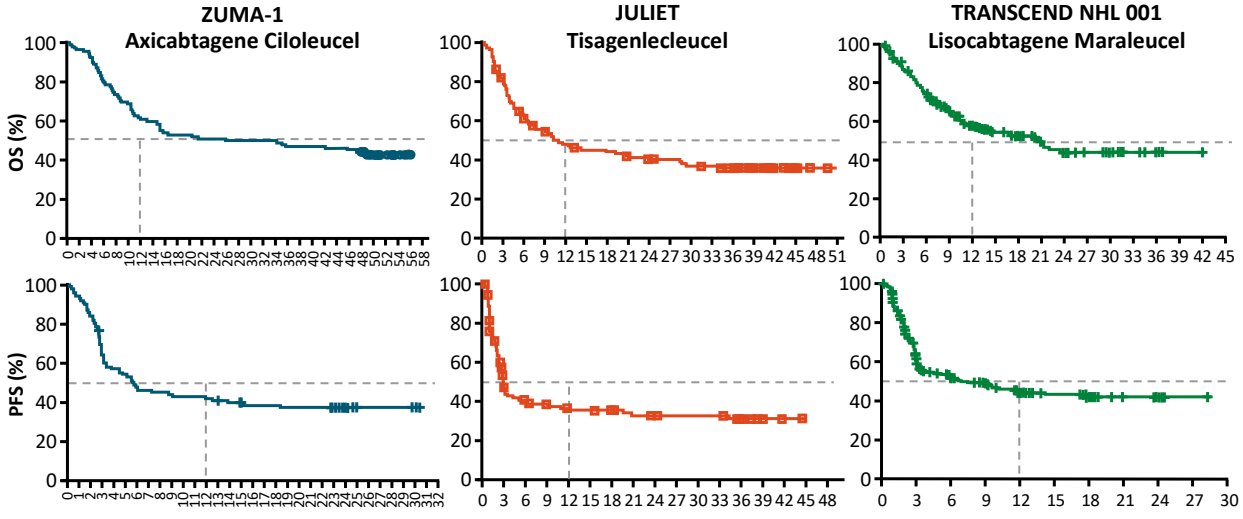
Pivotal Anti-CD19 CAR T-Cell Therapy Trials: DLBCL

	ZUMA-1[1,2]	JULIET[3]	TRANSCEND NHL 001[4]
CAR T-cell agent	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Study phase	II	II	I
Patient population	Adults with refractory DLBCL	Adults with R/R DLBCL	Adults with R/R DLBCL
Patients pheresed/ treated, n	111/101	165/111	344/269*
Bridging therapy	None allowed in pivotal trial, often used in standard practice	92%	59%
ORR, %	82%	52%	73%
CR, %	54%	40%	53%
	FDA approved	**FDA approved**	**FDA approved**

*256 included in the efficacy-evaluable set.

1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31. 3. Schuster. NEJM. 2019;380:45. 4. Abramson. Lancet. 2020;396:839.

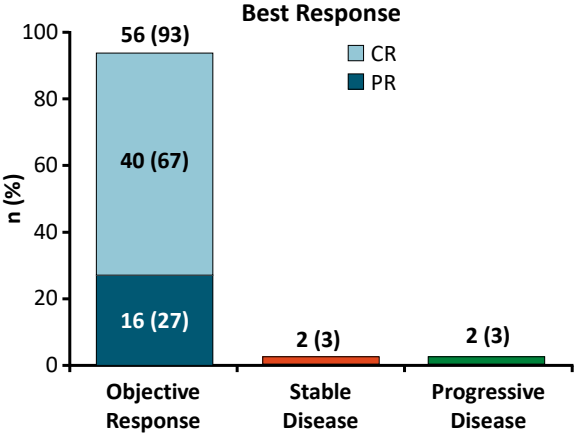
Pivotal Anti-CD19 CAR T-Cell Therapy Trials: DLBCL

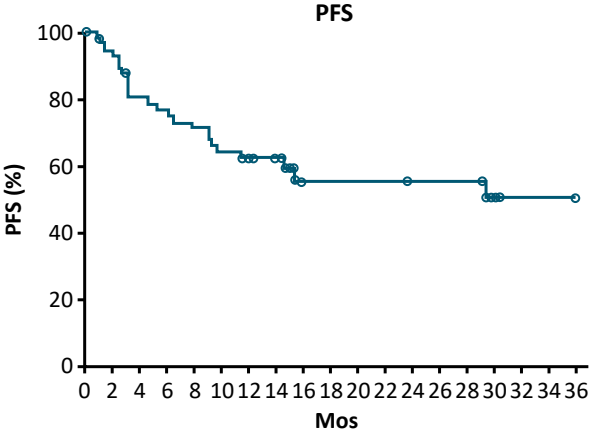


Locke. Lancet Oncol. 2019;20:31. Jacobson. ASH 2020. Abstr 1187. Jaeger. ASH 2020. Abstr 1194. Abramson. Lancet. 2020;396:839.

ZUMA-2: Brexucabtagene Autoleucel (KTE-X19) for Patients With R/R MCL

- Multicenter, single-arm, open-label phase II trial of brexucabtagene autoleucel for adults with relapsed/refractory mantle cell lymphoma (N = 68 received agent)





Wang. NEJM. 2020;382:1331. Wang. ASH 2020. Abstr 1120.

Recent Key Findings With CAR T-Cell Therapy for Lymphomas and ALL

Trial	Description	Response
NHL		
ELARA[1]	Phase II study of tisagenlecleucel for pts with R/R FL (N = 52)	▪ ORR 83%; CR 65%
ZUMA-5[2]	Phase II study of axicabtagene ciloleucel for pts with R/R indolent B-cell NHL (FL or MZL) with ≥ 2 prior therapies (N = 104)	▪ ORR 92%; CR 76%
ZUMA-12[3]	Phase II study of axicabtagene ciloleucel for pts with high-grade LBCL with positive PET after 2 cycles of anti-CD20 Ab + anthracycline (N = 32)	▪ ORR 85%; CR 74%
CLL		
TRANSCEND CLL 004[4]	Phase I/II study of lisocabtagene maraleucel for pts with R/R CLL/SLL who failed/were ineligible for BTK inhibitors (N = 23)	▪ ORR 82%; CR 46%
ALL		
ZUMA-3[5]	Phase I/II trial of brexucabtagene autoleucel for adult pts with R/R B- ALL (N = 45)	▪ ORR 70%, CR 68%

1. Fowler. ASH 2020. Abstr 1149. 2. Jacobson. ASH 2020. Abstr 700. 3. Neelapu. ASH 2020. Abstr 405.
4. Siddiqi. ASH 2019. Abstr 503. 5. Shah. ASCO 2019. Abstr 7006.

Select Ongoing Trials With Autologous CAR T-Cell Therapy for Lymphomas, CLL, and ALL

Trial	Phase	Treatment	Population
Lymphomas/CLL			
ZUMA-7 (NCT03391466)	III	Axicabtagene ciloleucel vs SoC	2nd line for transplant-eligible R/R large B-cell NHL
TRANSFORM (NCT03575351)	III	Lisocabtagene maraleucel vs SoC	2nd line for transplant-eligible R/R large B-cell NHL
BELINDA (NCT03570892)	III	Tisagenlecleucel vs SoC	2nd line for transplant-eligible R/R large B-cell NHL
ZUMA-8 (NCT03624036)	I/II	Brexucabtagene autoleucel	Relapsed/refractory CLL
ALL			
OBERON (NCT03628053)	III	Tisagenlecleucel vs blinatumomab or inotuzumab ozogamicin	Adults with B-ALL; R/R after 1-2 lines of therapy or ASCT
CASSIOPEIA (NCT03876769)	II	Tisagenlecleucel	Pediatric/young adult high-risk B-cell ALL; MRD+ after 1L
ZUMA-4 (NCT02625480)	I/II	Axicabtagene ciloleucel	Pediatric/adolescent pts with R/R B-ALL or B-NHL

Class Effects of the Cell-Mediated Immune Response: CRS and Neurotoxicity

	B-ALL		DLBCL			MCL	MM
	ELIANA[1]	ZUMA-3[2]	JULIET[3]	ZUMA-1[4]	TRANSCEND[5]	ZUMA-2[6]	CRB-401[7]
CAR T-cell agent	Tisagenlecleucel	Brex. autoleucel	Tisagenlecleucel	Axicabtagene ciloleucel	Lisocabtagene maraleucel	Brex. autoleucel	Idecabtagene Vicleucel
N treated	75	45	111	101	269	68	33
CRS, %	77*	93†	58*	93†	42†	91†	76
Grade ≥ 3 CRS, %	46*	29†	22*	13†	2†	15†	6
NT, %	40	78	21	64	30	63	42
Grade ≥ 3 NT, %	13	38	12	28	10	31	3

*Per Penn scale. †Per Lee Scale.

1. Maude. NEJM. 2018;378:439. 2. Shah. ASCO 2019. Abstr 7006. 3. Schuster. NEJM. 2019;380:45.
4. Neelapu. NEJM. 2017;377:2531. 5. Abramson. ASH 2019. Abstr 241. 6. Wang. NEJM. 2020;382:1331. 7. Raje. NEJM. 2019;380:1726.

Principles of Toxicity Management by Grade

Grade	CRS	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care	Supportive care	Supportive care
2	Tocilizumab	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Tocilizumab	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	Tocilizumab + high-dose steroids ICU/critical care	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care

- Always rule out/treat alternative causes
- If tocilizumab refractory, consider corticosteroids
- Patients with neurotoxicity should receive AEDs and appropriate CNS imaging, EEG monitoring
- Steroid dosing for neurotoxicity may vary between products
- Patients on steroids should receive appropriate fungal prophylaxis

MD Anderson. CAR cell therapy toxicity assessment and management. 2017. Neelapu. Nat Rev Clin Oncol. 2018;15:47.

Additional CAR T-Cell Toxicities

Toxicity	Management Strategies
Cytopenias	▪ Supportive care
Macrophage activation-like syndrome	▪ Measure ferritin, IL-2R, NK cell activation, coags ▪ Anakinra
Immunosuppression	▪ IVIg ▪ Antimicrobial prophylaxis

Axicabtagene ciloleucel PI. Tisagenlecleucel PI. Neelapu. Hematol Oncol. 2019;37(suppl 1):48. Mehta. Lancet Rheumatol. 2020;2:358.

Impact and safety of chimeric antigen receptor T-cell therapy in older, vulnerable patients with relapsed/refractory large B-cell lymphoma

Lin et al, Haematologica. 2021 Jan 1; 106(1): 255–258.

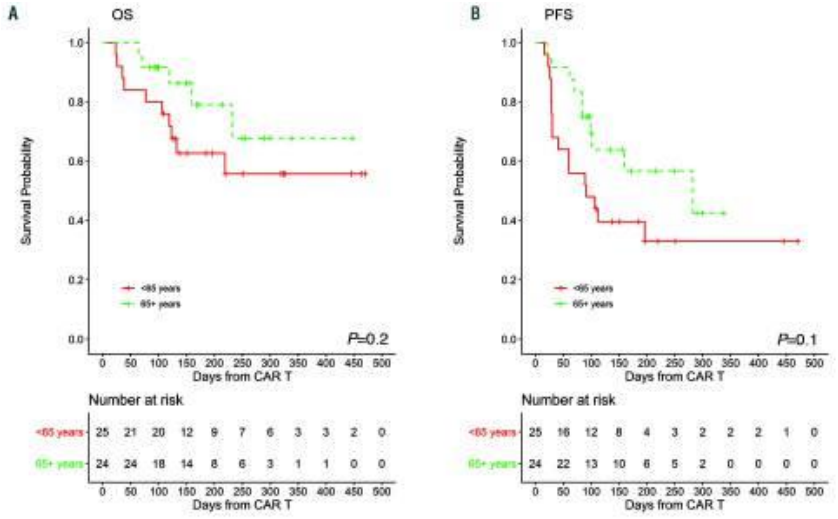
Patient Demographics

	Younger patients (<65 years, n=25)	Older patients (≥65 years, n=24)	P
Age in years, median (range)	56 (20 – 64)	72 (67 – 86)	
Female gender, n (%)	2 (8)	13 (54)	<0.001
CAR T, n (%)			0.11
Axicabtagene ciloleucel	21 (84)	15 (63)	
Tisagenlecleucel	4 (16)	9 (37)	
Advanced stage at CAR T, n (%)	14 (56)	14 (58)	0.78
Prior lines, median (range)	3 (2 – 9)	3 (2 – 9)	0.81
Baseline LDH, median (range)	298 (128 – 3722)	240 (146 – 1409)	0.12
Time to CAR T, median (range)	75 days (43 – 175)	92 days (33 – 272)	0.54
DCI/CCI, median, (range)	2 (2 – 4)	3 (2 – 7)	0.04
KPS <80, n (%)	7 (28)	9 (38)	0.55
Functional limitation, n (%)	5 (20)	8 (33)	0.35
Cognitive impairment, n (%)	8 (32)	11 (46)	0.76
Prior fall, n (%)	7 (28)	7 (29)	>0.99
Weight loss, n (%)	8 (32)	5 (21)	0.52
ICU admission, n (%)	9 (36)	6 (25)	0.54
CRS, n (%)			0.61
No CRS	7 (28)	4 (17)	
Grade 1-2 CRS	15 (60)	18 (75)	
Grade >2 CRS	3 (12)	2 (8)	
ICANS, n (%)			0.60
No ICANS	16 (60)	11 (46)	
Grade 1-2 ICANS	6 (24)	7 (29)	
Grade >2 ICANS	4 (16)	6 (25)	
Infections, ≥G3, n (%)	15 (60)	10 (42)	0.26
Prolonged cytopenia, n (%)	16 (64)	10 (42)	0.16
Metabolic toxicities, ≥ grade 3, n (%)	3 (12)	8 (33)	0.10
Other toxicities, ≥ grade 3, n (%)	9 (36)	12 (50)	0.39

CAR T: chimeric antigen receptor T-cell therapy; Time/CAR T: time (in days) from last relapse/disease progression to start of CAR T; LDH: lactate dehydrogenase; DCI/CCI: Deyo/Charlson Comorbidity Index; KPS: Karnofsky Performance Status; ICU: intensive care unit; CRS: cytokine release syndrome; ICANS, immune effector cell associated neurotoxicity syndrome.

Lin et al, Haematologica. 2021 Jan 1; 106(1): 255–258.

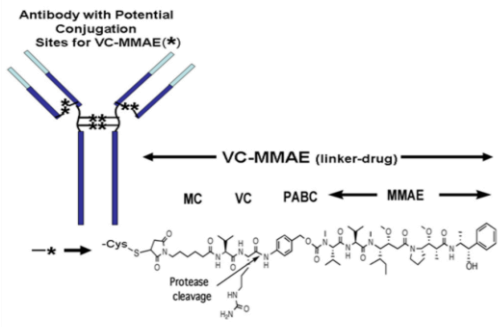
Survival Analysis

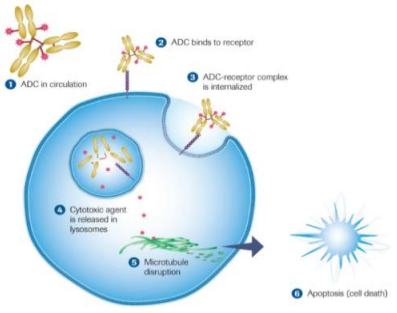


Lin et al, Haematologica. 2021 Jan 1; 106(1): 255–258.

Polatuzumab vedotin

- Polatuzumab vedotin (pola) is an antibody drug conjugate (ADC) consisting of a potent microtubule inhibitor monomethyl auristatin E (MMAE) conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker



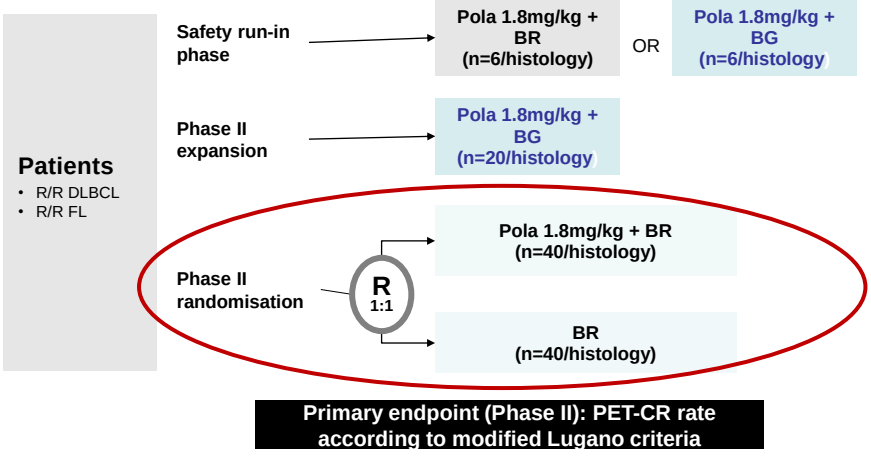


- Pola has demonstrated efficacy in R/R DLBCL in combination with rituximab[1,2]

Treatment	Best overall response
Pola +/- rituximab	51–56%[1,2]

1. Palanca-Wessels A, et al. Lancet Oncol, 2015;16:704–15
2. Morschhauser F, et al. Lancet Hematology, 2019;6:e254 –65

Randomised Phase II study of pola-BR versus BR (GO29365): study design

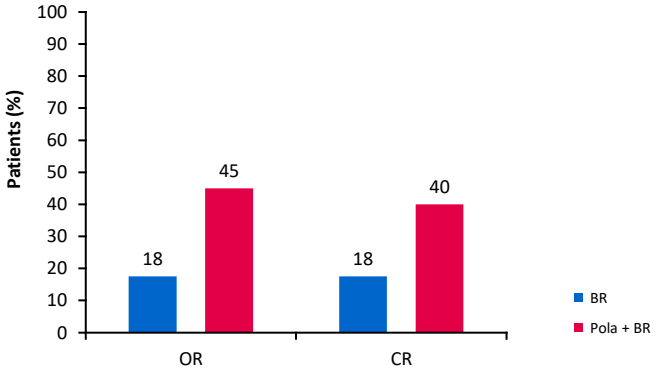


Sehn L, et al. Abstract #1683, ASH 2018

BG, bendamustine and obinutuzumab; BR, bendamustine and rituximab; FL, follicular lymphoma; PET-CR, positron electron tomography–complete response; pola, polatuzumab vedotin; R, randomisation; R/R, relapsed/refractory

Polatuzumab vedotin added to bendamustine/ rituximab

Response at EOT (IRC)[1*]



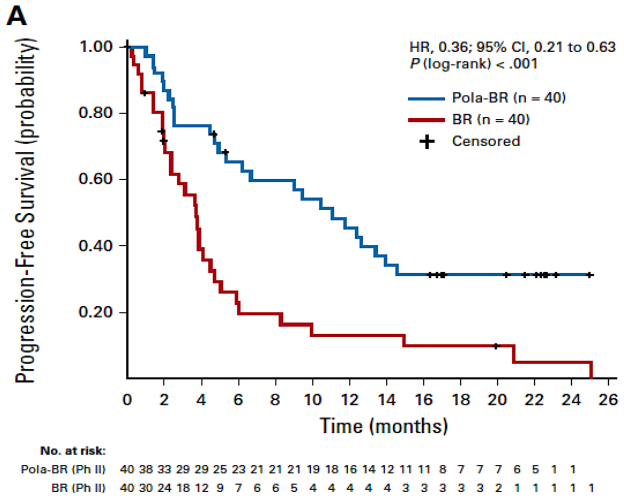
Seven patients have ongoing response durations of ≥20 months at data cut-off

1. Sehn L, et al. Abstract #1683, ASH 2018 | 2. Sehn L, et al. Abstract #7507. ASCO 2018

Data cut-off: 1. 30 April 2018, 2. May 2017
*Primary endpoint; PET-CR is assessed by modified Lugano criteria
BOR, best overall response; BR, bendamustine and rituximab; CR, complete response; EOT, end of treatment; INV, investigator; IRC, independent review committee; OR, objective response; pola, polatuzumab vedotin

Polatuzumab vedotin added to bendamustine/rituximab

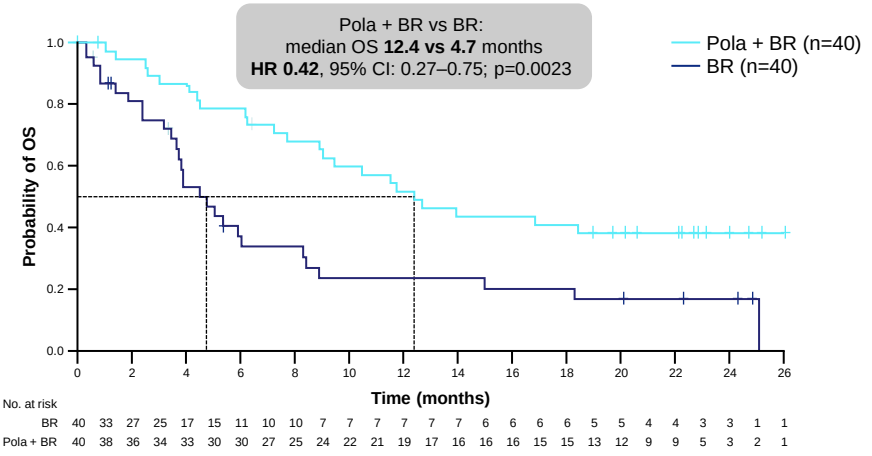
Progression Free Survival (IRC)



- Few patients with durable responses
- Toxicity: hematological, infectious, neurological

Sehn, JCO 2019

OS was significantly longer with pola + BR versus BR



Median follow-up: 22.3 months

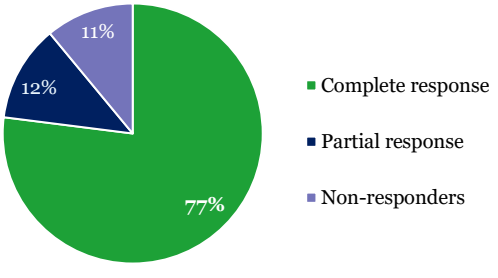
Sehn L, et al. Abstract #1683, ASH 2018

Data cut-off: 30 April 2018
BR, bendamustine and rituximab; pola, polatuzumab vedotin

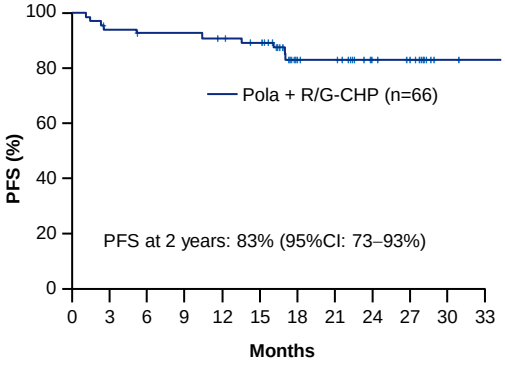
In frontline: Pola-R-CHP in a phase 1b/2 trial

1. The safety and tolerability of pola-R-CHP is similar to that of R-CHOP

2. Tumour responses to pola-R-CHP assessed by PET



3. PFS in patients with 1L DLBCL receiving pola + R/G-CHP

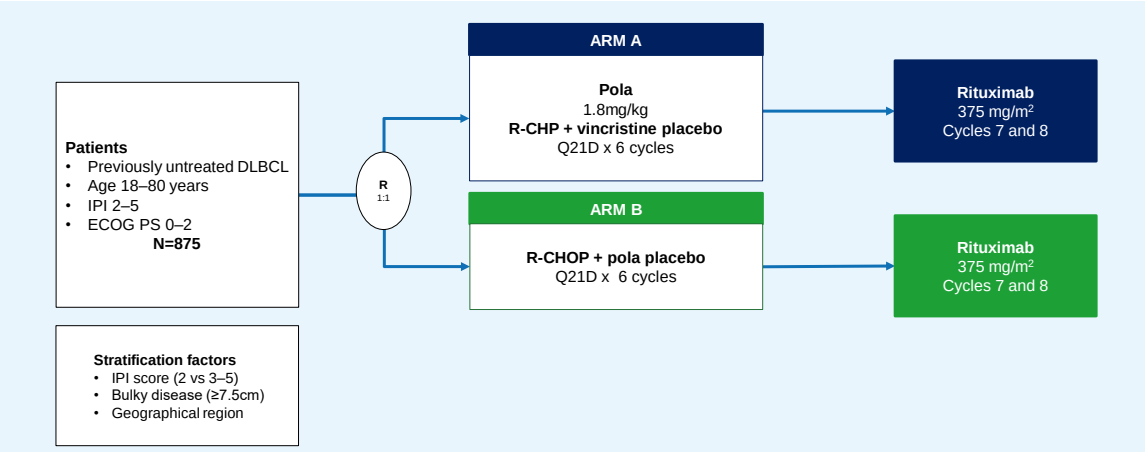


G, obinutuzumab; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Tilly H, et al. Lancet Oncol 2019; [Epub ahead of print]

POLARIX: Study design

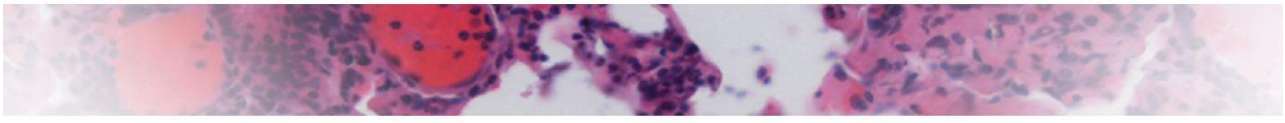
A double-blinded, phase 3, placebo-controlled trial



LYSA, the lymphoma study association; IPI, international prognostic index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; Q21D, every 21 days; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Collaboration with LYSA and LYSARC

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide



Efficacy and Safety of Loncastuximab Tesirine (ADCT-402) in Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Paolo F. Caimi[1], Weiyun Ai[2], Juan Pablo Alderuccio[3], Kirit M. Ardeshna[4], Mehdi Hamadani[5], Brian Hess[6], Brad S. Kahl[7], John Radford[8], Melhem Solh[9], Anastasios Stathis[10], Pier Luigi Zinzani[11], Jay Feingold[12], David Ungar[12], Yajuan Qin[12], Shui He[12], Carmelo Carlo-Stella[13]

[1]University Hospitals Cleveland Medical Center/Case Western Reserve University, Cleveland, OH, USA, [2]Division of Hematology and Oncology, Department of Medicine, University of California, San Francisco, CA, USA, [3]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA, [4]Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK, [5]Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, USA, [6]Division of Hematology and Medical Oncology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA, [7]Department of Medicine, Oncology Division, Washington University, St. Louis, MO, USA, [8]NIHR Clinical Research Facility, Christie NHS Foundation Trust and the University of Manchester, Manchester, UK, [9]Blood and Marrow Transplant Program at Northside Hospital, Atlanta, GA, USA, [10]Oncology Institute of Southern Switzerland, Bellinzona, Switzerland, [11]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy, [12]Clinical Development, ADC Therapeutics America, Inc., Murray Hill, NJ, USA, [13]Department of Oncology and Hematology, Humanitas Clinical and Research Center, Humanitas University, Milan, Italy

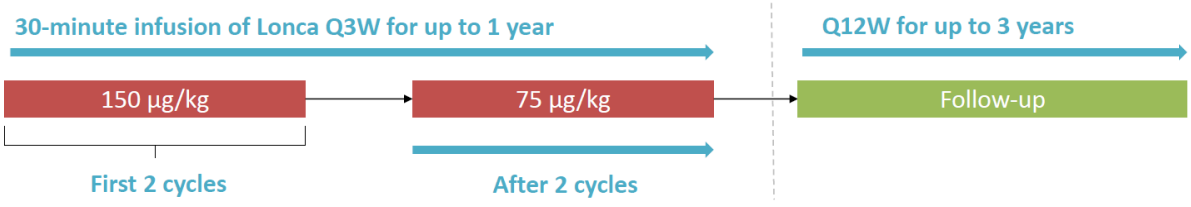
Poster slides, 62nd ASH Annual Meeting and Exposition Virtual Meeting, December 5–8, 2020

Poster session I, Saturday, December 5, 2020: 7:00 am – 3:30 pm (Pacific Time)

Introduction and Methods

- Patients with R/R DLBCL have a poor prognosis and unmet need for new treatment options[1,2]
- Lonca comprises a humanized anti-CD19 antibody conjugated to a potent PBD dimer toxin[3]

Lonca had substantial antitumor activity and an acceptable safety profile in this single-arm open-label Phase 2 study (NCT03589469) in adult patients with R/R DLBCL, who had failed ≥2 established therapies[4]



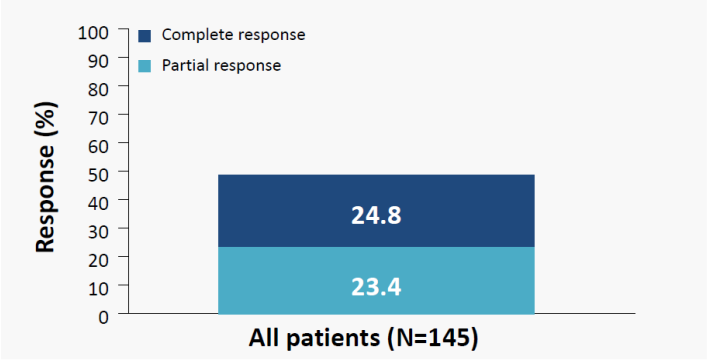
Here, we present updated results including analysis of response in subgroups with high risk for poor prognosis

Pre-specified analyses of ORR and DoR by demographic and clinical characteristics were performed

1. Levin A, Shah NN. *Am J Hematol* 2019;94:S18–S23; 2. Nagle SJ, et al. *Am J Hematol* 2013;88(10):890–4; 3. Zammarchi F, et al. *Blood* 2018;131(10):1094–105;
4. Carlo-Stella C, et al. EHA Congress 2020. Abstract S233.

DLBCL, diffuse large B-cell lymphoma; **DoR**, duration of response; **Lonca**, loncastuximab tesirine; **ORR**, overall response rate; **PBD**, pyrrolobenzodiazepine; **Q3W**, every 3 weeks; **Q12W**, every 12 weeks; **R/R**, relapsed/refractory.

Efficacy Results – ORR



Lonca ORR:
48.3%
(95% CI: 39.9, 56.7)

Lonca CRR:
24.8%
(95% CI: 18.0, 32.7)

Most responders had a response after 2 cycles; median time to first response was 41.0 days (range: 35–247)
Mean Lonca cycles: 4.5 (Std: ± 3.89) (Min, max: 1, 18)*

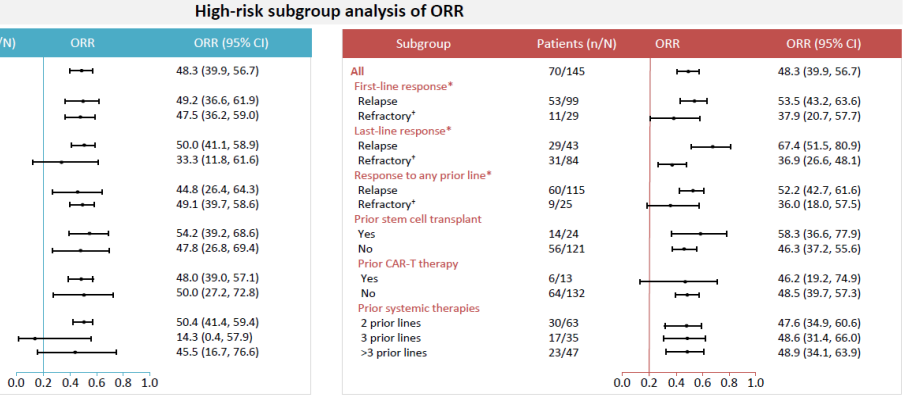
ORR was assessed by independent reviewer. Data cut-off: 06 August, 2020. *4 patients had treatment ongoing at data cut-off.
CI, confidence interval; **CRR**, complete response rate; **Lonca**, loncastuximab tesirine; **max**, maximum; **min**, minimum; **ORR**, overall response rate; **Std**, standard deviation.

Efficacy Results – ORR

High-risk subgroup analysis of ORR

Subgroup	Patients (n/N)	ORR	ORR (95% CI)
All	70/145		48.3 (39.9, 56.7)
Age			
<65 years	32/65		49.2 (36.6, 61.9)
≥65 years	38/80		47.5 (36.2, 59.0)
Double/triple hit			
No	65/130		50.0 (41.1, 58.9)
Yes	5/15		33.3 (11.8, 61.6)
Transformed disease			
Transformed	13/29		44.8 (26.4, 64.3)
De novo	57/116		49.1 (39.7, 58.6)
Cell-of-origin			
GCB	26/48		54.2 (39.2, 68.6)
ABC	11/23		47.8 (26.8, 69.4)
Double/triple expressor			
No	60/125		48.0 (39.0, 57.1)
Yes	10/20		50.0 (27.2, 72.8)
WHO classification			
DLBCL NOS	64/127		50.4 (41.4, 59.4)
PMBCL	1/7		14.3 (0.4, 57.9)
HGBCL	5/11		45.5 (16.7, 76.6)

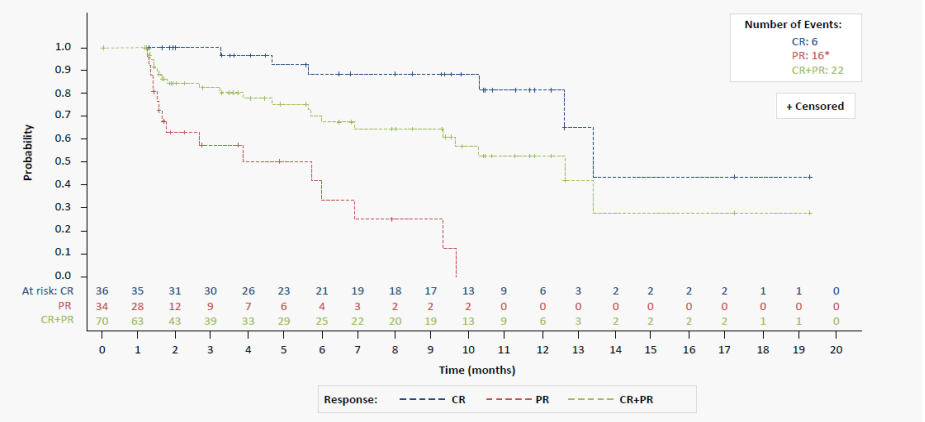
Subgroup	Patients (n/N)	ORR	ORR (95% CI)
All	70/145		48.3 (39.9, 56.7)
First-line response*			
Relapse	53/99		53.5 (43.2, 63.6)
Refractory†	11/29		37.9 (20.7, 57.7)
Last-line response*			
Relapse	29/43		67.4 (51.5, 80.9)
Refractory†	31/84		36.9 (26.6, 48.1)
Response to any prior line*			
Relapse	60/115		52.2 (42.7, 61.6)
Refractory†	9/25		36.0 (18.0, 57.5)
Prior stem cell transplant			
Yes	14/24		58.3 (36.6, 77.9)
No	56/121		46.3 (37.2, 55.6)
Prior CAR-T therapy			
Yes	6/13		46.2 (19.2, 74.9)
No	64/132		48.5 (39.7, 57.3)
Prior systemic therapies			
2 prior lines	30/63		47.6 (34.9, 60.6)
3 prior lines	17/35		48.6 (31.4, 66.0)
>3 prior lines	23/47		48.9 (34.1, 63.9)



Encouraging ORRs were seen in high-risk subgroups

ORR was assessed by independent reviewer. *Prior systemic therapies. †Refractory disease defined as no response to therapy. Data cut-off: 06 August, 2020.
ABC, activated B-cell-like; **CAR-T**, chimeric antigen receptor T-cell; **CI**, confidence interval; **CRR**, complete response rate; **DLBCL**, diffuse large B-cell lymphoma; **GCB**, germinal center B-cell-like; **HGBCL**, high grade B-cell lymphoma; **NOS**, not otherwise specified; **ORR**, overall response rate; **PMBCL**, primary mediastinal B-cell lymphoma; **WHO**, World Health Organization.

Efficacy Results – DoR



mDoR for the 70 responders:
12.58 months
(95% CI: 6.87, -)

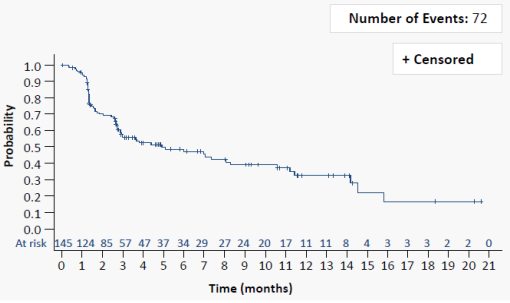
mDoR for patients with a CR:
13.37 months
(95% CI: 12.58, -)

mDoR was comparable to the whole study population in subgroups at high risk of poor prognosis
Patients continue to be followed for DoR

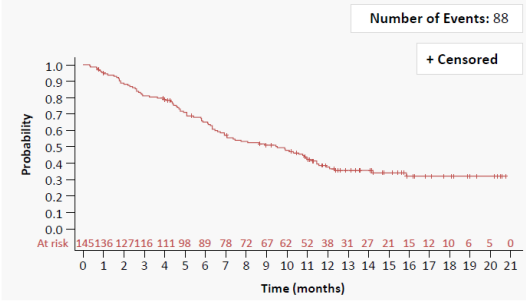
DoR was defined as the time from earliest date of first response until the first date of either disease progression or death due to any cause. *mDoR for patients with a PR: 5.68 months (95% CI: 1.64, 6.87).
Data cut-off: 06 August, 2020
CI, confidence interval; **CR** complete response; **mDOR**, median duration of response; **PR**, partial response.

PFS, OS, and Subsequent Treatment Results

Median PFS: 5.09 months (95% CI: 2.89, 8.31)



Median OS: 9.53 months (95% CI: 6.93, 11.24)



Subsequent Treatment

- **15 patients** received CD19-directed CAR-T therapy with an investigator-assessed ORR of 46.7% (6 CR; 1 PR)
- **9 patients** proceeded to SCT as consolidation after Lonca response

Data cut-off: 06 August, 2020.
CAR-T, chimeric antigen receptor T-cell; **CI**, confidence interval; **CR**, complete response; **Lonca**, loncastuximab tesirine; **ORR**, overall response rate; **OS**, overall survival; **PFS**, progression-free survival; **PR**, partial response; **SCT**, stem cell transplant.

Safety Results

TEAEs in ≥20% of the all-treated population

	Patients n (%)		
Preferred term	**<65 years (N=65)**	**≥65 (N=80)**	**Total (N=145)**
Patients with any TEAE	65 (100)	78 (97.5)	143 (98.6)
GGT increased	33 (50.8)	27 (33.8)	60 (41.4)
Neutropenia	34 (52.3)	24 (30.0)	58 (40.0)
Thrombocytopenia	28 (43.1)	20 (25.0)	48 (33.1)
Fatigue	21 (32.3)	19 (23.8)	40 (27.6)
Anemia	23 (35.4)	15 (18.8)	38 (26.2)
Nausea	17 (26.2)	17 (21.3)	34 (23.4)
Cough	19 (29.2)	13 (16.3)	32 (22.1)
Alkaline phosphatase increased	18 (27.7)	11 (13.8)	29 (20.0)
Peripheral edema	11 (16.9)	18 (22.5)	29 (20.0)

Most common (≥10%) grade ≥3 TEAEs were:

- Neutropenia (38 patients; 26.2%)
- Thrombocytopenia (26 patients; 17.9%)
- GGT increased (25 patients; 17.2%)
- Anemia (15 patients; 10.3%)

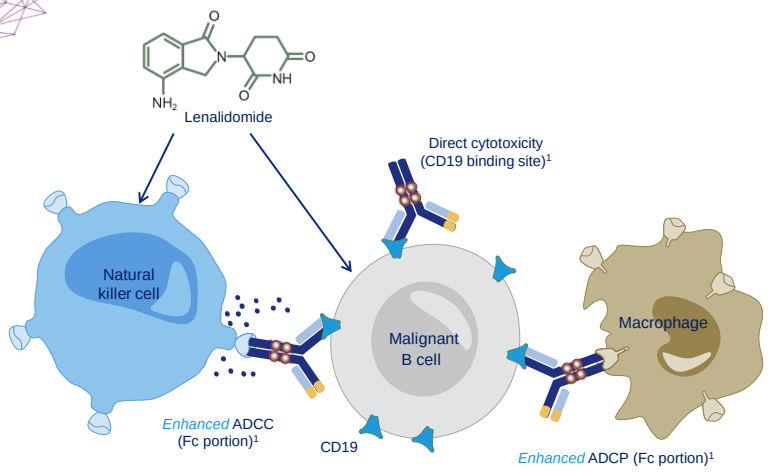
Treatment-related TEAEs leading to treatment discontinuation occurred in 26 (17.9%) patients, most commonly (≥2%):

- GGT increased (16 patients; 11.0%)
- Peripheral edema (4 patients; 2.8%)
- Localized edema (3 patients; 2.1%)

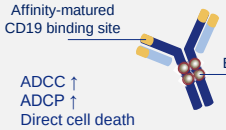
No increase in toxicity was seen in patients aged ≥65 years compared with younger patients

TEAEs were reported for the all-treated population. Data cut-off: 06 August, 2020.
GGT, gamma-glutamyltransferase; **TEAE**, treatment-emergent adverse event.

Tafasitamab-cxix and Lenalidomide: Rationale for an Immunological Combination



Tafasitamab-cxix (CD19-directed cytolytic mAb)[1–6]



- ADCC ↑
- ADCP ↑
- Direct cell death
- Phase IIa study showed single-agent activity in patients with R/R DLBCL and iNHL

Lenalidomide[4,5]

- T-cell and NK-cell activation/expansion
- Direct cytotoxic and immunomodulatory effects
- Well-studied as an anti-lymphoma agent, alone or in combination

CD19 = cluster of differentiation 19; mAb = monoclonal antibody; Fc = fragment crystallizable; ADCC = antibody-dependent cellular cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; R/R DLBCL = relapsed/refractory diffuse large B-cell lymphoma; iNHL = indolent non-Hodgkin's lymphoma; NK = natural killer.

1. Horton HM, et al. *Cancer Res* 2008;68:8049–57; 2. Woyach JA, et al. *Blood* 2014;124:3553–60; 3 Jurczak W, et al. *Ann Oncol* 2018;29:1266–72; 4. Witzig TE, et al. *Ann Oncol* 2015; 26:1667–77; 5. Czuczman MS, et al. *Clin Cancer Res* 2017; 23:4127–37. 6. MONJUVI Prescribing Information. Boston, MA: MorphoSys US, Inc.

L-MIND Study Rationale

Unmet need in r/r DLBCL

30%–40% of patients with DLBCL fail to respond or show relapse to initial therapy[1]

Patients who fail first-line therapy and are not eligible for HDC/ASCT have a poor outcome and require more therapeutic options[1]

Single-agent activity of Tafasitamab-cxix evaluated in r/r B-cell malignancies

A phase I dose-escalation study in 27 patients with R/R CLL showed the preliminary efficacy of Tafasitamab-cxix[2]

A phase II study of 92 patients demonstrated clinical activity of Tafasitamab-cxix in patients with R/R DLBCL and R/R FL, including those with rituximab-refractory tumors[3]

Lenalidomide may have synergistic effects with Tafasitamab-cxix

Lenalidomide has been well-studied as an anti-lymphoma agent, alone or in combination[4,5]

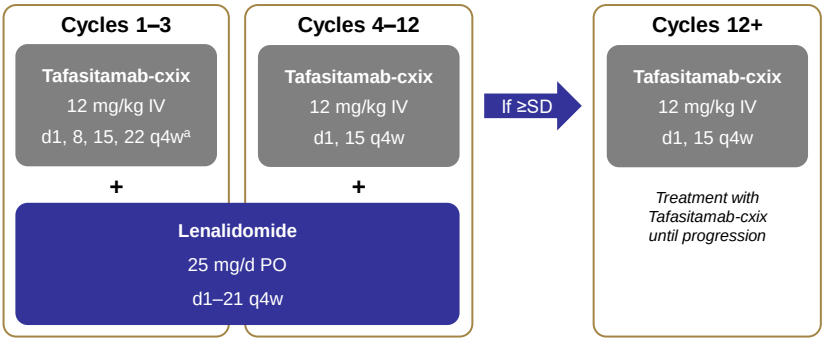
In an *in vitro* study, NK-cell mediated ADCC with Tafasitamab-cxix was further enhanced by lenalidomide[6]

R/R CLL = relapsed/refractory chronic lymphocytic leukemia; R/R FL = relapsed/refractory follicular lymphoma.

1. Crump M, et al. *Blood* 2017;130:1800–8; 2. Woyach JA, et al. *Blood* 2014;124:3553–60; 3 Jurczak W, et al. *Ann Oncol* 2018;29:1266–72; 4. Witzig TE, et al. *Ann Oncol* 2015; 26:1667–77; 5. Czuczman MS, et al. *Clin Cancer Res* 2017;23:4127–37 ; 6. Awan FT, et al. *Blood* 2010;115:1204–13.

Phase II L-MIND Study Design and Inclusion Criteria

- N=81
- Age ≥18 years
- R/R DLBCL
- Not eligible for HDT + ASCT
- 1–3 prior regimens
- Primary refractory patients were excluded[b]
- ECOG 0–2
- ***First Data Analysis: November 2018[1]***
- ***Updated Long Term Outcomes: November 2019[2]***



Primary endpoint:
ORR (ORR = complete response [CR] + partial response [PR])

Select Secondary endpoints:
PFS, DoR, OS, safety, exploratory and biomarker-based assays

[a]Loading dose on day 4 of cycle 1 only.
[b]Primary refractory defined as no response to, or progression/relapse during or within 6 months of front-line therapy.
R/R = relapsed or refractory; IV = intravenous; q4w = every 4 weeks; SD = stable disease; HDT = high dose therapy; ASCT = autologous stem cell transplantation; ECOG = Eastern Cooperative Oncology Group; PO = orally; ORR = overall response rate; PFS = progression-free survival; DoR = duration of response; OS = overall survival.
1. Salles G, Duell J, González Barca E, et al. Tafasitamab-cxix plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol.* 2020 Jun 5;S1470-2045(20)30225-4. doi: 10.1016/S1470-2045(20)30225-4. 2. Salles G, et al. EHA 2020. Abstract EP1201.

L-MIND Patient Characteristics

Characteristic	Specification	N=81
Age (years)[a]	Median (range)	72 (41–86)
Sex, n (%)	Male	44 (54)
	Female	37 (46)
Ann Arbor stage, n (%)[a]	I–II	20 (25)
	III–IV	61 (75)
Risk (IPI), n (%)[a]	0–2	40 (49)
	3–5	41 (51)
Elevated LDH, n (%)[a]	Yes	45 (56)
	No	36 (44)
Prior lines, n (%)[a]	Median	2
	1	40 (49)
	2	35 (43)
	3	5 (6)
	4	1(1)

Characteristic	Specification	N=81
Primary refractory, n (%)[a]	Yes	15 (18)[b]
	No	66 (82)
Refractory to previous therapy line, n (%)[a]	Yes	36 (44)
	No	45 (56)
Prior SCT, n (%)	Yes	9 (11)
	No	72 (89)
Cell of origin (by IHC), n (%) (Centrally assessed – Hans algorithm)	GCB	37 (46)
	Non-GCB	20 (25)
	Unknown	24 (30)

[a]At study entry.
[b]Primary refractory patients had a DoR to first line of 3–6 months.
IPI = International Prognostic Index; LDH = lactate dehydrogenase; SCT = stem cell transplant; IHC = immunohistochemistry; GCB = germinal center B-cell like.
Salles G, Duell J, González Barca E, et al. Tafasitamab-cxix plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol.* 2020 Jun 5;S1470-2045(20)30225-4. doi: 10.1016/S1470-2045(20)30225-4.

L-MIND: Updated Efficacy Outcomes (IRC)

Long term outcomes from L-MIND: Tafasitamab-cxix + Lenalidomide in R/R DLBCL (Phase II)

	Nov 2018[1] (n=80)	Nov 2019[3] (n=80)	Nov 2019[3] 2L (n=40)
ORR	60%	57.5%[a]	67.5
CR	42.5%	40.0%[a]	50.0
PR	17.5	17.5	17.5
mDoR	21.7 mo (21.7, NR)	34.6 mo (26.1, NR)	34.6 mo (21.7, NR)
mPFS	12.1 mo (5.7, NR)	12.1 mo (6.3, NR)	23.5 mo (7.4, NR)
mOS	NR (18.3, NR)	31.6 mo (13.8, NR)	NR (24.6, NR)
Patients still on study	N=28	N=22	

The US Prescribing Information(USPI) includes efficacy data on a subset of patients with centrally confirmed diagnoses of DLBCL[2]: N=71; ORR=55%; mDoR=21.7 mo

[a]For 3 patients, additional data accumulating after Nov '18 cut off changed the radiology adjudication within the Independent Review Committee (IRC).
mDoR = median duration of response; mOS = median overall survival.
1. Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or

Efficacy in L-MIND Study Population

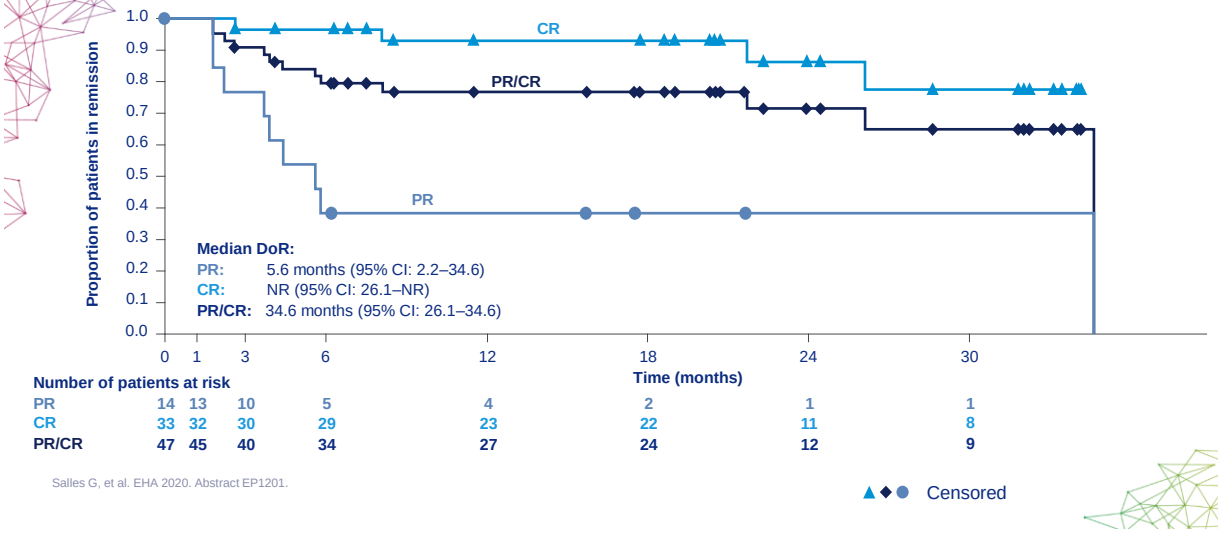
	12 Month Analysis*		24 Month Analysis†	
	N=80 (FAS)[1]	N=71**[2]	N=80 (FAS)[2]	N=71**[2]
ORR %	60	55	57.5	53.5
CR %	42.5	37	40	35.2
PR %	17.5	18	17.5	18.3
mDoR, months (95% CI)	21.7 (21.7–NR)	21.7 (0-24)	34.6 (26.1–NR)	34.6 (21.7–NR)
mPFS, months (95% CI)	12.1 (5.7–NR)	8.7 (4.3–NR)	12.1 (6.3–NR)	9.1 (4.7–36.4)
mOS, months (95% CI)	NR (18.3–NR)	NR (14.8–NR)	31.6 (18.3–NR)	24.8 (14.8–NR)

- *Data cut-off: 30 November 2018. †Data cut-off: 30 November 2019.CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; FAS, full analysis set; LT, long-term; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
- ** N=71 patients are L-MIND patients with DLBCL confirmed by central laboratory and were evaluable for efficacy as assessed by an Independent Review Committee using the International Working Group Response Criteria (Cheson 2007)

1. Salles G, Duell J, González Barca E, et al. Tafasitamab-cxix plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol. 2020.. 2.Data on File-Listing for Efficacy Data for Subgroups. MorphoSys 2020.

L-MIND Efficacy: DoR After ≥24 Months of Follow-up (IRC)

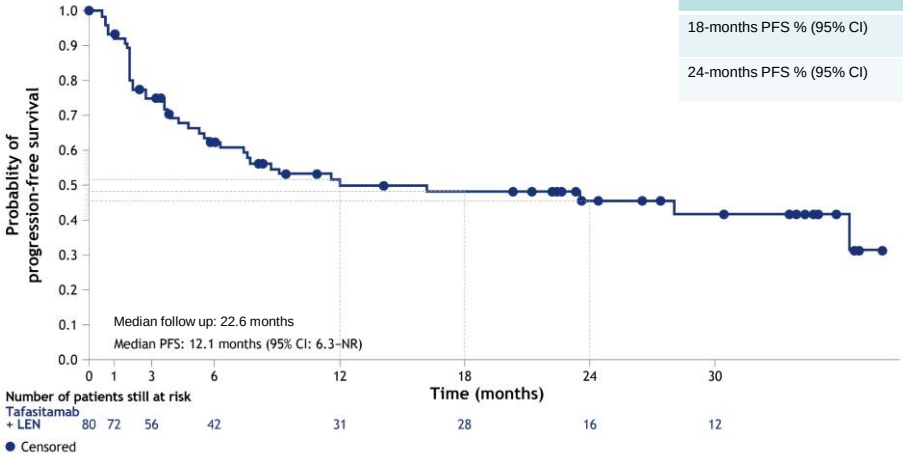
Long term outcomes from L-MIND: Tafasitamab-cxix + Lenalidomide in R/R DLBCL (Phase II)



Salles G, et al. EHA 2020. Abstract EP1201.

L-MIND Efficacy: PFS After ≥24 Months of Follow-up (IRC)

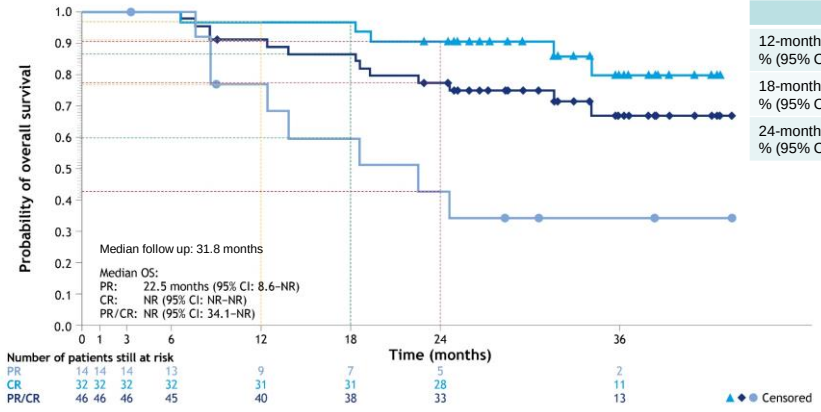
Long term outcomes from L-MIND: Tafasitamab-cxix + Lenalidomide in R/R DLBCL (Phase II)



12-months PFS % (95% CI)	51.6 (39.4, 62.5)
18-months PFS % (95% CI)	48.2 (36.0, 59.4)
24-months PFS % (95% CI)	45.5 (33.0, 57.2)

L-MIND Efficacy: OS After ≥24 Months of Follow-up

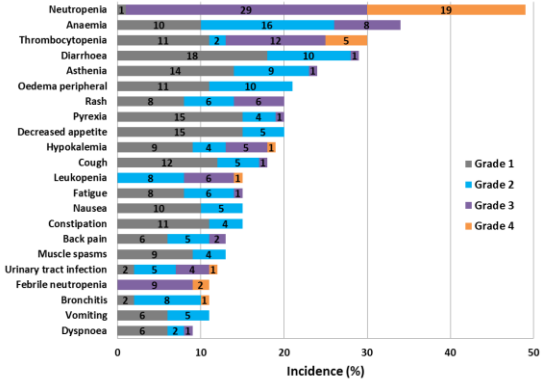
Long term outcomes from L-MIND: Tafasitamab-cxix + Lenalidomide in R/R DLBCL (Phase II)



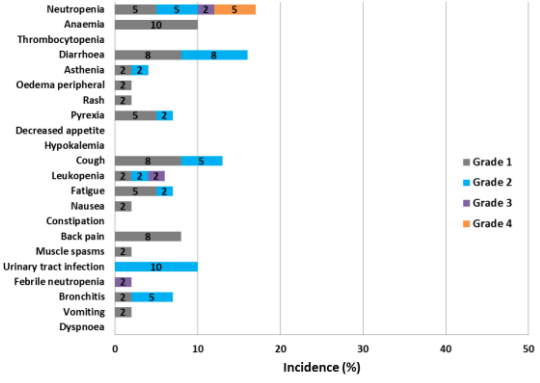
	PR	CR	PR/CR
12-months OS % (95% CI)	76.9 (44.2, 91.9)	96.9 (79.8, 99.6)	91.1 (78.0, 96.6)
18-months OS % (95% CI)	59.8 (28.5, 81.0)	96.9 (79.8, 99.6)	86.6 (72.5, 93.7)
24-months OS % (95% CI)	42.7 (15.9, 67.5)	90.6 (73.7, 96.9)	77.4 (62.1, 87.2)

Tafa-len (L-MIND): safety by treatment phase

Tafasitamab + LEN combination (up to 12 cycles) n=80, median exposure 6.5 months



Tafasitamab monotherapy (cycle 13 onwards or after LEN discontinuation) n=37, median exposure 8.7 months



- Incidence and severity of TEAEs is lower during the tafasitamab monotherapy phase
- 10 patients (12%) discontinued tafasitamab + LEN due to AE

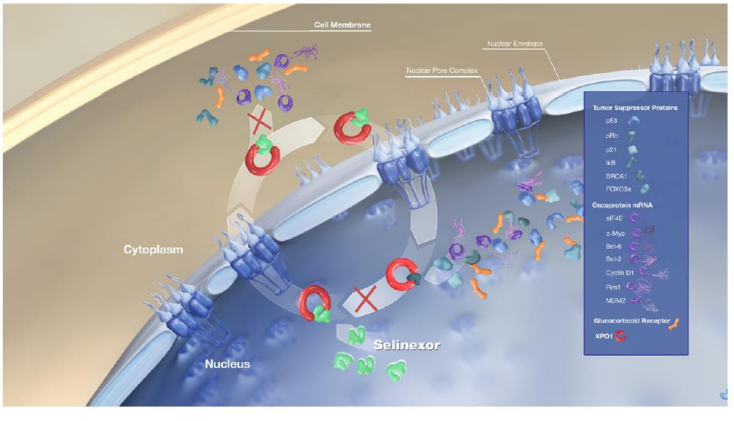
AE collection period included 30 days after end of treatment. | LEN, Lenalidomide.

Salles et al, Lancet Oncol 2020

A Phase 2b Study of Selinexor in Patients with Relapsed / Refractory Diffuse Large B-Cell Lymphoma: SADAL trial

N. Kalakonda, F. Cavallo, G. Follows, A. Goy, J.S.P. Vermaat, O. Casasnovas, O. Lavee, M. Maerevoet, J.M. Zijlstra, S. Bakhshi, R. Bouabdallah, S. Choquet, R. Gurion, B. Hill, U. Jaeger, J.M. Sancho, M. Schuster, C. Thieblemont, F. De la Cruz, M. Egyed, S. Mishra, F. Offner, T.P. Vassilakopoulos, K. Warzocha, M. Brown, D. McCarthy, X. Ma, K. Corona, J. Shah, E. Van Den Neste, M.A. Canales

Selinexor: Mechanism of Action



Exportin 1 (XPO1 or CRM1) mediates the nuclear export of proteins, mRNAs, rRNAs, snRNAs and impacts

- **Tumor suppressor proteins** (p53, IκB, FOXO etc.)
- **eIF4E** (Translational initiation factor) bound oncogenic mRNAs (c-Myc, Bcl-xL, cyclins etc.)

Selinexor is an oral selective **XPO1** inhibitor; preclinical data support that XPO1 inhibition:

- Reactivates multiple TSPs relevant to NHL, (p53, p21, IκB, FOXO etc.)
- Disrupts localization of eIF4e (overexpressed in most B-cell lymphomas[1]
- Reduces c-Myc, Bcl-2, and Bcl-6 levels[2-3]

1. Kodali 2011 2. Kuruvilla 2014 3. Schmidt 2013

3

SADAL: Study Design

Single Agent Oral Selinexor in Patients with Relapsed / Refractory DLBCL

Selinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma (**SADAL**): An Open-label, Phase 2b study

Patient Population
- Patients with de novo or t-DLBCL
- Relapsed or Refractory DLBCL
- Not eligible for ASCT

Main Inclusion / Exclusion
- 2 – 5 prior treatment regimens
- Platelet count >75,000/mm^3
- Cr Cl <30 ml/min – excluded

Oral Selinexor
60 mg twice-weekly
Days 1, 3 – 28 day cycle

→

Treatment until PD or intolerable toxicity;
Response assessed every 8 weeks per *Cheson 2014*

→

mITT Population for all Analysis and Safety
(≥Protocol Version 6 patients)

Objectives:

- **Primary Endpoint**: Overall response rate (ORR): Independent Central Radiological Review (ICRR); Lugano Classification (2014)
- **Secondary Endpoints**: Duration of response (DOR), Overall survival (OS), Safety

Modified Intent to Treat (mITT) Population: All patients who were randomized to the **60 mg Arm**

SADAL: Patient Characteristics

Characteristic	N
Enrolled* as of April 3, 2019	**127**
Median Age, Years (Range)	**67** (35–87)
Males (%) : Females (%)	**75** (59%) : **52** (41%)
Median Years from DLBCL Diagnosis (Range)	**2.6 yrs** (<1–26.2)
De novo DLBCL : Transformed DLBCL : Unknown	**96** (76%) : **30** (24%) : **1** (<1%)
GCB Subtype : Non-GCB Subtype : Unclassified	**59** GCB : **63** Non-GCB : **5** Unclassified
Median Prior Treatment Regimens (Range)	**2 (1–6)**
Prior Transplantation	39 (31%)

Phase II SADAL trial of selinexor: first inhibitor of nuclear export

	Overall response rate	Complete response	Partial response	Stable disease	Progressive disease or no response recorded
All patients	36/127 (28%) (20·7–37·0)	15 (12%) (6·8–18·7)	21 (17%) (10·5–24·2)	11 (9%) (4·4–15·0)	80 (63%) (54·0–71·4)
GCB subtype	20/59 (34%) (22·1–47·4)	8 (14%) (6·0–25·0)	12 (20%) (11·0–32·8)	7 (12%) (4·9–22·9)	32 (54%) (40·8–67·3)
Non-GCB subtype	13/63 (21%) (11·5–32·7)	6 (10%) (3·6–19·6)	7 (11%) (4·6–21·6)	3 (5%) (1·0–13·3)	47 (75%) (62·1–84·7)
Unclassified	3/5 (60%) (14·7–94·7)	1 (20%) (0·5–71·6)	2 (40%) (5·3–85·3)	1 (20%) (0·5–71·6)	1 (20%) (0·5–71·6)

Data are n/N (%; 95% CI). Responses were adjudicated according to central imaging assessment. GCB=germinal centre B cell. See results section in main text for one-sided 97·5% CI.

Table 2: **Responses in evaluable patients**

Median progression-free survival: 2.6 months (95% CI, 1.9 - 4.0)
Median overall survival: 9.1 months (95% CI, 6.6 - 15.1)

Kalakonda N et al. *Lancet Haematol*. 2020;7(7):e511-e522.

Phase II SADAL trial of selinexor: first inhibitor of nuclear export

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Data are n/N (%; 95% CI). Responses were adjudicated according to central imaging assessment. GCB=germinal centre B cell. See results section in main text for one-sided 97·5% CI.

Table 2: **Responses in evaluable patients**

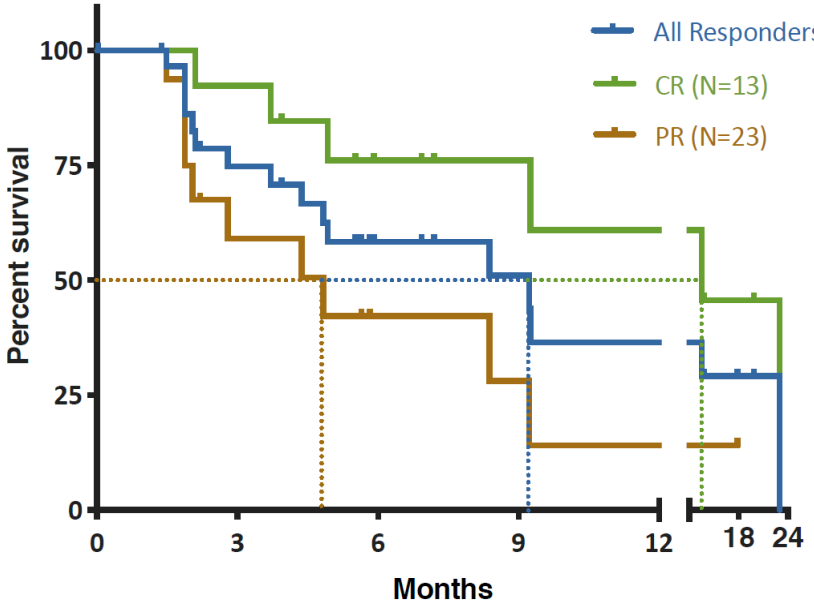
In patients with ≥ partial response,
- **median overall survival was not reached**,

In patients with stable disease,
- median overall survival was 18·3 months (95% CI 11·1–28·0).

Median progression-free survival: 2.6 months (95% CI, 1.9 - 4.0)
Median overall survival: 9.1 months (95% CI, 6.6 - 15.1)

Kalakonda N et al. *Lancet Haematol*. 2020;7(7):e511-e522.

SADAL: Duration of Response



Category	Median DOR (months)	95% CI
All Responders	9.2	(4.8 – 23.0)
CR Patients	13.5	(9.3 – 23.0)
PR Patients	4.8	(2.0 – NE)

Selinexor: first inhibitor of nuclear export
Management of side effects

Most common grade 3-4 AEs

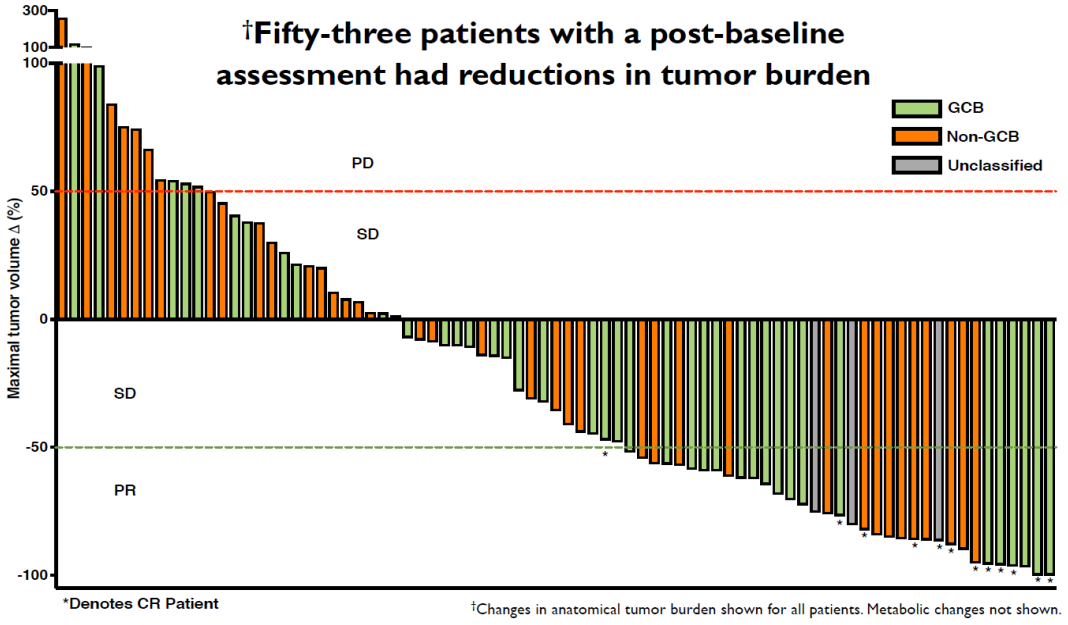
- Thrombocytopenia (46%); neutropenia (24%) and anemia (22%)
- Fatigue (11%), hyponatraemia (8%), and nausea (6%)

Supportive measures:

Cytopenia:
. growth factors, transfusions
. dose reduce from 60mg 2/week to 40mg 2/week then 60mg 1/week
Anorexia, weight loss
. olanzapine (2.5 to 5 mg QHS)
Nausea, vomiting
. 5HT3 antagonists, NK1R receptors antagonists**.**
Steroids… ,sodium intake…

Kalakonda N et al. *Lancet Haematol*. 2020;7(7):e511-e522.

SADAL: Tumor Responses: Anatomical



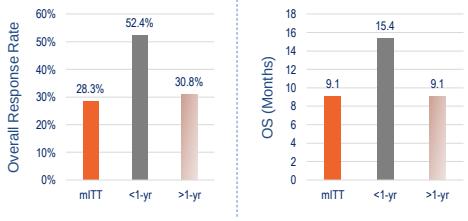
10

SADAL – Subgroup Analyses by Patient Characteristics:
By Refractory or Relapse <1 year To The Last Stem-Cell Transplant For DLBCL

Group	N	ORR, n (%)	DCR, n (%)	mDOR, months [95% CI]
Overall	127	36 (28.3%)	47 (37.0%)	9.3 [4.8, 23]
Less than 1-yr	21	11 (52.4%)	11 (52.4%)	8.4 [2.8, NE]
After 1-yr	13	4 (30.8%)	6 (46.2%)	14 [4.9, 23]

Group	N	mPFS, months [95% CI]	mOS, months [95% CI]
Overall	127	2.6 [1.9, 4.0]	9.1 [6.6, 15.1]
Less than 1-yr	21	4.6 [1.9, NE]	15.4 [7.8, NE]
After 1-yr	13	6.3 [1.9, 24.8]	9.1 [2.0, NE]

SADAL Subgroup Analysis
(Relapsed or Refractory < 1yr to Last Stem-Cell Transplant)



Anti-CD19 CAR-T Cell Therapies in R/R aggressive NHL

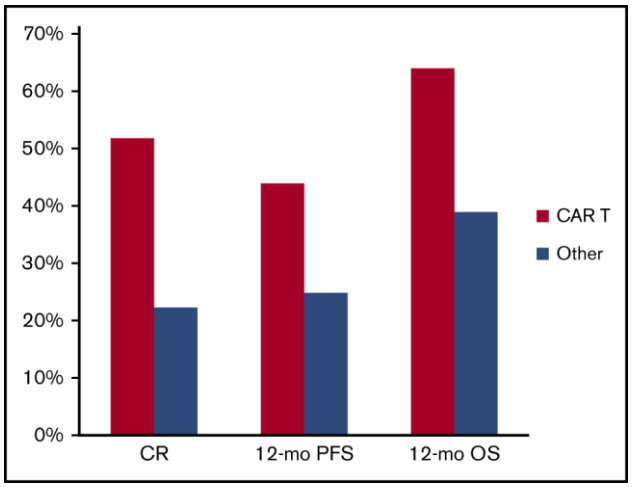
	KTE-C19 [1, 2] Axi-cel	CTL019 [3,4] Tisagenlecleucel	JCAR017 [5] Liso-cel
Vector	Gammaretroviral	Lentiviral	Lentiviral
Costimulatory domain	CD28	4-1BB	4-1BB
Disease state	DLBCL, TFL, PMBCL	DLBCL, TFL	DLBCL, t-iNHL, FL3B
ORR	84%	54%	73%
CR Rate	58%	40%	53%
Median follow-up (months)	27	32	12
Median PFS (months)	5.9	2.9	6.8
Median DOR (months)	NR	NR	NR
Median OS (months)	NR	11.1	21
Grade 3-4 CRS	11%	23%*	2%
Grade 3-4 Neurotox	32%	11%	10%

- CRS grading using UPenn scale

1. Neelapu S et al, NEJM 2017. 2. Locke F et al. , Lancet Oncol 2019
2. 3. Schuster S et al, NEJM 2019 4. .Bachanova V; et al., Hematol Oncol 2019 5. Abramson J et al, Lancet 2020

Can Alternate Therapies Compete with CAR T?

Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies



David Sermer,, Blood Adv, 2020,

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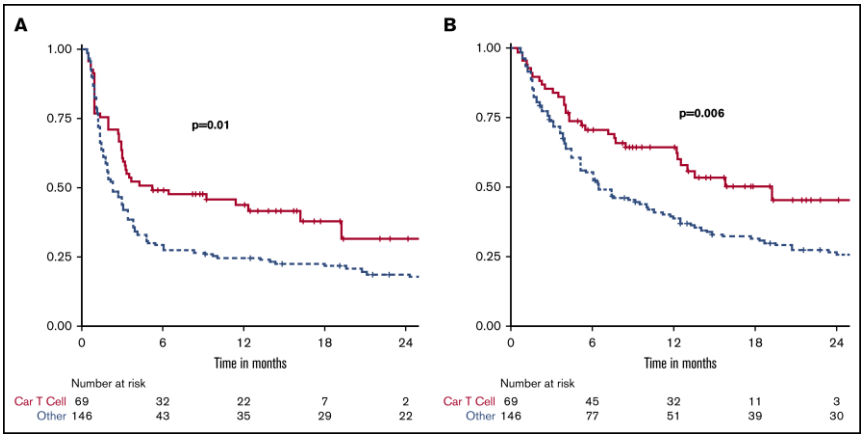
Helping hematologists conquer blood diseases worldwide

Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies



David Sermer,, Blood Adv, 2020,

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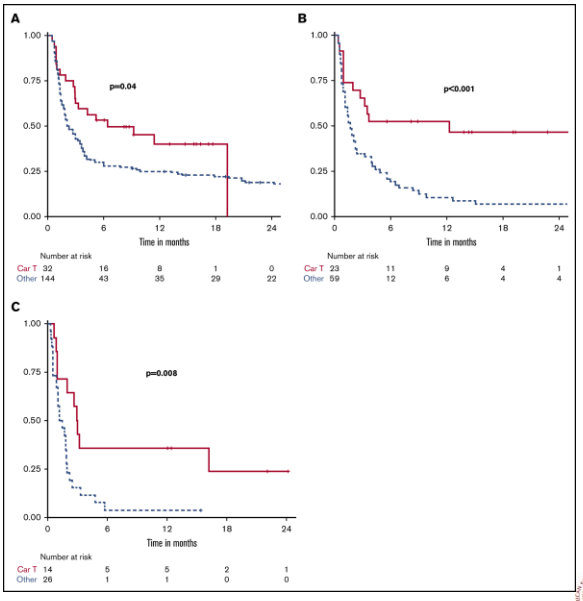
Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies



David Sermer,, Blood Adv, 2020,

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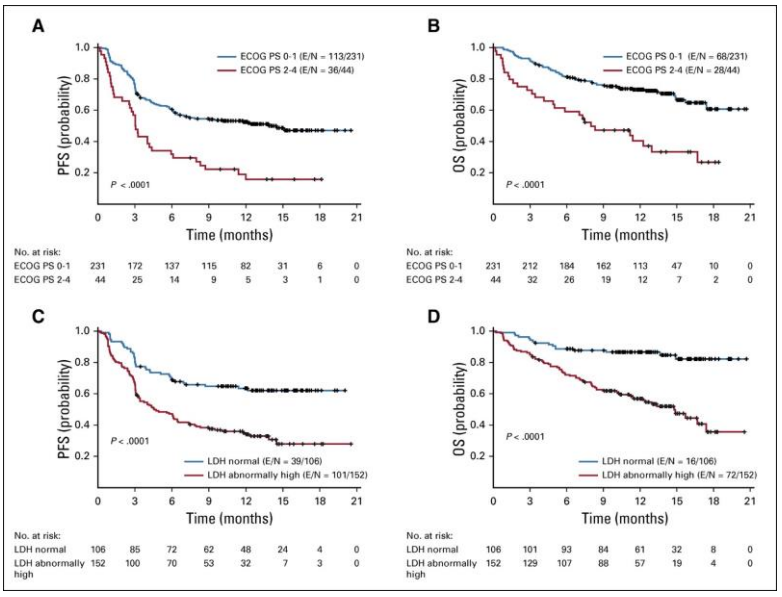
Helping hematologists conquer blood diseases worldwide

Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies

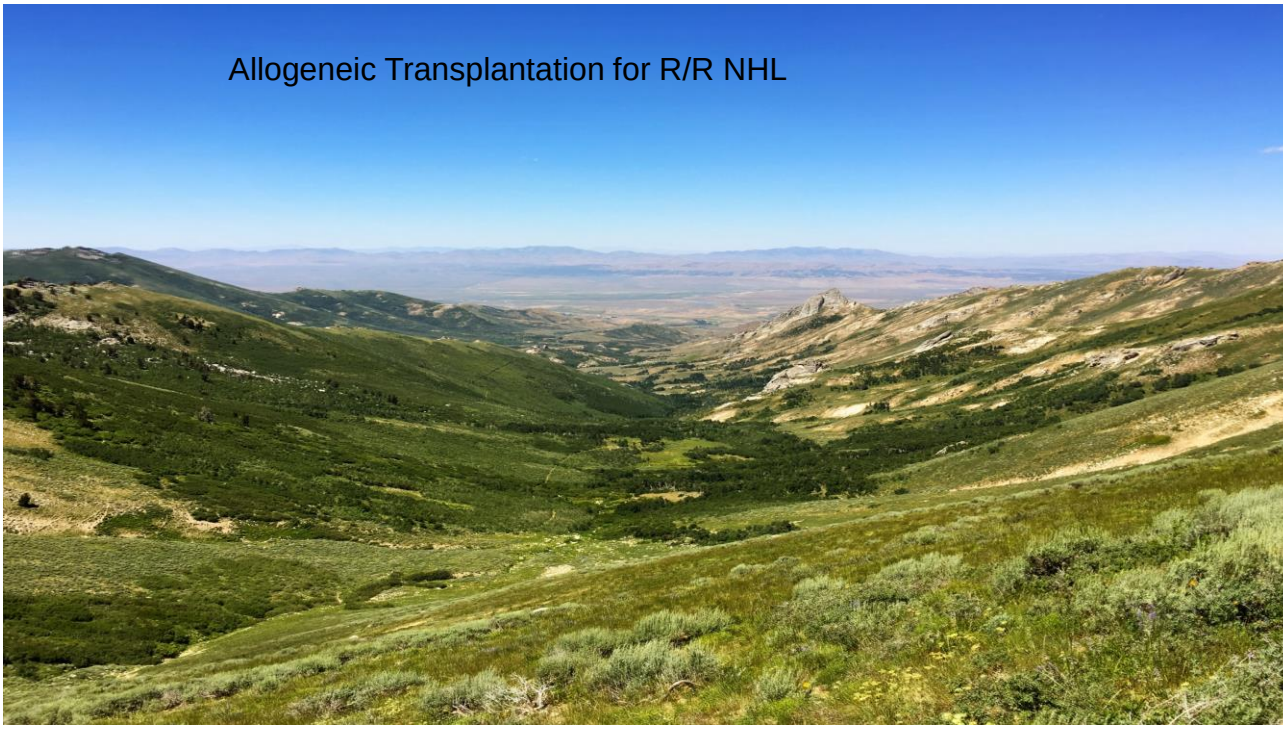
In this group of responders to alternate therapy, of the 21 patients who proceeded to consolidation with either autologous (n =11) or an allogeneic hematopoietic cell transplant (HCT; n =10), 3 (14%) relapsed. Of the 25 patients who did not undergo HCT, 14 (56%) ultimately relapsed.

David Sermer,, Blood Adv, 2020,

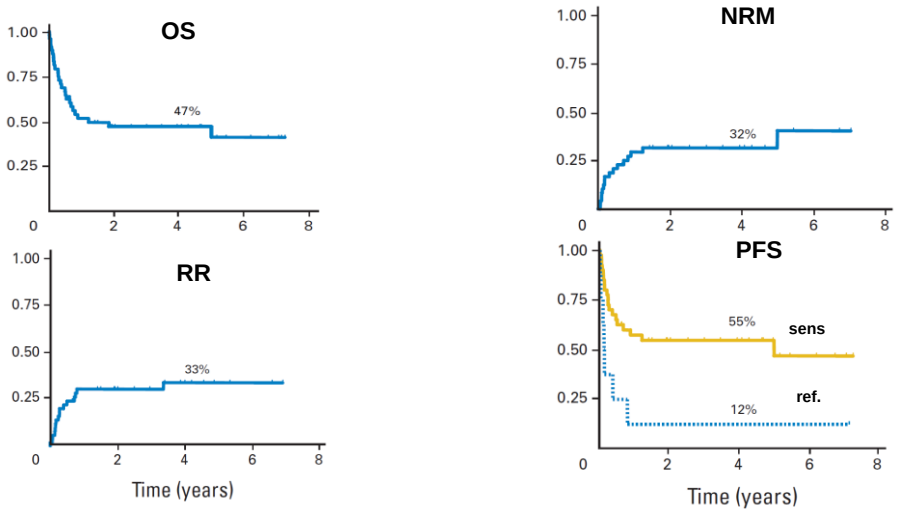
Axicabtagene Ciloleucel in “real world“
PFS and OS by Baseline ECOG and LDH



Loretta J. Nastoupil et al, JCO 2020



Allogeneic SCT in relapsed DLBCL
Reduced intensity conditioning : Results



Thomson et al. JCO 2009; 27 (3): 426

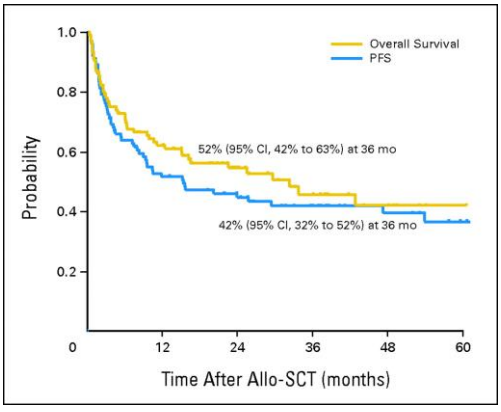
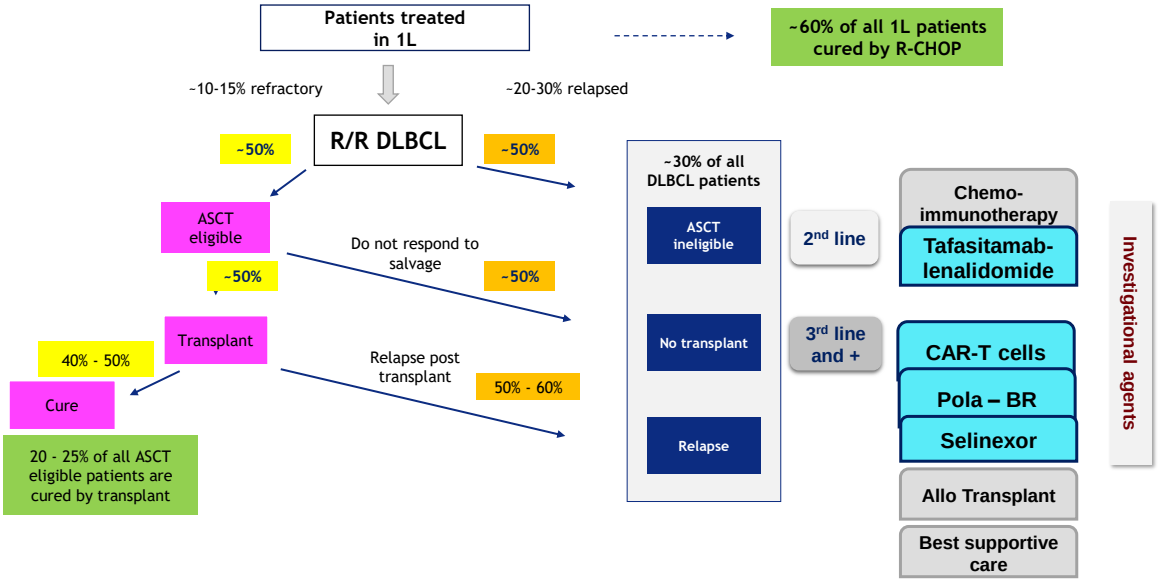


Fig 3. Progression-free survival (PFS) and overall survival of the whole series. Allo-SCT, allogeneic stem-cell transplantation; mo, months.

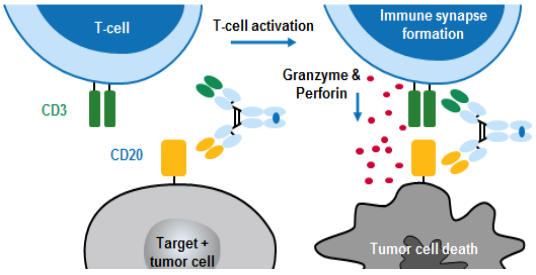
Published in: Roel J.W. van Kampen; Carmen Canals; Harry C. Schouten; Arnon Nagler; Kirsty J. Thomson; Jean-Paul Vernant; Agnes Buzyn; Marc A. Boogaerts; Jian-Jian Luan; Sébastien Maury; Noel J. Milpied; Jean-Pierre Jouet; Gert J. Ossenkoppele; Anna Sureda; *Journal of Clinical Oncology* **2011,** 29, 1342-1348.
DOI: 10.1200/JCO.2010.30.2596
Copyright © 2011

Relapsed and refractory DLBCL



Background

- Mosunetuzumab (RG7828; BTCT4465A)
  - Full-length, fully humanized IgG1 bispecific antibody[1]
  - Redirects T cells to engage and eliminate B cells; T-cell activation, cytokine elevation and increase in TILs observed (**Hernandez et al. ASH 2019 P-1585**)
  - No ex-vivo T cell manipulation required ('off-the-shelf' and no delay in treatment)



- GO29781
  - Phase I/Ib dose-escalation and expansion study in heavily pre-treated R/R B-cell NHL
  - Cycle 1 step-up dosing: mitigates CRS, allowing dose escalation to maximize therapeutic potential[2,3]
- Data for 270 R/R B-cell NHL pts, including 30 pts with prior CAR-T

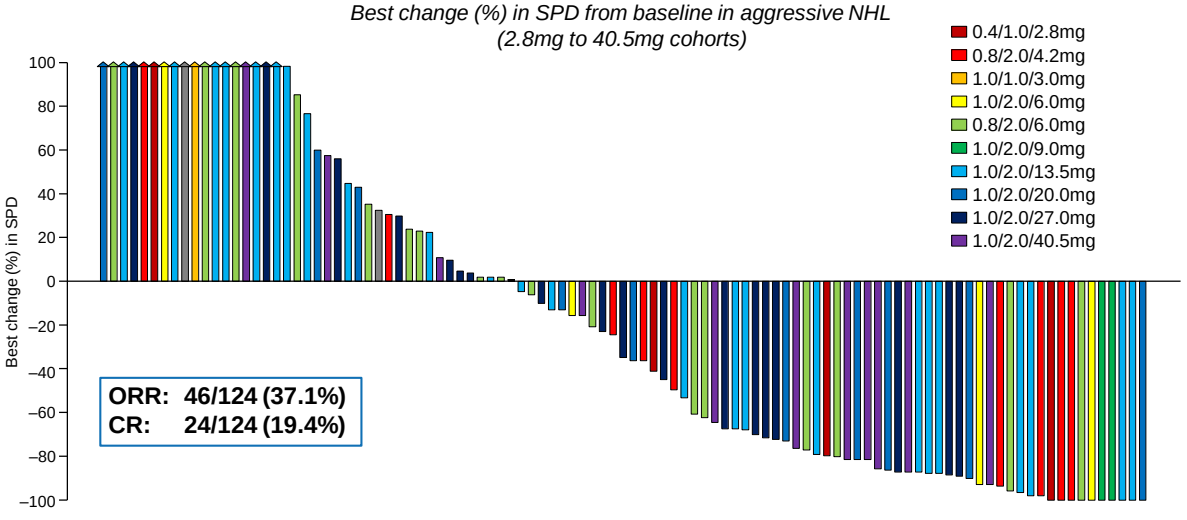
Registry number: NCT02500407

CRS, cytokine release syndrome; NHL, non-Hodgkin lymphoma; pts, patients; R/R, relapsed or refractory; TILs, tumor-infiltrating lymphocytes

1. Sun et al. Sci Transl Med 2015
2. Budde et al. ASH 2018; 3 Bartlett et al. ASCO 2019

Schuster S et al, ASH 2019

Mosunetuzumab: objective response rate in aggressive NHL



Aggressive NHL: DLBCL, trFL, MCL, Richter's transformation, transformed marginal zone lymphoma and FL (Grade 3B)
SPD: sum of the product of the diameters; CCOD: Aug 9, 2019

Schuster S et al, ASH 2019

Response rates and duration in aggressive NHL

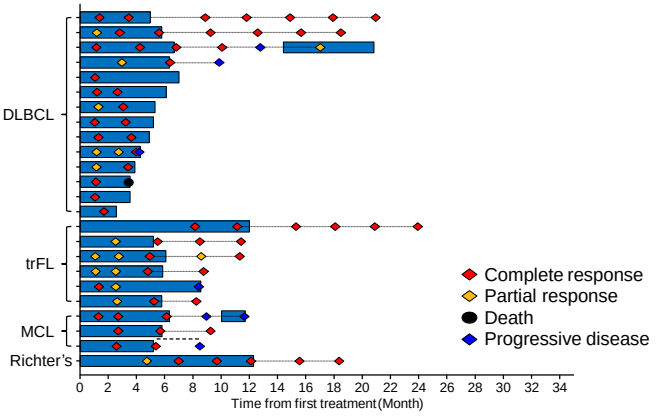
Investigator-assessed best objective response (pooled data from 2.8mg to 40.5mg cohorts)

	N*	ORR, n (%)	CR, n (%)
Aggressive NHL	124	46 (37.1%)	24 (19.4%)
DLBCL/trFL after ≥ 2 lines	98	37 (37.8%)	20 (20.4%)
• Refractory to anti-CD20	88/98	32 (36.4%)	18 (20.5%)
• With prior auto SCT	32/98	17 (53.1%)	11 (34.3%)

- Dose optimization is ongoing
- Increased efficacy in pts with higher exposure to mosunetuzumab, as measured by CD20 receptor occupancy (RO%)

Li et al. ASH 2019;Abstract 1285

Time on treatment and duration of response among aggressive NHL complete responders



- **17 CR pts (70.8%) remain in remission (up to 16 months off treatment)**
- **Mosunetuzumab tolerability profile appeared favorable**

*efficacy-evaluable pts: pts who were enrolled for at least 3 months, or had response data available at any time, or discontinued treatment for any cause; CCOD: Aug 9, 2019

Schuster S et al, ASH 2019

Bi-Specifics CD3 x CD20 in patients with DLBCL: update at ASH 2020

	Mosunetuzumab[1] (RG7828)	Odronextamab[1] (REGN1979)	Glofitamab[1] * (RG6026)	Epcoritamab[1] (GEN3013)
Patients	98	35	28	33
ORR	38%	40%	61%	76%
CR	20%	31%	54%	48%

1. Schuster SJ et al, ASH 2019, Abstract 6 (doses >=2.5 mg); 2. Bannerji R, et al. ASH 2020, Abstract 400 (doses 80-320); 3. Hutchings M, et al. ASH 2020, Abstract 403 (step up dosing from 2.5 to 16/30 mg); 4. Hutchings M, et al. ASH 2020, Abstract 402 (all doses).
2. * "aggressive lymphoma"

ETCTN

Experimental Therapeutics Clinical Trials Network

Team Driven. Cancer Therapy Focused.

A Phase I Trial of the Combination of Lenalidomide and Blinatumomab in Patients with Relapsed or Refractory Non-Hodgkins Lymphoma (NHL)

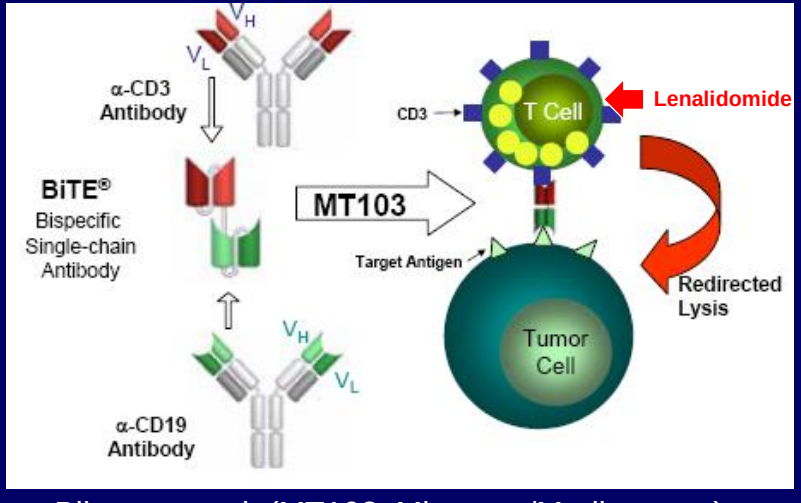
NCI Protocol # 9924

Joseph Tuscano

UC Davis Cancer Center

ASH 2019

Activating and Redirecting the Immune System to Enhance Efficacy

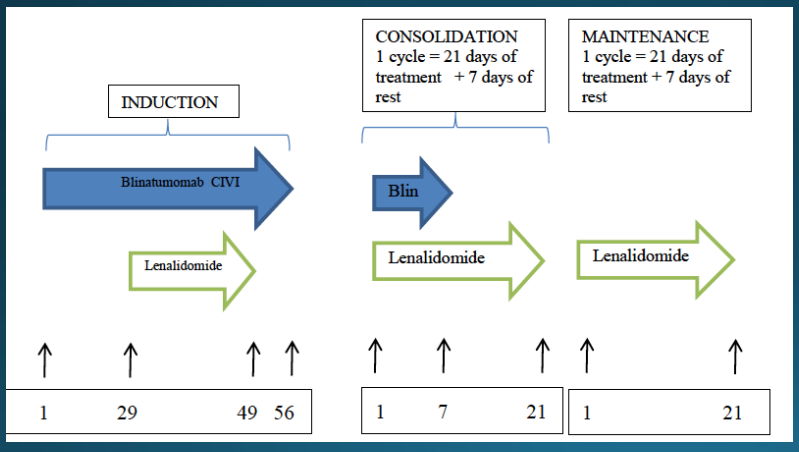


Blinatumomab (MT103; Micromet/Medimmune), a BiTE specific for CD19 and CD3

Patrick A. Baeuerle, Micromet, Inc. San Diego, December , 2009

Study Design

- **Escalation Phase**



Endpoints

Primary
- Toxicity
- MTD/RP2D determination of lenalidomide

Secondary
- Overall response rate (ORR)
- Complete response (CR) rate
- Progression free survival (PFS)
- Immune response biomarkers

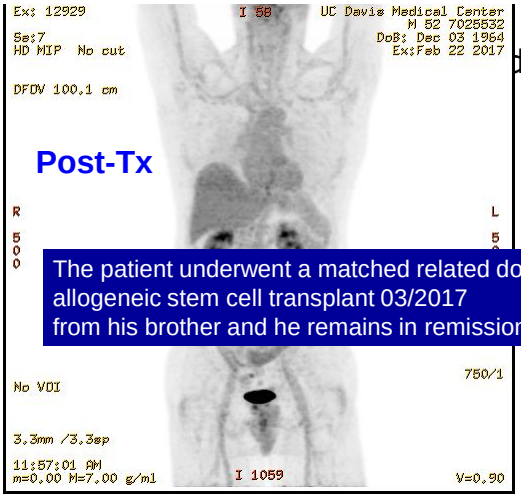
Results

- Clinical Response

Response Category	Intention to treat N (%)	Completed Induction N (%)
ORR	10 (56)	10 (91)
CR	6 (33)	6 (55)
PR	4 (22)	4 (36)
SD	1 6)	1 (9)
PD	4 (22)	0
NE	3 (17)	0

- Median follow-up time: 14.3 months
- 3 patients who achieved response underwent allogeneic stem cell transplant (SCT) and remained in remission 14.2 to 22.3 months thereafter

First Patient to Complete Therapy on 9924



patient was
d autologous stem cell

The patient underwent a matched related donor allogeneic stem cell transplant 03/2017 from his brother and he remains in remission

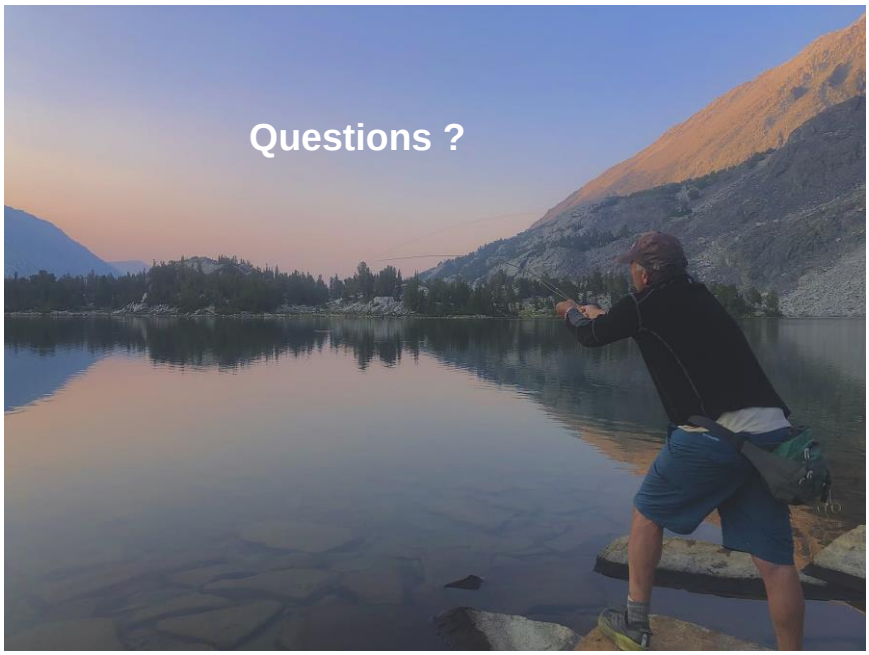
Novel agents in development for DLBCL

Class	Target	Agent	Overall response rate (%)	Complete response rate (%)	Reference
Monoclonal antibody	CD19	tafasitamab + lenalidomide	60	43	Salles et al
Antibody drug conjugates	CD19	loncastuximab tesirine	59	41	Kahl et al
	CD79b	polatuzumab vedotin	52	13	Palanca-Wessels et al
		polatuzumab vedotin + BR versus BR	45 17.5	40 17.5	Sehn et al
Bispecific antibodies	CD19/CD3	blinatumomab	43	19	Viardot et al
	CD20/CD3	mosunetuzumab	35	19	Schuster et al
		glofitamab	38	31	Dickinson et al
Other target inhibitors	BCL2	venetoclax	18	12	Davids et al
	XPO1	selinexor	28	12	Kalakonda et al
Checkpoint inhibitors	PD-1	nivolumab	≤ 10	≤ 3	Ansell et al
	CD47	magrolimab	40	33	Advani et al

Salles et al., Lancet Oncol. 2020; Kahl et al., Clin Cancer Res. 2019; Palanca-Wessels et al., Lancet Oncol. 2015; Sehn et al., JCO 2020; Viardot et al., Blood 2016; Schuster el al., ASH 2019; Dickinson et al., EHA 2020; Davids et al., JCO 2017; Kalakonda et al., Lancet Haematol. 2020; Ansell et al., JCO 2019; Advani et al., N Engl J Med., 2018

Conclusions

- Autologous Stem Cell transplantation remains the SOC for *eligible* patients with R/R DLBCL
- CAR T cell therapy is generally appropriate for R/R DLBCL that have failed AutoPSCT or are not good candidates for AutoPSCT (refractory dz etc)
  - Eligibility for CAR T is evolving (age, PS etc)
  - Insurance approval can be challenging but is getting better
  - Efficacy appears similar between different agents, but longer f/u is needed
  - Polatuzumab, Selinexor, Tafasitamab, and Loncastuximab are all recently FDA approved in R/R DLBCL
  - Tafasitamab's long term f/u data looks promising for responding patients
  - Selinexor has surprising response rates in the most difficult to treat DLBCL patients
    - Needs a partner-? venetoclax
  - No proven superiority for any of these agents
  - Consider for salvage therapy prior to, or after CAR T, in ineligible patients or as bridging therapy
  - Look for many combinations in coming years
  - When considering CD19-targeted therapy in patients relapsing after CD19-targeted CAR T consider a re-Bx to confirm CD19 expression
    - 10-25% will have CD19 loss after CAR T



ANCO

Hematologic Malignancies Update 2021

ACUTE MYELOID LEUKEMIA

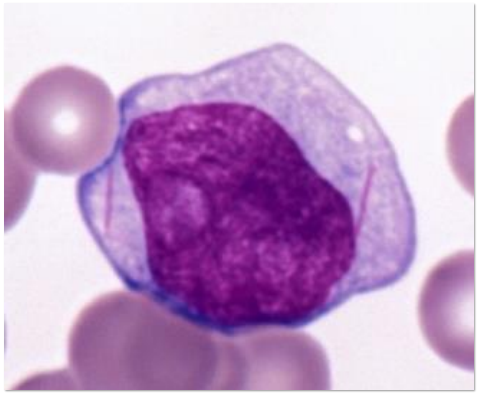
Gabriel N. Mannis, MD
Assistant Professor of Medicine
Division of Hematology
Stanford University
September 11, 2021

Disclosures

- **Consultancy:** AbbVie, Agios, Macrogenics, Pfizer
- **Advisory Role:** AbbVie, Agios, Astellas, BMS/Celegene, Genentech, Stemline
- **Research Funding:** Glycomimetics, Forty Seven/Gilead, Jazz

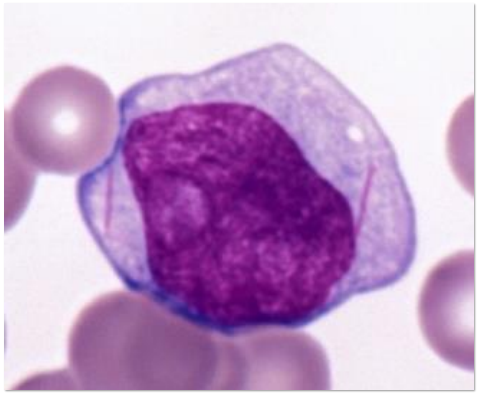
Overview

- **Newly diagnosed AML**
  - Current standard of care
  - Maintenance therapy
  - Future directions
- **Relapsed/refractory AML**
  - Current standard of care
  - Future directions

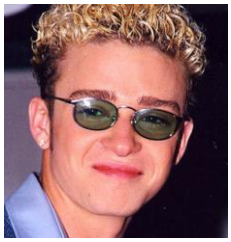


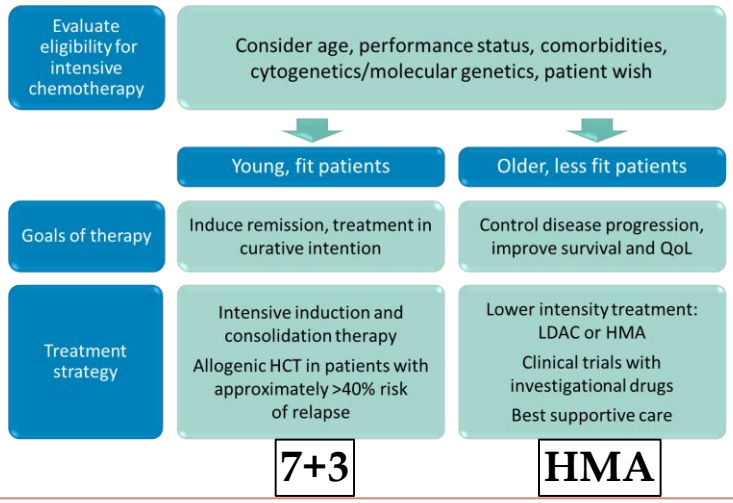
New since May

- **Updates from ASCO/EHA**
- **ASH 2021 preview**
- **New in the literature**
- **More pop culture references**



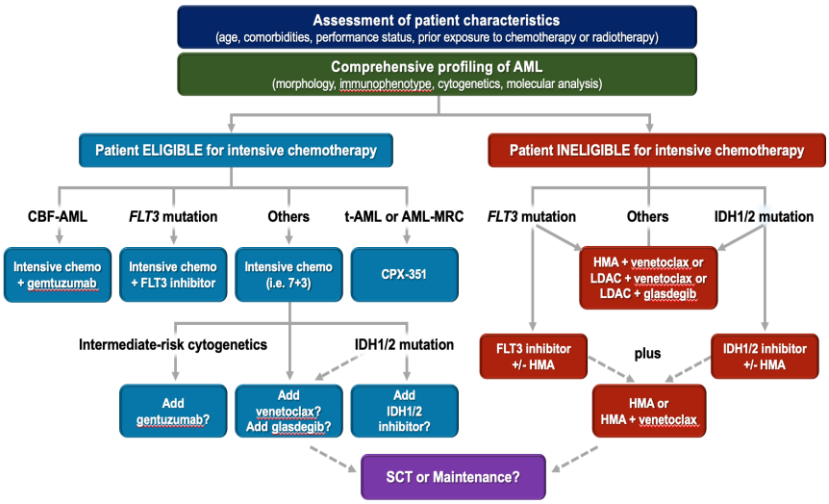
Treatment Paradigm for AML Therapy
(circa 2017)





FLT3
NPM1
CEBPA

Treatment Paradigm for AML Therapy
(2021)



2017-2020: FDA Approvals in AML

04/28/17: Midostaurin (Rydapt; FLT3 inhibitor)

08/01/17: Enasidenib (IDHIFA; IDH2 inhibitor)

08/03/17: Liposomal 7+3 (CPX-351/Vyxeos)

09/01/17: Gemtuzumab ozogamicin (Mylotarg; CD33 Antibody-Drug conjugate)

07/20/18: Ivosidenib (Tibsovo; IDH1 inhibitor)

11/21/18: Venetoclax (Venclexta; BCL2 inhibitor) + HMA/LDAC

11/21/18: Glasdegib (Daurismo; Hedgehog pathway inhibitor) + LDAC

11/28/18: Gilteritinib (Xospata; FLT3 inhibitor)

06/01/20: Oral azacitidine (Onureg; maintenance therapy)

A Simplified Approach

FIT	UNFIT
CURABLE	INCURABLE
ACTIONABLE TARGET	NO ACTIONABLE TARGET

Newly Diagnosed, "Fit" AML

ANCO
Educating and Empowering the Northern California Cancer Community

What defines fitness for intensive induction?

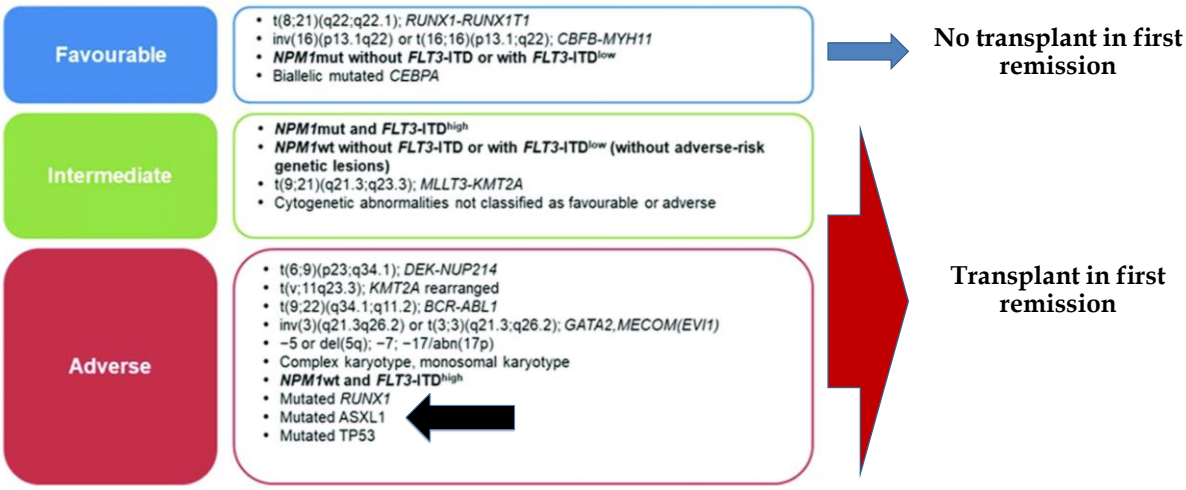
ANCO
Educating and Empowering the Northern California Cancer Community

- Age
  - <75? <65? <55?
- Co-morbidities
- Functional status
- Social support
- Disease biology
  - TP53 mutation
  - Complex/monosomal karyotype

Diagnostic Work-up for "Fit" AML in 2021

Next day	Morphology, Flow cytometry (CD33 expression), FISH for t(15;17)
2-3 days	FISH for inv(16), t(8;21), MDS panel; PCR for FLT3/NPM1/IDH
7-10 days	Conventional karyotyping
2-4 weeks	Next generation sequencing panel (30-500 genes)

ELN 2017 Risk Stratification



Dohner et al, *Blood* 2017

Implications of diagnostic testing for choice of initial therapy

- Midostaurin
- CPX-351
- Gemtuzumab ozogamicin
- Venetoclax-based?

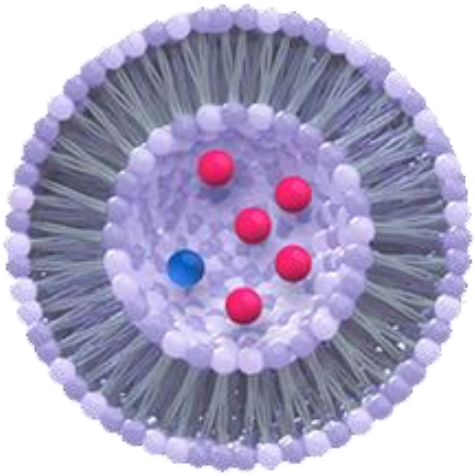
"Fit" AML Induction Therapy in 2021

***FLT3* mutation**	**7+3 + midostaurin**
CBF AML (CD33+)	**7+3 + gemtuzumab**
AML-MRC	**CPX-351***
None of the Above	**7+3 +/- gemtuzumab**

Areas of active investigation

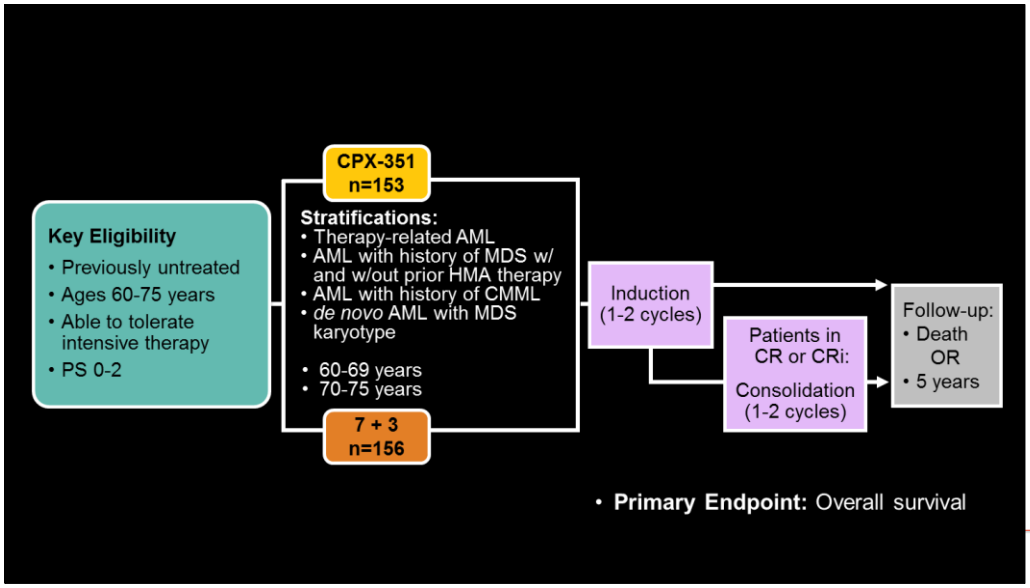
- 7+3 + novel FLT3 inhibitors
- Gemtuzumab for non-CBF favorable/intermediate-risk AML
- 7+3 + IDH inhibitors
- Venetoclax + hypomethylating agents
- *TP53*-mutated AML

CPX-351



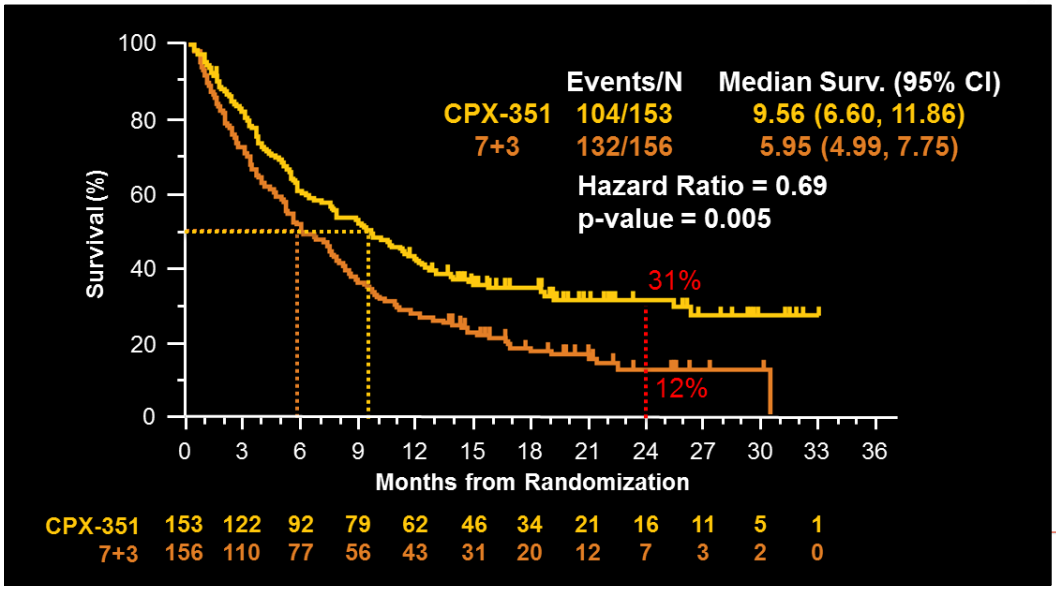
- Liposomal 7+3
- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin

CPX-351



Lancet et al, *JCO* 2018

CPX-351



Median OS:

9.56 months vs 5.95 months (HR 0.69, *P* = .005)

CR:

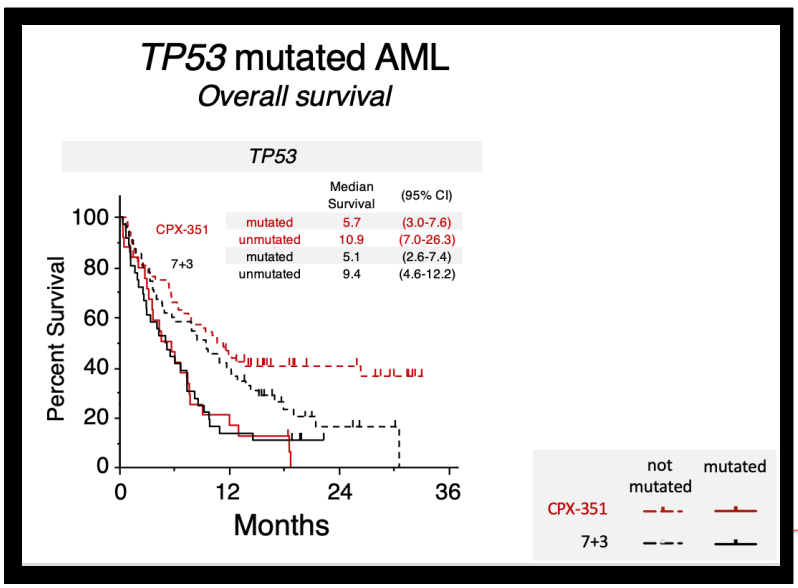
37% vs 26%

CR + CRi:

48% vs 33%

Lancet et al, *JCO* 2018

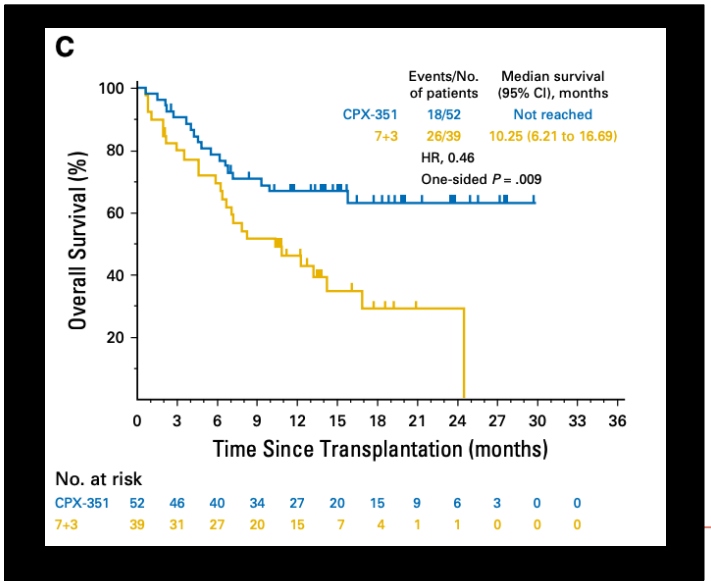
CPX-351



- **No clear benefit relative to 7+3 in *TP53*-mutated AML**
- **More active in "secondary-type" mutations (*SRSF2, U2AF1, SF3B1, ZRSR2, ASXL1, BCOR, EZH2, STAG2*)**
- **Less active in "activated signaling" mutations (*FLT3, NRAS, KRAS, PTPN11, NF1, CBL*)**

Lindsley et al, *ASH* 2019

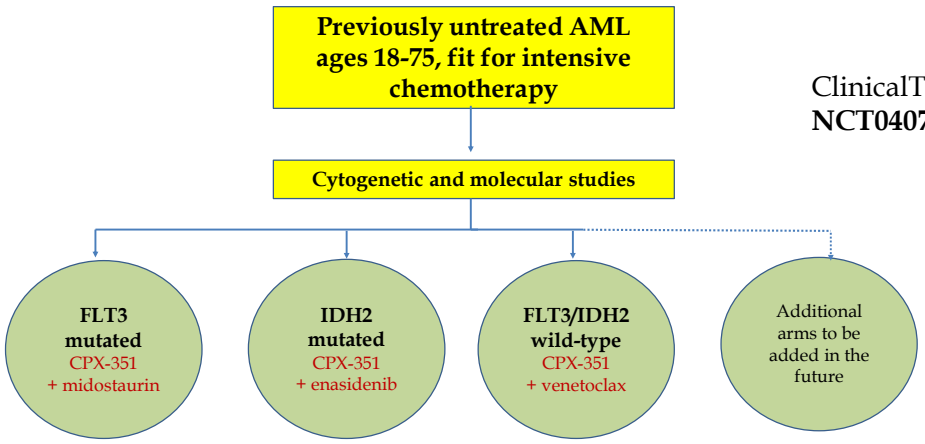
CPX-351



- **Post-transplant median OS not reached**
- **56% reduction in risk of death relative to 7+3**

Lancet et al, *JCO* 2018

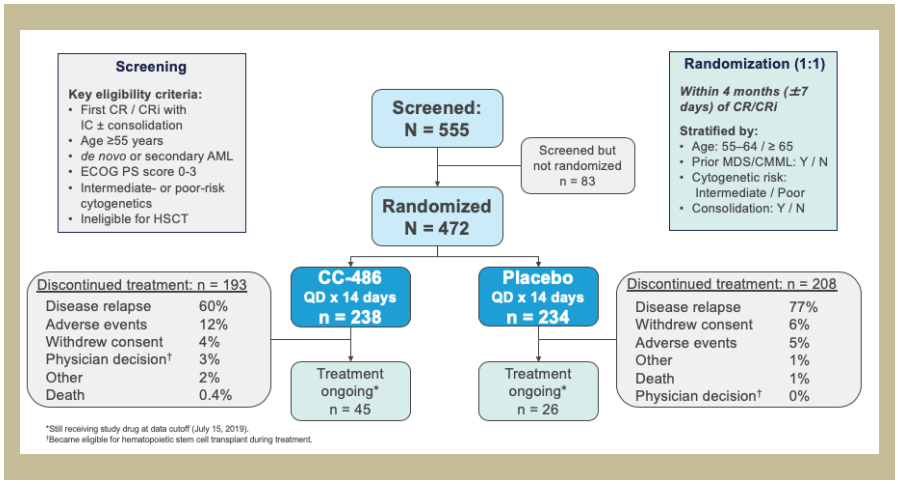
CPX-351: V-FAST Master Trial



ClinicalTrials.gov
NCT04075747

Maintenance Therapy

Oral azacitidine maintenance



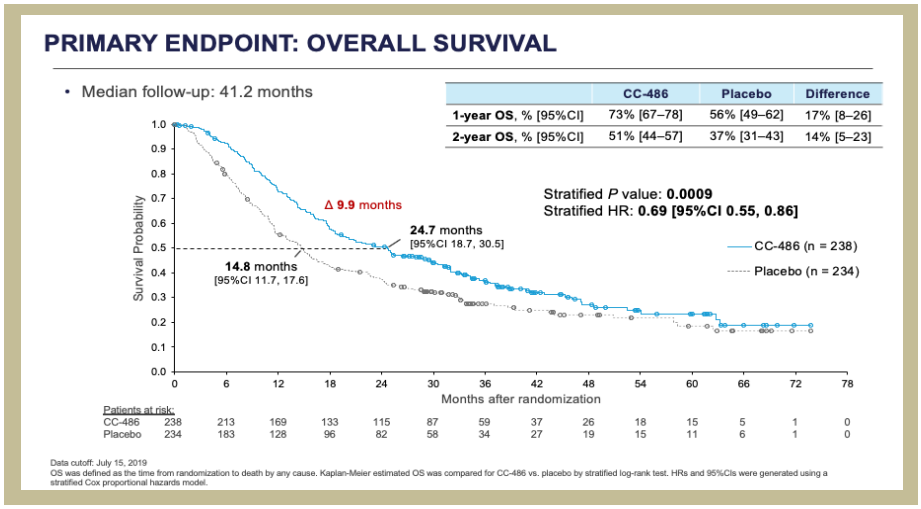
QUAZAR AML-001 Trial

Key eligibility:

- **First CR/CRi after intensive chemotherapy +/- consolidation**
- **Age ≥55**
- **Int/Poor risk**
- **Ineligible for HSCT**

Wei et al, *NEJM* 2020

Oral azacitidine maintenance

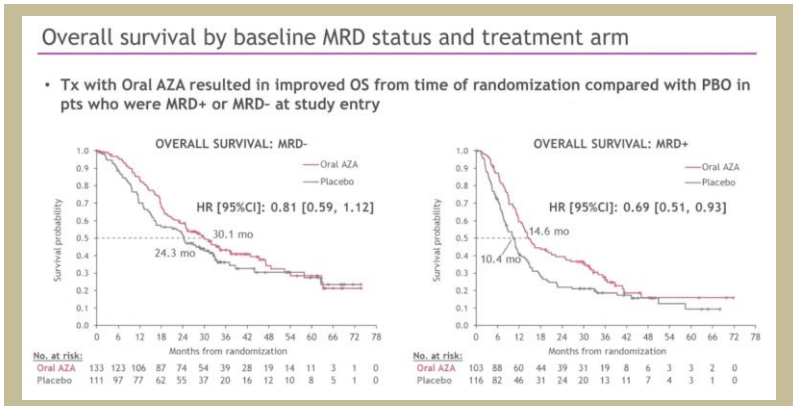


- **Median OS 24.7 vs 14.8 months (P < .001)**
- **Median RFS 10.8 vs 4.8 months (P < .001)**
- **Oral azacitidine is NOT bioequivalent to parenteral azacitidine**

Wei et al, *NEJM* 2020
Roboz et al, *ASH* 2020

Oral azacitidine

CC-486 Prolongs Survival for Patients with Acute Myeloid Leukemia in Remission after Intensive Chemotherapy Independent of the Presence of Measurable Residual Disease at Study Entry: Results from the QUAZAR AML-001 Maintenance Trial



- **At baseline, 44% MRD+ in oral AZA arm vs 51% in placebo arm**
- **Of MRD+ patients, 37% became MRD- in oral AZA arm vs 19% in placebo arm**

Roboz et al, *ASH* 2020

"Unfit" AML Induction Therapy in 2021

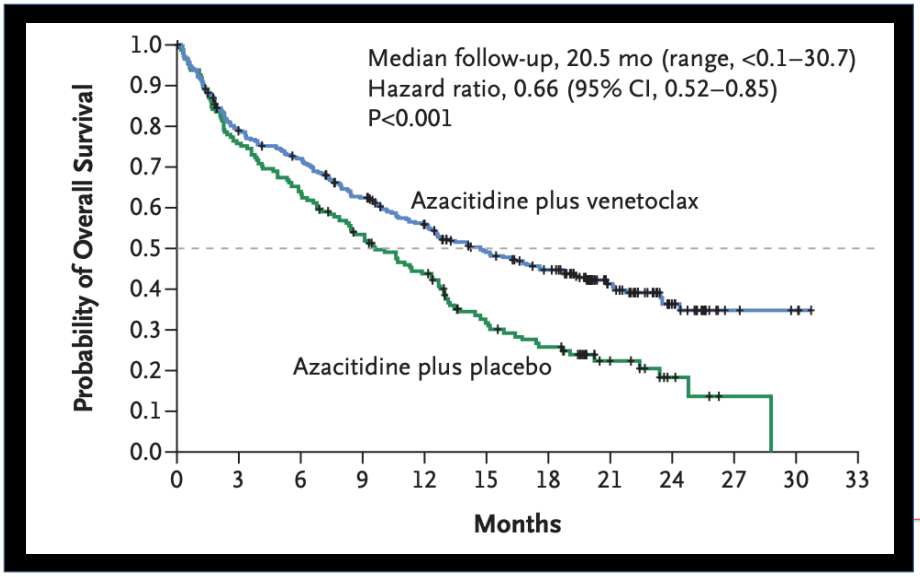
"Unfit" AML Induction Therapy in 2021

- **As defined in trials**
  - 75 years of age or older
  - ECOG 2-3 with LVEF <50%, active CHF, angina, or DLCO/FEV1 <65%
- **As defined in practice**
  - Very subjective

FDA approved frontline agents/combinations

- Venetoclax + Azacitidine/Decitabine/LDAC
- Glasdegib + LDAC
- Ivosidenib

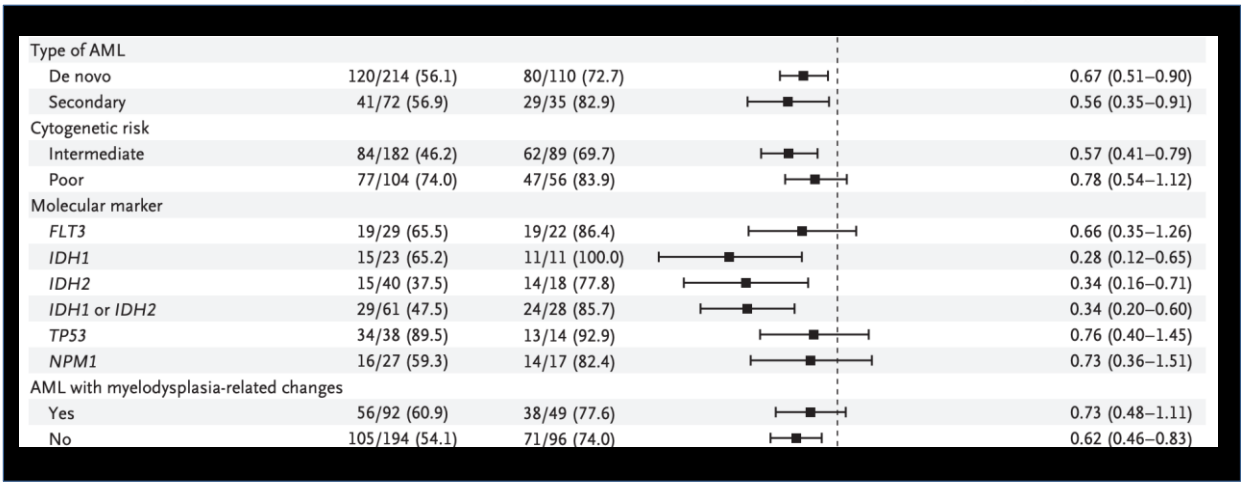
VIALE-A: Venetoclax + Azacitidine



- **433 patients randomized**
- **Median OS 14.7 vs 9.6 months (HR 0.66, *P* <.001)**
- **Median time to response 1.3 months vs 2.8 months**
- **Median duration of response 17.5 months vs 13.4 months**

DiNardo et al, *NEJM* 2020

VIALE-A: Venetoclax + Azacitidine

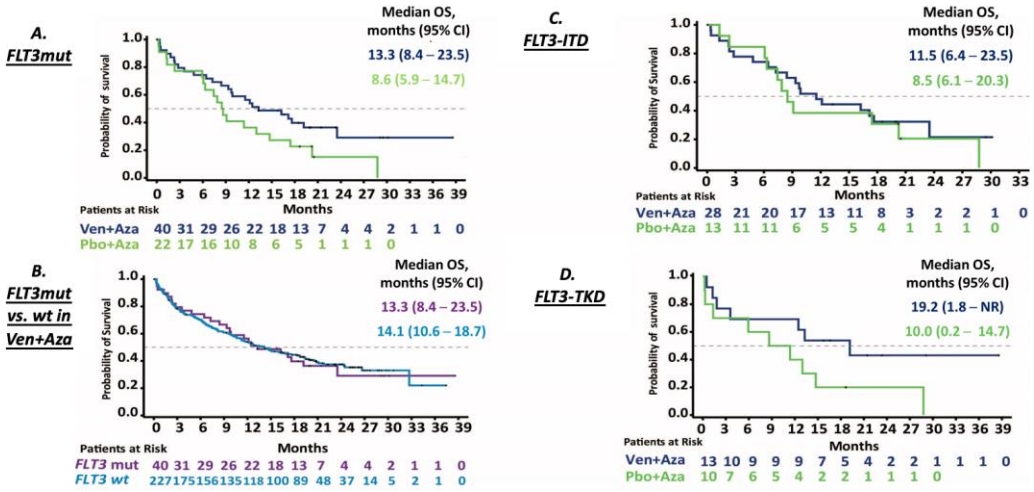


Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51–0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35–0.91)
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41–0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54–1.12)
Molecular marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)	0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16–0.71)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)	0.34 (0.20–0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36–1.51)
AML with myelodysplasia-related changes			
Yes	56/92 (60.9)	38/49 (77.6)	0.73 (0.48–1.11)
No	105/194 (54.1)	71/96 (74.0)	0.62 (0.46–0.83)

Areas of active investigation: FLT3i+ HMA, IDHi+ HMA, *TP53*-active agents, triplets

DiNardo et al, *NEJM* 2020

Impact of FLT3 on Ven/HMA response

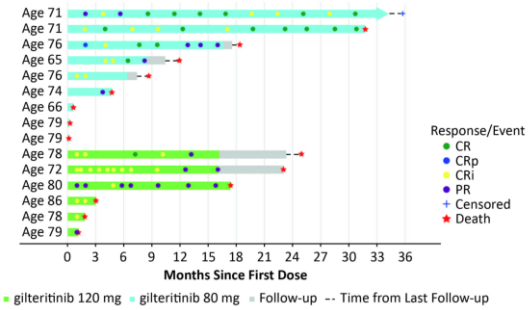


Konopleva et al, *ASH* 2020

Gilteritinib + Azacitidine

Phase 3, Multicenter, Open-Label Study of Gilteritinib, Gilteritinib Plus Azacitidine, or Azacitidine Alone in Newly Diagnosed *FLT3* Mutated (*FLT3*$^{mut+}$) Acute Myeloid Leukemia (AML) Patients Ineligible for Intensive Induction Chemotherapy

Figure. Treatment Response and Duration of Gilteritinib in Combination with Azacitidine in the Safety Cohort (n=15)



Phase 3 LACEWING Trial Fails to Meet Primary End Point of OS in Newly Diagnosed FLT3+ AML

December 21, 2020
Hannah Slater

Based on the recommendation of an independent data monitoring committee, Astellas has halted enrollment in the trial and is reviewing the results for further actions needed.

The phase 3 LACEWING trial of the FMS-like tyrosine kinase 3 (FLT3) inhibitor gilteritinib (Xospata) plus azacitidine versus azacitidine alone in patients with newly diagnosed *FLT3* mutation-positive acute myeloid leukemia (AML) who were ineligible for intensive induction chemotherapy did not meet its primary end point of overall survival (OS) at a planned interim analysis, according to Astellas Pharma, the developer of the agent.[1]

Based on these results, an independent data monitoring committee recommended the study be terminated for futility, citing that the results are unlikely to demonstrate a statistically significant increase in OS. Astellas indicated it has since halted enrollment in the trial and is reviewing the results for other action as needed.

Wang et al, *ASH* 2020

2021 ASCO ANNUAL MEETING

VENETOCLAX AND AZACITIDINE COMBINATION IN CHEMOTHERAPY INELIGIBLE UNTREATED PATIENTS WITH THERAPY-RELATED ACUTE MYELOID LEUKEMIA, ANTECEDENT MYELODYSPLASTIC SYNDROMES OR CHRONIC MYELOMONOCYTIC LEUKEMIA

Vinod Pullarkat M.D.[1], Keith W. Pratz M.D.[2], Hartmut Döhner M.D.[3], Christian Recher M.D.[4], Michael J. Thirman M.D [5], Courtney D. DiNardo M.D. [6], Pierre Fenaux M.D. [7], Andre C. Schuh M.D. [8], Andrew H. Wei M.D.[9], Arnaud Pigneux M.D. [10], Jun-Ho Jang M.D. [11], Gunnar Juliusson M.D. [12], Yasushi Miyazaki M.D. [13], Dominik Selleslag M.D. [14], Martha L. Arellano M.D. [15], Kiran Naqvi M.D. [16] Jun Yu Ph.D [17], Jean A. Ridgeway DNP, NP-C [17], Jalaja Potluri M.D. [17], Marina Konopleva M.D.[6]

[1]Department of Hematology and Hematopoietic Cell Transplantation and Gehr Family Center for Leukemia Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [2]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [3]Department of Internal Medicine III, Ulm University Hospital, Ulm, Germany; [4]Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [5]Section of Hematology/Oncology, Department of Medicine, The University of Chicago Medicine, Chicago, IL, USA; [6]Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]Hôpital St. Louis /Assistance Publique- Hôpitaux de Paris and Université de Paris, France; [8]Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [9]Australian Center for Blood Diseases, The Alfred Hospital and Monash University, Melbourne, Australia, [10]Department of Hematology, CHU de Bordeaux, France; [11]Department of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [12]Department of Hematology, Skåne University Hospital, Lund, Sweden; [13]Department of Hematology, Atomic Bomb Disease and Hibakusha Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan; [14]Algemeen Ziekenhuis Sint-Jan, Brugge, Belgium; [15]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA; [16]Genentech Inc., South San Francisco, CA, USA; [17]AbbVie Inc., North Chicago, IL, USA

4

Methods and patient categorization

Design:
Pooled analysis of patients enrolled in the randomized phase 3 VIALE-A trial **(NCT02993523)** and a prior phase 1b trial **(NCT02203773)**

Key patient inclusion criteria:
- Treatment-naïve AML patients with co-morbidities and/or age ≥ 75 years[1]
- Ineligible for intensive chemotherapy

Key patient exclusion criteria:
- No prior exposure to hypomethylating agents
- Patients with history of myeloproliferative neoplasm including myelofibrosis, essential thrombocytosis, polycythemia vera, chronic myeloid leukemia with or without *BCR-ABL1* translocation, and AML with *BCR-ABL1* translocation
- Patients with favorable-risk cytogenetics

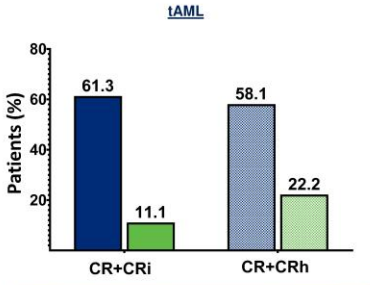
Key outcomes evaluated:
CR+CRi, CR+CRh, DoR, OS

Patient categorization	Ven+Aza			Pbo+Aza
	Viale-A (N=286)	Phase 1b (N=67)	Total (N=353)	Viale-A (N=145)
			Included in this analysis	
Therapy-related AML, n (%)	26 (9.1)	5 (7.5)	**31 (8.8)**	**9 (6.2)**
Antecedent MDS/CMML, n (%)	46 (16.1)	13 (19.4)	**59 (16.7)**	**26 (17.9)**
Antecedent MDS[2]	39 (13.6)	13 (19.4)	52 (14.7)	24 (16.6)
Antecedent CMML	7 (2.4)	0	7 (2.0)	2 (1.4)

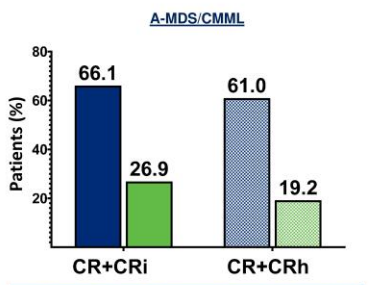
Data cutoff: Viale-A-Jan 04, 2020; phase 1b study-Jul 19, 2019
[1]Includes therapy-related patients with AML who were not previously treated for AML; [2]Antecedent MDS is any-time before transformation to AML
A-MDS/CMML: antecedent myelodysplastic syndrome or chronic myelomonocytic leukemia ; Aza: Azacitidine; CR: Complete remission; CRi: CR with incomplete hematologic recovery; CRh: CR with partial hematologic recovery; DoR: Duration of response; OS: Overall survival; Pbo: Placebo; Ven: Venetoclax; tAML: therapy-related acute myeloid leukemia;

6

Response rates and duration of response



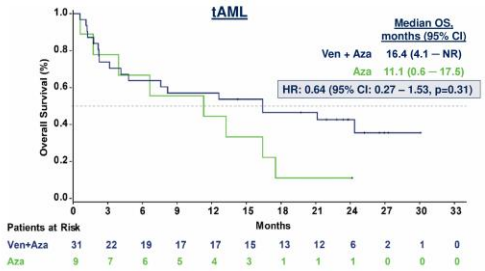
Median duration of response, months (95% CI)				
	n	CR+CRi	n	CR+CRh
Ven+Aza	19	NR (17.8, NR)	18	NR (17.8, NR)
Aza	1	8.5 (-)	2	4.6 (0.5, NR)

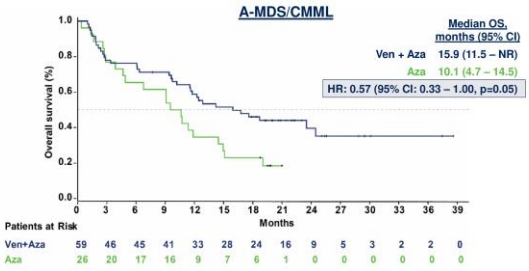


Median duration of response, months (95% CI)				
	n	CR+CRi	n	CR+CRh
Ven+Aza	39	17.3 (9.6, NR)	36	17.4 (10.6, NR)
Aza	7	5.8 (1.1, NR)	5	15.6 (1.1, NR)

Note: Patients with tAML received a median (Ven+Aza/Aza) of 5/4 cycles of treatment and patients with A-MDS/CMML received a median (Ven+Aza/Aza) of 9/5 cycles of treatment.
CR was defined as absolute neutrophil count >10^3/µL, platelets >10^5/µL, red cell transfusion independence (TI), and bone marrow with <5% blasts; CRi was defined as all criteria for CR, except for neutropenia ≤10^3/µL or thrombocytopenia ≤10^5/µL. CRh was defined as all the criteria for CR, except for neutropenia >0.5 X10^3/µL, and platelets >0.5 x 10^5 /µL.
Aza: Azacitidine; CR: Complete remission; CRi: CR with incomplete hematologic recovery; CRh: CR with partial hematologic recovery; Pbo: Placebo; Ven: Venetoclax; NR: Not reached

Overall survival





Median OS 16.4 months vs 11.1 months **Median OS 15.9 months vs 10.1 months**

2021 ASCO ANNUAL MEETING

MEASURABLE RESIDUAL DISEASE RESPONSE AND PROGNOSIS IN ACUTE MYELOID LEUKEMIA WITH VENETOCLAX AND AZACITIDINE

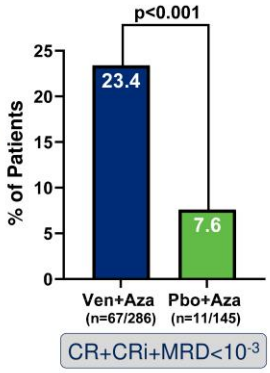
Keith W. Pratz[1], Brian A. Jonas[2], Vinod Pullarkat[3], Christian Recher[4], Andre C. Schuh[5], Michael J. Thirman[6], Jacqueline S. Garcia[7], Courtney D. DiNardo[8], Vladimir Vorobyev[9], Nicola S. Fracchiolla[10], Su-Peng Yeh[11], Jun Ho Jang[12], Muhit Ozcan[13], Kazuhito Yamamoto[14], Arpad Illes[15], Ying Zhou[16], Monique Dail[17], Brenda Chyla[16], Jalaja Potluri[16], Hartmut Döhner[18]

[1]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA, [2]Department of Internal Medicine, Division of Hematology and Oncology, University of California Davis School of Medicine, Sacramento, CA, USA, [3]Department of Hematology and Hematopoietic Cell Transplantation and Gehr Family Center for Leukemia Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA [4]Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [5]Department of Medical Oncology and Hematology, Princess Margaret Cancer Center, Toronto, Ontario, Canada, [6]Section of Hematology/Oncology, Department of Medicine, The University of Chicago Medicine, Chicago, IL, USA, [7]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, [8]Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [9]Department of Hematology, S. P. Botkin City Clinical Hospital, Moscow, Russia, [10]UOC Ematologia, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy, [11]Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan, [12]Department of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, [13]Department of Hematology, Ankara University School of Medicine, Ankara, Turkey, [14]Department of Hematology and Cell Therapy, Aichi Cancer Center Hospital, Nagoya, Japan, [15]University of Debrecen, Faculty of Medicine, Department of Hematology, Debrecen, Hungary, [16]AbbVie Inc., North Chicago, IL, USA, [17]Genentech Inc., South San Francisco, CA, USA, [18]Department of Internal Medicine III, University Hospital, Ulm, Germany

3

Introduction

- The VIALE-A trial demonstrated that the combination of venetoclax (Ven) and azacitidine (Aza) led to a significant improvement in composite complete remission* and measurable residual disease (MRD) response ($<10^{-3}$) as compared to Aza alone.[1]
- There is limited evidence in the literature of the clinical significance of MRD monitoring in treatment-naive patients ineligible for intensive induction chemotherapy.

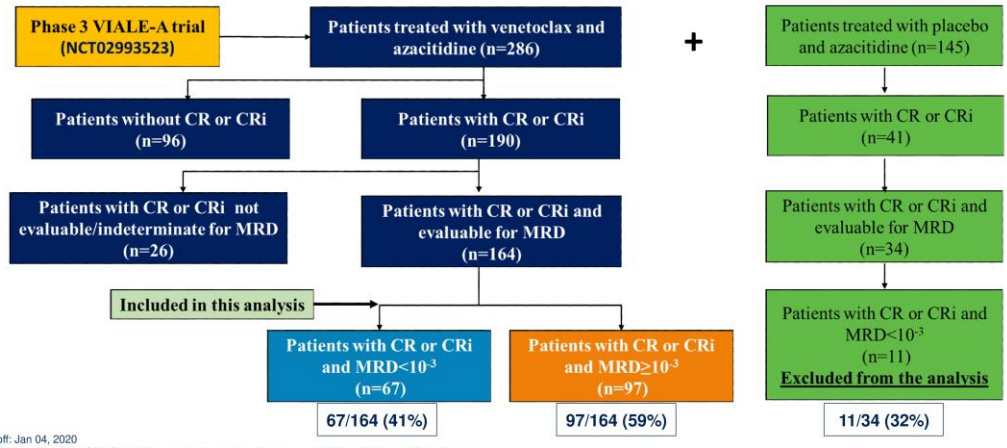


Objective: Evaluate the prognostic impact of MRD$<10^{-3}$ on outcomes among patients with AML treated with lower-intensity chemotherapy.

*Composite complete remission (CRc) is defined as complete remission (CR) + CR with incomplete hematologic recovery (CRi), AML: Acute myeloid leukemia; Pbo: Placebo
[1]DiNardo et al., *NEJM*, 2020

5

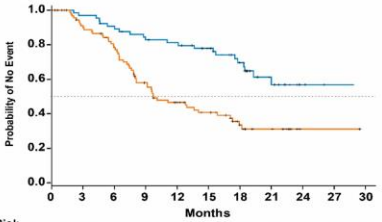
Analyzed patient population



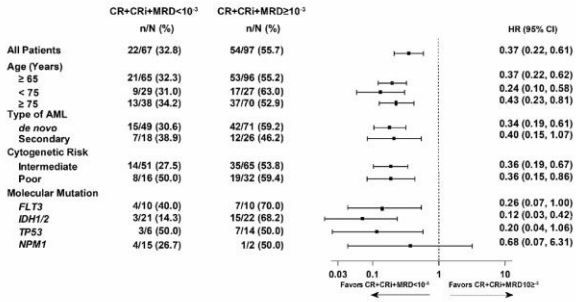
Data cutoff: Jan 04, 2020
CR: Complete remissions, CRi: CR with incomplete hematological recovery; MRD: Minimal residual disease
Patients were indeterminate if the BM samples had less than a hundred thousand CD45+ leukocytes

7

Duration of remission



Patients at Risk											
CR+CRi+MRD<10^{-3}	67	63	58	52	50	44	30	14	3	1	0
CR+CRi+MRD≥10^{-3}	97	80	67	46	34	27	14	9	1	1	0

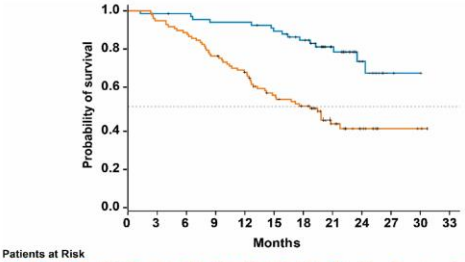


Duration of remission	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median DoR, months (95% CI)
CR+CRi+MRD<10^{-3}	22	81.2 (69.3, 88.9)	69.6 (55.9, 79.8)	NR (19.3 – NR)
CR+CRi+MRD≥10^{-3}	54	46.6 (35.6, 56.8)	33.5 (22.9, 44.5)	9.7 (8.0 – 15.8)

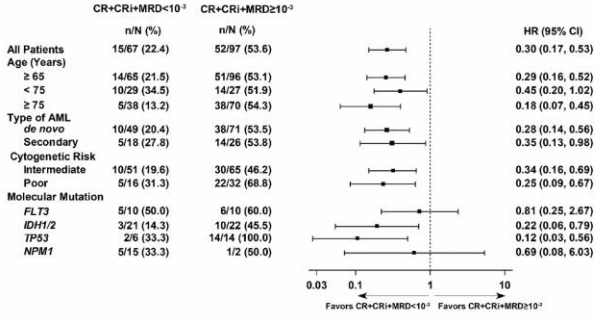
Patients who attained an MRD response at any time received a median treatment of 16·0 (range: 1·0 — 28·0) cycles with Ven+Aza; patients with MRD≥10^{-3} received a median of 9·0 (range: 2·0 — 30·0) cycles .
The median follow-up was 22·1 (range: 1·3— 30·1) months in patients with MRD<10^{-3} and 20·8 (range: 2·3 — 30·7) months in patients with MRD ≥10^{-3}.
Duration of remission for CRc was defined as the number of days from the date of first response (CR or CRi) per the modified IWG criteria for AML to the earliest evidence of confirmed morphologic relapse, confirmed progressive disease, or death due to disease progression.
NR: Not reached

9

Overall survival



Patients at Risk											
CR+CRi+MRD<10^{-3}	67	66	65	62	62	58	52	30	13	2	1	0
CR+CRi+MRD≥10^{-3}	97	92	86	74	64	49	42	21	10	3	2	0

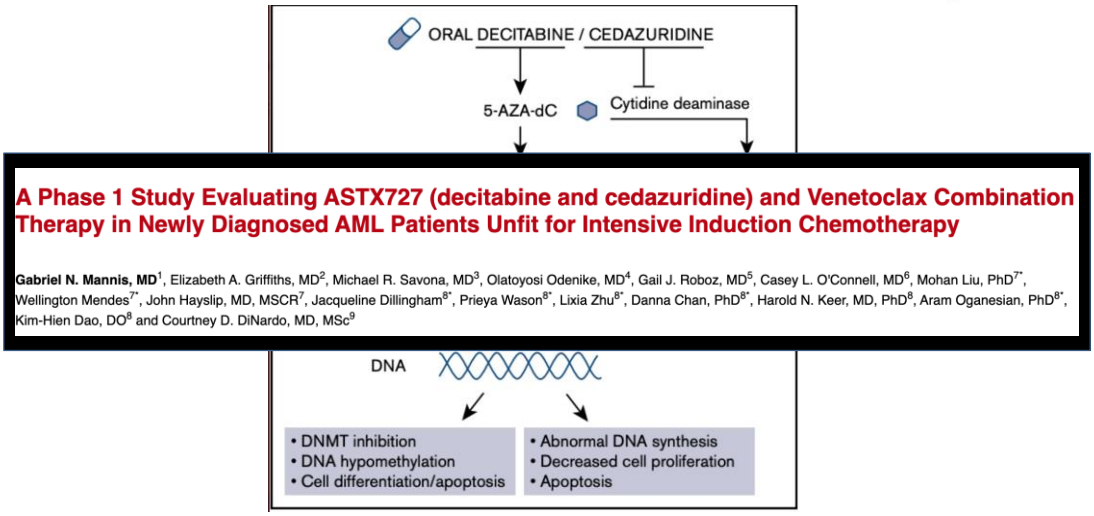


Overall survival	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median OS, months (95% CI)
CR+CRi+MRD<10^{-3}	15	94.0 (84.7, 97.7)	84.6 (73.3, 91.4)	NR (24.4 – NR)
CR+CRi+MRD≥10^{-3}	52	67.9 (57.6, 76.2)	50.1 (39.6, 59.8)	18.7 (12.9 — NR)

OS was defined as the time from randomization to the date of death from any cause.
AML: Acute myeloid leukemia; CI: Confidence interval; HR: Hazard ratio; NR: Not reached

Multivariate Cox regression analysis for overall survival		
Covariate	**Adjusted HR (95% CI)**	**P Value**
MRD response group (MRD<10^{-3} vs. MRD≥10^{-3})	0.285 (0.159, 0.510)	**<0.001**
Age group (≥75 years vs. <75 years)	0.884 (0.532, 1.467)	0.632
AML type (*de novo* vs. secondary)	1.004 (0.587, 1.716)	0.989
Cytogenetic risk (poor vs. intermediate)	2.062 (1.260, 3.374)	**0.004**

Oral HMA + Ven?



A Phase 1 Study Evaluating ASTX727 (decitabine and cedazuridine) and Venetoclax Combination Therapy in Newly Diagnosed AML Patients Unfit for Intensive Induction Chemotherapy

Gabriel N. Mannis, MD[1], Elizabeth A. Griffiths, MD[2], Michael R. Savona, MD[3], Olatoyosi Odenike, MD[4], Gail J. Roboz, MD[5], Casey L. O'Connell, MD[6], Mohan Liu, PhD[7*], Wellington Mendes[7*], John Hayslip, MD, MSCR[7], Jacqueline Dillingham[8*], Prieya Wason[8*], Lixia Zhu[8*], Danna Chan, PhD[8*], Harold N. Keer, MD, PhD[8], Aram Oganesian, PhD[8*], Kim-Hien Dao, DO[8] and Courtney D. DiNardo, MD, MSc[9]

Magrolimab + Azacitidine

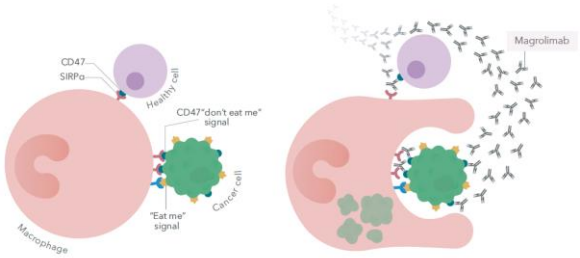
The First-in-Class Anti-CD47 Antibody Magrolimab Combined With Azacitidine Is Well Tolerated and Effective in AML Patients: Phase 1b Results

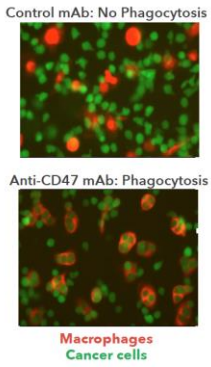
David A. Sallman[1], Adam S. Asch[2], Suman Kambhampati[3], Monzr M. Al Malki[4], Joshua F. Zeidner[5], William Donnellan[6], Daniel J. Lee[7], Paresh Vyas[8], Deepa Jeyakumar[9], Gabriel N. Mannis[10], Tiffany N. Tanaka[11], Wanxing Chai-Ho[12], Richard A. Larson[13], Andrew R. Whiteley[14], Guido Marcucci[4], Rami S. Komrokji[1], Guillermo Garcua-Manero[15], Joanna Van Elk[16], Ming Lin[16], Roy Maute[16], Jens-Peter Volkmer[16], Chris H. Takimoto[16], Mark P. Chao[16], and Naval G. Daver[15]

Sallman et al, *ASH* 2020

Magrolimab + Azacitidine

Magrolimab (Formerly 5F9) Is a First-in-Class Macrophage Immune Checkpoint Inhibitor Targeting CD47





- CD47 is a "do not eat me" signal that is overexpressed in multiple cancers, including acute myeloid leukemia, leading to macrophage immune evasion
- Magrolimab, an IgG4 anti-CD47 monoclonal antibody, eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dosed

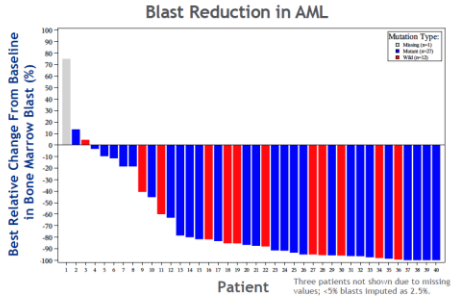
Sallman et al, *ASH* 2020

Magrolimab + Azacitidine

Magrolimab + AZA Induces High Response Rates in AML

Best Overall Response	All AML (N=43)	*TP53* mutant AML (29)
ORR	27 (63%)	20 (69%)
CR	18 (42%)	13 (45%)
CRi	5 (12%)	4 (14%)
PR	1 (2%)	1 (3%)
MLFS	3 (7%)	2 (7%)
SD	14 (33%)	8 (28%)
PD	2 (5%)	1 (3%)

Response assessments per 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown



Three patients not shown due to missing values; <5% blasts imputed as 2.5%.

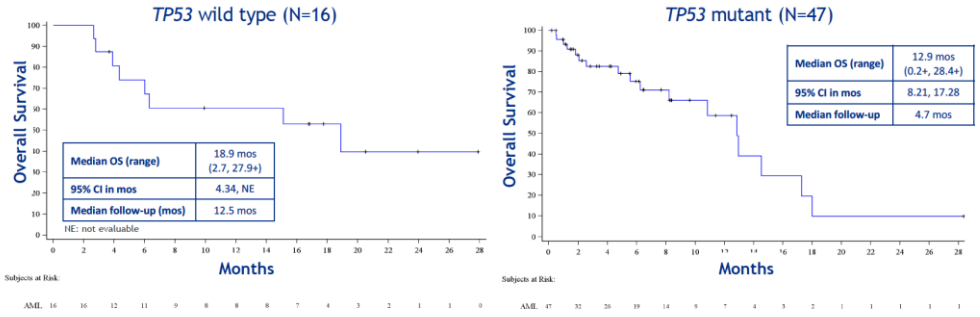
- Magrolimab + AZA induces a 63% ORR and 42% CR rate in AML including similar responses in *TP53*-mutant patients
- Median time to response is 1.95 months (range 0.95 to 5.6 mo), more rapid than AZA monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 18%-20%[1,2])

1. Fenaux P, et al. *J Clin Oncol*. 2010;28(4):562-569. 2. Dombret H, et al. *Blood*. 2015;126(3):291-299.

Sallman et al, *ASH* 2020

Magrolimab + Azacitidine

Preliminary Median Overall Survival is Encouraging in both *TP53* Wild Type and Mutant Patients

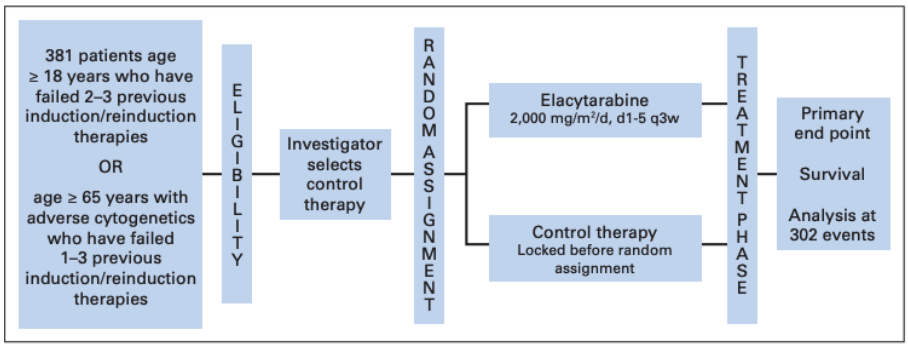


- The median OS is 18.9 months in *TP53* wild type patients and 12.9 months in *TP53* mutant patients
- This initial median OS data may compare favorably to venetoclax + hypomethylating agent combinations (14.7-17.5 mo in all-comers[1,3], 5.2-7.2 mo in *TP53* mutant[2,3])
- Additional patients and longer follow-up are needed to further characterize the survival benefit

Sallman et al, *ASH* 2020

Relapsed/Refractory AML

The Challenge of R/R AML



Elacytarabine vs Investigator's choice
(HiDAC, MEC, FLAG-Ida, HMA/LDAC, Hydroxyurea, Palliative Care)

Roboz et al, *JCO* 2014

The Challenge of R/R AML

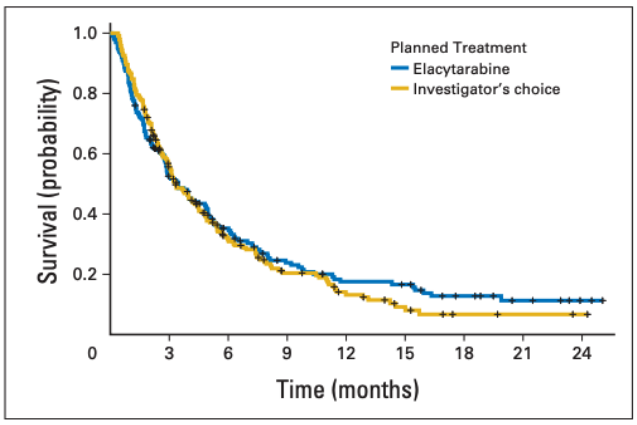
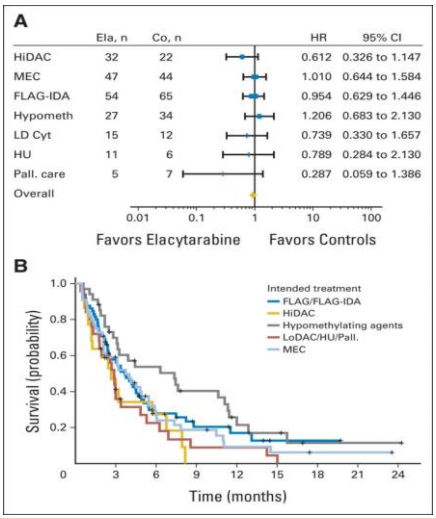


Fig 3. Overall survival estimates in the intention-to-treat population of elacytarabine versus investigator's choice by Kaplan-Meier test.



Roboz et al, *JCO* 2014

The Challenge of R/R AML

Have outcomes improved over time? **NO**

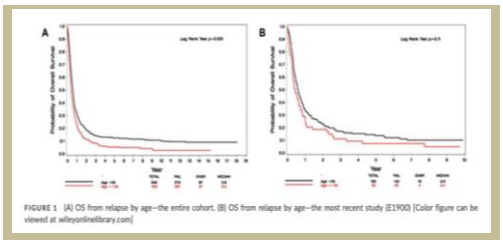
Received: 15 February 2018 | Revised: 29 May 2018 | Accepted: 29 May 2018
DOI: 10.1002/ajh.25162

RESEARCH ARTICLE

WILEY AJH

Very poor long-term survival in past and more recent studies for relapsed AML patients: The ECOG-ACRIN experience

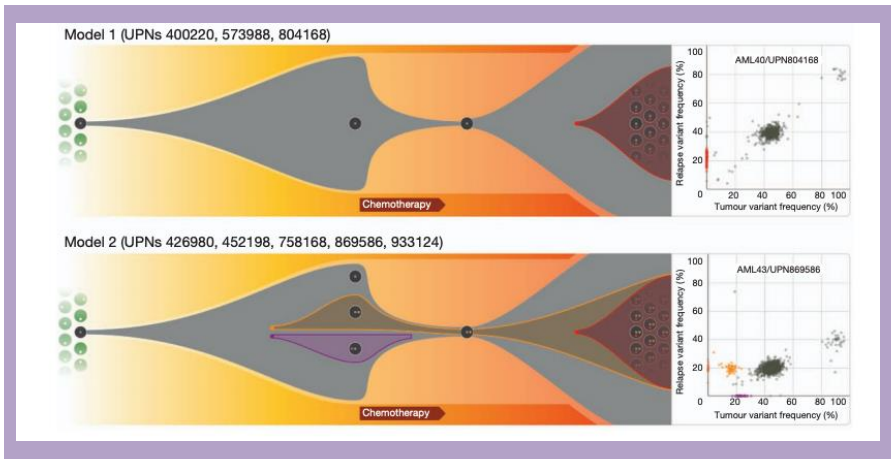
Chezi Ganzel[1] | Zhuoxin Sun[2] | Larry D. Cripe[3] | Hugo F. Fernandez[4] | Dan Douer[5] | Jacob M. Rowe[1,6] | Elisabeth M. Paietta[7] | Rhett Ketterling[8] | Michael J. O'Connell[8] | Peter H. Wiernik[9] | John M. Bennett[10] | Mark R. Litzow[8] | Selina M. Luger[11] | Hillard M. Lazarus[12] | Martin S. Tallman[5]



- **3012 newly diagnosed AML patients enrolled in 9 consecutive ECOG-ACRIN trials (1984-2008)**
- **1779 (59.1%) achieved CR1; of those 1048 (58.9%) relapsed**
- **Median OS from relapse = 0.5 years**
- **5 year OS = 10%**

Ganzel et al, *AJH* 2018

R/R AML: Mechanistic considerations



Re-emergence of the dominant clone

Expansion of a minor clone

Highlights the importance of repeating mutational testing at relapse

Ding et al, *Nature* 2012

R/R AML: Therapeutic options

NCCN Guidelines Version 2.2020
Acute Myeloid Leukemia (Age ≥18 years)

- CBC, platelets every 1–3 mo for 2 y, then every 3–6 mo up to 5 y
- Bone marrow aspirate and biopsy only if peripheral smear is abnormal or cytopenias develop
- Donor search should be initiated at first relapse in appropriate patients concomitant with institution of other therapy if no sibling donor has been identified

→ Relapse[z,fff] → Determine mutation status of actionable genes: *FLT3* (ITD or TKD), *IDH1*, *IDH2* →

Options:
Clinical trial (strongly preferred)
or
Targeted therapy (see AML-H) followed by matched sibling or alternative donor HCT
or
Chemotherapy[ggg] (see AML-H) followed by matched sibling or alternative donor HCT
or
Repeat initial successful induction regimen[hhh] if ≥12 months since induction regimen
or
Best supportive care (see NCCN Guidelines for Palliative Care)

R/R AML: Therapeutic options

NCCN Guidelines Version 2.2020
Acute Myeloid Leukemia (Age ≥18 years)

THERAPY FOR RELAPSED/REFRACTORY DISEASE[1]

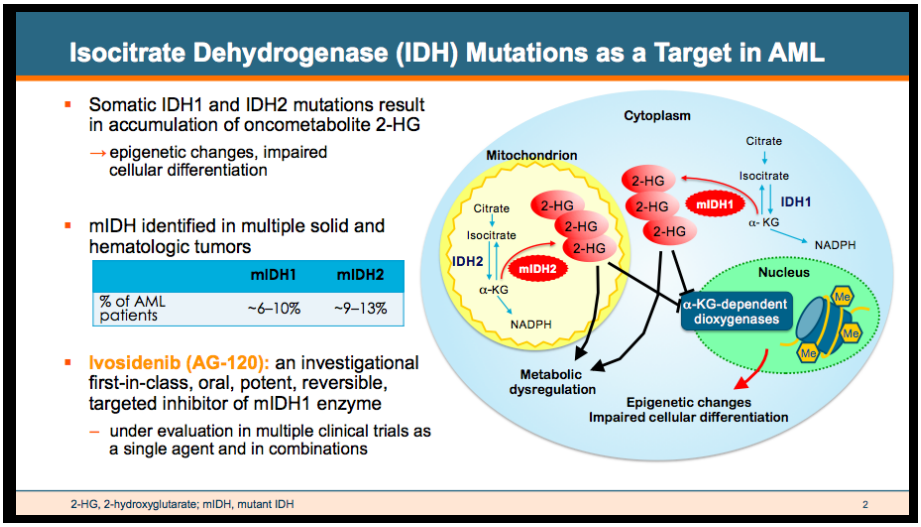
Clinical trial[1]

Targeted therapy:
- Therapy for AML with *FLT3*-ITD mutation
  - Gilteritinib[2] (category 1)
  - Hypomethylating agents (azacitidine or decitabine) + sorafenib[3,4]
- Therapy for AML with *FLT3*-TKD mutation
  - Gilteritinib[2] (category 1)
- Therapy for AML with *IDH2* mutation
  - Enasidenib[5]
- Therapy for AML with *IDH1* mutation
  - Ivosidenib[6]
- Therapy for CD33-positive AML
  - Gemtuzumab ozogamicin[7]

Aggressive therapy for appropriate patients:
- Cladribine + cytarabine + G-CSF ± mitoxantrone or idarubicin[8,9]
- HiDAC (if not received previously in treatment) ± (idarubicin or daunorubicin or mitoxantrone)
- Fludarabine + cytarabine + G-CSF ± idarubicin[10,11]
- Etoposide + cytarabine ± mitoxantrone[12]
- Clofarabine ± cytarabine + G-CSF ± idarubicin[13,14]

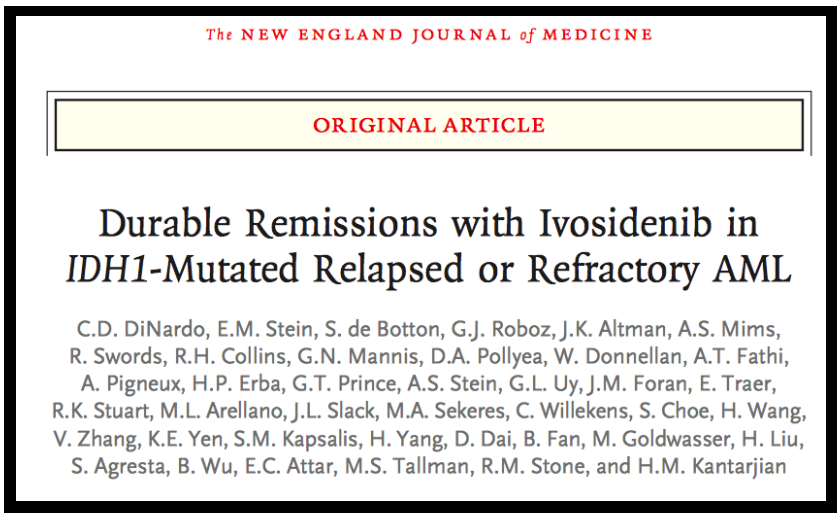
Less aggressive therapy:
- Hypomethylating agents (azacitidine or decitabine)
- Low-dose cytarabine (category 2B)
- Venetoclax + HMA/LDAC[15,16]

Targeted agents: IDH inhibitors



DiNardo et al, *ASH* 2017

Targeted agents: IDH inhibitors



DiNardo et al, *NEJM* 2017

Targeted agents: IDH inhibitors

Response in R/R AML (n=125)

	Primary R/R AML Set (n=125)
CR+CRh rate, n (%) [95% CI]	**38 (30.4%) [22.5, 39.3]**
Time to CR/CRh, median (range) months	2.7 (0.9, 5.6)
Duration of CR/CRh, median [95% CI] months	8.2 [5.5, 12.0]
CR rate, n (%) [95% CI]	27 (21.6%) [14.7, 29.8]
Time to CR, median (range) months	2.8 (0.9, 8.3)
Duration of CR, median [95% CI] months	9.3 [5.6, 18.3]
CRh rate, n (%)	11 (8.8%)
Overall Response Rate, n (%) [95% CI]	**52 (41.6%) [32.9, 50.8]**
Time to first response, median (range) months	1.9 (0.8, 4.7)
Duration of response, median [95% CI] months	6.5 [4.6, 9.3]

- **CR+CRh 30.4%**
- **ORR 41.6%**
- **Median time to CR 2.8 months**
- **Median duration of CR 9.3 months**

DiNardo et al, *NEJM* 2017

Targeted agents: IDH inhibitors

Table 2. Treatment-Related Adverse Events of Grade 3 or Higher Occurring in More than 1% of the Overall Population.*

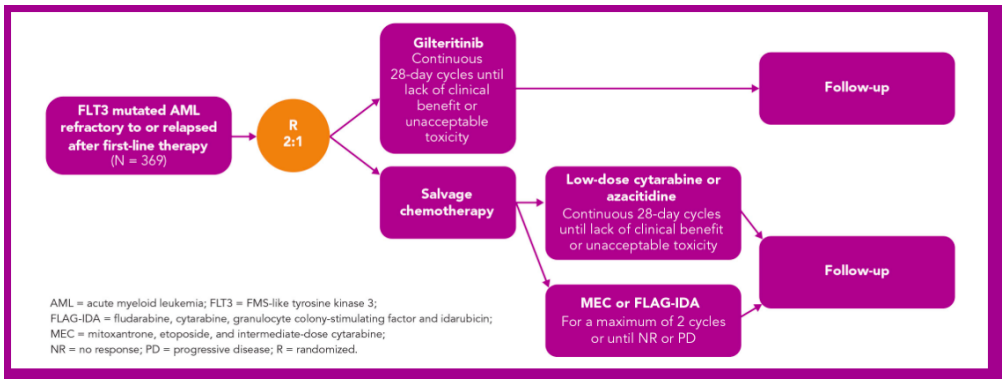
Event	Relapsed or Refractory AML and Starting Dose of Ivosidenib of 500 mg Daily (N=179)	Overall Population (N=258)
	no. of patients (%)	
≥1 Treatment-related adverse event of grade 3 or higher	37 (20.7)	66 (25.6)
Prolongation of the QT interval on ECG	14 (7.8)	18 (7.0)
IDH differentiation syndrome†	7 (3.9)	12 (4.7)
Anemia	4 (2.2)	6 (2.3)
Thrombocytopenia	3 (1.7)	5 (1.9)
Leukocytosis	3 (1.7)	3 (1.2)
Febrile neutropenia	1 (0.6)	3 (1.2)
Diarrhea	1 (0.6)	3 (1.2)
Platelet count decreased	3 (1.7)	3 (1.2)
Hypoxia	2 (1.1)	3 (1.2)

IDH differentiation syndrome

- **Occurs in 20-25% of patients**
- **Most frequently presents with dyspnea, hypoxia, edema, effusions, weight gain**
- **Requires concurrent evaluation for infection, disease progression**
- **Treated with steroids +/- diuretics +/- drug interruption**

DiNardo et al, *NEJM* 2017

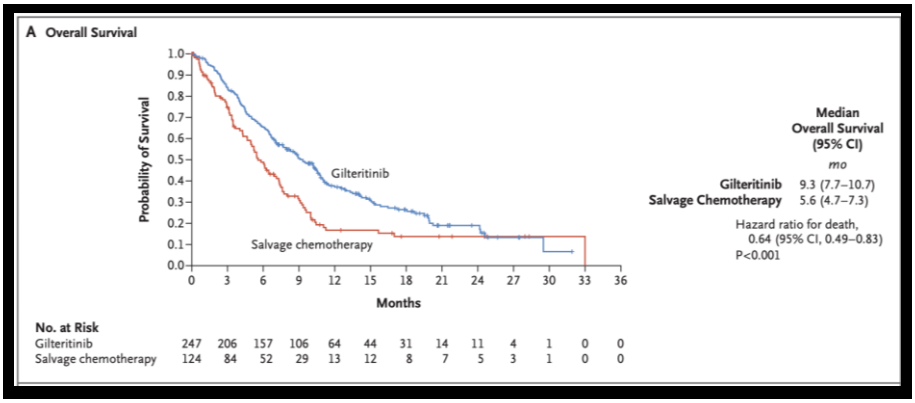
Targeted agents: Gilteritinib



ADMIRAL Trial

Perl et al, *NEJM* 2019

Targeted agents: Gilteritinib

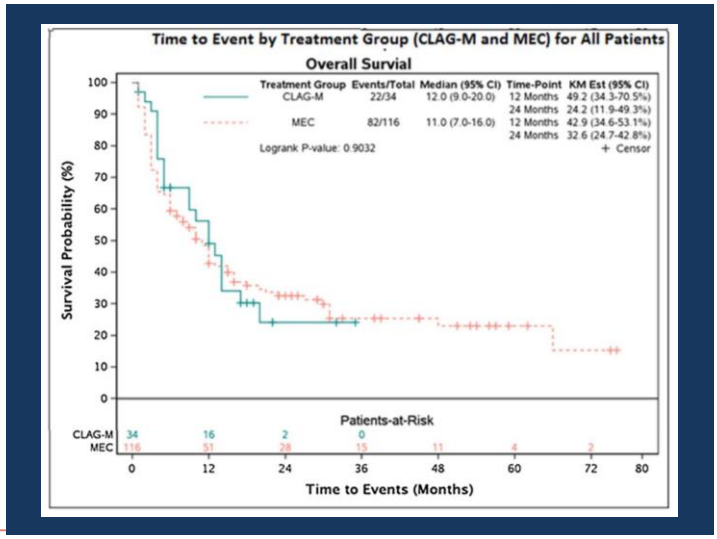


- **Median OS 9.3 vs 5.6 months (HR 0.64, p<0.001)**
- **ORR 68% vs 26%**
- **Composite CR 54% vs 22%**
- **True CR 21% vs 10.5%**
- **Median duration of CR 11 months**

Perl et al, *NEJM* 2019

HiDAC-based regimens

- MEC
- CLAG-M
- FLAG-Ida
- GCLAC



Scheckel et al, *Leuk Res* 2020

HiDAC-based regimens

original reports

Venetoclax Combined With FLAG-IDA Induction and Consolidation in Newly Diagnosed and Relapsed or Refractory Acute Myeloid Leukemia

Courtney D. DiNardo, MD, MSCE[1]; Curtis A. Lachowiez, MD[2]; Koichi Takahashi, MD, PhD[1]; Sanam Loghavi, MD[3]; Lianchun Xiao, MS[4]; Tapan Kadia, MD[1]; Naval Daver, MD[1]; Maria Adeoti, RN[1]; Nicholas J. Short, MD[1]; Koji Sasaki, MD[1]; Sa Wang, MD[3]; Gautam Borthakur, MD[1]; Ghayas Issa, MD[1]; Abhishek Maiti, MBBS[1]; Yesid Alvarado, MD[1]; Naveen Pemmaraju, MD[1]; Guillermo Montalban Bravo, MD[1]; Lucia Masarova, MD[1]; Musa Yilmaz, MD[1]; Nitin Jain, MD[1]; Michael Andreeff, MD, PhD[1]; Elias Jabbour, MD[1]; Guillermo Garcia-Manero, MD[1]; Steven Kornblau, MD[1]; Farhad Ravandi, MD[1]; Marina Y. Konopleva, MD, PhD[1]; and Hagop M. Kantarjian, MD[1]

DiNardo et al, *JCO* 2021

HiDAC-based regimens

TABLE 2. Patient Outcomes

Outcome	All (N = 68)	Phase IIA ND-AML (n = 29)	Phase IB R/R-AML (n = 16)	Phase IIB R/R-AML (n = 23)
ORR, No. (% [CI])	56 (82 [71 to 91])	28 (97 [85 to 99])[a]	12 (75 [48 to 93])	16 (70 [47 to 83])[a]
CRc (CR + CRi + CRh), No. (% [95% CI])	52 (76 [65 to 86])	26 (90 [73 to 98])	12 (75 [48 to 93])	14 (61 [39 to 80])
CR, No. (%)	37 (53)	20 (69)	6 (38)	11 (48)
CRh, No. (%)	10 (15)	5 (17)	2 (13)	3 (13)
CRi, No. (%)	5 (7)	1 (3)	4 (25)	—
MRD⁻ CR (flow cytometry), No. (% [95% CI])	43 (83 [70 to 92])	25 (96 [80 to 99])	7 (58 [28 to 85])	11 (79 [49 to 95])
OS				
Median, months (95% CI)	NR	NR	9 (4.9 to NE)	NR (6 to NE)
6-month, % (95% CI)	81 (71 to 91)	100	63 (43 to 91)	68 (49 to 94)
12-month, % (95% CI)	70 (58 to 83)	94 (84 to 100)	38 (20 to 71)	68 (49 to 94)

DiNardo et al, *JCO* 2021

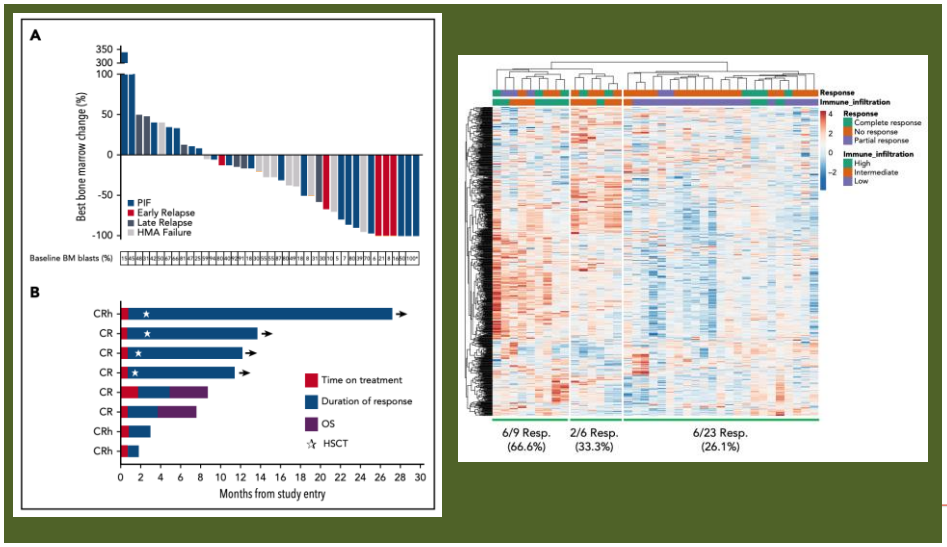
Venetoclax-based regimens

	DEC10 + ven (%)	HMA + ven
Number of patients	55	33
CR/CRi	23 (42)	17 (51)
MRD negative flow	14/26 (57)	8/15 (53)
Median OS (months)	7.8	NR

- Not an FDA-approved indication

Maiti et al, *ASCO* 2020
Aldoss et al, *Haematologica* 2018

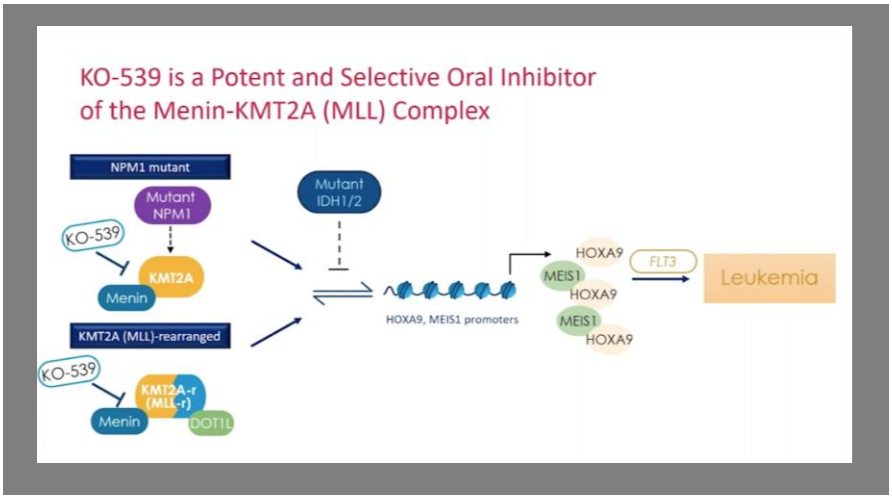
Novel agents: Flotetuzumab



- CD3 x CD123 bispecific Ab
- n=88 (30 with primary induction failure/early relapse @ RP2D)
- Among PIF/ER patients, ORR 30%
- Responses enriched in patients with "immune infiltrated" gene signature

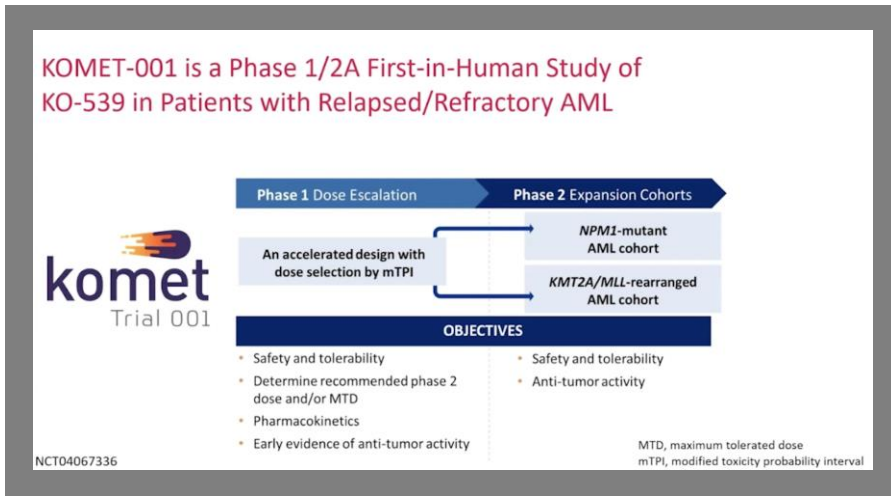
Uy et al, *Blood* 2021

Novel agents: Menin-MLL inhibitors



Wang et al, *ASH* 2020

Novel agents: Menin-MLL inhibitors



Wang et al, *ASH* 2020

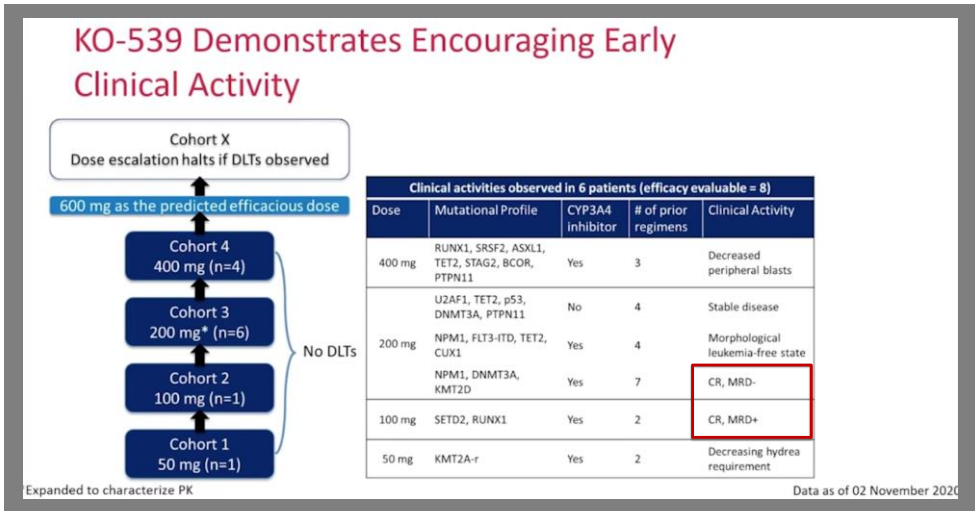
Novel agents: Menin-MLL inhibitors

Patient Demographics and Baseline Characteristics

KOMET-001 Patients	N=12
Median Age, y (min, max)	67 (33, 80)
Gender, n (%)	
Male	8 (66.7%)
Female	4 (33.3%)
Race, n (%)	
White	8 (66.7%)
Number of prior lines of therapies, median (range)	3 (2-7)
Number of patients with prior transplant	1

Wang et al, *ASH* 2020

Novel agents: Menin-MLL inhibitors



Clinical activities observed in 6 patients (efficacy evaluable = 8)

Dose	Mutational Profile	CYP3A4 inhibitor	# of prior regimens	Clinical Activity
400 mg	RUNX1, SRSF2, ASXL1, TET2, STAG2, BCOR, PTPN11	Yes	3	Decreased peripheral blasts
200 mg	U2AF1, TET2, p53, DNMT3A, PTPN11	No	4	Stable disease
	NPM1, FLT3-ITD, TET2, CUX1	Yes	4	Morphological leukemia-free state
	NPM1, DNMT3A, KMT2D	Yes	7	CR, MRD-
100 mg	SETD2, RUNX1	Yes	2	CR, MRD+
50 mg	KMT2A-r	Yes	2	Decreasing hydrea requirement

Wang et al, *ASH* 2020

Ongoing areas of investigation

- For patients with targetable mutations, when should targeted agents be used *in lieu* of cytotoxic chemotherapy?
- For patients with targetable mutations, when should targeted agents be used *in combination* with cytotoxic chemotherapy?
- For patients with multiple targetable mutations, which mutation should be targeted, or should targeted agents be combined?

Thanks!

ANCO
Educating and Empowering the Northern California Cancer Community

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Hematologic Malignancies Update: September 11, 2021

Tamer Othman, MD

Hematology/Oncology Fellow

Outline

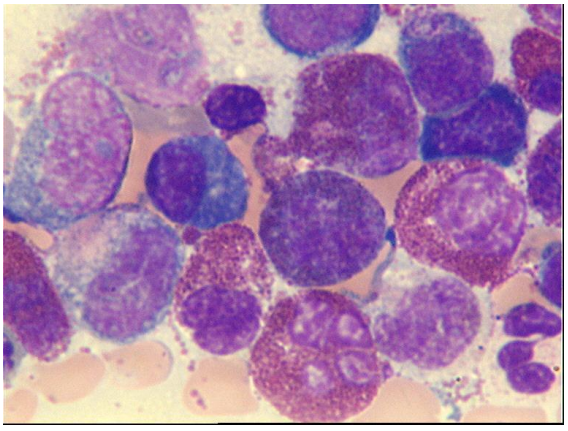
- Case 1: Leukemia
- Case 2: Lymphoma
- Case 3: Myeloma

Case 1: Leukemia

- HPI abridged
  - 60 yo M with a PMH of HTN, DM2, HLD, CVA who presented with a 2-month history of progressive cough, fatigue, dizziness, SOB, 35 lbs unintentional wt loss, and bruising
  - No prior history of malignancies or hematologic disorders
  - ECOG 0
- Notable physical exam findings
  - Subconjunctival pallor, palatal petechiae
- Pertinent labs/imaging
  - CBC: WBC 120.1 (ANC 9000), Hgb 3.3, MCV 102.7, plts 40
  - Peripheral smear shows 22% blasts, 6% eosinophils. No auer rods visualized.
  - Chemistry: Cr + AST/ALT/AP WNL, Tbili 1.9, K 4.4, Ca 8.7 phos 6.4, uric acid 9.3, LDH 981
  - Coags WNL
  - CXR and TTE without any abnormalities, EF=63%

Case 1: Leukemia

- Bone marrow biopsy (aspirate smear and core)
  - Markedly hypercellular (~90%) with ↑ blasts (~50%)
- Flow cytometry on BM
  - Immunophenotyping shows CD33+
- Cytogenetics
  - 46,XY,inv(16)(p13.1q22)
- Neotype myeloid panel
  - ASXL1 mutated



Case 1: Leukemia

- WHO 2016 diagnosis
  - AML with inv(16)(p13.1q22)
- ELN 2017 risk stratification
  - Favorable-risk[#]

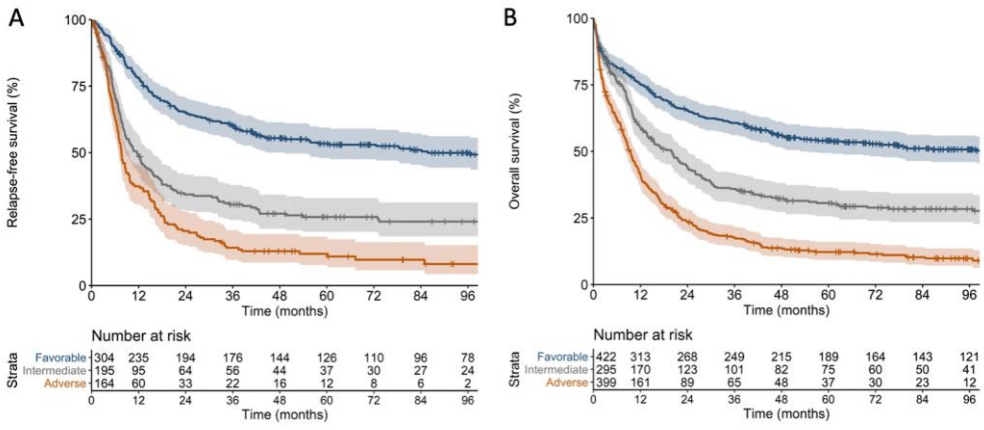
[#]ASXL1 mutations are only used as an adverse prognostic marker in the absence of a favorable-risk AML subtype

Table 5. 2017 ELN risk stratification by genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Case 1: Leukemia

Prognosis based on risk-stratification



Case 1: Leukemia

- Question for the audience
  - How would you treat this patient?
    - A. CPX-351 (Vyxeos)
    - B. Cytarabine x 7 days + daunorubicin x 3 days (7+3) + gemtuzumab ozogamicin (GO)
    - C. Hypomethylating agent + venetoclax
    - D. 7+3

Case 1: Leukemia

- Intensive chemotherapy or low-intensity therapy?
  - Balance chance of disease control and risk of major morbidity/early mortality
  - Intensive induction for pts <60 regardless of risk stratification
  - For ≥60, factor to consider
    - Organ function
    - Performance status
    - AML risk stratification
  - Pts ineligible for intensive chemo are more appropriate for HMA/Ven or targeted therapy[#]

[#]Rapid screening for actionable mutations should also be performed (i.e., FLT3, IDH1/2)

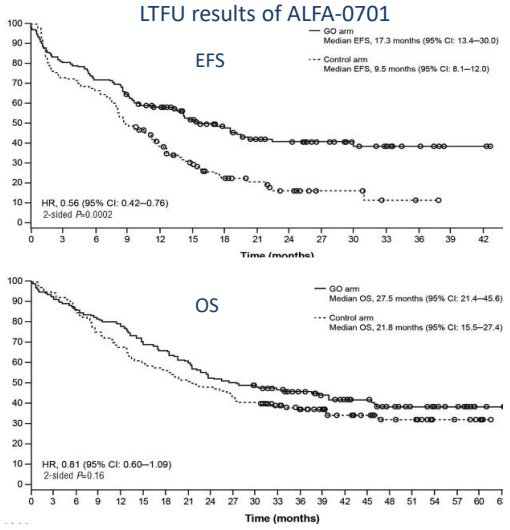
Case 1: Leukemia

- Treatment
  - The patient is started on 7+3+GO

Case 1: Leukemia

- GO is a CD33-targeting ADC
- Several trials looked at chemo + GO
- ALFA-0701 trial specifically looked at 7+3+GO
- Initial results showed OS and EFS benefit
- OS benefit lost in LTFU report

LTFU results of ALFA-0701



Castaigne et al, Lancet 2012; Lambert et al, Haematologica 2019; Hills et al, Lancet Oncol 2014

Case 1: Leukemia

- Induction course
  - C/b LLL pneumonia, strep bacteremia, FN, and sepsis
  - D14 BMBx – 5% cellularity and 1% blasts
  - D28 BMBx – CR: 90% cellularity and 3% blasts with ANC >1000 and plts >100
    - Cytogenetics 46,XY
    - Multicolor flow cytometry (MFC) MRD negative
    - Inv(16) real-time quantitative PCR (RQ-PCR) negative

Case 1: Leukemia

- Question for the audience
  - How would next manage this patient?
    - A. Consolidation with IDAC + GO
    - B. Referral for alloHCT
    - C. Both a and b

Case 1: Leukemia

Younger patients (18-60/65 y)	
• Favorable-risk genetics	• 2-4 cycles of IDAC (1000-1500 mg/m^2 IV over 3 h q12h, d1-3; or 1000-1500 mg/m^2 IV over 3 h d1-5 or 6)
• Intermediate-risk genetics	• Allogeneic HCT from matched-related or unrelated donor
	• 2-4 cycles of IDAC (1000-1500 mg/m^2 IV over 3 h q12h, d1-3; or 1000-1500 mg/m^2 IV over 3 h d1-5 or 6), or
	• High-dose therapy and autologous HCT
• Adverse-risk genetics	• Allogeneic HCT from matched-related or unrelated donor
Older patients (>60/65 y)	
• Favorable-risk genetics	• 2-3 cycles of IDAC (500-1000 mg/m^2 IV over 3 h q12h, d1-3; or 500-1000 mg/m^2 IV over 3 h d1-5 or 6)
• Intermediate/adverse-risk genetics	• No established value of intensive consolidation therapy; consider allogeneic HCT in patients with low HCT-Comorbidity Index, or investigational therapy

Case 1: Leukemia

- The patient receives IDAC + GO x 2 cycles followed by IDAC x 2 cycles
- Repeat BMBx showed CR, inv(16) undetectable in PB but now detectable in BM
- 1 month later inv(16) re-emerged in PB with new thrombocytopenia
- Repeat BMBx showed 28% blasts by IHC, consistent with relapsed AML
- He is started on decitabine/venetoclax

Case 1: Leukemia

- HMA/Ven in r/r AML
  - Retrospective data shows ORR 21-64%, mOS 3.4-8 mos
  - One non-randomized phase 2 clinical trial showed an ORR 62%, mOS 7.8 mos

Tenold et al, Front Oncol 2021; Aldoss et al, Haematologica 2018

Case 1: Leukemia

- After 1 cycle, patient achieves CR
  - BMBx shows normocellular marrow (30-40%) with 2% blasts by aspirate count
  - RQ-PCR inv(16) undetected

Case 1: Leukemia

- AlloHCT provides the best chance for long-term survival in r/r AML
  - AlloHCT with MAC is difficult to perform in older populations
  - RIC has made alloHCT more accessible
  - 1-year OS rates post-alloHCT >50% with lower-intensity conditioning
- HMA/Ven as a bridge to alloHCT
  - Not as well understood as those who receive more intensive treatments
  - Small retrospective studies support the viability of this pathway
    - 1-year post-alloHCT OS rates >60%

Herr et al, Leukemia, 2007; Storb et al, Best Pract Res Clin Haematol, 2007; Pollyea et al, Blood, 2020; Kennedy et al, Blood, 2020; Sandhu et al, Biol Blood Marrow Transplant, 2020

Case 1: Leukemia

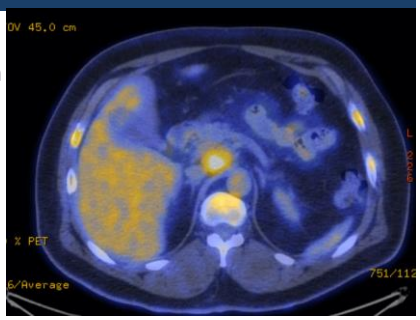
- Pt outcome
  - The patient undergoes RIC alloHCT with flu/mel
  - 7 months post-alloHCT, he remains AML-free without evidence of GVHD

Case 1: Leukemia

- Summary
  - If CD33+ with favorable- or intermediate-risk cytogenetics, add GO to intensive chemo
  - AlloHCT is not required in favorable-risk AML in CR1, but is for poor-risk, select cases of intermediate-risk, and r/r AML if eligible
  - HMA/Ven has efficacy in the r/r setting
  - HMA/Ven can be used to induce CR as a bridge to alloHCT

Case 2: Lymphoma

- HPI abridged
  - 55 yo M with no prior PMH presented with abdominal pain
  - ECOG 0
- Pertinent physical exam findings
  - Unremarkable abdominal exam, no appreciable LAD
- Pertinent labs
  - CBC, CMP, LDH unremarkable
- Imaging
  - CT imaging that revealed bulky mediastinal, retroperitoneal, retrocaval and mesenteric LAD, largest node measures 6.3 x 5.5 cm
  - PET/CT with extensive bulky mediastinal, retroperitoneal and mesenteric LAD, Deauville 5



Case 2: Lymphoma

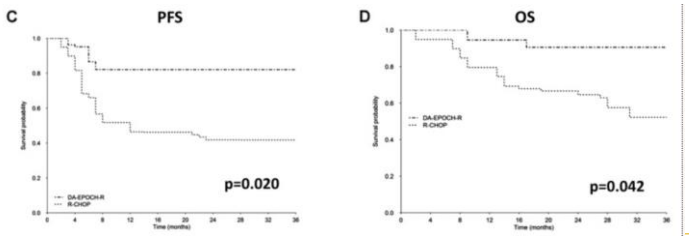
- Pathology
  - RP LN bx shows sheets of large abnormal lymphoid cells that are positive for B-cell markers (CD20 and PAX5), CD10+,BCL6+,MUM-
    - IHC shows MYC 70% and BCL2 80%
    - No MYC, BCL2, BCL6 rearrangements on FISH
  - BMBx unremarkable
- Diagnosis and prognostication
  - Diffuse large B-cell lymphoma, double-expressor phenotype
  - Stage III, IPI score 0, CNS-IPI score 0

Case 2: Lymphoma

- Initial management of newly diagnosed DLBCL
  - Alliance/CALGB 50303
    - R-CHOP and DA-R-EPOCH are equal in terms of EFS and OS for untreated stage II-IV DLBCL
    - DA-R-EPOCH more toxic
  - Stage III-IV without meeting double/triple-hit criteria
    - R-CHOP
      - Leads to cure rates >50%

Case 2: Lymphoma

- Double-expressor lymphomas (DEL)
  - Variable IHC cutoffs, but MYC ≥40%, BCL2 ≥50% accepted
  - Represents up to 1/3 of newly diagnosed DLBCL
  - Optimal treatment strategy is not clear, and outcomes are suboptimal with known treatments
    - Comprised only 15.6% of Alliance population
    - Inferior outcomes with R-CHOP vs non-DEL
      - 5-y PFS and OS 27% and 30%
    - Largest retrospective data suggests DA-R-EPOCH better for <65 yo



Hu et al, Blood 2013; Dodero et al, Leukemia 2019; Herrera et al, J Clin Oncol 2017

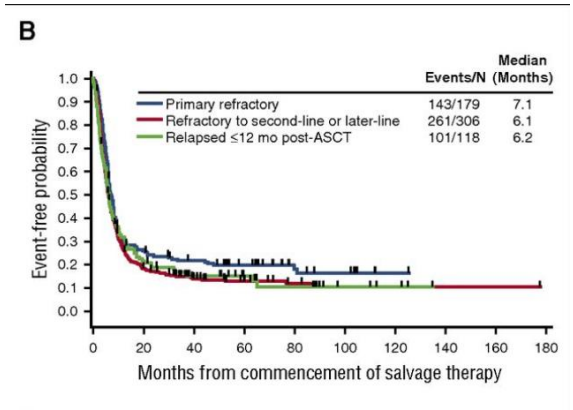
Case 2: Lymphoma

- Treatment and response assessment
  - The pt received 4 cycles of DA-R-EPOCH (was successfully escalated to dose level 4) and 4 doses of IT MTX
  - PET/CT after 2 and 4 cycles showed no improvement (Deauville 5)

Case 2: Lymphoma

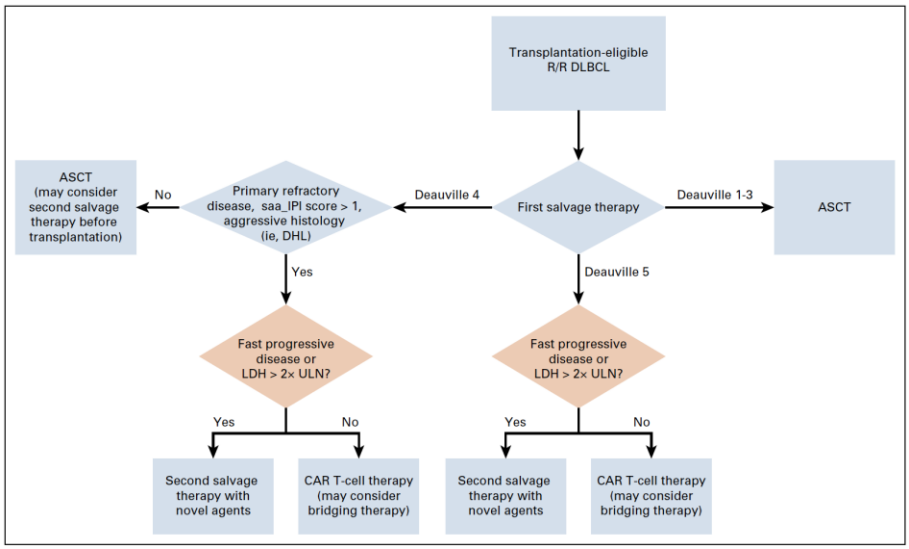
- SCHOLAR-1
  - Largest pooled analysis to evaluate responses and OS rates in pts with r/r DLBCL

Endpoint	N=636
ORR to next line of tx	26%
CR to next line of tx	7%
2-y OS	20%



Crump et al, Blood 2017

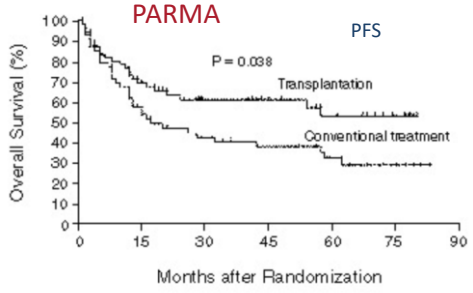
Case 2: Lymphoma

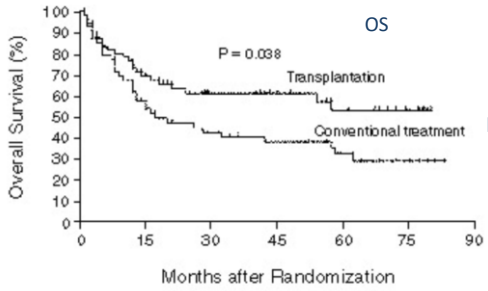


Alencar et al, J Clin Oncol 2020

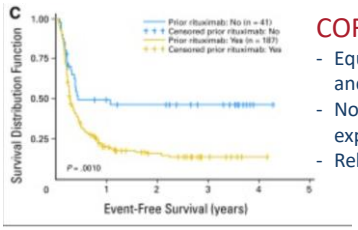
Case 2: Lymphoma

PARMA



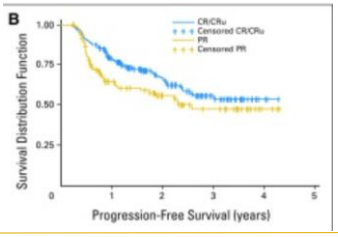


Pre-rituximab era



CORAL

- Equivalent outcomes between R-ICE and R-DHAP
- Not affected by prior rituximab exposure if relapse >1 year
- Relapse <1 y after Dx = worse prognosis



Philip et al, NEJM 1995; Gisselbrecht et al, J Clin Oncol 2010

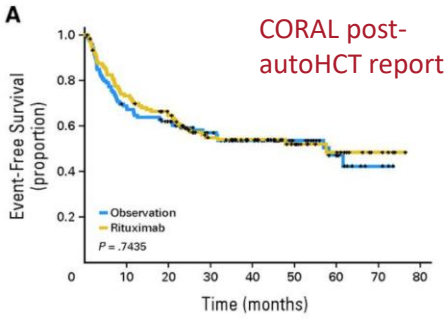
Case 2: Lymphoma

- Salvage treatment
  - Received R-ICE salvage therapy x 3 cycles, subsequent PET/CT with CR
  - Received R-BEAM and autoHCT

Case 2: Lymphoma

- Question for the audience:
  - Is post-autoHCT rituximab as maintenance therapy indicated?
    A. Yes
    B. No

Case 2: Lymphoma



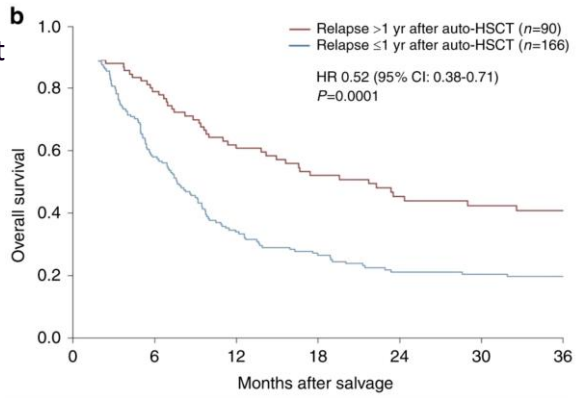
CORAL post-autoHCT report

More toxicity and death in the rituximab arm

Conclusion: Patients should not get rituximab maintenance post-autoHCT for DLBCL

Case 2: Lymphoma

- Post-autoHCT course
  - Uncomplicated early post-transplant course
  - Relapsed 7 months post-autoHCT (PET/CT shows Deauville 5, RP LN bx confirmed relapse)



E. González-Barca et al, Bone Marrow Transplant 2020

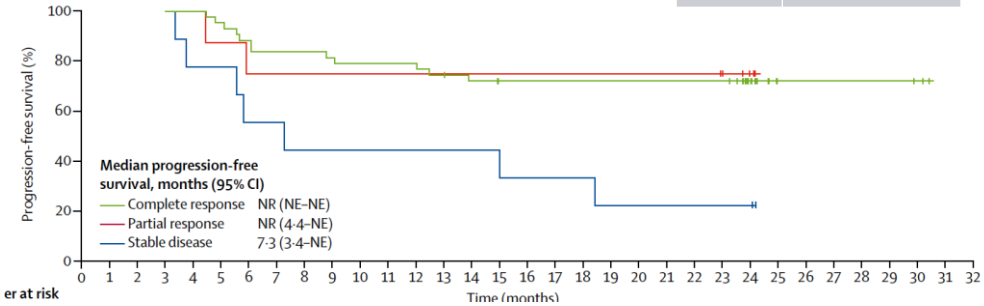
Case 2: Lymphoma

- Received additional cycle of R-ICE
- Received flu/cy lymphodepletion followed by CAR T-cell (Axi-Cel) infusion

Case 2: Lymphoma

- Anti-19 CAR T-cell efficacy in r/r DLBCL
  - Axi-Cel (Yescarta)
    - ZUMA-1 LTFU (median f/u 27 mos)

Variable	N=101
ORR	83%
CR	58%
mDOS	11.1 mos
mPFS	5.9 mos
mOS	NR



Locke et al, Lancet Oncol 2018

Case 2: Lymphoma

- Caveats to CAR T
  - Limited accessibility
  - Time to manufacture
    - 17 days in ZUMA-1, 54 days in JULIET (Tisagenlecleucel [Kymriah] trial)
    - The need for bridging therapy (not done in ZUMA-1) leads to ↑ treatment- and lymphoma-related mortality
    - Some patients who are apheresed may ultimately not receive CAR T-cells
  - Toxicity profile
    - Frequent grade ≥3 prolonged organ toxicity, hematologic, metabolic, and infectious complications
    - Deaths are more frequent in post-marketing reports
  - Limited long-term follow-up

Alencar et al, J Clin Oncol 2020

Case 2: Lymphoma

- Pt outcome
  - No further complications from CAR T infusion
  - Patient achieves CR on 1-month post-PET assessment
  - Remains in CR 3 months post-CAR T infusion

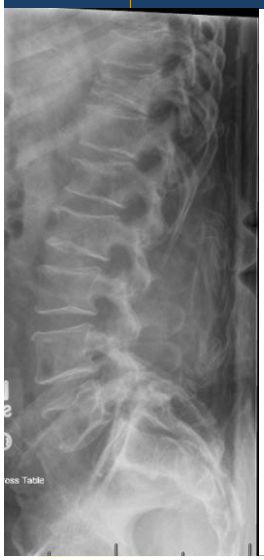
Case 2: Lymphoma

- Summary
  - DLBCL pts with primary refractory disease, relapsing ≤1 y of autoHCT, and DEL all remain an unmet medical need
  - AutoHCT remains a curative intervention in pts with chemosensitive disease, especially those who achieve CR at the time of transplant
  - No role for maintenance therapy post-autoHCT for DLBCL
  - CAR T-cells may provide pts ineligible for HCT a chance at long-term survival, but more long-term follow-up data is needed and logistical challenges limit universal adoption

Case 3: Myeloma

- HPI abridged
  - 54 yo M with a PMH of HTN presents to the ED after sudden onset back pain while chopping wood
  - No sx of hyperviscosity: vision changes/impairment, hearing loss, dizziness/vertigo, somnolence, coma, seizures, respiratory compromise, bleeding.
  - ECOG 0
- Physical exam remarkable only for midline tenderness to palpation at T11
- Labs
  - CMP: Cr 4.30, Ca++ 12.2, total protein 12.2, albumin 2.4
  - CBC: Hgb 7.9, MCV 100.2, other counts WNL and differential unremarkable
  - Misc chem: K:L 5.31, serum viscosity 1.89, LDH 330, B2MG 6.5
  - SPEP: M-spike 7.5 g/dL, IFE with 2 IgG kappa bands
  - UPEP: M-spike 4.1 mg/dL
  - IgA 36, IgM <25, IgG 7566

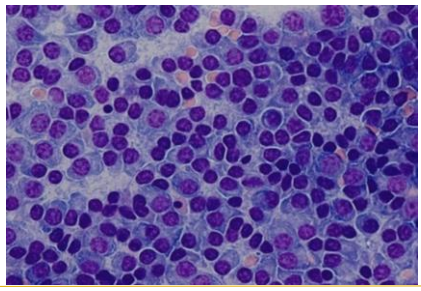
Case 3: Myeloma



Bone survey: Extensive lytic lesions involving the axial and appendicular skeleton, compression fracture at T11

BMBx: Hypercellular with sheets of kappa-restricted plasma cells (90% by CD138 IHC)

Cytogenetics and FISH unremarkable



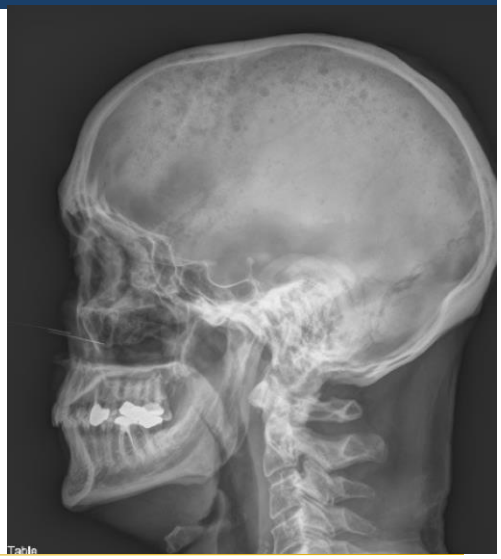


Image credit: doi:10.7759/cureus.5969

Case 3: Myeloma

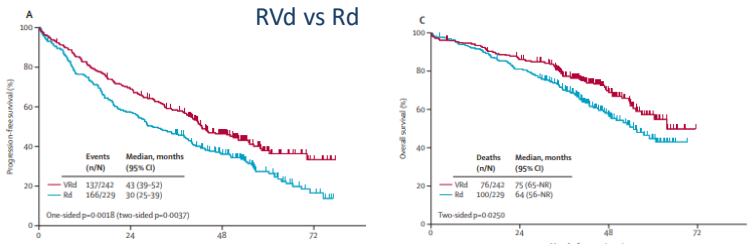
Question to the audience:

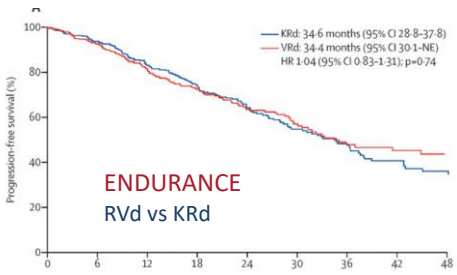
- What induction regimen would you treat him with?
  - A. RVd (lenalidomide, bortezomib, dexamethasone)
  - B. CyBorD
  - C. D-RVd (daratumumab, lenalidomide, bortezomib, dexamethasone)
  - D. KRd (carfilzomib, lenalidomide, dexamethasone)

Case 3: Myeloma

- Triplet therapy is SOC for fit pts
- Induction regimen of choice?

SWOG 0777
RVd vs Rd





ENDURANCE
RVd vs KRd

RVd is still the induction regimen of choice for HCT-eligible patients, but in patients with acute renal injury, CyBorD is preferred for at least 1 cycle

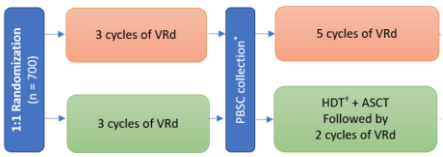
Kumar et al, Clin lymphoma myeloma leuk 2019; Kumar et al, Lancet Oncol 2020; Voorhees et al, Blood 2020

Case 3: Myeloma

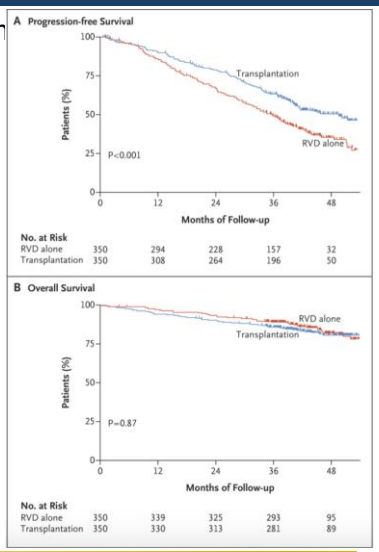
- The patient receives 1 dose of pamidronate and IVFs
- Evaluated by apheresis and renal, who thought plasmapheresis and HD were not indicated, respectively
- The patient receives CyBorD
- Cr normalizes by C1D7
- He is switched to RVd for C2-C7 with monthly denosumab and achieves VGPR (no BMBx repeated to determine if in CR)
- Receives melphalan 140 mg/m2 and undergoes autoHCT

Case 3: Myeloma

- AutoHCT in as a standard of care after triplet induction
  - Long-term follow-up of IFM 2009



- Relevance of PFS as an endpoint
  - Post-hoc analysis of 2 phase 3 trials showed of 1243 pts with PD, 43.7% had morbid PD
  - Prevention of morbid events
    - Fractures
    - Renal injury and HD requirement
    - Cord compression
    - Hypercalcemia

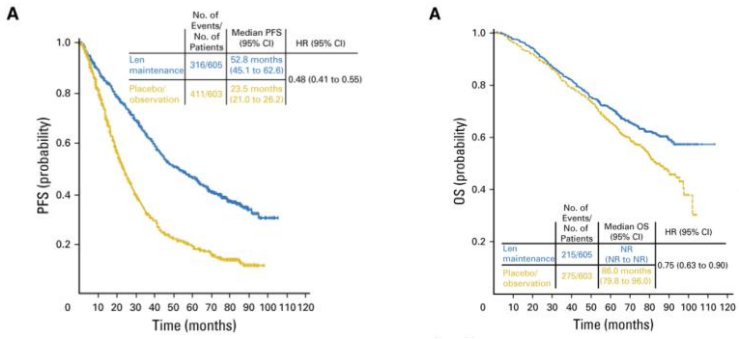


Case 3: Myeloma

- Question for the audience
  - What should he receive as post-autoHCT maintenance?
    - A. Bortezomib until disease progression
    - B. Lenalidomide until disease progression
    - C. Maintenance is not indicated

Case 3: Myeloma

Lenalidomide as maintenance therapy



PFS and OS benefit is seen with maintenance len, despite the ↑increased risk of SPM

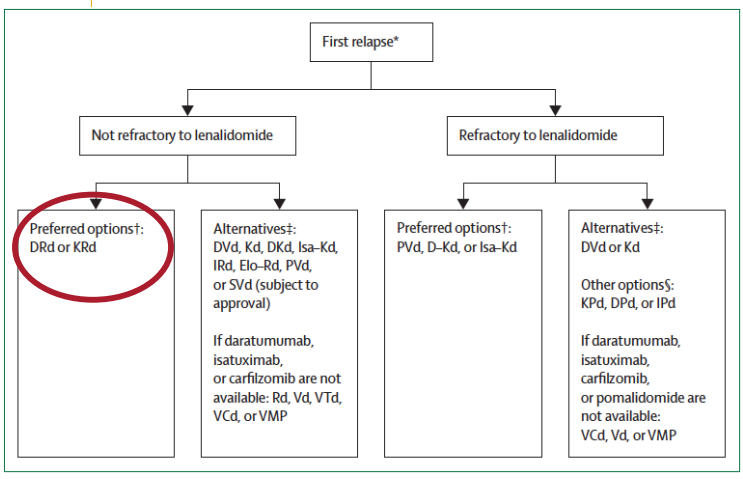
McCarthy et al, J Clin Oncol 2017

Case 3: Myeloma

- The patient is placed on lenalidomide maintenance and continues it until…
- SPEP shows biochemical progression 4 years post-autoHCT (serum M-protein ↑ by 1.3 g/dL above baseline)

Case 3: Myeloma

- Managing first relapse of myeloma

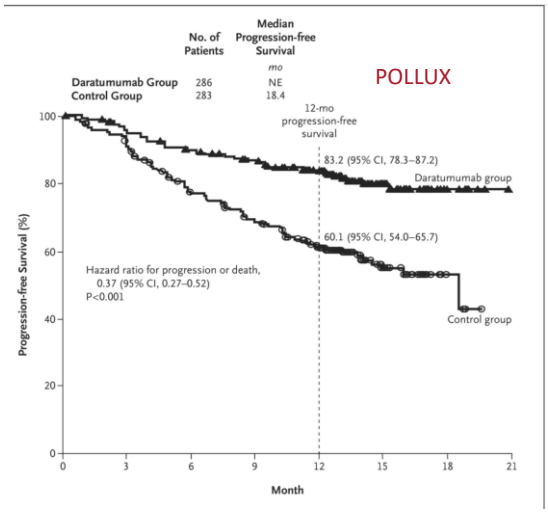


- Lenalidomide-refractory MM is defined as
  - PD during therapy
  - No response (< PR) to prior lenalidomide-containing therapy, or within 60 days of discontinuation from lenalidomide-containing regimens
  - Does not include low-dose maintenance lenalidomide

Shah, Blood 2015; Moreau, Lancet Oncol 2021

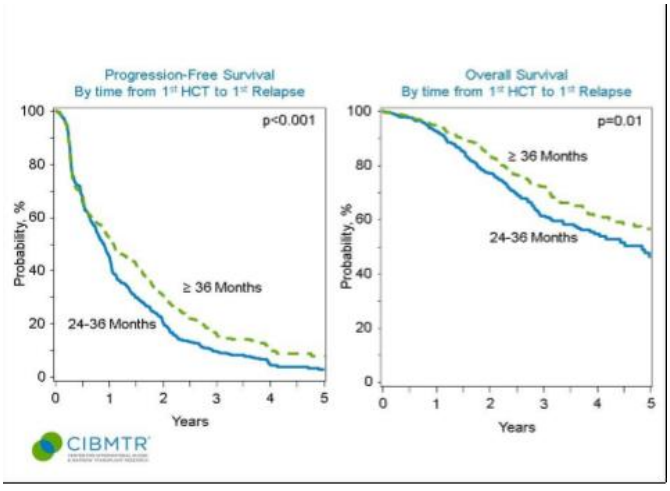
Case 3: Myeloma

He undergoes re-induction with daratumumab, lenalidomide, dexamethasone



Case 3: Myeloma

He achieves VGPR once again and undergoes 2nd autoHCT with high-dose melphalan conditioning



Case 3: Myeloma

- Pt outcome
  - Remains in remission 2 years out from autoHCT

Case 3: Myeloma

- Summary
  - In the absence of an AKI, RVd is the standard frontline treatment for multiple myeloma
  - AutoHCT for MM is still preferred in fit pts directly after induction, although depending on pt preferences, may be delayed until after first relapse
  - Lenalidomide maintenance should be considered for at least 2 years post-autoHCT if pt can tolerate
  - Many options exist for managing r/r MM, and choice should be tailored to prior treatment history and pt-related factors
  - A second autoHCT, especially if PFS ≥3 years after first autoHCT, is an acceptable treatment approach upon disease control with salvage regimens

Acknowledgements

- Dr. Joseph Tuscano