Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

November 14, 2020

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Northern California Cancer Community

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Association of Northern California Oncologists (ANCO)

presents

Hematologic Malignancies Updates: Leukemias, Lymphomas. & Myeloma

Saturday, November 14, 2020

9:00AM-12:30PM

Agenda & Schedule

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

9:05AM *ANCO Hematologic Malignancies Updates:*
How I Manage Acute Myeloid Leukemia in 2020
Rebecca Olin, MD, MSCE, *University of California, San Francisco*

9:50 AM *ANCO Lymphoma Update 2020*
Neel Gupta, MD, *Stanford University*

10:35AM Stretch Break and a word from our sponsors

11:00 AM *Updates in Multiple Myeloma: ANCO 2020*
Aaron Rosenberg, M.D., University of California, Davis

11:45AM *Case Presentations: Leukemia, Lymphoma, Myeloma*
Vanessa Kennedy, M.D., University of California, San Francisco

12:30PM ADJOURN

Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Program Faculty

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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:

Neel K. Gupta, MD, disclosed that he does not have any relevant financial relationships with any commercial interests.

Rebecca L. Olin, MD, MSCE*,* disclosed that she has received grant/research support from Astellas, Genentech, and Pfizer; and consulted for *AMGEN*.

Aaron S. Rosenberg, MD, MS disclosed that he is on a speakers bureau for Millenium Takeda, and Janssen,.

Vanessa Kennedy, MD, disclosed that she does not have any relevant financial relationships with any commercial interests.

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Agios

Amgen

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

ANCO Hematologic Malignancies Updates: How I Manage Acute Myeloid Leukemia in 2020

Rebecca L. Olin, MD, MSCE
University of California, San Francisco

How I Manage Acute Myeloid Leukemia in 2020

Rebecca Olin MD MSCE
Associate Professor, University of California San Francisco
Fall 2020

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UCSF

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Background: The AML field has exploded

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- 1970s: **7+3** was developed
- 2000-2010: **gemtuzumab ozogamycin** (Mylotarg) approved and then withdrawn
- April 28 2017: **midostaurin** (FLT3 inhibitor)
- August 1 2017: **enasidenib** (IDH2 inhibitor)
- August 3 2017: **CPX-351** (Vyxeos; liposomal dauno/cytarabine)
- September 1 2017: **gemtuzumab ozogamycin** (Mylotarg)
- July 20 2018: **ivosedinib** (IDH1 inhibitor)
- November 21 2018: **glasdegib +LoDAC** (hedgehog pathway inhibitor)
- November 21 2018: **venetoclax +HMA or +LoDAC** (BCL2 inhibitor)
- November 28 2018: **gilteritinib** (FLT3 inhibitor)
- September 1 2020: **oral azacitidine**

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Overview

- New medications and combinations
  - two brief cases
- Past vs present treatment algorithms
- On the horizon

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Bcl-2 Inhibition: Venetoclax

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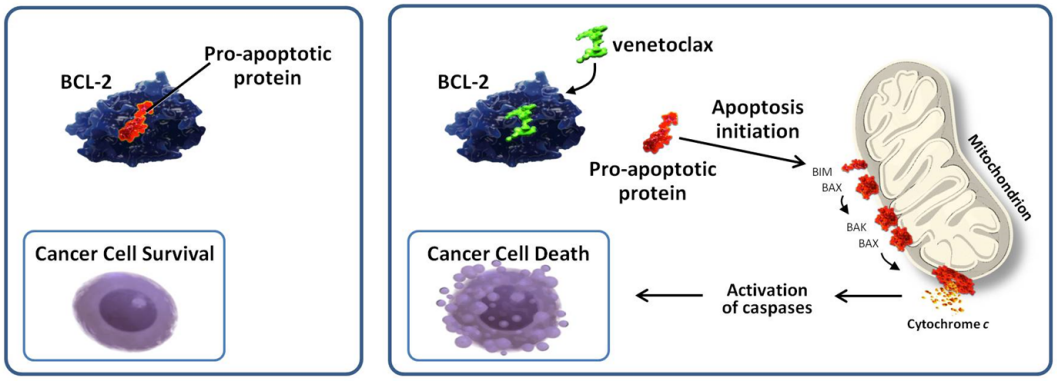
Restoration of apoptosis through BCL-2 inhibition



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

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

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HMA + Venetoclax

Venetoclax Dose Escalation Stage
(Target N~48) (45 enrolled)
Objective: To estimate safety, PK, RPTD and MTD

Arm A
Venetoclax (VEN) + Decitabine (DEC)
VEN: once daily
DEC: 20mg/m² IV; D1-5, 28D cycles

Arm B
Venetoclax (VEN) + Azacitidine (AZA)
VEN: once daily
AZA: 75mg/m² IV/SQ; D1-7, 28D cycles

Expansion stage with both HMAs

Safety Expansion Stage
(Target N=25 at each dose level)
Objective: To confirm safety and efficacy

DEC/AZA → **VEN 400 mg** 28/28 days

DEC/AZA → **VEN 800 mg** Cycle 1: 28/28 days Cycle 2: 21/28 days

Eligibility criteria:
- Adult patients ≥65 years of age with untreated AML who are not eligible for standard induction therapy
- Intermediate or Adverse risk cytogenetics

Study objectives:
Primary: Safety - AEs, early deaths, tolerability (duration of treatment), PK, MTD, RPTD
Secondary: Efficacy – ORR (CR+CRi+PR), DOR, TTP, PFS, OS
Exploratory: MRD and Biomarkers (BCL-2 family proteins)

Cohort	N	Composite response rate (CR + CRi) [n], n (%)
All patients	145	[54 + 43], 97 (67)
VEN 400 mg + HMA	60	44 (73)
VEN 400 mg + AZA	29	22 (76)
VEN 400 mg + DEC	31	22 (71)

DiNardo Blood 2019

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HMA + Venetoclax

Subgroup	Evaluable for response/OS, n (%)	CR + CRi, n (%)	n for Median duration of CR + CRi	Median duration of CR + CRi, mo (95%CI)	Median OS, mo (95%CI)
All patients	145	97 (67)	97	11.3 (8.9, NR)	17.5 (12.3-NR)
Cytogenetic risk					
Intermediate	74 (51)	55 (74)	55	12.9 (11, NR)	NR (17.5-NR)
Poor	71 (49)	42 (60)	42	6.7 (4.1, 9.4)	9.6 (7.2-12.4)
Age					
≥75 y	62 (43)	40 (65)	40	9.2 (6.4, 12.5)	11 (9.3-NR)
<75 y	83 (57)	57 (69)	57	12.9 (9.2, NR)	17.7 (14.2-NR)
AML					
De novo	109 (75)	73 (67)	73	9.4 (7.2, 11.7)	12.5 (10.3-24.4)
Secondary	36 (25)	24 (67)	24	NR (12.5, NR)	NR (14.6-NR)
Mutations*					
FLT3†	18 (12)	13 (72)	13	11 (6.5, NR)	NR (8-NR)
IDH1 or 2‡	35 (24)	25 (71)	25	NR (6.8, NR)	24.4 (12.3-NR)
NPM1	23 (16)	21 (91)	21	NR (6.8, NR)	NR (11-NR)
TP53	36 (25)	17 (47)	17	5.6 (1.2, 9.4)	7.2 (3.7-NR)

Adverse event (N = 145)	Total (N = 145) Gr3/4
Any event, n (%)	122 (84)
Nausea	2 (1)
Diarrhea	7 (5)
Constipation	2 (1)
Febrile neutropenia	63 (43)
Fatigue	8 (6)
Hypokalemia	15 (10)
Decreased appetite	3 (2)
Decreased WBC count	45 (31)
Vomiting	0
Anemia	36 (25)
Cough	0
Peripheral edema	0

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Practical Tips for HMA + Venetoclax

1. Dose ramp up may not be necessary
2. Antifungal prophylaxis may be needed, and dose of venetoclax must be adjusted accordingly
3. Bone marrow biopsy should occur after 1-2 cycles
4. Schedule of venetoclax should be adjusted in cytopenic patients who are otherwise responding

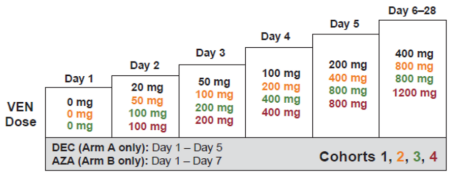

Table 7. Management of Potential VENCLEXTA Interactions with CYP3A and P-gp Inhibitors

Coadministered drug	Initiation and Ramp-Up Phase		Steady Daily Dose (After Ramp-Up Phase)[a]
Posaconazole	CLL/SLL	Contraindicated	Reduce VENCLEXTA dose to 70 mg.
	AML	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 70 mg	
Other strong CYP3A inhibitor	CLL/SLL	Contraindicated	Reduce VENCLEXTA dose to 100 mg.
	AML	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg	
Moderate CYP3A inhibitor	Reduce the VENCLEXTA dose by at least 50%.		
P-gp inhibitor			

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VIALE-A trial: Aza-Ven vs Aza-Placebo

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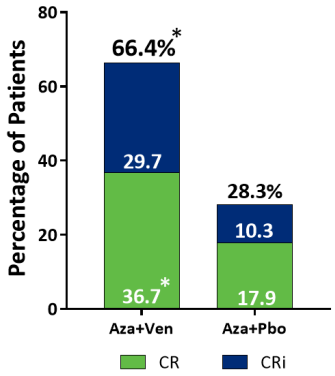
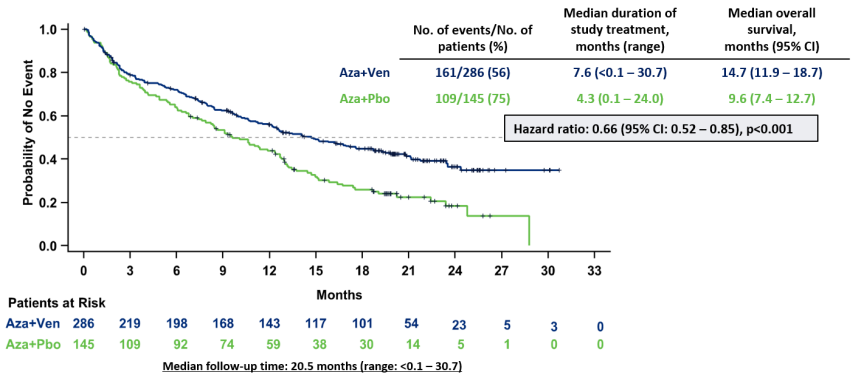
CR/CRi



Overall Survival



	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), p<0.001

Median follow-up time: 20.5 months (range: <0.1 – 30.7)

DiNardo EHA abstract 2020

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VIALE-A trial: CR/CRi by subgroups

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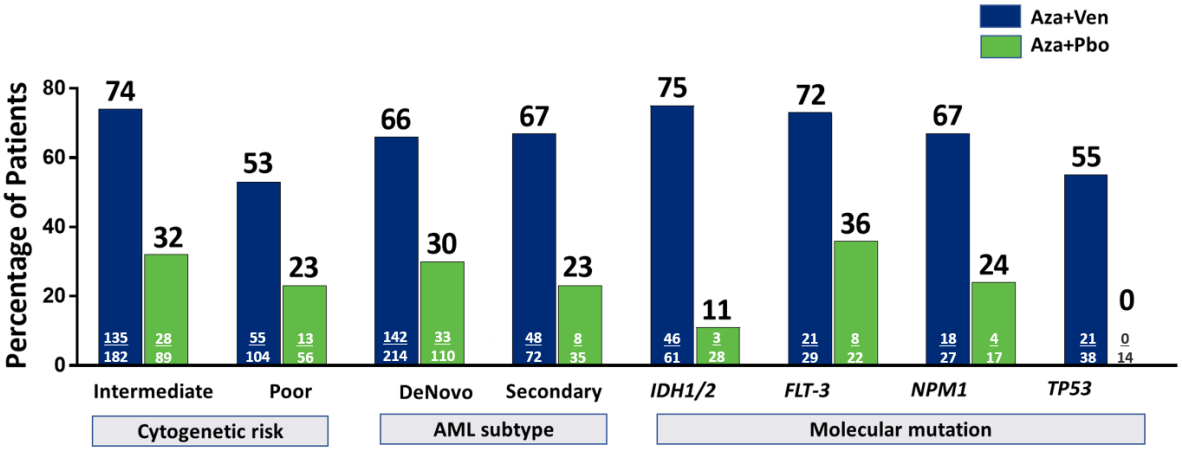

DiNardo EHA abstract 2020

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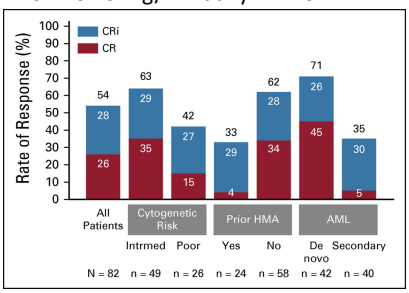
VIALE-C trial: LoDAC-Ven vs LoDAC-Placebo

Venetoclax 600 mg
LoDAC 20 mg/m2 daily D1-10



February 28, 2020

AbbVie Provides Update from Phase 3 Study Evaluating VENCLEXTA® (venetoclax) in Combination with Low-Dose Cytarabine in Newly-Diagnosed Patients with Acute Myeloid Leukemia (AML)

- Study did not demonstrate statistically significant improvement in the primary endpoint of OS (HR 0.75, 95% CI 0.52-1.07, p=0.11)
- OS was 7.2 months in venetoclax arm and 4.1 months in comparator arm

Select Secondary Endpoint Outcomes:*

Outcome	Venetoclax plus LDAC (n=143)	Placebo plus LDAC (n=68)
Complete Remission	27.3%	7.4%
Complete Remission or Complete Remission with Incomplete Blood Count Recovery (CR + CRi)	47.6%	13.2%
Complete Remission or Complete Remission with Partial Hematologic Recovery (CR + CRh)	46.9%	14.7%
Complete Remission or Complete Remission with Incomplete Blood Count (CR + CRi) by Initiation of Cycle 2	34.3%	2.9%

*Nominal p values <0.001

Wei JCO 2019; AbbVie press release

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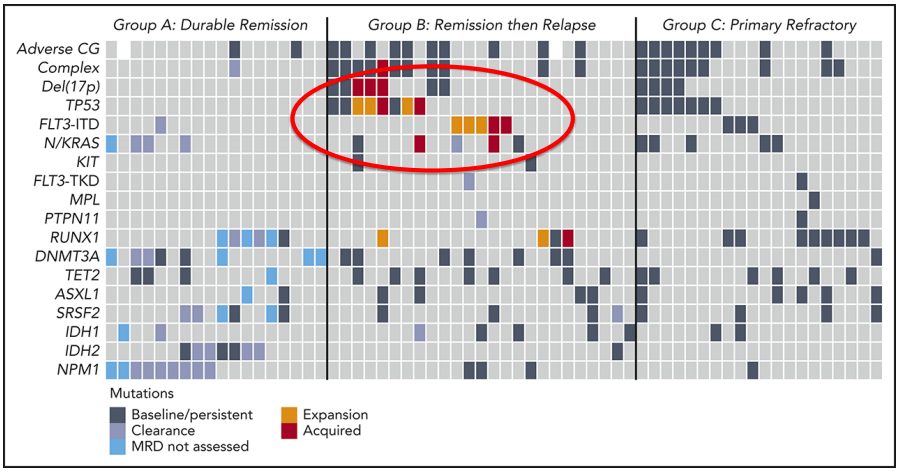
Venetoclax: Durable Remissions



Dinardo Blood 2020

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Venetoclax Plus Cytotoxic Chemotherapy

616.ACUTE MYELOID LEUKEMIA: NOVEL THERAPY, EXCLUDING TRANSPLANTATION | NOVEMBER 13, 2019

Phase I Trial of Escalating Doses of the Bcl-2 Inhibitor Venetoclax in Combination with Daunorubicin/Cytarabine Induction and High Dose Cytarabine Consolidation in Previously Untreated Adults with Acute Myeloid Leukemia (AML)

Richard M. Stone, MD, Daniel J. DeAngelo, MD PhD, Ilene Galinsky, Caroline Kokulis, Jeremy M. Stewart, BA, Michael McGinnis, Lillian Werner, MS, Anthony G. Letai, MD PhD, Marina Y Konopleva, MD PhD, Marlise Luskin, MDMS

616.ACUTE MYELOID LEUKEMIA: NOVEL THERAPY, EXCLUDING TRANSPLANTATION | NOVEMBER 13, 2019

A Phase Ib/II Study of the BCL-2 Inhibitor Venetoclax in Combination with Standard Intensive AML Induction/Consolidation Therapy with FLAG-IDA in Patients with Newly Diagnosed or Relapsed/Refractory AML

Iman Aboudalle, MD, Marina Y Konopleva, MD PhD, Tapan M. Kadia, MD, Kiran Naqvi, MDMPH, Kenneth Vaughan, RN, Mehmet Kurt, RN, Antonio Cavazos, Sherry A. Pierce, BSN, BA, Koichi Takahashi, MD, Lucia Masarova, MD, Musa E. Yilmaz, MD, Elias Jabbour, MD, Guillermo Garcia-Manero, MD, Steven M. Kornblau, MD, Farhad Ravandi, MD, Jorge Cortes, MD, Hagop M. Kantarjian, MD, Courtney D. DiNardo, MD MSc

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What's old is new again: CPX-351 (Vyxeos) and Gemtuzumab Ozogamycin (GO; Mylotarg)

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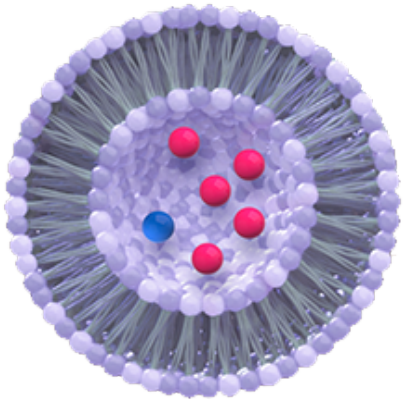
CPX-351 Uses a Nano-Scale Delivery Complex



- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

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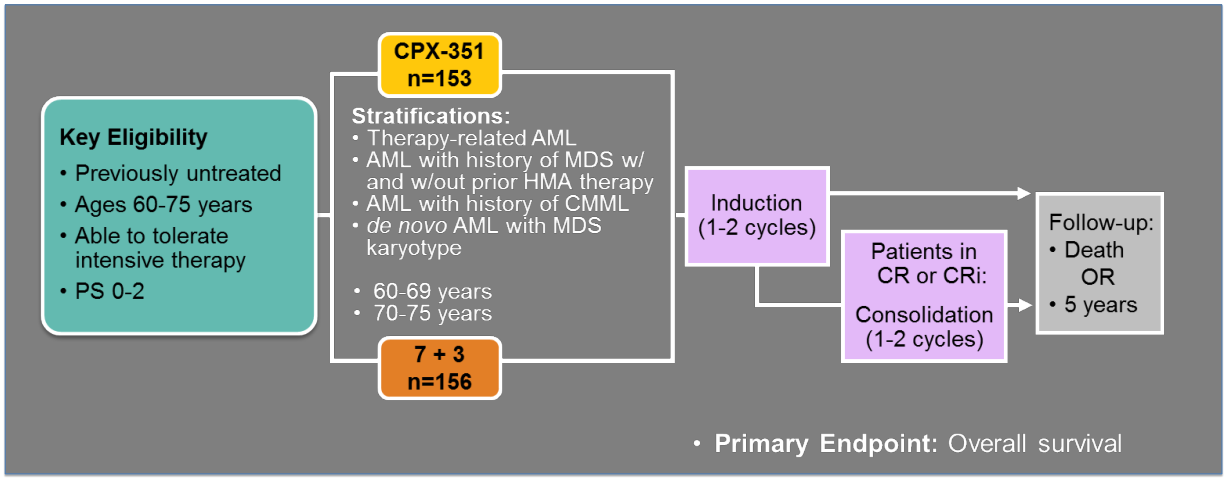
CPX-351: Phase 3 Study Design



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Treatment Schema

	CPX-351 1 unit = 1 mg cytarabine + 0.44 mg daunorubicin	7 + 3
First Induction	• 100 units/m^2 • Days 1, 3 and 5	• Cytarabine: 100 mg/m^2 x 7 d • Daunorubicin: 60 mg/m^2 x 3 d
Re-induction	• 100 units/m^2 • Days 1 and 3	• Cytarabine: 100 mg/m^2 x 5 d • Daunorubicin: 60 mg/m^2 x 2 d
Consolidation	• 65 units/m^2 • Days 1 and 3	• Cytarabine: 100 mg/m^2 x 5 d • Daunorubicin: 60 mg/m^2 x 2 d

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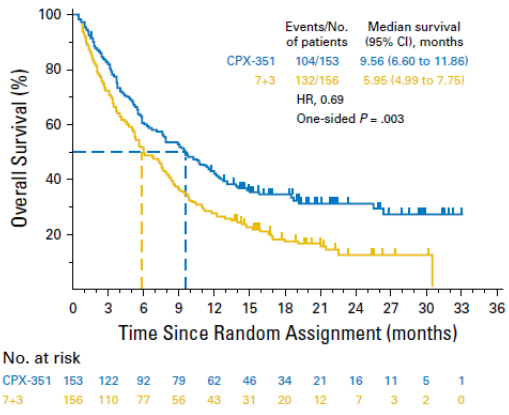
CPX-351: Improved Remission and Overall Survival

	CPX-351 n=153	7+3 n=156		
			Odds Ratio	*P* value
CR	37.3%	25.6%	1.67 (1.02, 2.74)	0.040
CR+CRi	47.7%	33.3%	1.77 (1.11, 2.81)	0.016
Stem Cell Transplant	34.0%	25.0%	1.54 (0.92, 2.56)	0.098



Lancet JCO 2018

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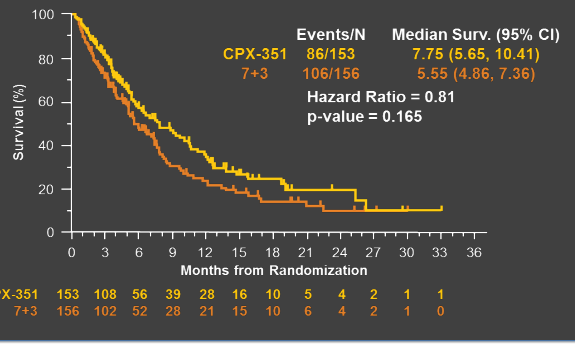
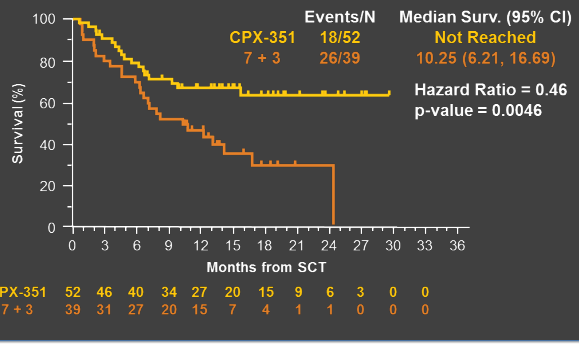
CPX-351: Effect of Allogeneic Transplant

HSCT Baseline Characteristics		CPX-351 n (%)	7+3 n (%)
Patients Who Went to Transplant		**52 (34)**	**39 (25)**
Age	60-69	36 (70)	33 (85)
	70-75	16 (31)	6 (15)

OS Censored at Time of Transplant



OS Landmarked at Time of Transplant



Lancet JCO 2018

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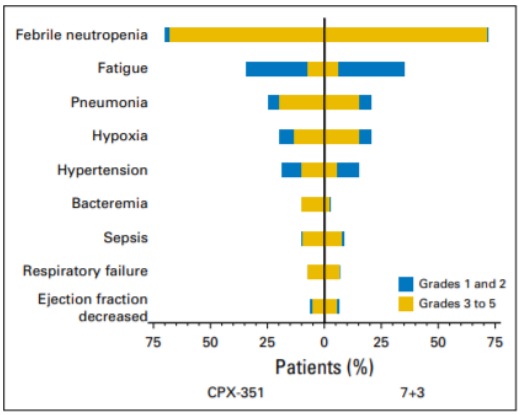
CPX-351: Safety



	Time to ANC recovery	Time to platelet recovery
CPX-351	35 days	36.5 days
7+3	29 days	29 days

Lancet JCO 2018

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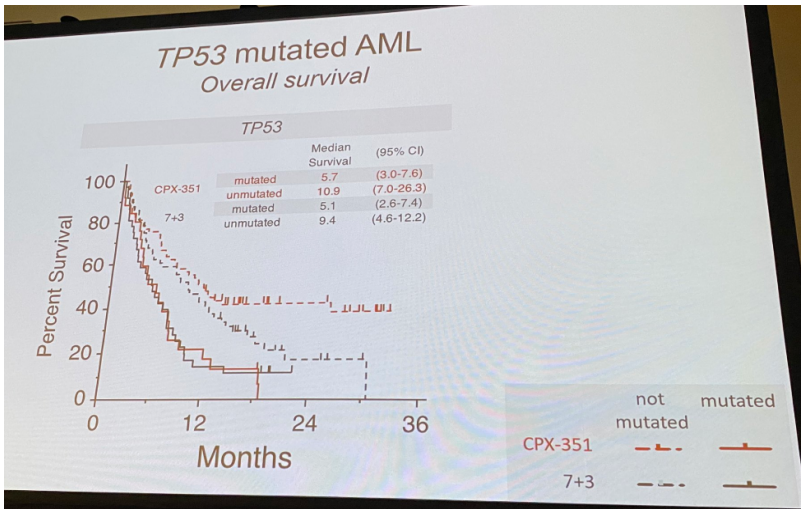
Caveat: TP53



Lindsley ASH abstract 2019

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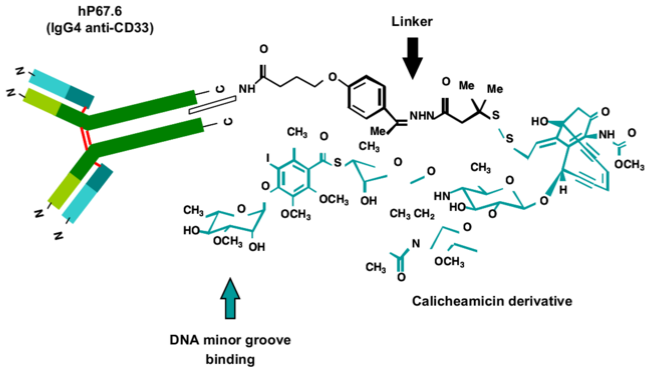
Gemtuzumab Ozogamycin (GO)

- CD33 antibody-drug conjugate (calicheamicin derivative)
- CD33 on >80% of AML



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ALFA 0701 Trial

Age 50-70
De Novo AML

R

Cytarabine 200 mg/m2 x7 days
Daunorubicin 60 mg/m2 x3 days
GO 3 mg/m2 on days 1,4,7
(max dose 5 mg)
→ 2 cycles HiDAC/dauno
GO 3 mg/m2 day 1

Cytarabine 200 mg/m2 x7 days
Daunorubicin 60 mg/m2 x3 days
→ 2 cycles HiDAC/dauno

Primary Endpoint: EFS
Secondary Endpoints: RFS, OS, safety

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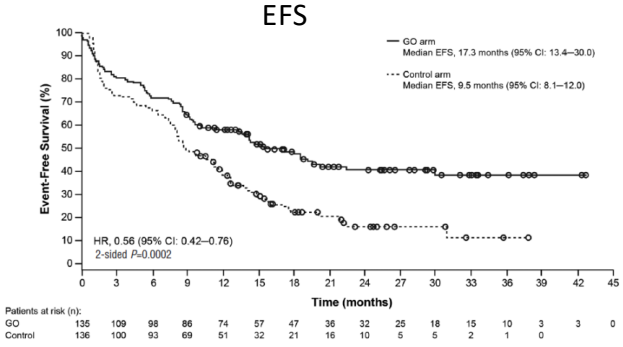
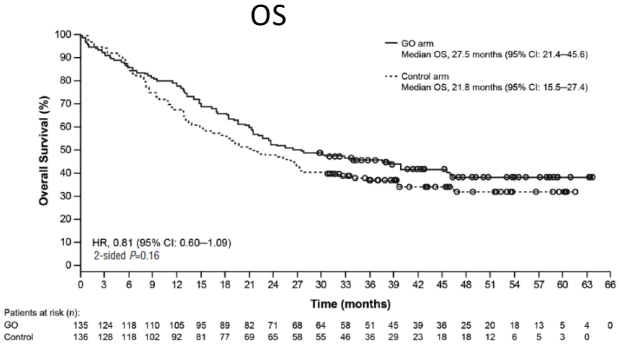
ALFA 0701: EFS and OS

EFS



OS



Lambert Haematologica 2019

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Study	Population	N	Age	GO dosing	Other rx	TRM	OS
US SWOG S0106	De novo or sAML	595	18-60	6 mg/m2 day 4	DA (60 mg/m2) vs DA (45 mg/m2) +GO		
UK MRC AML-15	De novo or sAML	1113	0-71	3 mg/m2 day 1	Randomization to DA or FLAG-Ida, both ± GO		*
French GOELAMS AML 2006	De novo, int cyto	238	18-60	6 mg/m2 day 4	DA ± GO	†	
UK NCRI AML16	AML and HR MDS	1115	51-84	3 mg/m2 day 1	Randomization to DA vs DClo, both ± GO		
French ALFA 0701	De novo	278	50-70	3 mg/m2 day 1,4,7	DA ± GO		

* Significant improvement in survival in favorable risk patients
† Significant increase in hepatotoxicity

Godwin Leukemia 2017

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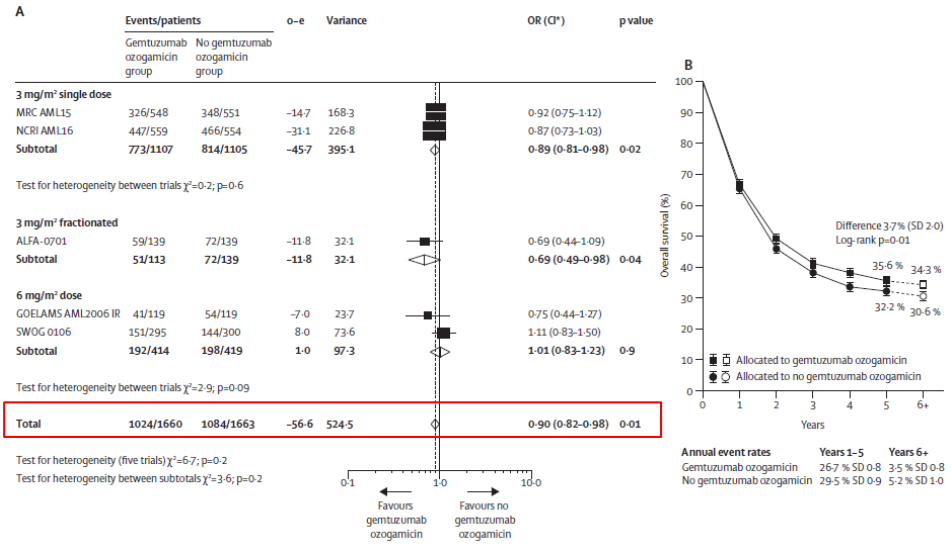
GO improved overall survival, by a small margin



Hills Lancet Oncol 2014

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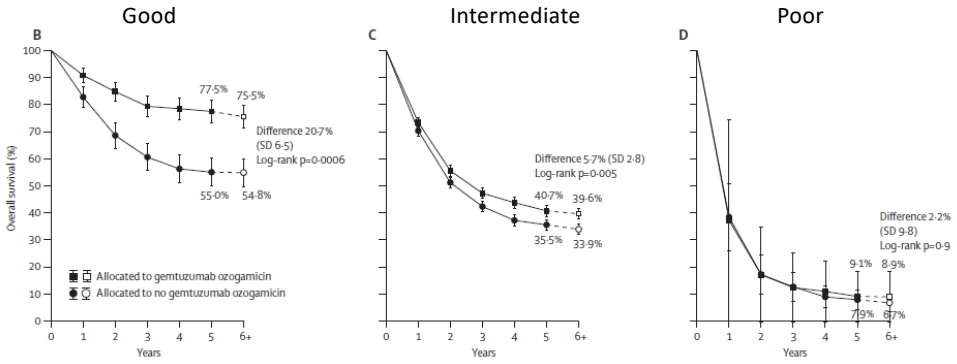
Effect of cytogenetic risk groups was significant



No effect of age, sex, diagnosis, induction type, FLT3, NPM1

Hills Lancet Oncol 2014

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What would you do?

68 year old with newly diagnosed AML, CD33+. Cytogenetics/FISH show monosomy 7. NGS panel is pending. Comorbidities include: hypertension, hyperlipidemia, type II diabetes, obesity, sleep apnea, and gout.

What is your preferred therapy?

A. Azacitidine + venetoclax
B. CPX-351
C. 7 + 3 + GO
D. Not sure – wait for NGS if possible

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FLT3 inhibitors: 1st line and in relapse

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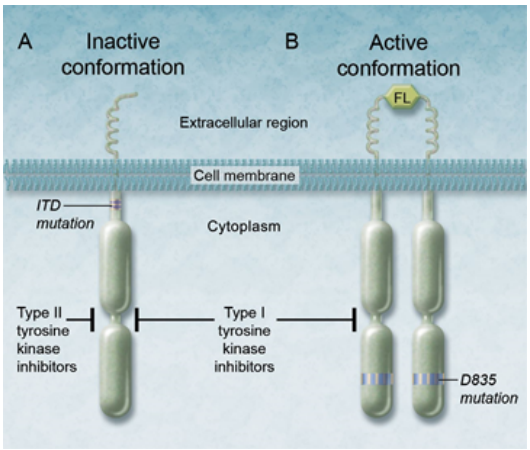
FLT3 inhibitors: types I vs II

Type II:
Sorafenib
Quizartinib (AC220)
Ponatinib
PLX3397



Type I:
Midostaurin
Lestaurtinib
Gilteritinib
Crenolanib

Sudhindra, A. & Smith, C.C. Curr Hematol Malig Rep 2014; Fathi Blood 2013

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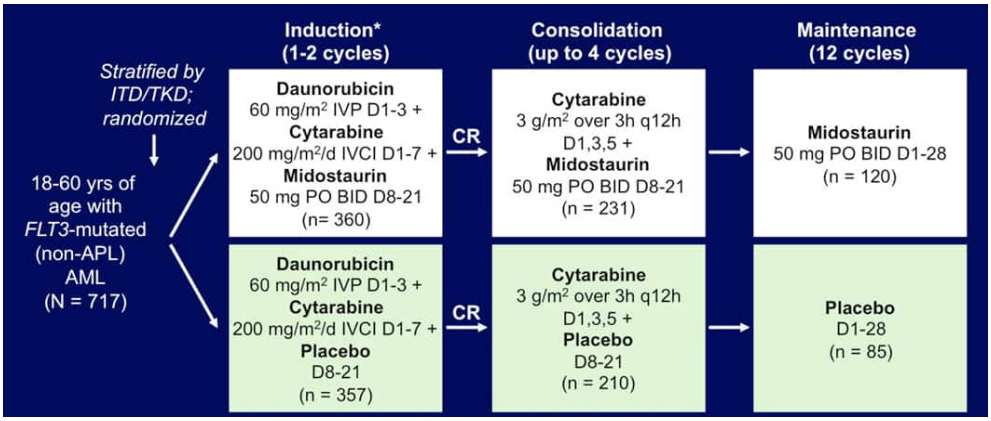
Midostaurin: RATIFY (C10603) Study Design

- Randomized, double-blind placebo controlled phase III study
- Primary endpoint: OS (not censored for SCT)



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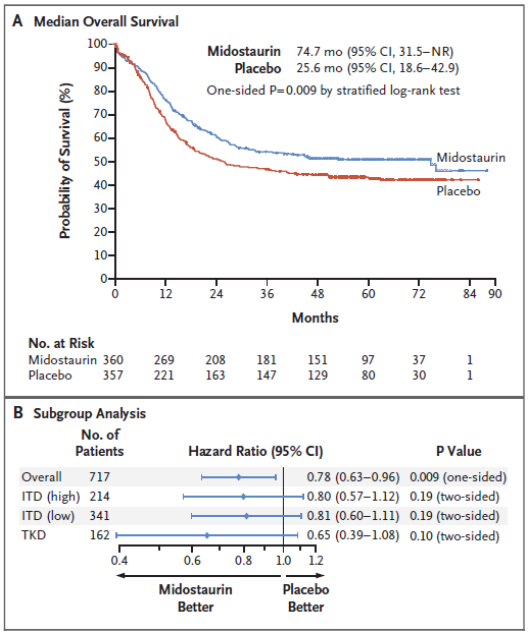

Table 2. Summary of Grade 3, 4, or 5 Adverse Events.

Adverse Event	Midostaurin Group (N=355)	Placebo Group (N=354)	P Value*
	no. of patients (%)		
Hematologic			
Thrombocytopenia	346 (97)	342 (97)	0.52
Neutropenia	338 (95)	339 (96)	0.86
Anemia	329 (93)	311 (88)	0.03
Leukopenia	93 (26)	105 (30)	0.32
Lymphopenia	68 (19)	78 (22)	0.35
Other blood or bone marrow event	1 (<1)	4 (1)	0.22
Bone marrow hypocellularity	0	1 (<1)	0.50
Nonhematologic			
Febrile neutropenia	290 (82)	292 (82)	0.84
Infection	186 (52)	178 (50)	0.60
Lymphopenia	68 (19)	78 (22)	0.35
Diarrhea	56 (16)	54 (15)	0.92
Hypokalemia	49 (14)	60 (17)	0.25
Pain	47 (13)	44 (12)	0.82
Increased alanine aminotransferase	45 (13)	33 (9)	0.19
Rash or desquamation	50 (14)	27 (8)	0.008
Fatigue	32 (9)	37 (10)	0.53
Pneumonitis or pulmonary infiltrates	28 (8)	29 (8)	0.89
Nausea	20 (6)	34 (10)	0.05
Hyponatremia	31 (9)	23 (6)	0.32
Hyperbilirubinemia	25 (7)	28 (8)	0.67
Mucositis or stomatitis	22 (6)	28 (8)	0.38
Hypophosphatemia	19 (5)	29 (8)	0.14
Hypocalcemia	24 (7)	21 (6)	0.76

Stone NEJM 2017

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Gilteritinib: ADMIRAL study design

Randomized 2:1

Adults w/FLT3-mutant AML refractory to initial induction or untreated first relapse after prior CRc (CR + Cri + CRp), ECOG perf status ≤ 2, normal liver and renal function, prior frontline midostaurin or sorafenib allowed, but no other prior FLT3 inhibitors (N = 371)

- **Gilteritinib 120 mg/day (n = 247)** → **HSCT** → **Gilteritinib 120 mg/day (n = 247)**
- **Salvage Chemotherapy* (n = 124)** → **HSCT**

*Salvage chemotherapy selected prior to randomization: MEC + FLAG-IDA (high intensity) for 1-2 cycles; Low-dose cytarabine + azacytidine (low intensity) administered until disease progression or intolerance

Primary endpoints: OS, CR/CRh

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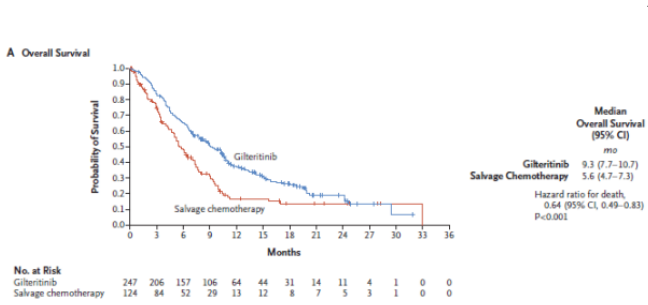
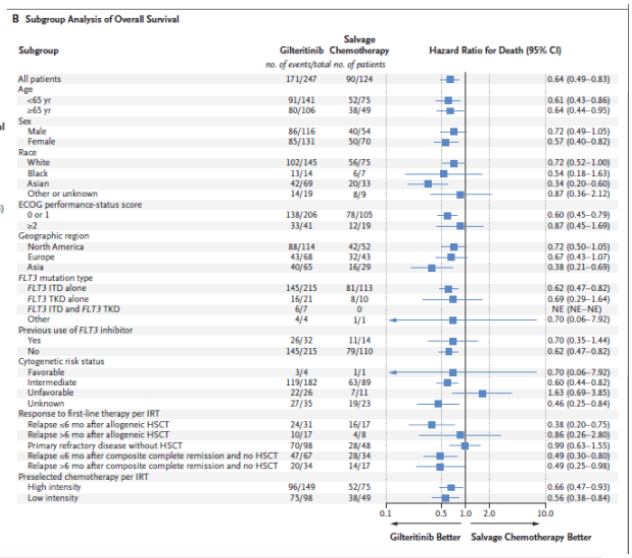
Gilteritinib: Efficacy and Safety





TEAEs G3+ in at least 10% - febrile neutropenia, anemia, thrombocytopenia, LFTs, hypokalemia

GI toxicity

Differentiation Syndrome

Pancreatitis

Prolonged QT

Perl NEJM 2019

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Next steps: Gilteritinib in combinations

613.ACUTE MYELOID LEUKEMIA: CLINICAL STUDIES | NOVEMBER 13, 2019

Phase II Randomized Trial of Gilteritinib Vs Midostaurin in Newly Diagnosed *FLT3* Mutated Acute Myeloid Leukemia (AML)

Selina M. Luger, MD FRCPC, Zhuoxin Sun, PhD, Sanam Loghavi, MD, Hillard M Lazarus, MD, Jacob M. Rowe, MB, BS, Martin S. Tallman, MD, Keith W. Pratz, MD, Mark Litzow, MD

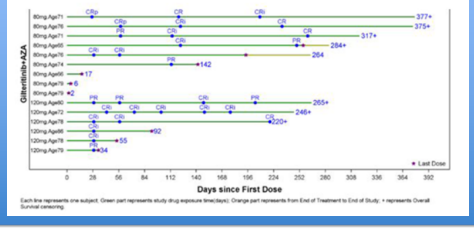
(7+3+midostaurin vs 7+3+gilteritinib)

616. ACUTE MYELOID LEUKEMIA: NOVEL THERAPY, EXCLUDING TRANSPLANTATION: POSTER II | NOVEMBER 29, 2018

Multicenter, Open-Label, 3-Arm 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: Findings from the Safety Cohort

Jordi Esteve, MD PhD, Rik Schots, Teresa Bernal Del Castillo, MD PhD, Je-Hwan Lee, MD PhD, Eunice S. Wang, MD, Shira Dinner, MD, Mark D. Minden, MD PhD, Olga Salamero, MD, Jorge Sierra, MD, Goichi Yoshimoto, MD PhD, Kamel Laribi, MD, Janusz Halka, MD, Pau Montesinos, MD PhD, Shufang Liu, Elizabeth Shima Rich, MD PhD, Erkut Bahceci, MD

Figure. Remission Response and Treatment Duration of Gilteritinib in Combination With Azacitidine



616.ACUTE MYELOID LEUKEMIA: NOVEL THERAPY, EXCLUDING TRANSPLANTATION | NOVEMBER 13, 2019

Venetoclax in Combination with Gilteritinib in Patients with Relapsed/Refractory Acute Myeloid Leukemia: A Phase 1b Study

Alexander E. Perl, MD, Naval G. Daver, MD, Keith W. Pratz, MD, Joseph Maly, MD, Wan-Jen Hong, MD, Erkut Bahceci, Bo Tong, PhD, Tian Tian, PhD, Kimberley Dilley, MD MPH

Table. Responses to Venetoclax plus Gilteritinib Treatment

Characteristic	Wild type *FLT3* n = 5	Mutant *FLT3* (9 ITD, 1 TKD) n = 10
Response, n (%)		
CR	0	1 (10)
CRi	0	1 (10)
CRp*	0	3 (30)
PR	0	0
MLFS	1 (20)	4 (40)
Resistant disease	3 (60)	1 (10)
Non-response evaluable	1 (20)	0
Early mortality, n (%)		
≤30 days	1 (20)	0

CI, confidence interval; CR, complete remission, CRi, CR with incomplete blood count recovery; CRp, CR without platelet recovery; MLFS, morphological leukemia free state

* The 1 patient with TKD *FLT3* had this response

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IDH1 and IDH2 inhibition: Ivosidenib and Enasidenib

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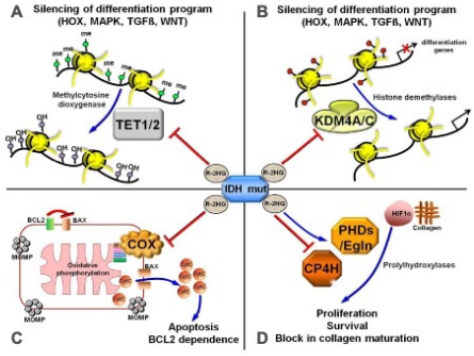
Targeting Mutant IDH1/2

- *IDH2* mutations lead to accumulation of 2-HG, an oncometabolite that competitively inhibits enzymes that utilize αKG as a substrate
  - αKG is a substrate for >60 αKG-dependent dioxygenases
- 2-HG–induced oncogenic activities are thought to include:



A and **B**: Differentiation block via inhibition of TET family enzymes and histone demethylases, yielding hypermethylated DNA and histones

C: BCL2 dependence via inhibition of Cyt C Oxidase in electron transport chain leading to lowered apoptotic threshold

D: Altered hypoxic response via dysregulated HIF-1α

Chan et al, *Nature Med*. 2015;21(2):178-84. Heuser et al, *Exp Hematology* 2015;43:685-97.
2-HG, 2-hydroxyglutarate; αKG, alpha ketoglutarate; BCL2, B-cell lymphoma 2; Cyt, cytochrome; HIF-1α, hypoxia-inducible factor 1-alpha; TET, ten-eleven translocation.

DiNardo, ASH 2019

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FDA Approved Uses of IDH inhibitors

Ivosidenib (IDH1)

Table 3. Investigator-Reported Hematologic Response, Time to Response, and Response Duration in Patients Receiving 500 mg of Ivosidenib Daily.*

Response	Primary Efficacy Population (N = 125)	Relapsed or Refractory AML (N = 179)	Untreated AML (N = 34)†	MDS (N = 12)‡
Overall response				
No. of patients	52	70	19	11
% (95% CI)	41.6 (32.9–50.8)	39.1 (31.9–46.7)	55.9 (37.9–72.8)	91.7 (61.5–99.8)
Median time to first response (range) — mo§	1.9 (0.8–4.7)	1.9 (0.8–4.7)	1.9 (0.9–2.9)	1.6 (1.0–2.8)
Median duration of response (95% CI) — mo	6.5 (4.6–9.3)	6.5 (4.6–9.3)	9.2 (1.9–NE)	NE (2.3–NE)

Enasidenib (IDH2)

Response	Enasidenib 100 mg per day (n = 109) No.	%	95% CI	Median	Range
ORR*†	42	38.5	29.4-48.3		
Best response					
CR	22	20.2	13.1-28.9		
CR with incomplete hematologic recovery/CR with incomplete platelet recovery	7	6.4			
Partial remission	3	2.8			

HEMATOLOGIC MALIGNANCIES—LEUKEMIA, MYELODYSPLASTIC SYNDROMES, AND ALLOTRANSPLANT

Ivosidenib (IVO; AG-120) in IDH1-mutant newly-diagnosed acute myeloid leukemia (ND AML): Updated results from a phase 1 study.

Gail J. Roboz, Courtney Denton Dinardo, Eytan M. Stein, Stéphane de Botton, Alice S. Mims, Gabrielle T. Prince, Jessica K. Altman, Martha Lucia Arellano, Harry Paul Erba, Daniel Aaron Pollyea, Anthony Selwyn Stein, Justin M. Watts, Amir Tahmasb Fathi, Hagop M. Kantarjian, Martin S. Tallman, Bin Fan, Hua Liu, Bin Wu, Eyal C. Attar, Richard M. Stone

- 75 or older or unfit for induction
- ORR 55% (95% CI 36-72%)
- CR+CRh 42% (95% CI 26-61%)
- Transfusion-independence rate of 42%

DiNardo NEJM 2018, Stein Blood 2017, Roboz ASCO abstract 2019

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Non-FDA approved uses of IDH inhibitors

Ivosidenib + AZA

HEMATOLOGIC MALIGNANCIES—LEUKEMIA, MYELODYSPLASTIC SYNDROMES, AND ALLOTRANSPLANT

Mutant IDH1 inhibitor ivosidenib (IVO; AG-120) in combination with azacitidine (AZA) for newly diagnosed acute myeloid leukemia (ND AML).

Courtney Denton Dinardo, Anthony Selwyn Stein, Eytan M. Stein, Amir Tahmasb Fathi, Olga Frankfurt, Andre C. Schuh, ...

ORR 78%, CR 57% (n = 18)

Enasidenib + AZA vs AZA

	ENA + AZA (n=68)	AZA Only (n=33)
Overall response (CR, CRi/CRp, PR, MLFS), n (%)	**48 (71)**	**14 (42)**
[ORR 95%CI]	[58, 81]	[26, 61]
P value	0.0064	
CR, n (%)	**36 (53)**	**4 (12)**
[CR rate 95%CI]	[41, 65]	[3, 28]
P value	0.0001	
CRi/CRp, n (%)	7 (10)	4 (12)
PR, n (%)	3 (4)	4 (12)
MLFS, n (%)	2 (3)	2 (6)
Stable disease, n (%)	13 (19)	13 (39)
Disease progression, n (%)	2 (3)	1 (3)
Not evaluable / Missing, n (%)	5 (7)	5 (15)

HEMATOLOGIC MALIGNANCIES—LEUKEMIA, MYELODYSPLASTIC SYNDROMES, AND ALLOTRANSPLANT

Phase Ib/II study of the IDH1-mutant inhibitor ivosidenib with the BCL2 inhibitor venetoclax +/- azacitidine in IDH1-mutated hematologic malignancies.

Curtis Andrew Lachowiez, Gautam Borthakur, Sanam Loghavi, Zhihong Zeng, Tapan M. Kadia, Lucia Masarova, Koichi Takahashi, George Dono Tippett, Kiran Naqvi, Prithviraj Bose, Elias Jabbour, Farhad Ravandi, Naval Guastad Daver, Guillermo Garcia-Manero, Bilyana Stoilova, Paresh Vyas, Hagop M. Kantarjian, Marina Konopleva, Courtney Denton Dinardo

Ivosidenib + Ven +/- AZA

ORR 67-100% across cohorts (n=18)

DiNardo ASCO 2019, DiNardo ASH 2019, Lachowiez ASCO 2020

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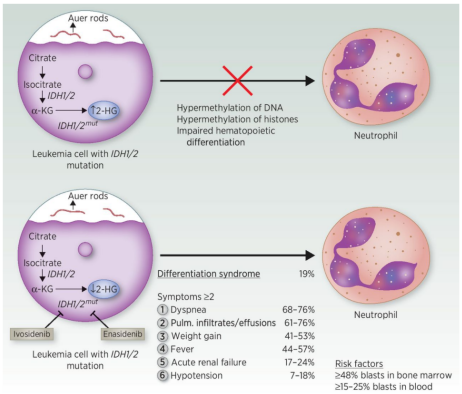
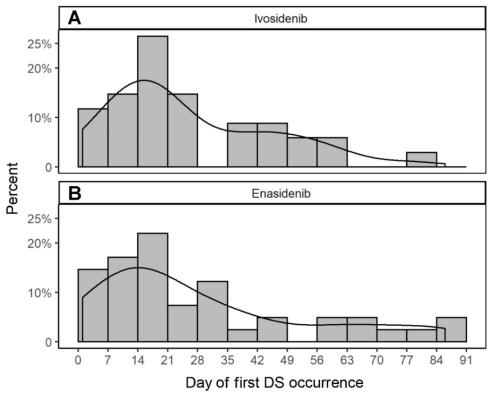
Differentiation Syndrome





Management: steroids, hydroxyurea, supportive care (O2, antibiotics, diuresis), consider stopping drug

Zeidner CCR 2020, Norsworthy CCR 2020

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Smoothened Inhibitor: Glasdegib

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Glasdegib: Inclusion Criteria

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Educating and Empowering the Northern California Cancer Community

- Age >=55
- Newly diagnosed AML or high risk MDS (>10% blasts)
- Not suitable for intensive chemotherapy, defined by one of the following:
  - Age >=75
  - Creatinine >1.3
  - Severe cardiac disease (eg LVEF <45%)
  - ECOG PS = 2

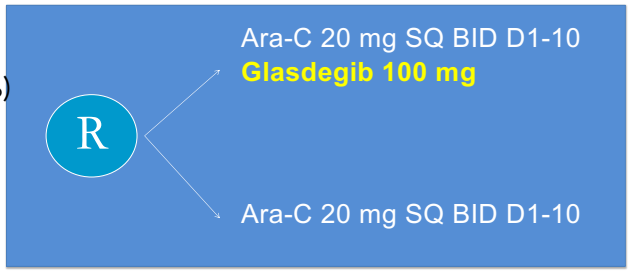

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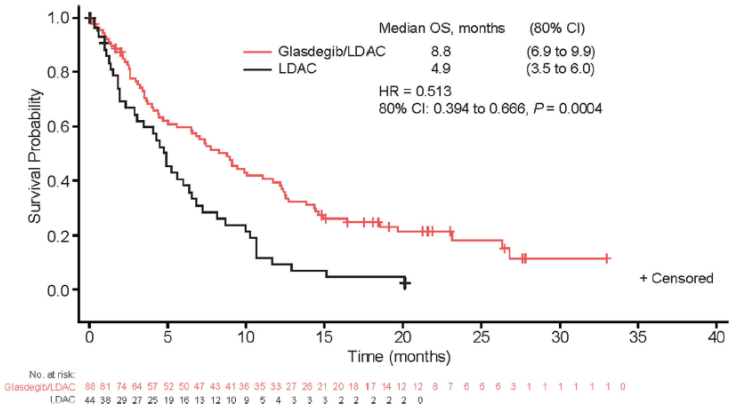
Table 2 Proportion of patients with investigator-reported CR, full analysis set

	Glasdegib 100 mg +LDAC, $N = 88$	LDAC, $N = 44$
Patients with CR, *n* (%)	15 (17.0)	1 (2.3)
80% CI[a]	11.9–22.2	0.0–5.2
Cytogenetic risk		
Good/intermediate	52	25
Patients with CR, *n* (%)	10 (19.2)	0 (0.0)
80% exact CI[b]	12.3–28.1	0.0–8.8
Poor cytogenetic risk	36	19
Patients with CR, *n* (%)	5 (13.9)	1 (5.3)
80% exact CI[b]	6.9–24.2	0.6–19.0
Combination versus LDAC		
Pearson Chi-square test for all enrolled patients (unstratified)		
P value		0.0142
CMH test for all enrolled patients stratified by cytogenetics[c]		
Odds ratio (80% CI)		5.03 (1.59–15.88)
P value		0.0152



Cortes Leukemia 2019

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What would you do?

70 year old with IDH1+ AML initially treated with azacitidine/venetoclax, with achievement of CR for 9 months. He then develops circulating myeloid blasts consistent with relapse. His functional status has

What is your preferred therapy?

A. Ivosidenib
B. 7 + 3
C. Await FLT3 PCR; consider gilteritinib if positive
D. Not sure – wait for NGS if possible

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So, how do I treat AML in 2020?

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Prior therapeutic algorithm

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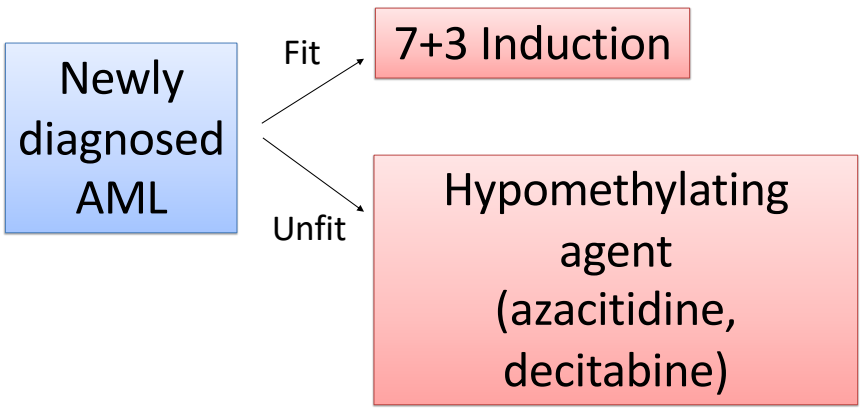

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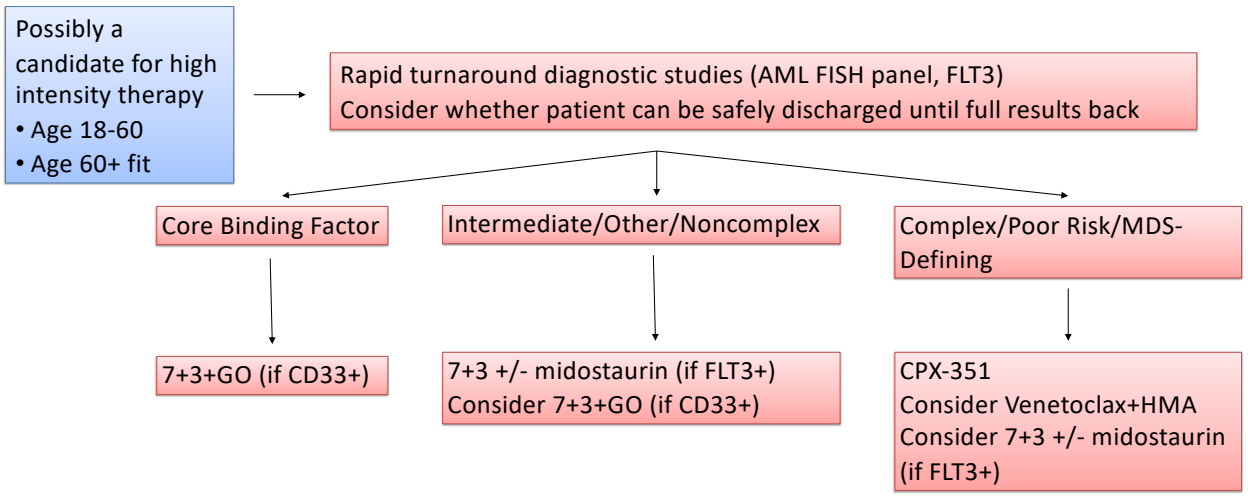
Therapeutic algorithm in 2020: Fit



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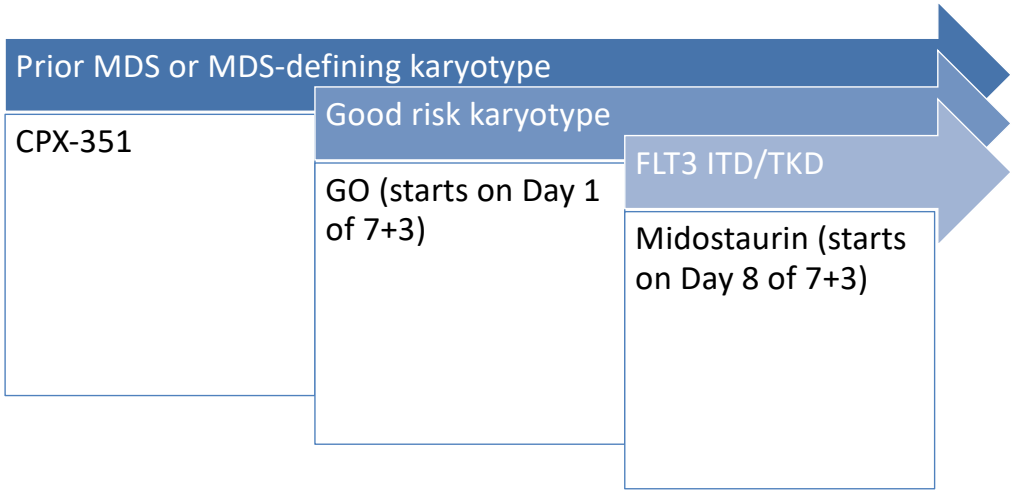
"Fit" Patients Need Rapid Cytogenetics and Molecular Testing



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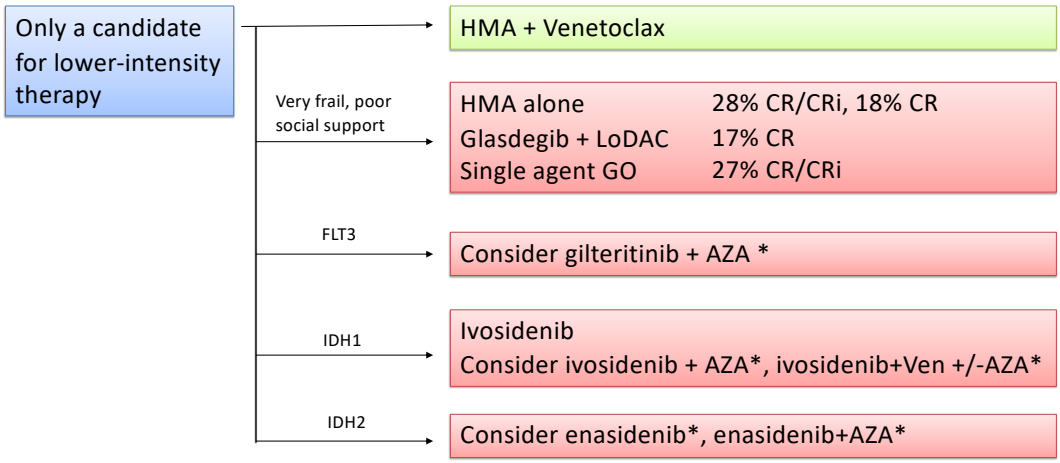
Therapeutic algorithm in 2020: Unfit



* Not FDA approved

DiNardo EHA abstract 2020; Cortes Leukemia 2019; Amadori JCO 2016

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What does "fit" or "unfit" mean?

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Newest Kids On The Block: Oral Hypomethylating Agents

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QUAZAR AML-001 Study Design

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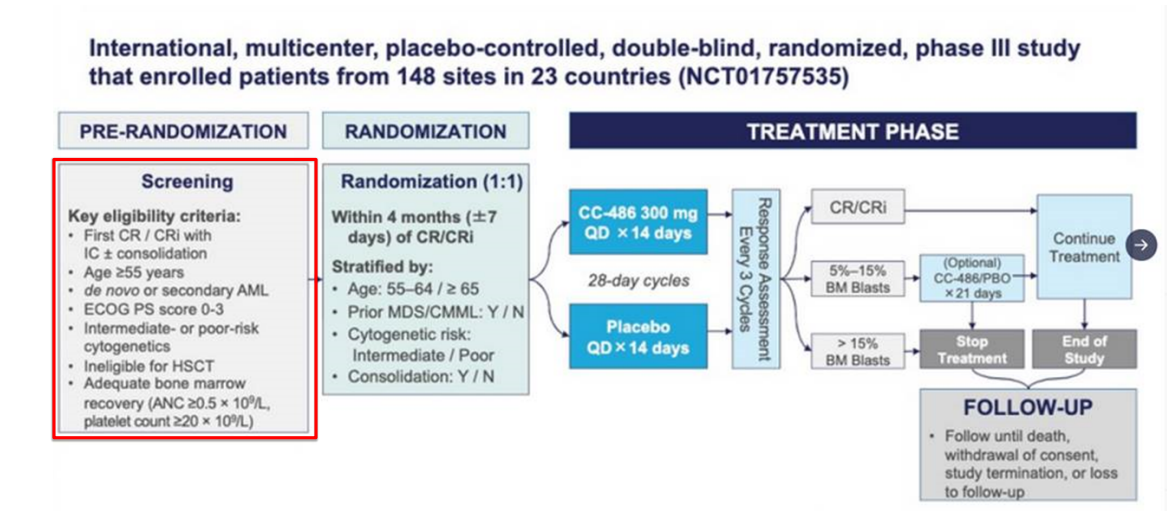

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QUAZAR AML-001

APPROVED Sept 1 2020

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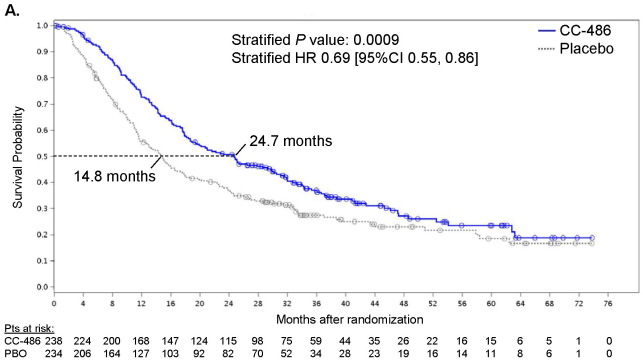
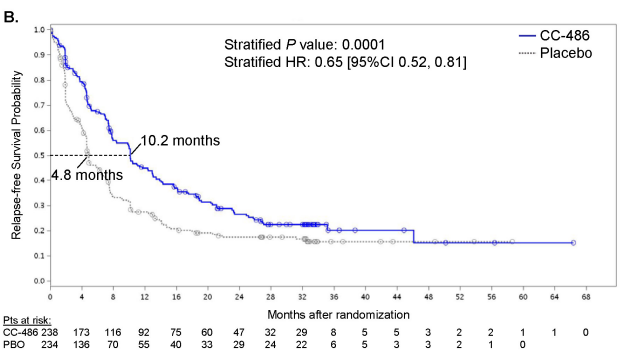
Overall Survival



Relapse-free Survival



95%CI, 95% confidence interval; HR, hazard ratio; PBO, placebo; Pts, patients

Wei, ASH LBA abstract 2019

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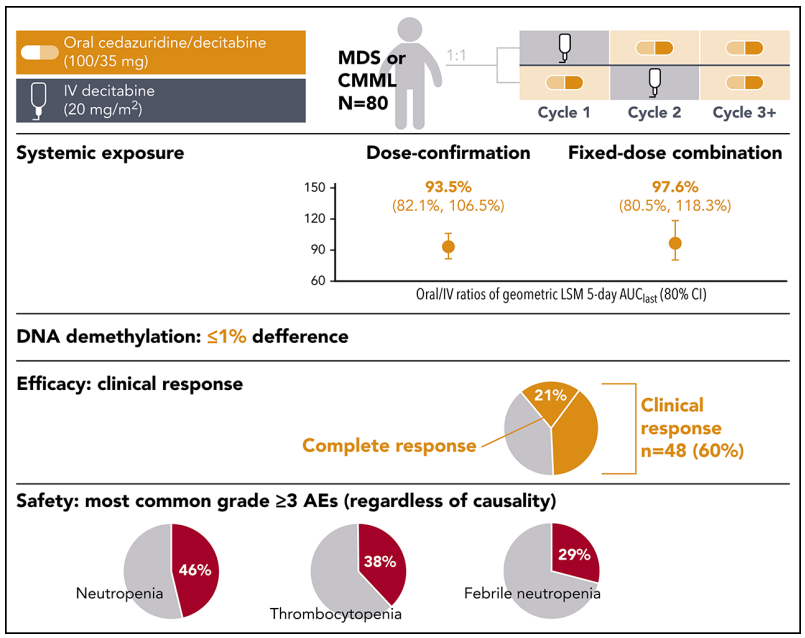

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APPROVED July 7 2020

Garcia-Manero Blood 2020

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BRIGHT FUTURE AHEAD
• New treatment options
• New combinations
• New challenges (such as molecular testing)

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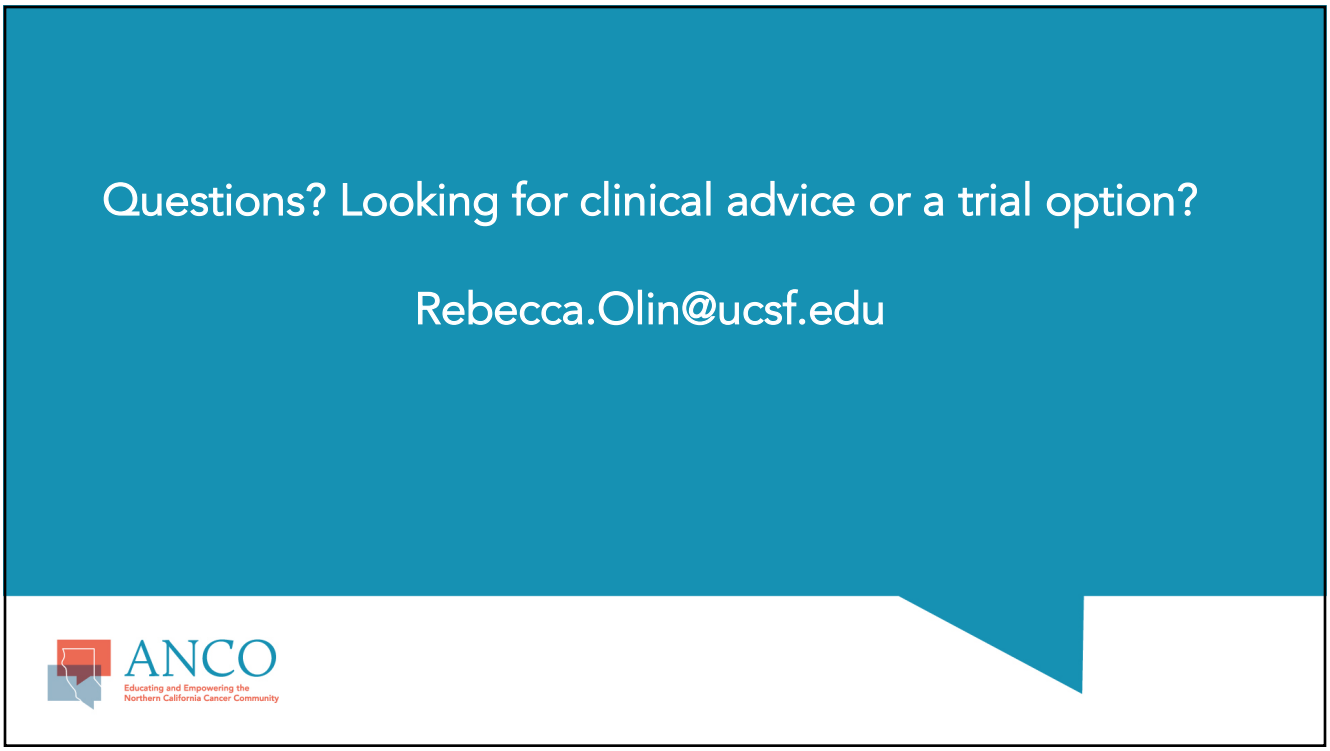
Questions? Looking for clinical advice or a trial option?
Rebecca.Olin@ucsf.edu
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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

ANCO Lymphoma Update 2020

Neel K. Gupta, **MD**
Associate Professor of Medicine
Stanford University

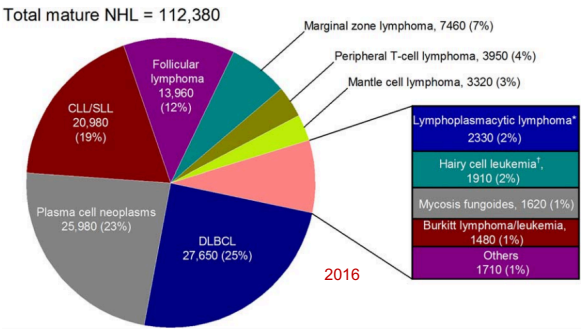
ANCO Hematologic Malignancies Update 2020: Non-Hodgkin's Lymphoma

Neel K. Gupta, MD
Clinical Assistant Professor
Divisions of Hematology and Oncology
Stanford University Department of Medicine
November 14, 2020

1

Overview:

- **Diffuse Large B-cell Lymphoma (DLBCL)**
  - SOC 1st line treatment
  - 2nd line treatment
  - New options for relapsed/refractory disease
- **Follicular Lymphoma (FL)**
  - SOC 1st line treatment
  - New options for relapsed/refractory disease
- **Mantle Cell Lymphoma (FL)**
  - 1st line treatment
  - Relapsed/refractory treatment options
  - New options for relapsed/refractory disease



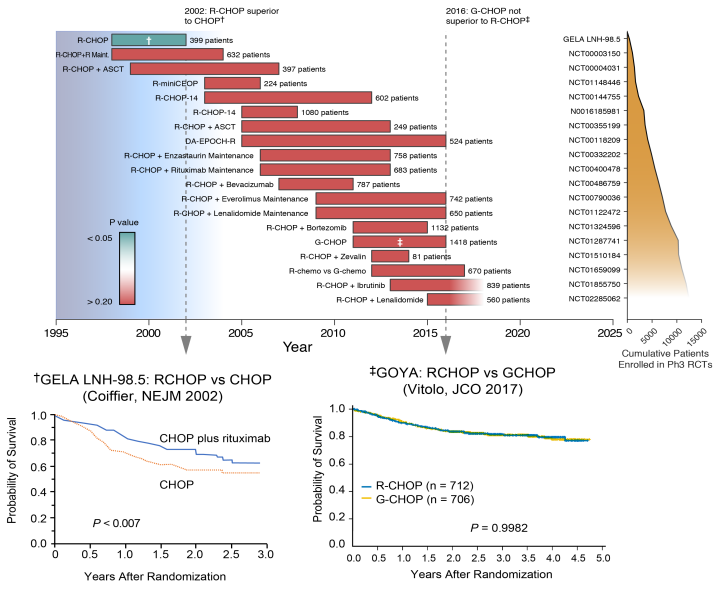
Teras et al, Cancer J Clin 2016;66:443-459

2

Diffuse Large B-cell Lymphoma (DLBCL)

- Standard of care 1st line therapy:
  - R-CHOP >>> **5-yr OS ~ 60%**
  - Attempts to improve upon R-CHOP >> ???

3



Courtesy of David Kurtz MD,PhD - Clinical Instructor, Stanford University

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Diffuse Large B-cell Lymphoma (DLBCL)

- Standard of care 1st line therapy:
  - R-CHOP >>> 5-yr OS ~ 60%
  - Attempts to improve upon R-CHOP >> ???

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Diffuse Large B-cell Lymphoma (DLBCL)

- Standard of care 1st line therapy:
  - R-CHOP >>> 5-yr OS ~ 60%
  - Attempts to improve upon R-CHOP >> FAIL

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Diffuse Large B-cell Lymphoma (DLBCL)

- Standard of care 1st line therapy:
  - R-CHOP >>> 5-yr OS ~ 60%
  - Attempts to improve upon R-CHOP >> FAIL
  - Current efforts to improve upon R-CHOP
    - EveR-CHOP (Johnston et al, Lancet Haem 2016; Witzig et al, Blood Cancer Journal 2017)

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Articles

Everolimus combined with R-CHOP-21 for new, untreated, diffuse large B-cell lymphoma (NCCTG 1085 [Alliance]): safety and efficacy results of a phase 1 and feasibility trial

Patrick B Johnston, Betsy LaPlant, Ellen McPhail, Thomas M Habermann, David J Inwards, Ivana N Micallef, Joseph P Colgan, Grzegorz S Nowakowski, Stephen M Ansell, Thomas E Witzig

Summary

Background The PI3K–mTORC pathway is upregulated in diffuse large B-cell lymphoma (DLBCL) and can be targeted with the mTOR complex 1 (mTORC1) inhibitor everolimus. Everolimus has activity in relapsed DLBCL. These data provide the rationale to combine everolimus with standard treatment for DLBCL of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone delivered in a 21-day cycle (R-CHOP-21) for six cycles.

Methods We did a phase 1 and feasibility study (NCCTG 1085) of oral everolimus 10 mg/day plus R-CHOP-21 in patients aged at least 18 years with new, untreated, CD20-positive DLBCL (stages II–IV) in the NCCTG (Alliance) National Cancer Institute Cooperative Group (USA). Patients received standard R-CHOP-21 (intravenous rituximab 375 mg/m², intravenous cyclophosphamide 750 mg/m², intravenous doxorubicin 50 mg/m², and intravenous vincristine 1·4 mg/m² [maximum 2·0 mg] all on day 1 of the 21-day cycle; and oral prednisone 100 mg/m² each day on days 1–5 of the cycle) for six cycles with scheduled subcutaneous pegfilgrastim 6 mg on day 2 of each cycle. We tested two schedules: everolimus given in the fasting state either on days 1–10 or days 1–14 of the R-CHOP cycle. The primary endpoint of the phase 1 portion of this study was to establish the maximum tolerated dose of everolimus that could be combined with R-CHOP-21. The primary endpoint of the feasibility portion of the study was to determine the feasibility of the regimen, which was assessed by determining the rate of significant toxicity. Secondary endpoints were the proportion of patients who achieved an overall response, a complete response, event-free survival at 12 months and 24 months from enrolment, progression-free survival, and overall survival; relapse of DLBCL; and duration of response. We deemed patients as assessable for the primary endpoint in the phase 1 portion if they completed the first cycle as planned. In the feasibility portion, all patients who received at least one dose of everolimus were included. This trial is registered with ClinicalTrials.gov, number NCT01334502.

Lancet Haematol 2016; 3: e309–16

Published Online June 5, 2016 http://dx.doi.org/10.1016/S2352-3026(16)30040-0

See Comment page e302

Mayo Clinic Division of Hematology (Prof T E Witzig MD), **Mayo Clinic College of Medicine and Mayo Foundation, Rochester, MN, USA** (P B Johnston MD, B LaPlant MS, E McPhail MD, Prof T M Habermann MD, D J Inwards MD, I N Micallef MD, J P Colgan MD, G S Nowakowski MD, Prof S M Ansell MD)

Correspondence to: Prof Thomas E Witzig, Mayo Clinic Division of Hematology, Rochester, MN 55905, USA **witzig.thomas@mayo.edu**

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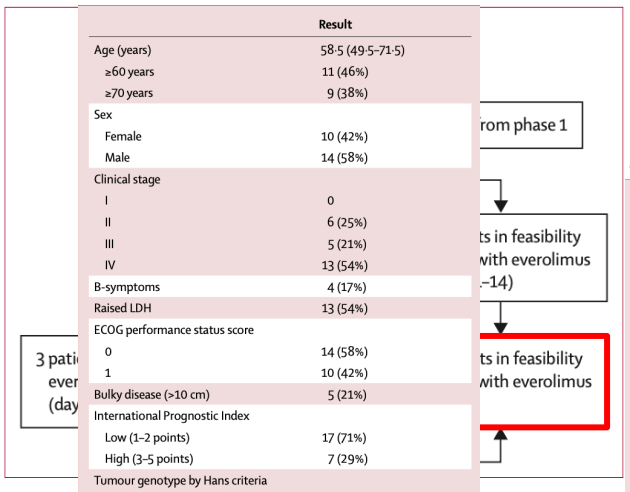
	Result
Age (years)	58·5 (49·5–71·5)
≥60 years	11 (46%)
≥70 years	9 (38%)
Sex	
Female	10 (42%)
Male	14 (58%)
Clinical stage	
I	0
II	6 (25%)
III	5 (21%)
IV	13 (54%)
B-symptoms	4 (17%)
Raised LDH	13 (54%)
ECOG performance status score	
0	14 (58%)
1	10 (42%)
Bulky disease (>10 cm)	5 (21%)
International Prognostic Index	
Low (1–2 points)	17 (71%)
High (3–5 points)	7 (29%)
Tumour genotype by Hans criteria	
Germinal centre type	11 (46%)
Non-germinal centre type	13 (54%)

Data are median (IQR) or n (%). LDH=lactic acid dehydrogenase. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics of the 24 eligible patients**



- 24 patients with newly diagnosed DLBCL given standard R-CHOP w/ pegGCSF + everolimus 10 mg daily
- Everolimus dose based on FDA-approved indications for other cancers

Table 2: adverse events in the study

	Grade 1–2	Grade 3	Grade 4
Haematological adverse events			
Anaemia	9 (38%)	3 (12%)	0
Leucocytosis	0	2 (8%)	0
Leucopenia	4 (17%)	7 (29%)	2 (8%)
Lymphopenia	0	4 (17%)	0
Neutropenia	4 (17%)	0	18 (75%)
Thrombocytopenia	15 (63%)	3 (13%)	3 (13%)
Non-haematological adverse events			
Febrile neutropenia	0	5 (21%)	0
Hypercholesterolaemia	14 (58%)	0	0
Hypertriglyceridaemia	15 (63%)	3 (13%)	0
Hyperglycaemia	0	1 (4%)	0
Diarrhoea	12 (50%)	0	0
Nausea	3 (13%)	0	0
Pneumonitis	3 (12%)	1 (4%)	0
Acneiform rash	0	1 (4%)	0
Maculopapular rash	5 (21%)	0	0
Dry skin	0	1 (4%)	0
Fatigue	11 (46%)	1 (4%)	0

Johnston et al, Lancet Haem 2016

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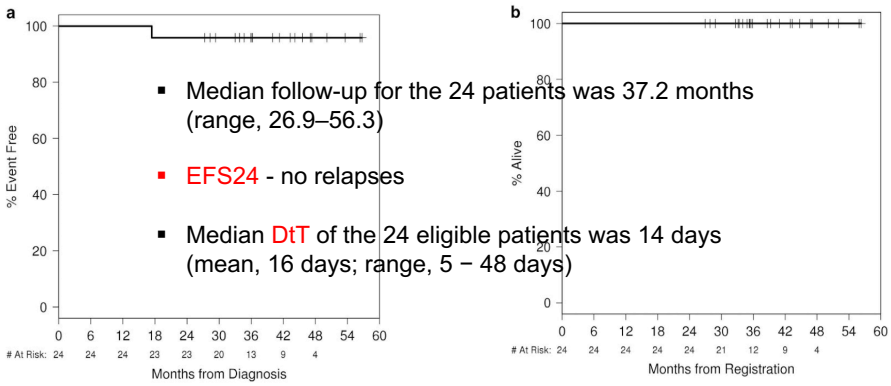
NCCTG N1085 (Alliance)



- Median follow-up for the 24 patients was 37.2 months (range, 26.9–56.3)
- EFS24 - no relapses
- Median DtT of the 24 eligible patients was 14 days (mean, 16 days; range, 5 − 48 days)

Figure 1. Event-free (**a**) and overall survival (**b**) of the 24 patients treated with everolimus and RCHOP on N1085 as updated through February 2017.

Witzig et al, Blood Cancer Journal 2017

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Clinical Trial Endpoints for Lymphoma

- **EFS24**
- **DtT (or DTI)**

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Clinical Trial Endpoints for Lymphoma

- **EFS24 = Event-Free Survival at 24 Months**
- **DtT (or DTI) = Diagnosis-to-treatment Interval**

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VOLUME 32 · NUMBER 10 · APRIL 1 2014
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Patients and Methods

Patients with newly diagnosed DLBCL treated with immunochemotherapy were prospectively enrolled onto the University of Iowa/Mayo Clinic Specialized Program of Research Excellence Molecular Epidemiology Resource (MER) and the North Central Cancer Treatment Group NCCTG-N0489 clinical trial from 2002 to 2009. Patient outcomes were evaluated at diagnosis and in the subsets of patients achieving event-free status at 12 months (EFS12) and 24 months (EFS24) from diagnosis. Overall survival was compared with age- and sex-matched population data. Results were replicated in an external validation cohort from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) Lymphome Non Hodgkinien 2003 (LNH2003) program and a registry based in Lyon, France.

Results

In all, 767 patients with newly diagnosed DLBCL who had a median age of 63 years were enrolled onto the MER and NCCTG studies. At a median follow-up of 60 months (range, 8 to 116 months), 299 patients had an event and 210 patients had died. Patients achieving EFS24 had an overall survival equivalent to that of the age- and sex-matched general population (standardized mortality ratio [SMR], 1.18; $P = .25$). This result was confirmed in 820 patients from the GELA study and registry in Lyon (SMR, 1.09; $P = .71$). Simulation studies showed that EFS24 has comparable power to continuous EFS when evaluating clinical trials in DLBCL.

Maurer, MS, Department of Health Sciences Research, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: maurer.matthew@mayo.edu.

0732-183X/14/3210w-1066w/$20.00
DOI: 10.1200/JCO.2013.51.5866

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Conclusion

Patients with DLBCL who achieve EFS24 have a subsequent overall survival equivalent to that of the age- and sex-matched general population. EFS24 will be useful in patient counseling and should be considered as an end point for future studies of newly diagnosed DLBCL.

J Clin Oncol 32:1066-1073. © 2014 by American Society of Clinical Oncology

ANCO Educating and Empowering the Northern California Cancer Community

Maurer et al, JCO 2016

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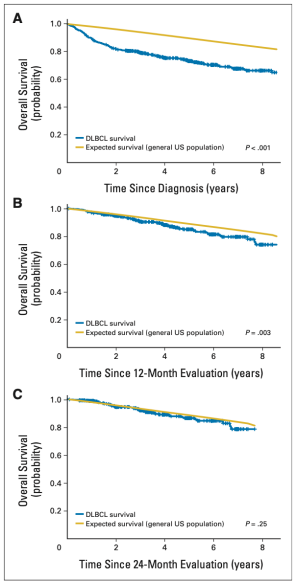

Fig 2. Overall survival versus expected survival in US cohort at diagnosis, in patients achieving event-free survival at 12 (EFS12) or 24 (EFS24) months. (A) Overall survival since diagnosis; (B) overall survival since EFS12 evaluation; (C) overall survival since EFS24 evaluation. DLBCL, diffuse large B-cell lymphoma.

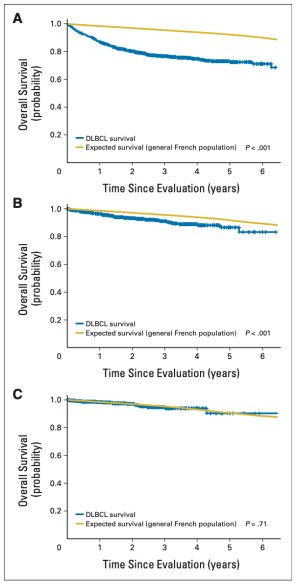

Fig 4. Overall survival versus expected survival in French cohort at diagnosis, in patients achieving event-free survival at 12 (EFS12) or 24 (EFS24) months. (A) Overall survival since diagnosis; (B) overall survival since EFS12 evaluation; (C) overall survival since EFS24 evaluation. DLBCL, diffuse large B-cell lymphoma.

ANCO Educating and Empowering the Northern California Cancer Community

Maurer et al, JCO 2016

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VOLUME 32 · NUMBER 10 · APRIL 1 2014
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Maurer et al, JCO 2016

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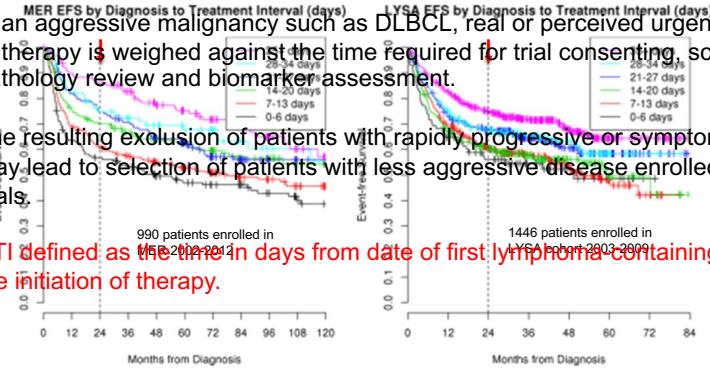
Diagnosis-to-Treatment Interval (DTI) Remains Associated with Adverse Clinical Characteristics and Outcome in Newly Diagnosed Patients with Diffuse Large B-Cell Lymphoma Treated on Clinical Trials

- S… el… If…
- L… g…
- A… fa… D… tc…
- In an aggressive malignancy such as DLBCL, real or perceived urgency of initiation of therapy is weighed against the time required for trial consenting, screening, pathology review and biomarker assessment.
- The resulting exclusion of patients with rapidly progressive or symptomatic disease may lead to selection of patients with less aggressive disease enrolled on clinical trials.
- DTI defined as the time in days from date of first lymphoma-containing biopsy to the initiation of therapy.



 Maurer et al, ASH 2017; Abstract 626

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Diffuse Large B-cell Lymphoma (DLBCL)

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  - R-CHOP >>> 5-yr OS ~ 60%
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  - Current efforts to improve upon R-CHOP
    - EveR-CHOP (Witzig et al, Blood Cancer Journal 2017; Johnston et al, Lancet Haem 2016)
    - Tazometostat + R-CHOP

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CLINICAL CANCER RESEARCH

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Clinical Trials: Targeted Therapy

A LYSA Phase Ib Study of Tazemetostat (EPZ-6438) plus R-CHOP in Patients with Newly Diagnosed Diffuse Large B-Cell Lymphoma (DLBCL) with Poor Prognosis Features

Clémentine Sarkozy, Franck Morschhauser, Sydney Dubois, Thierry Molina, Jean Marie Michot, Peggy Cullières-Dartigues, Benjamin Suttle, Lionel Karlin, Steven Le Gouill, Jean-Michel Picquenot, Romain Dubois, Hervé Tilly, Charles Herbaux, Fabrice Jardin, Gilles Salles, and Vincent Ribrag

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DOI: 10.1158/1078-0432.CCR-19-3741 Published July 2020 Check for updates

Article Figures & Data Info & Metrics PDF

Abstract

Purpose: The histone-methyl transferase EZH2, catalytic subunit of the PRC2 complex involved in transcriptional regulation, is mutated in approximately 25% of germinal center B-cell lymphomas. Aberrant proliferative dependency on EZH2 activity can be targeted by the orally available EZH2 inhibitor tazemetostat (EPZ-6438). We report the results of the phase Ib tazemetostat plus R-CHOP combination (NCT02889523), in patients 60 to 80 years of age with newly diagnosed diffuse large B-cell lymphoma.

July 2020
Volume 26, Issue 13
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Editorial Board (PDF)

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Diffuse Large B-cell Lymphoma (DLBCL)

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Phase Ib Study to Assess Safety and Preliminary Efficacy of Tafasitamab or Tafasitamab Plus Lenalidomide in Addition to R-CHOP in Patients With Newly Diagnosed DLBCL

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04134936

Recruitment Status : Recruiting
First Posted : October 22, 2019
Last Update Posted : April 3, 2020

See Contacts and Locations

Sponsor:
MorphoSys AG

Information provided by (Responsible Party):
MorphoSys AG

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Diffuse Large B-cell Lymphoma (DLBCL)

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- Standard of care 2nd line therapy
  - **Platinum-based chemotherapy f/b autoSCT** (PARMA, CORAL)

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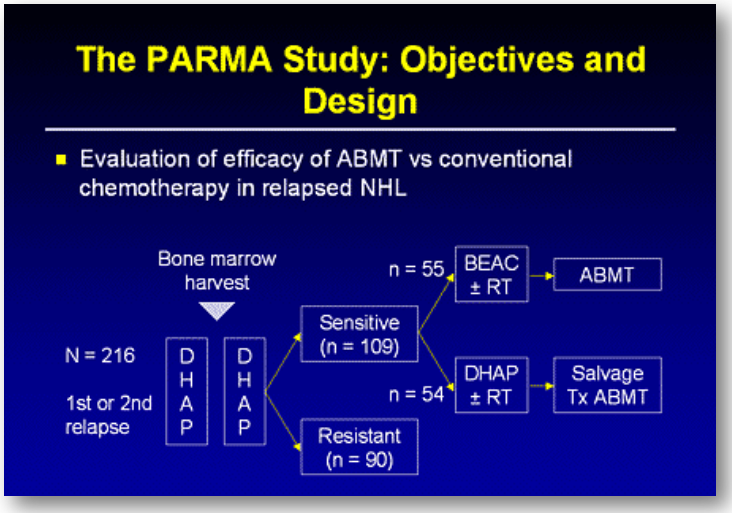
The PARMA Study: Objectives and Design

- Evaluation of efficacy of ABMT vs conventional chemotherapy in relapsed NHL



Philip et al, NEJM 1995

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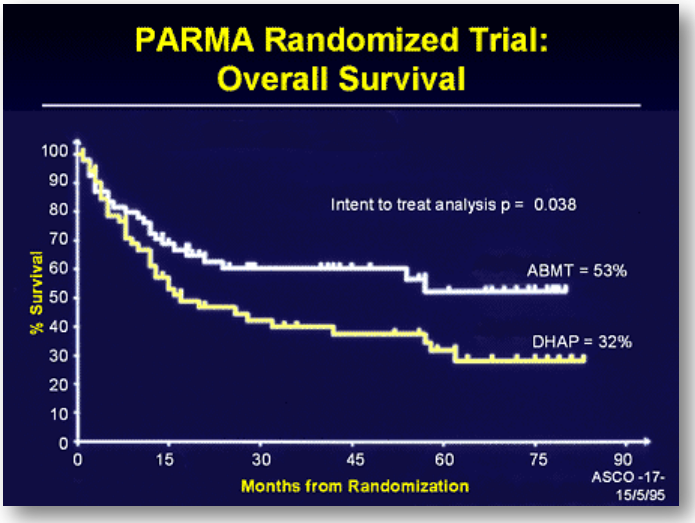

Philip et al, NEJM 1995

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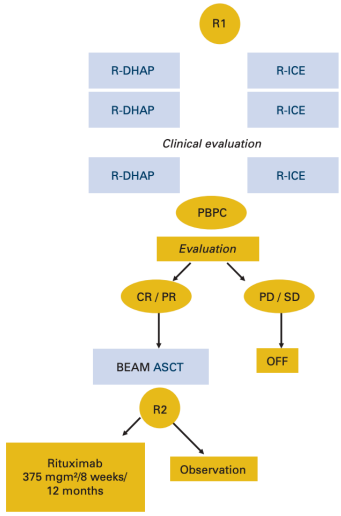


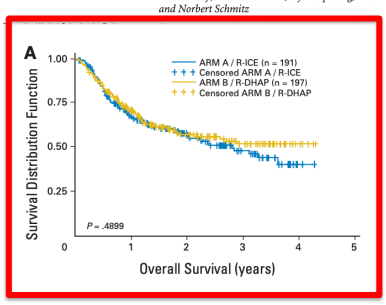
CORAL Study JCO 2010

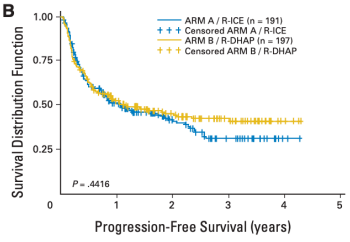
VOLUME 28 · NUMBER 27 · SEPTEMBER 20 2010

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era

Christian Gisselbrecht, Bertram Glass, Nicolas Mounier, Devinder Singh Gill, David C. Linch, Marek Trneny, Andre Bosly, Nicolas Ketterer, Ofer Shpilberg, Hans Hagberg, David Ma, Josette Brière, Craig H. Moskowitz, and Norbert Schmitz





Gisselbrecht et al, JCO 2010

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- Standard of care 2nd line therapy
  - Platinum-based chemotherapy f/b autoSCT (PARMA, CORAL) >>> 40 – 50% cured
  - Established regimens that allow stem-cell mobilization: R-ICE, R-DHAP, **R-GDP**

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VOLUME 32 · NUMBER 31 · NOVEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Comparison of Gemcitabine, Dexamethasone, and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12

Michael Crump, John Kuruvilla, Stephen Couban, David A. MacDonald, Vishal Kukreti, C. Tom Kouroukis, Morel Rubinger,† Rena Buckstein, Kevin R. Imrie, Massimo Federico, Nicola Di Renzo, Kang Howson-Jan, Tara Baetz, Leonard Kaizer, Michael Voralia, Harold J. Olney, A. Robert Turner, Jonathan Sussman, Annette E. Hay, Marina S. Djurfeldt, Ralph M. Meyer, Bingshu E. Chen, and Lois E. Shepherd

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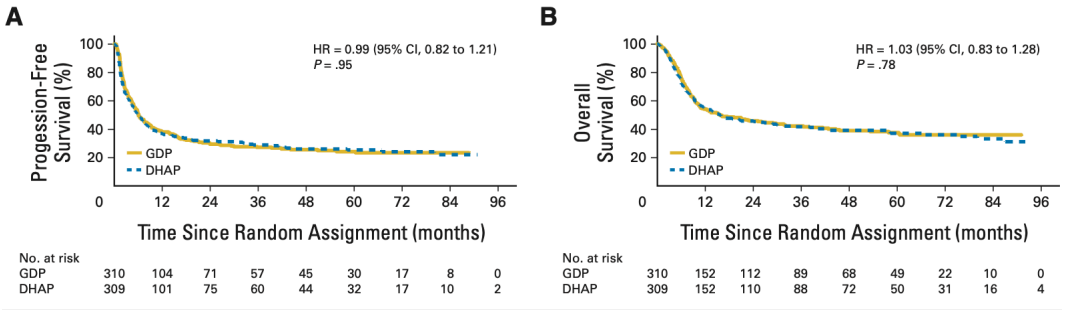
R-GDP vs R-DHAP: Crump et al, JCO 2014

- **R-GDP**
  - Rituximab D1
  - Gemcitabine 1000 mg/m2 D1 and 8
  - Dexamethasone 40 mg D1-4
  - Cisplatin 75 mg/m2 D1

- Non-inferior to R-DHAP
- Less toxic
- Outpatient
- Give pegGCSF on D8/9



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WHAT ABOUT REFRACTORY DLBCL PATIENTS?

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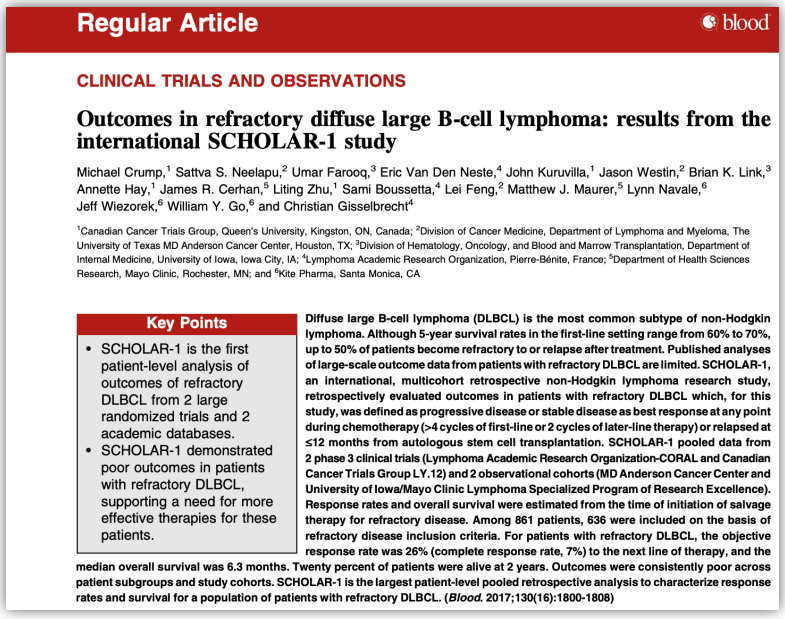

Regular Article

blood

CLINICAL TRIALS AND OBSERVATIONS

Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study

Michael Crump,[1] Sattva S. Neelapu,[2] Umar Farooq,[3] Eric Van Den Neste,[4] John Kuruvilla,[1] Jason Westin,[2] Brian K. Link,[3] Annette Hay,[1] James R. Cerhan,[5] Liting Zhu,[1] Sami Boussetta,[4] Lei Feng,[2] Matthew J. Maurer,[5] Lynn Navale,[6] Jeff Wiezorek,[6] William Y. Go,[6] and Christian Gisselbrecht[4]

[1]Canadian Cancer Trials Group, Queen's University, Kingston, ON, Canada; [2]Division of Cancer Medicine, Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Division of Hematology, Oncology, and Blood and Marrow Transplantation, Department of Internal Medicine, University of Iowa, Iowa City, IA; [4]Lymphoma Academic Research Organization, Pierre-Bénite, France; [5]Department of Health Sciences Research, Mayo Clinic, Rochester, MN; and [6]Kite Pharma, Santa Monica, CA

Key Points

- SCHOLAR-1 is the first patient-level analysis of outcomes of refractory DLBCL from 2 large randomized trials and 2 academic databases.
- SCHOLAR-1 demonstrated poor outcomes in patients with refractory DLBCL, supporting a need for more effective therapies for these patients.

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. Although 5-year survival rates in the first-line setting range from 60% to 70%, up to 50% of patients become refractory to or relapse after treatment. Published analyses of large-scale outcome data from patients with refractory DLBCL are limited. SCHOLAR-1, an international, multicohort retrospective non-Hodgkin lymphoma research study, retrospectively evaluated outcomes in patients with refractory DLBCL which, for this study, was defined as progressive disease or stable disease as best response at any point during chemotherapy (>4 cycles of first-line or 2 cycles of later-line therapy) or relapsed at ≤12 months from autologous stem cell transplantation. SCHOLAR-1 pooled data from 2 phase 3 clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational cohorts (MD Anderson Cancer Center and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence). Response rates and overall survival were estimated from the time of initiation of salvage therapy for refractory disease. Among 861 patients, 636 were included on the basis of refractory disease inclusion criteria. For patients with refractory DLBCL, the objective response rate was 26% (complete response rate, 7%) to the next line of therapy, and the median overall survival was 6.3 months. Twenty percent of patients were alive at 2 years. Outcomes were consistently poor across patient subgroups and study cohorts. SCHOLAR-1 is the largest patient-level pooled retrospective analysis to characterize response rates and survival for a population of patients with refractory DLBCL. (*Blood.* 2017;130(16):1800-1808)

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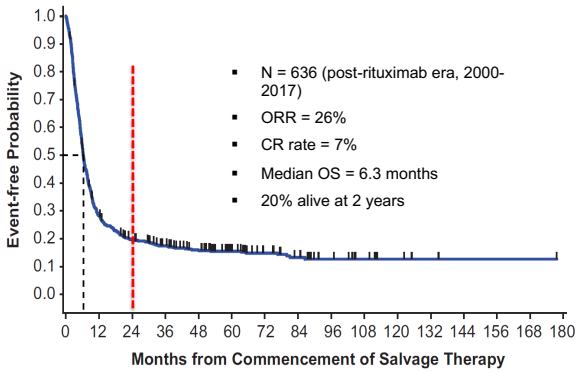
SCHOLAR-1

- A retrospective, international, patient-level, multi-institution study and the largest reported analysis of outcomes in patients with refractory large B cell lymphoma, demonstrated that these patients have a very poor prognosis

- Refractory DLBCL defined as progressive disease or stable disease as best response at any point during chemotherapy (> 4 cycles of first-line or 2 cycles of later-line therapy) or relapsed at ≤12 months from autologous stem cell transplantation



Crump M, et al. Blood 2017

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  - **PENDING RESULTS** of Zuma-7 (Kite/Gilead), BELINDA (Novartis), TRANSFORM (BMS)

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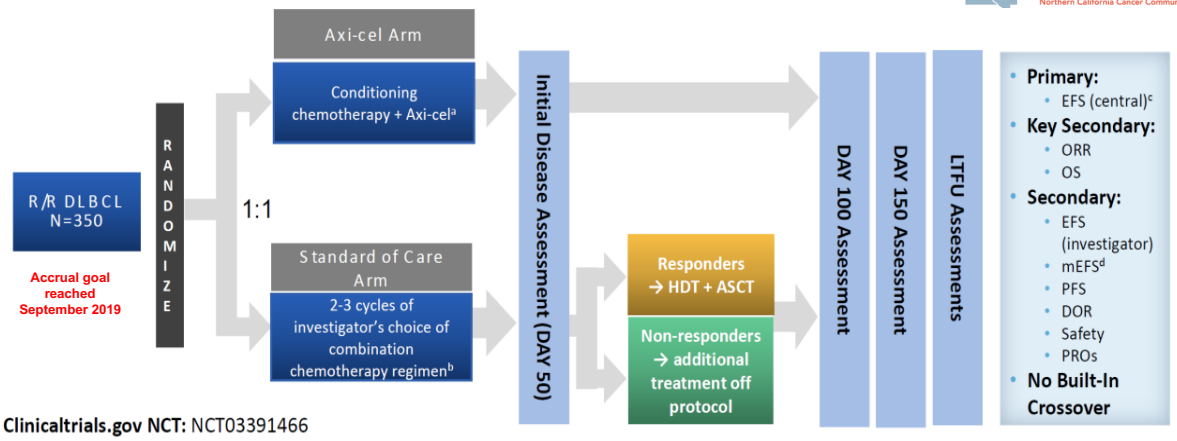
ZUMA-7 (Kite/Gilead)



Clinicaltrials.gov NCT: NCT03391466

ASCT=autologous stem cell transplantation; axi-cel=axicabtagene ciloleucel; CR=complete response; DLBCL=diffuse large B-cell lymphoma; EFS=event-free survival; mEFS=modified EFS; HDT=high dose therapy; HRQoL=health-related quality of life; ORR=objective response rate; PROs=patient reported outcomes; R/R=relapsed/refractory.

[a]Patients will receive a 3-day conditioning regimen consisting of fludarabine 30 mg/m^2/d + cyclophosphamide 500 mg/m^2/d (days −5 to −3) followed by 2 rest days (day −2 and day −1). On day 0, patients will receive a single infusion of axi-cel administered intravenously at 2 × 10^6 anti-CD19 CAR T cells/kg.

[b]Patients will receive 2-3 cycles of investigator's choice of salvage combination chemotherapy regimen (R-ICE, R-DHAP, R-ESHAP, or R-GDP) administered every 2-3 weeks.

[c]Defined as death, disease progression, or new lymphoma therapy. Best response of SD up to and including Day 150 assessment will be considered to have an EFS event.

[d]EFS except that failure to attain CR or PR by Day 150 assessment is not considered as an event.

Courtesy of David Miklos MD, PhD and Kite/Gilead

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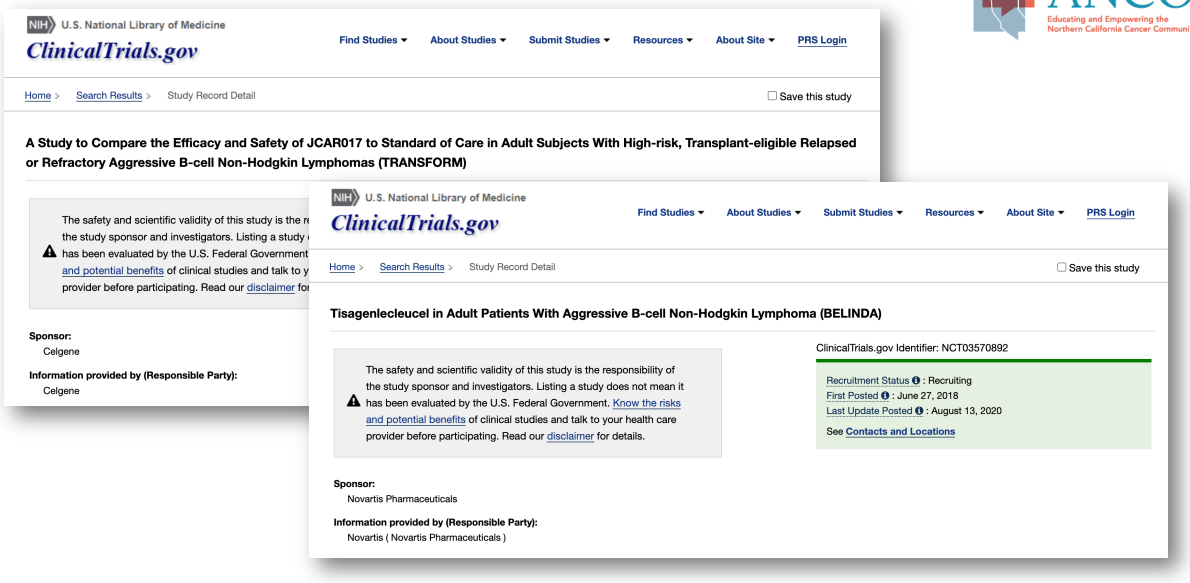

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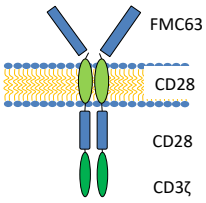
Two Anti-CD19 CAR T-cell Constructs FDA Approved as 3rd Line Therapy for R/R DLBCL

FDA approved 10/18/17

Axicabtagene ciloleucel (*aka* Axi-cel; Yescarta™) NCI

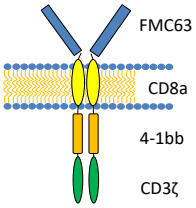


Retrovirus

Kite/Gilead KTE-C19

FDA approved 5/1/18

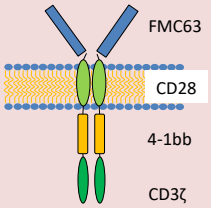
Tisagenlecleucel (*aka* Kymriah™) UPenn



Lentivirus

Novartis CTL-019

Lisocabtagene maraleucel (*aka* Liso-cel) FHCR



Lentivirus

Juno/Celgene JCAR 017

[1] Adapted from: van der Stegen SJ et al. Nat Rev Drug Discov. 2015 Jul;14(7):499-509; Courtesy of David Miklos MD, PhD

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Rel/Ref DLBCL Response to CAR19 Therapy

	FDA approved 10/18/17 ZUMA-1 Axi-cel (n=101)	FDA approved 5/1/18 JULIET Tisagenlecleucel (n=93)
ORR	82%	52%
CR	58%	40%
Median DOR	11.1 months	Not reached (est. 12 mo of 65%)

Neelapu SS et al. N Engl J Med; 2017; Locke F et al. Cancer Discovery 2018; Schuster SJ et al., N Engl J Med; 2018 - Courtesy of David Miklos MD, PhD

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Diffuse Large B-cell Lymphoma (DLBCL)

- Standard of care 1st line therapy:
  - R-CHOP >>> 5-yr OS ~ 60%
  - Attempts to improve upon R-CHOP >> FAIL
  - Current efforts to improve upon R-CHOP
    - EveR-CHOP
    - Tazometostat + R-CHOP
    - Tafasitamab + R-CHOP +/- lenalidomide
- Standard of care 2nd line therapy
  - Platinum-based chemotherapy f/b autoSCT (PARMA, CORAL)
  - Established regimens that allow stem-cell mobilization: R-ICE, R-DHAP, **R-GDP**
  - **PENDING RESULTS** of Zuma-7 (Kite/Gilead), BELINDA (Novartis), TRANSFORM (BMS)
- Recent, FDA-approved options for rel/ref disease:
  - CAR-T: axi-cel (Yescarta™; Kite/Gilead), tisagenlecleucel (Kymriah™; Novartis)
  - Polatuzumab + bendamustine + rituximab (PBR, FDA approval 6/10/19)

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June 10, 2019

← Home / Drugs / Development & Approval Process | Drugs / Drug Approvals and Databases / Resources for Information | Approved Drugs / FDA approves polatuzumab vedotin-piiq for diffuse large B-cell lymphoma

FDA approves polatuzumab vedotin-piiq for diffuse large B-cell lymphoma

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Resources for Information | Approved Drugs

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) Short Description

On June 10, 2019, the Food and Drug Administration granted accelerated approval to polatuzumab vedotin-piiq (POLIVY, Genentech, Inc.), a CD79b-directed antibody-drug conjugate indicated in combination with bendamustine and a rituximab product for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least two prior therapies.

Approval was based on Study GO29365 (NCT02257567), an open-label, multicenter clinical trial that included a cohort of 80 patients with relapsed or refractory DLBCL after at least one prior regimen. Patients were randomized (1:1) to receive either polatuzumab vedotin-piiq in combination with bendamustine and a rituximab product (P+BR) or BR for six 21-day cycles. Polatuzumab vedotin-piiq, 1.8 mg/kg by intravenous infusion, was given on day 2 of cycle 1 and on day 1 of subsequent cycles. Bendamustine (90 mg/m^2 intravenously) was administered on days 2 and 3 of cycle 1 and on days 1 and 2 of subsequent cycles. A rituximab product (375 mg/m^2 intravenously) was administered on day 1 of each cycle.

Content current as of: 06/10/2019

Regulated Product(s) Drugs

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-polatuzumab-vedotin-piiq-diffuse-large-b-cell-lymphoma

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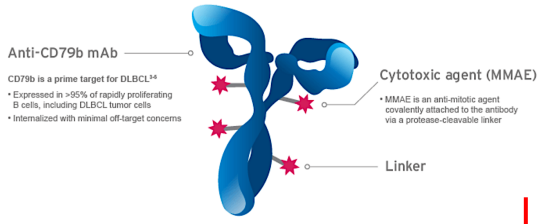
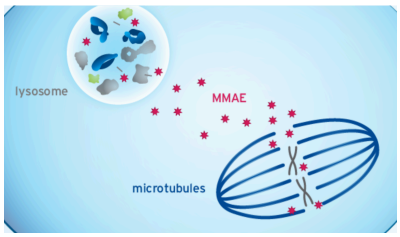
Polatuzumab vedotin – ADC



- Cytotoxin monomethyl auristatin E (MMAE)

+

- CD79b-targeted monoclonal antibody (mAb)



https://www.polivy.com/hcp/about-polivy/mechanism-of-action.html

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Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Laurie H. Sehn, MD, MPH[1]; Alex F. Herrera, MD[2]; Christopher R. Flowers, MD, MSc[3]; Manali K. Kamdar, MD, MBBS[4]; Andrew McMillan, PhD[5]; Mark Hertzberg, MBBS, PhD[6]; Sarit Assouline, MDCM, MSc[7]; Tae Min Kim, MD[8]; Won Seog Kim, MD, PhD[9]; Muhit Ozcan, MD[10]; Jamie Hirata, PharmD[11]; Elicia Penuel, PhD[11]; Joseph N. Paulson, PhD[11]; Ji Cheng, PhD[12]; Grace Ku, MD[11]; and Matthew J. Matasar, MD[13]

PURPOSE Patients with transplantation-ineligible relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) fare poorly, with limited treatment options. The antibody-drug conjugate polatuzumab vedotin targets CD79b, a B-cell receptor component.

METHODS Safety and efficacy of polatuzumab vedotin with bendamustine and obinutuzumab (pola-BG) was evaluated in a single-arm cohort. Polatuzumab vedotin combined with bendamustine and rituximab (pola-BR) was compared with bendamustine and rituximab (BR) in a randomly assigned cohort of patients with transplantation-ineligible R/R DLBCL (primary end point: independent review committee [IRC] assessed complete response [CR] rate at the end of treatment). Duration of response, progression-free survival (PFS), and overall survival (OS) were analyzed using Kaplan–Meier and Cox regression methods.

RESULTS Pola-BG and pola-BR had a tolerable safety profile. The phase Ib/II pola-BG cohort (n = 27) had a CR rate of 29.6% and a median OS of 10.8 months (median follow-up, 27.0 months). In the randomly assigned cohort (n = 80; 40 per arm), pola-BR patients had a significantly higher IRC-assessed CR rate (40.0% *v* 17.5%; *P* = .026) and longer IRC-assessed PFS (median, 9.5 *v* 3.7 months; hazard ratio [HR], 0.36, 95% CI, 0.21 to 0.63; *P* < .001) and OS (median, 12.4 *v* 4.7 months; HR, 0.42; 95% CI, 0.24 to 0.75; *P* = .002; median follow-up, 22.3 months). Pola-BR patients had higher rates of grade 3-4 neutropenia (46.2% *v* 33.3%), anemia (28.2% *v* 17.9%), and thrombocytopenia (41% *v* 23.1%), but similar grade 3-4 infections (23.1% *v* 20.5%), versus the BR group. Peripheral neuropathy associated with polatuzumab vedotin (43.6% of patients) was grade 1-2 and resolved in most patients.

CONCLUSION Polatuzumab vedotin combined with BR resulted in a significantly higher CR rate and reduced the risk of death by 58% compared with BR in patients with transplantation-ineligible R/R DLBCL.

J Clin Oncol 38:155-165. © 2019 by American Society of Clinical Oncology

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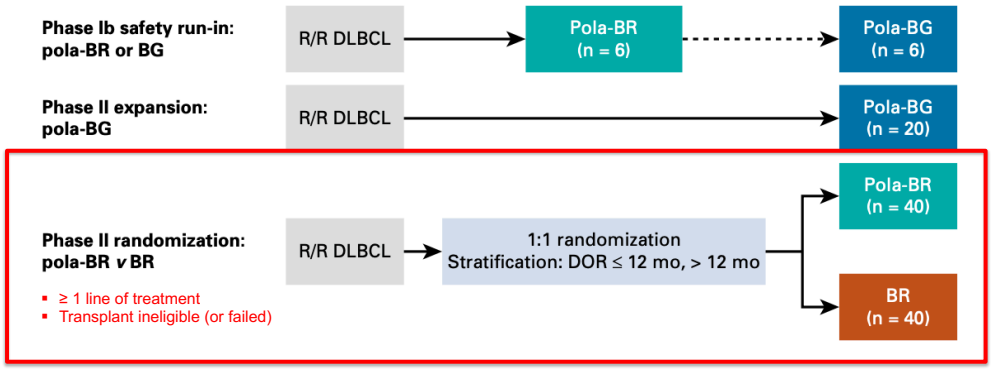
Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Laurie H. Sehn, MD, MPH[1]; Alex F. Herrera, MD[2]; Christopher R. Flowers, MD, MSc[3]; Manali K. Kamdar, MD, MBBS[4]; Andrew McMillan, PhD[5]; Mark Hertzberg, MBBS, PhD[6]; Sarit Assouline, MDCM, MSc[7]; Tae Min Kim, MD[8]; Won Seog Kim, MD, PhD[9]; Muhit Ozcan, MD[10]; Jamie Hirata, PharmD[11]; Elicia Penuel, PhD[11]; Joseph N. Paulson, PhD[11]; Ji Cheng, PhD[12]; Grace Ku, MD[11]; and Matthew J. Matasar, MD[13]

Figure 1A



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Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

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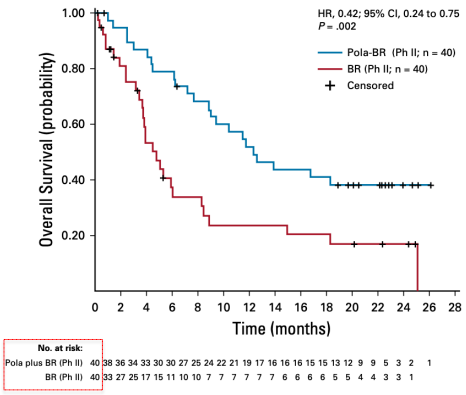
Figure 2C



- Median follow-up 22.3 months
- Median OS PBR vs BR = **12.4 v 4.7** months; HR, 0.42 (95% CI, 0.24 to 0.75) P = .002

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Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Laurie H. Sehn, MD, MPH[1]; Alex F. Herrera, MD[2]; Christopher R. Flowers, MD, MSc[3]; Manali K. Kamdar, MD, MBBS[4]; Andrew McMillan, PhD[5]; Mark Hertzberg, MBBS, PhD[6]; Sarit Assouline, MDCM, MSc[7]; Tae Min Kim, MD[8]; Won Seog Kim, MD, PhD[9]; Muhit Ozcan, MD[10]; Jamie Hirata, PharmD[11]; Elicia Penuel, PhD[11]; Joseph N. Paulson, PhD[11]; Ji Cheng, PhD[12]; Grace Ku, MD[11]; and Matthew J. Matasar, MD[13]

TABLE 3. Adverse Events in Patients Treated With Pola-BR Compared With BR

	Pola-BR (n = 39)*		BR (n = 39)*	
Adverse Event	**All Grades, No. (%)**	**Grades 3-4, No. (%)**	**All Grades, No. (%)**	**Grades 3-4, No. (%)**
Blood and lymphatic system disorders				
Anemia	21 (53.8)	11 (28.2)	10 (25.6)	7 (17.9)
Neutropenia	21 (53.8)	18 (46.2)	15 (38.5)	13 (33.3)
Thrombocytopenia	19 (48.7)	16 (41.0)	11 (28.2)	9 (23.1)
Lymphopenia	5 (12.8)	5 (12.8)	0	0
Febrile neutropenia	4 (10.3)	4 (10.3)	5 (12.8)	5 (12.8)
GI disorders				
Diarrhea	15 (38.5)	1 (2.6)	11 (28.2)	1 (2.6)
Nausea	12 (30.8)	0	16 (41.0)	0
Constipation	7 (17.9)	0	8 (20.5)	1 (2.6)
General disorders and administration site conditions				
Fatigue	14 (35.9)	1 (2.6)	14 (35.9)	1 (2.6)
Pyrexia	13 (33.3)	1 (2.6)	9 (23.1)	0
Metabolism and nutrition disorders				
Decreased appetite	10 (25.6)	1 (2.6)	8 (20.5)	0
Peripheral neuropathy				
Peripheral neuropathy†	17 (43.6)	0	3 (7.7)	0

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NCCN Guidelines Version 4.2020 Diffuse Large B-Cell Lymphoma

NCCN Guidelines Index
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Discussion

Second-line and Subsequent Therapy[d,i,j] (non-candidates for transplant)

- **Preferred regimens (in alphabetical order)**
  - **GemOx ± rituximab**
  - **Polatuzumab vedotin ± bendamustine ± rituximab (after ≥2 prior therapies)[k,l]**

- Recommended dose of polatuzumab vedotin-piiq is 1.8 mg/kg as an intravenous infusion over 90 minutes every 21 days for 6 cycles in combination with bendamustine and a rituximab
- Subsequent infusions may be administered over 30 minutes if the previous infusion is tolerated
- Pre-medicate with an antihistamine and antipyretic
- Administer prophylaxis for *Pneumocystis jiroveci* pneumonia and herpesvirus

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BCEL-C

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Diffuse Large B-cell Lymphoma (DLBCL)

- Standard of care 1st line therapy:
  - R-CHOP >>> 5-yr OS ~ 60%
  - Attempts to improve upon R-CHOP >> FAIL
  - Current efforts to improve upon R-CHOP
    - EveR-CHOP
    - Tazometostat + R-CHOP
    - Tafasitamab + R-CHOP +/- lenalidomide
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  - Polatuzumab + bendamustine + rituximab (PBR, FDA approval 6/10/19)
  - Tafasitamab + lenalidomide (FDA approval 7/31/20)

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July 31, 2020

U.S. FOOD & DRUG ADMINISTRATION

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FDA grants accelerated approval to tafasitamab-cxix for diffuse large B-cell lymphoma

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Drug Approvals and Databases

Resources for Information | Approved Drugs

On July 31, 2020, the Food and Drug Administration granted accelerated approval to tafasitamab-cxix (MONJUVI, MorphoSys US Inc.), a CD19-directed cytolytic antibody, indicated in combination with lenalidomide for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant.

Content current as of:
08/03/2020

Regulated Product(s)
Drugs
Prescription Drugs

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-tafasitamab-cxix-diffuse-large-b-cell-lymphoma

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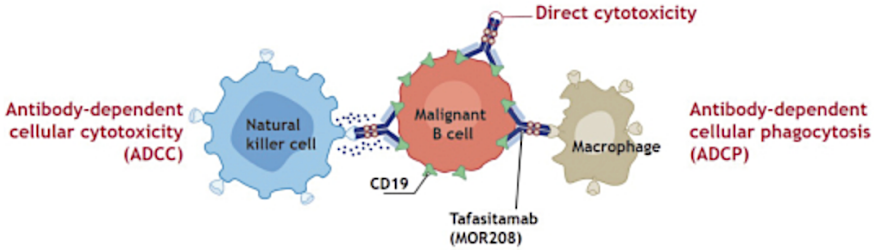
Tafasitamab – a novel anti CD19 mAb



https://www.morphosys.com/pipeline/proprietary-portfolio/tafasitamab-mor208

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Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study

Gilles Salles*, Johannes Duell*, Eva González Barca, Olivier Tournilhac, Wojciech Jurczak, Anna Marina Liberati, Zsolt Nagy, Aleš Obr, Gianluca Gaidano, Marc André, Nagesh Kalakonda, Martin Dreyling, Johannes Weirather, Maren Dimberger-Hertweck, Sumeet Ambarkhane, Günter Fingerle-Rowson, Kami Maddocks

Lancet Oncol 2020; 21: 978–88
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See Comment page 870

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Summary

Background Patients with relapsed or refractory diffuse large B-cell lymphoma who are ineligible for autologous stem-cell transplantation have poor outcomes and few treatment options. Tafasitamab (MOR208) is an Fc-enhanced, humanised, anti-CD19 monoclonal antibody that has shown preclinical and single-agent activity in patients with relapsed or refractory B-cell malignancies. Preclinical data suggested that tafasitamab might act synergistically with lenalidomide. We aimed to assess the antitumour activity and safety of tafasitamab plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma who were ineligible for autologous stem-cell transplantation.

Methods In this multicentre, open-label, single-arm, phase 2 study (L-MIND), patients older than 18 years with histologically confirmed diffuse large B-cell lymphoma, who relapsed or had refractory disease after previous treatment with one to three systemic regimens (with at least one anti-CD20 therapy), were not candidates for high-dose chemotherapy and subsequent autologous stem-cell transplantation, had an Eastern Cooperative Oncology Group performance status of 0–2, and had measurable disease at baseline were recruited from 35 academic and community hospitals in ten countries. Patients received coadministered intravenous tafasitamab (12 mg/kg) and oral lenalidomide (25 mg/day) for up to 12 cycles (28 days each), followed by tafasitamab monotherapy (in patients with stable disease or better) until disease progression. The primary endpoint was the proportion of patients with an objective response (centrally assessed), defined as a complete or partial response according to the 2007 International Working Group response criteria for malignant lymphoma. Antitumour activity analyses are based on all patients who received at least one dose of both tafasitamab and lenalidomide; safety analyses are based on all patients who received at least one dose of either study medication. Recruitment is complete, and the trial is in follow-up. This trial is registered with ClinicalTrials.gov, NCT02399085.

Findings Between Jan 18, 2016, and Nov 15, 2017, 156 patients were screened: 81 were enrolled and received at least one dose of either study medication, and 80 received at least one dose of both tafasitamab and lenalidomide. Median follow-up was 13·2 months (IQR 7·3–20·4) as of data cutoff on Nov 30, 2018. 48 (60%; 95% CI 48–71) of 80 patients who received tafasitamab plus lenalidomide had an objective response: 34 (43%; 32–54) had a complete response and 14 (18%; 10–28) had a partial response. The most common treatment-emergent adverse events of grade 3 or worse were neutropenia (39 [48%] of 81 patients), thrombocytopenia (14 [17%]), and febrile neutropenia (ten [12%]). Serious adverse events occurred in 41 (51%) of 81 patients. The most frequently reported serious adverse events (in two or more patients) were pneumonia (five [6%]), febrile neutropenia (five [6%]), pulmonary embolism (three [4%]), bronchitis (two [2%]), atrial fibrillation (two [2%]), and congestive cardiac failure (two [2%]).

Interpretation Tafasitamab in combination with lenalidomide was well tolerated and resulted in a high proportion of patients with relapsed or refractory diffuse large B-cell lymphoma ineligible for autologous stem-cell transplantation having a complete response, and might represent a new therapeutic option in this setting.

Salles et al, Lancet Oncology 2020

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MIND (

- Open label, multicenter single-arm trial with 81 patients
- Patients received tafasitamab-cxix 12 mg/kg intravenously D1,8,15,22 (C1-3) then D1,15 (C4 onward) with lenalidomide (25 mg D1-21 of each 28-day cycle) for maximum of 12 cycles
- This was followed by tafasitamab-cxix as monotherapy q2 weeks until progression or toxicity

	Patients in safety population (n=81)
Median age, years	72 (62–76)
Sex	
Male	44 (54%)
Female	37 (46%)
Race	
Asian	2 (2%)
White	72 (89%)
Other	1 (1%)
Data missing	6 (7%)
Median time since first DLBCL diagnosis, months	26·9 (17–51)
Previous lines of systemic therapy	
Median (range)	2 (1–4)
1	40 (50%)
2	35 (43%)
3	5 (6%)
4	1 (1%)
Previous anti-CD20 therapy	
Yes	81 (100%)
No	0 (0%)
Previous [illegible] therapy	
Yes	[illegible]
No	[illegible]
Primary refractory	
Yes	[illegible]
No	66 (81%)
Rituximab refractory	
Yes	34 (42%)
No	46 (57%)
Unknown	1 (1%)
Refractory to most recent previous therapy	
Yes	[illegible]
No	45 (56%)
Previous ASCT	
Yes	9 (11%)
No	72 (89%)
Ann Arbor stage at screening	
I or II	20 (25%)
III or IV	61 (75%)
ECOG performance status	
0	29 (36%)
1	45 (56%)
2	7 (9%)
IPI score at screening	
0–2 (low and low-intermediate risk)	40 (49%)
3–5 (intermediate-high and high risk)	41 (51%)

	Patients in safety population (n=81)
(Continued from previous column)	
Bulky disease*	
Present	15 (19%)
Absent	65 (80%)
Data missing	1 (1%)
Lactate dehydrogenase concentrations at screening	
Elevated	45 (56%)
Within reference range	36 (44%)
Cell of origin by immunohistochemistry	
Germinal centre B cell	38 (47%)
Non-germinal centre B cell	[illegible]
Unknown	22 (27%)
Cell of origin by gene-expression profiling	
Germinal centre B cell	7 (9%)
Non-germinal centre B cell	[illegible]
Unclassified	[illegible]
Unknown	49 (60%)
Patients with DLBCL arising from a previous indolent lymphoma	7 (9%)
Reasons for ASCT ineligibility	
Aged >70 years	37 (46%)
[illegible]	[illegible]
Refusal	13 (16%)
Comorbidities‡	11 (14%)
Other§	1 (1%)

Data are median (IQR) or n (%) unless otherwise stated. ASCT=autologous stem-cell transplantation. DLBCL=diffuse large B-cell lymphoma. ECOG=Eastern Cooperative Oncology Group. IPI=International Prognostic Index. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. *Defined as having a longest lesion diameter of ≥7·5 cm (by central radiological assessment). †Patients without a partial or complete response with salvage therapy or who had ASCT before enrolment. ‡All patients who are not chemorefractory and who have comorbidities (comorbidities are listed in appendix p 23). §Other reasons include inability to successfully collect stem cells.

Table 1: **Baseline characteristics of the safety population**

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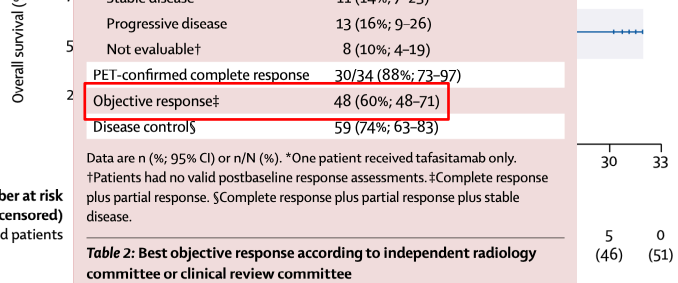
L-MIND (NCT02399085)

	Patients treated with tafasitamab plus lenalidomide (n=80)*
Best objective response	
Complete response	34 (43%; 32–54)
Partial response	14 (18%; 10–28)
Stable disease	11 (14%; 7–23)
Progressive disease	13 (16%; 9–26)
Not evaluable†	8 (10%; 4–19)
PET-confirmed complete response	30/34 (88%; 73–97)
Objective response‡	48 (60%; 48–71)
Disease control§	59 (74%; 63–83)

Data are n (%; 95% CI) or n/N (%). *One patient received tafasitamab only. †Patients had no valid postbaseline response assessments. ‡Complete response plus partial response. §Complete response plus partial response plus stable disease.

Table 2: **Best objective response according to independent radiology committee or clinical review committee**



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L-MIND (NCT02399085)

Table 3

	Grade 1–2	Grade 3	Grade 4	Grade 5
Haematological events				
Neutropenia	1 (1%)	22 (27%)	17 (21%)	0
Anaemia	22 (27%)	6 (7%)	0	0
Thrombocytopenia	11 (14%)	10 (12%)	4 (5%)	0
Leukopenia	5 (6%)	6 (7%)	1 (1%)	0
Febrile neutropenia	0	8 (10%)	2 (2%)	0
Lymphopenia	2 (2%)	2 (2%)	1 (1%)	0
Agranulocytosis	0	0	1 (1%)	0
Non-haematological events				
All rash*	22 (27%)	7 (9%)	0	0
Diarrhoea	26 (32%)	1 (1%)	0	0
Asthenia	17 (21%)	2 (2%)	0	0
Cough	17 (21%)	1 (1%)	0	0
Peripheral oedema	18 (22%)	0	0	0
Pyrexia	16 (20%)	1 (1%)	0	0
Decreased appetite	16 (20%)	0	0	0

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2020
Diffuse Large B-Cell Lymphoma

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Discussion

SUGGESTED TREATMENT REGIMENS[a,b]

An FDA-approved biosimilar is an appropriate substitute for rituximab.

Second-line and Subsequent Therapy[d,i,j] (intention to proceed to transplant)
- **Preferred regimens (in alphabetical order)**
  - **DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab**
  - **DHAX (dexamethasone, cytarabine, oxaliplatin) ± rituximab**
  - **GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab**
  - **ICE (ifosfamide, carboplatin, etoposide) ± rituximab**
- **Other recommended regimens (in alphabetical order)**
  - **ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab**
  - **GemOx (gemcitabine, oxaliplatin) ± rituximab**
  - **MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab**

Anti-CD19 CAR T-cell therapy[n,o]
- **Axicabtagene ciloleucel**
- **Tisagenlecleucel**

See First-line Therapy on BCEL-C 1 of 4.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

Second-line and Subsequent Therapy[d,i,j] (non-candidates for transplant)
- **Preferred regimens (in alphabetical order)**
  - **GemOx ± rituximab**
  - **Polatuzumab vedotin ± bendamustine ± rituximab (after ≥2 prior therapies)[k,l]**
- **Other recommended regimens (in alphabetical order)**
  - **CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab - PO and IV**
  - **CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab**
  - **DA-EPOCH ± rituximab**
  - **GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab**
  - **Gemcitabine, vinorelbine ± rituximab (category 3)**
  - **Rituximab**
  - **Tafasitamab[p] + lenalidomide**
- **Useful in certain circumstances**
  - **Brentuximab vedotin for CD30+ disease**
  - **Bendamustine[k] ± rituximab (category 2B)**
  - **Ibrutinib[m] (non-GCB DLBCL)**
  - **Lenalidomide ± rituximab (non-GCB DLBCL)**

Third-line and Subsequent Therapy (including patients with disease progression after transplant or CAR T-cell therapy)
- **Selinexor (only after at least two lines of systemic therapy)[q]**

[a] See references for regimens BCEL-C 3 of 4 and BCEL-C 4 of 4.
[b] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[d] Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
[i] If additional anthracycline is administered after a full course of therapy, careful cardiac monitoring is essential. Dexrazoxane may be added as a cardioprotectant.
[j] Rituximab should be included in second-line therapy if there is relapse after a reasonable remission (>6 mo); however; rituximab should often be omitted in patients with primary refractory disease.
[k] In patients intended to receive CAR T-cell therapy, bendamustine should be used with caution unless immediately prior to CAR T-cell therapy, since it could impact the success of the patient's T-cell collection.
[l] Bendamustine, rituximab, and polatuzumab vedotin-piiq is indicated for the treatment of adult patients with relapsed or refractory DLBCL and HGBL with translocations of *MYC* and *BCL2* and/or *BCL6* after ≥2 prior therapies.
[m] See Special Considerations for Use of Small-Molecule Inhibitors (NHODG-E).
[n] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (BCEL-D).
[o] Tisagenlecleucel is not FDA-approved for relapsed/refractory primary mediastinal large B-cell lymphoma.
[p] It is unclear if tafasitamab will have a negative impact on the efficacy of subsequent anti-CD19 CAR T-cell therapy.
[q] Selinexor is FDA approved only for DLBCL and transformed DLBCL arising from FL.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Diffuse Large B-cell Lymphoma (DLBCL)

- Standard of care 1st line therapy:
  - R-CHOP >>> 5-yr OS ~ 60%
  - Attempts to improve upon R-CHOP >> FAIL
  - Current efforts to improve upon R-CHOP
    - EveR-CHOP
    - Tazometostat + R-CHOP
    - Tafasitamab + R-CHOP +/- lenalidomide
- Standard of care 2nd line therapy
  - Platinum-based chemotherapy f/b autoSCT (PARMA, CORAL)
  - Established regimens that allow stem-cell mobilization: R-ICE, R-DHAP, **R-GDP**
  - **PENDING RESULTS** of Zuma-7 (Kite/Gilead), BELINDA (Novartis), TRANSFORM (BMS)
- Recent, FDA-approved options for rel/ref disease:
  - CAR-T: axi-cel (Yescarta™; Kite/Gilead), tisagenlecleucel (Kymriah™; Novartis)
  - Polatuzumab + bendamustine + rituximab (PBR, FDA approval 6/10/19)
  - Tafasitamab + lenalidomide (FDA approval 7/31/20)
  - Selinexor (FDA approval 6/22/20)

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June 22, 2020

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FDA approves selinexor for relapsed/refractory diffuse large B-cell lymphoma

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Resources for Information | Approved Drugs

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

On June 22, 2020, the Food and Drug Administration granted accelerated approval to selinexor (XPOVIO, Karyopharm Therapeutics) for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.

Approval was based on SADAL (KCP-330-009; NCT02227251), a multicenter, single-arm, open-label trial in patients with DLBCL after 2 to 5 systemic regimens. Patients received selinexor 60 mg orally on days 1 and 3 of each week.

Content current as of:
06/22/2020

Regulated Product(s)
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Oncology

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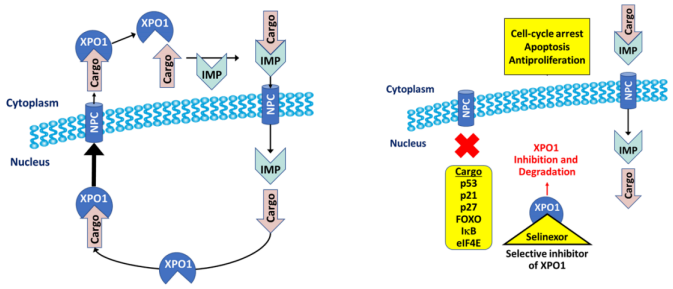
Selinexor

An **oral**, selective inhibitor of nuclear export (SINE) compound that specifically blocks the function of the protein XPO1, which is responsible for the nuclear export and functional inactivation of major tumor suppressor proteins



Abbreviations: IMP=importin; NPC=nuclear pore complex; TSP=tumor suppressor protein; XPO1=exportin 1

Karyopharm Therapeutics Inc, ODAC Briefing Document; 2/26/19

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Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial

Nagesh Kalakonda, Marie Maerevoet*, Federica Cavallo, George Follows, Andre Goy, Joost S P Vermaat, Olivier Casasnovas, Nada Hamad, Josée M Zijlstra, Sameer Bakhshi, Reda Bouabdallah, Sylvain Choquet, Ronit Gurion, Brian Hill, Ulrich Jaeger, Juan Manuel Sancho, Michael Schuster, Catherine Thieblemont, Fátima De la Cruz, Miklos Egyed, Sourav Mishra, Fritz Offner, Theodoros P Vassilakopoulos, Krzysztof Warzocha, Daniel McCarthy, Xiwen Ma, Kelly Corona, Jean-Richard Saint-Martin, Hua Chang, Yosef Landesman, Anita Joshi, Hongwei Wang, Jatin Shah, Sharon Shacham, Michael Kauffman, Eric Van Den Neste, Miguel A Canales*

Lancet Haematol 2020; 7: e511–22

See Comment page e500

Summary

Background Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) is an aggressive cancer with a median overall survival of less than 6 months. We aimed to assess the response to single-agent selinexor, an oral selective inhibitor of nuclear export, in patients with relapsed or refractory DLBCL who had no therapeutic options of potential clinical benefit.

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Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial

Nagesh Kalakonda*, Marie Maerevoet*, Federica Cavallo, George Follows, Andre Goy, Joost S P Vermaat, Olivier Casasnovas, Nada Hamad, Josée M Zijlstra, Sameer Bakhshi, Reda Bouabdallah, Sylvain Choquet, Ronit Gurion, Brian Hill, Ulrich Jaeger, Juan Manuel Sancho, Michael Schuster, Catherine Thieblemont, Fátima Da Ia Cruz, Miklos Egyed, Sourav Mishra, Fritz Offner, Theodoros P Vassilakopoulos, Krzysztof Warzocha, Daniel McCarthy, Xiwen Ma, Kelly Corona, Jean-Richard Saint-Martin, Hua Chang, Yosef Landesman, Anita Joshi, Hongwei Wang, Jatin Shah, Sharon Shacham, Michael Kauffman, Eric Van Den Neste, Miguel A Canales

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Lancet Haematol 2020; 7: e511–22

See Comment page e500

	Grade 1–2	Grade 3	Grade 4	Total (N=127)
Age, years				
Median (range)				75 (59%)
≥70 year				57 (41%)
Sex				
Female				8·1 (4·57–15·14)
Male				
ECOG performance-status				
0				
1				38 (30%)
2				89 (70%)
3				
Time since DLBCL diagnosis				
DLBCL type				
De novo DLBCL				91 (72%)
Transformed DLBCL				29 (23%)
DLBCL subtype				7 (6%)
GCB				21 (17%)
Non-GCB				
Unclassified				42 (33%)
Double hit or triple hit DLBCL				49 (39%)
Yes				36 (28%)
No				
Missing				
Creatinine Clearance, mL p				
<30				
30–<60				
≥60				
Lactic acid dehydrogenase				
Yes				
No				
Missing				
Number of previous systemic regimens for DLBCL				
Thrombocytopenia	20 (16%)	39 (31%)	39 (15%)	
Nausea	66 (52%)	8 (6%)	0	
Fatigue	46 (36%)	14 (11%)	0	
Anaemia	26 (21%)	27 (21%)	1 (1%)	
Decreased appetite	42 (33%)	5 (4%)	0	
Diarrhoea	41 (32%)	4 (3%)	0	
Constipation	39 (31%)	0	0	
Neutropenia	7 (6%)	20 (16%)	11 (9%)	
Weight loss	38 (30%)	0	0	
Vomiting	35 (28%)	2 (2%)	0	
Pyrexia	23 (18%)	5 (4%)	0	
Asthenia	21 (17%)	6 (5%)	0	
Cough	23 (18%)	0	0	
Upper respiratory tract infection	18 (14%)	1 (1%)	0	
Dizziness	18 (14%)	0	0	
Hypotension	13 (10%)	4 (3%)	0	
Oedema peripheral	14 (11%)	1 (1%)	0	
Dyspnoea	12 (10%)	1 (1%)	1 (1%)	
Hyponatraemia	4 (3%)	10 (8%)	0	

Data are n (%). Data are for events that occurred in at least 10% of the patients, for serious adverse events in ≥2% patients see appendix p 8. The Medical Dictionary for Regulatory Activities preferred terms were used. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). No Grade 5 events were reported in 10% or more of the patients.

Table 3: Treatment-emergent adverse events in 10% or more of patients

(Table 1 continues in next column)

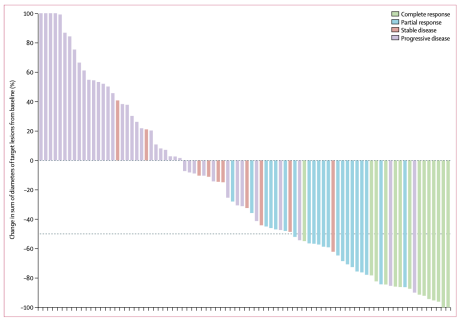

Figure 3: Changes in tumour burden for all patients
Response based on metabolic response or anatomic response if PET missing.

	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**

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2020
Diffuse Large B-Cell Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a,b]

An FDA-approved biosimilar is an appropriate substitute for rituximab.

Second-line and Subsequent Therapy[d,i,j] (intention to proceed to transplant)
- **Preferred regimens (in alphabetical order)**
  - **DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab**
  - **DHAX (dexamethasone, cytarabine, oxaliplatin) ± rituximab**
  - **GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab**
  - **ICE (ifosfamide, carboplatin, etoposide) ± rituximab**
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- **Selinexor (only after at least two lines of systemic therapy)[q]**

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BCEL-C

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  - Selinexor (FDA approval 6/22/20)

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Follicular Lymphoma (FL)

- **First-line therapy**:
  - Bendamustine + rituximab (Rummel et al, Lancet 2014)
  - R-CHOP
  - R-CVP
  - **Rituximab + lenalidomide** (Morschhauser et al, NEJM Sept 2018; Delfau-Larue et al, Blood Adv July 2020)

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September 6, 2018

The NEW ENGLAND JOURNAL of MEDICINE

July 16, 2020

REGULAR ARTICLE

blood advances

Rituximab Untr

F. Morschhauser, N
C. Fruchart, E.N. Lit
L. Ysebaert, N.L.
S. Le Gouill, G.M. Pi
K. Ando, M. Gomes
D. Liu, J. Wang, L. Y

Lenalidomide/rituximab induces high molecular response in untreated follicular lymphoma: LYSA ancillary RELEVANCE study

Marie-Helene Delfau-Larue,[1] Marie-Laure Boulland,[2] Asma Beldi-Ferchiou,[1] Pierre Feugier,[3] Hervé Maisonneuve,[4] Rene-Olivier Casasnovas,[5] François Lemonnier,[6] Gian Matteo Pica,[7] Roch Houot,[8] Loic Ysebaert,[9] Hervé Tilly,[10] Jean-Claude Eisenmann,[11] Steven Le Gouill,[12] Vincent Ribrag,[13] Pascal Godmer,[14] Sylvie Glaisner,[15] Guillaume Cartron,[16] Luc Xerri,[17] Gilles André Salles,[18] Thierry Fest,[2] and Franck Morschhauser[19]

[1]Biological Hematology and Immunology Department, Groupe Hospitalier Mondor, INSERM U955, Creteil, France; [2]Hematobiology Department, Centre Hospitalo-Universitaire (CHU) Pontchaillou, Rennes, France; [3]Service d'Hématologie, Centre Hospitalier Regional Universitaire de Nancy, Vandoeuvre les Nancy, France; [4]Service d'Onco-Hématologie, Centre Hospitalier Départemental Vendée, La Roche-sur-Yon, France; [5]Service d'Hématologie Clinique, CHU Le Bocage, Dijon, France; [6]Unité Hémopathies Lymphoïdes, University Hospital Mondor, Creteil, France; [7]Service Hématologie, Centre Hospitalier (CH) Métropole Savoie, Chambéry, France; [8]Service d'Hématologie Clinique, CHU Pontchaillou, Rennes, France; [9]Service d'Hématologie, Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France; [10]U1245 and Département d'Hématologie, Centre Henri Becquerel, Rouen, France; [11]Département d'Hématologie, CH de Mulhouse, Hôpital Emile Muller, Mulhouse, France; [12]Service d'hématologie clinique du CHU de Nantes, INSERM CRCINA Nantes-Angers, Nantes Excellence Trajectory Université de Nantes, Nantes, France; [13]Hematology Department, Gustave Roussy Cancer Campus Grand Paris, Villejuif, France; [14]Service Hematologie, Centre Hospitalier Bretagne-Atlantique, Vannes, France; [15]Service d'Hématologie, Centre René Huguenin, Saint-Cloud, France; [16]Department of Hematology, CHU Montpellier, Montpellier, France; [17]Departement de Bio-pathologie, Institut Paoli-Calmettes, Marseille, France; [18]Département d'Hématologie, Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, Lyon, France; and [19]Département d'Hématologie, Equipe d'Accueil 7365, CHU Lille, Lille, France

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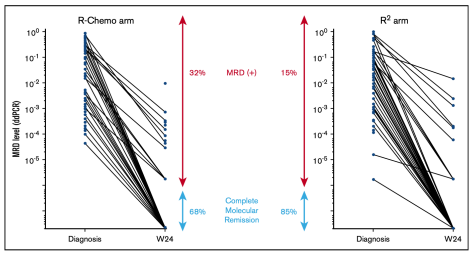


Figure 2. Molecular disease in BM samples according to treatment arm. MRD level was quantified using droplet digital PCR, and results are expressed as number of tumor cells/number of analyzed cells. Each dot represents a patient sample. The lines connect the diagnostic and W24 samples from the same patient. CMR was defined as negative MRD PCR with a sensitivity $\geq 10^{-4}$.

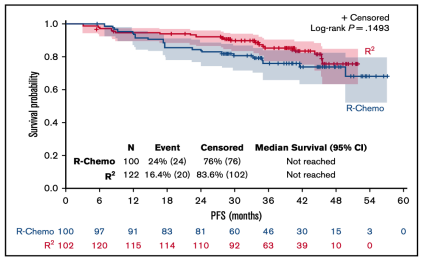
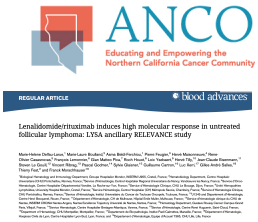


Figure 3. PFS survival in MRD-studied population by treatment arm.

- Of 440 French patients participating in the Lymphoma Study Association (LYSA) RELEVANCE MRD study, all 222 patients with a BIOMED-2–detectable BCL2-JH translocation at diagnosis were analyzed.
- Achievement of CMR (in PB and/or BM) had a significant impact on progression-free survival (PFS), with 3-year PFS of 84% and 55% for patients with CMR and detectable MRD, respectively (P 5 .015).
- CMR at week 24 was reached more frequently in the R2 arm (105/117; 90%) than in the R-Chemo arm (70/90; 77%) (P 5 .022).

In agreement with the clinical results of the RELEVANCE trial, results show that R2 immunomodulatory treatment in first-line FL can achieve high rates of CMR.



Delfau-Larue, Blood Advances 7/16/20

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Follicular Lymphoma (FL)

- **First-line therapy**:
  - Bendamustine + rituximab (Rummel et al, Lancet 2014)
  - R-CHOP
  - R-CVP
  - **Rituximab + lenalidomide** (Morschhauser et al, NEJM Sept 2018; Delfau-Larue et al, Blood Advances July 2020 regarding MRD negativity)
- **Treatment for relapsed/refractory disease**:
  - **Tazemetostat** (FDA approval 6/18/20; Morschhauser et al, Lancet Oncology 2020)

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FDA granted accelerated approval to tazemetostat for follicular lymphoma

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Drugs

Regulatory Science Research and Education

Development & Approval Process | Drugs

Drug Safety and

On June 18, 2020, the Food and Drug Administration granted accelerated approval to tazemetostat (TAZVERIK, Epizyme, Inc.), an EZH2 inhibitor, for adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and for adult patients with R/R FL who have no satisfactory alternative treatment options.

Today, the FDA also approved the cobas EZH2 Mutation Test (Roche Molecular Systems, Inc.) as a companion diagnostic for tazemetostat.

Content current as of:
06/18/2020

Regulated Product(s)
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Phase 2 Multicenter Study of Tazemetostat, an EZH2 Inhibitor, in Patients with Relapsed or Refractory Follicular Lymphoma

Table 1

	EZH2 MT cohort		EZH2 WT cohort	
Parameter	Response-evaluable population (n=43)	POD24 subgroup (n=17)	Response-evaluable population (n=53)	POD24 subgroup (n=30)
Objective response rate, n (%)	33 (77)	11 (65)	18 (34)	9 (30)
95% CI	61.4, 88.2	38.3, 85.8	21.5, 48.3	14.7, 49.4
Complete response, n (%)	3 (7)	1 (6)	3 (6)	0 (0)
Partial response, n (%)	30 (70)	10 (59)	15 (28)	9 (30)
Stable disease, n (%)	10 (23)	6 (35)	16 (30)	8 (27)
Treatment ongoing, n (%)	4 (9)	4 (24)	0 (0)	0 (0)
Progressive disease, n (%)	0 (0)	0 (0)	19 (36)	9 (30)
Progression-free survival, months	11.1[a]	13.8	5.7	5.6
95% CI	8.4, 15.7	3.8, NE	3.5, 11.1	1.9, 11.1
Median duration of response, months	8.3[a]	8.2	13.0	7.3
95% CI	4.0, 12.7	1.9, 12.7	7.3, NE	1.7, NE
Median (range) follow-up, months	15.9 (0.4–40.3)	14.5 (1.6–26.8)	24.9 (0.3–46.0)	26.0 (1.2–42.3)

- Approval based on two open-label, single-arm cohorts (Cohort 4 - EZH2 mutated FL and Cohort 5 - EZH2 wild-type FL) of a multi-center trial (Study E7438-G000-101, NCT01897571) in patients with histologically confirmed FL after at least 2 prior systemic therapies.
- EZH2 mutations identified prospectively using formalin-fixed, paraffin-embedded tumor samples, which were centrally tested using the cobas® EZH2 Mutation Test.
- Tazemetostat 800 mg orally twice daily until confirmed disease progression or unacceptable toxicity.
- Most common (≥20%) adverse reactions in patients with follicular lymphoma included fatigue, upper respiratory tract infection, musculoskeletal pain, nausea and abdominal pain. Serious adverse reactions occurred in 30%, most often from infection. Second primary malignancy was the most common reason for treatment discontinuation (2% of patients)

Morschhauser et al, ASH 2019, Morschhauser et al, Lancet Oncology 2020

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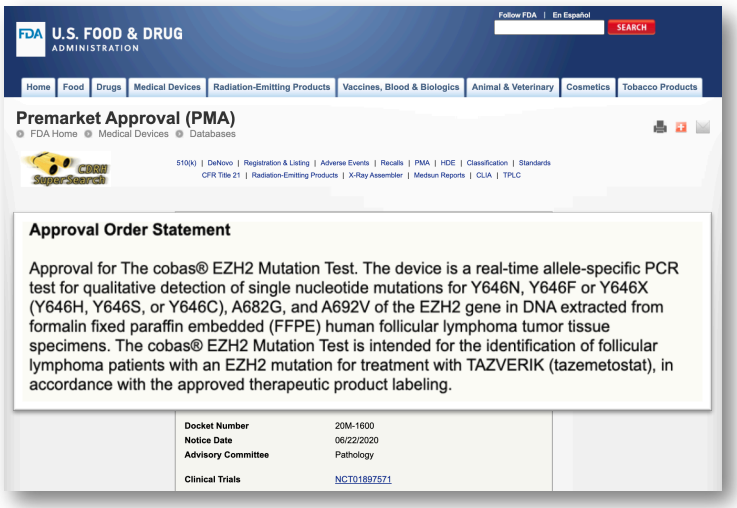

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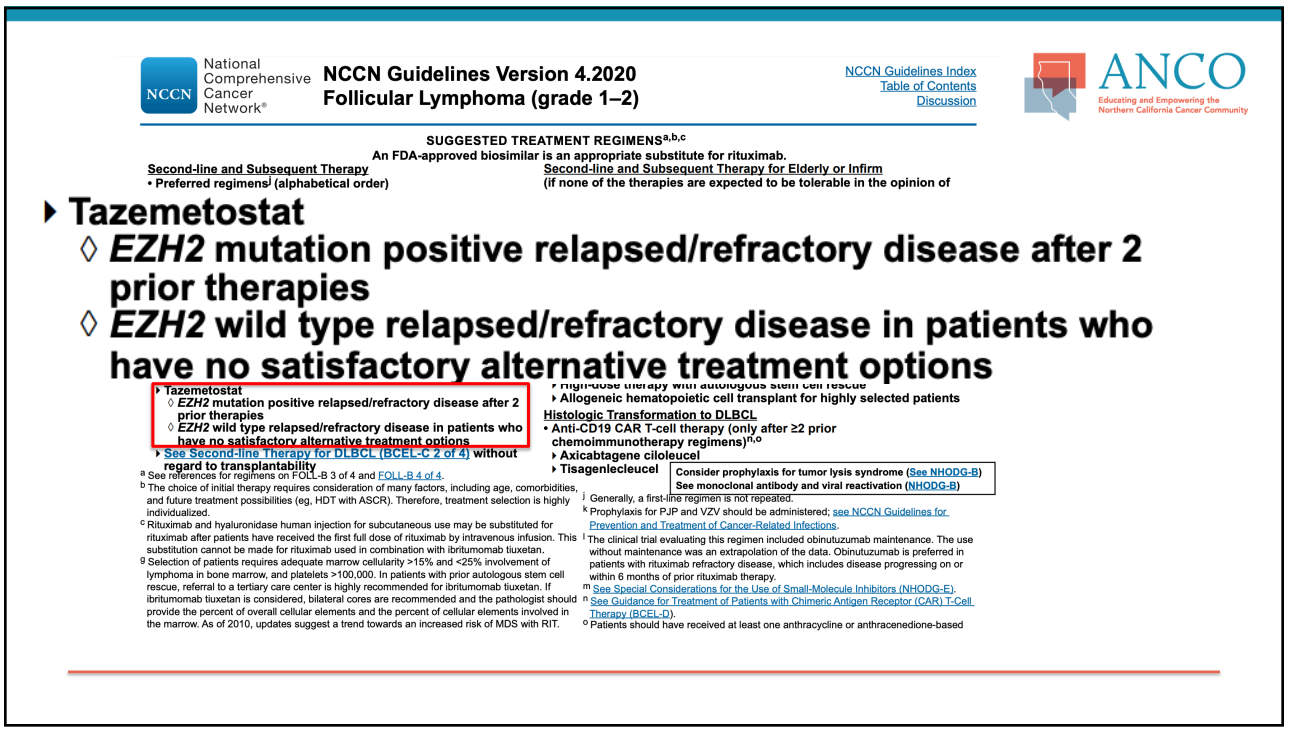

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Follicular Lymphoma (FL)

- **First-line therapy**:
  - Bendamustine + rituximab (Rummel et al, Lancet 2014)
  - R-CHOP
  - R-CVP
  - **Rituximab + lenalidomide** (Morschhauser et al, NEJM Sept 2018; Delfau-Larue et al, Blood Advances July 2020 regarding MRD negativity)
- **Treatment for relapsed/refractory disease**:
  - **Tazemetostat** (FDA approval 6/18/20; Morschhauser et al, ASH 2019)
- **CAR-T?**
  - Zuma-5 (EHA 2020)

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ZUMA-5: Study Design
(Jacobson et al, EHA 2020; abstract S287)

Phase 2 (N ≈ 160 planned for enrollment)

R/R iNHL	FL: n ≈ 125 (with n ≥ 80 evaluable for efficacy)
	MZL: n ≈ 35

Key eligibility criteria
- R/R FL (Grade 1 – Grade 3a) or MZL (nodal or extranodal)[a]
- ≥ 2 prior lines of therapy—must have included an anti-CD20 mAb combined with an alkylating agent

Conditioning regimen
- Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3

Axi-cel: 2 × 10^6 CAR+ cells/kg

Primary endpoint
- ORR (IRRC-assessed per the Lugano classification[1])

Key secondary endpoints
- CR rate (IRRC-assessed)
- DOR, PFS, OS
- AEs
- CAR T cell and cytokine levels

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.
[a] Patients with stable disease (without relapse) > 1 year from completion of last therapy were not eligible.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; iNHL, indolent non-Hodgkin lymphoma; IV, intravenous; mAb, monoclonal antibody; MZL, marginal zone lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory. – Courtesy of David Miklos MD, PhD

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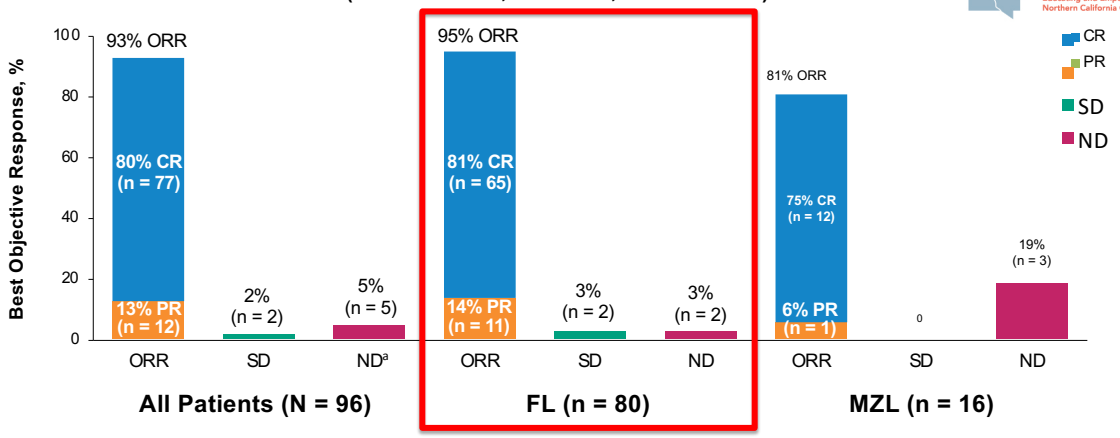
ZUMA-5: Responses
(Jacobson et al, EHA 2020; abstract S287)



- The median time to first response was 1 month (range, 0.8 – 3.1)
- Of the 80 patients with FL, 10 (13%) had an initial response of PR at Week 4 and later converted to CR

The investigator-assessed ORR (N = 96) was 95%, with a CR rate of 80%.
[a] For the 5 patients reported as ND, 4 (1 with FL and 3 with MZL) had no disease at baseline and postbaseline assessments by IRRC; 1 patient with FL died prior to the first scheduled assessment.
CR, complete response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; ND, undefined/not done; ORR, objective response rate; PR, partial response; SD, stable disease. - Courtesy of David Miklos MD, PhD

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Follicular Lymphoma (FL)

- **First-line therapy**:
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  - R-CHOP
  - R-CVP
  - **Rituximab + lenalidomide** (Morschhauser et al, NEJM Sept 2018; Delfau-Larue et al, Blood Advances July 2020 regarding MRD negativity)
- **Treatment for relapsed/refractory disease**:
  - **Tazemetostat** (FDA approval 6/18/20; Morschhauser et al, ASH 2019)
- **CAR-T?**
  - Zuma-5 (EHA 2020)
  - AlloGene (ALPHA, NCT03939026)

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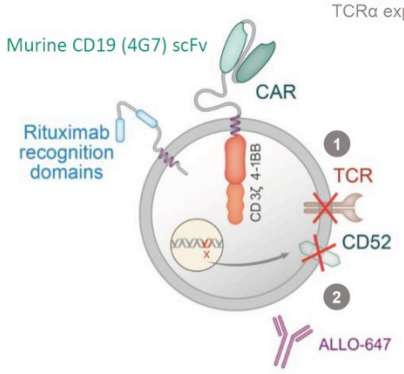
First-in-Human Data of ALLO-501 and ALLO-647 in Rel/Ref Large B-cell or Follicular Lymphoma

1.TALEN-mediated TRAC KO eliminates TCRα expression to minimize risk of GvHD



2. TALEN-mediated CD52 KO allows selective lymphodepletion with ALLO-647

Allogeneic CAR -T therapy may provide the benefits of CAR-T therapy while addressing **autologous CAR-T challenges**:

- **Access:**
  - Off the shelf therapy
  - Repeat dosing
- **Reliability:**
  - Less product variability
  - Made from healthy T cells
- **Less Expensive?**

Neelapu et al ASCO 2020 – Courtesy of David Miklos MD, PhD

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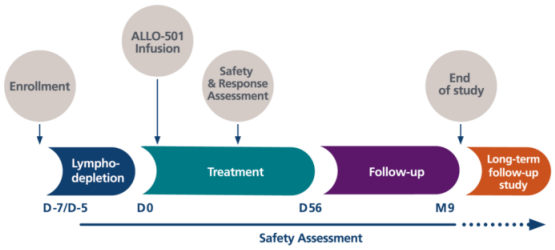
ALPHA Study (NCT03939026) Design and Endpoints
Phase 1, Open-label, Multicenter Dose Escalation Study



	DL1	DL2	DL3
Cell Dose	40 x 10^6 CAR+ T cells	120 x 10^6 CAR+ T cells	360 x 10^6 CAR+ T cells

- Lymphodepletion Regimens
  - LD1: Flu/Cy and ALLO-647 13 mg/d x 3 days
  - LD2/LD3: Flu/Cy and ALLO-647 30 mg/d x 3 days (concomitant/staggered)

Fludarabine (Flu): 30 mg/m2/d x 3 days **Cyclophosphamide (Cy)**: 300 mg/m2/d x 3 days

Primary Endpoints
•Safety and dose-limiting toxicity

Key Secondary Endpoints
•Overall response rate
•ALLO-501 cell kinetics
•ALLO-647 PK

Key Eligibility Criteria
•R/R LBCL or FL
•At least 2 prior lines of therapy, including an anti-CD20 monoclonal antibody
•ECOG 0 or 1
•Prior autologous CAR T if tumor remains CD19+
•Patients with Donor Specific Antibodies and rituximab > 15ng/ml were excluded

Neelapu et al ASCO 2020 – Courtesy of David Miklos MD, PhD

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Mantle Cell Lymphoma (MCL)

- **First-line therapy:**
  - BR +/- autoSCT
  - R-DHAP/R-CHOP >> autoSCT >> rituximab maintenance (OS benefit; Le Gouill et al, NEJM 2017)
  - Rituximab + lenalidomide (Ruan et al, NEJM 2015)
  - R-CHOP f/b rituximab maintenance (OS benefit; Kluin-Nelemans et al, NEJM 2012)
- **Treatment for relapsed/refractory disease:**
  - BTKi
    - Ibrutinib (FDA approval 12/13/13; Wang et al, NEJM 2013)
    - Acalabrutinib (FDA approval 10/31/17; Wang et al, Lancet 2018)
    - **Zanubrutinib** (FDA approval 11/14/19; Song et al, Clin Cancer Research, August 2020)

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TABLE II

Adverse events reported with Bruton tyrosine kinase inhibitors[a]

Variable	Key trial, by inhibitor			
	Ibrutinib Wang *et al.*, 2015[29] (*n*=111)	Acalabrutinib Wang *et al.*, 2018[14] (*n*=124)	Zanubrutinib Tam *et al.*, 2017[38] (*n*=65)	Tirabrutinib Walter *et al.*, 2016[39] (*n*=12)
Adverse events of interest (%)				
Bleeding	Observed All grades: 50 Grade 3 or greater: 6	Observed All grades: 31 Grade 3 or greater: 0.8 (1 case of grade 3 or greater GI hemorrhage with history of ulcer)	Observed All grades: 25 Grade 3 or greater: 3	All grades: not given No increased risk
Atrial fibrillation	Observed Grade 3 or greater: 4.6	Not observed	Observed All grades: 3	Observed, but not drug-related
Common toxicities, all grades (%)				
Diarrhea	54	31	23	21
Fatigue	50	27	18	Not given
Nausea	33	18	Not given	15
Headache	Not given	38	Not given	Not given

Adapted from Owen et al, Curr Oncol April 2019

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Mantle Cell Lymphoma (MCL)

- **First-line therapy:**
  - BR +/- autoSCT
  - R-DHAP/R-CHOP >> autoSCT >> rituximab maintenance (OS benefit; Le Gouill et al, NEJM 2017)
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- **Treatment for relapsed/refractory disease:**
  - BTKi
    - Ibrutinib (FDA approval 12/13/13; Wang et al, NEJM 2013)
    - Acalabrutinib (FDA approval 10/31/17; Wang et al, Lancet 2018)
    - **Zanubrutinib** (FDA approval 11/14/19; Song et al, Clin Cancer Research, August 2020)
  - Ibrutinib + venetoclax (Tam et al, NEJM 2018; phase III ongoing)
  - Rituximab + lenalidomide (FDA approval 6/5/13; Goy et al, JCO 2013)
  - Bortezomib-based regimens (BDR, VR)
- **CAR-T:**
  - **Tecartus** (brexucabtagene autoleucel, Kite/Gilead) (FDA approval 7/24/20; Wang et al, NEJM April 2020)

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U.S. FOOD & DRUG ADMINISTRATION

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FDA NEWS RELEASE

FDA Approves First Cell-Based Gene Therapy For Adult Patients with Relapsed or Refractory MCL

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Press Announcements

For Immediate Release: July 24, 2020

Today, the U.S. Food and Drug Administration approved Tecartus (brexucabtagene autoleucel), a cell-based gene therapy for treatment of adult patients diagnosed with mantle cell lymphoma (MCL) who have not responded to or who have relapsed following other kinds of treatment. Tecartus, a chimeric antigen receptor (CAR) T cell therapy, is the first cell-based gene therapy approved by the FDA for the treatment of MCL.

Content current as of:
07/24/2020

Regulated Product(s)
Biologics

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April 20, 2020

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan

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Wang et al, NEJM April 2020

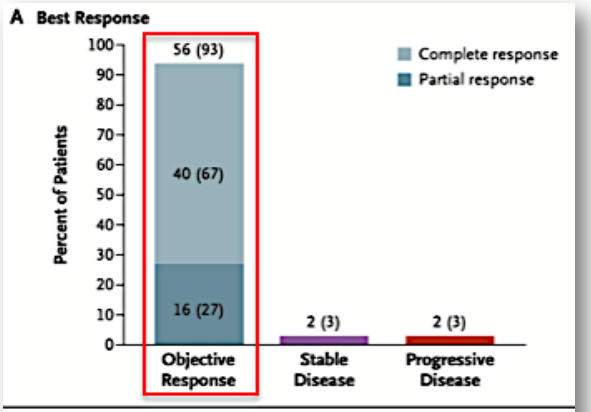

Figure 1. Objective Response, Duration of Response, Progression-free Survival, and Overall Survival.

Panel A shows the numbers and percentages of patients who had an objective response (complete response or partial response) among the 60 patients who had been treated with KTE-X19 and were included in the primary efficacy analysis. Panel B shows the Kaplan–Meier estimate of the duration of response, as assessed on the basis of review by the independent radiologic review committee, among the 56 patients in the primary efficacy analysis who had a response. Tick marks indicate censored data. Kaplan–Meier estimates of progression-free survival and overall survival among the 60 patients who were included in the primary efficacy analysis are shown in Panels C and D, respectively. NE denotes could not be estimated.

Table 1. Baseline Characteristics of All 68 Treated Patients.*

Characteristic	Patients
Median age (range) — yr	65 (38–79)
Intermediate or high risk according to Simplified MIPI — no. (%)†‡	38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL — no. (%)	21 (31)
Ki-67 proliferation index ≥30% — no./total no. (%)‡	40/49 (82)
TP53 mutation — no. (%)	6/36 (17)
Positive CD19 status — no./total no. (%)	47/51 (92)
Median no. of previous therapies (range)§	3 (1–5)
≥3 Previous lines of therapy — no. (%)	55 (81)
Previous autologous stem-cell transplantation — no. (%)	29 (43)
Previous BTK inhibitor therapy — no. (%)§	68 (100)
Ibrutinib	58 (85)
Acalabrutinib	16 (24)
Both	6 (9)
Relapsed or refractory disease — no. (%)	
Relapse after autologous stem-cell transplantation	29 (43)
Refractory to most recent previous therapy	27 (40)
Relapse after most recent previous therapy	12 (18)
Disease that relapsed or was refractory to BTK inhibitor therapy — no. (%)	68 (100)
Refractory to BTK inhibitor therapy	42 (62)
Relapse during BTK inhibitor therapy	18 (26)
Relapse after BTK inhibitor therapy	5 (7)
Could not take BTK inhibitor therapy because of adverse events¶	3 (4)

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Wang et al, NEJM April 2020

Table 3. Cytokine Release Syndrome and Neurologic Events among All 68 Treated Patients.*

Event	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			number of patients (percent)			
Symptom of cytokine release syndrome						
Any	62 (91)	20 (29)	32 (47)	8 (12)	2 (3)	0
Pyrexia	62 (91)	15 (22)	40 (59)	7 (10)	0	0
Hypotension	35 (51)	4 (6)	16 (24)	14 (21)	1 (1)	0
Hypoxemia	23 (34)	1 (1)	10 (15)	8 (12)	4 (6)	0
Chills	21 (31)	12 (18)	9 (13)	0	0	0
Tachycardia	16 (24)	11 (16)	5 (7)	0	0	0
Headache	15 (22)	7 (10)	8 (12)	0	0	0
Alanine aminotransferase increased	10 (15)	5 (7)	1 (1)	3 (4)	1 (1)	0
Aspartate aminotransferase increased	9 (13)	4 (6)	0	5 (7)	0	0
Fatigue	9 (13)	6 (9)	2 (3)	1 (1)	0	0
Nausea	9 (13)	5 (7)	4 (6)	0	0	0
Neurologic event	43 (63)	13 (19)	9 (13)	15 (22)	6 (9)	0
Tremor	24 (35)	19 (28)	5 (7)	0	0	0
Encephalopathy	21 (31)	5 (7)	3 (4)	7 (10)	6 (9)	0
Confusional state	14 (21)	3 (4)	3 (4)	8 (12)	0	0
Aphasia	10 (15)	3 (4)	4 (6)	3 (4)	0	0

* Shown are events of any grade that occurred in at least 15% of the patients and events of grade 3 or higher that occurred in at least 4% of the patients. Cytokine release syndrome was graded according to Lee et al.[21] The severity of neurologic events and symptoms of cytokine release syndrome were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

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FDA NEWS RELEASE

FDA Approves First Cell-Based Gene Therapy For Adult Patients with Relapsed or Refractory MCL

****No prior BTKi required****

81

Acknowledgements:

David Kurtz MD, PhD – Clinical Instructor

Matthew Frank MD, PhD – Assistant Professor

David Miklos MD, PhD – Associate Professor

ANCO!

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"Whoa—way too much information."

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Updates in Multiple Myeloma: ANCO 2020

Aaron S. Rosenberg, MD, MS
University of California, Davis

ANCO

Educating and Empowering the Northern California Cancer Community

Updates in Multiple Myeloma

Aaron Rosenberg, MD, MS
Assistant Professor of Medicine
Bone Marrow Transplantation Unit
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1

Disclosures

ANCO
Educating and Empowering the Northern California Cancer Community

- Speakers Bureau (unbranded)
  - Janssen, Millennium-Takeda
- Research
  - Amgen

- Bone Marrow Transplant Attending (probably more important than any of the above!)

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Outline

- Newly Diagnosed Multiple Myeloma
- New Treatments in 2020:
  - Belantamab Mafodotin
  - Selinexor with Bortez/Dex
- Survivorship in Myeloma
  - Second primary malignancies
  - Cardiovascular Endpoints

3

What is the current standard of care

NEWLY DIAGNOSED MYELOMA

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How Should Front Line Therapy be Approached?

- Incurable disease – thus goals of therapy tailored to individual patients
- In modern era of therapy, prolongation of life while minimizing toxicity is achievable
- Minimize morbidity – and adjust how aggressive you are to the end-organ damage in front of you

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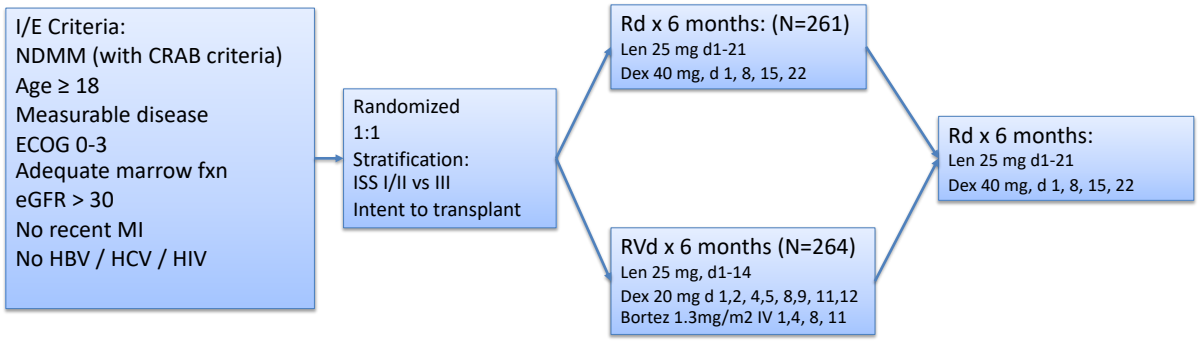
S0777: Trial Schema



Durie et al Lancet 2017
Durie et al Blood Canc Jour 2020

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S0777: PFS and OS

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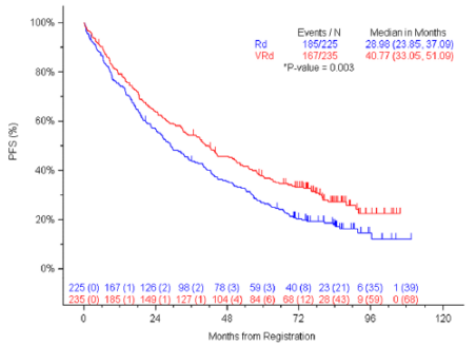
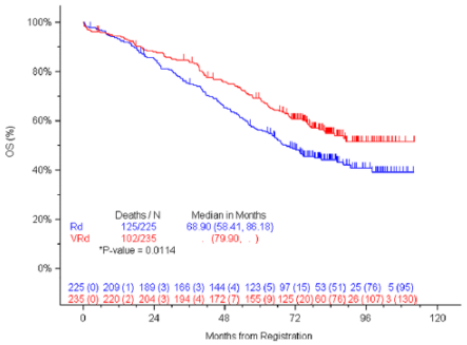
PFS



OS



Durie et al Lancet 2017
Durie et al Blood Canc Jour 2020

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S0777: Response Rates and Multivariable Analysis

ANCO
Educating and Empowering the Northern California Cancer Community

Table 2 Confirmed best responses in assessable patients.

	VRd[a] ($n = 215$)	Rd[a] ($n = 207$)
Complete response (CR)	24.2% (52)	12.1% (25)
Very good partial response (VGPR)	50.7% (109)	41.1% (85)
VGPR or better	**74.9% (161)**	**53.2% (110)**
Partial response (PR)	15.3% (33)	25.6% (53)
Overall response rate (ORR)	**90.2% (194)**	**78.8% (163)**
Stable disease (SD)	7.0% (15)	16.4% (34)
PD or Death	2.8% (6)	4.8% (10)

Table 3 Multivariate age-adjusted progression-free survival and overall survival.

	Variable	*n/N* (%)	PFS		OS	
			HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Multivariate	RVd arm	235/460 (51%)	0.77 (0.62, 0.95)	0.013	0.75 (0.58, 0.98)	0.033
	ISS Stage III	155/460 (34%)	1.34 (1.01, 1.77)	0.041	1.98 (1.38, 2.86)	<.001
	ISS Stage II	179/460 (39%)	1.12 (0.86, 1.47)	0.398	1.36 (0.95, 1.97)	0.096
	Intent to Transplant	315/460 (68%)	0.95 (0.74, 1.23)	0.714	0.73 (0.54, 0.99)	0.043
	Age > =65 yr	197/460 (43%)	1.27 (1.00, 1.61)	0.048	1.63 (1.21, 2.19)	0.001

Durie et al Lancet 2017
Durie et al Blood Canc Jour 2020

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S0777: Does Response Matter?

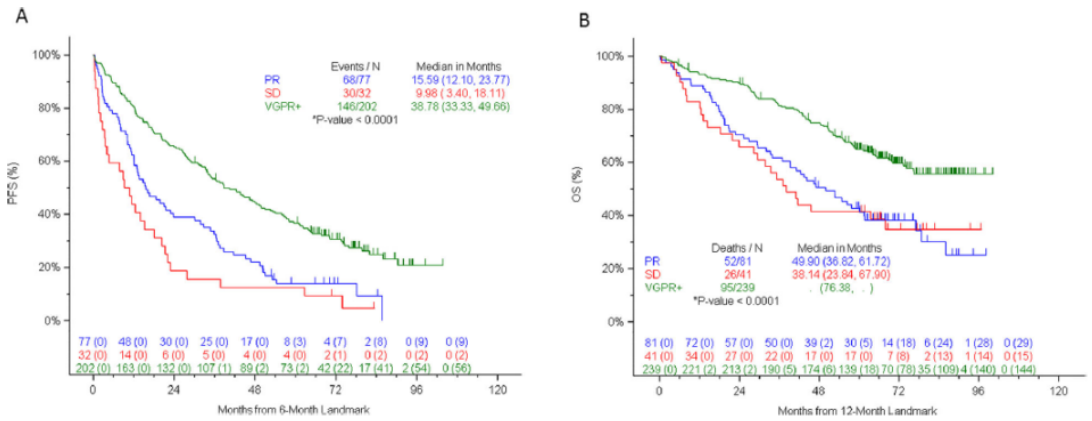

Fig. 2 Landmarked outcomes. a Progression-free Survival by best response at 6 months. **b** Overall Survival by best response at 12 months.

Durie et al Lancet 2017
Durie et al Blood Canc Jour 2020

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Table 5 Adverse events at least possibly attributable to study drug by category.

Adverse event description	Revlimid/dexamethasone (*N* = 222)					Velcade/Revlimid/dexamethasone (*N* = 234)				
	1	2	3	4	5	1	2	3	4	5
Allergy/immunology	12 (5%)	5 (2%)				10 (4%)	4 (2%)	2 (<1%)		
Auditory/ear	1 (<1%)	16 (7%)				1 (<1%)	8 (3%)			
Blood/bone marrow	22 (10%)	53 (24%)	68 (31%)	39 (18%)		27 (12%)	52 (22%)	70 (30%)	44 (19%)	
Cardiac arrhythmia	5 (2%)	4 (2%)	4 (2%)			10 (4%)	3 (1%)	3 (1%)		
Cardiac general	13 (6%)	9 (4%)	8 (4%)			15 (6%)	17 (7%)	21 (9%)		
Coagulation	1 (<1%)		3 (1%)					5 (2%)		
Constitutional symptoms	61 (27%)	77 (35%)	38 (17%)			60 (26%)	84 (36%)	51 (22%)		
Death					1 (<1%)					2 (<1%)
Dermatology/skin	60 (27%)	23 (10%)	9 (4%)			50 (21%)	41 (18%)	7 (3%)	1 (<1%)	
Endocrine	11 (5%)	8 (4%)				7 (3%)	12 (5%)			
Gastrointestinal	77 (35%)	71 (32%)	19 (9%)			64 (27%)	79 (34%)	51 (22%)	2 (<1%)	1 (<1%)
Hemorrhage/bleeding	13 (6%)	2 (<1%)				9 (4%)	3 (1%)	8 (3%)		
Hepatobiliary/pancreas			2 (<1%)							
Infection	1 (<1%)	31 (14%)	27 (12%)	4 (2%)		1 (<1%)	33 (14%)	34 (15%)	7 (3%)	1 (<1%)
Lymphatics	58 (26%)	19 (9%)	1 (<1%)			73 (31%)	26 (11%)	4 (2%)		
Metabolic/laboratory	56 (25%)	58 (26%)	51 (23%)	13 (6%)		50 (21%)	58 (25%)	57 (24%)	8 (3%)	
Musculoskeletal/soft tissue	25 (11%)	25 (11%)	16 (7%)	1 (<1%)		15 (6%)	31 (13%)	24 (10%)		
Neurology	78 (35%)	44 (20%)	21 (9%)	3 (1%)	1 (<1%)	42 (18%)	70 (30%)	77 (33%)	4 (2%)	
Ocular/visual	21 (9%)	8 (4%)	11 (5%)			39 (17%)	17 (7%)	6 (3%)		
Pain	44 (20%)	29 (13%)	10 (5%)			55 (24%)	43 (18%)	28 (12%)		
Pulmonary/upper respiratory	42 (19%)	27 (12%)	9 (4%)	1 (<1%)		56 (24%)	17 (7%)	15 (6%)	5 (2%)	
Renal/genitourinary	3 (1%)	2 (<1%)	9 (4%)	1 (<1%)		10 (4%)	3 (1%)	6 (3%)		
Secondary malignancy			5 (2%)	1 (<1%)				5 (2%)	2 (<1%)	
Sexual/reproductive function	1 (<1%)	1 (<1%)	1 (<1%)			3 (1%)	1 (<1%)			
Syndromes			2 (<1%)			1 (<1%)	2 (<1%)	4 (2%)		
Vascular		7 (3%)	15 (7%)	6 (3%)		1 (<1%)	9 (4%)	20 (9%)	4 (2%)	

Durie et al Lancet 2017
Durie et al Blood Canc Jour 2020

15

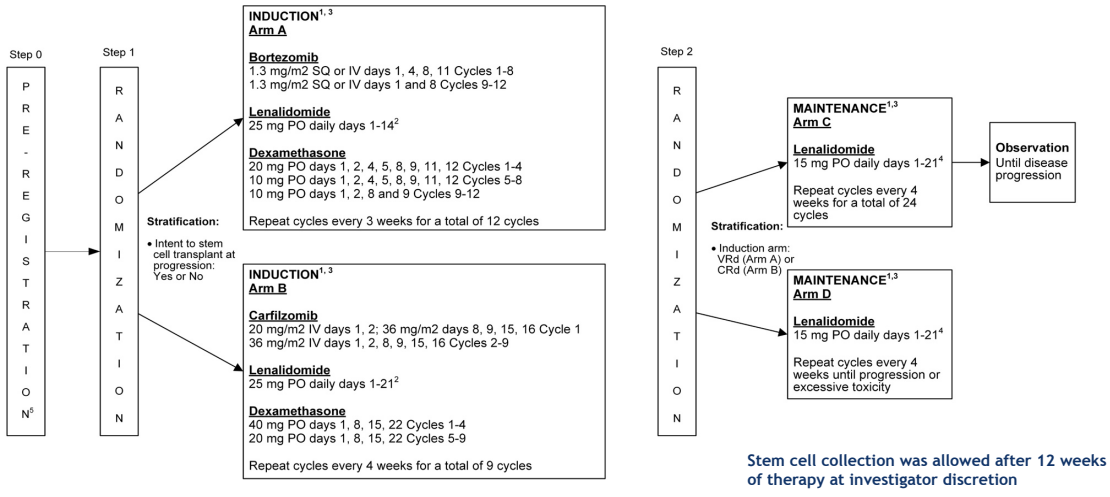
Can we do better than VRd?

Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial

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

16

Patient Randomization and Treatment Schedule



Stem cell collection was allowed after 12 weeks of therapy at investigator discretion

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Key Eligibility Criteria

- Previously untreated MM with no intent for immediate (upfront) SCT
- None of the following high-risk features (t(14;20), t(14;16), del17p, LDH > 2 X ULN, no plasma cell leukemia)
- ECOG performance status 0, 1, or 2 (PS 3 if secondary to pain)
- Adequate hematological parameters and organ function
- Measurable disease in serum, urine, or bone marrow
- No grade ≥2 peripheral neuropathy
- NYHA III or IV heart failure or MI < 6 months were excluded

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Baseline Demographics

Variable	Category	VRd (n=542) N (%)	KRd (n=545) N (%)	Total (n=1087) N (%)
Age (y), median (range)		64 (32-88)	65 (35-86)	65 (32-88)
	>/=70 years	167 (30.8)	177 (32.5)	344 (31.6)
	>/=65 years	264 (48.7)	288 (52.8)	552 (50.8)
Gender	Male	315 (58.1)	327 (60.0)	642 (59.1)
Race	White	443 (84.5)	448 (86.3)	891 (85.4)
	Black	68 (13.0)	59 (11.4)	127 (12.2)
	Other	13 (2.5)	12 (2.3)	25 (2.4)
ECOG PS	PS0	212 (39.1)	241 (44.2)	453 (41.7)
	PS1	270 (49.8)	249 (45.7)	519 (47.8)
	PS2-3	60 (11.1)	55 (10.1)	115 (10.5)
ISS Stage	I	144 (30.6)	157 (32.5)	301 (31.6)
	II	203 (43.1)	207 (42.9)	410 (43.0)
	III	124 (26.3)	119 (24.6)	243 (25.5)
Measurable Disease Type	SPEP&UPEP	115 (21.2)	114 (20.9)	229 (21.1)
	SPEP	305 (56.3)	296 (54.3)	601 (55.3)
	UPEP	57 (10.5)	79 (14.5)	136 (12.5)
	FLC	58 (10.7)	51 (9.4)	109 (10.0)
	Bone Marrow	4 (0.7)	4 (0.7)	8 (0.7)
	Not Measurable	3 (0.6)	1 (0.2)	4 (0.4)

Variable	VRd (n=542) median (IQR)	KRd (n=545) median (IQR)	Total (n=1087) median (IQR)
Bone marrow plasma cell (%)	52 (30-75)	50.5 (30-72)	51 (30-75)
Albumin (g/dL)	3.8 (3.4-4.2)	3.8 (3.4-4.2)	3.8 (3.4-4.2)
Beta 2 microglobulin (ug/mL)	3.6 (2.6-5.6)	3.9 (2.8-6)	3.8 (2.6-5.8)
Hemoglobin (g/dL)	11 (9.6-12.4)	11.2 (9.8-12.6)	11.1 (9.7-12.5)
Calcium (mg/dL)	9.3 (8.9-9.8)	9.4 (8.9-9.8)	9.3 (8.9-9.8)
Serum M Spike (g/dL)	3 (1.8-4.2)	2.9 (1.8-4.2)	3 (1.8-4.2)
Urine M Spike (mg/24hr)	297.8 (64.9-1099)	257.1 (49.4-1312.4)	275 (56.4-1157)
Creatinine (mg/dL)	1 (0.8-1.3)	1 (0.8-1.3)	1 (0.8-1.3)
Lactate Dehydrogenase (U/L)	171 (136-222)	166 (135-203)	168 (136-209)

Variable	Category	N (%)	N (%)	N (%)
Cytogenetics	Normal	326 (71.8)	331 (72.3)	657 (72.0)
	Abnormal	128 (28.2)	127 (27.7)	255 (28.0)
	Missing	88	67	175
t(11;14)	Abnormal	87 (20.6)	80 (18.7)	167 (19.7)
t(4;14)	Abnormal	44 (10.4)	36 (8.4)	80 (9.4)

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Induction Treatment Status

N=1053 starting assigned treatment

Reason	VRd (n=527) N (%)	KRd (n=526) N (%)	Total (n=1053) 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) N (%)	KRd (n=545) N (%)	Total (n=1087) 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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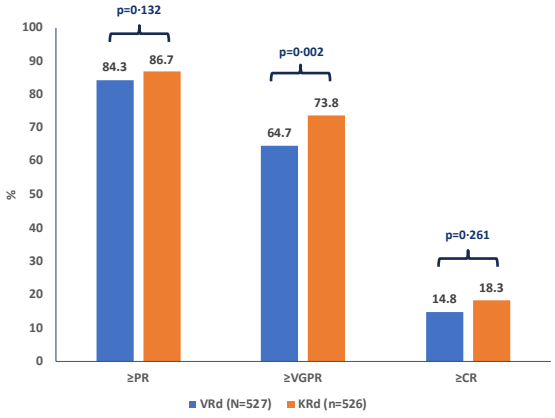
Response To Induction

Category	VRd (n=527) N (%)	KRd (n=526) N (%)	Total (n=1053) 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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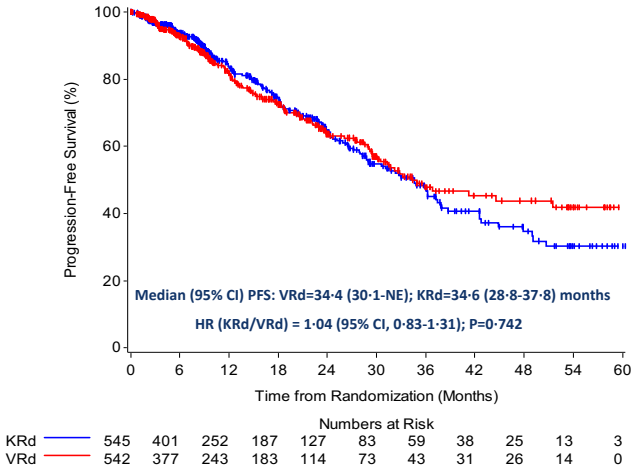
Progression Free Survival from Induction Randomization



- 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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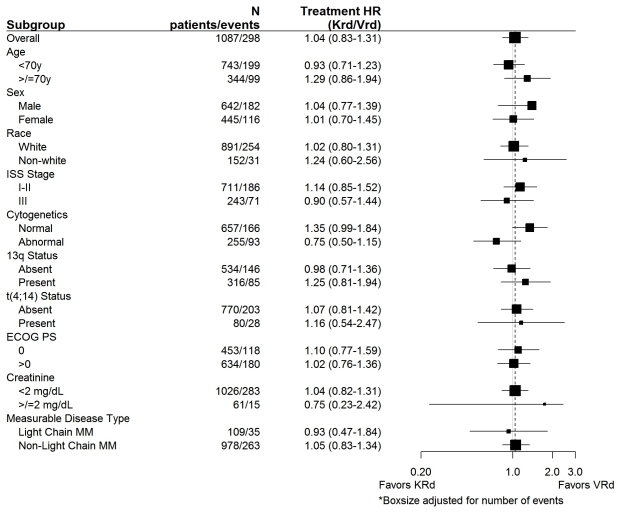
Progression Free Survival in Subgroups



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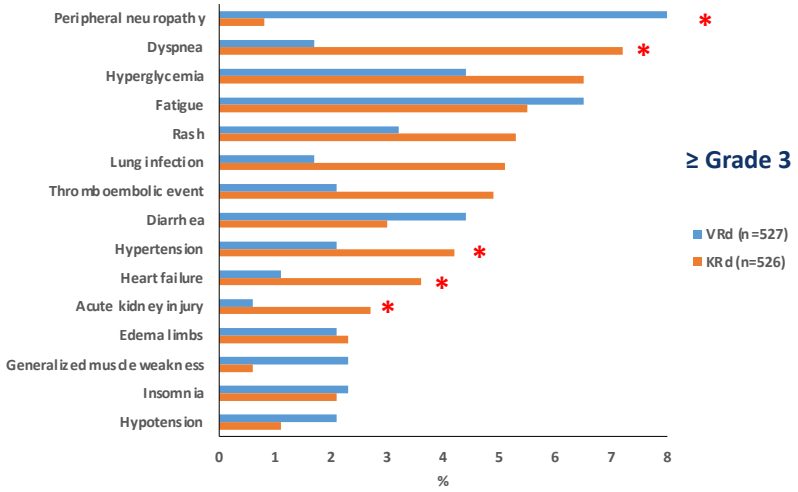
Non-hematologic: Treatment-Related AEs (≥2%)



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Can we do better than VRd?

Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial

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

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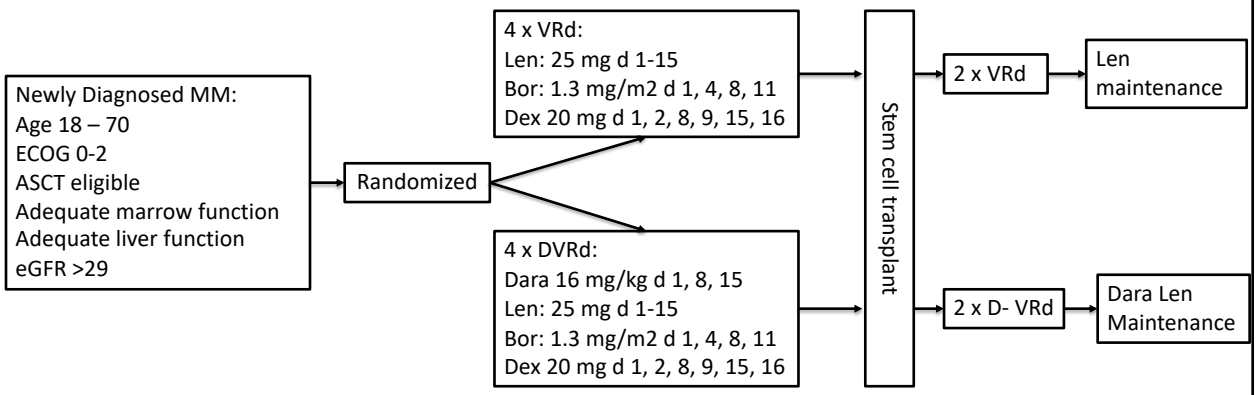
Design



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GRIFFIN: Demographics and Toxicity

Table 1. Patient demographic and disease characteristics in the intent-to-treat population at baseline

	D-RVd	RVd
Age, y	n = 104	n = 103
Median (range)	59 (29-70)	61 (40-70)
Category, n (%)		
<65	76 (73.1)	75 (72.8)
≥65	28 (26.9)	28 (27.2)
Sex, n (%)	n = 104	n = 103
Male	58 (55.8)	60 (58.3)
Female	46 (44.2)	43 (41.7)
ECOG performance status, n (%)*	n = 101	n = 102
0	39 (38.6)	40 (39.2)
1	51 (50.5)	52 (51.0)
2	11 (10.9)	10 (9.8)
ISS disease stage, n (%)†	n = 104	n = 103
I	49 (47.1)	50 (48.5)
II	40 (38.5)	37 (35.9)
III	14 (13.5)	14 (13.6)
Missing	1 (1.0)	2 (1.9)
Baseline creatinine clearance, mL/min, n (%)	n = 104	n = 103
30-50	9 (8.7)	9 (8.7)
>50	95 (91.3)	94 (91.3)
Cytogenetic risk profile, n (%)‡	n = 98	n = 97
Standard	82 (83.7)	83 (85.6)
High risk	16 (16.3)	14 (14.4)
Time since diagnosis of MM, mo	n = 103	n = 102
Median (range)	0.7 (0-12)	0.9 (0-61)

t(4;14), t(14;16), del(17p)

Adverse event, n (%)	D-RVd, n = 99		RVd, n = 102	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic				
Neutropenia	57 (57.6)	41 (41.4)	36 (35.3)	22 (21.6)
Thrombocytopenia	43 (43.4)	16 (16.2)	36 (35.3)	9 (8.8)
Leukopenia	36 (36.4)	16 (16.2)	29 (28.4)	7 (6.9)
Anemia	35 (35.4)	9 (9.1)	33 (32.4)	6 (5.9)
Lymphopenia	30 (30.3)	23 (23.2)	28 (27.5)	22 (21.6)
Nonhematologic				
Fatigue	68 (68.7)	6 (6.1)	62 (60.8)	6 (5.9)
Upper respiratory tract infection	62 (62.6)	1 (1.0)	45 (44.1)	2 (2.0)
Peripheral neuropathy*	59 (59.6)	7 (7.1)	74 (72.5)	8 (7.8)
Diarrhea	59 (59.6)	7 (7.1)	51 (50.0)	4 (3.9)
Constipation	51 (51.5)	2 (2.0)	40 (39.2)	1 (1.0)
Cough	50 (50.5)	0	27 (26.5)	0
Nausea	49 (49.5)	2 (2.0)	50 (49.0)	1 (1.0)
Pyrexia	45 (45.5)	2 (2.0)	28 (27.5)	3 (2.9)
Insomnia	42 (42.4)	2 (2.0)	31 (30.4)	1 (1.0)
Back pain	36 (36.4)	1 (1.0)	34 (33.3)	4 (3.9)
Peripheral edema	34 (34.3)	2 (2.0)	35 (34.3)	3 (2.9)
Arthralgia	33 (33.3)	0	33 (32.4)	2 (2.0)
Infusion-related reaction	42 (42.4)	6 (6.1)†	NA	NA

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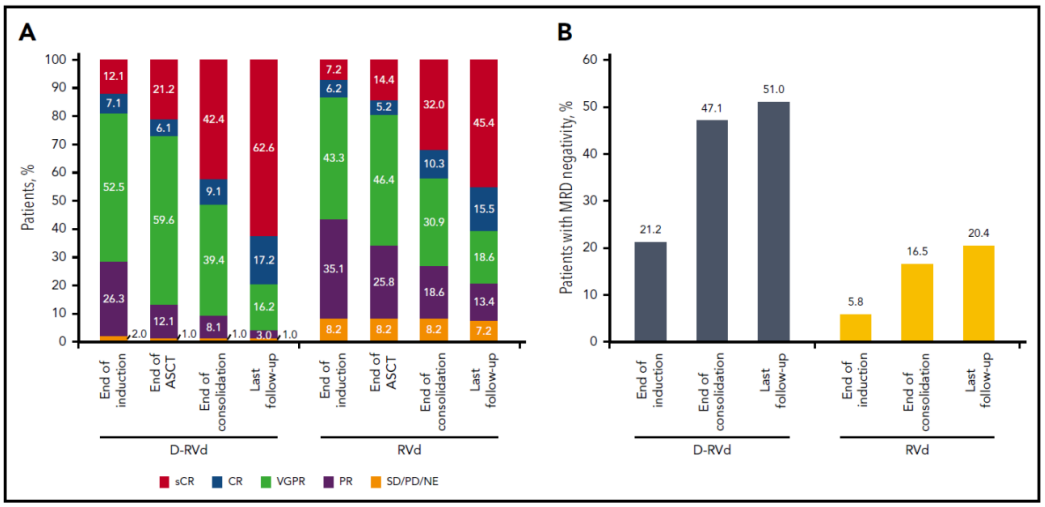
GRIFFIN: Responses deepen over time



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D-VRd: Subgroup analysis of sCR rates

B **Median follow-up, 22.1 months**

Subgroup	RVd *minimal residual disease negative, n (%)*	D-RVd	Odds Ratio (95% CI)
Sex			
Male	10/60 (16.7)	26/58 (44.8)	4.06 (1.73-9.54)
Female	11/43 (25.6)	27/46 (58.7)	4.13 (1.68-10.19)
Age			
<65 yr	16/75 (21.3)	38/76 (50.0)	3.69 (1.81-7.52)
≥65 yr	5/28 (17.9)	15/28 (53.6)	5.31 (1.57-17.97)
ISS disease stage			
I	6/50 (12.0)	25/49 (51.0)	7.64 (2.75-21.19)
II	10/37 (27.0)	20/40 (50.0)	2.70 (1.04-7.01)
III	5/14 (35.7)	8/14 (57.1)	2.40 (0.52-10.99)
Type of multiple myeloma			
IgG	11/52 (21.2)	29/55 (52.7)	4.16 (1.78-9.73)
Non-IgG	10/51 (19.6)	22/46 (47.8)	3.76 (1.53-9.26)
Cytogenetic risk			
High risk	4/14 (28.6)	6/16 (37.5)	1.50 (0.32-6.99)
Standard risk	17/83 (20.5)	45/82 (54.9)	4.72 (2.37-9.40)
ECOG PS score			
0	5/40 (12.5)	21/39 (53.8)	8.17 (2.64-25.25)
1 or 2	16/62 (25.8)	32/62 (51.6)	3.07 (1.44-6.53)

1 10 100

RVd better D-RVd better

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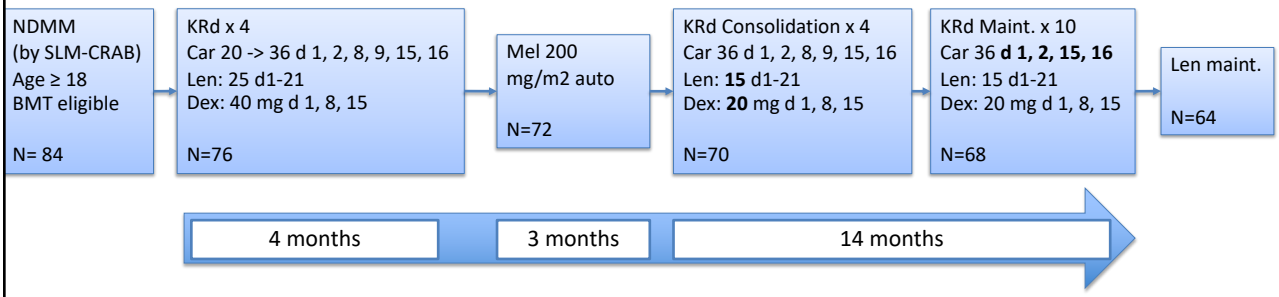
Is KRd really dead for NDMM? MMRC Extended KRd trial (The new total therapy?)



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MMRC Extended KRd: Demographics and Toxicity

Characteristic	N=76
Age	
Median years (range)	59 (40–76)
≥65 years, n (%)	21 (27.6)
Sex, n (%)	
Male	45 (59.2)
Female	31 (40.8)
ECOG performance status, n (%)	
0–1	65 (85.5)
Unknown	11 (14.5)
ISS Stage, n (%)	
I	31 (40.8)
II	31 (40.8)
III	10 (13.2)
Unknown	4 (5.3)
Cytogenetic risk by FISH*, n (%)	
High	27 (35.5)
Deletion 17p	11 (14.5)
Ultra-high risk†	8 (10.5)
Standard	49 (64.5)
Serum β_2-microglobulin, n (%)	
<3.5 mg/L	45 (59.2)
≥3.5 mg/L, %	24 (31.6
Unknown	7 (9.2)

*Defined per IMWG: t(4;14), del(17p), t(14;16), t(14;20), non-hyperdiploidy and gain(1q).

Table 3. Treatment-emergent adverse events during KRd*

	KRd +ASCT N=76	
	All Grade, n (%)	Grade 3/4, n (%)
Hematologic		
Thrombocytopenia	47 (62)	11 (14)
Anemia	32 (42)	9 (12)
Lymphopenia	32 (42)	24 (32)
Neutropenia	30 (39)	26 (34)
Non-hematologic		
Infection	56 (74)	17 (22)
Fatigue	51 (67)	4 (5)
Diarrhea	39 (51)	7 (9)
Hyperglycemia	33 (43)	6 (8)
Dyspnoea	30 (39)	2 (3)
Peripheral neuropathy	32 (42)	0
Rash	33 (43)	4 (5)
Hypophosphatemia	22 (29)	11 (14)
Hypertension	15 (20)	4 (5)
Thromboembolic events	14 (18)	5 (7)
Cardiac events†	10 (13)	2 (3)

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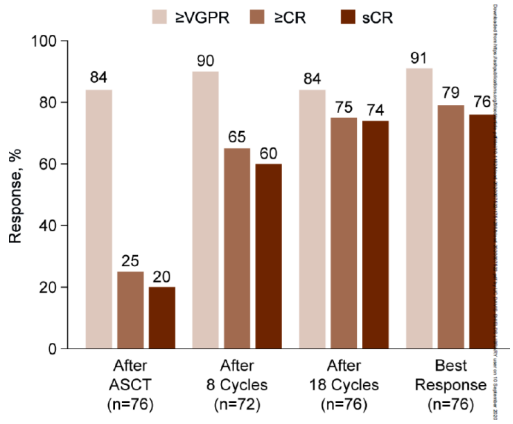
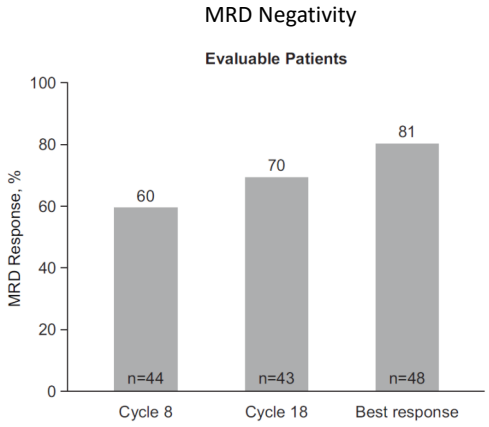
MMRC Extended KRd: Responses improve throughout KRd exposure





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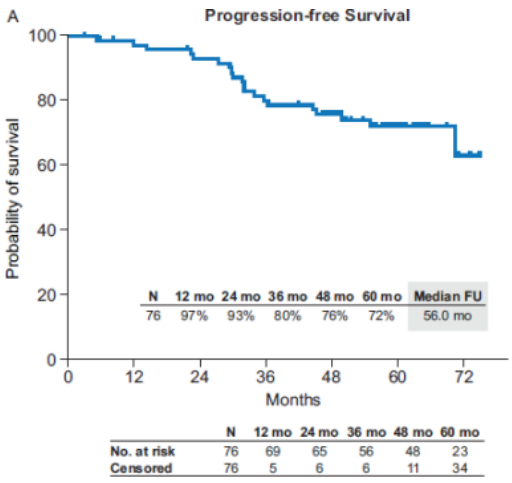
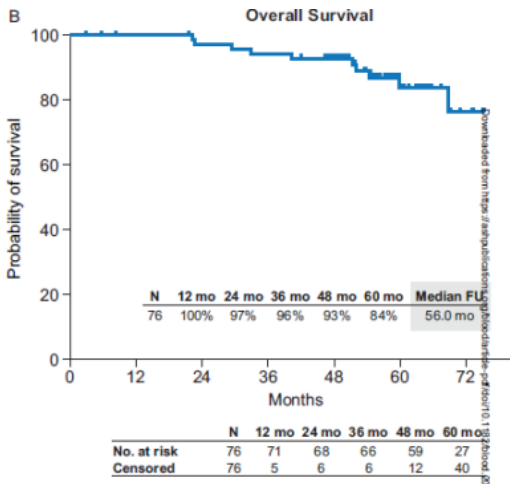
MMRC: Extended KRd PFS and OS





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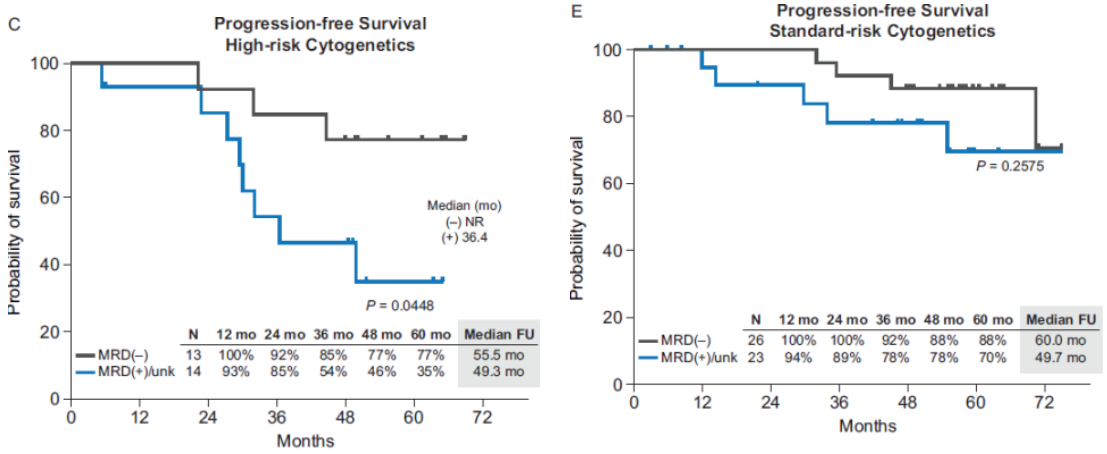
MMRC: Extended KRd: PFS by High Risk and Standard Risk Cytogenetics



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NDMM with Acute Kidney Injury

Randomized Trial Comparing Double Versus Triple Bortezomib-Based Regimen in Patients With Multiple Myeloma and Acute Kidney Injury Due to Cast Nephropathy

Frank Bridoux, MD, PhD[1,2,3]; Bertrand Arnulf, MD, PhD[4]; Lionel Karlin, MD[5]; Nicolas Blin, MD[6]; Nolwenn Rabot, MD[7]; Margaret Macro, MD[8]; Vincent Audard, MD, PhD[9]; Karim Belhadj, MD[10]; Brigitte Pegourie, MD[11]; Pierre Gobert, MD[12]; Emilie Cornec Le Gall, MD, PhD[13]; Bertrand Joly, MD[14]; Alexandre Karras, MD, PhD[15]; Arnaud Jaccard, MD, PhD[2,3,16]; Karine Augeul-Meunier, MD[17]; Salomon Manier, MD, PhD[18]; Bruno Royer, MD[19]; Denis Caillot, MD, PhD[20]; Mourad Tiab, MD[21]; Sébastien Delbes, MD[22]; Felipe Suarez, MD, PhD[23]; Cécile Vigneau, MD, PhD[24]; Sophie Caillard, MD, PhD[25]; Nina Arakelyan-Laboure, MD[26]; Damien Roos-Weil, MD, PhD[27]; Sylvie Chevret, MD, PhD[28]; and Jean Paul Fermand, MD[4]; for the MYRE study group

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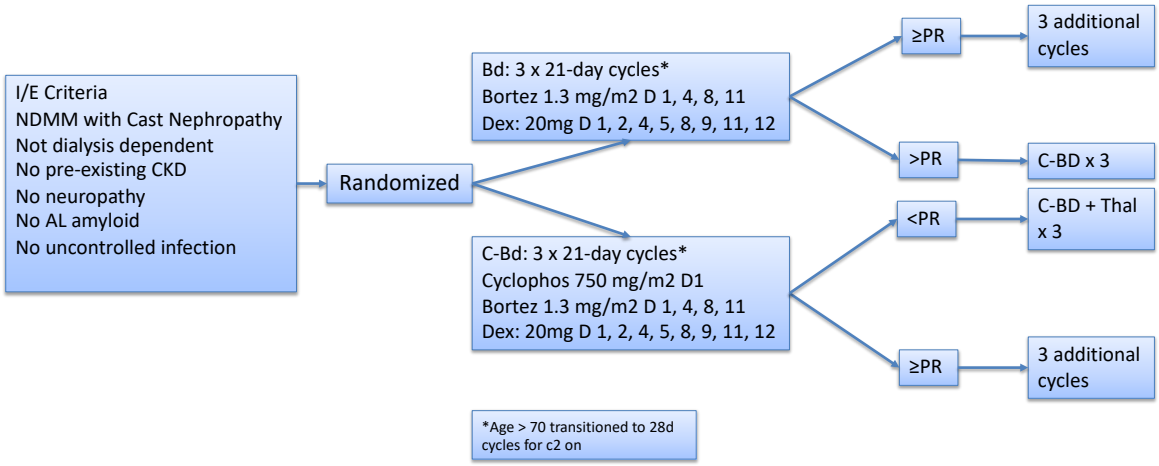
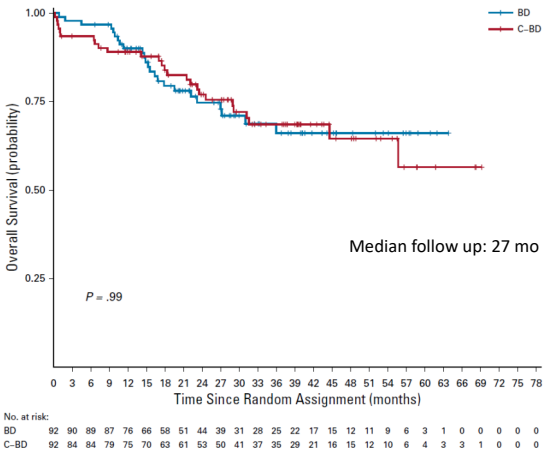
MYRE: Design



Bridoux et al JCO 2020

MYRE: Responses and OS

- Renal response at 3 months
  - BD: 44.6%
  - C-BD: 51.1%
  - Risk ratio 0.87 (0.64 – 1.18)
- Overall Response at 3 months
  - BD: 78.3%
  - C-BD: 77.2%
- ≥VGPR at 6 months
  - BD: 46.8%
  - C-BD51.1%
  - RR 0.88 (0.66 – 1.17)



Bridoux et al JCO 2020

Newly Diagnosed Multiple Myeloma: Summary

- The standard of care of NDMM should be RVd based on S0777 and E1A11: ENDURANCE
  - BUT…. E1A11 excluded t(14;16), t(14;20) and del(17p)
- The CR and MRD- rates with extended KRd in the high risk population are provocative
  - I may still consider this, since these patients were excluded from E1A11
- What about D-RVd?
  - If you're an "early adopter," or if you think MRD- rates are an adequate surrogate, GRIFFIN probably gives you enough push to adopt now
  - However, I personally would like to see some data on PFS
  - It will be hard to assess survival outcomes in GRIFFIN because of the difference in post-BMT maintenance
  - Interestingly, D-RVd did not seem to affect outcomes in high-risk populations. More to come with this, I'm sure (along with all the caveats that come with sub-group analyses)
- For NDMM with AKI:
  - Bolus dosing of cyclophosphamide is not effective
  - However, hyper-fractionated cyclophosphamide, or lower dose oral cyclophos may provide improved outcomes by providing more consistent cytotoxic therapy
  - Randomized trials are clearly needed in this population

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Relapsed Myeloma:
New Drugs 2020

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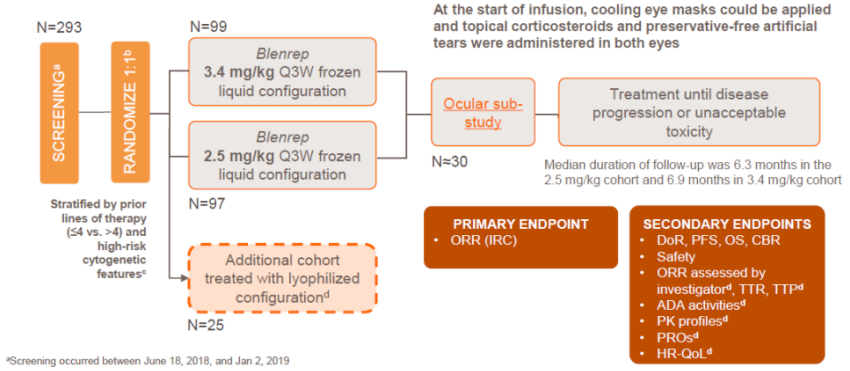
DREAMM-2: Study Design

A phase II, open label, randomized 2-dose study in RRMM who were refractory to an immunomodulatory drug, proteasome inhibitor and refractory/intolerant to an anti-CD38 monoclonal antibody.



[a]Screening occurred between June 18, 2018, and Jan 2, 2019
[b]DREAMM-2 was not designed to compare between the 2 doses
[c]Presence or absence of t(4;14), t(14;16) or 17p13del
[d]To be reported separately

ADA = anti-drug antibody; CBR = clinical benefit rate; DoR = duration of response; HR-QoL = health-related quality-of-life; IRC = independent review committee; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PK = pharmacokinetics; PRO = patient reported outcome; Q3W = every 3 weeks; TTP = time to progression; TTR = time to (best) response.

Lonial et al, Lancet Onc 2020

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DREAMM-2: Demographics

Characteristic	2.5-mg/kg Cohort (N=97)	3.4-mg/kg Cohort (N=99)
Age, median (IQR), years	65 (39–85)	67 (34–84)
18 to <65 years	45 (46)	36 (36)
65 to <75 years	39 (40)	46 (46)
≥75 years	13 (13)	17 (17)
Sex		
Male	51 (53)	56 (57)
Female	46 (47)	43 (43)
Race		
White	72 (74)	83 (84)
Black or African American	16 (16)	11 (11)
Renal impairment per eGFR (mL/min/1.73m²)		
Normal (≥90)	19 (20)	17 (17)
Mild (≥60 to <90)	48 (49)	52 (52)
Moderate (≥30 to <60)	24 (25)	22 (22)
Severe (≥15 to <30)	2 (2)	5 (5)
Time from initial diagnosis, median (IQR), years[a]	5.49 (4.01-7.02)	5.08 (4.16-7.48)
ISS Disease stage at screening		
Stage I	21 (22)	18 (18)
Stage II	33 (34)	51 (52)
Stage III	42 (43)	30 (30)
Unknown	1 (1)	0
Cytogenetic abnormalities		
t(11;14)	16 (16)	9 (9)
t(14;20)	3 (3)	0
Del 13	18 (19)	17 (17)
Hyperdiploidy	7 (7)	4 (4)
Other	28 (29)	23 (23)
High-risk cytogenetics	41 (42)	47 (47)
17p13del	16 (16)	22 (22)
t(4;14)	11 (11)	11 (11)
t(14;16)	7 (7)	2 (2)
1q21+	25 (26)	30 (30)

Characteristic	2.5-mg/kg Cohort (N=97)	3.4-mg/kg Cohort (N=99)
Type of myeloma		
IgG	65 (67)	73 (74)
Non-IgG	33 (33)	26 (26)
Extramedullary disease	22 (23)	18 (18)
Prior lines of therapy[b]		
Median (IQR)	7 (3–21)	6 (3–21)
≤4 lines	16 (16)	17 (17)
>4 lines	81 (84)	82 (83)
Prior therapies received		
Proteasome inhibitor	95 (98)	97 (98)
Bortezomib	74 (76)	64 (65)
Carfilzomib		
Immunomodulatory drug		
Lenalidomide	97 (100)	99 (100)
Pomalidomide	89 (92)	84 (85)
Anti-CD38 monoclonal antibody		
Daratumumab	97 (100)	96 (97)
Isatuximab	3 (3)	2 (2)
Refractory to prior therapies[c]		
Proteasome inhibitor		
Bortezomib	74 (76)	74 (75)
Carfilzomib	63 (65)	57 (58)
Immunomodulatory drug		
Lenalidomide	87 (90)	88 (89)
Pomalidomide	84 (87)	77 (78)
Anti-CD38 monoclonal antibody		
Daratumumab	97 (100)	91 (92)
Isatuximab	3 (3)	1 (1)

Lonial et al, Lancet Onc 2020

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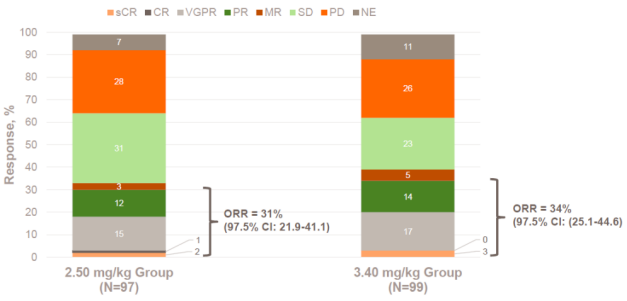
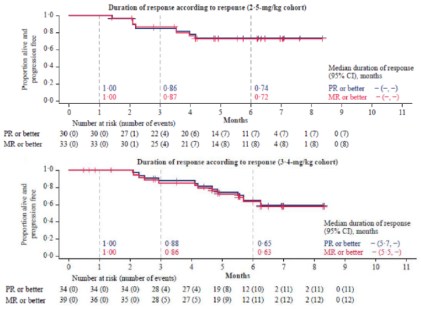
DREAMM-2: ORR and DOR





At a median duration of follow-up of 6.3 (IQR: 3.7–7.7) and 6.9 (IQR: 4.8–7.9) months, respectively, the median duration of response was not reached

Lonial et al, Lancet Onc 2020

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DREAMM-2: Special Attention to Occular Toxicity

Adverse Event of Special Interest	*Blenrep* 2.5-mg/kg Cohort (N=95)	*Blenrep* 3.4-mg/kg Cohort (N=99)
	Percentage of patients	
Thrombocytopenia[a]	35	59
Infusion-related reactions[b]	21	16
Keratopathy	71	75

Events reported based on Common Terminology Criteria for Adverse Events criteria v4.03[14] in the safety population (including all patients who received at least one dose of trial treatment)

[a]Thrombocytopenia includes the preferred terms thrombocytopenia, decreased platelet count, and cerebral hemorrhage. [b]Infusion-related reactions includes preferred terms infusion-related reaction, pyrexia, chills, diarrhea, nausea, vomiting if occurring within 24 hours.

	Blenrep 2.5-mg/kg Cohort (N = 17)		*Blenrep* 3.4-mg/kg Cohort (N = 12)	
	With corticosteroid eye drops	Without corticosteroid eye drops	With corticosteroid eye drops	Without corticosteroid eye drops
Median (IQR) days to initiation of drug-related change in corneal epithelium (based on exam findings)	24 (21-30)	27 (21-42)	25 (9-40)	25 (21-40)
Percentage of Patients with Grade 3 Events, %	29	18	42	50

Lonial et al, Lancet Onc 2020

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Thoughts:

- BelMaf is a promising agent
- Ocular toxicity is common, frequently requires dose reductions/holds
- Evaluation by an ophthalmologist or optometrist are required every cycle
  - Unique and potentially challenging collaborative practice
  - May prove to be a barrier

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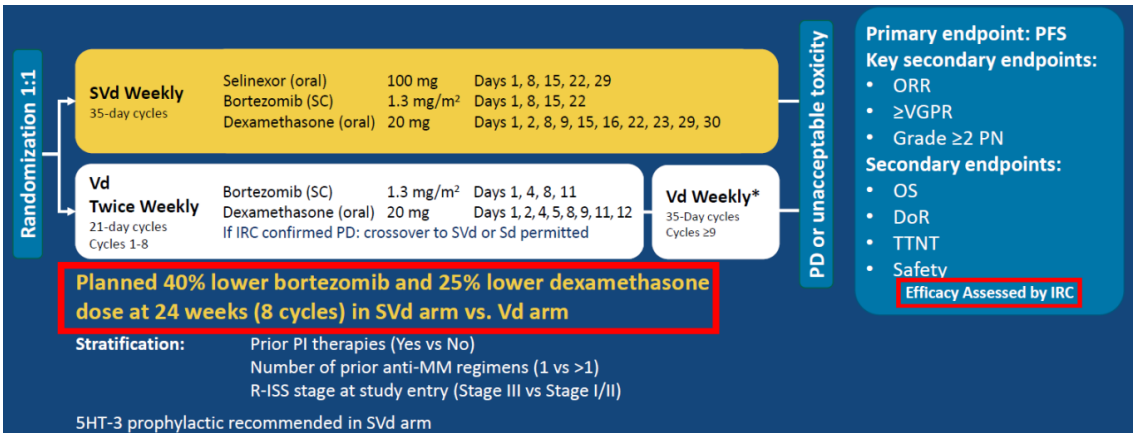
Selinexor Bortez Dex (SVd): BOSTON study



Dimopoulos et al ASCO 2020

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BOSTON: Key I/E criteria

Key Inclusion Criteria

- Progressive measurable MM per IMWG criteria[1]
- 1–3 prior anti-MM regimens (at least a PR to a prior PI, if received)
- Patients with moderate or severe renal impairment (CrCl ≥ 20mL/min) allowed, patients requiring dialysis excluded
- ECOG status score 0–2
- Adequate hepatic and hematopoietic function
  - ANC > 1,000/µL
  - Platelets > 75,000/µL

Key Exclusion Criteria

- > Grade 2 neuropathy or ≥ Grade 2 neuropathy with pain at baseline
- Prior exposure to a SINE, including selinexor
- Prior malignancy that required treatment/had evidence of recurrence
- Concurrent medical condition/disease/active infection
- Active plasma cell leukemia
- MM involving the CNS

Dimopoulos et al ASCO 2020

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BOSTON study: Demographics

Patient and Disease Characteristics Well Balanced Between Treatment Arms

Characteristic	SVd arm (n=195)	Vd arm (n=207)
Media Age, years (range)	66 (40, 87)	67 (38, 90)
≥75 years, n (%)	34 (17)	47 (23)
Male, n (%)	115 (59)	115 (56)
Creatinine Clearance, mL/min, n (%)		
<30	3 (2)	10 (5)
30-60	53 (27)	60 (29)
Time since initial diagnosis, years, (range)	3.8 (0.4, 23.0)	3.6 (0.4, 22.0)
High Risk Cytogenetic, [del (17p) or t (14;16) or t (4;14) or amp 1q21] n (%)*	97 (50)	95 (46)
R-ISS disease stage at screening, n (%)		
I or II	173 (89)	177 (86)
III	12 (6)	16 (8)
Unknown	10 (5)	14 (7)
Number of prior lines of therapy, n (%)		
1	99 (51)	99 (48)
2	65 (33)	64 (31)
3	31 (16)	44 (21)
Prior Therapies, n (%)		
Bortezomib	134 (68.7)	145 (70.0)
Carfilzomib	20 (10.3) 79.0%	21 (10.1) 80.1%
Daratumumab	11 (5.6)	6 (2.9)
Lenalidomide	77 (39.5)	77 (37.2)

Dimopoulos et al ASCO 2020

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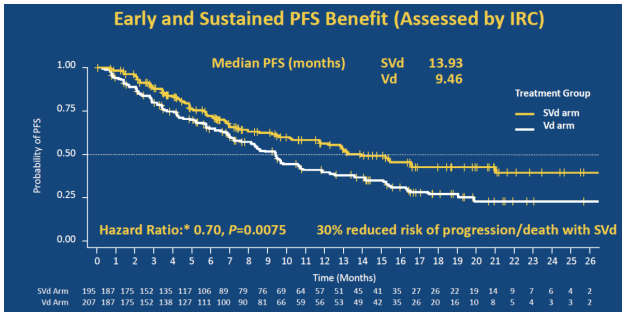
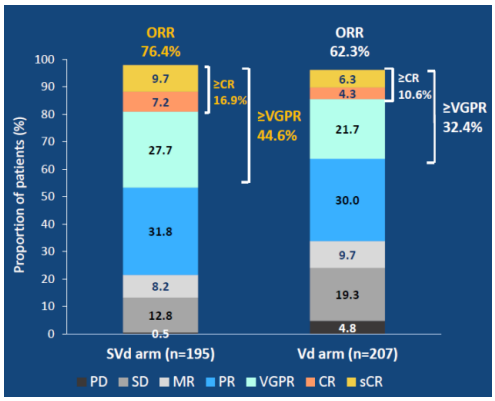
BOSTON study: PFS and ORR





Dimopoulos et al ASCO 2020

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BOSTON study: PFS and ORR

	SVd (n=195)		Vd (n=204)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Non-hematological (%)				
Nausea	50.3	7.7	9.8	0
Fatigue	42.1	13.3	18.1	1.0
Decreased Appetite	35.4	3.6	5.4	0
Diarrhea	32.3	6.2	25.0	0.5
Peripheral Neuropathy†	32.3	4.6	47.1	8.8
Upper Respiratory Tract Infection‡	29.2	3.6	21.6	1.5
Weight decreased	26.2	2.1	12.3	1.0
Asthenia	24.6	8.2	13.2	4.4
Cataract§	21.5	8.7	6.4	1.5
Vomiting	20.5	4.1	4.4	0

Dimopoulos et al ASCO 2020

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Thoughts

- Selinexor remains challenging to give
- Prophylactic olanzapine may help with anorexia and nausea
- Combinatorial therapy is rationale, since the mechanism of action is inhibiting nuclear export
- Hopefully we'll see additional data from STORM coming out soon with carfilzomib, daratumumab and pomalidomide dosing

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Survivorship in Multiple Myeloma:

Dealing with long term complications in an incurable disease

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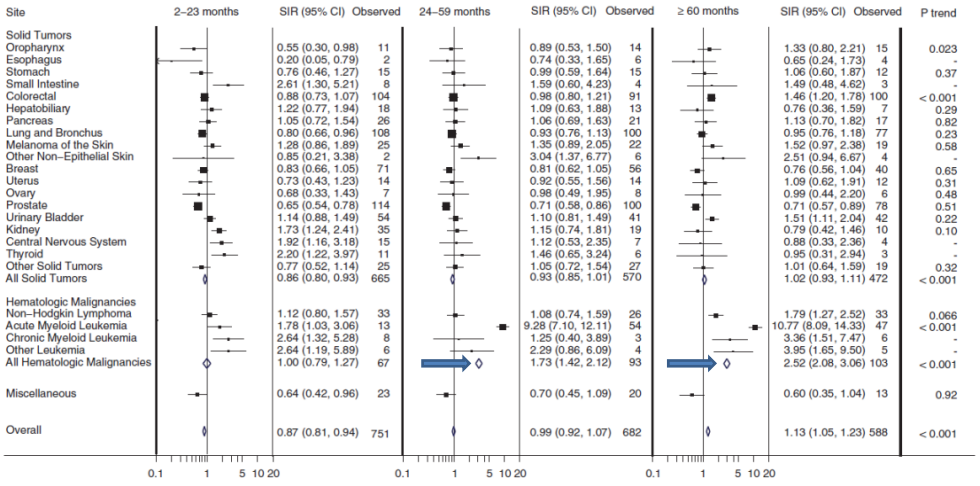
Second Primary Malignancies



Site	2–23 months SIR (95% CI)	Observed	24–59 months SIR (95% CI)	Observed	≥ 60 months SIR (95% CI)	Observed	P trend
Solid Tumors							
Oropharynx	0.55 (0.30, 0.98)	11	0.89 (0.53, 1.50)	14	1.33 (0.80, 2.21)	15	0.023
Esophagus	0.20 (0.05, 0.79)	2	0.74 (0.33, 1.65)	6	0.65 (0.24, 1.73)	4	-
Stomach	0.76 (0.46, 1.27)	15	0.99 (0.59, 1.64)	15	1.06 (0.60, 1.87)	12	0.37
Small Intestine	2.61 (1.30, 5.21)	8	1.59 (0.60, 4.23)	4	1.49 (0.48, 4.62)	3	-
Colorectal	0.88 (0.73, 1.07)	104	0.98 (0.80, 1.21)	91	1.46 (1.20, 1.78)	100	< 0.001
Hepatobiliary	1.22 (0.77, 1.94)	18	1.09 (0.63, 1.88)	13	0.76 (0.36, 1.59)	7	0.29
Pancreas	1.05 (0.72, 1.54)	26	1.06 (0.69, 1.63)	21	1.13 (0.70, 1.82)	17	0.82
Lung and Bronchus	0.80 (0.66, 0.96)	108	0.93 (0.76, 1.13)	100	0.95 (0.76, 1.18)	77	0.23
Melanoma of the Skin	1.28 (0.86, 1.89)	25	1.35 (0.89, 2.05)	22	1.52 (0.97, 2.38)	19	0.58
Other Non–Epithelial Skin	0.85 (0.21, 3.38)	2	3.04 (1.37, 6.77)	6	2.51 (0.94, 6.67)	4	-
Breast	0.83 (0.66, 1.05)	71	0.81 (0.62, 1.05)	56	0.76 (0.56, 1.04)	40	0.65
Uterus	0.73 (0.43, 1.23)	14	0.92 (0.55, 1.56)	14	1.09 (0.62, 1.91)	12	0.31
Ovary	0.68 (0.33, 1.43)	7	0.98 (0.49, 1.95)	8	0.99 (0.44, 2.20)	6	0.48
Prostate	0.65 (0.54, 0.78)	114	0.71 (0.58, 0.86)	100	0.71 (0.57, 0.89)	78	0.51
Urinary Bladder	1.14 (0.88, 1.49)	54	1.10 (0.81, 1.49)	41	1.51 (1.11, 2.04)	42	0.22
Kidney	1.73 (1.24, 2.41)	35	1.15 (0.74, 1.81)	19	0.79 (0.42, 1.46)	10	0.10
Central Nervous System	1.92 (1.16, 3.18)	15	1.12 (0.53, 2.35)	7	0.88 (0.33, 2.36)	4	-
Thyroid	2.20 (1.22, 3.97)	11	1.46 (0.65, 3.24)	6	0.95 (0.31, 2.94)	3	-
Other Solid Tumors	0.77 (0.52, 1.14)	25	1.05 (0.72, 1.54)	27	1.01 (0.64, 1.59)	19	0.32
All Solid Tumors	0.86 (0.80, 0.93)	665	0.93 (0.85, 1.01)	570	1.02 (0.93, 1.11)	472	< 0.001
Hematologic Malignancies							
Non–Hodgkin Lymphoma	1.12 (0.80, 1.57)	33	1.08 (0.74, 1.59)	26	1.79 (1.27, 2.52)	33	0.066
Acute Myeloid Leukemia	1.78 (1.03, 3.06)	13	9.28 (7.10, 12.11)	54	10.77 (8.09, 14.33)	47	< 0.001
Chronic Myeloid Leukemia	2.64 (1.32, 5.28)	8	1.25 (0.40, 3.89)	3	3.36 (1.51, 7.47)	6	-
Other Leukemia	2.64 (1.19, 5.89)	6	2.29 (0.86, 6.09)	4	3.95 (1.65, 9.50)	5	-
All Hematologic Malignancies	1.00 (0.79, 1.27)	67	1.73 (1.42, 2.12)	93	2.52 (2.08, 3.06)	103	< 0.001
Miscellaneous	0.64 (0.42, 0.96)	23	0.70 (0.45, 1.09)	20	0.60 (0.35, 1.04)	13	0.92
Overall	0.87 (0.81, 0.94)	751	0.99 (0.92, 1.07)	682	1.13 (1.05, 1.23)	588	< 0.001

0.1 1 5 10 20 0.1 1 5 10 20 0.1 1 5 10 20

Figure 2. Site-specific risk of developing SPM among 36 491 patients who were diagnosed with MM as a first primary cancer by latency. Abbreviations: SIR, standardized incidence ratio; CI, confidence intervals.

Razavi et al, Blood

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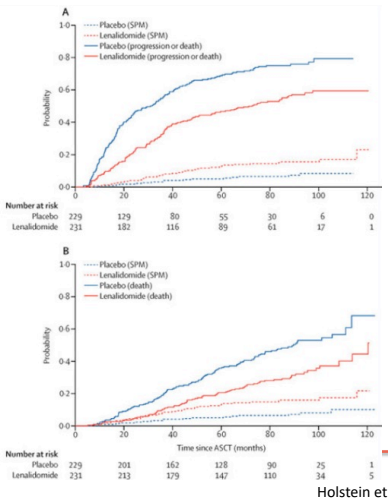
SPM Development: Post-BMT lenalidomide maintenance

Second primary malignancies

	SPM type		
Treatment Arm	**Haematologic (n)**	**Solid tumour (n)**	**Noninvasive (n)**
Len (231)	MDS/AML (10)	Breast (3)	SCC (5)
	B-cell ALL (6)	Colon (3)	BCC + SCC (3)
	Hodgkin lymphoma (1)	Prostate (2)	DCIS (2)
	Waldenstrom macroglobulinemia (1)	Endometrial (2)	BCC (1)
		Glioblastoma multiforme (1)	
		Melanoma (1)	
		Papillary Thyroid (1)	
		Salivary gland carcinoma (1)	
Placebo (229)			
Crossover to Len (86)	B-cell ALL (2)	Melanoma (2)	BCC (3)
	MDS (1)	Endometrial (1)	BCC + SCC (2)
		Renal cell (1)	
		Invasive SCC (1)	
		Breast (1)	SCC (1)
No crossover (143)		Melanoma (1)	
		Ovarian/endometrial (1)	
		Lung carcinoid (1)	



Holstein et al, Lancet Haem 2017

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SPM Development: Roll of ASCT (high dose chemotherapy)

Rationale

- Autologous stem cell transplant relies on high dose, genotoxic therapy
- This patient population is likely pre-disposed to SPMs due to underlying stem cell defects and alterations of the bone marrow microenvironment

Design

- Data: California Cancer Registry linked to the state wide discharge database
- Patients: all newly diagnosed myeloma patients surviving at least 1 year without SPM during first year
- Analysis: compare cumulative incidence of SPM development in aSCT to non-aSCT recipients

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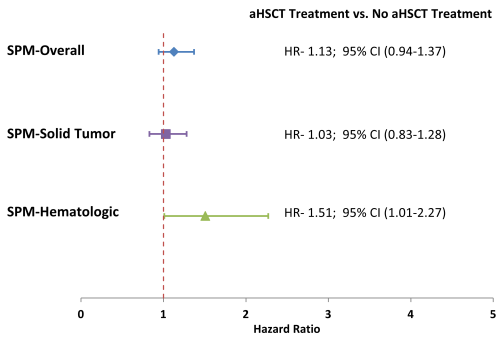
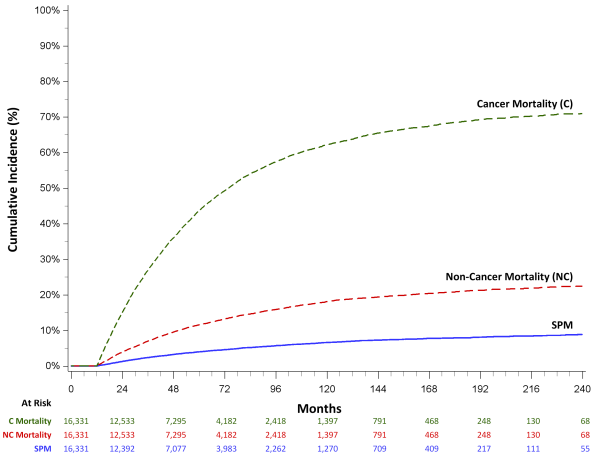
SPM Development: Contribution of Stem Cell Transplant





Rosenberg et al, under review

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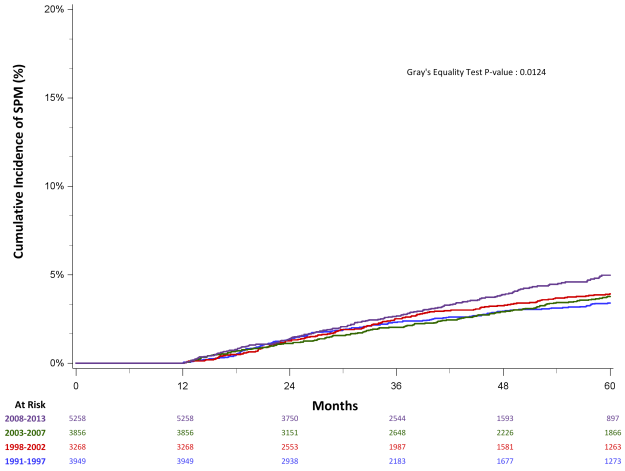
SPM Development: CCR offering concerning trends



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Cardiovascular disease in myeloma patients

Rationale

- Older patient population
- Potential cardiotoxic therapy
- More common in African Americans, a population a higher risk of cardiovascular outcomes

Design

- Data: California Cancer Registry linked to statewide discharge database
- Population: all newly diagnosed MM patients with no previous admission for cardiovascular events
- Outcome: cumulative incidence of admission for cardiovascular events

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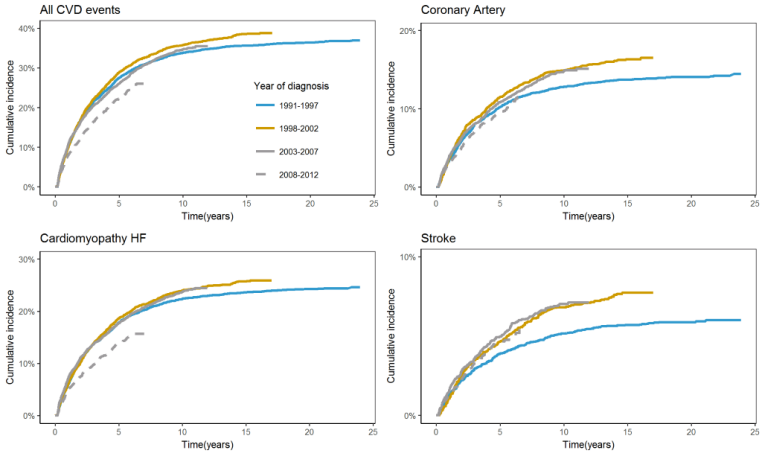
Cardiovascular endpoints



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Current Clinical Trial Portfolio

Treatment Line	Newly Diagnosed	BMT	Maintenance	Relapse: 1-3 prior lines	Relapse: Multiply R/R	Phase 1	CAR-T	Open?
SWOG 1803			Post-BMT maintenance,					Yes
PHI-100: KRD+AMG232				Not refractory to KRd, prior carfilzomib allowed				Yes
UCHMC 1915: Elo/Ipi								Awaiting SRC
UCHMC 1809: DIPd				No prior progression on Pom, no prior Dara or Ix				Yes
KITE-718-301							HLA restricted; must express MAGE A3/A6	Yes
POSIEDA							Prior Dara, PI, imid, no cardiovascular dz	Yes
SUTRO BCM-1						NHL+MM		Yes
UCHMC 20XX: BelMaf/Pom				2-4 prior lines of therapy	2-4 prior lines			Protocol Development
DREAMM				Patients with eGFR<30				Awaiting SRC
KPG 818						NHL+MM		Awaiting SRC
AEVI-007								Awaiting SRC

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Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Case Presentations: Leukemia, Lymphoma, Myeloma

Vanessa Kennedy, MD
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University of California, San Francisco

ANCO

Educating and Empowering the Northern California Cancer Community

Hematologic Malignancies Updates: Leukemias, Lymphomas, & Myeloma

Vanessa E. Kennedy, MD
Fellow, Hematology/Oncology, UCSF
November 14, 2020

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ANCO
Educating and Empowering the Northern California Cancer Community

CASE PRESENTATIONS

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Case 1: Leukemia

HPI:

- A 73-yo F presents to her PCP with 2 months of worsening fatigue and dyspnea
- She has HTN, HLD, and insulin-independent DM. She has no history of prior malignancy or chemotherapy. She lives with her partner and walks 30 minutes daily.
- **Labs:** WBC 9.4 (ANC 400), Hgb 8.3, Plts 84. She has no evidence of TLS or DIC
  - A peripheral smear shows 32% blasts

3

Case 1

Bone Marrow Biopsy

- **Acute Myeloid Leukemia (65% blasts)**
- **Aspirate:** Markedly increases blasts, morphology similar to that seen in peripheral blood
- **Flow:** Myeloid blasts are 70% of total events. Expressed weak: CD7, CD13, CD33, CD34, CD38, CD71, CD119.
- **Cytogenetics:** Normal
- **Molecular Testing:** TP53, IDH1 mutations

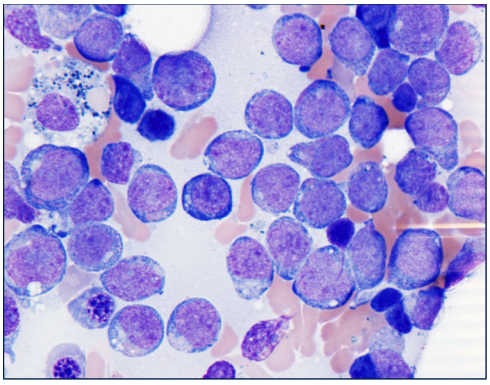

Image Credit: ASH Image bank

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Case 1: Question 1

How would you treat this patient?

A. CPX-351 (Vyxeos)

B. Azacitidine plus Venetoclax

C. Glasdegib plus LoDAC

D. Ivosidenib monotherapy

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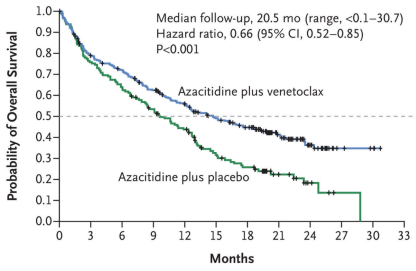
Case 1: Leukemia

- She is treated with **Azacitidine plus Venetoclax.**



Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
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)

DiNardo et al, *NEJM*, August 2020

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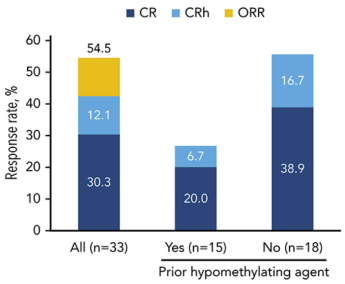
Case 1: Leukemia

- **Ivosidenib monotherapy** would also be an FDA-approved option, especially if she were considered unfit for Aza/Ven
- Response to ivosidenib monotherapy are not as promising as Aza/Ven

Table 3. Investigator-Reported Hematologic Response, Time to Response, and Response Duration in Patients Receiving 500 mg of Ivosidenib Daily.*

Overall response				
No. of patients	52	70	19	11
% (95% CI)	41.6 (32.9–50.8)	39.1 (31.9–46.7)	55.9 (37.9–72.8)	91.7 (61.5–99.8)
Median time to first response (range) — mo§	1.9 (0.8–4.7)	1.9 (0.8–4.7)	1.9 (0.9–2.9)	1.6 (1.0–2.8)
Median duration of response (95% CI) — mo	6.5 (4.6–9.3)	6.5 (4.6–9.3)	9.2 (1.9–NE)	NE (2.3–NE)



DiNardo et al, *NEJM*, 2018
Roboz et al, *Blood*, 2020

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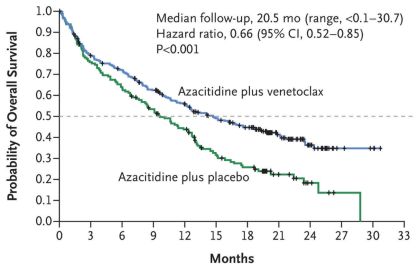
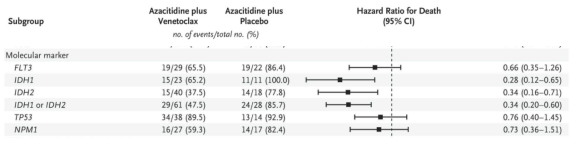
Case 1: Leukemia

- She is treated with **Azacitidine plus Venetoclax.**
- She tolerates this regimen well, but does require Venetoclax to be dose-adjusted from 28 days/cycle to 21 days/cycle due to persistent cytopenias.
- After 2 cycles, she receives a repeat bone marrow biopsy. She is in CR with incomplete count recovery (CRi). MRD is negative.





DiNardo et al, *NEJM*, August 2020

8

Case 1: Question 2

What would be your next step in management?

A. Continue Azacitidine/Venetoclax indefinitely

B. Continue IV Azacitidine monotherapy

C. Start oral Azacitidine monotherapy

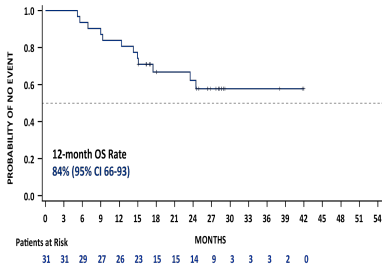
D. Referral for HCT

E. A and E

9

Case 1: Leukemia

- She continues on azacitidine and venetoclax.
- She is referred to a transplant center and, after comprehensive geriatric assessment, is deemed to be a candidate for HCT. Her sister is HLA typed and found to be a match.
- Outcomes of HCT after Ven-based regimens



Pratz et al, ASH 2019

10

Case 1: Take-home points

- In 2020, there are many new options for older patients with AML
  - There is increasing need to compare endpoints across trials as a single patient may have multiple reasonable options
- Azacitidine and Venetoclax improved OS in patients 75 years or older or unfit for standard induction with newly diagnosed AML
  - Patients with TP53 mutations can achieve remission with Aza/Ven, but are more likely to relapse
- Patients may still be evaluated for allogeneic stem cell transplant if receiving lower intensity therapy, and there are many geriatric-specific metrics for evaluating older adults as possible HCT candidates beyond chronologic age
  - When in doubt, refer

11

Case 2: Multiple Myeloma

HPI:

- A 60 yo M with well-controlled hypertension presents to urgent care with worsening back pain. He is otherwise healthy and rides his bicycle daily.
- **Labs:**
  - Hgb 9.8, Ca 11.8, Cr 1.0, LDH 400, Beta-2-microglobulin 4.1 mg/L, Albumin 3.8
  - SPEP/SIFE demonstrated M-protein of 3.8 g/dL
  - sFLC demonstrated kappa of 678, lambda 14, k/l ratio 0.02
  - Immunoglobulins: IgG 1030, IgA 117, IgM 45
  - UPEP unremarkable

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Case 2: Multiple Myeloma

HPI, continued:

- BMBx:
  - 45% atypical IgG kappa-restricted plasma cells
  - FISH: Trisomies involving chromosomes 3 and 11, but no IgH translocation, del(17p) or gain 1q
- MRI Spine: Lytic lesions at T9 and L1
- PET: Lytic lesions as above

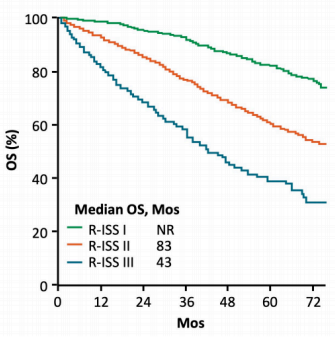
13

Case 2: Multiple Myeloma

HPI, continued:

- BMBx:
  - 45% atypical IgG kappa-restricted plasma cells
  - FISH: Trisomies involving chromsomes 3 and 11, but no IgH translocation, del(7p) or gain 1q

ISS Definition	
I	▪ Serum albumin ≥ 3.5 g/dL *AND* ▪ β_2-M < 3.5 mg/L
II	▪ Not stage I or III
III	▪ β_2-M ≥ 5.5 mg/L
R-ISS Definition	
I	▪ ISS stage I *AND* ▪ Normal LDH ▪ No t(4;14), t(14;16), or del(17p)
II	▪ Not stage I or III
III	▪ ISS stage III *AND* ▪ Serum LDH > ULN *OR* ▪ With t(4;14), t(14;16), or del(17p)



Palumbo et al, *J Clin Oncol*, 2015

14

Case 2: Question 1

How would you initially treat this patient?

A. Lenalidomide/Dexamethasone (Rd)

B. Bortezomib/Lenalidomide/Dexamethasone (VRd)

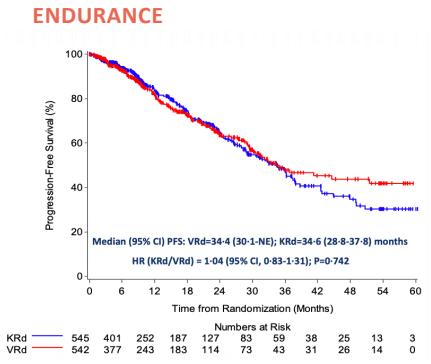
C. Carfilzolib/Lenalidomide/Dexamethasone (KRd)

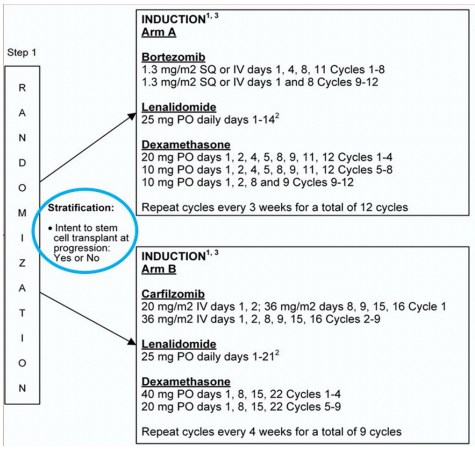
D. Daratumumab/Bortezomib/Lenalidomide/Dexamethasone (Dara-RVd)

15

Case 2: Multiple Myeloma

- He is started on **Bortezomib/Lenalidomide/Dexamethasone (RVd)**
- Why not KRd?



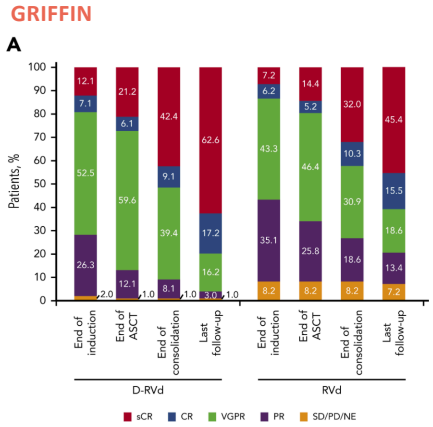


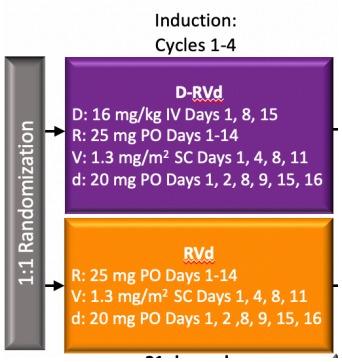
Kumar et al, *Lancet Oncology*, October 2020

16

Case 2: Multiple Myeloma

- He is started on **Bortezomib/Lenalidomide/Dexamethasone (RVd)**
- Why not RVd-Daratumumab?





Voorhees et al, *Blood,* August 2020

17

Case 2: Multiple Myeloma

- He is started on **Bortezomib/Lenalidomide/Dexamethasone (RVd)**
- After 4 cycles, he achieves a VGPR. He then proceeds to auto-HCT, which was uncomplicated.
- Following auto-HCT he resumes lenalidomide maintenance and achieves a CR.
- 24 months after starting maintenance, he presents to the emergency room with new shortness of breath and palpitations and is found to be in Afib with RVR. He is rate controlled and feels much better. During his hospitalization, he is found to have worsening anemia and a newly rising M-protein.

18

Case 2: Question 2

What should his next line of therapy be?

A. Daratumumab/Lenalidomide/Dexamethasone (Dara-Rd)

B. Daratumumab/Bortezomib/Dexamethasone (Dara-Vd)

C. Daratumumab/Carfilzolib/Dexamethasone (Dara-Kd)

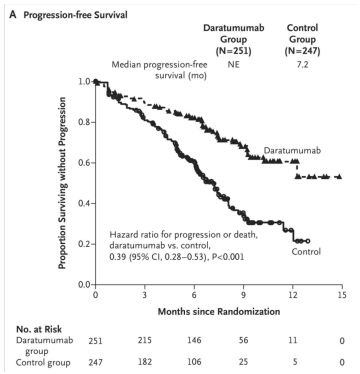
D. Pomalidomide/Bortezomib/Dexamethasone (PVd)

19

Case 2: Multiple Myeloma

- He is started on **Dara/Bortezomib/Dexamethasone.** Carfilzomib was avoided due to cardiac comorbidity and he is likely lenalidomide refractory as he progressed while on lenalidomide maintenance.

CASTOR



Palumbo et al, *NEJM*, 2016

20

Case 2: Multiple Myeloma

- He is started on **Dara/Bortezomib/Dexamethasone.** Carfilzomib was avoided due to cardiac comorbidity and he is lenalidomide refractory as he progressed while on lenalidomide maintenance.
- After 7 cycles, he develops progressive neuropathy to the point where he can no longer button his shirt. Repeat BMBx shows CR, MRD+. He is maintained on monthly Daratumumab monotherapy.
- 3 months later, he is found to have elevated M-protein and worsening anemia on routine labs. He is confirmed to have relapsed disease.

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Case 2: Question 3

What should his next line of therapy be?

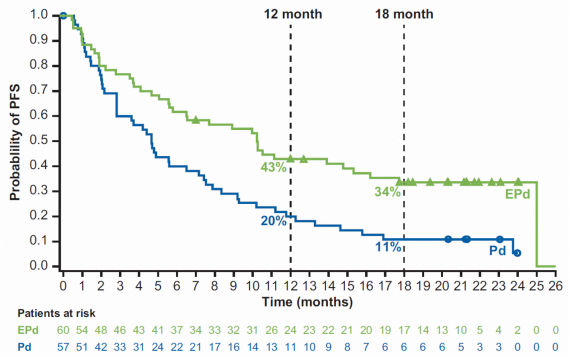
A. Carfilzomib/Daratumumab/Dexamethasone
B. Elotuzumab/Pomolidomide/Dexamethasone
C. Isatuximab/Pomalidomide/Dexamethasone
D. Pomalidomide/Cyclophosphamide/Dexamethasone
E. Belantamab Mafadotin
F. Selenexor/Bortezomib/Dexamethasone
G. Repeat ASCT

22

Case 2: Multiple Myeloma

- He is started on **elotuzumab/pomalidomide/dexamethasone** as he has not been exposed to these agents previously.

ELOQUENT-3



23

Case 2: Take-home points

- RVd is still considered standard of care for newly diagnosed standard-risk multiple myeloma.
- KRd did not improve PFS in comparison with RVd
  - **ENDURANCE** trial did not include patients with high-risk disease
  - Extended KRd may be an option in high-risk patients
- Dara-RVd is an emerging option for newly diagnosed, transplant eligible patients with MM
  - **GRIFFIN** trial improved stringent CR with Dara-RVd
  - Overall similar safety profile as RVd
  - Ongoing Phase III PERSEUS trial– we await survival data

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Case 2: Take-home points, cont.

- There are several options for relapsed disease without evidence of best sequencing.
- Choice of regimen is often impacted by side effect profile.

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Case 3: Lymphoma

HPI

- An otherwise-healthy 69 yo F presents with painless cervical adenopathy.
- **Labs:** CBC is normal, LDH and beta-2-macroglobulin are elevated
- **CT Neck/Chest/Abdomen/Pelvis:** Multiple cervical, axillary, and inguinal nodes measuring up to 3.5 cm in largest dimension as well as a retroperitoneal nodal conglomerate measuring 9 cm.
- **Core needle biopsy of cervical node:** Grade 2 follicular lymphoma
- **BMBx:** involvement by FL

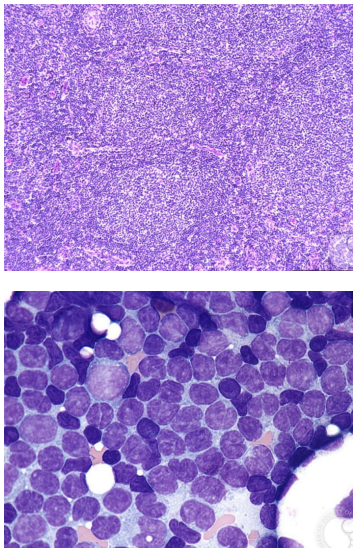

Image Credit: ASH Image bank

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Case 3: Question 1

How would you treat this patient?

A. R-CHOP

B. R-CVP

C. Bendamustine + Rituximab

D. Bendamustine + Obinutuzumab

E. Rituximab + Lenalidomide

F. Observation

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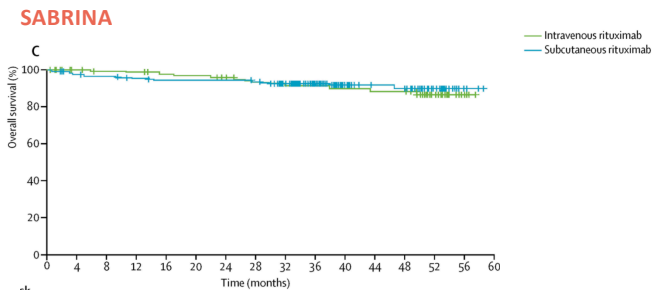
Case 3: Lymphoma

- She is started on treatment with **rituximab and bendamustine**.
- She feels strongly about limiting her time in the infusion center, and thus opts for **subcutaneous rituxumab**



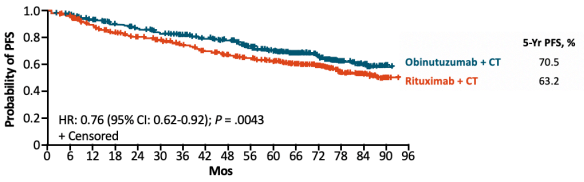
Davies et al, *Lancet Hematology*, 2017

28

Case 3: Lymphoma

- She is started on treatment with **rituximab and bendamustine**.
- What about **obinatuzumab and rituximab?** What about **rituximab and lenalidomide?**

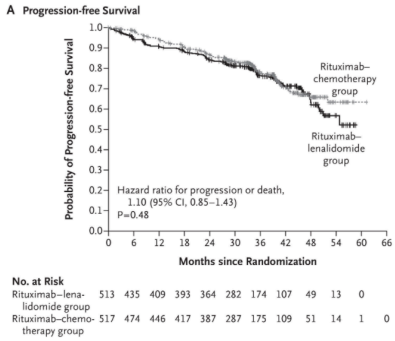
GALLIUM-3



- No significant difference in 5-yr OS between arms (90.2% vs 89.4%, respectively; HR: 0.87; 95% CI: 0.62-1.22; *P* = .41)
- Some increase in infusion reactions, cytopenias with Obinutuzumab

Townsend et al, ASCO, 2020.

RELEVANCE



Morschhauser et al, NEJM, 2018

29

Case 3: Lymphoma

- Five years after completion of maintenance rituximab, she develops recurrent back pain. She is more fatigued than previously, but otherwise has no B-symptoms. Her labs are normal.
- Repeat PET demonstrates recurrent axillary and retroperitoneal adenopathy measuring up to 5 cm, including an RP conglomerate measuring 9 cm. SUV max is 7 in the R axilla.
- An open biopsy of her axillary mass demonstrates recurrent grade 2 FL with no evidence of transformation.

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Case 3: Question 2

How would you treat this patient?

A. R-CHOP
B. Obinutuzumab plus Bendamustine
C. Rituximab plus Lenalidomide
D. Idelalisib
E. Tazemetostat
F. Observation

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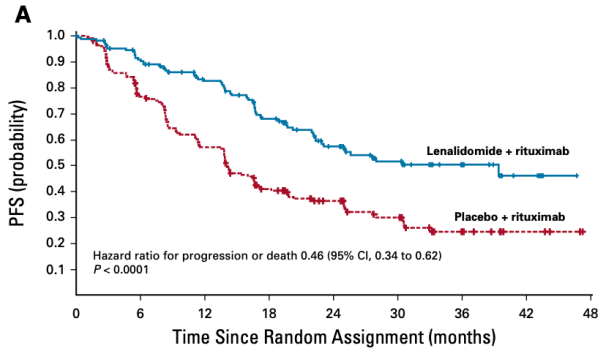
Case 3: Lymphoma

- She is treated with **rituximab plus lenalidomide (R^2) for** 6 months and achieves a PR. She continues obinatuzumab maintenance for 18 months.

AUGMENT



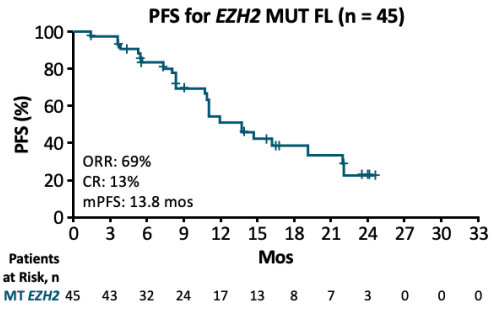
Leonard et al, *JCO*, 2019

32

Case 3: Lymphoma

- Two years later, she relapses with bulky axillary and cervical adenopathy, again confirmed to be grade 2 follicular lymphoma on core biopsy. Mutational testing confirms she has an ***EZH2*** **mutation.**

- She is still considers herself relatively healthy and walks 30 minutes per day, but she is now 78 years old and wishes to avoid toxicities if possible. She begins treatment with **tazemetostat.**



Morschhauser et al, ASH, 2019
Image from ClinicalCareOptions

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Case 3: Lymphoma

Agent	Idelalisib[1,2]	Copanlisib[3,4]	Duvelisib[5,6]
PI3K isoform target	Delta	Alpha, delta	Delta, gamma
Dose/delivery	150 mg orally BID	60 mg IV weekly (3 wks on, 1 wk off)	25 mg orally BID
Grade ≥ 3 AE, %	(n = 125)	(n = 142)	(n = 129)
▪ ↓ ANC/PLT level	27/6	24/7	25/12
▪ ALT/AST elevations	13/8	2/2	5/3
▪ Diarrhea/colitis	13/4	5/1	15/5
▪ Pneumonia	7	15	5
▪ Hyperglycemia	--	41	--
▪ Hypertension	--	24	--
Serious AEs of special interest	Sepsis, opportunistic infections, diarrhea/colitis, cutaneous rxn, pneumonitis, hepatotoxicity, intestinal perforation, anaphylaxis	Opportunistic infections, pneumonitis, severe cutaneous rxn	Opportunistic infections, diarrhea/colitis, cutaneous rxn, pneumonitis
Monitoring	LFTs, blood counts, signs of SAEs, PJP infection, CMV reactivation/infection	BP, blood sugar, blood counts, PJP infection, CMV reactivation/infection	LFTs, blood counts, signs of SAEs, PJP infection, CMV reactivation/infection

Slide credit: clinicaloptions.com

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Case 3: Take-home points

- Outcomes for patients with untreated FL have approved substantially in the era of rituximab based strategies
  - Median survival is now ~20 years
  - Rituximab-Bendamustin is still standard of care.
  - Obinatuzumab plus chemotherapy improves PFS compared to rituximab plus chemotherapy, but is associated with more cytopenias
  - Rituximab plus lenalidomide is a good option, especially for patients who wish to avoid chemotherapy

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Case 3: Take-home points

- There are multiple FDA-approved options for R/R FL
  - Bendamustine + Obinatuzumab for patients who relapsed after rituximab
  - Lenalidomide + Rituximab
  - Tazemetostat (R/R after >2 prior therapies with EZH2+, or if no other therapeutic options)
  - PI3K inhibitors (R/R after >2 prior therapies)
  - Cellular therapies, auto-HCT for advanced disease if patients are candidates
  - Always critical to rule out transformation in R/R disease

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Case 4: Leukemia

HPI:

- A 50 yo F presents to urgent care with worsening fatigue and easy bruising. She has hypothyroidism on levothyroxine but is otherwise healthy.
- **Labs:** WBC 7.3 (ANC 200), Hgb 7.9, Plts 11. She has no evidence of TLS or DIC.
  - A peripheral smear shows 19% blasts
- **Bone Marrow Biopsy:** Initial aspirate reveals 35% blasts.
  - Flow cytometry confirms 42% myeloid blasts expressing weak CD7, CD13, CD34, CD38, CD71, CD119.

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Case 4: Question 1

How would you treat this patient?

A. Admit, start 7 + 3 immediately

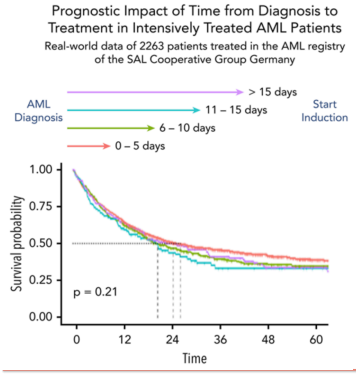
B. Admit, wait for cytogenetics and molecular testing, then start therapy

C. Discharge home while waiting for cytogenetics and molecular testing, then readmit once results are available to start therapy

38

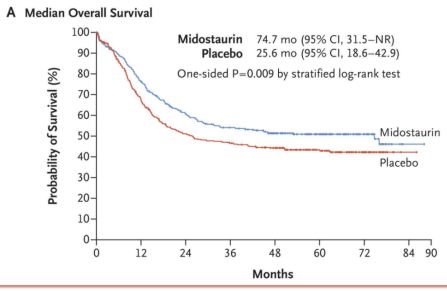
Case 4: Leukemia

- She is discharged home. Two days later, molecular testing reveals a FLT3-ITD mutation and cytogenetics are normal.
- She is started on **7 + 3** and **midostaurin** is added on day 8.



Röllig et al, Blood, August 2020

RATIFY



Stone et al, *NEJM*, 2017

39

Case 4: Leukemia

- Her Day 14 BMBx shows hypocellular marrow with no evidence of blasts. Her Day 34 BMBx shows normocellular marrow with no blasts, MRD negative by flow cytometry.
- She begins consolidation with HiDAC plus midostaurin.
- While undergoing unrelated donor search for allo-HCT, she develops new peripheral blasts and is found to have relapse, again with FLT3-positive disease.

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Case 4: Question 2

How would you treat this patient?

A. Repeat induction with 7 + 3 + Midostaurin

B. Repeat induction with MEC

C. Start gilteritinib monotherapy

D. Start gilteritinib plus venetoclax

E. Start azacitidine plus sorafenib

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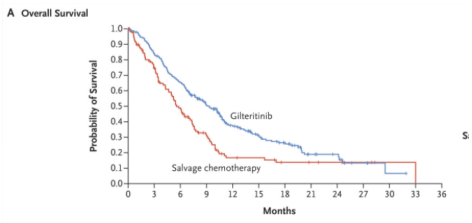
Case 4: Leukemia

- She begins **gilteritinib monotherapy**, which she tolerates well aside from mild neuropathy.
- After 2 months, she has a repeat BMBx and is found to have an MRD-negative CR. She proceeds to allogeneic HCT and remains in CR on her Day 90 BMBx
- Following transplant, she is restarted on gilteritinib monotherapy as part of a clinical trial.

ADMIRAL



Perl et al, *NEJM*, 2019

42

Case 4: Take-home points

- As stratification in frontline AML treatment evolves, time-to-diagnosis data suggests it may be feasible to wait for genetic and other laboratory results prior to starting induction
- **Midostaurin**, in combination with 7 + 3, remains standard of care for newly-diagnosed FLT3-mutated AML
- **Gilteritinib**, as monotherapy**,** is standard of care for relapsed/refractory FLT3-mutated AML
- There are many additional FLT3 inhibitors and FLT3 inhibitor combinations in active clinical development
- In the US, the role of post-transplant maintenance therapy is not standardized.
  - Most patients with FLT3-mutated AML will receive a post-HCT FLT3i, but the choice is not standardized. Post-transplant azacitidine is possible in non-FLT3 mutated patients.
  - There are on-going clinical trials, and off-label use is possible as well.

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Acknowledgements

- Rebecca Olin, MD
- Nina Shah, MD
- Bita Fahkri, MD

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