Best of ASH 2018: Myeloma

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Learning Objectives

- Understand the preferred frontline treatment options in NDMM in the US and recognize ongoing clinical trials with daratumumab in this setting
- Review the data challenging upfront ASCT in NDMM
- Review the role of ixazomib in myeloma maintenance therapy
- Recognize BCMA as an important new target in the treatment of multiple myeloma

Learning Objective 1: Triplet therapy is SOC for NDMM in 2019

- Which triplet is debatable
- Holds true for both transplant-eligible and –ineligible pts
- The addition of monoclonal antibody daratumumab to triplet backbones is being studied, but results are not mature

Reference: Rajkumar, SV, "Selection of initial chemotherapy for symptomatic multiple myeloma." UpToDate.com 1/3/2019. https://www.uptodate.com/contents/selection-of-initial-chemotherapy-for-symptomatic-multiple-myeloma

Top 5 Picks for MM

- Newly diagnosed
  - Griffin: Dara-RVd in transplant eligible (abstract 151)
  - MAIA: Dara-Rd in transplant ineligible (abstract LBA-2)
  - Forte: KRd – ASCT vs KRD 12 vs KCd-ASCT in transplant eligible (abstract 121)
- Maintenance
  - Tourmaline-MM3: Ixazomib vs placebo (abstract 301)
- Relapsed and Refractory
  - AMG 420: BCMA BiTE (abstract 1010)

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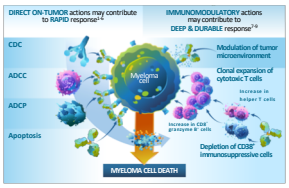
Griffin: Dara-VRd in Newly Dx'd MM Eligible for Transplant (Abstract 151)

- Phase II
- Safety run-in cohort of 16 pts

Blood 2018 132:151

Daratumumab

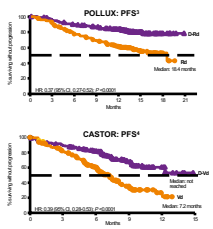


- Daratumumab
  - Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action
- Efficacy
  - Daratumumab-based combinations reduce risk of progression or death and induce rapid, deep, and durable responses across all lines of therapy[10-12]
- Approved
  - As **monotherapy** and in **combination** with standard of care regimens in RRMM in many countries
  - In **combination** with bortezomib, melphalan, and prednisone in transplant-ineligible NDMM in many countries

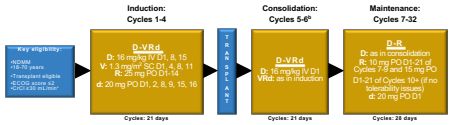
RRMM, relapsed or refractory multiple myeloma; NDMM, newly diagnosed multiple myeloma; CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis.

Background

- Attainment of sCR correlates with improved long-term outcomes after ASCT[1]
- Bortezomib, lenalidomide, and dexamethasone (VRd) followed by HDT, ASCT, and consolidation has yielded high response rates and PFS in NDMM[2]
- In 3 phase 3 studies, daratumumab added to other SoC regimens improved depth of responses, including sCR and MRD-negative rates, and PFS in patients with RRMM or NDMM[3-7]
- Hypothesis: the addition of daratumumab to VRd (D-VRd) will be safe and effective in transplant-eligible patients with NDMM



GRIFFIN: Safety Run-in Phase (N = 16)



- Patients who complete maintenance cycles 7-32 may continue single-agent lenalidomide thereafter

Safety run-in phase in 16 patients to assess dose-limiting toxicities during 1 Cycle of D-VRd

ECOG, Eastern Cooperative Oncology Group; CrCl, creatinine clearance; D, daratumumab; IV, intravenously; qd, daily; V, bortezomib; SC, subcutaneously; PO, orally; d, dexamethasone; LEN, lenalidomide; R, lenalidomide.
[a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min; [b]Consolidation was initiated 60-100 days post-transplant.

Demographics and Disease Characteristics

Characteristic	(N = 16)
Median (range) age, years	62.5 (46-65)
Male, n (%)	8 (50)
Race, n (%)	
White	11 (69)
Black/ African American	4 (25)
Asian	1 (6)
ECOG performance status, n (%)	
0	3 (19)
1	10 (63)
2	3 (19)
ISS, n (%)	
Stage I	12 (75)
Stage II	2 (13)
Stage III	2 (13)
High-risk cytogenetics[a], n (%)	5 (31)

[a]High-risk cytogenetics were defined by any of del(17p), t(4;14), t(14;16). All 5 patients with high-risk cytogenetics had a del(17p) abnormality. Percentages may not add up to 100% due to rounding.
ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group.

- As of October 24 2018, 16 patients were enrolled in the safety run-in and all completed ≥9 cycles of treatment, including ≥3 cycles of maintenance
- Patients have received a median (range) of 17 (10-19) cycles, including 4-13 maintenance cycles

Safety: Most Common TEAEs[a]

Hematologic TEAEs, n (%)	Any grade	Grade 3 or 4
Neutropenia	12 (75)	5 (31)[b]
Febrile neutropenia	2 (13)	2 (13)
Lymphopenia	12 (75)	3 (19)
Thrombocytopenia	8 (50)	4 (25)
Leukopenia	8 (50)	2 (13)
Anemia	7 (44)	1 (6)

Nonhematologic TEAEs, n (%)	Any grade	Grade 3 or 4
Diarrhea	9 (56)	1 (6)
Fatigue	9 (56)	1 (6)
Hypocalcemia	8 (50)	1 (6)
Constipation	8 (50)	0
Nausea	6 (38)	0
Vomiting	6 (38)	0
Peripheral edema	6 (38)	0
Pyrexia	6 (38)	0
Upper respiratory tract infection	6 (38)	0
Hypokalemia	6 (38)	0
Cough	5 (31)	0
Hypoalbuminemia	5 (31)	0
Hypomagnesemia	5 (31)	0
Insomnia	5 (31)	0
Pain in extremity	5 (31)	0
[illegible]europathy	5 (31)	0
[illegible]	4 (25)	4 (25)
[illegible]	4 (25)	2 (13)
[illegible]	4 (25)	2 (13)

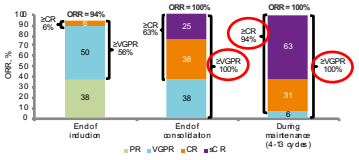
- TEAEs occurred in all 16 patients
  - TEAEs related to daratumumab[c] occurred in 15 patients (94%)
- Grade 3 or 4 TEAEs occurred in 14 patients (88%)
  - Grade 3 or 4 TEAEs related to daratumumab[c] occurred in 10 patients (63%)

✓ No one stopped treatment for AE.
✓ Stem cell collection was not impacted by addition of daratumumab.

10

Efficacy: Investigator-assessed Response Rate

- Median (range) follow-up: 16.8 (15.9-18.7) months



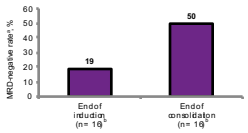
Responses continued to deepen over time

ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response.

11

MRD Negativity (10^{-5}; ITT) and Outcomes

- Median (range) follow-up: 16.8 (15.9-18.7) months



- 15/16 (94%) patients remain progression-free on study treatment

[a]Evaluated by next generation sequencing (NGS; ClonoSEQ v2.0).
[b]3 patients were evaluated for MRD at each timepoint.

50% of patients achieved MRD negativity at 10^{-5}

MRD rate expressed as a percentage of all patients (N=16). Note that 3 patients were not evaluable due to technical issues.

12

Griffin: Summary

- Addition of daratumumab to VRd backbone in transplant-eligible pts w/NDMM has impressive response rates and deep responses
- The Phase 2 randomized trial of D-VRd vs VRd is closed to accrual (N=222) – *await those results*
- Daratumuamb approved as front-line therapy in combination with VMP, but not yet with VRd.

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MAIA: Phase 3 Randomized Study of D-Rd vs Rd in Newly Dx'd MM Ineligible for Transplant (Abstract LBA-2)[1]

- Pre-specified interim analysis
- FIRST trial: Rd significantly prolonged PFS vs MPT in transplant-ineligible NDMM (26.0 vs 21.9 months)[2]
- Triplet regimens have consistently shown deeper responses and better PFS
  - *Does the addition of daratumumab improve PFS and responses in NDMM?*

1 - Facon T, Kumar SK, Plesner T, et al. Phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA). Abstract #LBA-2. Presented at the 2018 ASH Annual Meeting, December 4, 2018; San Diego, CA.
2 - N Engl J Med 371:906–917,2014

MAIA Study Design

Phase 3, Randomized, open-label, multi-center

Key eligibility criteria:
- transplant-ineligible NDMM
- ECOG 0-2
- CrCl ≥30 ml/min

N 1 Randomization

D-Rd (n = 368)
Daratumumab (16 mg/kg IV)
Cycles 1-2: qW
Cycles 3-6: q2W
Cycles 7+: q4W until PD
R: 25mgpo daily on days 1-21 until PD
D: 40mg po weekly until PD

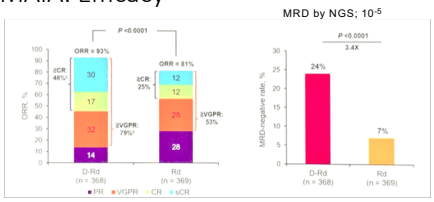
Rd (n = 369)
R: 25mg po daily on days 1-21 until PD
D: 40mg po weekly until PD

Primary Endpoint:
PFS

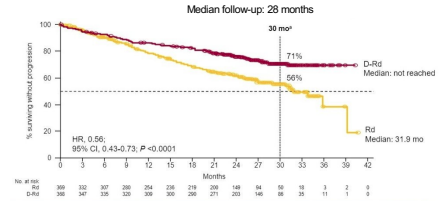
Key secondary endpoints:
≥CR
≥VGPR
MRD-negative rate (NGS; 10-5)
OS
Safety

Stratification factors:
ISS (I vs II vs III)
Region (NA vs other)
Age (<75 and ≥75 years)

MAIA: Efficacy



MAIA: PFS



MAIA: Summary

- Triplets continue to be better than doublets in MM
- How does DRd compare to VRd?
  - SWOG S0777: Phase 3, VRd vs Rd in NDMM without intent for immediate SCT[1]
    - PFS (months): VRd 43 vs Rd 30
    - OS (months): VRd 75 vs Rd 64
    - HR 0.7 (vs 0.5 in DRd)
    - Bortezomib only given x 8 cycles; Daratumumab given until PD[2]
  - RVD Lite: Phase 2, single arm in transplant-ineligible NDMM
    - 15 cycles RVD lite; no maintenance specified, but 66% got lenalidomide
    - PFS (months): 35.1
- Should DRd be the new SOC for transplant-ineligible NDMM?
  - I await more mature results and a direct comparison of regimens
  - Note: Daratumumab is not yet FDA-approved for frontline treatment of NDMM except in combination with VMP

[1]Lancet. 2017 Feb 4;389(10068):519-527.

[2]Br J Haematol. 2018 Jul;182(2):222-230.

Learning Objective 2: ASCT should still be considered in frontline treatment of NDMM

- ASCT has shown improved depth of response and PFS
- OS benefit remains of debate: IFM2009 trial showed better PFS with upfront vs delayed ASCT, but comparable OS – short follow-up as yet
- Ongoing US Trial: Determination (DFCI 10-106) – VRd – ASCT – lenalidomide maintenance

Blood. 2018 Dec 26. pii: blood-2018-08-825349

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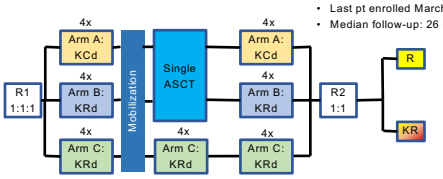
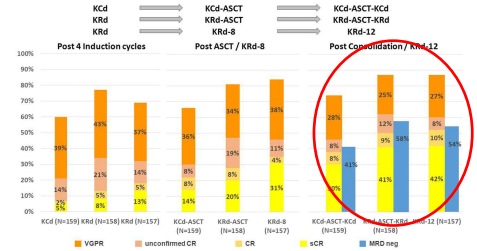
Forte: KRd – ASCT vs KRd 12 cycles vs KCd in NDMM (Abstract 121)

- Phase 2, Randomized
- NDMM, transplant eligible, <65 yr
- Last pt enrolled March 2017
- Median follow-up: 26 months



Blood 2018 132:121

FORTE: Results



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Forte: Safety

- Discontinuation for AEs similar in the 3 arms
  - KRd-ASCT: 6%
  - KRd12: 8%
  - KCd-ASCT: 7%

Forte: Summary

- At completion of consolidation, KRd regimens vs KCd-ASCT-KCd had
  - improved ≥VGPR rates, 89% vs 76%
  - Improved MRD negative rates, 56% vs 42% (statistically significant)
    - Second generation flow cytometry, 10^{-5} sensitivity
- Maintenance data are not mature
- When feasible, use lenalidomide over cyclophosphamide
- High-dose melphalan with ASCT is still the standard of care, but I await results of DETERMINATION (RVd with either upfront or delayed ASCT) and FORTE for OS data and factors that influence response to ASCT

Learning Objective 3: Lenalidomide maintenance after ASCT in standard-risk disease remains the SOC

- Lenalidomide maintenance has shown improved PFS and OS over placebo (53 vs 24 months; 62% vs 50% at 7 years) in standard-risk MM
- For high-risk MM, bortezomib is considered over lenalidomide, however, there is no trial comparing these head-to-head.

Rajkumar SV. "Autologous hematopoietic cell transplantation in multiple myeloma." UpToDate.com 1/3/2019. https://www.uptodate.com/contents/autologous-hematopoietic-cell-transplantation-in-multiple-myeloma?sectionName=MAINTENANCE&topicRef=6643&anchor=H13&source=see_link#H14

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Tourmaline-MM3: Maintenance Therapy with Ixazomib Significantly Prolongs PFS following ASCT in Newly Dx'd MM (abstract 301)

Phase 3, double-blind, placebo-controlled

Key eligibility criteria:

NDMM with ≥ PR after induction w/ IMiD or PI followed by 200 mg/m2 melphalan ASCT

Randomization 2:1

Ixazomib Maintenance (n = 395)

Ixazomib 3mg po days 1, 8, 15 – C1-4
Ixazomib 4mg po days 1, 8, 14 – C5+ (n=317)
Treatment for 1 cycle = 28 days; cycles

Placebo Maintenance (n = 261)

Placebo po days 1, 8, 15
1 cycle = 28 days

Primary Endpoint: PFS

Key Secondary Endpoint: OS

Stratification factors:
ISS (I vs II vs III)
Induction regimen
Response after ASCT (≥ VGPR vs PR

Lancet. 2019 Jan 19;393(10168):253-264.

Safety

- Only 7% discontinued ixazomib d/t AE
- Neuropathy not different, improved in 75% and resolved in 70%
- No increase in SPM

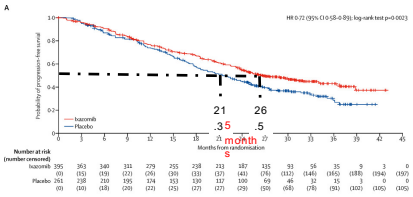
	Ixazomib group (n=254)			Placebo group (n=253)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Common haematological adverse events of any cause						
Neutropenia*	36 (9%)	12 (4%)	3 (1%)	20 (8%)	9 (3%)	0
Thrombocytopenia*	53 (13%)	14 (4%)	5 (1%)	8 (3%)	0	2 (1%)
Anaemia	79 (7%)	4 (1%)	0	35 (14%)	7 (2%)	0
Common non-haematological adverse events of any cause						
Infections and infestations (MedDRA SOC)†	242 (74%)	55 (14%)	3 (1%)	166 (64%)	21 (8%)	2 (1%)
Upper respiratory tract infection	101 (26%)	2 (1%)	0	54 (21%)	1 (<1%)	0
Viral upper respiratory tract infection	94 (24%)	0	0	69 (27%)	0	0
Pneumonia†	40 (10%)	23 (6%)	1 (<1%)	21 (8%)	11 (4%)	0
Gastrointestinal disorders (MedDRA SOC)	270 (69%)	25 (6%)	0	174 (68%)	3 (1%)	0
Nausea	154 (39%)	1 (<1%)	0	40 (15%)	0	0
Diarrhoea	137 (35%)	10 (3%)	0	61 (24%)	2 (1%)	0
Vomiting	106 (27%)	6 (2%)	0	28 (11%)	0	0
Rash‡	135 (28%)	7 (2%)	0	57 (23%)	0	0
Cough	87 (22%)	0	0	55 (23%)	1 (<1%)	0
Arthralgia	86 (22%)	3 (1%)	0	30 (12%)	1 (<1%)	0
Pyrexia	84 (21%)	1 (<1%)	0	28 (11%)	0	0
Fatigue	79 (20%)	5 (1%)	0	43 (17%)	1 (<1%)	0
Back pain	77 (19%)	4 (1%)	0	45 (18%)	4 (2%)	0
Peripheral neuropathy*	73 (19%)	1 (<1%)	0	38 (15%)	0	0
Headache	43 (11%)	0	0	21 (8%)	0	0
Influenza	42 (11%)	3 (1%)	0	30 (12%)	1 (<1%)	0
Other adverse events of clinical interest						
Acute renal failure	11 (3%)	3 (<1%)	0	8 (3%)	3 (<1%)	0
Cardiac arrhythmias	19 (5%)	7 (2%)	0	7 (3%)	2 (1%)	0
Liver impairment	24 (6%)	9 (2%)	0	11 (4%)	3 (1%)	1 (<1%)
Hypotension or orthostatic hypotension	4 (1%)	3 (<1%)	0	1 (<1%)	0	0
New primary malignant tumour	17 (1%)	–	–	8 (3%)	–	–

Response

- Deepened in both arms
- Not powered for MRD comparison

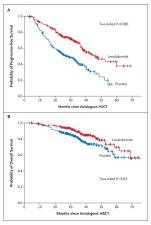
	Ixazomib group (n=395)	Placebo group (n=261)	HR (95% CI) or RR (95% CI); p value
Response at study entry*			
Complete response	60 (15%)	54 (21%)	–
Very good partial response	211 (54%)	152 (58%)	–
Converted to complete response during study	113/211 (43%)	48/152 (32%)	RR 1·37 (1·03–1·81)
Partial response	89 (23%)	35 (13%)	–
Converted to very good partial response or better during study	47/89 (53%)	11/35 (34%)	RR 1·56 (0·94–2·54)
Stable disease	7 (<1%)	1 (<1%)	–
Progressive disease	1 (<1%)	0	–
Either very good partial response or partial response	301 (76%)	187 (72%)	–
Deepening response during treatment	159/301 (46%)	60/187 (32%)	RR 1·41 (1·10–1·80); p=0·0041
MRD status			
MRD-positive status at study entry	225/282 (80%)	156/218 (81%)	–
Converted to MRD-negative status at any time point at study entry	28/225 (12%)	10/156 (7%)	–
By 6 months post-study entry	3/225 (1%)	0	–
By 12 months post-study entry	17/225 (8%)	8/139 (6%)	–
By 18 months post-study entry	21/225 (9%)	9/139 (6%)	–
By 24 months post-study entry	23/225 (10%)	10/139 (7%)	–
Time to MRD-negative status (months)	Not estimable	Not estimable	HR 1·64 (0·79–3·42); p=0·18
Progression-free survival (months)	23·1 (20·3–25·7)	18·5 (15·7–21·9)	HR 0·78 (0·54–0·92); p=0·010
MRD-negative status at study entry	117/357 (27%)	75/223 (33%)	–
Patients with MRD-negative status retained at any subsequent evaluation	73/117 (62%)	38/75 (51%)	p=0·11
Time to documented MRD-positive status, progression, or death (months)	Not estimable (28·6–not estimable)	24·6 (12·1–not estimable)	HR 0·57 (0·37–0·90); p=0·014
Progression-free survival (months)	28·6 (23·8–not estimable)	17·5 (13·1–not estimable)	HR 0·61 (0·39–0·97); p=0·034

Tourmaline-MM3: Results



How does this compare to lenalidomide maintenance?

- IFM 2005-02 study[1]: Len until progression vs placebo
  - PFS: 41 vs 23 months
- CALGB 100104[2]: Len until progression vs placebo
  - PFS: 46 vs 27 months



[1]N Engl J Med. 2012 May 10;366(19):1782-91.
[2]N Engl J Med. 2012; 366: 1770-1781

Tourmaline-MM3: Summary

- Ixazomib vs placebo resulted in 5 months additional PFS
- Good safety profile
- I would not use this in place of lenalidomide for maintenance at this time
- Await results of ongoing studies of ixazomib and lenalidomide in combination or alone, in high-risk patients, and in an alternating strategy

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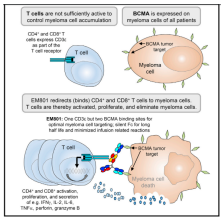
AMG 420 anti-BCMA BiTE (abstract 1010)

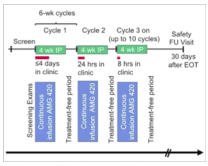
- B-cell Maturation Antigen (BCMA) is expressed on multiple myeloma cells, plasma cells, and mature B-cells
- AMG 420 is a mAb for CD3 joined by a flexible linker to mAb for BCMA
- T-cell mediated lysis of BCMA+ cells



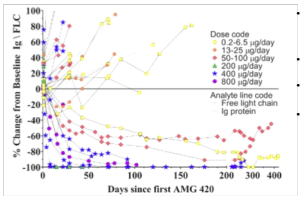
Note: this is not AMG 420, but a general representation of BiTE
Cancer Cell. 2017 Mar 13;31(3):396-410

AMG 420

- Phase 1, First-in-human dose escalation study
- RRMM with progression after >2 prior lines of treatment (including PI and IMiD)
- Tx for up to 5 cycles or PD, 5 additional cycles could be given
- 35 pts received drug as of May 2018



AMG 420 anti-BCMA BiTE (1010)



- 400 ug/day was MTD – CRS and polyneuropathy at 800 ug/day
- 7/10 pts in 400 ug/day group responded
- 4/10 were MRD-negative sCR
- 6/10 pts still responding at 7.5 months

AMG 420: Summary

- BCMA has been a good target in myeloma
  - mAb-drug conjugates
  - CAR-T
  - BiTE
- This construct showed very promising results, and would potentially offer "off-the-shelf" option for tx, rather than the wait time for CAR-T production
- FDA granted "Fast Track" designation

Final Summary

None of these data are as yet practice-changing in my opinion, but the mature data over the next few years will inform practice

Brandi_Reeves@med.unc.edu

Best of ASH 2018--Leukemia

Matthew Foster, MD

25 January 2019

UNC CANCER CARE

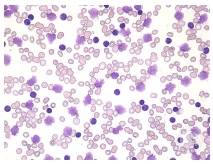
Outline

I. Chronic Lymphocytic Leukemia
II. Lower Risk MDS
III. AML in older adults

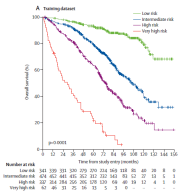
Outline

I. Chronic Lymphocytic Leukemia
II. Lower Risk MDS
III. AML in older adults

Chronic lymphocytic leukemia

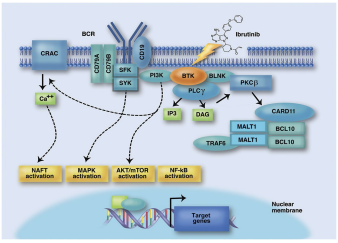


This image was originally published in ASH Image Bank. Maslak P. Smudge Cells - 1. ASH Image Bank. 2010; image number-00001023. © the American Society of Hematology



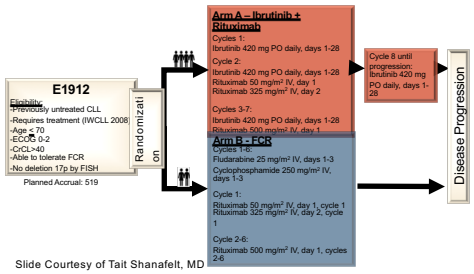
The International CLL-IPI Working Group. Lancet Oncol 2016; 17:779-90

Ibrutinib



Davide Rossi, and Gianluca Gaidano Blood 2014;123:1772-1774

Study design-E1912, abstract BA-4



Slide Courtesy of Tait Shanafelt, MD

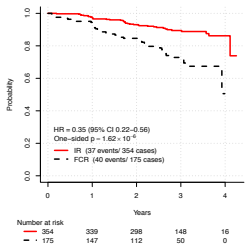
Patient Characteristics Were Well Balanced

Baseline characteristics		IR n=354	FCR n=175	Total
Median age (y)		58	57	58
Age ≥ 60		41.0%	40.0%	40.6%
Female		33.3%	31.4%	32.7%
ECOG = 0		63.8%	62.3%	63.3%
Rai stage 0		3.1%	5.1%	3.8%
Rai stage I-II		52.8%	53.7%	53.1%
Rai stage III-IV		44.1%	41.1%	43.1%
FISH	11q deletion	22.0%	22.3%	22.2%
	Trisomy 12	19.8%	15.4%	18.3%
	13q deletion	34.2%	33.1%	33.8
B2M >3.5 mg/L		51.9%	48.0%	50.6%
IGHV Unmutated*		75.0%	61.7%	71.1%

* Tested in 437 (82%) patients

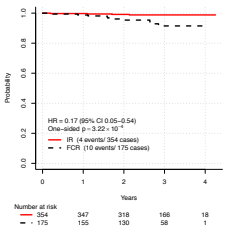
Slide Courtesy of Tait Shanafelt, MD

Progression-free Survival—Intent to treat



Slide Courtesy of Tait Shanafelt, MD

Overall Survival—Intent to treat



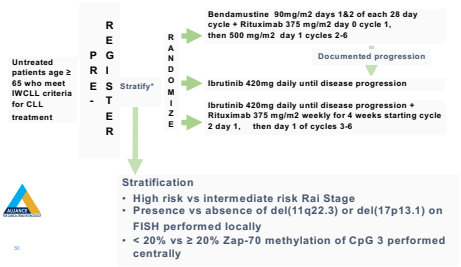
Slide Courtesy of Tait Shanafelt, MD

Grade 3-5 Treatment Related Adverse Events Throughout Observation

Adverse event	IR (%) N= 352	FCR (%) N=158	p value
Neutropenia	22.7%	43.7%	<0.001
Anemia	2.6%	12.0%	<0.001
Thrombocytopenia	2.9%	13.9%	<0.001
Any Infection	7.1%	19.0%	<0.001
Infection	5.4%	8.2%	0.24
Neutropenic fever	2.3%	15.8%	<0.001
Atrial fibrillation	2.9%	0.0%	0.04
Bleeding	1.1%	0.0%	0.32
Hypertension	7.4%	1.9%	0.01
Diarrhea	2.6%	0.6%	0.19
Any Grade 3 or higher AE	**58.5%**	**72.1%**	**P=0.004**

Slide Courtesy of Tait Shanafelt, MD

Schema-A041202, abstract 6



Slide Courtesy of Jennifer Woyach, MD

Patient Characteristics

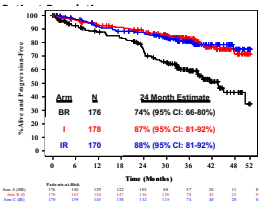
Characteristic	Total N=547	BR N=193	Ibrutinib N=182	IR N=182
Age (years), median (range)	71 (65-89)	70 (65-86)	71 (65-89)	71 (65-86)
Male, %	67	65	68	69
ECOG 0-1, %	97	95	97	99
White blood cell count $x10^9/\mu L$, median (range)	82 (4-518)	92 (7-518)	79 (6-438)	70 (4-481)
FISH Characteristics, %				
Del (17p)	6	8	5	6
Del (11q)	19	18	19	21
TP53 mutation, %	10	9	9	12
Complex Karyotype, %	29	27	24	36
Zap-70 Unmethylated, %	53	52	53	53
IGVH unmutated*, %	61	58	63	61

*N= 360 total

Slide Courtesy of Jennifer Woyach, MD

Primary Endpoint: Progression Free Survival

Eligible



Pairwise Comparisons

I vs BR:
Hazard Ratio 0.39
95% CI: 0.26-0.58
(1-sided P-value <0.001)

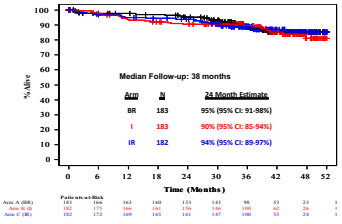
IR vs BR:
Hazard Ratio 0.38
95% CI: 0.25-0.59
(1-sided P-value <0.001)

IR vs I:
Hazard Ratio 1.00
95% CI: 0.62-1.62
(1-sided P-value 0.49)

Slide Courtesy of Jennifer Woyach, MD

Overall Survival

Intention-to-Treat Patient Population



Slide Courtesy of Jennifer Woyach, MD

Grade 3, 4, or 5 Adverse Events

During treatment or follow-up (excluding crossover)

Adverse Event	BR N=176	Ibrutinib N=180	IR N=181	P-value
All Hematologic – no. (%)	**107 (61)**	**74 (41)**	**70 (38)**	**<0.001**
Anemia	22 (13)	21 (12)	11 (6)	0.09
Neutropenia	71 (40)	27 (15)	39 (22)	<0.001
Thrombocytopenia	26 (15)	12 (7)	9 (5)	0.008
All Non-hematologic – no. (%)	**111 (63)**	**133 (74)**	**134 (74)**	**0.04**
Bleeding	0 (0)	3 (2)	5 (3)	0.46
Infections	26 (15)	37 (21)	37 (20)	0.62
Febrile neutropenia	13 (7)	3 (2)	1 (1)	<0.001
Atrial fibrillation	5 (3)	17 (9)	10 (6)	0.05
Hypertension	25	53 (29)	61 (34)	<0.001
Unexplained/unwitnessed death	2 (1)	7 (4)	4 (2)	0.24

- Deaths during active treatment + 30 days: 2 (1%), 13 (7%), 13 (7%)
- Deaths during active treatment + 30 days, up to 6 cycles: 2 (1%), 3 (2%), 6 (3%)

Slide Courtesy of Jennifer Woyach, MD

Outline

I. Chronic Lymphocytic Leukemia
II. Lower Risk MDS
III. AML in older adults

Myelodysplastic Syndromes

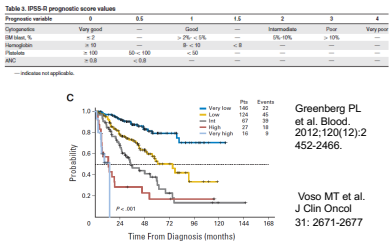


Table 3. IPSS-R prognostic score values

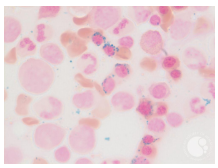
Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	< 2	—	> 2% - < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8 - < 10	< 8	—	—	—
Platelets	≥ 100	50 - < 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

— indicates not applicable.

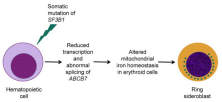
Greenberg PL et al. Blood. 2012;120(12):2 452-2466.

Voso MT et al. J Clin Oncol 31: 2671-2677

MDS with Ring Sideroblasts

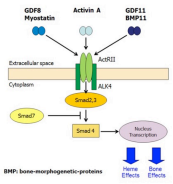


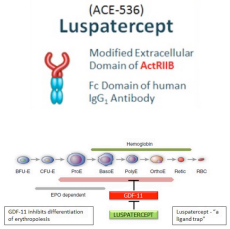
This image was originally published in ASH Image Bank. Vankalakunnan G., MDS-RS: ASH Image Bank. 2018; image number-00081622. © the American Society of Hematology



Cazzola M et al. Blood. 2013; 121(2):260-269.

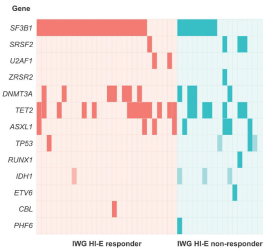
Luspatercept





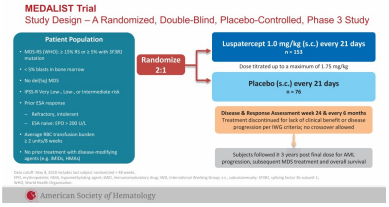
Fenaux P et al. Blood 2019 Jan 2 [Epub ahead of print]

Luspatercept response associated with SF3B1 mutations



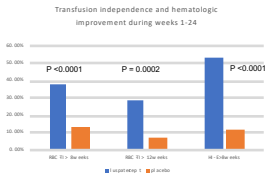
Platzbecker U et al. Lancet Oncol 2017;18:1338-47.

RCT Luspatercept vs Placebo



List A et al. ASH 2018 Abstract 1

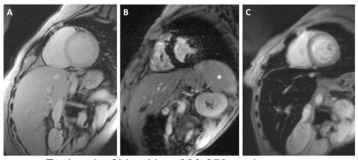
RCT Luspatercept vs Placebo



Median duration of transfusion independence (95% CI): 30.6 weeks (20.6-40.6) versus 13.6 (9.1-54.9)

List A et al. ASH 2018 Abstract 1

Iron overload in MDS



Hoffbrand AV et al. Blood. 2012; 120(18): 3657-69.

- Each unit of blood has 200-250 mg iron.
- Annual intake of excess iron for 2-4 units/month: 5-10 grams
- MDS patients with longer life expectancy who get >20-30 units and elevated ferritin previously recommended for chelation
- Previously unknown if benefits of chelation outweigh risks

Deferasirox vs placebo in lower risk MDS

Eligibility:

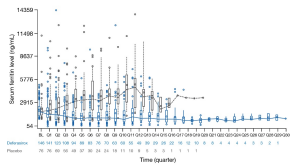
- IPSS low/Intermediate-1 MDS
- Ferritin >1000 ng/mL
- Transfusion history: 15-75 units RBC
- No cardiac or hepatic abnormalities

Composite Primary Endpont: Event-Free Survival (by independent review)

- Cardiac events
- Hepatic events
- Transformation to AML
- Death

Angelucci E et al. ASH 2018 Abstract 0234

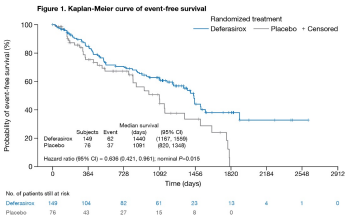
Changes in Serum Ferritin



Whiskers mark 10th and 90th percentiles, boxes show lower and upper quartiles, horizontal line shows the median and o represents the mean; values outside 10th–90th percentile are plotted as o
NE, not evaluable

Angelucci E et al. ASH 2018 Abstract 0234

Event-Free Survival

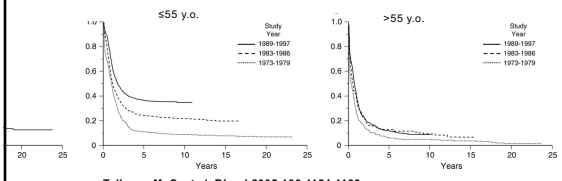


Angelucci E et al. ASH 2018 Abstract 0234

Outline

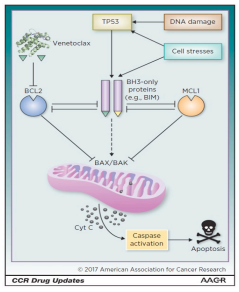
I. Chronic Lymphocytic Leukemia
II. Lower Risk MDS
III. AML in older adults

Lack of progress in older adults



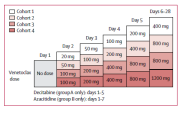
Tallman, M. S. et al. Blood 2005;106:1154-1163

Venetoclax



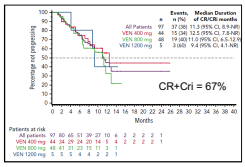
Roberts AW et al. Clin Cancer Res; 23(16); 4527-33.

Venetoclax + HMA phase 1b



DiNardo CD et al. Blood. 2019;133(1):7-17.

DiNardo CD et al. Lancet Oncol 2018;19:216-28.



14 ASH abstracts on Ven + HMA/LDAC

CR/CRi, n = 97	MRD < 10^{-3}	MRD ≥ 10^{-3}	Nonevaluable
n (%)	28 (29)	55 (57)	14 (14)
DOR, mo	NR	11.3	6.4
OS, mo	NR	NR	10.6