25th Multidisciplinary Management of Cancers: A Case-based Approach

# Hematologic Malignancies Tumor Board

Friday, March 7th, 2025
11:00 AM

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25th Multidisciplinary Management of Cancers: A Case-based Approach

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# Panelists

- Krishna Komanduri, MD (Chair) – UCSF
- Shagun Arora, MD – UCSF
- Michael Green, MD – The Permanente Medical Group
- Jarrod Holmes, MD – Providence Medical Group
- David Iberri, MD – Stanford
- Brian Jonas, MD, PhD – UC Davis
- Tom Martin, MD – UCSF
- William Shomali, MD – Stanford
- Cathy Smith, MD – UCSF
- Francisco Socola, MD – UC Davis
- Michael Randall, MD (Fellow, Case Presenter) – UCSF

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## Disclosures

| Full Name | Role | Type of Financial Relationship | Company |
|---|---|---|---|
| **Krishna Komanduri** | **Chair** | Advisory Board or Panel | Scientific Advisory Board - Aegle Therapeutics, CellChorus, Clinical Advisory Board - Optum Health |
| | | Consultant | Ad hoc Consulting- Iovance, Incyte, Cargo Therapeutics, CRISPR therapeutics, Genentech/Roche, and BMS. |
| **Michael Randall** | **Fellow** | Disclosed no relevant financial relationships. | |
| Shagun Arora | Panelist | Disclosed no relevant financial relationships. | |
| Michael Green | Panelist | Disclosed no relevant financial relationships. | |
| Jarrod Holmes | Panelist | Speaker's Bureau | Pharmacyclics and Glaxo Smith Kline. |
| David Iberri | Panelist | Disclosed no relevant financial relationships. | |

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### Disclosures

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|---|---|---|---|
| Brian Jonas | Panelist | Advisory Board or Panel | AbbVie, Kura, Rigel, Schrodinger, Syndax, and Treadwell |
| | | Consultant | AbbVie, BMS , Gilead, Kura, Rigel, Schrodinger, Syndax, and Treadwell |
| | | Grants/Research Support | Research funding to my institution from AbbVie, Amgen, Aptose, AROG, Biomea, BMS, Celgene,Forma, Forty-Seven, Genentech/Roche, Gilead, GlycoMimetics, Hanmi, Immune-Onc, Jazz,Kymera, Loxo, Pfizer, Pharmacyclics, and Treadwell |
| | | Other Financial or Material Support (royalties, patents, etc.) | Travel reimbursement/support from Rigel; Data monitoring committee for Gilead. |
| Tom Martin | Panelist | Consultant: | GSK, Pfizer, Lilly |
| | | Grants/Research Support: | Sanofi, AMGEN, BMS, and Janssen. |
| William Shomali | Panelist | Advisory Board or Panel | Blueprint Medicines |
| | | Consultant | Incyte |
| | | Grants/Research Support | Incyte and Blueprint Medicines |
| Cathy Smith | Panelist | Advisory Board or Panel | Biomea, Abbvie, and Genentech |
| | | Grants/Research Support | Erasca, Abbvie, Zentalis, and Biomea. |
| Francisco Socola | Panelist | Disclosed no relevant financial relationships. | |

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### Case #1: History

- A 49-year-old man presents to PCP with progressive fatigue/malaise, blurred vision and 10 lb weight loss over the past two months
- PMH: T2DM, HTN, mild asthma
- SH: Retired construction worker. Lives with his spouse in an apartment. Remote smoking history, no alcohol use.
- FH: No family history of hematologic malignancies
- Physical exam: ECOG PS 1, pale and fatigued-appearing, tachycardic with regular rhythm, scattered ecchymoses on extremities. No lymphadenopathy. Right retinal hemorrhage noted on ophthalmology exam.

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### Case #1: Labs & Imaging

- WBC 266, Hgb 9.4, Plt 52, MCV 93, ANC 5.3
  - 43.9% monocytes, 53.0% blasts
- Na 138, K 3.6, Cr 3.20 (baseline ~1.0), albumin 2.8
- LDH 645, uric acid 10.6
- INR 2.0, aPTT 41.8, fibrinogen 278

- A pheresis catheter was placed urgently and he underwent leukapheresis. He was given fluids, allopurinol and rasburicase with improvement in renal function.



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### Case #1: Bone Marrow Biopsy

- Pathology: 90% blasts by morphology; flow cytometry with atypical monocytic population (85%) consistent with AML with monocytic differentiation. Immunophenotype: CD13, CD33, CD34, CD38, weak CD71, CD117, HLA-DR
- Cytogenetics: 46, XY
- FISH: Negative AML FISH panel
- NGS/Molecular: Mutations include *FLT3-ITD* (allelic ratio 0.7), *DNMT3A* (VAF 50.6%, Tier 1), *NPM1* (VAF 44.3%, Tier 1), *TET2* (VAF 49.2%, Tier 1), *RAD21* (VAF 45.9%, Tier 2)



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### Case #1: Newly Diagnosed AML Risk Stratification

How would you characterize this patient's disease risk based on cytogenetics and molecular abnormalities?

A. Favorable
B. Intermediate
C. Poor
D. Unable to determine

- **Pathology**: 90% blasts by morphology; flow cytometry with atypical monocytic population (85%) consistent with AML with monocytic differentiation. Immunophenotype: CD13, CD33, CD34, CD38, weak CD71, CD117, HLA-DR
- **Cytogenetics**: 46, XY
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### Prognostic impact of FLT3 mutations in AML

| Risk category† | Genetic abnormality |
|---|---|
| Favorable | • t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡<br>• inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡<br>• Mutated *NPM1*†,§ without *FLT3*-ITD<br>• bZIP in-frame mutated *CEBPA*‖ |
| Intermediate | • Mutated *NPM1*†,§ with *FLT3*-ITD<br>• Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions)<br>• t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶<br>• Cytogenetic and/or molecular abnormalities not classified as favorable or adverse |
| Adverse | • t(6;9)(p23.3;q34.1)/*DEK*::*NUP214*<br>• t(v;11q23.3)/*KMT2A*-rearranged#<br>• t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*<br>• t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP*<br>• inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*<br>• t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged<br>• −5 or del(5q); −7; −17/abn(17p)<br>• Complex karyotype,** monosomal karyotype††<br>• Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡<br>• Mutated *TP53*[a] |

Curable with chemotherapy alone

High risk of relapse without allogeneic SCT

Döhner et al. *Blood* 2022

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- **Pathology**: 90% blasts by morphology; flow cytometry with atypical monocytic population (85%) consistent with AML with monocytic differentiation. Immunophenotype: CD13, CD33, CD34, CD38, weak CD71, CD117, HLA-DR
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Case #1: Initial Treatment – FLT3-ITD AML in a fit patient

How would you characterize this patient's disease risk based on cytogenetics and molecular abnormalities?


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## 24th Multidisciplinary Management of Cancers: A Case-Based Approach

- **Pathology**: 90% blasts by morphology; flow cytometry with atypical monocytic population (85%) consistent with AML with monocytic differentiation. Immunophenotype: CD13, CD33, CD34, CD38, weak CD71, CD117, HLA-DR
- **Cytogenetics**: 46, XY
- **FISH**: Negative AML FISH panel
- **NGS/Molecular**: Mutations include FLT3-ITD (allelic ratio 0.7), DNMT3A (VAF 50.6%, Tier 1), NPM1 (VAF 44.3%, Tier 1), TET2 (VAF 49.2%, Tier 1), RAD21 (VAF 45.9%, Tier 2)

Case #1: Initial Treatment – FLT3-ITD AML in a less fit patient

How would you characterize this patient's disease risk based on cytogenetics and molecular abnormalities?


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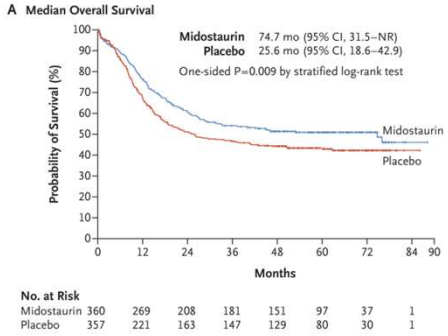
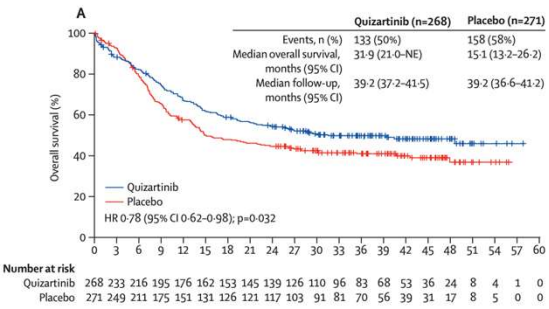
### Targeting FLT3 mutations in frontline AML therapy

**Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation**

R.M. Stone, S.J. Mandrekar, B.L. Sanford, K. Laumann, S. Geyer, C.D. Bloomfield, C. Thiede, T.W. Prior, K. Döhner, G. Marcucci, F. Lo-Coco, R.B. Klisovic, A. Wei, J. Sierra, M.A. Sanz, J.M. Brandwein, T. de Witte, D. Niederwieser, F.R. Appelbaum, B.C. Medeiros, M.S. Tallman, J. Krauter, R.F. Schlenk, A. Ganser, H. Serve, G. Ehninger, S. Amadori, R.A. Larson, and H. Döhner




**Quizartinib plus chemotherapy in newly diagnosed patients with *FLT3*-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial**




Stone et al. *NEJM* 2023; Erba et al. *Lancet* 2023

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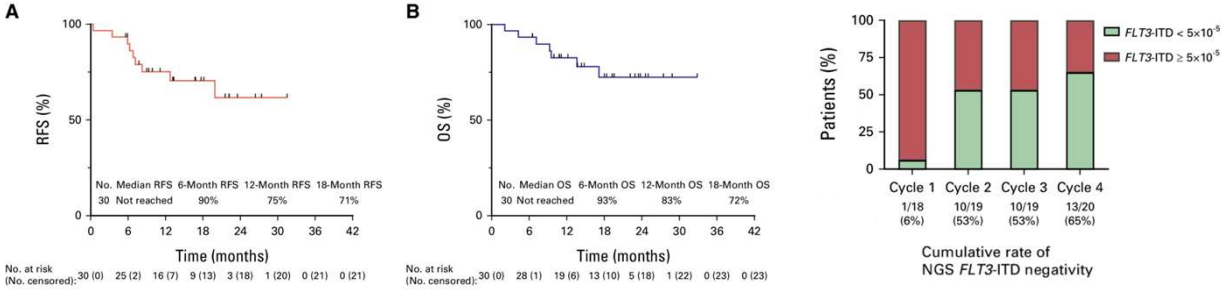
### Targeting FLT3 mutations in frontline AML therapy

**Azacitidine, Venetoclax, and Gilteritinib in Newly Diagnosed and Relapsed or Refractory *FLT3*-Mutated AML**

Nicholas J. Short, MD[1]; Naval Daver, MD[1]; Courtney D. Dinardo, MD[1]; Tapan Kadia, MD[1]; Lewis F. Nasr, MD, MSc[1]; Walid Macaron, MD, MSc[1]; Musa Yilmaz, MD[1]; Gautam Borthakur, MBBS[1]; Guillermo Montalban-Bravo, MD, MS[1]; Guillermo Garcia-Manero, MD[1]; Ghayas C. Issa, MD[1]; Kelly S. Chien, MD[1]; Elias Jabbour, MD[1]; Cedric Nasnas, MD[1]; Xuelin Huang, PhD[2]; Wei Qiao, PhD[2]; Jairo Matthews, BA[1]; Christopher J. Stojanik, BS[1]; Keyur P. Patel, MD, PhD[3]; Regina Abramova, BS, BSN, RN[1]; Jennifer Thankachan, BSN, MSN, RN[1]; Marina Konopleva, MD, PhD[1]; Hagop Kantarjian, MD[1]; and Farhad Ravandi, MD[1]

DOI https://doi.org/10.1200/JCO.23.01911




Short et al. *J Clin Oncol* 2024

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### Case #1: Continued

- Patient was treated with 7+3+quizartinib. Post-induction BMBx showed no evidence of disease with subsequent recovery of normal counts, consistent with CR. He underwent 2 cycles of consolidation with high-dose cytarabine + quizartinib while preparations were made for allogeneic hematopoietic stem cell transplant
- Prior to transplant, while he remained in CR by flow, targeted NGS for FLT3-ITD was positive at a level of $10^{-5}$
- He then underwent myeloablative allogeneic SCT, complicated by grade 1 GVHD of the skin and liver

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Case #1: Post-transplantation maintenance therapy for FLT3-mutated AML

What maintenance strategy, if any, would you adopt for this patient?


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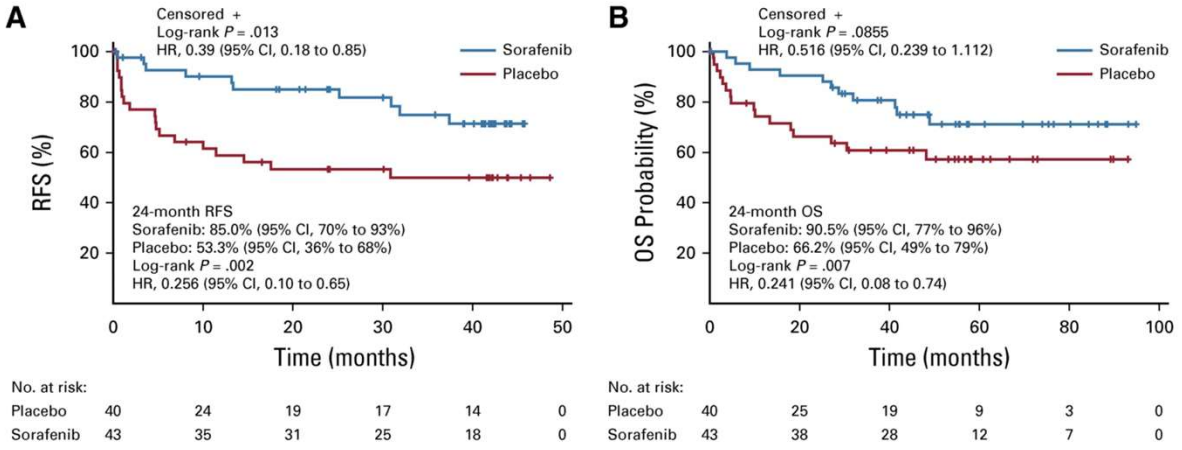
### SORMAIN: Sorafenib maintenance improves RFS and OS after alloSCT




Burchert et al. *J Clin Oncol* 2020



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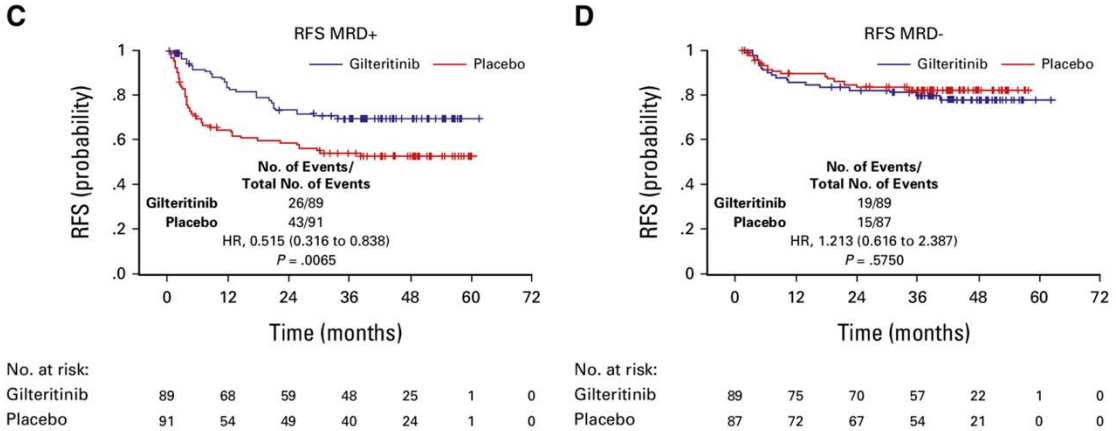
### BMT-CTN 1506: Gilteritinib as post-transplant maintenance for AML with FLT3-ITD




Levis et al. *J Clin Oncol* 2024



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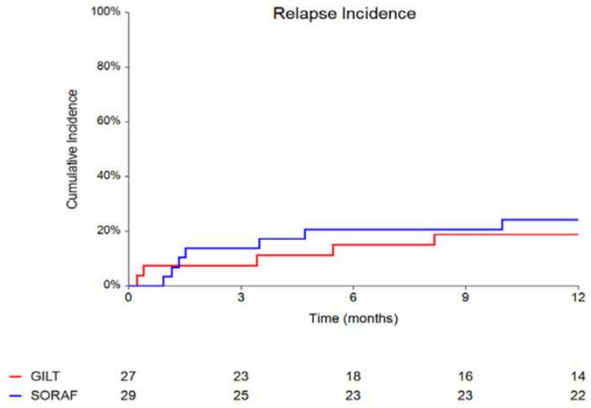
### Sorafenib or gilteritinib?

- No direct prospective comparison
- MSKCC retrospective: 55 patients
  - Gilteritinib (n=27)
  - Sorafenib (n=29)
- 1-year PFS was similar
  - 66% with gilteritinib
  - 76% with sorafenib (P = 0.4)
- As was relapse incidence
  - 19% with gilteritinib
  - 24% with sorafenib (P = 0.6)
- 86% of sorafenib patients discontinued maintenance vs. 56% of gilteritinib patients




Yeh et al. *Clin Lymphoma Myeloma Leuk* 2024.



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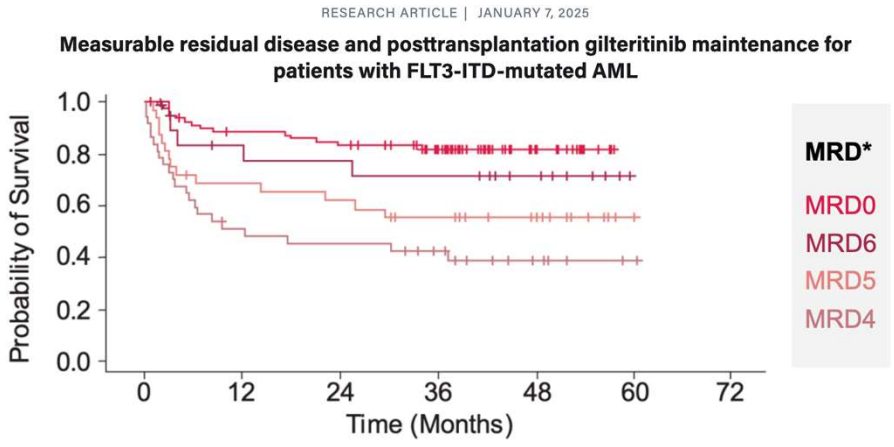
### Gilteritinib as post-transplant maintenance for AML with FLT3-ITD – correlation of MRD with survival




Levis et al. *Blood* 2025



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### Case #1: Key Points

- In the ENL 2022 risk stratification model, all AML with FLT3-ITD is intermediate risk
- For fit adults with FLT3 mutant AML, current SOC is intensive chemotherapy + quizartinib (for ITD) or intensive chemotherapy + midostaurin (for ITD or TKD)
- AZA/VEN/gilteritinib shows promise in a single-center study, but more studies are needed.
- Both sorafenib and gilteritinib improve RFS in patients with FLT-ITD AML after alloSCT
- BMT CTN 1506 demonstrated improved RFS with gilteritinib maintenance after alloSCT, driven by benefit in patients with detectable FTL3-ITD MRD

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### Case #2: History

- A 46-year-old man presents with an incidental finding of M-spike 3.1 on SPEP sent for workup of “chronic digestive issues”. He feels generally well with the exception of frequent loose stools
- PMH: IBS, diverticulitis, moderate OSA
- SH: Remote, brief smoking history. Lives with his spouse. Software engineer at Meta.
- FH: No family history of hematologic malignancies.
- Physical exam: Unremarkable

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### Case #2: Labs & Imaging

- CMP: Na 137, Cr 1.10 (baseline), Ca 9.3, total protein 7.5, albumin 4.3
- CBC: WBC 5.4, Hgb 15.0, Plt 215
- Beta 2 microglobulin: 2.96
- SPEP/IFE: M-spike 3.1 (IgG kappa)
- IgG 3276, IgA 50, IgM 26
- UPEP: Negative
- SFLC: Kappa 156.3, lambda 6.6, ratio 23
- Bone marrow biopsy: 25-30% kappa-restricted CD138+ plasma cells.
- Myeloma FISH: t(11;14), del(13q)
- PET/CT unremarkable. Overall, no myeloma-defining events

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### Smoldering myeloma

| Smoldering Myeloma (Asymptomatic)[a,b] | Multiple Myeloma (Symptomatic)[a,c] |
|---|---|
| • Serum monoclonal protein ≥3 g/dL<br>or<br>• Bence-Jones protein ≥500 mg/24 h<br>and/or<br>• Clonal bone marrow plasma cells (BMPCs) 10%–59%<br>and<br>• Absence of myeloma-defining events or amyloidosis | • Clonal BMPCs ≥10% or biopsy-proven bony or extramedullary plasmacytoma<br>and<br>Any one or more of the following myeloma-defining events:<br>• Calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)<br>• Renal insufficiency (creatinine >2 mg/dL) [>177 µmol/L] or creatinine clearance <40 mL/min<br>• Anemia (hemoglobin <10 g/dL or hemoglobin >2 g/dL below the lower limit of normal)<br>• One or more osteolytic bone lesions on skeletal radiography, CT, or FDG-PET/CT<br>• Clonal BMPCs ≥60%<br>• Involved:uninvolved serum FLC ratio (FLCr) ≥100 and involved FLC concentration 10 mg/dL or higher<br>• >1 focal lesions on MRI studies ≥5 mm |

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Case #2: Risk assessment in smoldering myeloma

How would you assess this patient's risk of progression to MM at 2 years?

- CMP: Na 137, Cr 1.10 (baseline), Ca 9.3, total protein 7.5, albumin 4.3
- CBC: WBC 5.4, Hgb 15.0, Plt 215
- Beta 2 microglobulin: 2.96
- SPEP/IFE: M-spike 3.1 (IgG kappa)
- IgG 3276, IgA 50, IgM 26
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A. Low-risk; 6.2% progression at 2 years

17%

B. Intermediate-risk; 17.9% progression at 2 years

34%

C. High-risk; 44.2% progression at 2 years

48%

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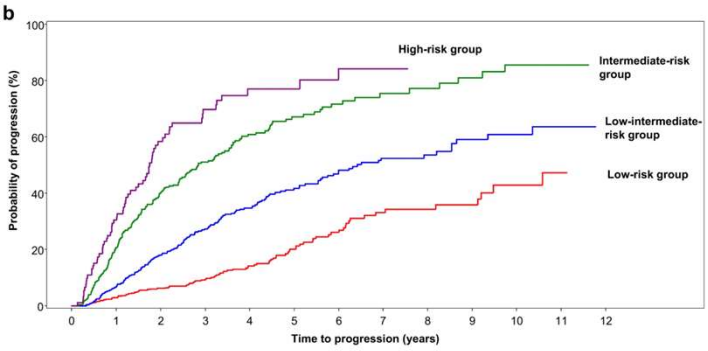
Assessing Risk of Progression in SMM

2/20/20 Risk Model:

- Serum M-protein >2 g/dL
- Free light chain ratio >20
- Marrow plasma cell infiltration >20%




| Risk Stratification groups | Number of risk factors | Hazard Ratio (95% CI) | Risk of progression (2 years) | # of patients |
|---|---|---|---|---|
| Low-Risk | 0 | Reference | 6.2% | 522 (38.3%) |
| Intermediate | 1 | 2.99 (1.97 – 4.54) | 17.9% | 445 (32.7%) |
| High | 2-3 | 9.02 (6.15 – 13.2) | 44.2% | 396 (29.1%) |

Mateos et al. *Blood Cancer J* 2020

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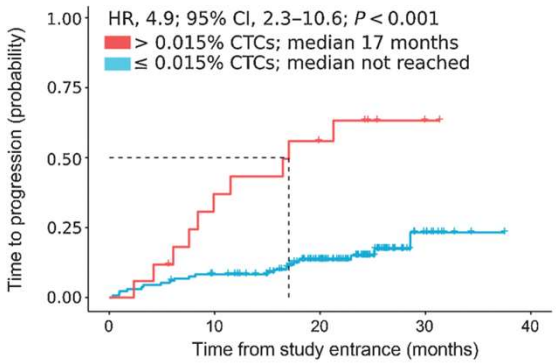
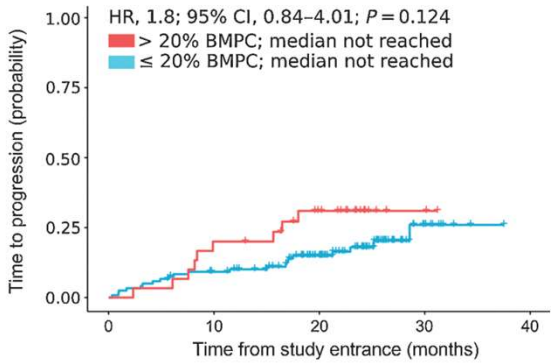
### Circulating Tumor Cells Predict SMM Progression Better than Bone Marrow Plasma Cells

- In our patient, peripheral blood flow cytometry shows 0.024% (1.8 cells/microliter) circulating tumor cells




Termini et al. *Clin Cancer Res* 2022

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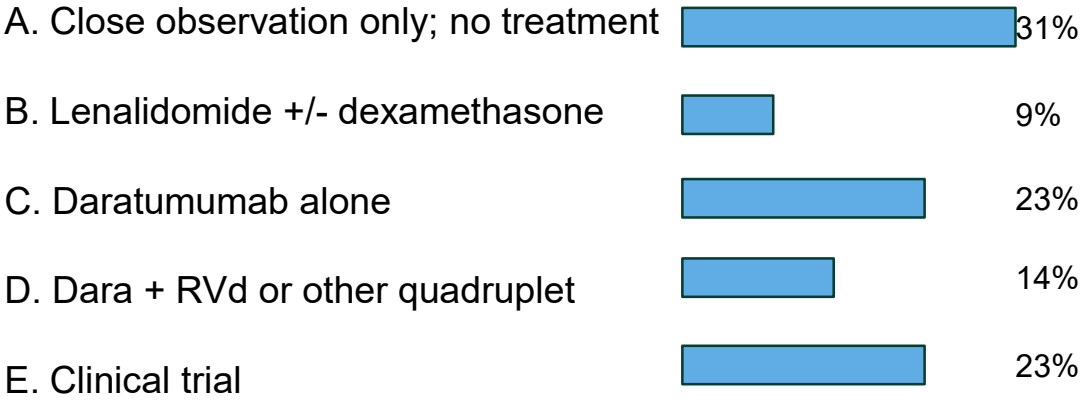
### Case #2: Management of high-risk smoldering myeloma

How would you approach treatment of this patient with high-risk smoldering myeloma wi
>0.015% CTCs?

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## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #2: Management of high-risk smoldering myeloma

**Topics of debate in SMM therapy**

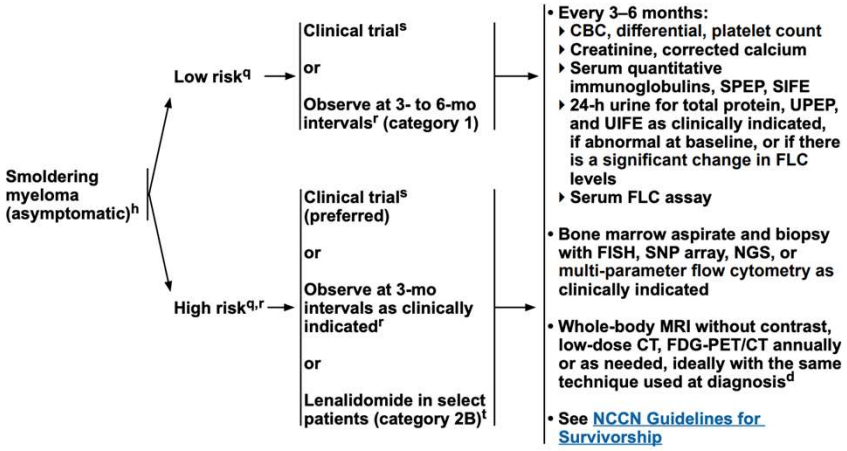
| Topic |
|---|
| What is the ideal time to start therapy? |
| Which patient populations should be treated? |
| Which therapies would best benefit patients with SMM? Cure vs control? |
| How long should patients with SMM be treated? |
| What are the most appropriate end points in clinical trials for SMM? |





## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### How should we approach high-risk smoldering myeloma?

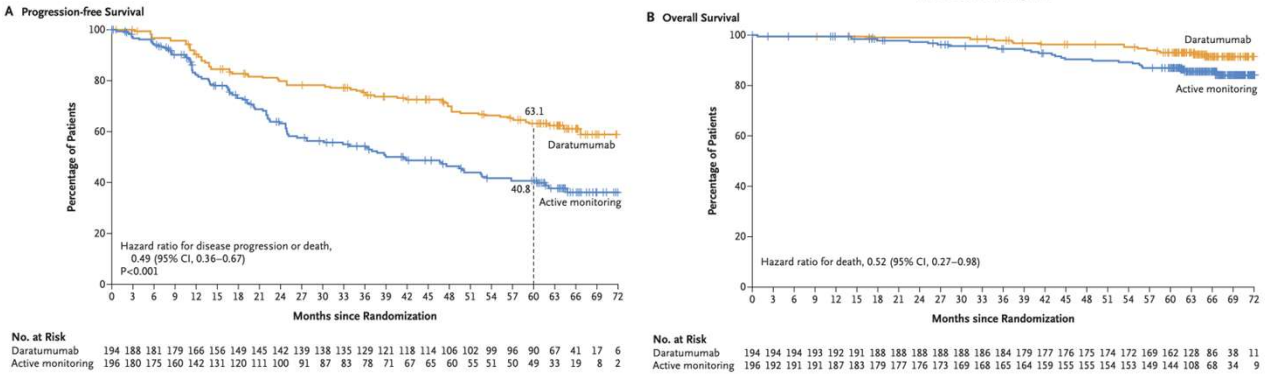


## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Treatment of High-Risk SMM: AQUILA

**Daratumumab or Active Monitoring for High-Risk Smoldering Multiple Myeloma**

M.A. Dimopoulos, P.M. Voorhees, F. Schjesvold, Y.C. Cohen, V. Hungria, I. Sandhu, J. Lindsay, R.I. Baker, K. Suzuki, H. Kosugi, M.-D. Levin, M. Beksac, K. Stockerl-Goldstein, A. Oriol, G. Mikala, G. Garate, K. Theunissen, I. Spicka, A.K. Mylin, S. Bringhen, K. Uttervall, B. Pula, E. Medvedova, A.J. Cowan, P. Moreau, M.-V. Mateos, H. Goldschmidt, T. Ahmadi, L. Sha, A. Cortoos, E.G. Katz, E. Rousseau, L. Li, R.M. Dennis, R. Carson, and S.V. Rajkumar, for the AQUILA Investigators*




Dimopoulos et al. *NEJM* 2024





## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Treatment of High-Risk SMM: AQUILA

**Daratumumab or Active Monitoring for High-Risk Smoldering Multiple Myeloma**

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**Table 3. Summary of Adverse Events (Safety Population).**

| Event | Daratumumab (N=193) | Active Monitoring (N=196) |
|---|---|---|
| | *number of patients (percent)* | |
| Any adverse event | 187 (96.9) | 162 (82.7) |
| Most common adverse events* | | |
| Fatigue | 66 (34.2) | 26 (13.3) |
| Upper respiratory tract infection | 58 (30.1) | 15 (7.7) |
| Diarrhea | 53 (27.5) | 10 (5.1) |
| Arthralgia | 52 (26.9) | 35 (17.9) |
| Nasopharyngitis | 49 (25.4) | 23 (11.7) |
| Back pain | 46 (23.8) | 38 (19.4) |
| Insomnia | 43 (22.3) | 5 (2.6) |
| Grade 3 or 4 adverse event | 78 (40.4) | 59 (30.1) |
| Most common grade 3 or 4 adverse event: hypertension | 11 (5.7) | 9 (4.6) |
| Serious adverse event | 56 (29.0) | 38 (19.4) |
| Most common serious adverse event: pneumonia | 7 (3.6) | 1 (0.5) |
| Adverse event that led to death† | 2 (1.0) | 4 (2.0) |
| Second primary cancer | 18 (9.3) | 20 (10.2) |

Dimopoulos et al. *NEJM* 2024

## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #2: Continued

- Over the next several months, patient's hemoglobin dropped by >2 g/dL and he thus met criteria for overt multiple myeloma. He was treated with Dara-RVd x 4 cycles and achieved a PR
- He proceeded to an autologous stem cell transplant with melphalan 200 mg/m$^2$ conditioning.
- ClonoSeq MRD sent from bone marrow at Day 80 demonstrates 2,199 residual clonal cells per million

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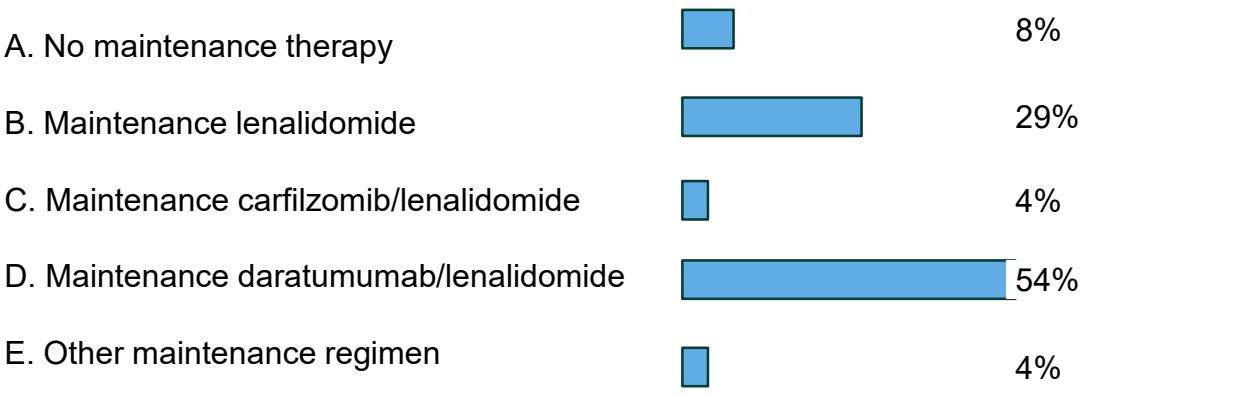
## 24th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #2: Post-transplant maintenance therapy

What next?

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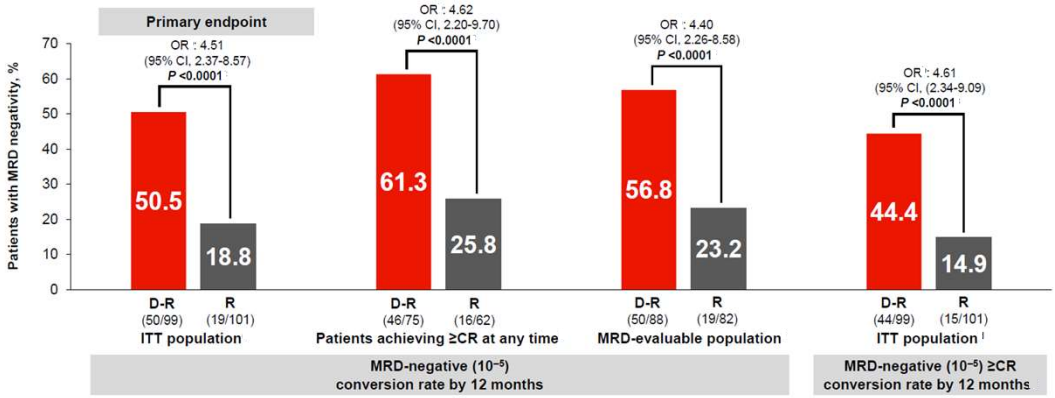
## Maintenance R vs D-R: AURIGA

MRD-Negative ($10^{-5}$) Conversion Rates From Baseline to 12 Months of Maintenance Treatment




- MRD-negative ($10^{-5}$) conversion rates by 12 months were improved with Dara-R vs R across all clinically relevant subgroups

Badros et al. *Blood* 2025







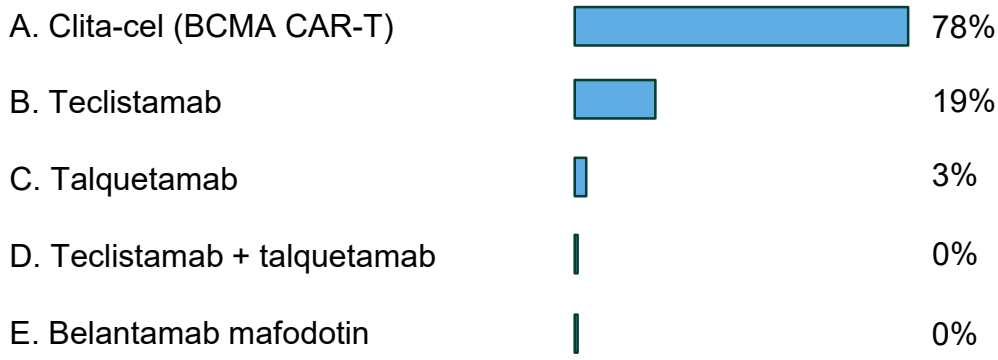
## Case #2: Continued

- The patient is started on maintenance therapy with lenalidomide + daratumumab. After 8 months, he experiences biochemical progression, demonstrating refractoriness to lenalidomide
- He is started on carfilzomib + pomalidomide + dexamethasone (KPd) and after initial partial response he experiences progression after 6 months, consistent with triple-class refractory disease

## 24th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #2: Relapsed/refractory multiple myeloma

What is the optimal next step in therapy?

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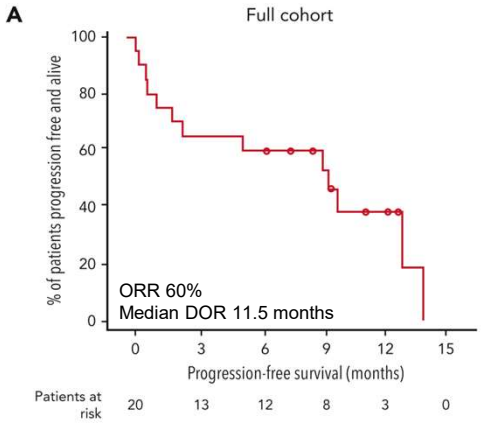
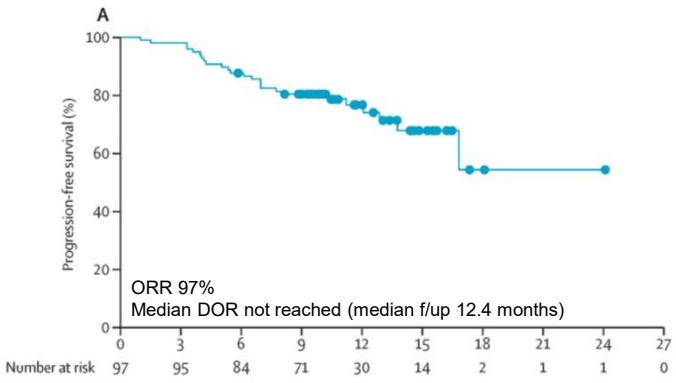
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Sequencing of CAR-T and bispecific antibodies in R/R MM: CAR-T after other BCMA immunotherapy




Berdeja et al. *Lancet* 2021; Cohen et al. *Blood* 2023

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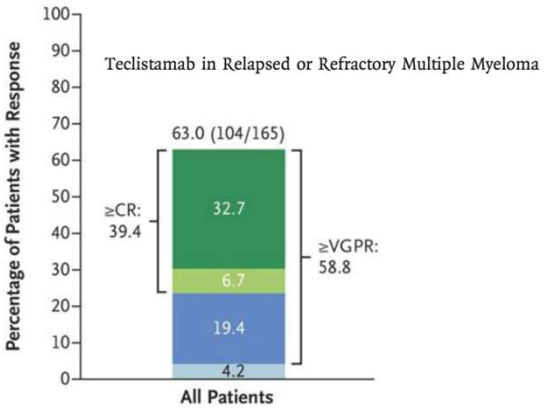
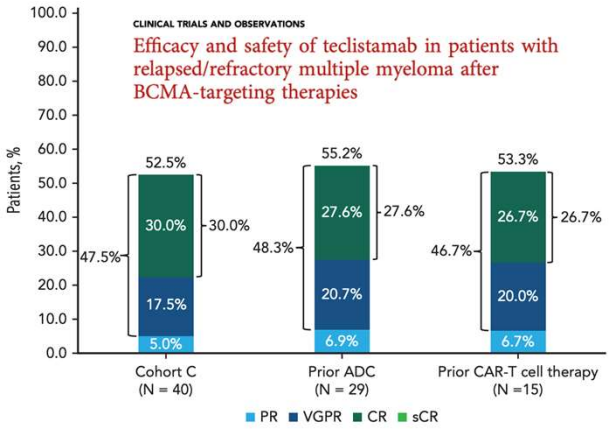
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Sequencing of CAR-T and bispecific antibodies in R/R MM: BCMA immunotherapy after CAR-T



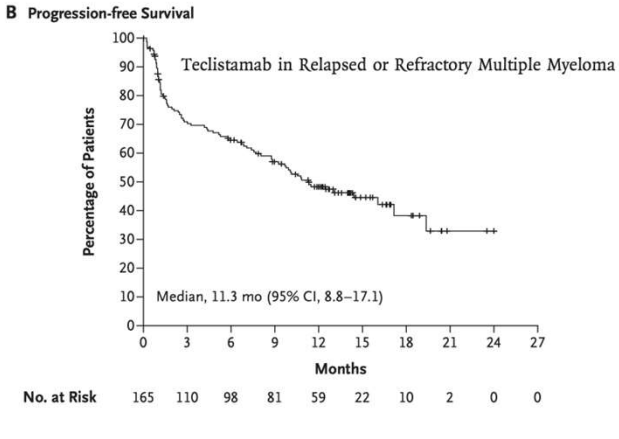

Moreau et al. *NEJM* 2022; Touzeau et al. *Blood* 2024

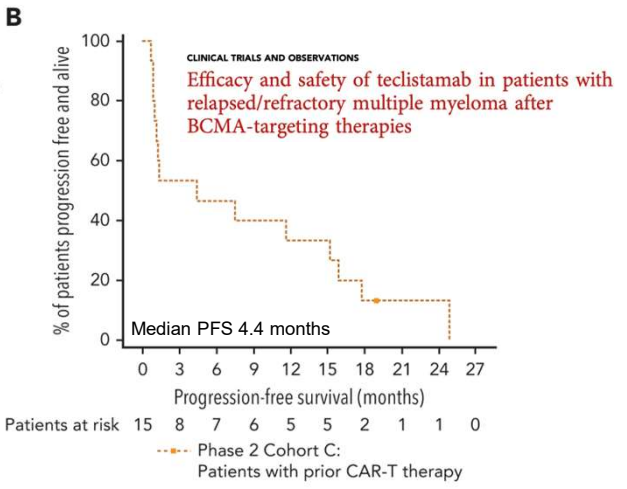




## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Sequencing of CAR-T and bispecific antibodies in R/R MM: BCMA immunotherapy after CAR-T




Touzeau et al. *Blood* 2024

## IMWG Immunotherapy Committee Recommendation on Sequencing T-cell Redirecting Therapy (TCRT) – January 2025

1. 2-week washout of PIs, IMiDs, mAbs, and corticosteroids before apheresis and before first TCRT dose
2. Avoid collection of cells for CART in patients currently receiving a T-cell engager (TCE); minimum of 4-week washout
3. Avoid high-dose alkylators and bendamustine in patients for whom next therapy is likely to be TCRT
4. Strongly consider bridging therapy after apheresis in patients with high disease burden and/or at risk of morbidity
5. BCMA-targeted TCRT should be used before a BCMA-targeted ADC, assuming equal access
6. BCMA CART therapy should be used before TCE, assuming equal access
7. In patients with rapidly progressing disease who may experience morbidity during CAR-T manufacturing, proceed with off-the-shelf TCE
8. Both BCMA-targeted and GPRC5D-targeted immunotherapy are safe and active inpatients with prior BCMA-targeted CART therapy, but responses to BCMA-targeting therapies are likely less frequent and durable
9. Recommend therapy with a different mechanism of action or targeting a different antigen for patients progressing while receiving or shortly after receiving BCMA-targeting TCE

Costa et al. *Leukemia* 2025



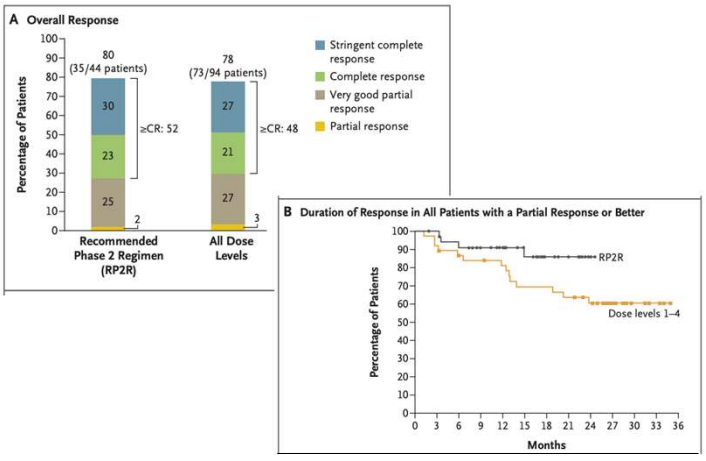




## RedirecTT-1

**Table 2. Hematologic and Nonhematologic Adverse Events, According to Grade, in 94 Patients Who Received Talquetamab plus Teclistamab at Any Dose Level.***

| Event | Any Grade | Grade 3 or 4 |
|---|---|---|
| | *number of patients (percent)* | |
| Any adverse event | 94 (100) | 90 (96) |
| Hematologic event | | |
| Neutropenia | 69 (73) | 64 (68) |
| Anemia | 53 (56) | 36 (38) |
| Thrombocytopenia | 40 (43) | 28 (30) |
| Nonhematologic event | | |
| Cytokine release syndrome | 74 (79) | 2 (2) |
| Taste changes† | 61 (65) | NA |
| Nonrash skin adverse event‡ | 57 (61) | 0 |
| Nail-related adverse event§ | 49 (52) | 0 |
| Pyrexia¶ | 48 (51) | 2 (2) |
| Diarrhea | 45 (48) | 3 (3) |
| Cough | 42 (45) | 1 (1) |
| Dry mouth | 40 (43) | 0 |
| Covid-19 | 38 (40) | 17 (18) |
| Rash adverse event‖ | 37 (39) | 1 (1) |
| Pneumonia | 34 (36) | 19 (20) |
| Weight decrease | 32 (34) | 5 (5) |
| Fatigue | 26 (28) | 8 (9) |




Cohen et al. *NEJM* 2025

## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #2: Key Points

- SOC for high-risk smoldering myeloma remains observation or enrollment on a clinical trial.
- AQUILA trial found a significant OS benefit for daratumumab (not yet FDA approved)
- AURIGA study showed that addition of daratumumab to lenalidomide post-transplant maintenance improved rates of MRD negativity (50.5% vs 18.8%) and PFS
- Sequencing, especially with multiple therapies targeting BCMA, is a major issue
- BCMA-targeted T-cell responses decline with successive lines of therapy. Consensus recommendations suggest using CAR T-cells first.

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## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #3: History

- A 58-year-old woman who is an avid marathon runner presents with progressive exercise intolerance and exertional dyspnea over the past six months
- PMH: Migraines; otherwise healthy. Hysterectomy 10 years ago
- SH: Lives in a single-family home with her spouse and adult daughter. She is a practicing radiologist. No history of alcohol or tobacco use. Runs 5-6 miles most days
- FH: Daughter with NF1/neurofibromatosis. No family history of hematologic malignancies
- Physical exam: Unremarkable

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## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #3: Labs and Bone Marrow Biopsy

- CBC (10 years ago): WBC 7.1 (ANC 4.4), Hgb 14.7, Plt 206
- CBC (4 years ago): WBC 4.1 (ANC 1.4), Hgb 13.6, Plt 172
- CBC (Now): WBC 2.5 (ANC 0.81), Hgb 11.6, Plt 148

- Bone marrow biopsy: hypercellular (70%), with trilineage hematopoiesis, blasts <5%. No dysplastic features that would suggest MDS.
- Bone marrow flow cytometry: 1.6% blasts, no immunophenotypically abnormal cell population
- Cytogenetics: 46-47,XY,+8,del(20)(q11.2q13.1)[19] / 46,XY[1]
- MDS FISH: positive for gain of 8 (73.0%), positive for deletion of 20q (84.5%)
- Myeloid mutation panel:
  - IDH1,p.(Arg140Gln), VAF 3.8%,Tier 1
  - TET2,p.(Arg1404*), VAF 2.6%,Tier 1
  - DNMT3A,p.(Pro2Leu), VAF 91.6%,Tier 2

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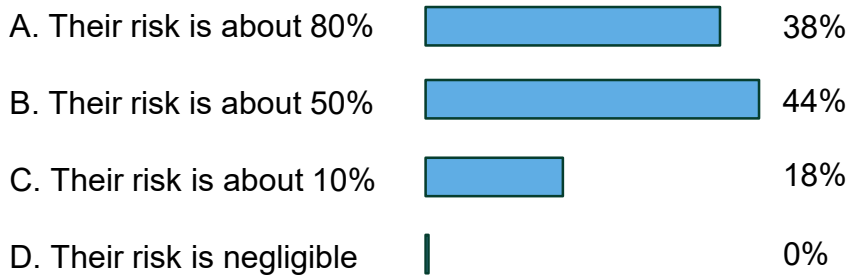
## 24th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #3: Risk assessment in CHIP/CCUS

How would you counsel this patient about their risk of developing a myeloid neoplasm within the next 10 years?

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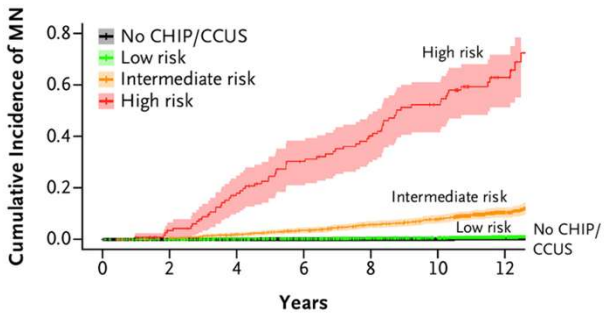
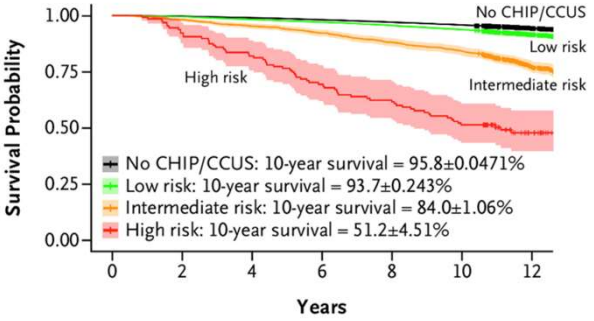
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Prognostic framework for CHIP/CCUS




Weeks et al. *NEJM Evidence* 2023



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## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Prognostic framework for CHIP/CCUS

**Table 2. CHRS Values.***

| Prognostic Variable | 0.5 | 1 | 1.5 | 2 | 2.5 |
|---|---|---|---|---|---|
| Single *DNMT3A* | Present | Absent | | | |
| High-risk mutation | | Absent | | | Present |
| Mutation number | | 1 | | ≥2 | |
| Variant allele fraction | | <0.2 | | ≥0.2 | |
| Red cell distribution width | | <15 | | | ≥15 |
| Mean corpuscular volume | | <100 | | | ≥100 |
| Cytopenia | | CHIP | CCUS | | |
| Age (yr) | | <65 | ≥65 | | |

Our patient: 1 for single DNMT3A (other mutations present), 2.5 for high-risk mutation (IDH1), 2 for ≥ mutations, 2 for VAF ≥ 0.2, 2.5 for RDW ≥15 (hers is 18.1), 2.5 for MCV ≥100 (hers is 101), 1.5 for CCUS, 1 for age <65 = 15 → High risk

Weeks et al. *NEJM Evidence* 2023



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## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #3: History continued

- She is managed expectantly with CBC q3months and counseled that her risk of developing an overt myeloid neoplasm in the next 10 years is at least 50%.
- Over the next two years, her anemia continues to deepen with nadir 8.1 and she becomes increasingly symptomatic. Repeat bone marrow biopsy shows:
  - CBC: WBC 3.4 (ANC 1.8), Hgb 8.1, Plt 130
  - Morphology: hypercellular (60%), with dyserythropoiesis and <5% blasts by morphology. Unusual morphology in megakaryocytes with large hyperchromatic forms.
  - Flow: 1.7% abnormal myeloid blast population
  - Cytogenetics: 47,XY,+8,del(20)(q11.2q13.1)[19] / 46,XY[1]
  - MDS FISH: positive for gain of 8 (60.0%), positive for deletion of 20q (63.5%)
  - Myeloid mutation panel: mutations in TET2, IDH1, DNMT3A (unchanged from prior)
- IPSS-R score is 3 (2 for intermediate-risk cytogenetics, 1 for anemia), IPSS-M score is -0.34 (moderate low)
- Erythropoietin level is 817 mIU/mL

Bernard et al. *NEJM Evidence* 2022

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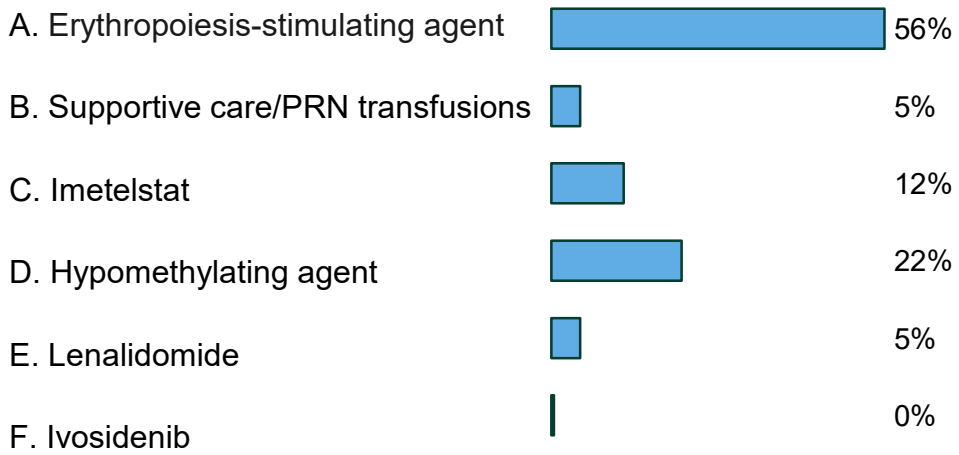
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #3: Management of symptomatic anemia in low-risk MDS

How would you treat this patient's anemia?

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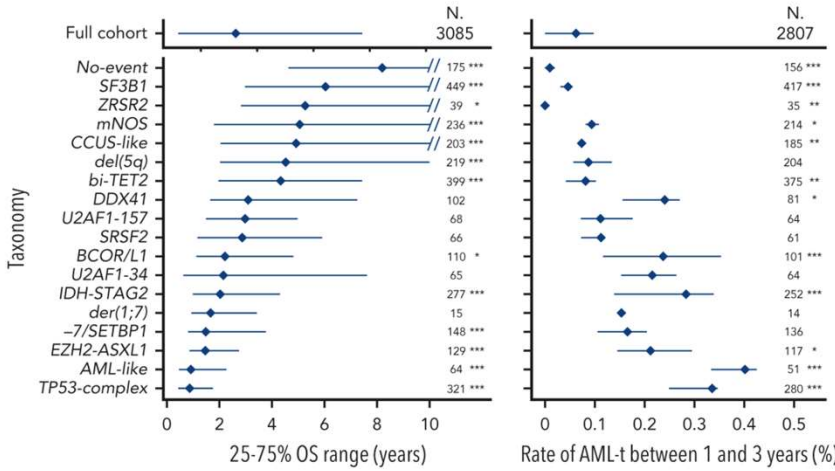
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Toward a molecular taxonomy of myelodysplastic syndromes




Median overall survival ranged from

**0.9 to 8.2 years**

The 2-year rate of transformation to AML ranged from

**0 to 40%**

Bernard et al. *Blood* 2024



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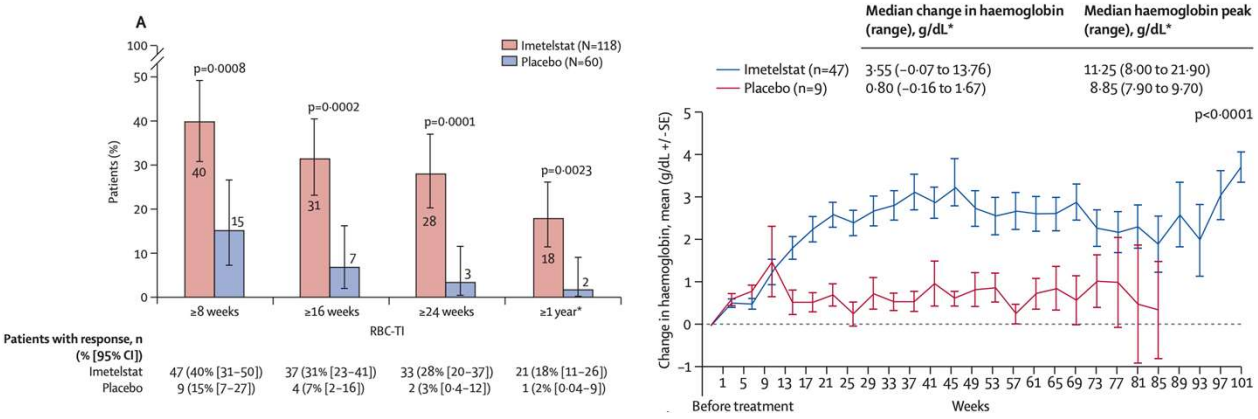
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Imetelstat in low-risk MDS (IMerge)




Platzbecker et al. *Lancet* 2024



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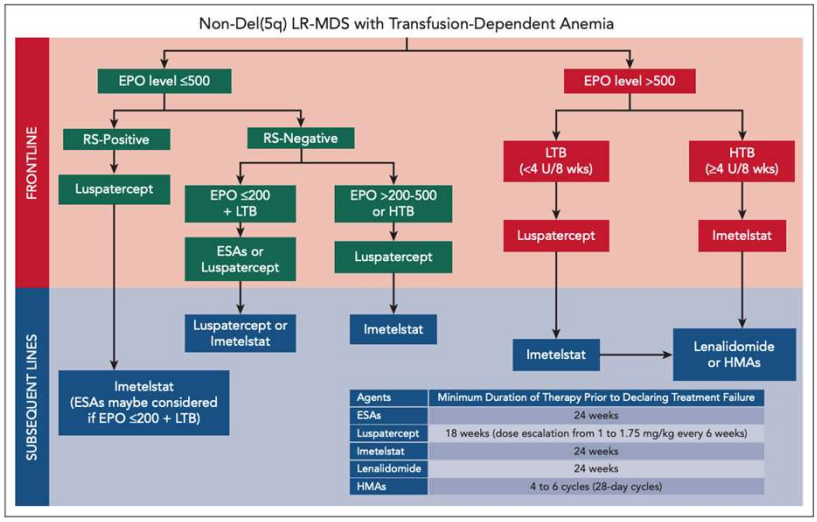
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach




Abaza and DeZern. *Blood* 2025

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## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #3: History continued

- She is offered treatment with azacitidine but prefers a non-chemotherapy approach so is prescribed imetelstat. Her hemoglobin improves to the 10-11 range for about 12 months before declining again
- She undergoes repeat bone marrow biopsy which is now consistent with higher-risk MDS with 7% blasts and new mutations in *RUNX1* and *U2AF1*
- Preparations are made for the patient to undergo allogeneic hematopoietic stem cell transplant

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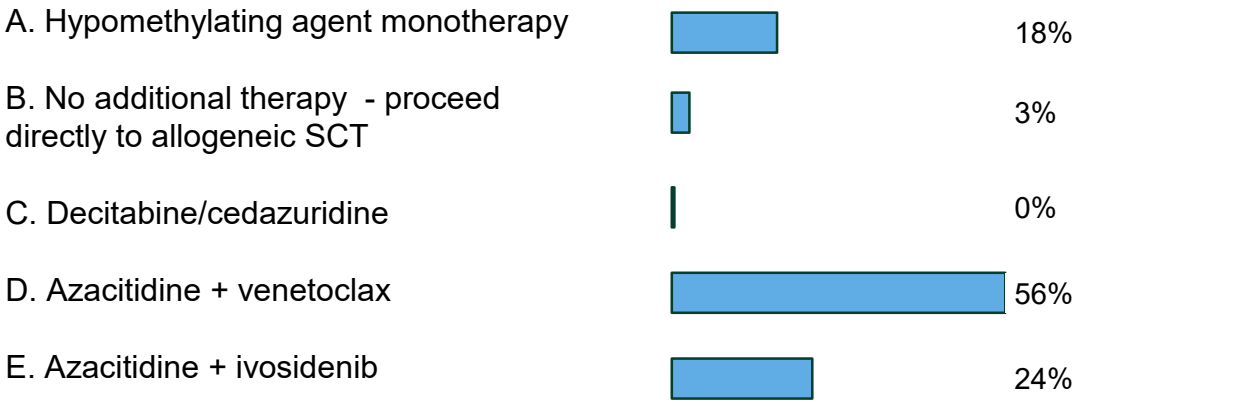
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #3: Management of symptomatic anemia in low-risk MDS

What would you do next, prior to transplant?

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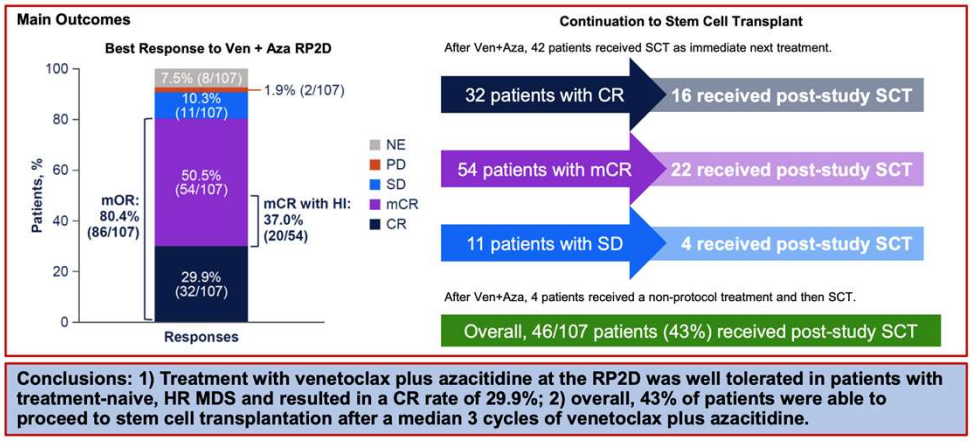
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Azacitidine + venetoclax for treatment-naïve high-risk MDS




**Conclusions: 1) Treatment with venetoclax plus azacitidine at the RP2D was well tolerated in patients with treatment-naive, HR MDS and resulted in a CR rate of 29.9%; 2) overall, 43% of patients were able to proceed to stem cell transplantation after a median 3 cycles of venetoclax plus azacitidine.**

*"The median OS of 26 months and a CR duration of 16.6 months appear more favorable than the historical outcomes observed with azacitidine monotherapy, including mOS of 24.5 months in the AZA-001 study and 13-19 months in recent, randomized studies of HR MDS"*

Garcia et al. *Blood* 2024

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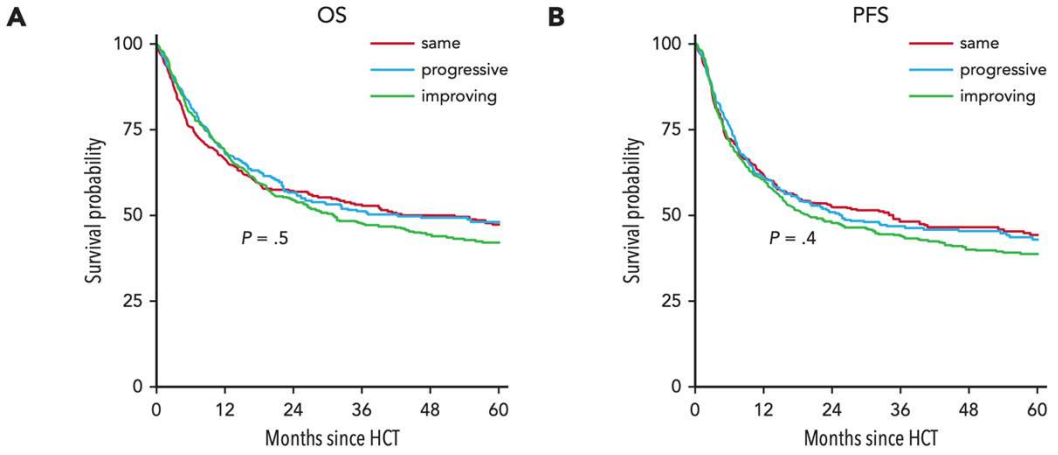
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### How important is IPSS-R downstaging prior to transplant?




Scheid et al. *Blood* 2024



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## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #3: Key Points

- Clonal hematopoiesis risk score can help guide prognosis and monitoring for CHIP/CCUS
- Classification is moving away from morphology/blast percentage and toward molecular classification
- Imetelstat is a new option for low-risk MDS
- Aza + VEN is safe and effective (based on Ph2b data) with Ph3 data pending
- Role of cytoreduction prior to allo-HCT is unclear. A prospective trial of upfront allo-HCT in higher-risk MDS patients with <10% blasts is ongoing (NCT04184505)



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## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #4: History

- A 61-year-old man presents with progressive fatigue, exercise intolerance, drenching night sweats, and palpable cervical lymphadenopathy
- PMH: Ulcerative colitis s/p colectomy; gout
- SH: Lives alone in a condo. Works as a city planner. Married with two adult children. Social alcohol use, no smoking history.
- FH: No family history of hematologic malignancies
- Physical exam: ECOG 1. Cervical, supraclavicular, and axillary adenopathy with several palpable nodes 1-3 cm in size. Spleen tip palpable 4 cm below the costal margin. No pallor, petechiae or ecchymosis.
- Labs:
  - CBC: WBC 78 (81% lymphocytes), Hgb 10.3, Plt 95
  - CMP unremarkable
  - LDH 240
  - Peripheral blood flow cytometry revealed a CD5, CD19, CD23 positive kappa-restricted B cell population
  - CLL FISH : del(11q22.3), +12, del(13q14.3); negative for t(11;14) and del(17p)
  - IGHV unmutated
  - NGS: KMT2D mutation

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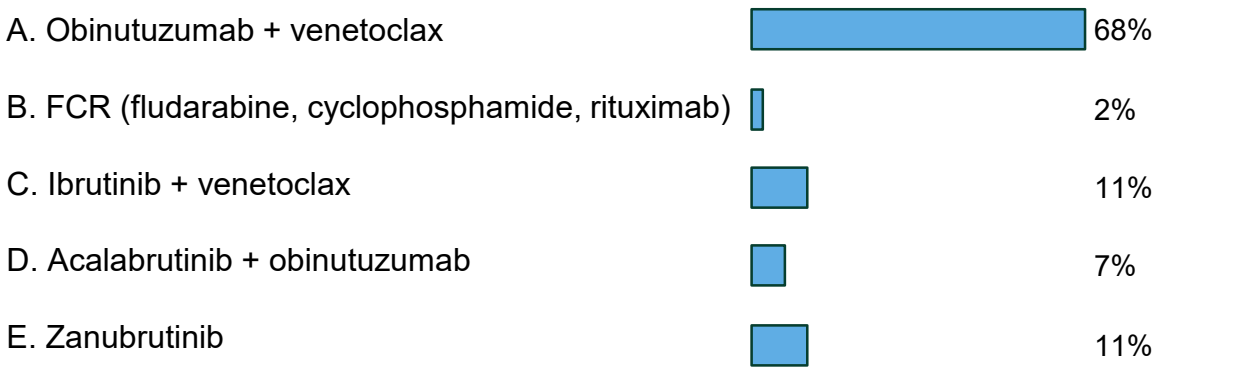
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #4: First-line management of CLL

What would you choose as initial treatment for this patient with treatment-naïve CLL, IGHV unmutated, with intact 17p/TP53?

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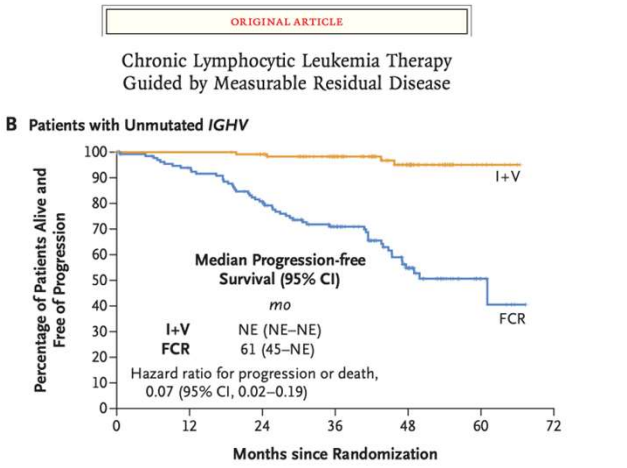
## FLAIR: MRD-Guided Therapy for Untreated CLL

- Phase 3 randomized trial comparing FCR to ibrutinib + venetoclax
- Duration of ibrutinib + venetoclax was double the time taken to achieve undetectable MRD in blood/bone marrow
- Notably, MRD was assessed by flow cytometry at a sensitivity of $10^{-4}$, not immunoglobulin gene sequencing (ClonoSeq), and was defined as 3 consecutive negative results at 3 month intervals
- At 3 years, 58% of patients in the I+V group had stopped therapy due to undetectable MRD




Munir et al. *NEJM* 2024







## AMPLIFY: Fixed-Duration Acalabrutinib + Venetoclax +/- Obinutuzumab in ND CLL

- Interim analysis presented at ASH 2024
- Patients randomized 1:1:1 to receive acalabrutinib-venetoclax (A+V), acalabrutinib-venetoclax-obinutuzumab (AVO), or investigator's choice of chemotherapy (FCR or BR)
- A+V and AVO therapy were time-limited to 14 x 28-day cycles
- Improved PFS and OS with A+V versus FCR/BR
- Differences between A+V and AVO were not statistically significant
- A+V is the first all-oral, fixed-duration combination likely to be approved for CLL in the United States

| | A+V | AVO | FCR/BR |
|---|---|---|---|
| 3 Year Progression Free Survival (PFS) | 76% | 83% | 66% |
| Overall Response Rate (ORR) | 93% | 93% | 75% |
| COVID-19 Deaths | 10 | 25 | 21 |
| Total Deaths | 18 | 37 | 42 |

Brown et al. ASH 2024

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### Case #4: History continued

- The patient prefers a fixed-duration regimen and so via shared decision-making elects to begin treatment with obinutuzumab + venetoclax, which he tolerates well
- At end of treatment, he achieves MRD negativity in the peripheral blood by ClonoSeq
- About 3 years later, he presents with headaches, cognitive changes, gait instability, and frequent falls
- MRI brain is unremarkable. Lumbar puncture is performed. Cell count with 350 WBC, 98% lymphocytes. Cytology demonstrates a “monotonous population of small lymphoid cells with scant cytoplasm and round nuclei with slightly irregular nuclear contours. No significant population of large lymphoid cells is seen.” Flow cytometry demonstrates a CD5+, CD19+ kappa-restricted lymphoproliferative disorder
- PB flow cytometry was negative for CLL. Subsequent bone marrow biopsy was unremarkable with no evidence of involvement by CLL by flow. BM MRD remained negative
- He is diagnosed with an isolated CNS relapse of CLL

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## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #4: Management of CLL with leptomeningeal involvement

What would you choose for the next line of treatment?

| | |
|---|---|
| A. High dose methotrexate | 0% |
| B. High-dose methotrexate followed by BTK inhibitor maintenance | 0% |
| C. Intrathecal methotrexate | 0% |
| D. Intrathecal methotrexate followed by BTK inhibitor maintenance | 0% |
| E. FCR | 0% |

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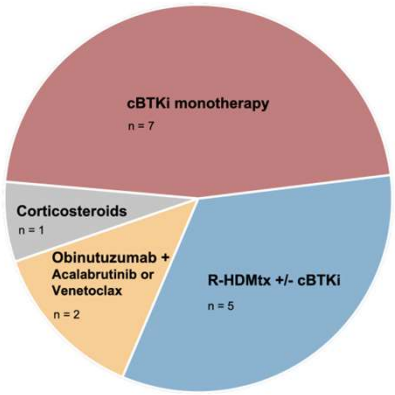
### CNS Involvement of CLL: A Rare Complication




- DFC EHA24: CNS involvement of CLL 2015 – 2023
- N=3580 CLL pts; 16 (0.4%) with CNS involvement
- Time from diagnosis to CNS CLL: 35 months
- Cases were enriched for unmutated IGHV (69%)
- Treatment (left) usually BTK inhibition +/- HD-MTX
- Median OS: 61 months (range 13 – 206)
- Median OS from CNS Dx: 21 months (range 0.3 – 164)

Mikhaleva et al. EHA 2024



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### Case #4: History continued

- The patient was treated with 5 cycles of high-dose methotrexate at 2.5 g/m$^2$ followed by continuous ibrutinib
- He was monitored with serial lumbar punctures and cleared his CNS disease after about 1 year
- He experienced systemic relapse without CNS relapse about 2 years later while still on ibrutinib



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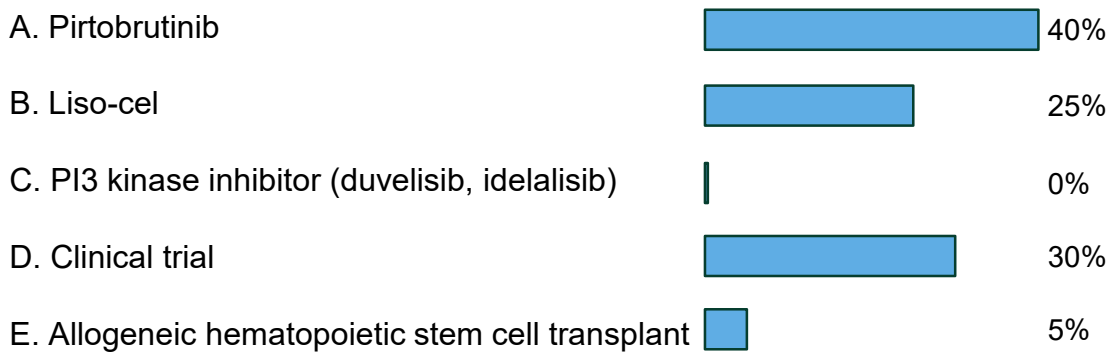
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Case #4: Treatment of double class-exposed CLL

What would you choose for the next line of treatment for this patient refractory to both BTKi and BCL2i?

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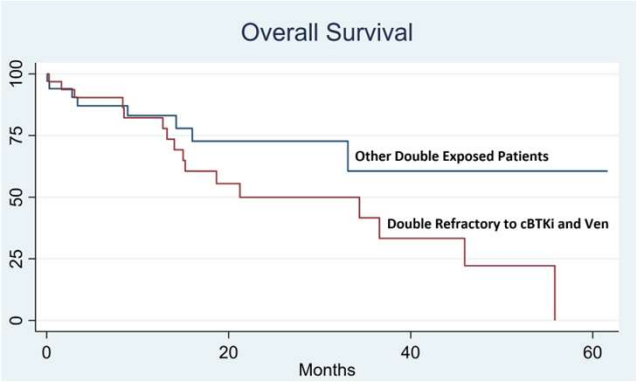
## 25th Multidisciplinary Management of Cancers: A Case-Based Approach

### Outcomes in patients with BTKi/BCL2i refractory CLL

- No clear consensus in DR CLL
- One single-center study reported the next therapy after DR landmark:
  - 34% received a non-covalent BTK inhibitor (pirtobrutinib)
  - 28% received concurrent covalent BTK inhibitor + BCL2 inhibitor
  - 24% received CAR T-cell therapy
  - 10% underwent allogeneic SCT
- Med OS after DR landmark 2.2 years




Yoon et al. ASH 2024; Samples et al. ASH 2023

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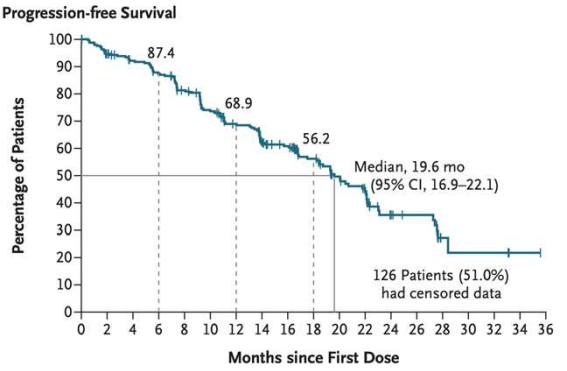
## BRUIN: Pirtobrutinib after failure of covalent BTK inhibitors in R/R CLL

**Table 2. Efficacy of Pirtobrutinib in Patients with CLL or SLL Who Had Previously Received a BTK Inhibitor.***

| Variable | Previous BTK Inhibitor (N=247) | Previous BTK Inhibitor + BCL2 Inhibitor (N=100) |
|---|---|---|
| Overall response — % (95% CI) | | |
| Including complete response, nodular partial response, or partial response | 73.3 (67.3–78.7) | 70.0 (60.0–78.8) |
| Including complete response, nodular partial response, partial response, or partial response with lymphocytosis | 82.2 (76.8–86.7) | 79.0 (69.7–86.5) |
| Best response — no. (%) | | |
| Complete response | 4 (1.6) | 0 |
| Nodular partial response | 1 (0.4) | 0 |
| Partial response | 176 (71.3) | 70 (70.0) |
| Partial response with lymphocytosis | 22 (8.9) | 9 (9.0) |
| Stable disease | 26 (10.5) | 11 (11.0) |
| Progression-free survival | | |
| Median (95% CI) — mo | 19.6 (16.9–22.1) | 16.8 (13.2–18.7) |
| Patients with censored data — no. (%) | 126 (51.0) | 44 (44.0) |
| Median follow-up — mo | 19.4 | 18.2 |




Mato et al. *NEJM* 2023

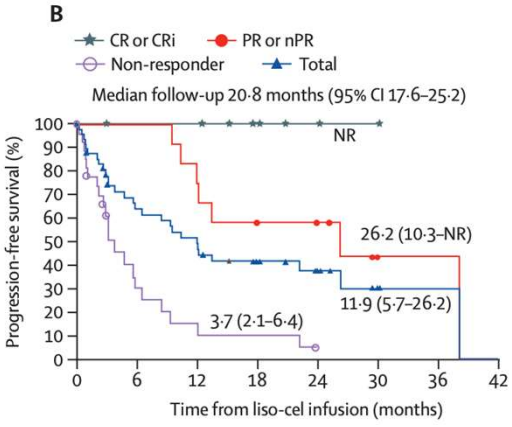




25th Multidisciplinary Management of Cancers: A Case-Based Approach

## TRANSCEND CLL 004: Lisocabtagene maraleucel in R/R CLL/SLL

- Overall high-risk population with 46% TP53 mutation or del(17p); 51% of patients with 5 or more prior lines of therapy
- 18% CR rate by iwCLL criteria, both in overall (n=96) and DR patients (n=53)
- ORR 48% (overall), 43% (DR)
- CRs were highly durable (100% 2-year PFS!)
- Grade 3+ CRS in 9%, Grade 3+ ICANS in 19%. No grade 5 CRS or ICANS
- More work needed to understand determinants of response




Siddiqi et al. *Lancet* 2023

25th Multidisciplinary Management of Cancers: A Case-Based Approach

## Case #4: Key Points

- Based on AMPLIFY acalabrutinib + VEN likely to be approved for treatment-naïve CLL.
- CLL CNS involvement: no prospective studies; experts use BTK inhibitors +/- HD MTX
- We need better therapies for BTK and BCL2 inhibitor (double refractory, DR) patients
- No randomized studies guide approach for DR CLL. In single-arm studies, PFS with pirtobrutinib is 19.6 months and PFS with liso-cel is 11.9 months
- Unknown whether CAR T-cell therapy is curative for a small proportion of patients with highly refractory CLL, and what this means for optimal sequencing

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