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Best of ASCO 2024 - Iowa City

Leukemias

Notable abstracts in leukemia and MDS

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Disclosure

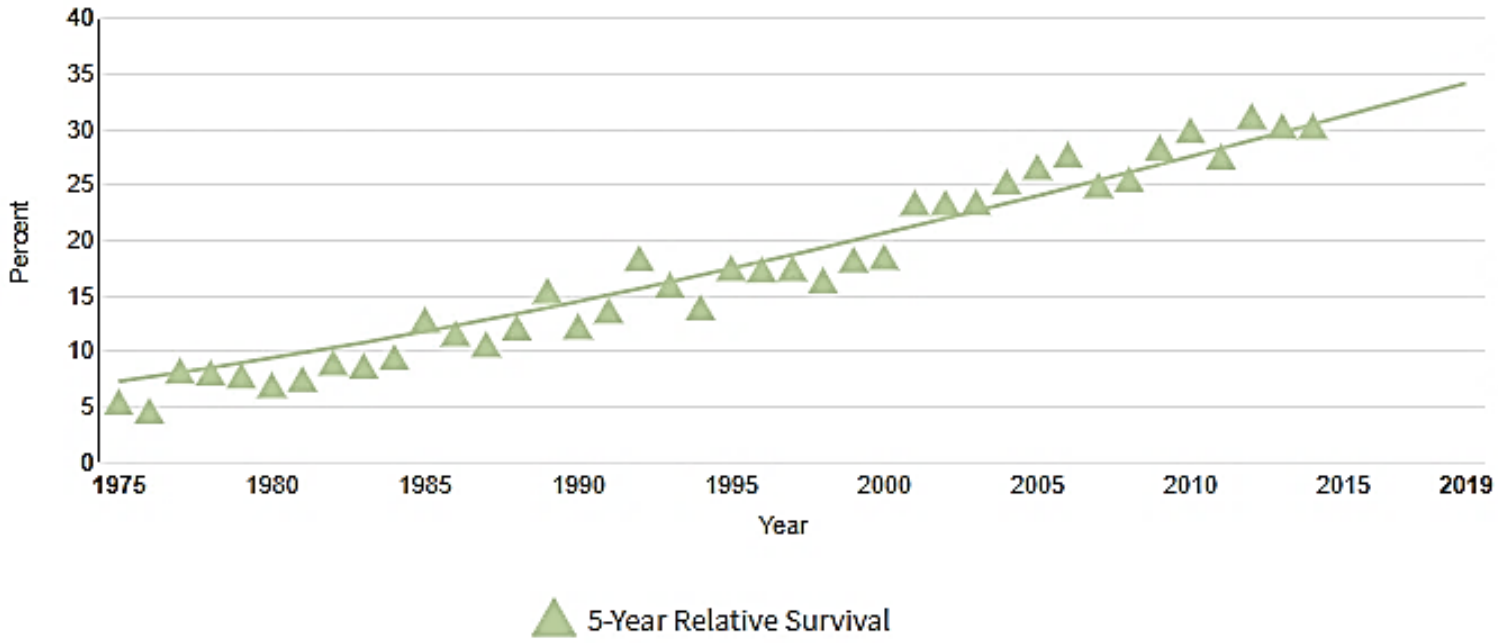
- I received research fundings from Arog Pharmaceuticals, Syros, Novartis, Gilead, Bristol Myers, Kura Oncology, Merck, and Juno Therapeutics for clinical trials running at the University of Iowa.
- I have no other relevant financial relationships with ineligible companies to disclose.
- Use of medications outside their FDA indication will be discussed.

In the histories of all the known cases of leukæmia we only find it once as yet recorded that the patient, after he had been for some time the subject of medical treatment, left the hospital considerably improved in health. In all the other cases the result was death. I do not wish by any means to infer from this that the disease in question is absolutely incurable; I hope on the contrary that for it too remedies will at length be discovered;

Rudolf Virchow, Lectures on Cellular Pathology at Pathological Institute of Berlin, Jan-April 1858

English translation; Source: Google Book,
URL: https://www.google.com/books/edition/_/JUth7ntb0_AC?hl=en

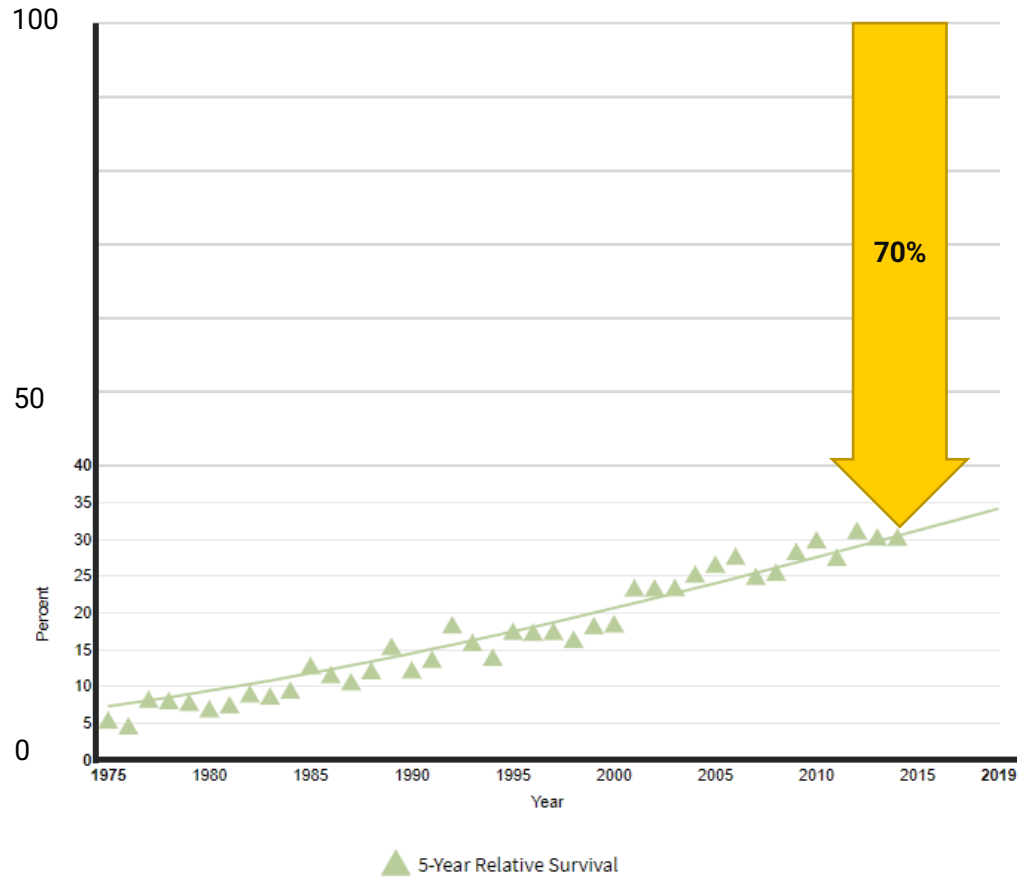
Survival of AML is getting better



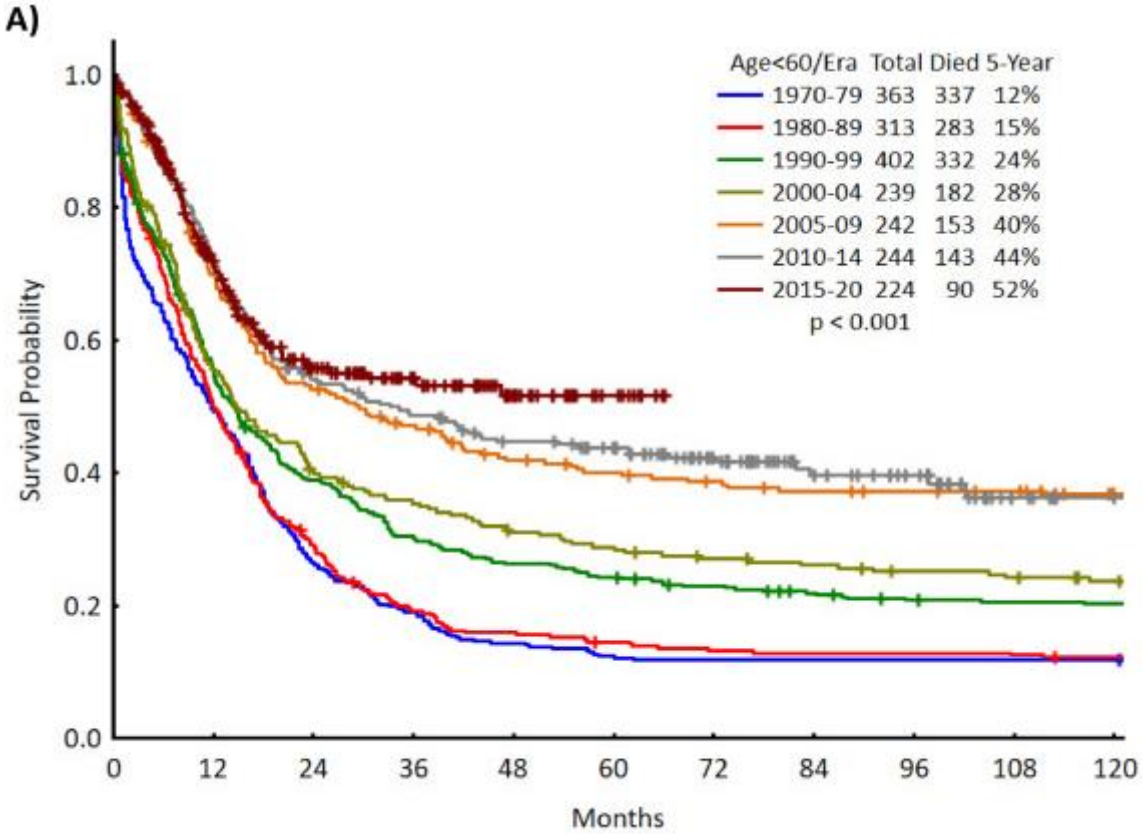
SEER 8 5-Year Relative Survival Percent from 1975–2014, All Races, Both Sexes.
Modeled trend lines were calculated from the underlying rates using the Joinpoint Survival Model Software.

Source: SEER cancer statistics:
https://seer.cancer.gov/statfacts/html/amyl.html

… But still poor.



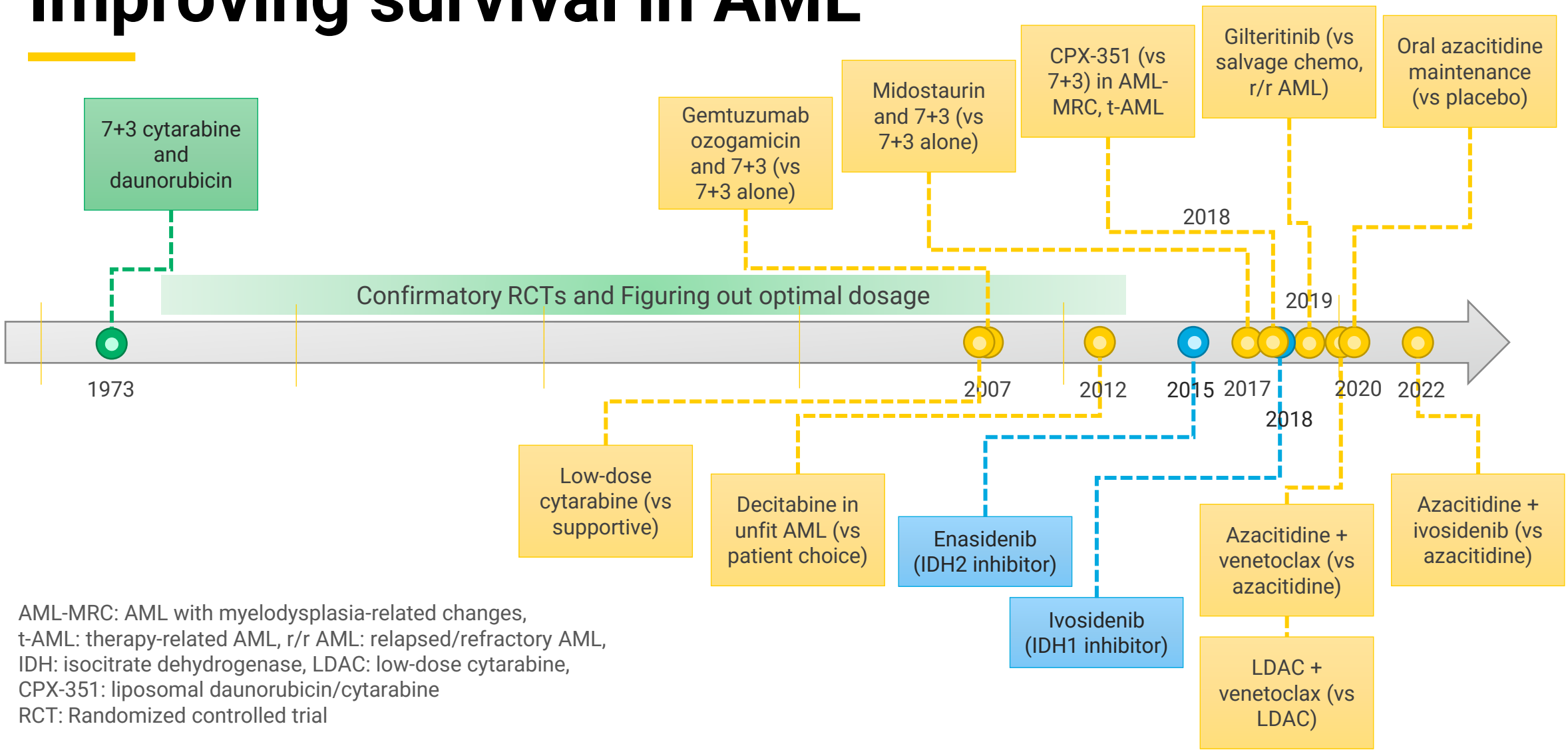
Source: SEER cancer statistics: https://seer.cancer.gov/statfacts/html/amyl.html



MD Anderson AML outcome (overall survival) in patients age < 60 years old

Kantarjian HM, et al. *Clin Lymphoma Myeloma Leuk.* 2021;21(9):580-597.

Improving survival in AML



AML-MRC: AML with myelodysplasia-related changes,
t-AML: therapy-related AML, r/r AML: relapsed/refractory AML,
IDH: isocitrate dehydrogenase, LDAC: low-dose cytarabine,
CPX-351: liposomal daunorubicin/cytarabine
RCT: Randomized controlled trial

Topics

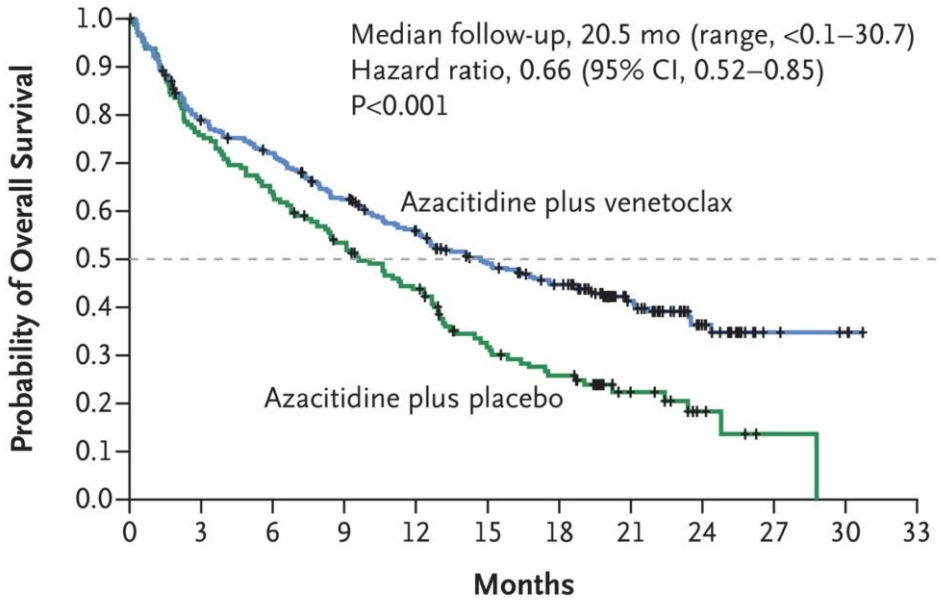
- Acute myeloid leukemia
- Acute lymphoblastic leukemia
- Myelodysplastic syndrome
- Chronic myeloid leukemia

Acute Myeloid Leukemia

- Abstract 6507: abbreviated 7+7 vs HMA/ven in older/unfit AML
- Abstract 6509: ASTREON: oral azacitidine in low/int-risk AML
- Abstract 6516: AML receiving GO receiving allo-HSCT
- Abstract 6511: BP1001/dec/ven in AML (Grb2 antisense oligonucleotide)

Lower intensity regimens in AML

- Prior to 2000, AML patients age > 60-70 were offered only palliative treatments or hospice.
- Birth of lower-intensity regimen in around 2005 onward
  - Low-dose cytarabine (2007, complete response rate 18%)
  - Hypomethylating agents: decitabine and azacitidine
  - **HMA/Venetoclax combination**



DiNardo CD, et al. *N Engl J Med* 2020; 383:617-629

The problem of “lower intensity” regimen

- VIALE-A study (azacitidine/venetoclax) utilized 28 days of venetoclax per 28-day cycle [1].
  - Most leukemia providers use 14-21 days of venetoclax to try to reduce hematologic toxicity and febrile neutropenia [2].
  - Are we able to use shorter duration of venetoclax to achieve similar efficacy and lower toxicity?
- Abstract 6507: A retrospective comparison of abbreviated course “7+7” vs standard hypomethylating agent plus venetoclax doublets in older/unfit patients with newly diagnosed acute myeloid leukemia [Alexandre Bazinet et al.]

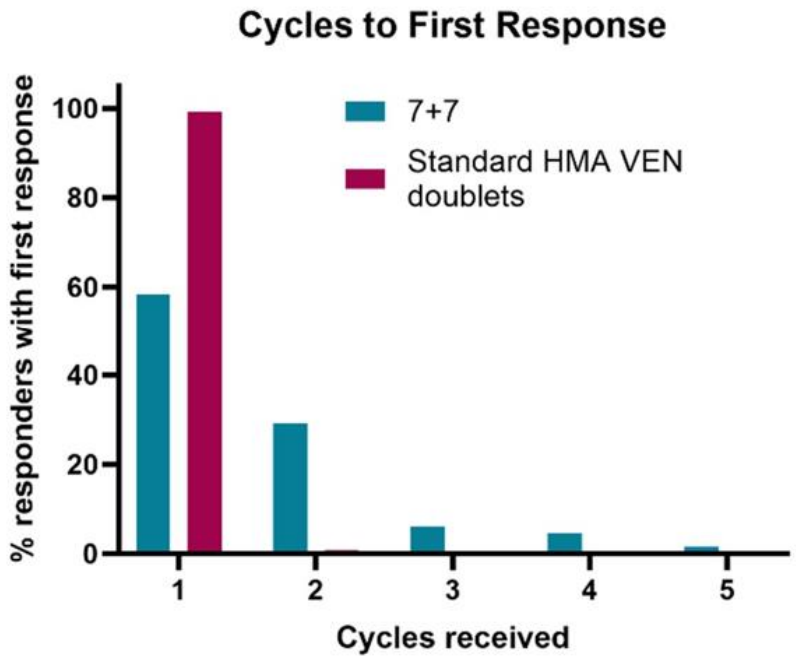
1. DiNardo CD, et al. *N Engl J Med* 2020; 383:617-629
2. Wang ES, Baron J. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):57-66.

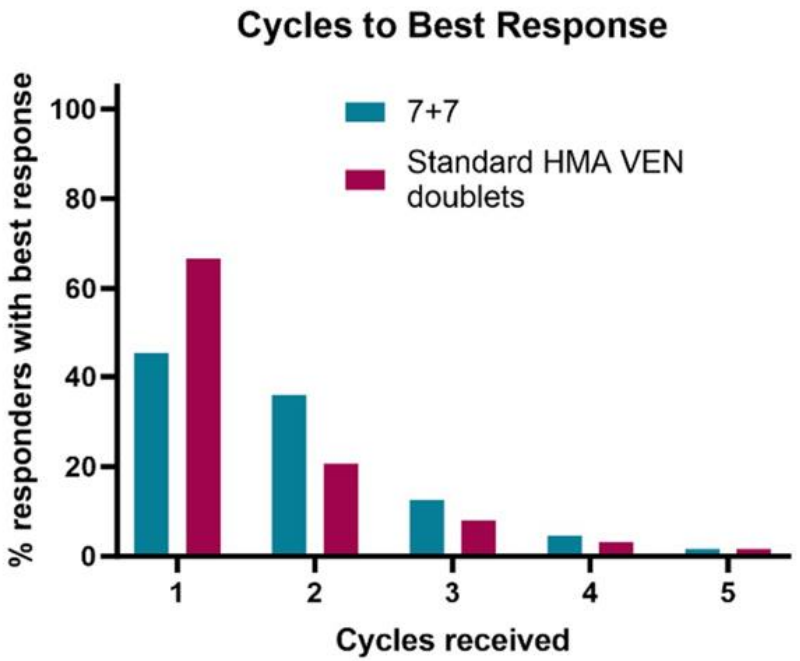
Azacitidine/venetoclax “7+7”

- Abstract 6507:
  - Design: Retrospective chart review
  - Setting: Academic medical centers (7 French centers [n=82 “7+7”] and MDACC [n=166 “others”])
  - Efficacy outcomes: ORR 79%, CRc 72% equal in both arms. “7+7” takes longer to achieve first/best response.
  - Toxicity outcomes: Neutropenic fever 48% vs 55%, platelet transfusion (62% vs 77%)
  - Limitation: Standard and comparator group were treated at different centers. Imbalance of characteristics (FLT3-ITD, allo-HSCT). Retrospective design. Variability of treatment regimens within the MDACC arm.

Alexandre Bazinet et al. JCO 42, 6507-6507(2024).

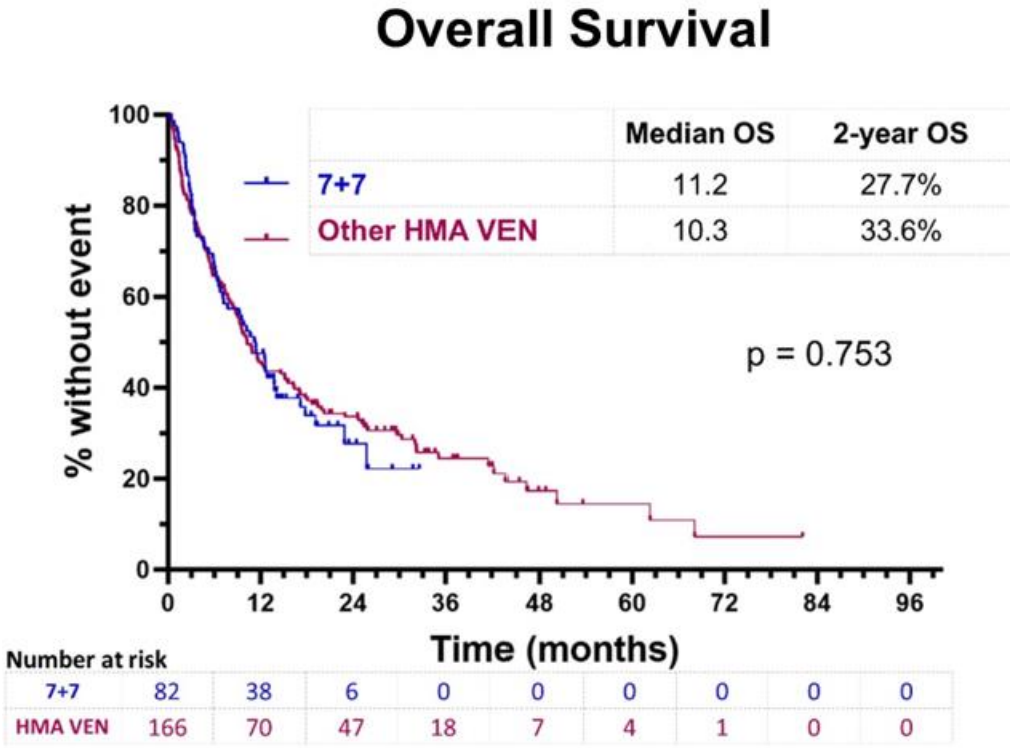
Cycles to first and best response

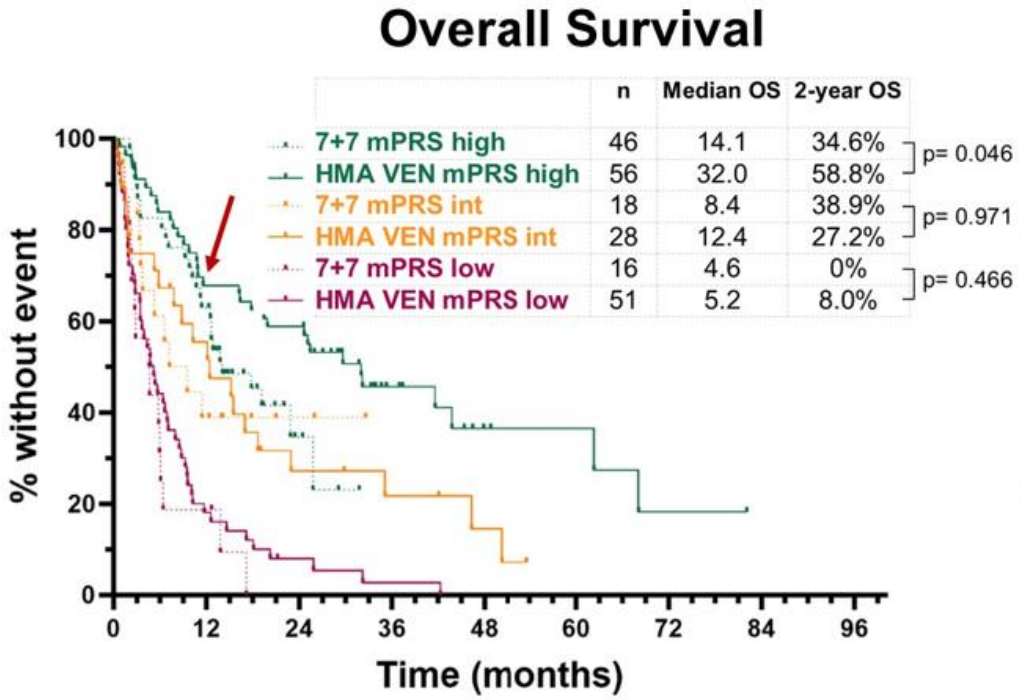




Alexandre Bazinet et al. JCO 42, 6507-6507(2024).

Overall survival





Alexandre Bazinet et al. JCO 42, 6507-6507(2024).

Acute Lymphoblastic Leukemia

- Abstract 6504: FELIX study obecabtagene in r/r B-ALL
- Abstract 6505: CN201 CD3xCD19 bispecific Ab for r/r B-ALL
- Abstract 6515: CD7-CAR-T in r/r T-ALL

B-ALL treatment efficacy improves with CAR-T persistence.

- Many evidence suggest CAR-T persistence is associated with a decrease in CD19-positive relapse.[1,2]
- There are attempts to improve CAR-T persistence by CAR-T engineering and dosing strategy.
  - CD19-targeting single-chain variable fragment (scFv) with lower affinity to CD19 may reduce CRS, decrease T cell exhaustion, and improved persistence.[3]
- Abstract 6504: Obecabtagene autoleucel in adults with r/r B-ALL: OS, EFS, and potential impact of CAR-T cell persistency and consolidative SCT in the open-label, single-arm FELIX phase IB/II study

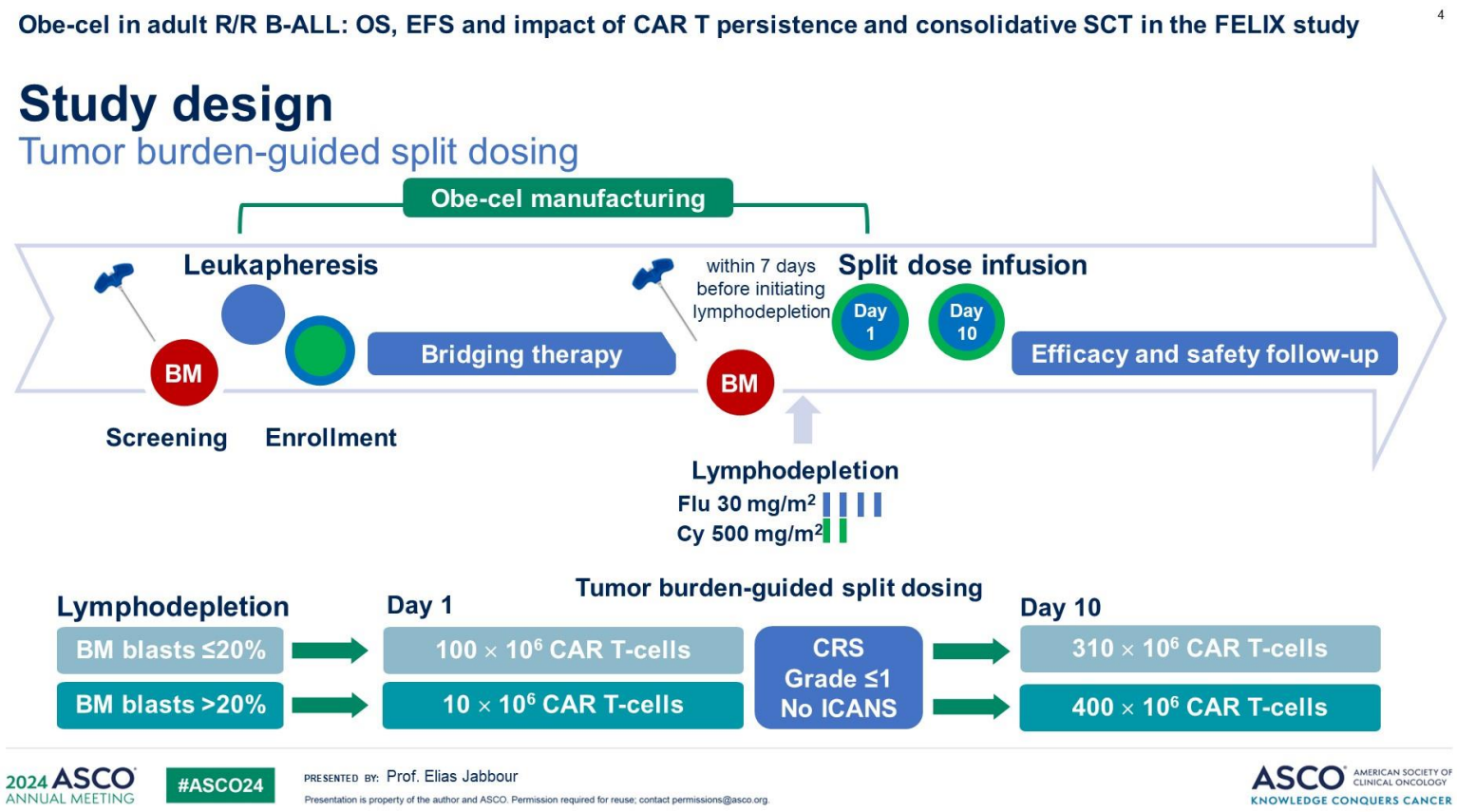
1. Mueller KT, et al. *Clin Cancer Res*. 2018;24(24):6175-6184.
2. Hay KA, et al. *Blood*. 2019;133(15):1652-1663.
3. Roddie C, Dias J, et al. *J Clin Oncol*. 2021;39(30):3352-3363.

New CAR-T design to improve persistency

- Abstract 6504
  - Design: Single arm phase Ib/II study
  - Population: adult r/r B-ALL
  - Intervention: Obe-cel with split dose infusion (days 1 and 10)
  - Results: N=127, median age 47 (20-81), 41% blinatumomab, 31.5% inotuzumab exposed, 44.1% prior allo-SCT.
  - Outcomes: CR or CRi 78%, 40% with ongoing remission, 18% underwent SCT
    - EFS 11.9 mo (censoring for SCT), OS 23.8 mo (censoring for SCT), 12-mo OS 63.7%
    - OS curve suggests long-term plateau.
    - CAR-T persistence is associated with EFS.
  - Limitation: Single arm study. Abstract did not discuss CRS/ICANS,

Elias Jabbour et al. JCO 42, 6504-6504(2024).

Abstract 6504 Study design



Elias Jabbour et al. JCO 42, 6504-6504(2024).

EFS in Obe-cel

Obe-cel in adult R/R B-ALL: OS, EFS and impact of CAR T persistence and consolidative SCT in the FELIX study

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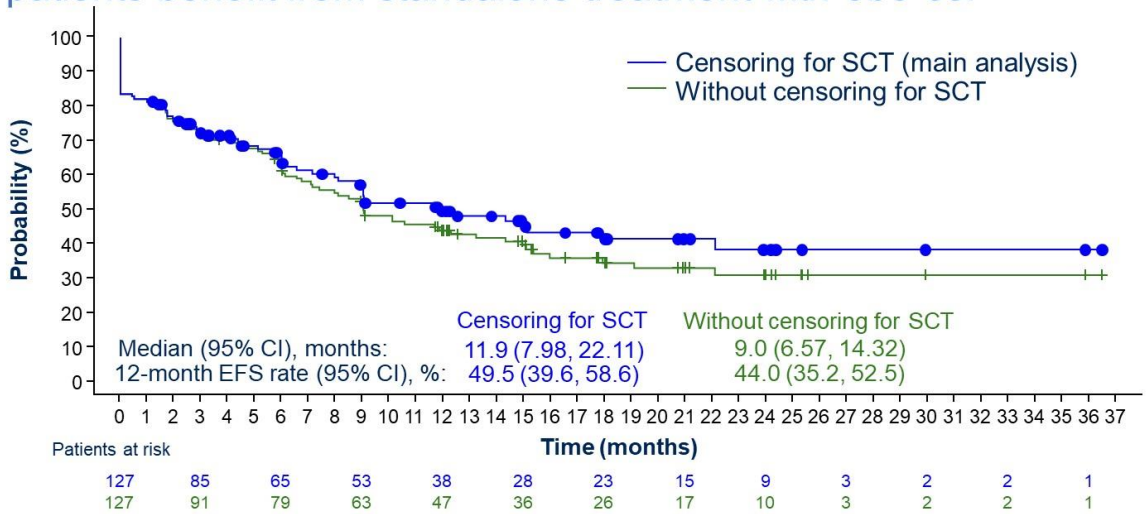
Event-free survival

Subset of patients benefit from standalone treatment with obe-cel



- All (18/18) patients who had SCT in remission were MRD-negative
- 10/18 patients (55.6%) had ongoing CAR T persistence prior to SCT (n = 2 ongoing without event; n = 8 relapse or death)
- Characteristics similar between patients who did and did not undergo consolidative SCT

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Prof. Elias Jabbour

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Elias Jabbour et al. JCO 42, 6504-6504(2024).

Myelodysplastic Syndrome

- LBA 6508 Palliative care for AML and MDS

Patients with AML/MDS have high symptoms burden and utilize significant healthcare resource

- Comparing to solid malignancies, patients with hematologic malignancy have more ER visits, hospital admissions, ICU admissions, and higher chemotherapy use.
  - These intensive treatments especially at the end of life result in high symptom burden and QoL impairment.
  - Many studies showed benefit of palliative care in solid malignancies.
  - Can palliative care improve symptom burden/QoL in this group of patients?
- LBA 6508: Multi-site randomized trial of a collaborative palliative and oncology care model for patients with acute myeloid leukemia and myelodysplastic syndrome receiving non-intensive therapy

Areej El-Jawahri et al. JCO 42, LBA6508-LBA6508(2024).

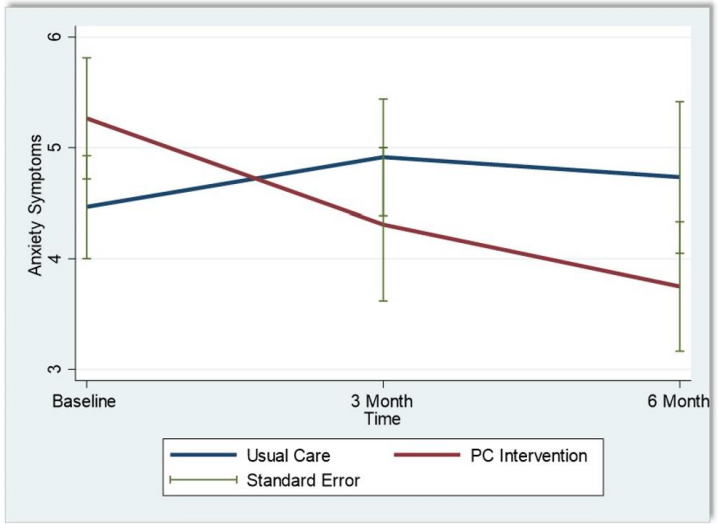
Palliative care in AML/MDS

- **LBA 6508**
  - Design: Randomized controlled trial, palliative care intervention vs usual care
  - Population: Adult with newly Dx AML or MDS within 30 days of non-intensive therapy
  - Setting: Single academic center (MGH)
  - Primary outcome: Time from documentation of EOL care preferences to death
  - Outcomes: N=115, primary outcome 41 days vs 1.5 days ($p < 0.001$), lower hospitalization in the last 30 days of life, higher hospice utilization, improved QoL
  - Limitation: Resource-intensive, no reported OS, unusually short duration of time to death in “usual care” arm.

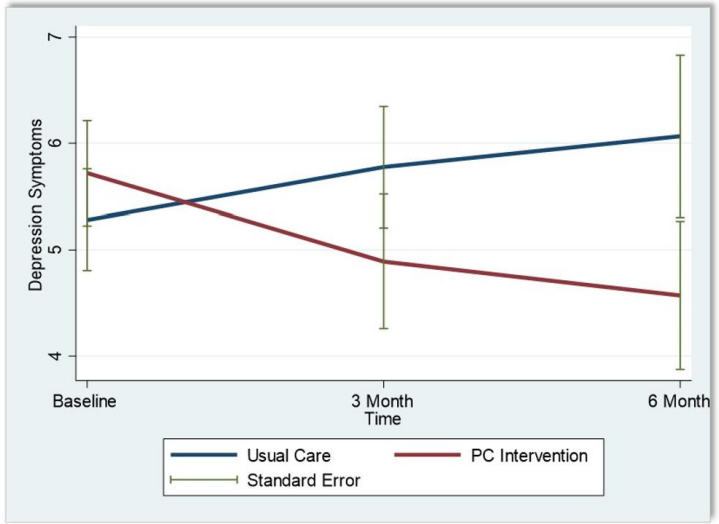
Areej El-Jawahri et al. JCO 42, LBA6508-LBA6508(2024).

Outcomes of palliative care intervention

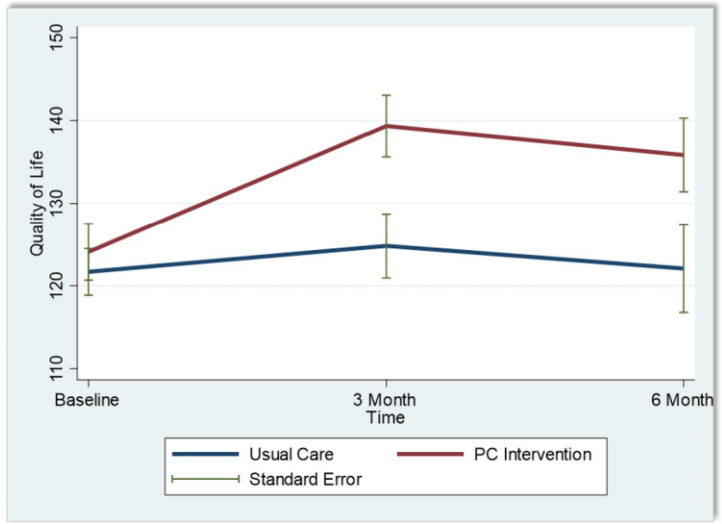
Anxiety Symptoms: Group X Time
B = -0.7 (95%CI -1.4 – 0.1), P=0.088



Depression Symptoms: Group X Time
B = - 0.7 (95%CI -1.6 – 0.2), P=0.124



Qualify of Life (QOL): Group X Time
B = 6.4 (95%CI 0.3 – 12.2), P=0.041



Areej El-Jawahri et al. JCO 42, LBA6508-LBA6508(2024).

Chronic Myeloid Leukemia

- LBA6500: Bringing highly effective agent into frontline treatment of CML: ASC4FIRST
- Abstract 6501: Confirmation of dosing strategy of ponatinib in CML and OS update from 4-year follow-up: OPTIC 4-year results, ponatinib in chronic-phase CML with T315I mutation

Bringing highly effective agents to frontline

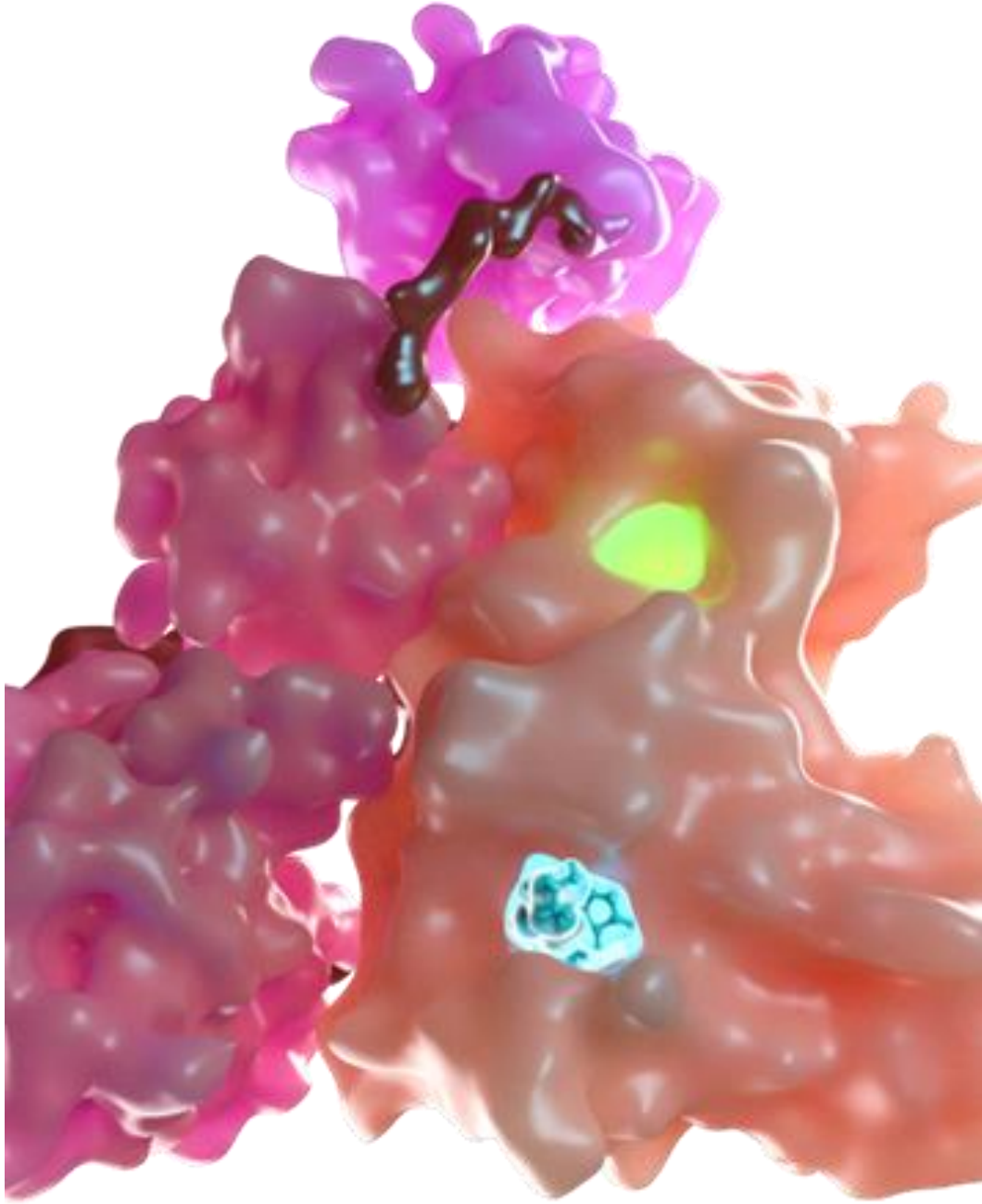
- Imatinib revolutionized CML treatment to TKI era, significant improved survival.
- Second-generation TKIs are more potent, can be used as frontline or after suboptimal response with imatinib.
  - Pleural effusion, GI events, and CV events are reported adverse events.

Hochhaus A, Baccarani M, Silver RT, et al. Leukemia. 2020;34(4):966-984.

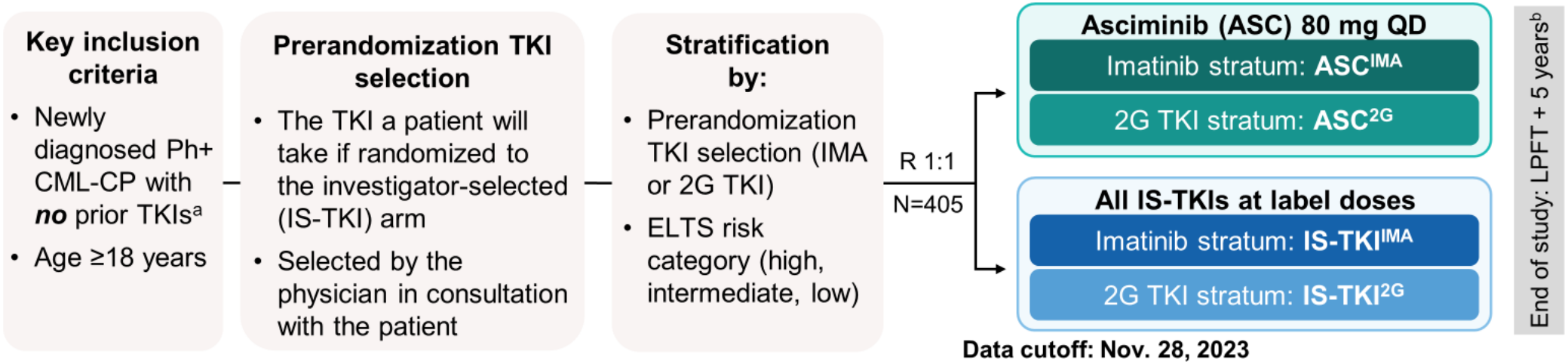
ASC4FIRST: frontline asciminib vs standard TKIs

Asciminib is currently approved as third-line treatment, specifically targets ABL1 myristoyl pocket, improved specificity and overcomes many resistant mutations.

Asciminib is also quite well tolerated, has a potential of being a frontline agent.



ASC4FIRST: Study design



Primary endpoints:
- MMR at week 48 for asciminib vs all investigator-selected TKIs
- MMR at week 48 for asciminib vs investigator-selected TKI within the imatinib stratum

ASC, asciminib; ELTS, EUTOS long-term survival score; EUTOS, European Treatment and Outcome Study; IMA, imatinib; LPFT, last person first treatment; Ph, Philadelphia chromosome; QD, once daily; R, randomized.
[a] Either imatinib, bosutinib, dasatinib, or nilotinib is allowed for up to 2 weeks prior to randomization. Treatment with other TKIs prior to randomization was not permitted.
[b] Patients will remain on study for 5 years after the last patient first dose, unless they have discontinued early due to treatment failure, disease progression, pregnancy, intolerance, or investigator or patient decision.

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ASC4FIRST: Results

- Median age: 52.0 vs 50.5 years old (asciminib vs std TKIs)
- Most are low-risk: 60.7% vs 61.3%
- Treatment discontinuation: 13.4% vs 29.9%
  - Unsatisfactory treatment effect: 6.0% vs 15.2%
  - Adverse event: 5.5% vs 10.3%
  - Similar trend for both imatinib and 2G TKI strata
- MMR rate at wk 48 is superior with asciminib: 67.7% vs 49.0%
  - Similar trend but less pronounced with 2G TKI stratum: 66.0% vs 57.8%

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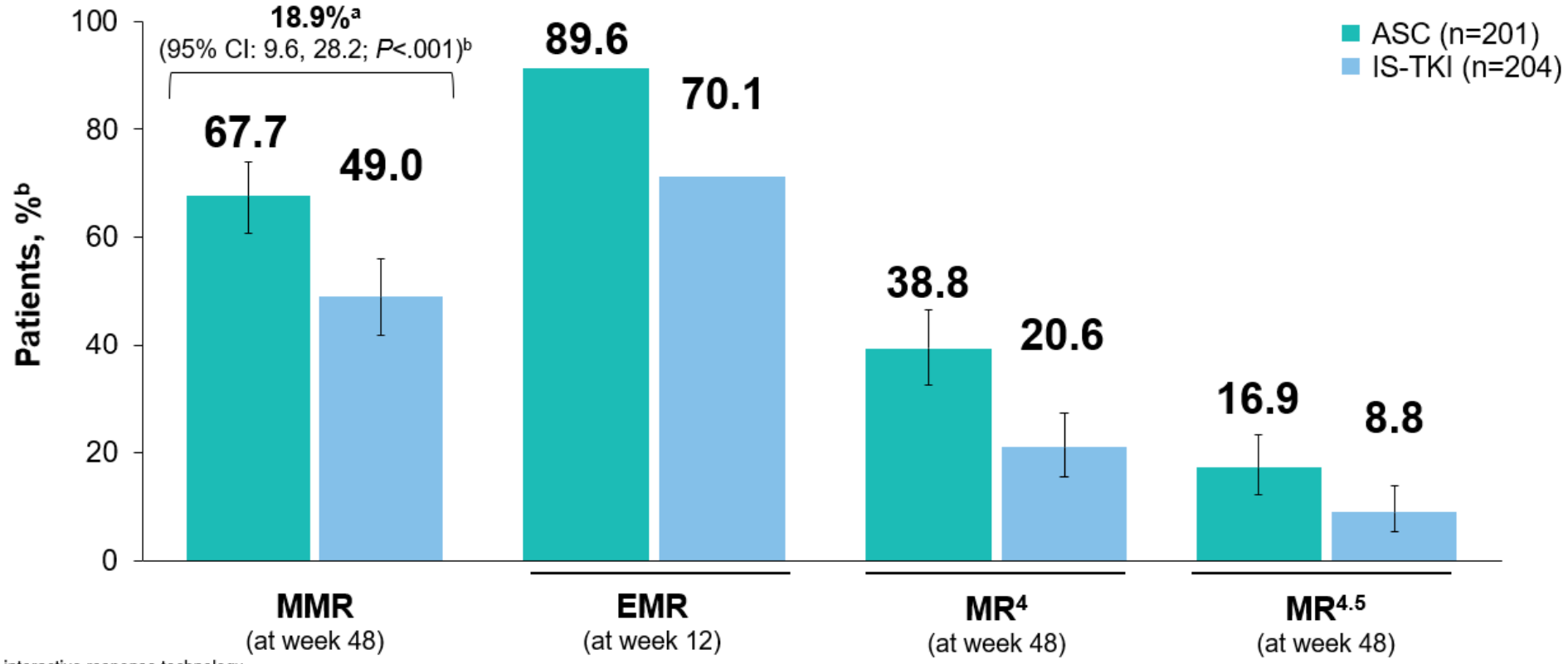
Asciminib shows better MMR rate at wk 48.



IRT, interactive response technology.
Error bars represent 95% CIs.
[a] The common treatment difference and its 95% CI are estimated using the Mantel-Haenszel method after stratifying for (a) pre-randomization selected TKI, and (b) baseline ELTS risk groups (both IRT data).
[b] Adjusted 1-sided p-value calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted p-value is ≤0.025.

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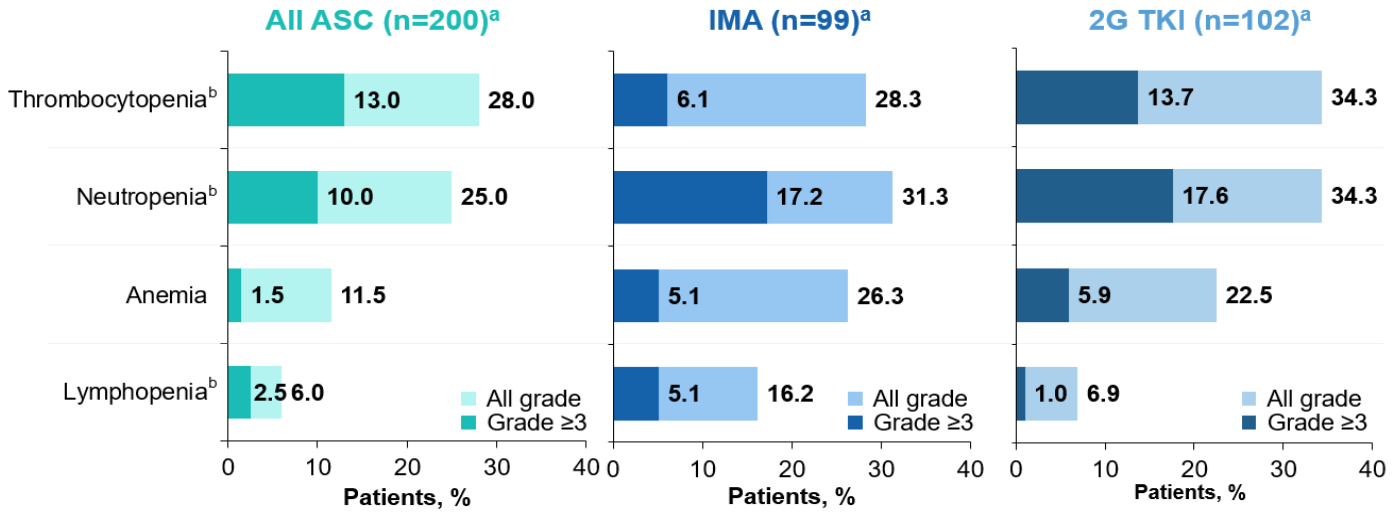
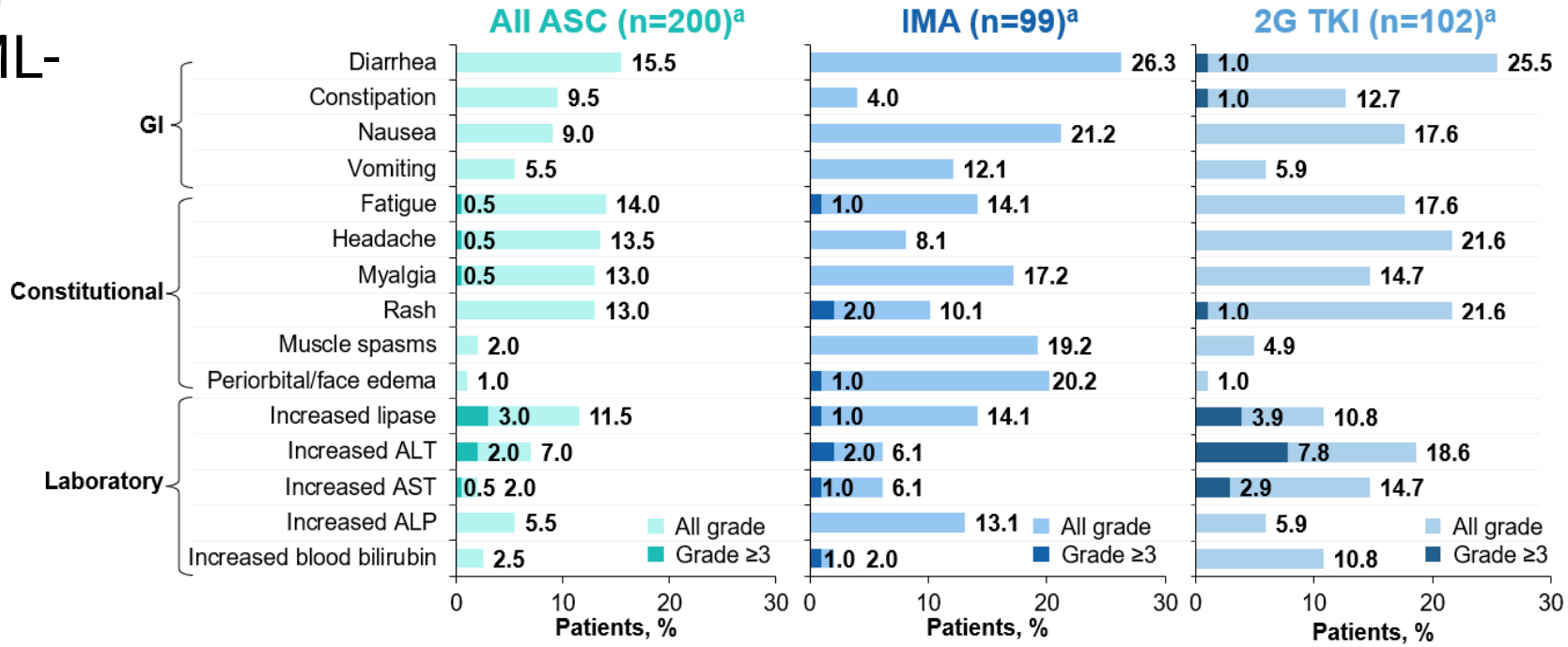
Ascinimib is quite well tolerated.

Asciminib has the potential to become a therapy of choice for newly diagnosed CML-CP.





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Questions?

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Thank you

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