Where Science Becomes Hope

CHRONIC MYELOID LEUKEMIA: SELECTION OF INITIAL THERAPY

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EMORY WINSHIP CANCER INSTITUTE
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DISCLOSURES

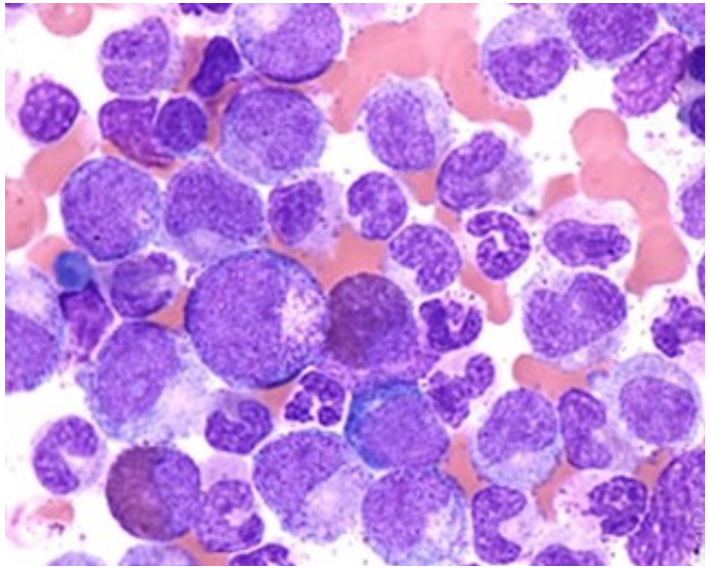
- No disclosures to report

LEARNING OBJECTIVES

- Develop a framework for individualized frontline treatment selection
- Review pivotal studies supporting use of the NCCN-recommended frontline agents
- Highlight emerging data in the frontline setting
- Discuss approach to treatment of accelerated/blast phase disease
- Introduce recent studies investigating predictors of response to some frontline therapies

CLINICAL CASE

- A fifty-year-old male with a history of hypertension, diabetes mellitus, hyperlipidemia, presents for evaluation of recently diagnosed CML.
- He was incidentally found to have hyperleukocytosis (WBC 70x10^3/mcL), anemia (hemoglobin 11.4g/dL), and thrombocytosis (Platelet count 550x10^3/mcL).
- Differential was notable for 50% neutrophils, 7% lymphocytes, 7% monocytes, 8% eosinophils, 6% basophils, 6% metamyelocytes, 15% myelocytes and 1% myeloblasts
- Bone marrow biopsy was consistent with chronic phase CML; karyotype revealed t(9;22)(q34;q11) in all 20 metaphases; no additional cytogenetic abnormalities



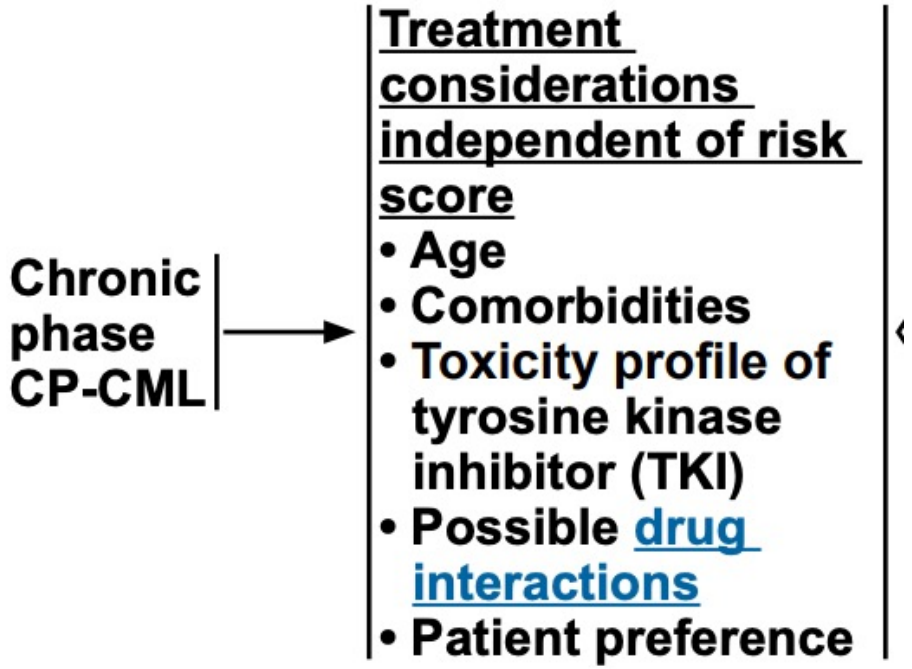
American Society of Hematology Image Bank #00002455

FRONTLINE TREATMENT RECOMMENDATION?

- Which therapy do you recommend?
- What factors are considered before arriving at this decision?
- How might the following factors impact your recommendation?
  - Co-morbidities such as IBD, pulmonary hypertension, CAD, severe GERD
  - High risk disease according to the EUTOS long-term survival score (ELTS)
  - Patient wishing for treatment free remission attempt as soon as possible

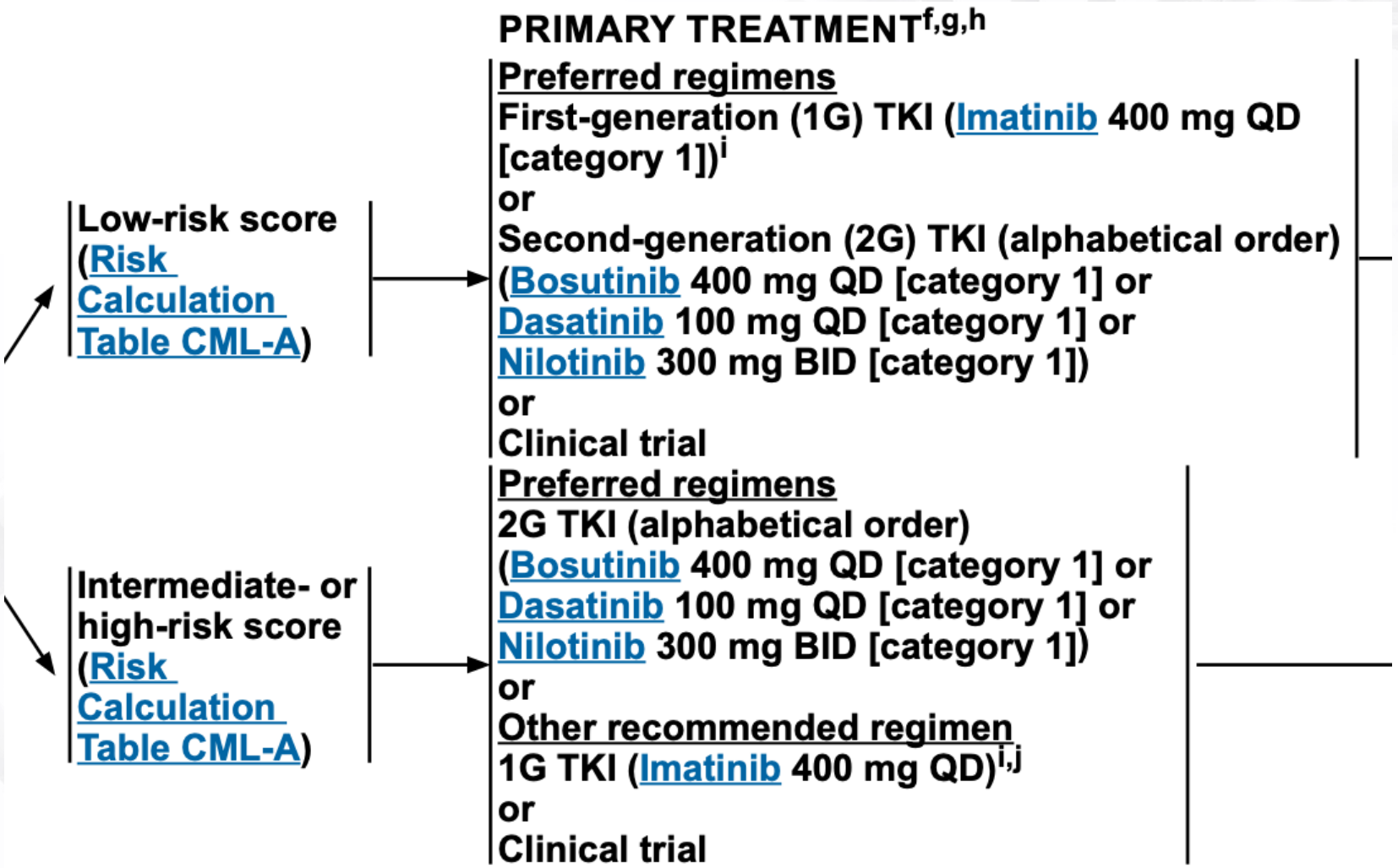
INITIAL CONSIDERATIONS

- Patient-, disease-, and drug-specific factors
- Patient goals may vary
  - Extend survival
  - Optimize quality of life
  - Treatment free remission attempt



NCCN v2. 2024

NCCN GUIDELINES



NCCN v2. 2024

FRONTLINE IMATINIB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia

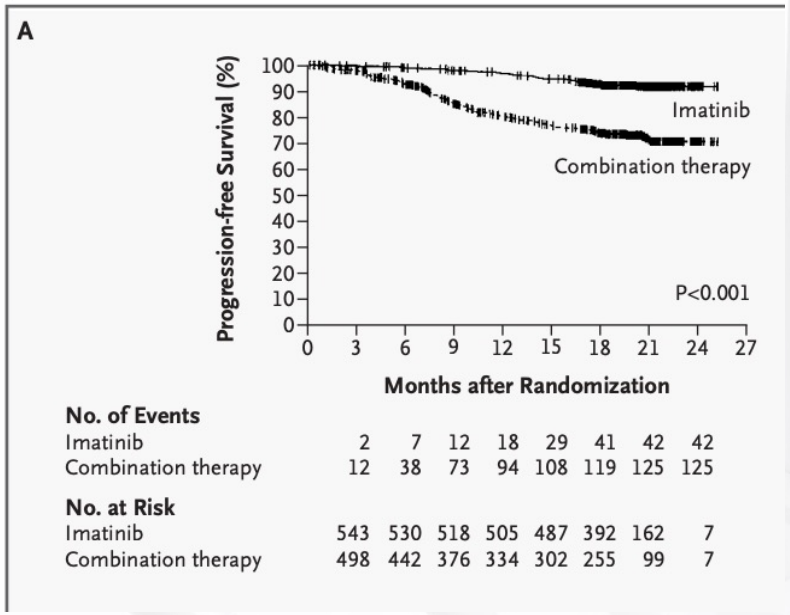


Table 3. Adverse Events.*

Adverse Event	All Grades		Grade 3 or 4	
	Imatinib (N=551)	Interferon Alfa plus Cytarabine (N=533)	Imatinib (N=551)	Interferon Alfa plus Cytarabine (N=533)
	percent			
Nonhematologic				
Superficial edema	55.5	9.2	0.9	0.6
Nausea	43.7	61.4	0.7	5.1
Muscle cramps	38.3	11.1	1.3	0.2
Musculoskeletal pain	36.5	42.0	2.7	8.3
Rash	33.9	25.0	2.0	2.3
Fatigue	34.5	65.5	1.1	24.4
Diarrhea	32.8	41.7	1.8	3.2
Headache	31.2	42.6	0.4	3.2
Joint pain	28.3	39.6	2.4	7.3
Abdominal pain	27.0	24.6	2.4	3.9
Nasopharyngitis	22.0	8.3	0	0.2
Myalgia	21.4	38.8	1.5	8.1
Hemorrhage	20.9	20.6	0.7	1.5
Hematologic				
Anemia	44.6	54.8	3.1	4.3
Neutropenia	60.8	67.2	14.3	25.0
Thrombocytopenia	56.6	78.6	7.8	16.5

O'Brien, et al. N Engl J Med 2003;348:994-1004.

FRONTLINE BOSUTINIB

Leukemia www.nature.com/leu

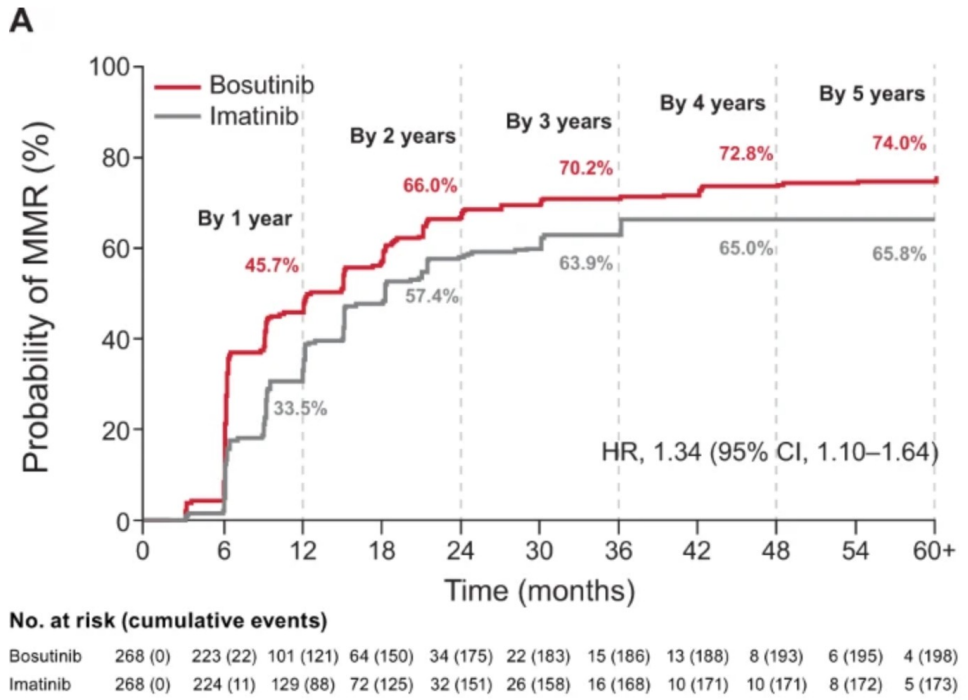
ARTICLE OPEN

Check for updates

CHRONIC MYELOGENOUS LEUKEMIA

Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: final results from the BFORE trial

Fig. 2: Cumulative incidence of molecular response.



No. at risk (cumulative events)

Bosutinib	268 (0)	223 (22)	101 (121)	64 (150)	34 (175)	22 (183)	15 (186)	13 (188)	8 (193)	6 (195)	4 (198)
Imatinib	268 (0)	224 (11)	129 (88)	72 (125)	32 (151)	26 (158)	16 (168)	10 (171)	10 (171)	8 (172)	5 (173)

Brummendorf, et al. Leukemia 2022; 36:1825–1833

FRONTLINE BOSUTINIB

- Treatment-emergent AEs
  - Gastrointestinal, liver, rash TEAEs more common in bosutinib arm
  - Edema, musculoskeletal TEAEs more common in imatinib arm

Table 4. Adverse Events, Safety Population

Adverse Event	Bosutinib (n = 268)		Imatinib (n = 265)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any adverse event	263 (98.1)	151 (56.3)	257 (97.0)	113 (42.6)
GI	218 (81.3)	29 (10.8)	163 (61.5)	9 (3.4)
Diarrhea	188 (70.1)	21 (7.8)	89 (33.6)	2 (0.8)
Nausea	94 (35.1)	0	103 (38.5)	0
Vomiting	48 (17.9)	3 (1.1)	43 (16.2)	0
Abdominal pain	48 (17.9)	5 (1.9)	19 (7.2)	1 (0.4)
Hematologic*	122 (45.5)	44 (16.4)	115 (43.4)	52 (19.6)
Thrombocytopenia*	94 (35.1)	37 (13.8)	52 (19.6)	15 (5.7)
Anemia*	50 (18.7)	9 (3.4)	50 (18.9)	12 (4.5)
Neutropenia*	30 (11.2)	18 (6.7)	55 (20.8)	32 (12.1)
Leukopenia*	15 (5.6)	3 (1.1)	29 (10.9)	8 (3.0)
Musculoskeletal	79 (29.5)	5 (1.9)	155 (58.5)	6 (2.3)
Muscle spasms	6 (2.2)	0	70 (26.4)	1 (0.4)
Arthralgia	30 (11.2)	2 (0.7)	35 (13.2)	0
Myalgia	8 (3.0)	1 (0.4)	41 (15.5)	2 (0.8)
Pain in extremity	12 (4.5)	1 (0.4)	33 (12.5)	0
Infections	119 (44.4)	9 (3.4)	125 (47.2)	13 (4.9)
Upper respiratory tract infection	23 (8.6)	1 (0.4)	27 (10.2)	0
Liver function†	107 (39.9)	65 (24.3)	36 (13.6)	11 (4.2)
ALT increased	82 (30.6)	51 (19.0)	15 (5.7)	4 (1.5)
AST increased	61 (22.8)	26 (9.7)	17 (6.4)	5 (1.9)

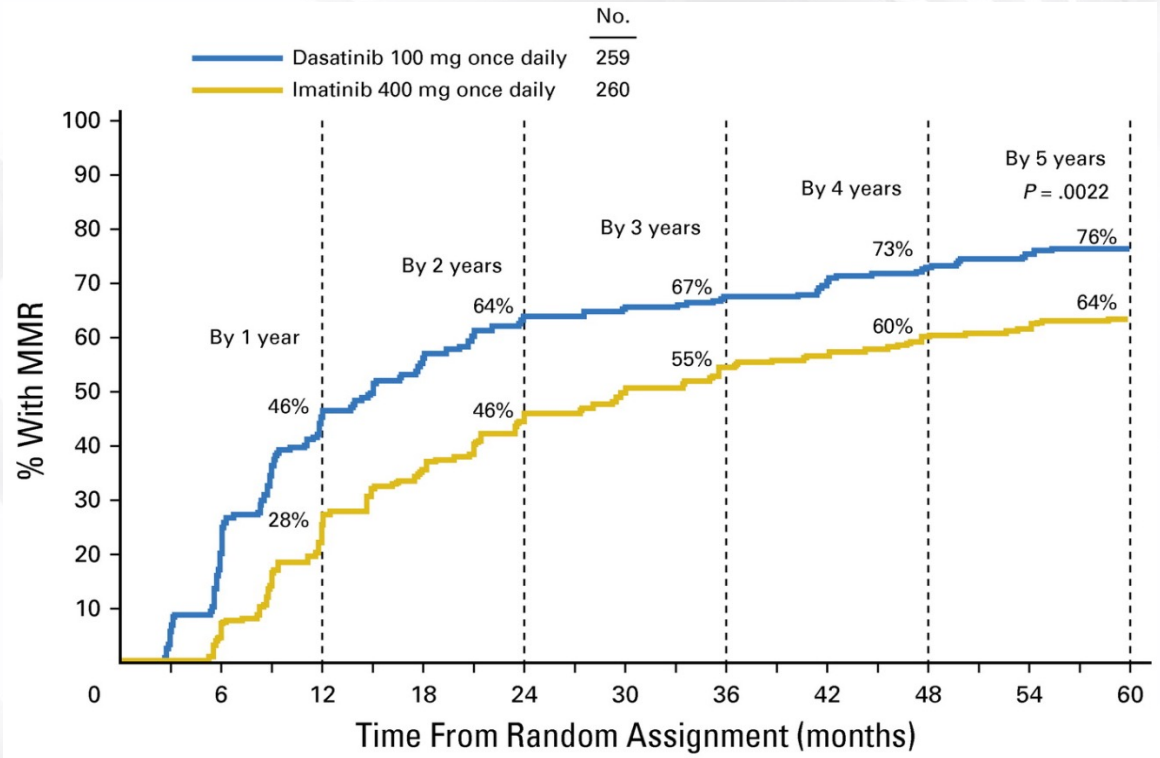
Cortes, et al. J Clin Oncol 2018; 36(3):231-237.

FRONTLINE DASATINIB

Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial

Authors: Jorge E. Cortes, Giuseppe Saglio, Hagop M. Kantarjian, Michele Baccarani, Jiří Mayer, Concepción Boqué, Neil P. Shah, Charles Chuah, Luis Casanova, Brigid Bradley-Garelik, George Manos, and Andreas Hochhaus | AUTHORS INFO & AFFILIATIONS

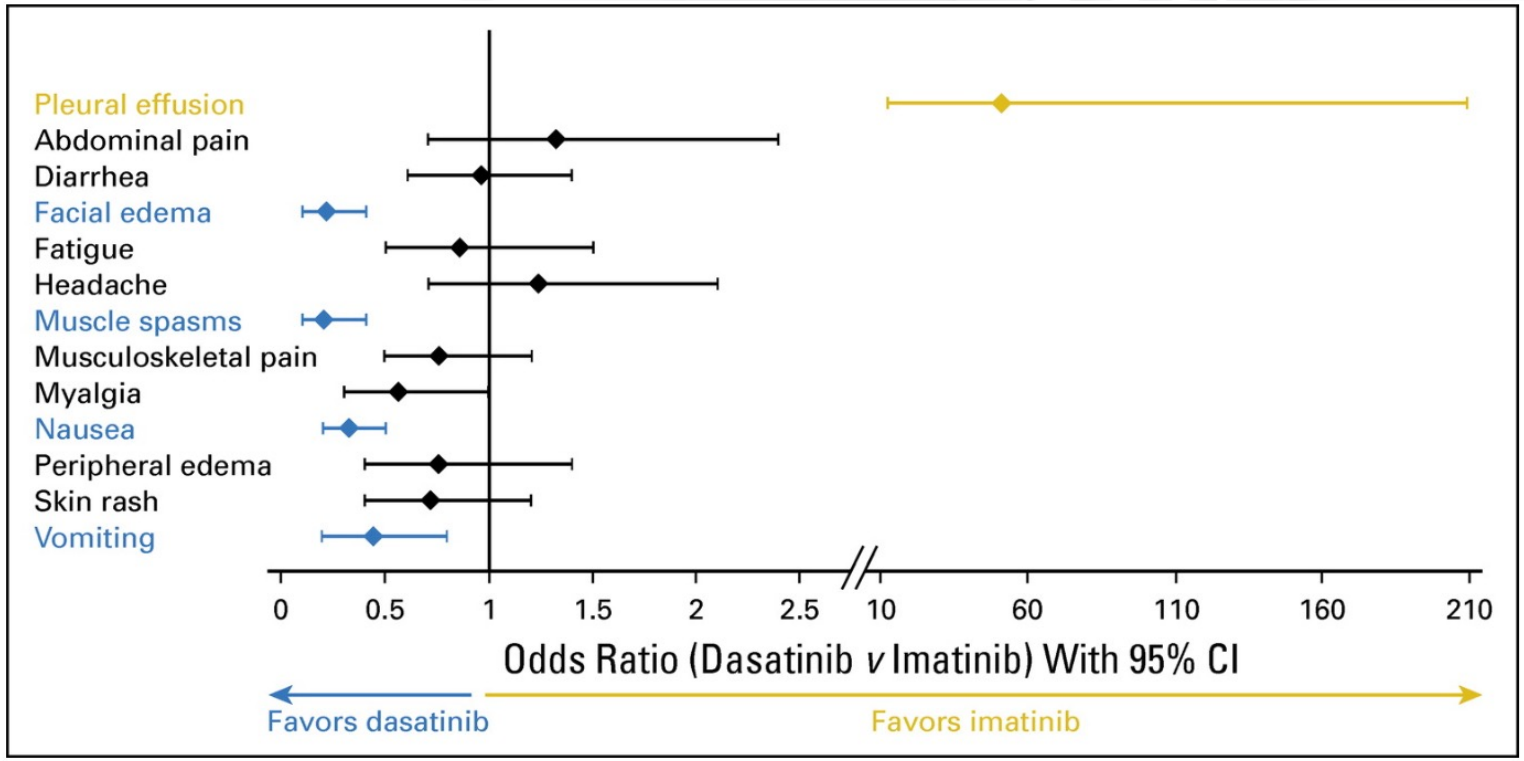
Publication: Journal of Clinical Oncology • Volume 34, Number 20 • https://doi.org/10.1200/JCO.2015.64.8899



Cortes, et al. J Clin Oncol. 2016;34:2333–40.

FRONTLINE DASATINIB

- Treatment-emergent AEs
  - Rates of grade 3 or 4 hematologic AEs were higher for dasatinib
  - Apart from pleural effusions, non-hematologic toxicities more common with imatinib



Cortes, et al. J Clin Oncol. 2016;34:2333–40.

FRONTLINE DASATINIB

- Drug-related pleural effusions
  - 28% vs 0.8%
    - 26% grade 1-2, 3% grade 3-4
    - More common in patients age ≥ 65 years
  - Management
    - Dose interruption (62%) and/or dose reduction (41%), diuretics (47%), corticosteroids (32%), or therapeutic thoracocentesis (12%)
    - Only 15 patients (6%) discontinued dasatinib due to pleural effusions

Cortes et al. J Clin Oncol. 2016;34:2333–40.

FRONTLINE DASATINIB 50MG

Low-Dose Dasatinib (50 mg Daily) Frontline Therapy in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia: 5-Year Follow-Up Results

Georgina Gener-Ricos, Fadi G. Haddad, Koji Sasaki, Ghayas C. Issa, Jeffrey Skinner, Lucia Masarova, Gautam Borthakur, Yesid Alvarado, Guillermo Garcia-Manero, Elias Jabbour, Hagop Kantarjian

Table 1 Baseline Patient Characteristics (n = 83)

Parameter	N (%) / Median (Range)
Age, years	47 (20-84)
Male sex	40 (48)
White blood cells, $x10^9$/L	43 (2.7-290)
Hemoglobin, g/dL	12.1 (8.1-17.1)
Platelets, $\times 10^9$/L	337 (98-1956)
PB basophils, %	3 (0-15)
PB blasts, %	0 (0-4)
BM blasts, %	1 (0-9)
Spleen size, cm	0 (0-11)
Sokal risk group	
Low	54 (65)
Intermediate	24 (29)
High	5 (6)

Gener-Ricos, et al. Clin Lymphoma Myeloma Leuk 2023; 23(10):742-748

FRONTLINE DASATINIB 50MG

- Less myelosuppression (grade 3-4 neutropenia (7%), thrombocytopenia (6%), anemia (5%))
- 13% developed pleural effusions
  - 11% grade 1-2, 2% grade 3-4

Table 2 Response Rates at 3, 6, 12, 24, and 60 Months of Low-Dose Dasatinib (50 mg) Daily

	Number of Responses/Total, (%)				
	3 mo	6 mo	12 mo	24 mo	60 mo
CCyR	41/81 (51)	72/81 (89)	77/80 (96)	76/78 (97)	51/51 (100)
MMR	25/81 (31)	54/81 (67)	65/80 (81)	72/78 (92)	51/51 (100)
MR4	5/81 (6)	28/81 (35)	51/80 (64)	58/78 (74)	46/51 (90)
MR4.5	3/81 (4)	21/81 (26)	43/80 (54)	55/78 (71)	46/51 (90)
CMR	1/81 (1)	13/81 (16)	27/80 (34)	40/78 (51)	42/51 (82)

Gener-Ricos, et al. Clin Lymphoma Myeloma Leuk 2023; 23(10):742-748

FRONTLINE NILOTINIB

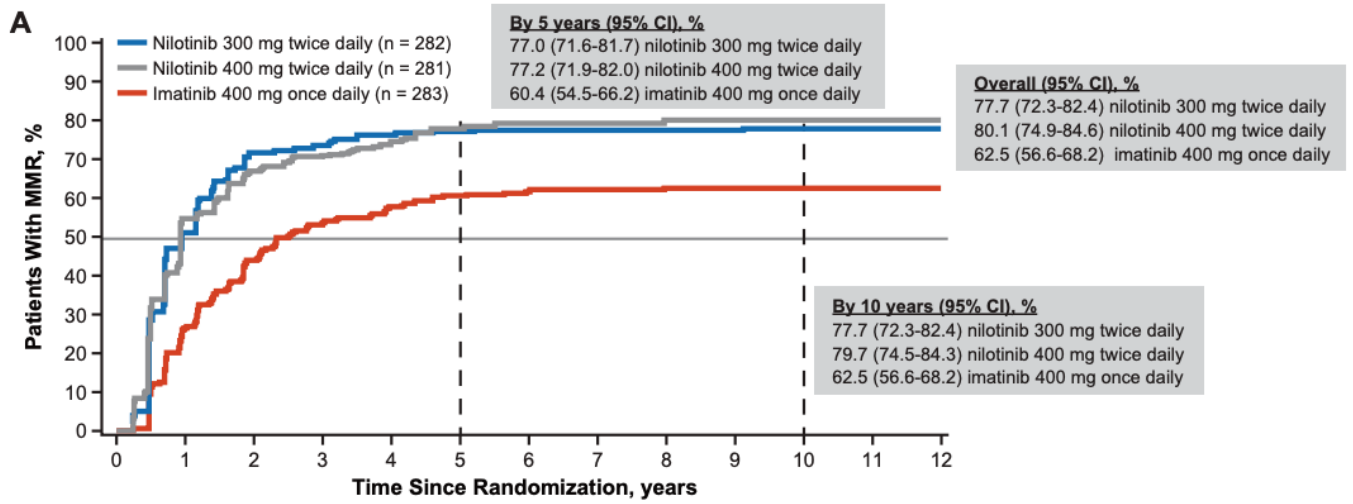
Leukemia (2021) 35:440–453
https://doi.org/10.1038/s41375-020-01111-2

ARTICLE

Chronic myelogenous leukemia

Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis

Hagop M. Kantarjian[1] · Timothy P. Hughes[2,3] · Richard A. Larson[4] · Dong-Wook Kim[5] · Surapol Issaragrisil[6] · Philipp le Coutre[7] · Gabriel Etienne[8] · Carla Boquimpani[9,10] · Ricardo Pasquini[11] · Richard E. Clark[12] · Viviane Dubruille[13] · Ian W. Flinn[14] · Slawomira Kyrcz-Krzemien[15] · Ewa Medras[16] · Maria Zanichelli[17] · Israel Bendit[18] · Silvia Cacciatore[19] · Ksenia Titorenko[20] · Paola Aimone[19] · Giuseppe Saglio[21] · Andreas Hochhaus[22]



Kantarjian, et al. Leukemia 2021; 35:440-453

FRONTLINE NILOTINIB

Table 4 Cardiovascular events (CVEs).

	Nilotinib 300 mg twice daily	Nilotinib 400 mg twice daily	Imatinib 400 mg once daily
CVEs, *n*[a]	279	277	280
Cumulative CVEs			
All CVEs	46 (16.5)	65 (23.5)	10 (3.6)
Ischemic heart disease	22 (7.9)	36 (13.0)	8 (2.9)
Peripheral arterial occlusive disease	18 (6.5)	20 (7.2)	0
Ischemic cerebrovascular disease	13 (4.7)	21 (7.6)	1 (0.4)
Other CVEs	4 (1.4)	4 (1.4)	1 (0.4)

Kantarjian, et al. Leukemia 2021; 35:440-453

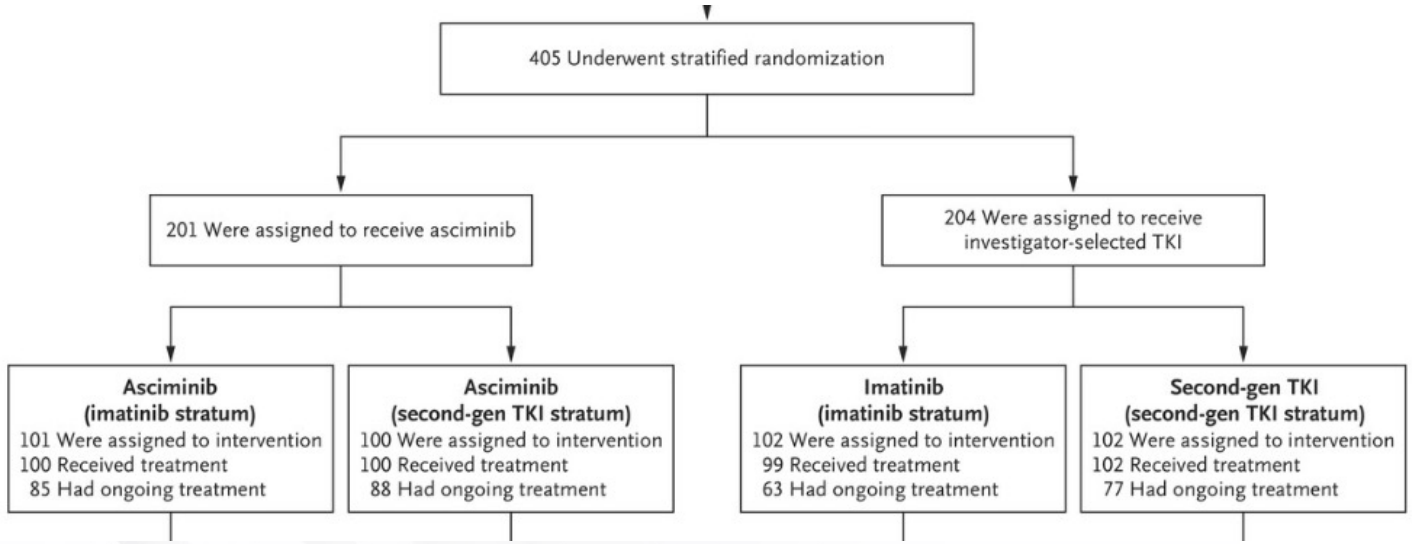
FRONTLINE ASCIMINIB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

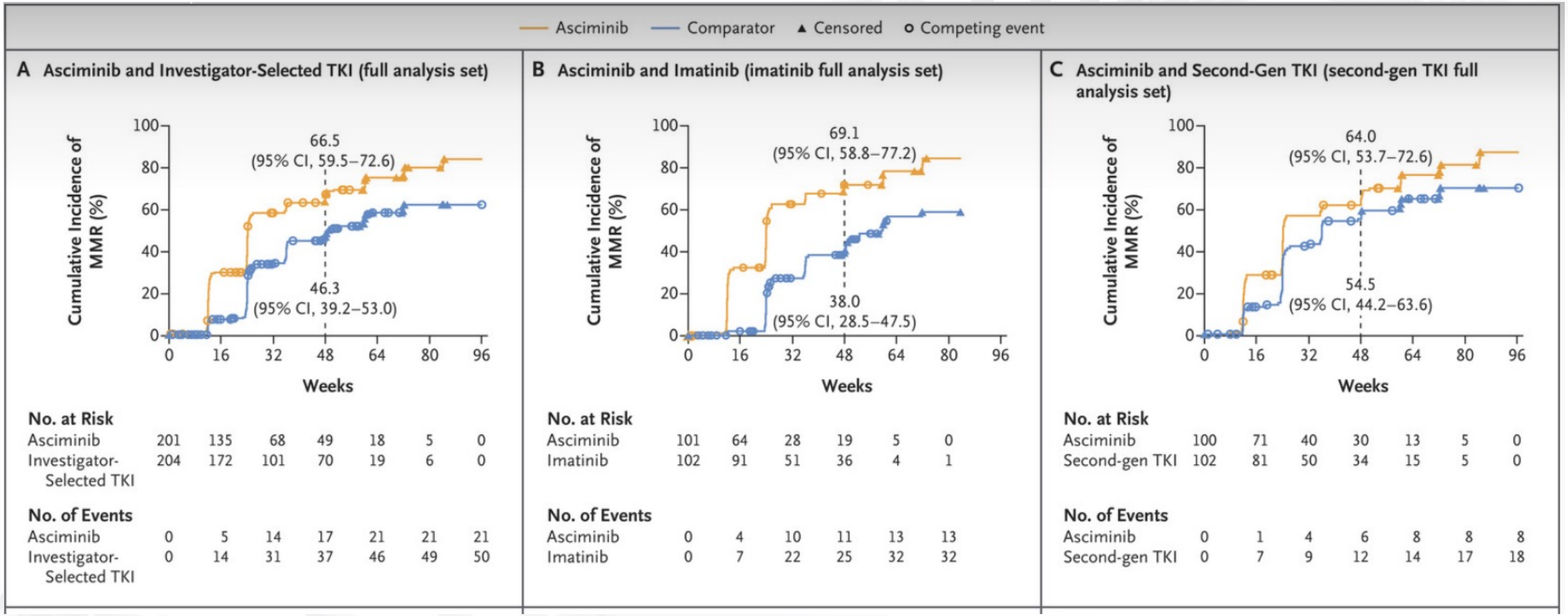
Asciminib in Newly Diagnosed Chronic Myeloid Leukemia

A. Hochhaus, J. Wang, D.-W. Kim, D.D.H. Kim, J. Mayer, Y.-T. Goh, P. le Coutre, N. Takahashi, I. Kim, G. Etienne, D. Andorsky, G.C. Issa, R.A. Larson, F. Bombaci, S. Kapoor, T. McCulloch, K. Malek, L. Yau, S. Ifrah, M. Hoch, J.E. Cortes, and T.P. Hughes, for the ASC4FIRST Investigators*



Hochhaus, et al. N Engl J Med 2024; DOI: 10.1056/NEJMoa2400858

FRONTLINE ASCIMINIB



Hochhaus, et al. N Engl J Med 2024; DOI: 10.1056/NEJMoa2400858

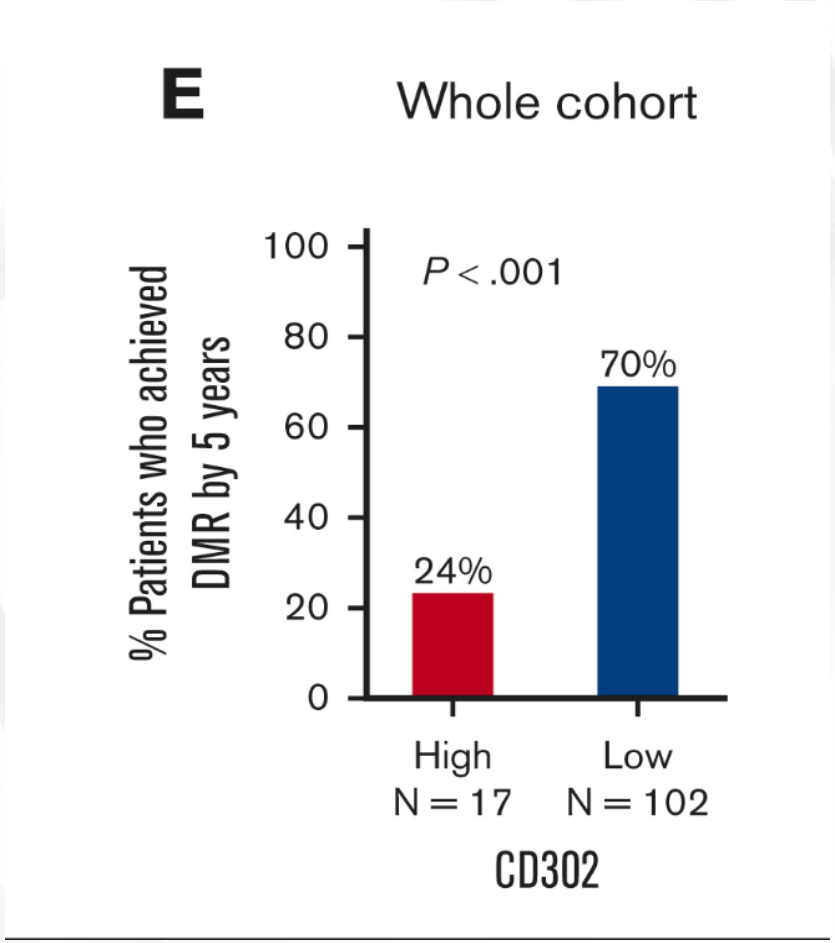
FRONTLINE ASCIMINIB

Adverse Event	Asciminib	
	All Asciminib (N=200)	
	Any Grade	Grade ≥3
At least one adverse event	187 (93.5)	76 (38.0)
Thrombocytopenia†	56 (28.0)	26 (13.0)
Neutropenia‡	50 (25.0)	20 (10.0)
Leukopenia§	38 (19.0)	4 (2.0)
Coronavirus disease 2019	35 (17.5)	0
Diarrhea	31 (15.5)	0
Fatigue	28 (14.0)	1 (0.5)
Headache	27 (13.5)	1 (0.5)
Myalgia	26 (13.0)	1 (0.5)
Rash	26 (13.0)	0
Anemia	23 (11.5)	3 (1.5)
Increased lipase	23 (11.5)	6 (3.0)

Hochhaus, et al. N Engl J Med 2024; DOI: 10.1056/NEJMoa2400858

FUTURE DIRECTIONS

- Predictors of response to frontline treatment?



Kok, et al. Blood Neoplasia (2024) 1 (2): 100014

CONCLUSIONS

- The decision regarding frontline treatment recommendations remains nuanced.
- After assessing individual treatment goals and patient-specific factors, the risks and benefits of each agent should be carefully assessed.
- It is then parament to ensure that patients are monitored optimally and managed appropriately at the earliest sign of true treatment resistance.
- Future research aims to develop strategies to identify predictors of response, minimize toxicities without compromising efficacy, and increase treatment free remission eligibility when desired.