3:40–4:45 PM

CML & MPN

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THE 2nd ANNUAL HemOnc Pulse LIVE | AUSTIN 2025

Updates in Chronic Myeloid Leukemia

Presenter

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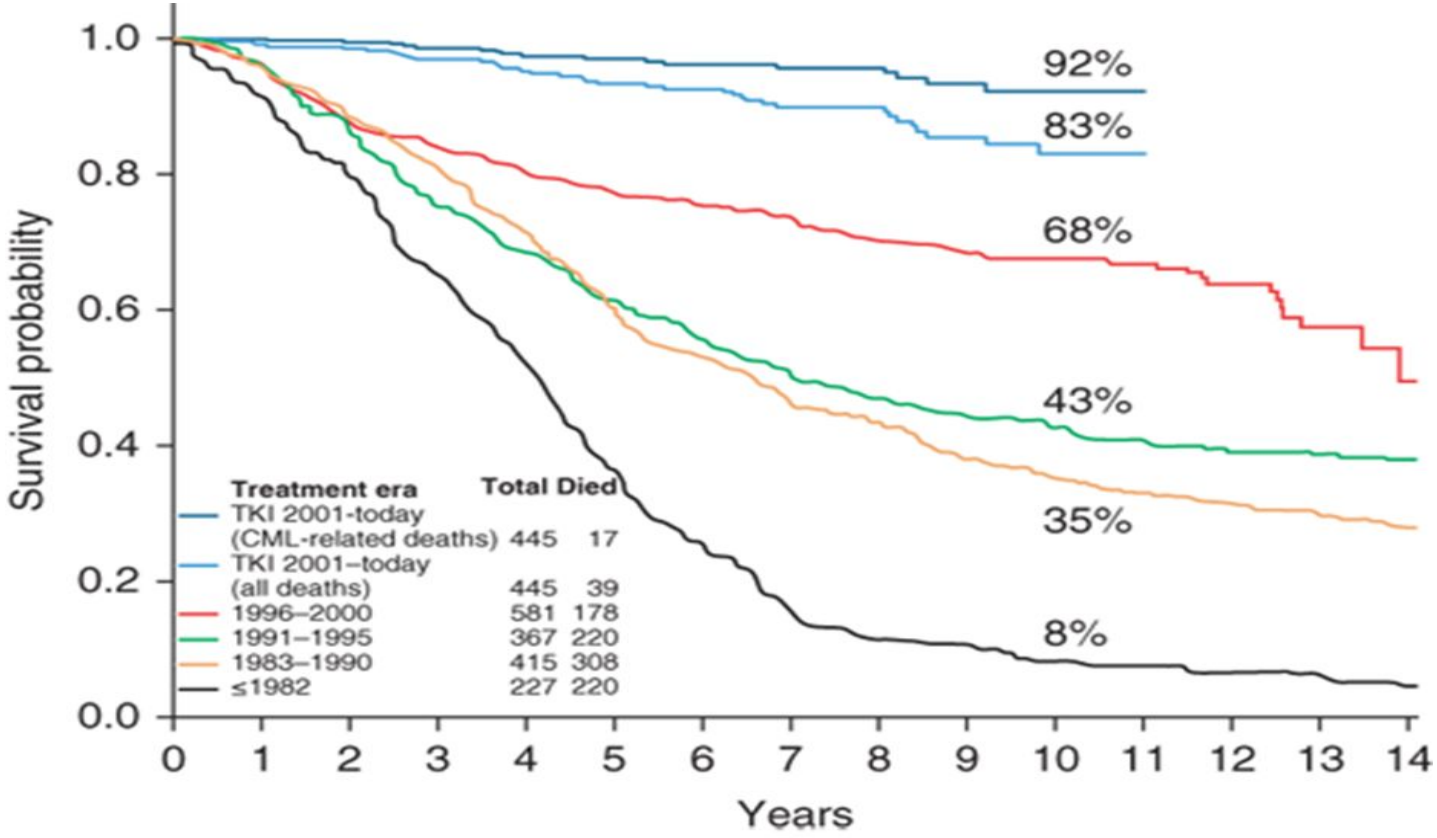
Disclosures

Consulting: Amgen

Advisory board: Sobi

What's New in 2024-2025?



TKI = tyrosine kinase inhibitor; CML = chronic myeloid leukemia.

Kantarjian H et al. *Harrison's Principles of Internal Medicine.* 20th ed. McGraw Hill; 2018.

First-Line Therapy

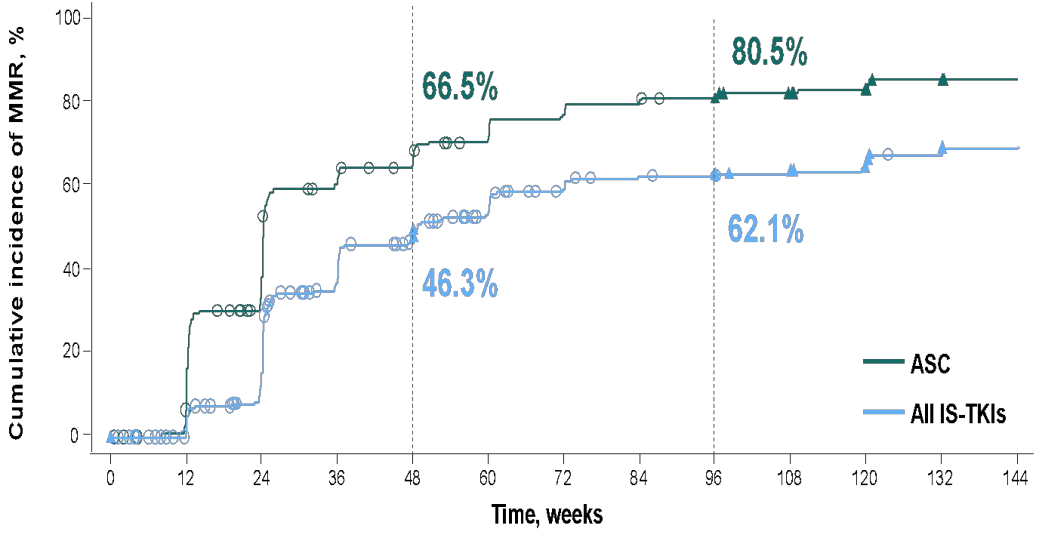
Asciminib in Newly Diagnosed CML-CP: ASC4FIRST

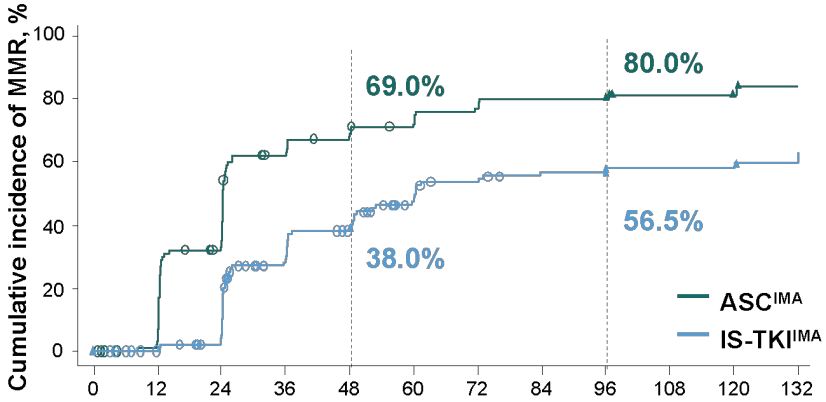
- 405 patients with newly diagnosed CML-CP randomized to asciminib (n=201) or investigator's choice (IS) of imatinib or second-generation TKIs (n=204)
- Patients in imatinib group were **older** (age ≥65 years) with **higher cardiovascular disease risk**, compared with those in 2G-TKI group

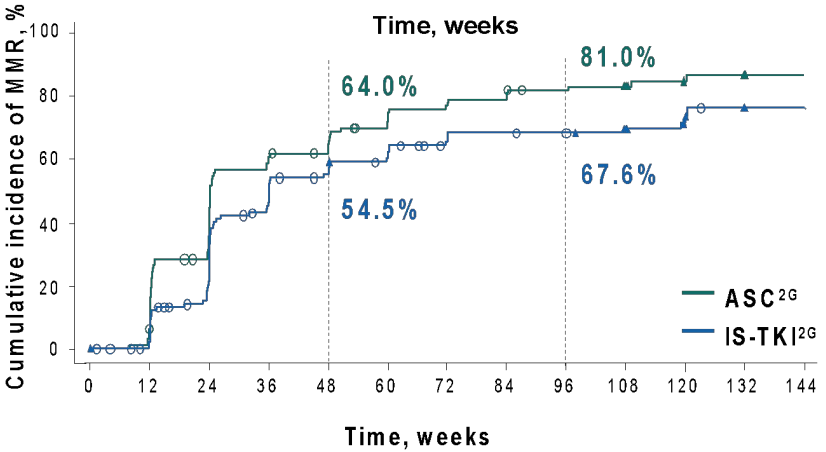
Rates at 48 weeks (%)	Primary End Point 1		Primary End Point 2	
	Asciminib (N=201)	**All TKIs (N=204)**	**Asciminib (N=101)**	**Imatinib (N=102)**
MMR	**67.7**	**49.0**	**69.3**	**40.2**
MR4	38.8	20.6	42.6	14.7
MR4.5	16.9	8.8	17.8	4.9

CML-CP = chronic phase CML; MMR = major molecular response.
Hochhaus A et al. *N Engl J Med.* 2024;391(10):885-898.

ASC4FIRST: Cumulative MMR at 96 Weeks



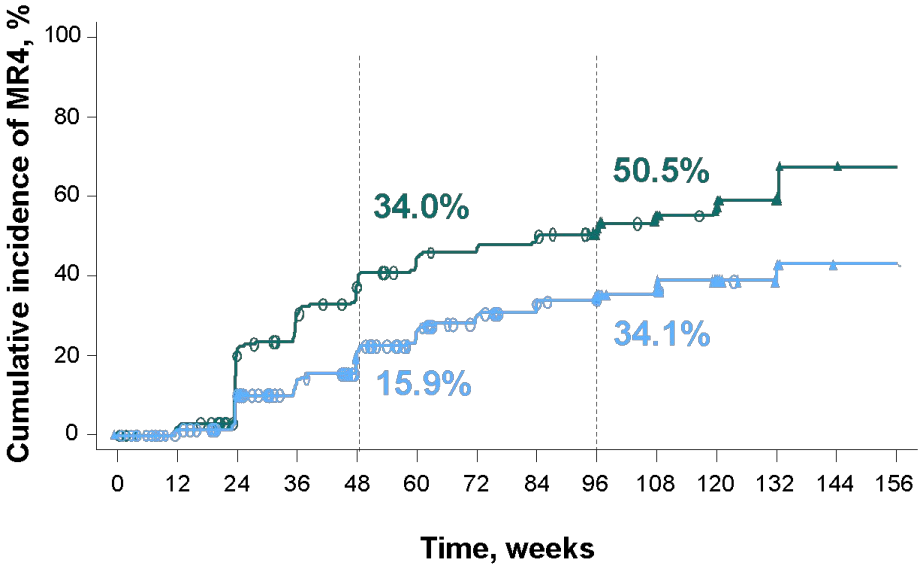




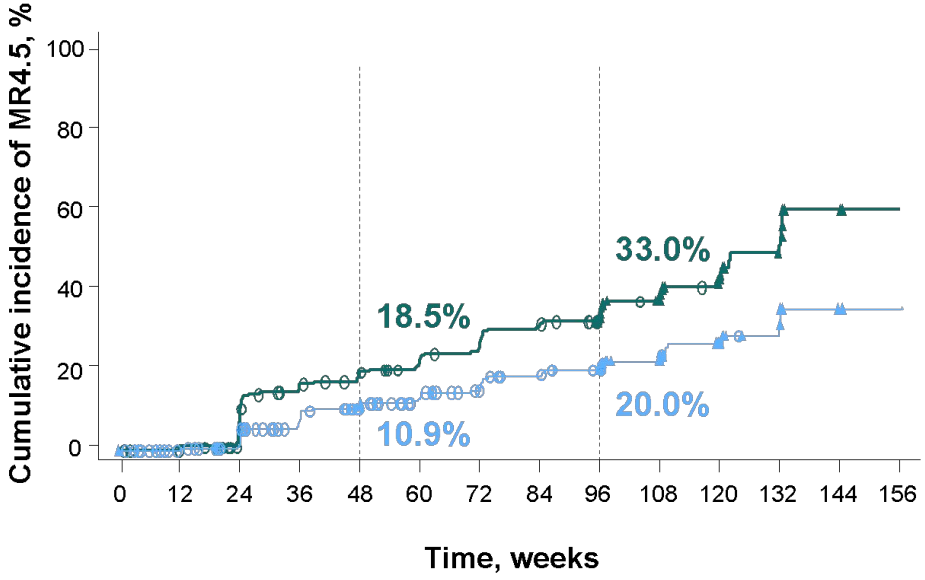
Cortes JE et al. *Blood*. 2024;144(suppl 1):475.

ASC4FIRST: Cumulative Deep Molecular Responses at 96 weeks

Cumulative MR4



Cumulative MR4.5



Cortes JE et al. *Blood*. 2024;144(suppl 1):475.

Post-Baseline Treatment-Emergent BCR::ABL1 Gene Mutations (by NGS)

Patients	Post-baseline mutations	Discontinuation reason	Post-protocol therapy (Second line and beyond)	Last disease/survival status
Asciminib	**Myristoyl pocket**			
1	A433D	Treatment failure per ELN	Bosutinib, dasatinib	CP/alive
2	A337V, V506M[b]		Dasatinib	CP/alive
3	A337T, A344P,[b] P465Q,[b] I502N[b]		Dasatinib	AP/alive
4	A433D		Dasatinib, olverembatinib	AP/alive
5	A337T, V506M[b]		Ponatinib	Discontinued study
6	L340Q		Not available	Discontinued study
7[c]	A337T	Confirmed loss of MMR	Dasatinib	Discontinued study
8	A337T, L340Q	Unsatisfactory therapeutic effect (other)	Dasatinib	CP/alive
9	A337T,[b] F497L[b]	Progressive disease (BP)	Ponatinib	CP/death post HSCT
10[c]	A337V	Ongoing on study	Not applicable	
Imatinib	**ATP-binding domain**			
1	L248V, E255V,[b] G250E[b]	Treatment failure per ELN	Flumatinib, olverembatinib	BP/death post HSCT
2[c]	F317L[b]		Imatinib	CP/alive
3	L248V, E450G[b]		Nilotinib	CP/alive
4[c]	E459K	Confirmed loss of MMR	Dasatinib	CP/alive
Nilotinib	**ATP-binding domain**			
5[c]	Y253H	Treatment failure per ELN	Dasatinib	CP/alive
6	Y253H		Dasatinib, ponatinib	CP/alive
7	Y253H[b]	Ongoing on study	Not applicable	

ATP = adenosine triphosphate; ELN = European Leukemia Network; BP = blast phase; CP = chronic phase; AP = accelerated phase; HSCT = hematopoietic stem cell transplantation.

Cortes JE et al. *Blood*. 2024;144(suppl 1):475.

ASC4FIRST: Side Effects

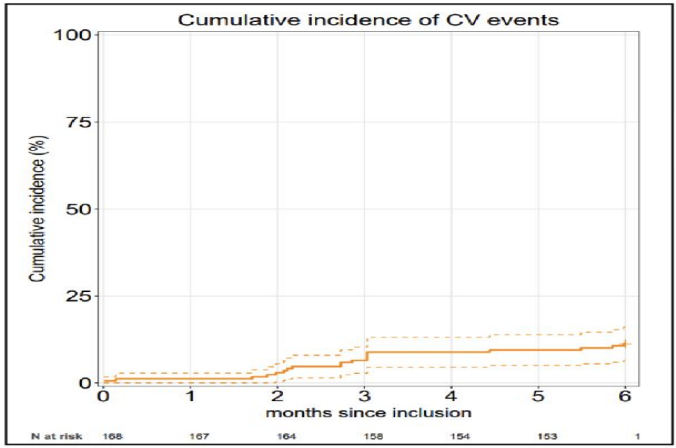
Rates by week 96 (%)	Asciminib	Imatinib	2G-TKI
Grade ≥3 AEs	44.5	49.5	59.8
AEs leading to discontinuation	5.0	13.1	12.7
AEs leading to dose adjustment/interruption	33.0	41.4	57.8
Patients with ≥1 AOE	2.0	0	2.9

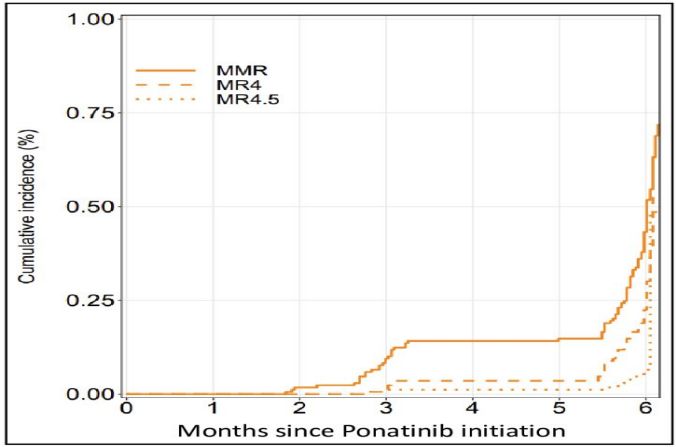
Since the week 48 cutoff, 2 additional patients had AOEs with asciminib and 1 with bosutinib

AE = adverse event; AOE = arterial occlusive event.
Cortes JE et al. *Blood*. 2024;144(suppl 1):475.

Trial of Imatinib After Ponatinib Induction (TIPI)

- **Ponatinib 30 mg/day for 6 months** then imatinib 400 mg/day until MR4.5 ≥ 2 years (TFR criteria)
- 169 patients, no significant CV disease, ELTS high risk in 16%
- 135 grade 3-5 AEs: grade 3 = 91%, grade 4 = 8%, and 1 fatal AE
- 6 grade 3-5 cardiac events (1 fatal cardiac arrest)
- 17 (12.5%) vascular events (15 hypertension, 1 pulmonary embolism?, 1 carotid stenosis)





CV = cardiovascular; TFR = treatment-free remission; ELTS = EUTOS long-term survival (ELTS) score; EUTOS = European Treatment Outcome Study.
Nicolini FE et al. *Blood*. 2023;142(suppl 1):445.

Trial of Imatinib After Ponatinib Induction (TIPI)

- Median follow-up 18 months, EMR with ponatinib = **97%**, loss of MMR on imatinib = **8%**

Molecular response rate (%)	Month 6 (end of ponatinib)	Month 9	Month 12	Month 18
MMR	44	59	65	68
MR4	23	32	33	40
MR4.5	7	8	10	13

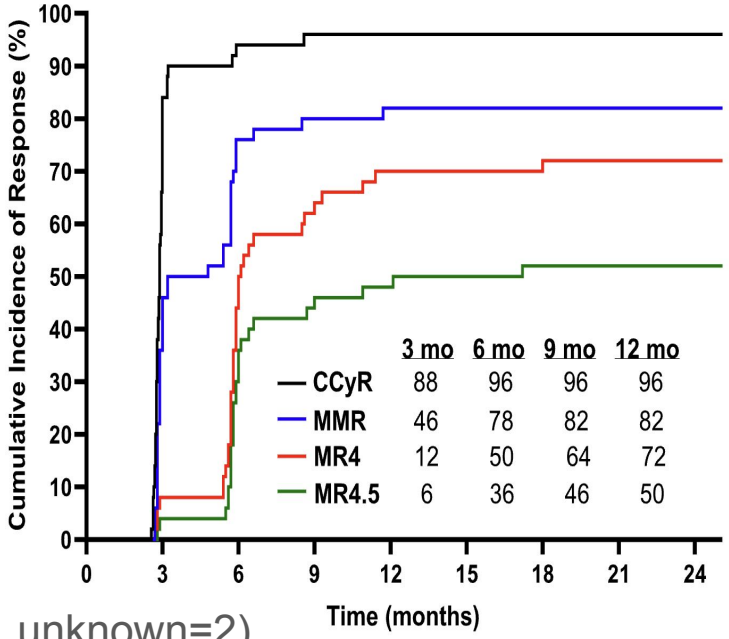
- Grade 3-5 AEs in **39 patients** between M6 and M18: 13 (33%) during imatinib treatment, none of them cardiovascular AE
- 3 deaths: 1 sudden at 2.5 months, 2 from blast phase crisis post SCT (months 3 and 8)

EMR = extramedullary relapse.

Nicolini FE et al. *Blood*. 2024;144 (suppl 1):478.

Ponatinib in Frontline CML-CP: MD Anderson Experience

- 51 patients treated at **45 mg/day**
- Median age, 48 years (21-75); 59% had ≥1 CV comorbidities
- Median time on treatment, **13 months** (2-25)
- Discontinuation due to FDA warning (42%), study (28%), toxicity (28%)
- No transformation, 1 patient had transplant
- **8 (16%) serious CV AEs** in 6 patients, 5 leading to permanent discontinuation
- **6-month MR4 = 61%, 12-month MMR = 82%**
- 10-year OS = 90%, 4 deaths (MDS=1, renal failure=1, unknown=2)



FDA = US Food and Drug administration; OS = overall survival; MDS = myelodysplastic syndrome.
Haddad FG et al. *Cancer*. 2024;130(19):3344-3352.

Impact of Additional Genetic Abnormalities on Outcomes in CML-CP

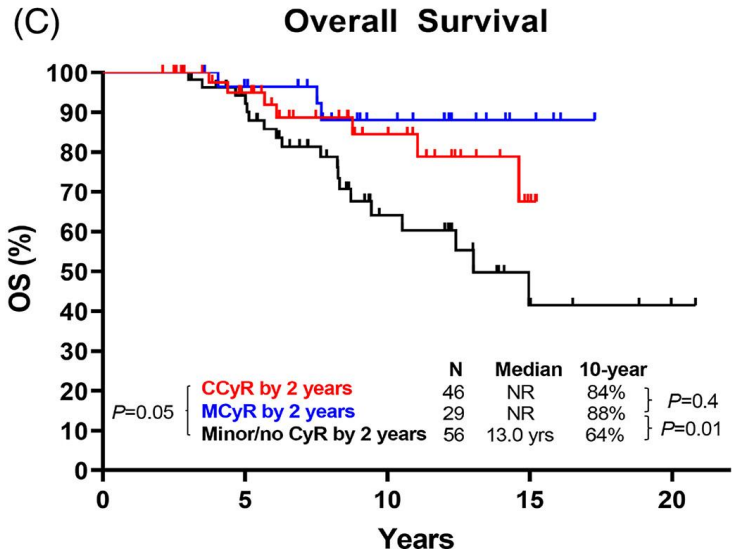
- Cohort of 515 patients (imatinib = 200, dasatinib = 76, nilotinib = 140, asciminib = 99)
- Incidence of cancer-related gene variants (CGVs) = **18%**, most frequently ***ASXL1* (8%)**
- **CGVs associated with**
  - **Higher rate of treatment failure**: 2-year FFS 76% vs 92% (*P*<0.001)
  - **Higher rate of acquisition of KD mutations** at 2 years: 11% vs 0.3% (*P*<0.001)
  - **Lower rate of MMR** at 12 months: 63% vs 82% (*P*=0.002)
- *ASXL1* particularly associated with **worse outcome**: 12-month MMR (55% vs 82%), 2-year FFS (68% vs 93%), 2-year KD mutation acquisition (27% vs <0.3%)
- No impact on overall survival or transformation-free survival

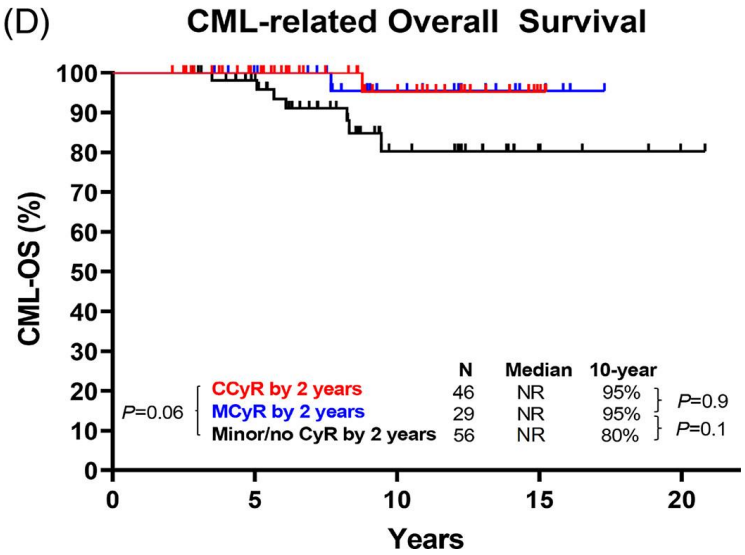
KD = kinase domain.

Shanmuganathan N et al. *Blood*. 2024;144(suppl 1):991.

Outcome of CML-CP With No MMR at 2 Years

- 131 patients with CML-CP and **no MMR after 2 years of TKIs**
- **79 (60%) achieved later MMR**, 24 (30%) on same TKI, 48 (61%) after changing TKI, 9 (11%) after transplant
- Overall: **10-year OS = 76%; 10-year CML-specific OS = 89%**

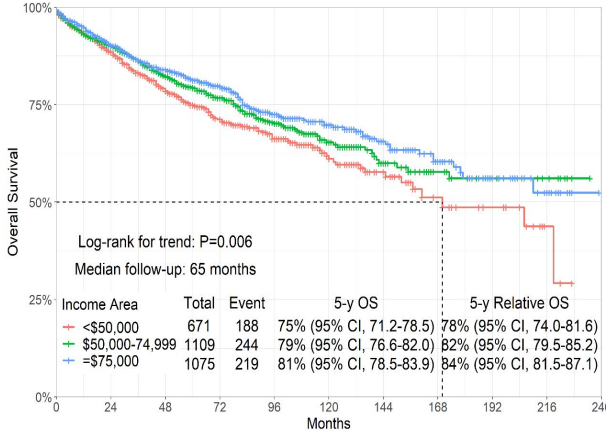


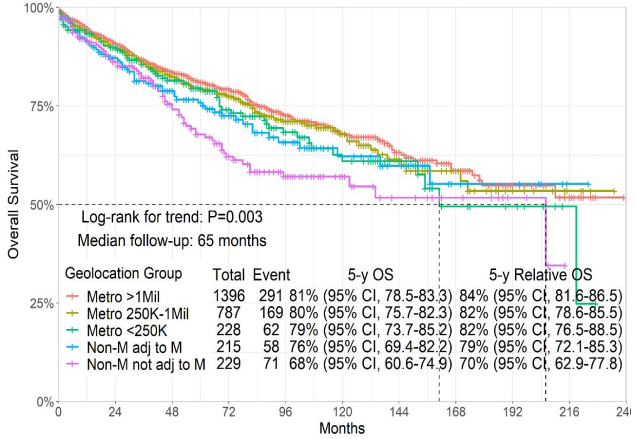


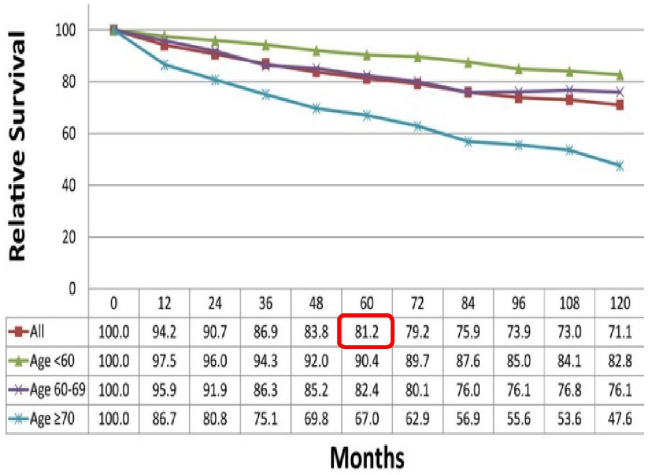
Bidikian A et al. *Am J Hematol.* 2023;98(4):639-644.

Outcomes of CML in the USA: SEER 2000-2019

- SEER database of 2,857 patients with CML
- Lower income = inferior survival (higher costs, out-of-pocket, lack of insurance)
- Smaller geographic populations = inferior outcomes
- Relative OS in USA ≈ 80% *vs* Europe ≈ 90%
- **Around 10%-15% of patients with CML in US not able to access optimal TKIs**







	0	12	24	36	48	60	72	84	96	108	120
All	100.0	94.2	90.7	86.9	83.8	81.2	79.2	75.9	73.9	73.0	71.1
Age <60	100.0	97.5	96.0	94.3	92.0	90.4	89.7	87.6	85.0	84.1	82.8
Age 60-69	100.0	95.9	91.9	86.3	85.2	82.4	80.1	76.0	76.1	76.8	76.1
Age ≥70	100.0	86.7	80.8	75.1	69.8	67.0	62.9	56.9	55.6	53.6	47.6

SEER = Surveillance, Epidemiology, and End Results Database

Sasaki K et al. *Cancer*. 2023;129(23):3805-3814.

Thank you!

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PANEL DISCUSSION

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