CML HORIZONS
HYBRID MEETING 2023

CML ADVOCACY - LEARN, SHARE, GROW
21TH INTERNATIONAL CONFERENCE FOR ORGANISATIONS REPRESENTING PATIENTS WITH CML

CML ADVOCATES NETWORK
Berlin, Germany
03-05 Nov 2023

LMIC - how do we deal with later lines?

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Making sense of later/ alternate lines of therapy in frontline

- Understanding of CML, has influenced the goals of therapy to be revisited - optimising treatment and outcomes. *(Need to be discerning)*

- Frontline Rx CML-CP, imatinib and the three 2nd Gen TKIs (comparable overall survival results.)

- The 2nd Gen TKIs delivers EMR & DMR, reducing the time to TFR. *(if that is an endpoint)*

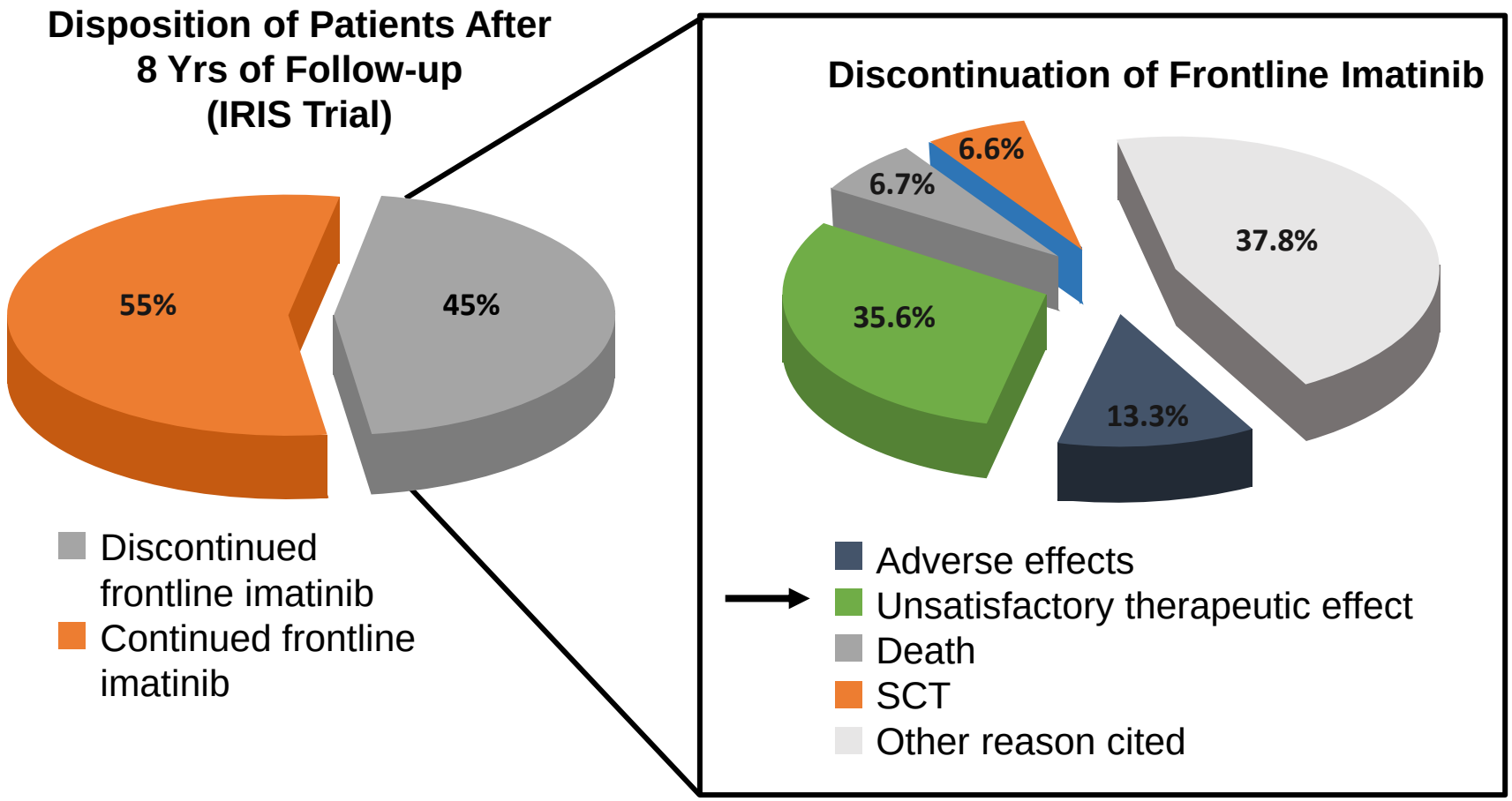
- The choice of the second-generation TKI over imatinib in frontline therapy determined by aims-
  - Survival, TFR,
  - The CML risk,
  - The drug cost, sustainability
  - The toxicity profile with respect to the patient's comorbidities,
  - long term use – drug induced effects, relevance in the older patient.

Making sense of later lines of therapy…. When need is absolute

- When there is intolerance to first line therapy (Imatinib). (the incidence of primary resistance is 10% and secondary 30%)
- When there is less than optimal response to Imatinib
- When there is progression on Imatinib.
- Reasonable in situation of high risk CML at diagnosis

2nd generation TKIs in presence of intolerance/ Resistance - Certainly

Intolerance/Resistance in Patients With CML on Imatinib



Deininger M, et al. ASH 2009. Abstract 1126.

Failure to frontline therapy in CML …

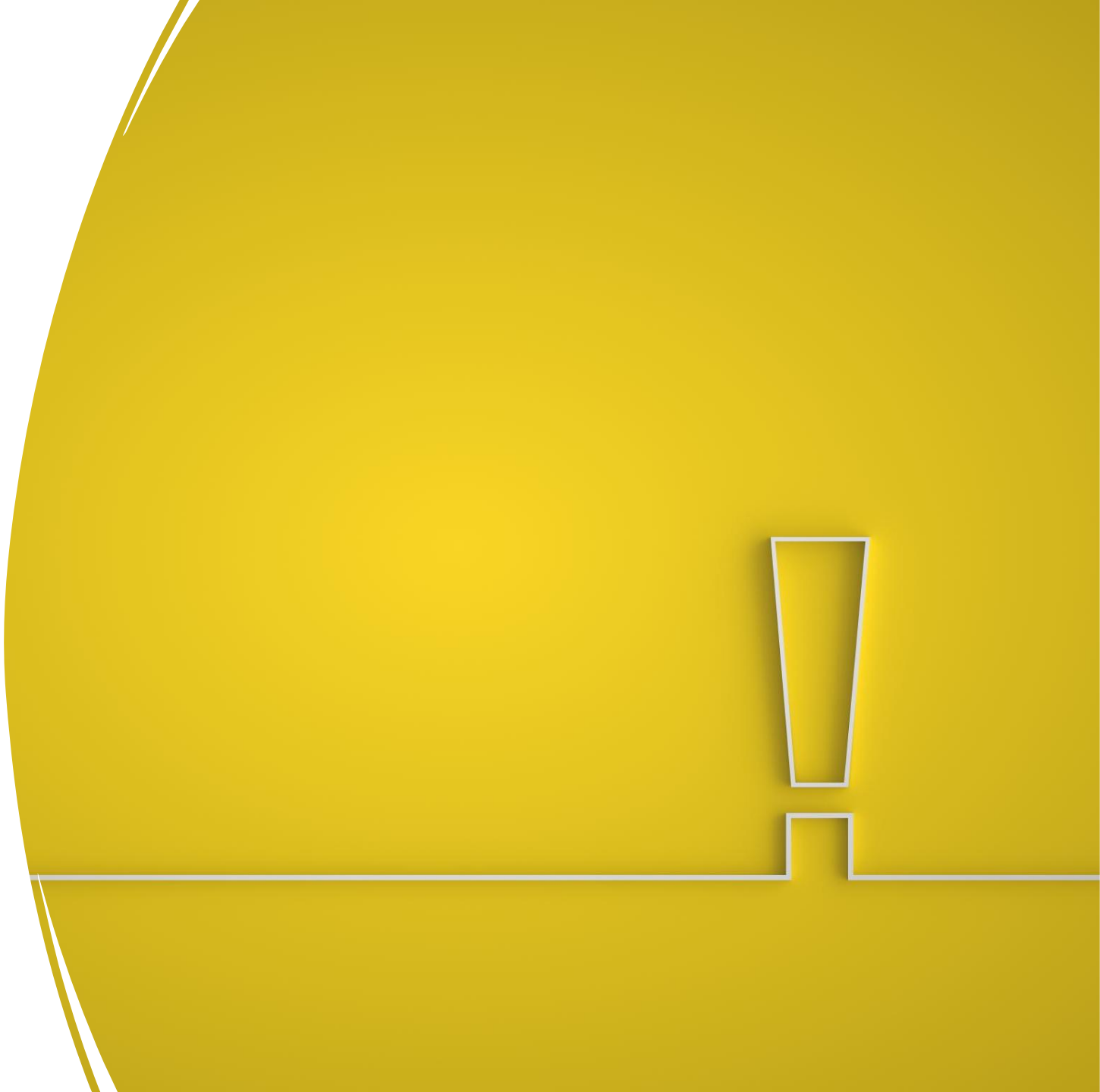
- TKI toxicities
- Treatment resistance .
- Poor compliance to therapy also triggered by inadequately managed drug toxicities, financial burdens and other causes.

TKI	Common side effects	Toxicities to watch for	[a]Prohibitive toxicities	[b]Lowest dose range
Imatinib	Rash, fluid retention, edema, weight gain, musculoskeletal aches, diarrhea, skin depigmentation	Renal toxicity	Neurotoxicity	100–200 mg/day
Nilotinib	Rash, headaches, increased bilirubin, impaired glycemic control, dyslipidemia	Renal toxicity, pancreatitis, Worsening diabetes	Arterio-occlusive and vaso-occlusive events	200 mg/day–200 mg BID
Dasatinib	Pleural effusion, cytopenia	Pulmonary hypertension, systemic hypertension	>1 episode of pleural effusion, pulmonary hypertension	20–50 mg/day
[c]**Bosutinib**	Gastrointestinal toxicity (diarrhea/colitis), renal dysfunction, liver dysfunction	Enterocolitis	Enterocolitis	100–200 mg/day
Ponatinib	Rash, hypertension	Pancreatitis, hepatic toxicity	Arterio-occlusive and vaso-occlusive events; refractory hypertension	15 mg/day

How can we overcome / mitigate toxicities with TKI in first and 2nd line

- Imatinib - fluid retention, periorbital edema, bone and muscle aches,
  - Rarely, weight gain, renal dysfunction and neurotoxicity (dementia-like; parkinsonism). – Reduce dose in responders
- Dasatinib is associated with pleural effusions, and myelosuppression; rarely, patients develop pulmonary hypertension and muscle aches. – Reduce dose, may be idiosyncratic too
- Bosutinib is associated with gastrointestinal (GI) toxicity (diarrhea), and hepatic and renal dysfunction. – Gradual increase in dose
- Nilotinib can exacerbate hyperglycemia and cause dyslipidemia – Reducing dose

- Using 2nd generation TKIs in frontline
- *Would being discretional help for better outcomes*



Discretional use in frontline

- The older patients, survival may be the primary aim, and TFR secondary. - Imatinib a preferable frontline TKI therapy.
- Patient co-morbidities: influence the choice of a TKI - CLD, HT, DM, hepatic or renal dysfunction, pancreatitis, enterocolitis, vaso-spastic or occlusive events, and others.
- Patients with higher-risk disease – 2nd gen TKIs may be favoured over imatinib.
- No advantage has been observed in lower-risk disease.
- The role for lower dose 2nd generation TKI – Dasatinib –MDACC data

Later lines of therapy with the objective of TFR

Using 2nd generation drugs in frontline – The ENEST ND/ ENEST CMR/ DASISION

	Ref. (Study)	Title	TKI
ASH 2011	Marin et al., abstract 785 (SPIRIT 2)	The Predictive Value of Early Molecular Response in Chronic Phase CML Patients Treated with Dasatinib First Line Therapy	Dasatinib
	Hochhaus et al., abstract 2767 (DASISION)	Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP): Analysis of Molecular Response Kinetics in the DASISION Trial	Imatinib and dasatinib
	Hanfstein et al., abstract 783 (CML IV)	Molecular and Cytogenetic Response After 3 Months of Imatinib Treatment Is Predictive for the Risk of Disease Progression and Death in Newly Diagnosed Chronic Myeloid Leukemia Patients – a Follow-up Analysis of the German CML Study IV	Imatinib (with and without interferon)
	Nicolini et al., abstract 1684	The Month Three Major Molecular Response in Chronic Phase Chronic Myeloid Leukemia on imatinib400, Nilotinib and Dasatinib Is a Major Prognostic Factor for Failure-Free and Progression-Free Survival	Imatinib, nilotinib, and dasatinib
JCO 2012	Marin et al., JCO 2012	Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors.	Imatinib and dasatinib
EHA 2012	Hochhaus et al., EHA 2012	Early BCR-ABL Transcript Levels Predict Future Molecular Response And Long-term Outcomes In Newly-diagnosed Patients With CML-CP: Analysis Of ENESTnd 3-year Data	Imatinib and nilotinib
	Jabbour et al., EHA 2012	An exploratory analysis from 3 year DASISION follow-up examining the impact on patient outcomes of early complete cytogenetic responses at 3 months and major molecular responses at 12 months	Imatinib and dasatinib
ASH 2012	Hochhaus et al., ASH 2012	Outcome of Patients with CML-CP Based on Early Molecular Response and Factors Associated with Early Response: 4-Year Follow-up Data from ENESTnd	Imatinib and nilotinib

Cumulative rates of MR 4.5 according to frontline TKI

Patients, %	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years
ENESTnd [29,31,40–42]						
Nilotinib 300 mg twice daily ($n = 282$)	11	25	32	40	53.5	55.7
p value versus imatinib	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Nilotinib 400 mg twice daily ($n = 281$)	7	19	28	37	52.3	54.8
p value versus imatinib	<0.0001	0.0006	0.0003	0.0002	<0.0001	<0.0001
Imatinib 400 mg once daily ($n = 283$)	1	9	15	23	31.4	32.9
ENEST1st[b] [45]						
Nilotinib 300 mg twice daily ($n = 1052$)	20.7	38.6	NR	NR	NR	NR
DASISION[c] [30,43]						
Dasatinib 100 mg once daily ($n = 259$)	5	19	24	34	42	NR
Imatinib 400 mg once daily ($n = 260$)	3	8	13	23	33	NR
p value	<0.2394	<0.0008	<0.0013	<0.0055	<0.0251	NR
CML-Study IV[d] [38]						
Imatinib 400 mg once daily ($n = 337$)	NR	20.9	NR	40.5	NR	55.6

Therefore, the question that emerges…. For TFR

- Can we persevere with Imatinib itself with the objective of a treatment free strategy? If not in a hurry, If 2nd gen TKI may not be the best due to co morbidities
- Is the 2nd Generation TKI going to do a better job in achieving this objective? Yes in achieving early and quicker deep response
- Are there prognostic factors to start with which are favorable or unfavorable? Debatable – no consensus
- Can we convert a less than optimum response to first line by switching and getting them onto a platform to explore TFR – Not certain.

TFR trial	Factors associated with TFR success	robability of maintaining TFR, % (95% CI)	Factors associated with TFR success
STIM1 [4,5,10,17,58]	Low Sokal risk, high NK cell counts[c]	months: 59 · months: 41[b]	Low Sokal risk, high NK cell counts[c]
TWISTER [7]	Duration of IFN treatment >12 months and achievement of UMRD ≤9 months after switching from IFN to imatinib treatment[e]	4 months: 47.1 (31.5–62.7)[d]	Duration of IFN treatment >12 months and achievement of UMRD ≤9 months after switching from IFN to imatinib treatment[e]
A-STIM [9]		2 months: 64 (54–75)[d] · months: 64 (54–75)[d] months: 61 (51–73)[d]	
KIDS [15]	Negativity of digital PCR at screening, duration of imatinib therapy ≥62 months, and imatinib withdrawal syndrome (i.e. aggravation or development of musculoskeletal pain and/or pruritus)[h]	2 months: 62.2[g] · months: 58.5[g]	Negativity of digital PCR at screening, duration of imatinib therapy ≥62 months, and imatinib withdrawal syndrome (i.e. aggravation or development of musculoskeletal pain and/or pruritus)[h]
ISAV [16]	Negativity of digital PCR prior to imatinib discontinuation and patient age (≥ 45 years)	4 months: 50.9	Negativity of digital PCR prior to imatinib discontinuation and patient age (≥ 45 years)
EURO-SKI [12,59,60]	High NK cell counts, low frequency of CD86-positive plasmacytoid dendritic cells[j]	months: 61.5 (54.4–68.3)	High NK cell counts, low frequency of CD86-positive plasmacytoid dendritic cells[j]
STOP 2G-TKI [8,13]	History of suboptimal response or resistance to imatinib[m]	2 months: 61.4 (48.1–74.6)[l] · months: 57.0 (43.3–70.6)[l]	History of suboptimal response or resistance to imatinib[m]
DADI [14]	History of imatinib resistance,[m] high NK cell counts, low γδ+ T-cell count, low CD4+ regulatory T-cell count	2 months: 48 (35–59)	History of imatinib resistance,[m] high NK cell counts, low γδ+ T-cell count, low CD4+ regulatory T-cell count

ADDRESSING THE MOST FREQUENT QUESTION IN CML MANAGEMENT: CHANGING TKI THERAPY IN A PATIENT WITH BCR::ABL1 TRANSCRIPTS (IS) < 1% BUT NOT IN MMR, DMR OR UNDETECTABLE LEVELS

- The absence of MMR by one year -“warning” in the ELN recommendations.
- Patients who do not have high-risk CML features (high-risk additional cytogenetic abnormality, mutations in genes such as ASXL1) and in whom TFR is not an aim - it is reasonable to continue the same TKI at the same dose, provided the patient tolerates the drug well, maintains compliance to therapy and is monitored every 3–6 months.
- As detailed earlier, in patients with persistent low-level BCR::ABL1 transcripts (IS) 0.1–1%, the long-term CML- specific survival is excellent (10-year OS rate about 90%).
- Changing to a third-generation TKI in such situations may increase the toxicities and cost, without improving the long-term outcome.

APPROACH TO PATIENTS WITH T315I MUTATION

- Ponatinib and asciminib
- Stem cell transplant – More doable in LMIC.
- Ponatinib may result in better responses compared with asciminib in T315I-mutated CML - preferred option in the absence of absolute contra- indications. (cost / efficacy)

Generic Availability in India – Can make this a possibility

TKIs	Strength	N	Rupees (app)	$ (app)
Imatinib	400mg	30	2200	30
Dasatinib	20mg 50mg	60 60	1200 2600	15 31
Nilotinib	150mg 200mg	30 30	1740 2040	21 25
Bosutinib	400mg 500mg	30 30	4800 5500	60 65
Ponatinib	15mg 45mg	30 30	18500 49500	225 600

Conclusions

- As patients with CML have a near-normal life span on TKI therapies, it has become increasingly important to clarify the goals of therapy (survival; TFR)
- Important to clarify the likelihood that such goals can be achieved on different TKIs, and then to revisit the treatment milestones that have been standard for the past 2 decades.
- It is also important to clarify the benefit versus toxicity (clinical and financial) of changing TKIs more frequently than necessary in pursuit of goals that may not be achievable
- In patients who are not candidates for TFR, any response below BCR::ABL1 (IS) transcripts <1% is a reasonable goal.
- More stringent molecular goals could be considered in patients in whom a TFR is an aim.
- In patients with non-prohibitive TKI toxicity, dose reductions should be the first step before a TKI change since dose reductions in the right context are effective and safer, often leading to better treatment compliance.