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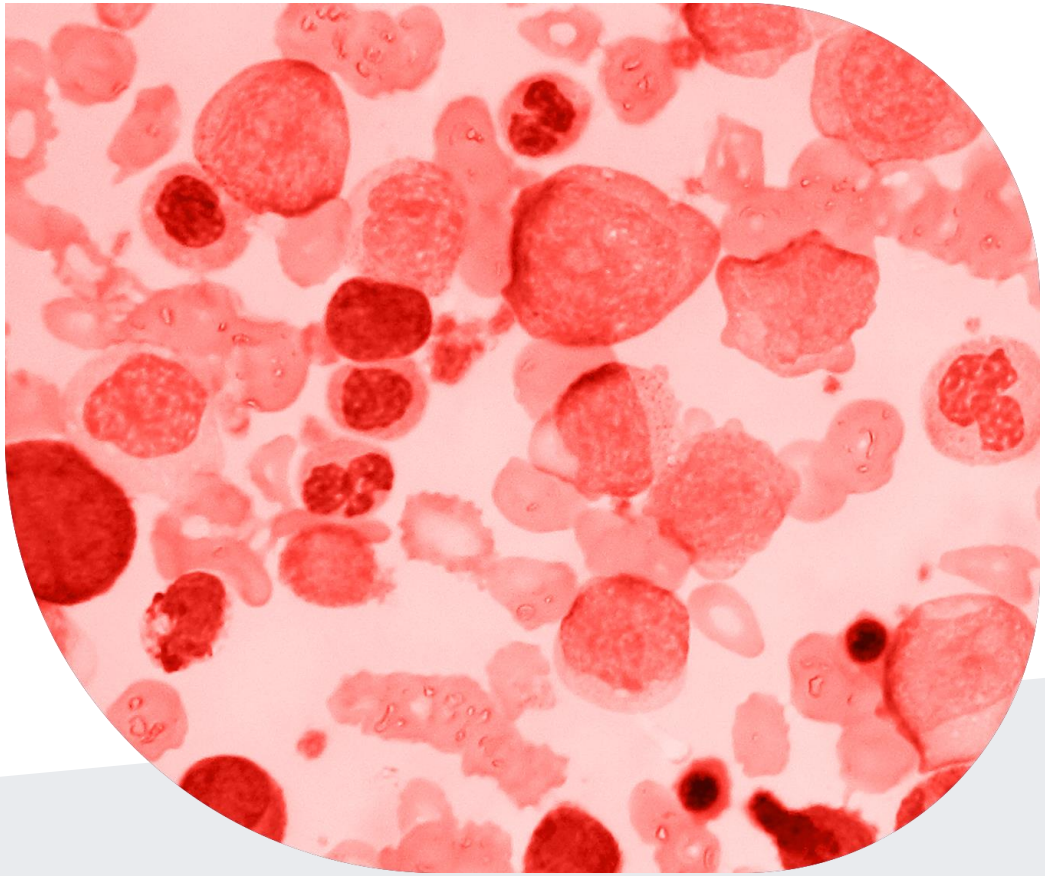
CML: the promise of treatment-free remission



February 2022

Edited by Prof. Gianantonio Rosti

Learning objectives

Following review of these slides the reader should understand:

- Why treatment free remission is a goal for CML therapy
- Studies demonstrating treatment free remission is an achievable goal
- The relevance of first-line TKI choice
- The potential issues that CML patients can experience from TKI withdrawal
- The unanswered questions in TKI withdrawal

CML, chronic myeloid leukaemia; TKI, tyrosine kinase inhibitor.

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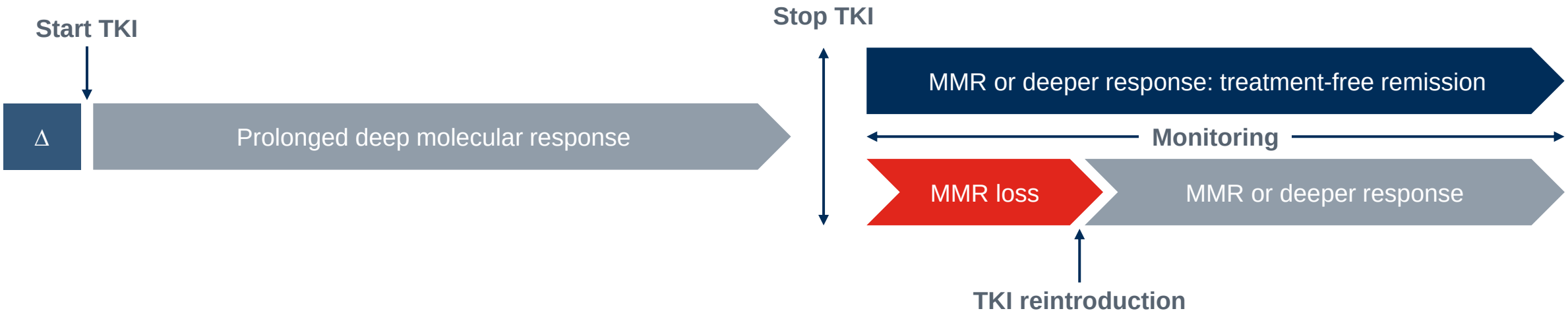
Background to CML treatment-free remission

- 30–50% of patients taking first-generation TKIs achieve undetectable or nearly undetectable molecular residual disease that is sustained if treatment compliance is good[1–3]
- For second generation TKIs, response is even higher: 80% of those receiving first-line dasatinib[4] and 75% receiving first-line nilotinib[5] achieve MR[4.5] and may be eligible for TFR
- As such the need for lifelong treatment in CML has been challenged. Several clinical trials have demonstrated that approximately 40–50% of patients in DMR can remain relapse-free after stopping TKI therapy[6–8]
- This has lead to the latest European LeukemiaNet (ELN) recommendations stating that TFR should be considered as a new goal for treatment of CML[9]



CML, chronic myeloid leukaemia; DMR, deep molecular response; MMR, major molecular response; MR, molecular response; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

1. Branford S, et al. *Blood* 2013;121:3818–24; 2. Hochhaus A, et al. *Leukemia* 2016;30:1044–54; 3. Cortes JE, et al. *J Clin Oncol* 2016;34:2333–40; 4. Maiti A, et al. Cancer 2020;126:1502–11; 5. Masarova L, et al. Cancer 2020;126:1448–59; 6. Etienne GJ, et al. *Clin Oncol* 2017;35:298–305; 7. Ross DM, et al. *Blood* 2013;122:515–22; 8. Saussele S, et al. *Lancet Oncol* 2018;19:747–57; 9. Hochhaus A, et al. Leukemia 2020;34:966–84.

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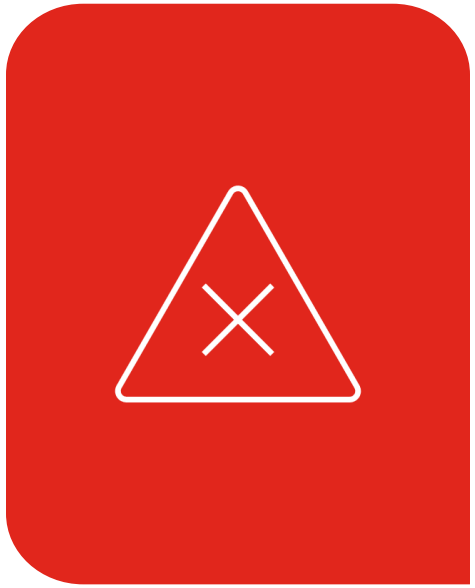
The case for stopping TKI treatment

- Long-term use of TKIs (particularly second-generation TKIs) are associated with adverse events including cardiovascular toxicities, pleural effusion, metabolic toxicities and pulmonary arterial hypertension[1,2]
- TKIs are also associated with less severe events (e.g. fatigue or musculoskeletal pain) that may affect patient quality of life[3]
- Females willing to become pregnant must stop TKIs for the risk of teratogenic effects.[4] Use of TKIs during pregnancy have been associated with spontaneous abortion, hypospadias, exencephaly, encephalopathies and abnormalities of the skull bones[4]
- Lower use of TKIs will also lead to cost savings: considering drug costs alone the EURO-SKI study estimated savings of €22 million for 596 patients who fully or temporarily discontinued treatment[5]
- However, many patients are unwilling to halt treatment. One survey found only 42% of respondents were willing to stop TKIs due to fears of disease recurrence and increased mortality[6]



TKI, tyrosine kinase inhibitor.

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Clinical trials: studies of imatinib discontinuation

Study	N	TFR eligibility*	Rate TFR (%)	Trigger to resume TKI	Relapsing patients	Achievement of second remission
STIM1[1,2]	100	>2/UMRD ≥2	41% at 12 months 38% at 24 months 38% at 60 months	Loss of UMRD on 2 consecutive tests or MMR on 1 test	42/69 (61%) – 12 months 61/100 (61%) – 60 months	26 of 42 (62%) 55 of 57 (96%)
TWISTER[3]	40	3/UMRD ≥2	47% at 24 months	Loss of UMRD on 2 consecutive tests or MMR on 1 test	22/40 (68%) – 27 months	22/22 (100%)
A-STIMI[4]	80	3/MR^4 ≥2	64% at 24 months 61% at 36 months	Loss of MMR, UMRD	31/49 (63%) – 36 months	23/31 (74%)
KID[5]	90	2/UMRD ≥1	50% after 12 months 50% after 24 months	Loss of MMR on 2 consecutive tests	37/90 (41%) – 26.6 months	32/37 (86%)
TRAD[6]	67	3/$MR^{4.5}$ ≥2	65% at 6 months	Loss of MMR^4 on 2 consecutive tests or MMR on 1 test	21/67 (31%) – NR	12/21 (57%, MMR)
EUROSKI[7]	755	3/MR^4 ≥2	62% (123/200) at 6 months	Loss of MMR	39% – 6 months 49% – 24 months	321/373 (86%, MMR)
ISAV[8]	107	2/UMRD ≥1	52% at 12 months	Loss of MMR	37/51 (73%) – 60 months	>95%
JALG-STIM213[9]	68	3/MMR ≥2	67% at 12 months	Loss of MMR	22/68 – 12 months	22/22 (100%)
DOMEST[10]	99	MR^4 ≥2	70% at 6 months 69% at 12 months 64% at 24 months	Loss of MR^4	26/99 – NR	25/26 (96%)

*Minimum TKI duration [yr]/ minimum DMR duration [yr].

DMR, deep molecular response; IM, imatinib; MMR, major molecular response; MR, molecular response; TFR, treatment-free response; UMRD, undetectable molecular residual disease.

1. Mahon FX, et al. *Lancet Oncol* 2010;11:1029–35; 2. Etienne G, et al. *J Clin Oncol* 2017; 35:298–305; 3. Ross DM, et al. *Blood* 2013;122:515–22; 4. Rousselot P, et al. *Blood* 2013;122:381; 5. Lee SE, et al. *Haematologica* 2016;101:717–23; 6. Kim DDH, et al. *Blood* 2016;128:1922; 7. Saussele S. et al. Lancet *Oncol* 2018;19:747–57; 8. Diral E, et al. *Blood* 2020;136:2237–40; 9. Takahashi N, et al. *Int J Hematol* 2018;107:185–93; 10. Fujisawa S, et al. *Int J Clin Oncol* 2019;24:445–53.

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Clinical trials: studies of nilotinib or dasatinib discontinuation

Study	N	TFR eligibility*	Rate TFR (%)	Trigger to resume TKI	Relapsing patients	Achievement of second remission
STAT2[1]	90	2 yr/MR[4.5]	63% IM first line at 12 months 70% IM then NIL at 12 months	NR	NR	NR
NILSt[2]	87	2 yr/MR[4.5] ≥2	80% at 12 months	Loss of MR[4.5]	34/87 (39%) – ~6 months	32/34 (94%)
ENESTFreedom[3]	190	3.6 yr/MR[4.5] ≥2	52% at 48 weeks 49% at 96 weeks	Loss of MMR	88/190 (46%) – 48 weeks 69/190 (36%) – 96 weeks	87/88 (99%)
ENESTop[4,5,6]	126	≥3 yr/MR 4.5	58% at 48 weeks 53% at 96 weeks 46% at 192 weeks 43% at 5 years	Loss of MR[4], or MMR	NR	52/56 (93%) at 96 weeks 56/59 (95%) at 192 weeks 58/59 (98%) at 5 years
DADI[7,8]	63	1 yr/DMR ≥2	49% at 6 months 48% at 12 months 44% at 3 years	Loss of MR[4]	33/63 (52%) – 7 months 35/63 (56%) – 21 months	29/33 (88%) – 3 months 33/33 (100%) – 6 months 33/35 (94%) – 6 months
D-STOP[9,10]	54	2 yr/DMR ≥2	68% at 6 months 63% at 12 months 59% at 36 months	Loss of MMR	22/54 (41%) – 7 months	22/22 (100%) – 12 months
DASFREE[11]	84	2 yr/MR[4.5] ≥1	48% at 12 months 46% at 2 years	Loss of MMR	46/84 (55%) – 2 years	43/45 (96%) – 3 months
DADI (First-line)[12]	58	3 yr/DMR ≥2	55% at 6 and 12 months	Loss of MR[4]	26/58 (45%) – 6 and 12 months	23/25 (92%) – 12 months
STOP 2G-TKI[13]	60	3 yr/MR4.5 ≥2	63% at 12 months 54% at 24 months	Loss of MMR	26/60 (43%) – 4 months	NR
LAST[14]	172	≥3 yr/MR4 ≥2	61% at 36 months	Loss of MMR	59/172 (39%) – 36 months	55/59 (93%) – NR
Etienne et al.[15]	95		55% at 12 months 47% at 24 months	Loss of MMR	NR	NR

*Minimum TKI duration[yr]/ minimum DMR duration [yr];. DMR, deep molecular response; IM, imatinib; MMR, major molecular response; MR, molecular response, NIL, Nilotinib; N/R, not reported.

1. Takahashi N, et al. *Blood* 2016:128:1889; 2. Kadowaki N, et al. *Blood* 2016;128:790; 3. Ross D, et al. *Haematologica* 2017;102,P601; 4. Hughes TP et al. *Haematologica* 2017;102:P257; 5. Hughes TP, et al. *J Clin Oncol* 2019;37:7005; 6. Mahon FX, et al. *Blood* 2020;136(suppl1):29–30; 7. Imagawa J, et al. *Lancet Hematol,* 2015;2:e528-35; 8. Okada M, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:353-60.e1; 9. Kumagai T. et al. *Cancer Sci* 2018;109:182–92; 10. Kumagai T, et al. *Cancer Sci* 2020; 111:2923–34; 11. Shah NP et al. *Leuk. Lymphoma*. 2020; 61:650-9; 12. Kimura S. et al. *Lancet Haematol* 2020;7:e218-25; 13. Rea D, et al. *Blood* 2017;129:846–54; 14. Atallah E, et al. *JAMA Oncol* 2021;7:42–50; 15. Etienne G, et al. *Cancers* 2020;12:2521.

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Clinical trials: real-world data

Study	N	TFR eligibility*	Type of TKI	TFR rate/result	Trigger to resume TKI	Relapsing patients	Achievement of second UMRD
Spanish[1]	236	3 yr/MR$^{4.5}$ ≥2	IM (n=175), NIL (n=41), DAS (n=17), BOS (n=1), PON (n=1)	64% at 4 years	Loss of MMR	20% at 6 months 26% at 12 months 33% at 3 years	NR
Italian[2]	293	MMR/DMR	IM (n=211), NIL (n=82), DAS (n=23), BOS (n=1)	68% at 12 months (IM) 73% at 12 months (2G)	Loss of MMR/DMR	114/293 (39%) – 12 months (75%)	94% MMR, 82% DMR
UK[3]	28	NR	IM (n=22), NIL (n=3), DAS (n=3)	Median TFR not reached (median 2.5 yr follow-up)	NR	10/28 (35.7%) – 6 months (90%)	60% MMR
German[4]	268	MR^{4}	NR	55%	NR	106/268 (40%)	NR
Portugal[5]	25	DMR	NR	76%	NR	56% after 4 months (median)	All patients regained ≥MMR
Andalusian[6]	71	MR$^{4.5}$ for 3 yr	IM (n=51), NIL (n=12), DAS (n=7)	78% at 9 months	NR	NR	NR
Swedish[7]	548	5 yr/>MR^{4}	IM (n=58), 2nd gen (n=42), Switched (22%)	23% at 1 month	NR	NR	NR
US[8]	100	MR$^{4.5}$	IM (n=47), DAS (n-35), NIL (n=14), BOS (n=2), PON (n=2)	100%	Loss of MR$^{4.5}$	35% at 30 months	26/28 (93%) regained MR$^{4.5}$
Japan[9]	53	DMR		53%			

*Minimum TKI duration[yr]/ minimum DMR duration [yr]. 2G, second generation; BOS, bosutinib; DAS, dasatinib; DMR, deep molecular response; IM, imatinib; MMR, major molecular response; MR, molecular response; NIL, nilotinib; NR, not reported; PON, ponatinib; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor; UMRD, undetectable molecular residual disease.

1. Hernández-Boluda JC, et al. *Blood Cancer Journal* 2018;8:91; 2. Fava C, et al. *Haematologica* 2019;104:1589–96; 3. Kwok M. et al. EHA Learning Center. 2019, PB1946; 4. Dengler J, et al. *Hemasphere* 2019;3(S1):PF418; 5. Cerveira N, et al. EHA Learning Center 2018; Abstract 216327:PB1963; 6. Alarcón-Payer C, et al. *HemaSphere* 2019; 3(S1):884; 7. Flygt H, et al. *Br J Haematol* 2021;193:915–21; 8. Chamoun K, et al. *J Hematol Oncol* 2019;12:1; 9. Ureshino H, et al. *Hematol Oncol* 2021;39:549–57.

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Clinical trials: second attempt at TKI discontinuation

Study	N	Trigger for reinitiation of TKI	TKI treatment at primary and secondary discontinuation	TFR following second discontinuation	Conclusion
TRAD[1]	75	Loss of $MR^{4.5}$	Primary: IM (n=75) Secondary: NIL (n=67)	N/A	Dasatinib can be safely administered in CML patients who lost molecular response after IM discontinuation with 100% of MMR rate at 3 months
RE-STIM[2,3]	106	Loss of MMR (66%) Loss of $MR^{4.5}$ (33%)	Primary: IM (n=101), NIL or DAS (n=5) Secondary: N/A	48% at 1 yr 44% at 2 yrs 39% at 3 yrs 33% at 4 yrs	TKIs could safely and successfully be discontinued a 2nd time in CP CML patients despite a 1st failure. The speed of molecular relapse after the 1st TKI discontinuation and TKI-free duration remain major factors significantly associated with TFR outcome
KID[4]	23	Loss of MMR	Primary: IM Secondary: IM	35% at 2.9 months	A second attempt at TFR with IM might be possible and the median time to MMR loss after second discontinuation was similar to that of the first discontinuation

CML, chronic myeloid leukaemia; CP, chronic phase; DAS, dasatinib; IM, imatinib; MR, molecular response; MMR, major molecular response; N/A, not applicable; NIL, nilotinib; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

1. Kim DDH, et al. *Blood* 2016;128:1922; 2. Legros L, et al. *Cancer* 2017;123:4403–10; 3. Legros L, et al. *Blood* 2019;134 (suppl 1):28; 4. Lee SE, et al. *Blood* 2020;136 (suppl 1):51–2.

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Criteria for TKI discontinuation: expert recommendations and guidelines

	ESMO (2017)[1]	NCCN (2018)[2]	FCMLG (2018)[3]	ELN (2020)[4]
Age (yr)	≥18	≥18	≥18	–
History CML	CP only/optimal response	CP only/ No prior history progression or treatment resistance	CP only/ No HSCT, progression, resistance, suboptimal response	CP only
Sokal score	Not a high score	–	–	–
BCR-ABL1 transcript	Quantifiable typical transcript	Quantifiable typical transcript	e13a2, e14a2 or e13a2 +e14a2	Typically e13a2 or e14a2
TKI duration	≥5 yrs	≥3 yrs	>5 yrs	Minimal criteria: 5 yr (>4 yr for 2GTKI) Optimal criteria: >5 yr
Duration DMR	≥MR^4 for ≥2 yrs	>2 yrs	>2 yrs	Minimal criterial: ≥MR^4 for >2 yrs Optimal criteria: >3 yrs if MR4 or >2 yrs if $MR^{4.5}$
Retreatment	N/A	Loss of MMR	Loss of MMR	Within 4 weeks of MMR loss
Frequency monitoring	Monthly for first 6 months Every 6 weeks for second 6 months Every 3 months thereafter	Monthly for first year Every 6 weeks in second year Every 12 weeks thereafter	Monthly for first 6 months Every 2 months from 6–12 months Every 3 months during second year Every 3-6 months thereafter	Monthly during first 6 months Every 2 months from month 6–12 Every 3 months thereafter

2GTKI, second generation TKI; CP, chronic phase; DMR, deep molecular response; ELN, European Leukemia Net; ESMO, European Society for Medical Oncology; FCMLG, French Chronic Myeloid Leukemia Study Group; HSCT, haematopoietic stem cell transplant; MMR, major molecular response; MR, molecular response; N/A, not available; NCCN, National Comprehensive Cancer Network; TKI, tyrosine kinase inhibitor.

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An example guide to selection of patients suitable for TFR

Criteria	Green	Yellow	Red
Sokal score at diagnosis	Non-high	High	–
BRC-ABL transcript at diagnosis	Typical – B2A2 or B3A2 (e13a2 or e14a2)	Atypical, but can be accurately quantified	Not quantifiable
CML past history	CP only	Resistance or KD mutation	Prior AP or BC
Response to first line TKI therapy	Optimal	Warning	Failure
Duration of all TKI therapy	>8 years	3–8 years	<3 years
Depth of deep molecular response	$MR^{4.5}$	$MR^{4.0}$	Not in $MR^{4.0}$
Duration of deep molecular response monitored in a standardised laboratory	>2 years	1–2 years	<1 year
	Strong recommendation to consider TKI withdrawal	Only consider TKI withdrawal in high priority circumstances (e.g. significant toxicity or planned pregnancy)	TKI withdrawal not recommended except in a clinical trial

AC, acute phase; CML, chronic myeloid leukaemia; CP, chronic phase; KD, kinase domain; MR, molecular response; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

Adapted from Hughes TP & Ross D. *Blood* 2016;128:17–23.

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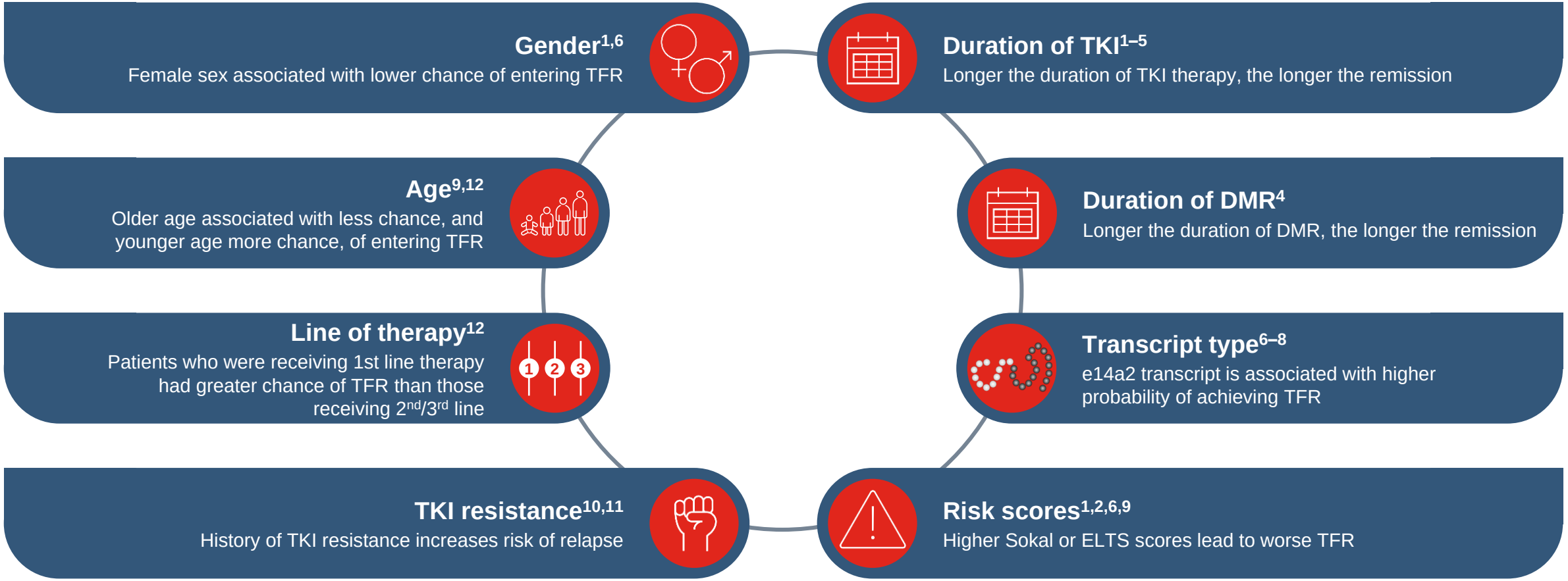
Factors predicting TFR success



DMR, deep molecular response; ELTS, EUTOS Long-Term Survival; EUTOS, European Treatment Outcome Study; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

1. Mahon FX et al. *Lancet Oncol. 2010*;11:1029–35; 2. Etienne G, et al. *J Clin Oncol.* 2017;35:298–305; 3. Lee SE, et al. *Haematologica* 2016;101:717–23; 4. Saussele S. et al. *Lancet Oncol.* 2018;19:747–57; 5. Fujisawa S, et al. *Int J Clin Oncol.* 2019;24:445–53; 6. Etienne G, et al. *Cancers* 2020;12:2521; 7. Castagnetti F et al. *Am J Hematol.* 2017;98:797–805; 8. Baccarani M, et al. *Leukemia* 2019;33:2358–64; 9. Fava C et al. *Haematologica* 2019;104:1589–96; 10. Imagawa J. et al. *Lancet Haematol.* 2015;2: e528-35; 11. Rea D et al. Blood 2017;129:846–54; 12. Shah NP et al. *Leuk. Lymphoma.* 2020;61:650–9.

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Low-level risk from TFR

- Sudden blast crisis (SBC) is categorized as rapid onset of blast crisis, during a documented ‘optimal‘ response to TKI therapy and within 3 months of a normal complete blood count.[1]
- There have been reported cases of SBC in some of the studies examining TFR, but the incidence of such events is very low,[2–4]
- In addition, while a proportion of patients do relapse, virtually all patients re-achieve a good response after restarting TKI, indicating that disease control can be maintained.

SBC, sudden blast crisis; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

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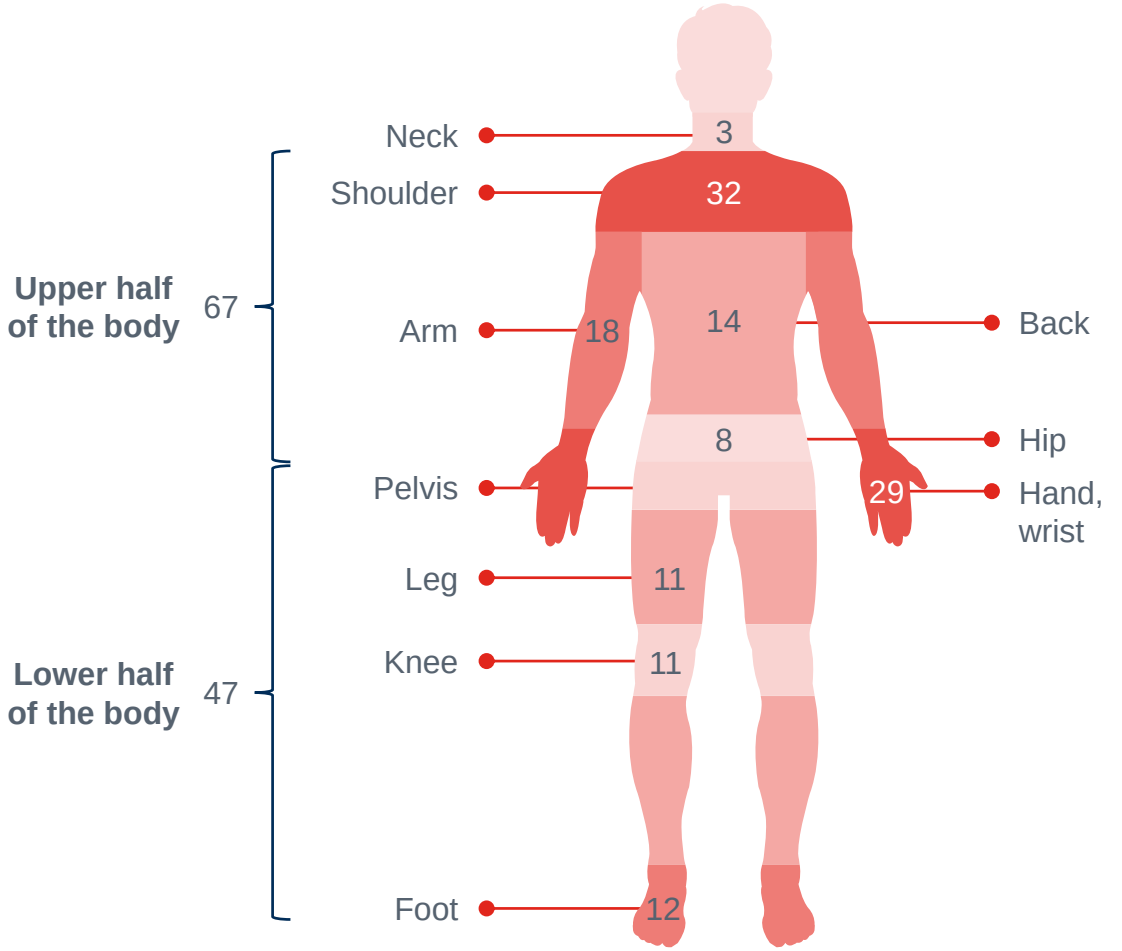
TKI withdrawal syndrome

- In a retrospective analysis of 427 CML patients (from STOP-TKI and EURO-SKI), 23% developed musculoskeletal symptoms on TKI withdrawal.[1] Longer duration of TKI treatment and history of osteoarticular symptoms predisposed patients[1]
- Withdrawal symptoms include diffuse myalgia, arthralgia, or musculoskeletal pain affecting arms, hips and extremities.[2]
- Symptoms resolve immediately for patients resuming TKIs,[3] and eventually go away for those continuing to stop treatment (may take many months)[4]
- Symptomatic treatment with mild analgesics (e.g. paracetamol and non-steroidal anti-inflammatory drugs) may help, but more severe cases require steroids[4]
- The mechanism of TKI withdrawal syndrome is not clear, it may be due to withdrawal of off-target TKI effects (i.e. targets other than ABL1)[4]
- Whether 'withdrawal syndrome' may be minimized by tapering TKI doses over several months before discontinuation remains an open question[5]



CML, chronic myeloid leukaemia; TKI, tyrosine kinase inhibitor.

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Conclusions

- DMR and TFR are feasible treatment goals in CML and expert recommendations on TKI discontinuation in clinical practice have been published
- About 40–60% of patients with long-lasting DMR on TKI therapy are likely to remain in prolonged TFR after treatment discontinuation
- Studies have shown that the use of 2nd generation TKIs may increase the proportion of potential candidates eligible for TKI discontinuation
- While a significant proportion of patients relapse during TFR, nearly all regain response once treatment is reinitiated
- There remains a possibility for patients who fail a first TFR to discontinue TKI again with close monitoring

CML, chronic myeloid leukaemia; DMR, deep molecular response; TFR, treatment-free response; TKI, tyrosine kinase inhibitor.

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