STOPPING TKI THERAPY IN CML

WHO, WHEN AND HOW?

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TREATMENT-FREE REMISSION IS POSSIBLE FOR SOME CML PATIENTS!

- TKI therapy has changed the outlook and management landscape for patients with CML
- Tradeoffs
  - Medical toxicities
  - Psychological burdens
  - Financial burden of long term use
- TKI discontinuation is feasible in some patients who achieve deep molecular responses
  - Which patients are good candidates?
  - How do we do it?
  - What if the disease comes back?
  - What's on the horizon?

A REFRESHER ON DEFINITIONS OF MOLECULAR RESPONSE

Depth of MR	BCR::ABL Transcript Level
MMR ($MR^{3.0}$)	≤ 0.1% IS
$MR^{4.0}$	≤ 0.01% IS
$MR^{4.5}$	≤ 0.0032% IS
$MR^{5.0}$	≤ 0.001% IS

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STOP IMATINIB (STIM) TRIAL

- First large prospective multicenter study of imatinib discontinuation (n=100 pts)
- Eligibility
  - CML in CP1 or AP treated with imatinib for ≥ 3 yrs
  - Sustained MR^5 for ≥ 2 yrs
  - No prior allo-transplant
- Results
  - K-M molecular recurrence free survival was 43% at 6 mos and 38% at 60 mos
    - Most relapses occurred within 6 mos of discontinuation
    - Latest relapse was at 19 mos
  - All relapsing pts responded to reintroduction of imatinib
  - Sokal score at dx and imatinib treatment duration were predictors of TFR

MahonFX, et al. Lancet Oncology. 2010; 11(11): 1029-35
Etienne G, et al. J Clin Oncol.2017; 35:298-305

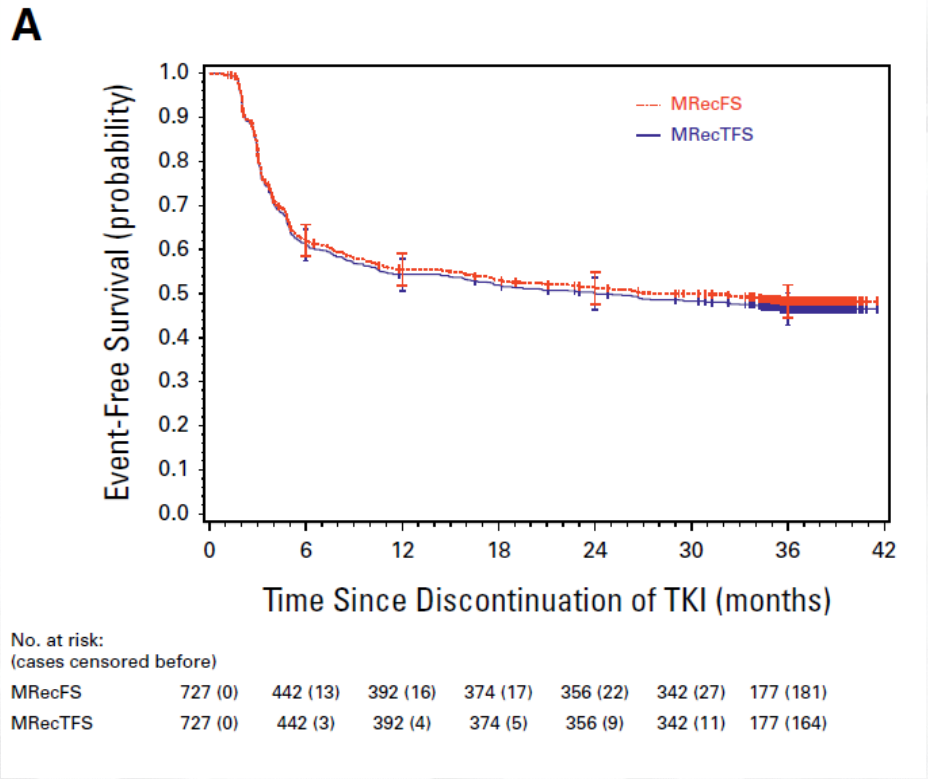
EURO-SKI STUDY

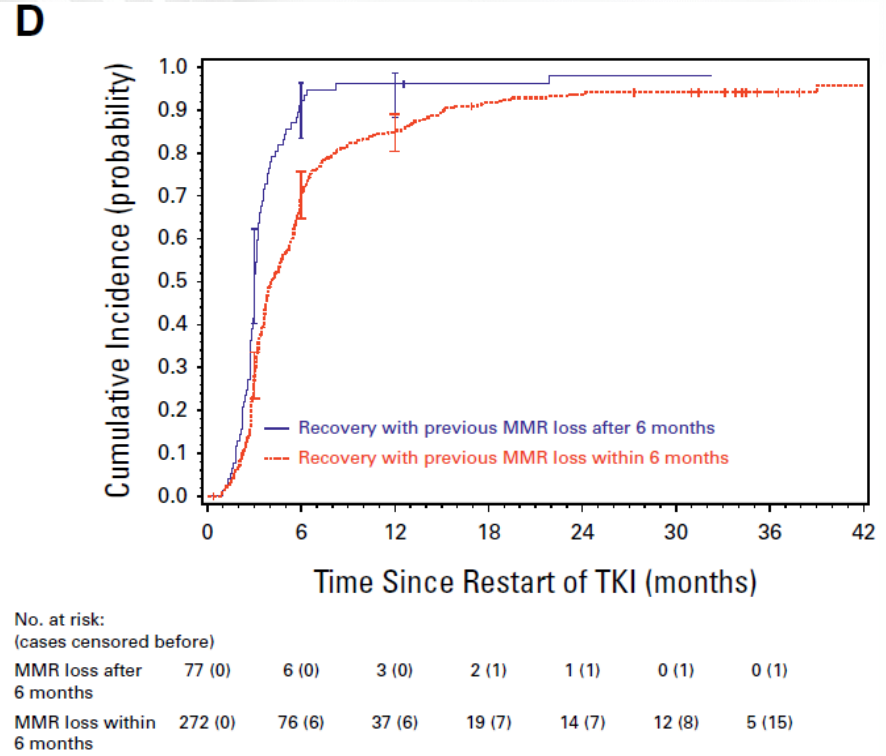
- Largest prospective trial of TKI discontinuation in adults with CML (n=758)
- Inclusions
  - CML in CP1
  - On any TKI for at least 3 years
    - Excluded pts with treatment failure to 1st line TKI
    - Majority of subjects were on imatinib prior to treatment discontinuation
  - $MR^{4.0}$ for at least 1 year
- Molecular monitoring monthly for the first 6 mos after TKI discontinuation
- Definition of failure: loss of MMR ($MR^{3.0}$)

Saussele, S et al. Lancet Oncology. 2018; 19: 747-757
Mahon, F-X et al. J Clin Oncol. 2024; 42(16): 1875-1880

EURO-SKI OUTCOMES

- Molecular Recurrence-Free Survival (MRecFS) at 6 mos and 36 mos: 61% and 46%, respectively
- Recovery of MR^4 after loss of MMR and restafrting TKI: 92% at 12 mos
- No instances of loss of hematologic remission or progression to accelerated phase or blast phase observed





Saussele, S et al. Lancet Oncology. 2018; 19: 747-757
Mahon, F-X et al. J Clin Oncol. 2024; 42(16): 1875-1880

EURO-SKI: OTHER LESSONS LEARNED

- Predictors of maintaining MMR at 6 mos
  - Duration of TKI treatment and DMR (every additional yr ~3% increase in probability of maintaining MMR)
  - Transcript type (e14a2)

- Predictors of MMR maintenance between 6-36 mos
  - Duration of TKI treatment (but not DMR)
  - Peripheral blast % and plt count at dx

- *Early (<6 mos) and later relapses may be biologically different*

WHAT IS THE BIOLOGY OF SUCCESSFUL TREATMENT FREE REMISSION?

- Numerous studies document stable low level persistence of *BCR::ABL* transcripts in some patients without clinical relapse after TKI discontinuation
  - Persistence in lymphocytes?
  - Persistence in non-proliferating neoplastic cells associated with leukemic stem cell exhaustion?

- What is the role of the immune system in maintaining treatment-free remission?

WHAT ABOUT PATIENTS WHO FAIL INITIAL TKI DISCONTINUATION?

- Numerous small studies indicate that a second attempt at TKI discontinuation can be successful in some patients who achieve a 2nd deep molecular response (at least MR^4)

- Time to molecular relapse after 1st attempt is most predictive of success with 2nd attempt at TKI discontinuation
  - Several studies suggest relatively favorable results if molecular relapse was > 3 mos after initial TKI discontinuation

- **No current consensus recommendations regarding TFR2 attempt**

Reviewed in: Ciftciler R, et al. Clin Lymphoma, Myeloma, Leukemia. 2023; 23: 8-14.

TKI WITHDRAWAL SYNDROME

- Occurs in 10-40% of pts after stopping TKI, typically within 3-4 mos
- Worsening musculoskeletal pain +/- rash
- More frequent in women
- Longer duration of TKI treatment and antecedent arthritis symptoms also associated with increased risk
- Tapering TKI seems to have little effect on incidence or severity
- Management is symptomatic
  - Analgesics, NSAIDs
  - Brief course of steroids may be useful if severe
  - Restarting TKI is NOT necessary
  - Symptoms generally resolve within a few months

RECOMMENDATIONS FOR A TREATMENT DISCONTINUATION TRIAL

Criteria	NCCN (2023)	ELN (2020)*
Disease Status	CML in CP1 with no prior treatment failure	same
BCR::ABL Testing	qPCR with sensitivity up to at last $MR^{4.5}$	same
Duration of TKI Therapy	> 3 yrs	> 5 yrs (imatinib) > 4 yrs (2GTKI)
Duration of DMR (MR^4)	> 2 yrs	same
Monitoring	Monthly x 6 months, then q 2 mos x 6 mos then q 3 mos	same
Resumption Criteria	Loss of MR^3	same

*Hochhaus A et al. Leukemia. 2020; 34: 966-84)

HOW MANY PATIENTS DO WE EXPECT TO BE ELIGIBLE FOR D/C OF TKI?

Study	TKI / Response	5 years (%)	10 yrs (%)
ENESTnd*	Nilotinib / MR^4	66	73
	Nilotinib/ $MR^{4.5}$	54	64
	Imatinib / MR^4	42	56
	Imatinib / $MR^{4.5}$	35	45
DASISION**	Dasatinib / $MR^{4.5}$	42	NA
	Imatinib / $MR^{4.5}$	33	NA

***Hochhaus, A et al. Leukemia. 2016; 30: 1044-54. Hughes,T et al. Blood. 2019; 134: 2924 (abstract).**
****Cortes, JE et al. J Clin Oncol. 2016; 34: 2333-40.**

MANAGEMENT OF CML DURING PREGNANCY

- Off target effects of TKIs lead to increased risk of miscarriage, hydrops fetalis, and congenital malformations
- Risk is greatest in first trimester, but consensus recommendations are that TKIs be avoided throughout pregnancy
- Once pregnancy is confirmed, TKI should be stopped
  - If pt is in DMR, can stop prior to attempt to conceive, with monthly monitoring
  - For pts in chronic phase not in DMR, monthly monitoring still appropriate
  - For pts beyond chronic phase, a frank discussion is in order, as it is less likely that disease control will be able to be maintained without TKI and/or chemotherapy
- For pts who lose hematologic control with rapidly rising WBC, interferon is ok throughout pregnancy

TKI DISCONTINUATION: TAKE HOME MESSAGES

- Who?
  - TKI treatment for at least 3 yrs
  - MR^4 for at least 2 yrs
  - **The longer TKI therapy and MR^4 the better**
- Monitor closely
  - Monthly mo 1-6, then q 2 months 7-12, then q 3 mos for at least 5 yrs
  - Resume TKI if PCR rises back to MR^3
- After failure, a second TKI discontinuation trial is not unreasonable, but probably want a long period of MR^4
- Pregnancy
  - Monitor monthly
  - Interferon ok if needed

A FEW ONGOING QUESTIONS

- Can addition of other agents to TKI therapy increase the likelihood of successful TKI discontinuation?
- What is the role of ultrasensitive molecular monitoring in refining decision-making in these patients?
- Role of novel biomarkers in predicting CML outcomes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