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Starting & stopping therapy in Chronic Myeloid Leukemia: What more is needed?

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  - Delta Fly Pharma
  - Novartis

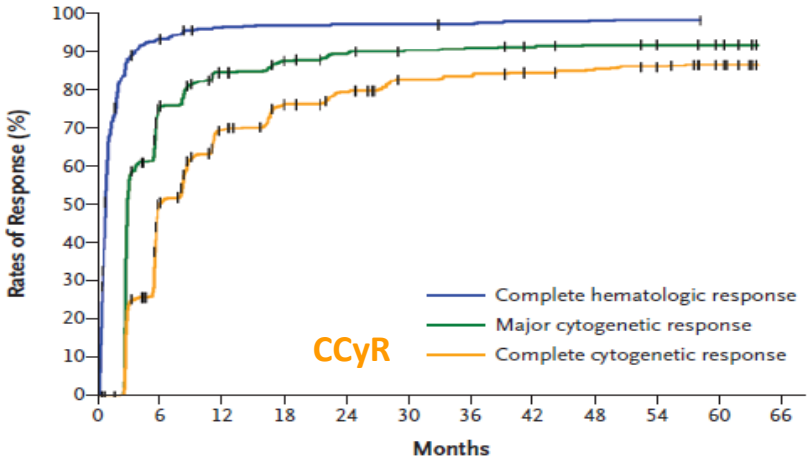
Learning Objectives –

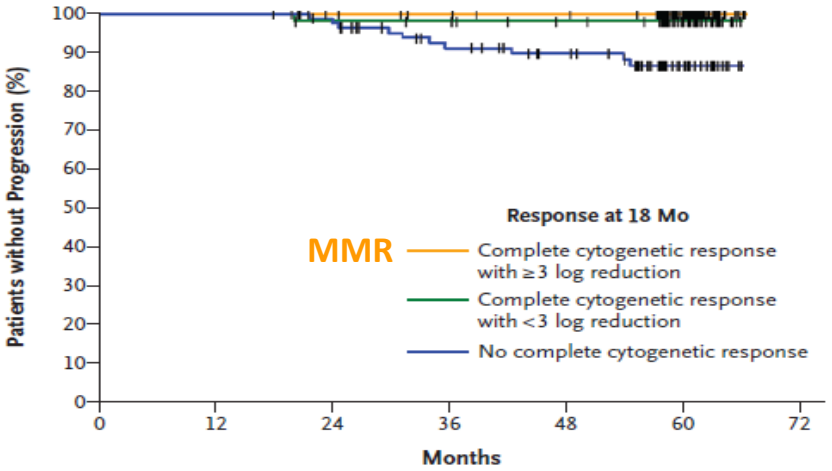
CML: Starting, switching, de-escalating, discontinuing

- Which TKI to start?
- Switching based on Early Molecular Response (EMR)
- Reducing dosages to reduce side-effects
- Asciminib (ABL001; Novartis) – a non-ATP competitive inhibitor of BCR/ABL1
- Discontinuation studies (18 so far)

ORIGINAL ARTICLE

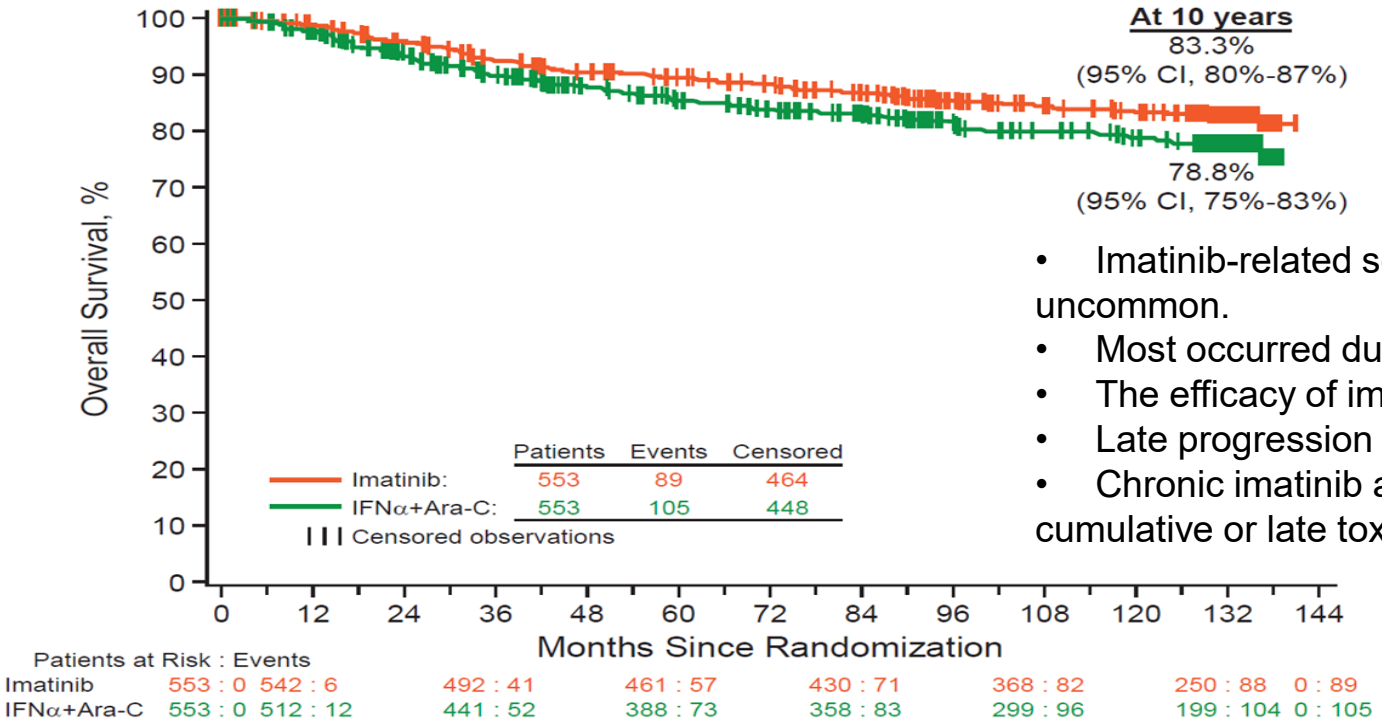
Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia





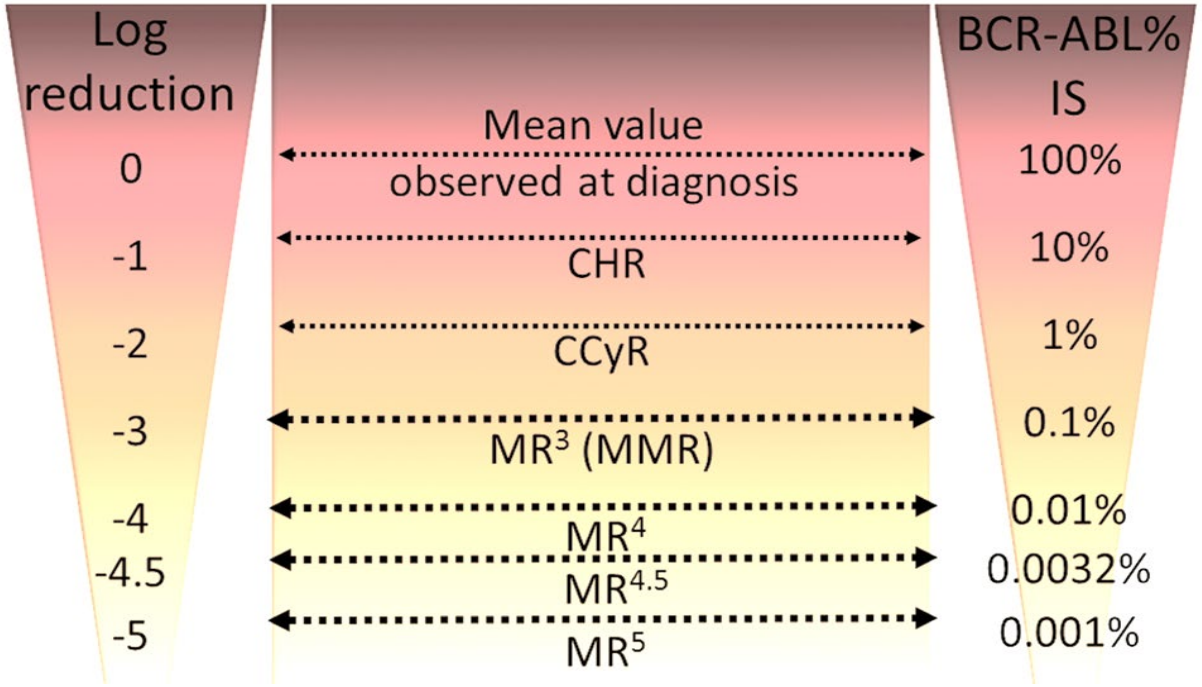
BJ Druker et al. New Engl J Med 2006;355:2408-17.

The IRIS Trial: Imatinib vs Interferon + AraC



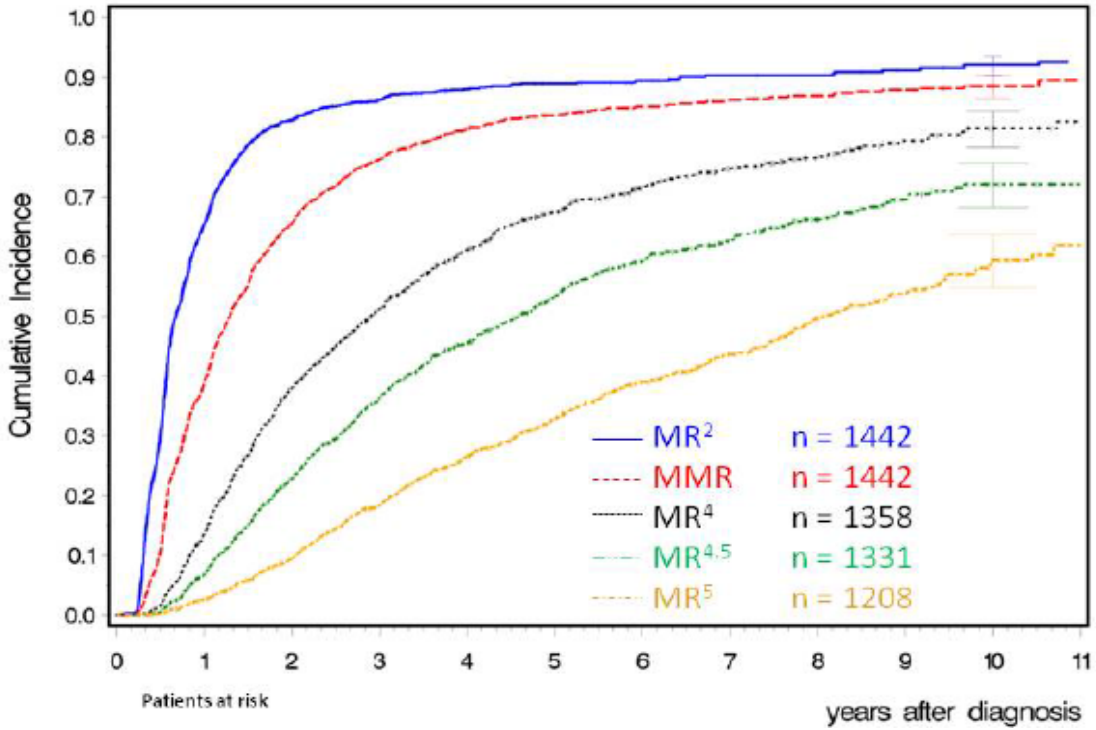
- Imatinib-related serious adverse events were uncommon.
- Most occurred during the 1st year of treatment.
- The efficacy of imatinib persisted over time.
- Late progression events were rare.
- Chronic imatinib administration did not have cumulative or late toxicities.

Quantitative RT-PCR for BCR-ABL1 transcripts (International Scale)



Baccarani M et al. Am Soc Clin Oncol Education Book. 2014: 167-75.

Safety & Efficacy of Imatinib over 10 years – German CML IV trial



Kalmanti et al. German CML Study Group. Leukemia 2015

Activity of TKIs Against 18 Imatinib-Resistant BCR/ABL Mutations

- These mutations are not detectable when chronic phase CML is first diagnosed.
- Occult subclones emerge under selective pressure from TKI therapy.

Redaelli et al, 2009

		IC_{50} fold increase (WT = 1)			
		Bosutinib	Imatinib	Dasatinib	Nilotinib
	Parental	38.31	10.78	> 50	38.43
	WT	1	1	1	1
P-LOOP	L248V	2.97	3.54	5.11	2.80
	G250E	4.31	6.86	4.45	4.56
	Q252H	0.81	1.39	3.05	2.64
	Y253F	0.96	3.58	1.58	3.23
	E255K	9.47	6.02	5.61	6.69
	E255V	5.53	16.99	3.44	10.31
C-Helix	D276G	0.60	2.18	1.44	2.00
	E279K	0.95	3.55	1.64	2.05
ATP binding region (drug contact sites)	V299L	26.10	1.54	8.65	1.34
	T315I	45.42	17.50	75.03	39.41
	F317L	2.42	2.60	4.46	2.22
SH2-contact	M351T	0.70	1.76	0.88	0.44
Substrate binding region (drug contact sites)	F359V	0.93	2.86	1.49	5.16
A-LOOP	L384M	0.47	1.28	2.21	2.33
	H396P	0.43	2.43	1.07	2.41
	H396R	0.81	3.91	1.63	3.10
	G398R	1.16	0.35	0.69	0.49
C terminal lobe	F486S	2.31	8.10	3.04	1.85

Sensitive	≤ 2
Moderately resistant	2.01–4
Resistant	4.01-10
Highly resistant	> 10

2013 European LeukemiaNet Recommendations for newly diagnosed CML

Time:	Optimal Response	Warning	Failure
3 months	**BCR/ABL ≤10% Ph+ cells ≤35% (PCyR)**	**BCR/ABL >10% Ph+ cells 35-95%**	**No CHR. Ph+ cells >95%**
6 months	**BCR/ABL <1% Ph⁺ cells 0% (CCyR)**	**BCR/ABL 1-10% Ph+ cells 1-35%**	**BCR/ABL >10% Ph+ cells >35%**
12 months	**BCR/ABL ≤0.1% (MMR)**	**BCR/ABL 0.1-1%**	**BCR/ABL >1% Ph+ cells >0%**
Thereafter	**Major Molecular Response [MMR] or better; Tolerating the drug; good adherence; monitored every 3 mos**	**-7 or del(7q) in Ph- cells**	**Loss of CHR or CCyR; confirmed loss of MMR. ABL mutations. New chromosome abnormalities**

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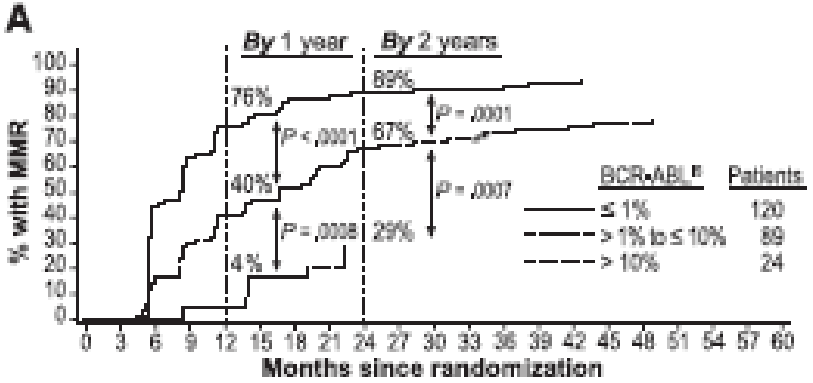
Baccarani et al. Blood 2013 Aug 8; 122(6): 872-84

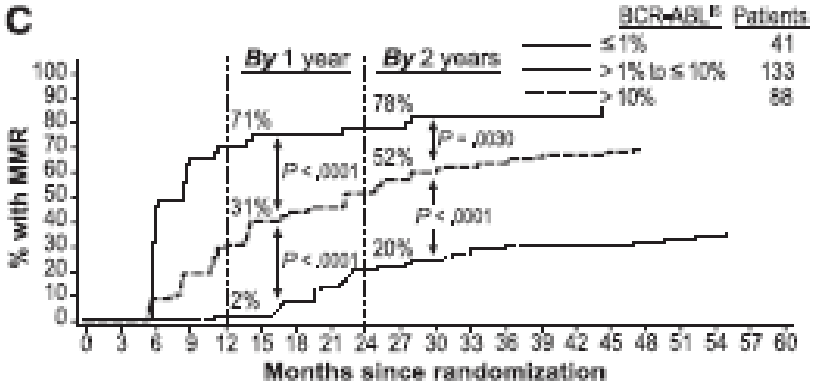
What is an Early Molecular Response?

- *BCR/ABL1* transcript level ≤10% (International Scale)
  - At 3 months
  - At 6 months
- Importance: predicts for MMR and Survival
- Limitations: not yet clear whether altering therapy for qRT-PCR level >1% leads to a better outcome.
- However, switching at 3 or 6 months if the *BCR/ABL1* level is still >10% seems reasonable.

Outcomes (MMR by 1-2 yrs) by EMR at 3 months (ENESTnd)



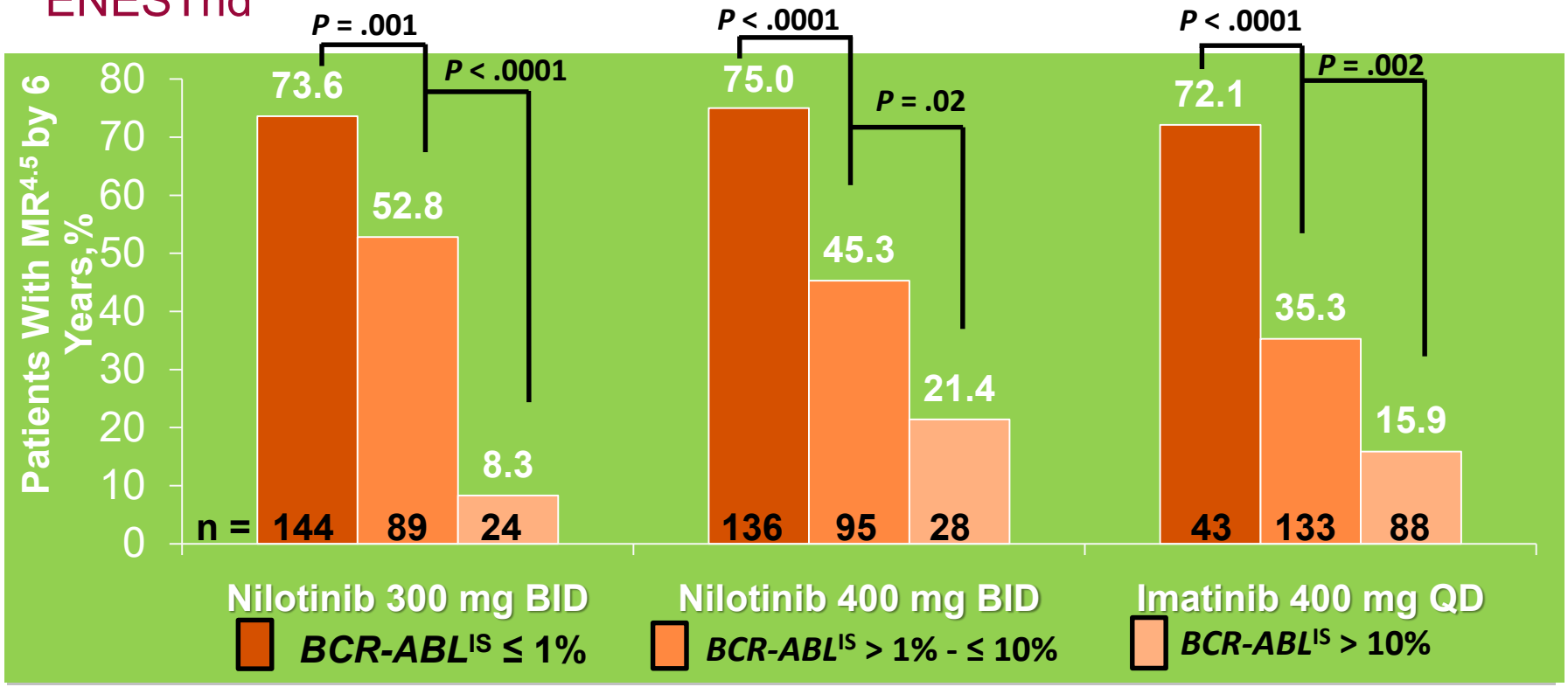
Nilotinib 300 mg BID



Imatinib 400 mg Daily

Hughes TP, et al. Blood 2014; 123(9); 1353-1360

Rate of MR$^{4.5}$ By 6 Years According To 3-Month *BCR-ABL*^{IS} Levels -- ENESTnd

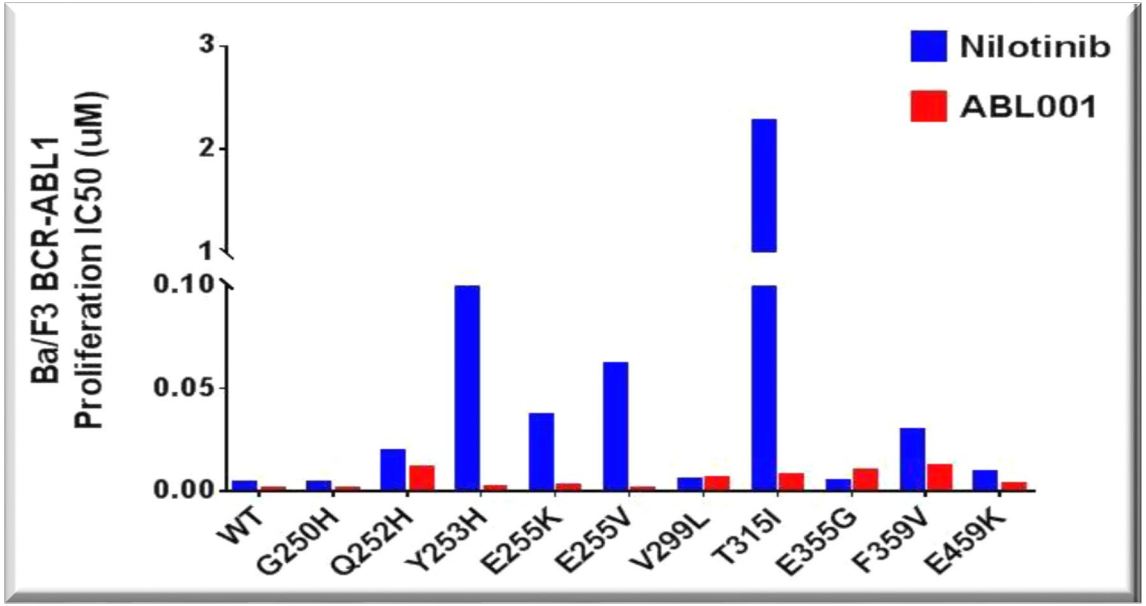


Larson RA, et al. Blood 2014; 124: abstr #4541

Investigational agents for CML

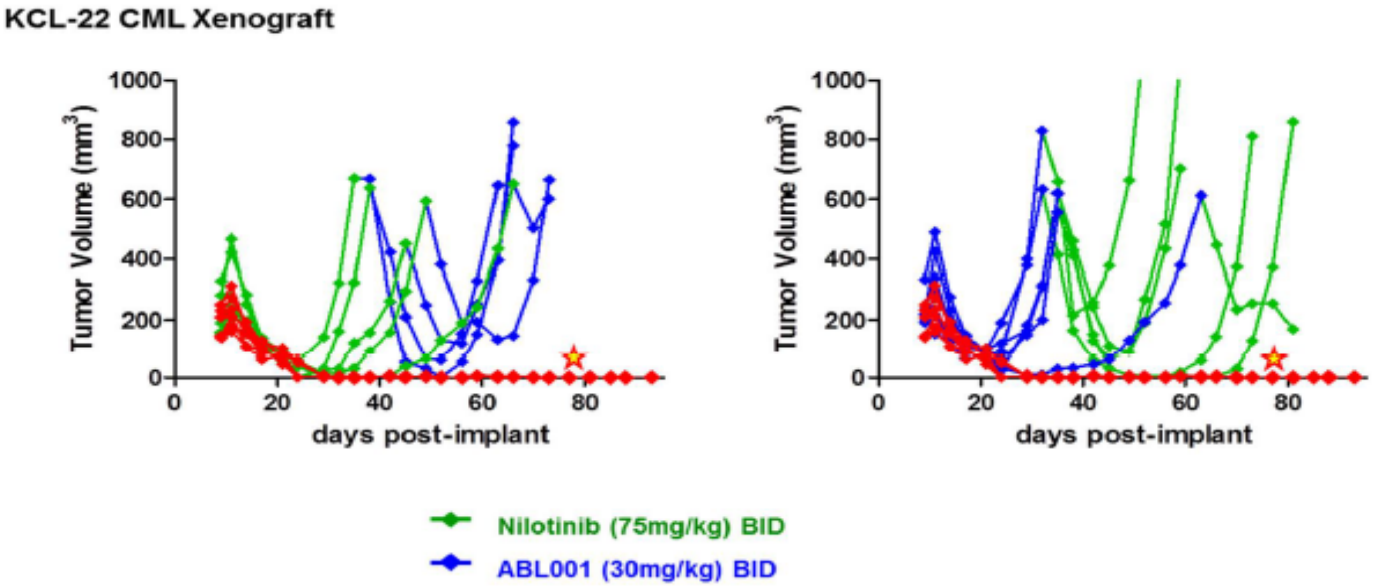
- **Asciminib** (ABL-001; Novartis)
- Ruxolitinib (JAK2 inhibition)
- **Selinexor** (KPT-330; Karyopharm)
- **Inecalcitol** (Hybrigenics)
- **Venetoclax** (BCL-2 inhibition)
- Other metabolic pathways
  - EZH2 inhibitors
  - Pioglitazone: PPAR-gamma agonist
  - Hedgehog pathway inhibitors
  - Tigecycline
  - Fingolimod (FTY720)
  - Autophagy inhibitors -- chloroquine

In contrast to nilotinib, ABL001 maintained activity against all BCR-ABL constructs, regardless of mutation, at concentrations below 50 nM.



ABL001 inhibited the proliferation of cells with a T315I mutation in the low nanomolar range; in contrast, nilotinib was inactive at concentrations up to 10 μM.

Combination versus sequential single-agent treatment of ABL001 and nilotinib on the emergence of resistance in KCL-22 xenograft model



Can TKI therapy ever be reduced or discontinued?

De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY)

- non-randomized, phase 2 trial at 20 hospitals in the UK
- CML in first chronic phase who had received TKI for ≥ 3 years
- Either in stable MR4 (BCR-ABL1:ABL1 ratio <0.01%) or in stable MMR (consistently <0.1%) for 12 months or longer.
- Patients decreased to half their standard TKI dose (imatinib 200 mg daily, dasatinib 50 mg daily, or nilotinib 200 mg twice daily) for 12 months.
- Molecular recurrence was defined as loss of MMR on two consecutive samples.
- The primary endpoint was the proportion of patients who lost MMR on de-escalation and regained MMR on TKI resumption.

Richard Clark et al. Lancet Oncology 2017

De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY)

- 49 patients enrolled into the MMR cohort and 125 into the MR4 cohort.
- During the 12 months of half-dose therapy, 12 patients (7%) had molecular recurrence, all of whom regained MMR within 4 months of full-dose TKI resumption (median time to recovery 77 days).
- Recurrence was significantly lower in the MR4 cohort (2%) than in the MMR cohort (19%).
- Adverse events (eg, lethargy, diarrhea, rash, and nausea) improved during the first 3 months of de-escalation, though not thereafter.
- TKI de-escalation is safe for most patients with excellent responses to TKI therapy, and is associated with improvement in symptoms.

Richard Clark et al. Lancet Oncology 2017

De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY)

Relapse-free survival

Red = MR4

Blue = MMR

Time to recover MMR

Red = MR4

Blue = MMR

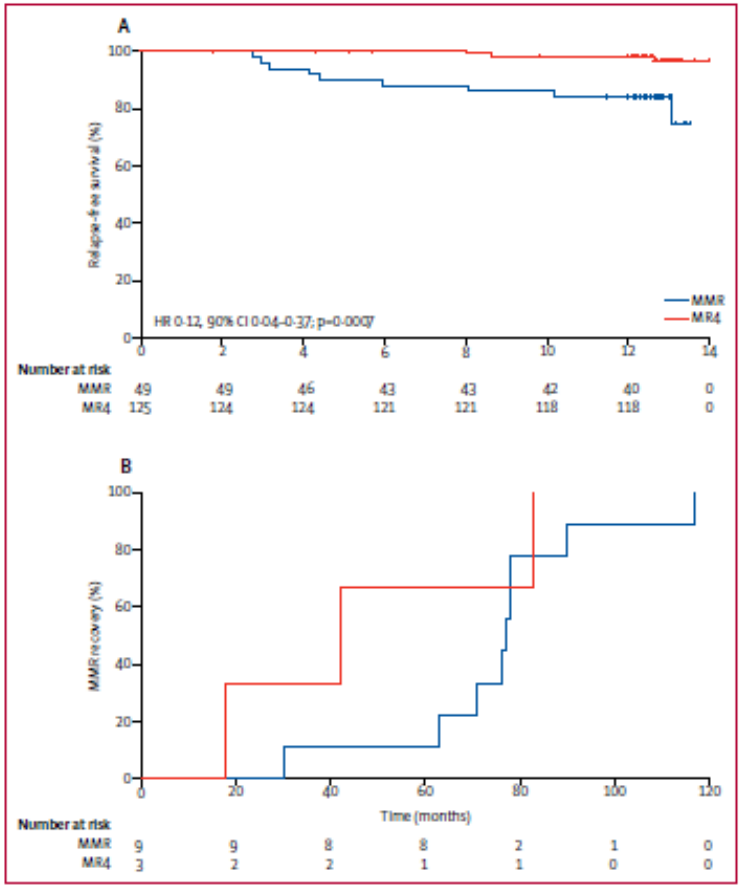


Figure 2: Relapse-free survival (A) and time to MMR recovery (B)
MMR=major molecular response (*BCR-ABL1*:*ABL1* ratio consistently ≤0·1%). MR4=deep molecular response (*BCR-ABL1*:*ABL1* ratio ≤0·01%). HR=hazard ratio.

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Richard Clark et al. Lancet Oncology 2017

What is “treatment-free remission” (TFR) and when it is appropriate to consider?

- Prospective discontinuation of TKI therapy with more frequent molecular monitoring.
  - Goal is to maintain deep molecular remission
  - Eliminate chronic side-effects (e.g. fatigue, rash, GI)
  - Reduce complications of treatment (vascular toxicity)
  - Reduce costs
- Best results are achieved after >5 years of total therapy and >2 years in deep molecular remission (<0.01% transcript level)

TFR – warnings!

- Psychological stress & anxiety
- Non-adherence to follow up (monitoring is mandatory)
- “TKI withdrawal” syndrome
- Molecular recurrence & hematologic relapse
- Need for retreatment

Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial

- 61 European centers in 11 countries.
- Chronic-phase CML
- Received any TKI for at least 3 years, and had a confirmed deep molecular response for at least 1 year.
- The primary endpoint was molecular relapse-free survival, defined by loss of MMR (>0.1% BCR-ABL1 on the International Scale)
- Interim analysis on the first 200 patients

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Susanne Saussele et al. Lancet Oncology 2018; 19: 747

Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial

- 758 were enrolled. Median follow-up was 27 months.
- Molecular relapse-free survival for these patients was 61% at 6 months and 50% at 24 months.
- Of 755 evaluable patients, 371 (49%) lost MMR after TKI discontinuation
- Six (1%) patients died in chronic-phase CML after loss of MMR and re-initiation of TKI therapy for reasons unrelated to CML.
- Two (<1%) patients lost MMR despite restarting TKI therapy.
- TKI discontinuation led to substantial cost savings (~ €22 million). No serious adverse events were reported

Susanne Saussele et al. Lancet Oncology 2018; 19: 747

Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial

Molecular recurrence

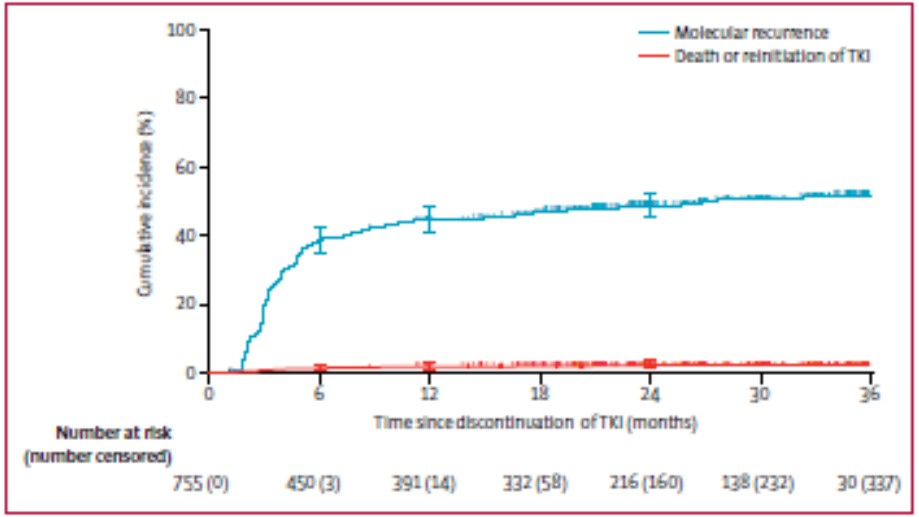

Figure 2: **Cumulative incidence of molecular recurrence after TKI discontinuation**
Bars at 6, 12, and 24 months indicate the upper and lower limits of the 95% CIs for the estimated incidences. TKI=tyrosine kinase inhibitor.

Molecular relapse-free survival

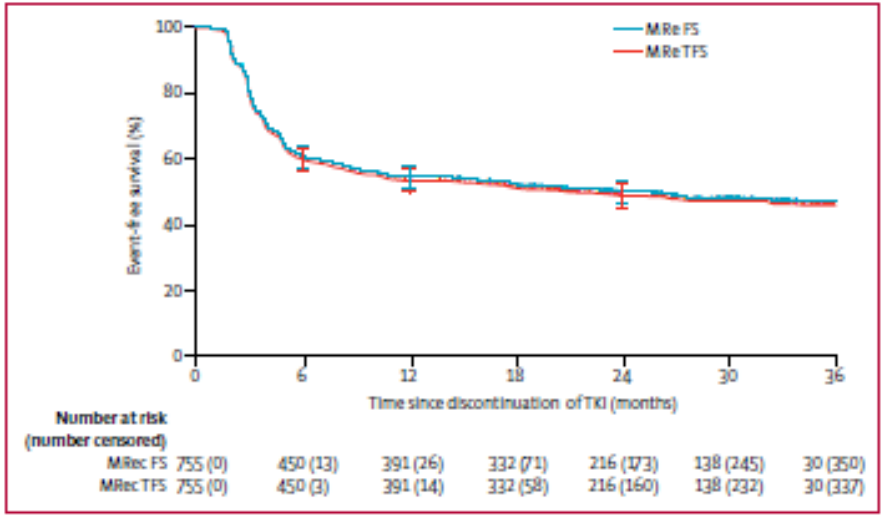

Figure 3: **MReFS and MReTFS after TKI discontinuation**
Bars at 6, 12, and 24 months indicate the upper and lower limits of the 95% CIs. MReFS=molecular relapse-free survival. MReTFS=molecular relapse-free and treatment-free survival. TKI=tyrosine kinase inhibitor.

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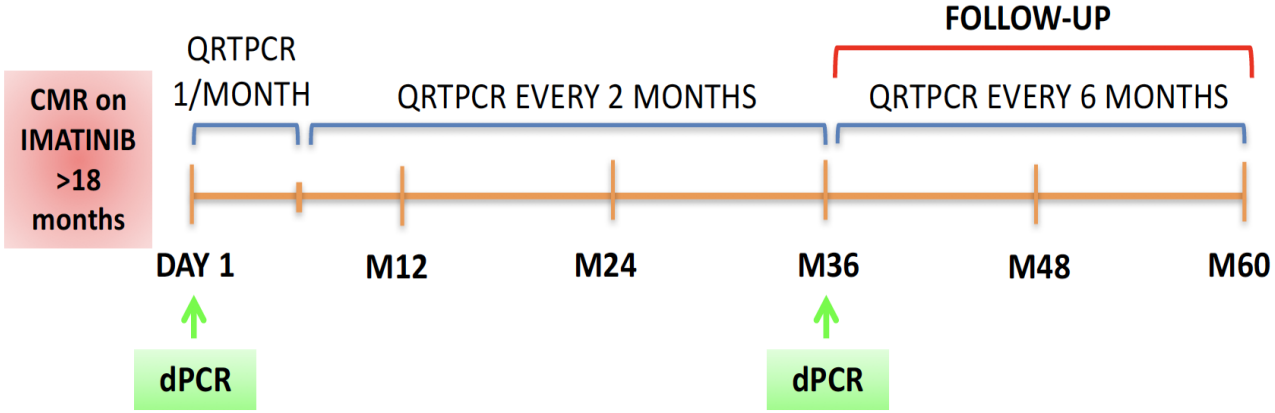
Susanne Saussele et al. Lancet Oncology 2018; 19: 747

Imatinib Suspension And Validation (ISAV) Study: final results at 79 months

Carlo Gambacorti Passerini MD, on behalf of ISAV investigators

STUDY DESIGN



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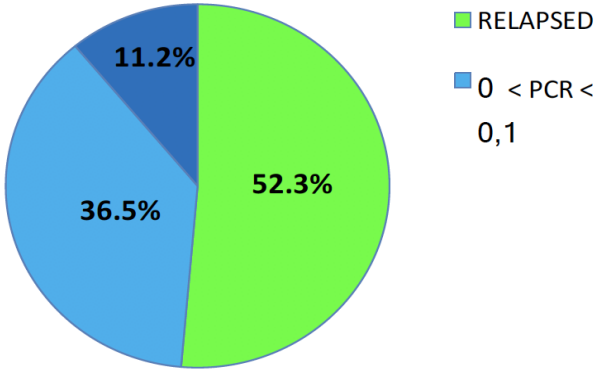
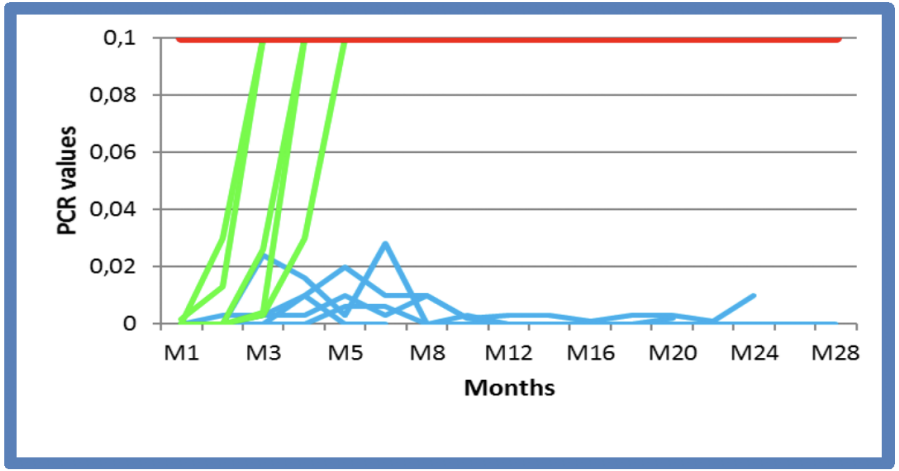
Gambacorti-Passerini et al. ASH 2018. Abstract #461

3 GROUPS OF PATIENTS





- A total of 56 (52.3% [95%CI 42.96-61.55]) patients relapsed
- 69.6% of relapses occurred within 9 mts from imatinib discontinuation;
  Three late relapses developed at month: **30.6**, **45.5** and **55.6**
- Loss of CCyR: 13 patients (10 recovered, 3 not assessed); No case of progression/resistance
- 77.6% of pts obtained again CMR and 22.4% MMR after imatinib resumption
- Median time from relapse to CMR/MMR after imatinib resumption: 1.8 mts [95% CI: 1.2–2.1]

Gambacorti-Passerini et al. ASH 2018. Abstract #461

ISAV study

Remaining challenges in CML

- Managing acute and chronic toxicities of TKI therapy.
- Identifying which patients can safely stop TKI therapy.
- Treating resistant and blast phase disease.