

FREE TREATMENT OR TREATMENT FREE?

The Next Challenges in CML

CML Horizon, 2023

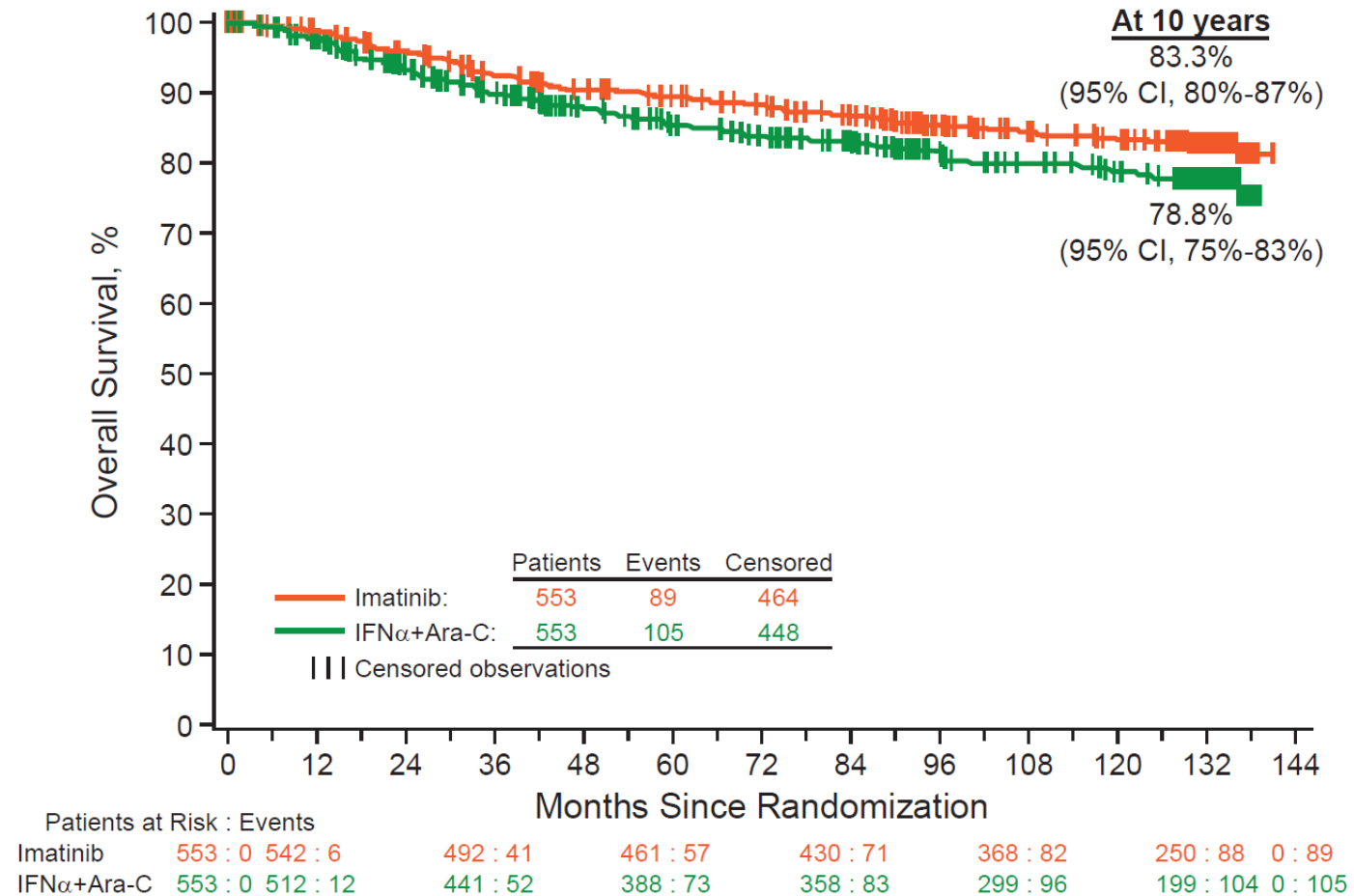
Michael Deininger MD PhD



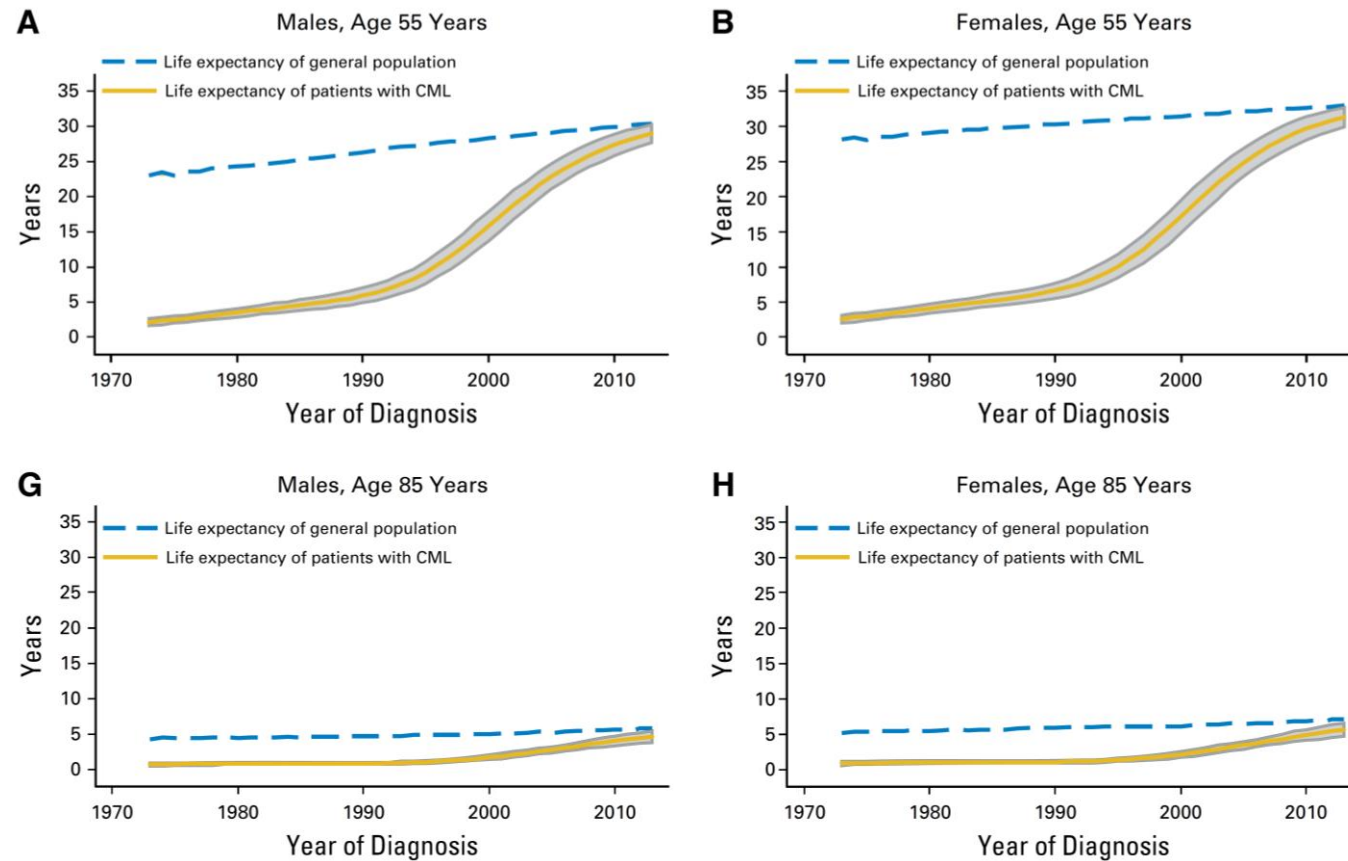
2022 CML Landscape in High Income Countries

- Perception of a solved problem
- Increasing prevalence
- Prospect of indefinite TKI therapy for the majority of patients
- Therapy setting moving from academia to community
- Ongoing struggle with high drug prices (not everywhere)
- Important questions moving outside the expertise of clinicians and leukemia biologists
- Reduced research funding and less interest to dedicate career to CML

IRIS Study: 10-year Follow-up

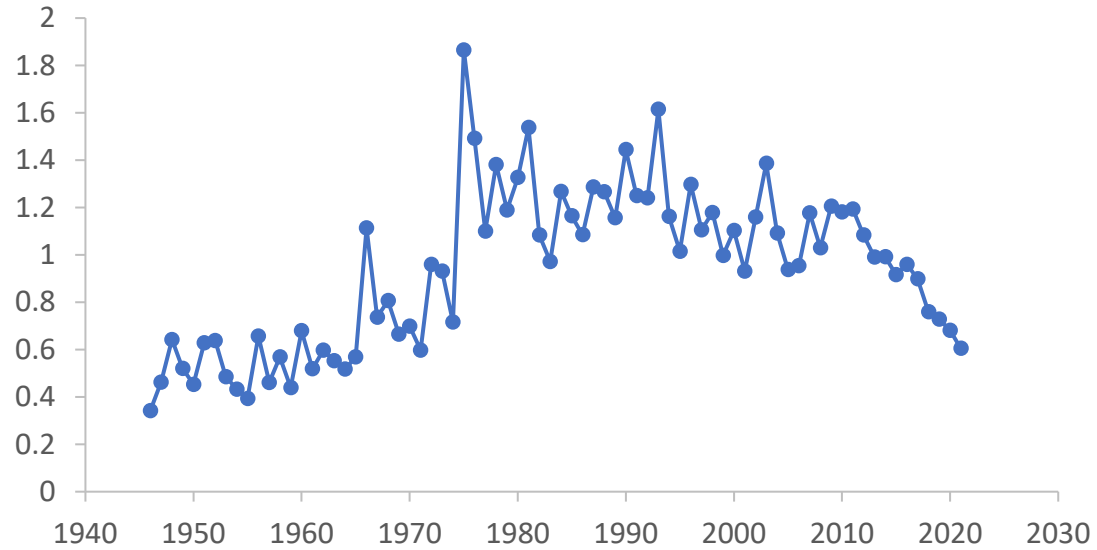


The Life Expectancy of Chronic Phase CML Patients Approaches that of the General Population (In Sweden)

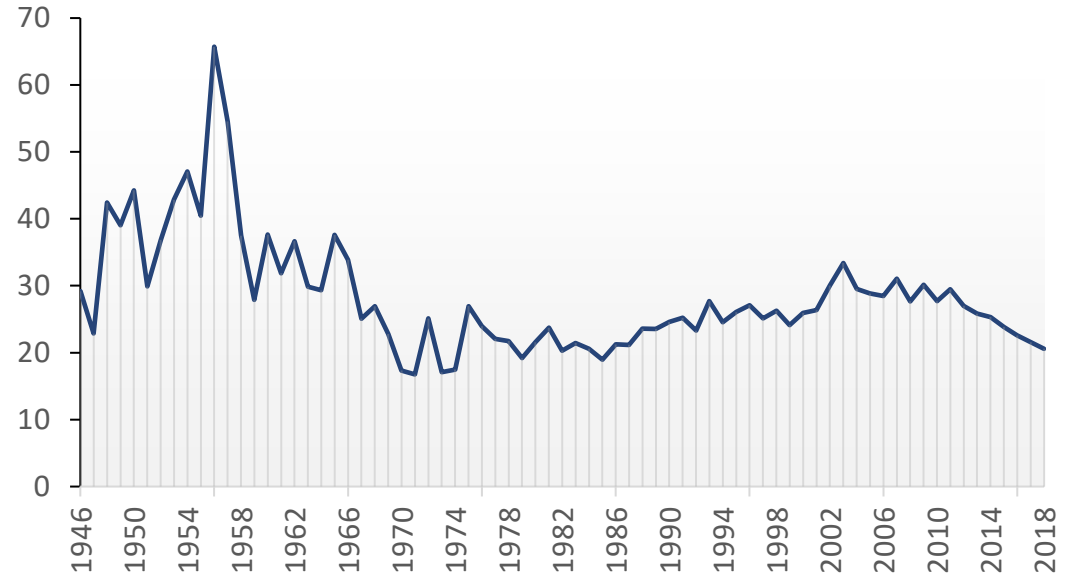


Trends in PubMed-listed Publications

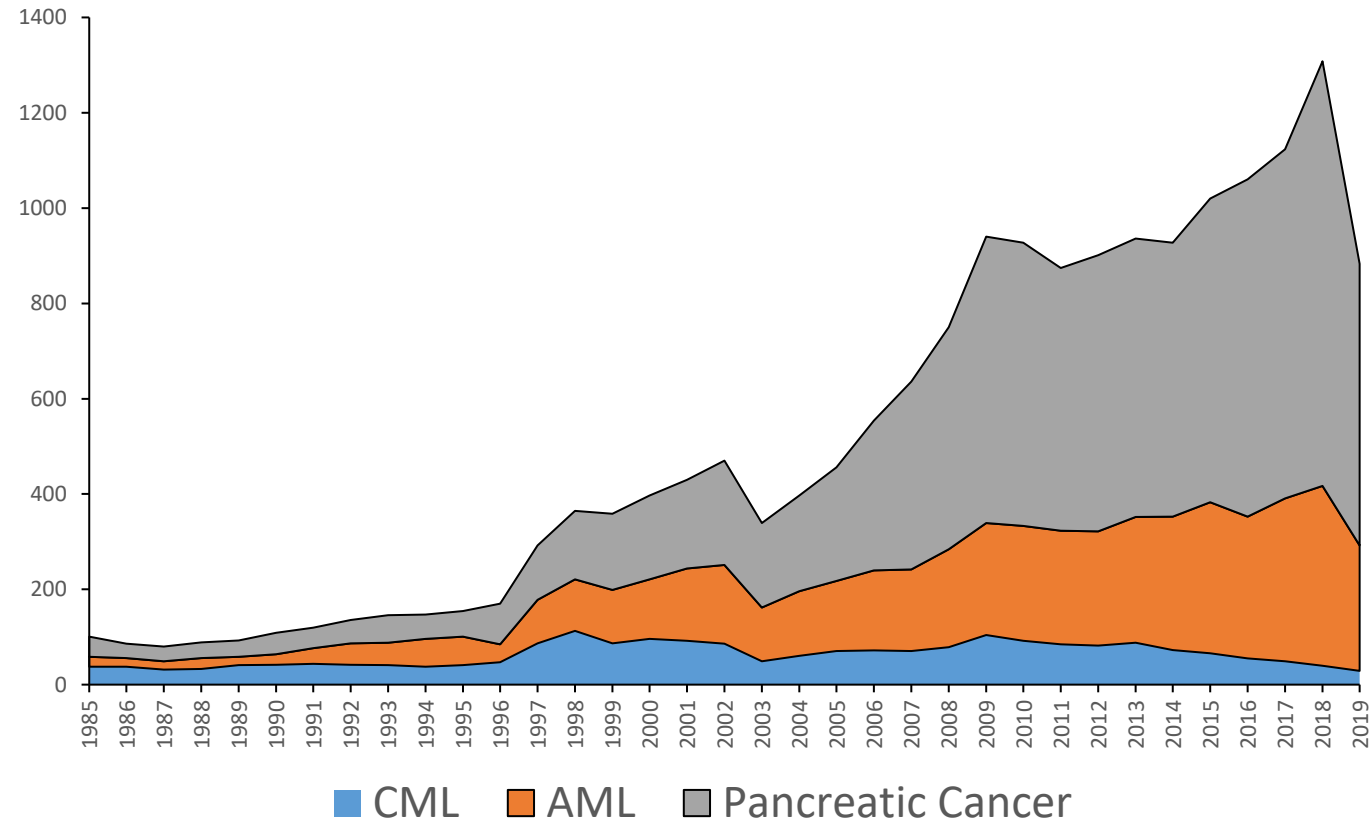
CML in the Title (% of Cancer)



CML as proportion of CML, AML, CLL, MDS

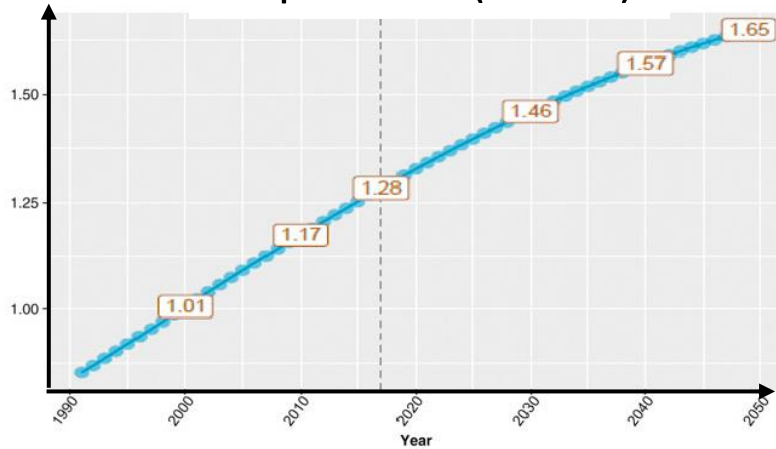


NIH/NSF Awards 1985 - 2019

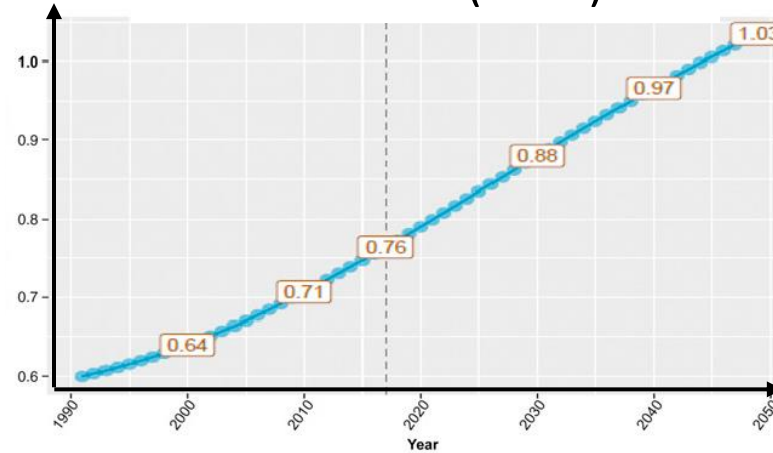


CML in India: Projections

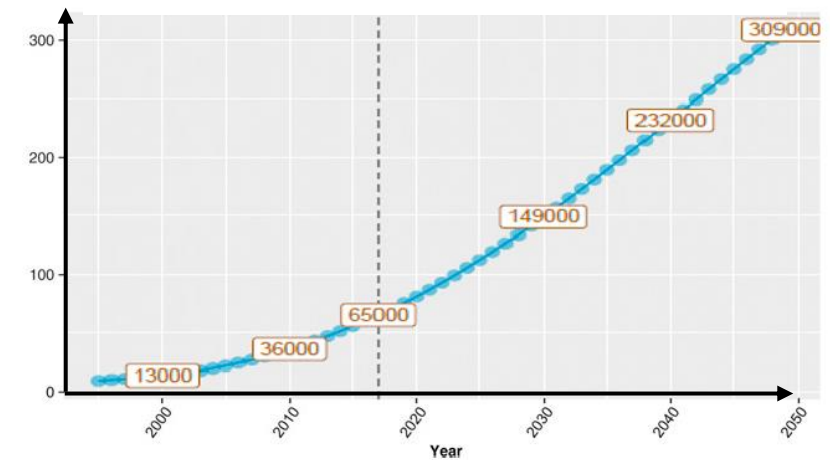
Population (billion)



Incidence ($\times 10^{-5}$)

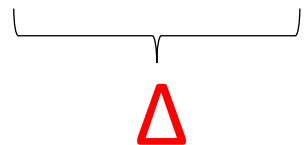


Number of Patients



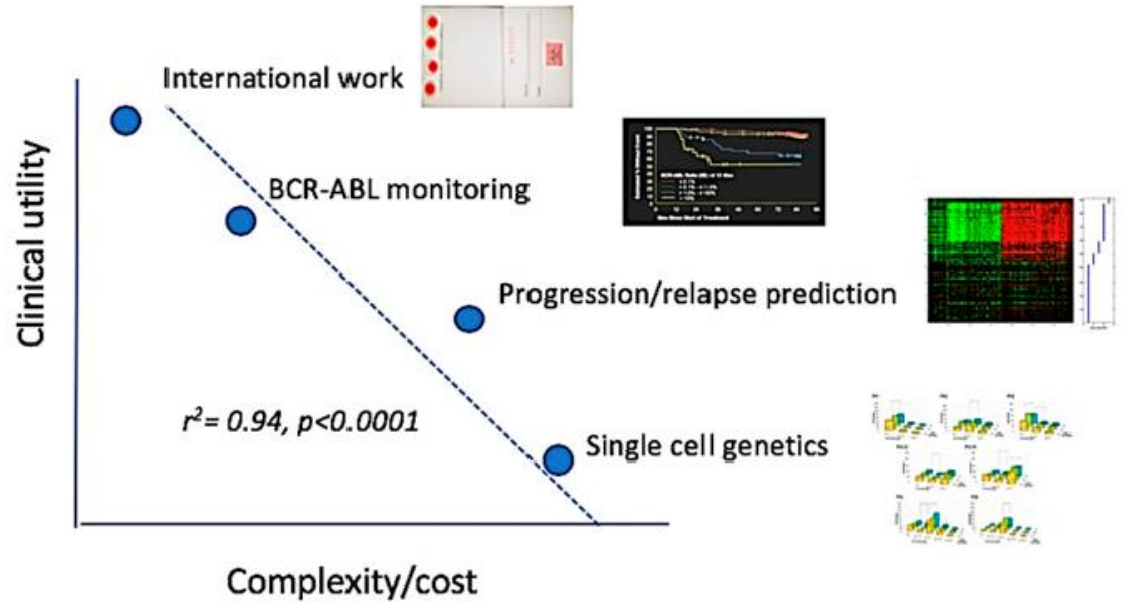
Access to Care vs. New Technology

Chronic phase	Advanced phases	
	Acc. phase	Blastic phase (blast crisis)
Median 4–6 years stabilization HIC LMIC	Median duration up to 1 year	Median survival 3–6 months Terminal phase



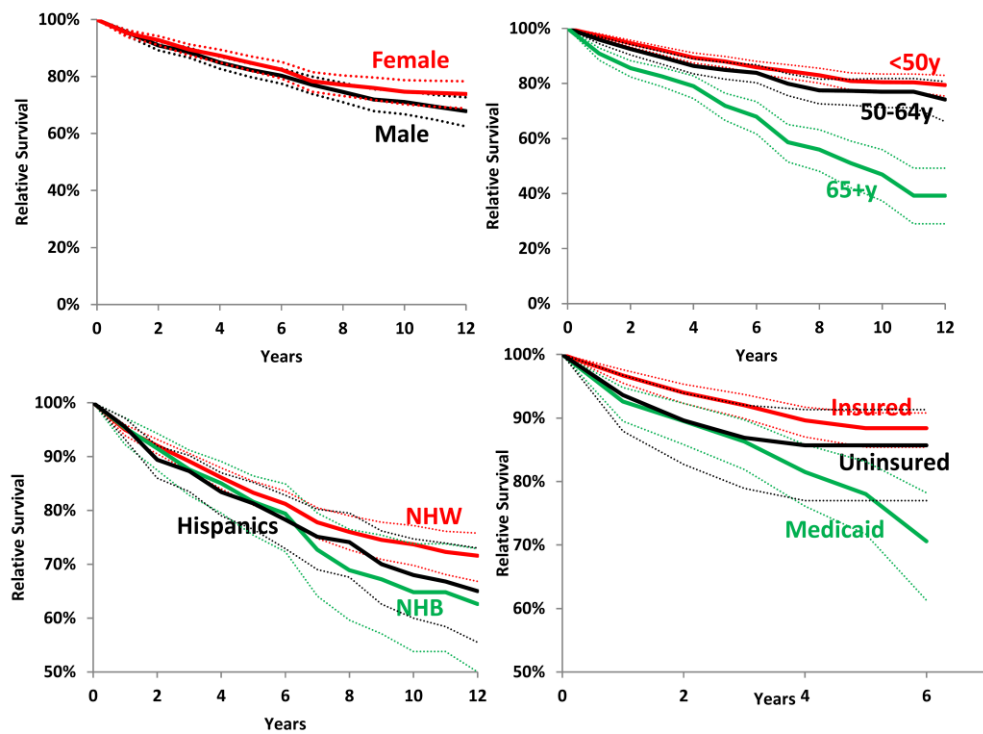
HIC = High income countries

LMC = Low and middle income countries

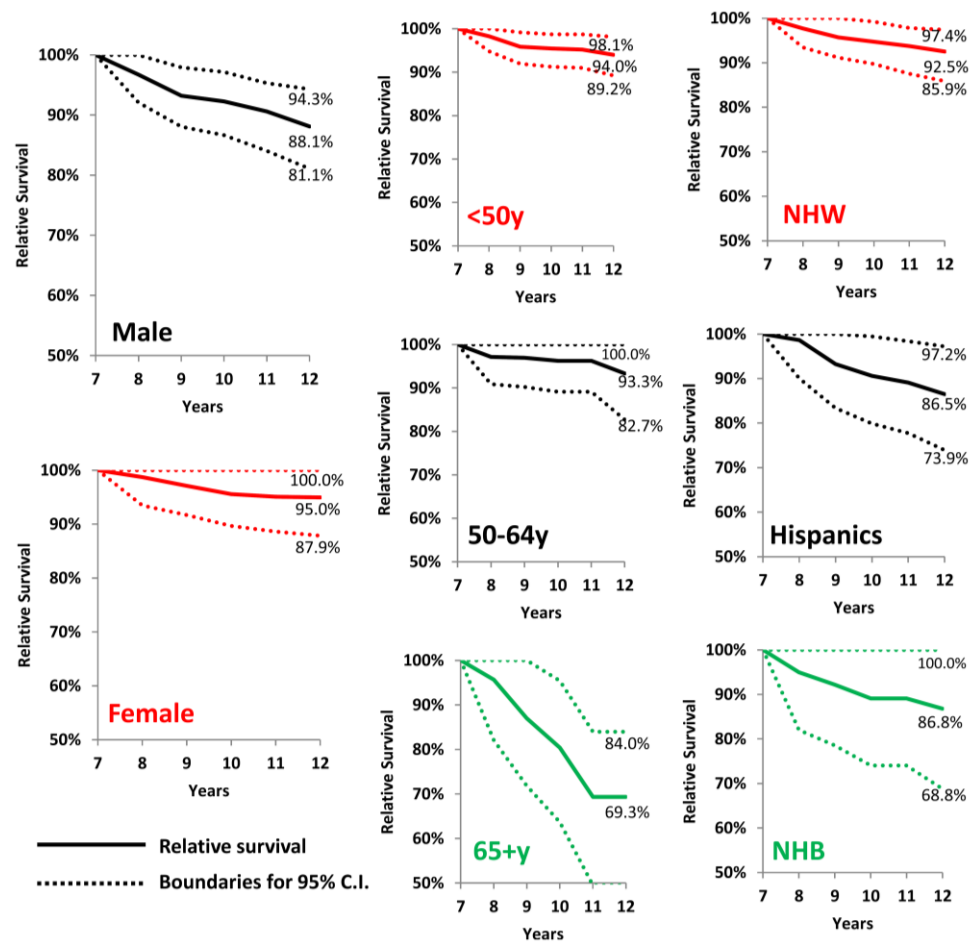


CML Survival in the US

Relative Survival from Diagnosis

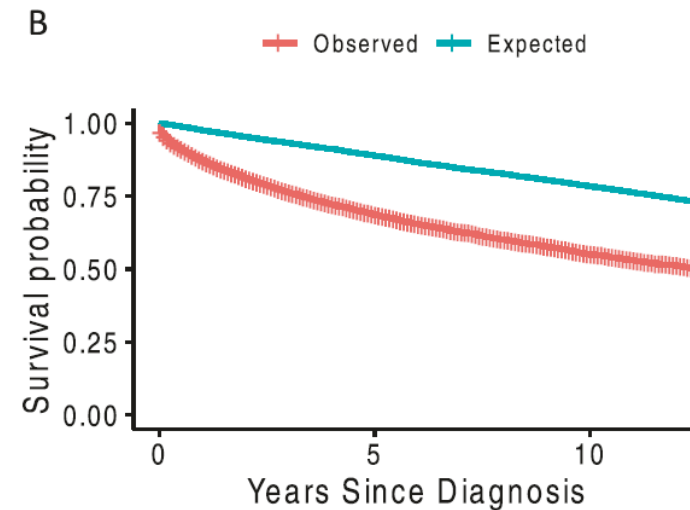
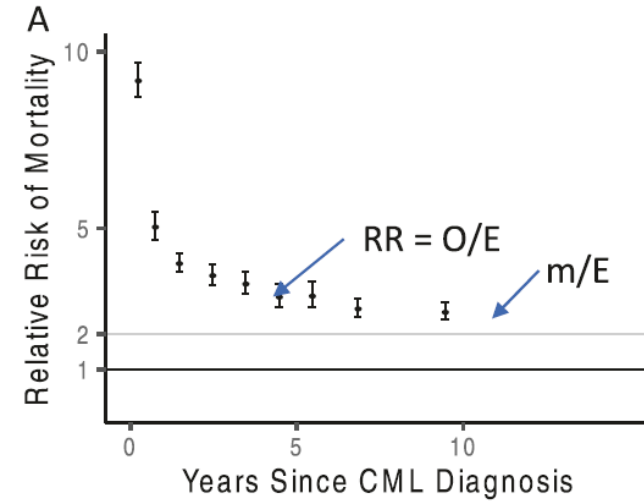
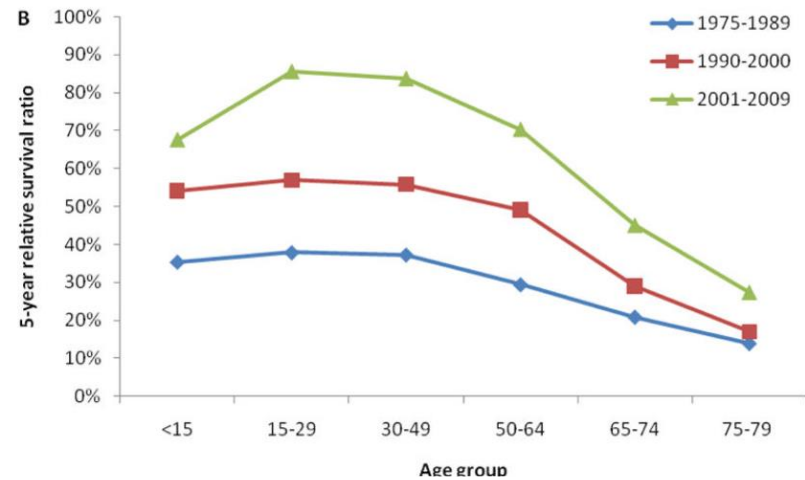
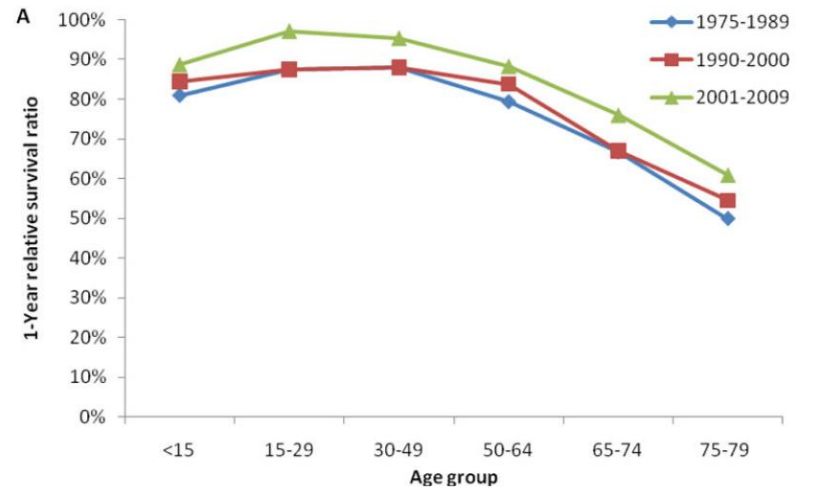


Landmark Analysis at 7 Years after Diagnosis



CML Survival in the US

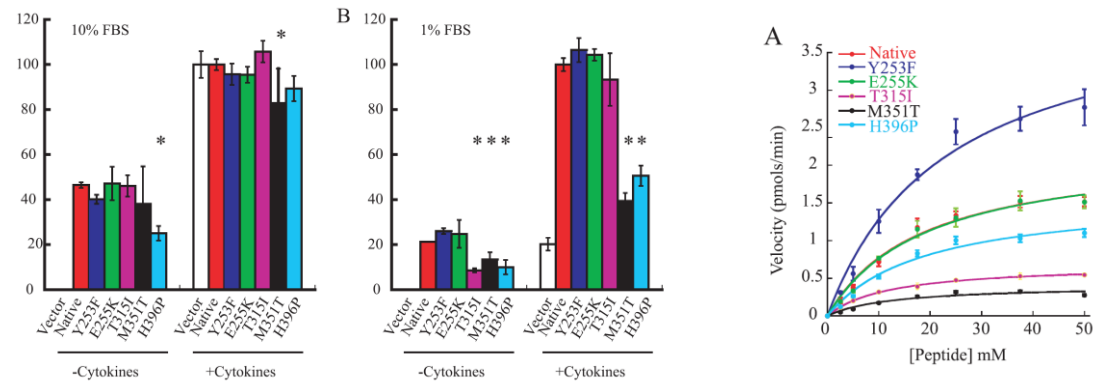
SEER11 2001-2009



Given limited resources, is it time to re-consider some of our approaches?

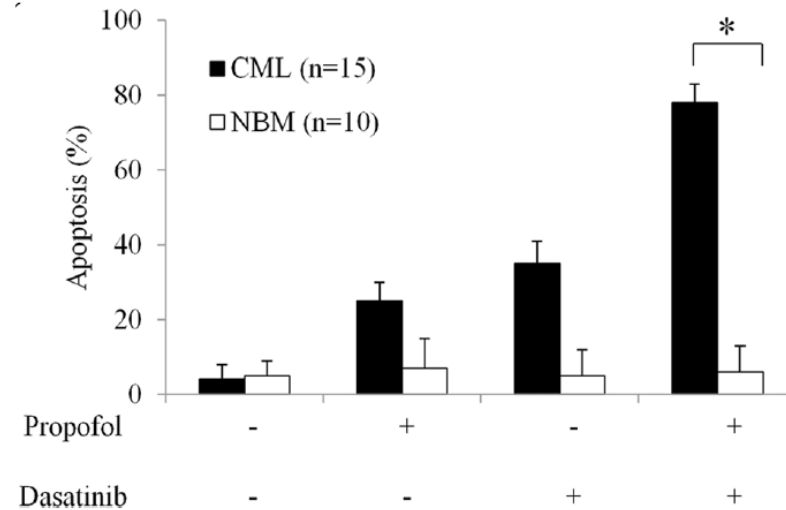
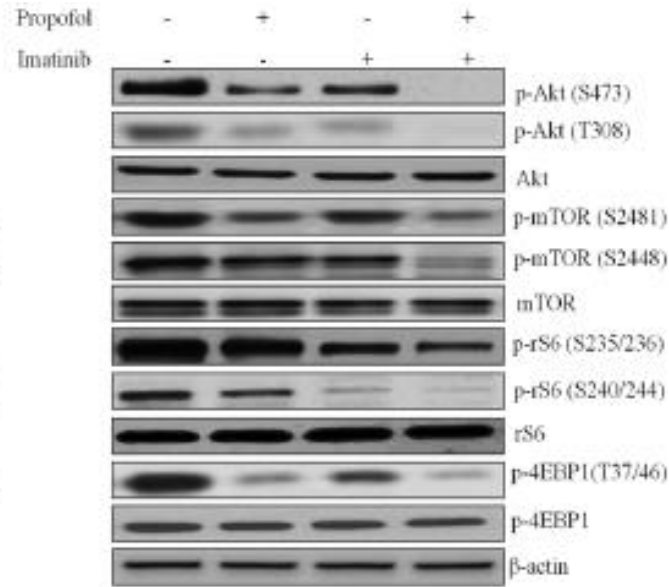
#2 Are We Getting a Little Obsessed with Details?

Biological differences between BCR::ABL1 kinase domain mutants



#3 Is Everything Knowable Worth Knowing?

Propofol enhances BCR-ABL TKIs' inhibitory effects in chronic myeloid leukemia through Akt/mTOR suppression



Michael Jackson
† June 25, 2009

“... that propofol has potential to be repurposed for CML treatment...”

How do we deploy limited resources to achieve maximum impact?

Free treatment for as many patients as possible?

OR

Freedom from treatment for as many patients as possible?

How are we going to get there?



Treatment Free Remission

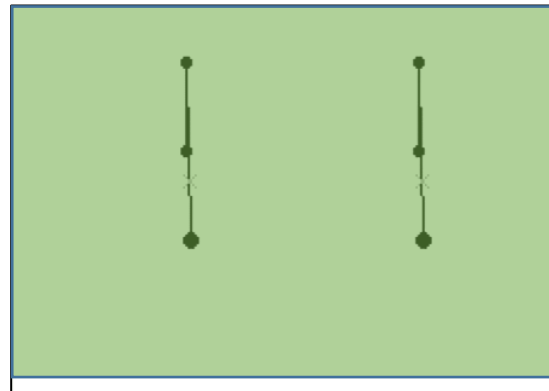
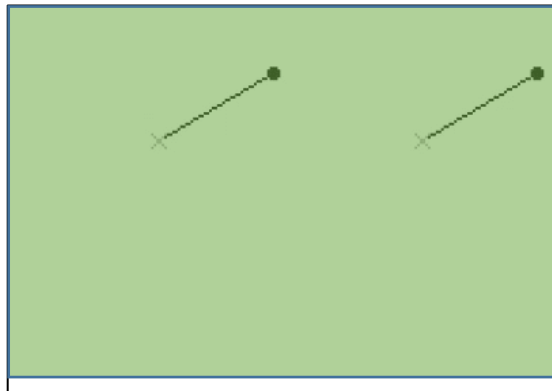
- Will we ever be able to predict TFR success?
- Do we use the right disease models to understand persistent leukemia?
- Is TKI plus X the answer?
- Are we translating the preclinical data?

Will it Ever be Possible Precisely to Predict TFR?

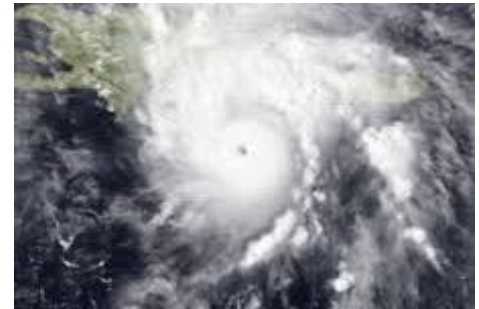
Associations with TFR

- Longer time of TKI therapy
- Longer time in deep remission
- Higher NK cells, lower T regulatory cells, lower CD86⁺ plasmacytoid DC
- Lower Sokal risk?
- Prior IFN- α ?
- Deeper response?
- Female gender?

Initial states differ by .01%



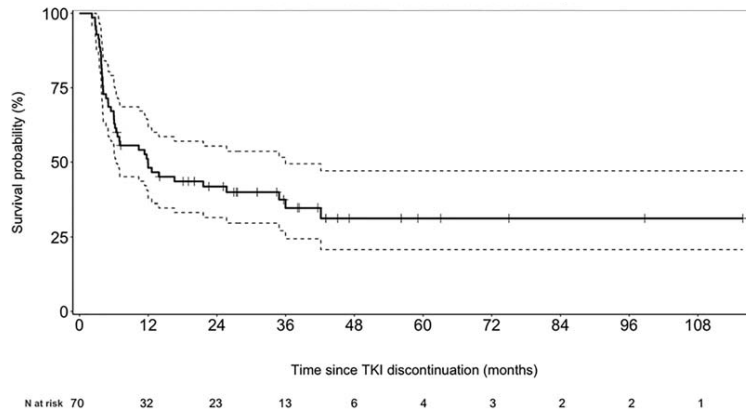
[Weather](#)
Forecast



How Many TFR Attempts Until it's Time to Give Up?

SUCCESS OF 2ND ATTEMPT

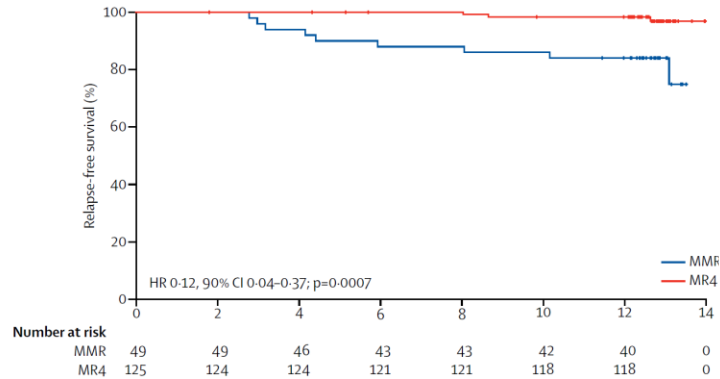
Recurrence Free Survival



Legros et al. Cancer. 2017;123(22):4403-4410

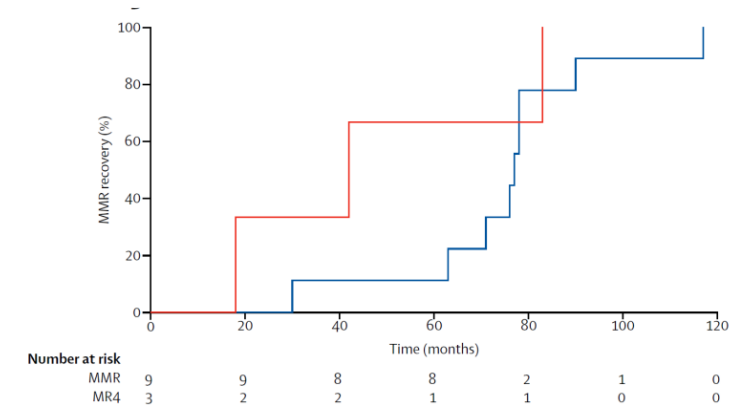
DESTINY TRIAL: Halving the TKI Dose

Recurrence Free Survival

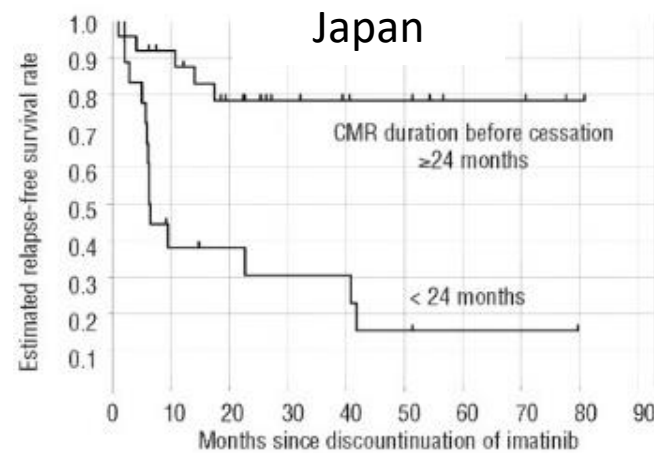
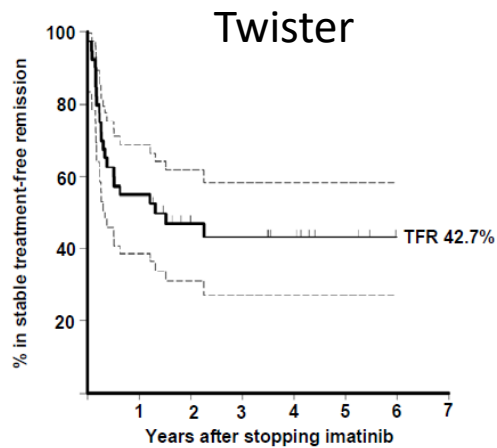
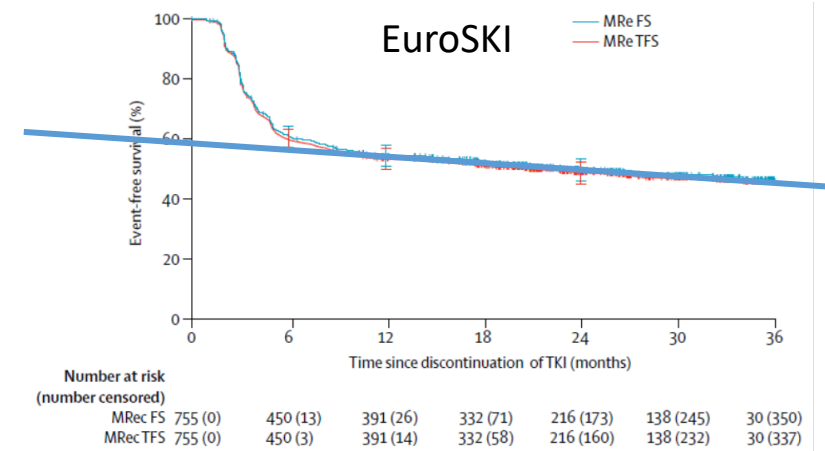
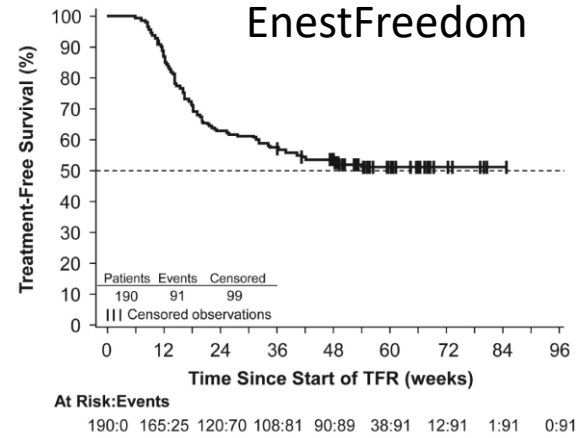
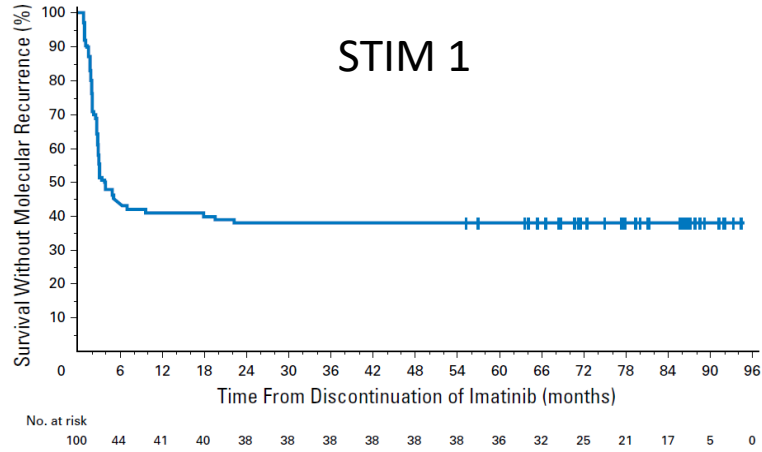


Clark et al. Lancet Haematol. 2017 310-e316. Epub 2017 May 26

Time to MMR Recovery



The Worry: Are 'Real World' TFR Curves not Plateauing?



The Holy Grail: Finding the Weak Spot in CML Stem Cells

Pathway	Publications Supporting Role in LSCs/MRD	Clinical Trial in CML		Status	Final Report
		Resistance± Progression	MRD		
WNT/ β -Catenin	Zhao et al. Cancer Cell 2007; McWeeney et al. Blood 2010; Heidel et al. Cell Stem Cell 2012; Schürch et al. JCI 2012; Lim et al. PNAS 2013; Zhang et al. Blood 2013; Eiring et al. Leukemia 2015; Agarwal et al. Blood 2017	NO	NO	MNK inhibitor withdrawn	NO
HDAC	Zhang et al. Cancer cell 2010	YES Panobinostat (2 trials)	NO	Lack of efficacy/abstract	NO
Hedgehog	Dierks et al. Cancer Cell 2008 Zhao et al. Nature 2009	YES LDE225+NIL BMS-833923+DAS	NO	Terminated/abstract Terminated/abstract	NO NO
5-Lipoxygenase	Chen et al. Nat Genet. 2009	YES Zileuton+IM	NO	Terminated/not reported	NO
BCL6	Hurtz et al. JExMed. 2011	NO	NO	NA	NA
MYC	Ravie et al. Cancer Cell 2013 Abraham et al. Nature 2016	NO	NO	NA	NA
PP2A	Neviani et al. JCI 2007; Neviani et al. Blood 2008; Neviani et al. JCI 2013; Lai et al. Sci Trans Med	NO	NO	NA	NA
SIRT1	Bhatia et al. Cancer Cell 2012	NO	NO	NA	NA
PRMT5	Jin et al. JCI 2016	NO	NO	NA	NA
Rad52	Cramer et al. Blood 2013	NO	NO	NA	NA
PIM2	Ma et al. PNAS 2019	NO	NO	NA	NA

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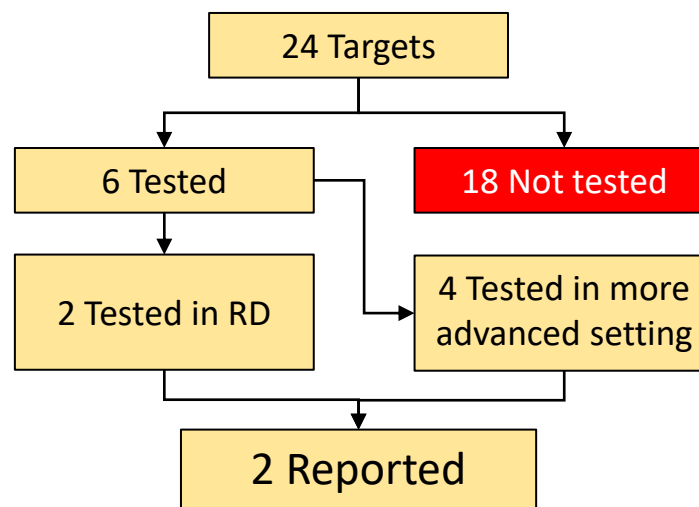
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PPRγ	Prost et al. Nature 2015	YES	YES Pioglitazone+IM (2 trials)	1) Complete (N=27; no control) 2) Ongoing	1) Rousselot et al. Cancer 2017 2) NA
Autophagy	Bellodi et al. JCI 2009 Baquero et al. Leukemia 2019	NO	YES ▪ HCHL+IM vs. IM ▪ N=62	▪ Tolerable; autophagy inhibition ▪ MMR at 12 months 80% vs 92% (p=0.2) ▪ MMR at 24 months 79% vs 88% (p=0.1)	NO
PML	Ito et al. Nature 2008	YES ATO+IM ATO+TKI	NO	Terminated/Not reported Complete/Not reported	NO
JAK2/STAT3/STAT5	Ye et al. Blood 2006; Traer et al. Leukemia 2012; Neviani et al. JCI 2013; Gallipoli et al. Blood 2014; Eiring et al. Leukemia 2015	YES Ruxolitinib+TKI	NO	1) Complete + NIL (N=12; no control) 2) Several ongoing	1) Sweet et al. Leuk Res 2018 2) NA
Mitochondrial protein translation	Kuntz et al. Nature Medicine 2017	NO	NO	NO	NA
TGFβ	Naka et al. Nature 2010	NO	NO	NO	NA
Musashi2	Ito et al. Nature 2010	NO	NO	NO	NA
ADAR1	Jiang et al. PNAS 2013	NO	NO	NO	NA

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		Resistance± Progression	MRD		
EZH2	Xie et al. Cancer Discov. 2016; Scott et al. Cancer Discov. 2016	NO	NO	NO	NA
CXCL2	Agarwal et al. Cell Stem Cell. 2019	NO	NO	NO	NA
miR-126	Zhang et al. Nat Med 2018	NO	NO	NO	NA
mir-183/EGR1/E2F1	Pellicano et al. Blood 2018	NO	NO	NO	NA



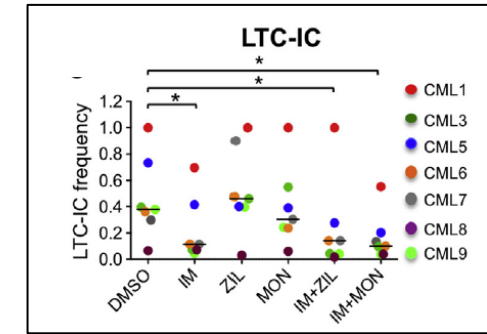
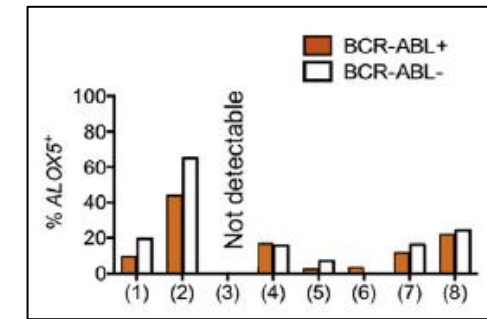
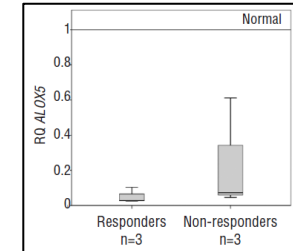
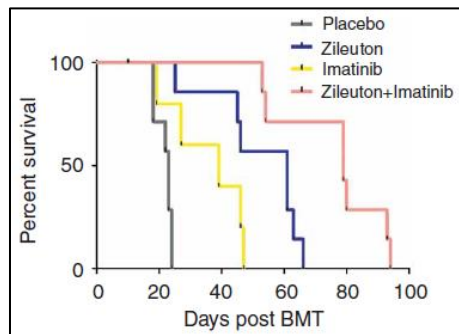
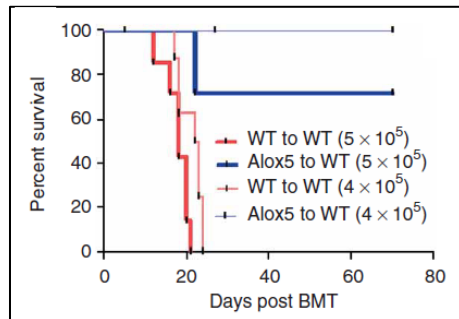
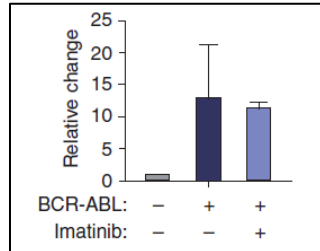
Not considered:

- IFN
- 5-Azacytidine
- Vaccines

#1 There is Insufficient Clinical Follow-Through



#2 Humans are not Large Mice



#3 It's messy

- We tend to like intuitive, clear-cut stuff
- Co-existing somatic mutations in a subset of early CP-CML add a level of complexity

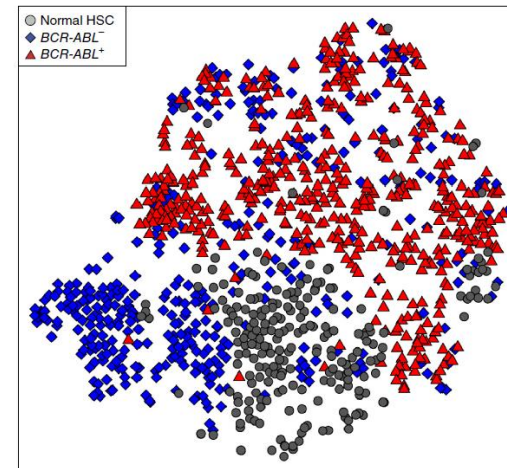
Relevant variants at diagnosis in chronic phase for patients treated with first-line TKI

Variants	MMR, n=19 patients	Poor outcome, n=27 patients
Ph-associated rearrangement	■	■
ASXL1 †	■	■
IKZF1 †	■	■
RUNX1 †		■
SETD1B		■
TP53 (I195T, R248Q-germ line) †		■
IDH1 (R132H) †		■
BCORL1 †		■
CBFB-MYH11 †		■
EZH2 †		■
KMT2D †		■
Patient number	26 24 25 61 27 28 29 30 31 32 33 34 35 36 37 62 63 64 65	11 40 4 8 44 5 7 47 51 43 16 17 49 41 9 14 46 42 6 10 45 12 13 48 15 50 18
Month of BC		6 1 3 5 5 3 4 12 4 30 39 47 3 6 23 7 4 3 6 6 12 15 15 25 47 60

Branford et al. Blood. 2018;132(9):948-961

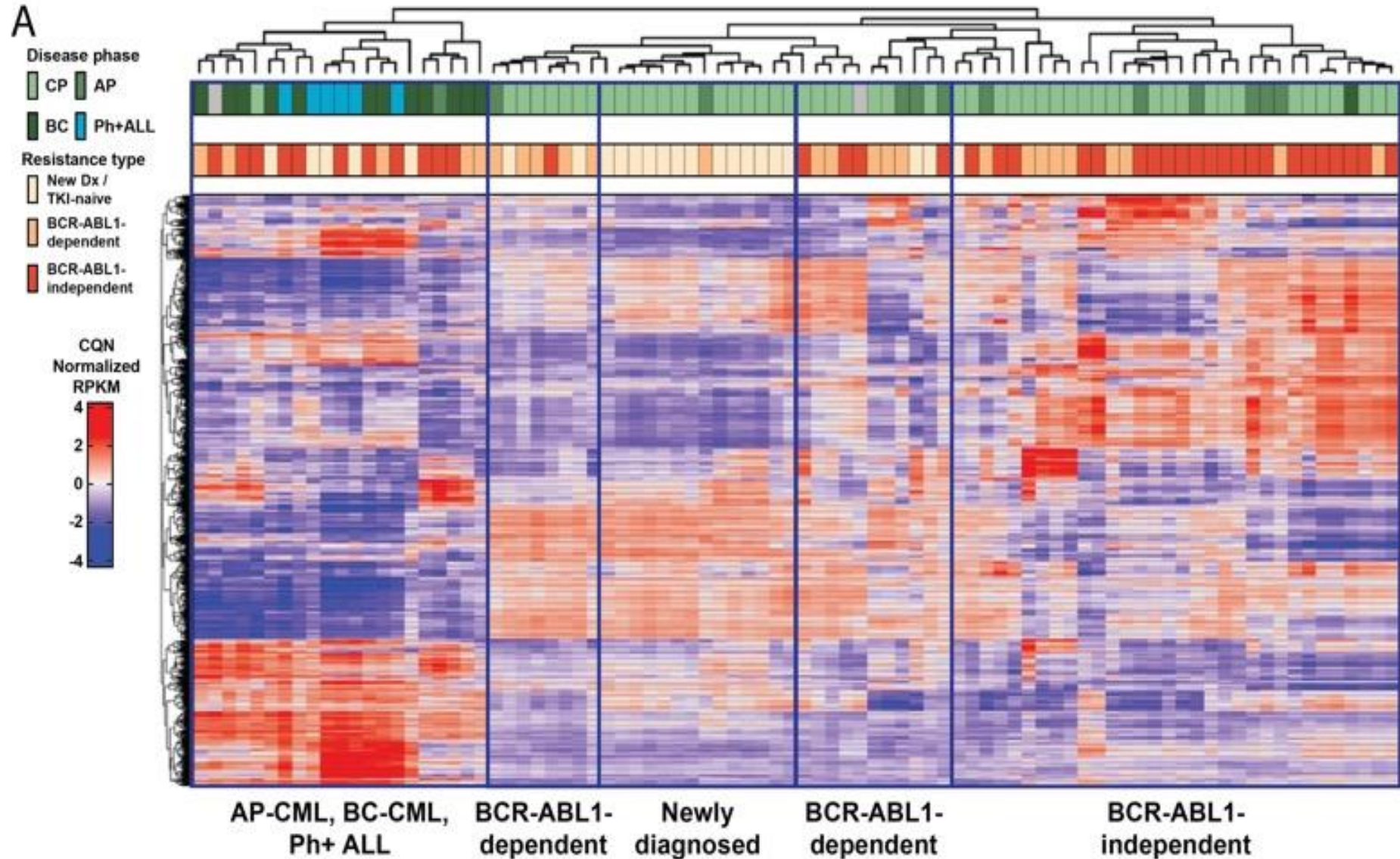
- Bulk sequencing obscures critical information
– such as what the residual normal cells are doing

Giustacchini et al. Nat Med. 2017;23(6):692-702



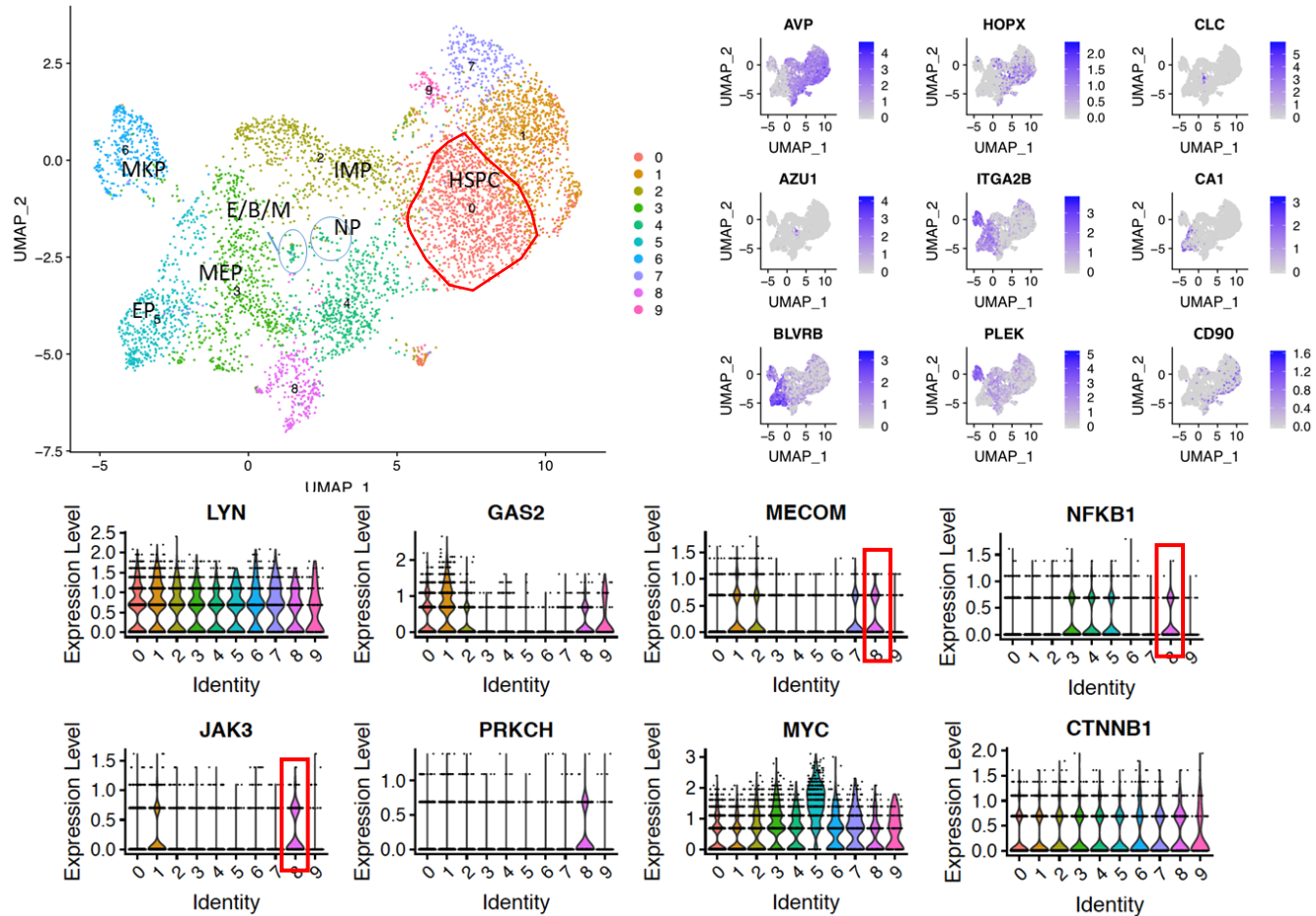
- We have not quite understood BCR-ABL1 independence

RNAseq on Patients with Clinical BCR-ABL1-dependent and – independent Resistance

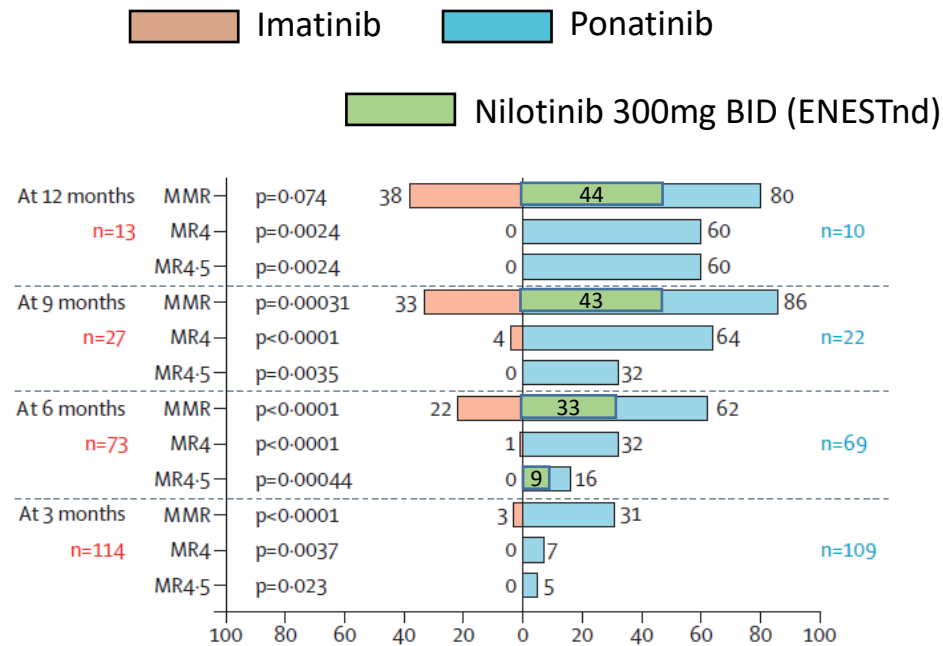


Collaboration with
Brian Druker,
OHSU, Jerry
Radich, FHCRC

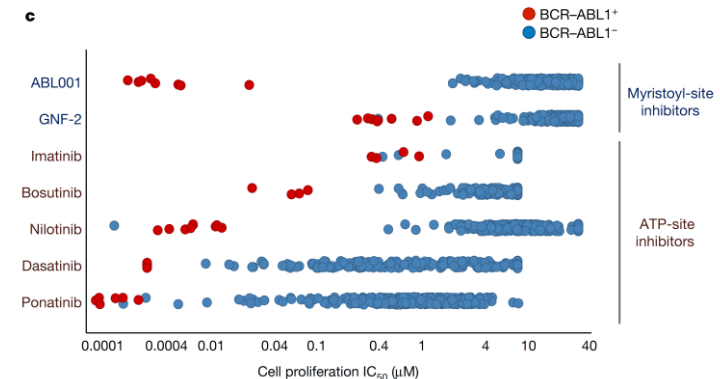
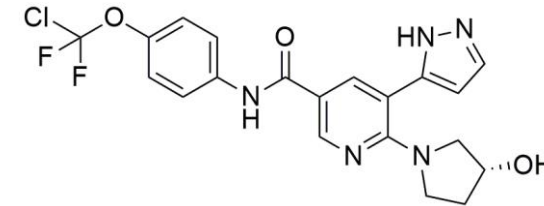
RNAseq on single CD34⁺ Cells from a Patient with BCR-ABL1-independent Resistance: BCR-ABL1T315I⁺ but not Responding to Ponatinib



How Far Can We Get with BCR::ABL1 Kinase Inhibition Alone? Responses to Ponatinib 45mg vs. Imatinib 400mg Daily (EPIC Trial)

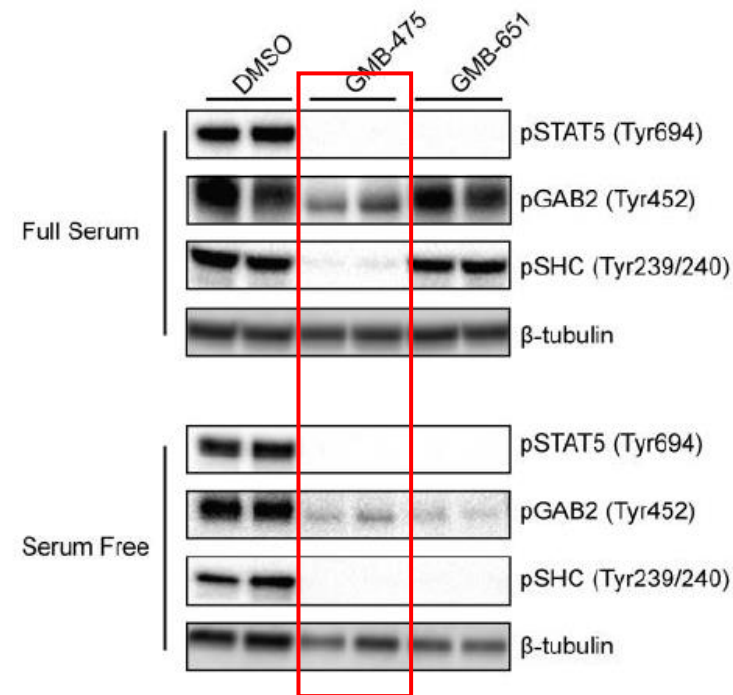
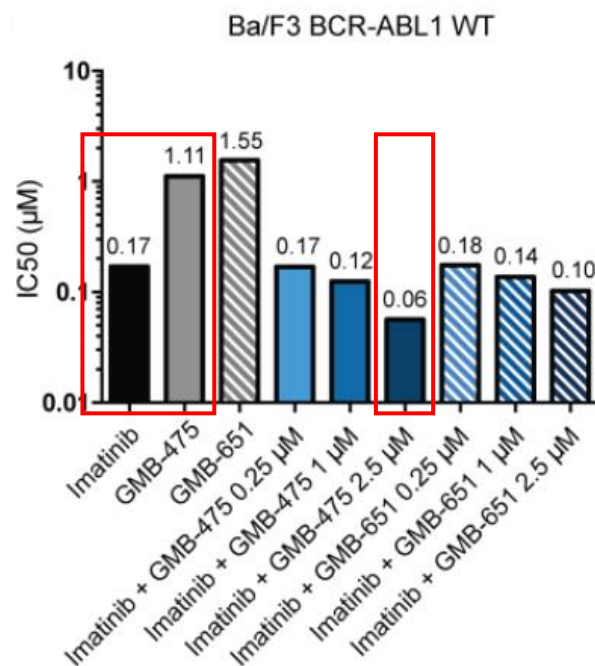
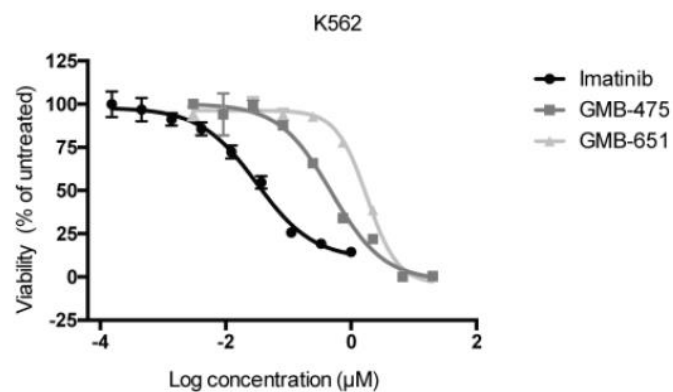
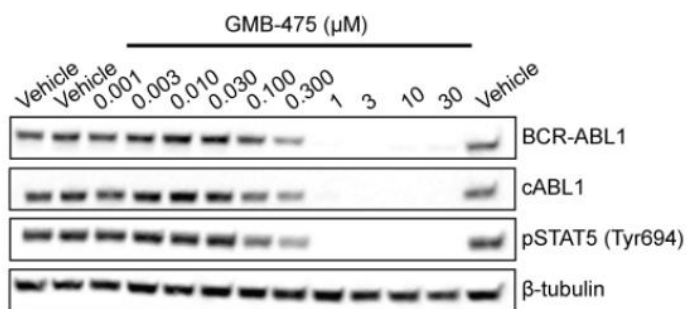


Asciminib



Cave: Low numbers at 9, 12 months due to study closure

GMB-475: PROTAC Binding to the Myristoyl Pocket to Target BCR-ABL1 Protein for Degradation



GMB-651: Diastereomeric control

The Next Frontiers

- Improving access to care
- Doing clinical trials
- Testing the limits of BCR::ABL1 inhibition
- Charting the CML ecosystem at the single cell level
- Maintaining the CML research community

