AT THE FOREFRONT
UChicago Medicine

Chronic Myeloid Leukemia: What more is needed?

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  - Astellas
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  - CVS/Caremark
  - Novartis
  - Pfizer

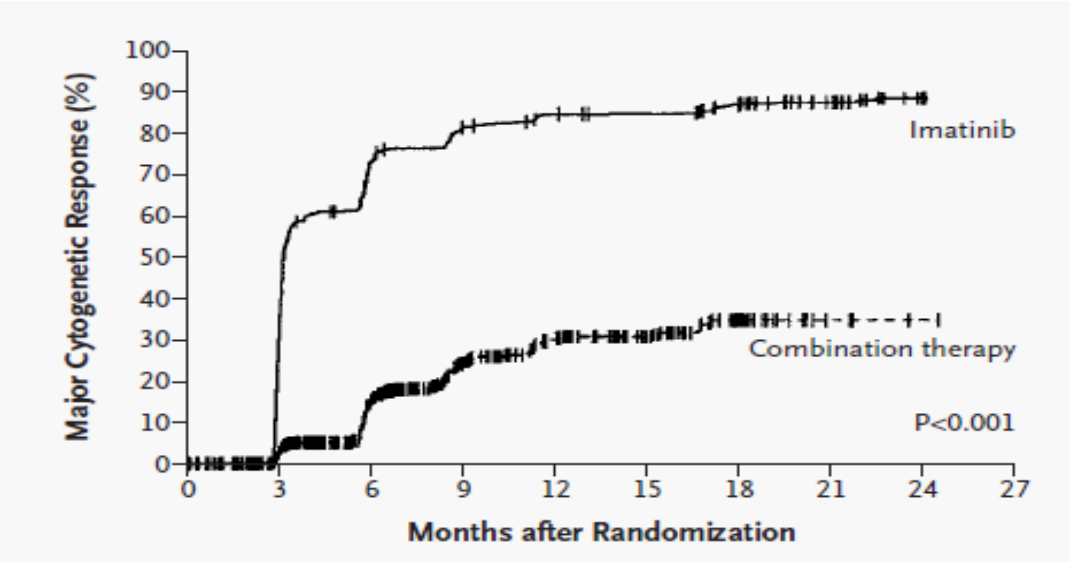
CML: Starting, switching, discontinuing

- 10-year follow up from the IRIS study
- Switching based on Early Molecular Response (EMR)
- Aciminib (ABL001; Novartis) – a non-ATP competitive inhibitor of BCR/ABL1
- Discontinuation studies (18 so far)
- Novel agents and combinations

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

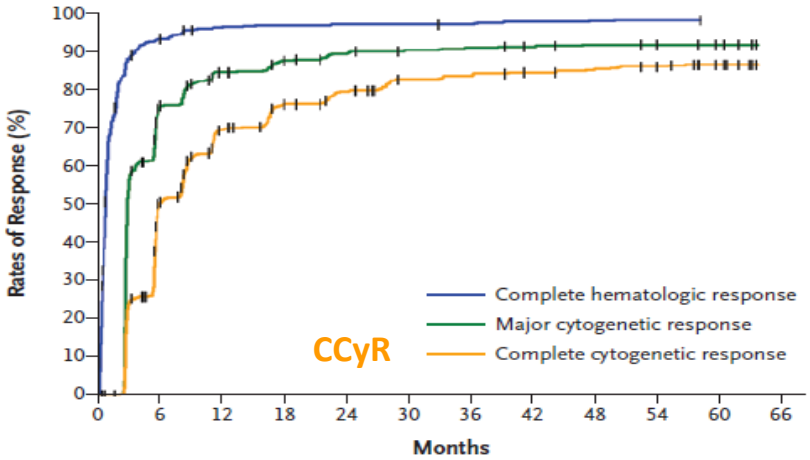
Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia

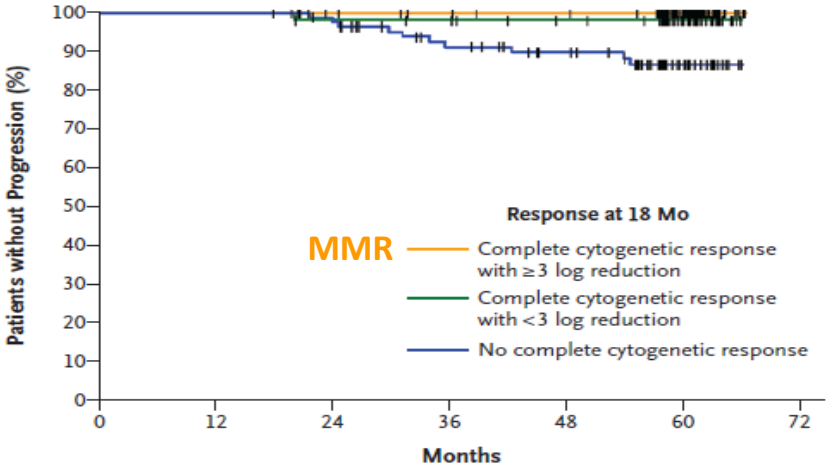


SG O'Brien et al. New Engl J Med 2003; 348: 994-1004.

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.

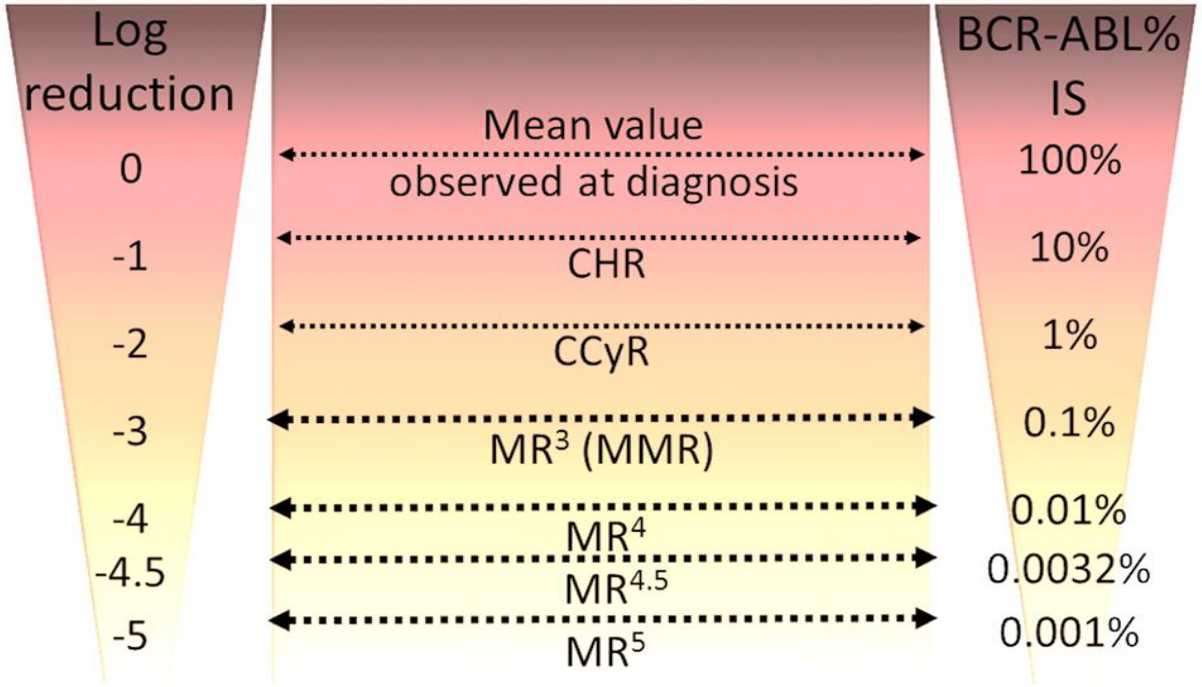
The IRIS Trial: Imatinib vs Interferon + AraC

A Hochhaus, RA Larson, F Guilhot, et al.
New Engl J Med 2017

Long-Term Outcomes of Imatinib Treatment for CML: IRIS

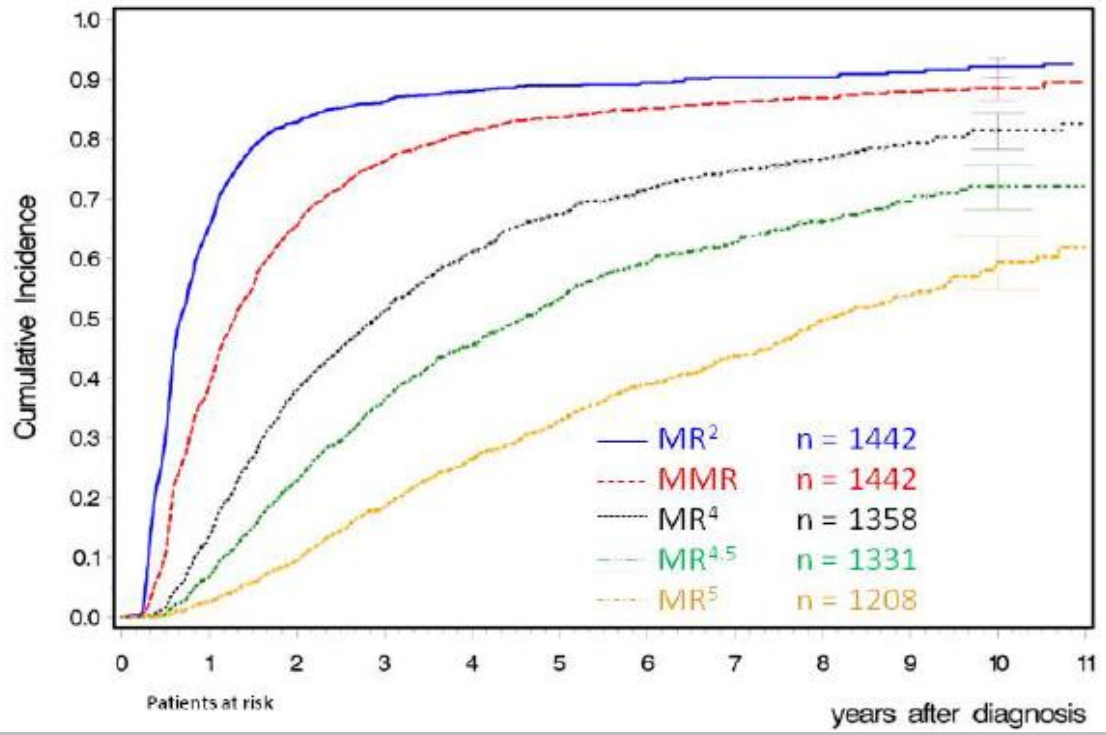
- Median follow-up now 10.9 years.
- Among patients on the imatinib arm, the estimated 10-year overall survival rate was 83.3%.
- 82.8% achieved a complete cytogenetic response.
- Imatinib-related serious adverse events were uncommon and most frequently occurred during the first year of treatment.
- 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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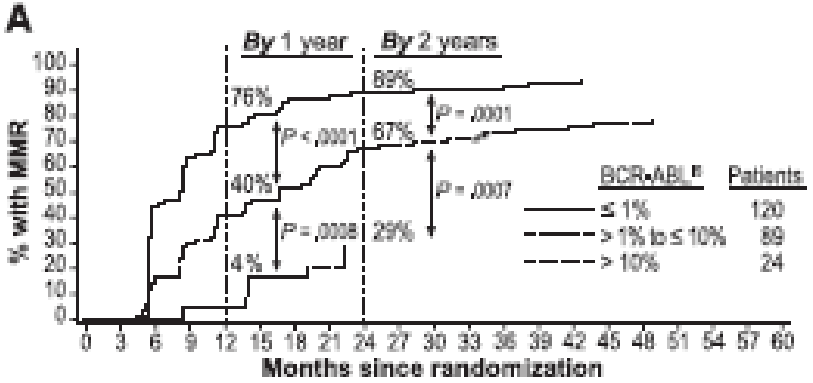
Baccarani et al. Blood 2013 Aug 8;122(6):872-84

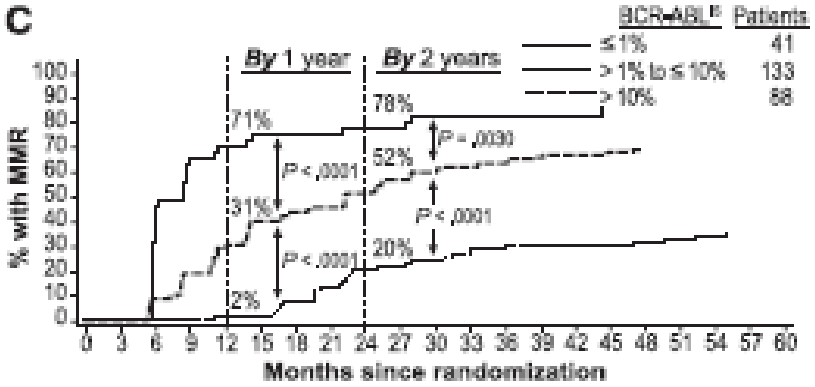
What is an Early Molecular Response?

- *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)



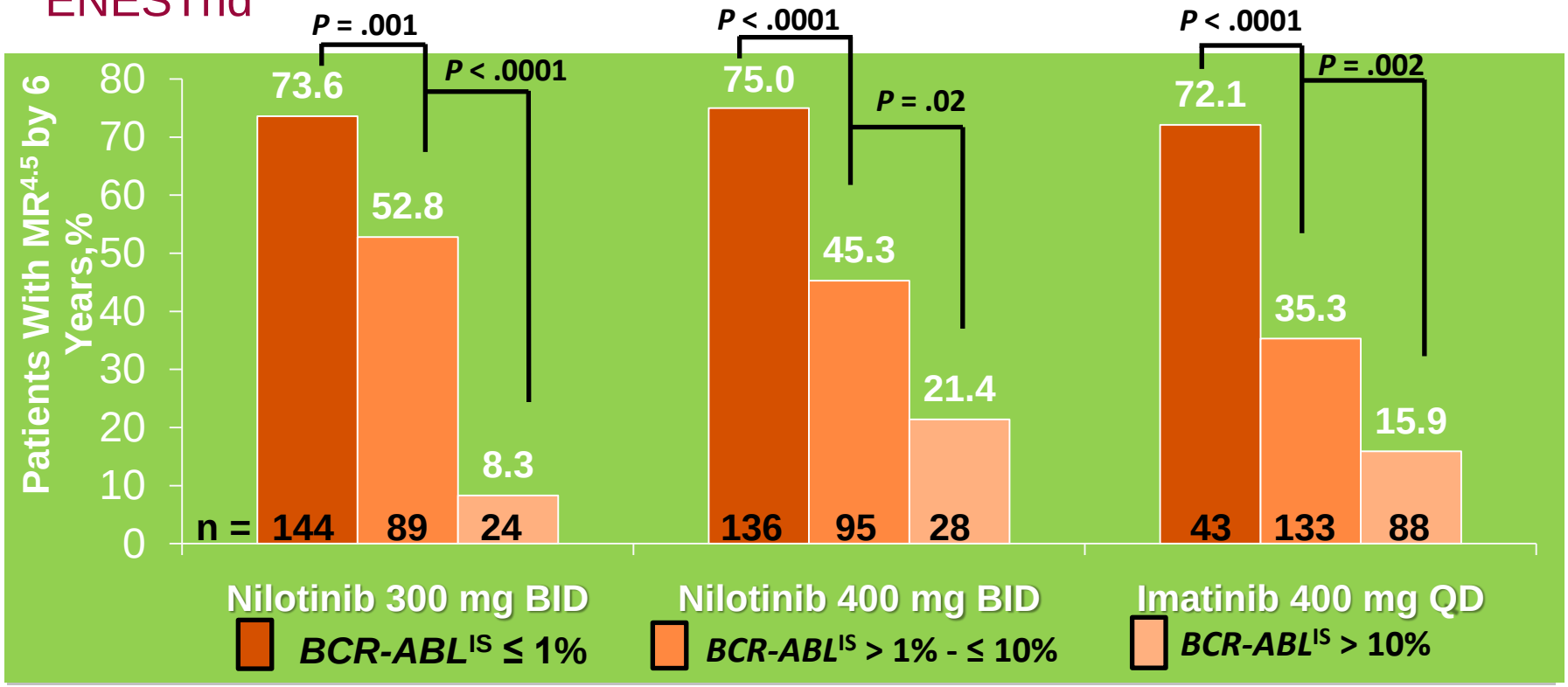
Nilotinib 300 mg BID



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



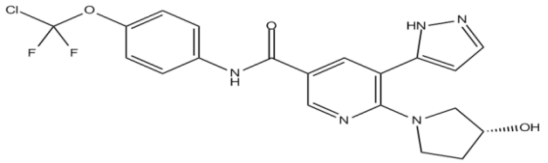
THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

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

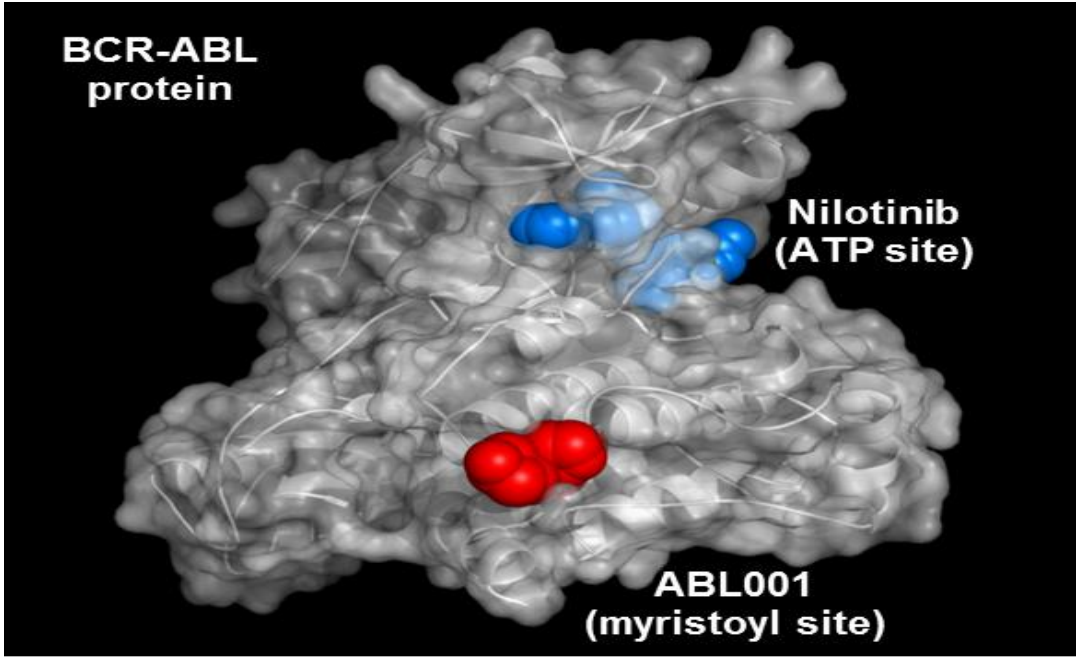
Investigational agents for CML

- **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

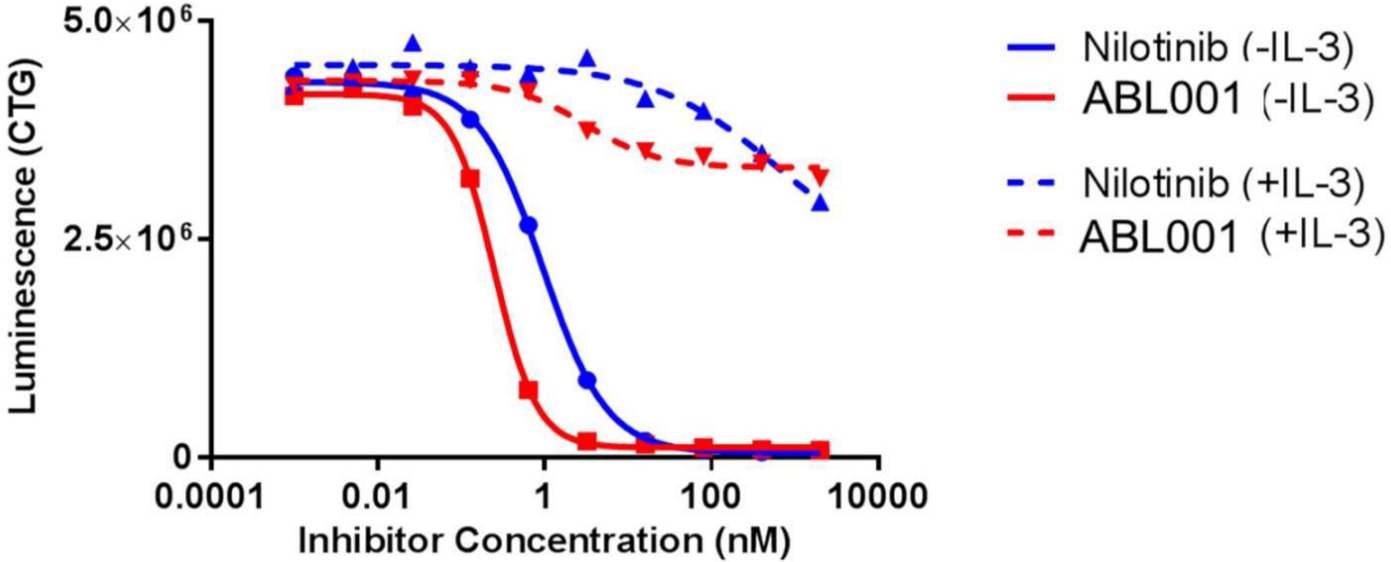
Asciminib (ABL001) Is a Potent, Specific Inhibitor of BCR-ABL1 with a Distinct Allosteric Mechanism of Action



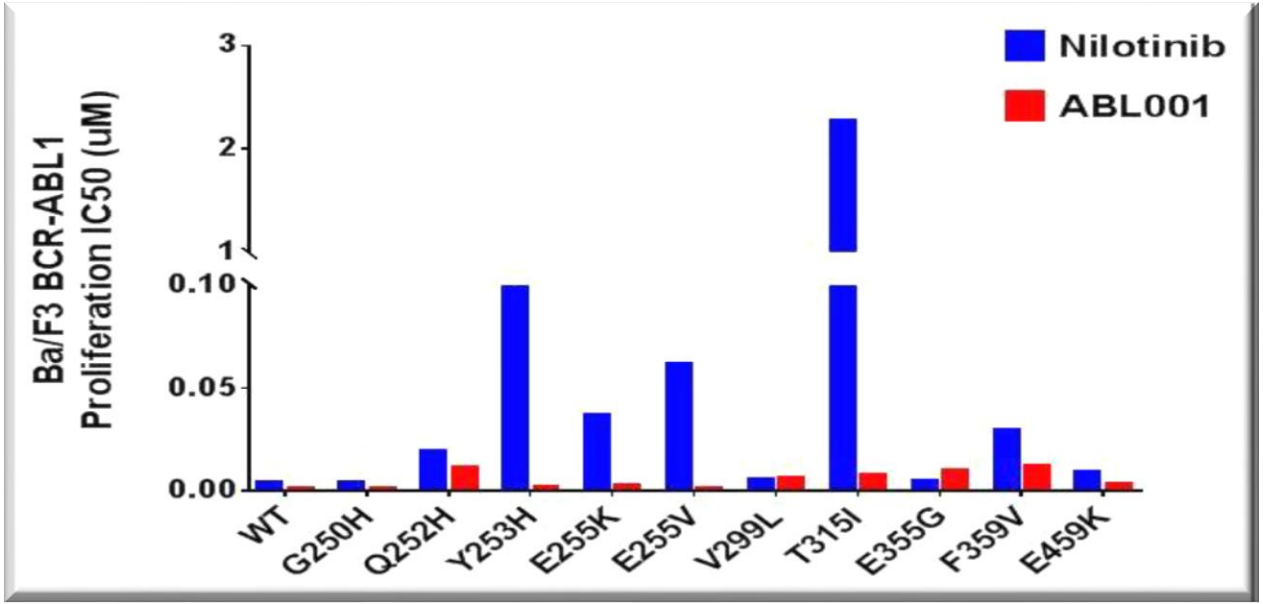
- Developed to gain potent BCR-ABL1 inhibition, maintained against BCR-ABL1 mutations that confer resistance to TKIs
- Combine with TKIs to prevent emergence of BCR-ABL1 mutations, increasing the depth of molecular response in a greater number of patients compared with single-agent treatment



Effect of ABL001 on proliferation of BaF3/BCR-ABL cells in absence and presence of IL3

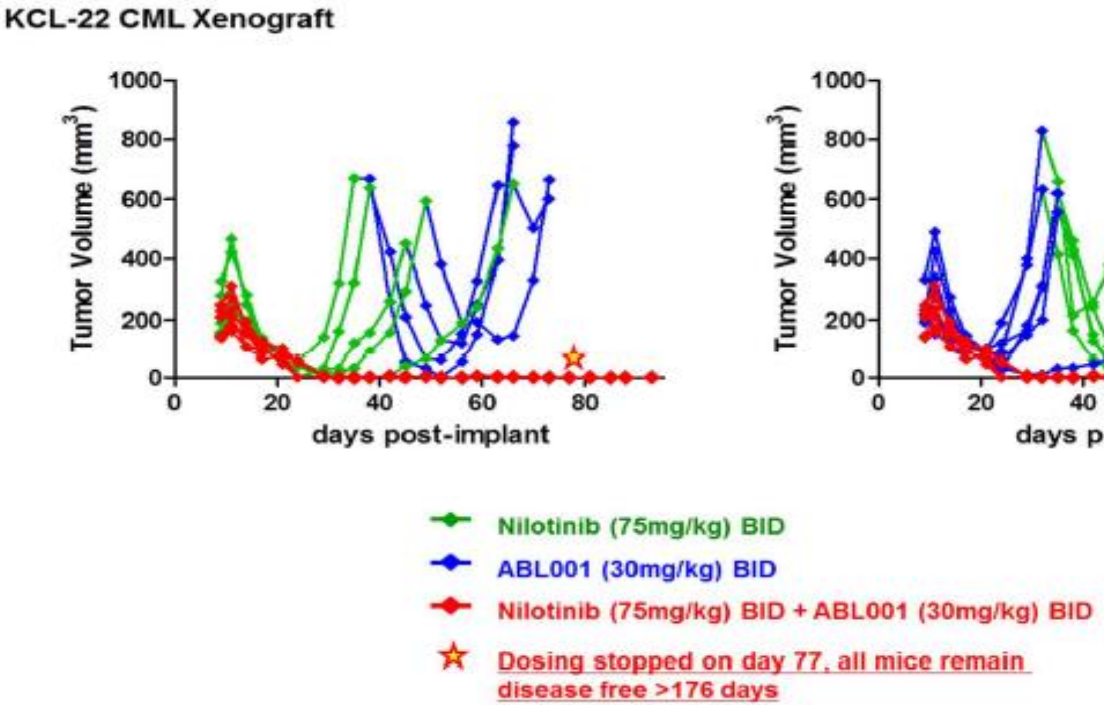


In contrast to nilotinib, ABL001 maintained activity against all BCR-ABL constructs, regardless of mutation, at concentrations below 50 nM.



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

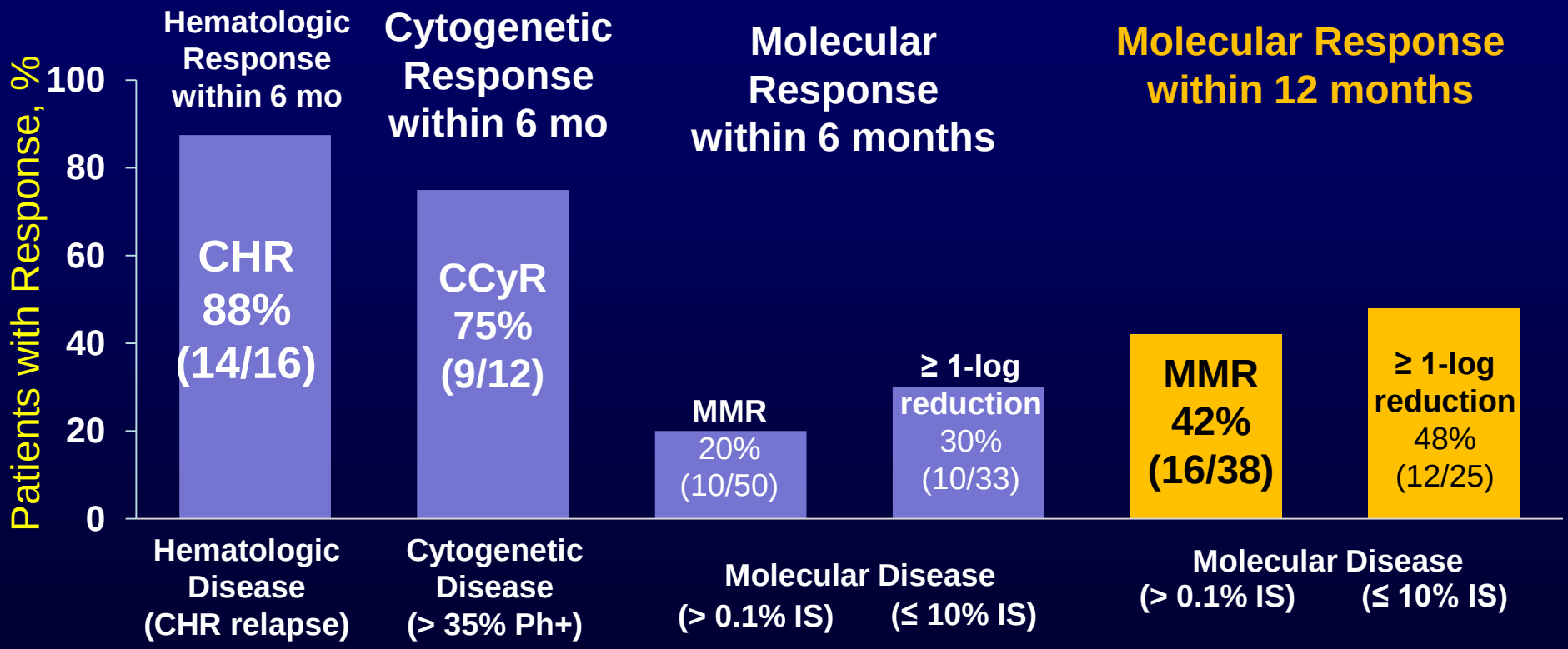


Expanded Phase I Study of ABL001, a Potent, Allosteric Inhibitor of BCR-ABL1, reveals Significant and Durable Responses in Patients with CML-Chronic Phase with Failure of Prior TKI Therapy

Timothy P. Hughes, Yeow-Tee Goh, Oliver Ottmann, Hironobu Minami, Delphine Rea, Fabian Lang, Michael Mauro, Daniel J. DeAngelo, Moshe Talpaz, Andreas Hochhaus, Massimo Breccia, Jorge Cortes, Michael Heinrich, Jeroen Janssen, Juan-Luis Steegmann, François-Xavier Mahon, Ally He, Varsha Iyer, David Hynds, Gary J. Vanasse, Dong-Wook Kim

American Society of Hematology

Responses in Patients with CML treated with Single-Agent ABL001 BID with ≥ 3 Months Exposure



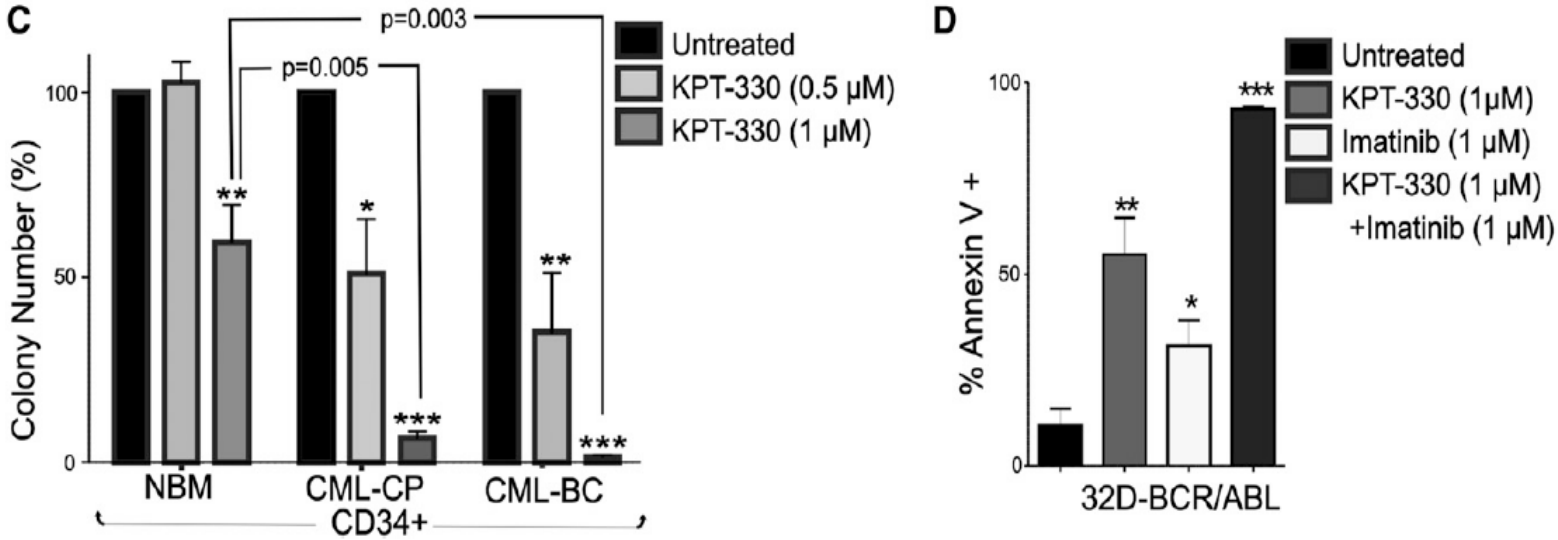
Conclusions

- ABL001 (aciminib) was generally well tolerated in heavily pretreated patients with CML resistant to (61%) or intolerant of prior TKIs.
- Clinical activity seen in patients with non-mutated *BCR-ABL1* as well as across multiple TKI-resistant mutations.
  - 42% achieved MMR by 12 months
  - Only 1 patient with progressive disease had detectable mutations in both kinase and myristoyl domains.
- Dose of 40 mg BID recommended for patients with CML-CP without T315I mutations.
- Phase III trial is randomizing aciminib vs bosutinib for TKI failures.

Selinexor: Exportin-1 (XPO1) inhibition in CML

- Chromosome Maintenance Protein-1 (CMP1)
- Karyopherins → transport RNA and proteins out of the nucleus
- Selective inhibitors of nuclear export (SINE)
- Ph+ leukemia → increased XPO1 expression
  - SET, IkB, FoxO3a, P53 are transported into the cytoplasm
    - Tumor suppressor PP2A is not activated (by SET).
  - Selinexor led to reactivation of PP2A in the nucleus.

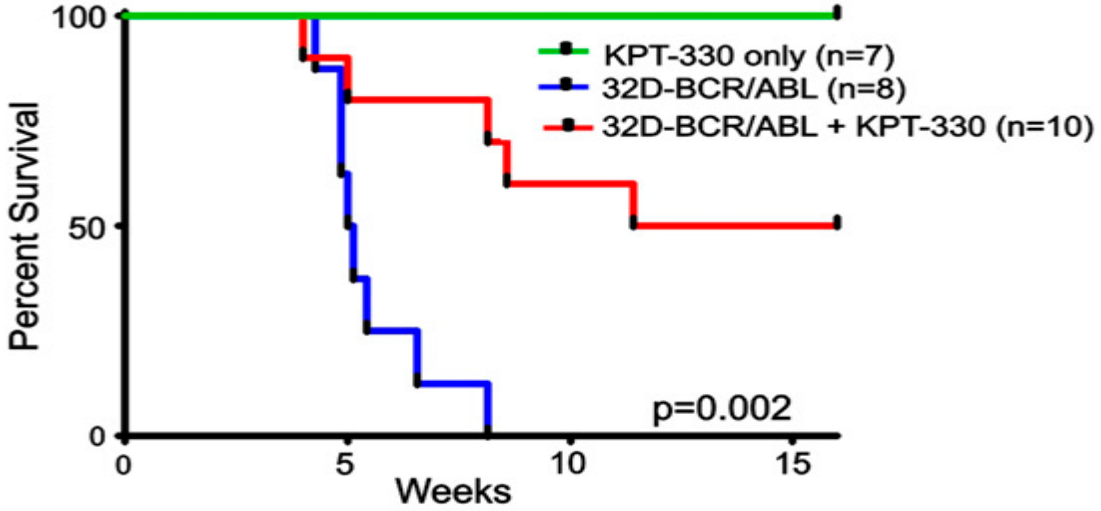
Selinexor (KPT-330) decreased the survival and clonogenic potential in CML-BC and Ph+ B-ALL cells.



*P= .05, **P= .01,***P =.001

Walker et al. Blood. 2013;122(17):3034-3044

Selinexor (KPT-330) increased survival in mice injected with 32D-BCR/ABL leukemia cells.



Walker et al. Blood. 2013;122(17):3034-3044

A 37-year old man with CML in accelerated phase received 4 weekly doses of selinexor

	Pretreatment	Selinexor (16.5 mg/m^2) for 3 doses
WBC (per ul)	>300,000	7000
Spleen (cm below Left Costal Margin)	13	4
Bone pain (0 – 4+)	3+	0

Walker et al. Blood. 2013;122(17):3034-3044

Inecalcitol,
an orally active vitamin D receptor agonist

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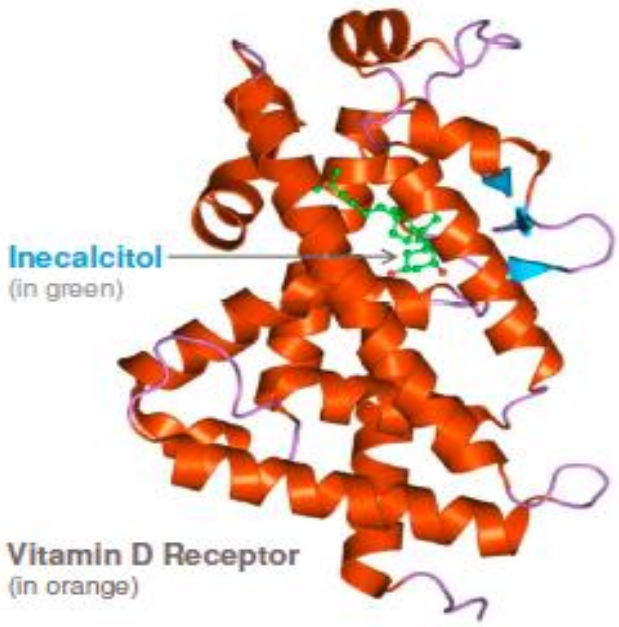


- The vitamin D receptor is a nuclear receptor regulating expression of genes involved in calcium homeostasis and cell proliferation.
- Inecalcitol binds to the vitamin D receptor in a different conformation than the natural vitamin D:
  - Stronger inhibition of cell proliferation
  - Less hypercalcemic toxicity
- Given orally at 4 mg daily.
- Orphan drug status in the US.
- A phase 2 trial in AML is under way in Europe

Inecalcitol, a Novel Adjuvant Therapy Inhibiting CML Stem Cells

- Activates a macrophage differentiation pathway in leukemic progenitors
- 3 to 10 times more potent than the active metabolite of vitamin D to inhibit the growth of human AML cell lines
- Stimulated differentiation into more mature and functional myeloid cells
- Induces apoptosis
- In a model of AML genetically induced in mice, the treatment with inecalcitol resulted in a significant delay in the onset of the disease.

Desterke et al. Blood 2015; 126:4020

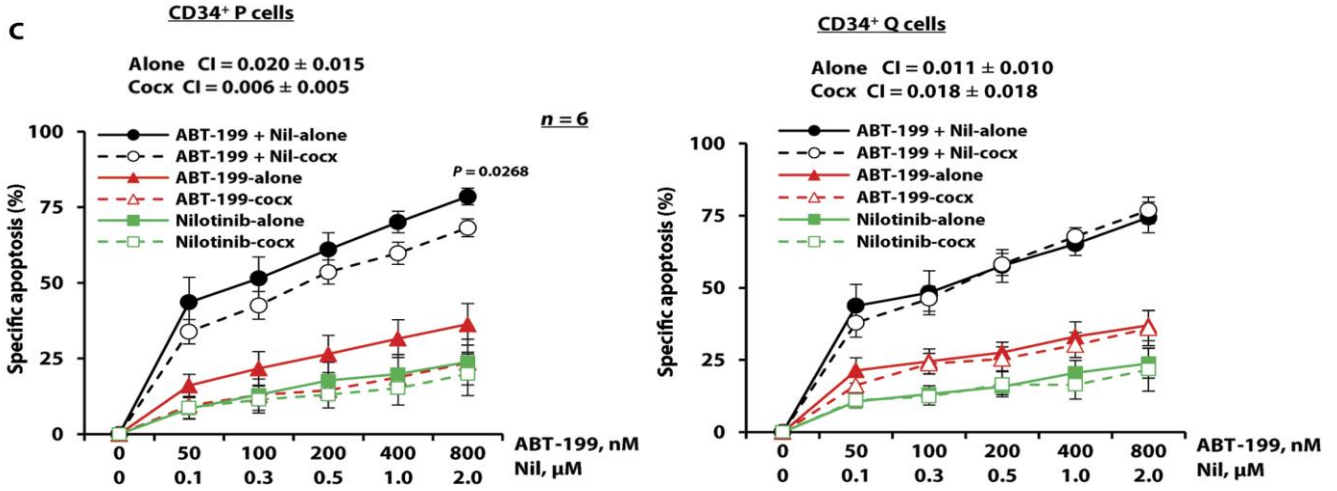
Inecalcitol, a Novel Adjuvant Therapy Inhibiting CML Stem Cells

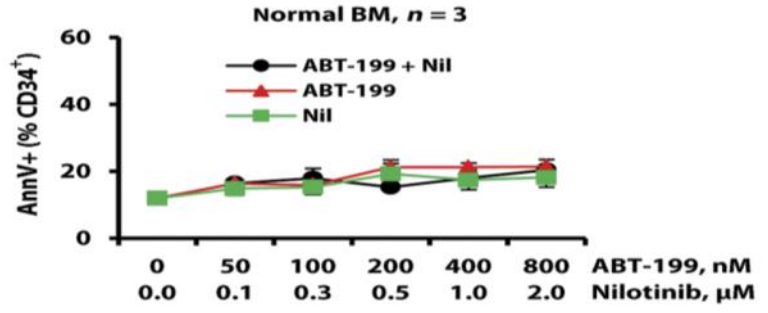
- The combination of inecalcitol and decitabine *in vitro*, or in mice *in vivo*, exerted a more potent effect than the addition of the individual activities of each compound alone.
- Decitabine increases expression of the gene coding for vitamin D receptors (by reducing the methylation of its promoter region).
- As a consequence, more vitamin D receptors are expressed and available to be activated by inecalcitol.

Desterke et al. Blood 2015; 126:4020

Venetoclax: targeting prosurvival BCL-2

Targeting of BCL-2 and BCR-ABL in proliferating and quiescent CD34+ cells from TKI-resistant Blast Crisis CML patients.





Carter et al. Sci Transl Med 2016

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.