Nuclear Export Inhibitor KPT-8602 Is Highly Active Against Leukemic Blasts and Leukemia-Initiating Cells in Patient-Derived Xenograft Models of AML

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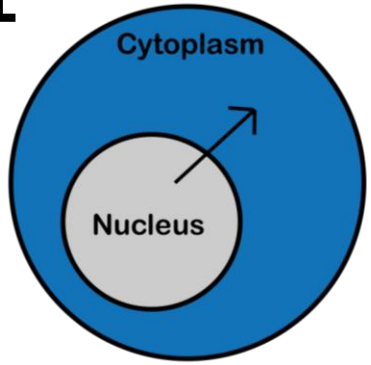
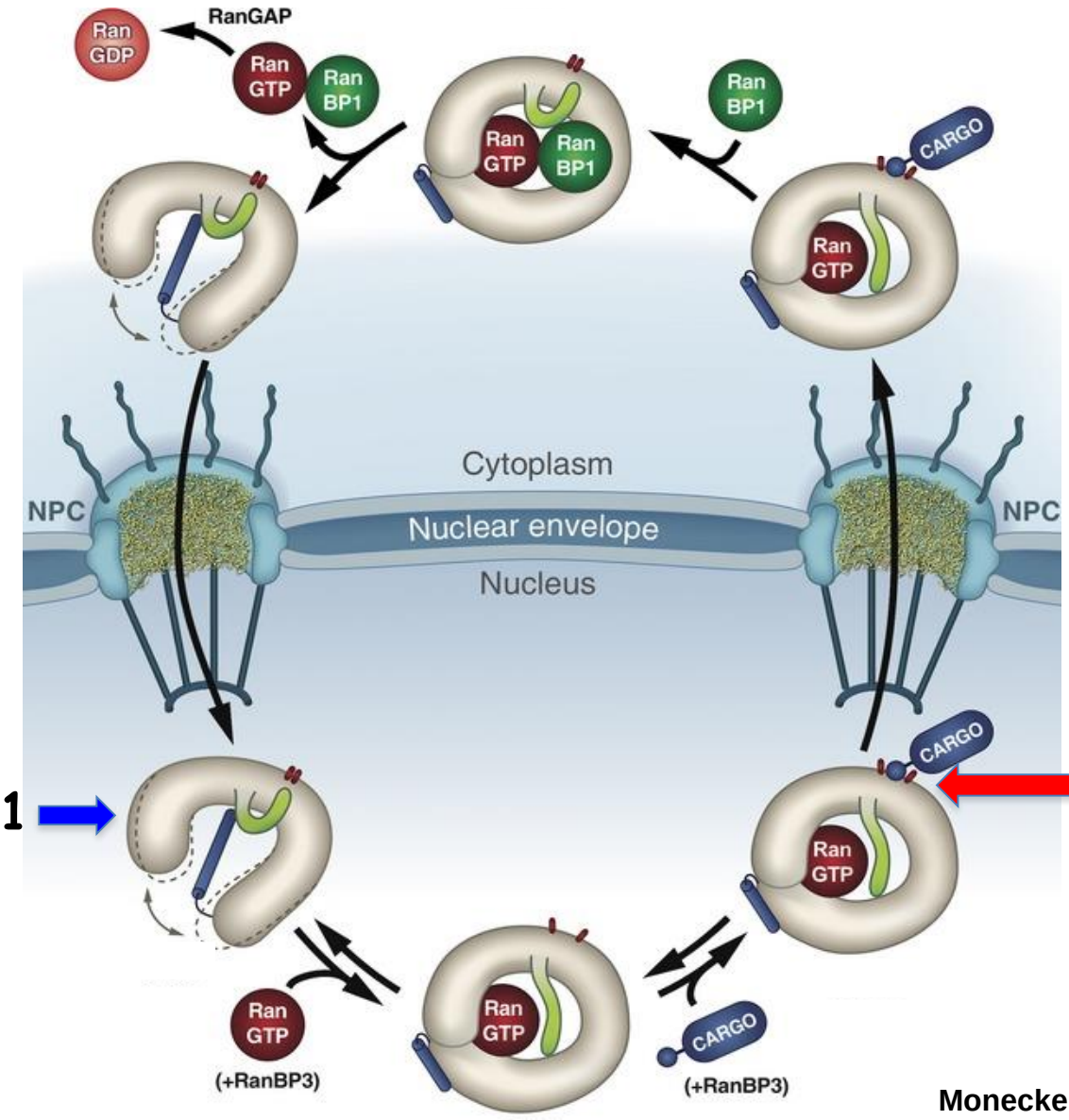
Nuclear Exporter CRM1/XPO1



- major protein nuclear export receptor
- exports ~ 220 macromolecules that contain leucine-rich nuclear export signals (NES)
- mediates export of RNA substrates (e.g. rRNAs, viral mRNAs, cellular mRNAs)
- transports a variety of cancer proteins, including tumor suppressors, transcription factors, and cell cycle regulators

Overview of the XPO1-Mediated Pathway of Nuclear Export



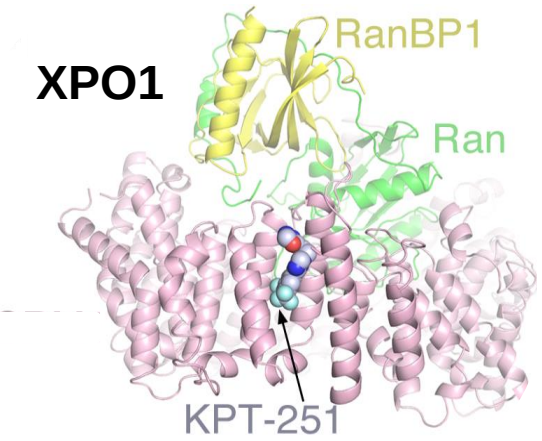
XPO1

Targeted Inhibitor (KPT-SINE)

Monecke et al, FASEB J Review, 2014

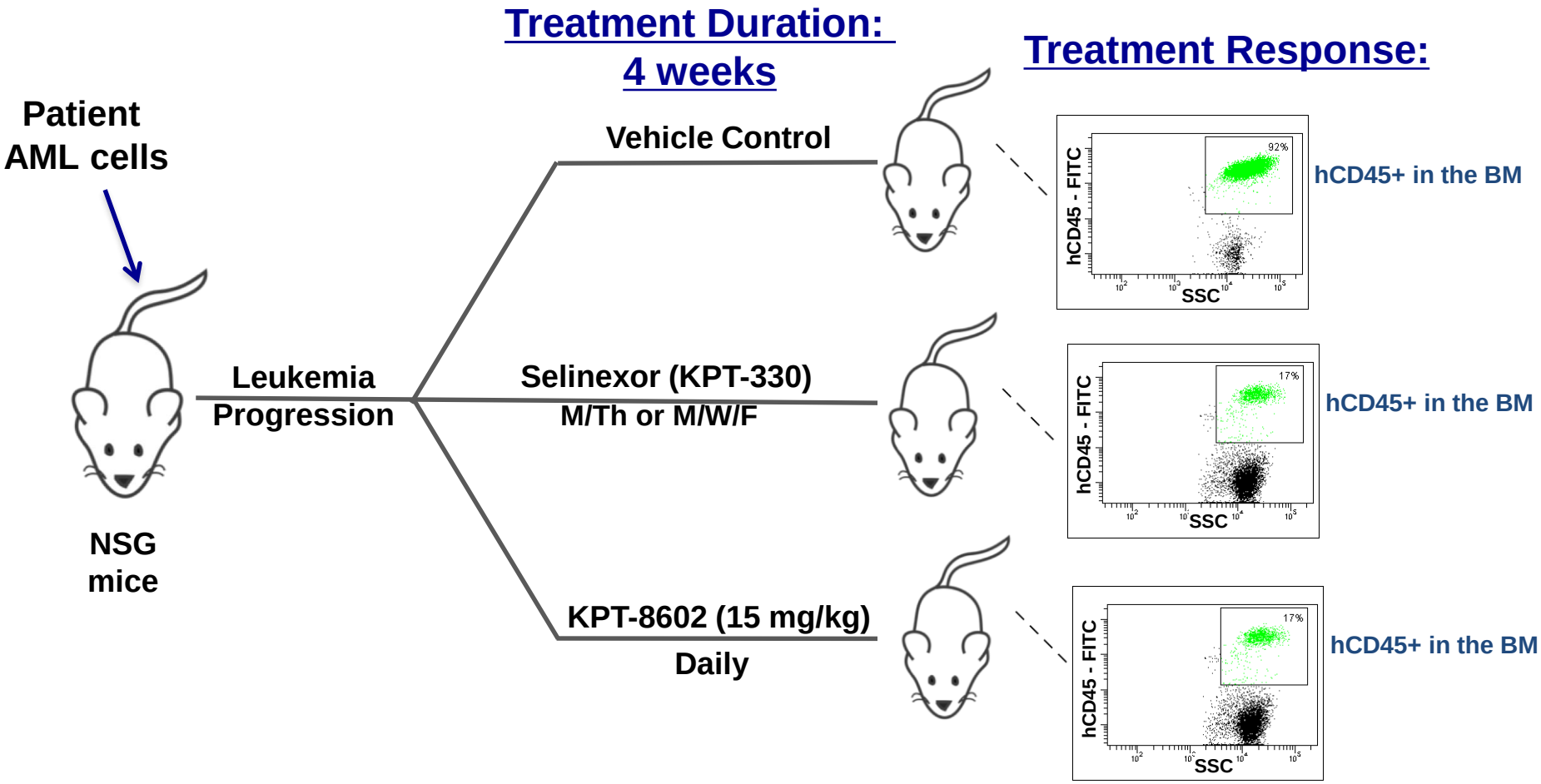
Novel XPO1 inhibitors: KPT-SINE

- Developed based on the crystal structure of CRM1/XPO1 (target Cys^{528} in the cargo-binding groove)
- Orally bioavailable

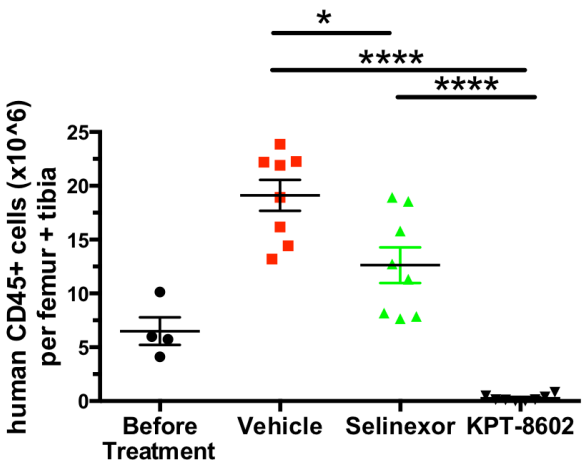


- Selinexor (KPT-330) is in clinical phase I/II trials in adults and children with AML – Preliminary results show that selinexor alone or in combination is active at inducing remission in patients with relapsed or refractory AML
- Next generation SINE compound, KPT-8602, has over 30 times lower brain penetration than selinexor
- KPT-8602 is a more reversible inhibitor of XPO1 as compared to KPT-330

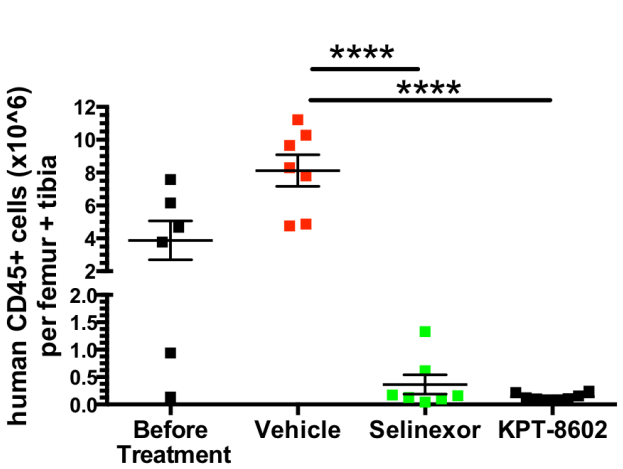
Experimental scheme to determine the activity of KPT-8602 against primary bulk cells



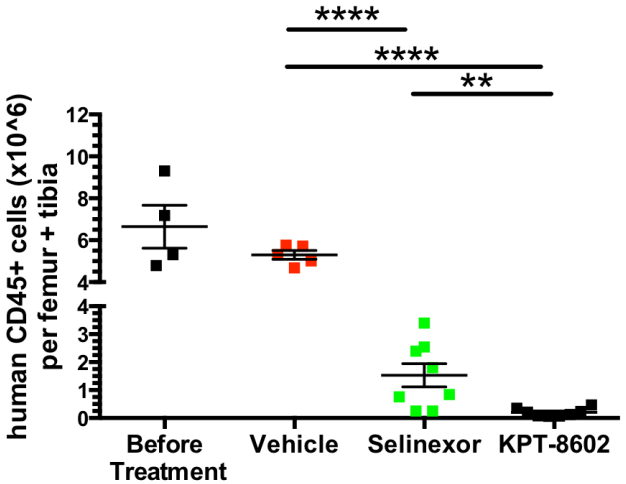
KPT-8602 is Highly Active against Bulk AML Cells in PDX Models of Patient AML



Cytogenetically Normal AML (AML-CN) with FLT3-ITD



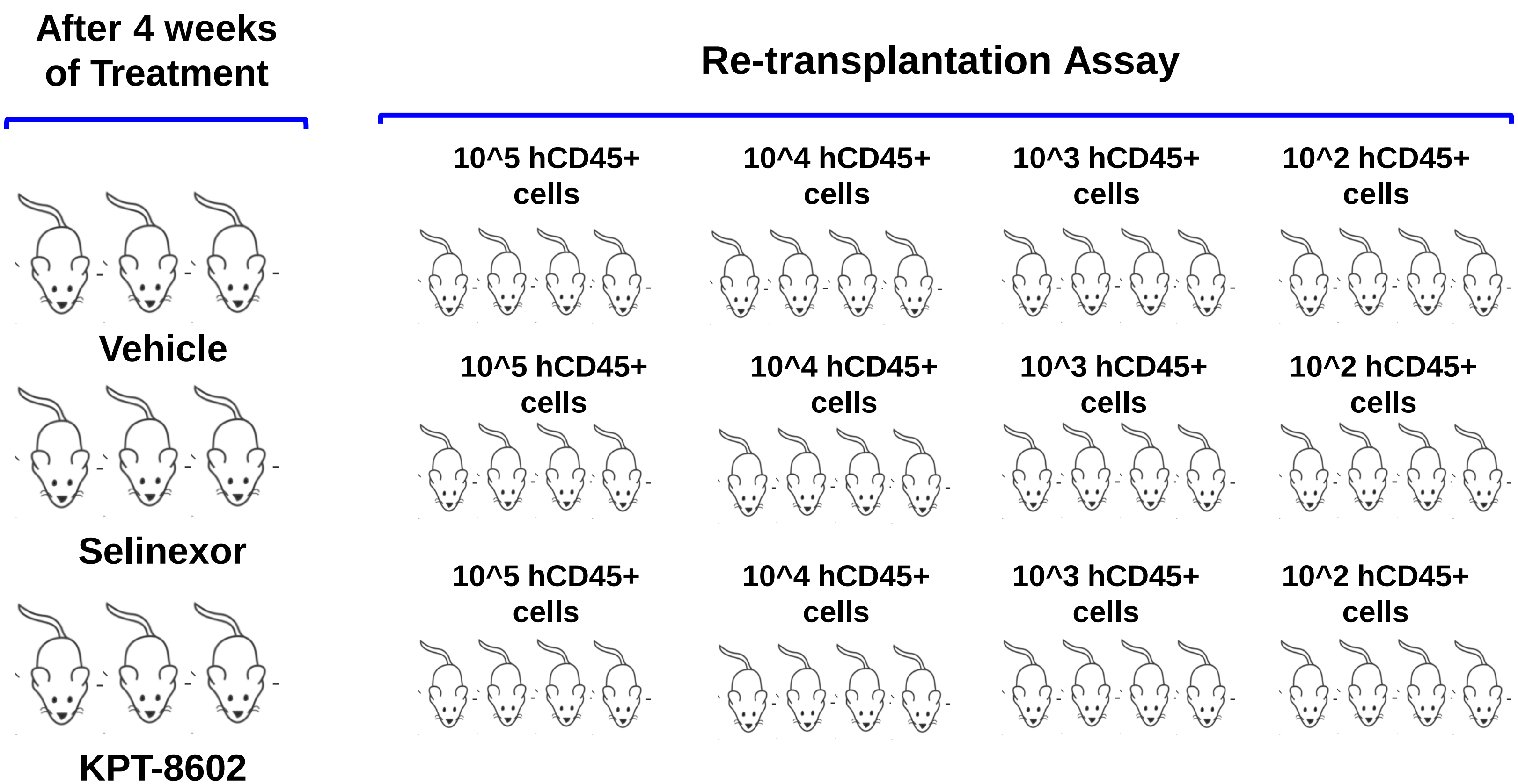
MDS/AML



Complex Karyotype AML (AML-CK)

KPT-8602 greatly reduces the number of bulk AML cells in PDX models of high-risk AML; 2 mice demonstrated no detectable AML cells in the bone marrow after 4 weeks of treatment

Experimental scheme: Response of LICs to KPT-8602 treatment



Compare LIC frequencies between experimental groups

KPT-8602 is Highly Active against AML LICs in PDX models

PDX model AML-CN	LIC freq.	Fold Reduction in LIC Frequency (compared to LIC frequency of Vehicle)
Vehicle	1/1155	1
Selinexor	1/128923	↓ 111-fold
KPT-8602	1/504215	↓ 437-fold

KPT-8602 induced ~ 437 fold reduction in LIC frequency in the surviving AML cell population

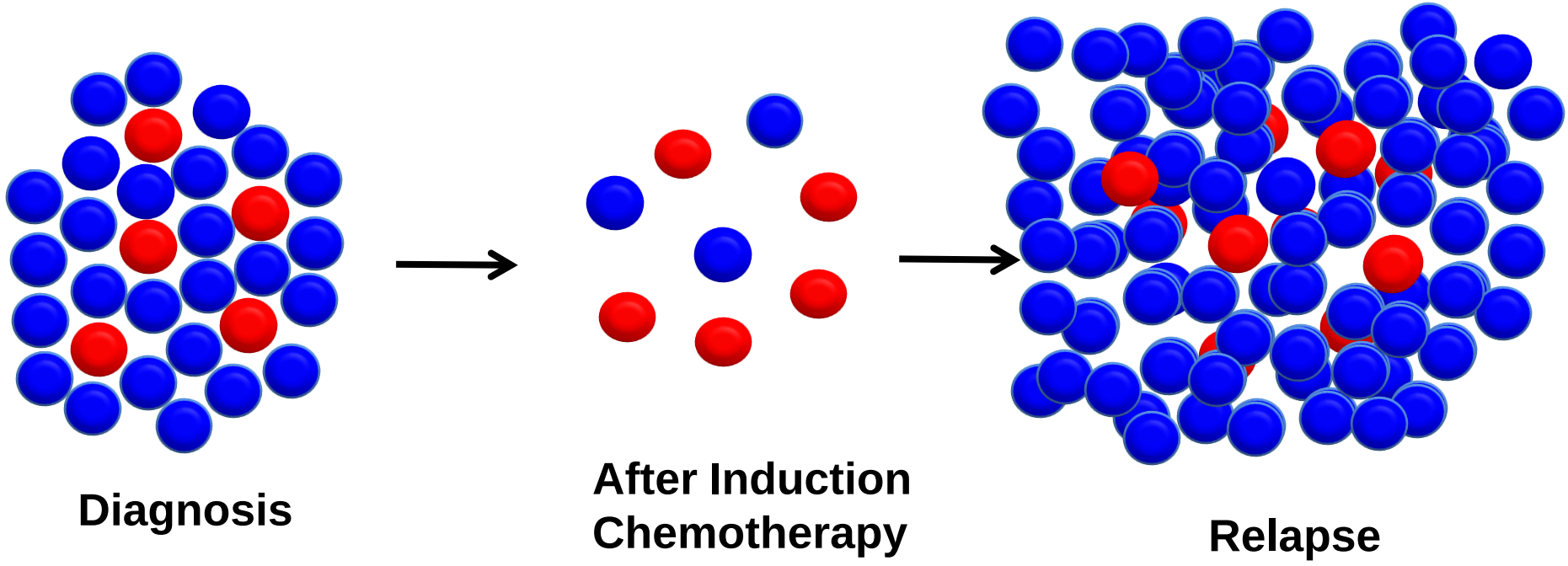
PDX model MDS/AML	LIC freq.	Fold Reduction in LIC Frequency (compared to LIC frequency of Vehicle)
Vehicle	1/4092	1
Selinexor	<1/771218	↓ >150-fold
KPT-8602	<1/681463	↓ >150-fold

KPT-8602 induced ~ 150 fold reduction in LIC frequency

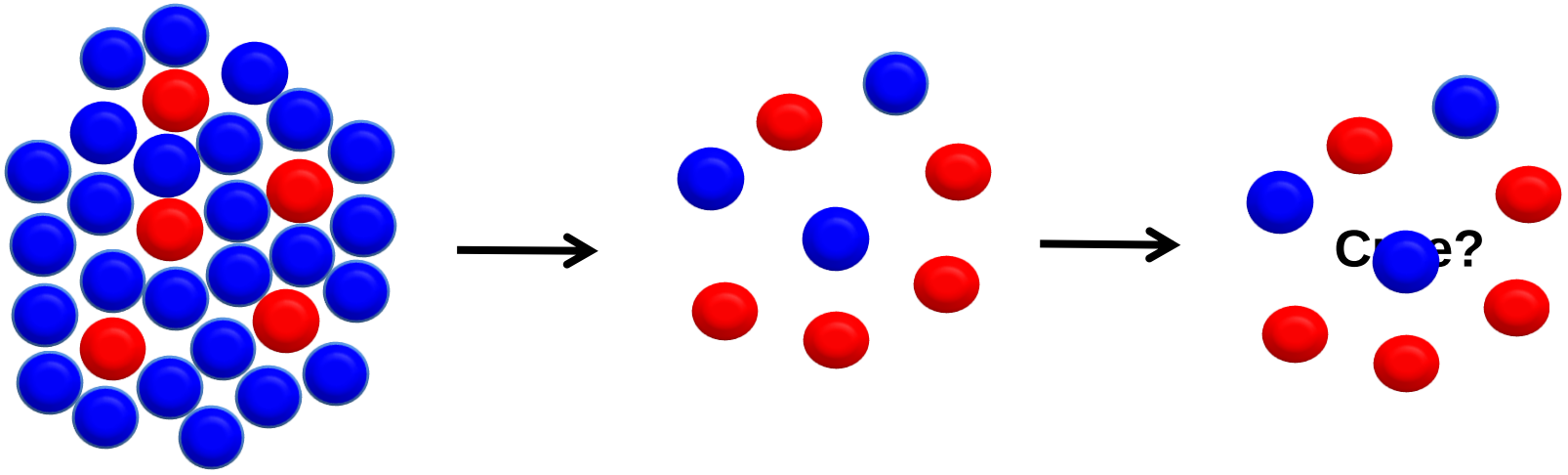
PDX model AML-CK	LIC freq.	Fold Reduction in LIC Frequency (compared to LIC frequency of Vehicle)
Vehicle	1/311	1
Selinexor	1/280	↓ 0.9-fold
KPT-8602	1/157733	↓ 507-fold

KPT-8602 induced ~ 507 fold reduction in LIC frequency

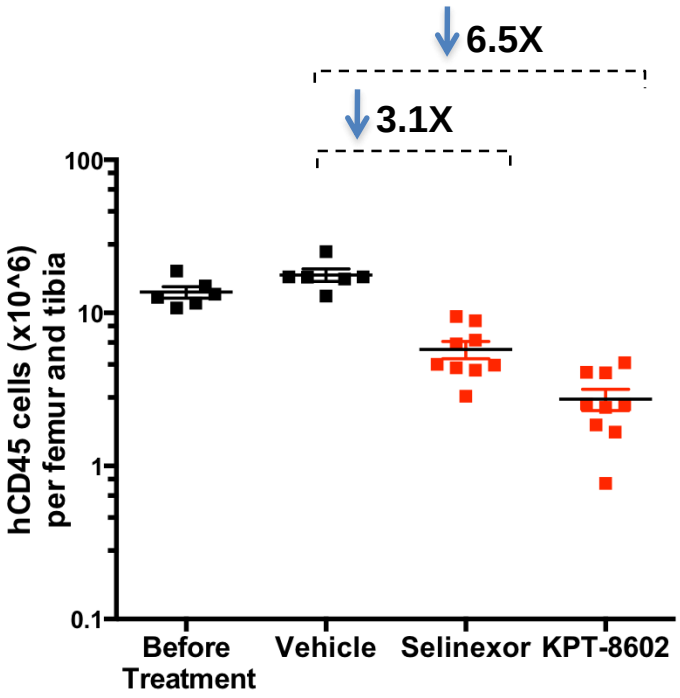
Cytotoxic chemotherapy targets AML bulk cells, but leaves LIC that cause relapse

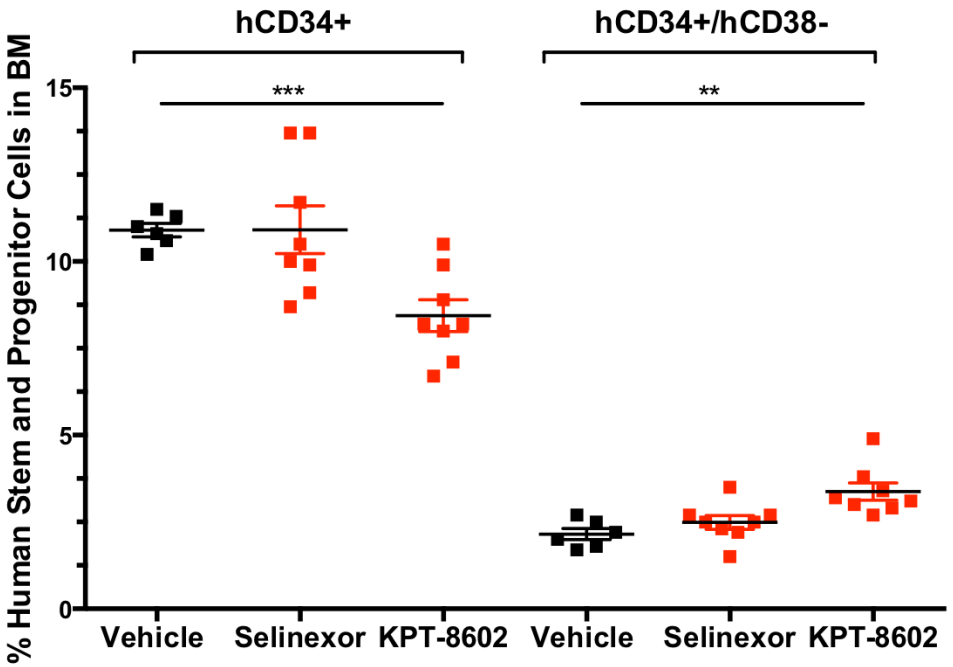


KPT-8602 targets AML bulk and Leukemia Initiating Cells (LICs) with high efficiency



The effects of KPT-8602 on normal human leukocytes and hematopoietic stem and progenitor cells





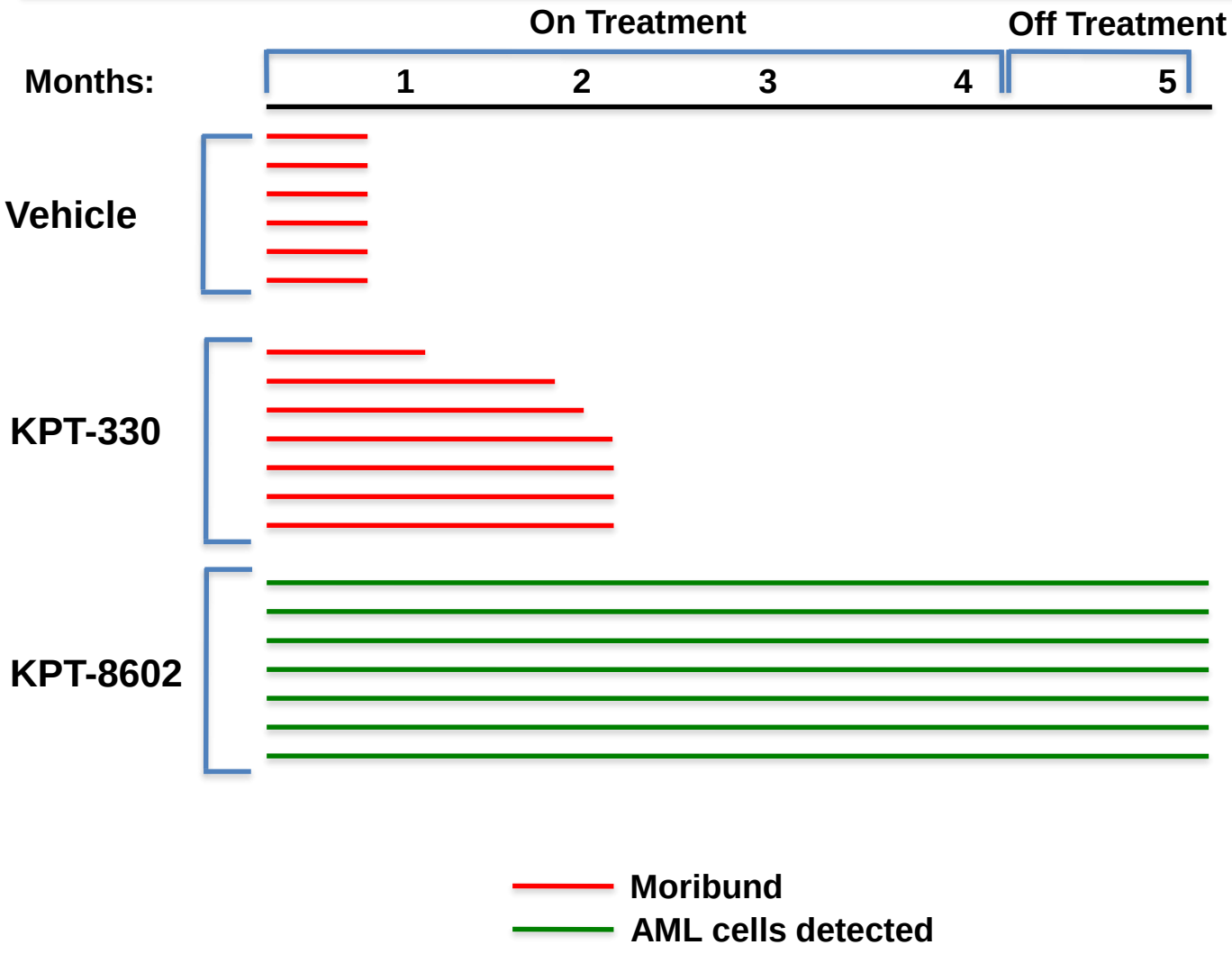
KPT-8602, like KPT-330, shows minimal toxicity against normal HSPCs

The effects of KPT-8602 on normal HSCs

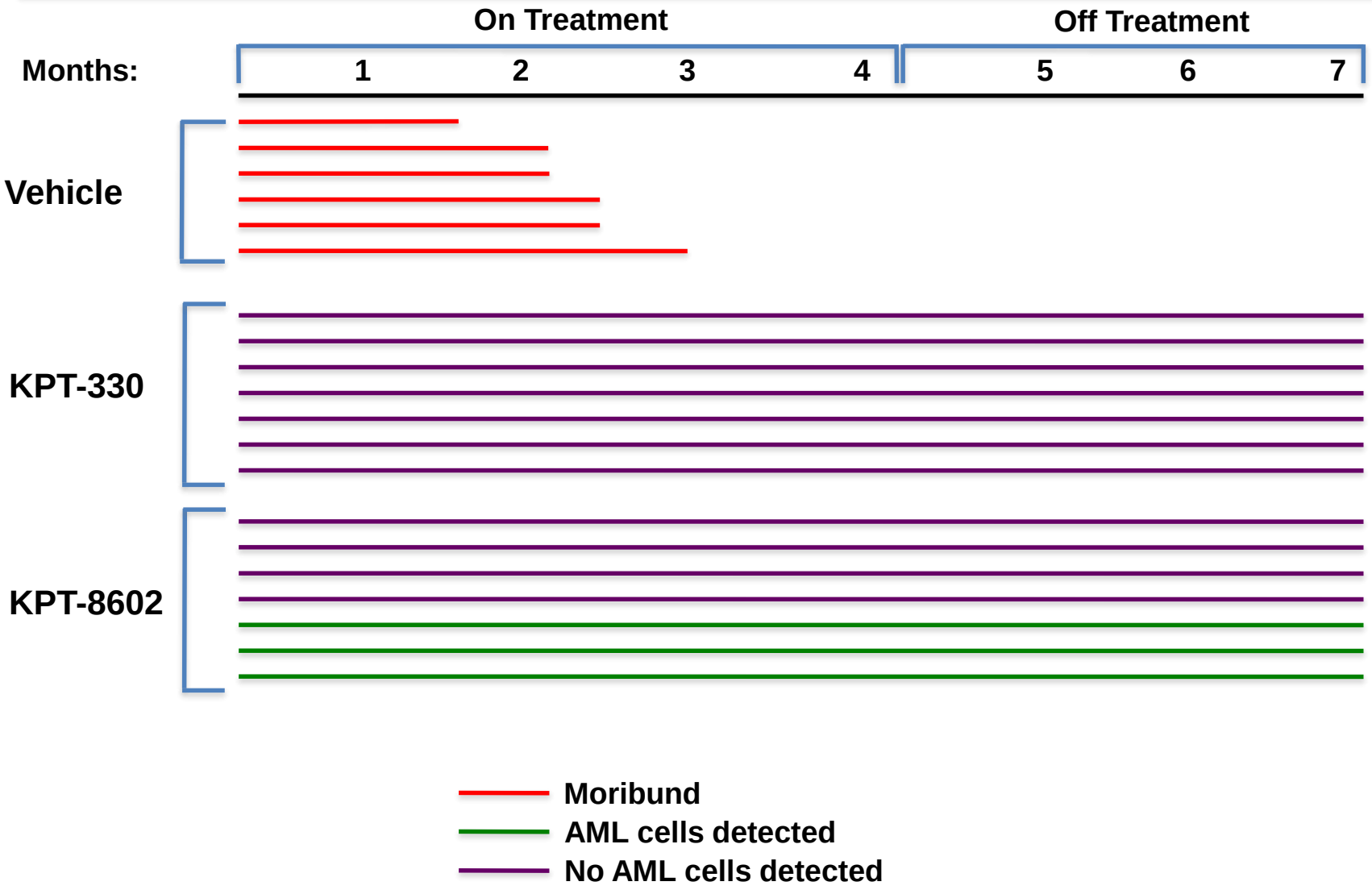
Normal human CD34+ Grafts	Secondary Transplant Normal HSC frequency	Fold Reduction in Normal HSC Frequency (compared to Frequency of Vehicle)
Vehicle	1/7389	1
Selinexor	1/20496	↓ 2.77
KPT-8602	1/6264	↓ 0.85

KPT-8602, like KPT-330, shows minimal toxicity against normal HSCs

The effects of KPT-8602 on Survival of Complex Karyotype AML PDX Mice



The effects of KPT-8602 on Survival of MDS/AML PDX Mice



Conclusions

- KPT-8602 is highly active against bulk AML cells and LICs, but spares normal hematopoietic stem and progenitor cells
- Both selinexor and KPT-8602 can completely eradicate leukemia cells in one of the two PDX models
- KPT-8602 can be given daily to mice and has better tolerability compared to selinexor
- Preliminary toxicology studies in rats and monkeys suggest that KPT-8602 has a substantially better tolerability profile, with reduced CNS-mediated side effects of anorexia and weight loss compared to selinexor.
- KPT-8602 will enter Phase I trials in early 2016 and based on our studies may prove useful to help eradicate LIC that may remain after induction chemotherapy