

PCI-32765 is an investigational drug limited to investigational use and has not been approved for marketing by the FDA

Targeting Bruton's Tyrosine Kinase with PCI-32765 Blocks Growth and Survival of Multiple Myeloma and Waldenström Macroglobulinemia Via Potent Inhibition of Osteoclastogenesis, Cytokines/Chemokine Secretion, and Myeloma Stem-Like Cells in the Bone Marrow Microenvironment

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Btk (Bruton's Tyrosine Kinase)

- Btk is a nonreceptor kinase resembling src family and expressed in hematopoietic cells except T and NK cells.
- Regulated by membrane recruitment, autophosphorylate at Y551 and Y223. Further phosphorylates PLCγ, leading to activation of MAPK, NFκB, and AKT signaling pathways.
- Important in B cell and myeloid function.
- Selective expression in osteoclasts (OC), but not osteoblasts (OB) suggests its role in osteoclastogenesis.
- However, Btk has not been characterized in multiple myeloma (MM) and Waldenström Macroglobulinemia (WM).

OBJECTIVES

Osteolytic bone disease is prominent in MM
OC ↑ OB ↓

- To define the role of Btk in MM-induced osteolysis
- To characterize Btk in MM and WM in the bone marrow (BM) microenvironment

To determine molecular targets of Btk signaling cascade in OC, MM and WM in the BM milieu & to support clinical trial of targeting Btk by PCI-32765 in these plasma cell cancers

PCI-32765

- Forms a specific and irreversible bond with cysteine-481 in Btk
- Potent Btk inhibition (IC₅₀ = 0.5 nM)
- Orally available
- Once daily dosing results in 24h sustained target inhibition
- Phase I/II Studies in NHL patients - promising clinical activities
 - 78% of MCL
 - 69% of CLL
 - 31% of FL
 - 29% of DLBCL
- Safe, lacks cumulative toxicity

CC(=O)N1CCCCC1N2C=NC3=C(N)N=CN=C32c4ccc(Oc5ccccc5)cc4

MW 440.5
 Horigberg 2010; Herman 2011; Chang 2011

PCI-32765 Inhibits Btk-mediated Osteoclastogenesis

CD14+ From Normal Donor Or MM Samples → M-CSF → M-CSF/RANKL → RANKL → Bone resorption

A RANKL/M-CSF min 0 5 10 30 60
 pBTK, pPLCγ2, Btk

B RANKL/M-CSF + - - -
 PCI-32765 + + - -
 pBtk, pPLCγ2, α-tubulin

C multi-labeled OC (% nuclei) vs PCI-32765 μM (0, 0.5, 1, 10). TRAP Staining, x40

PCI-32765 Blocks Bone Resorption

Dex PCI-32765 μM

1	2
1	1
1	0.1
1	-
-	1
-	0.1
-	-

* p<0.05

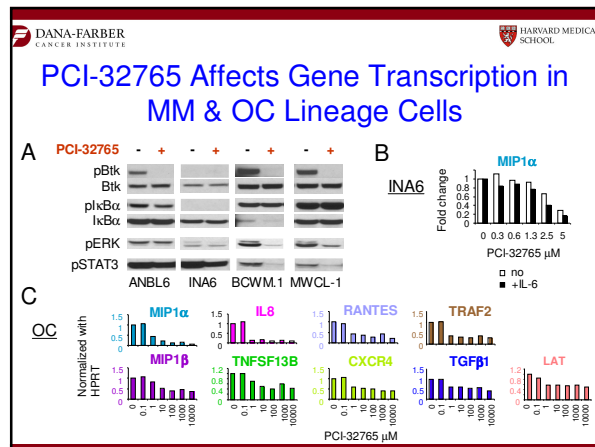
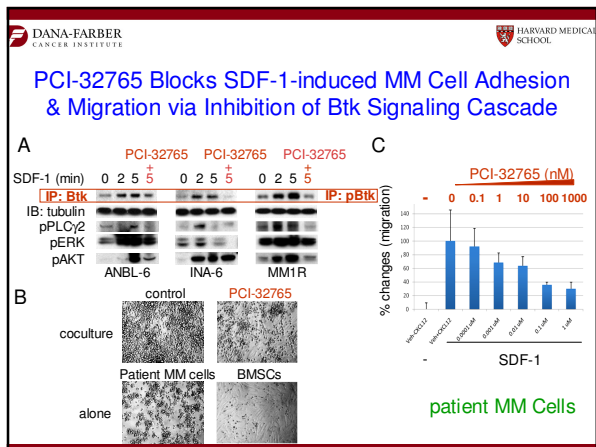
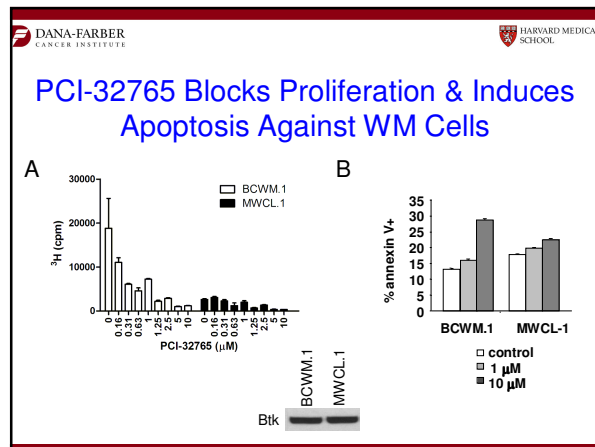
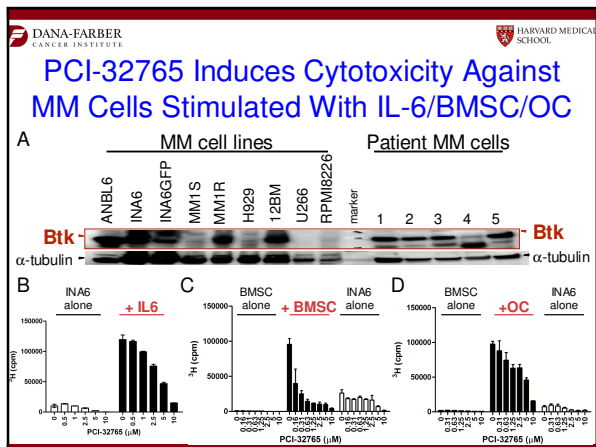
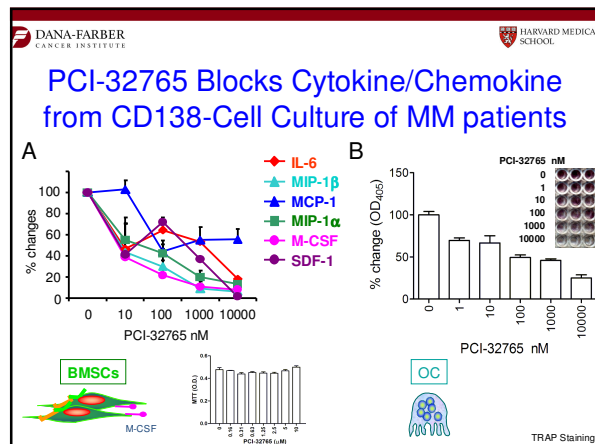
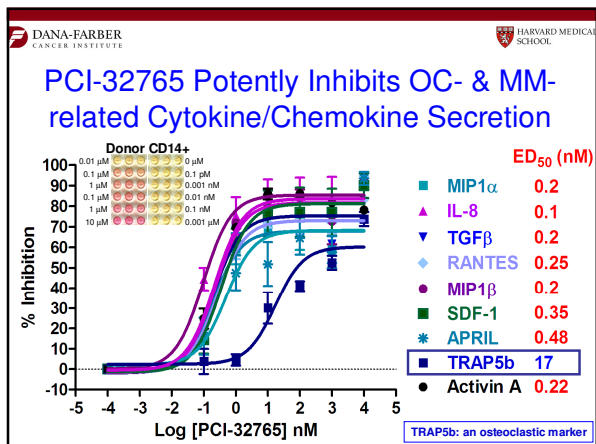
% eroded area

TRAP formation assay

PCI-32765 vs control images

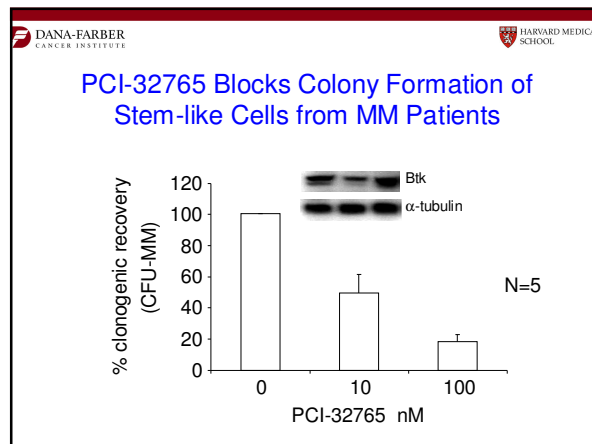
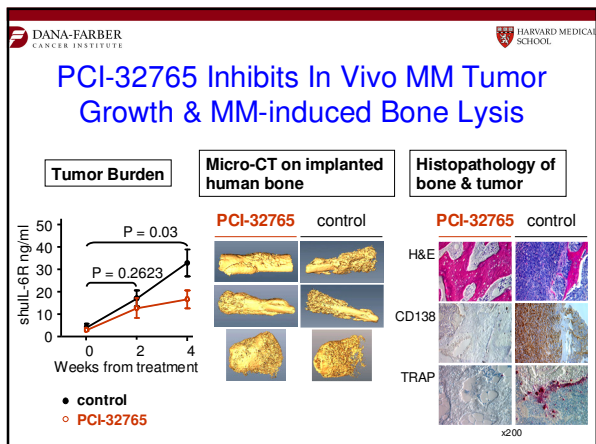
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