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Title of Presentation	A Roadmap Towards Targeting KIT D816V Mastocytosis with Non-TKI Compounds
abstract-hint	
Abstract of Presentation	A drug discovery approach was applied to malignant KIT D816V cells, derived from mastocytosis patient induced pluripotent stem cells (iPS cells), to screen a library of FDA approved and experimental drugs for specific killing of KIT D816V cells. We discovered the novel compound LDC 3416, which targets multiple malignant KIT D816V cell types, including hematopoietic stem/progenitor cells and mast cells. Importantly, by exploring the LDC 3416 targeting profile, we identified the phosphodiesterase 3A-Schlafen 12 (PDE3A-SLFN12) molecular glue pathway as a novel approach for specific killing of malignant KIT D816V cells. We found that the KIT D816V mutation leads to increased expression of PDE3A and SLFN12 and thus confers selective molecular vulnerability to PDE3A-SLFN12 molecular glues. Primary malignant mast cells of KIT D816V patients with indolent and advanced systemic mastocytosis also exhibit increased

	expression of PDE3A and SLFN12. We extended our study to include additional PDE3A-SLFN12 molecular glues and demonstrate their synergistic action with KIT D816V selective tyrosine kinase inhibitors (TKIs) in killing KIT D816V cells. Furthermore, the PDE3A-SLFN12 molecular glues also target KIT D816V megakaryocytes, a cell type that has been underestimated in our understanding of malignant mast cell pathophysiology and molecular targeting. The identified molecular glues, along with their synergy with TKIs and their simultaneous targeting of multiple KIT D816V cell types, open novel treatment options for KIT D816V mast cell malignancies and other KIT D816V associated diseases.