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Blood 142 (2023) 3300–3301

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Pacritinib Blocks Key Pro-Survival Signaling Related to Mutated MYD88, Produces High Levels of Apoptosis and Overcomes Mutated BTK ^{Cys481} Related BTK-Inhibitor Resistance

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Background: Somatic mutations in MYD88 are prevalent in many B-cell malignancies, including Waldenström Macroglobulinemia (WM; 95-97%), primary CNS lymphoma (70-80%), ABC DLBCL (40%), marginal zone lymphoma (5-10%) and CLL (5-15%). Mutated MYD88 drives oncogenic pro-survival signaling through multiple signaling cascades that include HCK-directed BTK, ERK and SYK, as well as IRAK1/IRAK4 activation. HCK is an SRC family member that mutated MYD88 transcriptionally upregulates, and its activation is triggered by IL-6/IL-6R/gp130/JAK2 signaling. BTK inhibitors are active in MYD88 mutated B-cell malignancies, but fail to produce complete responses, and show varying durations of response that are disease dependent and impacted by depth of response. Acquired resistance to BTK inhibitors is commonly related to a BTK ^{Cys481} mutation. Pacritinib is a kinase inhibitor, FDA-approved for myelofibrosis, that is well tolerated and targets pro-signaling cascades that are relevant to mutated MYD88 signaling, including IRAK1, JAK2, and SRC, a homologue of HCK (**Fig. 1**). Pacritinib may therefore represent a more effective option in blocking mutated MYD88 pro-survival signaling versus BTK-inhibitors.
Methods: We performed comparative studies to evaluate the activity of pacritinib and the covalent BTK-inhibitors ibrutinib and zanubrutinib on mutated MYD88 relevant pro-survival signaling, as well as proliferation and survival in MYD88 mutated cell lines and primary MYD88-mutated WM cells. Further to these studies, we assessed the activity of pacritinib in well-characterized mutant (BTK ^{Cys481Ser}) expressing covalent BTK-inhibitor resistant WM and ABC DLBCL lymphoma cell models.
Results: Pacritinib produced higher levels of apoptosis in MYD88-mutated WM (BCWM.1) and ABC DLBCL (TMD-8), and primary (CD19 $^{+}$) MYD88-mutated WM cells relative to the BTK inhibitors ibrutinib or zanubrutinib.The apoptotic activity of pacritinib showed dose dependence with high levels of apoptosis at 0.5 μM, which is well within its pharmacologically achievable levels. Importantly, pacritinib, in addition to its known effects on JAK2 and IRAK1 activation, also showed robust inhibition of p-HCK (Y411) and its downstream signaling partner p-BTK (Y223) in MYD88 mutated BCWM.1 and TMD-8 cells. By combination index and normalized isobologram analyses, pacritinib showed synergistic interactions with covalent BTK inhibitors, and more so with the BCL-2 inhibitor venetoclax in MYD88 mutated cell lines and primary WM cells. Lastly, pacritinib alone and combined with venetoclax induced high levels of apoptosis in BTK ^{Cys481Ser} expressing covalent BTK-inhibitor resistant MYD88 mutated WM and ABC DLBCL lymphoma cells.
Conclusions: Pacritinib more broadly extinguishes mutated MYD88 pro-survival signaling cascades (**Fig 1.)** and demonstrates high levels of apoptotic activityin mutated MYD88 WM and ABC DLBCL cells versus selective covalent BTK-inhibitors. Pacritinib also synergizes with covalent BTK- and BCL2 inhibitors and can overcome covalent BTK-inhibitor resistance related to mutated BTK ^{Cys481}. Our studies provide a framework for investigating pacritinib in MYD88 mutated lymphomas. A clinical trial of pacritinib in relapsed/refractory WM is being initiated.

Disclosures Sarosiek: *Cellectar:* Consultancy, Research Funding; *Beigene:* Honoraria, Research Funding; *ADC Therapeutics:* Research Funding. **Castillo:** *Pharmacyclics:* Consultancy, Research Funding; *Loxo:* Consultancy, Research Funding; *Cellectar:* Consultancy, Research Funding; *Kite:* Consultancy; *BeiGene:* Consultancy, Research Funding; *AstraZeneca:* Consultancy, Research Funding; *Mustang Bio:* Consultancy; *Abbvie:* Consultancy, Research Funding. **Treon:** *Eli Lilly:* Consultancy, Research Funding; *BeiGene:* Consultancy, Research Funding; *Abbvie/Pharmacyclics:* Consultancy, Research Funding; *Janssen:* Consultancy, Research Funding; *Bristoll Myers Squibb:* Consultancy, Research Funding.

https://doi.org/10.1182/blood-2023-190463

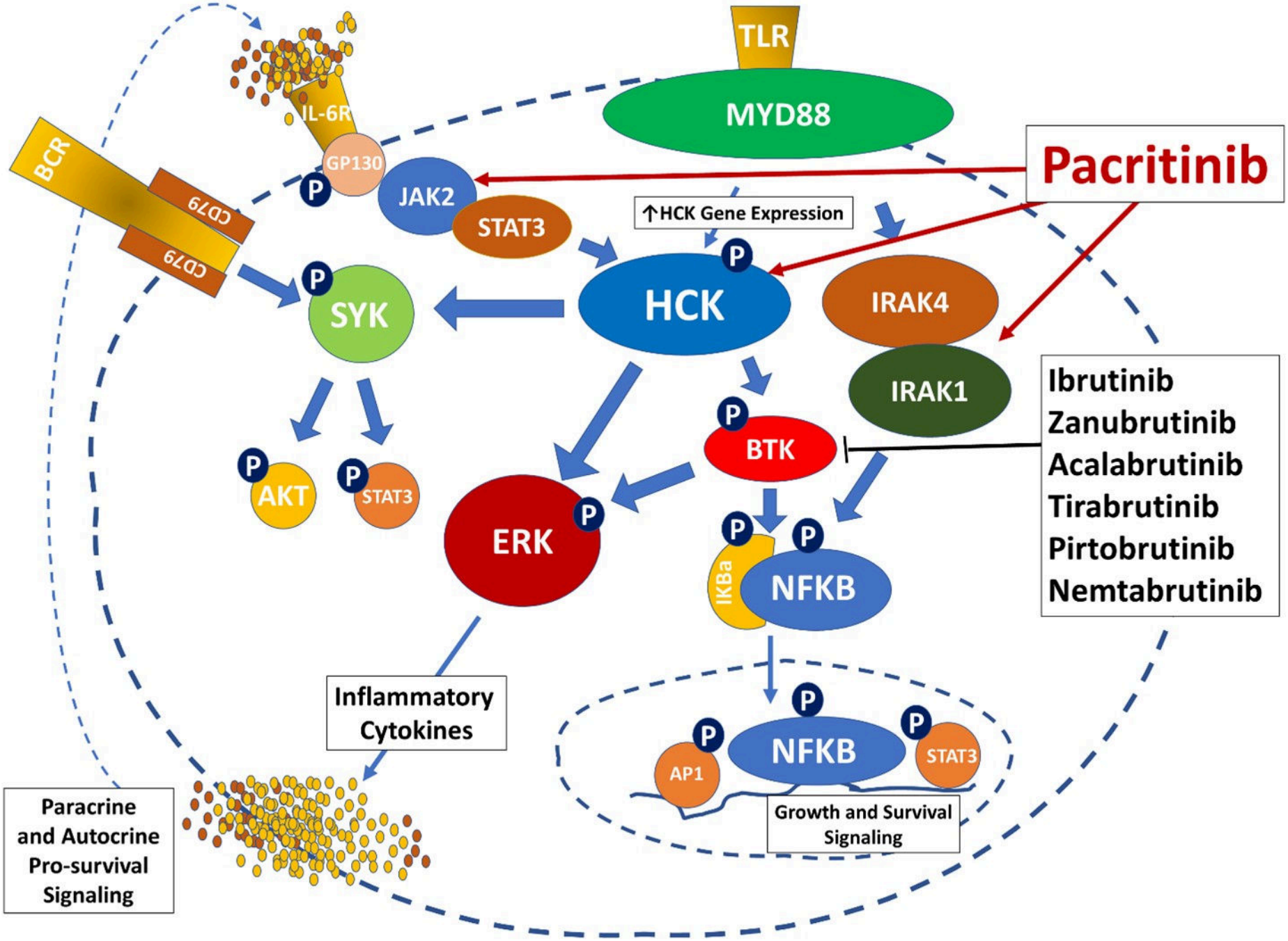

Fig. 1. Pro-survival signaling mediated by mutated MYD88. Targets for therapeutic intervention by pacritinib and BTK-inhibitors are identified.

Figure 1