PHASE 2 STUDY OF THE SYK INHIBITOR MIVAVOTINIB IN RELAPSED/REFRACTORY (R/R) NON-GCB DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) WITH OR WITHOUT MYD88 AND/OR CD79 MUTATIONS

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BACKGROUND

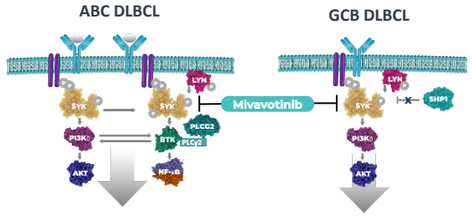
Diffuse Large B-Cell Lymphoma (DLBCL)

- Most common form of lymphoma (~30% of all NHL); 5-year survival rate of ~60%[1-3]
- Classified by cell-of-origin (COO) as germinal center B-cell (GCB; ~40%) or activated B-cell (ABC; ~50%) by gene expression profiling; ABC DLBCL confers poorer outcomes compared to GCB[4]
- High unmet need remains for patients ineligible for, or relapse after, CAR-T or autologous stem cell transplant (ASCT)
- No defined patient selection strategies to optimize therapy for patients with R/R DLBCL
- Unmet need for oral regimen with enriched efficacy in biomarker-defined DLBCL subset

Mivavotinib is an orally dosed, potent, selective Syk inhibitor

- Mivavotinib inhibits Syk, a signaling protein that activates key survival pathways in B-cell lymphomas
- The ABC or non-GCB DLBCL has increased reliance on the BCR pathway and Syk signaling as compared to GCB DLBCL[5]
- Syk activates multiple signaling pathways in ABC DLBCL compared to GCB DLBCL

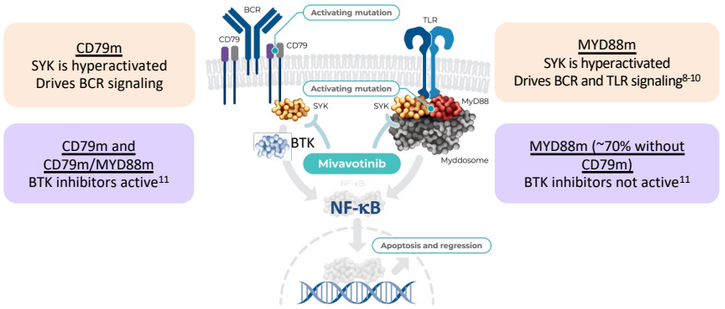
Figure 1. Syk inhibition in ABC or GCB DLBCL



Adapted from Efremov et al. Cancers 2020;12:1396-1434

THE ROLE OF SYK IN MYD88-/CD79-MUTATED DLBCL

Figure 2. Syk Inhibition with Mivavotinib in MYD88-/CD79-mutated DLBCL



- MYD88 and/or CD79 mutations are strongly enriched within ABC subtype and associated with poor outcomes[6,7]
- ABC DLBCL cell lines harboring MYD88/CD79 mutations showed Syk hyperactivation, with Syk driving signaling through both BCR and toll-like-receptor (TLR)-MYD88 pathways to activate NF-κB[8-10]
- Preclinically, mivavotinib showed the strongest anti-tumor activity in MYD88-/CD79-mutated ABC DLBCL cell lines

MIVAVOTINIB: ENRICHED SINGLE AGENT CLINICAL ACTIVITY IN NON-GCB (ABC) DLBCL

Figure 3. Best response by cell-of-origin. 53% ORR in non-GCB vs. 22% GCB

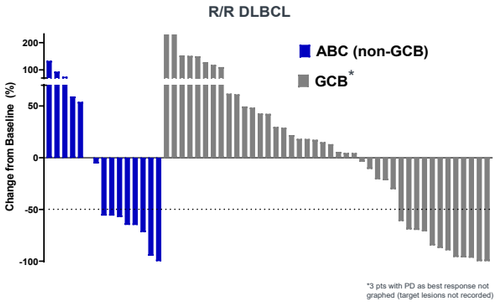
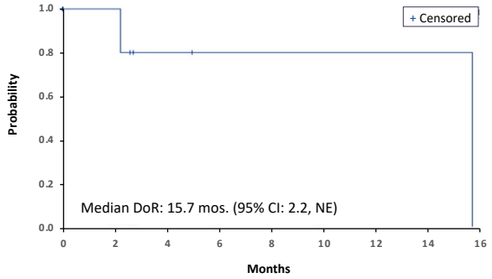


Figure 4. Duration of response in non-GCB responders (n=8)



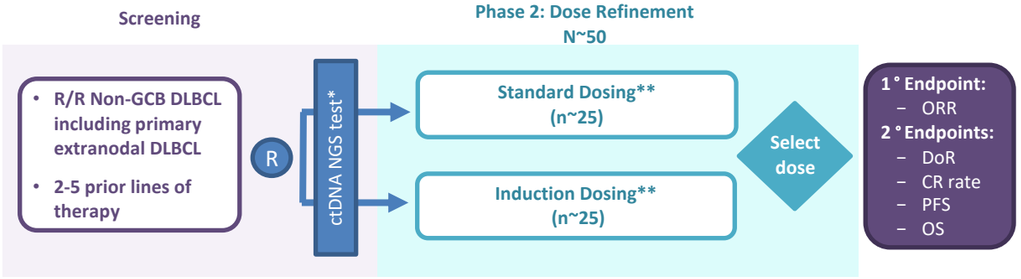
- In a combined analysis of two prior studies of mivavotinib monotherapy in R/R DLBCL, mivavotinib at the RP2D (100 mg once daily [QD]) showed a substantially higher ORR in non-GCB (53%: 8/15) than GCB DLBCL (22%: 10/45) in a heavily pre-treated population, with a favorable safety profile
- Median duration of response (DoR) in non-GCB responders was 15.7 months (95% CI 2.2, NE)
- Previous studies did not systematically evaluate activity according to MYD88/CD79b mutation status

STUDY CX-659-401 (NCT05319028)

OBJECTIVES: To confirm mivavotinib activity in non-GCB DLBCL patients, evaluate activity according to MyD88/CD79B mutational status, and optimize dosing in a biomarker-defined patient population

- DLBCL COO is identified at diagnosis using the standard Hans algorithm or by gene-expression profiling, assessed locally
- ctDNA-based liquid NGS to identify MYD88/CD79b mutations; NGS result not required prior to randomization
- Two dosing regimens of mivavotinib monotherapy will be evaluated

Figure 5. Study Schema



* Expect to enroll 50 patients assuming a mutation frequency of ~50% for MyD88 or CD79b
** Standard dosing: 100 mg QD
** Induction dosing: 120 mg QD x 14 days, then 80 mg QD

KEY ELIGIBILITY CRITERIA

Inclusion Criteria	Exclusion Criteria
• Age ≥ 18 years • ECOG performance status 0-2 • FDG-PET-avid measurable disease per 2014 Lugano criteria • Histologically confirmed de novo or transformed DLBCL that is non-GCB by immunohistochemistry (IHC) per Hans algorithm or ABC by gene expression profiling including primary mediastinal and primary extranodal DLBCL • Relapsed/refractory to ≥2 but no more than 5 prior lines of systemic anticancer therapy • Following standard 1st line R-CHOP (or equivalent), patients must have received 2nd line salvage therapy with or without autologous stem cell transplant (ASCT), and/or CAR-T therapy, unless ineligible for the above.	• DLBCL with primary brain or secondary central nervous system involvement with active disease • History of HIV, active infection with hepatitis B, or hepatitis C • Prior ASCT or CAR-T within 90 days prior to screening • Prior allogeneic stem cell transplantation • Unstable/inadequate cardiac function (myocardial infarction/symptomatic ischemia within 6 months; abnormal 12-lead ECG; congestive heart failure; evidence of current uncontrolled cardiovascular conditions including cardiac arrhythmias, angina, pulmonary hypertension, ECG evidence of acute ischemia or active conduction system abnormalities)

NOTE: Full eligibility criteria provided in protocol

SUMMARY

- High unmet need remains in patients with R/R non-GCB DLBCL
- Mivavotinib showed enriched ORR with durable responses in R/R non-GCB DLBCL in prior studies
- Syk hyperactivation in MYD88-/CD79b-mutated DLBCL suggests potential for further enrichment of single agent activity in this genetically defined subset of non-GCB patients
- Results of this study will inform the optimal dose and provide confirmatory efficacy and safety data of mivavotinib in patients with non-GCB DLBCL, including MYD88-/CD79b-mutated DLBCL to guide further expansion in these biomarker-defined cohorts

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