

Abivertinib – A Franchise Oral Therapeutic for Cancer, COVID-19 and Autoimmune Diseases

EXECUTIVE SUMMARY

Abivertinib – A Broad Pipeline for Cancer, COVID-19 and Autoimmune Diseases (\$61B Market)

Key Abivertinib Programs	Preclinical	Phase I	Phase II	Phase III / Pivotal	FDA Approved	Market Size (\$ B)*
NSCLC						\$13.2
Severe COVID-19 in ICU**						\$4.3
B Cell Lymphomas						\$1.2
Prostate Cancer***						\$9.0
Lupus***						\$4.0
MS***						\$28.6
GvHD***						\$0.3

*Source: IQVIA, GlobalData, and Sorrento Internal Research.

**Waiting for FDA Clearance for Phase 3.

***Pending Phase 2 IND filing.

TOTAL \$60.6

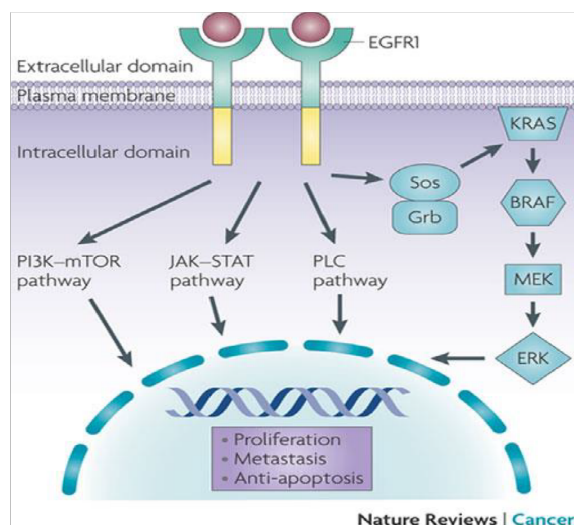
About Abivertinib:

- Abivertinib is a novel dual target, small molecule tyrosine kinase inhibitor (TKI) that selectively targets mutant forms of the epidermal growth factor receptor (EGFR) and Bruton's tyrosine kinase (BTK).
- Abivertinib is a third-generation epidermal growth factor receptor (EGFR) inhibitor that irreversibly targets mutant forms of EGFR in advanced non-small cell lung cancer (NSCLC) patients resistant to first-line EGFR kinase inhibitor therapies.
- Abivertinib also irreversibly binds to the BTK receptor, preventing the phosphorylation of the receptor that occurs during activation. Abivertinib has shown potent immunomodulatory activities *in vitro* with potent inhibition of key pro-inflammatory cytokine production, including IL-1 beta, IL-6 and TNF-alpha. These cytokines are associated with acute respiratory distress syndrome (ARDS) and cytokine release syndrome (CRS) or cytokine storm complicating COVID-19 resulting in disease progression with poor outcomes in patients.

Abivertinib Drug Targets:

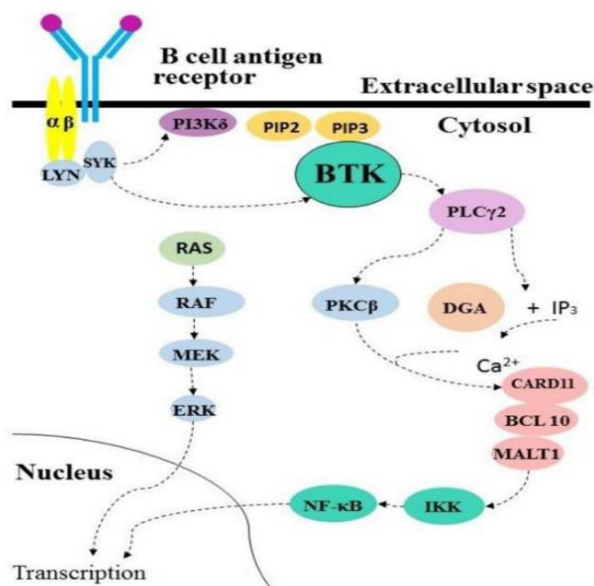
- **Abivertinib Targets Epidermal Growth Factor Receptor (EGFR) Mutations in Cancer Cells**

Figure 1. *EGFR Signaling Transduction Pathway in Regulation of NSCLC Cell Proliferation*



- **Abivertinib Targets Bruton's Tyrosine Kinase (BTK)**

Figure 2. *BTK Signaling Transduction Pathways in Regulation of Malignant B Lymphocyte Proliferation and Cytokine Expression*



Abivertinib - Mode of Actions

- **Abivertinib as EGFR Inhibitor for NSCLC**

Acquired T790M mutation in EGFR is the most common cause of resistance for patients with advanced NSCLC who have progressed after first line EGFR TKIs. The development of the third-generation (3G) EGFR TKIs focused on three key aspects: i) the inhibition of T790M isoform-specific kinase activity, ii) maintaining efficacy against exon 19 and 21 mutations, and iii) sparing the inhibition of wild-type EGFR. Abivertinib, discovered by ACEA Therapeutics (a wholly-owned subsidiary of Sorrento Therapeutics), is a pyrrolopyrimidine-based irreversible 3G EGFR TKI, and is structurally distinct from all other 3G pyrimidine-based EGFR inhibitors.

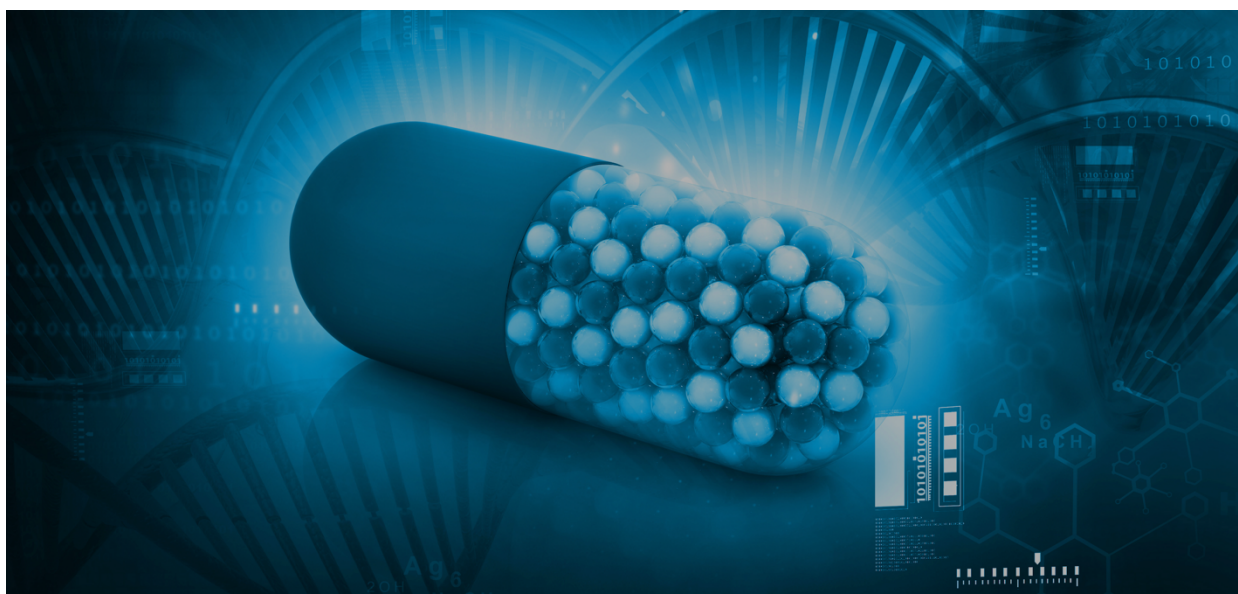
- **Abivertinib as BTK Inhibitor for B-Cell Malignancies**

Bruton's tyrosine kinase (BTK) is a clinically validated target for the treatment of B-cell malignancies, including relapsed or refractory (R/R) B-cell lymphoma, mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL)/small lymphocytic.

Abivertinib is also a potent BTK inhibitor, selectively, and irreversibly inhibiting the phosphorylation of BTK with IC50 value at 1.6 nM and its downstream target proteins at low nM range. Abivertinib occupied BTK targets in human peripheral blood mononuclear cells (PBMCs) with IC50 value at 0.78 nM.

- **Abivertinib as Potent Inhibitor of Cytokines for COVID-19 Associated Cytokine Storm**

BTK is a critical molecule in immune regulation and host inflammatory responses. Abivertinib has shown potent anti-inflammatory and immune modulation activities by inhibiting key pro-inflammatory cytokines including IL-1beta, IL-6 and TNF-alpha. These cytokines are associated with the acute respiratory distress syndrome (ARDS) in the COVID-19 patients.



Abivertinib – Clinical Experience and Preclinical Experiments

• Abivertinib for Cancer Indications

NSCLC (Pivotal Trial) - Among 209 response evaluable NSCLC patients who developed resistance to first line TKIs (Figure 3):

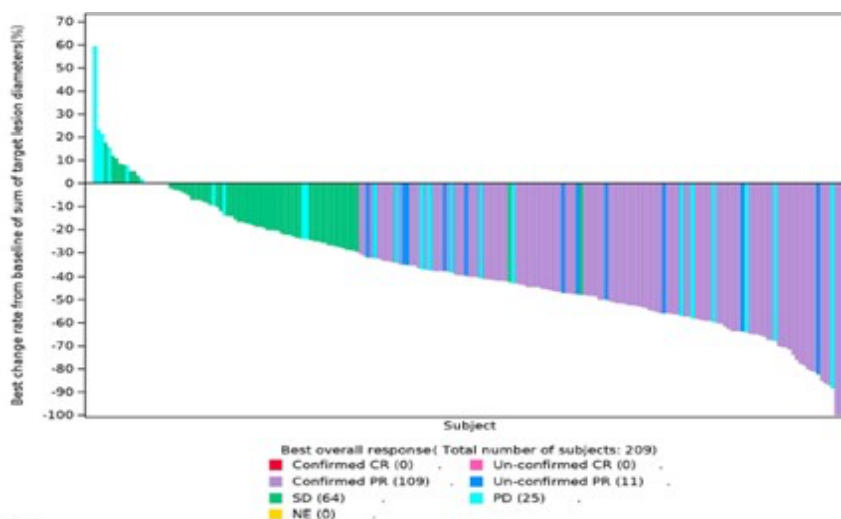
- 93.3 % (n/N: 195/209) subjects achieved tumor shrinkage at target lesions
- 57.4% (n/N: 120/209) subjects achieved the best overall responses (confirmed + unconfirmed PR)
- 52.2% (n/N: 109/209) subjects achieved confirmed PR
- 24.9 months OS

In the pivotal study conducted in China using Abivertinib as a second line treatment of 227 heavily pretreated NSCLC patients with resistant EGFR mutations were enrolled. Among 209 response evaluable patients, confirmed ORR was 52.2%. Disease control rate (DCR) was 88.0%. The median duration of response (DoR) and progression-free survival (PFS) was 8.5 months and 7.5 months, respectively. The median overall survival (OS) was 24.9 months.

The study result of the data as of March 2019 was published online in Clinical Cancer Research at: <https://clincancerres.aacrjournals.org/content/early/2021/11/04/1078-0432.CCR-21-2595>.

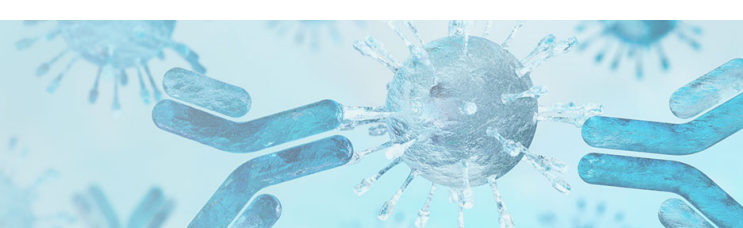
Abivertinib showed similar efficacy compared to Osimertinib, the only FDA-approved third generation EGFR inhibitor, but with a different resistant mechanism it can provide a potential alternative in NSCLC (Xu, X, et al Mol Cancer Ther 15: 2586-2597, 2016; Zhang, YC et al, EBioMedicine 43:180-187, 2019; Zhang, YC et al, Neoplasia 41: 41-51, 2019; Zhang YC et al, Sci. Bull. 64:499-503, 2019).

Figure 3. Waterfall plots for best percentage change in target-lesion size by investigator assessment are shown for evaluable patients in Phase 2.



The color key indicates the response to 300 mg BID of Abivertinib.

Abbreviation: CR, complete response; NE: not evaluable; PD, progressive disease; PR, partial response; SD, stable disease



B-Cell Lymphoma (Phase 1/2 Trial) (as of 08/28/2020)

- o 63.6% ORR (n/N: 14/22)
- o 95.5% DCR (n/N: 21/22)
- o 19.7 Months PFS

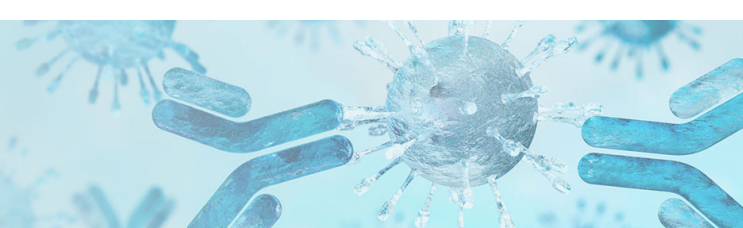
Table 1: Efficacy of Abivertinib for treatment of R/R B-Cell Lymphoma

	CLL n=7	MZL n=5	MCL n=4	LPL n=2	WM n=1	SLL n=1	FL n=1	DLBCL n=1	Total* N=22
ORR, n (%)	4 (57.1)	3 (60.0)	3 (75.0)	1 (50.0)	1 (100)	1 (100)	1 (100)	0	14 (63.6)
DCR, n (%)	7 (100)	5 (100)	4 (100)	2 (100.0)	1 (100)	1 (100)	1 (100)	0	21 (95.5)
PR, n (%)	4 (57.1)	3 (60.0)	3 (75.0)	1 (50.0)	1 (100)	1 (100)	1 (100)	0	14 (63.6)
SD, n (%)	3 (42.9)	2 (40.0)	1 (25.0)	1 (50.0)	0	0	0	0	7 (31.8)
PD, n (%)	0	0	0	0	0	0	0	1 (100)	1 (4.5)

- A Phase 1 study designed to determine the recommended Phase 2 dose (RP2D) of Abivertinib in patients with pre-treated R/R B-cell lymphoma (part 1) and to evaluate the safety and preliminary efficacy in patients with selected disease (part 2) was completed. Abivertinib has been investigated in an open-label phase 1 study with dose optimization (part 1) and dose expansion (part 2) (NCT03060850) in patients with R/R B-cell lymphoma. Twenty-nine patients were enrolled into 4 dose cohorts (200 mg QD, 150 mg BID, 200 mg BID and 300 mg BID). In all dose cohorts, Abivertinib occupied BTK target up to 100% in patient's PBMCs and achieved ORR of 54.2% and DCR of 95.8%. At 200 mg BID, the ORR was 81.8% (9/11) and the DCR was 100%. Abivertinib was shown to be well tolerated across the dosing cohorts. The most common adverse events (AEs) (all grades) regardless of causality were neutropenia (58.6%), thrombocytopenia (44.8%), diarrhea (34.5%), anemia (34.5%) and ALT elevation (34.5%). The most common (>10%) grade 3 or 4 AEs regardless of causality were neutropenia (24.1%), and thrombocytopenia (17.2%). Treatment-related serious adverse events (SAEs) occurred in 27.6% (8/29) of patients, and no death occurred during the treatment period. The SAEs associated with first generation BTK inhibitors such as Ibrutinib, including serious bleeding, atrial fibrillation, bruising, and tumor lysis syndrome, were not reported with Abivertinib treatment. Based on the safety and efficacy data, 150 mg BID was selected as RP2D for B-cell malignancies.
- The Phase 1 results were published in EHA, 2019. The abstract is available at: <https://library.ehaweb.org/eha/2019/24th/266315/min.yang.a.phase.i.study.of.the.btk.inhibitor.abivertinib.28ac001029.in.patients.html?f=listing%3D3%2Abrowseby%3D8%2Asortby%3D1%2Amedia%3D1>
- Abivertinib is effective for the treatment of R/R B-cell lymphoma in multiple disease types including MZL, MCL, CLL and follicular lymphoma (FL). Based on the effective dose cohorts (200mg QD, 150mg BID and 200mg BID) of 22 response evaluable subjects, the ORR was **63.6%**, DCR was **95.5**, and PFS was **19.7 months** (data cut off time: 08/28/2020)

Prostate Cancer (IND for Phase 2 Trial To-Be-Filed)

- Preclinical studies suggest that BTK inhibitors can inhibit prostate cancer (PCa) cell proliferation, migration and invasion and androgen synthesis, particularly from extragonadal precursor steroids. Kokabee and colleagues (Kokabee, L. *et al.*, Cancer Biol Ther. 16(11):1604-15, 2015.) and Zhu and colleagues (Zhu, Z. *et al.*, Onco Targets Ther. 13:4113-4122, 2020.) have shown that BTK expression is elevated in several PCa cell lines and tumors. Inhibition of BTK with BTK-C siRNA demonstrates that alternative BTK protein isoforms (i.e., BTK-C) contribute to PCa cell survival. Kokabee and Zhu found that BTK-C represents more than 50% of the total BTK expression in PCa cells. Ibrutinib and other BTK inhibitors were analyzed in LNCaP (AR+) and DU145 (AR-) prostate cancer cells (Kokabee 2015) and DU145 and PC3 prostate cancer cell lines (Zhu 2020) and showed significant dose-dependent responses with apoptosis of PCa cells. These data indicate that, in addition to its utility in B cell lymphomas, targeting BTK may be a potent therapeutic approach for advanced PCa, particularly castration-resistant metastatic PCa
- Assessment of Abivertinib anti-PCa activity in vitro revealed a dose-dependent sensitivity of metastatic PCa cell lines to Abivertinib: Abivertinib treatment induced apoptotic PCa cell death at low doses for lymph node metastasized PCa cells (LNCaP) while cancer cells isolated from bone marrow and brain PCa metastasis (PC3, DU145) responded at higher doses of Abivertinib (not shown).
- Oral administration of Abivertinib in mice bearing the human PCa tumor showed a dose-dependent anti-tumoral effect in a preclinical xenograft tumor model, using human DU145 cells isolated from advanced PCa brain metastasis.



Abivertinib for COVID-19 (Two Phase 2 trials Completed)

- 100 mg once-a-day oral capsule for hospitalized COVID-19 patients
- US trial (N=96) and Brazil trial (N=400)

For Severe Ordinal Scale (OS) Category 5 COVID-19 Patients (“At-Risk COVID-19 Patients”) identified to be beneficial with Abivertinib treatment at Day 28 (D28):

- **Abivertinib reduced the risk of death or respiratory failure by:**
 - **48% In the US trial:** (death or respiratory failure: 21.7% in the Abivertinib group vs. 41.7% in the placebo plus SoC control group)
 - **45% In the Brazil trial:** (death or respiratory failure: 30.4% Abivertinib vs. 55.6% placebo plus SoC controls)
 - **Abivertinib reduced the ICU stay by:**
 - **2 days in the US trial:** (8.6 days average stay in ICU in Abivertinib group vs. 10.6 days in placebo plus SoC control group)
- Abivertinib has the potential to fill the unmet need for At-Risk COVID-19 Patients and significantly reduce progression to intubation with invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO) and death.
 - Two Phase 2 studies of hospitalized patients with COVID-19-induced respiratory compromise were conducted as placebo-controlled studies in the setting of standard of care (SoC) treatments for COVID-19: US study (N=96) and Brazil study (N=400).
 - Preliminary results from these two Phase 2 studies demonstrated that subjects with milder COVID-19 respiratory compromise at baseline in the full analysis set (FAS) population, those with the 9-point Ordinal Scale (OS) category ≤ 4 (oxygen by mask or nasal prongs), experienced a slight protective effect with Abivertinib. For example, in the 45 subjects in the US study in this category, the Abivertinib group showed approximately a 4% improvement in the primary efficacy endpoint of alive and free of respiratory failure at Day 28 (D28). Whereas in the 33 subjects in OS category ≥ 5 (non-invasive ventilation or high-flow oxygen supplementation at baseline), the Abivertinib group showed a 20% improvement or a 5-fold improvement in response rate in this more at-risk population. Additionally, in the US study, the OS category ≥ 5 subjects in the Abivertinib group had a shorter ICU stay by 2 days (8.6 vs. 10.6 days) compared to the placebo group. The Brazil study data confirmed these results in the at-risk population of OS category 5 at baseline.
 - In summary, the Abivertinib group for the **At-Risk COVID-19 Patients** (OS category 5 or greater) showed a **48% (US)** and **45% (Brazil)** reduced risk of death or respiratory failure at one month (the primary endpoint), respectively. Death or respiratory failure in the US trial was 21.7% in the Abivertinib group vs. 41.7% for the placebo plus SoC control group and in Brazil: 30.4% Abivertinib vs. 55.6% placebo plus SoC controls, respectively. Compared to the lower risk COVID-19 patients (OS category 4 or less), the results with Abivertinib for category 5 patients showed 5-fold higher response rate. The overall safety summary showed that Abivertinib was well tolerated with

most events deemed unrelated. None of the deaths or SAEs were deemed by the investigators to be related to treatment. These safety results were confirmed in the Brazil study.

- Separate Phase 2 clinical trials recently concluded in the US and Brazil for the treatment of acute respiratory distress syndrome (ARDS) associated with SARS-CoV-2 viral infection. While all patient groups improved with treatment, the US study identified **At-Risk Patients** who were the best responders: those who were category 5 in the 9-point OS: those subjects who required oxygen supplementation with non-invasive ventilation or high flow oxygen at baseline. In the US study, At-Risk Patients were discharged on average 2 days sooner from the ICU. In both US and Brazil studies there were about 50% reduced risks of death or mechanical ventilation. Confirmatory results from two parallel studies in US and Brazil demonstrate the likelihood that a Phase 3 pivotal study in the higher risk category may show similar results of avoiding invasive mechanical ventilation, ECMO or death.

Abivertinib for Autoimmune Diseases

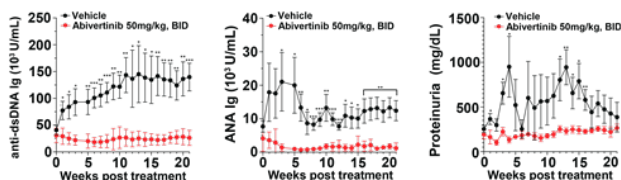
Systemic lupus erythematosus (SLE) (IND for Phase 2 Trial To-Be-Filed):

The therapeutic effect of Abivertinib for the treatment of Systemic lupus erythematosus (SLE) was studied in two mouse models (BXSB and MRL/lpr mice) that spontaneously develop lupus-like disease and recapitulate several pathological features of the human disease.

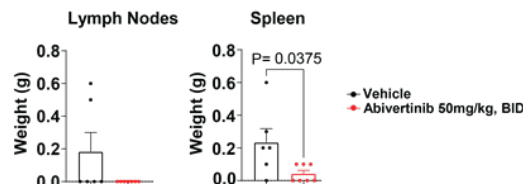
- In the study with BXSB mice, Abivertinib strongly suppressed both serum autoantibodies levels and proteinuria. In addition, Abivertinib also significantly reduced splenomegaly and lymphadenopathy.
- In studies using the MRL/lpr SLE model, Abivertinib also significantly reduced autoantibodies, proteinuria, lymphadenopathy, and splenomegaly.

Figure 4: Abivertinib Reduces Disease Severity in SLE Mouse Models

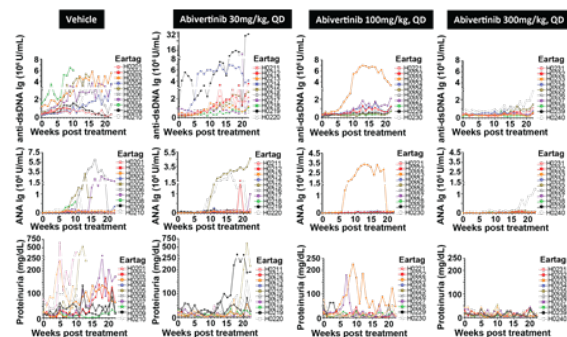
A. BXSB Mice – Autoantibodies and Proteinuria



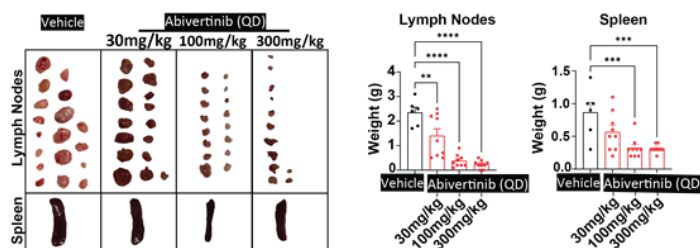
B. BXSB Mice – Splenomegaly and Lymphadenopathy



C. MRL/lpr Mice – Autoantibodies and Proteinuria



D. MRL/lpr Mice – Splenomegaly and Lymphadenopathy

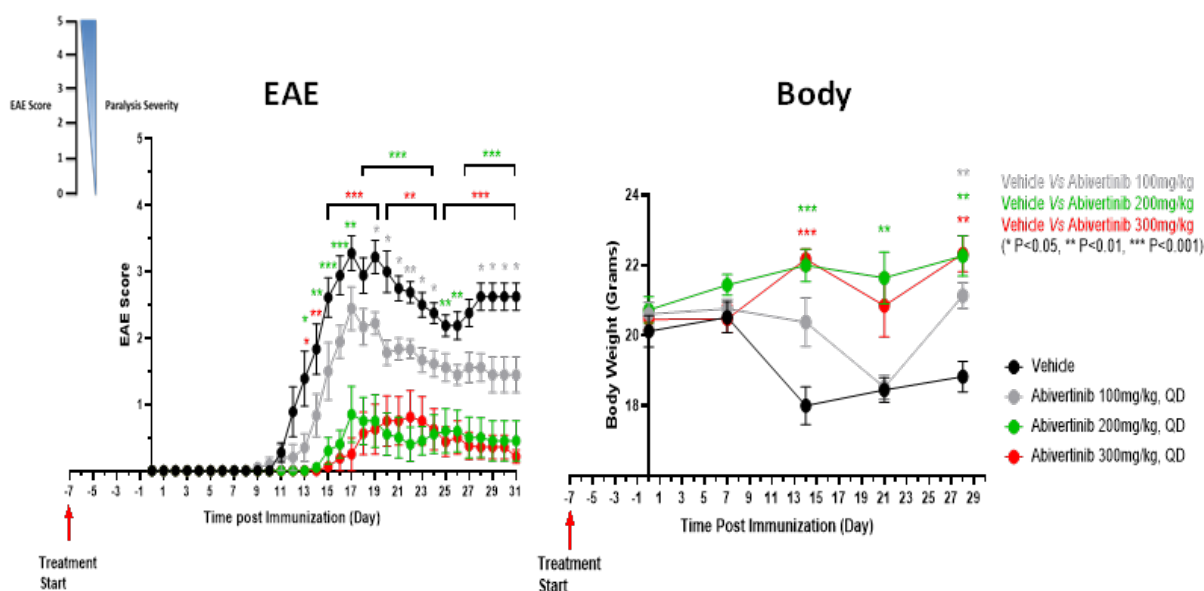


A and B: BXSB mice (n=7) were treated with Abivertinib (50 mg/kg PO, BID) or vehicle. Disease progression was monitored **A**) weekly by serologic analysis for anti-dsDNA and anti-nuclear (ANA) autoantibodies and by proteinuria. **B**) After 21 weeks of treatment, spleen and lymph node weights were examined. Quantifications for all animals are shown as bar graphs. **C and D**) Dose response study of Abivertinib in the lupus prone MRL/lpr strain. MRL/lpr mice (n=10) were treated with Abivertinib (30/100/300 mg/kg, PO, QD) or vehicle for 21 weeks and disease was monitored by **C**) Serum levels of anti-dsDNA and antinuclear (ANA) autoantibodies. **D**) Representative pictures of spleen and lymph nodes and corresponding tissue weights are shown. Data are shown as mean \pm SEM. Statistical analyses include unpaired t test and 1-way ANOVA. Asterisks indicate statistical significance * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001

Multiple Sclerosis (MS) (IND for Phase 2 Trial To-Be-Filed):

In this study, we investigated the immunological effects of Abivertinib using Experimental Autoimmune Encephalitis (EAE) mouse model. The results showed that Abivertinib dose-dependently ameliorated clinical EAE severity and associated body weight loss.

Figure 5. Abivertinib Pretreatment Attenuates Clinical Signs in EAE Mouse Model.



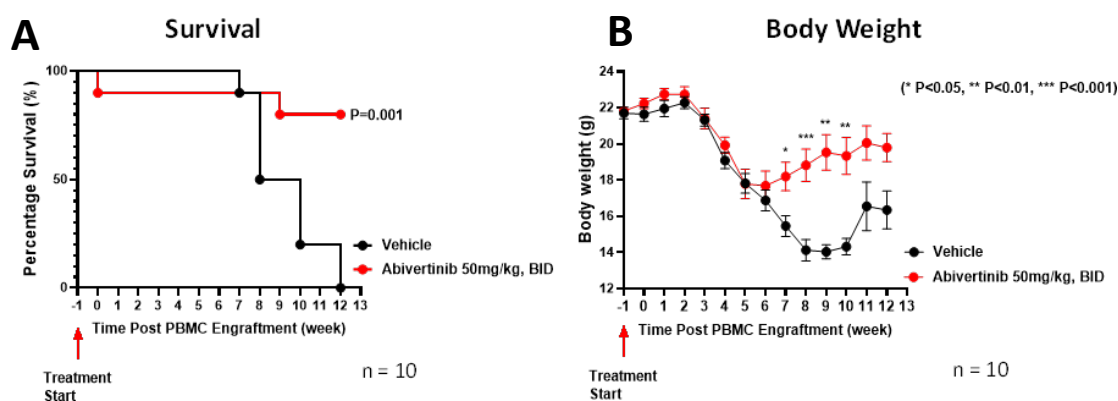
C57BL/6 mice were pretreated with 100mg/kg ($n = 10$), 200mg/kg ($n = 10$), 300mg/kg Abivertinib ($n = 10$) or vehicle control ($n=10$) daily by oral gavage beginning 7 days prior to the MOG immunization. Clinical EAE scores were assessed daily and body weight was measured once per week.

Data represent mean \pm SEM. Grey asterisks indicate statistical significance between vehicle and 100mg/kg Abivertinib treatment; Green asterisks indicate statistical significance between vehicle and 200mg/kg Abivertinib treatment; Red asterisks indicate statistical significance between vehicle and 300mg/kg Abivertinib treatment. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Graft-versus-Host Disease (GvHD) (IND for Phase 2 Trial To-Be-Filed):

We investigated the therapeutic effect of the BTK inhibitor, Abivertinib, against GvHD by using humanized-PBMC-NSG mice, which are widely used as models of human-to-mouse xenogeneic GvHD. Our study has shown that Abivertinib has beneficial effects such as improving the survival rate and preventing weight loss in GvHD mice.

Figure 6. Abivertinib Improves Survival and Reduces Body Weight Loss in Xenograft Mouse Model



Immunodeficient NSG recipients were engrafted with human PBMC at week 0. Groups ($n=10$) were either given daily oral gavage of vehicle, or Abivertinib 50mg/kg (BID) beginning one week prior to the PBMC transplantation and continued for 13 weeks. Mice were monitored for survival (A) and body weight (B). Data represent the mean \pm SEM in (B). Asterisk indicates statistical significance between vehicle treatment and Abivertinib treatment groups: * $P<0.05$, ** $P<0.01$, *** $P<0.001$.