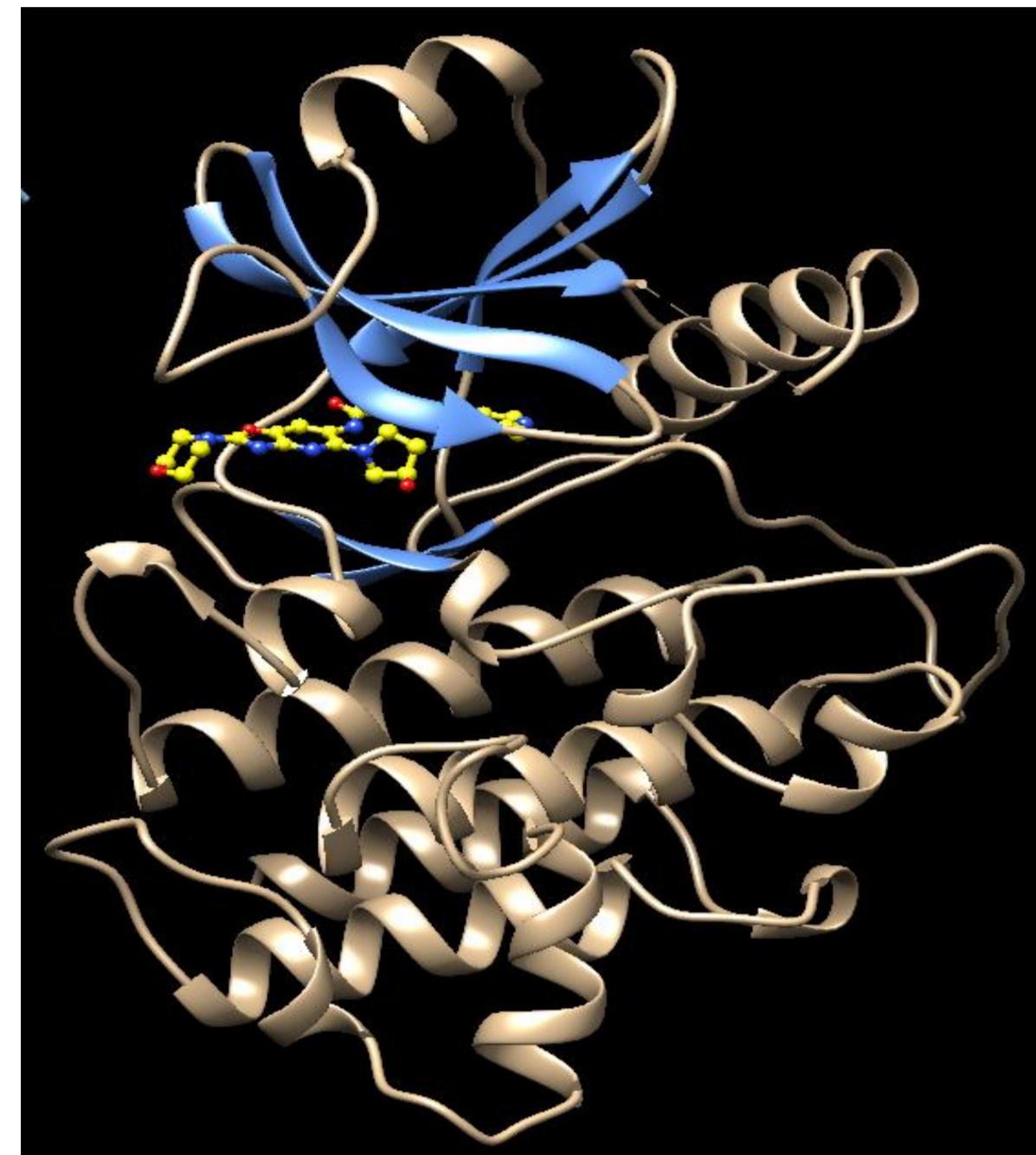


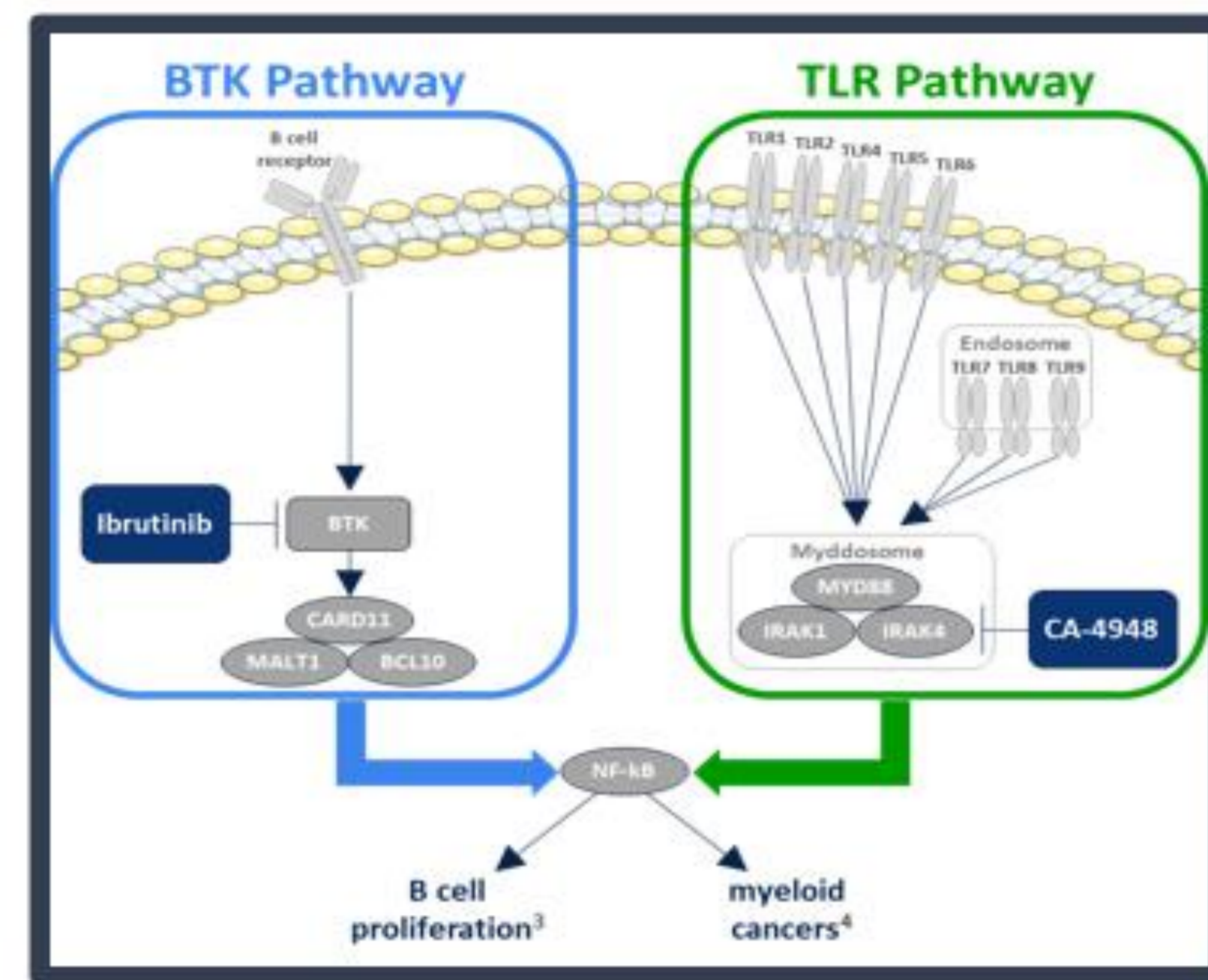
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INTRODUCTION



IRAK4/emavusertib Co-crystal Structure



BCR and TLR Pathways independently drive NF-κB overactivity (IMBRUVICA Package Insert, Rev 08/2018)

- Primary central nervous system lymphoma (PCNSL) is a rare and highly aggressive form of NHL isolated to the central nervous system or vitreoretinal space.
- Despite initial high response rates from first line therapies, the frequent relapse and poor long-term survival remain a significant unmet need.
- Upregulation of the B cell receptor (BCR)/NF-κB and Toll-like receptors (TLR)/NF-κB signaling axis have been identified as key pathways in the pathogenesis of B cell lymphoma and PCNSL.
- MYD88 L265P, a widely expressed somatic mutation in more than 70% of PCNSL patients activates NF-κB signaling through stimulation of BTK and IRAK4.

Emavusertib, a novel oral IRAK4 inhibitor, dosed twice daily has previously demonstrated:

- Single agent activity in R/R NHL patients⁽³⁾
- The ability to overcome tumor resistance to ibrutinib and PI3K inhibitors in preclinical studies⁽⁴⁾
- The ability to cross the blood-brain barrier, reversed IRAK4 pathway activity and caused tumor regression, including cure in a murine PDX model with transplanted A20 NHL to the brain⁽⁵⁾
- In-vivo synergy in B-cell NHL in combination with BTK inhibitors, including ibrutinib, acalabrutinib, and zanubrutinib, potentially enhancing patient sensitivity to BTK inhibitor therapy and promoting re-sensitization to BTKi treatment^(6, 7)
- Responses to BTK experienced patients in the early phase of this study.

STUDY OBJECTIVES

NCT03328078

Primary

- Safety of emavusertib in combination with ibrutinib in patients with PCNSL

Secondary

- To evaluate anti-cancer activity of emavusertib in combination with ibrutinib in patients with PCNSL
- To assess the ability of emavusertib to re-sensitize PCNSL patients who have progress on prior BTKi
- To assess the PK profile of emavusertib in combination with ibrutinib

Exploratory

- To assess the potential association between target-related biomarkers, selected genetic mutations, gene expression signatures, cell of origin, or other molecular classification subtypes and anti-cancer activity

STUDY DESIGN

Part B: Emavusertib in combination with ibrutinib expansion in PCNSL patients (NCT03328078)

Patient Population

- ~20 patients with R/R PCNSL
- Previously received ≤3 lines of prior anti-PCNSL therapy, including a BTKi
- Absence of residual grade ≥2 toxicity from prior therapy

Study Treatment 28-day cycle

- Emavusertib 100-200 mg BID
- + Ibrutinib 560 mg QD

Endpoints

- Primary:**
 - Safety (AEs, ECGs, lab values, vital signs, and physical examinations)
- Secondary:**
 - ORR, DCR, PFS, OS, PK

Primary Endpoint

- Incidence of AEs including serious adverse events (SAEs), ECGs, laboratory values, vital signs, and physical examinations.

Secondary Endpoints

- ORR: proportion of patients achieving CR + unconfirmed complete response (CRu) + PR.
- DCR: proportion of patients achieving CR + CRu + PR + stable disease.
- Progression-free survival (PFS) and Overall survival (OS).
- PK parameters including maximum observed plasma concentration (C_{max}) and area under the concentration curve (AUC) of emavusertib and ibrutinib.

Exploratory Endpoints

- Cell-free DNA sequencing in plasma and cerebrospinal fluid (CSF).
- The mutations in B-cell receptor (BCR) / toll-like receptor (TLR) pathways, eg, MYD88 and CD79B.
- Proteomics analysis in plasma and peripheral blood mononuclear cells.

ELIGIBILITY

Key inclusion criteria:

- Pathologically confirmed diagnosis of PCNSL with evidence of disease progression.
- Measurable disease, relapsed or refractory with no more than 3 lines of prior anti-PCNSL systemic therapies.
- Absence of residual Grade ≥2 toxicity from prior therapy.

Key exclusion criteria:

- Only intraocular PCNSL without brain lesion or CSF involvement
- Prior exposure to investigational agents within 28 days or 5 half-lives before start of treatment.
- History of Grade ≥ 3 rhabdomyolysis without complete recovery, or significant co-morbidity.

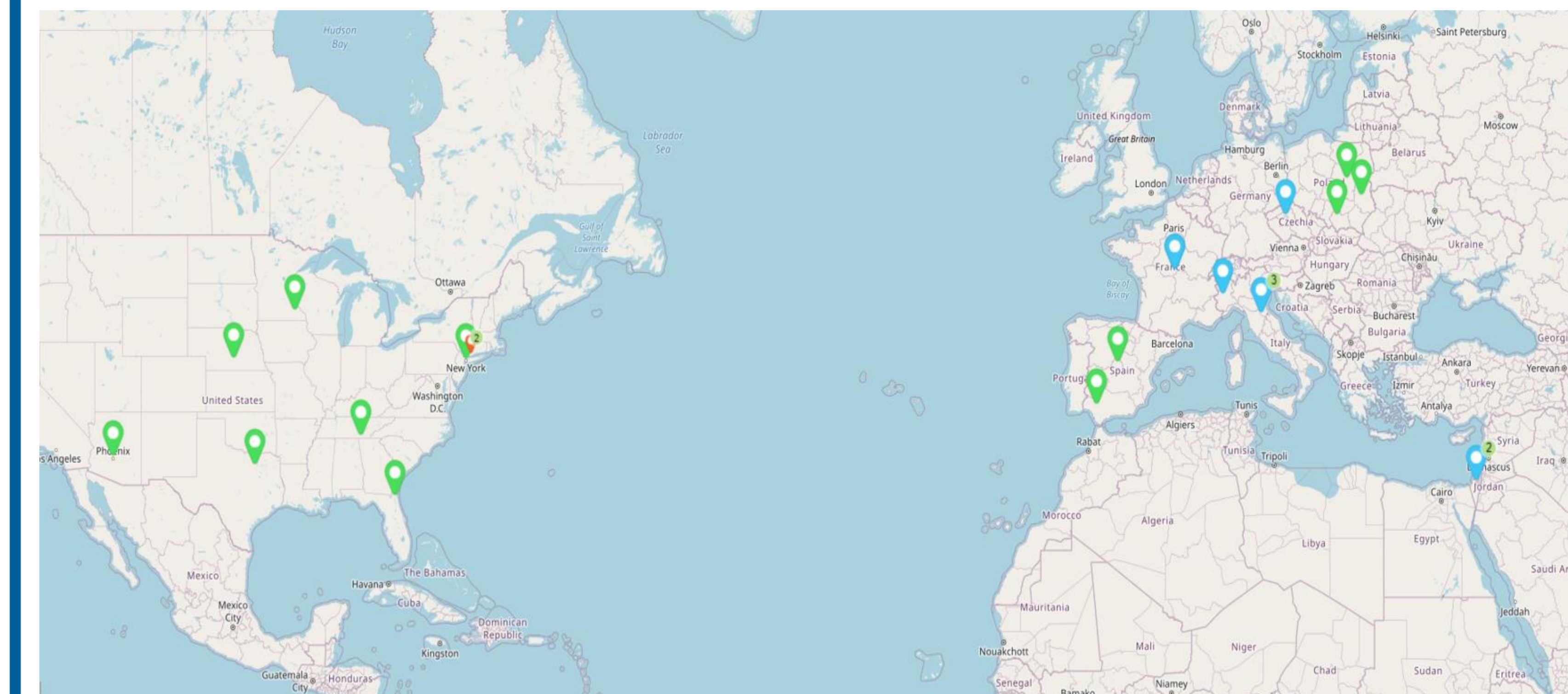
Key clinical assessments

- Brain imaging, CSF cytology and ocular examination.

STATISTICAL METHODS

- For safety, efficacy and PK, data will be summarized using descriptive statistics for continuous variables and using frequencies and percentages for discrete variables.

STUDY PROGRESS



- Enrollment ongoing.
- Current activated sites (green): USA (9 sites), Spain (2 sites) and Poland (3 sites).
- 8 additional sites (blue) planned to be activated in Italy, Israel, Czech Republic and France.

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Abbreviations

Interleukin-1 receptor kinase 4 (IRAK4), Bruton Tyrosine Kinase Inhibitor (BTKi), Relapsed/Refractory (R/R), Non-Hodgkin Lymphomas (NHL), Adverse Event (AE), Disease Control Rate (DCR), Objective Response Rate (ORR), Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Pharmacokinetic (PK), Cerebrospinal fluid (CSF).