An open-label trial of oral CA-4948, an IRAK4 inhibitor combined with ibrutinib in adult patients with relapsed or refractory hematologic malignancies

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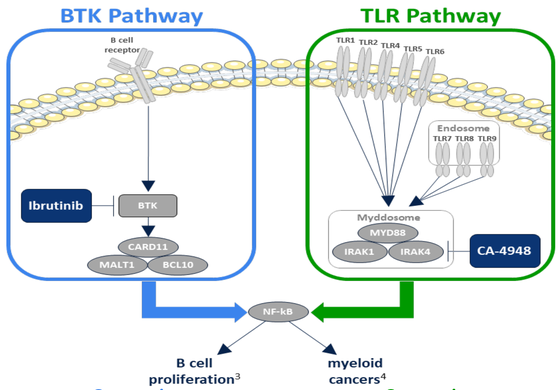
Introduction

Interleukin-1 receptor-associated kinase 4 (IRAK4) is essential for toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling in myeloid and lymphoid cells.IRAK4 forms Myddosome complex with myeloid differentiation primary response 88 (MYD88), driving maximal activation of Nuclear Factor Kappa B (NF-κB) and causing inflammatory and immune responses and tumor promotion.[5,6]



- **Oncogenic**
  Dysregulation drives excessive B Cell proliferation
- **Pathway validate**
  Waldenström's macroglobulinemia[1], MCL, MZL, CLL
- **BTK inhibition effective**
  Ibrutinib is FDA approved

- **Oncogenic**
  Dysregulation drives excessive B cell proliferation[2,3]
- **Dependent upon IRAK4**
  Signaling requires Myddosome, which requires IRAK4
- **Strong Synergy**
  Highly synergistic with BTK inhibition

CA-4948 is a novel small molecule, oral inhibitor of IRAK4. When combined with the Bruton kinase (BTK) inhibitor, ibrutinib, it has shown *in vivo* synergy in B-cell Non-Hodgkin Lymphoma (NHL) models.[7]

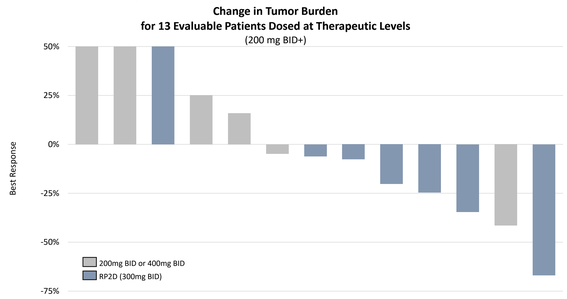
Methods

This is an ongoing trial of CA-4948 monotherapy and in combination with ibrutinib in R/R hematologic malignancies (NCT03328078).

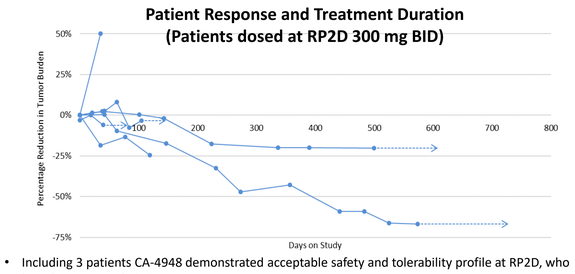
Part A1 is dose escalation monotherapy with a 3 + 3 design in patients with R/R NHL. Primary objectives include safety and tolerability, DLTs, MTD and RP2D. Secondary objectives include PK profile and preliminary anti-cancer activity of CA-4948.

Preliminary results (monotherapy)

CA-4948 was previously reported to be well-tolerated and active as monotherapy in heavily pretreated R/R NHL.



- 300 mg BID is the Recommended Phase 2 Dose (RP2D)

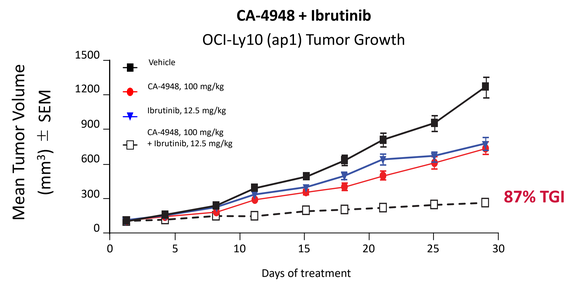


- Including 3 patients CA-4948 demonstrated acceptable safety and tolerability profile at RP2D, who have been on study 1-2 years

Trial in progress

In preclinical studies, CA-4948 when combined with ibrutinib blocks parallel BCR signaling and NF-κB pathway, showing synergy in *in vivo* B-cell NHL models, providing strong rationale for clinical evaluation.[8]

CA-4948 Exhibits Efficacy in DLBCL PDX Models in Combination with Ibrutinib



The safety data and clinical benefits lead to amendment of the current trial into a multi-center, open label trial of oral CA-4948 combination with ibrutinib in adult patients with R/R hematologic malignancies.

Part A2 inclusion

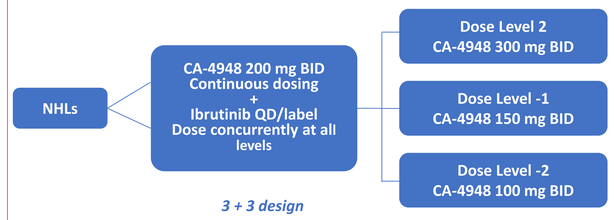
Histopathologically confirmed B-cell NHLs (WHO 2016 classification), including FL, MZL, MCL, DLBCL (including extranodal lymphomas of leg, testicle, or other sites, excluding mediastinal lymphoma), CLL/SLL, primary or secondary CNS lymphoma, and WM/LPL.

Part B inclusion

Cohorts 1-3 include MZL, ABC-DLBCL, or PCNSL who are BTK-inhibitor naïve. Cohort 4 includes ibrutinib pre-treated MCL, MZL, CLL/SLL, WM/LPL, ABC-DLBCL, or PCNSL with adaptive resistance.

Exclusions for both Parts A2 and B:

Significant acute or chronic toxicity from prior anti-cancer therapy that has not resolved to Grade ≤ 1, as determined by NCI CTCAE v4.03 within 7 days prior to start of study or serious co-morbidities.



Part A2 (Combination dose escalation phase)

Primary objectives: To determine the safety and tolerability, DLTs, MTD, and RP2D of oral CA-4948 in combination with ibrutinib

Secondary objectives: PK and preliminary efficacy

Exploratory objectives: Correlation with MYD88-L265P mutation status

Part B (Basket design of 4 expansion cohorts with a Simon 2-Stage approach)

Primary objectives: Efficacy; CR, ORR and DOR

Secondary objectives: Safety and tolerance, PFS, and population-PK

Exploratory objective: biomarkers correlations

Conclusions

CA-4948 showed preclinical synergistic activity in combination with ibrutinib. Clinical safety, tolerance, and preliminary efficacy in selected NHL cohorts are being studied in **Part A2** and **Part B**. This combination study is now enrolling.

References

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