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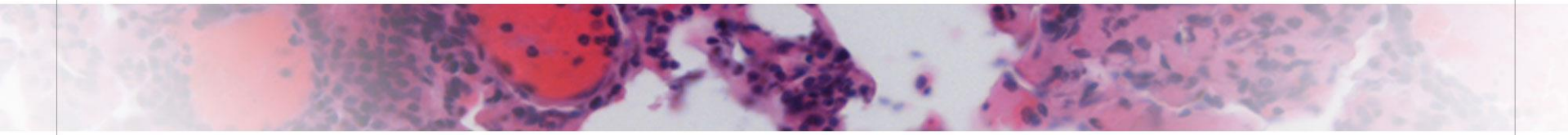

2945: A Multi-Center, Dose-Finding Study to Assess Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of a novel IRAK4 inhibitor CA-4948 in combination with ibrutinib, in Patients with Relapsed or Refractory Hematologic Malignancies

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Abstract

IRAK4 kinase activity is required for toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling in a variety of myeloid and lymphoid cell types. Recruitment of IRAK4 to these receptors and its subsequent activation is facilitated by the MYD88 adaptor protein, which is mutated in ~22% of diffuse large B-cell lymphoma (DLBCL) cases. The *MYD88*-L265P activating mutation is found in ~30% of the activated B-cell (ABC) and ~6% of germinal center B-cell (GCB) subtypes of DLBCL and leads to constitutive activation of NF-κB signaling that is associated with worse prognosis. In Waldenstrom macroglobulinemia (WM), the *MYD88*-L265P activating mutation is present in >90% of cases. Thus, the development of small molecule inhibitors targeting IRAK4 is an attractive anticancer strategy for *MYD88* mutation-containing cancers such as DLBCL and WM.

Background

- CA-4948 is a first-in-class small molecule inhibitor of IRAK4 kinase that modulates the TLR and IL-1R signaling cascades. CA-4948 has been developed as a novel agent for the treatment of hematologic cancers with dysregulated IRAK4 signaling and is currently in a Ph1 trial for R/R NHL (clinicaltrials.gov NCT03328078). Recent preclinical studies demonstrated the role of IRAK4 activation as a driver of secondary, adaptive tumor resistance and survival mechanisms of hematological and solid tumor malignancies [1] that could be blocked by CA-4948 to delay or reverse resistance.

- In preclinical studies, CA-4948 when combined with the BTK inhibitor ibrutinib demonstrated activity that blocks parallel BCR signaling and NF-kB activating pathway, showing synergy in in-vivo B-cell NHL models, providing strong rationale for clinical evaluation [2]. Based on the safety data and clinical benefits seen in the current R/R NHL study, leads to amendment of the current trial into an open label trial of oral CA-4948 combination with ibrutinib in adult patients with R/R malignancies.

1) Melgar, K. et al., 2019. Sci Transl Med, 11: eaaw8828
2) Booher, RN et al., 2018. Blood, 132 (Supplement 1): 4168

Interleukin-1 Receptor-Associated Kinase-4 (IRAK4)

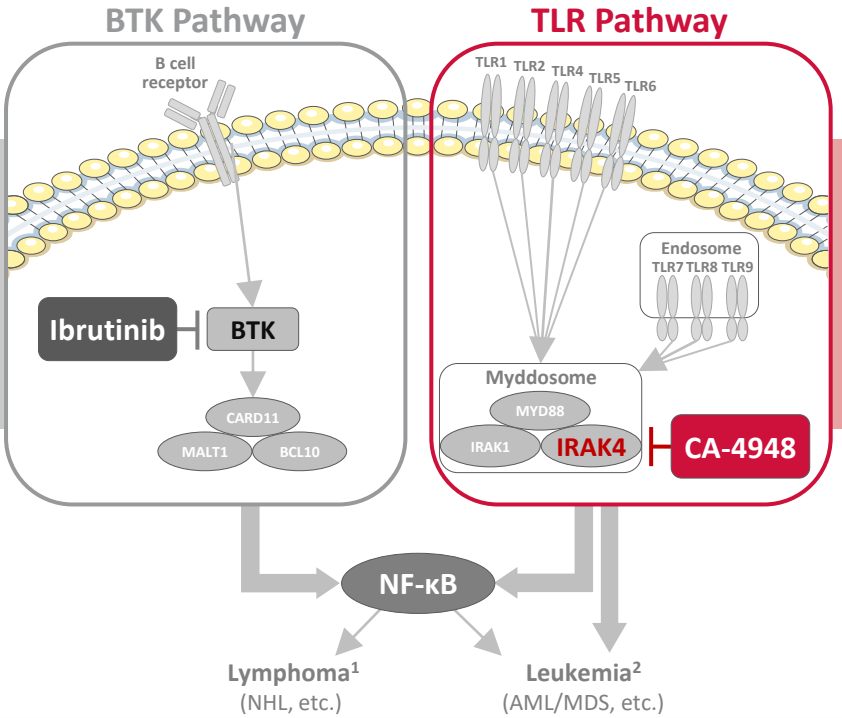
A novel target for addressing cancer through the TLR Pathway

BTK and TLR are parallel pathways that drive oncogenic activity as primary independent activators of NF-κB

BTK Pathway is Oncogenic
- Dysregulation drives excessive B Cell proliferation

Pathway is dependent upon BTK
- Signaling requires BTK

BTK inhibition is effective
- Ibrutinib is FDA approved[1]



TLR Pathway is Oncogenic
- Dysregulation drives excessive B cell proliferation[2,3]

Pathway is dependent upon IRAK4
- Signaling requires myddosome, which requires IRAK4

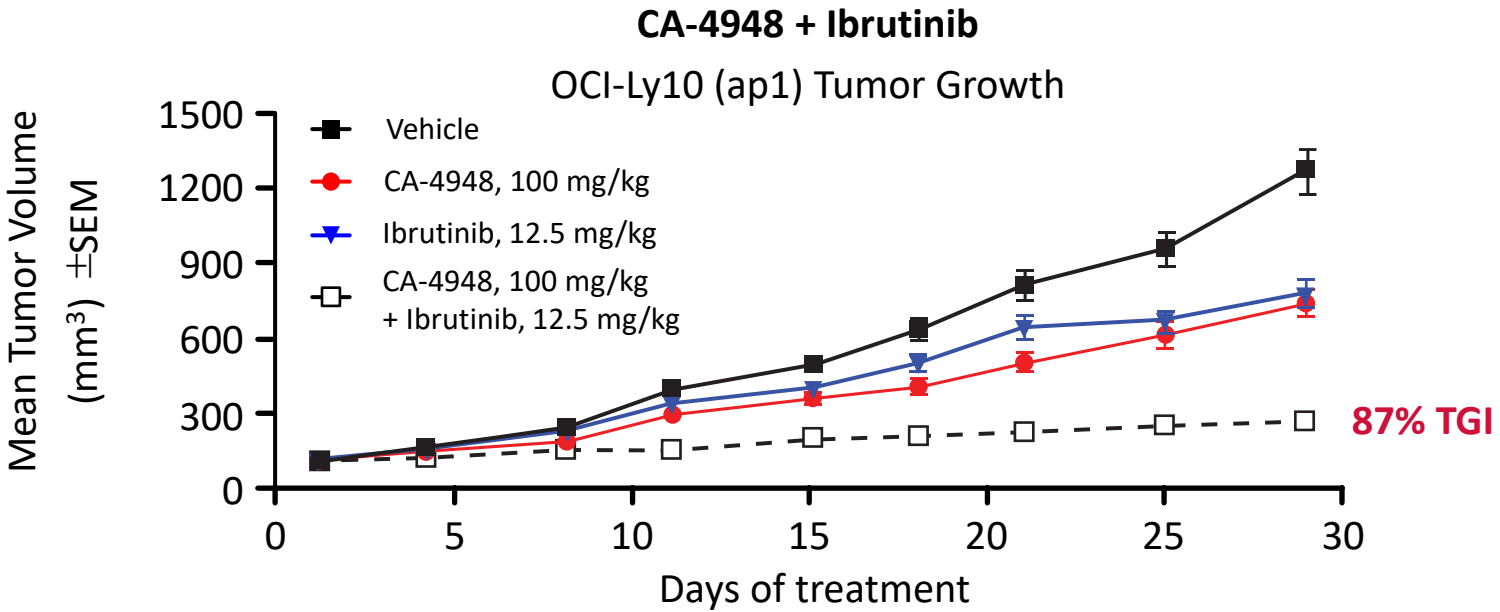
IRAK4 inhibition is effective
- Preliminary clinical data indicate efficacy

In November 2020, the NCI initiated a CRADA to conduct clinical and non-clinical studies of CA-4948 in its role as an anti-cancer agent that works via suppression of the TLR Pathway

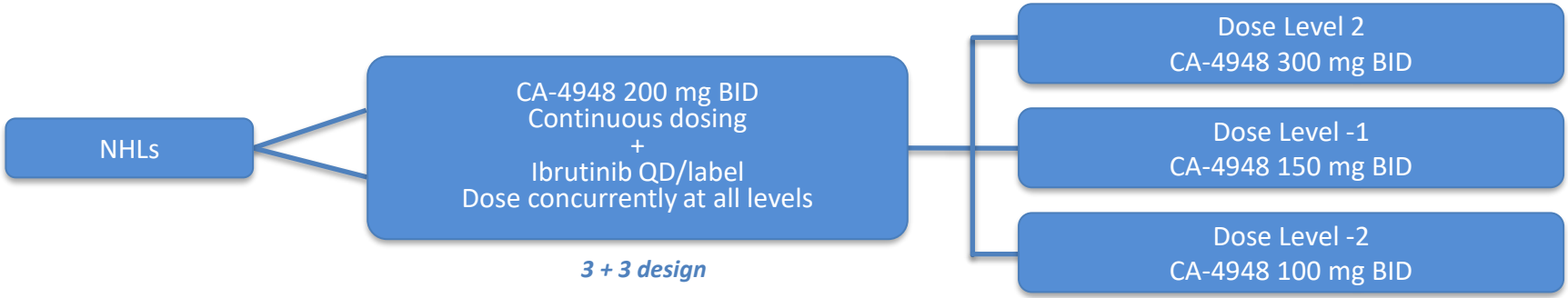
1) IMBRUVICA Package Insert. Rev 08/2018
2) Ngo et al. Nature. 2011 Feb 3;470(7332):115-9
3) Küppers et al. J Exp Med. 2015. 212(13): 2184
4) Smith et al. Nat Cell Biol 2019

In-Vivo Activity

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



Study Design and Methods



This is a multicenter, open-label trial of oral CA-4948 combined with ibrutinib in adult patients with relapsed or refractory hematologic malignancies. (NCT03328078). It has 2 parts: a dose escalation (Part A2), and an expansion basket of 4 cohorts (Part B).

Part A2 (Combination Dose Escalation Phase)

Is a truncated 3+3 design: CA-4948 dose starting is 200 mg BID with subsequent escalation to 300 mg BID. Both doses are safe and active against NHL as seen in the nearly completed monotherapy Part A1 of this trial. Patients will receive CA-4948 with ibrutinib at the labeled dose for the respective NHL subtype (560 mg or 420 mg) until toxicity or progression.

Part A2 Objectives

Primary objectives:

- To determine the safety and tolerability, dose limiting toxicity (DLTs), maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of oral CA-4948 in combination with ibrutinib

Secondary objectives:

- To assess ORR, duration of response (DOR) following treatment with CA-4948 in combination with ibrutinib
- To assess DCR and PFS following treatment with CA-4948 in combination with ibrutinib

Exploratory objectives:

- 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
  - MYD88 mutation status (L265P) will be determined
  - NF-κB activation will be assessed
  - Other potential predictive and PD biomarkers will be assessed
  - DLBCL subtype (cell-of-origin) will be evaluated

Part B Objectives

Dose Expansion Phase

Primary objectives:

- To assess CR rate or ORR of CA-4948 in combination with ibrutinib

Secondary objectives:

- To assess DOR, DCR, PFS and OS following treatment with CA-4948 in combination with ibrutinib
- To assess the safety and tolerability of CA-4948 in combination with ibrutinib
- To assess the population kinetics and estimated blood-brain barrier penetration in CNS lymphoma patients

Exploratory objectives:

- To assess the pharmacodynamic effects of CA-4948 in combination with ibrutinib on selected biomarkers in tumor tissue
- 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

Inclusion and Exclusion Criteria

Part A2 inclusion

Histopathologically confirmed B-cell NHL as per the WHO 2016 classification.

- Eligible NHL subtypes:
  - 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.
  - Patients with FL, MCL, MZL, WM/LPL, or CLL/SLL should meet clinical treatment criteria.

Part B Inclusion

- Cohorts 1-3 includes:
  - 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:

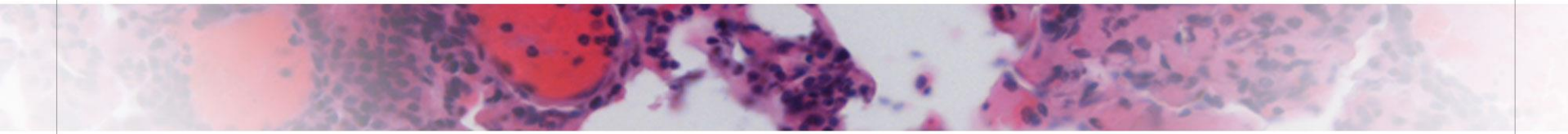
Significant acute or chronic toxicity from prior anti-cancer therapy that has not resolved to Grade ≤ 1, as determined by NCI CTCAE v 4.03 within 7 days prior to start of study or serious co-morbidities.

Sample Sizes and Statistical Considerations

- Approx. 18 patients in Part A2
- In Part B, a Simon 2-Step design will be applied to each cohort.
  - Early stopping rule for futility after approx. 20 patients in Stage 1
  - Full accrual with Stage 2 will add about 25 patients.
- Successful signal efficacy identification in a cohort may support further expansion or a subsequent controlled trial
- Safety population will include all patients in the study who received any test dose
- Efficacy population will have a valid baseline and post-baseline disease assessment
- Safety assessments:
  - TEAEs, safety labs, vitals, physical exams, PK, and ECGs
- Efficacy assessments:
  - Tumor imaging, para-protein determination, and histo/cyto-morphologic examinations

Summary

- Preclinical rationale as well as clinical safety and tolerance profile of CA-4948 support testing as **combination** therapy **with ibrutinib** in a two-part trial:
  - Part A2 - a truncated 3 by 3 dose escalation design of CA-4948 with full ibrutinib doses to establish safety and tolerance of the combination, and
  - Part B - a basket trial of 4 expansion cohorts for subsequent efficacy signal detection:
    - Cohorts 1-3 test the activity of the combination and BTK-inhibitor naïve NHL sub-populations, and cohort 4 examines the potential reversal of adaptive resistance to ibrutinib by adding CA-4948
- Now enrolling at selected US Cancer Centers, visit *clinicaltrials.gov* (NCT03328078).



Thank you

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