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POSTER ABSTRACTS

627.AGGRESSIVE LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Takeaim Lymphoma: An Open-Label, Dose Escalation and Expansion Trial of Emavusertib (CA-4948) in Combination with Ibrutinib in Patients with Relapsed or Refractory Hematologic Malignancies

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Background: Emavusertib (CA-4948) is a novel oral inhibitor of interleukin-1 receptor-associated kinase 4 (IRAK4), which is essential for toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling in B cell proliferation. Additional inhibitory activity against FMS-like tyrosine kinase 3 (FLT3) and CDC-like kinases (CLK1/2/4) is also present in emavusertib. IRAK4 forms a Myddosome complex with MYD88 adaptor protein and drives overactivation ofnuclear factor-kappa B (NF-κB), causing inflammation and tumor growth. Emavusertib has been reported to be well tolerated and active as monotherapy in heavily pretreated patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) (Nowakowski 2020). Preclinical studies demonstrated that tumor resistance and survival via IRAK4 activation could be delayed or reversed. Emavusertib crossed the blood-brain barrier in a murine PDX model of PCNS lymphoma, blocked the activated IRAK4 pathway, and induced tumor response and prolonged survival (von Roemeling 2022). In combination with Bruton tyrosine kinase (BTK) inhibitors, emavusertib showed *in vitro* synergy and re-sensitization of resistant cell lines, overcoming BTK resistance (Guidetti 2023a and 2023b). *In vivo* synergy in B-cell NHL was also demonstrated. Adaptive chemotherapy treatment resistance through IRAK4 upregulation and activation was also described in other disease models (Melgar 2019, Li 2019). This abstract presents preliminary efficacy and safety data of emavusertib + ibrutinib in R/R NHL patients.
Aim: Assessment of safety and clinical activity of emavusertib in combination with ibrutinib.
Methods: This is an ongoing open-label trial (NCT03328078) of emavusertib as monotherapy and in combination with ibrutinib. Part A1 - completed; dose escalation of emavusertib as monotherapy; the recommended phase 2 dose (RP2D) is 300 mg BID with continuous oral dosing (Nowakowski 2020). Part A2 - completed; dose escalation of emavusertib in combination with ibrutinib at 420 and 560 mg QD (Joffe 2022). Part B - ongoing; an expansion cohort of PCNSL patients with resistance to prior BTK inhibitors for additional safety and efficacy related to exposure: emavusertib at 100 or 200 mg BID + ibrutinib at 560 mg QD in 28-Day cycles.
Results: As of 19 July 2023, 18 heavily pretreated NHL (including five PCNSL) patients received emavusertib at 100, 200, or 300 mg BID in combination with full ibrutinib doses per label. Median age was 63.5 years (range 50-92). Median number of prior lines of anti-cancer therapies was 3 (range 1-10). Eleven of 18 patients failed prior BTK inhibitors. Median treatment duration was 95.5 days (21-587 days), suggesting acceptable safety and tolerability. No DLTs were observed at the 200 mg BID dose level, and two reversible DLTs (stomatitis and syncope) were observed at the 300 mg BID dose level. The preliminary efficacy data of 16 evaluable patients in combination with ibrutinib showed 5 CRs (2 MCL, 3 PCNSL) and 1 PR (1 CLL). All 3 PCNSL patients with CR were previously treated with BTK inhibitors.
Conclusion: The combination ofemavusertib plus ibrutinib (ema+ibr) is well tolerated with an acceptable long-term safety profile and promising efficacy, showing several objective responses in heavily pretreated and/or BTK inhibitor resistant pa-

tients. Emavusertib may have the potential to overcome BTK inhibitor resistance and the combination of ema+ibr has the potential to show increased anti-cancer activity compared to ibrutinib monotherapy.

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