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P1121 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

Topic: 18. Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

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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. IRAK4 forms a Myddosome complex with MYD88 adaptor protein and drives overactivation of **nuclear 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). 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, resulting in tumor response and prolonged survival. In combination with Bruton tyrosine kinase (BTK) inhibitors, emavusertib showed *in vivo* synergy in B-cell NHL. Here we present an update on the preliminary efficacy data of emavusertib + ibrutinib in R/R hematologic malignancies.

Aims: Assessment of safety and clinical activity of emavusertib in combination with ibrutinib at full prescribed dose.

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. ***Part A2*** (dose escalation in combination with ibrutinib), and ***Part B*** (a basket design of 4 expansion cohorts of emavusertib and ibrutinib: BTK-naïve MZL, DLBCL, or PCNSL and NHL with adaptive resistance to ibrutinib). The primary endpoints of ***Parts A1*** and ***A2*** include safety, tolerability, and RP2D. The primary endpoints of ***Part B*** include CR or ORR, with key secondary endpoints of DOR, DCR, PFS and OS following treatment of emavusertib at dose levels of 200 (DL1) or 300 mg BID (DL2) with ibrutinib at full prescribed dose.

Results:

As of December 7th, 2021, 35 heavily pretreated NHL patients have received emavusertib monotherapy (median age 66 years, range 50-87), of which six patients have been on emavusertib for approximately 1 year or longer, suggesting emavusertib has a long-term acceptable safety and tolerability profile at RP2D (dose level of 300 mg BID). In ***Part A2***, 10 patients are treated with emavusertib + ibrutinib (median age 65 years, range 56-82). Median number of prior lines of anti-cancer therapies is 3 (range 1-8). No DLTs were observed at 200 or 300 mg dose levels to date. The preliminary efficacy data of seven evaluable patients with combination therapy showed 1 CR (MCL), 2 PR (MCL and MZL), 3 SD, and 1 PD, 3 of whom had failed prior ibrutinib. The preliminary data indicate the combination therapy may overcome ibrutinib resistance.

Summary/Conclusion: Emavusertib as a monotherapy and in combination with ibrutinib is well tolerated with an acceptable long term safety profile and promising efficacy. ***Part A2*** is transitioning to ***Part B*** basket cohorts of MZL,

ABC-DLBCL, PCNSL and NHL with adaptive resistance to ibrutinib.