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616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

A Phase 1a/b Trial of Luxeptinib (CG-806) in Patients with Relapsed/Refractory B-Cell Malignancies or Acute Myeloid Leukemia and Evaluation of New G3 Formulation

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INTRODUCTION: Luxeptinib (CG-806; LUX) is an orally active noncovalent kinase inhibitor of Bruton's tyrosine kinase (BTK), wild type and mutant forms of Fms-like tyrosine kinase 3 (FLT3) (including the internal tandem duplicates (ITD), tyrosine kinase domain (TKD), and F691L mutant forms), and growth receptors like KIT, CSF1R, PDGFRα, and TRKs. In prior studies, LUX has been shown to suppress aberrant proliferative signaling in B cell malignancies and acute myeloid leukemia (AML) via regulation of BTK, LYN, SYK, AKT, ERK, and MAPK. LUX is cytotoxic to primary AML cells insensitive to other FLT3 inhibitors and to malignant B-cells insensitive to ibrutinib, at pM and nM concentrations, respectively.
AIMS: The primary objectives of these studies are to assess the safety, tolerability, and pharmacokinetics (PK) of LUX and determine recommended phase 2 doses for relapsed or refractory (R/R) AML and B cell malignancy patients.
METHODS: In two studies (NCT04477291; NCT03893682), LUX (original formulation, G1) was administered continuously as oral capsules BID in 28-day cycles of ascending cohorts (relapsed or refractory *de novo*, secondary, or therapy-related AML or

higher risk myelodysplastic syndrome (MDS), and relapsed and refractory for B cell lymphoma and chronic lymphocytic/small lymphocytic leukemia). A novel generation 3 (G3) formulation of LUX designed to increase bioavailability was tested at a single-dose (sub-study) for relative bioavailability (RBA), followed by continuous dosing in subsequent R/R AML patients.

RESULTS: In the B-cell study (as of 15 th May 2023), LUX has been administered to 36 patients at dose levels from 150 mg to 900 mg BID in patients with a median of 3 lines of prior treatment, with 47.2% having received a BTK-inhibitor. Only one (2.8%) patient had a DLT of hypertension and 14 (38.9%) experienced at least one drug related ≥Grade3 treatment emergent adverse event (TEAE). Two patients (900 mg) are currently on study with no DLT and no ≥Grade 3 related TEAEs. A Follicular lymphoma patient is at cycle 28, and achieved a best response as partial response (PR) with a decrease in lesion size of 76.2%; an SLL patient is at cycle 13, and achieved stable disease (SD) showing a decrease in lesion size of 43.1% (Figure A). The overall best response achieved among the 17 patients who have been on treatment for more than 12 weeks are stable disease (SD) (n=11), partial response (PR) (n=3), minor response (n=2) and complete response (CR) (n=1).

As of 5 th June 2023, in the AML trial, a total of 40 patients (16 (40%) FLT3-ITD, 21 (52.5%) FLT3-WT, 2 (5.0%) FLT3-TKD, and 1 (2.5%) unknown mutations) with a median of 3 prior treatments (range, 1 - 10) have been treated with LUX G1 formulation at dose levels from 450 mg - 900 mg BID (n=34) or with 50 mg BID of G3 formulation (n=6). Four (10%) experienced drug related SAE and 7 (17.5%) had a drug related grade ≥3 TEAEs. The most common related TEAEs were lymphocyte count decrease, platelet count decrease, and anemia (n=2; 5% patients each). One (2.5%) patient at 450 mg dose, reported complete remission without minimum residual disease (CRmrd) and remained on study for 56 weeks.

In the RBA sub-study, G3 (50 mg) produced comparable exposures to G1 (450-900 mg range) (Figure B) and was, therefore, selected as the starting dose for use in the R/R AML study. Six patients were treated with a continuous dosing of 50 mg BID G3; with plasma levels of 274 ng/mL and 195 ng/mL LUX observed by the end of C1D15 and C1D22 respectively. No drug related Grade ≥3 TEAEs or DLTs were observed in 50 mg BID G3 LUX treated patients; with no new safety signals observed for the G3 formulation. Based on these findings and expected exposures for higher dose levels, the cohort safety review committee has approved escalation of G3 dosing to 200 mg BID at which dosing is ongoing.

CONCLUSIONS: LUX has a favorable safety profile in patients at all tested dose levels, for multiple cycles, for both studies. Antitumor activity was observed in a heavily pretreated relapsed AML patient and in multiple B-NHL subtypes and CLL/SLL patients including several with prior ibrutinib exposure. Continuous dosing of patients with R/R AML and Higher-Risk MDS with the G3 formulation is ongoing; with updated clinical data (200 mg dose level) to be presented at the meeting.

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Figure: A-B

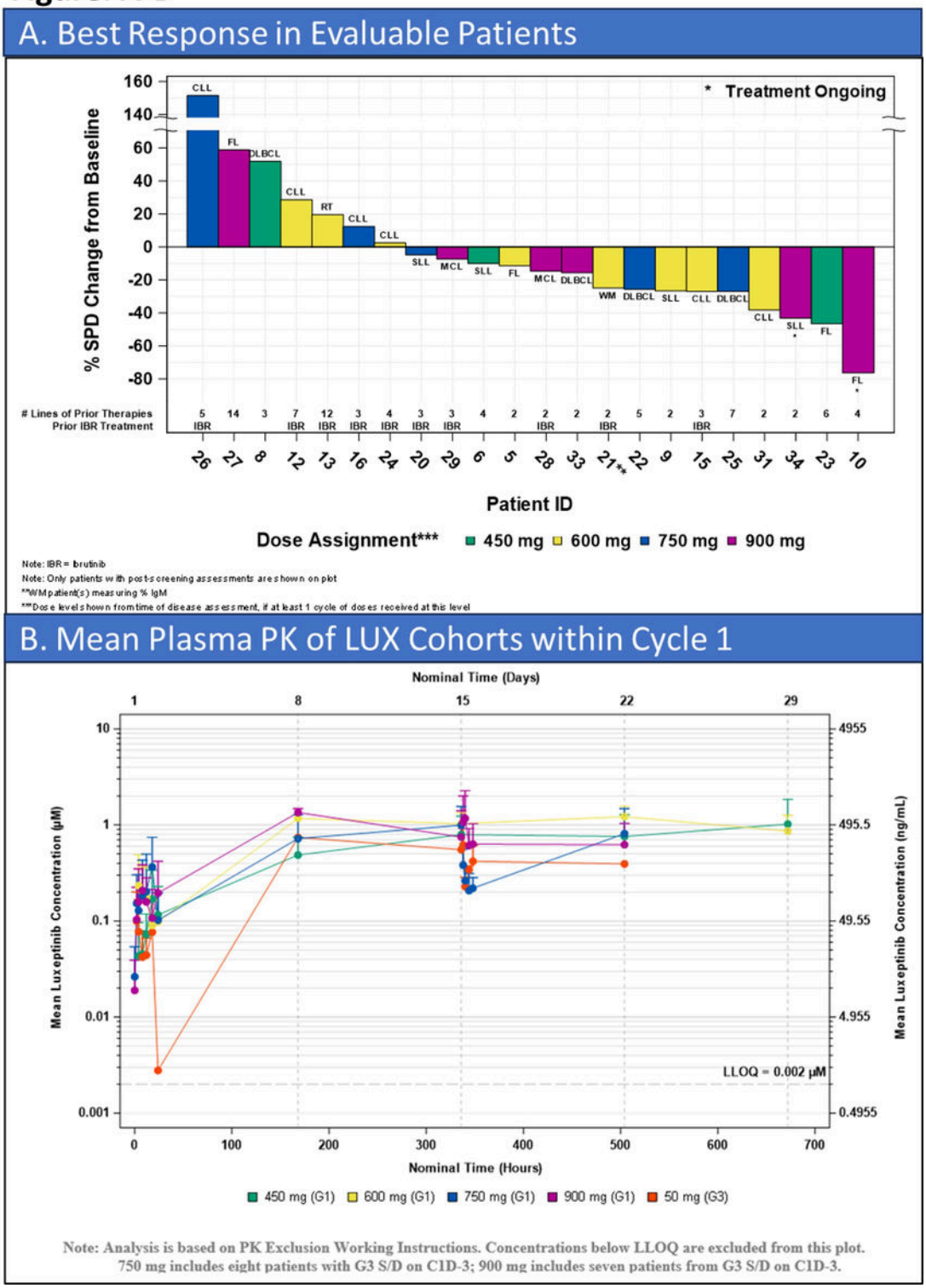

Figure 1

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