SMOOTHENED (SMO) INHIBITOR LDE225 COMBINED WITH NILOTINIB IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA (CML) RESISTANT/INTOLERANT (R/I) TO AT LEAST 1 PRIOR TYROSINE KINASE INHIBITOR: A PHASE 1B STUDY

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Background
Currently available therapies may have limited potential to eliminate leukemic stem cells (LSCs). LDE225 is an antagonist of the transmembrane protein SMO, which plays a role in the Hedgehog (Hh) pathway. Inhibition of the Hh pathway diminished survival signals in LSCs and increased the sensitivity of LSCs to tyrosine kinase inhibitors (TKIs).[1] Preclinical studies[2] have shown synergistic effects between SMO inhibitors and BCR-ABL TKIs. This combination is being explored in early phase clinical trials.

Aims
We evaluated the feasibility of the combination of nilotinib (NIL), a potent BCR-ABL TKI and LDE225 in patients with Philadelphia chromosome-positive CML in chronic phase R/I to at least 1 prior TKI.

Methods
This phase 1b, single-arm, multicenter study had the primary objective of determining the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D) of LDE225 (planned doses of 400/600/800 mg once daily) in combination with NIL 400 mg twice daily. Dose-limiting toxicities (DLT) were identified during the first 8 weeks of dosing. An adaptive Bayesian logistic regression model guided by the escalation with overdose control principle was used. Secondary objectives included safety, pharmacokinetics, and efficacy (as measured by the kinetics of molecular and cytogenetic responses).

Results
Eleven patients (cohort 1 [LDE225 400 mg + NIL]: n?=?4; median age 58 years; cohort 2 [LDE225 600 mg + NIL]: n?=?7, median age, 46 years) were enrolled. The median duration of exposure to study treatment in cohort 1 and cohort 2 was 11.27 and 8.25 months, respectively. Two patients in cohort 2 experienced 1 DLT (elevated creatine phosphokinase [CPK]: n?=?1, grade [G] 3; n?=?1, G4). One patient in cohort 1 experienced 1 serious adverse event (SAE; G4 elevated CPK), and 2 patients in cohort 2 experienced 2 SAEs each (G4 elevated CPK + G1 elevated troponin T and G3 appendicitis + G2 sepsis). The most frequently occurring (>?30%) adverse events (AEs; all grades) in the overall patient population included alopecia (73%), elevated CPK (64%), dysgeusia (64%), muscle spasms (64%), folliculitis (46%), and weight loss (37%). AEs leading to study discontinuation included 1 patient in cohort 1 (G1 elevated CPK) and 4 patients in cohort 2 (G1 folliculitis, G3 folliculitis, G2 dysgeusia, and G2 alopecia).
No deaths occurred during the study. No other clinically significant laboratory abnormalities were observed during the study.

One patient in cohort 1, who had a major molecular response (MMR; ≤ 0.1% BCR-ABL^{IS}) at baseline, achieved deep molecular response (MR$^{4.5}$; ≤ 0.0032% BCR-ABL^{IS}) temporarily at 2 months and 1 patient who had no MMR at baseline achieved MMR post baseline (from 1

month until 9 months). In cohort 2, 1 patient who had no MMR at baseline achieved MMR at 12 months.

The study was terminated early, as the benefit of addition of LDE225 to NIL did not appear to outweigh additional risks in patients with CML.

Summary

The MTD was not determined; no RP2D for the combination of NIL and LDE225 was found with respect to an acceptable risk/benefit ratio for patients with CML. No evidence of clinical benefit or impact of the combination was observed. The SAEs of elevated blood CPK were consistent with the safety profile of LDE225. No significant AEs were seen due to NIL. Study outcomes were similar to another phase 1 study, which showed lack of efficacy and tolerability when a SMO inhibitor was used in combination with dasatinib.[3]

References

[1]Dao KH, et al. *Clin Cancer Res*. 2013.

[2]David A, et al. *Hematologica*. 2011.

[3]Shah NP, et al. *Blood.* 2014.