A novel CSL-NICD inhibitor for the treatment of NOTCH-driven T-cell acute lymphoblastic leukemia: a case report

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BACKGROUND

The NOTCH pathway is a clinically validated target in oncology and can lead to cancer development like in T-cell acute lymphoblastic leukaemia (T-ALL). Furthermore, NOTCH aberrations may occur during the course of the disease, to a more aggressive phenotype and more malignant progression. Approximately 60% of T-ALL cases have NOTCH pathway activation due to mutations in at least one of the NOTCH receptors or FBXW7 gene. There is a high unmet medical need because none of the approved drugs is specifically targeting the NOTCH pathway in ALL. CB-103 is a highly specific inhibitor of oncogenic CSL-NICD gene transcription factor (GTF) complex which modulates transcription of oncogenic signature downstream of NOTCH signaling[1]. CB-103 has shown an outstanding safety profile in a phase I dose escalating study in patients with solid tumors[2]. The safety profile of CB-103 allows application of this novel inhibitor in human cancers as a single agent as well as in combination with other anticancer agents. Furthermore, clinical Proof of Concept (PoC) has been demonstrated with single agent treatment of patients with NOTCH activated Adenoid Cystic Carcinoma (ACC): A median PFS of 21.7 weeks has been achieved in advanced, metastatic ACC patients, previously progressing before treatment with CB-103. Strong target engagement was confirmed by assessment of surrogate tissue biomarkers in selected patients[2]. Here we present the first case of a relapsed/refractory (r/r) T-ALL patient with complete response, MRD free in the context of CB-103 treatment.

CASE NARRATIVE

A 24-year old male patient was diagnosed with T-ALL harbouring a NOTCH1 activating mutation in 29% of blasts in May 2020. After achieving CR with the GRAALL-2014/T high risk regimen in July 2020, the patient relapsed within a few months and became refractory to a series of salvage therapies (Table 1). When all standard treatments were exhausted, a sequential/combined therapy with agents specifically targeted to the molecular alterations detected in the leukaemic cells (BCL2, ABL1, CD-38 and NOTCH1) was adopted as the last attempt to transition the patient to HSCT. The effect of this treatment with Venetoclax, Ponatinib and Decitabine started, after some initial response, to level off and was not well tolerated leading to the necessity to step-wise stop this triple combination. At the same time, the persistence of the pathogenic NOTCH1 mutation was confirmed in a bone marrow biopsy. Under a compassionate use protocol the patient received CB-103*. In a rapid dose escalation CB-103 was added to treatment with Venetoclax and Decitabine, which were stepwise phased out while increasing the daily doses of CB-103. The patient was again induced into remission and was able to undergo allo-HSCT. CB-103 was continued throughout the transplantation and post HSCT to control the NOTCH1 mutation carrying clone. The patient remained disease-free for 9 months and then he developed extramedullary relapse for which he started targeted treatment.

* CB-103 was provided by Cellestia Biotech AG free of charge.

REFERENCES

1. Lehal R, et al. PNAS 2020;117:16292-301
2. Lopez Miranda E, et al. J Clin Oncol 2021;39:suppl 15; abstr 3020

CONTACT INFORMATION

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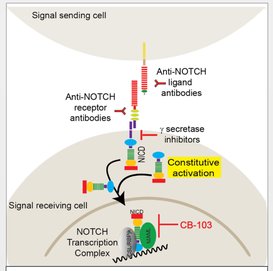

Figure 1:
Schematics of the NOTCH pathway

Induction	Prednisone, vincristine, cyclophosphamide, daunorubicin, L-asparaginase, intrathecal MTX, cytarabine, dexamethasone
1st and 2nd consolidation	Cytarabine, vincristine, methotrexate, mercaptopurine, cyclophosphamide, etoposide, intrathecal MTX, cytarabine, prednisone
Late intensification	Daunorubicin, vincristine, cyclophosphamide, prednisone, L-asparaginase, intrathecal methotrexate, cytarabine, dexamethasone
3rd consolidation	nelarabine, cyclophosphamide, etoposide, vincristine, methotrexate, mercaptopurine, intrathecal methotrexate, cytarabine, dexamethasone
Salvage attempts	- idarubicin, cytarabine - nelarabine, daratumumab, dasatinib - cyclophosphamide - venetoclax, ponatinib, decitabine

Table 1:
Drugs the patient received in the GRAALL protocol and in the r/r setting, prior to starting CB-103

Longitudinal follow up of pre-SCT leukocyte counts & co-medications

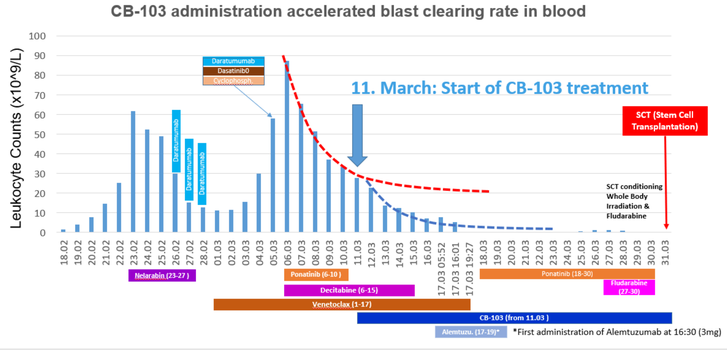

Figure 2: The graphic displays the variations in leukocyte counts, as measure of disease, over time given as calendar dates.
Clinically insufficient results were achieved with various treatment approaches during February and March. CB-103 was added on 11.03. and rapidly dose escalated (Figure 2). A bone marrow biopsy on the seventh treatment day revealed clearing of the blasts (Figure 3). As the cell population was CD52 positive, alemtuzumab was added later that day. For the next two weeks the patient stayed in remission. CB-103 was maintained during conditioning and allo-HSCT.

T-ALL patient bone marrow – clearing of T-ALL blast infiltration

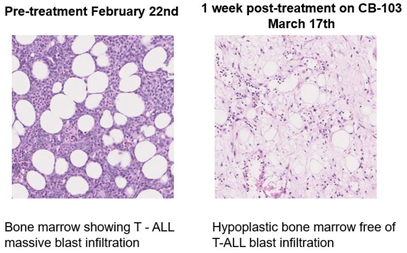

Figure 3:
Bone marrow biopsy obtained after one week of CB-103 administration, (H&E staining) (prior to alemtuzumab administration)

Target engagement markers

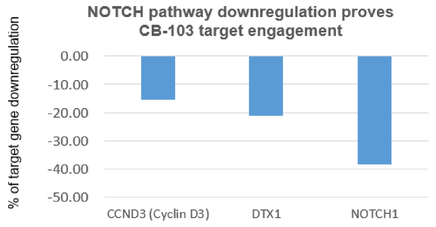

Figure 5: The graphic displays the variations in CCND3, DTX1 and NOTCH1 gene expression level already 1 hour after the first CB-103 administration at the low starting dose
RNA was extracted from circulating blasts at baseline and one hour after the first administration of CB-103. Gene expression profiling was performed with Nanostring technology using a NOTCH- pathway customised panel. A CSL-NICD-mediated, target gene downregulation was observed for NOTCH1-ICD, DTX1 and cyclin D3, as early as 1 hour post-CB-103 administration at the low starting dose

Liquid Bx longitudinal follow up pre-allo HSCT

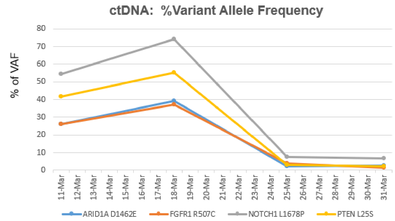

Figure 4: The graphic displays the variations in ctDNA: %Variant Allele Frequency over time given as calendar dates.
Liquid biopsy: NGS of circulating tumor DNA (ctDNA) was performed at different time points, to follow up the evolution of the identified T-ALL gene variants. The persistence of molecular markers at low %VAF were indicative of residual disease pre-SCT

Liquid Bx & T-ALL molecular markers longitudinal follow up post-allo HSCT : T-ALL molecular CR

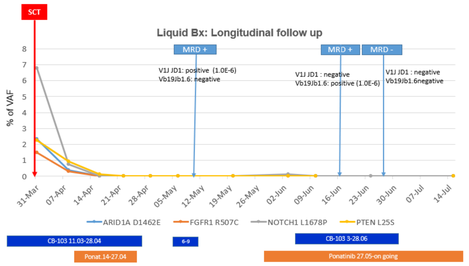

Figure 6: Change in levels of molecular markers of the blast clone over time
NGS of circulating tumor DNA (ctDNA) was performed at different time points, to follow up the identified T-ALL gene variants. Two weeks after SCT variants were not detectable in ctDNA (sensitivity ~0,5-1%), indicative of leukaemia growth control. On June 26, patient reached a molecular CR, with V1J JD1 and Vb19Jb1.6 molecular T-cell markers (RTqPCR) negative

RESULTS & CONCLUSIONS

CB-103 was well tolerated in combination with other anticancer drugs with only mild adverse events.
Within 1 week of starting CB-103, the bone marrow was free of T-ALL blast infiltration (MRD+). The patient underwent allo-HSCT. CB-103 was continued throughout the transplantation and post HSCT to control the NOTCH1 carrying clone. Sequential samples of ctDNA to monitor the disease after allo-HSCT showed a decrease of circulating variant allele frequency of the NOTCH1, FGFR1 and PTEN alterations reaching CRi, MRD negative, approximately 3 months after allo-HSCT. Downregulation of NOTCH target genes proved CB-103 target engagement. This is the first T-ALL patient treated with CB-103. The observed clinical response encourages further exploration of CB-103 in this indication. A clinical trial is open (NCT03422679).