Venetoclax added to HyperCVAD-Nelarabine and Pegylated Asparagine improves outcomes in patients with T-cell acute lymphoblastic leukemia/lymphoma

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Background

- Limited progress in the treatment of T-cell acute lymphoblastic leukemia (T-cell ALL) / Lymphoblastic lymphoma (T-LBL)
- Nelarabine is approved for the treatment of relapsed T-ALL
- Nelarabine improves disease free survival (DFS) but not overall survival (OS) in the frontline therapy of pediatric T-ALL; reduces risk of CNS relapse *(Dunsmore et al, JCO 2023)*
- T-ALL subtypes such as Early T-cell Precursor (ETP) ALL are sensitive to Bcl-2 inhibition *(Pullarkat el al, Cancer Discov, 2021)*
- Optimal combination of agents active against T-cell ALL/LBL are important to improve the depth and duration of first remission

Methods

Patients

- Adult patients ≥ 18 years of age
- Previously untreated or minimally pretreated T-ALL/T-LBL (failure to 1 induction course or CR after ≤ 2 cycles)
- ECOG PS ≤ 3
- Adequate renal and liver function

Treatment

- HyperCVAD backbone: **4 protocol amendments (5 treatment cohorts)**
- Nelarabine: 650 mg/m^2 IV x 5 days
- PegAsp: 1500 IU/m^2 (cap 3750 IU) on Day 5 of NEL [Age >60: 1000 IU/m^2 (cap 2000 IU)]
- Mediastinal RT (prior to start of maintenance) for bulky mediastinal disease (≥7 cm) at diagnosis or residual mediastinal disease.
- All patients received POMP (prednisone, vincristine, methotrexate and 6-mercaptopurine) maintenance for 30 months with early and late intensifications.

Cohorts	N	Year	Hyper-CVAD	Nelarabine (NEL)	Peg asparaginase (PegAsp)	Venetoclax (Ven)
1	30	2007-2011	Hyper-CVAD 1,3,5,7 MTX/Ara-C 2,4,6,8	After C8 for 2 cycles + Cycles 6-7 of maintenance	-	-
2	49	2011-2017		After C4 (4N) and C5 (5N) + Cycles 6-7 of maintenance	-	-
3	17	2017-2019			PegAsp with NEL in Cycles 4N and 5N + PegAsp with NEL in Cycles 6-7 of maintenance	-
4	16	2019-2021				Days 1-7 of all Induction/ consolidation cycles
5	33	2021-Ongoing				Days 1-7 of C1; Days 1-3 for C2-C8* only for ETP-ALL/LBL and/or MRD+ve

Treatment

- **Early intensification:**
  - C6 of maintenance- Nelarabine and PegAsp
  - C7 of maintenance- Nelarabine and PegAsp
- **Late intensification:**
  - C18 of maintenance- Methotrexate and PegAsp
  - C19 of maintenance- HyperCVAD
- Venetoclax was given for Cycles 1-8 (Omitted in the Nelarabine containing cycles [C4N and C5N]) in Cohort 4 and MRD/ETP direct in Cohort 5

Objectives

- Rates of CR/CRi in response evaluable patients (patients with active disease at enrollment)
- Duration of response, Progression Free Survival (PFS) and Overall Survival (OS) of full cohort stratified by ETP and Non-ETP subsets
- Primary endpoint: Improvement in DOR/PFS/OS of patients treated on the Venetoclax cohort (Cohort 4+%) compared to the Original Cohorts (Cohorts 1+2+3)
- Safety of Venetoclax added to HyperCVAD-Nel-PegAsp

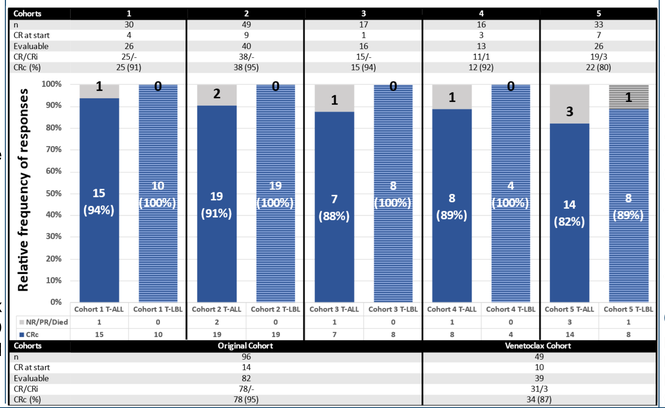
Results

- **Aug 20227 to Dec 2024: 145 patients treated**
- 96 patients (66%): Original Cohort
- 46 patients (34%) Venetoclax cohort
- Median age of 35 years (range 18-75 years)
- T-ALL: 91 (63%); T-LBL: 54 (37%)
- CNS disease: 7 patients (5%)
- ETP-ALL/LBL: 31/133 (23%) immunophenotyped
- In remission at enrollment: 121/145 (Response evaluable)
- Median follow up:
  - Full cohort: 62 months (95% CI 52-75 months)
  - Original cohort: 89 months (95% CI 74-105 months)
  - Venetoclax cohort: 24 months (95% CI 18-32 months)
- 10/33 (36.3%) patients in cohort 5 received venetoclax beyond one cycle (ETP=6, persistent disease/MRD positive =4). One patient with ETP-ALL in cohort 5 had progressive disease after C1 and was taken off study.

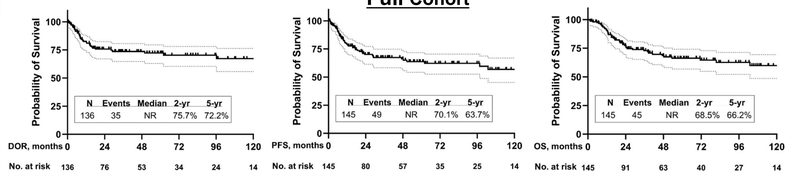
Baseline Characteristics of Study Patients

Treatment Cohorts		Full Cohort	Original cohort	Venetoclax Cohort
Variables		N(%), median [range]		
Number of patients		145	96	49
Age		35 [18-78]	35 [18-78]	37 [18-68]
	≥60 years	14 (10)	10 (10)	4 (8)
Gender	Male	110 (76)	75 (78)	35 (71)
ECOG PS	0	47 (32)	27 (28)	20 (41)
	1-2	89 (68)	69 (72)	29 (59)
Disease presentation	T-ALL	91 (63)	57 (59)	34 (69)
	T-LBL	54 (37)	39 (41)	15 (31)
EMD involvement	CNS	7 (5)	5 (5)	2 (4)
Immunophenotype	ETP	31/133 (23)	21/86 (24)	10/47 (21)
	Near ETP	21/133 (16)	15/86 (17)	6/47 (13)
Cytogenetics[$] (T-ALL)	Diploid	30/65 (46)	18/42 (43)	12/23 (52)
	High-risk	8/65 (12)	6/42 (14)	2/23 (9)
	Miscellaneous	27/65 (42)	18/42 (43)	9/23 (39)
Mutation profile (T-ALL)[$]	*NOTCH1/FBXW7*	20/32 (63)	5/8 (63)	15/24 (63)
	TP53	3/42 (7)	1/18 (6)	2/24 (8)
CR at enrollment		24 (17)	14 (15)	10 (20)

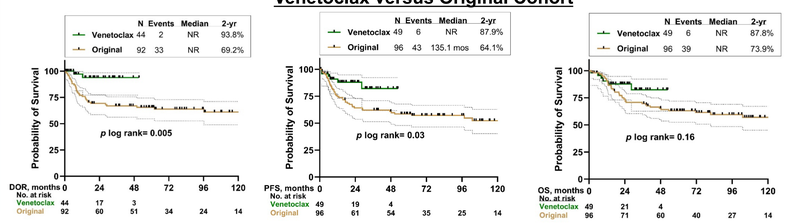
Frequency of responses on the study



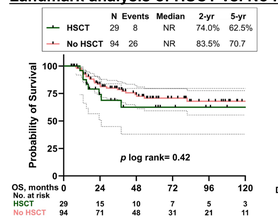
Full Cohort



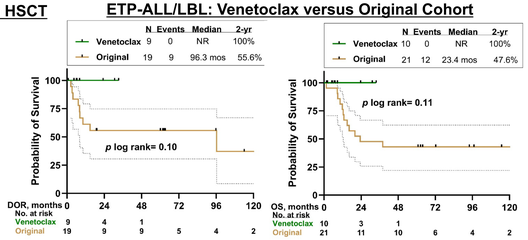
Venetoclax versus Original Cohort



Landmark analysis of HSCT vs. No HSCT



ETP-ALL/LBL: Venetoclax versus Original Cohort



Safety

- Most common serious adverse event (SAE): Febrile Neutropenia=87 (60%)
- Neurological SAE= 11 (8%); no treatment attributable central neurotoxicity.
- Thromboembolic events: 8 (5%); serious grade pancreatitis= 5 (3%)
- Comparable time to neutrophil and platelet recovery between the venetoclax and original cohorts

Conclusion

- Addition of venetoclax to HyperCVAD-Nel-PegAsp led to improvement in PFS, DOR and trend towards OS improvement compared to the original cohort in patients with T-ALL/LBL: Met protocol defined endpoint of 2-year improvement in PFS and OS by 10% compared to original cohort
- No noticeable safety signal with addition of venetoclax to HyperCVAD-Nel-PegAsp

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