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ORAL ABSTRACTS

614.ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Nelarabine (NEL), Pegylated Asparginase (PEG) and Venetoclax (VEN) Incorporated to HCVAD Chemotherapy in the Frontline Treatment of Adult Patients with T-Cell Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma (T-ALL/T-LBL)

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Background:
The incorporation of novel agents such as NEL and PEG to frontline therapy has been associated with improved outcomes in pediatric patients (pts) with T-ALL/LBL, but has not been extensively studied in the adult pts. BCL-2 upregulation has been demonstrated in T-lymphoblasts, especially of the early T-cell precursor (ETP) ALL and addition of VEN (BCL-2 inhibitor) may be beneficial.

Methods:
Pts with previously untreated or minimally pre-treated T-ALL/LBL were eligible if they had an ECOG PS ≤3, creatinine ≤ 2 mg/dL, total bilirubin ≤ 2 mg/dL and ALT/AST ≤ 4 x ULN. Pts received 8 cycles (C) of HCVAD (C 1,3, 5, 7) alternating with high dose Ara-C and methotrexate (MTX) (C 2, 4, 6, 8) at approximately 3-week intervals. Two cycles of NEL (650 mg/m ^{2} daily x 5) were initially administered after C8 (cohort 1). Later, after a protocol amendment, they were administered after C4 and C5 (cohort 2). Subsequently, the protocol was amended to add PEG (1500 IU/m ^{2} capped at 3750 IU; for pts age 60 or older, dose was 1000 IU/m ^{2}, capped at 2000 IU) on day 5 of the NEL cycles (cohort 3) and more recently, VEN 400 mg daily was added on the first 7 days of each of 8 cycles of therapy (cohort 4); this was later modified to be given for 7 days during the induction cycle to all pts and reduced to 3 days per post-induction cycle only in pts with ETP-ALL or those with persistent measurable residual disease (MRD) and all other pts did not receive VEN after C1 (cohort 5). Pts with ETP-ALL were referred for allogeneic stem cell transplant (allo-SCT) in first complete remission (CR). After the completion of the intensive phase; pts in all cohorts received 30 cycles of maintenance therapy with monthly POMP (prednisone, vincristine, MTX, prednisone) and early intensification with NEL/PEG on C6 and 7 and late intensification with MTX/PEG in C18 and HCVAD on C19. All pts received 8 intrathecal chemotherapy with MTX alternating with Ara-C and mediastinal radiation was considered in pts with bulky mediastinal disease.

Results:
Between 7/2007 and 12/2022, 133 pts were enrolled in the 5 study cohorts sequentially (cohort 1= 30, 2= 49, 3=17, 4=16, 5=21) **(Table 1).** Eighty pts (60%) had T-ALL, 52 T-LBL (39%) and 1 pt had ETP/myeloid bi-phenotypic leukemia. The median age for the entire cohort was 35 years (yrs) (range 18-78), 102 pts were male (77%), 83 pts (62%) were white and 18 pts (14%) had PS ≥2. Overall, 24 pts (18%) had an ETP phenotype and another 19 pts (14%) had a near-ETP phenotype. Six pts (5%) had central nervous system disease at diagnosis, 72 pts (54%) had mediastinal disease, 49 of 80 (61%) T-ALL pts had extramedullary disease and 20 pts (15%) were in complete remission (CR) at trial enrollment after minimal pre-enrollment therapy. Overall response (CR+CRp+CRi+PR) on trial was attained in 109/113 (95%) pts [CR= 101 (89%), CRi/CRp= 3 (3%), PR=5 (4%)]. CR/CRi/CRp was

attained in 36/41 (88%) pts with ETP/near-ETP ALL and 60/64 (94%) of confirmed near-ETP ALL pts (p=0.31). At a median follow-up of 62 months (mos), the median overall survival (OS) was not reached (NR), 3-yr OS was 71% and 5-yr OS was 64% . The 3-yr OS for pts treated with HCVAD+NEL (cohort 1+2), HCVAD+NEL+PEG (Cohort 3) and HCVAD+NEL+PEG+VEN (Cohort 4+5) were 66%, 88% and 76% respectively **(Figure 1**). Median OS was not reached for both VEN cohorts, while 3-yr OS was 72% in cohort 4 compared to 88% in cohort 5 (p=0.51), with significantly shorter follow-up for the latter (33 mos vs. 15 mos). Amongst the 124 pts who had CR/CRp/CRi, the median RFS was NR and 5-yr RFS was 68%. 24 (18%) pts underwent SCT in first remission, including 20 (83%) with ETP or near-ETP ALL. The median OS was shorter in the 44 ETP/near-ETP pts compared to the 77 pts with non-ETP phenotype (71 mos vs. NR, p=0.08). 30 and 60-day mortality was 0% and 1%. 10 pts (7.5%) died in remission (3, 5 and 2 pts in cohorts 1, 2 and 4 respectively) including 1 after SCT, 4 after developing therapy-related acute myeloid leukemia and 5 from infectious complications.

Conclusion: The ongoing phase 2 trial of NEL, ASP, VEN added to the HCVAD regimen shows promising long-term survival in adult pts with T-ALL/LBL with 3-yr OS of 76%-88% in pts treated with HCVAD+NEL+PEG +/- VEN. Larger prospective trials and longer follow-up are needed to demonstrate further benefit.

Disclosures Senapati: *Kite Pharma:* Other: Advisory Board. **Kantarjian:** *Novartis:* Honoraria; *KAHR Medical:* Honoraria; *Jazz Pharmaceuticals (Inst):* Honoraria, Research Funding; *Ipsen:* Honoraria; *Immunogen (Inst):* Honoraria, Research Funding; *Daiichih-Sankyo (Inst):* Honoraria, Research Funding; *AstraZeneca/MedImmune:* Honoraria; *Astellas Pharma:* Honoraria; *Ascentage Pharma Group:* Honoraria; *Amgen:* Honoraria; *Abbvie:* Consultancy, Honoraria; *Pfizer:* Honoraria; *Taiho Pharmaceutical:* Honoraria; *Precision Biosciences:* Honoraria; *Shenzhen Target Rx:* Honoraria; *Abbvie (Inst):* Research Funding; *Ascentage Pharma (Inst):* Research Funding; *Amgen (Inst):* Research Funding; *Bristol-Myers Squibb (Inst):* Research Funding; *Novartis (Inst):* Research Funding. **Jabbour:** *Ascentage Pharma Group:* Consultancy, Honoraria, Research Funding; *Adaptive Biotech:* Consultancy, Honoraria, Research Funding; *Pfizer:* Consultancy, Honoraria, Research Funding; *Abbvie:* Consultancy, Honoraria, Research Funding; *Bristol-Myers Squibb:* Consultancy, Honoraria, Research Funding; *Genentech:* Consultancy, Honoraria, Research Funding; *Hikma Pharmaceuticals:* Consultancy, Honoraria, Research Funding; *Amgen:* Consultancy, Honoraria, Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding. **Kadia:** *Celgene:* Research Funding; *Iterion:* Research Funding; *Sanofi-Aventis:* Consultancy; *Daiichi Sankyo, Genentech, Inc., Genzyme, Jazz Pharmaceuticals, Liberum, Novartis, Pfizer, PinotBio, Inc, Pulmotect, Inc, Sanofi-Aventis, Servier:* Consultancy; *Genzyme:* Honoraria; *Hikma Pharmaceuticals:* Speakers Bureau; *Amgen, Inc.:* Research Funding; *Astellas Pharma Global Development:* Research Funding; *Novartis:* Consultancy; *Cellenkos Inc.:* Research Funding; *Cure:* Speakers Bureau; *Jazz Pharmaceuticals, Pfizer, Pulmotect, Inc, Regeneron Pharmaceuticals, SELLAS Life Sciences Group:* Research Funding; *Janssen Research and Development:* Research Funding; *AbbVie, Amgen, Inc, Ascentage Pharma Group, Astellas Pharma Global Development, Astex, AstraZeneca, BMS, Celgene, Cellenkos Inc, Cyclacel, Delta-Fly Pharma, Inc, Genentech, Inc., Genfleet, Glycomimetics, Iterion, Janssen Research and Development:* Research Funding; *Liberum:* Consultancy; *Biologix, Cure, Hikma Pharmaceuticals:* Speakers Bureau; *Glycomimetics:* Research Funding; *Pulmotect, Inc.:* Consultancy, Research Funding; *Agios:* Consultancy; *Genentech:* Consultancy, Research Funding; *Delta-Fly Pharma, Inc.:* Research Funding; *GenFleet Therapeutics:* Research Funding; *Cyclacel:* Research Funding; *Pfizer:* Consultancy, Research Funding; *AstraZeneca:* Research Funding; *Ascentage Pharma Group:* Research Funding; *Regeneron Pharmaceuticals:* Research Funding; *SELLAS Life Sciences Group:* Research Funding; *Servier:* Consultancy; *Pinotb-Bio:* Consultancy; *BMS:* Consultancy, Research Funding; *Astex:* Honoraria. **Borthakur:** *Astex Pharmaceuticals, Ryvu, PTC Therapeutics:* Research Funding; *Pacylex, Novartis, Cytomx, Bio Ascend::* Membership on an entity's Board of Directors or advisory committees; *Catamaran Bio, Abbvie, PPD Development, Protagonist Therapeutics, Janssen:* Consultancy. **Konopleva:** *Reata Pharmaceuticals.:* Current holder of *stock options* in a privately-held company, Patents & Royalties; *Abbvie, Allogene Therapeutics, Cellectis, Forty Seven, Gilead Sciences, Genentech, Sanofi, MEI Pharma, Rafael Pharmaceuticals, Daiichi Sankyo Pharmaceutical, AstraZeneca Co., Menarini, Precision BioSciences.:* Research Funding; *AbbVie, Forty Seven, Precision Biosciences, Gilead Sciences, Genentech, Janssen, Sanofi, MEI Pharma, Daiichi Sankyo Pharmaceutical, AstraZeneca Co., Menarini.:* Consultancy. **Wierda:** *NIH P30 CA016672/MDACC Cancer Center Support Grant:* Research Funding; *GSK/Novartis:* Research Funding; *Nurix THerapeutics:* Research Funding; *AstraZeneca/Acerta Pharma:* Consultancy, Research Funding; *Numab THerapeutics:* Research Funding; *Oncternal Therapeutics, Inc.:* Research Funding; *Juno Therapeutics:* Research Funding; *Janssens Biotech:* Research Funding; *Cyclacel:* Consultancy, Research Funding; *GlaxoSmithKline:* Research Funding; *Loxo Oncology, Inc./Lilly:* Research Funding; *Janssens Biotech Inc:* Research Funding; *Gilead Sciences:* Research Funding; *Pharmacyclics LLC:* Research Funding; *AbbVie:* Consultancy, Research Funding; *Genentech:* Research Funding; *Accutar Biotechnology:* Research Funding; *National Comprehensive Cancer Network:* Other: Nonrelevant Financial Relationship/Chair, CLL). 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Table 1: Baseline characteristics and response

	N(%),[range]					
N	**133**	**30**	**49**	**17**	**16**	**21**
Median age	35 [18-78]	38 [19-76]	33 [18-78]	31 [18-65]	38 [18-52]	33 [20-62]
Male	102 (77)	22 (73)	39 (80)	14 (82)	12 (75)	15 (71)
ECOG PS ≥2	18 (14)	3 (10)	7 (14)	3 (18)	3 (19)	2 (10)
T-ALL , T-LL	80 (60), 52 (39)	19 (63), 11 (37)	28 (57), 20 (41)	9 (53), 8 (47)	11 (69), 5 (31)	13 (62), 8 (38)
CNS +ve at Diagnosis	6 (5)	2 (7)	2 (4)	1 (6)	1 (6)	0
Mediastinal disease	72 (54)	16 (53)	24 (49)	8 (47)	8 (50)	16 (76)
WBC (10^9/L)	7.8 [0.5-344.3]	7.6 [0.6-241.4]	7.7 [1.2-309.2]	7.4 [0.5-86.3]	9.3 [1.4-344.3]	11.3 [1.7-150.7]
BM Blast (%)	20 [0-97]	19.5 [0-95]	9 [0-96]	30 [1-94]	39 [0-90]	25 [1-97]
Immunophenotype						
Thymic	59 (44)	10 (33)	20 (41)	9 (53)	10 (63)	10 (48)
ETP	24 (18)	6 (20)	10 (20)	5 (29)	2 (13)	1 (5)
Near ETP	20 (15)	7 (23)	7 (14)	1 (6)	2 (13)	3 (14)
Early, non-ETP	3 (2)	0	1 (2)	0	2 (13)	0
Mature	15 (11)	3 (10)	6 (12)	1 (6)	0	5 (24)
NOS/NA	12 (9)	4 (13)	5 (10)	1 (6)	0	2 (10)
CR at start	20	4	9	1	3	3
ORR	109/113 (96)	25/26 (96)	39/40 (98)	16/16 (100)	13/13 (100)	16/18 (89)
CR/CRp	104/113 (92)	25/26 (96)	38/40 (95)	15/16 (94)	12/13 (92)	14/18 (78)
Median follow up (mos)	62	143	88	57	33	15
SCT in first remission	24 (18)	1 (3)	13 (26)	4 (23)	3 (19)	3 (14)

Abbreviations: ECOG, Eastern co-operative oncology group; PS, performance status; T-ALL, T-cell acute lymphoblastic leukemia; T-LL, T-cell lymphoblastic lymphoma; CNS, central nervous system; BM, bone marrow; ETP, early T-cell precursor; NOS, not otherwise specified; N/A, not available; CR, complete remission; ORR, overall response rate; SCT, allogeneic stem cell transplantation

Figure 1: Figure 1: Kaplan Meier estimates of overall survival (OS) of the study cohorts based on the drug combinations used

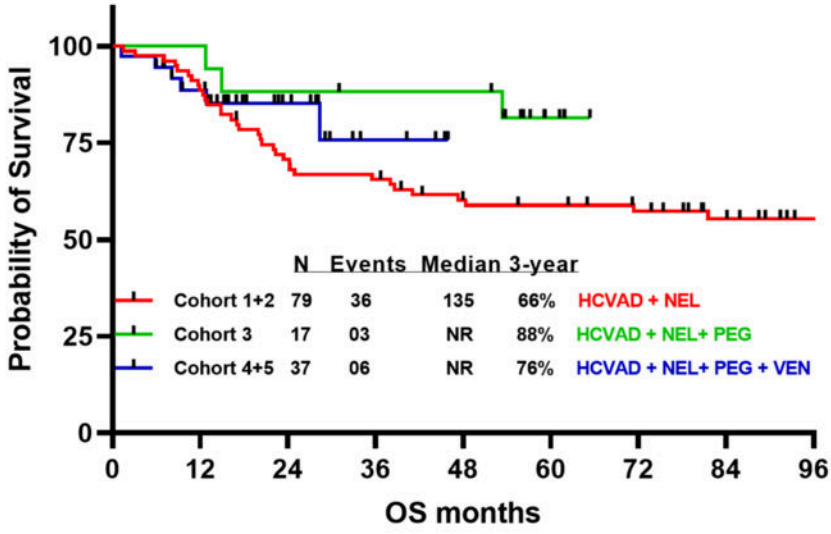

Figure 1

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