PHASE Ib PILOT STUDY OF ITACITINIB WITH ALEMTUZUMAB IN PATIENTS WITH T-CELL PROLYMPHOCYTIC LEUKEMIA

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Disclosure- none

Background

- T-cell prolymphocytic Leukemia (TPLL) is an incurable T-cell leukemia
  - Proliferation of mature, post-thymic prolymphocytes.
  - Aggressive course
  - Inherent resistance to conventional chemotherapy

- Strongly positive for CD52
- Alemtuzumab as monotherapy or combination therapies
    - Median overall survival (OS) from 7 to 17 months
    - No further improvement beyond that

- Majority TPLL have mutations in JAK/STAT genes

- Itacitinib (INCB039110) potently inhibits JAK1
  - Less for JAK2 and JAK3 or other non-JAK family kinases

- Itacitinib suppress
  - Cytokine signaling,
  - STAT phosphorylation
  - Cell growth in cytokine-dependent cell lines like IL 2, IL 23, and IL 6

- Early results using Itacitinib for MF and acute GVHD
- Dose 100 mg BID
- Similar grade ≥3 adverse events as placebo

- Single-center, single-arm, cohort expansion investigator-initiated phase 1b, 3+3 dose escalation pilot study
  - To assess the safety, tolerability, and efficacy of Itacitinib + Alemtuzumab

Methods

Inclusion

- Equal to or greater than 18 years, ECOG performance status ≤ 2, adequate organ function, and negative pregnancy test (where applicable)
- Frontline and relapsed/refractory (R/R)
- ClinicalTrials.gov (NCT03989466)

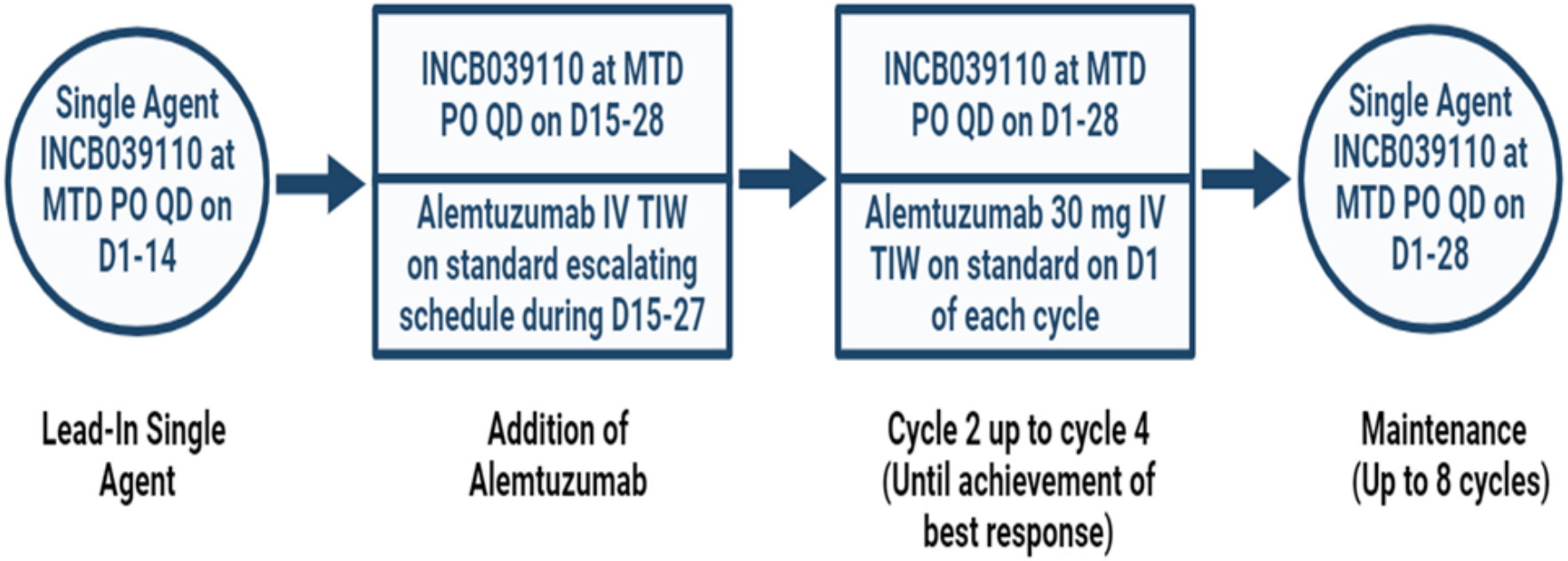
Exclusion

- Pregnant women, Uncontrolled intercurrent illness, on immunosuppressants for other disease, grade 2 or more neuropathy, prior treatment with JAK inhibitors, not practicing contraception (where applicable), known h/o HIV

Condition

- Stop taking CYP3A modulators for 72 hours before

Design



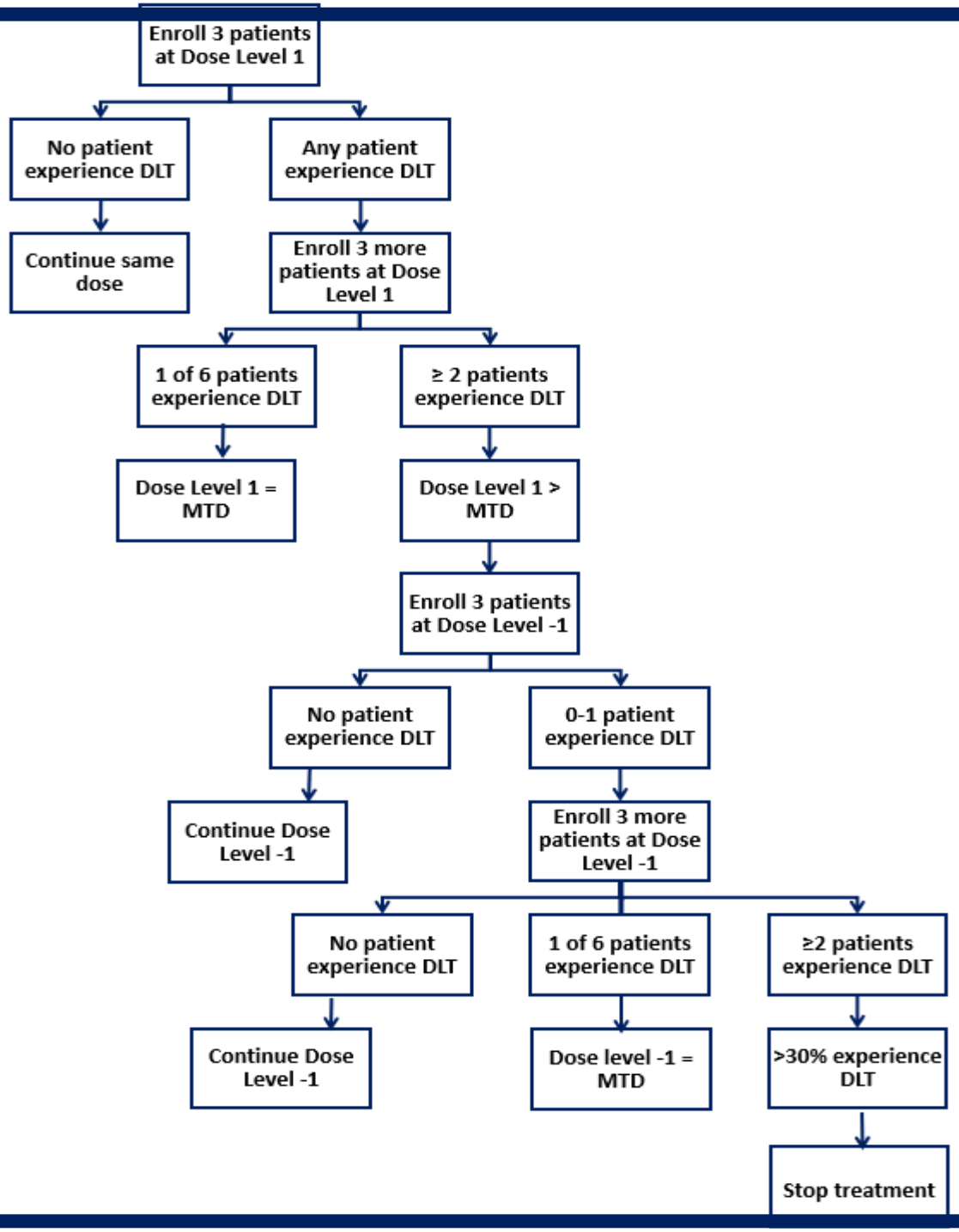
- 28 days defined as one cycle
- Days 1 to 14 involved single-agent lead-in Itacitinib oral administration
- From Day 15, combination therapy with Itacitinib and alemtuzumab ensues for up to 4 cycles, followed by single-agent Itacitinib maintenance for up to 8 cycles
- Continued Itacitinib post-treatment was allowed on a case-by-case basis after PI review for probable benefit after the 12-month course

Dose levels

Dose level	Itacitinib
1	200 mg PO daily
-1	100 mg PO daily
2	300 mg PO daily

3 + 3 algorithm

15 patients in Cycle 1 → to determine the maximum tolerated dose (MTD)



Safety and Response Assessment

- Patients who have received at least one cycle of therapy were evaluated for response
  - iwCLL Guidelines.
- First 6 weeks of study treatment were the DLT-defining period
- CTCAE (version 5)- to grade Adverse Events (AE)
- DLT
  - Grade 3 or greater non-hematologic toxicities
  - Grade 3 or 4 hematologic toxicity persisting for 42 days or more post-therapy interruption, with hypocellular bone marrow and no evidence of T-PLL

- *Events occurring commonly leukemia including anemia, <42 days myelosuppression, nonfebrile neutropenia, neutropenic fever without infection (grade 3), non-neutropenic fever (grade 3), infections with grade 3 and 4 neutropenia, infections without neutropenia (grade 3), tumor lysis syndrome, and supportive care-directed manageable adverse events were not included in the definition of DLT*

- Bone marrow aspiration and/or biopsy on Day 28 (+/- 7 days) of cycle one, on Day 28 (+/- 7 days) of Cycle 2, and then as required

Results

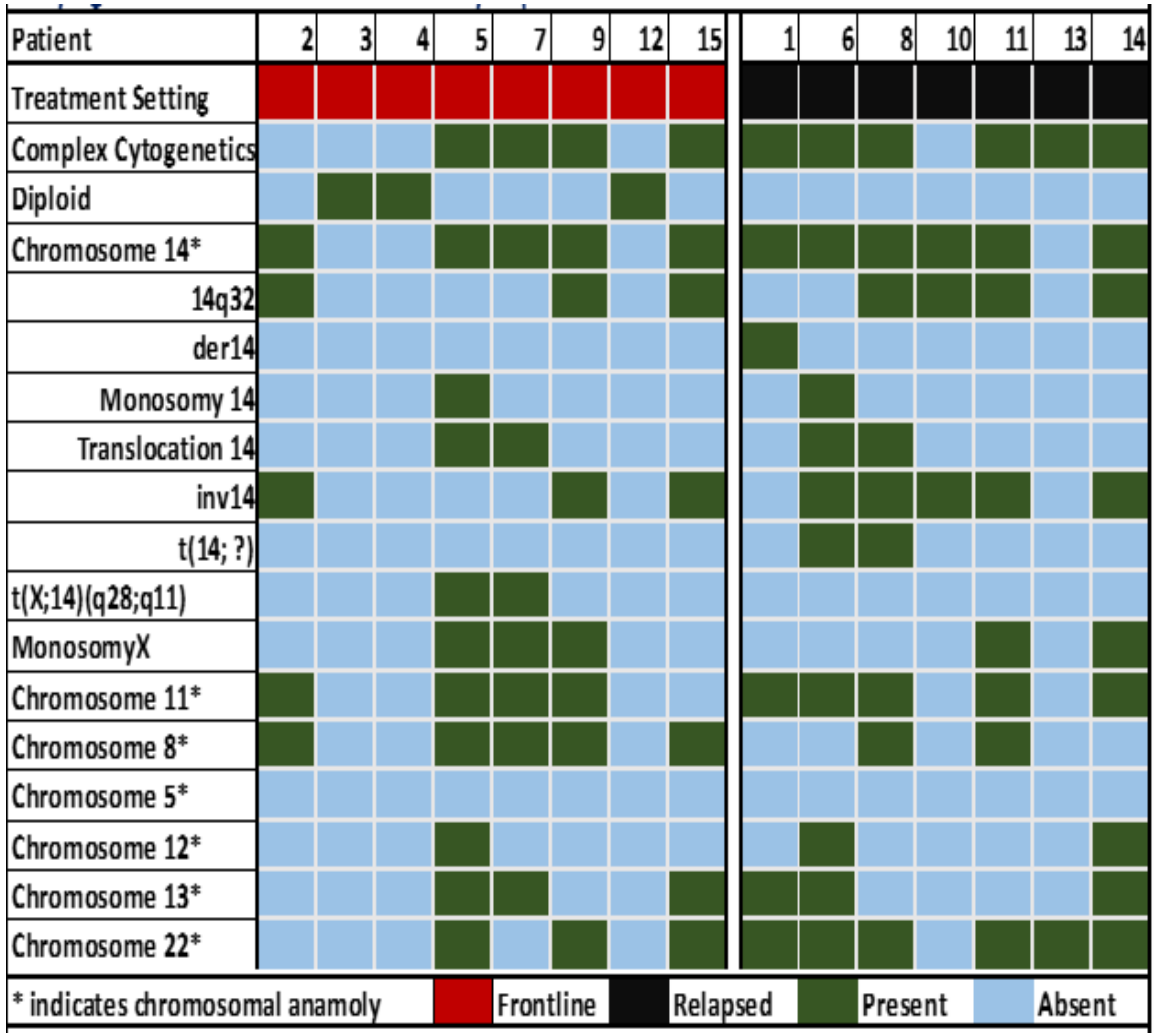
15 patients

- (53%) frontline
- 7 (47%) R/R

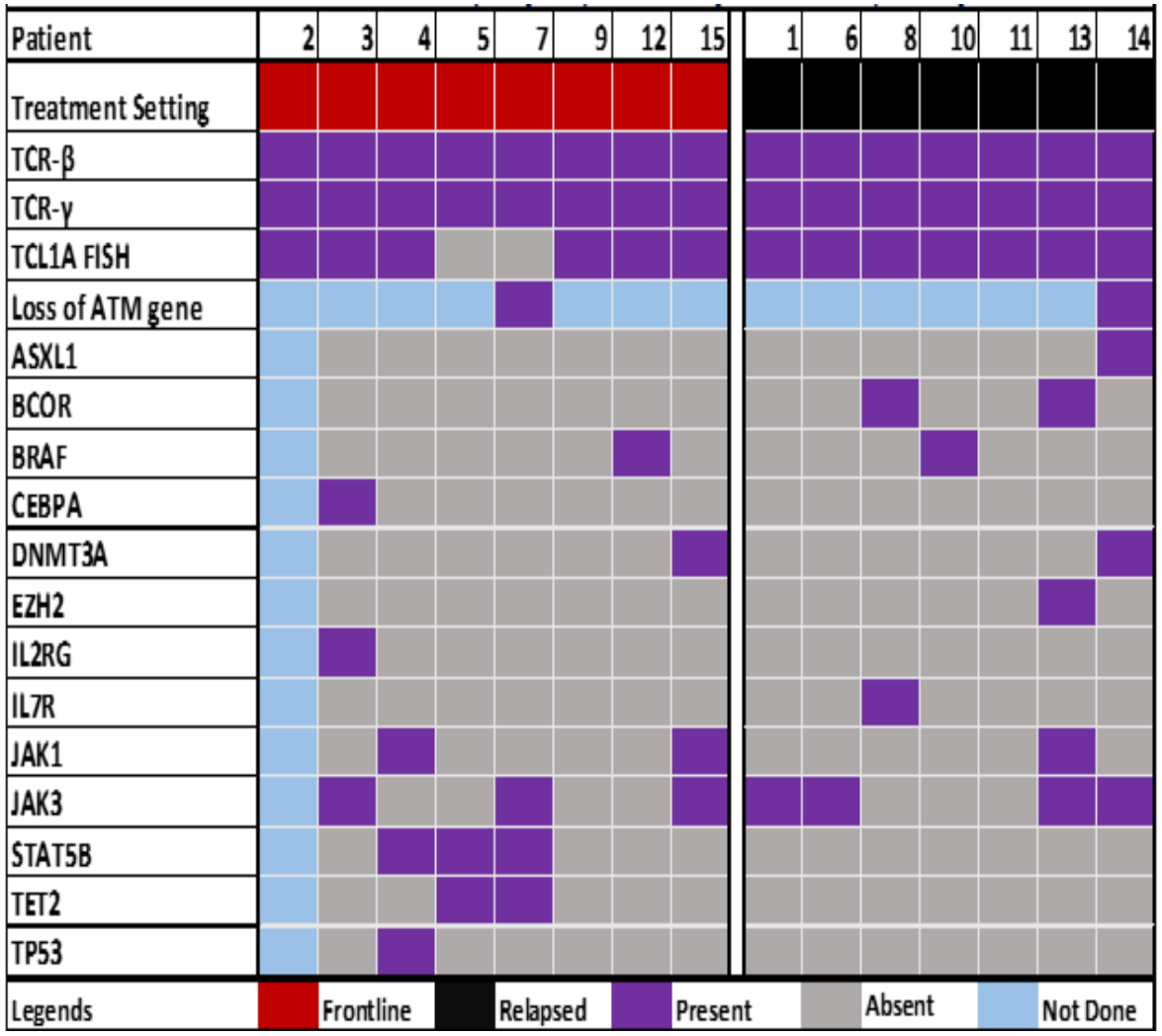
Baseline Characteristics	Frontline (n=8, 53%)		Relapsed/Refractory (n=7, 47%)		Total	
	Median	(range)	Median	(range)	Median	(range)
Age (years)	70.9	(39.1 - 83.4)	60.1	(45 - 80.6)	65.1	(39.1 - 83.4)
Hemoglobin (g/dL)	11.6	(9 - 13.3)	11.4	(7.2 - 14.8)	11.4	(7.2 - 14.8)
Hematocrit (%)	36.2	(28.6 - 42)	33.9	(20.4 - 42.2)	34.6	(20.4 - 42.2)
Platelet Count (K/uL)	111	(37 - 176)	95	(23 - 201)	108	(23 - 201)
White Blood Count (K/uL)	71	(9.6 - 181.6)	27	(2 - 68.6)	29	(2 - 181.6)
Lymphocyte Count (K/uL)	69	(2 - 92)	58	(19 - 84)	68	(2 - 92)
Monocyte Count (K/uL)	3	(2 - 14)	6	(1 - 22)	4	(1 - 22)
Neutrophil Count (K/uL)	10	(2 - 35)	22	(11 - 47.7)	14	(2 - 47.7)
Serum Lactate Dehydrogenase (U/L)	492	(244 - 610)	351	(220 - 1361)	485	(220 - 1361)
Serum β-2-microglobulin (mg/L)	2.8	(2.5 - 3)	5.3	(2.3 - 12.6)	3.0	(2.3 - 12.6)
Total Bilirubin (mg/dL)	0.5	(0.2 - 1.4)	0.7	(0.3 - 1.1)	0.5	(0.2 - 1.4)
Alanine transaminase (U/L)	19	(9 - 33)	27	(12 - 50)	21	(9 - 50)
Aspartate transaminase (U/L)	24	(14 - 32)	28	(18 - 94)	26	(14 - 94)
Serum Alkaline Phosphatase (U/L)	81	(68 - 149)	146	(46 - 355)	91	(46 - 355)
Serum Albumin (gm/dL)	4.1	(3.4 - 4.5)	4.3	(3.1 - 4.5)	4.2	(3.1 - 4.5)
Blood Urea Nitrogen (mg/dL)	16	(7 - 40)	20	(12 - 31)	19	(7 - 40)
Serum Creatinine (mg/dL)	1.0	(0.68 - 1.4)	1.0	(0.74 - 1.36)	1.0	(0.68 - 1.4)

		Frequency (%)		Frequency (%)		Frequency (%)	
Sex							
	Female	6	(75)	4	(57)	10	(67)
	Male	2	(25)	3	(43)	5	(33)
Race							
	White Hispanic or Latino	0		1	(14)	1	(7)
	White Non-Hispanic	6	(75)	5	(71)	11	(73)
	Other Hispanic or Latino	2	(25)	0		2	(13)
	Native American Non-Hispanic	0		1	(14)	1	(7)
ECOG PS							
	0	1	(12)	0		1	(7)
	1	5	(63)	7	(100)	12	(80)
	2	2	(25)	0		2	(13)
Prior Malignancy							
	Yes	3	(38)	3	(43)	6	(40)
	Chemotherapy	1	(12)	1	(14)	2	(13)
	Radiotherapy	1	(12)	1	(14)	2	(13)

Complex	10	(67)
Diploid	3	(20)
Chromosome 14 abnormality	11	(73)
14q32	7	(47)
inv14	8	(53)
translocations 14	4	(27)
Monosomy X	5	(33)
t(X;14)(q28;q11)	2	(13)
Chromosome 8 abnormality	7	(47)
Chromosome 11 abnormality	9	(60)
Chromosome 5 abnormality	0	
Chromosome 12 abnormality	3	(20)
Chromosome 13 abnormality	6	(40)
Chromosome 22 abnormality	9	(60)
TCL1A	13	(87)



10 patients (67%) had JAK/STAT mutations

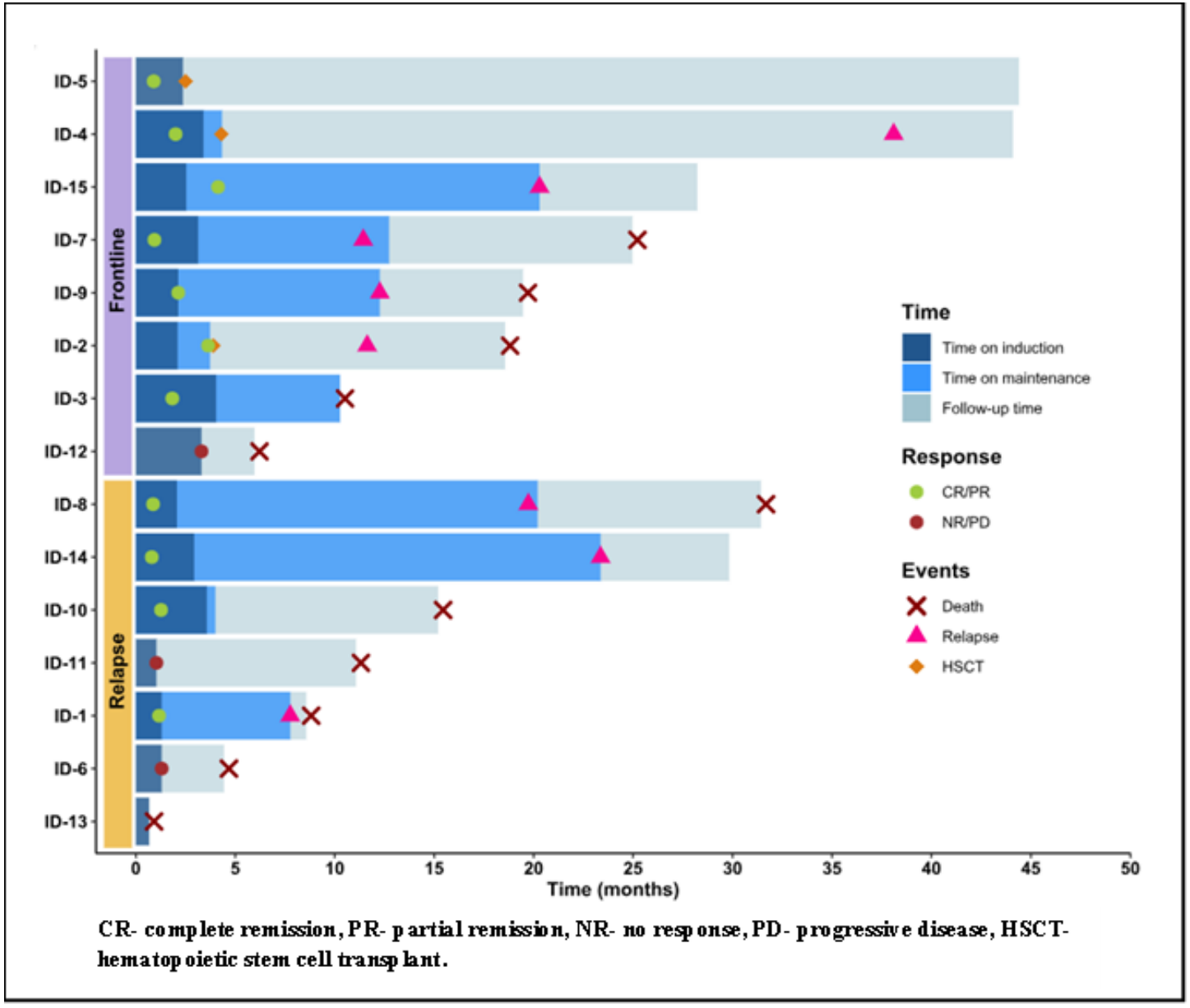


JAK3	**7**	**(47)**
JAK1	3	(20)
STAT5B	3	(20)
BCOR	2	(13)
BRAF	2	(13)
TP53	1	(7)

Chemotherapy Cycles	Frontline Median Frequency (range)		R/R Median Frequency (range)		All Median Frequency (range)	
Total Cycles	8	(2 - 21)	4	(1 - 25)	4	(1 - 25)
Induction Cycles	2	(2 - 4)	2	(1 - 3)	2	(1 - 4)
Alemtuzumab Induction Cycles	2	(2 - 4)	2	(1 - 3)	2	(1 - 4)
Itacitinib Induction cycles	2	(2 - 4)	2	(1 - 3)	2	(1 - 4)
Maintenance (Itacitinib) Cycles	5	(0 - 19)	1	(0 - 22)	2	(0 - 22)
Itacitinib Cycles Total	8	(2 - 21)	4	(1 - 25)	4	(1 - 25)
Time to Best Response (months)	2	(0.9 - 4.1)	1	(0.8 - 1.3)	1.3	(0.8 - 4.1)
Time to achieve MRD negative (months)	2	(0.8 - 7.5)	0.8	(0.8 - 1.2)	1.2	(0.8 - 7.5)

Response	Frontline		R/R		Total	
	Frequency (%)		Frequency (%)		Frequency (%)	
Best Response Achieved						
Complete Response (CR), N (%)*	6	(75)	3	(42.9)	9	(60.0)
Partial Response (PR), N (%)	1	(12.5)	1	(14.3)	2	(13.3)
Overall Response Rate (ORR), N (%)	7	(87.5)	4	(57.1)	11	(73.3)
No Response Achieved						
Died, N (%)	0		1	(14.3)	1	(6.7)
No Response (NR), N (%)	1	(12.5)	1	(14.3)	2	(13.3)
Progressive Disease (PD), N (%)	0		1	(14.3)	1	(6.7)
Total	1	(12.5)	3	(42.9)	4	(26.7)

Swimmer's Plot detailing the course of individual patients



CR- complete remission, PR- partial remission, NR- no response, PD- progressive disease, HSCT- hematopoietic stem cell transplant.

Survival Analysis of Study Population

Survival Times	Frontline			Relapsed/Refractory			Total		
	n	Median	(95% CI)	n	Median	(95% CI)	n	Median	(95% CI)
MRD-FS	6	5.0	(0.9 - NA)	3	6.5	(1.5 - NA)	9	6.5	(0.9 - 29.2)
CR Durability	6	10.5	(8.4 - NA)	3	13.9	(6.6 - NA)	9	13.9	(6.6 - 36.1)
DOR	7	10.5	(8 - 36.1)	4	13.9	(6.6 - NA)	11	13.9	(8 - 22.6)
EFS	8	11.6	(6 - 38.1)	7	11.1	(0.7 - 19.7)	15	11.6	(6 - 19.7)
OS	8	19.5	(6 - NA)	7	11.1	(0.7 - NA)	15	18.6	(6 - 31.4)

MRD-FS-Minimal residual disease-free survival, CR- Complete response, DOR- Duration of Response, EFS- Event-free survival, OS- Overall survival, NA- Not achieved.

Safety

- Dose reduction- 4 patients- coadministration of posaconazole (3 during maintenance, and 1 during induction phases)
- In the last group of 3 patients, 1 patient died on day 21 of cycle 1- declined transfusion- mortality was leukemia per se
- Only 1 treatment discontinuation due to AEs- maintenance cycle at 4 months
- MTD of the study was recorded as 200 mg daily Itacitinib
- Total of 150 events were documented

Grade	Number of Events
1	104
2	22
3	19
4	3
5	2

- None of the AEs had an incidence of >10%
- Only rash/skin disorders (=8%) had an incidence of >5%
- Rigor/Chills and Lung infections were 5% each with 8 occurrences
- Nausea and vomiting were non-serious with 3.8% and 2.6%
- Oral mucositis incidence was 2.6% with only 1 grade-3 incidence
- Unspecified infections- 4 (2 grade-2 and 2 grade-3)
- UTI- 2 grade-2
- Febrile Neutropenia- 1 grade-3
- Allergic reactions and hives with itching- 2 and 1 grade-3
- Deaths-2
  - 1 in C1 related to leukemia
  - 1 after C11 of unknown cause

Discussion

- Landscape of T-PLL treatment is limited
- Clinical real-world data and trials are limited
- Current knowledge of the treatment is limited from studies of the tertiary care centers
- Chemo-resistant leukemia especially with conventional cytotoxic drugs
  - Drugs or regimes that have been investigated- pentostatin, nelarabine, CHOP, Bendamustine- median OS around 10%- very limited to no CR
  - CIBMTR 30% 4-year OS
- Alemtuzumab prolongs OS- 10-48 months
  - Resposne rate 70%

- Itacitinib- specific JAK1 inhibitor expected to have activity in
  - activating JAK1 mutations
  - activating IL2GR mutations
  - potentially JAK3 mutations by function of its heterodimerization with JAK1
- Consolidation or maintenance therapy is not admirably adapted into practice and is often not stressed in the studies
- Our study allowed the use of Itacitinib as maintenance for up to eight cycles and with the permission to extend beyond based on the clinical judgment
- All CR had MRD negative
- 2 of 3 transplanted patients survive beyond 44 months which reinforces the utility of SCT in T-PLL upfront setting

Conclusion

- Itacitinib + Alemtuzumab combination is a safe option without any new concerning AE.
- The combination can be studied in prospective clinical trials.
- The maintenance Itacitinib beyond best response should be explored.

THANK YOU