



Promising Safety and Efficacy Results from an Ongoing Phase 1/2 Study of Pembrolizumab in Combination with Blinatumomab in Patients (pts) with Relapsed or Refractory (R/R) Acute Lymphoblastic Leukemia (ALL)

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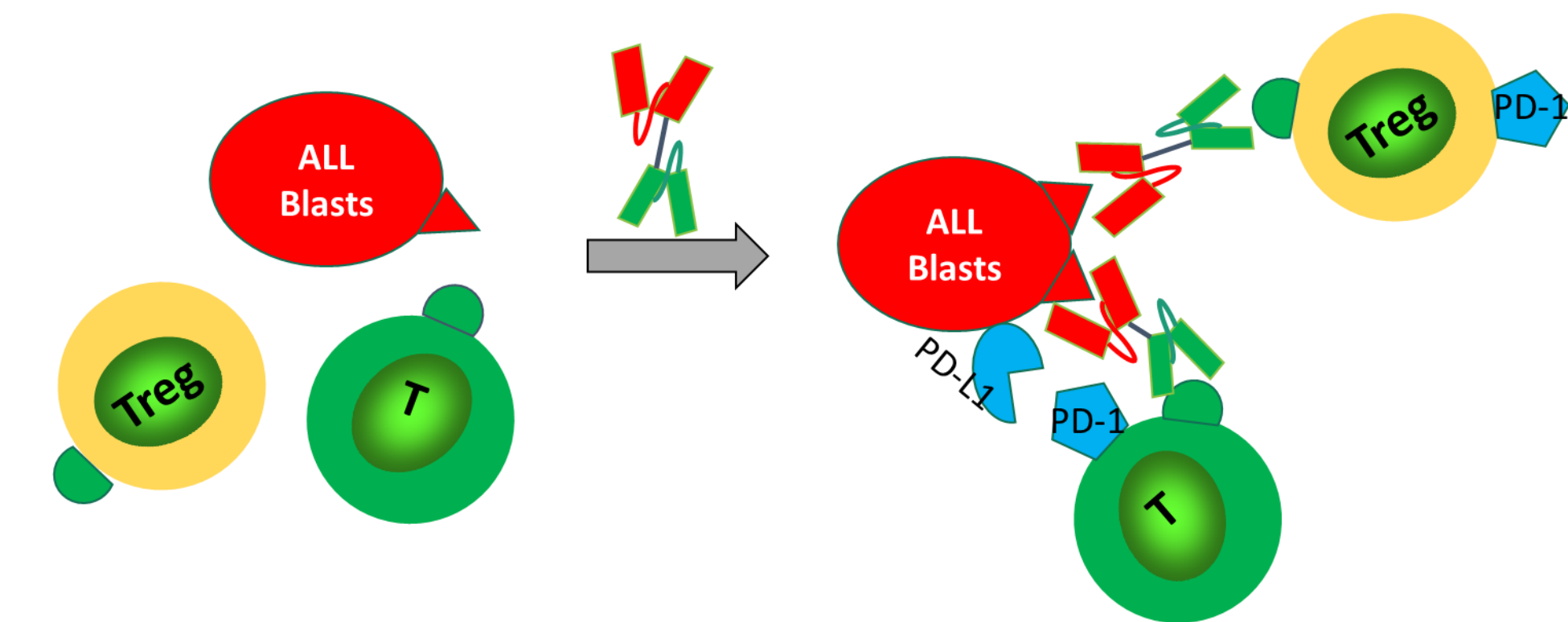
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Background

- Blinatumomab, a bispecific anti-CD19/CD3 antibody construct, has demonstrated single agent anti-leukemic activity with 42% CR/CRh in R/R B-ALL.
- Upregulation of Immune checkpoint inhibitory molecules has been shown to confer resistance to blinatumomab.
- Blocking PD-1/PD-L1/L2 pathway using anti-PD-1 antibodies has translated into overall survival benefit in patients with advanced melanoma, NSCLC and other solid and now hematologic malignancies.
- This pathway has been shown to directly regulate the development, maintenance, and function of regulatory T cells (Tregs), in addition to cytolytic T cells.
- R/R ALL patients who were refractory to blinatumomab had higher numbers of Tregs as compared to responders¹.
- Regulatory T cells incubated with blinatumomab and primary ALL blasts upregulated PD-1¹.
- Upregulation of PD-L1 on ALL blasts was reported to be one of the resistance mechanisms in patients treated with blinatumomab².

Hypothesis:

- Pembrolizumab can be safely administered together with blinatumomab.
- This combination will augment the therapeutic efficacy of blinatumomab in the treatment of patients with R/R ALL.



Objectives

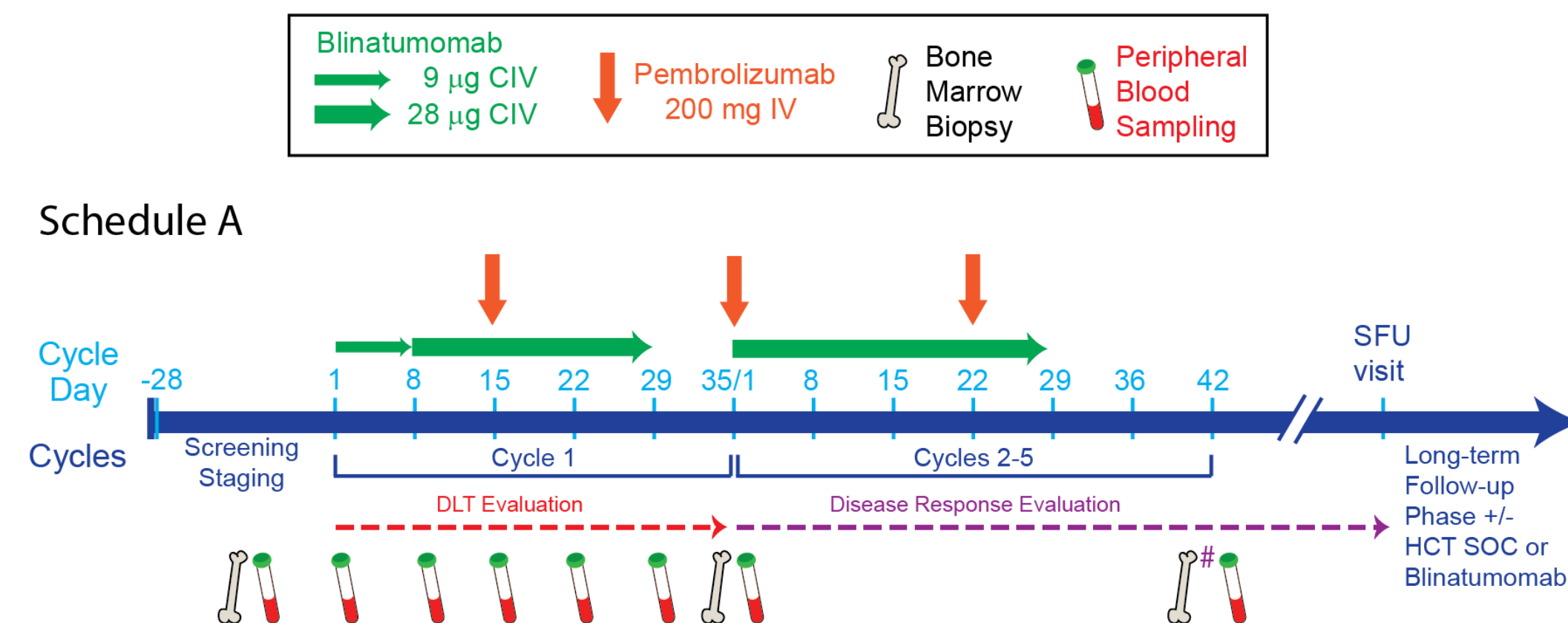
In adult patients with relapsed/refractory ALL:

Phase 1

- Assess the safety and tolerability of combination immunotherapy with blinatumomab and pembrolizumab by evaluation of toxicities including: type, frequency, severity, attribution, time course and duration.

- Determine the recommended phase 2 schedule of combination immunotherapy with pembrolizumab and blinatumomab.

Schema, Eligibility and Methods



- This study is being conducted as a single center, open-label, phase 1/2 clinical trial (NCT03512405) .

- Key eligibility: Patients ≥18 years old (yo); ECOG <1; r/r CD19+ R/R B-ALL, adequate organ function; no uncontrolled infection; no active CNS involvement; no prior allogeneic transplant; no prior PD-1/PD-L1 or blinatumomab use.

Phase 1:

- The phase 1 portion of the trial implemented traditional '3+3 rules' for enrollment with schedule 'reduction' (from Schedule A to Schedule B), or expansion of a cohort on the basis of the occurrence of dose limiting toxicities (DLTs) during cycle 1.

Schedule*	Cycle Length	Pembrolizumab: 200mg	Blinatumomab: 28 µg/day† CIV
A (starting schedule)	35 days cycle 1, 42 days cycles 2–5	cycle 1*: day 15 cycles 2-5: day 1 and 22	cycles 1-5: days 1 to 28
B*	42 days all cycles	cycle 1: day 22 cycles 2-5: day 1 and 22	cycles 1-5: days 1 to 28

- Depending on schedule assignment, the first cycle was either 35 days (Schedule A) or 42 days (Schedule B).

- After Cycle 1, patients were treated with planned 42-day treatment cycles until disease relapse, progression, unacceptable toxicity, or other criteria for removal from study treatment are satisfied.

- Patients underwent response evaluation using the NCCN ALL response criteria.

- The schedule that produced ≤1/6 DLTs in cycle 1 (Schedule A) was the maximum tolerated schedule/ recommended phase 2 dose. No patients were treated on Schedule B.

Results: Patients and Safety

- As of July 16, 2021, 7 pts were enrolled to phase 1 Schedule A with one unevaluable.
- Six treated and evaluable pts received a median of 1 (1-5) cycle of combination treatment.
- At baseline, the median age was 51 yo (29-74) with median 2 (1-2) prior lines of regimens, and median 76.5% (10-80) BM blasts.
- Two pts had extramedullary disease.
- In cycle 1, all 6-pts experienced grade (gr) 1-2 cytokine release syndrome/ infusion related reaction which were all reversible.
- Neurologic toxicities were all reversible with only 1 ≥ gr3 AE. All-non-hematologic gr3 toxicities, were reversible.
- No dose limiting toxicity, ≥ gr4 non-hematologic toxicity, or treatment related deaths were seen.

CTCAE 5.0 Scale Worst Grade Adverse Events in Cycle 1 Attributable to Pembrolizumab/Blinatumomab		Grade			
		Grade 1 N	Grade 2 N	Grade 3 N	Grade 4 N
Category	Adverse Events				
Blood and lymphatic system disorders	Anemia	0	0	3	0
	Febrile neutropenia	0	0	2	0
	Lymph node pain	1	0	0	0
	Sinus tachycardia	4	0	0	0
Cardiac disorders	Abdominal pain	1	0	0	0
	Diarrhea	1	1	0	0
	Nausea	1	2	0	0
	Vomiting	1	0	0	0
Gastrointestinal disorders	Chills	0	3	0	0
	Fatigue	0	2	1	0
	Fever	0	3	0	0
	Generalized edema	0	1	0	0
General disorders and administration site conditions	Malaise	1	0	0	0
	Pain	1	0	2	0
	Cytokine release syndrome	4	1	0	0
	Infusion related reaction	0	1	0	0
Immune system disorders	Alkaline phosphatase increased	1	0	0	0
	Aspartate aminotransferase increased	1	0	0	0
	Blood bilirubin increased	1	0	0	0
	Blood lactate dehydrogenase increased	1	0	0	0
Injury, poisoning and procedural complications	Lymphocyte count decreased	0	1	2	1
	Neutrophil count decreased	2	0	2	1
	Platelet count decreased	0	0	0	3
	Weight loss	0	2	0	0
Investigations	White blood cell decreased	0	2	0	4
	Hypocalcemia	2	1	0	0
	Hypokalemia	0	1	0	0
	Hypomagnesemia	1	1	0	0
Metabolism and nutrition disorders	Hyponatremia	1	0	0	0
	Hypophosphatemia	0	2	0	0
	Bone pain	0	1	0	0
	Myalgia	1	0	0	0
Musculoskeletal and connective tissue disorders	Neck pain	1	0	0	0
	Pain in extremity	2	0	0	0
	Generalized muscle weakness	0	2	0	0
	Dizziness	1	0	0	0
Nervous system disorders	Headache	0	3	1	0
	Lethargy	1	0	1	0
	Presyncope	0	1	0	0
	Tremor	2	0	0	0
Psychiatric disorders	Forgetfulness	1	0	0	0
	illegible handwriting	1	0	0	0
	Confusion	3	0	0	0
	Hyperhidrosis	0	1	0	0
Skin and subcutaneous tissue disorders	Pruritus	0	1	0	0
	Rash maculo-papular	2	0	0	0
	Flushing	1	0	0	0
	Hematoma	1	0	0	0
Vascular disorders	Hypertension	0	1	0	0
	Hypotension	0	1	0	0

Results: Response

- Median follow-up of 12.5 (3-20) months
- Five of 6 evaluable pts (83%) achieved MRD negative CR after a median of 1 (1-2) cycles.
- Five of 6 pts went off combination treatment prior to cycle 5: 1 pt (#2) after cycle 1 due to persistent disease and 4 pts (#1, 3, 4 and 7) in CR after day 1 cycle 2 pembrolizumab treatment, continuing on single agent blinatumomab prior to alloHCT, all engrafted.

Patient #	ELN Risk Level	# of Prior Tx	Prior Tx	Base-line Blast Count	Total # of cycles	Best Response (cycle)	MRD status	Transplant post tx yes/no (month)	Survival Status (A – Alive E – Expired) (months)
1	Poor Risk	1	1 cycle of Daunorubicin, Vincristine, Prednisone	80%	2	CR (1)	MRD-	Yes (3)	A (20)
2	Poor Risk	2	8 cycles – Dauno, Vincristine, Asparaginase, Cytosan, Methotrexate 2 cycles – Methotrexate and Vincristine	48%	1	Refractory Disease (1)	N/A	No	E (3)
3	n/a	2	Hyper- CVAD	10%	2	CR (1)	MRD-	Yes (3)	A (19)
4	n/a	1	8 cycles of Hyper CVAD plus Dasatinib	80%	2	CR (2)	MRD-	Yes (3)	E (10)
5	Poor Risk	2	8 cycles of Hyper CVAD POMP	74%	6	CR (1)	MRD-	No	A (15)
7	Un-class-ifiable	2	1 Cycle – Tx in Guatemala protocol HOP0612	79%	2	CR (1)	MRD-	Yes (3)	A (7)

Conclusions

- The combination of pembrolizumab and blinatumomab in phase 1 of this study in pts with B-ALL was deemed safe with manageable side effect profile and encouraging anti-leukemic activity.

- The RP2D was identified (Schedule A).

- The study is now open for phase 2 with the primary objective of overall response rate.

References

1. Topp, M.S., et al., Lancet Oncol, 2015. 16(1): p. 57-66.
2. Kohnke, T., et al., Journal of Hematology & Oncology, 2015. 8:111-115.

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