A Pilot Trial of Lirilumab with or without Azacytidine (AZA) for Patients with Myelodysplastic Syndrome

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Abstract

BACKGROUND: Experimental and clinical data suggest that enhancement of natural killer (NK) cell activity by blocking interactions between killer immunoglobulin-like receptors (KIR) and HLA molecules improve outcomes in myeloid malignancies. Lirilumab is a human IgG4 monoclonal antibody that blocks KIR/HLA-C interaction and augments NK cell activity. We designed a pilot study to evaluate the safety and efficacy of lirilumab as a single agent and in combination with azacytidine, in patients with myelodysplastic syndrome (MDS).

METHODS: Adult patients with MDS of any risk or chronic myelomonocytic leukemia who had not received prior therapy with a hypomethylating agent, adequate performance status (ECOG ≤ 2) and organ function were included. Lower-risk MDS patients (low and intermediate-1 by IPSS) were given lirilumab at the dose of 3 mg/kg in every 4 weeks. Higher-risk MDS patients received azacytidine (AZA) at the dose of 75 mg/m^2 on days 1-7 in combination with lirilumab 3 mg/kg on day 7 of 28-day cycle. Responses were evaluated on day 28 of course 1 and afterwards every 3 months or at any time with suspicion of progression or potential achievement of clinical response. Response assessment was performed using IWG-2006 criteria.

RESULTS: A total of 10 patients including 8 with higher and 2 with lower-risk disease were enrolled. The median age was 70 years (range, 50-84) and 40% of patients had complex cytogenetics. All patients had baseline next generation sequencing and frequently identified mutations included TP53 (n=5), TET2 (n=3) and NRAS (n=2). The median follow up was 9.5 months (range, 5-21 months) and patients received a median of 4 (range, 2-13) and 9 (range, 5-14) cycles of treatment with AZA plus lirilumab and single agent lirilumab, respectively. Two patients achieved complete remission (CR), 5 marrow CR and 3 had stable disease. Two achieved cytogenetic CR (40%) and 4 (40%) had hematologic improvement. The median EFS for the entire cohort was 8 months (95%CI, 4 months to not reached), and the median OS has not yet been reached. At 1 year 70% (n=6, 75% in the combination arm; n=1, 50% in the single agent arm) of the patients were alive. Eight patients discontinued the study due to disease progression (n=4), stem cell transplantation (n=3) and toxicities (myocarditis, non-therapy related, n=1). Five patients (n=4, 50% in the combination treatment arm; n=1, 50% in the single agent treatment arm) experienced a total of 8 episodes of grade ≥3 AEs attributable to study drug, with the most frequent being infection or neutropenic fever (6 out of 8, 75%). None of the patients had grade IV AEs.

CONCLUSION: Lirilumab either as a single as well as in combination with AZA has clinical activity in patients with MDS. Further studies are needed to confirm our findings.

Background

- Natural killer (NK) cells are essential components of the innate immune system and play a critical role in host immunity against various malignancies
- NK cell function is governed by a balance between signals received from inhibitory receptors, notably the killer immunoglobulin-like receptors (KIRs) and activating receptors
- Blockage of KIR receptors with a fully human monoclonal antibody is known to enhance NK-mediated lysis of tumor cells [1]
- Lirilumab (IPH2102/BMS-986015) is a fully humanized IgG4 monoclonal antibody that is designed to block the interaction between KIR2DL1/L2/L3 inhibitory receptors and their ligands
- Blockade of KIRs by lirilumab may improve outcomes in patients with myelodysplastic syndrome

Objectives

- Primary Objective:
  - To determine the safety of lirilumab, as a single agent or in combination and with AZA, in patients with MDS
- Secondary Objectives:
  - Event-free survival
  - Overall survival
  - Response by IWG criteria [2]

Methods/Study Design

- Single Institution Phase I/II Study Design
- Patients were assigned to 2 cohorts based on their IPSS[3] risk evaluation
  - Lower Risk MDS cohort (Lower and Intermediate-1)
    - Lirilumab single agent 3mg/kg IV; Q4 weeks
  - Higher Risk MDS cohort (Intermediate-2 and High)
    - AZA 75 mg/m^2 days 1-7 with lirilumab 3mg/kg IV on D7; Q4 weeks

Eligibility

- Previously untreated MDS of any risk or CMML
- ECOG Performance Status 0-2
- Adequate hepatic and renal function
- New York Heart Association heart failure class III/IV [4], patients with uncontrolled infection and autoimmune diseases excluded

Response Criteria

MDS

- Response by IWG criteria[2]

Overall Survival

- From start of treatment to last follow-up or death at any time; analysis performed using Kaplan-Meier method according to intention-to-treat principle

Event-free Survival

- From start of treatment to the date of lack of response, loss of response, transformation to AML, or death; analysis performed using Kaplan-Meier method according to intention-to-treat principle

Table 1: Patient Characteristics (n=10)

Characteristic	All patients N=10	Azacytidine + Lirilumab N=8	Lirilumab N=2
Age, in years, median (range)	70 (50-84)	70 (50-84)	74 (71-77)
Males, n(%)	7 (70)	6 (75)	1 (50)
ECOG performance status			
0	5 (50)	4 (50)	1 (50)
1	4 (40)	3 (38)	1 (50)
2	1 (10)	1 (12)	
IPSS risk group			
Intermediate-1	2 (20)	0	2 (100)
Intermediate-2	7 (70)	7 (88)	0
High	1 (10)	1 (12)	0
Laboratory values, median (range)			
Hemoglobin, g/dL	9.1 (7-13)	9.2 (8-13)	7.9 (6.7-9)
WBC	2.6 (1.6-63)	2.6 (1.6-25)	32 (1.6-63)
ANC	2 (0.6-21)	2 (0.6-14)	10.7 (0.7-21)
Platelets	62 (7-237)	44 (7-237)	77 (71-83)
PB blast %	0 (0-13)	0 (0-13)	0
BM blast %	11 (1-19)	13 (2-19)	4 (1-7)
LDH, IU/ml	707 (311-1766)	707 (311-1689)	1077 (389-1766)
Somatic mutation analysis, n(%)			
TET2	3 (30)	1 (12)	2 (100)
DNMT3A	1 (10)	1 (12)	0
ASXL1	1 (10)	0	1 (50)
JAK3	1 (10)	1 (12)	0
MPL	1 (10)	0	1 (50)
KRAS	1 (10)	1 (12)	0
NRAS	2 (20)	1 (12)	1 (50)
CBL	1 (10)	1 (12)	0
Tp53	5 (50)	4 (50)	1 (50)
SRSF2	1 (10)	1 (12)	0
STAG2	1 (10)	1 (12)	0
Cytogenetic classification, n(%)			
Good			
Normal	5 (50)	4 (50)	1 (50)
del 5q, del 20q	1 (10)	0	1 (50)
Poor			
Complex	4 (40)	4 (50)	0

Table 2: Overall Responses

Response	All patients N=10	Azacytidine + Lirilumab N=8	Lirilumab N=2
Number of treatment cycles, median (range)	4 (2-14)	4 (2-13)	9 (5-14)
Best Overall Response, n(%)			
CR	2 (20)	2 (25)	0
PR	0	0	0
mCR	5 (50)	4 (50)	1 (50)
SD	3 (30)	2 (25)	1 (50)
Cytogenetic response, n(%)			
Complete response	2/5 (40)	2/4 (50)	0/1 (0)
Partial response	0	0	0
Hematologic improvement, n(%)	4/10 (40)	4/8 (50)	0/2 (0)
HI-E	2/9 (22)	2/7 (29)	0/2 (0)
HI-P	3/8 (38)	3/6 (50)	0/2 (0)
HI-N	2/4 (50)	2/3 (70)	0/1 (0)

Abbreviations: CR=complete remission; mCR=marrow CR; PR=partial remission; SD=stable disease; HI-E=HI with erythroid response; HI-P=HI with platelet response; HI-N=HI with neutrophil response; WBC=white blood cells; ANC=absolute neutrophil count; PB=peripheral blood; BM=bone marrow

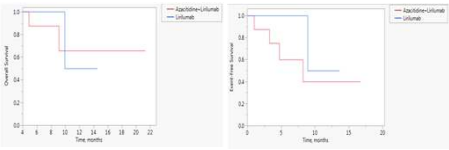
Table 3: Toxicities

Adverse Event	Grade 1-2, n (%)		Grade ≥3, n (%)	
	Azacytidine+ Lirilumab N=8	Lirilumab N=2	Azacytidine +Lirilumab N=8	Lirilumab N=2
Nausea	4 (50)	-	-	-
Constipation	4 (50)	-	-	-
Rash	3 (38)	-	1 (12)	-
Infusion reaction	2 (25)	-	-	-
Fatigue	1 (12)	-	-	-
Pruritis	1 (12)	-	-	-
Increased bilirubin	1 (12)	-	1 (12)	-
Infections	1 (12)	-	3 (38)	1 (12)

Results

- A total of 10 patients included (Table 1). Higher-risk MDS patients received a median of 4 cycles (range, 2-13 cycles) of treatment with lirilumab in combination with AZA, and lower-risk patients received a median of 9 cycles (range, 5-14 cycles) of single agent lirilumab.
- A total of 2 patients (20%) achieved CR (both are in combination arm), 5 patients (50%) had marrow CR (n=4, 50% and n=1, 50%; in combination and single arm, respectively) and 3 patients had stable disease (n=2, 25% and n=1, 50%; in combination and single arm, respectively (Table 2).
- Drug related AEs were reported in all patients in the higher-risk and in 1 patient in the lower-risk cohort. Five patients (n=4, 50% and n=1, 50%; in combination and single arm, respectively) experienced a total of 8 episodes of grade 3 AEs attributable to study drug with the most frequent being infection or neutropenic fever (6 out of 8, 75%) (Table 3).
- The median EFS for the entire cohort was 8 months (95%CI, 4 months to not reached), and the median OS has not yet been reached (Figure).

Figure: Overall and Event-Free Survival Curves



Conclusions

- This is the first report of efficacy and safety with the anti-KIR lirilumab in patients with MDS.
- Lirilumab is effective and well tolerated either as a single agent or in combination with AZA, in patients with MDS in the limited population studied.

References

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The authors have no relevant COI to disclose