Phase IB/II Study of Lirilumab in Combination with Azacytidine (AZA) in Patients (pts) with Relapsed Acute Myeloid Leukemia (AML)

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Abstract

Background: Inhibitory killer-cell immunoglobulin receptors (KIRs) negatively regulate NK cell-mediated killing of HLA class I-expressing tumors. Lack of KIR-HLA class I interactions has been associated with potent NK-mediated antitumor efficacy in AML patients in remission upon haploidentical stem cell transplantation (SCT) from KIR-mismatched donors (Ruggeri L et al., Science 2002). Blockade of KIR2DL1, 2 and 3 receptors induced augmented NK-cell mediated lysis of tumor cells (Romagne F et al., Blood 2009). Hypomethylating agents possess anti-leukemia activity and concomitantly alter immune regulation. Blockade of the KIR-receptors by lirilumab may improve response rates and abrogate immune-mediated resistance to hypomethylating agents.

Patients and Methods: Pts are eligible if they have AML and failed prior therapy (including prior therapy with a hypomethylating agent), have adequate performance status (ECOG ≤ 2), and organ function. AZA was given at the dosage of 75mg/m^2 on days 1-7; lirilumab was given on Day 8 at the dosage of 1 and 3 mg/kg in 2 consecutive cohorts of 6 pts each. Courses were repeated approximately every 4-5 weeks. No dose-limiting toxicities were observed and lirilumab 3mg/kg was established as the recommended phase 2-dose (RP2D) in combination with AZA. 9 additional pts have been treated at the RP2D. Responses were evaluated at the end of 3 courses of therapy.

Results: To date, 21 pts (11 de novo, 10 secondary AML), median age 60 years (range, 33 – 89), 48% with adverse cytogenetics, median prior therapies of 3 (range, 1-8), and prior allogeneic SCT in 6 (28%) have been enrolled. All 21 pts had baseline next generation sequencing for 28-genes and frequently identified mutations included *TP53* (n=6), *TET2* (N=6), *ASXL1* (n=5), *RUNX1* (n=5), *EZH2* (n=3), *DNMT3A* (N=2), and *CEBPA* (n=2). 12 pts are ≥ 3 months into therapy and evaluable for response at this time: 1 achieved complete remission (CR), 1 achieved complete remission with insufficient count recovery (CRi), 2 (17%) had ≥50% bone marrow (BM) blast reduction, 2 (17%) had hematologic improvement (HI) > 6 months, and 6 (50%) had progressed. Nine pts were too early for response assessment. The 4- and 8-week mortality is 0 and 5%, respectively. The median duration of response, overall survival (OS) and event-free survival for the 12 evaluable pts were 2.5 months (range, 1.1 – 3.0) 4.4 months and 3.2 months, respectively.
Grade 3/4 toxicities irrespective of causality were similar to those seen with AZA based therapies in salvage patients included 15 episodes of neutropenic infections, 6 pneumonia, 1 UTI, 1 skin infection, 2 abdominal pain, and 1 mucositis. Immune mediated toxicities were observed in 3 (14%) pts (1 pneumonitis Grade 3, 1 colitis Grade 2, 1 infusion reaction Grade 2), respectively. The immune mediated toxicities responded rapidly to steroids and all 3 pts could be rechallenged safely with lirilumab. Six pts were postSCT and no Grade 3/4 GVHD flares were noted. No pts have come off study due to toxicities and the azacytidine or lirilumab were not discontinued in any pts due to toxicities.
Multicolor flow-cytometry studies and Mass-cytometry (CyTOF) studies are being conducted by the Immunotherapy Platform on baseline and on-treatment BM aspirate (end of cycle 1, 2, 4, 8) and peripheral blood to assess NK- and T-cell costimulatory markers.

Conclusion: Full doses of AZA and lirilumab were well tolerated in heavily pretreated pts with relapsed AML with poor risk features, including pts with post-allogeneic SCT relapse. The efficacy data are still preliminary. AZA with lirilumab is being investigated in earlier salvage in AML and frontline and salvage settings in myelodysplastic syndrome.

Background

- Inhibitory cell killer immunoglobulin receptors (KIRs) negatively regulate NK-cell mediated killing of HLA class I-expressing tumors
- Preventing KIR-HLA class I interactions by haploidentical SCT From KIR-mismatched donors increased donor-versus-recipient NK-cell alloreactivity. This was able to reduce leukemia relapse and graft rejection (Ruggeri L et al., Science 2002)
- Blockade of KIR receptors with a fully human monoclonal antibody is known to enhance NK-mediated lysis of tumor cells, including autologous AML cells (Romagne et al., Blood 2009)
- Lirilumab is a fully human monoclonal antibody designed to act as a checkpoint inhibitor by blocking interactions between KIRDL-1,-2,-3 inhibitory receptors and their ligands.
- Lirilumab is being evaluated in salvage AML, MDS and as a maintenance in high-risk AML.
- Blockade of the KIR-receptors by lirilumab may improve response rates and abrogate immune-mediated resistance to hypomethylating agents.

Objective

- Primary Objective:
  - IWG-criteria CR/CRi/PR/HI at 3 months
- Secondary Objectives:
  - Progression-free survival
  - Overall survival
  - Correlation of baseline T-cell subpopulations, NK-cell population, costim receptors and costim ligands to response and survival
  - Identify and manage immune mediated toxicities

Methods/Study Design

- Single institution, single arm, phase Ib/II trial
- AZA 75 mg/m^2 days 1-7 with lirilumab 1 mg/kg or 3mg/kg on Day 8 (+/-3 days).
- In the dose-finding phase 0 of 6 pts had a dose limiting toxicity at lirilumab 1mg/kg.
- The next 6 patients received lirilumab 3 mg/kg.
- No DLTs were noted and lirilumab 3mg/kg with AZAZ was established as recommended phase 2 dose (RP2D).
- 13 additional pts treated at the RP2D.
- Courses were repeated approximately every 4-6 weeks.
- 25 patients enrolled before Aug 1, 2016 are evaluable for response.

Eligibility

- R/R AML (Any salvage)
- HR-MDS or HR-CMML to AML
- Therapy for prior MDS before progression to AML acceptable
- Adequate hepatic and renal function
- No uncontrolled infection
- Patients with uncontrolled infection, autoimmune diseases, and prednisone > 20 mg excluded

Statistics

- The study is continuously monitored for efficacy and toxicity
- Toxicity will be evaluated every 5 patients enrolled and the study will stop if excessive drug-related grade 3/4 toxicity (>30%) is highly probable (i.e., probability >97.5%) for the combination treatment, per predefined operating characteristics.
- The study will be continuously monitored for futility every 5-10 patients per predefined operating characteristics. The study will cease if the data suggest that it is unlikely (i.e., probability < 2.5%) that ORR rate of the combination treatment is greater than the ORR rate of standard treatment by 15.0%

Table 1: Dosing Schema

Dose level	5-azacytidine (mg/m2/d, Days 1-7)	Lirilumab (mg/kg, day 1 and 14)
-4	25	0.3
-3	50	0.3
-2	75	1.
-1	**75**	**1.0 (starting dose)**
0	**75**	**3.0 (target dose)**

Table 2: Patient Characteristics (n=25)

Characteristics	N (%) / Median [range]
Age, year	64 [30-89]
>60 years	14 (56)
Diagnosis	
AML de novo	19 (64)
Secondary AML	9 (36)
Median Prior Rx	3 [1-8]
Prior Therapy	
HMA-based	14 (56)
HiDAC-based	16 (64)
Int-dose AraC based	9 (36)
Molecular Rx	9 (36)
Prior Stem Cell Rx	7 28)
BM blast %	58 [17-95]
WBC (x 10^9/L)	1.9 [0.3-19]
Platelets (x10^9/L)	21 [2-137]
Cytogenetics	
Diploid	8 (32)
Miscellaneous	2 (8)
Adverse (-5/-7/complex)	13 (52)
Insufficient metaphase	2 (8)
Molecular (n=28)	
DNMT3A	1
ASXL1	9
CEBPA	1
RAS	4
TP53	7
IDH2	1
TET2	4
RUNX1	3
Median Follow-up, months	5.1 [3.1 -9.4+]

Table 3: Overall Responses (n=25)

Best Response (IWG)/Outcome	N (%) / Med [Range]
ORR	5 (20)
CR/CRp	2 (8)
HI	3 (12)
NR	14 (56)
8-week mortality	3 (12)
Median cycles to response	3 [1-11]

Table 4: Grade 3/4 toxicities irrespective of causality (n=25)

Grade 3/4 Toxicity	N (%)
Neutropenic infection	15 (60)
Pneumonia	6 (24)
Abdominal pain	2 (8)
Skin infection	1
UTI	1
Mucositis	1

Immune Mediated Toxicities

- Immune toxicities in 4 (16%) patients: Gr 2 (n=1) and Gr 3 colitis (n=1), 1 pneumonitis Gr 3, 1 skin rash Gr 3
- Immune toxicities responded rapidly to steroids
- All 4 patients could be rechallenged
- One patient came off therapy due to Gr 3 colitis

Fig 1: PFS and OS Aza+liri (n=25)

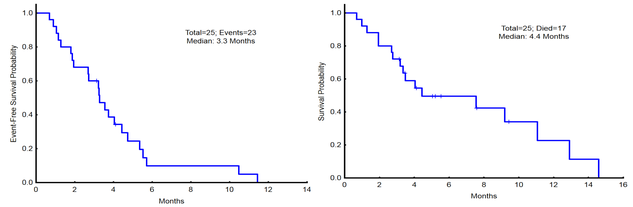


Fig 2: Response duration (n=5 responders)

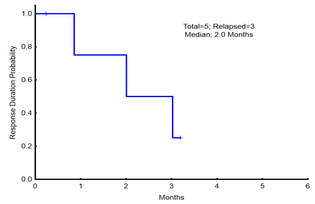
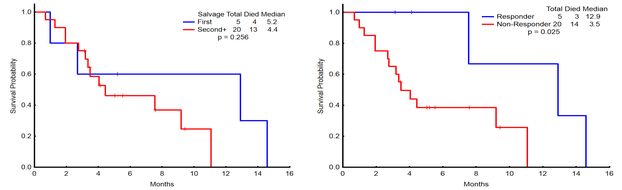


Fig 3: Median OS by salvage status and response



Conclusions

- Full dose Aza and full dose lirilumab well tolerated in heavily pretreated AML patients with high-risk features.
- Immune mediated toxicities occur; may be adequately managed with early recognition and steroids.
- The efficacy and immune correlative data is being evaluated
- Lirilumab is also being evaluated as a maintenance in high-risk AML and in frontline and salvage studies in MDS.

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The authors have no relevant COI to disclose