Lead-in Dose Optimization to Mitigate Cytokine Release Syndrome in AML and MDS Patients Treated with Flotetuzumab, a CD123 x CD3 Bispecific DART® Molecule for T-cell Redirected Therapy

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Background

- Flotetuzumab (MGD006/S80880): Novel T-cell redirecting CD123 x CD3 bispecific DART protein
- Cytokine secretion with ensuing potential for cytokine release syndrome (CRS) is inherent in T-cell activation and is observed with T-cell redirecting therapies
- Two flotetuzumab lead-in dose (LID) strategies, in conjunction with early intervention with tocilizumab, were assessed for their ability to mitigate CRS

Methods

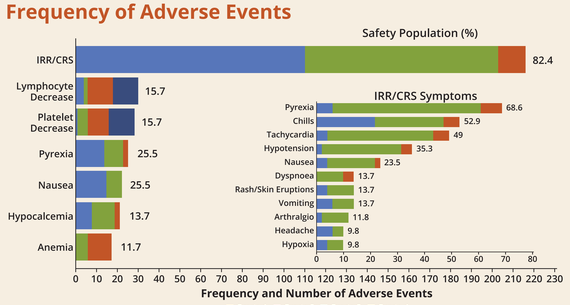
- Phase 1 study of patients with relapsed/refractory acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)
- LID-1 schema: Flotetuzumab administered at 100 ng/kg/day (d) for 4d followed by 3d pause and resumption at 300 or 500 ng/kg/d starting on Day 8 (one-step LID)
- LID-2 schema: Flotetuzumab administered at 30 ng/kg/d for 3d, 100 ng/kg/d for 4d and 300 or 500 ng/kg/d on Day 8 (two-step LID)

Lead-in Dose Schema (flotetuzumab ng/kg/d)

- IL-2, IL-6, IL-8, IL-10, TNF-α, INF-γ, and GM-CSF were measured and CRS severity graded according to Lee DW, et al. Blood, 2014
- Peak cytokine values during first reported CRS events, occurring within 10 days of start of first dose, were evaluated
- Median peak cytokine levels were compared between patients with and without 2-step LID
- Other potential CRS determinants evaluated

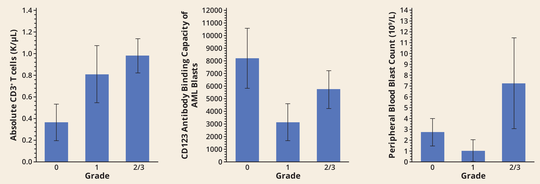
Results

Frequency of Adverse Events



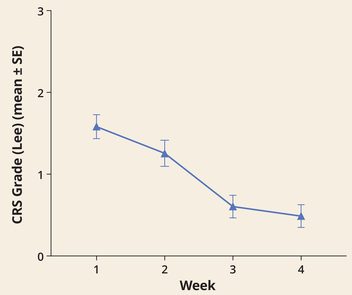
- Infusion-related reactions (IRR)/CRS occurred in 42/51 (82%) of patients and were generally manageable and reversible (Data cutoff 01 Nov 2017)
- Most events (36/42; 86%) Grade 1 and 2
- Most common symptoms: pyrexia (69%), chills (53%), tachycardia (49%) and hypotension (35%)

Determinants of IRR/CRS



- Preliminary data show relationship between baseline circulating T-cell number and maximum CRS grade during Week 1
  - Higher grade of CRS (≥2) in Week 1 associated with higher baseline levels of circulating T-cells
- Other variables (tumor burden, monocyte count, CD123 expression) did not trend with CRS grade (data not shown)

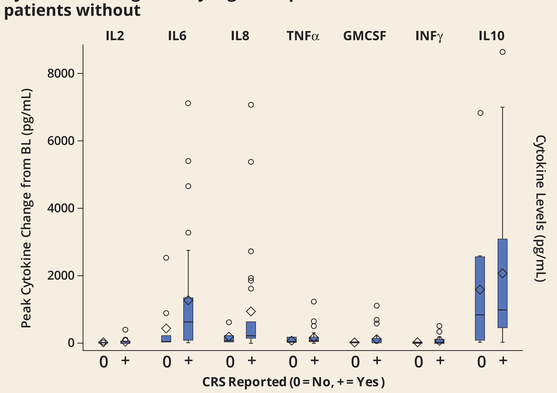
Mean Grade (± SE) of IRR/CRS Events by Week During Cycle 1



- CRS severity and incidence decreased upon repeated dosing of flotetuzumab during Cycle 1
- Among 36 patients with complete cytokine data, 27 reported at least one IRR/CRS event; 56% (15/27) experienced CRS within 2 days of start of flotetuzumab; and 44% (12/27) within 3–10 days (22% Gr 1, 44% Gr2, and 8% Gr 3)

Correlation Between Cytokine Levels and CRS

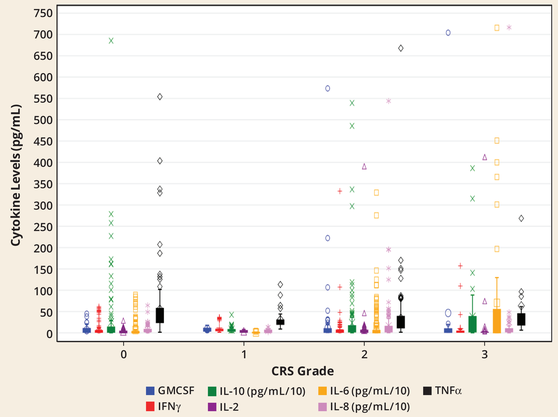
Cytokine levels generally higher in patients with CRS than in patients without



Median IL-6, 611.85 vs. 67.9 pg/mL; IL-8, 206.83, vs. 155.43 pg/mL; IL-10, 989.63, vs. 839.44 pg/mL

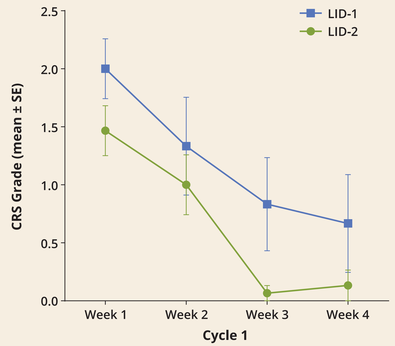
Correlation Between Cytokine Levels and CRS Grade

Cytokine levels increase with increasing CRS grade



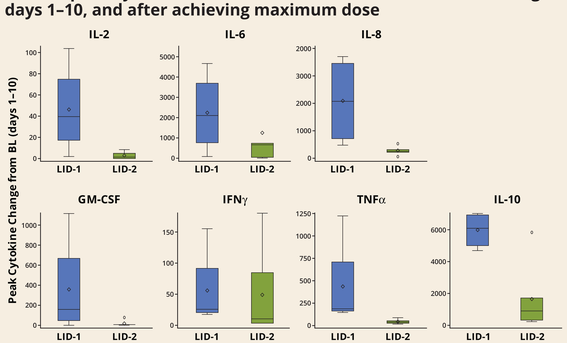
2-step Lead-in Dose Reduced Severity of CRS and Overall Cytokine Levels

Institution of two-step LID in Week 1 decreased CRS severity by mean 0.54 grade during Cycle 1



Mean CRS grade Week 1: 1.16 vs. 2; Week 2: 1 vs. 1.33; Week 3: 0.67 vs. 0.83; Week 4: 0.13 vs 0.67 (LID-2 vs. LID-1, respectively).

Median peak cytokine levels observed with LID were lower during days 1–10, and after achieving maximum dose



- Anti-leukemic activity with flotetuzumab has been reported (ASH Oral Presentation # 637 Preliminary Results of a Phase 1 Study of Flotetuzumab, a CD123 x CD3 Bispecific DART Protein, in Patients with Relapsed/Refractory Acute Myeloid Leukemia and Myelodysplastic Syndrome; Monday, December 11, 2017, 10:30 AM)
- IRR/CRS did not correlate with anti-leukemic activity in this patient population

Conclusions

- Preliminary flotetuzumab data suggest that a patient's baseline circulating T-cell number may be a potential predictor of CRS
- Cytokine levels correlate with T-cell activity and CRS severity; CRS severity did not correlate with anti-leukemic activity
- Two-step LID showed effectiveness in limiting IRR/CRS events and circulating cytokines over one-step LID

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