Biomarkers and Management of Cytokine Release Syndrome in AML Patients Treated with Flotetuzumab, a CD123 x CD3 Bispecific DART® Molecule for T-cell Redirected Therapy

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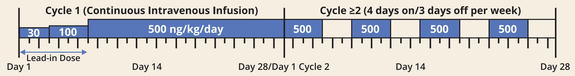
Background

- Flotetuzumab (MGD006/S80880): Novel CD123 x CD3 bispecific DART® protein being tested in a Phase 1/2 study in patients with relapsed/refractory acute myeloid leukemia (AML)
- As with all T-cell redirecting therapies, cytokine secretion is inherent in T-cell activation, with ensuing potential for cytokine release syndrome (CRS), an important side effect
- We have previously reported that multi-step lead-in dosing of flotetuzumab mitigates CRS severity[1]
- CRS diagnosis and treatment is guided by the occurrence of non-specific clinical signs, such as fever, chills, hypotension and tachycardia; therefore, identification of predictors of CRS will be useful for optimal patient management
- We report herein on potential biomarkers of CRS severity that may help guide CRS management

Methods

Dose and Dosing Schedules for Flotetuzumab (28-day cycles): Recommended Phase 2 Dose



- Incidence and severity of CRS were analyzed for correlation with cytokine levels and changes in bone marrow blasts
- CRS graded according to Lee *et al*., 2014
- Relation between immune cells (T-cell subsets, monocytes) with tumor burden, percent CD123+ AML blasts, and CD123 expression were interrogated as potential determinants of CRS
- Administration, dose, and frequency of IL-6 receptor antagonist tocilizumab were evaluated for their relationship with CRS severity, frequency, and cytokine levels

Results

Demographics

Characteristic	All Patients (n=31)
Age	
Mean ± SD	59.9 ± 15.24
Median (Range)	64.0 (29.0, 82.0)
Gender [n(%)]	
Female	15 (48.4)
AML Sub-classification	
Relapse*	9 (29.0%)
Failed 2 cycles of HMA	3 (9.7)
Refractory**	**19 (61.3%)**
AML Risk Stratification (ELN 2017)	
Adverse	**15 (48.4)**
Intermediate	8 (25.8)
Favorable	5 (16.1)
Unknown	3 (9.7)
# of Prior Lines of Therapy	
Mean ± SD	2.7 ± 1.90
Median (Range)	2.0 (1, 9)

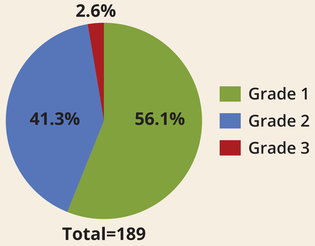
*Relapse includes progression after initial response to HMA.
**Refractory ≥2 induction attempts/CR with initial duration < 6 months/refractory ≥4 cycles of HMA.
Data cut-off Nov 1, 2018.

- 31 patients dosed; median age 64
- Most patients heavily pretreated with adverse cytogenetics (ELN 2017) and refractory to induction therapy; history of allogeneic stem cell transplant exclusionary

CRS Severity Predominantly Mild to Moderate

- 189 CRS events in 31 patients
- CRS events primarily mild-to moderate in grade (97.4% Grade 1–2)

CRS Grade by Event

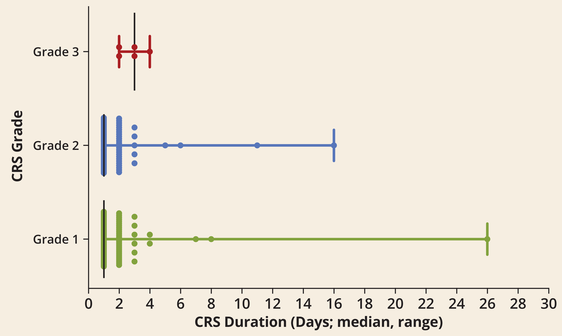


CRS Grade by Patient

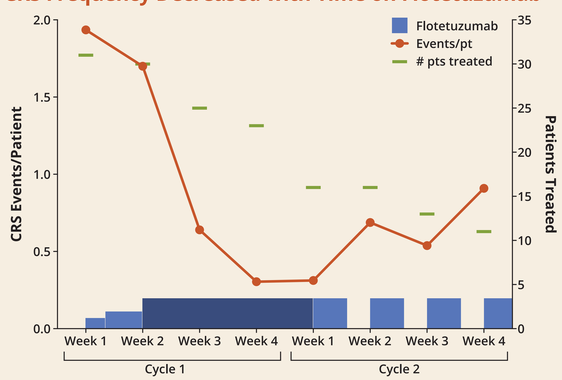
(n=31)	N (%)
Grade 1	8/31 (25.8%)
Grade 2	18/31 (58.1%)
Grade 3	4/31 (12.9%)

CRS Generally Limited to 1 Day

- Median overall CRS duration: 1 day (range 1–26)
- Median duration of CRS events with peak grade of 3: 3 days (range 2–3)

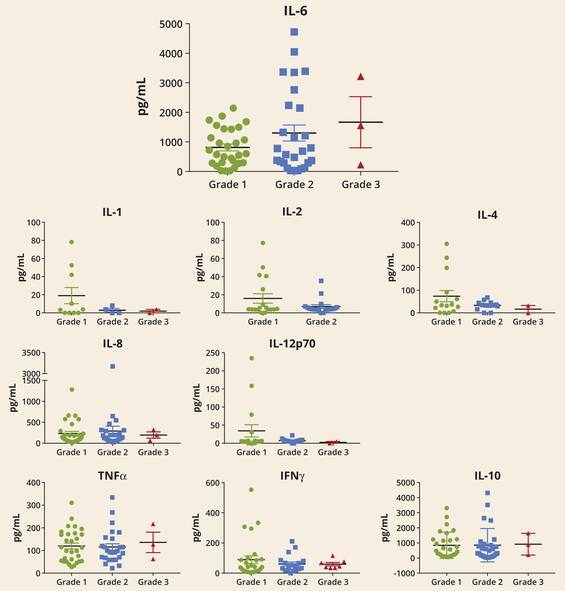


CRS Frequency Decreased with Time on Flotetuzumab



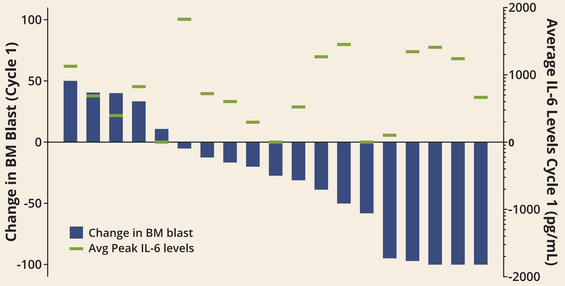
- 94.7% (179/189) of CRS events occurred Cycles 1 and 2
  - Most events (62.0%, 111/179) occurred within first week (Lead-in Dose) and during step up to 500 ng/kg/day in the 2nd week of Cycle 1
  - 12.8% of CRS events occurred in Weeks 3 and 4 of Cycle 1
  - In Cycle 2, 43/179 CRS events (24.0%) were reported, with an increase noted after dosing interruptions

Correlation of CRS Events and Peak Cytokine Levels



- IL-6 levels showed the strongest relationship with CRS severity, as previously reported[1].

IL-6 Levels Did Not Correlate with Flotetuzumab Anti-leukemic Activity



Companion presentation #764. December 3, 2018: 3:00 p.m.

Management of CRS Events

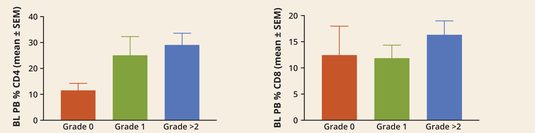
- Most CRS events were conservatively managed
- Aggressive early treatment with tocilizumab reduced CRS severity

Treatment	Grade 1		Grade 2		Grade 3	
	# Doses	# Patients	# Doses	# Patients	# Doses	# Patients
Tocilizumab	15	10	27	16	2	2
Vasopressors	0	0	3	2	0	0
Steroids	3	3	10	5	0	0
Oxygen	0	0	1	1	0	0

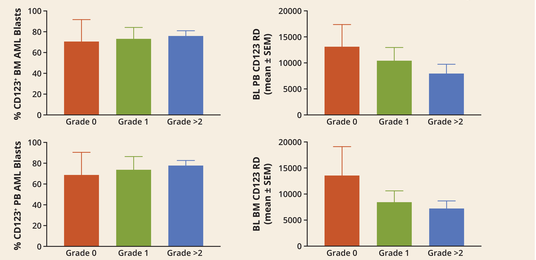
Twenty-one patients (70%) received at least one dose of tocilizumab (median 1 dose/pt; range 1–5 doses).
Eight patients (26.7%) required steroid for CRS management (median 2 doses/pt; range 1–2 doses).
Two patients (6.7%) received vasopressors (median 1.5 doses/pt; range 1–2).
One patient (3.3%) received oxygen for management of CRS.

Peak Levels of Circulating CD4 T Cells Correlate with CRS Severity

- CRS severity in days 1–8 (lead-in dose to max dose) in 40 patients treated at ≥500 ng/kg/day showed a relationship with baseline frequency of circulating CD4+ cells (Grade 0=6, Grade 1=11, ≥ Grade 2=23), while CD8+ cell frequency did not correlate with CRS severity

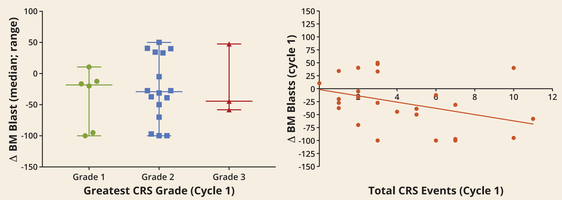


Disease Burden Does Not Correlate with CRS Severity



- Disease burden, % AML blasts, CD123 receptor density in bone marrow or peripheral blood did not show a relationship with CRS severity
- Other parameters tested such as monocyte levels and effector-to-target ratio in the peripheral blood did not correlate with CRS severity (not shown)

Relation of CRS Events and Anti-leukemic Activity



- CRS severity was not correlated with anti-leukemic activity
- Preliminary analysis shows potential relationship between # of CRS events and anti-leukemic activity

Conclusions

- The frequency of CD4+ cells at baseline may be a potential biomarker for identifying patients at risk of more severe CRS
- Early use of tocilizumab can effectively modify the activity of IL-6, a significant contributor to CRS, and ameliorate CRS severity
- CRS severity is associated with increased IL-6 levels. There is no relationship between average peak IL-6 levels and anti-leukemic activity. Furthermore, no link could be found between CRS severity and decrease in BM blasts. Therefore, targeting CRS severity and IL-6 levels does not influence the activity of flotetuzumab
- Early identification of patients at greater CRS risk together with multistep dosing[1] and early use of tocilizumab can ameliorate CRS with no impact on flotetuzumab anti-leukemic activity
- Investigation of lead-in dose strategy ongoing

Reference

1. Jacobs *et al*. ASH 2017, abstract #3856.

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