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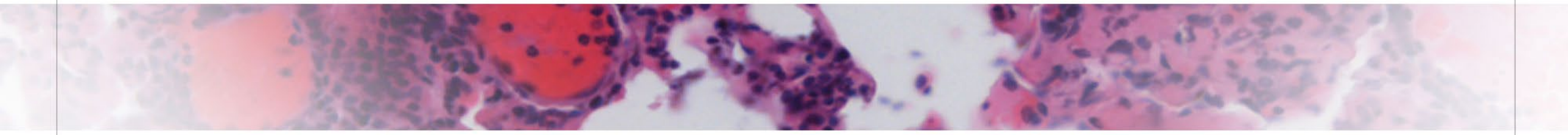

Prophylactic Ruxolitinib for Cytokine Release Syndrome (CRS) in Relapse/Refractory (R/R) AML Patients Treated with Flotetuzumab

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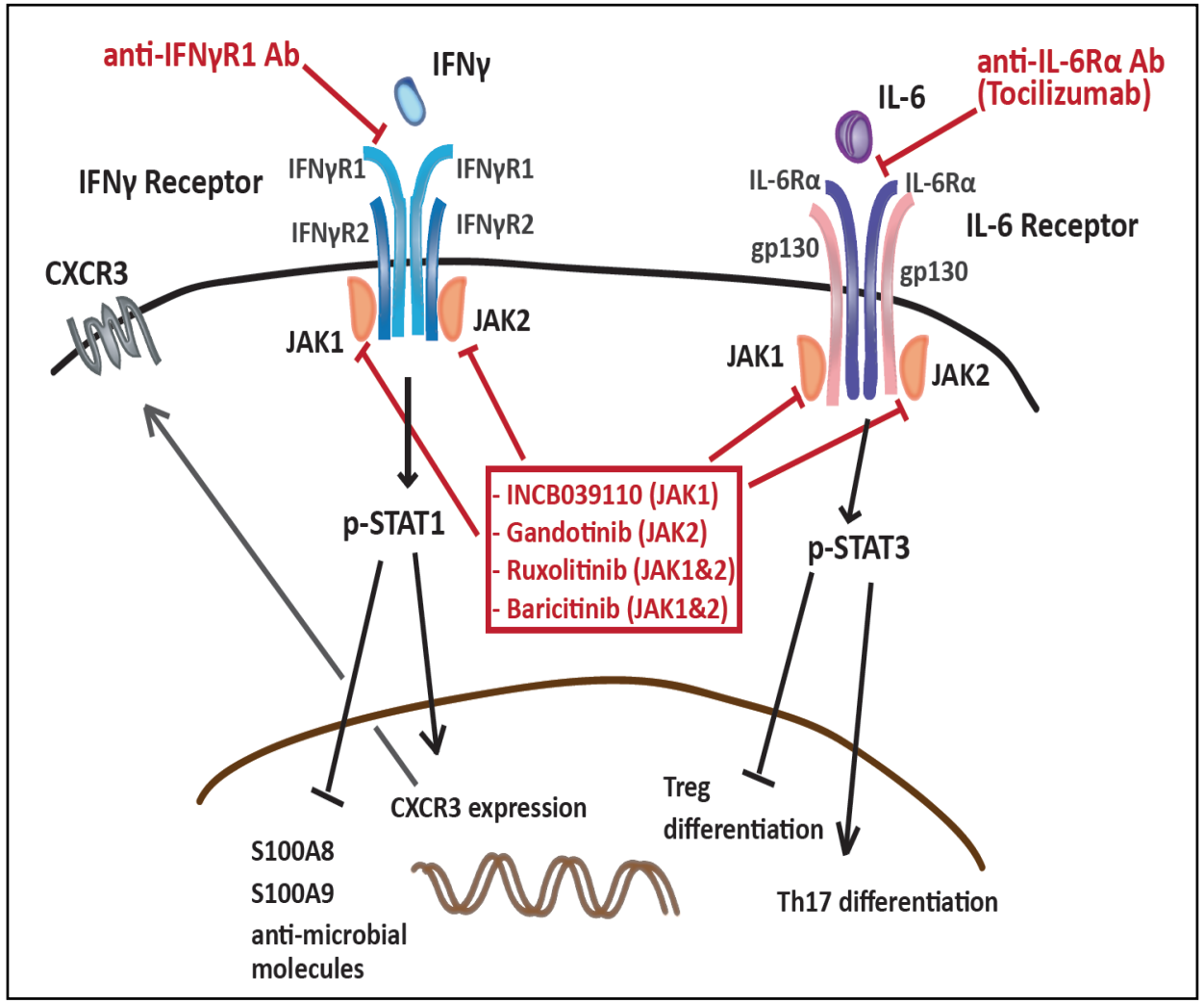
Background

- CRS is a potentially life-threatening toxicity observed following T cell-redirecting therapies and limits the therapeutic window of novel immunotherapeutic agents.

- Disruption of cytokine signaling via Janus kinase (JAK) pathway interference may blocking CRS by interfering with cytokines including IFNγ and IL6

We hypothesized that RUX may reduce the frequency and severity of CRS in R/R AML patients undergoing treatment with flotetuzumab (FLZ), aCD123 x CD3 bispecific DART® molecule.

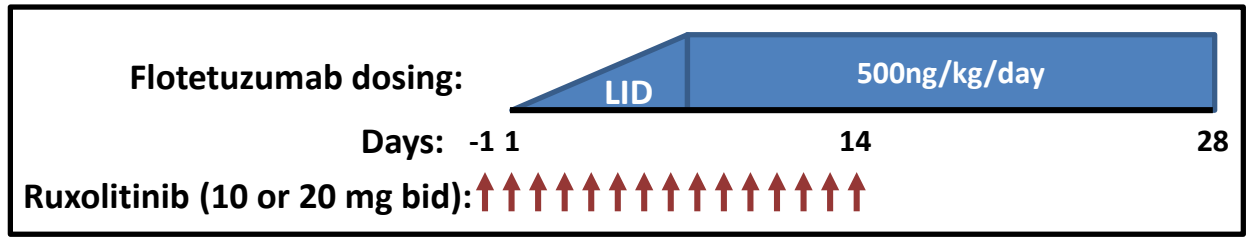


Patients and Methods

Characteristic		Non-RUX (n=21)	RUX (n=10)
Age	Median (Range)	58 (28-74)	65 (40-82)
Gender [n(%)]	Female	8 (38.1)	2 (20.0)
AML Status at Study Entry	Primary Induction Failure	12 (57.1)	6 (60.0)
	Early Relapse (CR1 < 6 months)	9 (42.8)	2 (20.0)
	Other	0	2 (20.0)
AML Risk Stratification (ELN 2017)	Adverse	15 (71.4)	8 (80.0)
	Intermediate	6 (28.6)	2 (20.0)
	Favorable	0	0
Secondary AML		11 (52.4)	1 (10.0)
Number of Prior Lines of Therapy	Median (Range)	2.0 (1.0, 3.0)	2.0 (1.0, 5.0)
Baseline BM blasts	Mean ± SD	39.1 ± 22.5	24.0 ± 21.8
	Median (Range)	40 (10.0, 84.0)	15.0 (5.0, 72.0)

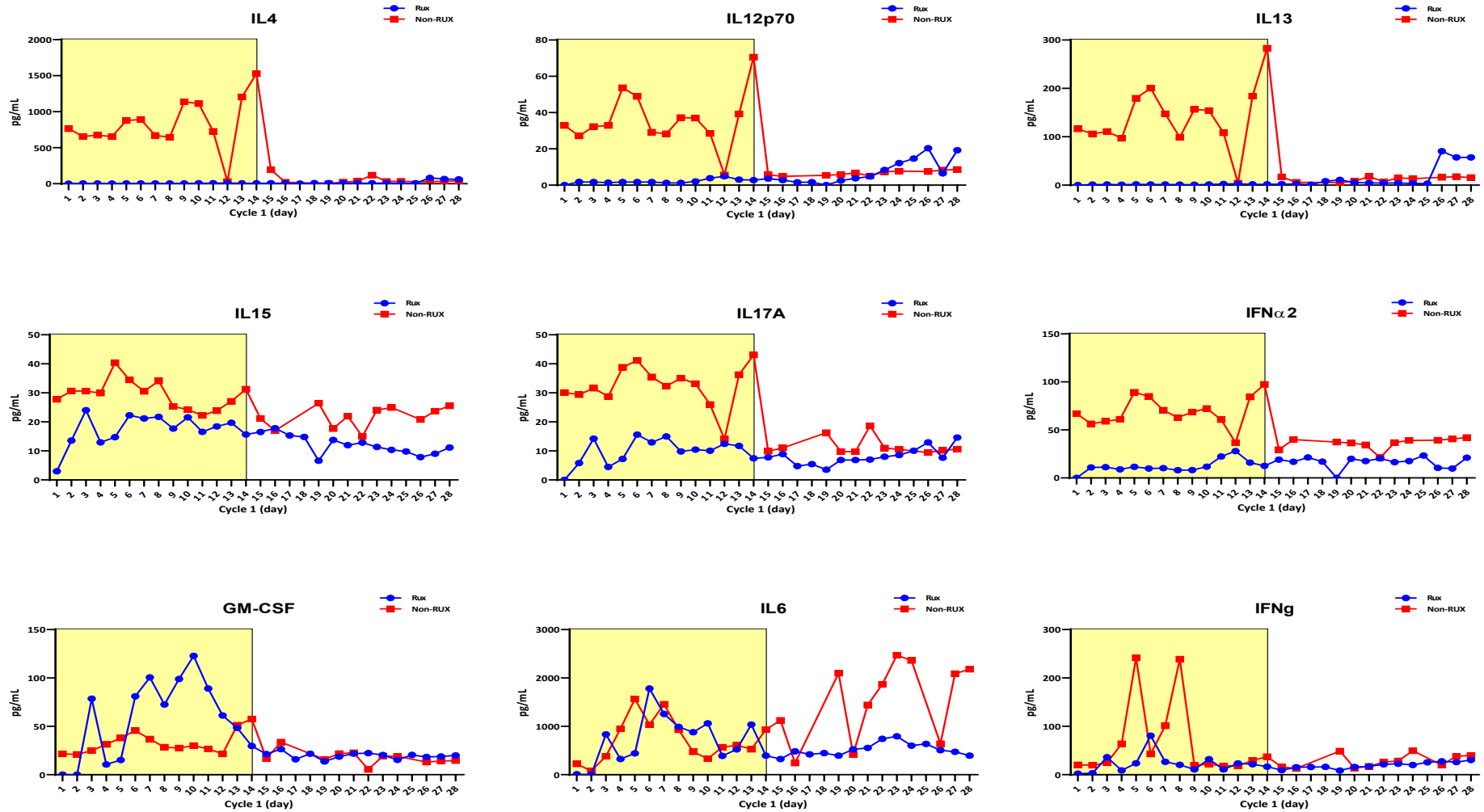
- Relapse/refractory (including primary induction failure, early relapse and late relapse) AML pts were included in this study.
- RUX pts were treated at a single site, Washington University, St. Louis, MO. Randomly selected comparator cohort (non-RUX) pts (n=21) were treated at other clinical sites at same dose during the same timeframe.

- FLZ was administered at 500 ng/kg/day continuously in 28-day cycles following multi-step lead-in dosing in week 1 of cycle 1.
- RUX was dosed at 10 mg (n=6) or 20mg (n=4) BID days -1 through 14.
- CRS was graded per Lee criteria[1].



Ruxolitinib modifies cytokine levels

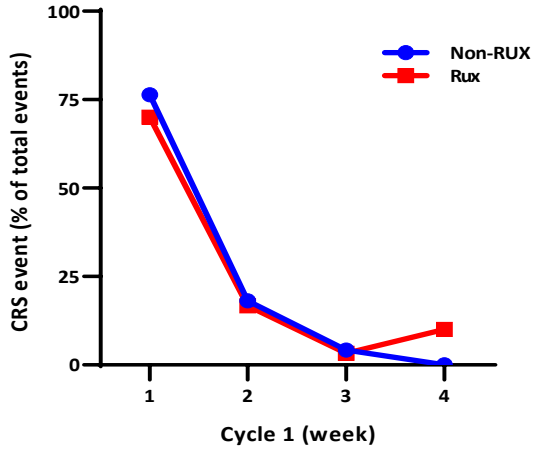
Cytokine analysis showed statistically significant ($p<0.05$) lower levels of IL4, IL12p70, IL13, IL15, IL17A, IFNα2, but higher levels of GM-CSF were measured in RUX vs non-RUX pts, specifically during co-administration with FLZ.

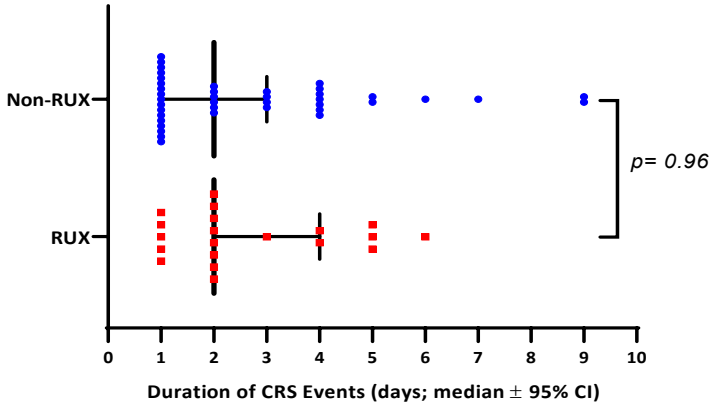


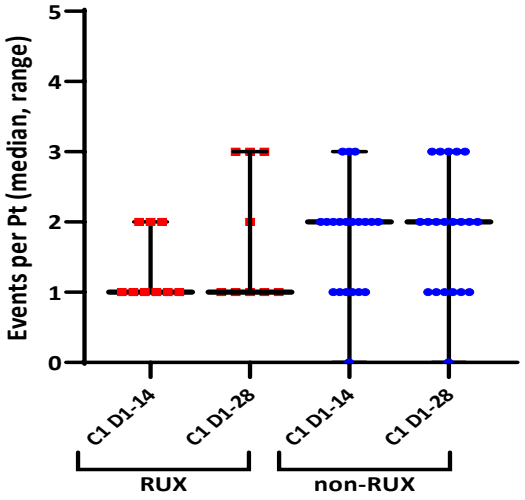
Cytokine levels for pts treated with FLZ at 500 ng/kg/day continuously in 28-day cycles following multi-step lead-in dosing in week 1 of cycle 1. RUX pts (blue) received ruxolitinib 10 mg or 20mg BID days -1 through 14 (yellow block).

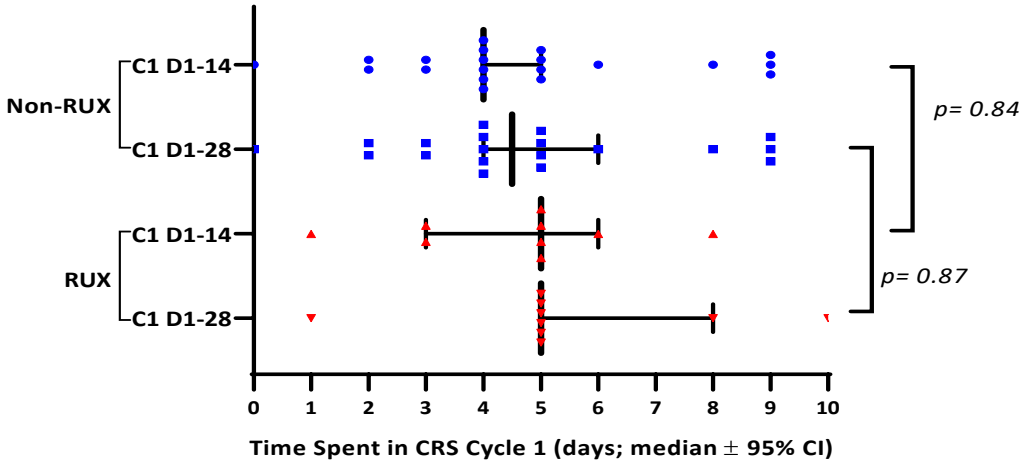
Ruxolitinib did not impact Incidence, Severity or Duration of Cytokine Release Syndrome

- *Most CRS events occurred in the first 2 weeks of FLZ administration in both groups.*
- *In the RUX and non-RUX groups median severity of CRS events were 1 and 2 per patient, respectively.*
- *Median CRS duration was equal for both groups.*









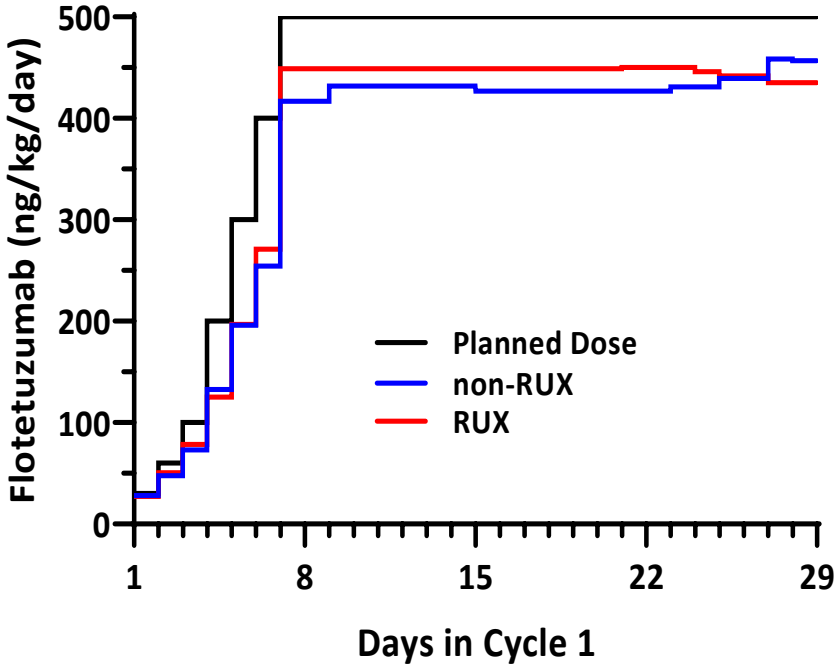
More CRS-directed treatments were used during cycle 1 for CRS management in the ruxolitinib group

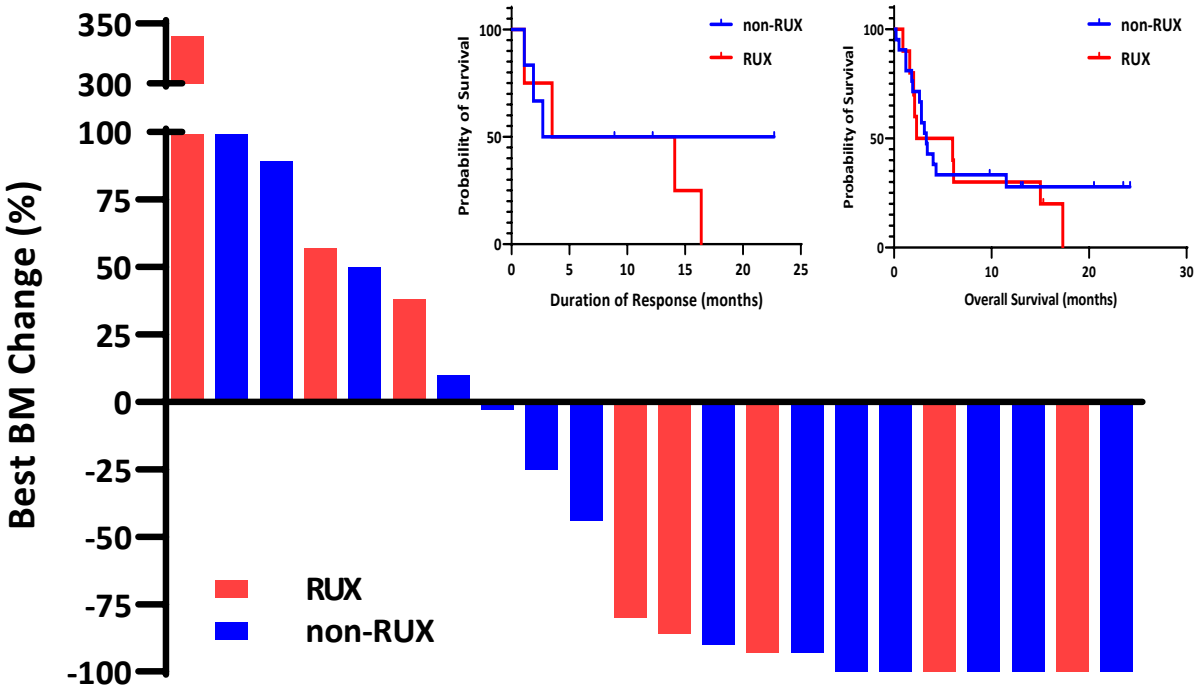
Doses administered			
	Tocilizumab	Steroids	Vasopressors
Non-RUX (n=21)	12	4	2
RUX (n=10)	13	1	1

Pts treated % (n)			
	Tocilizumab	Steroids	Vasopressors
Non-RUX (n=21)	33.3% (7)	14.3% (3)	4.8% (1)
RUX (n=10)	60% (6)	10% (1)	10% (1)

Ruxolitinib did not Impact Dose Intensity or Anti-leukemic Activity

- Dose intensity (DI) at FLZ dose of 500 ng/kg/day was comparable, with median DI of 95.6% and 98.3% in RUX and non-RUX cohorts, respectively.
- Complete response rate (BM < 5% blasts) was similar: 4 (40%) in RUX pts, and 6 (28.6%) in non-RUX pts
- Two RUX (50%) and 4 non-RUX (66.7%) responders transitioned to stem cell transplant





Conclusions

- Prophylactic RUX produced a clear difference in cytokine profiles but no discernable improvement in clinical CRS or response rates in FLZ treated patients.
- A larger study may be required to determine the prophylactic role of RUX in CRS.

Acknowledgements

We are grateful to the patients who participated in this study and their families

Clinical trial teams at the study centers:

Max S. Topp , MD, Universitätsklinikum Würzburg; Martin Wermke, MD,Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden; Norbert Vey, MD, Institut Paoli-Calmettes; Fabio Ciceri, MD, Matteo Carraba, MD, University Vita-Salute San Raffaele; Stefania Paolini, MD, Antonio Curti, M.D, PhD, Policlinico Sant'Orsola-Malpighi; Gerwin A. Huls, MD, University Medical Center Groningen; Bob Lowenberg, MD, Mojca Jongen-Lavrenic, MD, Erasmus University Medical Center; Geoffrey L. Uy, MD, Washington University School of Medicine; Harry Erba, MD PhD, Duke University Medical Center; Martha Arellano, MD, Emory University School of Medicine; Matthew C. Foster, MD, UNC Lineberger Comprehensive Cancer Center; John Godwin, MD, Providence Cancer Center; Farhard Ravandi-Kashani, MD, The University of Texas M D Anderson Cancer Center Department of Leukemia; Kendra Sweet, MD, Moffitt Cancer Center; Peter Sayre, MD, University of California, San Francisco; Anjali Advani, MD, Cleveland Clinic; Matthew Wieduwilt, MD, UCSD Moores Cancer Center; Ibrahim Aldoss, MD, City of Hope National Medical Center; Michael T. Byrne, DO, Vanderbilt-Ingram Cancer Center; Ashkan Emadi, MD, University of Maryland; Laura Michaelis, MD, Medical College of Wisconsin; Kristen Petit, MD, University of Michigan; Roland Walter, MD, PhD, Fred Hutchinson Cancer Research Center; Jessica Altman, MD, Northwestern Medicine

CP-MGD006-01 Team

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