soho2023
ELEVENTH ANNUAL MEETING

# T-Cell Exhaustion and Immune Checkpoint VISTA Overexpression are Associated with Suboptimal Response to Tyrosine Kinase Inhibitors in Patients with Chronic Myeloid Leukemia


Aram Bidikian, MD[1,2], Sreyashi Basu, PhD[1], Zhong He, PhD[1], Himachandana Atluri, MD[1], Jabra Zarka, MD[3], Michael Andreeff, MD, PhD[1], Koji Sasaki, MD, PhD[1], Elias Jabbour, MD[1], Jorge Cortes, MD[4], Padmanee Sharma, MD, PhD[1], Ghayas C. Issa MD[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA.
[2] Yale New Haven Hospital, Yale School of Medicine, New Haven, CT, USA
[3] University of Pittsburgh Medical Center, Pittsburgh, PA, USA.
[4] Georgia Cancer Center, Augusta, GA, USA


## INTRODUCTION

- The role of the immune system in eradicating CML has been demonstrated in
  - Successful graft-versus-leukemia effects
  - Requirement of active T and NK cells for sustained remission before therapy discontinuation.
- Further understanding of immune determinants of TKI response will help improve the odds of deeper molecular responses and treatment-free remission.

## METHODS

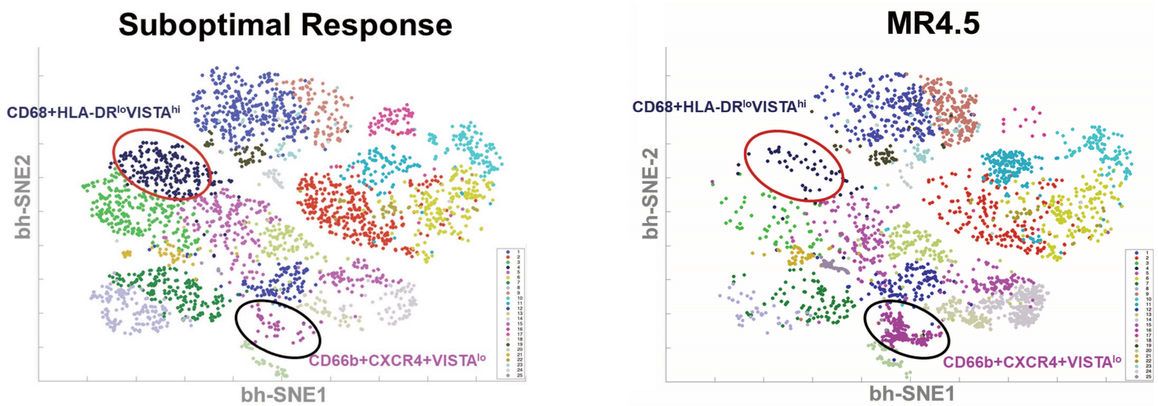
- We compared 20 patients that achieved MR4.5 to 32 patients with suboptimal response to therapy according to the European LeukemiaNet (ELN) response milestones.
- We prospectively collected longitudinal blood and bone marrow samples from these patients and characterized them using cytometry by time of flight (CyTOF).
- The CyTOF panel (36-plex) was custom-designed to include markers of leukemia/stem progenitor cells, lineage defining, intracellular signaling, immune exhaustion and activation markers.
- Samples were barcoded, pooled and processed simultaneously to overcome technical variations and batch effects.
- CD45hi cells (leukocytes) were grouped using PhenoGraph clustering, based on expression of these markers.

| Characteristics | Suboptimal Response | MR4.5 | *P* |
|---|---|---|---|
| **N** | 32 | 20 | |
| **Median age, years (range)** | 48 (23 – 75) | 49 (24 – 68) | 0.9 |
| **Female, no. (%)** | 17 (53) | 12 (60) | 0.8 |
| **WBC, median x10$^9$ (range)** | 12 (11 – 96) | 12 (2 – 145) | 0.9 |
| **BCR::ABL% (IS)*** | | | |
| At 3 months >10% | 1/9 (11%) | 0/12 (0%) | 0.4 |
| At 6 months >1% | 4/13 (31%) | 1/12 (8%) | 0.3 |
| At 12 months>0.1% | 8/13 (62%) | 1/12 (8%) | 0.01 |
| **Meeting at least one ELN response criterion** | 8/13 (62%) | 2/12 (17%) | 0.04 |
| **Frontline Treatment, no. (%)** | | | |
| Imatinib | 19 (59) | 10 (50) | 0.6 |
| Dasatinib | 9 (28) | 5 (25) | 0.9 |
| Nilotinib | 4 (13) | 2 (10) | 0.9 |
| Ponatinib | 0 (0) | 3 (15) | 0.05 |
| **Median line of treatment lines by time of sample collection (range)** | 2 (1 – 5) | 1 (1 – 3) | 0.02 |
| **Median *BCR::ABL* (%) at time of sample collection (range)** | 0.08 (0.007 – 100) | 0 (0 – 0.007) | <0.0001 |
| **Median time of sample collection from diagnosis (range)** | 57.6m (9 – 266) | 129.6m (56 – 256) | 0.09 |

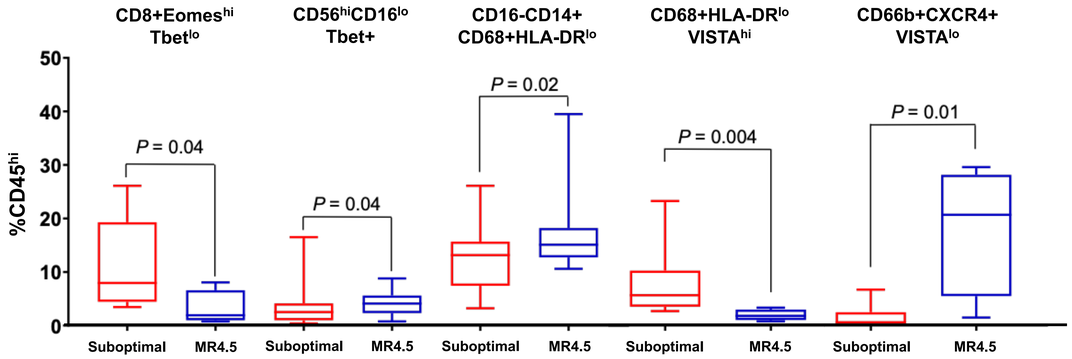
*Evaluable patients, Abbreviations: ELN, European LeukemiaNet; m, months

## RESULTS

- Suboptimal response to therapy was associated with
  - Higher proportion of exhausted CD8+ T-cells
  - Lower proportion of interferon gamma releasing NK-cells (CD56$^{hi}$CD16$^{lo}$Tbet+)
  - Higher proportion of macrophages expressing the immune regulatory ligand V-domain immunoglobulin suppressor of T-cell activation (VISTA)
  - Lower proportion of mature granulocytes with low expression of VISTA




tsNE plots comparing 25 distinct clusters of patients who achieved MR4.5 compared with patients who achieved suboptimal response




Prevalence of different immune cell subpopulations among patients with suboptimal response compared with patients who achieved MR4.5

## CONCLUSION

- T-cell exhaustion and immune checkpoint VISTA overexpression are associated with suboptimal response to therapy in CML.

## CONTACT INFORMATION


Ghayas C. Issa, MD
The University of Texas MD Anderson Cancer Center
1515 Holcombe Boulevard, Houston, TX 77030, USA.
**Email**: gcissa@mdanderson.org