Memorial Sloan Kettering Cancer Center

Mutations in Acute Promyelocytic Leukemia are Similar at Diagnosis and Relapse and ETV6 may be a Molecular Biomarker of Decreased Disease-Free Survival and High-Risk Disease Independent of White Blood Cell Count

Eytan M. Stein, Aaron D. Viny, Sean Devlin, Elisabeth M. Paietta, Janis Racevskis, Robert Gallagher, Jeffrey E. Lancet, Bayard L. Powell Frederick R. Appelbaum, Richard A. Larson, Peter Wiernik, Jacob M. Rowe, Ross L. Levine and Martin S. Tallman on behalf of the Eastern Cooperative Oncology Group

Background

- Relapse-free survival in patients with APL is defined based on white blood count (WBC) at presentation.
  - WBC below or equal to 10 x 10^9 are defined as having high relapse risk
  - WBC above 10 x 10^9 have increased relapse risk

- Consensus guidelines incorporate chemotherapy into treatments for high risk patients and use ATRA/Arsenic alone for low risk patients.

Background

- **E2491 - ECOG led study that randomized 401 patients with newly diagnosed APL to induction with ATRA vs. chemotherapy.**
  - **Patients who achieved a complete remission were re-randomized to ATRA maintenance vs. observation**

- **C9710 – 518 patients received ATRA/chemotherapy for induction and were randomized to arsenic trioxide vs. no arsenic for consolidation**

Goal of this Study

- Investigate the mutational profiles of patients treated on E2491 and C9710 at diagnosis and relapse
- Assess whether the mutational profiles of patients with a white count over 10K ("high risk) differed from those patients with a white count lower than or equal to 10K ("low risk")
- Define whether disease free survival can be defined based on mutational profile rather than WBC at diagnosis.

Methods

- 195 patients with genomic DNA available at the time of diagnosis.
  - 82 from E2491 and 113 from C9710
  - FLT3 mutational analysis (ITD and TKD) done on these patients
- Subset of 45 patients had whole genome sequencing (NY genome center)
- 12 patients with paired DNA available at the time of diagnosis and relapse

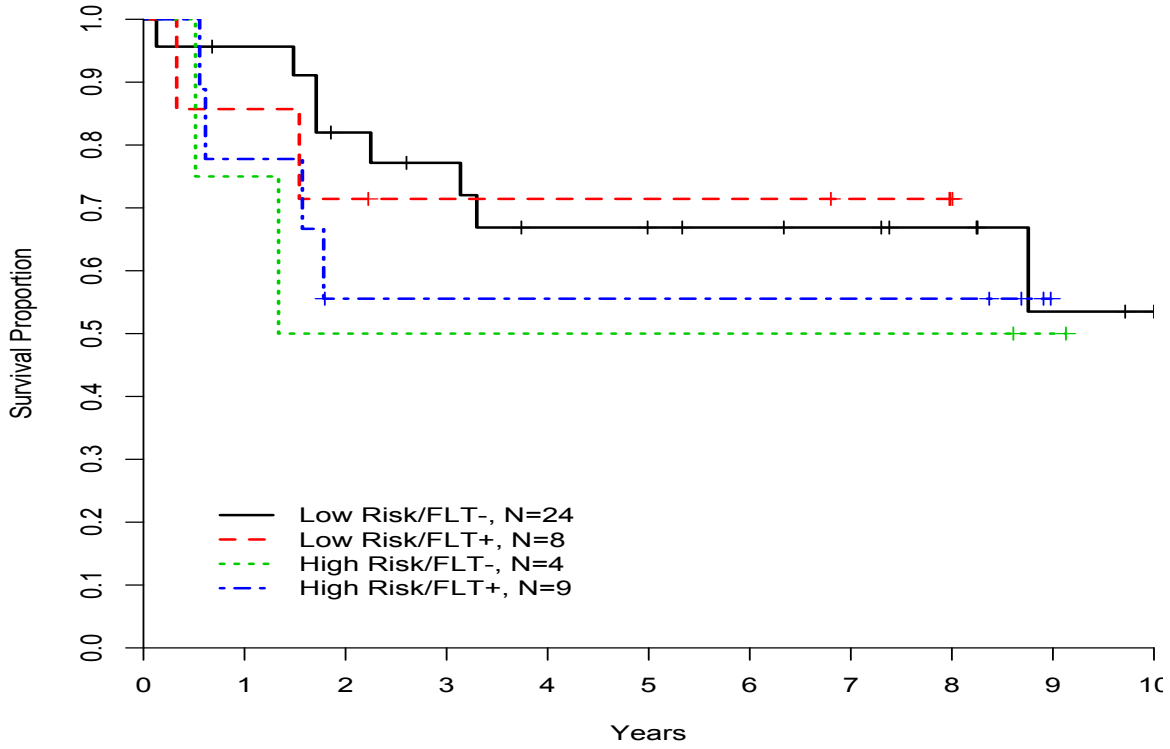
Results – FLT3

- **FLT3 ITD more common in patients with WBC over 10K at diagnosis**

	Low Risk	High Risk	P-value
FLT3 -D835	28/120 (23%)	9/37 (24%)	0.99
FLT3- ITD	24/120 (20%)	21/37 (57%)	< 0.001
FLT3 (D835/ ITD)	52/120 (43%)	30/37 (81%)	< 0.001

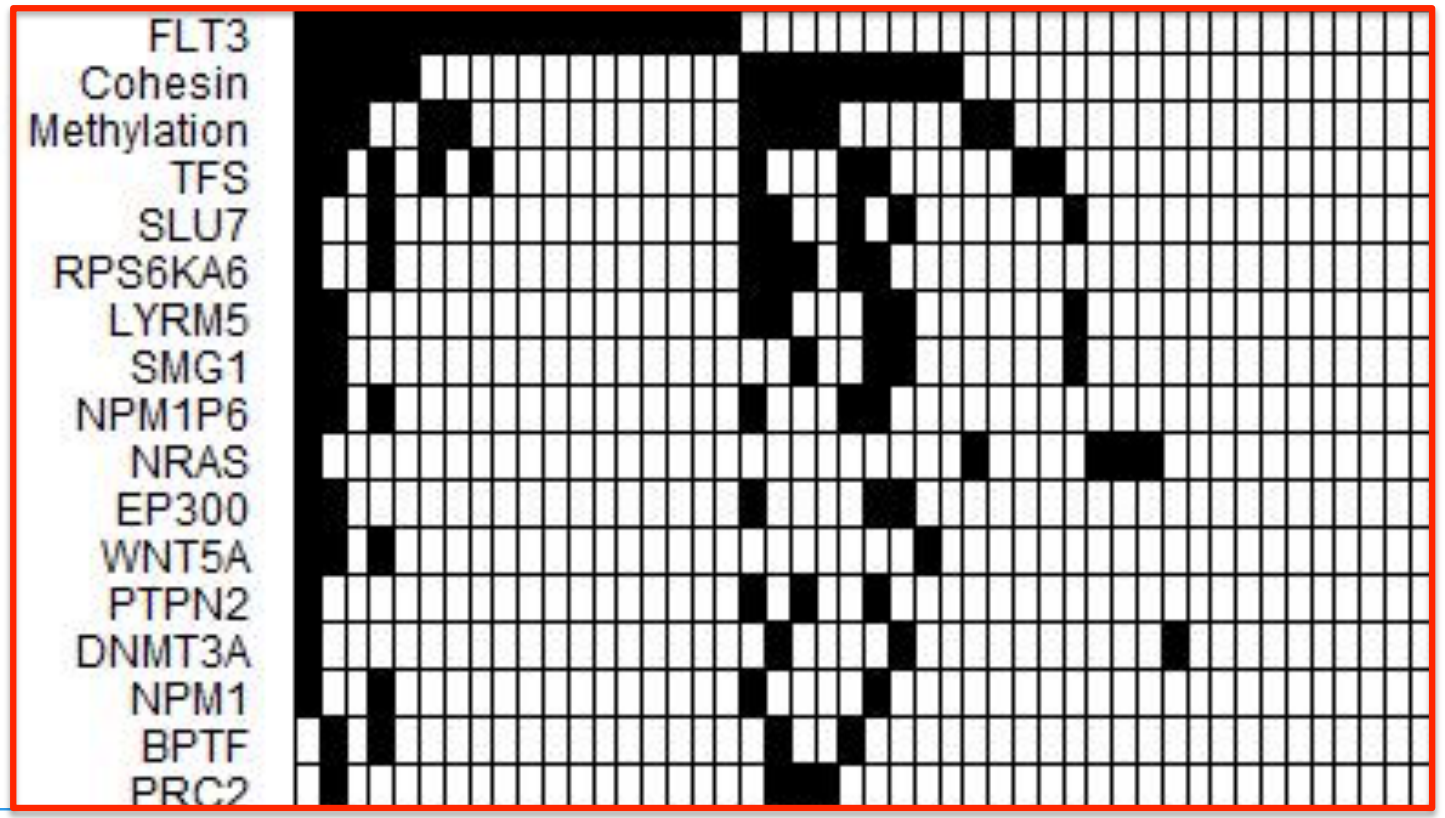
Disease Free Survival – FLT3

- **Despite FLT3 being more common in pts with WBC over 10K, FLT3 status in combination with WBC does not predict for disease free survival**



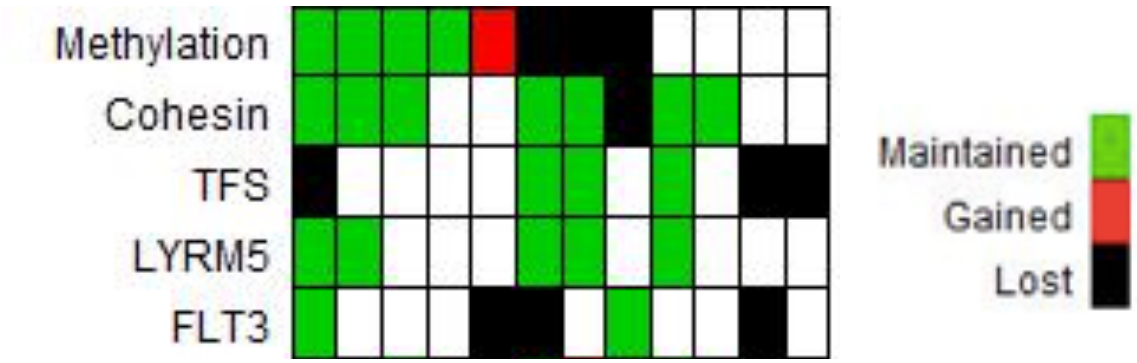
Mutations at Diagnosis

- **Mutations in Cohesin complex and methylation genes seen in 31% and 24% of patients, respectively, at time of diagnosis (n=45)**

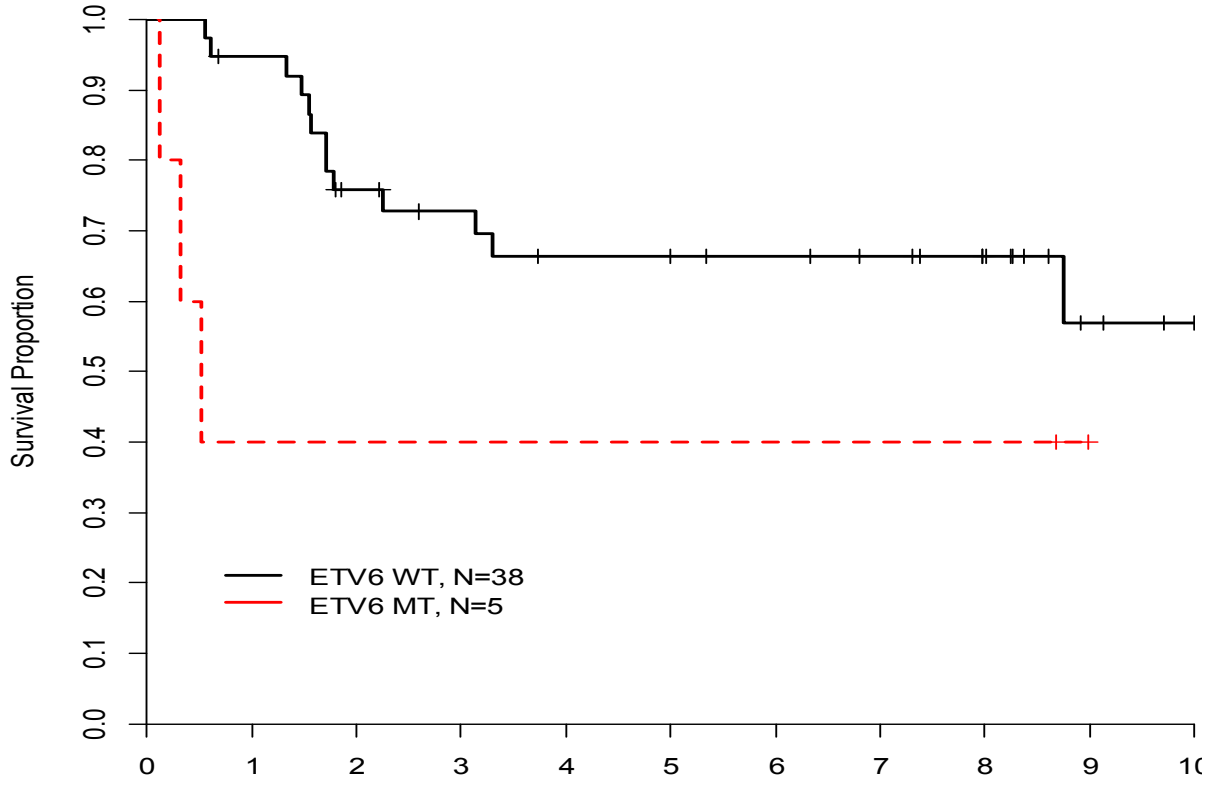


Mutations at Diagnosis vs. Relapse

- 12 patients with paired diagnosis/relapse DNA
- 7 with mutations in genes involved in DNA methylation at the time of diagnosis.
- At relapse, four patients retain the same mutations in methylation genes one patient acquires new mutations and three revert to a wild type state



Decreased Disease Free Survival in Patients with ETV6 mutations at Diagnosis



P-value: 0.07

Conclusions

- FLT3-ITD co-segregates with WBC over 10 x 10^9 in patients with APL, but does not by itself or in combination with WBC predict for decreased RFS.
- Mutations in genes involved in methylation and the cohesin complex are seen in patients with APL both at the time of diagnosis and relapse
- Mutational profiles at the time of APL relapse are largely similar to those seen at the time of diagnosis, suggesting that a novel mutational event and clonal evolution does not drive relapse.
- ETV6 may predict a group of patients with decreased RFS, independent of WBC and may serve as a molecular biomarker of high-risk disease.

Acknowledgements

Eastern Cooperative Oncology Group,

Alliance for Clinical Trials in Oncology,

Southwest Oncology Group,

leadership and statisticians