Kinetic Measurement of Leukemia-Cell Proliferation Rate by Deuterium Labeling Predicts Time to Initial Treatment

Abstract 829

Murphy EJ, Neuberg D, Rai KR, Rassenti L, Emson C, Li K, Kay NE, Wierda WG, Hayes GM, Brown JR, Byrd JC, McConnel C, Barrientos JC, Redd RA, Turner S, Busch R, Greaves A, Hellerstein M, Chiorazzi N, Kipps TJ

Cell Kinetics in CLL

- Traditionally thought of as a disease of failed cell death
- On average, birth rate of CLL cells < birth normal B cells
- It has also been shown that
  - Significant heterogeneity of birth rates between patients
  - Some individuals have significantly higher birth rates than normal B cells
  - Different clones have significantly different birth rates
- It is likely that defects in both cell production and destruction are present in CLL

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CLL Cell Birth Rate as a Prognostic Marker

- **Hypothesis: birth rate could be used as a prognostic marker for disease progression in CLL**
- **Study goals:**
  - **Assess CLL cell birth rates in untreated patients (Rai stage 0, 1, 2; diagnosis within 3 years)**
  - **Compare birth rate to other established prognostic markers**
  - **Assess all markers as predictors need for treatment (progression) during 2 years of patient follow-up**

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Demographics

	Total n = 97
Sex	
Female	39 (40%)
Male	58 (60%)
Age	
Median (range)	57 (40-85)
Rai stage at enrollment	
0	36 (37%)
I	44 (45%)
II	17 (18%)
Enrollment site	
Dana-Farber Cancer Institute	5 (5%)
North Shore - Long Island Jewish Health System	19 (20%)
Mayo Clinic	18 (19%)
MD Anderson Cancer Center	14 (14%)
Ohio State University	10 (10%)
University of California San Diego	31 (32%)
Months from CLL diagnosis to study entry	
Median (range)	12 (1-36)

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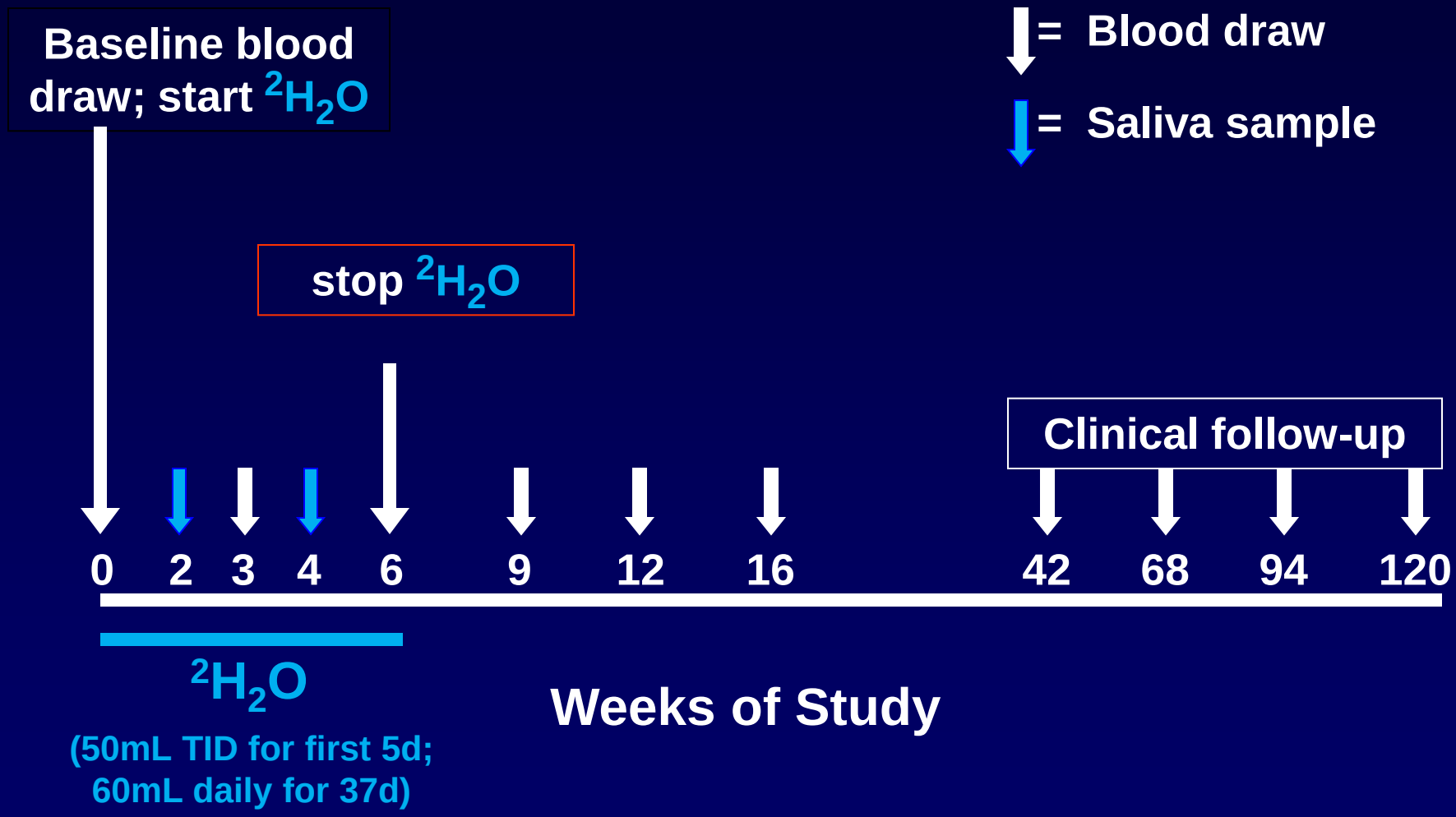
Measurement of CLL Cell Birth Rate

Heavy Water Study Protocol



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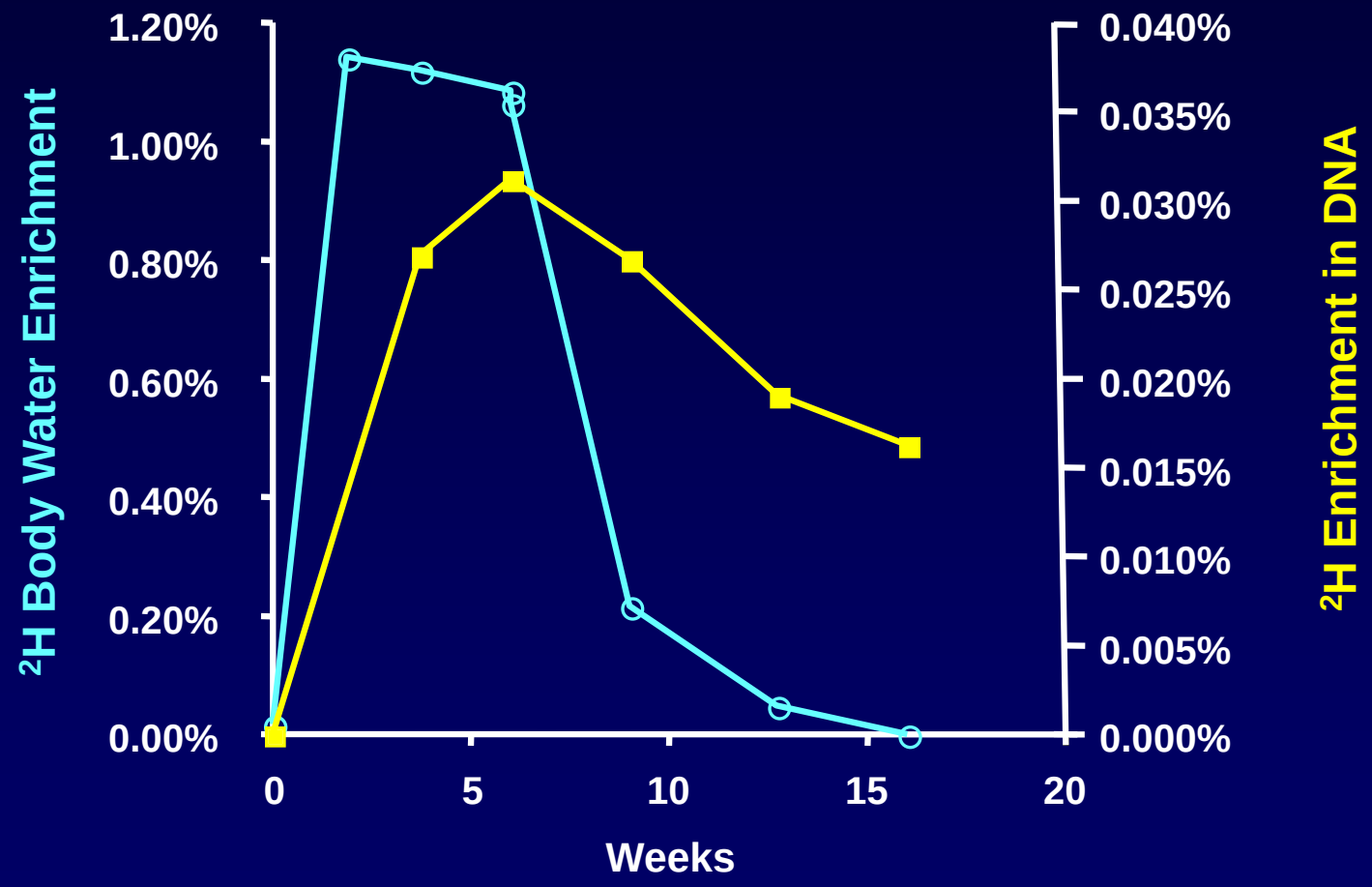
Heavy Water Studies

Body Water Enrichment and CLL cell incorporation



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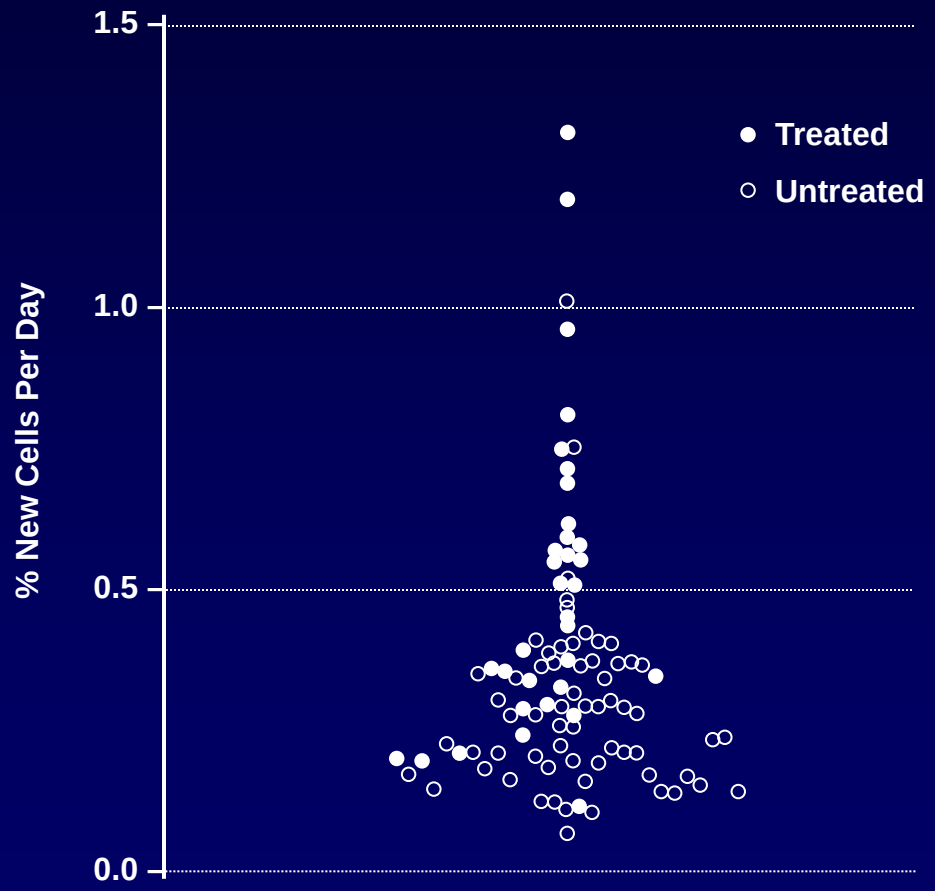
CLL Cell Birth Rates (n = 97)

Median Birth Rate 0.32% new cells per day
Range 0/07%-1.31% per day



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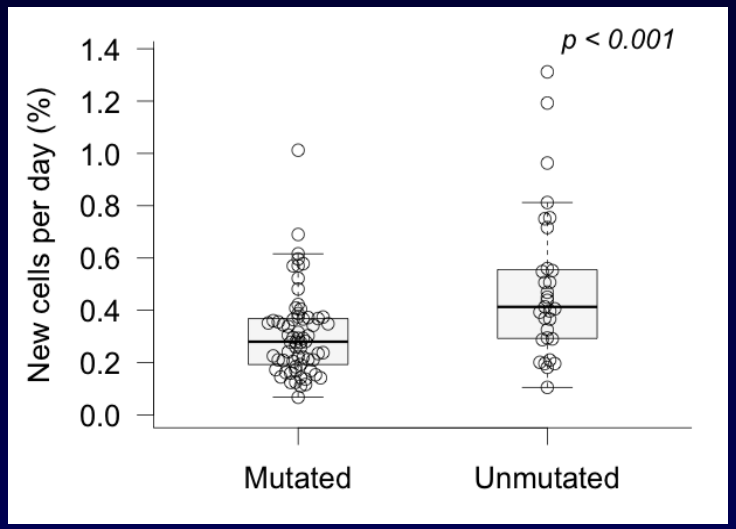
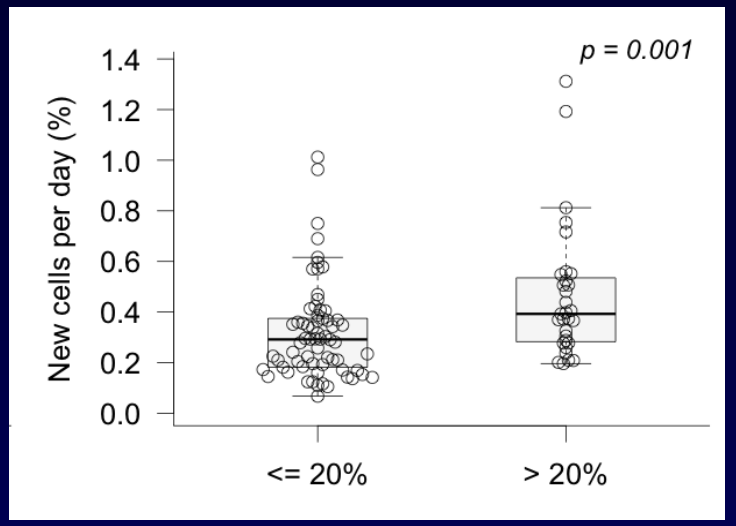
Birth Rate in Relation to Other Prognostic Factors

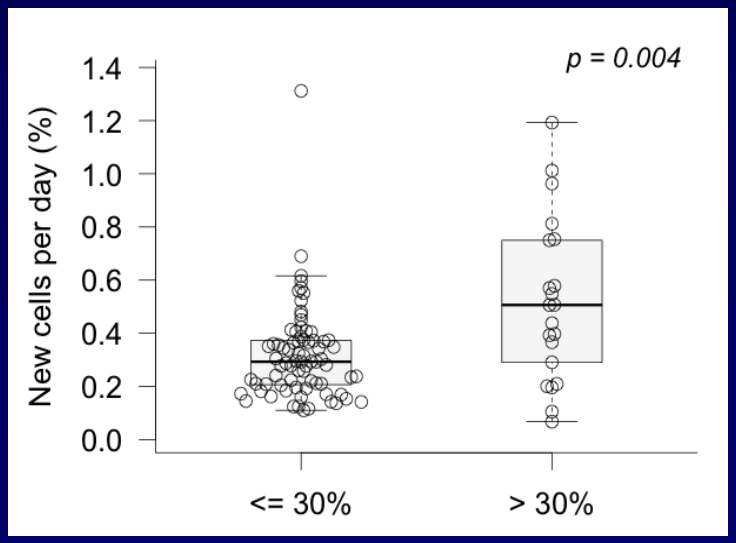
IGHV Mutation Status



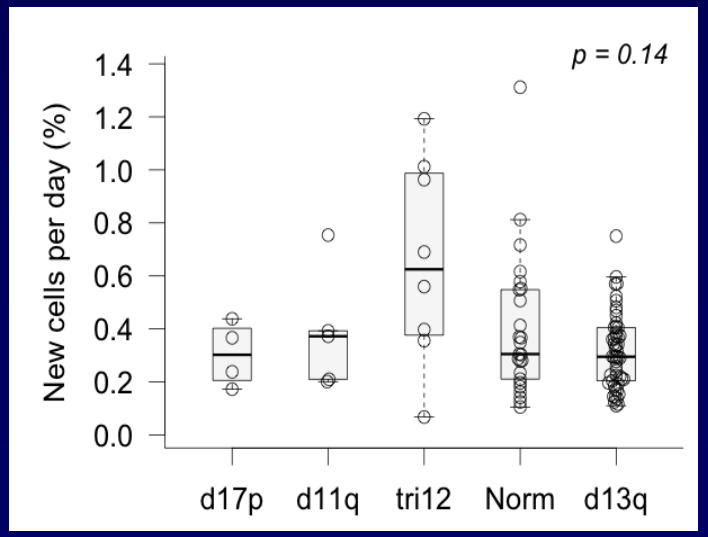
ZAP-70 Expression



CD38 Expression



Cytogenetics



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Treated Patients

	Total n = 97	Treated CLL	
		No n = 64	Yes n = 33
Sex			
Female	39 (40%)	26 (41%)	13 (39%)
Male	58 (60%)	38 (59%)	20 (61%)
Age			
Median (range)	57 (40-85)	58 (40-85)	56 (41-78)
Rai stage at enrollment			
0	36 (37%)	32 (50%)	4 (12%)
I	44 (45%)	24 (38%)	20 (61%)
II	17 (18%)	8 (12%)	9 (27%)
Enrollment site			
Dana-Farber Cancer Institute	5 (5%)	3 (5%)	2 (6%)
North Shore - Long Island Jewish Health System	19 (20%)	11 (17%)	8 (24%)
Mayo Clinic	18 (19%)	12 (19%)	6 (18%)
MD Anderson Cancer Center	14 (14%)	9 (14%)	5 (15%)
Ohio State University	10 (10%)	0 (14%)	1 (3%)
University of California San Diego	31 (32%)	20 (31%)	11 (33%)
Months from CLL diagnosis to study entry			
Median (range)	12 (1-36)	11 (1-36)	12 (1-36)

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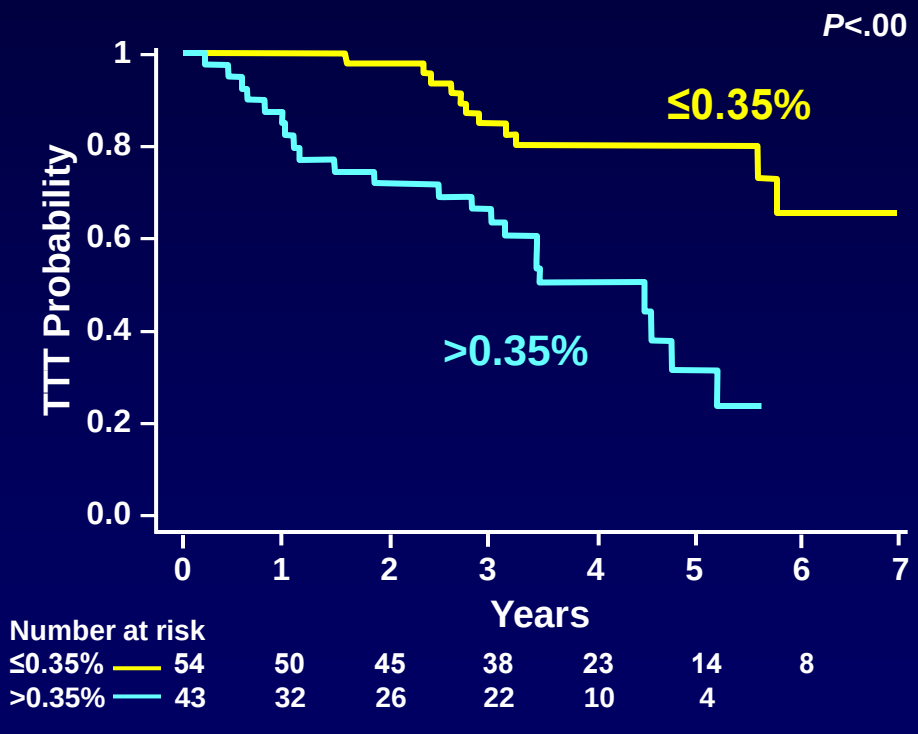
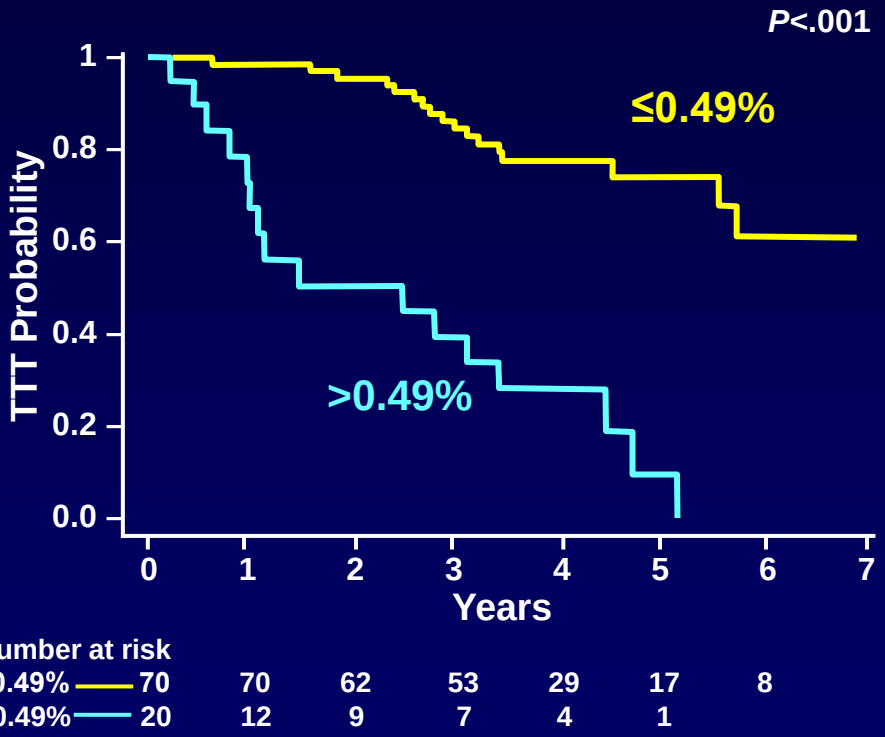
Birth Rate vsTime to Initial Therapy

Birth Rate >0.35% per day [1]



Birth Rate >0.49% per day



1. Messmer BT, et al. *J Clin Invest.* 2005;115(3):755-764.

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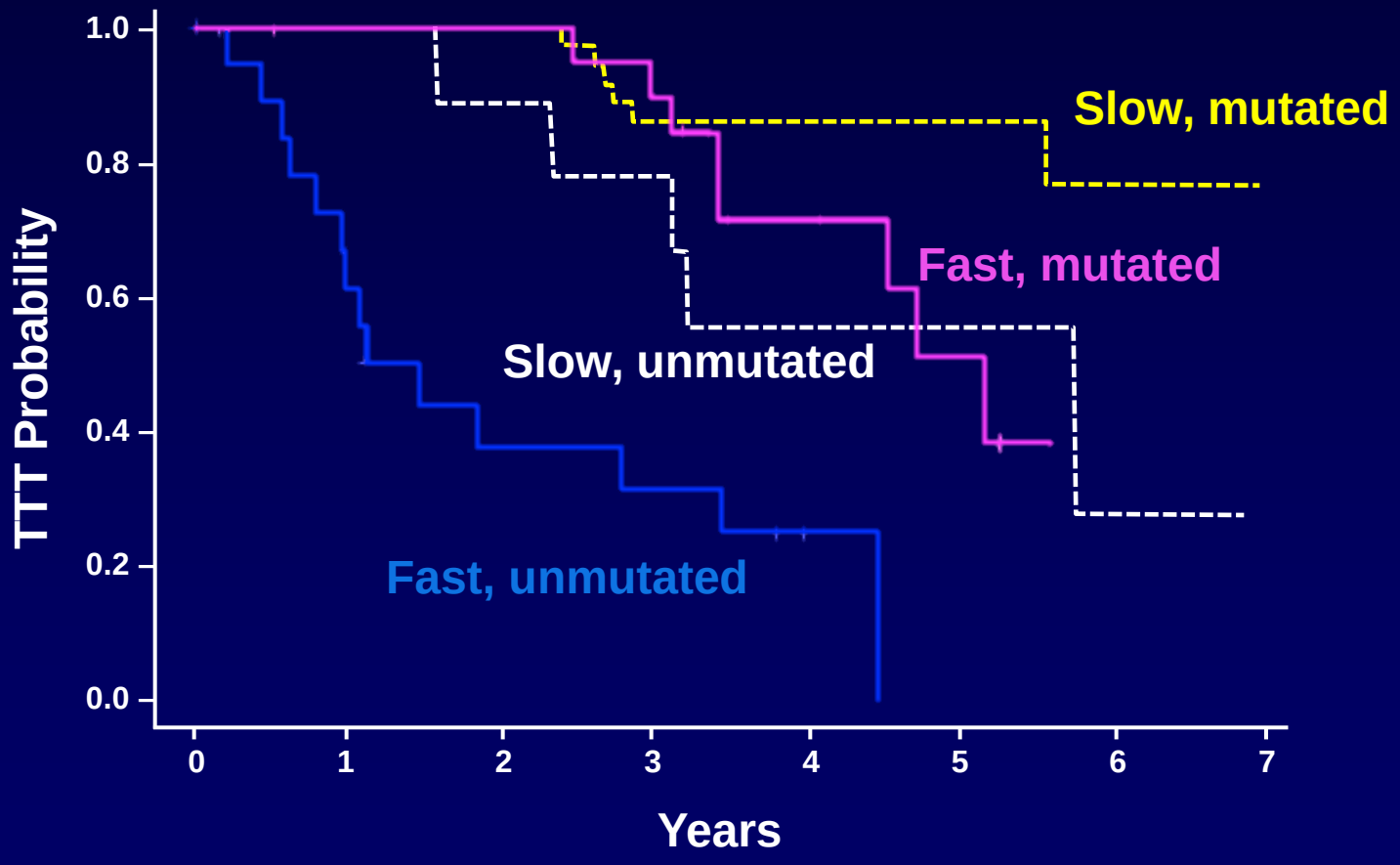
Time to Treatment Stratified by *IGHV* and Birth Rate



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Conclusions

- **Increased CLL cell birth rate in early-stage disease is a strong predictor of earlier treatment**
- **In a multivariable model, only birth rate and *IGHV* mutational status contributed significantly**
- **Within the groups of patients with mutated or unmutated *IGHV*, birth rate allowed further discrimination in a time-to-treatment analysis**
- **This direct measure of CLL-cell proliferation represents a new marker for prognostication for subjects with early-stage CLL**

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