



Rome,
March 23-24 2017

VOI Donna Camilla Savelli Hotel

Transformed Follicular Lymphoma Biology and Treatment

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Disclosures of Brian K. Link

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche	X					X	
Celgene						X	
AbbVie							DSMB
Gilead							DSMB
Millenium	x						



Established 1846

Population 1880 = 276

Iowa



Population 2015 = 117



Why do we care about transformed FL?

- FL – common
- Median survival 15-20 years
- Perhaps most people die of other causes
- Two biggest fears of FL patients and their docs
 - Early failure after immunochemotherapy
 - transformation

Key Questions in FL Transformation

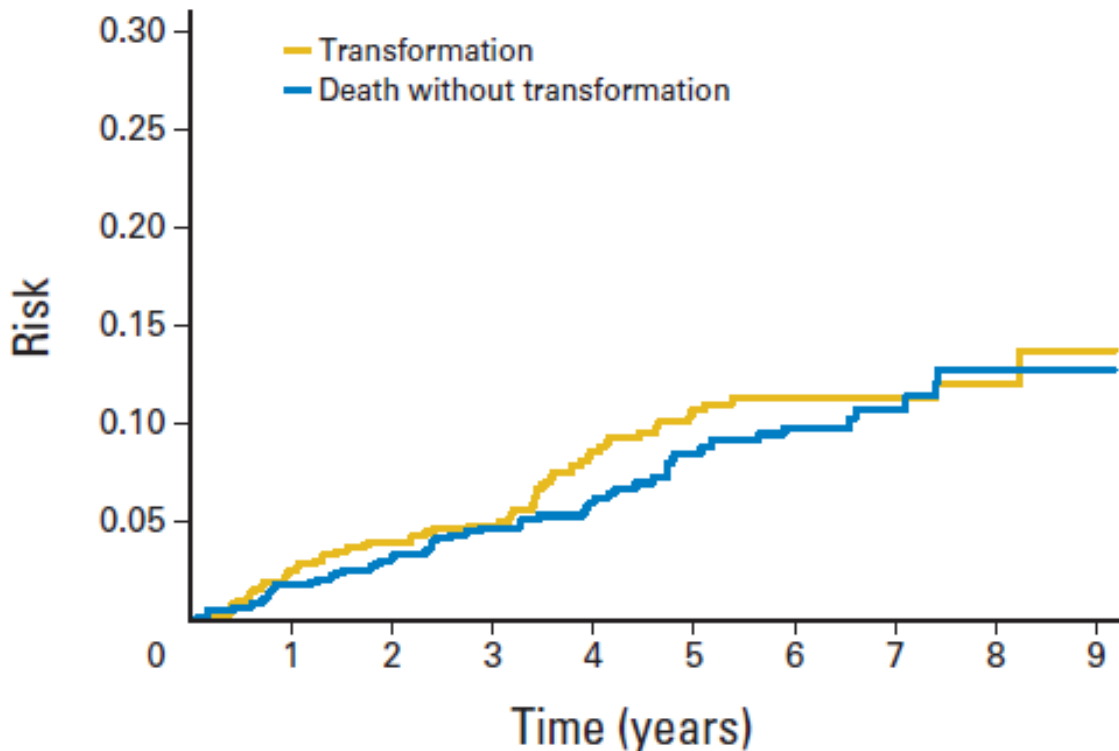
- Frequency and timing of FL transformation
- Risk factors at FL presentation
- Management strategies at FL diagnosis that may favorably or adversely impact tFL
- Heterogeneity of outcomes
- Optimal treatment strategies

Data to Understand Transformation in the immunochemotherapy era

- **Three Observational Cohort Series**
 - NCCN consortium cohort¹
 - 118 retrospectively ascertained at transformation
 - Biopsy proven
 - Iowa/Mayo MER Observation Cohort Study²
 - 631 FL patients ascertained at FL diagnosis
 - 51 of 60 transformed events were biopsy proven
 - National LymphoCare (NLCS)³
 - 2700 FL patients ascertained at FL diagnosis
 - 147 of 379 transformed events were biopsy proven
 - Considers 47 patients with “transformation at diagnosis”
- **Secondary Analysis of PRIMA phase III Trial⁴**
 - 1018 patients ascertained at FL diagnosis and randomized
 - At progression/relapse becomes observational cohort
 - 40 of 194 biopsied first relapses show transformation

Frequency and Timing of Transformation

- 2% per annum for first decade.
 - NCLS: 14.3% at 7 years
 - PRIMA: 9% at 6 years*
 - Iowa/Mayo MER: 10.7% at 5 years



Risk Factors at FL Presentation

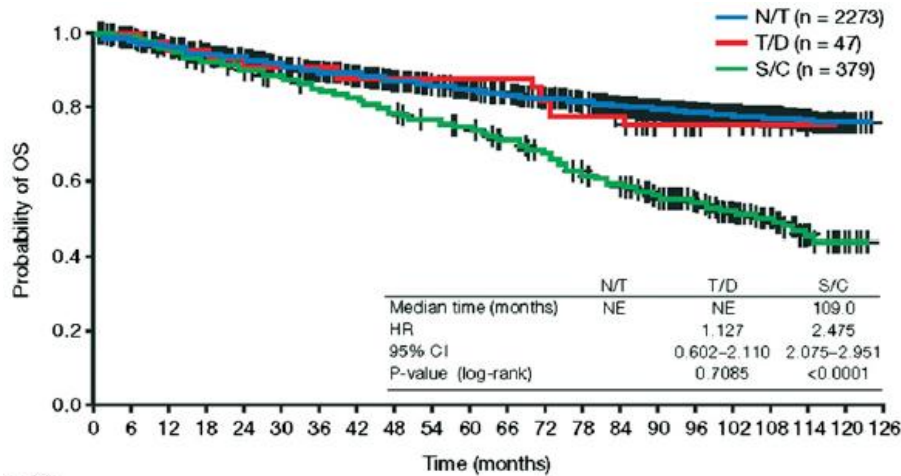
	PRIMA	NLCS	MER	NCCN
FLIPI >2	X		X	
Grade 3a	X			
Elevated LDH	X	X	X	
PS >1	X	X		
B symptoms	X	X		
Hgb <12	X		Protective	
Advanced age		(Protective)	X	
>1 EN site		X		

FL Initial Therapy and Risk of Transformation

	PRIMA	NLCS	MER
observation		Higher	Higher
anthracyclines	Neutral	Slightly protective	Neutral
rituximab	Maintenance protective	Maintenance protective	Monotherapy protective

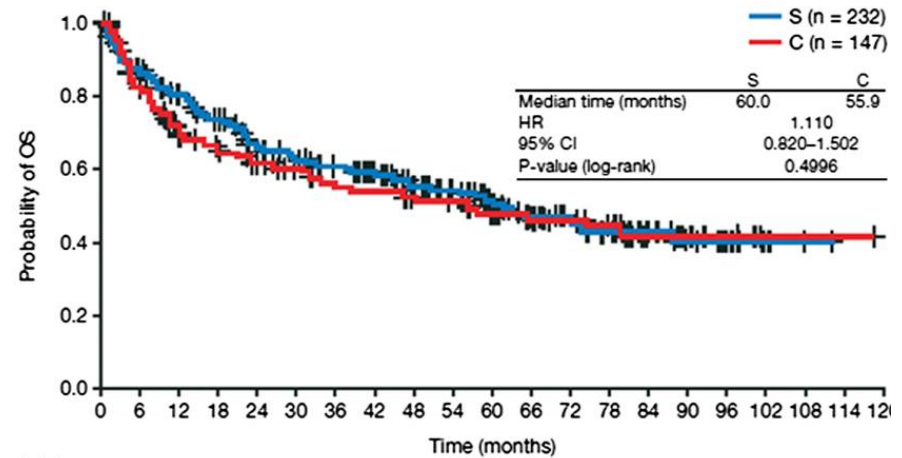
Outcomes After Transformation

- Median OS 4-5 years in all studies



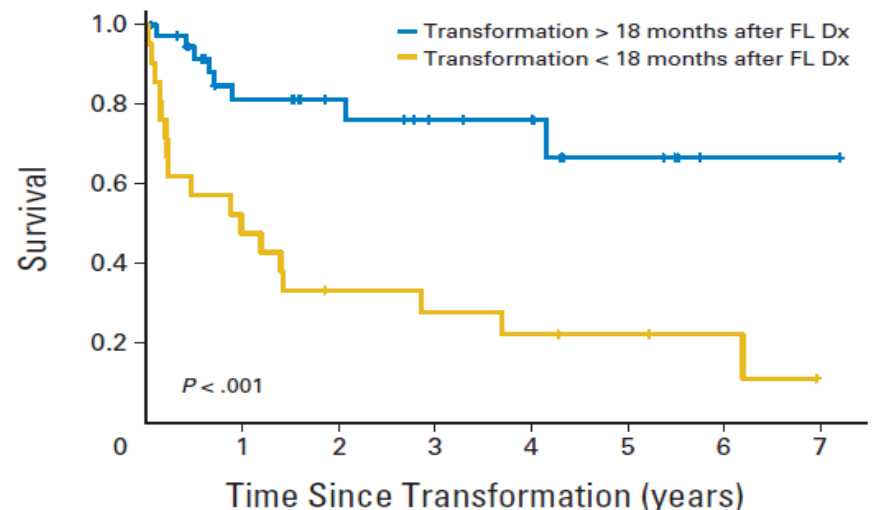
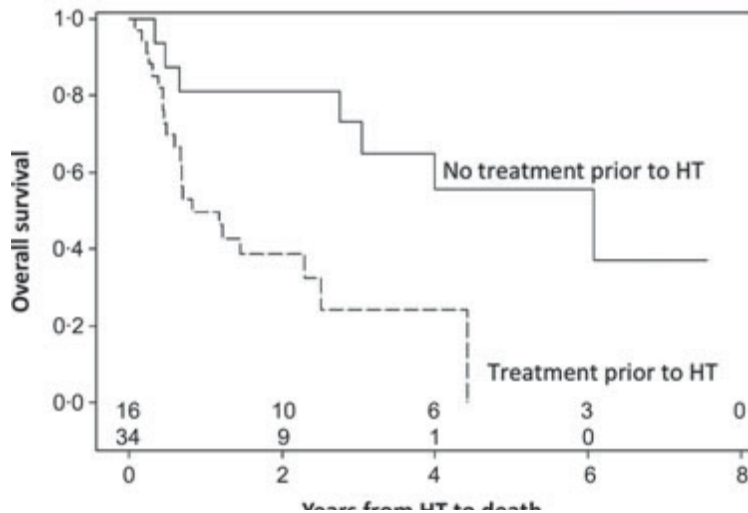
at risk

N/T	2273	2221	2121	2034	1943	1865	1802	1739	1678	1614	1559	1515	1469	1426	1360	1115	854	615	370	163	22	0
T/D	47	46	44	40	38	38	38	37	36	35	35	35	32	31	29	21	13	11	6	2	0	0
S/C	379	376	362	345	334	322	309	300	287	276	267	252	235	213	202	160	130	94	57	27	6	0



at risk

S	232	194	168	149	126	115	107	96	78	66	54	43	34	29	20	13	6	3	1	0	0
C	147	117	88	80	71	61	56	54	49	47	39	31	26	19	10	8	4	1	1	1	0



Biology of Transformation

Methods

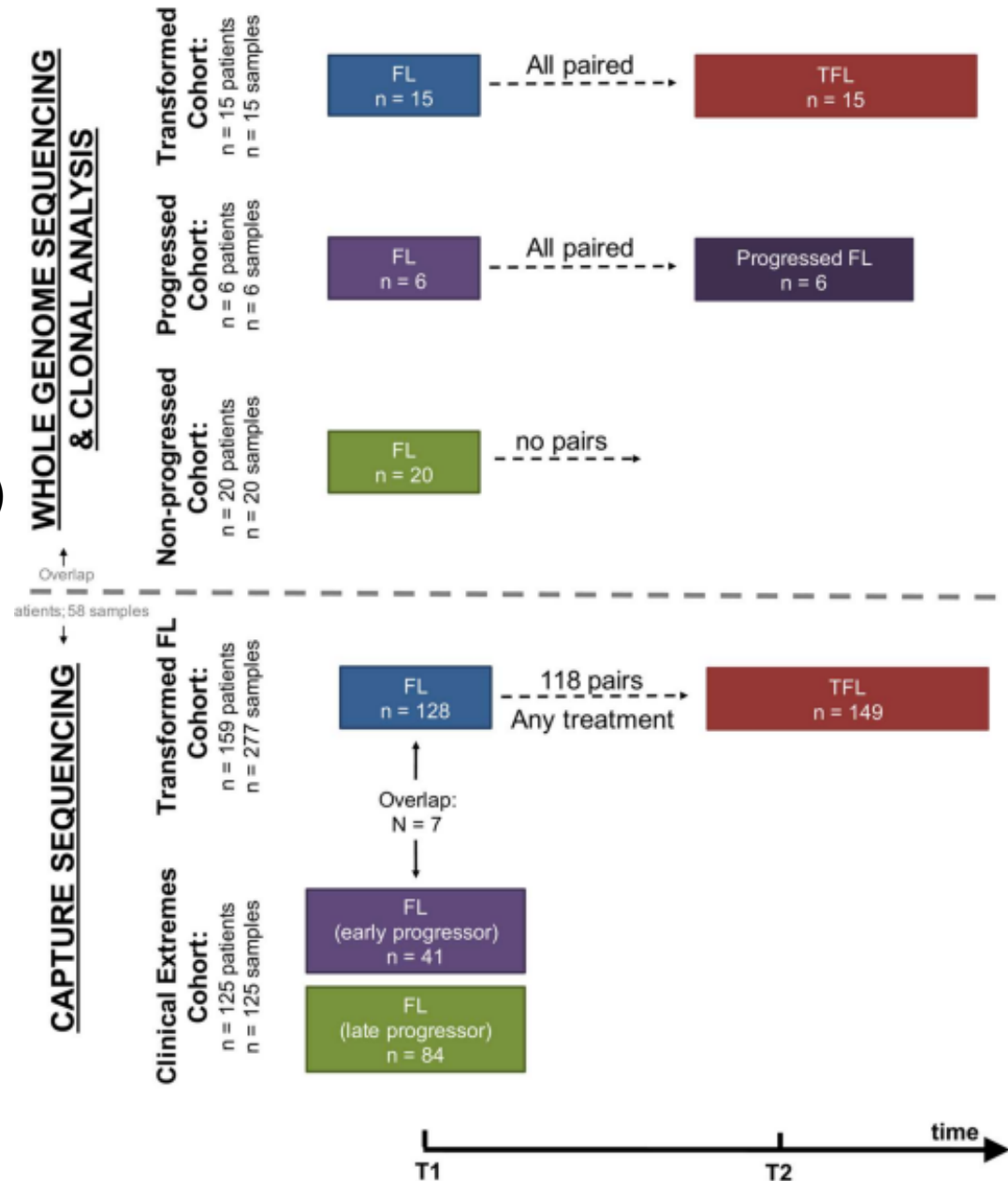
Specimens: BCCA, Belgium, and Mayo
:tumor and normal

15 transformed paired
6 early progressed paired
20 not progressed (unpaired)

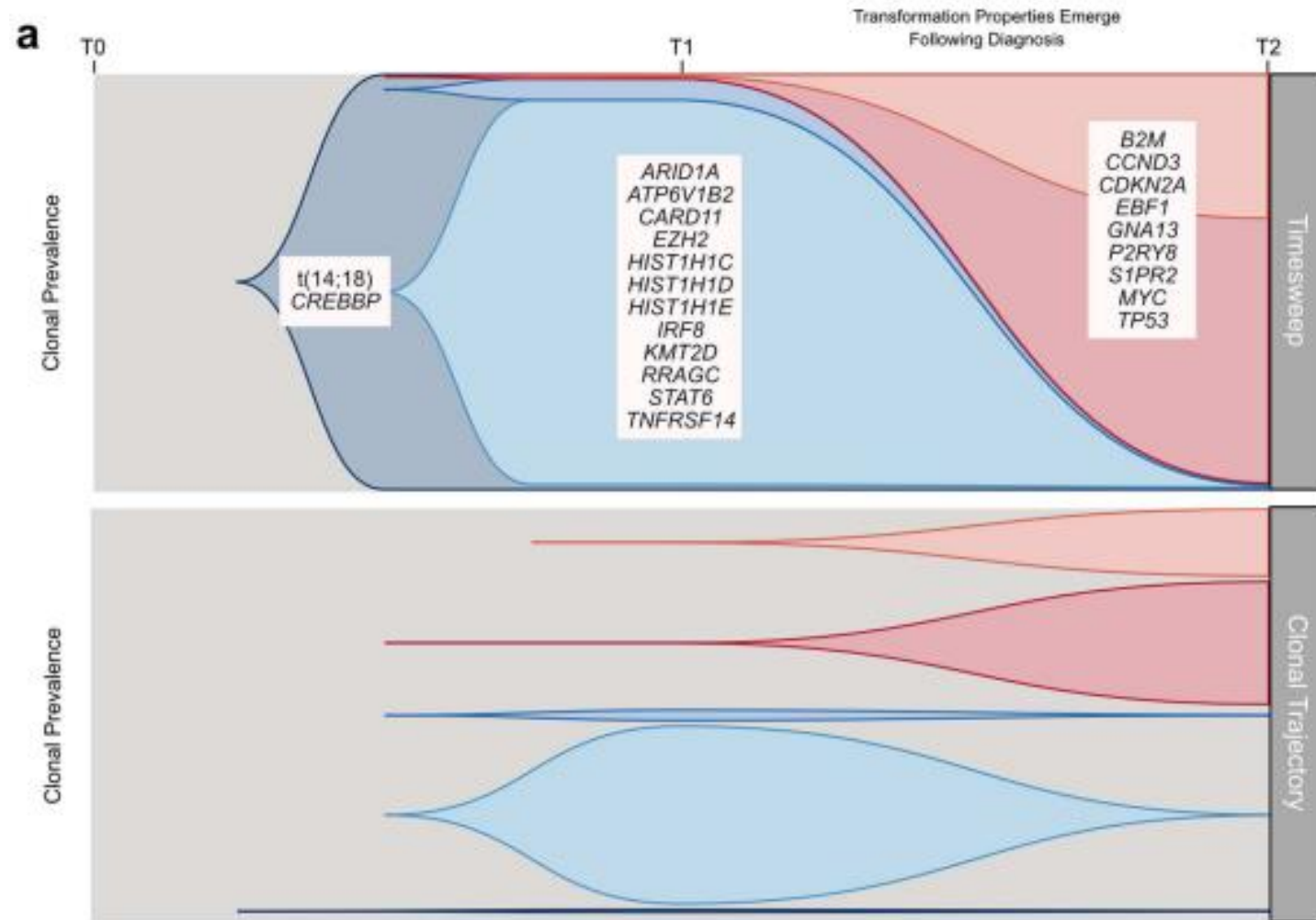
Expansion Cohort

Capture sequencing (94 genes)

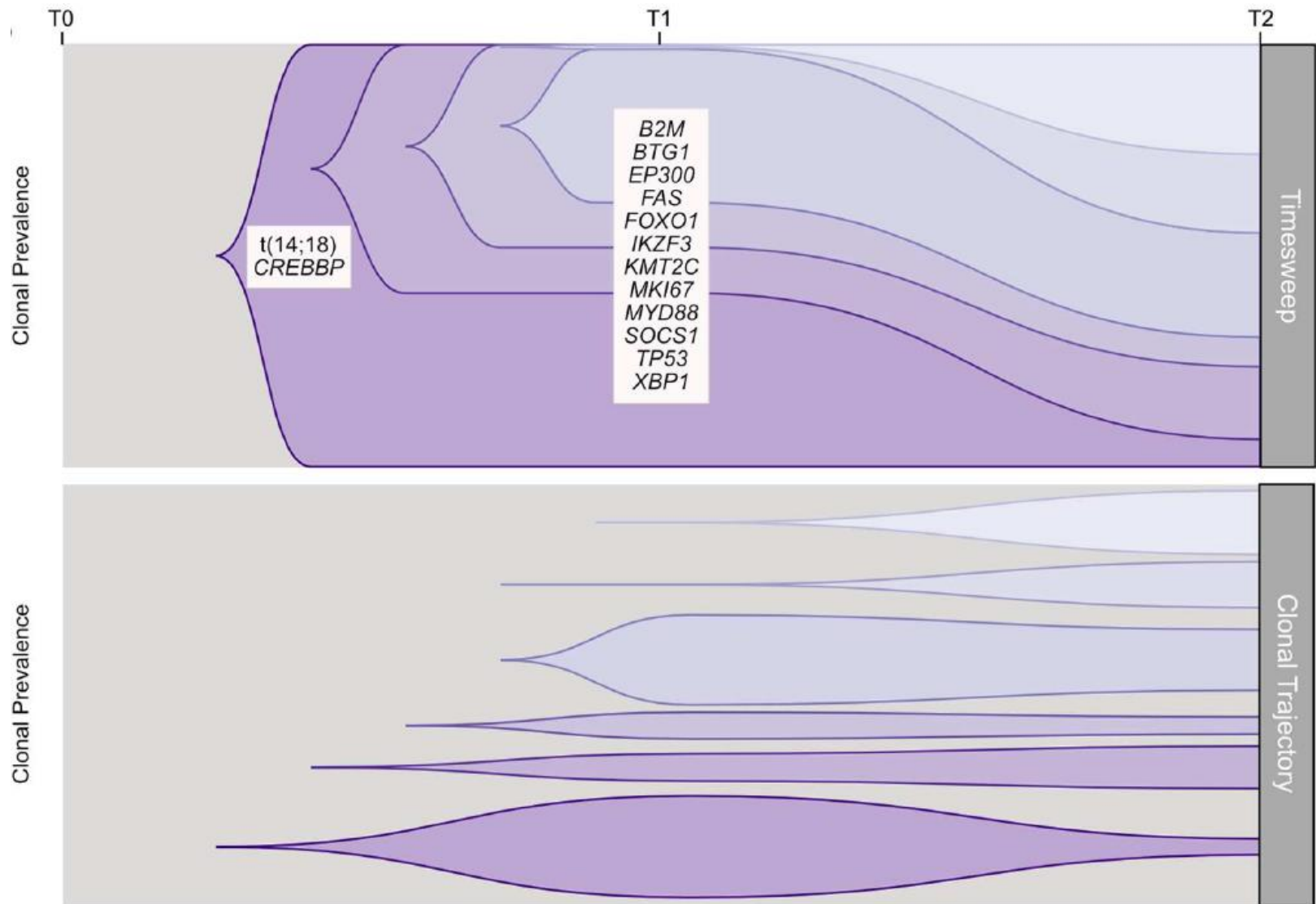
118 transformed pairs
41 early progressors
84 never progressors



Biology of Transformation

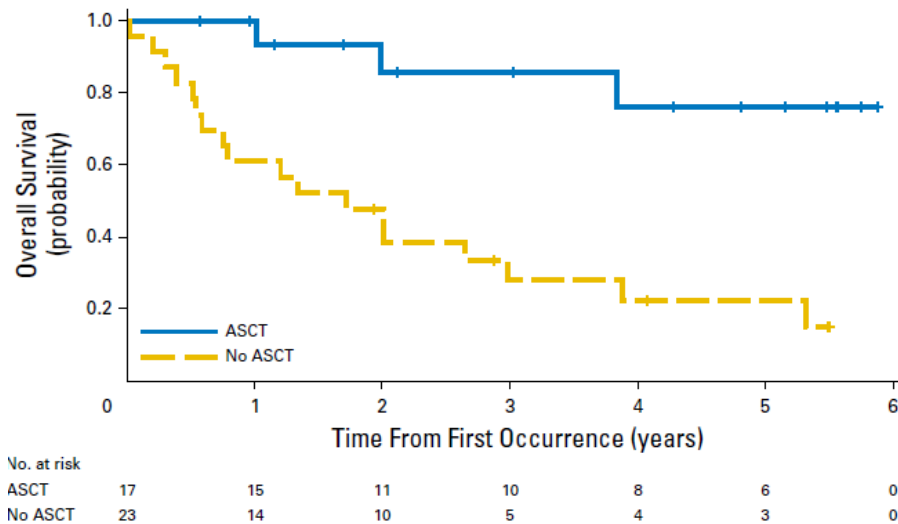
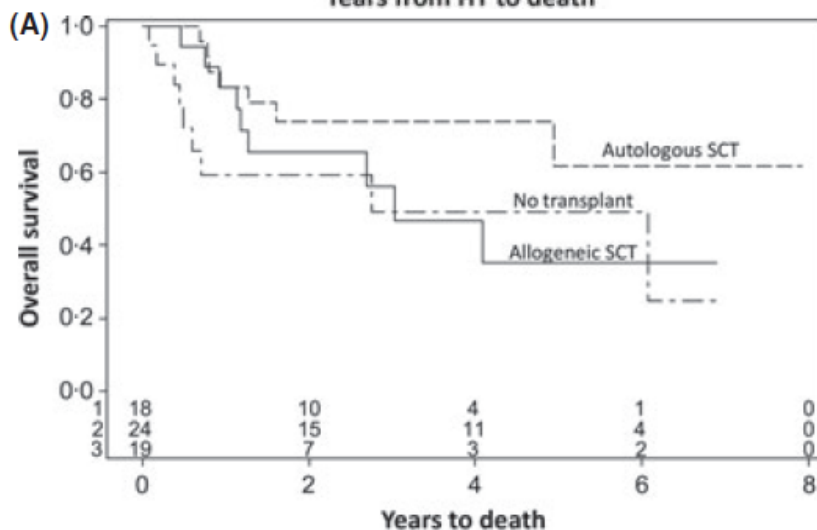
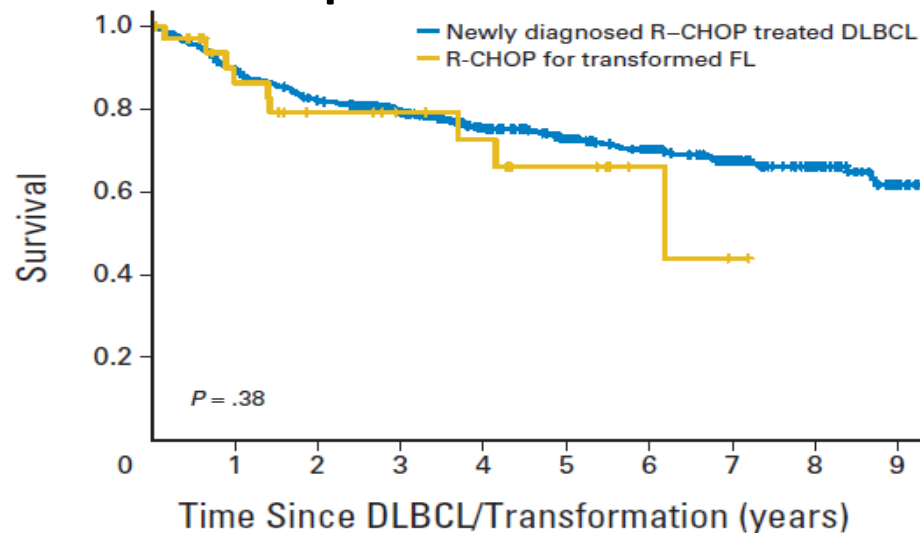
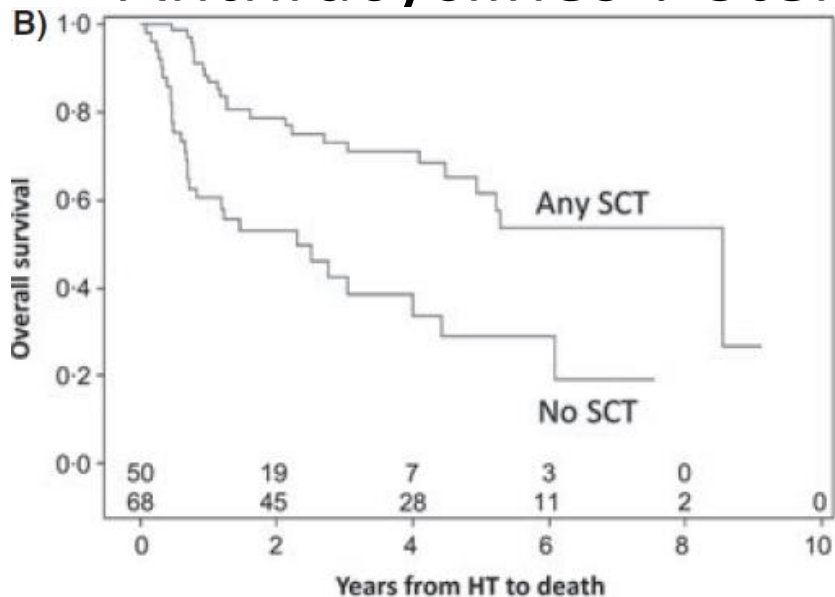


Biology of Early Progression



Optimal Management

- Anthracyclines ? Stem Cell Transplant ? Bexxar?



Conclusions FL Transformation

- Infrequent and minimally influenced by initial management factors except rituximab
- THEREFORE: Transformation deserves only limited consideration when choosing initial therapy or as an endpoint for trials of initial therapy
- Outcomes are disappointing but not dire
- Anthracycline – immunochemotherapy for those naive to such.
- Auto SCT is somewhat popular on the basis of consistent though potentially flawed retrospective series.