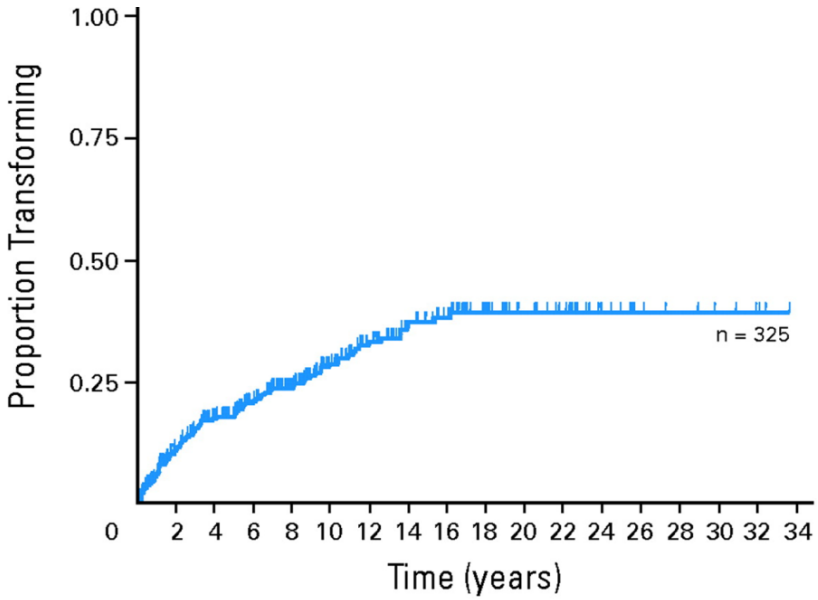
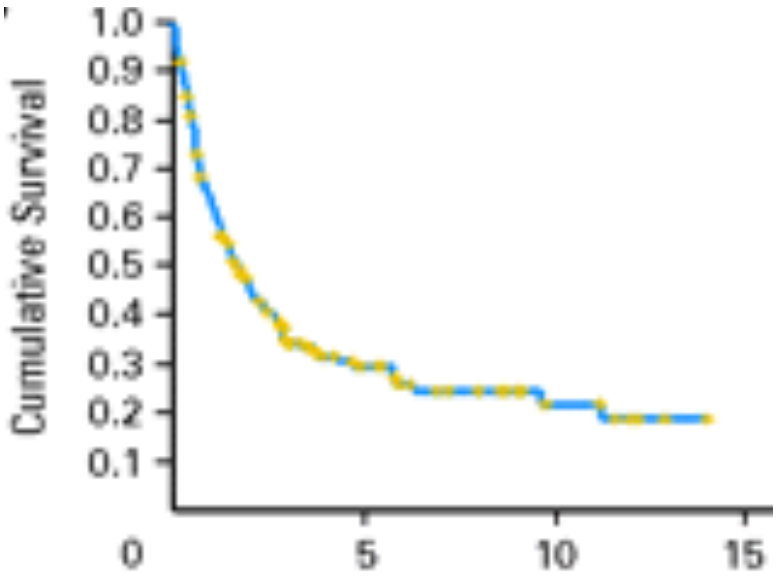
Transformed follicular lymphoma

Jonathan W. Friedberg M.D., M.M.Sc.

The past:
Incidence and Outcome of Transformed NHL





Steady risk of 3% per year for first 15 years of diagnosis
Treatment (or lack thereof) does not impact risk
Poor overall survival, particularly for advanced stage disease

Montoto et al, *JCO* 25: 2426
Al-Tourah et al, *JCO* 26: 5165

Key recent themes in transformed FL

- Remains an important cause of morbidity and mortality for patients with FL.
- Increased biological understanding of clonal hierarchy involved in transformation.
- Incidence of HT may be decreasing in rituximab era.
- Outcomes have improved significantly, for unclear reasons.
  - Heterogeneity of mutations have differential outcomes, i.e. “double hit” GCB DLBCL.
- These improved outcomes have led to significant OS improvements in FL.

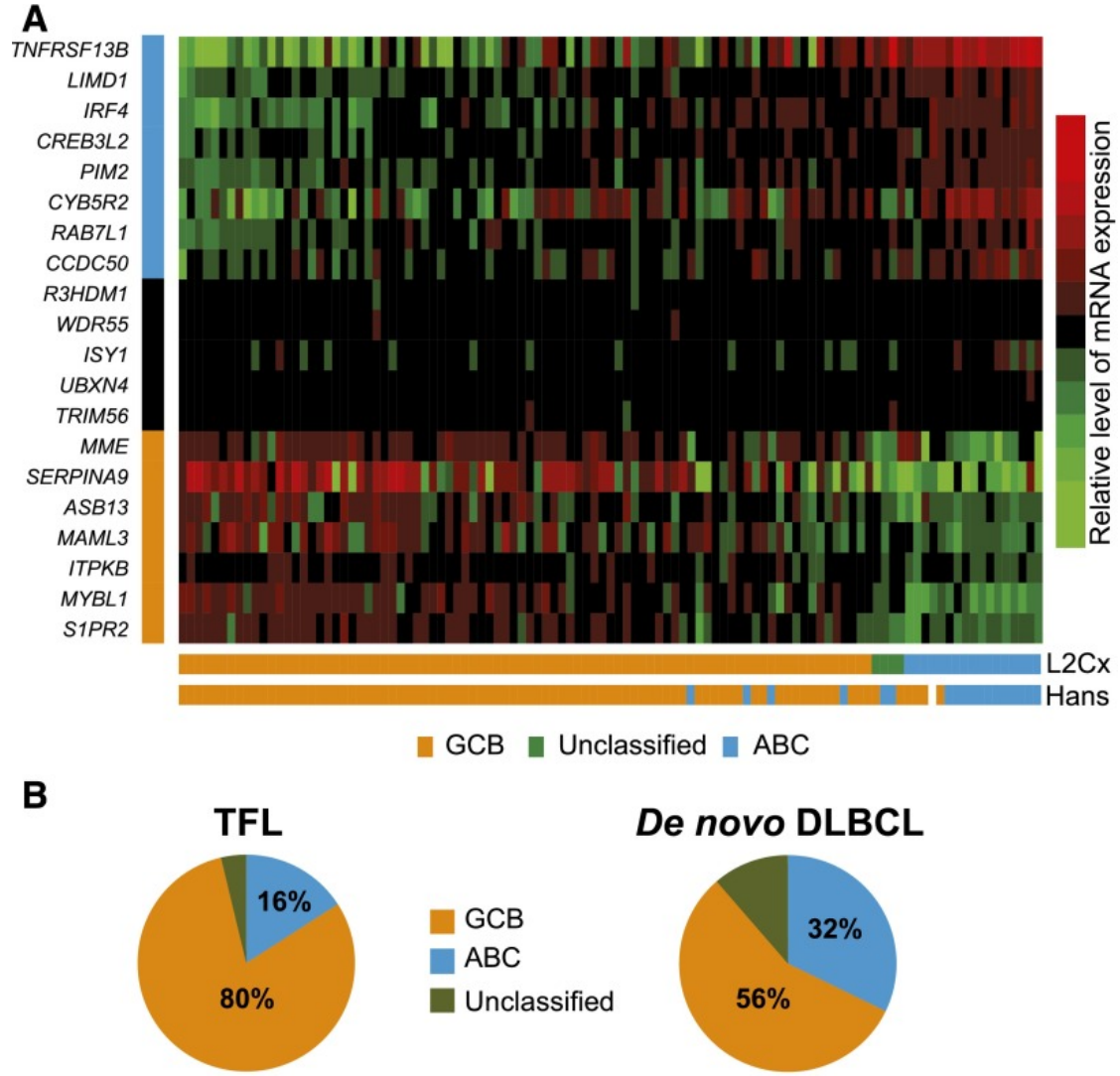
Biology and Pathogenesis of Transformation

Cell of origin of transformed FL

Using Lymph2Cx assay, Heterogeneity of transformed FL was demonstrated:

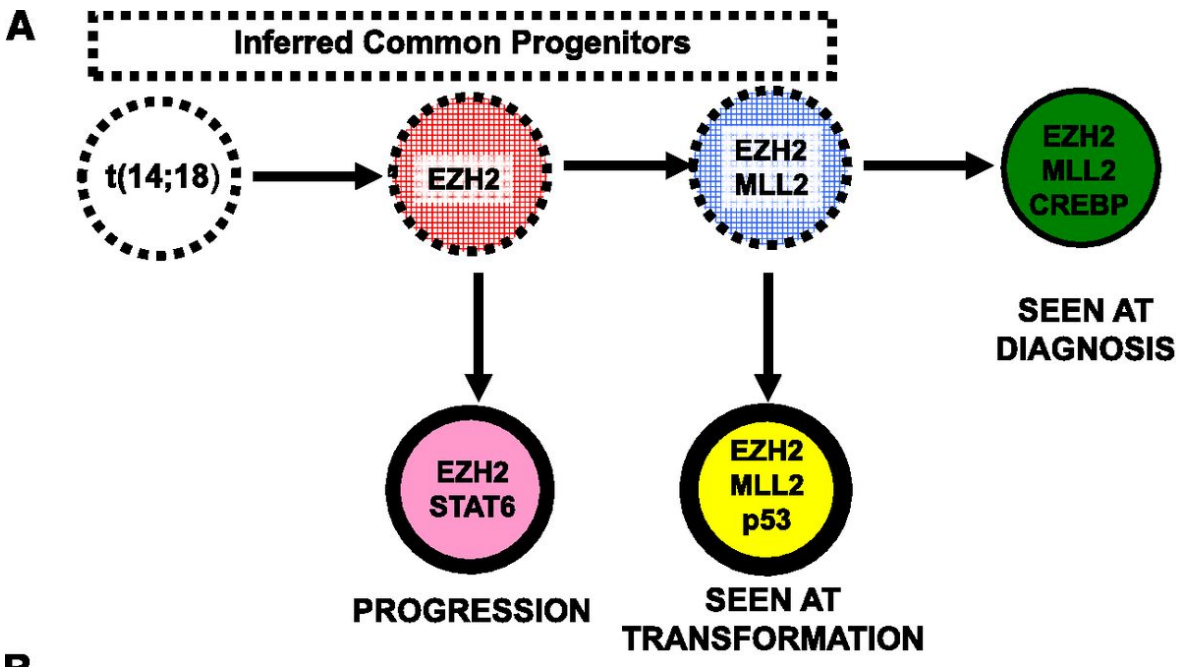
80% GCB subtype

Remainder ABC subtype, arising from BCL2 translocation-negative and/or IRF4-expressing FLs.



Kridel et al, *Blood* 126(18):2118-27, 2015

New biologic understanding of transformed FL

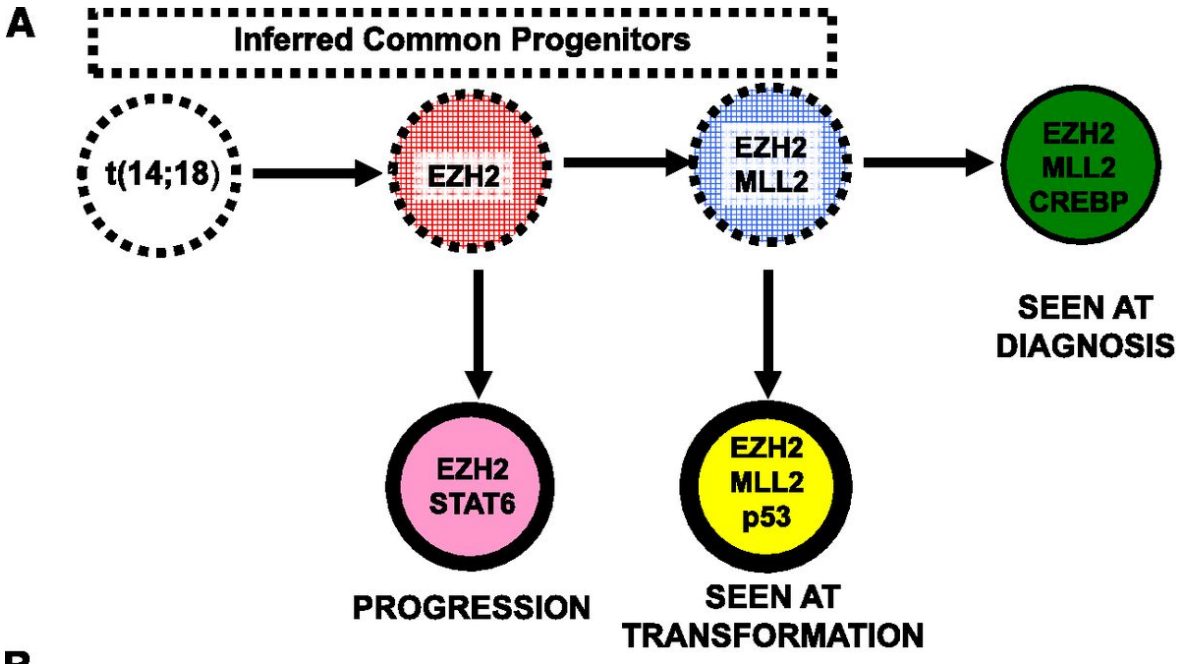


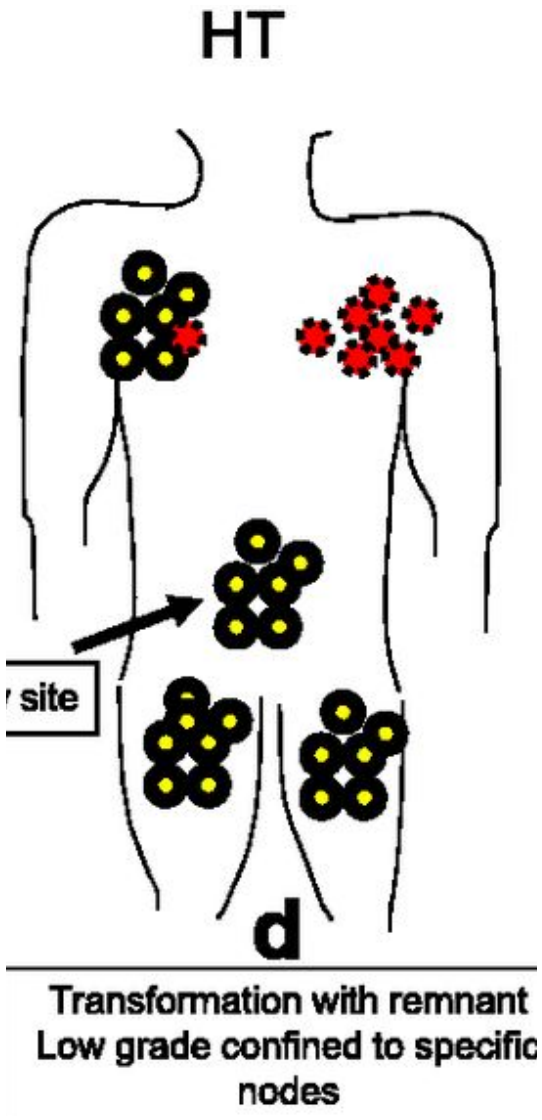
Numerous subclones present in FL.

Population that arises at HT is not directly descended from diagnosis or relapsed population.

Casulo, Burack, Friedberg *Blood* 125: 40-7

New biologic understanding of transformed FL





Casulo, Burack, Friedberg *Blood* 125: 40-7

RESEARCH ARTICLE

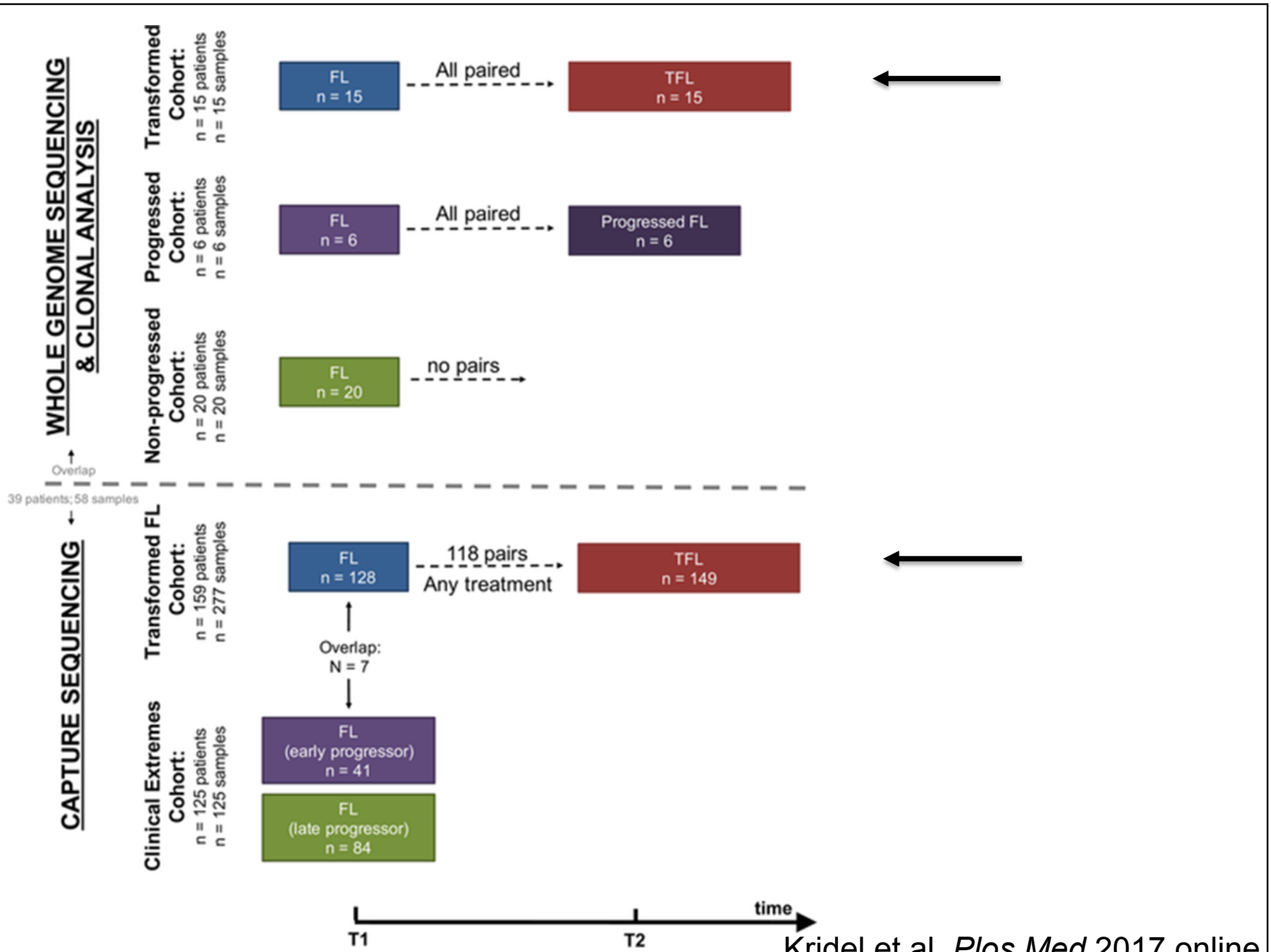
Histological Transformation and Progression in Follicular Lymphoma: A Clonal Evolution Study

Robert Kridel[1☯¤a], Fong Chun Chan[1,2☯], Anja Mottok[1,3], Merrill Boyle[1], Pedro Farinha[1], King Tan[1], Barbara Meissner[1], Ali Bashashati[4], Andrew McPherson[4], Andrew Roth[2,4], Karey Shumansky[4], Damian Yap[4], Susana Ben-Neriah[1], Jamie Rosner[4], Maia A. Smith[2,4], Cydney Nielsen[4], Eva GineÂ[1], Adele Telenius[1], Daisuke Ennishi[1], Andrew Mungall[5], Richard Moore[5], Ryan D. Morin[5,6], Nathalie A. Johnson[7], Laurie H. Sehn[1], Thomas Tousseyn[8,9], Ahmet Dogan[10,11], Joseph M. Connors[1], David W. Scott[1], Christian Steidl[1,3], Marco A. Marra[5], Randy D. Gascoyne[1,3], Sohrab P. Shah[3,4]*

PLoS MEDICINE

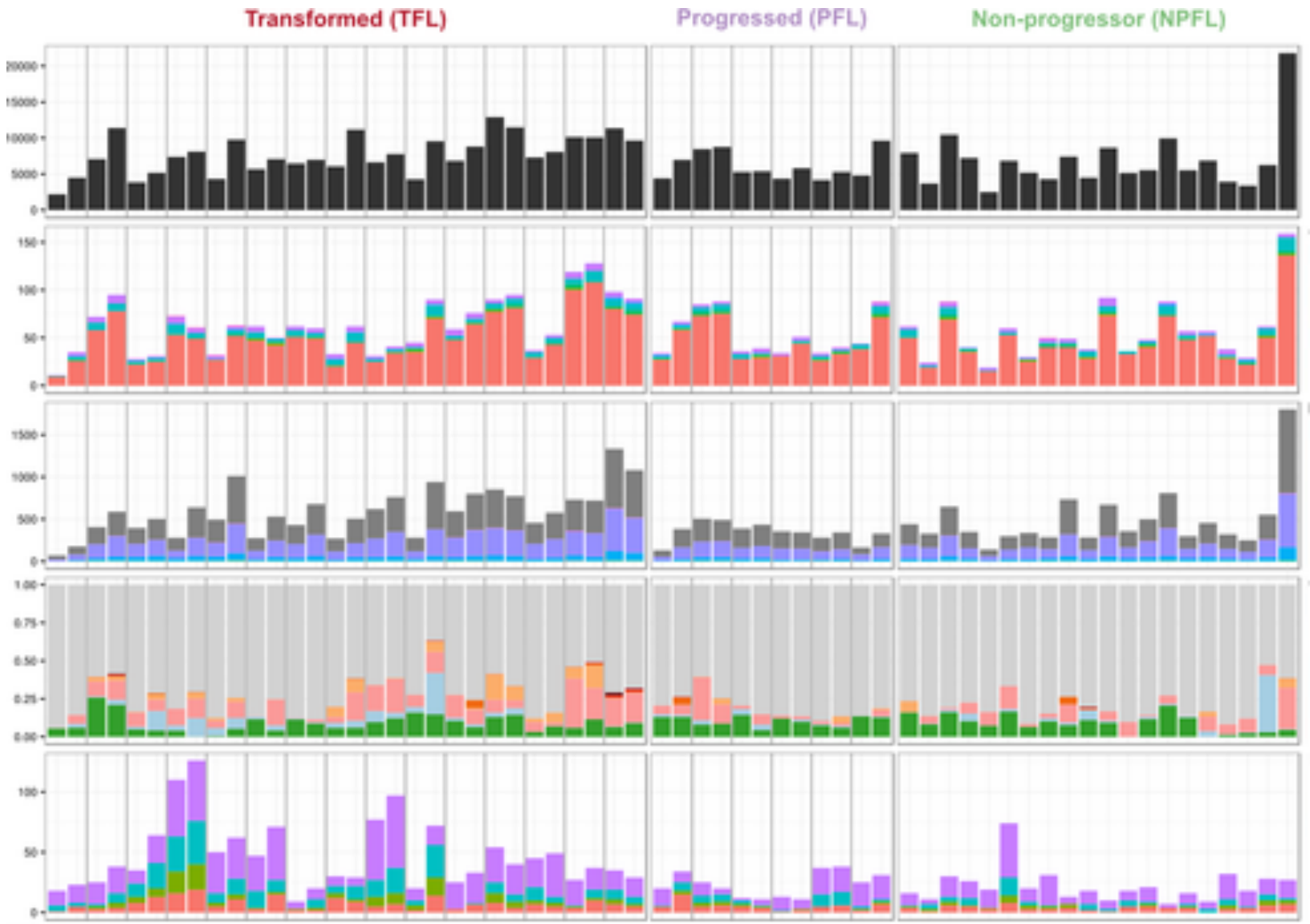
"We contended that detailed characterization of clonal dynamics would reveal fundamental biological properties with implications for future patient management strategies relating to both transformation and progression."

"We also sought to identify recurrent gene mutations associated with transformation and/or early progression in a large patient cohort."



Kridel et al, *Plos Med* 2017 online

High level WGS overview



Single nucleotide variants

Coding variants

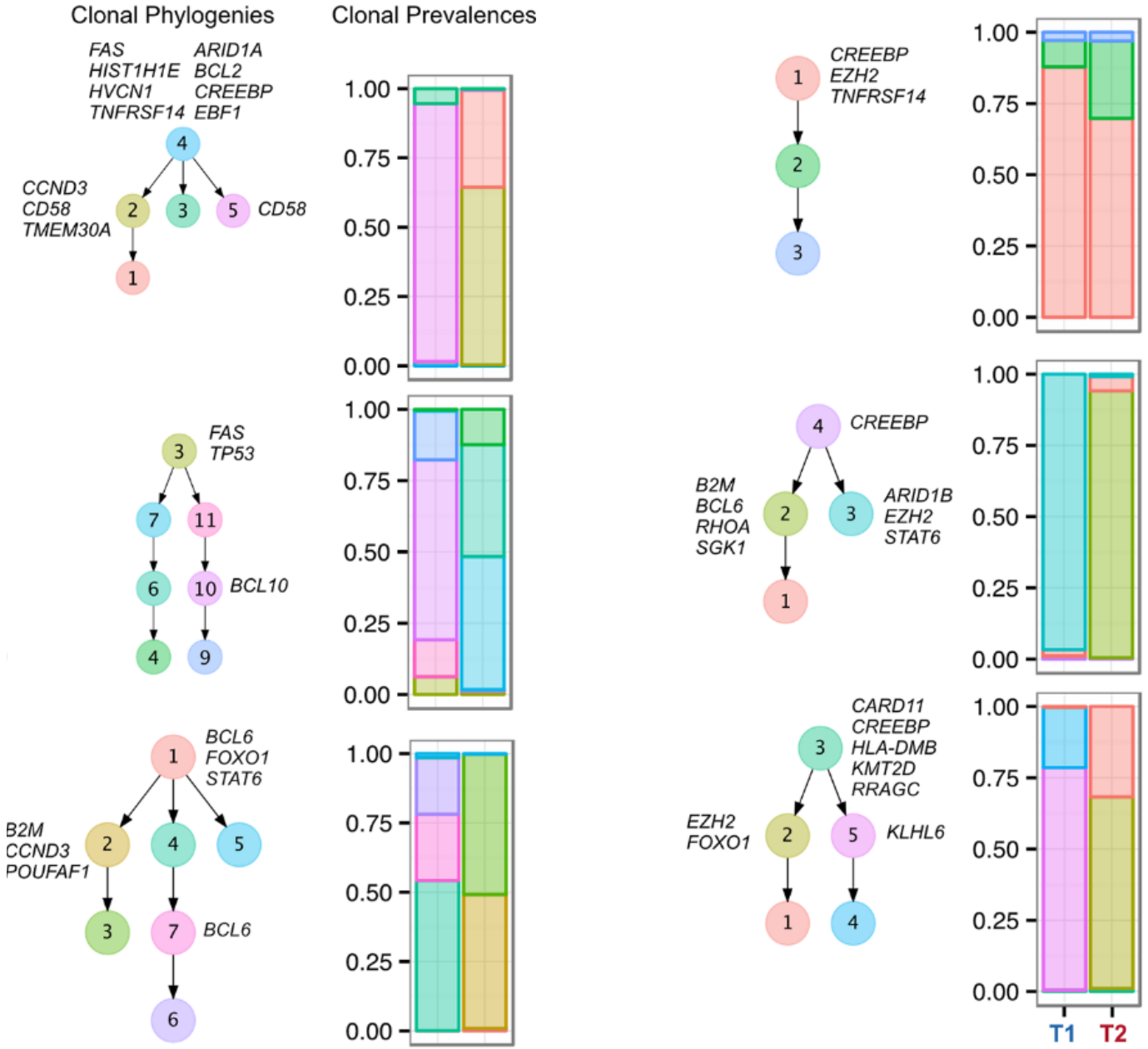
Insertions and deletions

Altered copy number fraction

Structural rearrangements

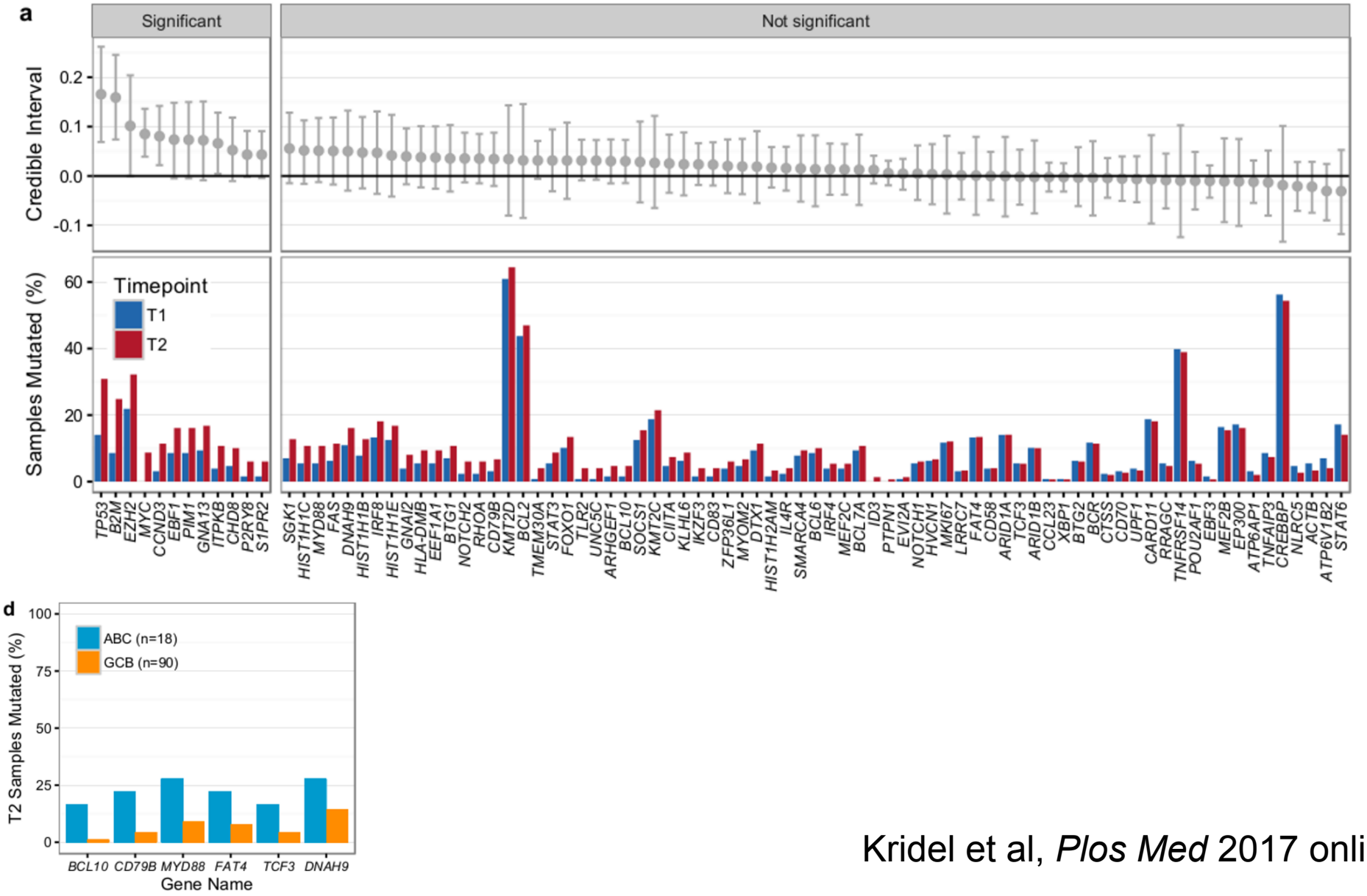
Kridel et al, *Plos Med* 2017 online

Clonal phylogenies of transformed FL



Kridel et al,
Plos Med
2017 online

Targeted sequencing of 86 genes in transformed follicular lymphoma samples



Kridel et al, *Plos Med* 2017 online

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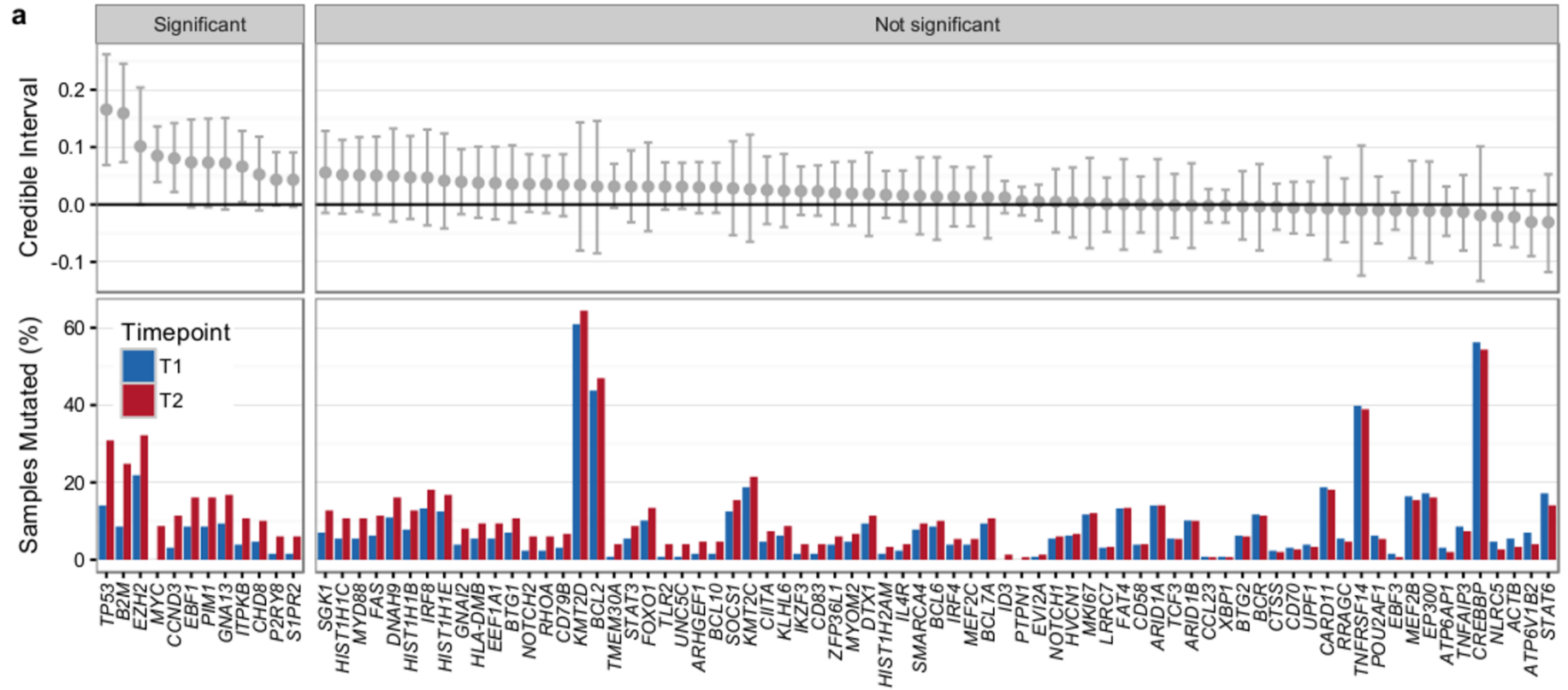
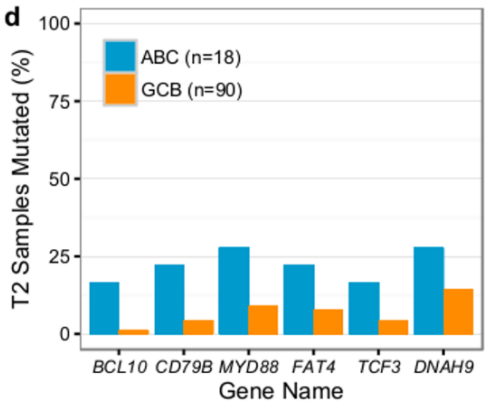




Bcl-2

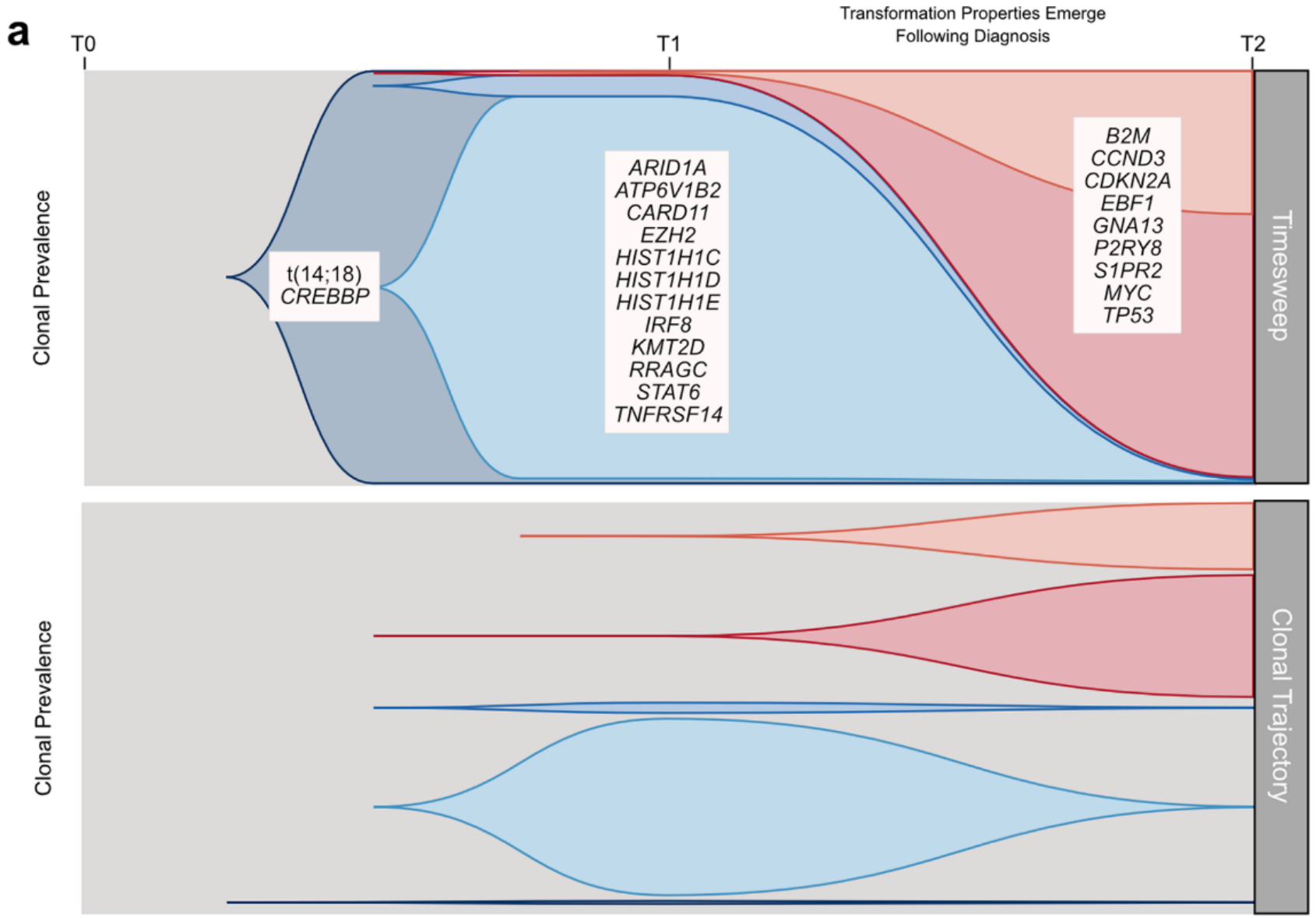
MLL2

CREBBP

TNFRSF14

Kridel et al, *Plos Med* 2017 online

Putting it together: Schematic model of evolutionary progression in transformed follicular lymphoma



Therapeutic implications of WGS studies in transformed FL

- Evolutionary processes driving FL transformation independent of selective pressures by treatment.
  - Patients on observation transform.

- Association of known driver events (i.e. CCND3 mutations) with transformation suggests a positive selection pressure.

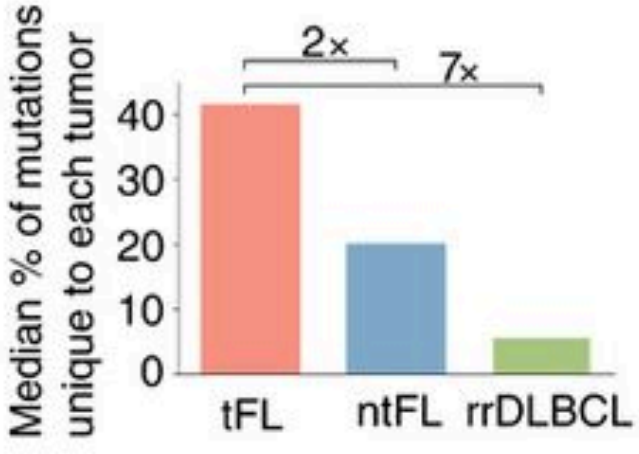
- Future work needed on how these driver events emerge and modify founder events to ultimately understand mechanism of transformation.

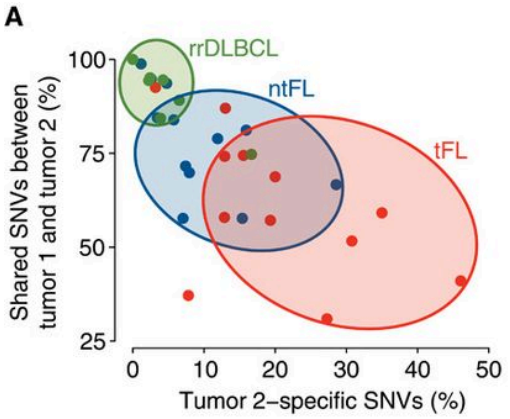
Kridel et al, *Plos Med* 2017 online

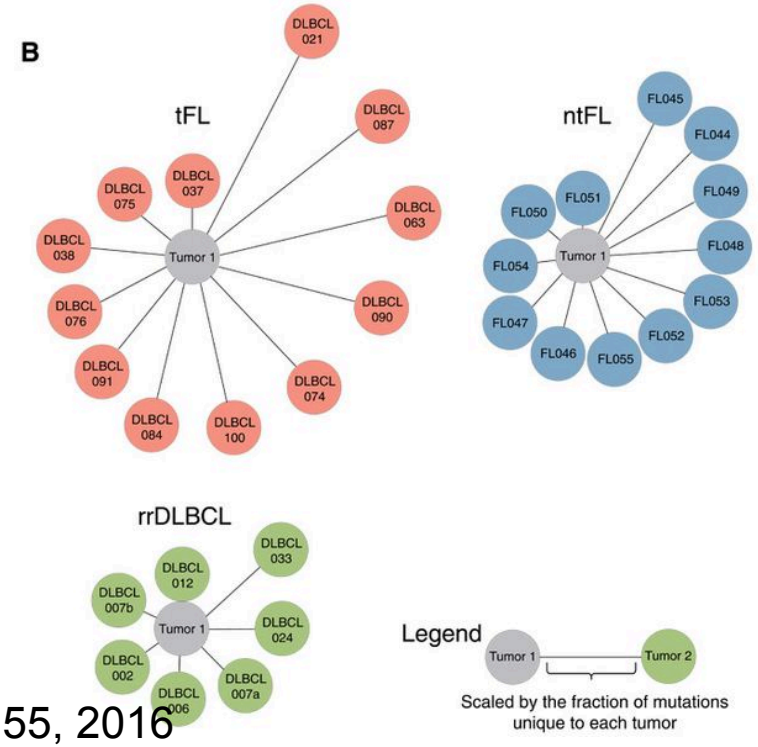
Patterns of genome evolution toward transformed lymphoma revealed by circulating tumor DNA

Distinct patterns of clonal evolution distinguish indolent follicular lymphomas from those that transform into DLBCL.

Circulating tumor DNA (ctDNA) profiling can reveal molecular determinants of adverse outcomes.

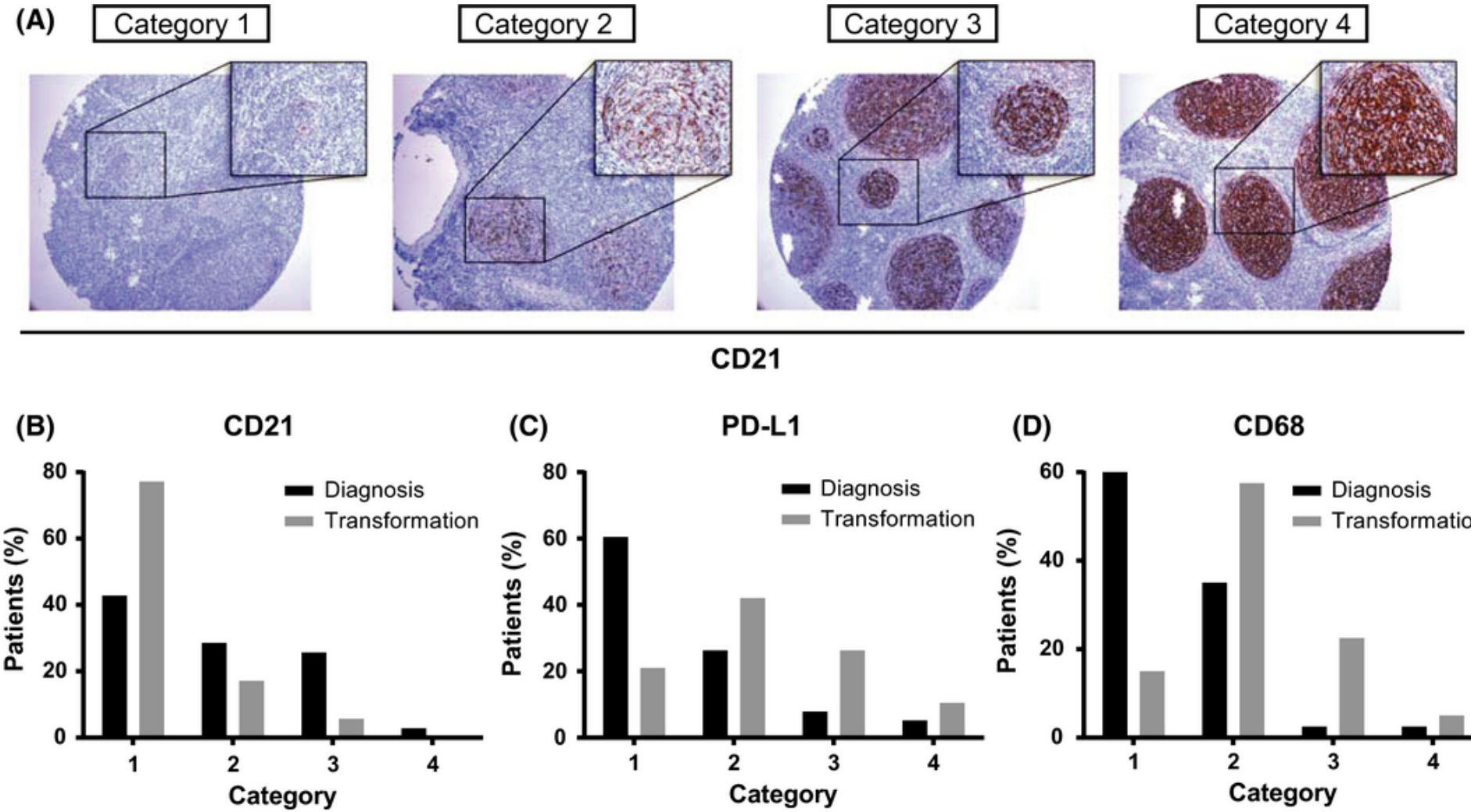






Scherer et al, *Science Translational Medicine* 8: 364ra155, 2016

Impact of the microenvironment: Better developed CD21+ FDC meshworks at diagnosis associated with shorter survival in tFL patients



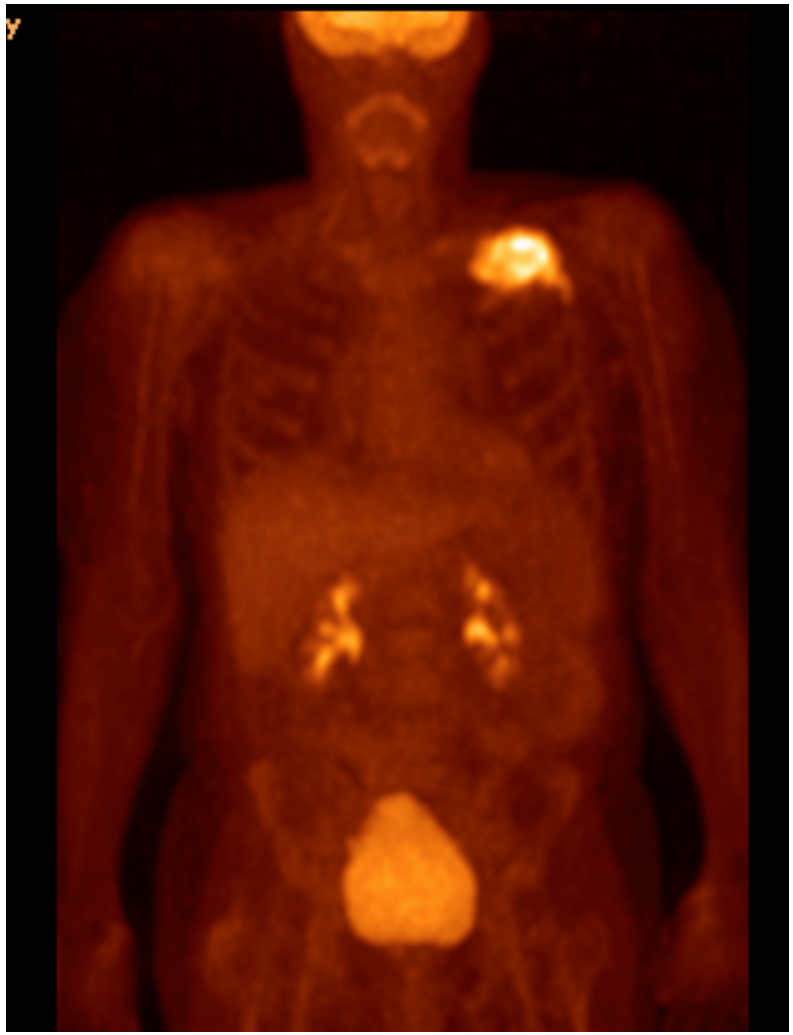
Blaker et al, *Brit J Haem* 175:102-14, 2106

Management of transformation

FDG-PET in transformed FL

- N=33 patients
  - SUV of the biopsy site ranged from 3-38, mean 14, median 12.
  - majority of transformations have a high SUV max for pretreatment staging study.

PET important tool to select biopsy site in suspected HT



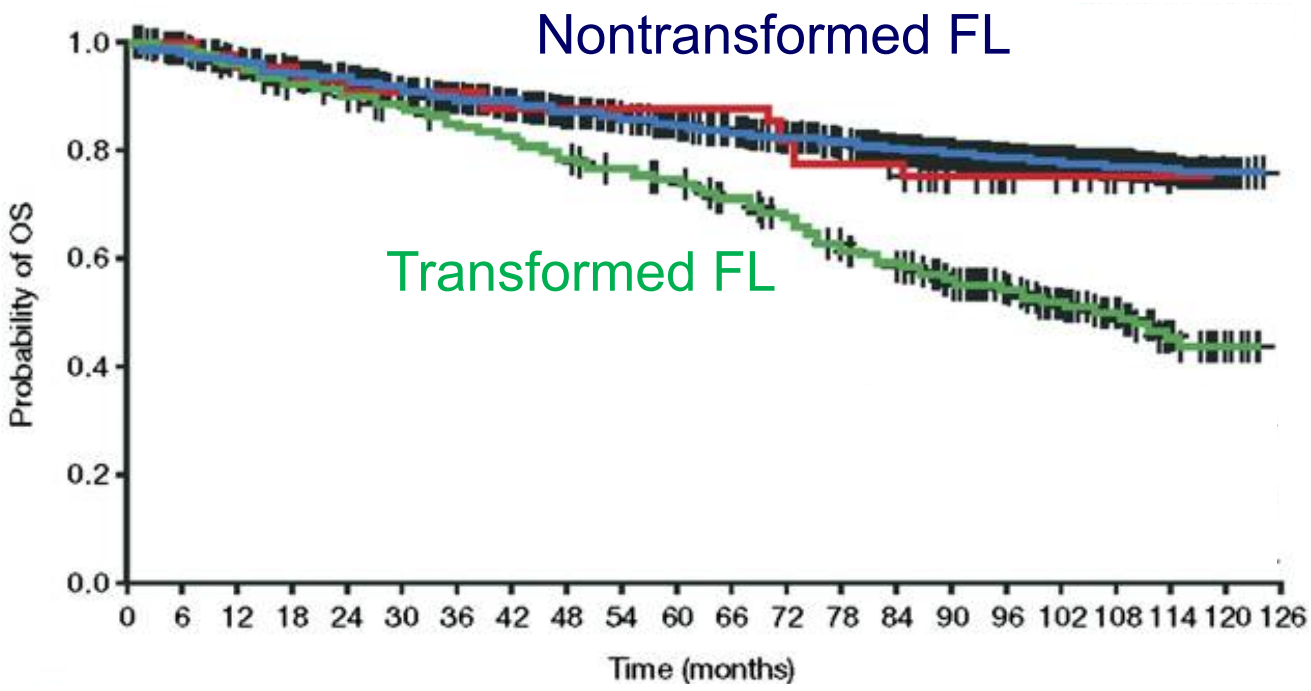
Noy et al, *Annals Oncol 20:508*

Improved OS for transformed FL, but still a major cause of mortality

Median OS 5 years.

Maintenance rituximab was associated with reduced transformation risk (HR, 0.67).

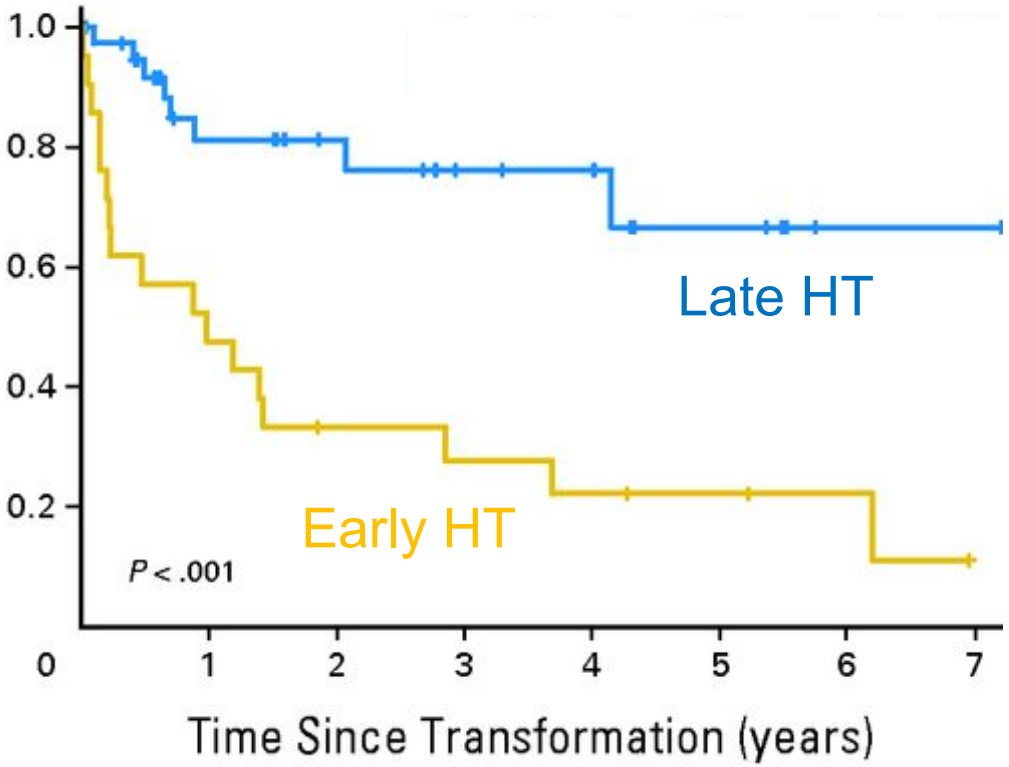
OVERALL SURVIVAL, NLCS



Wagner-Johnson et al, *Blood* 126:851-7, 2015

Outcome (OS) of HT has improved

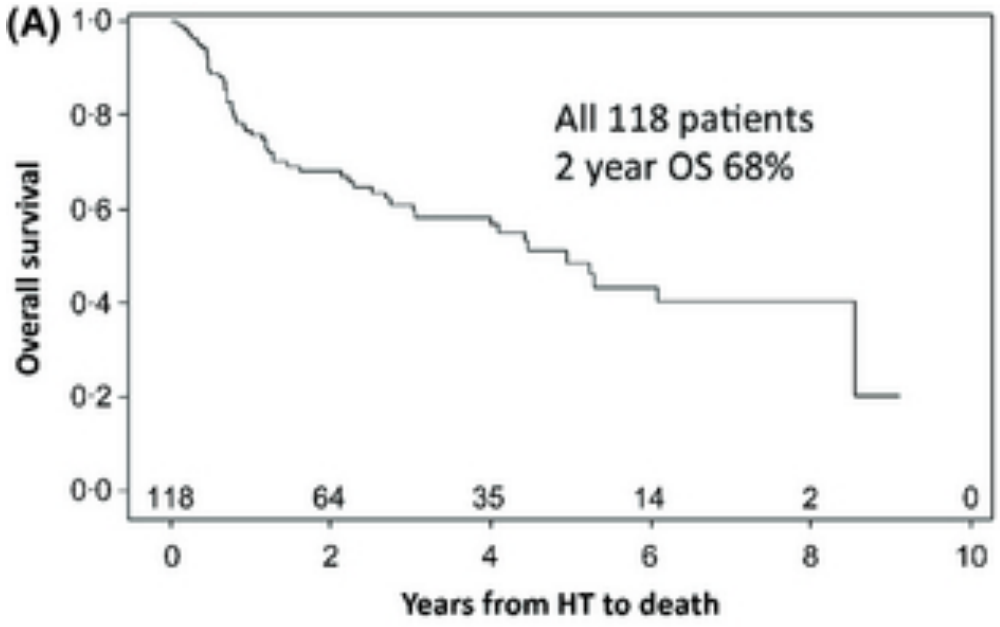
- N= 631 FL patients SPORE
  - 60 patients developed HT, 51 biopsy proven.
- Estimated HT rate of 2%/yr.
  - Median f/u 5 yrs.
- Median OS post HT 50 months
  - Superior in pts > 18 months after FL diagnosis compared with patients with earlier HT (P < .001).



Link et al, *JCO* 31:3272

Outcome (OS) of HT has improved

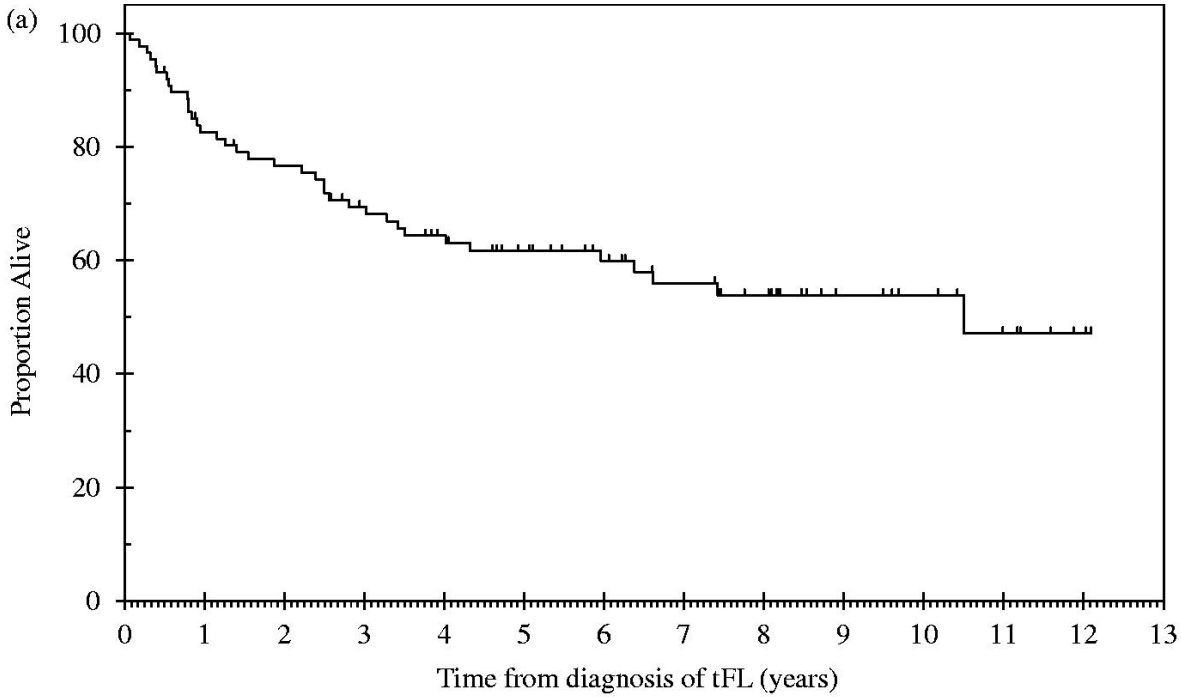
- NCCN database, N=118:
  - biopsy confirmed HT
  - Survival improved with no prior FL therapy



Ban Hoefen…Friedberg, *BJHaem* 163: 487

Outcome (OS) of HT has improved

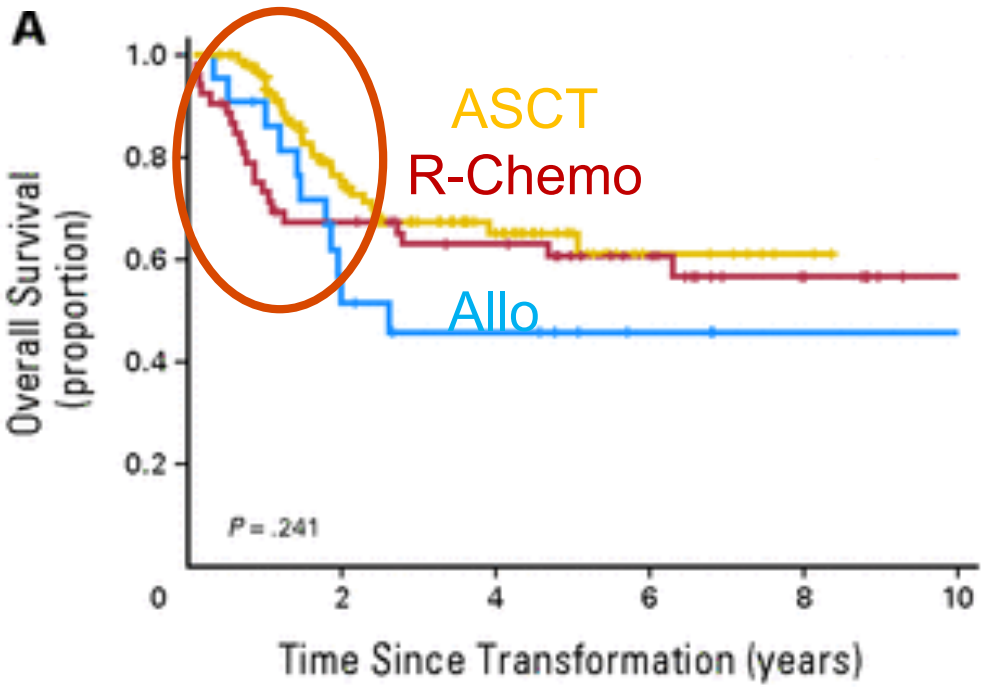
- Royal Marsden 2003-13 (N=87):
  - Median f/u 8 yrs
  - 89% no ASCT
  - RCHOP alone: 5yr OS 64%
    - Improved outcomes with rituximab maintenance



Gleeson et al, *Leuk Lymphoma* 58:1805-1813, 2017

Role of ASCT for HT

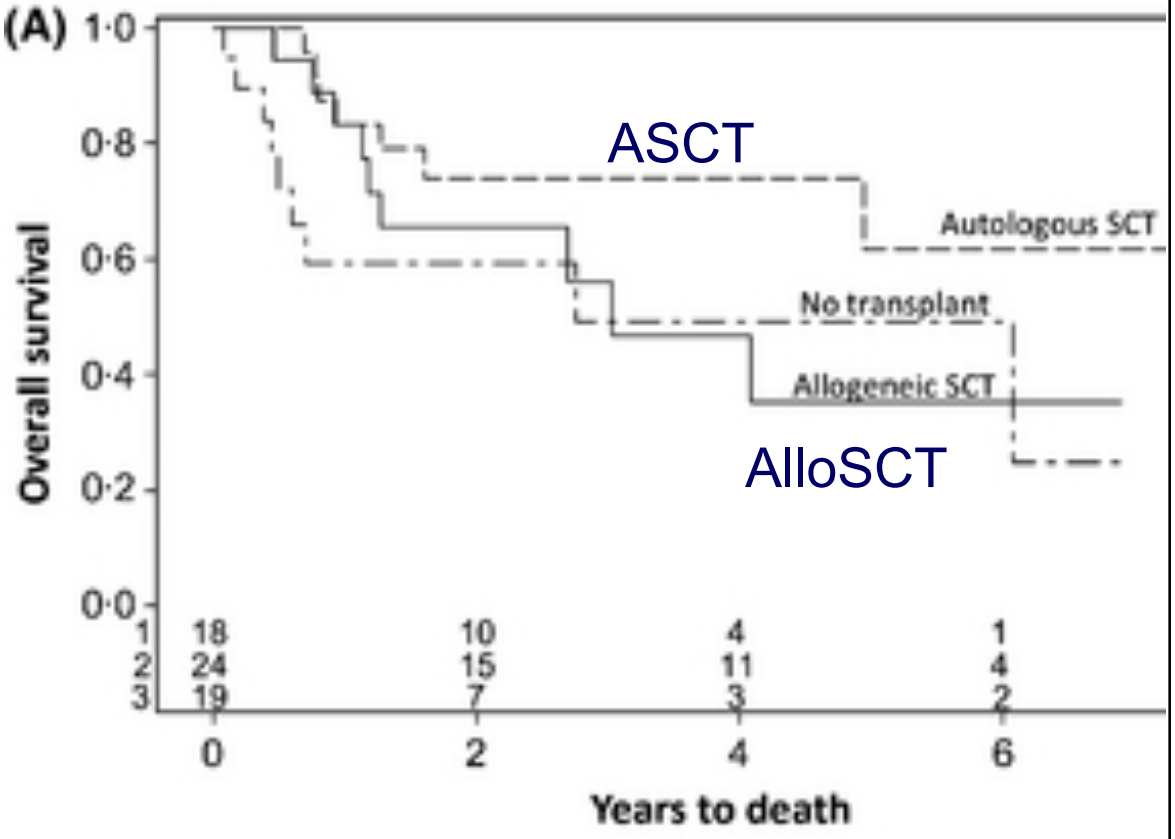
- N=172 Canadian Registry
  - 22 (13%) alloSCT
  - 97 (56%) ASCT
  - 53 (31%) R-Chemo
- ASCT had improved OS compared with R-Chemo alone (*P* = .12).
  - OS and PFS similar between those treated with ASCT and alloSCT.



Villa et al, *JCO* 31: 1164

Role of ASCT for HT

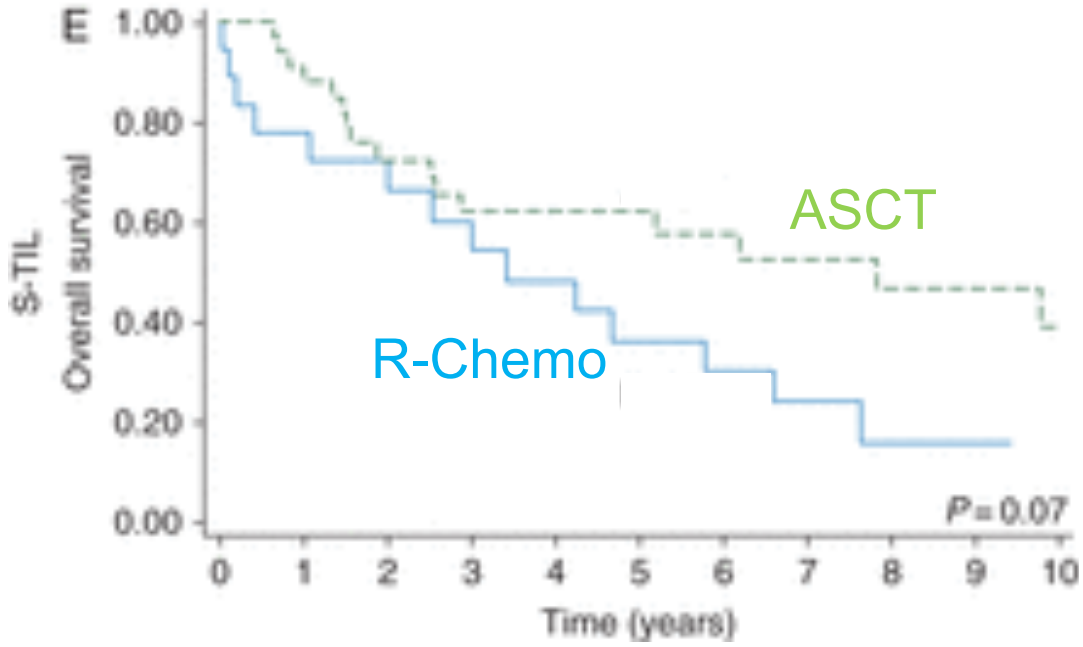
- NCCN database:
  - ASCT ≤60 years (*n* = 24), 2-year OS was 74%.
  - For non-transplanted aged ≤60 years (*n* = 19), the 2-year OS was 59%.



Ban Hoefen et al, *BJHaem* 163:487

Role of ASCT in HT

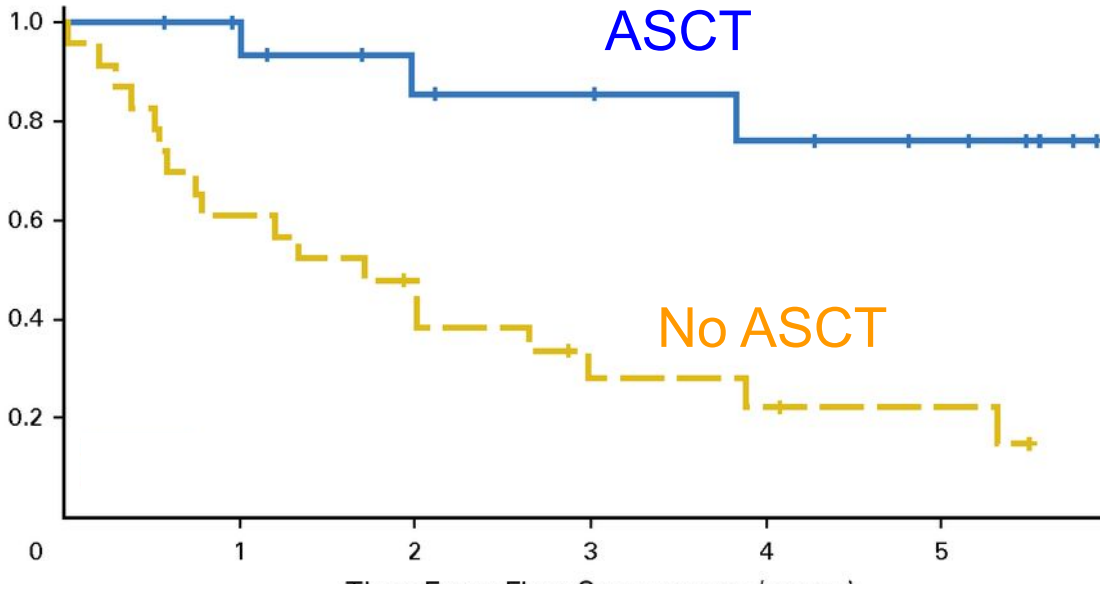
- N=85 pts from Denmark:
  - OS improved with ASCT for “sequential” rather than “composite” HT.
  - Median f/u 3.4 yrs.
  - Similar findings to other studies.



Madsen et al, *Annal Oncol* 26:393

Role of ASCT for HT

- PRIMA trial:
  - Median 6 year follow-up of 1018 FL patients.
  - Subset with histologic documentation
  - Early HT had poor outcome; median OS 6.4 years no HT vs. 3.8 years with HT.



Sarkozy et al, *JCO* 34:2575-82 2016

Challenges to interpretation of ASCT data

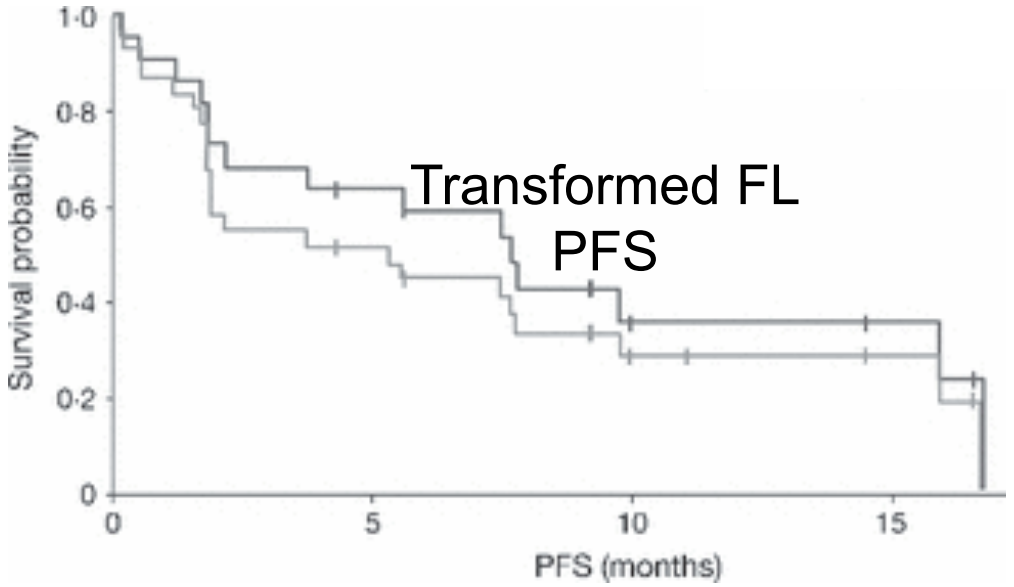
- No randomized or prospective trials
- Differential definitions
  - Clinical vs. pathological confirmation
  - Composite NHL vs. transformation
- Patient selection
  - Single institutional vs. registry
  - Elderly under-reported
- Rituximab era vs. no rituximab

Conclusions: ASCT for HT in rituximab era

- Outcomes in younger patients relatively favorable, with or without ASCT. Early HT has inferior prognosis.
- Nonrandomized studies suggest small benefit of ASCT, with relatively short follow-up.
- No clear role for alloSCT.
- Most patients older or frail and not ASCT candidates

Lenalidomide for HT

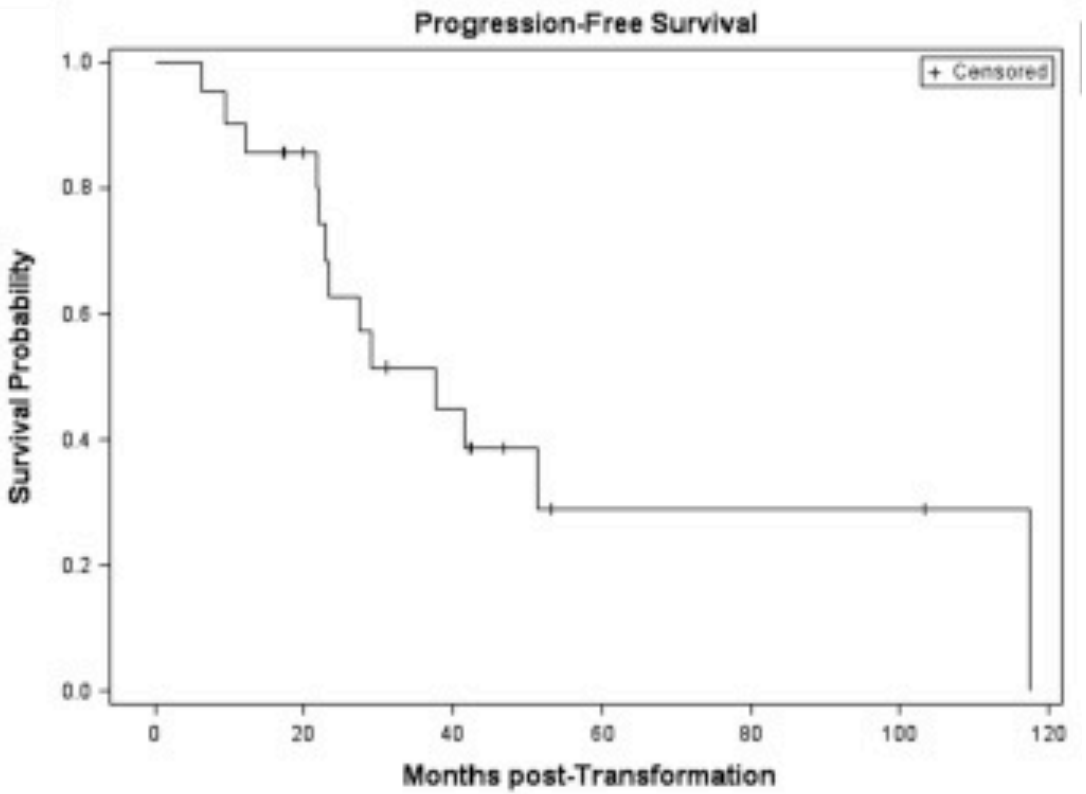
- N=33 pts
  - 25 mg dose
  - ORR 57%
  - Median DOR 1 yr
  - FL > other histologies



Czuczman et al, *BJHaem* 154: 477

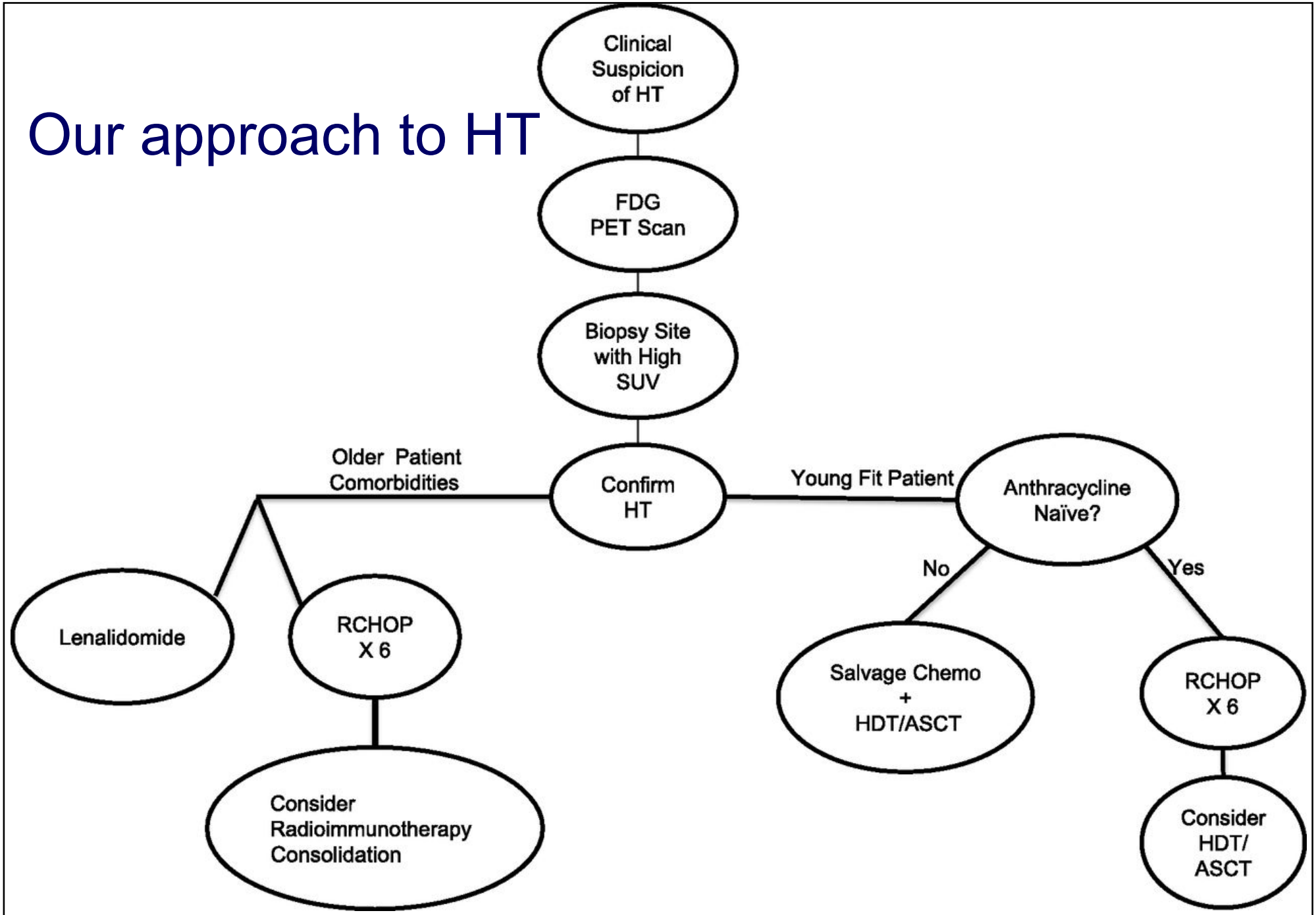
Consolidative RIT for HT: *Patients unfit for ASCT*

- N=21; R-CHOP + tositumomab or ibritumomab
- Median OS from HT: 84 months
- 2 cases of MDS/ AML

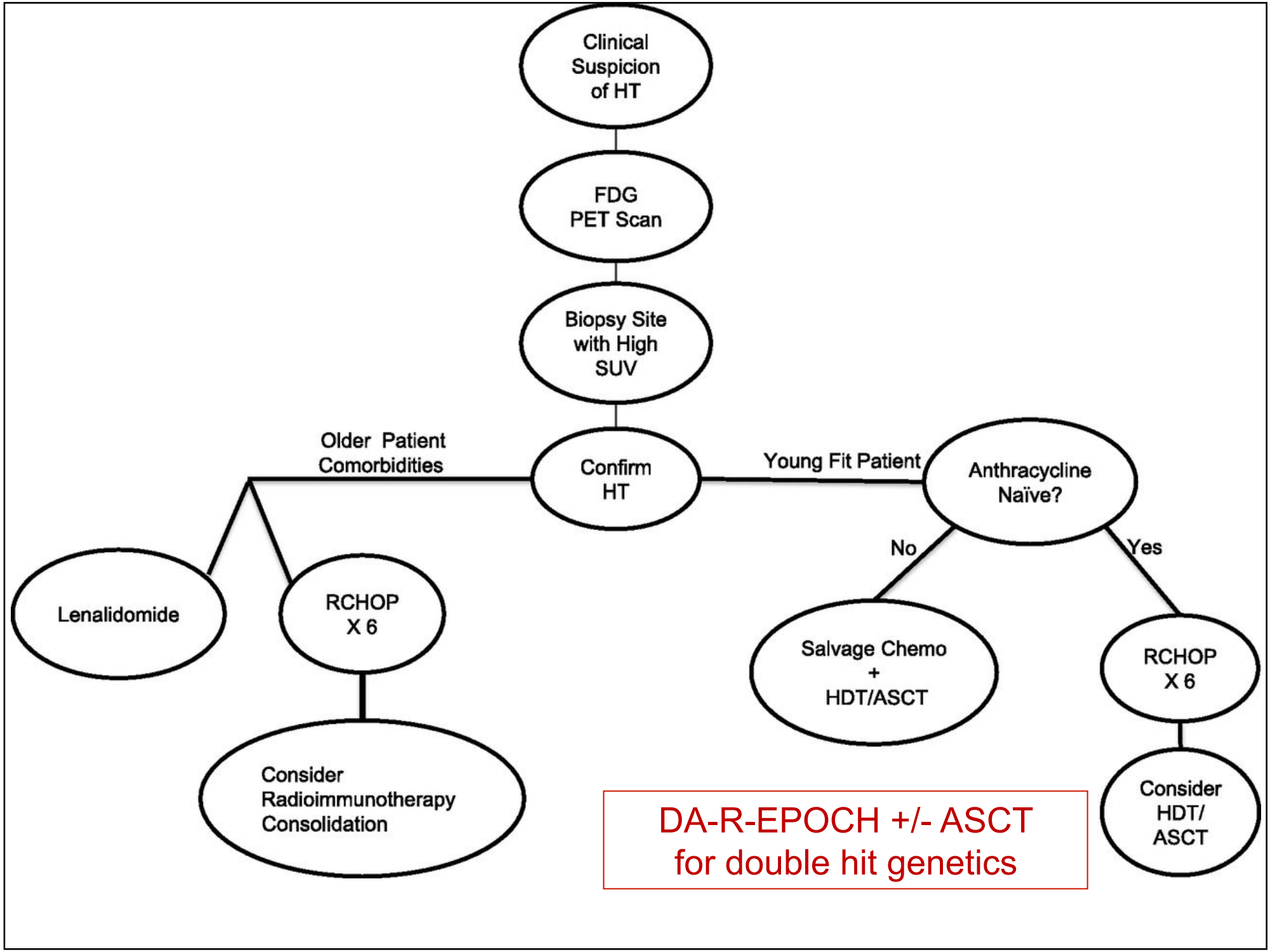


Reagan et al, *Clin Lymphoma* 16:322-8, 2016

Our approach to HT



Casulo, Burack, Friedberg *Blood* 125: 40, 2015


Clinical Suspicion of HT
FDG PET Scan
Biopsy Site with High SUV
Confirm HT
Older Patient Comorbidities
Young Fit Patient
Lenalidomide
RCHOP X 6
Consider Radioimmunotherapy Consolidation
Anthracycline Naïve?
No
Yes
Salvage Chemo + HDT/ASCT
RCHOP X 6
Consider HDT/ ASCT
DA-R-EPOCH +/- ASCT for double hit genetics


Acknowledgments
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UR
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