



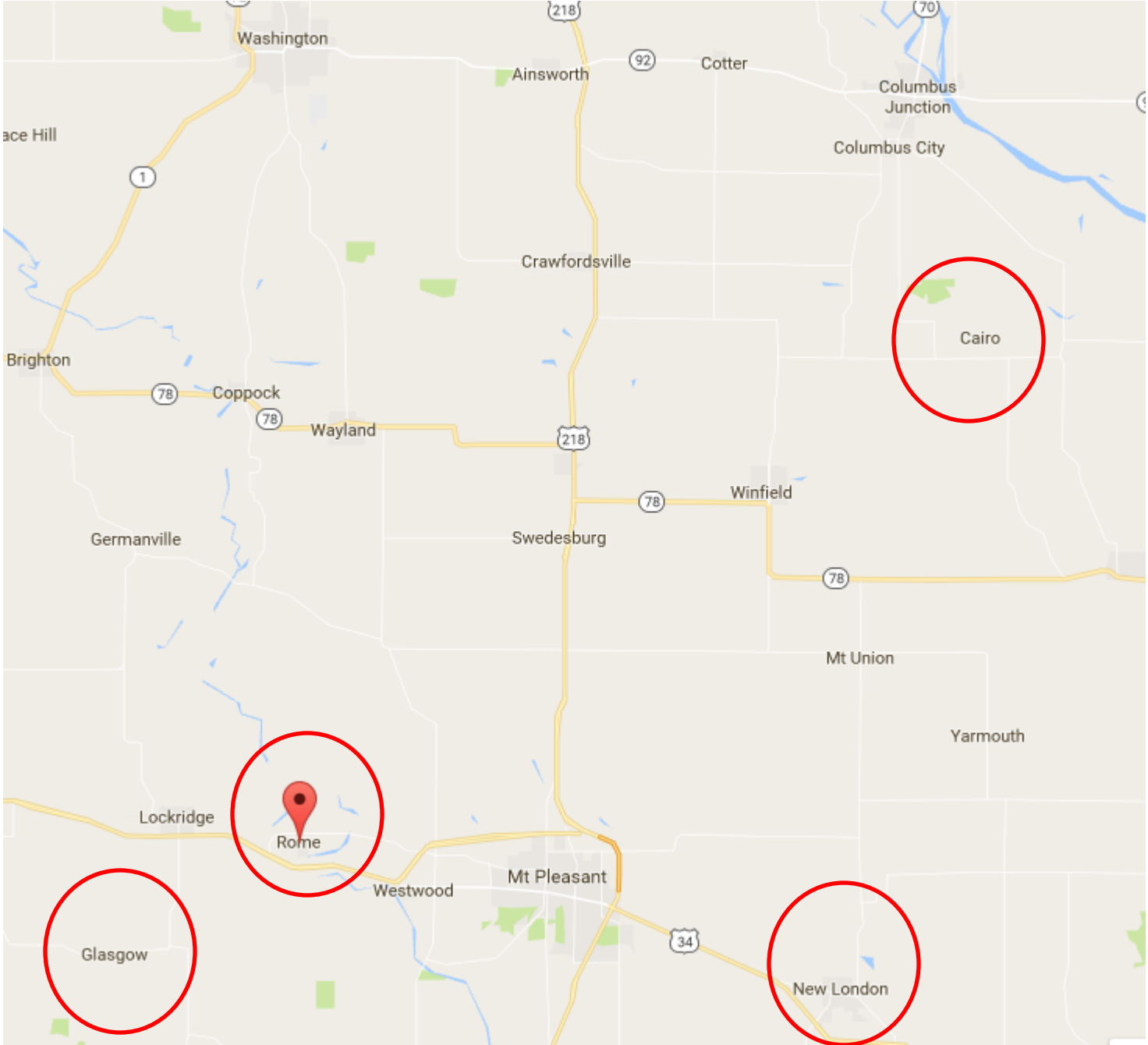
Rome,
March 23-24 2017

VOI Donna Camilla Savelli Hotel

Double Hit/Double Expressing Lymphomas

Clinical Presentation and Management

Brian K. Link
University of Iowa





Rome,
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VOI Donna Camilla Savelli Hotel

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						

B Cell Lymphomas with Myc/Bcl Terminology

- Double Hit Lymphomas
 - High grade B cell lymphomas with dual rearrangement
 - MYC + Bcl-2 or Bcl-6
 - Excluding:
 - follicular morphology
 - Non rearranged molecular derangement
- Dual Expressing Lymphomas
 - DLBCL NOS with IHC over expression of
 - Myc (40-50%)
 - Bcl-2 (50-70%)

B Cell Lymphomas with Myc/Bcl Frequency

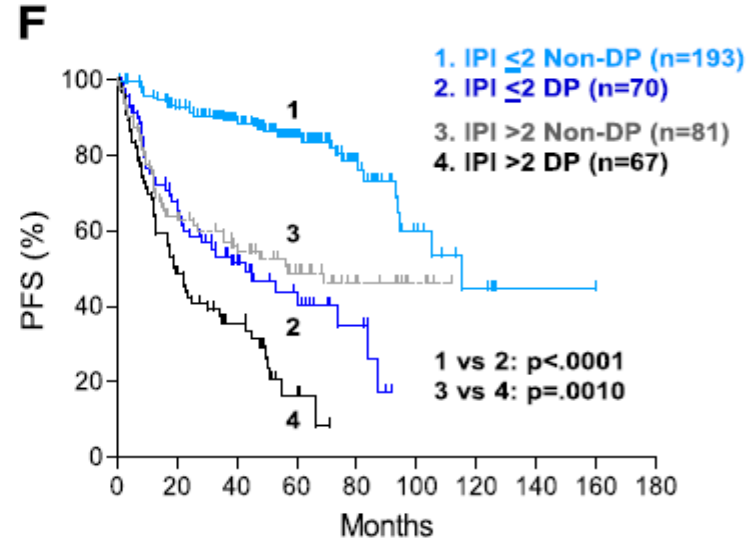
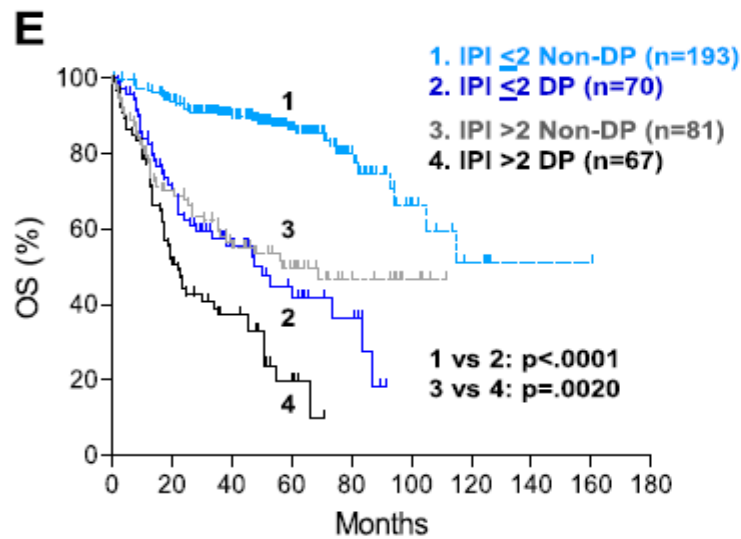
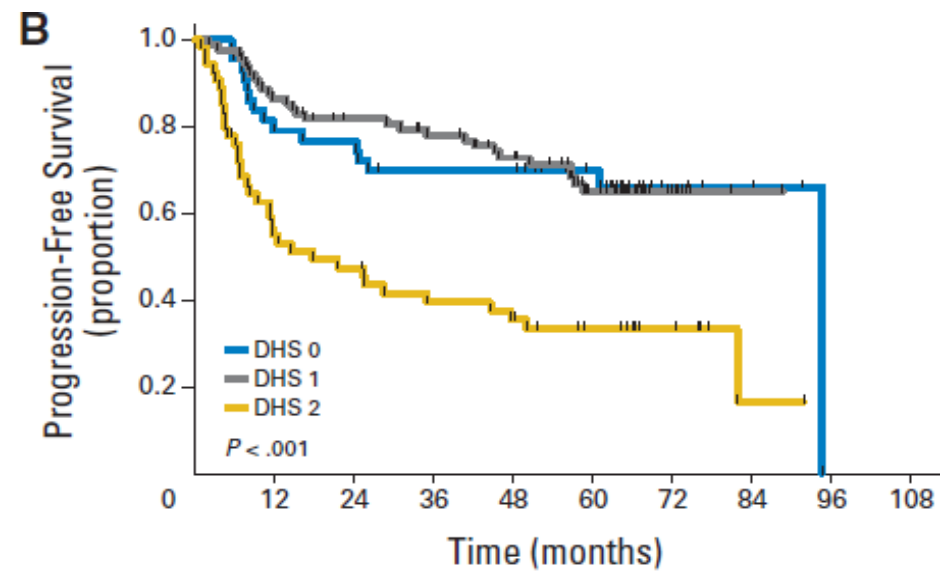
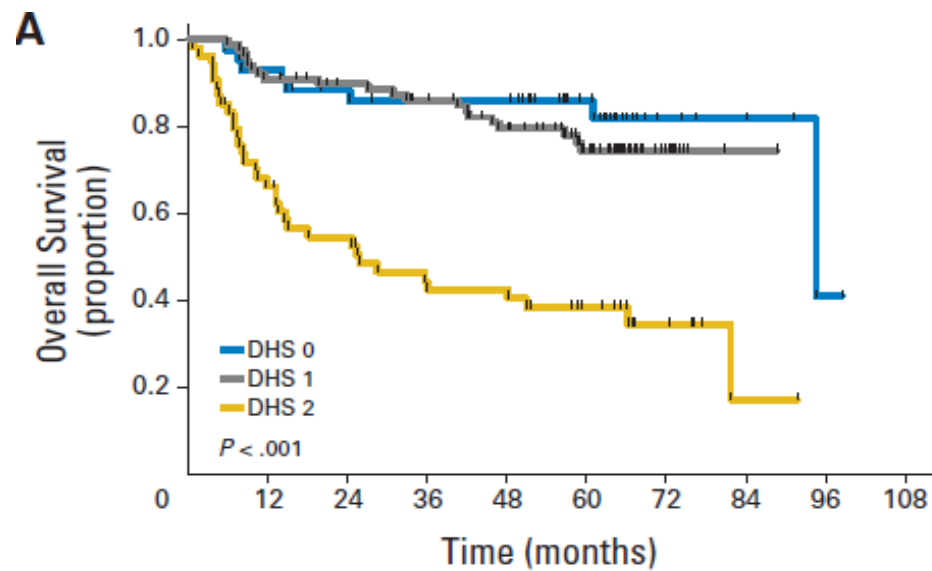
	DLBCL		HGBCL
	<u>GCB</u>	<u>ABC</u>	
MYC + by IHC	27%	35%	60%
translocation	21%	5%	60%
BCL-2+ by IHC	43%	63%	70%
translocation	25%	5%	40%
DE DLBCL	15%	23%	NA
MYC/BCL-2 trans	6%	1%	30%
MYC/BCL-6 trans	2%	2%	

Adapted from Sesques and Johnson BLOOD 2017

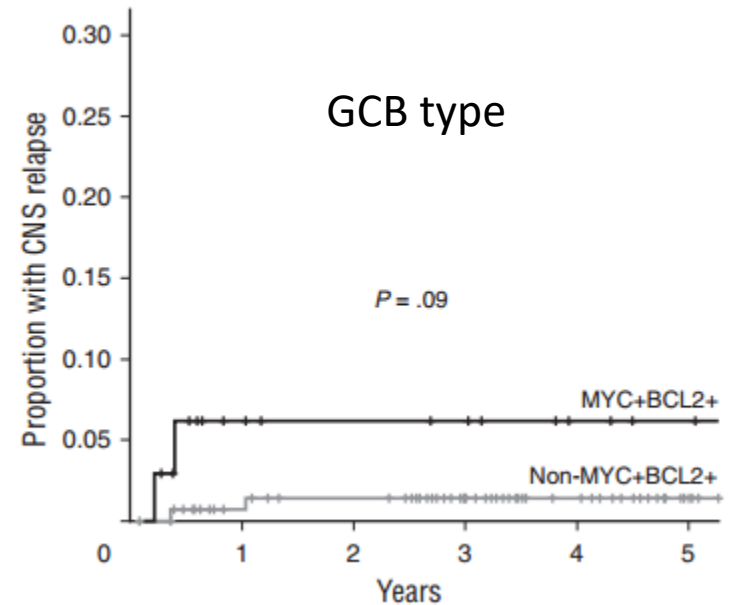
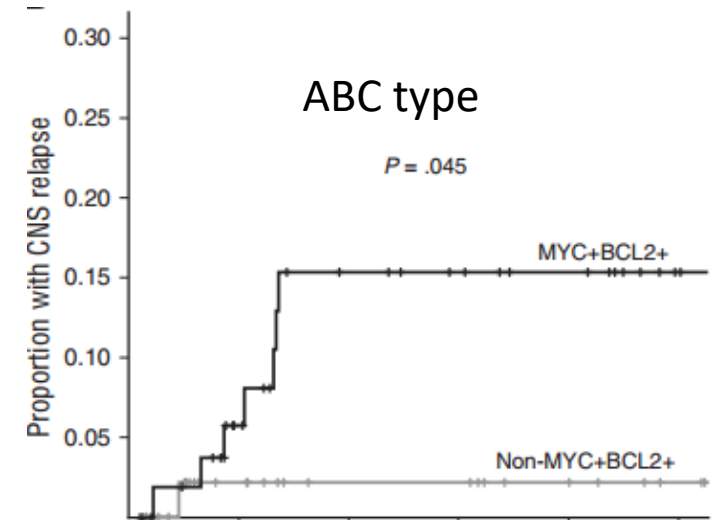
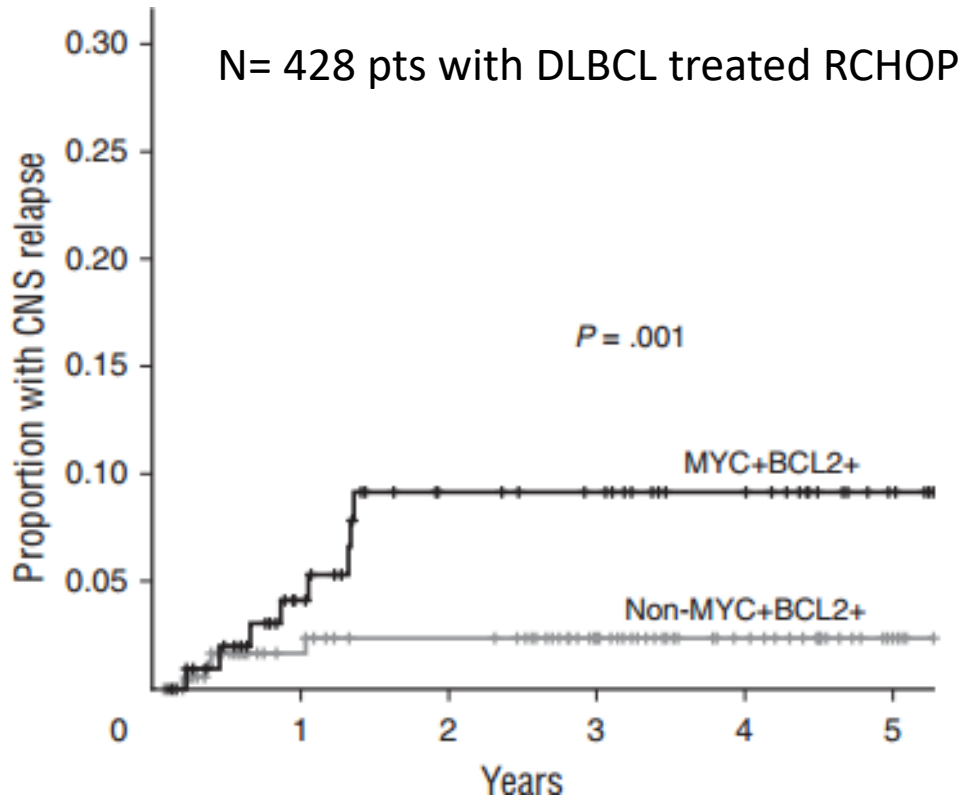
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Double Expression - Prognosis



CNS Relapse Risk in DE-DLBCL



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DH –Presentation

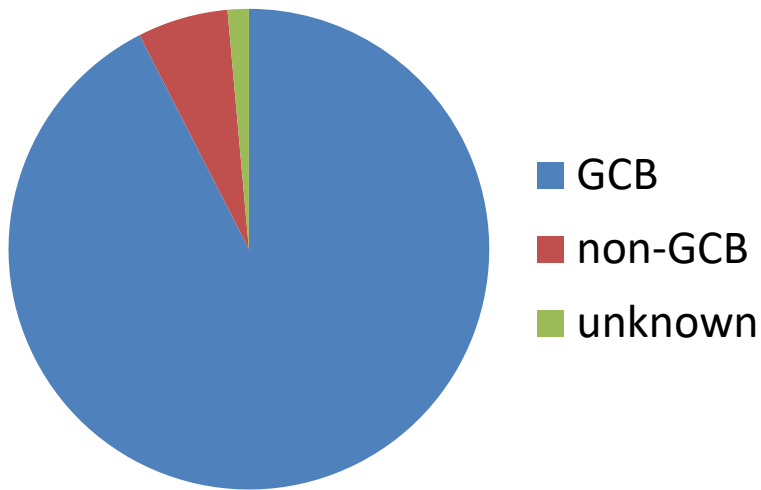
- 95% with DLBCL or high grade histology
 - Formerly classified as unclassifiable
 - Reclassified as HGBL-NOS
 - Can follow transformation from indolent
 - Rarely lymphoblastic leukemia/lymphoma
- 90% HGBL-DH present with high risk features
 - Leukocytosis
 - CNS disease
 - LDH 3x ULN

Mayo Clinic Series of DHBCL

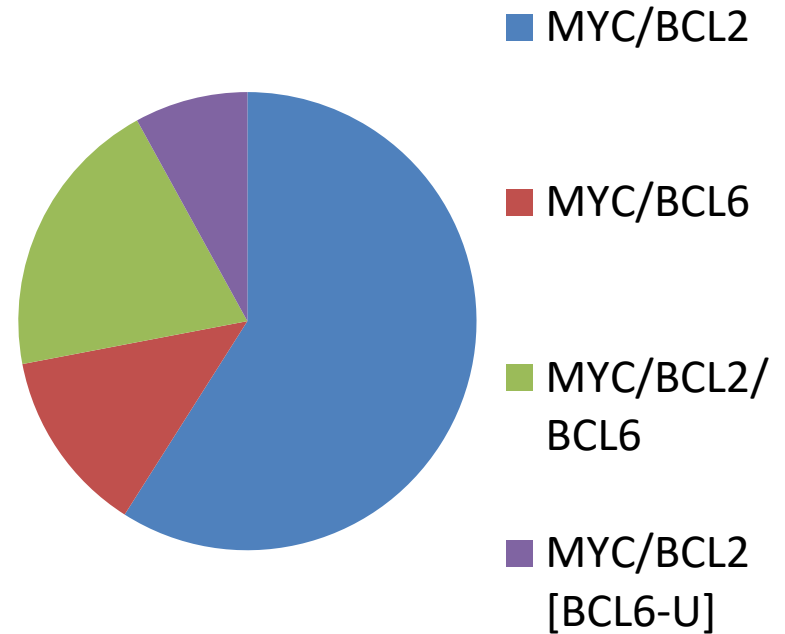
- **71 patients treated with anthracycline based therapy at the time of DH/TH diagnosis were included in this analysis.**
- **The median age was 61 years (range 29-82).**
- **60 patients were de-novo; 11 had a histologic transformation of previously diagnosed low-grade lymphoma**
- **Histology (central pathology re-review):**
 - **39 (60%) with high grade morphology**
 - **26 (40%) with DLBCL morphology (Abstract 1750)**

COO and Rearrangements

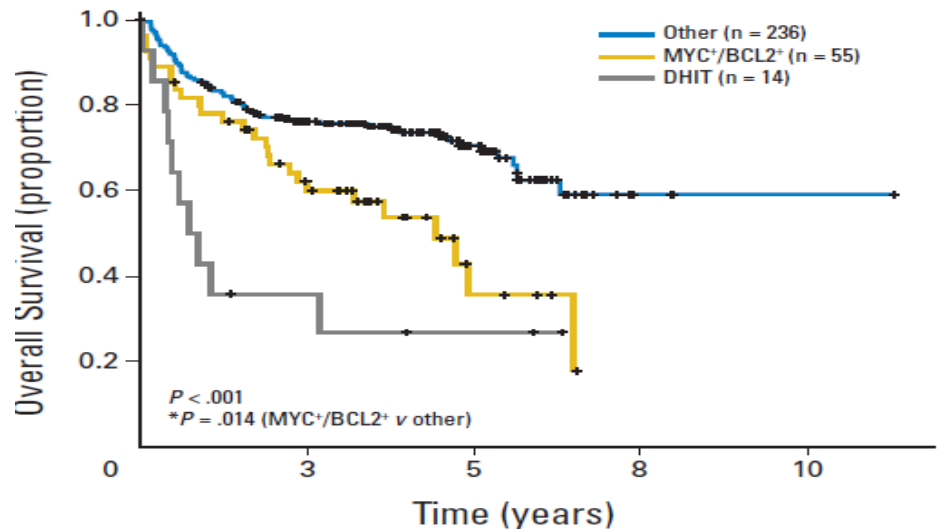
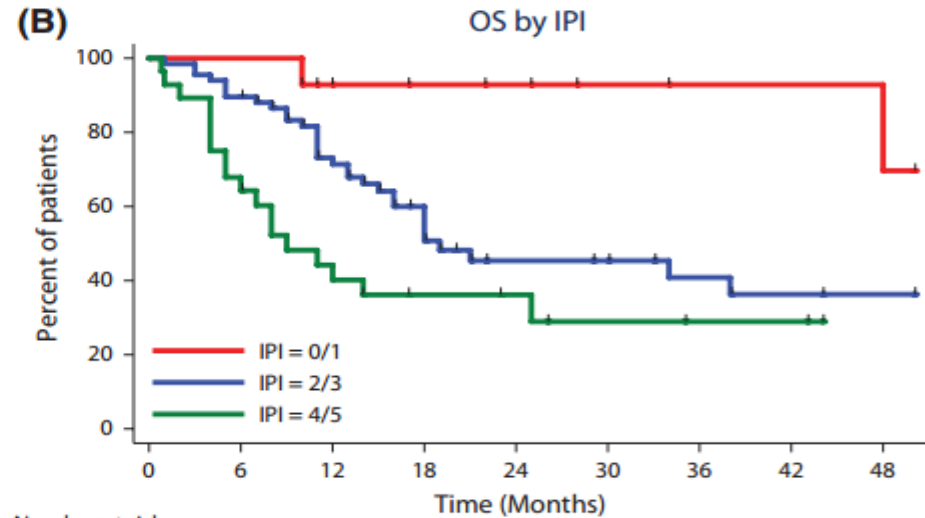
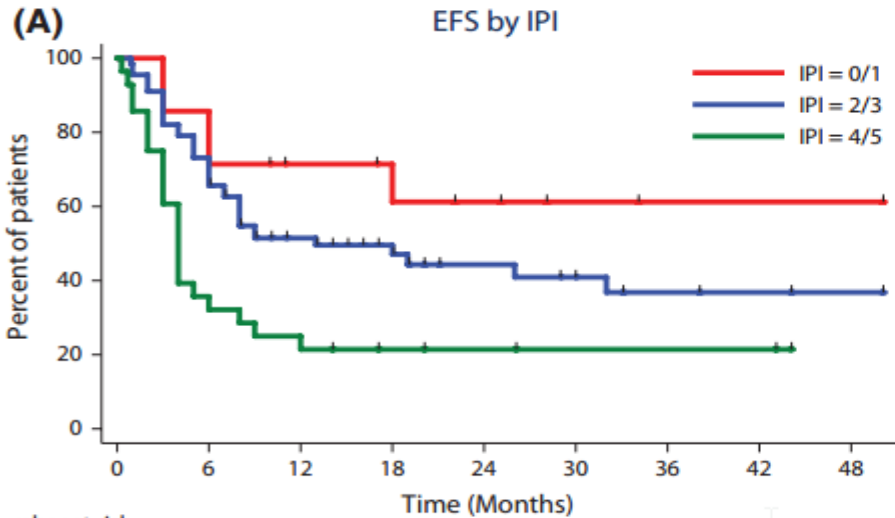
COO



Rearrangements



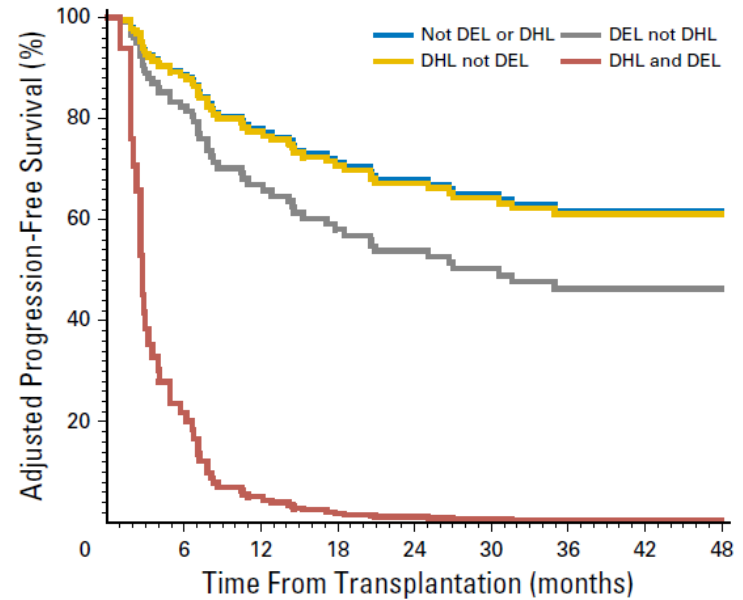
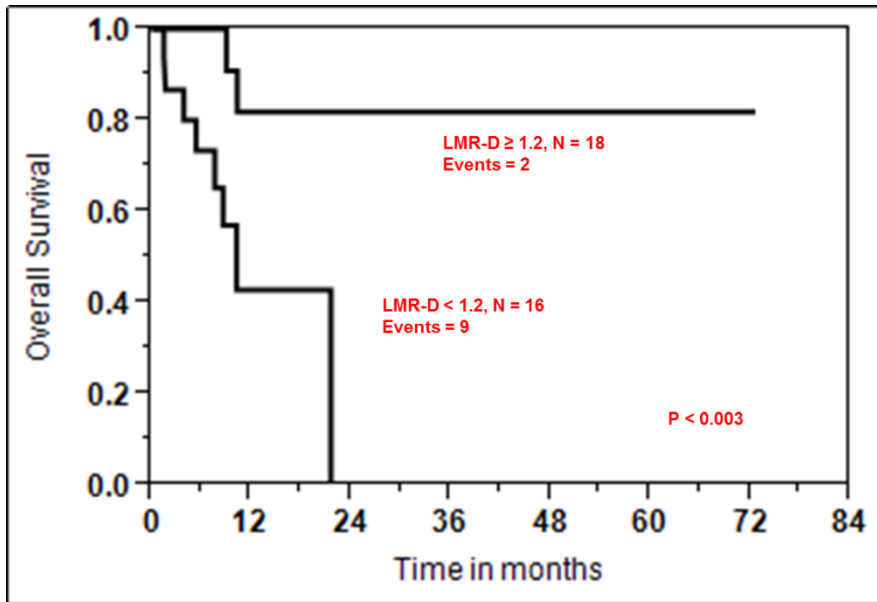
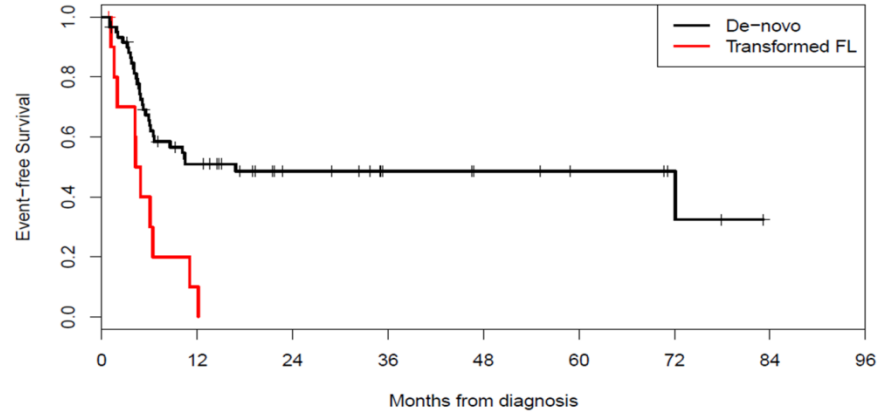
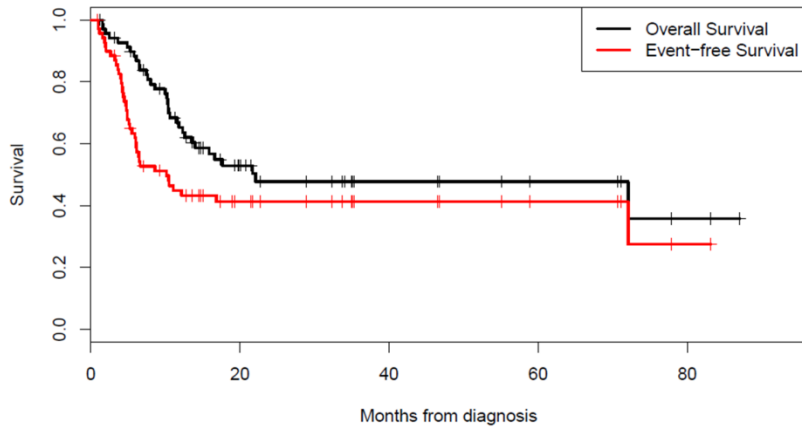
DH DLBCL - prognosis



Oki et al Br J. Haem 2014

Johnson et al J Clin Oncol 2012

DHL prognostic subsets



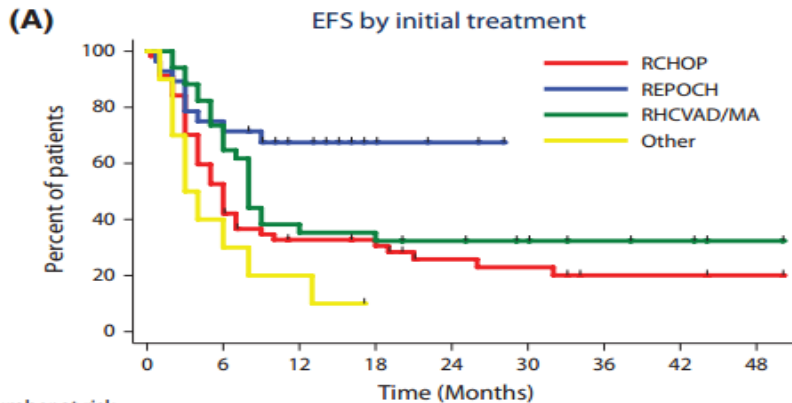
Rational testing for DE/DH lymphoma

- FISH testing too expensive for every DLBCL case
- High (>20%) yield in:
 - HGBCL NOS
 - Plasmablastic
 - FL → transformed to DLBCL
- DLBCL NOS - ?IHC screening?
 - Ki-67 logical but not yet demonstrated effective
 - MYC and BCL-2 IHC prognostic anyway
 - Test all GCB? – still only a 6% yield, but cuts waste in half
 - Test GCB with high MYC and BCL2?
 - Reduce testing by 90%
 - Yield is high (30%)
 - Sensitivity is low
 - most HGBCL-DH are not DE.
 - (the worst ones are)

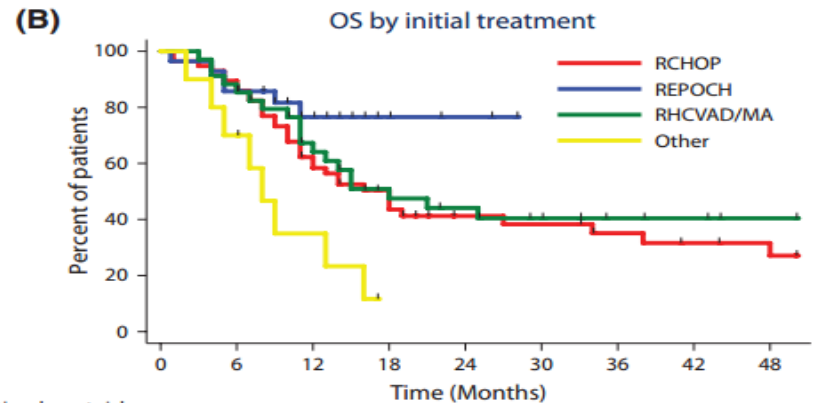
Rational therapy for DE DLBCL

- Outcomes after R-CHOP are generally poor
- Median age a bit older making escalation hard
- Da- R-EPOCH?
 - In a small NCI study DE-DLBCL not inferior
 - NCTN 50303 (R-CHOP v R-EPOCH) will be analyzed
- Novel potential targets:
 - NFkB given enriched for ABC type. (R² CHOP)
 - BCL-2 antagonists (venetoclax + chemo backbone)

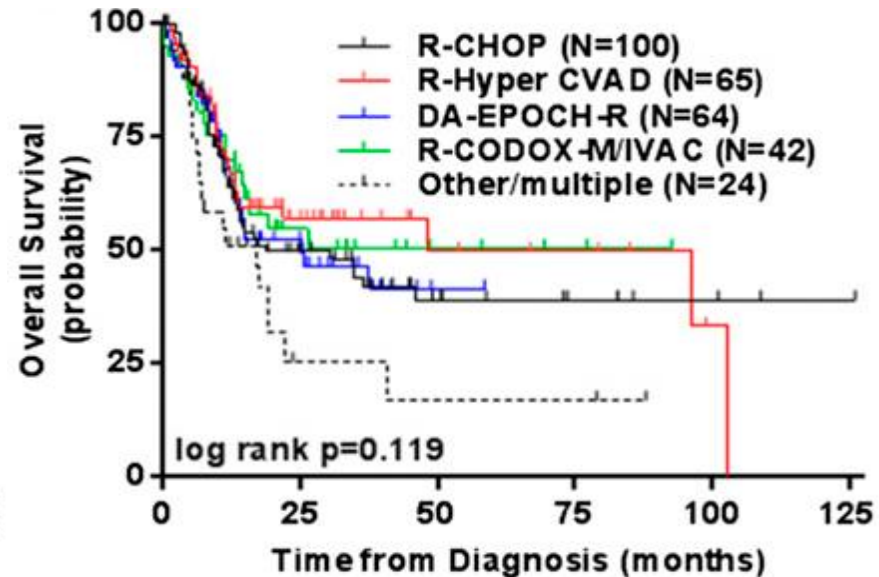
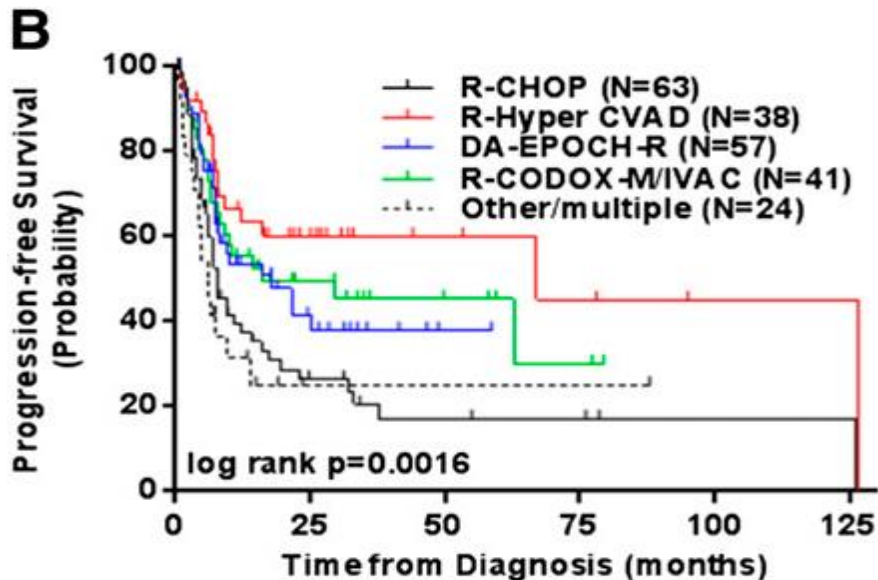
Rational Therapy for DH BCL



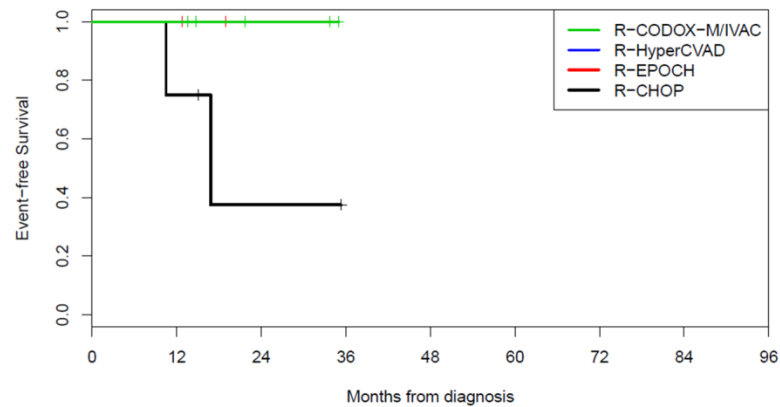
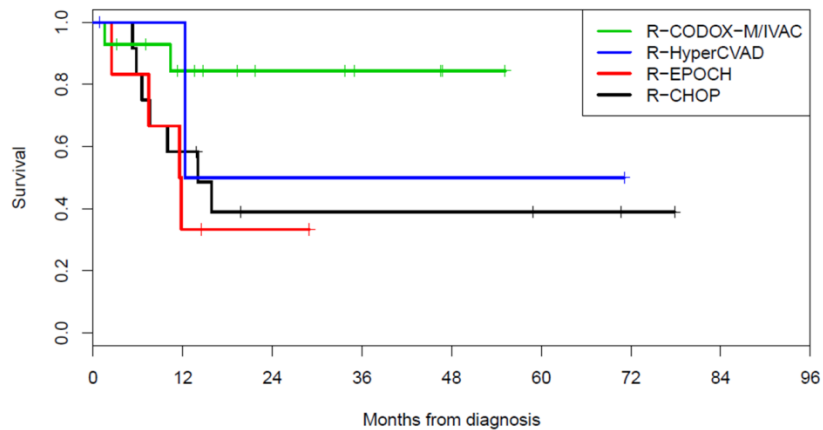
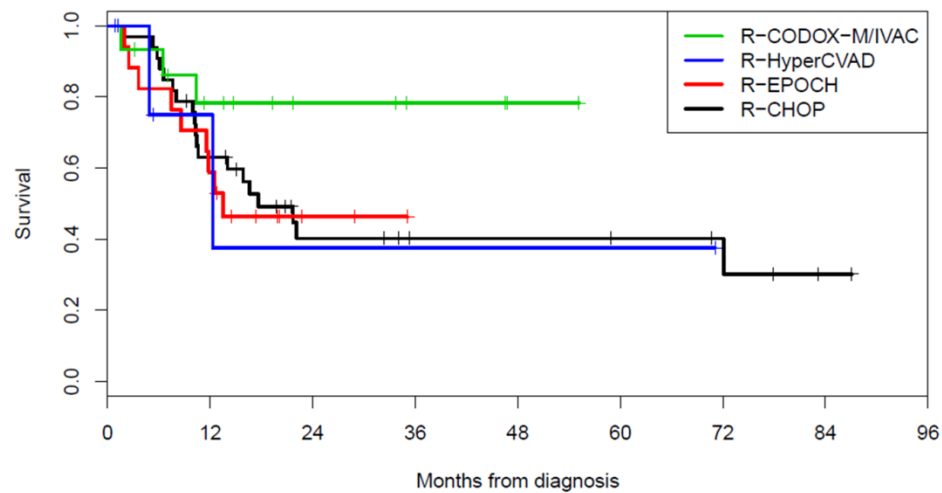
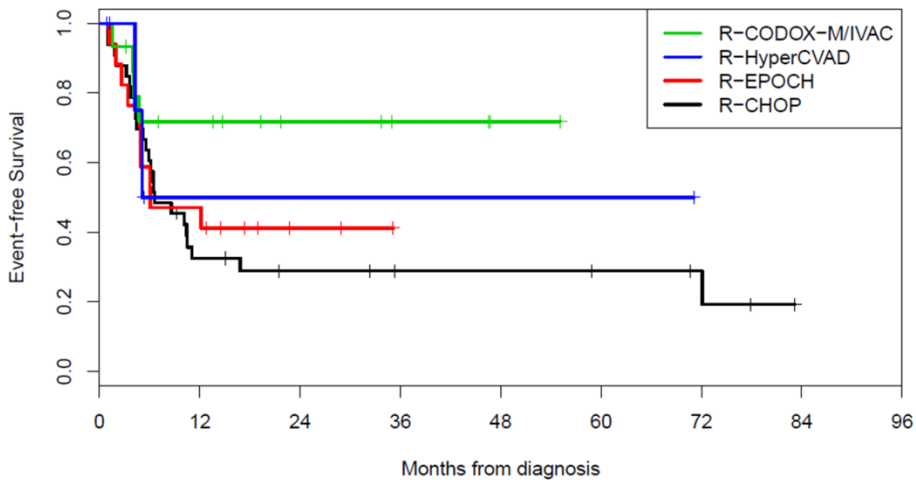
Number at risk	0	6	12	18	24	30	36	42	48
RCHOP	57	30	16	15	9	8	5	5	4
REPOCH	28	21	12	5	2	0	0	0	0
RHCVAD/MA	34	25	13	12	10	8	6	5	3
Other	10	4	2	0	0	0	0	0	0



Number at risk	0	6	12	18	24	30	36	42	48
RCHOP	57	51	32	22	14	13	10	8	7
REPOCH	28	24	14	5	2	0	0	0	0
RHCVAD/MA	34	30	21	15	12	9	6	5	3
Other	10	7	3	0	0	0	0	0	0

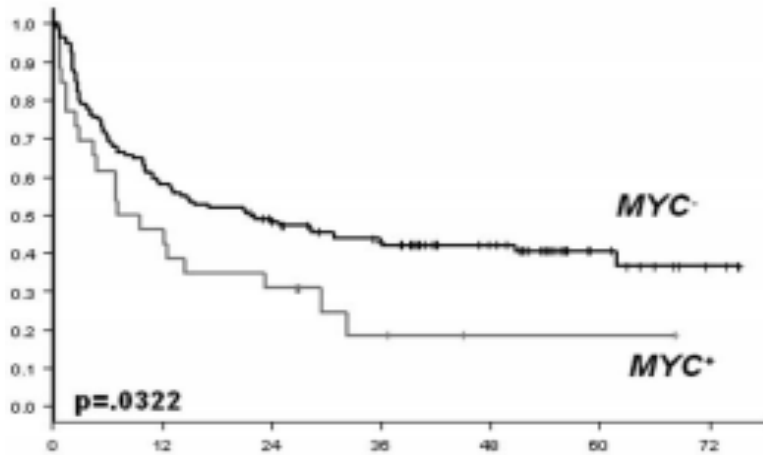


Rational Therapy for DH BCL

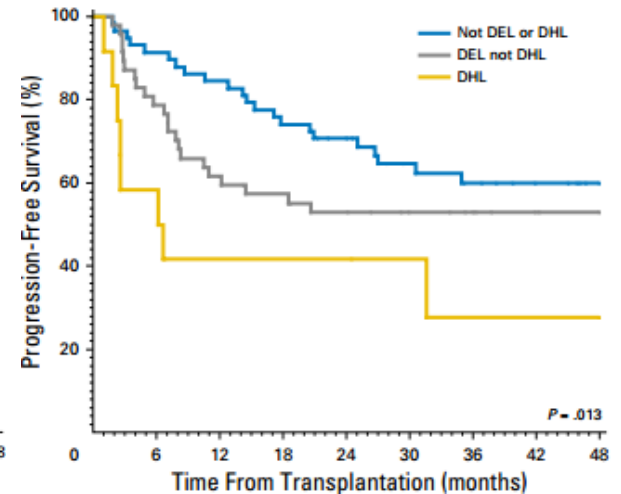
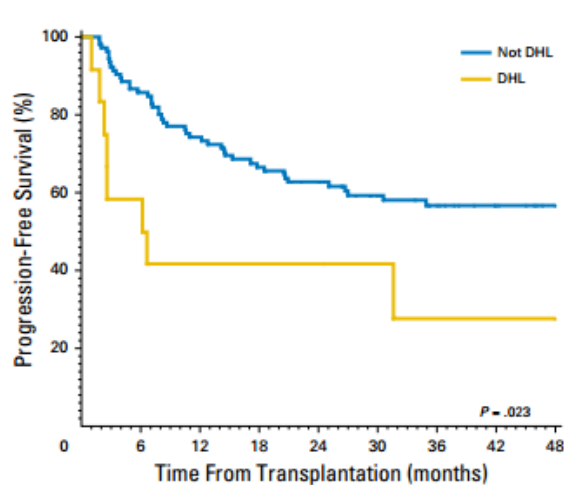
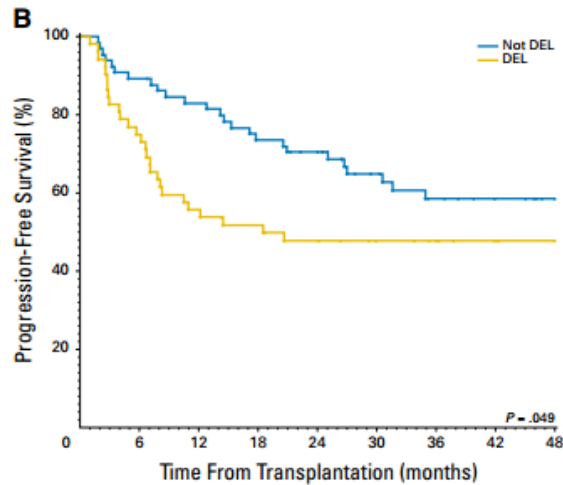
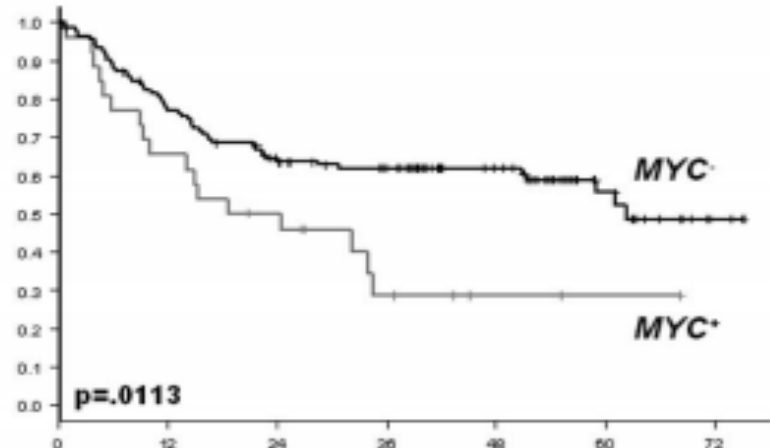


Salvage Therapy

Progression free survival



Overall survival



Summary

- Double Hit and Double Expressing BCL represent another step toward individualized management strategies.
- DHL is clearest threat but uncommon (5%)
- DEL probably a threat and more common (25%)
- Diagnostic testing strategies are in transition
- R-CHOP seems unappealing, but.....
 - 2017 should be enlightening
 - CNS attention is a high priority.