Rome,
March 23-24 2017

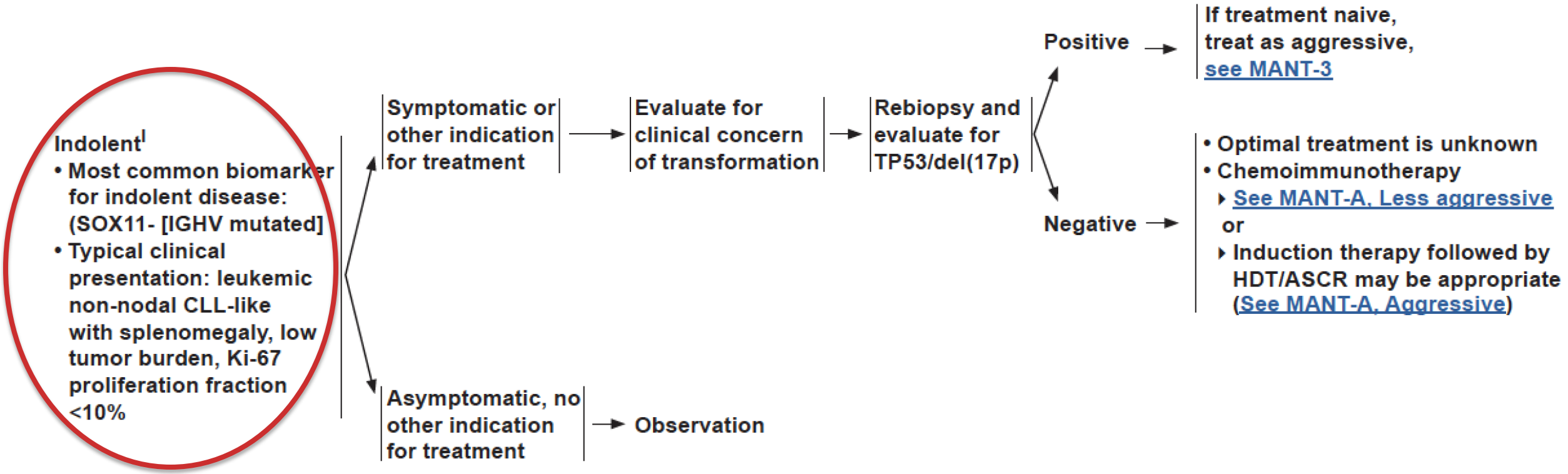
VOI Donna Camilla Savelli Hotel

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen			X				
Gilead			X				
Celgene			X				
Genentech			X				
Novartis			X				
Pharmacyclics			X				
Verastem			X				

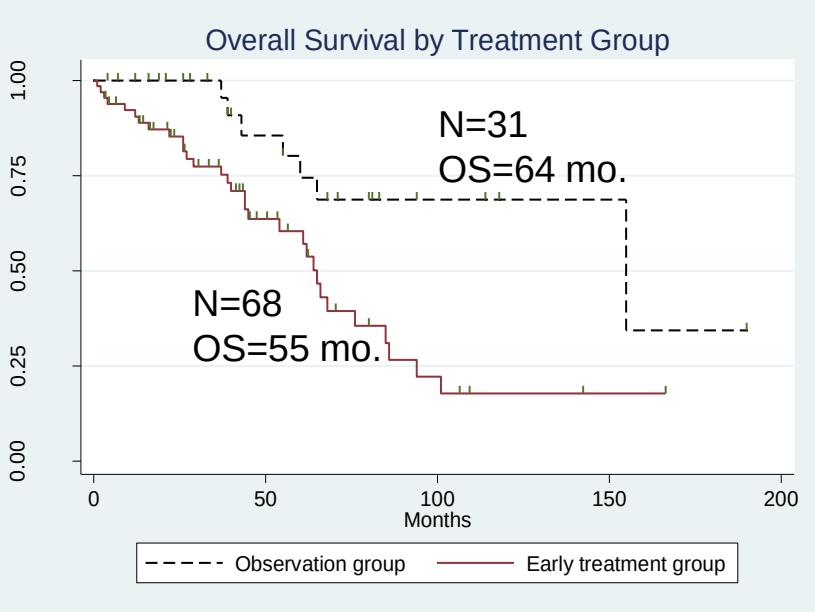
The US Approach to First-Line Treatment of Mantle Cell Lymphoma

March 26, 2017 pem9019@med.cornell.edu

Weill Cornell Medicine NewYork-Presbyterian


Indolent[l]
• Most common biomarker for indolent disease: (SOX11- [IGHV mutated]
• Typical clinical presentation: leukemic non-nodal CLL-like with splenomegaly, low tumor burden, Ki-67 proliferation fraction <10%
Symptomatic or other indication for treatment
Evaluate for clinical concern of transformation
Rebiopsy and evaluate for TP53/del(17p)
Positive
If treatment naive, treat as aggressive, see MANT-3
Negative
• Optimal treatment is unknown
• Chemoimmunotherapy
See MANT-A, Less aggressive
or
Induction therapy followed by HDT/ASCR may be appropriate (See MANT-A, Aggressive)
Asymptomatic, no other indication for treatment
Observation

Treatment may be safely deferred in some patients with MCL

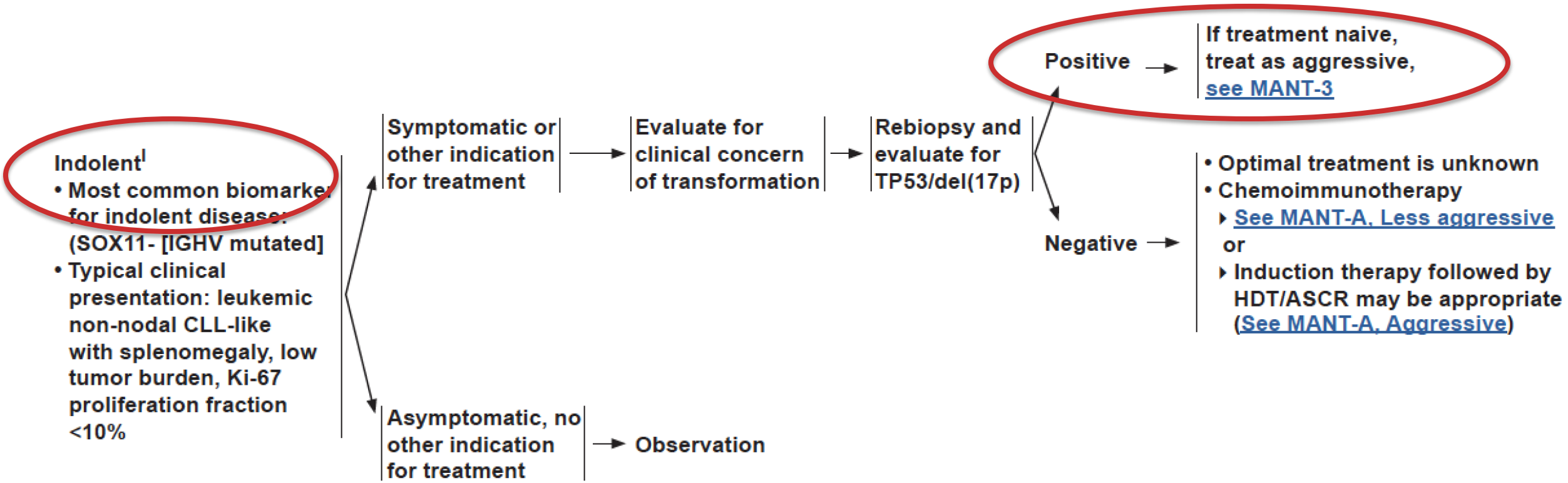


What characteristics are define these patients?

- **Not blastoid morphology[1]**
- **Normal LDH[2]**
- **Ki67 <30%[3]**
- **No B symptoms[4]**
- **Mutated IGHV[5]**
- **SOX11-**
- **Non-nodal[6]**
- **MIPI is NOT a defining characteristic**

Center	N	Defn. of deferred tx.	TTT	Impact on OS
Derriford[7]	16/52	3 mo.	11.1 mo.	No difference
FHCRC[8]	13/118	3 mo.	5 mo.	No difference
Nordic[2]	29/1389	NR	NR	79% vs. 61%
BCCA[3]	74/439	3 mo.	35.5 mo.	66 mo. vs. 50 mo.
NCDB[4]	492/8029	90 days	NR	HR 0.79

1-Martin JCO 2009, 2-Abrahamsson Blood 2014, 3-Abrisqueta ASH abstract 2015, 4-Cohen ASH abstract 2015, 5-Orchard Blood 2003, 6-Ondrejka Haematologica 2011, 7-Eve JCO 2009, 8-Budde JCO 2010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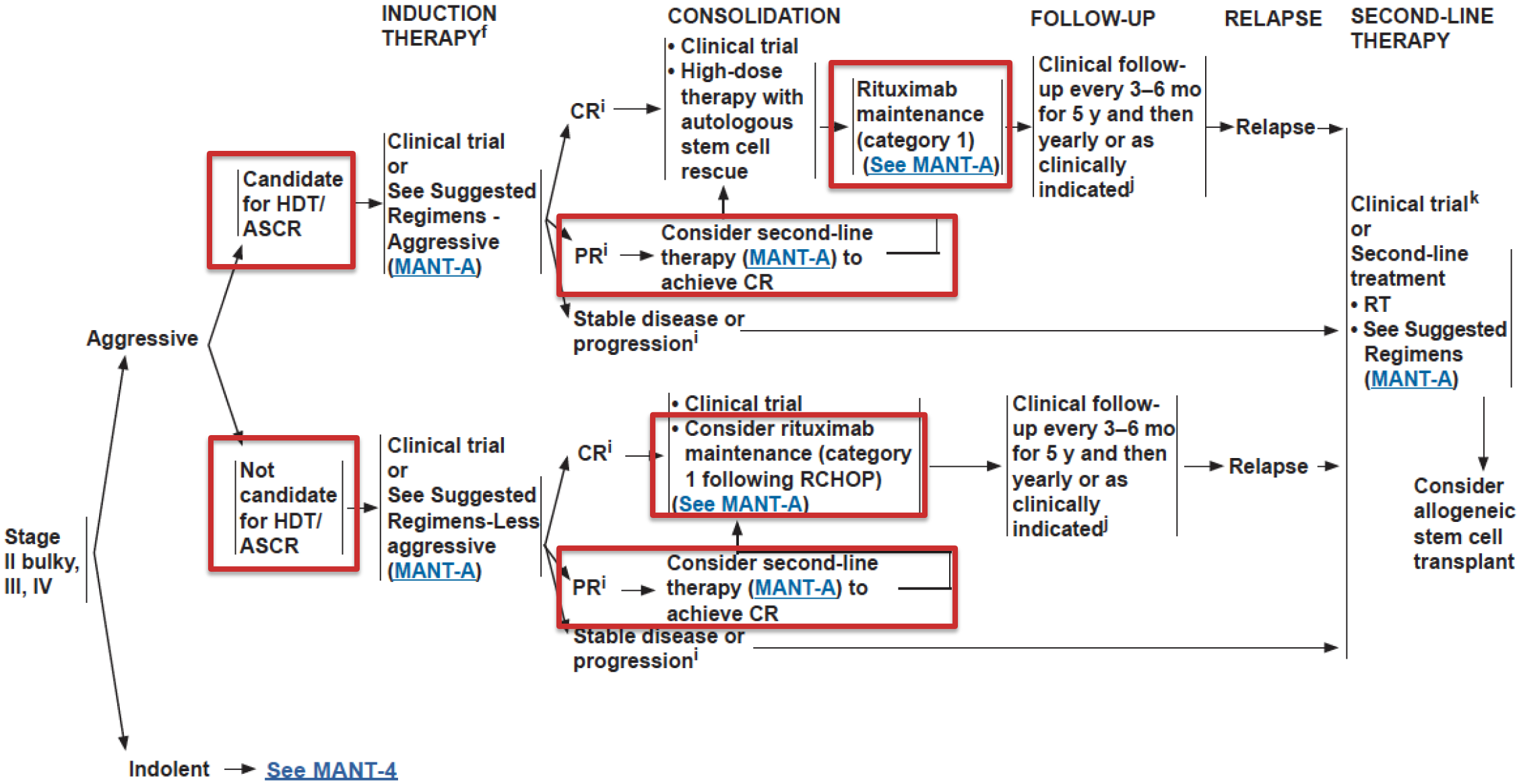
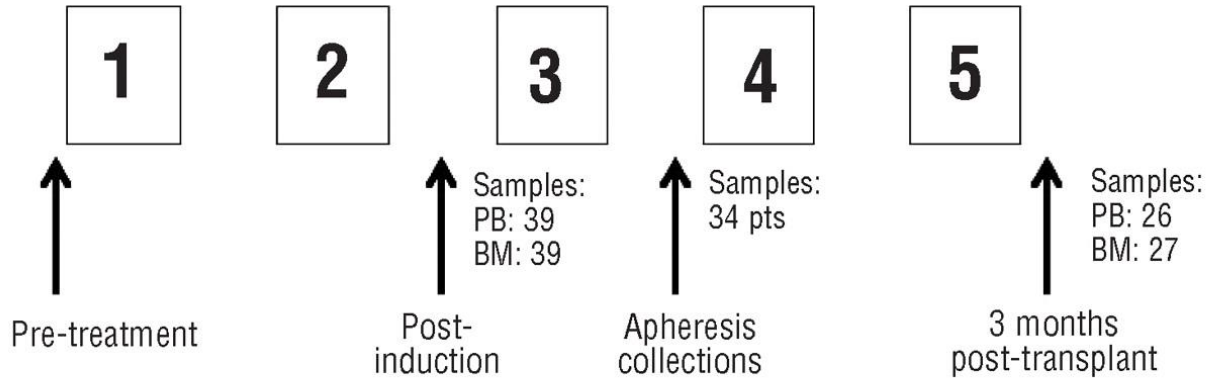

INDUCTION THERAPY[f]
CONSOLIDATION
FOLLOW-UP
RELAPSE
SECOND-LINE THERAPY
Stage II bulky, III, IV
Aggressive
Candidate for HDT/ ASCR
Clinical trial or See Suggested Regimens - Aggressive (MANT-A)
CR[i]
• Clinical trial
• High-dose therapy with autologous stem cell rescue
Rituximab maintenance (category 1) (See MANT-A)
Clinical follow-up every 3–6 mo for 5 y and then yearly or as clinically indicated[j]
Relapse
PR[i]
Consider second-line therapy (MANT-A) to achieve CR
Stable disease or progression[i]
Clinical trial[k] or Second-line treatment
• RT
• See Suggested Regimens (MANT-A)
Consider allogeneic stem cell transplant
Not candidate for HDT/ ASCR
Clinical trial or See Suggested Regimens-Less aggressive (MANT-A)
CR[i]
• Clinical trial
• Consider rituximab maintenance (category 1 following RCHOP) (See MANT-A)
Clinical follow-up every 3–6 mo for 5 y and then yearly or as clinically indicated[j]
Relapse
PR[i]
Consider second-line therapy (MANT-A) to achieve CR
Stable disease or progression[i]
Indolent
See MANT-4

Aggressive regimens

CALGB 59909

Eligibility:

- Age 18-69
- Stage III-IV
- No HIV
- LVEF>45%
- Cr≤2 mg/dL



Treatment 1: rituximab, methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisone, G-CSF

Treatment 2: rituximab, methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisone, G-CSF

Treatment 3: cytarabine, etoposide, rituximab, G-CSF

Treatment 4: ASCT, carmustine, etoposide, cyclophosphamide, G-CSF

Treatment 5: rituximab maintenance

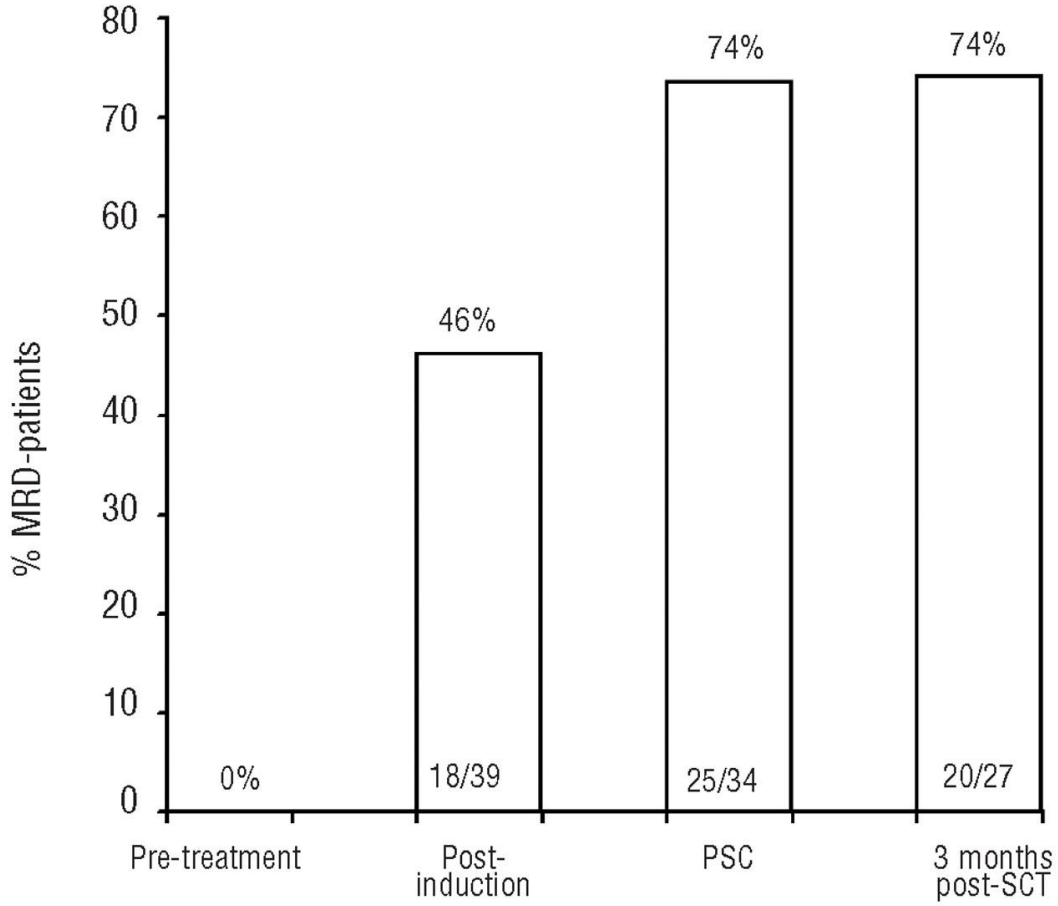
Table 2. Patient Demographics and Disease Characteristics

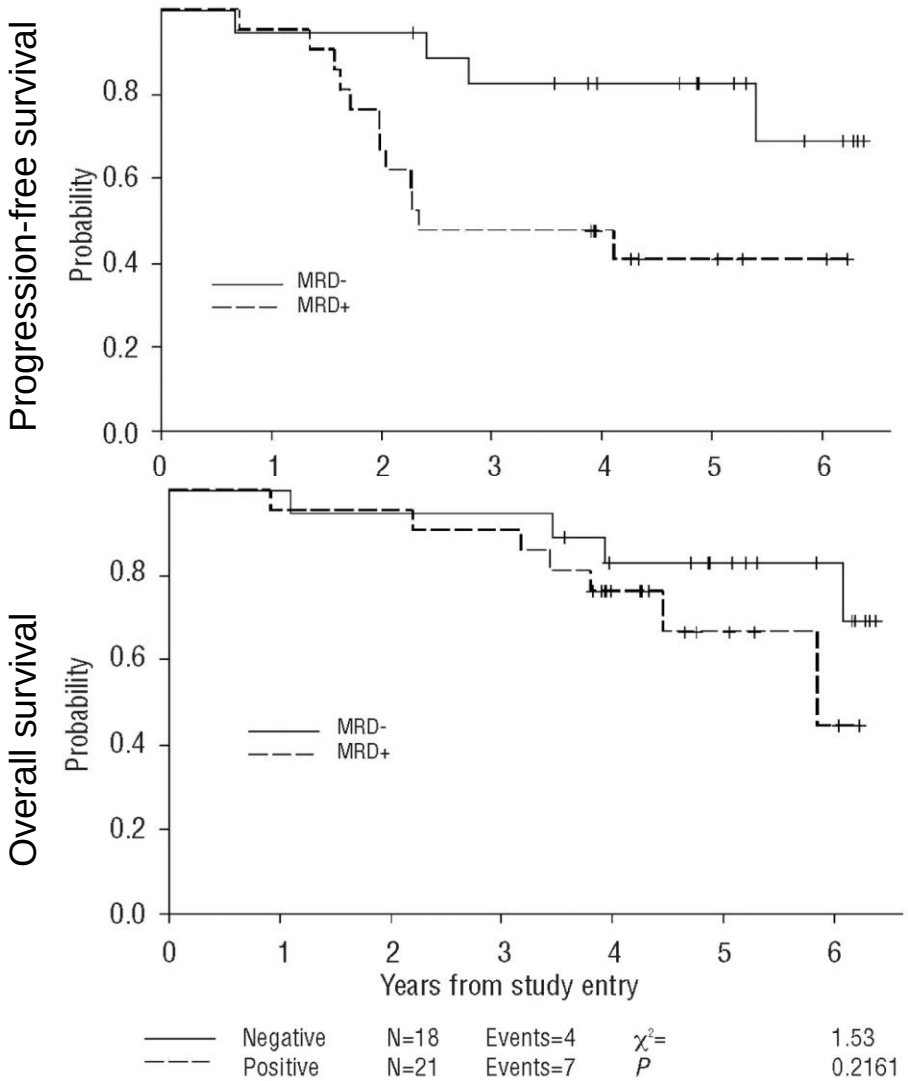
Characteristic	No. of Patients (n = 78)*	%
Prior chemotherapy and/or rituximab	6	8
Sex		
Male	64	82
Female	14	18
Age, years		
Median	57	
Range	37-69	
Histology		
Blastic	12	15
Diffuse	37	47
Nodular	21	27
Unknown	8	11
MIPI score[34]		
Low	41	53
Intermediate	24	31
High	12	15
Unknown	1	1

Abbreviations: LDH, lactate dehydrogenase; IU/L, international units/liter; CSF, cerebrospinal fluid; IPI, International Prognostic Index; MIPI, mantle-cell lymphoma IPI.
*Intent-to-treat.

Damon et al. JCO 2009
Liu H et al. Haematologica 2012;97:579-585

Post-induction MRD status in PB after induction was associated with PFS but not OS

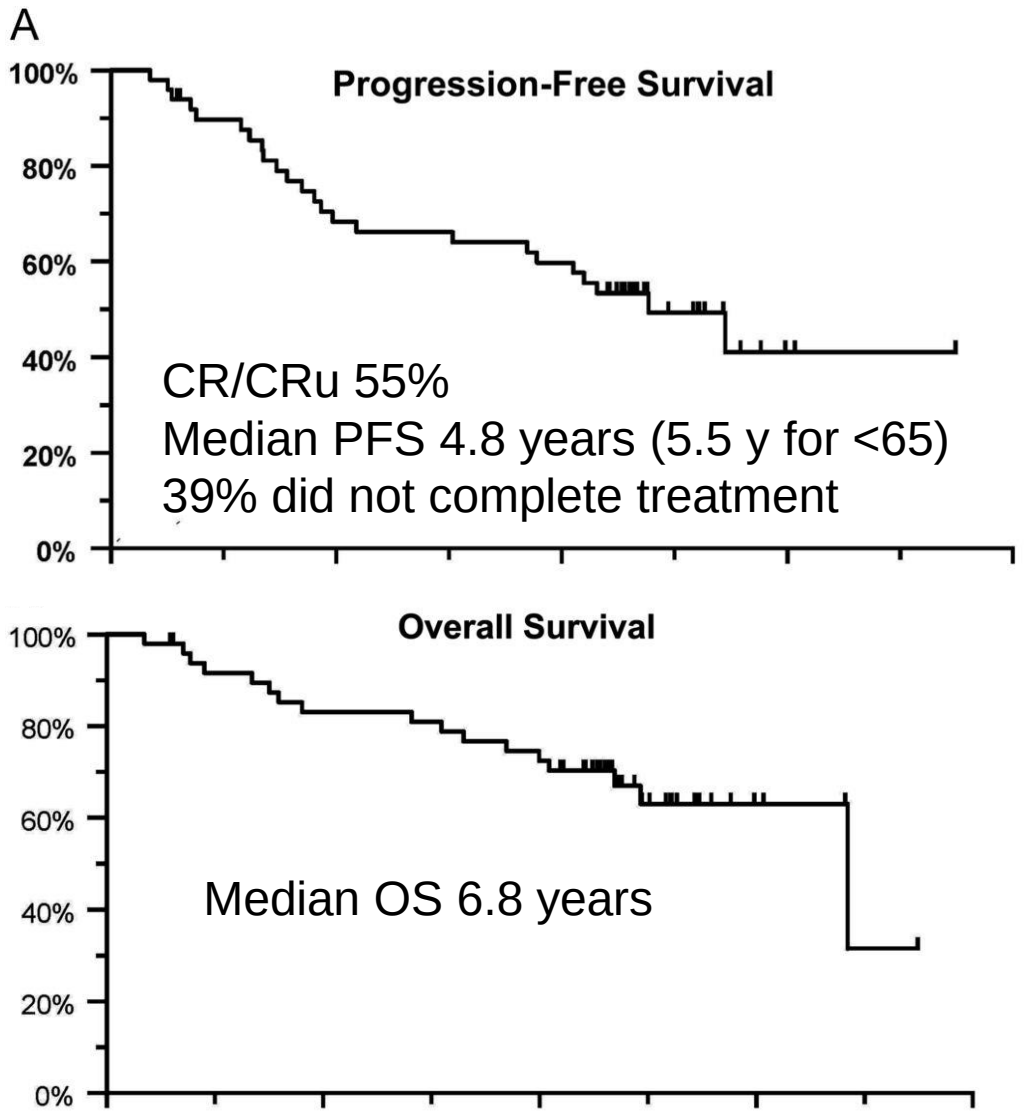




Liu H et al. Haematologica 2012;97:579-585

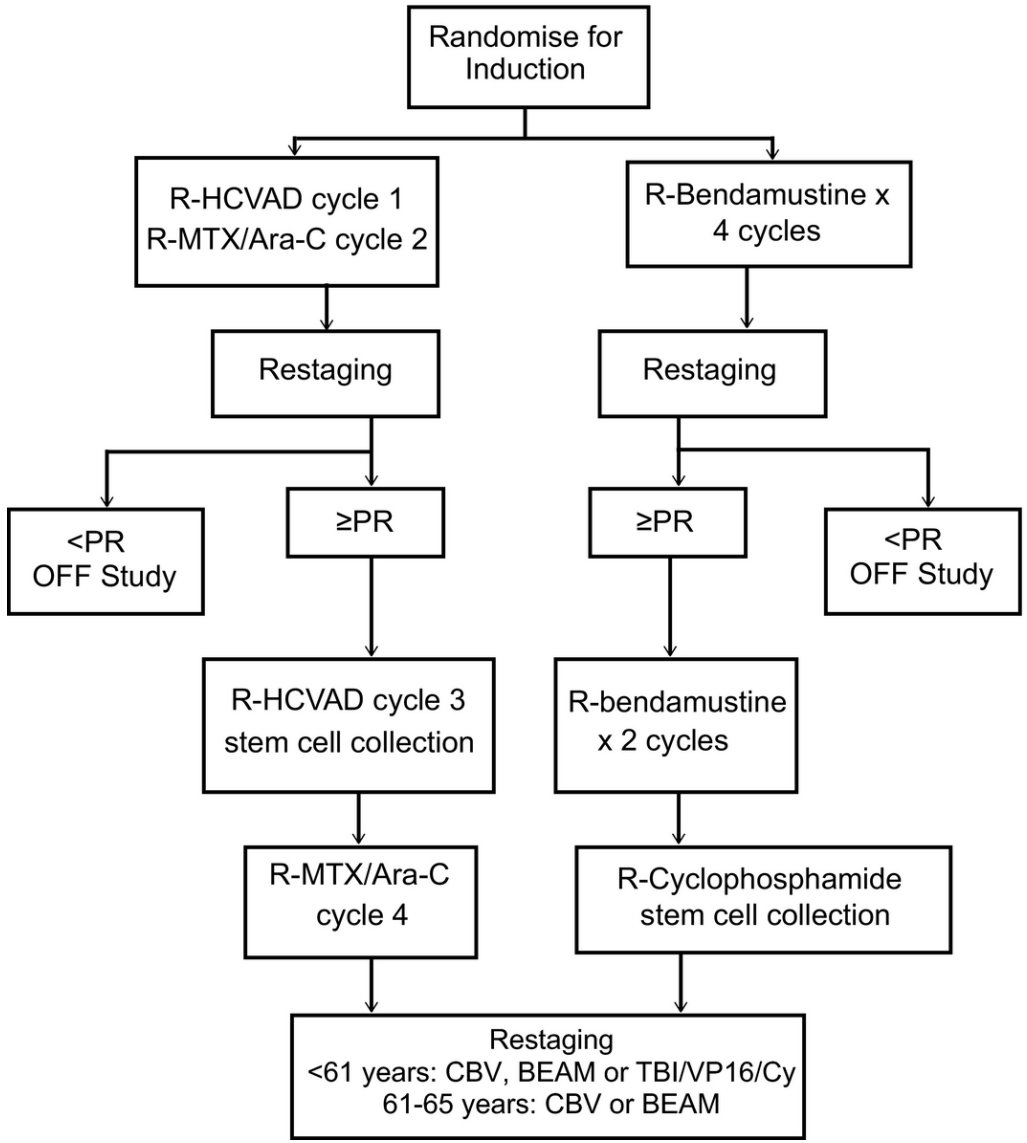
S0213 Trial of R-hyperCVAD/MTX-AraC

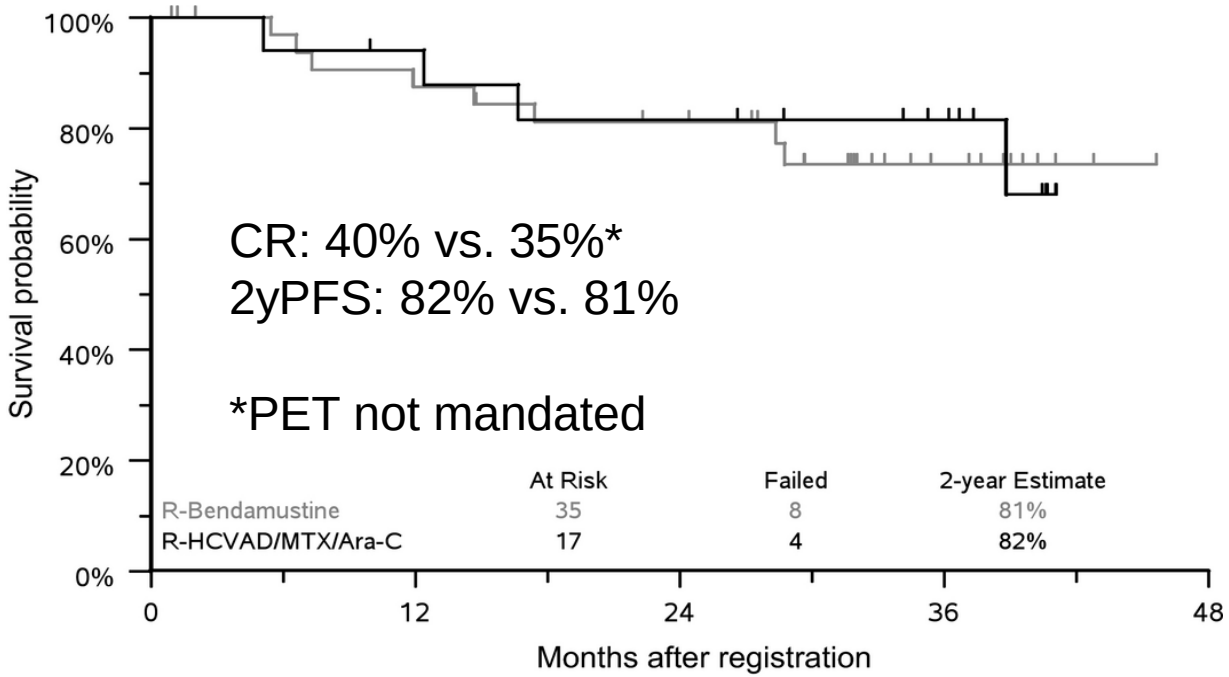
		Number of patients	Percent of patients
Total patients		49	
Age, years			
Median (range) (years)	57.4 (35.0–69.8)		
≤65		42	86
>65		7	14
Sex, male		38	78
ECOG PS 1 or 2		20	41
Stage III or IV		49	100
B symptoms		18	37
Blastoid variant		4	8
IPI			
Low		16	33
Low-intermediate		17	35
High-intermediate		11	22
High		5	10
MIPI			
Low		27	55
Intermediate		15	31
High		7	14
Ki-67[a]			
Median (range)	28 (5–78)		



Bernstein S H et al. Ann Oncol 2013;24:1587-1593

Not included in 2017 NCCN Guidelines
S1106: BR vs. R-hyperCVAD





Grade 3/4 Toxicities	R-HyperCVAD (N=17)	R-Bendamustine (N=35)
Anemia	59%	8.6%
Neutropenia	65%	34%
Febrile neutropenia	29%	14%
Thrombocytopenia	71%	17%

Chen et al. British Journal of Haematology Volume 176, Issue 5, pages 759-769, 19 DEC 2016

Less aggressive regimens

E1405: VcR-CVAD

VcR-CVAD induction chemotherapy

Bortezomib 1.3 mg/m² IV days 1 & 4

Rituximab 375 mg/m² IV day 1

Cyclophosphamide 300 mg/m² IV every 12 hours days 1-3 (total of 6 doses)

Doxorubicin 50 mg/m² IV by continuous infusion over 48 hours (days 1-2)

Vincristine 1 mg IV on day 3

Dexamethasone 40 mg orally days 1-4

Cycles repeat every 21 days X 6

G-CSF with each cycle

→ CR or PR →

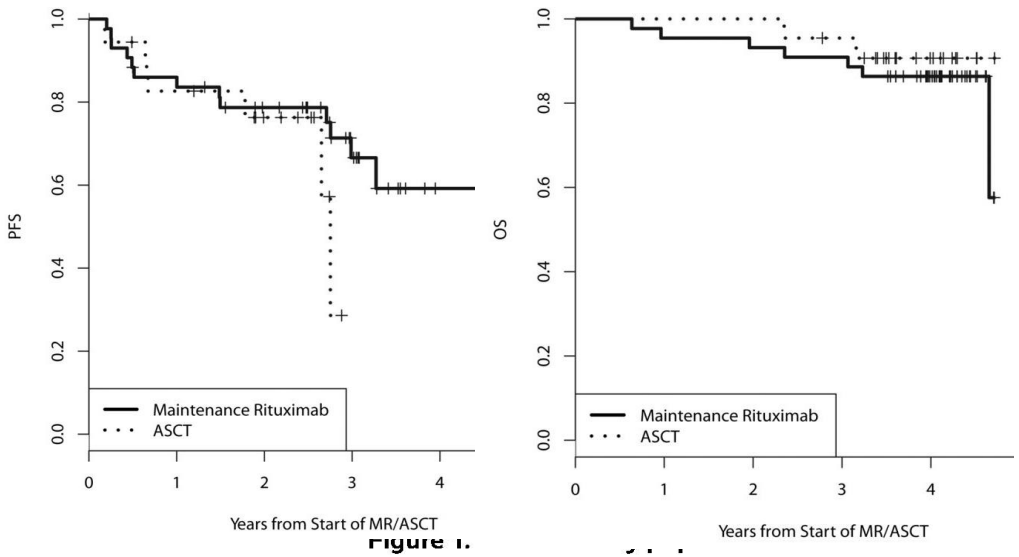
Maintenance rituximab

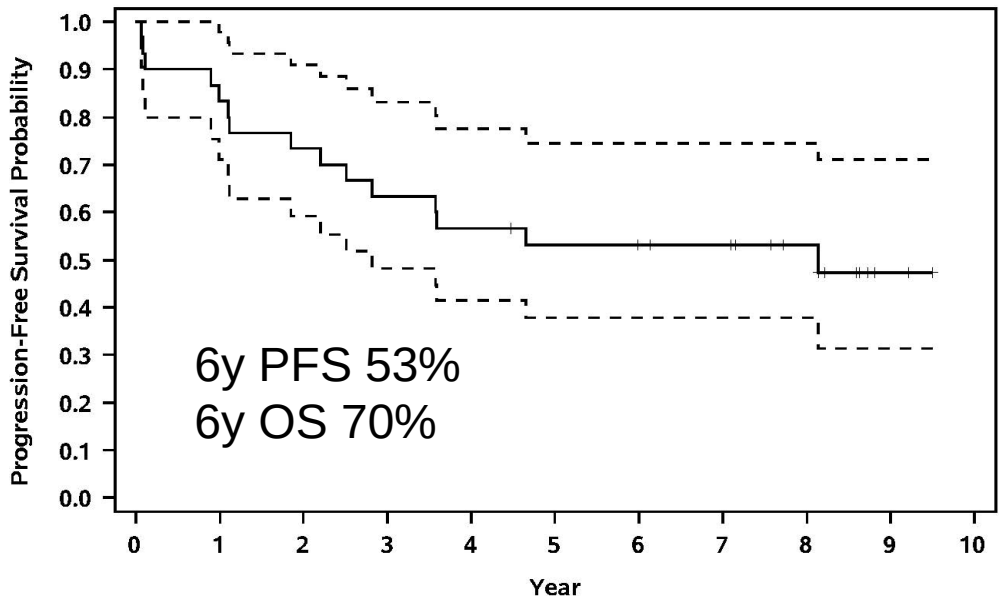
375 mg/m² IV weekly X 4 doses repeated every 6 months for 2 years (total of 16 doses)

Optional

Autologous stem cell transplant (per local institution standards)

	n	%
Age		
Median (range)	62 (40-76)	
MIPI score		
Low risk	28	41
Intermediate risk	26	38
High risk	15	22
Unknown*	6	

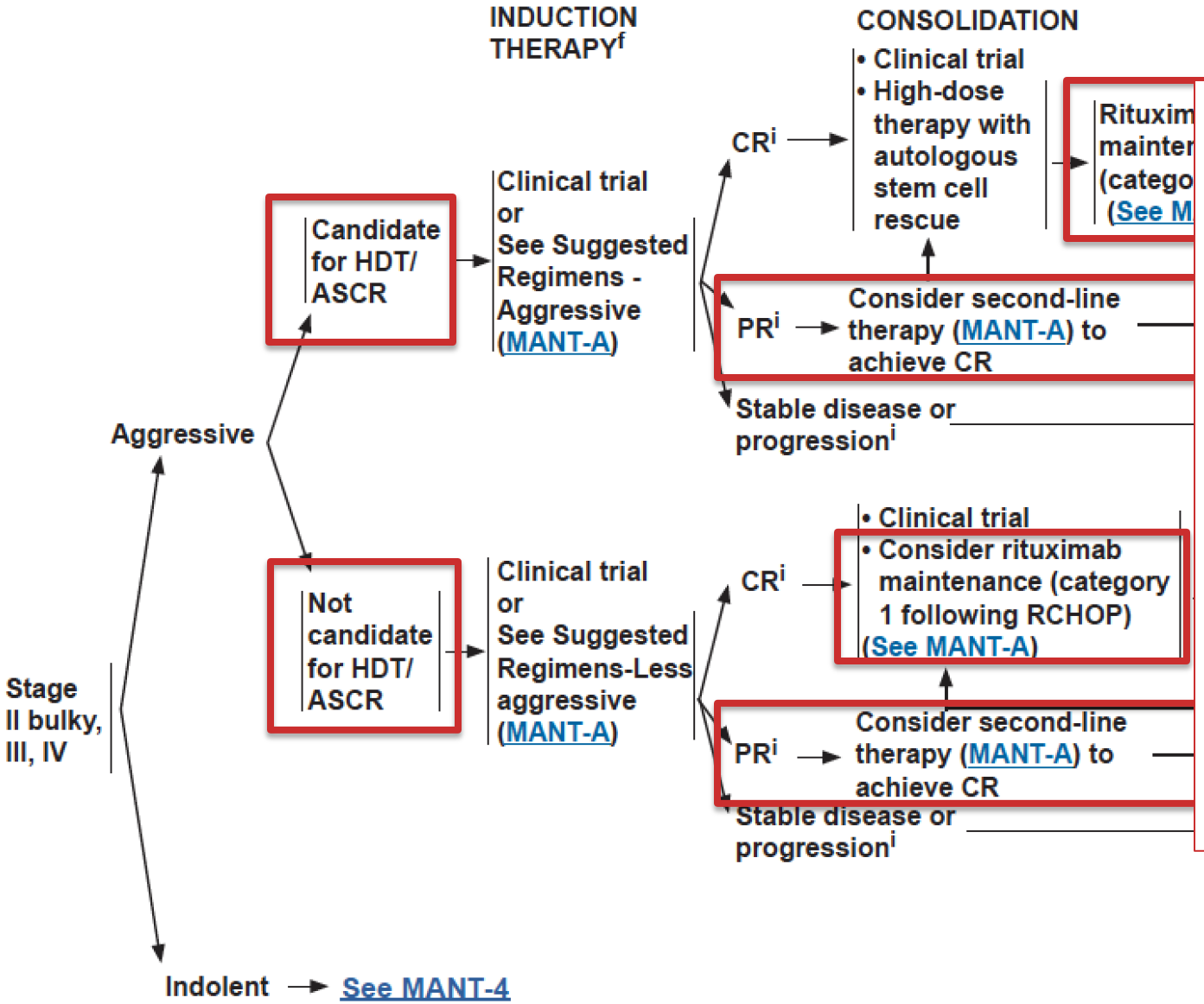




Chang J E et al. Blood 2014;123:1665-1673 and ASH 2016

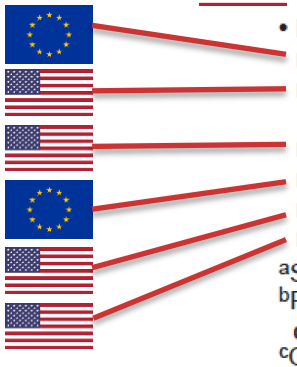
Other US Cooperative Group Studies

Study	Regimen	Eligibility	Enrolled	Outcome	Reference
ECOG E1499	RCHOP x 4 ^{90}Y-ibrutimomab tiuxetan	All ages	N=56 Ages 33-83 years MIPI low 50%	TTF 34 mo. OS 7.9 y	Smith JCO 2012 Smith Leuk 2017
SWOG S0601	VR-CHOP	All ages	N=65 Ages 36-85 MIPI low 45%	PFS 29.5 mo 5yOS 66%	Till BJH 2016
NCCTG N0189	Cladribine rituximab	All ages	N=29 Ages 41-86	TTP 12.1 mo.	Inwards Cancer 2008
ECOG E1411	BR vs. BVR Followed by R vs. LR	All ages	N=373	Ongoing	Ongoing



- **Most trials testing intensive regimens limit to age ≤65 or <70. The R-hyperCVAD regimen was more toxic between age 65-70.**
- **Most trials testing less intensive regimens were open to all ages.**
- **The recommendation to only proceed to ASCT in CR is supported by trials done outside of the NCI/NCTN structure**
  - **CR rate depends on response criteria**

SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)



Induction Therapy

- **Aggressive therapy**
  - CALGB regimen (Treatment 1, 2, 2.5: rituximab + methotrexate with augmented CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone]; Treatment 3: etoposide, cytarabine, rituximab; Treatment 4: carmustine, etoposide, cyclophosphamide/autologous stem cell rescue; Treatment 5: rituximab maintenance) (Treatment 2.5 is given if the pre-Treatment 3 bone marrow biopsy contains >15% MCL.)
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
  - NORDIC regimen (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine)
  - Alternating RCHOP/RDHAP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cisplatin, cytarabine)
  - RDHAP (rituximab, dexamethasone, cisplatin,[c] cytarabine)
  - Sequential RCHOP/RICE (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, ifosfamide, carboplatin, etoposide)
- **Less aggressive therapy**
  - Bendamustine + rituximab
  - VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone)
  - Cladribine + rituximab (category 2B)
  - CHOP + rituximab[d]
  - Lenalidomide + rituximab
  - Modified rituximab-HyperCVAD[b] in patients older than 65 y

[a]See references for regimens MANT-A 2 of 3 and MANT-A 3 of 3.
[b]Rituximab + ibrutinib can be used as a pre-treatment to limit the number of cycles of RHyperCVAD/rituximab maintenance.
[c]Oxaliplatin or carboplatin can also be used.
[d]There is a randomized trial that demonstrated that RCHOP was not superior to CHOP.

First-line Consolidation Candidate for HDT/ASCR

- High-dose therapy with autologous stem cell rescue[e] ± rituximab maintenance (category 1 for rituximab maintenance)

First-line Consolidation Not a Candidate for HDT/ASCR

- Rituximab maintenance (category 1 following RCHOP)

Second-line Therapy

- Bendamustine ± rituximab
- Bendamustine, bortezomib, and rituximab (category 2B)
- Bortezomib ± rituximab
- Cladribine + rituximab
- FC (fludarabine, cyclophosphamide) ± rituximab (category 3)
- Ibrutinib[f]
- Ibrutinib, lenalidomide, rituximab (category 2B)
- Lenalidomide ± rituximab
- PCR (pentostatin, cyclophosphamide, rituximab) (category 3)
- PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab (category 3)
- Venetoclax
- See Second-line Therapy for DLBCL (BCEL-C 2 of 4) without regard to transplantability

Second-line Consolidation

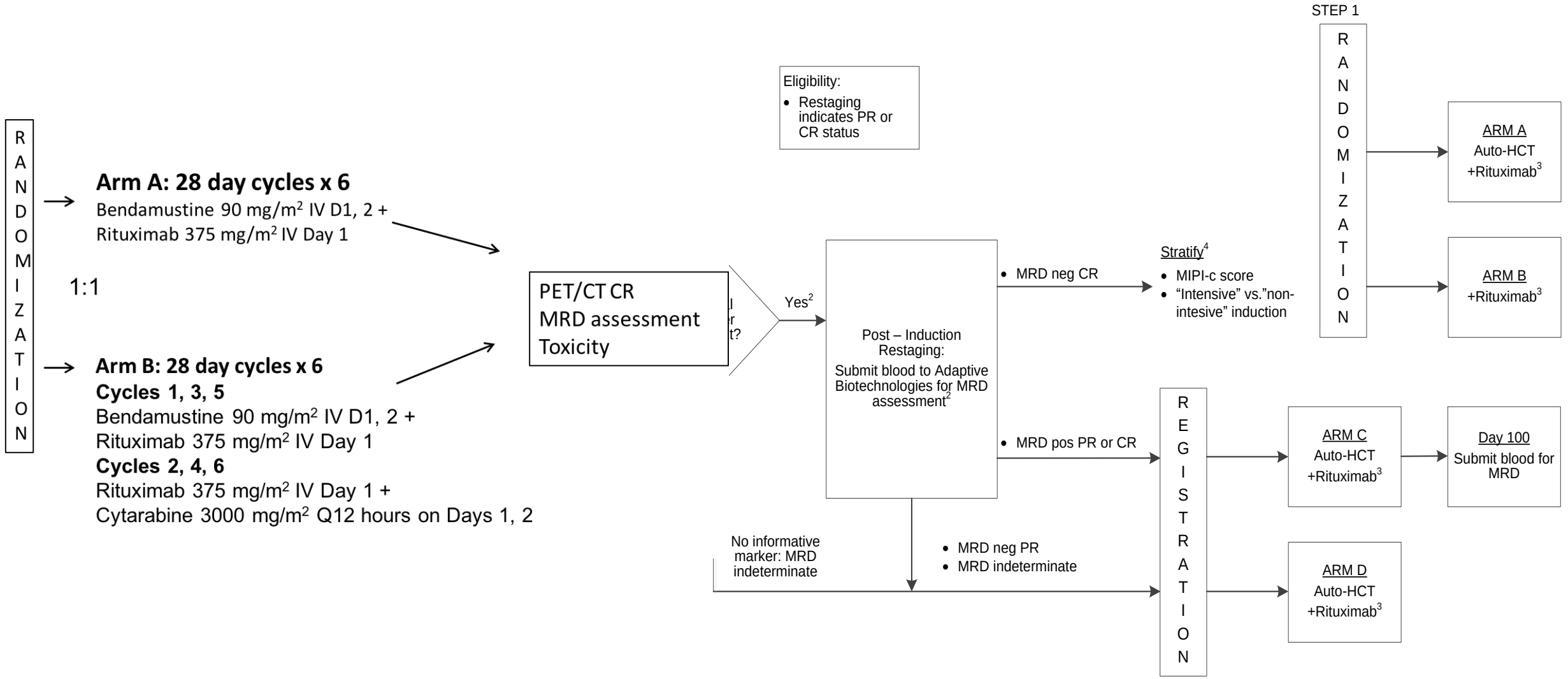
- Allogeneic stem cell transplant (nonmyeloablative or myeloablative)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[e]Randomized data with anthracycline-containing regimens suggest an improvement in progression-free survival with the addition of first-line high-dose therapy with autologous stem cell consolidation.
[f]See Special Considerations for Use of Small-Molecule Inhibitors (Ibrutinib and Idelalisib) (NHODG-E).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Intensive therapy trials



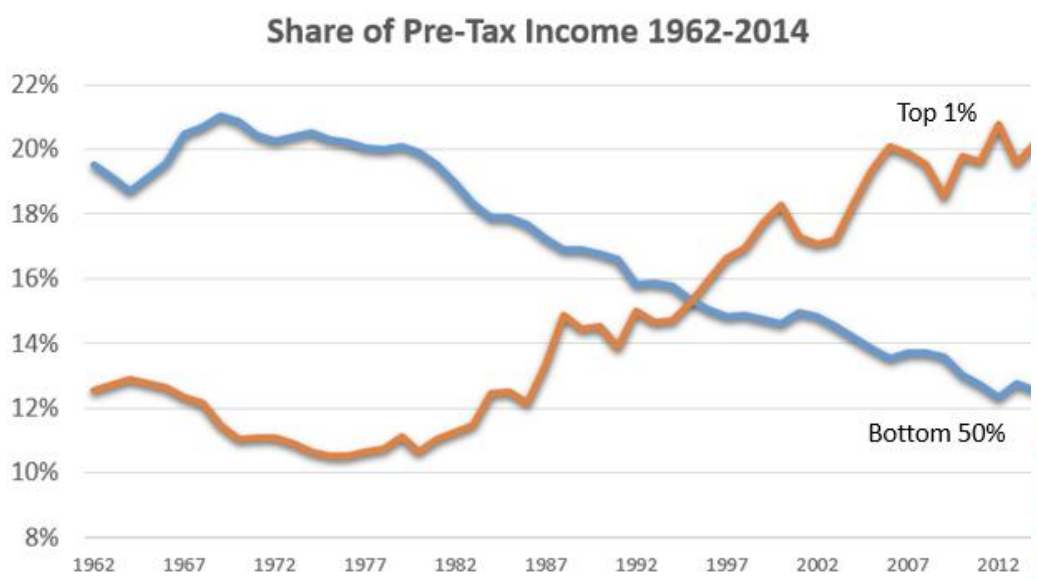
Less intense therapies: A phase 3 trial???

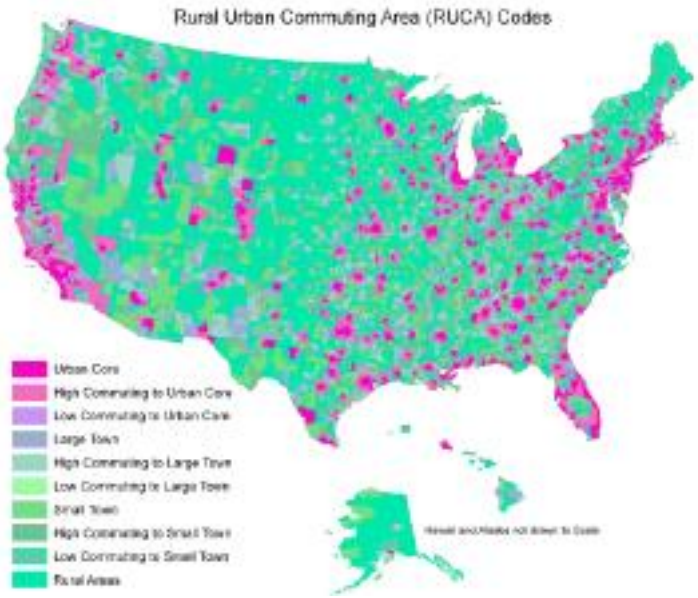
Bendamustine-rituximab plus X

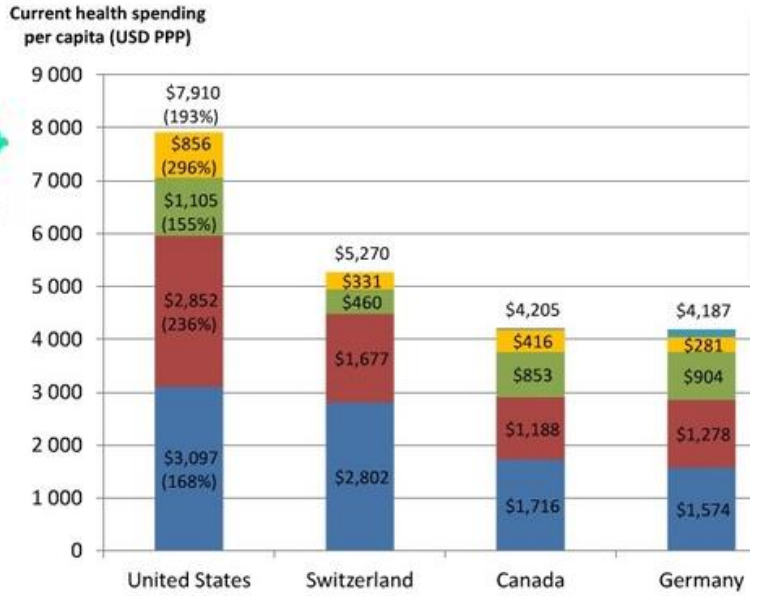
- E1411 – BR +/- bortezomib
- SHINE – BR +/- ibrutinib
- R-BAC500 – BR + cytarabine
- LenaBerit – BR + lenalidomide
- BeRT – BR + temsiroliums
- Next US study: BR + venetoclax?

The United States of America is a complicated place

Payer	Employer	Private	Medicaid	Medicare	Other public	Uninsured
US	49%	7%	20%	14%	2%	9%







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