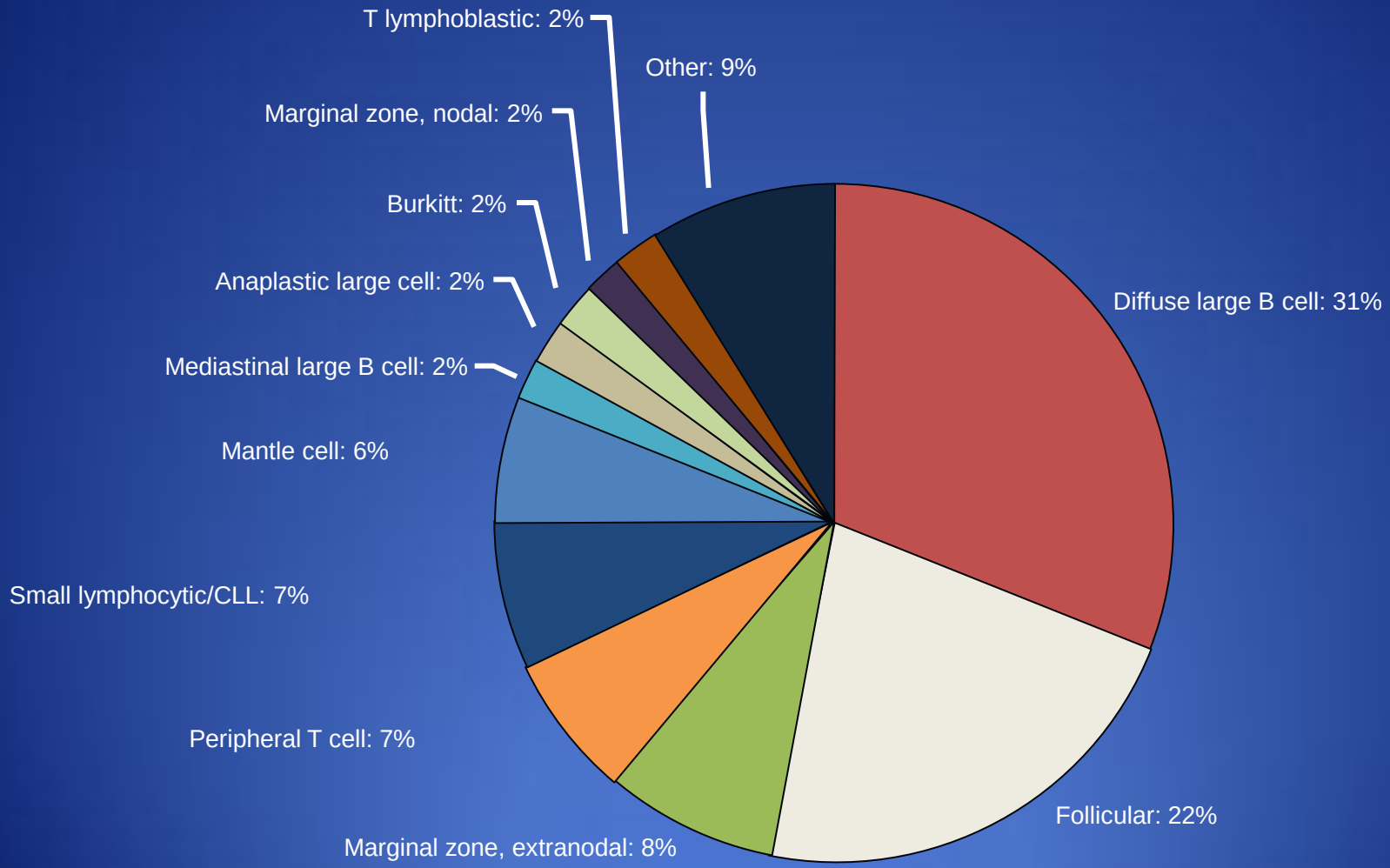
Lymphomas in 2010

Prof Paul Ruff
Division of Medical Oncology

Most Common Lymphomas: ~90% B-cell and ~10% T-cell



Armitage JO, et al. J Clin Oncol. 1998;16:2780-2795.

B- Cell Lymphoproliferative Disorders (~90%)

- "Low Grade":
- CLL/SLL
- Follicular
- Marginal
- Mantle Cell
- Hairy Cell Leukaemia

- Multiple Myeloma

- "High Grade":
- Diffuse Large B-Cell
- B-Lymphoblastic/ALL
- Burkitt's Lymphoma

Lymphomas: Ann Arbor Staging (1971)

- Stage I: One lymph node group
- Stage II: >1 lymph node group on same side of diaphragm
- Stage III: Lymph nodes on both sides of diaphragm
- Stage IV: Extralymphoid spread eg. marrow, lung, liver, brain
- A/B: presence or absence of symptoms: Night sweats, repeated fever >38ºC, >10% weight loss

Staging of Lymphomas

- Radiological staging essential for prognostic and therapeutic reasons
- Chest X-ray
- Spiral Chest CT if CXR suggests mediastinal or hilar adenopathy
- Spiral CT head and neck also be needed in some lymphoma patients
- MRI brain needed in AIDS lymphomas

Staging of Lymphomas

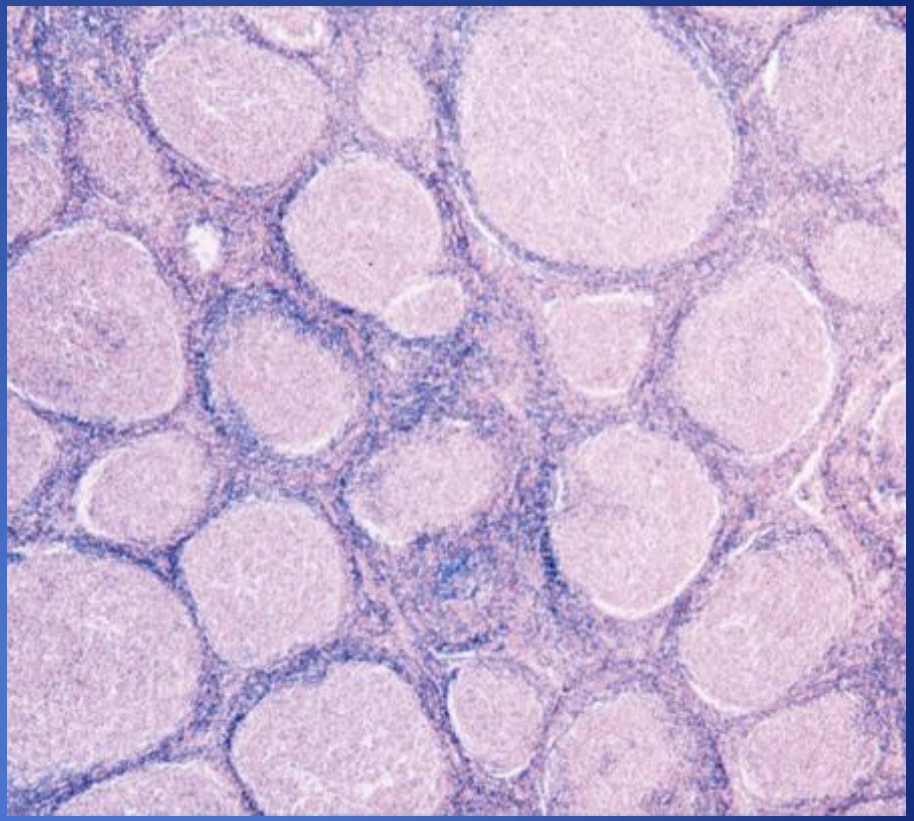
- Spiral CT abdomen and pelvis essential today
- Ultrasound sub-optimal for retroperitoneal structures and in obese patients
- Lymphangiogram obsolete but was used in Hodgkin's lymphoma pre-1990s when CT scanning was limited and inadequate
- Staging laparotomy no longer important with advent of better chemotherapy and reduced role of radiation in Hodgkin's lymphoma
- ?role of ^{18}FDG PET/CT scan in staging newly diagnosed patients

Staging of Lymphomas: Follow-up

- Spiral CT chest/abdomen to assess extent and size of lymph glands during and after completion of chemotherapy +/- radiation
- Exact tumour size essential in clinical trials
- Residual glands may not be malignant therefore a ^{18}FDG PET/CT scan very useful to define active tumour tissue versus residual fibrosis

Follicular NHL

- Common indolent NHL
  - 24,000 new cases diagnosed annually in USA
  - Rising in incidence
- Variable clinical course
  - Incurable with standard therapy; multiple remissions and relapses
  - Histological transformation
  - Median survival improving
- t(14;18)(q32;q21)
  - Oncogene: *bcl-2*



Follicular Lymphoma Classification

Grade	Characteristic
Grade 1	0-5 centroblasts/hpf
Grade 2	6-15 centroblasts/hpf
Grade 3	> 15 centroblasts/hpf
▪ 3a	Centrocytes present
▪ 3b	Solid sheets of centroblasts

Blood. 1997;89:3909-3918.

FLIPI Prognostic Score

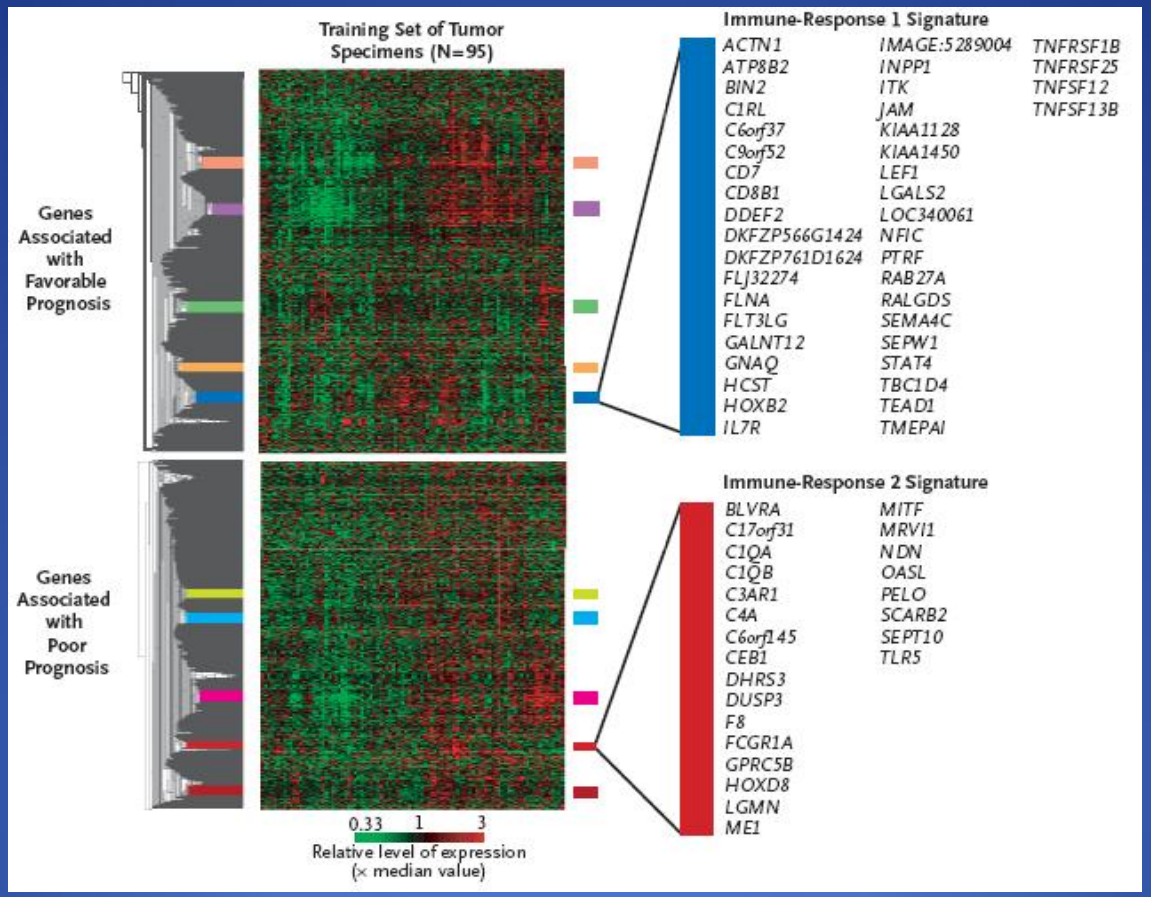
Characteristic	RR (Death)
Older than 60 yrs of age	2.38
Stage III-IV	2.00
Hemoglobin < 12.0 g/dL	1.55
Elevated LDH	1.50
Nodal sites > 4	1.39

FLIPI and OS

Risk Group	Risk Factors, n	5-Yr OS, %	10-Yr OS, %
Low	0-1	91	71
Intermediate	2	78	51
High	≥ 3	53	36

Solal-Céligny, et al. Blood. 2004;104:1258-1265.

Gene Expression: Follicular NHL



Predictive Power of Gene Expression Signature in Follicular Lymphoma

Expression Signature (Prognosis)	RR of Death	*P* Value
Immune response 1 (favorable)	0.15	< .0001
Immune response 2 (unfavorable)	9.35	< .0001

Dave SS, et al. N Engl J Med. 2004;351:2159-2169.

Follicular Lymphoma: Indications for Therapy

- Cytopenias secondary to bone marrow infiltration
- Threatened end-organ function
- Symptoms attributable to disease
- Bulk at presentation
- Steady progression during > 6 mos of observation
- Presentation with concurrent histologic transformation
- Massive splenomegaly
- Patient preference
- Candidate for clinical trial

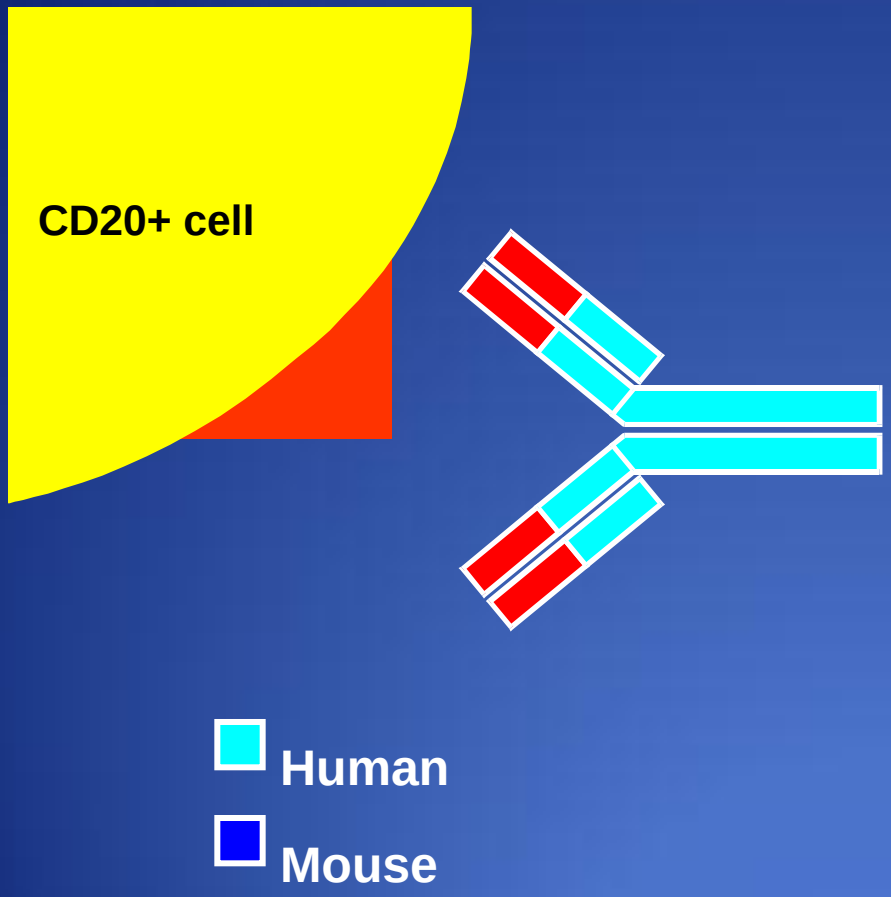
Treatment Options in 2010:

- Observation (watch and wait)
- Radiation
- Single-agent therapy
- Combination chemotherapy
- Interferon-α
- Monoclonal antibodies: especially rituximab
- Hematopoietic transplantation
- Antisense molecules
- Vaccines
- Targeted agents

Monoclonal Antibodies in B-Cell Lymphoma

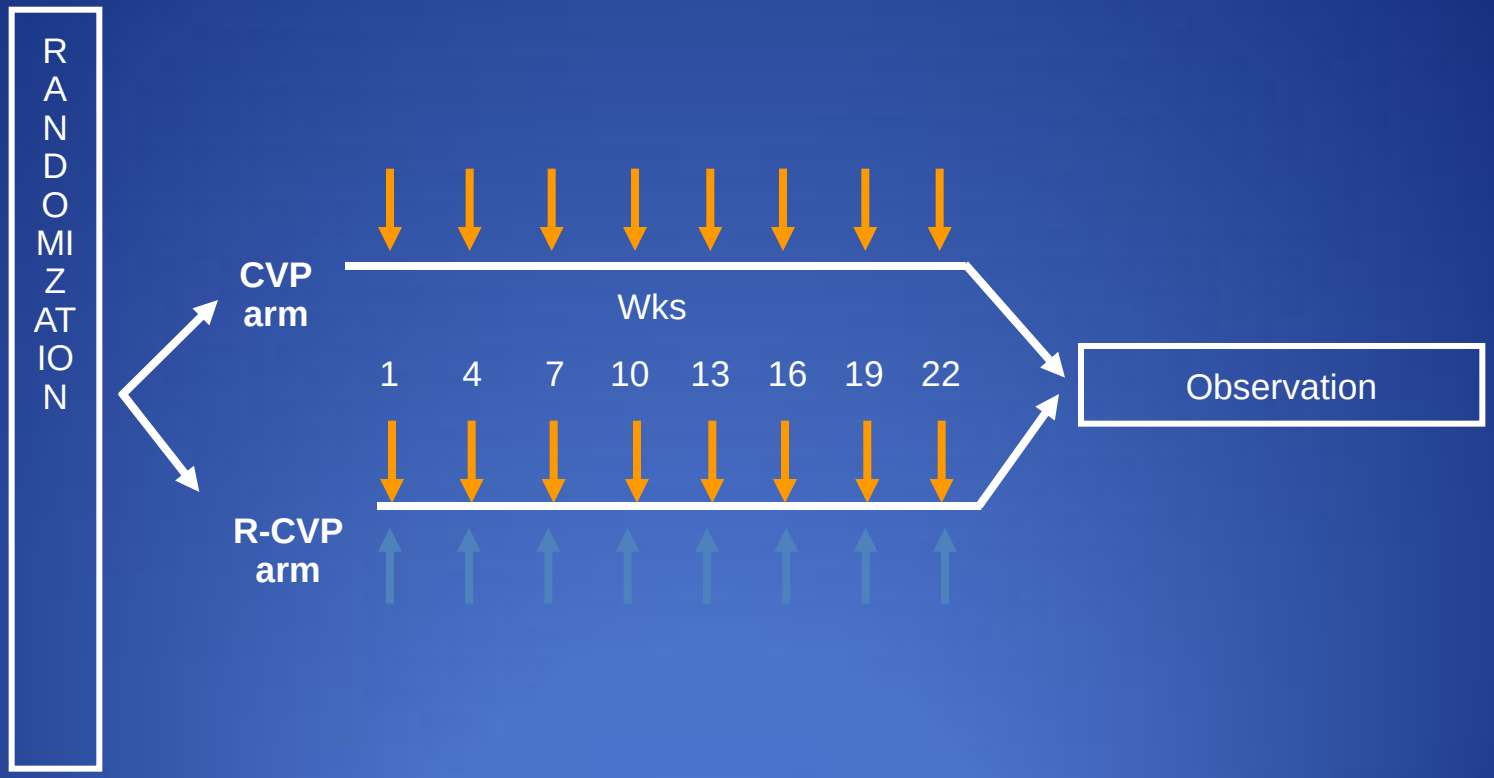
- Rituximab: Naked chimeric monoclonal antibody against CD20 antigen
- CD20 on cell surface of most B-cell malignancies except primitive B-cell ALL and post-mature myeloma cells
- Licensed as Mabthera® (RSA/Europe) or Rituxan® (USA) in CD20+ B-cell lymphomas

Key features of Rituximab



- Chimeric anti-CD20 MoAb
- Activates complement mediated cytotoxicity & antibody dependent cellular cytotoxicity (ADCC)
- Direct anti-tumor effects
- Synergistic activity with chemotherapy
- Sensitizes chemoresistant cell lines

CVP versus CVP + Rituximab for Stage III-IV Follicular Lymphoma



Marcus R, et al. J Clin Oncol. 2008;26:4579-4586.

CVP versus CVP + Rituximab for Advanced Follicular Lymphoma

Outcome	CVP	CVP + Rituximab
CR, %	10	41
Duration of response, mos	14	38
4-yr survival, %	77	83

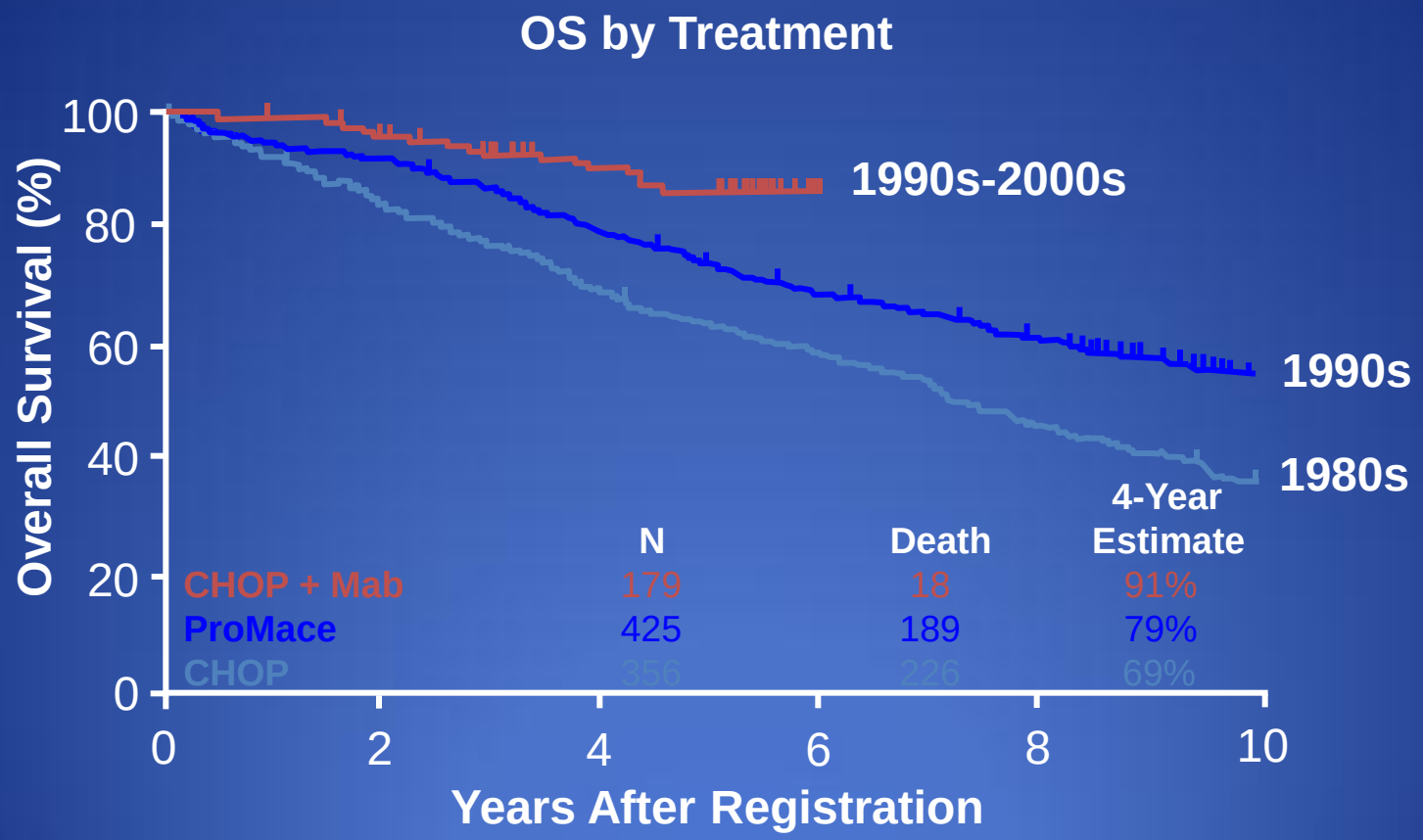
Marcus R, et al. J Clin Oncol. 2008;26:4579-4586.

Prolonged Survival With Chemo + Rituximab for FL

- CVP vs R-CVP[1]
- CHOP vs R-CHOP[2]
- MCP vs R-MCP[3]

1. Marcus R, et al. J Clin Oncol. 2008;26:4579-4586.
2. Hiddemann W, et al. Blood. 2005;106:3725-3732.
3. Herold M, et al. J Clin Oncol. 2007;25:1986-1992.

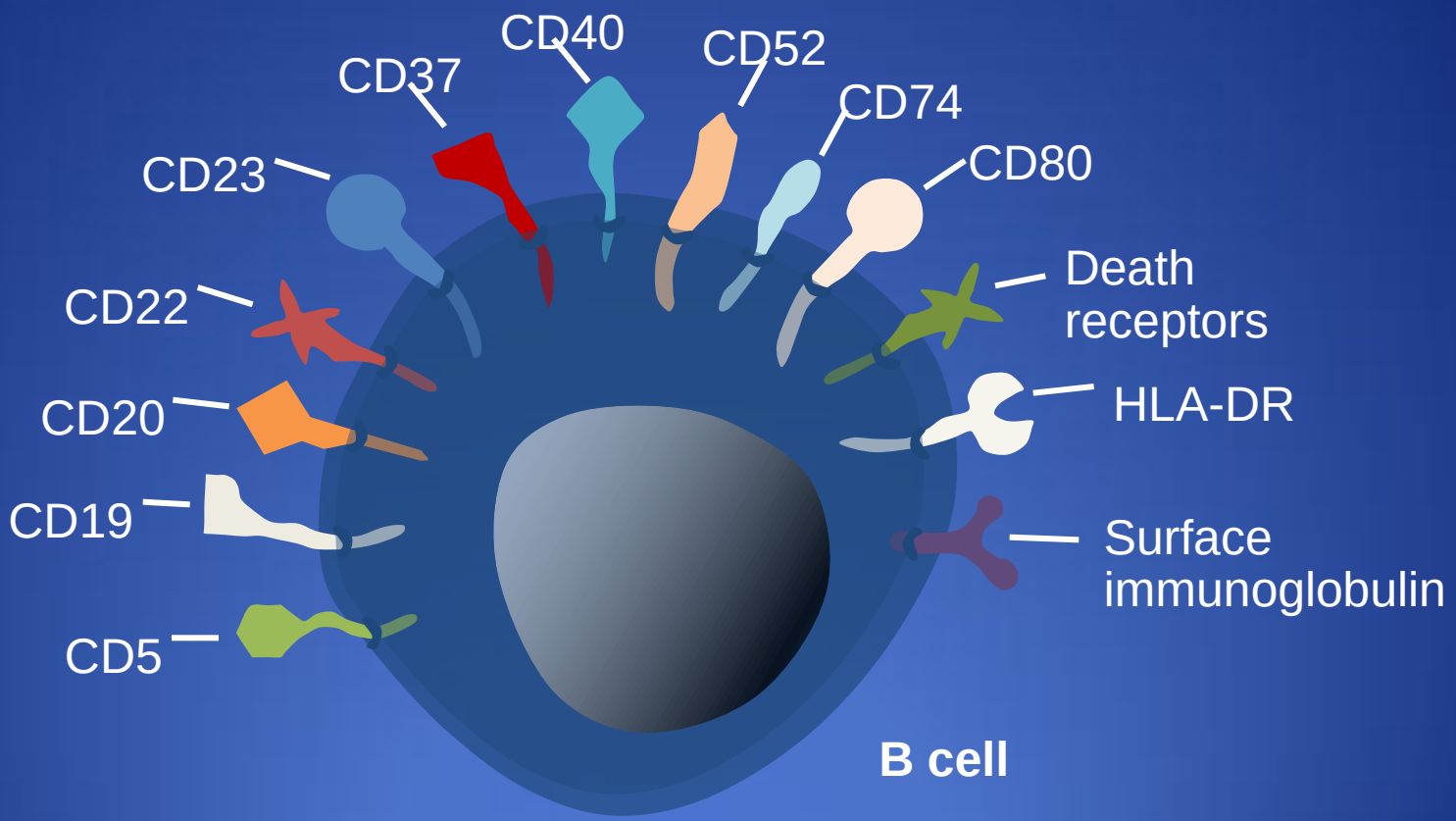
Improving Survival of Follicular NHL: Impact of Antibody-Based Therapy



Treatment of FL: Summary

- Rituximab prolongs PFS and OS in patients requiring treatment
- Despite progress, relapsing patterns continue to be observed
- Maintenance rituximab improves PFS
  - Longer-term follow-up will be of interest to determine whether there is a survival advantage
- Many unanswered questions
  - Role of watchful waiting
  - Role of maintenance therapy
  - Role of FLIPI or risk stratification in choosing therapy

Potential Antibody Targets for B-Cell Lymphomas



Cheson BD, et al. N Engl J Med. 2008;359;613-626.

New Antibodies for Follicular Lymphoma

Antibody	Type
Epratuzumab (humanized)	Anti-CD22
Ofatumumab (human)	Anti-CD20
Galiximab (chimeric)	Anti-CD80
Dacetuzumab (humanized)	Anti-CD40
Inotuzumab-ozogamicin (humanized)	Anti-CD22
Veltuzumab (humanized)	Anti-CD20
GA-101 (humanized)	Anti-CD20

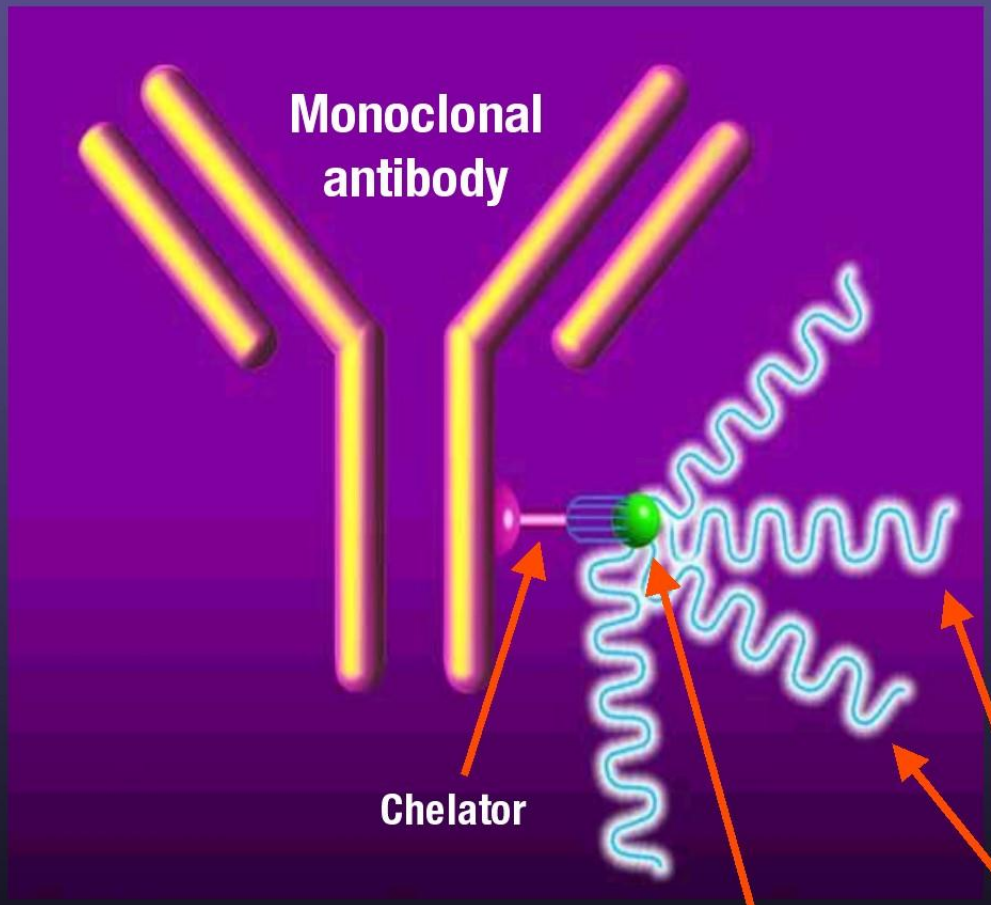
Rituximab-Refractory Indolent NHL

- Patients treated with rituximab who then
  - Fail to respond to rituximab therapy
  - Progress within 6 months of rituximab therapy
- In the US, often includes patients refractory to an R-chemo regimen or who progress during maintenance therapy
- Outcome of this group of patients has not been well evaluated, and optimal therapy is unknown

Rituximab-Refractory Indolent NHL: "Standard" Therapy Options

- Radioimmunotherapy
  - On label
  - Response rate high, time-to-progression variable
- ASCT
  - Randomized trial suggests benefit over standard therapy
  - Applicable to minority of patients
  - May be difficult with extensive previous therapy or marrow involvement
- AlloSCT
  - Potentially curative option
  - High transplantation-related mortality and morbidity
  - Donor a requirement

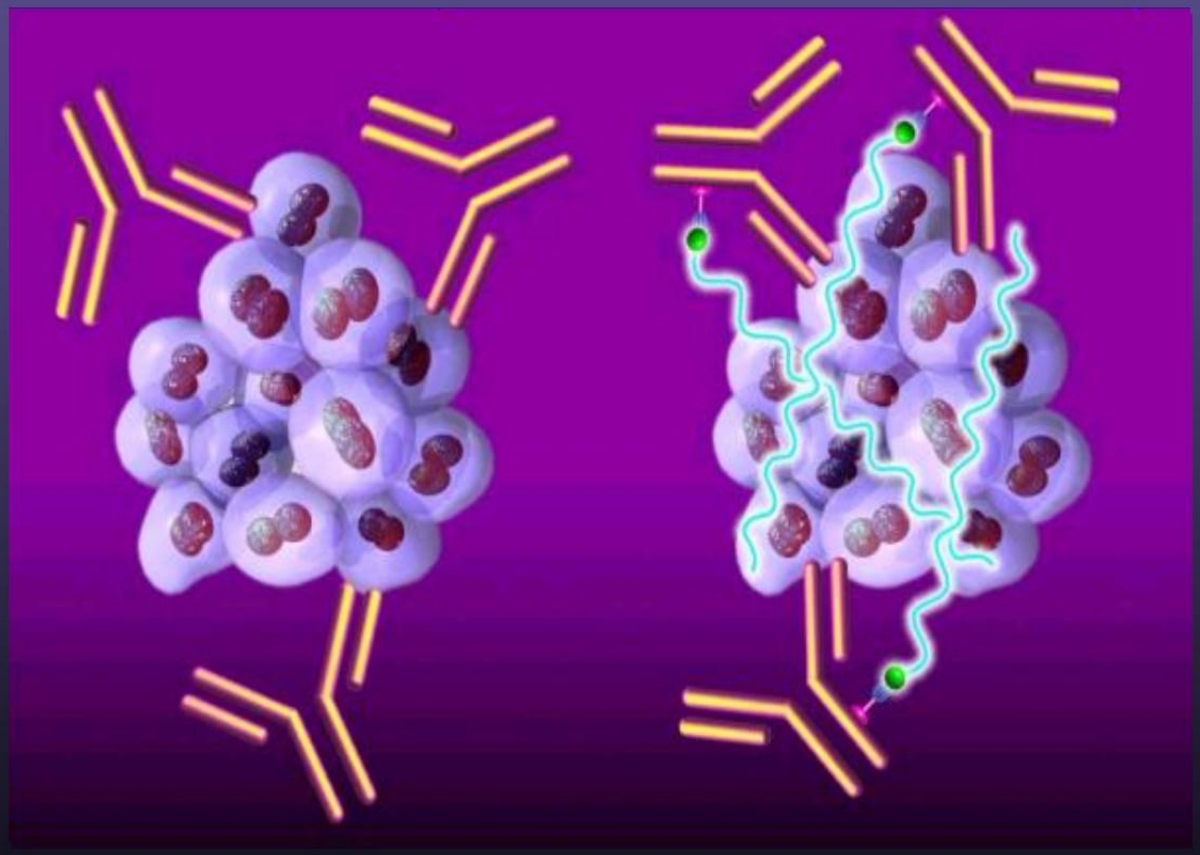
Yttrium-90 (Y-90) Zevalin Radioimmunotherapy Delivers Increased Cytotoxicity by Antibodies



- Ibritumomab
  - Murine monoclonal antibody parent of Rituximab
- Tiuxetan
  - Conjugated to antibody, forming strong urea-type bond
  - Stable retention of Y-90

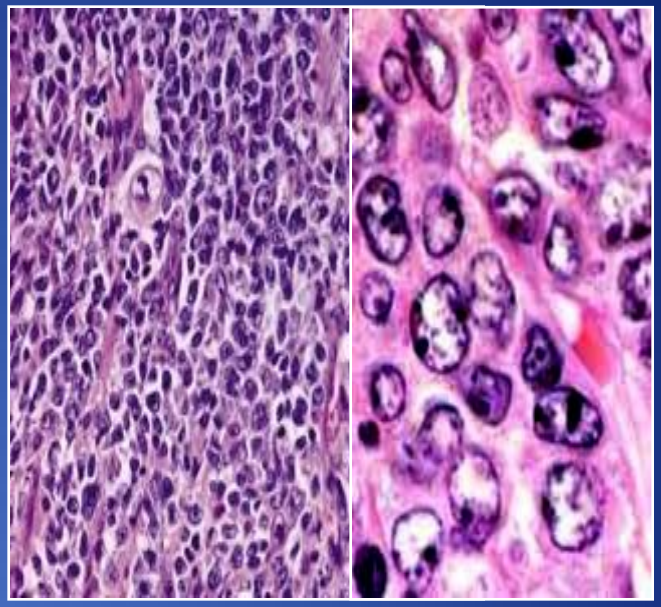
ZEVALIN™
Ibritumomab tiuxetan

Y-90 Zevalin Produces a Crossfire Effect



ZEVALIN™
Ibritumomab tiuxetan

Diffuse Large B-Cell Lymphoma



- Most common NHL: 31%
  - Peak incidence in 6th decade
- Curable in 50% or more of cases
- Median survival: wks to mos if not treated
- Clinical outcomes and molecular features highly heterogeneous
- Large cells with loss of follicular architecture of node
  - 30% to 40% present with rapidly enlarging, symptomatic mass with B symptoms
  - May present as extranodal disease (stomach, CNS, testis, skin)

Michallet AS, et al. Blood Rev. 2009;23:11-23.

DLBCL: Prognostic Factors (IPI)

Risk Group	Risk Factors, n	CR, %	5-Yr OS, %
Patients (all ages)			
▪ Low	0-1	87	73
▪ Low intermediate	2	67	51
▪ High intermediate	3	55	43
▪ High	4-5	44	26
Patients 60 yrs of age or younger			
▪ Low	0	92	83
▪ Low intermediate	1	78	69
▪ High intermediate	2	57	46
▪ High	3	46	32

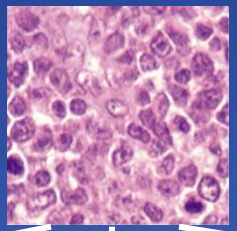
- Adverse risk factors correlated with response to chemotherapy and survival
  - Older than 60 yrs of age
  - LDH > normal
  - PS ≥ 2
  - Ann Arbor stage III/IV
  - Extranodal involvement > 1 site*

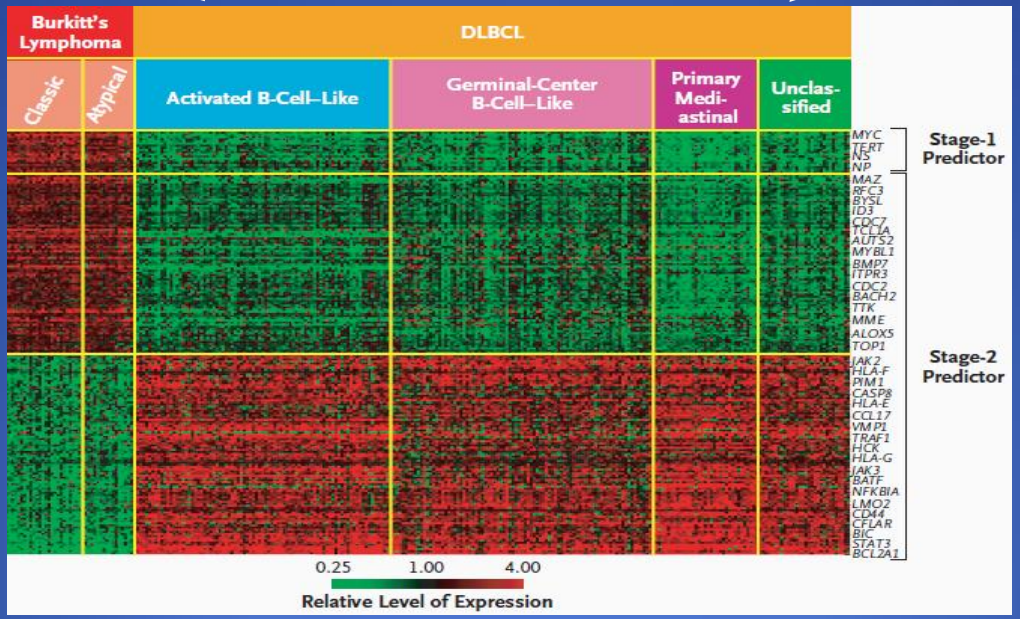
*Prognostic for patients older than 60 yrs of age only.

International NHL Prognosis Factors Project. N Engl J Med. 1993;329:987-994.

Gene Expression Defines Molecularly and Clinically Distinct Subgroups in DLBCL

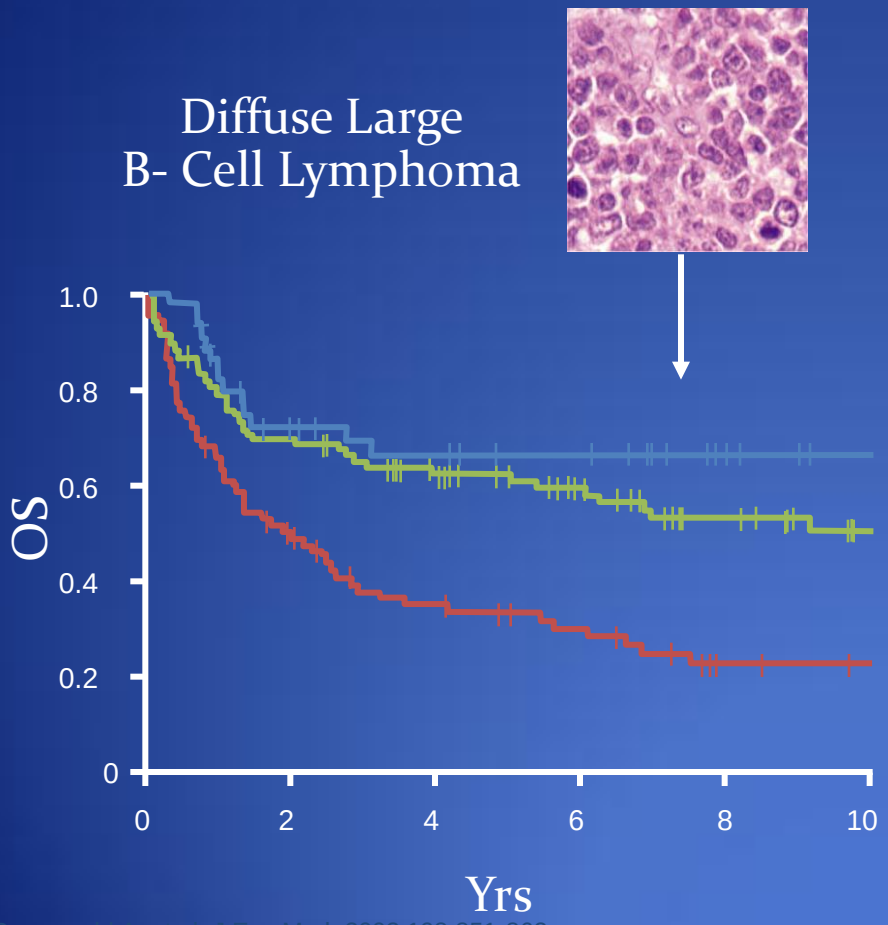
Diffuse Large B-Cell Lymphoma





Dave SS, et al. N Engl J Med 2006;354:2431-2442.

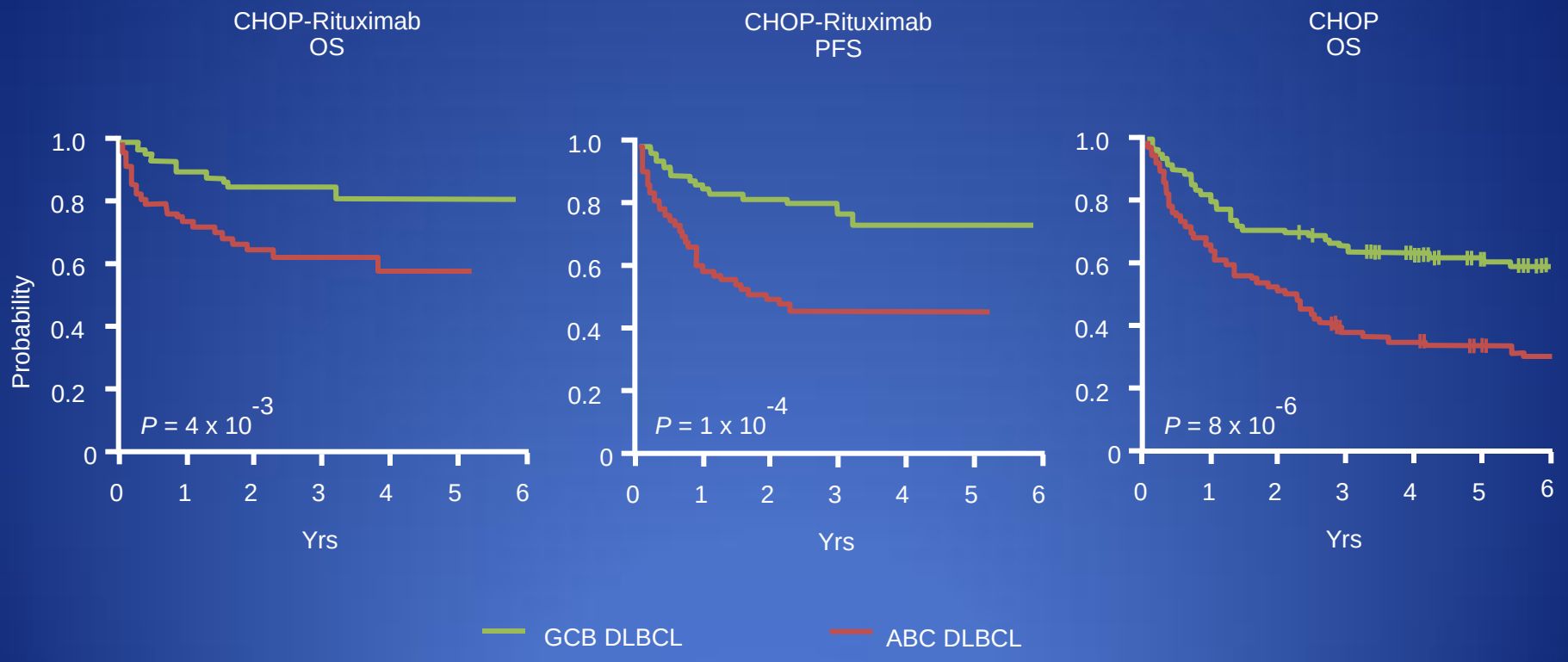
Gene Expression Defines Molecularly and Clinically Distinct Subgroups in DLBCL



DLBCL Subgroup	5-Yr OS, %
PMBL	64
GCB DLBCL	59
ABC DLBCL	30

Rosenwald A, et al. J Exp Med. 2003;198:851-862.
Originally published in The Journal of Experimental Medicine.

DLBCL Subtype Retains Prognostic Value With R-CHOP Therapy



Lenz G, et al. N Engl J Med. 2008;359:2313-2323.

DLBCL Treatment

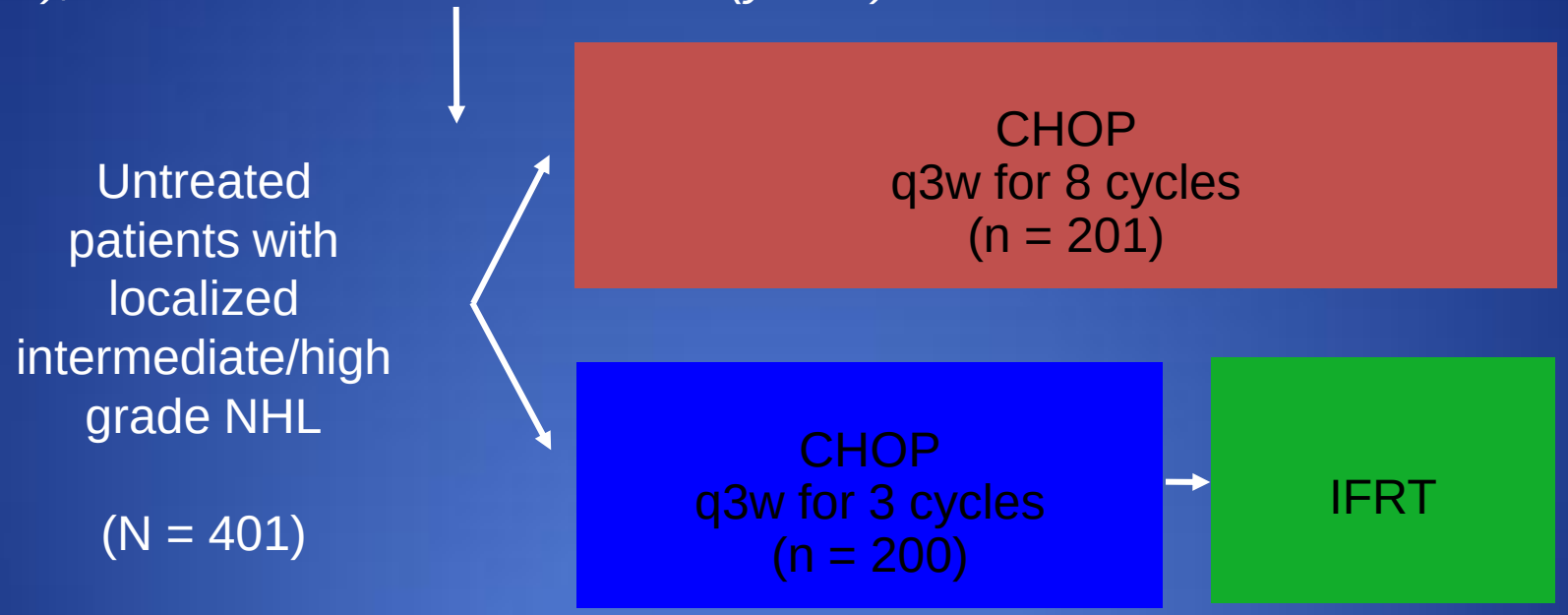
- Localized stage I/II disease:
  - Abbreviated course of chemotherapy with immunotherapy followed by radiation or a full course of chemotherapy

- Advanced-stage disease:
  - Chemoimmunotherapy plus combination of rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy for 6-8 cycles

NCCN practice guidelines in oncology: non-Hodgkin's lymphomas V.1.2010. Available at: http://nccn.org/professionals/physician_gls/PDF/nhl.pdf.

SWOG 8736: CHOP ± Radiotherapy in NHL in Localized DLBCL (Stage I and II)

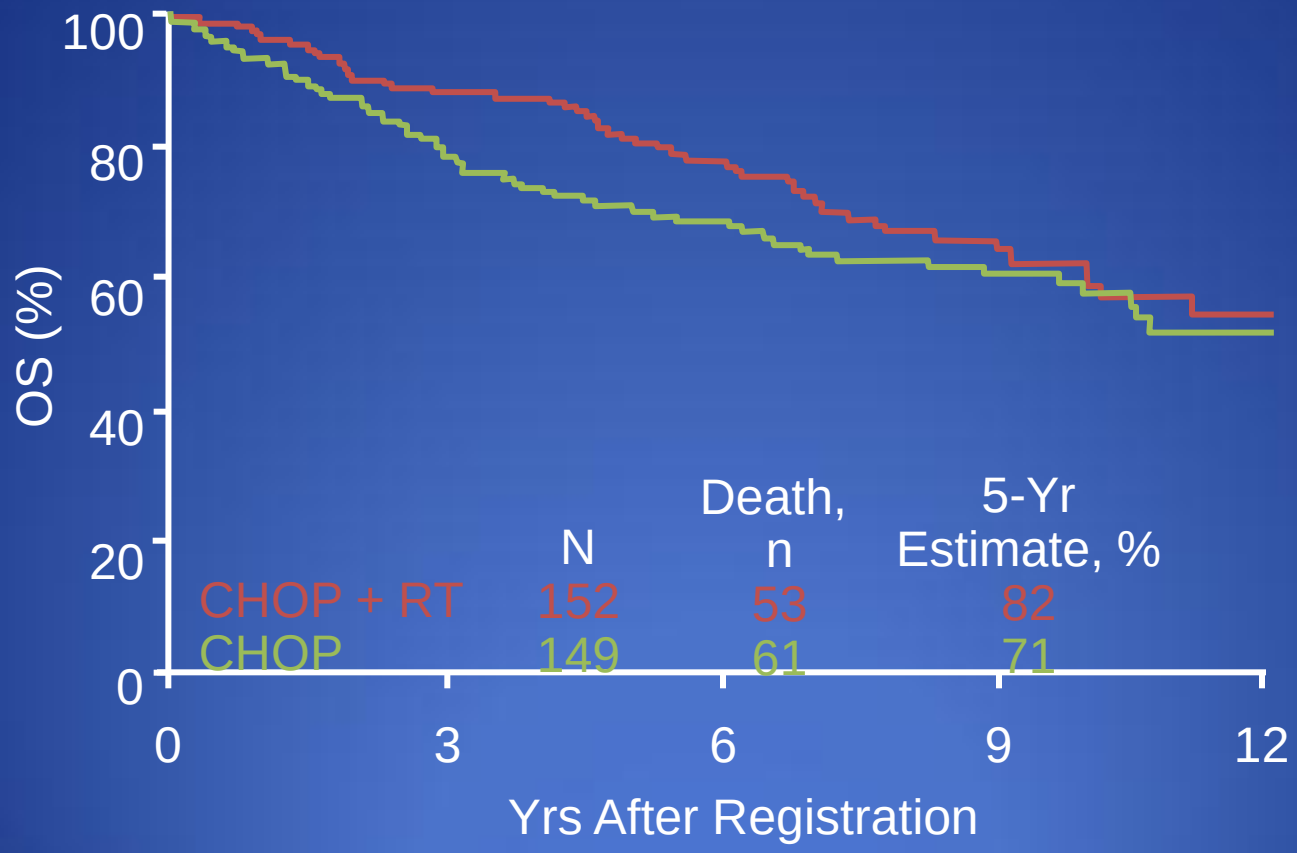
Stratified by age (< vs ≥ 65 yrs), histology (DLBCL vs others), disease site (GI vs other), stage (I vs II), resection of all visible tumors (y vs n)



- Endpoints: PFS, OS, toxicity

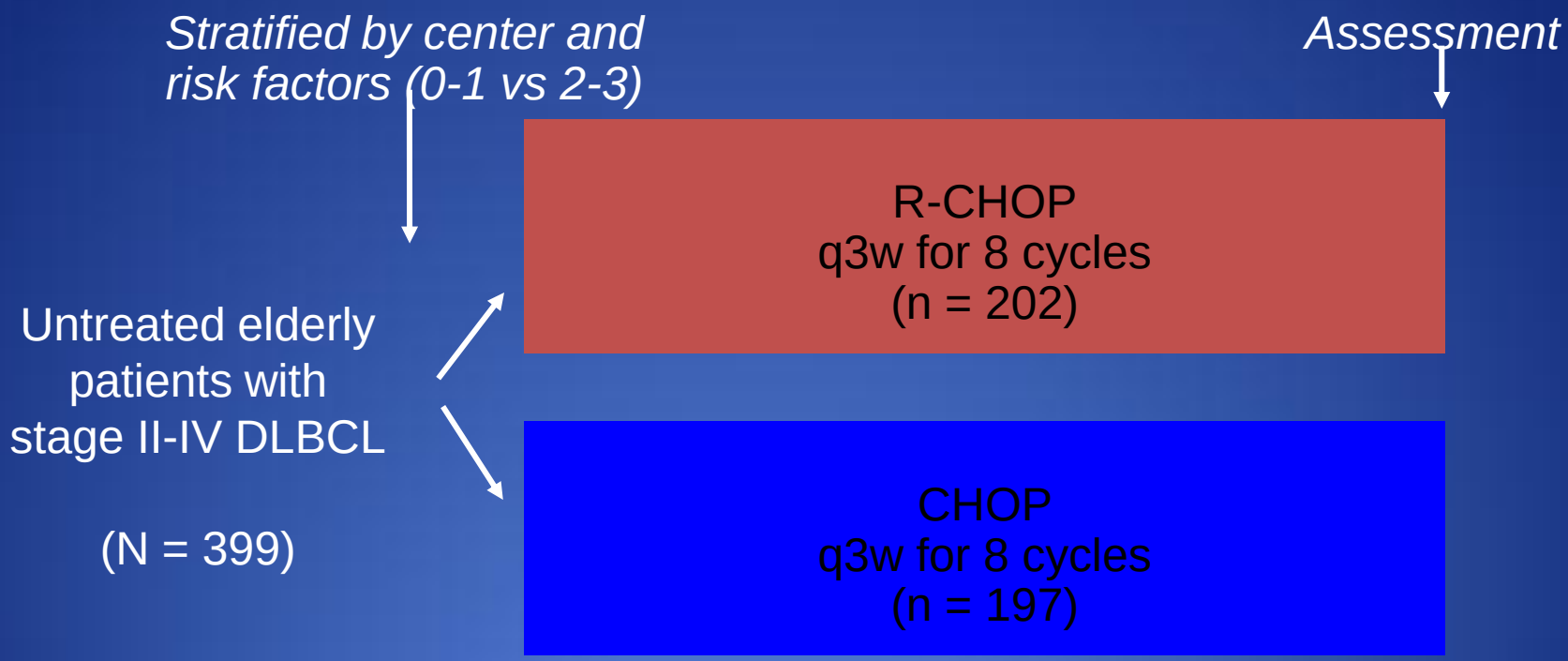
Miller TP, et al. N Engl J Med. 1998;339:21-26.

SWOG 8736: OS for DLBCL Patients Treated With CHOP ± Radiotherapy



Miller T, et al. ASH 2001. Abstract 3024.

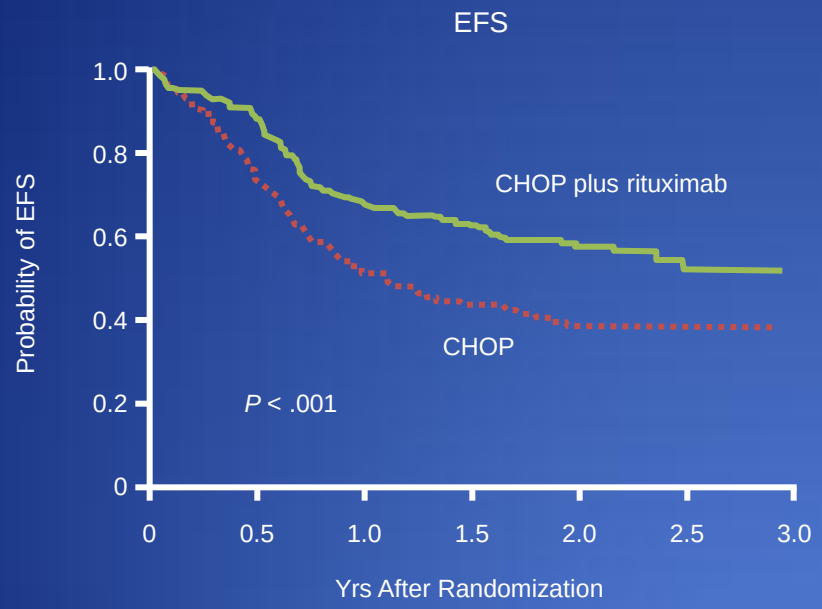
CHOP ± Rituximab in Advanced-Stage DLBCL: GELA LNH-98.5 Phase III Study



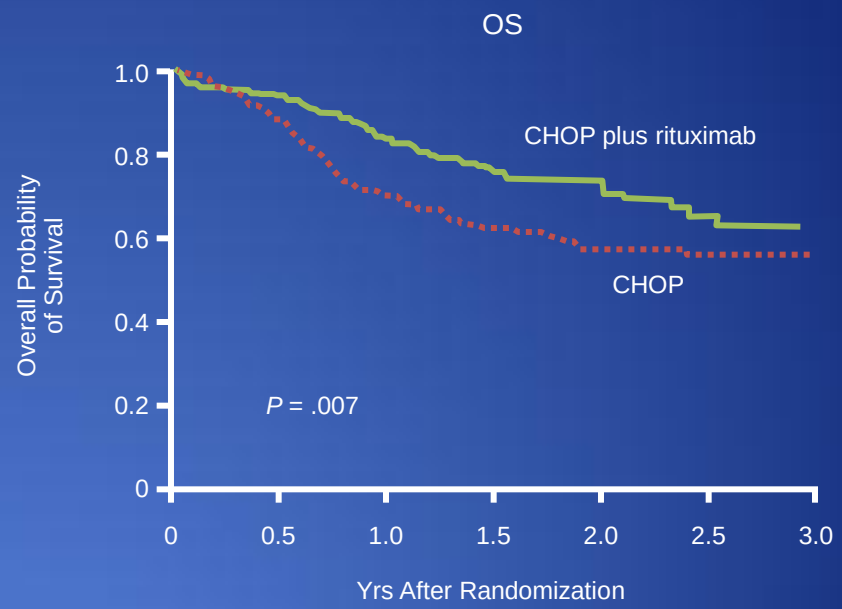
- Primary endpoint: EFS
- Secondary endpoints: OS, RR

Coiffier B, et al. N Engl J Med. 2002;346:235-242. Feugier P, et al. J Clin Oncol. 2005;23:4117-4126.

CHOP ± Rituximab in DLBCL: 3-Yr Survival Results (GELA LNH-98.5 Study)



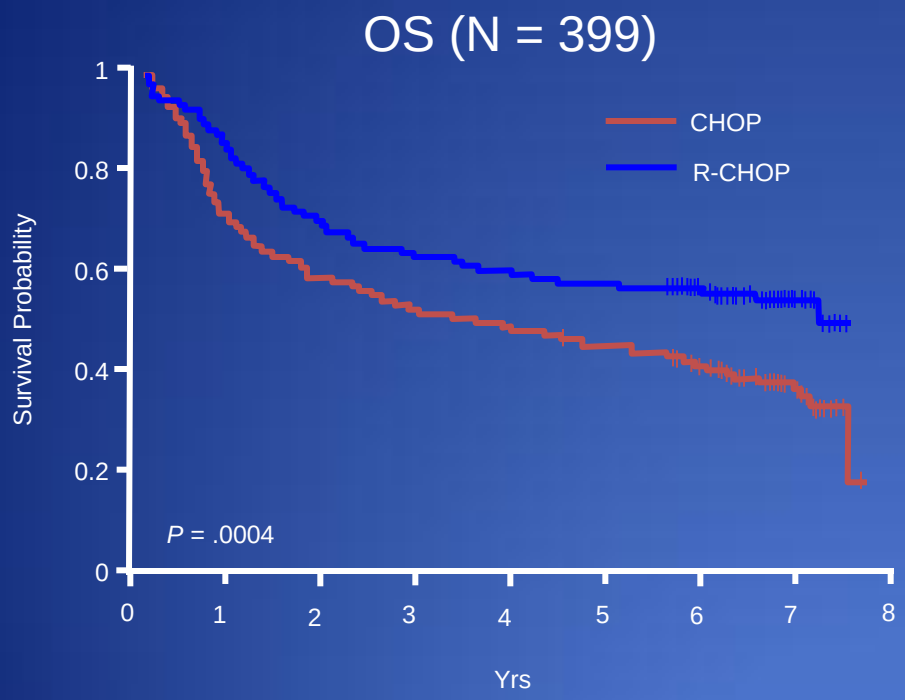
Pts at Risk, n						
CHOP plus rituximab	202	177	137	108	63	19
CHOP	197	144	101	72	42	17



Pts at Risk, n						
CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

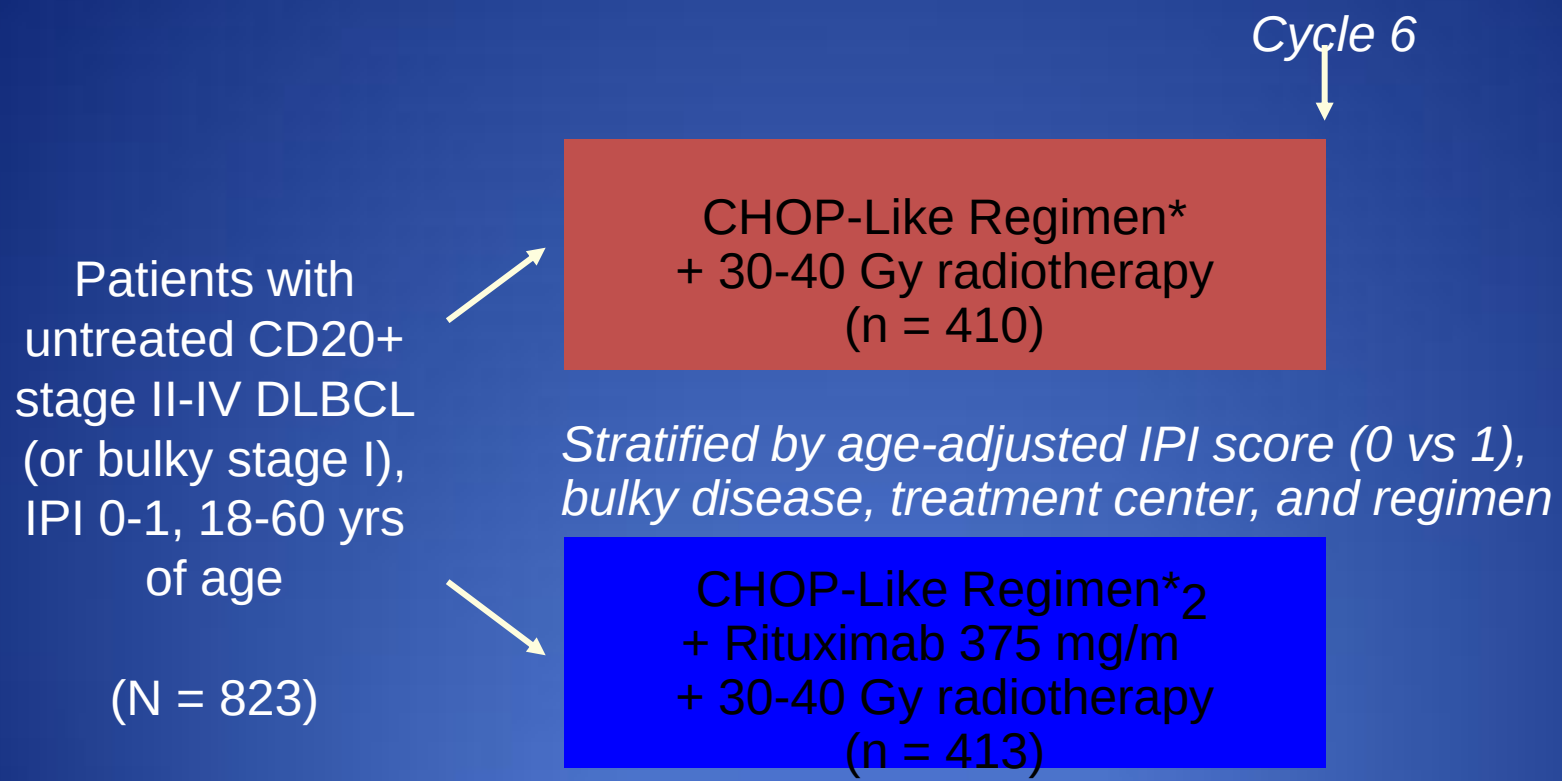
Coiffier B, et al. N Engl J Med. 2002;346:235-242.

CHOP ± Rituximab in DLBCL: 7-Yr Survival Results (GELA LNH-98.5 Study)



Coiffier B, et al. ASCO 2007. Abstract 8009.

MInT: Phase III Study of CHOP-like Chemo ± Rituximab in Adv. DLBCL (Younger Pts)



*CHOP-21, CHOEP-21, MACOP-B, or PMitCEBO.

Pfreundschuh M, et al. Lancet Oncol. 2006;7:379-391.

Impact of Rituximab: The MInT Trial Group

For rituximab plus chemotherapy vs chemotherapy alone, the impact of rituximab that was demonstrated in the GELA trial also held true in the MInT trial with benefits in:

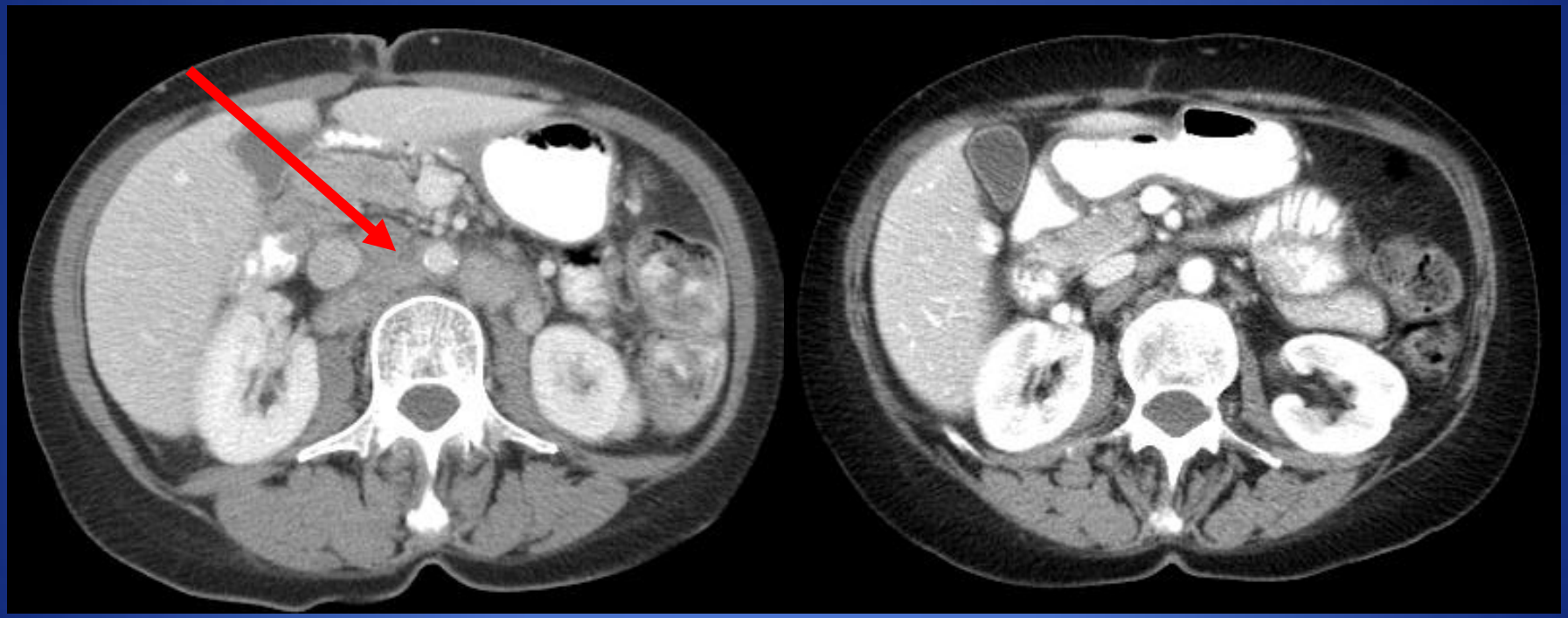
- EFS
- PFS
- OS

Pfreundschuh M. et al. Lancet Oncology. 2006; 7: 379-391.

Diffuse Large B-Cell Lymphoma: Nodal Response

Before Treatment

After Treatment

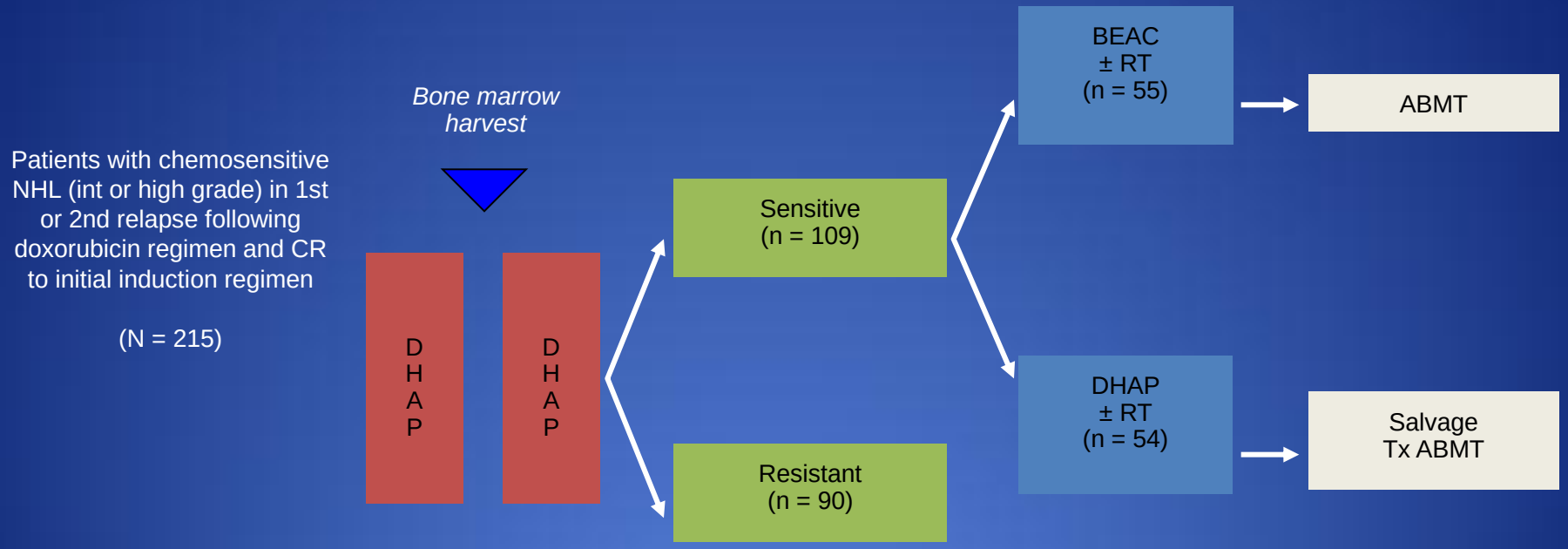


Guideline Recommendations for Treatment of Relapsed DLBCL

- Second-line therapy in candidates for high-dose therapy + ASCT
  - DHAP ± rituximab
  - ESHAP ± rituximab
  - GDP ± rituximab
  - GemOx ± rituximab
  - ICE ± rituximab
  - MINE ± rituximab
- Second-line therapy for patients who are not candidates for high-dose therapy
  - Clinical trial
  - Rituximab
  - CEPP ± rituximab
  - Lenalidomide
  - EPOCH ± rituximab

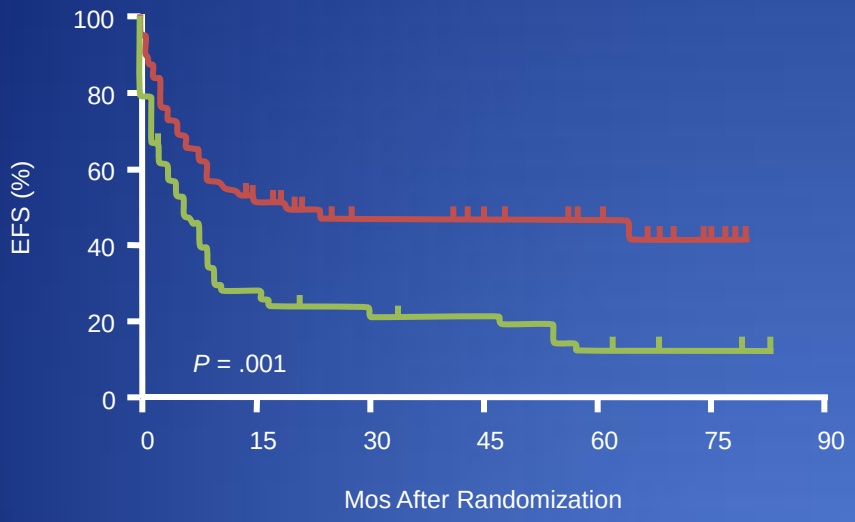
NCCN practice guidelines in oncology: non-Hodgkin's lymphomas V.1.2010. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf.

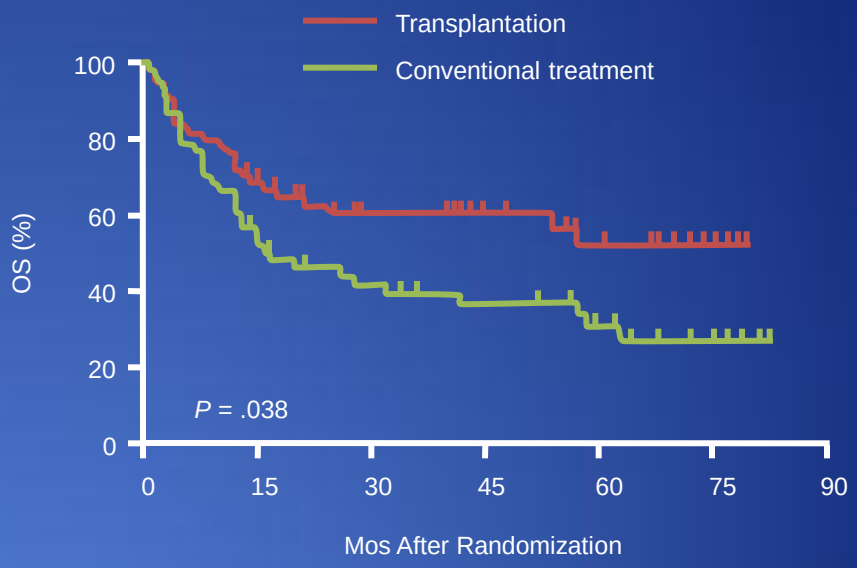
PARMA Study: ABMT vs Conventional Chemotherapy in Relapsed NHL



Philip T, et al. N Engl J Med. 1995;333:1540-1545.

PARMA Study: Bone Marrow Transplantation versus Salvage Chemotherapy





Investigational Therapies for DLBCL

- Bevacizumab: recombinant, humanized, monoclonal anti-VEGF antibody
- Epratuzumab: humanized, monoclonal anti-CD22 antibody
- Everolimus: mTOR inhibitor
- Lenalidomide: immunomodulator, antiangiogenic
- Radioimmunotherapy
- Tamatinib: inhibitor of Syk in B-cell signaling pathway
- Bortezomib: proteasome inhibitor
- Enzastaurin: PKCβ-selective inhibitor

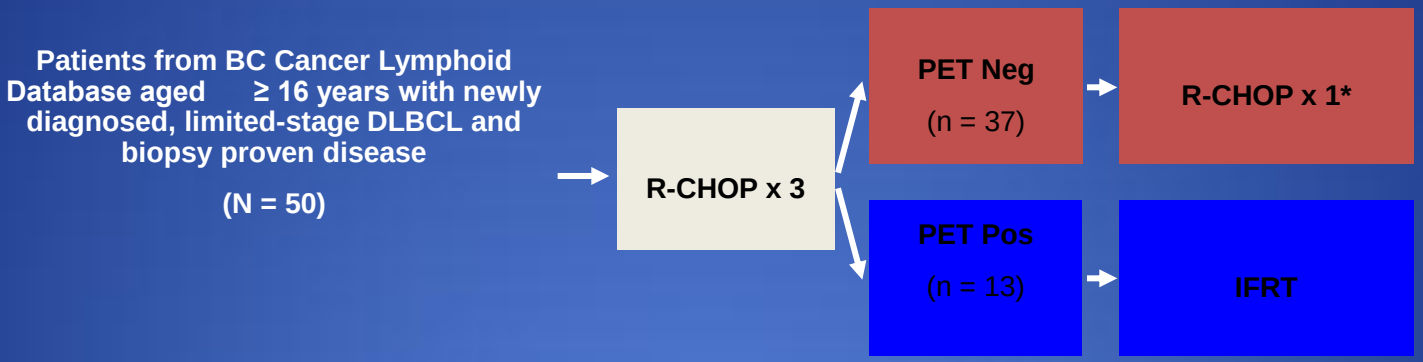
DLBCL Treatment: Summary

- Eminently curable with chemoimmunotherapy approaches, both for patients with limited-stage disease and for those with advanced-stage disease/localized stage I/II disease
- Modern era treatment
  - Combination of rituximab and chemotherapy, typically using the R-CHOP for an abbreviated course of therapy plus radiation for patients with limited-stage disease or possibly R-CHOP for 6-8 cycles for those patients without radiation
  - For patients with advanced-stage disease, R-CHOP chemotherapy for 6-8 cycles total

NCCN practice guidelines in oncology: non-Hodgkin's lymphomas V.1.2010. Available at: http://nccn.org/professionals/physician_gls/PDF/nhl.pdf.

PET to Determine Treatment Approach in DLBCL Following 3 R-CHOP Cycles

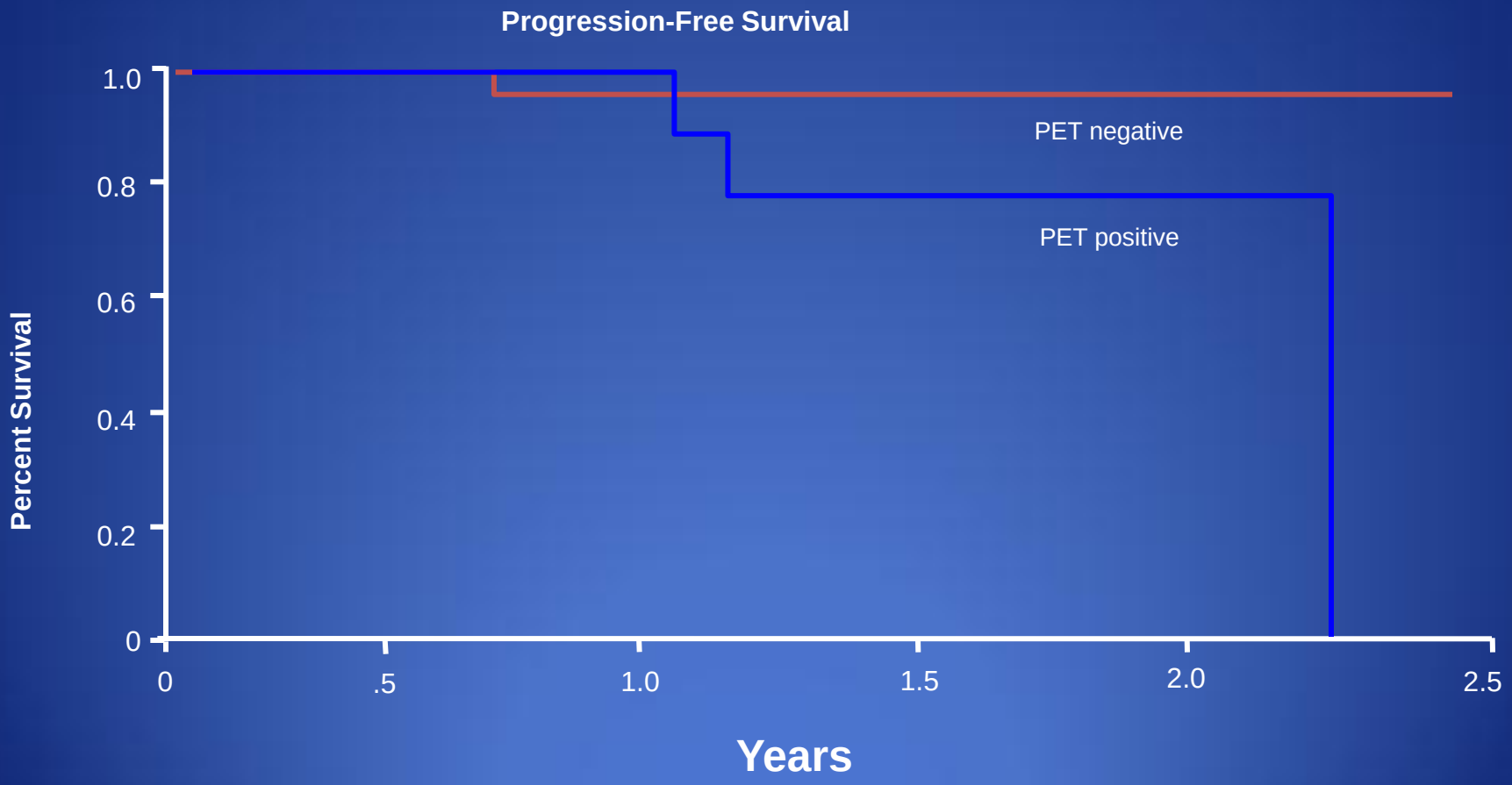
- Retrospective analysis of PET-guided treatment in patients with limited-stage DLBCL
  - Median follow-up: 20 months



*1 patient received subsequent IFRT because of chemotoxicity and 1 died prior to receiving further therapy.

Sehn LH, et al. ASH 2007. Abstract 787.

PET to Determine Treatment Approach in DLBCL Following 3 R-CHOP Cycles



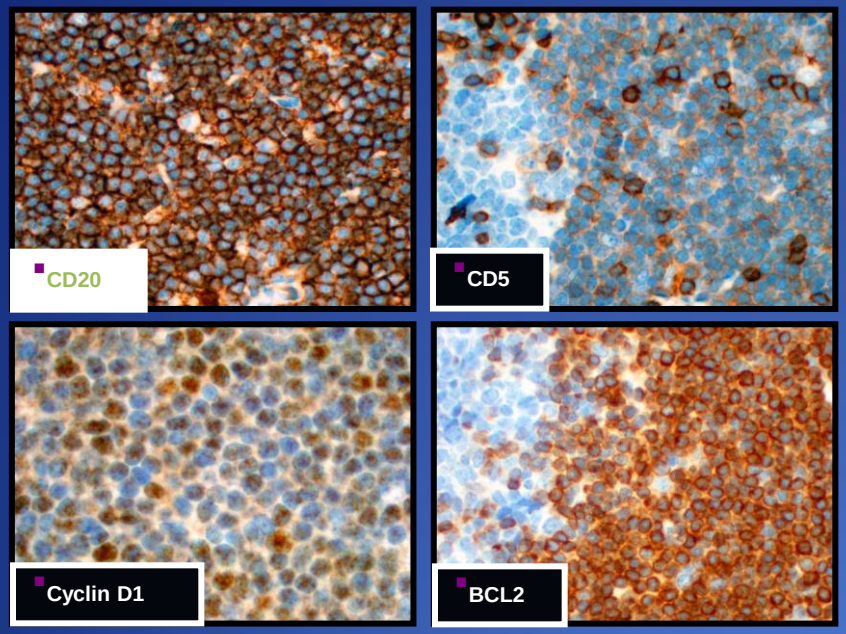
Sehn LH, et al. ASH 2007. Abstract 787.

Mantle Cell Lymphoma: Clinical Features

- Accounts for ~ 6% of B-cell NHL cases
- Moderately aggressive course
- 74% male
- Median age: 63 yrs
- > 90% stage III/IV, including marrow involvement
- Extranodal sites common
  - GI (upper and lower, can present as lymphomatous polyposis coli)
  - Leukemic phase, PB flow commonly positive

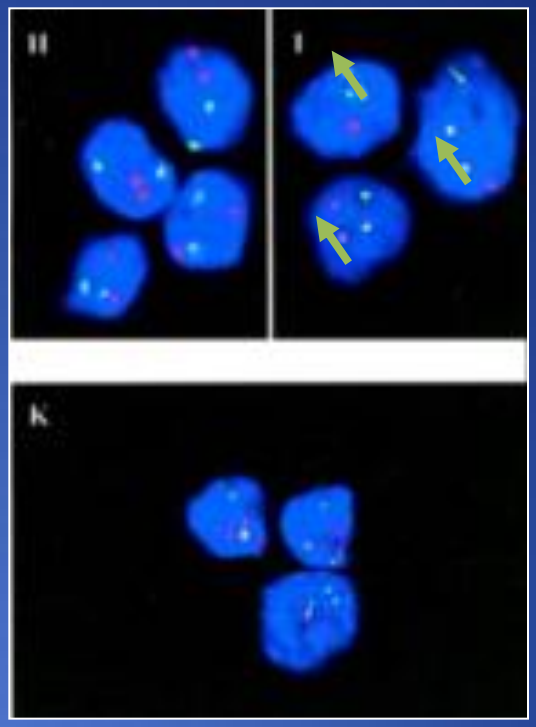
Armitage JO. Oncology (Williston Park). 1998;12(10 suppl 8):49-55. Fisher RI, et al. Hematology Am Soc Hematol Educ Program. 2004:221-226. O'Connor OA, et al. Leuk Lymphoma. 2008;49(Suppl 1):59-66.

MCL: Pathology



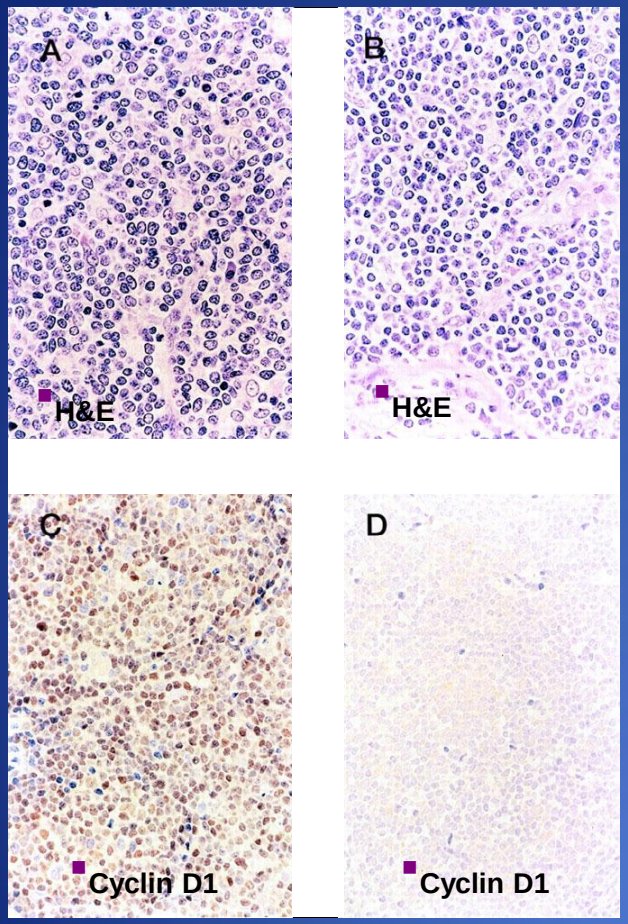
Typical immunophenotype:
CD20+, CD5+, CD23-, CCND1+, FMC7+, BCL2+

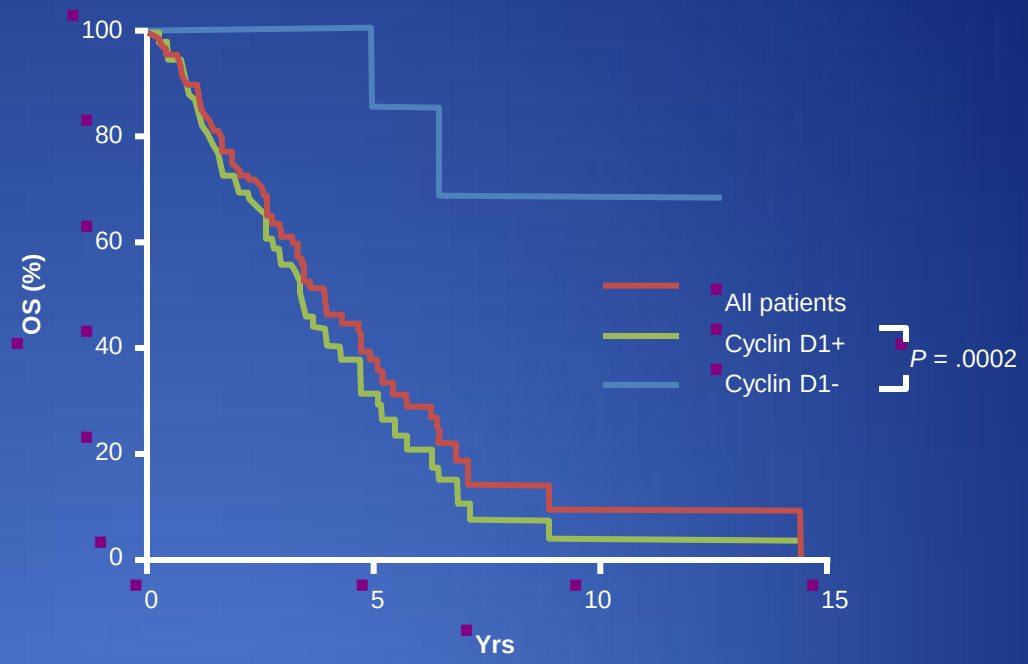
Morphological variants
Diffuse histology: 75%
Nodular: 10% to 15%
Mantle zone: 5% to 7%
Blastoid: 5%



t(11;14)(q13;q32) → CCDN1 driven by IgH locus
Occasion amplification; CCDN2 or CCDN3 translocation

MCL: Critical Role of Cyclin D1





- Most cases of lymphoma that are CD20+, CD5+, and CD23- and lack expression of cyclin D1 are not MCL but rather variant CLL

Improvement of OS in MCL During the Last Decade

- Median OS of patients with advanced MCL significantly increased from 2.7 to 4.8 yrs (HR: 0.44; *P* < .0001)
- 5-yr survival increased from 22% to 47%
- Patients with advanced MCL benefit from progress in medical treatment
  - Rituximab?
  - New agents?
  - Aggressive therapy with transplant?

Herrmann A, et al. J Clin Oncol. 2009;27:511-518.

MCL: Conventional Therapy

- CHOP ± rituximab
  - Median FFS: 15-18 mos
  - Few long-term survivors
  - Howard and colleagues[1] showed improved CR with rituximab but no improvement in PFS
- Fludarabine
  - Lower response rate than CHOP, similar FFS
  - Highly active when combined with cyclophosphamide but increased toxicity

1. Howard OM, et al. J Clin Oncol. 2002;20:1288-1294.

SWOG 0213: HyperCVAD + Rituximab in Newly Diagnosed MCL

- Multicenter, nonrandomized, prospective, phase II trial
- Recruited October 2002-September 2006 (N = 49)
- 8 cycles of hyperCVAD (fractionated cyclophosphamide, vincristine, doxorubicin, + dexamethasone) alternating every 21 days with rituximab + high-dose methotrexate/ cytarabine
- Prophylactic anti-infectious agents, G-CSF given

- Disease type
  - Nodular: 3 (6%)
  - Diffuse: 13 (27%)
  - Mantle zone: 28 (57%)
  - Blastic: 4 (8%)
  - Too early: 1 (2%)
- Stage III/IV disease: 49 (100%)
- Zubrod performance status
  - 0: 29 (59%)
  - 1/2: 20 (41%)

Epner EM, et al. ASH 2007. Abstract 387.

SWOG 0213: HyperCVAD + Rituximab in Newly Diagnosed MCL

Survival Outcome	At Risk, n	Progression/Death, n	1-Year Estimate, %
Progression-free	49	13	89
Overall	49	9	91

Epner EM, et al. ASH 2007. Abstract 387.

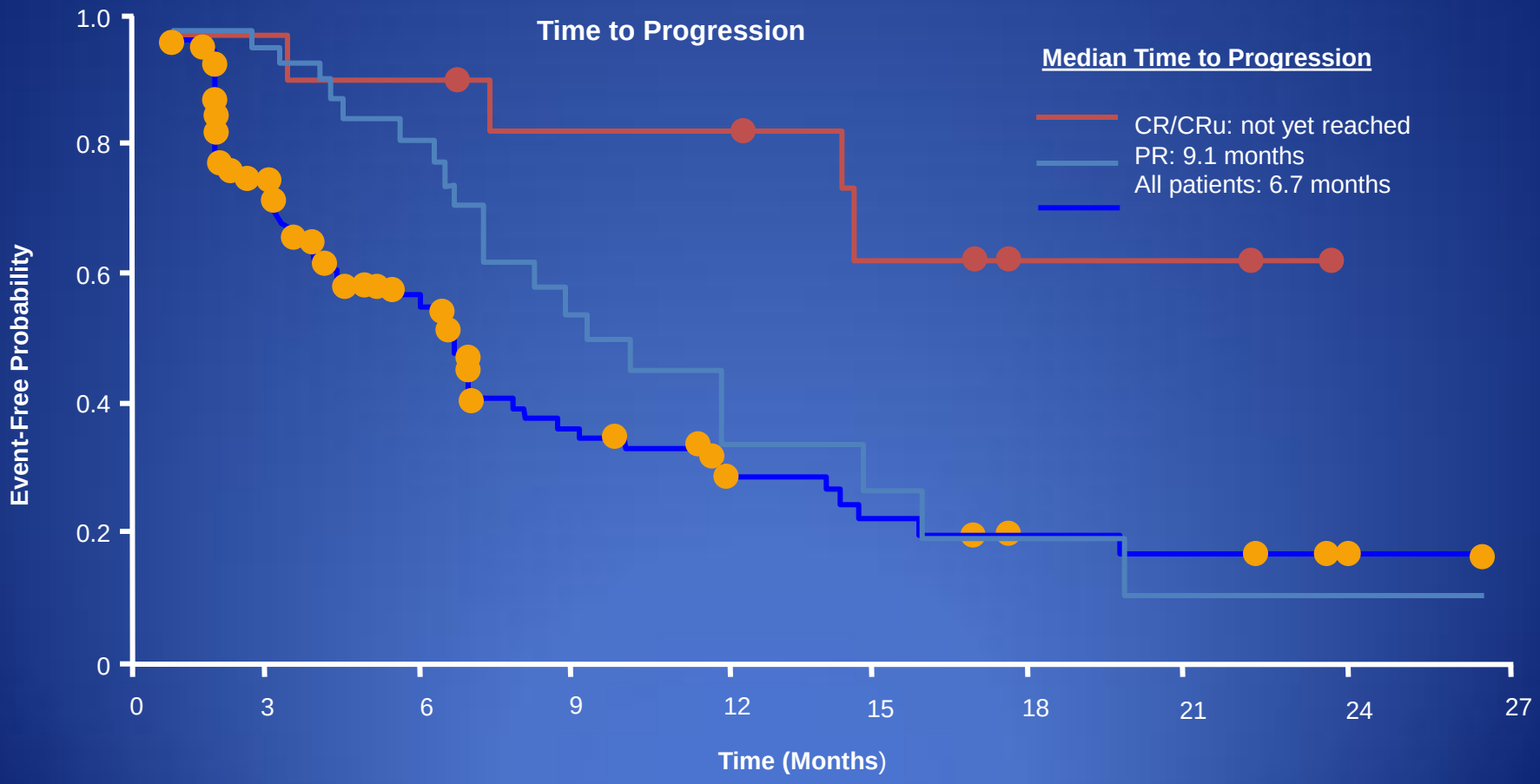
PINNACLE: Bortezomib in Patients With Relapsed/Refractory MCL

- Open-label, prospective, international, multicenter, phase II trial
- Bortezomib 1.3 mg/m^2 on Days 1, 4, 8, and 11 of 21-day cycle
  - Upon CR/CRu
    - Treatment continued for 4 additional cycles
  - If no CR/CRu
    - Treatment continued up to 17 cycles or until disease progression or toxicity

Characteristic	Patients (N = 155)
Median age, years (range)	65 (42-89)
Median time from diagnosis, yrs (range)	2.3 (0.2-11.2)
Median prior therapies	1
Stage IV MCL, %	77
IPI score ≥ 3, %	44
KPS < 90%, %	29
LDH > upper limit of normal, %	36
Bone marrow involvement, %	55

Goy A, et al. ASH 2007. Abstract 125.

PINNACLE: Bortezomib in Patients With Relapsed/Refractory MCL



Goy A, et al. ASH 2007. Abstract 125.

Conclusions

- Lymphomas are amongst the most curable adult malignancies
- Predominantly B-cell phenotype (~90%)
- CHOP-type chemotherapy standard since 1970s
- Radiation useful in localized disease
- Advent of rituximab, a chimeric anti-CD20 monoclonal antibody has revolutionized the treatment of most B-cell lymphomas
- T-cell lymphomas have a more aggressive course and are more difficult to treat.
- Evolving role of ^{18}FDG PET/CT scanning in monitoring lymphoma treatment