

Indolent Non-Hodgkin Lymphoma: A Brief Overview of Management

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Disclosures

- Honorarium
 - Celgene Corporation
 - Genentech/Roche
- Research Support
 - TG Therapeutics
 - Abbvie
 - Janssen
 - Celgene

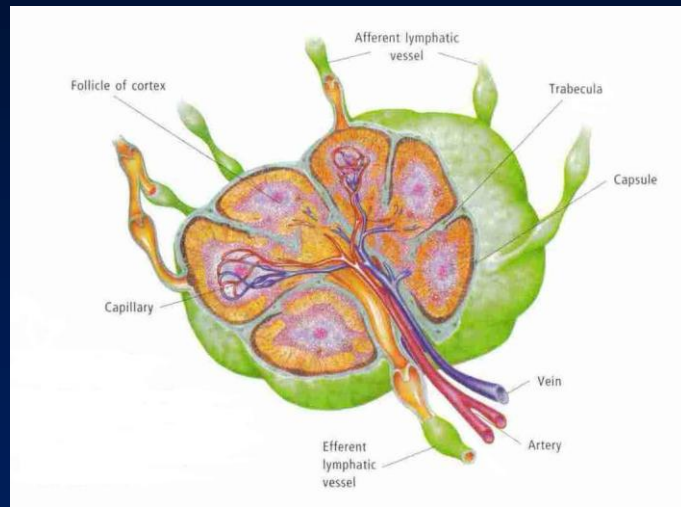
Presentation Overview

- Overview of Lymphoma
- Common Management Strategies and Outcomes
- New Developments
- Clinical Trials
- Questions

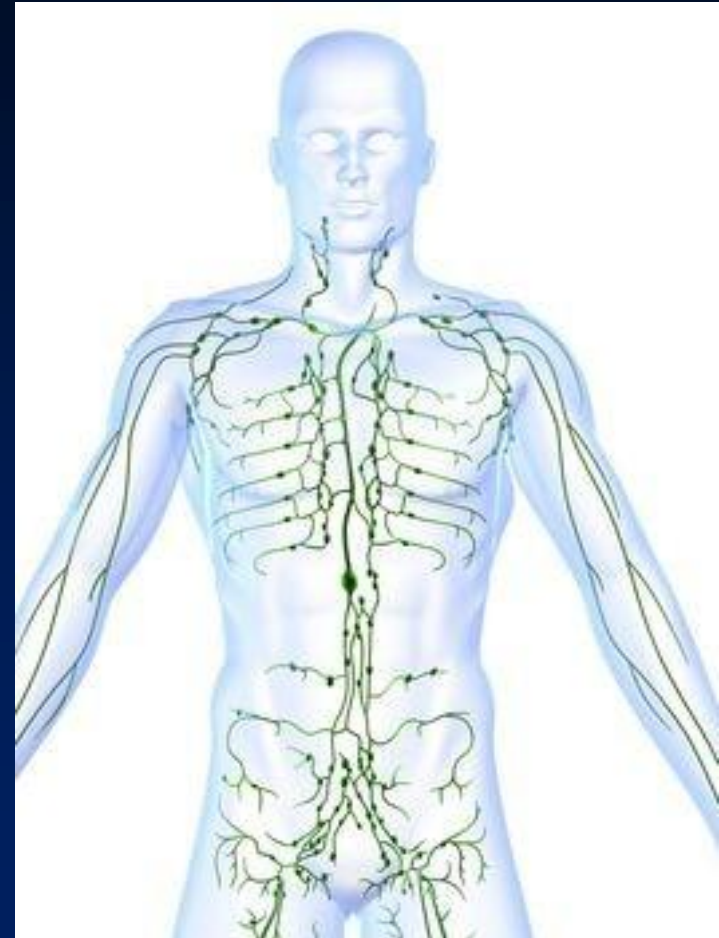
Lymphoma Overview

- Lymphoma is a hematologic malignancy (i.e., blood cancer) that arises from malignant transformation of peripheral blood, lymphatic system, and other bone marrow derived cells
- Over 70,000 new cases of lymphoma are diagnosed each year in the US
- Diverse group of diseases, comprising over 60 different subtypes of non-Hodgkin and Hodgkin lymphoma

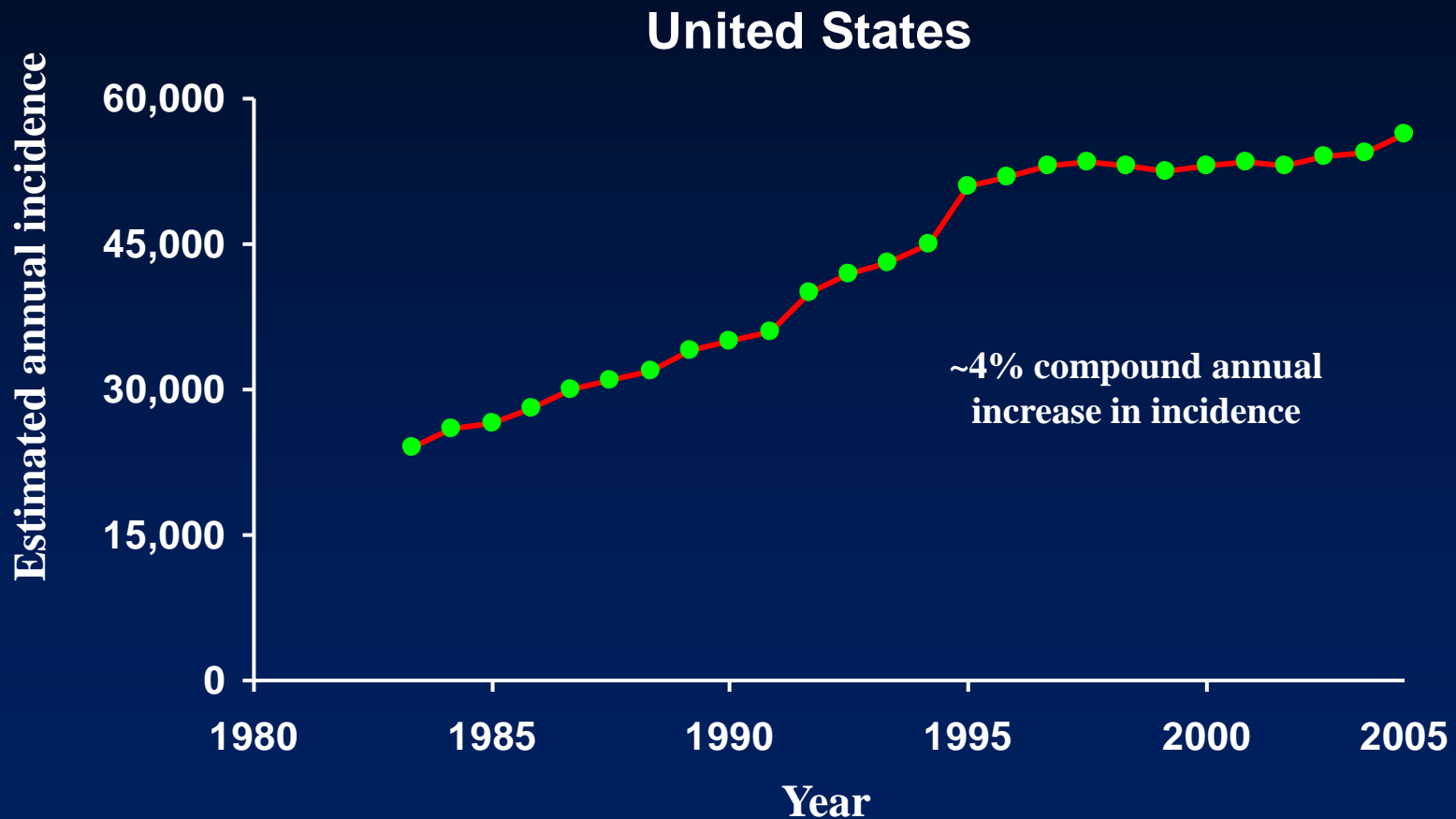
Lymphoma Overview



Lymph Node



NHL Epidemiology

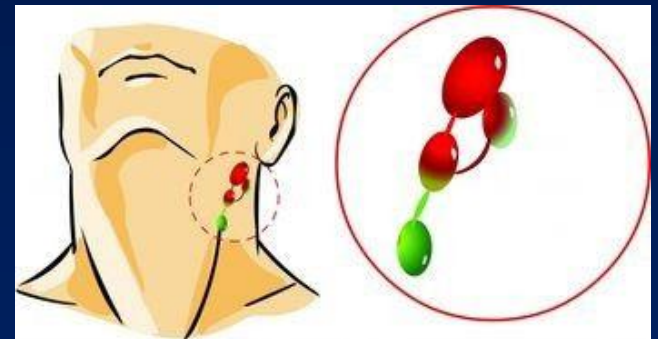


Risk Factors

- Immunodeficiency disorders
- Autoimmune disorders
- Organ transplantation
- Radiation exposure
- Bacteria or viruses
- Environmental exposure?

Symptoms

- Swelling of lymph nodes (often, but not always painless)
- Fever
- Night sweats
- Unexplained weight loss
- Lack of energy



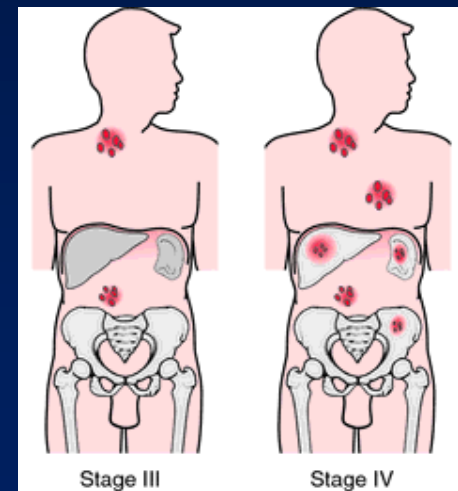
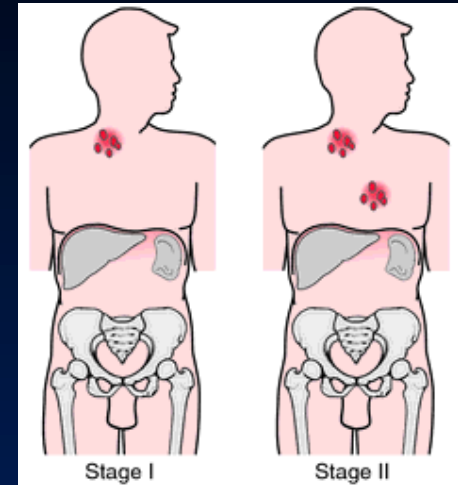
Diagnosis

- Physical examination
 - Lymphadenopathy, splenomegaly
- Biopsy
 - Adequate tissue is imperative
 - Excisional biopsy (optimal)
 - Multiple core biopsies may be acceptable
 - Fine needle aspiration is unacceptable
- Adequate immunophenotyping
 - Immunohistochemistry of paraffin sections
 - Flow cytometry to detect cell surface markers
- Cytogenetics/FISH to detect genetic abnormalities when appropriate



Stage

- Stage I - in a single lymph node or in one organ or area outside the lymph node
- Stage II - two or more lymph node regions on one side of the diaphragm
- Stage III - lymph nodes above and below the diaphragm
- Stage IV - in one or more organs or tissues (in addition to the lymph nodes); liver, blood or bone marrow

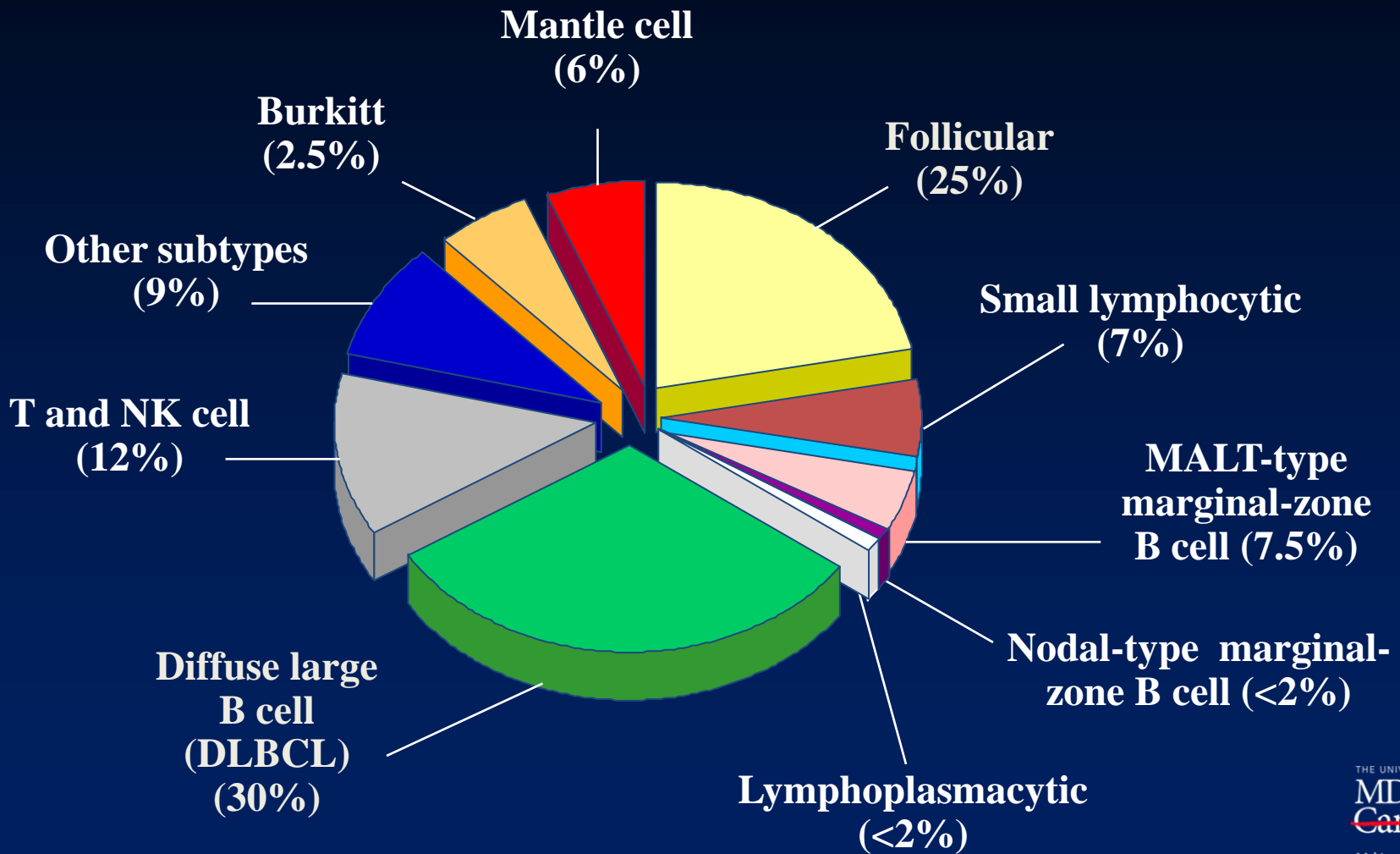


How Does One Decide Which Treatment to Recommend?

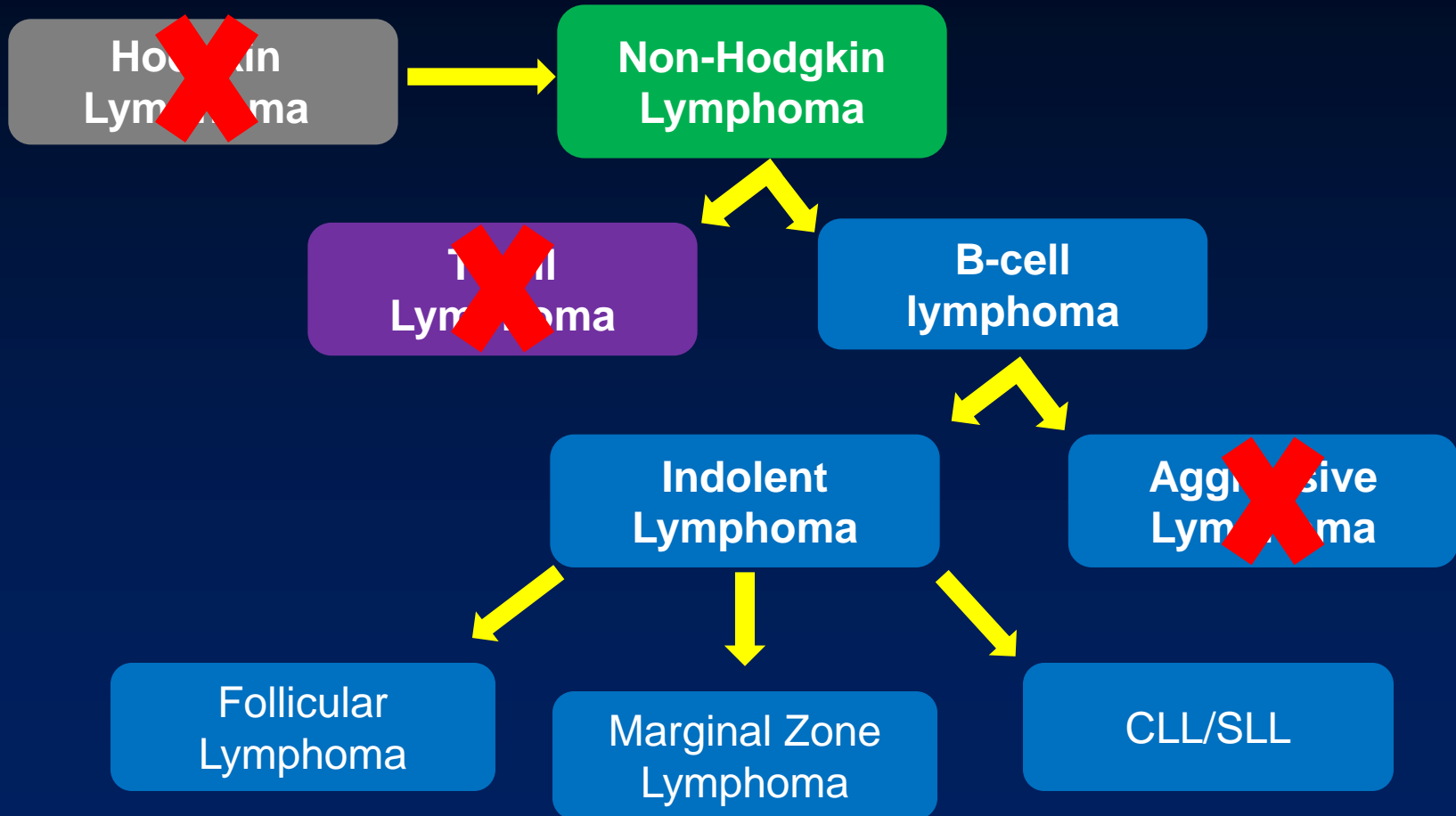
- Classification
 - Subtype
- Growth rate (grade)
 - Indolent vs. Aggressive
- Stage of disease
 - Local, distant, widespread
- Prognostic Factors
 - IPI, FLIPI, MIPI
- Disease Burden
 - GELF criteria

**Indolent NHL:
Common Management
Strategies and Outcomes**

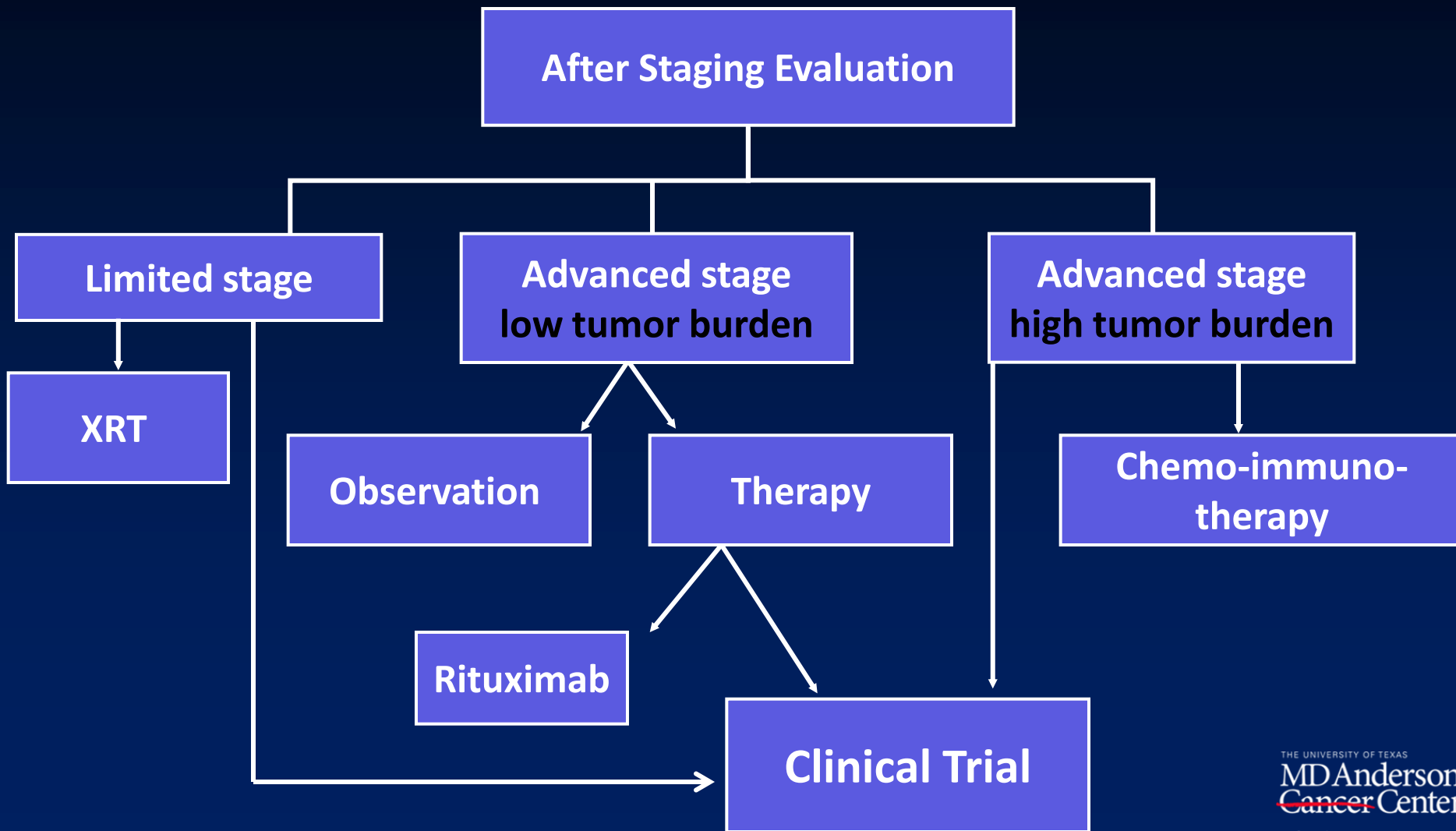
NHL Subtypes



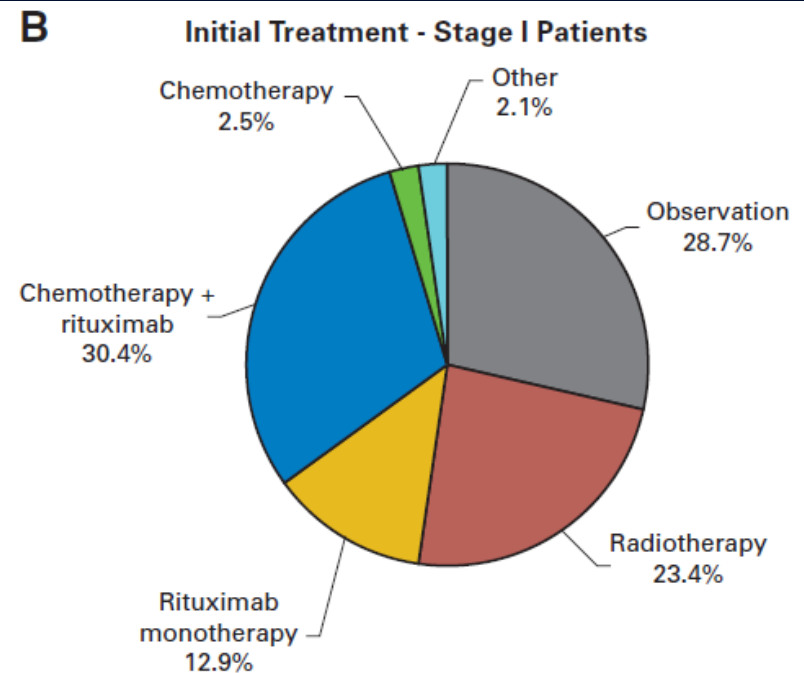
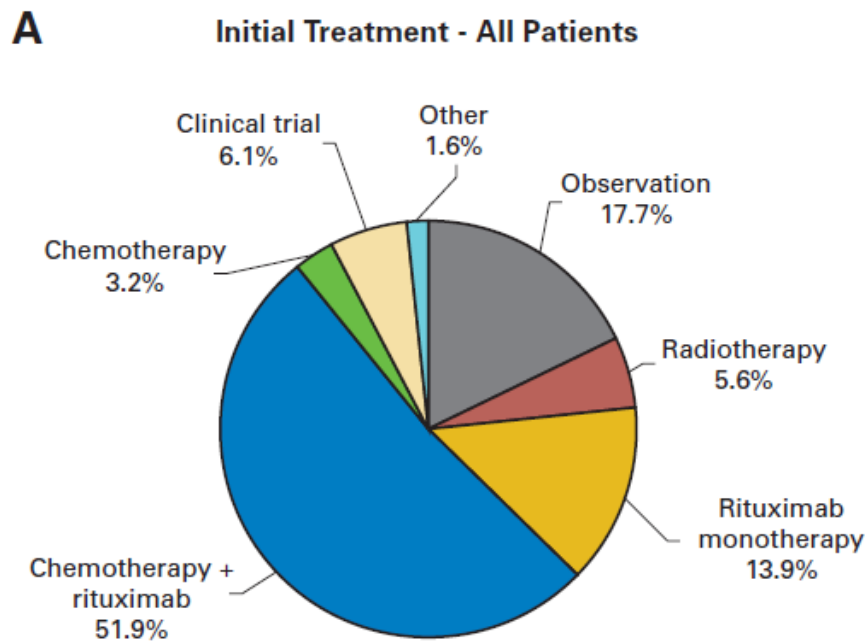
Indolent NHL



Treatment Options for Untreated Follicular Lymphoma



Initial Treatment of FL in the US

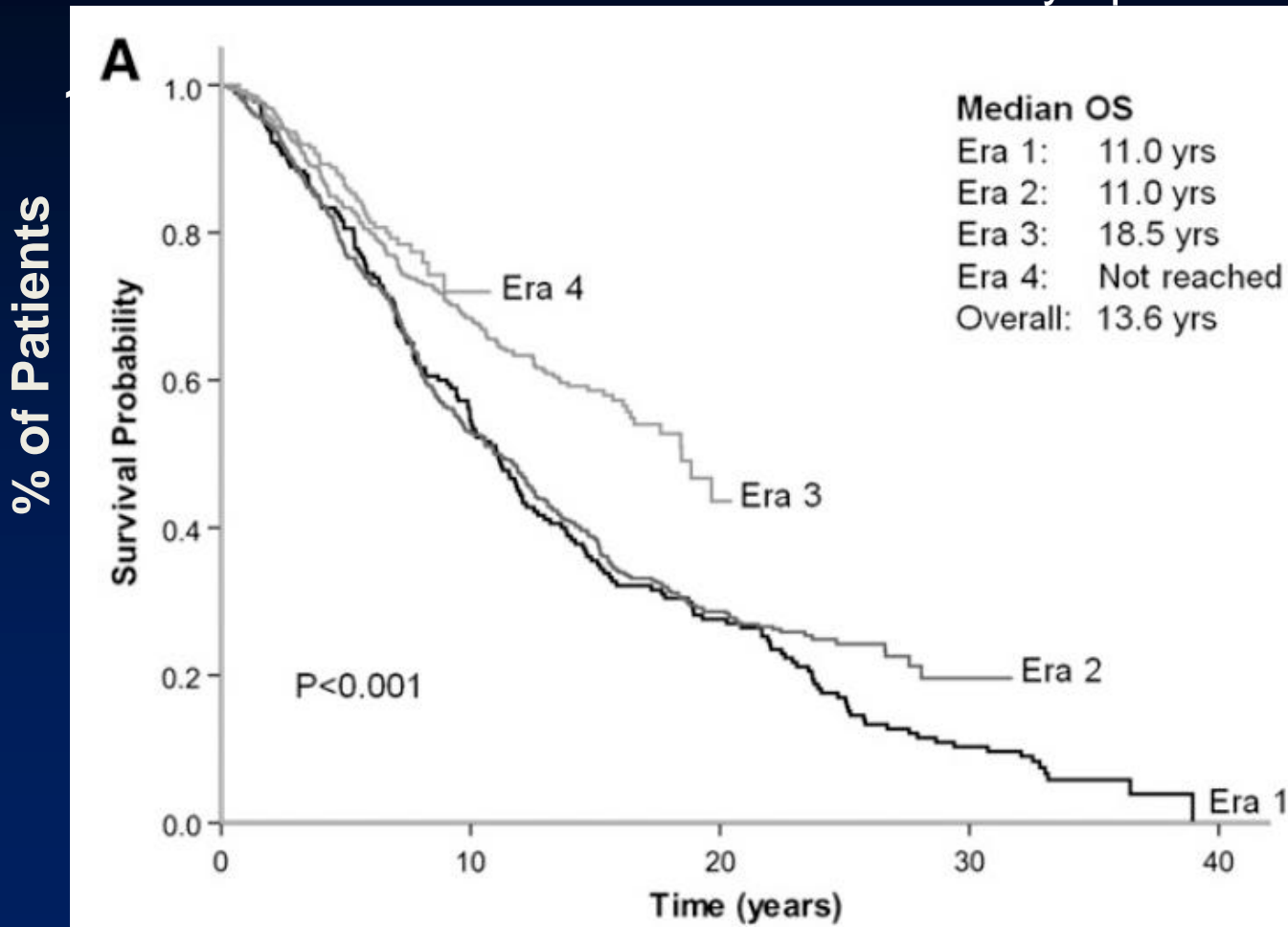


Watchful Waiting

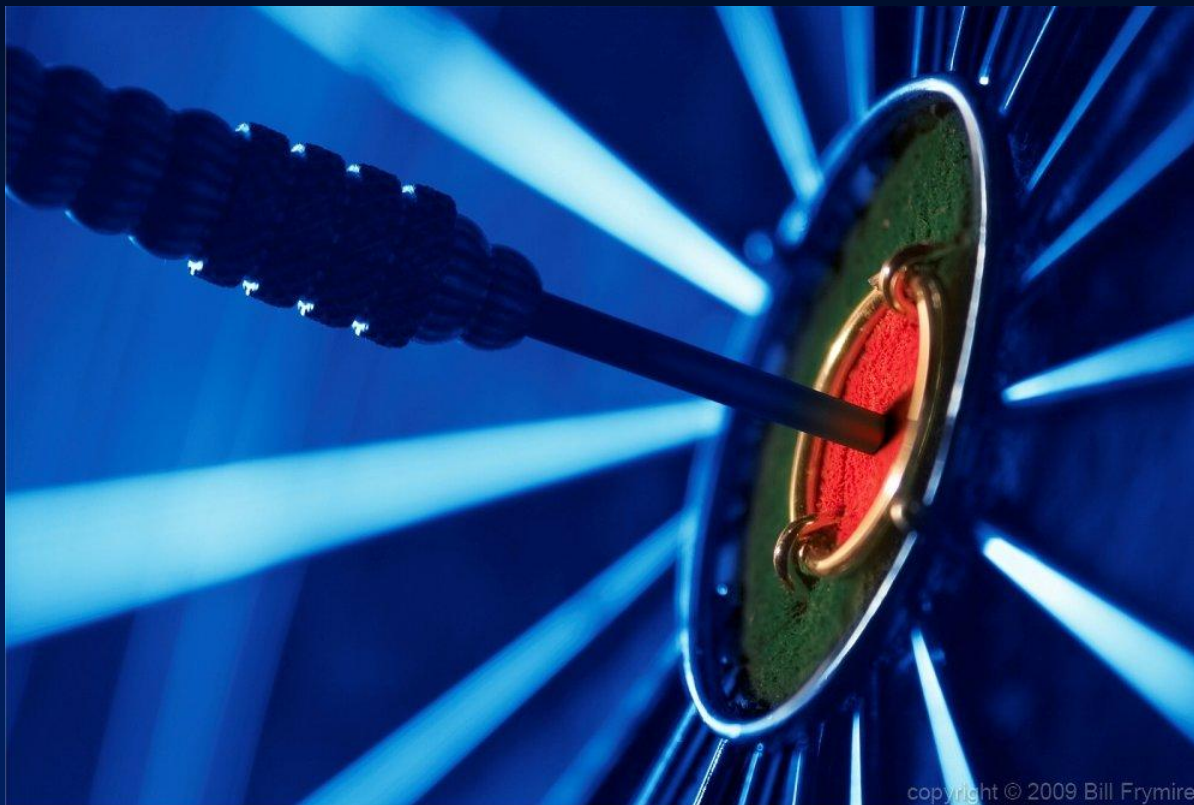
- “Watchful waiting” or “Watch and Wait”
 - Only for indolent, low-grade NHLs
 - Regular physical exam and lab evaluation
 - No treatment until patient has:
 - Symptoms- fever, chills, night sweats, weight loss
 - LN > 7 cm or ≥ 3 LNs > 3 cm in diameter
 - Splenomegaly
 - Cytopenias (anemia, thrombocytopenia), elevated LDH
 - Ascites or pleural effusion
 - Spontaneous regressions have occurred

The Natural History of Indolent NHL

Survival of Patients With Indolent Lymphoma:



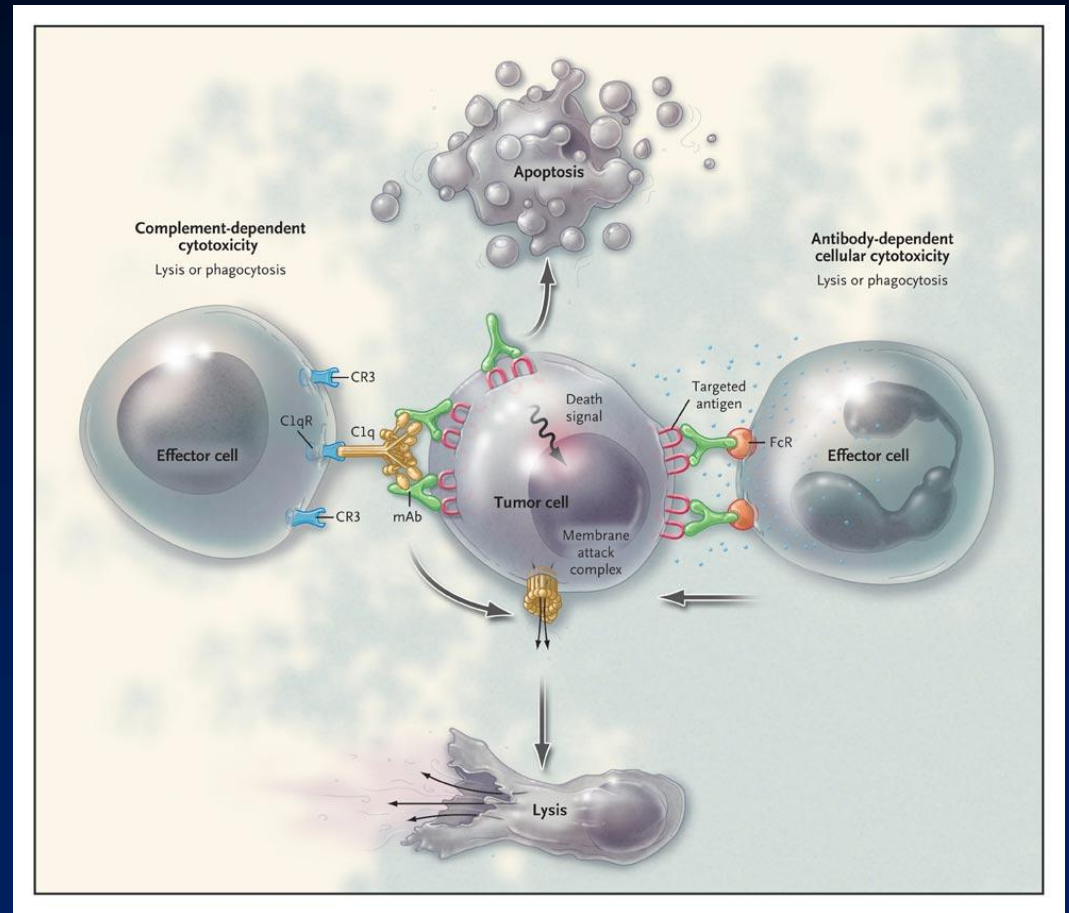
Targeted Immune Therapy



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Rituximab (Rituxan)

- Monoclonal antibody against CD20
- The first monoclonal antibody approved for use in cancer patients (1997)
- Given once per week for 4 weeks or in combination with standard chemotherapy

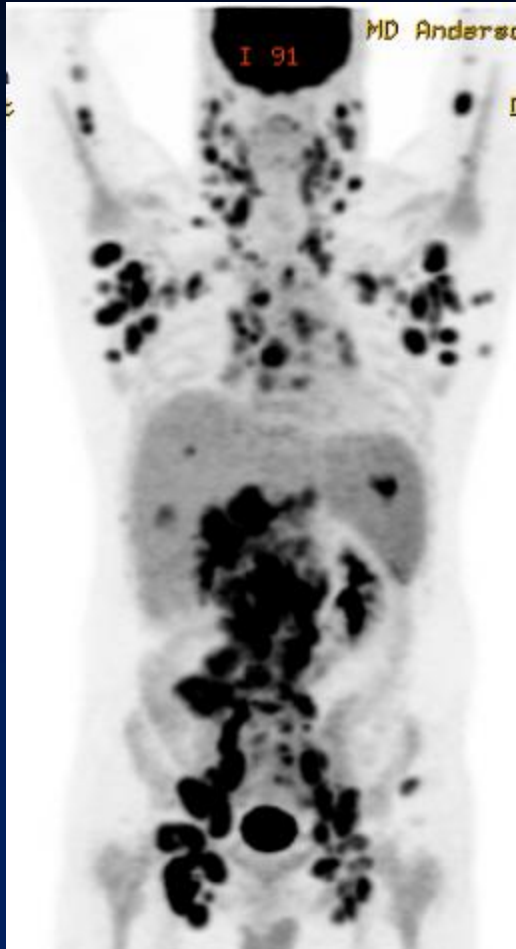


Effect of Frontline Follicular Lymphoma Therapies

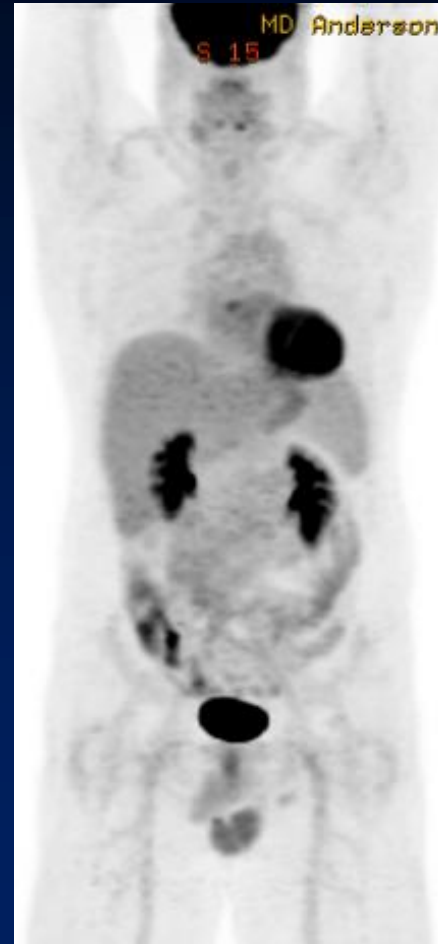
Regimen	Colombat et al	Rummel et al.	Hiddemann et al	Marcus et al
	Rituximab	Bendamustine + Rituximab	CHOP + Rituximab [†]	CVP +Rituximab
Stage III/IV, %	50 (II+)	100	100	100
Grade 3	No	No	No	9%
GELF Criteria for treatment, %	0	100	NR	80 [‡]
FLIPI ≥ 3, %	NR	46	NR	38
Bulky disease, %	0%	28	NR	39
ORR, %	73	94*	96	80
CR, %	26	41*	20	41
PFS	1 year 80%	2 year 78%*	2 year ≈ 85%	32 mo 50%

*Included indolent, MCL patients; [‡]BLNI, ECOG Criteria; [†]70% had INF maint, 23% had SCT consolidation

Dramatic Response to Therapy



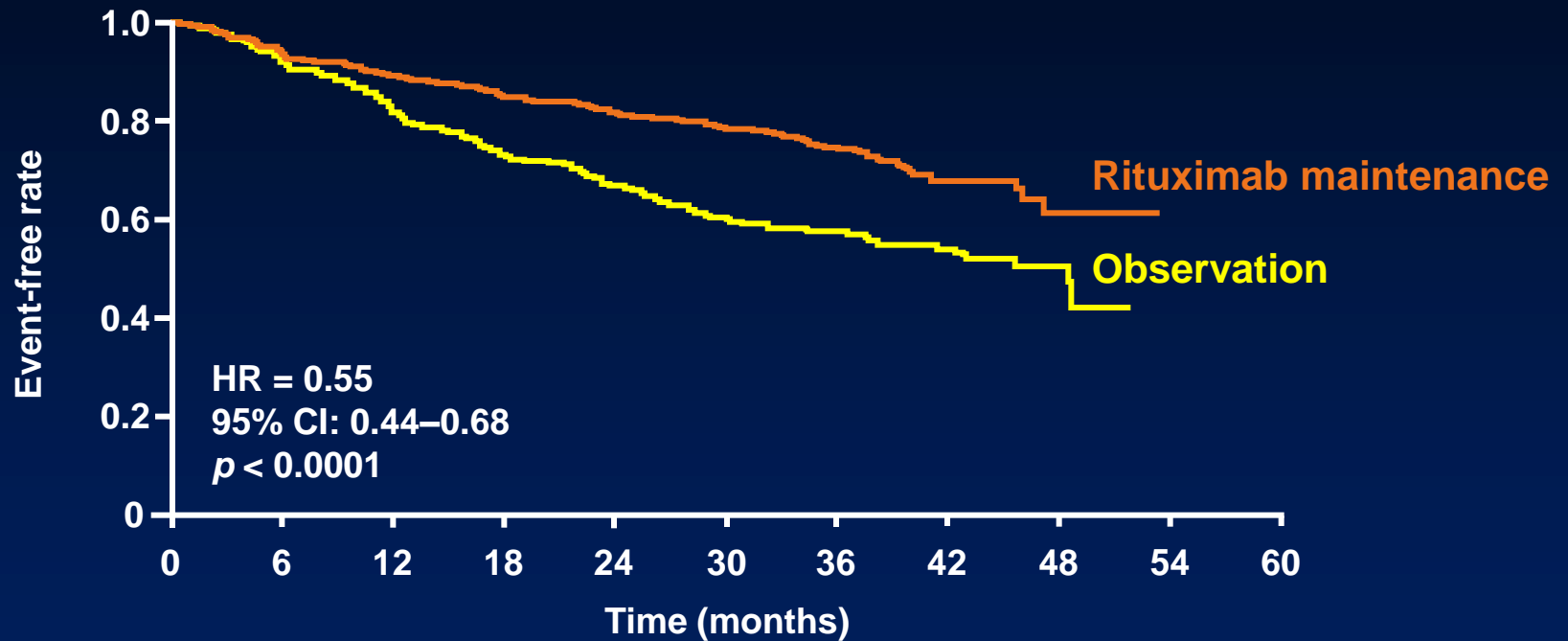
3 cycles of BR



Chemo Side Effects

- Non-drug specific
 - Fatigue, loss of appetite, low energy
 - Nausea, vomiting
 - Low blood counts
 - White cells: risk of infections
 - Platelets: risk of bruising/bleeding
 - Red cells: anemia
 - Hair loss, skin and nail changes
- Chemo agent-specific
 - Doxorubicin- heart toxicity (heart failure)
 - Vincristine- nerve ending toxicity (neuropathy)
 - Prednisone- high blood sugar, agitation, loss of sleep, stomach irritation, “shakiness”

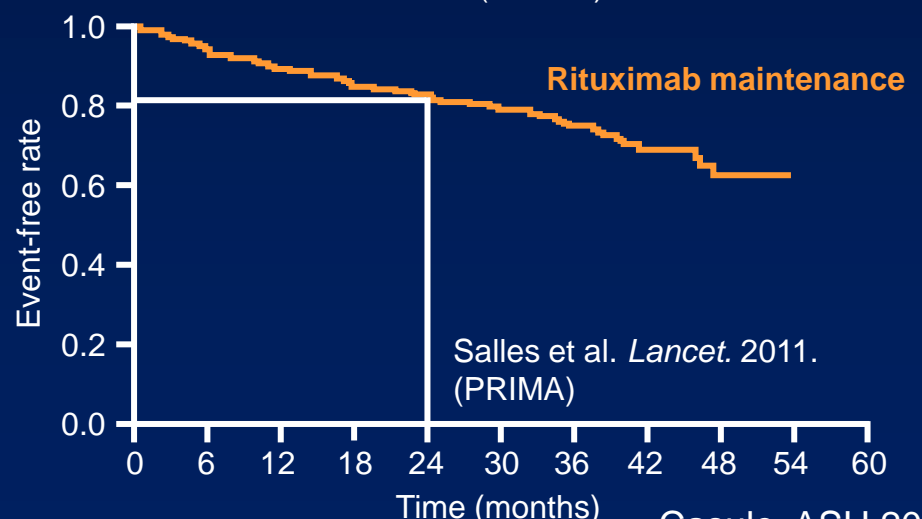
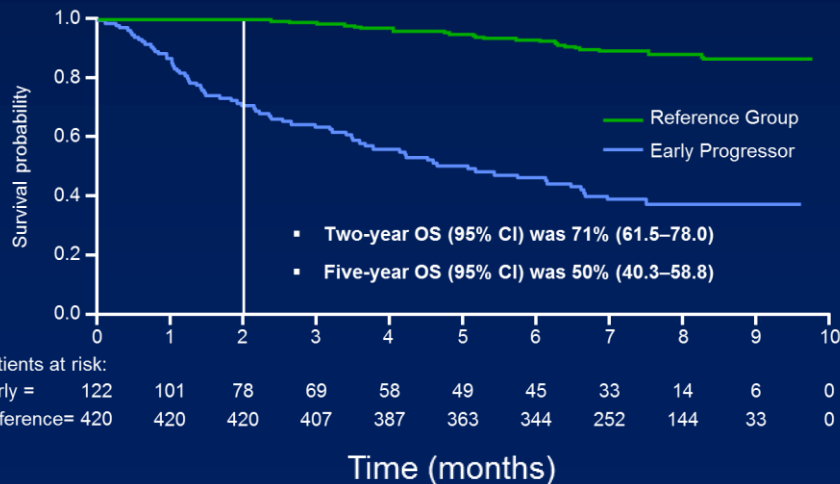
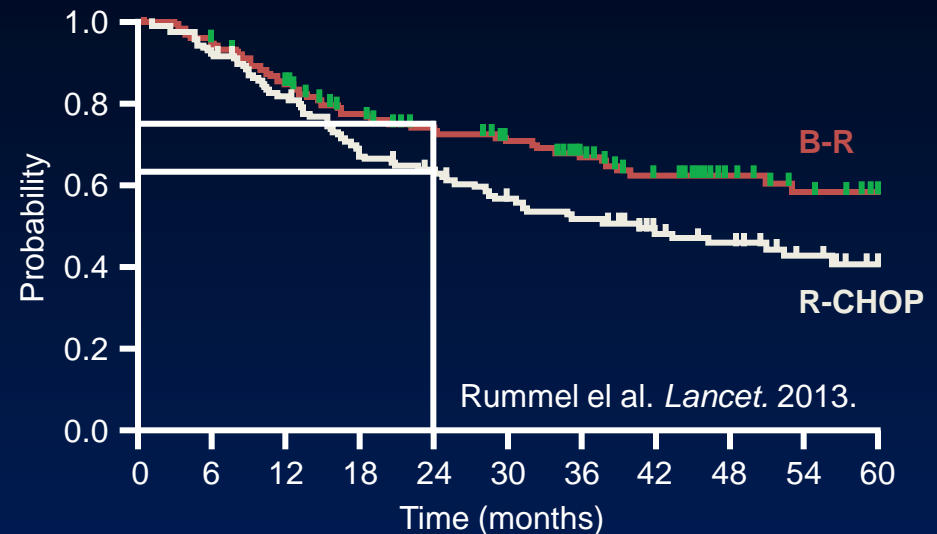
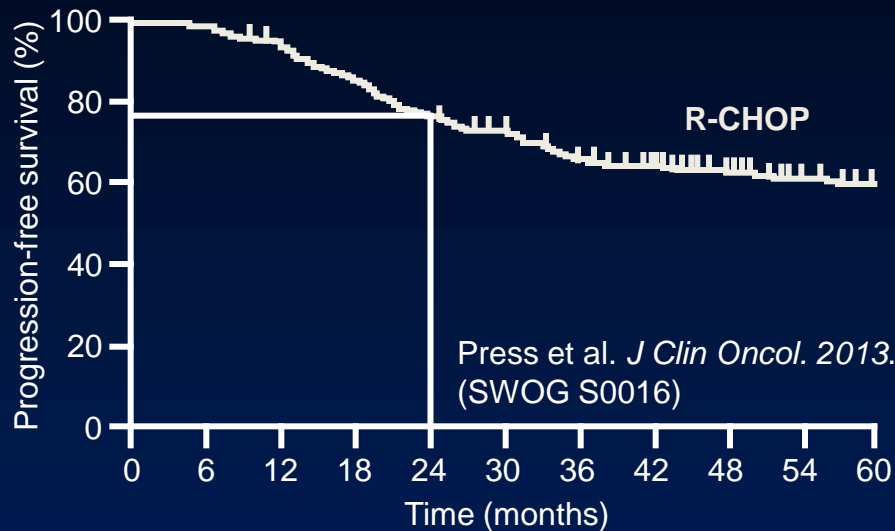
Rituximab Maintenance



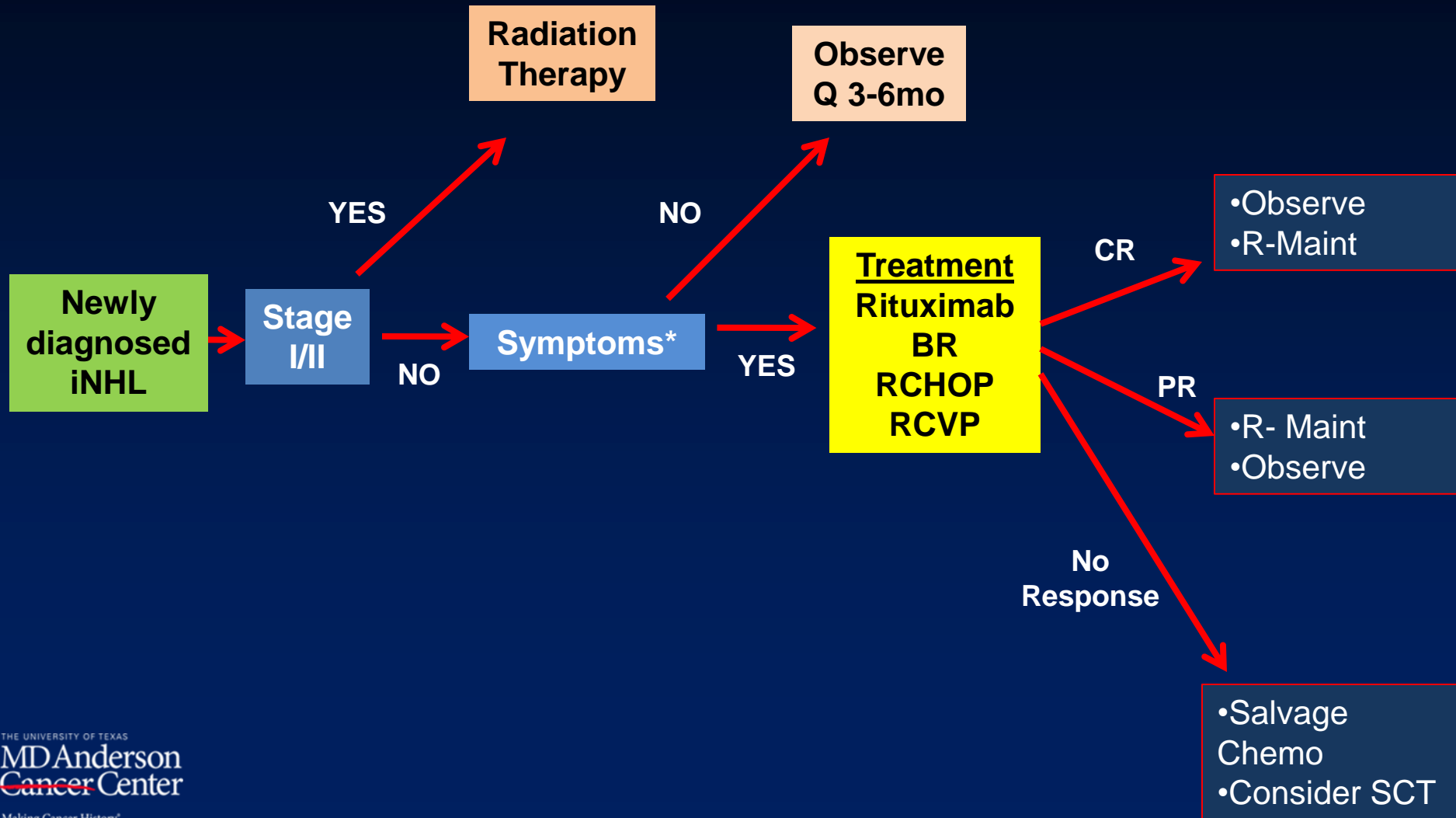
Patients at risk

Rituximab	505	472	445	423	404	307	207	84	17	0	—
Observation	513	469	415	367	334	247	161	70	16	0	—

“Early” Progression is Associated with Poor Outcomes



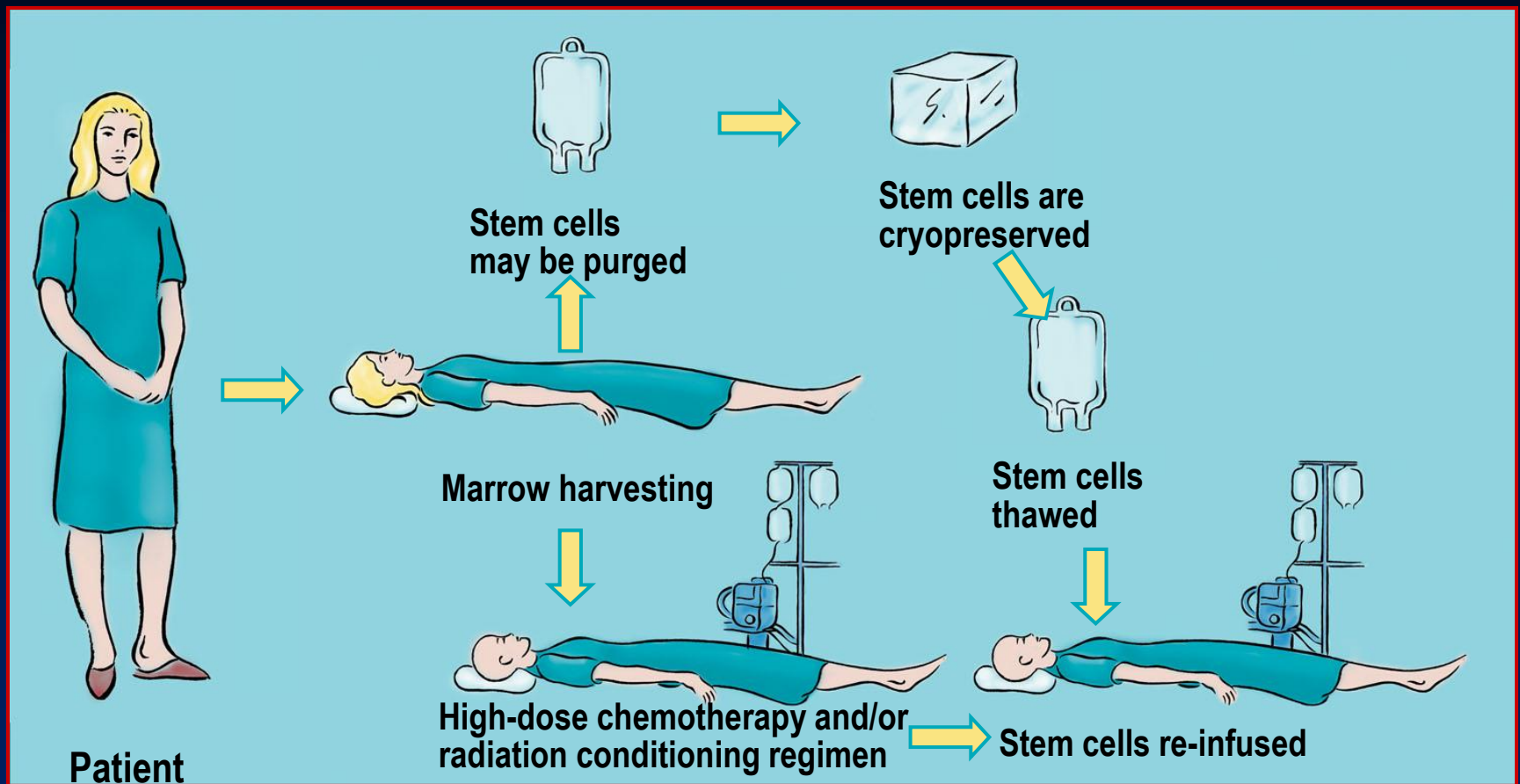
Standard Treatment of Nodal iNHL



Subsequent Therapy

- Rituximab
- Chemoimmunotherapy
 - BR
 - RCHOP
 - RCVP
 - RDHAP
 - RESHAP
 - RGDP
 - RICE
- Radioimmunotherapy
- Idelalisib
- Stem cell transplant for selected patients

Autologous Stem Cell Transplant: Procedure Overview



Autologous Stem Cell Transplant

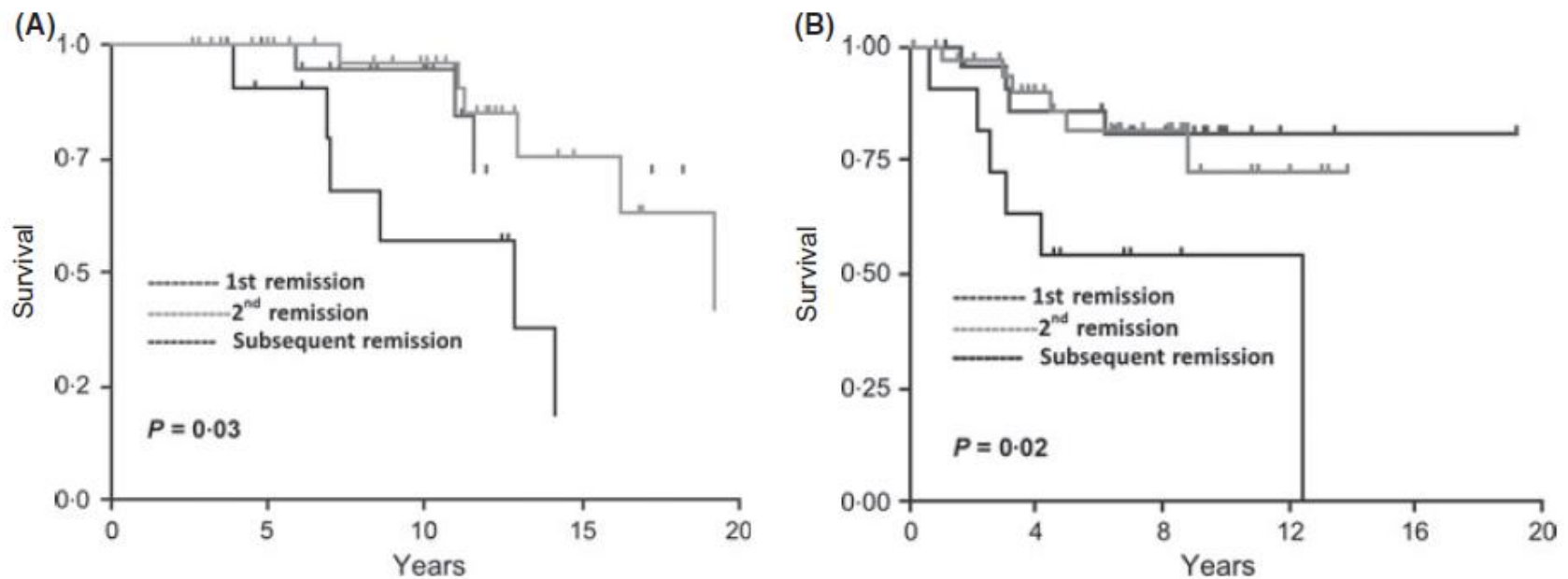
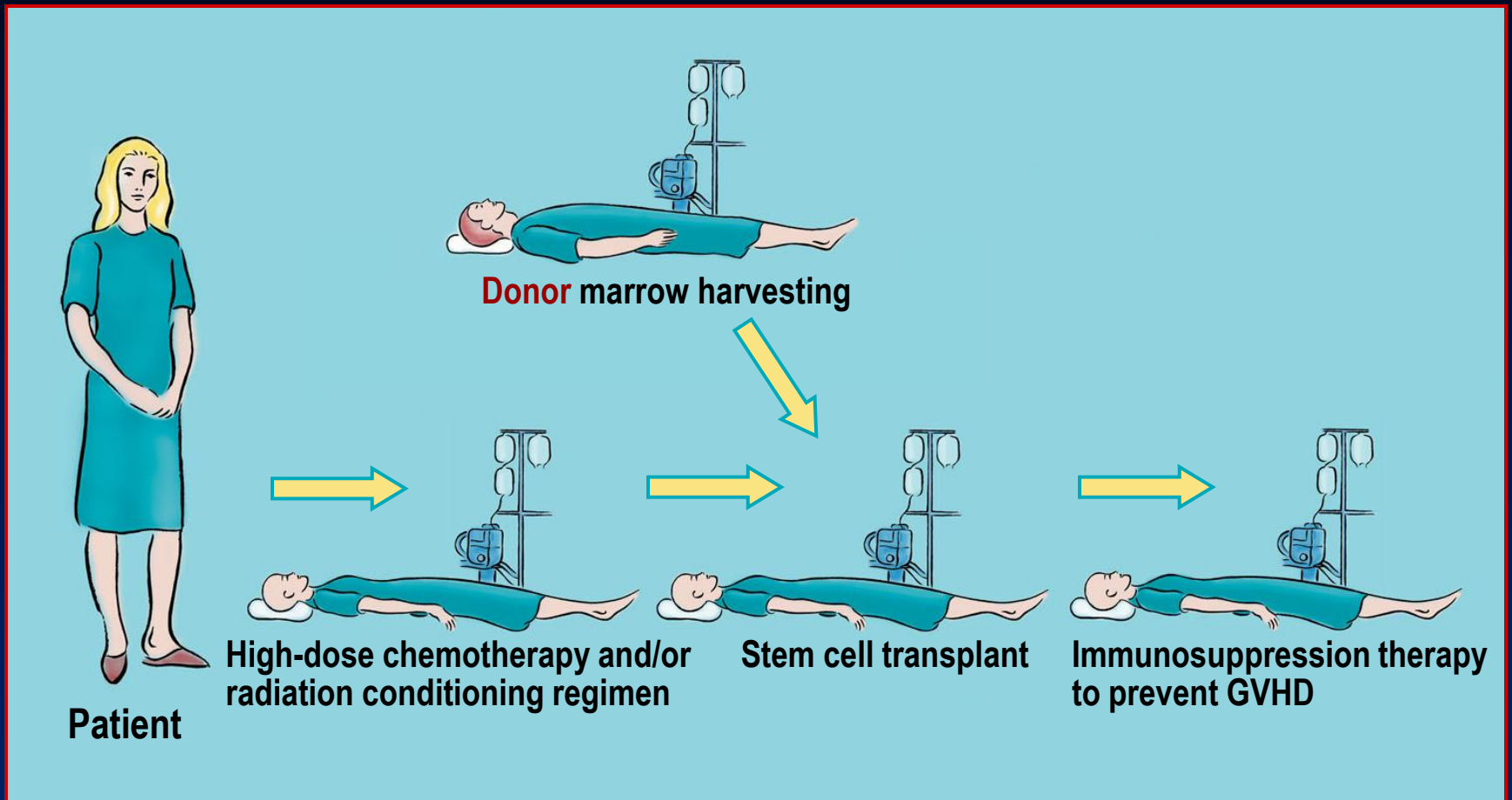
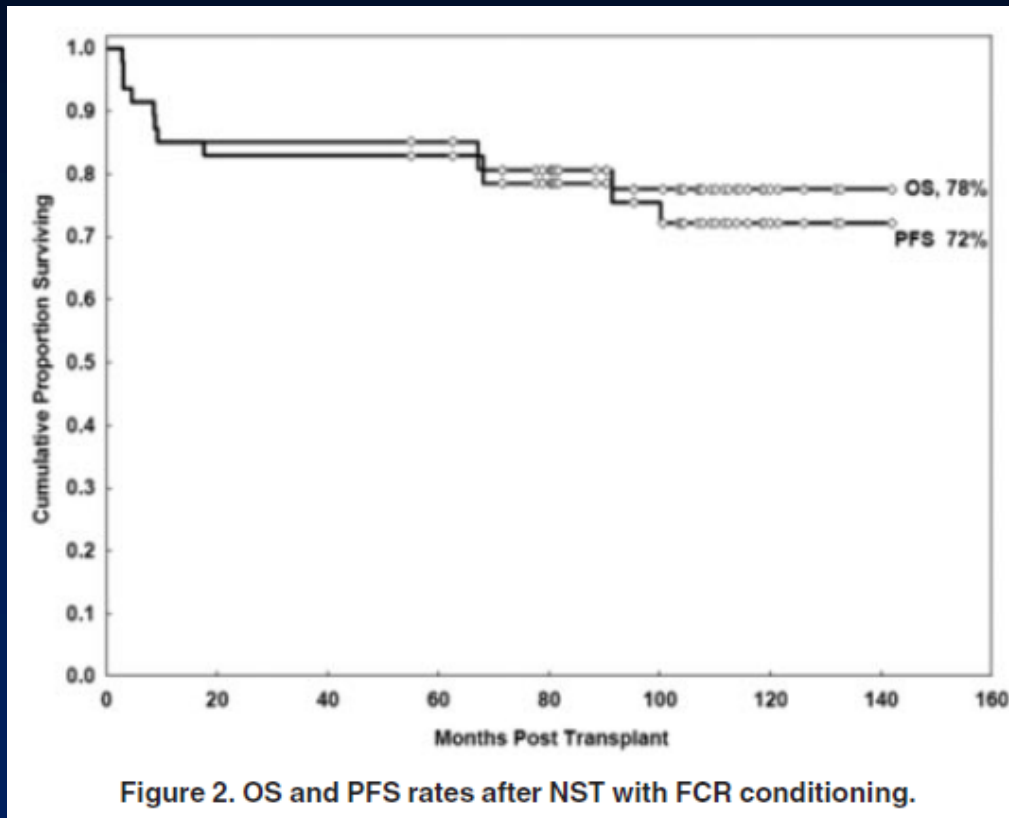


Fig 2. (A) Overall survival from date of diagnosis, by remission. (B) Overall survival from date of autologous stem cell transplantation, by remission.

Allogeneic Stem Cell Transplant Procedure Overview

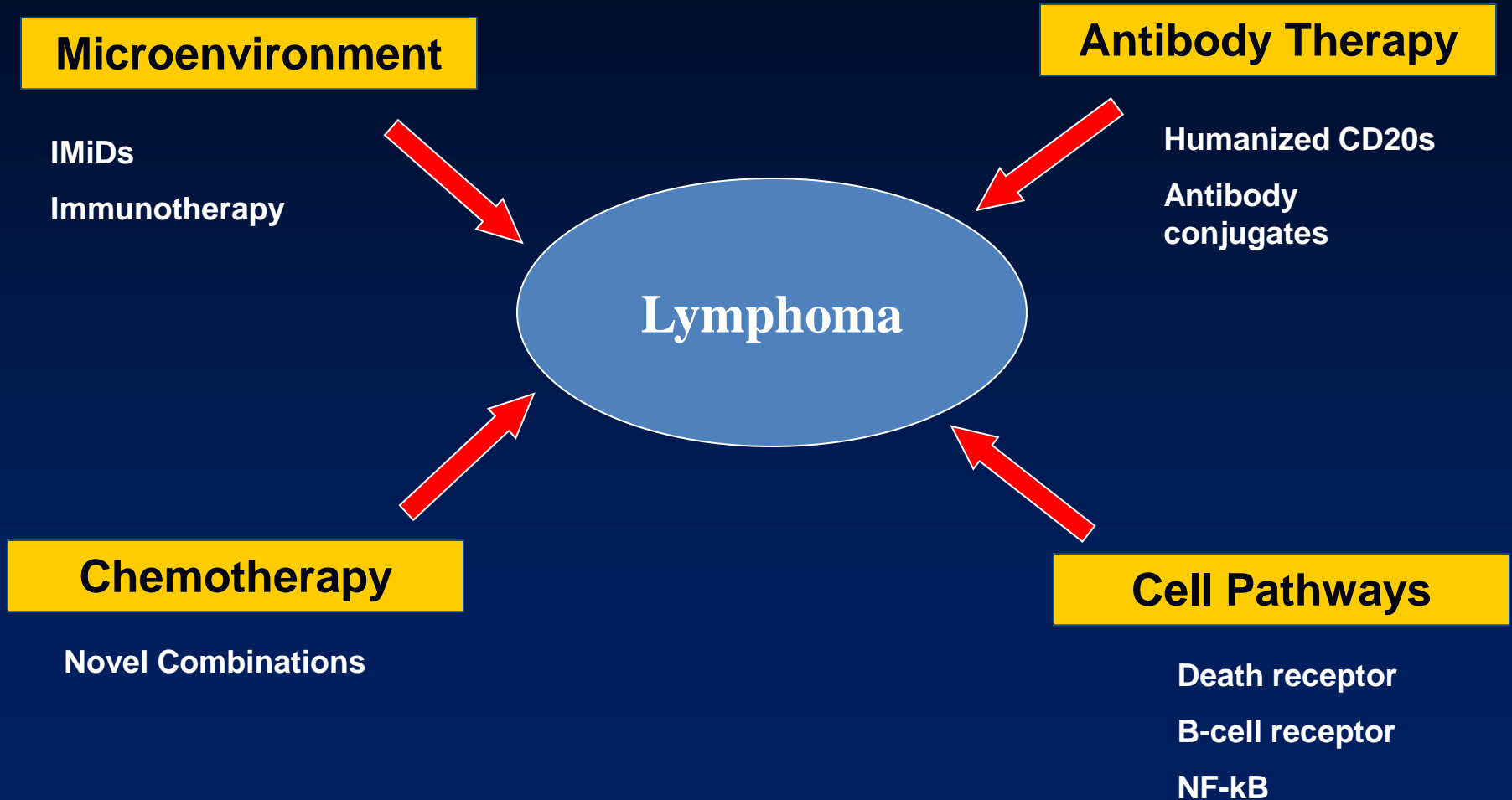


Allogeneic Stem Cell Transplant in Lymphoma

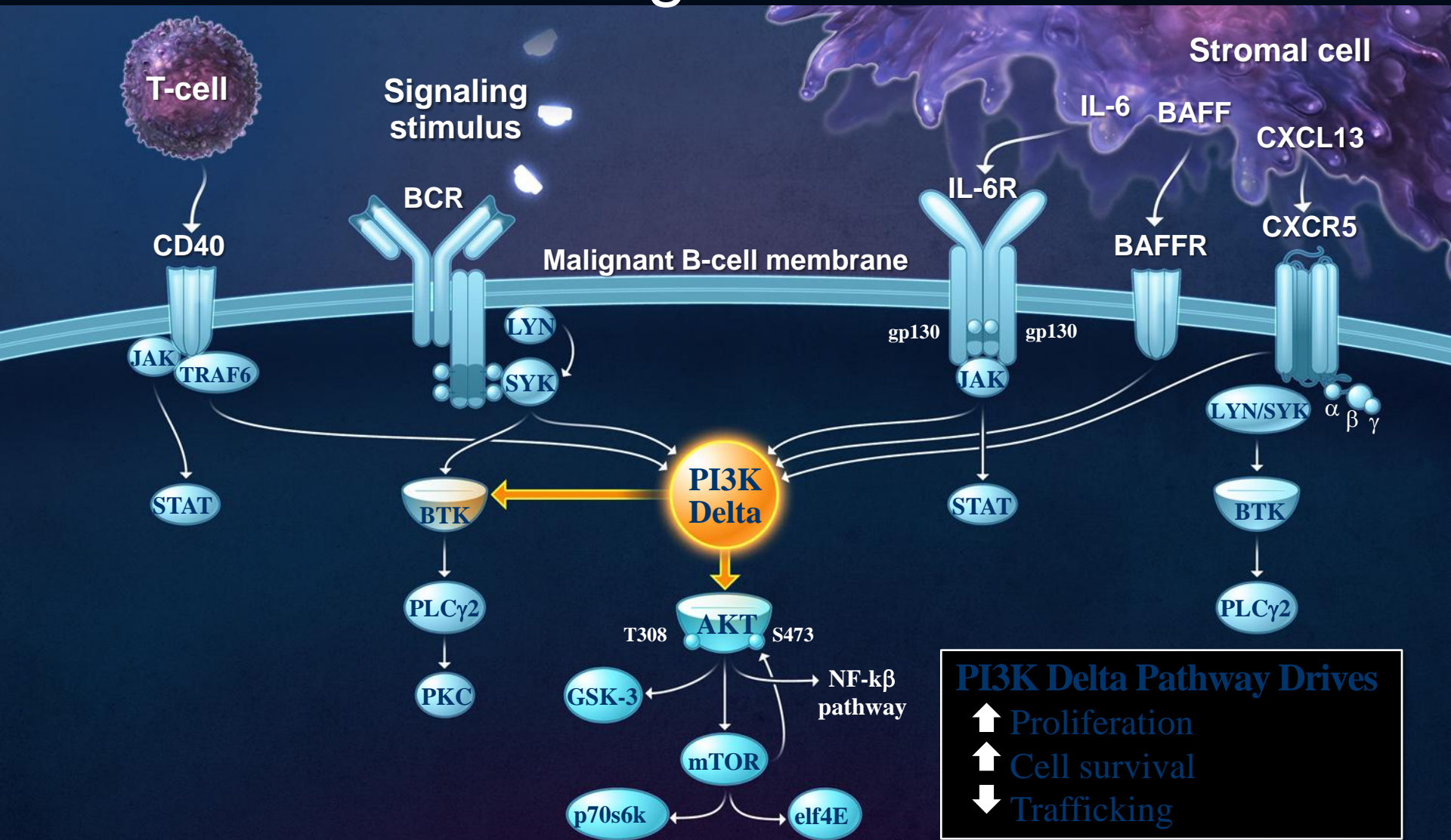


New Developments in the Management of iNHL

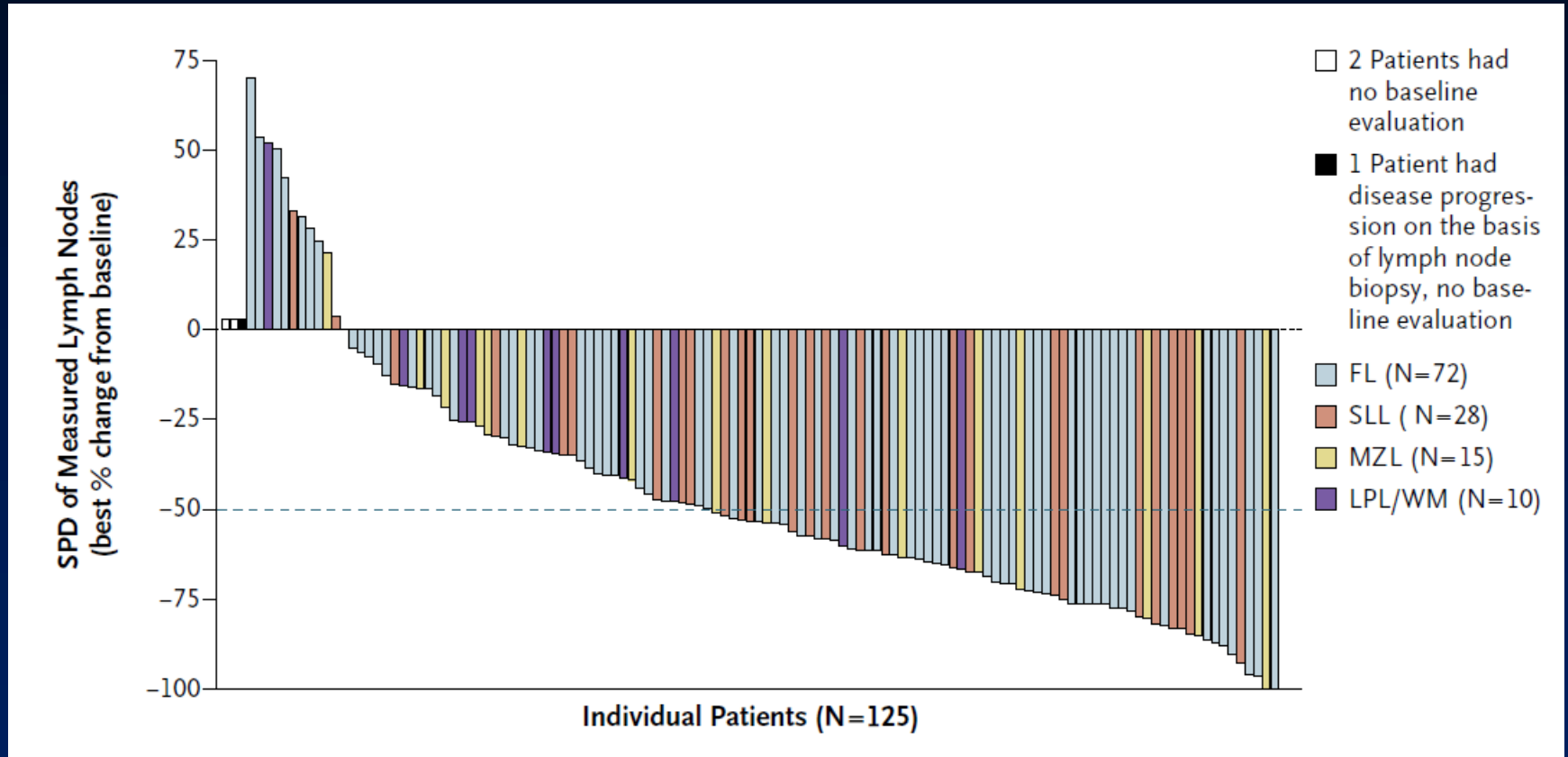
Emerging Therapy for Lymphoma



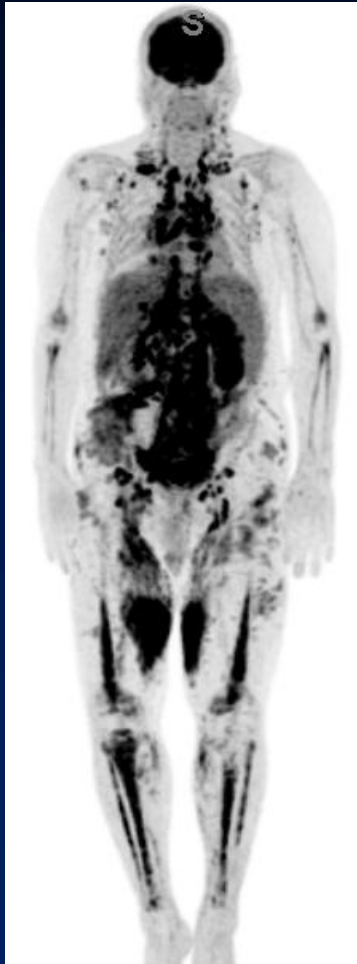
PI3K Delta Inhibition in B-Cell Malignancies



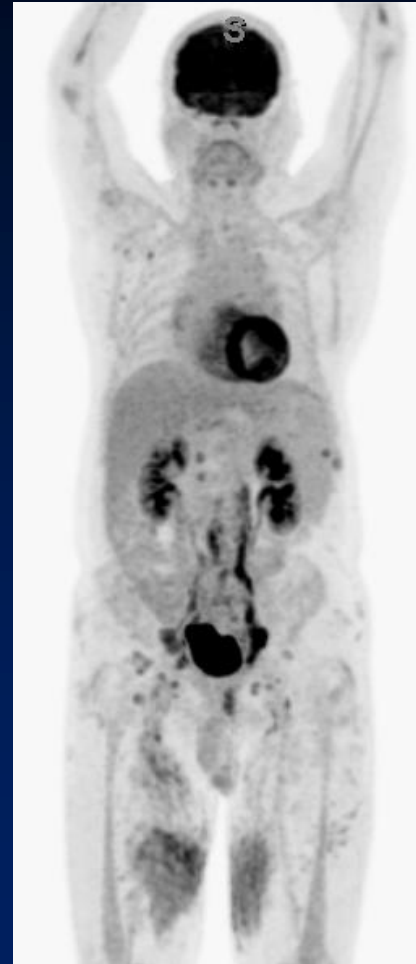
PI3K δ Inhibition with Idelalisib in Relapsed iNHL



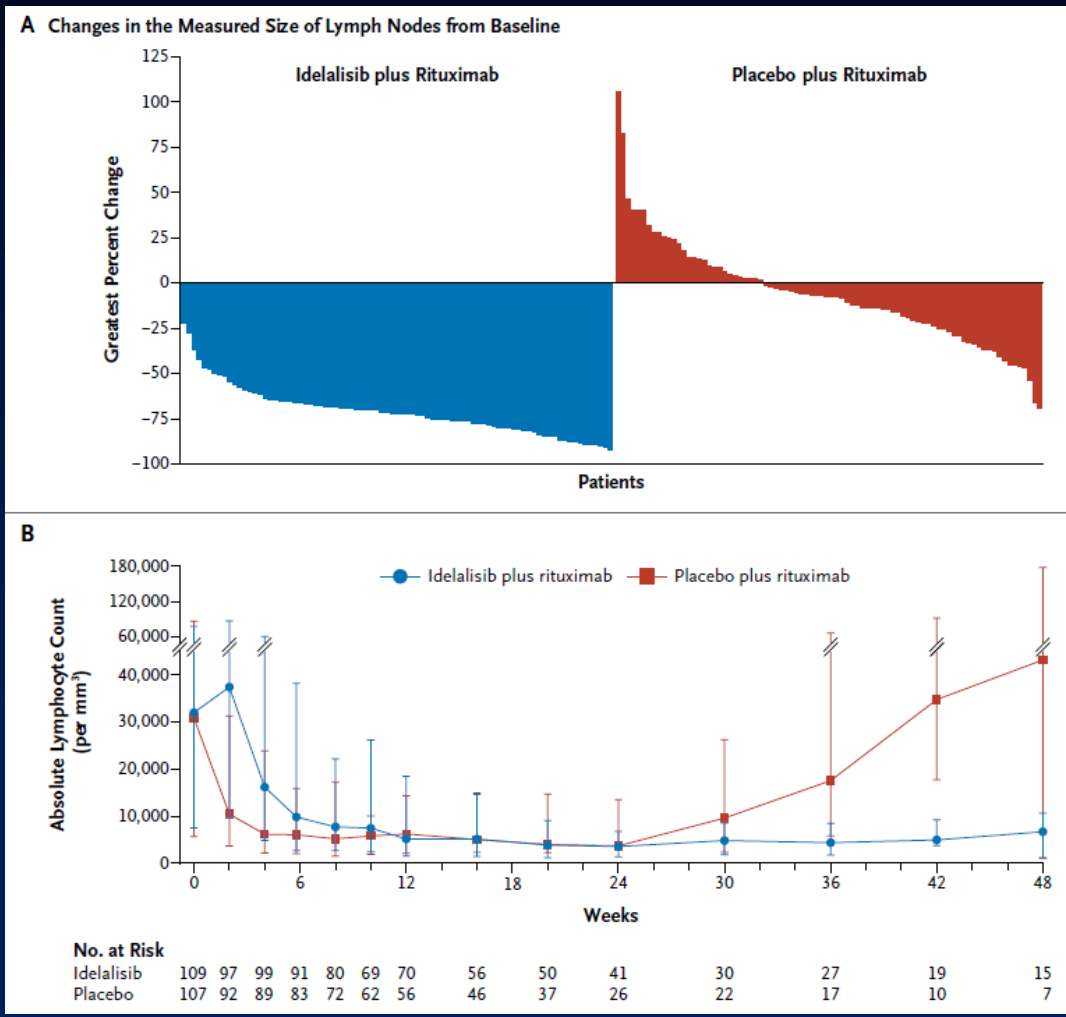
Idelalisib in Rel/Ref FL



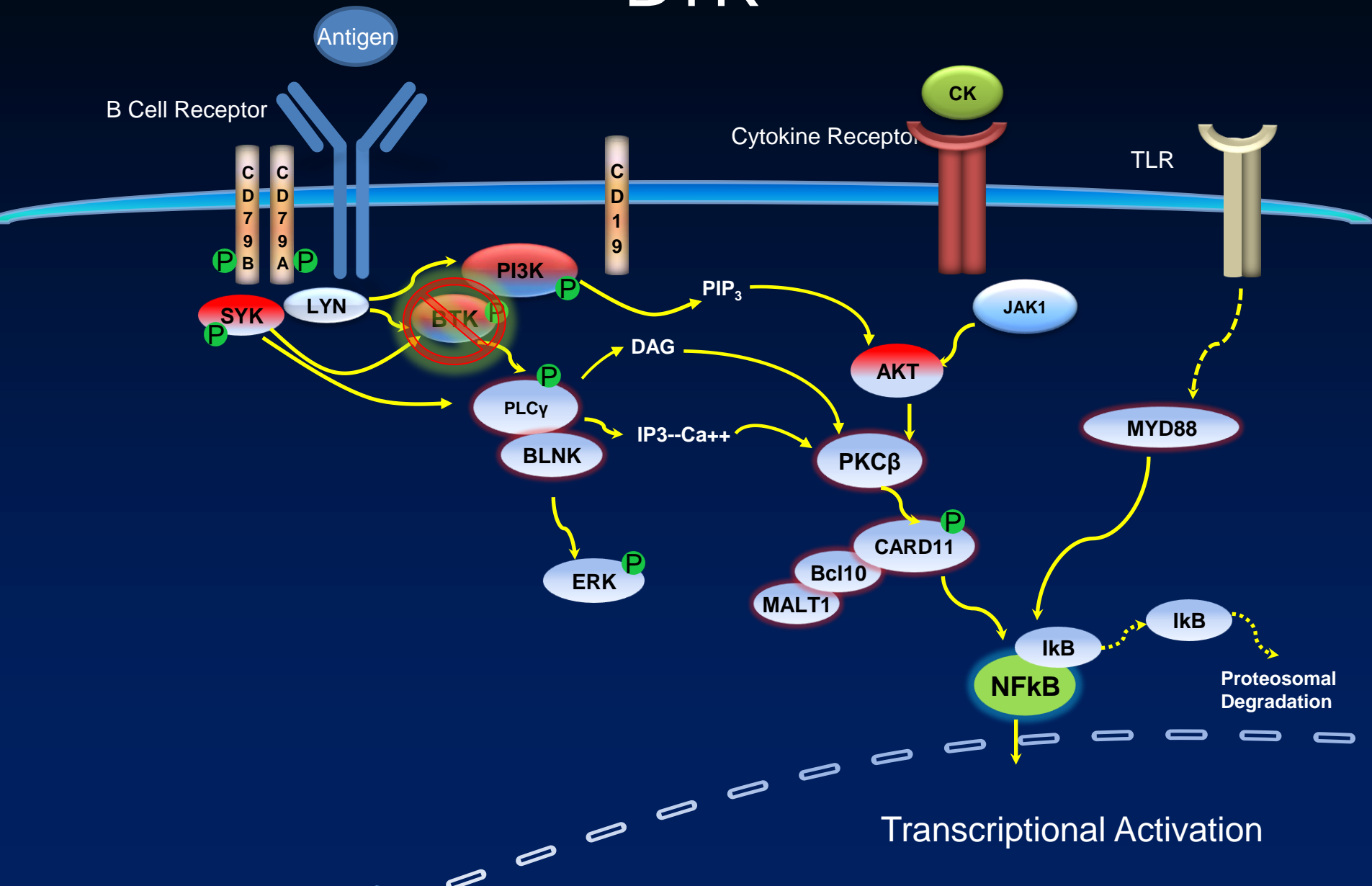
4 months of
idelalisib



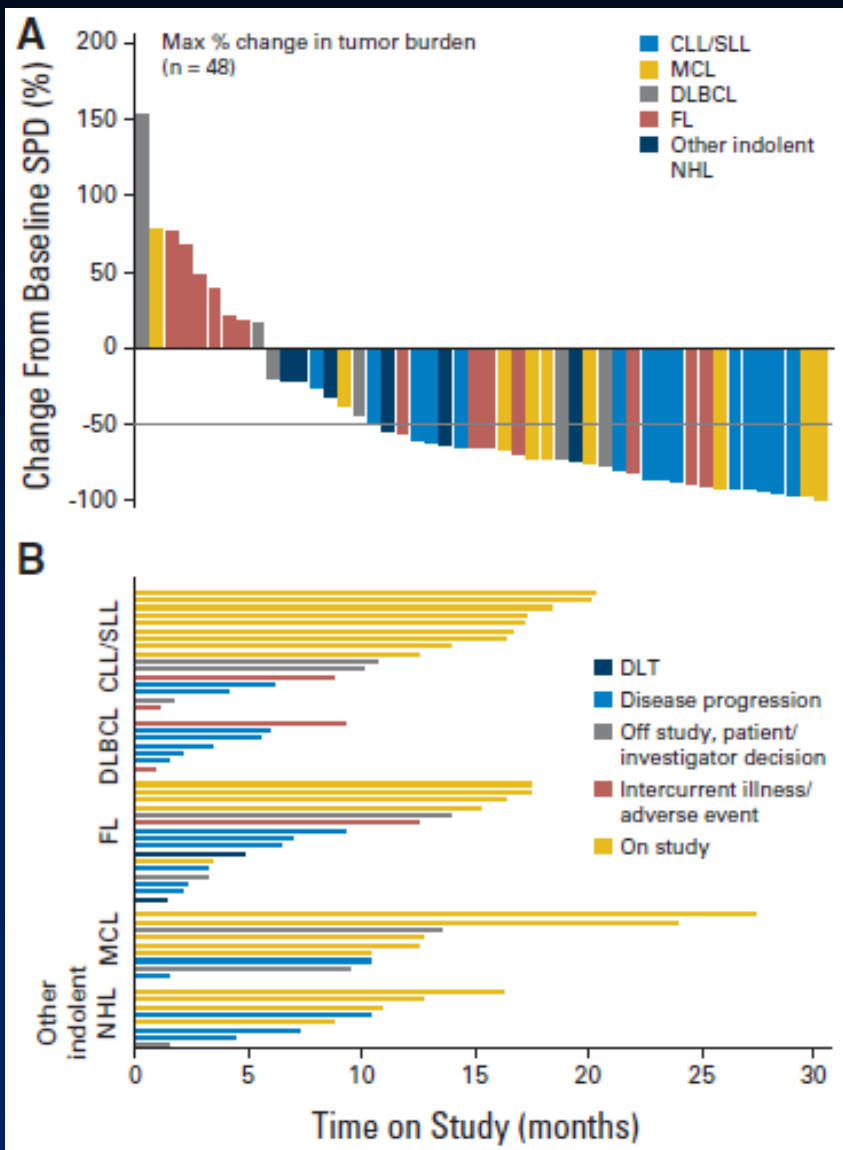
PI3K δ Inhibition with Idelalisib+ R in Relapsed CLL



Targeting B-Cell Receptor Signaling: BTK



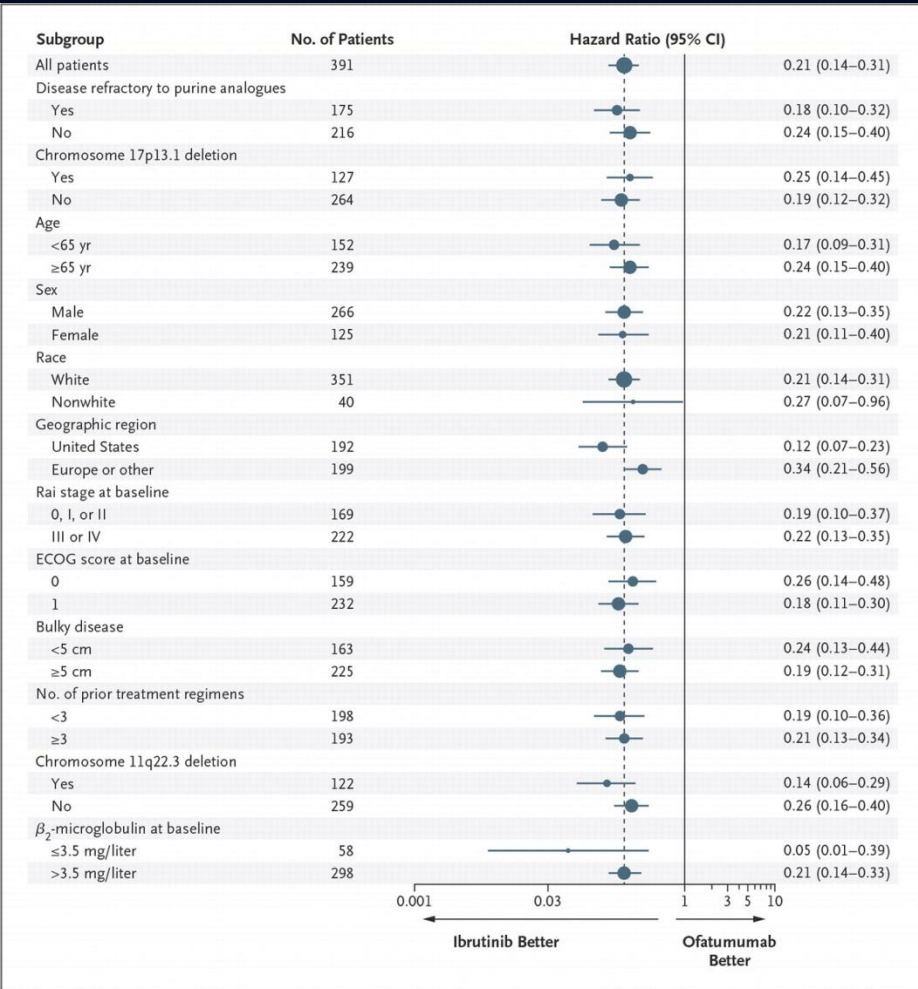
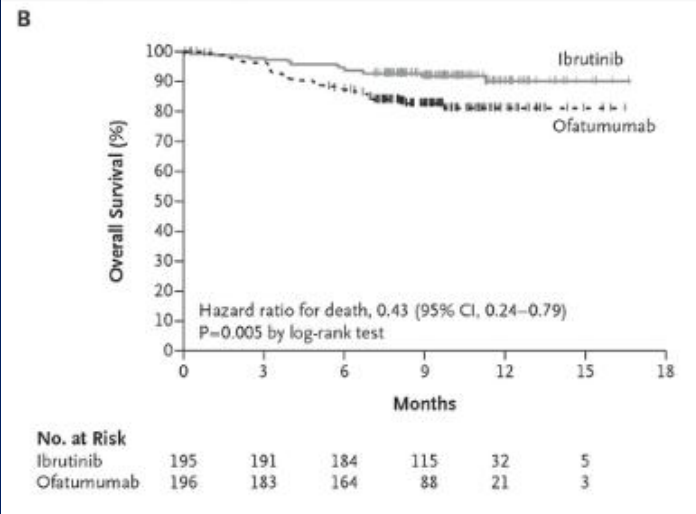
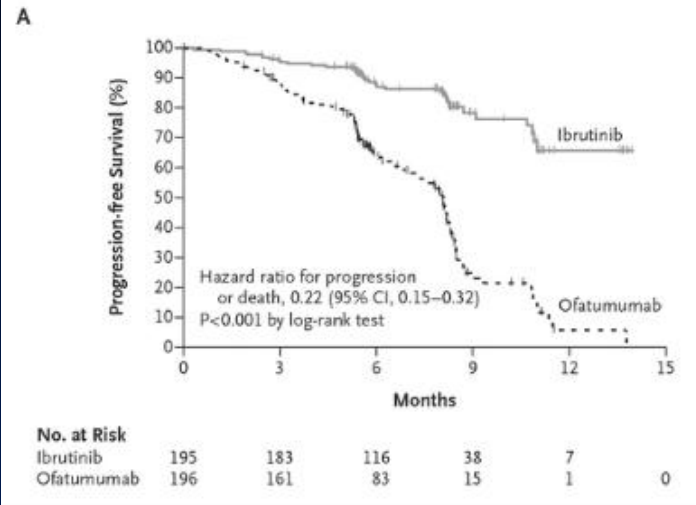
Ibrutinib in R/R B-cell Malignancies



Best Response	n	CR	PR	SD	ORR, IIT (N = 56)
CLL/SLL	16	2	9	3*	69%
MCL	9	3	4	1	78%
WM	4	0	3	1	75%
FL	16	3	3	4	38%
MZL/MALT	4	0	1	1	25%
DLBCL	7	0	2	1	29%
Total	56	8	22	11	54%

*One patient with CLL had nodal response with lymphocytosis.

Ibrutinib versus Ofatumumab in relapsed CLL



Marked Reductions in Peripheral Lymphadenopathy Observed

Pretreatment

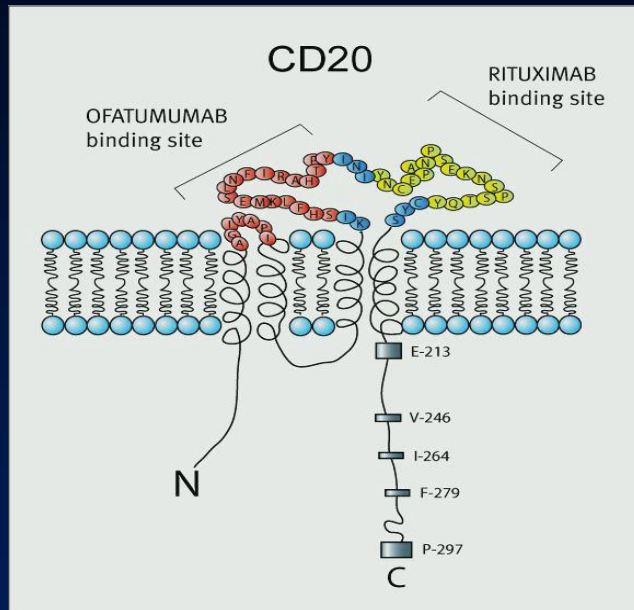
With Idelalisib Treatment



38-year-old patient with refractory CLL and 5 prior therapies

Antibody Therapy: Next Generation Molecules

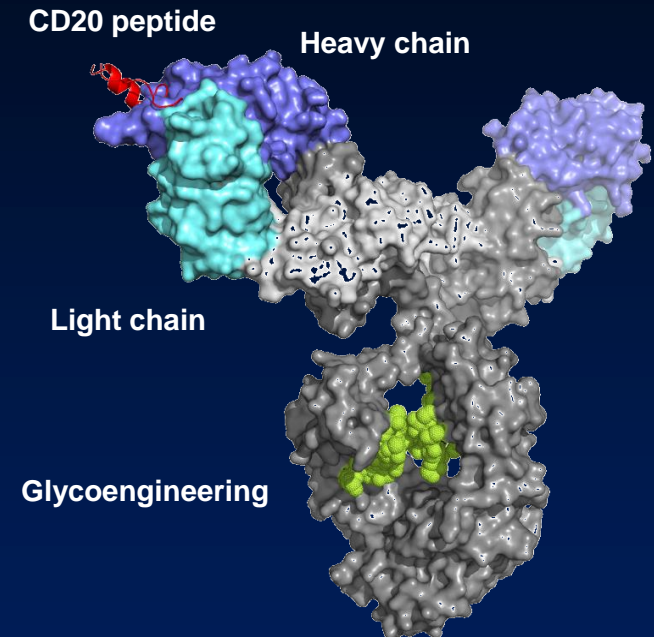
Ofatumumab



- Human IgG1 antibody
- Novel membrane-proximal small loop epitope
- Slow off-rate
- Induces ADCC
- Induces strong and rapid CDC

Image Courtesy of GlaxoSmithKline

Obinutuzumab



- Human IgG, type II antibody
- Increased ADCC
- Lower CDC
- Glycoengineering for increased affinity to FcγR11a

Image Courtesy of Genentech

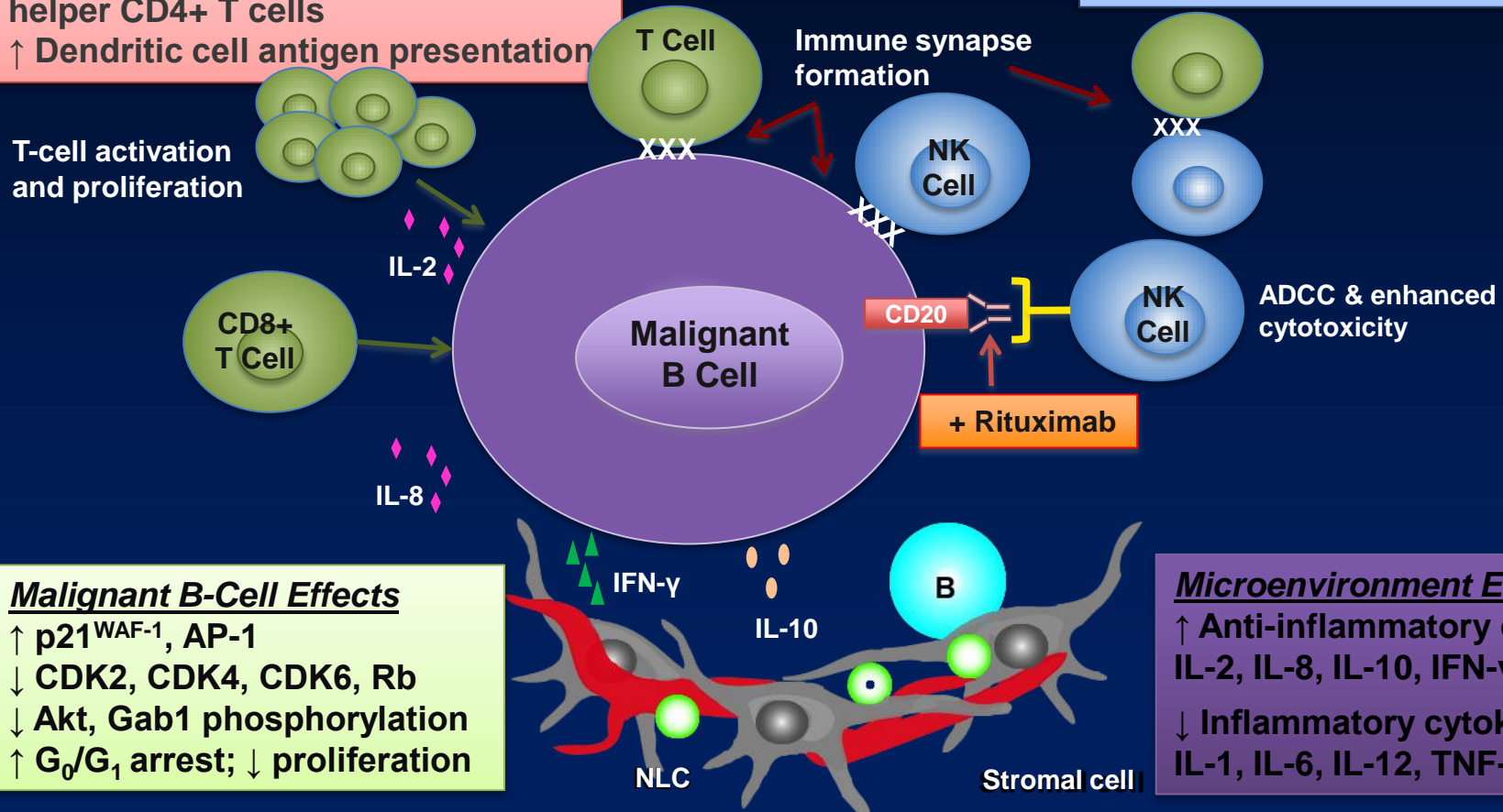
Mechanisms of Action of Lenalidomide in Lymphoma Cells and the Nodal Microenvironment

T-Cell Effects

Activation and proliferation
 ↑ Immune synapse formation
 ↑ CD8+ T-effector cell activity
 Stimulation of cytotoxic CD8+ and helper CD4+ T cells
 ↑ Dendritic cell antigen presentation

NK-Cell Effects

↑ Number and activity of NK cells
 ↑ Enhanced ADCC
 ↑ Immune synapse formation and direct NK killing



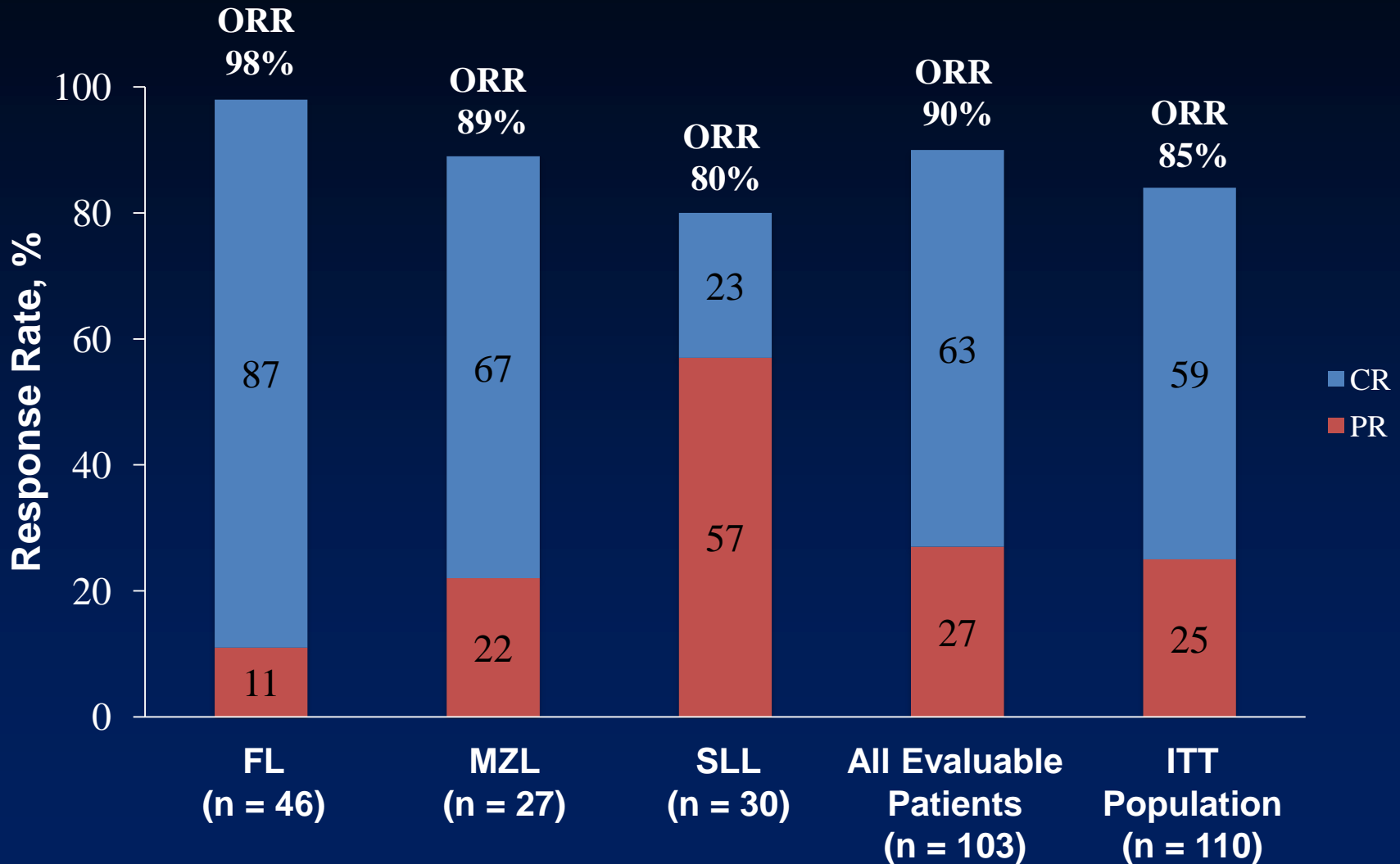
Malignant B-Cell Effects

↑ p21^{WAF-1}, AP-1
 ↓ CDK2, CDK4, CDK6, Rb
 ↓ Akt, Gab1 phosphorylation
 ↑ G₀/G₁ arrest; ↓ proliferation

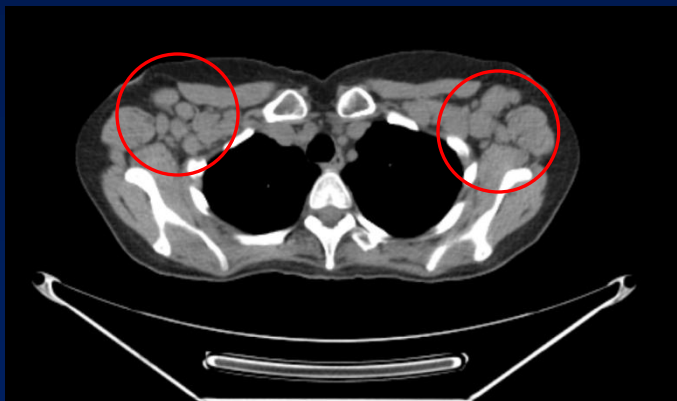
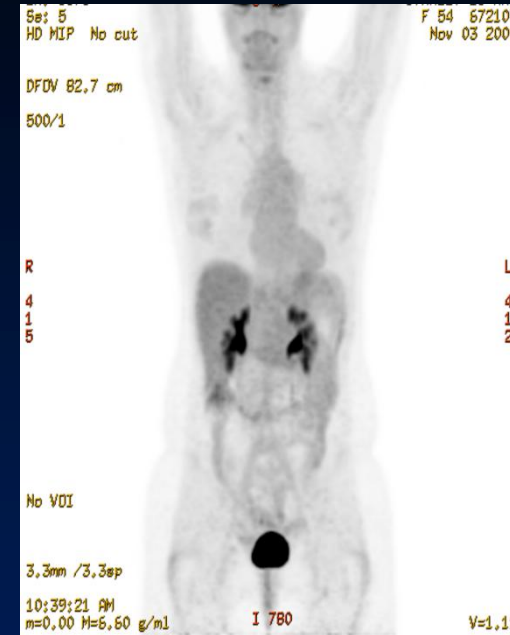
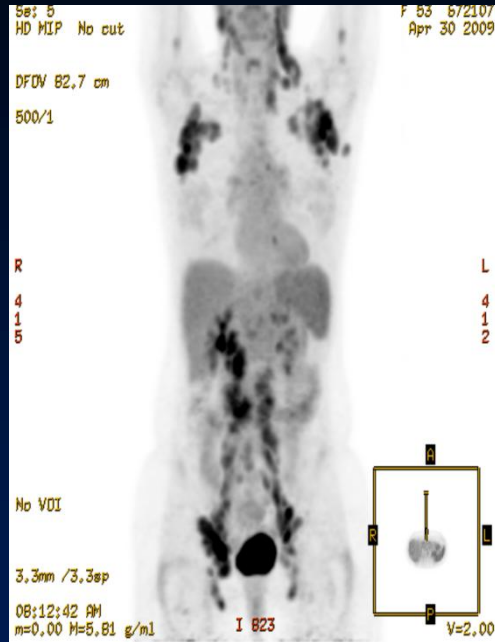
Microenvironment Effects

↑ Anti-inflammatory cytokines:
 IL-2, IL-8, IL-10, IFN- γ , TNF- α
 ↓ Inflammatory cytokines:
 IL-1, IL-6, IL-12, TNF- α

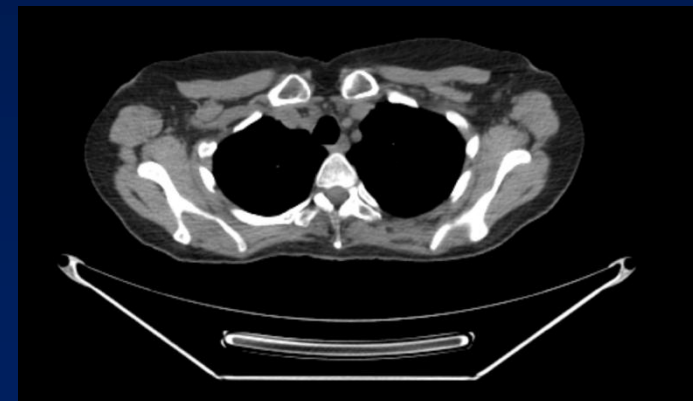
Lenalidomide + Rituximab (R2) in Untreated Indolent Lymphoma: Response Rates



Lenalidomide + Rituximab in Indolent Lymphoma



Baseline



S/P cycle 6

Clinical Trials

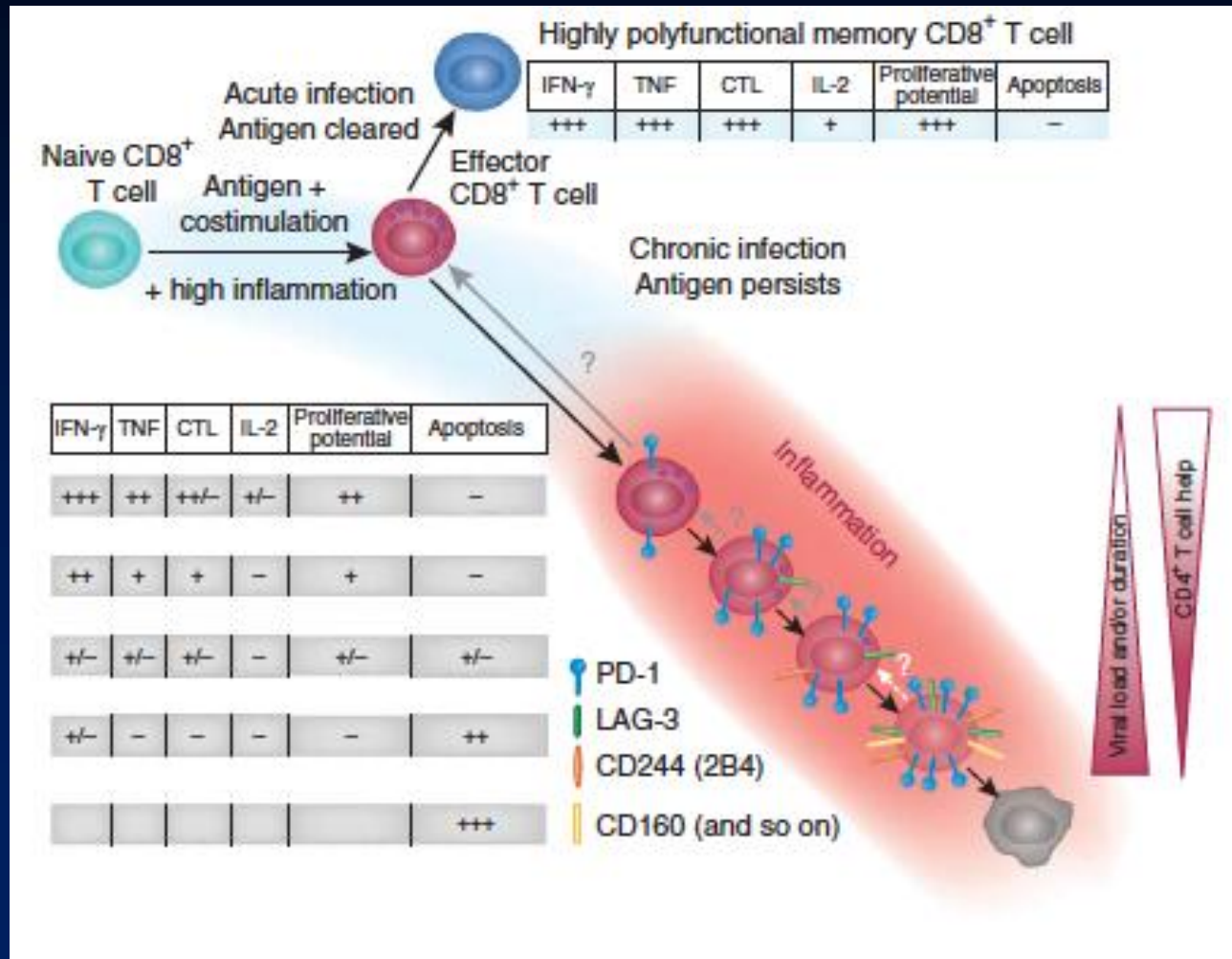
Challenges to Progress

- No accepted standard of care
- Heterogeneous outcomes with frontline therapy
- Relapse/resistance
- Evolving understanding of lymphoma biology

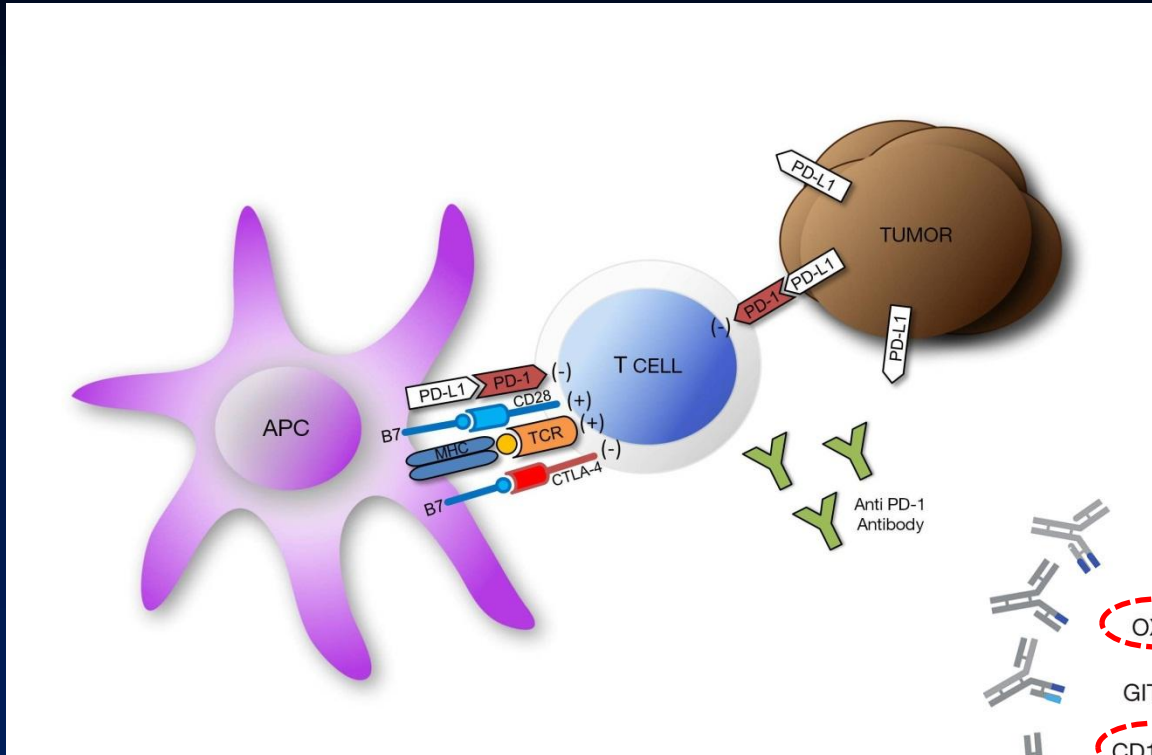
Why Consider a Clinical Trial

- May offer additional or better options than standard therapy
- Advance the care for lymphoma
- Risks must be weighed against potential benefits

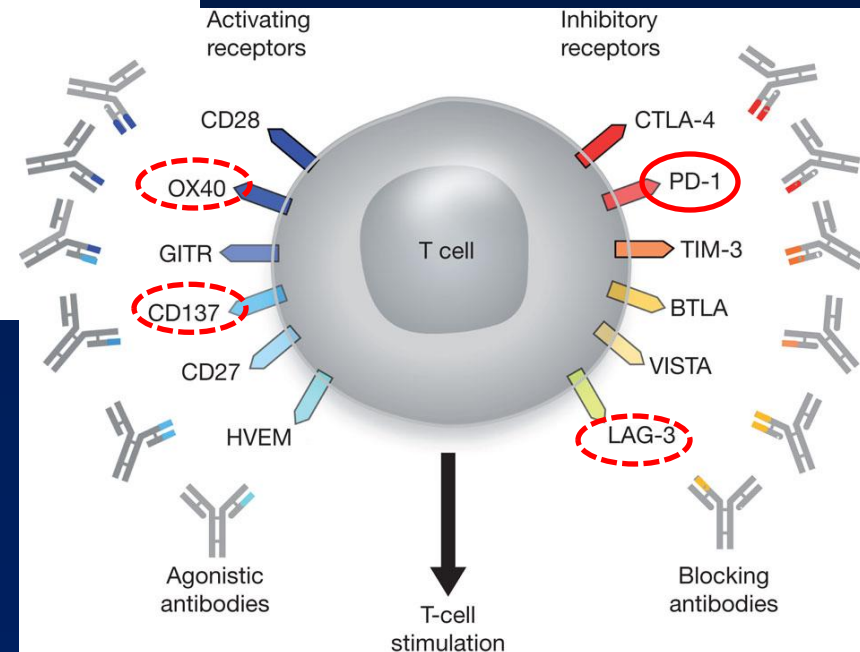
Progressive T cell dysfunction during chronic antigen exposure



New Agents- Immunotherapy



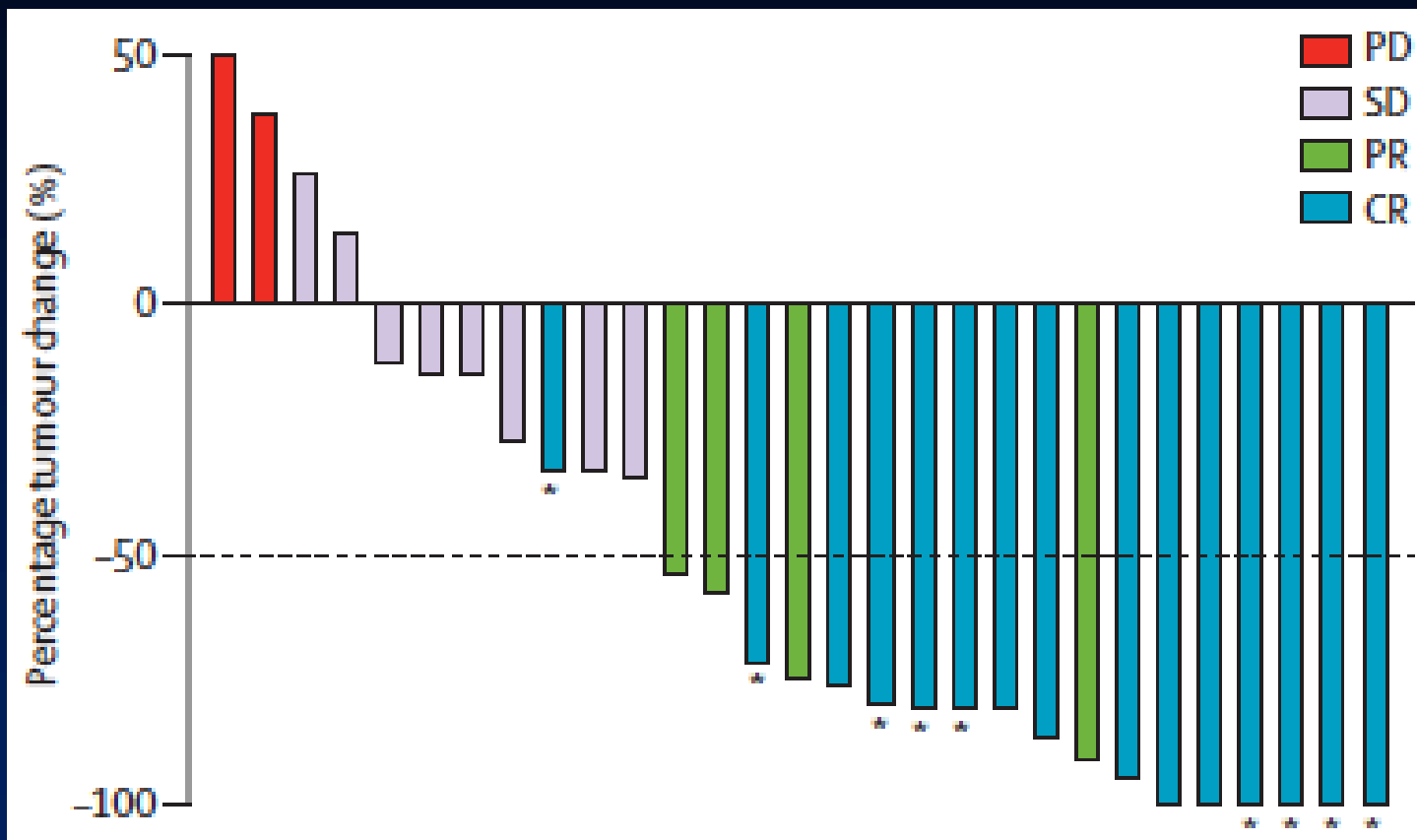
Nastoupil, in press.



Mellman et al, Nature, 2011

Pidilizumab + Rituximab in relapsed FL

66% ORR and 52% CR



Key Questions to Ask Your Doctor

- What type of lymphoma do I have? What is the specific subtype?
- Is it indolent or aggressive?
- What is the stage of my lymphoma?
- What are my treatment options?
- What side effects may I experience and how can I deal with them?
- Are there any clinical trials that I might benefit from, now or in the future?

Questions

