Oncology Grand Rounds
Lymphomas and Chronic Lymphocytic Leukemia

Nurse and Physician Investigators Discuss New Agents, Novel Therapies and Actual Cases from Practice

Thursday, May 4, 2017
6:00 PM – 8:00 PM

Faculty

Ann S LaCasce, MD, MMSc
Kim Leake, MSN, FNP-C, APN-1
Mollie Moran, MSN, CNP, AOCNP
Michael E Williams, MD, ScM

Moderator

Neil Love, MD

Research To Practice®

Oncology Grand Rounds Series

Wednesday	**Non-Small Cell Lung Cancer** 6:00 PM – 8:00 PM
Thursday	**Cancer Immunotherapy** 6:00 AM – 7:30 AM
	Breast Cancer 12:15 PM – 1:45 PM
	Lymphomas and CLL 6:00 PM – 8:00 PM
Friday	**Myeloproliferative Neoplasms** 6:00 AM – 7:30 AM
	Ovarian Cancer 12:15 PM – 1:45 PM
	Gastrointestinal Cancers 6:00 PM – 8:00 PM

Oncology Grand Rounds: Themes

Identifying and understanding oncology clinical scenarios

- Key determining factors; natural history and treatment
- Evaluating and managing clinical symptoms
- Patient and caregiver education

Integrating new agents and treatment strategies into practice

- Benefits and risks
- Prevention, identification and management of side effects/toxicity
- Identifying patients at high risk for toxicity

Psychosocial issues in clinical oncology

- Caring for family and loved ones, including minor children and grandchildren
- Job satisfaction and disappointment
- The bond that heals

Novel Agents Approved by the FDA in the Past 9 Weeks

Agent	Approval Date	FDA-Approved Use on Approval Date
Telotristat ethyl (tryptophan hydroxylase inhibitor)	February 28th	In combination with somatostatin analogue (SSA) therapy for the treatment of adults with carcinoid syndrome diarrhea inadequately controlled by SSA therapy alone
Ribociclib (CDK4/6 inhibitor)	March 13th	In combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer
Avelumab (anti-PD-L1 antibody)	March 23rd	For the treatment of patients (≥12 years) with metastatic Merkel cell carcinoma, including those who have not received prior chemotherapy
Niraparib (PARP inhibitor)	March 27th	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer whose tumors have completely or partially shrunk in response to platinum-based chemotherapy
Brigatinib (ALK inhibitor)	April 28th	For the treatment of patients with ALK-positive metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib
Midostaurin (FLT3 inhibitor)	April 28th	For the treatment of adults with newly diagnosed FLT3-positive acute myeloid leukemia in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
Durvalumab (anti-PD-L1 antibody)	May 1st	For the treatment of patients with PD-L1-positive inoperable or metastatic urothelial bladder cancer that has progressed during or after one standard platinum-based regimen

https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm537040.htm

- Chronic Lymphocytic Leukemia
- Follicular Lymphoma
- Hodgkin Lymphoma
- Mantle Cell Lymphoma
- Diffuse Large B-Cell Lymphoma
- T-Cell Lymphoma

About the Enduring Program

- The proceedings from this 7-part CNE series will be video recorded and used in a virtual meeting archive including a downloadable version of the slides.

- An email will be sent to all attendees when the web activity is available.
- To learn more about our education programs visit our website, www.ResearchToPractice.com

Download the RTPLive app on your smartphone or tablet to access program information, including slides being presented during the program:

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Submit a challenging case or question for discussion during the program.

Email to **DrNeilLove@ResearchToPractice.com**

Text to **(786) 759-1458**

(Your phone number will remain confidential and will not be disclosed.)

If you are unable to text or email, please complete a question/comment card located on your conference table and drop it in one of the designated bins located throughout the meeting room.

Make the Meeting Even More Relevant to You

Join the conversation by sharing photos and videos using the hashtag #RTPLive

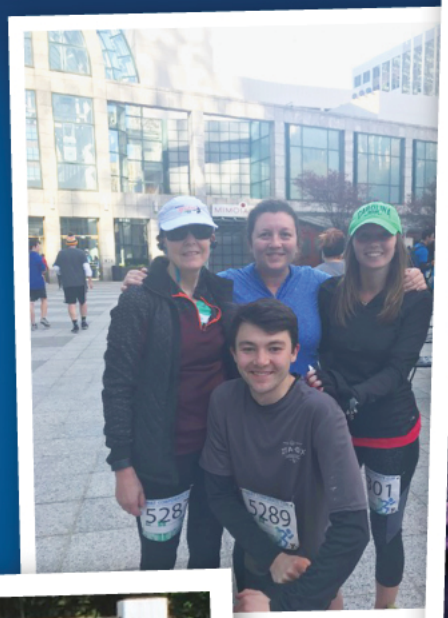
Facebook **@researchtopractice**

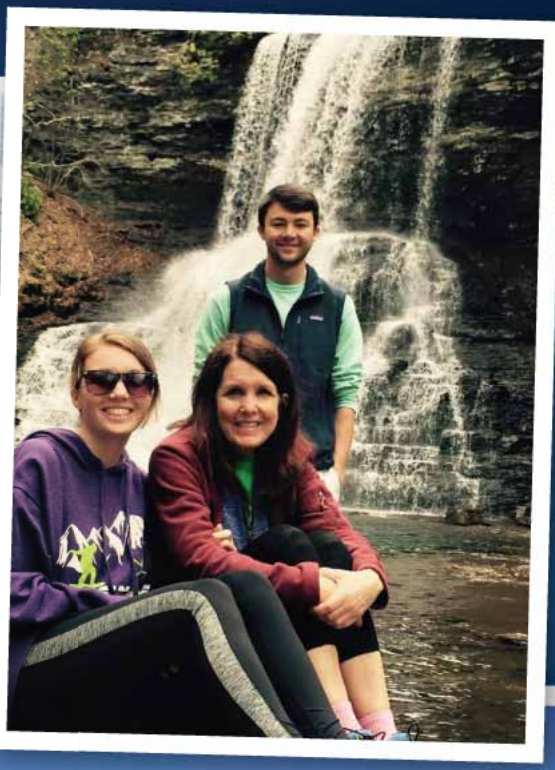
Twitter **@DrNeilLove**

Instagram **@researchtopractice**

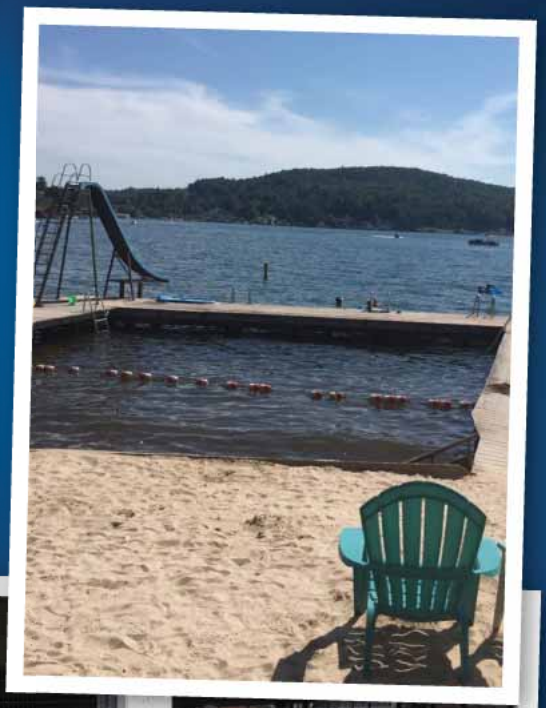
And get here early to participate in a brief video interview, where you can tell us about your experiences with oncology nursing. You may even see your post on the big screen during the events!

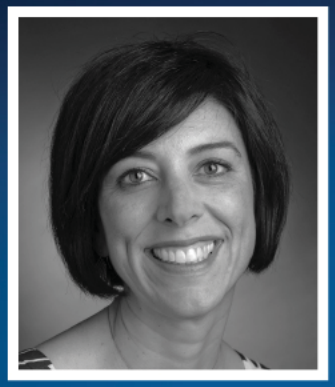
Kim Leake, MSN, FNP-C, APN-1
University of Virginia
School of Medicine
Charlottesville, Virginia



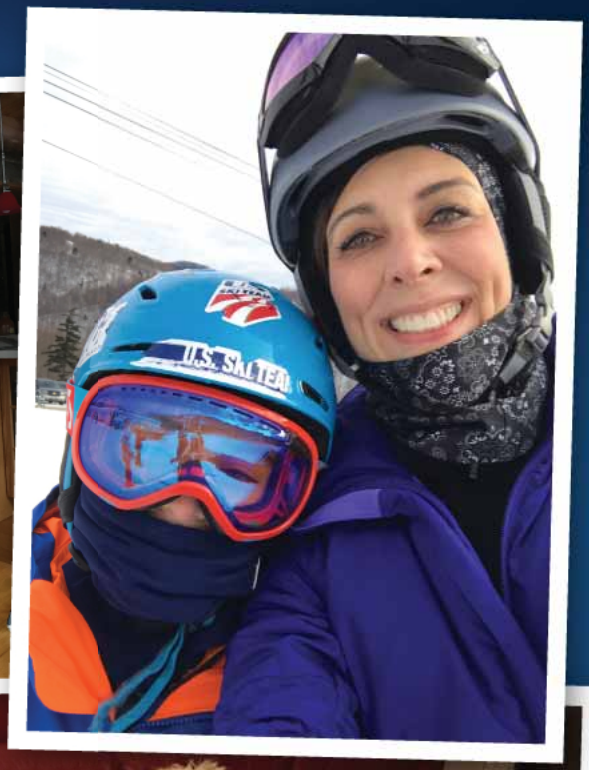


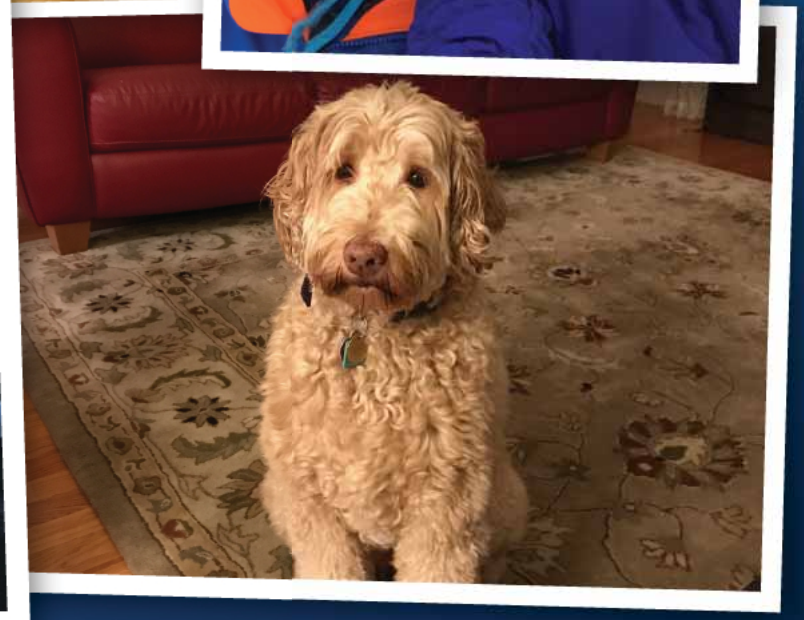
Mollie Moran, MSN, CNP, AOCNP
The Ohio State University
Columbus, Ohio



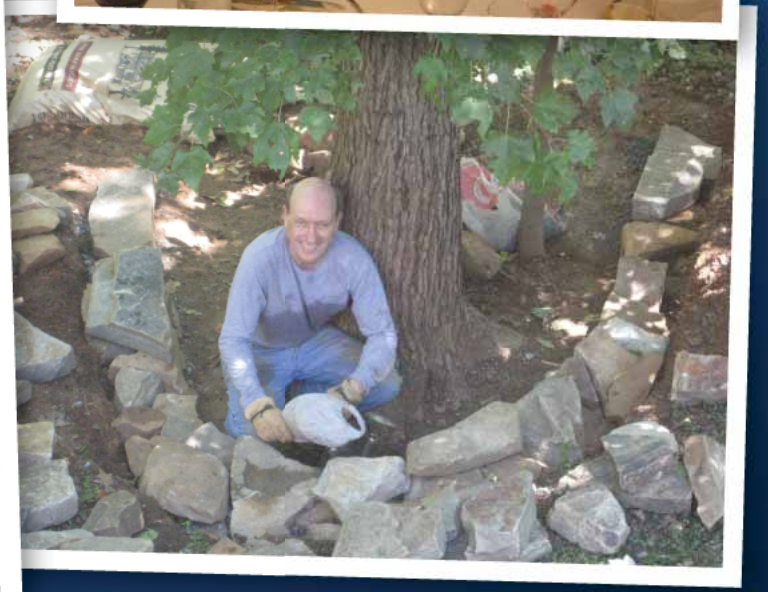


Ann S LaCasce, MD, MMSc
Dana-Farber Cancer Institute
Boston, Massachusetts





Michael E Williams, MD, ScM
University of Virginia
School of Medicine
Charlottesville, Virginia



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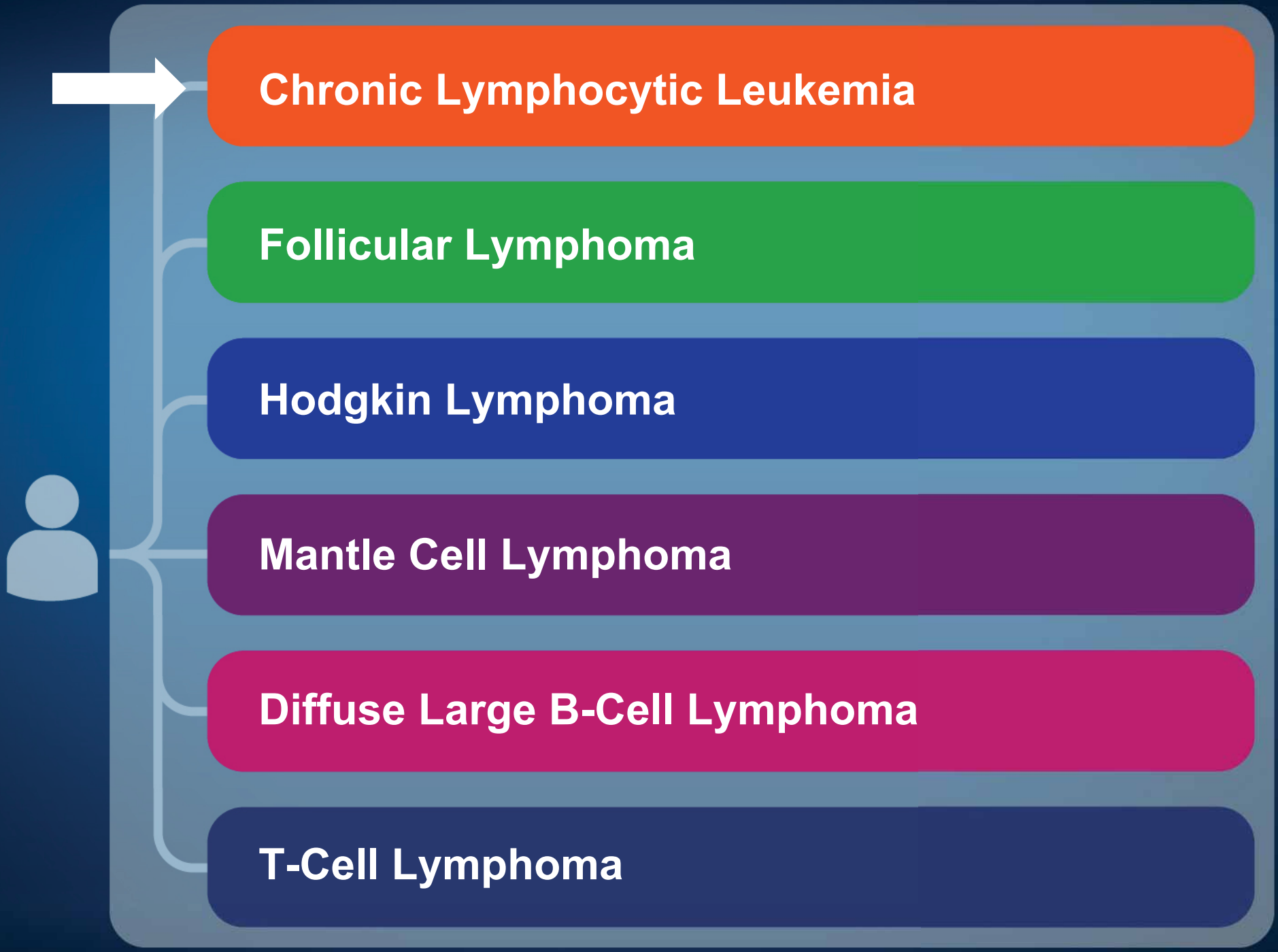

Chronic Lymphocytic Leukemia
Follicular Lymphoma
Hodgkin Lymphoma
Mantle Cell Lymphoma
Diffuse Large B-Cell Lymphoma
T-Cell Lymphoma

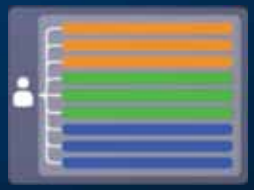
Overview of Chronic Lymphocytic Leukemia

- Estimated number of new cases and deaths in 2017:
  - New cases = 20,110
  - Deaths = 4,660
- 61% men, 39% women
- Five-year survival estimates (2006-2012) = 83%

Cancer Facts and Figures 2017; https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html

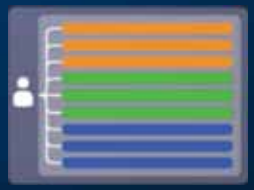
Key Determinants of Systemic Therapy Decision-Making in CLL

- Cytogenetics and other genomic factors
- Disease symptoms
- Age
- Comorbidities
- Supportive care issues
  - Hypogammaglobulinemia
  - Infection



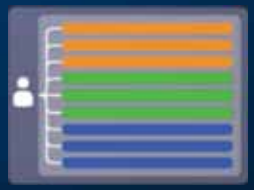
Treatment Approaches - CLL

- Observation off treatment
- Chemotherapy/anti-CD20 antibody (rituximab, obinutuzumab)
  - FCR, BR
  - Possibility of prolonged treatment-free intervals; tolerance in older patients
- Obinutuzumab/chlorambucil
  - Efficacy advantage over rituximab; infusion reactions



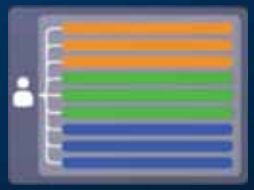
Treatment Approaches - CLL

- Ibrutinib
  - Possibility of prolonged disease control with minimal side effects; bleeding, atrial fibrillation, patients going for surgery; indefinite treatment
- Idelalisib
  - Efficacy in relapsed disease; autoimmune complications (colitis, hepatitis)
- Venetoclax
  - Efficacy up front and on relapse; prevention and management of tumor lysis syndrome
- Lenalidomide
  - Use as maintenance; disease flare



Key Considerations for the Management of CLL with Normal Cytogenetics

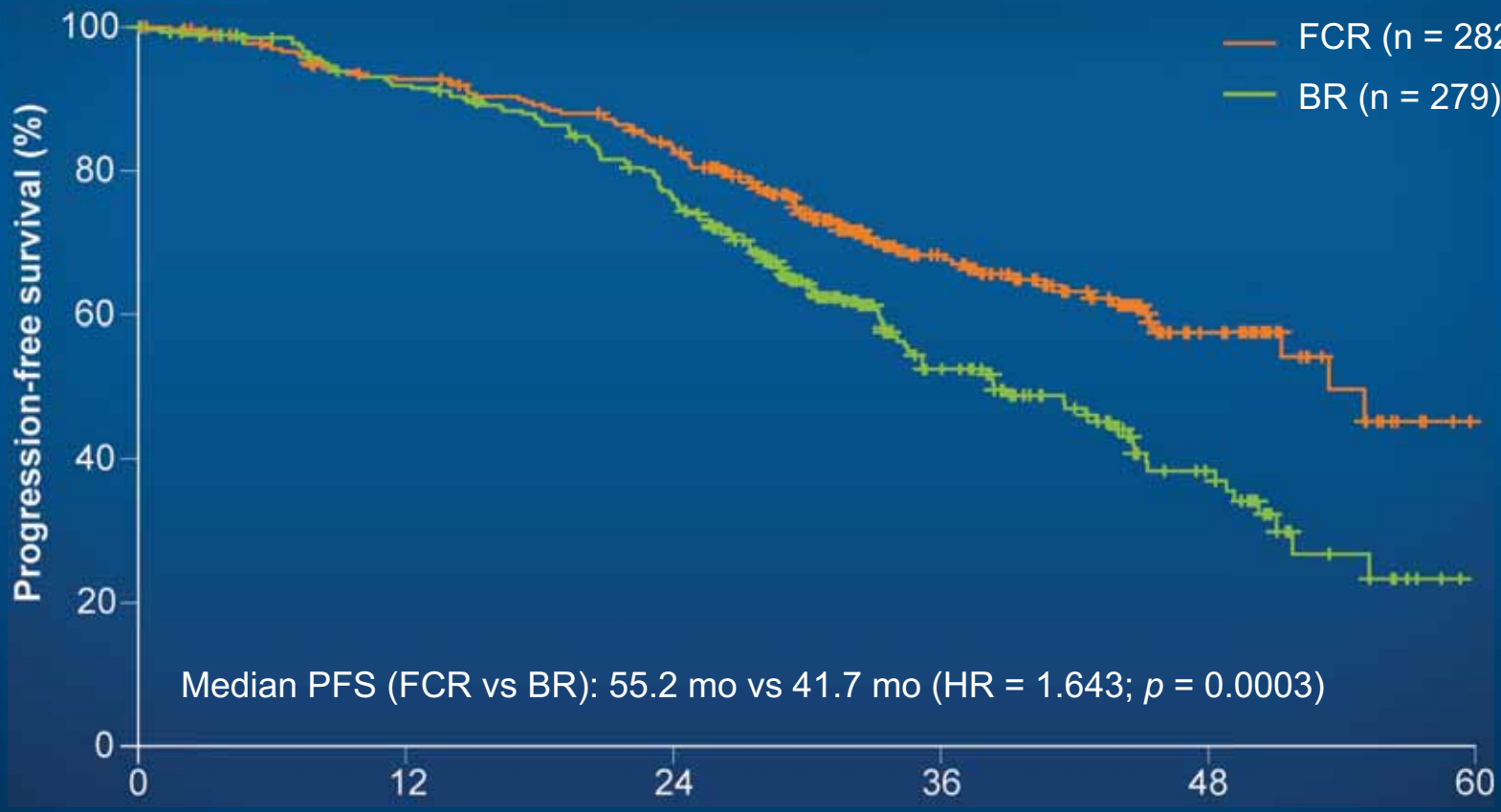
- Choice between:
  - Short-term potentially toxic treatment (chemo/anti-CD20 antibody [Ab])
  - Indefinite therapy that is better tolerated
- Maintenance treatment after chemo/anti-CD20 Ab
  - Anti-CD20 Ab or lenalidomide
- Therapeutic selection beyond front line; integrating novel therapies (eg, idelalisib, venetoclax)



74-Year-Old Man with CLL (Ms Leake)

- February 2016: Diagnosis of CLL/SLL Rai Stage I, trisomy 12
  - CT scan: Diffuse adenopathy in neck and chest
  - Normal blood counts
- Obinutuzumab/chlorambucil
- September 2016: Post-treatment scans show patient in PR
  - Interval reduction of known adenopathy in neck/chest; normal blood counts
- Recently, mild disease progression less than 6 months from completion of therapy
  - Increased cervical and bilateral inguinal adenopathy
  - No splenomegaly, normal blood counts
- June 2017: Repeat CT, consider re-checking peripheral blood by flow cytometry and FISH studies; next-line treatment…ibrutinib?

CLL10: Phase III Trial of FCR versus BR in Advanced CLL



- Median PFS in younger patients (≤65 yrs) was significantly longer with FCR than with BR
- In elderly patients (>65 yrs) there was no significant difference in median PFS between FCR and BR

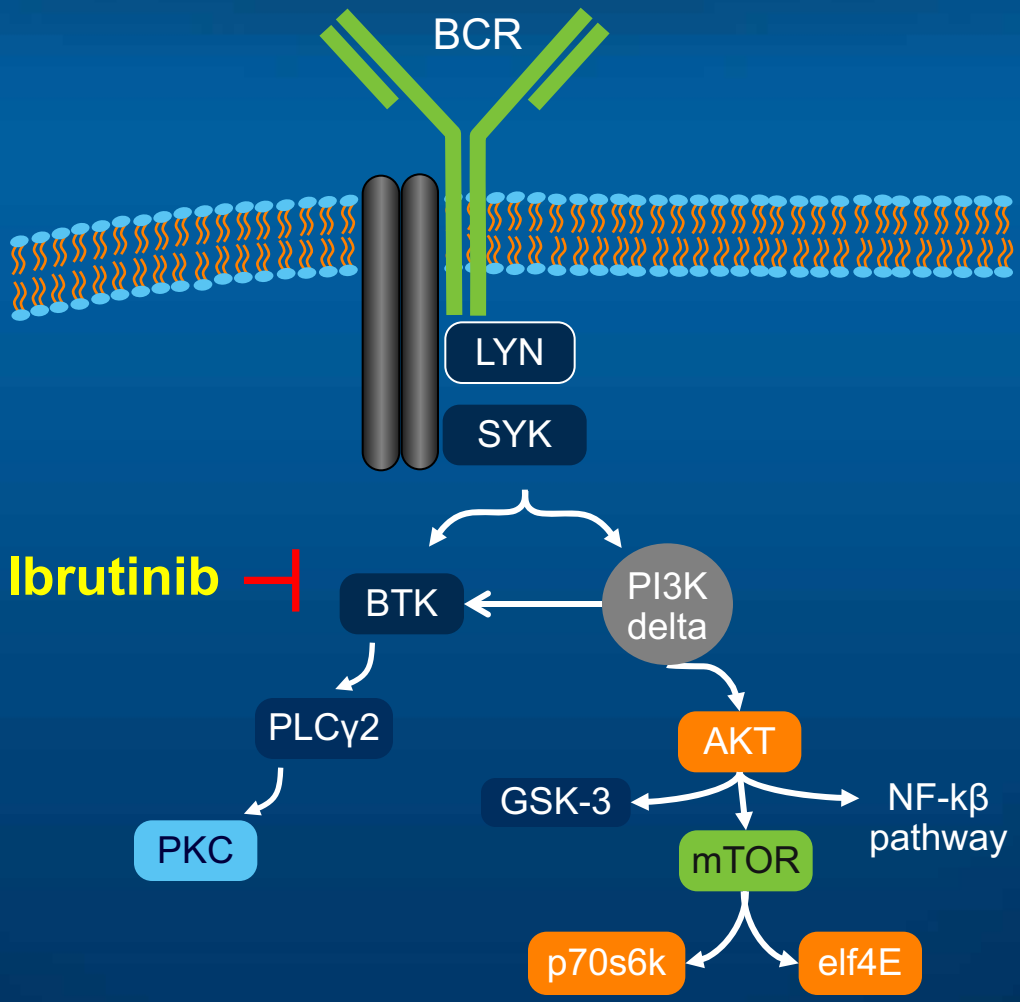
Eichhorst B et al. *Lancet Oncol* 2016;17(7):928-42.

Ibrutinib

- **Mechanism of action:**
  - An oral, selective inhibitor of Bruton tyrosine kinase activity
- **Indication in CLL:**
  - For patients with treatment-naïve CLL
  - For the treatment of CLL in patients who carry a del(17p) mutation
  - For patients with CLL who have received at least 1 prior therapy
- **Recommended dose for CLL:**
  - 420 mg orally once daily

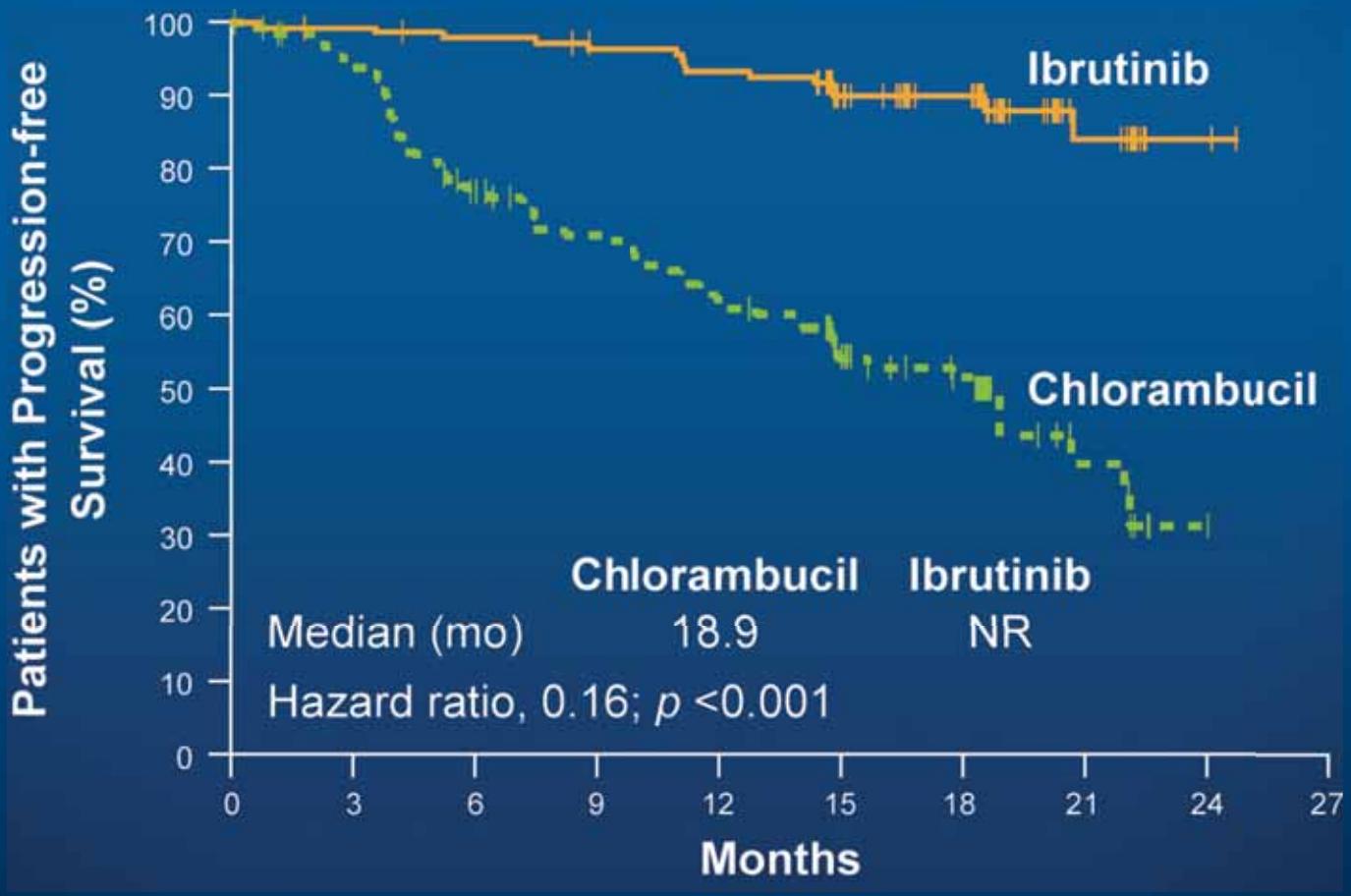
http://www.prnewswire.com/news-releases/imbruvica-ibrutinib-approved-by-us-fda-for-the-first-line-treatment-of-chronic-lymphocytic-leukemia-300231107.html
Ibrutinib package insert, April 2016

Mechanism of Action of Ibrutinib



Woyach JA et al. *Blood* 2012;120(6):1175-84.

RESONATE-2: PFS with Ibrutinib in Patients with Untreated CLL Aged ≥65 Years



Burger JA et al. *N Engl J Med* 2015;373(25):2425-37.

RESONATE-2: Select Ibrutinib-Associated Adverse Events (AEs)

- **Common AEs**
  - Diarrhea
  - Fatigue
  - Cough
  - Nausea
- **Grade ≥3 AEs**
  - Neutropenia
  - Anemia
- **AEs of special interest**
  - Major hemorrhage: 4% (no fatal events)
  - Atrial fibrillation: 6% (majority Grade 2)
  - Hypertension: 4% Grade ≥3 (no dose modifications required)

Burger JA et al. *N Engl J Med* 2015;373(25):2425-37.

Obinutuzumab

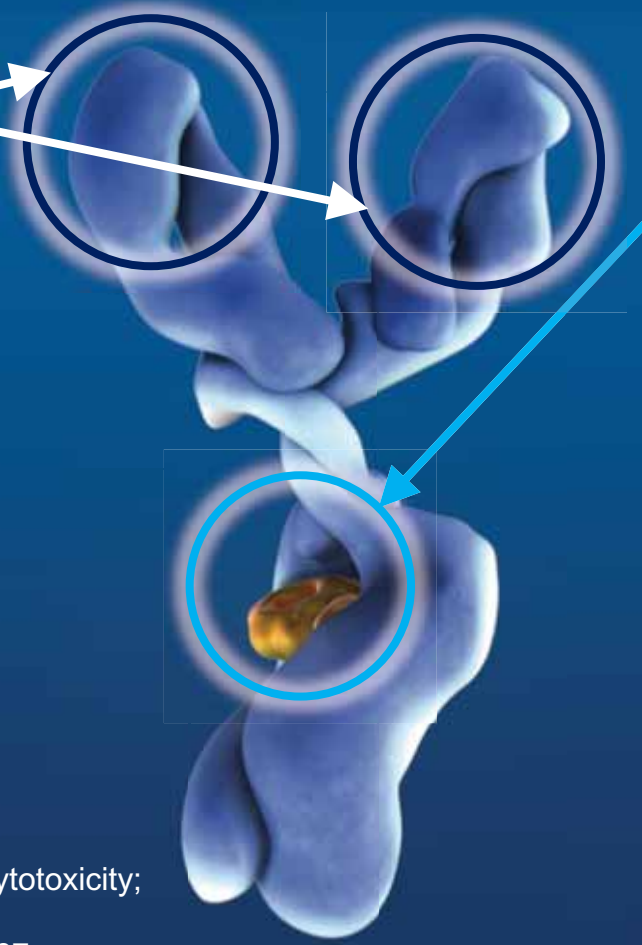
- **Mechanism of action:**
  - A humanized, glycoengineered CD20 monoclonal antibody that enhances antibody-dependent, cell-mediated cytotoxicity
- **Indication in CLL:**
  - In combination with chlorambucil for the treatment of previously untreated CLL
- **Recommended dose for CLL:**
  - 100 mg IV on day 1 and 900 mg IV on day 2 of cycle 1
  - 1,000 mg IV on days 8 and 15 of cycle 1 and 1,000 mg IV on day 1 of cycles 2-6

http://www.cancer.gov/about-cancer/treatment/drugs/fda-obinutuzumab
Obinutuzumab package insert, April 2016

Comparison of cell death induced by obinutuzumab and rituximab

Type II anti-CD20 antibody[1]

Enhanced DCD vs rituximab[2]



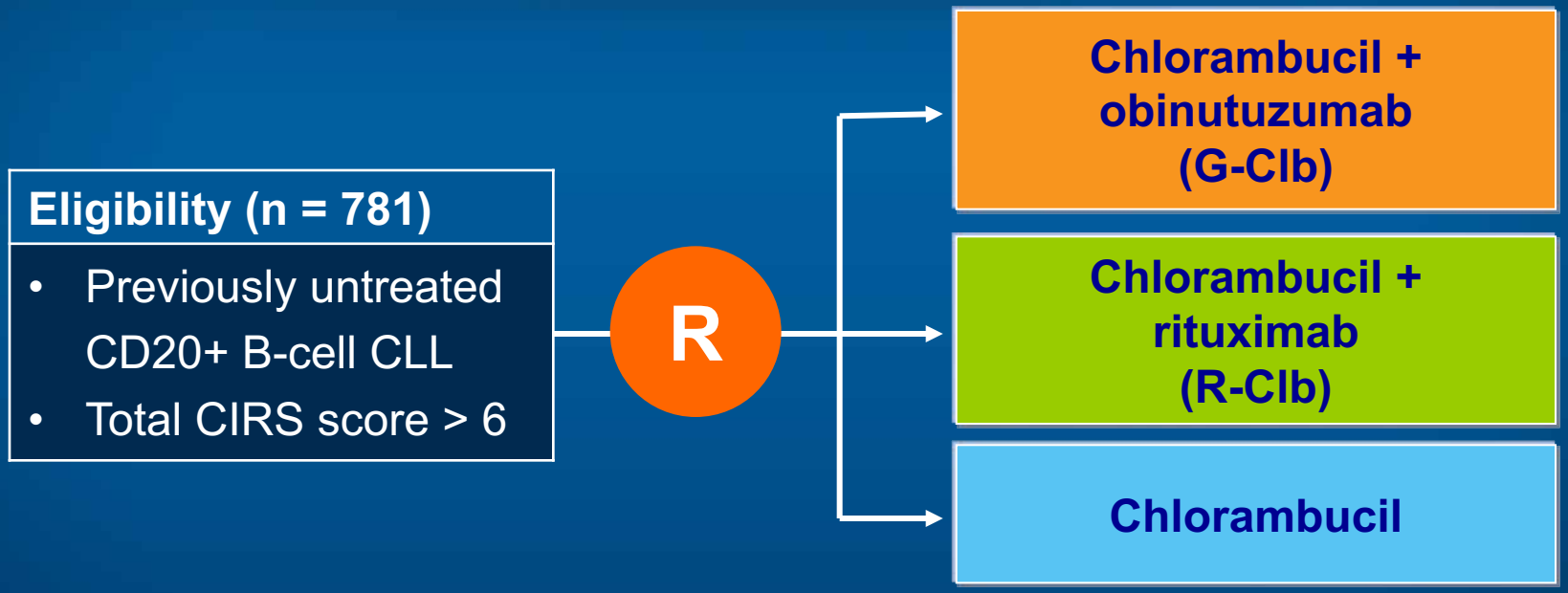
Glycoengineered Fc region[3]

Up to 100-fold increase in ADCC vs rituximab[3,4]

ADCC = antibody-dependent cell-mediated cytotoxicity;
DCD = direct cell death

1. Niederfellner G et al. *Blood* 2011;118:358-67.
2. Alduaij W et al. *Blood* 2011;117:4519-29.
3. Mössner E et al. *Blood* 2010;115:4393-402.
4. Herter S et al. Poster presentation at ASH 2010 (Abstract 3925).

CLL11: Obinutuzumab/Chlorambucil in Patients with CLL and Coexisting Conditions



	G-Clb	R-Clb
Median PFS	26.7 mo	16.3 mo
Median OS	Not reached	Not reached

Goede V et al. *N Engl J Med* 2014;370(12):1101-10.

Idelalisib

- **Mechanism of action:**
  - An orally available small molecule inhibitor of the phosphoinositide-3 kinase (PI3K) delta
- **Indication for CLL:**
  - In combination with rituximab for the treatment of CLL in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities
- **Recommended dose:**
  - 150 mg orally twice daily

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm406387.htm
Idelalisib package insert, April 2016

Serious Adverse Events Associated with Idelalisib

- Hepatotoxicity (elevations in ALT/AST)
- Diarrhea and colitis
- Dyspnea and pneumonitis
- GI perforation

- **See Risk Evaluation and Mitigation Strategy (REMS) to avoid serious or fatal toxicity**

http://www.accessdata.fda.gov/drugsatfda_docs/rems/Zydelig_2014-07-23_FACT%20SHEET.pdf

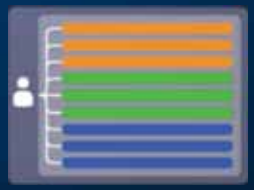
Front-Line Idelalisib Results in Frequent and Severe Immune-Mediated Toxicities

- An early fulminate hepatotoxicity develops in a subset of primarily younger patients who receive idelalisib monotherapy:
  - Median time to initial development of hepatotoxicity = 28 days
- This early hepatotoxicity is immune mediated as suggested by
  - Delayed time to onset
  - An immune cell infiltrate (activated T cells) in biopsies of affected organs
  - Abatement of toxicity with steroids

Lampson BL et al. *Proc ASH* 2015;Abstract 497.

Key Considerations for the Management of CLL with Del(17p)

- Lack of significant benefit with chemotherapy
- Current approved strategy: Ibrutinib → venetoclax
- Contraindications to ibrutinib



57-Year-Old Woman with Del(17p) and Trisomy 12 CLL (Ms Moran)

- April 2013: Diagnosis of CLL positive for del(17p) and trisomy 12
  - FCR x 1 cycle
  - Cycle 2: Fevers and refractory disease
- July 2013: Ibrutinib x 47 months
- March 2017: “BTK resistance” is noted (worsening counts and increased node size)
- March 19, 2017: Venetoclax 20 mg/day administered inpatient
- Patient is married with grown children and works as an executive assistant
  - She is concerned about missing work due to venetoclax and the need for hospitalization for venetoclax escalation

Cytogenetics of CLL and Prognosis

Approximately 80% of patients with CLL have acquired chromosomal abnormalities (as detected by FISH).

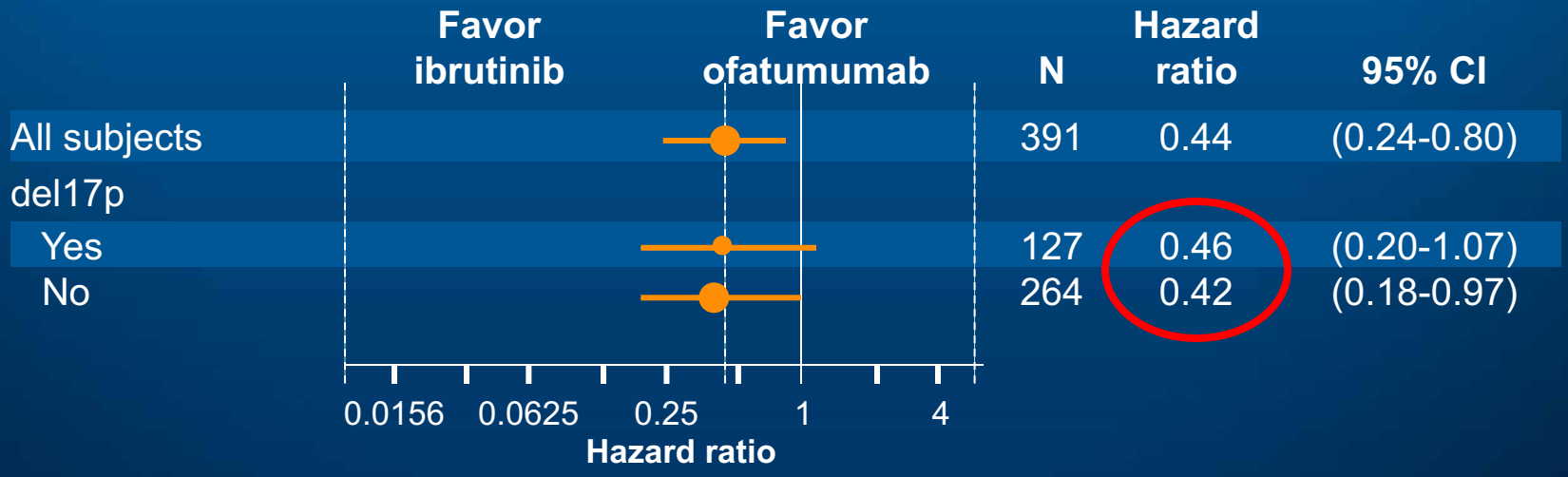
Cytogenetic Abnormality (n = 325)	Incidence	Median Survival
Del(13q)	55%	133 months
Del(11q)	18%	79 months
Trisomy 12q	16%	114 months
Del(17p)	7%	32 months

Dohner H et al. *N Engl J Med* 2000;343(26):1910-6.

RESONATE: Ibrutinib vs Ofatumumab in CLL

18-Month update[1]	Ibrutinib (N = 63)	Ofatumumab (N = 64)	Hazard ratio (*p*-value)
Progression-free survival	Not reached	8.1 mo	0.106 (<0.0001)
Overall response rate	90%	25%	— (<0.0001)

Overall Survival[2]



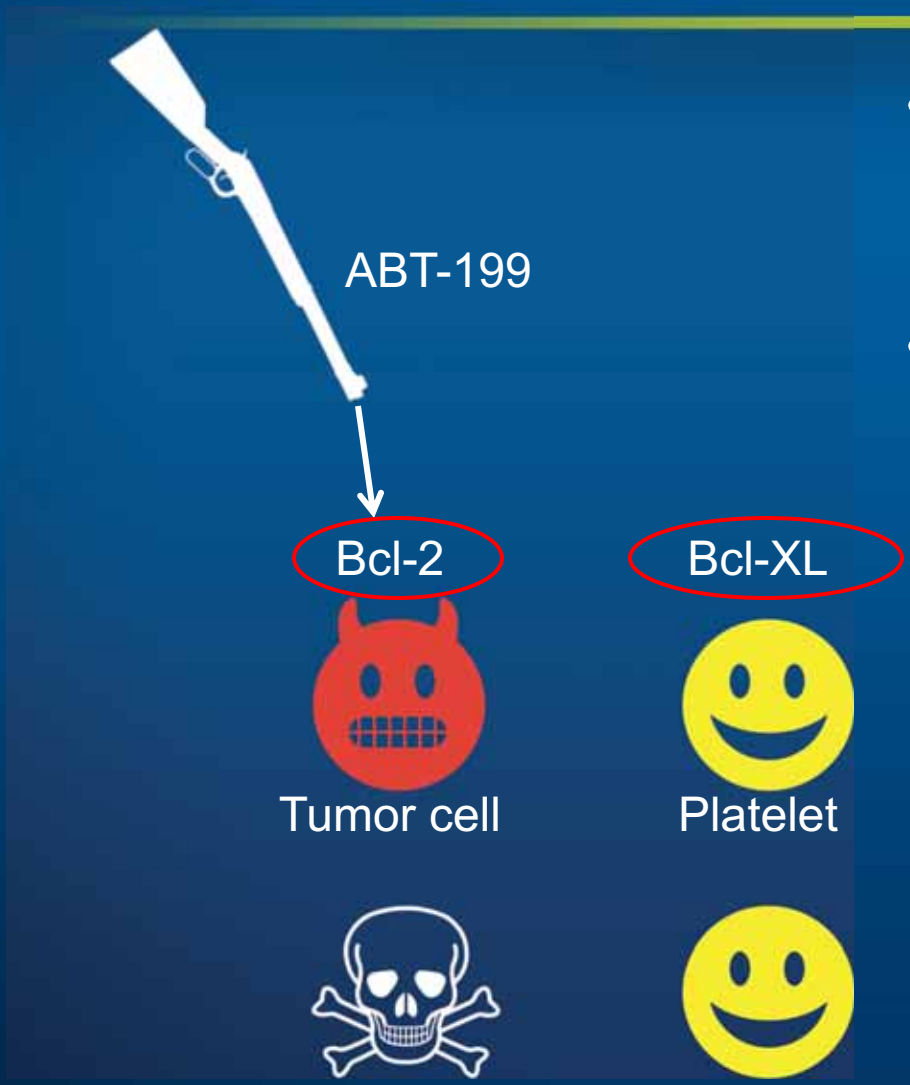
[1] Brown JR et al. International Congress on Hematologic Malignancies 2016;Abstract 386.
[2] Byrd JC et al. *N Engl J Med* 2014;371(3):213-23.

Venetoclax

- **Mechanism of action:**
  - An orally available Bcl-2 inhibitor
- **Indication:**
  - For the treatment of CLL in patients who carry a del(17p) mutation and who have received at least 1 prior therapy
- **Recommended dose:**
  - 20 mg orally once daily for 7 days, followed by a weekly ramp-up dosing schedule to the recommended dose of 400 mg. Administer with food

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm495253.htm
Venetoclax package insert, April 2016

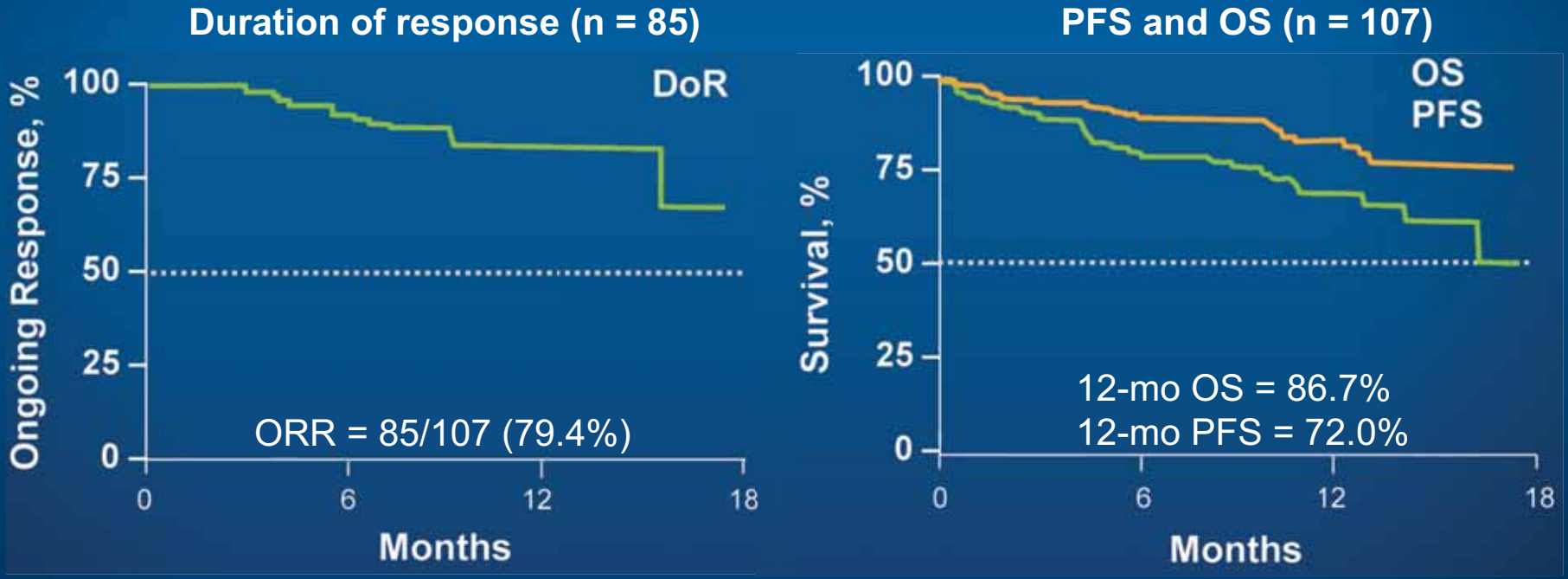
Mechanism of Action of Venetoclax (ABT-199)



- Bcl-2 functions to prevent cell death by apoptosis
- Venetoclax is specific for Bcl-2 and inhibits its function, thereby removing the block on apoptosis

Adapted from Davids MS, Letai A. *Cancer Cell* 2013;23(2):139-41.

Pivotal Phase II Trial of Venetoclax Monotherapy in R/R CLL with Del(17p)



- 18/45 (40%) patients achieved MRD negativity in peripheral blood.
- 6/10 (60%) patients with available bone marrow MRD results were MRD-negative in the bone marrow.

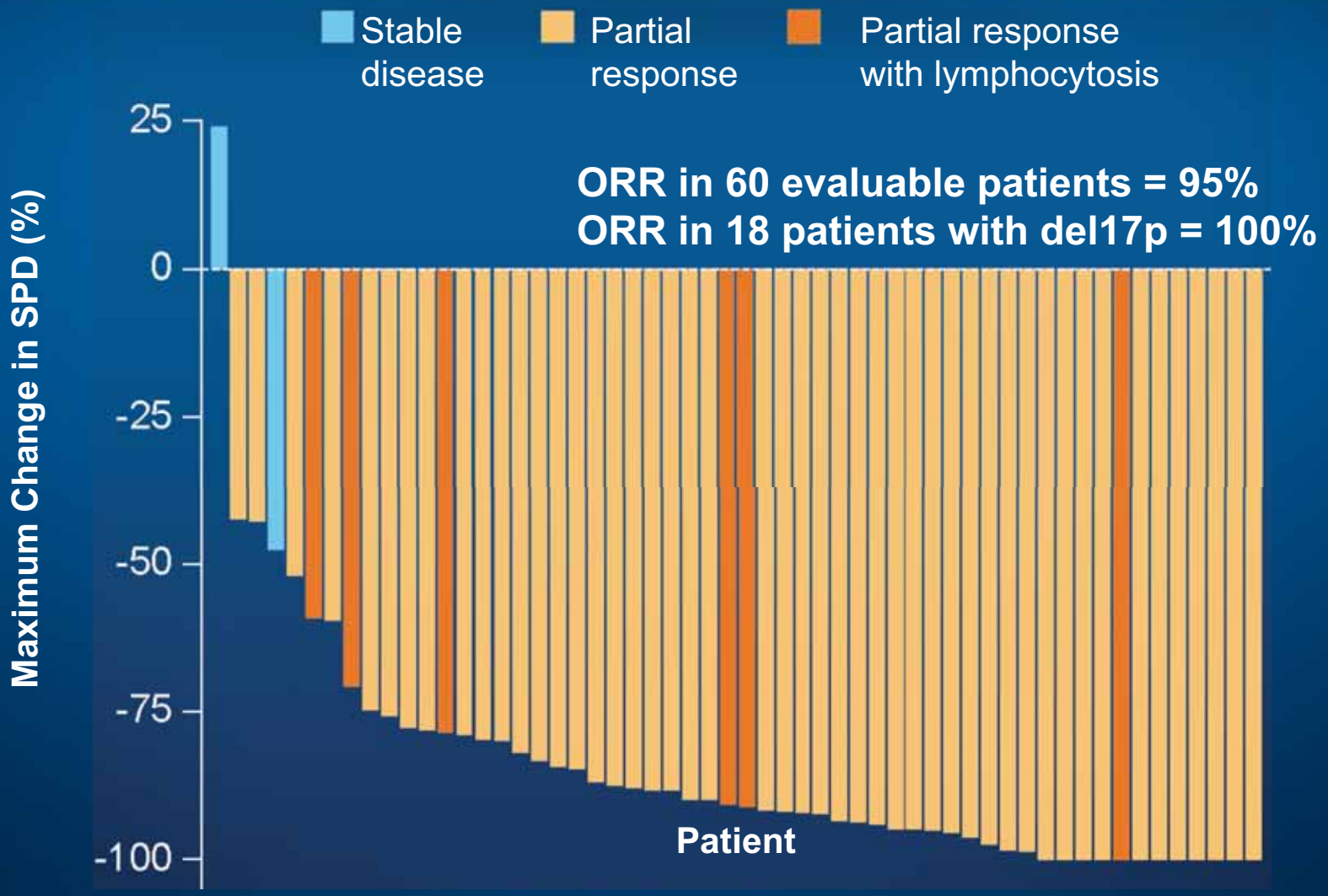
Stilgenbauer S et al. *Lancet Oncol* 2016;17(6):768-78.

Recommended TLS Prophylaxis and Monitoring During Venetoclax Therapy

Tumor burden		Prophylaxis		Blood chemistry monitoring
		Hydration	Anti-hyperuricemics	
Low	All LN <5 cm *AND* ALC <25 x 10^9/L	Oral (1.5-2 L)	Allopurinol	*Outpatient* • Pre-dose, 6-8 hrs, 24 hrs at 1st dose of 20 mg and 50 mg • Pre-dose at ramp-up doses
Medium	Any LN 5 cm to <10 cm *OR* ALC ≥25 x 10^9/L	Oral (1.5-2 L); consider additional IV	Allopurinol	*Outpatient* • Same as above • Consider hospitalization if CrCl <80 mL/min at 1st dose of 20 mg and 50 mg
High	Any LN ≥10 cm *OR* ALC ≥25 x 10^9/L *AND* Any LN ≥5 cm	Oral (1.5-2 L) and IV (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid elevated	*In hospital at 1st dose of 20 mg and 50 mg* • Pre-dose, 4, 8, 12 and 24 hrs *Outpatient at ramp-up doses* • Pre-dose, 6-8 hrs, 24 hrs

http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf

Response to Acalabrutinib in R/R CLL



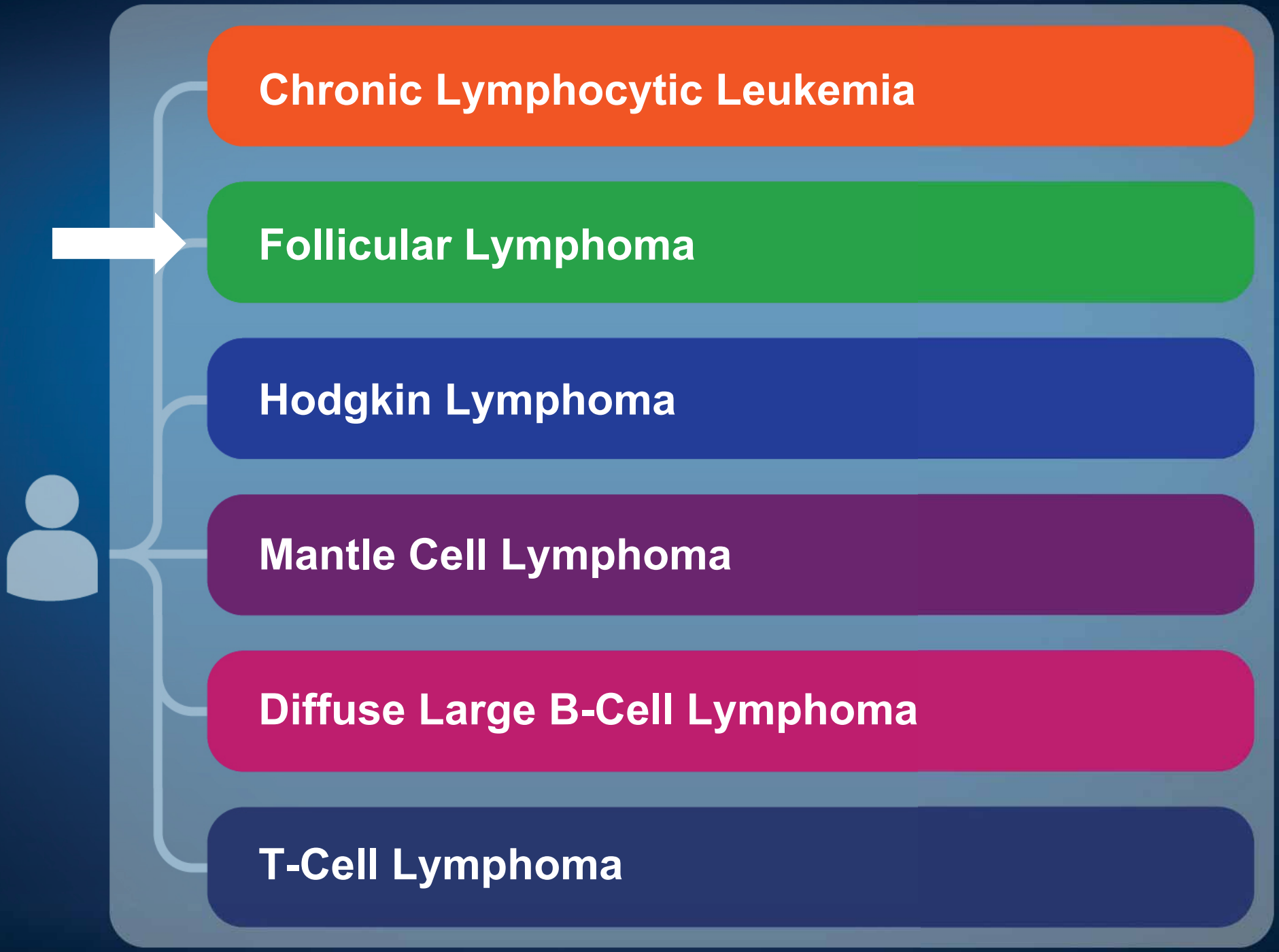
Byrd JC et al. *N Engl J Med* 2016;374(4):323-32.

Adverse Events Associated with Acalabrutinib

Adverse event (N = 61)	Any grade	Grade 3/4
Headache	43%	0%
Diarrhea	39%	2%
Increased weight	26%	2%
Pyrexia	23%	3%
Upper respiratory tract infection	23%	0%

- Major hemorrhage or atrial fibrillation: 0 cases
- No clinically significant changes in the numbers of T cells, NK cells and monocytes over time

Byrd JC et al. *N Engl J Med* 2016;374(4):323-32.


Chronic Lymphocytic Leukemia
Follicular Lymphoma
Hodgkin Lymphoma
Mantle Cell Lymphoma
Diffuse Large B-Cell Lymphoma
T-Cell Lymphoma

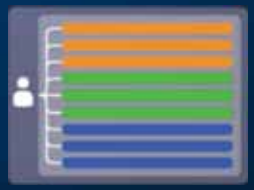
Overview of Follicular Lymphoma

- Estimated number of new cases in 2017: 15,893
- Stage at diagnosis (percent of patients who present with):
  - Stage I disease = 15%
  - Stage II disease = 14%
  - Stage III disease = 22%
  - Stage IV disease = 41%
- Five-year relative survival rate = 76%
- Ten-year relative survival rate = 62%

Cancer Facts and Figures 2017; cruk.org/cancerstats; http://www.lymphomation.org/statistics.htm#in-news; http://www.cancernetwork.com/cancer-management/non-hodgkin-lymphoma

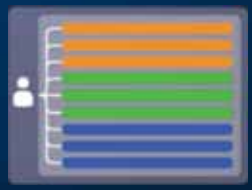
Key Determinants of Systemic Therapy Decision-Making in FL

- Extent of disease and symptoms
- Age
- Comorbidities



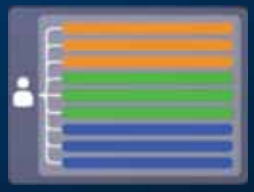
Approved Systemic Treatments and Promising Therapies in Development - FL

- Observation off treatment
- Rituximab monotherapy
- Chemotherapy/anti-CD20 Ab (bendamustine, rituximab, obinutuzumab)
- Lenalidomide/rituximab (R^2)
  - Use as maintenance; disease flare
- Radioimmunotherapy
- Idelalisib



Key Considerations for the Management of Newly Diagnosed FL

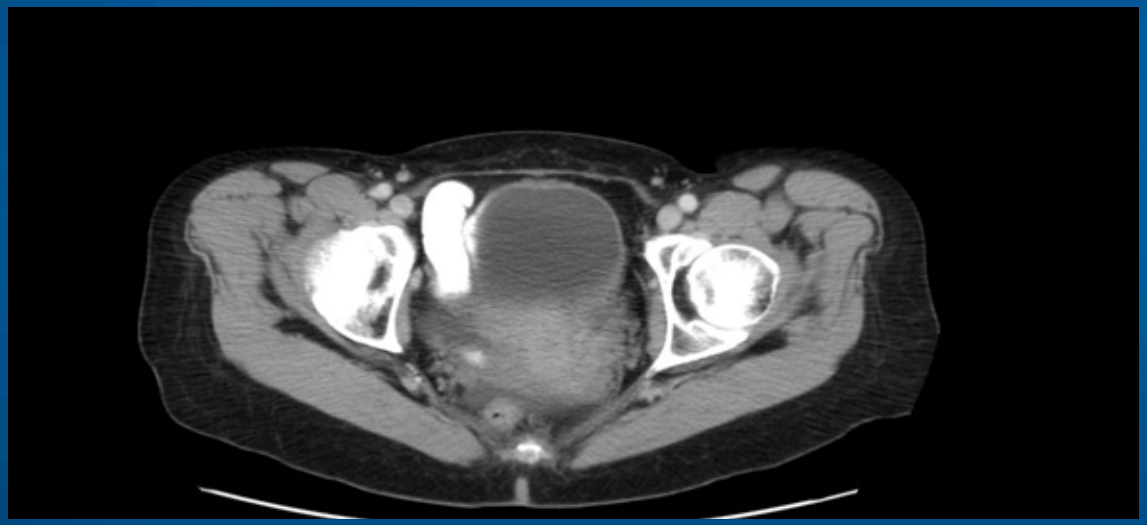
- "Watch and wait" vs rituximab monotherapy for low tumor burden
- Choice of up-front chemotherapy/anti-CD20 antibody regimen
- Use of maintenance rituximab
- Role of obinutuzumab in the management of treatment-naïve and relapsed FL
- Nonprotocol role of rituximab/lenalidomide (R^2)
- Appropriate integration of idelalisib into current treatment algorithms
- Ongoing investigation of other novel agents and strategies



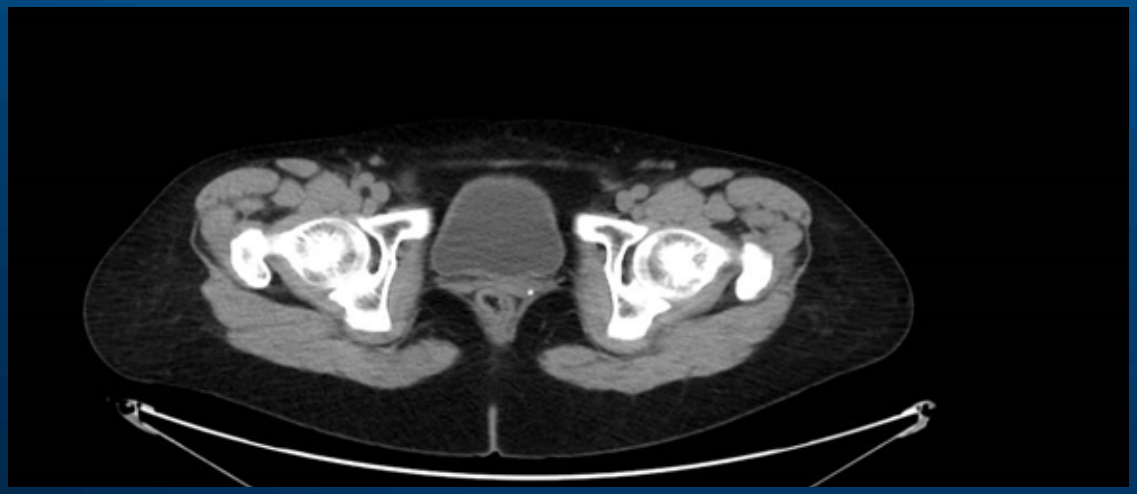
61-Year-Old Woman with Grade I FL (Ms Leake)

- 2008: Diagnosis of Stage IIA Grade I FL after CT scan of abdomen due to continued periumbilical cramping revealed adenopathy
  - Staging CT scans showed adenopathy in mesenteric nodes (2.3-cm x 1.6-cm and multiple subcentimeter nodes) and in node anterior to aortic bifurcation (1.3 cm x 0.8 cm)
  - No adenopathy in the neck, chest or pelvis noted
  - Patient did not have any B symptoms other than low-grade temperatures
- Rituximab (R) weekly x 4 doses administered → R maintenance (q3m) for 2 years
- June 2010: Restaging CT scan showed patient was in CR
- Post-treatment CT scans continued to show CR; no residual side effects from rituximab

61-Year-Old Woman with Grade I FL (Ms Leake)



Initial CT scan



Post-rituximab CT scan showing CR

March 29, 2017 Press Release

FDA Advisory Committee Unanimously Recommends Approval of Subcutaneous Rituximab

- The proposed indications for the treatment include previously untreated follicular lymphoma (FL), previously untreated diffuse large B-cell lymphoma (DLBCL), relapsed or refractory low-grade or follicular lymphoma and previously untreated and relapsed or refractory chronic lymphocytic leukemia (CLL)
- Subcutaneous rituximab can be administered in 5-7 minutes compared to 1.5 hours or more for intravenous rituximab
- A final approval decision is expected from the FDA by June 26, 2017

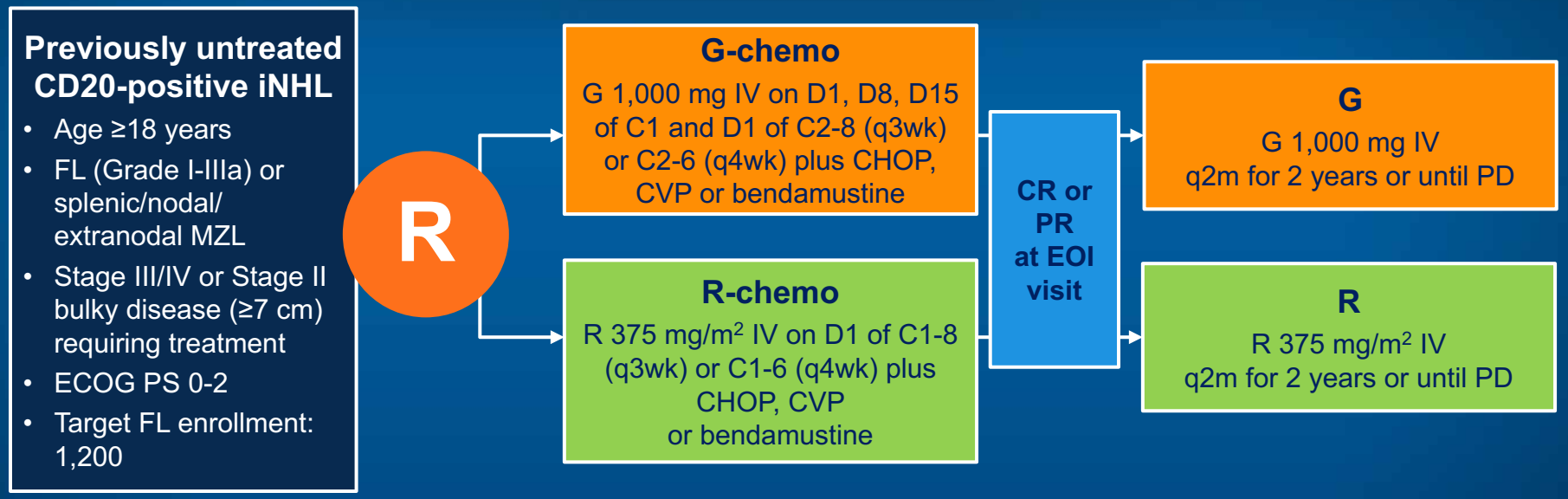
https://www.gene.com/media/press-releases/14658/2017-03-29/fda-advisory-committee-unanimously-recom

Phase III SABRINA Study: Efficacy of IV vs Subcutaneous Rituximab in Patients with Treatment-Naïve CD20+ Grade I-IIIa FL

Endpoint	Rituximab IV (N = 205)	Rituximab SC (N = 205)
ORR after induction	84.9%	84.4%
CR/CRu after induction	32.2%	32.2%
ORR after maintenance	78.1%	77.9%
CR/CRu after maintenance	56.2%	50.6%
PFS (% with event)	27.8%	24.4%
	HR = 0.84, p = 0.3696	
OS (% with event)	9.8%	7.8%
	HR = 0.81, p = 0.5398	

Davies AJ et al. *Proc ASH* 2016;Abstract 1103.

GALLIUM: Phase III Trial of Obinutuzumab-Based Induction and Maintenance in Newly Diagnosed FL



	G-Chemo (n = 601)	R-Chemo (n = 601)	HR (*p*-value)
3-year PFS rate	80.0%	73.3%	0.66 (0.0012)
3-year OS rate	94.0%	92.1%	0.75 (0.21)
ORR	88.5%	86.9%	—

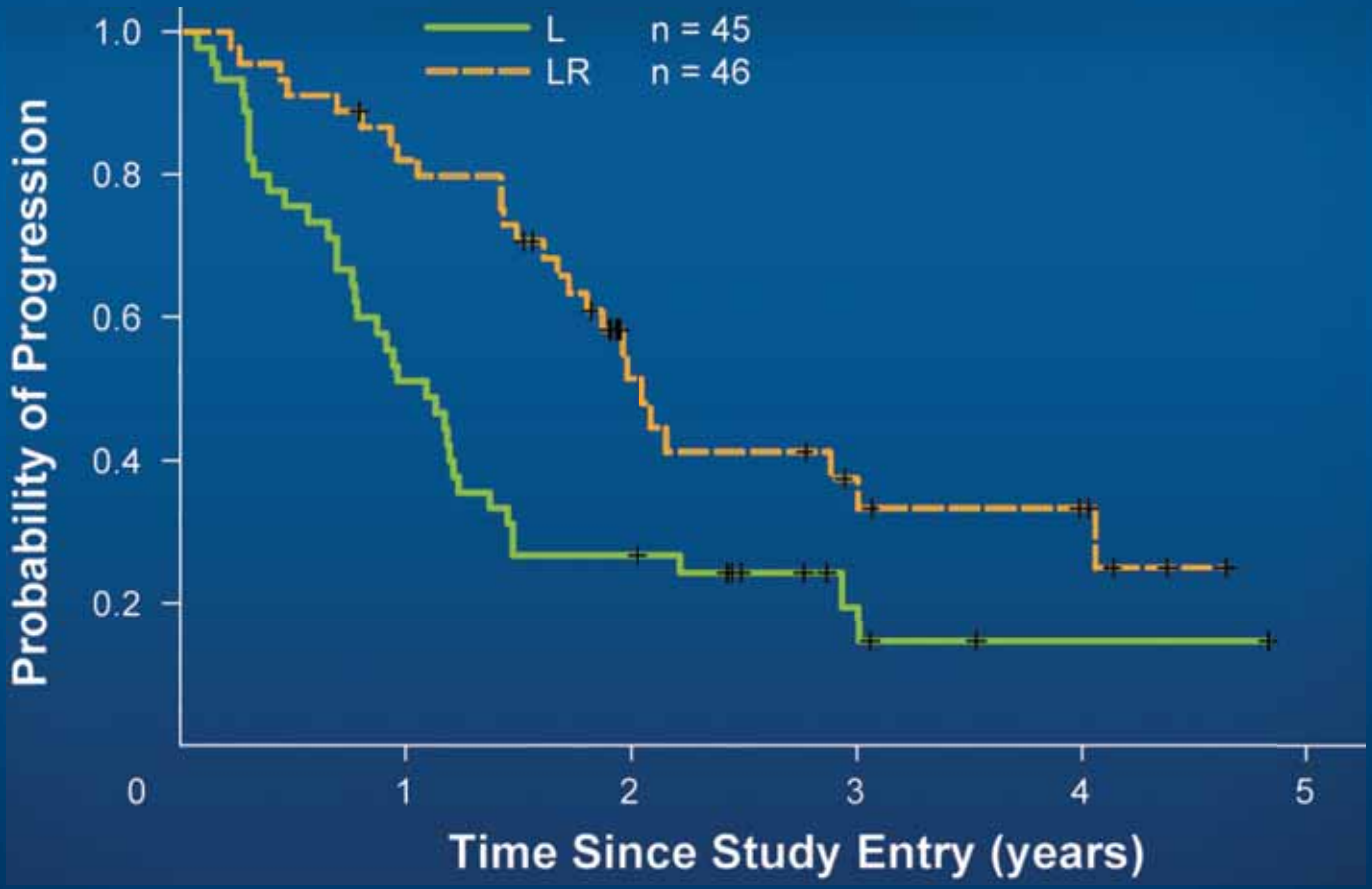
Marcus R et al. *Proc ASH* 2016;Abstract 6.

GALLIUM: Safety Summary

Adverse Events	R-Chemo (n = 597)	G-Chemo (n = 595)
Grade ≥3 AEs	67.8%	74.6%
Neutropenia	37.9%	43.9%
Febrile neutropenia	4.9%	6.9%
Thrombocytopenia	2.7%	6.1%
Infections	15.6%	20%
Infusion-related reaction	6.7%	12.4%
Grade 5 (fatal AEs)	3.4%	4.0%

Marcus R et al. *Proc ASH* 2016;Abstract 6.

CALGB 50401: A Phase II Study of Lenalidomide and Rituximab in Recurrent Follicular Lymphoma

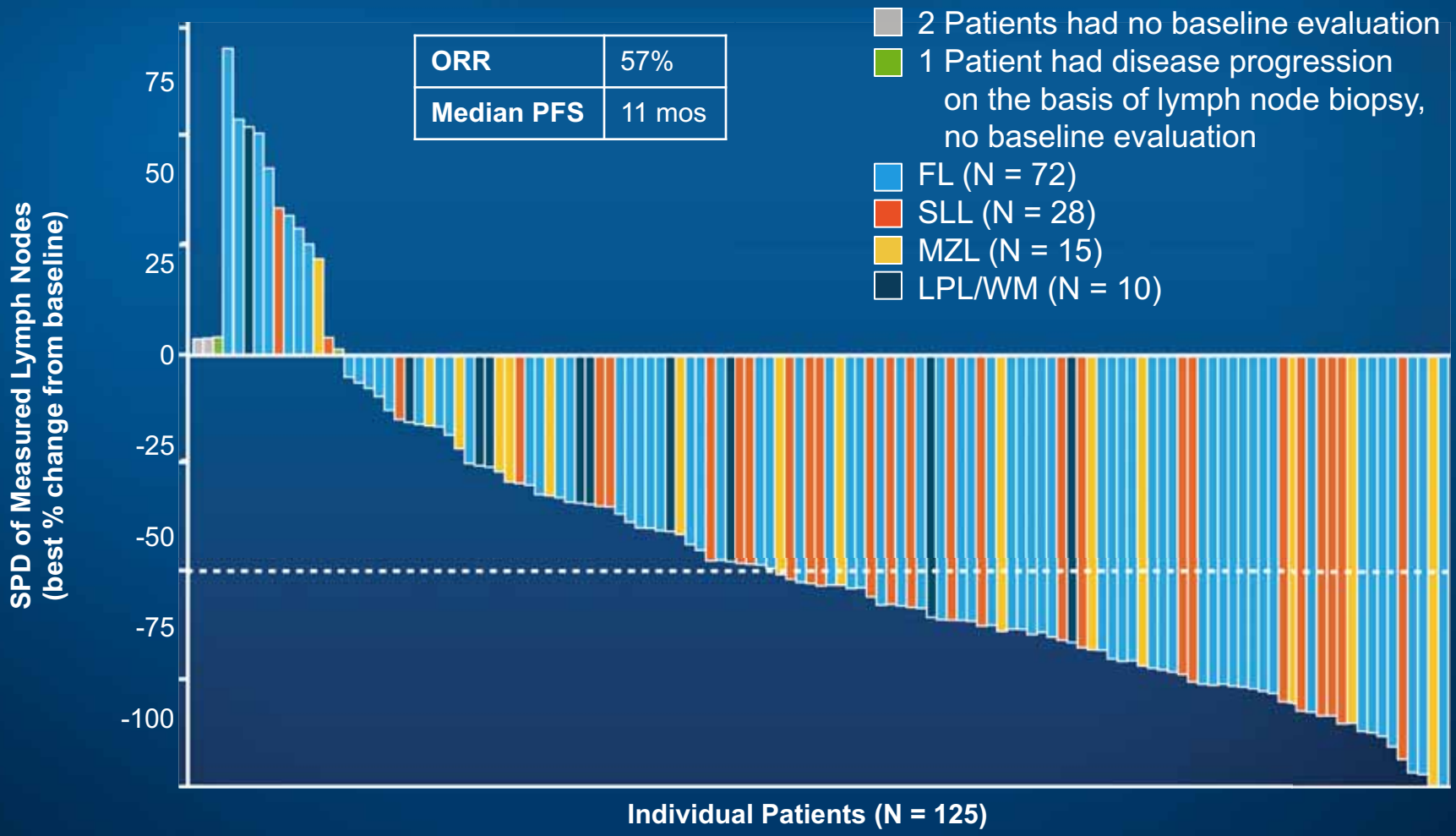


ASCO 2017, Saturday, June 3, 3:00 PM – 6:00 PM

Andorsky DJ et al. Phase IIIb randomized study of lenalidomide plus rituximab (R^2) followed by maintenance in relapsed/refractory NHL: Analysis of patients with double-refractory or early relapsed follicular lymphoma (FL). *Proc ASCO* 2017;Abstract 7502.

Leonard JP et al. *J Clin Oncol* 2015;33(31):3635-40.

Phase II Study of Idelalisib in Relapsed FL



Gopal AK et al. *N Engl J Med* 2014;370(11):1008-18.

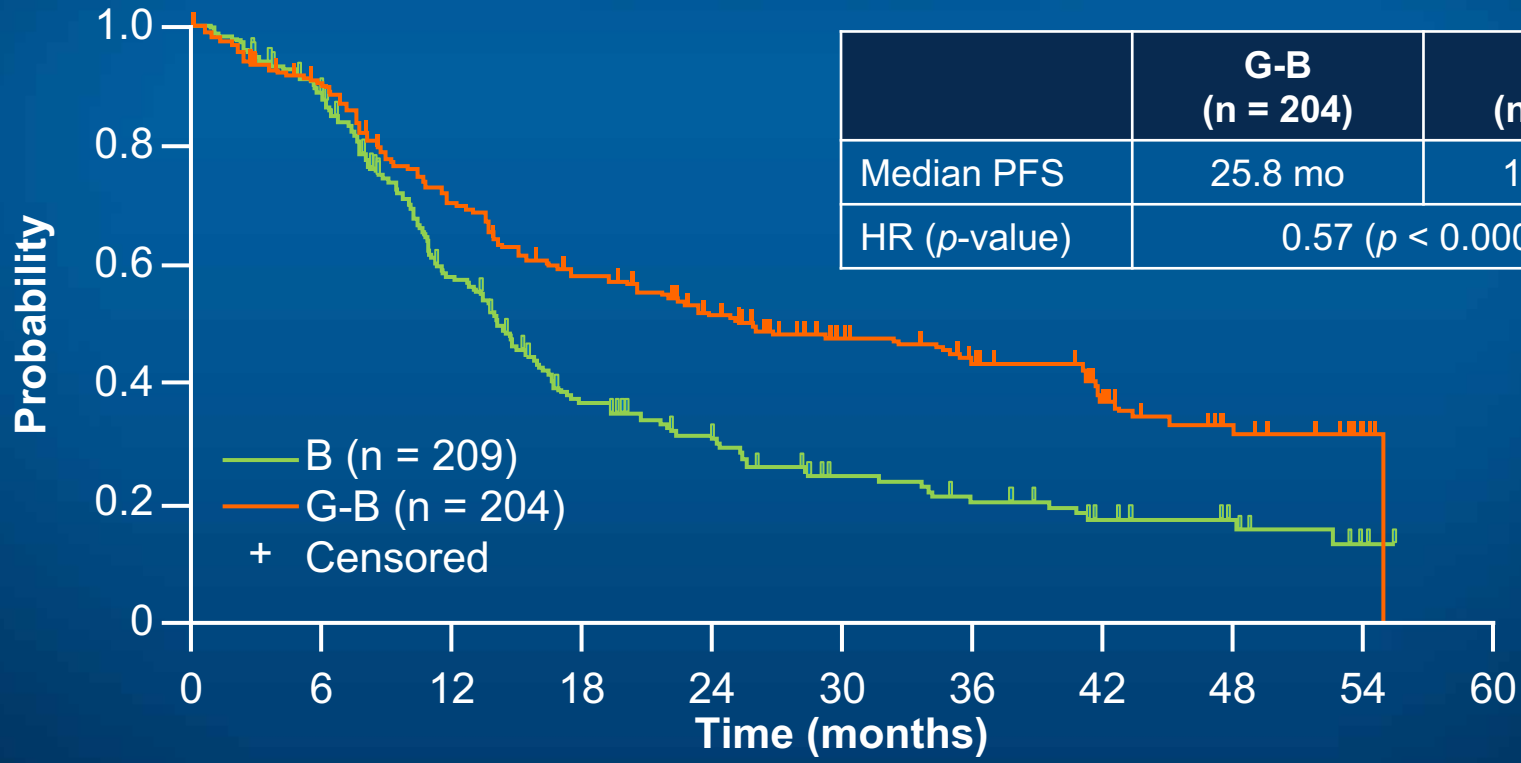
FDA Approval of Obinutuzumab in FL

- On February 26, 2016, the US Food and Drug Administration (FDA) approved obinutuzumab for use in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of follicular lymphoma (FL) in patients who experienced relapse after, or are refractory to, a rituximab-containing regimen.

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm488013.htm
Obinutuzumab package insert, April 2016

GADOLIN: Updated Efficacy Analysis of Obinutuzumab and Bendamustine (G-B) in Rituximab-Refractory Indolent NHL

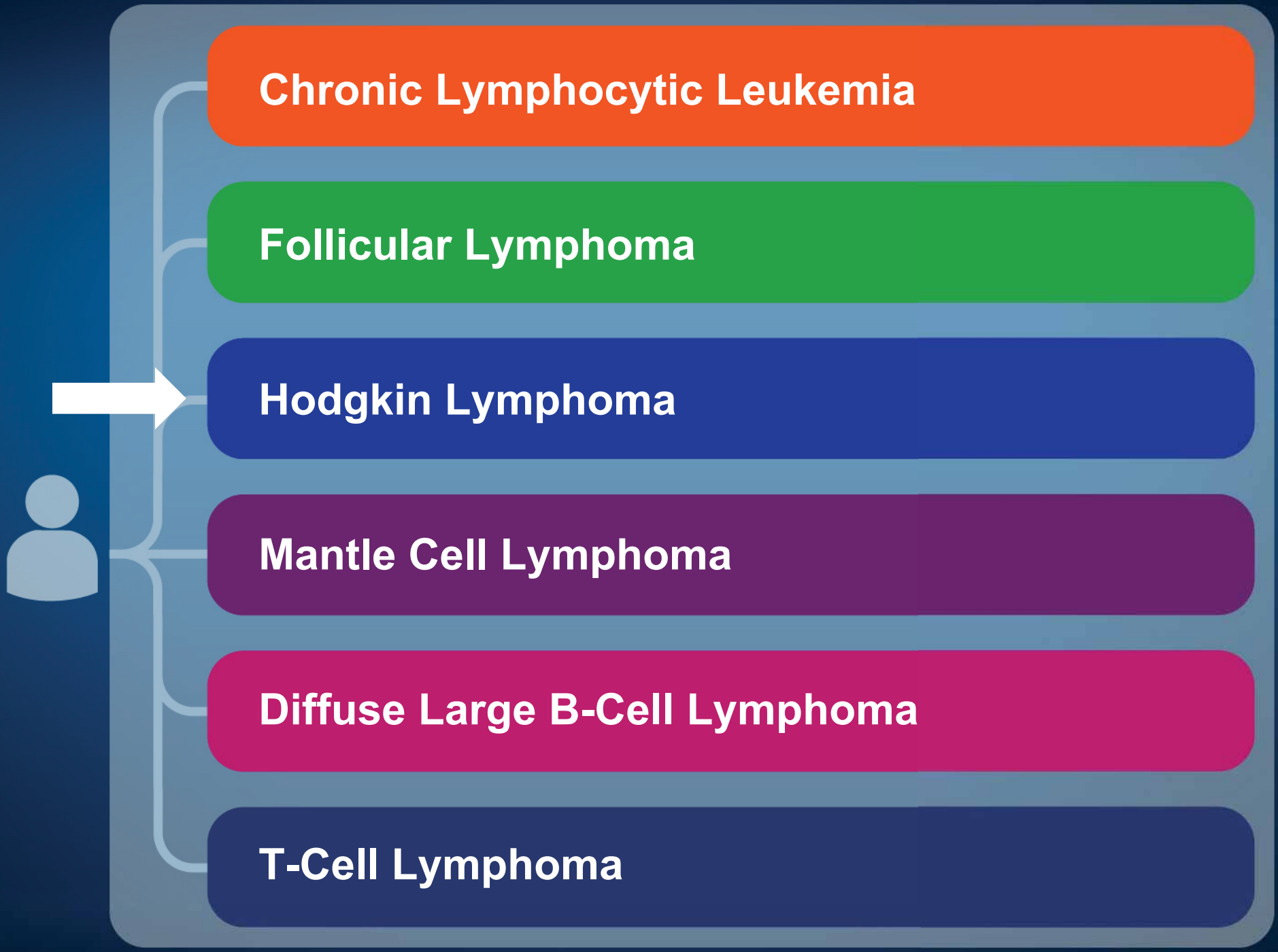
PFS (investigator-assessed, overall population iNHL)



	G-B (n = 204)	B (n = 209)
Median PFS	25.8 mo	14.1 mo
HR (*p*-value)	0.57 ($p < 0.0001$)	

- In patients with FL:
  - Median PFS was improved with G-B (25.3 mo vs 14.0 mo, HR = 0.52, $p < 0.0001$)
  - Median OS was significantly improved with G-B (Not reached vs 53.9 mo, HR = 0.58, $p = 0.0061$)

Cheson BD et al. *Proc ASH* 2016;Abstract 615.


Chronic Lymphocytic Leukemia
Follicular Lymphoma
Hodgkin Lymphoma
Mantle Cell Lymphoma
Diffuse Large B-Cell Lymphoma
T-Cell Lymphoma

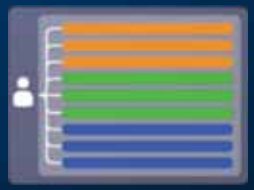
Overview of Hodgkin Lymphoma

- Estimated number of new cases and deaths in 2017:
  - New cases = 8,260
  - Deaths = 1,070
- Stage at diagnosis (percent of patients who present with):
  - Stage I disease = 16%
  - Stage II/III disease = 40%
  - Stage IV disease = 40%
- 56% men, 44% women
- Five-year survival estimates (2007-2013) = 86.4%
- Most commonly diagnosed in patients aged 20-34 (median age at diagnosis: 39)

Cancer Facts and Figures 2017; cruk.org/cancerstats; SEER.cancer.gov/statfacts/html/hodg.html

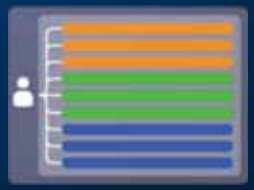
Approved Systemic Treatments and Promising Therapies in Development - HL

- Chemotherapy: ABVD
- Autologous stem cell transplantation
- Brentuximab vedotin
- Anti-PD-1 antibodies (nivolumab, pembrolizumab)



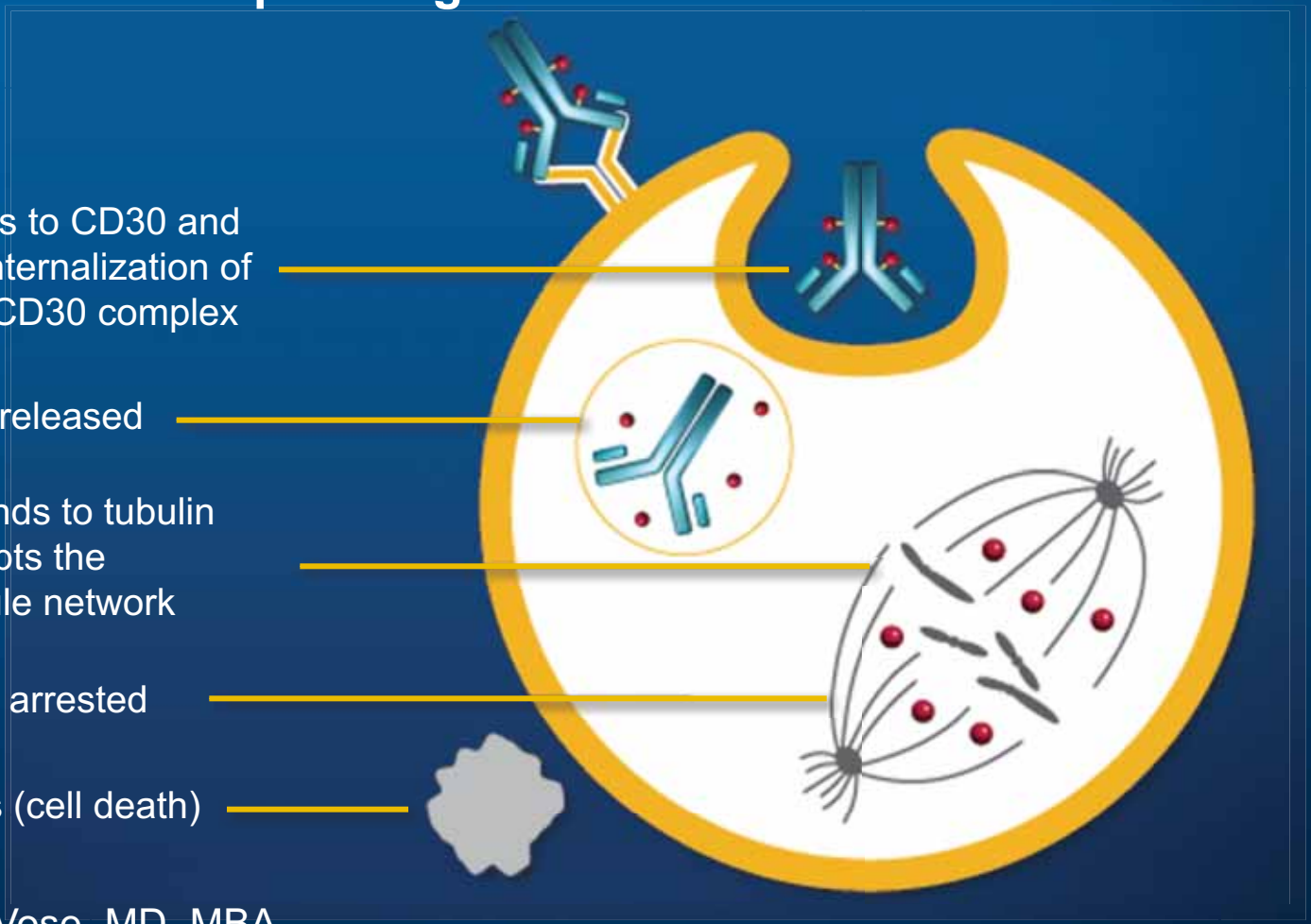
Key Considerations in the Management of Newly Diagnosed HL

- Disease stage and histologic subtype
- Patient age
- Comorbidities
- Clinical management of early-stage classical HL
  - Long-term effects of radiation therapy for localized disease
- Relative benefits and risks of various combination chemotherapy regimens for newly diagnosed advanced-stage HL
  - Recognition and management of bleomycin-induced pneumonitis



Mechanism of Action of Brentuximab Vedotin

Brentuximab vedotin is an antibody-drug conjugate (ADC) targeted to cells expressing CD30 on their surface



Courtesy of Julie M Vose, MD, MBA.

SGN35-015: A Phase II Trial of BV with DTIC or Bendamustine in Patients with Untreated HL (≥60 Years)

	BV (N = 27)	BV + DTIC (N = 22)	BV + bendamustine (N = 20)
ORR, n (%)	24 (92)	21 (100)	17 (100)
CR rate, n (%)	19 (73)	13 (62)	15 (88)
Median PFS, months	10.5	Not reached	Not reached
PFS rate at 18 months	34%	55%	57%
Median OS, months	40.1	Not reached	Not reached
OS rate at 18 months	88%	94%	75%

Friedberg JW et al. *Proc EHA* 2016;Abstract P023.

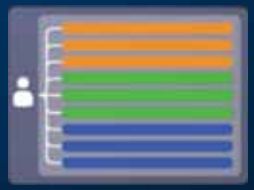
Ongoing Evaluation of Brentuximab Vedotin in Other Clinical Settings

- **Front Line**
  - ECHELON-1: A Phase III trial of BV + AVD versus ABVD in advanced classical HL (cHL)
  - AHOD1331: A Phase III trial of BV and combination chemotherapy for untreated high-risk cHL
  - BREACH: A Phase II trial of BV + AVD versus ABVD in untreated HL with unfavorable characteristics
- **First-Line Salvage**
  - Phase II study of BV in relapsed/refractory HL prior to ASCT (NCT02244021)[1]

www.clinicaltrials.gov. Accessed April 2017; [1] Chen RW et al. *Proc ASH* 2014;Abstract 501.

Key Considerations in the Management of Recurrent HL

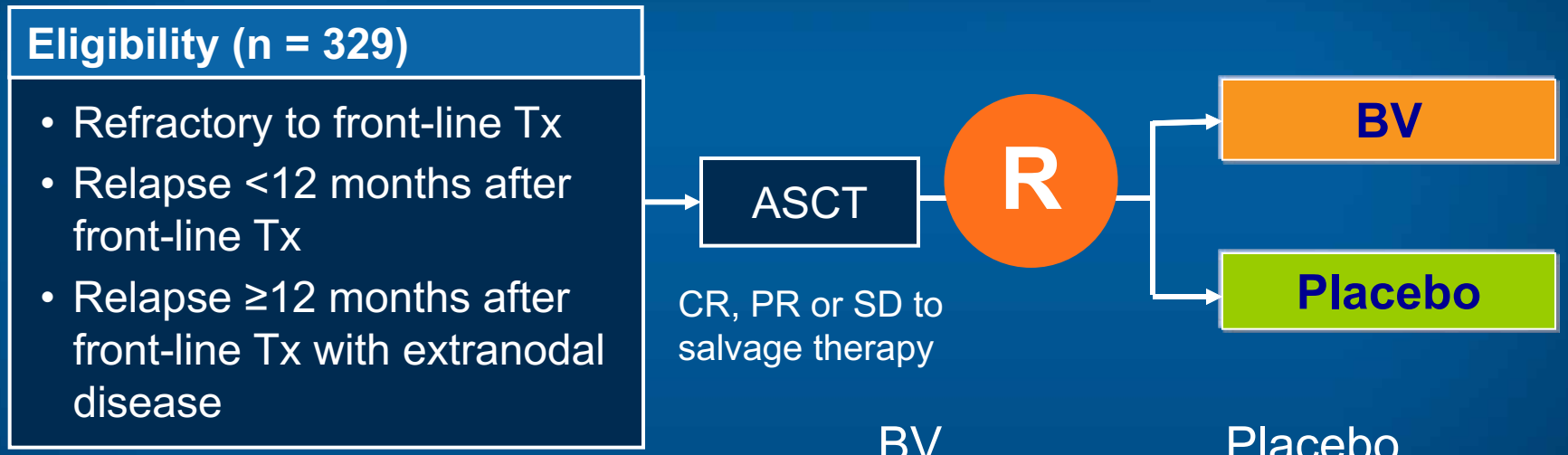
- Fitness to receive autologous stem cell transplant
- Utility of post-transplant consolidation
- Selection and sequencing of available therapeutic options



45-Year-Old Woman with Stage IV cHL (Ms Leake)

- 2011: Patient presented with jaundice and adenopathy of the right cervical lymph node
  - Biopsy results consistent with classic nodular sclerosing HL and diagnosis of Stage IVB mixed cellularity HL
- February 2011: COPP x 5 cycles
- November 2011−July 2012: Two separate rounds of BV re-initiated after disease progression noted on restaging scans
- January 2014−April 2014: ICE x 3 cycles → CR
  - ASCT was recommended, but patient elected not to proceed with transplant
- March 2015: BV x 3 cycles; Tx stopped due to worsening neuropathy
- Patient currently on nivolumab
  - Restage in 1 month and consider ASCT
- Multitude of ongoing psychosocial issues

AETHERA Phase III Trial: BV After Transplant



	BV	Placebo
• Median PFS	42.9 mo	24.1 mo

- PFS benefit consistent across subgroups and maintained after 3 years
- No OS benefit at interim analysis
- BV: Higher rates of peripheral neuropathy, neutropenia

Moskowitz CH et al. *Lancet* 2015;385(9980):1853-62; Sweetenham J et al. *Proc ASH* 2015;Abstract 3172.

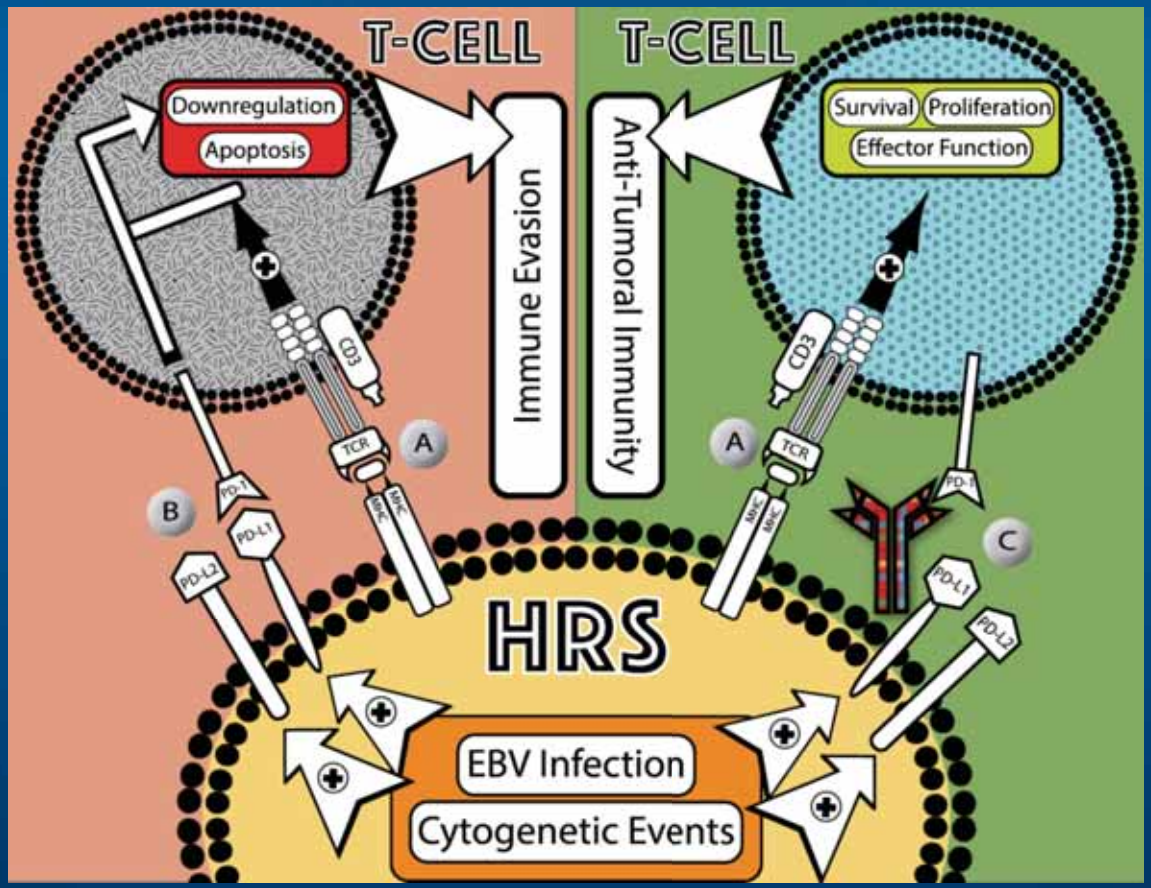
FDA Approval of BV as Consolidation Treatment

- On August 17, 2015, the US FDA approved brentuximab vedotin for the postautologous hematopoietic stem cell transplantation (auto-HSCT) consolidation treatment of classical Hodgkin lymphoma with high risk of relapse or progression.
- The recommended dose and schedule for brentuximab vedotin as postauto-HSCT consolidation is 1.8 mg/kg administered intravenously over 30 minutes every 3 weeks. Treatment should be initiated within 4 to 6 weeks after auto-HSCT or upon recovery from transplantation. The patient should continue treatment until a maximum of 16 cycles, disease progression or unacceptable toxicity.

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm458815.htm

Targeting the PD-1/PD-L1 Axis in HL

Binding of PD-1 receptor on T-cell with its ligands on tumor cells leads to decreased T-cell function and apoptosis

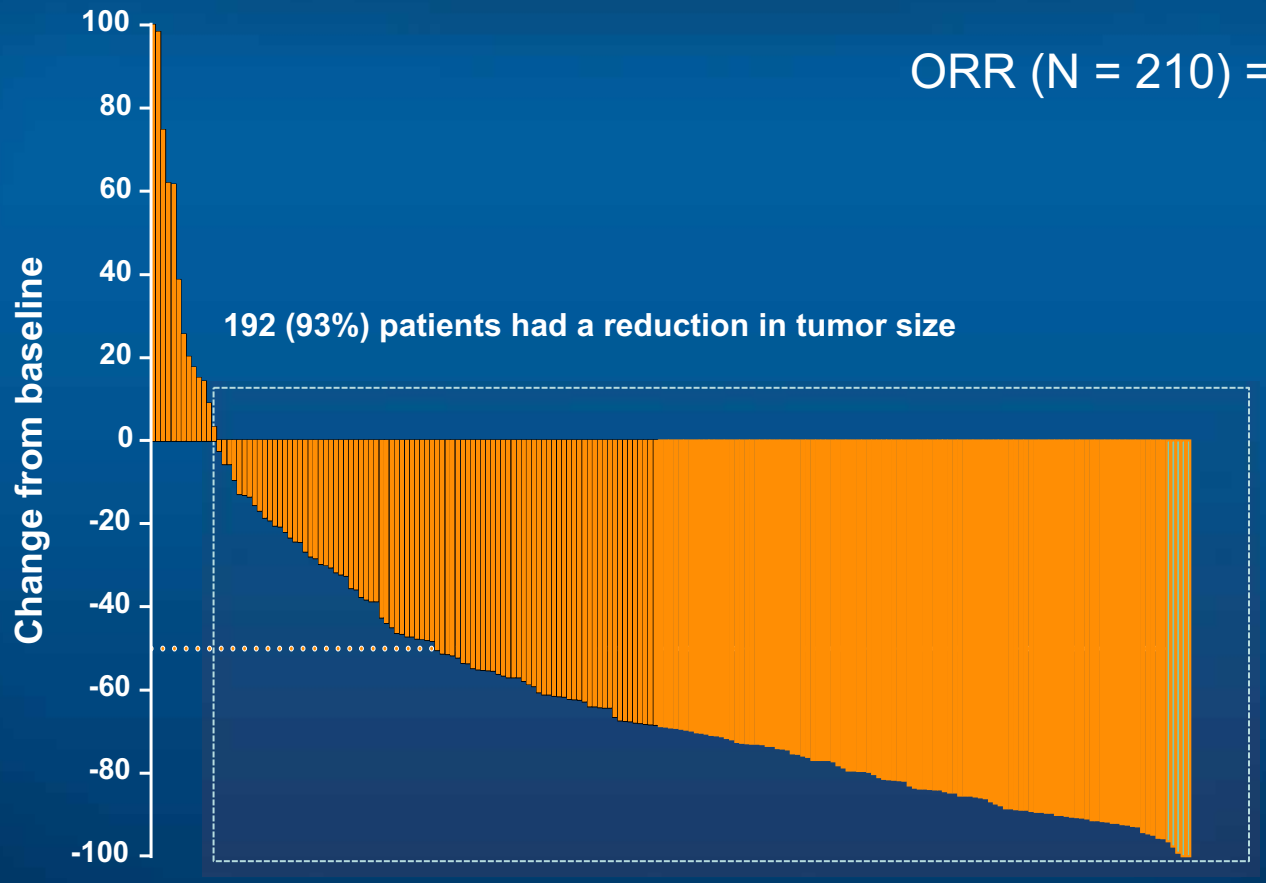


PD-1 antibodies restore antitumoral immunity by disrupting PD-1/PD-L1 interaction

Malignant Hodgkin and RS cells overexpress PD-L1/L2 ligands (due to cytogenetic events, infection with EBV)

Villasboas JC, Ansell SA. *Cancer J* 2016;22(1):17-22.

KEYNOTE-087: A Phase II Study of Pembrolizumab in Relapsed cHL



- Adverse events (any grade): hypothyroidism (12.4%), pneumonitis (2.9%), diarrhea (7.1%)

Moskowitz CH et al. *Proc ASH* 2016;Abstract 1107.

CheckMate 205: Phase II Study of Nivolumab in cHL After Failure of ASCT and BV

	Survival (by independent review)
Six-month PFS	76.9%
Six-month OS	98.7%

Younes A et al. *Lancet Oncol* 2016;17(9):1283-94.

Ongoing Evaluation of Immune Checkpoint Inhibitors in HL

- **KEYNOTE-204**: A Phase III trial of pembrolizumab or BV in relapsed/refractory cHL
- **NCT02758717**: A Phase II trial of nivolumab + BV in patients with newly diagnosed HL who are over the age of 60 years
- **NCT02572167**: A Phase I/II trial of nivolumab + BV in relapsed/refractory HL after failure of front-line therapy

www.clinicaltrials.gov. Accessed May 2017.

64-Year-Old Man with Stage III cHL (Ms Moran)

- November 2016
  - Altered mental state
  - Abdominal nodes by CT scan and biopsy of left iliac node positive for cHL (Stage III)
- February 2017: Enrollment on clinical trial of brentuximab vedotin + nivolumab in older patients (>60 years)
  - Cycle 3: Increased peripheral neuropathy
- Patient was in the process of retiring and planned to move south with his wife
  - Is now experiencing guilt over not doing what he “promised” his wife; couples counseling has been recommended

- Chronic Lymphocytic Leukemia
- Follicular Lymphoma
- Hodgkin Lymphoma
- Mantle Cell Lymphoma
- Diffuse Large B-Cell Lymphoma
- T-Cell Lymphoma

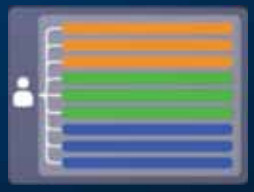
Overview of Mantle Cell Lymphoma

- Estimated number of new cases in 2017: 4,355
- Stage at diagnosis (percent of patients who present with):
  - Stage I disease = 2%
  - Stage II disease = 4%
  - Stage III disease = 9%
  - Stage IV disease = 73%
- 75%-80% men, 20%-25% women
- Five-year relative survival rate = 51%
- Ten-year relative survival rate = 34%

Cancer Facts and Figures 2016; cruk.org/cancerstats; http://www.lymphomation.org/type-MCL.htm; http://www.cancernetwork.com/cancer-management/non-hodgkin-lymphoma

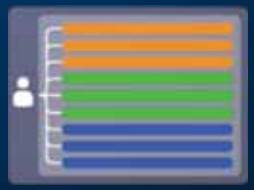
Key Considerations for the Management of Newly Diagnosed MCL

- Level of symptomatology and potential for observation off treatment
- Age and fitness to receive aggressive induction therapy, including transplant
- Selection of up-front regimen
- Maintenance rituximab after autologous transplant and in older patients
- Potential role of novel agents in the up-front setting
- Impact of gastrointestinal involvement

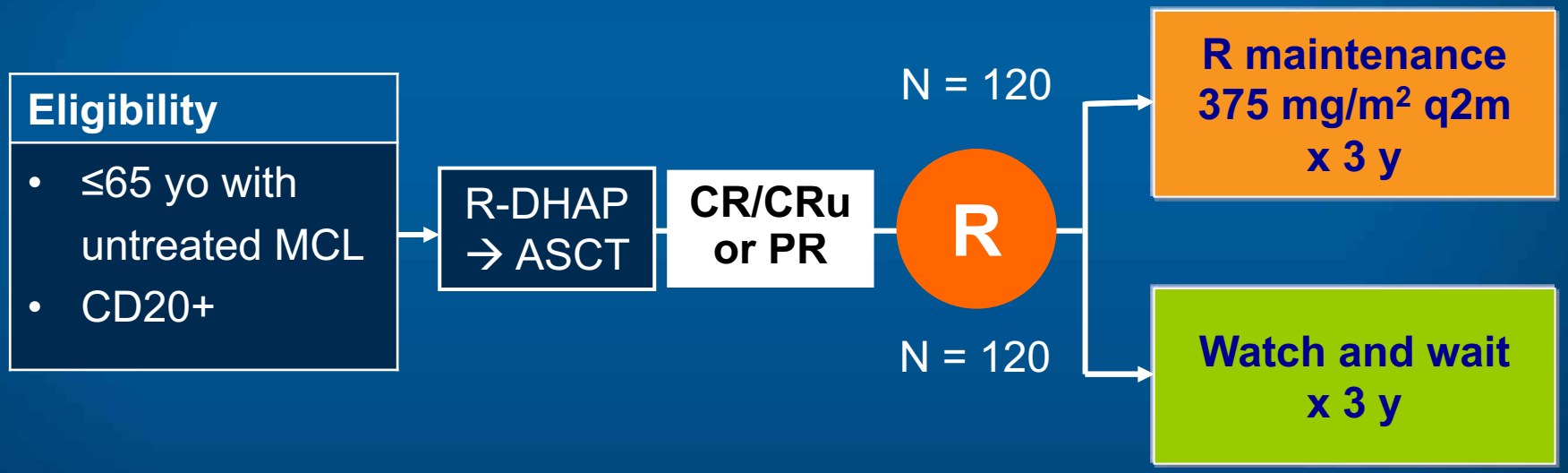


Systemic Treatments and Promising Therapies in Development - MCL

- Observation off treatment
- Chemotherapy/anti-CD20 antibody (bendamustine/rituximab)
- Ibrutinib
- Lenalidomide
- Bortezomib
- Venetoclax



LyMa Phase III Study of Maintenance Rituximab in Younger Patients

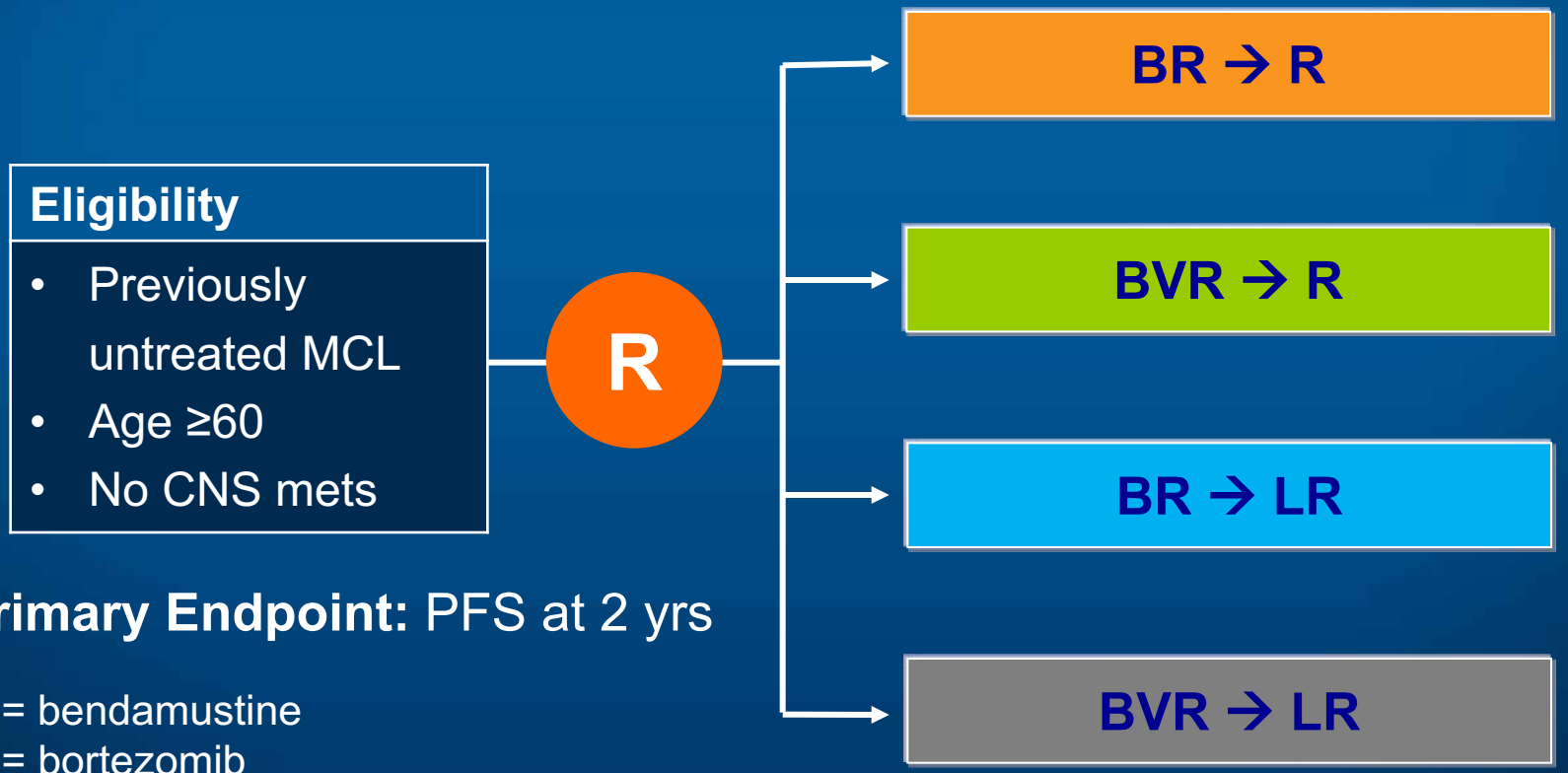


- Primary endpoint: Event-free survival
  - 4-year EFS: 78.9% (R maintenance) vs 61.4% (observation); $p = 0.0012$
- Patients in the R maintenance arm had a:
  - 60% reduction of risk of progression (HR = 0.4; $p = 0.0007$)
  - 50% reduction of risk of death (HR = 0.5; $p = 0.0454$)

Le Gouill S et al. *Proc ASH* 2016;Abstract 145. www.clinicaltrials.gov, May 2017 (NCT00921414)

ECOG-E1411 Phase II Study in Older Patients with Untreated MCL

Target Accrual: 332 (Active, recruiting)



Primary Endpoint: PFS at 2 yrs

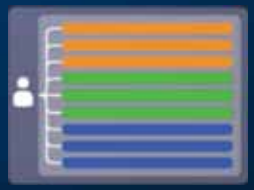
B = bendamustine
V = bortezomib
R = rituximab
L = lenalidomide

www.clinicaltrials.gov, May 2017

ClinicalTrials.gov identifier: NCT01415752

Key Considerations for the Management of Recurrent MCL

- Sequencing of available treatment options:
  - Bortezomib
  - Lenalidomide
  - Ibrutinib
- Clinical research on the use of venetoclax



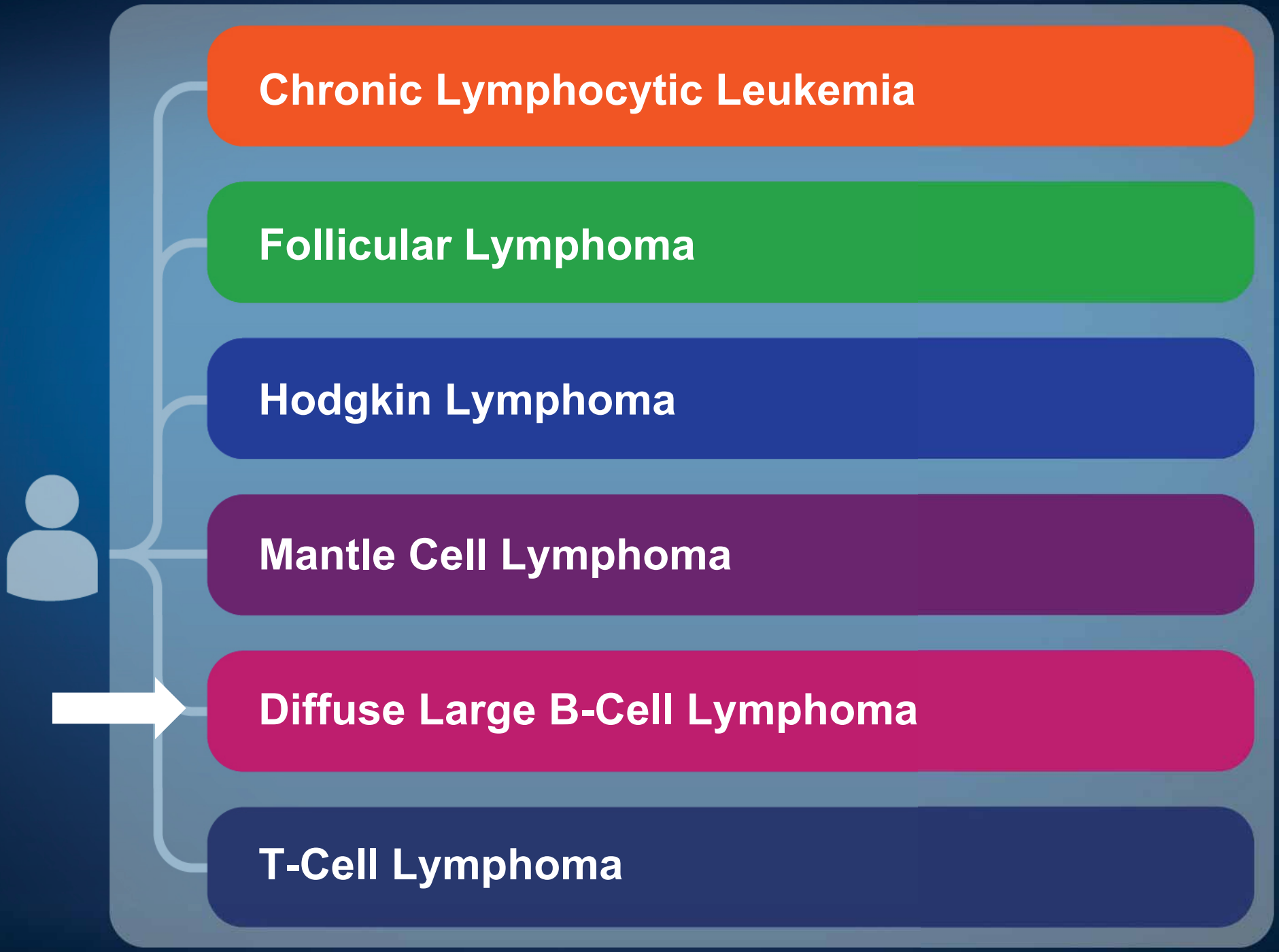
73-Year-Old Man with Stage IV MCL (Ms Leake)

- October 2007: Diagnosis of Stage IV MCL
  - Bortezomib x 1 cycle → EPOCH: Partial remission
- December 2010: B symptoms noted with marked fatigue and drenching night sweats
- January 2011–July 2011: Enrollment on clinical trial of lenalidomide + bendamustine
- August 2011–January 2012: Maintenance lenalidomide
- December 2012: Follow-up scans show disease progression
- March 2013: Enrollment on clinical trial of ibrutinib
  - Patient is in remission and remains on treatment; no tolerance issues

Ibrutinib in Relapsed/Refractory MCL

- Phase II trial of single-agent ibrutinib (N = 111)
  - ORR: 68% (CR: 21%)
  - mDoR: 17.5 months
  - mPFS: 13.9 months
  - Grade ≥3 AEs: Neutropenia, thrombocytopenia
  - Any grade AEs: Diarrhea, fatigue, nausea
- **Phase II trial of ibrutinib/rituximab (N = 50)**
  - ORR: 88% (CR: 44%)
  - ORR: 100% (CR: 54%) if Ki-67 <50%
  - Median DoR, PFS and OS: Not reached

Wang ML et al. *N Engl J Med* 2013;369(6):507-16. Wang ML et al. *Lancet Oncol* 2016;17(1):48-56.


Chronic Lymphocytic Leukemia
Follicular Lymphoma
Hodgkin Lymphoma
Mantle Cell Lymphoma
Diffuse Large B-Cell Lymphoma
T-Cell Lymphoma

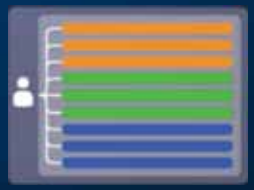
Overview of Diffuse Large B-Cell Lymphoma

- Estimated number of new cases in 2017: 22,500
- Stage at diagnosis (percent of patients who present with):
  - Stage I disease = 21%
  - Stage II disease = 17%
  - Stage III disease = 17%
  - Stage IV disease = 33%
- Five-year relative survival rate = 50%
- Ten-year relative survival rate = 46%

Cancer Facts and Figures 2016; cruk.org/cancerstats; http://www.lymphomation.org/statistics.htm#in-news; http://www.cancernetwork.com/cancer-management/non-hodgkin-lymphoma

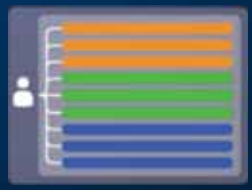
Approved Systemic Treatments and Promising Therapies in Development – DLBCL

- Chemotherapy/anti-CD20 Ab (R-CHOP)
- Lenalidomide
- Brentuximab vedotin
- Chimeric antigen receptor T-cell (CAR-T) therapy



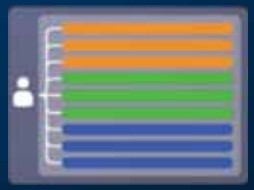
Key Considerations for the Management of Newly Diagnosed DLBCL

- Disease stage and tumor bulk
- Patient age and comorbidities
- Cell of origin and clinical implications
- Use of radiation therapy for limited-stage disease
- Role of consolidation therapy and autologous transplant
- CNS and antiviral prophylaxis



Key Considerations for the Management of Recurrent DLBCL

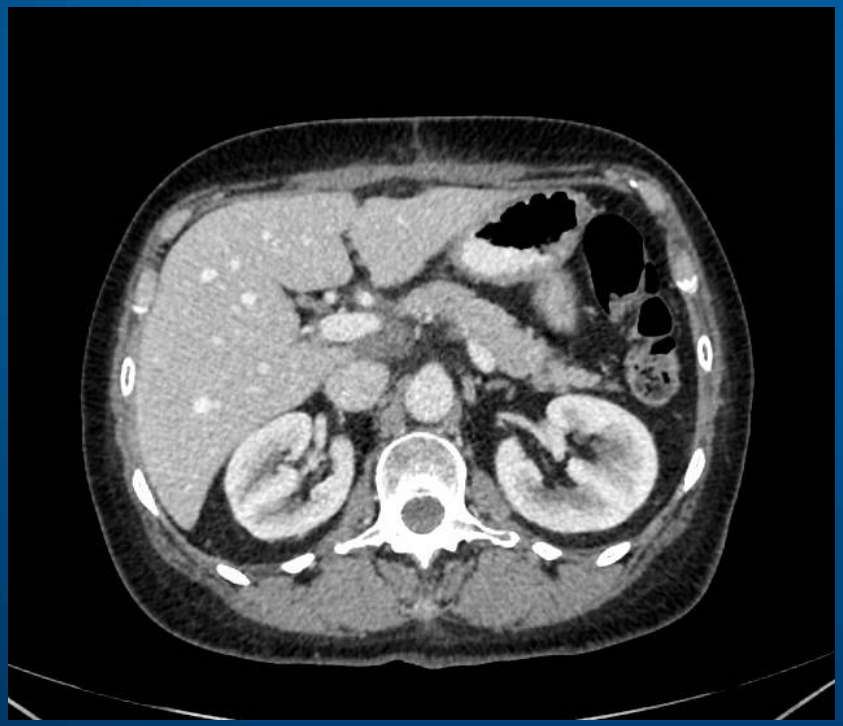
- Current role, if any, of lenalidomide
- Indications for CD30 testing and utility of BV in relapsed/refractory disease
- Novel agents currently under investigation in DLBCL



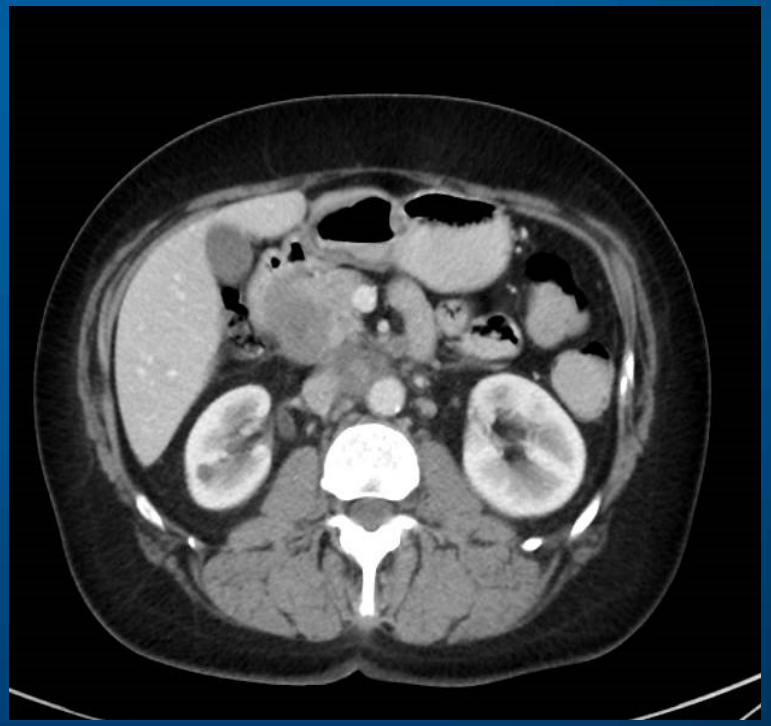
54-Year-Old Patient with Stage IVB DLBCL (Ms Leake)

- 2016: Stage IV DLBCL (GCB subtype) with extra-nodal involvement
  - Pancreas, parotid and bone involvement
  - Difficult to diagnose: Multiple biopsies were necrotic
  - PET: Marked uptake in the pancreatic head; cervical, axillary and subcarinal adenopathy
  - 30-lb weight loss, significant pain prior to diagnosis
- R-CHOP x 6, HD methotrexate (MTX) x 3, CNS prophylaxis
  - Restage after cycle 3: Clinical and radiographic response
  - Tolerated well but Grade 2 sensory neuropathy
    - Vincristine dose reduced 50%, then held
- Off all pain medication except gabapentin
- Plan to return in 6 weeks for restaging PET scan

54-Year-Old Patient with Stage IVB DLBCL (Ms Leake)

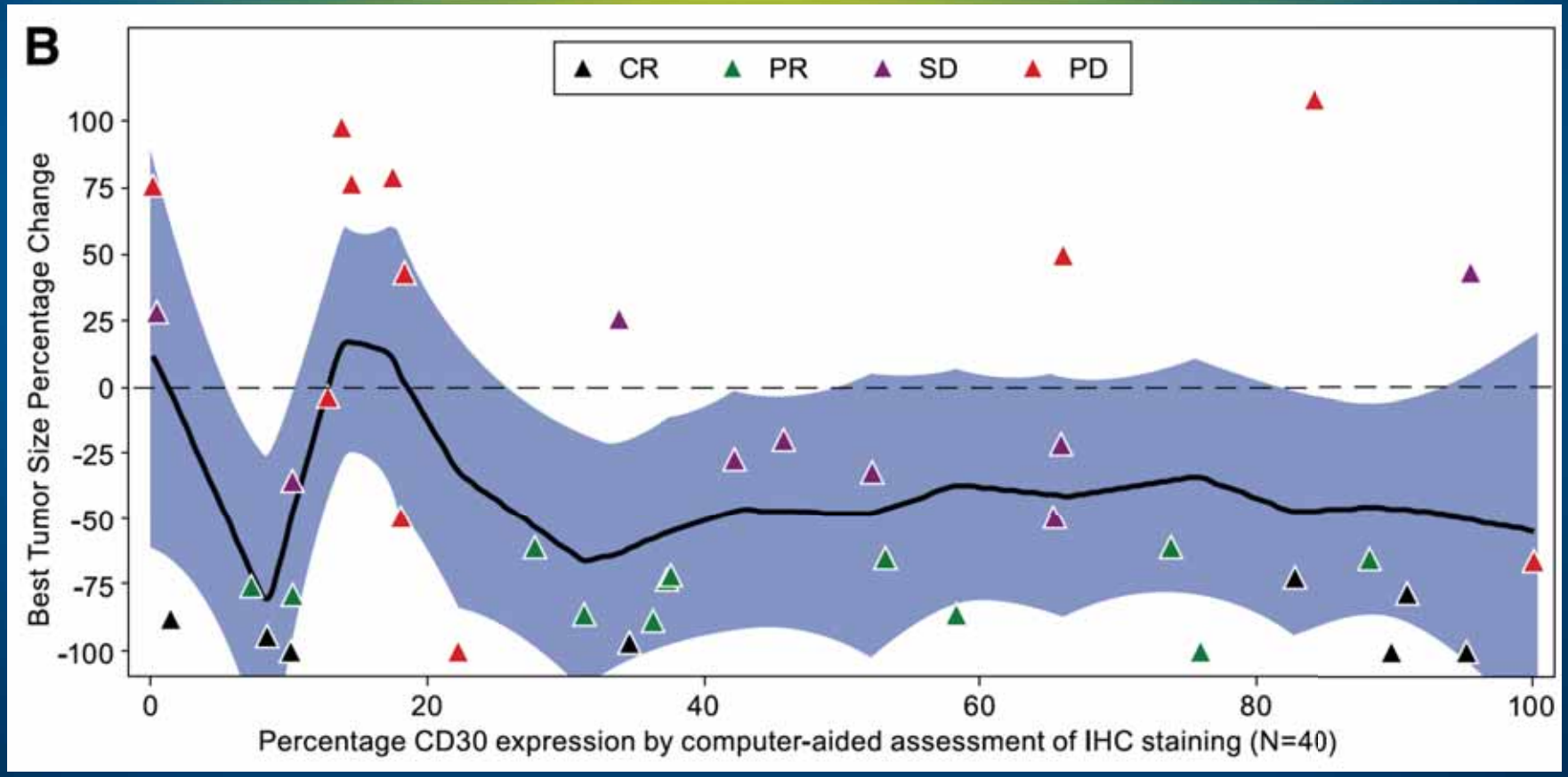


Initial CT scan



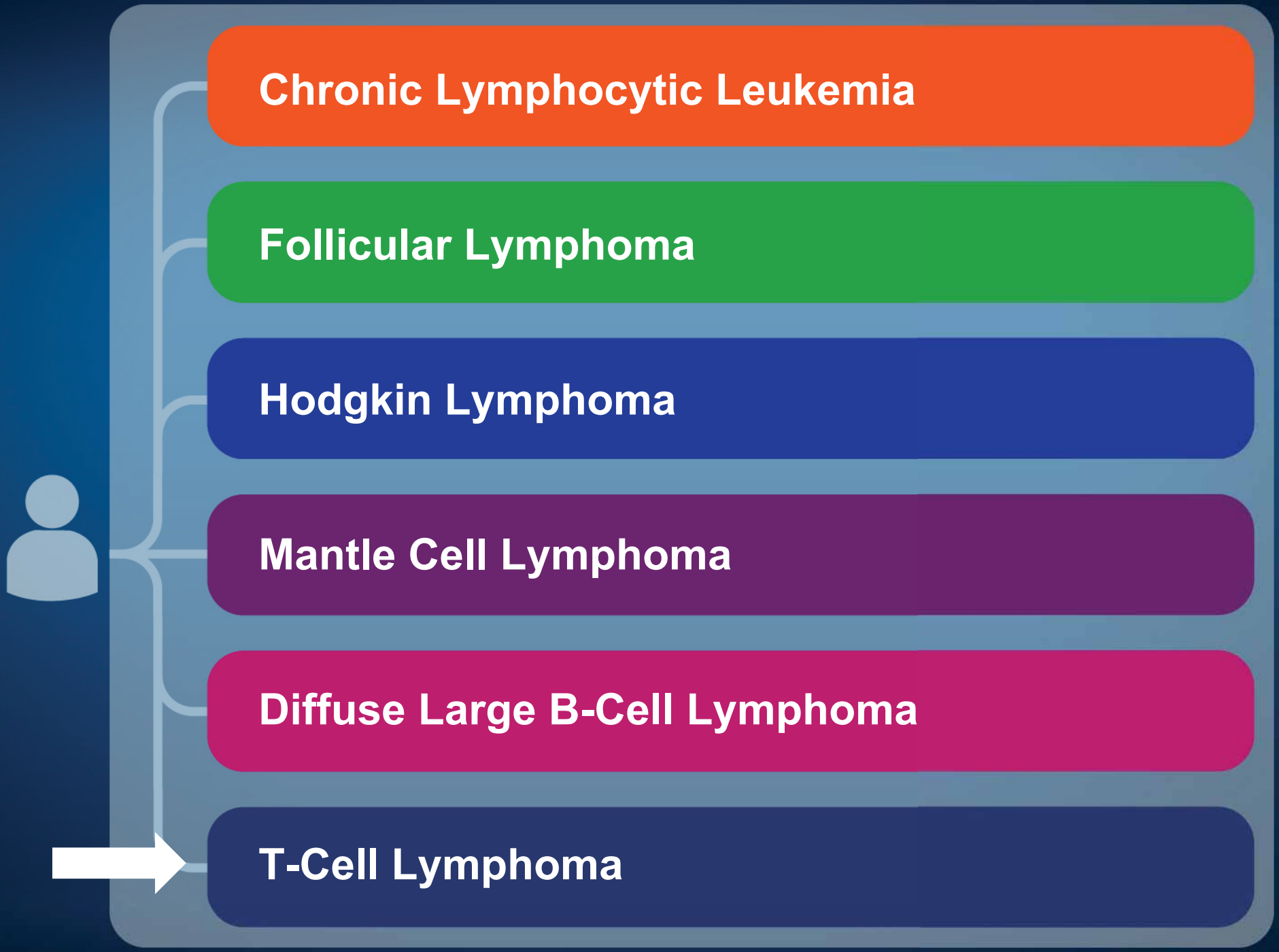
CT scan after 3 cycles of R-CHOP

Maximum Tumor Size Reduction by Quantitative CD30 Expression in Patients with DLBCL



- No statistical correlation between response and level of CD30 expression
- However, all responding patients had quantifiable CD30 by computer-assisted assessment of IHC

Jacobsen ED et al. *Blood* 2015;125(9):1394-402.


Chronic Lymphocytic Leukemia
Follicular Lymphoma
Hodgkin Lymphoma
Mantle Cell Lymphoma
Diffuse Large B-Cell Lymphoma
T-Cell Lymphoma

Overview of T-Cell Lymphomas

- Estimated number of new cases in 2017: 7,258
- Stage at diagnosis (percent of patients who present with):
  - Stage I disease = 19%
  - Stage II disease = 12%
  - Stage III disease = 15%
  - Stage IV disease = 27%
- Five-year relative survival rate = 88%
- Ten-year relative survival rate = 83%

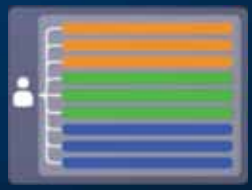
Cancer Facts and Figures 2016; cruk.org/cancerstats; http://www.lymphomation.org/statistics.htm#in-news; http://www.cancernetwork.com/cancer-management/non-hodgkin-lymphoma

Approved Systemic Treatments and Promising Therapies in Development – TCL

- Chemotherapy (CHOP)
- Autologous stem cell transplant
- Brentuximab vedotin
- Romidepsin
- Belinostat
- Pralatrexate

Key Considerations for the Management of PTCL NOS

- Disease stage and histology
- Patient age and comorbidities
- Up-front therapy and role of autologous stem cell transplant
- Sequencing of romidepsin, pralatrexate and belinostat for patients with relapsed/refractory TCL
- Role of CD30 testing; indications for treatment with BV, including in anaplastic large cell lymphoma



45-Year-Old Woman with Mycosis Fungoides (Ms Leake)

- April 2013: Patient with past medical history of psoriasis is noted to have increased lymphadenopathy during a hospitalization
  - Diagnosis of mycosis fungoides (Stage T3/N3/M0/B0, Stage IVA2)
- November 2013: Excisional biopsy confirms N3 mycosis fungoides
- December 2013: Interferon alpha (1 million U, M/W/F); poorly tolerated
- March 2015−February 2016: Local XRT on multiple occasions to several sites on body
- March 2016: Romidepsin x 2 cycles; no response
- May 2016: Gemcitabine (1.2 g/m^2); little response
- August 2016: BV initiated
- Patient lost to follow-up

ALCANZA: Phase III Trial of Brentuximab Vedotin versus Physician's Choice in CD30-Positive Cutaneous TCL

Patients with mycosis fungoides (n = 97)	BV (N = 48)	Physician's choice[a] (N = 49)
ORR lasting at least 4 months	50%	10%
ORR	65%	16%
CR	10%	0

[a] Methotrexate or bexarotene

Kim YH et al. *Proc ASH* 2016;Abstract 182.

Reminder

Please turn in your CNE course evaluation for credit as you exit the activity.

Thank you for joining us.