Applying Genomics to the Treatment of Rare Lymphomas and Leukemias (Hodgkin Lymphoma and Chronic Lymphocytic Leukemia)

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Learning Objectives

1. Identify key molecular attributes that have relevance in risk-adapted treatment of rare lymphomas, including Hodgkin lymphoma, mantle cell lymphomas, and marginal zone lymphomas
2. Determine which prognostic factors are clinically relevant in the era of novel agents for the treatment of chronic lymphocytic leukemia
3. Evaluate toxicity profiles and the best management of side effects associated with therapies used to treat rare lymphomas and leukemias
4. Discuss the role of the advanced practitioner in oncology in managing patients with these malignancies

Financial Disclosures

- Ms. Kurtin has acted as a consultant for AbbVie, Bristol-Myers Squibb, Celgene, Genentech, Incyte, Janssen, and Takeda.
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Hodgkin Lymphoma: Epidemiology

New Cases (US 2017)	Deaths (US 2017)	Age at Diagnosis	5-Year Overall Survival 2016
8,260	1,070	Bimodal age distribution	82.6%

Risk factors

- Socioeconomic factors
- Familial risk: genetic predisposition and common environmental exposure
- EBV: Geographic variability and variability by subtype: 30%–40% in Europe and North America, and as high as 80% in Central and South American
- Autoimmune disorders
- Tobacco use
- HIV on antiretroviral therapy
- Bone marrow microenvironment
- Genetic drivers: NF-κB, JAK-STAT pathways

HL = Hodgkin lymphoma; EBV = Epstein-Barr virus.

Epidemiology

- 0.5% of all new cancer cases
- More common in males
- Bimodal age distribution
  - First peak at age 20
  - Second peak at age 65
- Etiologic heterogeneity between HL subtypes

Survival

- In 2013, there were an estimated 193,545 people living with Hodgkin lymphoma in the United States

National Cancer Institute, Cancer Stat Facts: Chronic Lymphocytic Leukemia (CLL), http://seer.cancer.gov/statfacts/html/clyl.html; Kamper-Jorgensen M, et al. *Ann Oncol* 2013;24:2245-55.

Presenting Signs and Symptoms

Most common

- Asymptomatic lymphadenopathy
  - Most often in the neck or mediastinum (60%–70%)
- Cough, retrosternal chest pain, or shortness of breath
- Pruritus, severe in many cases
- Alcohol-induced pain in sites of disease

Others

- B symptoms are most common in stage III/IV disease
  - Fever (>100.4°F), night sweats, and weight loss
- Eosinophilia
- Bone pain
- Other symptoms may be present in patient with bulky abdominal disease

Mauch et al. *Cancer* 1993;71:2062.

Diagnostic Evaluation

ESSENTIAL

History

- B symptoms, alcohol intolerance, pruritus, fatigue, performance status

Physical exam

- Examine lymphoid regions, spleen, liver

Laboratory testing

- CBC, differential, platelets
- ESR
- Comprehensive metabolic panel
- LDH
- Pregnancy test for women of childbearing age

Imaging

- Diagnostic CT (with contrast)
- **PET/CT (skull base to mid-thigh)**

Excisional biopsy (recommended)

- Core needle biopsy may be adequate if diagnostic immunohistochemistry evaluation

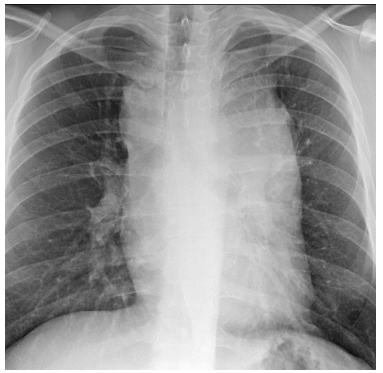
Psychosocial

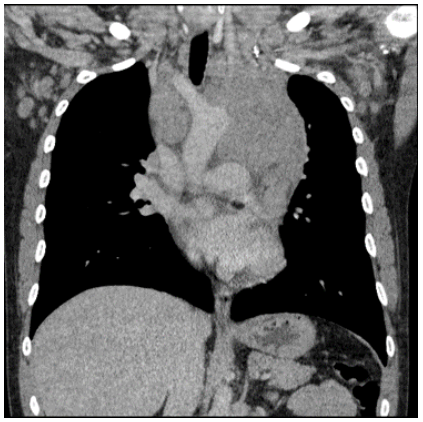
- Fertility, smoking cessation

ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; CT = computed tomography; PET = positron emission tomography; RT = radiation therapy; PFTs = pulmonary function tests; DLCO = diffusing capacity of the lungs for carbon monoxide

Case Study: 30-year-old Male

- Presented to ED with a 2-mo history of fevers, cough, night sweats, and 8-lb weight loss
- Past medical history: splenic laceration s/p splenectomy
- Was diagnosed with shingles 2 mo prior to ED visit
- CXR
  - CT chest: Large anterior mediastinal mass/nodal conglomerate with extensive lymphadenopathy
  - CT-guided biopsy: Fibrosis, non-diagnostic

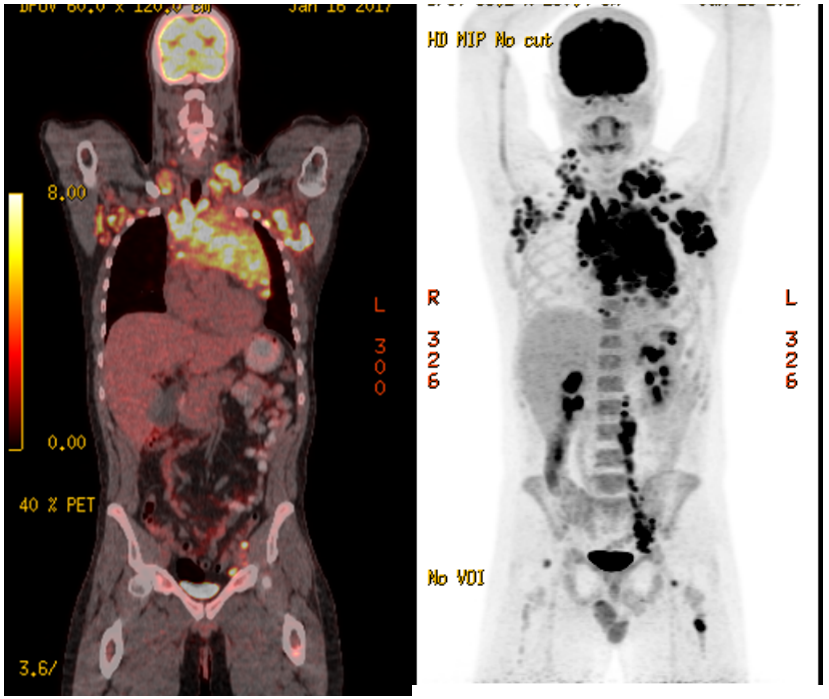




Images courtesy of Sandra Kurtin, PhDc, ANP-C, AOCN.

Case Study: 30-year-old Male With cHL

- Referred to hem/onc
- PET/CT obtained
- Excisional biopsy
  - CLASSICAL HODGKIN LYMPHOMA, NODULAR SCLEROSIS SUBTYPE
- Sections show effacement of nodal architecture by large nodules surrounded by sclerotic bands. The nodules contain large *Reed-Sternberg/Hodgkin cells* with the classical Hodgkin lymphoma phenotype (CD45-, CD20-, PAX5+, CD30+, CD15+).
- Sed rate: 79 (0–15 MM/HR)



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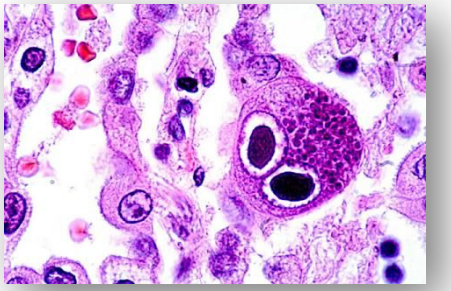
Classical HL

- Most common (95% of cases in Western countries)
- Derived from germinal center B cells, but typically fail to express many of the genes and gene products that define normal germinal center B cells

Characterized by the presence of the **Reed-Sternberg cell**



Typical immunophenotype

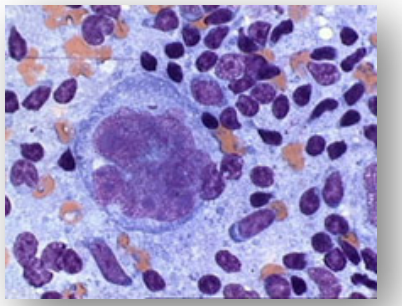
- CD15+, **CD30+,** PAX-5+ (weak); CD3-, CD20- (majority), CD45-, CD79a-

Four subtypes

- Based on differences in the appearance of the tumor cells and the composition of the microenvironment
  - Nodular sclerosis classical HL (NSHL): disease above the diaphragm and mediastinal node involvement most common
  - Mixed cellularity classical HL (MCHL): liver involvement more common
  - Lymphocyte rich classical HL (LRHL)
  - Lymphocyte depleted classical HL (LDHL): least common subtype; more likely to present with advanced stage disease, liver involvement, B symptoms

Swerdlow SH, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition, 2008; NCCN Guidelines Version 1.2017 Hodgkin Lymphoma.

Nodular Lymphocyte Predominant HL



- Relatively rare: 5% of HL cases
- Retain the immunophenotypic features of germinal center B cells
- Typical immunophenotype for nodular lymphocyte-predominant HL:
  - CD20+, CD45+, CD79a+, BCL6+, PAX-5+; CD3-, CD15-, **CD30**
- **Lacks Reed-Sternberg cell**; characterized by the presence of lymphocyte-predominant cells (popcorn cell)
- Treated with regimens used for follicular lymphoma
  - ABVD + rituximab
  - CHOP +rituximab
  - CVP + rituximab

Swerdlow SH, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition, 2008; NCCN Guidelines Version 1.2017 Hodgkin Lymphoma.

Clinical Staging of Hodgkin Lymphoma

Staging

- Early-stage favorable
  - Stage I-II
  - No unfavorable factors
- Early-stage unfavorable
  - Stage I-II
  - Any unfavorable factor
- Advanced-stage disease
  - Stage III-IV

Unfavorable factors

- Bulky disease
  - Large mediastinal adenopathy > 10 cm
  - MMR > 0.33
  - > 1/3 internal transverse diameter of the thorax at the T5-T6 interspace
- Extranodal involvement
  - > 3 nodal sites of disease
  - Most common is bone or bone marrow, followed by lung, liver, and muscle
- **Sedimentation rate (ESR) ≥ 50**
- Presence of B symptoms
  - Unexplained fevers > 38°C
  - Drenching night sweats
  - Weight loss of > 10% of their body weight within 6 mo of diagnosis

MMR = mediastinal mass ratio.

Ng AK, et al. *Semin Hematol* 2016;53:209-15.

Risk Stratification for cHL

Stage	Bulky Disease	Nodal Sites	ESR	Risk Stratification
IA	No	1	< 50	Early stage favorable
IB	No	1	Any	Early stage unfavorable
IIA (no E)	No	< 3	< 50	Early stage favorable
IIA +/- E	No	< 4	< 50	Early stage favorable
	No	Any	≥ 50	Early stage unfavorable
	Yes	Any	Any	Early stage unfavorable
IIB+/- E	No	Any	Any	Early stage unfavorable
	Yes	Any	Any	Early stage unfavorable
III-IV	Yes/No	Any	Any	Advanced-stage disease

cHL = classical Hodgkin lymphoma.

International Prognostic Score (IPS)* for Advanced Stage Disease

1 point for each factor

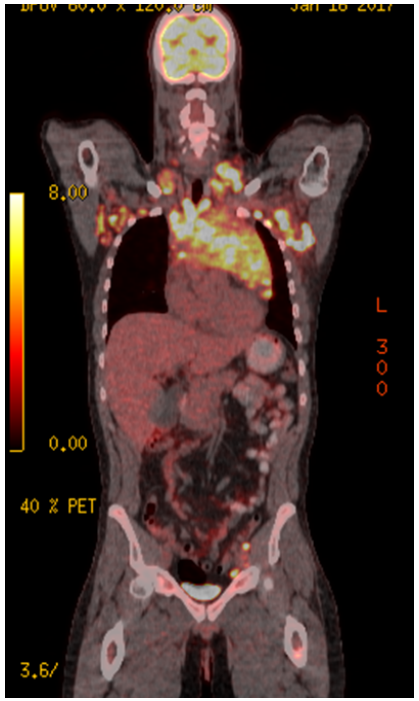
- Albumin < 4 g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Age ≥ 45 yr
- Stage IV disease
- Leukocytosis (WBC > 15,000/mm^3)
- Lymphocytopenia (ALC < 8%)
- WBC and/or lymphocyte count less than 600/mm^3

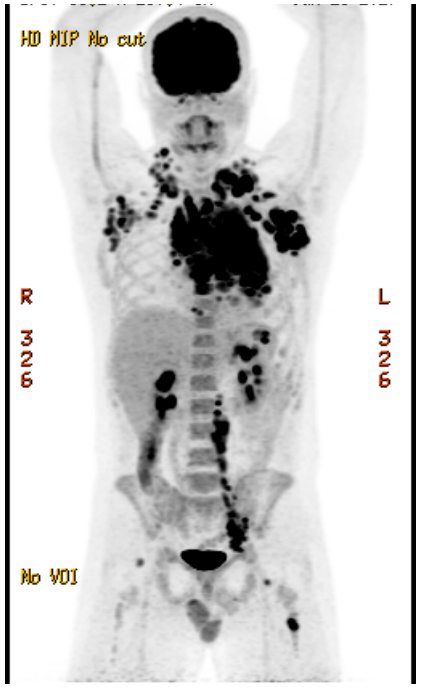
Number of factors	PFS at 5 years (%)	% of patients
0	84	7
1	77	22
2	67	29
3	60	23
4	51	12
≥ 5	42	7

Hasenclever & Diehl, *N Engl J Med* 1998;339:1506-1514

Case Study: 30-year-old Male With Stage IV High-Risk cHL

- WBC: 15.2
- Hgb: 11.1 g/dL
- Albumin 3.1
- Sed rate (ESR): 79 (0–15 MM/HR)
- PFT: DCLO 68% (74% corrected for Hgb)
- Echo: EF 59%





Images courtesy of Sandra Kurtin, PhDc, ANP-C, AOCN.

ABVD

Pre-treatment screening

- Echocardiogram
- PFTs with DLCO

Drugs

- Doxorubicin 25 mg/m^2 IV
- Bleomycin 10 units/m^2 IV
- Vinblastine 6 mg/m^2 IV
- Dacarbazine 375 mg/m^2

Schedule

- Days 1 and 15
- 2 cycles
- Re-image with PET/CT (skull base to mid-thigh)
- Then response-adapted treatment

Dose adjustment for baseline liver or renal dysfunction

- Bleomycin
  - Adjust for reduced CrCl, impaired pulmonary function
  - Discontinue if bleomycin lung toxicity is suspected
- Doxorubicin
  - Adjust in patients with increased bili AST/ALT
  - Adjust for reduced EF/cardiac dysfunction
- Vinblastine: adjust in patients with increased bili AST/ALT
- Dacarbazine: severe irritant, may require central line

CrCl = creatinine clearance; bili = bilirubin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; EF = ejection fraction.

ABVD: Adverse Events

- Emesis risk: HIGH (> 90)
  - Pre-medicate using 5HT3 antagonist, steroid
- Infusion reactions
  - Test dose of bleomycin may be administered
- Venous access
  - Doxorubicin and vinblastine are vesicants
  - Dacarbazine is an extreme irritant
- Infection prophylaxis
  - Primary prophylaxis with G-CSF is generally ***not*** indicated
  - Avoid concurrent administration with bleomycin – may increase bleomycin lung toxicity
- Neuropathy: vinblastine
- Pulmonary toxicity: bleomycin
  - Monitor for cough, exertional dyspnea
  - Repeat PFTs, CT chest is pneumonitis suspected
  - Start prednisone
  - Discontinue bleomycin if toxicity suspected

G-CSF = granulocyte colony-stimulating factor.

Canellos GP, et al. *N Engl J Med* 1992;327:1478; Bleomycin prescribing information, 2010, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/050443s036lbl.pdf.

Response-Adapted Frontline Therapy Deauville Criteria, PET 5-Point Scale

- Maximize cures while minimizing late effects
- Avoid under-treatment **or** overtreatment
- Reduce treatment-emergent adverse events
- Reduce potential long-term effects including secondary malignancies

Score	PET/CT Result
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Barrington SF, et al. *J Clin Oncol* 2014;32:3048-58; Hutchings M. Hematology Am Soc Hematol Educ Program 2012;2012:322-7; Johnson PW. Hematology Am Soc Hematol Educ Program 2016;316-22.

German Hodgkin Study Group (GHSG) HD10

Randomly assigned 1,370 patients with favorable prognosis early-stage HL:

- 4 cycles of ABVD followed by 30 Gy IFRT
- 4 cycles of ABVD followed by 20 Gy IFRT
- 2 cycles of ABVD followed by 30 Gy IFRT
- 2 cycles of ABVD followed by 20 Gy IFRT

At a median follow-up of 7.5 years:

Outcome	2 cycles of ABVD	4 cycles of ABVD
5-year OS	96.6%	97.1%
PFS	91.2%%	93.5%
FTF	91.1%	93%
8-year OS	94%	95%
Grade 3/4 AEs	33%	52%
Leukopenia	15%	24%
Infections	1.7%	5.1%
Hair loss	15%	28%

IFRT = involved-field radiation therapy; AEs = adverse events; OS = overall survival; PFS = progression-free survival; FTF = freedom from treatment failure.

Engert A, et al. *N Engl J Med* 2010;363:640.

Radiation Therapy in cHL

- Patient preference
- Risk of complications
- Young female patients (age < 30) where the radiation field includes the breasts—increased risk of secondary breast cancer
- Current RT: Uses lower dose and smaller field size, is likely associated with less long-term toxicity than higher-dose, larger field size treatment

BEACOPP

Age and PS-Adjusted Treatment-Related Mortality

- < 40 years with ECOG PS < 2 (2,164 patients) = TRM 0.7%
- < 40 years with ECOG PS ≥ 2 (108 patients) = TRM 0.9%
- 40 to 49 years with ECOG PS < 2 (592 patients) = TRM 1.7%
- **40 to 49 years with ECOG PS ≥ 2 (40 patients) = TRM 15 %**
- **≥ 50 years with ECOG PS < 2 (453 patients) = TRM 5.7%**
- **≥ 50 years with ECOG PS ≥ 2 (45 patients) = TRM 13.3%**

Drugs	Escalated BEACOPP	Standard BEACOPP
Bleomycin	10 units/m^2 IV on day 8	10 units/m^2 IV on day 8
Etoposide	200 mg/m^2 IV on days 1-3	100 mg/m^2 IV days 1-3
Doxorubicin	35 mg/m^2 IV on day 1	25 mg/m^2 IV on day 1
Cyclophosphamide	1,250 mg/m^2 IV on day 1	650 mg/m^2 IV on day 1
Vincristine	1.4 mg/m^2 (max 2 mg) IV on day 8	1.4 mg/m^2 (max 2 mg) IV on day 8
Procarbazine	100 mg/m^2 oral day 1-7	100 mg/m^2 oral days 1-7
Prednisone	40 mg/m^2 oral days 1-14	40 mg/m^2 oral on days 1-14
G-CSF	SC starting on day 8	

ECOG = Eastern Cooperative Oncology Group; PS = performance status; TRM = treatment-related mortality; SC = subcutaneously.

Wongso D, et al. *J Clin Oncol* 2013;31:2819-24.

Response-Adapted Studies of Reduced Therapy in PET-Negative Groups

Trial name	Stage	PET-negative patients	No. of cycles and type of initial therapy	% interim PET-negative	5-point PET score	No. of cycles and type of post-PET therapy	Time to analysis (years)	PFS (%)	OS (%)
NCRI RAPID	I IA-IIA nonbulky	420	3 ABVD	75	1–2	Nil vs IFRT	5	90.8 vs. 94	99 vs. 97.1
EORTC HD10	I-II favorable	381	2 ABVD	86	N/A	1 ABVD + INRT vs. 2 ABVD	1	100 vs. 94.9	N/A
	I-II unfavorable	519	2 ABVD	75		2 ABVD + INRT vs. 4 ABVD	1	97.3 vs. 94.7	
RATHL 2	II with adverse features, III, IV	935	2 ABVD	84	1–3	4 ABVD	3	85.7	97.2
						4 AVD	3	84.4	97.6
GITIL/FIL 0607	II with adverse features, III, IV	195	2 ABVD	80	1–3	4 ABVD 1 IFRT 4 ABVD	2	94	N/A
								88	
GHSG HD15	IIBX, III, IV	548	6-8 BEACOPPe or 8 BEACOPP-14	74 (PRs)	N/A	No IFRT for PET negative	4	92.6	95
LYSA AHL2011	IIB, III, IV	688	2 BEACOPPe	88	N/A	4 BEACOPPe	2	94	N/A
						4 ABVD	2	92	

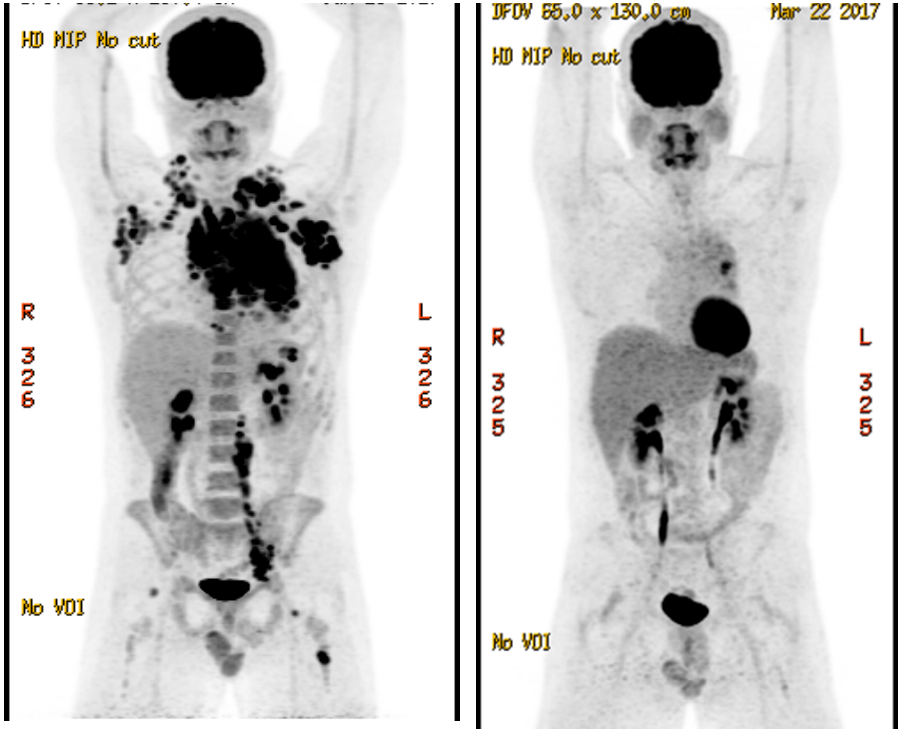
INRT = involved-node radiotherapy.

Case Study: 30-year-old Male With cHL

Completed 2 cycles of ABVD

- PET/CT - Deauville 3
  1. Good partial response to therapy.
  2. Marked decrease in FDG avidity in the large mediastinal nodal conglomerate with only mild residual focal activity remaining. This conglomerate has also significantly decreased in size.
  3. Resolution of the neck, axillary, pulmonary hilar, and retroperitoneal lymphadenopathy.
  4. Complete resolution of osseous involvement.
- PFTs show improvement in DLCO
- Echocardiogram with no change

Treatment Plan: 6 cycles of ABVD



Images courtesy of Sandra Kurtin, PhDc, ANP-C, AOCN.

cHL in Older Adults (age > 60)

Stage I-II favorable disease

- A(B)VD* (2 cycles) ± AVD (2 cycles) + 20-30 Gy ISRT (preferred)
- CHOP (4 cycles) + ISRT
- VEPEMB ± ISRT

Stage I-II unfavorable or stage III-IV disease

- A(B)VD (2 cycles) followed by AVD (4 cycles), if PET scan is negative after 2 cycles of ABVD
- Patients with a positive PET scan after 2 cycles of ABVD need individualized treatment
  - CHOP (6 cycles) ± ISRT
  - PVAG (6 cycles)
  - VEPEMB (6 cycles) ± ISRT

ISRT = involved-site radiation therapy; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; VEPEMB = vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone, and bleomycin; PVAG = prednisone, vinblastine, doxorubicin, and gemcitabine. * Bleomycin should be used with caution in older adults.

cHL in Older Adults (age > 60)

Relapsed or refractory disease

- Outcomes are uniformly poor for patients with relapsed or refractory disease
- No uniform recommendation can be made, although clinical trials or possibly single-agent therapy with a palliative approach is recommended
- Individualized treatment is necessary
- Palliative therapy options
  - Bendamustine
  - Brentuximab vedotin
  - Nivolumab (for patients previously treated with brentuximab vedotin)

Relapsed/Refractory Hodgkin Lymphoma

Case Study: 20-year-old Female

- cHL: Stage IIIBSE advanced disease
- Treated with ABVD x 6 (PET CR after cycle 2)
- Relapsed 8 months later
- Biopsy consistent with original diagnosis
  - Large CD30+, CD15+ CD45-, PAX5+
  - Mononuclear Hodgkin and Reed-Sternberg cells
- Treated with ICE chemotherapy regimen followed by autologous stem cell transplant

Regimens Used for R/R cHL

- **Brentuximab vedotin (only for cHL)**
- Bendamustine
- C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) (category 2B)
- DHAP (dexamethasone, cisplatin, high-dose cytarabine)
- ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin)
- Everolimus
- GCD (gemcitabine, carboplatin, dexamethasone)
- GVD (gemcitabine, vinorelbine, liposomal doxorubicin)
- ICE (ifosfamide, carboplatin, etoposide)
- IGEV (ifosfamide, gemcitabine, vinorelbine)
- Lenalidomide
- MINE (etoposide, ifosfamide, mesna, mitoxantrone)
- Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)
- **Nivolumab**
- **Pembrolizumab**

General Principles of Treatment for R/R cHL

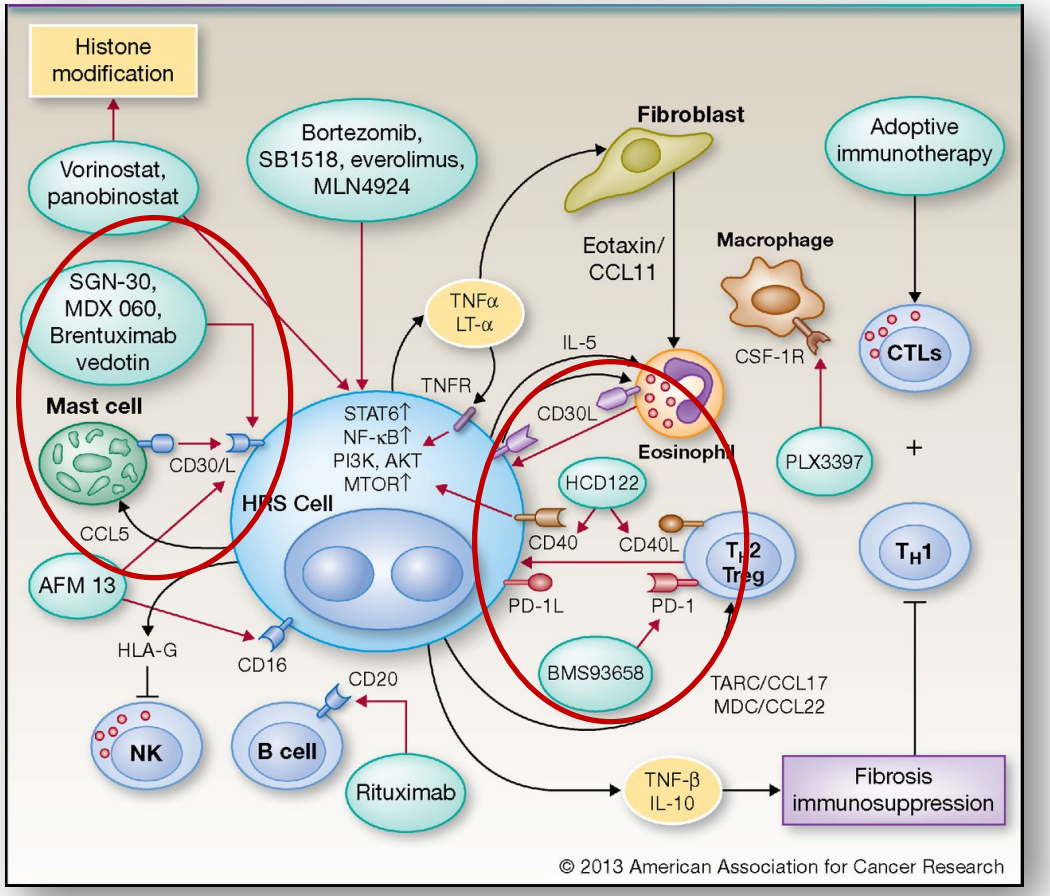
- Consider pattern of relapse and agents previously used
- HSCT should be considered for transplant-eligible patients who achieve a CR with second-line treatment
  - Patient not in CR may proceed, but will have a less favorable outcome
- Allogeneic stem cell transplant may be considered in eligible patients who fail autoHSCT and respond to third-line treatment
- Brentuximab vedotin is a treatment option if HDT/ASCR has failed or at least 2 prior multiagent chemotherapy regimens have failed
- Brentuximab vedotin can be used as second-line therapy prior to HDT/ASCR to minimize the use of more intensive chemotherapy
- Nivolumab or pembrolizumab are options for cHL that has relapsed or progressed following HDT/ASCR and post-transplant brentuximab vedotin

R/R = relapsed/refractory; HSCT = hematopoietic stem cell transplant; CR = complete response; autoHSCT = autologous hematopoietic stem cell transplant; HDT = high-dose therapy; ASCR = autologous stem cell rescue.

Novel Agents for the Treatment of cHL

HL and the Microenvironment: Potential Therapeutic Targets

Tailoring the therapy to the tumor biology of the patient may improve outcomes



Diefenbach & Steidl. *Clin Cancer Res*; 2013, 19(11); 2797–803.

Novel Agents in the Treatment of HL

Drug	Drug class	Target
Receptor-targeting therapies		
Brentuximab vedotin	ADC	CD30
Nivolumab	MoAb	PD-1
Rituximab	MoAb	CD20
Galiximab	MoAb	CD80
Microenvironment-targeting therapies		
Lenalidomide	Immunomodulator	T cells, NK cells, Tregs
Panobinostat	HDACi	HDAC
Mocetinostat	HDACi	HDAC
Inhibitors of signaling pathways		
Everolimus	mTOR inhibitor	mTORC1
Perifosine/sorafenib	AKT/MAPK inhibitor	AKT/MAPK

ADC = antibody-drug conjugate; MoAb = monoclonal antibody; NK = natural killer; HDACi = histone deacetylase inhibitor; mTOR = mechanistic target of rapamycin.

Diefenbach & Steidl. *Clin Cancer Res*. 2013;19(11):2797-803.

Brentuximab Vedotin

Class: Anti-CD30 MoAb

FDA Approval: August 19, 2011

Indication for cHL

- cHL after failure of autoHSCT
- cHL in transplant-ineligible candidates after failure of at least 2 multiagent chemotherapy regimens
- cHL at high risk of relapse or progression as post autoHSCT consolidation

Dosing and Administration

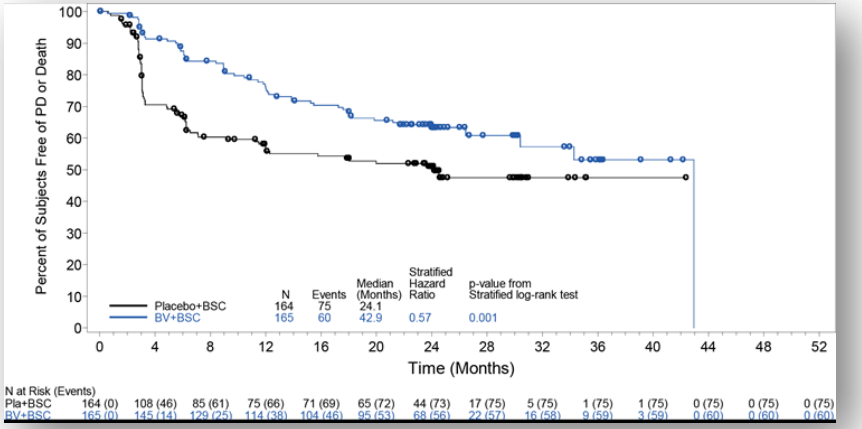
- 1.8 mg/kg intravenous infusion over 30 minutes every 3 weeks
- Reduce dose in patients with mild hepatic impairment
- Contraindication: concomitant use with bleomycin due to pulmonary toxicity

FDA = US Food and Drug Administration.

Brentuximab prescribing information, 2016, https://adcetris.com/pdf/ADCETRIS-brentuximab-vedotin-Prescribing-Information.pdf?v=20161101.

Brentuximab Vedotin Consolidation After AutoHSCT

- Randomized double-blind placebo-controlled trial (n = 329)
- cHL at high risk of relapse or progression post-autoHSCT
- 30-45 days post-autoHSCT, randomized to:
  - BV 1.8 mg/kg every 3 weeks for up to 16 cycles
  - Placebo every 3 weeks for up to 16 cycles
- Outcomes
  - Median number of cycles in each study arm was 15 (range, 1–16)
  - 80 patients (48%) in the BV arm received 16 cycles
  - Statistically significant improvement in PFS: BV 42.9 months, placebo 24.1, HR 0.57 (95% CI = 0.40–0.81; *p* = 0.001).



BV = brentuximab vedotin; HR = hazard ratio.

Epperla N, et al. (2015). *Bone Marrow Transplant*. doi:10.1038/bmt.2015.184

Brentuximab vedotin prescribing information, 2016, https://adcetris.com/pdf/ADCETRIS-brentuximab-vedotin-Prescribing-Information.pdf?v=20161101.

Nivolumab

Class: PD-1 blocking antibody

FDA Approval: March 17, 2016

Indication for cHL

- cHL that has relapsed or progressed after autoHSCT and post-transplantation brentuximab vedotin

Dosing and Administration

- 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity

Nivolumab prescribing information, 2014, http://packageinserts.bms.com/pi/pi_opdivo.pdf.

Nivolumab

- Drug-related adverse events
- No grade 4 or grade 5 drug-related AEs were reported

Serious adverse event	Any grade	Grade ≥ 3
MDS	1 (4)	1 (4)
Lymph node pain	1 (4)	0
Pancreatitis	1 (4)	1 (4)

Adverse event	Any grade	Grade ≥ 3
Any AE	18 (78)	5(22)
Rash	5 (22)	0
Thrombocytopenia	4 (17)	0
Fatigue	3 (13)	0
Pyrexia	3 (13)	0
Diarrhea	3 (13)	0
Nausea	3 (13)	0
Pruritus	3 (13)	0
Cough	2 (9)	0
Hypothyroidism	2 (9)	0
↓ ALC	2 (9)	1 (4)
Hypophosphatemia Hypercalcemia	2 (9)	0
Increased lipase	2 (9)	1 (4)
Stomatitis	2 (9)	1 (4)

Ansell SM, et al. *N Engl J Med* 2015;372;311-9.

Pembrolizumab

Class: IgG4 kappa humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2

FDA Approval: March 14, 2017

Indication for cHL

- Adult and pediatric patients with refractory cHL, or those who have relapsed after 3 or more prior lines of therapy

Dosing and Administration for cHL in Adults

- 200 mg every 3 weeks

Moskowitz CH, et al. ASH 2016. Abstract 1107; Pembrolizumab prescribing information, 2014, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.

Pembrolizumab KEYNOTE-087 Trial

- Multicenter non-randomized, open-label trial (n = 210)
- 3 cohorts defined by R/R cHL history
  - Cohort 1: progression after ASCT and subsequent brentuximab vedotin (BV; n = 69)
  - Cohort 2: failed salvage chemotherapy, ASCT ineligible, failed BV therapy (n = 81)
  - Cohort 3: failed ASCT, no BV after transplantation (n = 60)
  - Patients had received a median of four prior systemic therapies (range: 1–12)
- With a median follow-up of 9.4 months (range: 1–15)
  - ORR was 69% (95% CI = 62–75); PR = 47%, CR = 22%.
  - Median DOR = 11.1 months (range 0+ to 11.1)

ORR = objective response rate; PR = partial response; DOR = duration of response.

Moskowitz CH, et al. ASH 2016. Abstract 1107; Pembrolizumab prescribing information, 2014, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.

Pembrolizumab KEYNOTE-087 Trial

Response, n (%)	Patients With Primary Refractory Disease* (n = 73)	Patients Relapsed After ≥ 3 Lines of Therapy* (n = 146)
ORR ▪ CR ▪ PR	58 (79.5) 17 (23.3) 41 (56.2)	99 (67.8) 21 (21.2) 68 (46.6)
SD	4 (5.5)	24 (16.4)
PD	8 (11.0)	20 (13.7)
Undetermined	3 (4.1)	3 (2.1)

* Subgroups were not mutually exclusive

SD = stable disease; PD = partial disease.

Moskowitz CH, et al. ASH 2016. Abstract 1107; Pembrolizumab prescribing information, 2014, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.

KEYNOTE-087: Treatment-Related AEs

- 9 patients discontinued because of treatment-related AEs
- No treatment-related deaths (2 deaths on study)

Any-Grade AEs in ≥ 5% of Patients, n (%)	All Patients (N = 210)
Hypothyroidism	26 (12.4)
Pyrexia	22 (10.5)
Fatigue	19 (9.0)
Rash	16 (7.6)
Diarrhea	15 (7.1)
Headache	13 (6.2)
Nausea	12 (5.7)
Cough	12 (5.7)
Neutropenia	11 (5.2)

AEs, n (%)	All Patients (N = 210)
Any-grade grade 3/4 AE	23 (11)
Grade 3 AEs in ≥ 2 patients	
▪ Neutropenia	5 (2.4)
▪ Diarrhea	2 (1.0)
▪ Dyspnea	2 (1.0)
AEs of interest in ≥ 2 patients	
▪ Grade 1/2 infusion-related reactions	10 (4.8)
▪ Grade 2 pneumonitis	6 (2.9)
▪ Grade 1/2 hyperthyroidism	6 (2.9)
▪ Grade 2/3 colitis	2 (1.0)
▪ Grade 2/3 myositis	2 (1.0)

Moskowitz CH, et al. ASH 2016. Abstract 1107.

Pembrolizumab Warnings and Precautions

- A new “Warning and Precaution” was added for complications of alloHSCT after pembrolizumab
- Transplant-related deaths have occurred
- FDA has required the sponsor to further study the safety of alloHSCT after pembrolizumab therapy

Monitor closely for:

- Hyperacute GVHD
- Severe (grade 3 to 4) acute GVHD
- Steroid-requiring febrile syndrome
- Hepatic VOD
- Other immune-mediated adverse reactions

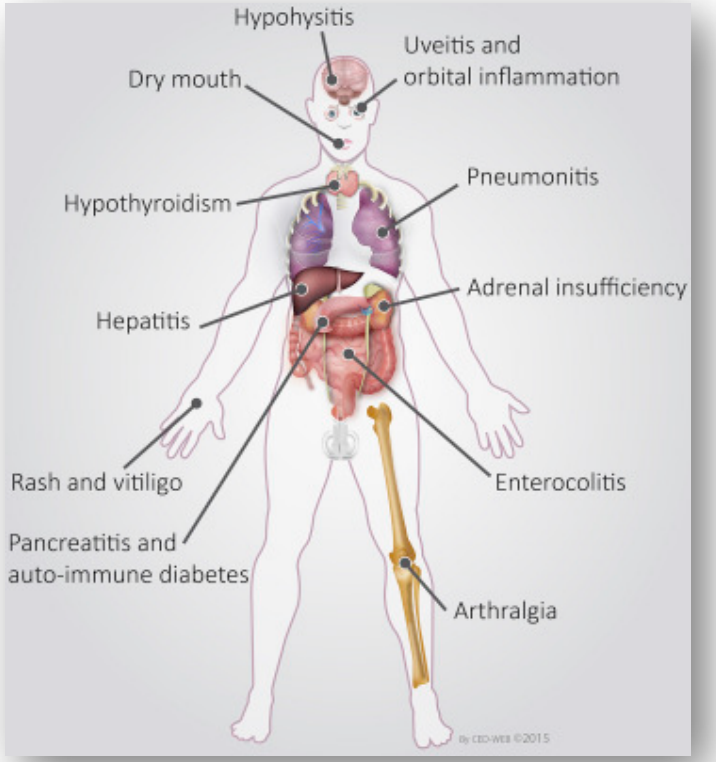
alloHSCT = allogeneic hematopoietic stem cell transplantation; GVHD = graft-versus-host disease; VOD = veno-occlusive disease.

Pembrolizumab prescribing information, 2014, https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.

AEs Associated With Immune Checkpoint Inhibition

Augmented immune response driven by T-cell activation creates the potential for autoimmune-related inflammation of normal tissues

Onset is often delayed compared to standard therapies



Michot JM, et al. *Eur J Cancer* 2016;54:139-48.

Treatment of Severe and Steroid-Refractory IRAEs

Type and Severity of irAE	Initial Management	Additional Immunosuppression	Immunosuppression Tapering Schedule
Colitis and/or diarrhea Grade 3-4 • Increase of ≥7 stools per day over baseline • Abdominal pain, fever, and change in bowel habits	• Admit to hospital for intravenous corticosteroid therapy (methylpredni-solone 1-2 mg/kg daily dose) • Supportive care including intravenous fluids, supple-mental oxygen, and antibiotics as needed • Withhold hepatotoxic drugs • Consider further diagnostic imaging or procedures	**Colitis and/or diarrhea** • If no improvement after 3 days, give infliximab 5 mg/kg • Can redose infliximab after 2 weeks if needed	**Colitis and/or diarrhea** • Rapidly tapering course of steroids as tolerated over 4-6 weeks • Increase steroids if diarrhea flares and then restart tapering
Hepatitis Grade 3-4 • Aspartate transaminase and/or alanine trans-aminase levels >5 times ULN • Total bilirubin level >3 times ULN		**Hepatitis** • If no improvement after 3 days, start mycopheno-late mofetil 500-1000 mg every 12 hours	**Hepatitis** • Rapidly tapering course of steroids as tolerated; discontinue mycophenolate mofetil once tapered to prednisone 10 mg daily
Pneumonitis Grade 3-4 • Severe, life-threatening symptoms • Worsening hypoxia		**Pneumonitis** • If no improvement after 48 hours, start additional agent as above or cyclophosphamide	**Pneumonitis** • Taper steroids slowly over 6 weeks • Mycophenolate mofetil management as above if needed

Friedman CF, et al. *JAMA Oncol* 2016;2:1346-53.

Mechanism of Action of Immune-Modulating Medications

Drug	Key mechanism of action
Steroids	Multiple effects on T cells, B cells, and phagocytes through inhibition of transcription of interleukins, reduction in synthesis of cytokines, inhibition of neutrophil apoptosis, and reduced macrophage function
Infliximab	Antibody that inhibits binding of the inflammatory cytokine TNF-α to its receptors
Mycophenolate mofetil	Inhibits IMPDH, an enzyme involved in nucleotide production, particularly in activated lymphocytes
Tacrolimus and cyclosporine	Calcineurin inhibitors that limit transcription of IL-2, involved in T-cell proliferation

TNF-α = tumor necrosis factor alpha; IMPDH = inosine monophosphate dehydrogenase; IL-2 = interleukin 2.

Spain L, et al. *Cancer Treat Rev* 2016;44:51-60.

Keys to Optimal Patient Management for Immune Checkpoint Inhibitors

- Time to onset for AEs is typically delayed
- Education of healthcare team, patients, and caregivers
- Rapid and timely intervention
  - Corticosteroids for some intolerable grade 2 irAEs and any grade 3/4 irAEs
  - Slow taper of glucocorticoids
- Reinitiation of treatment may be possible

Dadu et al. *Cancer J* 2016;22: 121–129

Chronic Lymphocytic Leukemia

CLL Epidemiology

New Cases (US 2016)	Deaths (US 2016)	Mean Age at Diagnosis	5-yr Overall Survival 2016
18,960	4,660	71 years	82.6%

Risk factors

- Age: CLL is extremely rare < 20 years of age
- White > Black >>> Asian
- Monoclonal B-cell lymphocytosis with elevated absolute lymphocyte count
- Rare familial cases
- No association with environmental or external factors, although association with Agent Orange exposure

Survival

- 5-year relative survival rate has increased from 67.5% (1975–1977) to 81.7% (2005–2011)
- Deaths associated with CLL are highest in patients aged 75–84
- Variable response to treatment and variation in survival
- Absolute survival has increased during past 2 decades

CLL = chronic lymphocytic leukemia.

NIH, Cancer Stat Facts: Chronic Lymphocytic Leukemia (CLL), http://seer.cancer.gov/statfacts/html/clyl.html;
US Department of Veterans Affairs, Public Health: Agent Orange,
http://www.publichealth.va.gov/exposures/agentorange/.

Clinical Characteristics of MBL, CLL, and SLL

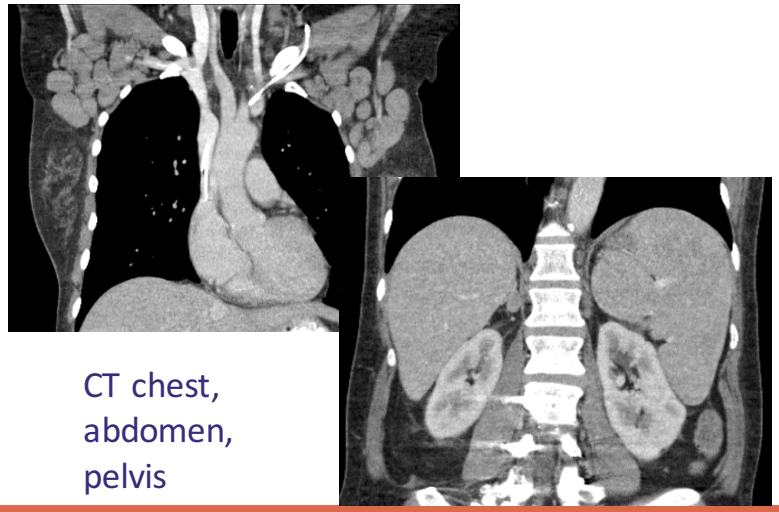
	MBL	CLL	SLL
Clonal B cells > 5 × 10^9/L	No	Yes	No
Lymph nodes > 1.5 cm	No	Yes/No	Yes
Enlarged spleen/liver	No	Yes/No	Yes/No
Anemia	No	Yes/No	Yes/No
Thrombocytopenia	No	Yes/No	Yes/No
Bone marrow involvement ≥ 30%	Yes/No	Yes	No
Molecular prognostic factors predictive of outcome	No	Yes	Yes
Higher risk of infection	No	Yes	Yes
Higher risk of autoimmune problems	No	Yes	Yes

MBL = monoclonal B-cell lymphocytosis.

Rawstron AC, et al. *N Engl J Med* 2008;359(6):575-83; Byrd JC & Flynn JM. Chronic Lymphocytic Leukemia, in *Abeloff's Clinical Oncology*, Fifth Ed, 2013. Churchill Livingstone, an imprint of Elsevier Inc.

Case Study 1: 72-year-old Female

- Presented with recurring pharyngitis, low-grade fevers, progressive fatigue, adenopathy, abdominal pain, > 10% weight loss
- Past medical history: HTN, GERD, hypothyroidism, cholelithiasis, shingles, exaggerated reaction to insect bites, chronic pain
- PE: Extensive adenopathy in the cervical, axillary, inguinal regions; splenomegaly



CT chest, abdomen, pelvis

- WBC: 230.7 x 1000/uL ALC: 223.78 x 1000/uL
- Hgb: 10.9 g/dL Platelets: 180 x 1000/uL
- LDH: 250 IU/L (ULN 243) β_2: 2.5 mg/L
- Flow cytometry: (peripheral blood) 84% of all cells are CD19 and CD20 positive, co-express CD5 and CD23, ZAP 70+
- Bone marrow
  - 80% involvement with small mature non-cleaved lymphocytes
  - Cytogenetics: 46,XX[15] Normal female karyotype
  - **FISH: 17p13 deletion in 92/200 cells scored (46%)**

Images courtesy of Sandra Kurtin, PhDc, ANP-C, AOCN.

Clinical Staging Predicts Outcome

Staging system		Clinical features	Median survival
Rai stage	0 (low risk)	Lymphocytosis in blood and marrow only	> 150 mo (12.5 yr)
	I and II (intermediate risk)	Lymphadenopathy, splenomegaly ± hepatomegaly	71-101 mo (5.9-8.4 yr)
	III and IV (high risk)	Anemia (Hb < 11.0 g/dL) thrombocytopenia (Plt < 100 × 10^9/L) ± lymphadenopathy and splenomegaly	19 mo
Binet group	A	Lymphocytosis < 3 areas of lymphadenopathy; no anemia or thrombocytopenia	Similar to age matched controls
	B	Lymphocytosis ≥ 3 areas of lymphadenopathy; no anemia or thrombocytopenia	7 yr
	C	Lymphocytosis Anemia (Hb < 10 g/dL) or thrombocytopenia (Plt < 100 × 10^9/L) ± ≥ 3 areas of lymphadenopathy	2 yr

Hb = hemoglobin; Plt = platelets.

Rai KR, et al. *Blood* 1975;46:219-34; Binet J, et al. *Cancer* 1981;148:198-206.

CLL International Prognostic Index

Prognostic Factor	Results	Points
FISH	Del17p/*TP53* mutation	4
Serum β_2	> 3.5 mg/dL	2
Rai stage	I-IV	1
IgHV	Unmutated	2
Age, years	> 65	1

Risk Category	Composite Risk Score	5-yr OS
Minimal risk	0-1	93%
Low risk	2-3	79%
Intermediate risk	4-6	64%
High risk	7-10	23%

IgHV = immunoglobulin heavy chain; OS = overall survival.

Parikh SA, et al. *Semin Oncol* 2016;42(2):233-40.

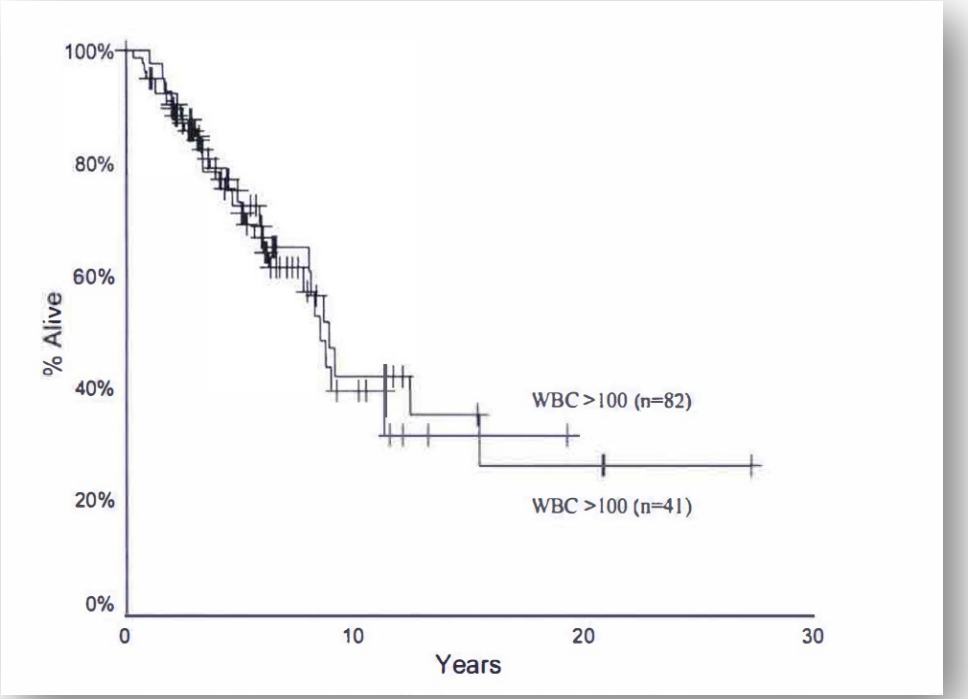
Genomic Alterations in CLL

Alteration	Risk (with sole abnormality)	Median Survival	Median TFS
13q deletion	Favorable	133 mo (11 yr)	92 mo (7.6 yr)
Normal	Neutral	111 mo (9.25 yr)	49 mo (4.1 yr)
Trisomy 12	Neutral	114 mo (9.5 yr)	33 mo (2.75 yr)
11q deletion	Unfavorable	79 mo (6.5 yr)	13 mo
17p deletion	Unfavorable	32 mo (2.6 yr)	9 mo

TFS = treatment-free survival.

Cramer P, et al. *Nat Rev Clin Oncol* 2011;8(1):38-47.

Elevated WBC Alone Is Not a Significant Adverse Prognostic Factor



Silverman JA, et al. *Leuk Lymphoma* 2002;43(6):1245-51.

Indications for Therapy Include the Extent and Severity of Disease Manifestations

Category	Reasons for Treatment
CLL-related symptoms	• Significant B symptoms (e.g., night sweats, fever without infection, severe fatigue, unintentional weight loss)
Tumor burden	• Massive nodes (i.e., 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy • Massive (i.e., 6 cm below the left costal margin) or progressive or symptomatic splenomegaly • Progressive lymphocytosis with an increase of > 50% over a 2-mo period • Lymphocyte doubling time < 6 months (if ALC > 30 x 10^9/L) • Threatened end-organ function (e.g., enlarged lymph node obstructing bowel) • Richter's transformation
Bone marrow failure	• Progressive anemia (Hb < 11 mg/dL) • Progressive thrombocytopenia (Plt < 100K)
Immune dysfunction	• Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy

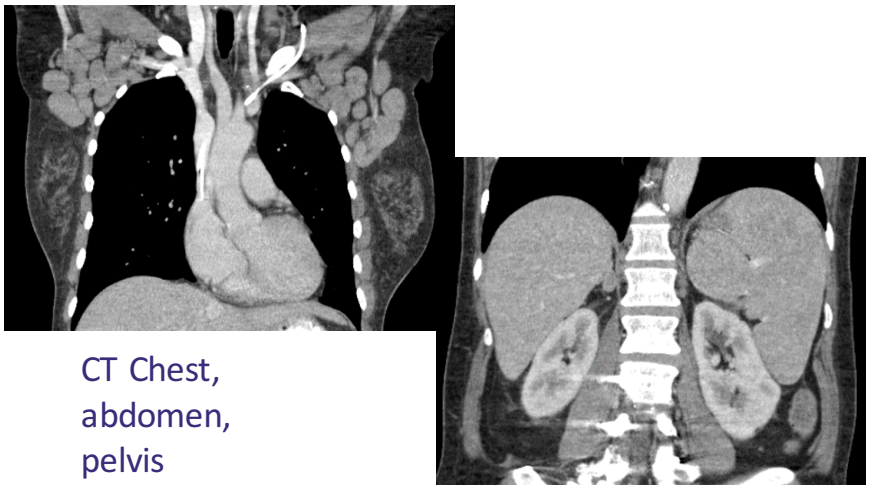
Hallek, M. *Am J Hematol* 2015;90(5):446-60; Hallek M, et al. *Blood* 2008;111(12):5446-56.

Case Study 1: 72-year-old Female

Rai stage: III (Hgb < 11 g/dL, splenomegaly, adenopathy, lymphocytosis)

CLL-IPI stage: **High risk**

17p+, Rai stage I-IV, IgHV unmutated, age > 65 = 8 points



CT Chest, abdomen, pelvis

Indication to Treat

- Progressive or symptomatic lymphadenopathy
- Fevers without infection

Images courtesy of Sandra Kurtin, PhDc, ANP-C, AOCN.

FDA-Approved Drugs to Treat CLL

Drug	Drug Class	Brand
Alemtuzumab	Anti-CD52 MoAb	Campath
Bendamustine	Nitrogen mustard/purine analog combined	Bendeka
Chlorambucil	Alkylating agent	Leukeran
Cyclophosphamide	Alkylating agent	Cytoxan
Fludarabine	Purine analog	Fludara
Ibrutinib	Bruton kinase inhibitor	Imbruvica
Idelalisib	PI3 kinase inhibitor	Zydelig
Lenalidomide	Immunomodulatory agent	Revlimid
Obinutuzumab	Anti-CD20 MoAb	Gazyva
Ofatumumab	Anti-CD20 MoAb	Arzerra
Rituximab	Anti-CD20 MoAb	Rituxan
Venetoclax	BCL2 inhibitor	Venclexta
Vincristine	Vinca alkaloid	Oncovin

CLL Front-Line Treatment

Stage	Fitness	Del(17p)/p53 mutation	Therapy
Binet A-B, Rai 0-II, inactive	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Fit and low comorbidity index (Go-Go)	No	Chemoimmunotherapy FCR (age < 70) BR (age > 65) Ibrutinib
		Yes	Ibrutinib* Alemtuzumab
	Unfit and/or complex comorbidities (Slow-Go)	No	Chlorambucil *+ MoAb Obinutuzumab*; rituximab; ofatumumab Ibrutinib*
		Yes	Ibrutinib* Rituximab Ofatumumab

*NCCN category 1

Hallek, M. *Am J Hematol* 2015;90(5):446-60; NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas, v.2.2017.

Fludarabine in CLL

- FDA approved in 1991 for use in CLL
- Remains a preferred regimen for younger and fit patients in combination with rituximab
  - Response rate 80% in previously untreated patients
- Hematologic and infectious toxicities common
  - ANC ≤ 500 in 59%
  - Long-term depletion of CD4+ T lymphocytes
  - ≥ 2-g drop in Hb in 60%
  - ≥ 50% drop in platelets in 55%

CLL10: Phase III FCR vs. BR in Frontline Response

Response, %	FCR (n = 284)	BR (n = 280)
CR	39.7%	30.8%
ORR	95.4%	95.7%

- Median observation time: 36 months
- Median PFS
  - ***FCR: 55.2 months vs. BR: 41.7 months (p < .001)***
- 3-year OS (no significant difference)
  - ***FCR: 90.6% vs. BR: 92.2% (p = .89)***

ANC = absolute neutrophil count.

NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas, v.3.2017;
Fludarabine package insert, Sagent Pharmaceuticals, 201,
https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020038s033lbl.pdf.

Ibrutinib

RESONATE (n = 391)

- Ibrutinib vs. ofatumumab in previously treated CLL/SLL
- At median 9.4 months of follow-up ibrutinib vs. ofatumumab:
  - ORR: 42.6% vs. 4.1%, $p < .001$
  - PFS: NR vs. 8.1 months (HR, 0.22; $p < .001$)
  - OS: 90% vs. 81% at 9.4 months of follow-up (HR, 0.43; $p = .005$)

RESONATE 2 (n = 269)

- Ibrutinib vs. chlorambucil in treatment-naive CLL/SLL age > 65
- At median 18.4 months of follow-up ibrutinib vs. chlorambucil
  - ORR: 86% vs. 35%, $p < .001$
  - PFS: NR vs. 18.9 months (HR, 0.16; $p = .001$)
  - OS: 98% vs. 85% at 24 months (HR, 0.16; $p = .001$)

NR = not reported; HR = hazard ratio.

Byrd JC, et al. *N Engl J Med* 2014;371(3):213-23; Burger JA, et al. *N Engl J Med* 2015;373(25):2425-37.

Lymphocytosis With Ibrutinib

Analysis of blood from 59 patients with CLL treated with ibrutinib on clinical trials

- Lymphocytosis is common
- Related to the trafficking of lymphocytes from nodal regions to peripheral blood
- Resolves within 8 months in the majority of patients (range 4–12 months)
- Persistent lymphocytes ***do not*** represent clonal evolution
- PFS is not inferior for patients with prolonged lymphocytosis vs. those with traditional responses

Woyach JA, et al. *Blood* 2014;123(12):1810-7.

Ibrutinib Toxicity

Common adverse events (≥ 20%)

- Thrombocytopenia
- Diarrhea
- Neutropenia
- Anemia
- Fatigue
- Musculoskeletal pain
- Peripheral edema
- Upper respiratory tract infection
- Nausea

Common grade 3/4 nonhematologic adverse events (≥ 5%)

- Pneumonia
- Abdominal pain
- **Atrial fibrillation**
- Diarrhea
- Fatigue
- Skin infections (5%)

- Treatment-emergent grade ≥ 3 cytopenias reported in nearly half of patients

Ibrutinib package insert, Janssen Pharmaceutical, 2013, https://www.janssenmd.com/pdf/imbruvica/PI-Imbruvica.pdf.

Ibrutinib and Atrial Fibrillation

- Risk of atrial fibrillation and atrial flutter
  - Patients with cardiac risk factors
  - Acute infections
  - History of atrial fibrillation
- Monitor closely for atrial fibrillation
- If symptomatic atrial fibrillation, consider discontinuation of ibrutinib

Ibrutinib package insert, Janssen Pharmaceutical, 2013, https://www.janssenmd.com/pdf/imbruvica/PI-Imbruvica.pdf.

Ibrutinib and Bleeding Risk

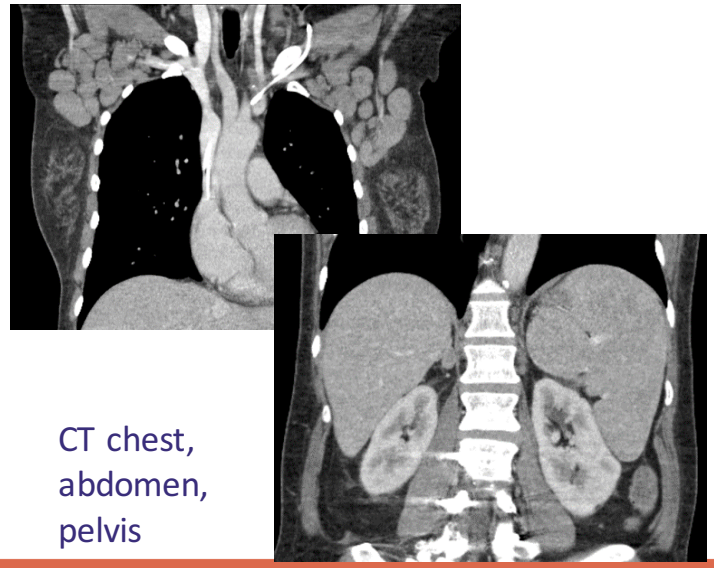
- Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients
- Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with ibrutinib
- The mechanism for the bleeding events is not well understood
- Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies
- Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre- and post-surgery depending on the type of surgery and the risk of bleeding

Ibrutinib package insert, Janssen Pharmaceutical, 2013, https://www.janssenmd.com/pdf/imbruvica/PI-Imbruvica.pdf.

Case Study 1: 72-year-old Female

Rai Stage: III (Hgb < 11 g/dL, splenomegaly, adenopathy, lymphocytosis)
CLL-IPI Stage: **High risk**

17p+, Rai stage I-IV, IgHV unmutated, Age > 65 = 8 points



CT chest, abdomen, pelvis

Indication to treat

- Progressive or symptomatic lymphadenopathy
- Fevers without infection

Treatment selection

- **Ibrutinib**
- **Rationale: 17p+, age > 65, comorbidities**

Images courtesy of Sandra Kurtin, PhDc, ANP-C, AOCN.

Relapsed/Refractory CLL

Definitions: Progression, Relapse, Refractory

Progression of disease

- Lymphadenopathy: Increase ≥ 50%
- Hepatomegaly: Increase ≥ 50%
- Splenomegaly: Increase ≥ 50%
- Blood lymphocytes: Increase ≥ 50% over baseline
  - ***Isolated progressive lymphocytosis in the setting of reduce lymph node size organomegaly or improvement in hemoglobin or platelets will not be considered progressive disease***
- Platelets: Decrease ≥ 50% over baseline secondary to CLL
- Hemoglobin: Decrease > 2 g/dL from baseline secondary to CLL

Relapse: Evidence of disease progression after a period of 6 months or more following an initial CR or PR

Refractory: Failure to achieve a response for having disease progression within 6 months of the last treatment

PR = partial response.

Hallek M, et al. *Blood* 2008;111(12):5446-56.

Clonal Evolution and RR CLL

- Clonal evolution (CE): the acquisition of new cytogenetic abnormalities during the disease course
  - Disease characteristics at relapse may be different than at initial diagnosis
  - Acquired mutations drive CLL relapse
- Clonal evolution in CLL by FISH has implications for overall survival:
  - Acquisition of high-risk abnormalities: (deletion 17p or 11q) associated with inferior overall survival
  - Acquisition of low/intermediate abnormalities: (trisomy 12, deletion 13q, and IGH translocation) had no difference in OS
- Richter's transformation is not clearly associated with known mutations

Woyach JA, et al. *N Engl J Med*. 2014;370:2286-2294; Huang SJ, et al, *Cancer Genet*. 2017;210:1-8.

CLL Second-Line Treatment

Response to First-Line therapy	Fitness	Therapy	
		Standard	Alternatives
Refractory or progression within 2 years	Fit and low comorbidity index (Go-Go)	Ibrutinib* Idelalisib + rituximab* Venetoclax (17p) Chemoimmunotherapy Allogeneic SCT (?)	Lenalidomide BR Other kinase inhibitors
	Unfit and/or complex comorbidities (Slow-Go)	Change therapy (include in trial)	Ibrutinib * Idelalisib + rituximab* Venetoclax (17p) Alemtuzumab (del17p) Rituximab Ofatumumab Lenalidomide FCR-lite HD Rituximab
Progression after 2 years	All	Repeat first-line therapy	

SCT = stem cell transplantation; HD = high dose; NCCN = National Comprehensive Cancer Network.

*NCCN category 1

Hallek, M. *Am J Hematol* 2015;90(5):446-60; NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas, v.2.2017.

Idelalisib

- Phase II, multicenter, randomized, double-blind, placebo-controlled, study comparing idelalisib/rituximab vs. rituximab/placebo
- 220 patients (↓ CrCl, myelosuppression, or major coexisting illnesses)
- Median PFS: NR in I/R vs. 5.5 months in R/P (HR, 0.15; $p < .001$)
- ORR: 81% (I/R) vs. 13% (R/P) (odds ratio, 29.92; $p < .001$) at 12 months of follow-up
- OS: 92% (I/R) vs. 80% (R/P) (HR, 0.28; $p = .02$) at 12 months of follow-up
- Serious adverse events occurred in 40% of the patients receiving idelalisib and rituximab and in 35% of those receiving placebo and rituximab

I/R = idelalisib/rituximab; R/P = rituximab/placebo; CrCl = creatinine clearance.

Idelalisib + Rituximab: Adverse Events

Adverse Event	Any Grade n (%)	Grade ≥ 3 n (%)
Pyrexia	32 (29)	3 (3)
Fatigue	26 (24)	3 (3)
Chills	24 (22)	2 (2)
Diarrhea	21 (19)	4 (4)
Dyspnea	12 (11)	2 (2)
Rash	11 (10)	2 (2)
ALT/AST elevation	38 (35)	6 (5)
Anemia	28 (25)	6 (5)
Neutropenia	60 (55)	37 (34)
Thrombocytopenia	19 (17)	11 (10)

Serious Adverse Event	Any Grade n (%)
Pneumonia	7 (6)
Pyrexia	7 (6)
Febrile neutropenia	5 (5)
Sepsis	4 (4)
Pneumonitis	4 (4)
Diarrhea	3 (3)
Neutropenia	3 (3)
Pneumocystis pneumonia	3 (3)
Neutropenic sepsis	3 (3)
Dyspnea	1 (1)
Cellulitis	1 (1)

ALT = alanine transaminase; AST = aspartate transaminase.

Idelalisib: Considerations for Patient Management

Manufacturer-Recommended Dose Modifications			
Toxicity	**Recommended Management**		
Pneumonitis, severe skin rash	Any symptomatic occurrence, discontinue idelalisib		
ALT/AST	> 3–5 x ULN	5–20 x ULN	> 20 x ULN
	• Continue idelalisib • Monitor weekly until ≤ 1 x ULN	• Hold idelalisib • Monitor weekly until ≤ 1 x ULN • Resume at 100 mg twice/day	Discontinue idelalisib
Bilirubin	> 1.5–3 x ULN	> 3–10 x ULN	> 10 x ULN
	• Continue idelalisib • Monitor weekly until ≤ 1 x ULN	• Hold idelalisib • Monitor weekly until ≤ 1 x ULN • Resume at 100 mg twice/day	Discontinue idelalisib
Diarrhea	Moderate	Severe or Hospitalized	Life-Threatening
	• Continue idelalisib • Monitor until resolved	• Hold idelalisib • Monitor weekly until resolved • Resume at 100 mg twice/day	Discontinue idelalisib

Idelalisib prescribing information, Gilead Sciences, Inc. 2014, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf.

Venetoclax in Relapsed CLL With del(17p)

- Proteins in the B-cell CLL/lymphoma 2 (BCL-2) family are key regulators of the apoptotic process
- Venetoclax induces p53-independent apoptosis of CLL cells
- Phase I study showed 79% response rate to venetoclax in patients with R/R CLL
  - ORR for R/R CLL with del(17p): 71% (95% CI = 52%–86%)
- A single dose of ABT-199 in 3 patients enrolled in the phase I trial with refractory CLL resulted in tumor lysis within 24 hours

R/R = relapsed/refractory.

Souers AJ, et al. *Nat Med* 2013;19(2):202-8; Roberts AW, et al. *N Engl J Med* 2016;374(4):311-22.

Venetoclax in R/R CLL With del(17p): Study Design

- Single-arm, multicenter phase II study, 107 patients with R/R CLL with del(17p)
- Titrated dosing of venetoclax (5 week ramp-up)*
  - 20 mg QD week 1
  - 50 mg QD week 2
  - 100 mg QD week 3
  - 200 mg QD week 4
  - 400 mg QD week 5+
- **Risk-based TLS prophylaxis used**
- Primary endpoint: ORR (IRC assessment)
- Secondary endpoints: CR/PR, time to first response, DoR, PFS, OS, safety
- Exploratory endpoint: **MRD**

QD = once per day; IRC = independent review committee; DoR = duration of response; MRD = minimal residual disease
* FDA approved dosing – ramp up dosing schedule was different in this clinical trial.

Phase II Trial Venetoclax Monotherapy in CLL With del(17p)

- Overall response: 79% (20% CR)
- 15-month PFS: 69%
- Among 87 patients with baseline lymphocytosis, only 4 failed to normalize ALC count to < 4 x 10^9/L
  - Median time to normalization: 22 days (range: 2–122)
- Among 96 patients with baseline lymphadenopathy, 89 had ≥ 50% reduction in nodal size of the largest target lesion (by SPD)
  - Median time to ≥ 50% reduction: 2.7 mo (range: 0.7–8.4 mo)

Roberts AW, et al. *N Engl J Med* 2016;374(4):311-22.

Venetoclax in R/R CLL With del(17p): Adverse Events

- Grade 3 or 4 neutropenia (in 41%)
  - Manageable with dose interruption or reduction, G-CSF, and/or antibiotics
- Mild diarrhea (52%)
- Upper respiratory tract infection (48%)
- Nausea (47%)

G-CSF = granulocyte colony-stimulating factor.

Roberts AW, et al. *N Engl J Med* 2016;374(4):311-22.

TLS Risk Stratification

- **TLS risk category, percent in the phase II study**
  - High: 42%
  - Medium: 40%
  - Low: 18%
- TLS occurred in 3 of 56 patients in the dose-escalation cohort, with 1 death
- After adjustments to the dose-escalation schedule, clinical TLS did not occur in any of the 60 patients in the expansion cohort
- The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS

Roberts AW, et al. *N Engl J Med* 2016;374(4):311-22.

TLS Risk Stratification and Prophylaxis

LOW Tumor Burden	All LN < 5 cm AND ALC < 25 x 10^9/L
Prophylaxis	Allopurinol Oral hydration (1.5–2 liters/day)
Setting	Outpatient
TLS Monitoring	Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg Pre-dose at subsequent ramp-up doses

MEDIUM Tumor Burden	LN 5 cm to < 10 cm OR ALC ≥ 25 x 10^9/L
Prophylaxis	Allopurinol Oral hydration (1.5–2 liters/day) Consider supplemental hydration for at risk patients
Setting	Outpatient*
TLS Monitoring	Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg Pre-dose at subsequent ramp-up doses

*Consider hospitalization for patients with CrCl < 80 mL/min at first dose of 20 mg and 50 mg.

Roberts AW, et al. *N Engl J Med* 2016;374(4):311-22; Venetoclax prescribing information, AbbVie and Genentech, 2016, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf.

TLS Risk Stratification and Prophylaxis (cont.)

HIGH Tumor Burden	**Any LN ≥ 10 cm OR ALC ≥ 25 x 10^9/L AND Any LN ≥ 5 cm**
Prophylaxis	Oral (1.5–2 liters) and IV (150–200 mL/hr as tolerated) Allopurinol; consider rasburicase if baseline uric acid is elevated
Setting	First dose at 20 mg and 50 mg inpatient Subsequent doses given outpatient
TLS Monitoring	20-mg and 50-mg dosing: Pre-dose, 4, 8, 12, and 24 hours Subsequent dosing: Pre-dose, 6 to 8 hours, 24 hours

Roberts AW, et al. *N Engl J Med* 2016;374(4):311-22; Venetoclax prescribing information, AbbVie and Genentech, 2016, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf.

Venetoclax Combinations in Relapsed/Refractory CLL

Agents	Phase	Setting	Results
Venetoclax + rituximab	Ib	Patients with R/R CLL/SLL (n = 49)	• ORR: 86% (MRD- in 53%) • PFS at 1 year: 87%; OS at 1 year: 94% • Tolerable safety profile
Venetoclax + obinutuzumab	Ib	Patients with R/R or treatment-naive CLL (n = 32)	• ORR: 100% (24% CR/CRi) • AEs appear to be manageable • Cytopenia is most frequent AE, but no patient discontinued treatment due to AEs • TLS prophylaxis effective even in patients with higher disease burden
Venetoclax + BR	Ib	Patients with R/R or treatment-naive CLL (n = 30)	• ORR: 100% (10% CR) • AEs appear to be manageable • Most common AEs: neutropenia and nausea

Cri = CR with incomplete blood count recovery.

Ma S, et al. ASH 2015. Abstract 830; Flinn IW, et al. ASH 2015. Abstract 494; Salles GA, et al. ASH 2015. Abstract 829.

Selected Studies Combining Ibrutinib and Venetoclax

Ongoing Studies	Study Investigator	Study Design	Estimated Date for Data Reporting
ML29533 (R/R, 1L)	Jones (OSU)	Phase Ib dose-escalation of venetoclax + obinutuzumab/ibrutinib up to 14 cycles in absence of unacceptable toxicity/PD followed by phase II	Phase Ib – ASH 2016
CLL13 (1L fit)	German CLL Study Group	Phase II open-label study of ibrutinib + venetoclax/obinutuzumab to 12 cycles	Pending finalization
10915/A15-746: CLARITY (R/R)	Hillmen (UK)	Phase II study of ibrutinib + venetoclax	Interim – pre-2021

PD = progressive disease.

https://clinicaltrials.gov/ct2/show/NCT02427451; https://clinicaltrials.gov/ct2/show/NCT02758665; Cancer Research UK, A study of venetoclax and ibrutinib for chronic lymphocytic leukemia (CLARITY), http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-of-venetoclax-and-ibrutinib-for-chronic-lymphocytic-leukaemia-clarity.

Second-Generation Bruton Kinase Inhibitors

- Acalabrutinib (ACP-196)
  - Acalabrutinib was granted Breakthrough Therapy Designation by the FDA in August 2017, for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy based on results of the ACE-LY-004 clinical trial
  - BGB-3111
- Both drugs are more selective for BTK and are designed to minimize off-target activity with minimal effects on other kinases such as TEC, EGFR, or ITK
- Expect limited utility in patients with mutations conveying resistance to ibrutinib

BTK = Bruton's tyrosine kinase.

Byrd JC, et al. *N Engl J Med* 2016;374:323-32; Tam C, et al. ASH 2015. Abstract 832.

Ofatumumab

- Fully human anti-CD20 monoclonal antibody
- FDA approved in 2009 for use in patients with CLL refractory to fludarabine and alemtuzumab
- Premedicate with acetaminophen, antihistamine, and corticosteroid
- Dosing is variable

Ofatumumab prescribing information, Novartis, 2011, https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/arzerra.pdf.

Ofatumumab (cont.)

- No black box warnings
- Warnings and precautions include
  - Infusion reactions (44% with first infusion; 29% with second infusion)
  - Cytopenias
  - Progressive multifocal leukoencephalopathy
  - Hepatitis B reactivation

Results in Fludarabine and Alemtuzumab Refractory	
Overall response rate (%)	42%
Complete response rate (%)	0%
Median duration of response (months)	6.5%

Ofatumumab prescribing information, Novartis, 2011, https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/arzerra.pdf.

Ofatumumab Side Effects

Adverse event	Total population (n = 154; %)
Neutropenia	60
Pneumonia	23
Fever	20
Cough	19
Diarrhea	18
Anemia	16
Fatigue	15
Rash	14
Dyspnea	14
Nausea	11
Upper respiratory tract infection	11
Bronchitis	11

Ofatumumab prescribing information, Novartis, 2011, https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/arzerra.pdf.

Obinutuzumab/Chlorambucil vs. Rituximab/Chlorambucil vs. Chlorambucil Alone

- 781 previously untreated patients with CLL/SLL with comorbidities: median age 73, median CrCl 62 mL/min, median CIRS score of 8

Regimen	ORR	PFS	OS
G/Clb (n = 238)	78.4% (CR 20.7%)	26.7 mo	20%
R/Clb (n = 233)	65.1% (CR 7%)	16.3 mo	
Clb (n = 118)		11.1 mo	9%
G/Clb vs. Clb		HR, 0.18; 95% CI = 0.13–0.24; p <.001	HR, 0.41; 95% CI = 0.23–0.74; p =.002
R/Clb vs. Clb		HR, 0.44; 95% CI = 0.34–0.57; p <.001	NR
G/Clb vs. R/Clb	HR, 0.39; 95% CI = 0.31–0.49; p < .001	HR, 0.39; 95% CI = 0.31–0.49; p <.001	NR

G/Clb = obinutuzumab/chlorambucil; R/Clb = rituximab/chlorambucil (R/Clb); Clb = chlorambucil alone; CIRS = Cumulative Illness Rating Scale.

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

Obinutuzumab Adverse Events Grade ≥ 3

- Vary with combinations
- Most common
  - Infusion-related reactions: more common with obinutuzumab (21%) than rituximab (4%) in this study
  - Cytopenias including leukopenia
  - Infections: pneumonia is most common

Ongoing Clinical Trials and Emerging Agents in CLL

Agent	Mechanism of Action	Initial Therapy	Relapsed Therapy
Duvelisib	PI3K-δ,γ inhibitor		Duvelisib vs. ofatumumab (phase III) Duvelisib/obinutuzumab after BTK inhibitor
Acalabrutinib (ACP-196)	Bruton tyrosine kinase inhibitor	Acalabrutinib alone vs. acalabrutinib plus obinutuzumab vs. obinutuzumab plus chlorambucil (phase III)	Acalabrutinib vs. ibrutinib (phase III)
Pembrolizumab	PD-1 inhibitor		Relapsed/refractory CLL (phase II)
CAR-T cells	Adoptive T-cell therapy		Relapsed/refractory CLL (phase I/II)