New Drug Update

Alex Ganetsky, PharmD, BCOP
Hematology/Oncology Clinical Pharmacy Specialist
Hospital of the University of Pennsylvania

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Disclosure

- I have no potential or actual conflicts of interest

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Objectives

- Describe the mechanisms of action of recently approved drugs for hematologic malignancies
- Discuss the efficacy data pertaining to each new drug
- Review the toxicity profile of each new drug

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Ibrutinib

- Oral irreversible tyrosine kinase inhibitor (TKI) of Bruton's tyrosine kinase (BTK)
  - Binds BTK at C481 residue
- Food and Drug Administration (FDA) approved indications
  - Relapsed chronic lymphocytic leukemia (CLL) patients who received ≥ 1 prior therapy
  - CLL with 17p deletion
  - Relapsed mantle cell lymphoma (MCL) patients who received ≥ 1 prior therapy
- Dosing
  - CLL 420 mg once daily
  - MCL 560 mg once daily
- Metabolism
  - Major CYP3A4 substrate

Bhatt V, et al. *Pharmacotherapy.* 2014;34:303-314.

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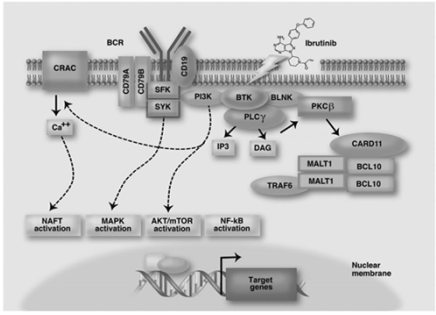
B-Cell Receptor (BCR) Signaling Pathway



Adapted from: Rossi D, et al. *Blood.* 2014;123:1772-4.

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Phase 1b/2: Ibrutinib in Relapsed/Refractory (R/R) CLL

- ≥ 2 prior therapies including purine analogue
  - Cohort 1: Ibrutinib 420 mg once daily (n=27)
  - Cohort 2: Ibrutinib 840 mg once daily (n=34)
- No response to chemoimmunotherapy
  - Cohort 3: Ibrutinib 420 mg once daily (n=24)

Byrd JC, et al. *N Engl J Med.* 2013; 369:32-42.

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Efficacy

Baseline Characteristics

- Median age 66 years
  - ≥ 70 years – 35%
- Median of four previous therapies
- Rai stage 3/4 – 65%
- 17p deletion – 33%

	No. of patients	ORR (95% CI)
All patients	85	71 (60 – 80)
Dose		
420 mg	51	71 (56 – 82)
840 mg	34	71 (52 – 85)
Age		
<70 years	55	69 (51 – 81)
≥70 years	30	71 (57 – 82)
Rai stage at baseline		
0 – II	29	69 (49 – 85)
III – IV	55	71 (57 – 82)
Previous chemotherapy		
< 3 regimens	27	74 (68 – 89)
≥ 3 regimens	58	69 (56 – 81)
17p deletion		
Positive	28	68 (48 – 84)
Negative	52	71 (57 – 83)
11q deletion		
Positive	31	77 (59 – 90)
Negative	49	65 (50 – 78)
IGHV		
Mutated	12	33 (10 – 65)
Unmutated	69	77 (65 – 86)

IGHV, immunoglobulin heavy chain variable; ORR, overall response rate.

Byrd JC, et al. *N Engl J Med.* 2013; 369:32-42.

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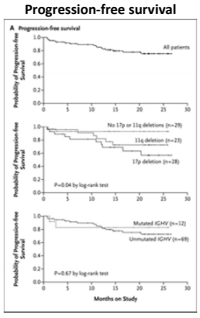
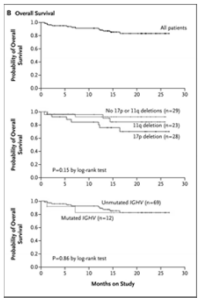
Efficacy

Progression-free survival



Overall survival



Adapted from: Byrd JC, et al. *N Engl J Med.* 2013; 369:32-42.

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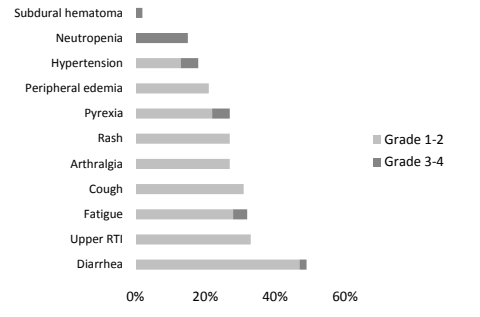
Safety



Byrd JC, et al. *N Engl J Med.* 2013; 369:32-42.

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RESONATE Trial: Ibrutinib vs Ofatumumab in R/R CLL

- Phase 3 (N=391)
- ≥ 1 prior CLL therapy
- Primary endpoint – Progression-free survival (PFS)

RANDOMIZE

- Ibrutinib 420 mg once daily (n=195)
- Ofatumumab 300 mg week 1 then 2000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks (n=196)

Byrd JC, et al. *N Engl J Med.* 2014;371:213-223.

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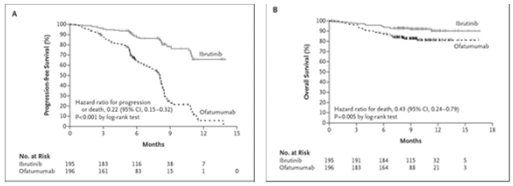
RESONATE Trial: Efficacy



- Trial terminated early due to significant improvement in efficacy with ibrutinib compared to ofatumumab
- PFS benefit with ibrutinib maintained in high-risk subgroups (17p del, 11q del, advanced age, Rai stage 3/4, bulky disease)
- Overall response rate (ORR) 63% vs 4%

Adapted from: Byrd JC, et al. *N Engl J Med.* 2014;371:213-223.

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RESONATE Trial: Safety

Grade ≥ 3 Adverse Event, %	Ibrutinib (n=195)	Ofatumumab (n=191)
Any	51	39
Neutropenia	16	14
Pneumonia	7	5
Thrombocytopenia	6	4
Anemia	5	8
Diarrhea	4	2
Atrial fibrillation	3	0
Hemorrhage	1	2

Byrd JC, et al. *N Engl J Med.* 2014;371:213-223.

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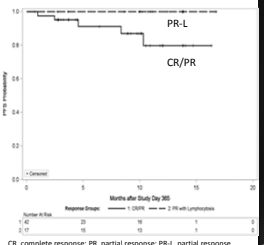
Early Lymphocytosis Associated with Ibrutinib

- Incidence of peripheral lymphocytosis (PL) with ibrutinib – 80%
- Class effect of all BCR antagonists
- Occurs by day 7 and may persist for months
- Reduction in lymph node size, spleen size, and improvement in cytopenias occurs in parallel with decline in PL



CR, complete response; PR, partial response; PR-L, partial response except lymphocytosis.
Image adapted from: Woyach JA, et al. *Blood.* 2014;213:10-17.

Woyach JA, et al. *Blood.* 2014;213:10-17.

Phase 2: Ibrutinib in R/R MCL

- Ibrutinib 560 mg once daily
- Patients enrolled received 1 – 5 prior MCL therapies

	No prior treatment with bortezomib (N=63)	Prior treatment with bortezomib (N=48)	All patients (N=111)
ORR, n(%) CR, n(%) PR, n(%)	43 (68) 12 (19) 31 (49)	32 (67) 11 (23) 21 (44)	75 (68) 23 (21) 52 (47)
Median duration of response, mo	15.8	NR	17.5
Median PFS, mo	7.4	16.6	13.9
Median OS, mo	NR	NR	NR

CR, complete response; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

- Comparable toxicity profile to ibrutinib CLL data

Wang ML, et al. *N Engl J Med.* 2013;369:507-516.

Precautions

- Mechanism of ibrutinib-associated bleeding poorly understood
- Ibrutinib should be held 3-7 days before and after surgical procedures due to risk of bleeding
- Increased risk of subarachnoid hemorrhage with concomitant warfarin

Byrd JC, et al. *J Clin Oncol.* 2014 July 21 [Epub ahead of print].

Potential Roles in HCT

- Treatment of chronic graft-versus-host disease (GVHD)
  - Rationale: B-cell inhibition via BTK and T-cell inhibition via interleukin-2-inducible kinase
  - Phase 1b/2 study currently ongoing evaluating ibrutinib in steroid dependent or refractory chronic GVHD
- Bridge therapy to HCT
- Maintenance therapy post-HCT

Dubovsky JA, et al. *J Clin Invest.* 2014 Oct 1 [Epub ahead of print].

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Audience Response Question

- Ibrutinib is currently FDA-approved for which of the following indications?

A. Relapsed acute myeloid leukemia
B. CLL with 17p deletion
C. Relapsed diffuse large B-cell lymphoma
D. Relapsed cutaneous T-cell lymphoma

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Summary

- Ibrutinib is the first orally available TKI to receive FDA approval for the treatment of CLL and MCL
- Ibrutinib has shown promising activity across a variety of B-cell malignancies
- Long-term toxicities have yet to be fully characterized
- Future research into combining ibrutinib with chemoimmunotherapy and/or emerging oral TKIs will further characterize its role in the treatment of hematologic malignancies

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Idelalisib

- Small molecule inhibitor of PI3Kδ
- FDA-approved indications
  - Relapsed CLL in combination with rituximab
  - Relapsed follicular lymphoma (FL) patients who received ≥ 2 prior therapies
  - Relapsed small lymphocytic lymphoma (SLL) patients who received ≥ 2 prior therapies
- Dosing
  - 150 mg orally twice daily
- Metabolism
  - Substrate of CYP3A4 (major), P-gp, UGT1A4
  - Inhibits CYP3A4 (strong), CYP2C19 (weak), CYP2C8 (weak), UGT1A1
- Black Box Warnings
  - Fatal and serious toxicities: hepatic, severe diarrhea, colitis, pneumonitis, intestinal perforation

Khan M, et al. *ISRN Oncol.* 2014:1-7.

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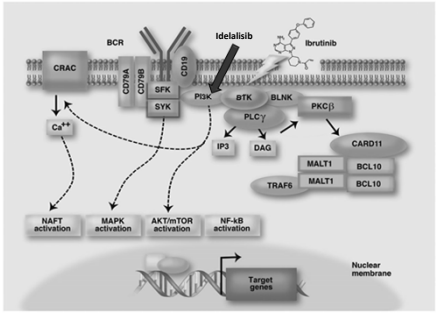
Idelalisib Mechanism of Action



Adapted from: Rossi D, et al. *Blood.* 2014;123:1772-4.

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Idelalisib + Rituximab in Relapsed CLL

- Phase 3 (N=220)
- Prior therapy included either CD20 monoclonal antibody-based regimen or ≥ 2 cytotoxic regimens
- CLL progression within 24 months after last treatment
- Primary endpoint - PFS

RANDOMIZE

- Idelalisib 150 mg twice daily + Rituximab* (n=110)
- Placebo + Rituximab* (n=110)

* Rituximab dosing: 375 mg/m² day 1 then 500 mg/m² every 2 weeks for 4 doses and then every 4 weeks for 3 doses for a total of 8 infusions.

Furman RP, et al. *N Engl J Med.* 2014;370:997-1007.

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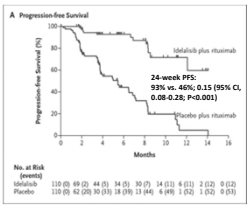
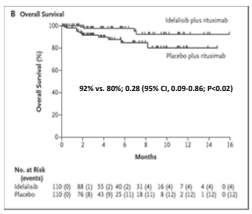
Efficacy





- Trial terminated at first interim analysis due to efficacy benefit in idelalisib/rituximab arm
- PFS significantly improved in high-risk subgroups randomized to idelalisib/rituximab arm (17p deletion, IGHV mutational status)
- ORR 81% vs. 13% (P<0.001) - All responses were PRs in both groups

Adapted from: Furman RP, et al. *N Engl J Med.* 2014;370:997-1007.

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Safety

Grade ≥ 3 Adverse Event, %	Idelalisib + Rituximab (n=110)	Placebo + Rituximab (n=107)
Any	56	48
Neutropenia	34	22
Thrombocytopenia	10	16
Anemia	5	14
ALT or AST elevation	5	1
Diarrhea	4	0

ALT, alanine aminotransaminase; AST, aspartate aminotransferase.

- Hepatotoxicity – related to nitrogen-based heterocyclic backbone
- Colitis – Decreased PI3Kδ results in intestinal inflammatory CD4+ T cell development (Th1 and Th17)

Furman RP, et al. *N Engl J Med.* 2014;370:997-1007. Steinbach EC, et al. *J Immunol.* 2014;192:3958-68.

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Phase 2: Idelalisib in R/R Indolent Non-Hodgkin's Lymphoma (NHL)

- Idelalisib 150 mg orally twice daily
- Inclusion - previously failed rituximab and alkylating agent
- Primary endpoint – ORR

Baseline Characteristics (N=125)	
Median age, y	64
Median number of prior regimens, n	4
Stage 3/4 disease, %	89%
Type of indolent NHL, %	
FL	58%
SLL	22%
MZL	12%

FL, follicular lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; SLL, small lymphocytic lymphoma.

Efficacy	
ORR, %	57%
CR, %	6%
PR, %	50%
Median time to response, mo	1.9
Median PFS, mo	11
Median OS, mo	20.3

CR, complete response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

- Safety: Grade ≥ 3 diarrhea/colitis 16% (median time to onset - 6 months)

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

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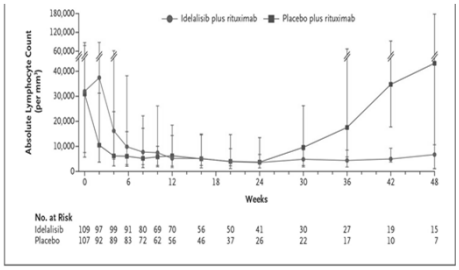
Impact of Rituximab on Idelalisib-Associated Lymphocytosis



Adapted from: Furman RP, et al. *N Engl J Med*. 2014;370:997-1007.

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Audience Response Question

- Which of the following is a black box warning associated with idelalisib?

A. Colitis
B. Nephrotoxicity
C. Myelosuppresion
D. Cardiomyopathy

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Summary

- FDA-approved for relapsed CLL/SLL and FL
- Key safety concerns – hepatotoxicity, colitis, pneumonitis
- Currently being evaluated as single-agent therapy and in combination for various B-cell malignancies
- Potential roles in HCT

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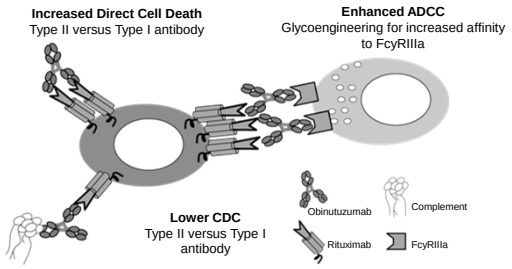
Obinutuzumab

- Humanized, glycoengineered type 2 CD20 monoclonal antibody
- FDA-approved indication
  - Previously untreated CLL in combination with chlorambucil
- Dosing
  - Cycle 1: 100 mg on day 1, 900 mg on day 2, and 1000 mg on days 8 and 15
  - Cycles 2 – 6: 1000 mg on day 1
- Black Box Warnings
  - Hepatitis B reactivation
  - Progressive multifocal leukoencephalopathy

Shah A. *Ann Pharmacother*. 2014;48:1356-61.

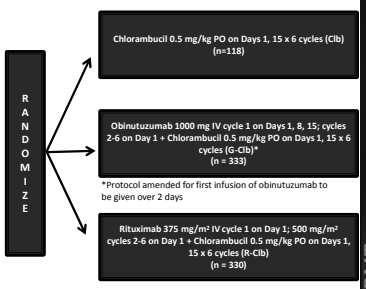
Mechanism: Type 1 vs Type 2 CD20 Monoclonal Antibody



Adapted from: Goede V et al. *Proc ASCO*. 2013;Abstract 7004.

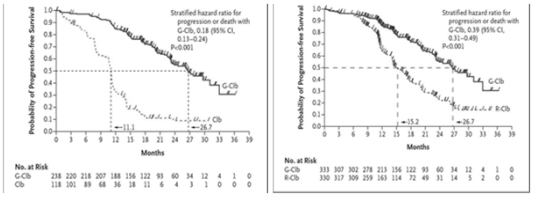
GCSG CLL11 Trial: Obinutuzumab in Patients with CLL and Coexisting Comorbidities

- Phase 3 (N=781)
- Previously untreated CLL
- Cumulative Illness Rating Scale > 6 and/or CrCl 30 – 69 mL/min
- Primary endpoint - PFS



Goede V, et al. *N Engl J Med*. 2014;370:1101-1110.

Efficacy



- PFS benefit with G-Clb maintained in all high-risk subgroups except del17p
- Improved OS with G-Clb compared Clb (0.41; 95% CI, 0.23-0.74; P=0.002) but not G-Clb vs R-Clb (0.66; 95% CI, 0.41-1.06; P=0.08)
- ORR: G-Clb 78.4% vs R-Clb 65.1% (P<0.001)

Adapted from: Goede V, et al. *N Engl J Med.* 2014;370:1101-1110.

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Safety

Grade ≥ 3 Adverse Event, %	Obinutuzumab + Chlorambucil (n=336)	Rituximab + Chlorambucil (n=321)
Any	70	55
Infusion-related reaction	20*	4
Neutropenia	33	28
Anemia	4	4
Thrombocytopenia	10	3
Infection	12	14
Pneumonia	4	5
Febrile neutropenia	2	1

*All during the first infusion. No grade 3/4 reactions during subsequent infusions.

Goede V, et al. *N Engl J Med.* 2014;370:1101-1110.

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Summary

- Obinutuzumab in combination with chlorambucil is effective and well-tolerated in treatment-naïve CLL
- Most appropriate for elderly and/or patients with comorbidities that are not candidates for aggressive chemoimmunotherapy

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Pomalidomide (POM)

- Immunomodulatory effects include:
  - Suppression of tumor necrosis factor-α
  - Costimulation of T-cell and natural killer cell function
  - Anti-angiogenesis
  - Cereblon inhibition
- FDA-approved indication
  - Patients with R/R multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy
- Dosing
  - 4 mg once daily days 1 – 21 of 28-day cycle
    - May be given in combination with dexamethasone (DEX)
- Metabolism
  - Substrate of CYP1A2 (major), CYP3A4 (major), CYP2C19 (minor), CYP2D6 (minor),and P-gp
- Black Box Warnings
  - Embryo-fetal toxicity
  - Venous thromboembolism

Holstein SA. *Clin Pharmacol Ther.* 2014;96:538-41.

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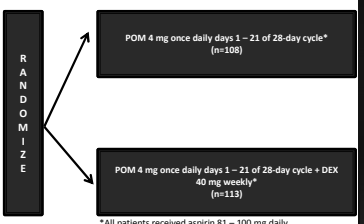
POM alone or in combination with low-dose DEX for R/R MM

- Phase 2 (N=221)
- ≥ 2 prior therapies (including lenalidomide and bortezomib) and progressed within 60 days of last treatment
- Primary endpoint - PFS



*All patients received aspirin 81 – 100 mg daily

Richardson PG, et al. *Blood.* 2014;123:1826-1832.

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Efficacy

- Median age: 63 years old
- Median prior therapies: 5
- Cytogenetic risk: high risk 27%, standard risk 45%

	POM + DEX (n=113)	POM alone (n=108)	P-value
Median PFS, months	4.2	2.7	0.003
Median OS, months	16.5	13.6	0.70
ORR	33	18	0.013
Median time-to-response, months	1.9	4.3	-
Median duration of response, months	8.3	10.7	-

DEX, dexamethasone; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POM, pomalidomide.

Richardson PG, et al. *Blood.* 2014;123:1826-1832.

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Safety

Grade 3-4 Adverse Event, %	POM + DEX (n=112)	POM alone (n=107)
Neutropenia	41	48
Anemia	22	24
Pneumonia	22	15
Thrombocytopenia	19	22
Fatigue	14	11
Acute renal failure	5	8
Deep vein thrombosis	2	3
Peripheral neuropathy	0	0

DEX, dexamethasone; POM, pomalidomide.

Richardson PG, et al. *Blood*. 2014;123:1826-1832.

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Summary

- Potential candidates for POM-based therapy
  - Patients who received prior lenalidomide and bortezomib and have become refractory to these agents
  - Patients who relapsed on lenalidomide and/or bortezomib and are refractory to subsequent therapy
  - Patients intolerant to other MM treatments
- Most common grade 3/4 adverse events (AEs) are myelosuppression and infection
  - Less constipation, asthenia, neuropathy, and rash compared with other immunomodulatory agents
- Thromboprophylaxis required for all patients on POM

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Blinatumomab

- Bispecific CD-19 directed CD3 T-cell engager
- FDA approval: R/R Philadelphia (Ph) chromosome-negative B-cell precursor acute lymphoblastic leukemia (ALL)
- Dosing
  - Hospitalization recommended for the first 9 days of the first cycle and the first 2 days of the second cycle
  - Cycle consists of 4 weeks of continuous infusion followed by 2-week treatment-free interval
  - Cycle 1: 9 mcg/day on days 1-7 and 28 mcg/day on days 8-28
  - Cycle 2: 28 mcg/day on days 1-28
  - Premedication with dexamethasone 20 mg IV 1 hour prior to first dose of each cycle and prior to a dose escalation
- Black Box Warnings
  - Cytokine release syndrome (CRS)
  - Neurologic toxicities

Blincyto [package insert]. Thousand Oaks, CA: Amgen Inc;2014.

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Blinatumomab for R/R ALL

- Phase 2, single-arm study
- R/R Ph- B-cell ALL

Efficacy Parameter	N=36
CR or CRh, %	69
CR, %	42
CRh, %	28
Median RFS, mo	7.6
Median OS, mo	9.8

CR, complete response; CRh, complete response with partial hematologic recovery; OS, overall survival; RFS, relapse-free survival.

- Most common any grade AEs were pyrexia (81%), fatigue (50%), headache (47%), tremor (36%), and leukopenia (19%)
- Nervous system or psychiatric toxicities occurred in 17% of patients
  - Pretreatment with cyclophosphamide/dexamethasone ameliorates severe CRS risk in patients with high tumor burden

Topp MS, et al. *J Clin Oncol.* 2014 Nov 10 [Epub ahead of print].

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Belinostat

- Pan-histone deacetylase inhibitor
- FDA Approved Indication
  - R/R peripheral T-cell lymphoma (PTCL)
- Dosing
  - 1000 mg/m^2 administered over 30 minutes by IV infusion on days 1 – 5 of a 21-day cycle
- BELIEF Trial
  - Phase 2, single-arm study in R/R PTCL after failure of ≥ 1 prior systemic therapies
  - Efficacy: ORR 26% (CR 10%, PR 16%), median duration of response 8.3 months
  - Safety: Most frequent grade 3/4 AEs were thrombocytopenia (13%), neutropenia (13%), anemia (10%), dyspnea (6%), and pneumonia (6%)

O'Connor OA, et al. *J Clin Oncol.* 2013;Abstr 8507.

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Defibrotide

- Sodium salt of a complex mixture of single-stranded oligodeoxyribonucleotides derived from porcine mucosal DNA
  - Anti-thrombic, anti-inflammatory, and anti-ischemic properties
- Multi-center, international phase 3 trial
- 102 patients (adult n=58; children n=44) with severe sinusoidal obstruction syndrome (SOS) received defibrotide 6.25mg/kg IV q6h daily (median 22 days)
  - Compared with 32 historical control patients
- 100-day OS: 38% vs. 25% (P<0.034)
- 100-day CR: 24% vs. 9% (P=0.013)
- Similar incidence of hemorrhagic AEs (65% vs. 69%)
- Results led to European Medicines Agency approval in October 2013 for the treatment of severe SOS in HCT

Richardson P, et al. Blood 2014;Abstr 2469.

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Audience Response Question

- POM + DEX demonstrated a higher rate of what endpoint compared to POM alone?

A. OS
B. PFS
C. Neutropenia
D. Peripheral neuropathy

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New Drug Update

Alex Ganetsky, PharmD, BCOP
Hematology/Oncology Clinical Pharmacy Specialist
Hospital of the University of Pennsylvania

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