New Drug Updates in Hematologic Malignancies

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2018 JADPRO Live
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Learning Objectives

1. Discuss the pharmacology and indications of medications approved in the year 2017-2018 for the management of patients with hematologic malignancies
2. Recall the pivotal clinical trial data considered by the FDA when approving new oncologic agents
3. Identify the signs and symptoms of serious or life-threatening adverse effects of newly approved oncology drugs
4. Describe the impact of these agents in advanced practice

Financial Disclosure

- Rebecca Nelson, PharmD, BCOP, has served on the speakers bureau and advisory board for BTG Inc.

Recap of 2016–2017 FDA Approvals

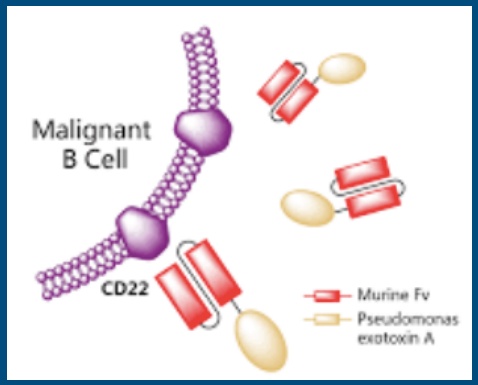
- Liposomal daunorubicin and cytarabine
- Gemtuzumab ozogamicin
- Tisagenlecleucel
- Inotuzumab ozogamicin
- Copanlisib
- Rituximab SC with hyaluronidase
- Midostaurin
- Enasidenib
- Ibrutinib

US Food and Drug Administration, Hematology/Oncology (Cancer) approvals & Safety Notifications, http://www.fda.gov/drugs/informationondrugs/approveddrugs.

2017–2018 FDA Approvals: Monoclonal Antibodies and CAR-T cells

- New approvals
  - Moxetumomab pasudotox-tdfk
  - Mogamulizumab-kpkc
  - Axicabtagene ciloleucel
- Expanded indications
  - Pembrolizumab
  - Tisagenlecleucel
  - Blinatumomab
  - Brentuximab vedotin
  - Obinutuzumab

US Food and Drug Administration, Hematology/Oncology (Cancer) approvals & Safety Notifications, http://www.fda.gov/drugs/informationondrugs/approveddrugs.



New Drug: Moxetumomab Pasudotox

Hairy Cell Leukemia

Approved: September 2018

US Food and Drug Administration, Hematology/Oncology (Cancer) approvals & Safety Notifications, http://www.fda.gov/drugs/informationondrugs/approveddrugs;
Image: www.pharmacodia.com

Moxetumomab Pasudotox

- **Mechanism:** CD22-directed antibody fused to a truncated bacterial toxin that inhibits protein synthesis and triggers apoptotic cell death.
- **Indication:** Adult patients with relapsed or refractory hairy cell leukemia who received at least 2 prior systemic therapies, including treatment with a purine nucleoside analog.
- **Dose:** 0.04 mg/kg IV over 30 minutes on days 1, 3, and 5 every 28 days for up to 6 cycles, disease progression, or unacceptable toxicity.

Moxetumomab Pasudotox (1053 Trial)

Phase III, single arm, open label

Efficacy measure	Result %, (95% CI)
Durable complete response rate[a,b]	30% (20, 41)
Overall response rate[c]	75% (64, 84)
Complete response rate[d]	41% (30, 53)
Partial response rate[e]	34% (24, 45)
Haematologic remission rate[b]	80%

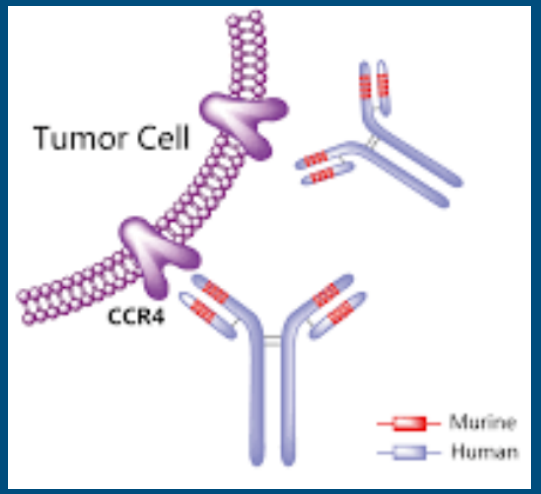
AstraZeneca Pharmaceuticals LP 2018. Lumoxiti (moxetumomab pasudotox-tdfk) Prescribing Information.

Moxetumomab Pasudotox (1053 Trial)

Phase III, single arm, open label

- Grade 3 or 4 adverse reactions (≥ 5%): hypertension, febrile neutropenia
- Capillary leak syndrome (CLS) and hemolytic uremic syndrome (HUS)
  - Grade 3 or 4 CLS occurred in 1.6% and 2% of patients, respectively.
  - Grade 3 or 4 HUS occurred in 3% and 0.8% of patients, respectively.
- **Adverse reactions** (≥ 20%): infusion-related reactions (50%), edema (39%), nausea (35%), fatigue (34%), headache (33%), pyrexia (31%), constipation (23%), anemia (21%), and diarrhea (21%).

New Drug: Mogamulizumab-kpkc



Relapsed/Refractory Mycosis Fungoides or Sézary Syndrome

Approved: August 2018

US Food and Drug Administration, Hematology/Oncology (Cancer) approvals & Safety Notifications, http://www.fda.gov/drugs/informationondrugs/approveddrugs. Image: www.pharmacodia.com

Mogamulizumab-kpkc

- **Mechanism**
  - Humanized IgG1 kappa monoclonal antibody that binds to CCR4 and aids in the trafficking of lymphocytes to various organs.
- **Indication**
  - Treatment of adult patients with relapsed or refractory mycosis fungoides or Sézary syndrome after at least 1 prior systemic therapy

Kyowa Kirin, Inc. 2018. Mogamulizumab-kpkc (Poteligeo) product information

Mogamulizumab-kpkc

- **Dose:** 1 mg/kg IV over 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent cycle
  - Pre-medicate with diphenhydramine and acetaminophen with the 1st infusion
- **Dose modifications**
  - Dermatologic toxicity
    - Grade 4 rash or SJS or TEN: Permanently discontinue
    - Grades 2 or 3 rash: Interrupt and administer at least 2 weeks of topical corticosteroids
    - Grade 1 rash: Consider topical corticosteroids
  - Infusion reactions
    - Temporarily interrupt for any infusion reaction
    - Permanently discontinue for any life-threatening infusion reaction

SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

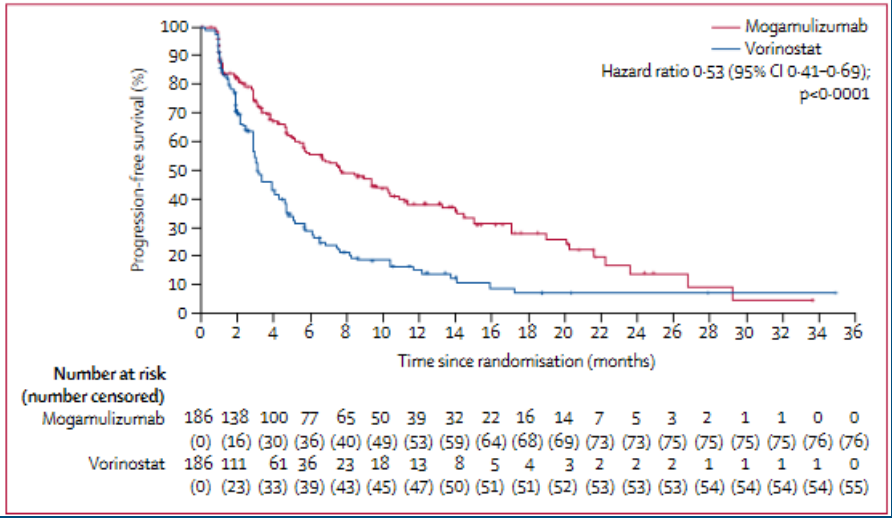
Kyowa Kirin, Inc. 2018. Mogamulizumab-kpkc (Poteligeo) product information

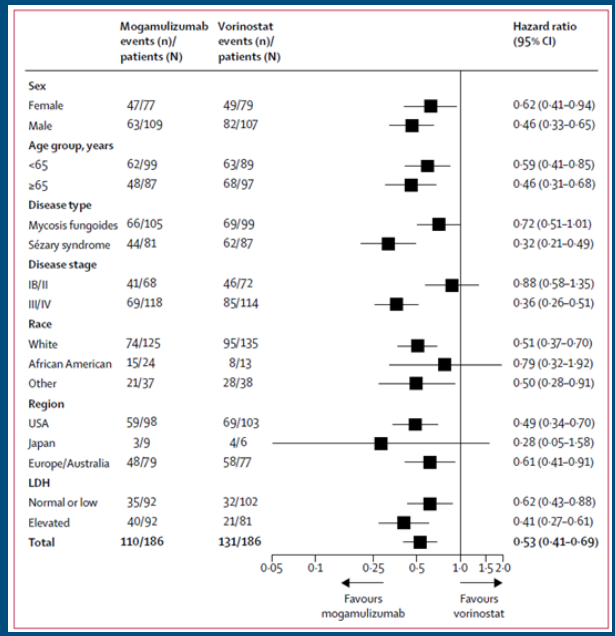
Mogamulizumab-kpkc

- Common adverse reactions (≥20%)
  - Rash, infusion related reactions, fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection
- Grade 3/4 adverse reactions (≥10%)
  - Edema, constipation, anemia, thrombocytopenia, headache, hypertension, cough

Kyowa Kirin, Inc. 2018. Mogamulizumab-kpkc (Poteligeo) product information

Mogamulizumab-kpkc (MAVORIC Trial)





Kim Y et al. *Lancet* 2018. S1470-2045(18)30379-6

Mogamulizumab-kpkc (MAVORIC Trial)

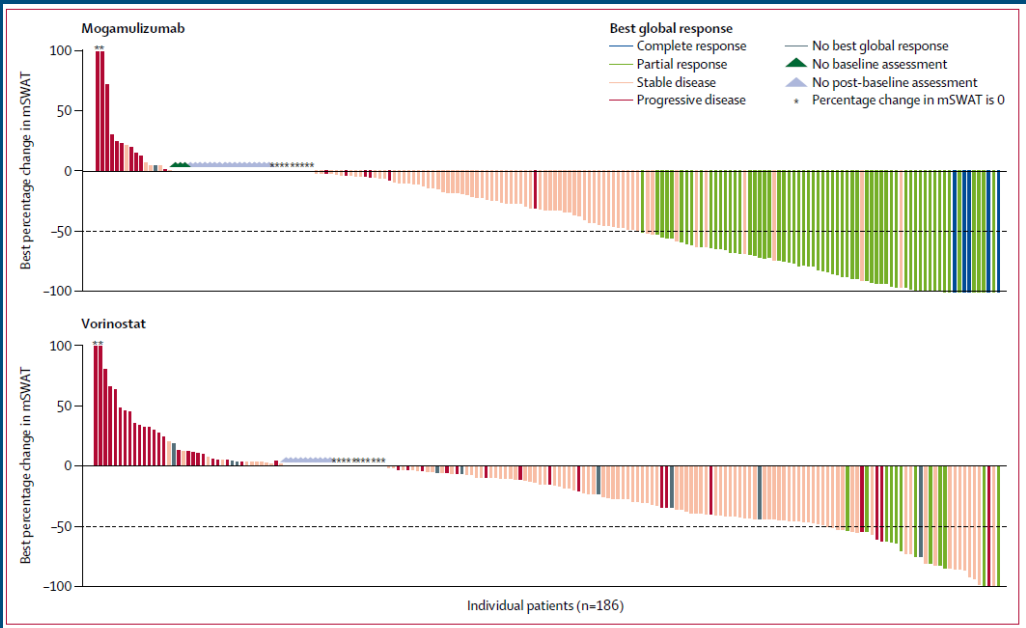


Figure 4: **Best global and skin responses**
Best skin response represented by maximum percentage change in skin mSWAT score. *Two patients in the mogamulizumab group and two in the vorinostat group had a more than 100% increase in mSWAT from baseline. mSWAT=modified Severity Weighted Assessment Tool.

	Mogamulizumab (n=186)	Vorinostat (n=186)
Proportion of patients with an overall response by global assessment*†	52/186 (28%)	9/186 (5%)
Overall responses in patient subgroups		
Mycosis fungoides	22/105 (21%)	7/99 (7%)
Sézary syndrome	30/81 (37%)	2/87 (2%)
Stage IB or IIA	7/36 (19%)	5/49 (10%)
Stage IIB	5/32 (16%)	1/23 (4%)
Stage III	5/22 (23%)	0/16 (0)
Stage IV	35/96 (36%)	3/98 (3%)
Duration of response, months	14·1 (8·4–19·2)	9·1 (5·6–NE)
Mycosis fungoides	13·1 (4·7–18·0)	9·1 (5·6–NE)
Sézary syndrome	17·3 (9·4–19·9)	6·9 (6·9–6·9)
Compartment response*‡		
Skin	78/186 (42%)	29/186 (16%)
Blood	83/122 (68%)	23/123 (19%)
Lymph nodes	21/124 (17%)	5/122 (4%)
Viscera	0/3 (0%)	0/3 (0%)

Data are n/N (%) or median (IQR). The proportion of patients achieving an overall response is based on the Global Composite Response score. NE=not estimable. *Proportion of patients with an overall response or compartmental response is the percentage of patients with confirmed complete response or confirmed partial response. †p<0·0001. ‡Denominator includes patients with measurable compartmental disease at baseline.

Table 2: **Measures of response by investigator assessment**

Kim Y et al. *Lancet* 2018. S1470-2045(18)30379-6

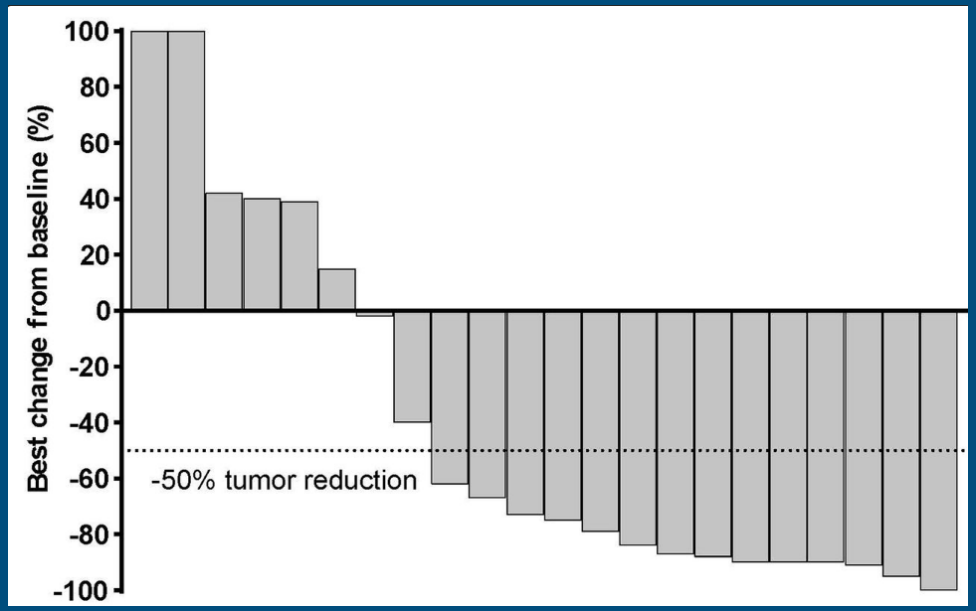
Expanded Indication: Pembrolizumab (KEYNOTE-170 Trial)

- Adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.
- Approval based on data from 53 patients with relapsed or refractory PMBCL enrolled in a multicenter, open-label, single-arm trial.
  - Patients were treated with pembrolizumab 200 mg IV every 3 weeks until unacceptable toxicity or documented disease progression, or for up to 24 months or progression
- **Common adverse reactions** (≥10%): musculoskeletal pain, upper respiratory tract infection, pyrexia, fatigue, cough, dyspnea, diarrhea, abdominal pain, nausea, arrhythmia, and headache.

PMBCL = primary mediastinal large B-cell lymphoma

Zinzani et al., *Blood.* 2017;130(suppl 1):2833

Expanded Indication: Pembrolizumab (KEYNOTE-170 Trial)



- Overall response was 45%
  - 11% complete responses
  - 34% partial responses
- Median duration of response was not reached within the follow-up period
  - Median 9.7 months
- Median time to first objective response was 2.8 months
- *Pembrolizumab is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy*

Zinzani et al., *Blood*. 2017;130(suppl 1):2833

Expanded Indication: Blinatumomab (BLAST Trial)

- Treatment of adult and pediatric patients with B-cell ALL in first or second complete remission with MRD greater than or equal to 0.1%
- Approval based on the open-label, multicenter, single-arm BLAST trial (n=86)
  - Inclusion
    - Received at least 3 chemotherapy lines of standard ALL therapy
    - Complete hematologic remission (defined as < 5% blasts in bone marrow, absolute neutrophil count > 1 Gi/L, platelets > 100 Gi/L)
    - MRD at a level of greater than or equal to 0.1% using an assay with a minimum sensitivity of 0.01%
- Blinatumomab was administered at a dose of 15 µg/m^2/day (equivalent to the dose of 28 µg/day) for all treatment cycles.
- Patients received up to 4 cycles of treatment.

ALL = acute lymphoblastic leukemia; MRD = minimal residual disease.

Gökbuget N et al., *Blood*. 2018 Apr 5;131(14):1522-1531

Expanded Indication: Blinatumomab (BLAST Trial)

	All patients	MRD responders*	MRD nonresponders*
OS			
Patients with events, n/N	48/110	31/85	14/22
Median† (95% CI)	36.5 (19.8-NR)	38.9 (33.7-NR)	12.5 (3.2-NR)
Estimated probability at 18 months (95% CI)†	0.67 (0.58-0.75)	0.70 (0.59-0.79)	0.34 (0.15-0.54)
P‡	—	.002	
Hematologic RFS			
Patients with events, n/N	62/110	40/85	12/15
Median† (95% CI)	18.9 (12.3-35.2)	23.6 (17.4-NR)	5.7 (1.6-13.6)
Estimated probability at 18 months (95% CI)†	0.53 (0.44-0.62)	0.58 (0.46-0.68)	0.20 (0.05-0.42)
P‡	—	.002	
Duration of hematologic remission§			
Patients with events, n/N	38/110	23/85	7/15
Median† (95% CI)	NR (NR-NR)	NR (NR-NR)	NR (3.7-NR)
Estimated probability at 18 months (95% CI)†	0.70 (0.61-0.78)	0.77 (0.67-0.85)	0.53 (0.30-0.80)
P¶	—	.14	

	All patients (N = 116)		
	Any grade	Grade 3	Grade 4
Any adverse event, n (%)	116 (100)	38 (33)	31 (27)
Non-neurologic adverse events, worst grade ≥3 occurring in ≥3% of patients			
Pyrexia	103 (89)	9 (8)	0 (0)
Headache	44 (38)	4 (3)	0 (0)
Neutropenia	18 (16)	2 (2)	16 (14)
Leukopenia	8 (7)	5 (4)	2 (2)
Anemia	7 (6)	4 (3)	1 (1)
ALT increased	7 (6)	2 (2)	4 (3)
Thrombocytopenia	6 (5)	2 (2)	3 (3)
AST increased	5 (4)	1 (1)	3 (3)
Any neurologic adverse event*	61 (53)	12 (10)	3 (3)
Neurologic events, worst grade ≥3			
Tremor	35 (30)	6 (5)	0 (0)
Aphasia	15 (13)	1 (1)	0 (0)
Dizziness	9 (8)	1 (1)	0 (0)
Confused state	6 (5)	1 (1)	0 (0)
Encephalopathy	6 (5)	3 (3)	2 (2)
Seizure	3 (3)	1 (1)	1 (1)
Disorientation	3 (3)	1 (1)	0 (0)
Depressed level of consciousness	1 (1)	1 (1)	0 (0)
Generalized tonic-clonic seizure	1 (1)	1 (1)	0 (0)

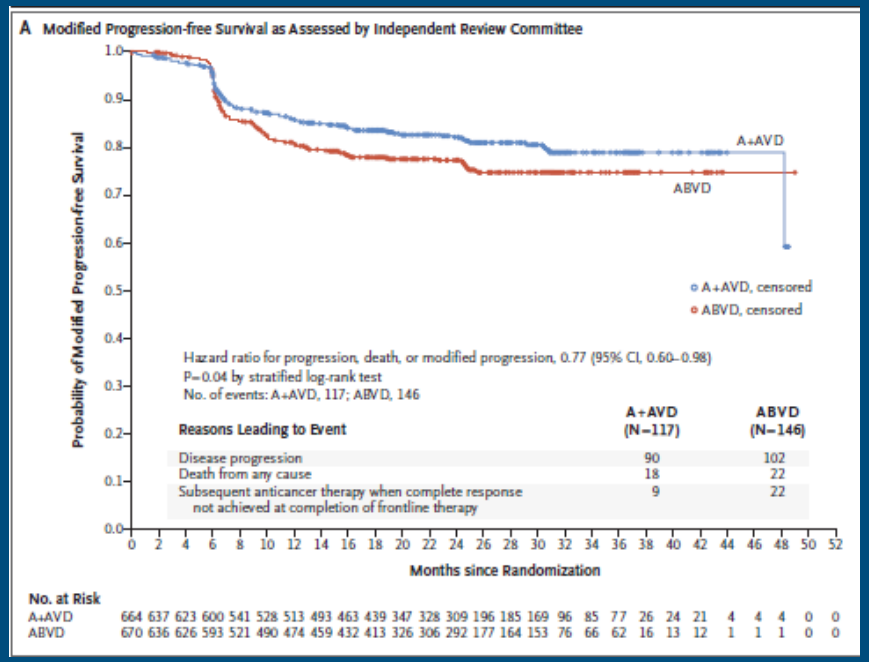
Gökbuget N et al., *Blood.* 2018 Apr 5;131(14):1522-1531

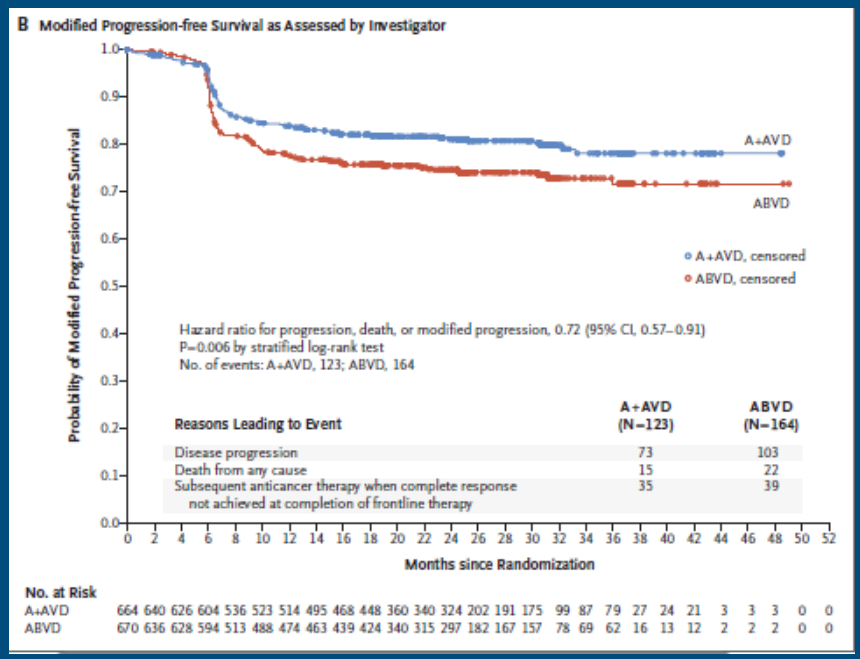
Expanded Indication: Brentuximab vedotin (ECHELON-1 Trial)

- Treatment of adult patients with previously untreated stage III or IV classical Hodgkin lymphoma in combination with chemotherapy
- Approval was based on a randomized, open-label, two-arm, multicenter trial (n=1,334)
  - Brentuximab vedotin (1.2 mg/kg (MAX 120 mg) plus doxorubicin, vinblastine, and dacarbazine (brentuximab vedotin + AVD) *or*
  - Bleomycin plus AVD (ABVD)
- Patients were randomized to receive up to 6 cycles on days 1 and 15 of each 28-day cycle

Connors et al., *N Engl J Med* 2018; 378:331-344

Expanded Indication: Brentuximab vedotin (ECHELON-1 Trial)





Connors et al., *N Engl J Med* 2018; 378:331-344

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Expanded Indication: Brentuximab vedotin (ECHELON-1 Trial)

Adverse Event (Grade ≥ 3)	A + AVD (N = 662)	ABVD (N = 659)
Neutropenia	357 (54%)	260 (39%)
Constipation	11(2%)	4 (<1%)
Vomiting	23 (3%)	9 (1%)
Fatigue	19 (3%)	7 (1%)
Peripheral neuropathy	27 (4%)	6 (<1%)
Diarrhea	19 (3%)	5 (<1%)
Pyrexia	19 (3%)	13 (3%)
Abdominal pain	21 (3%)	4 (<1%)

Connors et al., *N Engl J Med* 2018; 378:331-344

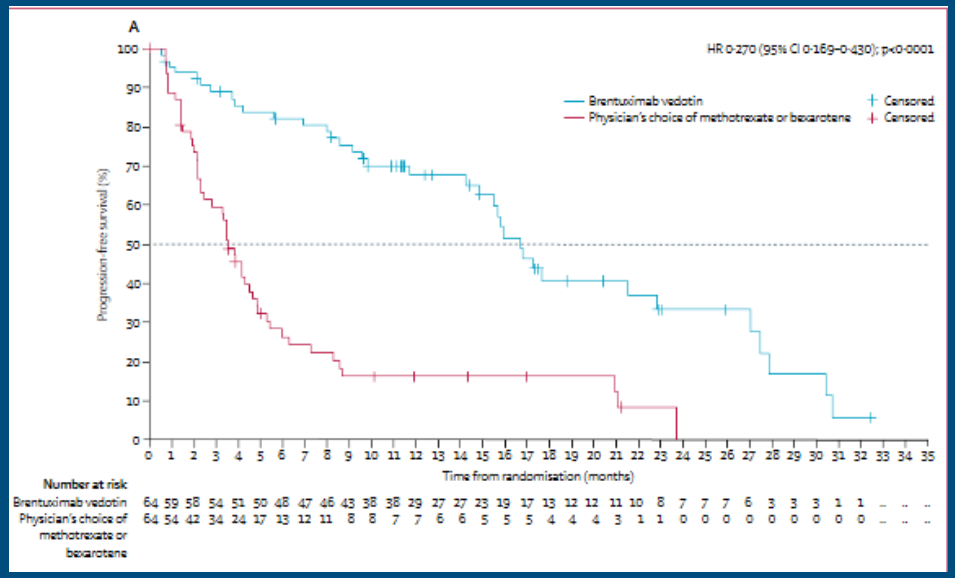
Expanded Indication: Brentuximab Vedotin (ALCANZA Trial)

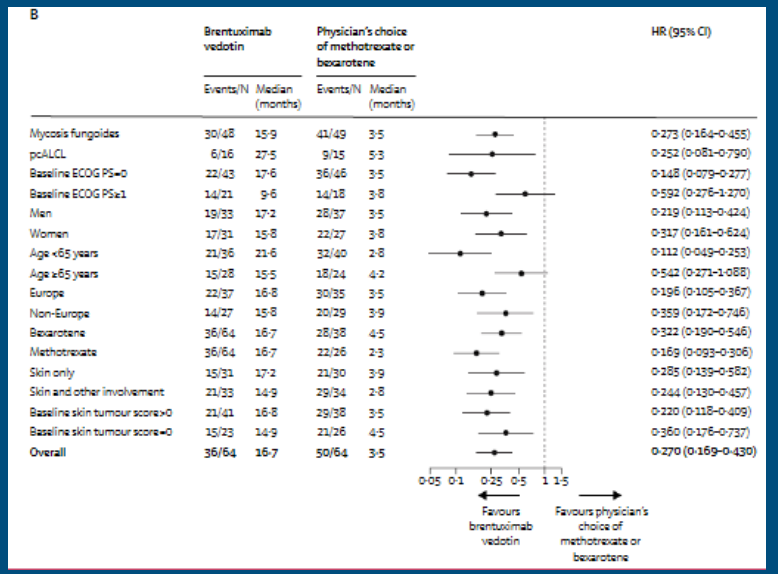
- Treatment of adult patients with pcALCL or CD30-expressing MF who have received prior systemic therapy
- Approval based on a phase III, randomized, open-label, multicenter clinical trial of brentuximab vedotin in 131 patients with MF or pcALCL who had previously received 1 prior systemic therapy and required systemic treatment.
  - Randomized to receive either brentuximab vedotin or the physician's choice of methotrexate or bexarotene.
- **Adverse reactions** (>20%): anemia, peripheral sensory neuropathy, nausea, diarrhea, fatigue, and neutropenia. The most common adverse event leading to discontinuation was peripheral neuropathy.
- **Dose:** 1.8 mg/kg up to a maximum of 180 mg every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity.

pcALCL = primary cutaneous anaplastic large cell lymphoma

Prince et al., *Lancet* 2017; 390: 555–66

Expanded Indication: Brentuximab Vedotin (ALCANZA Trial)





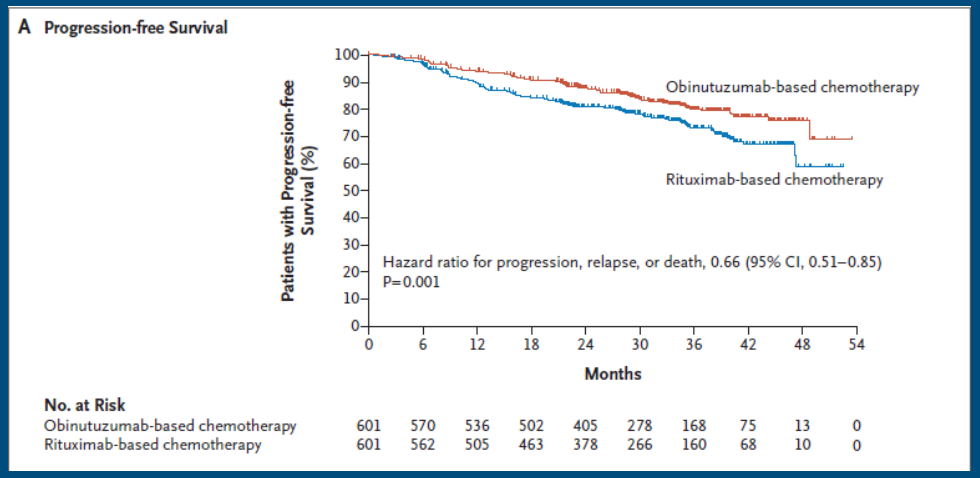
Prince et al., *Lancet* 2017; 390: 555–66

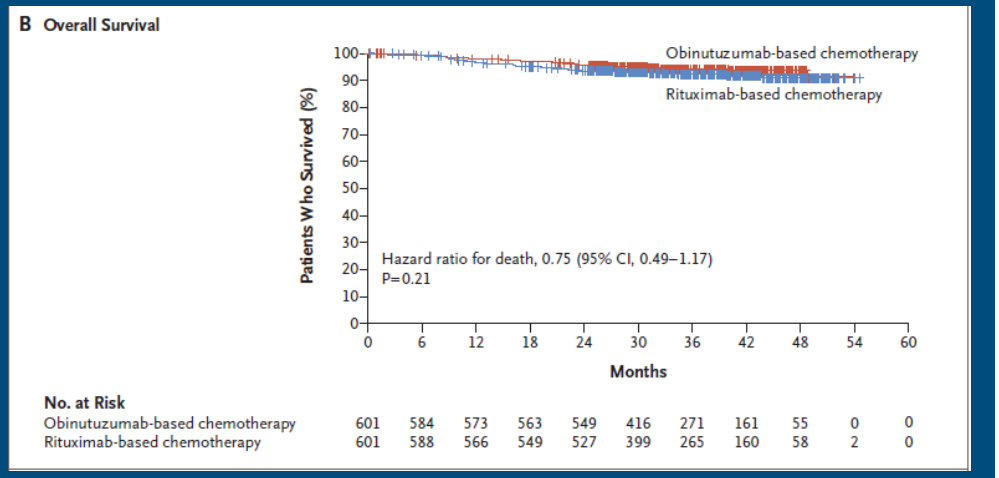
Expanded Indication: Obinutuzumab (GALLIUM Trial)

- Treatment of adult patients with previously untreated stage II bulky, III, or IV follicular lymphoma.
- Approval based on a multicenter, open-label, randomized phase 3 trial for patients with previously untreated non-Hodgkin lymphoma, including 1202 patients with FL.
- Randomized to obinutuzumab + chemotherapy or rituximab + chemotherapy, followed in responding patients by obinutuzumab or rituximab maintenance for up to 2 years.

Marcus R., et al., *N Engl J Med* 377;14

Expanded Indication: Obinutuzumab (GALLIUM Trial)





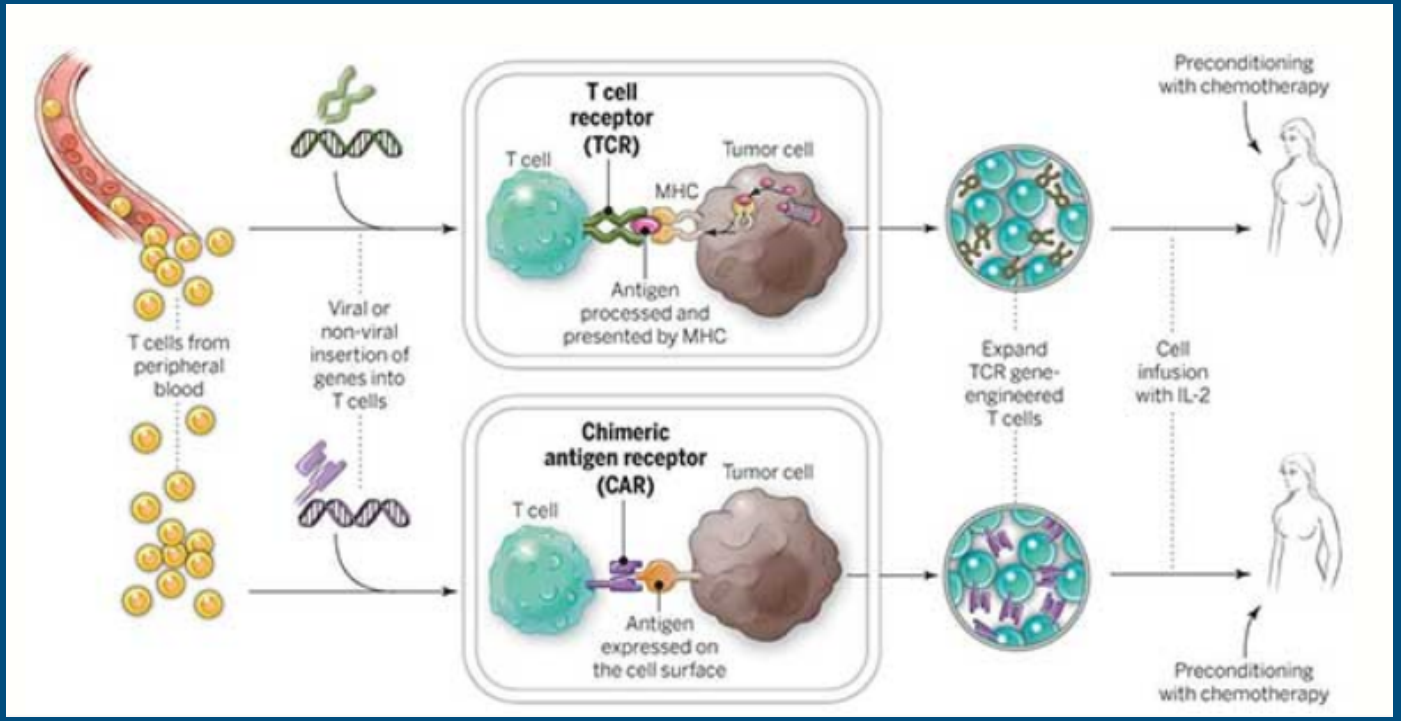
Marcus R., et al., *N Engl J Med* 377;14

Expanded Indication: Obinutuzumab (GALLIUM Trial)

- The obinutuzumab arm had a higher incidences of serious adverse compared to the rituximab arm (50% vs 43%), grade ≥ 3 reactions (79% vs. 72%) and fatal infections (2% vs. < 1%).
- Recipients of bendamustine had higher incidences of serious and fatal infections than recipients of CHOP or CVP.
- In patients with previously untreated FL, the recommended dose-schedule of obinutuzumab is 1000 mg intravenously on days 1, 8 and 15 of cycle 1; 1000 mg on day 1 of cycles 2-6 or cycles 2-8; and then 1000 mg every 2 months for up to 2 years.

Marcus R., et al., *N Engl J Med* 377;14

Chimeric Antigen Receptor (CAR) T Cells



Cancer.gov (https://www.cancer.gov/about-cancer/treatment/research/car-t-cells)

New CAR T-Cell Approval: Axicabtagene Ciloleucel

Relapsed/Refractory Large B-Cell Lymphoma

Approved: October 2017

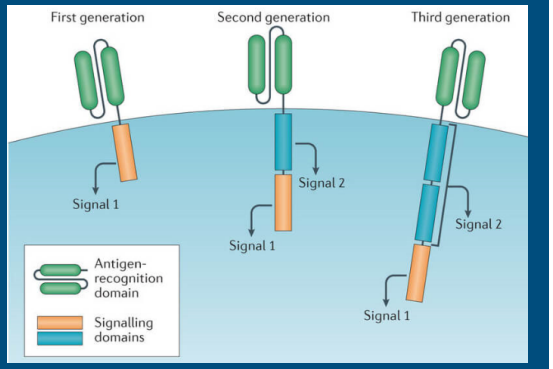


Image: Cancer.gov (https://www.cancer.gov/about-cancer/treatment/research/car-t-cells)

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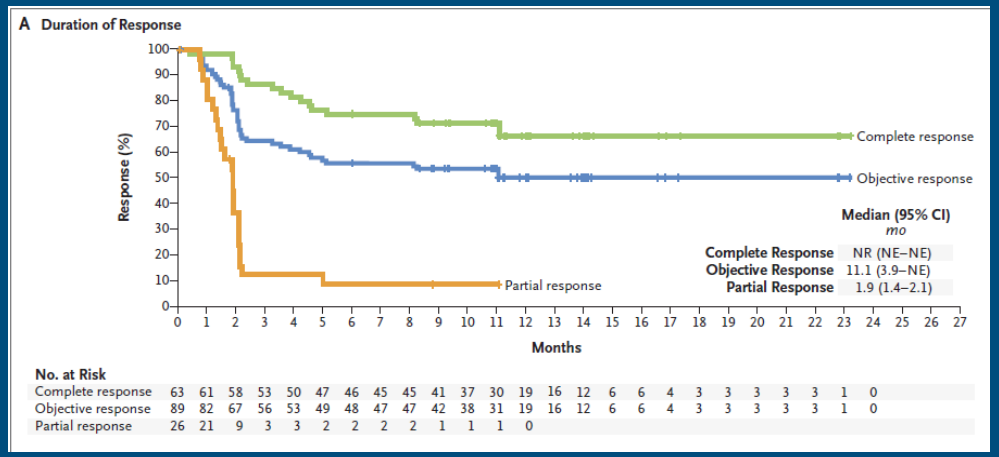
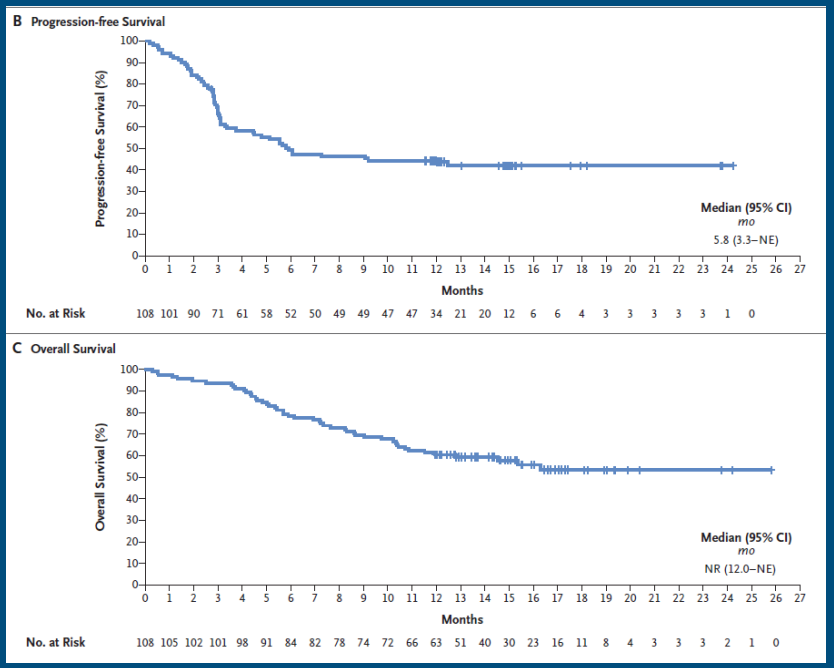
CAR-T Cells: Axicabtagene Ciloleucel

- **Mechanism:** Genetically modified CD19-directed autologous T cell immunotherapy
  - T cells are reprogrammed to identify and eliminate CD19-expressing malignant and normal cells.
  - This murine single-chain antibody recognizes CD19 and is fused to CD28 and CD3 zeta.
  - CD3 zeta is a critical component for initiating T-cell activation and secretion of inflammatory cytokines and chemokines, leading to destruction of CD19-expressing cells.
- **Indication:** Treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

Axicabtagene ciloleucel (YESCARTA) product information. 2017

CAR-T Cells: Axicabtagene Ciloleucel (ZUMA-1 Trial)





Neelapu SS et al., ***N Engl J Med*** **2017;377:2531-44.**

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CAR-T Cells: Axicabtagene Ciloleucel (ZUMA-1 trial)

- **Common grade 3 or higher adverse reactions** (≥10%): febrile neutropenia, fever, cytokine release syndrome (CRS), encephalopathy, infections, hypotension, and hypoxia.
  - Serious adverse reactions occurred in 52% of patients and included CRS, neurologic toxicity, prolonged cytopenias (including neutropenia, thrombocytopenia, and anemia), and serious infections.
- Fatal cases of CRS and neurologic toxicity occurred. FDA approved axicabtagene ciloleucel with a Risk Evaluation and Mitigation Strategy (REMS)
- **Dose:** Single IV infusion with a target of 2×10^6 CAR-positive viable T cells per kg body weight (maximum 2×10^8), preceded by fludarabine and cyclophosphamide lymphodepleting chemotherapy.
- Not indicated for the treatment of patients with primary central nervous system lymphoma.

Neelapu SS, et al., *N Engl J Med* 2017;377:2531-44.

Expanded Indication: Tisagenlecleucel (JULIET Trial)

- CD19-directed genetically modified autologous T-cell immunotherapy, for adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy including DLBCL not otherwise specified, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma
- Approval based on a single-arm, open-label, multi-center, phase II trial in 46 adult patients with relapsed or refractory DLBCL and DLBCL after transformation from follicular lymphoma.
- Patients received a single infusion of tisagenlecleucel following completion of lymphodepleting chemotherapy

Schuster et al., *Blood* 2017;130:577

Expanded Indication: Tisagenlecleucel (JULIET Trial)

- Overall response rate for 68 patients: 50% (95% CI: 37.6, 62.4)
- Complete response rate: 32% (95% CI: 21.5, 44.8)
- Median follow-up time: 9.4 months
- Duration of response (DOR) was longer in patients with best overall complete response, as compared to a best overall partial response.
  - Median DOR: not reached in patients who achieved a complete response
  - Median DOR: 3.4 months in patients who achieved a partial response
- **Common adverse reactions** (>20%): CRS, infections-pathogen unspecified, pyrexia, diarrhea, nausea, fatigue, hypotension, edema, and headache. Because of the serious risks of CRS and neurologic toxicities,
- FDA approved tisagenlecleucel with a REMS

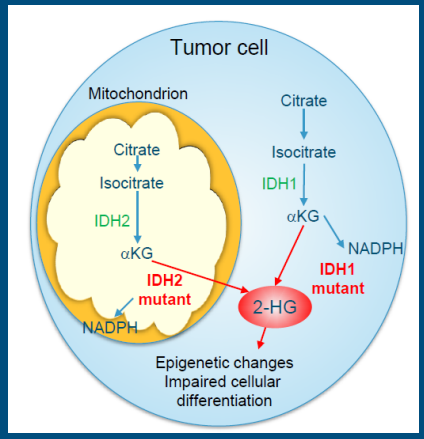
Schuster et al., Blood 2017 130:577

cytokine release syndrome (CRS)

2017-2018 FDA Approvals: Small-Molecule Inhibitors

- New drugs
  - Ivosidenib
  - Acalabrutinib
- Expanded indications
  - Nilotinib
  - Venetoclax
  - Bosutinib
  - Dasatinib

US Food and Drug Administration, Hematology/Oncology (Cancer) approvals & Safety Notifications, http://www.fda.gov/drugs/informationondrugs/approveddrugs.



New Approval: Ivosidenib

IDH1 Inhibitor in AML

Approved: July 2018

Dang et al. *Nature*.2009;462:739-744

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THE ANNUAL APSHO MEETING

Ivosidenib

- **Indication:** Treatment of adult patients with relapsed or refractory AML with a susceptible IDH1 mutation as detected by an FDA-approved test.
- **Mechanism:** Molecule inhibitor that targets the mutant isocitrate dehydrogenase 1 (IDH1) enzyme and reduces 2-hydroxyglutarate, blast counts, and induces differentiation of cells.

Ivosidenib (Tibsovo) product information. 2018

Ivosidenib

- **Dose:** 500 mg orally once daily with or without food until disease progression or unacceptable toxicity.
  - Avoid high-fat meals
  - Supplied as 250-mg tablets
- **Drug interactions:** Strong CYP3A4 inhibitor and inducer. Sensitive CYP3A4 substrate. Avoid or monitor concomitant QTc prolonging drugs.

Ivosidenib (Tibsovo) product information. 2018

Ivosidenib

- **Black Box Warning:** Differentiation syndrome; fatal if not treated. If suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.
- **Warnings**
  - QTc interval prolongation: Monitor electrocardiograms and electrolytes. If QTc interval prolongation occurs, dose-reduce or withhold, then resume dose or permanently discontinue.
  - Guillain-Barré syndrome: Monitor patients for signs and symptoms of new motor and/or sensory findings. Permanently discontinue in patients diagnosed with Guillain-Barré syndrome.

Ivosidenib (Tibsovo) product information. 2018

Ivosidenib

The most common adverse reactions (≥20%) were fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, mucositis, electrocardiogram QT prolonged, rash, pyrexia, cough, and constipation.

DiNardo et al., ***N Engl J Med*** **2018;378:2386-98**

Ivosidenib: Relapsed or Refractory AML (AG120-C-001 trial)

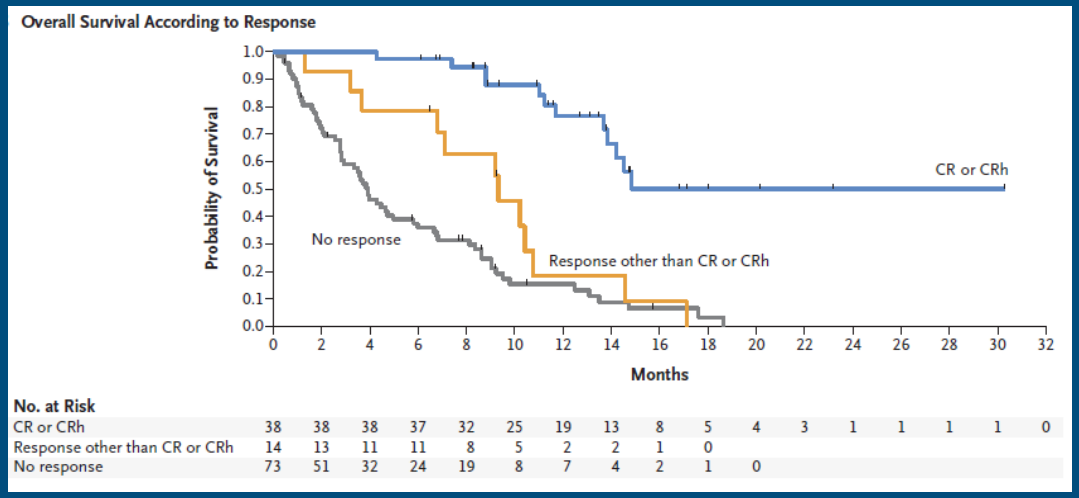


Table 2. Treatment-Related Adverse Events of Grade 3 or Higher Occurring in More than 1% of the Overall Population.*

Event	Relapsed or Refractory AML and Starting Dose of Ivosidenib of 500 mg Daily (N=179)	Overall Population (N=258)
	no. of patients (%)	
≥1 Treatment-related adverse event of grade 3 or higher	37 (20.7)	66 (25.6)
Prolongation of the QT interval on ECG	14 (7.8)	18 (7.0)
IDH differentiation syndrome†	7 (3.9)	12 (4.7)
Anemia	4 (2.2)	6 (2.3)
Thrombocytopenia	3 (1.7)	5 (1.9)
Leukocytosis	3 (1.7)	3 (1.2)
Febrile neutropenia	1 (0.6)	3 (1.2)
Diarrhea	1 (0.6)	3 (1.2)
Platelet count decreased	3 (1.7)	3 (1.2)
Hypoxia	2 (1.1)	3 (1.2)

DiNardo et al., *N Engl J Med* 2018;378:2386-98

New Approval: Acalabrutinib

Bruton Tyrosine Kinase (BTK) Inhibitor in Mantle Cell Lymphoma

2018 JADPRO Live
THE ANNUAL APSHO MEETING

Acalabrutinib

- **Mechanism:** Selective and irreversible second generation BTK inhibitor that decreases malignant B-cell proliferation and survival.
- **Indication:** Treatment of mantle cell lymphoma in patients who have received at least 1 prior line of therapy.
- **Dosing:** 100 mg every 12 hours until disease progression or unacceptable toxicity

Acalabrutinib (Calquence) product information. 2017

Acalabrutinib

- **Drug interactions**
  - Strong CYP3A inhibitor: Avoid (hold acalabrutinib if interaction is less than 7 days)
  - Moderate CYP3A inhibitor: Reduce acalabrutinib dose to 100 mg once daily
  - Strong CYP3A inducer: Avoid (if unable to avoid, increase acalabrutinib dose to 200 mg every 12 hours)
- Due to potential bleeding risk, consider interrupting treatment for 3-7 days prior to and after surgery

Acalabrutinib (Calquence) product information, 2017

Acalabrutinib

- **Dose adjustments**
  - Hematologic* and non-hematologic** toxicity
    - 1st and 2nd occurrence: Hold, resume at 100 mg BID once resolved to grade 1
    - 3rd occurrence: Hold, resume to 100 mg daily once resolved to grade 1
    - 4th occurrence: Discontinue
- **Adverse reactions:** Headache, skin rash, diarrhea, nausea, neutropenia, anemia, myalgia

*Grade 3 thrombocytopenia with bleeding, grade 4 thrombocytopenia, or grade 4 neutropenia lasting longer than 7 days

**Grade 3 or higher toxicity

Acalabrutinib (Calquence) product information, 2017

Acalabrutinib (ACE-LY-004 Trial)

Phase II, open-label, single-arm clinical trial (n=124) adult patients with relapsed or refractory MCL

Efficacy Measure	Result
Overall Response Rate	80% (95% CI: 72, 87)
Complete Response	40% (95% CI: 31, 49)
Partial Response	40% (95% CI: 32, 50)

Acalabrutinib (Calquence) product information, 2017

Expanded Information: Nilotinib (ENESTfreedom Trial) and (ENESTop Trial)

- ENESTfreedom, n=190
- Newly diagnosed patients who discontinued nilotinib after receiving it for 3 or more years
  - 51.6% remained in the TFR phase after 1 yr (48 wk)
  - 48.9% remained in the TFR phase after 2 yr (96 wk)
  - 96-wk data cutoff, among patients who restarted treatment due to loss of molecular response
  - 98.9% regained major molecular response
  - 92% regained MR4.5 by the cutoff date

- ENESTop n=126
- Patients who discontinued nilotinib after 3 or more years after switching from imatinib
  - 57.9% remained in the TFR phase after 48 wk
  - 53.2% remained in the TFR phase after 96 wk
  - 96-wk data cutoff, among patients who restarted treatment due to loss of molecular response
  - 92.9% regained molecular response (MR4.0 or M4.5).

TFM = treatment-free remission

Hochhaus et al., Leukemia. 2017 Jul;31(7):1525-1531; Mahon et al., Ann Intern Med. 2018 Apr 3;168(7):461-470

Expanded Information: Nilotinib (ENESTfreedom Trial) and (ENESTop Trial)

- No patient in either trial progressed to accelerated or blast phases of CML during TFR
- Common adverse reactions in patients who discontinued nilotinib include musculoskeletal symptoms including body aches, bone pain, and extremity pain
- Long-term outcomes of patients discontinuing vs. continuing treatment are unknown at this time

Hochhaus et al., Leukemia. 2017 Jul;31(7):1525-1531; Mahon et al., Ann Intern Med. 2018 Apr 3;168(7):461-470

Expanded Indication: Bosutinib (BFORE trial)

- Treatment of patients with newly-diagnosed chronic phase (Ph+) CML
- Approval based on data from an open-label, randomized, multicenter trial in 487 patients with Ph+ newly-diagnosed chronic phase CML who were randomized to receive either bosutinib 400 mg once daily or imatinib 400 mg once daily.
- Efficacy outcome measure was MMR at 12 months, defined as ≤0.1% BCR ABL ratio on international scale was statistically significant
  - MMR at 12 months
    - 47.2% (95% CI: 40.9, 53.4) in the bosutinib arm
    - 36.9% (95% CI: 30.8, 43.0) in the imatinib arm
- **Common adverse reactions** (≥20%): diarrhea, nausea, thrombocytopenia, rash, increased alanine aminotransferase, abdominal pain, and increased aspartate aminotransferase.

MMR = major molecular response

Cortes et al., *J Clin Oncol* 36:231-237

Expanded Indication: Dasatinib Phase I/Phase II Clinical Trials

- Approved for treatment of pediatric patients with (Ph+) chronic phase CML
- 97 pediatric patients with chronic phase CML evaluated in two trials
- Phase I, open-label, non-randomized, dose-ranging trial, and a phase II, open-label, non-randomized trial
  - 51 patients exclusively were newly diagnosed with chronic phase CML
  - 46 patients were resistant or intolerant to previous treatment with imatinib
  - Patients treated with dasatinib tablets 60 mg/m^2 once daily until disease progression or unacceptable toxicity
- After 24 months of treatment
  - 96.1% of newly diagnosed patients (95% CI: 86.5, 99.5) had (CCyR).
  - 82.6% of patients resistant or intolerant to imatinib (95% CI: 68.6, 92.2) had (CCyR).
  - Median durations of CCyR, major cytogenic response (MCyR), and major molecular response (MMR) could not be estimated as more than half of the responding patients had not progressed at the time of data cut-off (~5 years).
- **Adverse reactions** (≥10%): headache, nausea, diarrhea, skin rash, vomiting, pain in extremity, abdominal pain, fatigue, and arthralgia

CML = chronic myeloid leukemia.

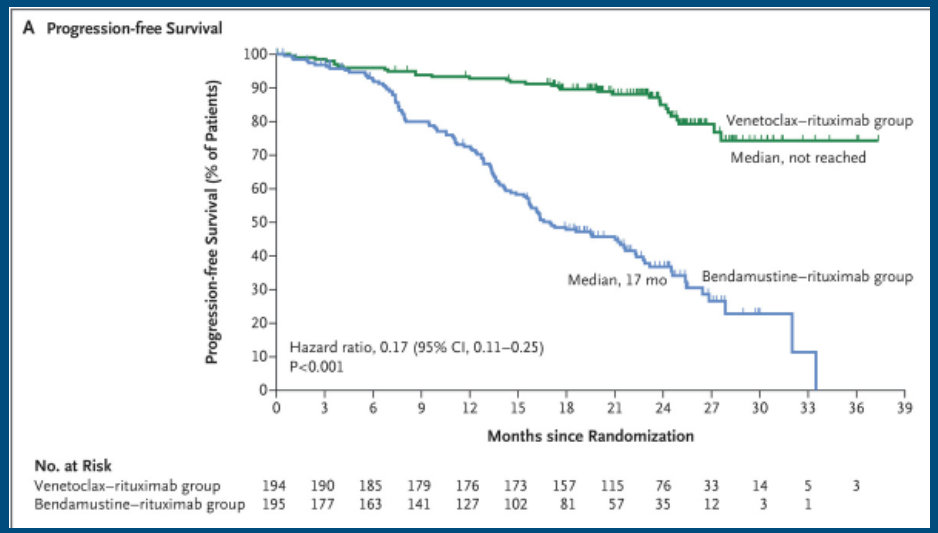
Expanded Indication: Venetoclax (MURANO Trial)

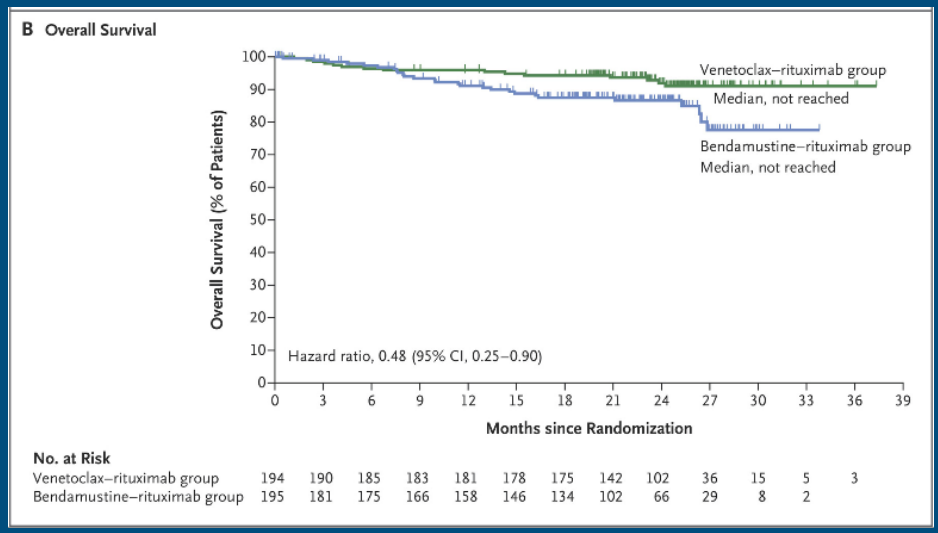
- Patients with CLL or SLL, with or without 17p deletion, who have received at least 1 prior therapy
- Randomized, multicenter, open-label trial (n=389)
  - Venetoclax with rituximab (VEN+R) vs.
  - Bendamustine with rituximab (B+R)
- Patients in the VEN+R arm completed a 5-week ramp-up venetoclax schedule and then received venetoclax 400 mg once daily for 24 months measured from the rituximab start date.
- Rituximab was initiated after venetoclax ramp-up and given for 6 cycles (375 mg/m^2 intravenously on cycle 1 day 1 and 500 mg/m^2 intravenously on day 1 of cycles 2-6, with a 28-day cycle length).
- The comparator arm received 6 cycles of B+R (bendamustine 70 mg/m^2 on days 1 and 2 of each 28-day cycle and rituximab at the above described dose and schedule).

CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma.

Seymour, M.B et al. *N Engl J Med* 2018; 378:1107-1120

Expanded Indication: Venetoclax (MURANO Trial)





Seymour, M.B et al. *N Engl J Med* 2018; 378:1107-1120

Venetoclax (MURANO Trial)

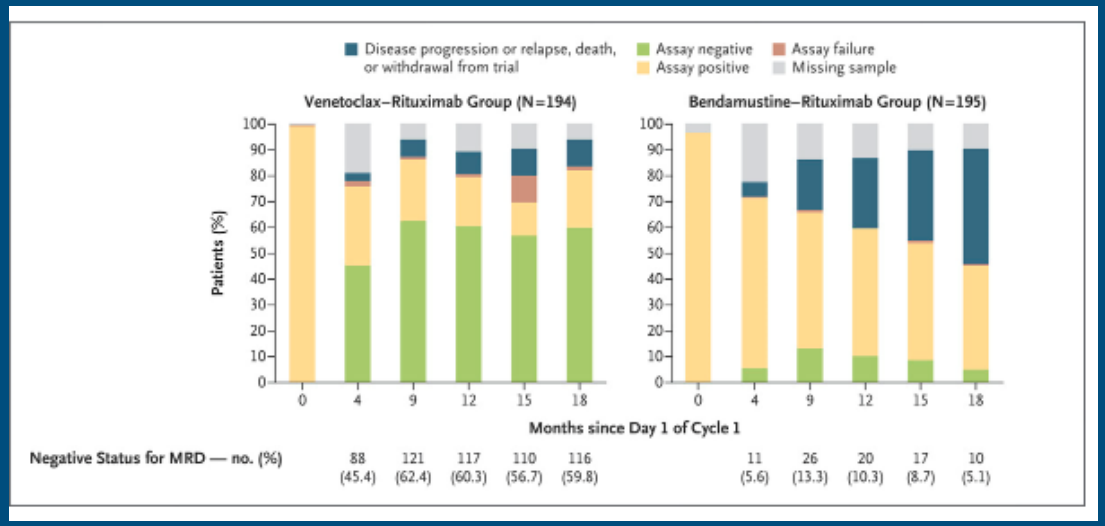


Table 2. Adverse Events.*

Event	Venetoclax–Rituximab Group (N=194)	Bendamustine–Rituximab Group (N=188)
Grade 3 or 4 adverse event — no. of patients (%)	159 (82.0)	132 (70.2)
Total no. of events	335	255
Grade 3 or 4 adverse events with at least 2% difference in incidence between groups — no. of patients (%)	130 (67.0)	104 (55.3)
Neutropenia†	112 (57.7)	73 (38.8)
Infections and infestations	34 (17.5)	41 (21.8)
Anemia	21 (10.8)	26 (13.8)
Thrombocytopenia	11 (5.7)	19 (10.1)
Febrile neutropenia	7 (3.6)	18 (9.6)
Pneumonia	10 (5.2)	15 (8.0)
Infusion-related reaction	3 (1.5)	10 (5.3)
Tumor lysis syndrome‡	6 (3.1)	2 (1.1)
Hypotension	0	5 (2.7)
Hyperglycemia	4 (2.1)	0
Hypogammaglobulinemia	4 (2.1)	0
Serious adverse events with at least 2% incidence in either group — no. of patients (%)	90 (46.4)	81 (43.1)
Pneumonia	16 (8.2)§	15 (8.0)
Febrile neutropenia	7 (3.6)	16 (8.5)
Pyrexia	5 (2.6)	13 (6.9)
Anemia	3 (1.5)	5 (2.7)
Infusion-related reaction	1 (0.5)	6 (3.2)
Sepsis	1 (0.5)	4 (2.1)
Tumor lysis syndrome	4 (2.1)	1 (0.5)
Hypotension	0	5 (2.7)
Fatal adverse events — no. of patients (%)	10 (5.2)§	11 (5.9)

Seymour, M.B et al. *N Engl J Med* 2018; 378:1107-1120

Other FDA Approvals

- Lusutrombopag (July 2018)
  - Thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a medical or dental procedure
- Methoxy polyethylene glycol-epoetin beta (June 2018)
  - Treatment of pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA
- Fulphila (pegfilgrastim-jmdb) as a biosimilar for Neulasta (June 2018)
  - Decrease the chance of infection as suggested by febrile neutropenia in patients with non-myeloid cancer who are receiving myelosuppressive chemotherapy that has a clinically significant incidence of febrile neutropenia

US Food and Drug Administration, Hematology/Oncology (Cancer) approvals & Safety Notifications, http://www.fda.gov/drugs/informationondrugs/approveddrugs.

Other FDA Approvals

- Avatrombopag (May 2018)
  - Thrombocytopenia in adults with chronic liver disease scheduled to undergo a procedure
- Retacrit as a biosimilar to Epogen/Procrit (May 2018)
  - Treatment of anemia due to chronic kidney disease (CKD) in patients on dialysis and not on dialysis, use of zidovudine in patients with HIV infection, and the effects of concomitant myelosuppressive chemotherapy. It is also approved for the reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery
- Fostamatinib disodium hexahydrate (April 2018)
  - Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment

US Food and Drug Administration, Hematology/Oncology (Cancer) approvals & Safety Notifications, http://www.fda.gov/drugs/informationondrugs/approveddrugs.

AML: Venetoclax + Decitabine/Azacitidine

Multicenter, open-label phase Ib dose-escalation and dose-expansion trial

Outcome	All Patients* (N = 145)	Venetoclax 400 mg		Venetoclax 800 mg	
		Azacitidine (n = 29)	Decitabine (n = 31)	Azacitidine (n = 37)	Decitabine (n = 37)
CR + CRi, %	67	76	71	57	73
▪ CR	37	38	45	30	38
▪ CRi	30	38	26	27	35
MRD negativity in patients with CR/CRi, n/N (%)	28/97 (29)	10/22 (45)	7/22 (32)	7/21 (33)	3/27 (11)
Median DoR in patients with CR/CRi, mos (95% CI)	--	NR (5.6-NR)	12.5 (5.1-NR)	11.7 (4.6-12.9)	9.2 (5.9-NR)
▪ Intermediate risk	12.9 (11.0-NR)	--	--	--	--
▪ Poor risk	6.7 (4.1-9.4)	--	--	--	--
▪ de novo AML	9.4 (7.2-11.7)	--	--	--	--
▪ Secondary AML	NR (12.5-NR)	--	--	--	--
Median OS, mos (95% CI)	17.5 (12.3-NR)	NR (11.0-NR)		17.5 (10.3-NR)	

DiNardo CD, et al. ASCO 2018. Abstract 7010

AML: Venetoclax + Decitabine/Azacitidine

Multicenter, open-label phase Ib dose-escalation and dose-expansion trial

- Venetoclax plus decitabine or azacitidine was well tolerated with deep, durable responses in elderly patients with previously untreated AML
  - CR/CRi rate in all patients: 67%
  - CR/CRi rates observed in high-risk subgroups: poor-risk cytogenetics (59%), secondary AML (67%), and ≥ 75 years of age (64%)
- Median OS was 17.5 mo in all patients (1-yr survival rate ~ 50%)
- MRD negativity observed in 45% of patients who received venetoclax 400 mg + azacitidine
- Venetoclax at 400 mg QD in combination with decitabine or azacitidine offers optimal risk–benefit profile

DiNardo CD, et al. ASCO 2018. Abstract 7010

Pipeline Drugs

- FLT3 inhibitors
  - Lestaurtinib, quizartinib, gilteritinib, crenolanib
- BTK inhibitors
  - Vecabrutinib
- P13K inhibitor
  - Duvelisib
  - Umbralisib
  - Buparlisib

PratzKW, et al. *Blood.* 2010;115:1425-1432; Levis MJ, et al. ASCO 2015. Abstract 7003; Greenwell IB, et al. *Oncology (Williston Park).* 2017;31(11):821-8.

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