Meet The Professor Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Jonathan W Friedberg, MD, MMSc

Samuel E Durand Professor of Medicine Director, James P Wilmot Cancer Institute University of Rochester Rochester, New York



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Dr Love — Disclosures

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Dr Friedberg — Disclosures

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We Encourage Clinicians in Practice to Submit Questions



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ONCOLOGY TODAY WITH DR NEIL LOVE

Key Presentations on Non-Hodgkin and Hodgkin Lymphomas from the 2020 ASH Annual Meeting



DR LAURIE SEHN BC CANCER CENTRE FOR LYMPHOID CANCER









Dr Laurie Sehn Key Presentations on N Oncology Today with Dr Neil Love —

(15) (30)

Meet The Professor Optimizing the Selection and Sequencing of Therapy for Patients with ER-Positive Breast Cancer

Thursday, October 28, 2021 5:00 PM – 6:00 PM ET

> Faculty Matthew P Goetz, MD



Meet The Professor Management of BRAF-Mutant Melanoma

Monday, November 1, 2021 5:00 PM – 6:00 PM ET

Faculty Prof Georgina Long, AO, BSc, PhD, MBBS



Meet The Professor Optimizing the Selection and Sequencing of Therapy for Patients with Urothelial Bladder Carcinoma

Tuesday, November 2, 2021 5:00 PM – 6:00 PM ET

> Faculty Andrea Apolo, MD



Meet The Professor Optimizing the Selection and Sequencing of Therapy for Patients with HER2-Positive Breast Cancer

Wednesday, November 3, 2021 5:00 PM – 6:00 PM ET

Faculty Adam M Brufsky, MD, PhD



Key Considerations in the Optimal Clinical Care of Patients with Small Cell Lung Cancer A CME/MOC-Accredited Virtual Event

Thursday, November 4, 2021 5:00 PM – 6:00 PM ET

> Faculty Anne Chiang, MD, PhD David R Spigel, MD



Meet The Professor Optimizing the Management of Acute Myeloid Leukemia

Monday, November 8, 2021 5:00 PM – 6:00 PM ET

> Faculty Keith W Pratz, MD



Meet The Professor Optimizing the Management of Metastatic Castration-Resistant Prostate Cancer

> Tuesday, November 9, 2021 5:00 PM – 6:00 PM ET

> Faculty Simon Chowdhury, MD, PhD



Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.



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Meet The Professor Program Participating Faculty



Nancy L Bartlett, MD Professor of Medicine Koman Chair in Medical Oncology Washington University School of Medicine St Louis, Missouri



Jonathan W Friedberg, MD, MMSc Samuel E Durand Professor of Medicine Director, James P Wilmot Cancer Institute University of Rochester Rochester, New York



Carla Casulo, MD Associate Professor of Medicine Division of Hematology/Oncology Director, Hematology/Oncology Fellowship Program University of Rochester Wilmot Cancer Institute Rochester, New York



Christopher R Flowers, MD, MS Chair, Professor Department of Lymphoma/Myeloma The University of Texas MD Anderson Cancer Center Houston, Texas



Brian T Hill, MD, PhD Director, Lymphoid Malignancy Program Cleveland Clinic Taussig Cancer Institute Cleveland, Ohio



Meet The Professor Program Participating Faculty



Brad S Kahl, MD

Professor of Medicine Washington University School of Medicine Director, Lymphoma Program Siteman Cancer Center St Louis, Missouri



Michael E Williams, MD, ScM

Byrd S Leavell Professor of Medicine Chief, Hematology/Oncology Division Physician Lead, Cancer Service Line University of Virginia School of Medicine Charlottesville, Virginia



Loretta J Nastoupil, MD Associate Professor Section Chief, Indolent Lymphoma Section Chief, New Drug Development Department of Lymphoma/Myeloma The University of Texas MD Anderson Cancer Center Houston, Texas



Moderator Neil Love, MD Research To Practice Miami, Florida



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Mamta Choksi, MD Florida Cancer Specialists and Research Institute New Port Richey, Florida



Zanetta S Lamar, MD Florida Cancer Specialists and Research Institute Naples, Florida



Justin Peter Favaro, MD, PhD Oncology Specialists of Charlotte Charlotte, North Carolina



Namrata I Peswani, MD Hematologist Oncologist UT Southwestern Medical Center Harold C Simmons Comprehensive Cancer Center Richardson, Texas



Lowell L Hart, MD Scientific Director of Research Florida Cancer Specialists Fort Myers, Florida



Mitchell R Smith, MD, PhD Clinical Professor of Medicine George Washington University Washington, DC



Meet The Professor with Dr Friedberg

Introduction

MODULE 1: Case Presentations

- Dr Choksi: A 58-year-old woman with Grade 1 follicular lymphoma
- Dr Favaro: A 68-year-old woman with a relapsed Grade 3A follicular lymphoma 8 years after prior treatment
- Dr Lamar: A 65-year-old man with mantle cell lymphoma, blastoid variant
- Dr Smith: A 71-year-old man with relapsed mantle cell lymphoma
- Dr Peswani: An 80-year-old man with newly diagnosed diffuse large B-cell lymphoma
- Dr Hart: A 51-year-old man with classic Hodgkin lymphoma

MODULE 2: Journal Club with Dr Friedberg

MODULE 3: Beyond the Guidelines

MODULE 4: Key Data Sets



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An Oncology Renaissance Jonathan W. Friedberg, MD, MMSc^{1,2,3}

J Clin Oncol 2021;39(25):2737-8.



"You don't know where you're going now, but you know you won't be back... Meet me in a land of hope and dreams."

-Bruce Springsteen


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Case Presentation – Dr Choksi: A 58-year-old woman with Grade 1 follicular lymphoma



- 10/2018: Diagnosed with low-grade lymphoma \rightarrow Observation
- 10/2020: Recurrent LAD, biopsy-confirmed Grade 1 follicular lymphoma
- 2/2021 PET/CT: Worsening B symptoms and disease above and below the diaphragm
- 3/2021: Bendamustine/obinutuzumab
 - Nausea/vomiting requiring IV hydration
- Re-staging CT: No evidence of intra-abdominal disease, 1.1-cm lesion in spleen

Questions

- Among the numerous treatment options for follicular lymphoma, what are your preferences? How do you decide which ones to consider?
- Which patients do you consider for rituximab versus obinutuzumab?



Dr Mamta Choksi

Case Presentation – Dr Favaro: A 68-year-old woman with a relapsed Grade 3A follicular lymphoma 8 years after prior treatment



Dr Justin Favaro

- 2014: Follicular lymphoma s/p R-CHOP x 6, with complete response
 - Myositis, treated with chonic methotrexate and IVIG
- 2012: Screening colonoscopy; Polyp biopsied: Grade 3A follicular lymphoma
- Bendamustine/rituximab

Questions

- In the setting of relapsed follicular lymphoma, once the patient achieves a complete response with salvage chemotherapy, how do you decide who to place on maintenance rituximab? Do you still use consolidation with radioimmunotherapy, or do you just observe patients after they go into a complete response?
- Where do you fit autologous transplantation and CAR T-cell therapy into relapsed follicular lymphoma?



Case Presentation – Dr Lamar: A 65-year-old man with mantle cell lymphoma, blastoid variant

- Diagnosed with mantle cell lymphoma, blastoid variant
 - Ki67 was not very elevated
- Clinical trial: Bendamustine/rituximab with or without acalabrutinib
- Plans for intrathecal chemotherapy disrupted due to COVID-19

Question

• How do you approach treatment of patients on BTK inhibitors that may be at risk for CNS involvement?



Dr Zanetta Lamar



Case Presentation – Dr Smith: A 71-year-old man with relapsed mantle cell lymphoma



Dr Mitchell Smith

- Presents with weight loss, early satiety and PCP notes cervical and axillary LAN and palpable spleen
- Work up and nodal biopsy confirms mantle cell lymphoma, CD5+, CD23-, Ki67: 35%, No del17p or pp53 mutations
- BR x 6, achieving PET-negative CR \rightarrow Maintenance rituximab x 2 years
- Two years after completing maintenance: Recurrent LAN, splenomegaly PET and biopsy-confirmed recurrent mantle cell lymphoma
- Acalabrutinib BID schedule
- 18 months later: Now 77 years old, PS: 1 with enlarging nodes

Question

 What would you recommend for this patient? How do you decide between the various treatment options available?



Case Presentation – Dr Peswani: An 80-year-old man with newly diagnosed diffuse large B-cell lymphoma

- Presents with neck swelling
- Excisional biopsy shows diffuse large B-cell lymphoma and further workup reveals involvement of axillary/inguinal lymph nodes and bone marrow involvement
- R-miniCHOP x 6 cycles with CR
- Patient desired to travel to see family and got vaccinated against COVID
- Tests for detection of COVID antibodies are negative

Questions

- Are you recommending for your patients to get vaccinated against COVID?
- If this patient's disease recurs, would you consider tafasitamab/lenalidomide as the next line of therapy for this patient? What is your experience with this combination?
- Would this patient be a candidate for CAR T-cell therapy?



Dr Namrata Peswani



Case Presentation – Dr Hart: A 51-year-old man with classic Hodgkin lymphoma

- PMH: multiple sclerosis managed with teriflunomide
- 10/2018: Diagnosed with bone marrow biopsy-confirmed classic Hodgkin lymphoma (55% cellularity) after routine follow-up MRI showed diffuse osseous metastases and enlarged lymph nodes in abdomen and pelvis; no B symptoms
- 4/2019: ABVD treatment completed
- 8/2019: Follow-up imaging showed possible progression and biopsy showed recurrence in left pelvis
- Brentuximab vedotin plus bendamustine → BEAM chemotherapy and autotransplant
 → brentuximab vedotin as maintenance
- Experiencing neuropathy

Question

• What would be the risk/benefit ratio of trying a checkpoint inhibitor for this patient as we know this class of agent is extremely efficacious in Hodgkin lymphoma?



Dr Lowell Hart



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Journal Club with Dr Friedberg

- Brice P et al. Classical Hodgkin lymphoma. Lancet 2021;[Online ahead of print].
- Herrera AF et al. SWOG S1826: A phase III, randomized study of nivolumab plus AVD or brentuximab vedotin plus AVD in patients with newly diagnosed advanced stage classical Hodgkin lymphoma. ASH 2020;Abstract 2969.
- Hutchings M et al. Brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine in patients with advanced-stage, classical Hodgkin lymphoma: A prespecified subgroup analysis of high-risk patients from the ECHELON-1 study. *Hematol Oncol* 2021;39(2):185-95.
- Kumar A et al. Brentuximab vedotin combined with chemotherapy in patients with newly diagnosed early-stage, unfavorable-risk Hodgkin lymphoma. J Clin Oncol 2021; 39(20):2257-65.
- Yasenchak CA et al. Frontline brentuximab vedotin as monotherapy or in combination for older Hodgkin lymphoma patients. ASCO 2020; Abstract 8032.



Journal Club with Dr Friedberg (continued)

- Craddock C and Friedberg JW. Immunotherapy for hematologic malignancies. J Clin Oncol 2021;39(5):343-5.
- Nowakowski GS et al. Addition of lenalidomide to R-CHOP improves outcomes in newly diagnosed diffuse large B-cell lymphoma in a randomized phase II US Intergroup Study ECOG-ACRIN E1412. J Clin Oncol 2021;39(12):1329-38.
- Reagan PM and Friedberg JW. Axicabtagene ciloleucel and brexucabtagene autoleucel in relapsed and refractory diffuse large B-cell and mantle cell lymphomas. *Future Oncol* 2021;17(11):1269-83.



Journal Club with Dr Friedberg (continued)

- Smith MR et al. ECOG-ACRIN E1411 randomized phase 2 trial of bendamustine-rituximab (BR)-based induction followed by rituximab (R) ± lenalidomide (L) consolidation for mantle cell lymphoma: Effect of adding bortezomib to front-line BR induction on PFS. ASCO 2021;Abstract 7503.
- Munshi PN et al. American Society of Transplantation and Cellular Therapy, Center of International Blood and Marrow Transplant Research, and European Society for Blood and Marrow Transplantation clinical practice recommendations for transplantation and cellular therapies in mantle cell lymphoma. *Transplant Cell Ther* 2021;27(9):720-8.



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Diffuse Large B-Cell Lymphoma



Which third- and fourth-line therapy would you generally recommend first for a 65-year-old patient with DLBCL who responds to R-CHOP and then R-DHAP followed by transplant on relapse but subsequently develops disease progression?





Which third- and fourth-line therapy would you generally recommend first for an 80-year-old patient with DLBCL who experiences disease progression on front-line R-CHOP and is not eligible for high-dose therapy?

Dr Bartlett	Loncastuximab tesirine → tafasitamab/ lenalidomide	Dr Hill	Tafasitamab/ lenalidomide → loncastuximab tesirine
Dr Casulo	Polatuzumab vedotin/BR → tafasitamab/lenalidomide	Dr Kahl	Tafasitamab/ lenalidomide → loncastuximab tesirine
Dr Flowers	CAR T-cell therapy → tafasitamab/ lenalidomide	Dr Nastoupil	CAR T-cell therapy → polatuzumab vedotin/BR
Dr Friedberg	Tafasitamab/ lenalidomide → loncastuximab tesirine	Dr Williams	Tafasitamab/ lenalidomide → loncastuximab tesirine



Do you generally use either tafasitamab/lenalidomide or loncastuximab tesirine in a patient who has experienced disease progression on or after CD19-directed CAR T-cell therapy?

Dr Bartlett	Yes, either	Dr Hill	Yes, tafasitamab/ lenalidomide
Dr Casulo	Yes, either	Dr Kahl	Yes, either
Dr Flowers	Yes, either	Dr Nastoupil	Yes, either
Dr Friedberg	Νο	Dr Williams	Yes, either



At what point in the treatment course are you referring patients with DLBCL for consultation regarding CAR T-cell therapy?





Do you believe that CAR T-cell therapy is more <u>efficacious</u> than autologous stem cell transplantation for DLBCL as second-line treatment after R-CHOP?

Dr Bartlett	Yes, but I'm still not sure	Dr Hill	Yes – for chemorefractory disease
Dr Casulo	Yes, but I'm still not sure	Dr Kahl	Yes, but l'm still not sure
Dr Flowers	Yes (but may vary by CAR-T product)	Dr Nastoupil	Yes
Dr Friedberg	Yes	Dr Williams	Yes, but I'm still not sure



A patient should be in adequate physical condition to undergo autologous stem cell transplant in order to be a suitable candidate for CAR T-cell therapy.





Do you believe that CAR T-cell therapy is more <u>tolerable</u> for most patients than autologous stem cell transplantation?





Hodgkin Lymphoma



What initial treatment would you recommend for a 26-year-old patient with classical Hodgkin lymphoma (HL) with anemia, diffuse adenopathy, hepatosplenomegaly and diffuse bone marrow involvement?

Dr Bartlett	Brentuximab vedotin + AVD	Dr Hill	ABVD
Dr Casulo	Brentuximab vedotin + AVD	Dr Kahl	Brentuximab vedotin + AVD
Dr Flowers	Brentuximab vedotin + AVD	Dr Nastoupil	Brentuximab vedotin + AVD
Dr Friedberg	Brentuximab vedotin + AVD	Dr Williams	Brentuximab vedotin + AVD

A = doxorubicin; V = vinblastine; D = dacarbazine; B = bleomycin



An 85-year-old frail patient with advanced-stage symptomatic HL is not a candidate for aggressive chemotherapy but is seeking active treatment. Regulatory and reimbursement issues aside, what would you recommend?

Dr Bartlett	Brentuximab vedotin + nivolumab	Dr Hill	Brentuximab vedotin
Dr Casulo	Brentuximab vedotin/ dacarbazine	Dr Kahl	Pembrolizumab
Dr Flowers	Brentuximab vedotin + nivolumab	Dr Nastoupil	Brentuximab vedotin + nivolumab
Dr Friedberg	Brentuximab vedotin + nivolumab	Dr Williams	Brentuximab vedotin



Regulatory and reimbursement issues aside, in general, what is your preferred second-line therapy for a patient with HL who is experiencing disease relapse after up-front ABVD and is not considered a candidate for transplant?

Dr Bartlett	Brentuximab vedotin + nivolumab	Dr Hill	Pembrolizumab
Dr Casulo	Pembrolizumab	Dr Kahl	Brentuximab vedotin + nivolumab
Dr Flowers	Brentuximab vedotin + nivolumab	Dr Nastoupil	Brentuximab vedotin + nivolumab
Dr Friedberg	Brentuximab vedotin	Dr Williams	Brentuximab vedotin



Regulatory and reimbursement issues aside, what is your preferred next line of therapy for a patient with HL who is experiencing disease relapse after ABVD and autologous stem cell transplant?





Have you administered or would you administer brentuximab vedotin in combination with an immune checkpoint inhibitor to a patient with HL outside of a clinical trial setting?





Follicular Lymphoma



What treatment do you generally recommend for an <u>otherwise</u> <u>healthy 65-year-old</u> patient with symptomatic FL requiring treatment?

Dr Bartlett	Bendamustine/ rituximab (BR)	Dr Hill	BR
Dr Casulo	BR	Dr Kahl	BR
Dr Flowers	BR	Dr Nastoupil	BR
Dr Friedberg	BR	Dr Williams	BR



What treatment do you generally recommend for a patient with symptomatic FL requiring treatment who refuses to receive cytotoxic chemotherapy?

Dr Bartlett	Rituximab alone (R)	Dr Hill	Lenalidomide/ rituximab
Dr Casulo	R or Lenalidomide/ rituximab	Dr Kahl	Lenalidomide/ rituximab
Dr Flowers	Lenalidomide/ rituximab	Dr Nastoupil	Lenalidomide/ rituximab
Dr Friedberg	Lenalidomide/ rituximab	Dr Williams	Lenalidomide/ rituximab



Regulatory and reimbursement issues aside, what is your usual second-line therapy for a 65-year-old patient with FL who achieves a complete response to 6 cycles of bendamustine/rituximab (BR) but then experiences disease <u>relapse 4 years later</u>?





What is your usual third- and fourth-line treatment for a patient with FL (EZH2 wild type) who receives first-line BR, second-line lenalidomide/rituximab and then develops disease progression?





What is your usual third- and fourth-line treatment for a patient with FL with an EZH2 mutation who receives first-line BR, second-line lenalidomide/rituximab and then develops disease progression?





Are you typically assessing EZH2 mutation status for your patients with FL?





Which PI3K inhibitor do you use most commonly?





How would you generally sequence PI3K inhibitors and tazemetostat for a patient with relapsed FL who is eligible to receive both?

Dr Bartlett	PI3K inhibitor → tazemetostat	Dr Hill	Tazemetostat → PI3K inhibitor
Dr Casulo	Tazemetostat → PI3K inhibitor	Dr Kahl	Tazemetostat → PI3K inhibitor
Dr Flowers	Tazemetostat → PI3K inhibitor	Dr Nastoupil	Tazemetostat → PI3K inhibitor
Dr Friedberg	Tazemetostat → PI3K inhibitor	Dr Williams	Tazemetostat → PI3K inhibitor



At what point in the treatment course are you referring patients with FL for consultation regarding CAR T-cell therapy?




Mantle Cell Lymphoma



In general, what would be your most likely treatment recommendation for a 70-year-old patient with mantle cell lymphoma who responds to BR and then ibrutinib on relapse but subsequently develops rapid tumor progression?

Dr Bartlett	Brexucabtagene autoleucel	Dr Hill	Brexucabtagene autoleucel
Dr Casulo	Brexucabtagene autoleucel	Dr Kahl	Brexucabtagene autoleucel
Dr Flowers	Brexucabtagene autoleucel	Dr Nastoupil	Brexucabtagene autoleucel
Dr Friedberg	Brexucabtagene autoleucel	Dr Williams	Venetoclax + rituximab as bridge to brexucabtagene autoleucel



At what point in the treatment course are you referring patients with mantle cell lymphoma for consultation regarding CAR T-cell therapy?

Dr Bartlett	At third relapse	Dr Hill	At first relapse
Dr Casulo	At second relapse	Dr Kahl	At second relapse
Dr Flowers	At first relapse	Dr Nastoupil	At first relapse
Dr Friedberg	At second relapse after BTKi	Dr Williams	At second relapse



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Phase III Study Shows Polatuzumab Vedotin with R-CHP Is the First Regimen in 20 Years to Significantly Improve Outcomes in Previously Untreated Aggressive Form of Lymphoma Press Release – August 9, 2021

"Pivotal Phase III POLARIX trial comparing polatuzumab vedotin in combination with chemotherapy regimen R-CHP versus the standard of care R-CHOP in treatment of firstline diffuse large B-cell lymphoma (DLBCL) met its primary endpoint of investigator assessed progression-free survival.

Prolonging survival without disease advancement could be transformative for newly diagnosed DLBCL patients, as currently 40% of patients relapse after disease progression.

Data will be submitted to health authorities globally as soon as possible and presented at an upcoming medical meeting."



https://finance.yahoo.com/news/phase-iii-study-shows-genentechs-050000152.html

POLARIX Phase III Trial Design





Courtesy of Gilles Salles MD, PhD.

Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Laurie H. Sehn, MD, MPH¹; Alex F. Herrera, MD²; Christopher R. Flowers, MD, MSc³; Manali K. Kamdar, MD, MBBS⁴;

Andrew McMillan, PhD⁵; Mark Hertzberg, MBBS, PhD⁶; Sarit Assouline, MDCM, MSc⁷; Tae Min Kim, MD⁸; Won Seog Kim, MD, PhD⁹; Muhit Ozcan, MD¹⁰; Jamie Hirata, PharmD¹¹; Elicia Penuel, PhD¹¹; Joseph N. Paulson, PhD¹¹; Ji Cheng, PhD¹²; Grace Ku, MD¹¹; and Matthew J. Matasar, MD¹³

J Clin Oncol 2020;38(2):155-65.



Polatuzumab Vedotin with Bendamustine/Rituximab for Transplant-Ineligible R/R DLBCL: End-of-Treatment CR Rate

	Phase II Randomized	
Outcome	Pola-BR $(n = 40)$	BR (n = 40)
End of treatment		
IRC, objective response	18 (45.0)	7 (17.5)
Complete response	16 (40.0)	7 (17.5)
Partial response	2 (5.0)	0
Stable disease	6 (15.0)	1 (2.5)
Progressive disease	8 (20.0)	10 (25.0)
Missing or unevaluable [†]	8 (20.0)	22 (55.0)
Progressive disease Missing or unevaluable [†]	8 (20.0) 8 (20.0)	10 (25.0) 22 (55.0)



Polatuzumab Vedotin with Bendamustine/Rituximab for Transplant-Ineligible R/R DLBCL: Overall Survival





Sehn LH et al. J Clin Oncol 2020;38(2):155-65.

FDA Approves Selinexor for R/R DLBCL

Press Release – June 22, 2020

"The Food and Drug Administration granted accelerated approval to selinexor for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.

Approval was based on SADAL (KCP-330-009; NCT02227251), a multicenter, single-arm, open-label trial in patients with DLBCL after 2 to 5 systemic regimens. Patients received selinexor 60 mg orally on days 1 and 3 of each week."



Lancet Haematol 2020;7:e511-22.

Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial

Nagesh Kalakonda*, Marie Maerevoet*, Federica Cavallo, George Follows, Andre Goy, Joost S P Vermaat, Olivier Casasnovas, Nada Hamad, Josée M Zijlstra, Sameer Bakhshi, Reda Bouabdallah, Sylvain Choquet, Ronit Gurion, Brian Hill, Ulrich Jaeger, Juan Manuel Sancho, Michael Schuster, Catherine Thieblemont, Fátima De la Cruz, Miklos Egyed, Sourav Mishra, Fritz Offner, Theodoros P Vassilakopoulos, Krzysztof Warzocha, Daniel McCarthy, Xiwen Ma, Kelly Corona, Jean-Richard Saint-Martin, Hua Chang, Yosef Landesman, Anita Joshi, Hongwei Wang, Jatin Shah, Sharon Shacham, Michael Kauffman, Eric Van Den Neste, Miguel A Canales



SADAL: Efficacy and Safety of Selinexor for R/R DLBCL After at Least 2 Previous Lines of Chemoimmunotherapy





Kalakonda N et al. Lancet Haematol 2020;7:e511-22.

FDA Grants Accelerated Approval to Tafasitamab-cxix for DLBCL Press Release – July 31, 2020

"The Food and Drug Administration granted accelerated approval to tafasitamab-cxix, a CD19directed cytolytic antibody, indicated in combination with lenalidomide for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant.

The efficacy of tafasitamab-cxix with lenalidomide was evaluated in L-MIND (NCT02399085), an open label, multicenter single-arm trial in 81 patients. Patients received tafasitamab-cxix 12 mg/kg intravenously with lenalidomide (25 mg orally on days 1 to 21 of each 28-day cycle) for maximum of 12 cycles, followed by tafasitamab-cxix as monotherapy."



Lancet Oncol 2020;21:978-88



Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study

Gilles Salles*, Johannes Duell*, Eva González Barca, Olivier Tournilhac, Wojciech Jurczak, Anna Marina Liberati, Zsolt Nagy, Aleš Obr, Gianluca Gaidano, Marc André, Nagesh Kalakonda, Martin Dreyling, Johannes Weirather, Maren Dirnberger-Hertweck, Sumeet Ambarkhane, Günter Fingerle-Rowson, Kami Maddocks



L-MIND: Best Objective Response According to Independent Radiology Committee or Clinical Review Committee

	Patients treated with tafasitamab plus lenalidomide (n=80)*
Best objective response	
Complete response	34 (43%; 32–54)
Partial response	14 (18%; 10–28)
Stable disease	11 (14%; 7–23)
Progressive disease	13 (16%; 9–26)
Not evaluable†	8 (10%; 4–19)
PET-confirmed complete response	30/34 (88%; 73–97)
Objective response‡	48 (60%; 48–71)
Disease control§	59 (74%; 63–83)

Data are n (%; 95% CI) or n/N (%). *One patient received tafasitamab only. †Patients had no valid postbaseline response assessments. ‡Complete response plus partial response. §Complete response plus partial response plus stable disease.



FDA Grants Accelerated Approval to Loncastuximab Tesirine-Ipyl for Large B-Cell Lymphoma Press Release – April 23, 2021

"The Food and Drug Administration granted accelerated approval to loncastuximab tesirine-lpyl, a CD19-directed antibody and alkylating agent conjugate, for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.

Approval was based on LOTIS-2 (NCT03589469), an open-label, single-arm trial in 145 adult patients with relapsed or refractory DLBCL or high-grade B-cell lymphoma after at least two prior systemic regimens. Patients received loncastuximab tesirine-lpyl 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles. Patients received treatment until progressive disease or unacceptable toxicity."



Lancet Oncol 2021;22:790-800



Paolo F Caimi, Weiyun Ai, Juan Pablo Alderuccio, Kirit M Ardeshna, Mehdi Hamadani, Brian Hess, Brad S Kahl, John Radford, Melhem Solh, Anastasios Stathis, Pier Luigi Zinzani, Karin Havenith, Jay Feingold, Shui He, Yajuan Qin, David Ungar, Xiaoyan Zhang, Carmelo Carlo-Stella



Mechanism of Action of Loncastuximab Tesirine





LOTIS-2: Response and Survival with Loncastuximab Tesirine for R/R DLBCL

Response	As-treated population (N = 145)		
Overall response rate	70/145 (48.3%)		
Complete response rate	35/145 (24.1%)		
Complete response	35 (24%)		
Partial response	35 (24%)		
Stable disease	22 (15%)		
Progressive disease	30 (21%)		
Not evaluable	23 (16%)		
Survival	As-treated population (N = 145)		
Median progression-free survival	4.9 months		
Median overall survival	9.9 months		



LOTIS-2: Common Treatment-Emergent Adverse Events

Treatment-Emergent AEs	Grade 1-2	Grade 3-4	
Anemia	16%	10%	
Thrombocytopenia	15%	18%	
Neutropenia	14%	26%	
Leukopenia	6%	9%	



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Adverse Cardiovascular and Pulmonary Events Associated With Chimeric Antigen Receptor T-Cell Therapy

Adam Goldman, MD, MPH,^{a,b} Elad Maor, MD, PHD,^{a,b} David Bomze, MD, MPH, MSc,^b Jennifer E. Liu, MD,^{c,d} Joerg Herrmann, MD,^e Joshua Fein, MD,^f Richard M. Steingart, MD,^{c,d} Syed S. Mahmood, MD, MPH,^g Wendy L. Schaffer, MD, PHD,^{c,d} Miguel-Angel Perales, MD,^{d,h} Roni Shouval, MD, PHD^{d,h}



Cardiovascular and Pulmonary Toxicities of CAR T-Cell Therapy



Goldman A et al. J Am Coll Cardiol 2021;78(18):1800-13.



Phase III ZUMA-7 Trial of Axi-cel Meets Primary Endpoint Press Release – June 30, 2021

"The ZUMA-7 trial (NCT03391466) demonstrated superiority of axicabtagene ciloleucel (axi-cel) compared with standard of care (SOC) autologous stem cell transplant (ASCT) after meeting the primary end point of event-free survival (EFS) improvement for patients with relapsed or refractory large B-cell lymphoma (LBCL), according to a press release from the company responsible for manufacturing the chimeric antigen receptor (CAR) T-cell therapy. A statistically significant EFS benefit (HR, 0.398; P <0.0001) was observed as well as improvement in the secondary end point of objective response rate (ORR).

The top-line results of the randomized ZUMA-7 trial paint the picture of a potential paradigm shift in the treatment of large B-cell lymphoma, Frederick L Locke, MD, ZUMA-7 lead principal investigator and co-leader of the Immuno-Oncology Program at Moffitt Cancer Center in Tampa, Florida, said in the press release. Investigators mentioned that these data are still immature and further analyses are planned for the future. The trial was conducted under a Special Protocol Agreement from the FDA where the trial design, end points, and statistical analysis were agreed in advance."





Phase III TRANSFORM Trial of Liso-cel Meets Primary Endpoint Press Release – June 10, 2021

"Data from the Phase 3 TRANSFORM trial (NCT03575351) of the chimeric antigen receptor (CAR) T-cell therapy lisocabtagene maraleucel (liso-cel) as second-line therapy for patients with relapsed/refractory large B-cell lymphoma (LBCL) resulted in a statistically significant improvement in the primary end point of event-free survival versus therapy with the standardof-care comparator arm, according to the company responsible for developing the agent.

Additionally, the toxicity profile observed with liso-cel was consistent with the safety data reported in the TRANSCEND NHL 001 trial (NCT02631044) which led to the FDA approving the CD19-directed therapy for patients with certain types of non-Hodgkin lymphoma, including diffuse large B-cell lymphoma (DLBCL), following 2 or more prior therapies. These data represent the first time a treatment for relapsed/refractory LBCL has demonstrated benefit over high-dose chemotherapy and hematopoietic stem cell transplant (HSCT).

Results regarding the primary end point will be evaluated and shared at an upcoming medical conference as well as with regulatory authorities."



BELINDA Study Investigating Tisagenlecleucel as Second-Line Treatment in Aggressive B-Cell Non-Hodgkin Lymphoma Fails to Meet Primary Endpoint

Press Release – August 24, 2021

"The Phase III BELINDA study investigating tisagenlecleucel in aggressive B-cell non-Hodgkin lymphoma (NHL) after relapse or lack of response to first-line treatment did not meet its primary endpoint of event-free survival compared to treatment with the standard-of-care (SOC). SOC was salvage chemotherapy followed in responding patients by high-dose chemotherapy and stem cell transplant. The safety profile was consistent with the established safety profile of tisagenlecleucel."

https://www.novartis.com/news/media-releases/novartis-provides-update-belinda-study-investigating-kymriah-second-line-treatment-aggressive-b-cell-non-hodgkin-lymphoma



Summary of CAR T-Cell Pivotal Studies in DLBCL

	Axi-cel ZUMA-1 (N = 108 infused)	Tisagenlecleucel JULIET (N = 108 infused)	Liso-cel TRANSCEND (N = 294 infused)	
CAR	α CD19	α CD19	α CD19	
Transmembrane domain	CD28	CD28	CD28	
Co-stimulatory doman	CD28	4-1BB	4-1BB	
T-cell activation domain	CD3ζ	CD3ζ	CD3ζ	
Leukapheresis	Fresh product	Cryopreserved product	Fresh product	
Outpatient administration	Not allowed	Allowed	Allowed	
Bridging therapy, %	Not allowed	92%	59%	
Lymphodepletion chemotherapy	Cy/Flu <mark>500/30</mark> mg/m ² × 3d	Cy/Flu <mark>250/25</mark> mg/m ² x 3d Bendamustine 90 mg/m ² x 2d	Cy/Flu <mark>300/30</mark> mg/m ² x 3d	



Summary of Efficacy Outcomes in Pivotal Studies of CAR T-Cell Therapy for DLBCL

	Axi-celTisagenlecleucelZUMA-1JULIET(N = 108 infused)(N = 115 infused)		Liso-cel TRANSCEND (N = 294 infused)
Overall response rate	74%	52%	73%
Complete response rate	54%	40%	53%
24-month OS rate	50.5%	40.0%	44.9%
Indication	DLBCL, High grade, PMBCL, tFL	DLBCL, High grade, tFL	DLBCL, HGBCL, PMBCL, tFL, tIND



Cytokine Release Syndrome and Neurologic Events in Pivotal Studies of CAR T-Cell Therapy for DLBCL





Westin JR et al. Am J Hematol 2021;[Online ahead of print].

CAR-T-Associated Cytokine Release Syndrome (CRS) and Neurologic Toxicity

CRS — May be mild or life-threatening

- Occurs with CART19 activation and expansion
- Dramatic cytokine elevations (IL-6, IL10, IFN_Y, CRP, ferritin)
- Fevers initially (can be quite high: 105°F)
- Myalgias, fatigue, nausea/anorexia
- Capillary leak, headache, hypoxia and hypotension
- CRS-related mortality 3% to 10%

Neurologic toxicity — May be mild or life-threatening

- Mechanism unclear, referred to as immune effector cell-associated neurotoxicity syndrome (ICANS)
- Encephalopathy
- Seizures
- Delirium, confusion, aphasia, agitation, sedation, coma



Hodgkin Lymphoma





Articles

Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial

David J Straus, Monika Długosz-Danecka, Joseph M Connors, Sergey Alekseev, Árpád Illés, Marco Picardi, Ewa Lech-Maranda, Tatyana Feldman, Piotr Smolewski, Kerry J Savage, Nancy L Bartlett, Jan Walewski, Radhakrishnan Ramchandren, Pier Luigi Zinzani, Martin Hutchings, Javier Munoz, Hun Ju Lee, Won Seog Kim, Ranjana Advani, Stephen M Ansell, Anas Younes, Andrea Gallamini, Rachael Liu, Meredith Little, Keenan Fenton, Michelle Fanale, John Radford



ECHELON-1: Five-Year Update



- Five-year PFS was higher with A + AVD than with ABVD for both PET-2-negative and positive patients
- Peripheral neuropathy continued to improve or resolve over time with both A + AVD and ABVD; more patients had ongoing peripheral neuropathy in the A + AVD group than in the ABVD group (19% vs 9%).



Straus DJ et al. Lancet Haematol 2021;8(6):e410-21.

Brentuximab Vedotin Combined With Chemotherapy in Patients With Newly Diagnosed Early-Stage, Unfavorable-Risk Hodgkin Lymphoma

Anita Kumar, MD¹; Carla Casulo, MD²; Ranjana H. Advani, MD³; Elizabeth Budde, MD⁴; Paul M. Barr, MD²; Connie L. Batlevi, MD, PhD¹; Philip Caron, MD¹; Louis S. Constine, MD²; Savita V. Dandapani, MD⁴; Esther Drill, MD¹; Pamela Drullinsky, MD¹; Jonathan W. Friedberg, MD²; Clare Grieve, BA¹; Audrey Hamilton, MD¹; Paul A. Hamlin, MD¹; Richard T. Hoppe, MD³; Steven M. Horwitz, MD¹; Ashlee Joseph, BA¹; Niloufer Khan, MD¹; Leana Laraque, BA¹; Matthew J. Matasar, MD¹; Alison J. Moskowitz, MD¹; Ariela Noy, MD¹; Maria Lia Palomba, MD¹; Heiko Schöder, MD¹; David J. Straus, MD¹; Shreya Vemuri, BA¹; Joanna Yang, MD⁵; Anas Younes, MD⁶; Andrew D. Zelenetz, MD, PhD¹; Joachim Yahalom, MD¹; and Craig H. Moskowitz, MD⁷

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J Clin Oncol 2021;[Online ahead of print].



Multicenter Pilot Study of BV + AVD with or without Consolidative Radiation Therapy for Early-Stage, Unfavorable-Risk Hodgkin Lymphoma

 Patients who achieved a negative end-of-therapy (EOT) PET-4 scan after 4 cycles of BV + AVD were studied with de-escalating radiation dose and field

Clinical endpoint	Cohort 1 30-Gy ISRT (n = 29)	Cohort 2 20-Gy ISRT (n = 29)	Cohort 3 30-Gy CVRT (n = 29)	Cohort 4 No radiation (n = 29)	All patients (n = 114)
EOT CR rate	27 (93%)	29 (100%)	27 (93%)	28 (97%)	111 (96%)
2-year PFS rate	93.1%	96.6%	89.7%	96.6%	94%

"BV + AVD x four cycles is a highly active and well-tolerated treatment program for ES, unfavorable-risk Hodgkin lymphoma, including bulky disease. The efficacy of BV + AVD supports the safe reduction or elimination of consolidative radiation among PET-4–negative patients."



Frontline Brentuximab Vedotin as Monotherapy or in Combination for Older Hodgkin Lymphoma Patients

Yasenchak CA et al. ASH 2020;Abstract 471.


Best Responses per Investigator – Efficacy Evaluable Set

Efficacy Evaluable Set	Part A BV mono N=25	Part B BV+DTIC N=19	Part C BV+benda N=17	Part D BV+nivo N=19
ORR, n (%)	23 (92)	19 (100)	17 (100)	18 (95)
Best overall response				
Complete response	18 (72)	13 (68)	15 (88)	15 (79)
Partial response	5 (20)	6 (32)	2 (12)	3 (16)
Stable disease	2 (8)	0	0	1 (5)
Progressive disease	0	0	0	0
Duration of response, n	23	19	17	18
Median (min, max)	9.1 (2.8, 81.4+)	45.4 (0.0+, 67.3)	39.0 (0.0+, 56.8+)	NR (1.4+, 27.5+)

Patients who were not efficacy-evaluable included:

- Patients with no post-baseline response assessment due to deaths (n=3) and patient withdrawal (non-AE related, n=2) on or before the first scheduled post-baseline scan at Cycle 2
- One patient lost to follow-up
- One patient who was not an eligible cHL subtype (nodular lymphocyte-predominant HL) but still achieved partial response after receiving BV

Lancet Oncol 2021;22(4):512-24.

Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study

John Kuruvilla, Radhakrishnan Ramchandren, Armando Santoro, Ewa Paszkiewicz-Kozik, Robin Gasiorowski, Nathalie A Johnson, Laura Maria Fogliatto, Iara Goncalves, Jose S R de Oliveira, Valeria Buccheri, Guilherme F Perini, Neta Goldschmidt, Iryna Kriachok, Michael Dickinson, Mieczyslaw Komarnicki, Andrew McDonald, Muhit Ozcan, Naohiro Sekiguchi, Ying Zhu, Akash Nahar, Patricia Marinello, Pier Luigi Zinzani, on behalf of the KEYNOTE-204 investigators*



KEYNOTE-204: Interim Analysis



- The most common Grade 3-5 TRAEs in the pembrolizumab and brentuximab vedotin study arms included pneumonitis (4% vs 1%), neutropenia (2% vs 7%), and peripheral neuropathy (1% vs 3%).
- Serious TRAEs occurred in 16% of patients receiving pembrolizumab and 11% of patients receiving brentuximab vedotin.



Kuruvilla J et al. Lancet Oncol 2021;22(4):512-24.

J Clin Oncol 2020;38(32):3794-804.

Anti-CD30 CAR-T Cell Therapy in Relapsed and Refractory Hodgkin Lymphoma

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Carlos A. Ramos, MD^{1,2}; Natalie S. Grover, MD^{3,4}; Anne W. Beaven, MD^{3,4}; Premal D. Lulla, MD^{1,2}; Meng-Fen Wu, MS^{1,5}; Anastasia Ivanova, PhD^{3,6}; Tao Wang, PhD^{1,5}; Thomas C. Shea, MD^{3,4}; Cliona M. Rooney, PhD^{1,7,8}; Christopher Dittus, DO^{3,4}; Steven I. Park, MD³; Adrian P. Gee, PhD^{1,7}; Paul W. Eldridge, PhD³; Kathryn L. McKay, MS³; Birju Mehta, MS¹; Catherine J. Cheng, MS³; Faith B. Buchanan, PA³; Bambi J. Grilley, RPh¹; Kaitlin Morrison, PhD³; Malcolm K. Brenner, MD, PhD^{1,2,7}; Jonathan S. Serody, MD^{3,4,9}; Gianpietro Dotti, MD^{3,9}; Helen E. Heslop, MD^{1,2,7}; and Barbara Savoldo, MD, PhD^{3,9,10}



Anti-CD30 CAR T-Cell Therapy After Lymphodepletion Regimens for R/R Hodgkin Lymphoma (HL)

- Two parallel Phase I/II studies (NCT02690545 and NCT02917083) at 2 independent centers involving patients with relapsed or refractory HL
- Anti-CD30 CAR T cells were administered after lymphodepletion with either bendamustine alone, bendamustine and fludarabine or cyclophosphamide and fludarabine

Response	All Patients $(N = 37)$	Benda (n = 5)	Benda-Flu (n = 15)	Cy-Flu (n = 17)
ORR				
CR + PR	23 (62)	0 (0)	12 (80)	11 (65)
Response rate				
CR	19 (51)	0 (0)	11 (73)	8 (47)
PR	4 (11)	0 (0)	1 (7)	3 (18)

 Cytokine release syndrome was observed in 10 patients, all of which were Grade 1. No neurologic toxicity was observed





Preliminary Results of a Phase 2 Study of Camidanlumab Tesirine (Cami), a Novel Pyrrolobenzodiazepine-Based Antibody-Drug Conjugate, in Patients with Relapsed or Refractory Hodgkin Lymphoma

Herrera AF et al. ASH 2020;Abstract 2020.



Response to Camidanlumab Tesirine in Patients with R/R Classical Hodgkin Lymphoma





Herrera AF et al. ASH 2020; Abstract 2020.

Follicular Lymphoma



Approved PI3K Inhibitors for FL: Indication and Dosing

	Idelalisib ¹	Copanlisib ²	Duvelisib ³	Umbralisib ⁴
Mechanism of action	Selective ΡΙ3Κδ inhibitor	Dual inhibitor of PI3Kδ,α	Dual inhibitor of ΡΙ3Κδ,γ	Dual inhibitor of PI3Kδ and casein kinase CK1ε
Indication	Relapsed FL after at least 2 prior systemic therapies	Relapsed FL after at least 2 prior systemic therapies	R/R FL after at least 2 prior systemic therapies	R/R FL after at least 3 prior systemic therapies
Dosing	150 mg orally, twice daily	60 mg as a 1-hour IV infusion weekly (3 weeks on, 1 week off)	25 mg orally, twice daily	800 mg orally, once daily

¹Gopal AK et al. *N Engl J Med* 2014;370(11):1008-18; Idelalisib package insert, January 2018.

² Dreyling M et al. *J Clin Oncol* 2017;35(35):3898-905; Copanlisib package insert, September 2017.

³ Flinn IW et al. J Clin Oncol 2019; [Epub ahead of print]; Zinzani PL et al. EHA 2017; Abstract S777; Duvelisib package insert,

September 2018. ⁴ Umbralisib package insert, February 2021.



Lancet Oncol 2021;22:678-89



Copanlisib plus rituximab versus placebo plus rituximab in patients with relapsed indolent non-Hodgkin lymphoma (CHRONOS-3): a double-blind, randomised, placebo-controlled, phase 3 trial

Matthew J Matasar, Marcelo Capra, Muhit Özcan, Fangfang Lv, Wei Li, Eduardo Yañez, Katya Sapunarova, Tongyu Lin, Jie Jin, Wojciech Jurczak, Aryan Hamed, Ming-Chung Wang, Ross Baker, Igor Bondarenko, Qingyuan Zhang, Jifeng Feng, Klaus Geissler, Mihaela Lazaroiu, Guray Saydam, Árpád Szomor, Krimo Bouabdallah, Rinat Galiulin, Toshiki Uchida, Lidia Mongay Soler, Anjun Cao, Florian Hiemeyer, Aruna Mehra, Barrett H Childs, Yuankai Shi, Pier Luigi Zinzani



CHRONOS-3: Progression-Free Survival in R/R Indolent NHL





Matasar MJ et al. Lancet Oncol 2021;22:678-89.

FDA Grants Accelerated Approval to Umbralisib for Marginal Zone Lymphoma and Follicular Lymphoma

Press Release – February 5, 2021

"The Food and Drug Administration granted accelerated approval to umbralisib, a kinase inhibitor including PI3K-delta and casein kinase CK1-epsilon, for the following indications:

- Adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen;
- Adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy.

Approval was based on two single-arm cohorts of an open-label, multi-center, multi-cohort trial, UTX-TGR-205 (NCT02793583), in 69 patients with MZL who received at least one prior therapy, including an anti-CD20 containing regimen, and in 117 patients with FL after at least 2 prior systemic therapies. Patients received umbralisib 800 mg orally once daily until disease progression or unacceptable toxicity."

www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-umbralisib-marginal-zone-lymphomaand-follicular-lymphoma



^(a) Umbralisib, a Dual PI3K δ /CK1 ϵ Inhibitor in Patients With Relapsed or Refractory *Data Lymphona* Nathan H. Fowler, MD¹; Felipe Samaniego, MD¹; Wojciech Jurczak, MD, PhD²; Nilanjan Ghosh, MD, Ph James A. Reeves, MD⁶; Wanda Knopińska-Posłuszny, MD⁷; Chan Y. Cheah, DMSc⁸; Tycel Phillips, MD⁹; Ew Bruce D. Cheson, MD¹¹; Paolo F. Caimi, MD¹²; Sebastian Grosicki, MD, PhD¹³; Lori A. Leslie, MD¹⁴; Jul Gustavo Fonseca, MD¹⁶; Sunil Babu, MD¹⁷; Daniel J. Hodson, MD¹⁸; Spencer H. Shao, MD¹⁹; John M. E Jeff P. Sharman, MD²¹; Jennie Y. Law, MD²²; John M. Pagel, MD, PhD²³; Hari P. Miskin, MSc²⁴; Peter S Owen A. Q'Conner, MD, PhD^{24,25}; Michael S. Weise, JD²⁴, and Pier Luigi Zinzapi, MD, PhD^{25,27}

Nathan H. Fowler, MD¹; Felipe Samaniego, MD¹; Wojciech Jurczak, MD, PhD²; Nilanjan Ghosh, MD, PhD³; Enrico Derenzini, MD^{4,5}; James A. Reeves, MD⁶; Wanda Knopińska-Posłuszny, MD⁷; Chan Y. Cheah, DMSc⁸; Tycel Phillips, MD⁹; Ewa Lech-Maranda, MD, PhD¹⁰; Bruce D. Cheson, MD¹¹; Paolo F. Caimi, MD¹²; Sebastian Grosicki, MD, PhD¹³; Lori A. Leslie, MD¹⁴; Julio C. Chavez, MD¹⁵; Gustavo Fonseca, MD¹⁶; Sunil Babu, MD¹⁷; Daniel J. Hodson, MD¹⁸; Spencer H. Shao, MD¹⁹; John M. Burke, MD²⁰; Jeff P. Sharman, MD²¹; Jennie Y. Law, MD²²; John M. Pagel, MD, PhD²³; Hari P. Miskin, MSc²⁴; Peter Sportelli, BS²⁴; Owen A. O'Connor, MD, PhD^{24,25}; Michael S. Weiss, JD²⁴; and Pier Luigi Zinzani, MD, PhD^{26,27}

J Clin Oncol 2021;39:1609-18



Umbralisib for Heavily Pretreated R/R Indolent NHL





FDA Grants Accelerated Approval to Tazemetostat for Follicular Lymphoma Press Release: June 18, 2020

"The Food and Drug Administration granted accelerated approval to tazemetostat, an EZH2 inhibitor, for adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and for adult patients with R/R FL who have no satisfactory alternative treatment options.

Today, the FDA also approved the cobas[®]. EZH2 Mutation Test (Roche Molecular Systems, Inc) as a companion diagnostic for tazemetostat.

Approval was based on two open-label, single-arm cohorts (Cohort 4 - EZH2 mutated FL and Cohort 5 - EZH2 wild-type FL) of a multi-center trial (Study E7438-G000-101, NCT01897571) in patients with histologically confirmed FL after at least 2 prior systemic therapies. EZH2 mutations were identified prospectively using formalin-fixed, paraffin-embedded tumor samples, which were centrally tested using the cobas EZH2 Mutation Test. Patients received tazemetostat 800 mg orally twice daily until confirmed disease progression or unacceptable toxicity."

Lancet Oncol 2020;21:1433-42

Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial



Franck Morschhauser, Hervé Tilly, Aristeidis Chaidos, Pamela McKay, Tycel Phillips, Sarit Assouline, Connie Lee Batlevi, Phillip Campbell, Vincent Ribrag, Gandhi Laurent Damaj, Michael Dickinson, Wojciech Jurczak, Maciej Kazmierczak, Stephen Opat, John Radford, Anna Schmitt, Jay Yang, Jennifer Whalen, Shefali Agarwal, Deyaa Adib, Gilles Salles



Response to Tazemetostat in Patients with R/R FL and EZH2-Mutated or EZH2 Wild-Type Tumors





Morschhauser F et al. Lancet Oncol 2020;21:1433-42.

Structure of Selected Bispecific Antibodies

Bi-Specific Antibody	Targets	Design	Ig Fragment Formats
blinatumomab	CD19 x CD3	cos	 two murine scFv joined by a glycine-serine linker monovalent CD19 and monovalent CD3 binding cloned from anti-CD19 (clone HD37) and anti-CD3 (clone L2K-07) murine mAbs
mosunetuzumab	CD20 x CD3		 humanized mouse heterodimeric IgG1-based antibody monovalent CD20 and monovalent CD3ε binding modified Fc devoid of FcγR and complement binding
glofitamab	(CD20) ₂ x CD3		 humanized mouse IgG1-based antibody bivalent CD20 and monovalent CD3ε binding modified Fc devoid of FcγR and complement binding
odronextamab	CD20 x CD3		 fully human IgG4-based heterodimeric antibody monovalent CD20 and monovalent CD3ε binding Fc-dependent effector function-minimized antibody with Fc of the anti-CD3ε heavy chain modified to reduce Protein A binding common κ light chain from anti-CD3ε mAb
epcoritamab	CD20 x CD3		 humanized mouse IgG1-based heterodimeric antibody monovalent CD20 and monovalent CD3 binding IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield

Ig, immunoglobulin; scFv, single-chain variable fragment; mAb, monoclonal antibody; Fc, fragment crystallizable; FcyR, Fc gamma receptor



FDA Grants Breakthrough Therapy Designation for the CD20 x CD3 Bispecific Cancer Immunotherapy Mosunetuzumab for Follicular Lymphoma

Press Release: July 14, 2020

"[The] investigational CD20xCD3 T-cell engaging bispecific mosunetuzumab has been granted Breakthrough Therapy Designation (BTD) by the US Food and Drug Administration (FDA) for the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma who have received at least two prior systemic therapies.

This designation was granted based on encouraging efficacy results observed in the phase I/Ib GO29781 study [NCT02500407] investigating mosunetuzumab in R/R non-Hodgkin lymphoma (NHL). The safety profile of this T-cell engaging bispecific was consistent with its mechanism of action."



Mosunetuzumab Shows Promising Efficacy in Patients with Multiply Relapsed Follicular Lymphoma: Updated Clinical Experience from a Phase I Dose-Escalation Trial

Assouline SE et al. ASH 2020;Abstract 702.



Investigator-Assessed Best Response to Mosunetuzumab in Patients with Follicular Lymphoma Who Have Received at Least 2 Prior Systemic Therapies



Response rates are based on the revised response criteria for malignant lymphoma (Cheson, et al. J Clin Oncol 2007). CAR-T, chimeric antigen receptor T-cell; PI3Ki, phosphoinositide 3-kinase inhibitor; POD24, patients with progressive disease within 24 months of starting first-line therapy. Cytokine release syndrome (CRS) rate: 35% (N = 22)

- Classified as serious adverse event in N = 4
- No patient required tocilizumab, intensive care unit admission or use of vasopressors for CRS management

Neurologic adverse event rate: 45% (N = 28)

• All Grade 1/2



Glofitamab, a Novel, Bivalent CD2O-Targeting T-Cell–Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial

Martin Hutchings, PhD¹; Franck Morschhauser, MD, PhD²; Gloria Iacoboni, MD^{3,4}; Carmelo Carlo-Stella, MD⁵; Fritz C. Offner, MD, PhD⁶; Anna Sureda, MD, PhD⁷; Gilles Salles, MD⁸; Joaquín Martínez-Lopez, MD, PhD, MBA⁹; Michael Crump, MD¹⁰; Denise N. Thomas, MSc¹¹; Peter N. Morcos, PharmD¹¹; Cristiano Ferlini, MD¹¹; Ann-Marie E. Bröske, PhD¹²; Anton Belousov, PhD¹³; Marina Bacac, PhD¹³; Natalie Dimier, PhD¹⁴; David J. Carlile, PhD¹⁴; Linda Lundberg, PhD¹⁵; David Perez-Callejo, MD, PhD¹⁵; Pablo Umaña, PhD¹³; Tom Moore, MD¹²; Martin Weisser, MD¹²; and Michael J. Dickinson, MBBS, DMedSci¹⁶

J Clin Oncol 2021;39:1959-70.



Response to Glofitamab in Patients with R/R B-Cell Lymphomas





Hutchings M et al. J Clin Oncol 2021;39:1959-70.

FDA Grants Accelerated Approval to Axicabtagene Ciloleucel for Relapsed or Refractory Follicular Lymphoma Press Release – March 5, 2021

"The Food and Drug Administration granted accelerated approval to axicabtagene ciloleucel for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Approval in FL was based on a single-arm, open-label, multicenter trial (ZUMA-5; NCT03105336) that evaluated axicabtagene ciloleucel, a CD19-directed chimeric antigen receptor (CAR) T cell therapy, in adult patients with relapsed or refractory FL after two or more lines of systemic therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. Following lymphodepleting chemotherapy, axicabtagene ciloleucel was administered as a single intravenous infusion."



Primary Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

Caron Jacobson, MD¹; Julio C. Chavez, MD²; Alison Sehgal, MD³; Basem William, MD⁴; Javier Munoz, MD, MS, FACP⁵;
 Gilles Salles, MD, PhD⁶; Pashna Munshi, MD⁷; Carla Casulo, MD⁸; David Maloney, MD, PhD⁹; Sven de Vos, MD, PhD¹⁰;
 Ran Reshef, MD¹¹; Lori Leslie, MD¹²; Ibrahim Yakoub-Agha, MD, PhD¹³; Olalekan Oluwole, MD, MPH, MBBS¹⁴;
 Henry Chi Hang Fung, MD¹⁵; Joseph Rosenblatt, MD¹⁶; John Rossi, MS¹⁷; Lovely Goyal, PhD¹⁷; Vicki Plaks, LLB, PhD¹⁷;
 Yin Yang, MS¹⁷; Jennifer Lee, BS¹⁷; Wayne Godfrey, MS, MD¹⁷; Remus Vezan, MD, PhD¹⁷; Mauro Avanzi, MD, PhD¹⁷; and Sattva S. Neelapu, MD¹⁸

¹Dana-Farber Cancer Institute, Boston, MA, USA; ²University of South Florida H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; ³UPMC Hillman Cancer Center, Pittsburgh, PA, USA; ⁴The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; ⁵Banner MD Anderson Cancer Center, Gilbert, AZ, USA; ⁶Centre Hospitalier Lyon Sud, Pierre-Bénite, France; ⁷Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA; ⁸University of Rochester Medical Center - James P. Wilmot Cancer Center, Rochester, NY, USA; ⁹Fred Hutchinson Cancer Research Center, Seattle, WA, USA; ¹⁰Ronald Reagan University of California Los Angeles Medical Center, Santa Monica, CA, USA; ¹¹Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY, USA; ¹²John Theurer Cancer Center, Hackensack, NJ, USA; ¹³CHU de Lille, Univ Lille, INSERM U1286, Infinite, 59000 Lille, France; ¹⁴Vanderbilt University Medical Center, Nashville, TN, USA; ¹⁵Fox Chase Cancer Center, Philadelphia, PA, USA; ¹⁶University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; ¹⁷Kite, a Gilead Company, Santa Monica, CA, USA; and ¹⁸The University of Texas MD Anderson Cancer Center, Houston, TX, USA



ASH 2020; Abstract 700.

ZUMA-5: ORR by IRRC Assessment for Patients with Follicular Lymphoma Receiving Axicabtagene Ciloleucel



- The median time to first response was 1 month (range, 0.8 3.1)
- Among the 25 patients with FL who initially had a PR, 13 (52%) subsequently converted to a CR after a median of 2.2 months (range, 1.9 – 11.2)



ZUMA-5: Progression-Free and Overall Survival



- With a median follow-up of 17.5 months, median PFS and median OS were not reached
 - The 12-month PFS rate was 73.7% (95% CI, 63.3 81.6) for all patients
 - The 12-month OS rate was 92.9% (95% CI, 85.6 96.5) for all patients



ZUMA-5: Cytokine Release Syndrome and Neurologic Events

Cytokine release syndrome (CRS)	FL (n = 124)	MZL (n = 22)
Any grade	78%	100%
Grade ≥3	6%	9%
Median time to onset (range)	4 (1-15) days	4 (1-9) days
Median duration of events (range)	6 (1-27) days	6 (2-14) days
Patients with resolved events	99%	100%
Neurologic events		
Any grade	56%	77%
Grade ≥3	15%	41%
Median time to onset (range)	7 (1-177) days	7 (3-19) days
Median duration of events (range)	14 (1-452) days	10 (2-81) days
Patients with resolved events	96%	82%



Oral Presentation 7508

2021 AS

ANNUAL MEETING

Efficacy and Safety of Tisagenlecleucel in Adult Patients With Relapsed/Refractory Follicular Lymphoma: Primary Analysis of the Phase 2 ELARA Trial

<u>Stephen J. Schuster</u>,¹ Michael Dickinson,² Martin Dreyling,³ Joaquin Martinez-Lopez,⁴ Arne Kolstad,⁵ Jason Butler,⁶ Monalisa Ghosh,⁷ Leslie Popplewell,⁸ Julio C. Chavez,⁹ Emmanuel Bachy,¹⁰ Koji Kato,¹¹ Hideo Harigae,¹² Marie José Kersten,¹³ Charalambos Andreadis,¹⁴ Peter A. Riedell,¹⁵ Ahmed Abdelhady,^{16a} Aiesha Zia,¹⁷ Mony Chenda Morisse,¹⁶ Nathan Hale Fowler,^{18,19,*} Catherine Thieblemont^{20,*}

¹University of Pennsylvania, Philadelphia, PA; ²Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia; ³Medizinische Klinik III, LMU Klinikum, Munich, Germany; ⁴Hospital 12 De Octubre, Complutense University, CNIO, Madrid, Spain; ⁵Oslo University Hospital, Oslo, Norway; ⁶Royal Brisbane Hospital, Herston, Australia; ⁷Michigan Medicine University of Michigan, Ann Arbor, MI; ⁸City of Hope National Medical Center, Duarte, CA; ⁹Moffitt Cancer Center, Tampa, FL; ¹⁰Hospices Civils de Lyon and Université Claude Bernard Lyon 1, Lyon, France; ¹¹Kyushu University Hospital, Fukuoka, Japan; ¹²Tohoku University Hospital, Sendai, Japan; ¹³Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands, on behalf of HOVON/LLPC; ¹⁴Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; ¹⁵University of Chicago, Chicago, IL; ¹⁶Novartis Pharmaceuticals Corporation, East Hanover, NJ; ¹⁷Novartis Pharma AG, Basel, Switzerland; ¹⁸The University of Texas MD Anderson Cancer Center, Houston, TX; ¹⁹BostonGene, Waltham, MA; ²⁰APHP, Hôpital Saint-Louis-Université de Paris, Paris, France

*Dr Fowler and Dr Thieblemont are co-senior authors. *Analysis completed while employed by Novartis Pharmaceuticals Corporation.



Stephen J. Schuster, MD

Stephen.Schuster@pennmedicine.upenn.edu

ELARA Primary Endpoint: Complete Response Rate by IRC

Best Overall Response Rate

Response Rate, %	Patients Evaluable for Efficacy⁵ (n=94)
CR	66.0 ^b
PR	20.2
ORR (CR+PR)	86.2

- Investigator-assessed CRR was 69.1%^c (ORR 90.4%)
- CRRs/ORRs were comparable among key high-risk subgroups
- Median DOR Was Not Reached at 11 Months Median Follow-Up Kaplan-Meier Plot of Duration of Response (DOR, CR+PR), by IRC Probability of Event Free (%) Assessment (Efficacy Analysis Set) **Censoring times** All patients (N=81) 40 -Number of events (n) All patients: 16 Kaplan-Meier medians All patients: NE months, 95 % CI (NE, NE) 0 9 10 11 12 13 15 17 Time (mo) No. at risk All patients 81 74 72 0
- Median follow-up for efficacy (n=94): 10.9 (4.3-19.7) months
- Probability for a responding patient to remain in response ≥6 months was 79% (95% CI, 66-87)
- 12 of 31 PRs (38.7%) converted to CRs; all but 1 occurred between Month 3 and Month 6
- · Median time to next antilymphoma treatment was not reached



Mantle Cell Lymphoma



Multicenter Phase II ZUMA-12 Schema: First-Line Therapy

Eligibility criteria

- Age ≥ 18 years
- High-risk LBCL
 - HGBCL, with MYC and BLCL2 and/or BCL6 translocations, or
 - LBCL with IPI score ≥ 3 any time before enrollment
- 2 cycles of anti-CD20 plus anthracycline-containing regimen
- Positive interim PET (DS 4 or 5)
- ECOG PS score 0 or 1



- Conditioning
 - Flu 30 mg/m² i.v. and Cy 500 mg/m² i.v.
 on Days -5, -4, and -3
- Axi-cel

Enro

pheresis

nc

motherap

- Single i.v. infusion of 2×10^6 CAR T cells/kg on Day 0

Primary endpoint

• CR^b

Key secondary endpoints

- ORR
- DOR
- EFS
- PFS
- OS
- Safety
- CAR T cells in blood and
 - cytokine levels in serum



ZUMA-12: Interim Safety and Efficacy Results with Axi-cel as First-Line Treatment

ORR and CR in response-evaluable cohort (N = 27)



Safety	CRS (N = 32)	Neurologic events (N = 32)
Any grade, n (%)	32 (100%)	22 (69%)
Grade ≥3, n (%)	3 (9%)	8 (25%)
Grade 4, n (%)	0	2 (6%)
Grade 5, n (%)	0	0
Most common any- grade symptoms, n (%)	Pyrexia: 32 (100%) Chills: 8 (25%) Hypotension: 8 (25%)	Encephalopathy: 10 (31%) Confusional state: 9 (28%)



FDA Approves Brexucabtagene Autoleucel for Relapsed or Refractory Mantle Cell Lymphoma Press Release – July 24, 2020

"The Food and Drug Administration granted accelerated approval to brexucabtagene autoleucel, a CD19-directed genetically modified autologous T cell immunotherapy, for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

Approval was based on ZUMA-2 (NCT02601313), an open-label, multicenter, single-arm trial of 74 patients with relapsed or refractory MCL who had previously received anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor. Patients received a single infusion of brexucabtagene autoleucel following completion of lymphodepleting chemotherapy. The primary efficacy outcome measure was objective response rate (ORR) per Lugano [2014] criteria as assessed by an independent review committee."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-brexucabtagene-autoleucel-relapsed-or-refractorymantle-cell-lymphoma



N Engl J Med 2020;382(14):1331-42

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ORIGINAL ARTICLE

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan



ZUMA-2: Response Rates, Survival and Select Safety Outcomes with Brexucabtagene Autoleucel for Mantle Cell Lymphoma




Meet The Professor Optimizing the Selection and Sequencing of Therapy for Patients with ER-Positive Breast Cancer

Thursday, October 28, 2021 5:00 PM – 6:00 PM ET

> Faculty Matthew P Goetz, MD

> > Moderator Neil Love, MD



Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

