Enhancing Patient Care for CAR T-Cell Therapy in NHL:

Comprehensive Solutions for Your Community

This activity is supported by an educational grant from Bristol Myers Squibb

FACULTY

Paolo F. Caimi, MD

Associate Professor
Cleveland Clinic Lerner College of Medicine
Staff Physician, Department of Hematology and Oncology
Cleveland Taussig Cancer Institute
Cleveland, OH, USA

Catherine Coombs, MD

Associate Clinical Professor
Division of Hematology-Oncology
Department of Medicine
University of California, Irvine School of Medicine
Orange, CA, USA

Christopher Flowers, MD, MS

Division Head *ad Interim*, Division of Cancer Medicine
Department Chair, Department of Lymphoma-Myeloma, Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, TX, USA

Activity Overview

Target Audience

This activity is intended for hematologists/oncologists (community and academic), PAs, NPs, and other members of the interprofessional, multidisciplinary cancer care team on a global level that interface with patients with NHL.

Educational Objectives

After completing this activity, the participant should be better able to:

- Assess the expanding treatment landscape for patients with NHL, including new and emerging non-CART options such as bispecific antibodies, and its impact on individualized treatment selection and treatment sequencing.
- Analyze available CAR T-cell therapies for patients with relapsed/refractory NHL based on the latest safety and efficacy trial data and currently approved indications.
- Conduct comprehensive evaluation to determine eligibility and potential benefits of CAR T-cell therapy based on recent clinical trial data, guideline recommendations, as well as patient-, disease-, and treatment-specific factors.
- Identify suitable candidates that might benefit from CAR T-cell therapy in an outpatient setting versus an inpatient setting to support patient preference and satisfaction.
- Apply a multidisciplinary approach to coordinate care between referring physician, establishing outpatient CART centers, and cross-collaboration with clinical teams to ensure individualized and optimal patient management.

Copyright 2024 © Medical Learning Institute Inc.

Agenda

- ✓ Part 1: Exploring Innovative NHL Treatment Alternatives: Expert Insights on Integrating Clinical Guidelines into Decision-Making
- ✓ Part 2: Constructing Patient Case Studies: Expert Conversations on Selecting Treatment Options and Patient Scenarios
- ✓ Part 3: Cultivating Personalized Treatment Strategies through a Multidisciplinary Approach: Expert Discourse on Coordinated Care, Outpatient CAR T, and Patient-Centric Factors
- ✓ Key Takeaways and Conclusions
- ✓ Q&A with Expert Faculty

Accreditation Information

In support of improving patient care, Medical Learning Institute Inc. is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physician Continuing Medical Education
Medical Learning Institute, Inc. (MLI) designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™.
Physicians should claim only the credit commensurate with the extent of their participation in the activity.

ECMEC® Credit

The European Union of Medical Specialists-European Accreditation Council for Continuing Medical Education (UEMS-EACCME®) has an agreement of mutual recognition of continuing medical education (CME) credit with the American Medical Association (AMA). European physicians interested in converting *AMA PRA Category 1 Credit(s)*™ into European CME credit (ECMEC®) should contact the UEMS (www.uems.eu)

MOC Statement

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Participation information will be shared through the ACCME's Program and Activity Reporting System (PARS).

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

Physician Associate

Medical Learning Institute, Inc. has been authorized by the American Academy of PAs (AAPA) to award AAPA Category 1 CME credit for activities planned in accordance with AAPA CME Criteria. This activity is designated for 1.0 AAPA Category 1 CME credit. PAs should only claim credit commensurate with the extent of their participation.

Nursing Continuing Professional Development
Successful completion of this nursing continuing professional development activity will be awarded 1.0 contact hour and 0.65 contact hour in the area of pharmacology.

Interprofessional Continuing Education (IPCE) Statement

This activity was planned by and for the healthcare team, and learners will receive 1.0 Interprofessional Continuing Education (IPCE) credit for learning and change

Copyright 2024 © Medical Learning Institute Inc.

Disclosures

Christopher Flowers, MD, MS, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: AbbVie, Bayer, BeiGene, Celgene, Denovo Biopharma, Foresight Diagnostics, Genentech/Roche, Genmab, Gilead, N-Power Medicine, Pharmacyclics/Janssen; *Research funding:* 4D, AbbVie, Acerta, Adaptimmune, Allogene, Amgen, Bayer, Celgene, Cellectis, EMD, Gilead, Genentech/Roche, Guardant, Iovance, Janssen Pharmaceutical, Kite, MorphoSys, Nektar, Novartis, Pfizer, Pharmacyclics, Sanofi, Takeda, TG Therapeutics, Xencor, Ziopharm, Burroughs Wellcome Fund, Eastern Cooperative Oncology Group, National Cancer Institute, V Foundation, Cancer Prevention and Research Institute of Texas: CPRIT Scholar in Cancer Research; *Stock Options:* Foresight Diagnostics (Advisor w/individual stock options), N Power (Advisor w/individual stock options)

Catherine C. Coombs, MD, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: AbbVie, Allogene, AstraZeneca, BeiGene, Janssen, Genentech, Lilly, MEI Pharma, Mingsight, Octapharma; *Speakers' Bureau:* AbbVie, AstraZeneca, BeiGene, Genentech, Lilly; *Research funding:* AbbVie, CarnaBio, Lilly; *Own stock:* Pfizer, bluebird bio, Geron
The following relationships have ended within the last 24 months:
Consultant/Advisor: Allogene, Mingsight

Paolo F. Caimi, MD, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: Arvinas, Bristol Myers Squibb, Genentech, Novartis, Takeda, Sobi, Recordati Rare Diseases; *Research funding:* AbbVie, ADC Therapeutics, Genentech, Genmab, Recordati Rare Diseases
The following relationships have ended within the last 24 months:
Consultant/Advisor: ADC Therapeutics

Planning Committee and Content/Peer Reviewers
The planners and content/peer reviewers from Medical Learning Institute, Inc., the accredited provider, do not have any relevant financial relationships to disclose with ineligible companies unless listed below.

All of the relevant financial relationships of individuals for this activity have been mitigated.

Disclosure & Conflict of Interest Policy

Medical Learning Institute Inc is committed to providing high quality continuing education to healthcare professionals, as individuals and teams, with a protected space to learn, teach, and engage in scientific discourse free from influence from ineligible companies that may have an incentive to insert commercial bias into education. To that end, MLI requires faculty, presenters, planners, staff, and other individuals who are in a position to control the content of this CE activity to disclose all financial relationships they have had in the past 24 months with ineligible companies as defined by the ACCME, as related to the content of this CE activity, regardless of the amount or their view of the relevance to the education. All identified COI will be thoroughly vetted and mitigated according to MLI policy. These disclosures will be provided to learners prior to the start of the CE activity.

Disclosure of Unlabeled Use

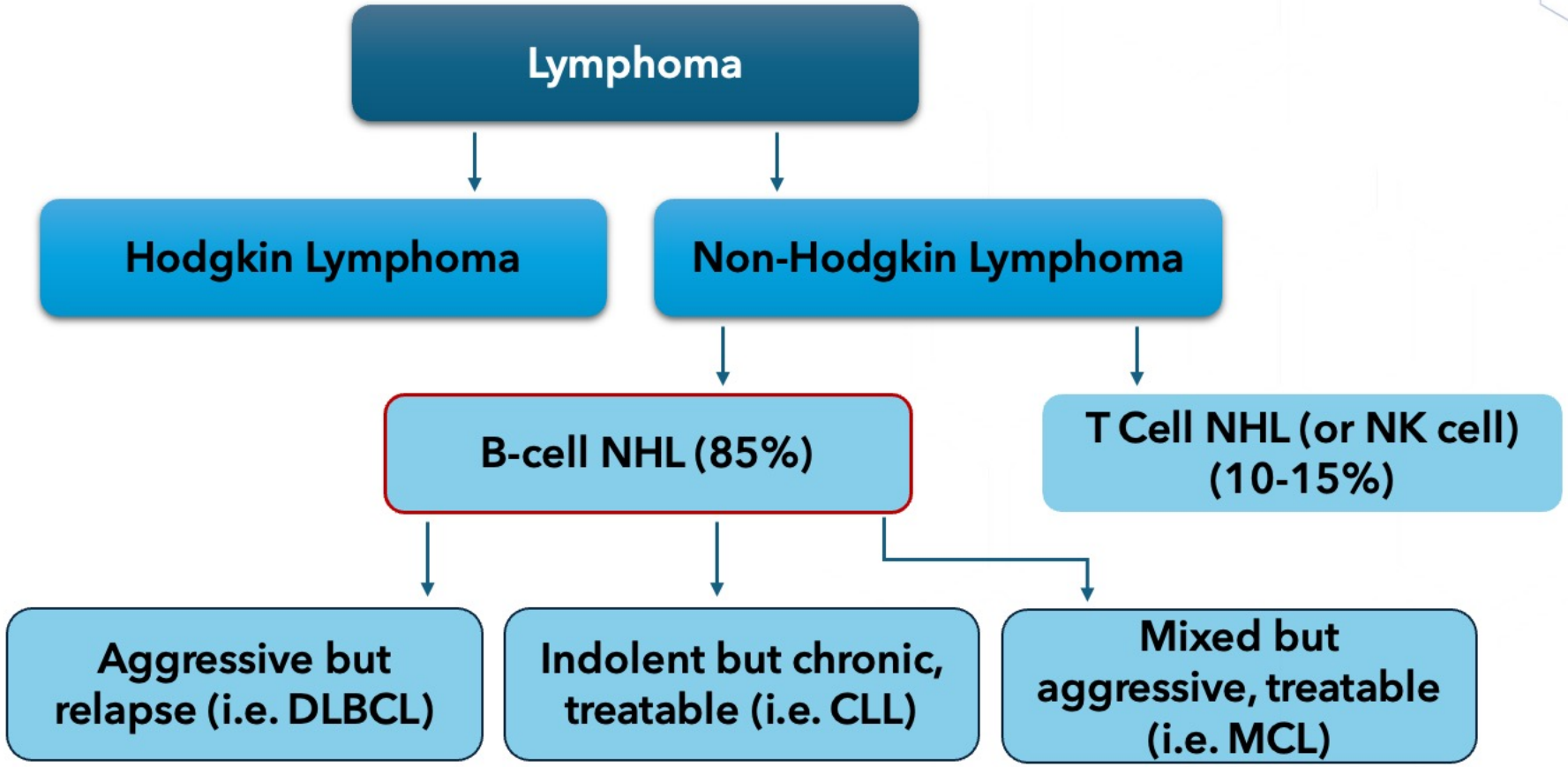
This educational activity may contain discussions of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this CE activity do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the CE activity are those of the presenters and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this CE activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this CE activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Copyright 2024 © Medical Learning Institute Inc.

Non-Hodgkin Lymphoma Malignancies



Adapted from MD Anderson. https://www.mdanderson.org/cancer-types/non-hodgkin-lymphoma.html. 2024.

© 2024

Treatment Guidelines for DLBCL

Second-Line Therapy
(relapsed disease <12 mo or primary refractory disease)

- CAR T-cell therapy
- Axicabtagene ciloleucel (CD19-directed) (category 1)
- Lisocabtagene maraleucel (CD19-directed) (category 1)

Bridging Therapy Options
(typically 1 or more cycles as necessary until CAR T-cell product is available)

- DHA + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) + rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- Gemox + rituximab
- ICE ± rituximab
- Polatuzumab vedotin-piiq ± rituximab ± bendamustine (bendamustine should be considered/added only after leukapheresis)
- ISRT (can be used as monotherapy or sequentially with systemic therapy)

Second-Line Therapy
(no intention to proceed to transplant)

Preferred regimens (in alphabetical order)
- CAR T-cell therapy (CD19-directed) (if eligible)
  - Lisocabtagene maraleucel
  - Polatuzumab vedotin-piiq ± bendamustine[1] ± rituximab
- Tafasitamab-cxixl + lenalidomide

Other recommended regimens (in alphabetical order)
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- DA-EPOCH ± rituximab
- GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx ± rituximab
- Rituximab

Useful in certain circumstances
- Brentuximab vedotin for CD30+ disease
- Ibrutinib[n] (non-GCB DLBCL)
- Lenalidomide ± rituximab (non-GCB DLBCL)

Third-Line and Subsequent Therapy

Preferred regimens
- T-cell engager therapy
  - CAR T-cell therapy (preferred if not previously given) (in alphabetical order)
    - ◇ Axicabtagene ciloleucel (CD19-directed)
    - ◇ Lisocabtagene maraleucel (CD19-directed)
    - ◇ Tisagenlecleucel (CD19-directed)
  - Bispecific antibody therapy (only after at least two lines of systemic therapy; including patients with disease progression after transplant or CAR T-cell therapy) (in alphabetical order)
    - ◇ Epcoritamab
    - ◇ Glofitamab

Other recommended regimens
- Loncastuximab tesirine
- Selinexor (including patients with disease progression after transplant or CAR T-cell therapy)

NCCN Guidelines Version 2.2024. Diffuse Large B-Cell Lymphoma.

© 2024

Treatment Guidelines for FL

Suggested Treatment Regimens
An DFA-approved biosimilar is an appropriate substitute for rituximab

Second-Line Therapy

Preferred Regimens (in alphabetical order)
- Bendamustine + Obinutuzumab or rituximab (not recommended if treated with prior bendamustine)
- CHOP + Obinutuzumab or rituximab
- CVP + Obinutuzumab or rituximab
- Lenalidomide + rituximab

Other recommended regimens
- Lenalidomide (if not candidate for anti-CD-20 mAb therapy)
- Lenalidomide + Obinutuzumab
- Obinutuzumab
- Rituximab

Second-Line Therapy For Older or Infirm
(if none of the therapies are expected to be tolerable in the opinion of treating physician)

Preferred regimens
- Rituximab (375 mg/m2 weekly for 4 doses)
- Tazemetostat (irrespective of *EZH2* mutation status)

Other recommended regimen
- Cyclophosphamide ± rituximab

Second-Line Extended Therapy (optional)

Preferred regimens
- Rituximab maintenance 375 mg/m2 one dose every 12 weeks for 2 years (category 1)
- Obinutuzumab maintenance for rituximab-refractory disease (1g every 8 weeks for total of 12 doses)

Second-Line Consolidation Therapy (optional)

- High-dose therapy with autologous stem cell rescue (HDT/ASCR)

Suggested Treatment Regimens
An DFA-approved biosimilar is an appropriate substitute for rituximab

Third-Line and Subsequent Therapy
Subsequent systemic therapy options include second-line therapy regimens (FOLL-B 2 of 6) that were not previously given

Preferred Regimens (in alphabetical order)
- T-cell engager therapy
  - Bispecific antibody therapy
  - Epcoritamab-bysp
  - Mosunetuzumab-axgb
- Chimeric antigen receptor (CAR) T-cell therapy
  - Axicabtagene ciloleucel (CD19-directed)
  - Lisocabtagene maraleucel (CD19-directed)
  - Tisagenlecleucel (CD19-directed)

Other recommended regimens
- EZH2 inhibitor
  - Tazemetostat (irrespective of EZH2 mutation status)
- BTK inhibitor (BTKi)
  - Zanubrutinib + obinutuzumab

Third-Line Consolidation Therapy

Useful in Certain Circumstances
- Allogeneic hematopoletic cell transplantation (HCT) in selected cases

On May 15, 2024, the FDA has granted accelerated approval for lisocabtagene maraleucel, a CAR T-cell therapy, for the treatment of adult patients with R/R FL who have received two or more prior lines of systemic therapy

R/R FL, relapsed/refractory follicular lymphoma
NCCN Guidelines Version 2.2024. Follicular Lymphoma.

© 2024

Treatment Guidelines for MCL

Suggested Treatment Regimens
An DFA-approved biosimilar is an appropriate substitute for rituximab

Second-Line and Subsequent Therapy

Preferred Regimens (in alphabetical order)
- Covalent BTKi (continuous)
  - Acalabrutinib
  - Zanubrutinib
- Lenalidomide + rituximab

Other recommended regimen
- Covalent BTKi (continuous)
  - Ibrutinib ± rituximab

Useful in Certain Circumstances (in alphabetical order)
- Bendamustine + rituximab (not recommended if treated with prior bendamustine)
- Bortezomib ± rituximab
- DHA (dexamethasone, cytarabine) + Platinum (carboplatin, cisplatin, or oxaliplatin) + rituximab (if not previously given)
- GemOx (gemcitabine, oxaliplatin) + rituximab
- Ibrutinib + venetoclax
- RBAC500 (rituximab, bendamustine, cytarabine) (not recommended if treated with prior bendamustine)
- Venetoclax (continuous) ± rituximab

Progressive disease after prior covalent BTKi
- Non-covalent BTKi (continuous)
  - Pirtobrutinib
- CAR T-cell therapy
  - Brexucabtagene autoleucel (CD19-directed)
  - Lisocabtagene maraleucel (CD19-directed)

On May 30, 2024, the FDA has granted accelerated approval for lisocabtagene maraleucel, a CAR T-cell therapy, for the treatment of adult patients with R/R MCL who have received after at least 2 lines of systemic therapy, including a BTK inhibitor

NCCN Guidelines Version 2.2024. Mantle Cell Lymphoma.

© 2024

Treatment Guidelines for CLL

Suggested Treatment Regimens
CLL/SLL Without del (17p)/*TP53* Mutation

Second-Line or Third-Line Therapy

Preferred Regimens
- Acalabrutinib (category 1)
- Venetoclax + rituximab (category 1)
- Zanubrutinib (category 1)

Other Recommended Regimens
- Ibrutinib (category 1)
- Venetoclax
- Ibrutunib + venetoclax (category 2B)

Useful in Certain Circumstances
- For relapse after a period of remission (if previously used)
- Venetoclax ± anti-CD20 mAb (venetoclax + Obinutuzumab preferred)
- Resistance or intolerance to prior covalent BTKi therapy
  - Pirtobrutinib

Therapy for Relapsed or Refractory Disease After Prior BTKI- and Venetoclax-Based Regimens

Other Recommended Regimens (alphabetical order by category)
- Chimeric antigen receptor (CAR) T-cell therapy
  - Lisocabtagene maraleucel (CD19-directed)
- Small-molecule inhibitors
  - Duvelisib
  - Idelalisib ± rituximab
  - Pirtobrutinib (if not previously given)
  - Ibrutinib + venetoclax (category 2B)
- FCR
- Lenalidomide ± rituximab
- Obinutuzumab
- Bendamustine + rituximab (category 2B for patients ≥65y or patients <65y with significant comorbidities)\
- HDMP + anti-CD20 mAb (category 2B)

Suggested Treatment Regimens
CLL/SLL With del (17p)/*TP53* Mutation
(alphabetical by category)
CIT is not recommended since del(17p)/TP53 mutation is associated with low response rates.

Second-Line or Third-Line Therapy

Preferred Regimens
- Acalabrutinib (category 1)
- Venetoclax + rituximab (category 1)
- Venetoclax
- Zanubrutinib (category 1)

Other Recommended Regimens
- Ibrutinib (category 1)
- Ibrutunib + venetoclax (category 2B)

Useful in Certain Circumstances
- For relapse after a period of remission (if previously used)
- Venetoclax ± anti-CD20 mAb (venetoclax + obinutuzumab preferred)
- Resistance or intolerance to prior covalent BTKi therapy
  - Pirtobrutinib

Therapy for Relapsed or Refractory Disease After Prior BTKi- and Venetoclax-Based Regimens

Other Recommended Regimens (alphabetical order by category)
- CAR T-cell therapy
  - Lisocabtagene maraleucel (CD19-directed)
- Small-molecule inhibitors (in aphpabetical order by category)
  - Duvelisib
  - Idelalisib ± rituximab
  - Pirtobrutinib (if not previously given)
  - Ibrutinib + venetoclax (category 2B)
- Alemtuzumab ± rituximab
- HDMP + anti-CD20 mAb
- Lenalidomide ± rituximab

NCCN Guidelines Version 3.2024. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.

© 2024

Approved CAR T-Cell Therapies

Generic Name	Brand Name	FDA approval (year)	Targeted antigen	Targeted hematologic malignancies	Pivotal trial(s)
Tisagenlecleucel (tisa-cel)	Kymriah	2017	CD19	Adults with R/R LBCL after 2 or more lines of systemic therapy	JULIET
				Adults with R/R FL after 2 or more lines of systemic therapy	ELARA
Axicabtagene ciloleucel (axi-cel)	Yescarta	2017		Adults with R/R LBCL after 2 or more lines of systemic therapy	ZUMA-1
				Adults with R/R FL after 2 or more lines of systemic therapy*	ZUMA-5
				Adults with LBCL that are refractory to first-line chemoimmunotherapy or that relapses ≤ 12 months	ZUMA-7
Lisocabtagene maraleucel (liso-cel)	Breyanzi	2021		Adults with R/R LBCL after 2 or more lines of systemic therapy	TRANSCEND NHL-001
				Adults with LBCL that are refractory to first-line chemoimmunotherapy or that relapses ≤ 12 months and not eligible for HSCT due to age or comorbidities	TRANSFORM
				Adult patients with R/R CLL/SLL who have been treated with at least 2 lines of therapy, including a BCL-2 inhibitor and a BTK inhibitor*	TRANSCEND CLL-004
				Adults with R/R FL after 2 or more lines of systemic therapy*	TRANSCEND FL
				Adults with R/R MCL after at least 2 lines of systemic therapy, including a BTK inhibitor*	TRANSCEND NHL-001
Brexucabtagene autoleucel (brexu-cel)	Tecartus	2020		Adult patients with R/R MCL*	ZUMA-2

*Indication is approved under accelerated approval.
BCL-2, B-cell lymphoma 2; BCMA, B-cell maturation antigen; BTK, Bruton tyrosine kinase; CD19, Cluster of Differentiation 19; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FL, follicular lymphoma; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory.
U.S. Food & Drug Administration. Cellular & Gene Therapy Products.; U.S. Prescribing Information.

© 2024

Approved Bispecific Antibody Therapies

Generic Name	Brand Name	FDA approval (year)	Targeted antigen	Targeted hematologic malignancies	Pivotal trial(s)
Mosunetuzumab	Lunsumio	2022	CD20	Adults with R/R FL after ≥2 lines of systemic therapy	GO29781
Glofitamab	Columvi	2023		Adults with R/R DLBCL, NOS or LBCL arising from FL after ≥2 lines of systemic therapy	NP30179
Epcoritamab	Epkinly	2023		Adults with R/R DLBCL, NOS including arising from indolent lymphoma and high-grade DLBCL after ≥2 lines of systemic therapy	EPCORE NHL-1

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; R/R, relapsed/refractory.

Mitra A, et al. *Front Immunol*. 2023 May 15;14:1188049.

© 2024

Inpatient & Outpatient CAR T-Cell Therapy

Inpatient

Many centers require admission for minimum of 7 days

After discharge, patients remain within proximity (1-2 hours) of treating center for up to 4 weeks and avoid driving for up to 8 weeks following CAR T-cell infusion

Patients monitored for ongoing cytopenias, CAR-T related side effects, or any other symptoms through the disease response assessment (typically at 4 weeks after CAR T)

Outpatient

Available at some centers and for some products

Patient should have lodging within 1-2 hours of the treating center for a minimum of 4 weeks

Patients seen frequently following infusion for ongoing cytopenias, TEAEs, or other symptoms by disease response assessment (typically at 4 weeks post-CAR T therapy)

Educate the patient on home temperature (+/- BP) monitoring, side effect monitoring, use of symptoms trackers

Patient to be admitted at onset of fever and/or any side effect concerning for CRS or neurotoxicity

TEAE, treatment emergent adverse events.

Myers GD, et al. *J Immunother Cancer*. 2021 Apr;9(4):e002056.

© 2024

BYOCS Live: Decision Points Determined by Learners and Discussion with Expert Faculty

BUILD YOUR OWN CASE STUDY LIVE

Paolo Caimi, MD

Catherine Coombs, MD

Christopher Flowers, MD

MLI

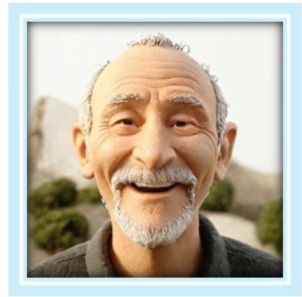
Patient Cases

Mr. Rosenstein

64-year-old fit male
from Maine

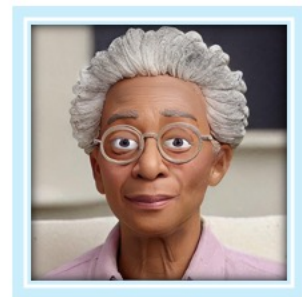
Ms. Blanchard

58-year-old fit female
from Utah



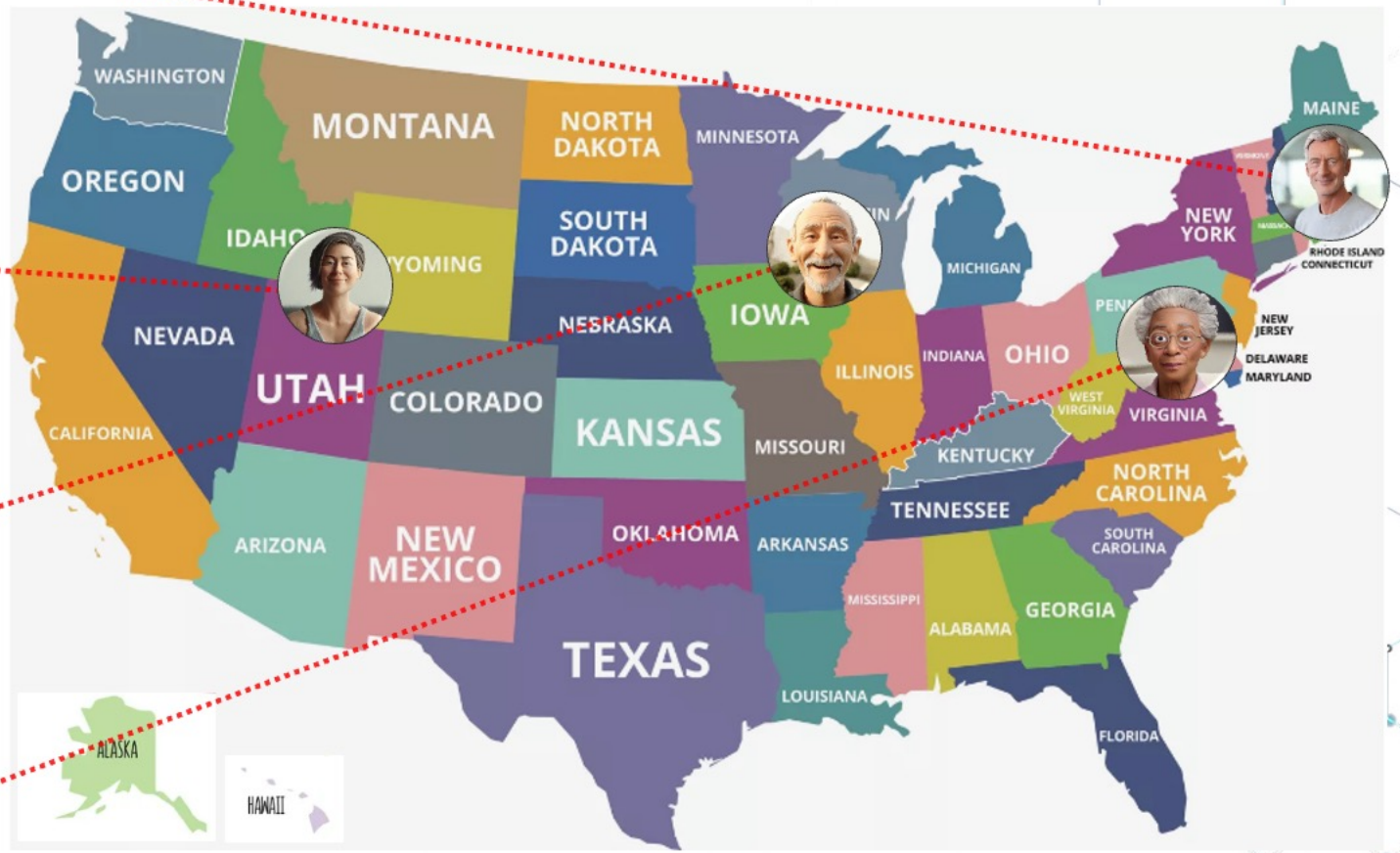
Mr. Campbell

81-year-old frail male
from Iowa



Ms. Souza

78-year-old frail female
from Virginia

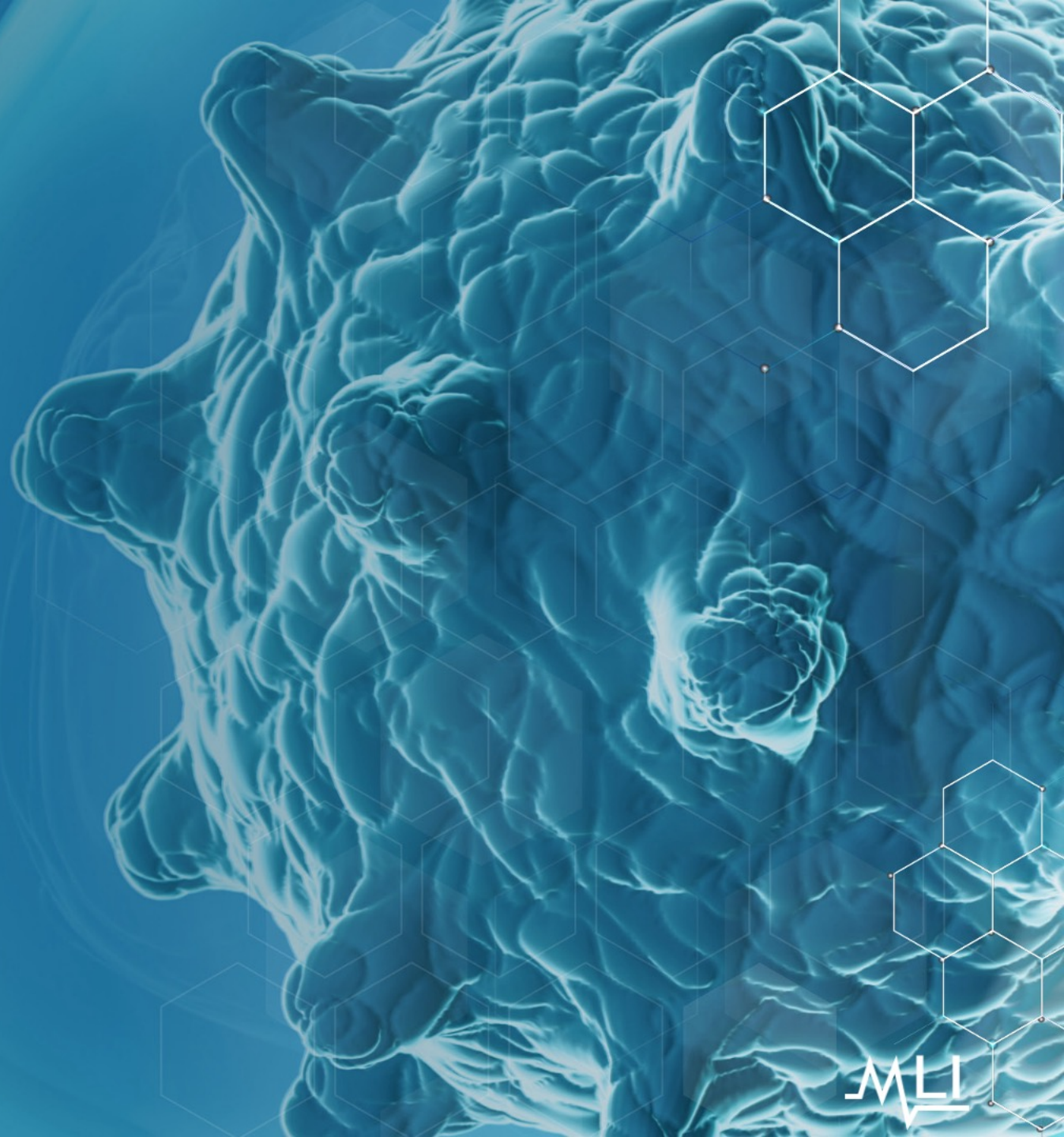


© 2024

CASE STUDY #1

MCL

NEXT



Mr. Rosenstein
64-year-old fit male from Maine
R/R MCL

- Medical History
  - Hypertension (controlled on metoprolol)
  - Family history of prostate cancer
- Initially diagnosed with stage II indolent extranodal localization of MCL
  - *IGHV* mutated
  - *TP53* not performed
  - *SOX11* negative
  - Classic histology
  - Low proliferation index by Ki-67
- Current symptoms: Watch and wait for 2 years from initial MCL diagnosis; 59-years-old when received auto-SCT as frontline therapy along with bendamustine-rituximab followed by rituximab + cytarabine; currently experiencing MCL relapse
  - Hepatomegaly by palpitation
  - GI involvement (15% via lower endoscopy; received radiotherapy)
  - Recent persistent fatigue
  - ECOG PS: 1
- Subjective symptoms:
  - GI discomfort
- Expresses the following preferences:
  - Time-limited therapy
  - Simple regimen that doesn't impact QOL

© 2024

Ms. Souza
78-year-old frail female from Virginia
R/R MCL

- Medical History
  - T1D
  - Mother history of ovarian cancer; sister history of breast cancer
- Initially diagnosed with stage III indolent, extranodal localization of MCL
  - *IGHV* mutated
  - *TP53* WT
  - *SOX11* negative
  - Low proliferation index by Ki-67
  - Classic histology
- 77-years-old when received initial induction of rituximab and bendamustine ± rituximab maintenance for treatment of MCL; relapsed 1 year after start and received ibrutinib and became intolerant
- Current symptoms:
  - Lymphadenopathy (2 cm nodes on axilla)
  - Bone pain and increased fatigue
  - Easy bruising and bleeding
  - ECOG PS: 3
- Subjective symptoms:
  - Weakness and loss of reflexes
  - Pain
- Expresses the following preferences:
  - Doesn't want to travel to a hospital
  - QOL vs prolong survival

© 2024

CASE STUDY #2

CLL

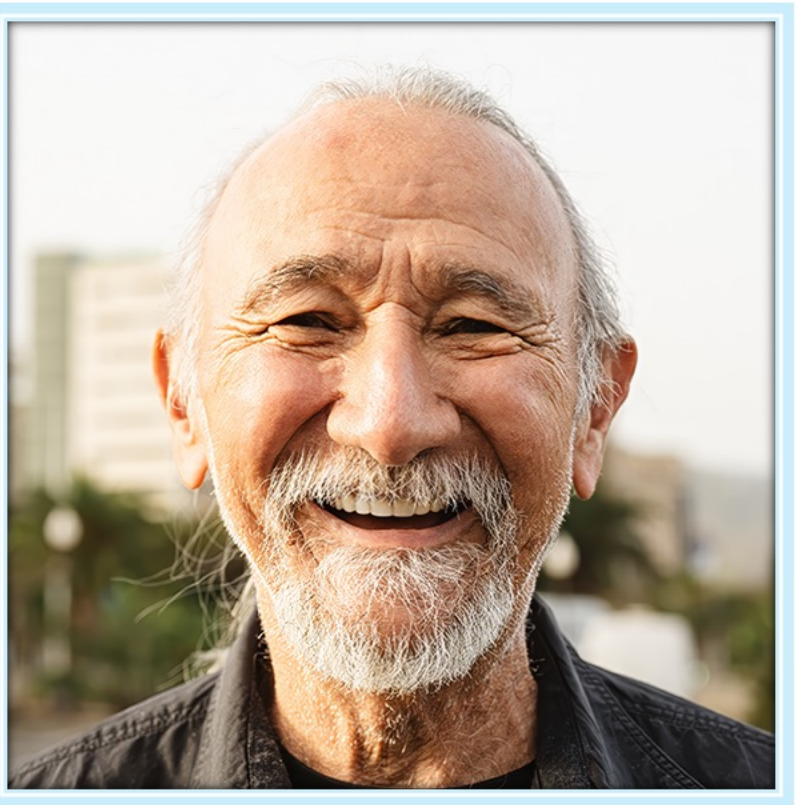
NEXT →

Ms. Blanchard
58-year-old fit female from Utah
R/R CLL

- Medical History
  - No significant medical history
  - No history of pregnancy
- Initially diagnosed with stage I indolent CLL with watch and wait approach
  - Del(*17p*) absent on FISH testing
  - *TP53* unmutated
  - Complex karyotype
- 54-years-old when initially received ibrutinib + rituximab for the treatment of CLL but eventually became intolerant and received venetoclax and disease was refractory
- Current symptoms:
  - Night sweats
  - Fatigue
  - ECOG PS: 0
- Subjective symptoms:
  - Weakness and loss of reflexes
- Headache and tingling
- Expresses the following preferences:
  - No preference for regimen
  - Therapy that prolongs survival

© 2024

Mr. Campbell
81-year-old frail male from Iowa
R/R CLL

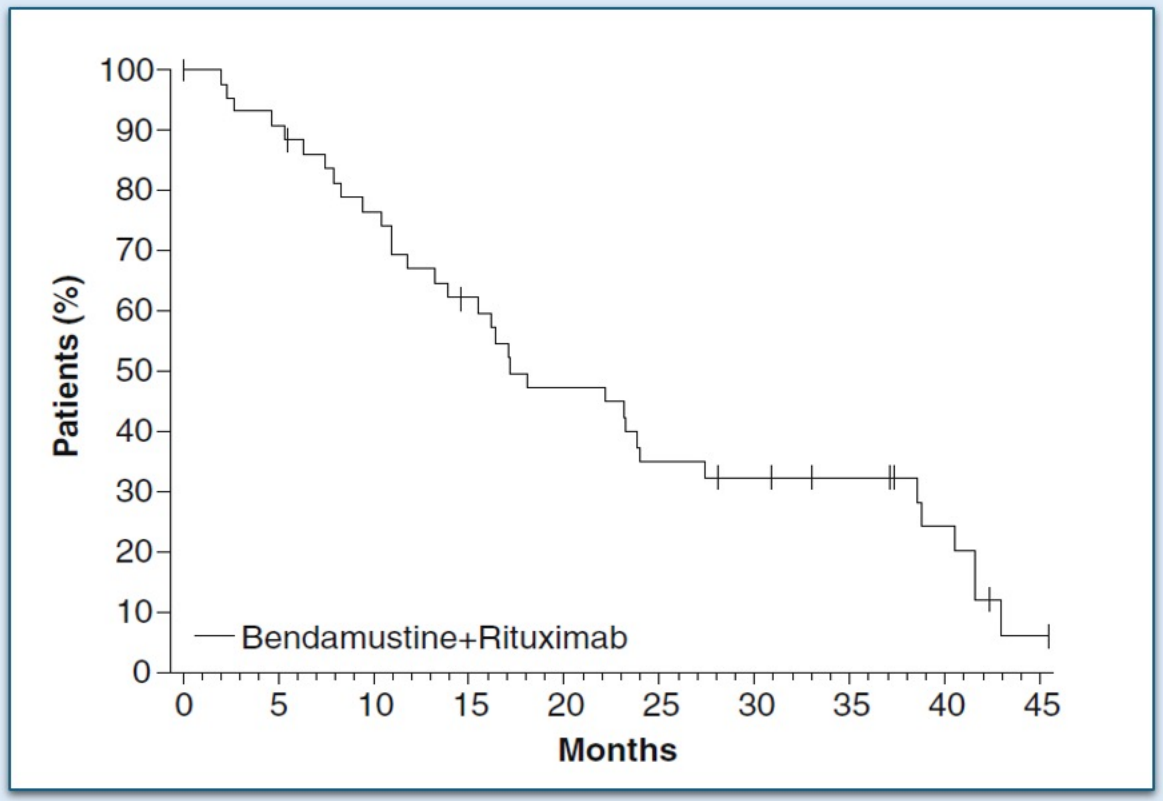


- **Medical History**
  - Hypertension (controlled on furosemide)
  - Type 2 diabetes (controlled on metformin)
  - Previously diagnosed enlarged benign prostate
- **Initially diagnosed with stage III aggressive CLL**
  - *IGHV* unmutated
  - *TP53* mutated; *TP53* deletion positive
  - del(*17p*) unmutated
  - del(*11q*) mutated
- **Relapsed 6 months after frontline therapy of bendamustine and rituximab for treatment of CLL then received acalabrutinib before becoming refractory 2 years later**
- **Current symptoms:**
  - Lymphadenopathy (2 cm nodes on axillae/groin)
  - Lymphocytosis (4,000/mcL)
  - Anemia (Hb: 10 g/dL, Hct: 37%, RBC: 4.1 cells/mcL)
  - Fever and rapid weight loss
  - ECOG PS: 3
- **Subjective symptoms**
  - Fatigue
  - Nausea
- **Expresses the following preferences:**
  - Concerned about future relapse
  - Would prefer not to travel to hospital

© 2024

Bendamustine + Rituximab

Phase II, multicenter, open-label, single-arm, trial evaluating the efficacy of bendamustine + rituximab (n=45) for patients with R/R MCL



PFS	Median PFS (95% CI), mo
Median PFS	17.2 (0.03 – 45.37)
1-year PFS	67.0

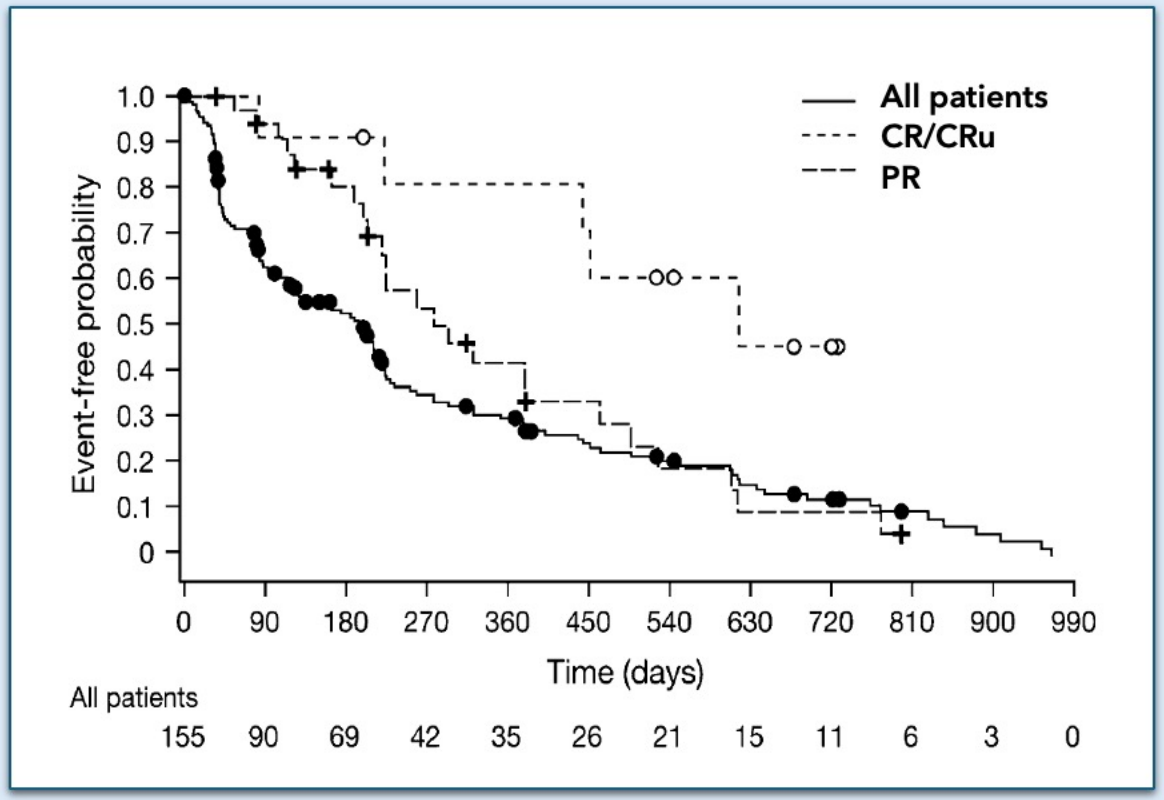
B-R; bendamustine + rituximab; CI, confidence interval; MCL, mantle cell lymphoma; mo, months; PFS, progression-free survival; R/R, relapsed/refractory.

Czuczman MS et al. *Ann Hematol*. 2015;94(12):2025-2032.

© 2024

Bortezomib Monotherapy

Phase II, multicentre, time-to-event PINNACLE study evaluating the efficacy of bortezomib (n=155) in patients with R/R MCL



PFS	Median PFS (95% CI), mo
All patients	6.5 (4.0 – 7.3)
CR/CRu (n=11)	20.3 (14.6 – NE)
PR (n=34)	9.7 (7.2 – 15.2)

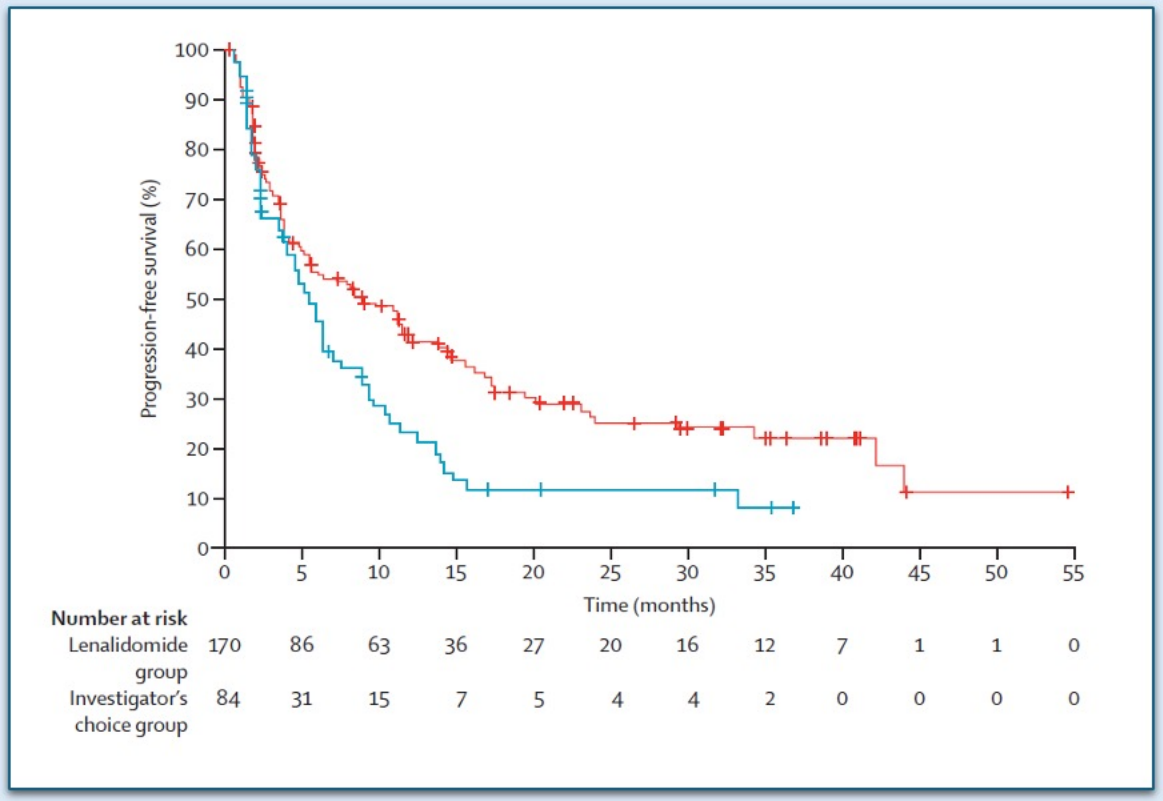
CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; MCL, mantle cell lymphoma; mo, months; NE, not estimatable; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory.

Goy A et al. *Ann Oncol*. 2009(3):520-525.

© 2024

Lenalidomide Monotherapy (1/2)

Phase II, randomized, multicenter, SPRINT study evaluating the efficacy of lenalidomide (n=170) vs investigators choice (n=84) in patients with R/R MCL



PFS	Median PFS (95% CI), mo
Lenalidomide	8.7 (5.5 – 12.1)
Investigator's choice	5.2 (3.7 – 6.9)
HR (95% CI)	0.6 (0.4 – 0.8)

Investigator's choice included rituximab, gemcitabine, fludarabine, chlorambucil, or cytarabine

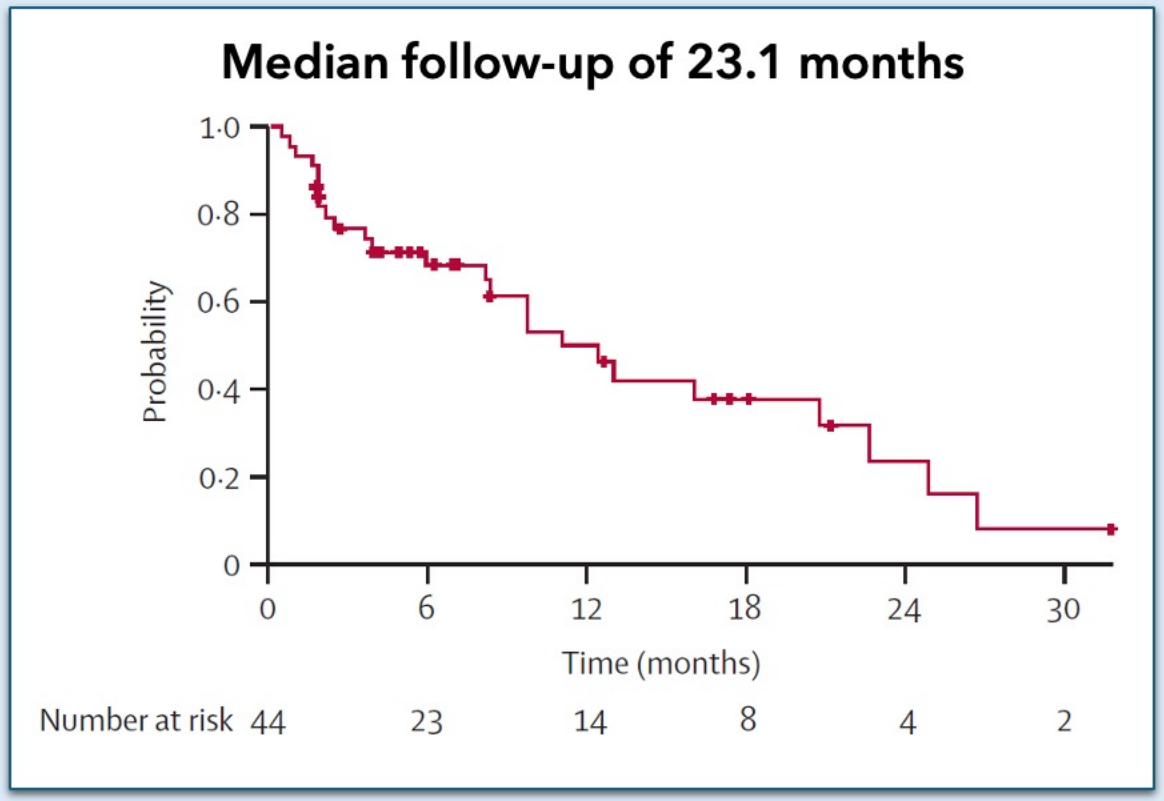
CI, confidence interval; HR, hazard ratio; MCL, mantle cell lymphoma; mo, months; PFS, progression-free survival; R/R, relapsed/refractory.

Trněný M et al. *Lancet Oncol*. 2016(3):319-331.

© 2024

Lenalidomide + Rituximab (2/2)

Phase I/II, single-arm, open-label trial at a single-arm, evaluating the efficacy of lenalidomide + rituximab (n=52) in patients with R/R MCL



PFS	Median PFS (95% CI), mo
L-R	11.1 (8.3 – 24.9)

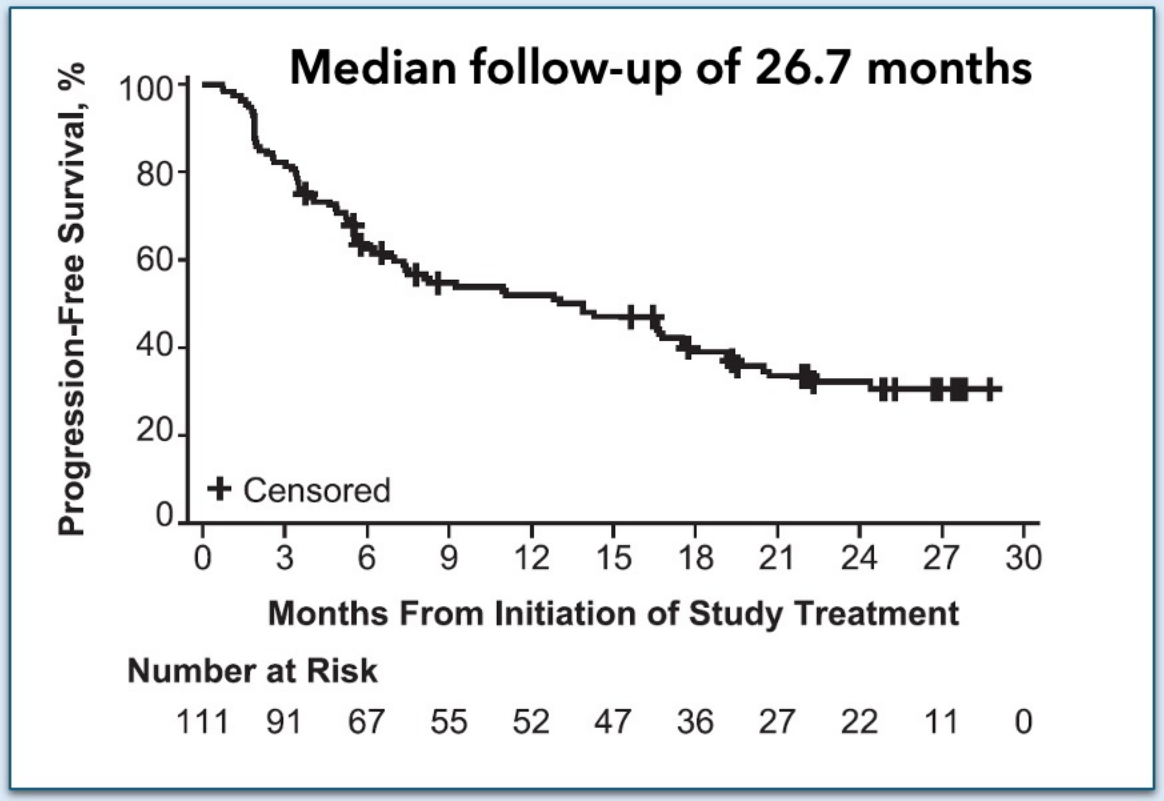
CI, confidence interval; L-R, lenalidomide + rituximab; MCL, mantle cell lymphoma; mo, months; PFS, progression-free survival; R/R, relapsed/refractory.

Wang M et al. *Lancet Oncol*. 2012(7):716-723.

© 2024

Ibrutinib Monotherapy (1/7)

Phase II, open-label, multicenter study evaluating the efficacy of single agent ibrutinib (n=111) in patients with R/R MCL



PFS	Median PFS (95% CI), mo
All treated patients	13.0 (7.0 – 17.5)

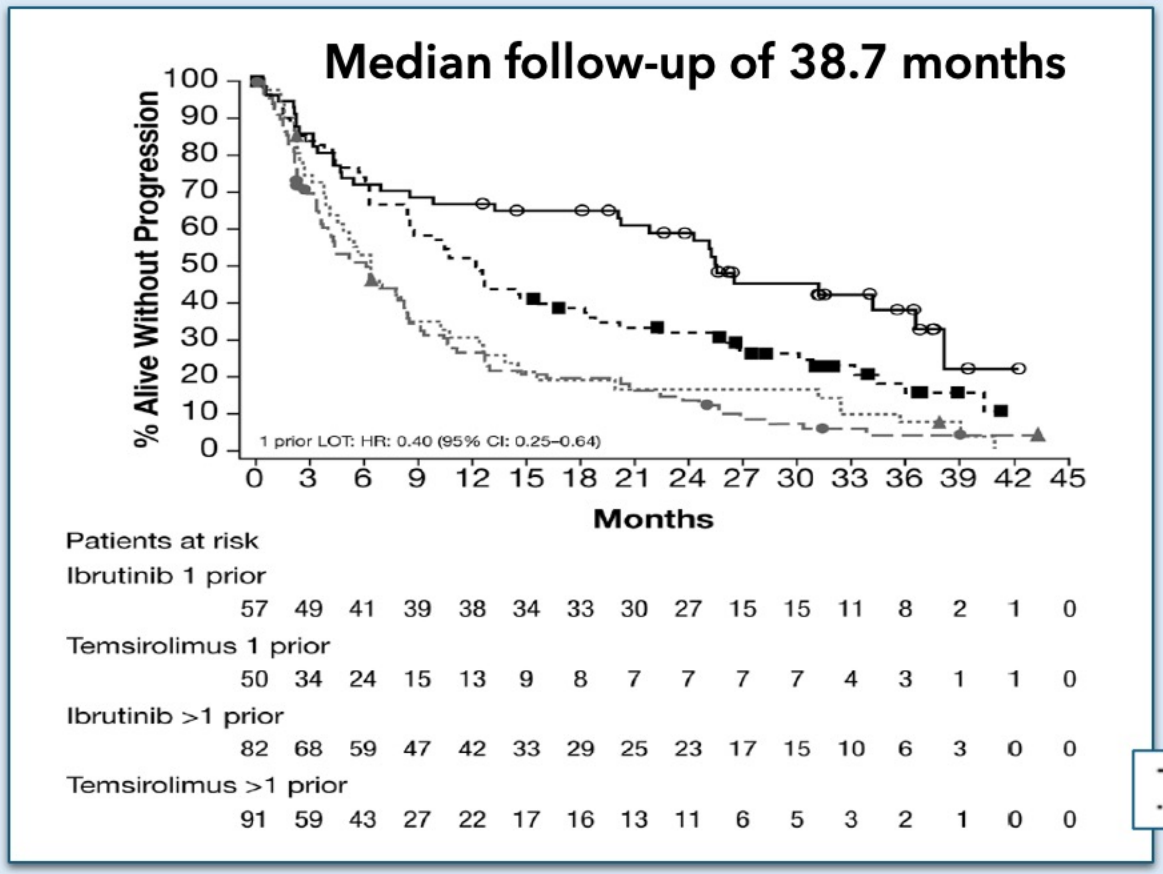
CI, confidence interval; MCL, mantle cell lymphoma; mo, months; PFS, progression-free survival; R/R, relapsed/refractory.

Wang M et al. *Blood*. 2015(6):739-745.

© 2024

Ibrutinib vs Temsirolimus (2/7)

3-year follow-up, randomized, international, open-label RAY study evaluating the efficacy of ibrutinib (n=139) vs temsirolimus (n=141) in patients with R/R MCL



PFS	Median PFS, mo
Ibrutinib	15.6
Temsirolimus	6.2
HR (95% CI)	0.45 (0.4 – 0.6)

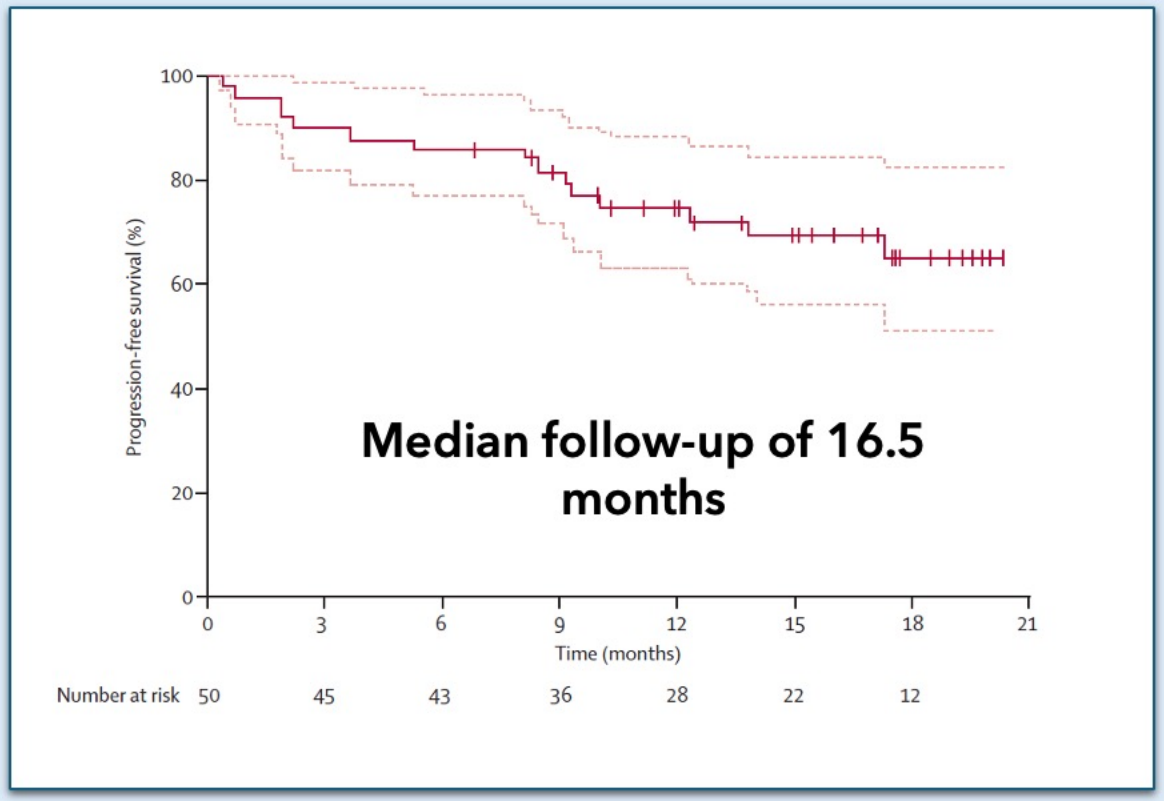
CI, confidence interval; HR, hazard ratio; MCL, mantle cell lymphoma; mo, months; PFS, progression-free survival; R/R, relapsed/refractory.

Rule S et al. *Leukemia*. 2018(8):1799-1803.

© 2024

Ibrutinib + Rituximab (3/7)

Phase II, single-center, open-label study evaluating the efficacy of ibrutinib + rituximab (n=50) in patients with R/R MCL



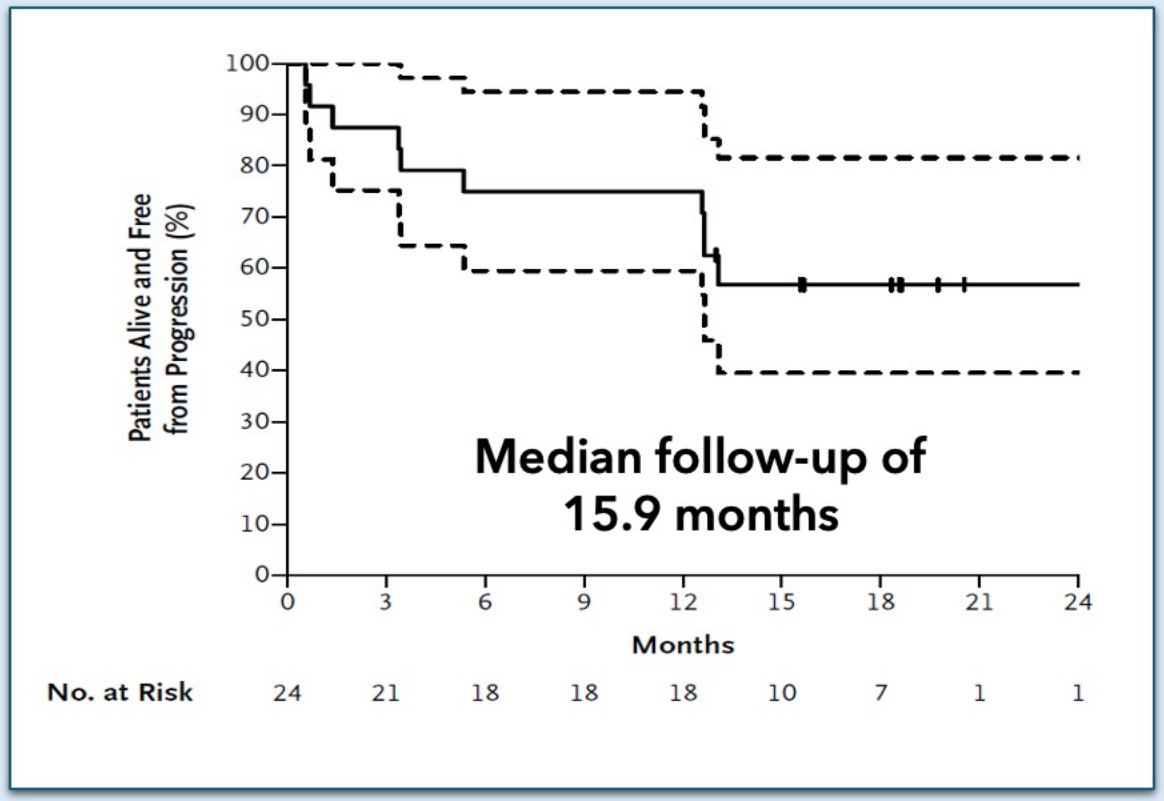
PFS	Median PFS (95% CI), mo
12-month PFS	75.0 (63.0 – 88.0)
15-month PFS	69.0 (57.0 – 84.0)

CI, confidence interval; MCL, mantle cell lymphoma; mo, months; PFS, progression-free survival; R/R, relapsed/refractory.
Wang M et al. *Lancet Oncol*. 2016(1):48-56.

© 2024

Ibrutinib + Venetoclax (4/7)

Phase II, single group, open-label, AIM study evaluating the efficacy of ibrutinib + venetoclax (n=24) in patients with R/R MCL



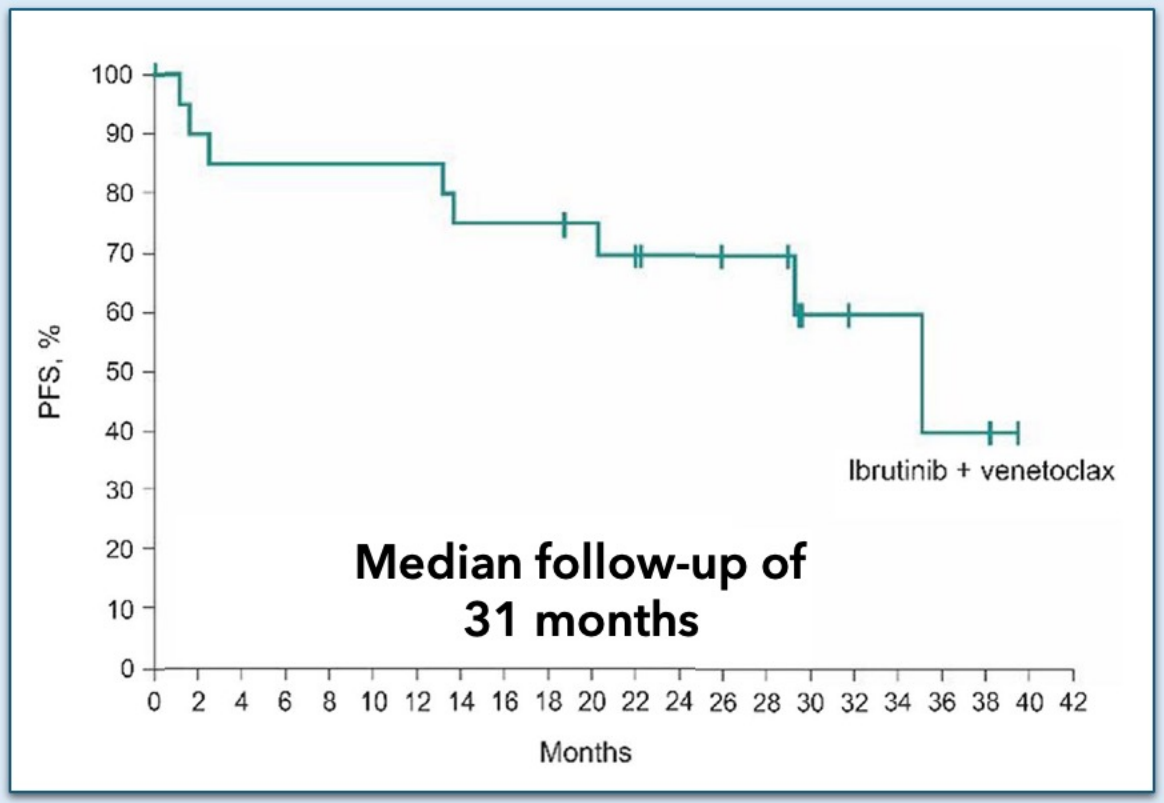
PFS	Median PFS (95% CI), mo
12-month PFS	75.0 (60.0 – 94.0)
18-month PFS	57.0 (40.0 – 82.0)

CI, confidence interval; MCL, mantle cell lymphoma; mo, months; PFS, progression-free survival; R/R, relapsed/refractory.
Tam C et al. *N Engl J Med*. 2018(13):1211-1223.

© 2024

Ibrutinib + Venetoclax (5/7)

Phase III, multinational, open-label SRI cohort, SYMPATICO study evaluating the efficacy of concurrent ibrutinib + venetoclax (n=24) in patients with R/R MCL



PFS	Median PFS (95% CI), mo
12-month PFS	35.0 (13.7– NE)
30-month PFS	60.0 (31.0 – 80.0)

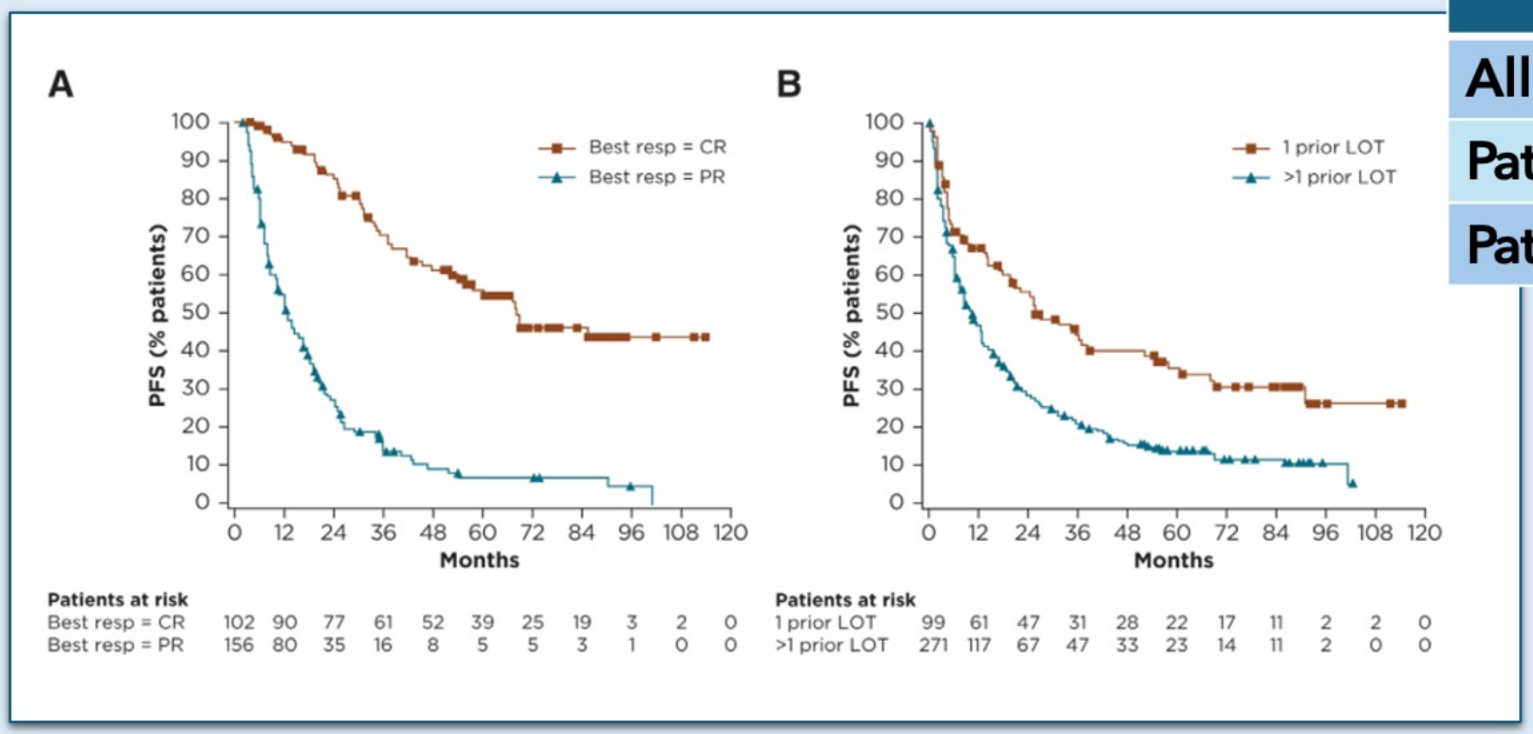
CI, confidence interval; MCL, mantle cell lymphoma mo, months; NE, not estimable; PFS, progression-free survival; R/R, relapsed/refractory; SRI, safety run-in.

Wang M et al. *J Hematol Oncol*. 2021;14(1):179.

© 2024

Pooled Analyses of Ibrutinib (6/7)

Long-term Outcomes With Ibrutinib Treatment for Patients With R/R MCL: A Pooled Analysis of 3 Clinical Trials With Nearly 10 Years of Follow-up



PFS (n=99)	Median PFS (95% CI), mo
All Patients	12.5 (9.8 – 16.6)
Patients with CR	68.5 (51.7 – NE)
Patients with PR	12.6 (10.3 – 16.6)

1 Prior LOT
25.4 (17.5 – 51.8)

>1 Prior LOT
10.3 (8.1 – 12.5)

CI, confidence interval; CR, complete response; LOT, line of therapy; MCL, mantle cell lymphoma, NE, not estimable, PR, partial response; R/R, relapsed/refractory.

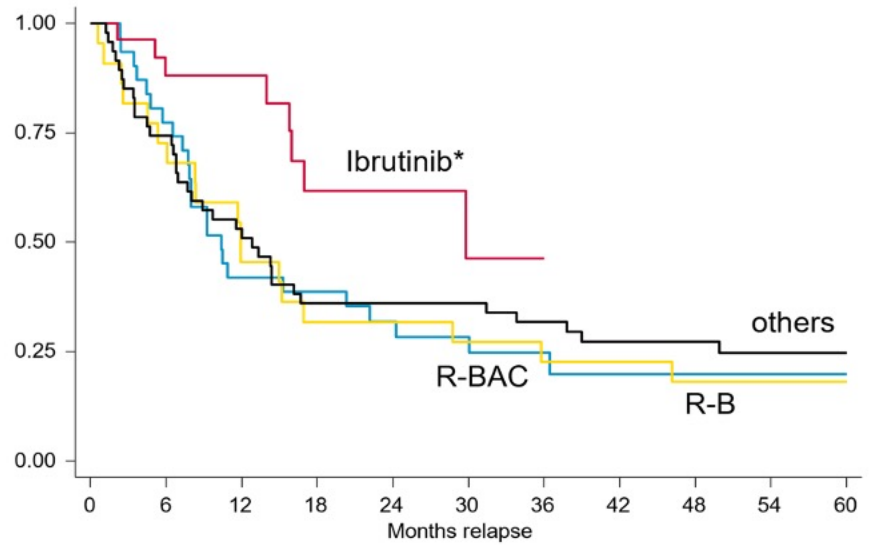
Dreyling M et al. *Hemasphere*. 2022;6(5): e712.

© 2024

Comparison Among 2L Regimens (7/7)

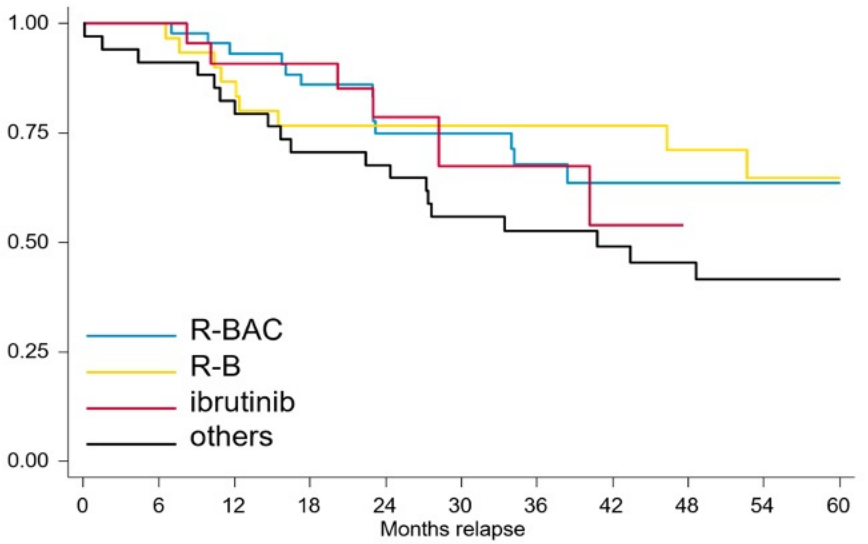
R-B (21%), R-BAC (29%), ibrutinib (19%), and others (31%)

Early POD



At risk:											
BAC	31	24	13	12	9	8	5	4	3	3	3
BR	22	16	10	7	7	6	5	5	4	3	2
ibru	27	21	16	8	5	3	0	0	0	0	0
other	47	35	24	17	17	17	15	11	11	10	6

Late POD



At risk:											
BAC	45	45	40	35	26	23	16	14	12	8	7
BR	32	30	26	23	22	20	16	15	13	10	9
ibru	23	22	20	18	10	6	6	4	0	0	0
other	34	31	27	24	23	19	16	13	12	8	7

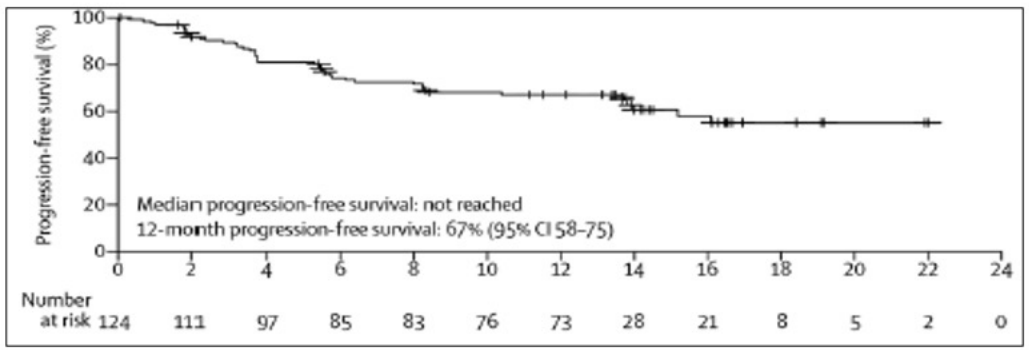
*Ibrutinib vs R-B and R-BAC (P=0.02); vs others (P=0.03)
MCL, mantle cell lymphoma; RB, rituximab-bendamustine; R-BAC, R-B and cytarabine; R/R, relapsed/refractory.
Visco C et al. *Leukemia*. 2021;35(3):787-795.

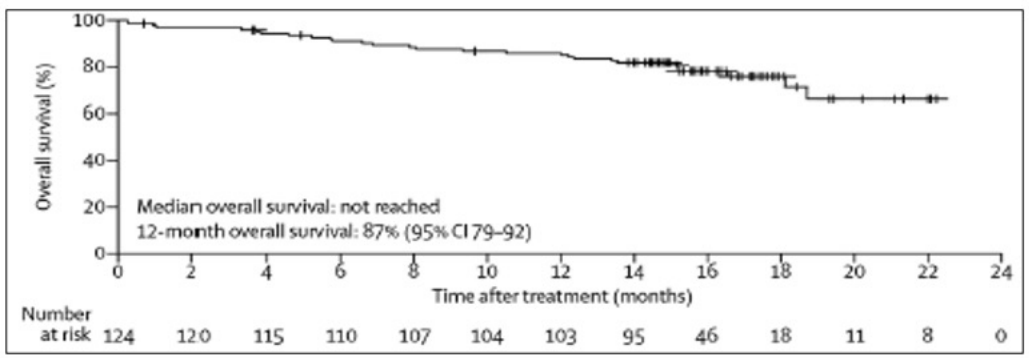
© 2024

Acalabrutinib

Phase II ACE-LY-004 study evaluating the efficacy of acalabrutinib (n=124) in patients with R/R MCL

Median follow-up of 15.2 months





Response Category	IRC-Assessed Response (%)
Overall response	99 (80; 72–87)
CR	49 (40; 31–49)
PR	50 (40; 32–50)
SD	9 (7; 3–13)
PD	11 (9; 5–15)
NE	5 (4; 1–9)

The number of patients with CR was lower in the 93 patients with Ann Arbor stage IV disease (29%), bone marrow involvement (9/64, 14%), and extranodal disease (25/90, 28%).

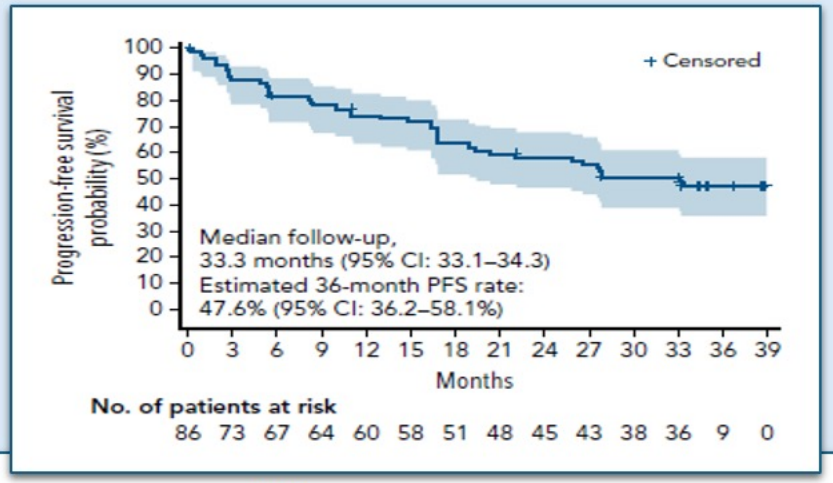
CR, complete response; NE, not estimated; PD, partial disease; PR, partial response, R/R, relapsed/refractory, SD, stable disease.

Wang M, et al.Lancet (2018); 391(10121): 659-667

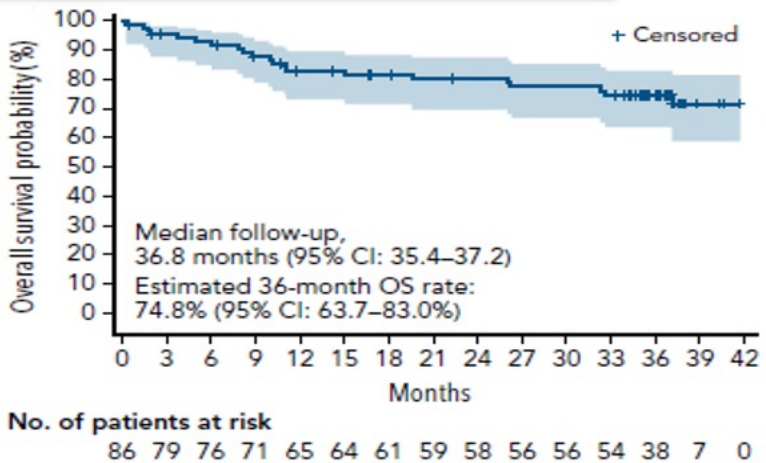
© 2024

Zanubrutinib

Phase II study evaluating long-term efficacy of zanubrutinib (n=86) in patients with R/R MCL



Median follow-up of 35.3 months



Response Category	n=86
Overall response	83.7 (74.2-90.8)
CR	67 (77.9)
PR	5 (5.8)
SD	1 (1.2)
PD	8 (9.3)
Discontinued before 1st assessment	5 (5.8)
Response duration, months	
Median (range; 95% CI)	NE (2.3-36.2+; 24.9-NE)
EFR at 30 months, % (95% CI)	57.3 (44.9-67.9)

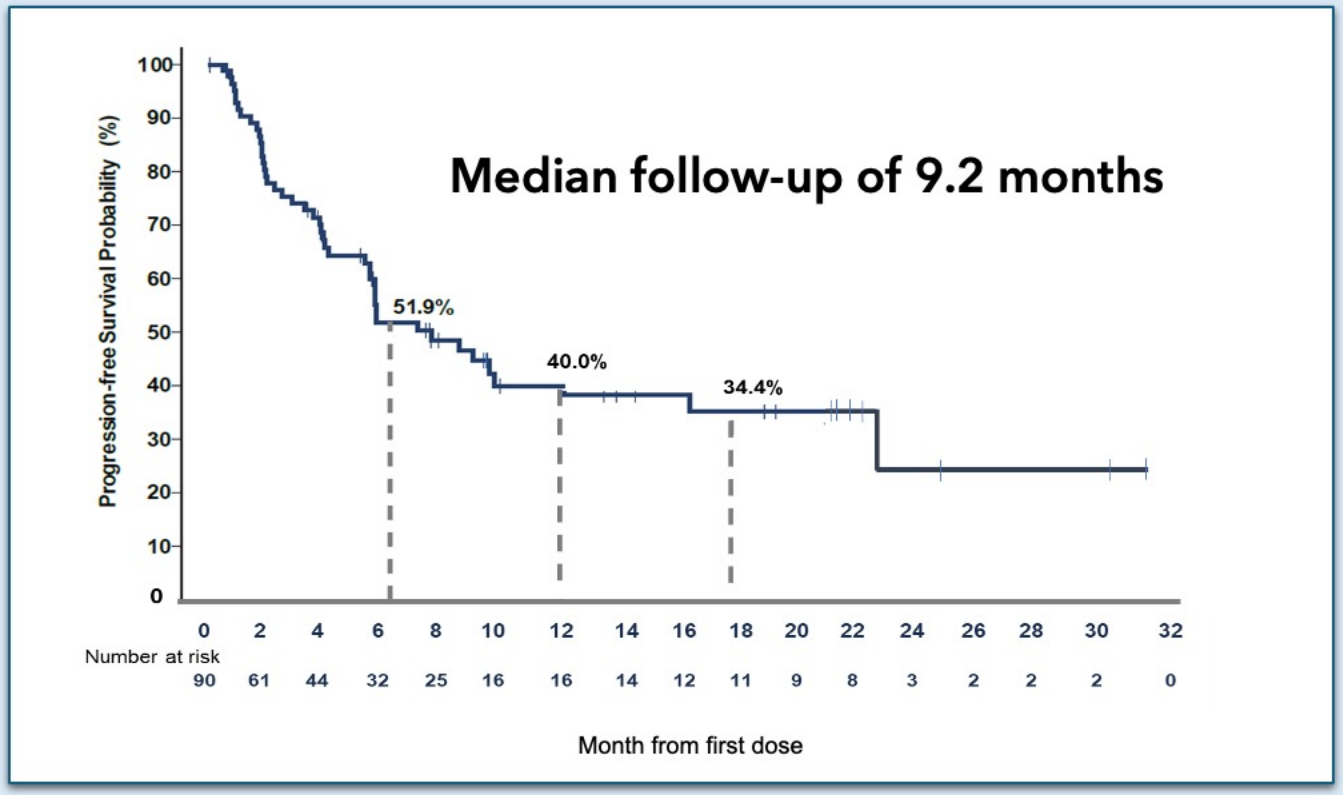
CR, complete response; EFR, event-free rates; NE, not estimated; PD, partial disease; PFS, progression-free survival; OS, overall survival PR, partial response, R/R, relapsed/refractory, SD, stable disease.

Song U, et al. *Blood* (2022); 139(21):3148-3158.

© 2024

Pirtobrutinib Monotherapy

Phase I/II, first-in-human, open-label, multicenter, BRUIN study evaluating the efficacy of pirtobrutinib (n=90) in patients with covalent BTK inhibitor pretreated MCL



PFS	Median PFS (95% CI), mo
12-month PFS	7.4 (5.3 – 12.5)

Overall ORR (95% CI)
cBTKi pre-treated (n=90): 57.8% (46.9-68.1)
cBTKI naïve (n=14): 85.7% (57.2-98.2)

BTK, Bruton kinase; CI, confidence interval; MCL, mantle cell lymphoma mo, months; PFS, progression-free survival; R/R, relapsed/refractory.

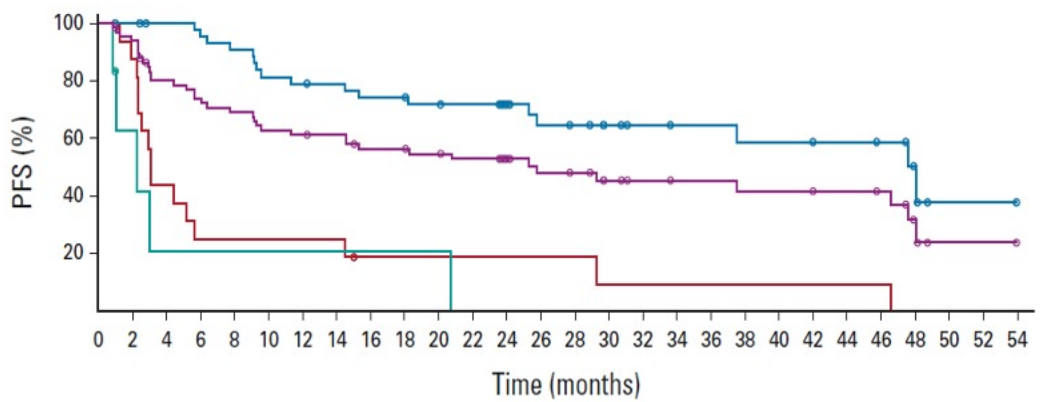
Wang M et al. *J Clin Oncol*. 2023(41):3988-3997.

© 2024

Brexucabtagene Autoleucel

3-year follow-up, ZUMA-2 study evaluating the efficacy of brexucabtagene autoleucel (n=68) in patients with R/R MCL, including high-risk subgroups

Median follow-up of 35.6 months



No. at risk:

All-treated patients	68	62	51	47	44	40	39	38	34	34	32	30	24	20	19	15	13	12	12	11	11	10	10	9	4	1	1	0
Patients with CR	46	45	43	42	39	35	34	33	31	31	29	28	22	18	17	14	12	11	11	10	10	9	9	8	4	1	1	0
Patients with PR	16	14	7	4	4	4	4	4	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	0	0	0	0
Patients with NR	6	3	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

PFS	Median PFS (95% CI), mo
All treated patients	25.8 (9.6 – 47.6)
CR	48.0 (25.8 – NE)
PR	3.1 (2.3 – 5.6)
No response	2.3 (0.9 – NE)

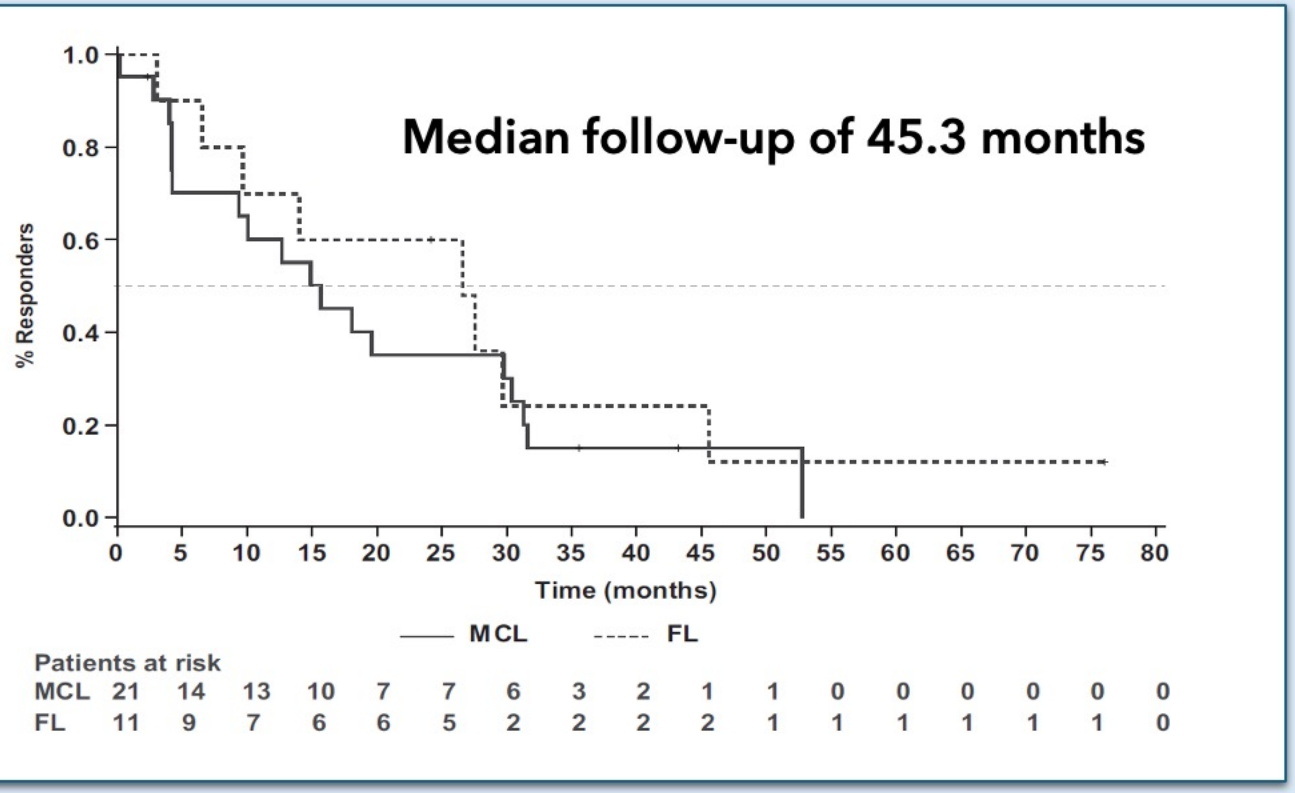
CI, confidence interval; CR, complete response; MCL, mantle cell lymphoma mo, months; NE, not estimatable; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory.

Wang M et al. *J Clin Oncol*. 2022(41):555-567.

© 2024

Venetoclax Monotherapy

3-year follow-up, phase I, first-in-human, study evaluating the efficacy of venetoclax monotherapy (n=106) in patients with R/R NHL (R/R MCL; n=28)



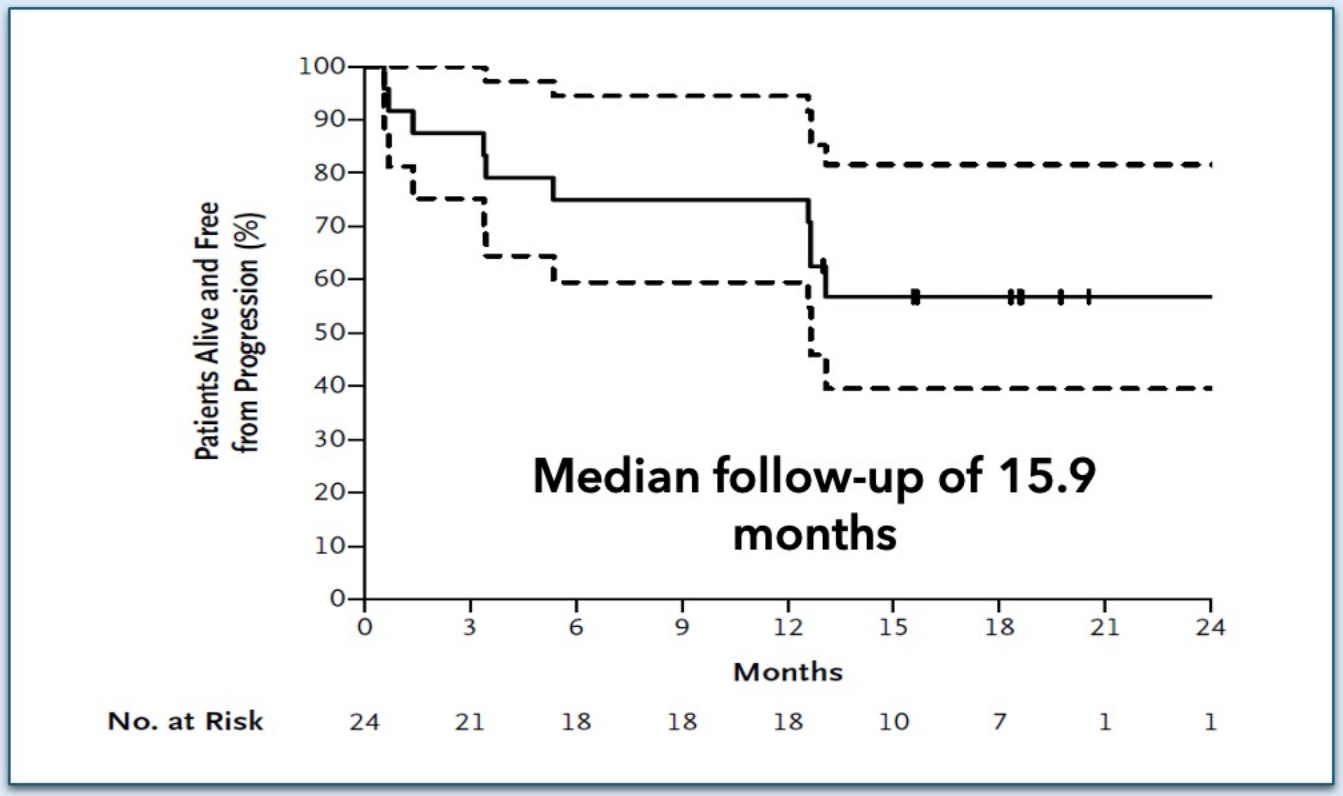
PFS	Median PFS (95% CI), mo
12-month PFS	11.3 (5.4 – 21.0)

CI, confidence interval; MCL, mantle cell lymphoma mo, months; PFS, progression-free survival; R/R, relapsed/refractory.
Davids MS et al. *Clin Cancer Res*. 2022(17):4690-4695.

© 2024

Venetoclax + Ibrutinib

Phase II, single group, open-label, AIM study evaluating the efficacy of ibrutinib + venetoclax (n=24) in patients with R/R MCL



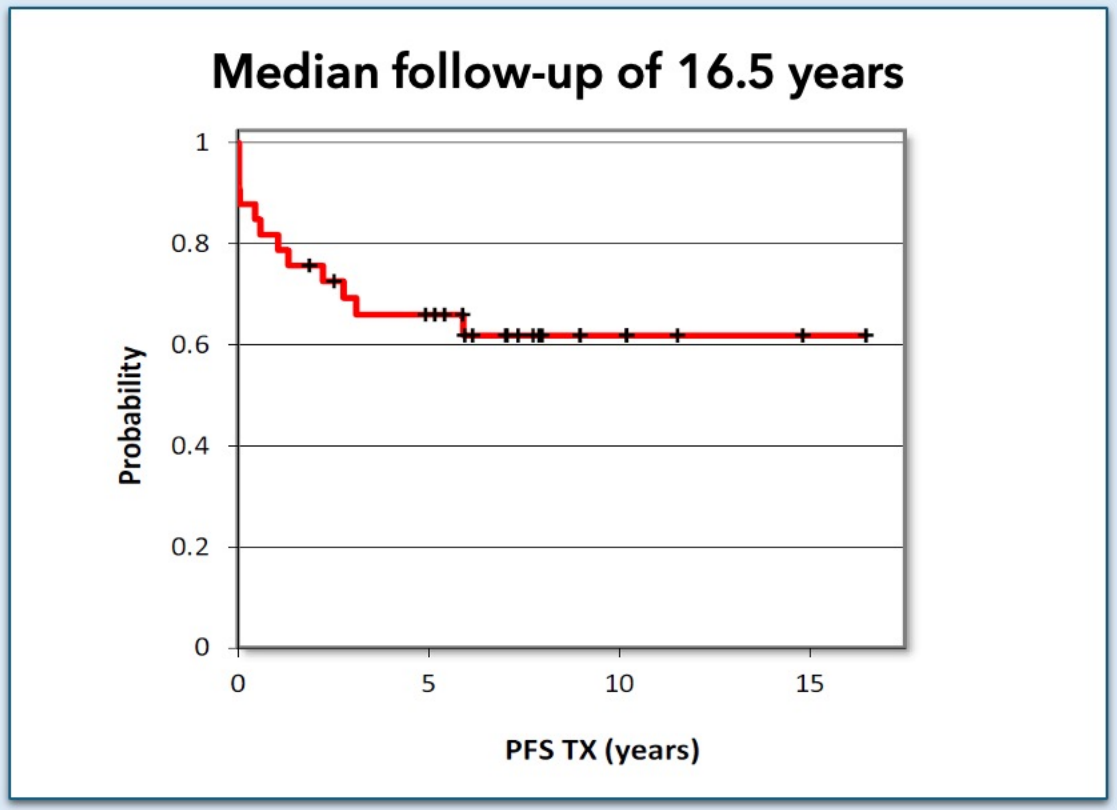
PFS	Median PFS (95% CI), mo
12-mo PFS	75.0 (60.0 – 94.0)
18-mo PFS	57.0 (40.0 – 82.0)

CI, confidence interval; MCL, mantle cell lymphoma; mo, months; PFS, progression-free survival; R/R, relapsed/refractory.
Tam C et al. *N Engl J Med*. 2018(13):1211-1223.

© 2024

Allo-SCT (1/2)

OSHO studies evaluating the efficacy of allogeneic STC (n=33) in patients with de novo MCL and R/R MCL



PFS	Median PFS (95% CI), yrs
All patients	5.9 (0.02 – 16.5)

50% survival was not reached

CI, confidence interval; MCL, mantle cell lymphoma; PFS, progression-free survival; R/R, relapsed/refractory; STC, stem cell transplant; TX, treatment; yrs, years.

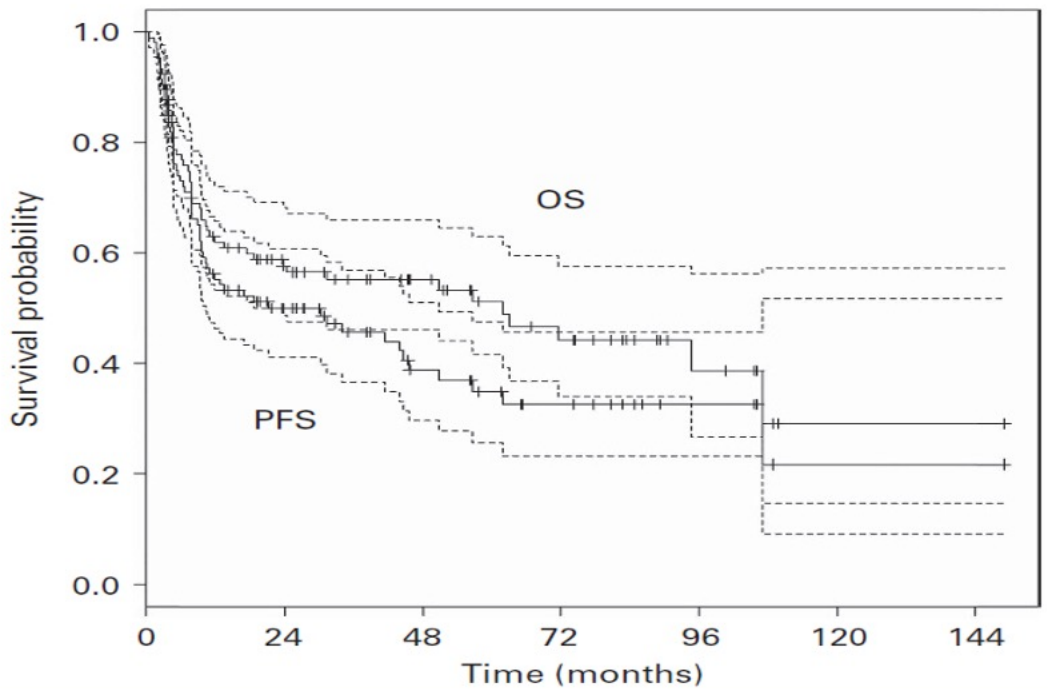
Krüger WH et al. *Ann Hematol*. 2021(6):1569-1577.

© 2024

Allo-SCT (2/2)

SFGM-TC study evaluating the efficacy of allogeneic-STC (n=106) in fit patients with R/R MCL who failed after autologous-SCT

Median follow-up of 45 months



PFS	Median PFS (95% CI), mo
All patients	30.1
OS	**Median PFS (95% CI), mo**
All patients	62.0

TRM at 1 year and 3 years were 28% and 32%, respectively

Mo, months; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; SCT, stem cell transplant; TRM, treatment-related mortality.

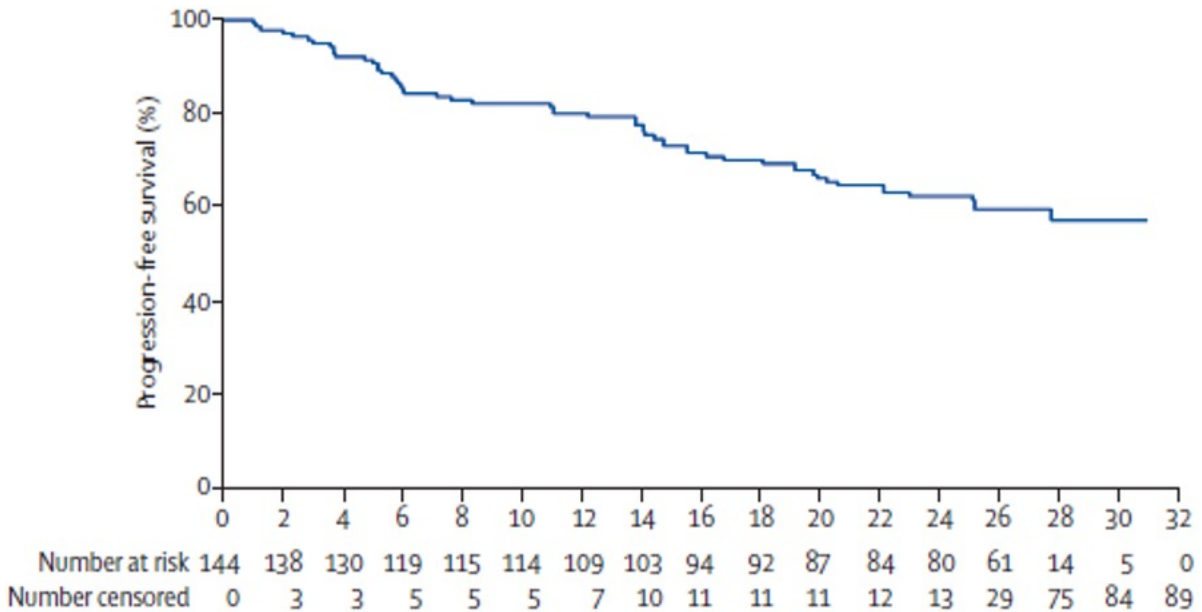
Tessoulin B et al. *Bone Marrow Transplant*. 2016;51(9):1184-1190.

© 2024

Ibrutinib (1/3)

Phase II RESONATE-17 study evaluating the efficacy of ibrutinib in patients (n=145) with R/R CLL and del(17p)

Median follow-up of 11.5 months



39 (27%) of 144 patients had progressive disease, including 17 with Richter's transformation

R/R CLL, relapsed/refractory chronic lymphocytic leukemia.
O'Brien S, et al. *Lancet Oncol*. 2016 Oct;17(10):1409-1418.

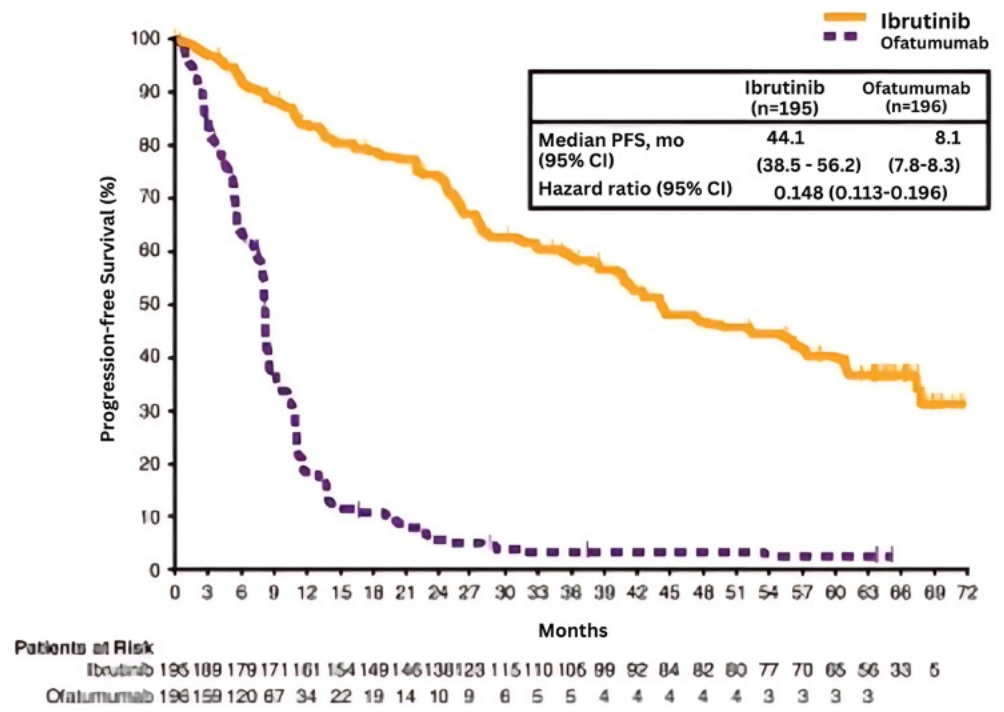
© 2024

Ibrutinib (2/3)

RESONATE study 6-year follow-up evaluating the efficacy of ibrutinib vs ofatumumab in patients (n=145) with R/R CLL and del(17p)

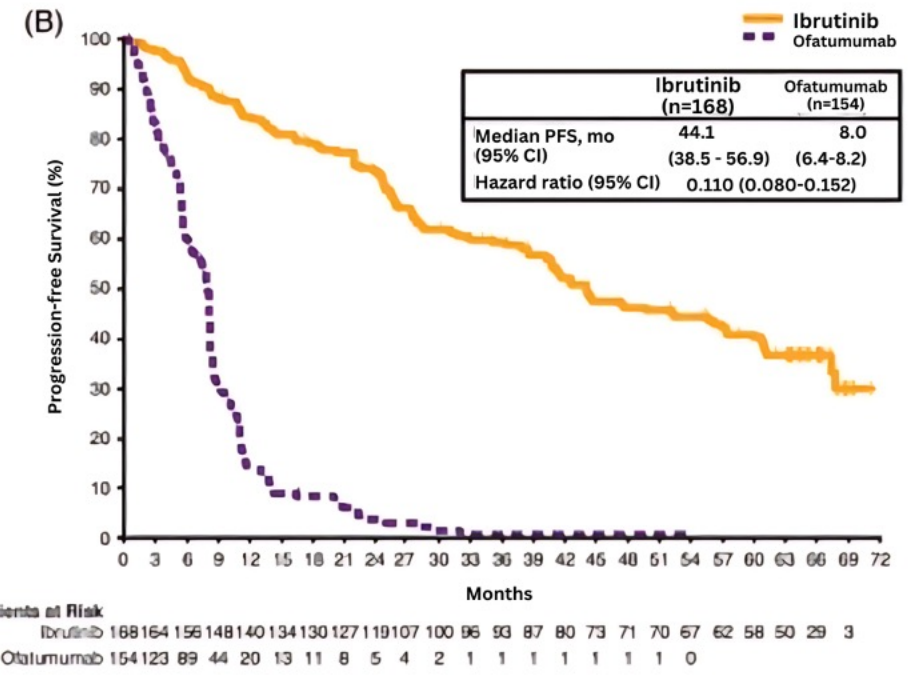
Median follow-up of 65.3 months

PFS in the ITT population



	Ibrutinib (n=195)	Ofatumumab (n=196)
Median PFS, mo (95% CI)	44.1 (38.5 - 56.2)	8.1 (7.8-8.3)
Hazard ratio (95% CI)	0.148 (0.113-0.196)	

PFS in the high-risk population (patients with del(17p), *TP53* mutation, del(11q), and/or unmutated *IGHV* status



	Ibrutinib (n=168)	Ofatumumab (n=154)
Median PFS, mo (95% CI)	44.1 (38.5 - 56.9)	8.0 (6.4-8.2)
Hazard ratio (95% CI)	0.110 (0.080-0.152)	

PFS, progression-free survival; R/R CLL, relapsed/refractory chronic lymphocytic leukemia.

Munir T, et al. *Am J Hematol*. 2019 Dec;94(12):1353-1363.

© 2024

Ibrutinib (3/3)

Phase II CLARITY study evaluating the efficacy of ibrutinib + venetoclax in patients (n=53) with R/R CLL

Median follow-up of 21.1 months

Response Month 14, No. of No. Evaluated (%)

Patient Group	CR	CRi	PR	OR	PB MRD Negative	PM MRD Negative	Trephine Normal
All patients	22 of 53 (42)	5 of 53 (9)	20 of 53 (38)	47 of 53 (89)	28 of 53 (53)	19 of 53 (36)	39 of 48 (81)
FCR/BR relapse < 36 months	8 of 21 (38)	2 of 21 (10)	8 of 21 (38)	18 of 21 (86)	14 of 20 (70)	9 of 20 (45)	18 of 19 (95)
Prior idelalisib	3 of 11 (27)	1 of 11 (9)	4 of 11 (36)	8 of 11 (73)	6 of 9 (67)	5 of 9 (56)	7 of 9 (78)

BM, bone marrow; BR bendamustine and rituximab; CR, complete response; CRi, with incomplete bone marrow recovery; FCR, flurarabine, cyclophosphamide, and rituximab; MRD, measurable residual disease; PB, peripheral blood; PR, partial disease; R/R CLL, relapsed/refractory chronic lymphocytic leukemia.

Munir T, et al. *Am J Hematol*. 2019 Dec;94(12):1353-1363.

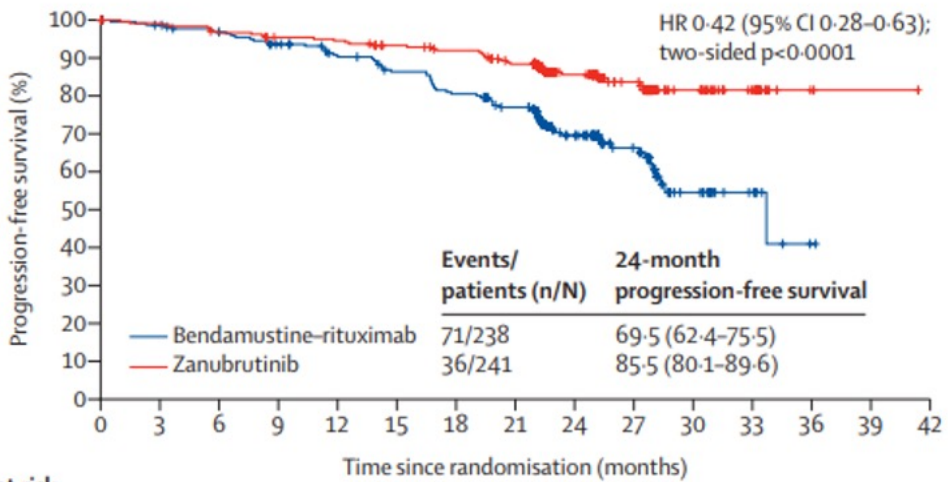
© 2024

Zanubrutinib (1/2)

Phase III SEQUOIA study evaluating the efficacy zanubrutinib vs bendamustine and rituximab (n=137) in patients with R/R CLL

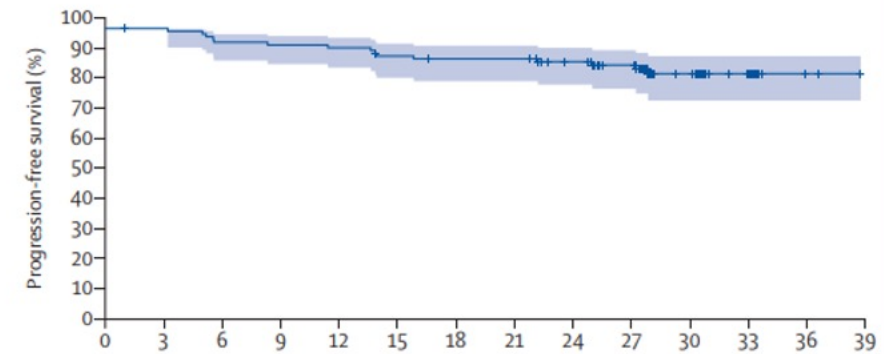
Median follow-up of 26.2 months

PFS among all patients without del(17)(p13·1)



Number at risk (number censored)															
Bendamustine–rituximab	238 (0)	218 (17)	210 (21)	200 (24)	187 (30)	176 (33)	164 (33)	150 (40)	89 (89)	54 (121)	20 (148)	8 (160)	1 (166)	0 (167)	.. ..
Zanubrutinib	241 (0)	237 (2)	230 (3)	224 (6)	222 (6)	214 (11)	208 (14)	195 (19)	123 (86)	79 (128)	31 (174)	17 (188)	2 (203)	1 (205)	0 (205)

PFS among all patients with del(17)(p13·1)



Number at risk (number censored)														
	110 (0)	109 (1)	104 (1)	103 (1)	102 (1)	98 (2)	96 (3)	96 (3)	86 (12)	74 (23)	37 (58)	19 (76)	2 (93)	0 (95)

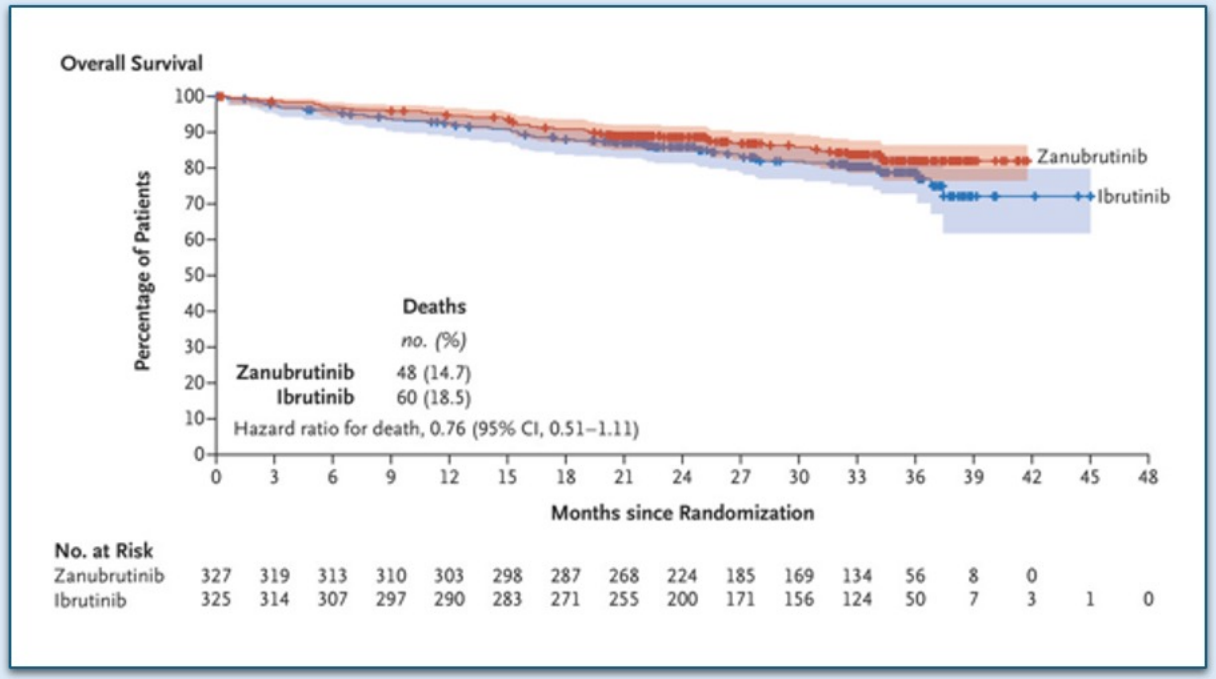
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
Tam CS et al. *Lancet Oncol*. 2022 Aug;23(8):1031-1043.

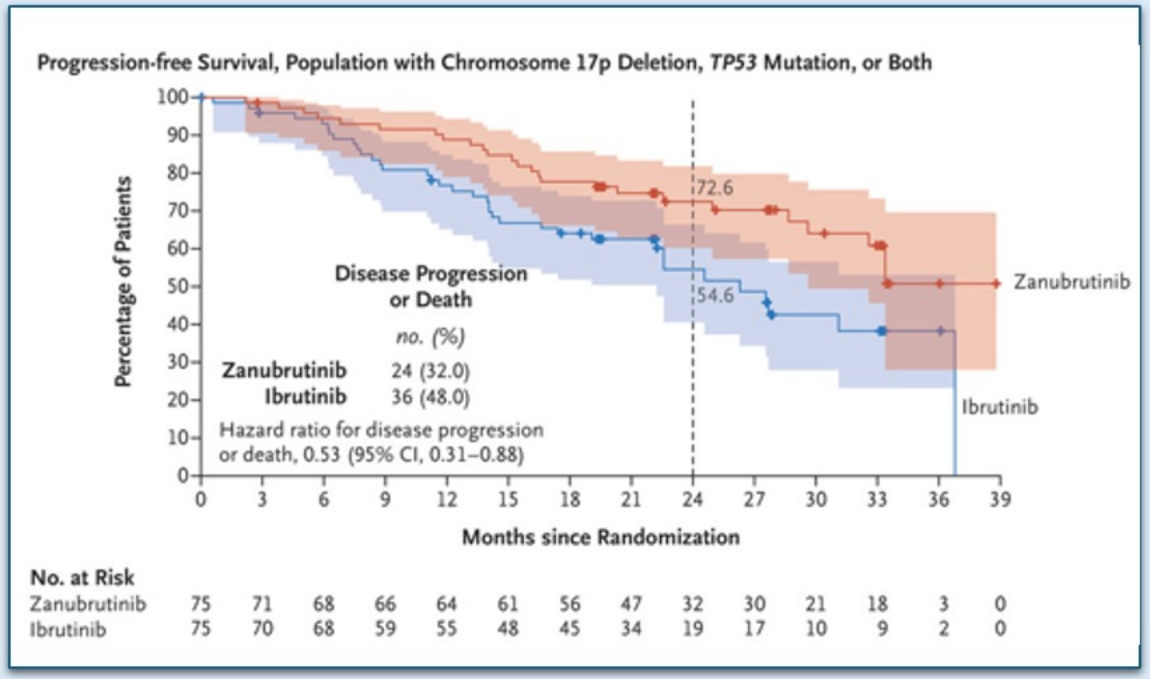
© 2024

Zanubrutinib (2/2)

Phase III study evaluating the efficacy zanubrutinib vs ibrutinib (n=652) in patients with R/R CLL

Median follow-up of 29.6 months





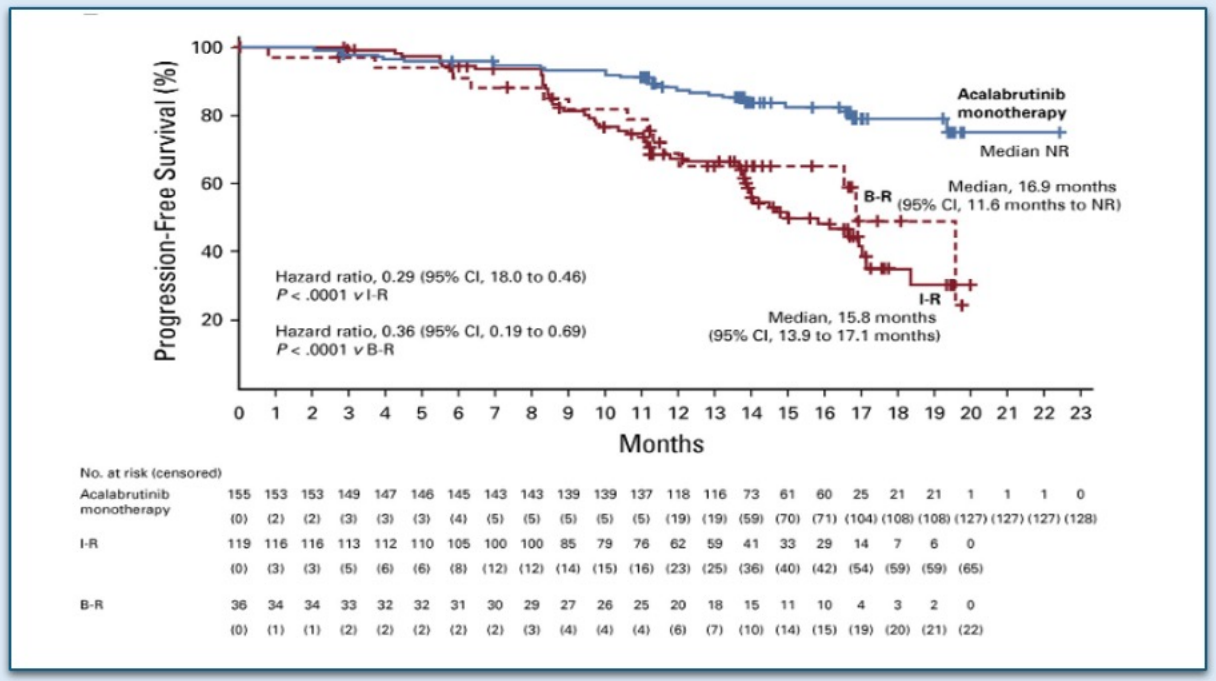
Brown JR, et al. N Engl J Med. 2023 Jan 26;388(4):319-332.

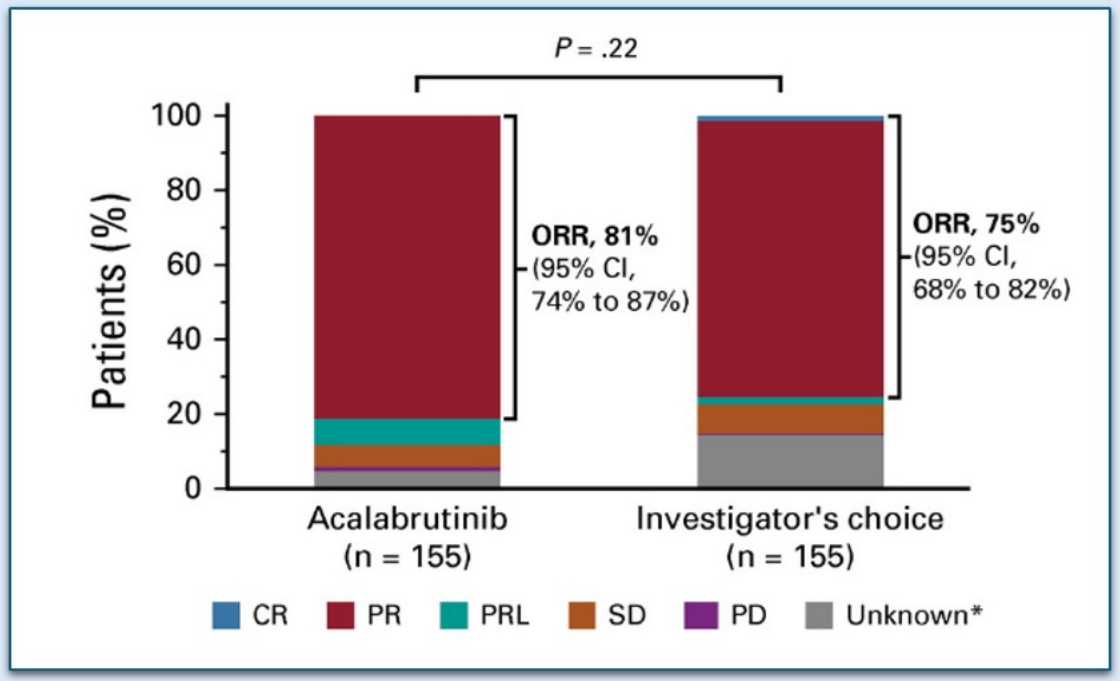
© 2024

Acalabrutinib (1/2)

Phase III ASCEND study evaluating the efficacy acalabrutinib vs idelalisib + rituximab or bendamustine + rituximab (n=398) in patients with R/R CLL

Median follow-up of 16.1 months





B, bendamustin; CI, confidence interval; CR, complete response; I, ibrutinib; ORR, overall response rate; PD, progressive disease; PRL, partial response with lymphocytosis; R, rituximab; R/R CLL, relapsed/refractory chronic lymphocytic leukemia; SD, stable diease.

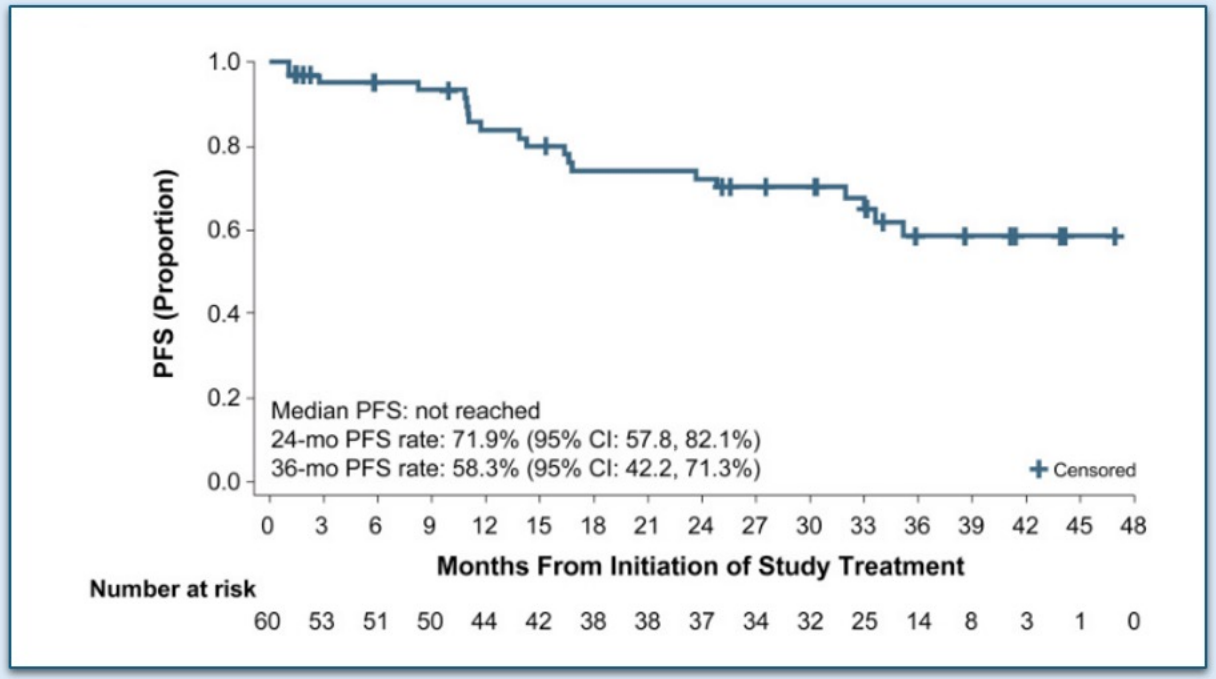
Ghia P, et al. *J Clin Oncol*. 2020 Sep 1;38(25):2849-2861.

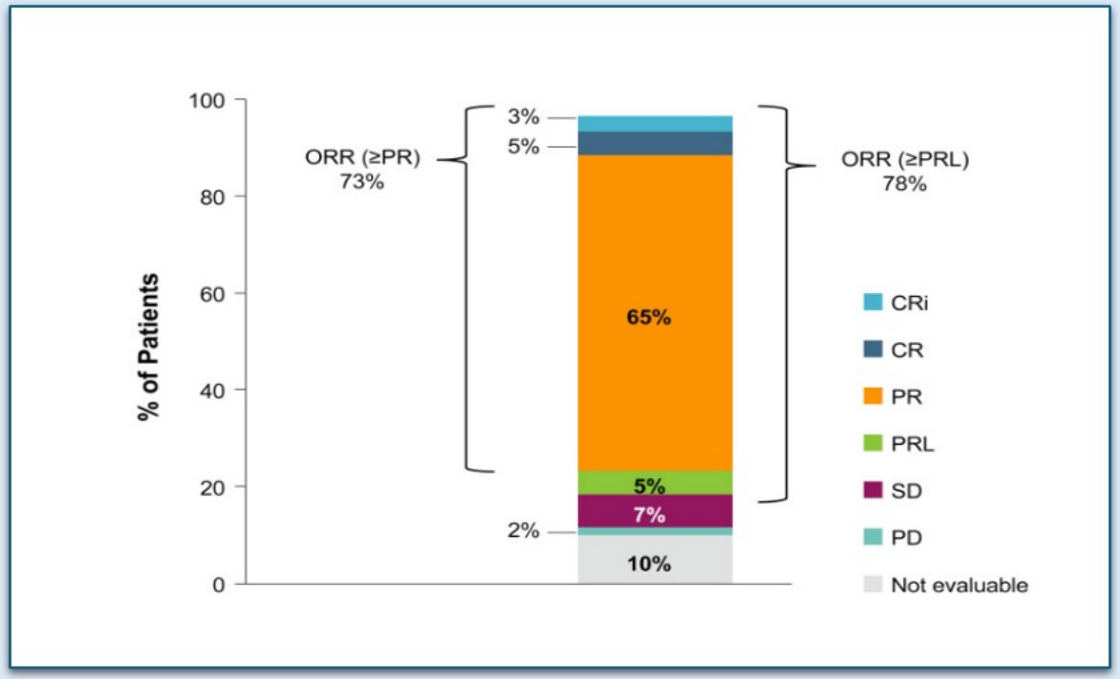
© 2024

Acalabrutinib (2/2)

Phase III study evaluating the efficacy acalabrutinib in patients with ibrutinib-intolerant (n=60) R/R CLL

Median follow-up of 35 months





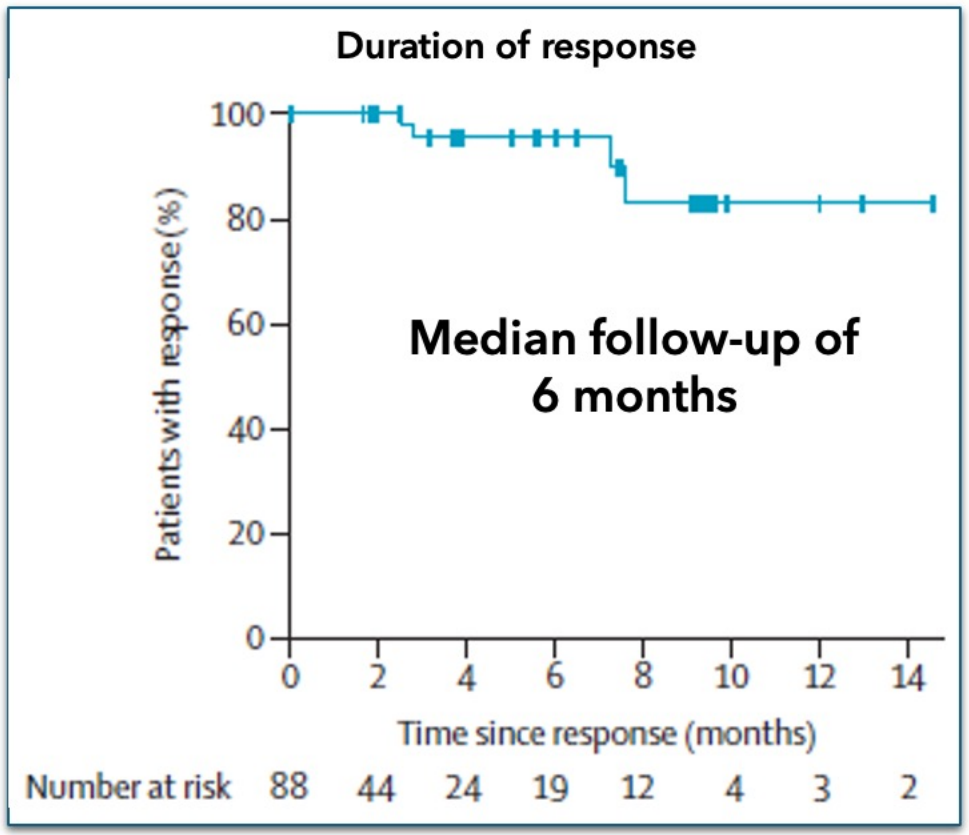
CR, complete remission; Cri, CR with incomplete bone marrow recovery; ORR, overall response rate; PD, progressive disease; PR, partial remission; PRL, partial remission with lymphocytosis; R/R CLL, relapsed/refractory chronic lymphocytic leukemia; SD, stable disease.

Rogers KA, et al. *Haematologica*. 2021 Sep 1;106(9):2364-2373.

© 2024

Pirtobrutinib

Phase I/II, first-in-human, open-label, multicenter, BRUIN study evaluating the efficacy of pirtobrutinib (n=323) in patients with R/R B-cell malignancies (n=121 with CLL/SLL)



	No. lines of previous systemic therapy	Treated	Efficacy, evaluable*	Responders	ORR
All pts	3 (2-5)	170	139	88	63% (55-71)
Pts who had previous therapy					
BTK	4 (2-5)	146	121	75	62% (53-71)
BCL2	5 (4-7)	57	48	31	65% (50-78)
P13K	4 (3-6)	36	30	18	60% (41-77)
BTK+BCL2	5 (4-7)	54	45	29	64% (49-78)
C+CD20+BTK	4 (3-6)	113	93	62	67% (56-76)
C+CD20+BTK +BCL2	5 (4-7)	48	39	27	69% (52-83)
C+CD20+BCL2 +P13K	6 (4-9)	14	12	7	58% (28-85)
CAR T-cell	6 (4-9)	10	10	9	90 (56-100)

*Efficacy evaluable includes patients who had at least one post-baseline response assessment or who discontinued treatment before their first post-baseline response assessment.

Mato AR, et al. Lancet. 2021(397): 892-901.

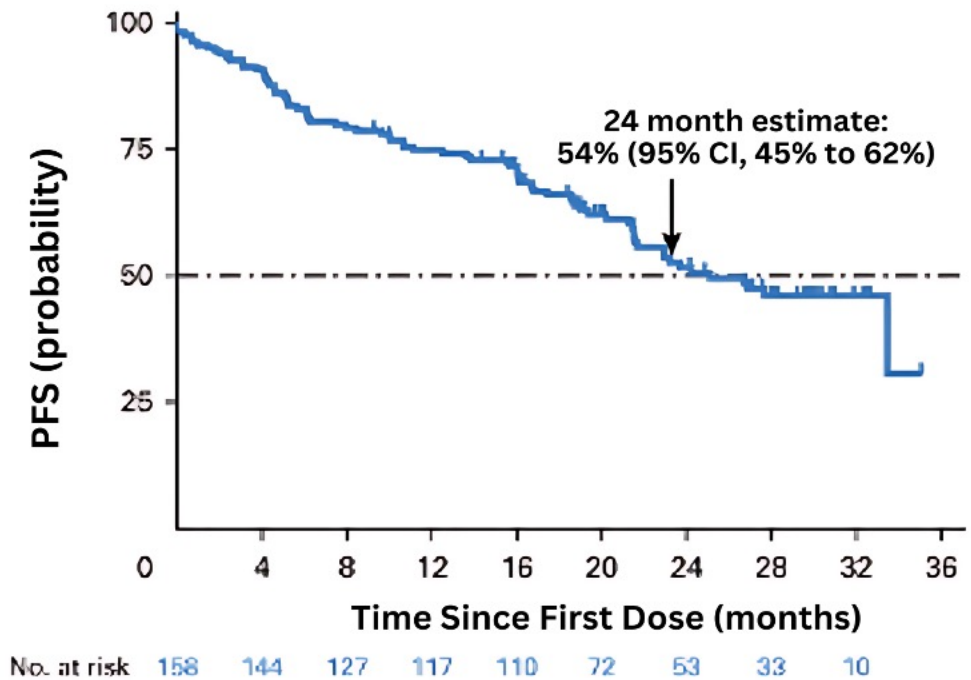
© 2024

Venetoclax (1/3)

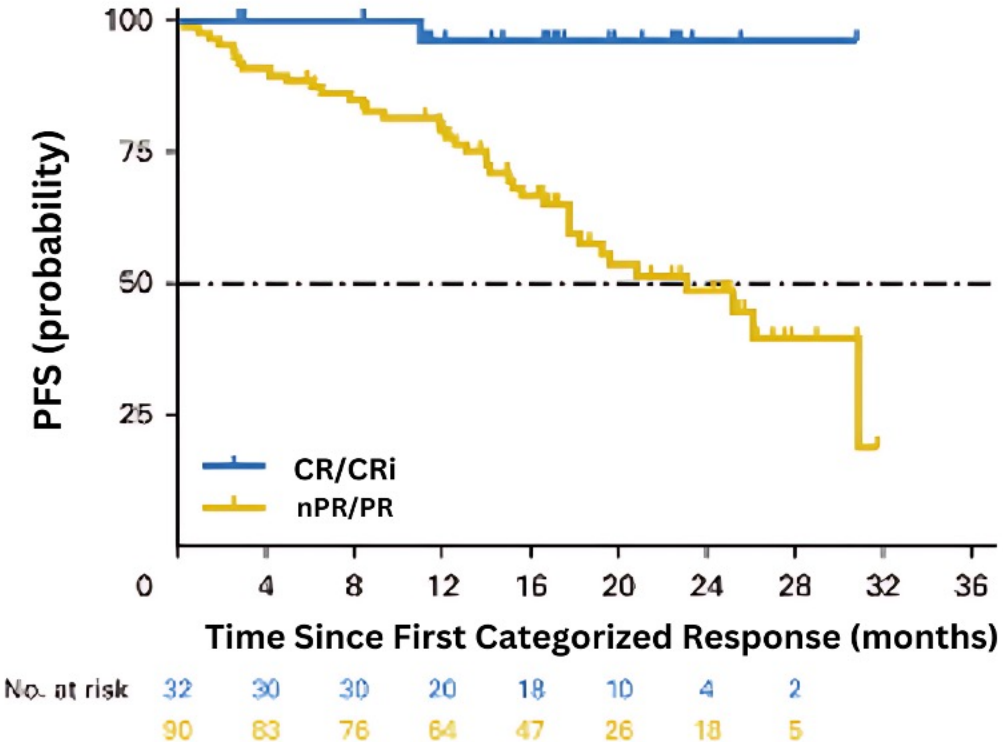
Phase II study evaluating the efficacy of venetoclax in patients (n=107) with R/R CLL and del(17p)

Median follow-up of 12 months

Progression-free survival



PFS since the time of first categorized response for patients who achieving CR/CRi or nPR/PR



CR/CRi, complete remission/complete remission with incomplete marrow recovery; nPR/PR, nodular partial remission/partial remission; PFS, progression-free survival; R/R CLL, relapsed/refractory chronic lymphocytic leukemia.

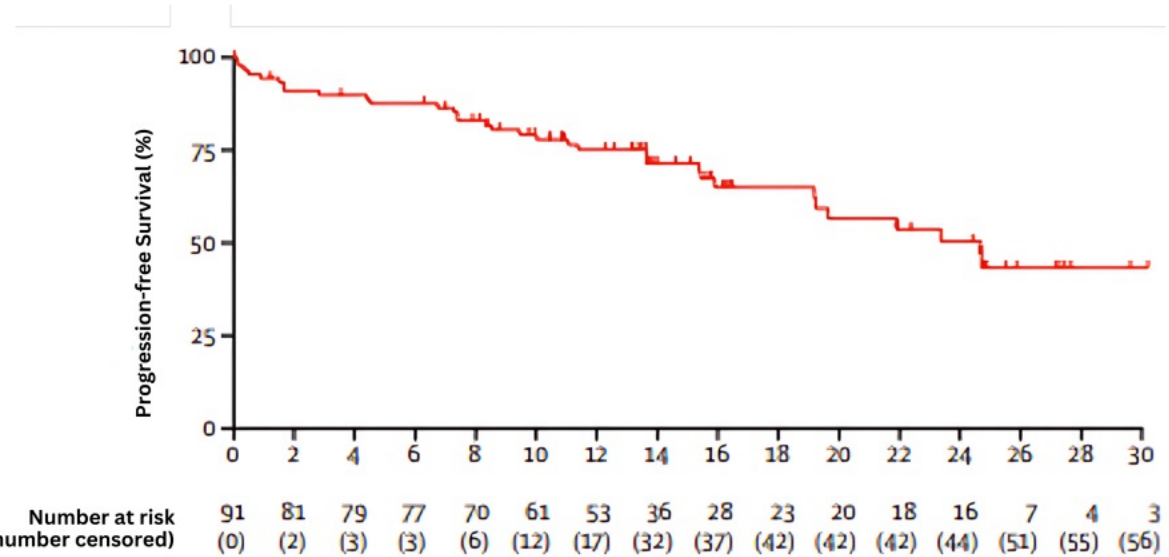
Stilgenbauer S, et al. *J Clin Oncol*. 2018 Jul 1;36(19):1973-1980.

© 2024

Venetoclax (2/3)

Phase II study evaluating the efficacy of venetoclax post ibrutinib in patients (n=127) with R/R CLL

Median follow-up of 14 months



Primary Study	All patients (n=91)
Overall response	59 (65%, 53-74)
CR or CR with incomplete bone marrow recovery	8 (9%)
Nodular PR	3 (3%)
PR	48 (52%)
SD	22 (24%)
DP	5 (5%)
Discontinued before assessment	6 (7%)

CR, complete response; DP, disease progression; PR, partial response; R/R CLL, relapsed/refractory chronic lymphocytic leukemia; SD, stable disease.

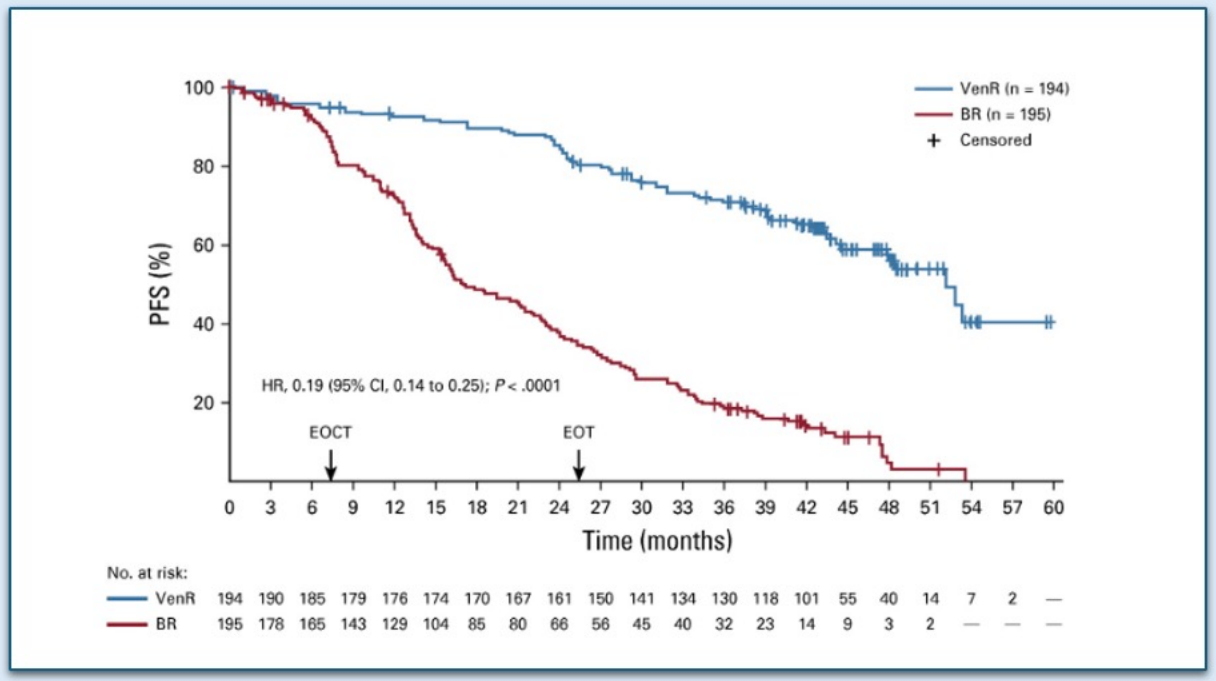
Jones JA, et al. *Lancet Oncol.* 2018 Jan;19(1):65-75.

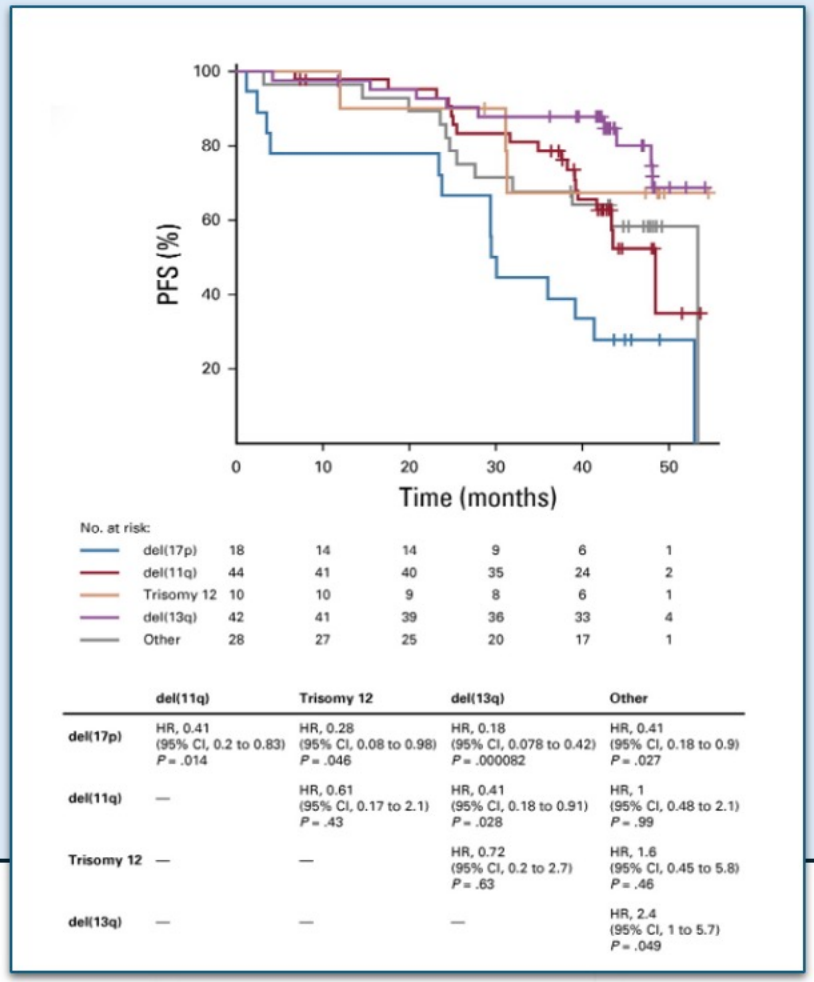
© 2024

Venetoclax + Rituximab (3/3)

Phase III MURANO study evaluating the efficacy of venetoclax + rituximab in patients (n=389) with R/R CLL

4-year follow-up





	del(11q)	Trisomy 12	del(13q)	Other
del(17p)	HR, 0.41 (95% CI, 0.2 to 0.83) P = .014	HR, 0.28 (95% CI, 0.08 to 0.98) P = .046	HR, 0.18 (95% CI, 0.078 to 0.42) P = .000082	HR, 0.41 (95% CI, 0.18 to 0.9) P = .027
del(11q)	—	HR, 0.61 (95% CI, 0.17 to 2.1) P = .43	HR, 0.41 (95% CI, 0.18 to 0.91) P = .028	HR, 1 (95% CI, 0.48 to 2.1) P = .99
Trisomy 12	—	—	HR, 0.72 (95% CI, 0.2 to 2.7) P = .63	HR, 1.6 (95% CI, 0.45 to 5.8) P = .46
del(13q)	—	—	—	HR, 2.4 (95% CI, 1 to 5.7) P = .049

BR, bendamustine; CI, confidence interval; EOCT, end of combination therapy; EOT, end of treatment; HR, hazard ratio; PFS, progression-free disease; R/R CLL, relapsed/refractory chronic lymphocytic leukemia; VenR, venetoclax + rituximab.

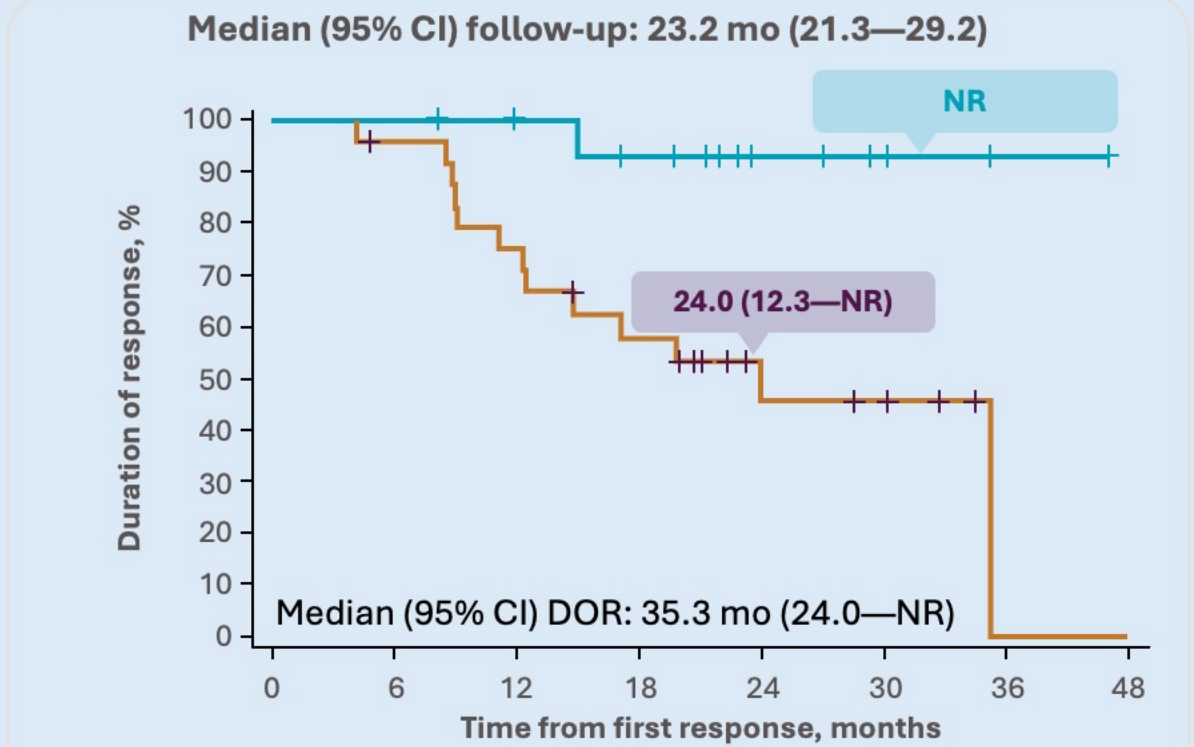
Kater AP, et al. *J Clin Oncol.* 2020 Dec 1;38(34):4042-4054.

© 2024

Lisocabtagene maraleucel

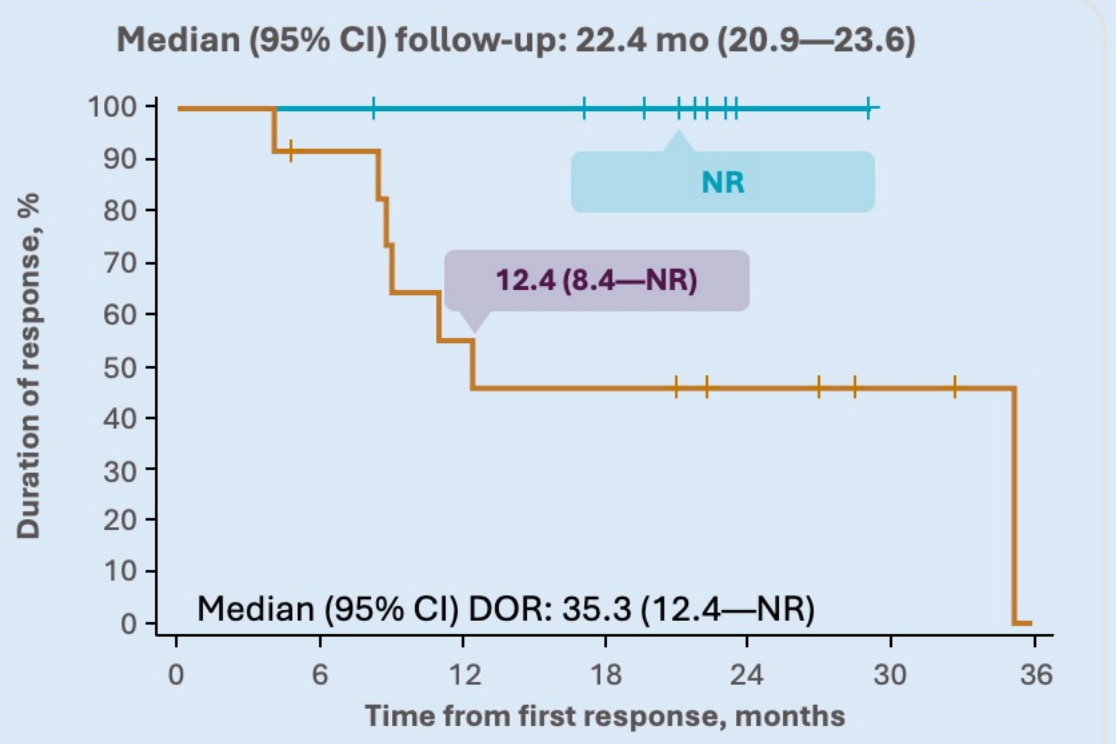
Phase I/II TRANSCEND CLL-004 study evaluating the efficacy liso-cel in patients (n=137) with R/R CLL/SLL

(A) Full study population at DL2 (n = 88)



No. at risk								
CR/CRi	17	17	14	12	5	3	1	0
PR/nPR	25	23	16	13	6	5	0	0

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 50)



No. at risk							
CR/CRi	10	10	9	8	1	0	0
PR/nPR	12	10	6	5	3	2	0

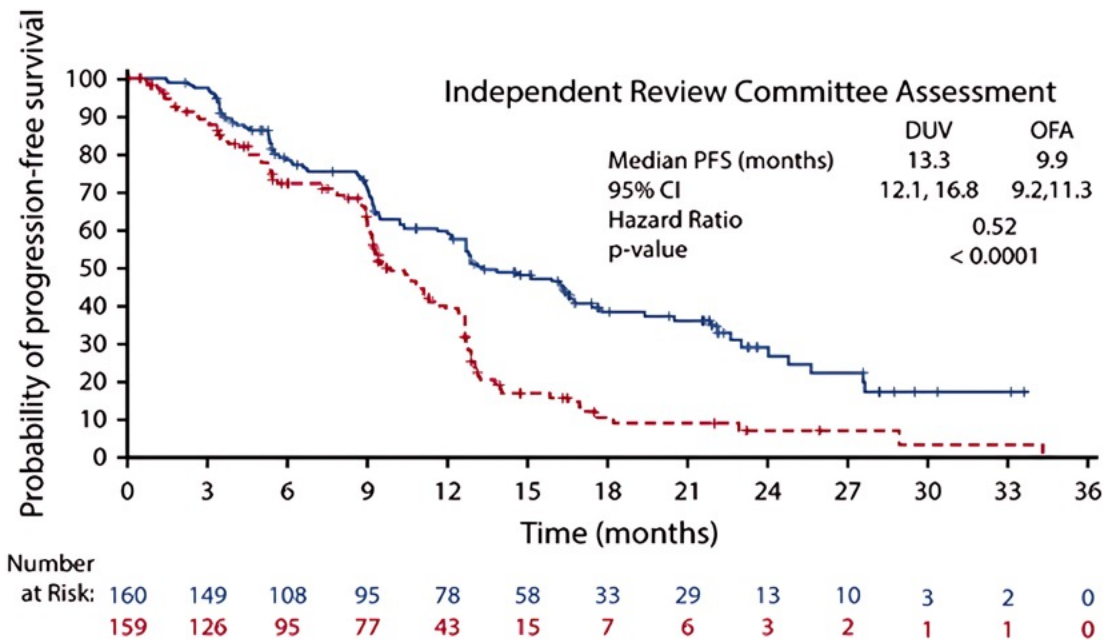
Data on KM curves are expressed as median (95% CI, if available).
DOR, duration of response; NR, not reached; R/R CLL, relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma.
Siddiqi T, et al. ASH 2023 [Presentation #330].

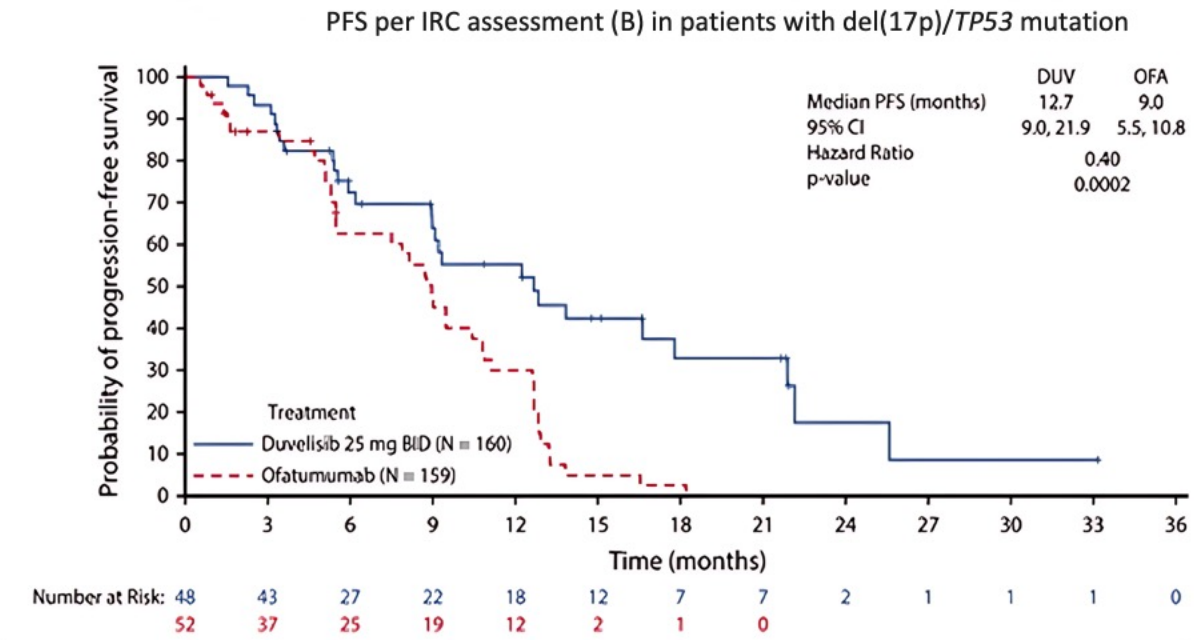
© 2024

Duvelisib

Phase III, DUO study evaluating the efficacy of duvelisib vs ofatumumab in patients with (n=319) with R/R CLL/SLL

Median follow-up of 22.4 months





CI, confidence interval; DUV, duvelisib; OFA, ofatumumab; PFS, progression-free survival; R/R CLL/SLL, relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma.

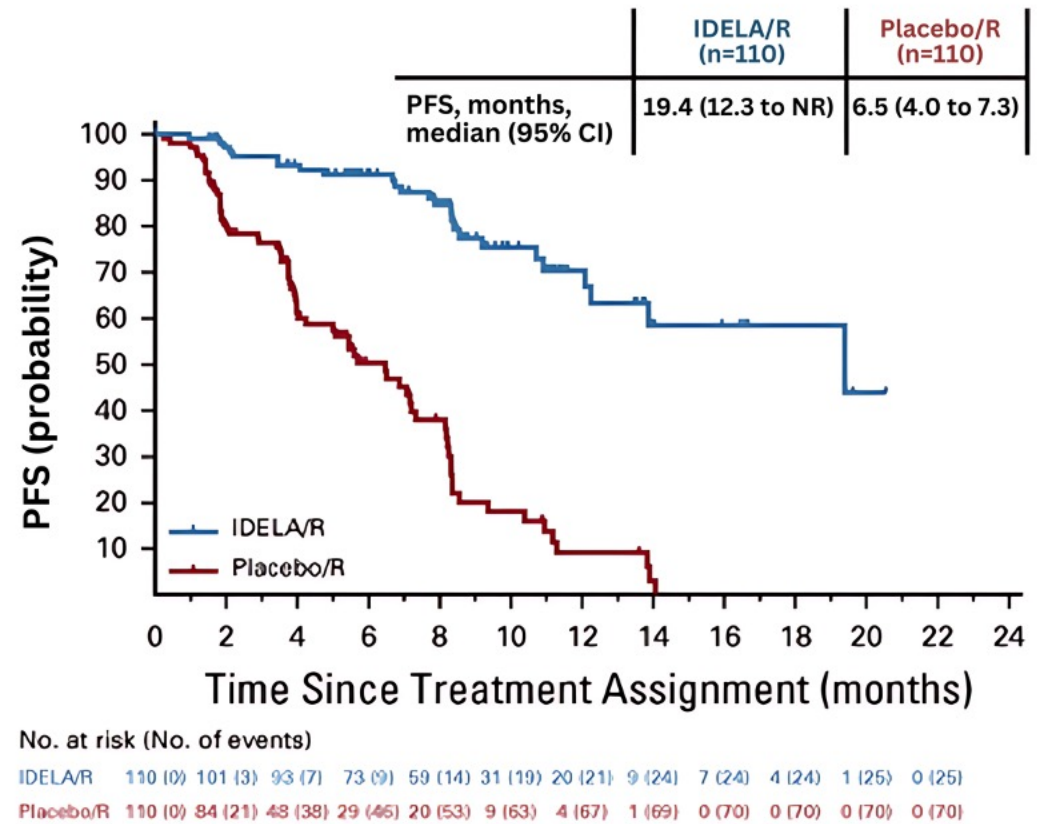
Flinn IW, et al. *Blood*. 2018 Dec 6;132(23):2446-2455.

© 2024

Idelalisib

Phase III study evaluating the efficacy of idelalisib ± rituximab in patients (n=220) with R/R CLL

Median follow-up of 18 months



Primary Study	IDELA/R (n=110) n (%)	Placebo/R (n=110) n (%)
Overall RR	92 (83.6)	17 (15.5)
95% CI	75.6 - 90.0	9.3 - 23.6
CR	0	0
PR	92 (83.6)	17 (15.5)
SD	13 (11.8)	71 (64.5)
PD	1 (0.9)	16 (14.5)
NE	4 (3.6)	6 (5.5)

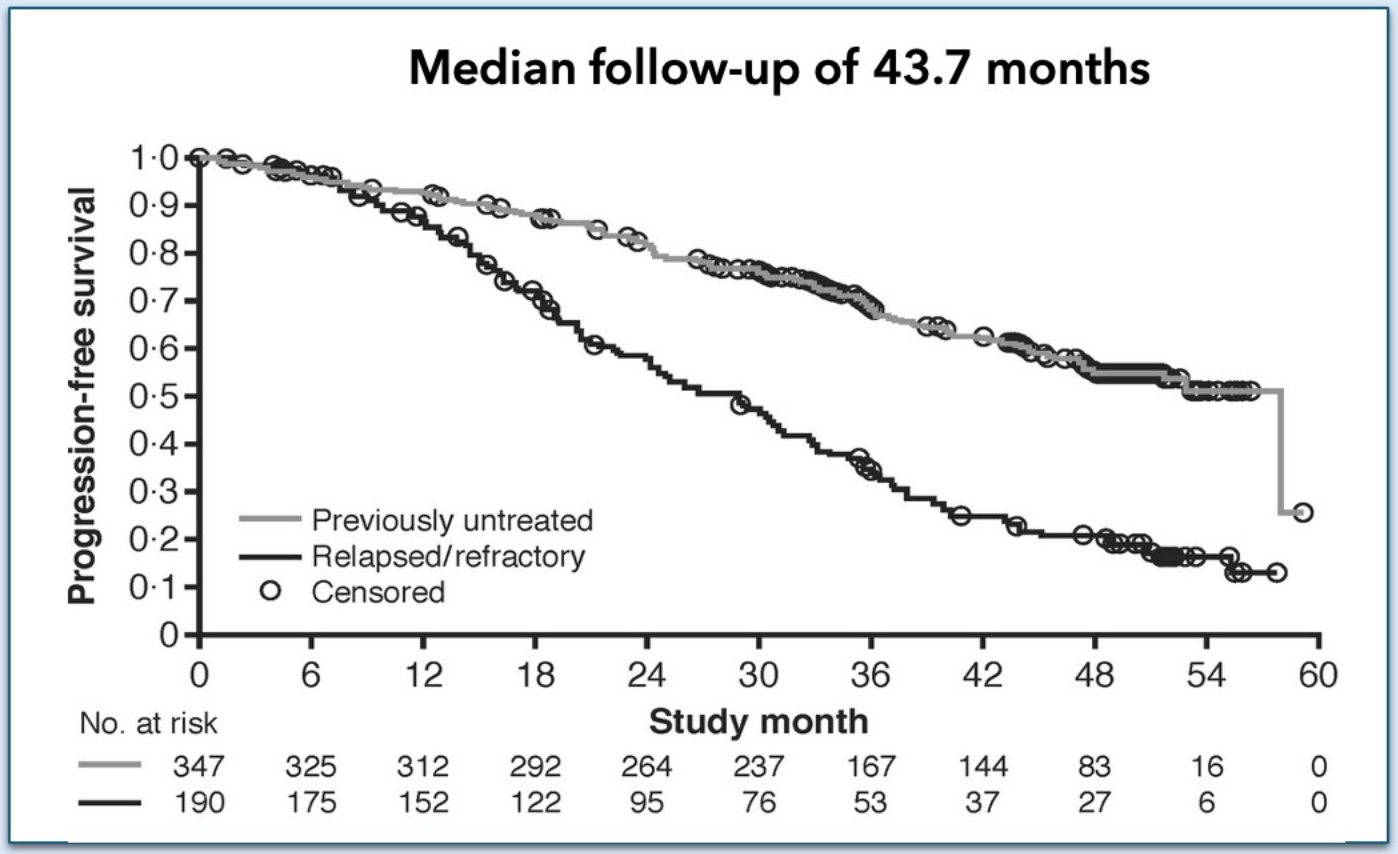
CI, confidence interval; IDELA, idelalisib; PD, progressive disease; R, ritutximab; RR, response rate; R/R CLL, relapsed/refractory chronic lymphocytic leukemia.

Sharman JP, et al. *J Clin Oncol.* 2019 Jun 1;37(16):1391-1402.

© 2024

Obinutuzumab

Phase IIIb, GREEN study evaluating the efficacy of obinutuzumab in patients (n=341) with R/R CLL and untreated patients with CLL



G-mono	1L (N=63)	R/R (N=65)
BOR, n (%)	49 (77.8)	39 (60.0)
95% CI	65.5; 87.3	47.1; 72.0
CR, n (%)	32 (50.8)	18 (27.7)
95% CI	37.9; 63.6	17.3; 40.2
Median (range) PFS, months	30.2	17.6
OS		
No pts at risk at 3 yrs	31	34
3-yr rate, 95% CI	0.86 (0.73; 0.93)	0.69 (0.55; 0.80)
No pts at risk at 4 yrs	14	16
4-yr rate, 95% CI	0.83 (0.67; 0.91)	0.59 (0.43; 0.71)

1L, first line; BOR, best overall response; CI, confidence interval; G-mono, obinituzumab; PFS, progression-free survival; R/R CLL, relapsed/refractory chronic lymphocytic leukemia.

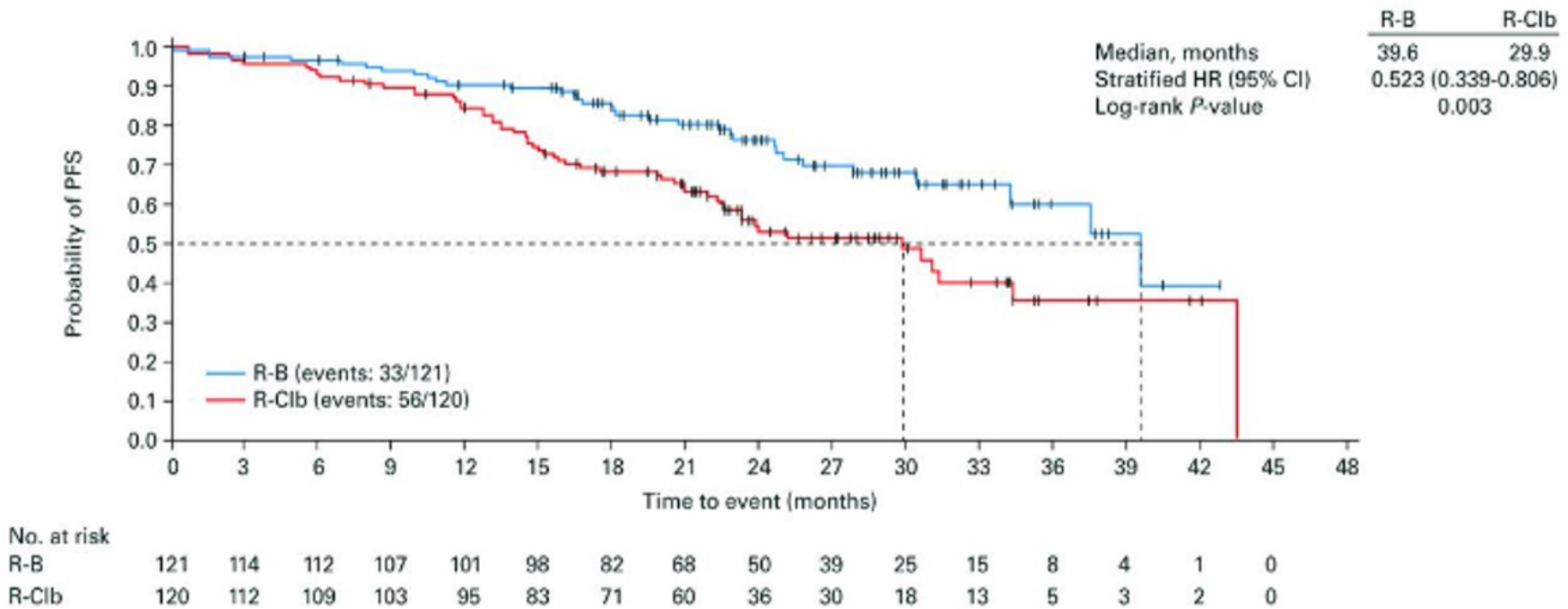
Stilgenbaurer S, et al. *Br J Haematol.* 2021 Apr;193(2):325-338.

© 2024

Rituximab

Open-label MABLE study evaluating the efficacy of rituximab plus bendamustine or chlorambucil in patients (n=357) with R/R CLL

Median follow-up of 23.5 months (R-B) and 23.3 months (R-Clb)



	R-B	R-Clb
Median, months	39.6	29.9
Stratified HR (95% CI)	0.523 (0.339-0.806)	
Log-rank *P*-value	0.003	

No. at risk

R-B	121	114	112	107	101	98	82	68	50	39	25	15	8	4	1	0
R-Clb	120	112	109	103	95	83	71	60	36	30	18	13	5	3	2	0

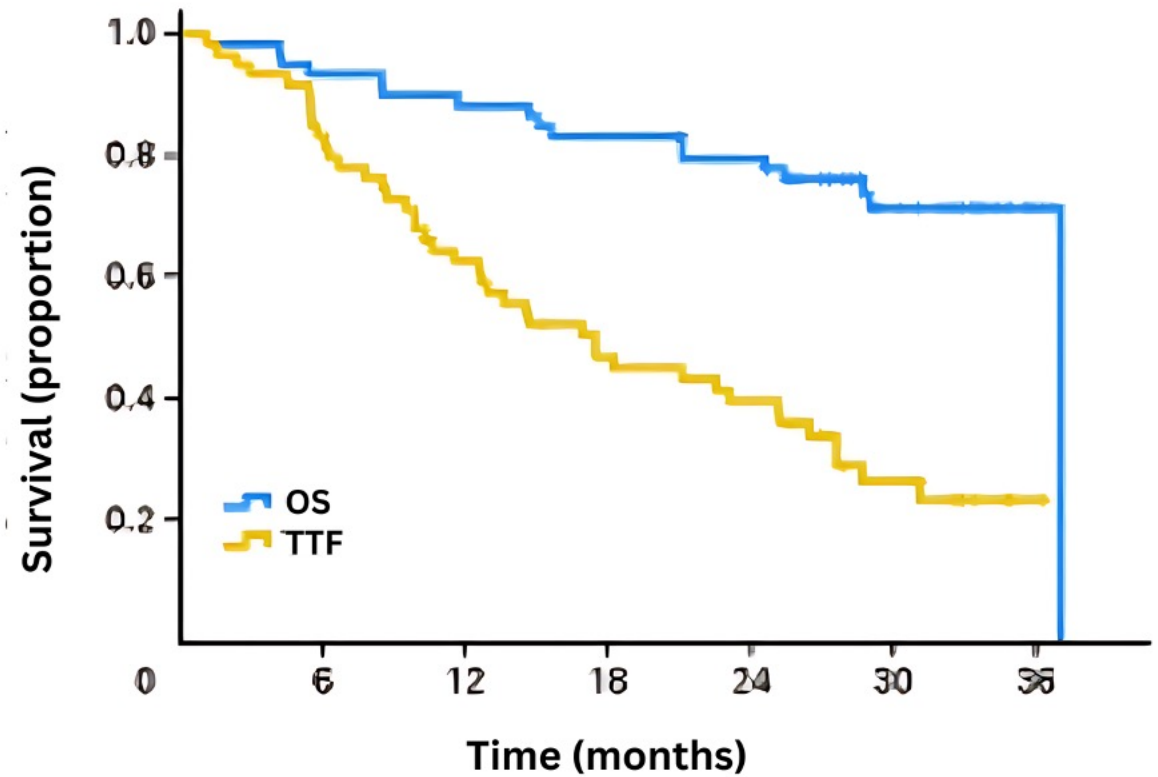
R-B, rituximab-bendamustin; R-Clb, rituximab-chlorambucil; R/R CLL, relapsed/refractory chronic lymphocytic leukemia.
Michallet AS, et al. *Haematologica*. 2018 Apr;103(4):698-706.

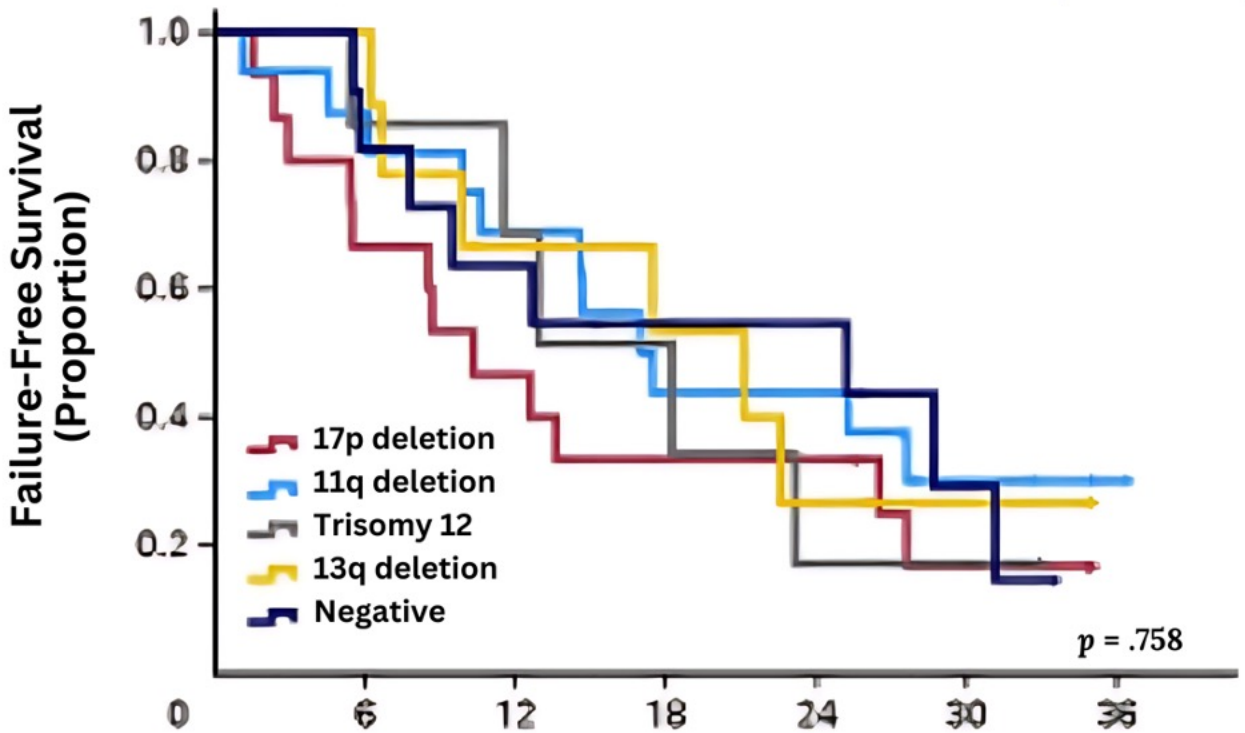
© 2024

Lenalidomide

Phase II study evaluating the efficacy of lenalidomide + rituximab in patients (n=59) with R/R CLL

Median follow-up of 33 months





OS, overall survival; R/R CLL, relapsed/refractory chronic lymphocytic leukemia; TTF, time-to-treatment failure.

Badoux XC, et al. *J Clin Oncol*. 2013 Feb 10;31(5):584-91.

© 2024

Safety of Bendamustine + Rituximab

NEXT

Grade 3/4 laboratory toxicities and adverse events (n=45)

Laboratory Hematologic Toxicities	n (%)
Lymphopenia	40 (89)
Leukopenia	20 (44)
Neutropenia	20 (44)
Thrombocytopenia	3 (7)
Anemia	2 (4)

Non-hematologic AEs Occurring in ≥ 2 Patients	n (%)
Hypokalemia	3 (7)
Muscle weakness	3 (7)
Hypotension	3 (7)
Pneumonia	2[a] (4)
Back pain	2 (4)
Decreased appetite	2 (4)
Device-related infection	2 (4)
Hyponatremia	2 (4)
Pleural effusion	2 (4)
Syncope	2 (4)
Weight decreased	2 (4)

[a]Once additional case of pneumonia was fatal.
AEs, adverse events; n, number.
Czuczman MS et al. *Ann Hematol*. 2015;94(12):2025-2032.

© 2024

Chemotherapeutic Combination TEAEs

- Neutropenia
- Thrombocytopenia
- Lymphopenia
- Leukopenia
- Anemia
- Pneumonia
- Infection

Commonly occurs with: Bendamustine

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR

- Assess during each visit and more frequently as needed
- Compare to similarly reported analyses to assess for manageability and reversibility

MITIGATE SYMPTOMS

- Consider prophylaxis for patients at increased risk of opportunistic infection
- Consider switching to another novel chemotherapy-free agent or clinical trial
- Dosing adjustment when using R-BAC or VR-CAP

TEAE, treatment-emergent adverse events.
Rummel MR et al. *Lancet Oncol*. 2016(1):57-66.

© 2024

Safety of Lenalidomide Monotherapy (1/2)

NEXT

Treatment-Emergent Hematological AEs (≥10% Grade 1–2, ≥5% Grade 3–4)

Lenalidomide (n=167) n (%)				Investigator's Choice (n=83) n (%)		
Hematological	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Anemia	34 (20)	12 (7)	2 (1)	13 (16)	5 (6)	1 (1)
Thrombocytopenia	31 (19)	25 (15)	5 (3)	10 (12)	16 (19)	7 (8)
Leukopenia	15 (9)	11 (7)	2 (1)	9 (11)	5 (6)	4 (5)
Neutropenia	12 (7)	40 (24)	33 (20)	1 (1)	13 (16)	15 (18)
Febrile neutropenia	0	7 (4)	3 (2)	0	2 (2)	0

AEs, adverse events.
Trněný M et al. *Lancet Oncol*. 2016(3):319-331.

© 2024

Safety of Lenalidomide Monotherapy (2/2)

Treatment-Emergent Non-Mehatological Aes (≥10% Grade 1-2, ≥5% Grade 3-4)

Non-Hematological AE's	Lenalidomide (n=167) n (%)			Investigator's Choice (n=83) n (%)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Fatigue	33 (20)	2 (1)	0	4 (5)	0	0
Diarrhea	32 (19)	5 (3)	1 (1)	8 (10)	0	0
Constipation	28 (17)	1 (1)	0	5 (6)	0	0
Nasopharyngitis	25 (16)	0	0	5 (6)	0	0
Asthenia	24 (14)	2 (1)	0	11 (13)	0	0
Pyrexia	24 (14)	3 (2)	1 (1)	9 (11)	1 (1)	0
Upper RTI	19 (11)	1 (1)	0	4 (5)	1 (1)	0
Cough	19 (11)	0	0	3 (4)	1 (1)	0
Decreased appetite	18 (11)	1 (1)	0	3 (4)	0	0
Nausea	18 (11)	0	0	12 (14)	0	0
Rash	18 (11)	0	0	3 (4)	0	0
Peripheral edema	16 (10)	1 (1)	0	9 (11)	0	0
Vomiting	10 (6)	0	0	9 (11)	0	0
Pneumonia	5 (3)	5 (3)	1 (1)	2 (2)	2 (2)	0

AEs, adverse events; RTI, respiratory tract infection.
Trněný M et al. *Lancet Oncol*. 2016(3):319-331.

© 2024

Safety of Lenalidomide + Rituximab (1/2)

NEXT

Common AEs in phase 2 (n=44) after 379 cycles of lenalidomide plus rituximab

Hematological	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	31 (70)	6 (14)	1 (2)	0
Neutropenia	20 (45)	22 (50)	16 (36)	13 (30)
Febrile neutropenia	1 (2)	7 (16)	2 (5)	0
Thrombocytopenia	23 (52)	9 (20)	8 (18)	2 (5)
Leukopenia	26 (59)	14 (32)	10 (23)	3 (7)
Lymphopenia	27 (61)	21 (48)	12 (27)	4 (9)

AEs, adverse events; n, number.
Wang M et al. *Lancet Oncol*. 2012(7):716-723.

© 2024

Safety of Lenalidomide + Rituximab (2/2)

NEXT

Common AEs in phase 2 (n=44) after 379 cycles of lenalidomide plus rituximab

Non-Hematological	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Pruritus	19 (43)	3 (7)	0	0
Fatigue	39 (89)	17 (39)	2 (5)	0
Constipation	27 (61)	3 (7)	0	0
Neuropathy	27 (61)	5 (11)	1 (2)	0
Cough	17 (39)	1 (2)	1 (2)	0
Nausea	15 (34)	5 (11)	0	0
Vomiting	11 (25)	4 (9)	0	0
Memory impairment	11 (25)	2 (5)	0	0
Mood alteration	11 (25)	1 (2)	0	0
Ataxia	1 (2)	0	1 (2)	0
Dizziness	14 (32)	4 (9)	0	0
Diarrhea	22 (50)	7 (16)	0	0
Rash	21 (48)	6 (14)	2 (5)	0
Myalgia	20 (45)	8 (18)	2 (5)	0

AEs, adverse events; n, number.
Wang M et al. *Lancet Oncol*. 2012(7):716-723.

© 2024

Lenalidomide TEAEs

- Neutropenia
- Thrombocytopenia
- Anemia
- Leukopenia
- Rash
- Fatigue
- Diarrhea
- Pneumonia

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR

- Assess during each visit and more frequently as needed
- Compare to similarly reported analyses to assess for manageability and reversibility

MITIGATE SYMPTOMS

- Utilize patient self-reporting at early signs of rash
- Provide appropriate and prompt intervention by grading of rash symptoms

TEAE, treatment-emergent adverse events.

Trněný M et al. *Lancet Oncol*. 2016(3):319-331. Wang M et al. *Lancet Oncol*. 2012(7):716-723. Tinsley et al. *Clin Lymphoma Myeloma Leuk*. 2015(Suppl):S64-S69.

© 2024

Safety of Brexucabtagene Autoleucel

NEXT

Adverse Events Occurring After the Previous Report2 (July 24, 2019 Data Cutoff Date) in the All-Treated Population (N=68)

	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CRS or neurologic events	2 (3)	1 (1)	0	1 (1)	0	0
CRS	0	0	0	0	0	0
Neurologic events	2 (3)	1 (1)	0	1 (1)	0	0
Serious neurological event	1 (1)	0	0	1 (1)	0	0

[a]CRS events were graded per revised Lee et al. 2014 grading system; all other AEs were graded per Common Terminology Criteria for Adverse Events version 4.03. [b]This serious neurologic event of encephalopathy began on day 397; the event resolved on day 408 and was considered unrelated to KTE-X19
AE, adverse events; CRS, cytokine release syndrome; N, number.
Wang M et al. *J Clin Oncol*. 2022(41):555-567.

© 2024

CAR T Therapy TEAEs (1/3)

NEXT

- CRS
- Neurological toxicity
- B cell aplasia
- Thrombocytopenia
- Neutropenia
- Immune-mediated pancytopenia

Commonly occurs with:
- Lisocabtagene maraleucel
- (liso-cel)
- Brexucabtagene autoleucel (brexu-cel)

PREVENT
- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR
- Monitor and assess CRS and ICANs by grade
- Provide brain imaging for neurologic symptoms (MRI > CT)

MITIGATE SYMPTOMS
- Low-grade CRS and neurotoxicity can be managed by supportive care or corticosteroids
- Provide prophylactic antiseizure medication if needed
- Provide monthly immunoglobulin G for patients at risk of infection

CRS, cytokine release syndrome; TEAE, treatment-emergent adverse events.

Wang M et al. J Clin Oncol. 2022(41):555-567. Adkins S. *J Adv Pract Oncol*. 2019(Suppl 3):21-28.

© 2024

Management of CRS (2/3)

Grade	Management	Notes
Grade 1	Observe	• Early fever (within 72 hrs) or significant comorbidities can consider early tocilizumab.
Grade 2	Tocilizumab 8 mg/kg (Consider alternative agents after 2 doses) *No more than 3 doses in a 24hr period or 4 doses in total.	• For patients with early fevers or significant co-morbidities, consider early dexamethasone (10mg x1). • Patients not responding to tocilizumab should could initiation of dexamethasone (10mg q12-24hrs).
Grade 3	Tocilizumab 8 mg/kg (Consider alternative agents after 2 doses) *No more than 3 doses in a 24hr period or 4 doses in total.	• Dexamethasone (10mg q12-24hrs) with tocilizumab initial tocilizumab. • For patients refractory to dexamethasone can increase to 20mg q6-12 hrs.
Grade 4	Tocilizumab 8 mg/kg (Consider alternative agents after 2 doses) *No more than 3 doses in a 24hr period or 4 doses in total.	• In dexamethasone refractory patients, consider high dose methylprednisolone 2mg/kg x12 hrs. • For refractory patients consider alternative therapies.

Always look for infections and treat infectious complications, especially in patients with neutropenia

CRS, cytokine release syndrome.

Wang M et al. J Clin Oncol. 2022(41):555-567. Adkins S. *J Adv Pract Oncol*. 2019(Suppl 3):21-28.

© 2024

Management of ICANS (3/3)

Grade	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care (± steroids)*	Supportive care (± tocilizumab)
2	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care

Neurology consultation
Low threshold for inpatient management
(if outpatient at time of onset)
Multidisciplinary team approach

ICANS Pearls

- Levetiracetam for seizure prophylaxis for the first 30 days
- Can be biphasic
- Early phase overlaps with CRS
  - Often mild (grade 1/2) and short lived (2-4 days)
  - May respond to tocilizumab
- Delayed phase may occur 2-4 weeks after CAR T-cell infusion
  - May be more severe and prolonged
  - Corticosteroids preferred therapy
  - Tocilizumab generally not effective

ICANS, immune effector cell-associated neurotoxicity syndrome.
*High-burden, high-risk products; older; comorbidities, etc.
Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47; Neelapu SS. *Hematol Oncol*. 2019;37(suppl 1):48-52..

© 2024

Safety of Ibrutinib Monotherapy (1/3)

Summary of SAEs (≥2% of Patients) Regardless of Attrition (N=111)

SAE*, n (%)	Any Grade	Grade 3-4	Grade 5
Disease progression	11 (10)	3 (3)	8 (7)
Pneumonia	8 (7)	7 (6)	1 (1)
Atrial fibrillation	7 (6)	6 (5) ‡	0
Urinary tract infection	4 (4)	3 (3)	0
Febrile neutropenia	3 (3)	3 (3)	0
Abdominal pain	3 (3)	3 (3)	0
Acute renal failure	3 (3)	2 (2)	1 (1)
Subdural hematoma	3 (3)	2 (2)	0
Pyrexia	3 (3)	1 (1)	0
Confusional state	3 (3)	1 (1)	0

*SAEs were updated with an estimated median follow-up of 26.7 months. †Mantle cell lymphoma reported as a SAE by investigators. ‡One additional patient had a grade 3 atrial fibrillation that was not considered an SAE.
SAEs, serious adverse events; n, number.
Wang M et al. *Blood*. 2015(6):739-745.

© 2024

Safety of Ibrutinib Monotherapy (2/3)

Prevalence of Select AEs by 6-Month Intervals

Select SAE*, n (%)	1-6 mo (n=111)	7-12 mo (n=72)	13-18 mo (n=51)	19-26 mo (n=41)	>24 mo (n=22)
Any diarrhea	49 (44)	21 (29)	15 (29)	8 (20)	6 (27)
Grade 3†	5 (5)	0	0	1 (2)	0
SAE	1 (1)	0	0	0	0
Any infection	76 (69)	43 (60)	30 (59)	22 (54)	9 (41)
Grade	20 (18)	11 (15)	6 (12)	5 (12)	1 (5)
SAE	16 (14)	9 (13)	4 (8)	5 (12)	1 (5)
Any bleeding	46 (41)	17 (24)	17 (33)	14 (34)	5 (23)
Major bleeding	6 (5)	1 (1)	3 (6)	2 (5)	2 (9)

*AEs were updated with an estimated median follow-up of 26.7 months. †No grade 4 or 5 diarrhea.
Mo, months; n, number; SAEs, serious adverse events
Wang M et al. *Blood*. 2015(6):739-745.

© 2024

Safety of Ibrutinib vs Temsirolimus (3/3)

TEAEs in ≥20% of Patients in Either Treatment Arm

Hematologic AEs n (%)	Ibrutinib (N=139)		Temsirolimus (N=139)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Thrombocytopenia	18.0	9.4	56.1	43.2
Anemia	19.4	8.6	43.9	20.1
Neutropenia	15.8	12.9	26.6	17.3

Non-Hematologic AEs	Ibrutinib (N=139)		Temsirolimus (N=139)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Diarrhea	33.1	3.6	30.9	4.3
Fatigue	23.7	5.0	28.8	7.2
Cough	23.0	0.7	22.3	0
Upper RTI	20.1	2.2	11.5	0.7
Pyrexia	18.7	0.7	20.9	2.2
Nausea	14.4	0	21.6	0
Peripheral edema	13.7	0	23.7	2.2
Epistaxis	9.4	0.7	23.7	1.4
Stomatitis	2.9	0	20.9	3.6

RTI, respiratory tract infection; TEAEs, treatment-emergent adverse events.

Rule S et al. *Leukemia*. 2018(8):1799-1803.

© 2024

Safety of Ibrutinib + Rituximab

Treatment-Emergent Adverse Events (n=50)

Hematologic AEs n (%)	Grade 1-2	Grade 3	Grade 4
Thrombocytopenia	24 (48)	2 (4)	0
Anemia	24 (48)	0	0
Neutropenia	10 (20)	1 (2)	1 (2)
Leukopenia	5 (10)	0	0
Leucocytosis	2 (4)	1 (2)	0

Non-Hematologic AEs n (%)	Grade 1-2	Grade 3	Grade 4
Fatigue	47 (94)	2 (4)	0
Diarrhea	39 (78)	1 (2)	1 (2)
Myalgia	34 (68)	1 (2)	0
Hypertension	13 (26)	1 (2)	0
Pneumonitis	2 (4)	1 (2)	0
Non-itchy rash (arms)	1 (2)	2 (4)	0
Skin infection	1 (2)	1 (2)	0
Urinary tract infection	3 (6)	1 (2)	0
Atrial fibrillation	1 (2)	6 (12)	0
Acute renal failure	0	1 (2)	0

AEs, adverse events.
Wang M et al. *Lancet Oncol*. 2016(1):48-56.

© 2024

Safety of Ibrutinib + Venetoclax (1/2)

Adverse Events and Serious Adverse Events*

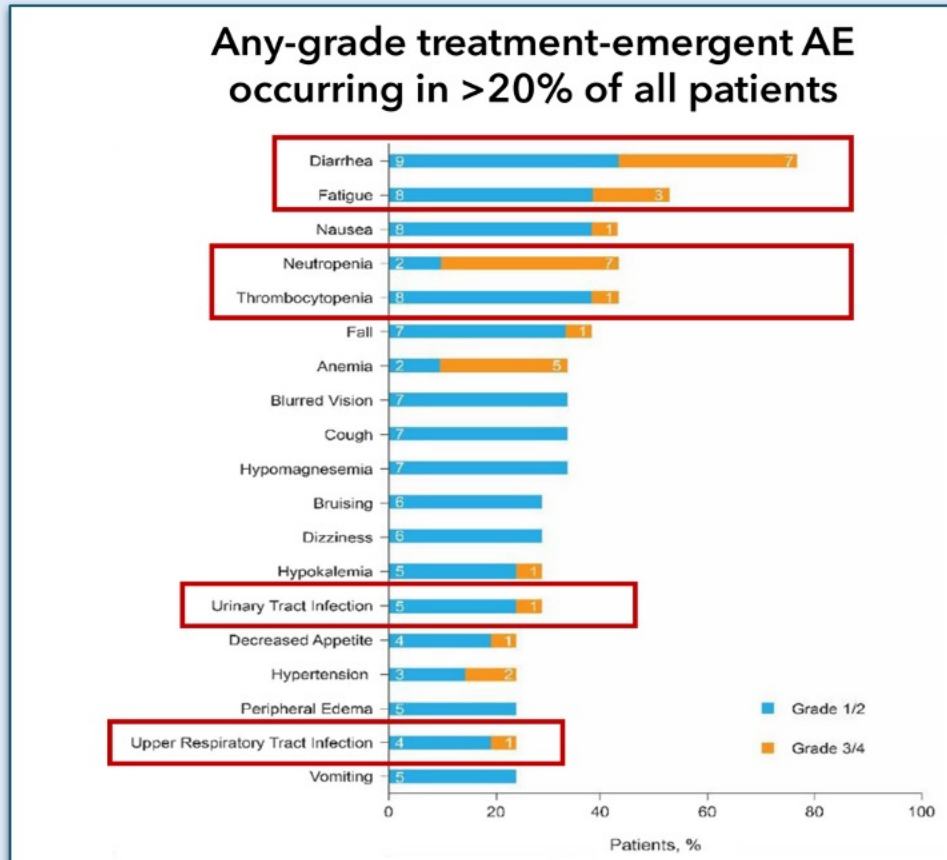
Event n (%)	Any Grade (N=24)	Grade ≥3 (N=24)
Any AE	24 (100)	17 (71)
Diarrhea	20 (83)	3 (12) †
Fatigue	18 (75)	0
Nausea or vomiting	17 (71)	0
Bleeding, bruising, post-operative hemorrhage	13 (54)	1(4)
Cough or dyspnea	11 (46)	1(4)
Soft tissue infection	10 (42)	2 (8) ‡
Neutropenia	8 (33)	8 (33)
Anemia	7 (29)	3 (12)
Rash	7 (29)	0
Thrombocytopenia	5 (21)	4 (17)
Atrial fibrillation	2 (8)	2 (8)

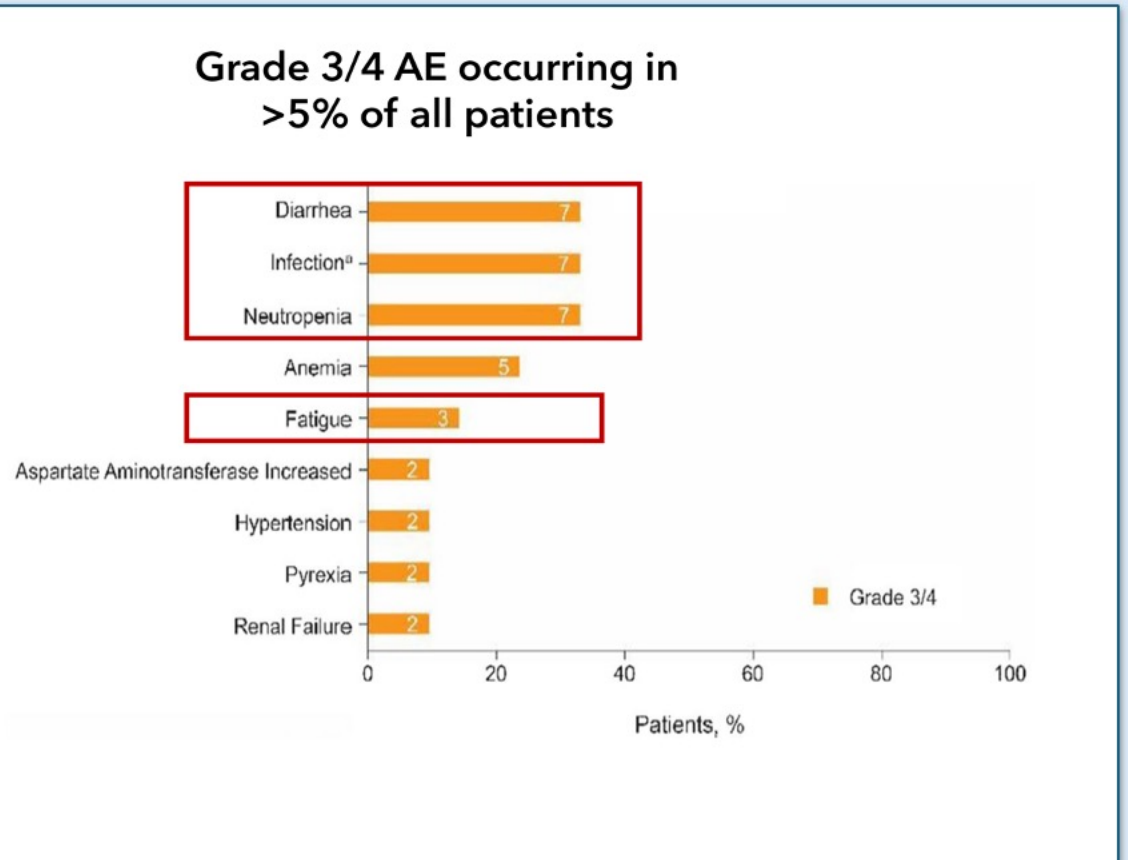
Event n (%)	Any Grade (N=24)	Grade ≥3 (N=24)
Any serious AEs	14 (58)	--
Diarrhea	3 (12)¶	--
Tumor lysis syndrome	2 (8)	--
Atrial fibrillation	2 (8)	--
Pyrexia	2 (8)	--
Pleural effusion	2 (8)	--
Cardiac failure	1 (4) ‡	--
Soft-tissue infection	1 (4) ‡	--

*Listed are the adverse events that were reported in at least 15% of the patients, as well as events of special interest (the tumor lysis syndrome and atrial fibrillation). †The three cases of grade 3 diarrhea lasted 4 days, 1 week, and 2 weeks. ‡Data include one fatal adverse event. The two fatal events that were considered by the investigators to be unrelated to disease progression were soft-tissue infection (malignant otitis externa) and cardiac failure. §Listed are the serious adverse events that were reported in at least two patients, as well as fatal events. ¶Data include one patient with microscopic colitis that had been diagnosed on the basis of colonoscopy and biopsy.
AEs, adverse events; n, number.
Tam C et al. *N Engl J Med*. 2018(13):1211-1223.

© 2024

Safety of Ibrutinib + Venetoclax (2/2)





[a]AEs of infection were bronchitis (n = 1), candida infection (n = 1), cellulitis (n = 1), fungal abscess central nervous system (n = 1, recovered), infection (not specified, n = 1), pneumonia (n = 2), sepsis (n = 1), staphylococcal bacteremia (n = 1), upper respiratory tract infection (n = 1), and urinary tract infection (n = 1).
AEs, adverse events.
Wang M et al. *J Hematol Oncol*. 2021;14(1):179.

© 2024

Safety of Acalabrutinib in R/R MCL

NEXT

Events	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Headache	47 (38%)	30 (24%)	15 (12%)	2 (2%)	0
Diarrhea	38 (31%)	21 (17%)	13 (10%)	4 (3%)	0
Fatigue	34 (27%)	24 (19%)	8 (6%)	1 (1%)	0
Myalgia	26 (21%)	19 (15%)	6 (5%)	1 (1%)	0
Cough	24 (19%)	21 (17%)	3 (2%)	0	0
Nausea	22 (18%)	12 (10%)	9 (7%)	1 (1%)	0
Vomiting	19 (15%)	14 (11%)	5 (4%)	0	0
Most common grade 3 or worse events:					
Anemia	15 (12%)	1 (1%)	3 (2%)	10 (8%)	1 (1%)
Neutropenia	13 (10%)	0	0	6(5%)	7 (6%)
Pneumonia	7 (6%)	0	1 (1%)	6 (5%)	0

- No cases of atrial fibrillation
- Bleeding events (mostly contusion and petechiae) occurred in 39 (31%) of patients.
  - All grade 1 or 2 except for one grade 3 gastrointestinal hemorrhage in one patient with a history of gastrointestinal ulcer

Wang M, et al. Lancet (2018); 391(10121): 659-667.

© 2024

Safety of Zanubrutinib in R/R MCL

AE of special interest	Any grade AE	Grade ≥3 AE
Any AE of special interest	76 (88.4)	34 (39.5)
Infections	56 (65.1	16 (18.6)
Bleeding	31 (36.0)	1 (1.2)
Major hemorrhage	3 (3.5)	1 (1.2)
Second primary malignancies	0	0
Skin cancers	0	0
Neutropenia	43 (50.0)	17 (19.8)
Thrombocytopenia	8 (9.3)	0
Anemia	15 (17.4)	5. (5.8)
Hypertension	14 (16.3)	3 (3.5)
Atrial fibrillation/flutter	0	0
Ventricular arrhythmia	--	0

AE, adverse events.
Song U, et al. Blood (2022); 139(21):3148-3158.

© 2024

Covalent BTK Inhibitor TEAEs

- Thrombocytopenia
- Neutropenia
- Atrial fibrillation/flutter
- Infection
- Bleeding
- Hypertension
- Fatigue
- Rash

Commonly occurs with:
- Ibrutinib
- Zanubrutinib
- Acalabrutinib

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR

- Assess during each visit and more frequently as needed
- Monitor for signs of atrial fibrillation, bleeding, hypertension during treatment

MITIGATE SYMPTOMS

- Administer direct oral anticoagulants and discontinue BTK inhibitor if atrial fibrillation not controlled
- Use antihypertensive medication for hypertension
- Consider prophylaxis for patients at increased risk of opportunistic infection

BTK, Bruton kinase; RTI, respiratory tract infection; TEAEs, treatment-emergent adverse events.

1Wang M et al. *J Clin Oncol*. 2023(3):555-567. Wang M et al. *Leukemia*. 2019(11):2762-2766. Tam CS et al. *Blood Adv*. 2021(12):2577-2585. O'Brien SM et al. *Front Oncol*. 2021(11):720704. Brown JR, et al. *N Engl J Med*. 2023 Jan 26;388(4):319-332. Ghia P, et al. *J Clin Oncol*. 2020 Sep 1;38(25):2849-2861.

© 2024

Safety of Pirtobrutinib Monotherapy

NEXT

Adverse events in at least 10% of all MCL patients (n=164)

AEs of special interest*	TEAE (≥10%), %		TRAE	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infections	59 (36)	28 (17)	24 (14)	5 (3)
Bleeding	45 (27)	6 (4)	26 (16)	1 (1)
Thrombocytopenia	24 (15)	11 (7)	2 (1)	0
Neutropenia[b]	23 (14)	22 (13)	15 (9)	14 (9)
Bruising[c]	27 (17)	0	19 (12)	0
Hemorrhage	25 *(15)*	6 (4)	11(7)	1 (1)
Atrial fibrillation/ atrial flutter	6 (4)	2 (1)	1 (1)	0

AEs of special interest*	TEAE (≥10%), %		TRAE	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	49 (30)	4 (2)	34 (21)	4 (2)
Diarrhea	35 (21)	0	20 (12)	0
Dyspnea	27 (17)	3 (2)	15 (9)	1 (1)
Contusion	24 (15)	0	16 (10)	0
Anemia	21 (13)	8 (5)	10 (6)	4 (2)
Back pain	21 (13)	2 (1)	2 (1)	0
Cough	20 (12)	0	10 (6)	0
Pyrexia	19 (12)	0	6 (4)	0
Constipation	18 (11)	0	3 (2)	0
Nausea	18 (11)	0	7 (4)	0
Pneumonia	17 (10)	14 (9)	5 (3)	4 (2)
Myalgia	17 (10)	0	14 (9)	0

[a]Adverse events of special interest are those that were previously associated with cBTK inhibitors and are all composite terms. [b]Combines neutrophil count decreased, neutropenia, febrile neutropenia, and neutropenic sepsis.
[c]Bruising includes contusion, petechia, ecchymosis, and increased tendency to bruise. [d]Of 6 total afib/aflutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation
MCL, mantle cell lymphoma; TEAE, treatment-emergent adverse events; TRAE, treatment-related adverse events.
Wang M et al. J Clin Oncol. 2023(41):3988-3997.

© 2024

Non-Covalent BTK Inhibitor TEAEs

- Thrombocytopenia
- Neutropenia
- Atrial fibrillation/flutter
- Infection
- Bleeding
- Hypertension
- Fatigue
- Pneumonia

Commonly occurs with:
- Pirtobrutinib

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR

- Assess during each visit and more frequently as needed
- Monitor for signs of hypertension during treatment

MONITOR SYMPTOMS

- Administer direct oral anticoagulants and discontinue BTK inhibitor if atrial fibrillation not controlled
- Use antihypertensive medication for hypertension
- Suggest use of Imodium for diarrhea symptoms
- Provide appropriate and prompt intervention by grading of rash symptoms

TEAE, treatment-emergent adverse events.
Wang M et al. *J Clin Oncol*. 2023(3):555-567.

© 2024

Safety of Venetoclax Monotherapy

TEAEs	35.2				New events with onset 12-24 mo (N=33)				New events with onset>24 mo (N=15)			
	n/N	%	P-Y[c]	IR[b]	n/N	%	P-Y	IR	n/N	%	P-Y	IR
Any AE	62/64	97	3.1	1984.7	26/33	79	7.6	340.7	13/15	87	9.3	139.6
Hematologic	18/64	28	37.1	48.5	5/33	15	21.8	22.9	0/15	0	40.1	0
Neutropenia	13/64	20	39.1	33.3	1/25	4	17.7	5.6	0/13	0	38.0	0
Thrombocytopenia	9/64	14	44.1	20.4	1/29	3	19.9	5.0	0/14	0	34.5	0
Anemia	7/64	11	45.3	15.4	2/31	7	21.0	9.5	0/13	0	36.6	0
Non-hematologic												
Nausea	34/64	53	21.4	158.5	1/11	9	6.1	16.3	1/2	50	2.9	34.3
Diarrhea	30/64	47	27.0	111.3	3/13	23	5.3	56.6	1/1	100	1.7	58.1
Fatigue	22/64	34	35.2	3/21	3/21	14	12.5	24.0	2/7	29	18.5	10.8
Upper RTI	15/64	23	39.7	1/20	1/20	5	13.9	7.0	3/8	38	11.2	26.7
Constipation	12/64	19	41.3	0/29	0/29	0	20.8	0	2/13	15	32.8	6.1
Headache	12/64	19	41.1	2/25	2/25	8	15.0	13.3	0/8	0	14.6	0
Vomiting	11/64	17	40.0	27.5	1/24	4	15.3	6.5	3/10	30	19.1	15.7
Decreased appetite	10/64	16	42.1	23.7	1/25	4	17.1	5.8	0/10	0	28.0	0
Cough	10/64	16	42.0	23.8	2/26	7	17.1	11.7	2/9	22	16.1	12.5

[a]Hematologic and nonhematologic adverse events ≥15% occurrence by incidence rate sorted by first events with onset ≤12 months. [b]Incidence rate ¼ number of patients with an event per 100 person-years at risk. [c]Person-years for the calculation of the incidence rate is the total time at risk of an event across all patients. Only new events not reported before this time period were counted in the summary of events with onset in one time period.
AE, adverse events; IR, incidence rate; mo, months; N, number PY, person-years; RTI, respiratory tract infection; TEAE, treatment-emergent adverse events.
Davids MS et al. *Clin Cancer Res*. 2022(17):4690-4695.

© 2024

BCL-2 Inhibitor TEAEs

- Thrombocytopenia
- Neutropenia
- Anemia
- Diarrhea
- Fatigue
- Upper RTI
- Nausea
- Headache
- Vomiting

Commonly occurs with:
- Venetoclax

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR

- Assess during each visit and more frequently as needed
- Monitor for signs of infection and bleeding during treatment

MITIGATE SYMPTOMS

- Use prophylactic measures to reduce opportunistic infection and tumor lysis syndrome
- Delays between venetoclax cycles may be need to address cytopenia and neutropenia
- Consider venetoclax dosing adjustment to address cytopenia
- Avoid grapefruit products to avoid CYP3A4 inhibitors

RTI, respiratory tract infection; TEAE, treatment-emergent adverse events.

Davids MS et al. *Clin Cancer Res*. 2022(17):4690-4695. Richard-Carpentier G et al. *Ther Adv Hematol*. 2019(10): 2040620719882822.

© 2024

Safety of Allo-SCT (1/2)

Patient	OSHO Trial	G	Age at SCT (yrs)	Follow-up after allo-ACT	Causes of death
#1	#60	M	65	N/A	PD
#2	#60	M	64	Day +8	Infection in aplasia
#3	#60	M	61	Day +8	Kidney/lung toxicity IV plus pneumonia
#4	#60	M	64	Day +481	Septic cardiomyopathy
#5	#74	F	63	Day +15	Bleeding d/t Aspergillosis of CNS
#6	#74	M	69	Day +312	Infection
#7	#74	M	59	Day +9	Infection
#8	#74	M	59	Day +1009	Infection
#9	#74	M	63	Day +229	PD
#10	#60	M	60	Day +2168	PD

Incidence of chronic GVDH was 15% (limited disease n=5, extensive disease n=1) without dynamic or mortality since 2014

Allo-SCT; allogeneic stem cell transplant; d/t, due to; F, female; G, gender; GVHD, graft-versus-host-disease; M, male; N/A not applicable; PD, progressive disease.
Krüger WH et al. Ann Hematol. 2021(6):1569-1577.

© 2024

Safety of Allo-SCT (2/2)

Patient Outcomes	n (%)
Relapse post RIC-allo-SCT, number of patients (8)	
Yes	24 (24)
aGVHD, number of patients (1)	
No aGVHD	48 (46)
I-II	37 (35)
III-IV	20 (19)
cGVHD*, number of patients (13)	
Yes	48 (59)
Extensive cGHVD	28 (58)
Toxicity-related mortality according to the period after RIC-allo-SCT, percentage	
6 months	17
1 year	29
3 years	32

*Limited to patients whose follow-up reached day 100.
aGVHD, acute GVHD; cGVHD, chronic GVHD; NA, not asserted; OS, overall survival; Ric-allo-SCT, reduced-intensity conditioning allogeneic stem cell transplantation.
Tessoulin B et al. *Bone Marrow Transplant*. 2016;51(9):1184-1190.

© 2024

Allogeneic Stem Cell Transplant TEAEs

- GVHD
- Infection
- Bleeding
- Anemia
- Mucositis
- Abdominal pain
- Diarrhea

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR

- Assess patient quality of life symptoms via patient-reported outcomes or other tools to identify impact of GVHD
- Monitor for signs of fibrillation or bleeding during treatment
- Assess infections that may be a result of graft failure

MITIGATE SYMPTOMS

- Provide therapies to prevent acute GVHD from occurring
- Use direct oral anticoagulants if needed to control bleeding
- Consider prophylaxis for patients at increased risk of opportunistic infection
- Use of human keratinocyte growth factor for mucositis

GVHD, graft-versus-host-disease; TEAEs, treatment-emergent adverse events.
Davids MS et al. *Clin Cancer Res*. 2022(17):4690-4695.

© 2024

Safety of Lenalidomide in R/R CLL

AE of Interest	Grade 3-4		Grade 4 only	
	No	%	No	%
Hematologic				
Neutropenia	43	73	30	51
Thrombocytopenia	20	34	9	15
Anemia	9	15	1	1.7
Infection				
Pneumonia/bronchitis	6	10	--	--
UTI	1	2	--	--
Other infection	2	3	--	--
Any infectious event	9	15	--	--
Fever				
Neutropenic fever	6	10	--	--
Febrile, non-neutropenic	2	3	--	--
Any febrile or infectious events	14	24	--	--

AE, adverse events; R/R CLL, relapsed/refractory chronic lymphocytic leukemia; UTI, urinary tract infection.
Badoux XC, et al. *J Clin Oncol*. 2013 Feb 10;31(5):584-91.

© 2024

Lenalidomide TEAEs

- Neutropenia
- Thrombocytopenia
- Anemia
- Leukopenia
- Rash
- Fatigue
- Diarrhea
- Pneumonia

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR

- Assess during each visit and more frequently as needed
- Compare to similarly reported analyses to assess for manageability and reversibility

MITIGATE SYMPTOMS

- Utilize patient self-reporting at early signs of rash
- Provide appropriate and prompt intervention by grading of rash symptoms

TEAE, treatment-emergent adverse events.

Trněný M et al. *Lancet Oncol*. 2016(3):319-331. Wang M et al. *Lancet Oncol*. 2012(7):716-723. Tinsley et al. *Clin Lymphoma Myeloma Leuk*. 2015(Suppl):S64-S69.

© 2024

Safety of Lisocabtagene maraleucel in R/R CLL

NEXT

Cytokine release syndrome	Full population (n=117)
Any grade	99 (85%)
Grade 1	43 (37%)
Grade 2	46 (39%)
Grade 3	10 (9%)
Grade 4	0
Grade 5	0
Time to onset, days*	4 (1 – 7)
Time to resolution, days*	6 (4 – 11)

Neurological Events	Liso-cel group (n=92)
Any grade	53 (45%)
Grade 1	13 (11%)
Grade 2	18 (15%)
Grade 3	21 (18%)
Grade 4	1 (1%)
Grade 5	0
Time to onset, days*	7 (4 – 11)
Time to resolution, days*	7 (4 – 16)

*Any event that stopped and started again within 7 days was considered a single episode; time to resolution was defined as the number of days from onset of the first event to when the last event of the first episode ended; patients with an unresolved episode were excluded. †Neurological events were defined as investigator-identified neurological adverse events related to liso-cel.

Siddiqi T, et al. *Lancet* 2023; 402: 641–54.

© 2024

CAR T Therapy TEAEs (1/3)

NEXT

- CRS
- Neurological toxicity
- B cell aplasia
- Thrombocytopenia
- Neutropenia
- Immune-mediated pancytopenia

Commonly occurs with:
- Lisocabtagene maraleucel
- (liso-cel)
- Brexucabtagene autoleucel (brexu-cel)

PREVENT
- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR
- Monitor and assess CRS and ICANs by grade
- Provide brain imaging for neurologic symptoms (MRI > CT)

MITIGATE SYMPTOMS
- Low-grade CRS and neurotoxicity can be managed by supportive care or corticosteroids
- Provide prophylactic antiseizure medication if needed
- Provide monthly immunoglobulin G for patients at risk of infection

CRS, cytokine release syndrome; TEAE, treatment-emergent adverse events.

Wang M et al. J Clin Oncol. 2022(41):555-567. Adkins S. *J Adv Pract Oncol*. 2019(Suppl 3):21-28.

© 2024

Management of CRS (2/3)

Grade	Management	Notes
Grade 1	Observe	• Early fever (within 72 hrs) or significant comorbidities can consider early tocilizumab.
Grade 2	Tocilizumab 8 mg/kg (Consider alternative agents after 2 doses) *No more than 3 doses in a 24hr period or 4 doses in total.	• For patients with early fevers or significant co-morbidities, consider early dexamethasone (10mg x1). • Patients not responding to tocilizumab should could initiation of dexamethasone (10mg q12-24hrs).
Grade 3	Tocilizumab 8 mg/kg (Consider alternative agents after 2 doses) *No more than 3 doses in a 24hr period or 4 doses in total.	• Dexamethasone (10mg q12-24hrs) with tocilizumab initial tocilizumab. • For patients refractory to dexamethasone can increase to 20mg q6-12 hrs.
Grade 4	Tocilizumab 8 mg/kg (Consider alternative agents after 2 doses) *No more than 3 doses in a 24hr period or 4 doses in total.	• In dexamethasone refractory patients, consider high dose methylprednisolone 2mg/kg x12 hrs. • For refractory patients consider alternative therapies.

Always look for infections and treat infectious complications, especially in patients with neutropenia

CRS, cytokine release syndrome.

Wang M et al. J Clin Oncol. 2022(41):555-567. Adkins S. *J Adv Pract Oncol*. 2019(Suppl 3):21-28.

© 2024

Management of ICANS (3/3)

Grade	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care (± steroids)*	Supportive care (± tocilizumab)
2	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care

Neurology consultation
Low threshold for inpatient management
(if outpatient at time of onset)
Multidisciplinary team approach

ICANS Pearls

- Levetiracetam for seizure prophylaxis for the first 30 days
- Can be biphasic
- Early phase overlaps with CRS
  - Often mild (grade 1/2) and short lived (2-4 days)
  - May respond to tocilizumab
- Delayed phase may occur 2-4 weeks after CAR T-cell infusion
  - May be more severe and prolonged
  - Corticosteroids preferred therapy
  - Tocilizumab generally not effective

ICANS, immune effector cell-associated neurotoxicity syndrome.
*High-burden, high-risk products; older; comorbidities, etc.
Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47; Neelapu SS. *Hematol Oncol*. 2019;37(suppl 1):48-52..

© 2024

Safety of Ibrutinib vs Acalabrutinib in R/R CLL (1/2)

Events, n (%)	Any Grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation†	25 (9.4)	42 (16.0)*	13 (4.9)	10 (3.8)
Ventricular arrhythmias	0	3 (1.1)	0	1 (0.4)
Bleeding events	101 (38.0)	135 (51.3)*	10 (3.8)	12 (4.6)
Major bleeding events	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
HTN†	25 (9.4)	61 (23.3)*	11 (4.1)	24 (9.1)*
Infections	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis†	7 (2.6)	17 (6.5)*	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

†2-sided P-value for event comparisons <0.05 without multiplicity adjustment. *Higher incidence indicated for terms with statistical differences.
AE, adverse events; HTN, hypertension; R/R CLL, relapsed/refractory chronic lymphocytic leukemia;.
Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-52.

© 2024

Safety of Ibrutinib vs Zanubrutinib in R/R CLL/SLL (2/2)

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, months	38.3 (0.4, 54.9)	35.0 (0.1, 58.4)
Any grade adverse event	320 (98.8)	323 (99.7)
Grade 3 to 5	235 (72.5)	251 (77.5)
Grade 5	41 (12.7)	40 (12.3)
Serious adverse event	165 (50.9)	191 (59.0)
Adverse event leading to:		
Dose reduction	47 (14.5)	59 (18.2)
Dose interruption	196 (60.5)	201 (62.0)
Treatment discontinuation	64 (19.8)	85 (26.2)
Hospitalization	150 (46.3)	180 (55.6)

R/R CLL, relapsed/refractory chronic lymphocytic leukemia/small lymphocytic leukemia.

Brown JR, et al. Presented at: 65th American Society of Hematology Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA. Paper No. 0202.

© 2024

Safety of Acalabrutinib in R/R CLL (1/2)

TEAEs observed in ≥10% of patients in any treatment group or grade ≥3 in ≥5% of any treatment group	Acalabrutinib (n=154)		I+R (n=118)		B+R (n=35)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
All	48 (31)	22(14)	59 (50)	42 (36)	8 (23)	7 (20)
Neutropenia	14 (9)	10 (6)	24 (20)	23 (19)	5 (14)	6 (17)
Diarrhea	2 (1)	0	26 (22)	2 (2)	0	0
Pyrexia	1 (1)	0	7 (6)	1 (1)	1 (3)	0
Cough	0	0	1 (1)	0	0	0
Upper respiratory tract infection	3 (2)	0	4 (3)	0	1 (3)	0
Headache	1 (1)	0	0	0	0	0
Thrombocytopenia	2 (1)	4 (3)	7 (6)	2 (2)	0	1 (3)
Anemia	16 (10)	2 (1)	8 (7)	0	3 (9)	0
Fatigue	2 (1)	0	0	0	1 (3)	0
Nausea	0	0	1 (1)	0	0	0
Pneumonia	8 (5)	0	10 (8)	0	1 (3)	0
Rash	0	0	4 (3)	0	0	0

B, bendamustine; I, ibrutinib; TEAE, treatment-emergent adverse events; R, rituximab.
Ghia P, et al. J Clin Oncol. 2020 Sep 1;38(25):2849-2861.

© 2024

Safety of Acalabrutinib in R/R CLL (2/2)

AE	No. of patients with ibrutinib intolerance[a]	Total	Acalabrutinib experience for same patient		
			Lower grade	Same grade	Higher grade
Atrial fibrillation	16[b]	2	2	0	0
Diarrhea	7	5	3	2	0
Rash	7	3	3	0	0
Bleeding[c,d]	6	5	3	2	0
Arthralgia	7[e]	2	1	1	0
Total16	41	24	18	6	1

[a]Among 60 patients meeting the study enrollment criteria, 41 patients had a medical history of one or more (43 events in total) of the following categories of ibrutinib-intolerance events: atrial fibrillation, diarrhea, rash, bleeding, or arthralgia. [b]Includes patients with atrial flutter (n=2). [c,d]Events categorized as bleeding including in ecchymosis, hemorrhage, epistaxis, contusion, hematuria, and subdural hematoma. All but one patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib treatment. [e]Includes on patient with arthritis.
AE, adverse events.
Rogers KA, et al. *Haematologica*. 2021 Sep 1;106(9):2364-2373.

© 2024

Safety of Zanubrutinib in R/R CLL (1/2)

NEXT

AEs occurring in at least 10% of patients, or grade 3 or worse in at least 5% of patients in any group	Zanubrutinib (n=240*)			B-R (n=227†)			Zanubrutinib (n=111)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Any	87 (35%)	28 (36%)	11 (5%)	88 (39%)	81 (36%)	12 (5%)‡	48 (43%)	10 (9%)	3 (3%)
Serious	49 (20%)	12 (5%)	11 (5%)	70 (31%)	19 (8%)	12 (5%)	34 (31%)	1 (1%)	3 (3%)
All bleeding adverse events¶	8 (3%)	0	1 (<1%)	3 (1%)	1 (<1%)	0	6 (5%)	0	0
All cardiac adverse events¶	10 (4%)	0	2 (1%)	9 (4%)	1 (<1%)	1 (<1%)	3 (3%)	1 (1%)	1 (1%)

*One patient in group A did not receive zanubrutinib and is not included in the safety analysis. †11 patients did not receive bendamustine–rituximab and are not included in the safety analysis. ‡Includes one patient who had a grade 5 event (confusion) that began prior to but ended after the data cutoff. §Due to amphotericin B infusion. ¶Grouped analyses.
AE, adverse events; R/R CLL, relapsed/refractory chronic lymphocytic leukemia.
Tam CS et al. Lancet Oncol. 2022 Aug;23(8):1031-1043. doi: 10.1016/S1470-2045(22)00293-5.

© 2024

Safety of Zanubrutinib in R/R CLL (2/2)

Grade ≥3 adverse events reported in >2% of the patients in either trial group	Zanubrutinib (N=324)	Ibrutinib (N=324)
Neutropenia	52 (16.0)	45 (13.9)
Hypertension	48 (14.8)	36 (11.1)
Covid-19–related pneumonia	23 (7.1)	13 (4.0)
Covid-19	22 (6.8)	16 (4.9)
Pneumonia	19 (5.9)	26 (8.0)
Decreased neutrophil count	17 (5.2)	14 (4.3)
Syncope	9 (2.8)	4 (1.2)
Thrombocytopenia	9 (2.8)	12 (3.7)
Anemia	7 (2.2)	8 (2.5)
Atrial fibrillation	6 (1.9)	12 (3.7)

AE, adverse events.
Brown JR, et al. N Engl J Med. 2023 Jan 26;388(4):319-332.

© 2024

Covalent BTK Inhibitor TEAEs

- Thrombocytopenia
- Neutropenia
- Atrial fibrillation/flutter
- Infection
- Bleeding
- Hypertension
- Fatigue
- Rash

Commonly occurs with:
- Ibrutinib
- Zanubrutinib
- Acalabrutinib

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR

- Assess during each visit and more frequently as needed
- Monitor for signs of atrial fibrillation, bleeding, hypertension during treatment

MITIGATE SYMPTOMS

- Administer direct oral anticoagulants and discontinue BTK inhibitor if atrial fibrillation not controlled
- Use antihypertensive medication for hypertension
- Consider prophylaxis for patients at increased risk of opportunistic infection

BTK, Bruton kinase; RTI, respiratory tract infection; TEAEs, treatment-emergent adverse events.

1Wang M et al. *J Clin Oncol*. 2023(3):555-567. Wang M et al. *Leukemia*. 2019(11):2762-2766. Tam CS et al. *Blood Adv*. 2021(12):2577-2585. O'Brien SM et al. *Front Oncol*. 2021(11):720704. Brown JR, et al. *N Engl J Med*. 2023 Jan 26;388(4):319-332. Ghia P, et al. *J Clin Oncol*. 2020 Sep 1;38(25):2849-2861.

© 2024

Safety of Pirtobrutinib in R/R CLL

AE	Grades 3 or 4	Any Grade
Fatigue	2 (1%)	27 (8%)
Diarrhea	0	28 (9%)
Contusion	0	29 (9%)
Neutropenia	17 (5%)	20 (6%)
Nausea	0	10 (3%)
Cough	0	2 (1%)

AE of special interest	Grades 3 or 4	Any Grade
Bruising	0	37 (12%)
Rash	0	18 (6%)
Arthralgia	0	5 (2%)
Hemorrhage	0	5 (2%)
Hypertension	0	4 (1%)
Atrial fibrillation or flutter	0	0

AE, adverse events.
Mato AR, et al. *Lancet*. 2021(397): 892-901.

© 2024

Non-Covalent BTK Inhibitor TEAEs

- Thrombocytopenia
- Neutropenia
- Atrial fibrillation/flutter
- Infection
- Bleeding
- Hypertension
- Fatigue
- Pneumonia

Commonly occurs with:
- Pirtobrutinib

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR

- Assess during each visit and more frequently as needed
- Monitor for signs of hypertension during treatment

MONITOR SYMPTOMS

- Administer direct oral anticoagulants and discontinue BTK inhibitor if atrial fibrillation not controlled
- Use antihypertensive medication for hypertension
- Suggest use of Imodium for diarrhea symptoms
- Provide appropriate and prompt intervention by grading of rash symptoms

TEAE, treatment-emergent adverse events.
Wang M et al. *J Clin Oncol*. 2023(3):555-567.

© 2024

Safety of Venetoclax in R/R CLL (1/2)

Grade 3 or 4 AE	All patients (N=158)
	119 (75)
Neutropenia	63 (40)
Thrombocytopenia	23 (15)
Anemia	23 (15)

Serious AE	All patients (N=158)
	91 (58)
Pneumonia	16 (10)
Autoimmune hemolytic anemia	8 (5)
Pyrexia	8 (5)
Febrile neutropenia	7 (4)
Tumor lysis syndrome	5 (3)
Anemia	5 (3)
Neutropenia	4 (3)
Thrombocytopenia	4 (3)
General physical health deterioration	4 (3)

AE, adverse events; R/R CLL, relapsed/refractory chronic lymphocytic leukemia.
Stilgenbauer S, et al. *J Clin Oncol*. 2018 Jul 1;36(19):1973-1980.

© 2024

Safety of Venetoclax in R/R CLL (2/2)

AE	Grade 3	Grade 4	Grade 5
Anemia	26 (29%)	0	0
AHA	0	2 (2%)	0
Febrile neutropenia	12 (13%)	0	0
Neutropenia	18 (20%)	28 (31%)	0
Thrombocytopenia	11 (12%)	15 (17%)	0
CRS	1 (1%)	0	1 (1%)
Hypertension	6 (7%)	0	0
Fatigue	4 (4%)	2 (2%)	0
Pneumonia	5 (5%)	1 (1%)	0
UTI	1 (1%)	1 (1%)	0

AE, adverse events; AHA, autoimmune hemolytic anemia; CRS, cytokine release syndrome; R/R CLL, relapsed/refractory chronic lymphocytic leukemia; urinary tract infection.

Jones JA, et al. Lancet Oncol. 2018 Jan;19(1):65-75.

© 2024

Safety of Venetoclax + rituximab in R/R CLL

No new SAEs related to study drug at 5-year follow-up	
3 additional second primary malignancies	BR, n=1 melanoma VenR, n=2 melanoma and breast cancer
No new reports of Richter transformation after an additional 12-month follow-up	VenR, n=7 BR, n=6

BR, bendamustine; R/R CLL, relapsed/refractory chronic lymphocytic leukemia; SAE, serious adverse events; VenR, venetoclax + rituximab.

Kater AP, et al. *J Clin Oncol*. 2020 Dec 1;38(34):4042-4054.

© 2024

BCL-2 Inhibitor TEAEs

- Thrombocytopenia
- Neutropenia
- Anemia
- Diarrhea
- Fatigue
- Upper RTI
- Nausea
- Headache
- Vomiting

Commonly occurs with:
- Venetoclax

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR

- Assess during each visit and more frequently as needed
- Monitor for signs of infection and bleeding during treatment

MITIGATE SYMPTOMS

- Use prophylactic measures to reduce opportunistic infection and tumor lysis syndrome
- Delays between venetoclax cycles may be need to address cytopenia and neutropenia
- Consider venetoclax dosing adjustment to address cytopenia
- Avoid grapefruit products to avoid CYP3A4 inhibitors

RTI, respiratory tract infection; TEAE, treatment-emergent adverse events.

Davids MS et al. *Clin Cancer Res*. 2022(17):4690-4695. Richard-Carpentier G et al. *Ther Adv Hematol*. 2019(10): 2040620719882822.

© 2024

Safety of Duvelisib in R/R CLL/SLL

AEs	All Grades		Grade 3 and Above	
	Duvelisib, n (%)	Ofatumumab, n (%)	Duvelisib, n (%)	Ofatumumab, n (%)
Any AEs	156 (99)	144 (93)	138 (87)	75 (48)
Hematologic AEs				
Neutropenia	52 (33)	32 (21)	48 (30)	27 (17)
Anemia	36 (23)	16 (10)	20 (13)	8 (5)
Thrombocytopenia	23 (15)	9 (6)	12 (8)	3 (2)
Nonhematologic AEs				
Diarrhea	80 (51)	19 (12)	23 (15)	2 (1)
Pyrexia	45 (29)	16 (10)	4 (3)	1 (1)
Nausea	37 (23)	17 (11)	0	0
Cough	33 (21)	22 (14)	2 (1)	0

AE, adverse events.
Flinn IW, et al. *Blood*. 2018 Dec 6;132(23):2446-2455.

© 2024

Safety of Idelalisib in R/R CLL

NEXT

AE of Interest	IDELA/R (n=110)		Placebo/R (n=110)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Diarrhea	32 (29.1)	10 (9.1)	19 (17.6)	0
Colitis	8 (7.3)	5 (4.5)	1 (0.9)	0
Pyrexia	55 (40.0)	3 (2.7)	20 (18.5)	1 (0.9)
Rash	27 (24.5)	4 (3.6)	7 (6.5)	1 (0.9)
Pneumonitis	6 (5.5)	4 (3.6)	1 (0.9)	1 (0.9)
Febrile neutropenia	5 (4.5)	5 (4.5)	6 (5.6)	5 (4.6)
PJP	4 (3.6)	4 (3.6)	1 (0.9)	1 (0.9)
CMV	1 (0.9)	0	0	0

AE, adverse events; CMV, cytomegalovirus; IDELA, idelalisib; PJP, pneumocystis jirovecii pneumonia; R/R CLL, relapsed/refractory chronic lymphocytic leukemia.
Sharman JP, et al. *J Clin Oncol*. 2019 Jun 1;37(16):1391-1402.

© 2024

Phosphoinositide 3-kinase (small molecule) inhibitors TEAEs

- Thrombocytopenia
- Neutropenia
- Anemia
- Diarrhea
- Colitis
- Pneumonitis
- Fatigue
- Nausea
- Pyrexia

Commonly occurs with:
- Duvelisib
- Idelalisib

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)

MONITOR

- Assess during each visit and more frequently as needed
- Be familiar with black box warnings for both agents:
  - FATAL AND SERIOUS TOXICITIES: INFECTIONS, DIARRHEA OR COLITIS, CUTANEOUS REACTIONS, AND PNEUMONITIS
- PJP and antiviral prophylaxis as well as CMV monitoring in all patients treated with idelalisib

MITIGATE SYMPTOMS

- Intermittent dosing or combine PI3K inhibitors with another novel agent as a continuous regimen or a fixed duration regimen, such as CAR T-cell therapy

CMV, cytomegaly virus; PJP, *Pneumocystis jirovecii* pneumonia; TEAE, treatment-emergent adverse events.

Flinn IW, et al. *Blood*. 2018 Dec 6;132(23):2446-2455. Sharman JP, et al. *J Clin Oncol*. 2019 Jun 1;37(16):1391-1402. Skånland SS, et al. *Haematologica*. 2023 Jan 1;108(1):9-21.

© 2024

Misperceptions Regarding CAR T-cell Therapy

CAR T-cell therapy does not have to be a last resort and can be explored earlier in therapy

Serious toxicities (AEs) are typically managed in the acute post infusion period (while still at CAR T site)

Long-term follow-up, while required, is not as extensive as during the initial treatment and often can be performed by referring provider (with support of CAR T center)

Insurance status and support network should not be deterrents to initiating CAR T referrals

There are support services to address emotional, financial, and logistic concerns

Hesitancy to participate in clinical trials should be addressed using an evidence-based, unbiased approach

Bixby TJ, et al. *Oncol Ther*. 2023 Sep;11(3):303-312. Li W, et al. *Ann Transl Med*. 2020 Sep;8(17):1093. Hoffmann MS, et al. *Transplant Cell Ther*. 2023 Jul;29(7):440-448.

© 2024

Strategies to Optimize Multidisciplinary, Interprofessional Collaboration With Community Oncologists

- Routinely provide patient education about what to expect before, during, and after CAR T-cell therapy
- Make timely and appropriate referrals for patients who could benefit from CAR T-cell therapy
- Assess patient/caregiver needs and familiarize yourselves with services and therapies available at outside centers
- Learn how to recognize and monitor for treatment-related toxicities including emergencies
- Be familiar with assistance for patient logistics throughout the CAR T process, including transportation, housing, finances, etc.
- Understand the role of each member within the team

Beaupierre A, et al. *J Adv Pract Oncol*. 2019 May-Jun;10(Suppl 3):29-40.

© 2024

Increasing Patient Participation in Clinical Trials

Lack of diversity is a barrier to the interpretation of safety and efficacy data across population subgroups, which is imperative in reducing disparities and advancing health equity

Barriers

- Medical mistrust
- Trial availability
- Patient acess
- Patient eligibility criteria
- Enrollment practices
- Negative beliefs, norms, and attitudes

Solutions

- Provide patient education to increase interest
- Incorporate engagement among academic, community, government, and industry stakeholders
- Increase clinical trial center locations
- Utilize digital tools to improve accessibility of clinical research
- Improve representation among investigators and clinical research staff

Gray DM et al. *Lancet Gastroenterol Hepatol*. 2021(8):605-607. Kelsey MD et al. *Contemp Clin Trials*. 2022(116):106740.

© 2024

Ongoing Clinical Trials and Emerging Immunotherapy Options

CAR T-cell Options

- Dual targeting CAR T, targeting multiple antigens to reduce risk of antigen-negative relapse
- New and improved autologous CAR T with alternative manufacturer strategies
- Allogeneic or "off-the-shelf" CAR T-cell therapies
- Moving CAR T treatment earlier
- Point-of-care manufacture at clinical sites

Other Emerging Options

- Bispecific antibodies, including CELMoDs
- BCL2 antagonists
- Zilovertamab vedotin
- Proteolysis targeting chimeras (PROTACS)

Kumar A et al. *Am Soc Clin Oncol Educ Book*. 2022(42):1-15. Thakurta A, et al. *Oncotarget*. 2021 Jul 20;12(15):1555-1563. Castelli S, et al. *Cell Res*. 2022 Dec;32(12):1036-1037.

© 2024

Key Points

- The treatment landscape for NHL is expanding rapidly to include various CAR T-cell therapies and numerous other emerging options
- Engaging patients in shared decision-making is crucial to optimize the selection of therapy based on patient- and disease-specific factors
- The need for a multidisciplinary approach between referring and outpatient community centers is crucial as treatment modalities continue to evolve

Paolo Caimi, MD

Catherine Coombs, MD

Christopher Flowers, MD

Copyright 2024 © Medical Learning Institute Inc.