What is new in the relapsed/refractory indolent lymphoma landscape?

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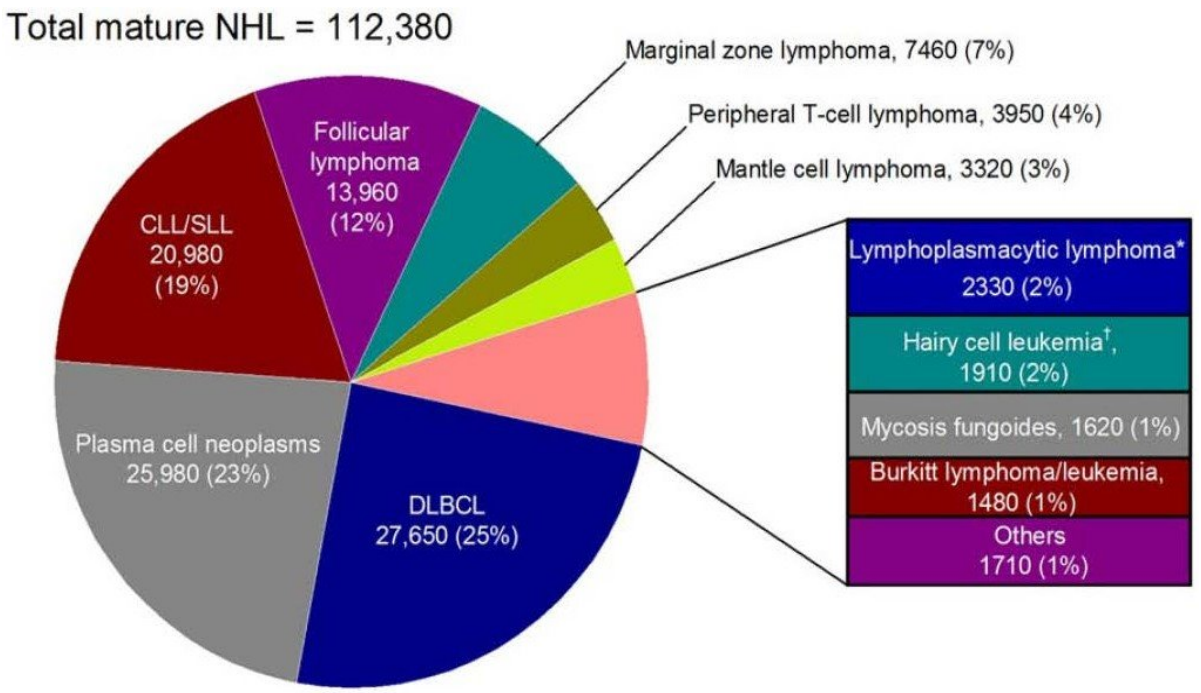
3/1/2025

Disclosures

No disclosures to report

What are indolent lymphomas?

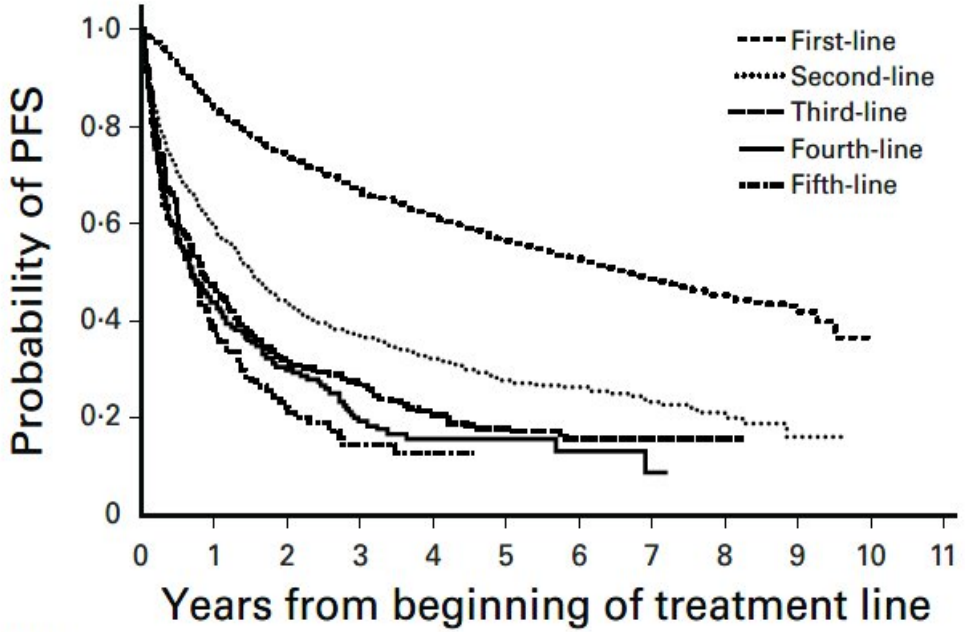
- NHL accounts for 4% of all cancers
- Incidence rates have declined by about 1% per year for NHL since 2015
- From 2013-2022, death rate decreased by 2% per year
- Indolent lymphoma subtypes progress slowly
- Up to 40% of all NHL cases in US can be considered indolent
- Follicular lymphoma most common indolent subtype, followed by marginal zone lymphoma



Teras & Flowers. CA Cancer J Clin. 2016;66:443-459.
https://www.lls.org/lymphoma/non-hodgkin-lymphoma/nhl-subtypes/treatment-indolent-nhl-subtypes

Each relapse leads to shorter PFS

- While treatable, course generally characterized by periods of remission followed by relapse
- PFS decrease most pronounced after 1st relapse

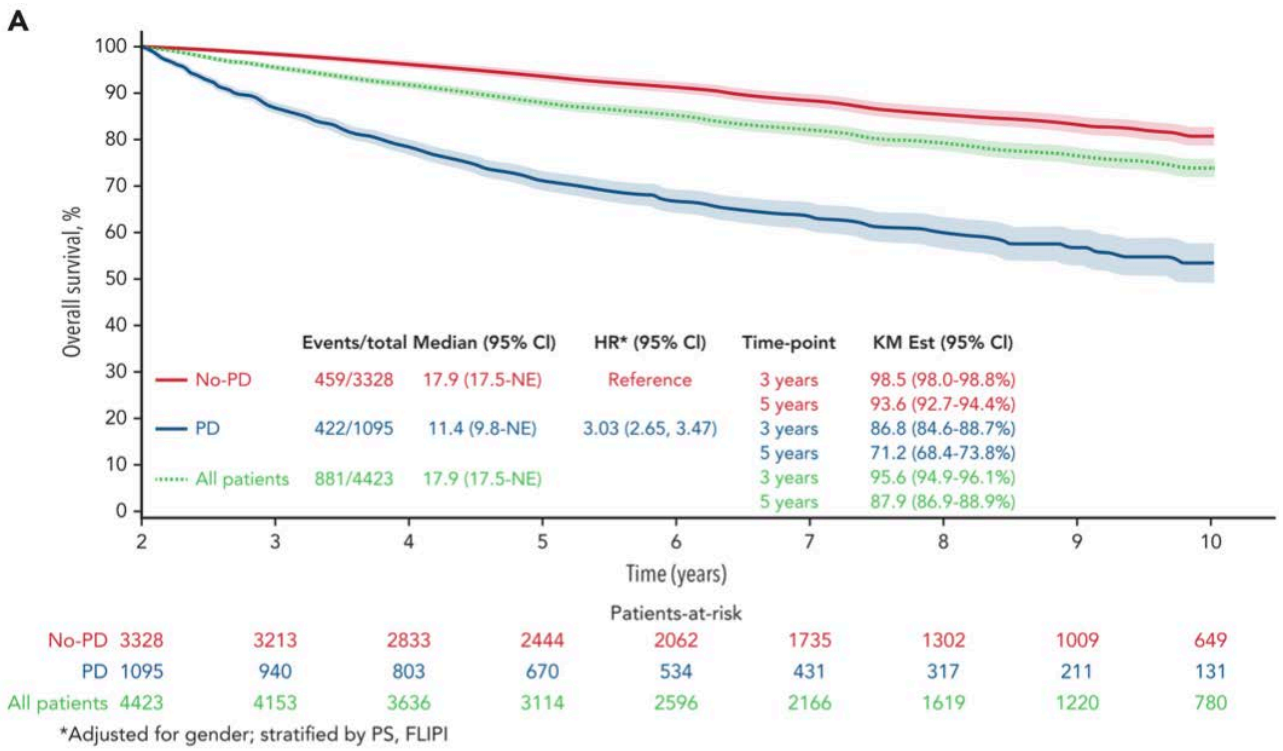


No. at risk												
First-line	2429	1916	1602	1381	1202	1035	869	635	329	96	1	0
Second-line	889	489	331	256	199	137	104	57	24	5	0	
Third-line	438	181	109	78	50	30	18	5	1	0		
Fourth-line	229	91	49	24	14	8	3	1	0			
Fifth-line	123	42	19	9	5	0						

Link & Friedberg. Br J Haematol. 2019;184:660.

Time to relapse predicts poor outcomes

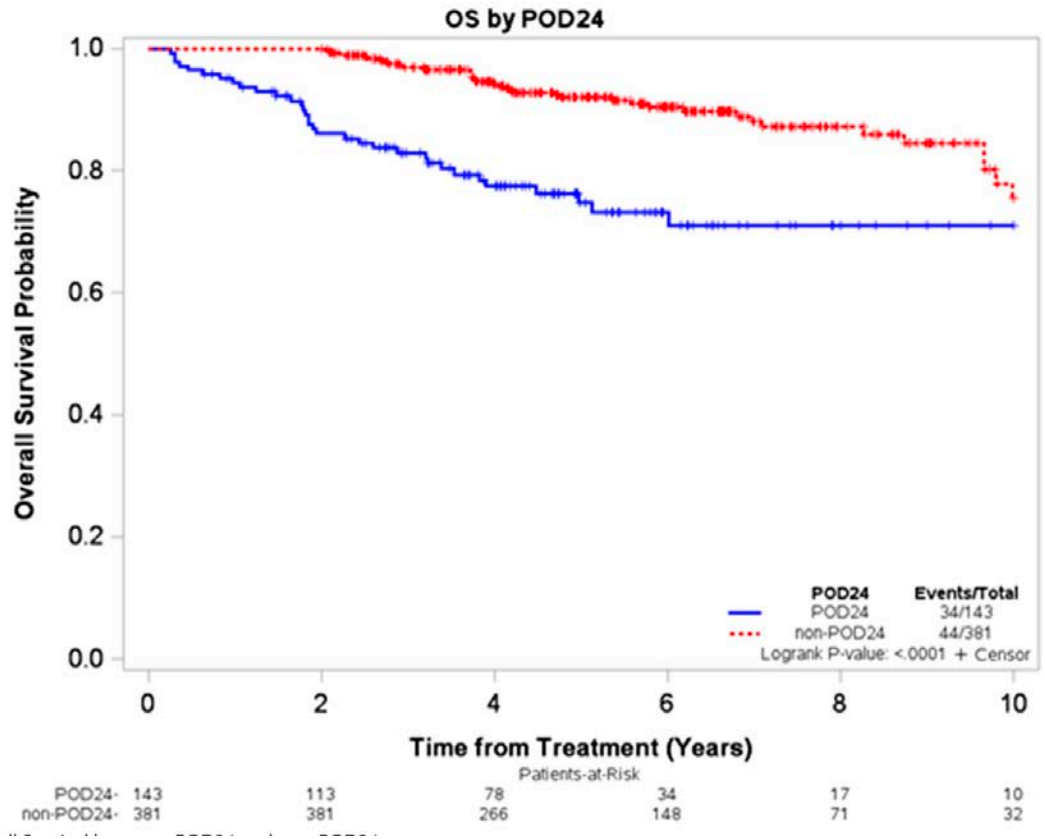
- POD24
- Of 5225 patients evaluated nearly 1/3 (29.3%) had disease progression by 24 months
- While effect of POD on OS was seen among all types of treatment, most pronounced in those who received R-chemo



Casulo et al. Blood (2022) 139 (11); 1684-1693.

Seen across other indolent lymphoma subtypes

- MZL POD24
- Patients with POD24 had inferior OS, regardless of type of systemic therapy received
- Had higher rates of transformation compared to those who did not have progression within 24 months of treatment



Epperla et al. J Hematol Oncol 16, 49 (2023).

Do all relapses require treatment?

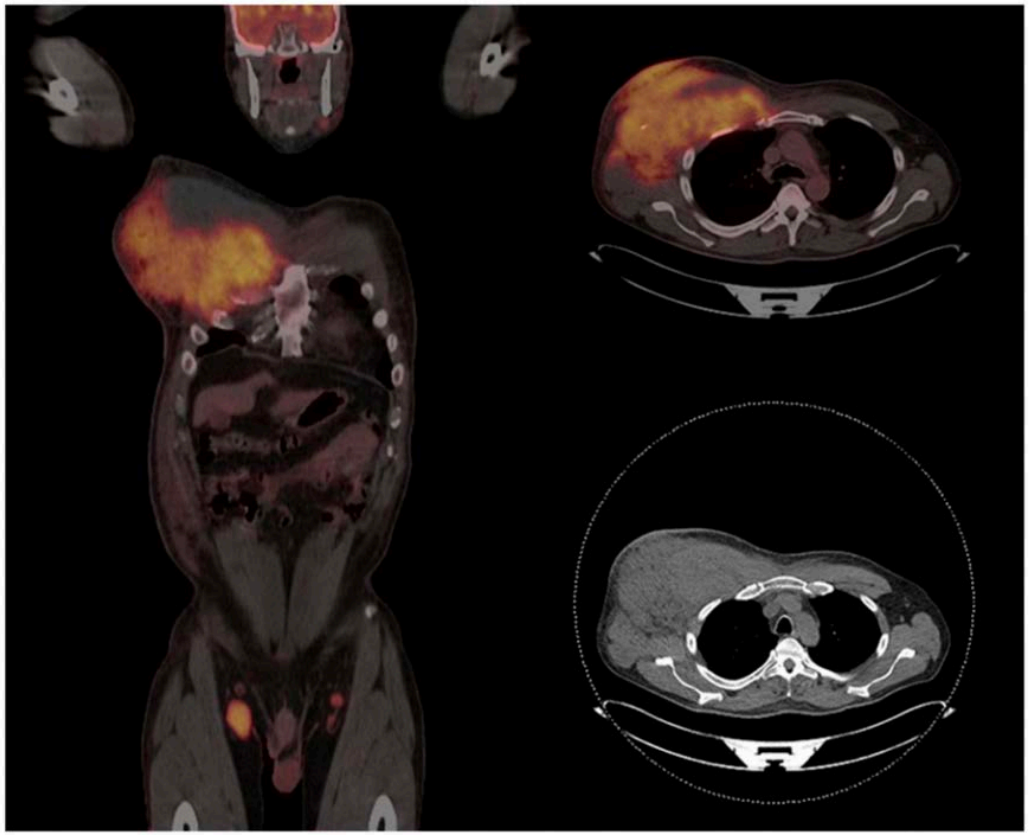
- Not necessarily
- Most asymptomatic patients can be closely observed

GELF Criteria
Tumor >7cm
≥ 3 nodal sites (each >3cm)
B symptoms
splenomegaly
Compression syndrome
Pleural effusions or ascites
Leukemic phase
Cytopenias

Barraclough et al. Blood (2019) 134 (supplement_1); 3986.

No…but make sure it is still indolent

- Roughly 14% of FL patients experienced transformation with 6.8 years median follow up
- When to an indolent lymphoma has transformed
  - Rapidly enlarging adenopathy
  - PET with higher SUV than expected in indolent lymphoma
  - Significantly elevated LDH
- May not be able to be biopsied
- Treat like an aggressive B cell lymphoma



Smith *Hematology Am Soc Hematol Educ Program* (2020) 2020 (1); 306-311.

Your patient with relapsed FL meets indication for treatment

Now what?

Second line treatment FL

SECOND-LINE THERAPY[h]

Preferred regimens (in alphabetical order)
- Bendamustine[d,i] + obinutuzumab[j] or rituximab (not recommended if treated with prior bendamustine)
- CHOP + obinutuzumab[j] or rituximab
- CVP + obinutuzumab[j] or rituximab
- Lenalidomide + rituximab
- Tafasitamab-cxix[k] + lenalidomide + rituximab (≥1 prior systemic therapy including an anti-CD20 mAb)

Other recommended regimens (in alphabetical order)
- Lenalidomide (if not a candidate for anti-CD20 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/m^2 weekly for 4 doses)
- Tazemetostat[l] (irrespective of *EZH2* mutation status)

Other recommended regimen
- Cyclophosphamide ± rituximab

SECOND-LINE EXTENDED THERAPY (optional)

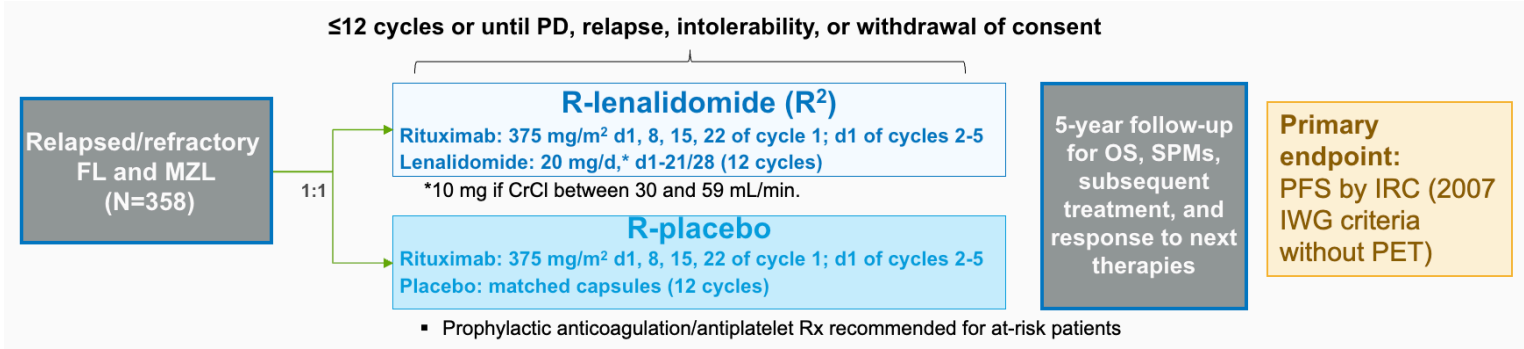
Preferred regimens
- Rituximab maintenance 375 mg/m^2 one dose every 12 weeks for 2 years (category 1)
- Obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for total of 12 doses)

SECOND-LINE CONSOLIDATION THERAPY (optional)

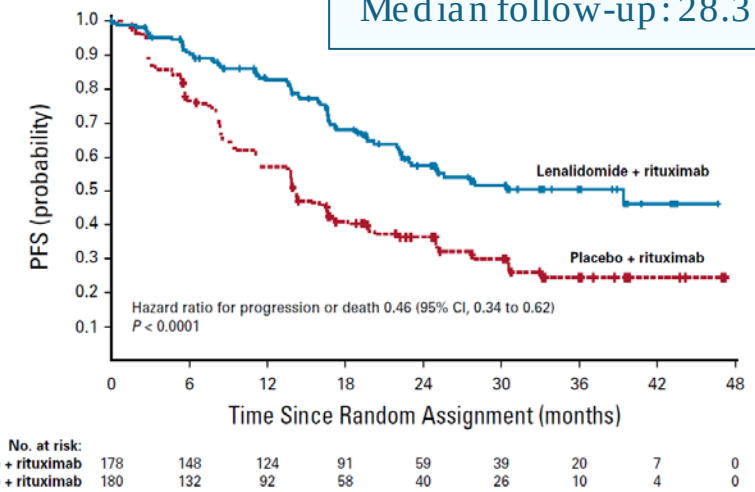
- High-dose therapy with autologous stem cell rescue (HDT/ASCR)

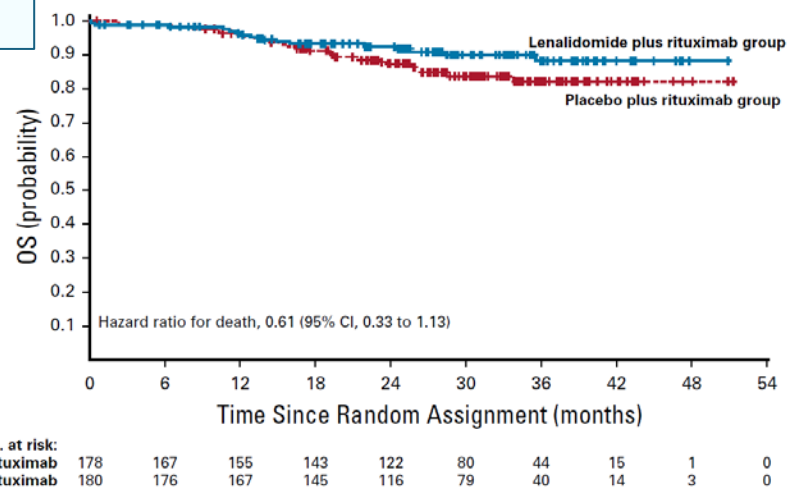
R^2: AUGMENT trial

- Phase 3 study of R^2 vs R in R/R FL and MZL
- Inclusion Criteria:
  - R/R MZL or FL (grades 1-3a) in need of treatment
  - ≥1 prior chemotherapy, immunotherapy or chemoimmunotherapy and ≥2 previous doses rituximab
  - Cannot be refractory to rituximab



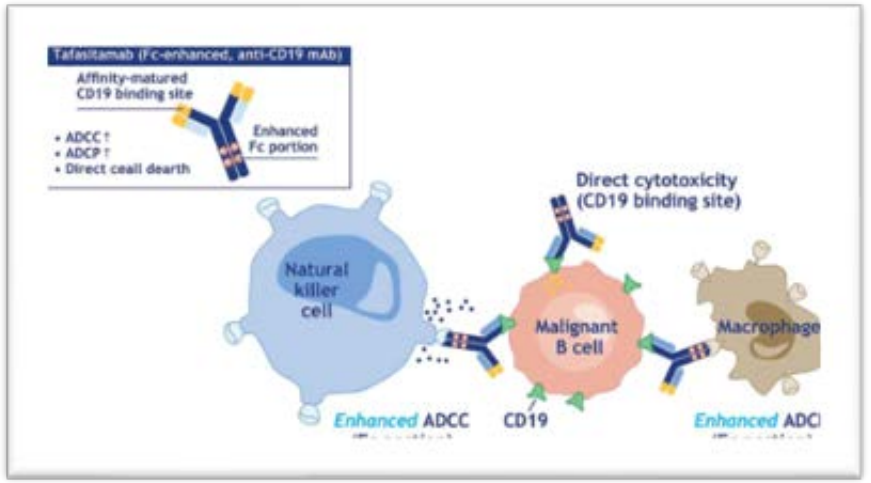
Median follow-up: 28.3 months





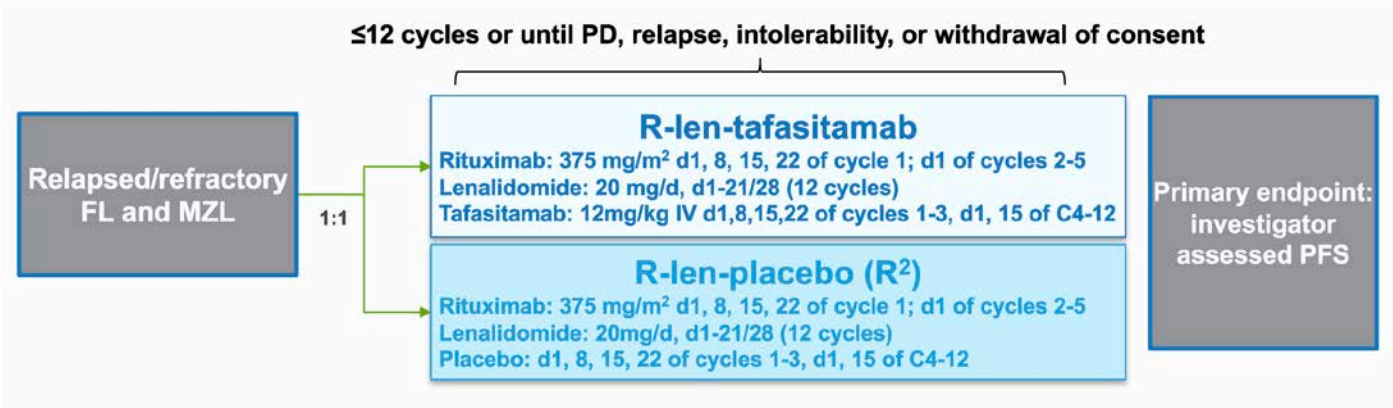
Leonard et al. JCO 37, 1188-1199 (2019).

Tafa-len-R: inMIND trial



Inclusion Criteria:

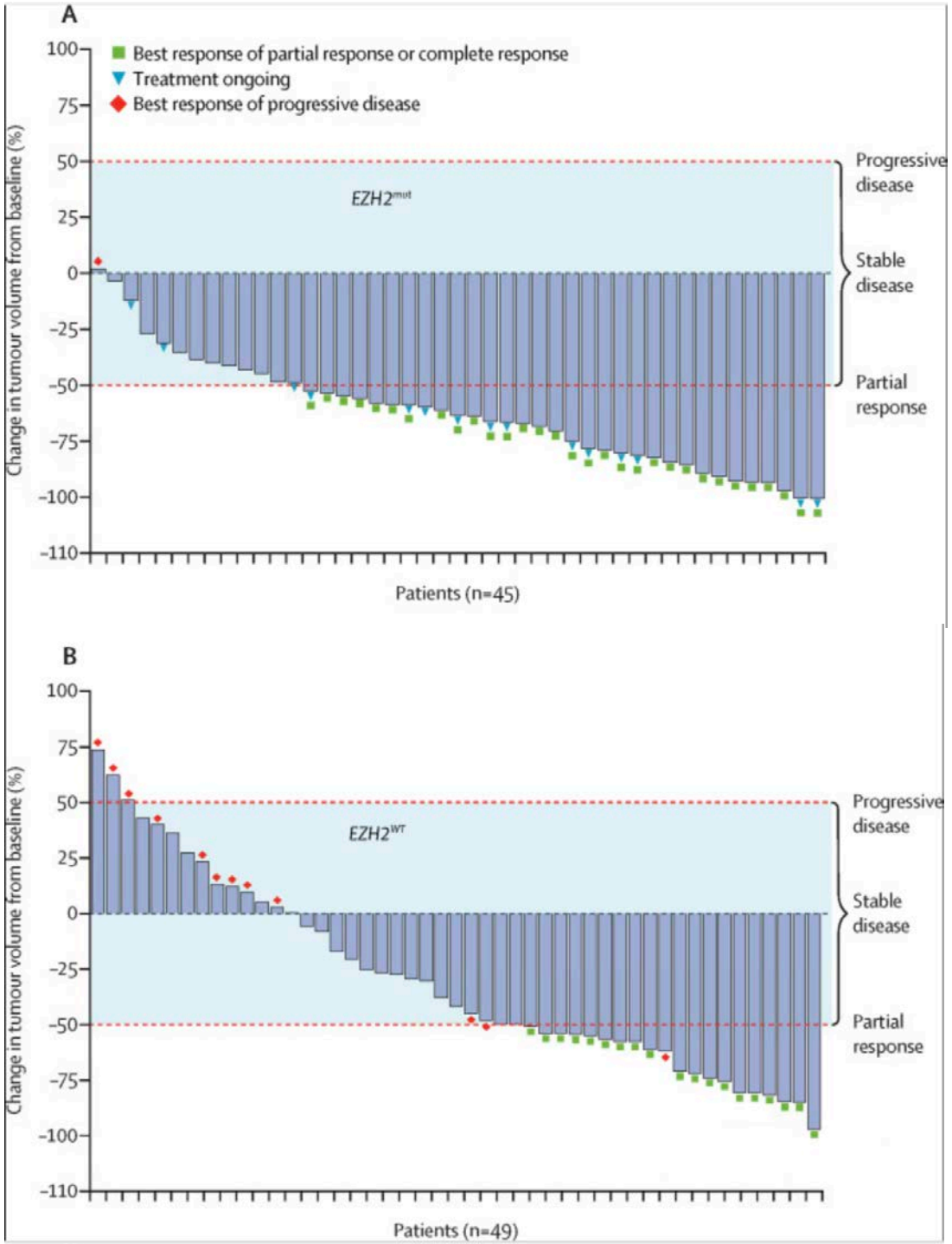
- ≥18 years with R/R CD19+ and CD20+ FL (grade 1-3A)
- ECOG ≤2
- Requiring treatment after ≥1 prior systemic therapy including an anti-CD20 mAB



- With median follow up of 14.1 months, results in lower risk of progression, relapse, or death vs placebo
- Median PFS not reached with tafa-len-R vs placebo (16.0 months)
- OS data was immature but trend favoring tafa (HR [95 % CI] 0.59 [0.31, 1.13]

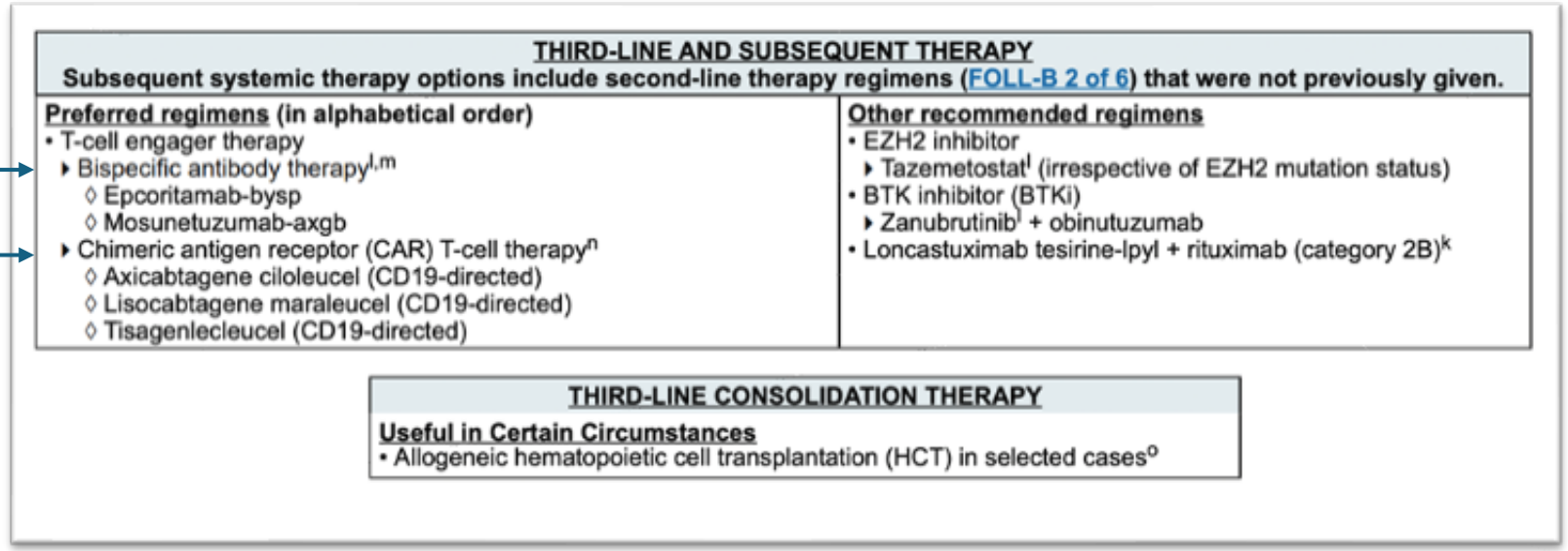
Tazemetostat

- First-in-class, oral EZH2 inhibitor
- Single-arm, phase 2 trial
- Inclusion criteria:
  - Patients ≥18 years with FL (grade 1-3b)
  - Relapsed or refractory to >2 systemic therapies
  - Sufficient tumor tissue for central testing of mutation status



Morschhauser et al. Lancet Oncology, 21;11, 1433-1442 (2020).

Third line and beyond



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[l,m]
    - Epcoritamab-bysp
    - Mosunetuzumab-axgb
  - Chimeric antigen receptor (CAR) T-cell therapy[n]
    - Axicabtagene ciloleucel (CD19-directed)
    - Lisocabtagene maraleucel (CD19-directed)
    - Tisagenlecleucel (CD19-directed)

Other recommended regimens

- EZH2 inhibitor
  - Tazemetostat[l] (irrespective of EZH2 mutation status)
- BTK inhibitor (BTKi)
  - Zanubrutinib[l] + obinutuzumab
- Loncastuximab tesirine-lpyl + rituximab (category 2B)[k]

THIRD-LINE CONSOLIDATION THERAPY

Useful in Certain Circumstances

- Allogeneic hematopoietic cell transplantation (HCT) in selected cases[o]

CAR-T products approved for FL

Axicabtagene ciloleucel (Yescarta)

- ZUMA-5
  - Inclusion criteria: r/r FL (grade 1-3a) or MZL (nodal and extranodal) with 2 or more lines of previous therapy
  - Primary endpoint: ORR

Tisagenlecleucel (Kymriah)

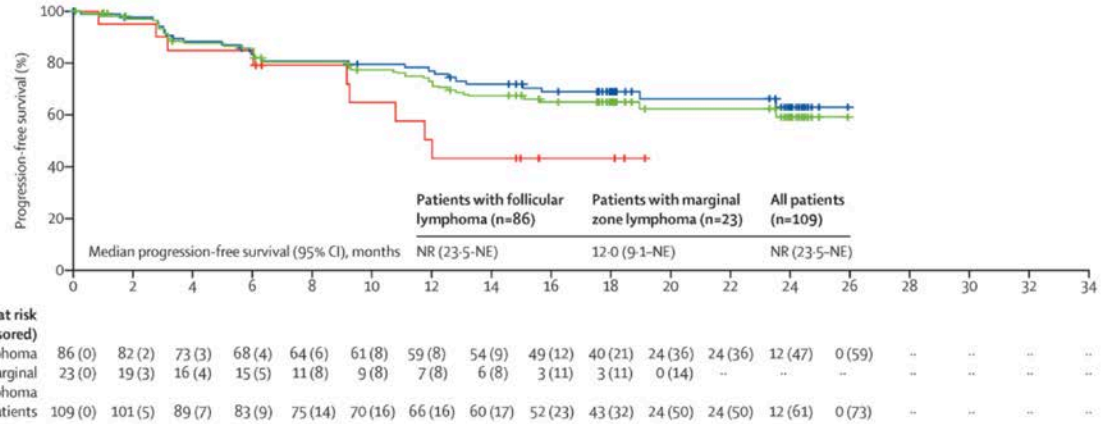
- ELARA
  - Inclusion criteria: r/r FL (grade 1-3a) with 2 or more lines of previous therapy
  - Primary endpoint: CR

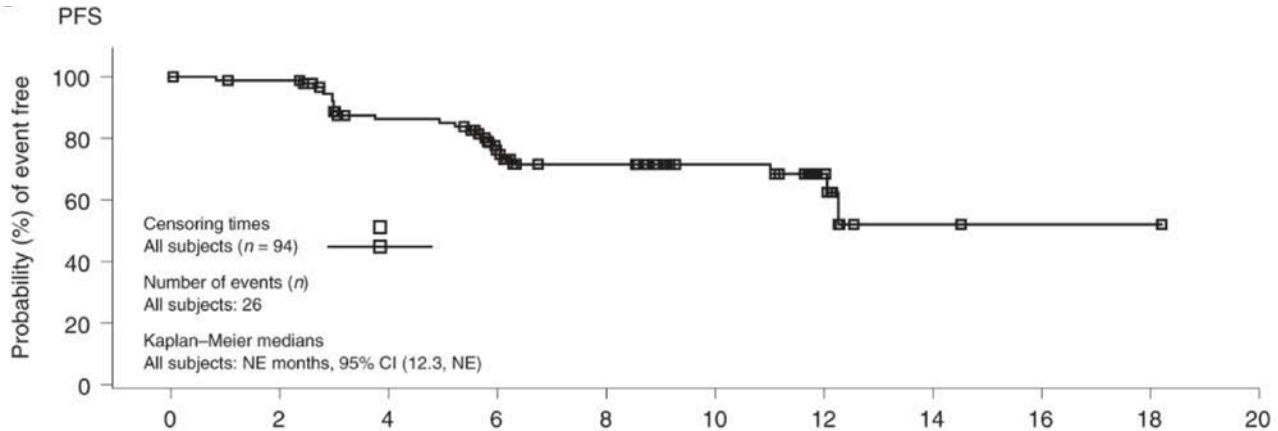
Lisocabtagene maraleucel (Breyanzi)

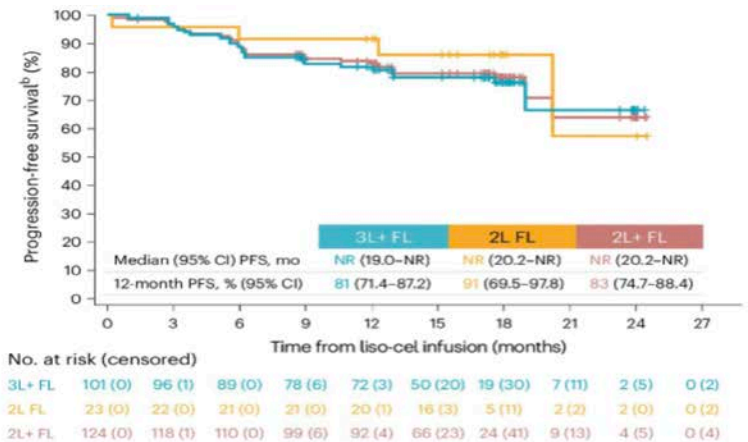
- TRANSCEND
  - Inclusion Criteria: r/r FL with 2 or more lines of therapy OR FL with 1 prior line of therapy with high risk disease (POD24 or mGELF)
  - Primary endpoint: ORR

Morschhauser et al. Nature Medicine 30, 2199-2207 (2024).
Jacobson et al. The lancet Onc 23 1 91-203 (2022).
Fowler et al. Nat Med. 2022; 28(2):325-332.

Study	ORR/CR	Median PFS
ZUMA-5 (Yescarta)	ORR: 92%; (95% CI, 85-97) CRR: 79%	Not reached (18-month estimated PFS 64.8%)
ELARA (Kymriah)	ORR: 86.2% (95% CI, 77.5-92.4) CR 69%	Not reached (12-month PFS 67%)
TRANSCEND (Breyanzi)	ORR: 97% (95% CI, 91.6–99.4) CR: 94%	Not reached (12-month PFS 81%)







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Foweler et al. Nat Med. 2022; 28(2):325-332.

Adverse Effects

Product	CRS (grade ≥3)	ICAN (grade ≥3)
Yescarta	78% (6%)	56% (18%)
Kymriah	48.5% (0%)	23% (1%)
Breyanzi	58% (1%)	15% (2%)

Morschhauser et al. Nature Medicine 30, 2199-2207 (2024).
Jacobson et al. The lancet Onc 23 1 91-203 (2022).
Foweler et al. Nat Med. 2022; 28(2):325-332.

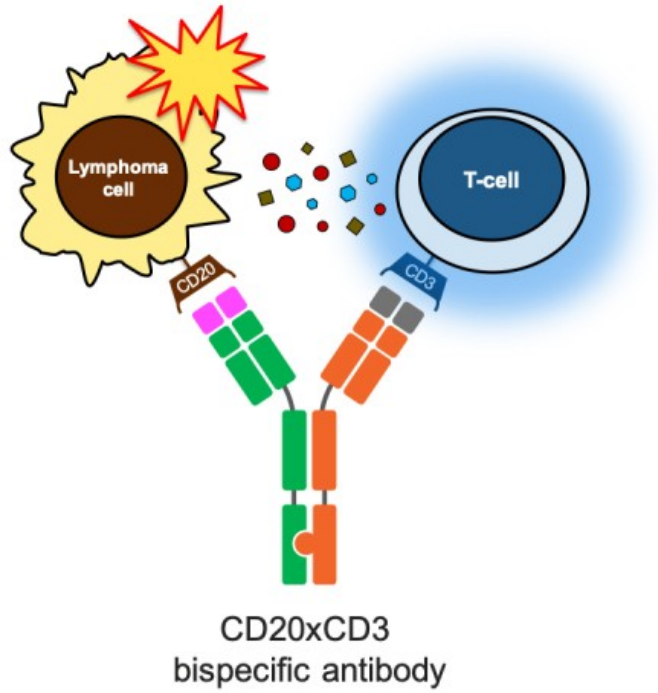
Bispecific Antibody Therapy

Mosunetuzumab

- FDA approval: December 2022

Epcoritamab

- FDA approval: June 2024



https://www.mskcc.org/clinical-updates

Mosunetuzumab

ORR (CR): 80% (60.0%)

18 month PFS: 47%

CRS: 44% (majority grade 1-2)

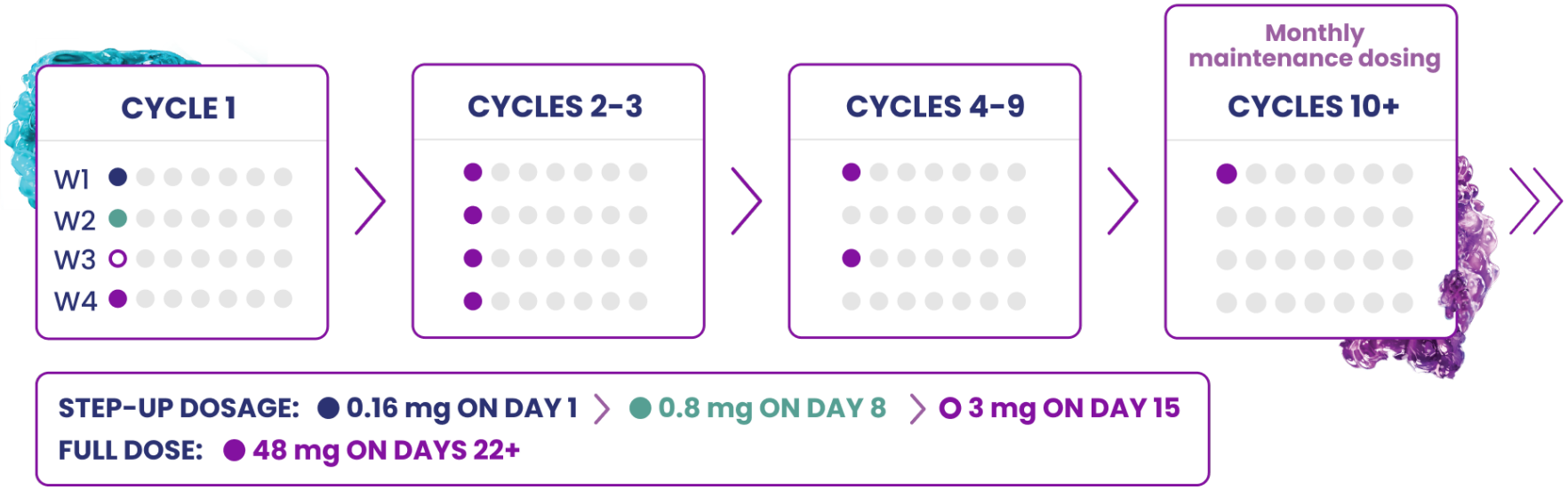
ICAN: 5%

https://www.lunsumio.com/taking-lunsumio/how-to.html

Budde et al. Lancet Oncol 2022; 23: 1055-65

Epcoritamab

- ORR (CR): 82% (60%)
- 18 month PFS: 49.4%
- CRS: 49% (majority grade 1-2)
- ICAN: 6%



https://www.epkinlyhcp.com/fl/dosing-administration

Linton et al. Lancet Haematology, Volume 11, Issue 8, e593-605.

Where did the PI3Kinhibitors go?

- Idelalisib
  - Voluntary withdrawal of FL and SLL indication in 2022
- Copanlisib
  - Voluntary withdrawal of NDA for NHL in 2021
  - Voluntary withdrawal from market for FL in 2023
- Duvelisib
  - Voluntary withdrawal of FL indication in 2021
- Umbralisib
  - Voluntary withdrawal from the market for FL and MZL in 2022

Relapsed/refractory MZL

Similar to FL with some key differences

SECOND-LINE AND SUBSEQUENT THERAPY

Preferred regimens (in alphabetical order)
- Bendamustine[d] + obinutuzumab (not recommended if treated with prior bendamustine)
- Bendamustine[d] + rituximab (not recommended if treated with prior bendamustine)
- BTKis
  - Covalent BTKi
    - ◊ Acalabrutinib[e,f]
    - ◊ Zanubrutinib[e] (after at least one prior anti-CD20 mAb-based regimen)
  - Non-covalent BTKi
    - ◊ Pirtobrutinib (after prior covalent BTKi)[e]
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
- CVP (cyclophosphamide, vincristine, prednisone) + rituximab
- Lenalidomide + rituximab

Other recommended regimens (in alphabetical order)
- Ibrutinib[e,g]
- Lenalidomide + obinutuzumab
- Rituximab (if longer duration of remission)

SECOND-LINE AND SUBSEQUENT THERAPY FOR OLDER OR INFIRM (if combination chemoimmunotherapy is not expected to be tolerable in the opinion of treating physician)

Preferred regimens (in alphabetical order)
- BTKis
  - Covalent BTKi
    - ◊ Acalabrutinib[e,f]
    - ◊ Zanubrutinib[e] (after at least one prior anti-CD20 mAb-based regimen)
  - Non-covalent BTKi
    - ◊ Pirtobrutinib (after prior covalent BTKi)[e]
- Lenalidomide + rituximab
- Rituximab (375 mg/m^2 weekly for 4 doses)

Other recommended regimens (in alphabetical order)
- Chlorambucil ± rituximab
- Cyclophosphamide ± rituximab
- Ibrutinib[e,g]

SECOND-LINE EXTENDED THERAPY (optional)

Preferred regimen
- If treated with bendamustine + obinutuzumab for recurrent disease then obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for total of 12 doses)

SECOND-LINE CONSOLIDATION THERAPY (optional)
- HDT/ASCR

THIRD-LINE AND SUBSEQUENT THERAPY
Subsequent systemic therapy options include second-line therapy regimens (MZL-A 2 of 4) that were not previously given.

Preferred regimen
- CAR T-cell therapy
  - Axicabtagene ciloleucel[h] (CD19-directed) (if not previously given)

THIRD-LINE CONSOLIDATION THERAPY (optional)
- Allogeneic HCT in highly selected cases[i]

What is next?

- Combination therapies
- Moving third line therapies up in the order
- Providing durable first line responses

Conclusion

- While survival is high, relapse is a challenge when treating indolent lymphomas
- Multiple therapies available, sequencing based on patient characteristics
- Other indolent lymphomas often excluded from trials, need for trials including these patients
- Expect new therapies to be approved in the upcoming years

Thank you!

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