IOWA | Carver College of Medicine

Best of ASCO 2024 Lymphoma Abstracts

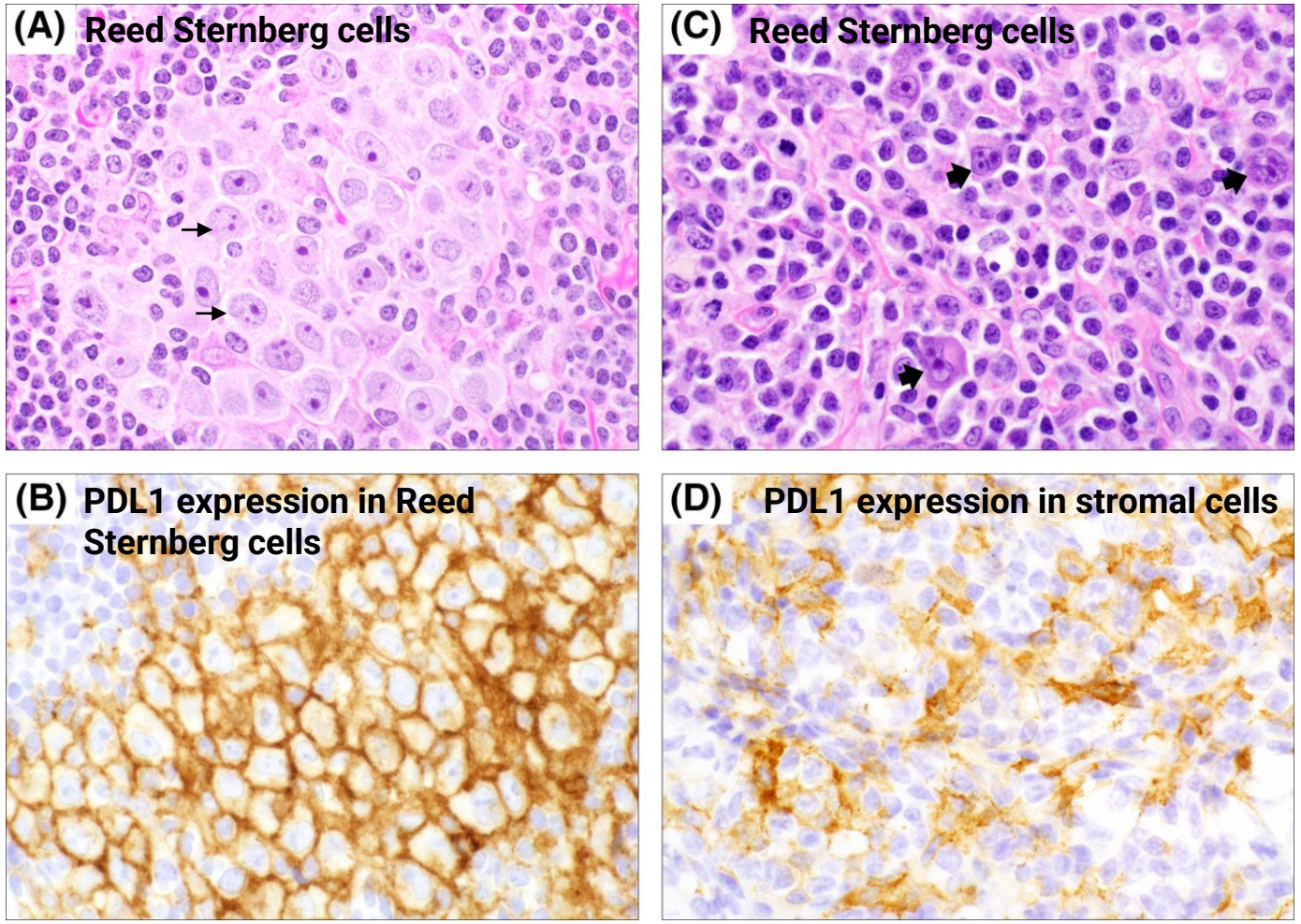
PRESENTED BY: NANMENG YU, MD, PHD, UNIVERSITY OF IOWA

August 24, 2024

Disclosure

- I have no relevant financial relationships with ineligible companies to disclose.

Classical Hodgkin Lymphoma (cHL)



- Bimodal presentation
  - Young adults (age 15-44)
  - Older adults (age >55)
- Histological features
  - Reed-Sternberg cells
  - Immune cell infiltrates
- Immunophenotype
  - CD30+
  - CD15+
  - PDL1+ and/or PDL2+

Wang, Hao-Wei, et al. *British journal of haematology* 184.1 (2019): 45-59.

Early Stage cHL

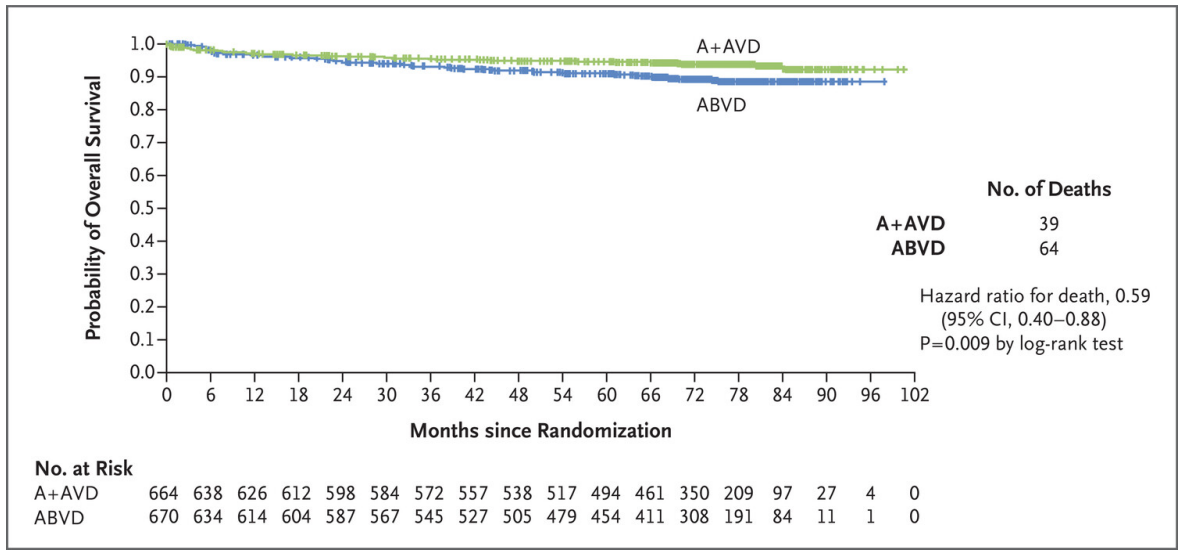
- Early stage favorable (HD10)
  - ABVD x 2 + IFRT 20Gy
  - 10yr PFS 87%, OS 94%
- Stage IA and IIA, non bulky (RAPID)
  - ABVD x 3-4, IFRT 30Gy
  - 3yr PFS 83-94.6%, OS 97.1-99%
- Early stage unfavorable, including bulky (HD11)
  - ABVD x 4 + 30Gy RT
  - 5yr PFS 86%, OS 94%
- Stage II, bulky or >3 sites (RATHL)
  - ABVD x2 + Interim PET
  - Interim PET neg AVD; PET pos escBEACOPP

Randomized studies incorporating novel agents ongoing

Engert, A, et al. NEJM 363.7 (2010): 640-652.
Radford, J, et al. NEJM 372.17 (2015): 1598-1607.
Eich, HT, et al. JCO 28.27 (2010): 4199-4206.
Johnson, P, et al NEJM 374.25 (2016): 2419-2429.

Advanced Stage cHL

- Brentuximab-vedotin + AVD vs ABVD (Echelon-1)
  - 6yr OS 93.9% vs 89.4%
  - 6yr PFS 82.3% vs 74.5%

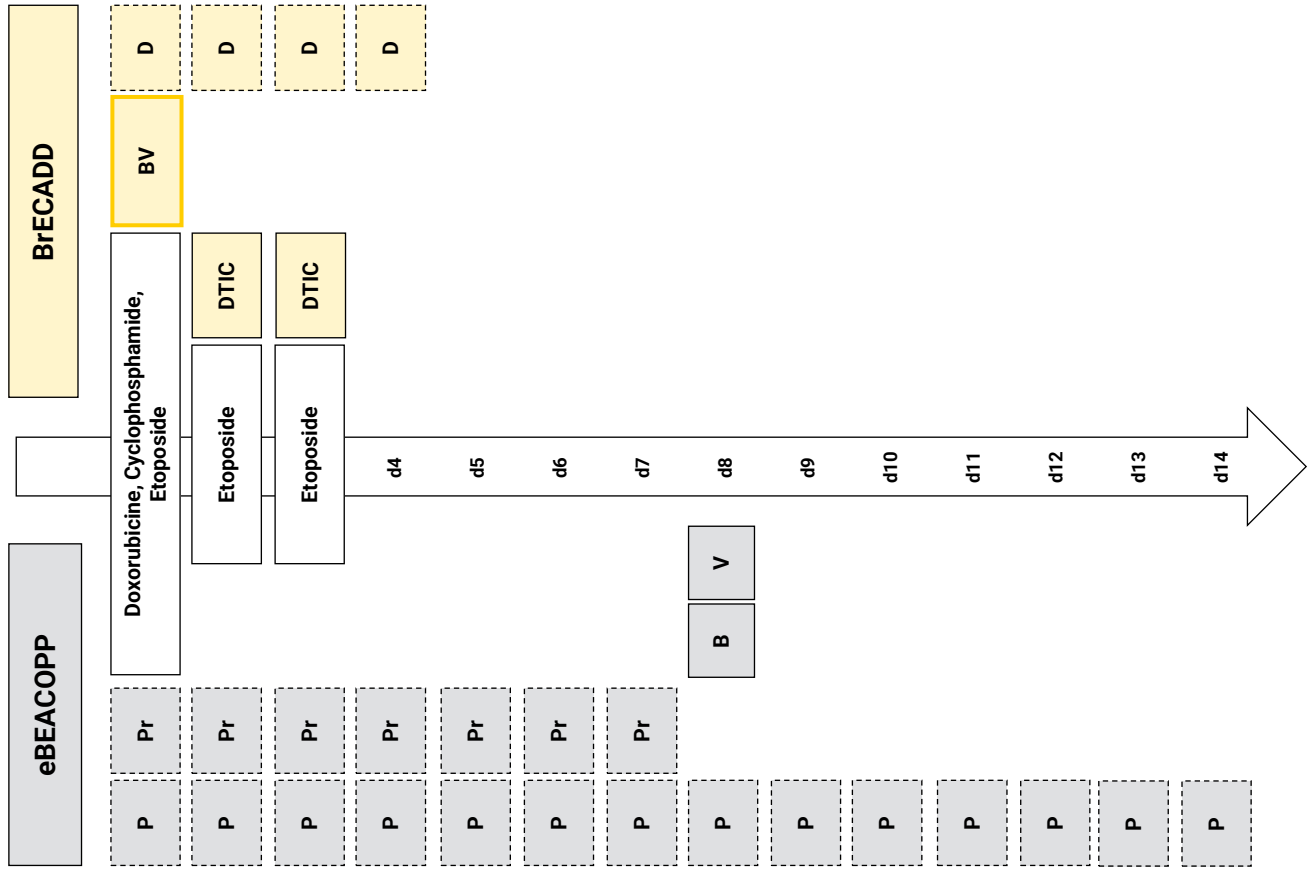


Ansell SM, et al. N Engl J Med. 2022 Jul 28;387(4):310-320.

- Nivolumab AVD vs Brentuximab-vedotin AVD (SWOG S1826)
  - 1yr PFS 94% vs 86%
  - Febrile neutropenia 5.6% vs 6.4%
  - Pneumonitis 2% vs 3.2%
  - ALT elevation 30.7% vs 39.8%
  - Hypo/hyperthyroidism 7%/3% vs <1%
  - Sensory neuropathy 28.1% vs 54.2%
  - Motor neuropathy 4% vs 6.8%

Herrera, AF, et al. ASCO 2023

Abstract #7000: BrECADD vs BEACOPP in advanced stage Hodgkin Lymphoma (GHSG HD21)

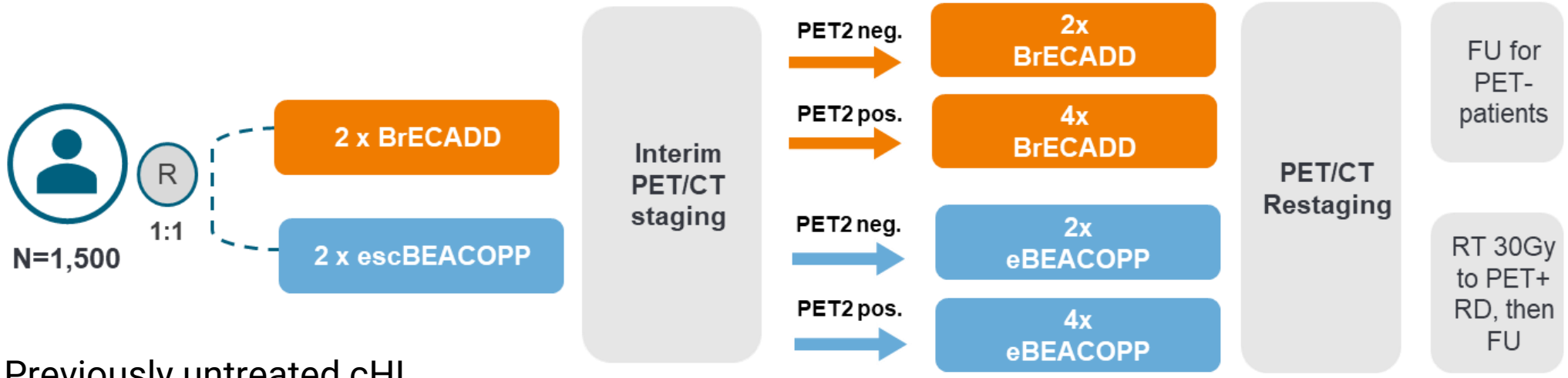


- The Kairos backbone **doxorubicin, cyclophosphamide, etoposide** was retained
- Introducing **Brentuximab Vedotin** (BV), **therefore omitting Bleomycin** (B, **pulmonary toxicity**) **and Vincristine** (V, **neuropathy**)
- Replacing **Procarbazine** (Pr) with the **less geno- and gonadotoxic Dacarbazine** (DTIC)
- Replacing 14 days of **Prednisone** (P) to 4 days of **Dexamethasone** (D)

HD21: Study Design and Endpoints

Primary objectives:

- Demonstrate **superior tolerability** defined by treatment-related morbidity with BrECADD.
- Demonstrate **non-inferior efficacy** of 4-6 x BrECADD compared with 4-6 x BEACOPP determined by PFS (NI margin 6%, HR to be excluded 1.69)



- Previously untreated cHL
- Stages IIB + large mediastinal mass or extranodal disease, III-IV
- Age <60

HD21: Treatment related morbidity endpoint

1. **Significant reduction of acute and severe treatment related adverse events favoring**
   - **BrECADD** (312/738 patients [42%])
   - eBEACOPP (430/732 patients [59%]), relative risk 0·72; 95% CI 0·65–0·79, p<0·0001
2. This benefit was observed for all subgroups (e.g. age, sex, IPS)

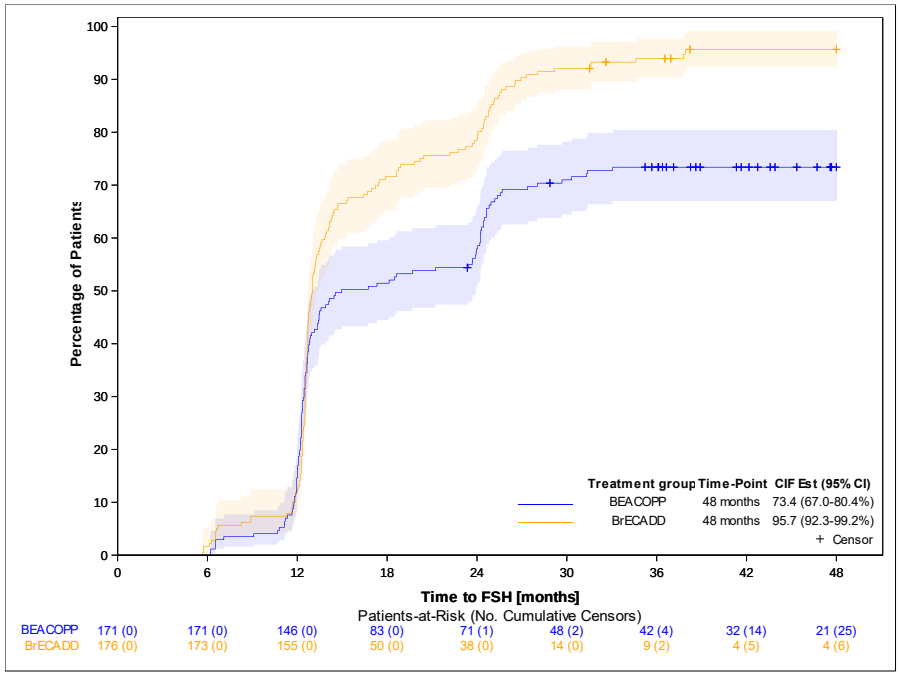
	BEACOPP (%)	BrECADD (%)
RBC transfusion freq	52	24
Platelet transfusion freq	34	17
Peripheral sensory neuropathy		
All grades	49	39
Grade 2	14	6
Grade 3	2	1

HD21: Resolution of treatment-related adverse events over time

Persistence of treatment-related morbidity at 12 months followup

Treatment related morbidity	BEACOPP (N=657)	BrECADD (n=677)
Anemia, thrombopenia, or infection of CTCAE grade 4	1 (<1)	0 (0)
Organ toxicity of CTCAE grade 3-4	6 (1)	2 (<1)
Treatment related morbidity	7 (1)	2 (<1)

Recovery of gonadal function (FSH) in female patients (18-40 yo at diagnosis) at 4yr follow up



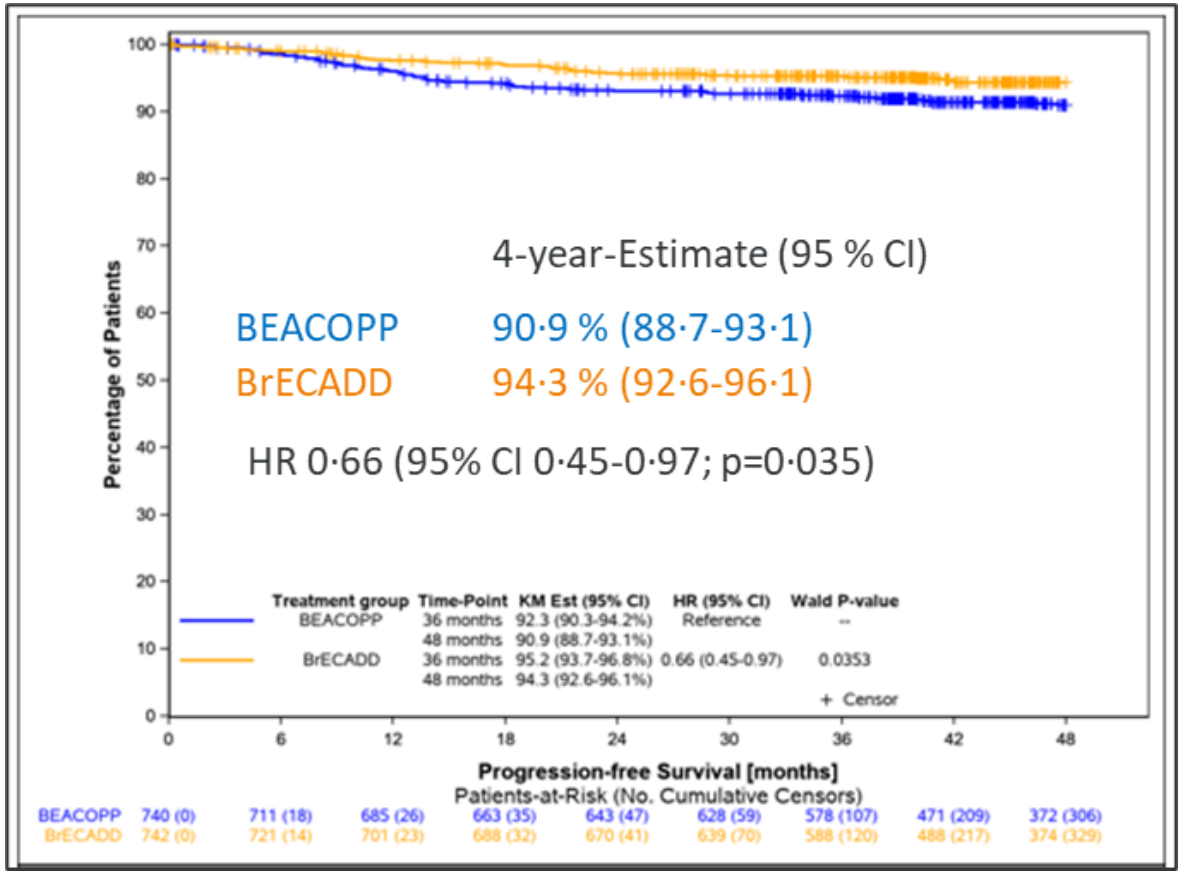
95.7% BrECADD

73.4% eBEACOPP

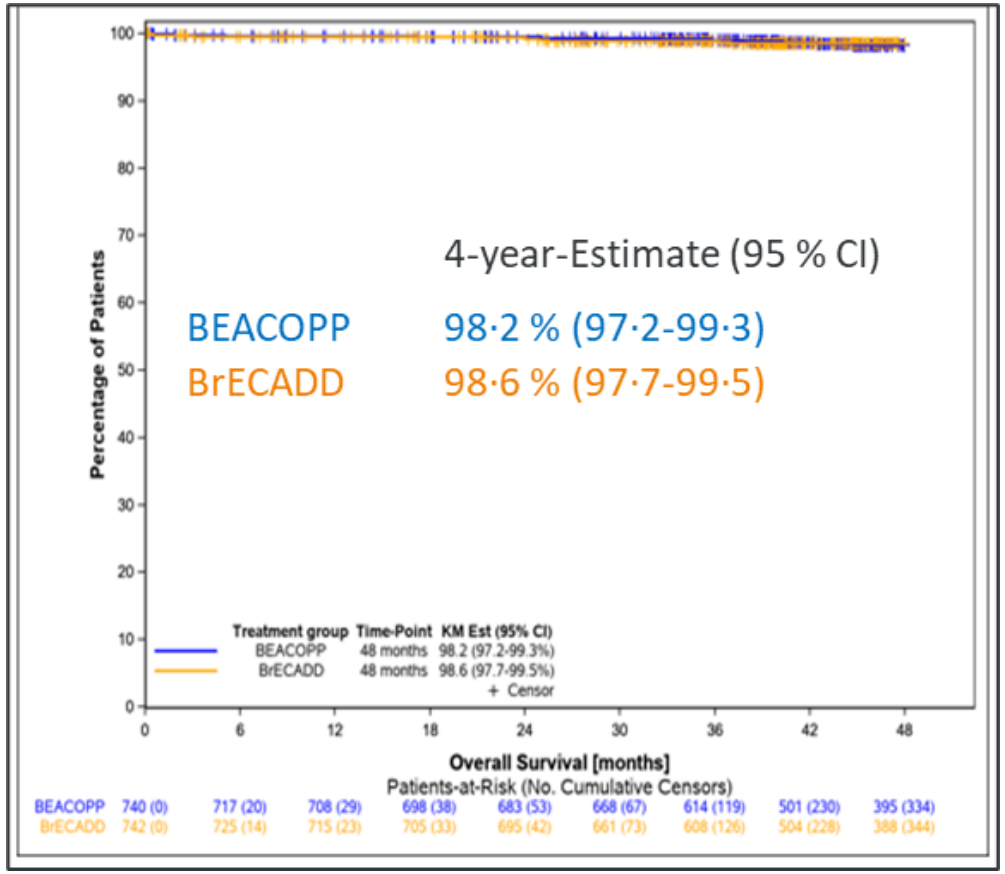
- Recovery in women was similar for 4 and 6 cycles of BrECADD (96%, 92%)
- Recovery in men was 87% (BrECADD) vs 40% (eBEACOPP)

HD21 Final Analysis: (mFU 48 m)

Progression-free survival



Overall survival

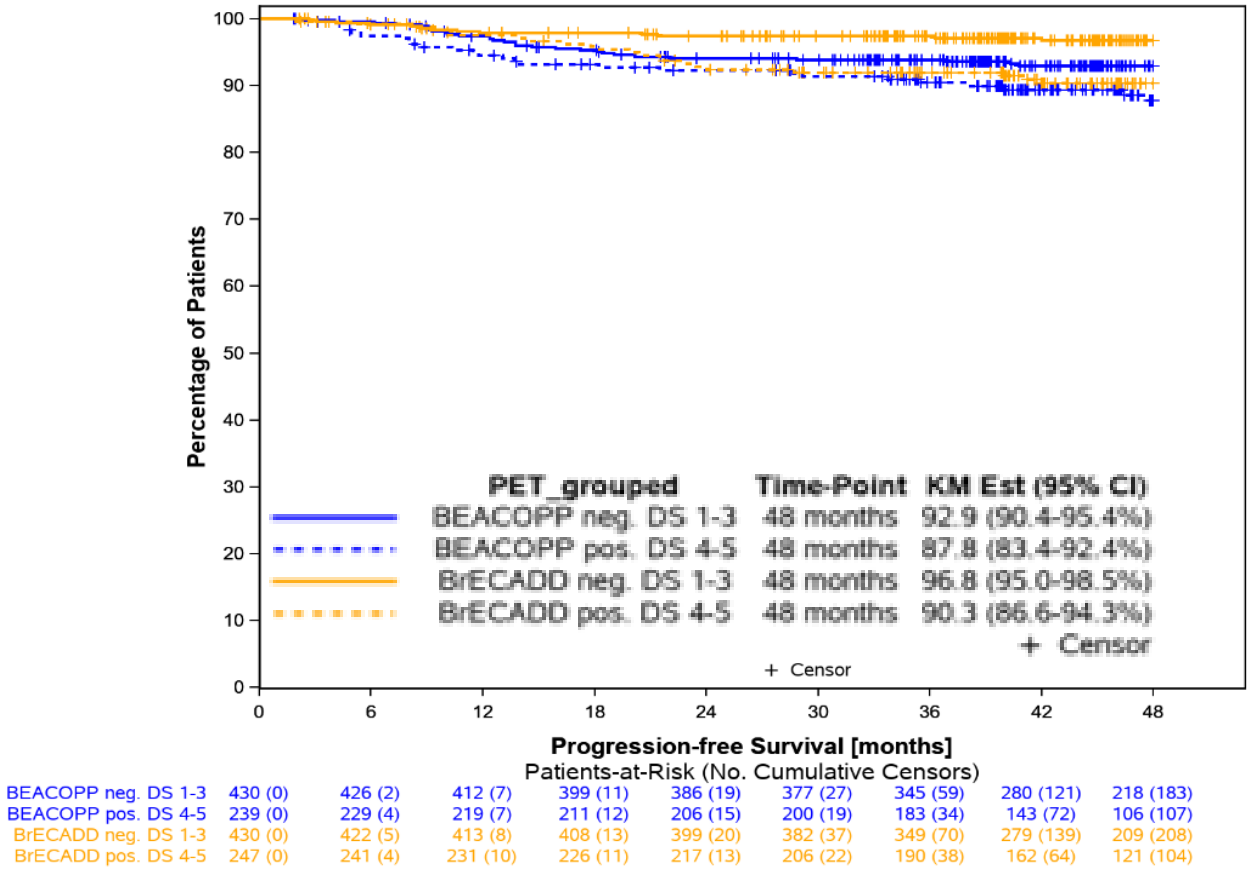


HD21:Response after two cycles of chemotherapy and PFS

PET2 and PET-EOT

	BEACOPP N=740 (%)	BrECADD n=742 (%)
Response at PET/CT2		
Central PET2 review (post-amendment)	669 (90)	677 (91)
CMR (DS1-3) PET/CT2	**430/669 (64)**	**430/677 (64)**
Response at EOT		
RTx recommended (i.e. no mCR, DS 4,5)	127 (17)	125 (17)
RTx documented	112 (15)	104 (14)

PFS by risk factor PET2-status



PFS benefit for BrECADD versus eBEACOPP was observed across all larger subgroups

HD21: Summary and conclusions

- **BrECADD is significantly better tolerated than eBEACOPP** including:
  - resolution of treatment-related adverse events after 12 months in > 99% of patients
  - and a very high recovery rate of gonadal function similar to ABVD in women.
- **Efficacy of BrECADD is superior to eBEACOPP** reaching a **PFS of 94.3%** with mature FU of 4-years
  - most patients (64%) receiving only 4 cycles (i.e. 12 weeks) and low cumulative doses of cytotoxic drugs below critical thresholds (e.g. doxorubicin at 160 mg/m²)
- Mature followup with high cure rates in all subgroups
- Not tested in pediatric and elderly population

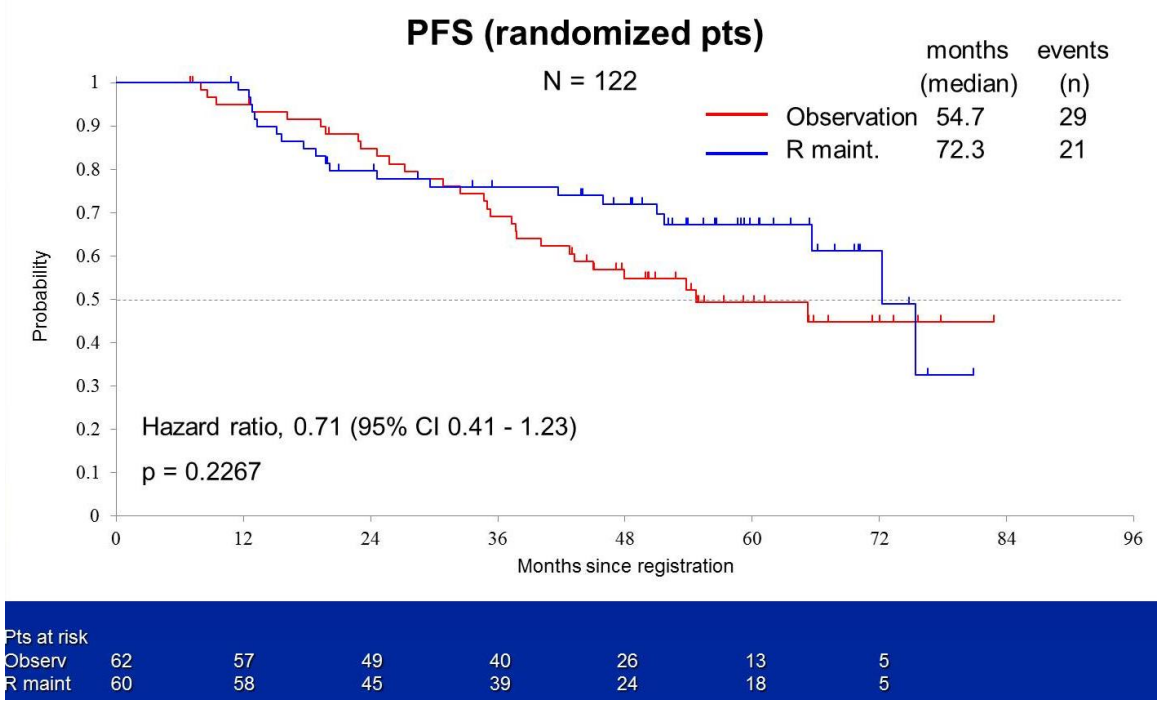
Mantle Cell Lymphoma

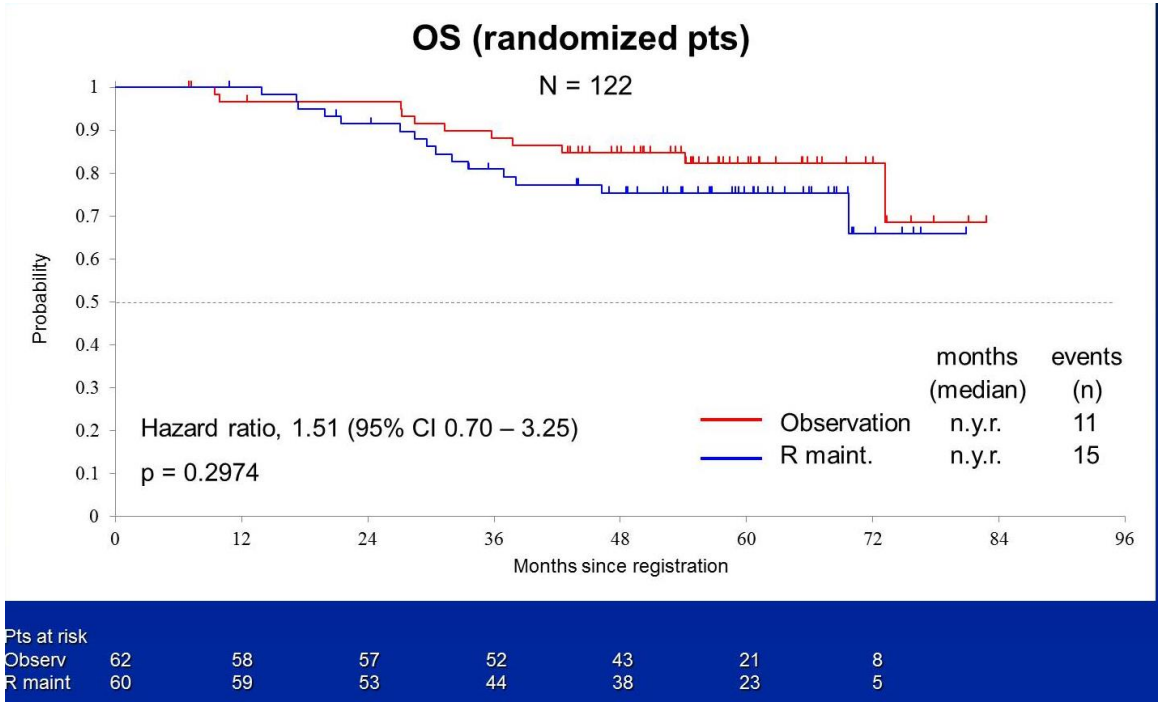
- Bendamustine and rituximab (BR) is a standard-of-care first-line (1L) immunochemotherapy regimen for older or unfit patients with mantle cell lymphoma (MCL) unable to undergo consolidative autologous HSCT.
- Rituximab maintenance improved survival outcomes after intensive chemoimmunotherapy with 1L R-CHOP and 1L R-DHAP and ASCT.
- **The role of rituximab maintenance after 1L BR has not been established.**
- In the prospective MAINTAIN trial, rituximab maintenance after 1L BR did not improve progression-free survival (PFS) or overall survival (OS).
- However, several retrospective studies have suggested potential benefits of rituximab maintenance after 1L BR.

Rummel M, et al. Lancet, 2013; Flin IW, et al. J Clin Oncol, 2019; Kluin-Nelemans HC, et al. N Engl J Med, 2012; Rummel M, et al. ASCO 2016; Hill B, et al. ASH 2019; Martin P et al, J Clin Oncol, 2023; Di M, et al, Haematologica, 2023.

StiL NHL7-2008 MAINTAIN trial

- Randomized phase 2 trial (Germany and Austria 2009-2012)
- Median follow-up approximately 5 years
- **Rituximab maintenance after 1L BR – no PFS or OS benefit observed**

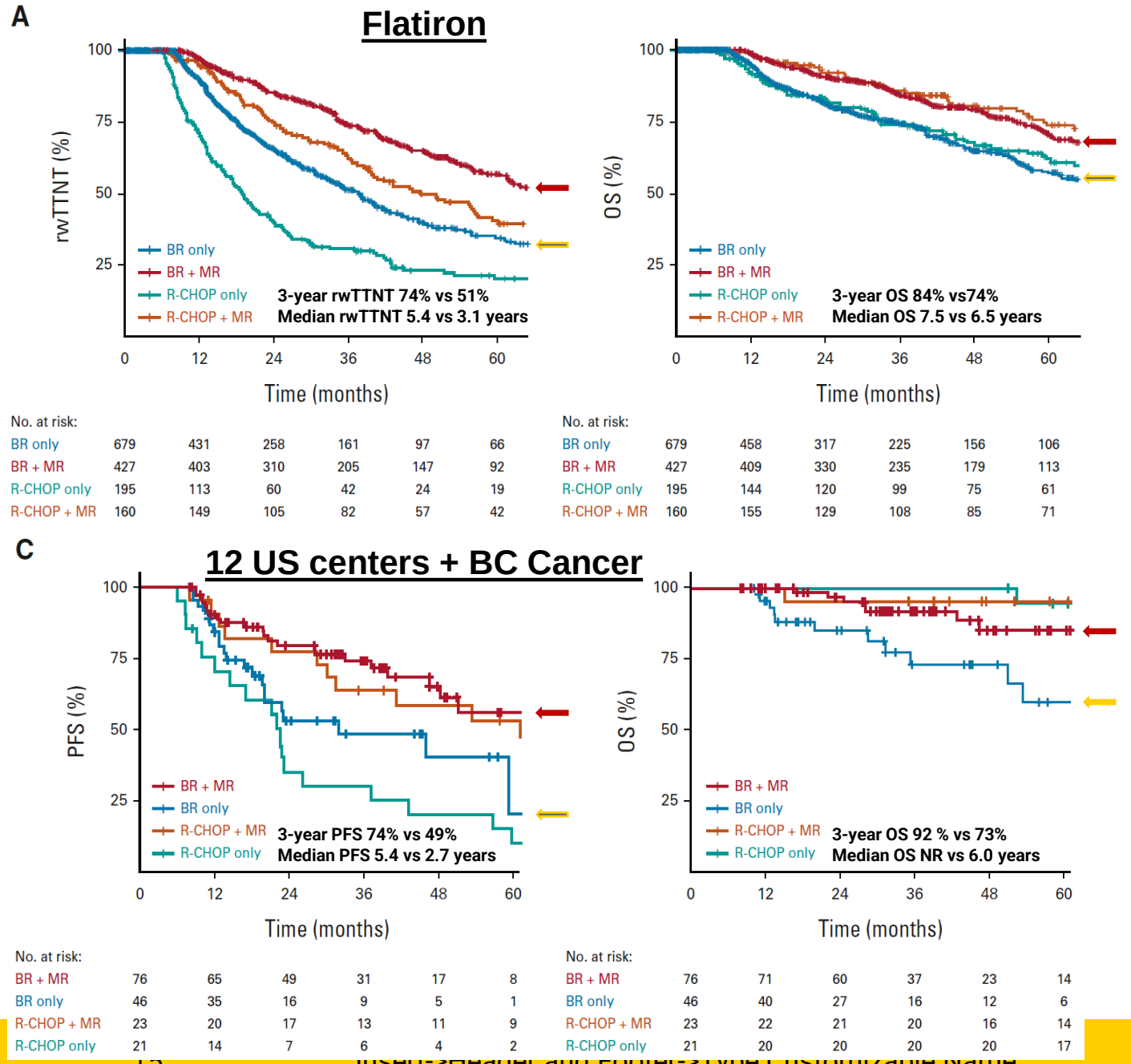




Rummel M, et al. ASCO 2016.

Retrospective evidence

- Flatiron database (community practice, 2011-2021)
- 12 US centers + BC Cancer retrospective cohort (2000-2015)
- Patients who underwent ASCT were excluded in this analysis
- **Rituximab maintenance showed rwTTNT/PFS and OS benefits after 1L BR** in both cohorts



Martin P, et al. J Clin Oncol, 2023.

Abstract 7006: Benefit of Rituximab Maintenance After First-line Bendamustine-Rituximab in Mantle Cell Lymphoma

Objective

- To examine the potential benefit of rituximab maintenance after 1L BR in a large observational cohort study.

Inclusion criteria

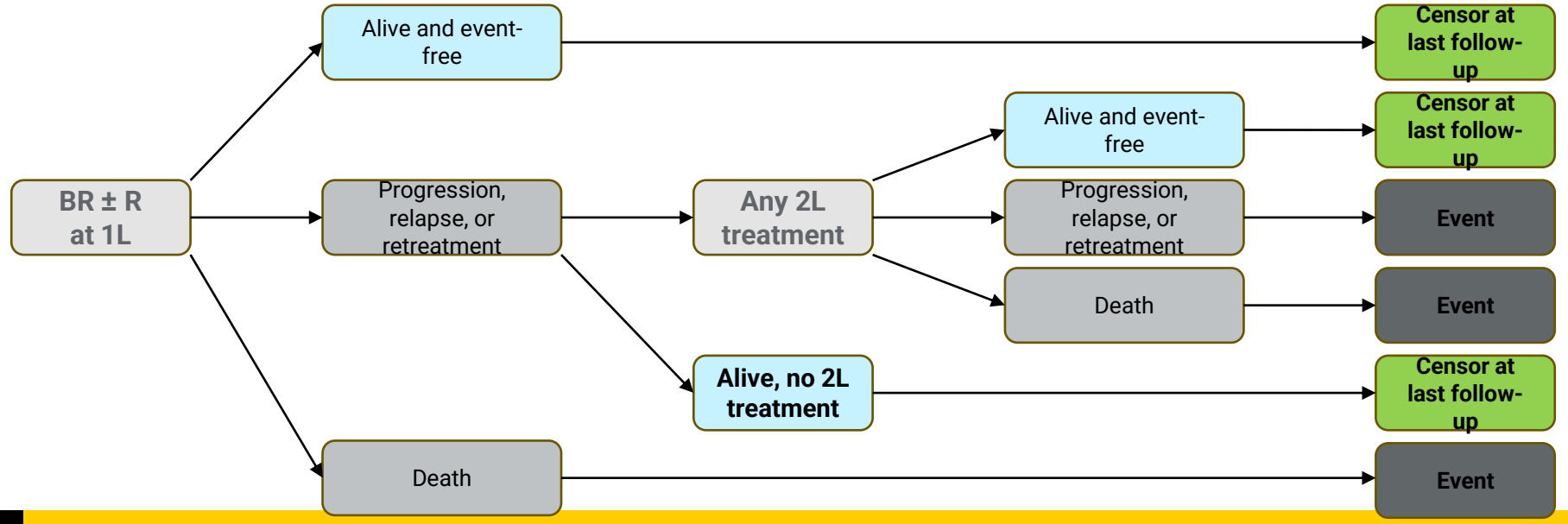
- Confirmed diagnosis of MCL with t(11;14)(q13;q32) translocation and/or cyclin D1 expression.
- Age ≥18 years old at diagnosis.
- Received BR in first line, with or without rituximab maintenance therapy.

Exclusion criteria

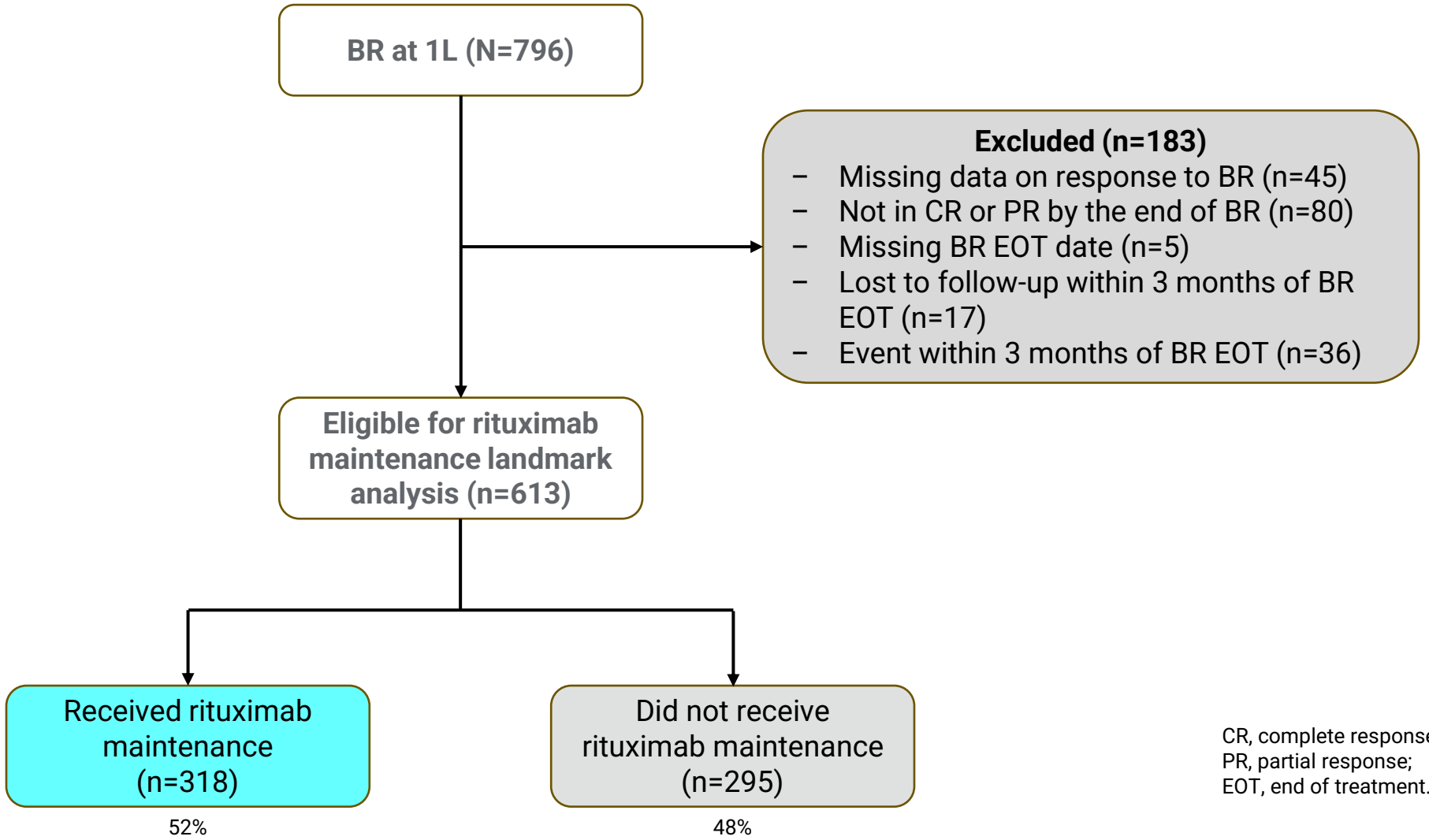
- Received first-line treatment on the SHINE or ECHO trial.
- Received a BTKi in combination with BR.
- Received other active MCL therapy in combination with BR, e.g., venetoclax, bortezomib, cytarabine, etc. *Pre-phase steroid is allowed.*
- Underwent ASCT consolidation after BR.
- Received maintenance therapy other than rituximab.

Methods – Data Analysis

- **Landmark analysis**, starting from 3 months after the end of BR.
- Event-free survival (EFS) was defined as time from the landmark to the first event (progression, relapse, retreatment, or death).
- EFS2 was defined as time from the landmark to progression, relapse, or retreatment following 2L treatment, or death.
- OS was defined as time from the landmark to death.



Consort diagram



CR, complete response;
PR, partial response;
EOT, end of treatment.

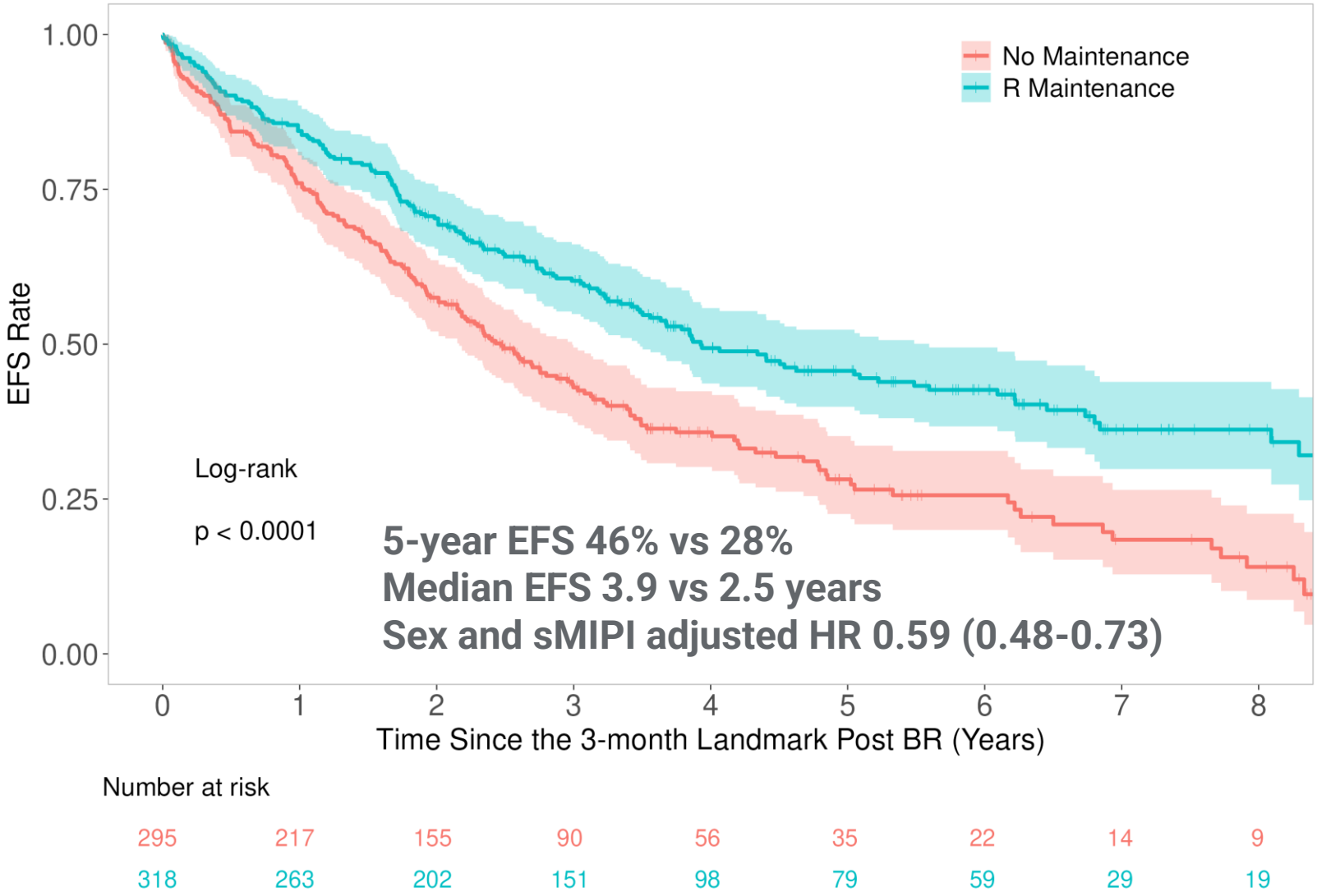
Baseline characteristics at diagnosis

Variable	R Maintenance (n=318)	No R Maintenance (n=295)
Age		
Median (range / IQR)	69 (32–91 / 64–74)	71 (34–90 / 64–76)
≥65	243 (76.4%)	224 (75.9%)
Sex, male	247 (77.7%)	202 (68.5%)
ECOG PS		
0-1	270 (93.1%)	222 (88.8%)
≥2	20 (6.9%)	28 (11.2%)
Missing	28	45
Bone marrow involvement		
Yes	197 (74.9%)	171 (69.2%)
No	66 (25.1%)	76 (30.8%)
Unknown	55	48
Stage		
I-II	15 (4.8%)	32 (11.0%)
III-IV	295 (95.2%)	258 (89.0%)
Missing	8	5
Simplified MIPI		
0-3 (low)	61 (23.2%)	47 (19.7%)
4-5 (intermediate)	100 (38.0%)	104 (43.7%)
6-11 (high)	102 (38.8%)	87 (36.6%)
Missing	55	57

Variable	R Maintenance (n=318)	No R Maintenance (n=295)
Bulky disease (≥5 cm)		
Yes	63 (27.4%)	51 (23.0%)
No	167 (72.6%)	171 (77.0%)
Unknown	88	67
Ki-67		
<30%	100 (48.8%)	83 (41.9%)
30-49%	65 (31.7%)	61 (30.8%)
≥50%	40 (19.5%)	54 (27.3%)
Unknown	113	97
Blastoid or pleomorphic		
Yes	28 (10.3%)	27 (10.6%)
No	244 (89.7%)	228 (89.4%)
Unknown	46	40
***TP53* mutation or deletion**		
Yes	18 (33.3%)	20 (29.9%)
No	36 (66.7%)	47 (70.1%)
Unknown	264	228
Complex karyotype		
Yes	27 (17.6%)	23 (17.2%)
No	126 (82.4%)	111 (82.8%)
Unknown	165	161

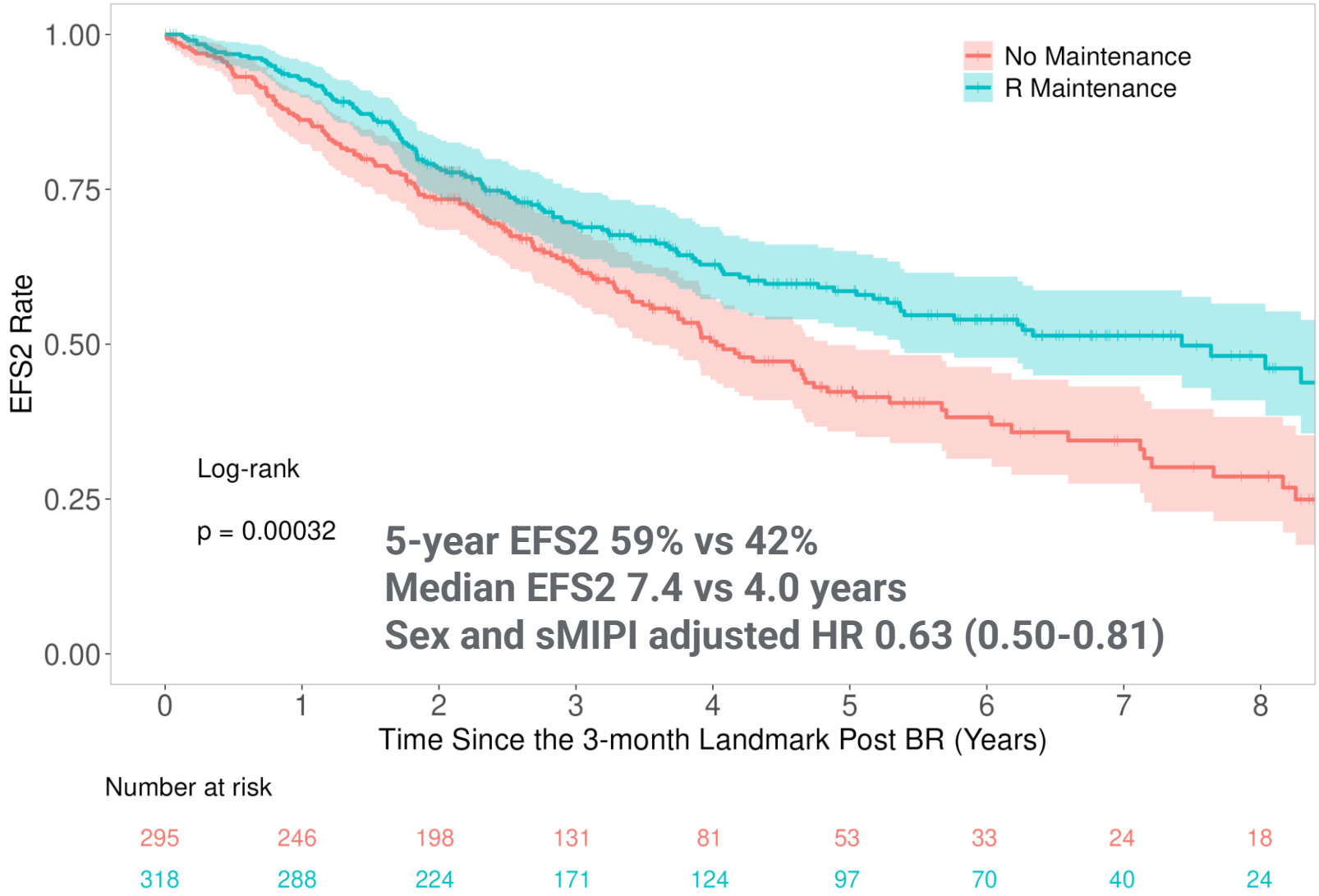
Wang, Y et al, ASCO 2024 Abstract # 7006

EFS by rituximab maintenance



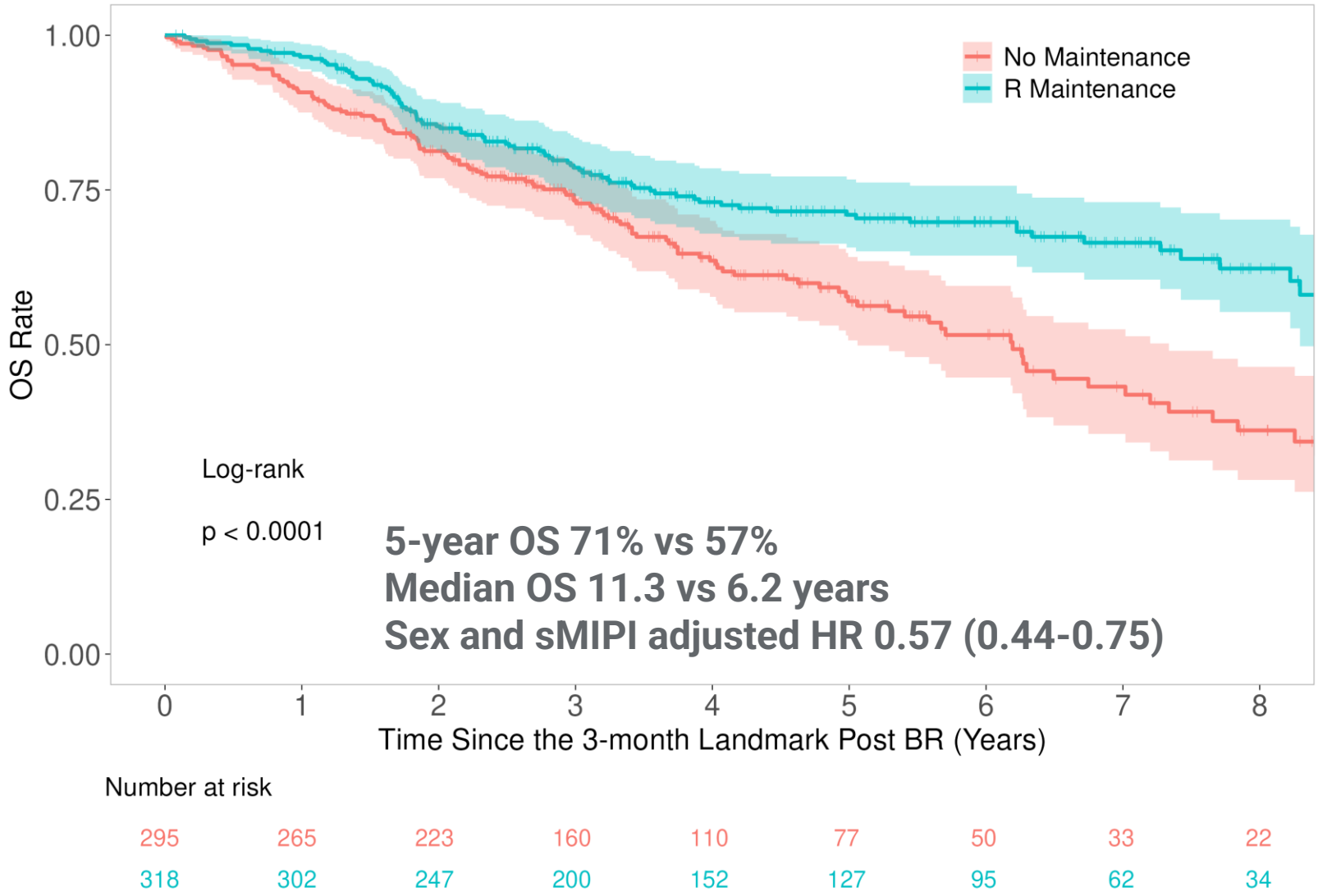
Wang, Y et al, ASCO 2024 Abstract # 7006

EFS2 by rituximab maintenance



Wang, Y et al, ASCO 2024 Abstract # 7006

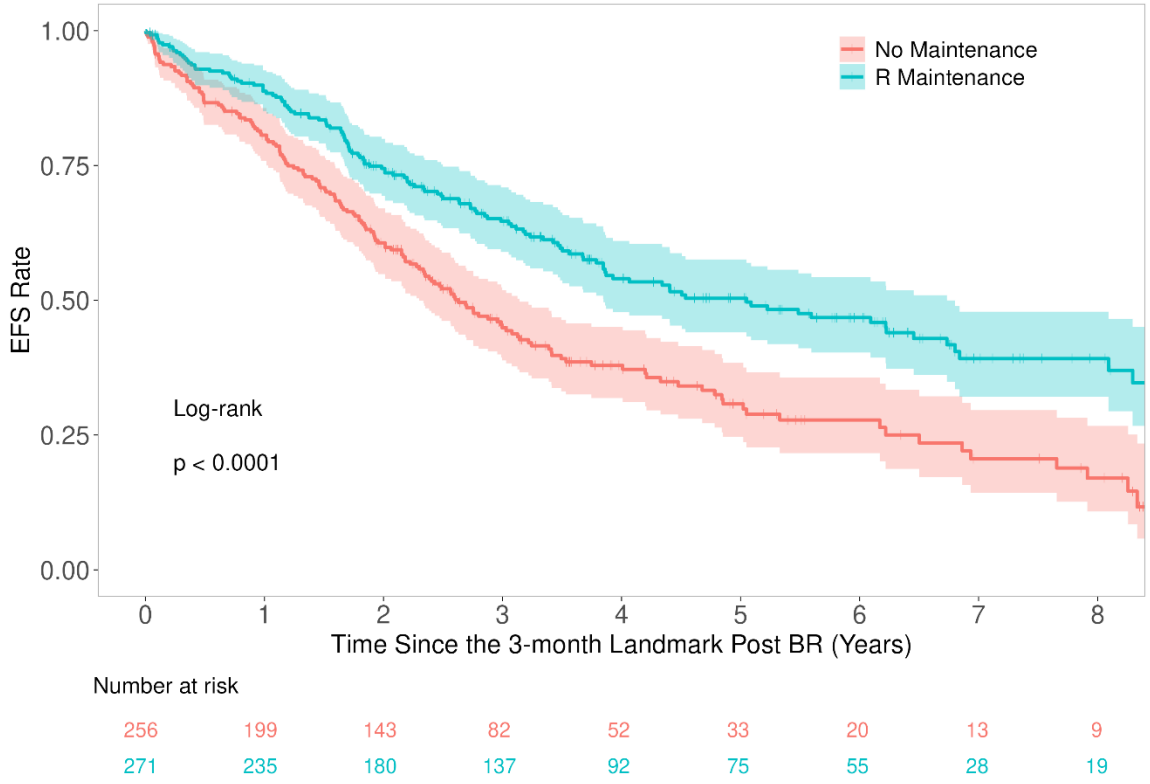
OS by rituximab maintenance



Wang, Y et al, ASCO 2024 Abstract # 7006

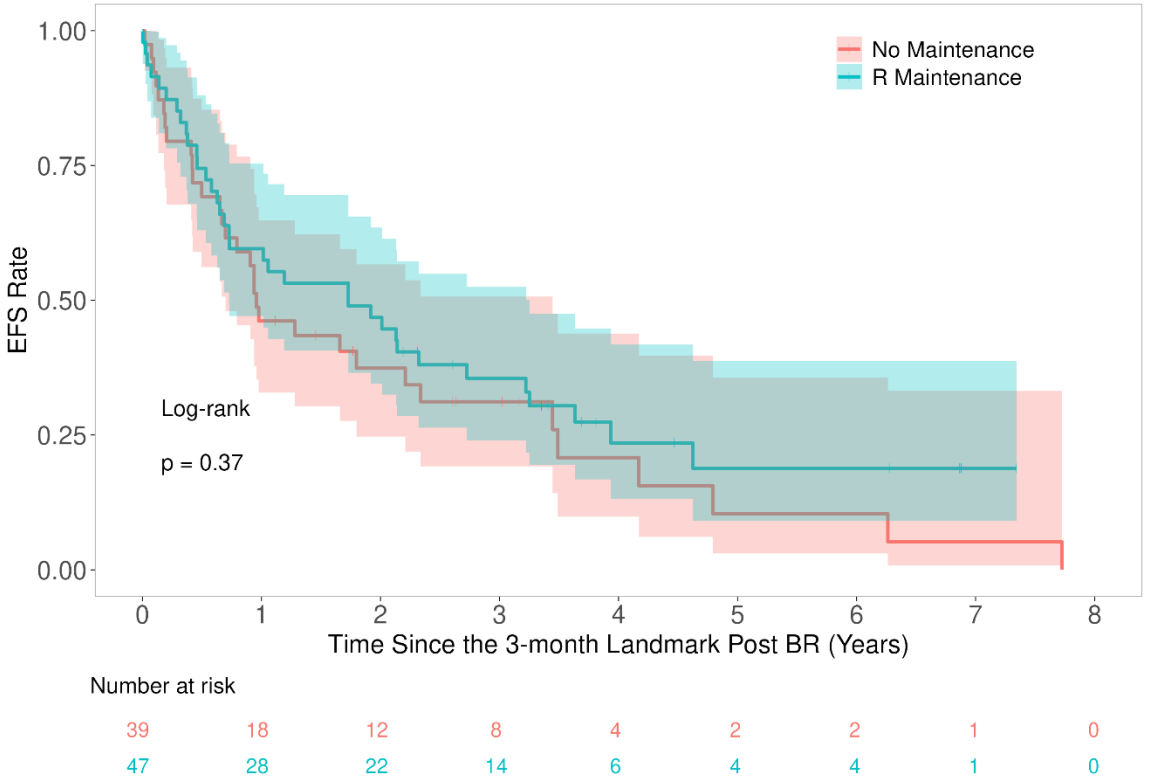
EFS by rituximab maintenance stratified by response to BR

Patients in CR after 1L BR



5-year EFS 50% vs 31%
Median EFS 5.1 vs 2.6 years
Sex and sMIPI adjusted HR 0.56 (0.44-0.71)

Patients in PR after 1L BR

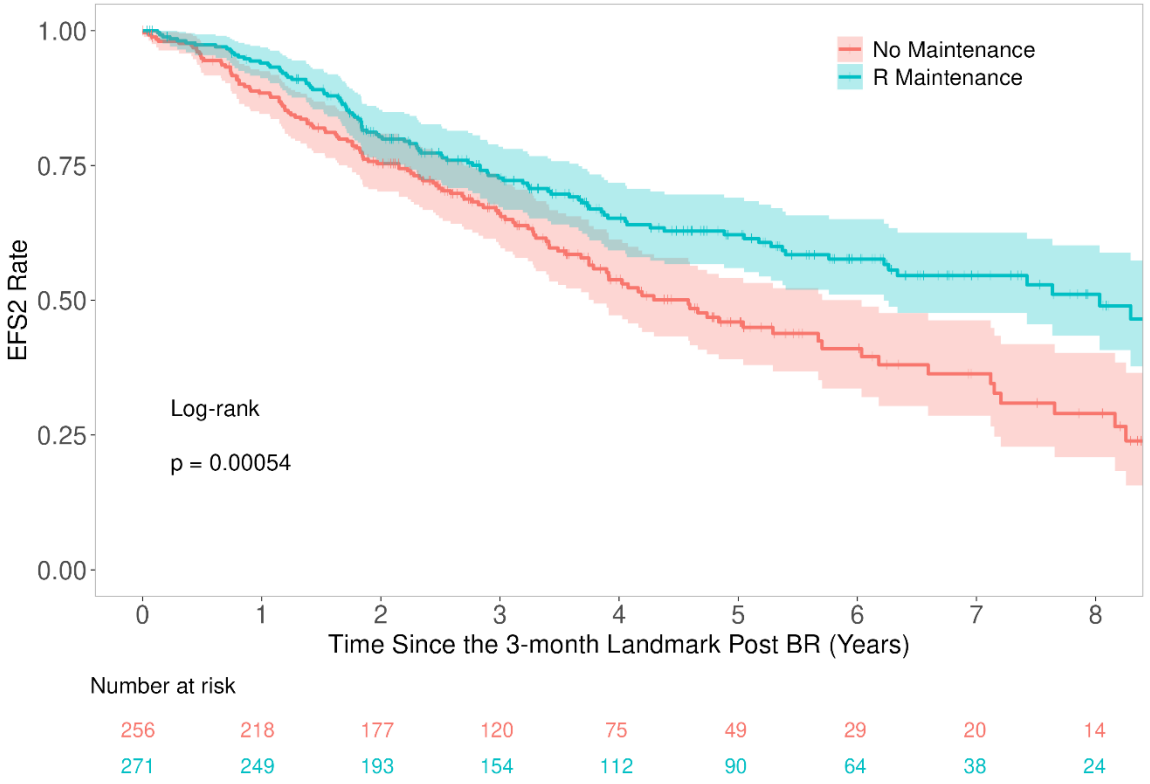


5-year EFS 19% vs 10%
Median EFS 1.7 vs 1.0 years
Sex and sMIPI adjusted HR 0.82 (0.49-1.37)

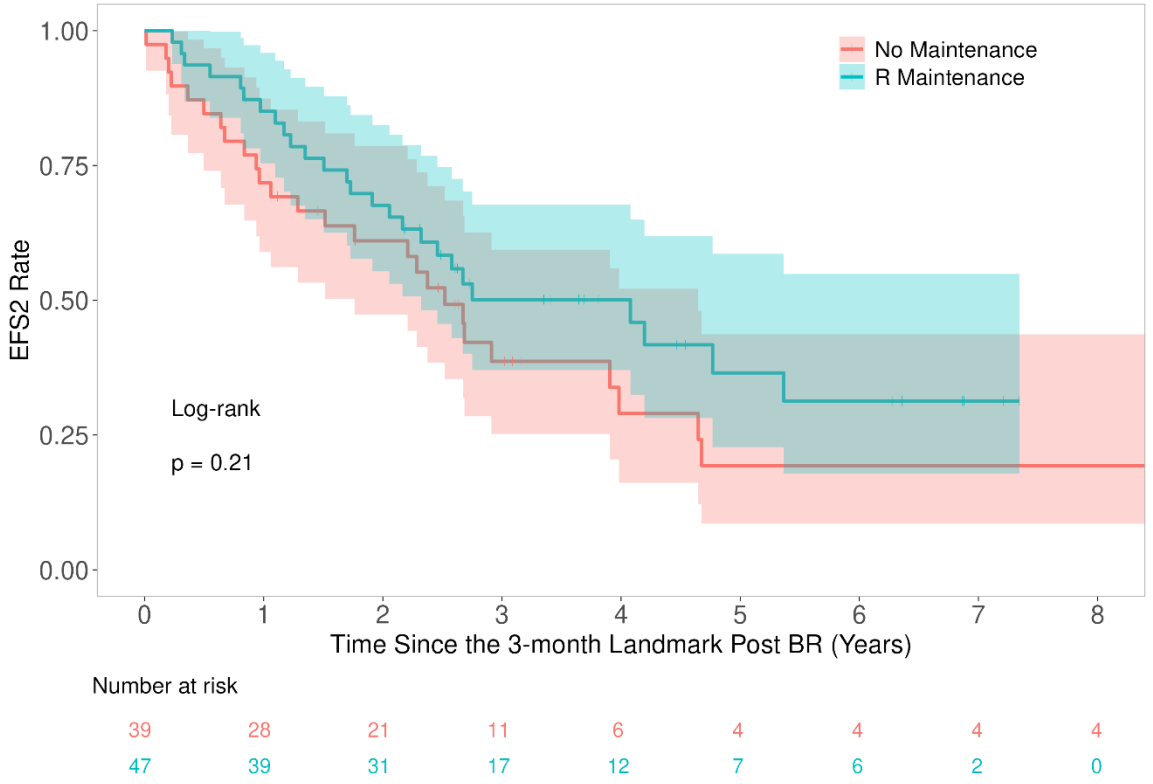
Wang, Y et al, ASCO 2024 Abstract # 7006

EFS2 by rituximab maintenance stratified by response to BR

Patients in CR after 1L BR



Patients in PR after 1L BR



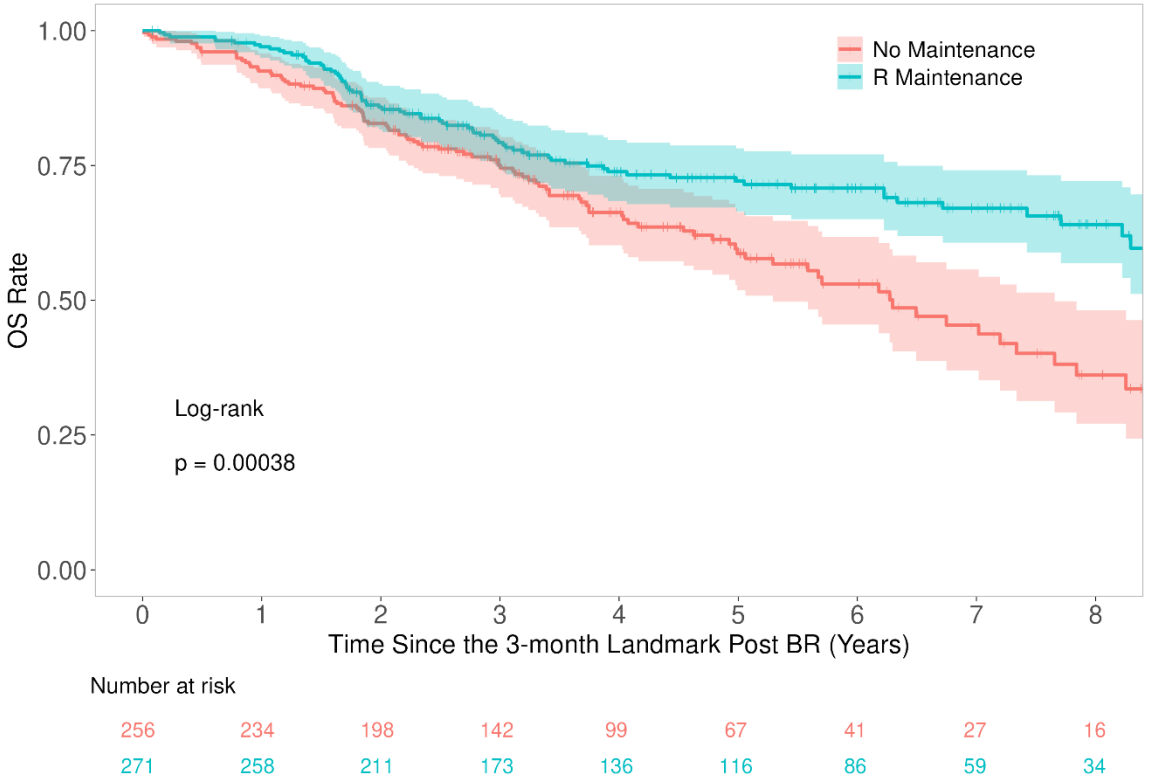
5-year EFS2 62% vs 46%
Median EFS2 8.0 vs 4.6 years
Sex and sMIPI adjusted HR 0.62 (0.48-0.81)

5-year EFS2 37% vs 19%
Median EFS2 4.1 vs 2.5 years
Sex and sMIPI adjusted HR 0.69 (0.39-1.22)

Wang, Y et al, ASCO 2024 Abstract # 7006

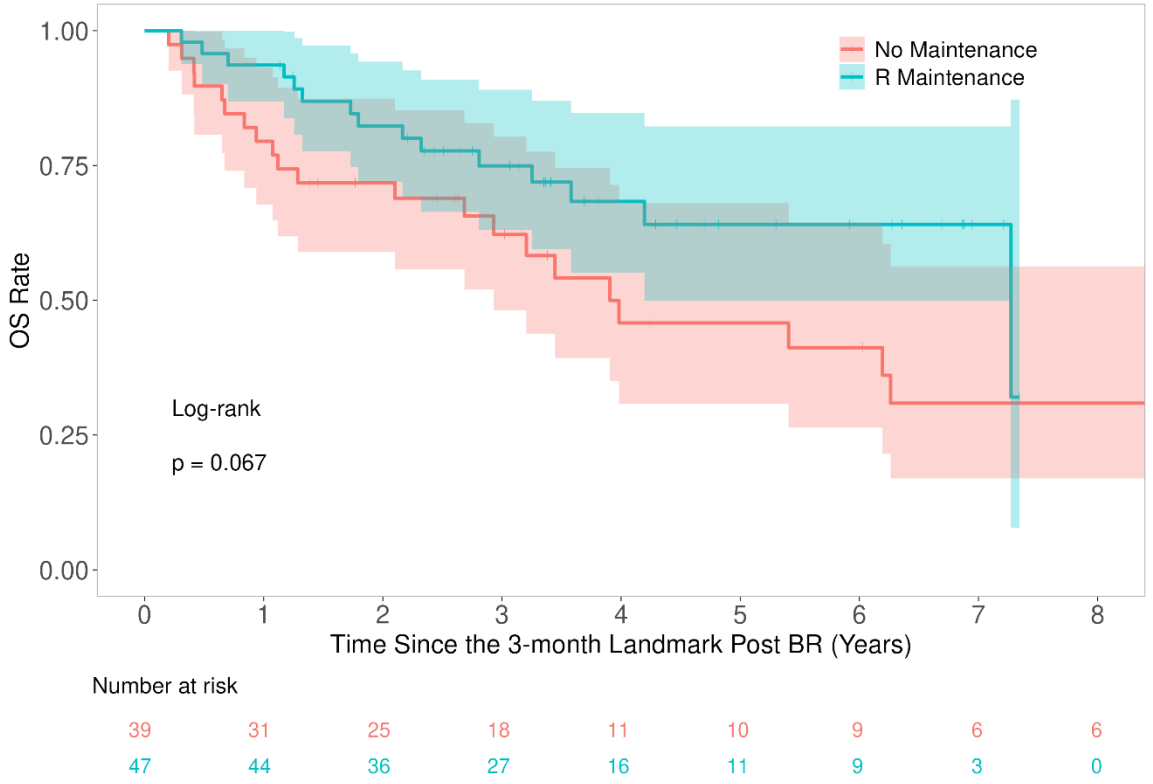
OS by rituximab maintenance stratified by response to BR

Patients in CR after 1L BR



5-year OS 72% vs 59%
Median OS 11.3 vs 6.3 years
Sex and sMIPI adjusted HR 0.59 (0.44-0.79)

Patients in PR after 1L BR



5-year OS 64% vs 46%
Median OS 7.3 vs 3.9 years
Sex and sMIPI adjusted HR 0.48 (0.24-0.98)

Wang, Y et al, ASCO 2024 Abstract # 7006

Summary and Conclusions

- **In this large multicenter study, rituximab maintenance after 1L BR was associated with improved EFS, EFS2 and OS.**
- The EFS, EFS2 and OS benefits of rituximab maintenance were clear in patients who achieved CR to 1L BR, but uncertain in those who achieved PR due to a small sample size in this subset.
- **Within the constraints of observational data, these results provide support for rituximab maintenance therapy after 1L BR in patients with MCL.**

Richter's Transformation (RT)

- Aggressive histological transformation from CLL
  - ~90% DLBCL
  - ~10% Hodgkin Lymphoma
  - ~<1% Other uncommon lymphomas
- Occurs at rate of 0.5-1% per year in patients with CLL
- Standard of care treatment for transformation to DLBCL
  - 1st line R-CHOP CR rate 30-45%, median OS 6-12 months
  - No standard second line approach

Abstract 7010: Real-world outcomes of lisocabtagene maraleucel (liso-cel) in patients with Richter transformation from the CIBMTR

Key eligibility criteria

- Patients with Richter's transformation (RT) and evidence of single infusion with commercially available liso-cel in the US
  - >1 visit after infusion and
  - ≥ 6 months followup before data cutoff date Aug, 4 2023

Baseline Characteristics

- 30 patients with RT
- Received treatment for CLL before RT - 24 (77%)
- Received treatment for RT before lisocel infusion – 30 (100%)
- Prior agents used for RT – BTKi, BCL2i, anti-CD20, chemoimmunotherapy
- Bridging therapy prior to lisocel infusion – 13/27 (48%)

Response to Liso-cel

- ORR 76% (CR 66%, PR10%) with median followup of 12.3 months.
- Median time to 1st response 1.1 months (range 0-3.1)
- PFS
  - Median NR
  - 6 month 65%
  - 12 month 54%
- OS
  - Median NR
  - 6 month 79%
  - 12 month 67%

Winter, AM. et al, ASCO 2024 Abstract # 7010

Safety of Liso-cel

	CRS n (%)	ICANs n(%)
Grade 1	11 (37%)	1 (3%)
Grade 2	7 (23%)	4 (13%)
Grade 3		5 (17%)
Grade 4	1 (3%)	3 (10%)
Grade 5	1 (3%)	

Other significant adverse events

- Prolonged cytopenias : 5 (17%)
- Clinically significant infections: 13 (43%)
- Hypogammaglobulinemia: 22 (73%)
- Grade ¾ organ toxicity: 2 (7%)

Deaths

- 7 due to disease progression
- 1 due to CRS (patient also had hemophagocytic lymphohistiocytosis)

Summary and Conclusions

- Largest multicenter real world study of patients with RT who received commercial liso-cel in the US.
- ORR of patients with RT to liso-cel comparable to other patient populations with relapsed/refractory large B cell lymphoma.
- The probability of 1 year survival after infusion was 67%. Higher than many other treatment options.
- Acceptable incidence of CRS and ICANs

IOWA | Carver College of Medicine

Questions?

Nanmeng Yu, MD, PhD
Clinical Assistant Professor
Division of Hematology, Oncology,
Blood and Marrow Transplant
Department of Internal Medicine

Email: nanmeng-yu@uiowa.edu

IOWA | Carver College of Medicine

Thank you

Nanmeng Yu, MD, PhD
Clinical Assistant Professor
Division of Hematology, Oncology,
Blood and Marrow Transplant
Department of Internal Medicine

Email: nanmeng-yu@uiowa.edu