When Not to Watch and Wait:

Emerging Strategies in the Treatment of Indolent Lymphoma and Mantle Cell Lymphoma

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UVA Cancer Center
An NCI Comprehensive Cancer Center

UVA Health

Disclosures: Michael E. Williams, MD, ScM

- Clinical trial grant support (PI) to University of Virginia:
  - Allos, Janssen, Kymera, Pharmacyclics
- Consultant:
  - Astra-Zeneca, Beigene, Celgene, Gilead, Janssen, Kite Pharma, Kymera, Pharmacyclics, Zentalis

- Off-label use:
  - Ibrutinib front-line in MCL
  - Lenalidomide front-line in FL

Presentation Outline

- Focus on Follicular and Mantle Cell Lymphoma
  - Similar progress in MZL, WM/LPL, CLL/SLL

- Follicular lymphoma
  - Low-tumor burden disease: RESORT Trial
  - Chemo-free: RELEVANCE Trial

- Mantle cell lymphoma:
  - Is front-line AutoSCT consolidation still needed?
  - Chemo-free: SYMPATICO Trial

FL Initial Therapy: 2024

- Watch/Wait patients
  - **Low tumor burden (GELF criteria*), asymptomatic**

- Low tumor burden, symptomatic or patient desires Rx
  - **Rituximab x 4 doses, no maintenance** (RESORT Trial, update, Kahl et al *JCO* 2024)

- High tumor burden
  - **R-chemo → R maintenance x 2 y** (PRIMA Trial)
  - **Lenalidomide/Rituximab** (RELEVANCE Trial)

*No B or systemic symptoms; <3 nodal areas >3cm; no nodal mass >7cm; no splenomegaly; no organ compression/compromise; no cytopenias; no effusions; normal LDH and β2M (Brice et al, *JCO* 1997)

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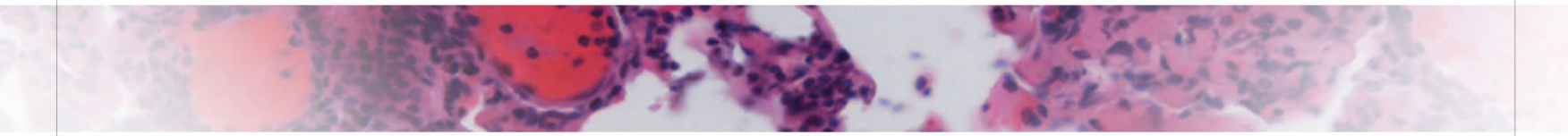
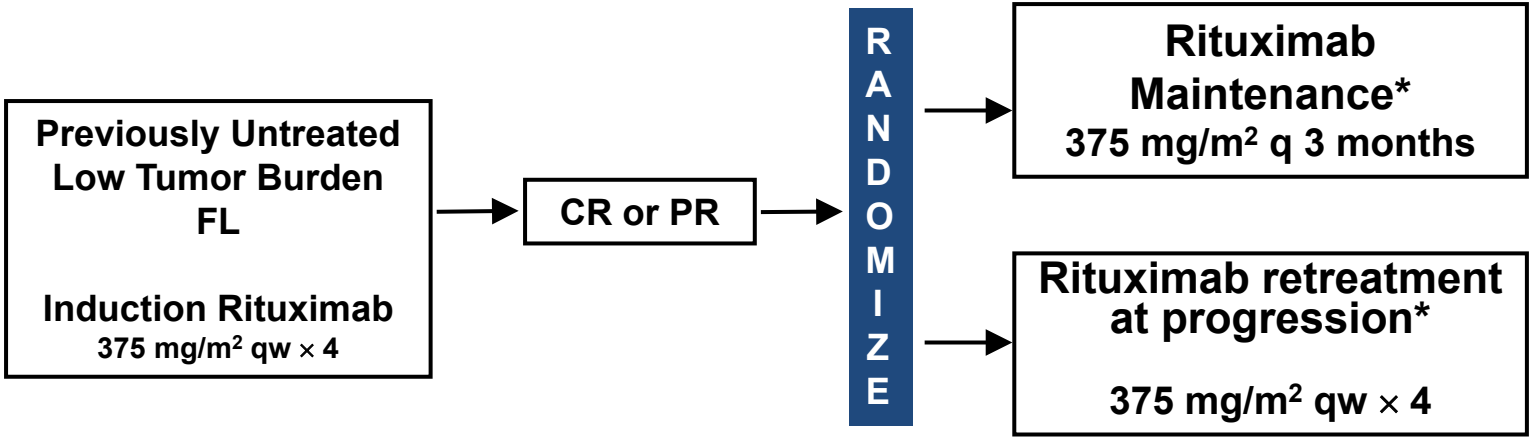


Long Term Follow Up of RESORT – Rituximab Extended Schedule Or Retreatment Trial (E4402)

Brad Kahl, Fangxin Hong, Yemi Jagede, Christopher Peterson, Lode Swinnen, Thomas Habermann, Stephen Schuster, Matthias Weiss, Paul Fishkin, Christopher Ehmann, Tim Fenske, Michael Williams

Presented at ASH 2021; updated and pre-published in *JCO* Jan., 2024

E4402 (RESORT) Schema (ASH 2021)



***Continue until treatment failure**

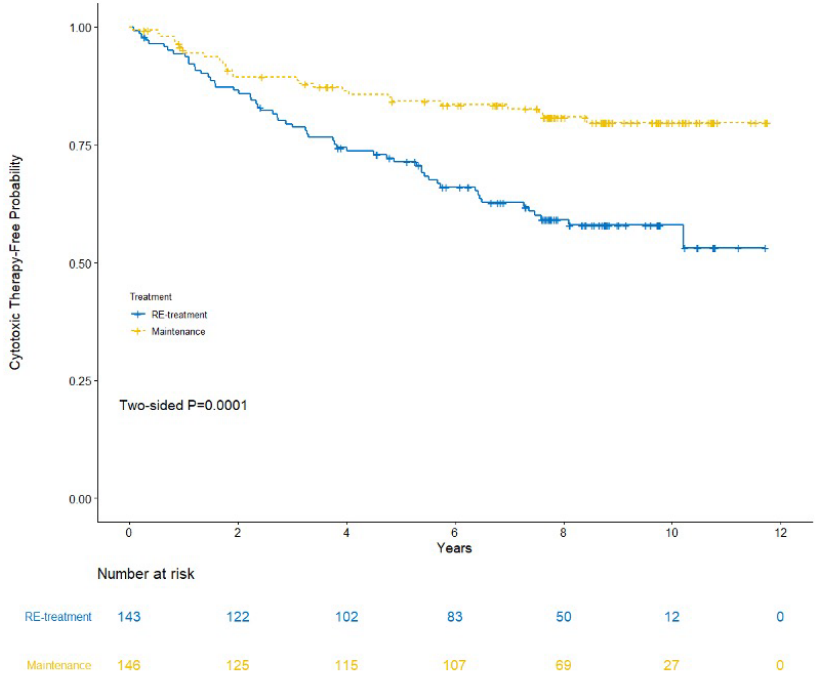
- No response to re-treatment or PD within 6 months of R
- Initiation of cytotoxic therapy or inability to complete planned R therapy

RESORT: Freedom from First Cytotoxic Therapy (ASH 2021)

	3 year	5 year	7 year
MR	89%	84%	83%
RR	79%	71%	63%

HR 2.37 (1.5-3.76)

Median follow up 8.7 years



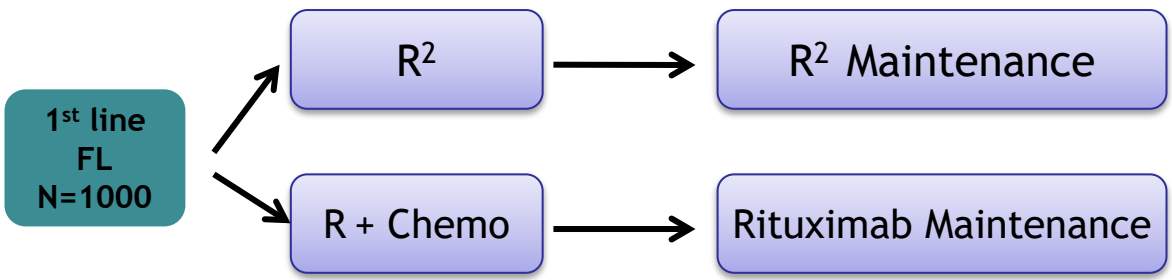
RESORT LTFU: Conclusions (ASH 2021; Kahl et al, *JCO* 2024)

- Time to treatment failure outcomes unchanged with LTFU
- MR benefit for time to first cytotoxic therapy increased over time
  - …but **63% of patient on RR strategy remained chemo-free at 7 years**
- Duration of response favored MR
  - …but **30% of RR patients remained in 1st remission at 10 years**
- No long term safety signals with prolonged MR (2nd CA, Ig levels)
- No OS benefit for MR
- 4x less drug utilized with the RR strategy
- ***A rituximab retreatment strategy remains our recommendation***

DRIVE Rank Score: 1-2 (incomplete information on minority groups)

Advanced-Stage Follicular Lymphoma: RELEVANCE Study

Rituximab and Lenalidomide vs. R-Chemotherapy



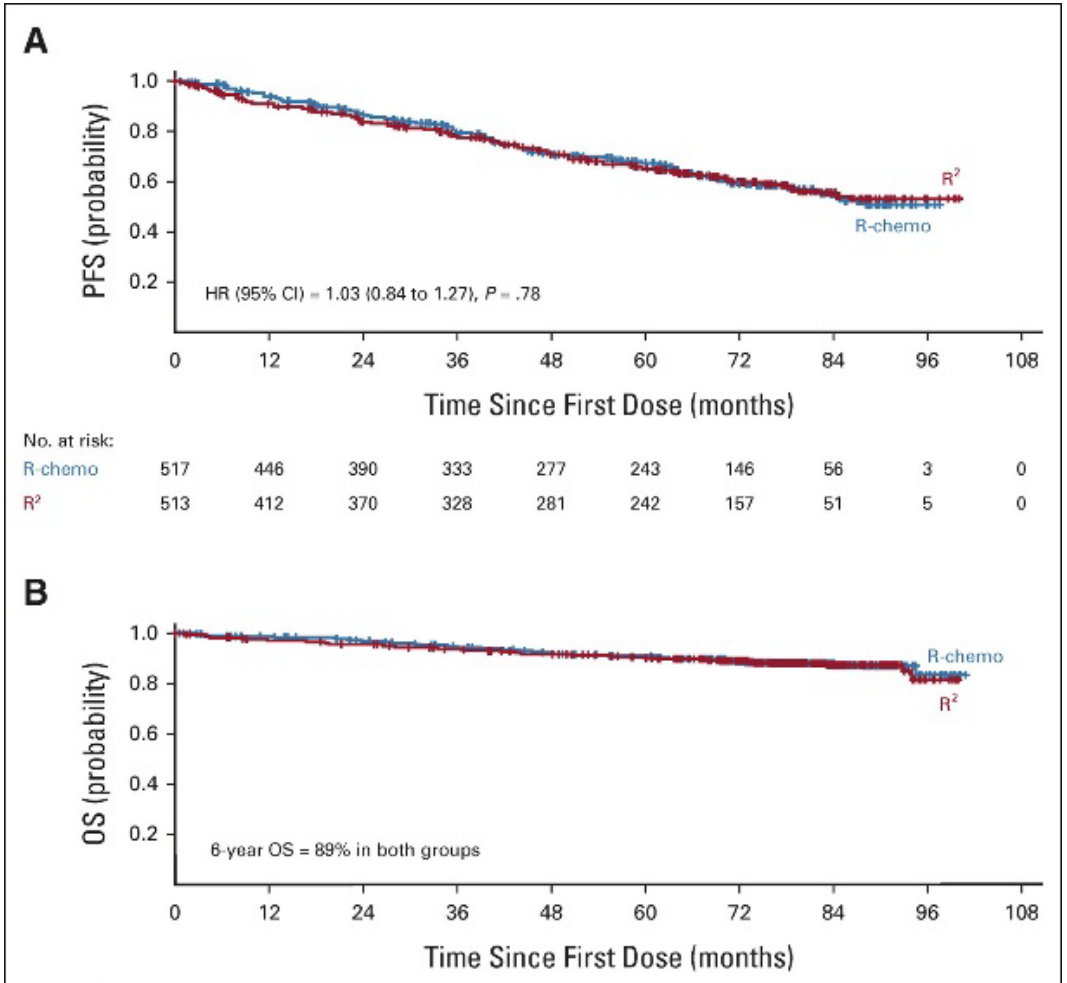
- R + chemo: Investigator's choice of R-CHOP, R-CVP, BR
- Lenalidomide 20 mg for 6 cycles, then 10 mg if CR
- Study group of Adult Lymphoma (GELA) + North American Multicenter Cooperative group

Morschhauser et al, *NEJM* 2018

Six-Year Results From RELEVANCE: Untreated Advanced Follicular Lymphoma

- Patients were randomized to R2 (513 patients) vs R-CHOP (372), R-Bendamustine (117), or R-CVP (28)
  - All patients received Rituximab maintenance x 2 years
- No differences in treatment response at the time of relapse
- No differences in overall survival
- **Conclusion:** R2 showed comparable efficacy and safety versus R-chemo and *provides an acceptable chemo-free alternative*

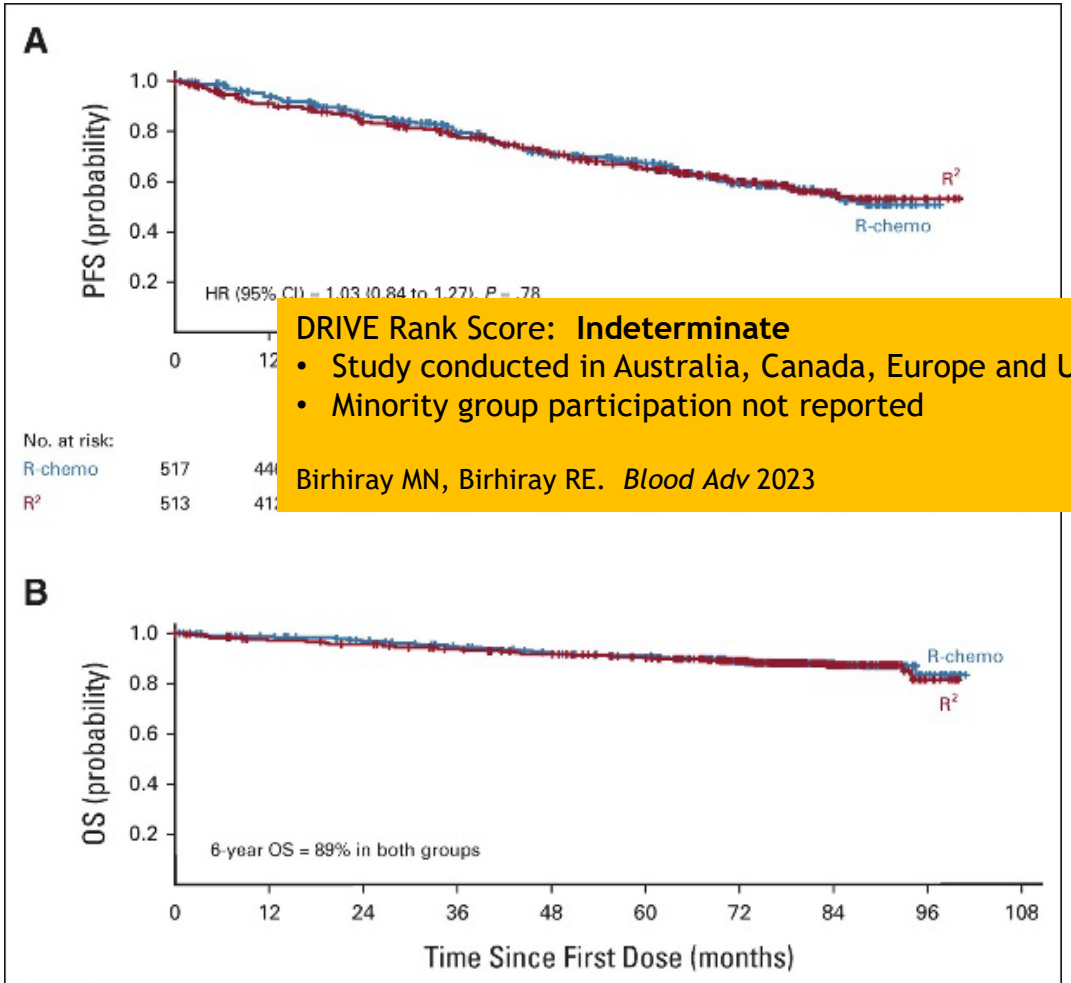
Morschhauser et al, *JCO* 2022



Progression-free survival

Overall survival

Morschhauser et al, *JCO* 2022



Progression-free survival

DRIVE Rank Score: **Indeterminate**

- Study conducted in Australia, Canada, Europe and U.S.
- Minority group participation not reported

Birhiray MN, Birhiray RE. *Blood Adv* 2023

Overall survival

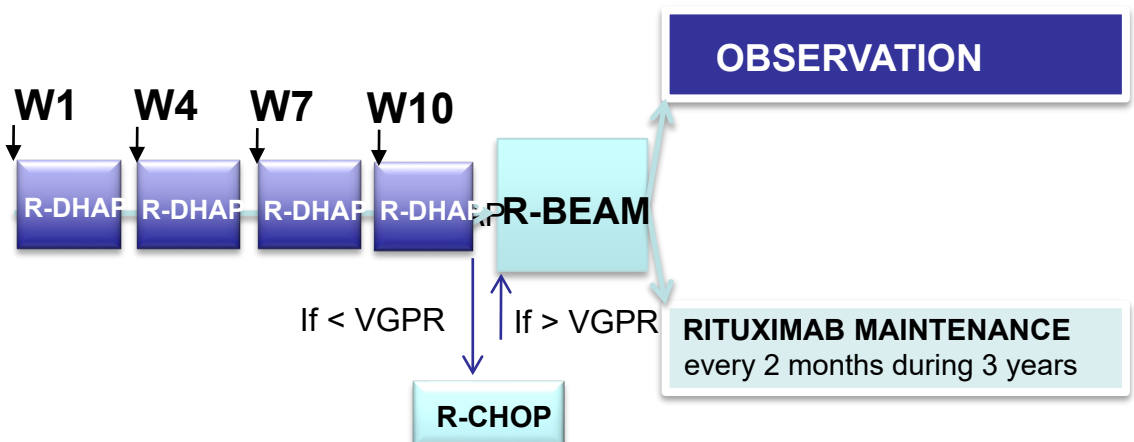
Morschhauser et al, *JCO* 2022

Mantle Cell Lymphoma

MCL Initial Therapy: 2024

- Watch/Wait patients
  - Indolent, CLL-like subtype, or low tumor burden, asymptomatic (15-20% of pts)
- Older, less fit patients
  - Bendamustine/Rituximab, Lenalidomide/Rituximab
  - Utilize BTKi in TP53 deleted/mutated pts
- Younger, medically fit patients
  - R-Benda-based regimen +/- AraC and/or Acalabrutinib *(ECOG 4181; results pending)*
  - Rituximab plus high-dose cytarabine-based regimen → Auto SCT→ Maintenance R *(LeGouill et al, NEJM 2017; Sarkozy et al, JCO 2023)*
  - **Is ASCT needed if MRD negative after induction therapy?** *(ECOG 4151)*
  - **Is ASCT needed if BTKi included in front-line therapy?** *(TRIANGLE, ASH 2022)*

LyMa trial: ASCT +/- Rituximab maintenance in MCL (LeGouill et al, *NEJM* 2017)



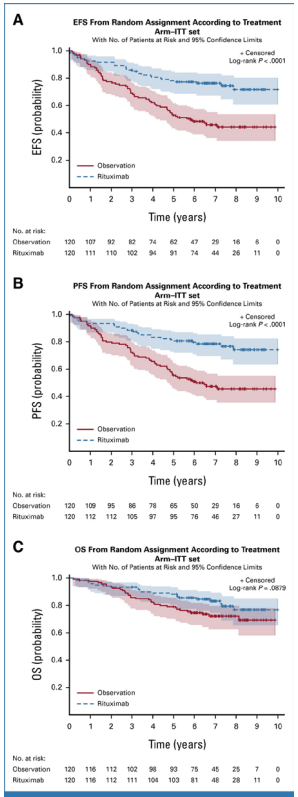
R-DHAP: Rituximab 375mg/m2; aracytine 2g/m2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m2 d1 (or **oxaliplatin** or carboplatin)

R-BEAM: Rituximab 500mg/m2 d-8; BCNU 300mg/m2 d-7; Etoposide 400mg/m2/d d-6 to -3; aracytine 400mg/m2/d d-6 to d-3; melphalan 140mg/m2 d-2

LyMa trial: ASCT +/- Rituximab maintenance in MCL: Long-term Follow-Up

Conclusions:

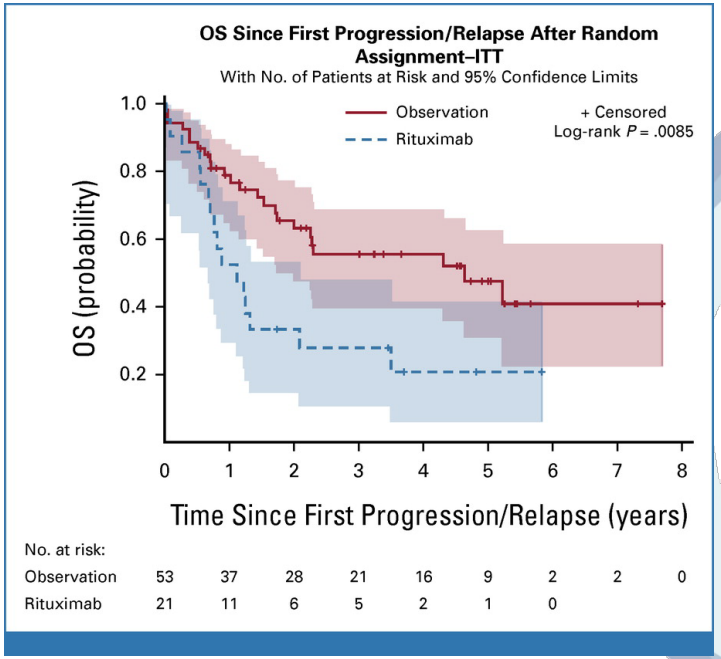
- PFS benefit of RM after ASCT remains after 7-year follow-up
- RM was not associated with an increase in infection-related mortality, making this strategy a safe standard of care
- POD24-relapsing patients in the RM arm had poorer OS than those in the Obs arm, despite similar salvage strategies



EFS
p<.0001

PFS
p<.0001

OS
p=.09



Sarkozy et al. *JCO* 2023

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Sarkozy et al. *JCO* 2023

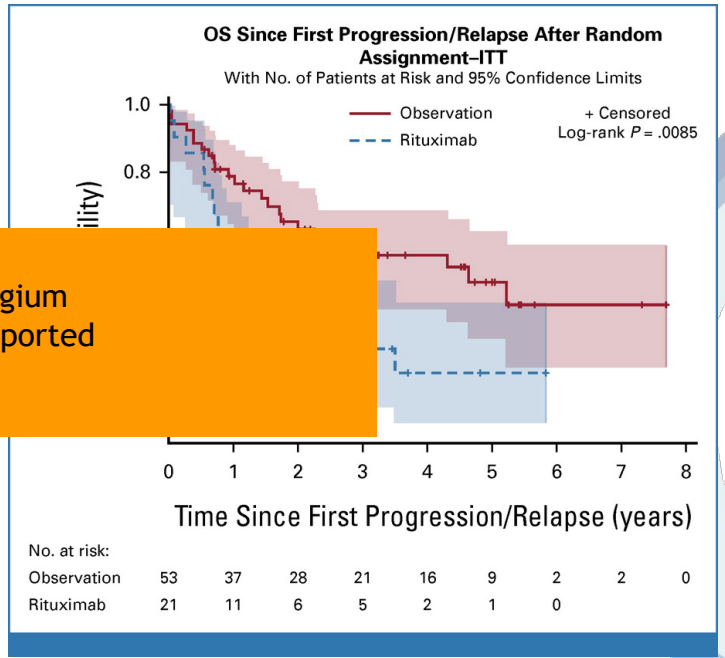
EFS
p<.0001

OS
p=.09

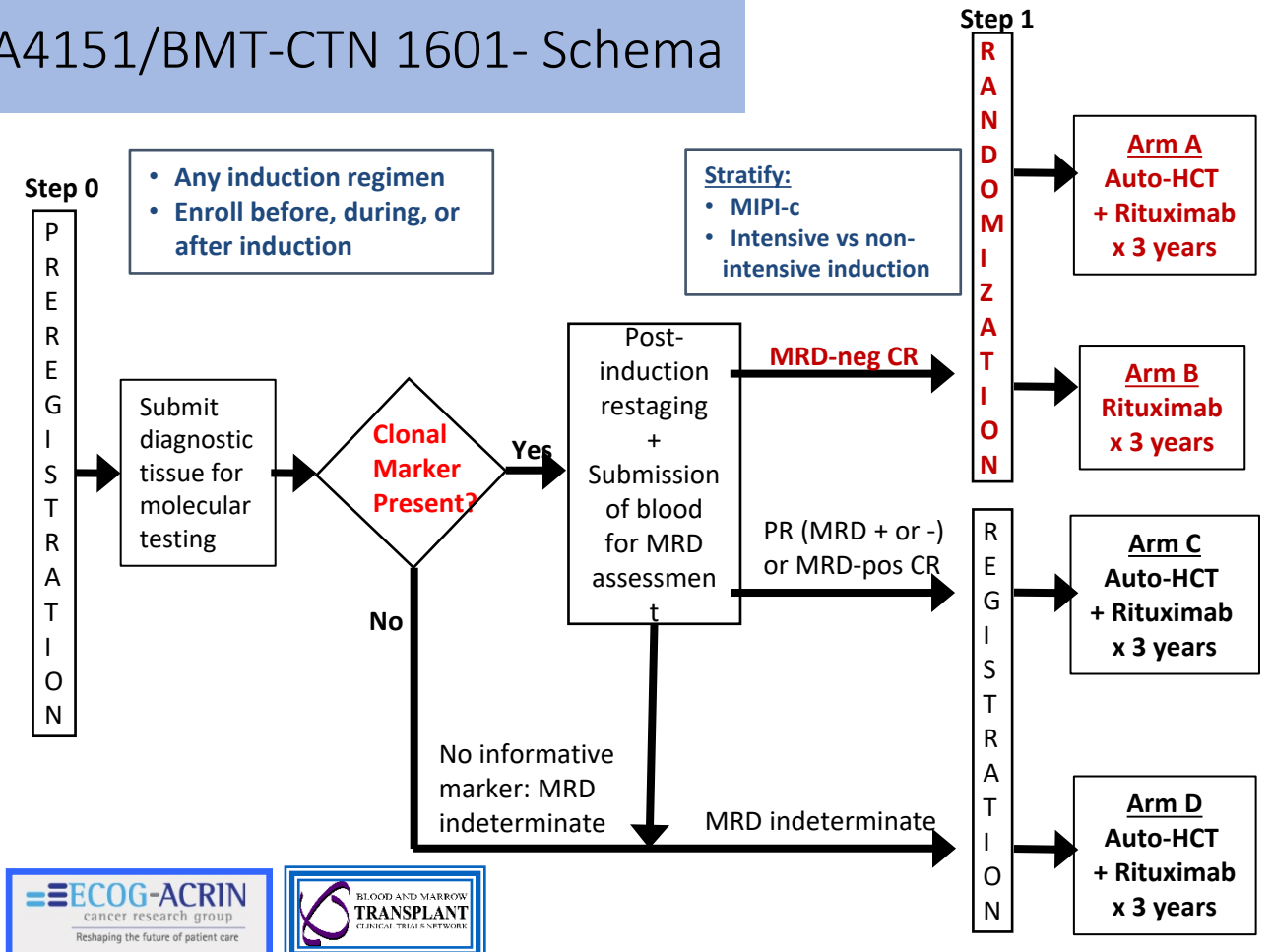
DRIVE Rank Score: **Indeterminate**

- Study conducted in France and Belgium
- Minority group participation not reported

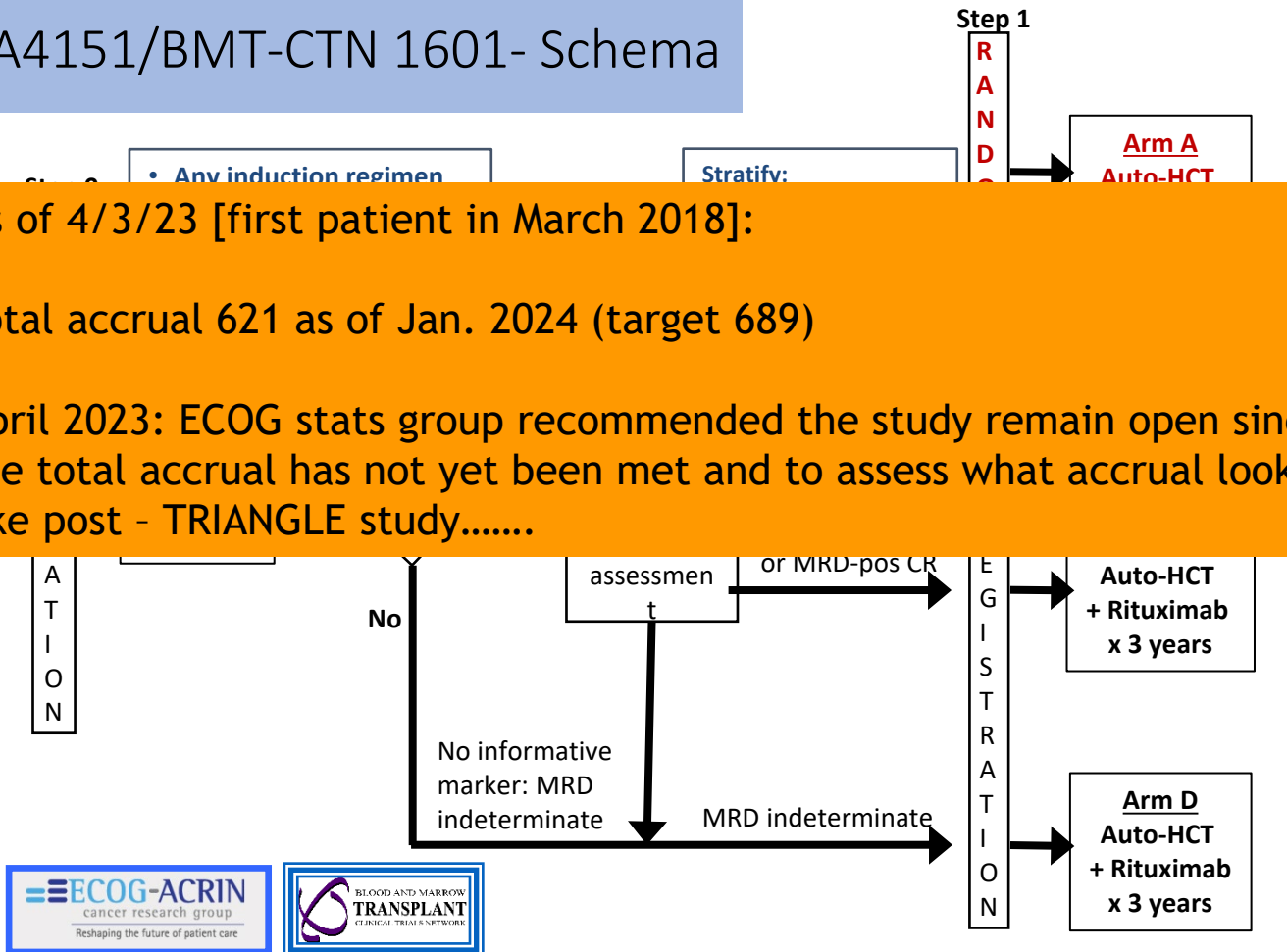
Birhiray MN, Birhiray RE. *Blood Adv* 2023



EA4151/BMT-CTN 1601- Schema



EA4151/BMT-CTN 1601- Schema



As of 4/3/23 [first patient in March 2018]:

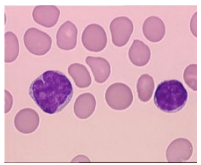
Total accrual 621 as of Jan. 2024 (target 689)

April 2023: ECOG stats group recommended the study remain open since the total accrual has not yet been met and to assess what accrual looks like post – TRIANGLE study…….

- *ASH 2022: Plenary Session, Abstract #1(slides courtesy of M. Dreyling)*

TRIANGLE:

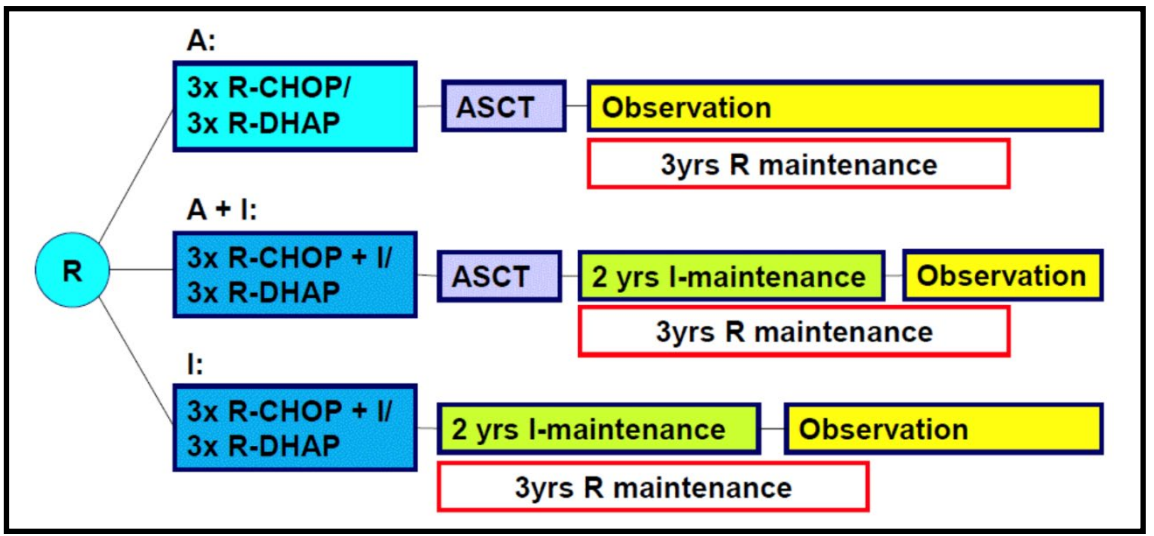
AUTOLOGOUS TRANSPLANTATION AFTER A RITUXIMAB/IBRUTINIB/ARA-C CONTAINING INDUCTION IN GENERALIZED MANTLE CELL LYMPHOMA – A RANDOMIZED EUROPEAN MCL NETWORK TRIAL



M Dreyling, J Doorduijn, E Giné, M Jerkeman, J Walewski, M Hutchings, U Mey, J Riise, M Trneny, V Vergote, M Celli, O Shpilberg, M Gomes da Silva, S Leppa, L Jiang, C Pott, W Klapper, D Gözel, C Schmidt, M Unterhalt, M Ladetto*, E Hoster*

LMU University Hospital Munich, Germany; Erasmus MC Cancer Institute, University Medical Center Rotterdam, Netherlands; Hospital Clinic of Barcelona, Spain; Skane University Hospital and Lund University, Lund, Sweden; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Rigshospitalet, Copenhagen University Hospital, Denmark; Kantonsspital Graubuenden, Chur, Switzerland; Oslo University Hospital, Oslo, Norway; Charles University and General University Hospital, Prague, Czech Republic; University Hospitals Leuven, Belgium; Ospedale degli Infermi di Rimini, Italy; Assuta Ramat Hahayal Medical Center, Tel Aviv, Israel; Instituto Português de Oncologia, Lisboa, Portugal; Helsinki University Hospital Comprehensive Cancer Center, Finland; IBE, LMU University Munich, Germany; University of Schleswig-Holstein, Kiel, Germany; Az Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

Front-line MCL, ASCT-eligible: TRIANGLE study

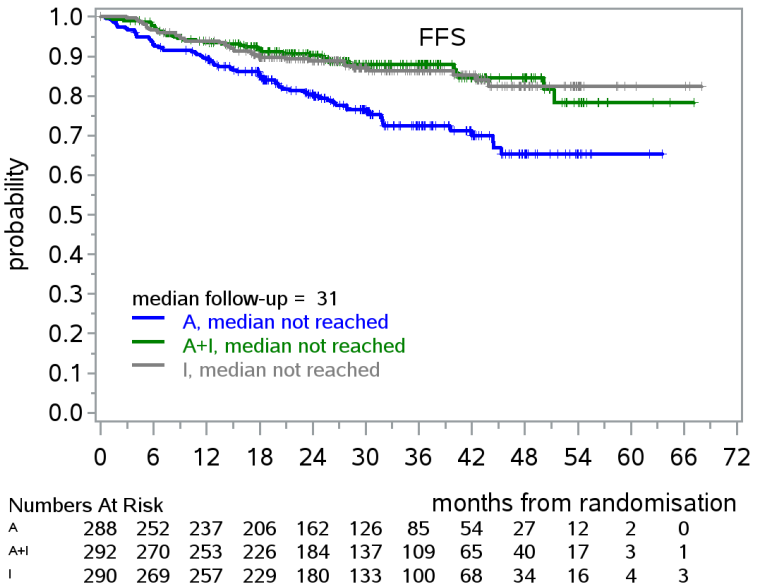


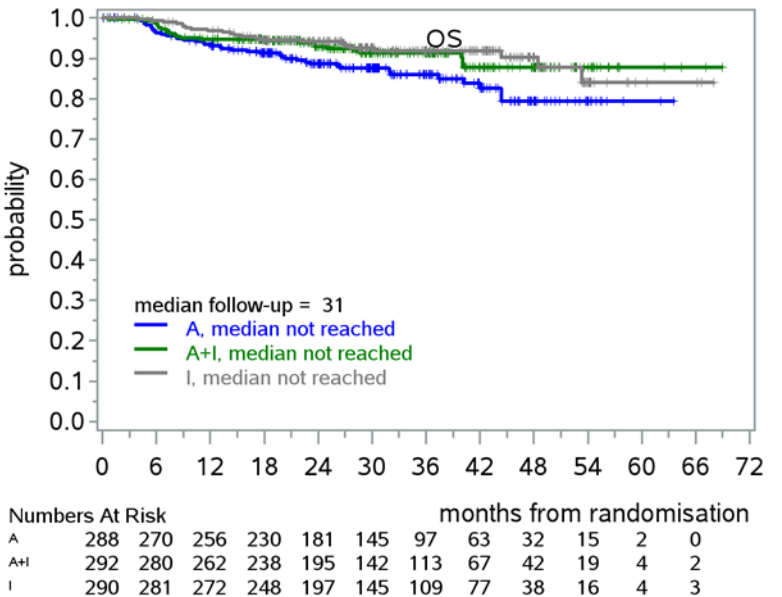
Between 2016-2020, 870 patients randomized 1:1:1

R maintenance allowed per institutional guidelines (54-58% of pts received R maint)

Dreyling et al, ASH Plenary 2022, Abstract 1

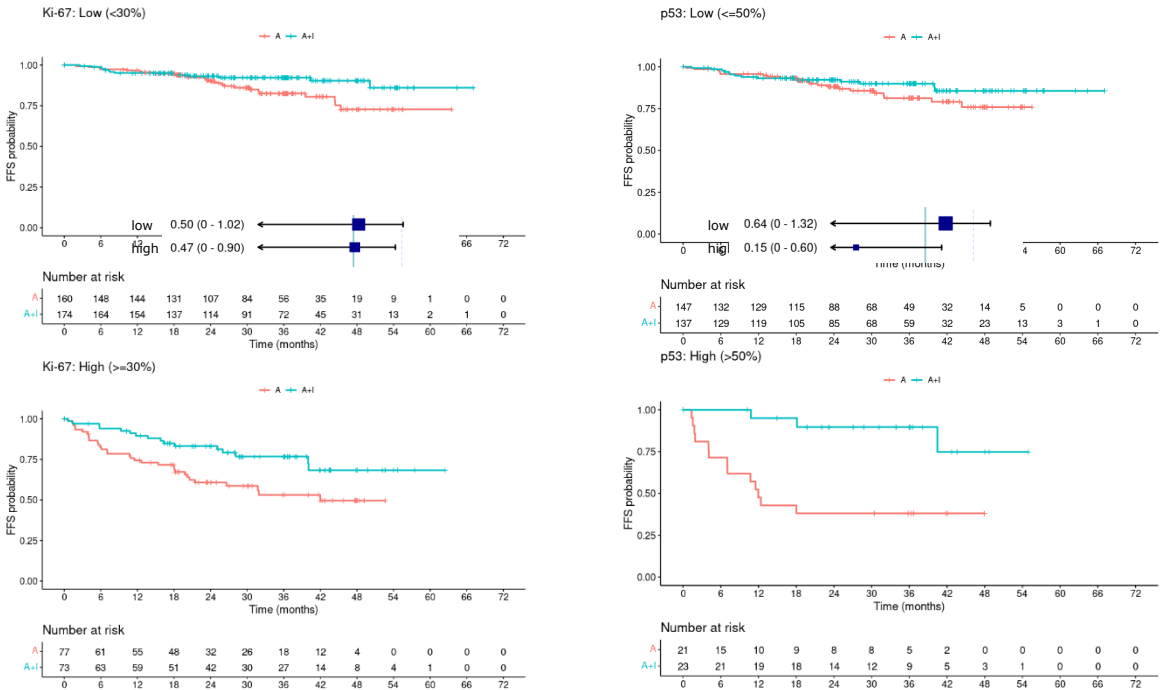
TRIANGLE: FFS and OS





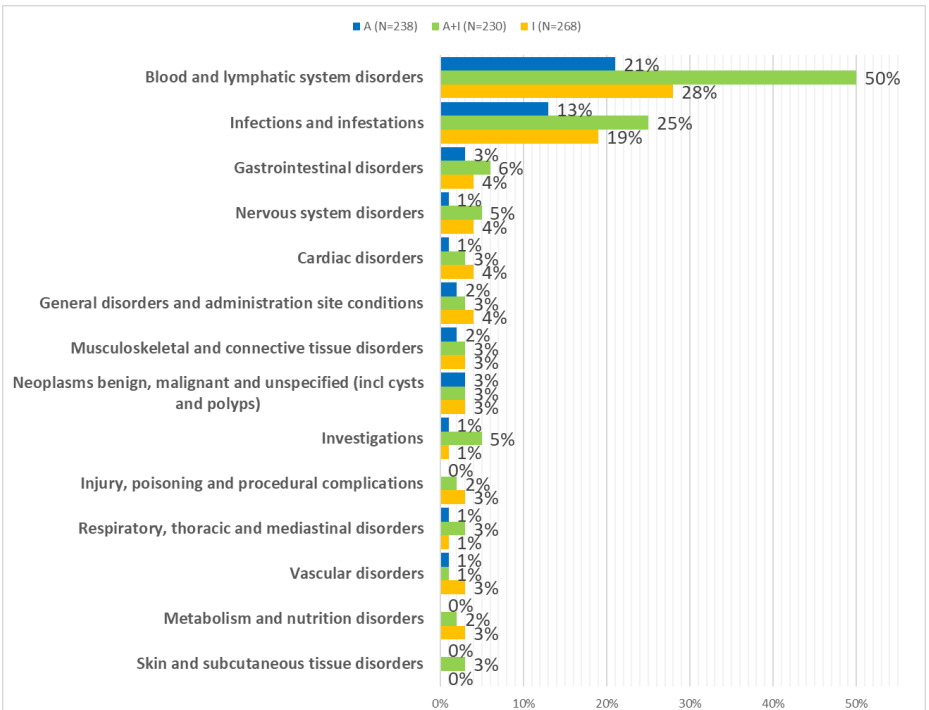
A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

TRIANGLE: FFS Superiority of A+I vs. A by Ki-67 score and p53 expression



A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I

TRIANGLE: Grade 3-5 AEs (including maintenance and follow-up)



Grade 3-5

Adverse Events by Preferred Term	A (N=238)		A+I (N=230)		I (N=268)	
Neutropenia	40	17%	101	44%	62	23%
Febrile neutropenia	6	3%	14	6%	7	3%
Thrombocytopenia	5	2%	13	6%	8	3%
Leukopenia	4	2%	10	4%	6	2%
Anaemia	4	2%	6	3%	4	1%
Lymphopenia	3	1%	1	0%	5	2%

Grade 5

Patients with at least one grade 5 AE by SOC

Adverse Events by System Organ Class	A (N=238)		A+I (N=230)		I (N=268)	
Infections and infestations	3	1%	2	1%	2	1%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0%	1	0%	0	0%
Cardiac disorders	0	0%	0	0%	1	0%
Respiratory, thoracic and mediastinal disorders	0	0%	1	0%	0	0%
Vascular disorders	1	0%	0	0%	0	0%

A arm: R-CHOP/R-DHAP+ASCT; **A+I arm:** IR-CHOP/R-DHAP+ASCT+I; **I arm:** IR-CHOP/R-DHAP+I. I: ibrutinib

Dreyling et al, Abs. 1, ASH Plenary 2022

Do preliminary results from TRIANGLE change practice?

- Follow up is relatively short (median 31 mo)
- Awaiting full publication of TRIANGLE results (in press, *Lancet* 2024)
- Higher cytopenic and infectious complications during Ibrutinib maintenance
  - **Did this differ in the ~50% of patients also receiving concurrent R maintenance?**
- Ibrutinib withdrawn from U.S. market for MCL (April 2023)
  - **Will a 2nd gen BTK-i be covered 1L for this indication? (NCCN 2023 includes TRIANGLE 1st line)**
  - **How to pair BTK-i with other induction regimens (RCHOP/RHDAP not often used in U.S.)?**
- EA4151 is asking a different question (i.e., benefit of auto SCT in MRD-neg patients)
  - Anticipated to complete accrual in 2024
  - Many centers still offering 1L auto-HCT and enrolling on EA4151

DRIVE Rank Score: Indeterminate, full publication pending

Modified from T Fenske; ECOG presentation, April 2023

SYMPATICO Trial: Mantle cell lymphoma
Ibrutinib/Venetoclax vs Ibr/Placebo

- BTKi is a standard of care for relapsed MCL
  - Ibrutinib, acalabrutinib, zanubrutinib
- Ibr/Ven combination is synergistic
- R/R MCL* → Ibr/Ven x 2 y vs Ibr/Placebo x 2 y
  Ibr continued until progression or Rx intolerance
- **CR and PFS significantly higher for Ibr/Ven vs Ibr/Placebo (n=267)**
- *No unexpected toxicities with the combination*
- **Conclusion: Positive trial showing efficacy of Ibr/Ven in R/R MCL**
  - Challenged by voluntary removal of Ibr for the FDA's MCL indication in 2023
  - Emerging data may support the use of an alternative BTKi plus Ven

DRIVE Rank Score: Indeterminate, pending full publication

*A cohort of previously untreated pts was also accrued, results not reported

Wang M, et al. ASH 2023: Late-breaking abstract-2

Figure. PFS per INV Assessment Using Global Censoring (primary endpoint)

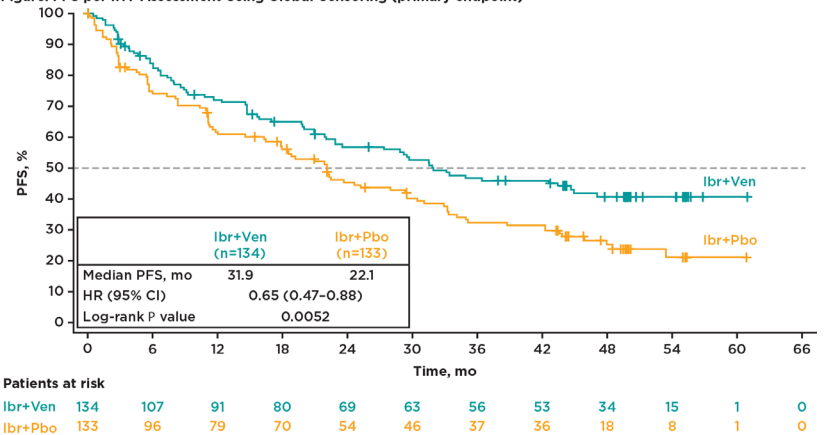


Table. Primary and Secondary Efficacy Endpoints

	Ibr+Ven (n=134)	Ibr+Pbo (n=133)	HR (or rate ratio) (95% CI)[a]	*P* value[b]
Median PFS by INV, mo				
Global censoring[c]	31.9	22.1	0.65 (0.47–0.88)	0.0052
US FDA censoring[d]	42.6	22.1	0.60 (0.44–0.83)	0.0021
Median PFS by IRC, mo				
Global censoring[c]	31.8	20.9	0.67 (0.49–0.91)	0.0108
US FDA censoring[d]	43.5	22.1	0.63 (0.45–0.87)	0.0057
Median TTNT, mo	NR	35.4	0.60 (0.40–0.89)	0.0096
ORR, %	82	74	1.10 (0.97–1.25)	0.1279
CR rate, %	54	32	1.66 (1.24–2.22)	0.0004
Median duration of response, mo	42.1	27.6		
Median duration of CR, mo	NR	40.8		
Median OS, mo (interim analysis)	44.9	38.6	0.85 (0.62–1.19)	0.3465

[a]HRs are reported for PFS, TTNT, and OS; rate ratios are reported for CR rate and ORR.
[b]*P* values were determined by stratified log-rank test for PFS, TTNT, and OS, and by stratified Cochran-Mantel-Haenszel test for CR rate and ORR (stratification factors: prior lines of therapy [1–2 vs ≥3] and TLS risk category [low vs increased risk]).
[c]Global censoring: pts without PD or death were censored at last follow-up without PFS event.
[d]US FDA censoring: pts without PD or death, with subsequent anticancer therapy, or with 2 or more missed visits prior to the PFS event were censored at last follow-up without PFS event.

My thanks for your attention!