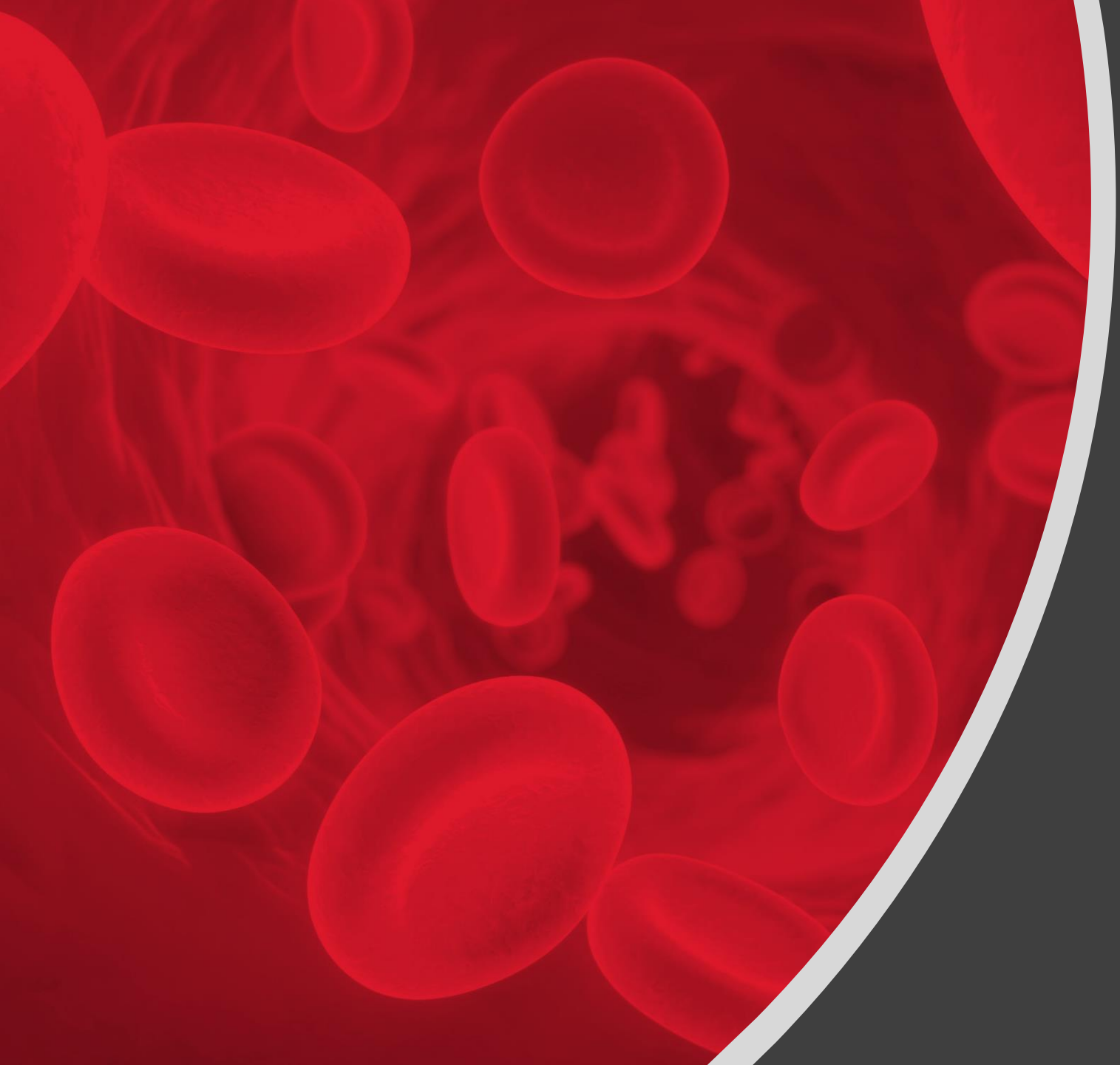


HIGHLIGHTS OF ASH 2022

07 February 2023

David Macdonald, MD, FRCPC

Hematologist, The Ottawa Hospital

Part 1. CLL

- Targeted therapy (Ven-O) beats Chemoimmunotherapy (again!)
- Combination BTKi and VEN – the way of the future?
- Novel BTK inhibitors – if at first you don’t succeed…

345. Genetic Markers and Front Line FCR/BR vs. RVe, GVe and GIVe Treatment – Outcome Results from the CLL13/GAIA Trial (Tausch E, et al.)

Tausch E, et al.

CLL13 / GAIA study

Fit patients with untreated CLL: CRS ≤ 6 & normal CrCl

No *TP53* mutation or del(17p) in central screening

Randomized

CIT: FCR/BR*
6 cycles, n=230

RVe
12 cycles, n=230

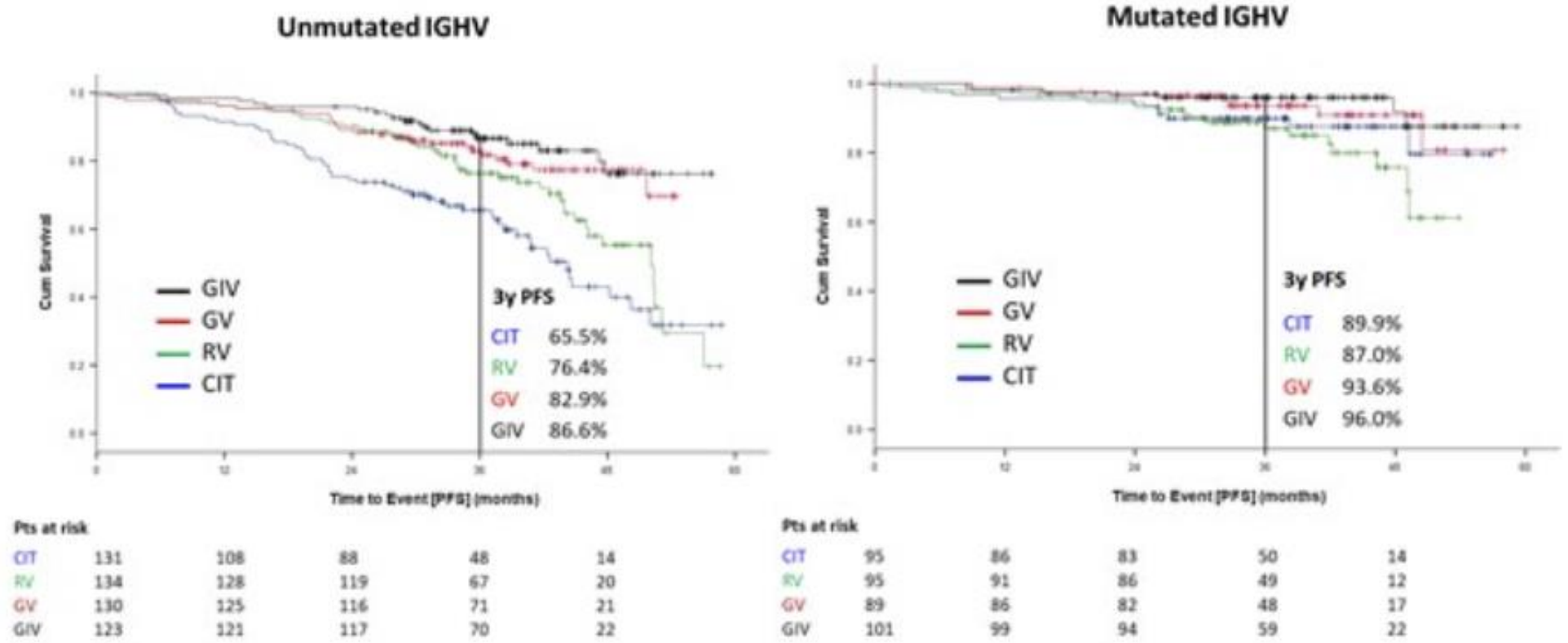
GVe
12 cycles, n=230

GIVe
15# cycles, n=230

CLL13 / GAIA study

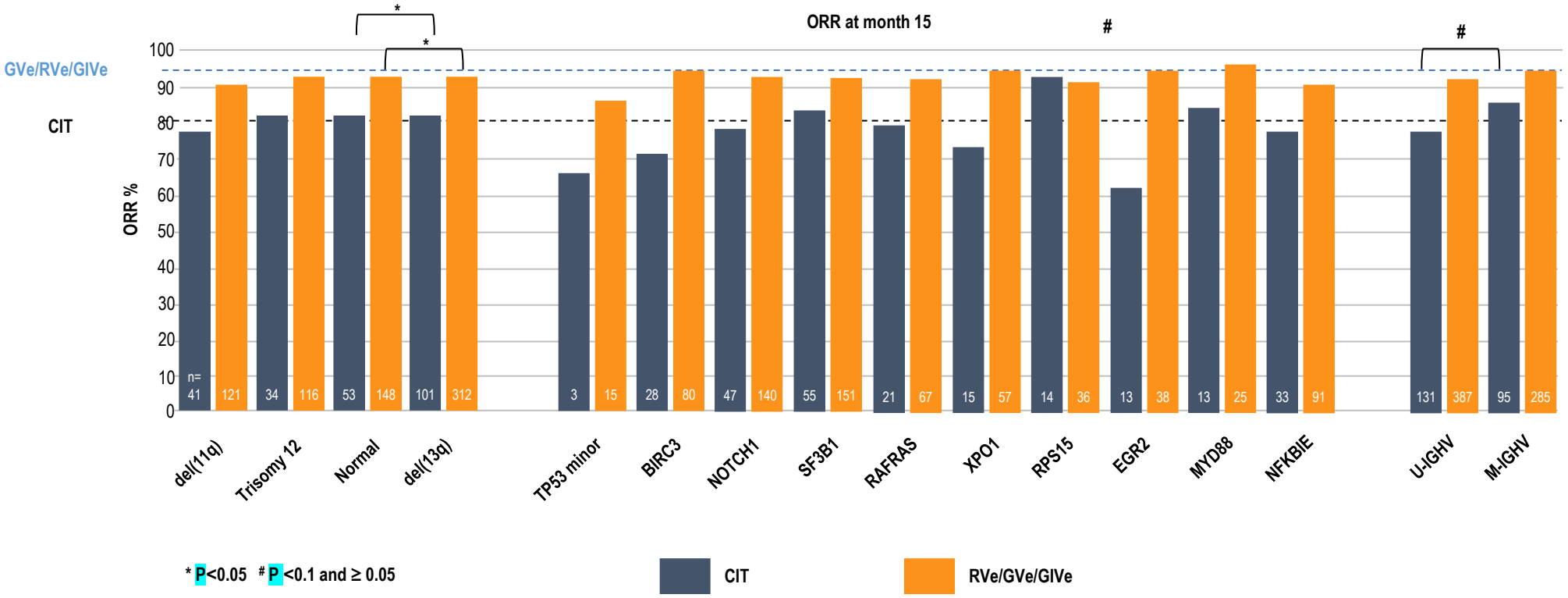
From EHA (June 2022)

B. Progression-free survival according to treatment arm and IGHV status



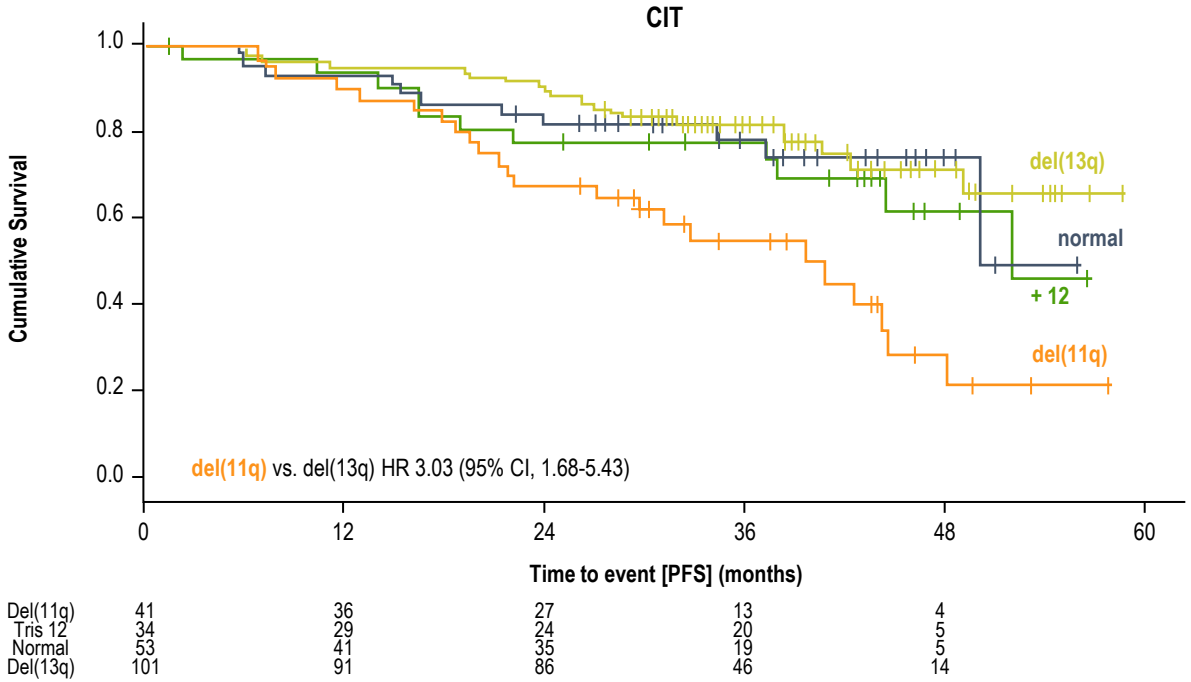
CLL13 / GAIA study

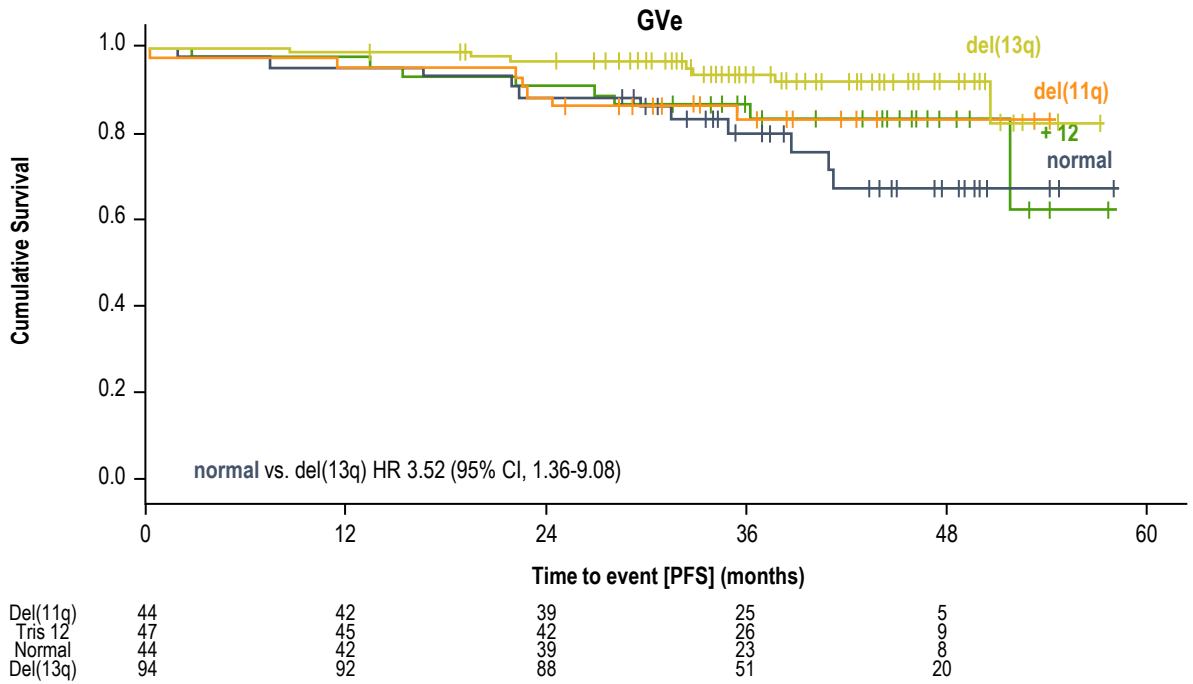
ORR by Genetic Subgroups



- Patients with del(13q) had the best ORR with either RVe/GVe/GIVe or CIT
- uIGHV and mutated EGR2 showed a trend for lower ORR with CIT (both P=0.08)

CLL13 / GAIA study



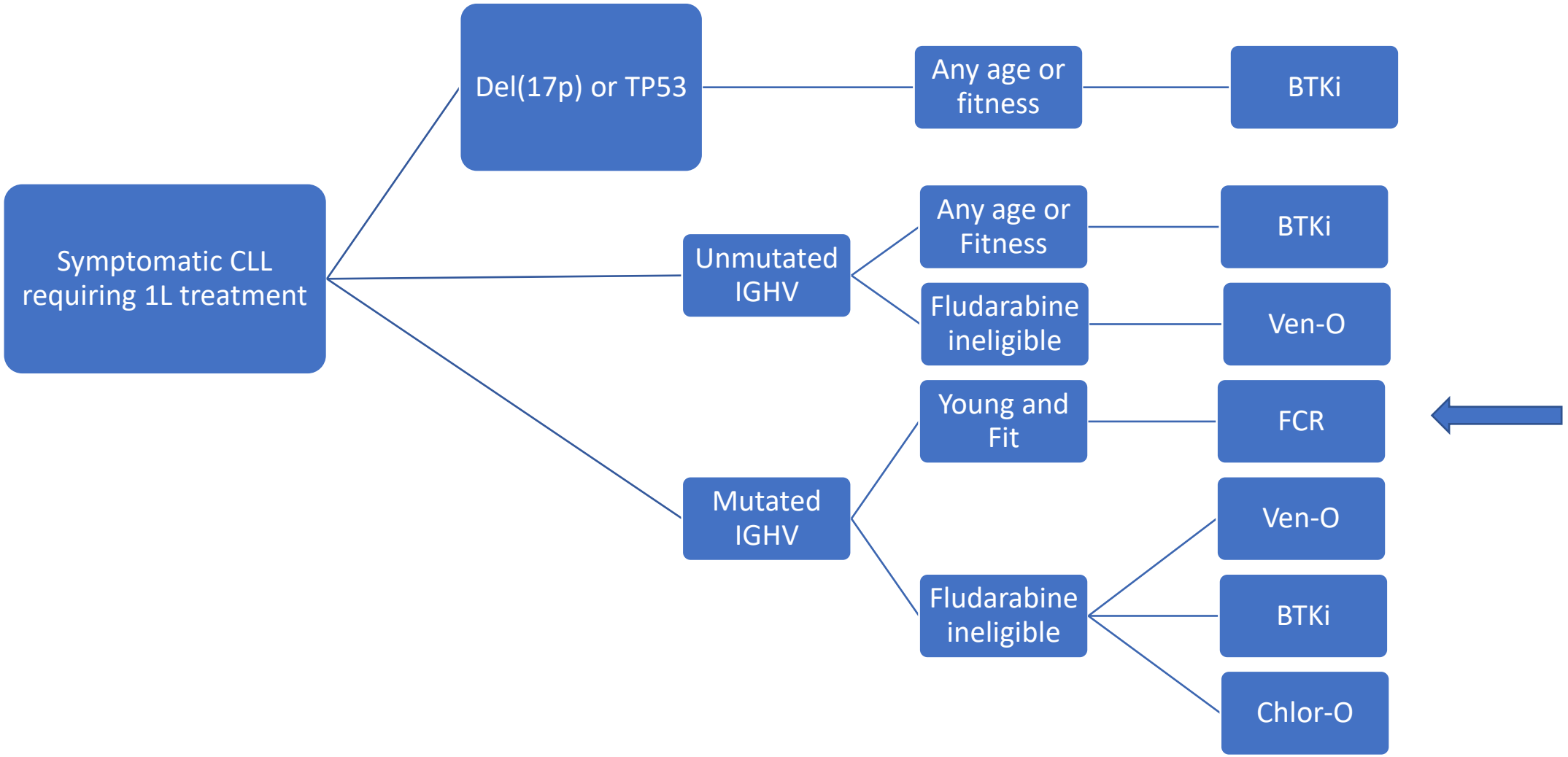


	mPFS (months)		3 year PFS (%)	
	CIT	GVe	CIT	GVe
del(11q)	39.5	NR	54.9	83.0
del(13q)	NR	NR	81.9	93.8

CLL13 / GAIA conclusions

- **Venetoclax and obinutuzumab (with or without ibrutinib) resulted in better response rates than chemoimmunotherapy, regardless of genetic risk factors (excluding del(17p) or TP53 mutations)**
- **Del(11q) was only associated with shorter PFS when treated with CIT, but not with RVe/GVe/GIVe.**
- **Del(13q) was associated with significantly longer PFS with GVe therapy.**

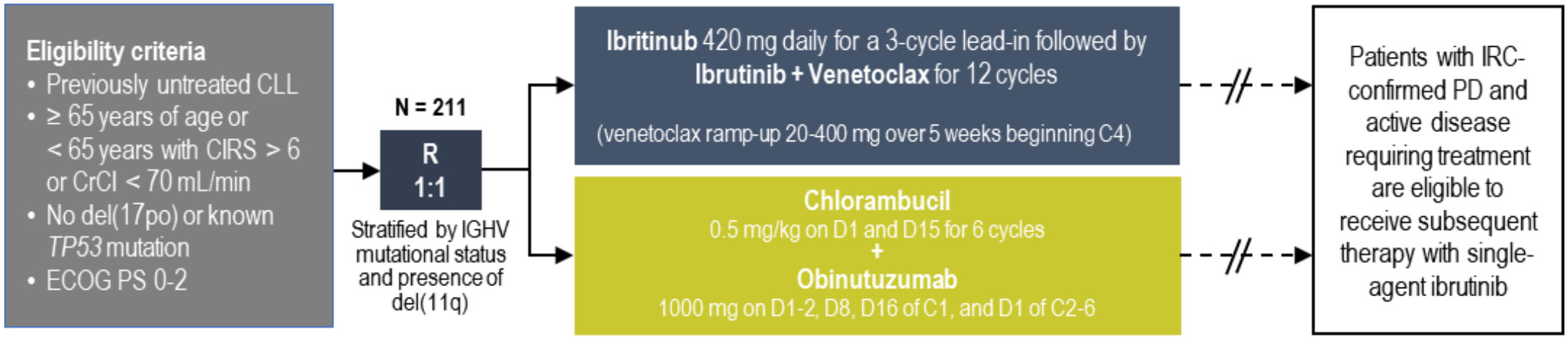
CLL13 / GAIA – Ontario context



93. Residual Disease Kinetics Among Patients with High-Risk Factors Treated with First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): The Glow Study

Niemann C, et al.

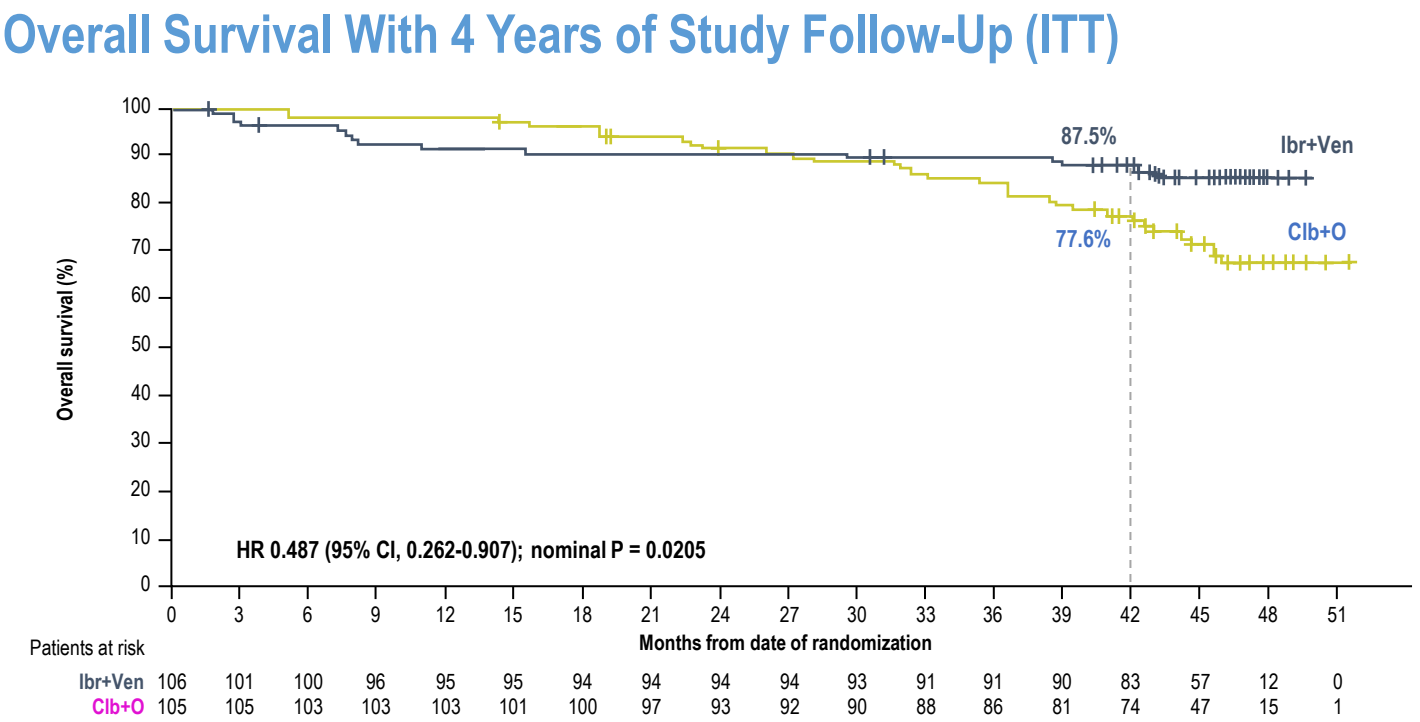
GLOW study


Eligibility criteria
• Previously untreated CLL
• ≥ 65 years of age or < 65 years with CIRS > 6 or CrCl < 70 mL/min
• No del(17p) or known *TP53* mutation
• ECOG PS 0-2
N = 211
R 1:1
Stratified by IGHV mutational status and presence of del(11q)
Ibritinub 420 mg daily for a 3-cycle lead-in followed by **Ibrutinib + Venetoclax** for 12 cycles
(venetoclax ramp-up 20-400 mg over 5 weeks beginning C4)
Chlorambucil
0.5 mg/kg on D1 and D15 for 6 cycles
+
Obinutuzumab
1000 mg on D1-2, D8, D16 of C1, and D1 of C2-6
Patients with IRC-confirmed PD and active disease requiring treatment are eligible to receive subsequent therapy with single-agent ibrutinib

GLOW study

- Primary Endpoint: 3.5-year PFS was 74.6% vs 24.8% (HR 0.214; P<0.0001)
- OS was 87.5% vs 77.6% (P=0.0205)
- 40% had uMRD ($<10^{-4}$) by 2 years, and >25% had deep uMRD ($<10^{-5}$)
- uMRD rates were higher and achieved faster in patients with uIGHV vs mIGHV
- uMRD was better sustained in mIGHV CLL
- Estimated PFS was ≥90% at 2 years post-treatment for uMRD at EOT+3, irrespective of IGHV status

GLOW study



Ontario Context:

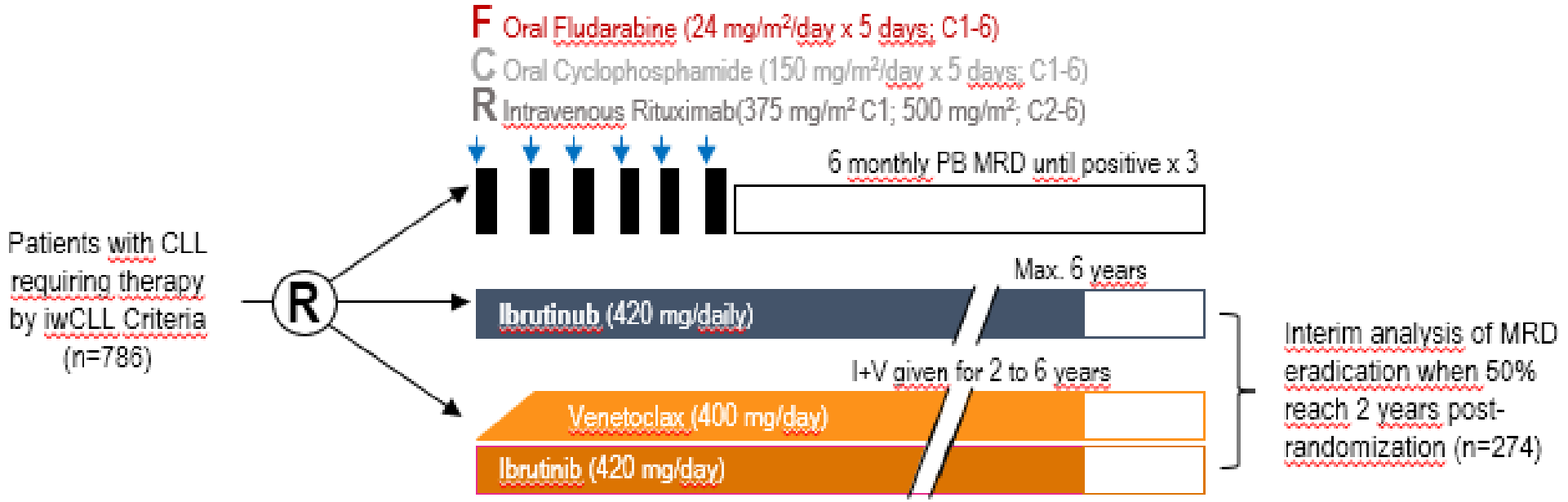
- Combination Ibr+Ven is still experimental and is not available outside of clinical trials
- Clb-O would no longer be considered the standard to compare to – the current question is if Ibr-Ven is better than Ven-O

94. Combination of Ibrutinib Plus Venetoclax with MRD-Driven Duration of Treatment Results in a Higher Rate of MRD Negativity in IGHV Unmutated Than Mutated CLL: Updated Interim Analysis of FLAIR Study

Munir T, et al.

FLAIR Study

Phase 3 FLAIR Study Design



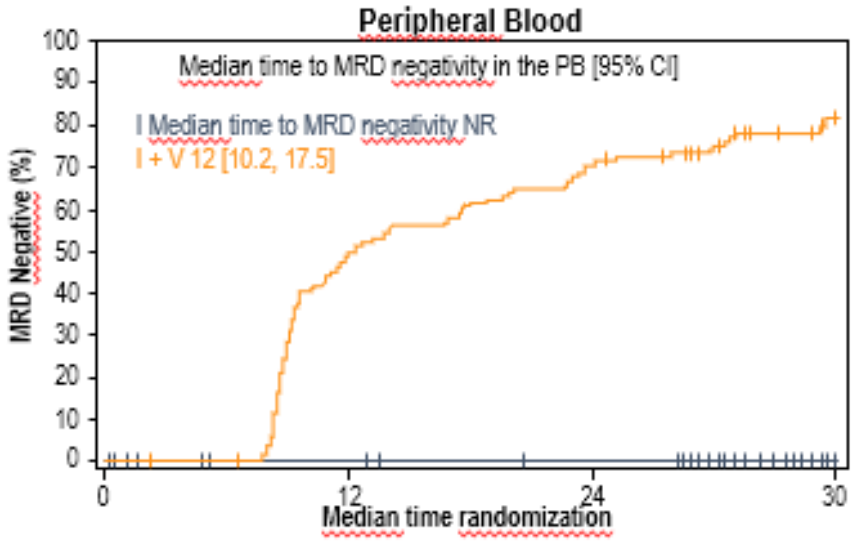
Duration of therapy in I and I+V arms depended on MRD status:
PB MRD every 6 mts; if negative, repeat after 3 mts and then PB and BM at 6 mts – if all MRD negative, then first PB MRD negative result is time to MRD negativity, and planned duration of treatment is twice that period

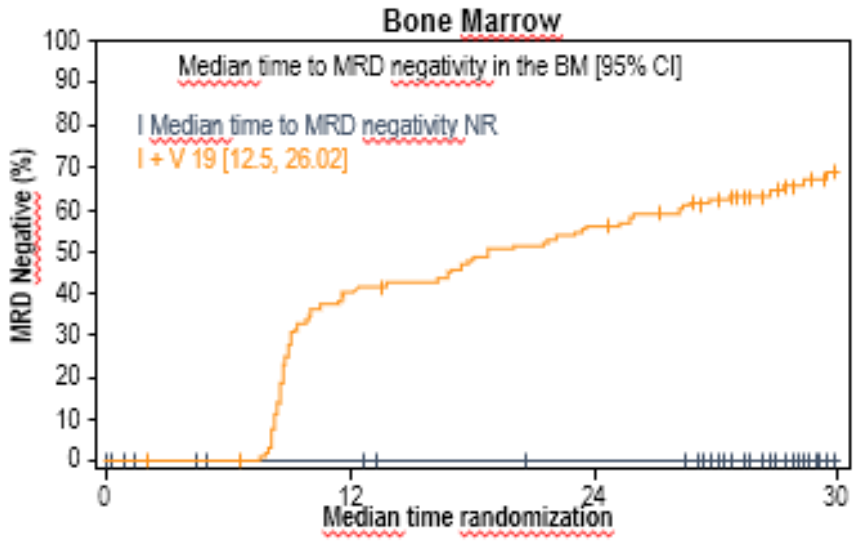
FLAIR Study

- Primary objectives:
  - To compare if I+V is superior to FCR for PFS
  - To compare if I+V is superior to I for MRD

The answer will be yes – we know this from Gaia study

Time to MRD Negativity in PB and BM by Arm





MRD Negative Remission Within 2 Years by Subgroup (I+V)

IGHV unmutated: 79.7%

IGHV mutated: 56.4%

11q del: 82.8%

Tri 12: 67.9%

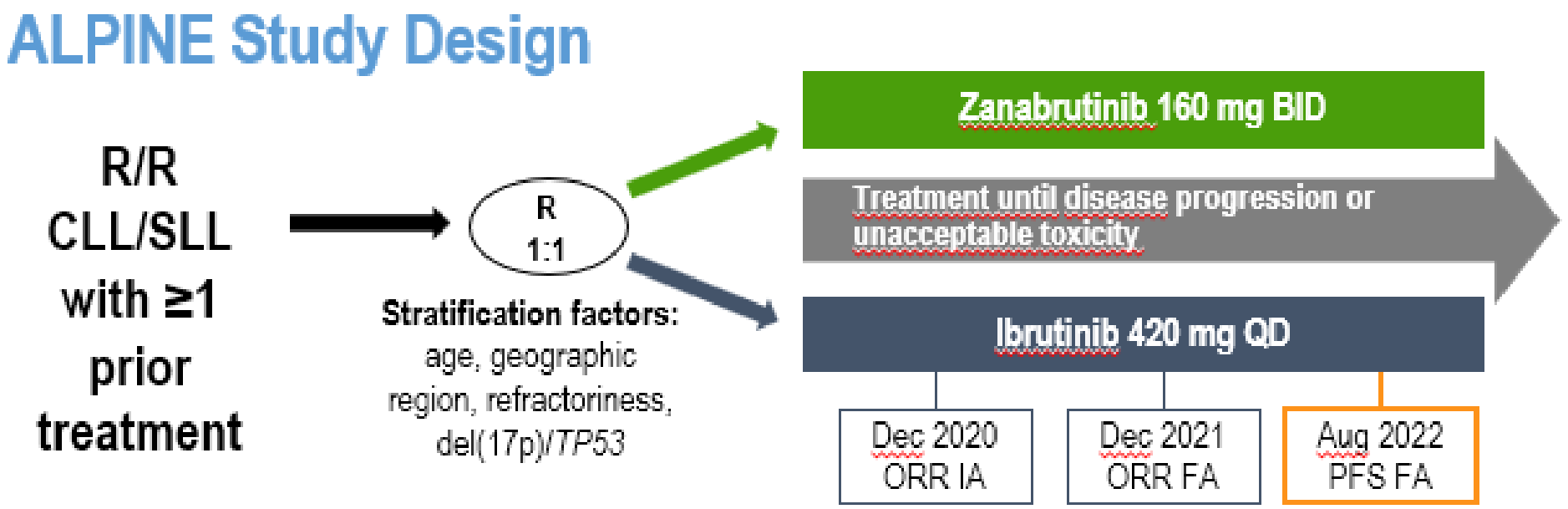
Normal karyotype: 67.9%

13q del: 54.5%

LBA-6. Zanubrutinib demonstrates superior progression-free survival (PFS) compared with ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL): Results from the final analysis of ALPINE randomized phase 3 study

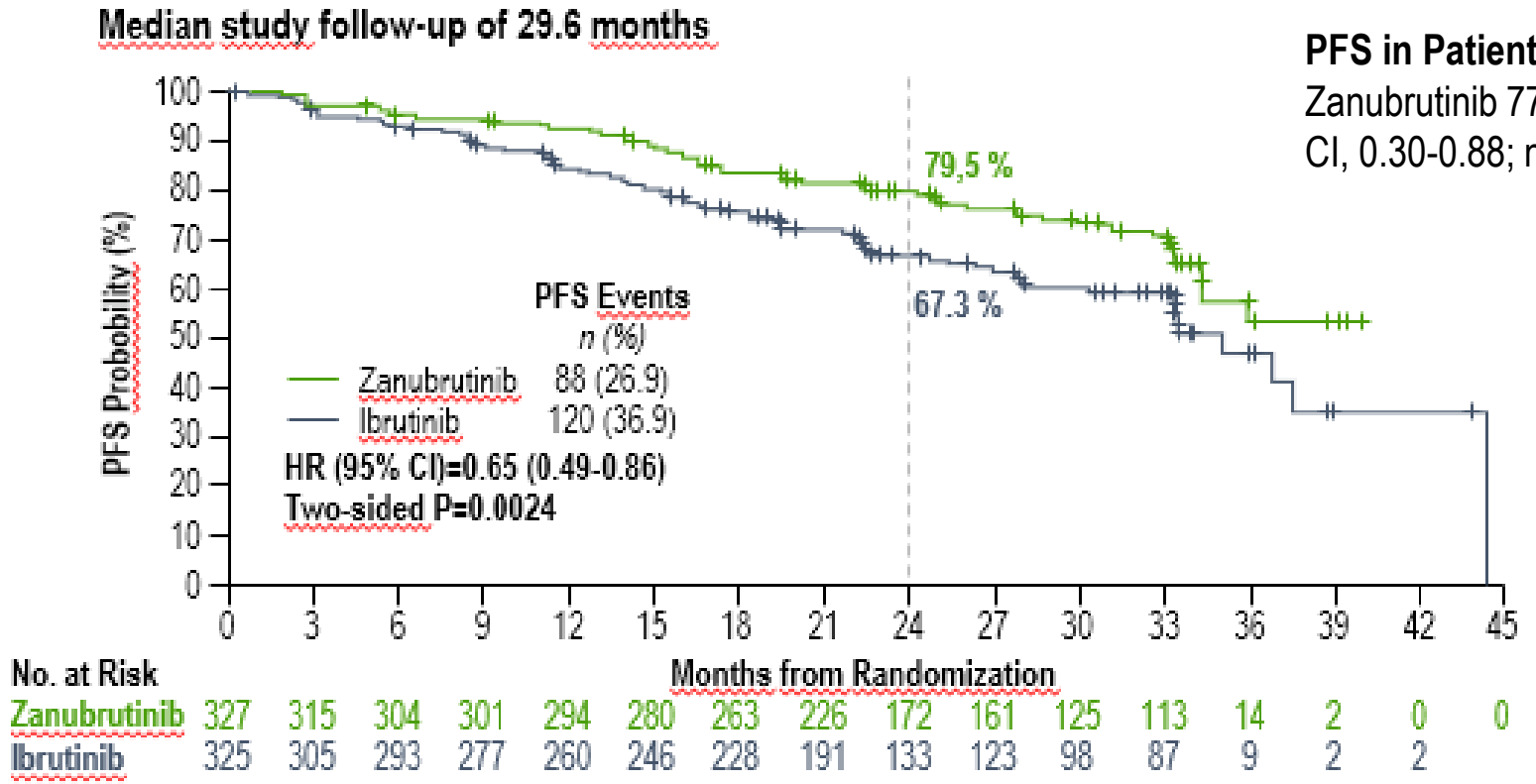
Brown J, et al.

ALPINE Study



ALPINE STUDY

PROGRESSION FREE SURVIVAL



PFS in Patients with del(17p)/*TP53*^{mut}
Zanubrutinib 77.6% vs ibrutinib 55.7% (HR 0.52, 95% CI, 0.30-0.88; nominal P=0.0134)

ALPINE – Overall Safety

N (%)	Zanubrutinib (N=324)	Inrutinib (N=324)
Any grade event	318 (98.1)	321 (99.1)
SAE	136 (42.0)	162 (50.0)
AE leading to discontinuation	50 (15.4)	72 (22.2)
Afib/flutter	17 (5.2)	43 (13.3)

ALPINE – Cardiac Safety

	Zanubrutinib (N=324)	Ibrutinib (N=324)
Cardiac adverse events	69 (21.3%)	96 (29.6%)
Serious cardiac adverse events	6 (1.9%)	25 (7.7%)
Cardiac adverse events leading to treatment discontinuation	1 (0.3)	14 (4.3)
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	0	5 (1.5)
Cardiac arrest	0	2 (0.6)
Cardiac failure	0	2 (0.6)
Congestive cardiomyopathy	0	1 (0.3)
Myocardial infarction	0	1 (0.3)
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)
Cardiac failure acute	0	1 (0.3)

ALPINE – Conclusions in Ontario Context

- In Ontario, both ibrutinib and acalabrutinib are funded for front-line (in high risk patients) and at relapse (in all patients)
- Acalabrutinib is already beginning to be recommended over ibrutinib for most patients, based on head to head comparison that shows better safety and equal efficacy
- This ALPINE comparison shows zanubrutinib is more effective than ibrutinib in relapsed patients
  - We do not know if it is more effective than acalabrutinib
  - We do not know if it is better than ibrutinib in front-line patients
- Zanubrutinib is currently available through compassionate access

- For patients ***currently on ibrutinib***, it **may be** reasonable to consider switching to zanubrutinib if having side effects on ibrutinib

961. Efficacy of Pirtobrutinib in Covalent BTK-Inhibitor Pre-Treated Relapsed / Refractory CLL/SLL: Additional Patients and Extended Follow-up from the Phase 1/2 BRUIN Study

Mato A, et al.

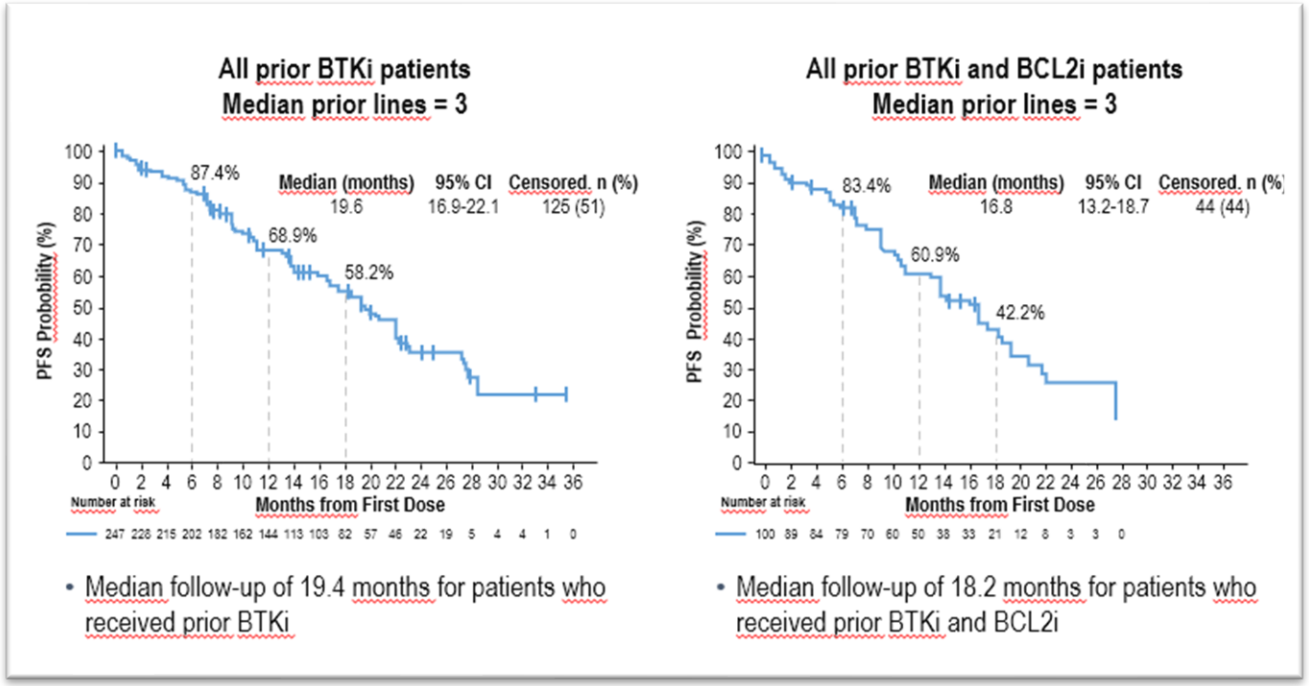
BRUIN Study

- 1st and 2nd gen BTKi are non-reversible, covalent binders of BTK
- Main mechanism of resistance to BTKi is mutation of C481 binding site
- 3rd gen BTKi Pirtobrutinib and Nemtabrutinib are reversible, non-covalent binders of BTK, and do not depend on binding at C481
- BRUIN – a Phase I/II study of pirtobrutinib in heavily pre-treated high risk CLL patients who have had prior BTK inhibitor

BRUIN Study – response rates and PFS

	Prior BTKi n=247	Prior BRKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

[a]ORR includes patients with a best response of CR, PR, and PR-L.



BRUIN Study – Ottawa Context

- Non-covalent, reversible BTK inhibitors might represent a future option for patients developing resistance on ibr / acala / zanu
- Remains to be seen if this mechanism of action makes them better than ibr/acala/zanu for patients who haven't had prior BTKi

- We have a clinical trial open using nemtabrutinib in relapsed CLL
- We will be opening a clinical trial of nemtabrutinib versus ibrutinib in previously untreated and relapsed CLL patients

Part 2. Mantle Cell Lymphoma

- Practice-changing study

1. Efficacy and Safety of Ibrutinib Combined with Standard First-Line Treatment or As Substitute for Autologous Stem Cell Transplantation in Younger Patients with Mantle Cell Lymphoma: Results from the Randomized Triangle Trial By the European MCL Network

Martin Dreyling, Jeanette K. Doorduijn, Eva Gine, Mats Jerkeman, Jan Walewski, Martin Hutchings, Ulrich Mey, Jon Riise, Marek Trneny, Vibeke K.J. Vergote, Melania Celli, Ofer Shpilberg, Maria Gomes da Silva, Sirpa Leppa, Linmiao Jiang, Christiane Pott, Wolfram Klapper, Döndü Gözel, Christian Schmidt, Michael Unterhalt, Marco Ladetto, and Eva Hoster

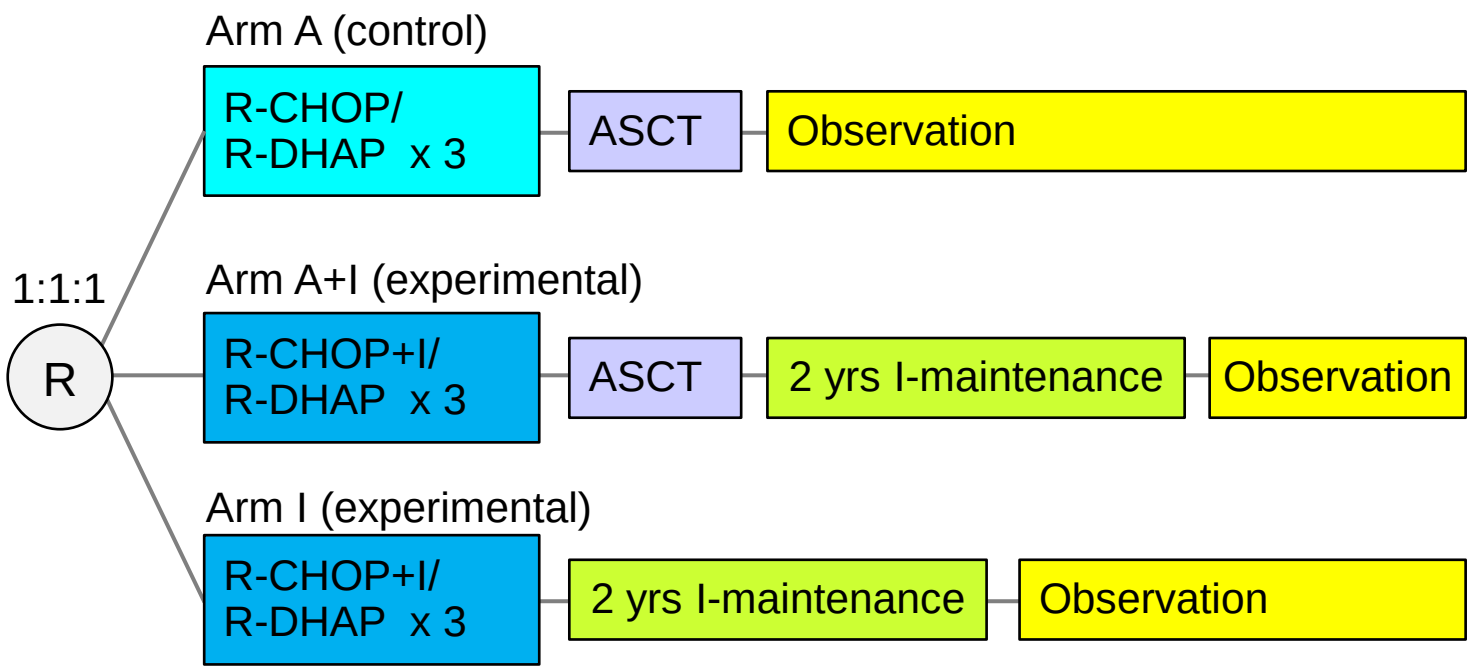
TRIANGLE: Trial Design

- MCL patients
- Previously untreated
- Stage II-IV
- Younger than 66 years
- Suitable for HA and ASCT
- ECOG 0-2

Primary outcome: FFS

Secondary outcomes:

- Response rates
- PFS, RD
- OS
- Safety



- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58%) /165 (57%)/158 (54%) of A/A+I/I randomized patients

Dreyling M, et al. Oral Abstract 1. ASH 2022.

TRIANGLE: Baseline Characteristics

Characteristic	Overall (n=870)	A (n=288)	A+I (n=292)	I (n=290)
Median age, years (range)	57 (27-68)	57 (31-65)	57 (36-68)*	58 (27-65)
Male sex	76%	76%	74%	79%
No MCL	8 (1%)	2 (CLL, FL)	4 (1 NHL NOS, 1 HD, 2 MZL)	2 (HCL, DLBCL)
Ann Arbor Stage (n=864)				
I	0%	0%	0%	0%
II	5%	4%	4%	6%
III	9%	8%	7%	10%
IV	87%	88%	89%	84%
ECOG > 1	1%	2%	1%	2%
MIPI Low	58%	58%	58%	58%
MIPI Intermediate	27%	27%	27%	27%
MIPI High	15%	14%	15%	16%

* 2 patients aged 66/68 randomized

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 M, et al. Oral Abstract 1. ASH 2022.

TRIANGLE: Response at End of Induction

	Overall	A	A+I/I	A+I	I
ED	2 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)	0 (0%)
PD	17 (2%)	11 (4%)	6 (1%)	3 (1%)	3 (1%)
SD	7 (1%)	4 (1%)	3 (0.5%)	1 (0.4%)	2 (0.7%)
PR	458 (55%)	158 (58%)	300 (54%)	152 (54%)	148 (53%)
CR	347 (42%)	98 (36%)	249 (45%)	124 (44%)	125 (45%)
CR+PR	805 (97%)	256 (94%)	549 (98%)	276 (98%)	273 (98%)
Total	831	272	559	281	278
NE	29	11	18	8	10
ND	10	5	5	3	2

- CR- and OR-Rates significantly higher in the combined I induction (A+I/I) versus control (A) (CR: p=0.0203, OR: p=0.0025)

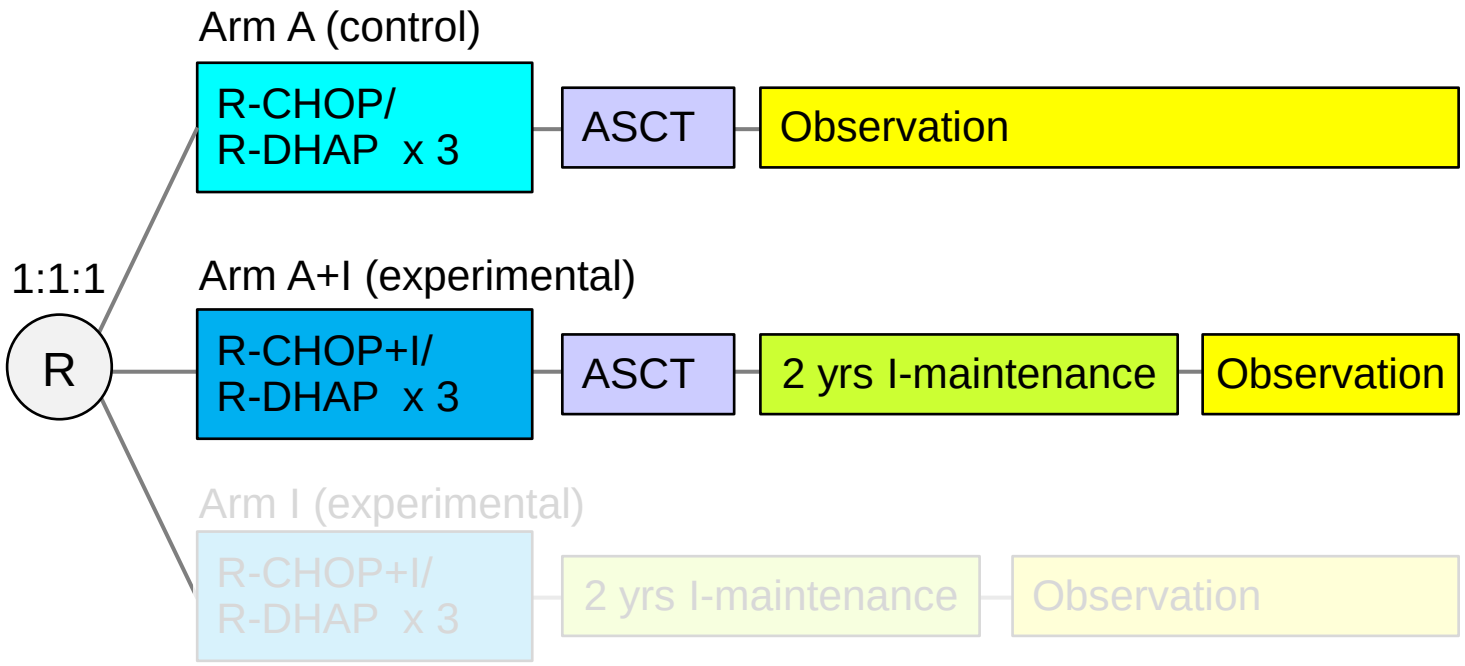
A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Dreyling M, et al. Oral Abstract 1. ASH 2022.

TRIANGLE: Evaluation of primary endpoint FFS

Test 1: FFS Superiority of A+I vs. A

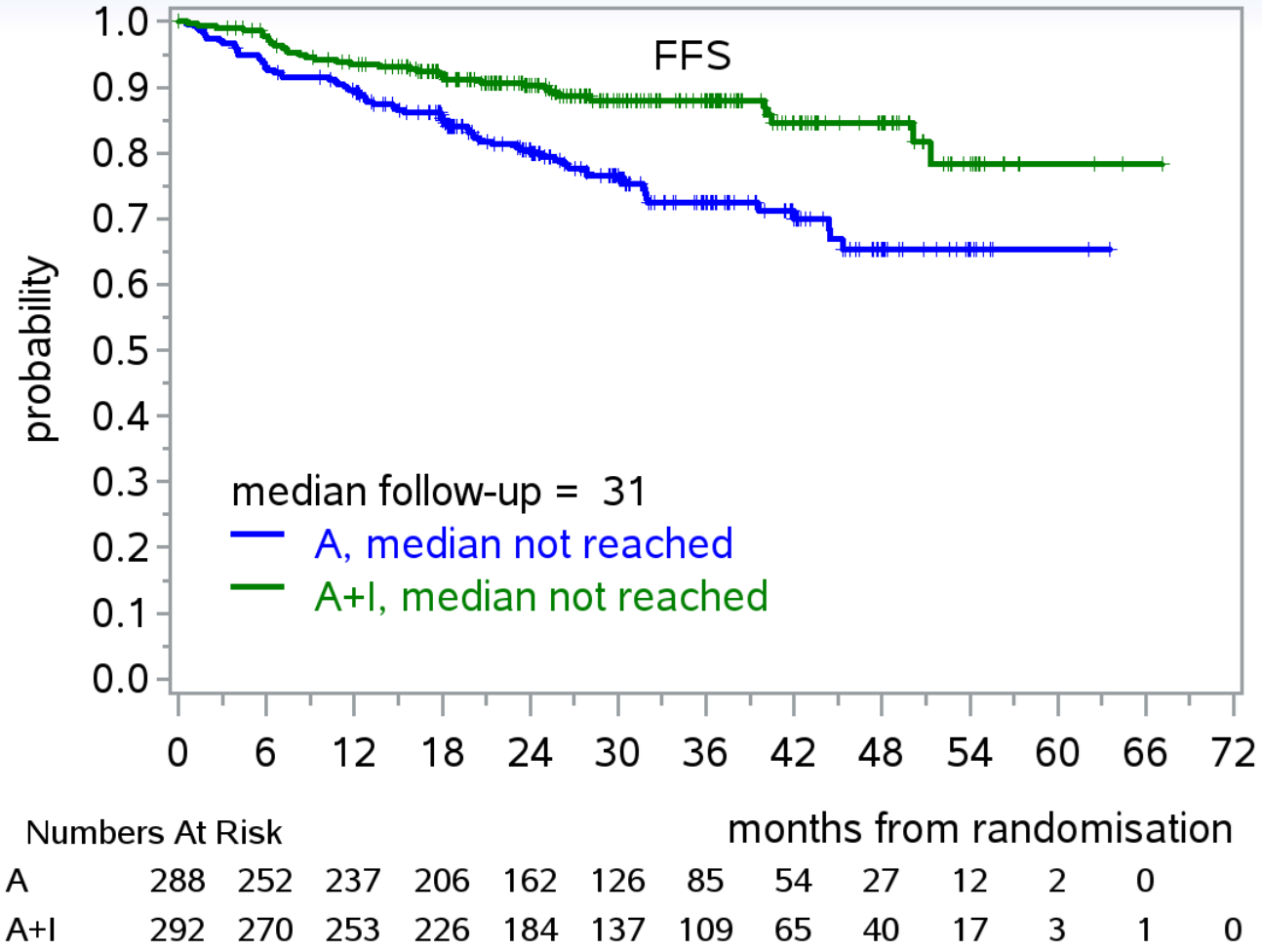
- 90% power to detect HR of 0.60
- One-sided alpha 0.016665



All three hypotheses were monitored with regular sequential analyses to allow for early stop for efficacy or futility (truncated sequential probability ratio test, *Whitehead*, 1985)

Dreyling M, et al. Oral Abstract 1. ASH 2022.

TRIANGLE: FFS Superiority of A+I vs. A



- Superiority of A+I vs. A (FFS) is confirmed
- Kaplan-Meier plots:
  - 3-year FFS A+I: 88%
  - 3-year FFS A: 72%
- p-value (corrected for sequential design) p=0.0008
- HR (A+I vs. A): HR=0.52

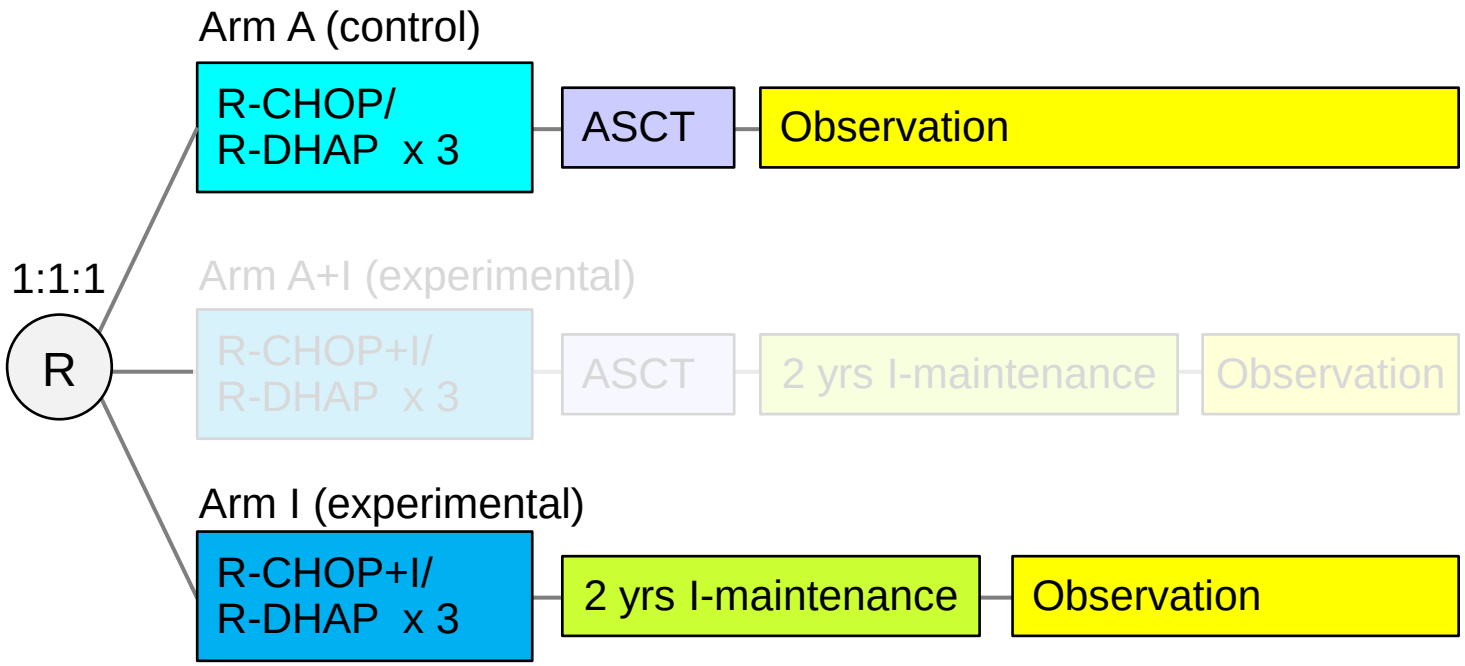
A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I

Dreyling M, et al. Oral Abstract 1. ASH 2022.

TRIANGLE: Evaluation of primary endpoint FFS

Test 2: FFS <u>Superiority of A</u> vs. I

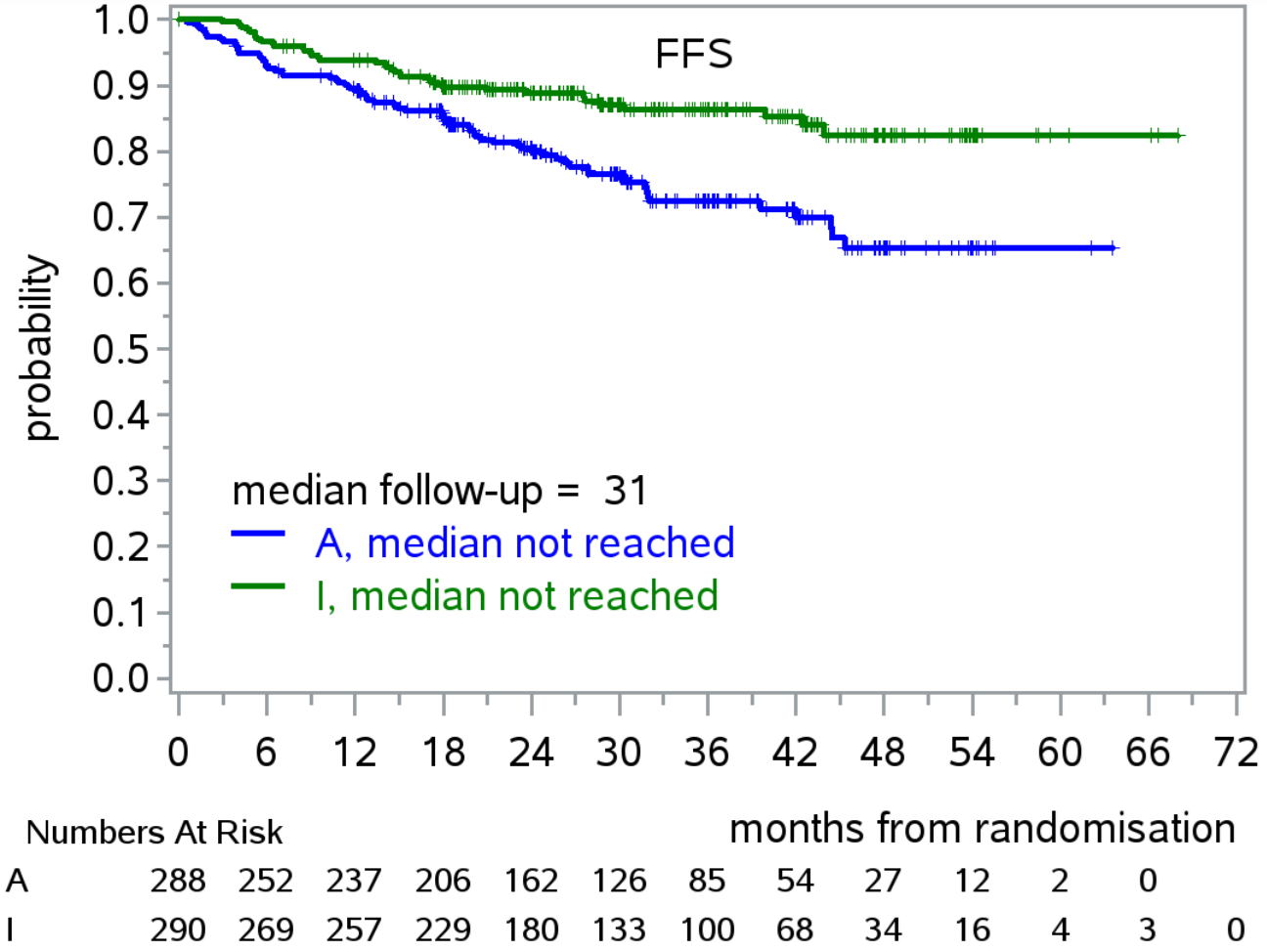
- 95% power to detect HR of 0.60
- One-sided alpha 0.016665



All three hypotheses were monitored with regular sequential analyses to allow for early stop for efficacy or futility (truncated sequential probability ratio test, *Whitehead*, 1985)

Dreyling M, et al. Oral Abstract 1. ASH 2022.

TRIANGLE: No FFS Superiority of A vs. I

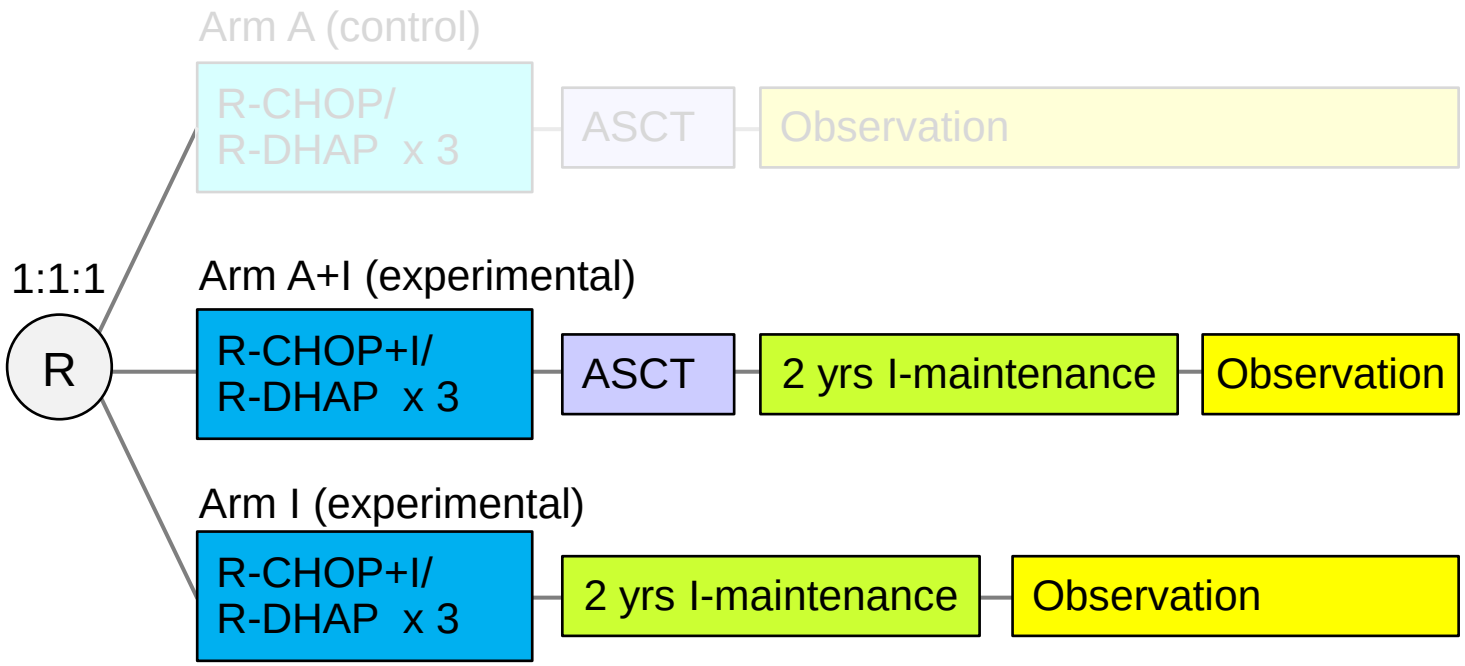


- Superiority of A vs. I (FFS) was rejected
- Kaplan-Meier plots:
  - 3-year FFS A: 72% (MCL Younger: 75%)
  - 3-year FFS I: 86%
- p-value corrected for sequential design: p=0.9979
- HR (A vs. I): HR=1.77

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

Dreyling M, et al. Oral Abstract 1. ASH 2022.

TRIANGLE: Evaluation of primary endpoint FFS

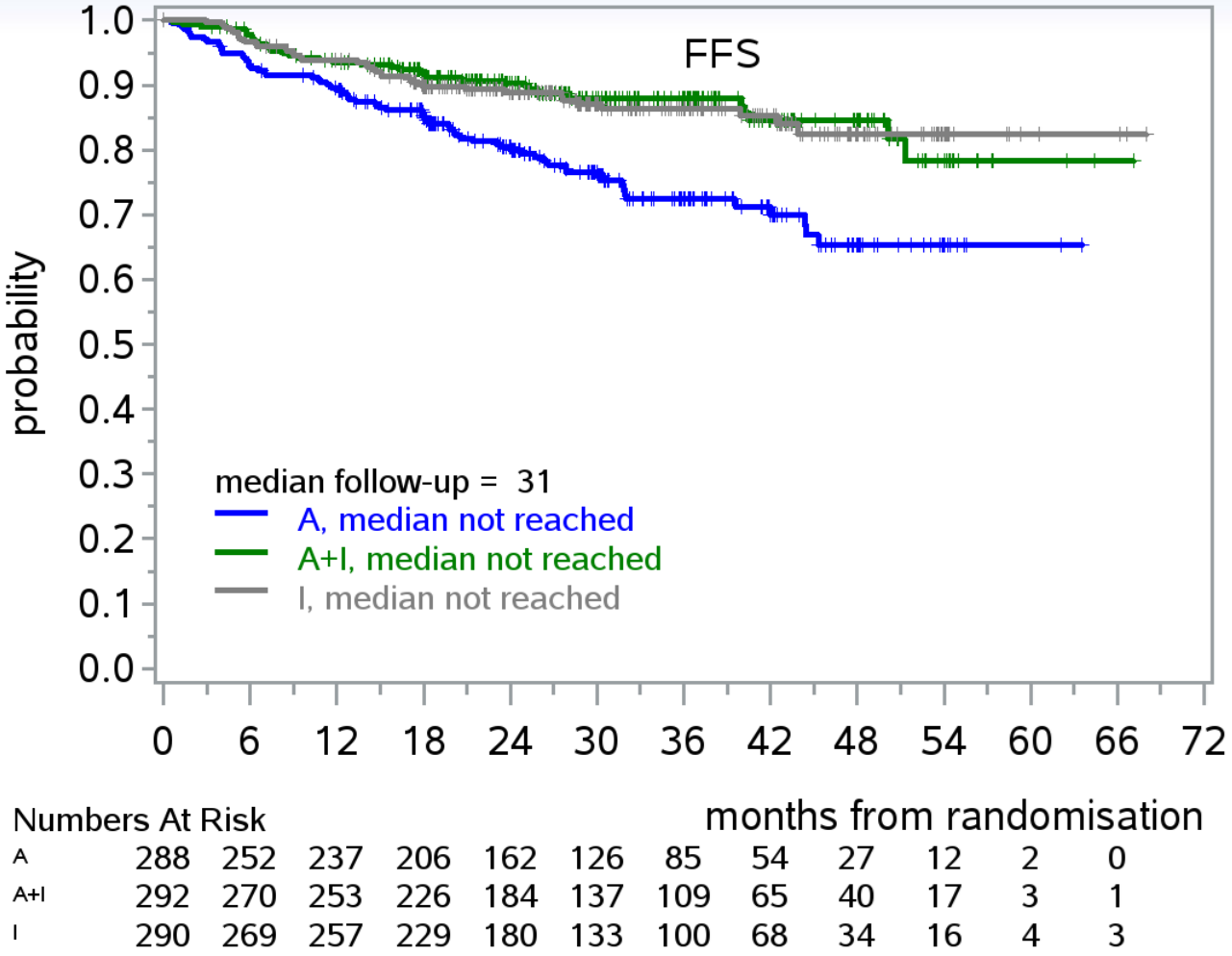


Test 3: FFS <u>Superiority of A+I</u> vs. I

- 90% power to detect HR of 0.60
- One-sided alpha 0.016665

All three hypotheses were monitored with regular sequential analyses to allow for early stop for efficacy or futility (truncated sequential probability ratio test, *Whitehead*, 1985)

TRIANGLE: FFS Superiority of A+I vs. I ?



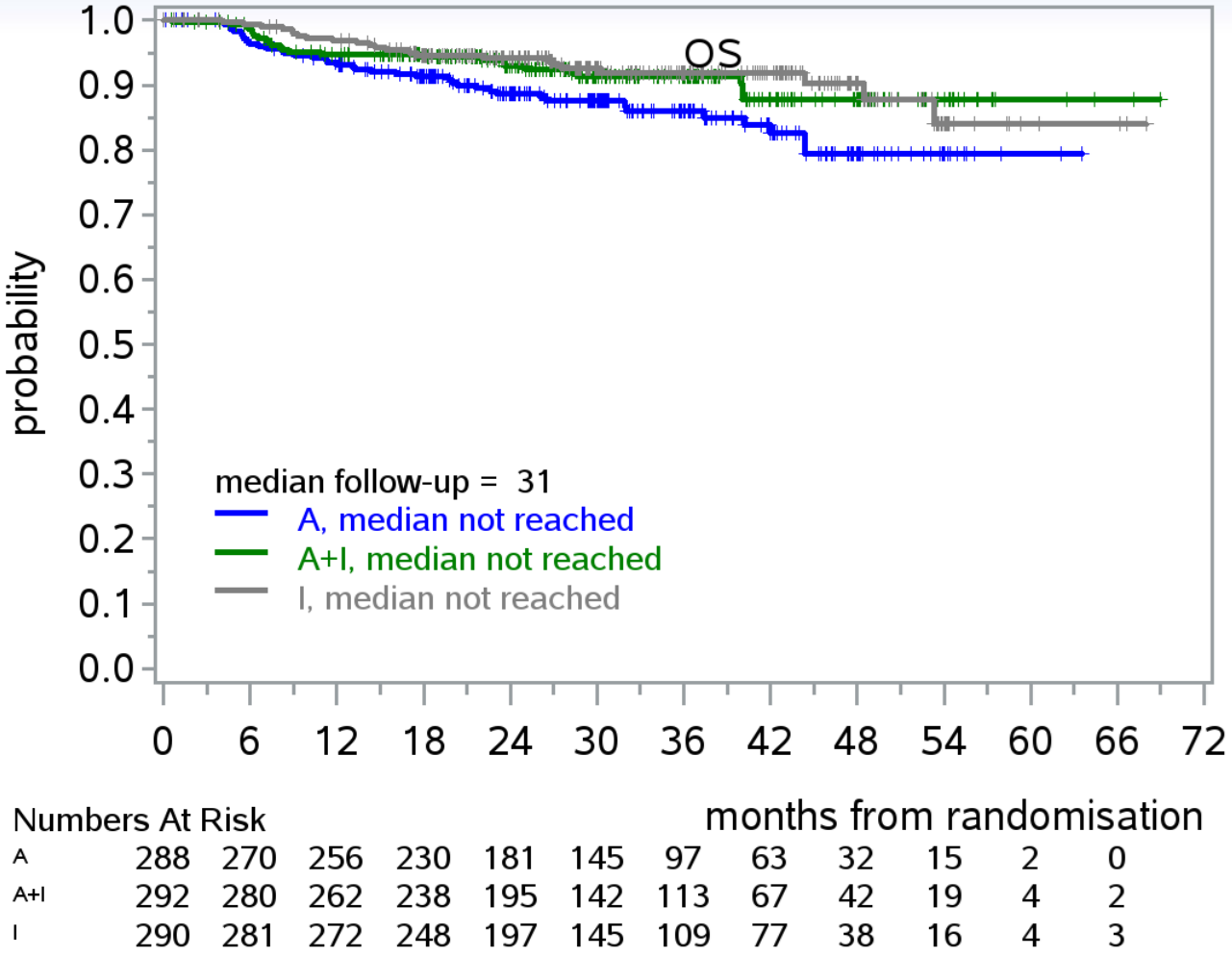
- Test A+I vs. I ongoing, no decision yet

Next lymphoma treatment (among patients with first treatment failure)	A (n=68)		A+I (n=35)		I (n=37)	
Treatment with Ibrutinib	34	79%	4	24%	3	11%
Treatment without Ibrutinib	9	21%	13	76%	24	89%
No treatment	25		18		10	

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

Dreyling M, et al. Oral Abstract 1. ASH 2022.

TRIANGLE: Overall survival

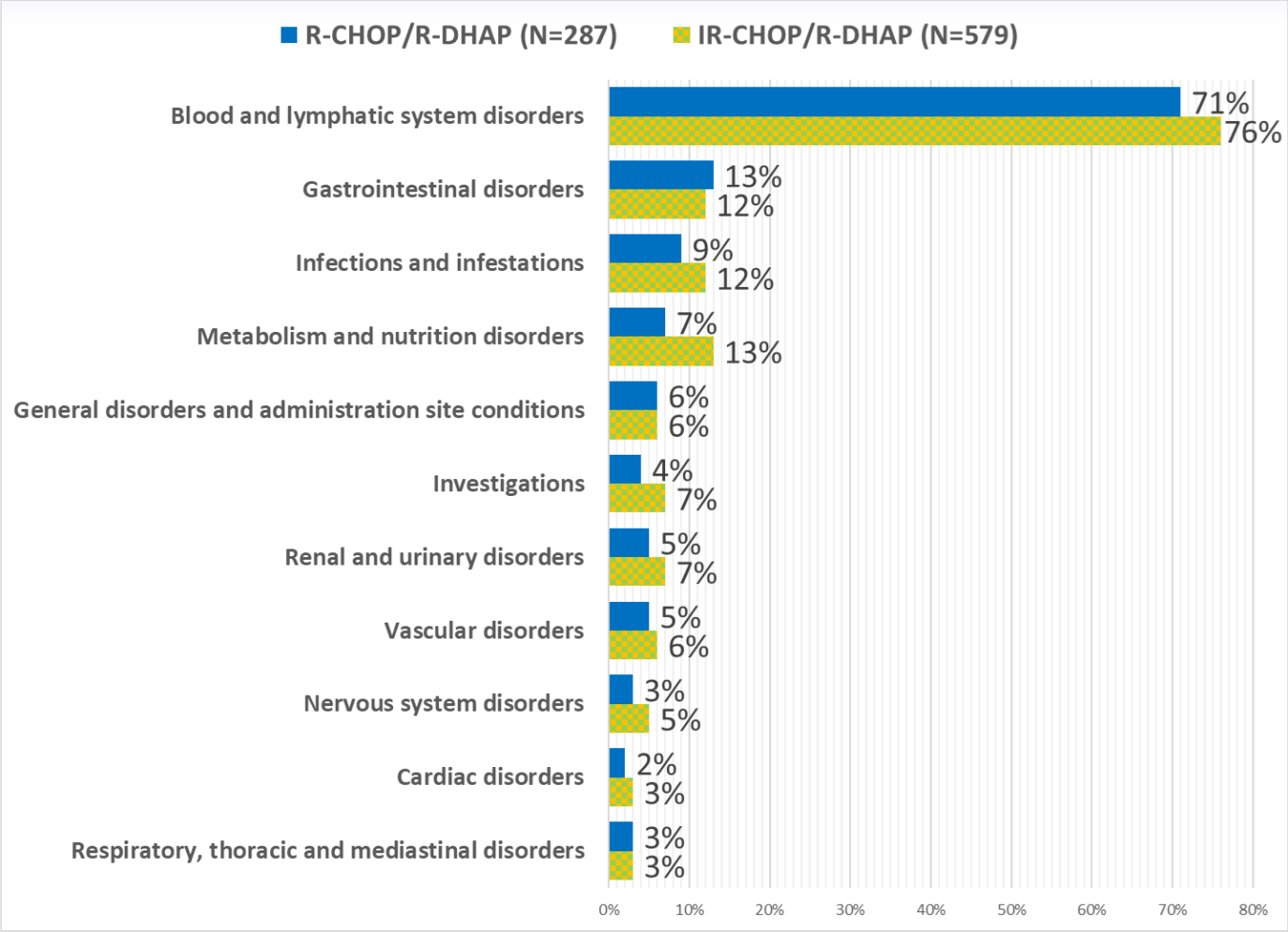


- 3-year OS:
  - A: 86% (MCL Younger exp.: 84%)
  - A+I: 91%
  - I: 92%
- Too early to evaluate statistical significance

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 M, et al. Oral Abstract 1. ASH 2022.

TRIANGLE: Grade 3-5 AEs (induction period; >2%)



Grade 3-5

Adverse Events by Preferred Term	R-CHOP/R-DHAP (N=287)		IR-CHOP/R-DHAP (N=579)	
Thrombocytopenia	169	59%	351	61%
Neutropenia	134	47%	283	49%
Anaemia	62	22%	140	24%
Leukopenia	44	15%	88	15%
Febrile neutropenia	25	9%	70	12%
Lymphopenia	15	5%	38	7%

Grade 5

Adverse Events by System Organ Class	R-CHOP/R-DHAP (N=287)		IR-CHOP/R-DHAP (N=579)	
Gastrointestinal disorders	2	1%	0	0%
Infections and infestations	1	0%	1	0%
Psychiatric disorders	0	0%	1	0%

Dreyling M, et al. Oral Abstract 1. ASH 2022.

Conclusions: current Triangle results

Based on FFS (primary endpoint):

- A+I (auto SCT + ibrutinib) is superior to A (auto SCT only)
- A (auto SCT) is not superior to I (ibrutinib without auto SCT)
- Currently, no decision whether autologous SCT adds to I (ibrutinib) but toxicity favors Ibrutinib only

Numerical overall survival benefit in the ibrutinib arms (I, A+I)

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 M, et al. Oral Abstract 1. ASH 2022.

Impact on Ontario Practice

- Control Arm (RCHOP/RDHAP +ASCT) is highly relevant
- FFS is improved with addition of Ibrutinib to SOC
  - Uncertain if this would be fundable – there is a signal for OS but we might have to wait and see
  - Uncertain how incorporation of BTKi into first-line would impact second line, where BTKi is current SOC (ie sequencing question)
    - Note CAR-T currently funded in 3L (after BTKi failure)
- Can this data justify removing ASCT from our 1L SOC?
  - ASCT was not superior compared to I-chemo (no ASCT) – but this is somewhat unconventional (ie is it the same as a non-inferiority design?)

Part 3. Follicular Lymphoma

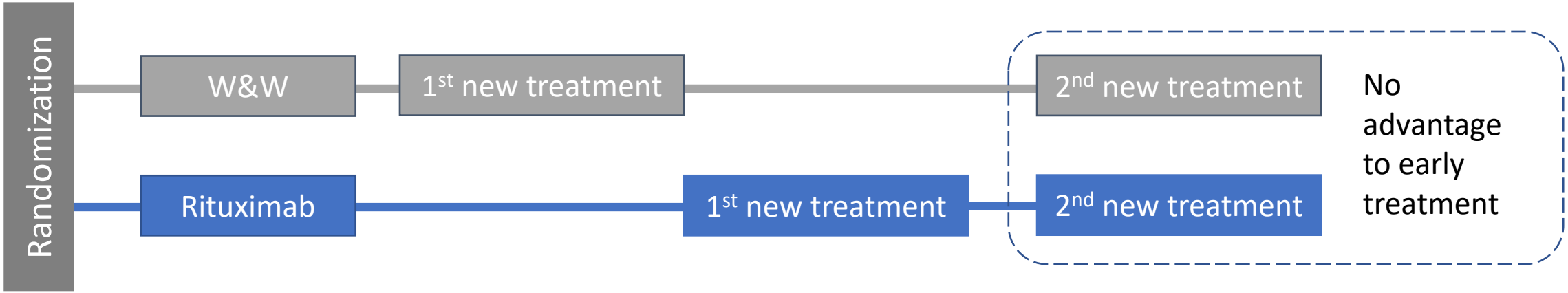
- Out with the Old
  - Rituximab monotherapy in front-line treatment
- In with the new
  - Rituximab plus lenalidomide (R^2) in relapsed follicular lymphoma
  - Immunotherapy

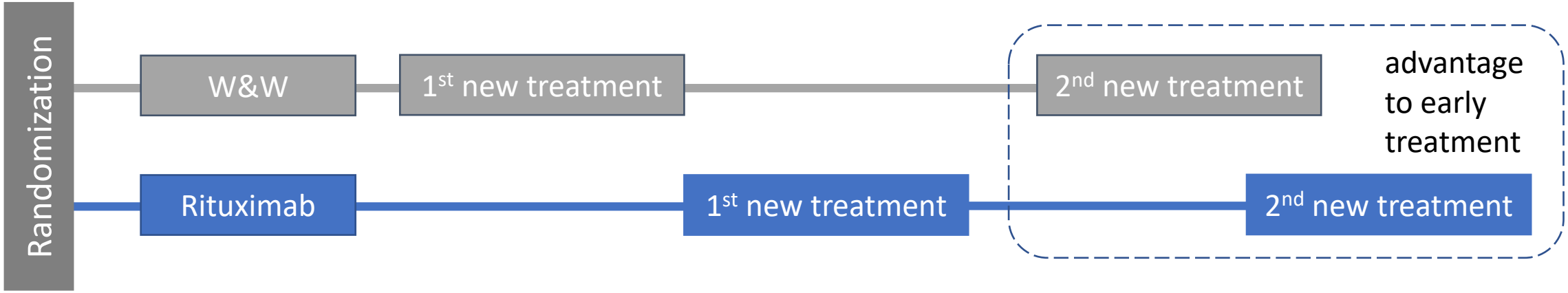
607. Long Term Follow-up of International Randomized Phase 3 Study of Rituximab Versus a Watch and Wait Approach for Patients with Asymptomatic, Low Tumour Burden Follicular Lymphoma Shows Rituximab Is Highly Effective at Delaying Time to New Treatment without Detrimental Impact Following Next Line of Therapy

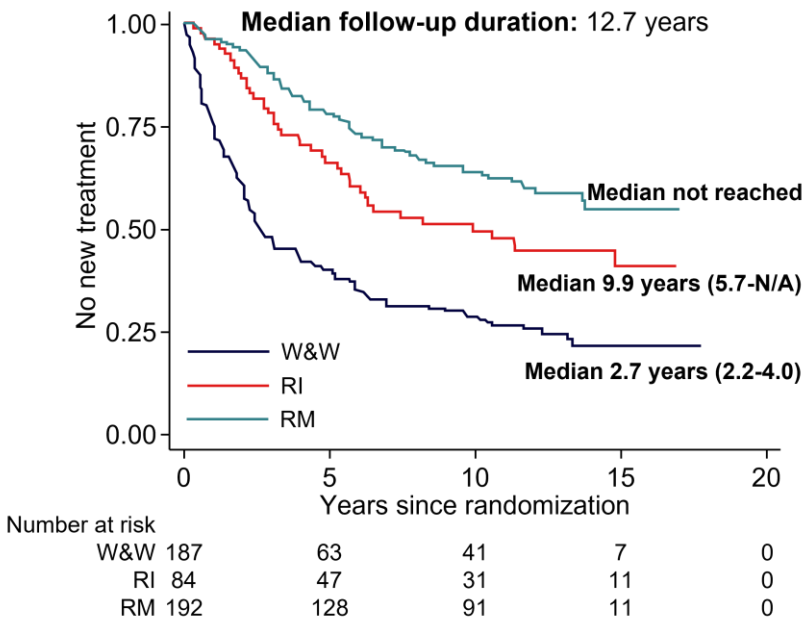
Michael Northend, William Wilson, Laura Clifton-Hadley, Zaynab Rana, Tanya-Louise Martin, Moya Young, Fiona Miall, David Cunningham, Jan Walewski, Burhan Ferhanoglu, Amanda Johnston, John F. Seymour, David C. Linch and Kirit M. Ardeshna

If we randomize low burden asymptomatic FL patients to watch and wait or immediate treatment with Rituximab:

1. **The time to next treatment is longer in the up-front Rituximab group (published 2014**
2. **But what about the time to second new treatment?**

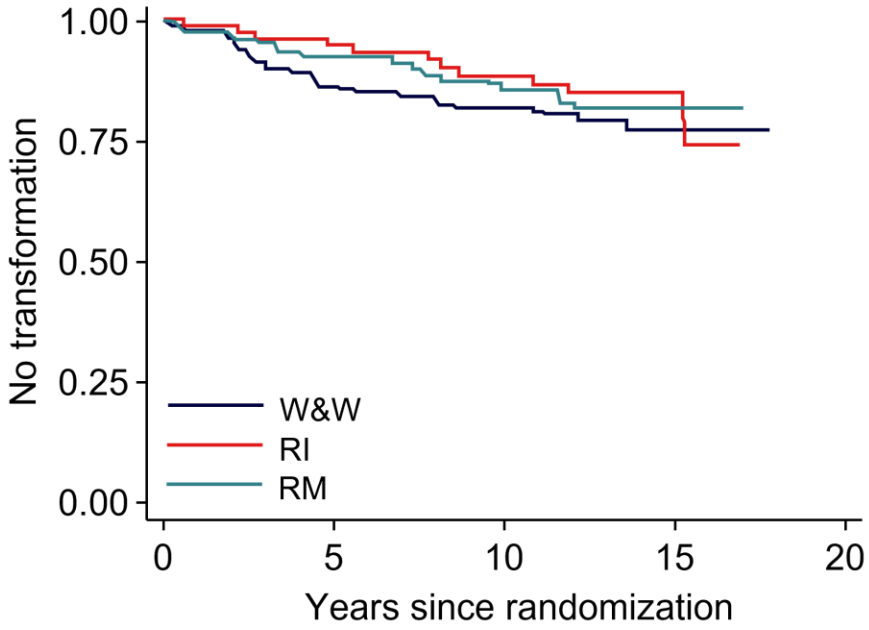






Arm	TT2NT events
W&W	35 (18.7%)
RI	13 (15.4%)
RM	27 (14.0%)

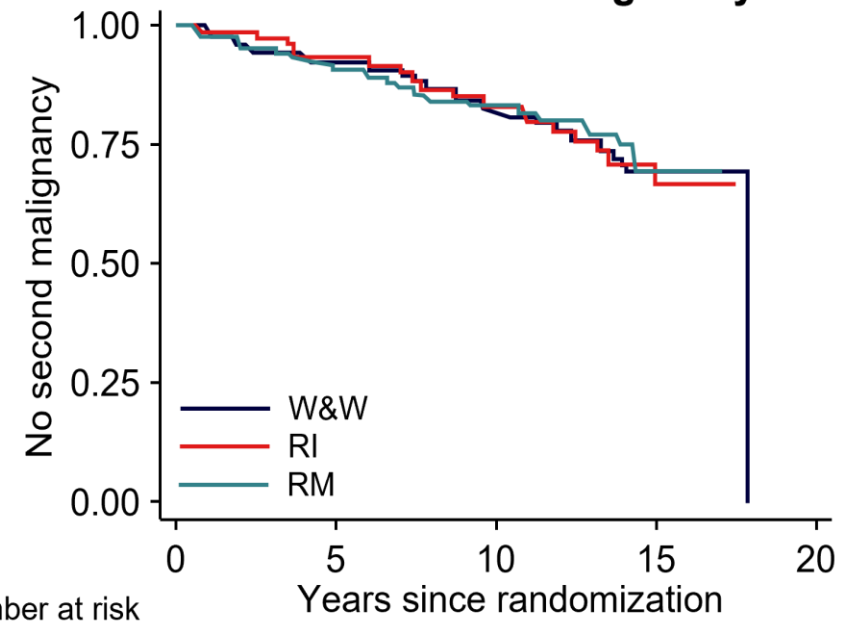
Time to transformation



Number at risk

W&W	187	131	105	23	0
RI	84	64	52	20	0
RM	192	149	117	16	0

Time to second malignancy



Number at risk

W&W	187	140	104	21	0
RI	84	62	48	17	0
RM	192	144	111	14	0

- 92 patients developed a second primary malignancy during follow-up:
  - **20%** of patients in the W&W arm (N=38)
  - **21%** of patients in the RI arm (N=18)
  - **19%** of patients in the RM arm (N=36)

Conclusions

- After long median follow-up (12.7 years) the median improvement in TTNT was large and sustained
- The greatest effect on TTNT was seen when R-induction was followed by maintenance
- There was no difference in time to 2nd new systemic treatment *"showing no detrimental effect of early use of rituximab"*
- Rituximab did not have any impact on rates of high-grade transformation or Second Malignancy
- "Early treatment with rituximab – either induction alone or induction followed by maintenance – should be considered a standard option for the treatment of patients with asymptomatic LTBFL"

Impact on Ontario Practice

- In Canadian practice, we can not use and re-use rituximab an unlimited number of times. We have a bias that if early treatment doesn't result in longer survival, then we should delay the start of treatment until it is needed

- Interpretation of this study:

  - United States – SUPPORTS that there is no detrimental effect to upfront treatment in asymptomatic low tumour burden patients

  - Canada – SUPPORTS that there is no detrimental effect to a watch and wait strategy

230. Five-Year Results and Overall Survival Update from the Phase 3 Randomized Study Augment: Lenalidomide Plus Rituximab (R^2) Vs Rituximab Plus Placebo in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

John P. Leonard, MD[1], Marek Trneny, MD[2], Fritz Offner, MD, PhD[3], Jiri Mayer, Prof, MD[4*], Huilai Zhang[5*], Grzegorz S. Nowakowski, MD[6], Phillip Scheinberg, MD[7], Argyrios Gkasiamis, MD[8], Joanna Mikita-Geoffroy, PhD[9*], Everton Rowe, PhD[8*] and John G. Gribben

Background

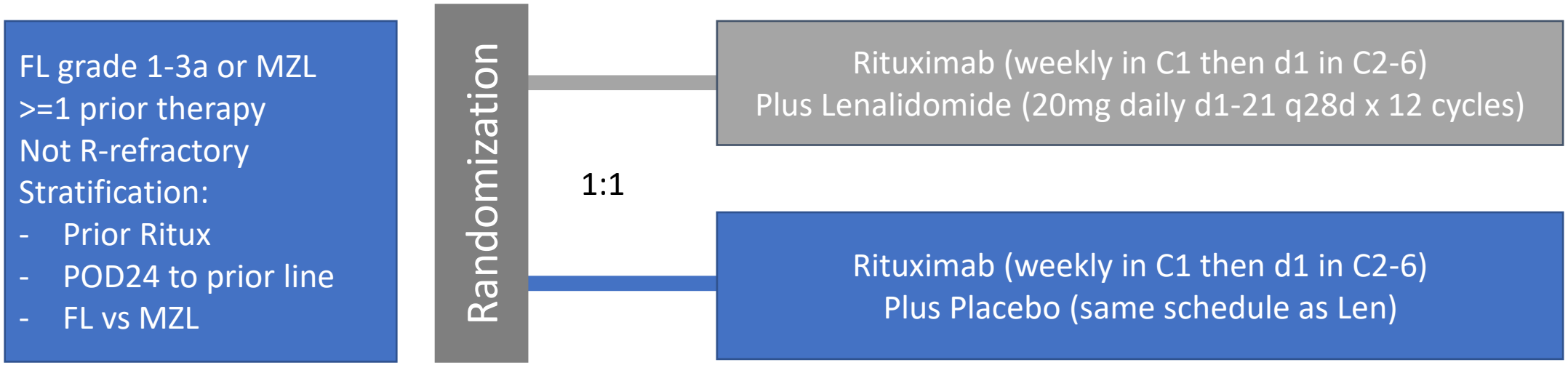
AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma

J Clin Oncol 37:1188-1199.

John P. Leonard, MD[1]; Marek Trneny, MD[2]; Koji Izutsu, MD[3]; Nathan H. Fowler, MD[4]; Xiaonan Hong, MD[5]; Jun Zhu, PhD[6]; Huilai Zhang, MD[7]; Fritz Offner, MD, PhD[8]; Adriana Scheliga, MD[9]; Grzegorz S. Nowakowski, MD[10]; Antonio Pinto, MD[11]; Francesca Re, MD[12]; Laura Maria Fogliatto, MD, PhD[13]; Phillip Scheinberg, MD[14]; Ian W. Flinn, MD, PhD[15]; Claudia Moreira, MD[16]; José Cabeçadas, MD[17]; David Liu, MD, PhD[18]; Stacey Kalambakas, MD[18]; Pierre Fustier, PhD[19]; Chengqing Wu, PhD[18]; and John G. Gribben, MD, DSc[20]; for the AUGMENT Trial Investigators

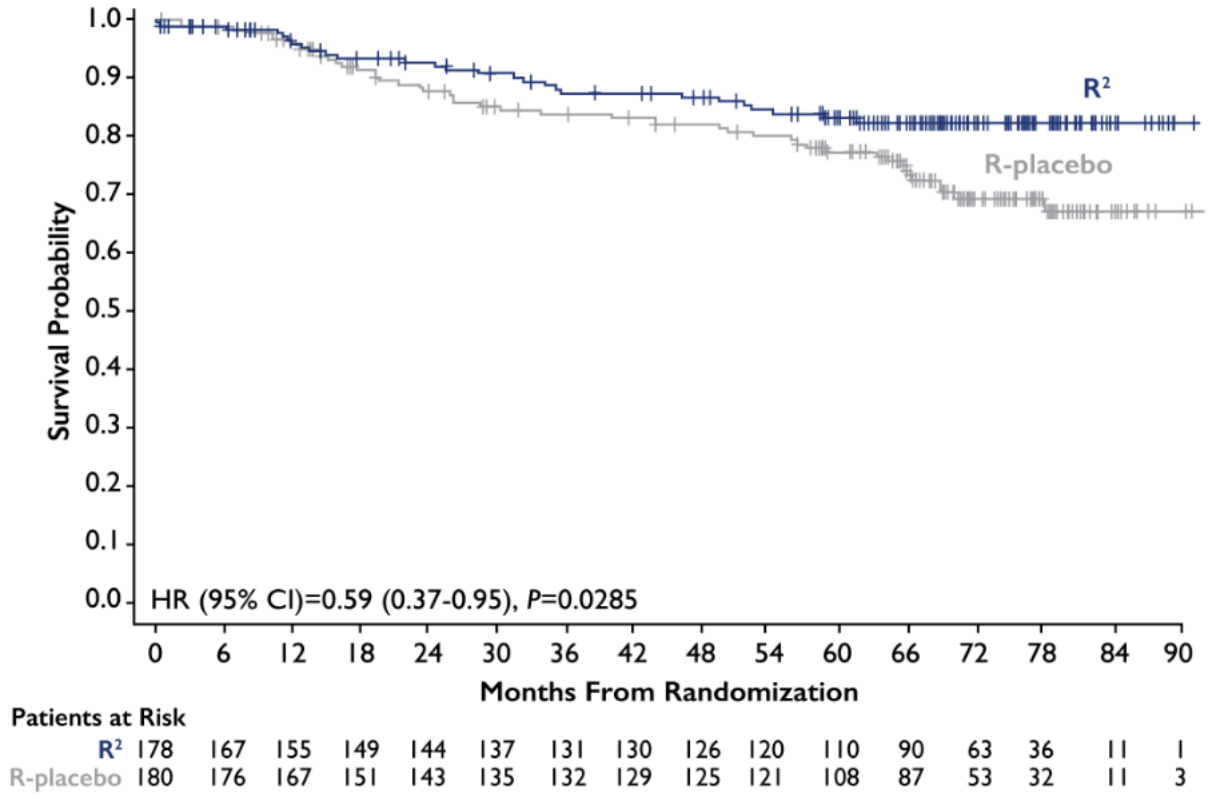
- lenalidomide + rituximab (R^2) showed superior efficacy vs rituximab + placebo (R-placebo) in patients (pts) with relapsed refractory (R/R) indolent non-Hodgkin lymphoma (iNHL)
- Based on these AUGMENT study results, R^2 was approved for the treatment of adult pts with previously treated follicular lymphoma (FL) or marginal zone lymphoma (MZL) in the US, Japan, and Brazil, and for FL in Europe.
- Reported here are updated long-term follow-up results from AUGMENT.

Methods


FL grade 1-3a or MZL
>=1 prior therapy
Not R-refractory
Stratification:
- Prior Ritux
- POD24 to prior line
- FL vs MZL
Randomization
1:1
Rituximab (weekly in C1 then d1 in C2-6)
Plus Lenalidomide (20mg daily d1-21 q28d x 12 cycles)
Rituximab (weekly in C1 then d1 in C2-6)
Plus Placebo (same schedule as Len)

Results

- N=358, median follow-up of 65.9 mo
- median PFS by Investigator: 27.6 mo for R^2 vs 14.3 mo for control, HR = 0.50 (95% CI, 0.38-0.66; *P* < 0.0001)
- median OS was not reached for either group
  - there was an improvement in OS for R^2 (HR = 0.59, 95% CI, 0.37-0.95, *P* = 0.0285).
  - 5-y OS rates for the R^2 vs control groups were 83.2% (95% CI, 76.3-88.3) vs 77.3% (95% CI, 70.1-83.1).
- Median TTNLT (after 12 cycles of time-limited therapy) was 73.1 mo for R^2 vs 31.8 mo for control with HR = 0.53 (95% CI, 0.39-0.71; *P* < 0.0001).



Safety

- The updated overall safety profile of both groups was consistent with the 1st analysis.
  - SPMs occurred in 13 (7%) R^2-treated and 21 (12%) control pts
  - 9 pts died of SPM (n = 3 R^2, n = 6 R-placebo)
  - Fewer histological transformations occurred in the R^2 arm than in the control group (n = 10 vs n = 15, respectively). The incidence rate of histological transformation was 1.24% (95% CI, 0.66-2.3) in the R^2 arm and 1.85% (95% CI, 1.12-3.07) in the control arm.

Conclusions

- R^2 continues to demonstrate superior efficacy over rituximab monotherapy (plus placebo) as measured by PFS
- The updated results for OS are consistent with the improvement observed in PFS. The OS KM curve separation after 5 y continues to favor R^2, providing evidence for a survival benefit.
- The safety profile of R^2 and R-placebo remain consistent with the primary analysis, with continued lower rates of SPM and rates of histologic transformation comparable to historical experience.
- These updated results, including OS data, provide further support for the use of the R^2 regimen as a standard of care for pts with R/R iNHL.

Impact on Ontario Practice

- R^2 has not been frequently used in Ontario as it is difficult to access
- The control arm of single agent rituximab is not relevant in Ontario/Canada
- This does represent a reasonable option when no other options exist, if a patient can access these medications through compassionate access / private insurance

Immunotherapy

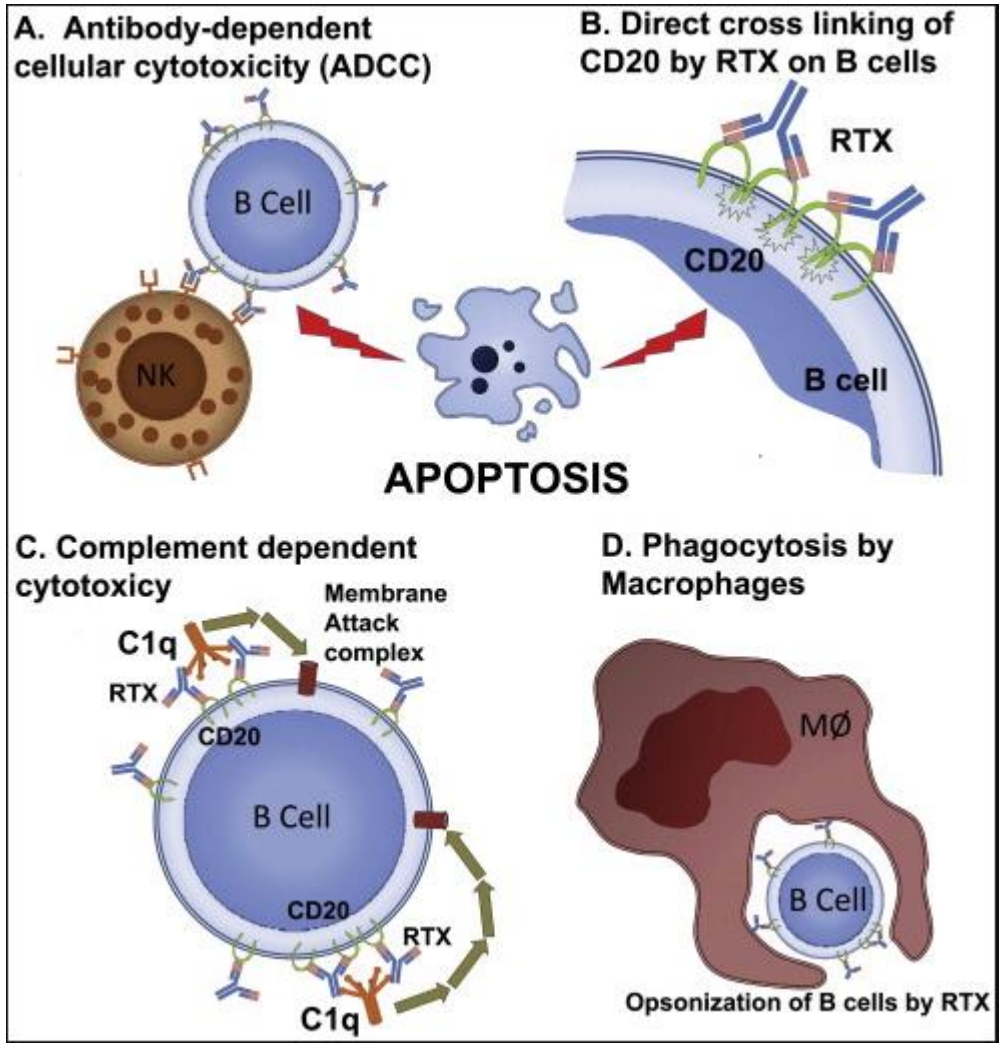
- What is immunotherapy?
  - Treatment that takes advantage of our own immune system, to attack cancer cells within our bodies
  - A class of treatment, not a single treatment
  - Has side effects, and CAN cause harm to healthy tissue / organs

Immunotherapy

- Immunotherapy examples
  - Monoclonal antibodies – Rituximab, Obinutuzumab
  - Immunoconjugates – Brentuximab vedotin, Polatuzumab vedotin

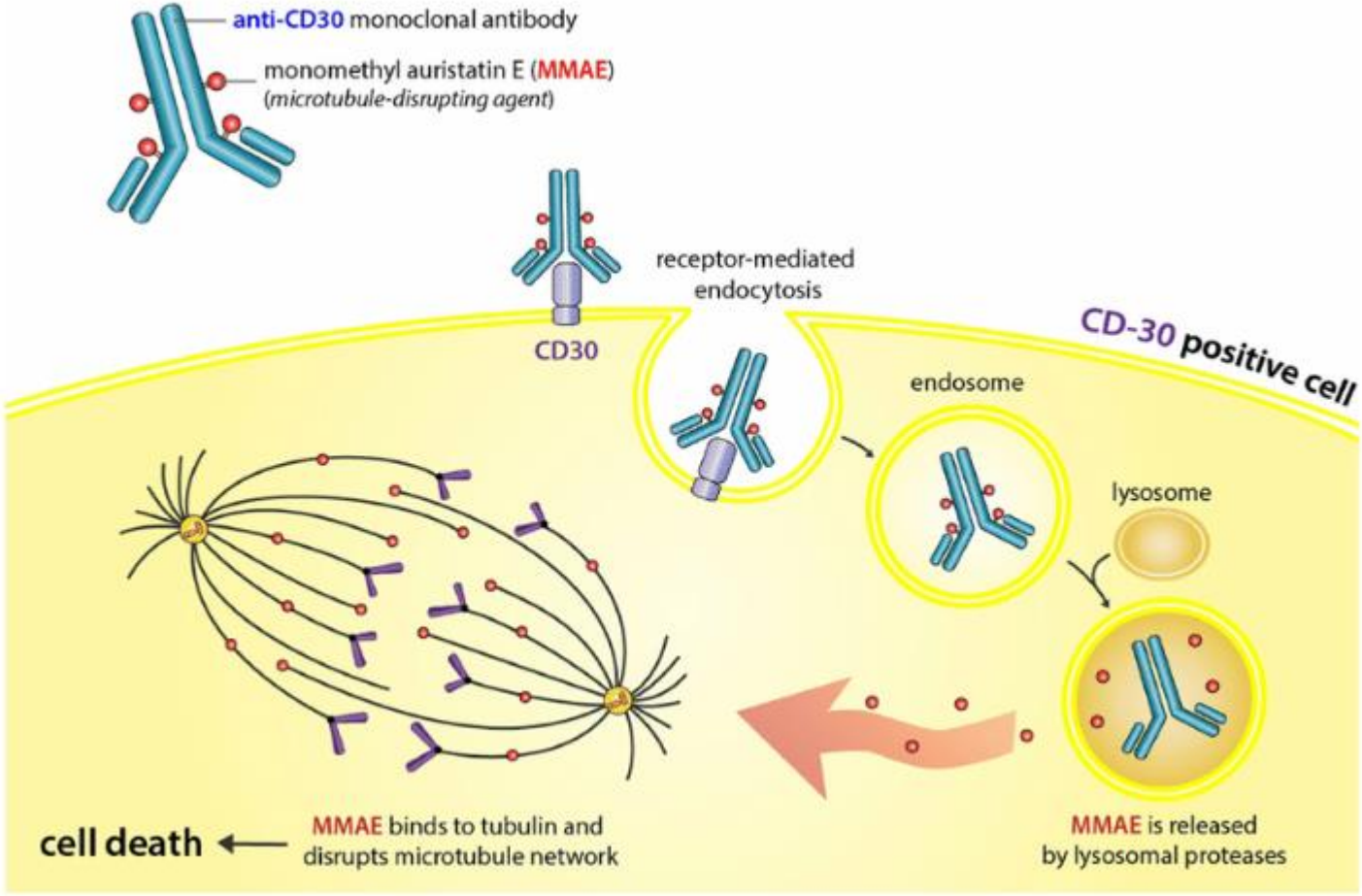
  - Therapies that “activate” our T-cells to recruit them to fight the cancer
    - “Checkpoint inhibitors” – nivolumab, pembrolizumab
    - CAR-T therapy – chimeric antigen receptor T cells
    - BiTE therapy – Bispecific T cell Engager therapy

4 ways that anti-CD20 monoclonal antibodies kill B cells



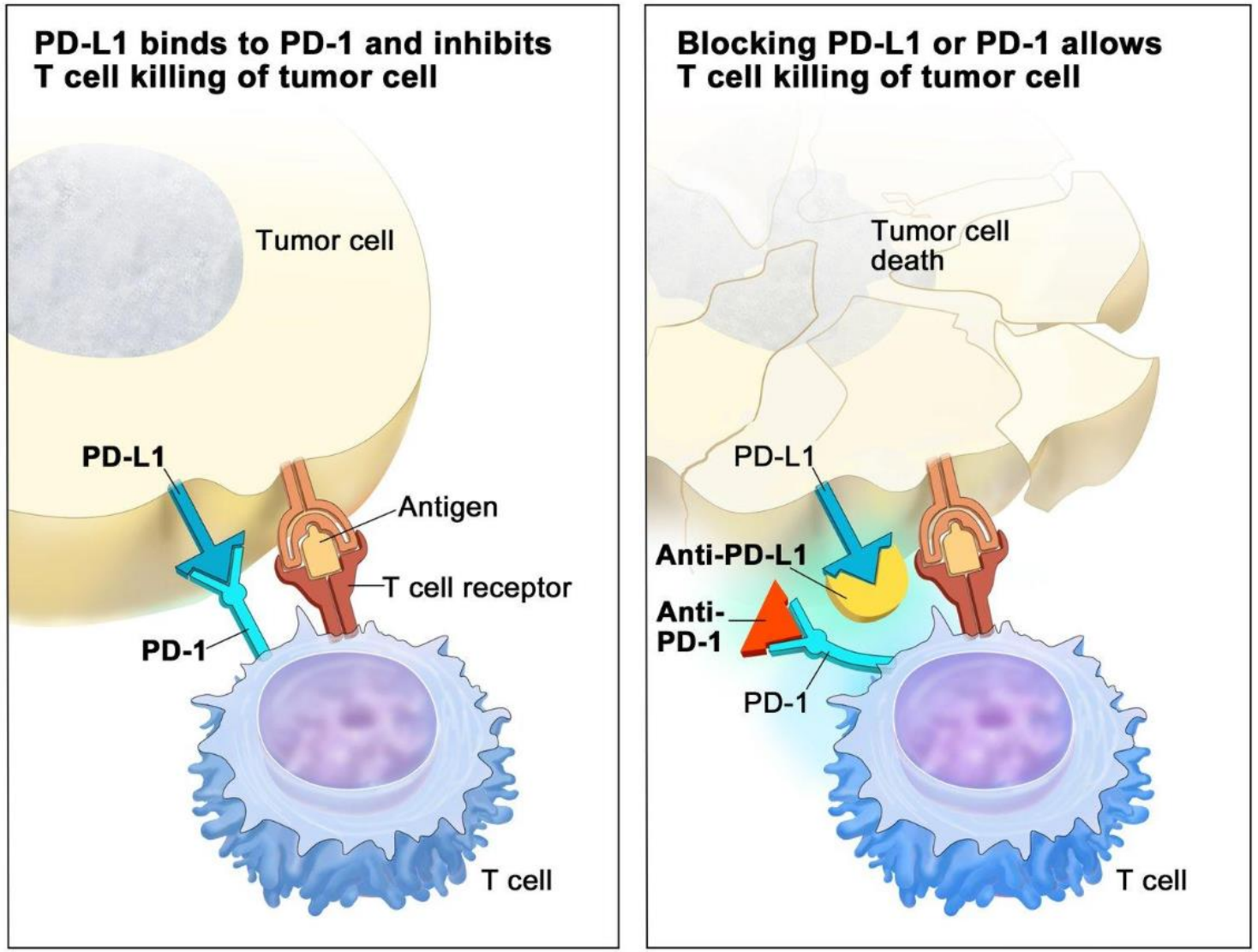
Gurcan, International Immunopharmacology, 2009

How immunoconjugates work



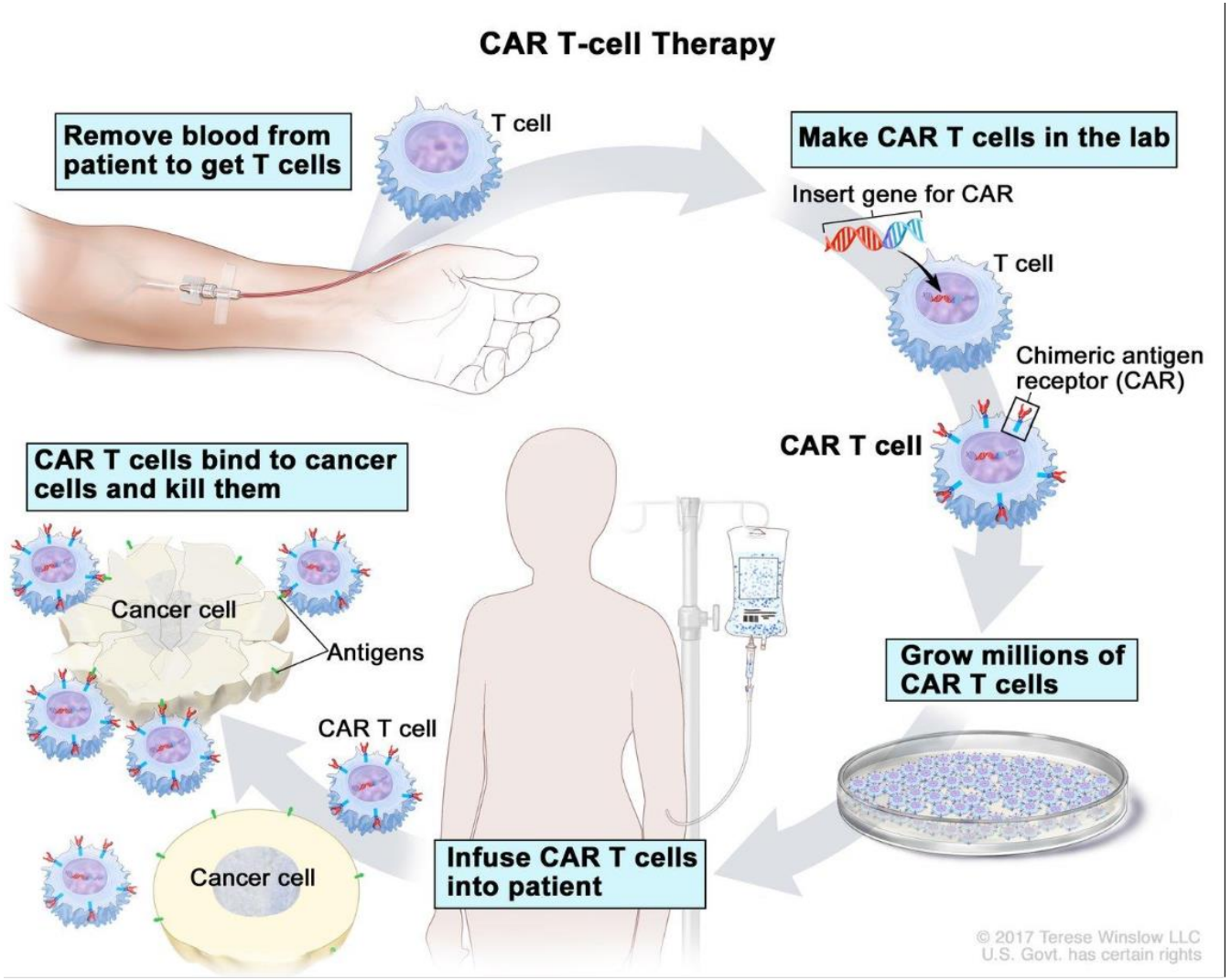
Collins, Lymphoma and Chronic Lymphocytic Leukemias, 2014

How Checkpoint Inhibitors work



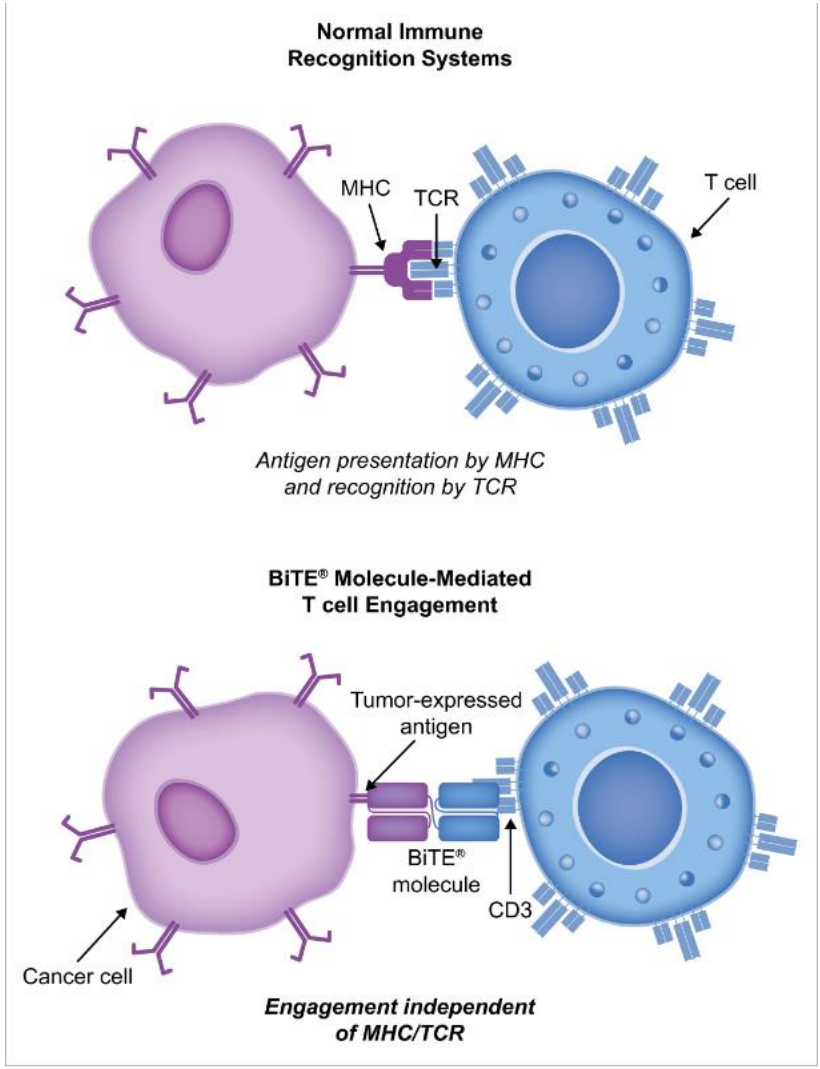
Source: National Cancer Institute Website:
https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors

How CAR T-cell Therapy works



Source: National Cancer Institute Website:
https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/T-cell-transfer-therapy

How BiTE Therapy works



Einsele, Cancer, 2020

610. Mosunetuzumab Monotherapy Demonstrates Durable Efficacy with a Manageable Safety Profile in Patients with Relapsed/Refractory Follicular Lymphoma Who Received ≥2 Prior Therapies: Updated Results from a Pivotal Phase II Study

Nancy L. Bartlett, Laurie H. Sehn, Matthew J. Matasar, Stephen J. Schuster, Sarit Assouline, Pratyush Giri, John Kuruvilla, Miguel Canales, Sascha Dietrich, Keith Fay, Matthew Ku, Loretta J. Nastoupil, Michael C. Wei, Shen Yin, Iris To, Huang Huang, Juliana Min, Elicia Penuel and Elizabeth L. Budde

Mosunetuzumab - Background

- Mosunetuzumab (Mosun) is a CD20xCD3 T-cell engaging bispecific monoclonal antibody (Bi-mAb) that redirects T cells to eliminate malignant B cells.
- Mosun is the first Bi-mAb approved for the treatment of patients (pts) with relapsed/refractory (R/R) follicular lymphoma (FL; EMA 2022) and is a fixed-duration treatment that can be administered in an outpatient setting.
- In a Phase II study (NCT02500407), Mosun demonstrated a high rate of complete response (CR) with a manageable safety profile in pts with R/R FL who had received ≥2 prior therapies (Budde et al. Lancet Oncol 2022).
- Current abstract presents updated data for this cohort after a median follow-up of 27 months.

Mosunetuzumab – Study Design

FL grade 1-3a
>=2 prior lines therapy, including alkylator and anti-CD20

8 x 21d cycles

C1D1 1mg
C1D8 2mg
C1D15 60mg
C2 60mg
C3+ 30mg

CR – treatment complete

PR, SD 9 more cycles (total 1 year)

Primary endpoint – CR rate by IRC

Post hoc analysis:
- Mosun versus last prior therapy
- Correlate tumour response with CRS

Mosunetuzumab - Results

- N=90, median age was 60 years (range: 29–90), and 77% of pts had stage III/IV disease.
- Median number of prior lines of therapy was three (range: 2–10);
- 53% of pts were double refractory to prior anti-CD20 therapy and alkylator therapy; and 52% of pts had progressive disease within 24 months from the start of their first-line therapy.
- median time on study was 26.7 months (range: 2.0–36.2); 54 pts (60%) had completed initial treatment and 36 pts (40%) had discontinued initial treatment (25 pts [28%] due to progressive disease). Two pts (2%) were undergoing retreatment, 72 pts (80%) were in follow-up, and 16 pts (18%) had discontinued the study.
- No new CRS events, or fatal, serious, or gr ≥3 adverse events (AEs) were reported since the previous analysis, and no evidence of chronic toxicity was observed. Overall, the rate of AEs leading to discontinuation was low (4.4%) and no treatment-related gr 5 AEs were observed. CRS events (44.4% of pts) were mostly confined to C1 (84.5% of events) and 97.2% were gr 1/2 in severity; all CRS events resolved. No correlation was observed between the occurrence of CRS and tumor response. ORR was 77.5% and 78.0%, respectively, in pts with or without CRS events.

Mosunetuzumab – Response Rates

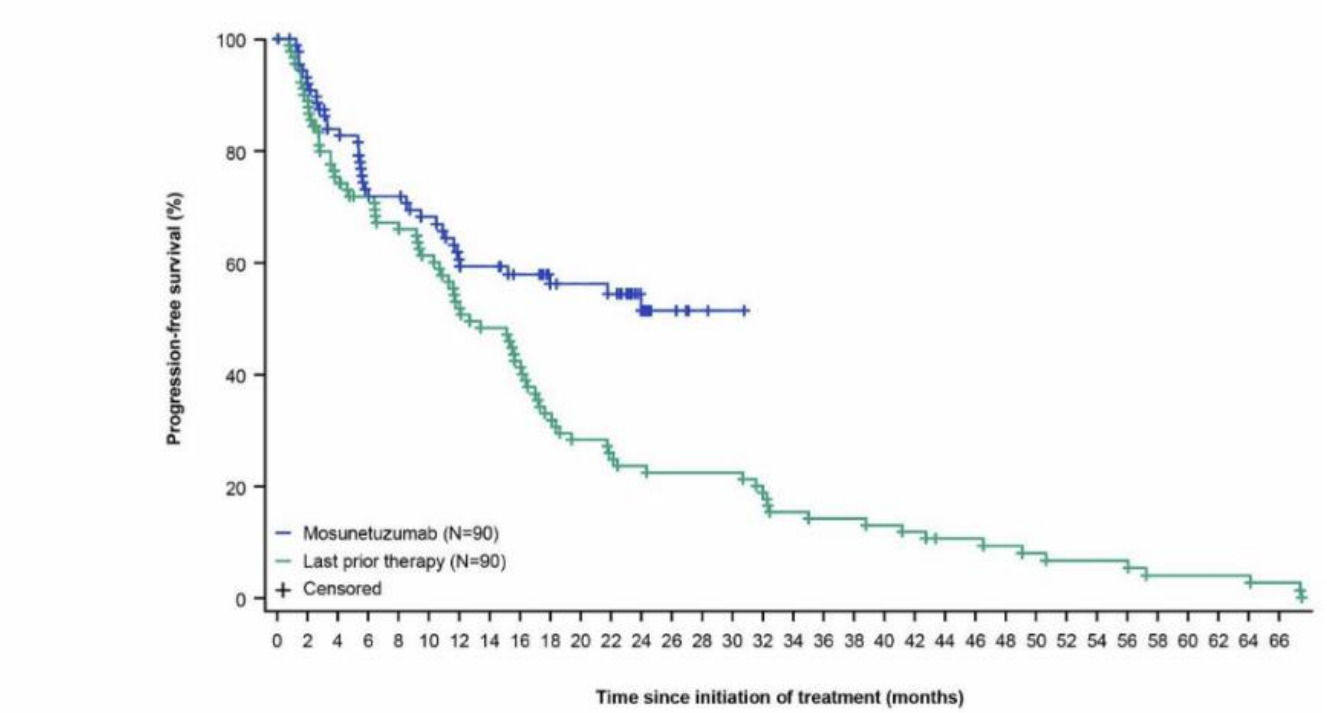
Table: Summary of efficacy with mosunetuzumab and last prior therapy received

Efficacy endpoints assessed by investigators	R/R FL N=90	
	Mosunetuzumab	Last prior therapy
ORR, % (95% CI)	77.8 (67.8–85.9)	55.6 (44.7–66.0)
CR, % (95% CI)	60.0 (49.1–70.2)	35.6 (25.7–46.4)
Median DOR, months (95% CI)	NR (22.8–NR)	11.8 (10.3–16.9)
24-month event-free rate, % (95% CI)	60.8 (46.8–74.2)	28.6 (16.0–41.3)
Median DOCR, months (95% CI)	NR (NR–NR)	15.1 (11.2–26.3)
24-month event-free rate, % (95% CI)	79.5 (66.7–92.2)	34.4 (17.9–50.8)
Median PFS, months (95% CI)	NR (12.0–NR)	12.6 (10.3–16.3)
24-month event-free rate, % (95% CI)	51.4 (39.4–63.3)	23.5 (14.5–32.5)
Median TTNT, months (95% CI)	NR (18.0–NR)	16.8 (14.4–20.4)
24-month event-free rate, % (95% CI)	55.3 (44.6–66.1)	33.3 (23.6–43.1)

CI, confidence interval; CR, complete response; DOCR, duration of complete response; DOR, duration of response in all responders; FL, follicular lymphoma; NR, not reached; ORR, objective response rate; PFS, progression-free survival; R/R, relapsed/refractory; TTNT, time to next therapy or death.

Mosunetuzumab – Progression Free Survival

Figure: Progression-free survival (investigator assessed) with mosunetuzumab vs last prior therapy



Patients remaining at risk

Mosunetuzumab (N=90)	90	80	71	60	59	54	46	45	40	33	32	31	16	6	2	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Last prior therapy (N=90)	90	81	66	61	56	52	44	41	36	28	24	22	20	19	19	19	16	13	12	12	11	10	8	8	7	6	5	5	5	3	3	3	3	2

NR, not reached.

Mosunetuzumab - Conclusions

- with a median follow-up of 27 months, durable responses continued to be observed with Mosun in pts with R/R FL.
- Compared with pts' last prior therapy, Mosun demonstrated higher ORR and CR rates, with longer DOR, DOCR, PFS and time to next therapy, although limitations should be noted for retrospective comparisons and the absence of standardized imaging assessment for the last prior therapy.
- The safety profile, characterized by a low rate of AEs leading to treatment discontinuation and predominantly low-grade CRS events, was consistent with previous reports and supports the administration of Mosun as an outpatient regimen.
- Clinical response was observed regardless of occurrence of CRS, suggesting the Mosun dose and schedule used is effective at dissociating cytokine toxicity from treatment efficacy.

Two BiTE Abstracts at ASH

	Mosunutuzumab (Abstract 610) N=90	Odronextamab (Abstract 949) N=96*
Number prior therapies	>=2	>=2
Median age (range)	60 (29-90)	59 (22-84)
Proportion of patients POD24 from first line	52%	48%
Overall Response Rate	78%	81%
CR rate	60%	75%
Median DOR	NR (60% at 24m)	18.2m
Median PFS	NR (51% at 24m)	20.2m
AE leading to discontinuation	4.4%	11.5%
CRS	44% (97% were Grade 1/2)	51% (100% were Grade 1/2) after dosing modification

*96pts submitted at abstract deadline, but N=131 presented at ASH

Mosunetuzumab – Ontario Impact

- At present time, CAR-T and BiTE products are not yet funded in Ontario for FL. CAR-T submissions are underway
  - Mosunutuzumab is available through Roche compassionate access program for FL patients with >=3 prior lines of therapy and not eligible for ASCT or CAR-T. This presentation justifies consideration in 3L
- Both products moving forward to Phase 3, and trials planned in 1L and 2L
- Will there be cost savings, and logistical/capacity advantages to outpatient BiTE products over CAR-T in future FL paradigm?
  - Administration in “non-CART centres”

SUMMARY – ASH 2022: some lessons

- CLL
  - Gaia – I study that excluded del(17p), venetoclax-containing regimens worked better than chemotherapy, regardless of genetic risk factors
  - GLOW – Ibr+ven better than Chlor-Obin in older CLL patients – OS benefit!
  - FLAIR – time-limited ven+ibr is better than FCR for PFS (known), but also better than ibr at achieving uMRD
  - ALPINE – in relapsed CLL, zanubrutinib works better than ibrutinib (PFS)
  - BRUIN – in patients previously treated with ibr or acala, the new BTKi pirtobrutinib can still be effective
- Mantle Cell Lymphoma
  - TRIANGLE – adding ibrutinib to front-line standard of care improves FFS (and maybe OS); adding ibrutinib might also make ASCT unnecessary – **potentially practice-changing**
- Follicular Lymphoma
  - upfront treatment with Rituximab is not better than watch and wait
  - AUGMENT – R2 (Rituximab and lenalidomide) improves survival compared to rituximab alonein relapsed follicular lymphoma
  - Immunotherapy – yes, it is *finally* coming to follicular lymphoma

Final Comments on Clinical Trials

- ASH would not be possible if it weren't for 1000s of patients, volunteering to participate in a clinical trial
- ASH summaries give us a glimpse of what may be available in the future
- Many patients in these clinical trials have had access to treatments that benefited them, including prolonging their life, treatments that might not be available to non-trial patients for 5-10 years
- Clinical trials have Built-In Layers of Safety