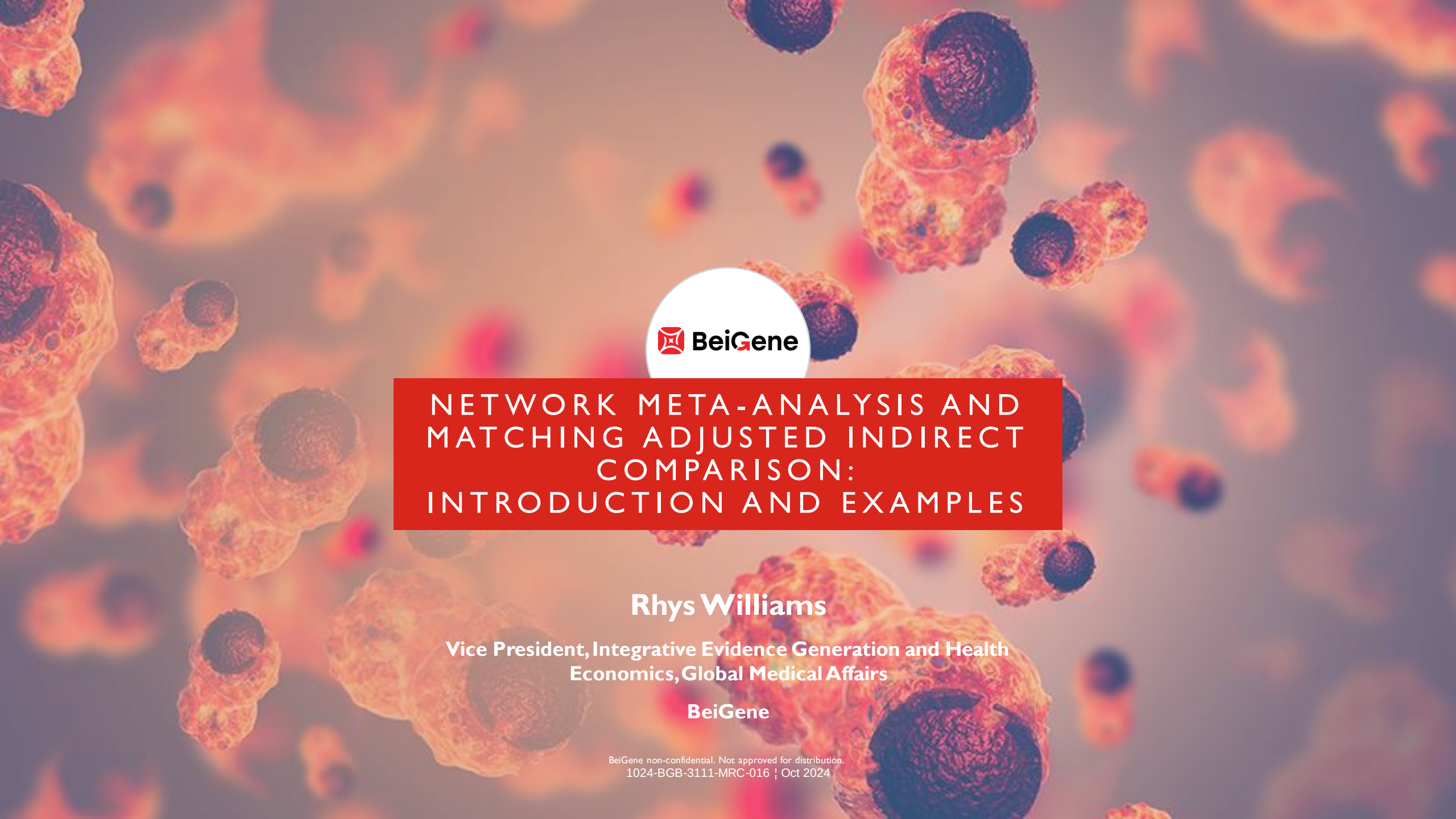

NETWORK META-ANALYSIS AND MATCHING ADJUSTED INDIRECT COMPARISON: INTRODUCTION AND EXAMPLES

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Conflict-of-Interest Statement

- Rhys Williams is an employee of BeiGene and owns stock in BeiGene.

Disclaimers

- The information contained herein is intended for healthcare professionals only and is given for educational purposes only. This document is not intended for professional counseling or advice.
- Matching adjusted indirect comparisons (MAICs) are a methodology to compare data across clinical trials and represent a lower level of evidence than randomized controlled trials.
  - This analysis should be interpreted with caution and should not drive treatment decisions for individual patients
  - Based on the variables selected for matching, outcomes may differ

Research Question: What is the relative efficacy of the BTKis in treatment of R/R CLL?

- Next-generation BTKis have led to changes in the treatment algorithm for patients with high-risk R/R CLL [1]
- Moreover, improved understanding of the CLL genome has facilitated the identification of specific high-risk genetic features of disease, allowing a more personalized approach to treatment [2-6]
- Multiple BTKis are available to treat R/R CLL [7]
- Different methodologies were evaluated[8,9] to estimate relative efficacy of approved and recommended BTKis used to treat R/R CLL

BTKi=Bruton's tyrosine kinase inhibitor, CLL=chronic lymphocytic leukemia, IGHV=immunoglobulin heavy chain variable, NMA=network meta-analysis, R/R=relapsed/refractory.

1. Shadman M. JAMA. 2023;329(11):918-932. 2. Moia R, et al Cancers (Basel). 2020;12(3):642. 3. Hampel PJ, et al Leuk Lymphoma. 2021;62(6):1289-1301. 4. Eichhorst B, et al Ann Oncol. 2021;32(1):23-33. 5. Stephens DM. J Natl Compr Cancer Netw. 2023;21(5.5):563-566. 6. Moia R, et al Expert Rev Hematol. 2020;13(2):109-116. 7. Tam C. *Blood Adv* 2024; 8(9): 2300-2309 8. Shadman M, et al. ASCO 2024 Annual Meeting;abstract 7048. Comparative efficacy of Bruton tyrosine kinase inhibitors in the treatment of relapsed/refractory chronic lymphocytic leukemia: A network meta-analysis (NMA). | Journal of Clinical Oncology (ascopubs.org). 9. Shadman M, et al. Poster Presentation at EHA 2024. https://www.beigenemedical.com/CongressDocuments/Shadman_BGB-3111-305_ASCEND_MAIC_EHA_Poster_2024.pdf

Introduction to Network Meta-Analysis (NMA) and A Case Study Addressing Our Research Question

What is Network-Meta Analysis (NMA)

Any set of studies that links three or more interventions via direct comparisons forms a **network of interventions**. [1]

In a network of interventions there can be multiple ways to make **indirect comparisons** between the interventions. [1]

These are comparisons that have not been made directly within studies, and they can be estimated using mathematical combinations of the direct intervention effect estimates available. [1]

Network meta-analysis combines direct and indirect estimates across a network of interventions in a single analysis.[1]

Example: A network diagram with four competing interventions and two arm and three arm direct comparisons available for some of the trials

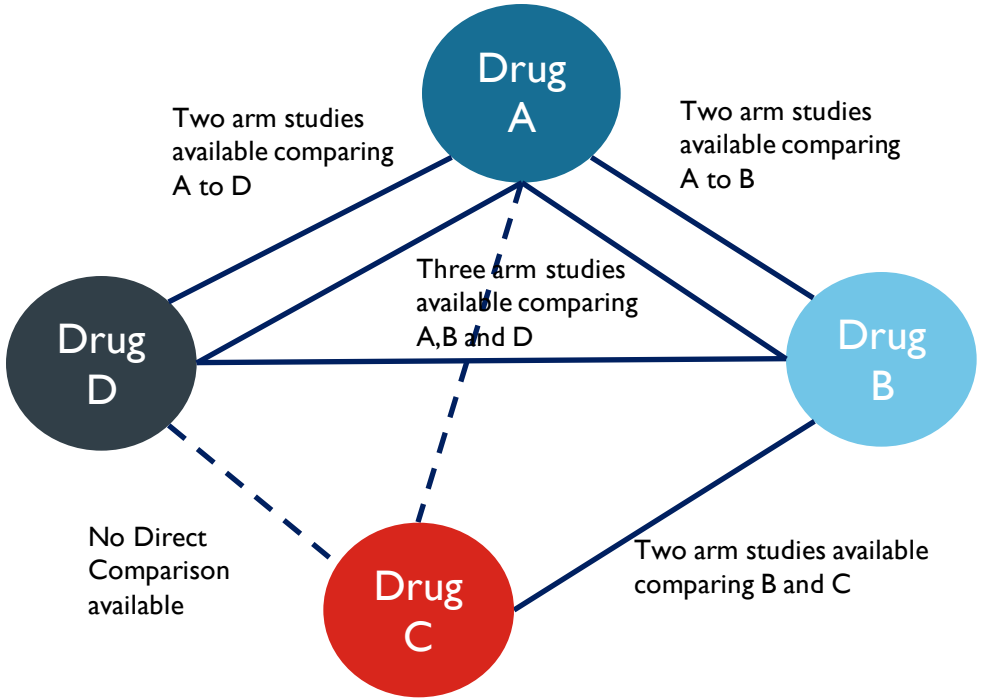


Diagram created by the speaker based on Rouse B, et al. Intern Emerg Med. 2016 Dec 2; 12(1):103-111

1. Rouse B, et al. Intern Emerg Med. 2016 Dec 2; 12(1):103-111

Network Diagram for Our Research Question

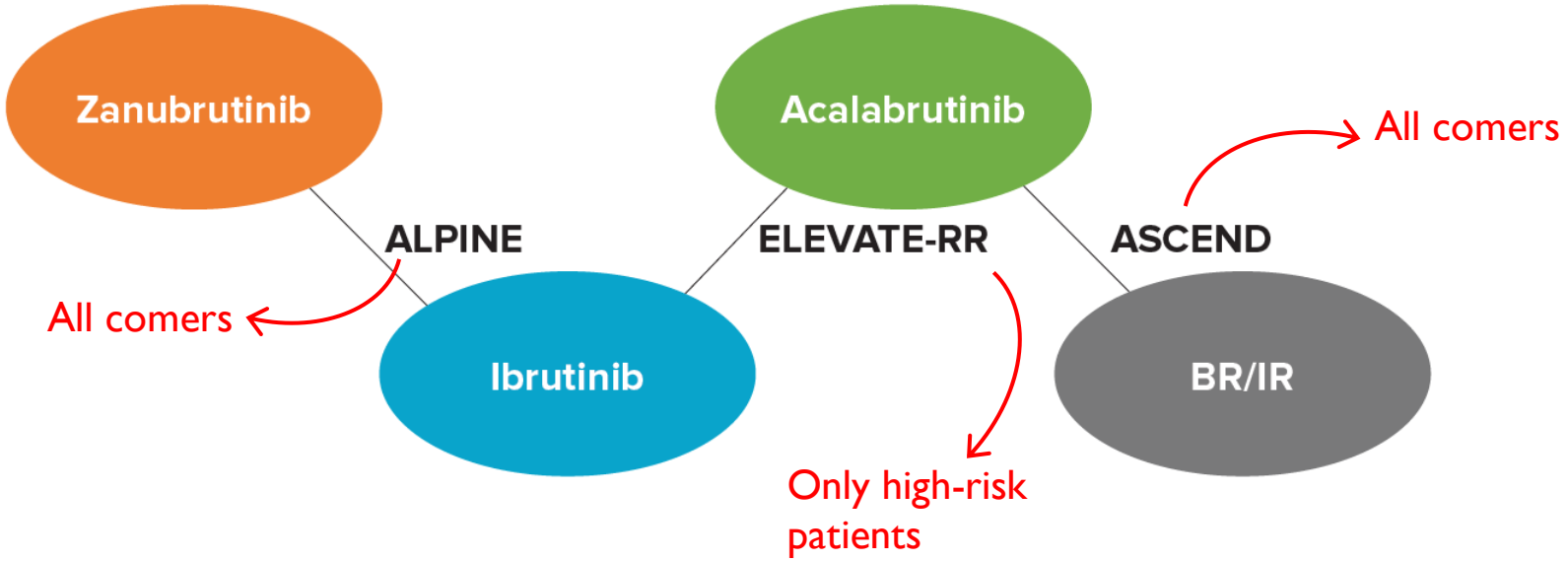


Diagram created by the speaker based on Shadman M et al J Clin Oncol. 2024;42(suppl 16):7048

- When exploring this research question using a Network Meta-Analysis (NMA), the population had to be restricted to only high-risk patients given ELEVATE-RR[1] trial who closes the network includes only high-risk population.
- This reduced the population included from ALPINE[2] and ASCEND[3]
- Given that data from ALPINE were collected during the COVID-19 pandemic, data were analyzed with and without adjustment for COVID-19-related deaths[4]

1. Byrd JC, et al J Clin Oncol. 2021;39(31):3441-3452 2. Brown JR, et al N Engl J Med. 2023;388(4):319-332 3. Ghia P, et al Hemasphere. 2022;6(12):e801 4. Shadman M et al J Clin Oncol. 2024;42(suppl 16):7048

Results

BTKis in R/R CLL: NMA

- In high-risk populations as defined by the individual trials, zanubrutinib was found to be proved significant clinical benefit compared to ibrutinib, acalabrutinib, and BR/IR for progression-free survival, representing risk reductions of 51%, 46%, and 88% respectively, with COVID-19 adjustment

NMA Results Using COVID-19 Adjusted Data from ALPINE Trial – Hazard Ratios and Probability Better for Zanubrutinib vs Comparators

Zanubrutinib vs.	HR [95%CrI]	Probability Better (%)
Acalabrutinib		
PFS	0.54 [0.32, 0.92]	98.6
OS	0.72 [0.35, 1.48]	81.7
Ibrutinib		
PFS	0.49 [0.30, 0.78]	99.9
OS	0.59 [0.31, 1.12]	94.8
BR/IR		
PFS	0.12 [0.05, 0.26]	100
OS	0.64 [0.24, 1.74]	80.7

BR/IR=bendamustine + rituximab or idelalisib + rituximab, CrI=credible intervals, Prob=probability better.
Shadman M, et al. ASCO 2024 Annual Meeting;abstract 7048. Comparative efficacy of Bruton tyrosine kinase inhibitors in the treatment of relapsed/refractory chronic lymphocytic leukemia: A network meta-analysis (NMA). | Journal of Clinical Oncology (ascopubs.org)

Results

BTKis in R/R CLL: NMA

- The table below presents results for zanubrutinib vs acalabrutinib from when data from ALPINE were and were not adjusted for COVID-19 deaths

NMA Results With and Without COVID-19 Adjustment from ALPINE Trial – Hazard Ratios and Probability Better for Zanubrutinib vs Acalabrutinib

Zanubrutinib vs. Acalabrutinib	High-Risk With COVID-19 adjustment	High-Risk With COVID-19 adjustment
HR [95%CrI], Probability Better (%)		
PFS	0.54 [0.32, 0.92], 98.6	0.58 [0.34, 0.98],98.0
OS	0.72 [0.35, 1.48], 81.7	0.84 [0.43, 1.65], 69.1
OR [95%CrI], Probability Better (%)		
ORR	1.91 [0.75, 5.00], 91.7	1.69 [0.61, 4.97], 84.4
CR	2.07 [0.50, 9.67], 84.4	1.84 [0.50, 7.20], 81.6

CR=complete response, CrI=credible intervals,OR=odds ratio; ORR=overall response rate; PFS=progression-free survival
Shadman M et al J Clin Oncol. 2024;42(suppl 16):7048

Limitations

- The definition of high-risk varied between the studies included in this NMA. The ELEVATE-RR trial exclusively enrolled patients with del(17p)/del(11q)[1], while ALPINE[2] and ASCEND[3] did not limit enrollment to this population.
- It is expected that the trials included would have differences in terms of baseline characteristics, however NMAs do not consider any adjustments on the characteristics of the populations.[4]
- The analysis was limited to high-risk R/R CLL patients.[5]

Strengths

- Randomization is preserved with NMAs.[4]
- As no adjustment is made for population characteristics, there is no reduction in sample size as with MAICs.[6]
- This analysis included scenarios with adjustment for the impact of COVID- with results shown to be consistent across different scenarios.[5]

NMA=network meta-analysis; R/R CLL=relapsed/refractory chronic lymphocytic leukemia.

1. Byrd JC, et al J Clin Oncol. 2021;39(31):3441-3452 2. Brown JR, et al N Engl J Med. 2023;388(4):319-332 3. Ghia P, et al Hemasphere. 2022;6(12):e801 4. Watt J, et al. Journal of Investigative Dermatology. 2019;139(1):4-12 5. Shadman M, et al. Poster Presentation at ASCO 2024;abstract 7048 6. Choy E et al. Arthritis Research & Therapy. 2019; 21(32):2019

Introduction to Matching-Adjusted Indirect Comparison (MAIC) and A Case Study Addressing Our Research Question

Matching Adjusted Indirect Comparison

Introduction to MAICs

- MAIC is a statistical method where published estimates of a trial can be combined with Individual Patient Data (IPD) of another trial to obtain indirect estimates[1,2]
- This approach is a form of **propensity score weighting** in which patients in one treatment group (in this case the trial with IPD) are weighted based on their closeness to the other treatment group (in this case the trial with only published aggregate data) [1,2]

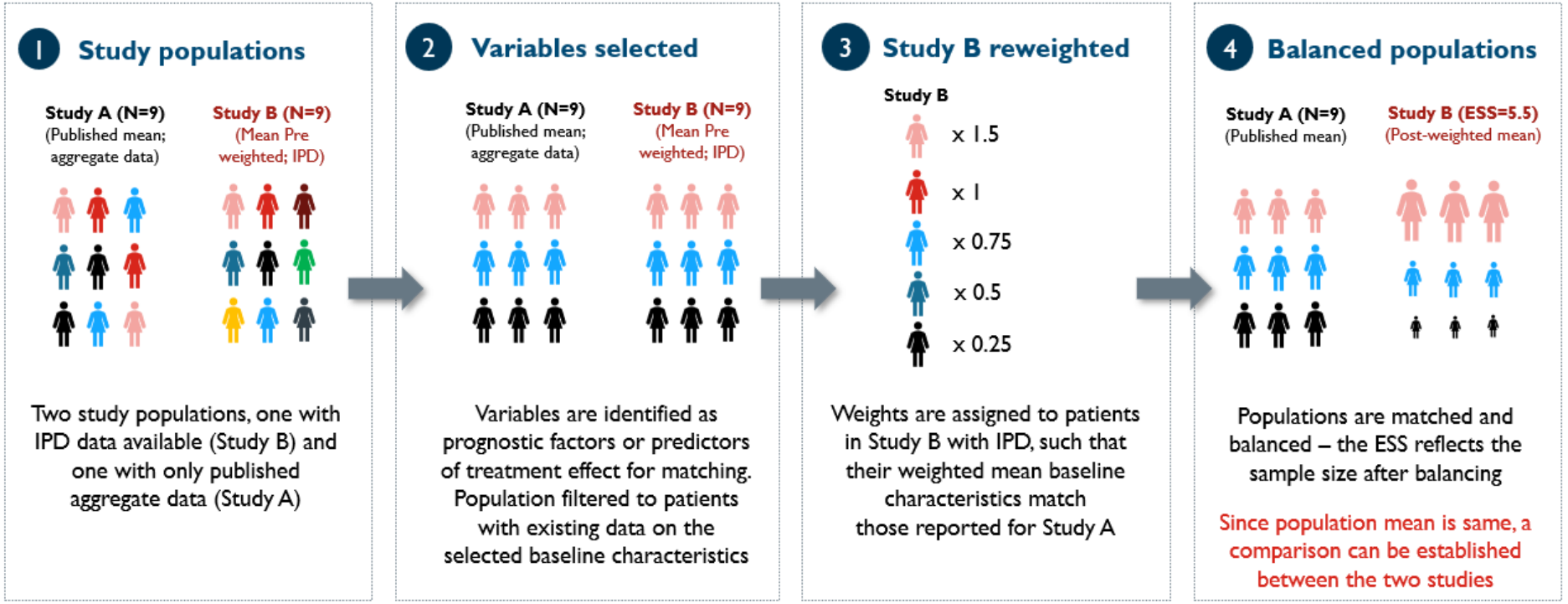


Diagram created by the speaker based on Phillippo[1] and Signorovitch[2]

ESS=effective Sample Size, IPD=Individual Patient Data, MAIC=Matching Adjusted Indirect Comparison.

1.Phillippo D, et al. NICE DSU Technical Support Document 18; 2016: https:// research-information.bris.ac.uk/en/publications/nice-dsu-technical-supportdocument-18-methods-for-population-adj; Access date: October 18, 2024 2. Signorovitch JE, et al. Value in Health 2012;15:940-947.

Anchored vs. Unanchored MAIC

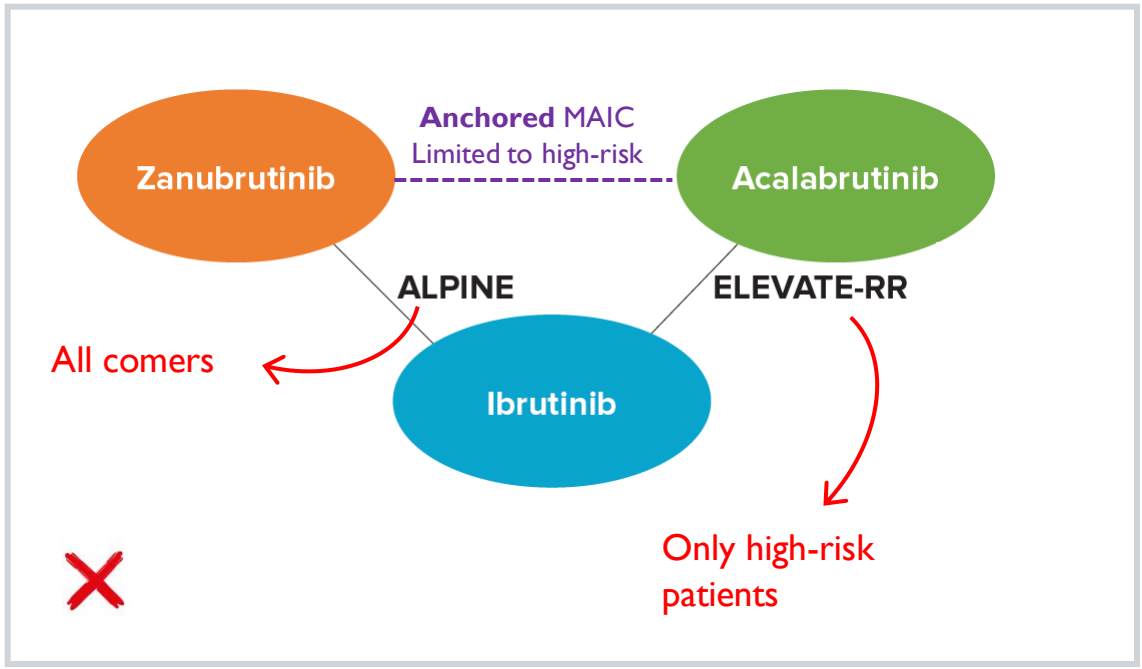
Introduction to MAICs

"Anchored" indirect comparisons:
Where the evidence is connected by a common comparator

"Unanchored" indirect comparisons:
Where the evidence is disconnected due to a lack of a common comparator or single-arm studies

MAIC=Matching Adjusted Indirect Comparison.
Phillippo D, et al. NICE DSU Technical Support Document 18; 2016: https:// research-information.bris.ac.uk/en/publications/nice-dsu-technical-supportdocument-18-methods-for-population-adj Access date: October 18, 2024

MAIC options for Our Research Question



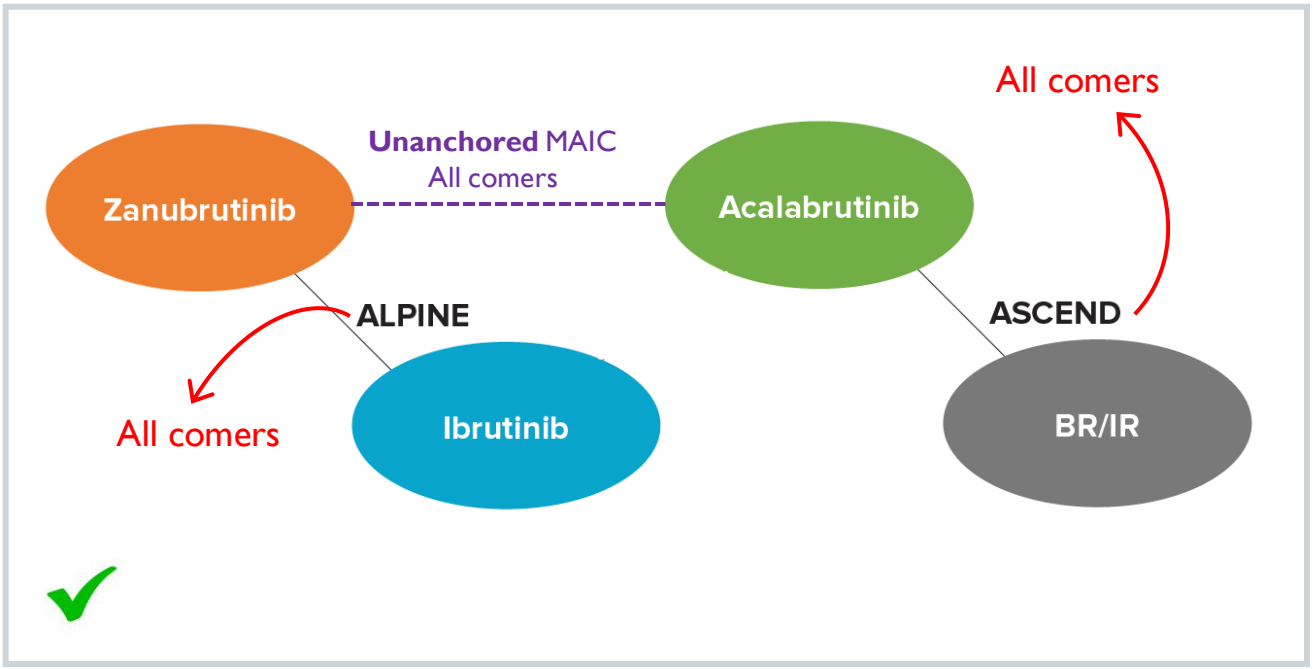


Diagram created by the speaker based on Byrd[1] , Brown [2] and Ghia [3]

- When exploring this research question using a Matching-Adjusted Indirect Comparison (MAIC), two options were possible: anchored and unanchored MAIC
- With an anchored MAIC, the population had to be restricted to only high-risk patients given ELEVATE-RR trial[1] who closes the network includes only high-risk population. This would reduce the starting population. The population would further reduce with matching and adjustment.
- Therefore, an unanchored MAIC comparing zanubrutinib (ALPINE[2]) and acalabrutinib (ASCEND[3]) was preferred. [4]

1. Byrd JC, et al J Clin Oncol. 2021;39(31):3441-3452 2. Brown JR, et al N Engl J Med. 2023;388(4):319-332 3. Ghia P, et al Hemasphere. 2022;6(12):e801 4. Shadman M et al J Clin Oncol. 2024;42(suppl 16):7048

Study Methods

ALPINE vs ASCEND MAIC

ALPINE (N=327)

Individual Patient-Level Data
(DCO: September 2023; median follow-up: 39 months)

ASCEND (N=155)

Published Aggregate Data
(DCO: October 2020; median follow-up: 36 months)

Adjustment for impact of COVID-19 within ALPINE

Variable identified as prognostic factors or predictors of treatment effect for matching

Age, gender, ECOG PS, geographic region, mutated IGHV, del(17p), del(11q), *TP53* mutation status, complex karyotype,* bulky disease, cancer type, beta$_2$-microglobulin,* Rai/Binet stage, number and type of prior therapies, absolute lymphocyte and neutrophil counts, and platelet count

Sensitivity analyses of scenarios to consider impact of matching for different sets of variables

Matching, reweighting, and adjusting for variables

- Zanubrutinib unadjusted (ITT) population (ALPINE), **n=327**.
- Zanubrutinib ITT population filtered to patients with existing data on the selected baseline characteristics and excluding patients with SLL, **n=308**.
- After population adjustment, **ESS=184.8** for zanubrutinib (60% of the starting filtered population).

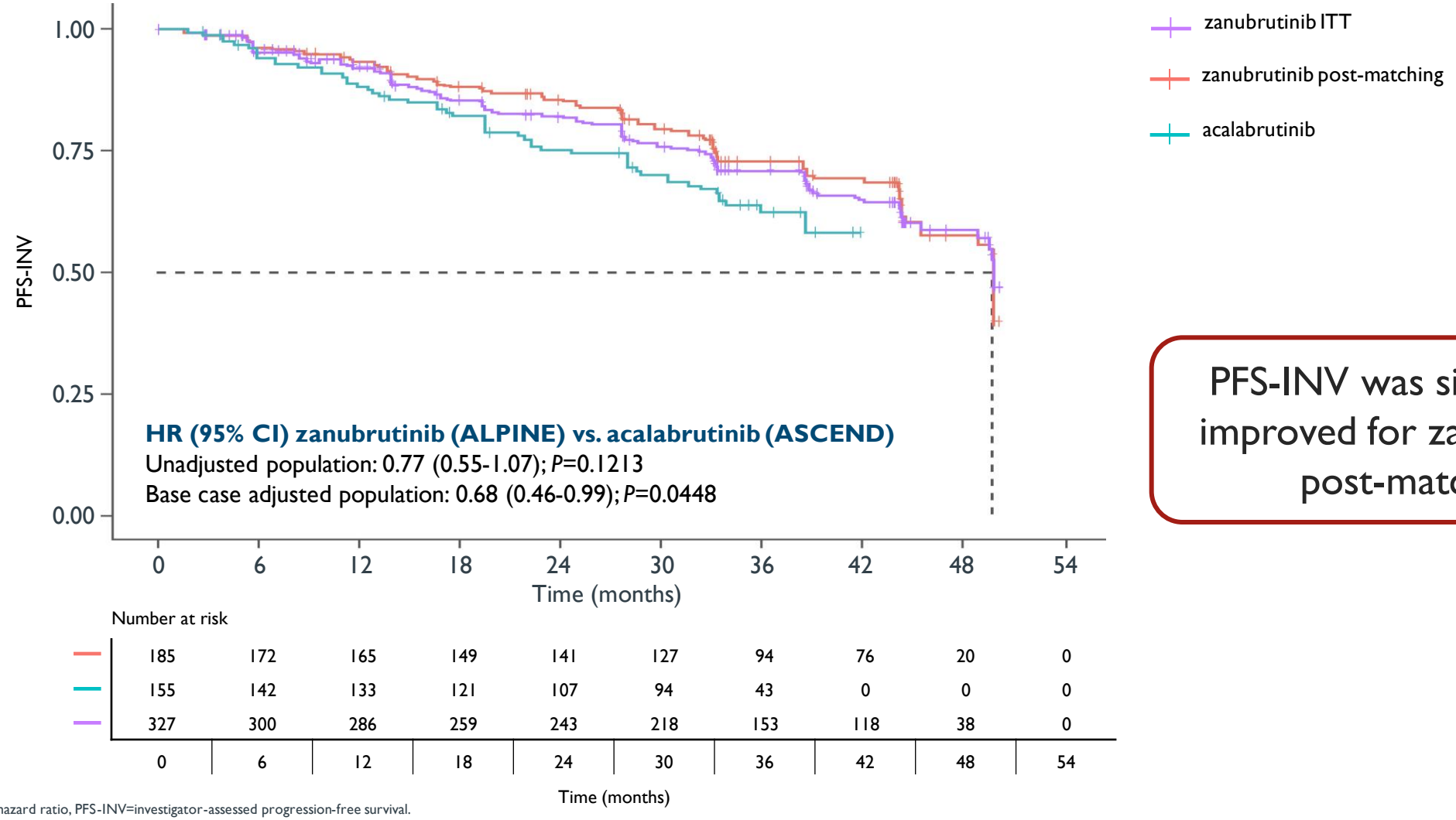
Outcomes

PFS-INV	HRs for PFS-INV and OS: Weighted Cox proportional hazard model
OS	
CR	OR for CR: Weighted logistic regression model

*Covariates not matched in the base case.
CR=complete response, DCO=data cut-off, del(11q)=chromosome 11q deletion, del(17p)=chromosome 17p deletion, ECOG PS=Eastern Cooperative Oncology Group performance status, ESS=effective sample size, HR=hazard ratio, IGHV=immunoglobulin heavy chain variable, IPD=individual patient-level data, OR=odds ratio, OS=overall survival, PFS-INV=investigator-assessed progression-free survival, SLL=small lymphocytic lymphoma.
Shadman M, et al. Poster Presentation at EHA 2024 https://www.beigenemedical.com/CongressDocuments/Shadman_BGB-3111-305_ASCEND_MAIC_EHA_Poster_2024.pdf

PFS-INV for zanubrutinib pre- and post-matching and acalabrutinib

ALPINE vs ASCEND MAIC



PFS-INV was significantly improved for zanubrutinib post-matching

CI=confidence interval, HR=hazard ratio, PFS-INV=investigator-assessed progression-free survival.
Shadman M, et al. Poster Presentation at EHA 2024. https://www.beigenemedical.com/CongressDocuments/Shadman_BGB-3111-305_ASCEND_MAIC_EHA_Poster_2024.pdf

Limitations

- Unanchored MAICs break the randomization and make the strong assumption that cross-trial differences can be entirely explained by variables selected for matching.[1]
- Including all variables in the matching would considerably reduce the ESS, given the differences across the two trial populations and the possibility of missing data on some variables.[1]

Strengths

- Several scenarios with different variables includes and different ESS resulted in consistent conclusions.[2]
- After adjustment, the resulting ESS was rather high given the starting population included the whole ALPINE sample size.[2]

BR/IR=bendamustine + rituximab or idelalisib + rituximab, NMA=network meta-analysis.

1. Signorovitch JE, Value in Health. 2012;15(6):940-947 2. Shadman M, et al. Poster Presentation at EHA 2024. https://www.beigenemedical.com/CongressDocuments/Shadman_BGB-3111-305_ASCEND_MAIC_EHA_Poster_2024.pdf

Differentiation from previous[2] ALPINE vs ASCEND MAIC

ALPINE vs ASCEND MAIC

These results differ from a previously presented MAIC[2] comparing the two trials because limitations of that analysis have been identified and specifically addressed in this analysis – namely:

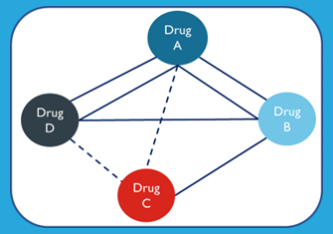
- Selecting comparable published median follow-ups – and the latest analysis of ALPINE
- Accounting for the impact of COVID-19 on ALPINE
- Using clinically-relevant matching criteria
- Ensuring the base case had a large enough sample size – while ensuring adequate sensitivity analyses
- Reporting essential efficacy outcomes
- Leaving safety comparisons for a more robust hypothesis-generating comparison tool – meta-analysis

MAIC=matching-adjusted indirect comparison.

1. Shadman M, et al. Poster Presentation at EHA 2024 https://www.beigenemedical.com/CongressDocuments/Shadman_BGB-3111-305_ASCEND_MAIC_EHA_Poster_2024.pdf; 2. Kittai AS, et al. Am J Hematol. 2023;98:E387–E3

NMA vs. MAIC: Which One to Use?

NMA VS MAIC[1]

	Network Meta Analysis (NMA)	Matching-Adjusted Indirect Comparison (MAIC)
		
1	Compares multiple treatments using published **aggregate data**	Compares published data with **IPD** (Individual Patient Data)
2	Requires a common comparator (connected evidence network, controlled trials)	May not require a common comparator (unanchored comparisons, single arm trials)
3	Assumes trials are comparable in terms of design and population (heterogeneity cannot be handled)	Some of the heterogeneity can be handled between trials by matching the patient population
5	Traditional and established methodology	Evolving method
6	There is no loss of information in methodology as all the available information is used	In an attempt to handle the heterogeneity, there is a risk of reduction of patient sample size

MAIC=matching-adjusted indirect comparison; NMA=network meta analysis
1. Extracted from Choy E et al Arthritis Res Ther. 2019;21:32

Feel free to contact us for any queries

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