Generating the Relevant Comparative Evidence to Support Market Access in Absence of a Randomized Comparative Trial Versus the Right Comparator or, Versus any Comparator

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Context: market access

- First requirement: regulatory approval to market the drug (FDA/ EMA)
- Approval is nothing without reimbursement!
- We have to get “the payers” convinced of the value of our drug

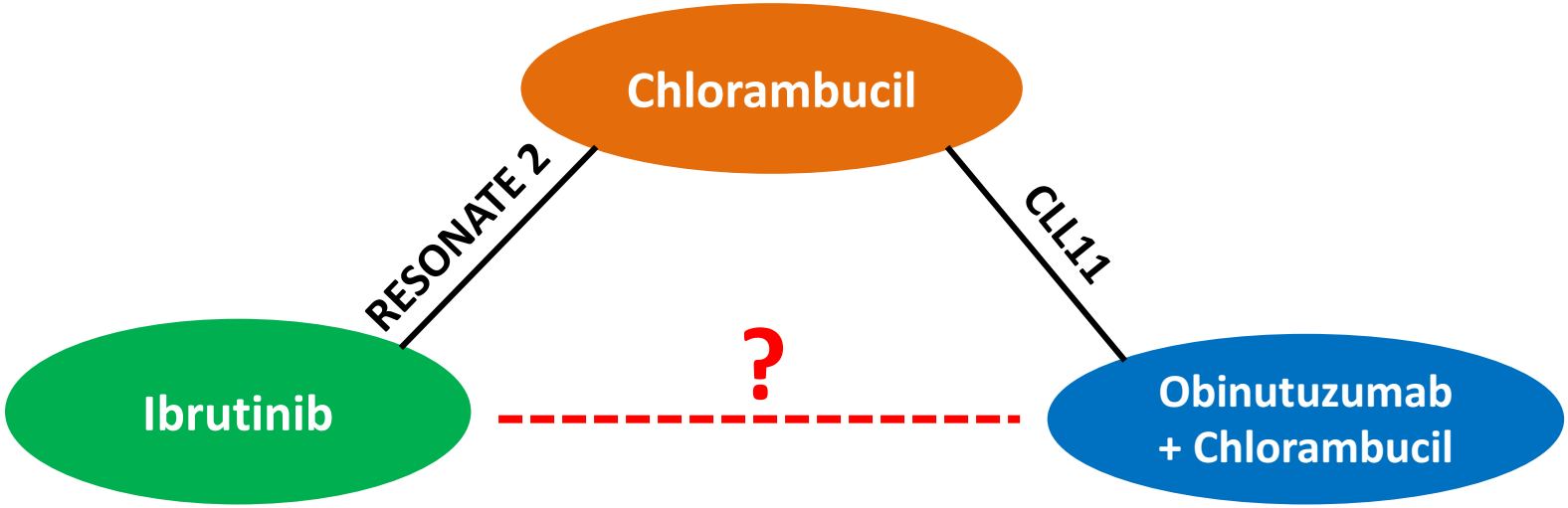
  $\Rightarrow$Health technology assessment (HTA)

The Role of HTA

- Reliable and timely provision of (synthesized, appraised) evidence:
  - Is the drug safe?
  - For whom does it work and when?
  - Is it better than what we already have?
  - Does it provide value for money?
  - Can we afford it? Can we afford not to?
  - What ‘s the trade-off?
  - What else needs to be considered?

Introduction

- E.g. Chronic Lymphocytic Leukemia (CLL)



There is no RCT comparing Ibrutinib with Obinutuzumab + Chlorambucil!

Introduction

- Randomization is the most powerful method to prevent confounding!
- However, we cannot always perform a RCT…
- An unadjusted comparison, comparing a treatment arm from one trial with that of another is unacceptable!

$\Rightarrow$ Breaks randomization and introduces bias

- What can we do to preserve randomization or to reduce the bias?

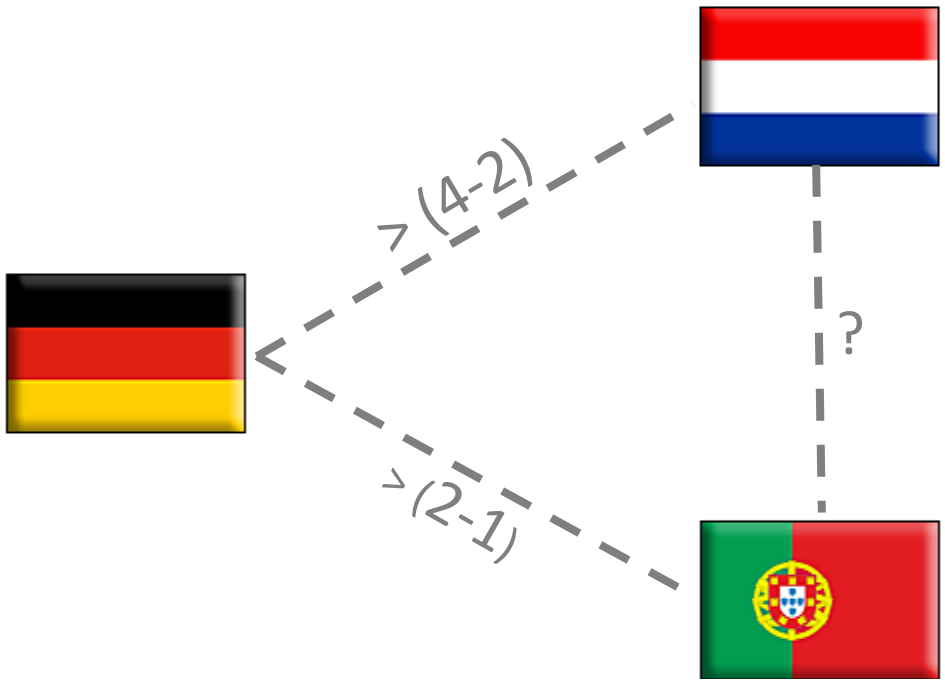
That depends on the available data!

What can we do to reduce the bias?

		TRIAL B (comparator drug)	
		IPD	**AD**
TRIAL A (J&J drug)	**IPD**	Modeling	ANCHORED MAIC • unbalanced pop. UNACHORED MAIC • single arm trial • no common comparator
	AD	ANCHORED MAIC • unbalanced pop. UNACHORED MAIC • single arm trial • no common comparator	IC or MTC/NMA

IPD: individual patient level data
AD: aggregate data

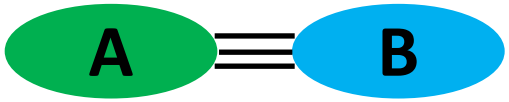
Concept of an NMA/MTC



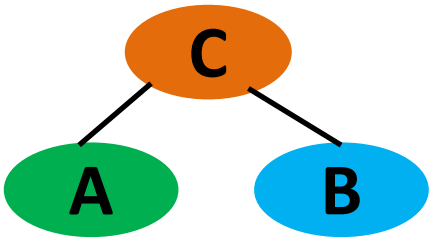
Indirect comparison

Pairwise meta-analysis

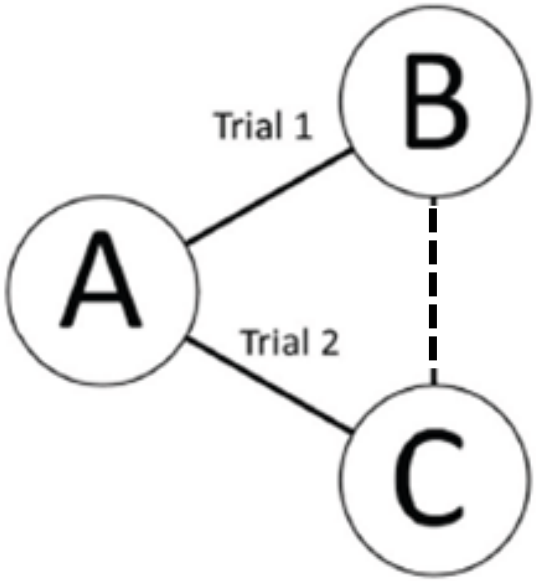
(direct comparison)

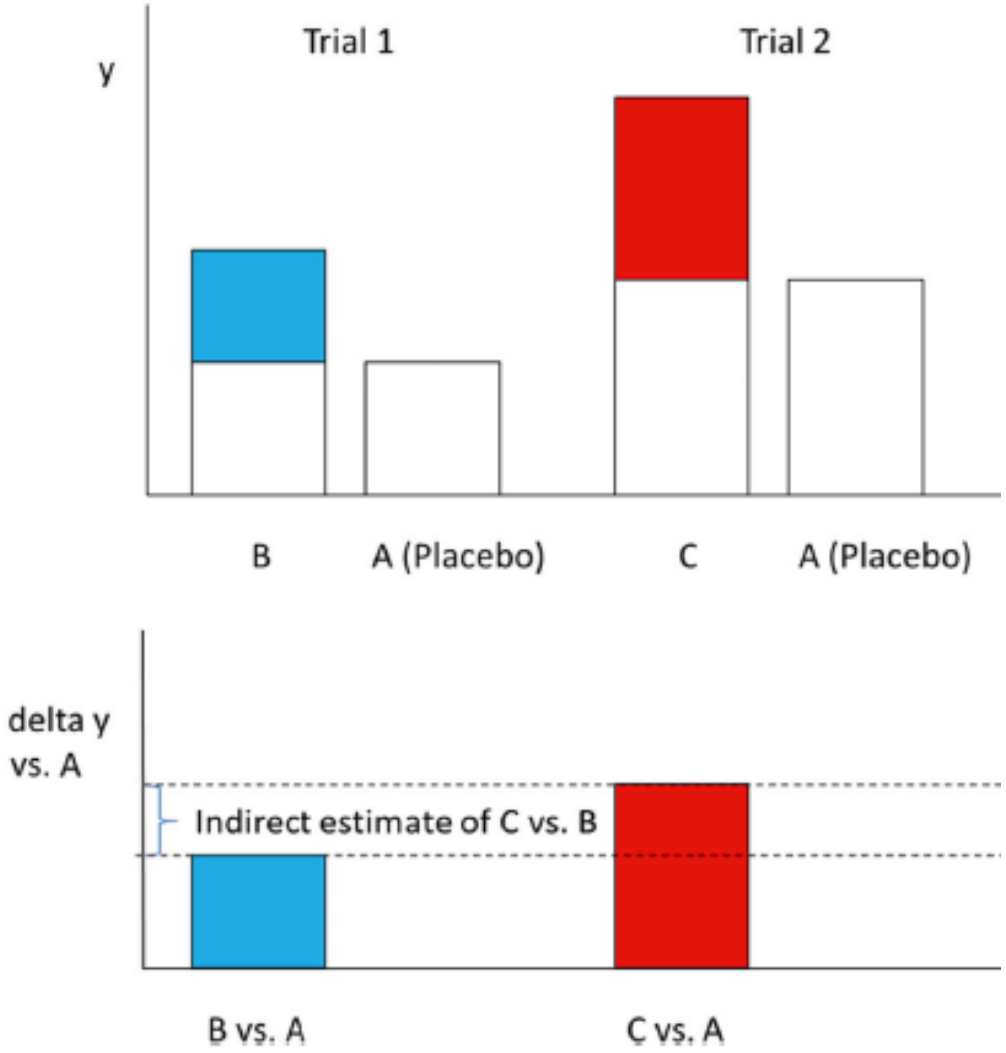


Indirect comparison



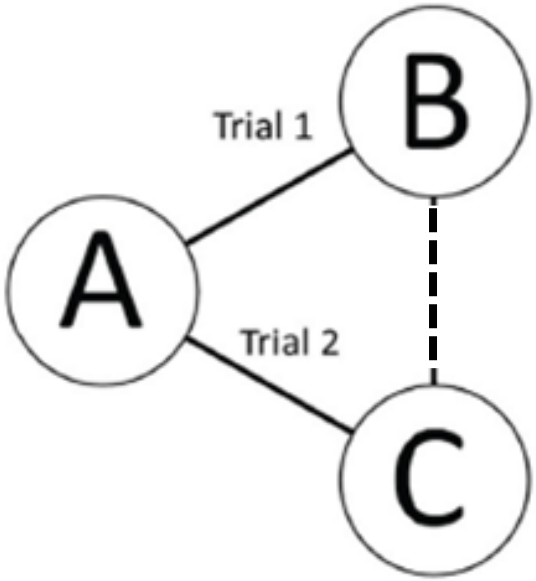
Indirect comparison





Source: Jansen et al. 2014

BUCHER approach



$$OR_{BC} = \frac{OR_{BA}}{OR_{CA}}$$

$$\log(OR_{BC}) = \log\left(\frac{OR_{BA}}{OR_{CA}}\right)$$

$$= \log(OR_{BA}) - \log(OR_{CA})$$

$$Var[LOR_{BC}]$$

$$= Var[LOR_{BA} - LOR_{CA}]$$

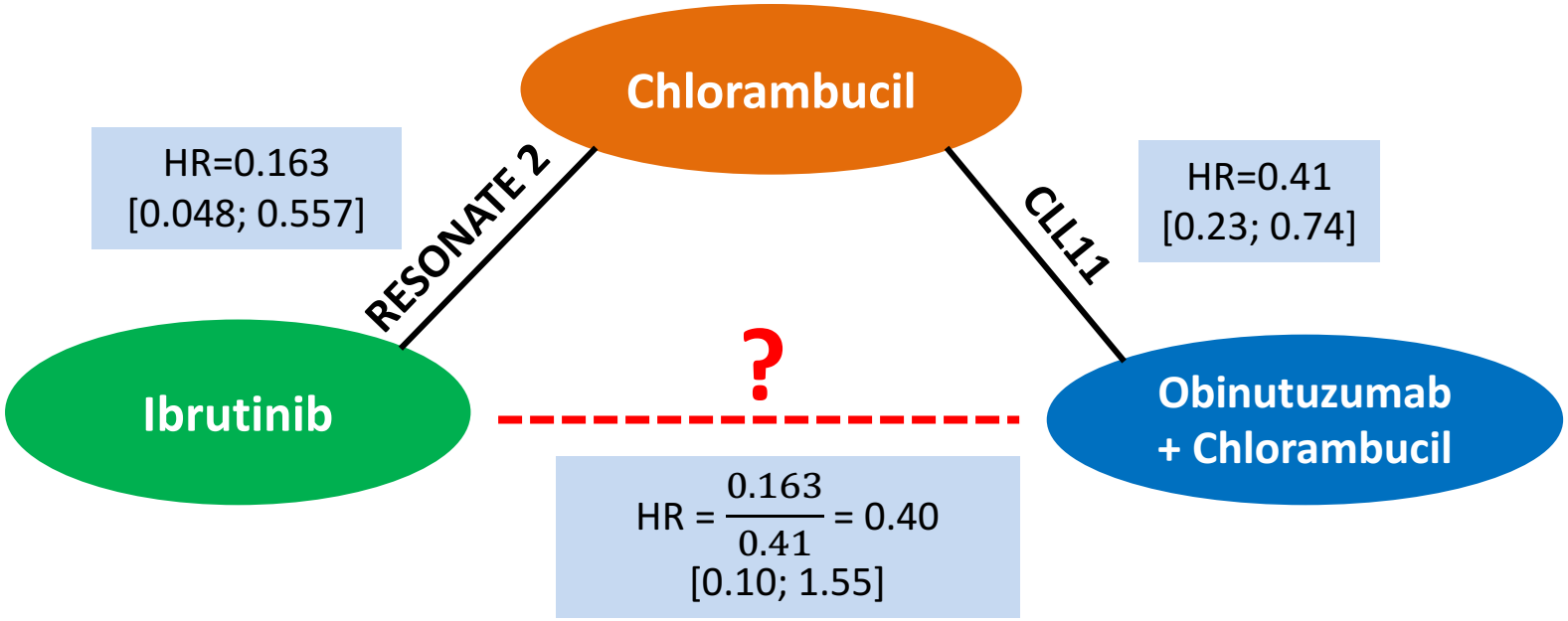
$$= Var[LOR_{BA}] + Var[LOR_{CA}]$$

$$LOR_{BC} = LOR_{BA} - LOR_{CA}$$

$$Var[LOR_{BC}] = Var[LOR_{BA}] + Var[LOR_{CA}]$$

Example: Bucher

- Chronic Lymphocytic Leukemia (CLL)
- Overall survival

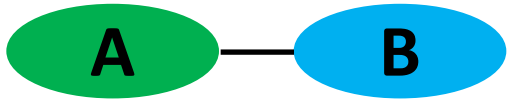


Van Sanden et.al. 2017 , Adv Ther 34(7):1650-1661

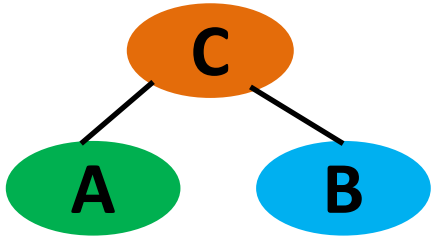
Network meta-analysis

Pairwise meta-analysis

(direct comparison)



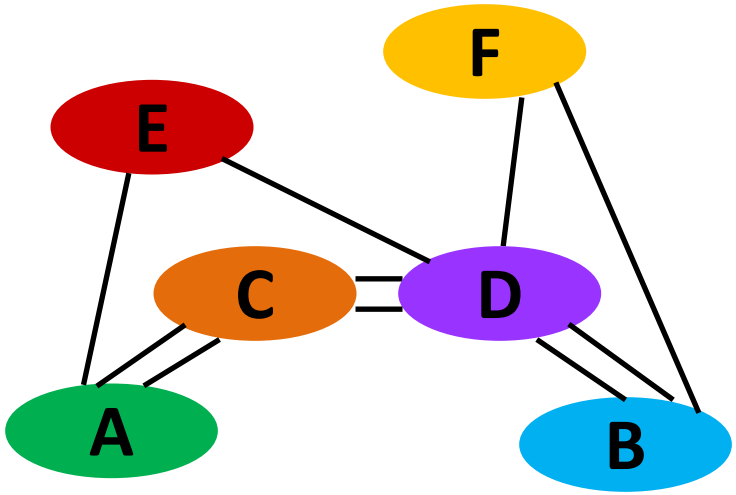
Indirect comparison



Special case

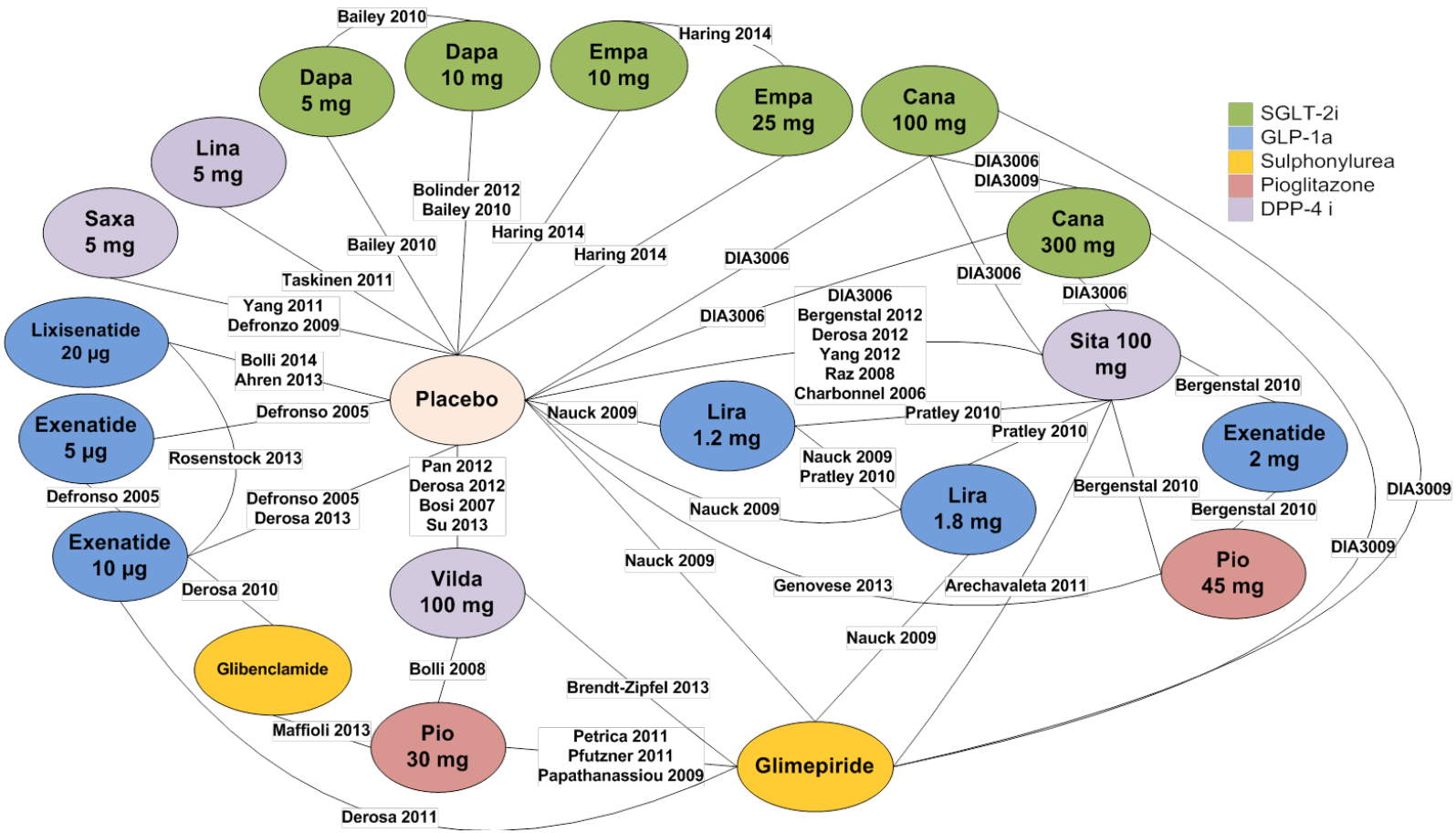
Mixed treatment comparison (MTC) or Network meta-analysis (NMA)

(Combines direct + indirect comparison)



Example: diabetes

Network of evidence : HbA1c (add-on to MET – 26 weeks)



MTC/NMA

- Based on comparing relative treatment effects vs a common comparator
- **Analysis: Frequentist vs Bayesian approach?**
  - Bucher approach (frequentist) for simple indirect comparison
  - Bayesian analysis with non-informative priors

    Posterior probability distribution allows calculating the probability of which of the competing interventions is best and other probability statements

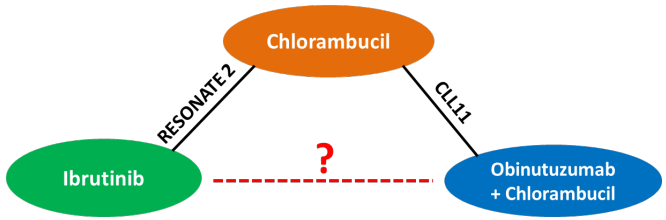
    Providing information that is directly relevant to health-care decision makers

    Ref. Jansen et al. 2011, Value in Health 14, 4 1 7 – 4 2 8

Example: Bucher vs Bayesian

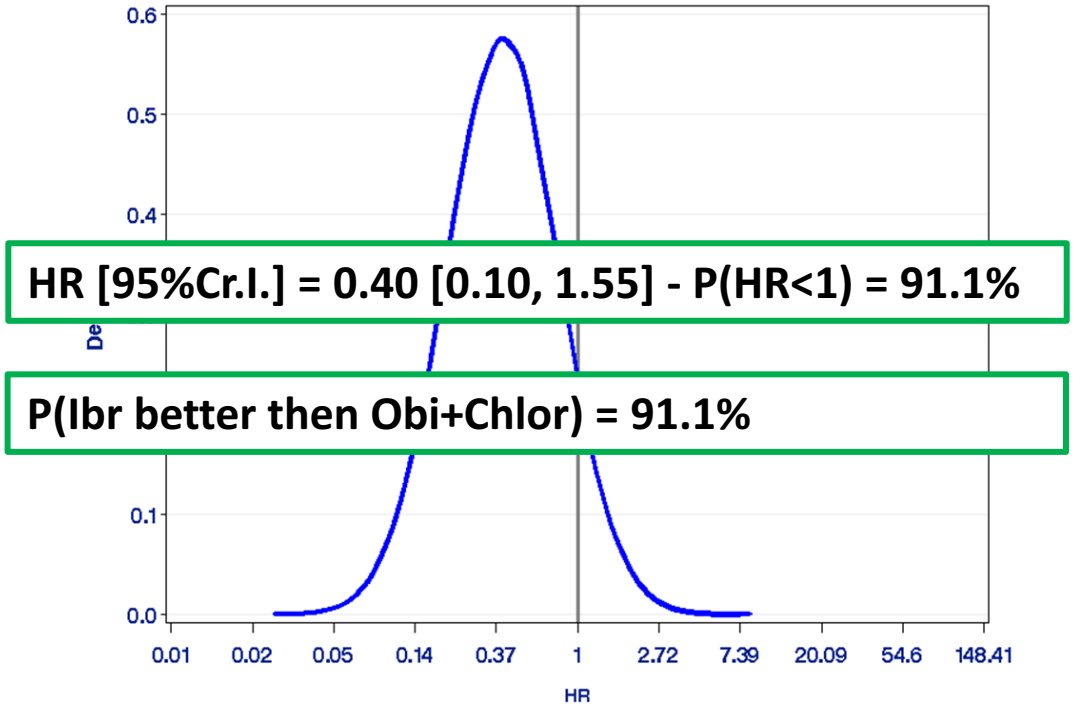
- BUCHER: HR [95%CI] = 0.40 [0.10; 1.55]

  $\Rightarrow$ Not statistically significant at the 5% s.l.



- BAYESIAN analysis:

Posterior distribution for the HR for Ibr vs Obi+Chlor



HR [95%Cr.I.] = 0.40 [0.10, 1.55] - P(HR<1) = 91.1%

P(Ibr better then Obi+Chlor) = 91.1%

Van Sanden et.al. 2017 , Adv Ther 34(7):1650-1661

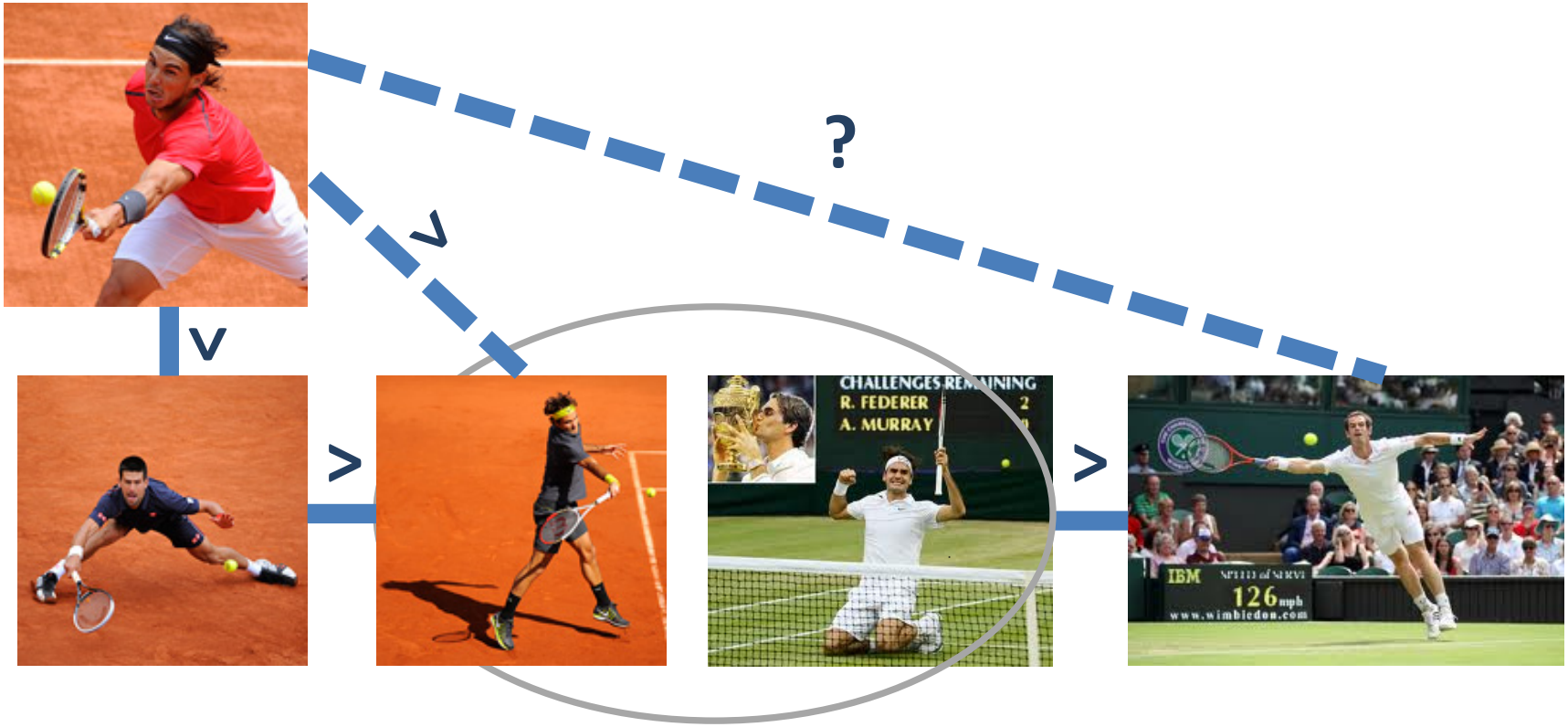
MTC/NMA

- Based on comparing relative treatment effects vs a common comparator
- Analysis: Frequentist vs Bayesian approach
- **RE or FE model?**

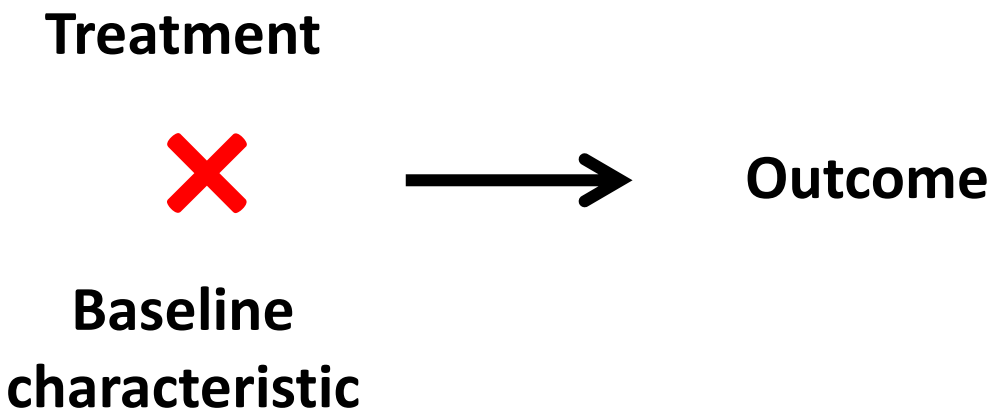
MTC/NMA

- Based on comparing relative treatment effects vs a common comparator
- Analysis: Frequentist vs Bayesian approach
- RE or FE model
- **Assumptions?**
  - Confounding is not a problem as it does not effect the relative treatment effect!
  - Populations have to be balances with respect to treatment effect modifiers (TEM)!

Treatment effect modification



Treatment effect modification



Size (or even direction) of the observed association differs across trial populations!

How to deal with TEM?

- Meta-regression
  - Characteristic of interest has to be available in all publications
  - Not always possible due to low number of studies (≈ 10 studies per covariate needed)

- Subgroups analysis
  - If available in publications
  - ⇒ Increased uncertainty (lower patient numbers)

- Sensitivity analysis (e.g. Excluding trials)

- Make populations more comparable (e.g. Anchored MAIC)

If you can not correct for TEM, try to at least identify the direction of the bias!

Treatment effect modification

Summary:

- If no differences between trials
  $\Rightarrow$ NMA/MTC is valid!

- If differences between trials
  - No impact on relative treatment effect
    $\Rightarrow$ NMA/MTC is valid!
  - Impact on relative treatment effect
    $\Rightarrow$ NMA/MTC is biased!

What can we do to reduce the bias?

		TRIAL B (comparator drug)	
		IPD	**AD**
TRIAL A (J&J drug)	**IPD**	Modeling	ANCHORED MAIC • unbalanced pop. UNACHORED MAIC • single arm trial • no common comparator
	AD	ANCHORED MAIC • unbalanced pop. UNACHORED MAIC • single arm trial • no common comparator	IC or MTC/NMA

IPD: individual patient level data
AD: aggregate data

MAIC

- Matching-adjusted indirect comparison
  (Signorovitch et al., 2012)
  - To balance the populations of an indirect comparison
    ⇒ Still comparing relative treatment effects

    ANCHORED MAIC
  - Can also be used to balance the populations in case of single arm trials or no common comparator in multi-arm trials
    ⇒ Comparing absolute treatment effects
    ⇒ Use of relative effect measures or validation of matching are not possible!

    UNACHORED MAIC

Matching-adjusted indirect comparison

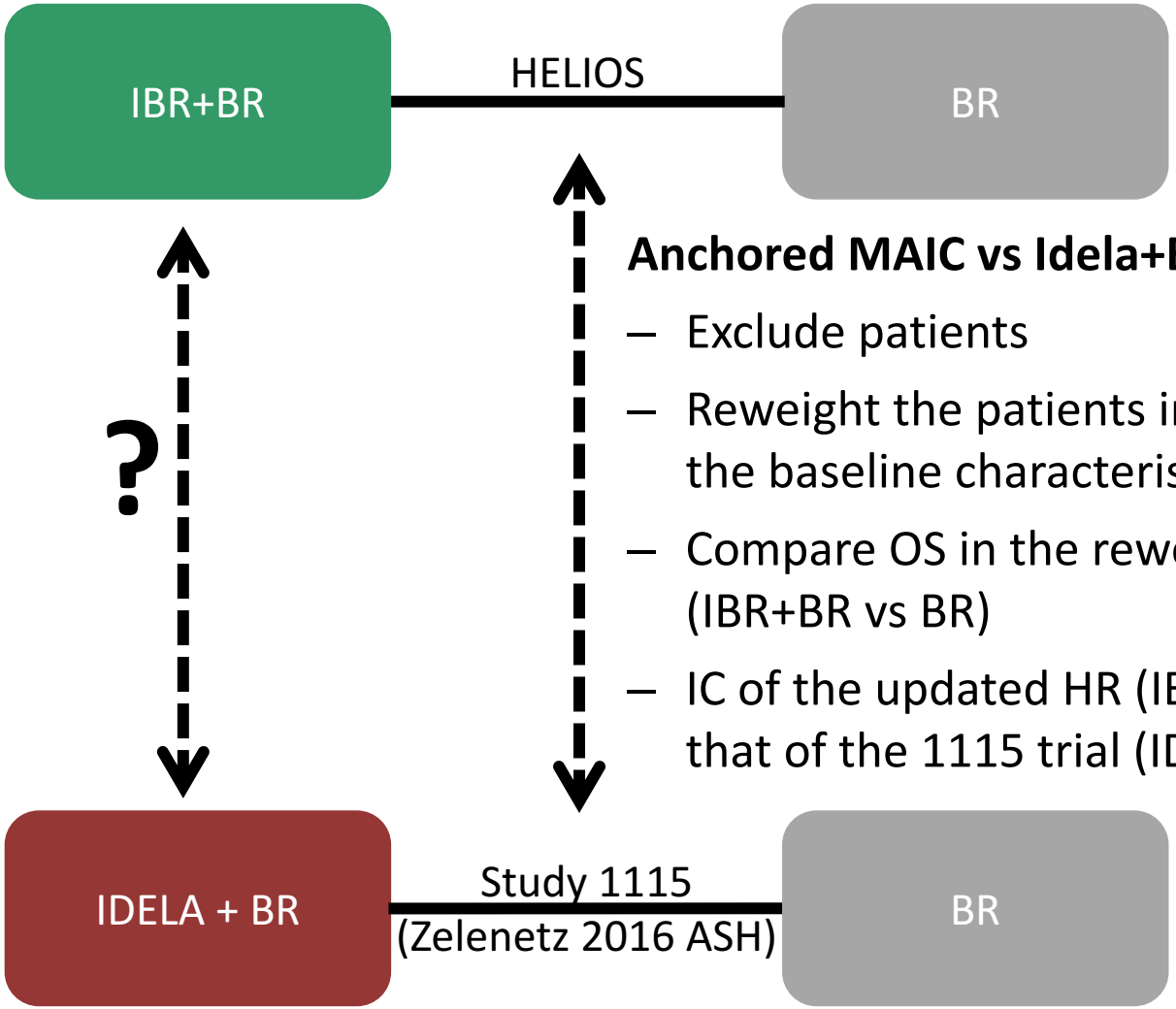
- How does it work?
  - Exclude patients from IPD data that where also excluded from AD trial
  - Re-weight patients in IPD data (= pseudo population)
    - $\Rightarrow$ Match baseline characteristics to those reported in trials with AD data
    - $\Rightarrow$ Balances trial populations
  - Compare outcome of the pseudo population with that of the published trial
- Weights=

  Inverse of odds of having enrolled in the IPD trial vs having enrolled in the AD trial

Matching-adjusted indirect comparison

- Limitations
  - Depends heavily on the available evidence in publications
    - E.g. If information about a characteristic is not reported, or a different scale/scoring system is used, we cannot match on it
  - Depends on the ability to match with the publication
    - E.g. If the populations are too different, matching will be impossible or will lead to high uncertainty (very small N_{eff}) in the final comparison

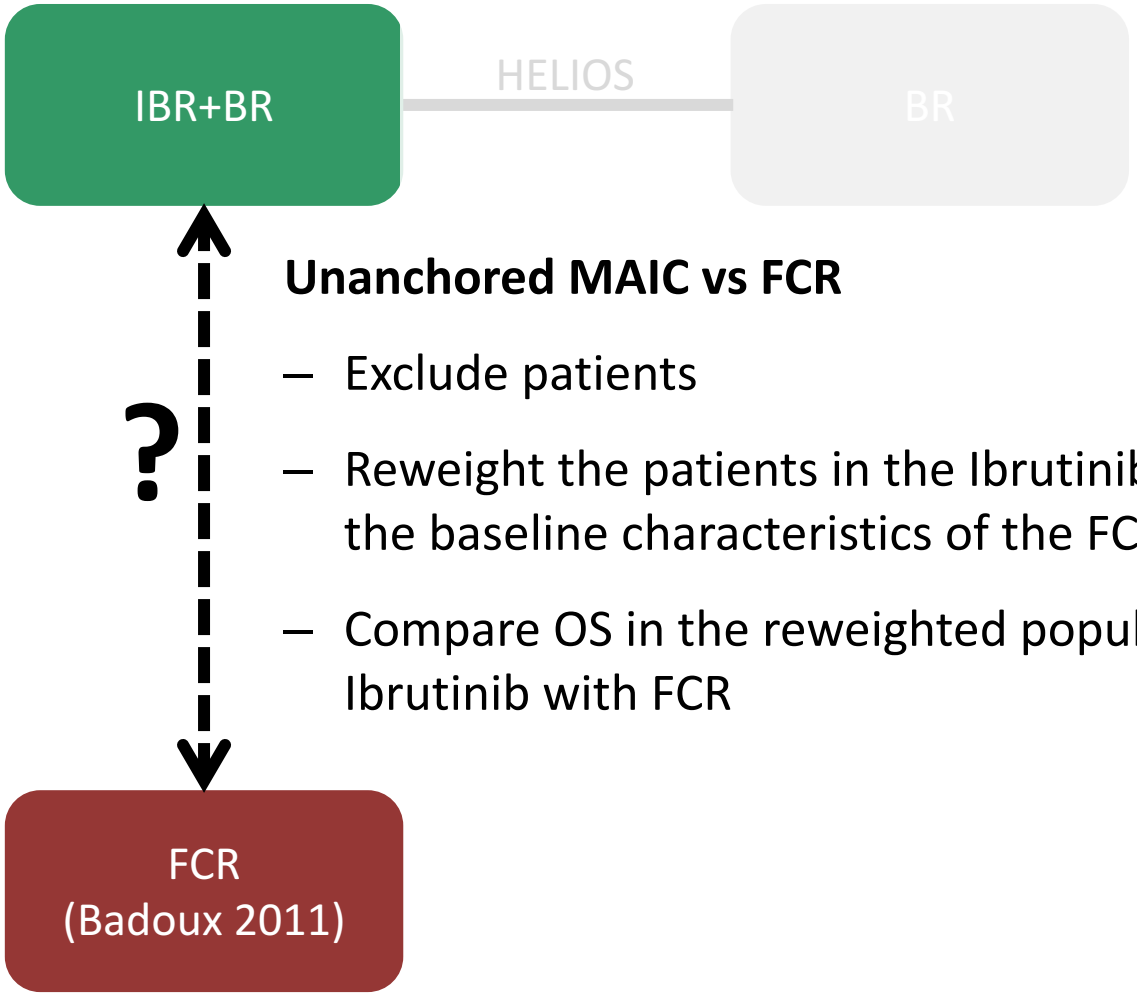
Example: IBR+BR in R/R CLL (HELIOS)



Anchored MAIC vs Idela+BR

- Exclude patients
- Reweight the patients in the HELIOS trial to match the baseline characteristics of the 1115 trial
- Compare OS in the reweighted population of Helios (IBR+BR vs BR)
- IC of the updated HR (IBR+BR vs BR) of HELIOS vs. that of the 1115 trial (IDELA+BR vs BR)

Example: IBR+BR in R/R CLL (HELIOS)



Unanchored MAIC vs FCR

- Exclude patients
- Reweight the patients in the Ibrutinib arm to match the baseline characteristics of the FCR arm
- Compare OS in the reweighted population for Ibrutinib with FCR

MAIC vs MAIC

ANCHORED MAIC: to balance population of an ITC

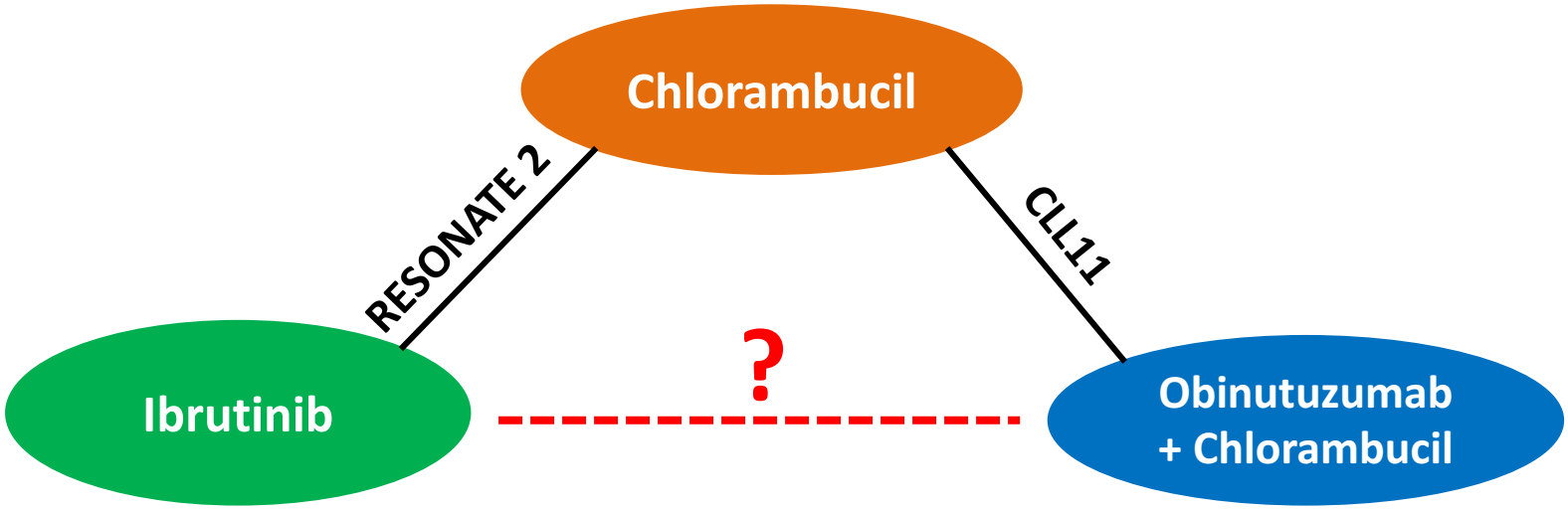
- Match “trials”
- Compares matching adjusted relative treatment effect of IPD trial with relative treatment effect of AD trial
- Within-study randomization is more or less preserved!

UNANCHORED MAIC: if no common comparator available

- Match treatment arms
- Compare matching adjusted absolute treatment effect of IPD trial arm with absolute treatment effect of AD trial arm
- No randomization, but bias is reduced by matching!

Example: Anchored MAIC

- Chronic Lymphocytic Leukemia (CLL)
- Overall survival



- BUCHER: HR [95%CI] = 0.40 [0.10; 1.55]
- Bayesian: HR [95%Cr.I.] = 0.40 [0.10; 1.55] - P(HR<1) = 91.1%

Van Sanden et.al. 2017 , Adv Ther 34(7):1650-1661

Example: Baseline characteristics

	CLL11 (Goede 2014)	RESONATE-2	RESONATE-2	RESONATE-2	RESONATE-2
	ITT	ITT	After exclusion*	Base case matched (n=13 variables)	SA matched (n=12 variables)
N (Neff)	589	269	191	115 (35)	152 (48)
CIRS score (median)	8	5	6	8	8
CIRS score ≤ 6 (%)	26	64	56	26	26
Age (median)	73	73	73	73	73
Age (≥ 75 years) (%)	43	35	40	43	43
Binet Stage A (%)	22	19	19	22	22
Binet Stage B (%)	42	43	40	42	42
Binet Stage C (%)	36	38	41	36	36
β2-Microglobulin ≥ 3.5 mg/L (%)	35	71	77	35	35
del11q (%)	17	22	24	17	17
ECOG (median)	1	1	1	1	1
Creatinine clearance (median, mL/min)	62	61.21	55.35	62.02	62.02
Male (%)	62	63	59	62	62
Unmutated IGHV (%)	61	59	58	61	57†

Exclusion: Excludes patients from RESONATE-2 with CIRS ≤6 and creatinine clearance ≥70 mL/min, patients with creatinine clearance ≤ 30 mL/min, and SLL patients

Example:Within-trial comparison of OS

Trial	N (Neff)	Treatment vs. chlorambucil	HR	[95%CI]	p-value
CLL11	589	Obinutuzumab + chlorambucil	0.41	[0.23, 0.74]	0.002
RESONATE-2 (ITT)	269	Ibrutinib	0.163	[0.048; 0.557]	0.0038
RESONATE-2 (after exclusion)*	191	Ibrutinib	0.065	[0.008; 0.491]	0.0081
RESONATE-2 (matched n=13)	115 (35)	Ibrutinib	0.085	[0.002; 3.447]	0.1922
RESONATE-2 (matched n=12)	152 (48)	Ibrutinib	0.081	[0.003; 1.872]	0.1167

Example:Between-trial comparison of OS

Ibrutinib vs obinutuzumab+chlorambucil

Trial	HR	[95%CrI]	P(HR<1)
RESONATE-2 (ITT)	0.4	[0.10, 1.54]	0.91
RESONATE-2 (after exclusion)*	0.16	[0.02, 1.34]	0.95
RESONATE-2 (matched n=13)	0.21	[0.00, 8.89]	0.79
RESONATE-2 (matched n=12)	0.2	[0.01, 5.16]	0.83

Potential to reduce the bias

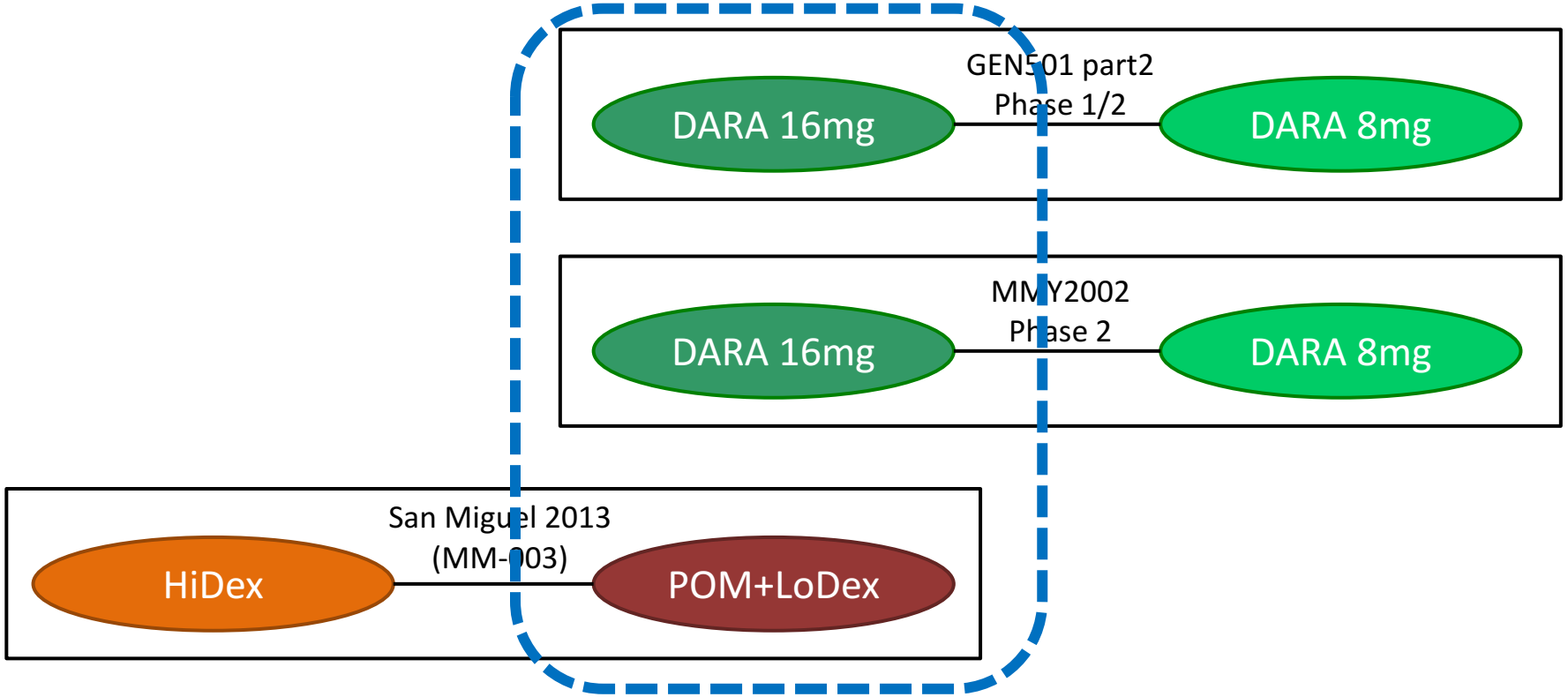
- RCT ★★★★★
- Unadjusted comparison **0**

		TRIAL B (comparator drug)	
		IPD	**AD**
TRIAL A (our drug)	**IPD**	Modeling ★★★★	ANCHORED MAIC ★★★ • unbalanced pop. UNACHORED MAIC ★(★) • single arm trial • no common comparator
	AD	ANCHORED MAIC • unbalanced pop. UNACHORED MAIC • single arm trial • no common comparator	IC or MTC/NMA ★★(★)

Backup slides

Example: Unanchored MAIC

- IC of OS & PFS between of Daratumumab and Pomalidomide (Multiple Myeloma)



Example: Unanchored MAIC

POOL:
- DARA 16mg from GEN501
- DARA 16mg from MMY2002

- Exclude Poma experienced patients (sensitivity analysis)
- Reweight the patients in the pool to match the baseline characteristics of the Poma arm
- Compare OS in the reweighted population for Dara with Poma

POM+LoDex from MM-003

Example: Unanchored MAIC

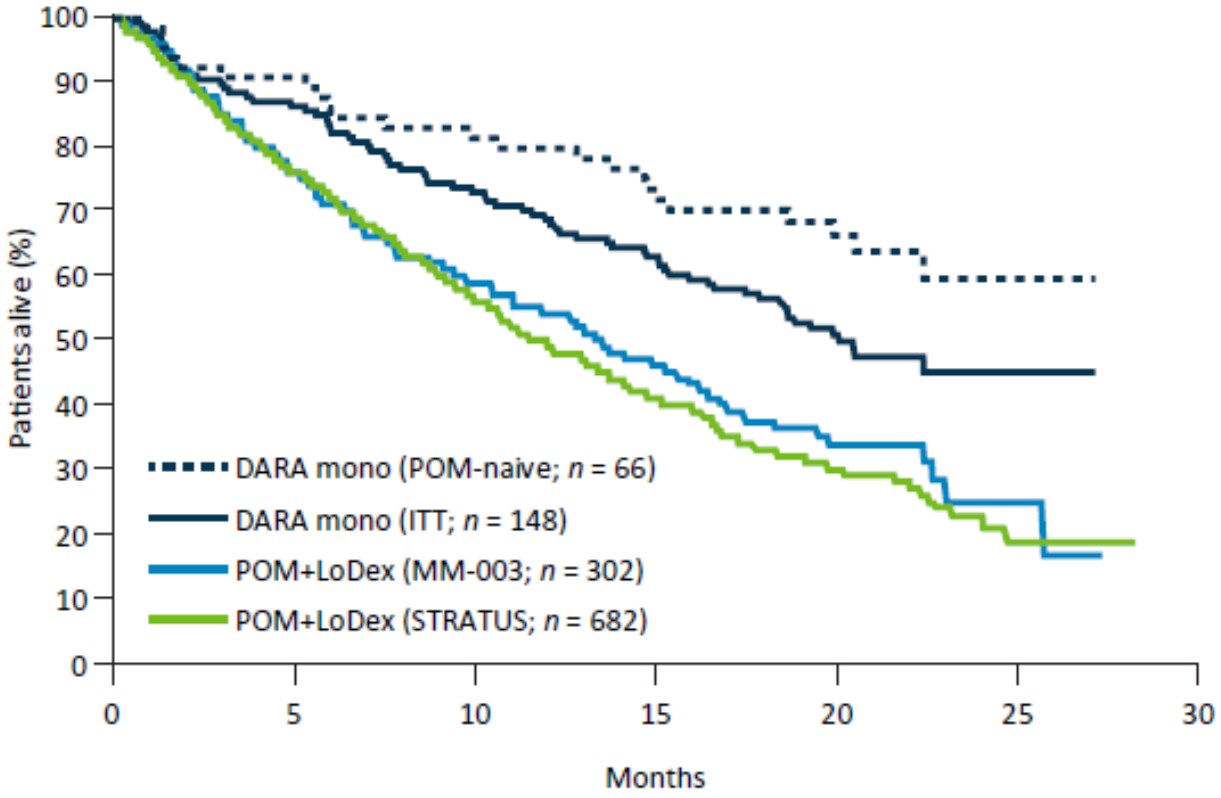


Figure 1. Naïve unadjusted comparisons of overall survival among patients treated with DARA versus POM + LoDex [12, 27, 28]. Data for POM + LoDex are from the MM-003 and STRATUS studies.

Van Sanden et.al. 2017 , The Oncologist 22:1-9

Example: Unanchored MAIC

Table 1. Baseline demographics and characteristics of DARA-treated and POM + LoDex–treated patients (MM-003)

Characteristics	POM + LoDex (MM-003)	DARA (pooled)	DARA (pooled; matched)	DARA (pooled; POM-naïve only)	DARA (pooled; POM-naïve only; matched)
n **(N_{eff})**	**302**	**148**	**136 (55)**	**66**	**66 (19)**
Refractory (%)					
Lenalidomide	95	84	95	76	95
Bortezomib	79	84	79	77	79
Both	75	77	75	67	75
Mean number of prior regimens					
n	5.00	5.38	5.00	4.38	5.00
>2 (%)	94	93	94	85	94
CrCl, mL/minute (%)					
<30	1	3	1	5	1
30–60	31	36	31	30	31
≥60	68	60	68	65	68
ECOG status (%)					
0	37	28	37	30	37
1	46	66	46	65	46
2	17	7	17	5	17
Mean time since diagnosis, years	6.20	6.34	6.20	5.96	6.20
Myeloma subtype (%)					
IgA	26	18	26	15	26
IgG	62	49	62	47	62
IgM	0	1	0	0	0
IgD	1	3	1	3	1
Light chain kappa	8	15	8	15	8
Light chain lambda	3	11	3	15	3
Race (%)					
White	96	85	96	93	—
Asian	2	3	2	0	—
Black	2	12	2	7	—
Bone lesions (%)	68	75	68	79	—
Prior ASCT (%)	71	78	71	70	—
Age					
Mean, years	63.6	63.2	63.6	62.9	—
Age >65 years (%)	45	41	45	41	—
Age >75 years (%)	8	9	8	12	—

Example: Unanchored MAIC

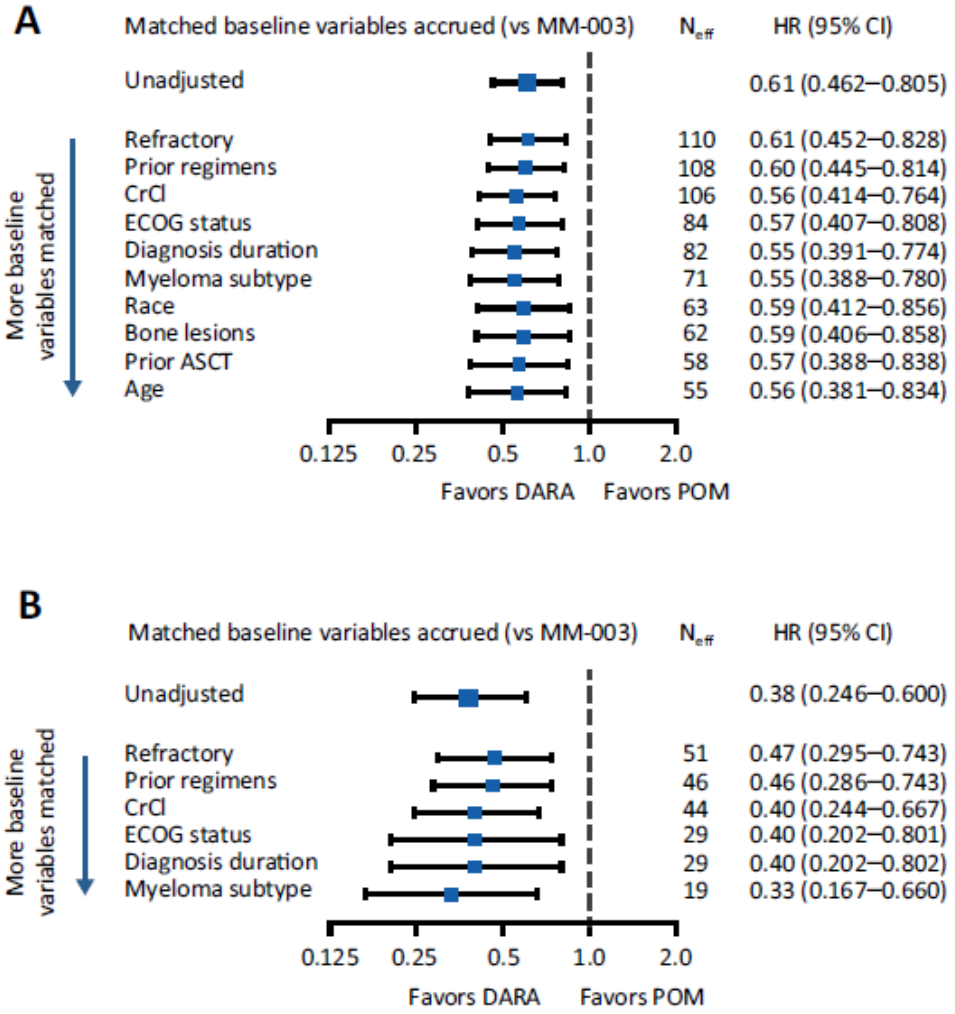


Figure 3. HRs for overall survival with different numbers of baseline characteristics matched in the intent-to-treat population **(A)** and the POM-naïve population **(B)**. Data for POM + LoDex are from the MM-003 and STRATUS studies. The covariate list used to determine the HRs is cumulative from the top to the bottom of the figures.

Example: Unanchored MAIC

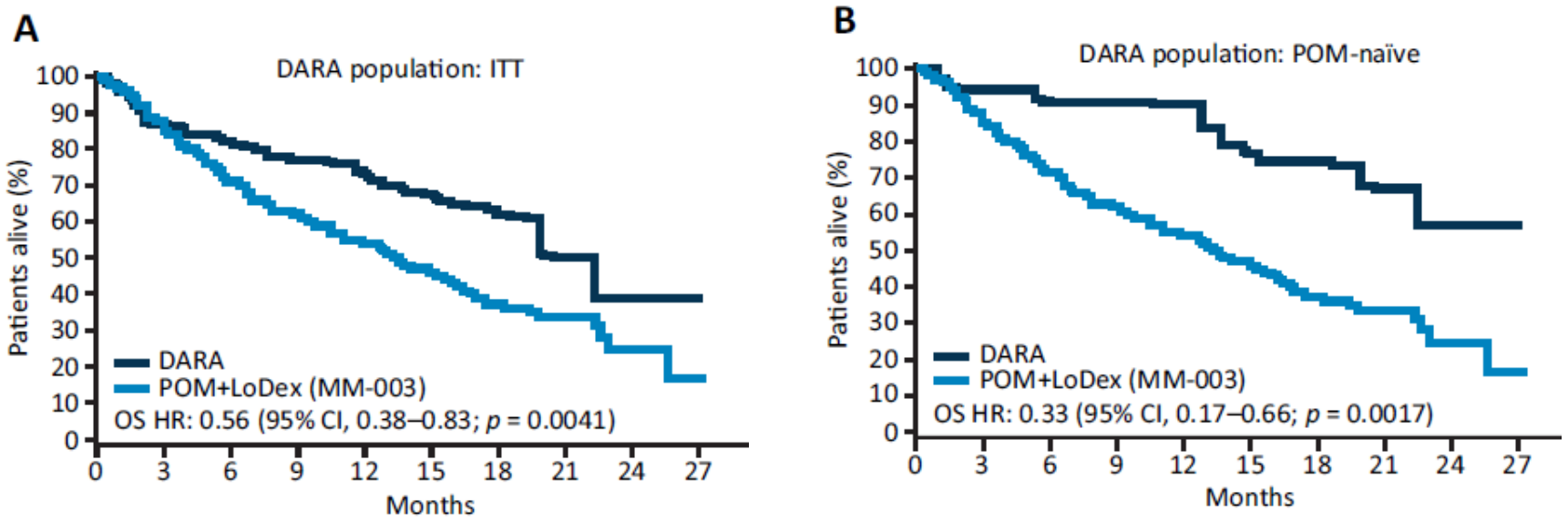


Figure 2. Matching adjusted indirect comparison of OS among patients treated with DARA versus POM + LoDex in the ITT population **(A)** and in the POM-naïve population **(B)**. Data for POM + LoDex are from the MM-003 and STRATUS studies.