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Are We Going Backwards? Where Are We Going With Single-Arm Trials?

Tuesday, 8 November 2022 | 10:15 – 11:15

Treatment Effect and Single-arm Trials

Adrian Vickers, PhD, MSc

Statistics Director
RTI Health Solutions

Treatment Effect and Single-arm Trials

Two options:

1 Estimate a relative treatment effect

- Individual patient-level data (IPD) from another trial or real-world evidence (RWE) are used to create a synthetic control arm for the single-arm trial (SAT).
  - The relative difference can be used to make comparisons with other treatments.

2 Compare absolute treatment effects

- Data from the SAT are compared to summary data from another trial, often another SAT.
  - Data are weighted to match the other trial (e.g., matching-adjusted indirect comparison [MAIC]).

1 Synthetic Control Arm

- Assumes we have access to IPD from a similar trial or from RWE
  - Similar trial
    - Similar study design – endpoint definitions, etc.
    - Synthetic control represents a single treatment.
  - RWE
    - Different design – assessment criteria, patients assessed less frequently, etc.
    - Only a blended control arm may be feasible.

1 Methods to Create a Synthetic Control Arm

- Statistical methods are used to match or weight the external data to the SAT, with many options available.
- Assumptions and issues
  - The fit of the models and their assumptions cannot be tested.
    - A range of models are needed to show the uncertainty in the matching/weighting.
  - All methods assume there are no unmeasured confounders.

2 Compare the Absolute Treatment Effects

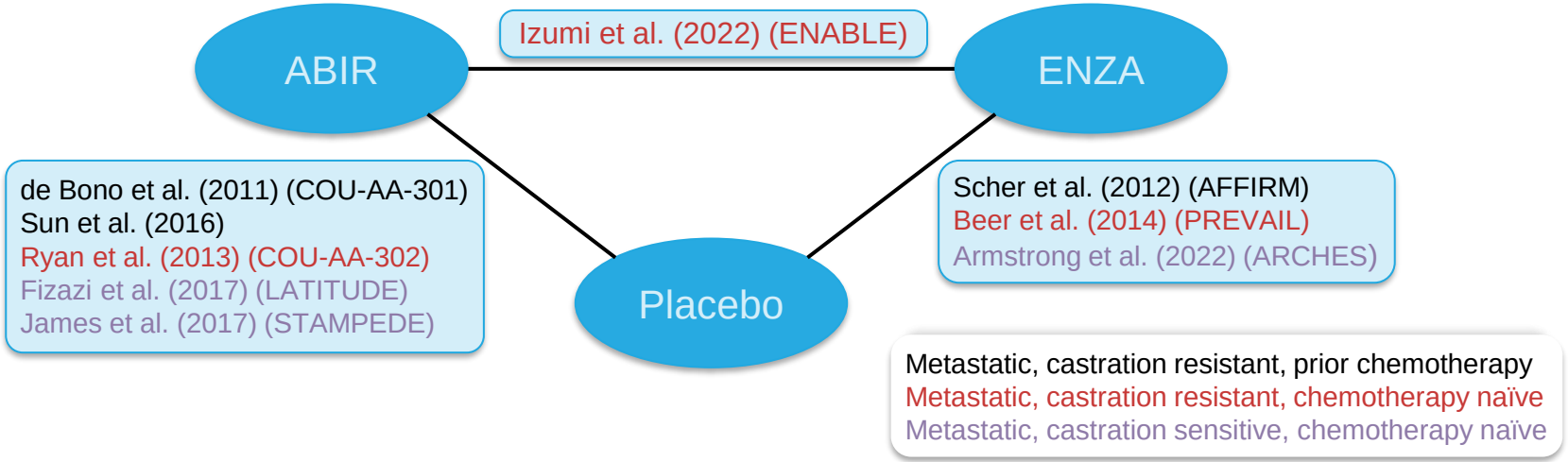
- Direct comparison made with summary data from another trial.
  - Naïve comparison or adjust for patient characteristics (e.g., MAIC)
- Assumes **all prognostic effects are accounted for** and there are **no treatment effect modifiers.**

2 Compare the Absolute Treatment Effects – Case Study

- This example will be speculative – we don't have access to the IPD.
- However, it should demonstrate some of the common issues of performing an MAIC.
- The example is from a network of evidence where there is no evidence of treatment-effect modifiers, either within or between trials.
  - A network meta-analysis (NMA) will be used to estimate a treatment effect for only abiraterone (ABIR) vs. enzalutamide (ENZA) in prostate cancer.
  - Comparisons will then be made using only the single-arm data (minus the control).

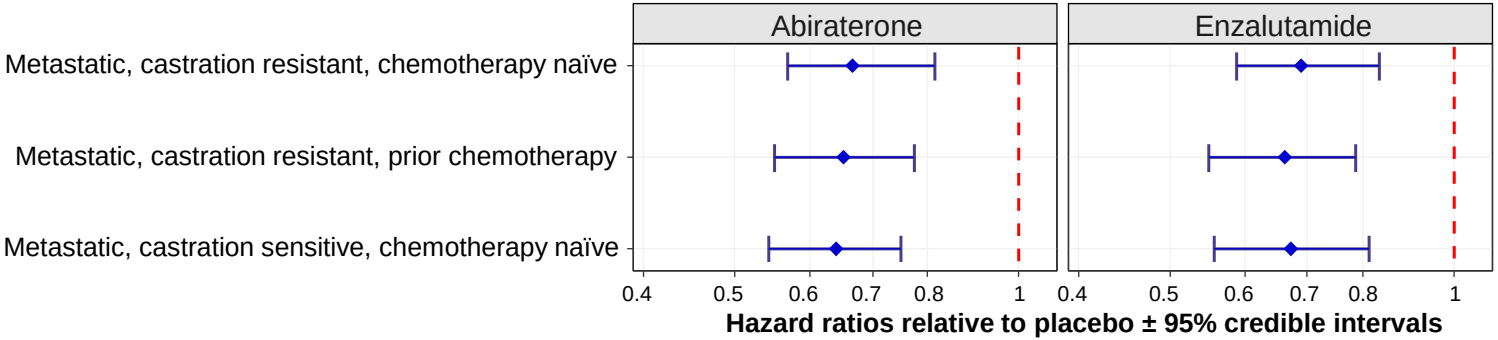
Network of Evidence – ABIR vs. ENZA

- Random-effects NMA with a hierarchical exchangeable structure for patient population.
  - Allows some variation between populations, and information to be borrowed from other populations.



Network Meta-Analysis Results

- Constant and relatively large treatment effects in all 3 populations.



- ABIR vs. ENZA was equivalent in all 3 populations.

Population	Hazard ratio	Lower 95%CrI	Upper 95%CrI	*P*
Metastatic, castration resistant, prior chemotherapy	0.98	0.78	1.25	0.8853
Metastatic, castration resistant, chemotherapy naïve	0.97	0.78	1.22	0.7787
Metastatic, castration sensitive, chemotherapy naïve	0.96	0.74	1.21	0.6880

CrI = credible interval.

Prognostic Effects

- Armstrong (2018) identified 11 significant prognostic effects from the PREVAIL trial (1,717 patients).
  - In order of importance:
    1. Prostate-specific antigen
    2. Haemoglobin
    3. Time since diagnosis
    4. Serum albumin
    5. Liver metastases
    6. Lactate dehydrogenase
    7. Treatment (enzalutamide versus placebo)
    8. Neutrophile to lymphocyte ratio
    9. No. bone metastases
    10. Pain score
    11. Alkaline phosphate

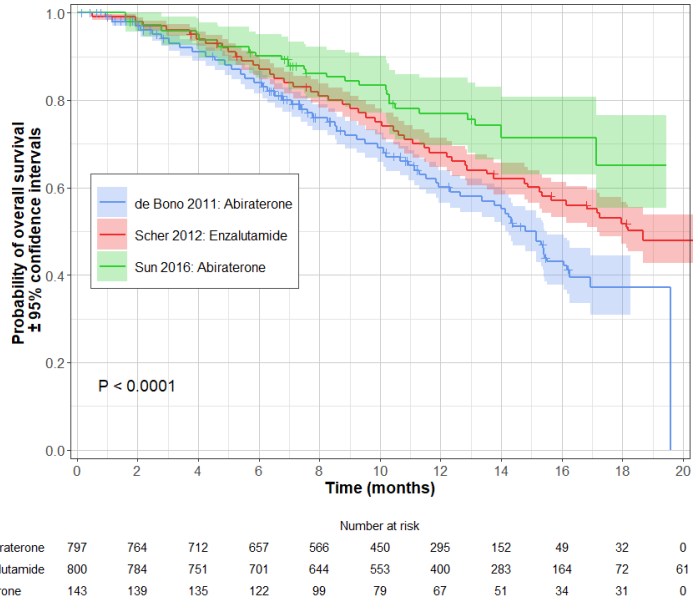
RED = MORE IMPORTANT THAN THE TREATMENT EFFECT

  - Additional evidence suggested age and Eastern Cooperative Oncology Group (ECOG) were also important.

What if we Only Had Single-arm Data?
Metastatic, Castration Resistant, Prior Chemotherapy

- Many important variables not reported; studies appear similar, but survival rates differ. Likely to conclude abiraterone is better or worse than enzalutamide depending on which trial we have data for.

	Rank importance	de Bono et al. (2011) COU-AA-301	Sun et al. (2016)	Scher et al. (2012) AFFIRM
Treatment being investigated		ABIR	ABIR	ENZA
Prostate-specific antigen (ng/mL)	1	129	NR	108
Hemoglobin (g/dL)	2	11.8	NR	12.0
Years since diagnosis	3	NR	3.8	5.9
Serum albumin (g/L)	4	NR	NR	38.0
Disease location - liver	5	11%	4%	12%
Lactate dehydrogenase (LDH) (U/L)	6	223	NR	NR
Neutrophile to lymphocyte ratio	8	NR	NR	NR
No. bone metastases	9	NR	NR	NR
Pain (≥ 4)	10	NR	NR	23%
Alkaline phosphate (U/L) (median)	11	NR	NR	NR
Age (median)	Significant	69	68	69
Asian (%)	Unknown	NR	100%	NR
Disease location - bone	Significant	89%	95%	92%
Disease location - node	Unknown	45%	25%	56%
ECOG (≥ 1)	Significant	NR	NR	NR
ECOG (≥ 2)	Significant	10%	7%	9%
Number of missing prognostic effects		8	9	6
Likely conclusion if single arm studies		ABIR worse than ENZA (de Bono et al. [2011])		
		ABIR better than ENZA (Sun et al. [2016])		

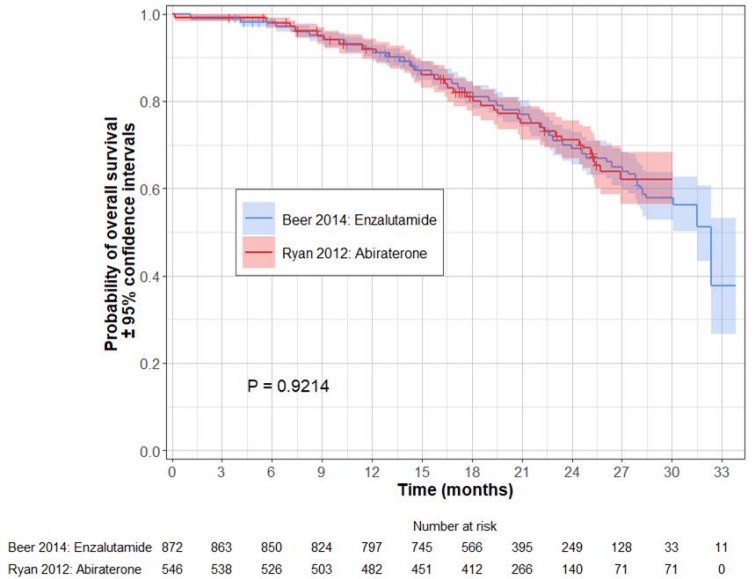


NR = not reported | Red = wrong direction for MAIC | Green = correct direction for MAIC

What if we Only Had Single-arm Data?
Metastatic, Castration Resistant, Chemotherapy Naïve

- Some important variables not reported (although all were included in the PREVAIL trial). Studies appear similar; survival rates are the same. Likely to conclude equal efficacy.

	Ryan et al. (2013) COU-AA-302	Beer et al. (2014) PREVAIL
Treatment being investigated	ABIR	ENZA
Prostate-specific antigen (ng/mL)	42	54
Hemoglobin (g/dL)	NR	13.0
Years since diagnosis	5.5	5.2
Serum albumin (g/L)	NR	54.1
Disease location - liver	NR	5%
Lactate dehydrogenase (LDH) (U/L)	187	185
Neutrophile to lymphocyte ratio	NR	NR
No. bone metastases	NR	NR
Pain (≥ 4)	2%	NR
Alkaline phosphate (U/L) (median)	NR	94.0
Age (median)	71	72
Asian (%)	NR	10%
Disease location – bone	NR	85%
Disease location – node	49%	50%
ECOG (≥ 1)	NR	NR
ECOG (≥ 2)	0%	0%
Number of missing prognostic effects	8	4
Likely conclusion if single arm studies	Equal efficacy	

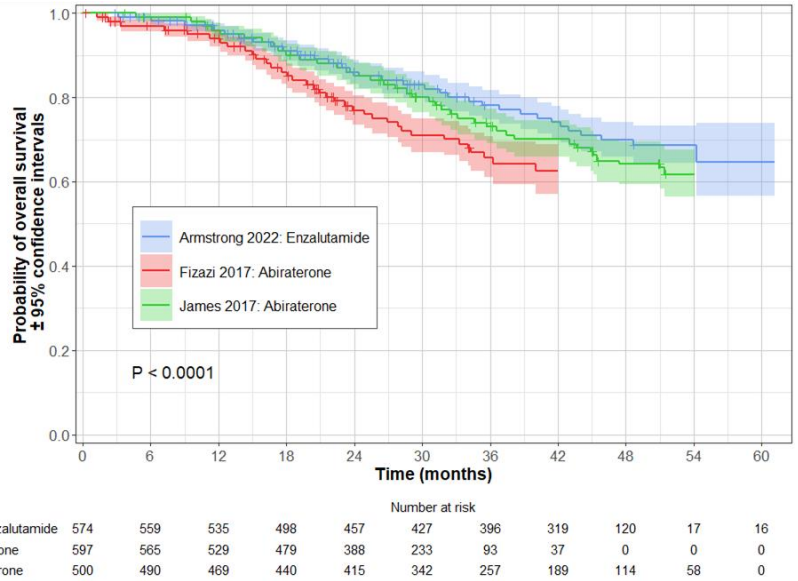


NR = not reported | Red = wrong direction for MAIC | Green = correct direction for MAIC

What if we Only Had Single-arm Data?
Metastatic, Castration Sensitive, Chemotherapy Naïve

- Most variables not reported (including Armstrong, who published the prognostic effects paper in 2018). Survival rates differ. Likely to conclude abiraterone is worse than enzalutamide or similar, depending on which trial we have data for.

	Fizazi et al. (2017) LATITUDE	James et al. (2017) STAMPEDE	Armstrong et al. (2022) ARCHES
Prostate-specific antigen (ng/mL)	NR	NR	5.4
Hemoglobin (g/dL)	NR	NR	NR
Years since diagnosis	NR	NR	NR
Serum albumin (g/L)	NR	NR	NR
Disease location - liver	5%	NR	NR
Lactate dehydrogenase (LDH) (U/L)	NR	NR	NR
Neutrophile to lymphocyte ratio	NR	NR	NR
No. bone metastases	NR	NR	NR
Pain (≥ 4)	29%	NR	NR
Alkaline phosphate (U/L) (median)	NR	NR	NR
Age (median)	68	NR	70
Asian (%)	NR	NR	13%
Disease location - bone	97%	NR	NR
Disease location - node	47%	NR	NR
ECOG (≥ 1)	NR	NR	22%
ECOG (≥ 2)	NR	NR	0%
Number of missing prognostic effects	11	16	11
Likely conclusion if single arm studies	ABIR worse than ENZA (Fizazi et al. [2017])		
	Similar efficacy (James et al. [2017])		



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Conclusion

1 Estimate a relative treatment effect with a synthetic control arm

- We do not know how reliable the results are from synthetic control arms.
  - At best, these will have a pseudo-control arm because there may be unknown confounders.

2 Compare absolute treatment effects (e.g., MAIC)

- The reporting of patient characteristic data from clinical trials is not intended for population adjustment methods, which assume all important variables are included.
  - A population adjusted comparison may be no better than a naïve comparison
    - In the case study, 60% probability (3 of 5) of drawing the wrong conclusion.
    - An MAIC might have only improved this to 40% probability (2 of 5) of drawing the wrong conclusion.

Are Single-arm Trials a Step Backwards?

- Single-arm designs have been used before any validation has been performed on whether they provide any useful information to assess relative effects.
  - The data presented here suggest that it may be impossible to obtain meaningful results from an MAIC using only single-arm data due to the way data from trials are reported.
- A small randomised controlled trial with the best current treatment as a control is more informative than a single-arm trial.

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