Network meta-analysis of treatments for previously untreated metastatic PD-L1-positive triple-negative breast cancer

Basel Biometric Section Seminar

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2015 - 2019: F. Hoffmann-La Roche Ltd
2019 - today: Institute of Health Economics and Health Policy, Bern University of Applied Sciences

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Challenges

- Comparator in pivotal study (nab-paclitaxel) not approved in Europe.
- Comparator in pivotal study (nab-paclitaxel) not previously investigated.
- Lack of Kaplan-Meier plots on triple-negative sub-populations in HER2-negative studies.
- PD-L1 status had not been measured in previous studies.

IMpassion130 study

Global, randomized, double-blind, phase 3 study [1, 2]

- P Previously untreated locally advanced or metastatic triple-negative breast cancer.
- I Atezolizumab + nab-paclitaxel.
- C Placebo + nab-paclitaxel.
- O Progression-free and overall survival in intent-to-treat and PD-L1-positive ($\geq$1% PD-L1 expression) populations as co-primary endpoints.

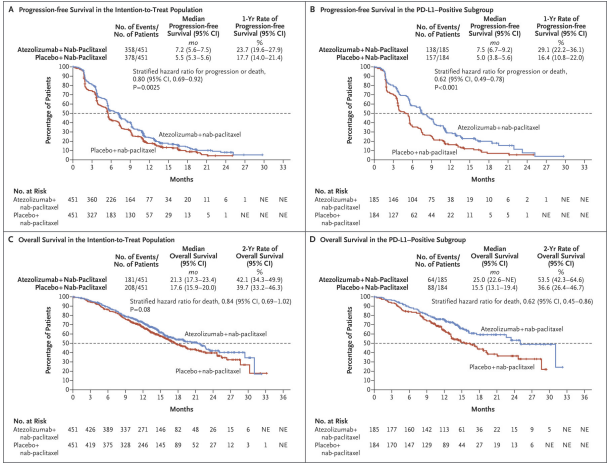
IMpassion130 study

Hazard ratio of atezolizumab + nab-paclitaxel versus nab-paclitaxel

	Progression-free survival [1]	Overall survival [2]
Intent-to-treat	**0.80** (0.69, 0.92)	0.86 (0.72, 1.02)
PD-L1-positive	**0.62** (0.49, 0.78)	**0.71** (0.54, 0.94)

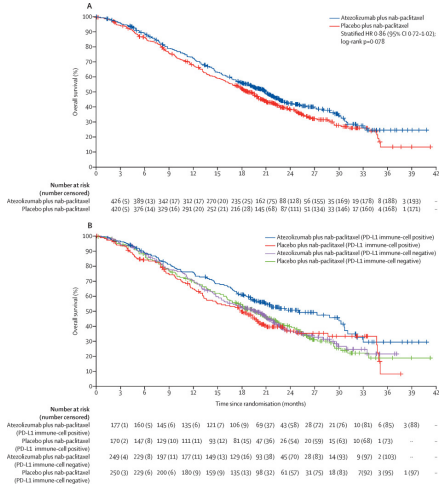
IMpassion130 study

Progression-free and overall survival (April 17, 2018 data cut [1])



IMpassion130 study

Overall survival (January 2, 2019 data cut [2])



Network meta-analysis

P Previously untreated locally advanced or metastatic **PD-L1-positive** triple-negative breast cancer.

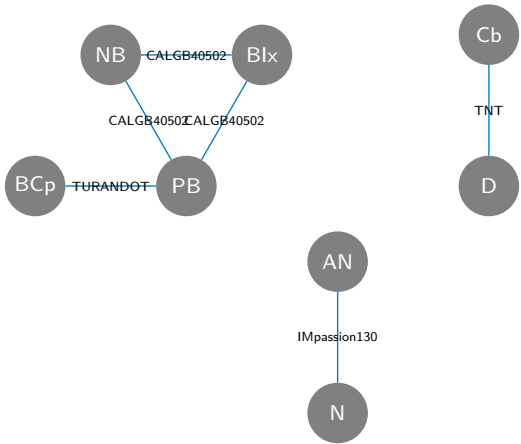
I Atezolizumab + nab-paclitaxel (AN).

C Nab-paclitaxel (N), paclitaxel (P), paclitaxel + bevacizumab (PB), nab-paclitaxel + bevacizumab (NB), bevacizumab + ixabepilone (BIx), bevacizumab + capecitabine (BCp), capecitabine (Cp), docetaxel (D), docetaxel + bevacizumab 15mg (DB15), docetaxel + bevacizumab 7.5mg (DB7.5), carboplatin (Cb).

O Progression-free, overall survival, objective response rates, adverse event rates, treatment discontinuation rates due to adverse events.

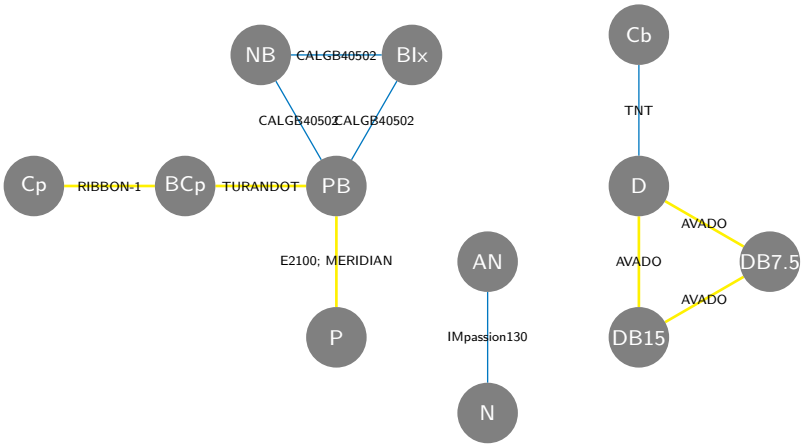
Progression-free survival data

Kaplan-Meier data from published triple-negative studies



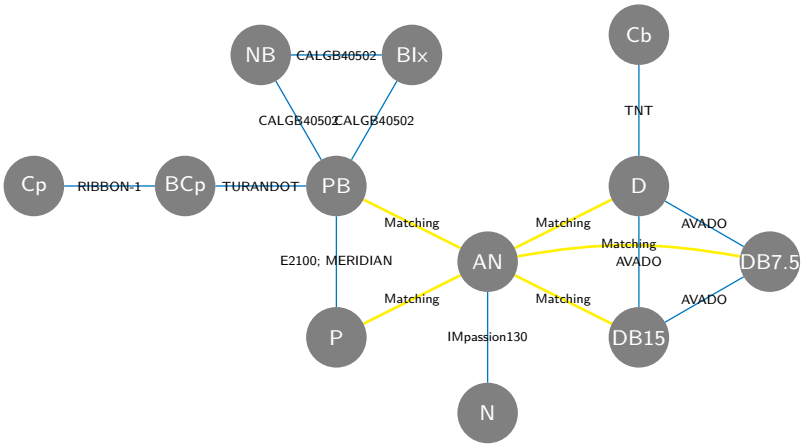
Progression-free survival data

Triple-negative subgroups of Roche sponsored HER2- studies



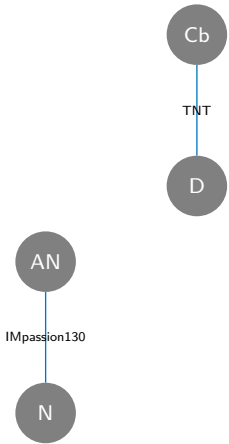
Progression-free survival data

Matching adjustment



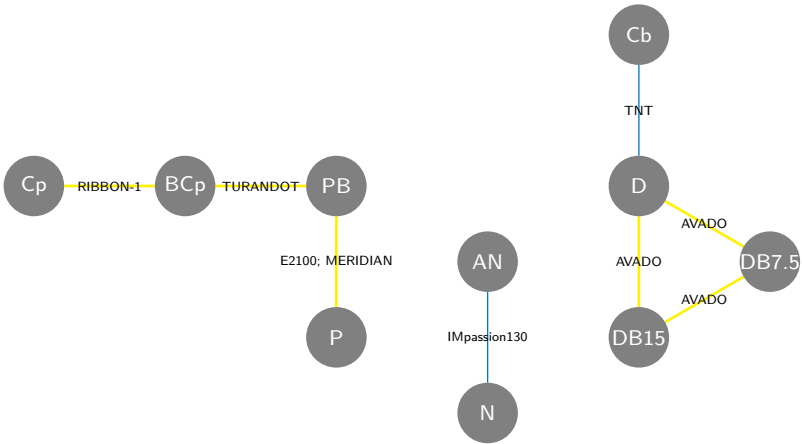
Overall survival data

Kaplan-Meier data from published triple-negative studies



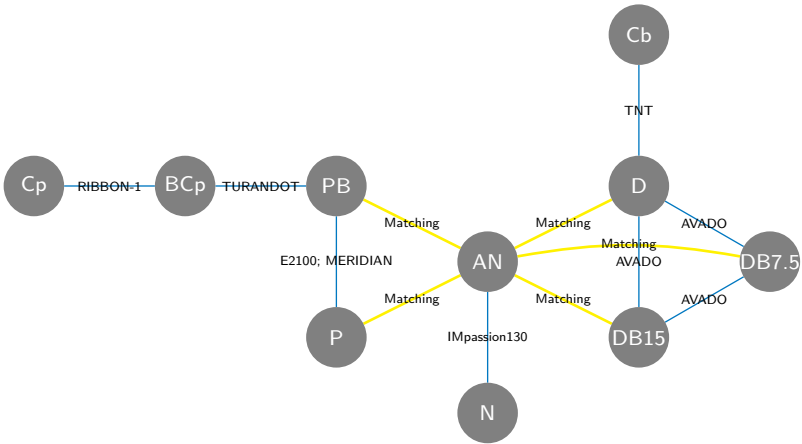
Overall survival data

Triple-negative subgroups of Roche sponsored HER2- studies



Overall survival data

Matching adjustment



Covariate balancing propensity score model

Generalized method of moments estimation [3]

$$\beta_{GMM} = \arg\min_{\beta \in \Theta} g_\beta(T, X)^T \sum_\beta (T, X)^{-1} g_\beta(T, X)$$

Just-identified model with first moment condition

$$\begin{aligned}
g_\beta &= \tfrac{1}{N} \textstyle\sum_{i=1}^{N} w_\beta(T_i, X_i) X_i \quad \text{...First moment condition} \\
w_\beta(T_i, X_i) &= \tfrac{T_i - \pi_\beta(X_i)}{\pi_\beta(X_i)(1-\pi_\beta(X_i))} \\
\pi_\beta(X_i) &= \tfrac{\exp(X_i^T \beta_{GMM})}{1+\exp(X_i^T \beta_{GMM})} \quad \text{...Propensity score}
\end{aligned}$$

Covariate balancing propensity score model

Standardized mean difference between weighted atezolizumab + nab-paclitaxel arm (n=185) and unweighted comparison study

	E2100	MERIDIAN	AVADO
Effective sample size	79.04	87.1	69.78
Age	<0.001	<0.001	<0.001
Height		<0.001	
BMI		<0.001	<0.001
Race white	<0.001	<0.001	<0.001
Race black	<0.001	<0.001	<0.001
Race asian	0.002	<0.001	<0.001
Region North America & EU		<0.001	
Region Asia		<0.001	<0.001
ECOG 0		<0.001	<0.001
Number of sites	<0.001	<0.001	
Number of sites 3			<0.001
Sum of largest diameters		<0.001	
Time from initial to metastatic diagnosis	<0.001		<0.001
Time from metastatic diagnosis to randomization		<0.001	<0.001
Bone metastases	<0.001	<0.001	
Liver metastases	<0.001	<0.001	<0.001
Lung metastases	<0.001	<0.001	<0.001
Prior anthracyclines	<0.001	<0.001	<0.001
Prior taxanes	<0.001	<0.001	<0.001
Diastolic blood pressure		<0.001	
Body temperature		<0.001	

Entropy balancing

Minimize entropy distance [4]

$$\begin{aligned} \min_{w_i} \quad & H(w) = \sum_{i|D=0} w_i log(\frac{w_i}{q_i}) \\ \text{s.t.} \quad & \sum_{i|D=0} w_i c_{ri}(X_i) = m_r \\ & \sum_{i|D=0} w_i = 1 \end{aligned}$$

$q_i = \frac{1}{n_0}$ ...Base weight

$c_{ri}(X_i) = m_r$ ...R balance constraints

$\sum_{i|D=0} w_i X_{ij}^{D=0} = E[X_{ij}^{D=1}]$ ...e.g. first moment balance

Entropy balancing

Standardized mean difference between weighted treatment arm and unweighted control arm (R Lalonde example dataset [5])

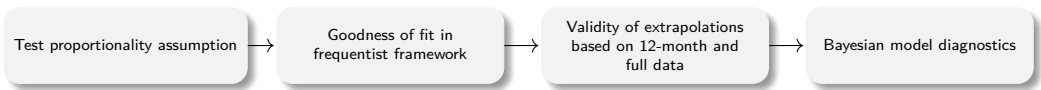
	CBPS	Entropy balancing
Effective sample size	657.98	664.15
Age	0.007	<0.001
Education	0.005	<0.001
Race black	0.005	<0.001
Race Hispanic	0.001	<0.001
Married	0.006	<0.001
No degree	0.004	<0.001

Model

Candidate models

- log-normal model of hazard ratios
- Discrete-time fractional polynomial models (Powers {0}, {1}, {0, 0}, {0, 1}, {1, 1})
- Discrete-time piecewise exponential models (one or two cut-points from 2 to 9 months)

Model selection



Model

Base case models

- Progression-free survival: Piecewise exponential with cut-points at 2 and 4 months
- Overall survival: Piecewise exponential with cut-point at 5 months

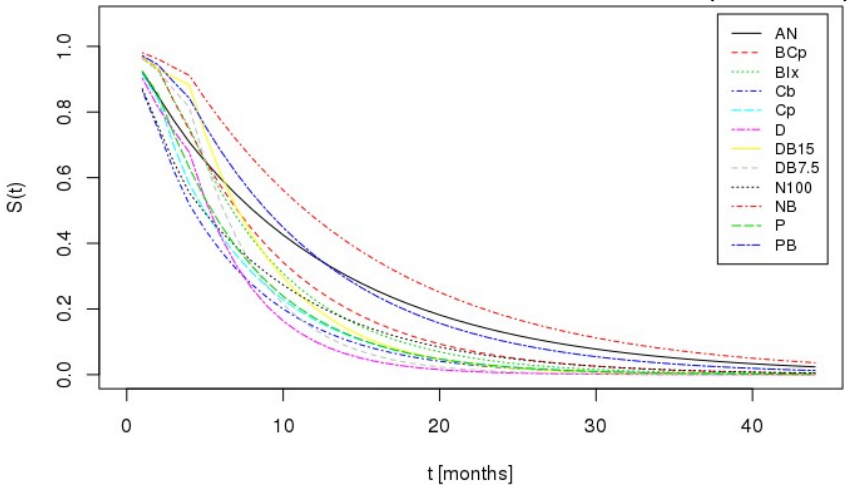
Results
Goodness of fit in frequentist framework

Progression-free survival			Overall survival		
Model	AIC	BIC	Model	AIC	BIC
FP (2nd order, p1=0, p2=0)	1874.24	2124.19	FP (Weibull, p1=0)	1505.57	1647.17
FP (2nd order, p1=0, p2=1)	1897.85	2147.81	FP (2nd order, p1=0, p2=0)	1506.32	1718.71
FP (2nd order, p1=1, p2=1)	1933.89	2183.84	FP (2nd order, p1=0, p2=1)	1510.28	1722.67
FP (Weibull, p1=0)	2007.56	2174.20	PWE (cutpoints at 5)	1517.39	1658.98
PWE (cutpoints at 2, 4)	2009.66	2259.62	PWE (cutpoints at 3, 6)	1517.55	1729.95

Results

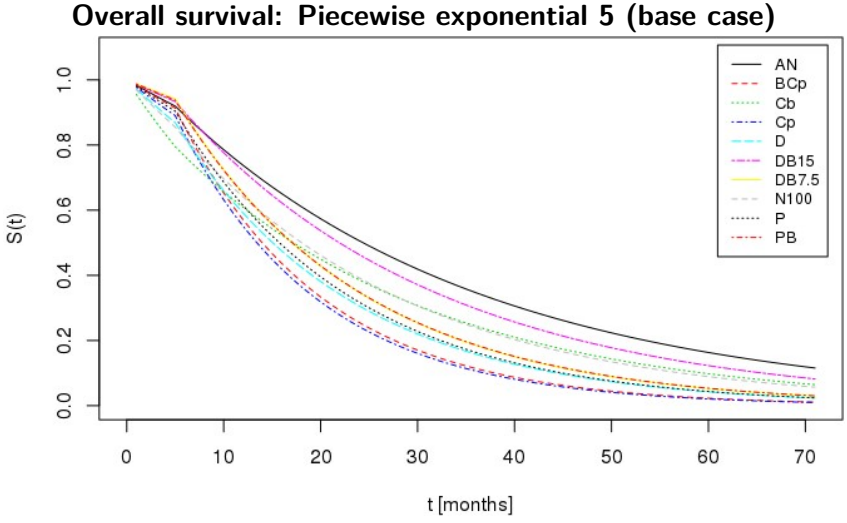
Extrapolations in reference study based on full data

Progression-free survival: Piecewise exponential 2, 4 (base case)



Results

Extrapolations in reference study based on full data

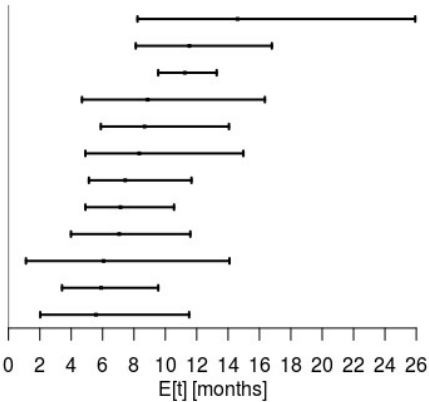


Results

5-year restricted mean progression-free survival times

Expected progression-free survival times

Treatment	Median	95% ll	95% ul
NB	14.6	8.23	25.93
PB	11.53	8.11	16.79
AN	11.24	9.55	13.27
BCp	8.87	4.69	16.35
DB15	8.68	5.89	14.06
Blx	8.34	4.9	14.97
DB7.5	7.44	5.13	11.67
P	7.14	4.9	10.55
N100	7.06	3.98	11.59
Cp	6.06	1.12	14.09
D	5.91	3.42	9.55
Cb	5.57	2.02	11.52

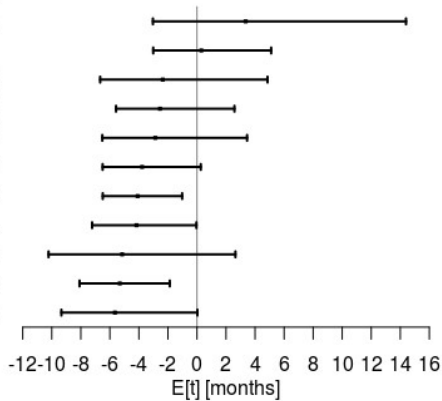


Results

5-year restricted mean progression-free survival times

Difference to atezolizumab + nab-paclitaxel

Treatment	Median	95% ll	95% ul
NB	3.35	-3.03	14.4
PB	0.3	-3.01	5.11
BCp	-2.36	-6.67	4.86
DB15	-2.54	-5.57	2.58
Blx	-2.87	-6.52	3.45
DB7.5	-3.78	-6.5	0.26
P	-4.08	-6.49	-1.02
N100	-4.17	-7.22	-0.04
Cp	-5.15	-10.22	2.65
D	-5.31	-8.09	-1.88
Cb	-5.65	-9.34	0.03

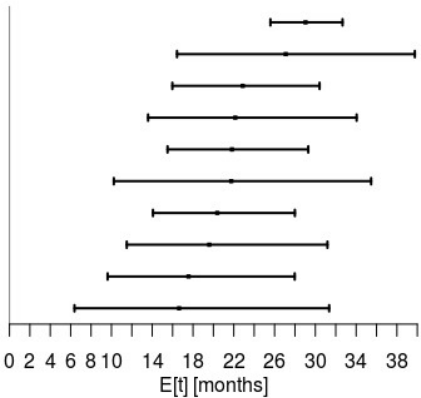


Results

5-year restricted mean overall survival times

Expected overall survival times

Treatment	Median	95% ll	95% ul
AN	29.04	25.59	32.67
DB15	27.09	16.43	39.76
N100	22.88	15.98	30.41
DB7.5	22.15	13.59	34.05
PB	21.82	15.5	29.3
Cb	21.75	10.23	35.47
P	20.38	14.07	27.99
D	19.6	11.5	31.19
BCp	17.56	9.62	27.98
Cp	16.64	6.38	31.35

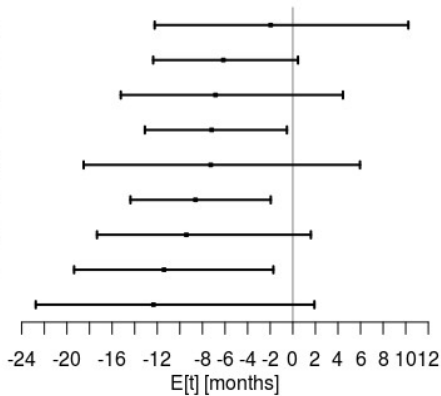


Results

5-year restricted mean overall survival times

Difference to atezolizumab + nab-paclitaxel

Treatment	Median	95% ll	95% ul
DB15	-1.96	-12.23	10.23
N100	-6.15	-12.36	0.46
DB7.5	-6.84	-15.23	4.44
PB	-7.19	-13.1	-0.52
Cb	-7.26	-18.52	5.95
P	-8.62	-14.37	-1.95
D	-9.42	-17.34	1.6
BCp	-11.4	-19.36	-1.72
Cp	-12.33	-22.76	1.91



Discussion

+ Individual-level data from HER2- studies.
+ Pre-specified analysis and model selection.
+ Scenario analyses.
+ Multiple matching adjustments using individual data.
+ Large sets of matching variables.
+ Good balance with covariate-balancing propensity scores.

Discussion

- Low effective sample size in weighted atezolizumab + nab-paclitaxel arms.
- Assumption of constant hazard rate in the tail.
- Piecewise exponential model sensitive to choice of cut-points and data in the tail.
- Large uncertainty about the relative effectiveness of paclitaxel because of different shapes of the hazard curves in the E2100 and MERIDIAN studies.
- Results are sensitive to the choice of matching studies and to pooling paclitaxel and nab-paclitaxel.
- Uncertainty about the effect of PD-L1 on the relative efficacy of comparators is a major limitation.
- Clinicians questioned relative ordering of docetaxel, paclitaxel and nab-paclitaxel.
- Payers criticized use of matching adjustment and high uncertainty around parameter estimates.

Conclusion

- ⇒ Consider economic evaluation in trial design.
- ⇒ Investigate association of biomarkers with effectiveness of previously investigated therapies.
- ⇒ Entropy balancing should be considered for estimation of propensity scores.
- ⇒ Flexible alternatives to second-order fractional polynomial models are needed.

Thank you very much!

References

[1] Schmid, P., Adams, S., Rugo, H.S., Schneeweiss, A., Barrios, C.H., Iwata, H., DiÃ©ras, V., Hegg, R., Im, S.A., Shaw Wright, G., Henschel, V., Molinero, L., Chui, S.Y., Funke, R., Husain, A., Winer, E.P., Loi, S. and Emens, L.A. (2018). Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. New England Journal of Medicine, 379(22), 2108–2121, doi:10.1056/NEJMoa1809615, pMID: 30345906.

[2] Schmid, P., Rugo, H.S., Adams, S., Schneeweiss, A., Barrios, C.H., Iwata, H., Diéras, V., Henschel, V., Molinero, L., Chui, S.Y. et al. (2019). Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (impassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology.

[3] Imai, K. and Ratkovic, M. (2014). Covariate balancing propensity score. Journal of the Royal Statistical Society: Series B (Statistical Methodology), 76(1), 243–263.

[4] Hainmueller, J. (2012). Entropy balancing for causal effects: A multivariate reweighting method to produce balanced samples in observational studies. Political Analysis, 20(1), 25–46.

[5] Dehejia, R.H. and Wahba, S. (1999). Causal effects in nonexperimental studies: Reevaluating the evaluation of training programs. Journal of the American statistical Association, 94(448), 1053–1062.