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Eliciting Unreported Subgroup-Specific Survival from Aggregate Randomized Controlled Trial Data

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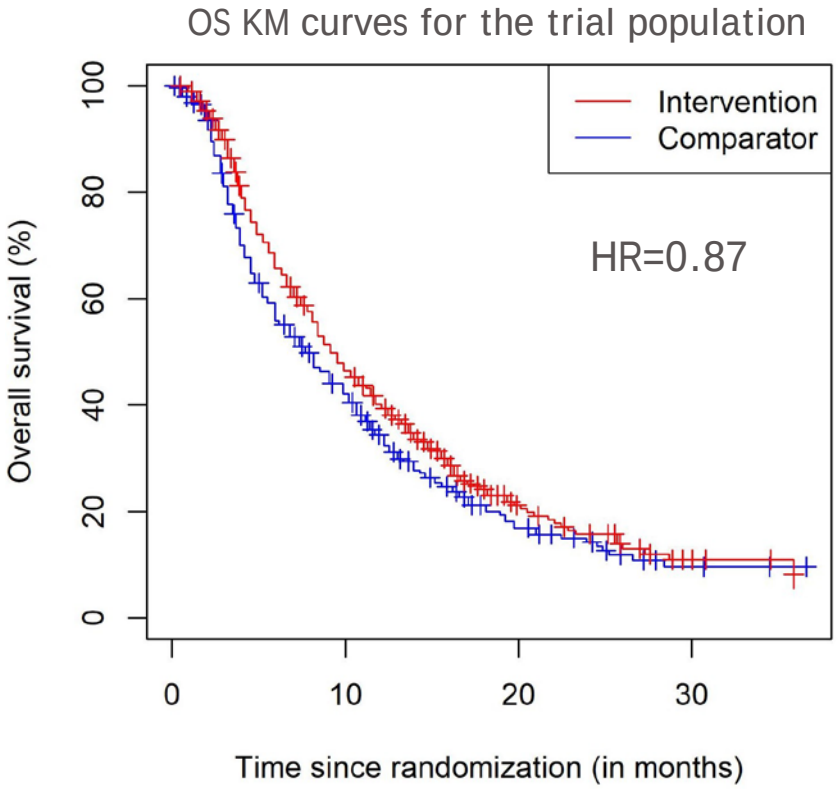
Disclosures

- Oguzhan Alagoz is a paid consultant for Bristol Myers Squibb. He was also a paid consultant for Biovector Inc. and UW Health, outside of the submitted work.

Background

- Analyses of randomized controlled trials (RCTs) typically report
  - Kaplan-Meier (KM) survival curves for intervention and comparator arms for the overall trial population
  - Subgroup-specific survival information is provided only in a limited extent: forest plots displaying hazard ratios across selected subgroups (sometimes limited to only those based on stratification factors)
- In the absence of clear HTA guidelines, subgroup-specific KM curves are essential for tailored analyses to address reimbursement restrictions

Example: REACH trial of 1L treatment for advanced hepatocellular carcinoma



Example: If subgroup-specific survival with respect to α-fetoprotein levels were sought

	Ramucirumab arm		Placebo arm		HR (95% CI)
Geographical Region	Patients (n)	Events (n)	Patients (n)	Events (n)	
Europe & North America	157	114	156	120	0.92 (0.72-1.20)
East Asia	126	104	126	104	0.84 (0.63-1.10)
Subgroups (α-fetoprotein)					
Subgroup 1 (<400)	160	116	150	108	1.09 (0.84-1.43)
Subgroup 2 (≥400)	119	99	131	116	0.67 (0.51-0.90)

- Highlighted information with circles could be leveraged to elicit subgroup-specific survival data

- There is no HTA guidance or established modeling framework to achieve this

Plot is adopted from Zhu AX, et al. *Lancet Oncol* 2015;16:859–870. Note: Vertical markers represent censoring information

Purpose: Why do we need subgroup-specific survival?

Objective:

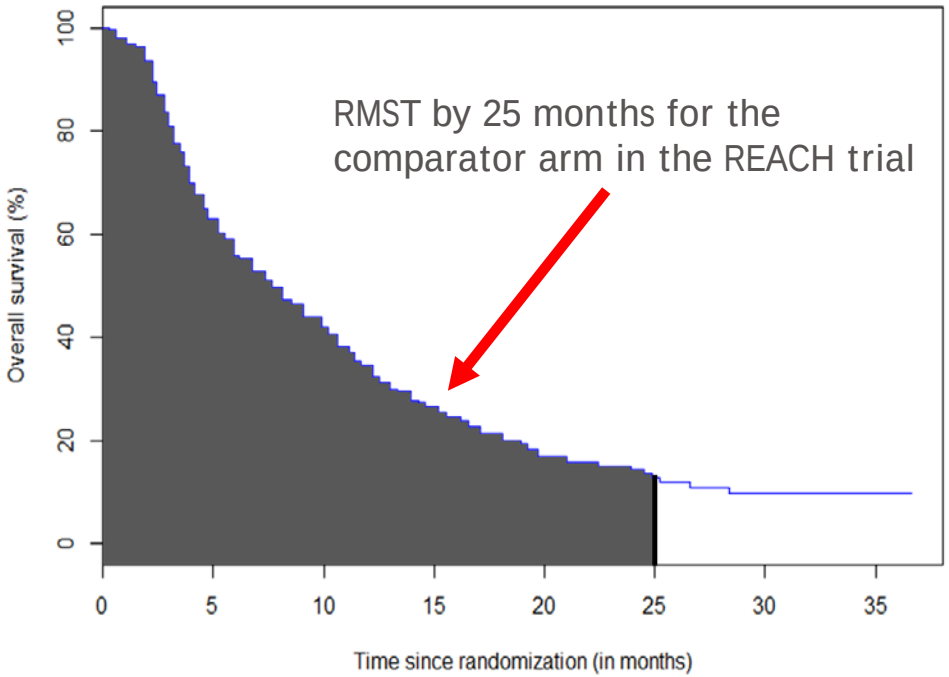
- Estimate unreported subgroup-specific survival times using published KM curves for overall trial population and hazard ratios reported in the forest plots

Opportunity for unmet need:

- In-depth *cost-effectiveness analyses* and *meta-analyses* focusing on a subpopulation
- Rigorous head-to-head comparison of survival outcomes between *clinical trials* focusing on a subpopulation
- More effective utilization of published comparator data

Restricted Mean Survival Time (RMST)

Our method uses RMST as a metric for objective function and defines it via conditioning on subgroups in each arm



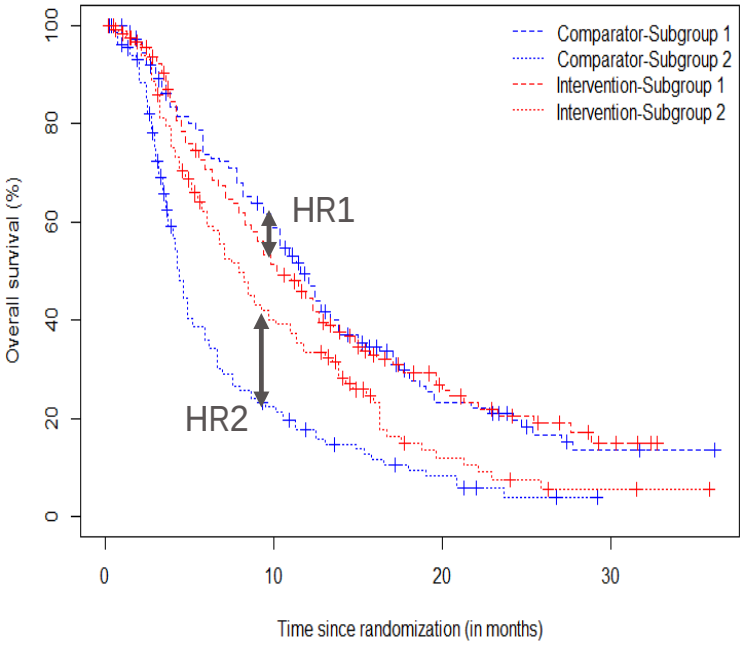
Note: RMST cutoff time is equal to 25 months in this example, however, our approach chooses RMST cutoff time flexibly and systematically based on number-at-risk data from both arms of the trial

Plot is adapted from the comparator (placebo) arm of Zhu AX, et al. *Lancet Oncol* 2015;16:859–870.

Methodological framework

Synopsis of the analytical approach: **RMST for the overall population in ach arm can be expressed as a weighted average of the RMSTs of a pre-specified list of mutually exclusive and exhaustive subgroups**

Reported subgroup-specific OS KM curves in the REACH trial



RMST for the intervention arm for the overall population by t^*

Prevalence of subgroup 1 in the intervention arm

RMST of the intervention arm for subgroup 1 by t^*

RMST of the intervention arm for subgroup 2 by t^*

$$RMST_i(t^*) = p(i,1) \times RMST_{i,1}(t^*) + (1 - p(i,1)) \times RMST_{i,2}(t^*)$$

Hazard ratios from the forest plots connect the hazard rates of the subgroups

$$RMST_c(t^*) = p(c,1) \times RMST_{c,1}(t^*) + (1 - p(c,1)) \times RMST_{c,2}(t^*)$$

RMST of the comparator arm for the overall population by t^*

Prevalence of subgroup 1 in the comparator arm

RMST of the comparator arm for subgroup 1 by t^*

RMST of the comparator arm for subgroup 2 by t^*

When the survival of each subgroup is exponentially distributed, the algebraic representation of hazard ratios via hazard rates enable closed form expressions for RMSTs for all subgroups

Plot is adapted from Zhu AX, et al. *Lancet Oncol* 2015;16:859–870. Note: Vertical markers represent censoring information

Methodological framework

- Devise an optimization-based approach that derives subgroup-specific survival distributions via
  - Enforcing hazard ratios across each pair of subgroup that are reported in forest plots
  - Minimizing the sum of squares of differences between predicted and observed RMSTs across both intervention and comparator arms

Objective function of the optimization model

Predicted RMST for the intervention arm

Reported RMST for the intervention arm

$$\min \left(p(i,1)RMST_{i,1}(t^*) + \left(1 - p(i,1)\right) \times RMST_{i,2}(t^*) - RMST_i(t^*) \right)^2$$

$$+ \left(p(c,1) \times RMST_{c,1}(t^*) + \left(1 - p(c,1)\right) \times RMST_{c,2}(t^*) - RMST_c(t^*) \right)^2$$

Predicted RMST for the comparator arm

Reported RMST for the comparator arm

Case Study

Test case	Tumor type	Trial	Subgroup 1	Subgroup 2
1	HCC	REACH	α-fetoprotein < 400 ng/mL	α-fetoprotein ≥ 400 ng/mL
2†		REACH	East-Asian	Non-East Asian
3		REACH-2	REACH-2 trial patients	REACH trial patients with α-fetoprotein ≥ 400 ng/mL
4		RESORCE	Last sorafenib dose 800 mg/day	Last sorafenib dose < 800 mg/day
5	EC/GC	KEYNOTE-181	PD-L1 CPS ≥ 10%	PD-L1 CPS < 10%*
6†		KEYNOTE-181	SCC	Adenocarcinoma*
7†	EC/GC	KEYNOTE-061	ECOG Status 0	ECOG Status 1
8		REGARD	Age < 65	Age ≥ 65
9†	CRC	RAISE	KRAS status wild-type	KRAS status mutant
10		RAISE	Tumor side (left)	Tumor side (right)
11		CORRECT	Japanese	Non-Japanese

†Test cases in which subgroups are used for stratifying randomization
*Subgroup-specific KM curves are not reported; thus these subgroups were not used for validation
HCC: hepatocellular carcinoma, EC: esophageal cancer, GC: gastric cancer, CRC: colorectal cancer

- We identified 8 distinct RCTs from the literature with 40 subgroups overall to test the performance of the approach
- We only included studies that reported subgroup-specific KM curves from pre-treated advanced-stage gastro-intestinal tumors

Performance measures

1. **Survival prediction accuracy:** proportion of the number of months in which predicted survival rate fell within the 95% CI of the reported survival rate

2. **Best-fit exponential alignment:** model-predicted subgroup-specific hazard rate vs. 95% CI of the estimated hazard rate from the best-fitting exponential distribution to the reported subgroup-specific KM curves

3. **Median time alignment:** predicted median time vs. 95% CI of the reported median time

4. **RMST deviation:** % deviation between the model-predicted RMST and estimated RMST (from reported trial data) for all subgroups

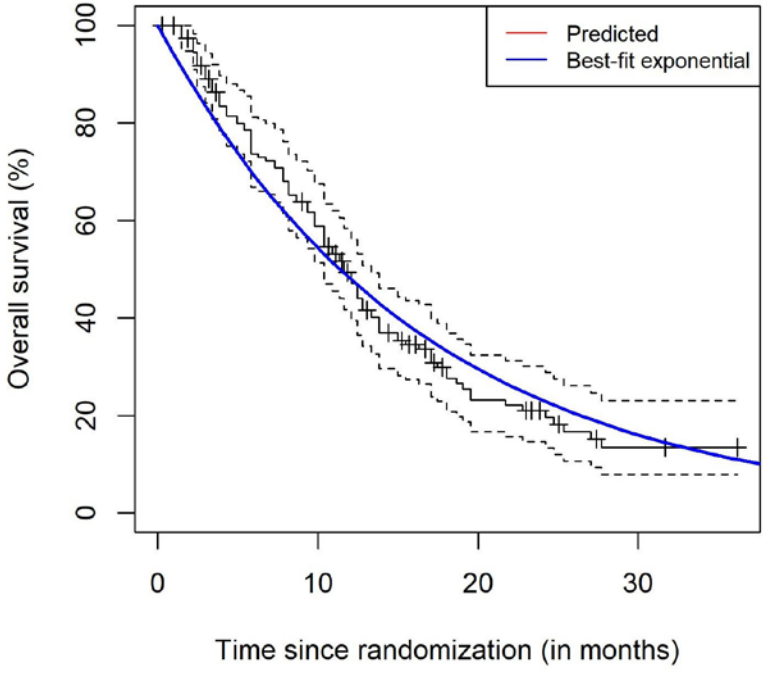
5. **RMST alignment:** model-predicted RMST vs. 95% CI of the estimated RMST for all subgroups

6. **Average survival time deviation:** average absolute difference between model-predicted and reported survival times across all months for all subgroups

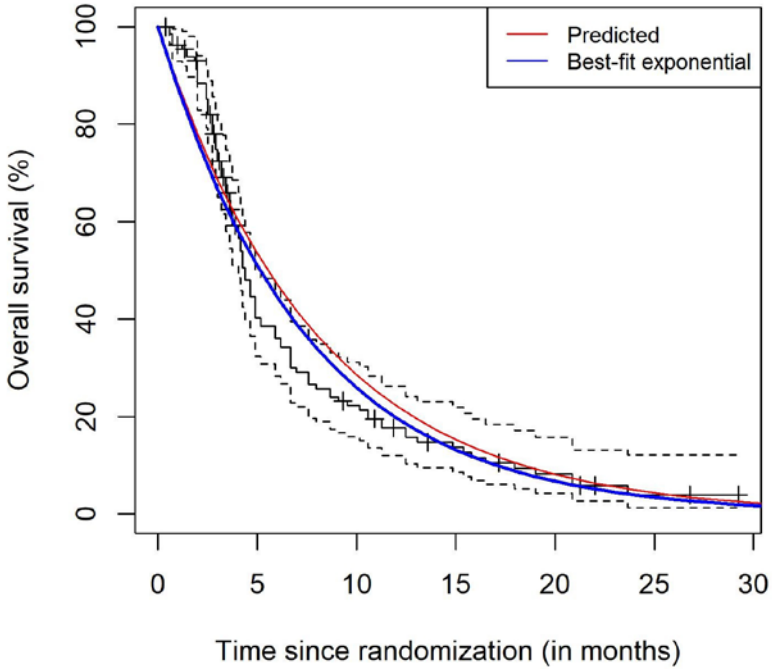
7. **Visual inspection:** comparing the quality of the fit between the predicted and reported subgroup-specific survival curves

Visual Comparison: Example from the placebo arm of the REACH trial

α-fetoprotein < 400 ng/mL subgroup



α-fetoprotein ≥ 400 ng/mL subgroup

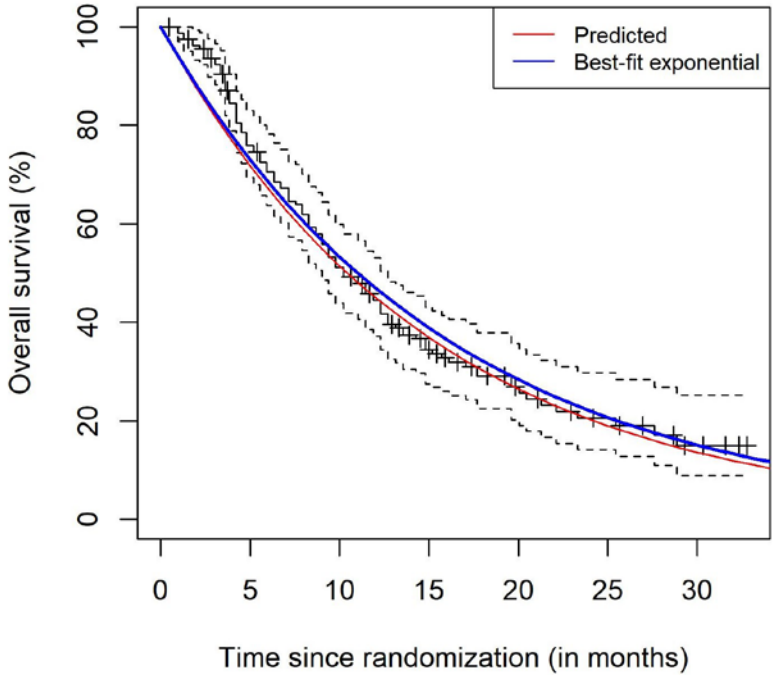


Plot is adapted from Zhu AX, et al. *Lancet Oncol* 2015;16:859–870.

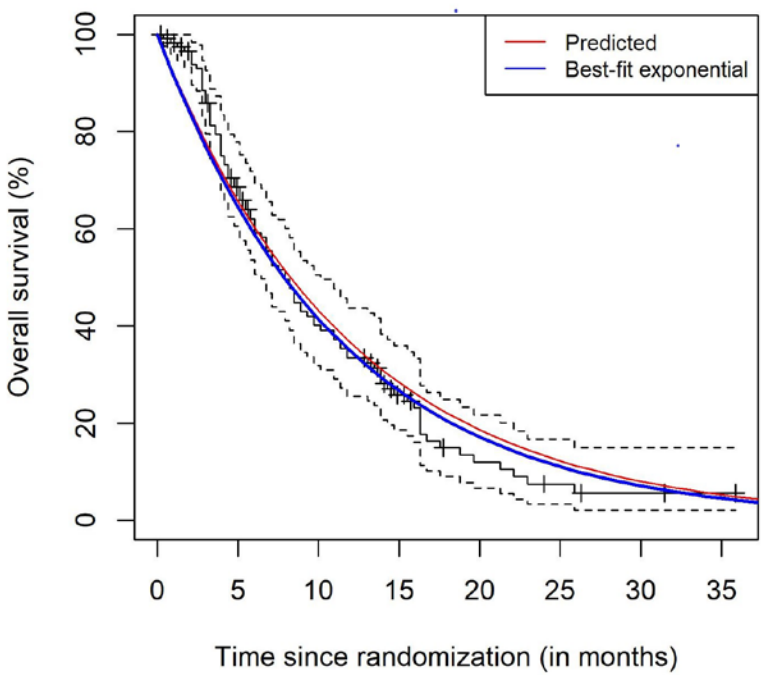
Note: Vertical markers represent censoring information. Predicted and best-fit exponential rate parameters perfectly overlap for the α-fetoprotein < 400 ng/mL subgroup, hence the red line is not visible

Visual Comparison: Example from the Ramucirumab arm of the REACH trial

α-fetoprotein < 400 ng/mL subgroup



α-fetoprotein ≥ 400 ng/mL subgroup



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Performance summary

		Performance metrics					
Test Set	**Total number of subgroups**	**1**	**2**	**3**	4	**5**	**6**
Complete test data	40	71%	35 (88%)	32 (80%)	10%	34 (85%)	5.55%
Reduced test data (subgroups used for randomization)	14	72%	14 (100%)	13 (93%)	8%	14 (100%)	4.97%

- Model-predicted medians were in alignment with the 95% CI of the reported medians in majority of the test cases

- When test data is limited to the cases where subgroups were defined according to randomization stratification factors, model's performance increases remarkably

Performance metrics: 1. Survival prediction accuracy 2. Best-fit exponential alignment 3. Median time alignment 4. RMST deviation 5. RMST alignment 6. Average survival time deviation

Summary and limitations

- Our proposed method worked very well for majority of the cases.
- In a few cases where our proposed approach did not succeed, we drew the following observations:
  - The subgroup is not used for stratifying randomization; therefore covariates/effect modifiers may not have been balanced between the subgroups.
  - Model performance is sensitive to the horizon over which RMST is considered. In the trials with earlier plateauing behavior, model performance was not as desired.
- Exponential distribution was chosen for analytical tractability but may not well represent the survival and hazard trend in the trial data in general.
- Next step: pilot testing the approach for subgroup-specific economic analyses

Questions? Comments?

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