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Surrogate Endpoints Under Attack: Is It Still Worth Performing Surrogacy Validation? Lessons from NSCLC

Choosing the right analytical method is critical!

by Dr Billy Amzal

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Context and challenges

- Previous studies revealed difficulty in demonstrating strong relationship between surrogacy endpoints such as PFS and ORR with hard outcomes such as OS
- **Hyper-progression** on immune-oncology treatments and **cross-over** result in bias
- Data aggregation (extracted study results) limits the statistical methods to adjust for confounders
- The choice of the statistical methods may result in avoidable bias and imprecision:
  - ✓ Covariate adjustment may reduce bias and increase precision
  - ✓ If the functional relationship is mis-specified, the available data may not be used efficiently
  - ✓ Popular methods such as meta-regression disregard that also the surrogate parameter is measured with error

Objective

- To explore methods to efficiently and accurately analyze surrogacy

OUR APPROACH

- **Exploratory** analyses on a large database of NSCLC trials
  - ✓ **Comprehensive**: >1000 clinical studies
  - ✓ **Up-to-date**: includes publications until June 2021
  - ✓ Leveraging **both trial-level** (hazard ratios) **and arm-level** results (median survival times)
- So to assess:
  - ✓ Surrogacy vs. **Subgroups ?**
  - ✓ **Model benchmarking:** what is the best performing surrogacy model?

Findings from exploratory analyses: Usage of appropriate methods may increase precision

Surrogacy strength…

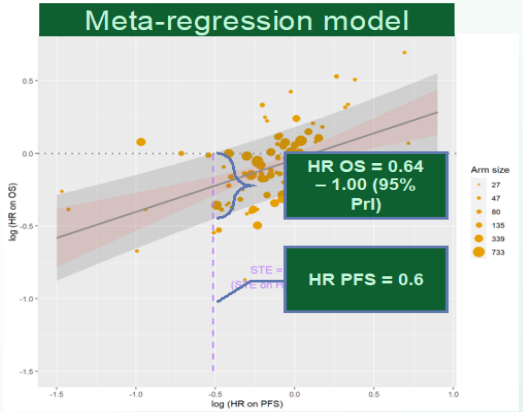
1. …depends on the model parameterization
   - ✓ …improves by applying non-linear (quadratic) model structures e.g., PFS vs. OS: R^2 = 0.260 for the linear model, and R^2 = 0.287 for the quadratic model*
   - ✓ …improves by applying a joint/bi-variate model for the surrogate and the final outcome e.g., ORR vs. mOS: R^2 = 0.764 for the joint model, and R^2 = 0.336 for the meta-regression model*

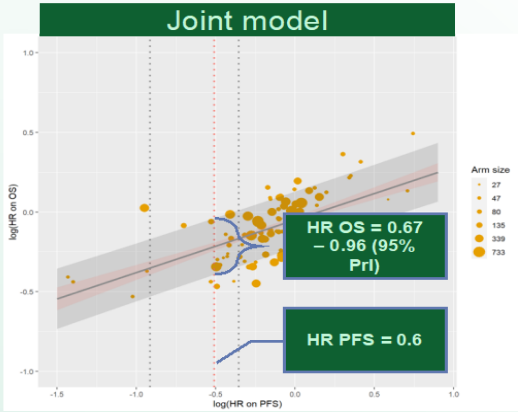
2. …varies across subgroups and can thus be improved by adjusting vs. relevant covariates
   - E.g., mPFS vs. mOS: R^2 = 0.501 for trials with high percentage of patients who never smoked as compared to R^2 = 0.339 overall

* Adjusted R^2 presented

mOS: median overall survival, mPFS: median progression-free survival, ORR: overall response rate

Joint model reduces uncertainty of surrogate to final endpoint prediction





Model	# comparisons	R2 [95% CI]	Adj. R2 [95% CI]	HR PFS	Predicted HR OS with 95% PrI
Meta-regression model	95	0.268 [0.121, 0.415]	0.26 [0.114, 0.407]	0.4	0.69 [0.539, 0.884]
				0.6	0.798 [0.637, 1.001]
				0.7	0.844 [0.676, 1.054]
Joint model		0.477 [0.273, 0.643]	0.471 [0.265, 0.639]	0.4	0.703 [0.587, 0.843]
				0.6	0.804 [0.674, 0.96]
				0.7	0.846 [0.709, 1.01]

Take-home messages

1. This negates the simplistic message that “surrogacy is weak” as previously published
   → Surrogacy strength improves in certain subgroups

2. Indicates a clear correlation between PFS gain and OS gain
   →Progression rates reduction of X% translates into mortality rates reduction $\frac{X}{2}\%$
   →Longer median PFS seems to be associated with longer median OS

3. Confirms that the surrogacy question needs appropriate methods (e.g., using non-linear and/or joint models) to be robust and fair
   → Example: very weak surrogacy in immunotherapy-treated subgroups (R^2=0.007) and strong surrogacy in chemo-treated subgroups (R^2=0.843)

Discussion: Surrogacy validation using RWD?

1. How is it possible?
   - ✓ Mapping key variables from RCT to RW
   - ✓ Accounting for drivers of effectiveness
   - ✓ Using proper analytical integration e.g via joint Bayesian regression models
2. When is it required?
   - ✓ When data are too sparse or too short term
   - ✓ For more ”real-world” or payers relevance
   - ✓ To expand validation and generalizability
3. Example?

Case study: PFS-OS surrogacy analysis in real world

BUSINESS CASE

Surrogacy between PFS and OS is usully assessed based on RCT data only.

In the studied drug class and population, very sparse data available.

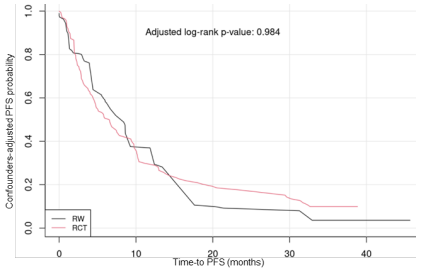
Can RW data be leveraged to enhance power and strength of surrogacy?

OUR APPROACH

We **projected multiple RCTs** for the drug class and indication of interest **in an EHR database** (Flatiron).

We then modeled the PFS to OS surrogacy at patient- & unit-level through a joint GLM model.

Example: endpoint analysis in RCT vs RW

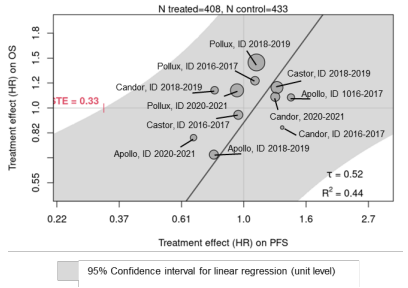


IMPACT

Moderate PFS-OS surrogacy was observed. Surrogacy threshold effect* was found.

Real world surrogacy analysis informs RCT design by checking the endpoints relevance, and reinforces market access and reimbursement dossiers.

Surrogacy at individual & unit level



*Surrogacy threshold effect (STE) indicates the minimum PFS hazard ratio improvement leading to a statistically significant OS improvement.

Back-up

Examples of “relevant” subgroups/covariates

- mPFS as surrogate for mOS

Covariate	R^2 in subgroups		
	Low	Medium	High
Age	**0.543**	0.251	0.078
% white	0.142	**0.570**	0.283
% black	0.201	**0.674**	0.278
% Asian	0.317	**0.553**	0.142
% never smoked	0.012	0.188	0.501
% with adenocarcinoma	0.502	-	0.209
% with prior platin	**0.620**	-	0.168
% with brain metastasis*	**0.545**	0.250	0.348

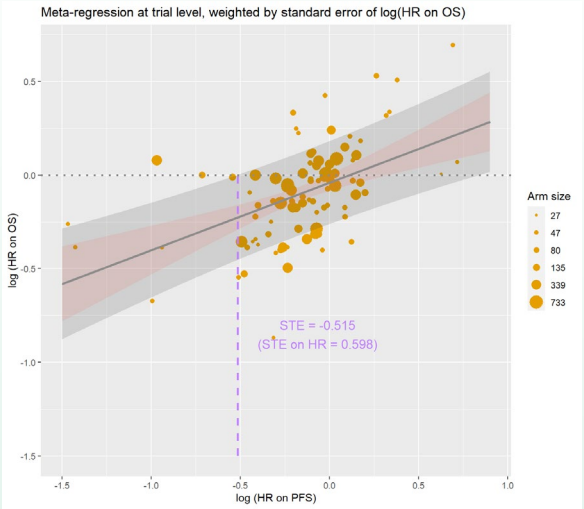
* > 60% of trials with missing data on this covariate

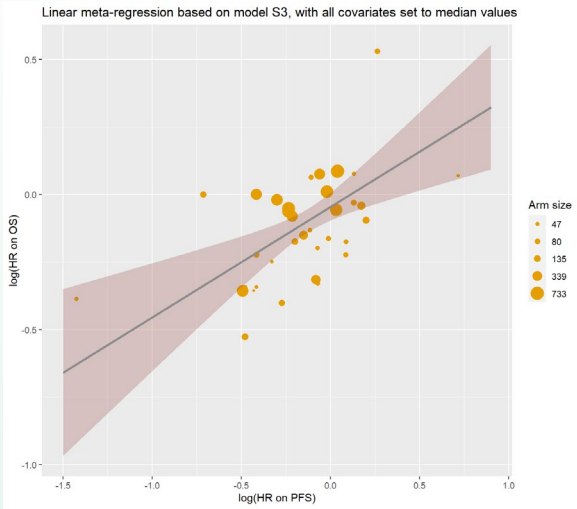
- PFS as surrogate for OS

Covariate	R^2 in subgroups		
	Low	Medium	High
% with PS = 0	**0.486**	0.358	0.032
% with PS ≥ 2	0.448	0.121	**0.595**
% black	0.158	0.279	**0.585**
% males	**0.468**	0.339	0.074
% with ≥ 2 prior chemos	0.336	**0.460**	0.000
Treatment class	0.007 (immuno)	0.225 (targeted)	**0.843 (chemo)**

Covariate selection for PFS as surrogate for OS

Covariate	Selected (forward)	Selected (correlation, backward)
Age	✓	✓
Age ≥ 65		
Male	✓	
White race		
Black race		
Asian race		
Never smoked	✓	✓
Adenocarcinoma	✓	✓
EGFR mutation	✓	
KRAS mutation		
Prior chemo ≥ 2	✓	✓
Prior platin		
PS = 0		
PS = 1		
PS ≥ 2		
Brain metastasis		





Model	# studies	R^2	Adjusted R^2
Whole population, no covariates	95	0.268	0.260
Reduced population, no covariates	35	0.265	0.243
Model after backward selection	35	0.579	0.470

Thank you

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