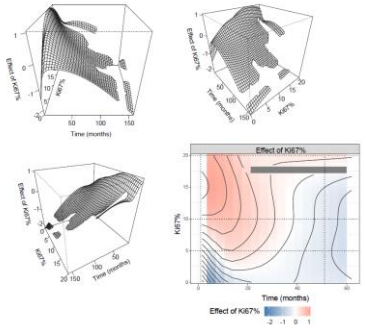
Investigación con RWD: aspectos clave en tumores neuroendocrinos



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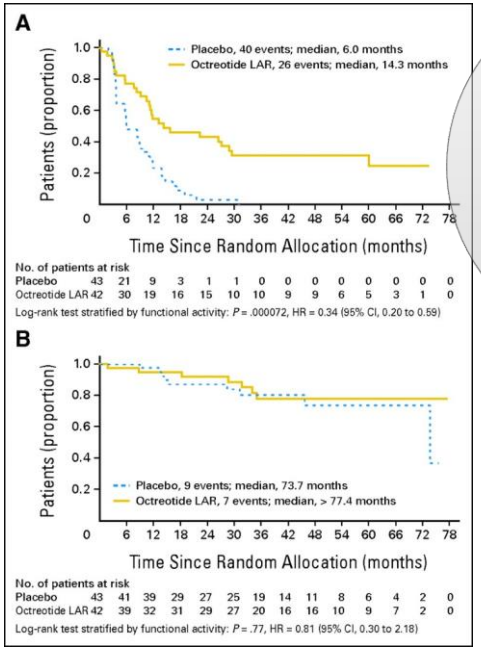
IMIB
Instituto Murciano de Investigación Biosanitaria

UNIVERSIDAD DE MURCIA

Here we had a clinical conundrum.
Even in supposedly well characterized tumors…

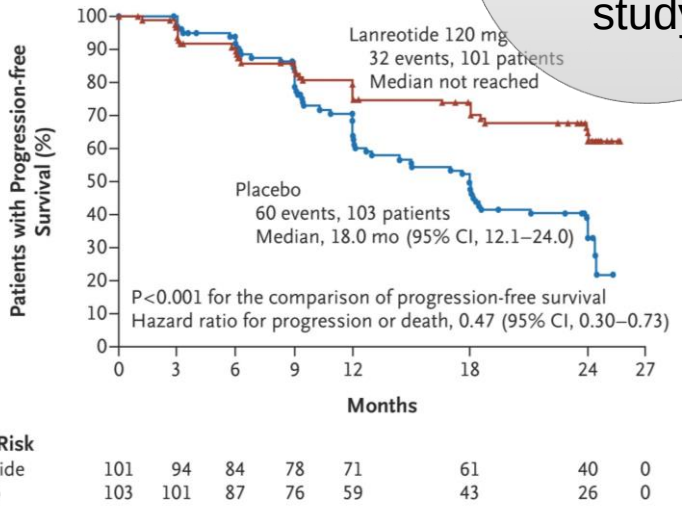


Approximately 25% of the tumors show progression to SSA at six months

(A) Conservative intent-to-treat analysis of time to progression or tumor-related death. (B) Intent-to-treat analysis of overall survival. HR, hazard ratio, in patients with midgut NETs with Ki-67 ≤2%

Anja Rinke et al. JCO 2009;27:4656-4663

Median PFS was longer in the CLARINET study



Caplin, Martyn E., et al. New England Journal of Medicine 371.3 (2014): 224-233.

The only covariate predictive of PFS in the PROMID trial was a liver burden >10%

Factor	Bivariate Analysis			Multivariate Analysis		
	P	HR	95% CI	*P*	HR	95% CI
Octreotide LAR *v* placebo*				< .0001	0.27	0.14 to 0.49
Functional active tumor *v* inactive tumor	.2420	1.38	0.81 to 2.37			
Liver involvement > *v* ≤ 10%	.0009	2.81	1.53 to 5.18	.0023	2.63	1.41 to 4.90
Chromogranin A elevated *v* not elevated	.3098	1.36	0.75 to 2.48			
Karnofsky performance status ≤ *v* > 80%	.6518	1.21	0.54 to 2.71			
Age ≥ *v* < 63 years	.1709	1.47	0.85 to 2.56			
Primary tumor not resected *v* resected	.1040	1.60	0.91 to 2.80	.6784	1.45	0.60 to 2.20
Time since diagnosis ≥ *v* < 4.3 months	.0806	0.62	0.36 to 1.06	.2883	0.71	0.38 to 1.34

Unplanned subgroup analysis

The CLARINET study showed benefit to be independent of the hepatic load, tumor grade (G1 vs. G2), and location

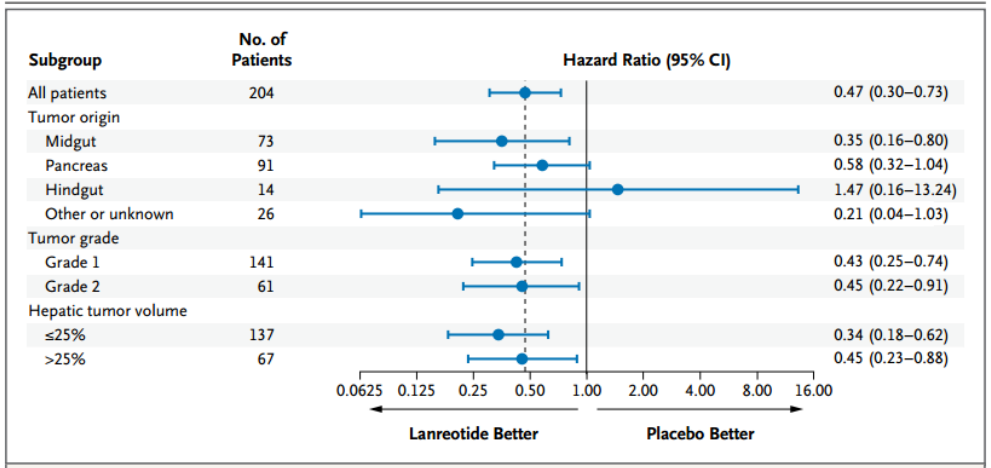


Figure 2. Progression-free Survival, According to Subgroups (Intention-to-Treat Population).

Shown are the hazard ratios for centrally assessed disease progression or death in subgroups defined according to baseline tumor origin and grade and hepatic tumor volume. Subgroup variables were predefined in all cases, although the number of categories for hepatic tumor volume was simplified post hoc from five (estimated hazard ratios ranging from 0.24 to 0.54) to two. The hazard ratio for "all patients" was derived from a Cox proportional-hazards model with terms for study treatment, presence or absence of tumor progression at baseline, and receipt or nonreceipt of previous therapy. The hazard ratio for each subgroup was derived from a Cox proportional-hazards model with a single term for study treatment.

Caplin, Martyn E., et al. "Lanreotide in metastatic enteropancreatic neuroendocrine tumors." New England Journal of Medicine 371.3 (2014): 224-233.

Perhaps in the future,
we should administer risk-based treatments

Targeted therapies
PRRT
Several combinations…

Don't be boring & do things lovingly

original report

Prediction of Progression-Free Survival in Patients With Advanced, Well-Differentiated, Neuroendocrine Tumors Being Treated With a Somatostatin Analog: The GETNE-TRASGU Study

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abstract

PURPOSE Somatostatin analogs (SSAs) are recommended for the first-line treatment of most patients with well-differentiated, gastroenteropancreatic (GEP) neuroendocrine tumors; however, benefit from treatment is heterogeneous. The aim of the current study was to develop and validate a progression-free survival (PFS) prediction model in SSA-treated patients.

PATIENTS AND METHODS We extracted data from the Spanish Group of Neuroendocrine and Endocrine Tumors Registry (R-GETNE). Patient eligibility criteria included GEP primary, Ki-67 of 20% or less, and first-line SSA monotherapy for advanced disease. An accelerated failure time model was developed to predict PFS, which was represented as a nomogram and an online calculator. The nomogram was externally validated in an independent series of consecutive eligible patients (The Christie NHS Foundation Trust, Manchester, United Kingdom).

RESULTS We recruited 535 patients (R-GETNE, n = 438; Manchester, n = 97). Median PFS and overall survival in the derivation cohort were 28.7 (95% CI, 23.8 to 31.1) and 85.9 months (95% CI, 71.5 to 96.7 months), respectively. Nine covariates significantly associated with PFS were primary tumor location, Ki-67 percentage, neutrophil-to-lymphocyte ratio, alkaline phosphatase, extent of liver involvement, presence of bone and peritoneal metastases, documented progression status, and the presence of symptoms when initiating SSA. The GETNE-TRASGU (Treated With Analog of Somatostatin in Gastroenteropancreatic and Unknown Primary NETs) model demonstrated suitable calibration, as well as fair discrimination ability with a C-index value of 0.714 (95% CI, 0.680 to 0.747) and 0.732 (95% CI, 0.658 to 0.806) in the derivation and validation series, respectively.

CONCLUSION The GETNE-TRASGU evidence-based prognostic tool stratifies patients with GEP neuroendocrine tumors receiving SSA treatment according to their estimated PFS. This nomogram may be useful when stratifying patients with neuroendocrine tumors in future trials. Furthermore, it could be a valuable tool for making treatment decisions in daily clinical practice.

J Clin Oncol 37. © 2019 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of neoplasms that follow a variable clinical course and are defined by the WHO 2010 classification into three subgroups on the basis of proliferation index[1]; however, within each category, cases with a different clinical and biologic behavior continue to coexist.[2]

Somatostatin analogs (SSAs) are currently the recommended first-line treatment of most patients who are diagnosed with advanced, well-differentiated GEP-NETs[3,4] as they provide prolonged progression-free survival (PFS) with an acceptable toxicity profile. PFS is often used as an outcome measure of patients with GEP-NETs because it is a surrogate variable for overall survival (OS).[5,6] Despite SSAs being the

TRASGU

PREDICTIVE TOOL IN NEUROENDOCRINE TUMORS TREATED WITH SOMATOSTATIN ANALOGUE

We successfully overcame the challenge of placing an asturian mythological creature at the top of international oncological literature

*Study GETNE-**TRASGU** (Treated With Analog of Somatostatin in Gastroenteropancreatic and Unknown Primary NETs)*


EL TRASGU

TRASGU-GETNE AFT model

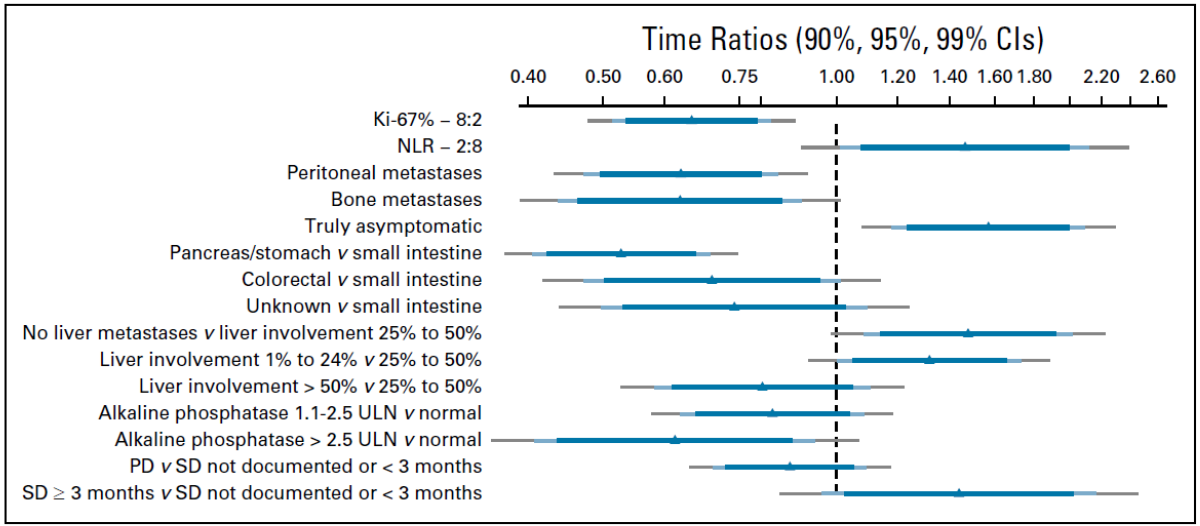
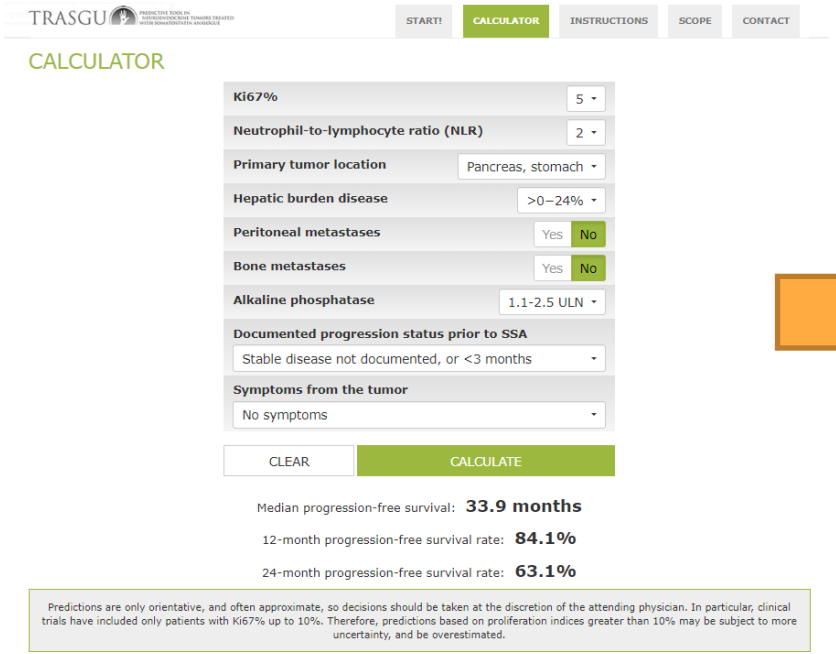
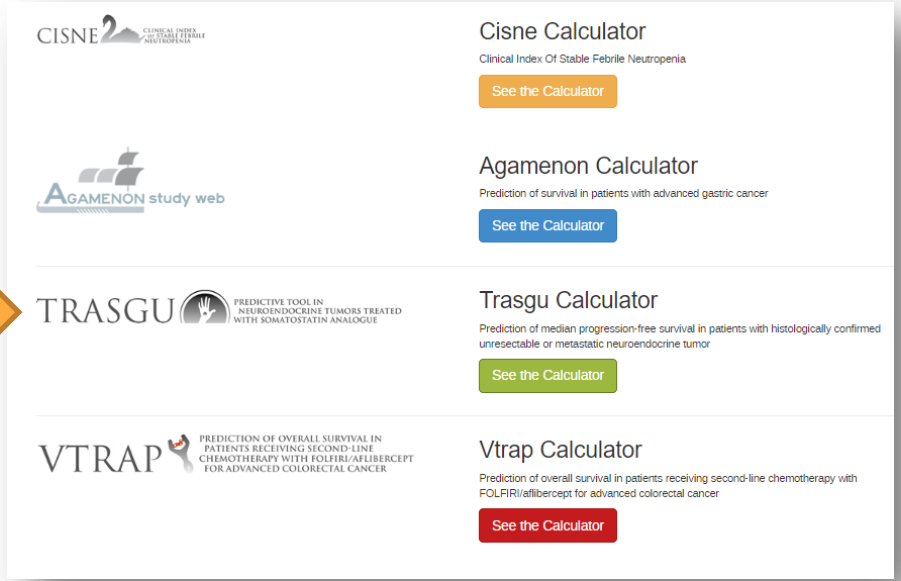


FIG 2. Effect of GETNE-TRASGU (Spanish Group of Neuroendocrine and Endocrine Tumors–Treated With Analog of Somatostatin in Gastroenteropancreatic and Unknown Primary Neuroendocrine Tumors) covariates on progression-free survival. Adjusted time ratios are derived from a multivariable log-normal accelerated failure time model and represent its exponentiated coefficients (Table 2). Interpretation of the adjusted time ratios (TR): TR $>$ 1 means that an increase in the value of the covariate is associated with longer survival. TR $<$ 1 means that an increase in the value of the covariate is associated with shorter survival. NLR, neutrophil-to-lymphocyte ratio; PD, progressive disease; SD, stable disease; ULN, upper limit of normal.

GETNE-TRASGU. JCO 2019

GETNE-TRASGU calculator

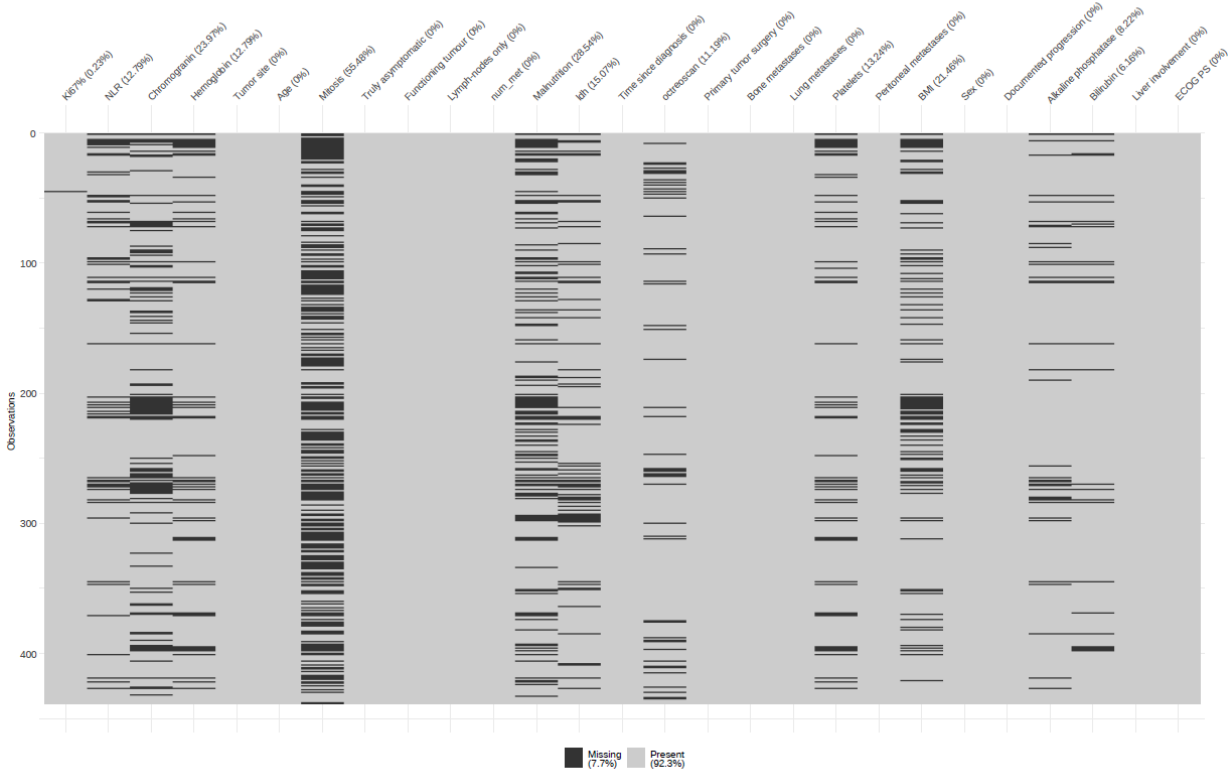




http://www.iricom.es/prognostictools/

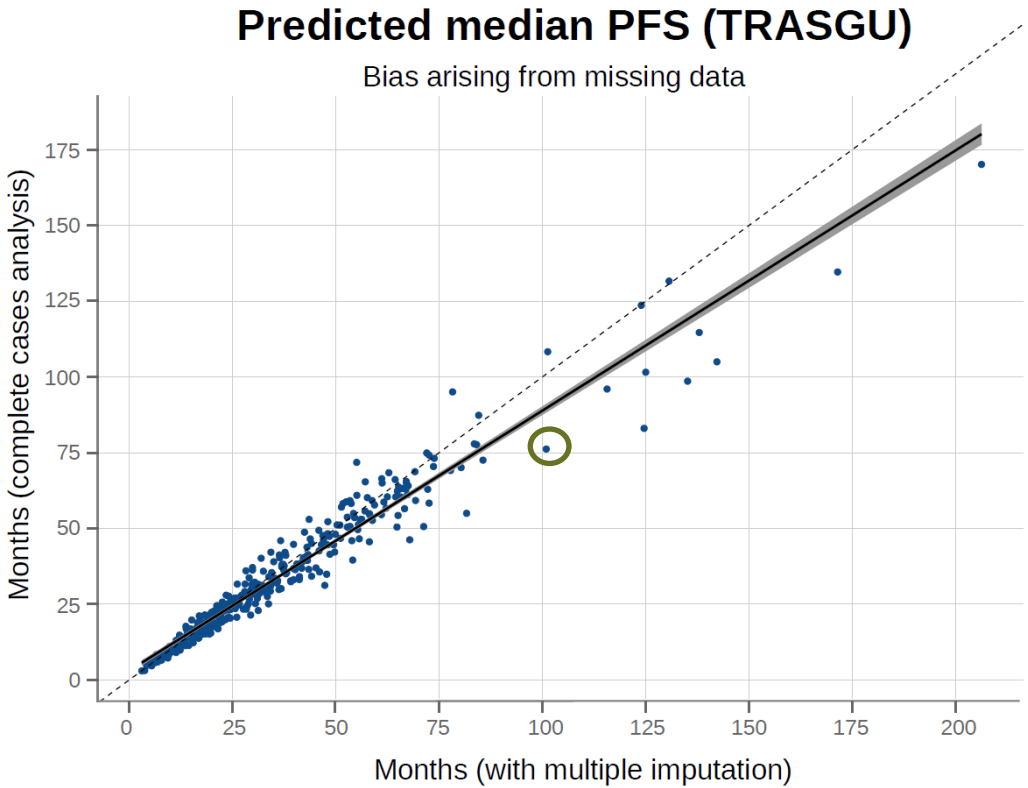
Challenges begin now; not considering missing data produces bias…

Annex Table 1. Pattern of missing values in the data set



Multiple imputation is required to preserve the message of what is seen from the influence of what is not seen

PFS predicted in the TRASGU study (complete cases vs imputed data analysis)



Prolonged OS in NET patients means dynamic effects should not be neglected

"There is nothing permanent except change"

Heraclitus of Ephesus
(535 BC – 475 BC)

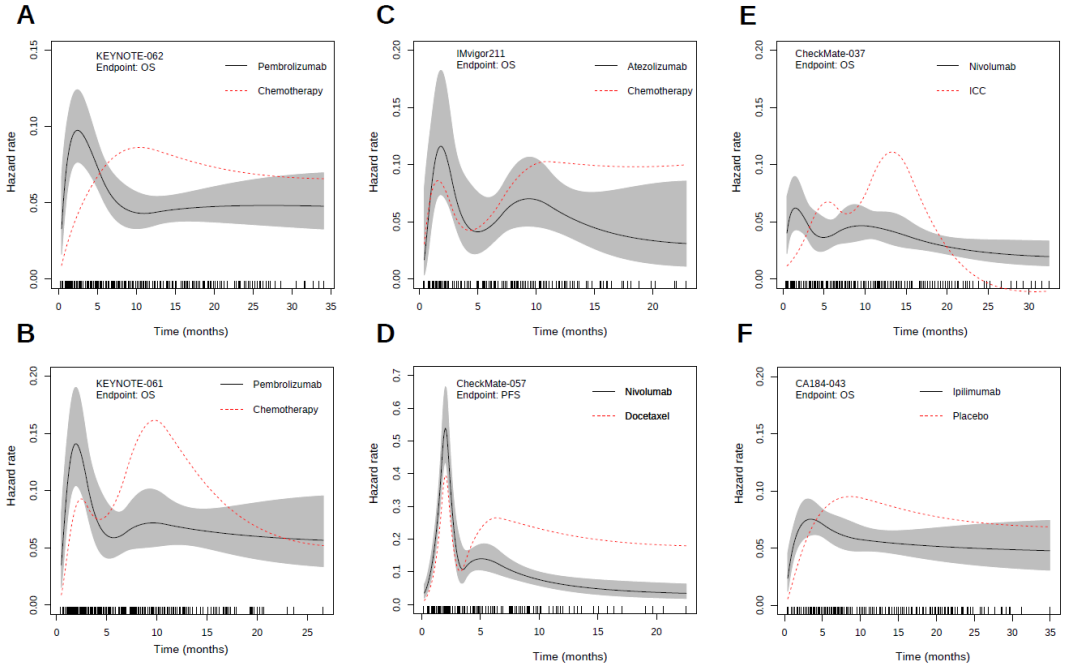
Reasons for not detecting non-PH in NETs are:

- Nobody checks it
- Dichotomization
- Small series
- No antiangiogenic for GINETs
- Short follow-up…

Flexible models for non-proportional hazards: seeking inspiration from shipbuilders

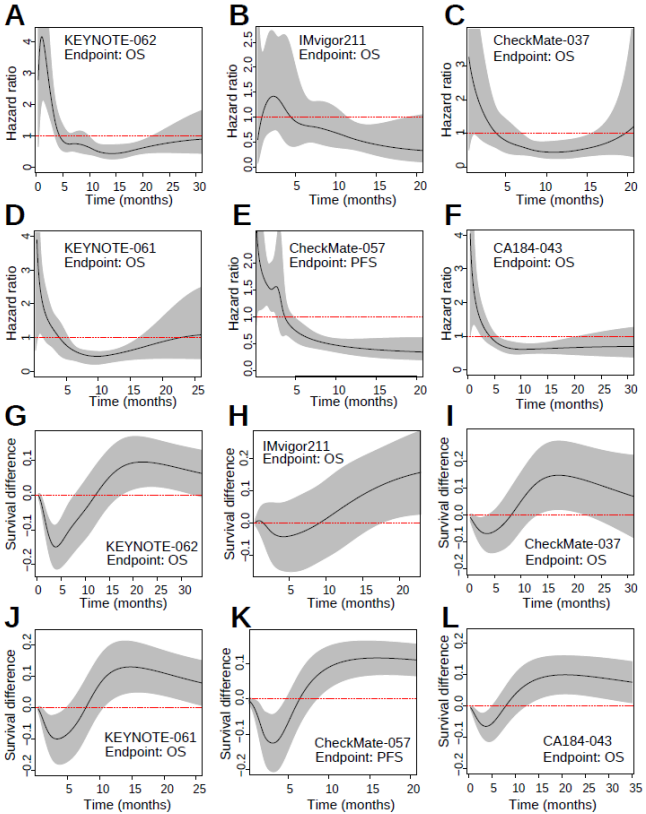
If the PH assumption is not fulfilled we will have to be honest and recognize that collapsing a complex effect to a single number does not correctly reflect reality

Non-proportional hazards will be a burning issue in the next years

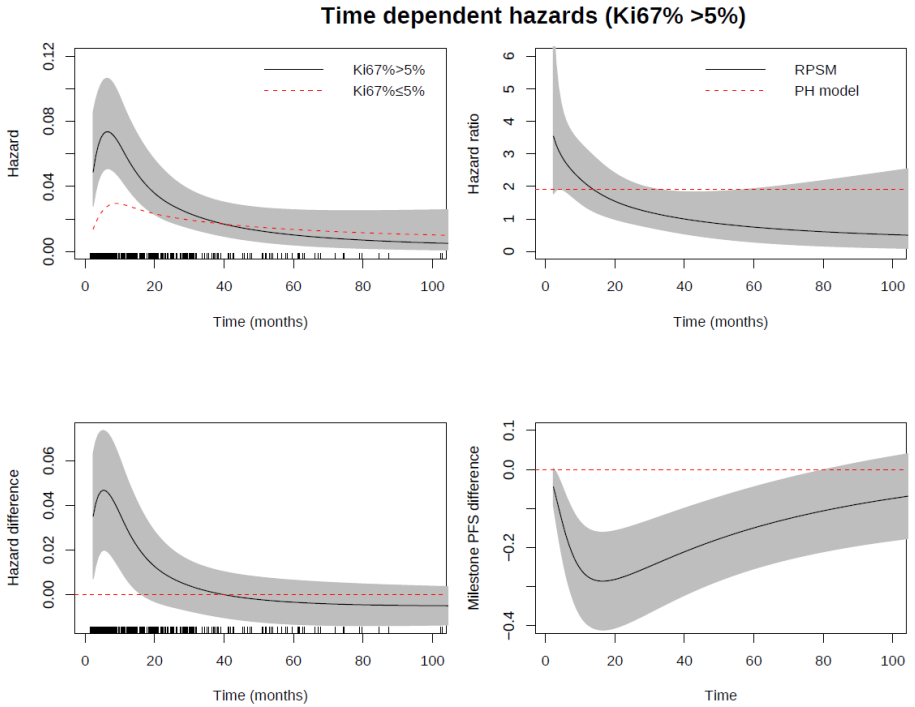


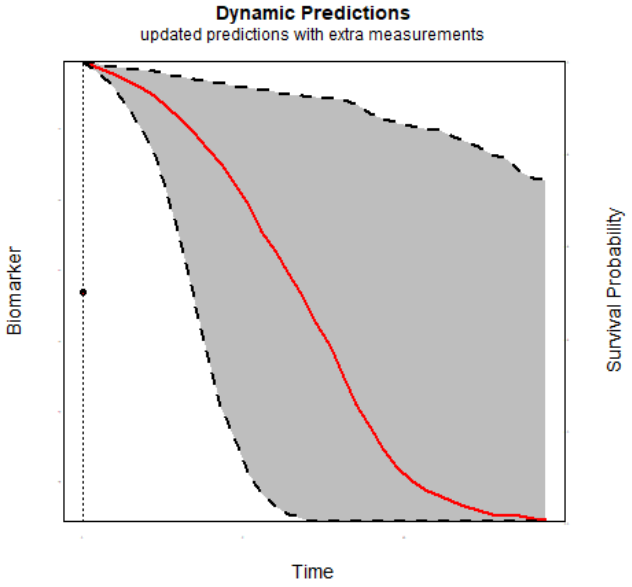
Example: 6 recent phase III trials with ICIs declared negative, despite the existence of benefit
Flexible model to assess fluctuating hazard rates during immunotherapy

Time-varying hazard ratios and milestone survival rates suggest real benefit!



Ki67% against time interactions (study GETNE-TRASGU)

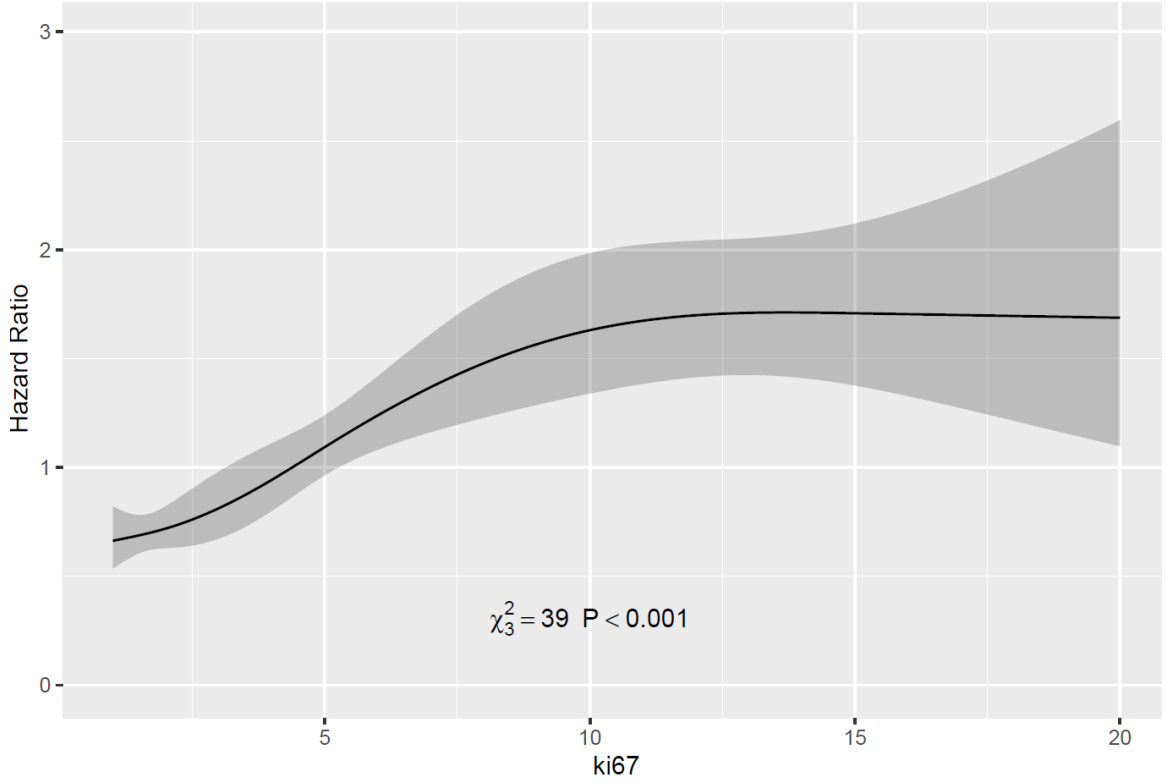




(Hypothetical)

Data are non-proportional (dynamic effect)

Ki67% as a continuous non-linear biomarker

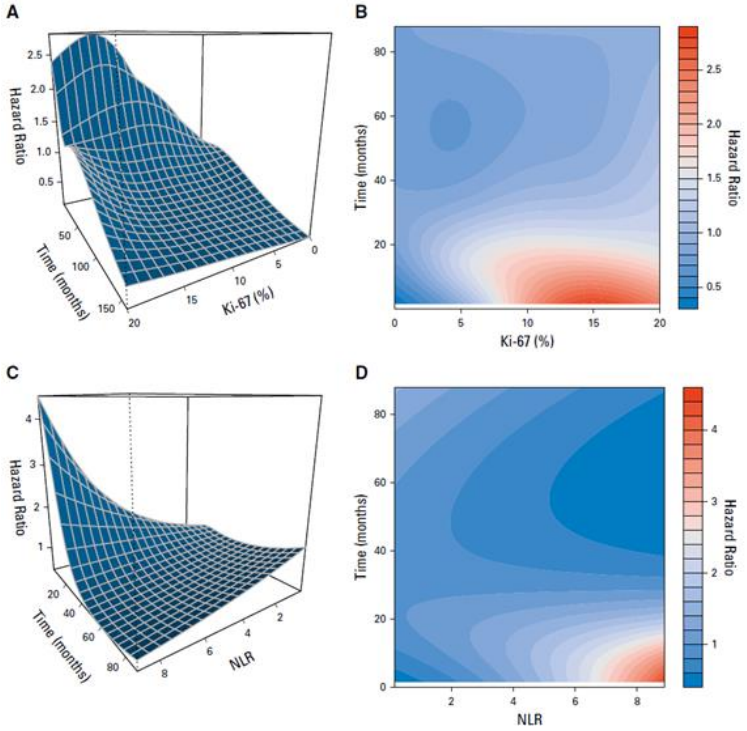


True discontinuities are infrequent in nature or knowledge: cut-off points based on Ki67% yields biologically implausible findings

WHO 2%
WHO 2017 3%
Scarpa 5%
Panzuto 5%
Nuñez 10%

"There may be said to be two classes of people in the world; those who constantly divide the people of the world into two classes, and those who do not".
Robert Benchley ('Vanity Fair',1920)

Continuous variables interact with hazards in non-linear ways, and both the baseline hazard and variable effects are dynamic: the silliness of thresholds !



Retwitteaste

Frank Harrell
@f2harrell

Beautiful analyses by @kimtruss showing continuous time-dependent effect of CONTINUOUS biomarker. Good example of (1) silliness of thresholds and (2) community-assisted analysis:

Traducir Tweet

Hazard ratio plots with non-linear & time-varying effects in R
I am pretty sure they have a zero width confidence interval at the reference value when using rcs in rms and applying ...
discourse.datamethods.org

3:22 p. m. · 1 sept. 2019 · TweetDeck

8 Retweets **50** Me gusta

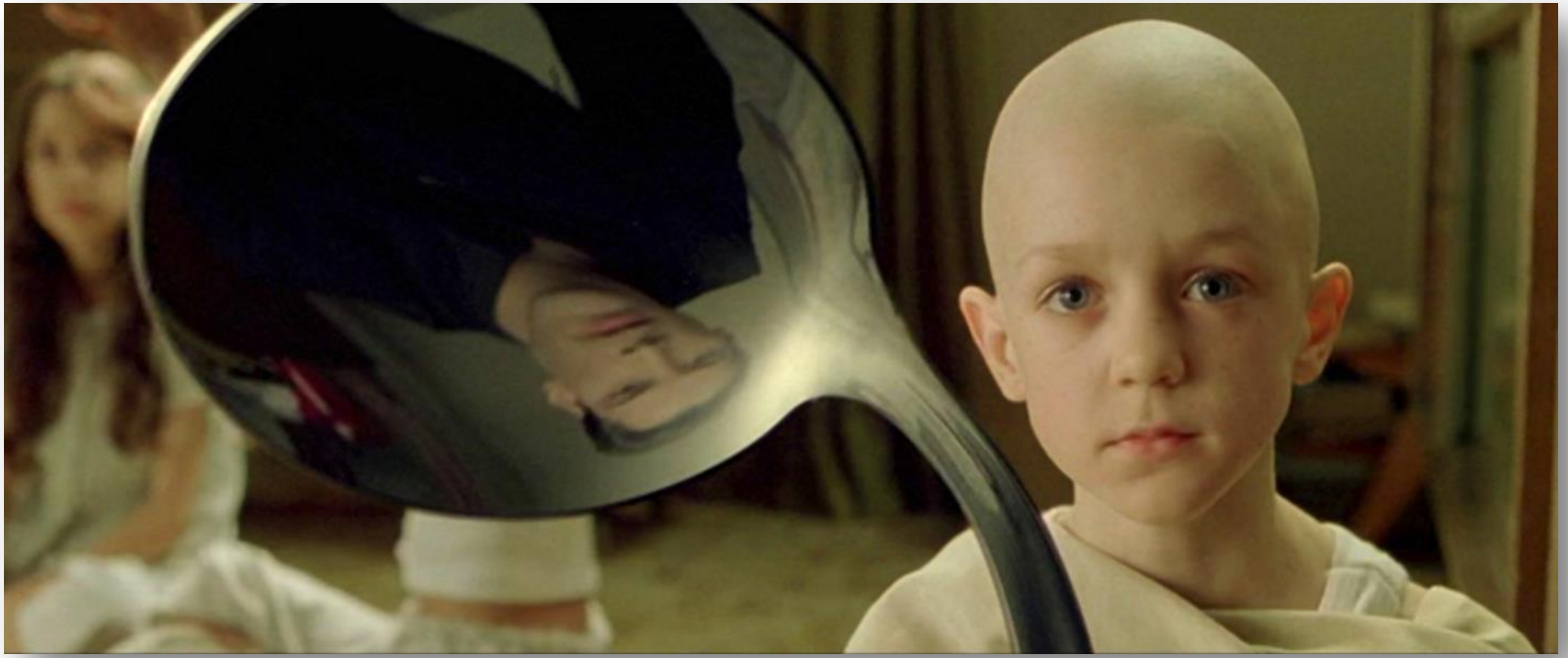
GETNE-TRASGU. JCO 2019

Our GETNE-TRASGU classification proposal (ie., trial stratification)

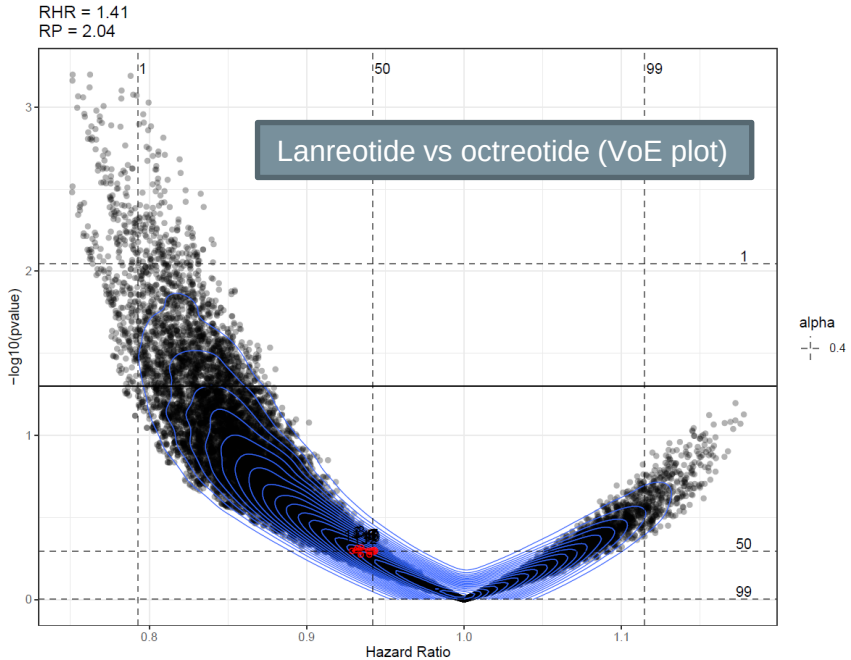
Location – histology – Ki67% (average/maximum – timepoint)

Examples:
r-NEC-60
i-NET-1
p-NET-5
p-NET-20
Etc

Let's be honest, a single parameter measuring treatment effects may not even exist



The comparison between octreotide and lanreotide is a possible natural development of TRASGU

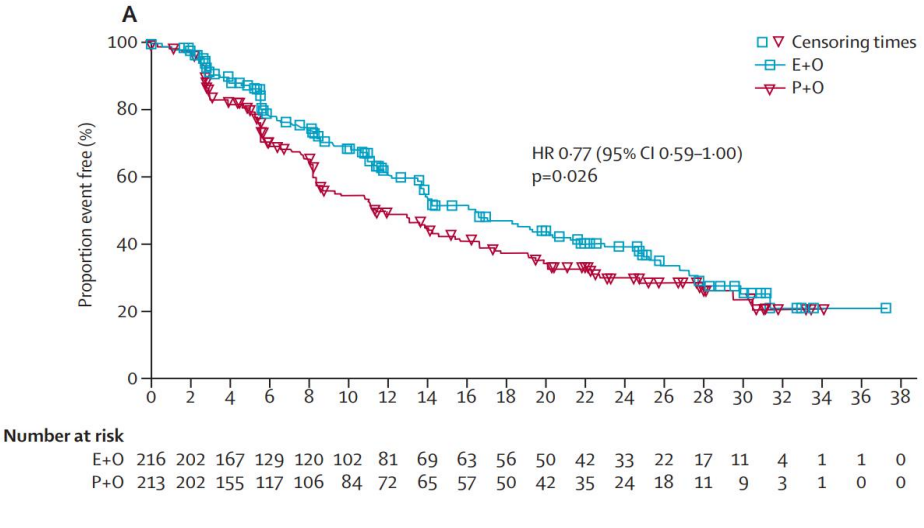


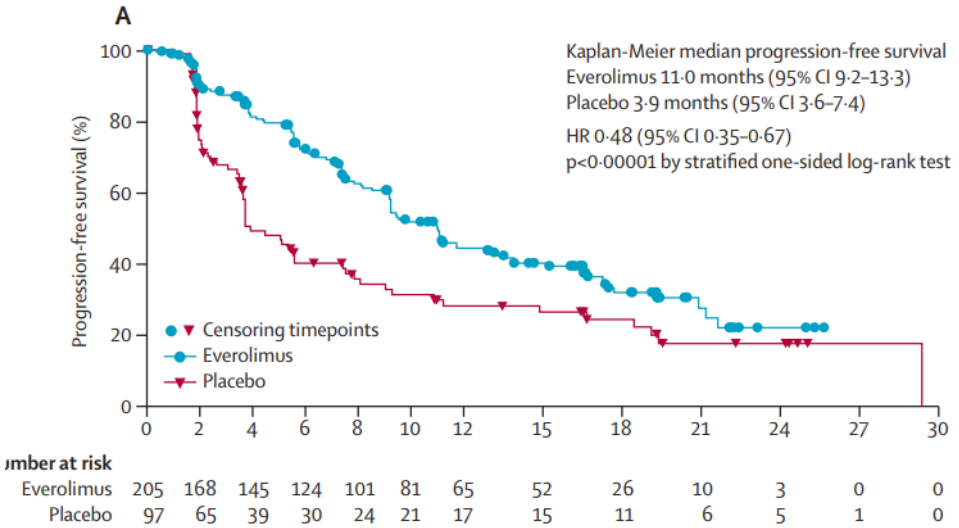
!?

Model specification has a decisive influence on the results of observational studies

Patel et al. Assessment of vibration of effects due to model specification can demonstrate the instability of observational associations. J Clin Epid, 2015

Adjustment for known prognostic covariates can lead to substantial increases in model efficiency, and may be incorporated into the analysis of RCTs





RADIANT-2
Multivariate (pos hoc) analysis:
HR 0·62; 95% CI 0·51-0·87; p=0·003

RADIANT-4
Análisis estratificado

In the field of RWD, a dishonest analyst can wreak havoc…

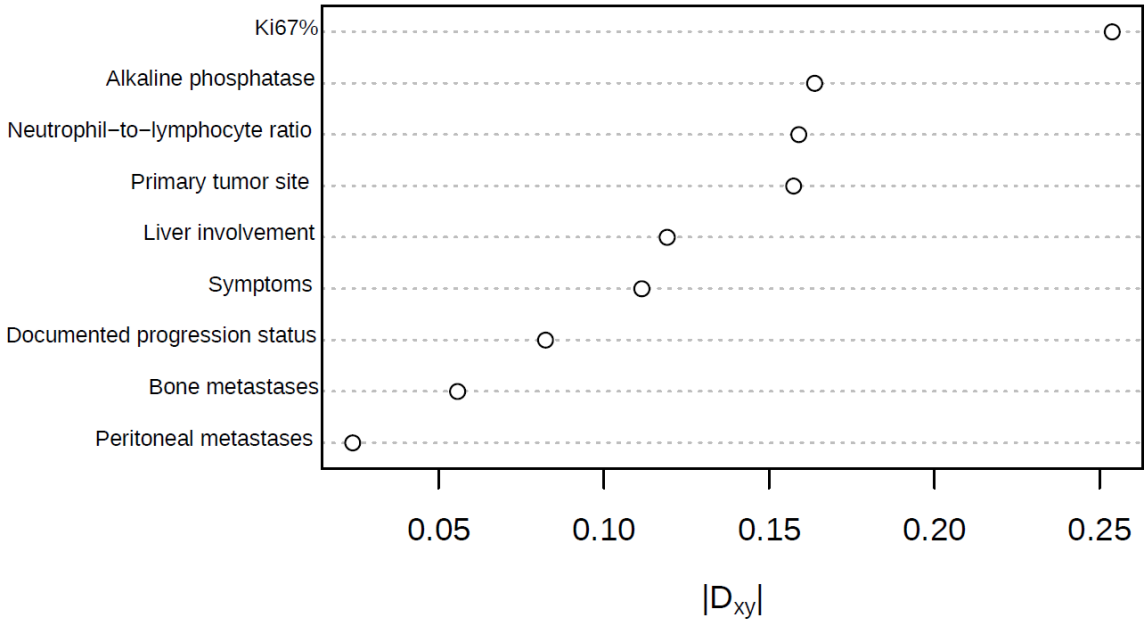
Modern procrustean analysis

"If you torture your data long enough, they will tell you whatever you want to hear"

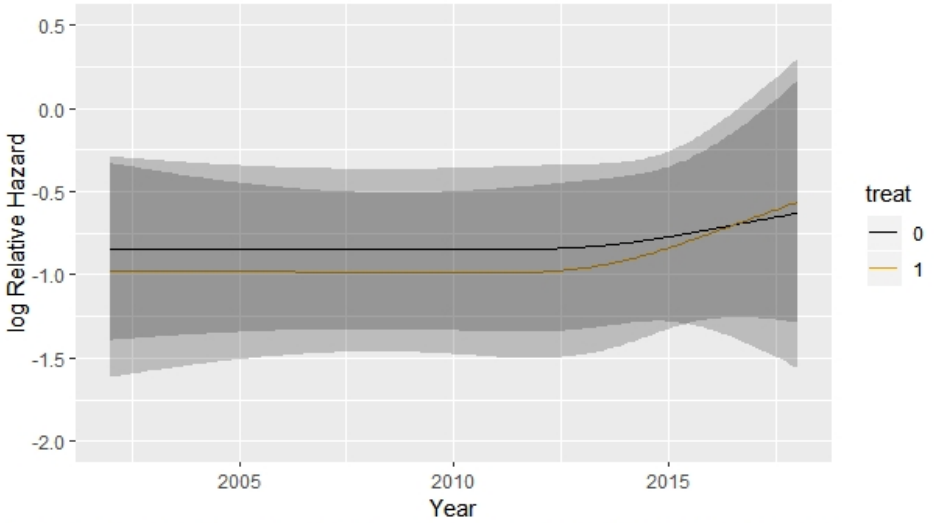
NEJM 1993, 329:1196-1199

The selection of confounding factors is one of the most important issues and should be theoretical

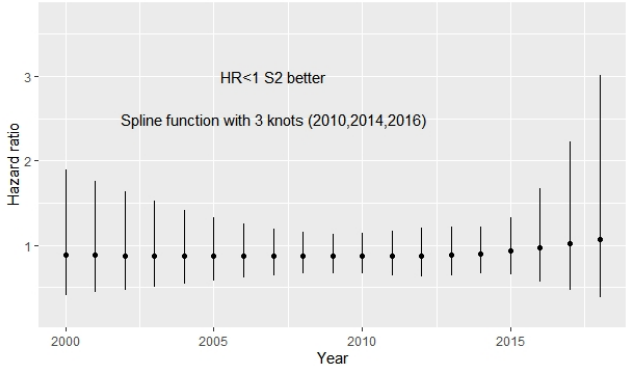
Annex 3. Somers' Dxy rank correlation between predictors and progression-free survival

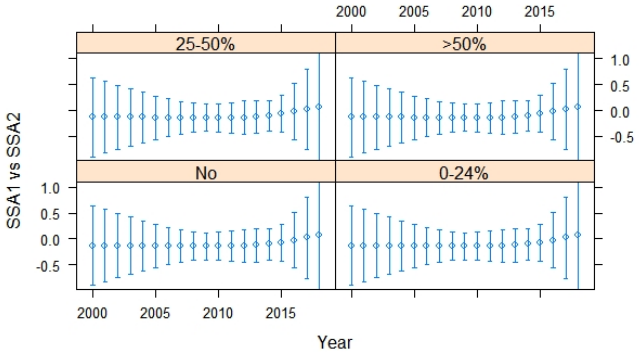


Explore interactions with year of treatment



The stability of treatment effects over time in different subgroups is complex to analyze in a clinical trial

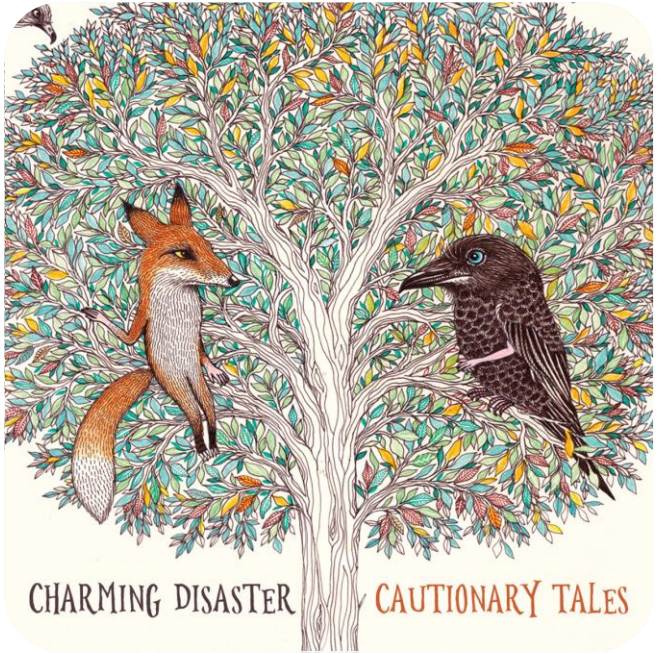




Effect by year & liver burden

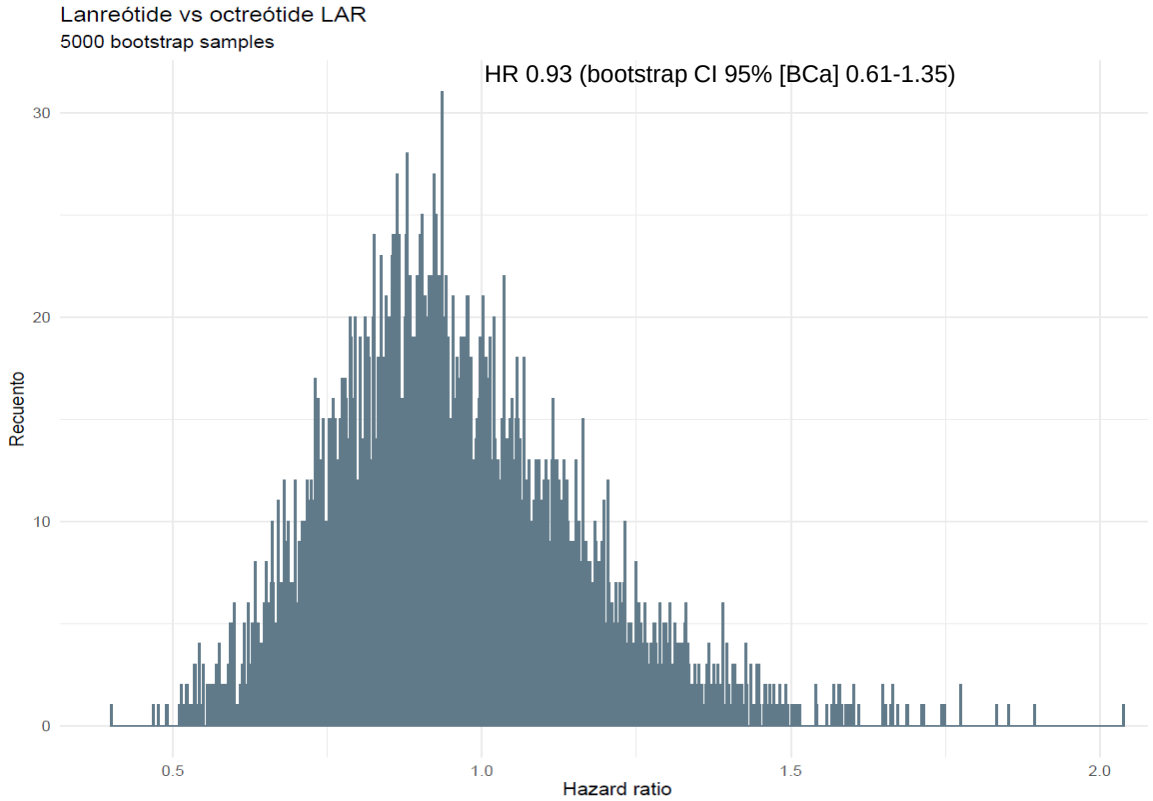
No estimate obtained from RWD is an island in itself; covariate effects are a piece of a continent, a part of a whole

- What is RWD in NETs for?
  - ✓ Not just a rebranding for bias-prone observational studies !!
- Cautionary tales from RWD
- Results should not interpreted aloof from the previous evidence (e.g, no data, solid RCT, weak evidence, etc.)
  - ✓ There's a method that fits great

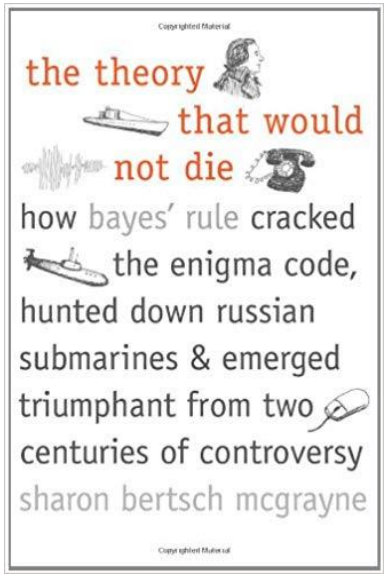


Karim et al. Effectiveness in the Absence of Efficacy: Cautionary Tales From Real-World Evidence. JCO 2019

Lanreotide vs octreotide (PFS; Bootstrapping Cox's Regression Model)

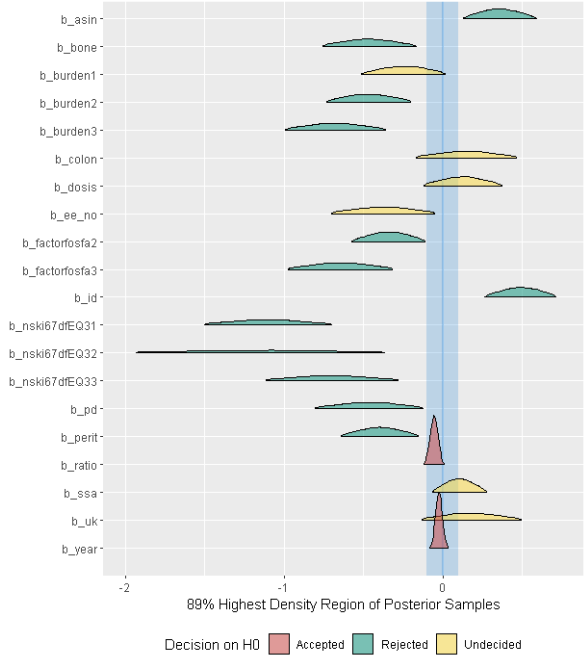


There's a better method to gradually reveal the truth from RWE



Bayesian methods are a rational choice for registry analysis

Are lanreotide & octreotide similar or different?

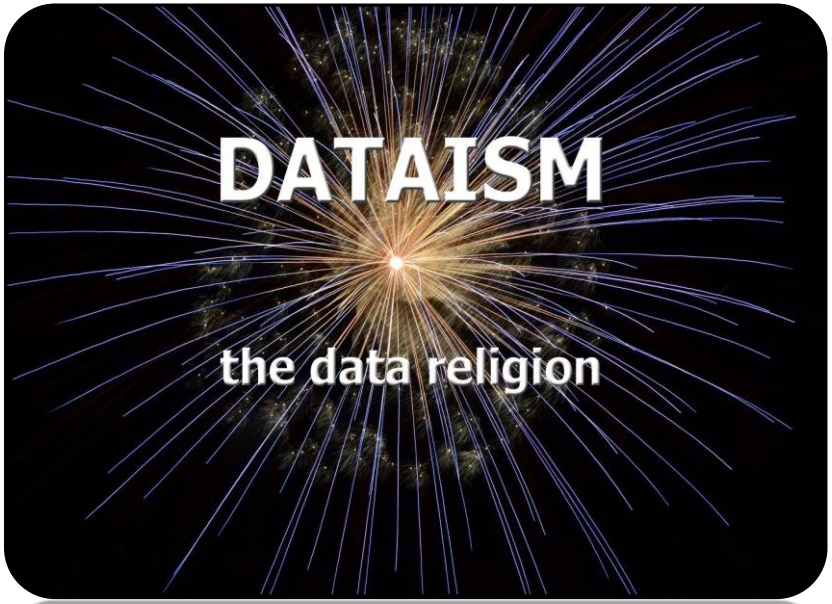


- Prob dirección= 84%
- Prob ROPE= 47%
- Prob superior >30% = 2%

It is essential to support the correct interpretation of data in clinical registries

"Dataism declares that the universe consists of data flows, and the value of any phenomenon or entity is determined by its contribution to data processing"
-*Yuval Noah Harari*

"Dataism is nihilism. It gives up on any and all meaning. Data are numbers and not narrative; they are additive. Meaning, on the other hand, is based on narration. Data simply fills up the senseless void"
-*Byung-Chul Han*



RGETNE is fun + phenomenal = funomenal

Thanks!!!

ENETS

Certificate

We are pleased to confirm that

was awarded **Third Place for Poster in the Clinical Science Category**
"Nomogram to Predict Progression-free Survival in Patients with Well-differentiated, Stage IV Gastroenteropancreatic Neuroendocrine Tumors Treated with Somatostatin Analogues: Data of TR"

Barcelona, Spain, March 8, 2019

Prof. Dermot O'Toole
Chairman of ENETS