Exploring the key clinical empirical observations relevant to adaptive dosing

Acknowledgements: Leon Aarons and Nicola Mellilo

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The scandal of poor medical research

BMJ 1994 ; 308 doi: https://doi-org.manchester.idm.oclc.org/10.1136/bmj.308.6924.283 (Published 29 January 1994)
Cite this as: *BMJ* 1994;308:283

Doug Altman “We need less research, better research, and research done for the right reasons”

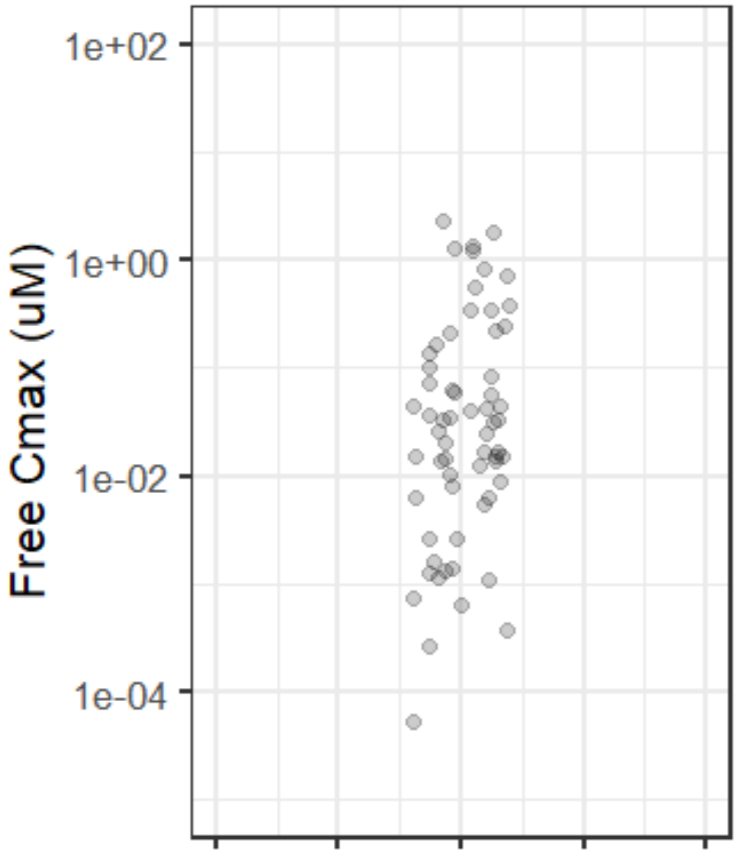
Outline

- Brief note on Preclinical Cancer Evolution studies
- Surrogate Biomarkers for Dose Adjustments
- Brief note on selection bias/observational studies

Preclinical Studies

- Biggest criticism of preclinical studies in general involving drugs is…

- Plot shows the mean free Cmax, maximal concentration, in plasma of targeted agents that have been approved
- Its rare to be above 1uM – average concentrations over a 24 hour period will be even lower!
- **Resistance in the clinic is happening at sub uM concentrations!**
- Let's explore a preclinical study on adaptive therapy…



Example

ARTICLE

DOI: 10.1038/s41467-017-01516-1 OPEN

Spatial competition constrains resistance to targeted cancer therapy

Katarina Bacevic[1], Robert Noble[2,5], Ahmed Soffar[1,6], Orchid Wael Ammar[1], Benjamin Boszonyik[1], Susana Prieto[1], Charles Vincent[3], Michael E. Hochberg[2,4], Liliana Krasinska[1] & Daniel Fisher[1]

- Article discusses resistance to CDK inhibitors such as Palpociclib (clinical mean free Cmax of 15nM, 0.015uM)

"cells were grown in the absence or presence of palbociclib (1 µM or 10 µM; PD0332991, PD) for 24 h, 48 h and 72 h,"

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- Another drug used NU6102 has an IC50 of 5 and 10 nM against its primary targets CDK1/Cyclin B and CDK2/Cyclin A3 – doses of 50uM were used in the experiments!

Quote from a colleague:

"Show me a drug that requires 50uM to be active and I will show you the door"

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"cells were grown in the absence or presence of palbociclib (1 µM or 10 µM; PD0332991, PD) for 24 h, 48 h and 72 h,"

Is there any preclinical ADT study that has used clinically relevant drug concentrations?

- Another drug used NU6102 has an IC50 of 5 and 10 nM against its primary targets CDK1/Cyclin B and CDK2/Cyclin A3 – doses of 50uM were used in the [illegible]

In-vivo studies haven't even measured drug levels – they vary a lot across animals!

Quote from a colleague:

"Show me a drug that requires 50uM to be active and I will show you the door"

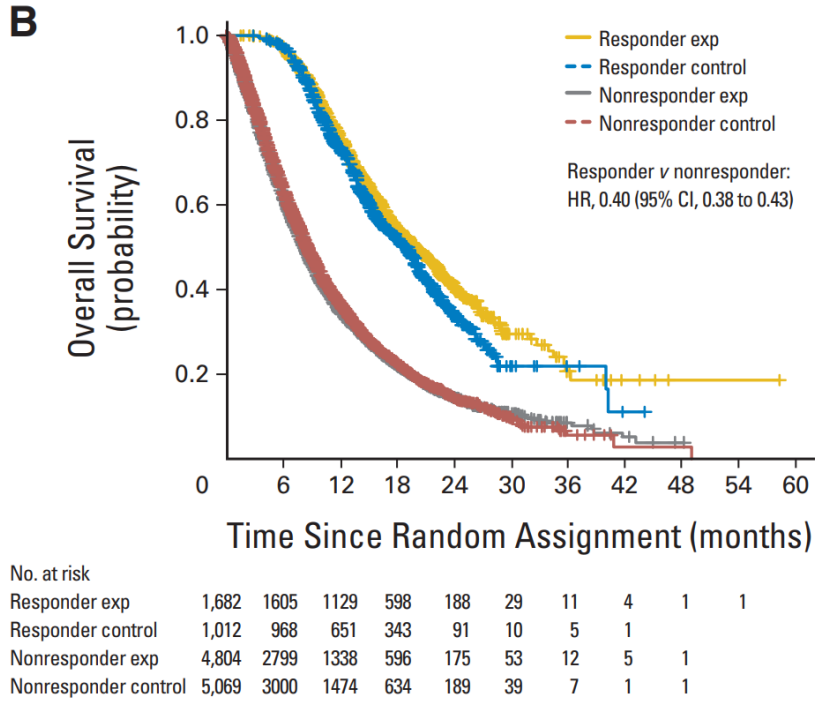
Adaptive therapy in the clinic – anyone for selection bias?

- Example in NSCLC
- Patients who respond to treatments in Oncology do live longer than those that don't
  - Response here is a 30% or more reduction in Sum of Longest Diameters (RECIST)
- The chances of having a patient respond in trials is ~20-30% on average
  - There are drugs that can lead to increase in response rate - but its not that many!
- In the example here its 20%!

VOLUME 33 · NUMBER 9 · MARCH 20 2015
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Overall Response Rate, Progression-Free Survival, and Overall Survival With Targeted and Standard Therapies in Advanced Non–Small-Cell Lung Cancer: US Food and Drug Administration Trial-Level and Patient-Level Analyses

Gideon M. Blumenthal, Stella W. Karuri, Hui Zhang, Lijun Zhang, Sean Khozin, Dickran Kazandjian, Shenghui Tang, Rajeshwari Sridhara, Patricia Keegan, and Richard Pazdur



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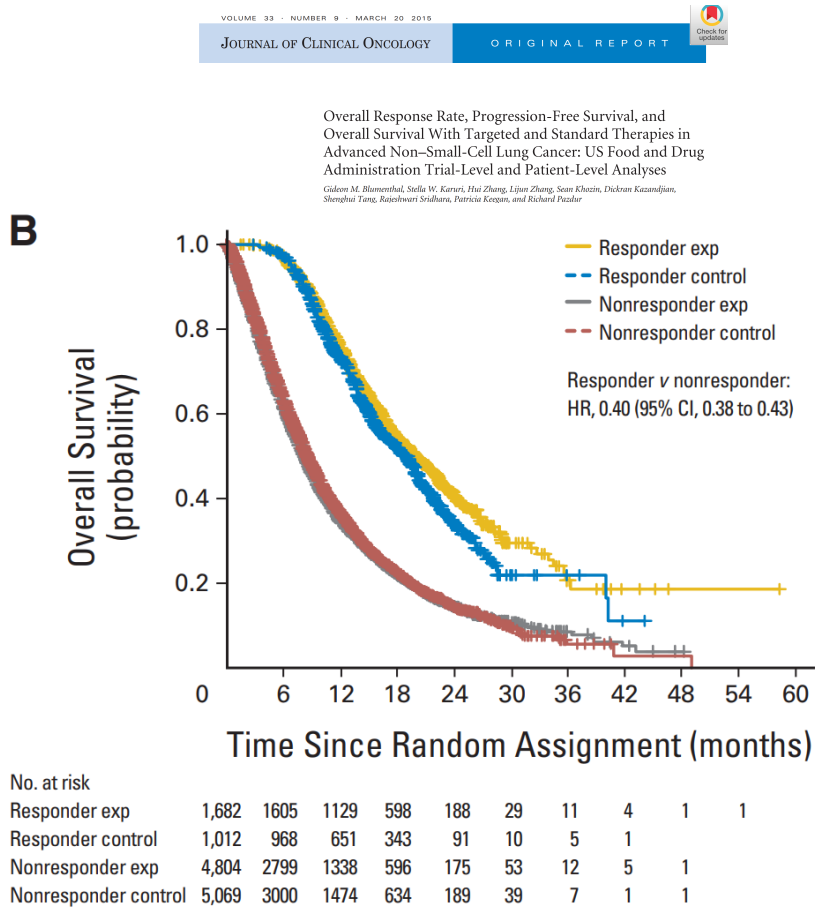


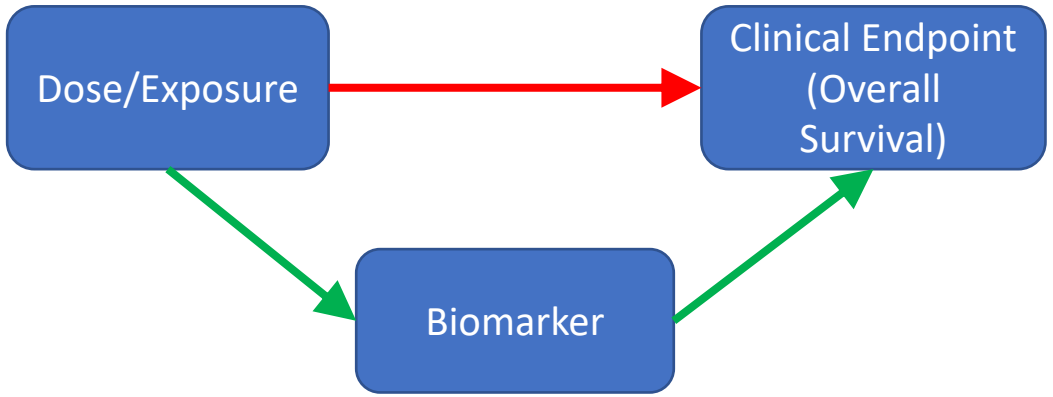
Adaptive therapy goal is to optimise treatment for the 20-30% of patients who will do well anyway!

Where would you invest time/resource on the 20-30% that do well or the 70-80% that don't?

Surrogate Biomarkers - ADT

In order to apply ADT a biomarker that fully captures the drug effect on the efficacy end-point is needed – these don't really exist so…

How much of the drug effect does a biomarker have to capture such that your dosing decisions don't lead to reduced efficacy?



Biomarker could be PSA, Imaging, Radiological Progression etc.

Let's consider the prostate cancer ADT trial…

Surrogate Biomarkers - ADT

- Overall Survival is the key end-point not PSA progression/radiological progression etc. in metastatic castration resistant prostate cancer
  - PSA/radiological progression are not surrogates!
  - Abiraterone – CTC counts are known to be a better dynamic biomarker than PSA
- In the ADT study:
  - Selection bias – patients have to respond to receive therapy – not the case in original trial
    - **Comparisons to the original trial are biased to favour ADT and are invalid – trial patients are not chosen based on responding to abiraterone**
  - **"Control"** arm is discussed but not disclosed on clinicaltrials.gov
    - **Prognostic factors are a plenty…**

VOLUME 33 · NUMBER 12 · APRIL 20 2015
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Circulating Tumor Cell Biomarker Panel As an Individual-Level Surrogate for Survival in Metastatic Castration-Resistant Prostate Cancer

Howard I. Scher, Glenn Heller, Arturo Molina, Gerhardt Attard, Daniel C. Danila, Xiaoyu Jia, Weimin Peng, Shahneen K. Sandhu, David Olmos, Ruth Riisnaes, Robert McCormack, Tomasz Burzykowski, Thian Kheoh, Martin Fleisher, Marc Buyse, and Johann S. de Bono

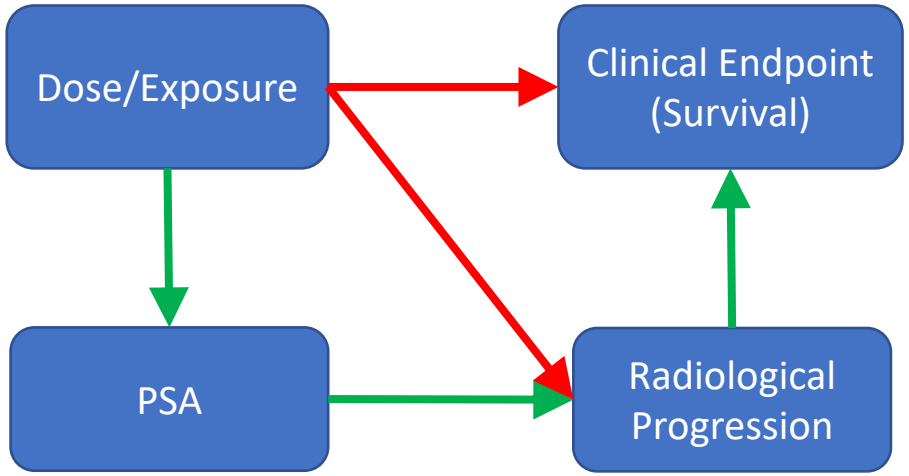
ARTICLE
DOI: 10.1038/s41467-017-01968-5 OPEN

Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer

Jingsong Zhang[1], Jessica J. Cunningham[2], Joel S. Brown[2,3] & Robert A. Gatenby[2,4]

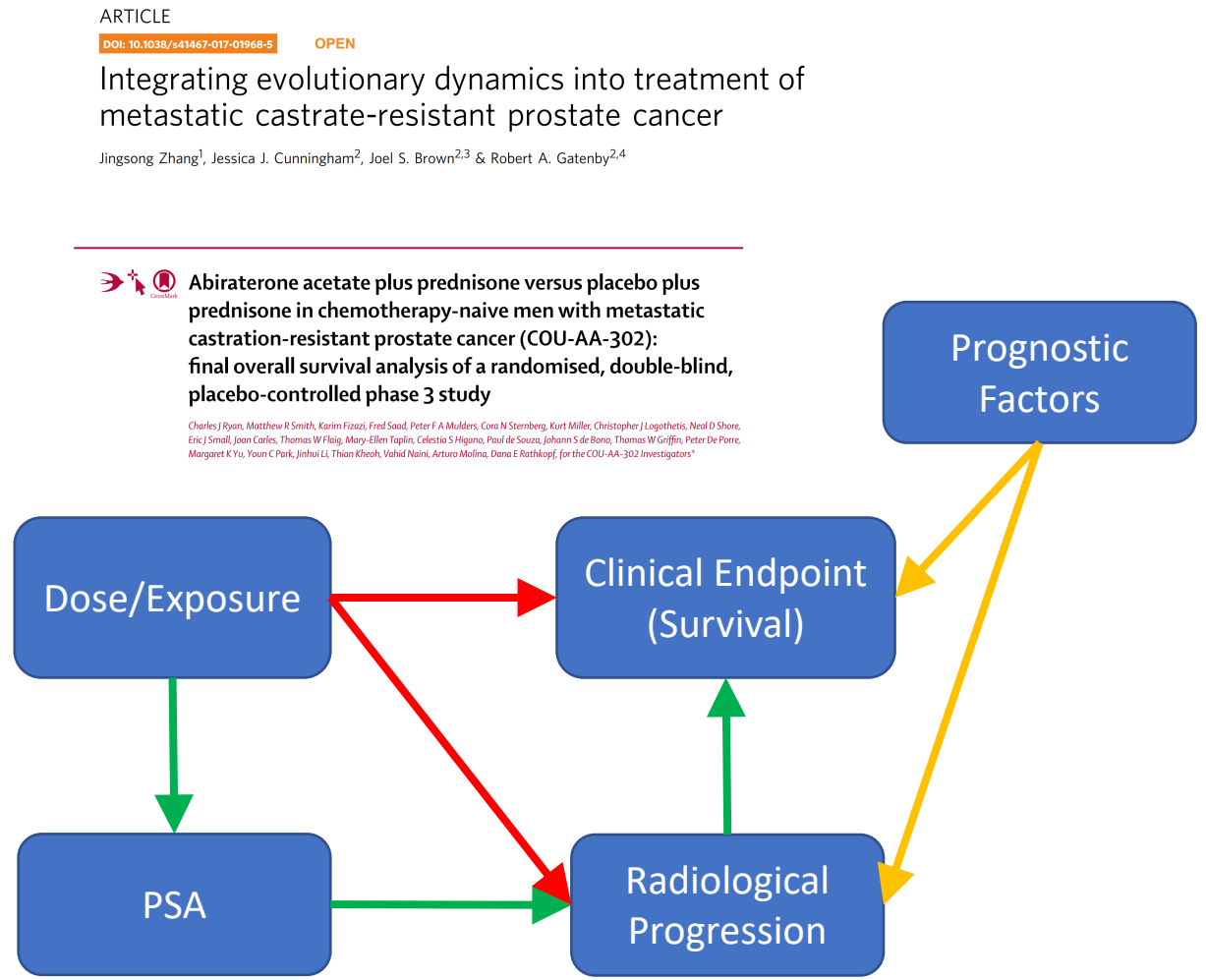
Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study

*Charles J Ryan, Matthew R Smith, Karim Fizazi, Fred Saad, Peter F A Mulders, Cora N Sternberg, Kurt Miller, Christopher J Logothetis, Neal D Shore, Eric J Small, Joan Carles, Thomas W Flaig, Mary-Ellen Taplin, Celestia S Higano, Paul de Souza, Johann S de Bono, Thomas W Griffin, Peter De Porre, Margaret K Yu, Youn C Park, Jinhui Li, Thian Kheoh, Vahid Naini, Arturo Molina, Dana E Rathkopf, for the COU-AA-302 Investigators**



Biomarkers – ADT – Observational Studies

- Known prognostic factors: Age, PSA, LDH, Hb, ALP, site of metastasis etc…
  - **Note these are easy to collect and are routinely collected**
  - **No excuse for not reporting these!**
- These factors are known to correlate to end-points independent of the drug dose/exposure
- When analysing a treatment effect you do want to assess these – this cannot be done on total 27 patients (11 treated & 16 “control”)
  - **You would have a minimum of one parameter per prognostic factor – you can see the problem!**
- Be very sceptical of conclusions from what is essentially an observational study with little information on prognostics factors!



All those PSA modelling studies…

2576 *Vol. 8, 2576–2579, August 2002* Clinical Cancer Research

Quantifying the Amount of Variation in Survival Explained by Prostate-specific Antigen[1]

David A. Verbel,[2] Glenn Heller, William K. Kelly, and Howard I. Scher

Departments of Epidemiology and Biostatistics [D. A. V., G. H.] and Medicine [W. K. K., H. I. S.], Memorial Sloan-Kettering Cancer Center, New York, New York 10021

INTRODUCTION

PSA[3] is the most widely used marker in the management of prostate cancer today. It has been evaluated for screening, to define prognosis, and to assess therapeutic outcomes in several well-defined clinical states (1). The extensive use of PSA in these areas and observed statistical associations between various

between PSA and survival ($P < 0.01$, two-sided test). However, time-dependent PSA explains only 17% of the variation in survival.

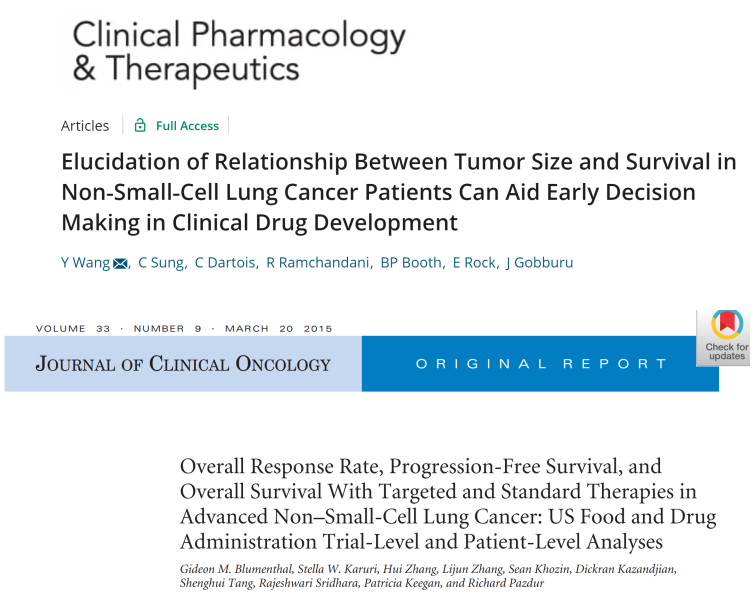
Conclusions: **Use of this methodology demonstrates that there remains sufficient variation in survival unaccounted for by PSA measurements in this patient cohort. Other factors, perhaps unknown, exist that determine survival outcome. Consideration of PSA alone as a surrogate can produce misleading information regarding the risk of death; its use as a surrogate for survival is not warranted when designing a clinical trial in this patient population.**

Most biomarkers only explain a modest amount of the survival variance - we've known this for decades…

Clinical Observations Tumour Burden Time-series

What have we learnt from decades of analysing tumour burden time-series data from clinical trials (1000s of patients time-series data)…

1. **The more we shrink tumours (by 1st visit 6-8 weeks) the longer the patient lives**
   a) The link between tumour shrinkage an end-points like PFS/OS is **NOT** drug independent


Clinical Pharmacology & Therapeutics

Articles | Full Access

Elucidation of Relationship Between Tumor Size and Survival in Non-Small-Cell Lung Cancer Patients Can Aid Early Decision Making in Clinical Drug Development

Y Wang, C Sung, C Dartois, R Ramchandani, BP Booth, E Rock, J Gobburu

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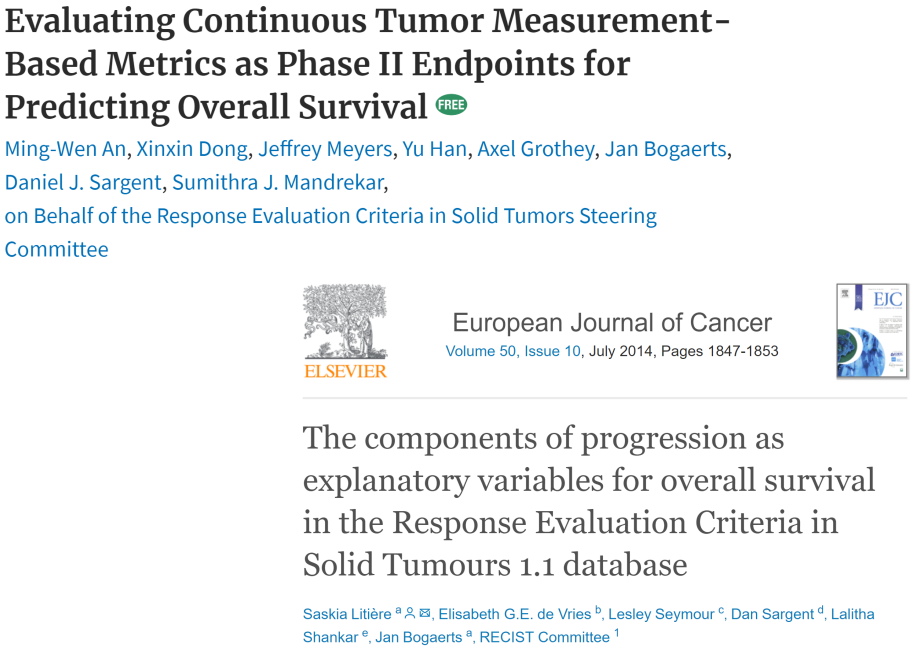
Evaluating Continuous Tumor Measurement–Based Metrics as Phase II Endpoints for Predicting Overall Survival FREE

Ming-Wen An, Xinxin Dong, Jeffrey Meyers, Yu Han, Axel Grothey, Jan Bogaerts, Daniel J. Sargent, Sumithra J. Mandrekar, on Behalf of the Response Evaluation Criteria in Solid Tumors Steering Committee

ELSEVIER

European Journal of Cancer

Volume 50, Issue 10, July 2014, Pages 1847-1853

The components of progression as explanatory variables for overall survival in the Response Evaluation Criteria in Solid Tumours 1.1 database

Saskia Litière [a], Elisabeth G.E. de Vries [b], Lesley Seymour [c], Dan Sargent [d], Lalitha Shankar [e], Jan Bogaerts [a], RECIST Committee [1]

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What have we learnt from decades of analysing tumour burden time-series data from clinical trials (1000s of patients time-series data)…

2. **There is no correlation between how fast you shrink tumours and how quickly the tumours grow back (mCRPC, metastatic melanoma and NSCLC)**

On the relationship between tumour growth rate and survival in non-small cell lung cancer

Research article | Mathematical Biology | Clinical Trials | Oncology | Pharmacology | Statistics

Tumor Growth Rates Derived from Data for Patients in a Clinical Trial Correlate Strongly with Patient Survival: A Novel Strategy for Evaluation of Clinical Trial Data

Wilfred D. Stein[a,b], William Doug Figg[a], William Dahut[a], Aryeh D. Stein[c], Moshe B. Hoshen[d], Doug Price[a], Susan E. Bates[a], and **Tito Fojo[a]**

Cancer Chemotherapy and Pharmacology (2018) 81:325–332
https://doi.org/10.1007/s00280-017-3486-3

ORIGINAL ARTICLE

CrossMark

Model based analysis of the heterogeneity in the tumour size dynamics differentiates vemurafenib, dabrafenib and trametinib in metastatic melanoma

Cancer Therapy: Clinical

Clinical Cancer Research

Tumor Regression and Growth Rates Determined in Five Intramural NCI Prostate Cancer Trials: The Growth Rate Constant as an Indicator of Therapeutic Efficacy

Wilfred D. Stein[1,3], James L. Gulley[2], Jeff Schlom[2], Ravi A. Madan[1,2], William Dahut[1], William D. Figg[1], Yang-min Ning[4], Phil M. Arlen[2], Doug Price[1], Susan E. Bates[1], and Tito Fojo[1,5]

Clinical Observations Tumour Burden Time-series

What have we learnt from decades of analysing tumour burden time-series data from clinical trials (1000s of patients time-series data)…

3. **Tumour burden is a time-dependent prognostic factor**
   - Probability of experiencing an event (progression/death) in a time interval (t, t+dt) is conditional on surviving up until that time window
   - Probability of surviving up until that time window is dependent on level of tumour burden leading up to that time-window

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Predictive value of serum CA-125 levels in patients with persistent or recurrent epithelial ovarian cancer or peritoneal cancer treated with bevacizumab on a Gynecologic Oncology Group phase II trial

Leslie M. Randall, MD[1], Michael W. Sill, PhD[2], Robert A. Burger, MD[3], Bradley J. Monk, MD[4], Barbara Buening, MD[5], and Joel I. Sorosky, MD[6]

Individual Prediction in Prostate Cancer Studies Using a Joint Longitudinal Survival–Cure Model

Menggang Yu, Jeremy M. G Taylor & Howard M Sandler

Let’s assume the perfect biomarker exists…

Tumour Burden – Time-dependent predictor of PFS/OS…

- What have people shown:

Semi-parametric Cox Model: $h(t) = h_0(t)e^{a_0 TB(t)}$

Parametric Survival Models: $h_0(t)$ – baseline hazard is replaced by numerous distributions – exponential, Weibull, log-normal etc.

Literature: coefficient a_0 good precision and is positive

- Over time your risk of experiencing an event (radiological progression/death) is proportional to the amount of tumour burden you have…
- Let's consider an individual patient…

Tumour Burden as a Time-Dependent Covariate

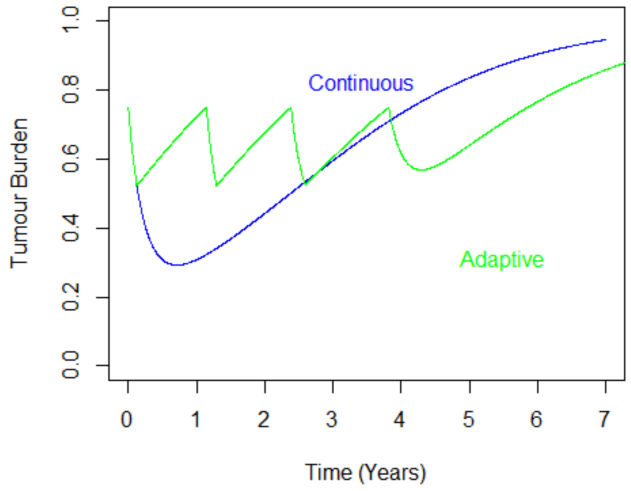
- Choice of dynamical model that generates time-series is irrelevant -

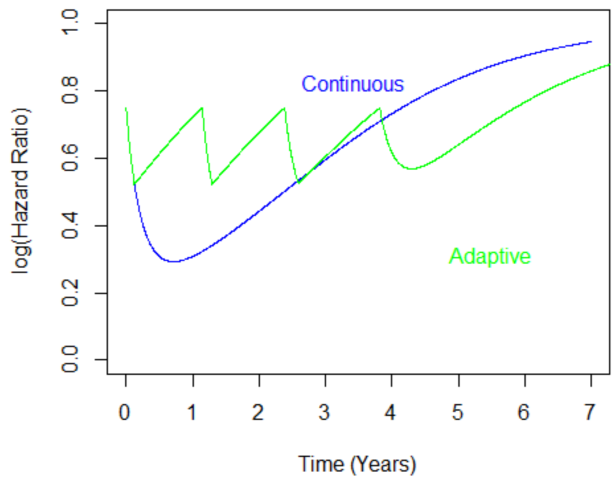
Y-axis is Tumour Burden

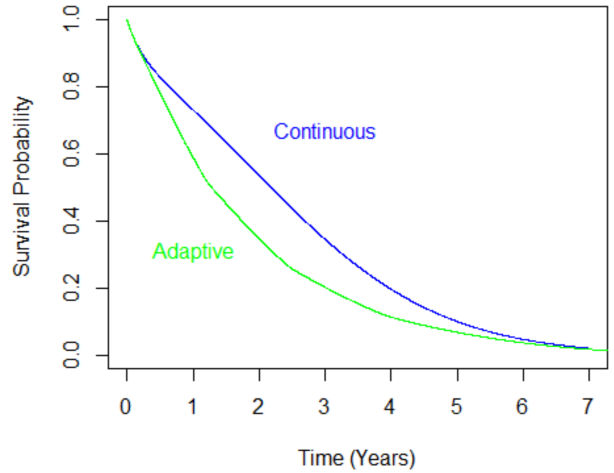
Tumour Burden is directly proportional to hazard

Y-axis is ~prob(event)

Simulate Literature Models linking TB to Events







When you link the output of the dynamical model to the survival models already established the optimal strategy is to reduce the tumour burden as quickly as possible and keep it low – continuous dosing!

Summary/Questions – ADT community

1. Why isn't there a randomized control trial exploring ADT?
   a) Public health is not going to benefit from lots of under-powered, poorly analysed small trials
2. Why aren't clinically relevant drug concentrations being used in preclinical experiments?
   a) For many oral targeted drugs resistance is occurring with concentrations order few 100 nM at most
3. Why does the community ignore literature analyses done for the last 20-30 years showing that tumour burden is a time-dependent prognostic factor when exploring theoretical models of ADT?
   a) Many papers provide mathematics/code etc. on how to combine tumour burden time-series with a time-to-event model
4. In the theoretical models why has the community not explored the known fact that treatment effect is not fully captured by any one single biomarker?
5. How does the community feel about the selection bias?
   a) Your hypothesis **MAY** only benefit 20-30% of patients who also happen to be the ones who benefit the most from continuous therapy

The scandal of poor medical research

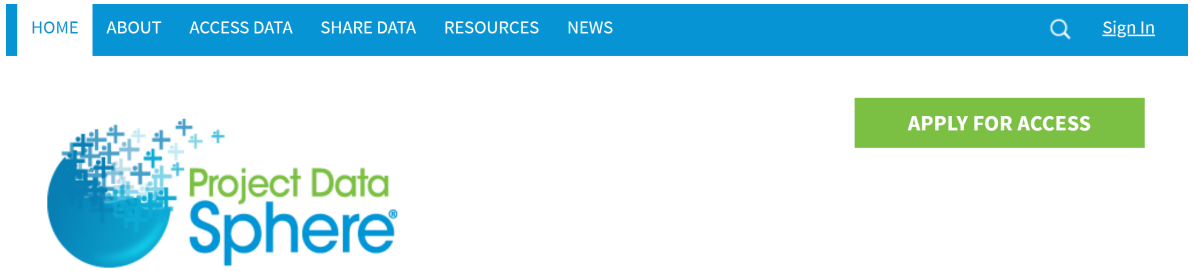
BMJ 1994 ; 308 doi: https://doi-org.manchester.idm.oclc.org/10.1136/bmj.308.6924.283 (Published 29 January 1994)

Cite this as: *BMJ* 1994;308:283

Doug Altman "What, should we think about researchers who use the wrong techniques (either wilfully or in ignorance), use the right techniques wrongly, misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions? We should be appalled. Yet numerous studies of the medical/scientific literature, in both general and specialist journals, have shown that all of the above phenomena are common. This is surely a scandal."

Useful links

Dedicated Oncology individual patient data from trials – amazing resource that is underused



Growing use of mathematical/statistical modelling in the NHS – annual conferences, workshops etc.