Phase 2 and 3 Immunotherapy Clinical Trials

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Disclosures

- Research support from Merck, Bristol-Myers Squibb

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- Research support from Merck, Bristol-Myers Squibb
- Nothing but grief from CTEP

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Disclaimer

There is no universal best practice for Phase 2 or 3 clinical trials.

- The design of any clinical trial is a function of:
  - The objective(s) of the trial;
  - The nature of the endpoint (e.g., efficacy is delayed);
  - The nature of the treatment (e.g., combination);
  - Existing pre-clinical data;
  - Existing clinical data;
  - Other treatments for the disease (e.g., SOC);
  - The applicable regulatory environment;
  - The treatment's developmental program.
- All of these issues must be considered when designing a specific trial.

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Whirlwind tour of Phase 2 and 3 trial designs for cytotoxics

By federal statute (Title 21 Part 312)), in the 1980-90's:

- Phase 1 trials assessed *safety*
- Phase 2 trials assessed *efficacy*
- Phase 3 trials *confirmed* safety and efficacy
- Phase 4 trials expanded labeleing

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Phase 2 and 3 designs for cytotoxics

- Phase 2
  - Single arm, single cohort (Gehan)
  - Single arm, two cohorts contingent on efficacy (Simon)
  - Single arm, continuous monitoring for safety and efficacy (Thall)
  - Sequential (seamless) Phase 1/2 and simultaneous Phase 1/2 (CRM-like)
  - Randomized
  - Umbrella and basket (Phase 2, 3 or 2/3)
- Phase 3
  - Randomized, maybe stratified, multi-center, generally with OS or PFS as primary endpoints
  - Group sequential (e.g., O'Brien-Fleming, Lan-DeMets)
  - Seamless Phase 2/3 (Berry)

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Sample sizes from the 1980-90s

Phase 1	Establish Safety	10s
Phase 2a	Identify Efficacy Signal	< 200
Phase 2b	Determine Dose	$200 - 1500$
	Study Special Populations	< 500
Phase 3	Confirm Safety & Efficacy (two independent trials)	$400 - 10000+$
Phase 4	Study Special Populations	< 1000
	Acquire New Labeling	$400 - 10000+$
	Promotion	Not Specified

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Faster tracks to market

Orphan, 1983 Treatment for rare diseases can be approved based on smaller (e.g., Single Arm Phase 2) trials

Fast Track, 1988 Treatment for life-threatening disease can be approved for marketing after single Phase 2 trial

Priority Review, 1992 Industry pays $$$ for accelerated paper-shuffling

Accelerated Approval, 1992 Treatment for life-threatening disease can be approved on basis of a surrogate endpoint

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Faster tracks to market (con't)

Breakthrough Therapy, 2012 Active FDA consultation throughout development program minimizes the number of trials

Rare Pediatric Disease Priority Review Voucher, 2014 Vouchers to sponsors of rare pediatric disease products for priority review of a subsequent marketing application for a different product.

21st Century Cures Act

- "Data summaries"
- "Real world evidence:" observational studies, insurance claims data, "patient input," anecdotal data

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Differences between cytotoxics and immunotherapies relevant to trial design

What features of immunotherapies make designs useful for cytotoxics *potentially* less efficient or invalid?

- Dose escalation until MTD may not be relevant
- Adverse events may be delayed in onset, and may be inconsistently reported
- Dose-response function may not be monotonic
- Relationship between duration of exposure and efficacy may be unclear
- Efficacy endpoints may be different (e.g., iRECIST, iiRC, PFS, time to next therapy)

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Differences between cytotoxics and immunotherapies relevant to trial design (con't)

What features of immunotherapies make designs useful for cytotoxics *potentially* less efficient or invalid?

- Clinical response may be significantly delayed
- Some patients may be "functionally" cured
- An immunotherapy may be combined with a cytotoxic or a second immunotherapy
- Phase 3 trial might be conducted after treatment acquires labeling or might not be conducted

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Reporting efficacy

- RECIST is commonly used to characterize response to chemotherapies, but has been challenged by immunotherapies
  - Tumors can continue to grow and even increase in growth rate before shrinking
  - New tumors may appear after treatment and then shrink or disappear
- These are not necessarily new problems; for example, pseudo-progression has long been recognized in brain tumors treated with RT
- Generally, progression needs to be confirmed; different criterial (e.g., iRECIST) have been proposed
- There are also statistical issues with reporting delayed clinical effects (see below)

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Reporting toxicity

- Immune-related adverse events (irAE)
  - Enterocolitis, hepatotoxicity, dermatitis, neuropathy, endocrinopathy
  - Different criteria for immune effector cells and checkpoint inhibitors
  - Not as specific as might be desired
- Immune-mediated adverse events (imAR)
  - Similar AEs grouped into contiguous events
  - Exclude grade 1
  - Include hepatic laboratory abnormalities of lower grades
  - Consideration of duration and concomitant medications
  - More complicated and more treatment-specific than irAE

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Reporting recommendations

- When possible, established reporting guidelines should be employed
- Modifications to published guidelines must be clearly stated
- Modifications must be clearly stated in trial protocols and those protocols should be available (clinicaltrials.gov)
- Meta-analyses should be approached with caution
- Multi-center trials from less resourced consortia should be approached with caution

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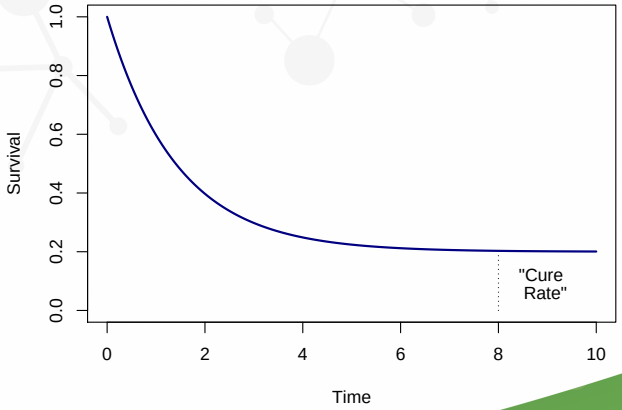
Cures

Patients who do not experience events in the feasible observation period may be considered “cured.”



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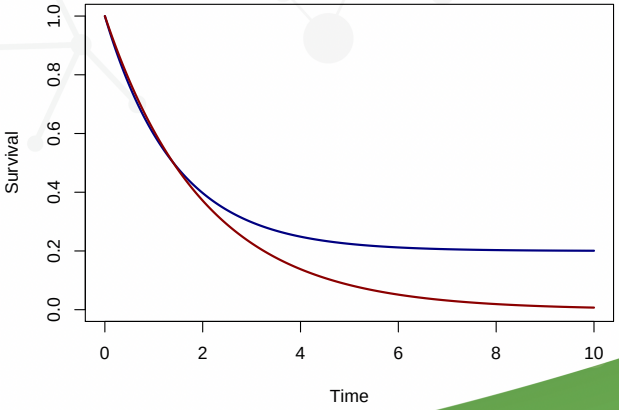
Cures

Survival functions with different probabilities of cure will likely violate the assumption of proportional hazards. This will induce statistical bias in Cox models and reduce the efficiency of the log-rank test.



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Cures

- The sample size may be too small
  - The statistical power of time-to-event analyses is a function of the number of observed events, and only indirectly of the sample size.
  - If the number of events is estimated based on the median survival when a significant proportion of patients experience functional cure, the power may be adversely affected.
  - In the graph above, both populations have a median survival of 1.4 years. At 5 years, the expected number of events out of 100 patients is 92 in the red population and 76 in the blue population.

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Cure model

- An obvious model to address this is to assume a proportion π of patients is cured (the "cure rate"), so that the survival function $S(t)$ is:

$$S(t) = \pi + (1 - \pi)S_U(t),$$

where $S_U(t)$ is a proper survival function for the "uncured" patients, say, exponential:

$$S_U(t) = e^{-\beta t} \Rightarrow S(t) = \pi + (1 - \pi)e^{-\beta t}$$

- This model, however, poses certain inferential problems (hazards are still not proportional), and a preferred model is the *promotion time cure model*.

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Promotion time cure model

- In the promotion time cure model (PTCM)[1], for the i^{th} patient,

$$S_i(t|\boldsymbol{x}_i) = \exp\{-\theta(\boldsymbol{x}_i)F(t)\},$$

  where θ is some function of the covariates (e.g., treatment assignment) and $F(t) = 1 - S^*(t)$ for some proper survival function $S^*(t)$
- This model will have proportional hazards if all the covariates are modeled through $\theta(\cdot)$, say,

$$\theta(\boldsymbol{x}_i) = \exp(\boldsymbol{x}_i'\boldsymbol{\beta})$$

- Noting that $\lim_{t\to\infty} F(t) = 1$, the probability of cure is:

$$\pi_i = \exp\{-\theta(\boldsymbol{x}_i)\} = \exp\{-\exp(\boldsymbol{x}_i'\boldsymbol{\beta})\}$$

[1] There are *many* variants

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PTCM

- $F(t)$ can be modeled by a parametric function (e.g., exponential, Weibull), or by a non-parametric function, as in a Cox model
- If $F(t)$ is parametric, then the model parameters can be estimated by the method of maximum likelihood
- The model parameters can also be estimated using Markov Chain Monte Carlo, if one is of the Bayesian persuasion

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PTCM

- If one is not of the Bayesian persuasion and one employs the exponential link function, as above, then the parameters of the PTCM can be estimated using proportional hazards (Cox) regression (PH).
  - Promotion time cure model:

$$S_{PTCM}(t|\boldsymbol{X}) = \exp\{-\exp(\boldsymbol{X}^T\boldsymbol{\beta}_{PTCM})\exp(\beta_{0,PTCM})F(t)\}$$

  - Proportional hazards regression:

$$h(t|\boldsymbol{X}) = \exp(\boldsymbol{X}^T\boldsymbol{\beta}_{PH})h_0(t)$$

- Then:

$$\begin{aligned}\hat{\boldsymbol{\beta}}_{PTCM} &= \hat{\boldsymbol{\beta}}_{PH}\\ \hat{\beta}_{0,PTCM} &= \log\{\hat{H}_{PH}(T_n)\},\end{aligned}$$

where $\boldsymbol{X} = \boldsymbol{0}_{n\times p}$ and T_n is the largest event time.

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Implementation of a basket trial

- A PTCM is nested in a hierarchical Bayesian framework in the basket trial HCC 19-135, "A randomized non-inferiority trial evaluating the length of treatment with PD-1/PD-L1 inhibitors in patients with advanced solid tumors" (PI: A. Wozniak)
- Randomize 578 patients who have already taken checkpoint inhibitors for 12 months to continue versus stop treatment 1:1
- The "treatment" is stopping the checkpoint inhibitor
- Primary endpoint: PFS

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Implementation of a basket trial (con't)

- Diseases with similar median PFS and estimated proability of cure define three disease groups:
  - 2^{nd}-line gastric and esophageal cancer, 2^{nd}-line bladder cancer, 2^{nd}-line NSCLC;
  - 2^{nd}-line anal cancer, 2^{nd}-line melanoma, 2^{nd}-line hepatocellular cancer, 2^{nd}-line renal cancer, 1^{st}-line triple-negative breast cancer;
  - 1^{st}-line melanoma, 1^{st}-line NSCLC, 1^{st}-line renal cancer.

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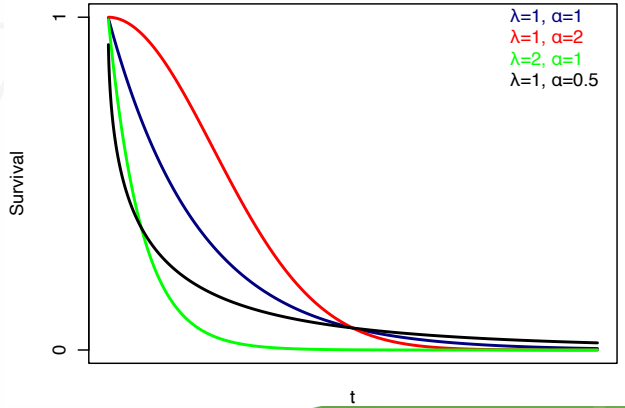
Implementation of a basket trial (con't)

The PTCM $S_i(t|\boldsymbol{x}_i) = \exp\{-\exp(\boldsymbol{\beta}'\boldsymbol{x}_i)(1 - S^*(t))\}$ is embedded in a hierarchical Bayesian framework:

- $S^*(t)$ is a Weibull distribution: $S^*(t\,|\,\lambda, \alpha) = e^{-e^{\lambda} t^{\alpha}}$



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Implementation of a basket trial (con't)

The PTCM $S_i(t|\boldsymbol{x}_i) = \exp\{-\exp(\boldsymbol{\beta}'\boldsymbol{x}_i)(1 - S^*(t))\}$ is embedded in a hierarchical Bayesian framework:

- $S^*(t)$ is a Weibull distribution: $S^*(t\,|\,\lambda, \alpha) = e^{-e^{\lambda} t^{\alpha}}$
- There are three disease clusters; the entries of $\boldsymbol{x}_i$ are $(0, 1)$ values indicating tumor type and treatment (I_t, I_1, I_2, I_3) snd $\boldsymbol{\beta}$ is written as $[\beta_1, \beta_2, \beta_3, \delta_1, \delta_2, \delta_3]$
- The covariates are:

$$\begin{aligned}\exp(\boldsymbol{\beta}'\boldsymbol{x}_i) \;=\; & \exp\{\beta_1(1 - I_t)I_1 + (\beta_1 + \delta_1)I_tI_1 + \\ & \beta_2(1 - I_t)I_2 + (\beta_2 + \delta_2)I_tI_2 + \\ & \beta_3(1 - I_t)I_3 + (\beta_3 + \delta_3)I_tI_3\}\end{aligned}$$

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Implementation of a basket trial (con't)

- The priors for the βs and δs, where $\mathcal{N}(\mu, \tau)$ indicates a normal distribution with mean μ and tolerance (1/variance), τ :

$$\beta_j : \mathcal{N}(0, 0.01) \quad \delta_j : \mathcal{N}(\delta, 0.01) \quad \delta : \mathcal{N}(0, 0.01)$$

- Priors for λ and α in $S^*(t \,|\, \lambda, \alpha)$ are also needed:

$$\lambda_j : \mathcal{N}(0, 0.1) \quad \alpha : \mathcal{G}(1, 1),$$

  where $\mathcal{G}(\cdot, \cdot)$ is the gamma distribution.
- The overall treatment effect is estimated by δ; at any time this quantity plus its 95% credible interval can be estimated.

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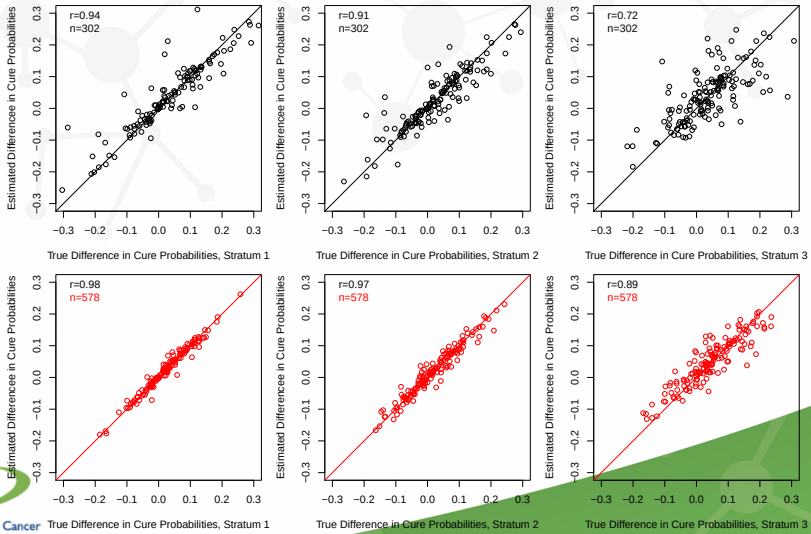
Implementation of a basket trial (con't)

Fragment of trial simulations:



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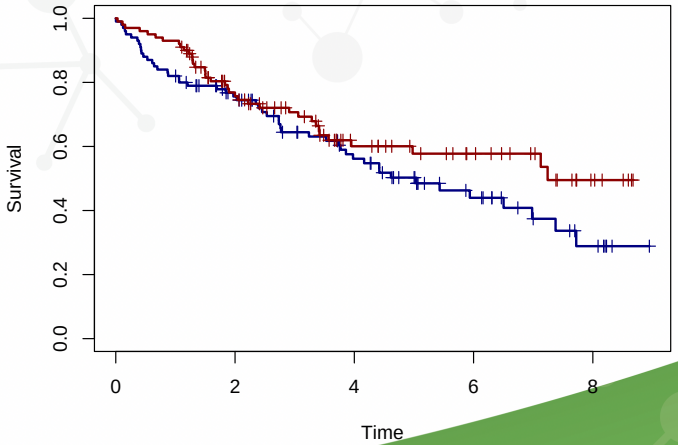
PTCM

- While it has been asserted that there is a loss of power and increase in bias when a PTCM model is employed when there are no cures, I have not seen anything more than assertions
- Monte Carlo simulation can be used to study these issues as designs are developed

Delayed efficacy

A delay in treatment activity will cause a delayed divergence in the survival curves, which will manifest as non-proportional hazards:



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Delayed efficacy

- Non-proportional hazards
  - Bias the tests in Cox models
  - Reduce the power of log-rank tests used to compare Kaplan-Meier curves
- Weighted log-rank give different weights $w(t)$ to events occurring earlier or later in the series
  - Weighting function should be pre-specified to preserve Type 1 error (however, see below)
  - Over-weighting earlier events can be useful when there are expected to be significant dropouts
  - When efficacy is delayed, later events are over-weighted

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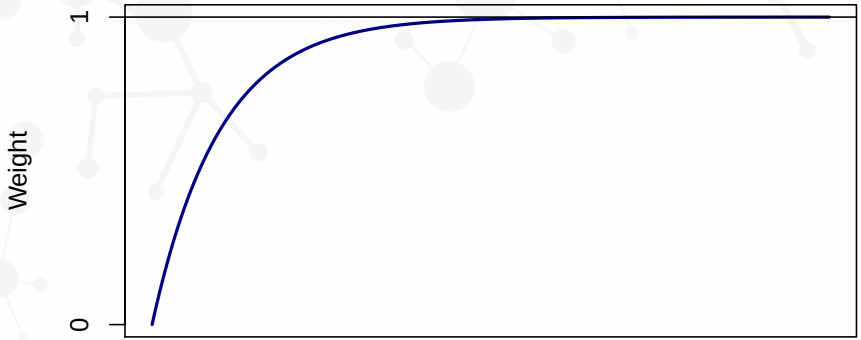
Weighting for delayed efficacy

Later events are weighted higher in the log-rank test:



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Time-varying treatment effects in Cox models

- In the standard proportional hazards (Cox) model, the hazard function of the i^{th} participant is:

$$h(t|\boldsymbol{x}_i) = h_{\circ}(t)e^{\boldsymbol{\beta}'\boldsymbol{x}_i},$$

  where $\boldsymbol{x}_i$ are the covariates for the i^{th} partipant.

- In the weighted Cox model, a weight function independent of i multiplies the covariate cross-product:

$$h(t|\boldsymbol{x}_i^*) = h_{\circ}(t)e^{A(t)\boldsymbol{\beta}'\boldsymbol{x}_i},$$

  where $A(t) = w(t)/\max(w(t))$ of the weight function $w(t)$ used in the weighted log-rank test.

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Time-varying treatment effects in Cox models

- The Cox model specified by the hazard function:

$$h(t|\boldsymbol{x}_i) = h_o(t)e^{A(t)\boldsymbol{\beta}'\boldsymbol{x}_i},$$

  is a proportional hazards regression model with time-varying covariates and can be analyzed by standard software (e.g., R, SAS Stata).

- If we write $X^*(t) = A(t)\boldsymbol{x}_i$, and

$$h(t|\boldsymbol{x}_i) = h_o(t)e^{\boldsymbol{\beta}'\boldsymbol{x}_i^*(t)}$$

  then the component of $\boldsymbol{\beta}$ corresponding to treatment assignment represents the difference between treatments in the maximum effects.

- If the weighting model is correct, the corresponding score test has optimal power.

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Time-varying treatment effects in Cox models

- The Schoenfeld residuals from a Cox regression can be inspected to determine if the assumption of proportional hazards has been grossly violated
- The optimality of power cannot be asserted if the model is not "correct," but it is not clear how to choose the "correct" model
- It is asserted that even a "pretty good" weighting model will be better than an unweighted model when there is a known delay in efficacy
- The robustness of any assumption should be tested in simulations

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Interim analyses for efficacy or futility

- Pocock and O'Brien-Fleming interim analyses are generally performed at some proportion (e.g., $1/2$) of the information (number of events) that will be accrued if the trial is brought to full term.
- Both delayed effect and functional cure can disrupt the assumed connection between information and sample size.
- Error spending (e.g., Lan & DeMets) is more flexible
- Care must be exercised in either case to avoid excessive false-positive and false-negative conclusions

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Combination trials

- Attribution and mitigation strategies may be complicated and impede interpretation of results
- Increasingly complex treatment regimens defy simple analyses
- Now, there is no simple modeling fix for these issues. This could change

Brisk conclusion

- Assumptions made for traditional (80s-90s) trial designs may be violated by immunotherapies
- Differences in reporting of adverse events and toxicities may make comparisons across trials and meta-analyses risky
- Bayesian methods may be more flexible and robust than frequentist group sequential design
- Monte Carlo simulations should be used to determine the robustness of any design against departures from assumptions
- Different primary endpoints and statistical models may be required when testing treatments with delayed effect and/or functional cures

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References

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- Weighted log-rank test: Chen T (2013) Statistical Issues and Challenges in Immuno-Oncology. *JITC* 1:18.
- Promotion time cure model: Amico M & Van Keilegom I (2018) Cure Models in Survival Analysis. *Annual Review of Statistics and Its Application* 5:311–42.
- irAE: Postow M, Sidlow R & Hellman M (2018) Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. *NEJM* 378: 158-68.
- Criteria for reporting: see links, above

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Footnote

Wretched habits from the Reagan era:

- Trickle-down economics
- No matter what CTEP says, the 3+3 dose-escalation design is a bad idea for cytotoxics and an even worse idea for immunotherapy
- A 6-patient run-in is an utter waster of time
- Fifteen-patient expansion cohorts are intellectually lazy, you're better than that

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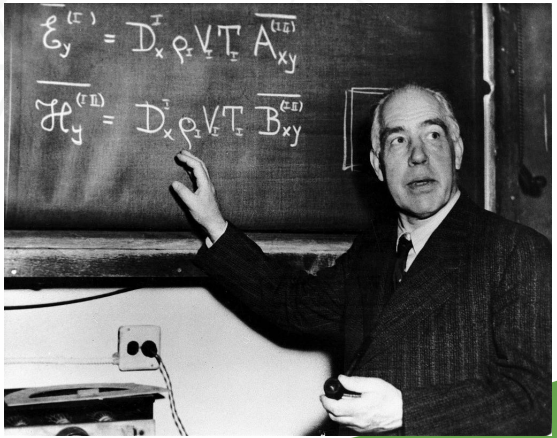
Other footnote

Prediction is difficult, especially about the future.

–Niels Bohr (1885-1962)



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