CREDIT SUISSE

Mistakes and casualties in biotech or "Why we are so dumb"

Cancer Progress

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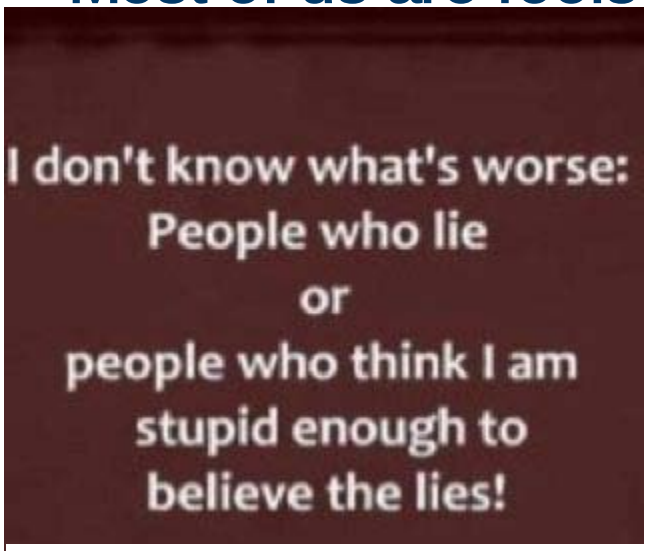
Confidential
March 7, 2017

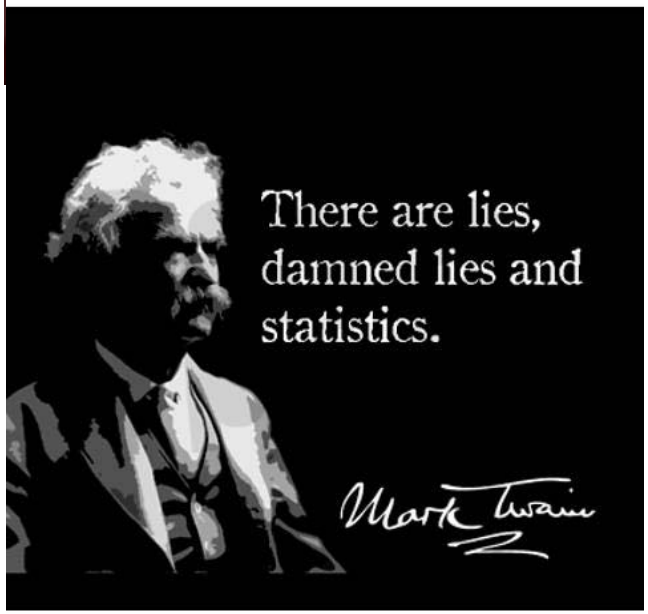
Most of us are fools



"In expert tennis, 80 percent of the points are won, while in amateur tennis, 80 percent are lost. The same is true for wrestling, chess and investing: Beginners should focus on avoiding mistakes, experts on making great moves." -- Erik Falkenstein

"No one can foresee the consequences of trivia and accident, and for that reason alone, the future will forever be filled with surprises." -- Dan Gardner

“The stock market is filled with individuals who know the price of everything, but the value of nothing.”
– Phillip Fisher



”People are too stupid to know how dumb they really are”
@GSElevator

“The four most dangerous words in investing are: ‘this time it’s different.’”
– John Templeton

“The book of Genesis says of the Flood that “… all the high hills that were under the whole heaven were covered…” Taken literally, this seems to indicate that there were 10,000 to 20,000 feet of water on the surface of the earth, equivalent to more than half a billion cubic miles of liquid! Since, according to biblical accounts, it rained for forty days and forty nights, or for only 960 hours, the rain must have fallen at a rate of at least fifteen feet per hour, certainly enough to sink any aircraft carrier, much less an ark with thousands of animals on board.”
— John Allen Paulos, Innumeracy: Mathematical Illiteracy and Its Consequences

Diligence is challenging

"Tell me where I'm going to die, so I won't go there…"

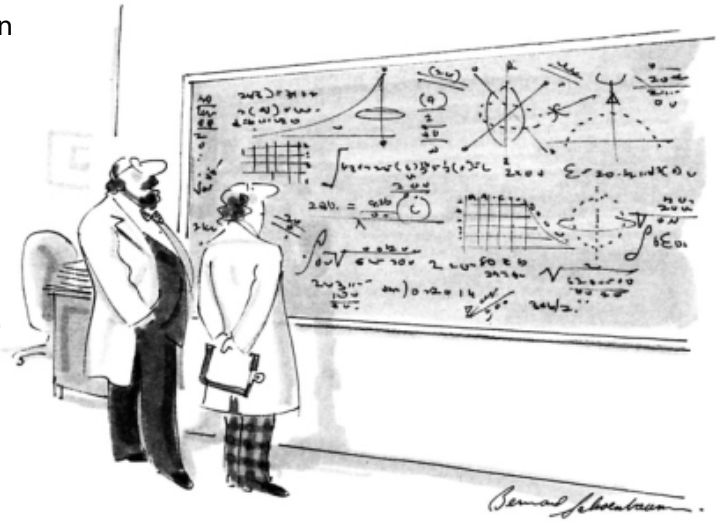
Typical mistakes

R&D/ technical

- Nonclinical: misunderstanding of science / mechanism / toxicology, CMC
- Seller may not be transparent on all information
- Clinical / observational trials: results not put in context, population not examined for representativeness, sanctity of data put aside
- Clinical / comparative trials: multiplicity error ignored, biomarkers pursued recklessly, biases not fully taken into account (e.g., ascertainment, selection, publication), missing data not treated conservatively
- Regulatory: FDA suggestions / correspondence ignored

Commercial and strategic assessment

- Errors of commission from:
  - Overly optimistic market builds
  - Overlooking competition / disruptive new entrants
  - Misevaluating sustainability of seller's aggressive marketing practices
  - Being overly driven to "do something"
- Errors of omission from:
  - Risk aversion / conservatism (e.g., with IP)
  - Consensus driven decision making
  - R&D not separated enough from BD
  - Lack of senior involvement in process till end



"Way too much information—just say that we successfully reached all endpoints."

Smoke and mirrors in data reporting and trial design

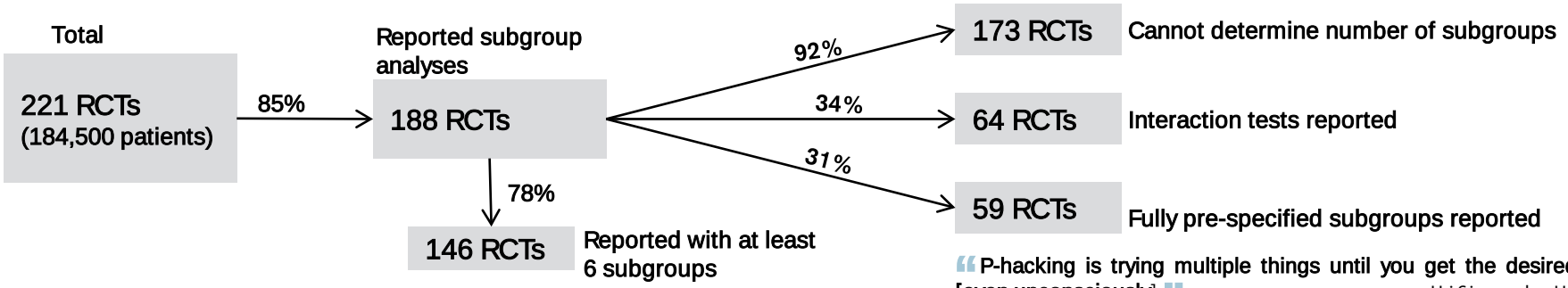
Companies are not transparent with information[1]

(n=61) Comparison of FDA letters with public announcements	% of FDA letters
Overall public statements about FDA decisions that are accurate	14%
Efficacy-related statements in CRL press releases that are accurate	16%
Safety-related statements in CRL press releases that are accurate	15%
Press releases not issued for CRL's	18%
Press releases that **do not include any statements that match the statements** included in the CRL	21%
CRLs that **include a new clinical trial requirement that reported the recommendation policy**	59%

Uncontrolled trials generally overestimate a drug's effect

	Identical chemotherapeutic agents	
	Phase 2	Phase 3
# of studies	49	43
Mean # of patients enrolled	52	363
% randomized	4%	100%
Mean RR[2] (range)	43.2 (16%–87%)	34.2 (11%–86%)

Overuse and lack of clarity of subgroup analyses[3]



"P-hacking is trying multiple things until you get the desired result [even unconsciously]." – Uri Simonsohn, Upenn
"Torture the data enough and it will confess"

Misunderstanding evidence leads to a porous drug filter

Symptoms

- Belief in past techniques (non-predictive, preclinical models, historical controls, invalidated biomarkers, retrospectively derived analyses, …)
- Prioritization of timelines/costs over definitive results
- The desire to avoid negative results overrides that of getting the right answer
- Easily "fooled by randomness"

Signs include

- Many publications of small, inconclusive P2 clinical trials
- Studies often not leading to additional definitive randomized controlled studies
- High P3 failure rate (for those trials that do lead to P3)

Source: Zia et al JCO 23 October 1, 2005 p. 6982-6991 and Ratain, AACR-NCI-EORTC 2007.
(1) BMJ 2015;350:h2758; doi: 10.1136/bmj.h2758, 8 April 2015.
(2) Reported response rate.
(3) Source: Zhang et al JCO 20 May, 2015 p. 1697-1702.

Uncontrolled studies do have some advantages over RCTs

Evaluation Characteristics	Randomized Controlled Study	Statistical Process Control
• Show treatment effect not due to chance	• Large sample size	• Dramatic sequential change (eg rabies)
• Causation	• Randomization	• Plausible process change which can be replicated
• Use of knowledge from prior trials	• Not used	• Used
• Ease of recruitment/ ethics/ cost	• Difficult when placebo is known to fail; $$$	• More straightforward, $
• Speed of answer	• Typically years	• Fast if dramatic (one patient?)
• Biases?	• Less an issue IF well conducted and communicated. Often see ascertainment bias, data dredging, missing data, wrong controls	• Many, especially selection and investigator biases, so need to “raise the bar”

Qual Saf Health Care 2005, Diaz

What is Dramatic?

Metrics

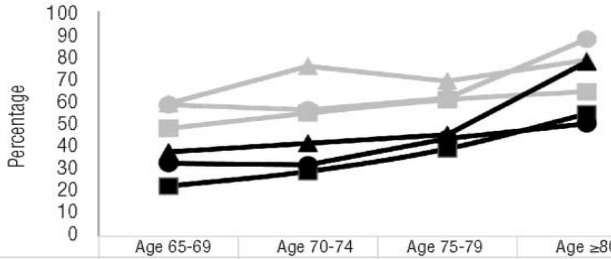
KOL opinion– "this is better than anything I have ever seen." SENSITIVE, NOT SPECIFIC

Prognostic criteria—"this is better than what would be expected of the best prognostic group in this cancer."

Statistical—Shewhart control charts; binomial distribution

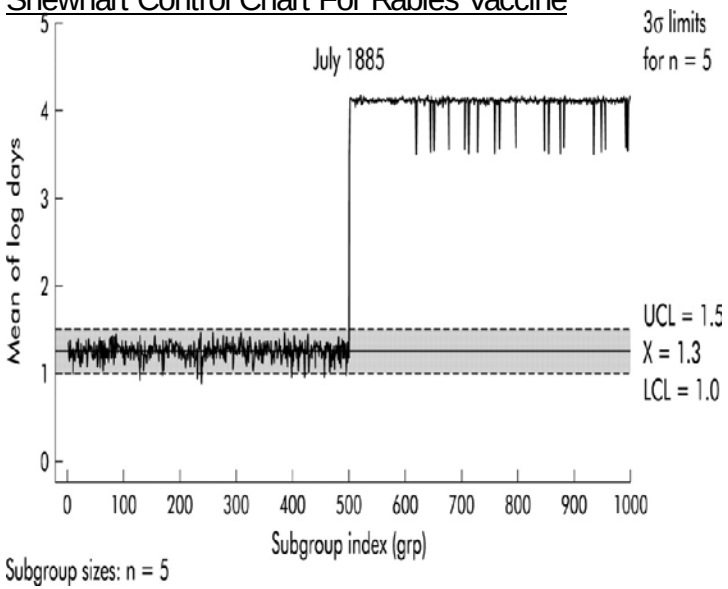
Apples to apples—how does this compare with other small, single arm studies?—POWERFUL METHOD

AML early death rate by age, prognostic criteria, therapy



	Age 65-69	Age 70-74	Age 75-79	Age ≥80
No therapy, CCI=0	47.9	54.7	60.7	64.3
No therapy, CCI=1	58.5	56.1	61.5	87.8
No therapy, CCI=2	58.9	75.6	69	78.3
Therapy, CCI=0	22.3	28.8	38.9	54.4
Therapy, CCI=1	32.4	31.8	43.4	50
Therapy, CCI=2	37.5	41.3	45.2	77.5

Shewhart Control Chart For Rabies Vaccine



Small p2 trials CRPC circa 2007

Drug	# patients, prior therapy	PSA response >50%, median durability	Recist response
Ketoconazole	38, naïve to taxanes	55%, 6 months	0
Satraplatin	39, naïve to taxanes	26%	0
Abireterone	33 naive 47 + prior taxanes	88% 51%	NR 27%

So was I right???