The role of Single Arm Trials in Oncology Drug Development

EMA-ESMO Workshop on single-arm trials for cancer drug market access
30th June 2016

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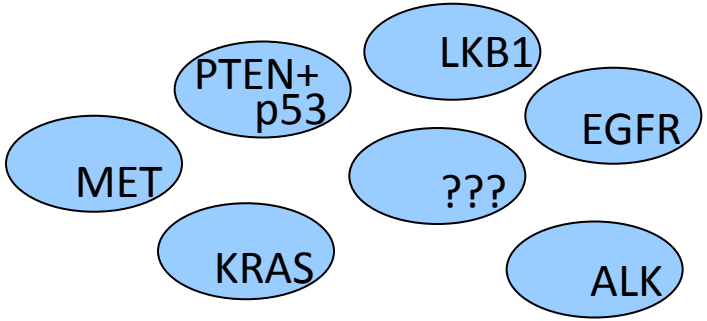
Challenges with "old paradigm"



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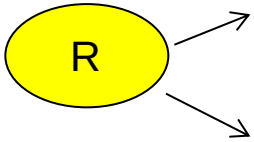


Platinum doublet

Platinum doublet
+ drug X

HIGH RISK
"FAILURE" OR
DETECTION
CLINICALLY SMALL
EFFECT

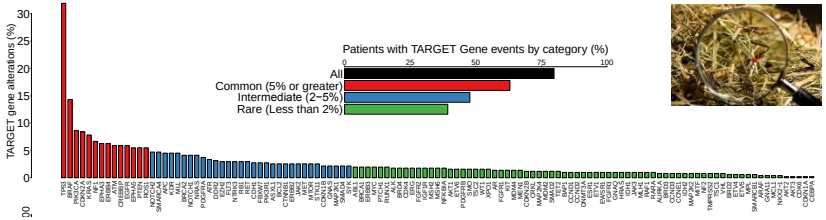
Challenges with "new paradigm"

ROS1 → Targeted Therapy

Large Magnitude, Durable ORR

N=50-200

1. Feasibility of screening/enrolling pts for RCT?



2. Equipoise Lost?

The New York Times
September 18, 2010

New Drugs Stir Debate on Rules of Clinical Trials
By AMY HARMON

> "But critics of the trials argue that the new science behind the drugs has eclipsed the old rules — and ethics — of testing them. They say that in some cases, drugs under development, PLX4032 among them, may be so much more effective than their predecessors that putting half the potential beneficiaries into a control group, and delaying access to the drug to thousands of other patients, causes needless suffering."

Clinical Equipoise: the assumption that there is no one "better" intervention (experiment vs control) present during the design of an RCT

When there is no clinical equipoise, should a RCT be conducted?
Who is "requiring" these RCTs? Regulators? Payers? Drug Sponsors (competitive advantage)?

When may randomized controlled trials be unnecessary?

Hazardous journeys

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

BMJ 2003; 327:1459

Unprecedented effects vs. historic control

- Penicillin for CAP
- Insulin for diabetes
- Multi-agent chemo for testicular cancer

Cautionary tale: autologous SCT for Metastatic Breast Ca

Objective Response Rate (ORR) in Single arm Trials (SAT) for regulatory approval

- Large magnitude, durable ORR
- Why ORR and not PFS or OS?
  - Tumor regression directly attributable to the drug(s)
    - Spontaneous remission- rare to non-existent
    - Historical control: 0%
  - "prolonged" Stable Disease, PFS or OS in a single arm study could be due to natural history of the tumor and not the intervention

The Role of Nonrandomized Trials in the Evaluation of Oncology Drugs

R Simon[1], GM Blumenthal[2], ML Rothenberg[3], J Sommer[4], SA Roberts[5], DK Armstrong[6], LM LaVange[2] and R Pazdur[3]

- The mechanism of action is supported by strong scientific rationale and/or preclinical data
- The drug is intended for a well-defined patient population
- The drug produces substantial, durable tumor responses that clearly exceed those offered by any existing available therapies
- The benefits outweigh the risks
- Randomization is unethical or infeasible

Clin Pharm and Ther, 97:502-507

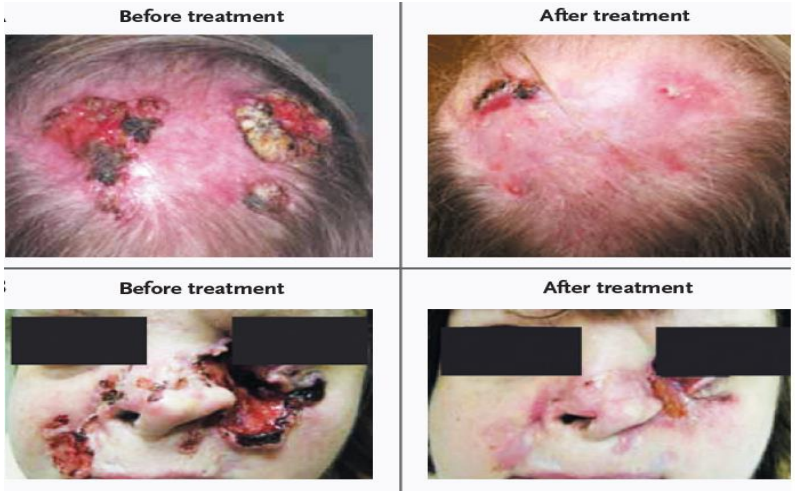
Accelerated Approvals based on ORR in SAT- partial list

Drug	Disease	N	ORR (95% CI)	CR	mDOR (months)	Year	NME?
Imatinib	CML-CP	532	88	16	NA	2001	Y
	CML-AP	235	63	4	NA		
	CML-BP	260	25	1	NA		
Brentuximab Vedotin	Hodgkin	102	73 (65,83)	32	6.7 (4,14.8)	2011	Y
	ALCL	58	86 (77,95)	57	12.6 (5.7,NE)		
Crizotinib	ALK+ NSCLC	136	50 (42,59)	<1	9.6 (1.4,9.7)	2011	Y
	ALK+ NSCLC	119	61 (52,70)	<1	11.1 (0.9,17.6)		
Osimertinib	EGFR T790M	411	59 (54,64)	<1	12.4	2015	Y
Ceritinib	ALK+ NSCLC (2L)	165	44 (36,52)	2.5	7.1 (5.6, NE)	2014	Y
Alectinib	ALK+ NSCLC (2L)	87	38 (28,49)	NA	7.5 (4.9, NE)	2015	Y
	ALK+ NSCLC(2L)	138	44 (36,53)	NA	11.2 (9.6, NE)		
Pembrolizumab	PDL1+ NSCLC (2L)	61	41 (29,54)	0	44% >6m	2015	N
Daratumumab	Myeloma (4L)	106	29 (21,39)	0	7.4	2015	Y
Ibrutinib	Mantle Cell	111	66 (56,75)	17	17.5 (15.8,NR)	2016	N

Traditional approvals based on ORR in SAT- partial list

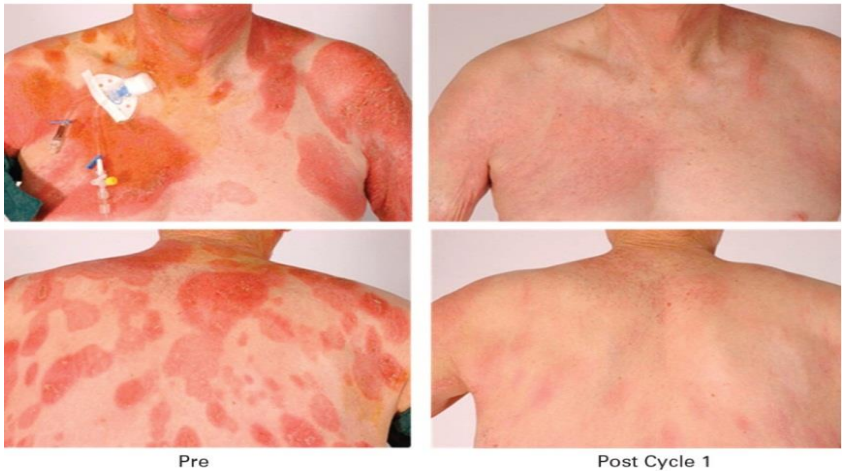
Drug	Disease	N	ORR (95% CI)	CR %	mDOR (months)	Year	NME?
Bexarotene	CTCL	62	32	2		1999	Y
Imatinib	DFSP	18	83	39	6.2	2006	N
	HES/CEL	176	74	61	1.5+ to 44		
	ASM	28	61	29	1 to 30		
	MDS/MPD	31	84	45	4.6+ to 15+		
Vorinostat	CTCL	74	30		5.6	2006	Y
Vismodegib	mBCC	33	30 (16,48)	0	7.6 (5.6,NE)	2012	Y
	laBCC	63	43 (31,56)	21	7.6 (5.7,9.7)		
Bosutinib	CML (2L)	503	53		18	2012	Y
Denosumab	GCTB	187	25 (19, 32)	0	>8 months	2013	N
Crizotinib	ROS1 NSCLC	50	66 (51,79)	2	18.5	2016	N

ORR as a measure of direct clinical benefit



Vismodegib Response

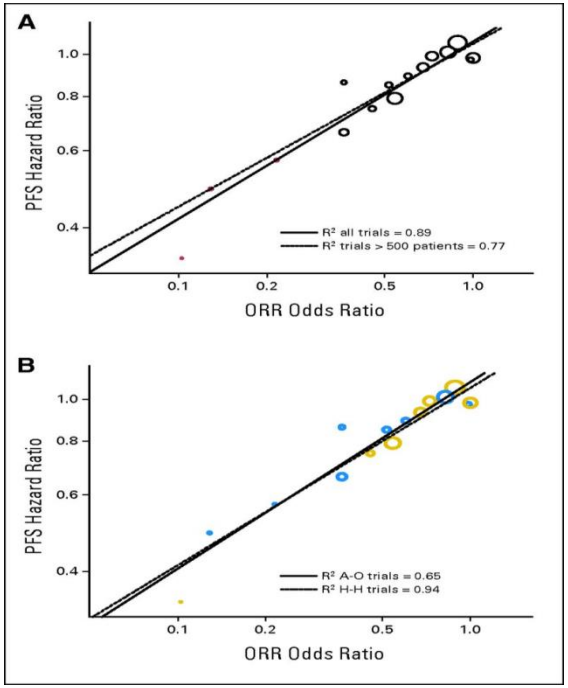
Von Hoff et al., NEJM, 2009; 361: 1164-72

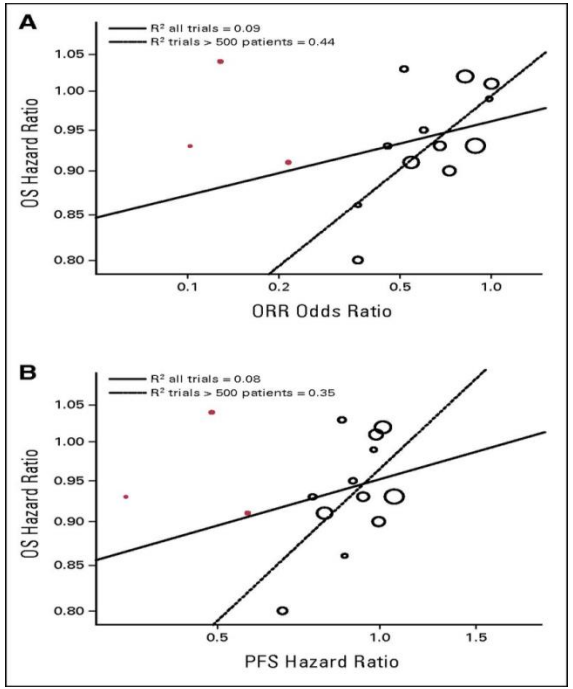


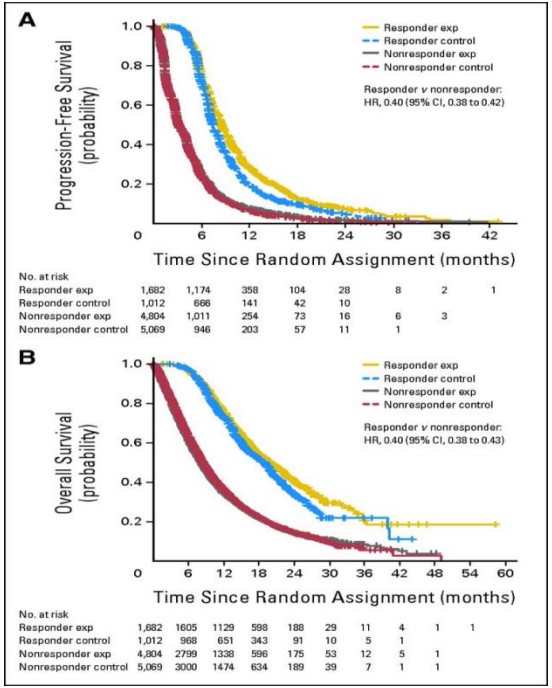
Romidepsin Response

Piekarz et al., JCO, 2009; 27: 5410-5417

FDA meta-analysis of 14 trials, >14,000 patients: ORR strongly associated with PFS on trial level







Blumenthal GM, Karuri S, Zhang H, Zhang L, Khozin S, Kazandjian D, Tang S, Sridhara R, Keegan P, Pazdur R. J Clin Oncol. 2015 Mar 20;33(9):1008-14.

Prognosis in biomarker-selected subsets

Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring *ALK* gene rearrangement: a retrospective analysis

Alice T Shaw, Beow Y Yeap, Benjamin J Solomon, Gregory J Riely, Justin Gainor, Jeffrey A Engelman, Geoffrey I Shapiro, Daniel B Costa, Sai-Hong I Ou, Mohit Butaney, Ravi Salgia, Robert G Maki, Marileila Varella-Garcia, Robert C Doebele, Yung-Jue Bang, Kimary Kulig, Paulina Selaru, Yiyun Tang, Keith D Wilner, Eunice L Kwak, Jeffrey W Clark, A John Iafrate, D Ross Camidge

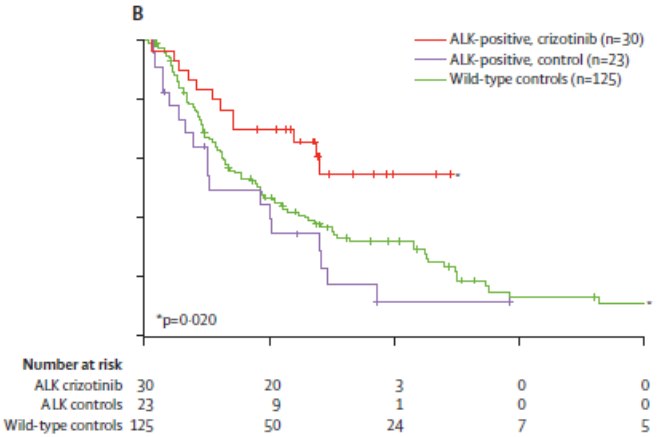
Summary

Background *ALK* gene rearrangement defines a new molecular subtype of non-small-cell lung cancer (NSCLC). In a recent phase 1 clinical trial, the ALK tyrosine-kinase inhibitor (TKI) crizotinib showed marked antitumour activity in patients with advanced, ALK-positive NSCLC. To assess whether crizotinib affects overall survival in these patients, we did a retrospective study comparing survival outcomes in crizotinib-treated patients in the trial and crizotinib-naive controls screened during the same time period.

Methods We examined overall survival in patients with advanced, ALK-positive NSCLC who enrolled in the phase 1 clinical trial of crizotinib, focusing on the cohort of 82 patients who had enrolled through Feb 10, 2010. For comparators, we identified 36 ALK-positive patients from trial sites who were not given crizotinib (ALK-positive controls), 67 patients without *ALK* rearrangement but positive for *EGFR* mutation, and 253 wild-type patients lacking either *ALK* rearrangement or *EGFR* mutation. To assess differences in overall survival, we assessed subsets of clinically comparable ALK-positive and ALK-negative patients.

Findings Among 82 ALK-positive patients who were given crizotinib, median overall survival from initiation of crizotinib has not been reached (95% CI 17 months to not reached); 1-year overall survival was 74% (95% CI 63–82), and 2-year overall survival was 54% (40–66). Overall survival did not differ based on age, sex, smoking history, or ethnic origin. Survival in 30 ALK-positive patients who were given crizotinib in the second-line or third-line setting was significantly longer than in 23 ALK-positive controls given any second-line therapy (median overall survival not reached [95% CI 14 months to not reached] *vs* 6 months [4–17], 1-year overall survival 70% [95% CI 50–83] *vs* 44% [23–64], and 2-year overall survival 55% [33–72] *vs* 12% [2–30]; hazard ratio 0·36, 95% CI 0·17–0·75; p=0·004). Survival in 56 crizotinib-treated, ALK-positive patients was similar to that in 63 ALK-negative, EGFR-positive patients given EGFR TKI therapy (median overall survival not reached [95% CI 17 months to not reached] *vs* 24 months [15–34], 1-year overall survival 71% [95% CI 58–81] *vs* 74% [61–83], and 2-year overall survival 57% [40–71] *vs* 52% [38–65]; p=0·786), whereas survival in 36 crizotinib-naive, ALK-positive controls was similar to that in 253 wild-type controls (median overall survival 20 months [95% CI 13–26] *vs* 15 months [13–17]; p=0·244).

Interpretation In patients with advanced, ALK-positive NSCLC, crizotinib therapy is associated with improved survival compared with that of crizotinib-naive controls. *ALK* rearrangement is not a favourable prognostic factor in advanced NSCLC.



Need large, high quality registries to provide useful prognostic information (e.g. French NSCLC registry)

Reasons for discomfort with SAT

- Fear of “cherry picking” patients
  - Randomization addresses known and unknown bias
- Fear of “dialing up the dose” to get a response but compromising long term toxicity
- Lack of comparative safety data
- Limited data on prognosis in a biomarker defined subset

When are RCTs necessary to assess benefit-risk?

- The majority of cases
- When the response rate/ durability is mild to modest
  - Cytostatic or immunologic MOA
- Highly toxic/ poor understanding of toxicity
- Lack understanding of the natural history of the disease
- When the biomarker strategy has not been optimized
- Settings with plethora of available, effective therapies

Recent challenges with SAT (#1)

- Rociletinib- 3rd generation EGFR T790M TKI
  - Key Uncertainties:
    - dose: 500mg BID vs 625 mg BID
    - efficacy: ORR and DoR better than available therapy?
    - safety: risk of QTc prolongation leading to Torsades de pointes and cardiac death (particularly in NAT2 slow acetylators)
  - April 2016: ODAC voted 12 to 1 to recommend postponing approval decision until results of RCT reported

Recent challenges with SAT (#2)

- Ponatinib – 3rd generation TKI CML/ Ph+ALL (including T315I)
  - December 2012: accelerated approval CML resistant to prior TKI or PH+ALL resistant to TKI based on SAT
  - October 2013: Sponsor announced temporary suspension of marketing for implementation of risk mitigation strategy and updates to PI to convey increased risk of cardiovascular AEs, including vascular and arterial occlusions
  - December 2013: Sponsor announced resumption of marketing with new safety measures to address risk of serious cardiac AEs

Alternate Designs

- Adaptive randomization (e.g. I-SPY2)
- Randomized dose finding trials
- Pragmatic “real world” RCTs
- Master protocols: multiple novel agents against standard of care (pair-wise comparisons)

Responses may be qualitatively or quantitatively different but still "Partial Responses" by RECIST

Response seen from across the room

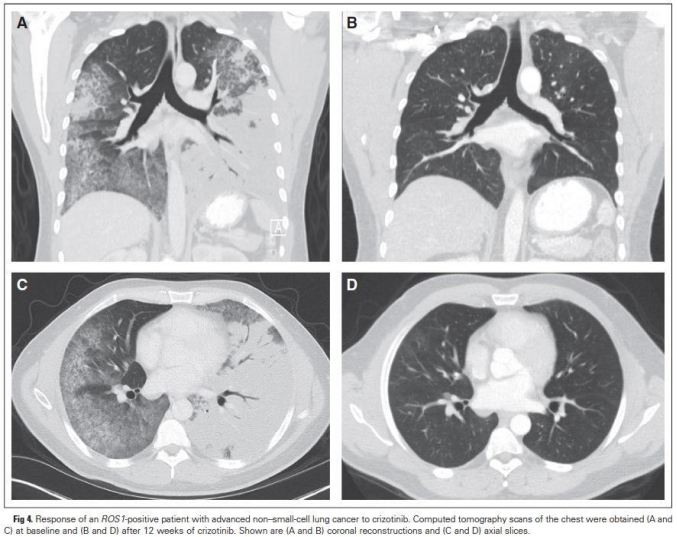
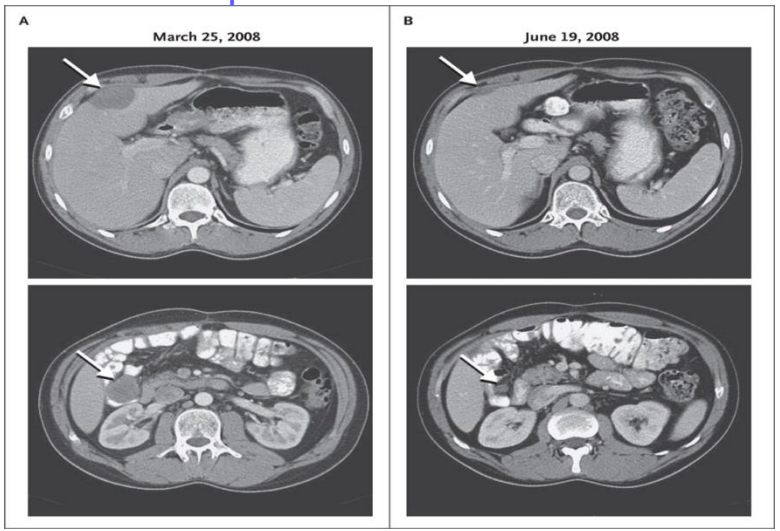


Fig 4. Response of an *ROS1*-positive patient with advanced non–small-cell lung cancer to crizotinib. Computed tomography scans of the chest were obtained (A and C) at baseline and (B and D) after 12 weeks of crizotinib. Shown are (A and B) coronal reconstructions and (C and D) axial slices.

Bergethon et al., JCO, 2012; 30(8): 863-70

Response where you need an arrow to point it out



Butrynski et al., NEJM, 2010; 363: 1727-1733

Parting Thoughts

- ORR of large magnitude and durability in SAT is established mechanism for approval (accelerated and in some cases traditional) in oncology
- Majority approved based on ORR are “breakthrough”, transformative
- ORR in SAT limitations: optimizing dose, optimizing biomarker strategy, and assessing safety
- Big data/ data sharing/ master protocols necessary to pool resources, drive down cost, and study rare and underserved subsets of patients
- Alternate trial designs should be utilized (e.g. common control, randomized dose finding, pragmatic RCTs)
- Alternate metrics for response needed (depth, durability, volume)
- Need global discussion (regulatory bodies, payers, national institutes) to decrease number of RCTs where equipoise is lacking

Thank You

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