Session 2: Case Studies and Lessons Learned From Recent Experiences- Reaction

The Drug Development Paradigm in Oncology: A Workshop
The National Academies of
*Sciences * Engineering * Medicine*
#OncologyDrugDev

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Highly effective drugs in refractory cancers: Do randomized controlled trials versus chemo always make sense?

- FDA oncology has long track record of accelerated (and sometimes full approval) based on ORR/DoR in single arm trials
- When is a RCT versus an incumbent, marginal, toxic control not necessary?[a,b]
- When is equipoise lost?[c]
- Who is mandating these types of RCTs?
    - FDA often gets blamed, but we often take activist role in ensuring flexibility (PFS vs OS, allowing cross-over, earlier looks at data leveraging known P2 data)
- Can RWE play a role for post-marketing studies?

[a]Blumenthal GM, Pazdur R: Response rate as an approval endpoint in oncology: Back to the Future. Jama Oncol 2016

[b]Simon R, Blumenthal GM, Rothenberg M, et al: The role of nonrandomized trials in the evaluation of oncology drugs. Clin Pharmacol Ther 2015

[c]Harmon A. New Drugs Stir Debate on Rules of Clinical Trials. New York Times; Sept 18, 2010

Balancing speed, quality of evidence, risk, and access

- Rociletinib ODAC[a]:
  - Use of unconfirmed ORR[b]
  - dose finding not optimal (e.g. 500 mg bid vs 625 bid)
  - Pharmacogenomic interaction leading to increased exposure to toxic metabolite (particularly NAT2 slow acetylators)
    - Increased QTc risk→ increased risk of torsades or other serious ventricular arrhythmia
- Many other drugs approved with uncertainties (dose/schedule), optimal biomarker, etc., etc.

[a]http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM494782.pdf

[b]Sequist LV, Soria JC, Camidge DR. Update to Rociletinib Data with the RECIST Confirmed Response Rate. NEJM 2016; 374:2296-2297

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

Response seen from across the room

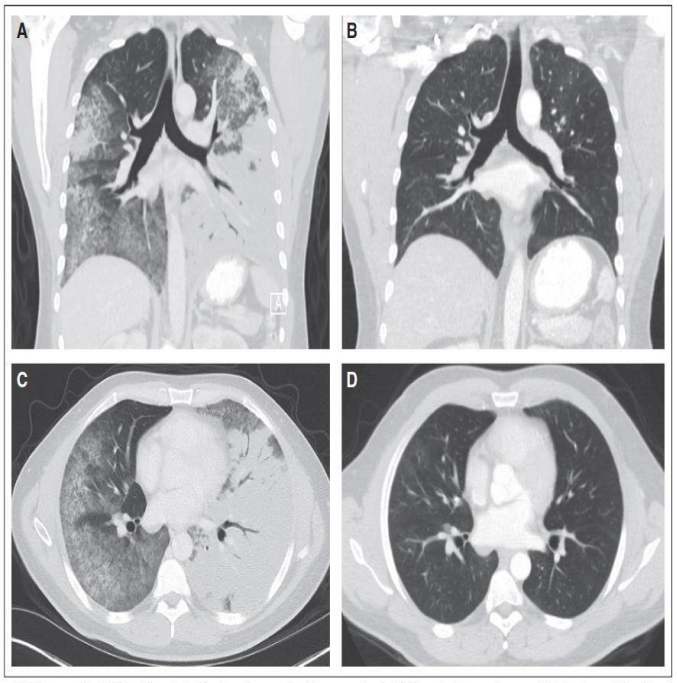
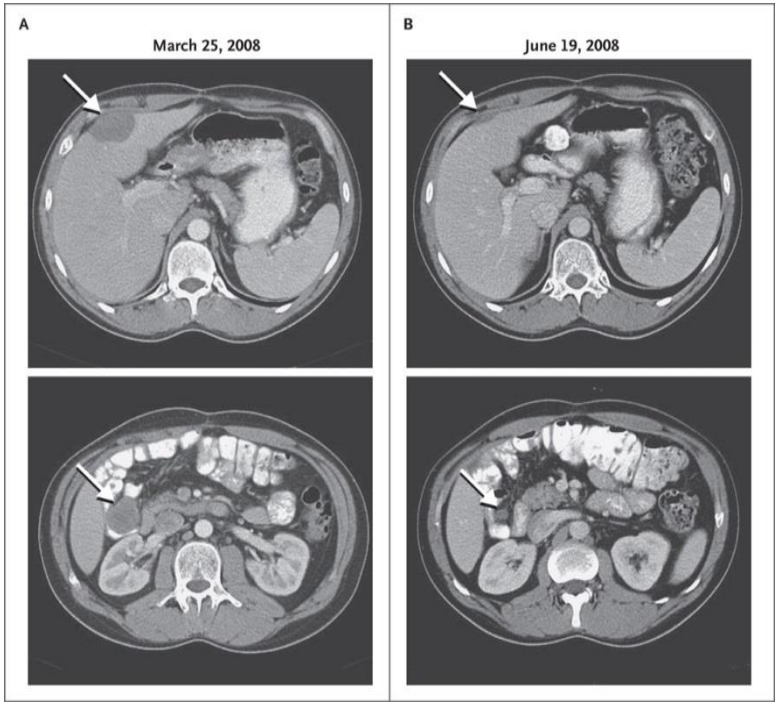


Fig 4. Response of an *ROS1*-positive patient with advanced non–small-cell lung cancer to crizotinib. Computed tomography scans of the chest were obtained (A and C) at baseline and (B and D) after 12 weeks of crizotinib. Shown are (A and B) coronal reconstructions and (C and D) axial slices.

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

Enable a culture of data sharing for better early safety and efficacy read-outs

Efficacy

- Project DataSphere
  - tumor growth kinetics
- FNIH VolPact
- irRECIST
- Liquid Biopsy Atlas
  - cfDNA
  - CTCs
  - exosomes

Safety

- Pre-competitive partnership to analyze biomarkers to predict rare but serious toxicity?
  - (e.g. autoimmune events with checkpoint inhibitors)