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
\(^c\)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\textsuperscript{a}:
  
  • Use of unconfirmed ORR\textsuperscript{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\textarrow increased risk of torsades or other serious ventricular arrhythmia

• Many other drugs approved with uncertainties (dose/schedule), optimal biomarker, etc., etc.

\textsuperscript{a}http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM494782.pdf
\textsuperscript{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

Response where you need an arrow to point it out

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

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)