Top 10 Myths about the FDA

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Myth #1

FDA takes longer to approve oncology drugs than other countries.

Myth #1

- From 2003 to 2010, FDA approved 32 new anti-cancer drugs while the European Medicines Agency (EMA) approved 26;
  - 23 approved by both agencies
    - Median time from application submission to approval:
      - 11.5 months at the EMA
      - 6 months at the FDA

Roberts S et al. Health Affairs, 30, no. 7 (2011): 1375-1381.

Myth #2: Dose

FDA and industry agree that more always is better for dosing in an oncology setting (MTD is best).

Myth #2: MTD is best

NMEs with Dose-related PMR/PMC

2011	2012	2013	2014
1. Ipilumumab	1. Glucarpidase	1. Pomalidomide	1. Ramucirumab
2. Vandetanib	2. Axitinib	2. Ado-trastuzumab	2. Siltuximab
3. Abiraterone	3. Vismodegib	3. Radium RA-223	3. Ceritinib
4. Rivoroxaban	4. Peginesatide	4. Trameitinib	4. Belinostat
5. Vemurafenib	5. Pertuzumab	5. Dabrafenib	5. Idelalisib
6. Brentuximab vedotin	6. Carfilzomib	6. Afatinib	6. Pembrolizumab
7. Crizotinib	7. Ziv-aflibercept	7. Obinutuzumab	7. Blinatumomab
8. Deferipone	8. Tbo-filgrastim	8. Ibrutinib	8. Nivolumab
9. Ruxolitinib	9. Enzalutamide		9. Olaparib
10. Asparaginase	10. Bosutinib		
	11. Regorafenib		
	12. Omacetaxine Mepesuccinate		
	13. Cabozantinib		
	14. Ponatinib		

Myth #2: Dose

- Case study: Zykadia (ceritinib)
  - Initially approved at 750 mg daily
  - 71% of patients with a dose reduction or interruption in registration trial, many due to GI ARs
  - 10% of patients discontinued due to AR
  - Food effect trial showed increased exposures when taken with food
  - PMR to study approved dose versus lower doses with food, which may also improve GI ARs

Myth #2: Dose

- Case study: Faslodex (fulvestrant)
  - Initially approved at 250 mg
  - Post-marketing study to examine 500 mg vs 250 mg in a randomized trial
  - Trial results showed that 500 mg dose improves overall survival

Myth #3

FDA's OHOP requires two randomized trials with overall survival (OS) as the endpoint, only allows enrollment of US patients, and does not permit crossover.

Myth #3: Two trials

- Two trial requirement
  - Exception to the rule in oncology: one key trial
    - High unmet medical need
    - Serious, life-threatening illnesses
    - Difficult to repeat a positive trial

Myth #3: OS only

- Overall survival as the only regulatory endpoint

Myth #3: OS only

Year	2012	2013	2014
Total NMEs	14	8	9
Total indications	15	8	11
ORR	6	2	9
PFS	3	5	1
OS	3	1	1
Other	3	0	0

Myth #3: OS only

- Two most recent approvals in ovarian cancer:
  - Olaparib in 4th-line setting: **ORR**
  - Avastin in platinum-resistant setting: **PFS**

Myth #3: U.S.A.!

- You don't have to a trial entirely or even mostly in a U.S. population, but the results DO have to be relevant to the U.S. population
  - Patient population
  - Control arm
  - Biomarker data
  - Supportive care measures
  - Available prior/subsequent therapy

Myth #3: Crossover

- Recent approvals where crossover permitted at time of progression:
  - dabrafenib and trametinib in metastatic melanoma
  - erlotinib, afatinib and crizotinib in non-small cell lung cancer
- Key questions to ask before writing crossover into a protocol:
  - Do both arms have access to same drugs
  - Are there agents available that have shown an OS improvement for this patient population

Myth #4

FDA advisory committees, such as the Oncologic Drugs Advisory Committee (ODAC), are the final decision makers in drug approval.

Myth #5

FDA staff lack scientific and clinical expertise.

Myth #5: Expertise

- Multidisciplinary team
  - Chemistry and manufacturing
  - Microbiology
  - Pharmacology/toxicology
  - Clinical pharmacology
  - Biostatistics
  - Clinical medicine
- All clinical reviewers trained in hematology and/or oncology
  - Over half still practice medicine (Hopkins, NCI, Georgetown)

Myth #6

FDA rejects most requests for expanded access to investigational drugs (a.k.a. compassionate use), and adverse events observed in an expanded access program could jeopardize approval.

Myth #6: Expanded access

- Steps to gain access to investigational drug:
  - Physician contacts company that makes drug
  - Company agrees to provide drug to patient
  - Single-patient IND submitted to FDA by physician
  - Reviewed by FDA staff within 24-48 hours

Myth #6: Expanded access

- Adverse events observed in expanded access programs
  - Challenge to determine causality of an AE
    - Patients heavily pre-treated
    - No control

Myth #7

FDA determines the cost of anticancer agents.

Myth #8

The FDA is responsible for all drug shortages due to changes in manufacturing standards that impose burdens on companies.

Myth #9

FDA does not take the voice of the patient into account in approval decisions and discourages use of patient-reported outcome measures.

Myth #9: PROs

- Voting patient rep on ODAC
- 2009 FDA Guidance on PROs in clinical trials
- Example: ruxolitinib in myelofibrosis
  - 6-item, validated PRO tool
  - Key secondary endpoint
  - Patients given hand-held devices to record their responses
  - Supported the primary endpoint (splenic response rate) for FULL approval

Myth #9: PRO tools

How strong is your pain

People agree that the following 5 words represent pain of increasing intensity. They are:

1	2	3	4	5
Mild	Discomforting	Distressing	Horrible	Excruciating

To answer each question below, write the number of the most appropriate work in the space beside the question.

1. Which word describes you pain right now? _____

Myth #9: PRO tools

- Not included in statistical plan
- No validation for specific patient population
- Does not differentiate between improvement or decrement
- Does not differentiate between disease symptoms and drug-related adverse events
- Missing data

Myth #10

The FDA chooses to withhold its reasons for a negative review and non-approval of a drug.

Myth #10

- Reviews and approval letters for new products that receive approval are posted on the drugs@FDA website
  - Supplements may have reviews posted if FOIA requests are made
- By law, FDA is not permitted to post reviews or letters to the applicant for products that do not receive approval

Myth #10

- Exception to the law: discussion of an application at an ODAC

Bonus Myth #11: Regulatory agencies around the world are islands unto themselves

- We talk to each other!

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