Access to Experimental Therapies / FDA Expanded Access Programs
Outline

• Overview of expanded access
• CDER/OHOP experience and data regarding expanded access
• Drug development considerations for expanded access
  – Single patient requests
  – Oncology case studies where expanded access facilitated drug approval
• Evidence pertaining to risks related to expanded access
• Conclusions
Criteria for Expanded Access

• Serious or immediately life threatening disease or condition
• No comparable or satisfactory alternative therapy
• Potential benefit justifies the risks
• Providing access will not interfere with clinical investigations that could support marketing approval

21 CFR 312.305
Types of expanded access

• Single patient (emergency or non-emergency)
• Intermediate size population
• Treatment IND
• EA protocols can also be submitted by commercial sponsors to an existing IND

Ultimately, approval represents the most optimal mechanism for patient access to new drugs
Expanded access requirements

• Patient, physician, and drug provider (sponsor) willing to participate (e.g., provide letter of authorization)

• Submission of an application (e.g., using Form FDA 3926 for single patient IND requests)
  – Emergency EA request can be granted via phone or email prior to submission of complete application

• IRB/consent (initial emergency EA treatment can begin prior to IRB notification)
Form 3926

• Simplified process for EA requests
• One and a half page form that contains required elements for single patient request (except LOA)
• Protocols (treatment plan) or additional information, if necessary, can be attached
CDER Experience (over 10 years)

- 10939 requests for EA
  - 8922 new EA IND applications
- 99.3% allowed to proceed
  - 24 SPIs (non-emergency requests) placed on hold (10 later allowed to proceed)
  - 38 eINDs denied
    - Most common reason was request not an emergency

Jarrow et al., TIRS, 2016 (online prior to publication)
Overview of SPIs in oncology

• FDA analysis of 1332 SPIs/eINDs from 2012 – 2014
  – Two placed on hold (one subsequently allowed to proceed)
  – Four withdrawn prior to FDA decision
  – Median review time for SPIs (2 days)
  – Median review time for eINDs (< 24 hours)
  – ~157 Unique drugs
  – Estimated 2/3 from major university hospital

Lemery et al., ASCO (poster presentation), 2016
Oncology Experience SPIs

• 61% of requests were for drugs subsequently approved

• Limited demographic data in submissions

• Age 62%; race/ethnicity 10%; sex 65%
  – (sex imputed for SPIs for patients with ovarian or prostate cancer)
  – 8% of requests (with data) were for pts age ≤ 17 yrs

• Annual reports received: ~ 15%
Data received in SPI withdrawal letters

• 100 SPI withdrawal letters reviewed
  – Most 83% contained *some* disease-related information
  – However, information generally not useful
    e.g., Patient stopped drug due to progression (without information such as prior response, listings of adverse events, or date of relapse)

• SPI information conclusion:
  – Without planning, unlikely to get useful/interpretable information from SPI EA requests
How could SPI EA information be used in an NDA/BLA?

• Could provide supplemental data, especially for rare diseases and drugs with high response rates (e.g., breakthrough drugs)

• Could provide data in patients who do not meet eligibility criteria of clinical trials (e.g., real-world experience)

• Single patient protocols under a sponsor’s IND might facilitate this approach
  – e.g., collection of data (even if limited)
Assessing treatment effects in ultra-rare diseases

• Strategies to facilitate development
  – Broaden eligibility criteria
  – Increase number of sites
  – EA if cannot enroll into trial (may not be possible to have a trial site available in all localities)
    • Provide real world experience
Case Studies that have supported approval or labeling

- Glucarpidase
- Uridine triacetate
- Eculizumab
- Dinutuximab
Case Study #1: glucarpidase

- Approved for toxic plasma methotrexate concentrations in patients with impaired renal function
  - NCI EA study primary basis for approval
  - Efficacy assessed on pre- and post-treatment plasma samples measuring methotrexate
Case study #2: uridine triacetate

• Approved for 5FU or capecitabine overdose or severe toxicity
• Approved based on effects observed in two open-label access studies (n=60) (n=75)
• Survival assessed in these patients (97%) as were PD effects
Case study #3: eculizumab

- Retrospective EA data in 19 patients supported efficacy supplement
  - EA data supported extrapolation to pediatric patients with atypical hemolytic uremic syndrome
- Results consistent with results in adults in prospective studies – decrease in dialysis requirements and improvements in eGFR
Case study #4: dinutuximab

• Approved for pediatric patients with high-risk neuroblastoma
• Primary basis for approval was randomized trial (n = 226)
• Data from an EA study (n = 793) provided safety information considered for approval
  – Safety data are described in labeling
What is the evidence regarding risks of EA?

• EA studied over 10 year period (1/2005 to 1/2014)

• Over 10,000 EA IND requests
  – Only 2 (of 1033) commercial programs with referenced INDs were placed on hold/partial hold due a serious adverse event in an EA IND.
    • One hold removed months later
    • Other was a partial hold limited to a specific population

Source: Jarow et al., TIRS, 2016.
What is the reality in oncology?

• FDA review staff are trained oncologists who understand context of adverse events in EA
  – Patients have late stage cancers
  – May have other co-morbidities

• While not related to EA, FDA’s safety reporting guidance describes
  – Anticipated events
  – Events that cannot be interpreted in a single patient, e.g.,
    • an MI in a 80 year old person
    • a patient with colon cancer who develops GI obstruction or perforation
Data regarding non-approval decisions in oncology

- Review of all CR (or not-approvable) letters for NDA (NME) marketing applications reviewed from 3/2005 to 3/2015.
- Fifteen letters
  - Most Due to lack of efficacy (67%)
  - Others due to trial design flaws (33%)
  - None due to EA

Source: Khozin et al., Nature Reviews Drug Discovery, 2015
EA Takeaways

• Provide treatment options for patients with life-threatening conditions and no available therapies – i.e., “compassionate use”

• Most requests are not primarily intended to support development/provide information about a drug
Takeaways (for development)

• EA may be a means to obtain important data, especially in rare diseases and in drugs with large treatment effects (e.g., breakthrough)

• *If* EA data may be useful
  – Try to recognize early
  – Be proactive to obtain useful data (e.g., through single patient protocols or treatment INDs later in development)

• Concerns regarding negative effects on drug development are not supported by available data
Takeaway

• While safety is assessed, it is exceedingly rare for a serious adverse event to result in a clinical hold to a commercial IND (0.2%).
  – Both holds were subsequently lifted
• In oncology, drugs not approved due to lack of efficacy or trial design issues (not EA)
  – Risk-benefit important but *highly unlikely* to be affected by a serious event in a single patient
  – Safety risks are accepted by patients/oncologists if a drug provides benefit