Breakthrough Designation: The First Two Years

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History of Legislation

- Nov, 2011 FOCR/Brookings Annual Conference on Clinical Cancer Research
  - Discussed expedited pathway for new cancer drugs with unprecedented activity
- Senate introduction March 2012: "Advancing Breakthrough Therapies for Patients Act"; (Bennett, Hatch, Burr)
- House introduction May 2012: "Breakthrough Therapies Act"; (DeGette, Bilray)
- FDASIA passed July 9, 2012
- 1st designation given in Jan 2013

Activity Since Enactment (dynamic)

	CDER	CBER
• Requests	206	37
• Granted	62	7
• Denied	101	27
• Withdrawn	2	0
• Rescinded	0	0

2013: 3 Approvals

- Guzyva: CLL
- Imbruvica: Mantle Cell Lymphoma
- Solvaldi: Chronic Hepatitis C

2014: 9 Approvals to Date—4/9 for Non-oncologic Indications

- Kalydeco, supplement: Cystic Fibrosis
- Arzerra, supplement: CLL
- Zykadia: NSCLC, alk+
- Zydelig: CLL
- Imbruvica, supplement: CLL
- Promacta, supplement: aplastic anemia
- Keytruda: metastatic melanoma
- Ofev: Idiopathic pulmonary fibrosis
- Esbriet: Idiopathic pulmonary fibrosis

FDA Initial Activities

- Set up tracking mechanism and process for review of requests
- Developed template for review and presentation
- Set up procedure for CDER Medical Policy Council review and recommendation
- Response letter templates

Medical Policy Council Activities

- Nine policy/procedure meetings
- Three quarterly progress updates from review offices
- Fifty-one face-to-face discussions for 72 requests
- Ninety-two email reviews

Evaluation of Program

- Have conducted initial evaluation of 1st 2 years of the program (by Office of Strategic Programs, CDER)
- Characteristics of program/reactions and opinions of staff
- Have not polled industry
- Plan further evaluation

Role of MPC

- 93% agreement with Division recommendations
- 47/50 instances, division recommended granting and MPC concurred
- 79/87 instances, division recommended to deny and MPC concurred
- In 2 cases, division said deny and MPC recommended granting; were granted
- In 6 cases, division said grant and MPC recommended denial; all ultimately denied

What is the Bar?

- Biggest factor seems to be magnitude of treatment effect
- In the clinical data submitted, successful requests show, in general, a reduction in the risk (e.g. of progression) of over 50%
- Of course, when the endpoint is survival, lesser improvements are still impressive
- Because of the wide range of conditions and endpoints studied, precise “bar” difficult
- In general, improvements of 10% over comparator do not seem to be BT territory

Is the Bar Consistent?

- Hard to compare across different indications
- We looked across Offices/Divisions for simple rates: no clear pattern
- ODE 3 has the highest percentage of grants but does not have a huge amount of requests
- MPC process intended to maintain consistency
- We will continue to evaluate this issue

Some characteristics of granted and denied BTDRs from FDA Evaluation

- On average, granted BTDRs tended to have **higher enrollment**, submit **more and larger phase trials**, and have a **genetic/targeted** component to their indications compared to denied BTDRs
- There is not much difference between BTDRs that were granted or denied in terms of rare/orphan status or randomized trials submitted

Variable	Grants (Means/%)	Denials (Means/%)
Number of Grants/Denials	50	86
Trial Enrollment[1]	184.3 (median 88)	114.4 (median 51)
Trial Count[2]	1.52	1.23
Maximum Trial Phase	1.94	1.73
Randomized/Blinded[3]	56%/32%	56%/46%
Available Therapy	64%	49%
Rare and/or Orphan	60%	55%
Genetic/Targeted	38%	20%

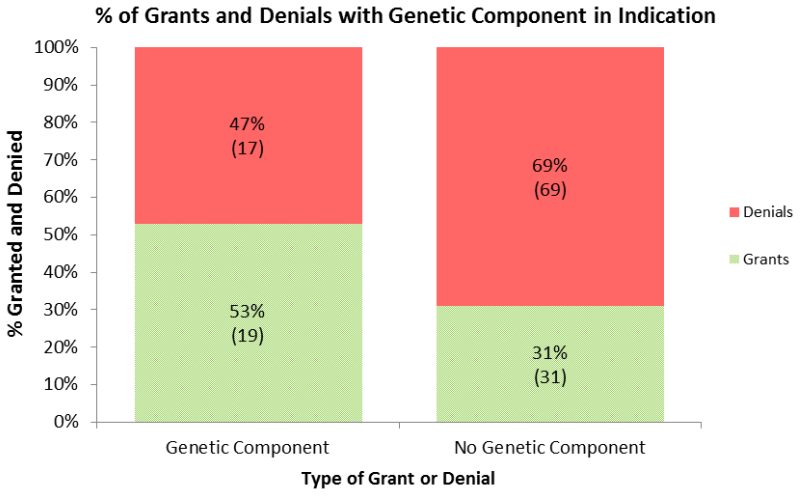
[1]"Trial enrollment" indicates the average enrollment of all trials submitted as evidence per BTDR

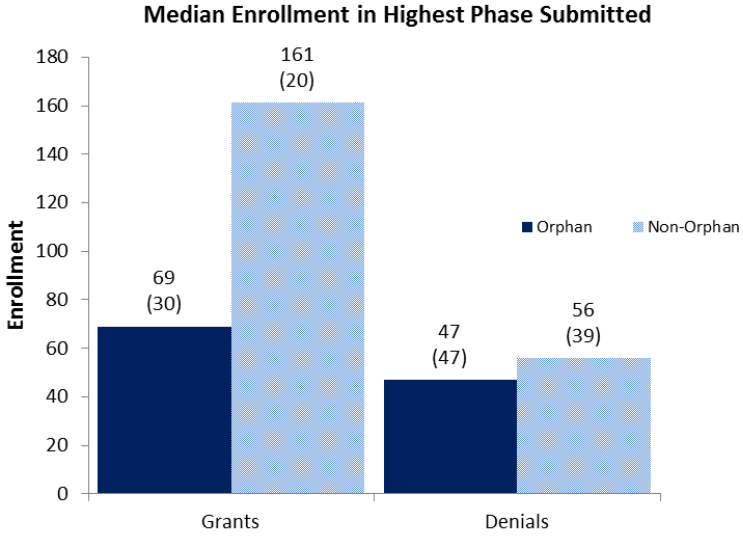
[2]"Trial count" indicates the average number of trials submitted as evidence per BTDR

[3]If more than one trial supported an BTDR, and one of those trials was randomized, the BTDR was flagged as "randomized"

Therapies with a genetic component[1] in their indication were more likely than those without to be granted BT status but orphan and/or rare status[2] did not make a difference

- While orphan and/or rare status and inclusion of a genetic component are not related to BTDR evidence submitted, they may reflect a future designation trend
- 38% of grants and 20% of denials had genetic components but 53% of therapies with a genetic component to their indication were granted compared to 31% of therapies without these components
- 60% of grants and 55% of denials had rare and/or orphan status but non-orphan/rare grants and denials had higher median trial enrollments (133% and 19%) than orphan/rare grants and denials



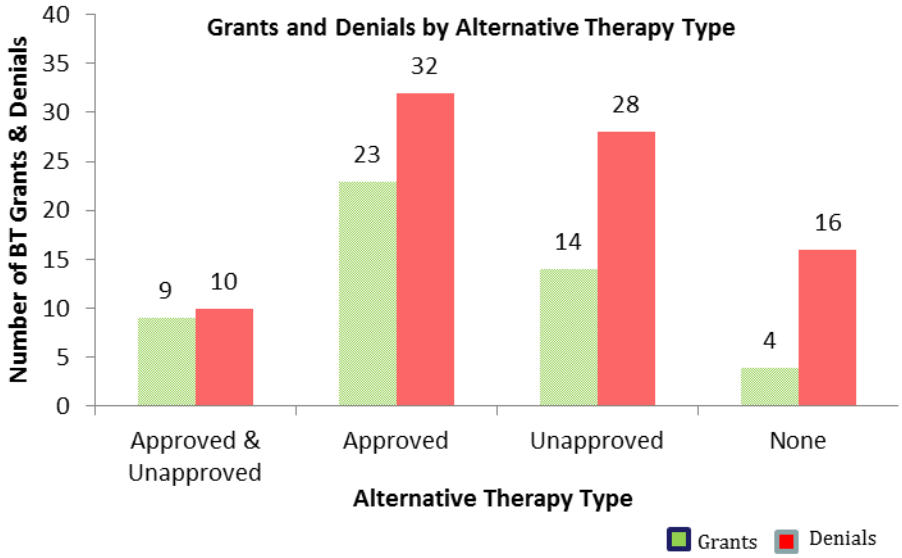


[1]The inclusion of a genetic component in the indication is used as a proxy for targeted therapy

[2]Grants and denials were categorized as orphan and/or rare status if they had either status in DAARTS at the time of data collection

Grants were more likely than denials to have some form of alternative therapy

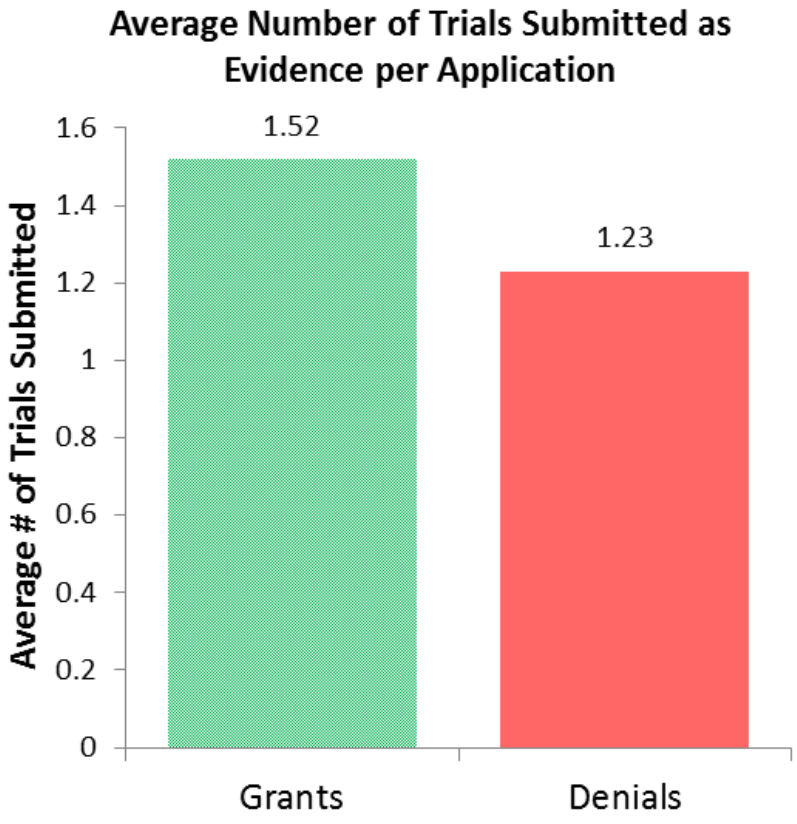
- Result is surprising given that a lack of alternative therapies would seem to indicate an advantage
- Expedited programs guidance specifies that only "approved" therapies be considered, but division briefing packets to the MPC mentioned "unapproved"[1] therapies for 44% of grants and 46% of denials
- There is no way of knowing if unapproved therapies factored into BT decisions
- 64% of grants and 49% of denials had approved alternative therapies
- 8% of grants and 19% of denials had no alternative therapies



[1]"Unapproved" therapy defined as off-label use (not considered SOC) or drugs in pipeline for same indication; "Unapproved" and "approved" categorizations were verified by medical officers

Grants submitted evidence from more trials than denials

- On average, grants submitted evidence from 24% more trials than denials, indicating that more evidence may inspire confidence
- The maximum number of relevant trials submitted with a BTDR was 5
- 4 denials submitted no trial data[1] and 3 BTDRs (2 grants, 1 denial) submitted only expanded access data[2]

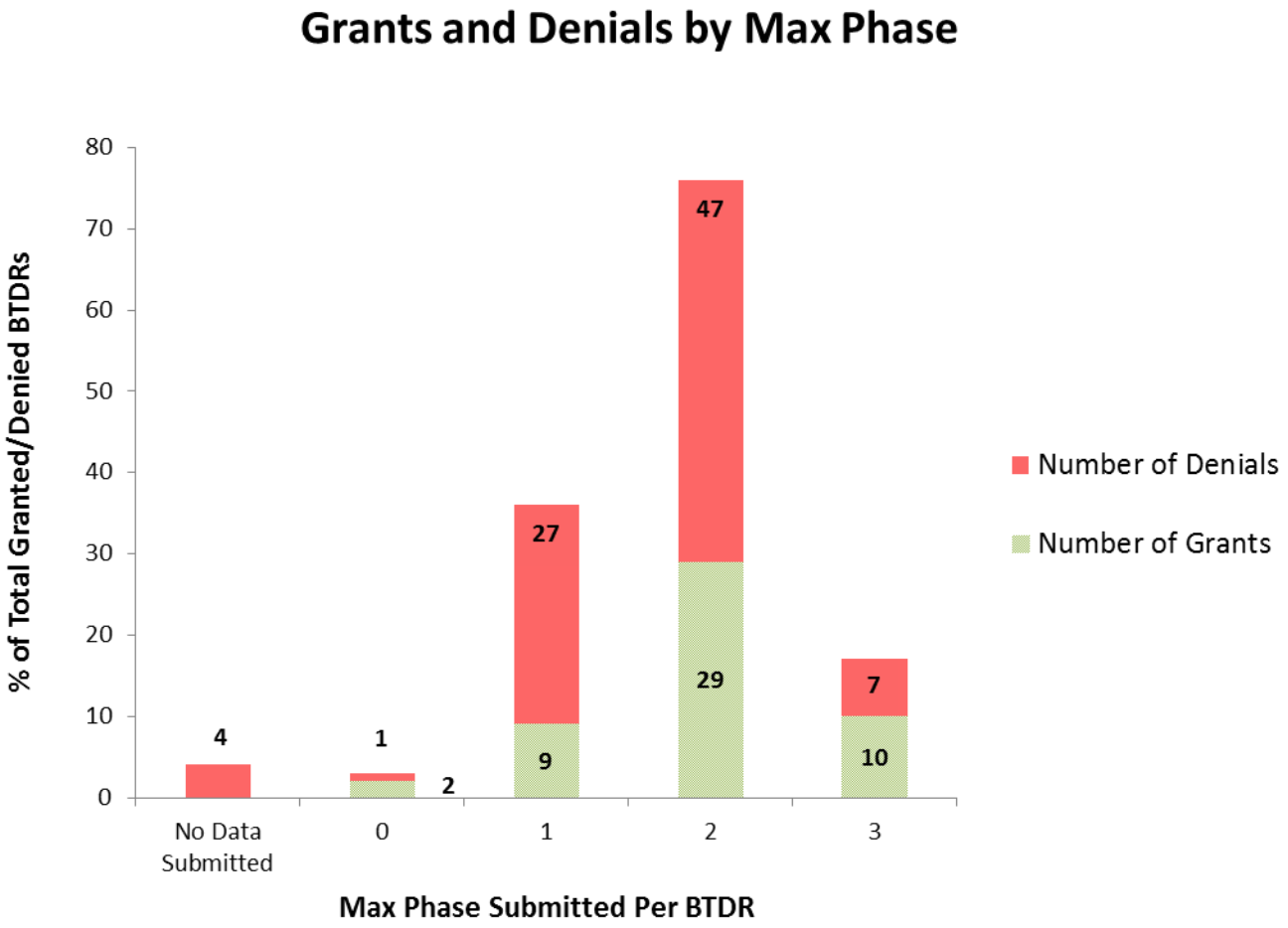


[1]BTDRs submitting no trial data were coded as having submitted 0 trials

[2]BTDRs submitting only expanded access data were coded as having submitted 1 trial

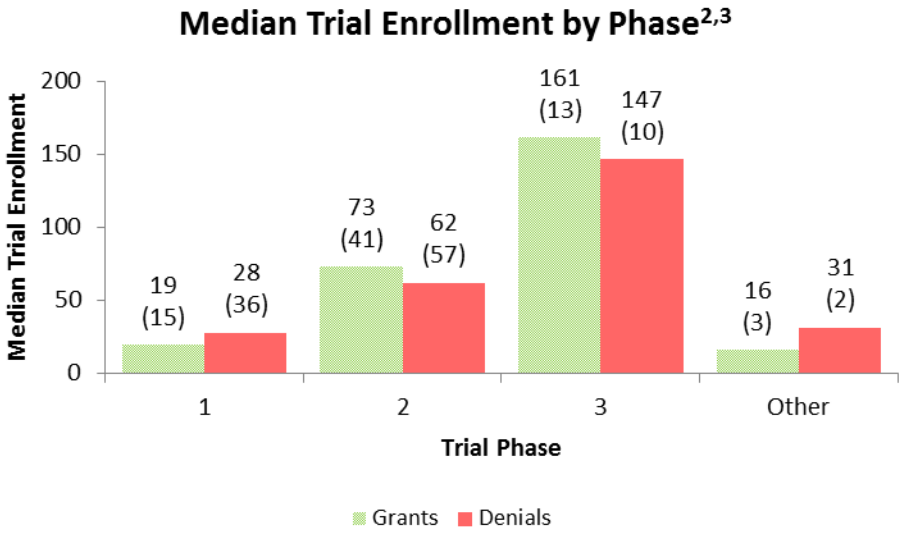
Over half of all grants and denials submitted a maximum trial phase of II

- 63% of denials submitted trial data of phase II or higher
- 78% of grants submitted trial data of phase II or higher
- Data suggests that most sponsors are adhering to the expedited programs guidance and submitting at phase II or earlier



Median trial enrollment for grants was slightly higher than denials in phases II and III

- Median[1] enrollment for grants was 18% and 10% higher than denials for phase II and III trials respectively, which may indicate that higher trial enrollment inspires more confidence
- Median enrollment for grants was 32% less than denials for phase I trials, but many BTDRs submitted higher phase data as well, relegating many phase I trials to a supporting role

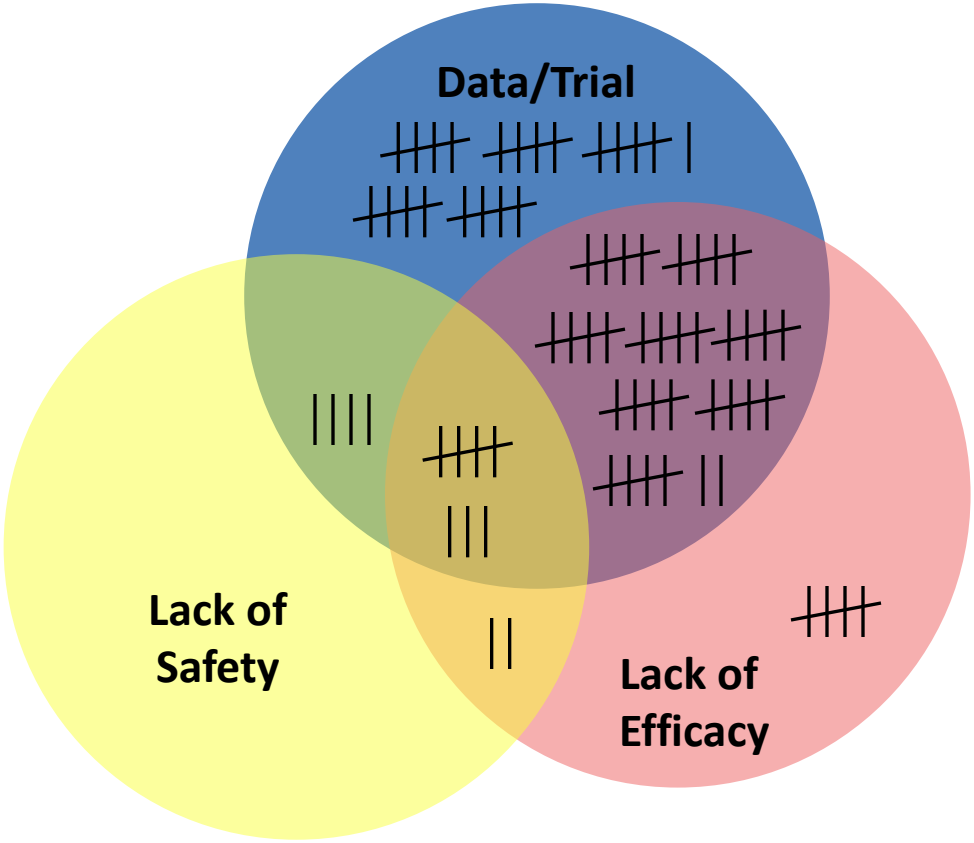


[1] Median enrollment data is presented to account for the influence of a few large trials in each phase that positively skews the overall data

[2]Enrollment numbers include total enrollment for all trials submitted as evidence (i.e. gave a treatment effect) specific to BTDR indication

[3]"Other" represents BTDRs that submitted expanded access data

Most denials cited trial design and trial data issues[1]



Denials	N=86
Reasons for Denial	
Lack of efficacy	**57 (66%)**
Lack of safety	**14 (16%)**
All data/trial problems	**80 (92%)**
No clinical data	5 (6%)
Trial design flaws	22 (43%)
Invalid endpoint	25 (29%)
Sample size	31 (36%)
Post hoc analysis	13 (15%)
Trial results too preliminary	21 (24%)
Treatment effects not isolated	10 (12%)
Concomitant treatments	3 (3%)
Misc/other	17 (20%)

[1]Many denials cited multiple reasons for denial; reasons gathered from denial letters and MO QCs ; "Condition not serious" was only cited as a reason for denial for two drugs and was not included in this analysis

BT Designation ≠ Approval: Serelaxin

- Serelaxin (Novartis): an intravenous drug being studied for heart failure
- Single Phase 3 trial—difficulties with primary EPs (symptoms) but possible improvement in mortality
- BT designation awarded June 2013
- March 2014: Cardiorenal AC votes 11:0 that more data needed
- May 2014: FDA requests data from ongoing outcomes trial

Benefits of Designation

- Focused attention on the development program by FDA staff
- Medical Policy Council input into regulatory approach
- Manufacturing: early consultation with the quality regulators; use of clinically relevant specifications and benefit/risk analysis
- Point of view of drug sponsors will be obtained

What about Effect on FDA/CDER Workload

- CDER currently has over 600 vacancies
- Clearly BT designation program has associated workload, but overall impact hard to measure
- Evaluation gave some indication of impact on reviewers
- As a result of the evaluation, we are undertaking to streamline some parts of the process, although the MPC is reluctant to cease oversight of certain actions, at the moment

Summary

- Response to Breakthrough Therapy Designation Program has exceeded expectations
- A number of BT designated drugs have undoubtedly reached patients sooner as a result
- No letup in applications, so expect a robust program going forward
- Impact of FDA resources still being evaluated