Introduction to US FDA's Expedited Programs

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Overview

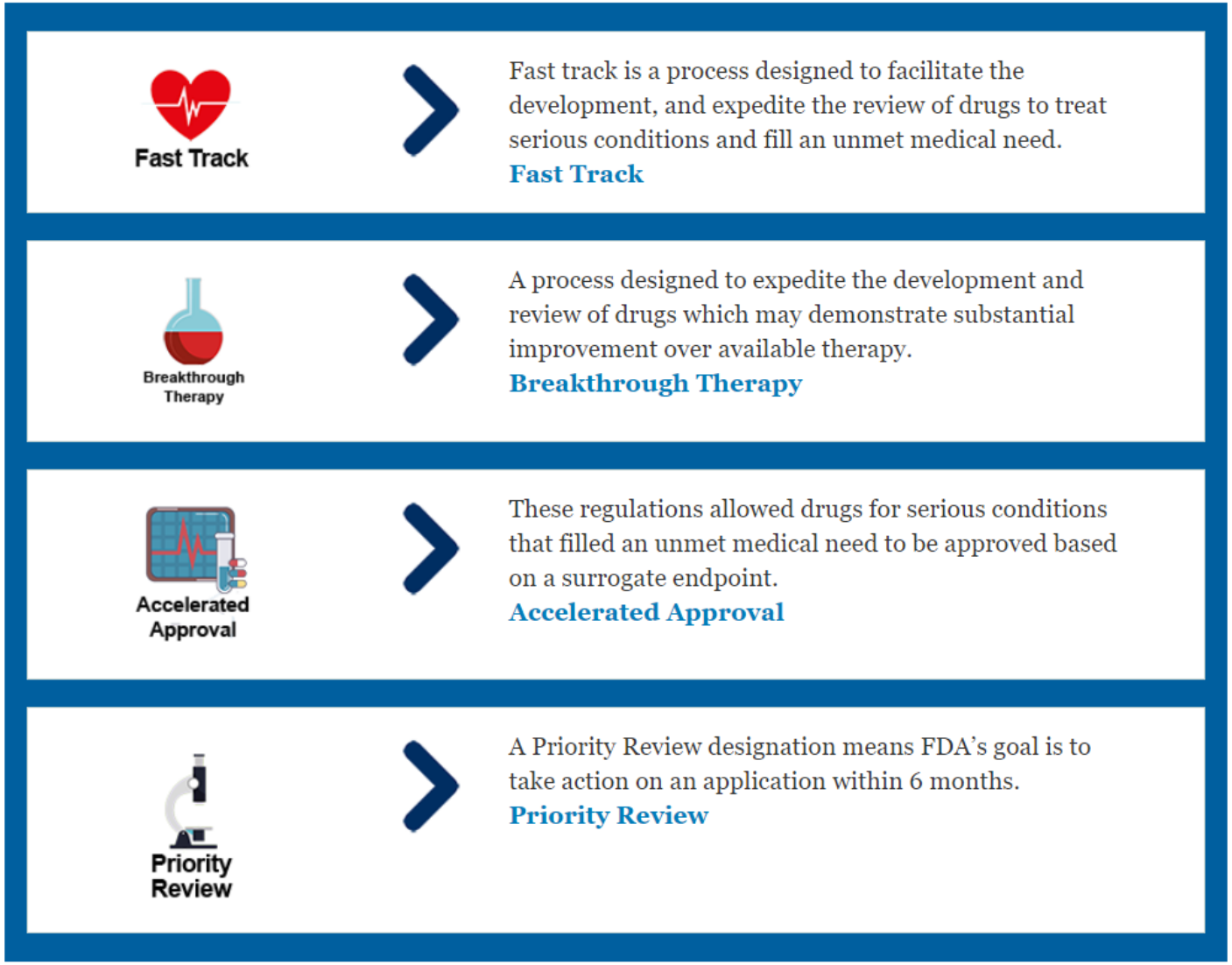
Overview of FDA's Expedited Drug Approval Programs

	FAST TRACK	ACCELERATED APPROVAL	PRIORITY REVIEW	BREAKTHROUGH THERAPY
Date established	1988	1992	1992	2012
Qualifying criteria	• Must be intended to treat serious condition • May address an unmet medical need • Supporting data can be clinical or nonclinical	• Must treat a serious condition • Early evidence shows substantial improvement over existing therapies • May use surrogate endpoints to demonstrate clinical benefit	• Must treat a serious condition • Provides significant improvement in safety or effectiveness over existing therapies	• Must treat a serious condition • Early evidence shows substantial improvement over existing therapies • Supporting data must be clinical
Time frame for application and FDA response	Can be requested with an investigational new drug (IND) submission or any point after applying. The FDA has 60 days to respond to request.	No formal process. Drug sponsors are encouraged to discuss the possibility with the FDA during drug development.	Requested at time of drug approval application. The FDA has 60 days to respond to request.	Can be requested with IND submission or any point after applying. The FDA has 60 days to respond to request.
Key program features	• Earlier and more frequent communication with the FDA during development • Rolling review of application • Designation may be withdrawn if drug no longer meets qualifying criteria	• Approval is granted on a conditional basis. Drug sponsor must conduct post-approval trials to confirm benefits • Application is submitted in one package • Drug is subject to expedited withdrawal	• Drug review process is shortened to six months (from the standard 10 months)	• All fast-track designation features • Intensive FDA guidance throughout development process, involving senior FDA officials • Designation may be withdrawn if drug no longer meets qualifying criteria

Source: FDA's "Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics" (June 2013)

*Fast-track designations created in 1997 but the table shows 1988

FDA's Description



https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review

On AA, it is rather "a regulatory pathway" than "These regulations".

Characteristics of FDA Expedited Programs (Hwang et al., 2017)

Table. Characteristics of the FDA's Expedited Programs for Drugs Treating Serious Diseases[a]

Characteristics	Accelerated Approval Program	Priority Review Program[b]	Fast-Track Program	Breakthrough Therapy Program
Year issued or enacted	1992[c]	1992[d]	1997[e]	2012
Approval based on effect on a surrogate measure or intermediate end point reasonably likely to predict clinical benefit	✓			
Shorter FDA review time		✓		
Rolling review of application			✓	✓
Actions to expedite development process			✓	✓
Organizational commitment and intensive guidance on efficient drug development[f]				✓

Abbreviation: FDA, US Food and Drug Administration.

[a] Drugs may qualify for more than 1 expedited program.

[b] Priority review aims to provide FDA decision within 6 mo vs 10 mo for standard review.

[c] The FDA's subpart H (21 CFR §314.500-§314.560; drugs) and subpart E (21 CFR §601.40-§601.46; biologics) regulations were issued in 1992.

[d] From 1975 through 1992, the FDA prioritized drug review using a 3-tiered system: type A, type B, and type C.

[e] The FDA's subpart E regulations (21 CFR §312.80-§312.88) were issued in 1988; Congress codified fast-track in 1997.

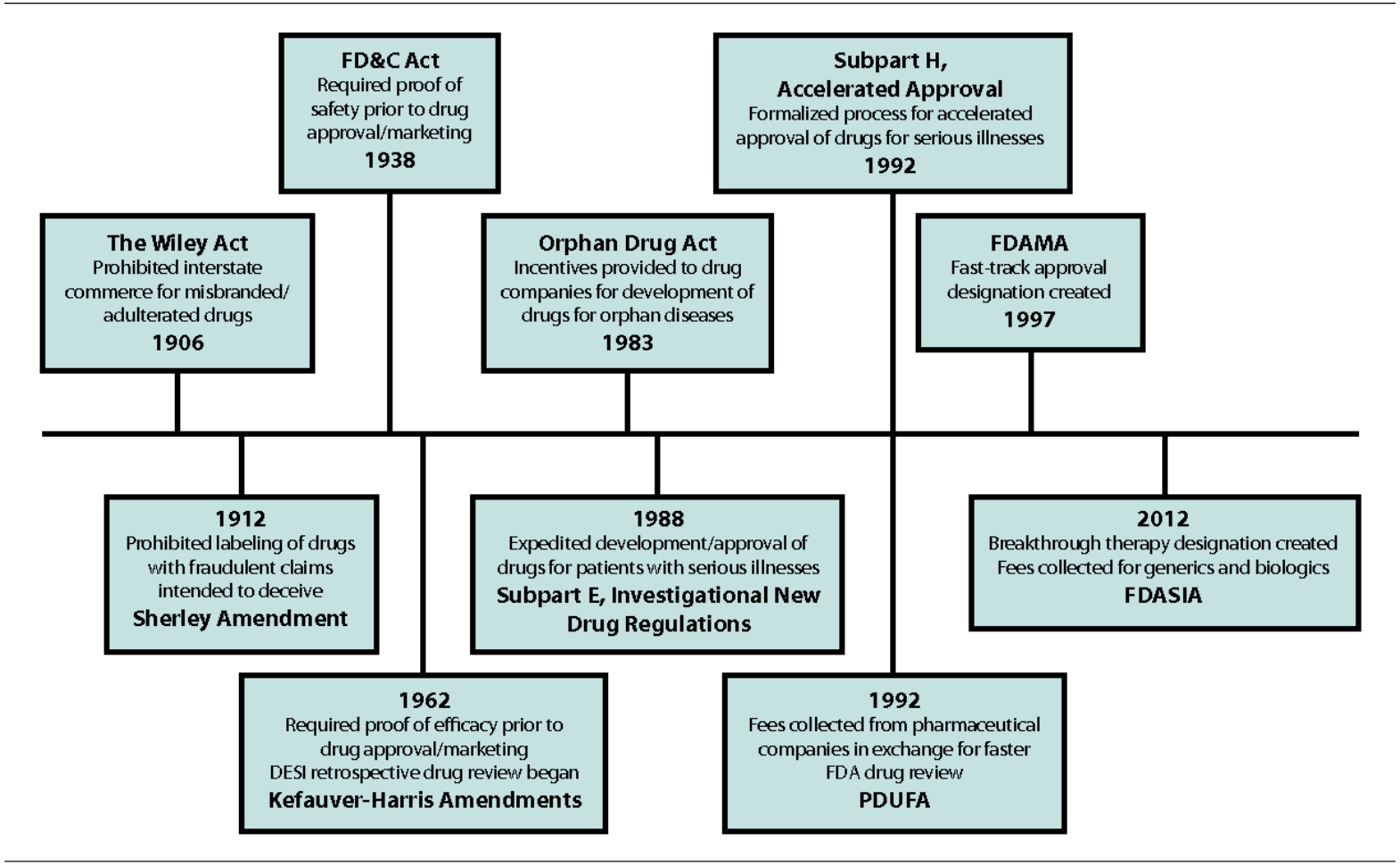
[f] The 1988 subpart E regulations also provided for early consultation and the involvement of senior FDA officials.

*For FT & BT also likely to have shortened review time.
*Rolling review must be asked by the sponsors and they are not always given.

History

- 1962: KHDA made drug development extremely costly and lengthy. “Thalidomide crisis”
- 1992: Accelerated approval program
  - Surrogate endpoint
  - Requirement of completion of postapproval studies
- 1992: Priority Review
  - A part of PDUFA 1992
- 1997: Fast-track program
  - Approved drugs based on phase 2 trials alone
- 2012: Breakthrough therapy program
  - Similar to the Fast-track, but with more formalized internal review processes
  - Can be approved basis of “alternative clinical trial designs” that may be smaller and require less time to complete
- 2012: FDA Safety Innovation Act
  - Allows FDA to base accelerated approval for drugs for serious conditions
- 2016: 21st Century Cures Act
  - FDA to “maximize” use of such expedited measures

Timeline


FD&C Act
Required proof of safety prior to drug approval/marketing
1938
Subpart H, Accelerated Approval
Formalized process for accelerated approval of drugs for serious illnesses
1992
The Wiley Act
Prohibited interstate commerce for misbranded/ adulterated drugs
1906
Orphan Drug Act
Incentives provided to drug companies for development of drugs for orphan diseases
1983
FDAMA
Fast-track approval designation created
1997
1912
Prohibited labeling of drugs with fraudulent claims intended to deceive
Sherley Amendment
1988
Expedited development/approval of drugs for patients with serious illnesses
Subpart E, Investigational New Drug Regulations
2012
Breakthrough therapy designation created
Fees collected for generics and biologics
FDASIA
1962
Required proof of efficacy prior to drug approval/marketing
DESI retrospective drug review began
Kefauver-Harris Amendments
1992
Fees collected from pharmaceutical companies in exchange for faster FDA drug review
PDUFA

Goals

- To facilitate the development of drugs that address an unmet medical needs in the treatment of serious or life-threatening conditions
- To ensure that therapies for serious or life-threatening conditions are approved and available to patients as soon as the minimum bar is passed
- To allow for “earlier” attention to drugs that may be promising in tough diseases
- To provide a chance for collaboration between the regulatory agency and the drug sponsors (e.g., expediting the development and review process)

Overview - Jarrow et al. (2020)

Box 2. Special Approval Programs

Orphan Drug Act (1983). US legislation creating incentives for the development of rare disease treatments, defined in 1984 as diseases or conditions affecting fewer than 200 000 people in the United States.

Fast-Track (1987). A program intended to expedite the development, evaluation, and marketing of new therapies for serious and life-threatening conditions by, among other things, eliminating phase 3 trials.

Accelerated approval (1992). A program intended to expedite the development and marketing of new therapies for serious and life-threatening conditions by allowing the use of surrogate measures only reasonably likely to predict clinical benefit as end points for the pivotal clinical trials forming the basis for drug approval.

Priority review (1992). Under the Prescription Drug User Fee Act, the FDA committed to first-cycle review deadlines for new drug applications of 6 months for priority applications and 12 months for standard applications (shortened to 10 months by 2002).

Breakthrough Therapy (2012). Experimental therapies designated in this program are eligible for greater FDA attention and expedited response timelines during the clinical development process.

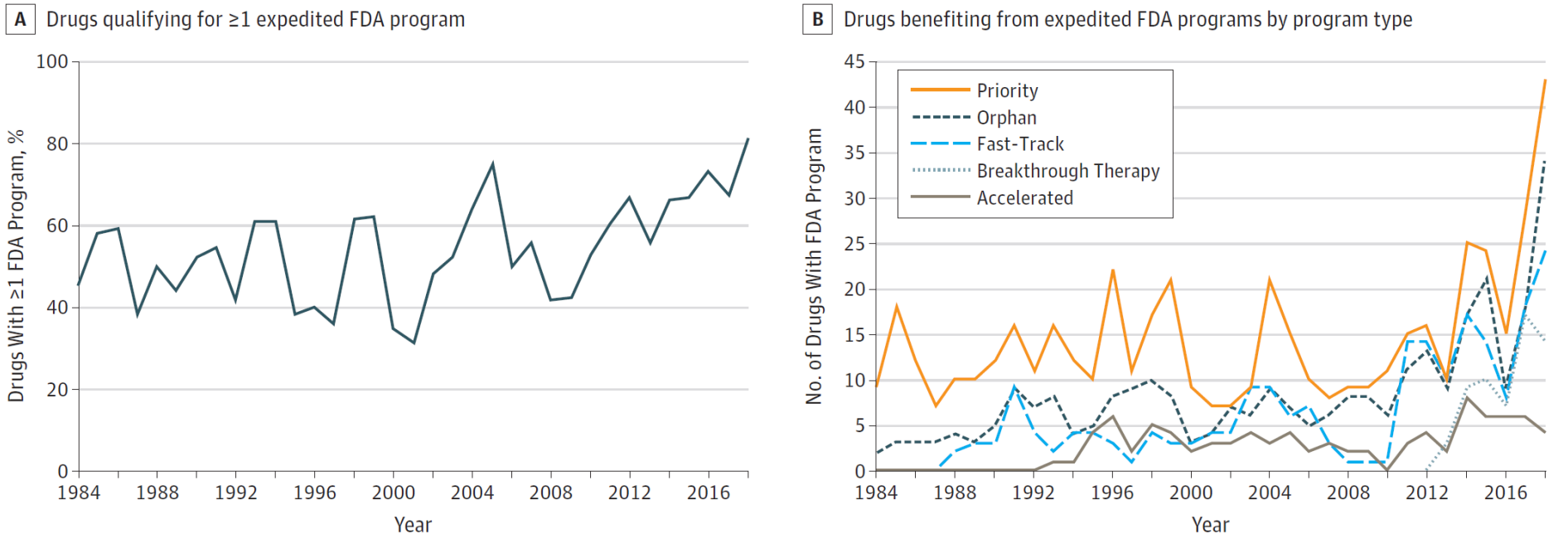
Abbreviation: FDA, US Food and Drug Administration.

- Expedited Development
  - Increased from 11% in 89-98 to 34% in 09-18
  - Approvals based on AA increased from 9% in 93-01 to 13% in 11-18.
  - 27% of new drugs approval in 14-18 were breakthrough designated
  - Breakthrough Therapy resulted in significantly shorter total development time (4 years vs 8 years)
    - Misinterpreted by physicians as implying higher levels of efficacy than has necessarily been demonstrated
  - 52% of all breakthrough designated drugs approved in 13-16 were approved on the bases of phase 1 or phase 2; 45% on the basis of single trial; 42% w/o using either placebo or control
    - These figures were higher for oncology
    - However, follow-up study of 33 breakthrough and 25 non-break through cancer medicines, no significant differences in response rates, novel mechanisms, rates of death, or serious side effects.
- 48% qualified for at least expedited program in 86-96 while 64% in 08-18.

*Fast-track designations created in 1997 but the table shows 1988

of Drugs Benefiting from Expedited Programs (Jarrow et al., 2020)

Figure 4. Number of Drugs Benefiting From Expedited Programs, 1984 to 2018

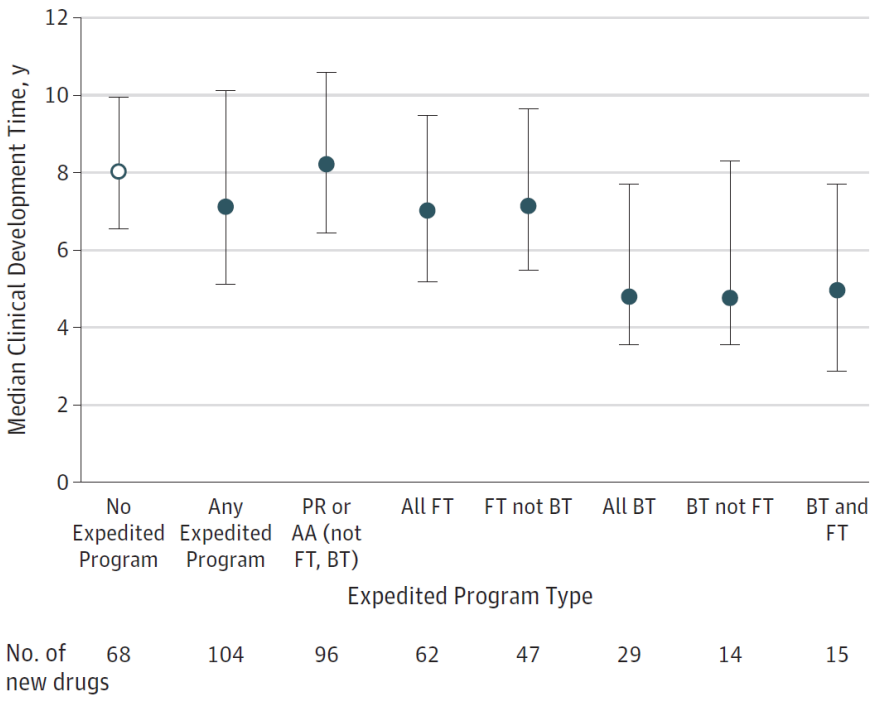


A, Forty-eight percent of drugs (150/313) qualified for at least 1 expedited program from 1986-1996, 51% (163/319) from 1997-2007, and 64% (243/380) from 2008-2018. B, Drugs may benefit from more than 1 program. Before the establishment of the 2-tiered priority review classification system in 1992, the US Food and Drug Administration (FDA) used a 3-tiered classification system. For drugs approved between 1984 and 1992, types A (important therapeutic gain) and B (modest therapeutic gain) were considered to correspond to priority review and type C (little or no therapeutic gain) to standard review. Drugs were categorized as subpart E (fast-track) drugs using the FDA's annual summaries, other public reports, and information provided by the FDA under the Freedom of Information Act. Accelerated approvals were identified using FDA documents and the FDA's annual summaries of novel new drugs. Drugs were categorized as having an Orphan Drug Act designation using the FDA's monthly drug approval reports database and the FDA's orphan drug database (expanded access not included).

Median Clinical Development Times for New Approvals 2012-2016 (Hwang et al., 2016)

- The median development time for drugs in at least 1 expedited program was 7.1 years (interquartile range [IQR], 5.1-10.1) compared with 8.0 years for nonexpedited drugs.

Figure. Median Clinical Development Times for New Drugs Approved by the FDA, 2012-2016



AA indicates accelerated approval; BT, breakthrough therapy; FDA, US Food and Drug Administration; FT, fast-track; PR, priority review. Clinical development times were calculated from the date of the Investigational New Drug (IND) application to the date of FDA approval. Any expedited program means any of PR, AA, FT, or BT. Development times were not available for 2 drugs in the study cohort. Error bars indicate interquartile ranges.

Priority Review

Eligibility & Benefits

- Eligibility
  - An application for a drug
    - That treats a serious condition AND, if approved, would provide a significant improvement in safety of effectiveness OR
    - That proposes a labeling change pursuant to a report on a pediatric study under 505A OR
    - That has been designated as qualified infections disease product OR
    - Submitted with a priority review voucher
- Benefits
  - Shorter clock for review of marketing application compared with standard review
    - 6 months instead of 10 months under standard review
- FDA Process
  - FDA informs the applicant of a Priority Review designation within 60 days of the receipt of the original BLA, NDA, or efficacy supplement
  - “Priority Review designation” does not alter the scientific / medical standard for approval or quality of evidence necessary.

Accelerated Approval

Eligibility & Benefit

- Eligibility
  - A drug that:
    - Treats a serious condition AND
    - Provides meaningful advantage over available therapies AND
    - Demonstrates effect on surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality that is reasonability likely to predict an effect on IMM or other clinical benefit
- Benefits
  - Approval based on an effect on surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict drug's clinical benefit

What is surrogate endpoint?

- Surrogate endpoint is a marker
  - A laboratory measurement
  - Radiographic image
  - Physical sign or other measure that is thought to predict clinical benefit

- Intermediate clinical benefit (that is considered reasonably likely to predict the clinical benefit such as an effect on irreversible morbidity and mortality (IMM))

Accelerated approvals for oncology products from 95-10 (Mullard, 2011)

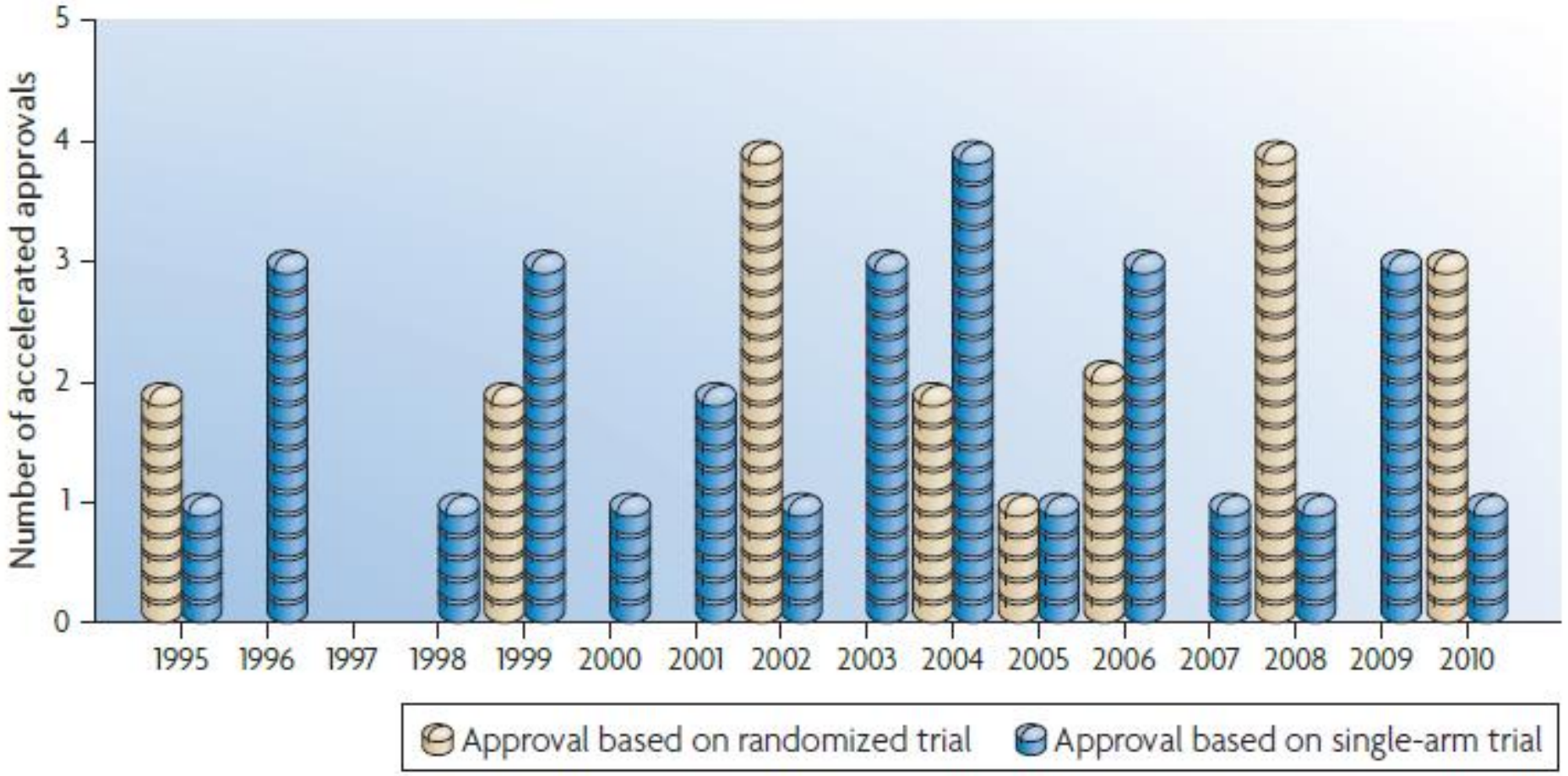


Figure 1 | **Accelerated approvals for oncology products from 1995 to 2010.**

Fast-track

Eligibility & Benefits

- Eligibility
  - A drug that:
    - Is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical needs OR
    - That has been designated as qualified infectious disease product
- Benefits
  - FDA takes actions to expedite development and review
    - More frequent meetings with FDA
    - More frequent written communication from FDA
  - Eligible for rolling review
    - Can submit the applications in sections (as each section is completed)
  - Eligible for accelerated approval / priority review if relevant criteria are met
- FDA Process
  - Must be requested by the drug company
  - The request can be initiated at anytime during the drug development process
  - Decision will be made within 60 days

Examples of serious conditions

- “Determining whether a condition is serious is a matter of judgment, but generally is based on whether the drug will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the condition, if left untreated, will progress from a less severe condition to more serious one”
- Examples
  - AIDS
  - Alzheimer's
  - Heart failure
  - Cancer
  - Diseases such as epilepsy, depression and diabetes are also considered to be serious conditions

Fast Track effect on Market capitalization and stock price (Cohen, 2004)

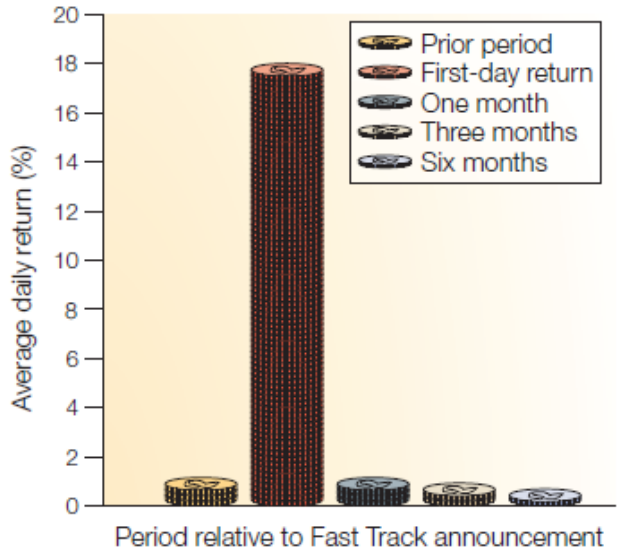


Figure 2 | **The Fast Track effect.** Shown is the acute effect of Fast Track announcement on stock price among US-based companies: APHT, CELG (2), DNA, DNDN, GNTA, HGSI, IBPI, ILXO, INGN, MLNM, OXGN, PARS, PCYC, SNUS, SPPI, SUPG, TELK, TLRK, TNOX, VXGN. Prior period is from open 27 January 27 2003 to close on the last trading day prior to announcement. First-day return is from close prior to announcement to close after it. The one-, three- and six-month periods are from close prior to announcement to respective closes after. Average daily return in the prior period was 0.684%±1.40% versus average first-day return of 19.0%±29.4% ($p = 0.008$). There was no difference between prior period average daily return and one-, three- or six -month returns. Source: Crownstone Research.

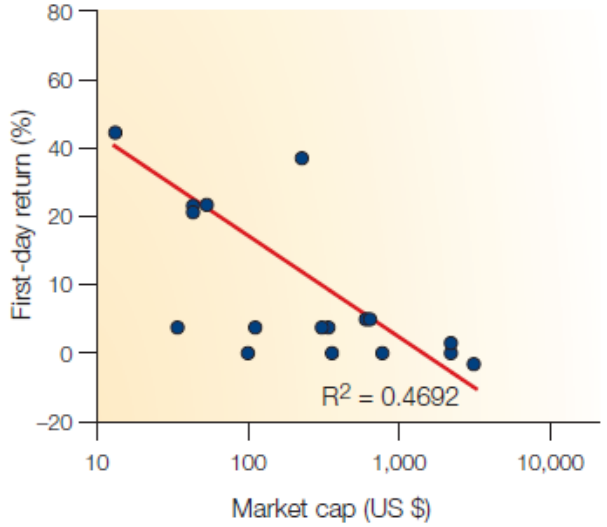


Figure 3 | **Relationship between Fast Track effect and market capitalization.** Data shown are from companies in FIG. 2, excluding two large outliers (Intrabiotics: one-day return 111%; and Genentech: market cap ~38B); market cap as of close prior to Fast Track announcement. An R^2 of 0.47 indicates that roughly 47% of the variation in one-day price appreciation can be explained by the market cap of the company alone. There was a strong relationship between market cap and the Fast Track effect, with greater price appreciation among lesser valued companies. All companies are micro- or small-cap. Source: Crownstone Research.

First decade of Fast Track Program (Reichert et al., 2008)

- Anticancer (32%); Anti-infective (22%); cardiovascular (11%); immunological (8%); and neurological (8%)

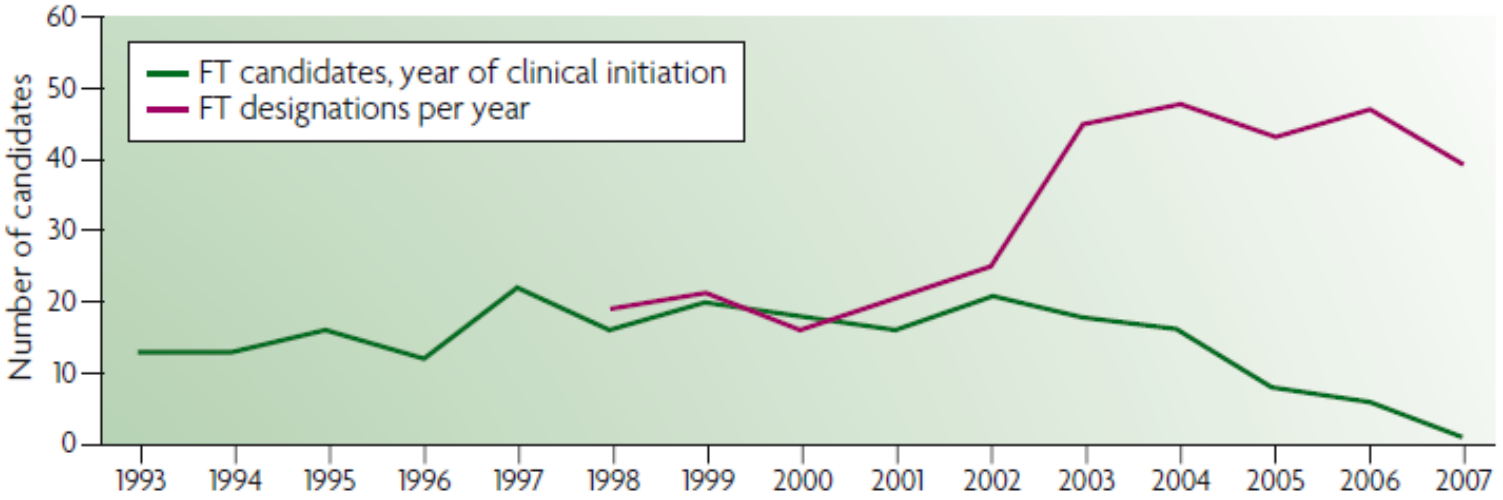


Figure 1 | **Use of Fast Track (FT) designation, introduced in 1998, has increased significantly since 2002.** The data set included 301 Fast Track therapeutic candidates; 80 candidates with FT designations entered clinical study prior to 1993; year unknown for 5 candidates.

First decade of Fast Track Program (Reichert et al., 2008) - Continued

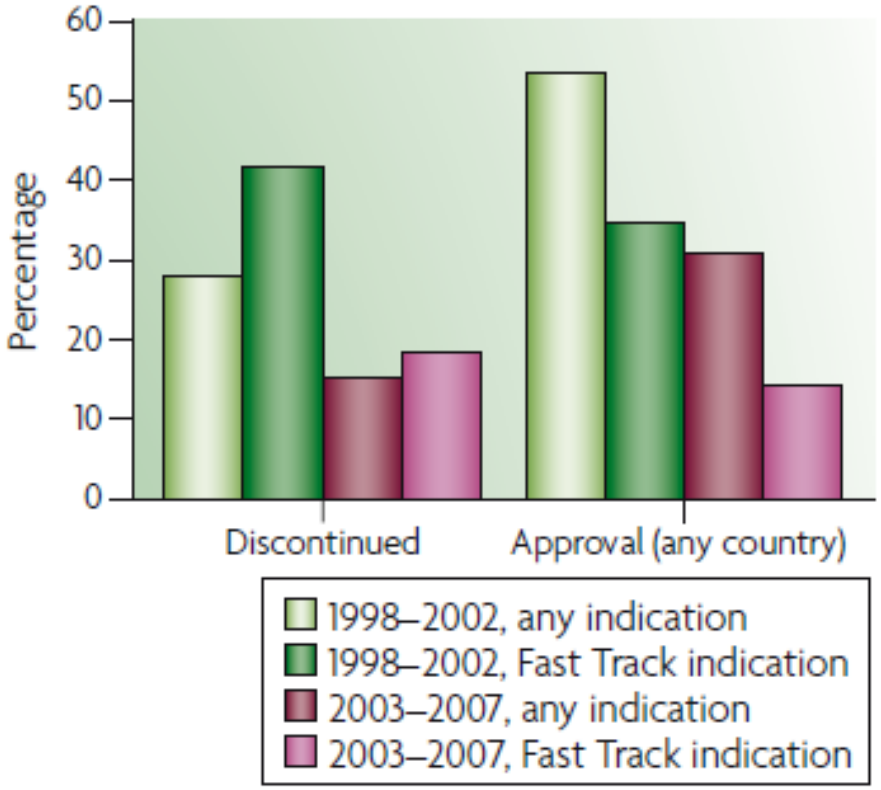


Figure 2 | **Fast Track indications were more frequently terminated and less frequently approved than other indications.** 1998–2002 and 2003–2007 are periods of Fast Track designation.

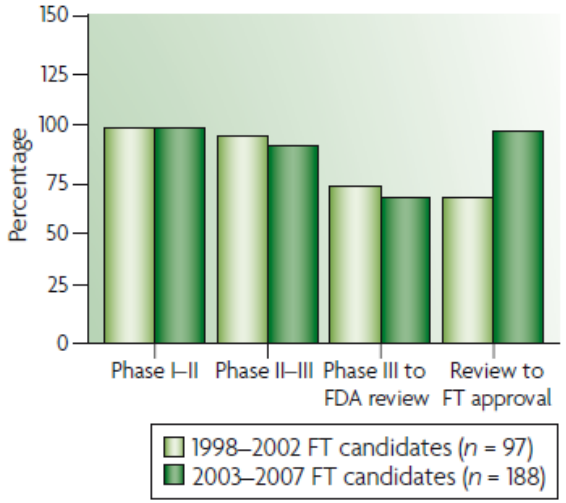


Figure 3 | **Phase transition probabilities were high in early development.** Clinical phase transition probabilities represent the likelihood that a candidate that begins a particular development phase will transition to the next phase. Phase transition probabilities were calculated as follows: the number of products that completed a given phase (e.g., Phase I) and entered the next phase (e.g., Phase II) was divided by the difference between the number of products that entered the phase and those that were still in the phase at the time of the calculation. Transitions occurring between phases of clinical studies conducted worldwide were included. FT, Fast Track.

Breakthrough Therapy

Eligibility & Benefits

- Eligibility
  - A drug that treats:
    - Serious condition AND
    - **Preliminary clinical evidence** (= KEY difference with Fast-track) indicates that the drug may demonstrate substantial improvement over available therapy on one more clinically significant endpoints
- Benefits
  - All fast-track designation benefits
    - Eligible for rolling review
  - Intensive guidance on efficient drug development, beginning as early as Phase 1
  - Organizational commitment involving senior managers
- FDA Process
  - Requested by drug company
  - If a sponsor has not requested breakthrough therapy, FDA may suggest that the sponsor consider submitting if after reviewing submitted data and information, the agency thinks the drug development program may meet the criteria for breakthrough
  - The remaining drug development program can benefit from the designation
  - Ideally, BT designation request should be received by FDA no later than the end of phase 2 meetings; FDA does not anticipate that BT designation request will be made after the submission of BLA or NDA
  - Response within 60 days of receipt of the request

Fast Track vs. Breakthrough (Darrow et al., 2018)

Table 2. Comparison of Selected Features of the Fast-Track and Breakthrough Designations.

Element	Fast Track (1988)	Breakthrough (2012)
Early meetings, efficient trial design	"A key component of the [fast track] procedures is early consultation . . . . Such consultation is intended to improve . . . efficiency" by ensuring "proper [trial] design"[10]	"Intensive Guidance . . . Beginning . . . Early"[13]; "taking steps to ensure that the design of the clinical trials is . . . efficient."[1]
Speed of development and review	"These procedures are modeled after the . . . development, evaluation, and approval of zidovudine," which "took only 2 years"[10]	"the Secretary shall . . . expedite the development and review of such drug"[1]
Senior FDA staff involvement	"the [FDA] Commissioner and other agency officials will monitor [and facilitate] progress"[15]	"involving senior managers and experienced review staff . . . in a collaborative, cross-disciplinary review"[1]
Cross-disciplinary lead	Not discussed	"assigning a cross-disciplinary project lead"[1]
Rolling review of new drug application	Included (authorized in 1997)[16]	Included[13]
Magnitude of expected benefit	"dramatic responses (i.e., great benefit)"[10]	"substantial improvement"[1]

*Fast-track designations created in 1997 but the table shows 1988

Disclosed breakthrough therapy designations (Chizkov & Million, 2015)

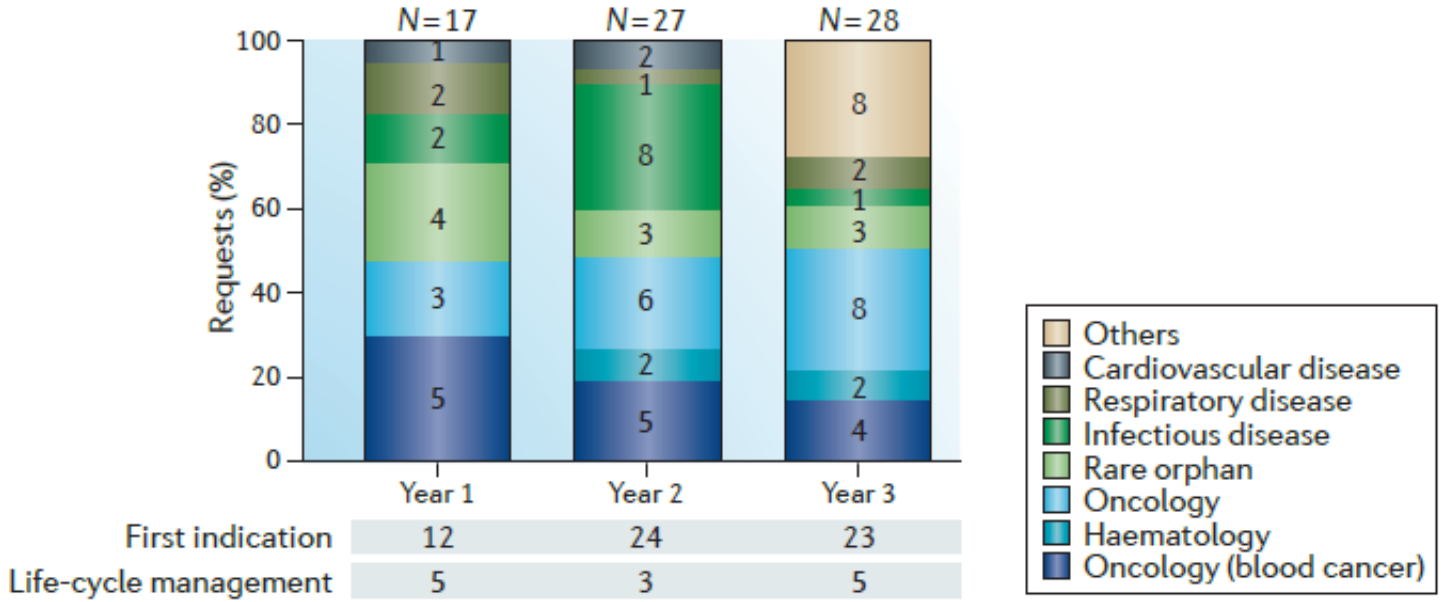


Figure 1 | **Disclosed breakthrough therapy designations by year and therapeutic area.** Year 1: July 2012–June 2013; Year 2: July 2013–June 2014; Year 3: July 2014–June 2015. The US Food and Drug Administration (FDA) had received 309 requests as of 11 June 2015, of which 29% (90) had been granted. The FDA does not disclose information regarding sponsors that have submitted requests. The charts are based on the 72 designations that have been disclosed by the sponsor companies; 18 have not been disclosed at the time of writing. In the key, 'Others' include: immunology, gastrointestinal disease, dermatology, ophthalmology and neurological disorders.

Characteristics of breakthrough therapy designations (Mullard, 2013)

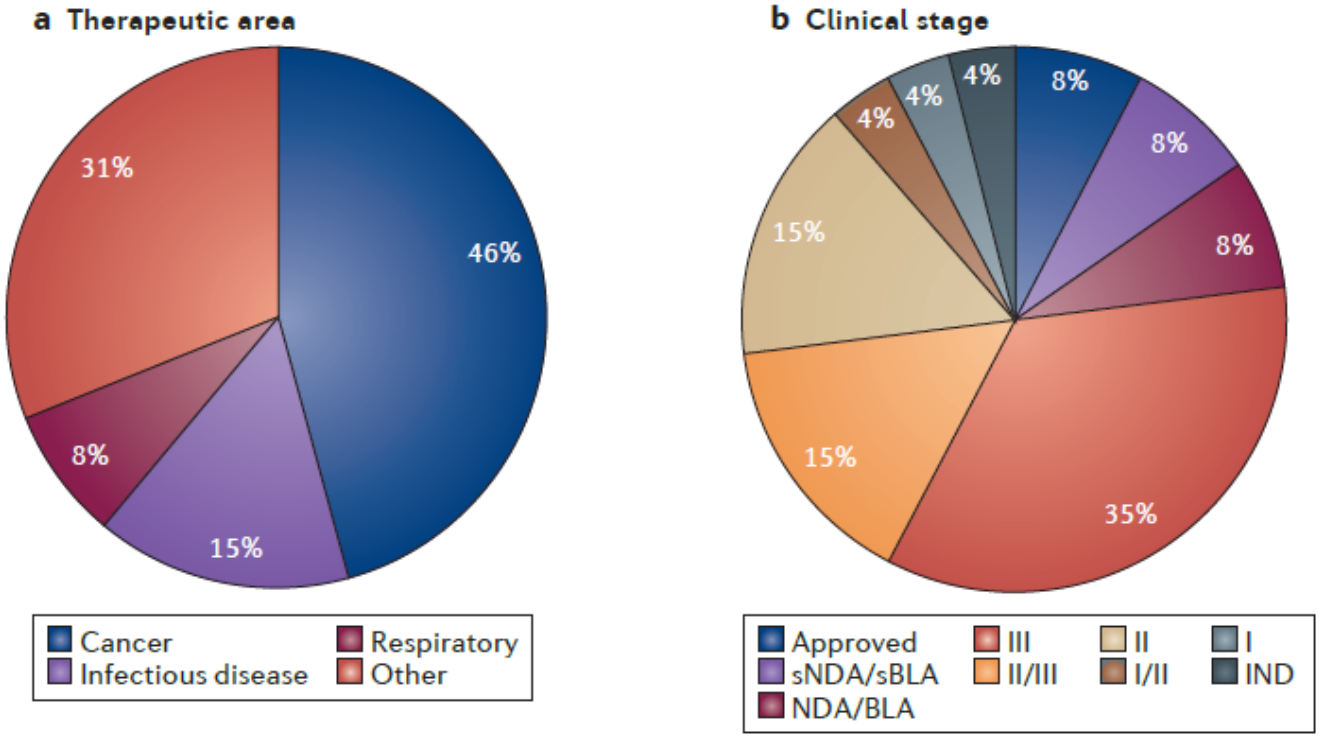


Figure 1 | **Breakthrough designations by therapeutic area and clinical stage. a** | Cancer therapies make up the bulk of the breakthrough designations. **b** | Clinical trial status is accurate as of mid-November. IND, investigational new drug; sBLA, supplemental biologics license application; sNDA, supplemental new drug application.

Novel cancer drugs with breakthrough designations (Shea et al., 2016)

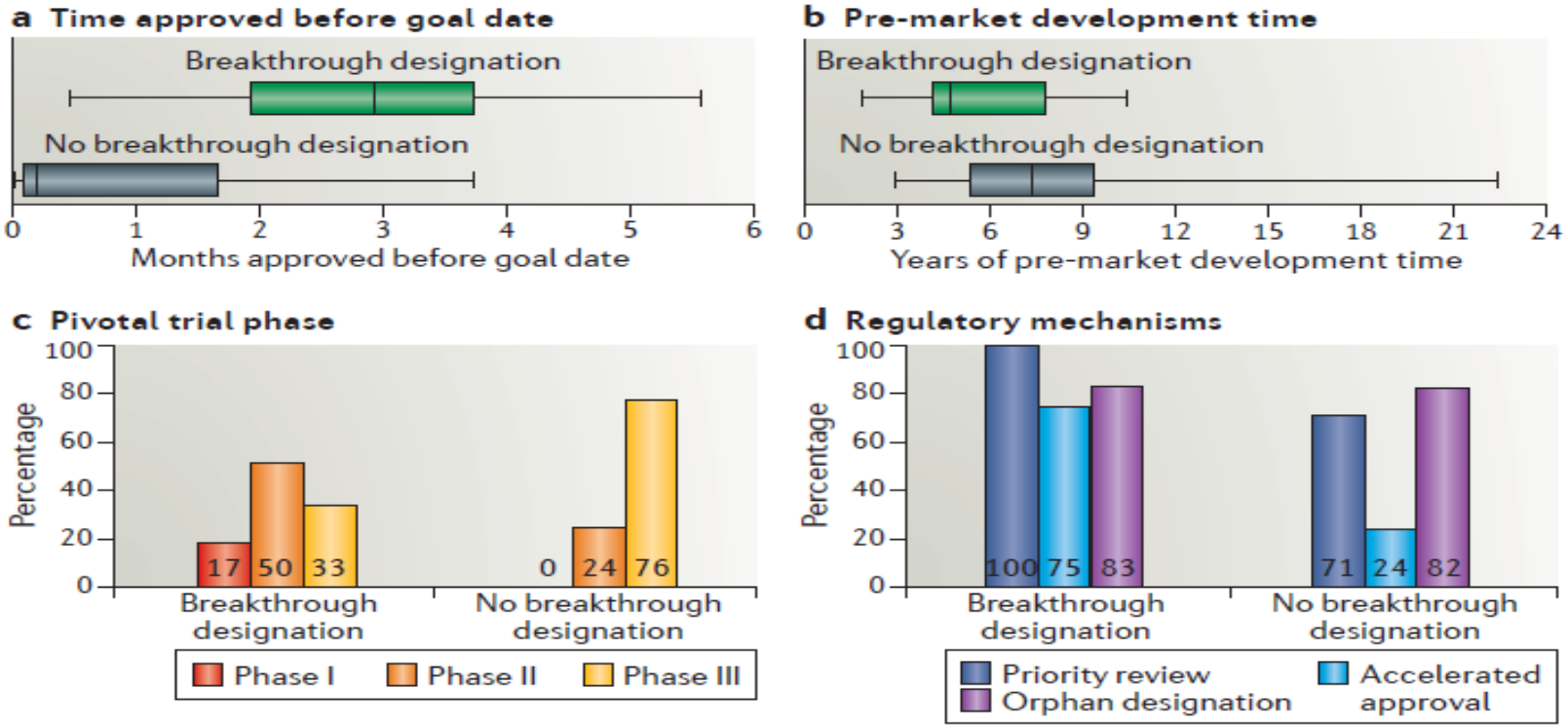
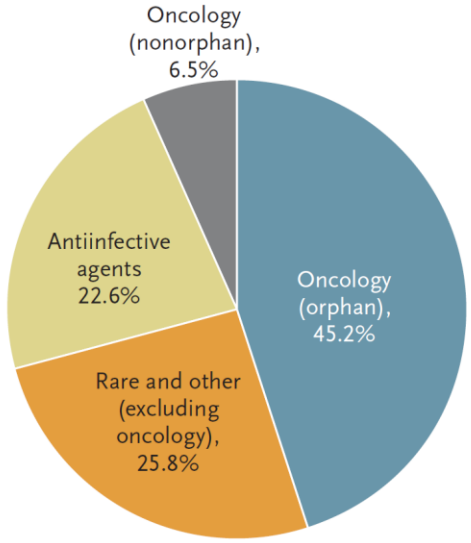


Figure 1 | **Characteristics of novel anticancer agents with and without breakthrough therapy designation, approved between 2013 and 2015. a** | Speed of regulatory review, which is shown by the time between marketing approval and the Prescription Drug User Fee Act (PDUFA) goal date. **b** | Pre-market development times, which have been calculated as the time between first clinical studies and submission of application for marketing approval. Box plots in panels **a** and **b** show interquartile ranges in the shaded areas and maximum and minimum values in whiskers. **c** | Development phase of pivotal registration trial (or trials). **d** | Use of additional regulatory mechanisms for drugs with and without breakthrough therapy designation.

Indications of Breakthrough Therapies at Initial Approval (Darrow et al., 2018)



Oncology (orphan)	Rare and Other (excluding oncology)	Antiinfective Agents
Blood Ibrutinib Blinatumomab Idelalisib Venetoclax Obinutuzumab Daratumumab Elotuzumab Lung Alectinib Osimertinib Ceritinib Skin Pembrolizumab Nivolumab Ovary Rucaparib Soft-tissue sarcoma Olaratumab	Cystic fibrosis Ivacaftor–lumacaftor Dabigatran reversal Idarucizumab Parkinson's delusions Pimavanserin Hyperphosphatasia Asfotase alfa Lysosomal acid lipase deficiency Sebelipase alfa Hereditary orotic aciduria Uridine triacetate Idiopathic pulmonary fibrosis Pirfenidone Nintedanib	Meningitis B vaccines Bexsero (GlaxoSmithKline) Trumenba (Pfizer) Hepatitis C Sofosbuvir Sofosbuvir–ledipasvir Sofosbuvir–velpatasvir Dasabuvir–ombitasvir–paritaprevir–ritonavir Elbasvir–grazoprevir

Oncology (nonorphan)
Breast Palbociclib Bladder Atezolizumab

Figure 1. Indications of Breakthrough Therapies at Initial Approval.

Breakthrough Therapy
Breakthrough, Approved Drugs, excluding new indication (Darrow et al., 2018)

Table 1. Breakthrough-Designated, Approved Drugs, Excluding New Indications, 2013–2016.

Drug	Approval Year	Indication	Concurrent Participation in Other FDA Programs*		
			Orphan	Fast Track	Accelerated
Obinutuzumab	2013	Cancer	+		
Ibrutinib	2013	Cancer	+	+	+
Ceritinib	2014	Cancer	+		+
Idelalisib†	2014	Cancer	+	+	
Pembrolizumab	2014	Cancer	+		+
Blinatumomab	2014	Cancer	+		+
Nivolumab	2014	Cancer	+	+	+
Palbociclib	2015	Cancer			+
Osimertinib	2015	Cancer	+	+	+
Daratumumab	2015	Cancer	+	+	+
Elotuzumab	2015	Cancer	+		
Alectinib	2015	Cancer	+		+
Venetoclax	2016	Cancer	+		+
Atezolizumab	2016	Cancer			+
Olaratumab	2016	Cancer	+	+	+
Rucaparib	2016	Cancer	+		+
Ivacaftor–lumacaftor	2015	Cystic fibrosis	+	+	
Idarucizumab	2015	Dabigatran side effects	+	+	+
Sofosbuvir–ledipasvir	2014	Hepatitis C genotype 1		+	
Dasabuvir–ombitasvir–paritaprevir–ritonavir	2014	Hepatitis C genotype 1		+	
Elbasvir–grazoprevir	2016	Hepatitis C genotypes 1 and 4			
Sofosbuvir	2013	Hepatitis C genotypes 1–4		+	
Sofosbuvir–velpatasvir	2016	Hepatitis C genotypes 1–6		+	
Uridine triacetate	2015	Hereditary orotic aciduria	+		
Asfotase alfa	2015	Hypophosphatasia	+	+	
Sebelipase alfa	2015	Lysosomal acid lipase deficiency	+	+	
Meningococcal group B vaccine (Trumenba, Pfizer)	2014	Vaccine		+	+
Meningococcal group B vaccine (Bexsero, GlaxoSmithKline)	2015	Vaccine		+	+
Pimavanserin	2016	Parkinson's disease psychosis			
Pirfenidone	2014	Pulmonary fibrosis	+	+	
Nintedanib	2014	Pulmonary fibrosis	+	+	

* All drugs that were approved and had a breakthrough designation received priority review.
† Idelalisib received accelerated approval on July 23, 2014, for relapsed follicular B-cell non-Hodgkin's lymphoma and relapsed small lymphocytic lymphoma, but its breakthrough designation was granted for relapsed chronic lymphocytic leukemia (also approved on July 23, 2014).

Physicians' Perceptions
On FDA Approvals & Breakthrough Therapy Designations (Kesselheim, et al, 2016)

	No. of Responses/ Total Respondents[a]	% (95% CI)[b]
3 Questions on the FDA Approval Process		
1. FDA approval typically means that a drug is as effective as other drugs approved to treat the same condition.		
True	495/682	73 (69-76)
False[c]	187/682	27 (24-31)
2. FDA approval typically means that a drug has benefits that outweigh its harms.		
True[c]	585/686	85 (82-88)
False	101/686	15 (12-18)
3. In order for a drug to get FDA approval, it has to have…		
A statistically significant result	90/687	13 (11-16)
A clinically important result	76/687	11 (9-14)
Both results	480/687	70 (66-73)
Neither of the results[c]	41/687	6 (4-8)
Physicians with number of correct answers		
0	67/675	10 (8-12)
1	423/675	63 (59-66)
2	176/675	26 (23-30)
3	9/675	1 (1-3)

5 Questions About Breakthrough Therapies		
1. The FDA has recently started designating some new prescription drugs it reviews and approves as breakthrough drugs. Before taking this survey, how familiar were you with the "breakthrough" designation?		
Very familiar	24/689	3 (2-5)
Familiar	118/689	17 (14-20)
A little familiar	255/689	37 (33-41)
Not familiar at all	292/689	42 (39-46)
2. In general, I am certain that an FDA-approved breakthrough drug represents a major advance over currently approved treatments for its indication.		
Very certain	39/686	6 (4-8)
Fairly certain	399/686	58 (54-62)
Fairly uncertain	213/686	31 (28-35)
Very uncertain	35/686	5 (4-7)
3. What is the minimum level of evidence that the FDA requires manufacturers to gather for the FDA to label a drug as a breakthrough?		
Strong evidence (eg, randomized trials evaluating clinical outcomes)	352/683	52 (48-55)
Preliminary evidence (eg, uncontrolled studies or studies testing surrogate outcomes)[c]	307/683	45 (41-49)
Very preliminary evidence (eg, in vitro laboratory or animal studies)	24/683	4 (2-5)
4. When the FDA calls a drug a breakthrough, does that mean that there is high-quality evidence that the drug is more effective than currently approved treatments?		
Yes	523/683	77 (73-80)
No[c]	160/683	23 (20-27)
5. When the FDA calls a drug a breakthrough, does that mean that there is high-quality evidence that the drug is safer than currently approved treatments?		
Yes	177/675	26 (23-30)
No[c]	498/675	74 (70-77)
Physicians with number of correct answers out of 3, %		
0	142/670	21 (18-24)
1	215/670	32 (29-36)
2	196/670	29 (26-33)
3	117/670	17 (15-21)

Hypothetical Scenario (Kesselheim, et al, 2016)

Hypothetical Scenario		
Imagine your patient has a serious medical condition for which there has been no effective treatment. The FDA recently approved 2 new drugs to treat this condition. Both drugs are oral tablets to be taken once a day, have similar adverse effect profiles, and are equally covered by the patient's insurance. Which would you choose first?		
Axabex, an FDA-designated breakthrough drug	640/684	94 (91-95)
Zykanta, a drug with early promising study results but has not been shown to improve survival or disease-related symptoms	44/684	6 (5-9)

Table 2. Effect of the Different Versions of the Mock US Food and Drug Administration (FDA) Press Release for the Hypothetical Drug Procampa on Physicians' Perceptions

	Mock FDA Press Release Version			
	Facts Alone (n = 180)	Breakthrough (n = 147)	Breakthrough/ Expedited (n = 179)	Breakthrough/ Warning (n = 181)
I Believe Procampa Improves Survival of Patients, No. of Respondents (%)[a]				
Strongly agree	24 (13)	15 (10)	27 (15)	10 (6)[b]
Somewhat agree	92 (51)	78 (53)	81 (45)	80 (45)
Somewhat disagree	52 (29)	45 (31)	53 (30)	62 (35)
Strongly disagree	12 (7)	9 (6)	18 (10)	27 (15)
I Believe That There Is Strong Evidence of Procampa's Benefit to Patients, No. of Respondents (%)[a]				
Strongly agree	22 (12)	20 (14)	26 (15)	13 (7)[c]
Somewhat agree	88 (49)	66 (45)	72 (40)	73 (41)
Somewhat disagree	56 (31)	48 (33)	68 (38)	72 (40)
Strongly disagree	14 (8)	13 (9)	13 (7)	22 (12)
If I Had Patients With Late-Stage Lung Cancer, I Would Suggest They Try Procampa, No. of Respondents (%)[a]				
Strongly agree	65 (36)	58 (39)	69 (39)	57 (31)
Somewhat agree	102 (57)	78 (53)	90 (50)	104 (57)
Somewhat disagree	11 (6)	7 (5)	17 (10)	18 (10)
Strongly disagree	2 (1)	4 (3)	3 (2)	2 (1)

Efficacy, Safety, and Approval of Breakthrough Designations vs Nonbreakthrough
Characteristics of New Cancer Drugs Approved by US FDA 2012 to 2017 (Hwang et al., 2018)

- "Breakthrough-designated cancer drugs were associated with faster times to approval, but there was no evidence that these drugs provide improvements in safety or novelty; nor was there a statistically significant efficacy advantage when compared with non–breakthrough-designated drugs"

Table 1. Characteristics of New Cancer Drugs Approved by the US Food and Drug Administration, 2012 to 2017

Characteristic	No. (%)
Cancer type	
Breast	6 (10)
Chronic lymphocytic leukemia	3 (5)
Chronic myeloid leukemia	3 (5)
Colorectal	3 (5)
Multiple myeloma	6 (10)
Non–small-cell lung cancer	6 (10)
Ovarian	3 (5)
Skin	8 (14)
Other blood cancers	9 (16)
Other solid tumors	11 (19)
Approval year	
2012	11 (19)
2013	8 (14)
2014	9 (16)
2015	14 (24)
2016	4 (7)
2017	12 (21)
Expedited program*	
None	3 (5)
Priority review	46 (79)
Accelerated approval	26 (45)
Fast track designation	28 (48)
Breakthrough therapy designation	25 (43)
Orphan drug status	
Yes	42 (72)
No	16 (28)
Novel mechanism of action	
Yes	22 (38)
No	36 (62)

NOTE. Study cohort (N = 58). Sums may not total to 100% because of rounding.
*Drugs may qualify for more than one expedited program.

Time from IND to FDA Approval (Hwang et al., 2018)

Table 2. Time to US Food and Drug Administration Approval of Cancer Drugs, 2012 to 2017

Characteristic	No. (%)	Time from IND to Approval: Years, Median (IQR)	*P*
Any expedited program			
Yes	55 (95)	6.8 (4.9-9.6)	.25
No	3 (5)	8.3 (6.7-14.1)	
Expedited program*			
All PR	46 (79)	6.4 (4.8-9.5)	.32
All AA	26 (45)	5.5 (4.4-8.3)	.05
All FT	28 (48)	6.5 (5.1-8.2)	.18
All BTD	25 (43)	5.2 (4.2-8.3)	.01
Accelerated approval*			
AA and BTD	17 (29)	4.8 (3.9-7.3)	.009
AA but no BTD	9 (16)	8.3 (6.2-10.2)	
Combinations of programs*†			
PR only	7 (12)	10.7 (6.6-19.6)	.73
FT only	5 (9)	6.8 (5.0-7.0)	.30
PR, FT	9 (16)	6.1 (5.2-7.4)	.17
PR, BTD	5 (9)	9.3 (4.6-14.1)	.88
PR, AA, FT	3 (5)	5.1 (5.0-9.6)	.28
PR, AA, BTD	11 (19)	4.8 (3.9-7.3)	.05
PR, FT, BTD	3 (5)	6.1 (5.2-7.4)	.51
PR, AA, FT, BTD	6 (10)	4.8 (2.7-8.1)	.12
Cancer type			
Solid	37 (64)	6.8 (4.9-9.5)	.52
Blood	21 (36)	7.0 (5.1-9.6)	
Orphan drug status			
Yes	42 (72)	7.0 (4.8-9.5)	.88
No	16 (28)	6.8 (5.3-10.4)	
Novel mechanism of action			
Yes	22 (38)	7.0 (5.2-9.6)	.46
No	36 (62)	6.9 (4.8-9.6)	

Abbreviations: AA, accelerated approval; BTD, breakthrough therapy designation; FT, fast track; IND, Investigational New Drug; IQR, interquartile range; PR, priority review.

*Drugs may qualify for more than one expedited program. *P* values for comparison with drugs receiving no expedited program.

†Only combinations of expedited programs with more than two observations are presented.

Efficacy, Safety, and Approval of Breakthrough Designations vs Nonbreakthrough

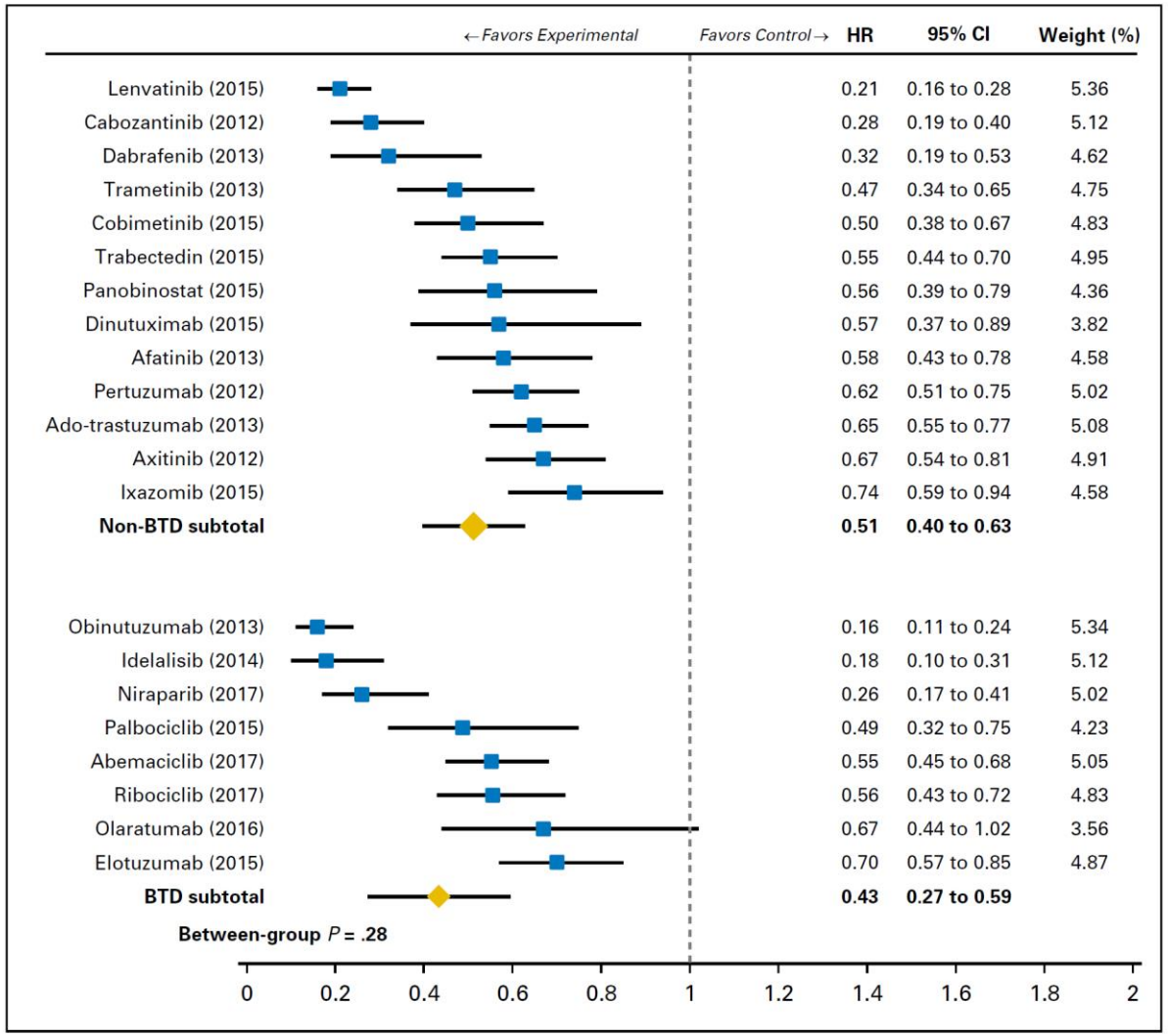
Pivotal Trial End Points and Outcomes (Hwang et al., 2018)

Table 3. Pivotal Trial End Points and Outcomes of US Food and Drug Administration–Designated Breakthrough Versus Nonbreakthrough Cancer Drugs, 2012 to 2017

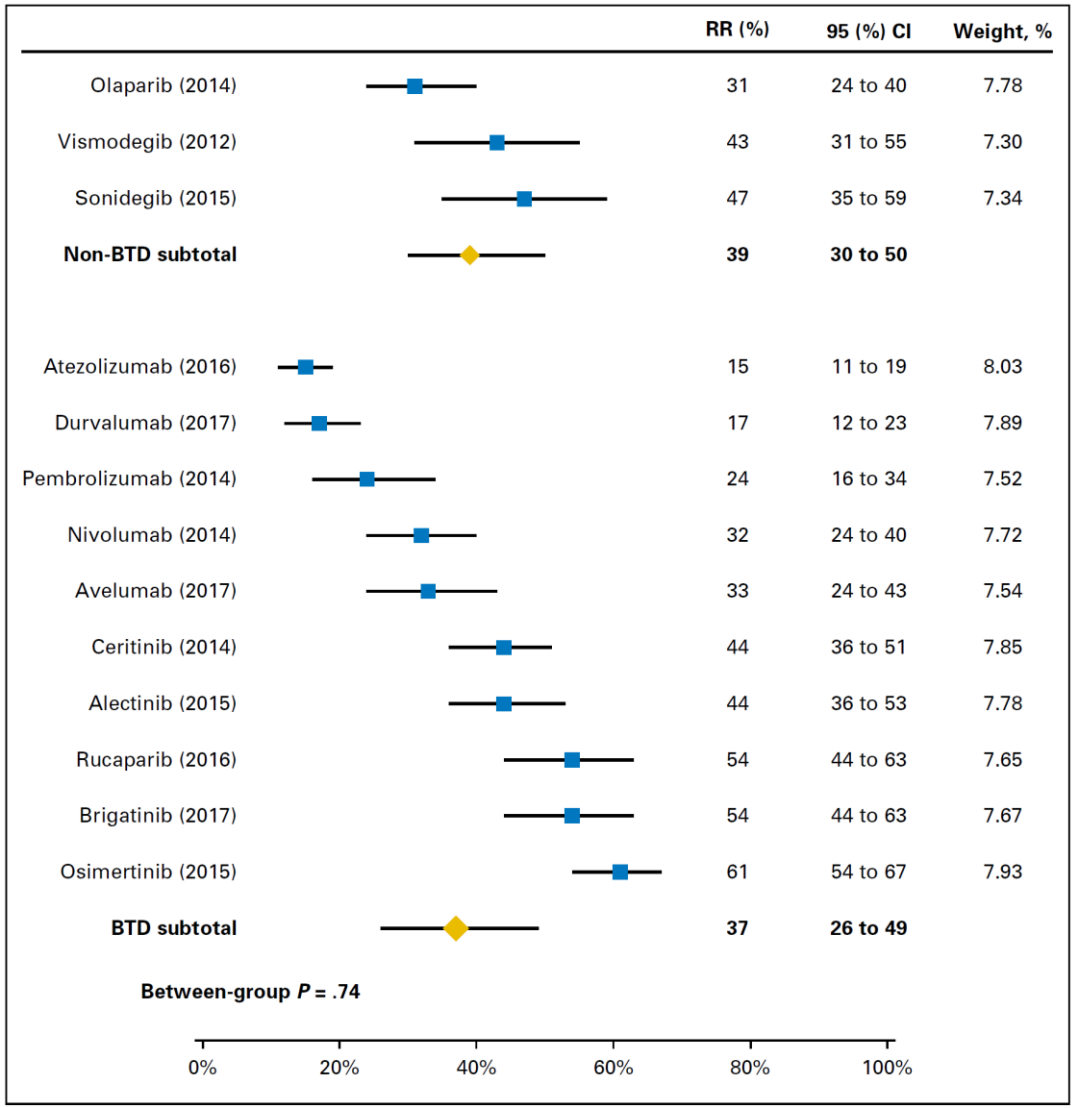
End Point or Outcome	Breakthrough-Designated Drugs (n = 25)	Nonbreakthrough Drugs (n = 33)	*P*
Primary trial end point, No. (%)			
Response rate*	16 (64)	12 (36)	.03
Progression-free survival†	8 (32)	11 (33)	
Invasive disease-free survival	0 (0)	1 (3)	
Overall survival‡	1 (4)	9 (27)	
Efficacy§			
Response rate, %			
Median (IQR)	38 (24-54)	43 (34-47)	.73
Pooled estimate (IQR)‖	37 (26-49)	39 (30-50)	.74
Progression-free survival†			
Gain, months, median (IQR)	8.6 (4.5-11.9)	4.0 (3.0-6.0)	.11
Pooled hazard ratio (IQR)‖	0.43 (0.27-0.59)	0.51 (0.40-0.63)	.28
Clinically meaningful improvement, No. (%)¶	5 (83)	9 (75)	.99
Novelty			
Novel mechanism of action, No. (%)	9 (36)	13 (39)	1.00
Safety			
Serious adverse events, No. patients (%)	2,586 of 6,857 (38)	4,347 of 11,933 (36)	.93‖
Deaths not caused by progression, No. patients (%)	347 of 6,265 (6)	517 of 12,188 (4)	.99‖

NOTE. Sums may not total to 100% because of rounding.
Abbreviation: IQR, interquartile range.
*For solid tumors, assessed as complete and partial responses.
†Median progression-free survival was not reached for the experimental group in the pivotal trials for three drugs at the time of Food and Drug Administration approval.
‡Includes two drugs approved on the basis of both overall survival and progression-free survival.
§Evaluated for solid tumor response rate (n = 13), progression-free survival gain (n = 18), and hazard ratio (n = 21).
‖From random-effects meta-regression.
¶On the basis of ASCO criteria of improvement in progression-free survival of ≥ 3 months.

Forest plot of hazard ration for PFS (Hwang et al., 2018)



Forest plot of hazard ration for Response Rate (Hwang et al., 2018)



Useful Links

- FDA
  - https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review
- Guidance for Industry “Expedited Programs for Serious Conditions – Drugs and Biologic
  - https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf

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