122. Kongress der Deutschen Gesellschaft für Innere Medizin e.V.

Demographischer Wandel fordert Innovation

09. - 12. April 2016

Status quo und zukünftige Anforderungen an wissenschaftliche Erkenntnisse zu Wirksamkeit und Sicherheit bei der Zulassung onkologischer Wirkstoffe im Zeitalter der Präzisionsmedizin

Wolf-Dieter Ludwig

HELIOS Klinikum Berlin-Buch

Klinik für Hämatologie, Onkologie, Tumorimmunologie und Palliativmedizin

The Use of Superlatives in Cancer Research

10 „Superlativ Begriffe

21.6.-25.6.2015

Google‘s news search

Artikel N=94

Drug	Superlative Frequency, No. (%)[a] (N = 97)	Superlative(s) Used (Frequency)	Drug Classification	FDA-Approved Drug(s)	Clinical Data?
Ipilimumab and nivolumab (Yervoy-Opdivo combination)	20 (21)	Breakthrough (7), miracle (5), game changer (5), revolutionary (2), groundbreaking (1)	Immunotherapy–checkpoint inhibitor	Yes	Yes
Pembrolizumab (Keytruda)	12 (12)	Revolutionary (5), game changer (2), groundbreaking (2), cure (2), miracle (1)	Immunotherapy–checkpoint inhibitor	Yes	Yes
Palbociclib (Ibrance)	10 (10)	Groundbreaking (6), game changer (2), revolutionary (1), miracle (1)	Targeted therapy	Yes	Yes
Trastuzumab emtansine (Kadcyla)	7 (7)	Revolutionary (4), miracle (3)	Targeted therapy	Yes	Yes
Dinutuximab (Unituxin)	4 (4)	Game changer (1), groundbreaking (1), breakthrough (1), miracle (1)	Targeted therapy	Yes	Yes
MPDL3280A	3 (3)	Game changer (2), revolutionary (1)	Immunotherapy–checkpoint inhibitor	No	Yes
Olaparib (Lynparza)	3 (3)	Revolutionary (2), breakthrough (1)	Targeted therapy	Yes	Yes
T-VEC	3 (3)	Breakthrough (3)	Immunotherapy–vaccine	No	Yes
Pertuzumab (Perjeta)	3 (3)	Groundbreaking (3)	Targeted therapy	Yes	Yes
Unnamed	3 (3)	Breakthrough (1), miracle (1), game changer (1)	…	…	…
Radium-223 dichloride (Alpharadin or Xofigo)	2 (2)	Game changer (2)	Radiotherapeutic drug	Yes	Yes
BPM31510	2 (2)	Revolutionary (2)	Cytotoxic therapy	No	Yes

JAMA Oncology January 2016 Volume 2, Number 1

Zulassungsstudien bei onkologischen Wirkstoffen: Status quo - *Agenda*

- neu zugelassene onkologische Wirkstoffe (FDA/EMA): 2014/2015
- Anforderungen an die Zulassung
- Zulassung: Was wissen wir und was sollten wir wissen?
- frühe Nutzenbewertung onkologischer Wirkstoffe
- Resümee/Ausblick

2014 FDA drug approvals

The FDA approved 41 new therapeutics in 2014, but the bumper year fell short of the commercial power of the drugs approved in 2013.

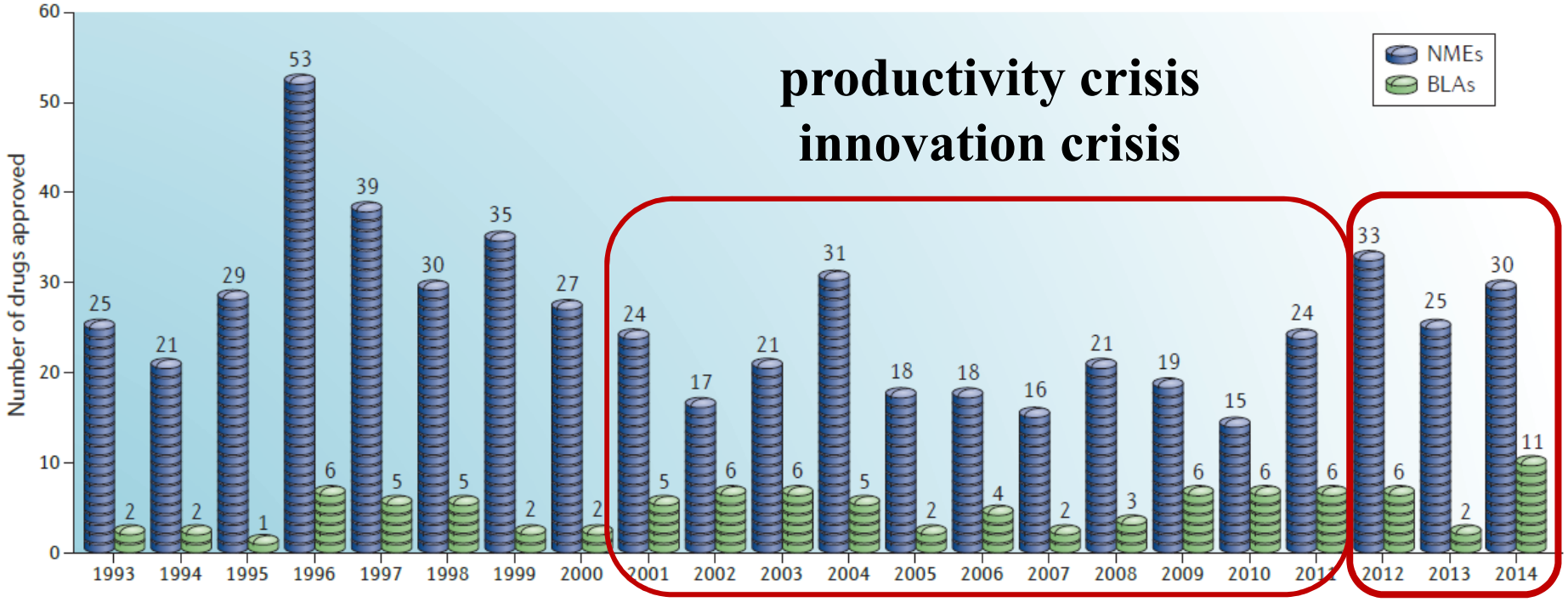
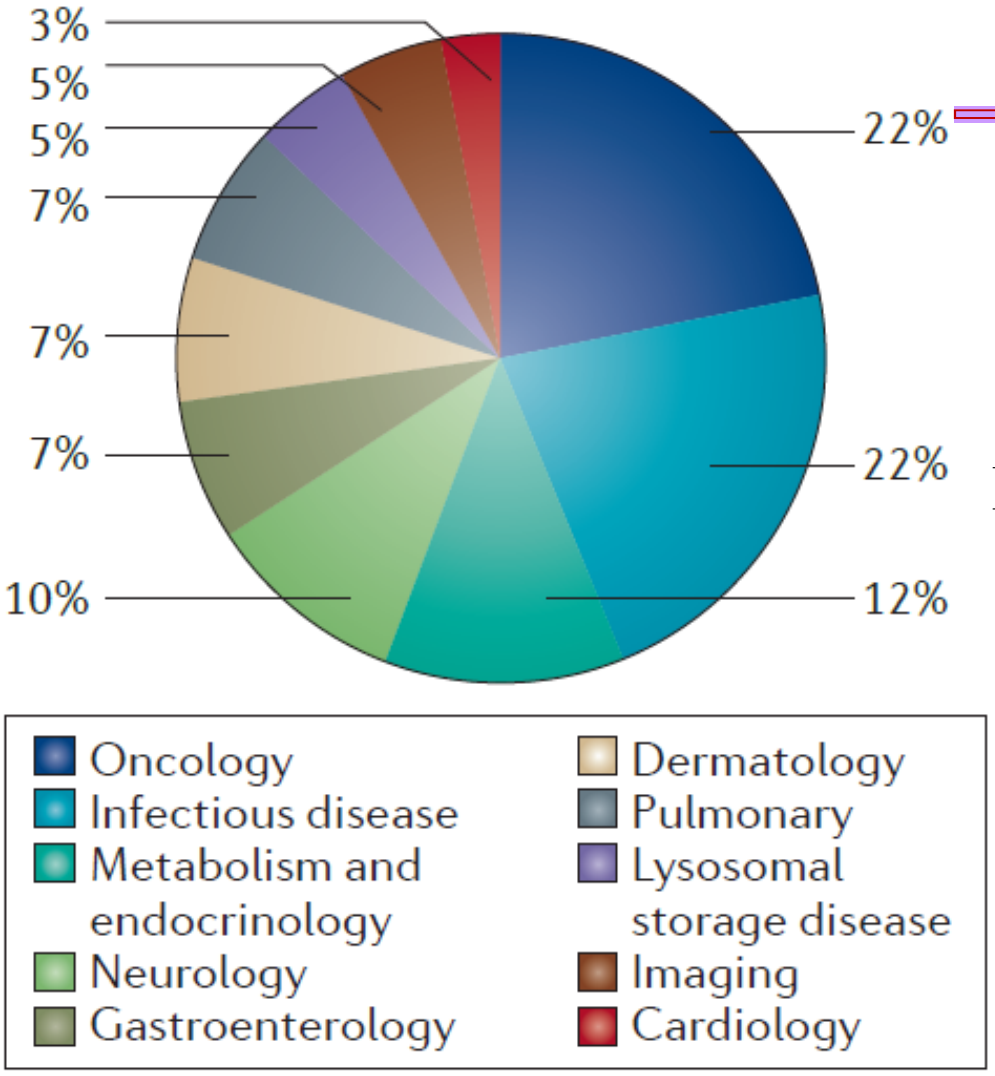


Figure 1 | **Novel approvals since 1993.** This figure shows the new molecular entities (NMEs) and biologics license applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER) since 1993. Approvals by the Center for Biologics Evaluation and Research (CBER) are not included in this drug count. Data are from Drugs@FDA and the US Food and Drug Administration (FDA).

Zulassungen nach Anwendungsgebiet 2014



N=10

Orphan N= 9

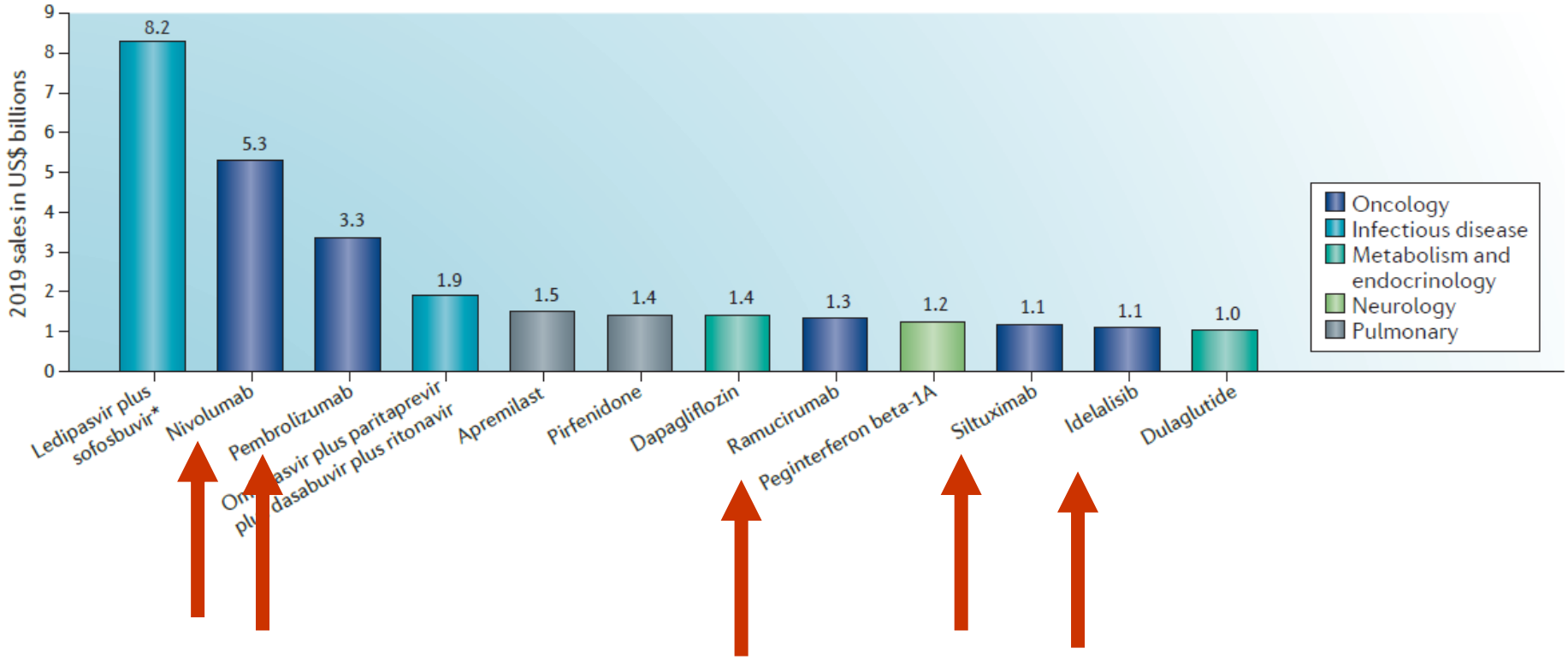
Priority N= 9

Accelerated N=7

Breakthrough N=6

„Biologicals“ N=5

Arzneimittel zugelassen in 2014:
erwartete „Blockbuster“ 2019 (5/12 Onkologie)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Annual report 2014

Deutschland 2014

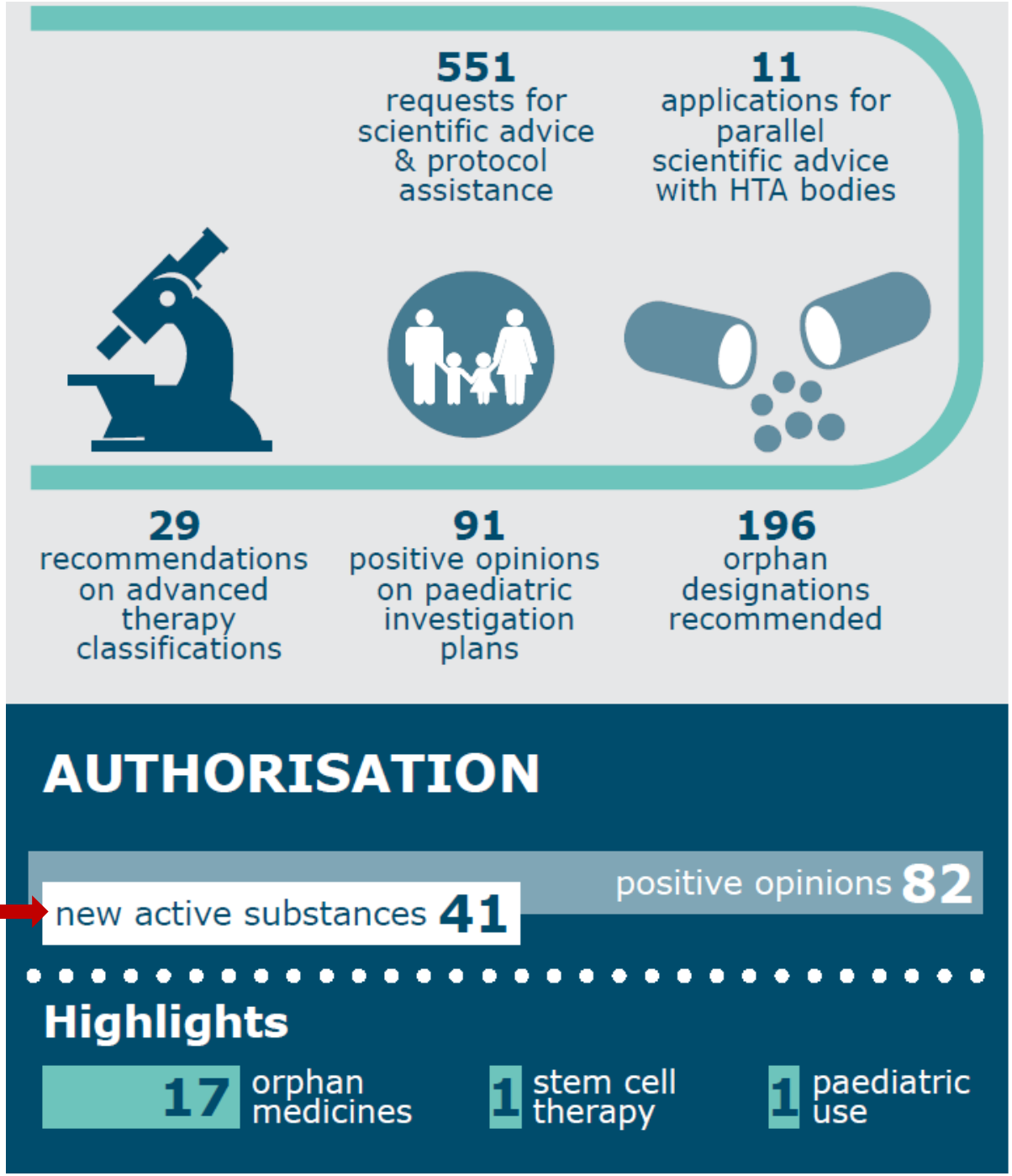
46 Arzneimittel

mit neuen Wirkstoffen

14 Orphan Drugs

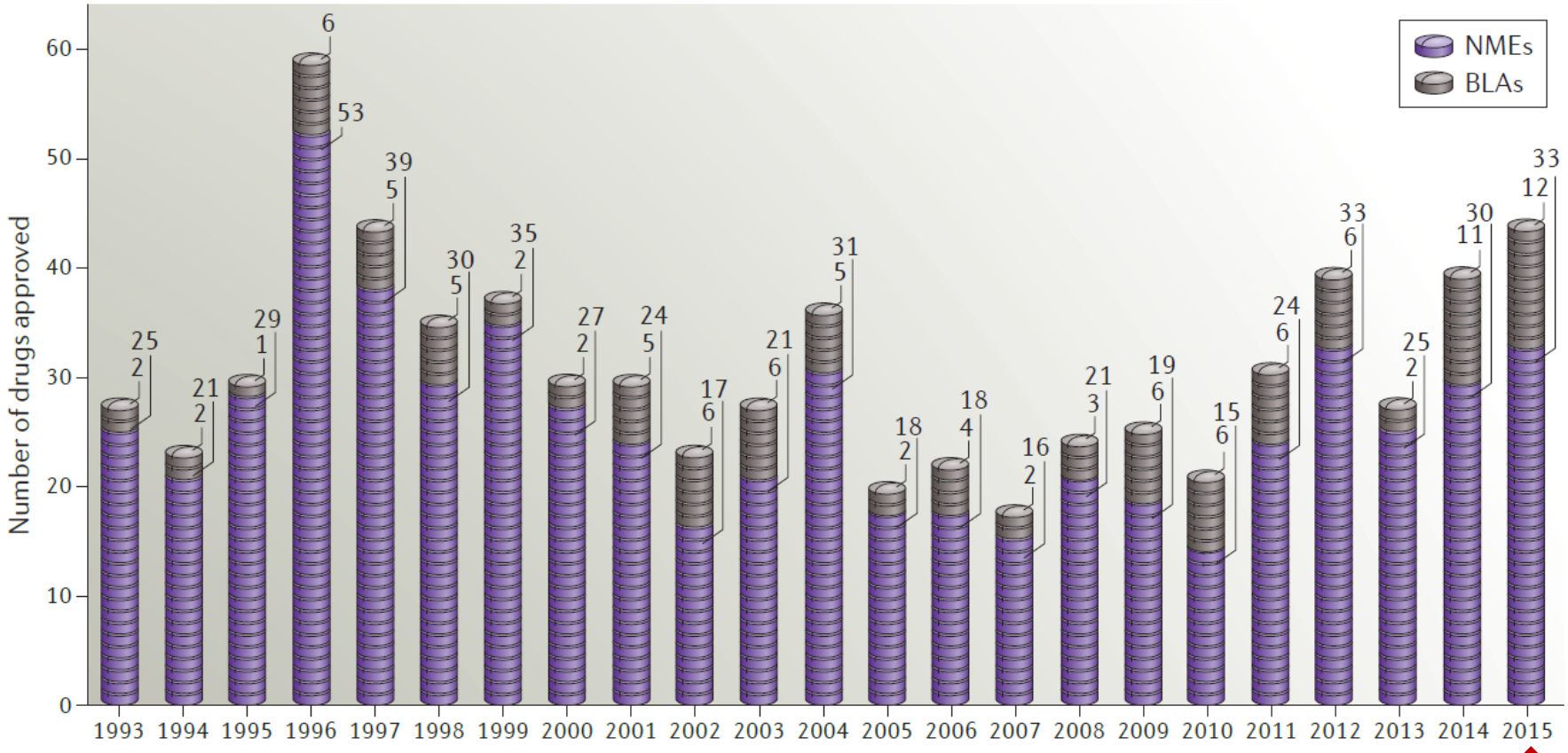
7 Onkologika

(4 als Orphan Drugs)

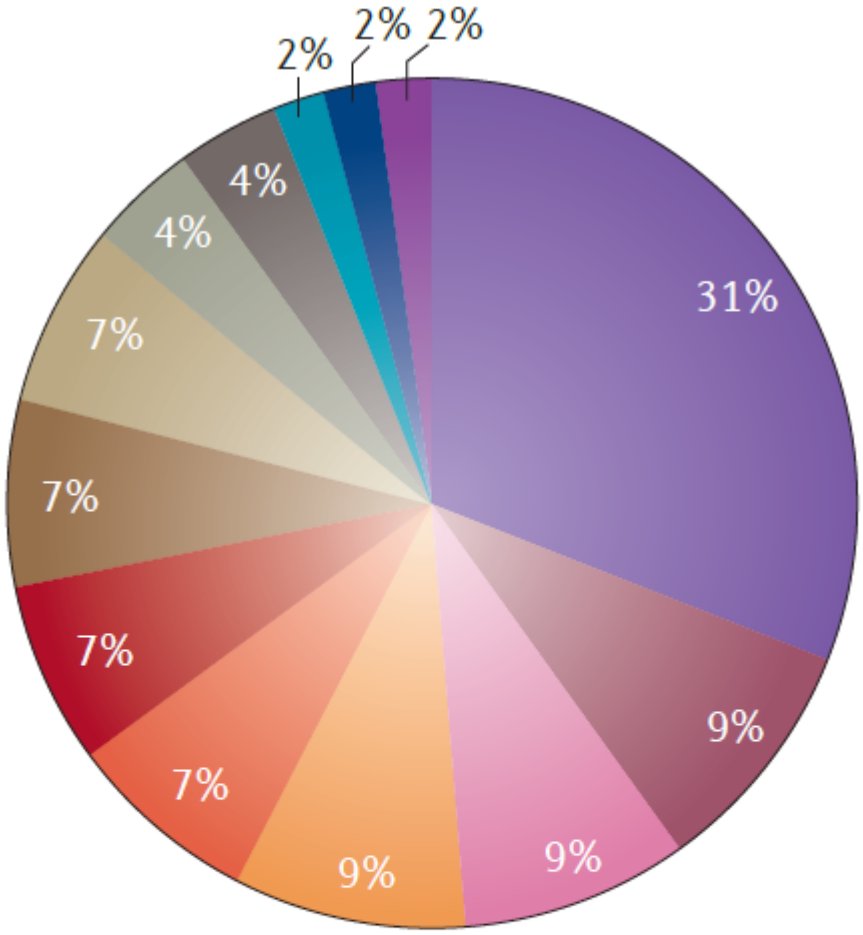


2015 FDA drug approvals

FDA approval rate continues to surge, with 45 green lights for new drugs granted in 2015.



Zulassungen nach Anwendungsgebiet
FDA 2015



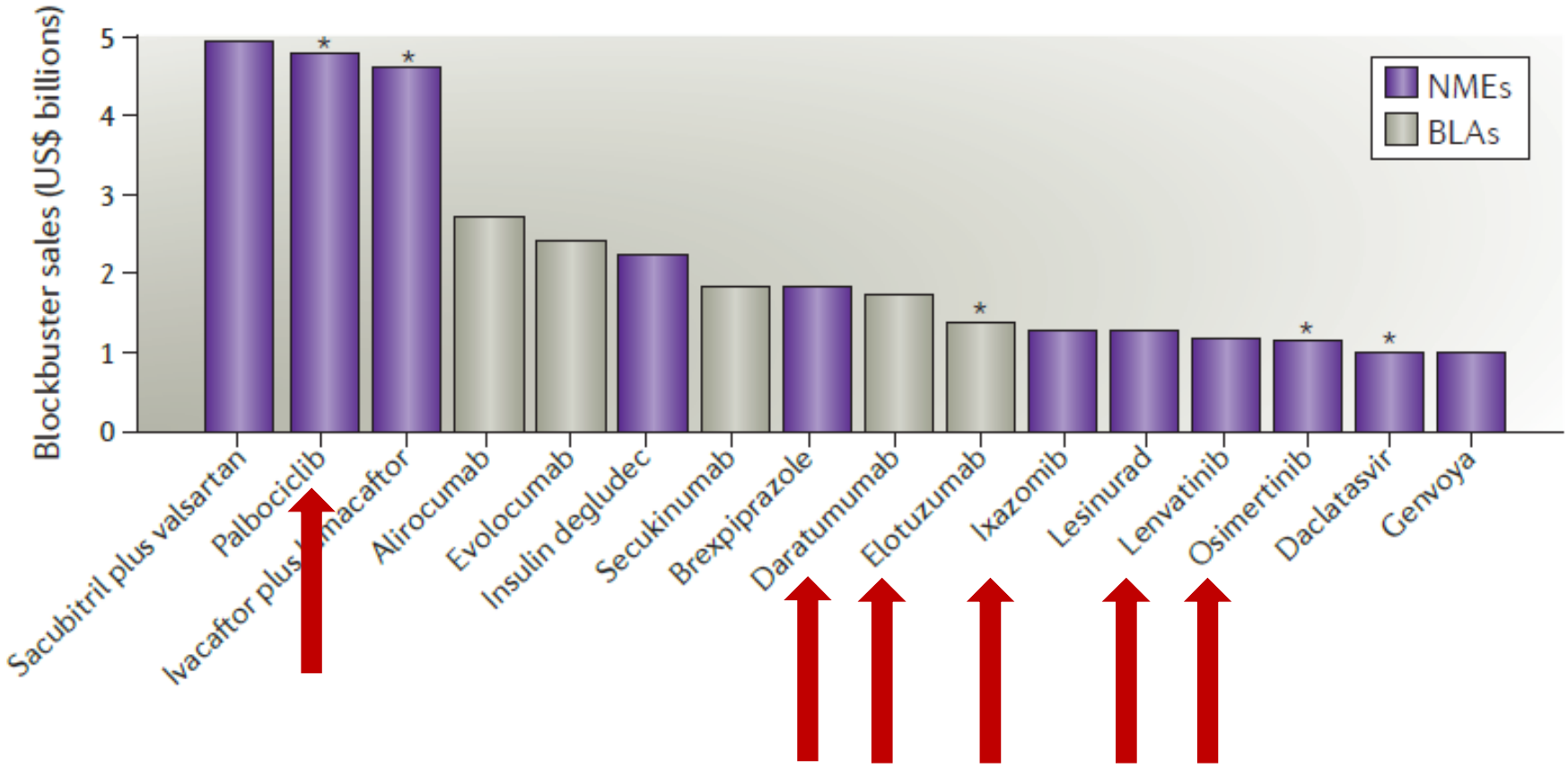
NATURE REVIEWS | DRUG DISCOVERY VOLUME 15 | FEBRUARY 2016 |

Onkologie
N=14

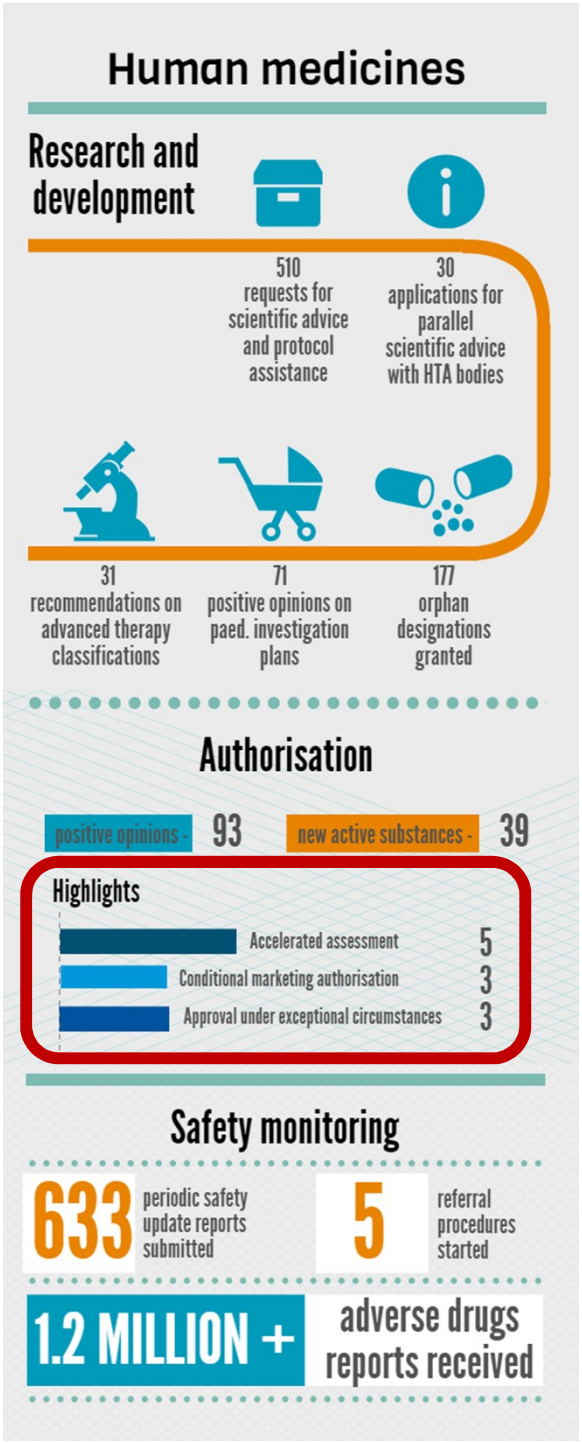
„Orphans“	N=11
„Priority“	N=11
„Breakthrough“	N= 5
„Standard“	N= 3

Arzneimittel zugelassen in 2015:
erwartete „Blockbuster“ 2020 (6/16 Onkologie)

N=16



NATURE REVIEWS | DRUG DISCOVERY VOLUME 15 | FEBRUARY 2016 |



Deutschland 2015

37 Arzneimittel

mit neuen Wirkstoffen

12 Orphan Drugs

12 Onkologika

(6 als Orphan Drugs)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Annual Report 2015

Marketing authorization of 39 new substances

May 2015

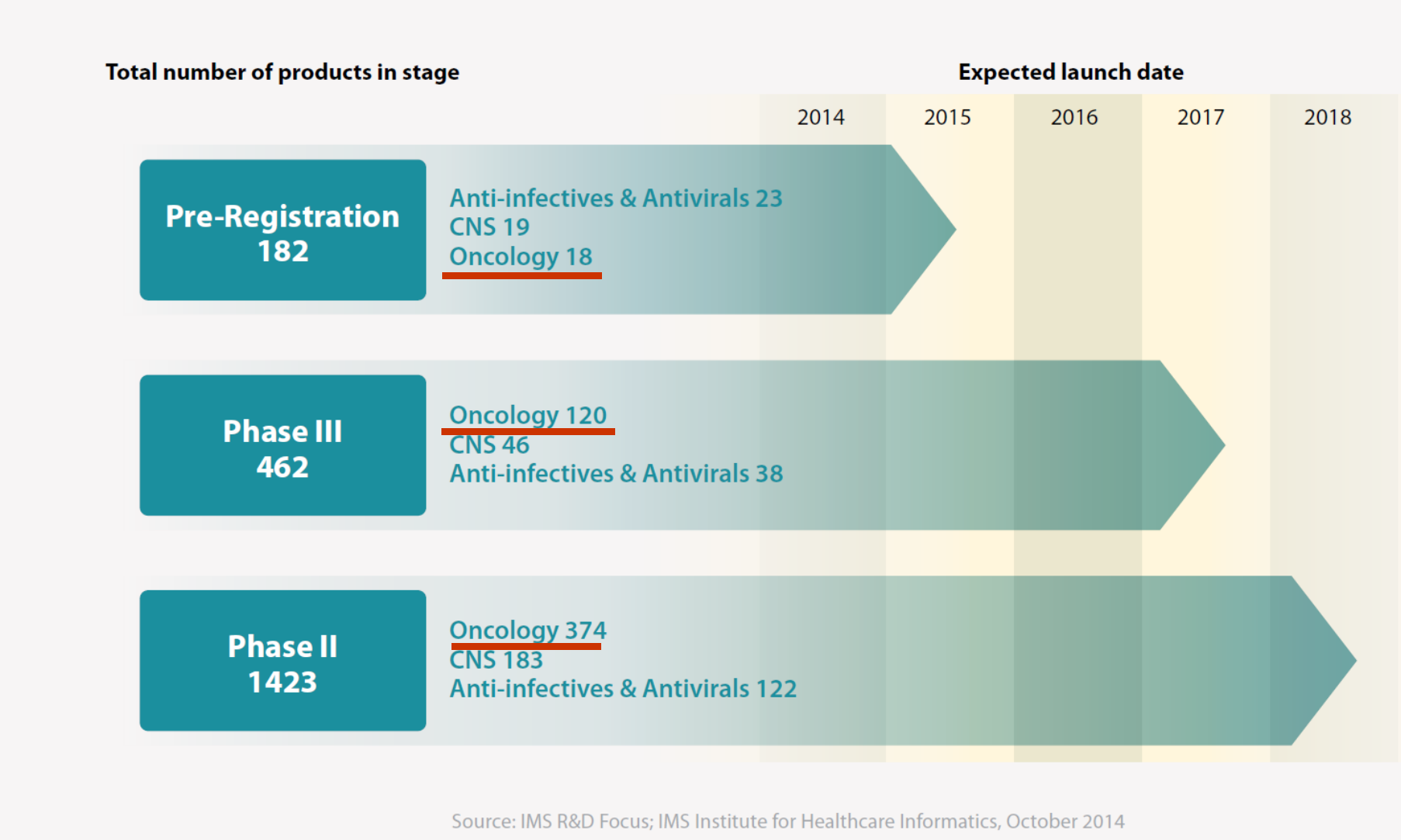
Developments in Cancer Treatments, Market Dynamics, Patient Access and Value

Global Oncology Trend Report 2015

Global Oncology Trends Report 2015. Report by the IMS Institute for Healthcare Informatics.

Oncology products continue to drive the pipeline:

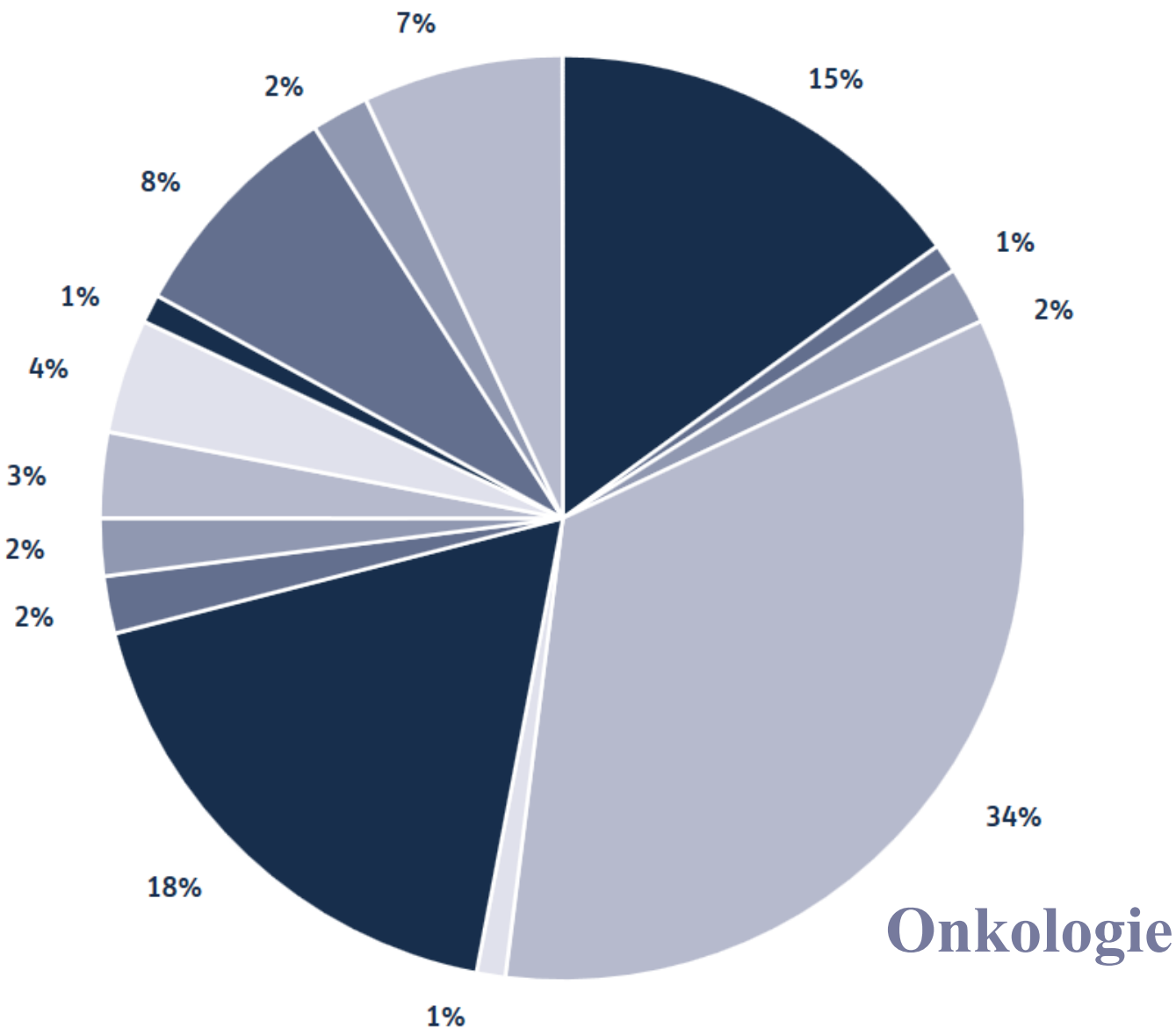
„approx. 30% of the total pipeline of pharmaceutical companies and 25% of the late-stage pipeline (phase II through pre-registration“)



„double the size of the next highest class, i.e., products developed for treatment of CNS disorders“

Medikamentenprojekte der vfa-Mitgliedsunternehmen mit Aussicht auf eine Zulassung bis 2019

Verteilung auf verschiedene medizinische Gebiete; Gesamtzahl der Projekte: 328

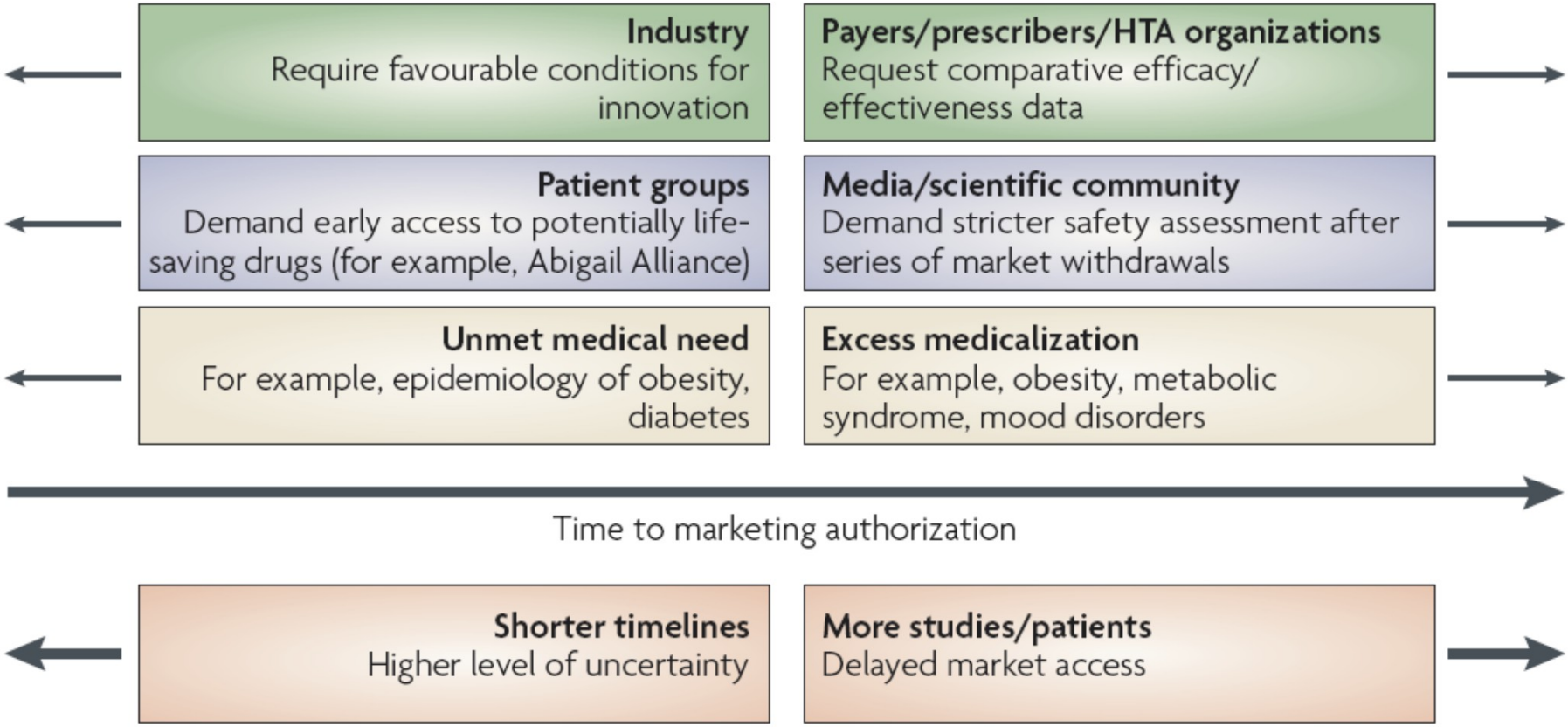


Zulassungsstudien bei onkologischen Wirkstoffen: Status quo - *Agenda*

- neu zugelassene onkologische Wirkstoffe (FDA/EMA): 2014/2015
- Anforderungen an die Zulassung
- Zulassung: Was wissen wir und was sollten wir wissen?
- Nutzenbewertung onkologischer Wirkstoffe
- Resümee/Ausblick

Das Dilemma der Zulassungsbehörden

Eichler H-G et al.



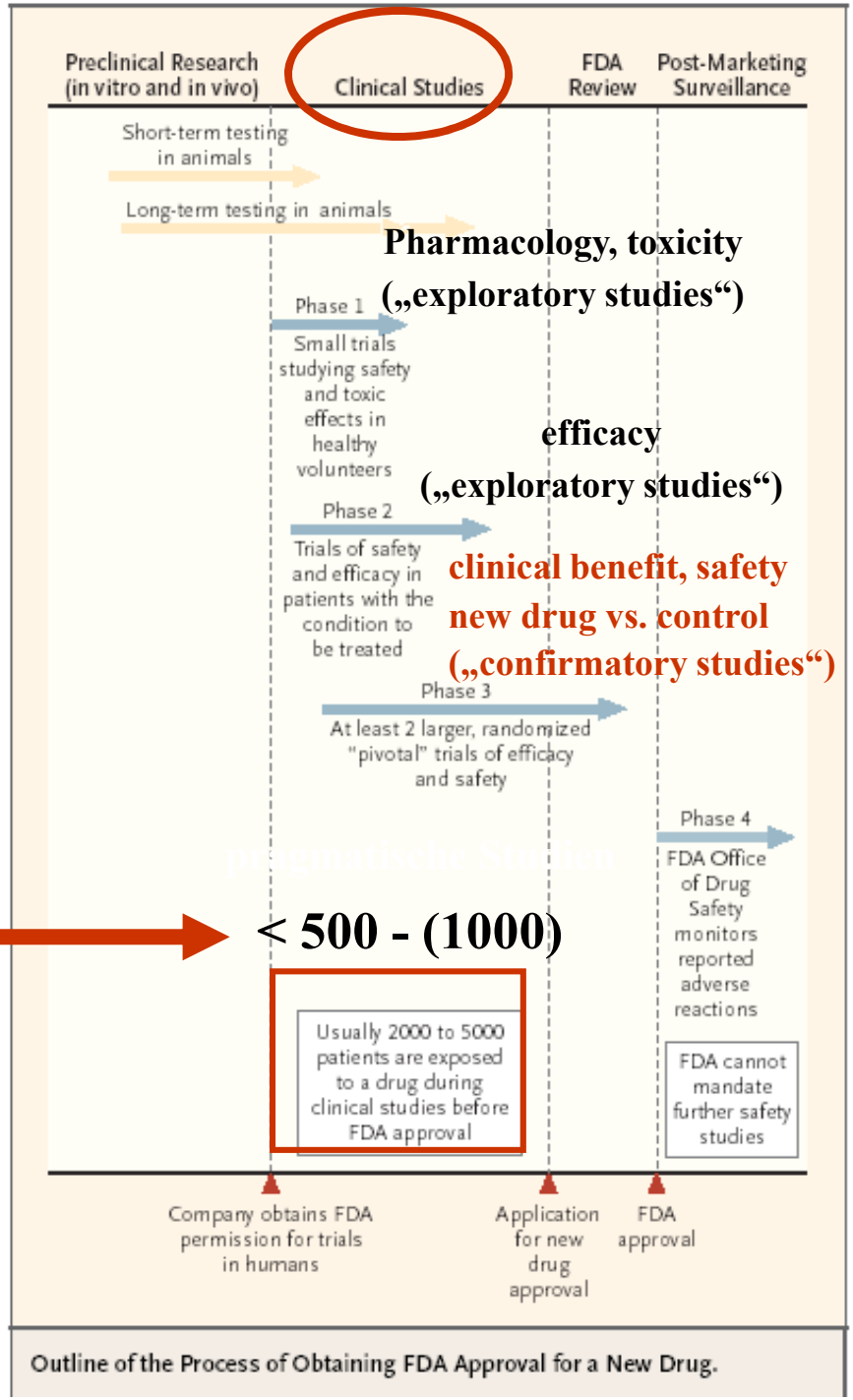
Drug Approval Process

„Complicated balance between
patient benefit,
regulatory requirements,
and economic interests“

Oncology

Median clinical/approval phase:
(Median)
„breakthrough“ 5,2 vs. 7,4 Jahre

Okie S: NEJM 2005; 352:1173



Outline of the Process of Obtaining FDA Approval for a New Drug.

Trends in utilization of FDA expedited drug development and approval programs, 1987-2014: cohort study

Aaron S Kesselheim, Bo Wang, Jessica M Franklin, Jonathan J Darrow

doi: 10.1136/bmj.h4633 | *BMJ* 2015;351:h4633 | thebmj

Table 1 | Food and Drug Administration expedited development and review programs

Program name	Year instituted	Characteristics of qualifying products	Does it formally change evidentiary standard?	Phase during which it exerts most direct effect
Orphan drug	1983	Treats disease occurring in <200 000 people per year in United States	No	Drug development
Fast track	1988	Treats life threatening or severely debilitating diseases	Yes; can approve after single phase 2 study	Drug development and FDA review
Priority review	1992	Seems to offer therapeutic advance over available therapy	No	FDA review
Accelerated approval	1992	Treats serious or life threatening illnesses	Yes; can approve on basis of surrogate endpoint reasonably likely to predict patient benefit	Drug development and FDA review
Breakthrough therapy	2012	Treats serious disease for which preliminary clinical evidence suggests substantial improvement over existing therapies on one or more clinically important endpoints	No	Drug development and FDA review

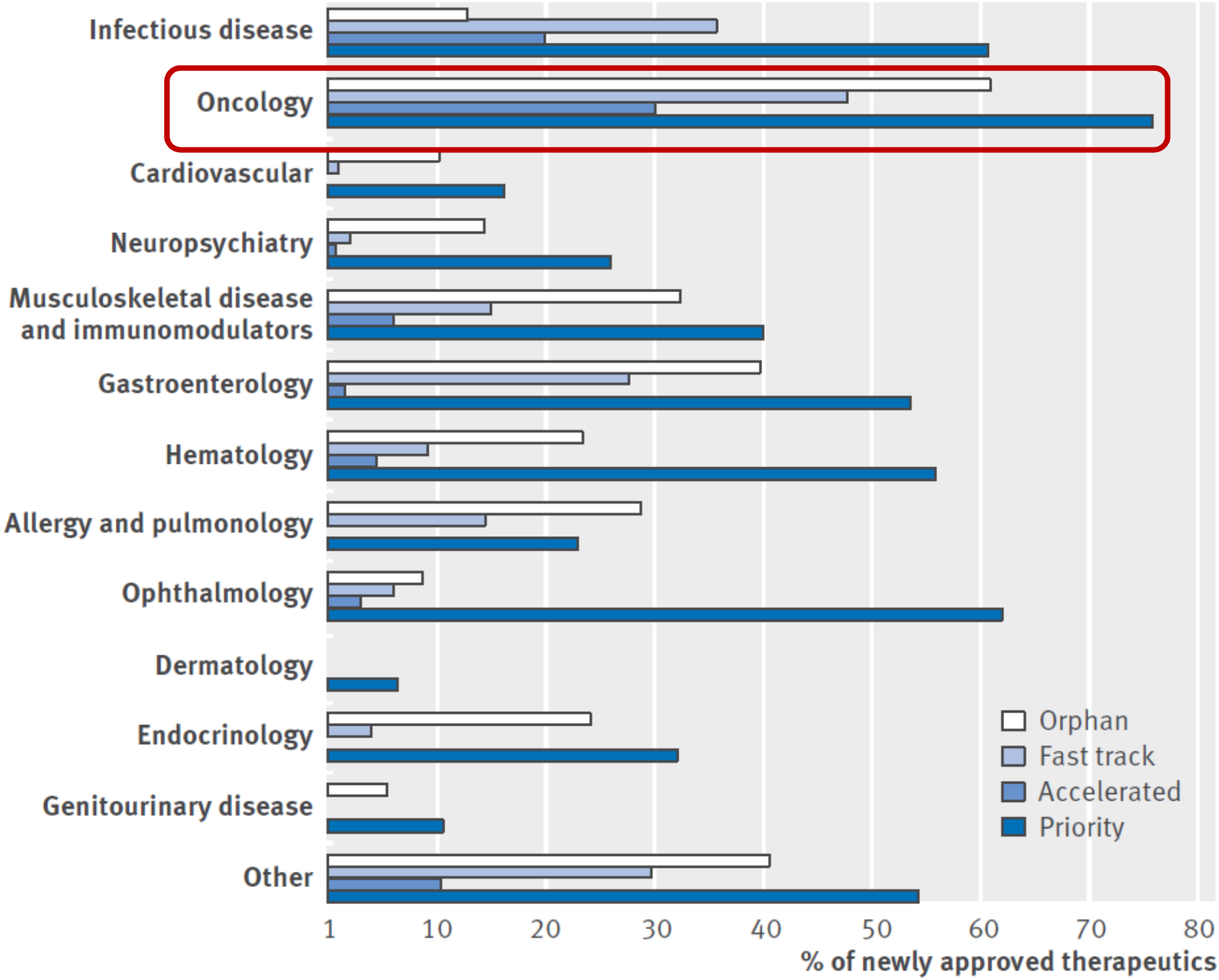
Trends in utilization of FDA expedited drug development and approval programs, 1987-2014: cohort study

Table 2 | Characteristics of new therapeutics approved by Food and Drug Administration, 1987-2014

Characteristics	No (%)*
Therapeutic area:	
Infectious disease	109 (14)
Oncology	107 (14)
Cardiovascular disease and its risk factors†	99 (13)
Neuropsychiatry	97 (13)
Musculoskeletal disease and immunomodulators	80 (10)
Gastroenterology	58 (7)
Hematology	43 (6)
Allergy and pulmonology	35 (5)
Ophthalmology	34 (4)
Dermatology	31 (4)
Endocrinology	25 (3)
Genitourinary disease	19 (2)
Other	37 (5)
Expedited programs:	
Orphan drug	195 (25)
Fast track	144 (19)
Accelerated approval	68 (9)
Priority review	331 (43)
Innovativeness‡	
First in class drug	252 (33)
Non-first in class drug	508 (67)

*Total of 774 approved therapeutics in our database.
†Including diabetes mellitus, hyperlipidemia, and hypertension.
‡FDA classification available for 760 of these therapeutics.

doi: 10.1136/bmj.h4633 | *BMJ* 2015;351:h4633 | the bmj


Infectious disease
Oncology
Cardiovascular
Neuropsychiatry
Musculoskeletal disease and immunomodulators
Gastroenterology
Hematology
Allergy and pulmonology
Ophthalmology
Dermatology
Endocrinology
Genitourinary disease
Other
Orphan
Fast track
Accelerated
Priority
1
10
20
30
40
50
60
70
80
% of newly approved therapeutics

Expediting Drug Development — The FDA's New "Breakthrough Therapy" Designation

Rachel E. Sherman, M.D., M.P.H., Jun Li, J.D., Ph.D., Stephanie Shapley, M.B.A., Melissa Robb, R.N., and Janet Woodcock, M.D.

N ENGL J MED 369;20 NEJM.ORG NOVEMBER 14, 2013

Bedeutung der „post-market confirmatory trials"

Table 2. Comparison of the FDA's Various Expedited Programs for Serious Conditions.*

Variable	Fast-Track Designation	Breakthrough-Therapy Designation	Accelerated-Approval Pathway	Priority-Review Designation
Qualifying criteria	A drug that is intended to treat a serious condition and for which nonclinical or clinical data demonstrate the potential to address an unmet medical need†	A drug that is intended to treat a serious condition and that preliminary clinical evidence indicates may demonstrate substantial improvement over available therapies on a clinically significant end point or end points	A drug that treats a serious condition, generally provides a meaningful advantage over available therapies, and demonstrates an effect on a surrogate end point that is reasonably likely to predict clinical benefit or on a clinical end point that is reasonably likely to predict an effect on "irreversible morbidity or mortality" or other clinical benefit	An application (original or efficacy supplement) for a drug that treats a serious condition and that if approved would provide a significant improvement in safety or effectiveness‡
Features	Opportunities for frequent interactions with FDA; possible eligibility for priority review; rolling review	All fast-track designation features; intensive guidance on an efficient drug-development program, beginning as early as phase 1; organizational commitment involving FDA senior managers	Approval based on an effect on a surrogate or intermediate clinical end point that is reasonably likely to predict a drug's clinical benefit	Shorter period for review of marketing application (6 months, as compared with the 10-month standard review)

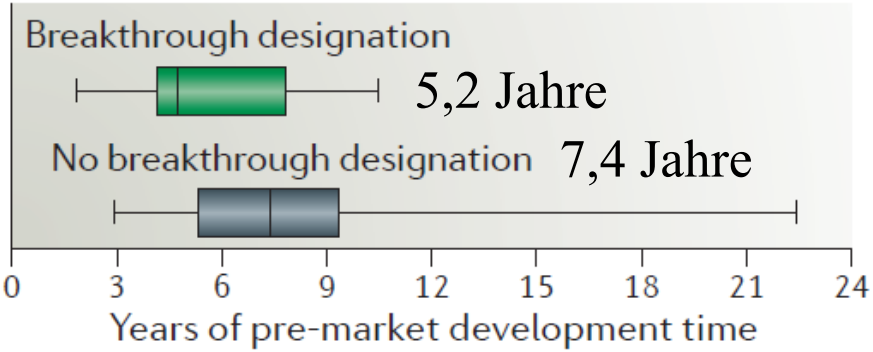
Impact of breakthrough therapy designation on cancer drug development

NATURE REVIEWS | DRUG DISCOVERY

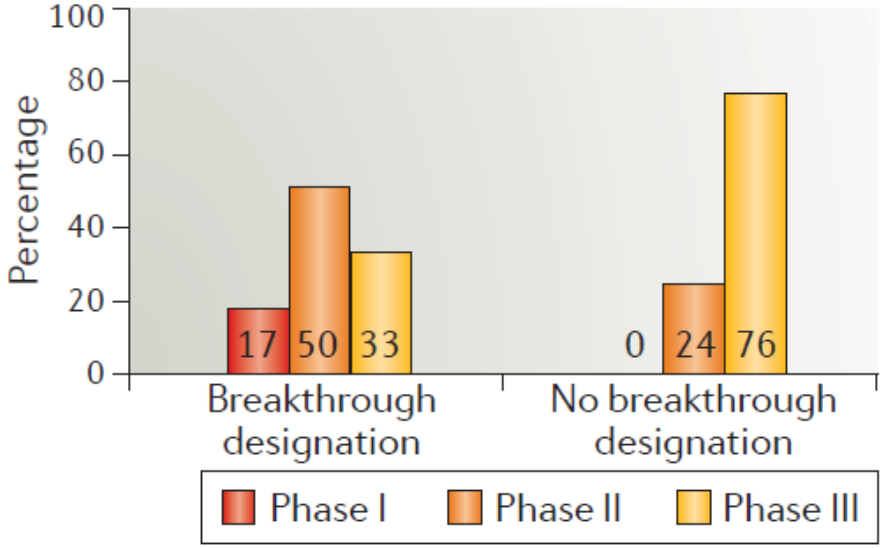
doi:10.1038/nrd.2016.19
Published online 2 Mar 2016

01/2013-12/2015: Onkologie 12/29 (41%)

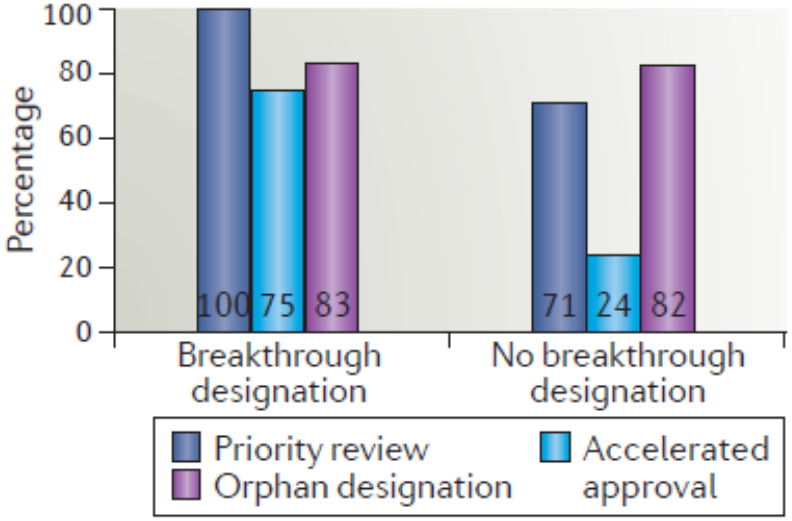
b Pre-market development time



c Pivotal trial phase



d Regulatory mechanisms



FDA fails to monitor fast tracked drugs after approval, says US watchdog

BMJ 2016;352:i371

Owen Dyer

Under half of the post-market studies that the FDA had required manufacturers to carry out had been completed by the set deadline, and many had not yet begun. Those that were carried out were often not reviewed on time, the report found. And the agency was three issues behind schedule in publishing its statutorily required quarterly reports on safety issues.

FDA Lacks Reliable Information for Postmarket Safety Reporting and Oversight

GAO

FDA lacks reliable, readily accessible data on tracked safety issues and postmarket studies needed to meet certain postmarket safety reporting responsibilities and to conduct systematic oversight. CDER's internal evaluations of data in its DARRTS database revealed problems with the completeness, timeliness, and accuracy of the data. These problems, as well as problems with the way data are recorded that impair their accessibility, have prevented FDA from publishing some required postmarket safety reports in a timely manner, and have restricted its ability to perform systematic oversight. Internal control standards for the federal government specify that information should be recorded in a form and within a time frame that enables staff to carry out their responsibilities and that relevant, reliable, and timely information should be available for external reporting purposes.[40] Although FDA has taken some steps to address the problems with its data, it lacks comprehensive plans for doing so.

Original Article

Approvals of drugs with uncertain benefit–risk profiles in Europe

Rita Banzi *, Chiara Gerardi, Vittorio Bertele', Silvio Garattini

Laboratory of Regulatory Policies, IRCCS—Istituto di Ricerche Farmacologiche Mario Negri, Via La Masa 19, 20156 Milan, Italy

Box 2
EMA procedures to grant marketing authorisations when data are incomplete.

	Exceptional circumstances	Conditional approval
Defined by	EC regulation 726/2004 Article 14(8) [7]	EC regulation 726/2004 Article 14(7) [7]
Since	1995	2006
Relevant guidance	Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to Article 14(8) of EC regulation 726/2004 [7]	EC regulation 507/2006 [8]
Ground for applicability	Inability to provide comprehensive data on the efficacy and safety under normal conditions	To meet unmet medical needs of patients and in the interests of public health
Conditions	• The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. • In the present state of scientific knowledge, comprehensive information cannot be provided. • It would be contrary to generally accepted principles of medical ethics to collect such information.	• Treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases. • Medicinal products to be used in emergency situations in response to public health threats recognised either by the World Health Organisation or by the EU. • Orphan medicinal products.
Specific obligations	Aimed at the provision of information on the safe and effective use of the product (normally not leading to completion of a full dossier).	To confirm that the risk–benefit balance is positive and resolving any questions relating to the quality, safety and efficacy of the product (the authorisation is not intended to remain conditional indefinitely).
Re-assessment of benefit–risk profile	Annual	Annual
Renewal of the marketing authorisation	After five years (like the regular marketing authorisation)	Annual
Accelerated assessment procedure	Yes	Yes

European Medicines Agency
Regulatory tool for early access

- Conditional marketing authorisation (CMA)
- Use of „exceptional circumstances“
- Accelerated assessment (150 instead of 210 day without clock stops)
- Orphan drug legislation
- Coming soon: **PRI**ority **ME**dicines; adaptive pathways;?

- ➢ Medicinal products fulfilling unmet medical need, e.g. for severe, life-threatening or rare diseases
- ➢ Positive benefit-risk balance to be demonstrateted
- ➢ Specific obligations from ongoing and new studies
- ➢ Yearly renewal
- ➢ Early dialogue, involving also other stakeholders (e.g., HTAs, HCP, patient organisations)

Use of the Conditional Marketing Authorization Pathway for Oncology Medicines in Europe

J Hoekman[1,2], WPC Boon[1,2], JC Bouvy[1], HC Ebbers[1], JP de Jong[3] and ML De Bruin[1]

Conditional marketing authorization (CMA) in the European Union (EU) is an early access pathway for medicines that show promising therapeutic effects, but for which comprehensive data are not available. Using a mixed quantitative-qualitative research design, we evaluated how CMA has been used in marketing authorization of oncology medicines in the period 2006 to 2013. We show that compared to full marketing authorization, CMA is granted based on less comprehensive data. However, this is accompanied by significantly longer assessment times and less consensus among regulators about marketing authorization. Moreover, development time from first-in-human testing to marketing authorization did not differ between full marketing authorization and CMA, but was significantly longer for CMA compared to accelerated approved products in the United States (US). Results indicate that CMA is not used by companies as a prospectively planned pathway to obtain early access, but as a "rescue option" when submitted data are not strong enough to justify full marketing authorization.

Conditional Marketing Authorisation

Cancer
12 (52%)

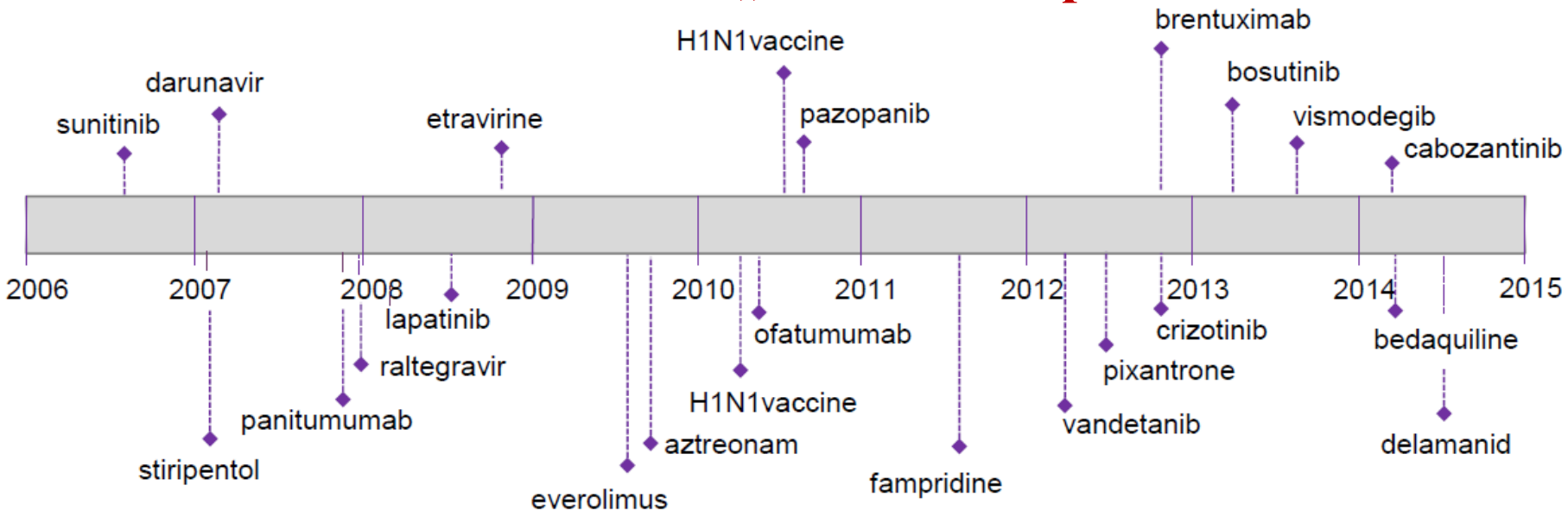
HIV
3 (13%)

23

Other
6 (26%)

Influenza
2 (9%)

weniger Patienten (N=154) untersucht als bei regulärer Zulassung
selten RCTs mit „harten“ Endpunkten



Zulassungsstudien bei onkologischen Wirkstoffen: Status quo - *Agenda*

- neu zugelassene onkologische Wirkstoffe (FDA/EMA): 2014/2015
- Anforderungen an die Zulassung
- Zulassung: Was wissen wir und was sollten wir wissen?
- frühe Nutzenbewertung onkologischer Wirkstoffe
- Resümee/Ausblick

Guideline on the evaluation of anticancer medicinal products in man

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Draft Agreed by Oncology Working Party	**September 2011**
Adoption by CHMP for release for consultation	15 December 2011
End of consultation (deadline for comments)	31 May 2012
Discussed at SAG-Oncology	05 November 2012
Agreed by Oncology Working Party	28 November 2012
Adopted by CHMP	13 December 2012
Date coming into effect	01 July 2013

This guideline replaces guideline / NfG Reference.

Keywords	Cancer, malignancy, biomarker, targeted drugs, pharmacogenomics

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guideline on the evaluation of anticancer medicinal products in man

The purpose of this guideline is to provide guidance on all stages of clinical drug development for the treatment of malignancies, including drug resistance modifiers or normal tissue protective compounds. Supportive measures such as anti-emetics and haematopoietic growth factors, however, are covered by separate guidelines.

Convincingly demonstrated favourable effects on overall survival (OS) are from both a clinical and methodological perspective the most persuasive outcome of a clinical trial. Prolonged progression-free or disease-free survival (PFS/DFS), however, are in most cases as such considered relevant measures of patients benefit, but the magnitude of the treatment effect should be sufficiently large to outbalance toxicity and tolerability problems. In order to capture possible negative effects on the activity of next-line therapies and also treatment related fatalities, informative data on overall survival compatible with a trend towards favourable outcome are normally expected at time of submission. This has consequences with respect to interim analyses, other than for futility, and cross-over, which thus should be undertaken only when available survival data provide the information needed for a proper evaluation of benefit/risk.

Guideline on the evaluation of anticancer medicinal products in man

In section 8, definitions and abbreviations used in this guideline are summarised. Appendix 1 provides methodological guidance on the use of PFS as endpoint in confirmatory studies. A planned appendix 2 will focus on the use of patient reported outcome (PRO) measures and health-related quality of life (HRQoL) from a regulatory perspective. A revised paediatric guideline is also foreseen as Appendix 3 and Appendix 4 is dedicated to condition specific guidance.

Number of Patients Studied Prior to Approval of New Medicines: A Database Analysis

Ruben G. Duijnhoven[1,2], Sabine M. J. M. Straus[2,3], June M. Raine[4], Anthonius de Boer[1], Arno W. Hoes[5], Marie L. De Bruin[1,2]*

Original Investigation

Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012

Nicholas S. Downing, AB; Jenerius A. Aminawung, MD, MPH; Nilay D. Shah, PhD; Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS

JAMA. 2014;311(4):368-377. doi:10.1001/jama.2013.282034

Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012

Nicholas S. Downing, AB; Jenerius A. Aminawung, MD, MPH; Nilay D. Shah, PhD; Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS

Was fehlt?

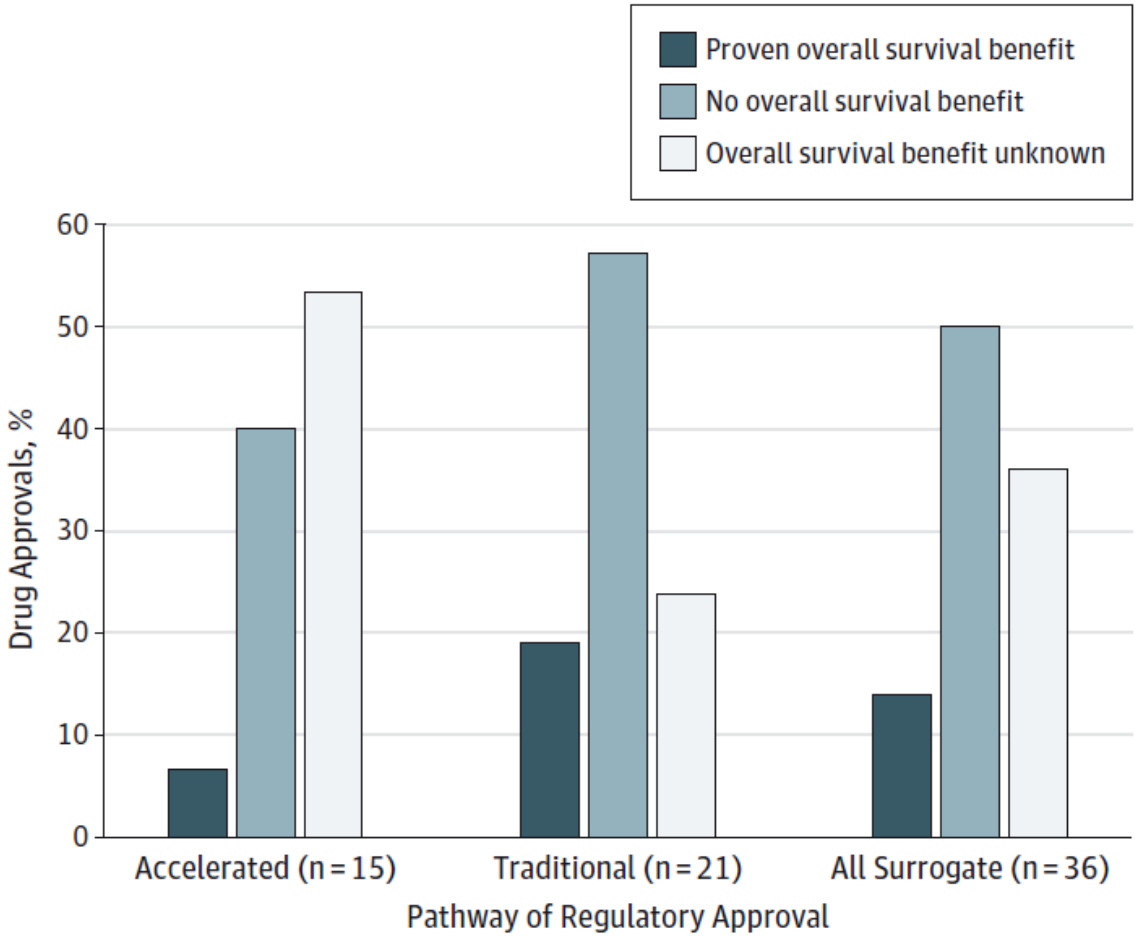
CONCLUSIONS AND RELEVANCE The quality of clinical trial evidence used by the FDA as the basis for recent approvals of novel therapeutic agents varied widely across indications. This variation has important implications for patients and physicians as they make decisions about the use of newly approved therapeutic agents.

Agent/Indication Characteristic (Pivotal Trials)	No. (%) [95% CI]							
	Randomized	Double-Blinded	Comparator: Active	Comparator: Placebo	Comparator: None	End Point: Surrogate Outcome	End Point: Clinical Outcome	End Point: Clinical Scale
All (N = 448)	400 (89.3) [86.4-92.2]	356 (79.5) [75.7-83.2]	143 (31.9) [27.6-36.3]	247 (55.1) [50.5-59.8]	58 (12.9) [9.8-16.1]	219 (48.9) [44.2-53.5]	130 (29.0) [24.8-33.2]	99 (22.1) [18.2-26.0]
Therapeutic area								
Cancer (n = 55)	26 (47.3) [33.7-60.9]	15 (27.3) [15.1-39.4]	10 (18.2) [7.7-28.7]	16 (29.1) [16.7-41.5]	29 (52.7) [39.1-66.3]	46 (83.6) [73.5-93.7]	9 (16.4) [6.3-26.5]	0
Infectious disease (n = 57)	53 (93.0) [86.1-99.8]	45 (78.9) [68.0-89.9]	39 (68.4) [56.0-80.9]	13 (22.8) [11.6-34.0]	5 (8.8) [1.2-16.3]	33 (57.9) [44.7-71.1]	24 (42.1) [28.9-55.3]	0
Cardiovascular disease, diabetes mellitus, hyperlipidemia (n = 73)	72 (98.6) [95.9-100.0]	68 (93.2) [87.2-99.1]	26 (35.6) [24.4-46.9]	45 (61.6) [50.2-73.1]	2 (2.7) [0.0-6.6]	62 (84.9) [76.5-93.3]	11 (15.1) [6.7-23.5]	0

Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals

FDA: 2008-2012

Figure 2. Overall Survival Results for Cancer Drug Approvals Granted on the Basis of a Surrogate End Point



JAMA Internal Medicine Published online October 19, 2015

Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals

Since 2008, the FDA has approved a higher percentage of drugs than previously,[4] and cancer drugs are approved on the basis of surrogates that have poor correlations with overall survival.[2] Our results suggest that the FDA may be approving many costly, toxic drugs that do not improve overall survival. Enforcement of postmarketing studies is therefore of critical importance.

JAMA Internal Medicine Published online October 19, 2015

„Orphan Drugs“ (OD) –

- **Verordnung (EG) Nr. 847/2000 der EC vom 27.4.2000**
- **Prävalenz:** nicht mehr als 5 von 10.000 Personen betroffen
- **Patienten mit seltenen Leiden denselben Anspruch auf Qualität, Unbedenklichkeit und Wirksamkeit von OD wie andere Patienten; ⟶ für OD normale Bewertungsverfahren**
- Definitionen: u.a. **„erheblicher Nutzen“ („significant benefit“)**; **„klinisch überlegen“**: AM im Vergleich zu einem zugelassenen AM für seltene Leiden **nachweislich zusätzlich einen oder mehrere erhebliche therapeutische Vorteile**:
  - größere Wirksamkeit
  - größere Sicherheit bei einem erheblichen Teil der Zielpopulation(en)
  - bedeutenden Beitrag zur Diagnose oder Behandlung von Patienten

Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer

The Orphan Drug Act is widely regarded as a watershed piece of legislation that has helped spur the development of numerous useful drugs for rare medical conditions. However, given the limited evidentiary basis on which orphan cancer drugs are approved, the act may need to be amended so that its resources can be more selectively guided to first-in-class drugs or those that treat a condition for which no other treatments are available, and to ensure that orphan products are rigorously evaluated and closely followed up once they are approved.

JAMA. 2011;305(22):2320-2326

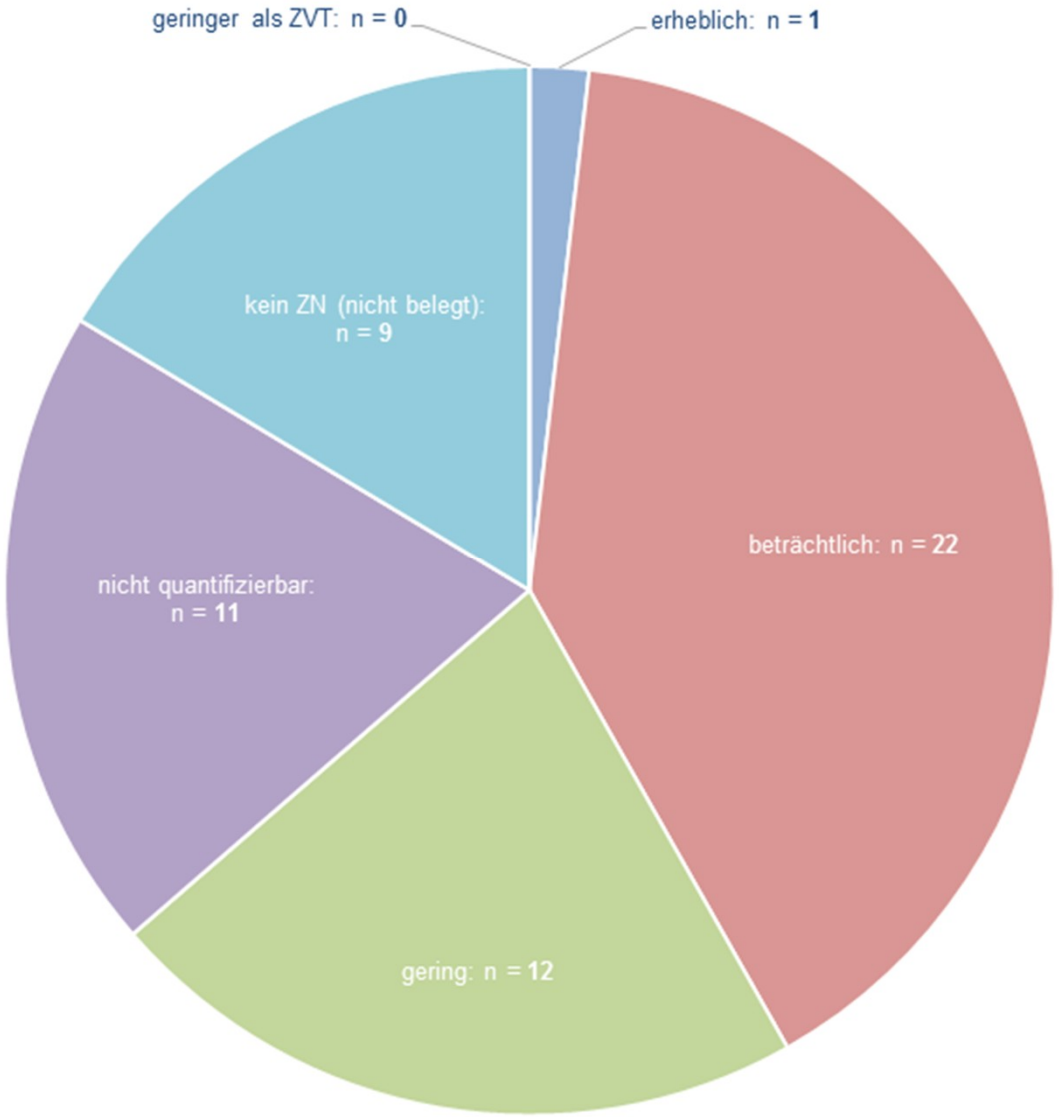
Zulassungsstudien bei onkologischen Wirkstoffen: Status quo - *Agenda*

- neu zugelassene onkologische Wirkstoffe (FDA/EMA): 2014/2015
- Anforderungen an die Zulassung
- Zulassung: Was wissen wir und was sollten wir wissen?
- frühe Nutzenbewertung onkologischer Wirkstoffe
- Resümee/Ausblick

AMNOG – Nutzenbewertung nach § 35a SGB V

Höchste Zusatznutzenkategorie je Verfahren nach § 35a SGB V

Ausmaß des Zusatznutzens (Verfahren onkologischer Wirkstoffe)



Anzahl Beschlüsse

n = 55

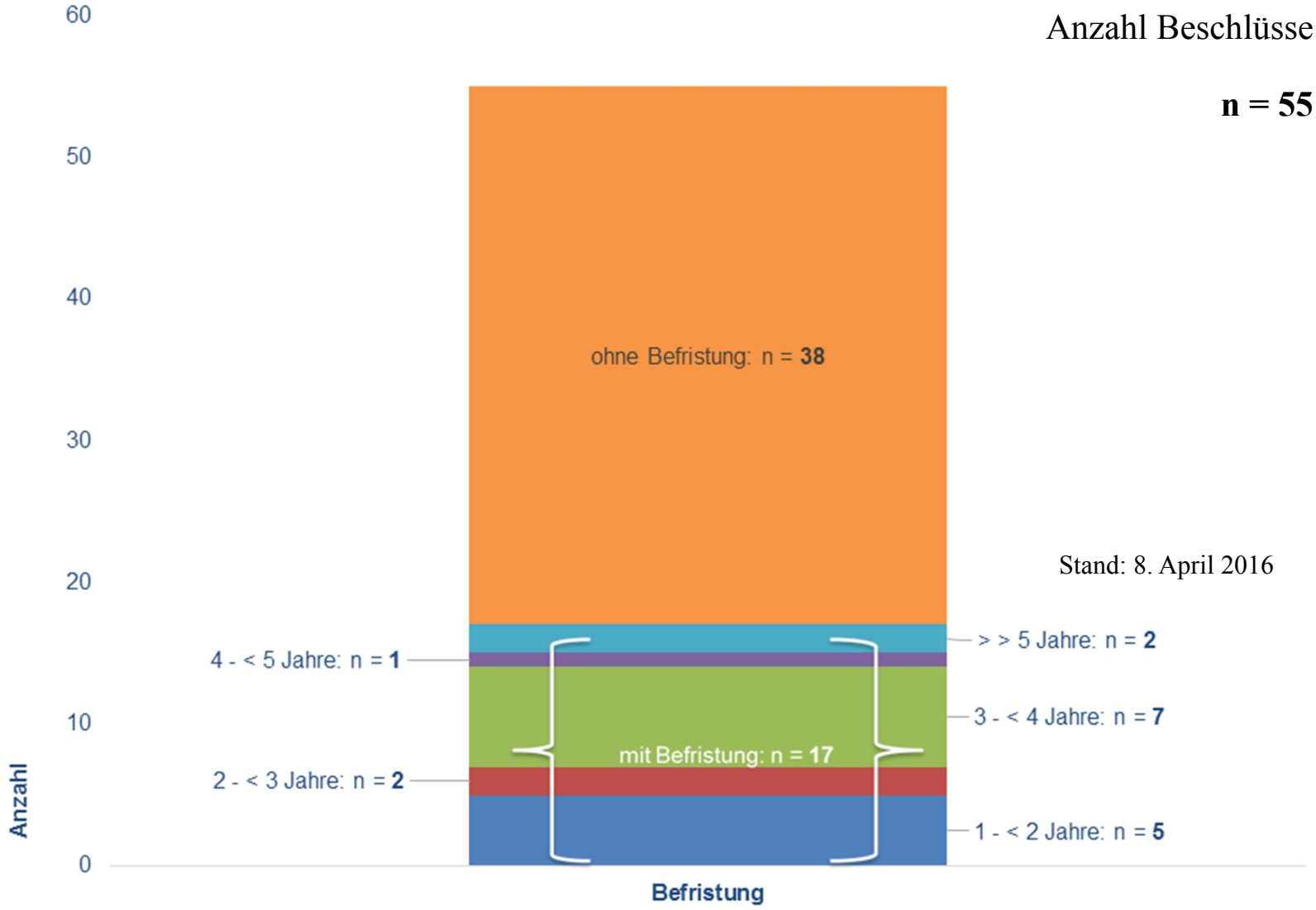
Stand: 1. April 2016

AMNOG – Nutzenbewertung nach § 35a SGB V

Zeitliche Befristung des Beschlusses (Verfahren onkologischer Wirkstoffe)

Anzahl Beschlüsse

n = 55



Stand: 8. April 2016

Resümee
Ausblick

Antonello da Messina
(approx. 1430-1479)
Saint Jerome in His Study

Why do cancer drugs get such an easy ride?

Rushed approvals result in a poor deal for both patients and cancer research

Donald W Light *professor*[1], Joel Lexchin *professor* [2]

- **Methodological weaknesses in oncology trials**

➢ Oncology drugs most likely to be approved through an accelerated pathhway

➢ Cancer using surrogate measures instead of survival and other patient-centered outcomes

➢ „Easy ride syndrome“, only small benefits to patients

➢ Regulators should require clear evidence that new drugs are clinically effective

- **> 100 oncologists (USA) protested against high prices charged for cancer drugs**

BMJ 2015;350:h2068 doi: 10.1136/bmj.h2068 (Published 23 April 2015)

Erkenntnislücken bei Arzneimittelzulassung und Marktüberwachung

- Klinische Studien (RCTs) **nicht repräsentativ** für Verordnung von Arzneimitteln nach Zulassung („real-life“ Patienten)
- Positive und **negative Effekte (Nutzen) von Arzneimitteln bzw. Therapiestrategien** unter Alltagsbedingungen i. R. von Zulassungsstudien **nicht ausreichend beurteilbar**

➢ **nach Zulassung von Arzneimitteln:**

  – > 50% Änderungen von Fachinformation/Packungsbeilage
  – ca. 7,5% - 20% neue Warnhinweise („black box warnings“)
  – ca. 3% Marktrücknahmen

- **Konsequenzen?; systematische Post-Marketing Studien (PAES, PASS) unverzichtbar und häufig neu # besser**

▼ This medicinal product is subject to additional monitoring.

By Cassie Frank, David U. Himmelstein, Steffie Woolhandler, David H. Bor, Sidney M. Wolfe, Orlaith Heymann, Leah Zallman, and Karen E. Lasser

DOI: 10.1377/hlthaff.2014.0122
HEALTH AFFAIRS 33,
NO. 8 (2014): 1453–1459

Era Of Faster FDA Drug Approval Has Also Seen Increased Black-Box Warnings And Market Withdrawals

Post-market safety warnings for drugs approved in Canada under the Notice of Compliance with conditions policy

Joel Lexchin

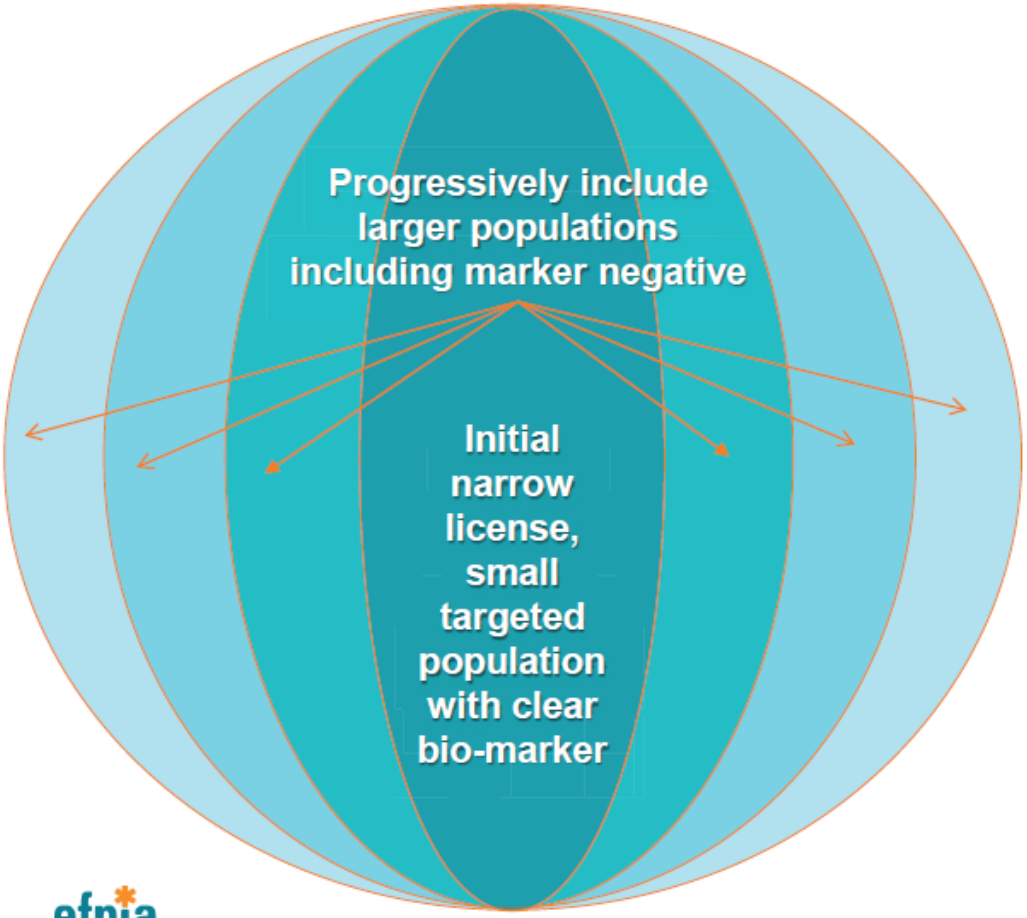
School of Health Policy and Management, York University, 4700 Keele St., Toronto, Ontario, Canada M3J 1P3

WHAT THIS STUDY ADDS

- In Canada drugs approved with limited safety and efficacy data are more likely to receive a serious safety warning compared with drugs approved through a standard review process.
- The increased risk of receiving a safety warning may be because these drugs spend less time in the review process and because less safety data are available when they are reviewed.

Medicine adaptive pathways to patients (MAPPs): using regulatory innovation to defeat Eroom's law

An example of how MAPPs could work in practice



Managing uncertainty:

1. Starts by targeting the most likely to respond
2. Robust capture of real-time data of the actual trial experience
3. All key stakeholders (patients, regulators, practitioners, industry) are aligned with the process starting at the design stage

efpia

NRDD vol. 10, July 2011

Chin Clin Oncol 2014;3(2):21

Science Drives Innovation: EMA needs to be prepared to receive the pass!

„The innovators perspective“

- Science drives Innovation:
  Regulation impacts investments

- A regulatory system designed in the 1950s for small molecule pill-based medicines will not meet the needs of 21st Century science

- Regulatory reform needs to match the pace and trajectory of scientific innovation

- The EMA is the access enabler as the key link between the science and the patient

Complex Biologics,
Gene Therapy
Regenerative Medicine
Precision Medicine
Diagnostic/device/drug combos
Nanomedicine
Synthetic Biology…

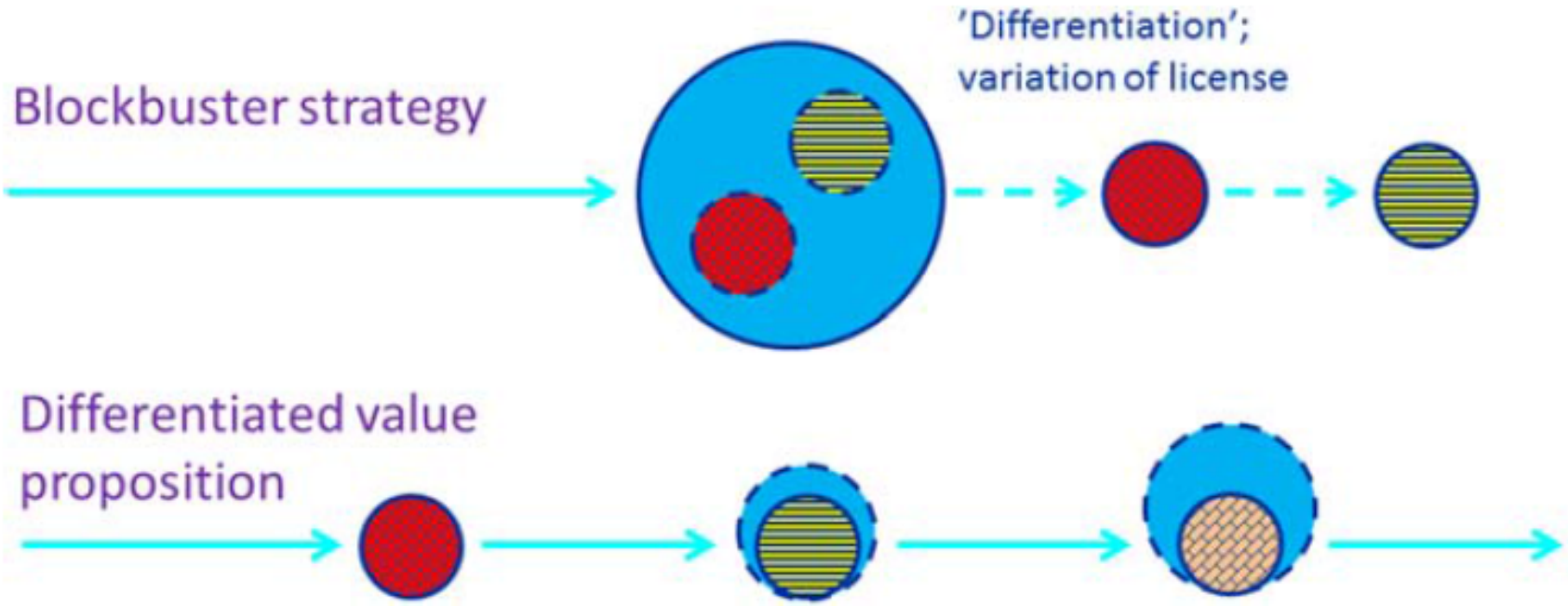
Elias Zerhouni M.D.
President, Global R&D, Sanofi

SANOFI

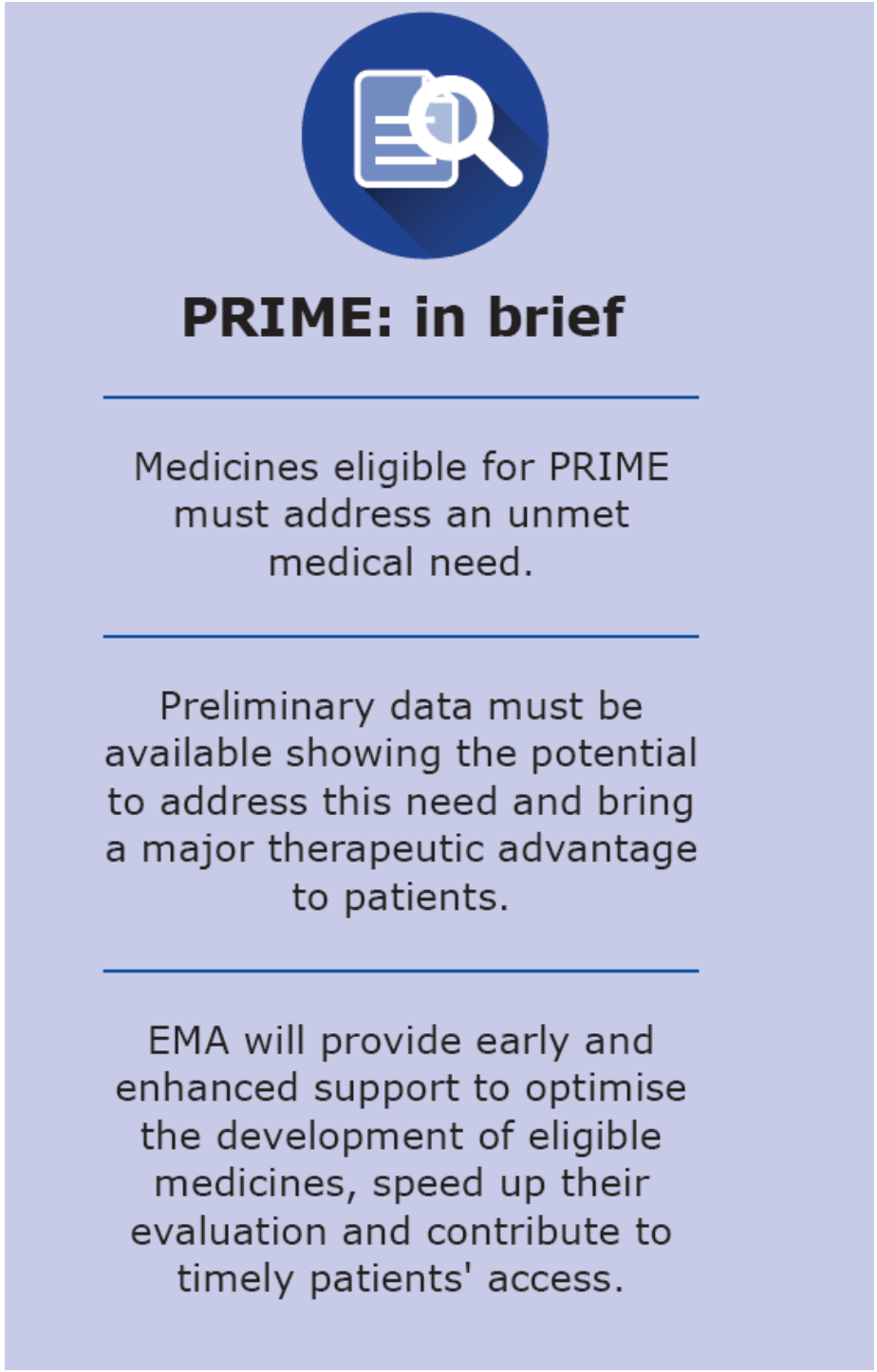
Innovation drives regulatory science?

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 97 NUMBER 3 | MARCH 2015

From Adaptive Licensing to Adaptive Pathways: Delivering a Flexible Life-Span Approach to Bring New Drugs to Patients



Methodik?, Off-Label Use, Post-Zulassungsstudien, große Unsicherheit bzgl. Wirksamkeit/Toxizität


PRIME: in brief
Medicines eligible for PRIME must address an unmet medical need.
Preliminary data must be available showing the potential to address this need and bring a major therapeutic advantage to patients.
EMA will provide early and enhanced support to optimise the development of eligible medicines, speed up their evaluation and contribute to timely patients' access.


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
PRIME – PRIORITY MEDICINES

März 2016

ILLUSTRATION BY GREG CLARKE

Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says **Nicholas J. Schork**.