Building a Community Research Program

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Disclosures

- **Leadership** (No Personal or Institutional Payment)

  ASCO NSCLC Guideline Committee Member, ACCC Board of Trustees

- **Consulting** (No Personal Payment; Payment to Sarah Cannon)

  Aeglea Biotherapeutics, Agios, Amgen, AnHeart Therapeutics, Apollomics, Arcus, Arrys Therapeutics, Ascendis Pharma, Astellas, AstraZeneca, Bayer, Beigene, BIND Therapeutics, BioNTech RNA Pharmaceuticals, Blueprint Medicine, Boehringer-Ingelheim, Bristol-Myers Squibb, Calithera, Celgene, Celldex, Clovis, Cyteir Therapeutics, Daiichi Sankyo, Denovo Biopharma, Eisai, Elevation Oncology, Endeavor, Erasca, Faeth Therapeutics, FujiFilm Pharmaceuticals, G1 Therapeutics, Gilead Sciences, GlaxoSmithKline, GRAIL, Hutchinson MediPharma, ImClone Systems, Incyte, Ipsen Biopharmaceuticals, Janssen, Jazz Pharmaceuticals, Kronos Bio, Lilly, Loxo Oncology, Lyell Immunopharma, MacroGenics, MedImmune, Merck, Molecular Templates, Nektar Therapeutics, Neon Therapeutics, Novartis, Novocure, PureTech Health, Razor Genomics, Repare Therapeutics, Rgenix, Roche/Genentech, SeaGen, Shenzhen Chipscreen Biosciences, Synthekine, Taiho, Tango Therapeutics, Tarveda, Tesaro, Tizona Therapeutics, Transgene, UT Southwestern, Verastem, Zai Laboratory

- **Contracted Research** (No Personal Payment; Payment to Sarah Cannon)

  AstraZeneca, Beigene, Bristol-Myers Squibb, EMD Serono, Evidera, GlaxoSmithKline, Ipsen Biopharmaceuticals, Janssen, Jazz Pharmaceuticals, Lilly, Molecular Templates, Monte Rosa Therapeutics, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche/Genentech, Sanofi-Aventis

The Business of Drug Development and the Business of Treating Cancer

The Value of Cancer Drugs

- Regulators
- Payers
- Academia
- Pharma/Biotech
- Distributors
- Clinicians
- Patients

The Business of Treating Cancer

48yo OB/GYN Physician

Physician spouse

3 children

Advanced ALK+ NS-NSCLC (chest, brain, bones)

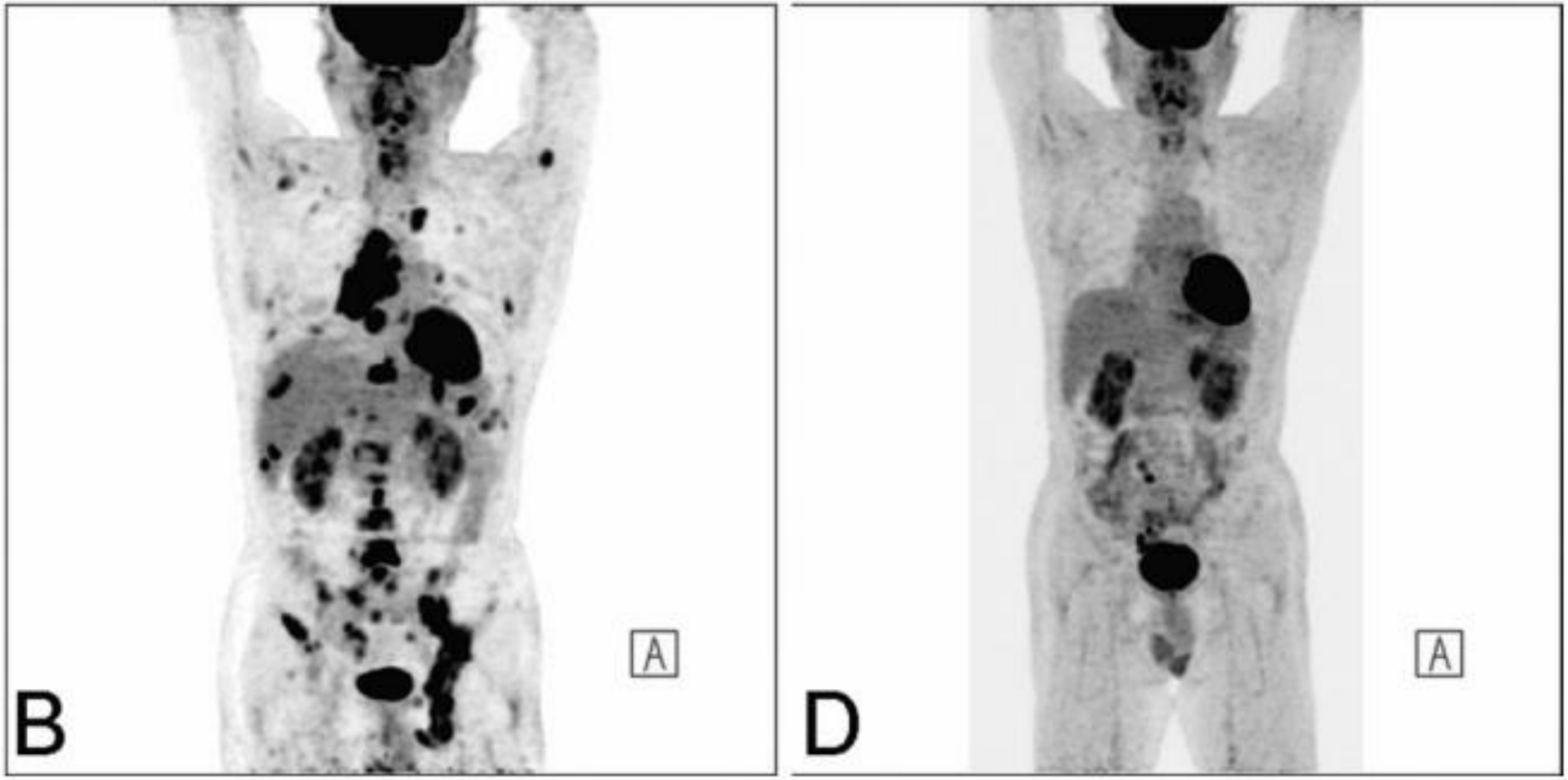
REPORT

Fusion of a Kinase Gene, *ALK*, to a Nucleolar Protein Gene, *NPM*, in Non-Hodgkin's Lymphoma

STEPHAN W. MORRIS, MARK N. KIRSTEIN, MARCUS B. VALENTINE, KRISTOPHER G. DITTMER, DAVID N. SHAPIRO, DAVID L. SALTMAN, AND A. THOMAS LOOK Authors Info & Affiliations

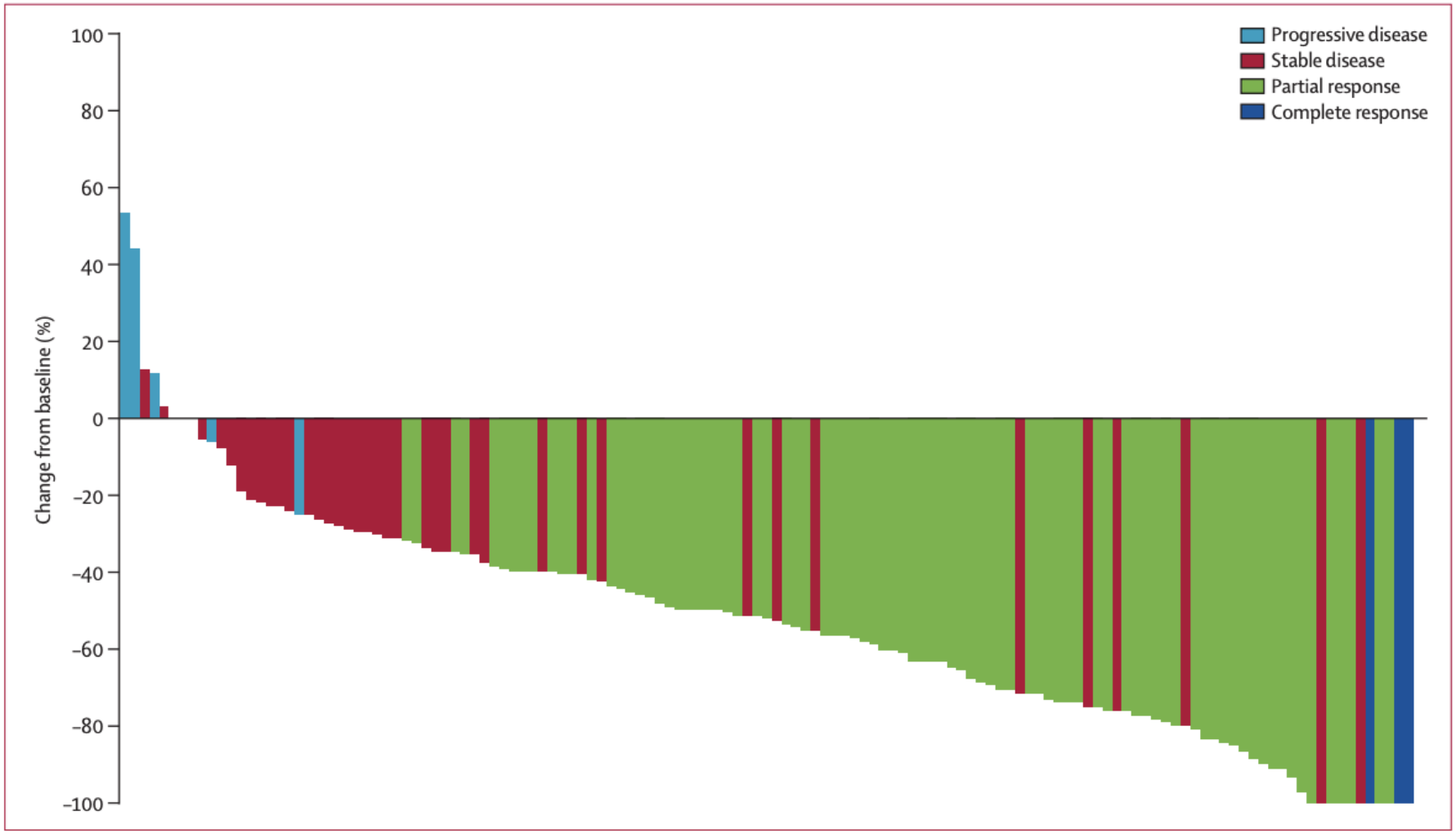
SCIENCE • 4 Mar 1994 • Vol 263, Issue 5151 • pp. 1281-1284 • DOI: 10.1126/science.8122112

42 Days on a an Experimental ALK Inhibitor



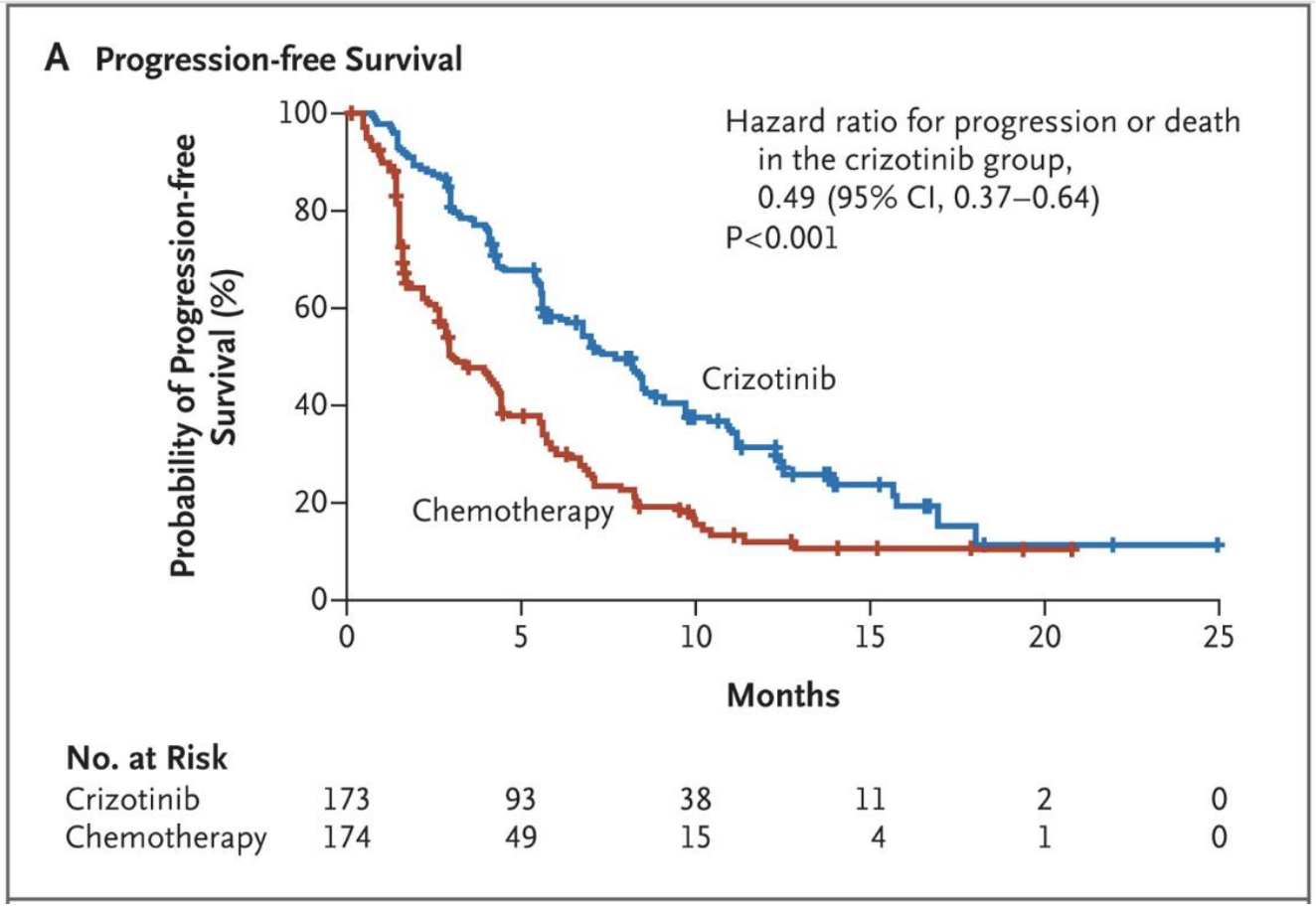
Nakajima, JTO 2010

Crizotinib in ALK+ NSCLC



Camidge, Lancet Onc 2012

Crizotinib c. Chemotherapy in ALK+ NSCLC



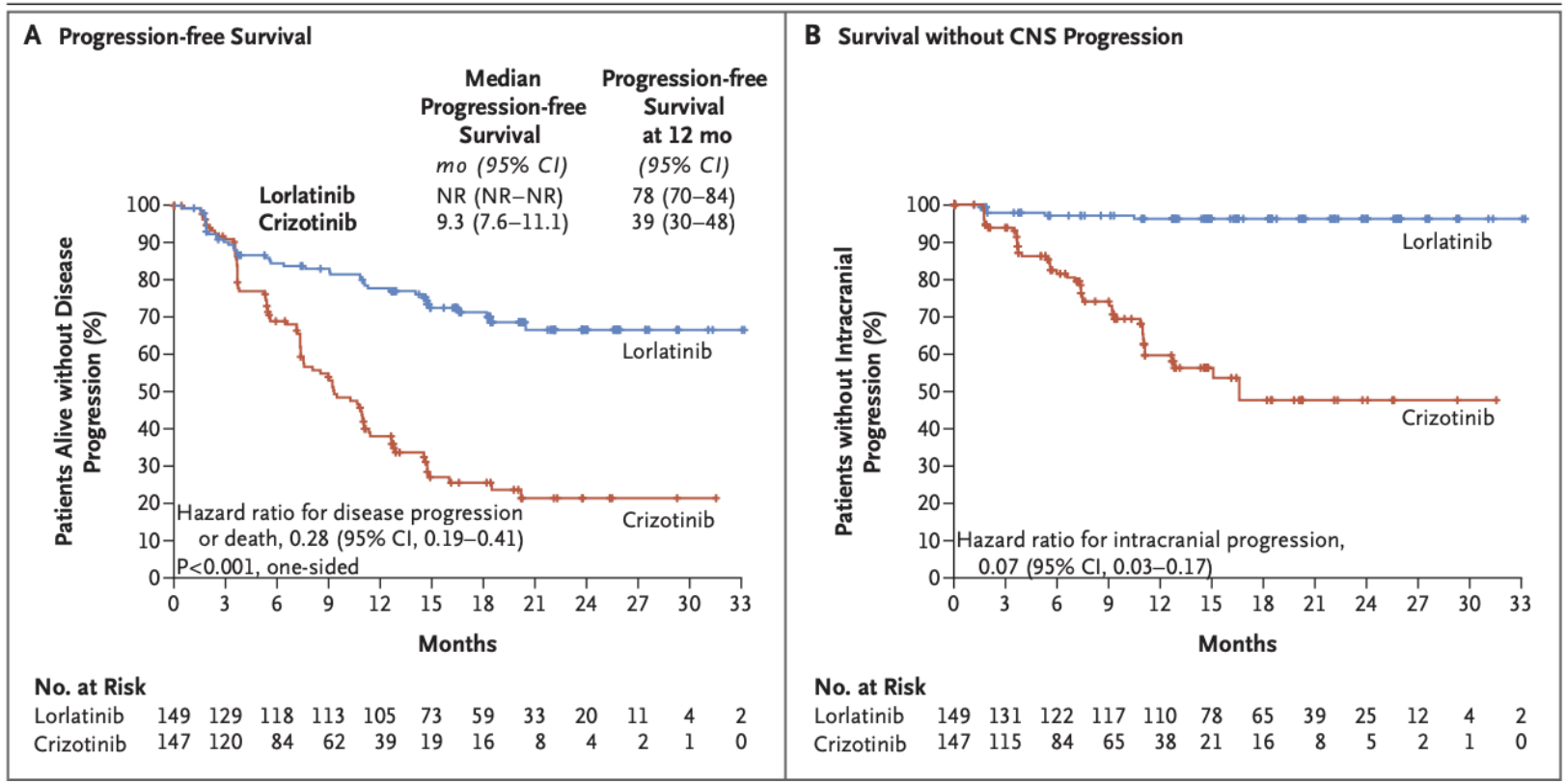
Shaw, NEJM 2013

The NEW ENGLAND JOURNAL of MEDICINE

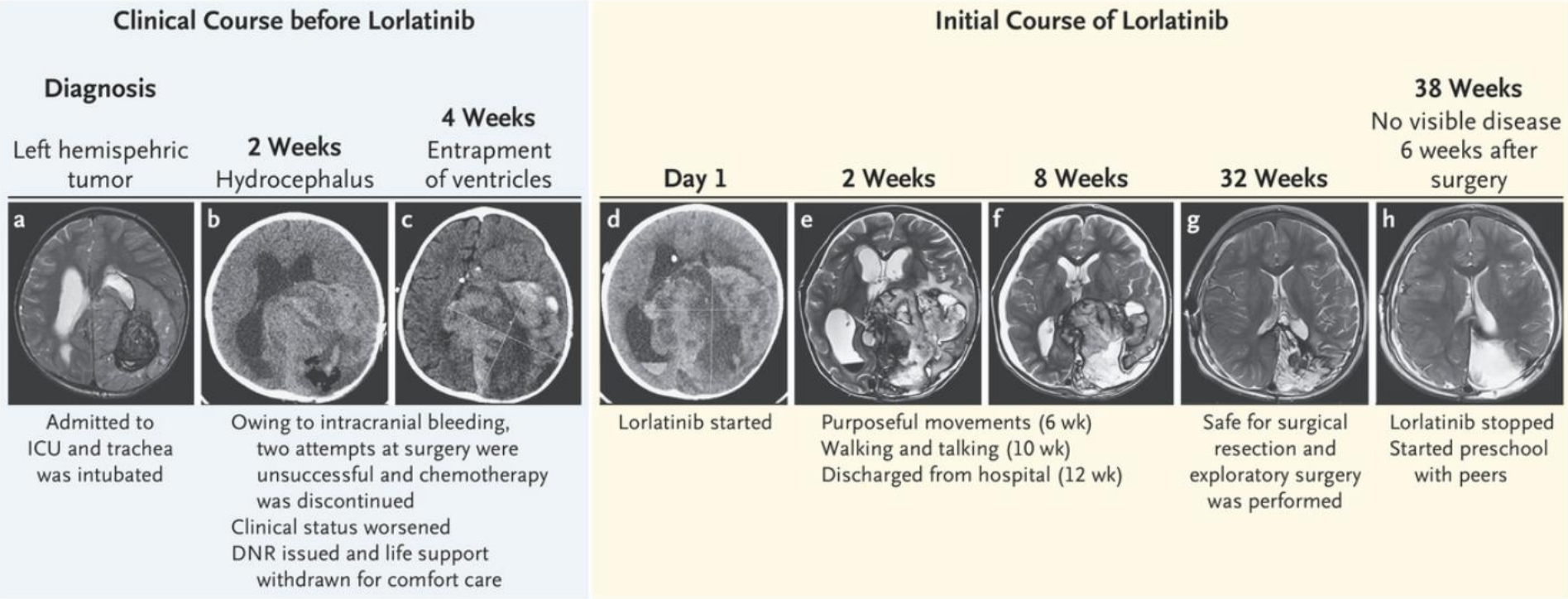
ORIGINAL ARTICLE

First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Todd M. Bauer, M.D., Filippo de Marinis, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Geoffrey Liu, M.D., Julien Mazieres, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Tony Mok, M.D., Anna Polli, B.Sc., Holger Thurm, M.D., Anna M. Calella, Ph.D., Gerson Peltz, M.D., M.P.H., and Benjamin J. Solomon, M.B., B.S., Ph.D., for the CROWN Trial Investigators*



The Potential of Development



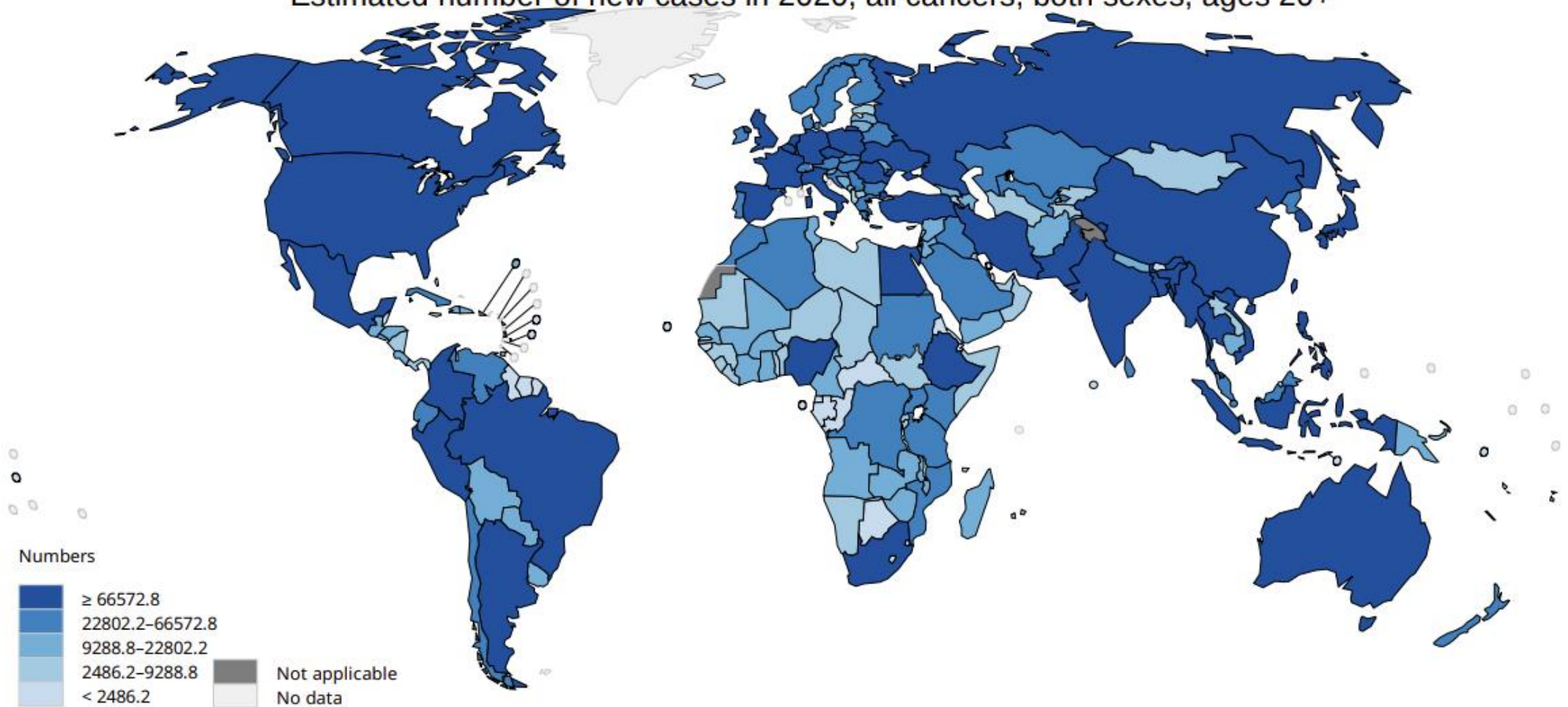
Bagchi, NEJM 2021

Outline

- The Case for Drug Development and Current Metrics
- Accelerating Discovery to Approval
- Research and Care

THE CASE FOR DRUG DEVELOPMENT AND CURRENT METRICS

Estimated number of new cases in 2020, all cancers, both sexes, ages 20+



Data source: GLOBOCAN 2020
Map production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization

Estimated number of new cases in 2020, all cancers, both sexes, ages 20+

Population	Value
China	4532103.0
United States of America	2266967.0
India	1283489.0
Japan	1025731.0
Germany	625597.0
Brazil	583304.0
Russian Federation	586352.0
France	465125.0
United Kingdom	455120.0
Italy	412936.0

https://gco.iarc.fr/today/online-analysis-map?v=2020&mode=population&mode_population=continents&population=900&populations=900&key=total&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=4&ages_group%5B%5D=17&nb_items=10&group_cancer=1&include_nmsc=0&include_nmsc_other=0&projection=natural-earth&color_palette=default&map_scale=quantile&map_nb_colors=5&continent=0&show_ranking=0&rotate=%255B10%252C0%255D

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https://gco.iarc.fr/today/online-analysis-map?v=2020&mode=population&mode_population=continents&population=900&populations=900&key=total&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=4&ages_group%5B%5D=17&nb_items=10&group_cancer=1&include_nmsc=0&include_nmsc_other=0&projection=natural-earth&color_palette=default&map_scale=quantile&map_nb_colors=5&continent=0&show_ranking=0&rotate=%255B10%252C0%255D

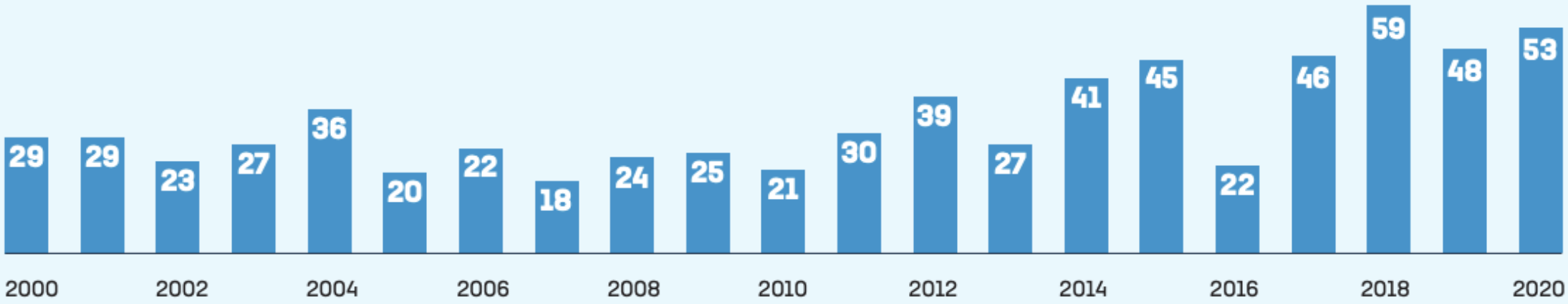
The Case for Drug Development

- 2020 — 18.1 million new cancer cases
  9.9 million cancer deaths globally

- 2040 — 28.0 million new cancer cases
  16.2 million cancer deaths

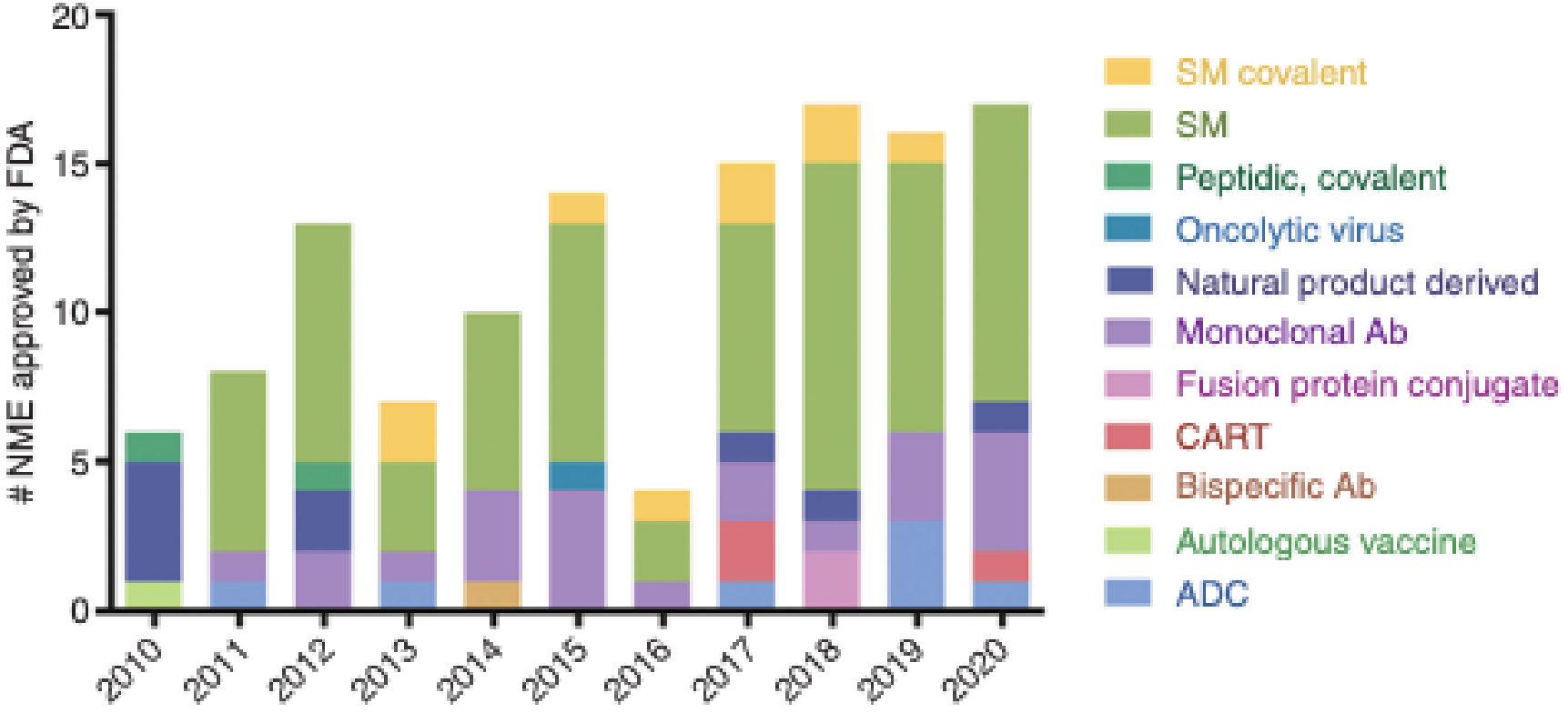
Jemal, CA Facts & Figures 2022

FIGURE 1. Annual New FDA Approved Medicines Since 2000



https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/G-I/Innovation_in_Biopharmaceuticals.pdf

Cancer Drug Approvals



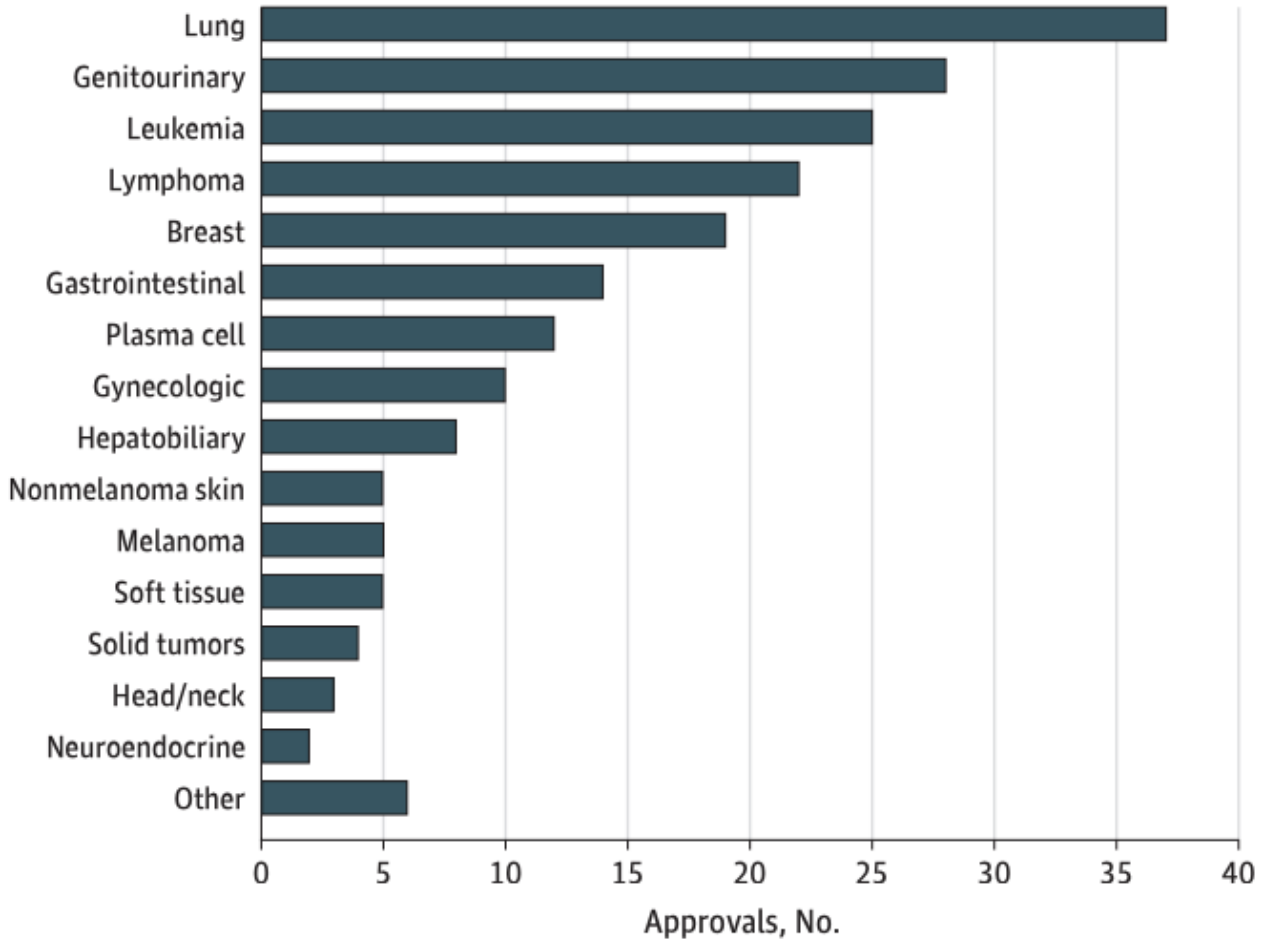
Rudolph, Cancer Discov 2021

2021 FDA Cancer Drug Approvals (18)

• FAM-Trastuzumab Deruxtecan	HER2 Adv BC
• Alpelisib	*PIK3A*-related overgrowth spectrum
• Axicabtagene Ciloleucel	NHL
• Lutetium Vipivotide Tetraxetan	Prostate CA
• Pembrolizumab	Endometrial – MSI-H/dMMR; RCC (Early); Melanoma (Pediatrics)
• Nivolumab / Retalimab	Adv Melanoma
• Olaparib	*BRCA* Early BC
• Nivolumab	Early NSCLC
• Pacritinib	PCV/ET
• Ciltacabtagene Autoleucel	Myeloma
• Tebentafusp-Tebn	Uveal Melanoma
• Rituximab	NHL (Pediatric)
• Daratumumab plus Hyaluronidase	Myeloma
• Carfilzomib	Myeloma
• Pafolacianine	Ovarian CA (Imaging)
• Sirlolimus	Perivascular Epithelioid marker

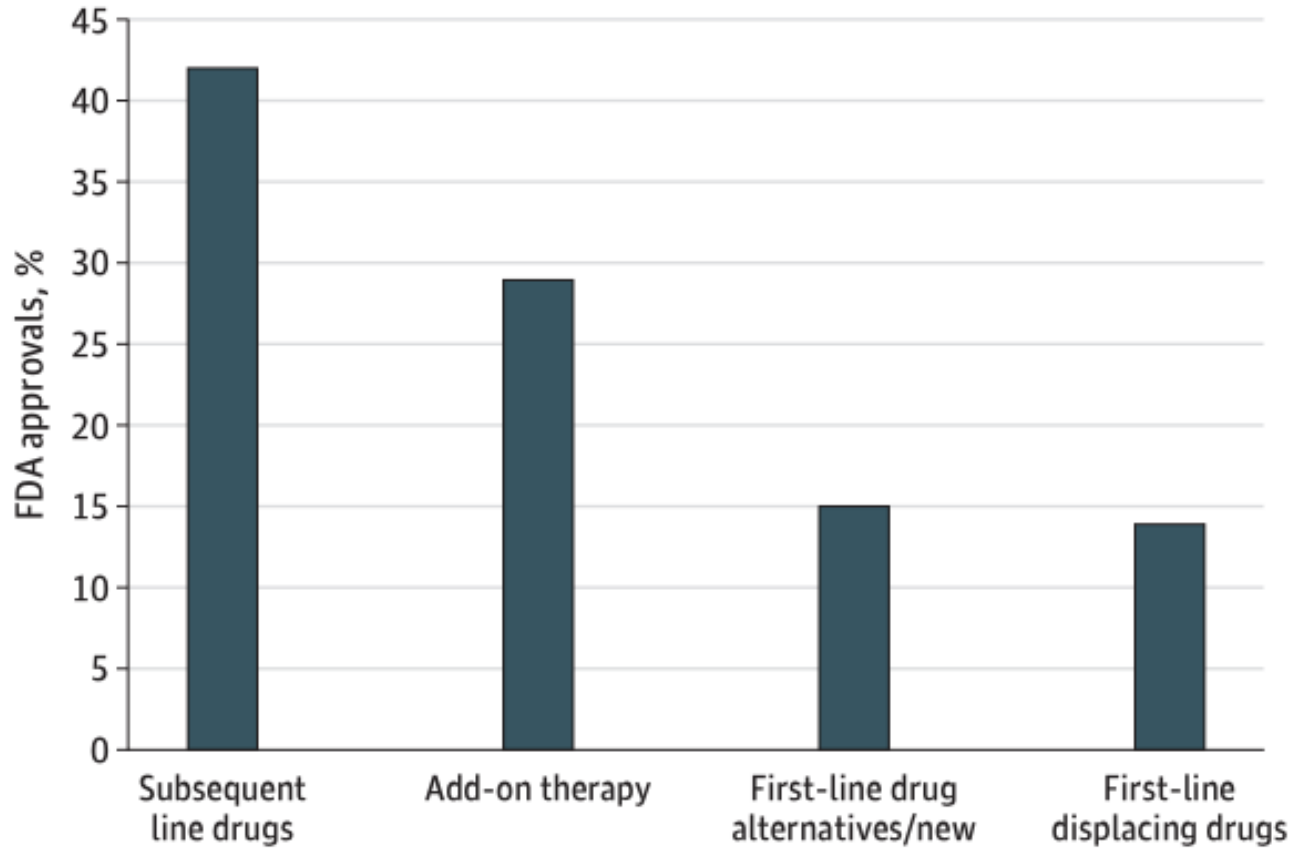
Bell, ASCO Post 2022

Figure 2. Number of Oncologic Approvals Between May 1, 2016, and May 31, 2021, by Tumor Organ System



JAMA Network Open. 2022;5(3):e222265. doi:10.1001/jamanetworkopen.2022.2265

Figure 1. Percentage of US Food and Drug Administration (FDA) Approvals Between May 1, 2016, and May 31, 2021, by Setting of Therapy



JAMA Network Open. 2022;5(3):e222265. doi:10.1001/jamanetworkopen.2022.2265

FIGURE 3. Distribution of Projects by Therapeutic Area and Phase

Therapeutic Area	Preclinical / Research Project	Number of Clinical Projects by Phase				Total Clinical Phase Projects
		Phase I	Phase II	Phase III	U.S. Filed / Approved	
Blood	236	80	159	73	8	320
Cancer	5,273	2,686	2,931	520	61	6,198
• Cancer, Blood & blood forming malignancies	701	681	591	86	23	1,381
• Cancer, Miscellaneous cancer	1,752	146	76	20	4	246
• Cancer, Solid tumors, Bladder	48	38	70	13	4	125
• Cancer, Solid tumors, Breast	231	137	162	36	2	337
• Cancer, Solid tumors, Colorectal	121	76	136	19	-	231
• Cancer, Solid tumors, Lung	79	14	20	2	-	36
• Cancer, Solid tumors, Melanoma	112	69	112	17	1	199
• Cancer, Solid tumors, Prostate	112	67	88	21	1	177
• Cancer, Solid tumors, Other	2,117	1,458	1,676	306	26	3,466

https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/G-I/Innovation_in_Biopharmaceuticals.pdf

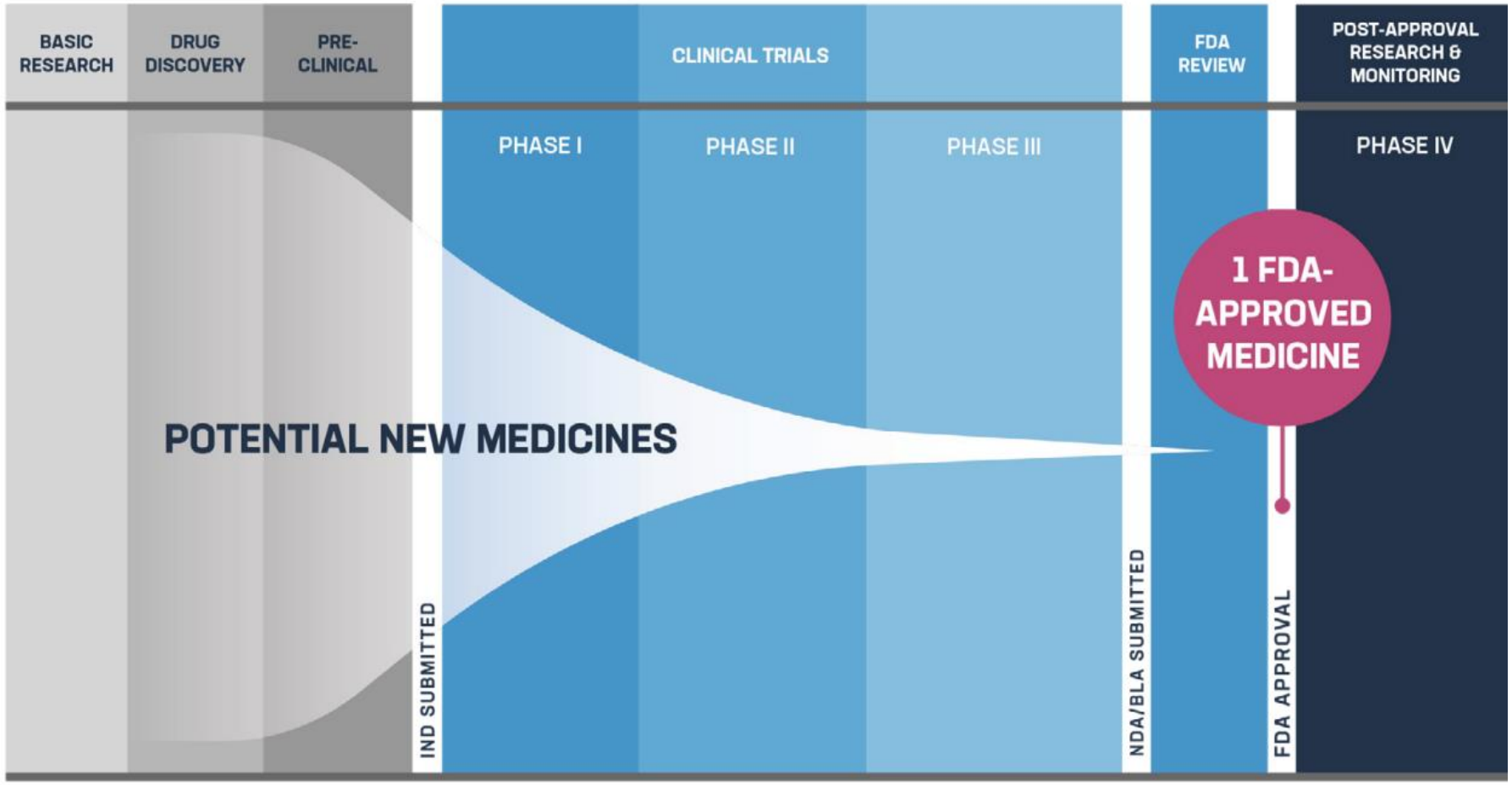
FIGURE 5. Potential First-in-Class Medicine Development Projects, by Therapeutic Area

Therapeutic Area	Preclinical / Research Project	Number of Clinical Projects by Phase				Total Potential First-in-Class Clinical Phase Projects
		Phase I	Phase II	Phase III	U.S. Filed / Approved	
Blood	188	61	112	42	3	218
Cancer	4,701	2,173	1,812	204	26	4,215
• Cancer, Blood & blood forming malignancies	584	539	330	33	9	911
• Cancer, Miscellaneous cancer	1,625	119	33	10	4	166
• Cancer, Solid tumors, Bladder	44	33	41	3	3	80
• Cancer, Solid tumors, Breast	194	106	109	11	-	226
• Cancer, Solid tumors, Colorectal	110	54	89	10	-	153
• Cancer, Solid tumors, Lung	69	10	10	1	-	21
• Cancer, Solid tumors, Melanoma	97	64	86	6	-	156
• Cancer, Solid tumors, Prostate	100	55	60	9	1	125
• Cancer, Solid tumors, Other	1,878	1,193	1,054	121	9	2,377

https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/G-I/Innovation_in_Biopharmaceuticals.pdf

ACCELERATING DISCOVERY TO APPROVAL

Cancer Drug Development



Key: IND=Investigational new drug application, NDA=New drug application, BLA=Biologics license application

*The average R&D cost required to bring a new FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Reproduced from: https://www.phrma.org/policy-issues/Research-Development/Clinical-Trials

FDA Fast Track Reviews:

- Serious Conditions
  - Will the drug have an impact?

- Unmet medical need
  - No therapy exists
  - Or may be better than what's available (must show an advantage)
    - *Superior Effectiveness*
    - *Decreases/Avoids serious side effects*

- Designation is eligible for:
  - Frequency of meetings/communication
  - Eligible for Accelerated Approval or Priority review
  - Rolling Review

- Requested by the company

https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track

EXHIBIT 1

Overview of the Food and Drug Administration's (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 a 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 sixty 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 sixty days to respond to request.	Can be requested with IND submission or any point after applying. The FDA has sixty 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 ten 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 Information in this table was adapted from the FDA's "Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics" (June 2013).

FDA Expedited Review Impact

Table 1 | **Regulatory factor impact**

Regulatory factor	Effect (years)	95% CI
Accelerated approval	−3.0	(−4.5, −1.5)
Breakthrough designation	−1.3	(−2.6, 0.0)
Orphan designation	+1.5	(+0.4, +2.6)
>1 Review cycle	+1.8	(+0.4, +3.2)

Effect size of US FDA regulatory factors on shortening (−) or increasing (+) clinical development times. See Supplementary Box 1 for details of the dataset and analysis. CI, confidence interval.

Brown, Can Drug Disc 2021

How Long Does it Take to Develop Innovative Drugs?

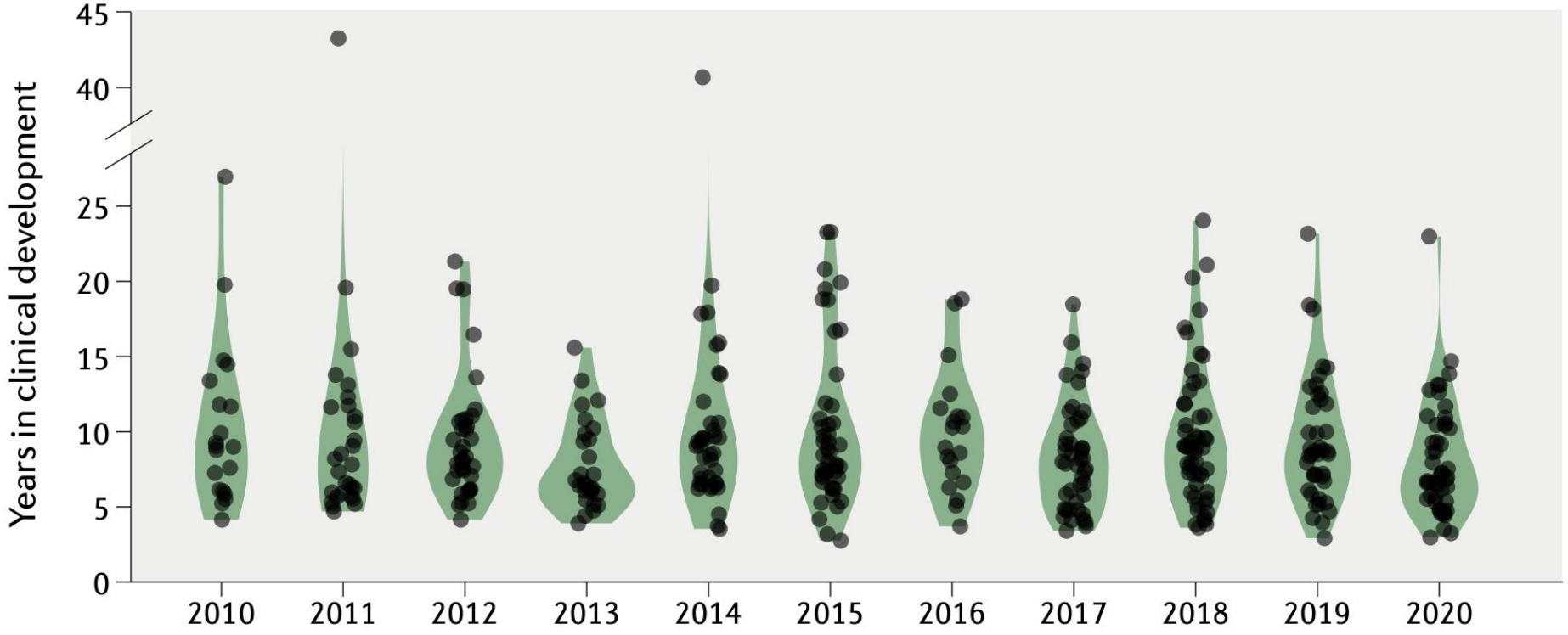


Fig. 1 | **Clinical development times for innovative drugs.** Development times for each year's cohort of drugs have remained stable over the past decade; the median was 8.3 years. See Supplementary Box 1 for details of the dataset and analysis.

Brown, Can Drug Disc 2021

A Race Against the Clock: FIH to Approval

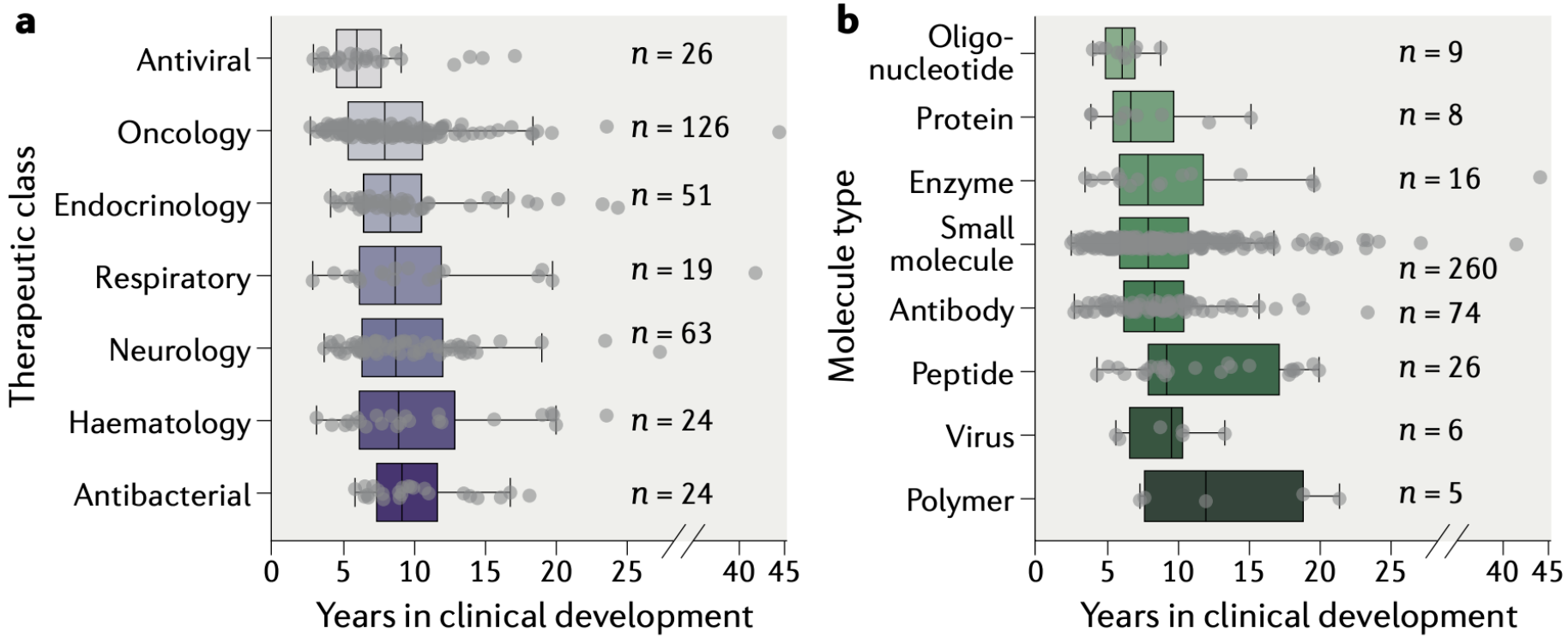


Fig. 2 | **Clinical development times for innovative drugs as a function of therapeutic class and molecule type. a** | Therapeutic class; one-way ANOVA $P = 0.04$. **b** | Molecule type; one-way ANOVA $P < 0.01$. See Supplementary Box 1 for details of the analysis.

Brown, Can Drug Disc 2021

A Race Against the Clock: FIH to Approval

2010 – 2020 Shortest Development Record

984 Days

Fig. s

and molecule type. a | Therapeutic class; one-way ANOVA $P = 0.04$. **b** | Molecule type; one-way ANOVA $P < 0.01$. See Supplementary Box 1 for details of the analysis.

Brown, Can Drug Disc 2021

A Race Against the Clock: FIH to Approval

2010 – 2020 Shortest Development Record

Osimertinib

FIH	March 6, 2013
FDA Accelerated Approval	November 13, 2015
FDA Full Approval	March 31, 2017

Fig. s
and molecule type. a | Therapeutic class; one-way ANOVA $P = 0.04$. **b** | Molecule type; one-way ANOVA $P < 0.01$. See Supplementary Box 1 for details of the analysis.

Brown, Can Drug Disc 2021

The Cost of Time

- FDA Priority Review Vouchers
  - Reducing review goal dates from 10 months to 6 months
  - A value of US$100 million+ on the open market
  - Projects cost of extra development time at ~$1 million a day

Brown, Can Drug Disc 2021

The Cost of Business

Drug (Manufacturer)	FDA Approval Date	No. of Drugs in Devel-opment	R&D Start Date	Basis of FDA Approval	Orphan Drug Exclusivity	Time to Approval, y	Total R&D Costs in Millions, $[a]	R&D Costs, Including 7% per Annum Cost of Capital, in Millions, $[a]	Time Since Approval, y	Revenue Since Approval in Millions, $[a]	Revenue as Part of R&D Spending, %
Eculizumab (Alexion Pharmaceuticals[b])	March 2007	3	January 1992	Regular (other)	Yes	15.2	817.6	1088.0	8.8	12 987.8	1588.5
Pralatrexate (Allos Therapeutics)	September 2009	3	December 2002[c]	Accelerated (RR)	Yes	6.8	178.2	217.4	3.0	304.8[d]	171.0
Brentuximab vedotin (Seattle Genetics)	August 2011	3	January 2001	Accelerated (RR)	Yes	10.6	899.2	1119.2	5.3	1034.3	115.0
Ruxolitinib (Incyte Corporation)	November 2011	5	January 2004	Regular (other)	Yes	7.8	1097.8	1374.3	5.1	2251.5	205.1
Enzalutamide (Medivation)	August 2012	2	August 2005[c]	Regular (OS)	No	7.0	473.3	554.9	4.0	21 068.3[d]	4451.4
Vincristine liposome (Talon Therapeutics)	September 2012	4	May 2006[c]	Accelerated (RR)	Yes	6.3	157.3	203.6	0.8	204.1[d]	129.8
Cabozantinib (Exelixis)	November 2012	11	January 2004	Regular (PFS)	Yes	8.8	1950.8	2601.7	4.1	341.9	17.5
Ponatinib (Ariad Pharmaceuticals)	December 2012	3	January 2007	Accelerated (RR)	Yes	5.9	480.1	548.4	4.1	5457.9[d]	1136.8
Ibrutinib (Pharmacyclics)	November 2013	4	April 2006[c]	Accelerated (RR)	Yes	7.6	328.1	388.7	1.3	22 275.0[d]	6789.1
Irinotecan liposome (Merrimack Pharmaceuticals)	October 2015	5	December 2009[c]	Regular (OS)	Yes	5.8	815.8	959.8	1.3	1065.2	130.6

Prasad, JAMA Int Med 2017

R&D Spend on New Agents (2009-2018)

Therapeutic Area[a]	Sample Size	Expenditure in US$, Millions (95% CI)[b]	
		Median	Mean
Antineoplastic and immunomodulating agents	20	2771.6 (2051.8-5366.2)	4461.2 (3114.0-6001.3)
Alimentary tract and metabolism	15	1217.6 (613.9-1792.4)	1430.3 (920.8-2078.7)
Nervous system	8	765.9 (323.0-1473.5)	1076.9 (508.7-1847.1)
Antiinfectives for systemic use	5	1259.9 (265.9-2128.3)	1297.2 (672.5-1858.5)
Dermatologicals	4	747.4	1998.3
Cardiovascular system	3	339.4	1152.4
Musculoskeletal system	3	1052.6	937.3
Blood and blood-forming organs	2	793.0	793.0
Sensory organs	2	1302.8	1302.8
Other[c]	1	1121.0	1121.0

Wouters, JAMA 2020

“It's hard enough to develop drugs when you know their mechanism of action. It's really difficult when you don't know the mechanism of action.”

Bill Kaelin, M.D.

Winner of The Nobel Prize In Physiology Or Medicine, 2019

The Chance for Success

Table 1. Clinical Trial Success Rates by Phase (on Aggregate and by Therapeutic Area)[a]

Source	Phase 1 to Approval, %[b]	Phase 2 to Approval, %[c]	Phase 3 to Approval, %[d]	FDA Submission to Approval, %[e]
Aggregate rates				
Wong et al[18]	13.8	21.0	59.0	83.2
Thomas et al[19]	9.6	15.3	49.6	85.3
Hay et al[20]	10.4	16.2	50.0	83.2
Therapeutic-area-specific rates[18]				
Oncology	3.4	6.7	35.5	81.7
Metabolism and endocrinology	19.6	24.1	51.6	80.4
Cardiovascular	25.5	32.3	62.2	84.5
Central nervous system	15.0	19.5	51.1	82.2
Autoimmune and inflammation	15.1	21.2	63.7	80.3
Ophthalmology[f]	32.6	33.6	74.9	80.4
Infectious disease	25.2	35.1	75.3	84.9
Other[g]	20.9	27.3	63.6	80.4

Wouters, JAMA 2020

Picking Winners

- 97% of drug-indication pairs tested in clinical trials in oncology never advance to approval
- Lack of efficacy and DLTs are the primary reason for failure
- Lin et al – used CRISPR to investigate 10 drugs (7 in active clinical trials)

Lin, Sci Trans Med 2020

Picking Winners

- Protein targets (of these drugs) were nonessential for cancer cell proliferation

  Discovered that a drug candidate in clinical development was effective at killing cancer cells even when its target protein was knocked out

- Efficacy of each drug was unaffected by the loss of its putative target, indicating that these compounds kill cells via off-target effects

- Paper Conclusion:

  Stringent genetic validation of the MOA in the preclinical setting would decrease the number of therapies tested in human patients that fail to provide any clinical benefit.

Lin, Sci Trans Med 2020

RESEARCH AND CARE

National Comprehensive Cancer Network (NCCN)

"The Best Management of Any Patient with Cancer is in a Clinical Trial. Participation in Clinical Trials is Especially Encouraged"

- *82 cancer guidelines*
- *13 million downloads each year*

Research and Care: Natural Allies

- Patients and Oncologists want the best options in care

- Research offers innovative options:

  Standard of Care or Better

  Pathway Driven

  Personalized

- Patients will seek research and expanded options

Research and Improved Outcomes

- Enhanced oversight
  Data and Safety
  Regulatory / Ethics

- Meta-analysis of 20k women
  25% better odds of improved outcomes (v. non-trial participants)

- Centers that offer research provide better care and have lower mortality

Nijjar, BGOJ 2017, Majumdar AIM 2008

EOM Aims and Research

- Enhance quality of care
- Reducing program spending
- Deliver evidenced-based care centered around patients
- Generate the best possible patient outcomes
- Target the right treatments for the right patients

The Challenge of Clinical Research

- Research depends on enrollment
- Enrollment to cancer clinical trials is low (<5%)
- Multiple barriers to enrollment:
  - *Time (staff/MD)*
  - *Equipment/Supplies/Facility*
  - *Trial complexity / Eligibility / Feasibility*
  - *Engagement*
  - *Competition w/ SOC*

Unger, JCO 2016

Limitations of Finding Value in Research

- Traditional outcomes (OS, safety) may neglect pt priorities and preferences
  e.g. older pts prioritize other outcomes (independence, cognition, etc)
- Inducements
- Competing goals (Pathways, Reimbursement)
- COIs
- Audits
- Not all research is 'imperative' – the number of clinical trials that could be performed is almost infinite (and resources are limited)
- Not all trials written to keep up (control changes)

Fried, NEJM 2002, Basu and Meltzer, AIM 2009

Research and Care: Shared Goals

- Extend survival - Decrease disease - Reduce symptoms - Improve QOL
- Research Drives Best Practice – Up to Date Care in Fast Advancing Field
- Research has the potential of bringing innovation to the clinic
  Early Access
  Early Adoption (risk/benefits)
  Opportunity to Best Predict Cost-Effectiveness
  Opportunity to 'Fit' Innovation into Routine Practice (e.g. CART, Bispecifics)

Now More than Ever

FDA NEWS RELEASE

FDA Takes Important Steps to Increase Racial and Ethnic Diversity in Clinical Trials

Agency's Focus on Inclusion in Trials for All Medical Products Aligns with Biden Administration's Cancer Moonshot Goal of Addressing Inequities and Beyond

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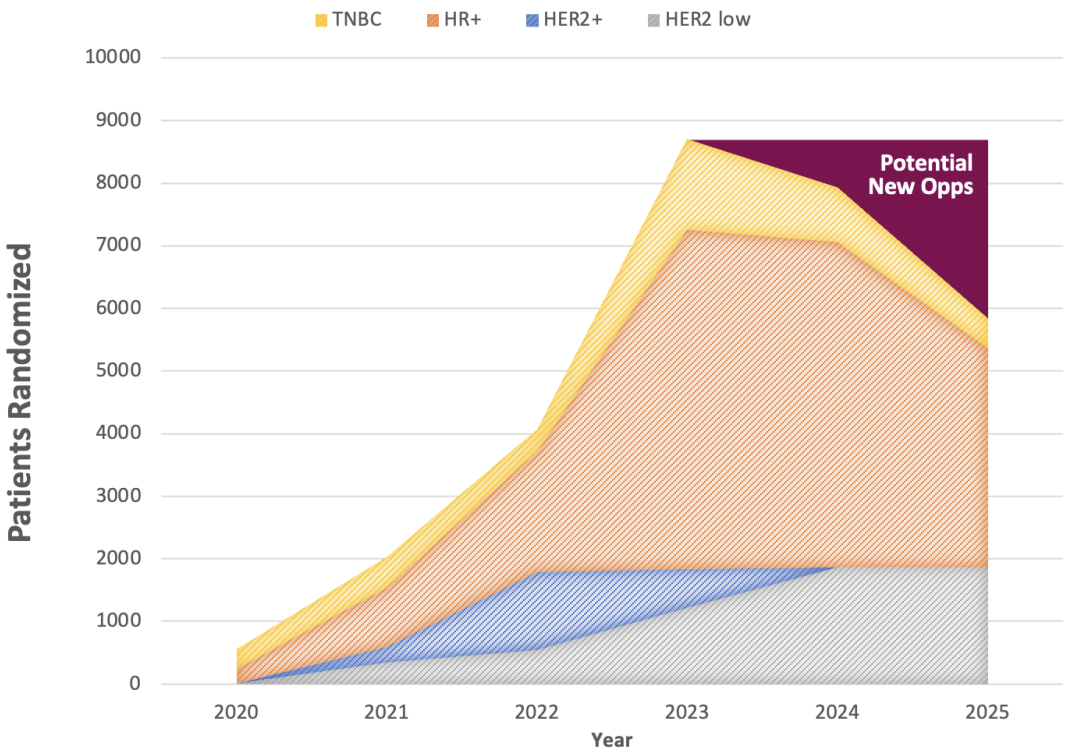
For Immediate Release: April 13, 2022

Español

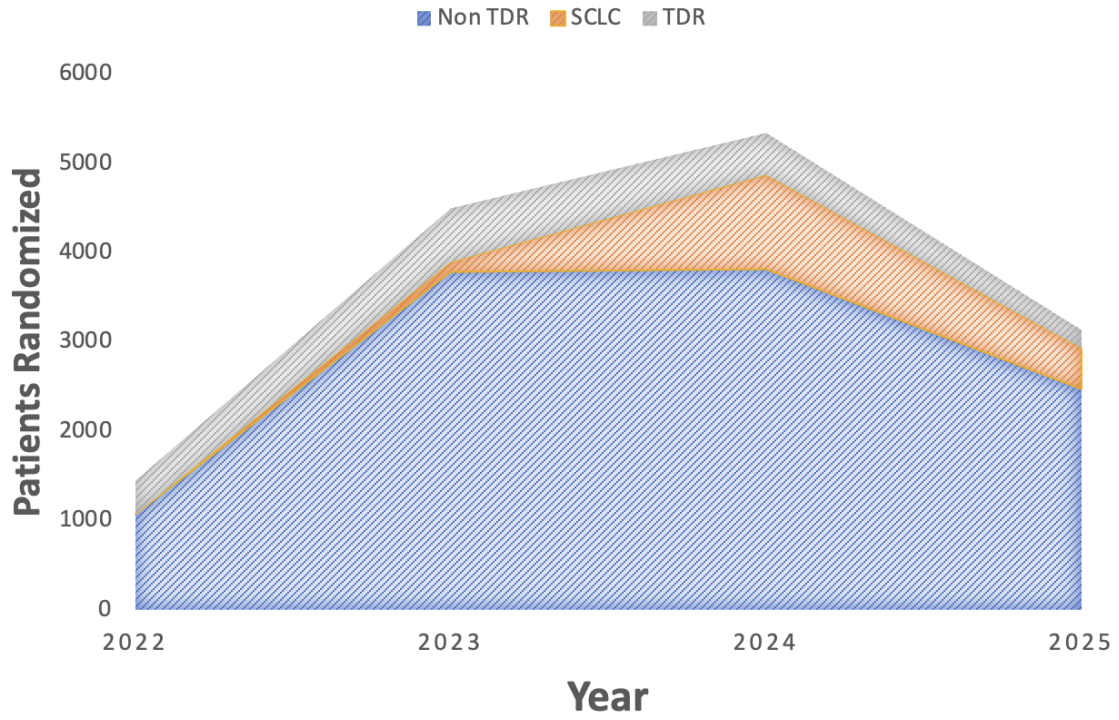
Today, the U.S. Food and Drug Administration issued a new draft guidance to industry for developing plans to enroll more participants from underrepresented racial and ethnic populations in the U.S. into clinical trials – expanding on the agency's previous guidances for industry to improve clinical trial diversity.

Now More than Ever

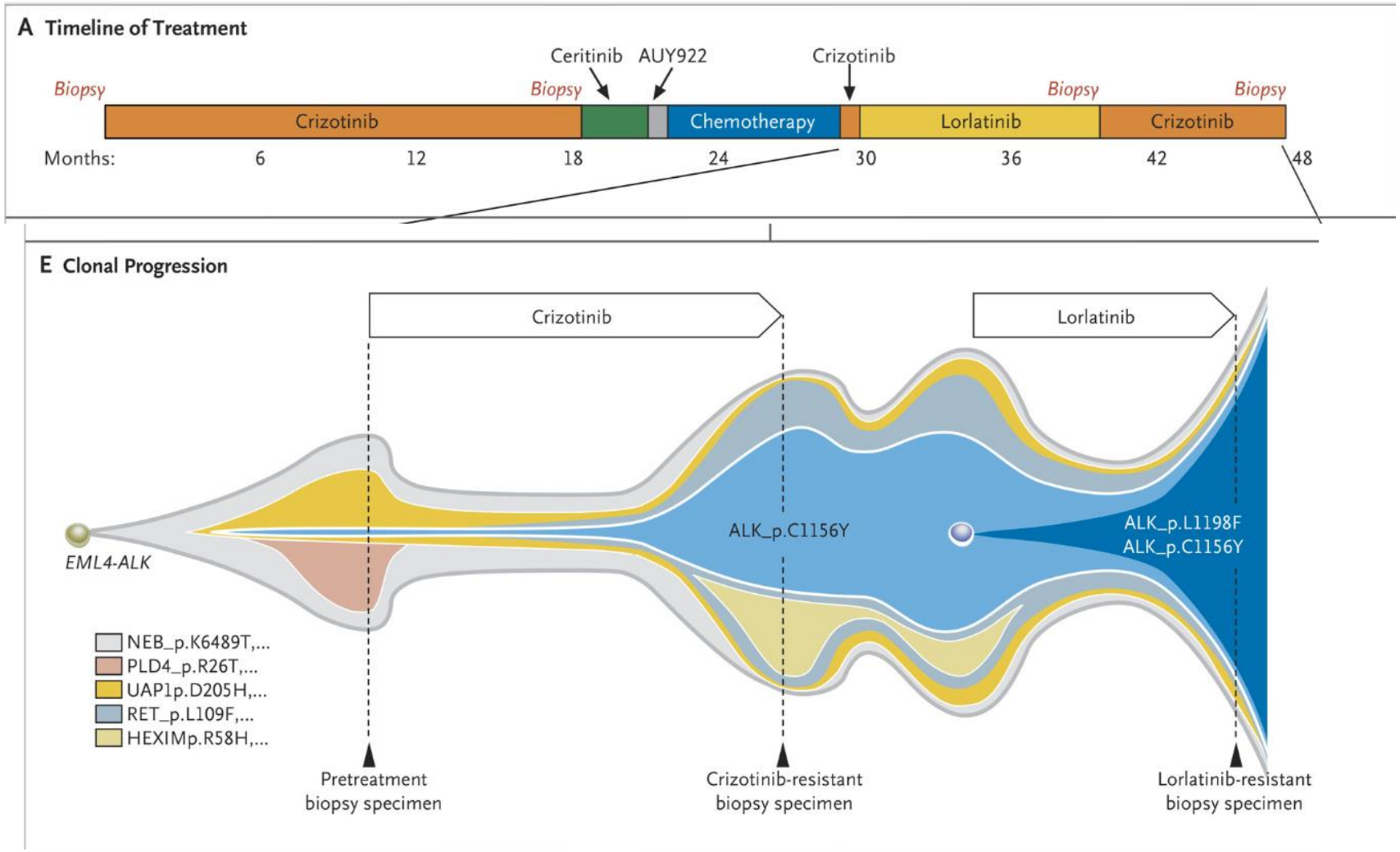
26,000+ Patients for PIII trials



14,000+ Patients by 2026



The Imperative to Innovate



Shaw, NEJM 2016

Summary

- The Business of Drug Development is the Business of Cancer Care
- Innovation and Discovery are at Record Levels – and there are Opportunities to Accelerate Time to Approval
- Patients and Research are at the Center of How We Advance Care