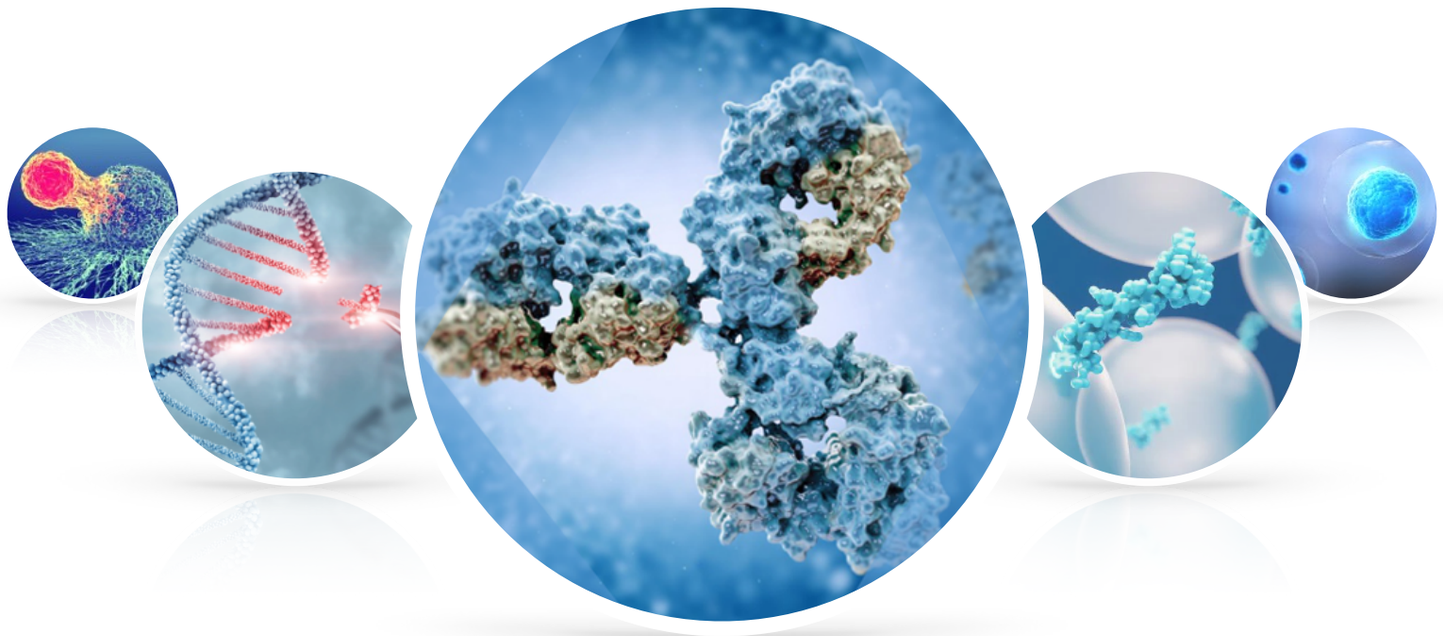
Clinical Trials

From fundamentals to advances in biologics



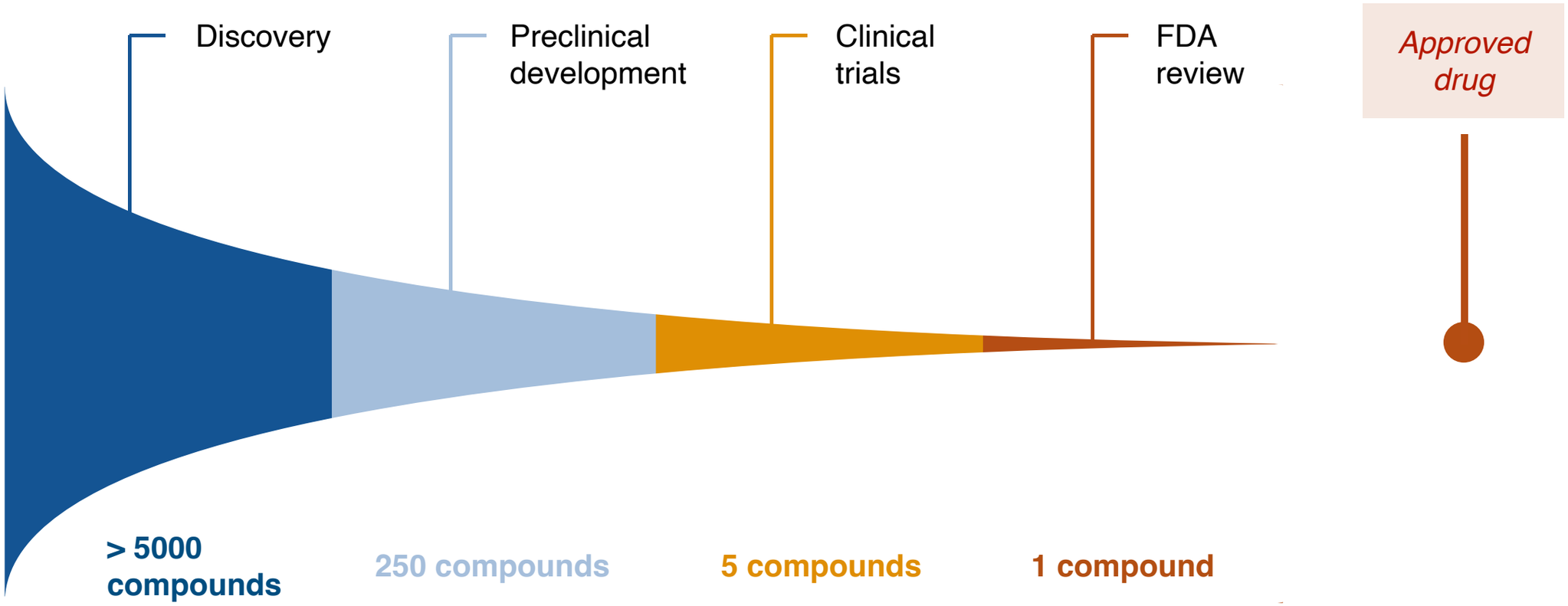
Roderick (Chenmengxiao) Pan

MacMillan Group

Princeton University

Apr. 4th, 2025

Drug development is a challenging process



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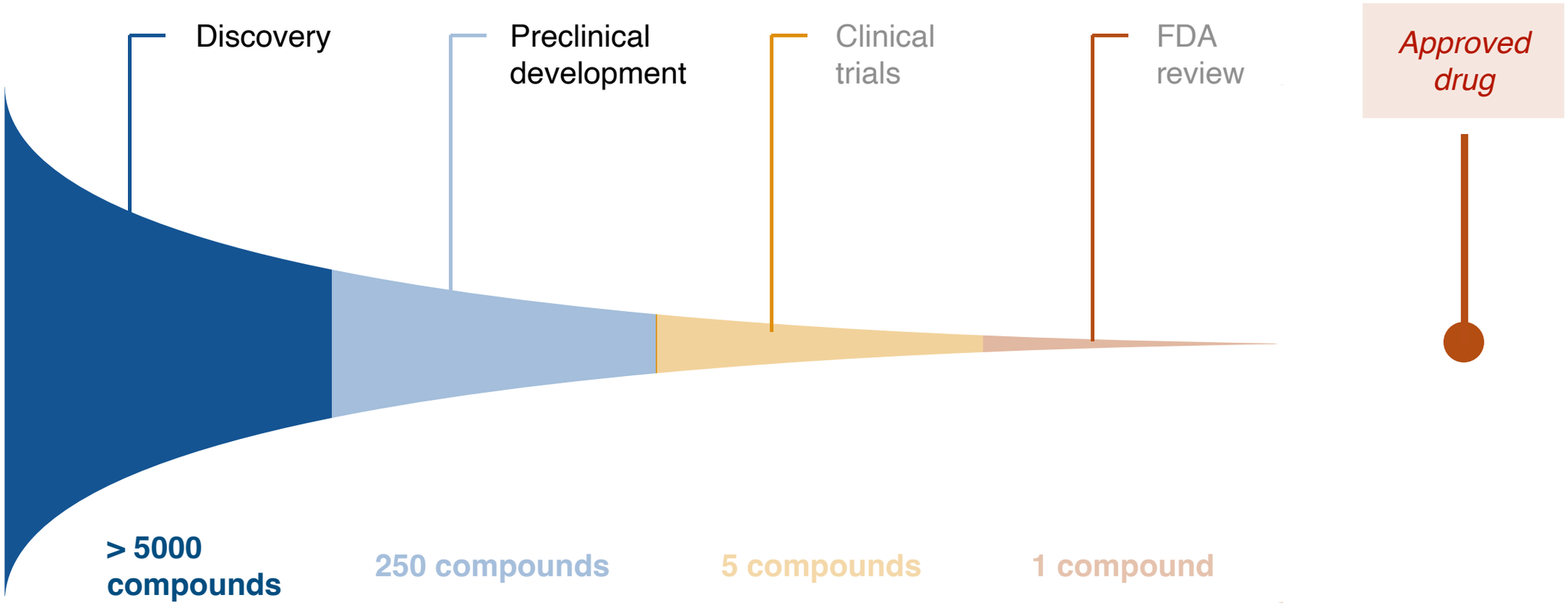
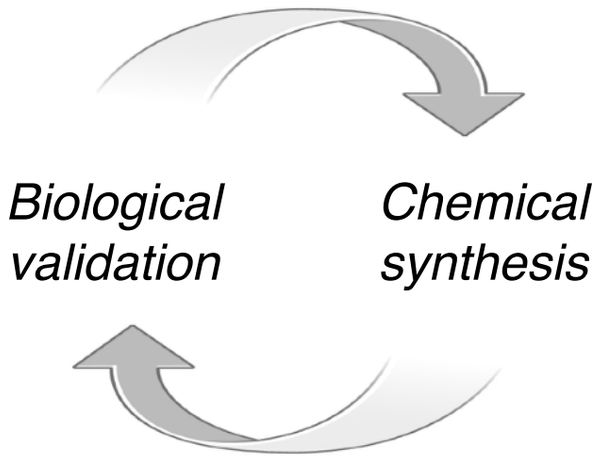


Science in our lab is mostly centered on discovery and preclinical



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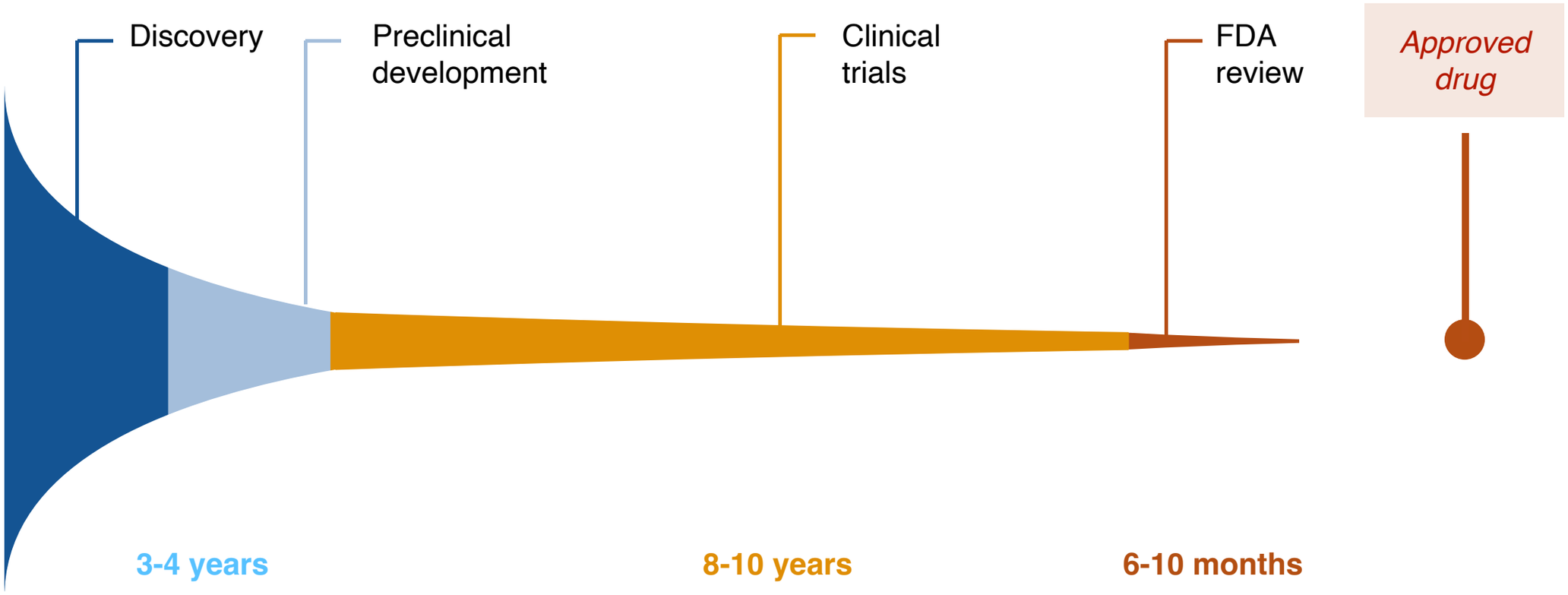

What are clinical trials?

Why should we care about clinical trials?

What will the future drug development look like?

Outlines

Introduction to fundamentals

Design and conduct of clinical trials

Real-world case studies

Special considerations for biologics

Emerging trends and future directions

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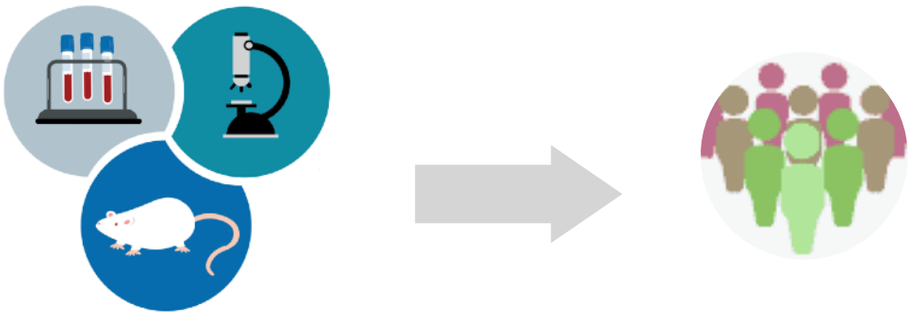
Introduction to fundamentals

Definition

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.



Preclinical
validations in animal models

Clinical
validations in humans

https://grants.nih.gov/policy-and-compliance/policy-topics/clinical-trials/definition

Introduction to fundamentals

Trial phases

https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#Clinical_Research_Phase_Studies

Introduction to fundamentals

Trial phases

Initial approval to conduct clinical trials

Final approval to sell and prescribe

Safety & dosage

20 - 100
healthy volunteers

Months to 1 year

https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#Clinical_Research_Phase_Studies

Introduction to fundamentals

Trial phases

Initial approval to conduct clinical trials

Final approval to sell and prescribe

Phase I → *Phase II* → *Phase III* → *Phase IV*

Safety & dosage

20 - 100 healthy volunteers

Months to 1 year

Efficacy & side effects

50 - 300 patients

1 - 2 years

~ 70%

https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#Clinical_Research_Phase_Studies

Introduction to fundamentals

Trial phases

Initial approval to conduct clinical trials

Final approval to sell and prescribe

Safety & dosage	*Efficacy & side effects*	*Large population*
20 - 100 healthy volunteers	*50 - 300 patients*	*300 - 3000 patients*
Months to 1 year	*1 - 2 years*	*2 - 4 years*

~ 70%

~ 30%

https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#Clinical_Research_Phase_Studies

Introduction to fundamentals

Trial phases

Initial approval to conduct clinical trials

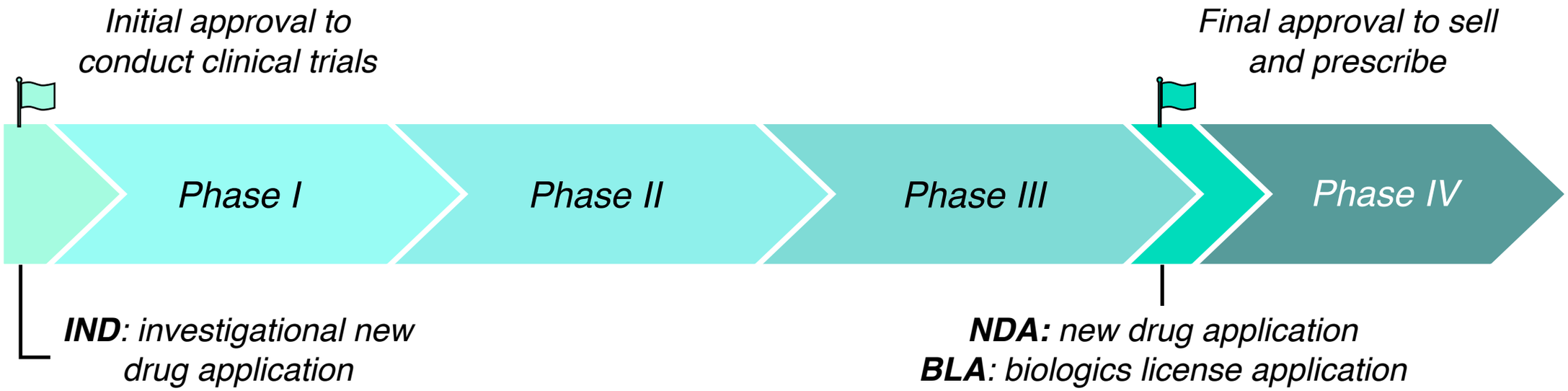
Final approval to sell and prescribe

Safety & dosage	*Efficacy & side effects*	*Large population*	*Long-term effects*
20 - 100 healthy volunteers	*50 - 300 patients*	*300 - 3000 patients*	*Thousands of patients (observational)*
Months to 1 year	*1 - 2 years*	*2 - 4 years*	*1+ year*
	~ 70%	*~ 30%*	*~ 50%*

https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#Clinical_Research_Phase_Studies

Introduction to fundamentals

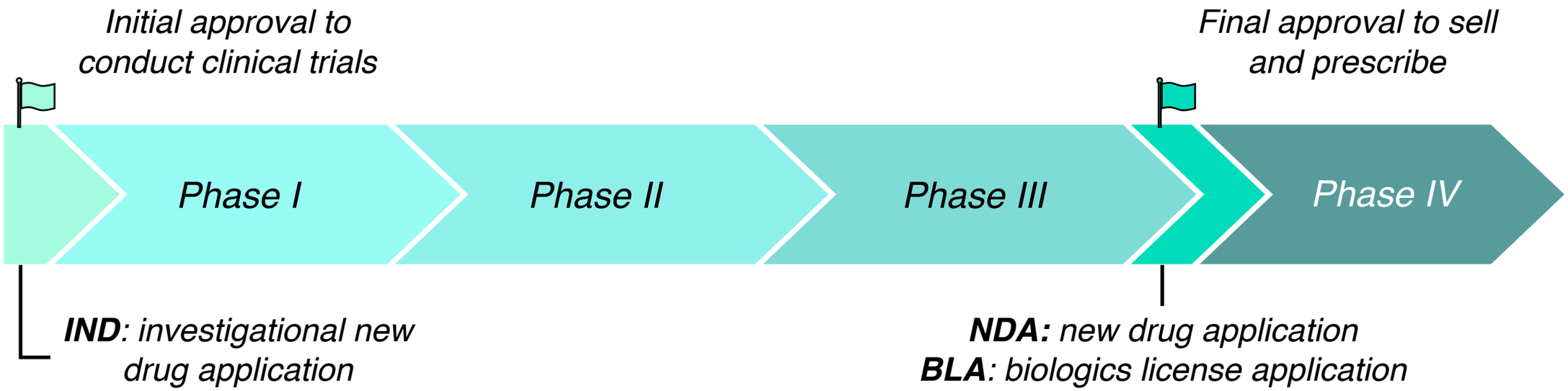
Trial phases



https://www.fda.gov/drugs/novel-drug-approvals-fda/novel-drug-approvals-2024
https://www.fda.gov/patients/drug-development-process/step-4-fda-drug-review

Introduction to fundamentals

Trial phases



- *Standard review*

⏳⏳

Longer processing
<10 months

(17/50 in 2024)

https://www.fda.gov/drugs/novel-drug-approvals-fda/novel-drug-approvals-2024
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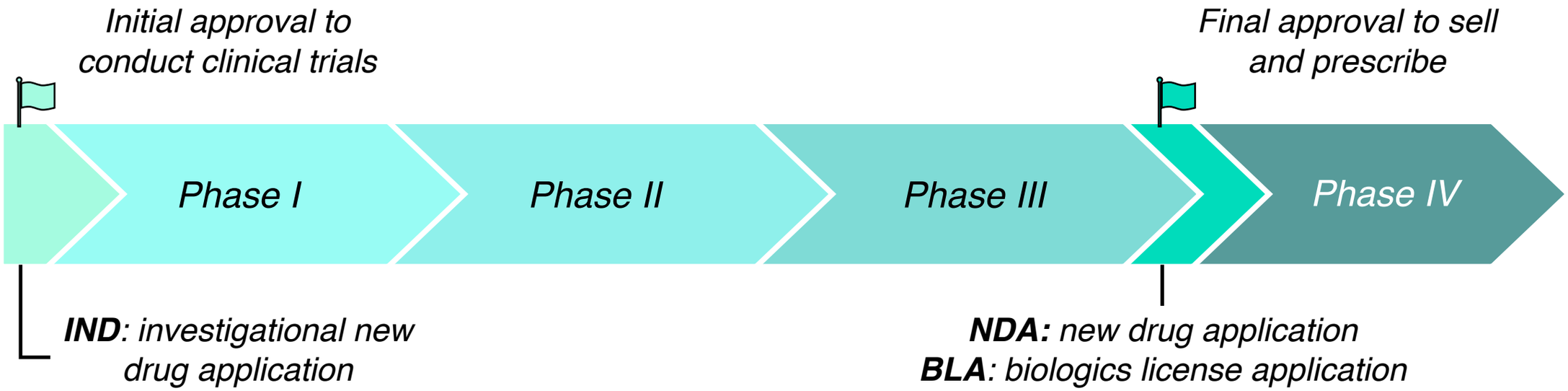
Introduction to fundamentals

Trial phases



- *Standard review*

Longer processing <10 months

(17/50 in 2024)

- *Expedited programs*

Shorter processing <6 months

(33/50 in 2024)

Fast track

Breakthrough therapy

Accelerated approval

Priority review

(Can check all 4 boxes if approved)*

https://www.fda.gov/drugs/novel-drug-approvals-fda/novel-drug-approvals-2024
https://www.fda.gov/patients/drug-development-process/step-4-fda-drug-review

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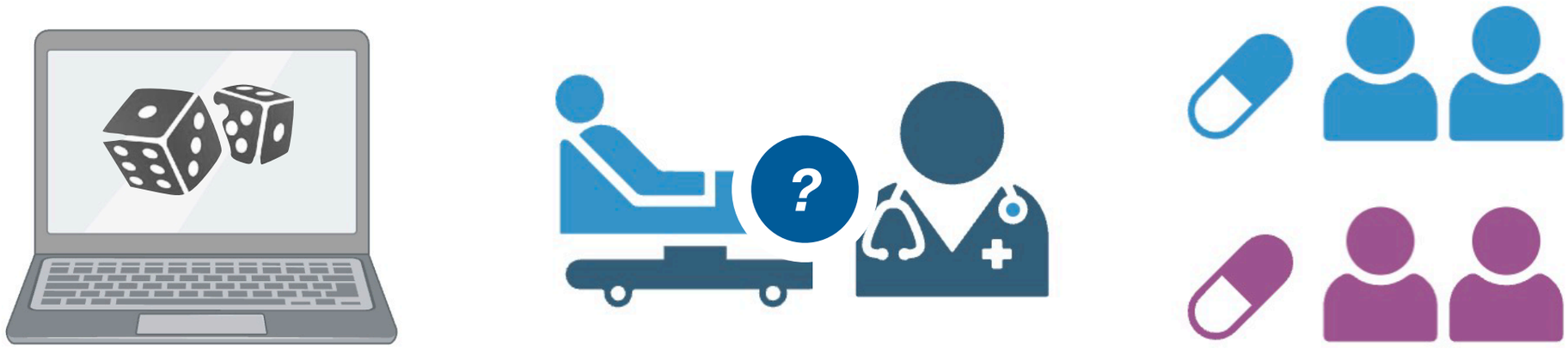
The gold standard



Randomized, double-blinded, controlled
trials are widely recognized as gold-standard trials

Often seen in Phase 2 and Phase 3 trials

Pre-specified and reviewed before performing the trials

*Hariton E, Locascio JJ. BJOG. **2018**;125(13).*

Design and conduct of clinical trials

Randomization

To ensure benefits and risks are equally shared,
and avoid selection bias

Simple randomization

It creates imbalances in group numbers

⇩

Diminished credibility

Berger VW, Bour LJ, Carter K, et al. BMC Med Res Methodol. ***2021****;21(1):168.*

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Design and conduct of clinical trials

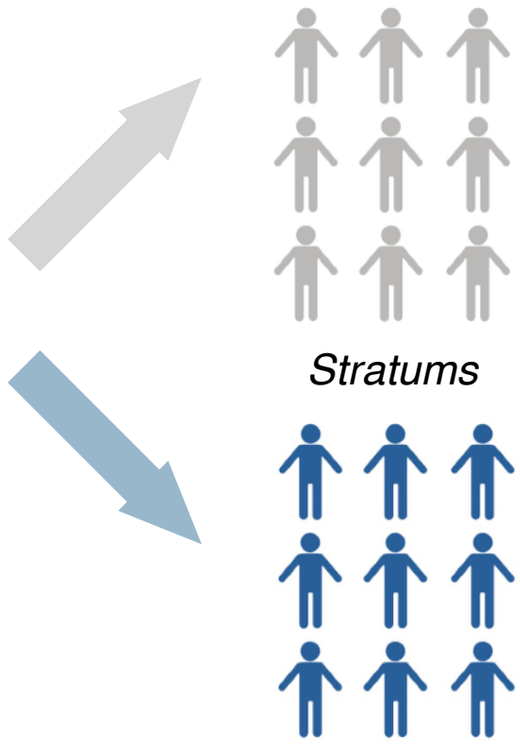
Randomization

***Restricted randomization** is widely applied*
pre-set ratio based on specified covariates

Stratification

Targeted patients

Disease level, gender, genetic variation, age, biomarker…



Stratums

Treatment A

Treatment B

Treatment C

Treatment A’

Treatment B’

Treatment C’

*Berger VW, Bour LJ, Carter K, et al. BMC Med Res Methodol. **2021**;21(1):168.*

Design and conduct of clinical trials

Randomization

***Restricted randomization** is widely applied*
pre-set ratio based on specified covariates

Stratification

Patient recruitment is a dynamic process

A dynamic allocation method is required to maintain effective randomization and ratio throughout the trial

*Berger VW, Bour LJ, Carter K, et al. BMC Med Res Methodol. **2021**;21(1):168.*

Design and conduct of clinical trials

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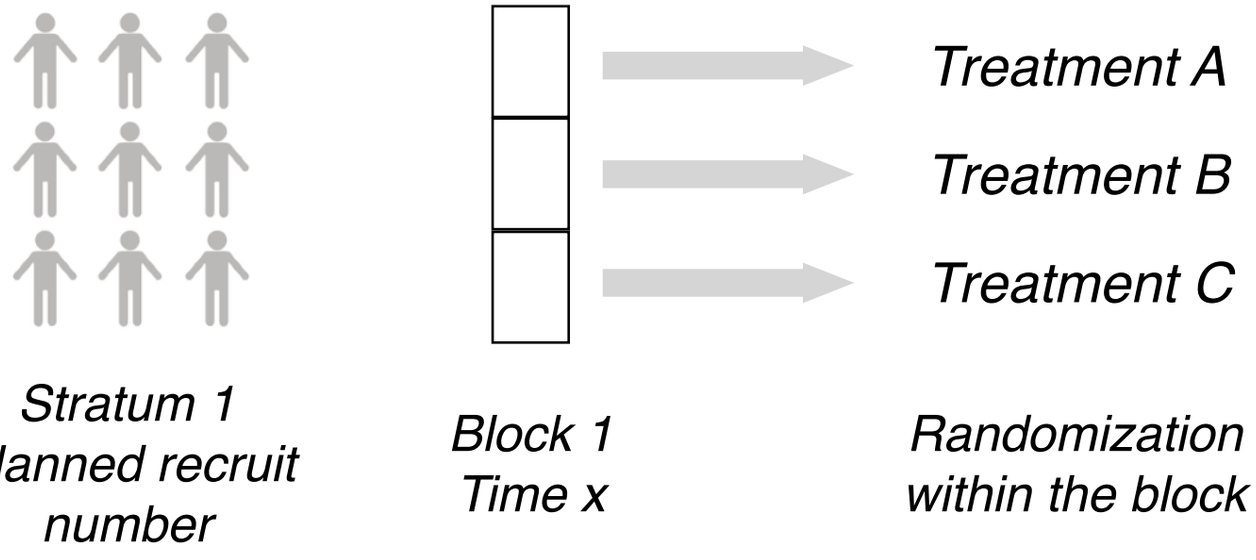
Stratification + Blocking



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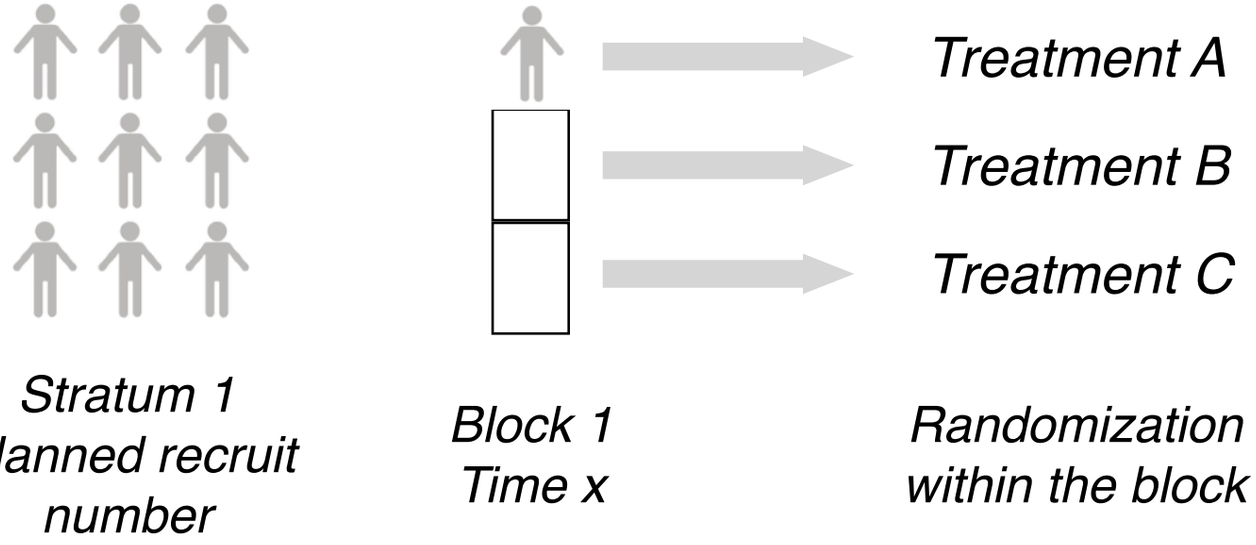

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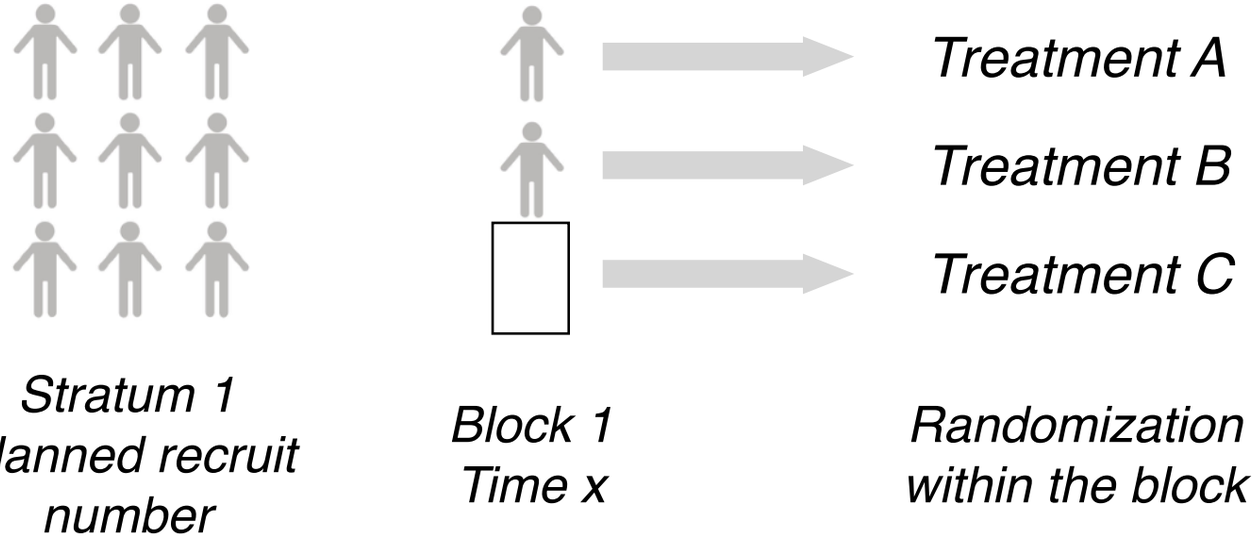

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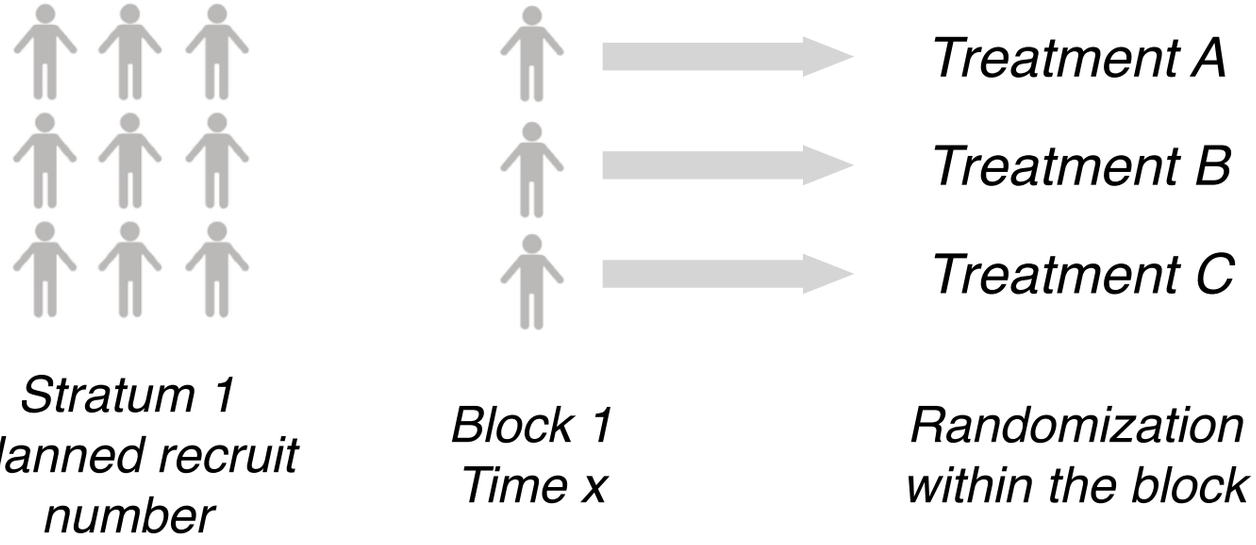

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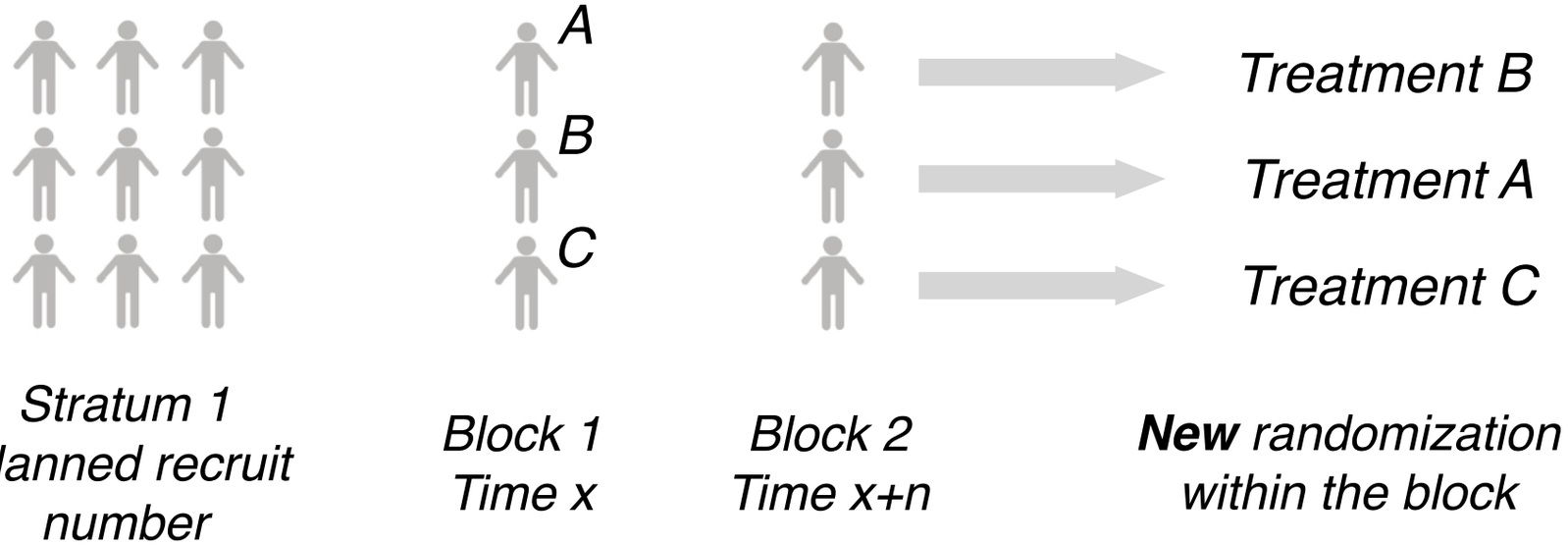

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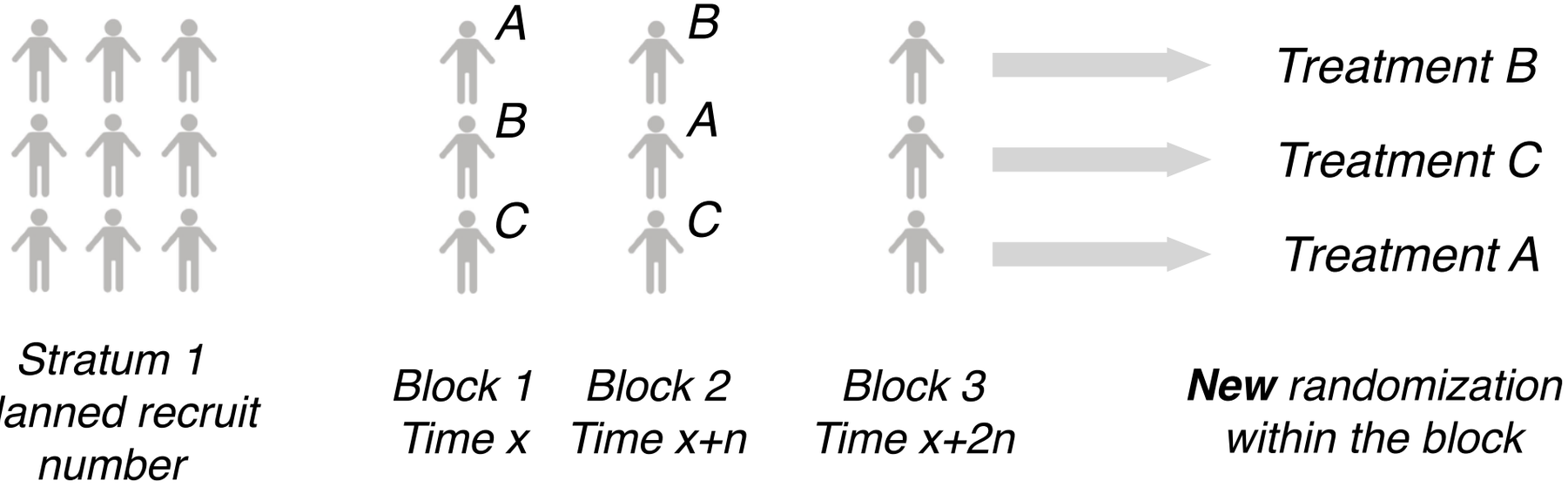

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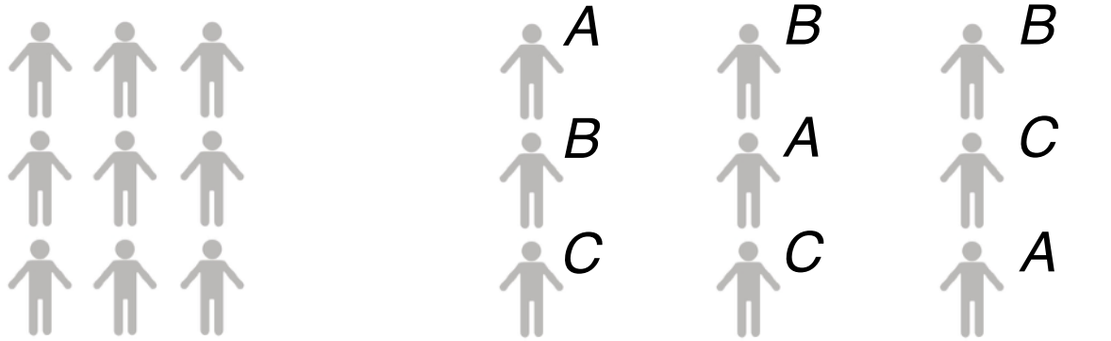


Stratum 1
Planned recruit number

Block 1
Time x

Block 2
Time x+n

Block 3
Time x+2n

Maintains allocation ratio throughout the trial

Flexibility in recruitment

*Berger VW, Bour LJ, Carter K, et al. BMC Med Res Methodol. **2021**;21(1):168.*

Design and conduct of clinical trials

Blinding / Masking

***Blinding** promotes objectivity*
psychological factors can greatly impact results

*Instead, there's **a detailed protocol** to*
ensure proper masking and later unmasking

*Yu R, Coleman DA. Contemp Clin Trials Commun. **2015**;1:22-27.*

Design and conduct of clinical trials

Blinding / Masking

***Blinding** promotes objectivity*
psychological factors can greatly impact results

Single-blinded	***Double-blinded***	***Triple-blinded***
		
Only masking patients	*Masking both patients and physicians*	*Masking patients, physicians, and ground-level data collectors and analyzers*

Is it possible? Is it ethical?

*Yu R, Coleman DA. Contemp Clin Trials Commun. **2015**;1:22-27.*

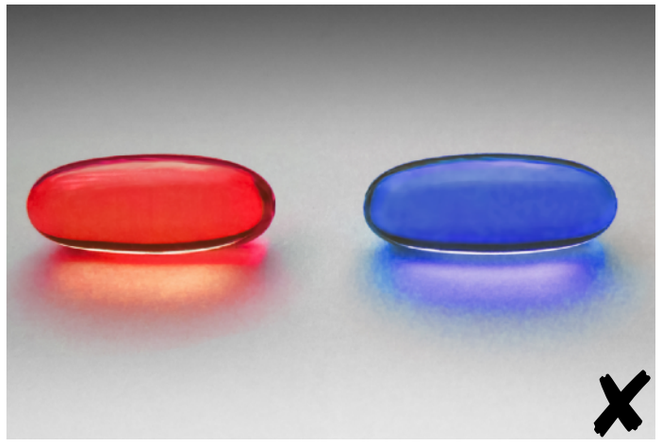
Design and conduct of clinical trials

Blinding / Masking

***Blinding** promotes objectivity*
psychological factors can greatly impact results

Is it possible? Is it ethical?

Coded, identical-looking kits



A red capsule and a blue capsule

*Yu R, Coleman DA. Contemp Clin Trials Commun. **2015**;1:22-27.*

Design and conduct of clinical trials

Blinding / Masking

***Blinding** promotes objectivity*
psychological factors can greatly impact results

Is it possible? Is it ethical?

Coded, identical-looking kits

- *Pills, injections…*
- *Behavioral intervention…*
- *Surgery? Sham surgery…*
- *Treating placebo to dying patients…*

*Yu R, Coleman DA. Contemp Clin Trials Commun. **2015**;1:22-27.*

Design and conduct of clinical trials

Controlled comparison

Treatment A

Treatment B

Parallel tests

Treatment A: the new treatment

Treatment B: placebo

} *Superiority*

Treatment A: the new treatment

Treatment B: standard of care

} *Superiority, equivalency or non-inferiority*

https://trials.lilly.com/en-US/blog/clinical-trial-design-parallel-crossover-studies

Design and conduct of clinical trials

Controlled comparison

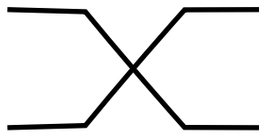
Treatment A

Treatment B

Parallel tests

Treatment A

Treatment B



Treatment A

Treatment B

Crossover tests

Time x *Wash out* *Time y*

Each patient serve as his/her own control

Chronic conditions, fast-responsive treatment (20%)

https://trials.lilly.com/en-US/blog/clinical-trial-design-parallel-crossover-studies

Design and conduct of clinical trials

Clinical trial protocol

Well-designed protocol of patient recruitment and treatment

⇩

What treatment outcomes should be measured?

Hariton E, Locascio JJ. BJOG. ***2018****;125(13).*

Design and conduct of clinical trials

Outcomes / Endpoints

- *Primary endpoints*

  Addressing primary hypothesis, mostly important

- *Secondary / surrogate endpoints*

  Other potential treatment effects

  Mechanism, safety

- *Other outcomes*

  Compliance

  Exploratory

Yu R, Coleman DA. Contemp Clin Trials Commun. ***2015****;1:22-27.*

Design and conduct of clinical trials

Outcomes / Endpoints

Semaglutide Phase 3 trials on Type II Diabetes: SUSTAIN 3

***Primary**: Change in HbA1c*
(Glycosylated Hemoglobin, correlated to average blood sugar level in past 2-3 months)

***Secondary**: Change in*

1) *Body weight*
2) *Fasting plasma glucose*
3) *Blood pressure*
4) *Satisfaction questionnaire status*
5) *Patients number achieving HbA1c Equal to or Below 6.5%*

2013-2015, https://clinicaltrials.gov/study/NCT02054897

Design and conduct of clinical trials

Outcomes / Endpoints

*Semaglutide Phase 3 trials also gathered evidence for **Alzheimer's disease***

***Other outcomes** included measurement of*

- *reduced inflammatory markers*
- *dementia-related phenotypes*
- *cognitive decline…*

⇩

Huge repurposing campaign: EVOKE and EVOKE 3+

Leverage safety and dosing results from previous trials I & II

*Mosenzon O, Capehorn MS, De Remigis A, et al. Cardiovasc Diabetol. **2022**;21(1):172.*
*Cummings JL, Atri A, Feldman HH, et al. Alzheimers Res Ther. **2025**;17(1):14.*

Design and conduct of clinical trials

Clinical trial protocol

Well-designed protocol of patient recruitment and treatment

Carefully-selected outcomes and measurements

⇩

Good clinical trial designs are vital for trial success

Hariton E, Locascio JJ. BJOG. ***2018****;125(13).*

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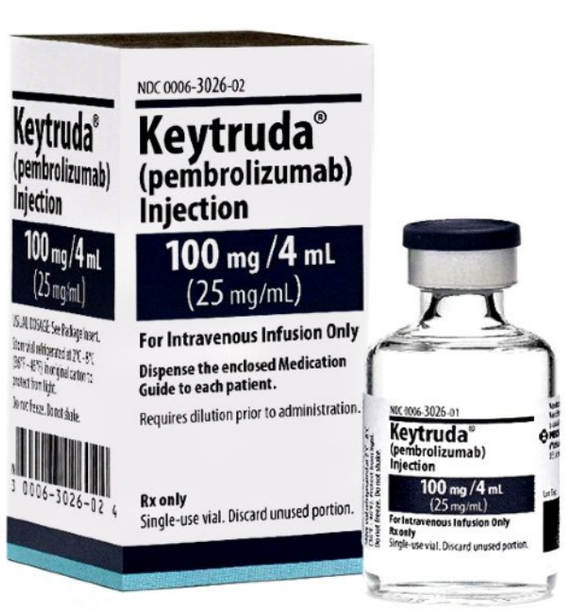
European Society of Medical Oncology conference, Oct. 2016

Reveal of Phase 3 data from two head-to-head competing products



Keytruda
(pembrolizumab)

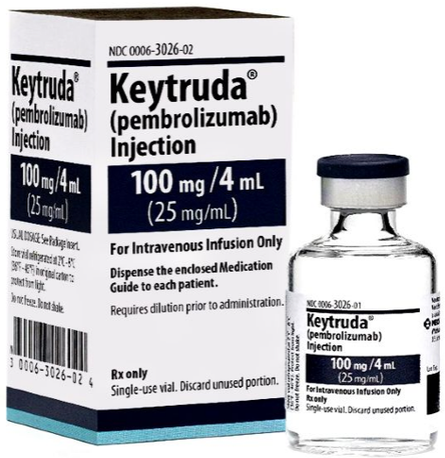
MERCK

Opdivo
(nivolumab)

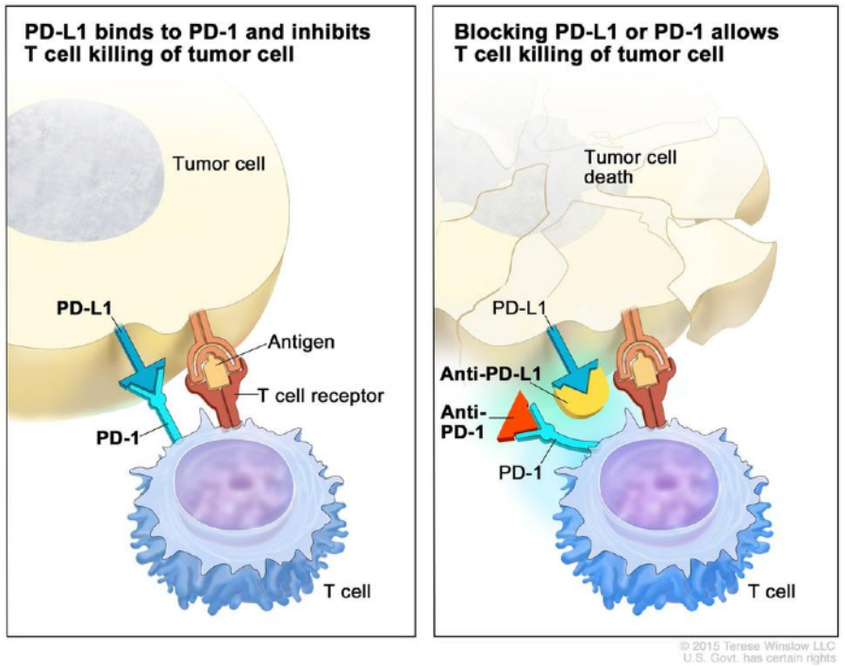
Bristol Myers Squibb™

- *Early dominance of the market*

Anti-PD1 antibody therapy



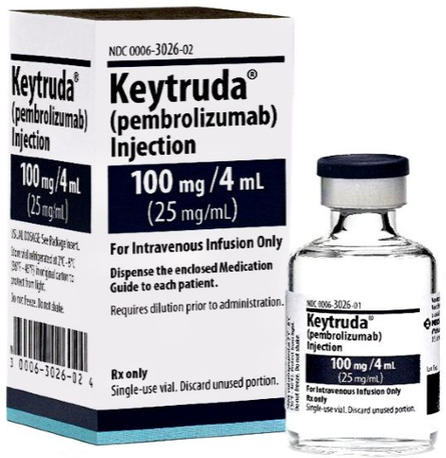
Keytruda
(pembrolizumab)



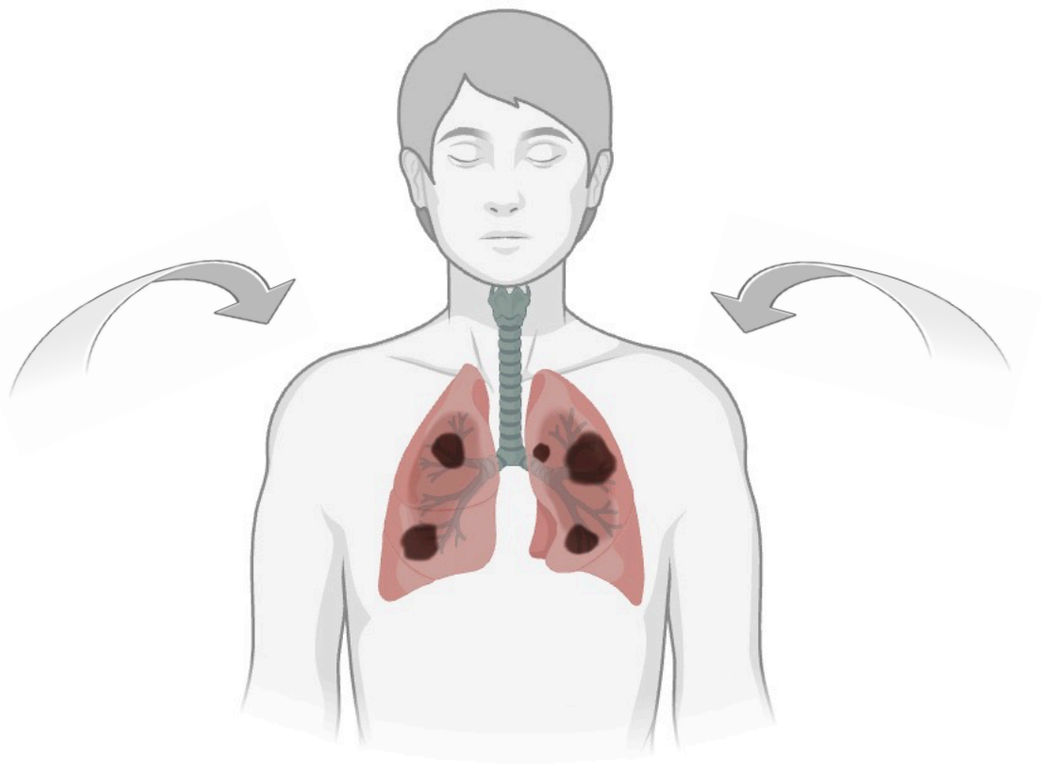
Opdivo
(nivolumab)

https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors

Non-small cell lung cancer (NSCLC)



Keytruda (pembrolizumab)



85% of all lung cancers

Opdivo (nivolumab)

1.28 million new NSCLC cases from 2010 to 2017 in US

Both trials compares with chemotherapy as first-line treatment

https://my.clevelandclinic.org/health/diseases/6203-non-small-cell-lung-cancer

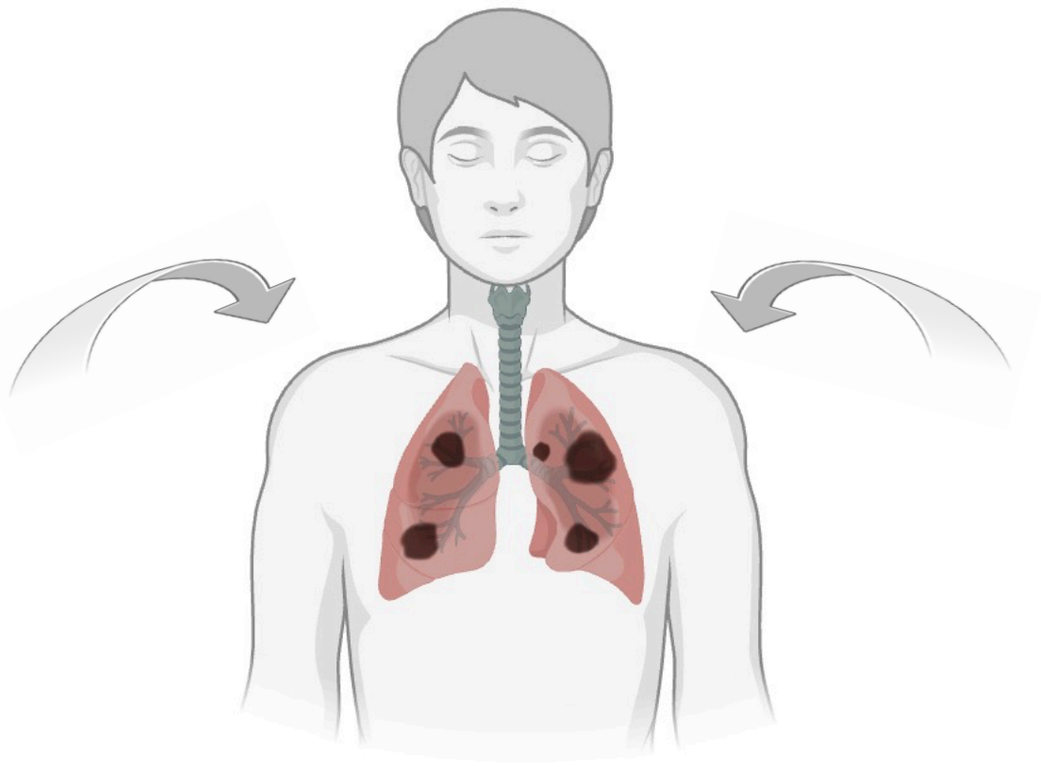
Non-small cell lung cancer (NSCLC)

KEYNOTE-024

“  ”

Keytruda (pembrolizumab)

MERCK



85% of all lung cancers

1.28 million new NSCLC cases from 2010 to 2017 in US

CHECKMATE-026

“  ”

Opdivo (nivolumab)

Bristol Myers Squibb™

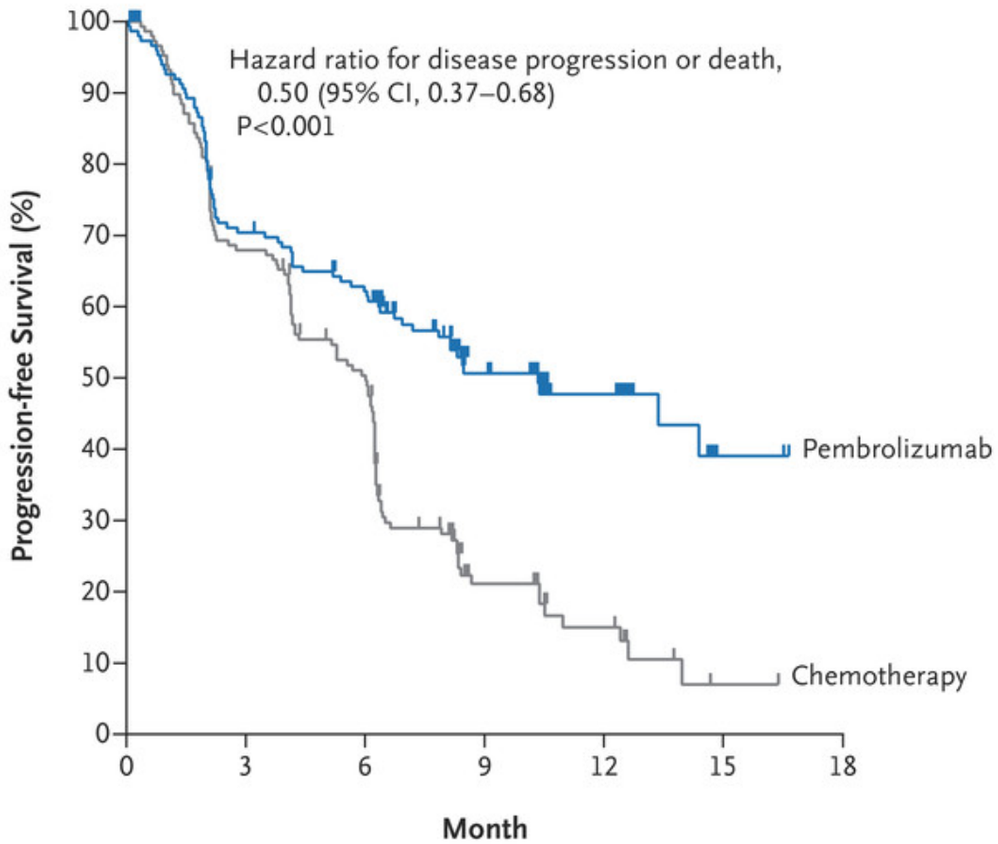
Keytruda reached all primary endpoints while Opdivo failed

https://my.clevelandclinic.org/health/diseases/6203-non-small-cell-lung-cancer

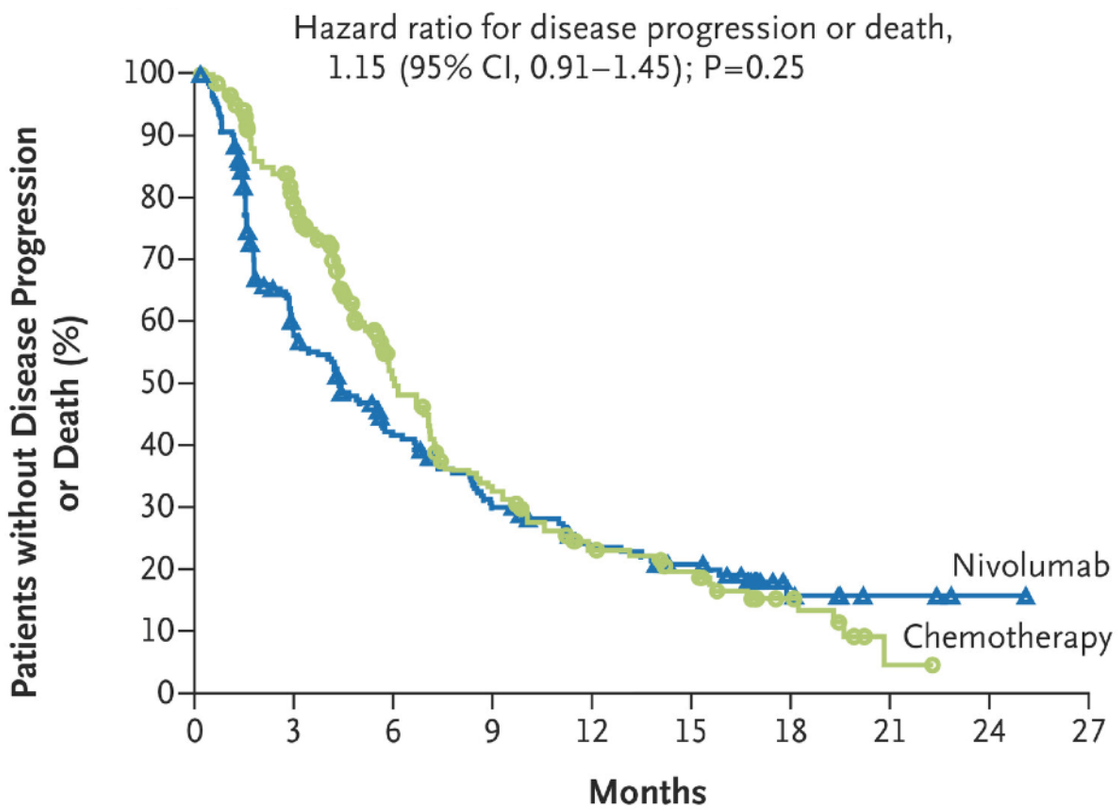
Keytruda vs. Opdivo trials

First-line monotherapy against NSCLC

KEYNOTE-024



CHECKMATE-026



Keytruda increased patients progression-free survival (PFS)

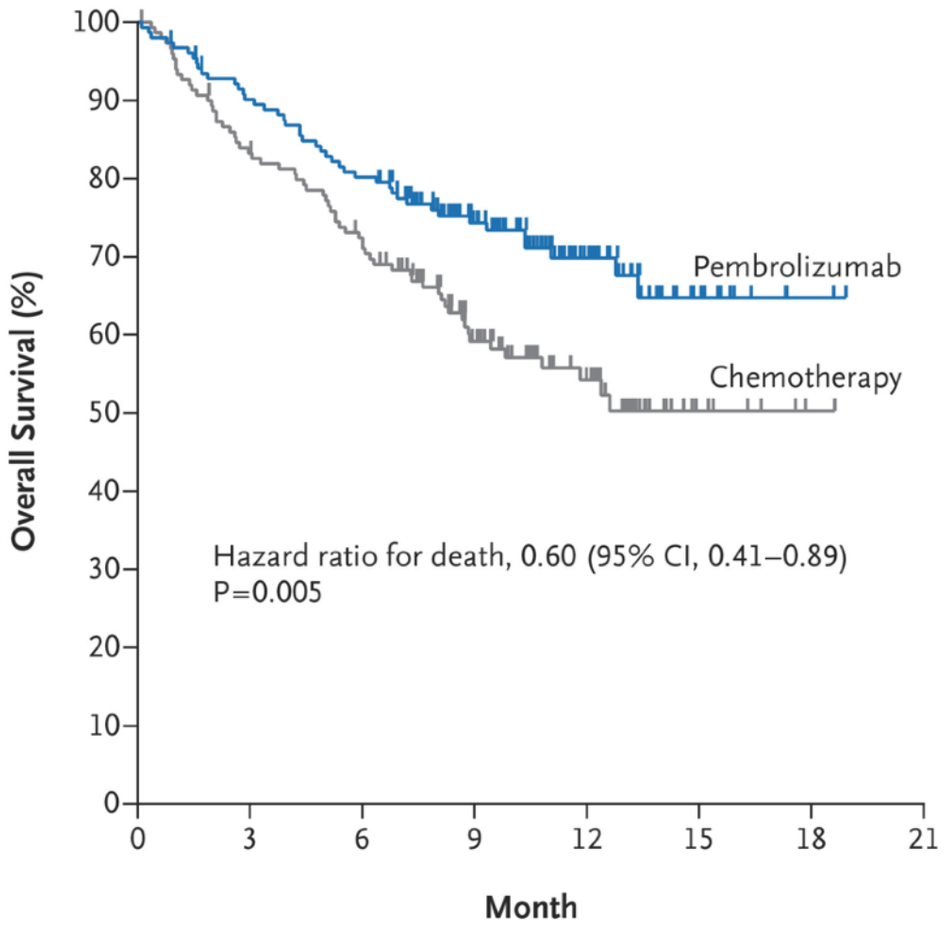
Reck M, Rodríguez-Abreu D, et al. N Engl J Med. ***2016****;375(19):1823-33.*

Carbone DP, Reck M, et al. N Engl J Med. ***2017****;376(25):2415-26.*

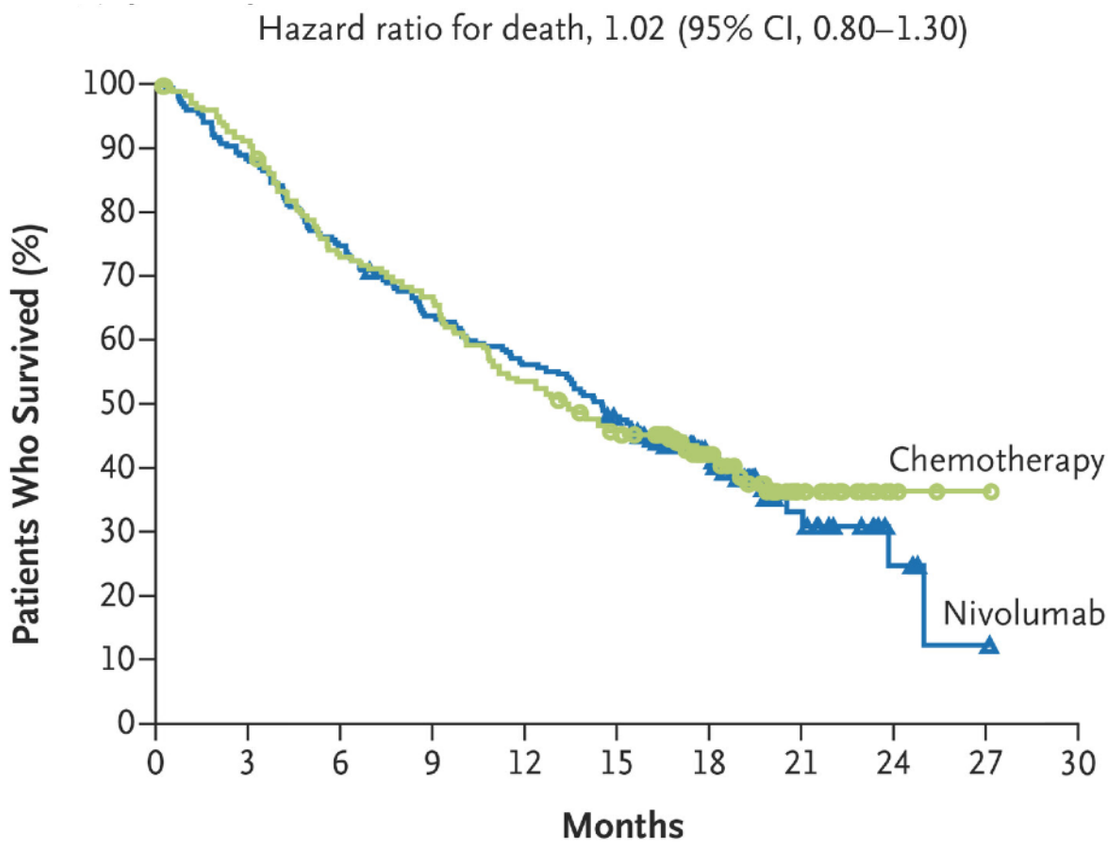
Keytruda vs. Opdivo trials

First-line monotherapy against NSCLC

KEYNOTE-024



CHECKMATE-026



Keytruda increased patients overall survival (OS)

Reck M, Rodríguez-Abreu D, et al. N Engl J Med. ***2016****;375(19):1823-33.*

Carbone DP, Reck M, et al. N Engl J Med. ***2017****;376(25):2415-26.*

Keytruda vs. Opdivo trials

First-line monotherapy against NSCLC

KEYNOTE-024

“ In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy.”

CHECKMATE-026

Nivolumab was not associated with significantly longer progression-free survival than chemotherapy among patients with previously untreated stage IV or recurrent NSCLC with a PD-L1 expression level of 5% or more. Overall survival was similar between groups. Nivolumab had a favorable safety profile, as compared with chemotherapy, with no new or unexpected safety signals.

*Reck M, Rodríguez-Abreu D, et al. N Engl J Med. **2016**;375(19):1823-33.*

*Carbone DP, Reck M, et al. N Engl J Med. **2017**;376(25):2415-26.*

Keytruda vs. Opdivo trials

First-line monotherapy against NSCLC

KEYNOTE-024

*“ In patients with advanced NSCLC and **PD-L1 expression on at least 50% of tumor cells**, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy.”*

CHECKMATE-026

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A difference in patient recruitment threshold profoundly impacted results

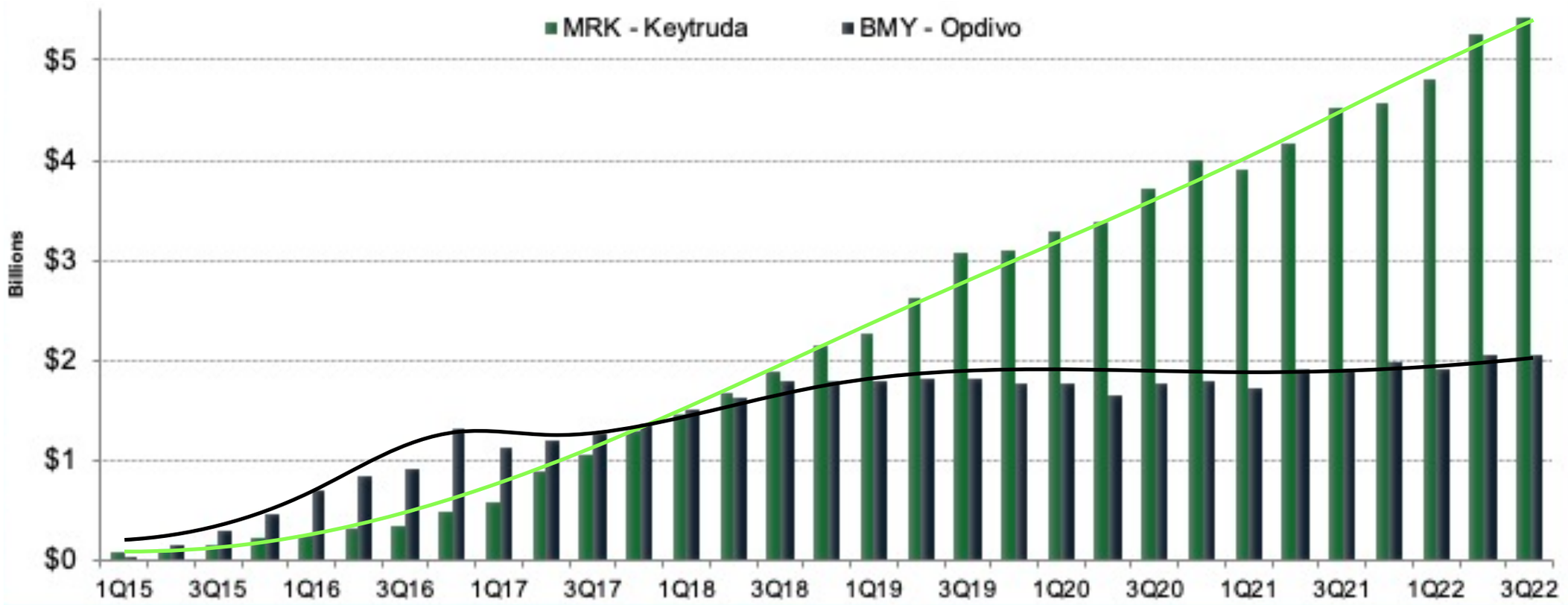
And more profoundly on product sales…

*Reck M, Rodríguez-Abreu D, et al. N Engl J Med. **2016**;375(19):1823-33.*

*Carbone DP, Reck M, et al. N Engl J Med. **2017**;376(25):2415-26.*

Keytruda vs. Opdivo trials

Trend in sales



@BradLoncar

Keytruda's sales quickly surpass opdivo in 2018, then top in 2023

Keytruda's sales in NSCLC significantly contributed to its global sales

~ $10 Billion global sales in 2022 (50%)

Keytruda vs. Opdivo trials

First-line monotherapy against NSCLC

KEYNOTE-024

“ In patients with advanced NSCLC and ***PD-L1 expression on at least 50% of tumor cells****, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy.”*

CHECKMATE-026

Nivolumab was not associated with significantly longer progression-free survival than chemotherapy among patients with previously untreated stage IV or recurrent NSCLC ***with a PD-L1 expression level of 5% or more****. Overall survival was similar between groups. Nivolumab had a favorable safety profile, as compared with chemotherapy, with no new or unexpected safety signals.*

What has contributed to this difference in trial strategies?

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Keytruda vs. Opdivo trials

First-line monotherapy against NSCLC

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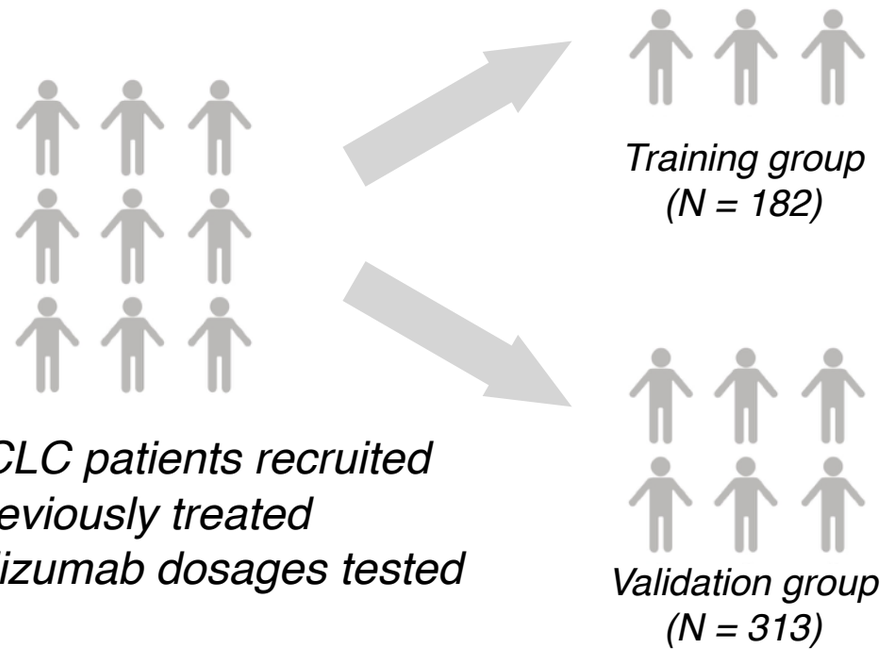
Keytruda vs. Opdivo trials

Keytruda's concern on PD-L1 level

KEYNOTE-001: a large international Phase 1 trial on NSCLC



"…We also sought to define and validate a tumor PD-L1 expression level associated with an enhanced likelihood of benefit from pembrolizumab."

https://clinicaltrials.gov/study/NCT01295827

Garon EB, Rizvi NA, Hui R, et al. N Engl J Med. ***2015****;372(21), 2018-2028.*

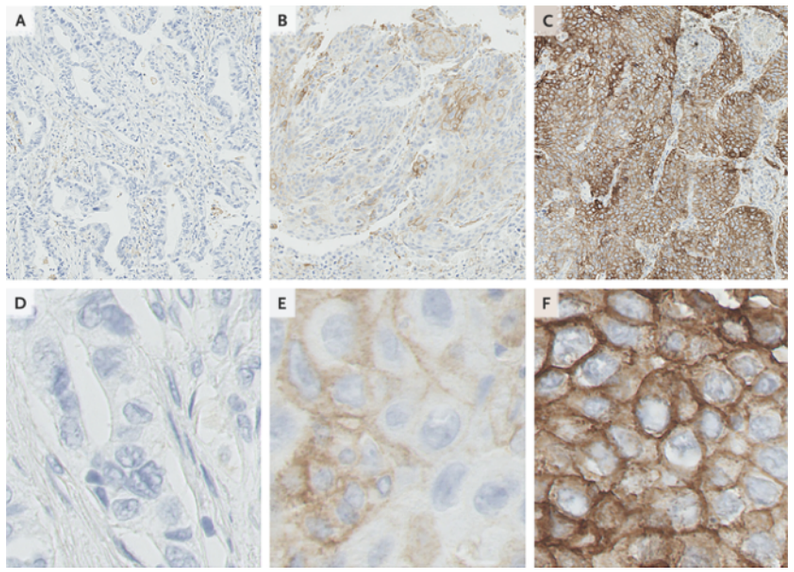
Keytruda vs. Opdivo trials

Keytruda's concern on PD-L1 level

KEYNOTE-001: a large international Phase 1 trial on NSCLC

Training group
(N = 182)

Individual tumor PD-L1 expression tested
Biopsy immunohistochemistry (IHC)



< 1% *1 - 49%* *≥ 50%*

Initial test found the cutoff:
***PD-L1 expression in at least 50%** of the tumor cells*

Better response rate, PFS and OS

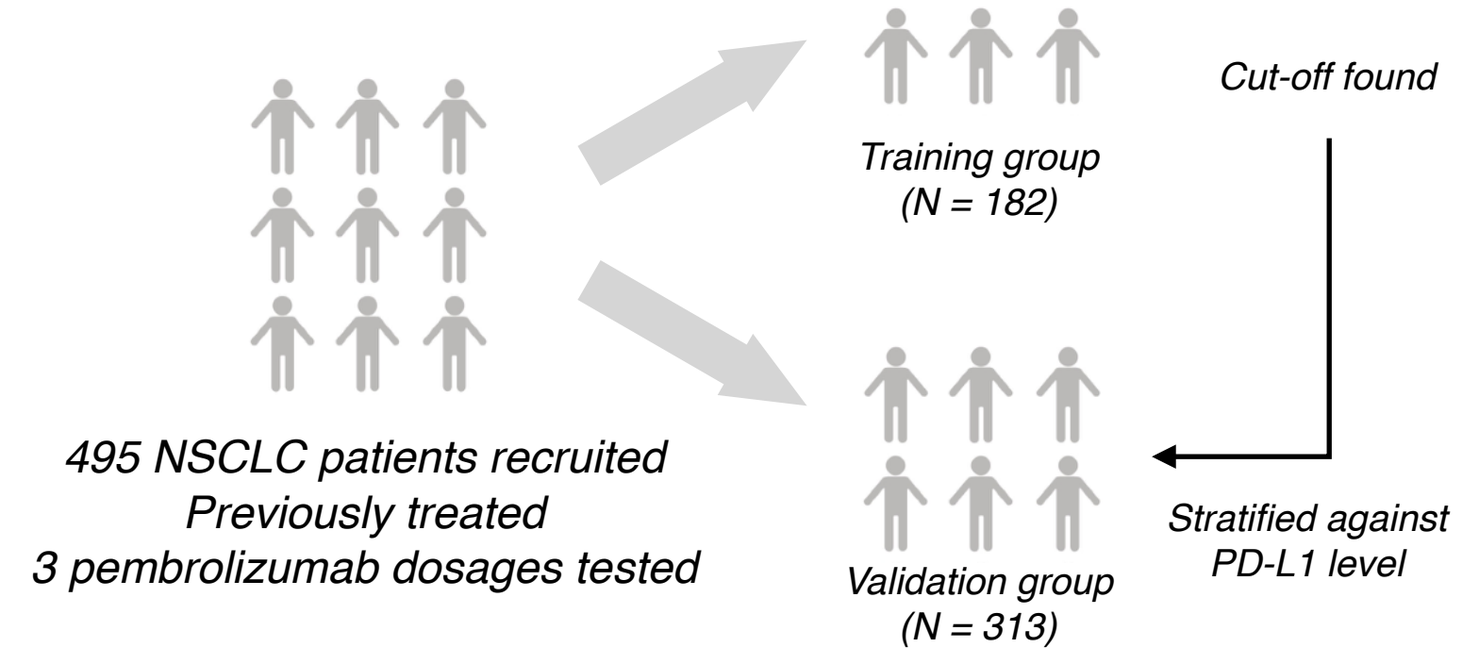
https://clinicaltrials.gov/study/NCT01295827

*Garon EB, Rizvi NA, Hui R, et al. N Engl J Med. **2015**;372(21), 2018-2028.*

Keytruda vs. Opdivo trials

Keytruda's concern on PD-L1 level

KEYNOTE-001: a large international Phase 1 trial on NSCLC



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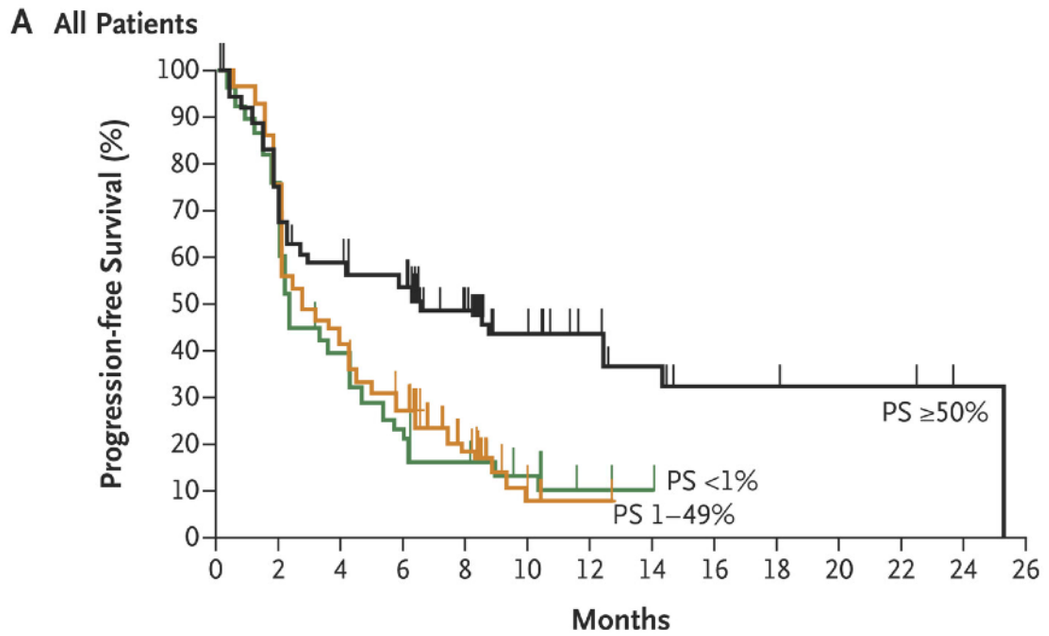
Keytruda vs. Opdivo trials

Keytruda's concern on PD-L1 level

KEYNOTE-001: a large international Phase 1 trial on NSCLC

Validation group
(N = 313)



No. at Risk														
PS ≥50%	119	86	66	60	38	20	13	8	4	3	3	3	1	0
PS 1–49%	161	122	70	45	21	4	1	0	0	0	0	0	0	0
PS <1%	76	52	29	17	11	6	2	0	0	0	0	0	0	0

Better response rate, PFS and OS validated in patient group
with ≥ 50% PD-L1 tumor expression

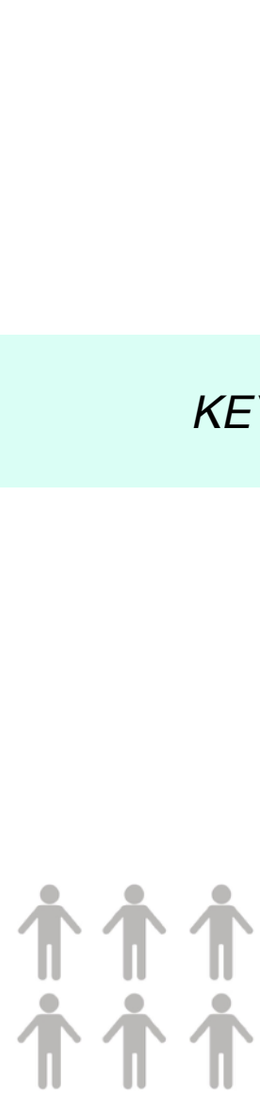
https://clinicaltrials.gov/study/NCT01295827

Garon EB, Rizvi NA, Hui R, et al. N Engl J Med. ***2015****;372(21), 2018-2028.*

Keytruda vs. Opdivo trials

Keytruda's concern on PD-L1 level

KEYNOTE-001: a large international Phase 1 trial on NSCLC



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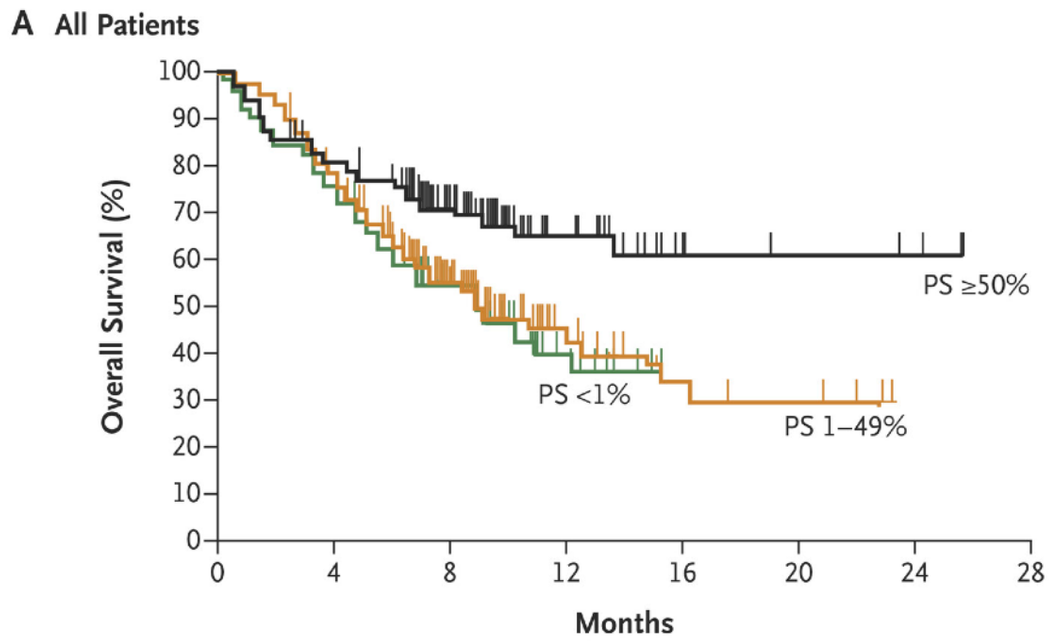
(N = 313)



No. at Risk								
PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

Better response rate, PFS and OS validated in patient group
with ≥ 50% PD-L1 tumor expression

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Keytruda vs. Opdivo trials

Keytruda's concern on PD-L1 level

KEYNOTE-010: pioneer Phase 2/3 study on NSCLC

1034 NSCLC patients recruited
Previously treated
≥1% PD-L1–positive staining

Pembrolizumab (2 mg/kg)

Pembrolizumab (10 mg/kg)

Docetaxel, SOC

Primary endpoint: better survival for

1) *All patients treated with Pembrolizumab*

2) *Patients with ≥ 50% PD-L1 expression*

https://clinicaltrials.gov/study/NCT01905657

*Herbst RS, Baas P, Kim DW, et al. The lancet. **2016**;387(10027), 1540-1550.*

Keytruda vs. Opdivo trials

Keytruda's concern on PD-L1 level

KEYNOTE-010: pioneer Phase 2/3 study on NSCLC

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Pembrolizumab (2 mg/kg)

Pembrolizumab (10 mg/kg)

Docetaxel, SOC

Primary endpoint: better survival for

1) *All patients treated with Pembrolizumab*

No sig. benefit for pem. against chemo

2) *Patients with ≥ 50% PD-L1 expression*

Huge improvement for pem. against chemo

https://clinicaltrials.gov/study/NCT01905657

*Herbst RS, Baas P, Kim DW, et al. The lancet. **2016**;387(10027), 1540-1550.*

Keytruda vs. Opdivo trials

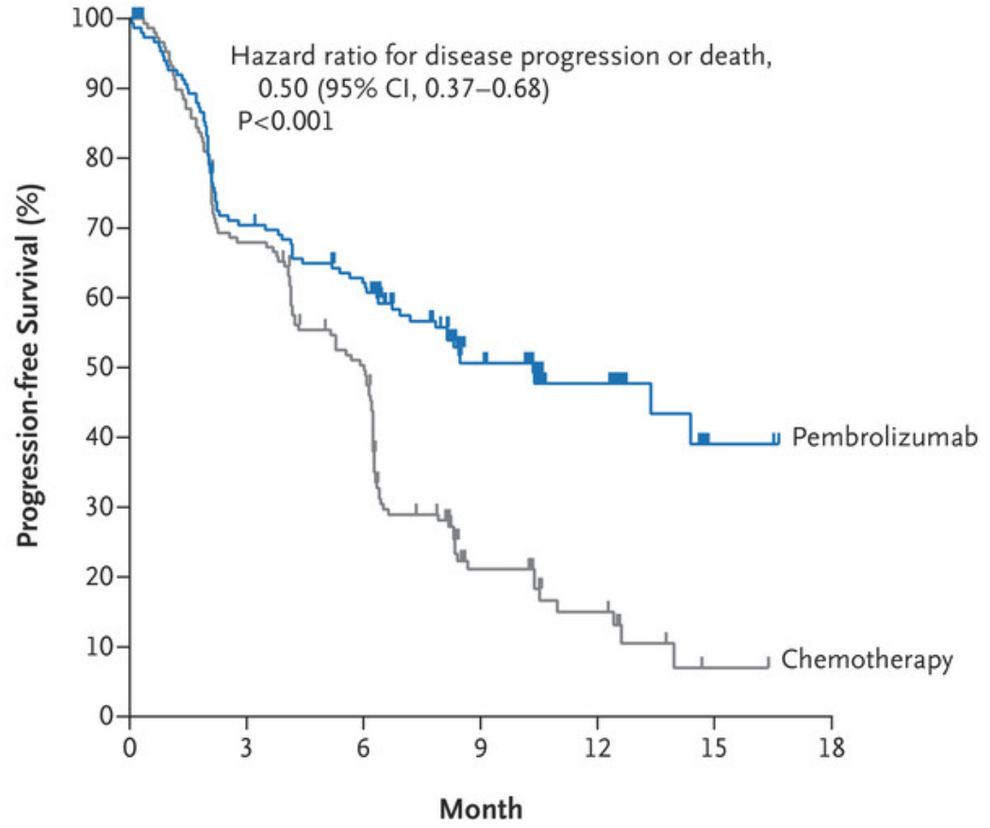
Keytruda's concern on PD-L1 level

KEYNOTE-024: final Phase 3 study on NSCLC

305 NSCLC patients recruited
Previously untreated
≥50% PD-L1–positive staining

Pembrolizumab (200 mg fixed dose)

Doctor's choice of chemotherapy
Crossover was allowed



Perbrolizumab/Keytruda outperformed first-line chemotherapy

Strong evidence for FDA approval of Keytruda as a first-line monotherapy

https://clinicaltrials.gov/study/NCT02142738

Reck M, Rodríguez-Abreu D, Robinson AG, et al. N Engl J Med. ***2016****;375(19), 1823-1833.*

Keytruda vs. Opdivo trials

First-line monotherapy against NSCLC

KEYNOTE-024

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Keytruda vs. Opdivo trials

Opdivo's confidence in the leap

For savvy business reasons, Bristol-Myers opted to target a broad patient population, hoping for the widest approval for Opdivo possible. It was suggested in early 2016 — that despite no data or approval in the first-line setting — physicians were already prescribing Opdivo off label to about 20% of first-line NSCLC patients. Analysts predicted the first-line setting could be a $12 billion market. Evercore ISI analyst Mark Schoenebaum previously estimated that Opdivo would bring in approximately $9 billion in revenues by 2019, with more than half of that coming from the NSCLC indication.

"Gambled big"

Is this the whole story?

https://www.biopharmadive.com/news/biomarkers-bristol-myers-opdivo-lost-lung-cancer/435891/

Keytruda vs. Opdivo trials

Opdivo's confidence in the leap

Approved as second-line treatment in 2015

For savvy business reasons, Bristol-Myers opted to target a broad patient population, hoping for the widest approval for Opdivo possible. It was suggested in early 2016 — that despite no data or approval in the first-line setting — physicians were already prescribing Opdivo off label to about 20% of first-line NSCLC patients. Analysts predicted the first-line setting could be a $12 billion market. Evercore ISI analyst Mark Schoenebaum previously estimated that Opdivo would bring in approximately $9 billion in revenues by 2019, with more than half of that coming from the NSCLC indication.

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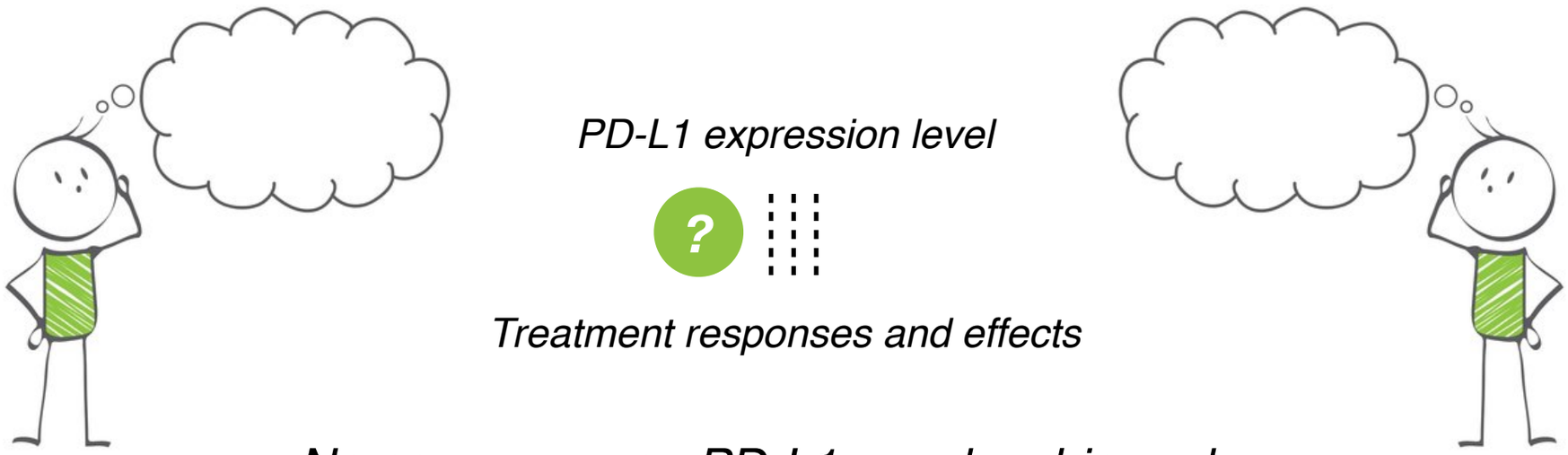
Keytruda vs. Opdivo trials

Opdivo's confidence in the leap



No consensus on PD-L1 as a key biomarker

> Merck, on the other hand, decided to take the more conservative approach. The New Jersey drugmaker opted on the side of precision medicine and used a pro-biomarker strategy, testing patients before trials and only allowing those patients into clinical trials that expressed certain levels of the PD-L1 biomarker. Investors weren't initially keen on this strategy — it limited the potential first-line indication to just 30% of that market, or $4 billion. Now, it seems to be paying off.

https://insights.citeline.com/PS056912/Building-A-Better-Biomarker-PD-L1-Expression-Under-Spotlight-At-ASCO/
https://www.biopharmadive.com/news/biomarkers-bristol-myers-opdivo-lost-lung-cancer/435891/

Keytruda vs. Opdivo trials

Opdivo's confidence in the leap

CHECKMATE-017: Phase 3 trial on squamous NSCLC, second-line

…overall survival, response rate, and progression-free survival were significantly better with nivolumab than with docetaxel, ***regardless of PD-L1 expression level.***

CHECKMATE-057: Phase 3 trial on non-squamous NSCLC, second-line

…overall survival was longer with nivolumab than with docetaxel. ***(In all PD-L1 level)***

Both observed better treatment effects in patients with higher PD-L1 level

CHECKMATE-026: Phase 3 trial on all NSCLC, first-line

Targeting all patients with PD-L1 tumor-expression level of 1% or more

Brahmer J, Reckamp KL, Baas P, et al. N Engl J Med. ***2015****;373(2):123-135.*
Borghaei H, Paz-Ares L, Horn L, et al. N Engl J Med. ***2015****;373(17), 1627-1639.*
https://www.onclive.com/view/checkmate026-underscores-predictive-value-of-high-pdl1-expression

Keytruda vs. Opdivo trials

Opdivo's confidence in the leap

CHECKMATE-017: Phase 3 trial on squamous NSCLC, second-line

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CHECKMATE-026: Phase 3 trial on all NSCLC, first-line

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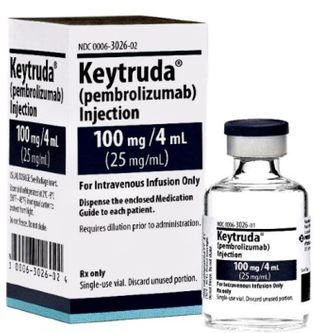
https://www.onclive.com/view/checkmate026-underscores-predictive-value-of-high-pdl1-expression

Keytruda vs. Opdivo trials

Era of indication expansion



Keytruda
(pembrolizumab)

Opdivo
(nivolumab)

MERCK

Bristol Myers Squibb™

2.5 M patients,
No.1 in 2023

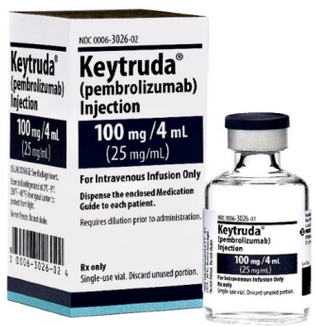
1.8 M patients,
No.9 in 2023

Both are great therapeutics!

https://www.biopharmadive.com/news/cancer-immunotherapy-decade-keytruda-opdivo-pd1-oncology/725774/

Keytruda vs. Opdivo trials

Era of indication expansion



Keytruda (pembrolizumab)

MERCK

Hundreds of new clinical trials for Keytruda against various cancers in the last decade

Expenses: $46 billion till 2024, another $20 billion by 2030

In 2024, reaching 40 indications!

Monotherapy	*Combination therapy*	*Inter-organizational alliances*

+ chemo

+

Opdivo holds over 20+ indications now

https://www.cancerresearch.org/blog/june-2024/keytruda-receives-40th-fda-approval

*Kodama K, Djurian A, Lim Y. Drug Discov Today. **2022**;27(12):103390.*

Outlines

Introduction to fundamentals

Design and conduct of clinical trials

Real-world case studies

Special considerations for biologics

Emerging trends and future directions

Outlines

Introduction to fundamentals

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Real-world case studies

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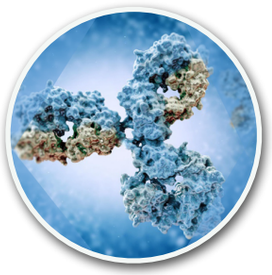
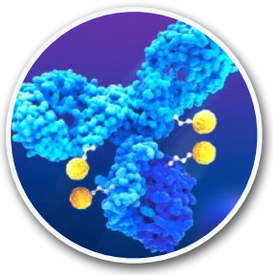
Special considerations for biologics

Definition

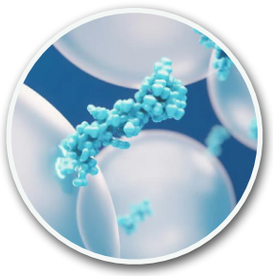
Medications derived from living organisms or containing components of living organisms



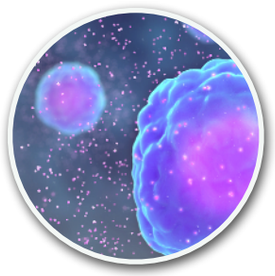
Antibodies (Monoclonal/ bispecific)



ADC



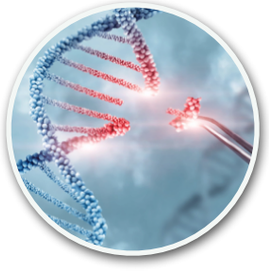
Peptide > 40 AAs



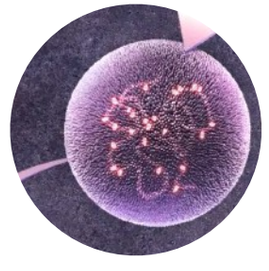
Cytokines, growth factors…

T cell therapy

Stem cell therapy



Gene therapy



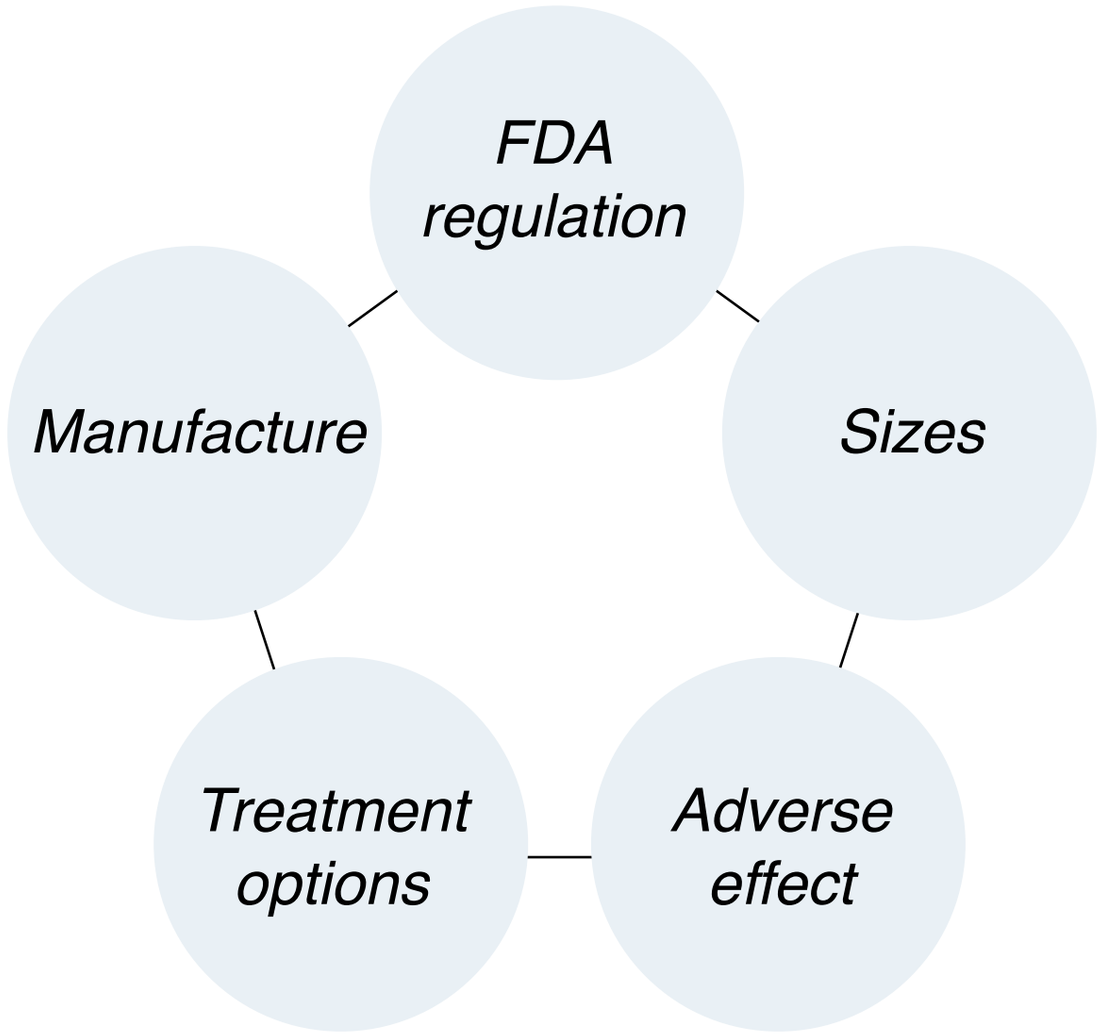
mRNA vaccines

…

https://www.fda.gov/drugs/types-applications/therapeutic-biologics-applications-bla

Special considerations for biologics

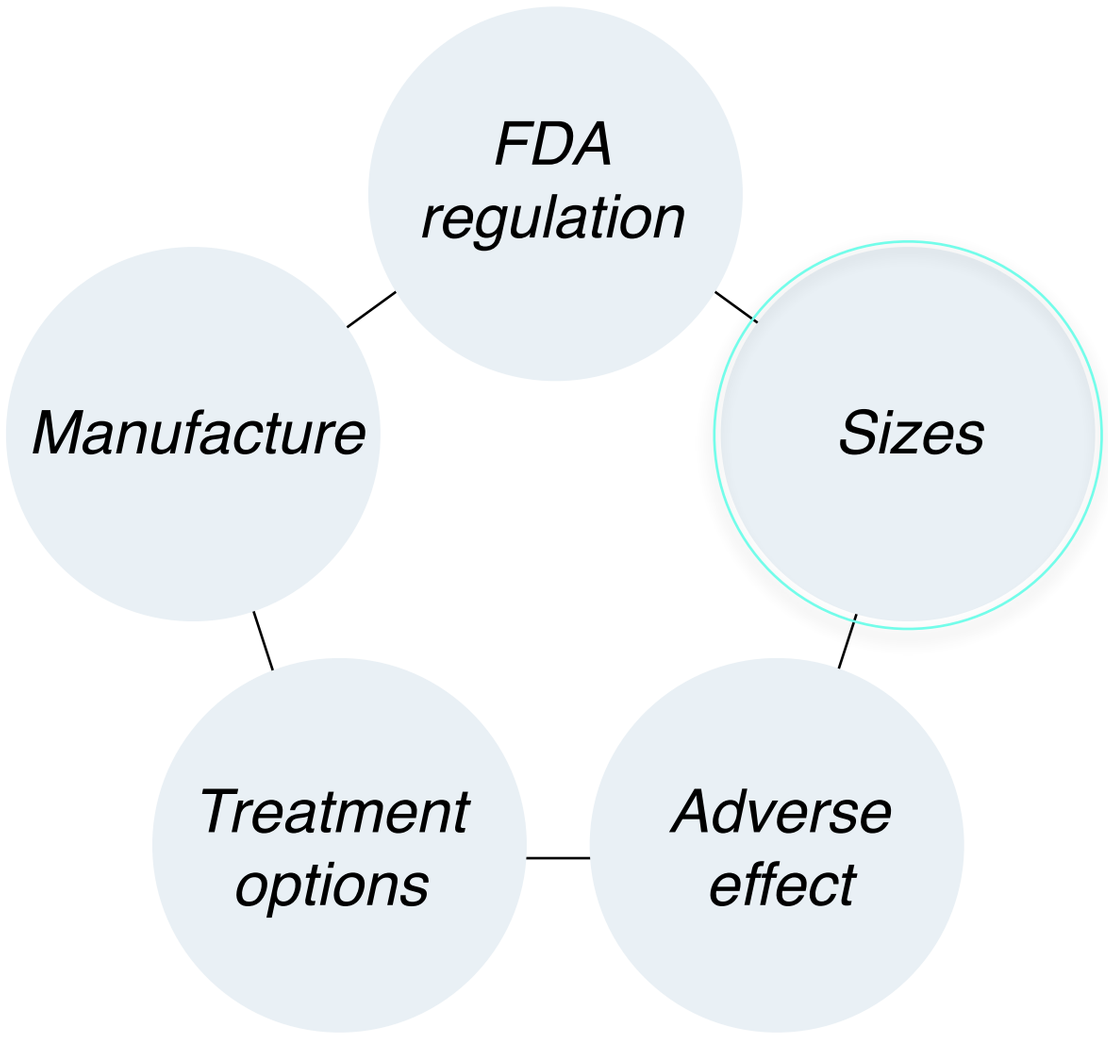
Differences compare to small molecule



https://www.allucent.com/resources/blog/what-are-regulatory-differences-between-nda-and-bla
https://www.allucent.com/resources/blog/points-consider-drug-development-biologics-and-small-molecules

Special considerations for biologics

Differences compare to small molecule



Small molecule drugs

20 to 100 atoms
Mw less than 1000 g/mol
or 1 kDa

Biologics

Antibodies: 150-200 kDa

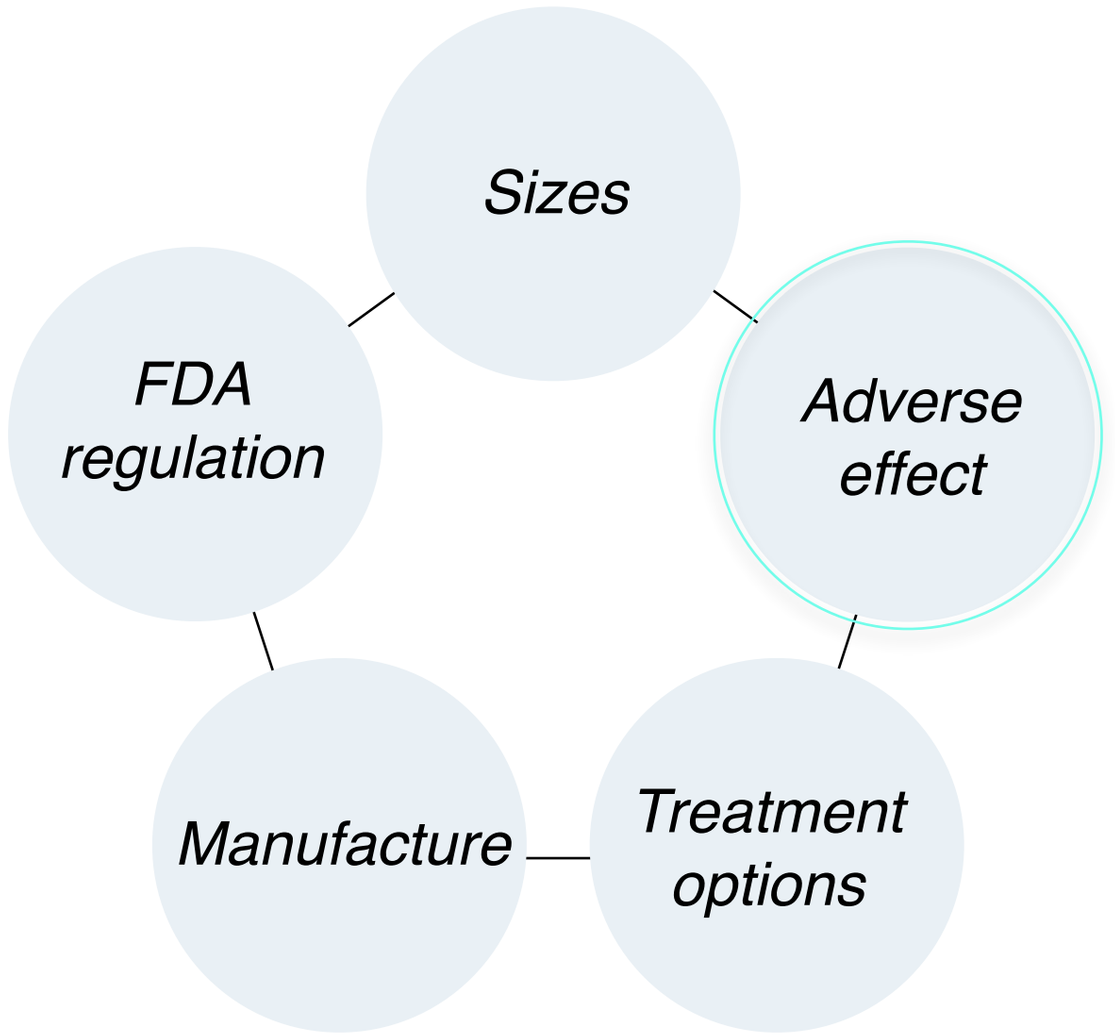
Cells: 10 picogram/per cell

Certain indications hard to target

https://www.allucent.com/resources/blog/what-are-regulatory-differences-between-nda-and-bla
https://www.allucent.com/resources/blog/points-consider-drug-development-biologics-and-small-molecules

Special considerations for biologics

Differences compare to small molecule



Small molecule drugs

Off-target effects

Biologics

Off-target effects

+ immunogenicity

https://www.allucent.com/resources/blog/what-are-regulatory-differences-between-nda-and-bla
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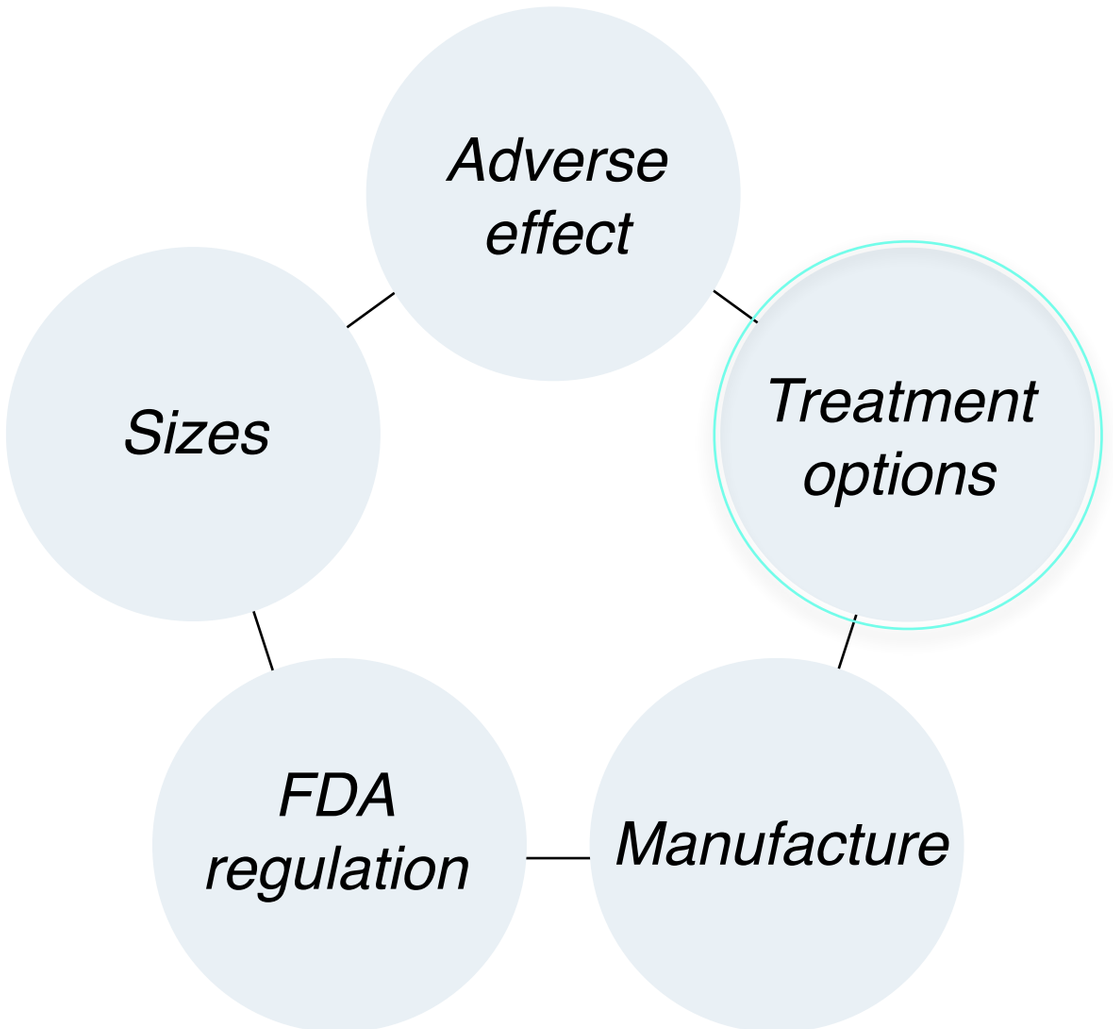
Special considerations for biologics

Differences compare to small molecule



Small molecule drugs

Many through oral administration

Biologics

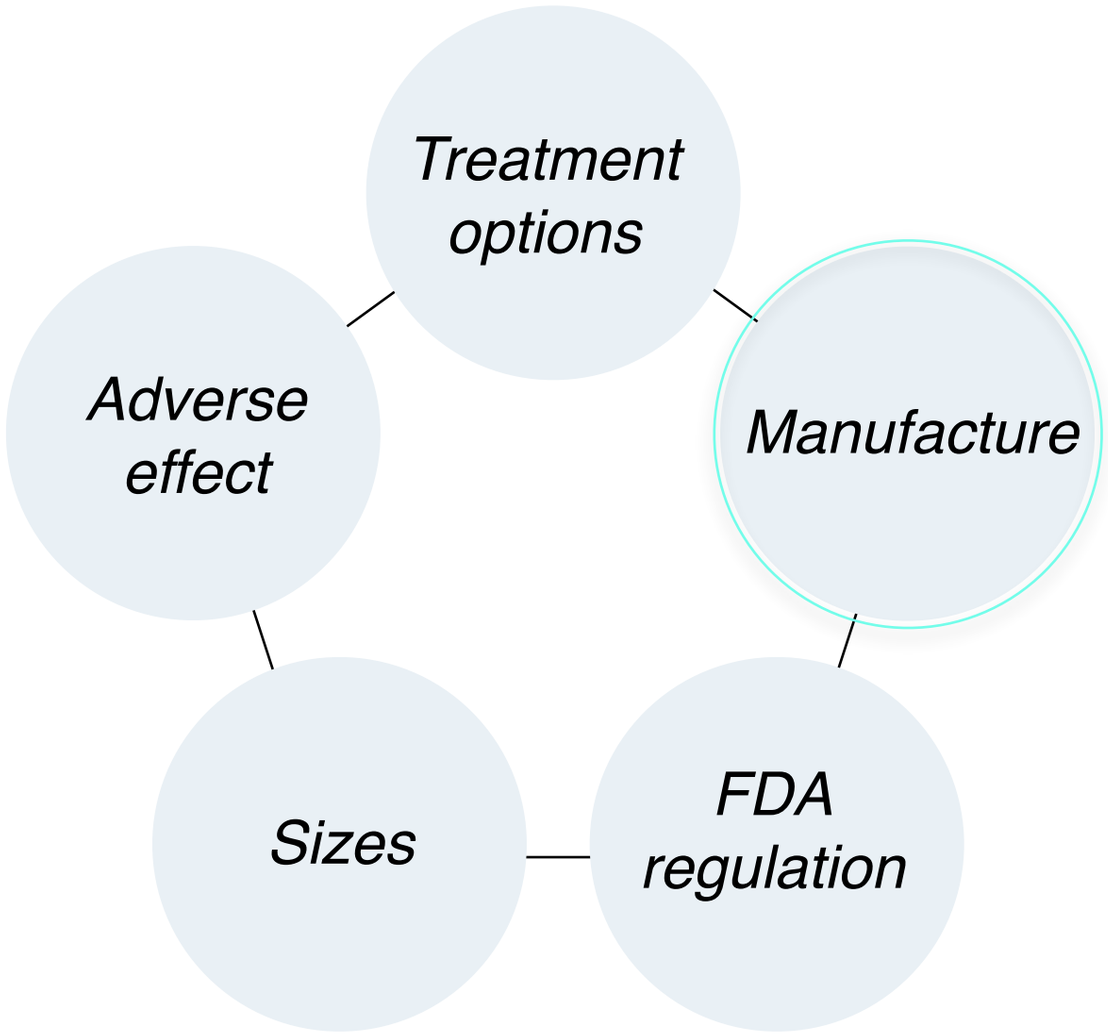
Many through IV injection

Higher standard of clinic care

https://www.allucent.com/resources/blog/what-are-regulatory-differences-between-nda-and-bla
https://www.allucent.com/resources/blog/points-consider-drug-development-biologics-and-small-molecules

Special considerations for biologics

Differences compare to small molecule



Small molecule drugs

Established synthesis facility

Biologics

More complicated, expensive & time consuming

Personalized therapy

https://www.allucent.com/resources/blog/what-are-regulatory-differences-between-nda-and-bla
https://www.allucent.com/resources/blog/points-consider-drug-development-biologics-and-small-molecules

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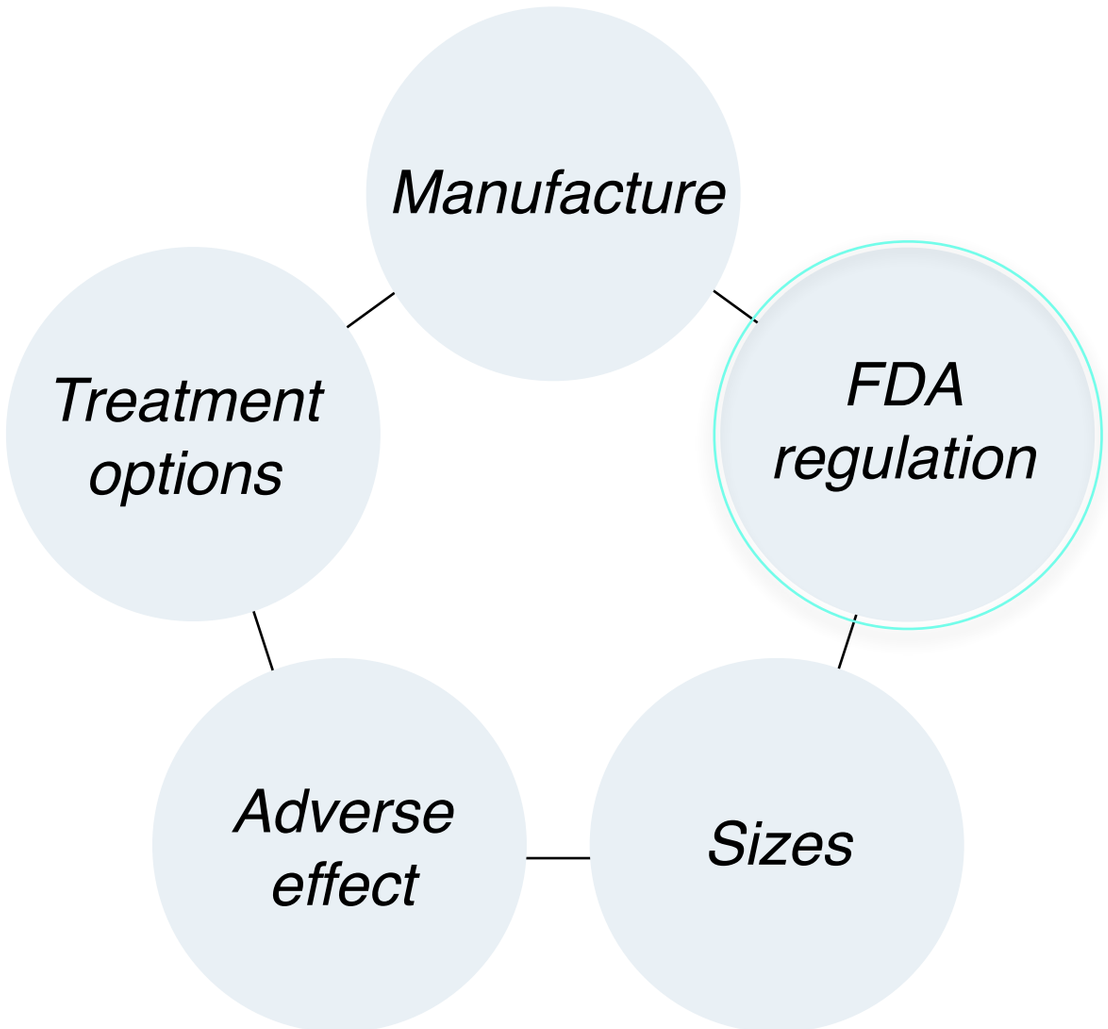


Small molecule drugs

Established protocol/ revision

Biologics

Difficulty in characterization

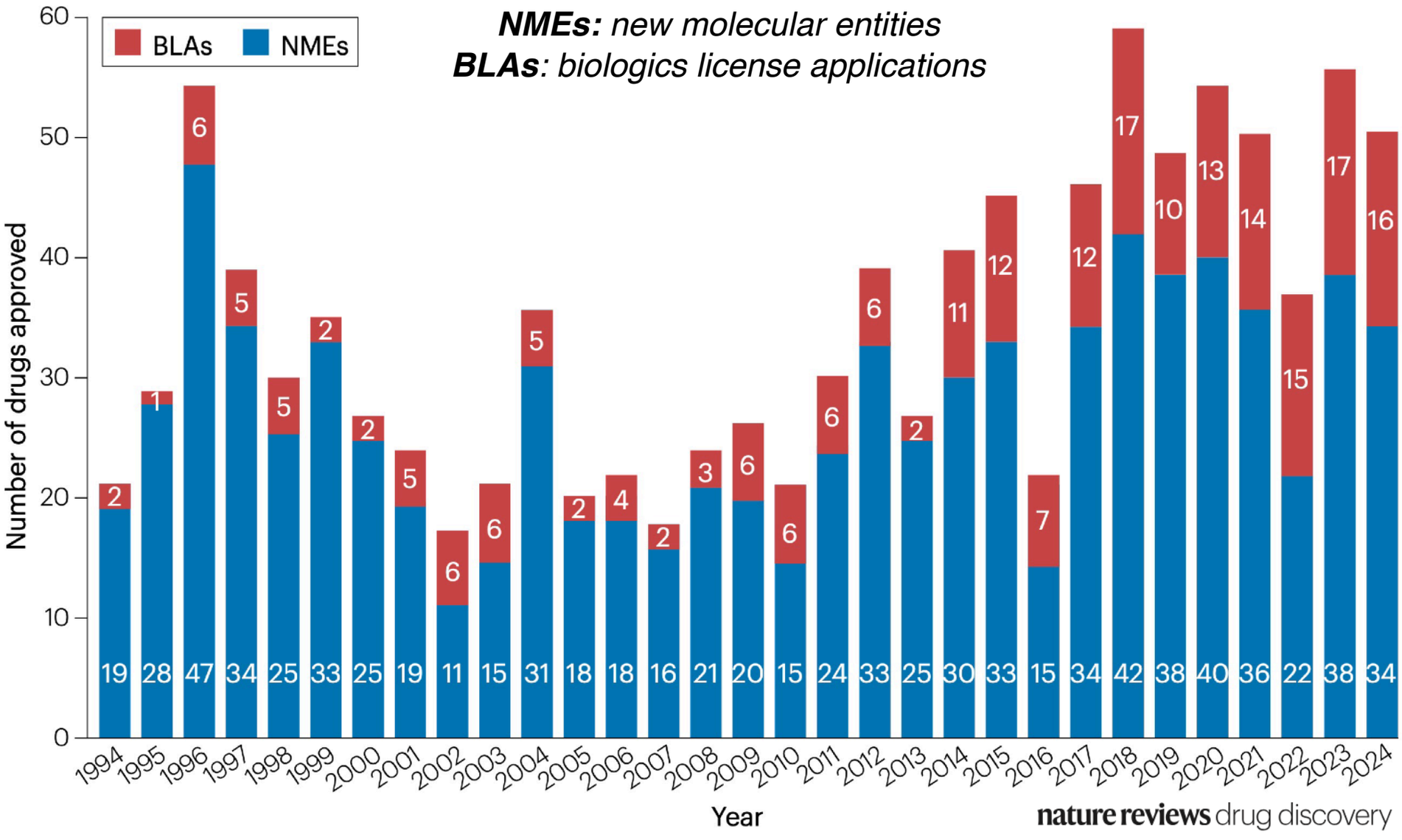
Higher requirement for purity and consistency

https://www.allucent.com/resources/blog/what-are-regulatory-differences-between-nda-and-bla
https://www.allucent.com/resources/blog/points-consider-drug-development-biologics-and-small-molecules

Special considerations for biologics

A gold rush

NMEs: *new molecular entities*
BLAs*: biologics license applications*



Sales of biologics is fast growing, soon reaching those of small molecules

https://www.nature.com/articles/d41573-025-00001-5

Special considerations for biologics

Life-cycle management

*Biologics approved by FDA are granted **12 years of exclusivity***

*blocking **biosimilar** (follow-on, me-too) applications for 4 years and approval for another 8 years*

Orphan Drug Exclusivity (ODE) – 7 years
New Chemical Entity (NCE) Exclusivity – 5 years

Developing a biologics therapy is not necessarily
more time-consuming than developing a small molecule therapy

*Nat Biotechnol. **2019**;37(7):708-711*

“12 years of protection from biosimilar competition is excessive”

*…could **increase competition** among biological products,*
*which has the potential to **reduce drug spending** in the U.S.*

@ Policy proposal from Pew Health in 2017

Special considerations for biologics

Life-cycle management

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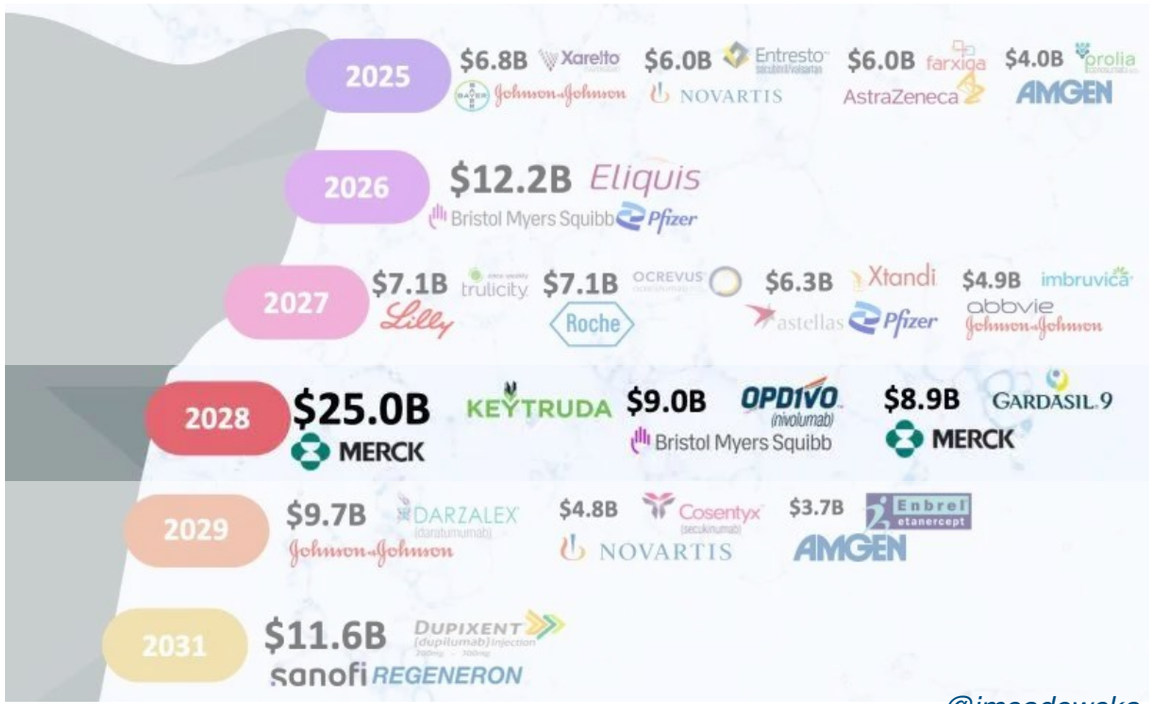


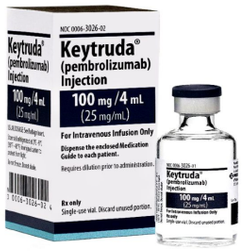
@jmsadowska

Both Keytruda and Opdivo face exclusivity ending in 2028

Emerging anti-PD-1 biosimilars acquiring market shares outside US

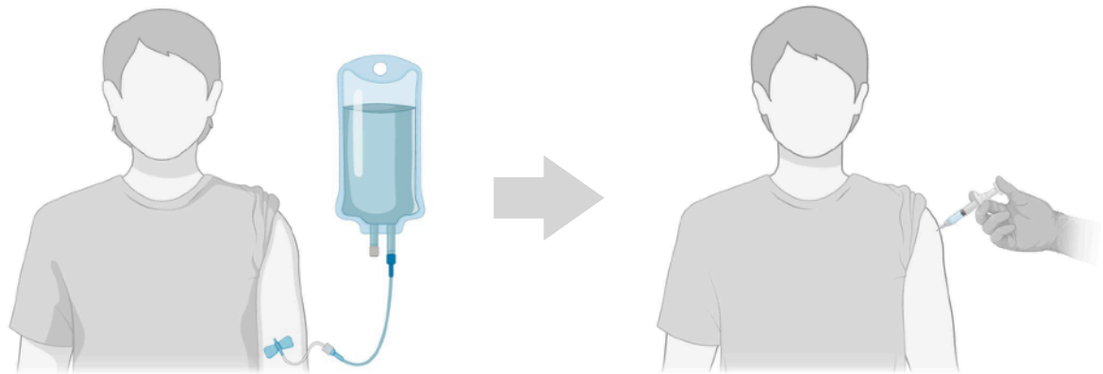
Special considerations for biologics

Life-cycle management



Keytruda
(pembrolizumab)

MERCK



Intravenous
> 30 min

Subcutaneous
~ few min

pivotal Phase 3
MK-3475A-D77 trial

metastatic NSCLC

Noninferiority

"Product hopping"

"Merck's patents on the subcutaneous version of Keytruda could protect that formulation until at least 2040"

https://firstwordpharma.com/story/5927667

https://www.merck.com/news/merck-announces-phase-3-trial-of-subcutaneous-pembrolizumab-with-berahyaluronidase-alfa-met-primary-endpoints/

Outlines

Introduction to fundamentals

Design and conduct of clinical trials

Real-world case studies

Special considerations for biologics

Emerging trends and future directions

Outlines

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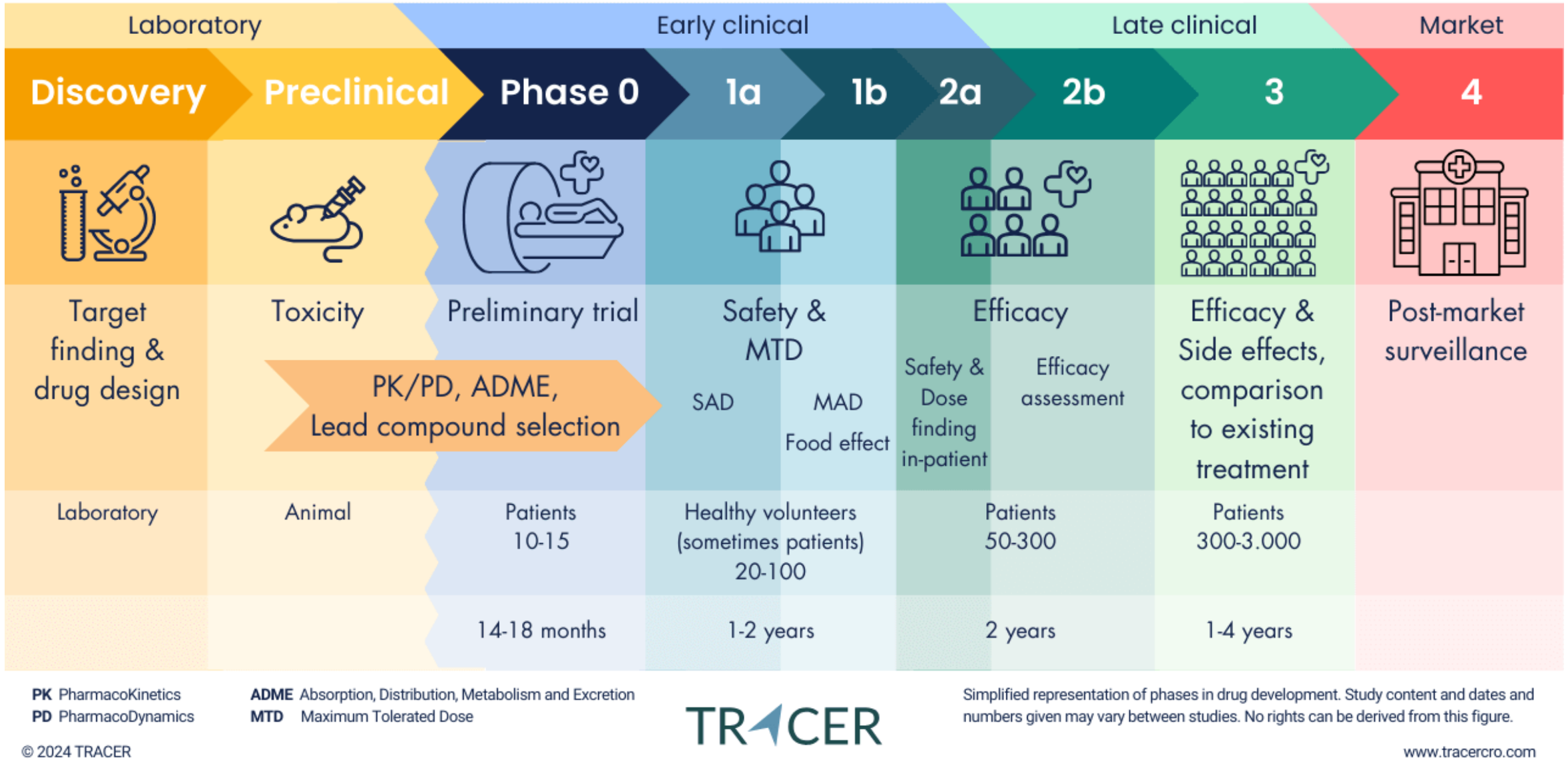
Emerging trends and future directions

Emerging trends and future directions

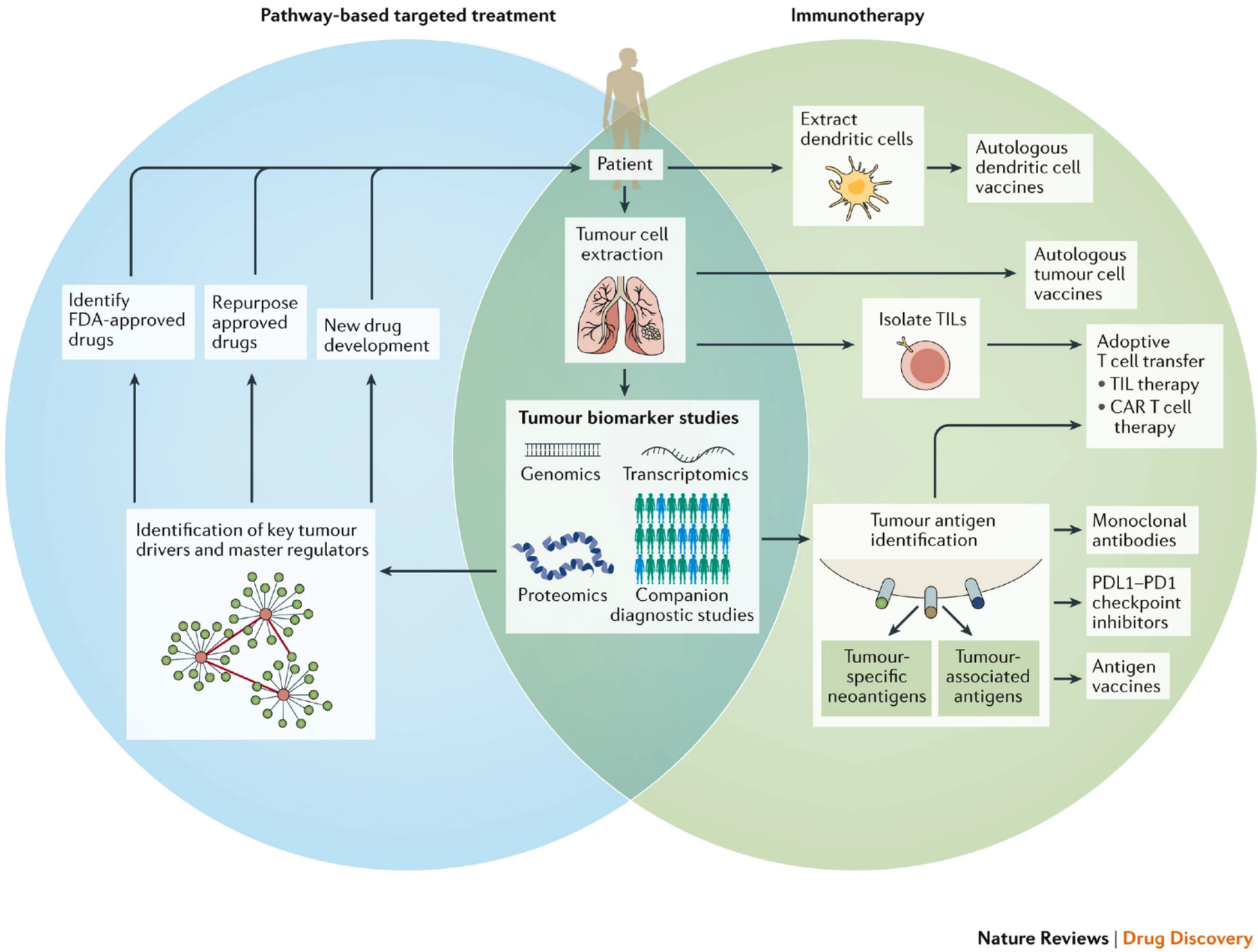
Dynamic design of trial phases



*Rossoni C, et al. Clin Trials. **2019**;16(6):635-644.*
https://www.tracercro.com/early-phase-clinical-trials/

Emerging trends and future directions

Biomarker strategy and precision medicine



Dugger SA, Platt A, Goldstein DB. Nat Rev Drug Discov. ***2018****;17(3):183-196.*

Emerging trends and future directions

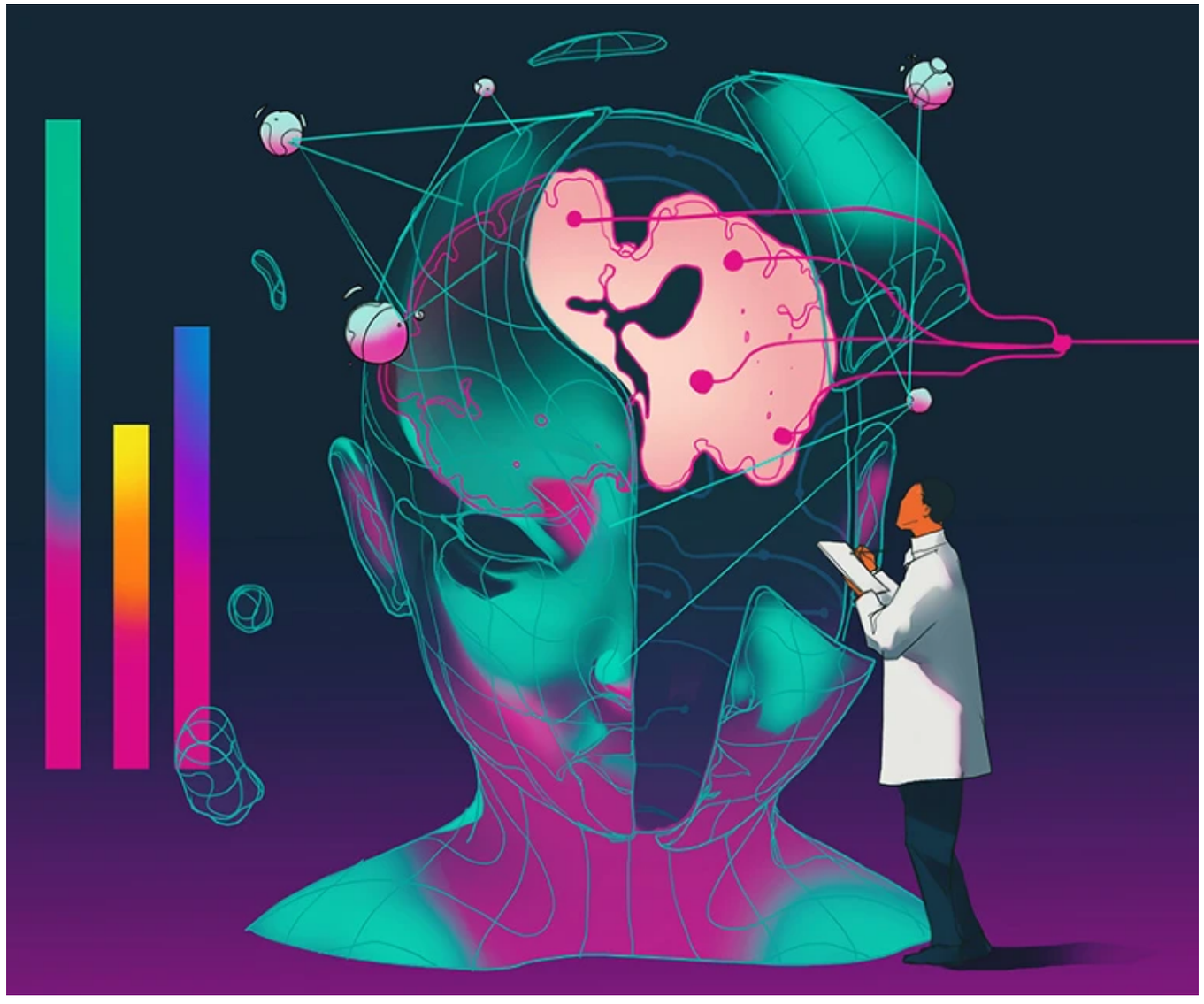
Globalization or de-globalization

Outside US contract research organization (CRO)

https://www.grandviewresearch.com/industry-analysis/global-clinical-trials-market

Emerging trends and future directions

The role of artificial intelligence



From study design to patient recruitment…

https://www.nature.com/articles/d41586-024-00753-x

Thanks

Hope you find it helpful