Memorial Sloan Kettering Cancer Center

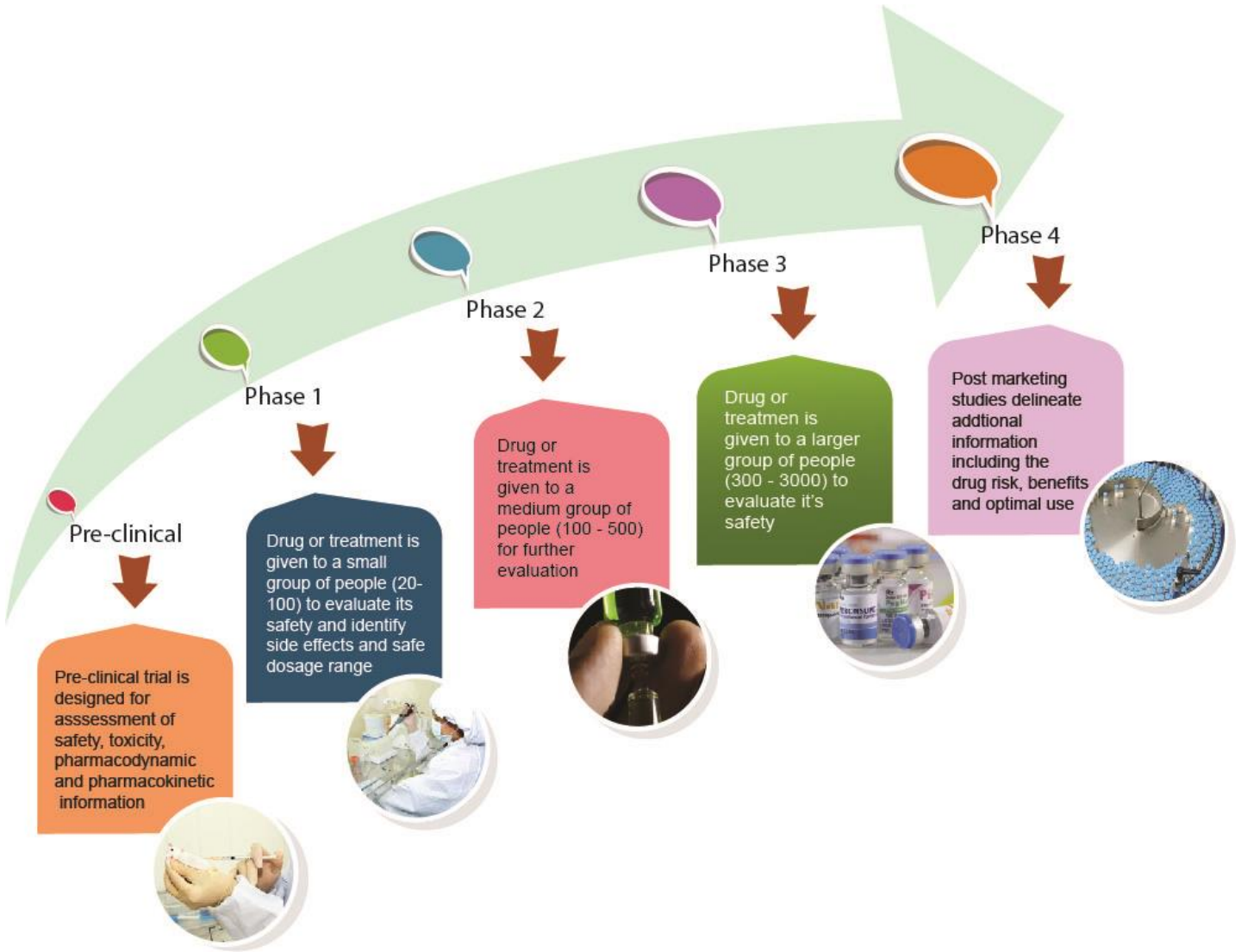
Early Phase Clinical Trials

changing the way we treat cancer

Alexander Drilon MD
Chief, Early Drug Development Service
Memorial Sloan Kettering Cancer Center

What are the phases of clinical trials?

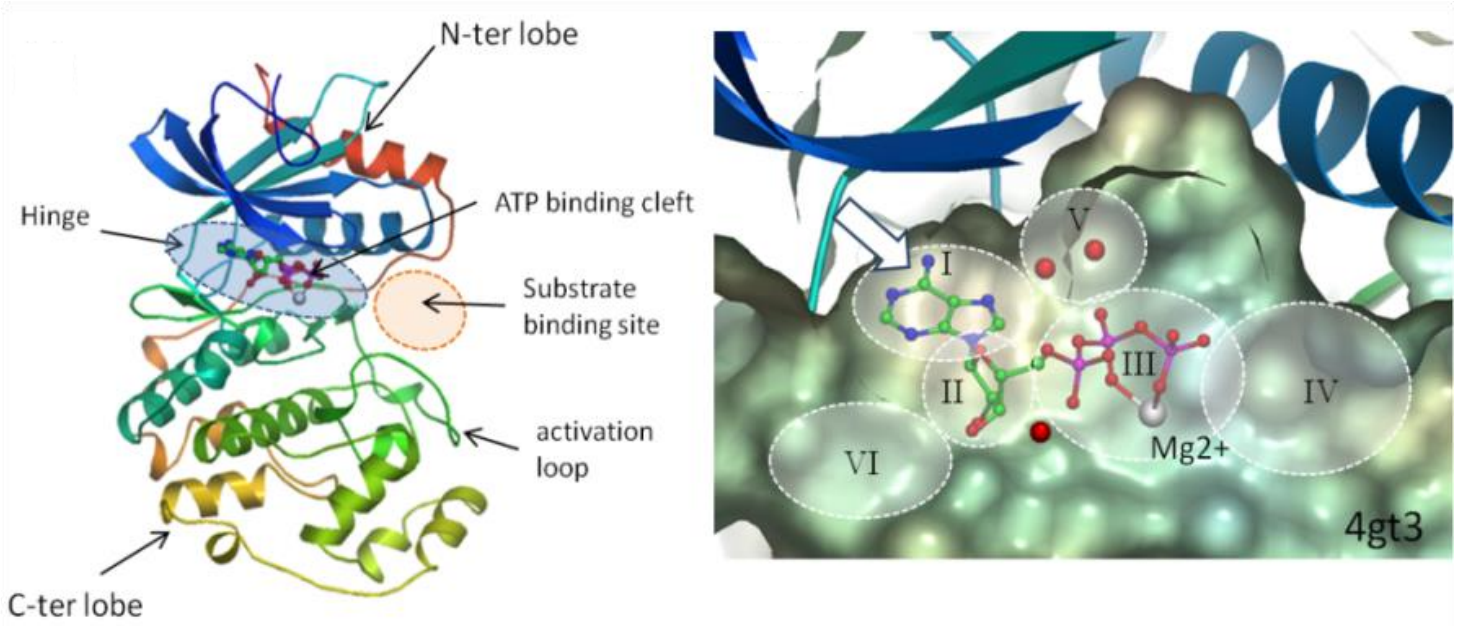
Clinical Trial Phases



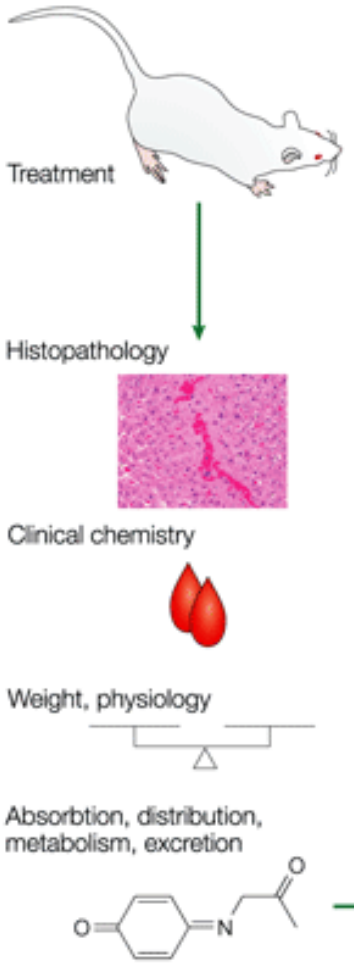
How is a new drug tested before it goes into clinical trials?

Sources of New Drugs

- **Rational drug development**
  - design small molecules based on structural data
    - computer-aided: virtual screening of a large collection of compounds, evaluation of docking to active site



Preclinical Testing



Determine

- Drug properties and distribution
- Side-effects
  - 2-3 species
- Effectiveness in cancer models
- Starting dose in patients

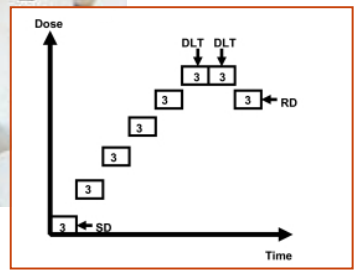
Memorial Sloan Kettering
Cancer Center

What happens in a phase I clinical trial?

Phase I Trial

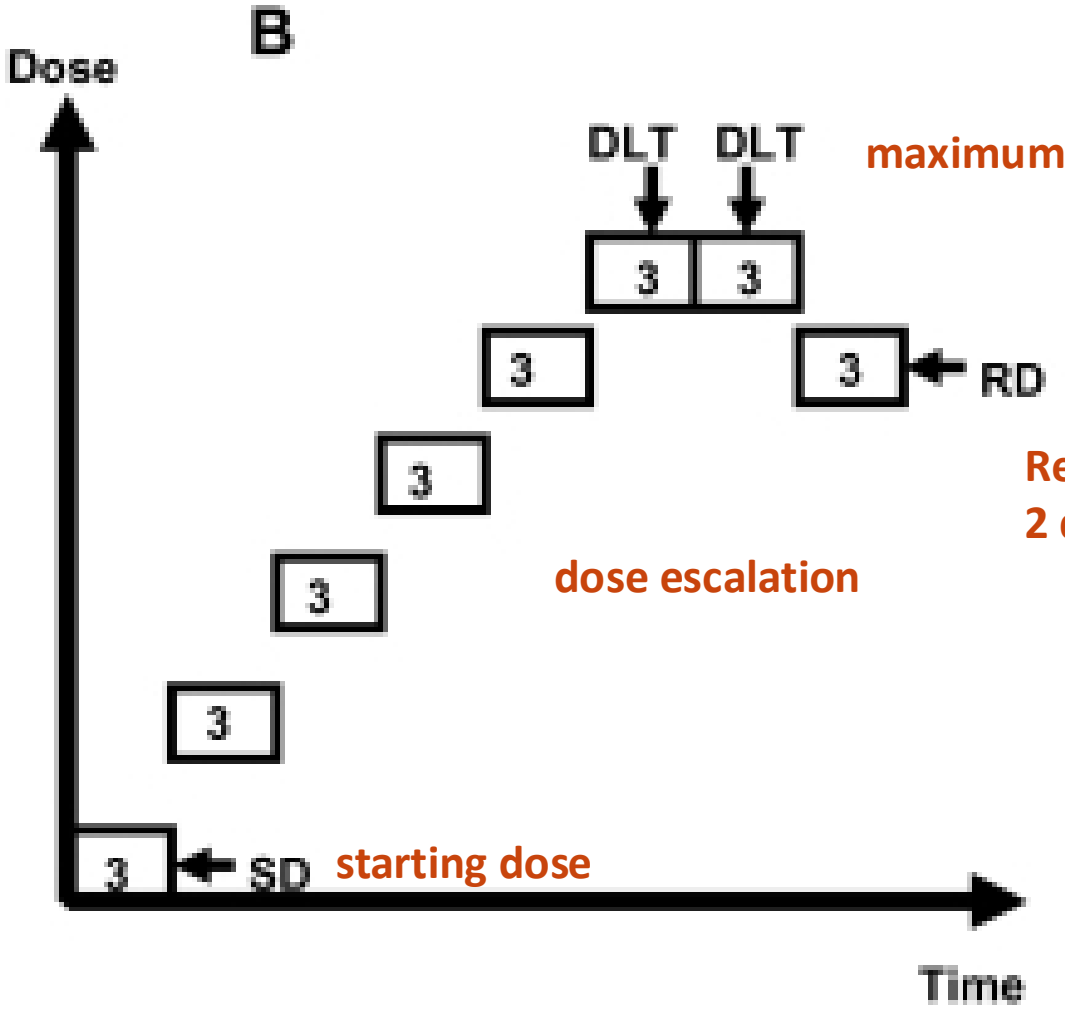
- **Objectives**
  - Identify dose
  - Identify adverse events (side-effects)
  - Characterize drug
    - Pharmacokinetics
    - Pharmacodynamics
  - Identify preliminary activity







Common phase I trial design: finding the right dose



maximum tolerated dose (MTD)

Recommended phase 2 dose (RP2D)

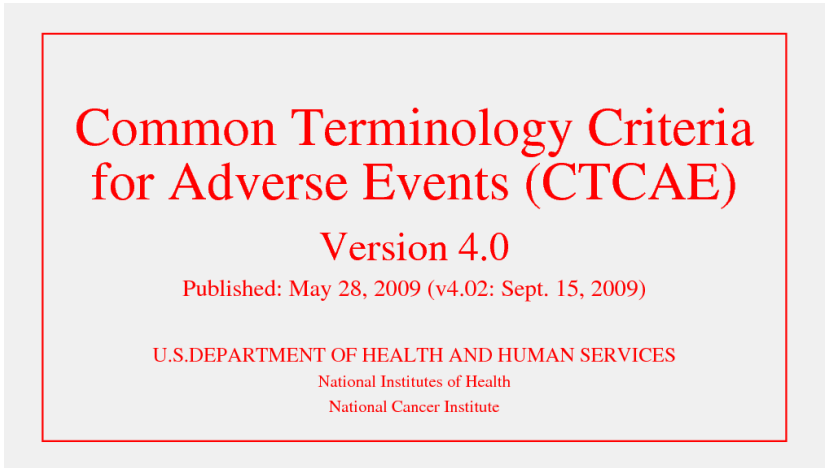
dose escalation

starting dose

Accurately capturing side effects

ADVERSE EVENT	GRADE 1	2	3	4	5
Diarrhea	Increase of four stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of four to six stools per day over baseline; IV fluids indicated less than 24 hours; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Increase of seven or more stools per day over baseline; incontinence; IV fluids 24 hours or more; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living	Life-threatening consequences (e.g., hemodynamic collapse)	Death

Note. From "Common Terminology Criteria for Adverse Events [v3.0]," by National Cancer Institute, 2006. Retrieved November 13, 2007, from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.

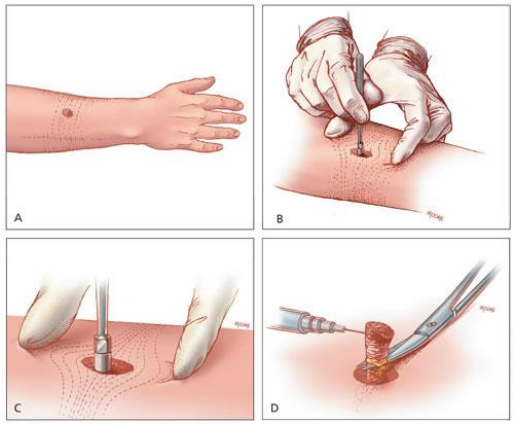


Assessments on phase I trials

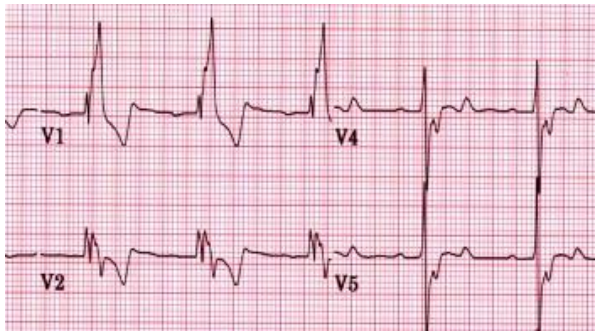
Blood-based biomarkers



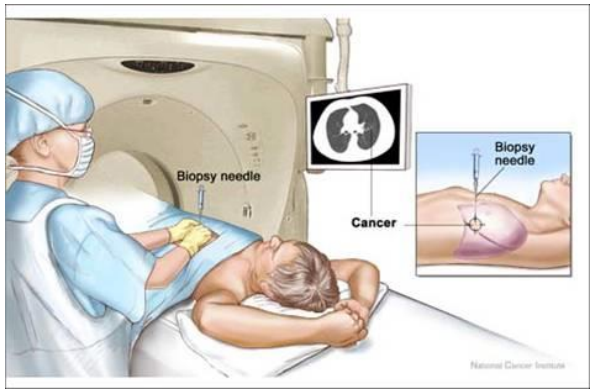
Skin biopsies



EKGs



Tumor biopsies



How are phase I trials changing?

The number of cancer targets has increased.

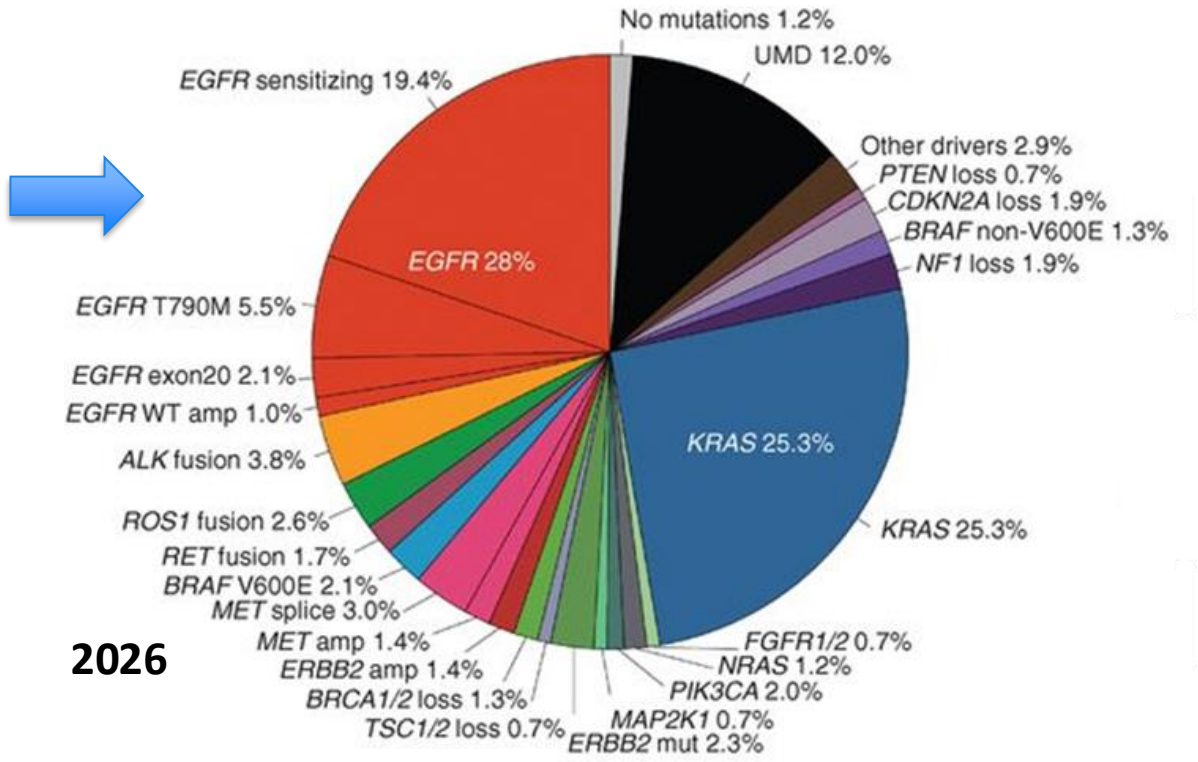
Many lung cancer targets have been found over the last two and a half decades.

First 860 lung adenocarcinomas profiled with MSK-IMPACT

- All with recurrent/metastatic disease



1999



2026

Jordan et al, Cancer Discov 2017

Targeted therapies have been developed for many target proteins that drive cancer.

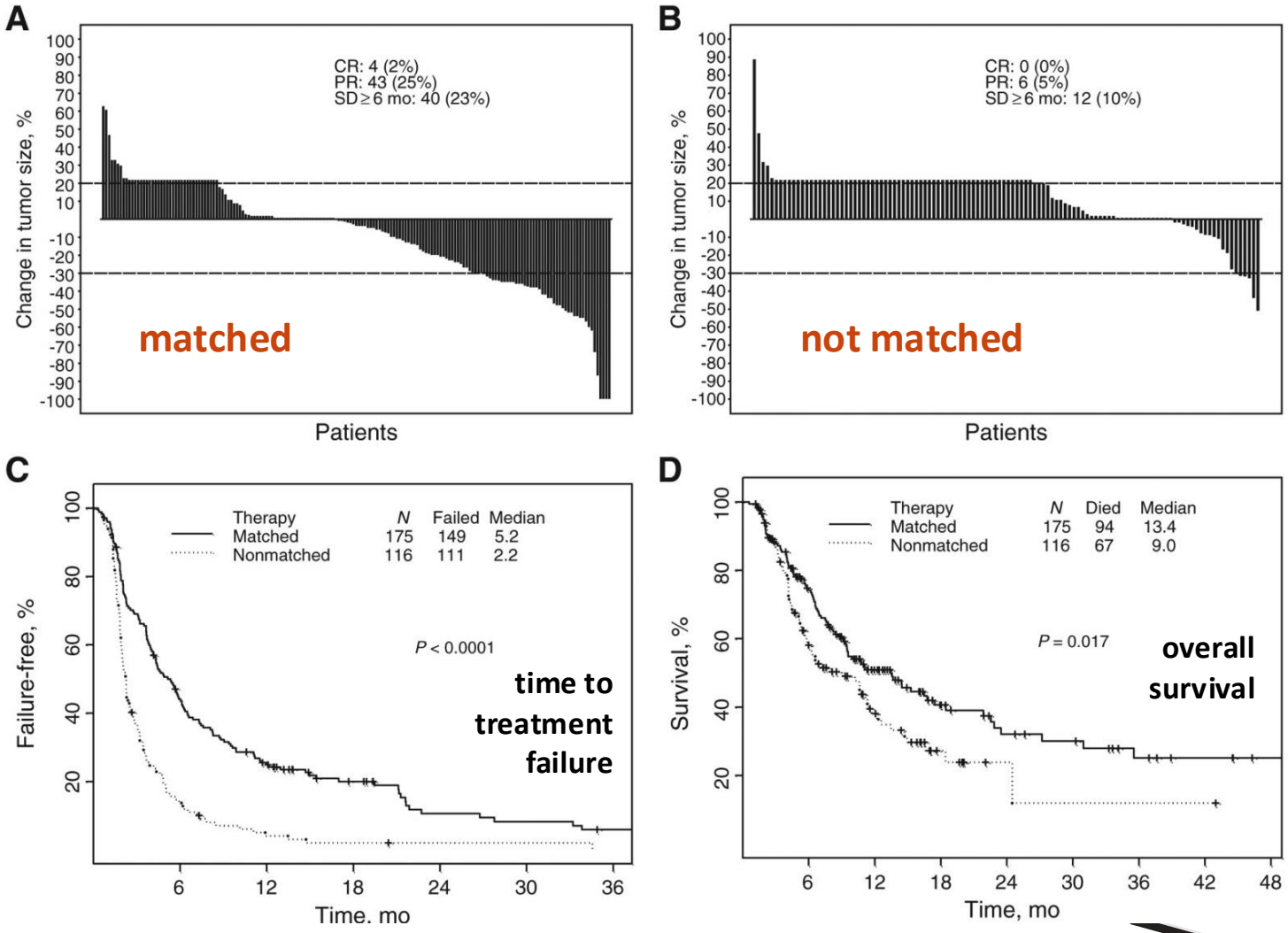


Memorial Sloan Kettering Cancer Center

How are phase I trials changing?

These trials can give patients access to exciting new therapies matched to their cancer's target.

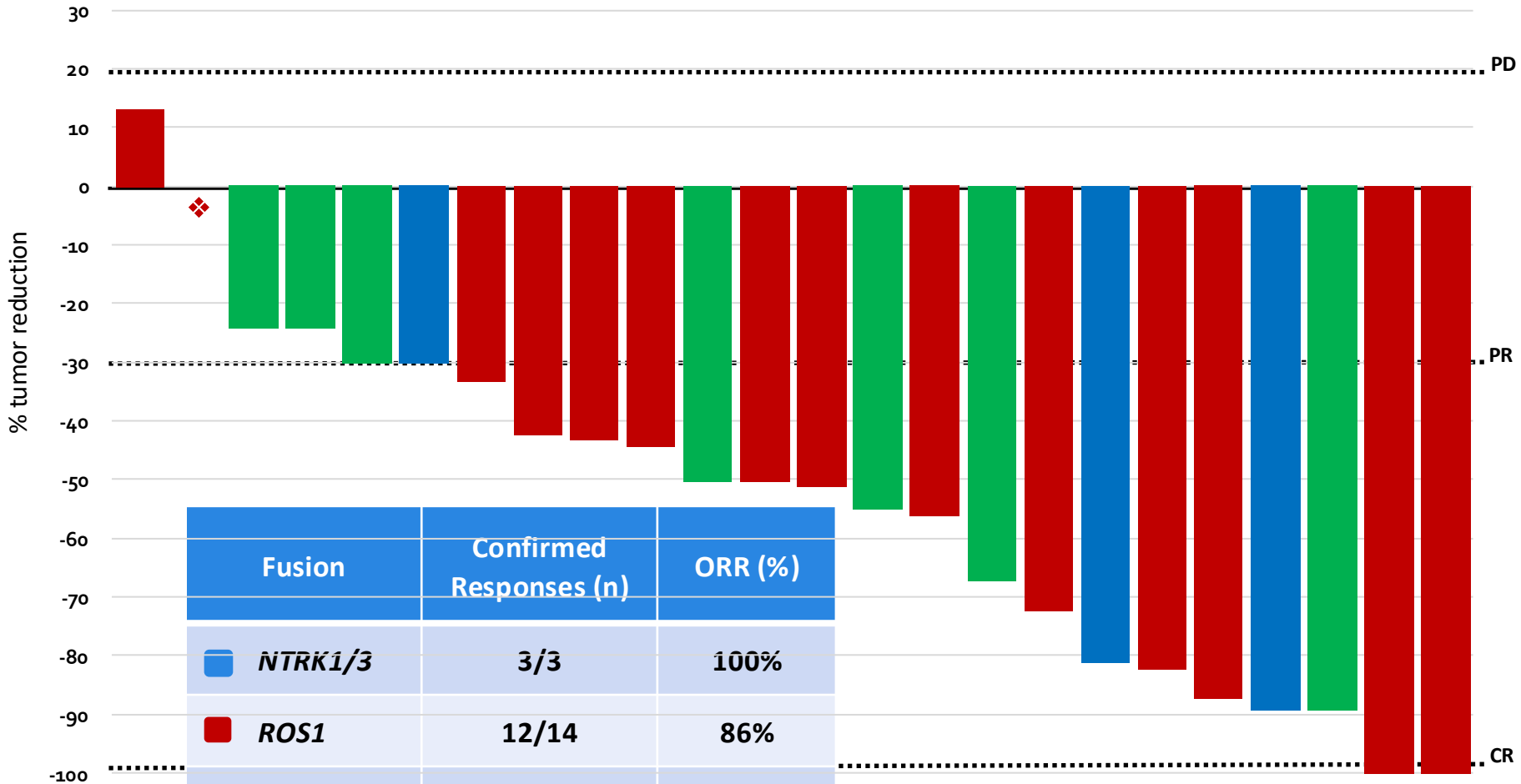
Improved patient biomarker matching improves outcomes



Memorial Sloan Kettering Cancer Center

Phase I trials have very quickly established the activity of new treatments

Best Response to Entrectinib in TKI Treatment-Naïve *NTRK*-, *ROS1*-, and *ALK*-rearranged Tumors (n=24)

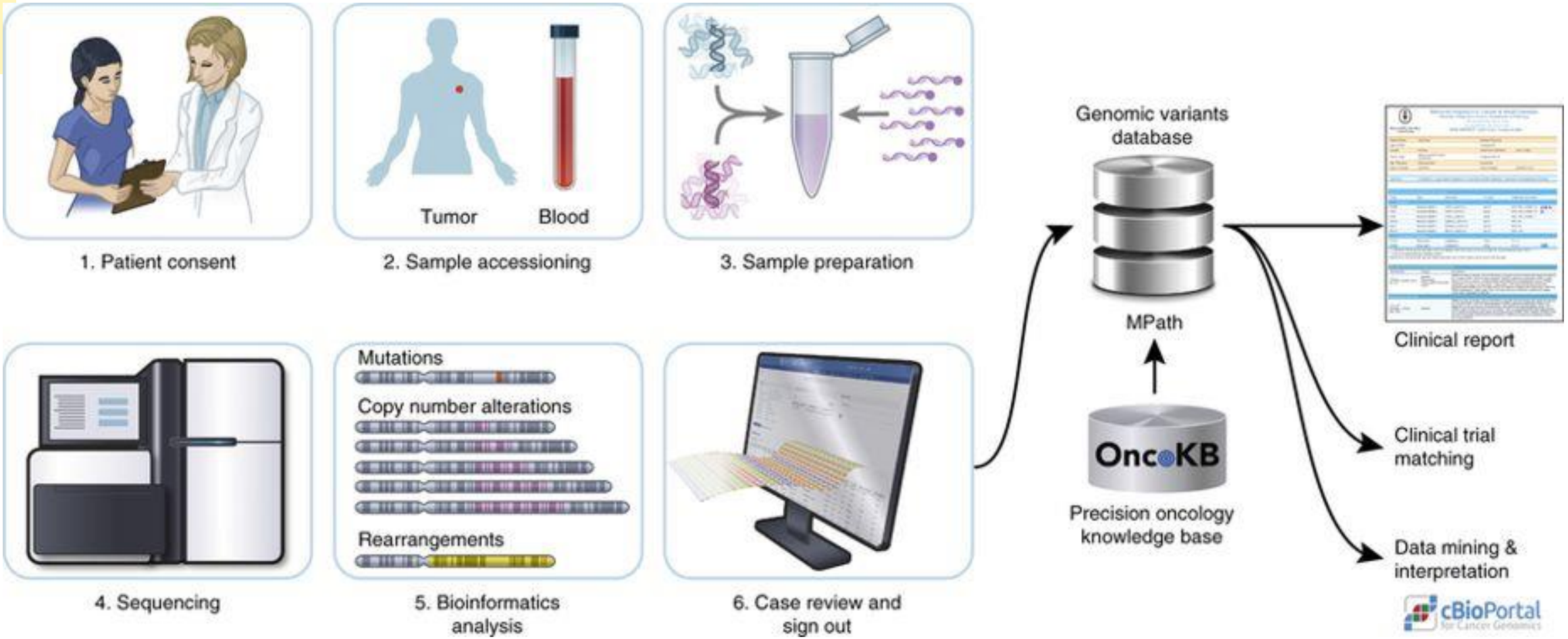


Fusion	Confirmed Responses (n)	ORR (%)
NTRK1/3	3/3	100%
ROS1	12/14	86%
ALK	4/7	57%

How are phase I trials changing?

Systems are in place to get patients to clinical trials faster.

Systems are in place at MSK to quickly match cancers to new and exciting therapies on phase I clinical trials.



Memorial Sloan Kettering Cancer Center

Both tumor and liquid biopsies are performed to identify targets for new therapies.



MSK-IMPACT
Tumor DNA NGS



MSK-ACCESS
Plasma cfDNA NGS



Memorial Sloan Kettering Cancer Center

Increased target identification increases clinical trial participation.

Clinical Trial Matching System

cBioPortal FOR CANCER GENOMICS

OncoTree

Kundra et al. JCO Clin Cancer Inform 2024

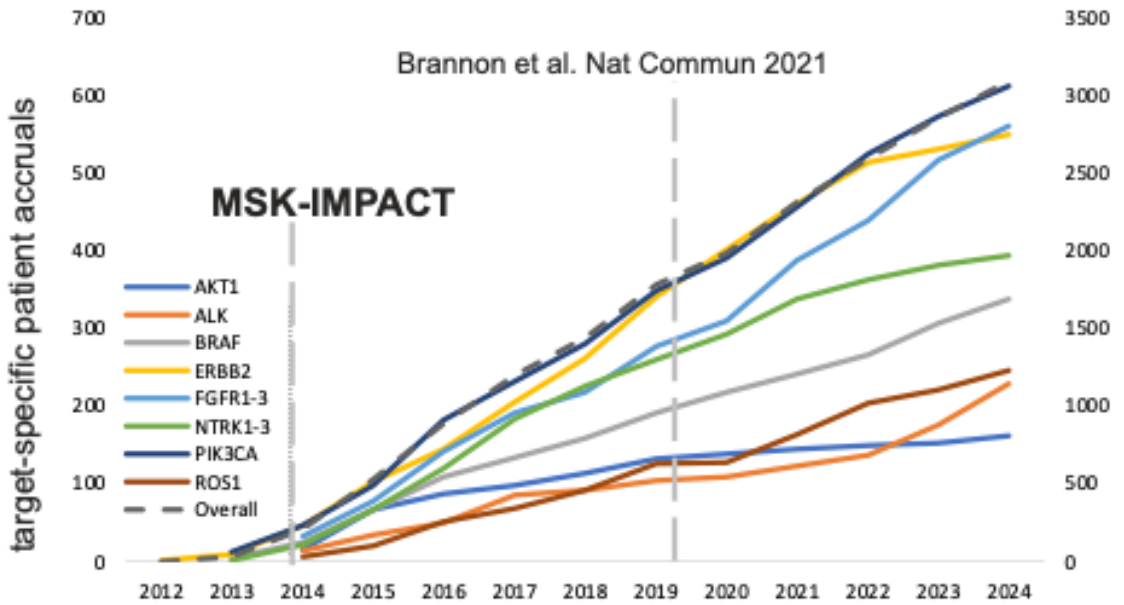
OncoKB

Suehnholz et al. Cancer Discov 2024

darwin Memorial Sloan Kettering Cancer Center

MSK-ACCESS

- NYS Approval May 2019
- 15,129 samples run
- 10,370 patients



Tumor genome matched patient accruals to MSK phase I/II unit clinical trials

Memorial Sloan Kettering Cancer Center

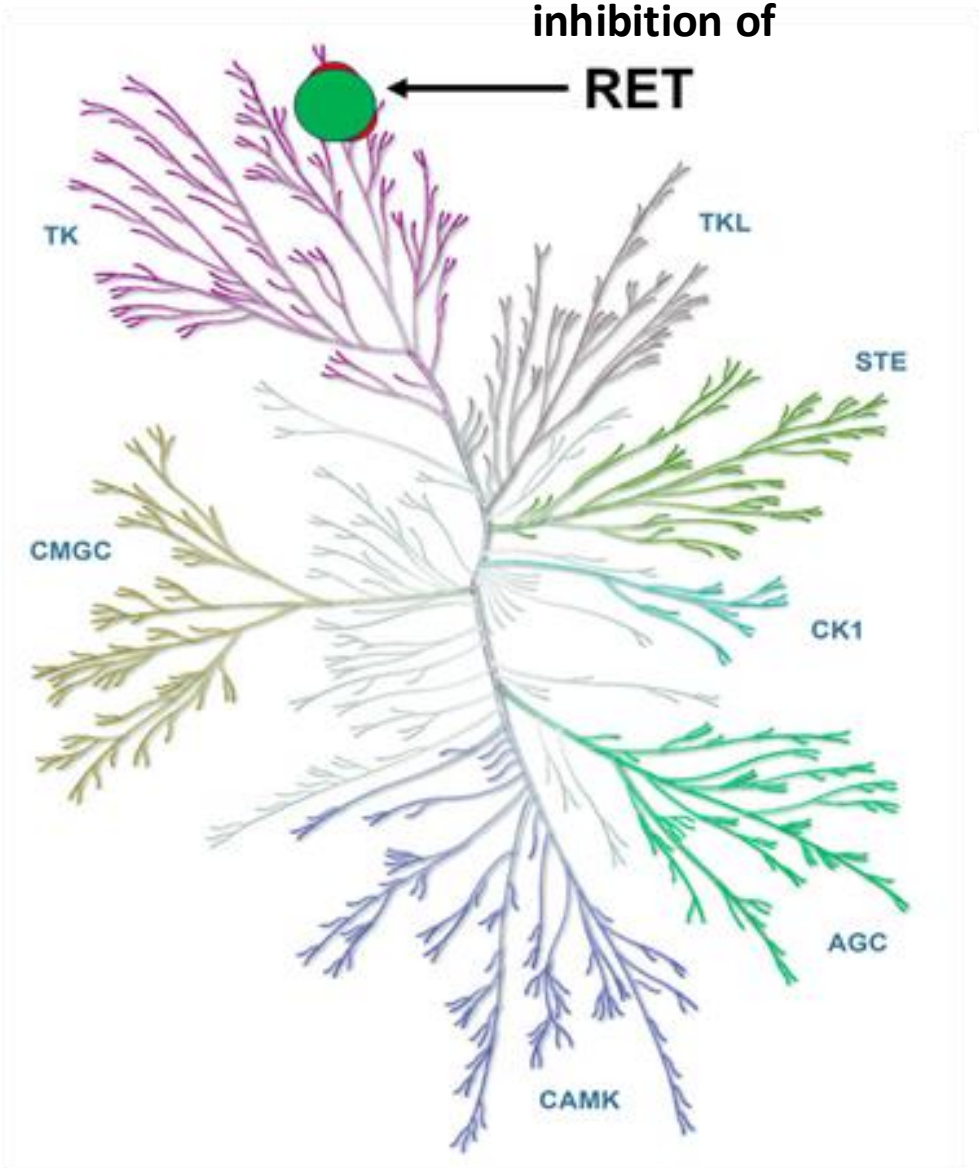
How are phase I trials changing?

Drug designs are improving.

CASE STUDY:

Selpercatinib for RET-dependent cancers

- **Drug Selection and Trial**
  - Research team recognized novel approach to targeting RET gene
  - MSK-IMPACT identified a significant patient pool



CASE STUDY:

Selpercatinib for RET-dependent cancers

Result

vs. standard of care

2.5x
RESPONSE RATE

60%
REDUCTION IN TOXICITY

May 2020

FDA
APPROVAL FOR LUNG AND THYROID

What are phase II trials?



Memorial Sloan Kettering
Cancer Center

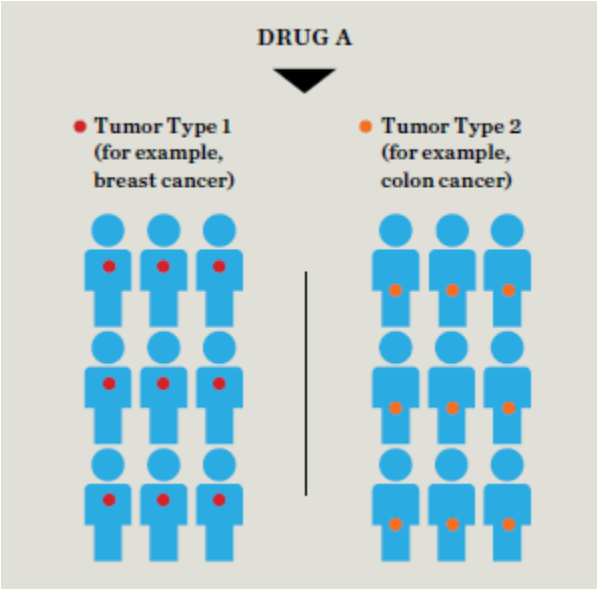
Phase II Trial

- **Dose is already known**
- **Objectives**
  - Identify activity of a new treatment
  - Further characterize safety profile

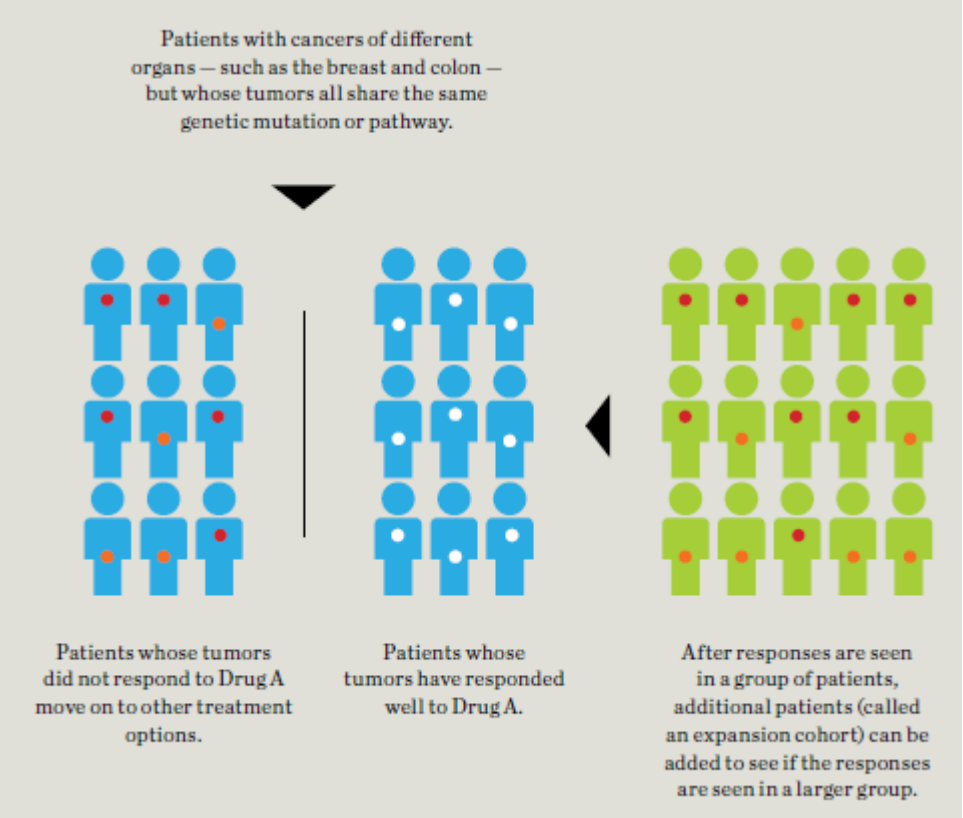




Basket Trials



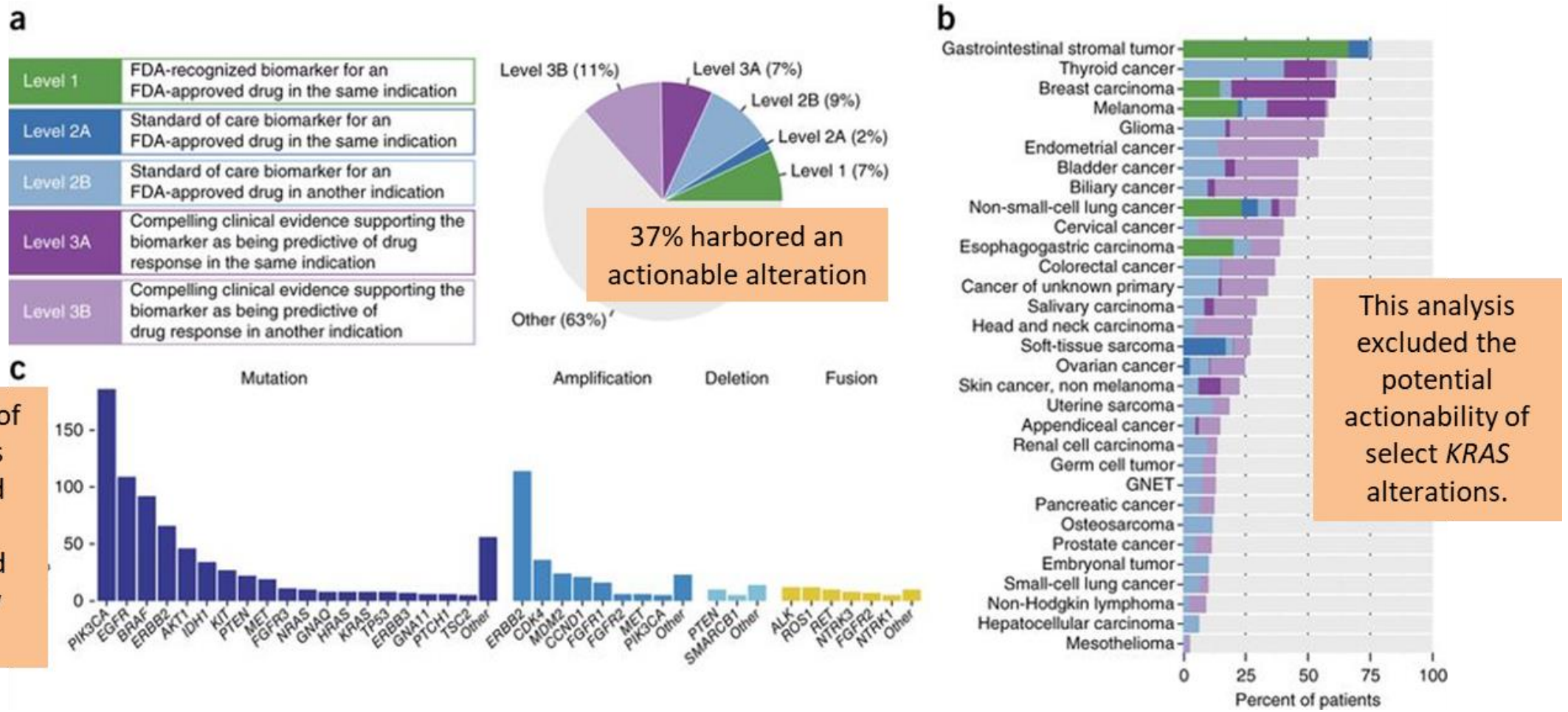
Traditional Approach
-histology-specific



Basket Trial Approach
-molecularly enriched
-non-histology-specific

Memorial Sloan Kettering Cancer Center

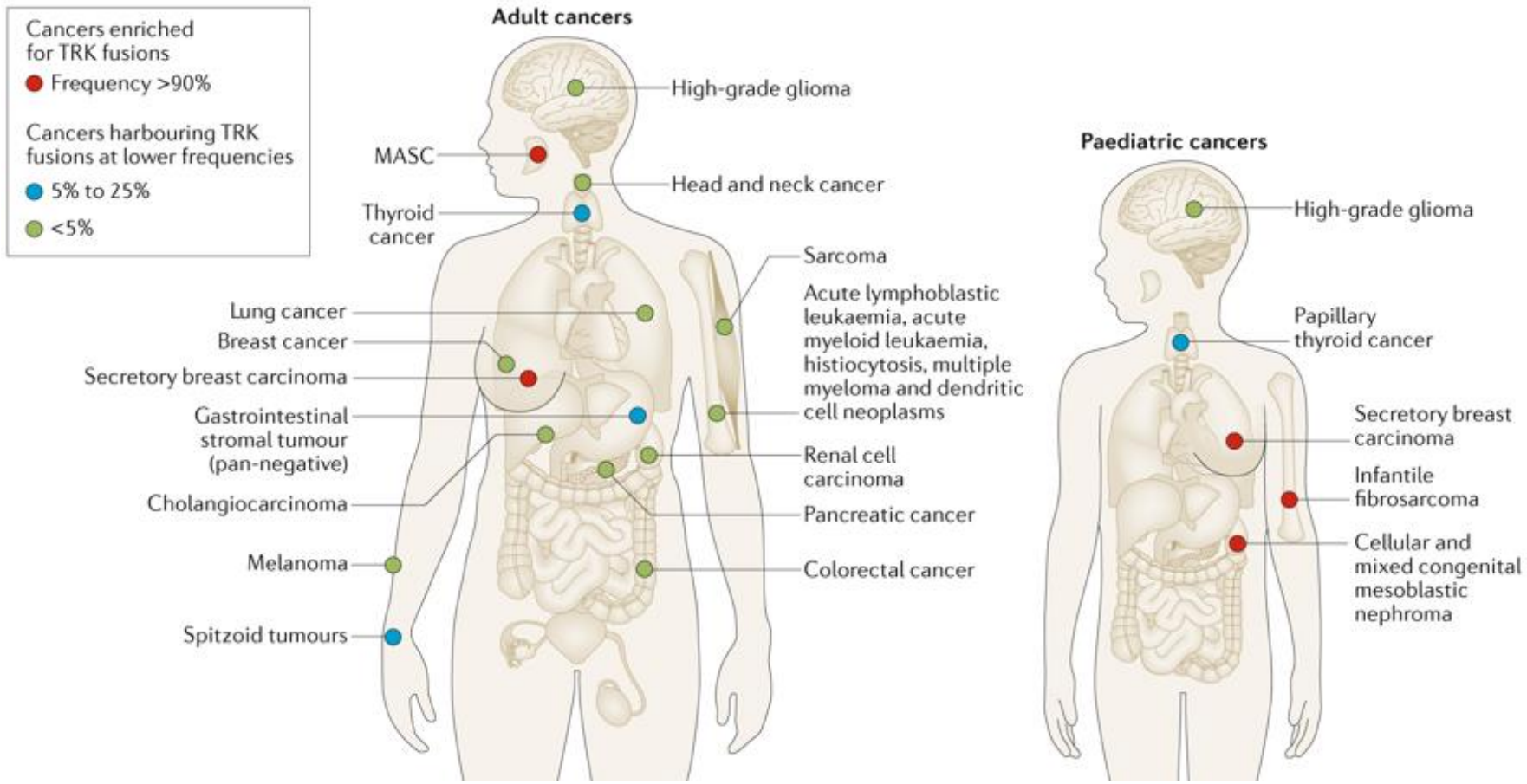
Target identification has also increased in other cancers.



Zehir et al, Nature Med 2017

Memorial Sloan Kettering Cancer Center

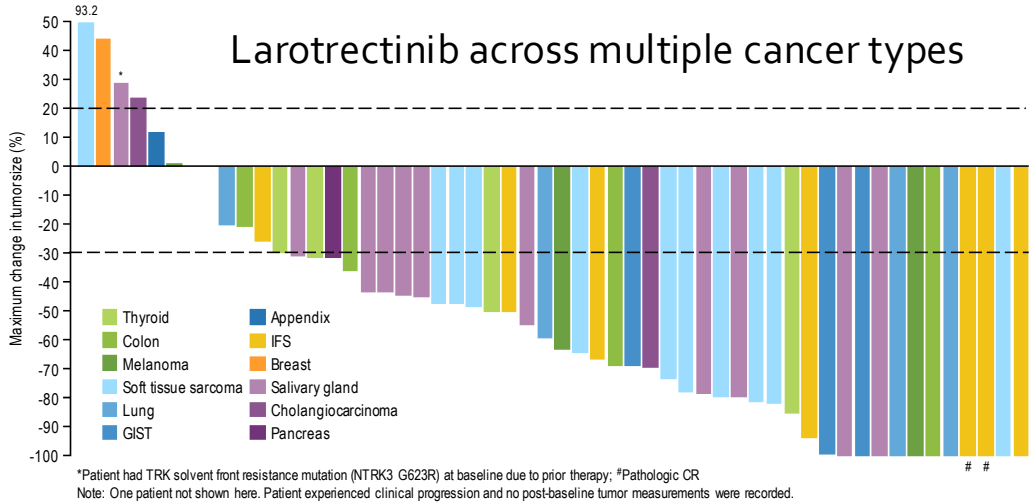
NTRK fusions are found across diverse adult and pediatric cancers



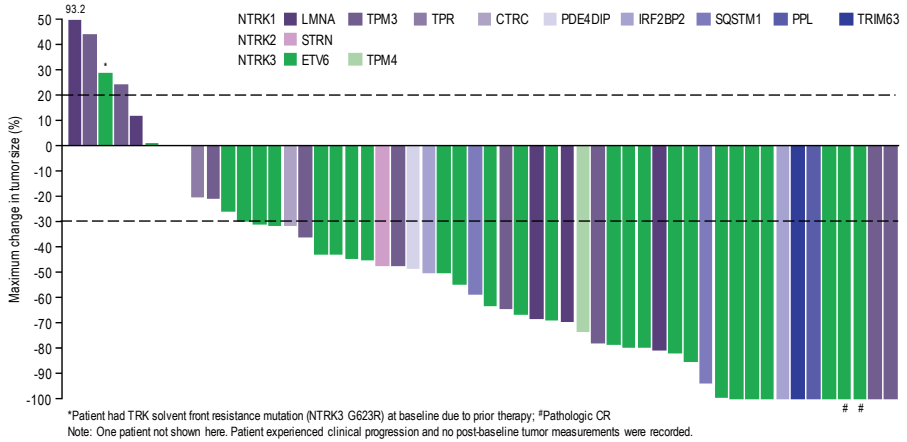
Cocco et al, Nat Rev Clin Oncol 2018

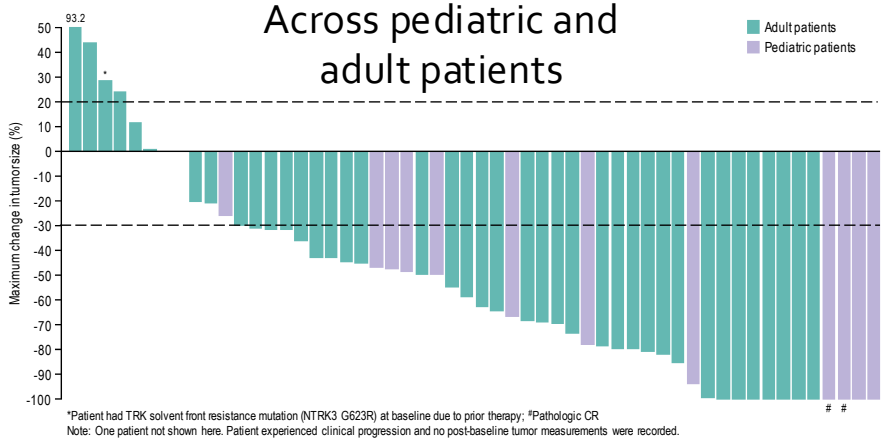
Memorial Sloan Kettering Cancer Center

First generation TRK inhibition is active in *NTRK* fusion-positive adult and pediatric cancers



Across fusion types





Drilon et al, NEJM 2017

Memorial Sloan Kettering Cancer Center

TRK inhibitors are approved in a tumor-agnostic fashion for adult and pediatric cancers with *NTRK* fusions

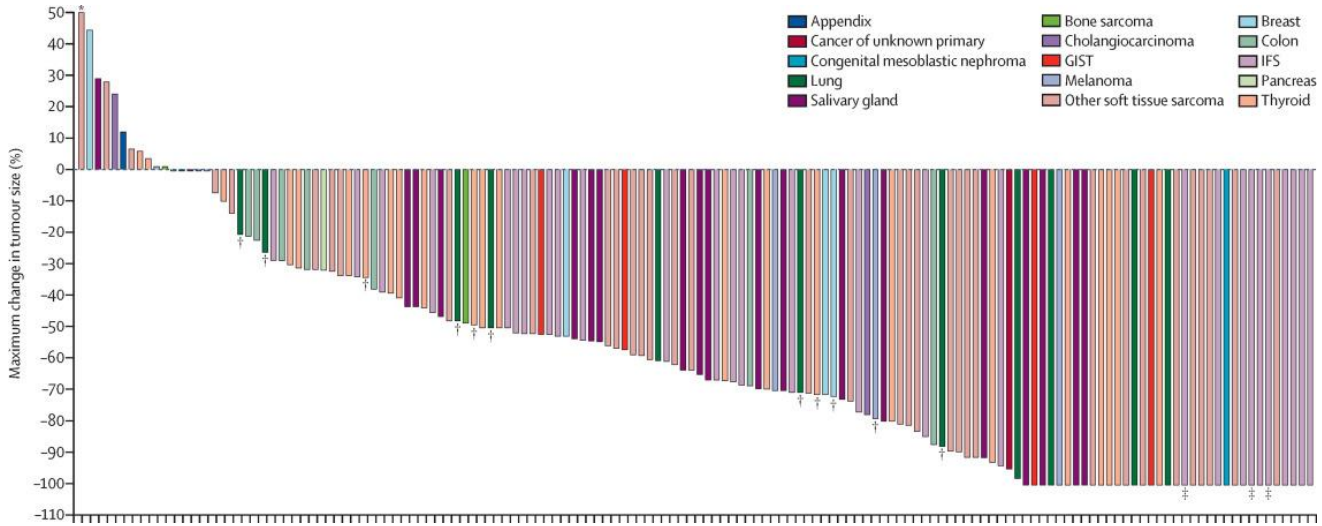
Larotrectinib

ORR 79%

(95% CI 72-85%, n=159)

Median DoR 35.2 months

Median PFS 28.3 months



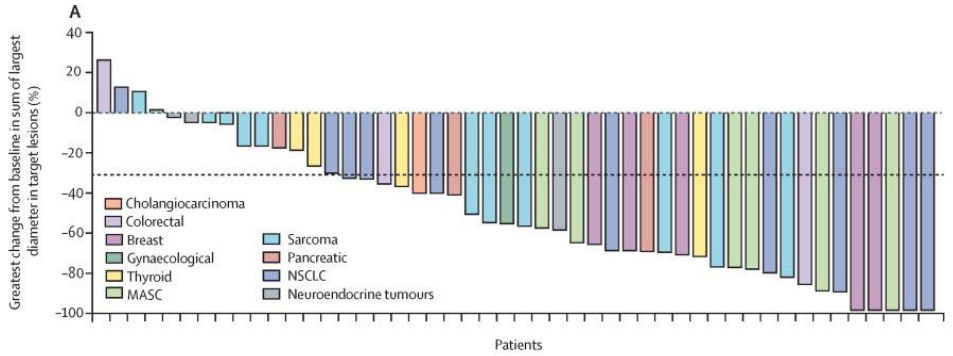
Entrectinib*

ORR 57%

(95% CI 43-71%, n=54)

Median DoR 10 months

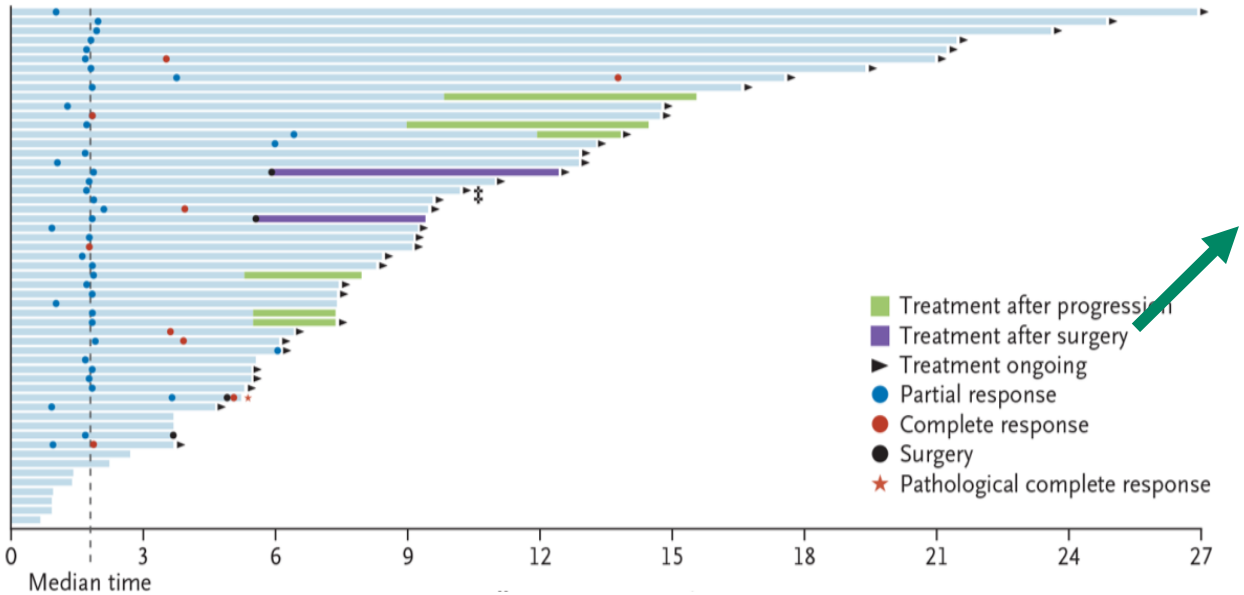
Median PFS 11 months

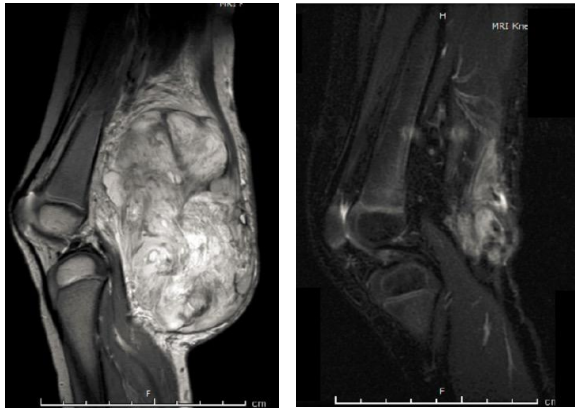


Hong et al, Lancet Oncol 2020; Doebele et al, Lancet Oncol 2020

Memorial Sloan Kettering Cancer Center

Larotrectinib trial uncovers the potential for neoadjuvant targeted therapy





Baseline Cycle 3

2-year-old requiring leg amputation for TRK fusion-positive sarcoma

- dramatic response to larotrectinib
- underwent limb-sparing surgery with no functional deficits
- pathologic complete response

Drilon et al, N Engl J Med 2017

Memorial Sloan Kettering Cancer Center

Larotrectinib for TRK-dependent cancers

Result

November 2018

FDA APPROVAL FOR NTRK FUSION+ CANCERS

landmark approval

first tumor-agnostic approval of targeted therapy in a molecular subset of cancers including adult and pediatric patients

The Early Drug Development Service at Memorial Sloan Kettering Cancer Center

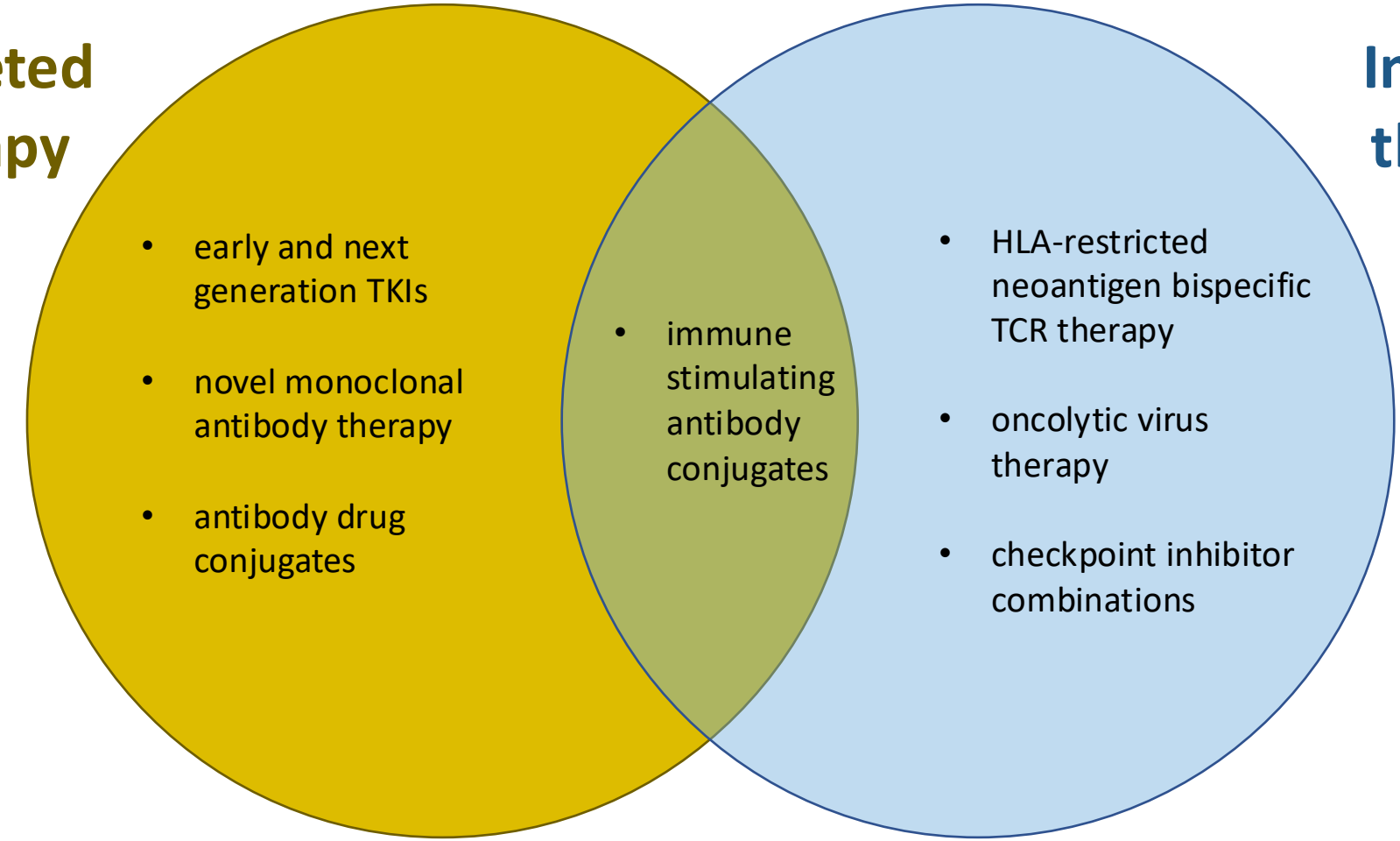


Memorial Sloan Kettering
Cancer Center

The Early Drug Development Service at MSKCC

Our goal is to develop the newest precision medicine treatments for patients with cancer.

Early Drug Development Pipeline



Our track record

10

drug approval indications

across 40 countries

in the last three years

larotrectinib for TRK+ cancers

entrectinib for TRK+ cancers

entrectinib for ROS1+ lung

tazemetostat for epithelioid sarcoma

selpercatinib for RET+ lung

selpercatinib for RET+ thyroid

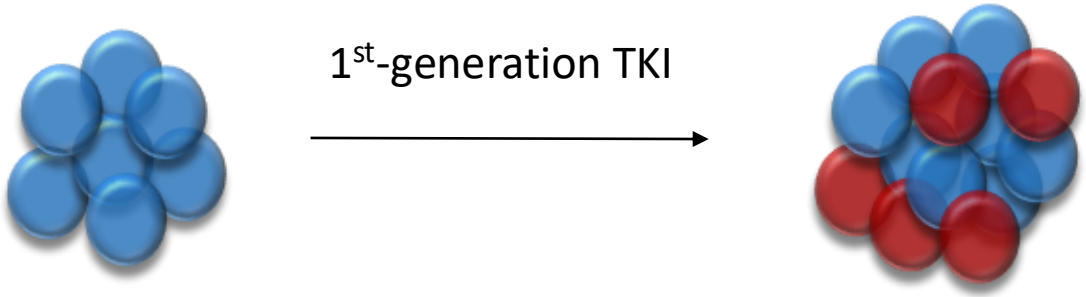
sotorasib for KRAS G12C+ lung

repotrectinib for ROS1+ lung

repotrectinib for NTRK+ cancers

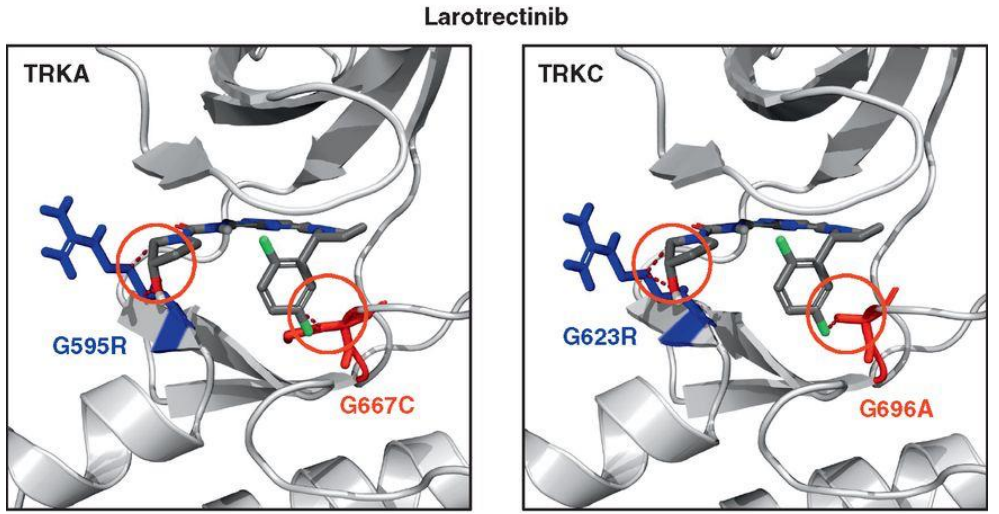
zenocutuzumab for NRG1+ lung/panc

TRK fusion-positive cancers can develop on-target resistance to TRK inhibitor therapy



NTRK fusion

NTRK fusion
NTRK mutation

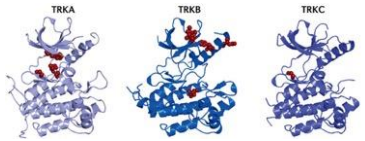


Memorial Sloan Kettering Cancer Center

Next-generation treatments can address resistance to prior therapies.

1st gen drug → 2nd gen drug

Larotrectinib
Entrectinib



Selitrectinib
Repotrectinib
Taletrectinib
SIM1803-1A
PBI-200



Memorial Sloan Kettering Cancer Center

Summary

- Phase I and II clinical trials have undergone a substantial transformation in the last two decades.
- These trials have improved patient access to exciting new therapies and helped get new treatments approved for patients with lung cancer around the world.
- New therapies with better designs are being developed, including those designed to work after prior treatments have stopped working.