Four Essential Factors
for Success in Oncology trials

2024.12.3

Sung Young Lee

Senior Vice President, Head of Clinical Strategy and Operation,

ImmuneOncia Therapeutics Inc.

Contents

1. Indication: biomarker driven, rare disease

2. Study design: master protocol, optimal dose finding

3. Immune response management

4. Data monitoring

5. Conclusion

Contents

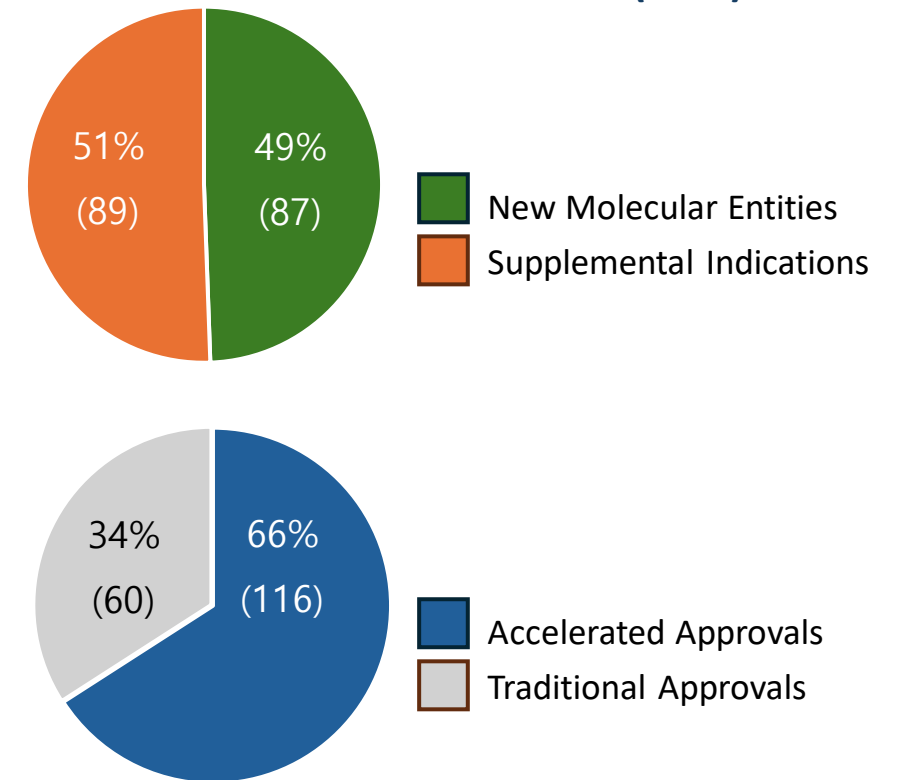# US FDA Approval of Malignant Hematology and Oncology Drugs and Biologics Based on Single-Arm Trials by Year, 2002-2021

AA (accelerated approval)
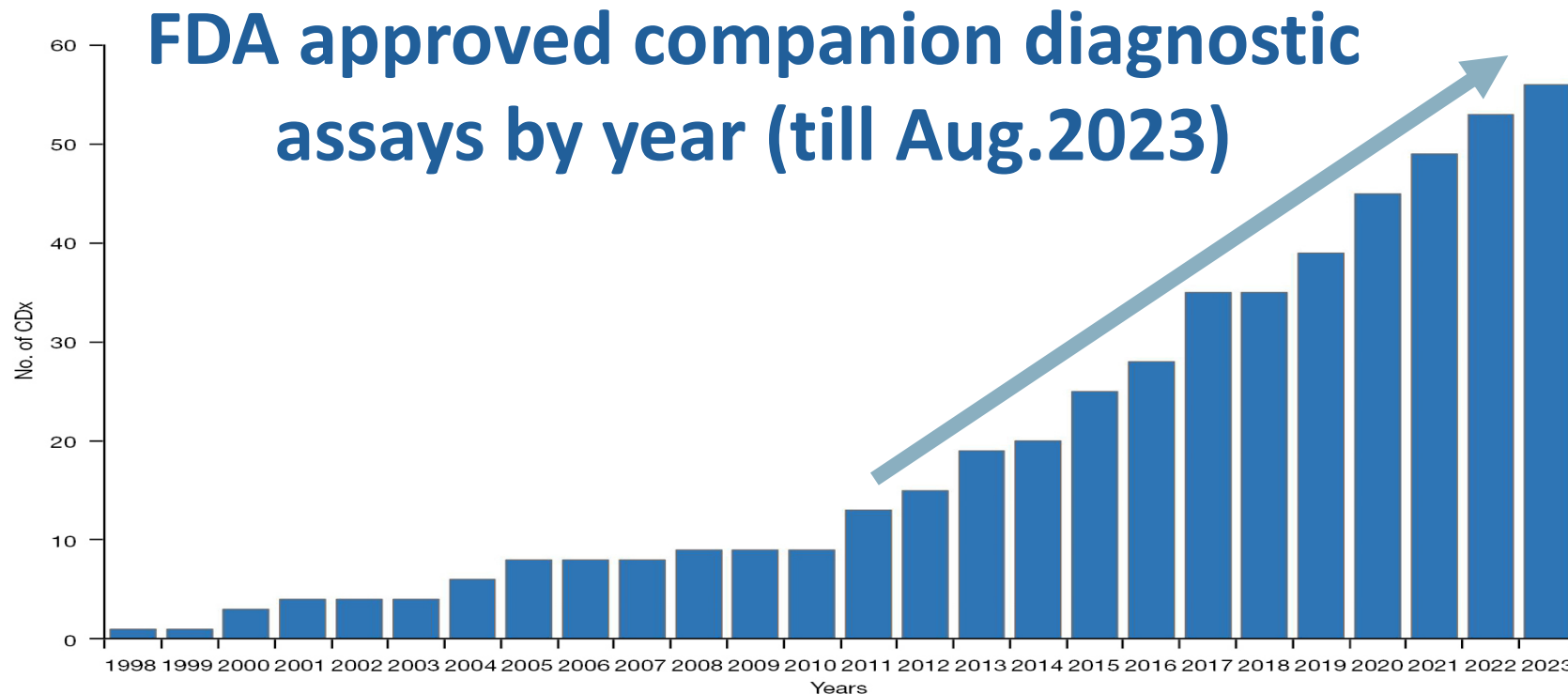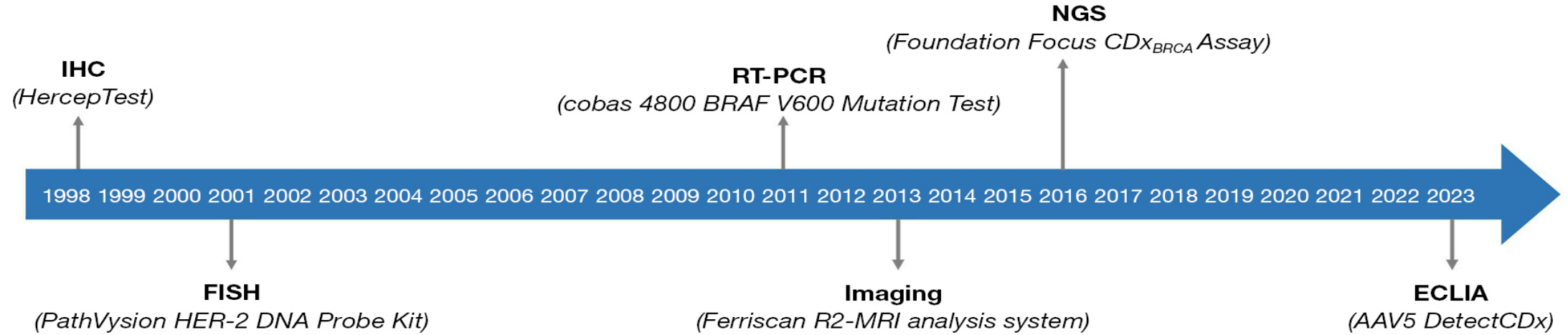NME (new molecular entity)
TA (traditional approval)

Source: Sundeep Agrawal et al (JAMA Oncology, 2022)

Different Companion Diagnostic Platforms

NGS
(Foundation Focus CDx$_{BRCA}$ Assay)

IHC
(HercepTest)

RT-PCR
(cobas 4800 BRAF V600 Mutation Test)

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023

FISH
(PathVysion HER-2 DNA Probe Kit)

Imaging
(Ferriscan R2-MRI analysis system)

ECLIA
(AAV5 DetectCDx)

FDA approved companion diagnostic assays by year (till Aug.2023)

IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; RT-PCR, real-time polymerase chain reaction; NGS, next-generation sequencing; ECLIA, electrochemiluminescence immunoassay.

Source: Jan Trøst Jørgensen (CCO, 2023)

FDA List of Cleared or Approved Companion Diagnostic Devices Biomarkers by August 2023

No.	Biomarker	Drug (generic name)
1	*ALK*/ALK	Alectinib; brigatinib; ceritinib; crizotinib; lorlatinib
2	Anti-AAV5 Antibodies	Valoctocogene roxaparvovec*
3	*BRAF*	Dabrafenib; trametinib; vemurafenib
4	*BRCA1/BRCA2*	Niraparib; olaparib; rucaparib; talazoparib
5	*BRCA1/BRCA2/ATM*	Olaparib
6	c-KIT/*KIT*	Imatinib mesylate
7	**dMMR**	**Dostarlimab; pembrolizumab**
8	*EGFR*/EGFR	Afatinib; amivantamab; cetuximab; dacomitinib; erlotinib; gefitinib; mobocertinib; osimertinib; panitumumab
9	*ESR1*	Elacestrant
10	*EZH2*	Tazemetostat
11	*FGFR2*	Infigratinib; pemigatinib
12	*FGFR3*	Erdafitinib
13	*FLT3*	Gilteritinib; midostaurin; quizartinib
14	*FOLR1*	Mirvetuximab soravtansine
15	*HER2*/HER2	Pertuzumab; trastuzumab; trastuzumab deruxtecan; trastuzumab emtansine
16	*HLA*	Tebentafusp

No.	Biomarker	Drug (generic name)
17	*IDH1*	Ivosidenib; olutasidenib
18	*IDH2*	Enasidenib
19	Ki-67	Abemaciclib
20	*KRAS*	Cetuximab; panitumumab
21	*KRAS/NRAS*	Panitumumab
22	*KRAS G12C*	Sotorasib, adagrasib
23	Liver imaging	Deferasirox*
24	*MET*	Capmatinib
25	MSI-H	Pembrolizumab
26	*NTRK1/2/3*	Entrectinib; larotrectinib
27	*PDGFRA*	Avapritinib
28	*PDGFRB*	Imatinib mesylate
29	PD-L1	Atezolizumab; cemiplimab; pembrolizumab
30	*PIK3CA*	Alpelisib
31	*POMC/PCSK1/ LEPR*	Setmelanotide acetate*
32	*RET*	Pralsetinib; selpercatinib
33	***ROS1***	**Crizotinib; entrectinib**
34	t(9;21) Ph chromosome	Nilotinib
35	**TMB-H**	**Pembrolizumab**
36	*TP53*	Venetoclax

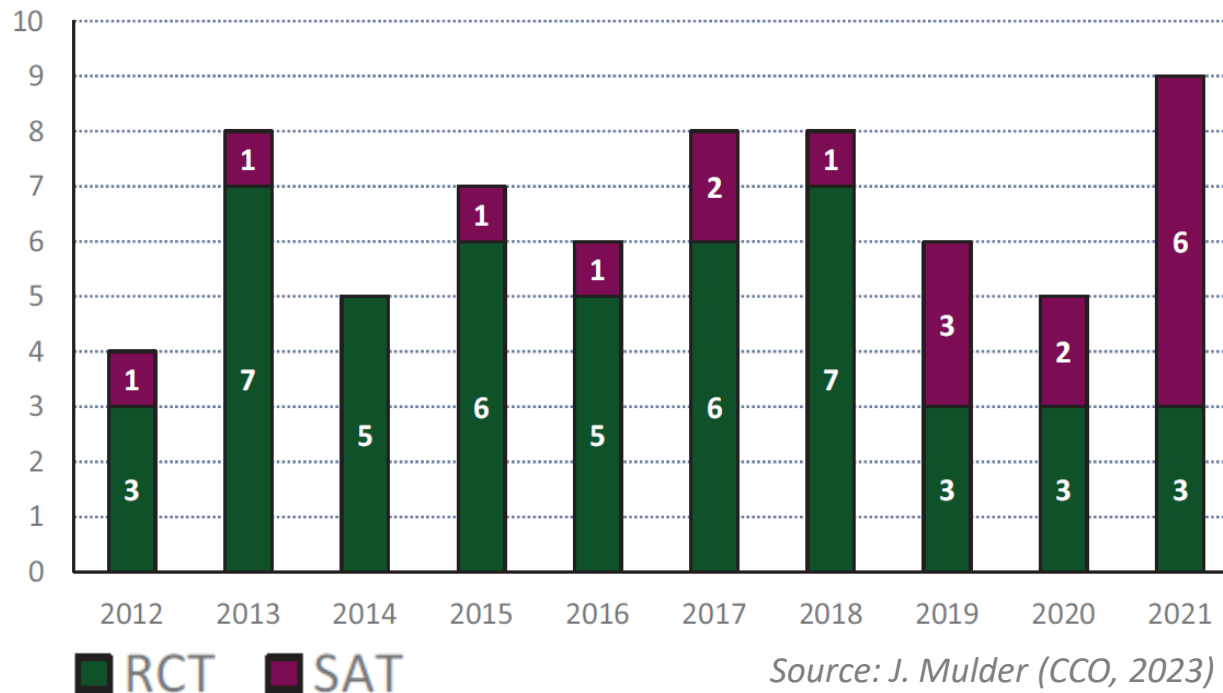*, non-oncological and hematological drugs

EMA Approval for Solid Tumor based on Single-Arm Trials by Year, 2012-2021

66 drugs approved for solid tumor
→ 18 drugs based Single-Arm Trial

⟹ 15 drugs Biomarker-based Indication

Number of Medicinal Products Approved for Solid Tumors

Source: J. Mulder (CCO, 2023)

Medicinal product	Therapeutic area	Biomarker-based indication
Alectinib	Lung cancer	Yes
Amivantamab	Lung cancer	Yes
Avapritinib	Sarcoma	Yes
Avelumab	Skin cancer	No
Cemiplimab	Skin cancer	No
Ceritinib	Lung cancer	Yes
Crizotinib	Lung cancer	Yes
Dostarlimab	Endometrial cancer	Yes
Entrectinib	Lung cancer	Yes
Larotrectinib	Cancer (NTRK+)	Yes
Lorlatinib	Lung cancer	Yes
Osimertinib	Lung cancer	Yes
Pemigatinib	Bile duct cancer	Yes
Pralsetinib	Lung cancer	Yes
Rucaparib	Ovarian cancer	Yes
Selpercatinib	Lung cancer, Thyroid cancer	Yes
Trastuzumab deruxtecan	Breast cancer	Yes
Vismodegib	Skin cancer	No

Indication for Expedited Approval Pathway

Indication for Expedited Approval

- **FDA / EMA**
  - ✓ Serious or Life-Threatening Conditions
  - ✓ Unmet Medical Needs
  - ✓ Improved Therapeutic Benefit
  - ✓ Orphan Diseases (Rare Diseases)

- **MFDS**
  - ✓ Serious or Life-Threatening Conditions
  - ✓ Unmet Medical Needs
  - ✓ Improved Therapeutic Benefit
  - ✓ Orphan Diseases (Rare Diseases)
  - ✓ Pandemic Infectious Disease
  - ✓ Companion Diagnostics with Expedited Drug Approval

What are **Rare Diseases**?

- **FDA Orphan Drug Designation** program grants orphan designation for drugs intended for diseases or conditions that affect fewer than **200,000 people in the US.** (US population 312.7 million →0.064%)

- **Orphan Designation in EMEA**: a medicine must be intended for the treatment, prevention, or diagnosis of a life-threatening or chronically debilitating disease that is prevalent in **less than 5 in 10,000 people in the EU** (<0.05%)

- **MFDS Rare Disease Management Act** as 'diseases with **a prevalence of 20,000 or fewer individuals**, or diseases for which the prevalence cannot be determined due to difficulty in diagnosis and are classified according to the procedures and standards specified by the Ministry of Health and Welfare.

Accelerated Approval of Oncology Drugs, Single Arm Trial

Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2023
Clinical/Medical

Draft Guidance, March 2023

- ✓ **First recommendation: RCT**
- ✓ **Alternative recommendation: Single-arm trial**
  - **Endpoint:** surrogate endpoint (e.g. ORR)
  - **Comparison:** historical data prespecified
  - **Sample size:**
    - adequate precision around the point estimate,
    - provide robust estimation of the duration of response, and
    - sufficiently describe the safety profile
  - **Statistical consideration**
    - Analysis in safety population
    - Pre-specified plan for sample size increase
    - Central independent review for efficacy
    - Disease control rate and clinical benefit rate are not acceptable.
  - **Postmarking confirmatory trial may be needed.**
    - Separate RCT to evaluate PFS or OS

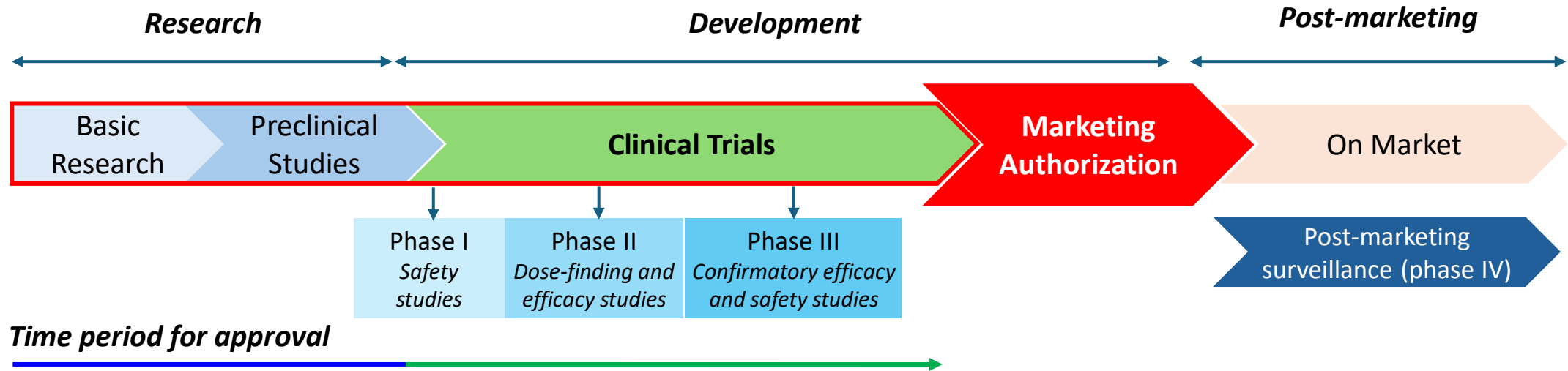# Benefits and Limitations of Single-Arm and Randomized Trial Designs

	Single Arm Trials	Randomized Trials
Benefits	- Shorter completion time - Smaller sample size - Efficacy signals can be detected early - Objective, **verifiable end point (RR) with supportive duration of response**	- Mitigates bias **Can evaluate time-to-event end points (eg, PFS, OS)** - Robust comparative safety evaluation
Limitations	- RR and DOR infeasible in tumor types with diffuse or poorly circumscribed tumors (eg, bone-only metastases, peritoneal carcinomatosis) **Comparison with historical control can be problematic** - Attribution of adverse events is limited - Cannot distinguish contribution of effect if multiple drugs given - May not allow for optimal dose selection	- Longer time to trial completion - Larger sample size **Difficult to accrue necessary sample size for rare tumors** - Potential loss of equipoise when early activity noted in drug development - End points, such as OS and PFS, may be confounded by subsequent therapies and censoring methods, respectively

DOR (duration of response), OS (overall survival), PFS (progression-free survival), RR (response rate)
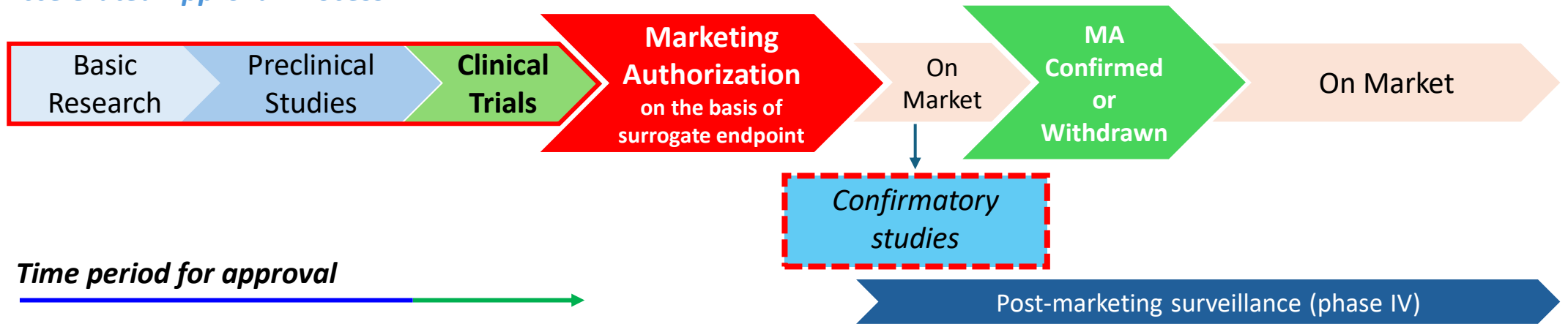
Source: Sundeep Agrawal et al. (JAMA Oncology, 2022)

FDA Accelerated Approval Process

Regular/Traditional Drugs Development Process

Research | **Development** | **Post-marketing**

Basic Research → Preclinical Studies → **Clinical Trials** → **Marketing Authorization** → On Market

Phase I *Safety studies* | Phase II *Dose-finding and efficacy studies* | Phase III *Confirmatory efficacy and safety studies*

Post-marketing surveillance (phase IV)

Time period for approval

Accelerated Approval Process

Basic Research → Preclinical Studies → **Clinical Trials** → **Marketing Authorization on the basis of surrogate endpoint** → On Market → **MA Confirmed or Withdrawn** → On Market

Confirmatory studies

Post-marketing surveillance (phase IV)
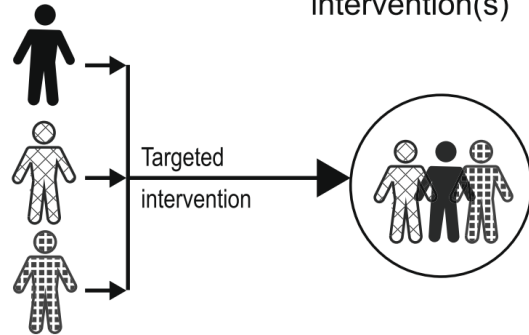
Time period for approval

Contents

1. Indication: biomarker driven, rare disease

2. **Study design: master protocol, optimal dose finding**

3. Immune response management

4. Data monitoring

5. Conclusion

Master Protocols for Oncology Drugs and Biologics
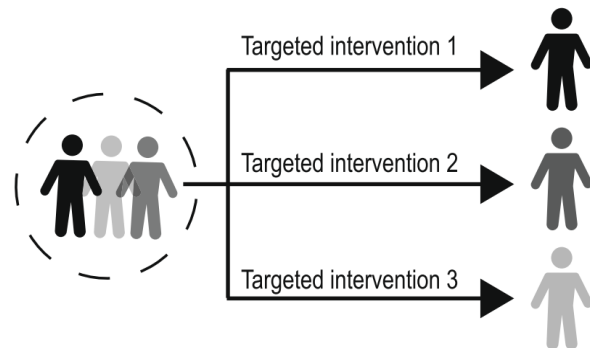

Basket trial

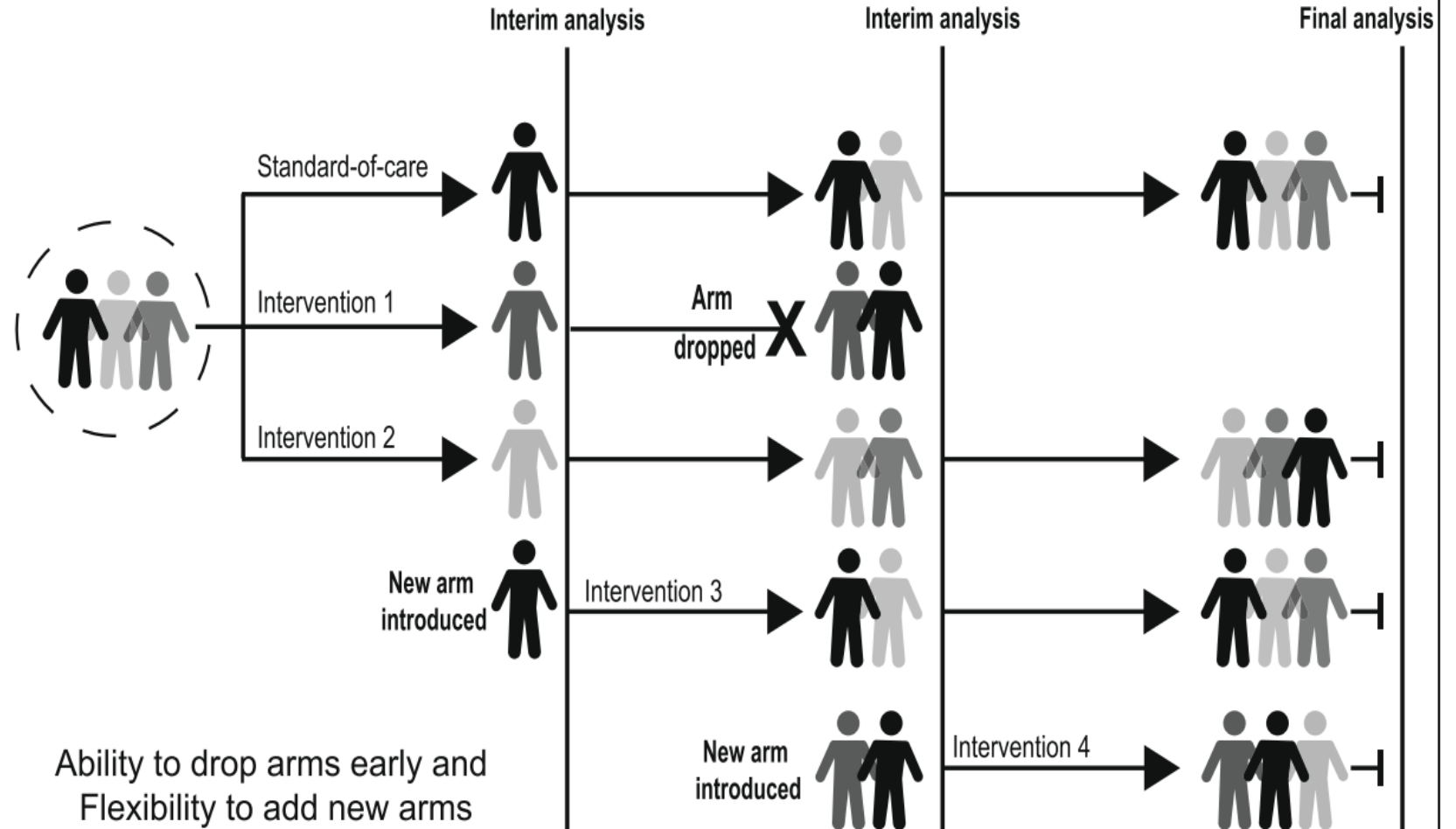Multiple diseases → Common targeted intervention(s)

Targeted intervention

Umbrella trial

Single disease → Multiple targeted interventions

Targeted intervention 1
Targeted intervention 2
Targeted intervention 3

Platform trial

Interim analysis — Interim analysis — Final analysis

Standard-of-care

Intervention 1 — Arm dropped X

Intervention 2

New arm introduced — Intervention 3

New arm introduced — Intervention 4

Ability to drop arms early and Flexibility to add new arms
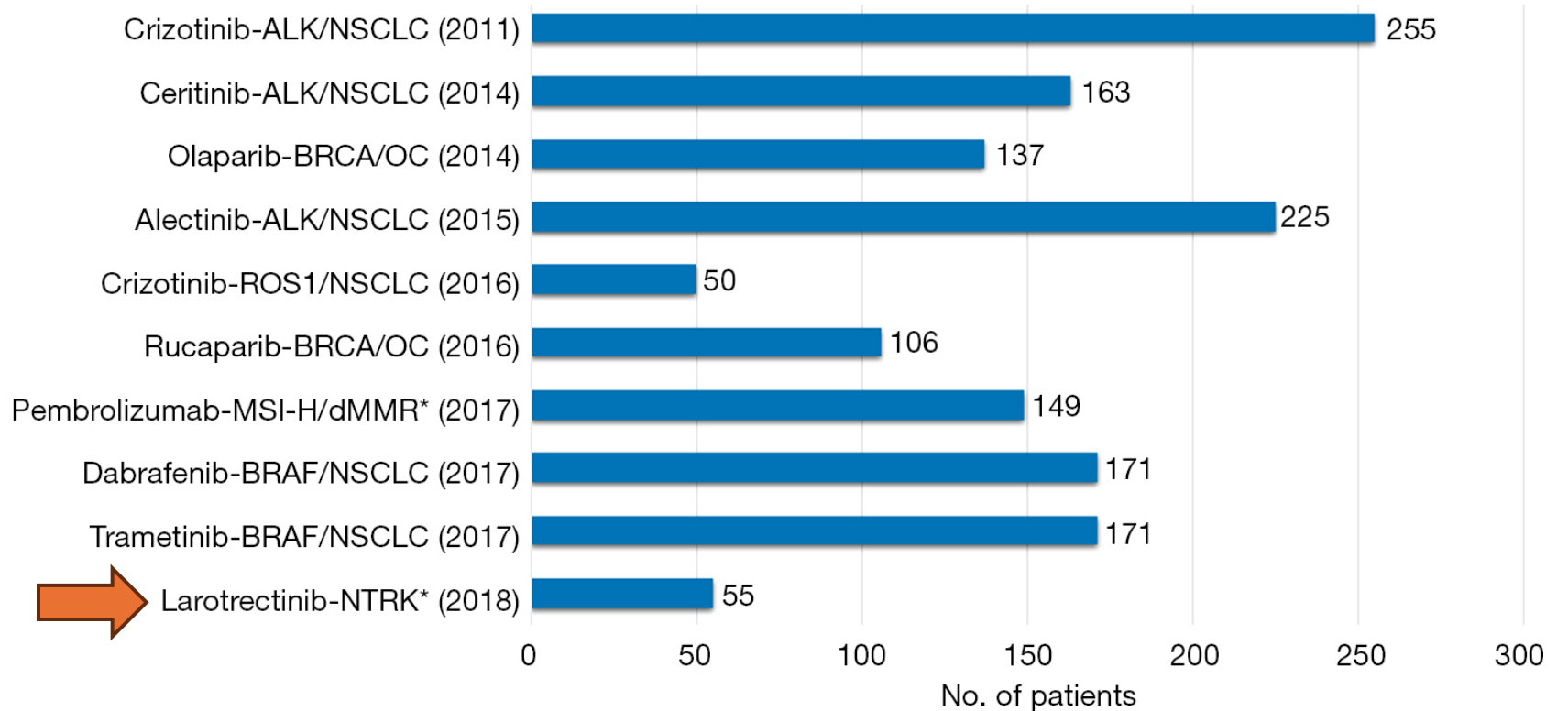
Drug-diagnostic combinations that have obtained US FDA approval based on the efficacy data from single-arm enrichment phase I/II trials
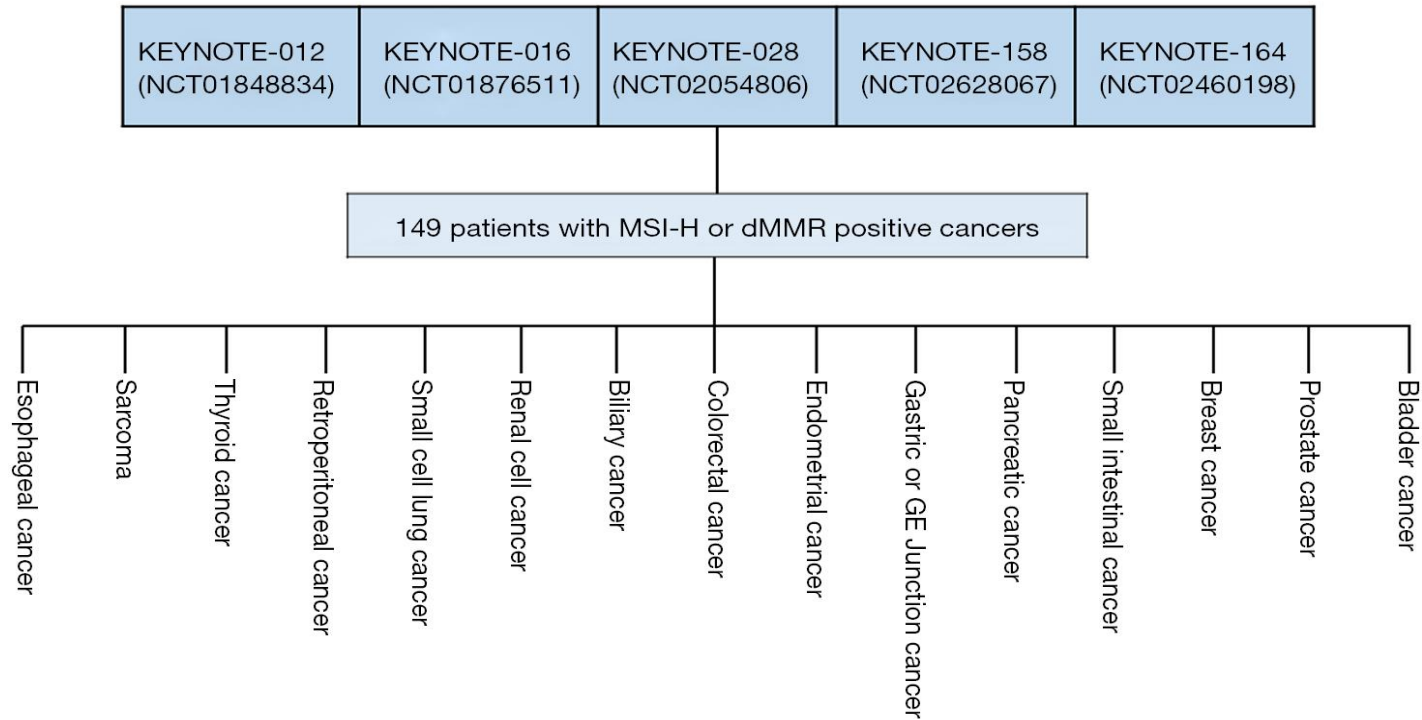
a star (*) were developed based on a "basket" trial-like approach with pooling of data from several individual clinical trials.

Drug-diagnostic combination	No. of patients
Crizotinib-ALK/NSCLC (2011)	255
Ceritinib-ALK/NSCLC (2014)	163
Olaparib-BRCA/OC (2014)	137
Alectinib-ALK/NSCLC (2015)	225
Crizotinib-ROS1/NSCLC (2016)	50
Rucaparib-BRCA/OC (2016)	106
Pembrolizumab-MSI-H/dMMR* (2017)	149
Dabrafenib-BRAF/NSCLC (2017)	171
Trametinib-BRAF/NSCLC (2017)	171
Larotrectinib-NTRK* (2018)	55

No. of patients

Source: Jan Trøst Jørgensen (Annals of Translational Medicine, 2019)

ALK (Anaplastic Lymphoma Kinase), NSCLC (Non-Small Cell Lung Cancer), BRCA (Breast Cancer gene), OC (Ovarian Cancer), MSI-H (Microsatellite Instability High), dMMR (deficient Mismatch Repair), BRAF (serine/threonine-protein kinase B-Raf), NTRK (Neurotrophic Tyrosine Receptor Kinase)

"Basket" Trial-like approach with pooling of data from several individual clinical trials

KEYNOTE-012 (NCT01848834)	KEYNOTE-016 (NCT01876511)	KEYNOTE-028 (NCT02054806)	KEYNOTE-158 (NCT02628067)	KEYNOTE-164 (NCT02460198)

149 patients with MSI-H or dMMR positive cancers

- Esophageal cancer
- Sarcoma
- Thyroid cancer
- Retroperitoneal cancer
- Small cell lung cancer
- Renal cell cancer
- Biliary cancer
- Colorectal cancer
- Endometrial cancer
- Gastric or GE Junction cancer
- Pancreatic cancer
- Small intestinal cancer
- Breast cancer
- Prostate cancer
- Bladder cancer

Source: Jan Trøst Jørgensen (Annals of Translational Medicine, 2019)
MSI-H (Microsatellite Instability High), dMMR (deficient Mismatch Repair)

- **5 single arm Basket Trials**
- **15 different indications**
- **Biomarker diagnosis for total 149 pts**
  - ✓ dMMR identified by IHC – 47 patients
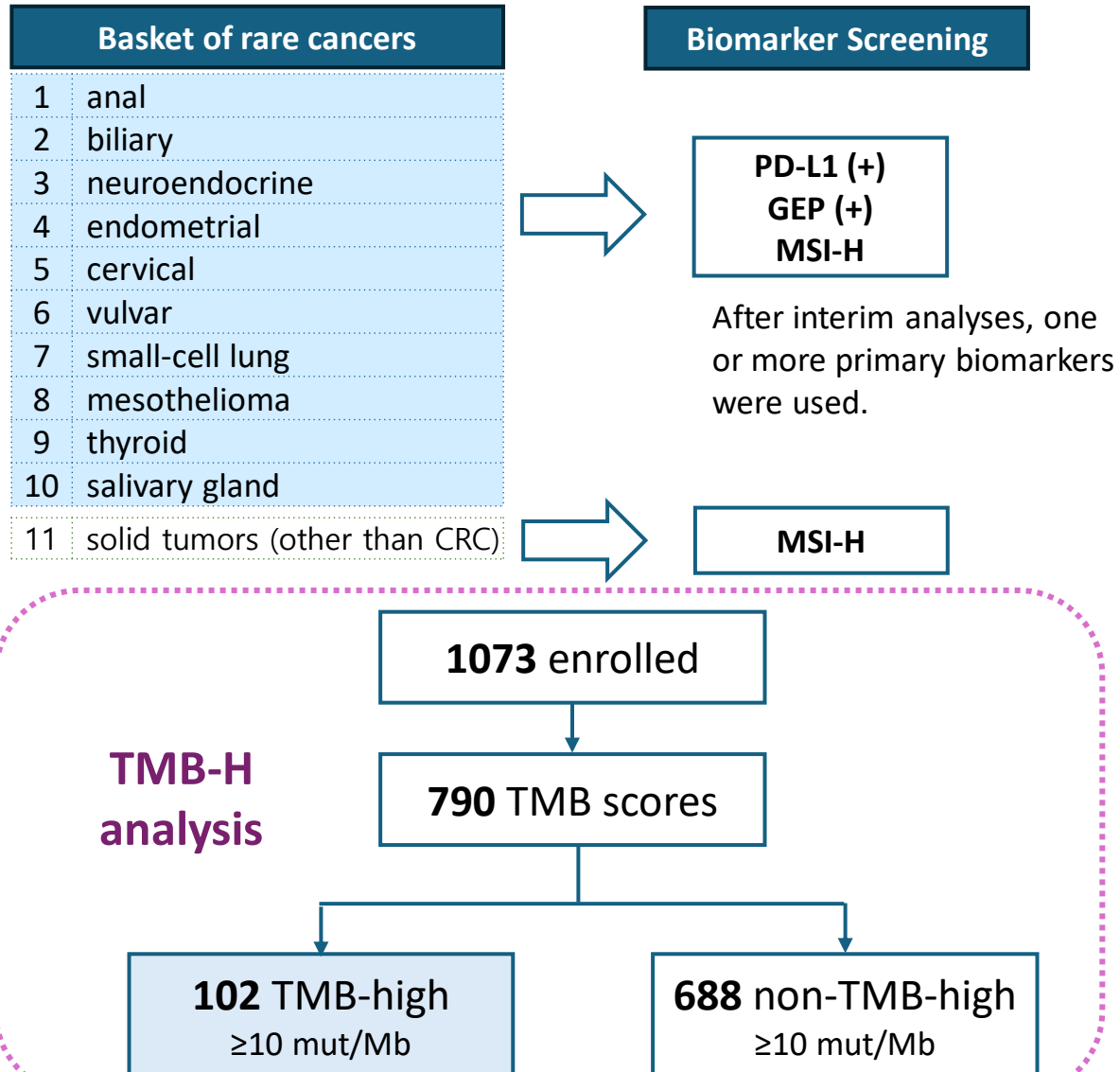 - ✓ MSI-H assessed by PCR – 60 patients
  - ✓ Both – 42 patients

On May 23, 2017, FDA granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, **MSI-H or dMMR solid tumors** that have progressed following prior treatment.

KEYNOTE-158 Study

21 countries in Africa, the Americas, Asia, and Europe
Pembrolizumab 200 mg IV Q3W, up to 35 cycles

Basket of rare cancers
1 anal
2 biliary
3 neuroendocrine
4 endometrial
5 cervical
6 vulvar
7 small-cell lung
8 mesothelioma
9 thyroid
10 salivary gland
11 solid tumors (other than CRC)

Biomarker Screening

**PD-L1 (+)
GEP (+)
MSI-H**

After interim analyses, one or more primary biomarkers were used.

MSI-H

TMB-H analysis

1073 enrolled

790 TMB scores

102 TMB-high
≥10 mut/Mb

688 non-TMB-high
≥10 mut/Mb

- **1 single arm Basket Trial**
- **10 different indications**
- **Biomarker diagnosis for total 102 pts**
  - ORR 29% (95% CI: 21,39)
  - Response durations ≥12 months 57%
  - Response durations ≥24 months 50%

On June 16, 2020, FDA granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic **tumor mutational burden-high** [TMB-H; ≥10 mutations/megabase (mut/Mb)] **solid tumors**, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

PD-L1 (Programed Death Ligand 1 expression),
GEP (tumor Gene expression profile),
MSI-H (Microsatellite Instability High),

Umbrella trials have an inherent key methodological characteristic of using **multiple predictive risk factors** to determine patient subgroups.

NCT02688894
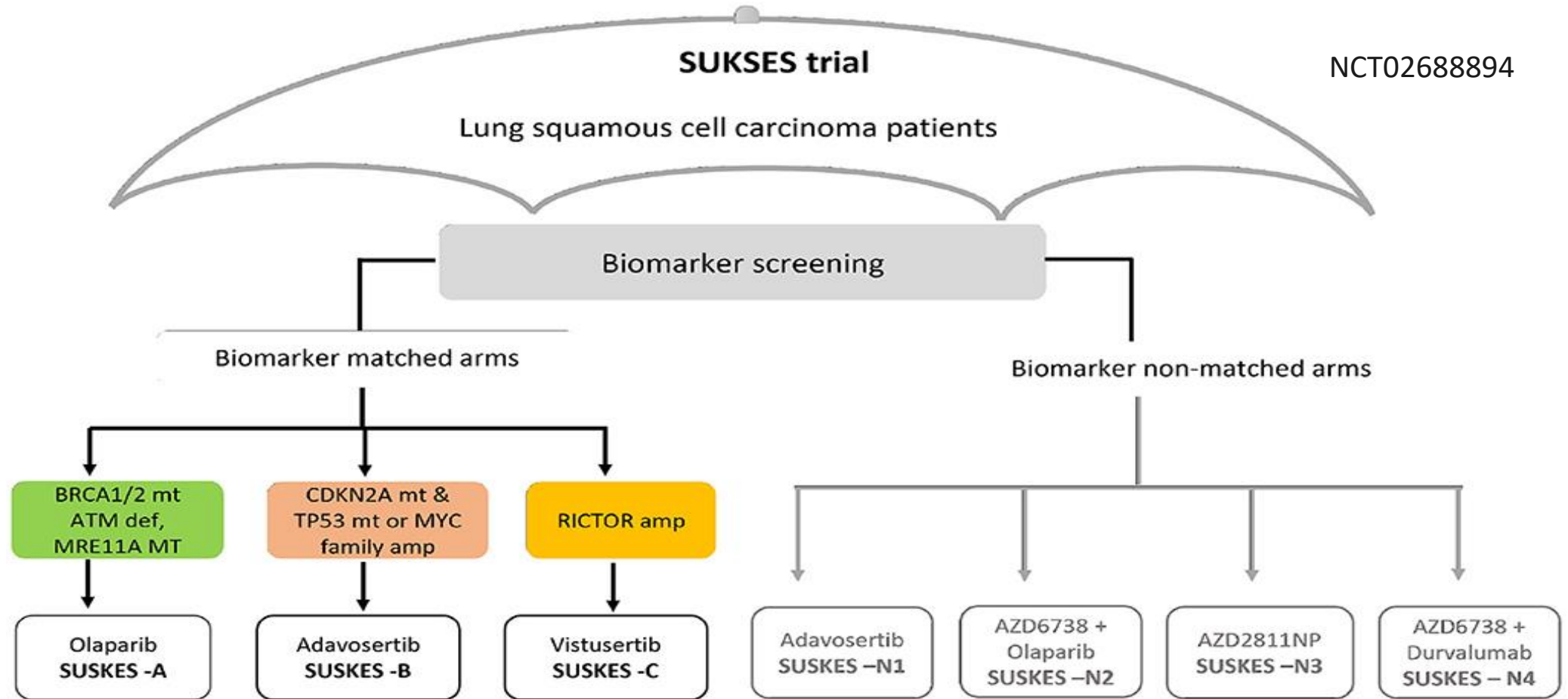
Source: Park et al. (CA Cancer J Clin. 2020)

Umbrella study example: SUKSES trial, LUNG-MAP trial, plasmaMATCH

Complex Innovative Trial Designs

Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

---

Guidance for Industry

Guidance, December 2020

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
December 2020

- **Complex adaptive, Bayesian, and other novel clinical trial designs**
  - ✓ Adaptive Designs for Clinical Trials of Drugs and Biologics (FDA, 2019)
  - ✓ Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials (FDA, 2010)

- **Decisions allocated to IDMC (DSMB)**

- **Use of Phase 2 control data in Phase 3 Study**

Real World Data and Real World Evidence

Considerations for the Design
and Conduct of Externally
Controlled Trials for Drug and
Biological Products

Guidance for Industry

DRAFT GUIDANCE

Draft Guidance, February 2023

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

February 2023
Real-World Data/Real-World Evidence (RWD/RWE)

49539091dft

Real-World Evidence:
Considerations Regarding
Non-Interventional Studies
for Drug and Biological
Products

Guidance for Industry

DRAFT GUIDANCE

Draft Guidance, March 2024

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

March 2024
Real World Data/Real World Evidence (RWD/RWE)

55680653dft

Real World Evidence for Regulatory Decision-Making

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

Guidance, August 2023

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

August 2023
Real-World Data/Real-World Evidence (RWD/RWE)

54767258fnl

Non-interventional Study

Collection

RWD — **Analysis** → **RWE**

Use

- ✓ Registries,
- ✓ EHRs,
- ✓ Medical claims, etc.

- ✓ **NDAs/BLAs**
- ✓ Post-marketing safety reporting

의료정보 데이터베이스 연구에 대한 가이드라인
Guidelines for Research on Medical Information Databases
(MFDS, 2021)

- ✓ Observational cohort study
- ✓ Case-control study
- ✓ Nested case-control study
- ✓ Case only study

Optimizing the Dosage of Oncology Treatment

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2024
Clinical/Medical

Guidance, August 2024

Dosage optimization **prior to approval** is recommended because delaying until after approval may result in large numbers of patients being exposed to a poorly tolerated dosage or one without maximal clinical benefit.

Sponsors should note that development of a drug under an FDA **expedited program** is **not a sufficient justification** to avoid identifying an optimized dosage(s) prior to submitting a marketing application.

Perceived **difficulty in manufacturing** multiple dose strengths is **an insufficient rationale** for not comparing multiple dosages in clinical trials.

If sufficient relevant data are not available to support the proposed dosage(s) for a **new combination or indication and usage**, **additional dose-finding** should be conducted.

Study Design and Consideration for Optimal Dose Finding

Design

- Multiple dosages

- Randomization (Stratified)

- Double blind

- **Adaptive design**

- Sample size: sufficient assessment of **safety and antitumor activity for each dosage** (not to be powered statistically)

- Drug interactions with concomitant medications

- Food effect on PK and safety for oral agent

PK

- Adequately characterize the PK (e.g., linearity, absorption, distribution, elimination)

- At the first dose and at **steady-state**

- PK, PD, population PK, and dose- and exposure-response analyses

  - ✓ Safety: laboratory data and adverse events

  - ✓ Activity: tumor-assessment based endpoints, biomarkers

  - ✓ Specific population: weight, age, sex, race and ethnicity, organ impairment, genetic factors

 - ✓ Intrinsic factors: genetic variation, organ impairment

Source: Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases Guidance for Industry (US FDA, 2024)

Exposure-Efficacy and Safety Relationships by Different Molecules

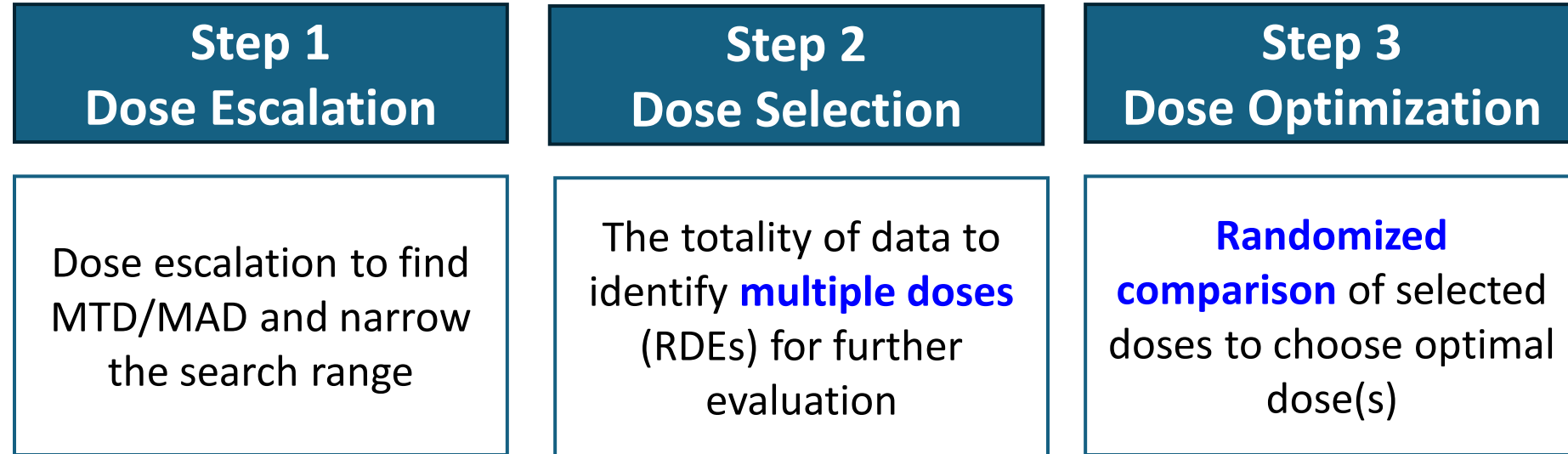Source: P. Soltantabar et al. (Critical Reviews in Oncology / Hematology, 2023)
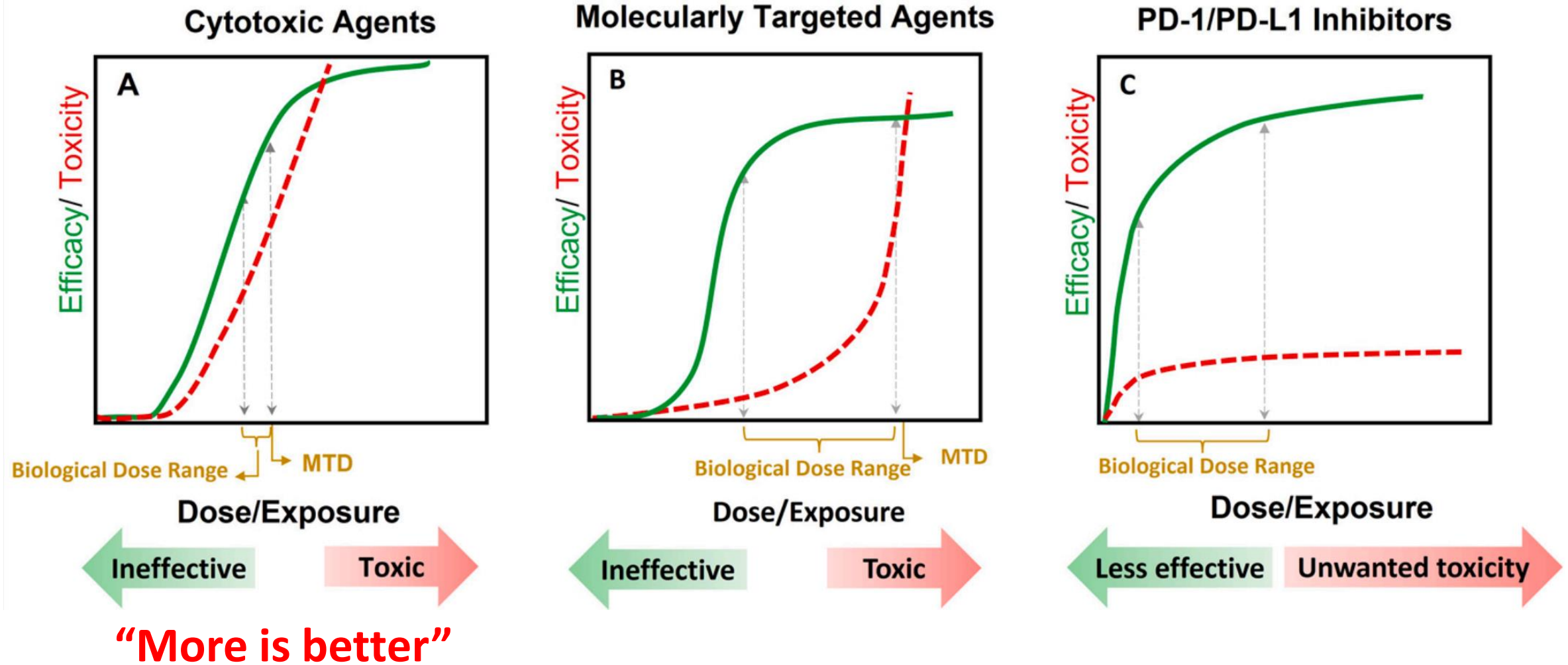
Development of Innovative Cancer Therapies (MDICT) Guideline (ESMO 2022)
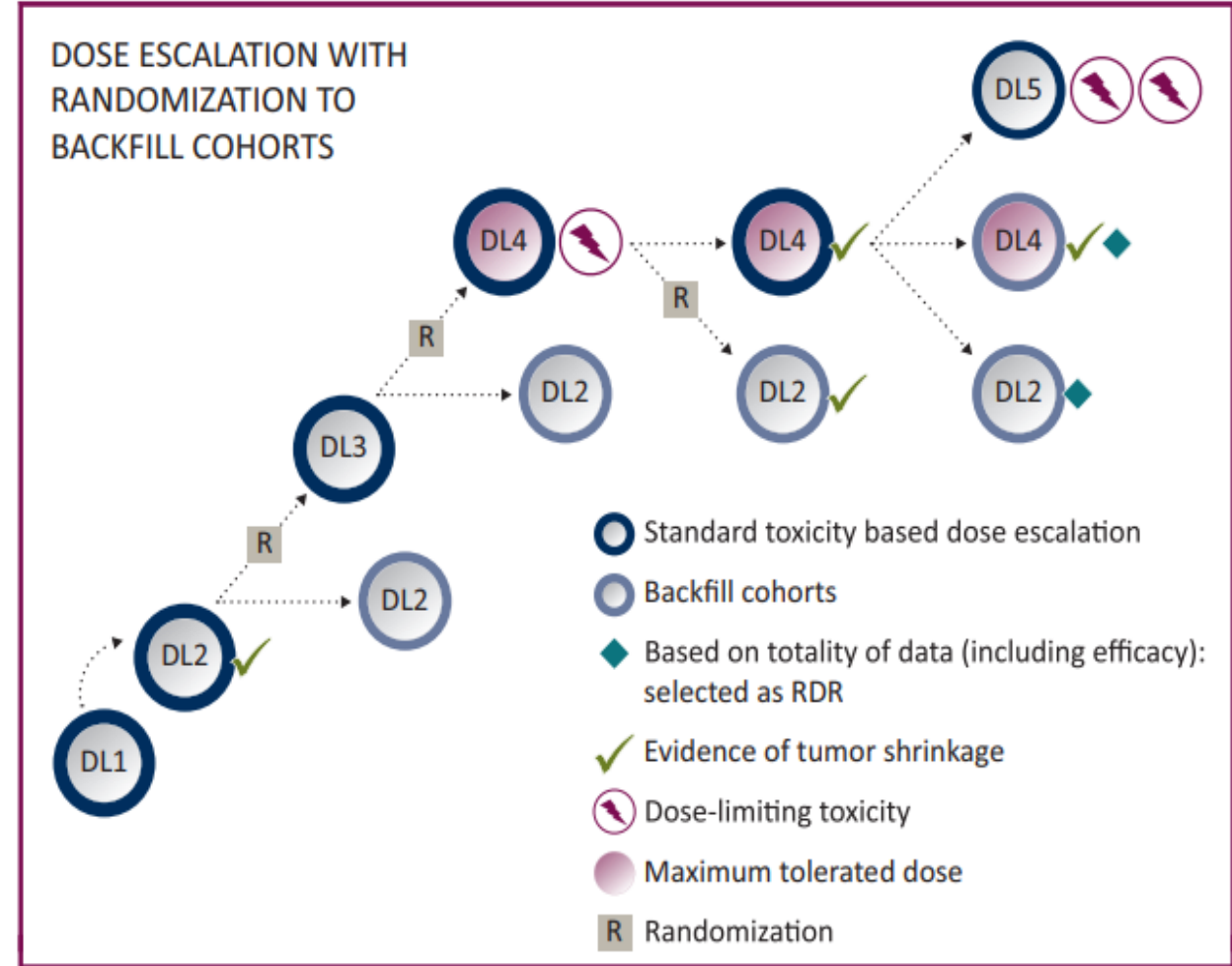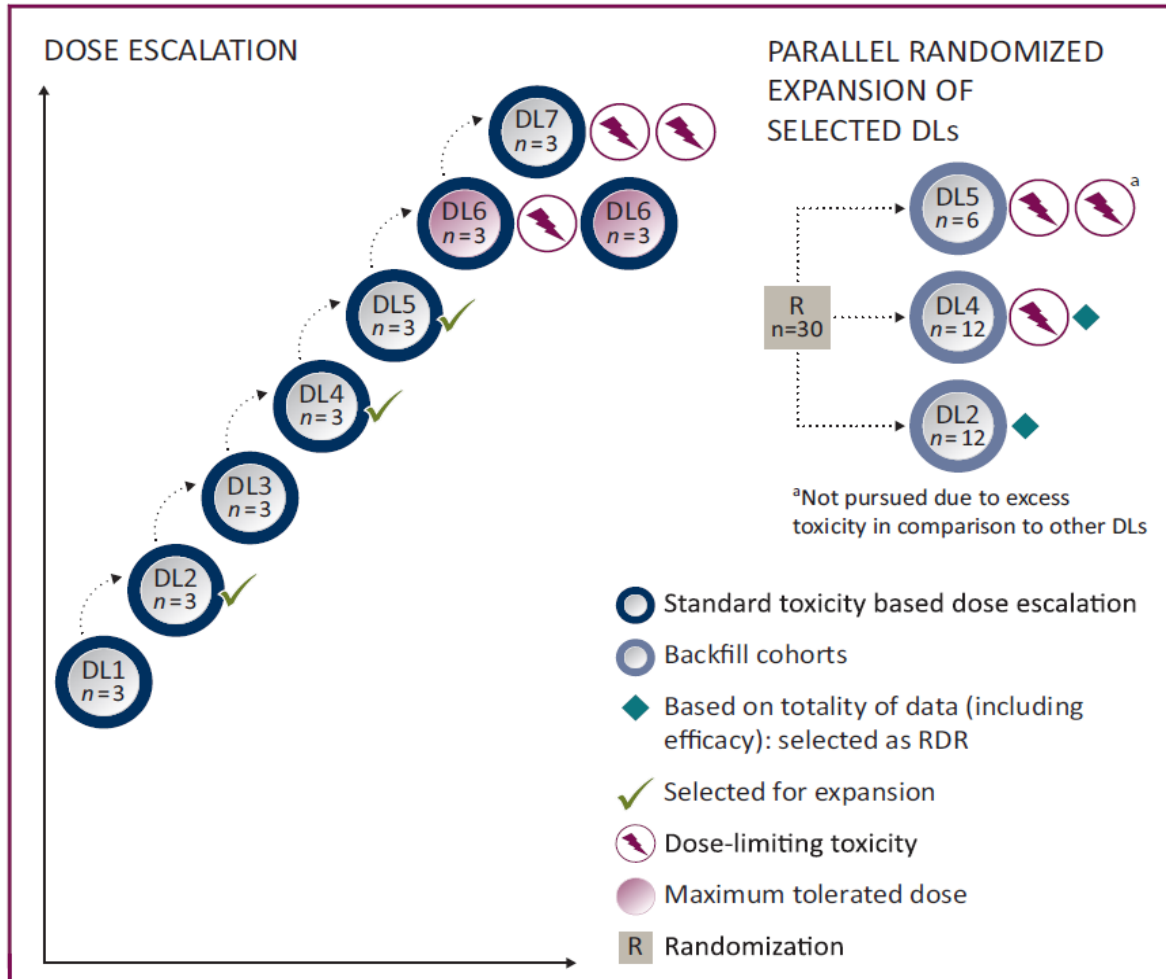
DL, dose level; MAD, maximum administered dose; MRAD, minimally reproducibly active dose; MTD, maximum tolerated dose; PD, pharmacodynamics; PER, predicted effective range; PK, pharmacokinetics; RD, recommended dosage; RDR, recommended dosage range; RP2D, recommended phase II dose.

Source: D. Araujo et al. (Annals of Oncology, 2022)

Dose Optimization Process

Step 1 Dose Escalation	Step 2 Dose Selection	Step 3 Dose Optimization
Dose escalation to find MTD/MAD and narrow the search range	The totality of data to identify **multiple doses** (RDEs) for further evaluation	**Randomized comparison** of selected doses to choose optimal dose(s)

Example for Accelerated Approvals Based on a Surrogate Endpoint
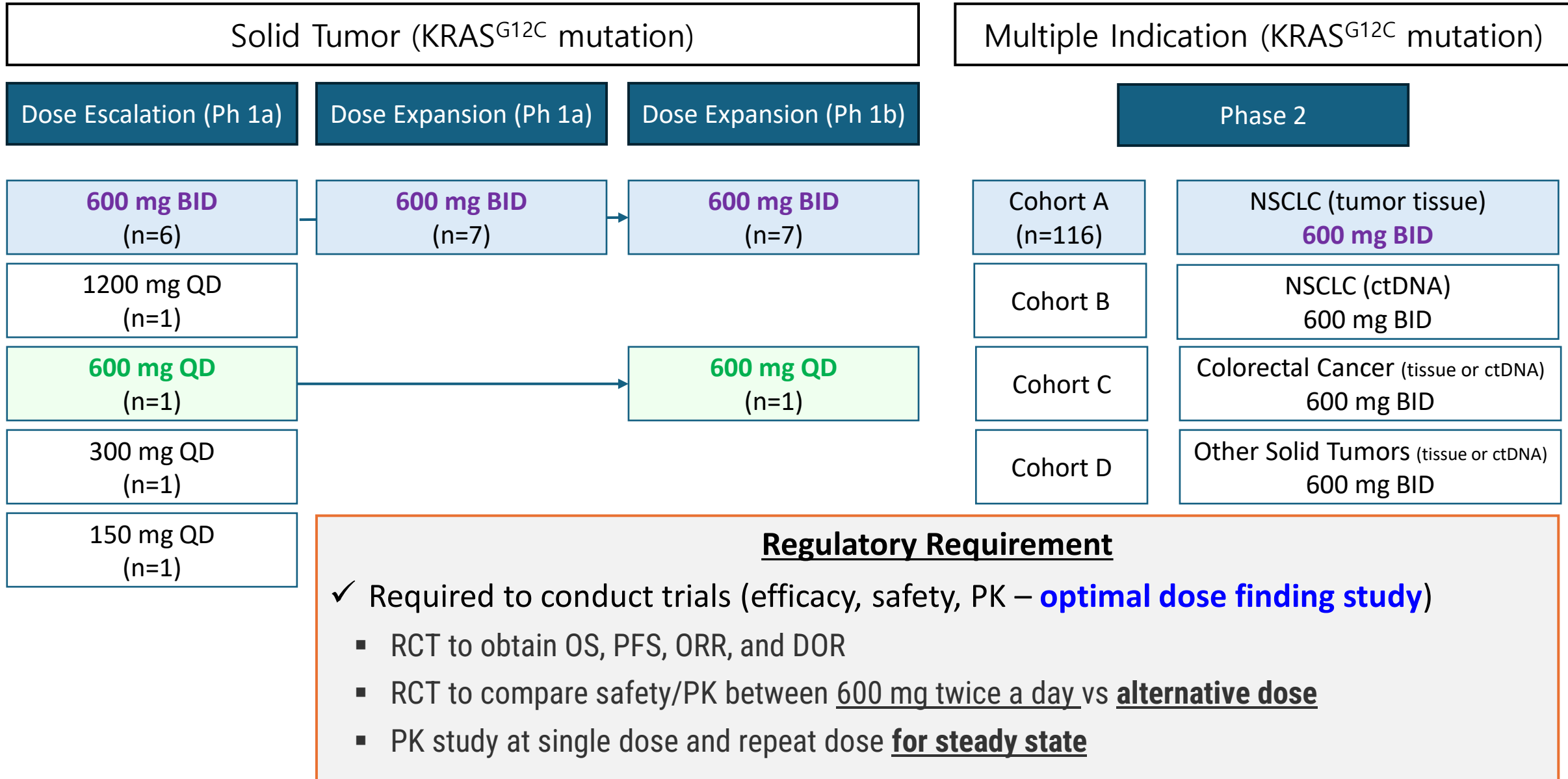# (US FDA as of September 30, 2024)

KRAZATI is an inhibitor of the RAS GTPase family indicated for the treatment of adult patients with **KRAS G12C-mutated** locally advanced or metastatic **non-small cell lung cancer (NSCLC)**, as determined by an FDA approved test, who have received at least one prior systemic therapy (submitted on 12/21/2023, **approved on 6/21/2024**).

Key Consideration
Adaptive design

Summary of Protocol Amendment for Pivotal Study 849-001 (Phase 1/2)

Document	Summary of Changes
Amendment 1	• Responded to IND feedback on the definition for dose limiting toxicity during dose escalation and the schedule for selected safety assessments
Amendment 2	• Added Phase 1 evaluation of the twice daily adagrasib regimen
Amendment 3	• Implemented the Phase 2 dosing regimen • Added pilot Phase 1 combination regimen evaluations
Amendment 4	• Revised the statistical design and increased the sample size for Cohort A to enable the pivotal evaluation of clinical efficacy following EOP1 meeting • Added a pilot Phase 1 combination regimen evaluation
Amendment 5	• Added a Phase 1b evaluation in a selected patient population
Amendment 6	• Provided guidance for conduct of the study during the COVID-19 public health emergency, in accordance with FDA guidance • Expanded the design for a pilot Phase 1 combination sub-study • Added several Phase 1b evaluations in selected patient populations • Revised the statistical design for a Phase 2 Cohort • Added a Phase 2 evaluation
Amendment 7	• Added a Phase 2 evaluation • Expanded a Phase 1b cohort

Source: Drugs@FDA

KRAZATI Pivotal Study 849-001 Design for NSCLC

Solid Tumor (KRAS^{G12C} mutation)	Multiple Indication (KRAS^{G12C} mutation)

Dose Escalation (Ph 1a)	Dose Expansion (Ph 1a)	Dose Expansion (Ph 1b)	Phase 2	

600 mg BID (n=6)	**600 mg BID** (n=7)	**600 mg BID** (n=7)	Cohort A (n=116)	NSCLC (tumor tissue) **600 mg BID**
1200 mg QD (n=1)			Cohort B	NSCLC (ctDNA) 600 mg BID
600 mg QD (n=1)		**600 mg QD** (n=1)	Cohort C	Colorectal Cancer (tissue or ctDNA) 600 mg BID
300 mg QD (n=1)			Cohort D	Other Solid Tumors (tissue or ctDNA) 600 mg BID
150 mg QD (n=1)				

Regulatory Requirement

✓ Required to conduct trials (efficacy, safety, PK – **optimal dose finding study**)

- RCT to obtain OS, PFS, ORR, and DOR
- RCT to compare safety/PK between <u>600 mg twice a day</u> vs **alternative dose**
- PK study at single dose and repeat dose **for steady state**

Drugs@FDA: FDA-Approved Drugs

Share Tweet Linkedin Email Print

U.S. FOOD & DRUG ADMINISTRATION

Home / Drugs / Drug Approvals and Databases / Drugs@FDA

Drug Approval Package: AUGTYRO

Share Tweet Linkedin Email Print

Company: Bristol-Myers Squibb Company
Application Number: 218213
Approval Date: 11/15/2022

Drugs@FDA information available about AUGTYRO ⓘ

Persons with disabilities having problems accessing the PDF files below may call (301) 796-3634 for assistance.

✔ **FDA Approval Letter and Labeling**

- Approval Letter(s) (PDF)
- Printed Labeling (PDF)

▤ **FDA Application Review Files**

- Product Quality Review(s) (PDF)
- Multi-Discipline Review (PDF)
- Proprietary Name Review(s) (PDF)
- Officer/Employee List (PDF)
- Other Review(s) (PDF)
- Risk Assessment and Risk Mitigation Review(s) (PDF)
- Administrative and Correspondence Documents (PDF)

Source: https://www.accessdata.fda.gov/scripts/cder/daf/

Home / Drug Databases / PMC Home

Postmarketing Requirements and Commitments: Searchable Database

Revise Search | New Search

You searched for: Both CBER and CDER; Repotrectinib; All Statuses; Neither

«« « 1 of 2 » »»

Applicant:	BRISTOL MYERS SQUIBB CO
Product:	Augtyro (repotrectinib)
NDA/BLA Number:	218213
NDA/BLA Approval Date:	11/15/2023
Annual Report Due Date: (must be submitted within 60 days of this date)	11/15/2024
Annual Report Received:	

Requirement/Commitment Number: 1

Required Under:	Pediatric Research Equity Act
Original Projected Completion Date:	03/31/2027
Description:	PMR 4547-1: Conduct a clinical study (ongoing CARE study) to assess the appropriate dose of repotrectinib and to assess safety, tolerability, pharmacokinetics (PK), and efficacy of repotrectinib, in pediatric and young adult patients with advanced or metastatic solid tumors, primary central nervous system (CNS) tumors, or anaplastic large cell lymphoma (ALCL), with ALK, ROS1, or NTRK alterations. At least 3 patients 6 years of age or younger will be evaluated in the dose-finding phase.
Current Status:	Pending

Source: https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

Approval History in patients with ROS1 positive NSCLC

	2016.3.11 Accelerated Approval (Supplement)	**2019.8.15** Accelerated Approval (New)	**2023.11.15** Accelerated Approval (New)
Drug	**Crizotinib (**Xalkori®, Pfizer)	**Entrectinib (**Rozlytrek®, Genentech)	**Repotrectinib (Augtyro®, BMS)**
Indication	ROS1-positive NSCLC	ROS1-positive NSCLC	ROS1-positive NSCLC, previously treated with another ROS1-targeted drug
Data	**Efficacy: 50 patients** **- One single arm study** • **ORR** by IRR: 66% (95% CI 51, 79) • **Median DOR**: 18.3 months (12.7, NR) • **Responders with DOR ≥12 months**: 64% **Safety: 50 patients**	**Efficacy: 51 patients** **- Three single arm studies, pooled analysis** • **ORR** by IRR: 78% (95% CI 65, 89) • **Median DOR**: 15.7 months (11.4, 34.8) • **Responders with DOR ≥12 months**: 55% **Safety: 355 patients**	**Efficacy: 71 + 56 patients** **- One single arm study** • **ORR** by IRR: 79%, 38% • **Median DOR**: 34.1 mo., 14.8 mo. • **Responders with DOR ≥12 months**: 86%, 60% **Safety: 351 patients**

Crizotinib Regulatory Consideration

✓ **Rare population (1%~2% of NSCLC)**
✓ Limited efficacy of alternative therapies (RR approximately 10%~35% with relatively short DoR)
✓ **Safety profile already well characterized in other disease areas that used RCTs**
✓ Conducting subsequent RCT could violate principles of clinical equipoise

Entrectinib Supportive Data

✓ Compare efficacy data from 69 patients with ROS1-positive NSCLC receiving **Crizotinib** in **the real world captured by the Flatiron Health Analytic Database**.

Repotrectinib Regulatory Requirement

✓ Required to conduct trials (safety, PK – **optimal dose finding study**)

RWE (Entrectinib 비교 자료)
ESMO 2024 발표

DOR (duration of response), RCT (randomized controlled trials), ORR (objective response rate)
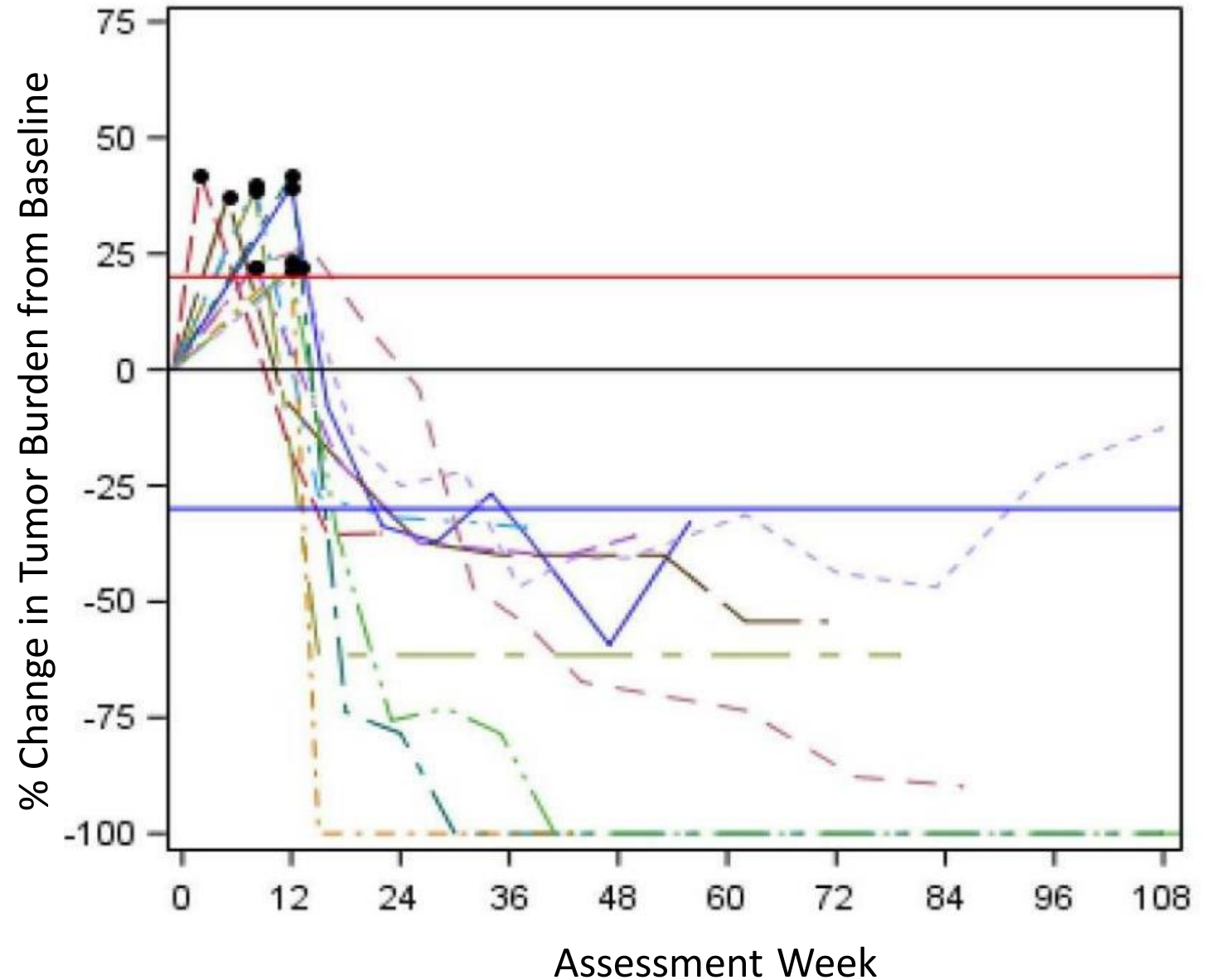*Source: Drugs@FDA*

Contents

Pseudo Progression during Immunotherapy (Example #1)

n=11 responders by iRECIST; black circle represents timing of progression based on increase in target lesions by RECIST V.1.1

Source: Comparison of iRECIST versus RECIST V.1.1 in patients treated with an anti-PD-1 or PD-L1 antibody: ***pooled FDA analysis*** *(Flora Mulkey et al, 2020)*

Pseudo Progression during Immunotherapy (Example #2)

Metastatic Head and Neck Squamous Cell Carcinoma

Source: Akshay Bedmtha and Ashish Kaushai (Images in Cancer Clinical Research, 2022)

PET-CT

CT

A B C

Baseline **12 weeks** **24 weeks**
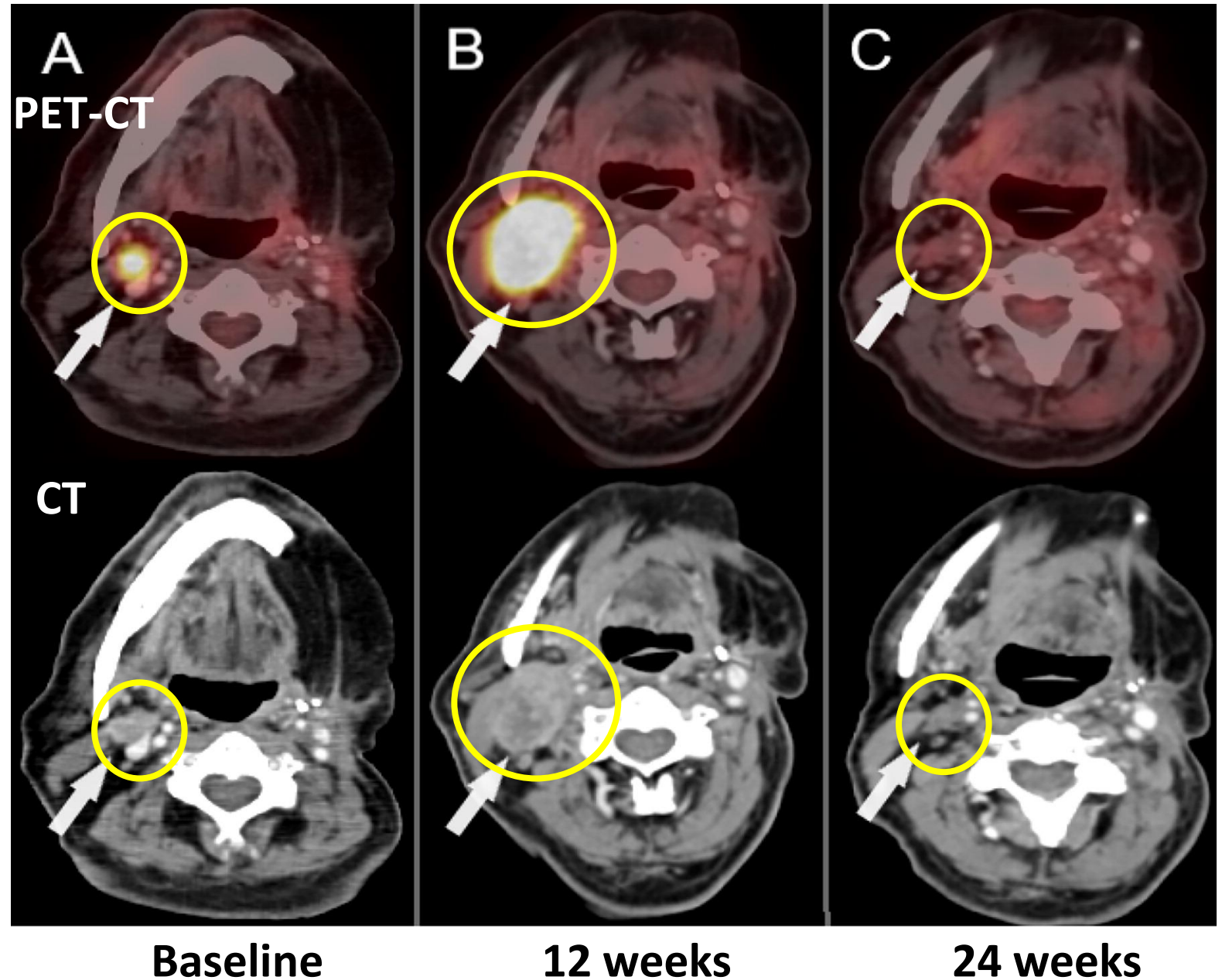
Key Consideration in Immune Checkpoint Trials

Accurate Guideline !

Solid Tumor

- ✓ RECIST 1.1: primary evaluation
- ✓ iRECIST: treatment

Lymphoma

- ✓ Lugano classification (Cheson, 2014): primary evaluation
- ✓ LYRIC modification (Cheson, 2016): treatment, primary evaluation

Continuous Education !

1 **Consider Pseudo Progression**

2 **Confirmed PD required**

3 **Efficacy assessment after EOT due to PD**

iRECIST

If feasible, even patients who **discontinue study treatment for PD** are recommended to continue to have disease assessments **until they start any new anticancer therapy**.

Contents

Various committee for clinical trial monitoring and oversight

Use of Data Monitoring Committees in Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

February 2024
Clinical/Medical
Revision 1

Draft Guidance, February 2024

- Steering Committee (BLIND)

- Endpoint Assessment / Adjudication Committees (BLIND)

- Clinical Site Monitor (BLIND)

- Entities Reviewing Safety Data (UNBLIND)

- Adaptation Committee (UNBLIND)

- DMC / DSMB / IDMC (UNBLIND)

Previous guideline
Establishment and Operation of Clinical Trial Data Monitoring Committees 21 issued in March 2006

Monitoring Committee for Study Quality

	Steering Committee	**DSMB (IDMC)**
Members	✓ **Principal Investigator** ✓ **Key Investigators** ✓ **Sponsor / Medical Monitor**	✓ **Physicians (one is Chair)** ✓ **Statistician** ✓ **(Pharmacologist)** *Independent!*
Assessment/ Decision	▪ **Blinded data** ✓ **Study Design (protocol)** ✓ Enrollment/Treatment Status → **Facilitate Enrollment** ✓ Efficacy, Safety, Case review → **Subject management** ✓ **Study go/no decision**	▪ Open session: **blinded data** ▪ Close session: **unblinded data (unblinded statistician assigned)** ✓ Efficacy, Safety, PK/PD ✓ External data ✓ **Study go/no decision** ✓ **Sample size (adaptive, Bayesian, etc.)**
Timepoint	✓ **Monthly** ✓ **Ad-hoc (emergency)**	✓ **Decision required for sample size and next phase** ✓ **1-2 times/year, Ad-hoc (emergency)**

Data and Safety Monitoring Board (DSMB in US)
Independent Data Monitoring Committee (IDMC in EU)

Key Items for Central Data Monitoring

At Each Enrollment

Eligibility Criteria

- ✓ Prior treatment history
- ✓ Pre-existing condition
- ✓ Concomitant medication

Example

- Multiple prior treatment and Multiple metastasis
- Nausea/Vomiting/Abdominal Pain due to tumor rupture (hepatocellular carcinoma)
- Heparin due to stroke
- Antibiotics due to infection

Weekly or Bi-weekly

Efficacy Data

- ✓ Measurable lesion at baseline
- ✓ Overall response at each assessment

Example

- LN size at baseline (≥ 1.5cm)
- Assessment date for PD
- Assessment date for CR/PR/SD
- Immune response at early timepoint

QC visit, Audit

At Each SAE, Monthly

Safety Data
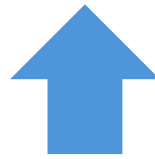
- ✓ SAE
- ✓ Grading
- ✓ Drug relationship

Example

- Frequent follow-up information for SAE (clinical meaningful update is required)
- Comprehensive queries for SAE
- Grade 2 without treatment
- Consider combination therapy (Standard of Care)

Contents

To obtain accelerated approval based on one single-arm trial !

↑

✓ *Why biomarker-driven study is needed*

✓ *Development strategy using single-arm trial for rare disease*

✓ *What is important for a successful phase 1 clinical trial?*

✓ *How to improve the data quality of complex structures*

Consideration for successful oncology drug development

Indication selection

- ✓ Rare disease
- ✓ Biomarker driven

Accelerated Approval !

Data Monitoring

- ✓ Central Data Monitoring
- ✓ Steering Committee, IDMC

Quality Improvement !

Immune Response

- ✓ Accurate guidance
- ✓ Pseudo progression

Increase Efficacy !

Study Design

One Single Arm Study

- ✓ RR with supportive DOR
- ✓ Adaptive design (phase 1 & 2), Bayesian

Optimal Dose Finding

- ✓ Multiple dose (double blind, random)
- ✓ PK/PD, Safety, Efficacy

External Data Comparison

- ✓ Historical data
- ✓ RWD, RWE

Efficient Trial !

Immune(면역) + Ciencia(과학)

**Changing the Standard of cancer treatment
By Bringing Korea's 1st immuno-oncology Drug**

국내 최초의 면역항암제 상용화