U.S. FOOD & DRUG ADMINISTRATION

From Seamless Trial Designs to Seamless Indications in Oncology: Regulatory Considerations

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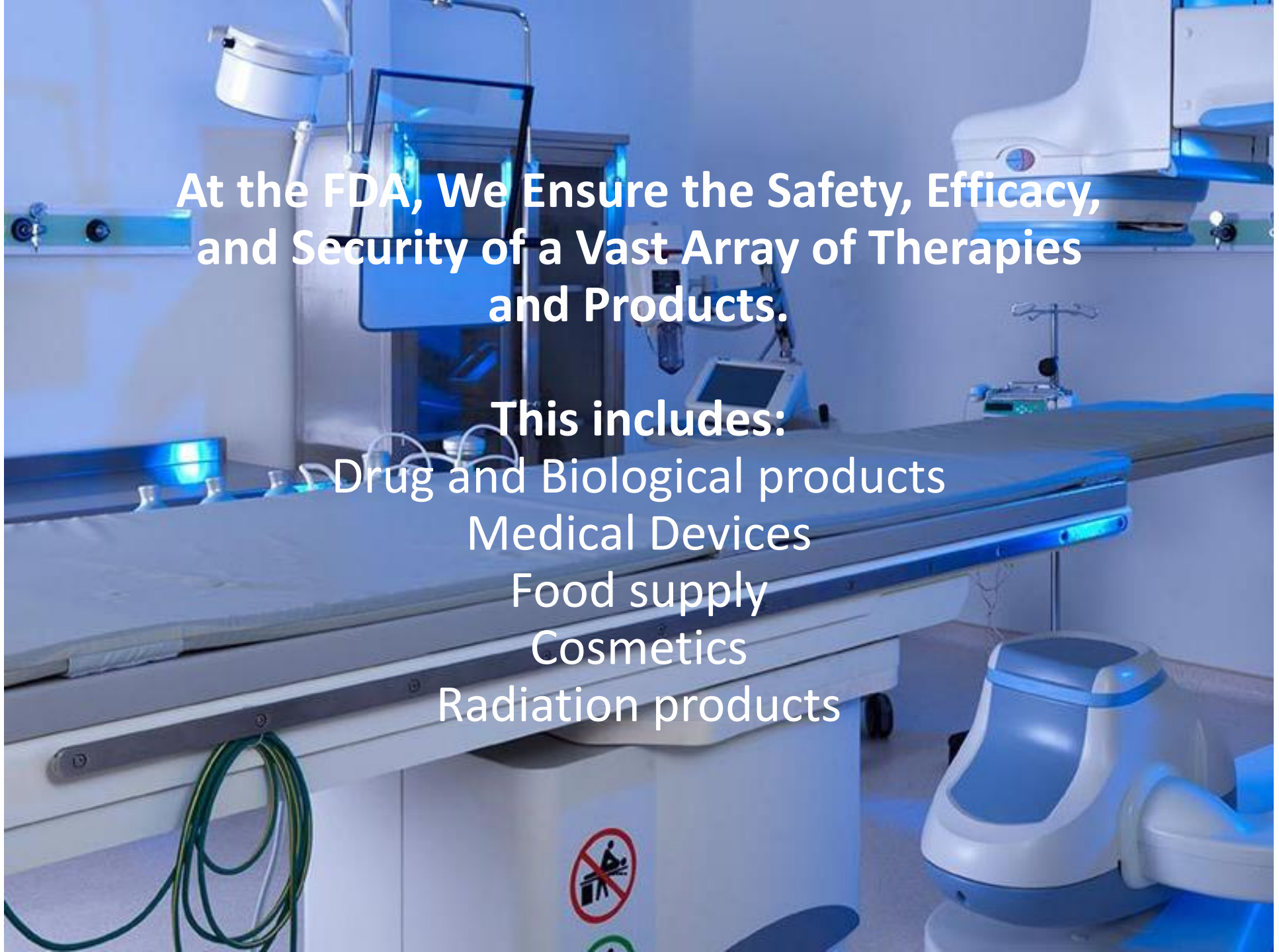
February 21, 2019

Outline

- **Background**
  - **FDA Oncology**
  - **Expedited Programs**
  - **Endpoints**
- **Evolving Drug Development Paradigm in Oncology**
  - **Expansion Cohorts – FIH Trials**
  - **Master Protocols**
  - **Tissue Agnostic Indications**



At the FDA, We Ensure the Safety, Efficacy, and Security of a Vast Array of Therapies and Products.

This includes:

Drug and Biological products

Medical Devices

Food supply

Cosmetics

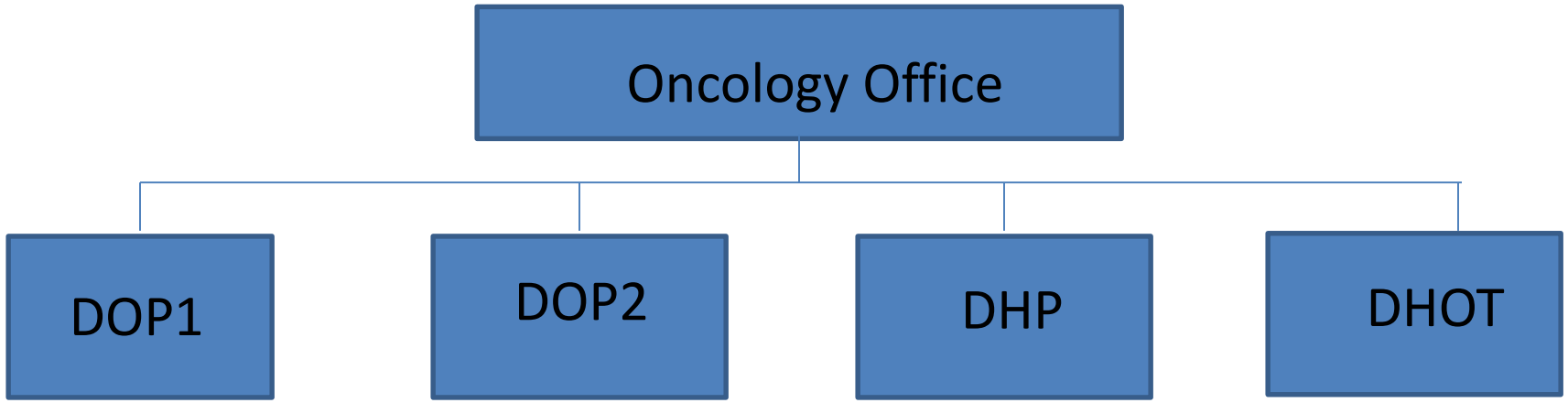
Radiation products

FDA Centers Active in Oncology

- **Center for Drugs Evaluation and Research**
  - Drugs – small molecules
  - Biologics – monoclonal antibodies, therapeutic proteins, cytokines
- **Center for Biologics Evaluation and Research**
  - Cellular and gene therapies, oncoloytic viruses, therapeutic vaccines
- **Center for Devices and Radiological Health**
  - Devices, including companion diagnostics, Radiologics

Office of Hematology and Oncology

- **Disease-specific structure**



- Breast Cancer
- Gynecologic Cancer
- GU Malignancies

- Thoracic - Head and Neck
- Gastrointestinal
- Melanoma-Sarcoma
- Pediatric-Neuroendocrine-Rare Tumors

- Benign Heme
- Lymphomas
- Leukemias
- Transplant

- Toxicologists supporting each clinical division

Oncology Center of Excellence

- FDA Inter-center Institute as Part of 21st Century Cures Act
- Integrated approach to clinical evaluation of cancer products
- Leverages combined skills of regulatory scientists and reviewers from the 3 key centers who review cancer products

Safety and Efficacy Requirements: Drugs and Biologics

- **FD&C Act "Safe and Effective"**
  - Adequate and well-controlled investigations (typically 2 or more trials)
  - Experts qualified to evaluate effectiveness of the drug
  - Reach a conclusion that the drug will have the effect it purports
- **PHS Act "Safe Pure and Potent"**
  - FDA Modernization Act – Minimize differences in review and approval between drugs and biologics
- For all intents and purposes, Safety and Efficacy of Drugs and Biologics use a similar evidentiary framework

Regular Approval

- **Substantial Evidence of Safety And Efficacy**
  - Adequate and Well-controlled Clinical Trials
- **Direct Evidence of Clinical Benefit**
  - Improvement in survival, physical functioning, tumor-related symptoms
- **Established Surrogate for Clinical Benefit**
- **No Comparative Efficacy Requirement for Regular Approval**

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Accelerated Approval

- **One of Four FDA Expedited Programs for Drugs - Serious or Life-Threatening Illnesses**
- **Meaningful Therapeutic Benefit “Over Existing Treatments”**
- **Based on “Surrogate” or Intermediate Endpoint Reasonably Likely to Predict Clinical Benefit**
- **Confirmatory Trials to Verify and Describe Clinical Benefit**

The strength of an efficacy endpoint rests in

- what is being measured (endpoint selection),
- how it's being measured (measurement characteristics) and
- how much an effect we are witnessing (magnitude of effect)

Efficacy Endpoints: Categories

Direct Measures of Clinical Benefit

- **Endpoints Directly Measure How a Patient "Feels, Functions or Survives"**
  - **Overall survival (OS); measures of symptoms or function**

Surrogate Measures Predict (?) Clinical Benefit

- **Endpoints Not Direct Measures of Clinical Benefit**
- **Commonly Radiographic Measurements of Tumor Burden Changes (Specified Thresholds)**
  - **Time-dependent–e.g., progression-free survival (PFS)**
  - **Time-independent–e.g., objective response rate (ORR)**

FDA Guidance For Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Direct Measures of Efficacy: Overall Survival- Gold Standard

Strengths:

- Direct measure of benefit
- Least prone to bias, no interpretation of the event (death yes or no)
- Event timing (date of death) typically known to the day
- Includes information regarding safety
- Deaths due to drug toxicity are part of the endpoint

Limitations

- Last Event in a Disease's Natural History = Longer and Larger Trial
- Requires randomized controlled trial
- Comparison with historical control limited (differing populations, differing standards of care, etc.)
- May be confounded by cross-over (depending on magnitude of effect) and subsequent therapies if given unequally between arms

Meaningful Clinical benefit of a survival advantage is still based on toxicity of drug and **magnitude** of OS result

Surrogate Endpoints: Radiographic Evidence of Anti-Tumor Effect

Response Rate (RR)

- Shrinking a tumor
- ***Critically important: tumor location, number of CRs, duration of response***

Time to Progression (TTP), Progression Free Survival (PFS)

- Time from Randomization to Growth of Tumor past predefined threshold
- PFS counts death as a progression event and is preferred

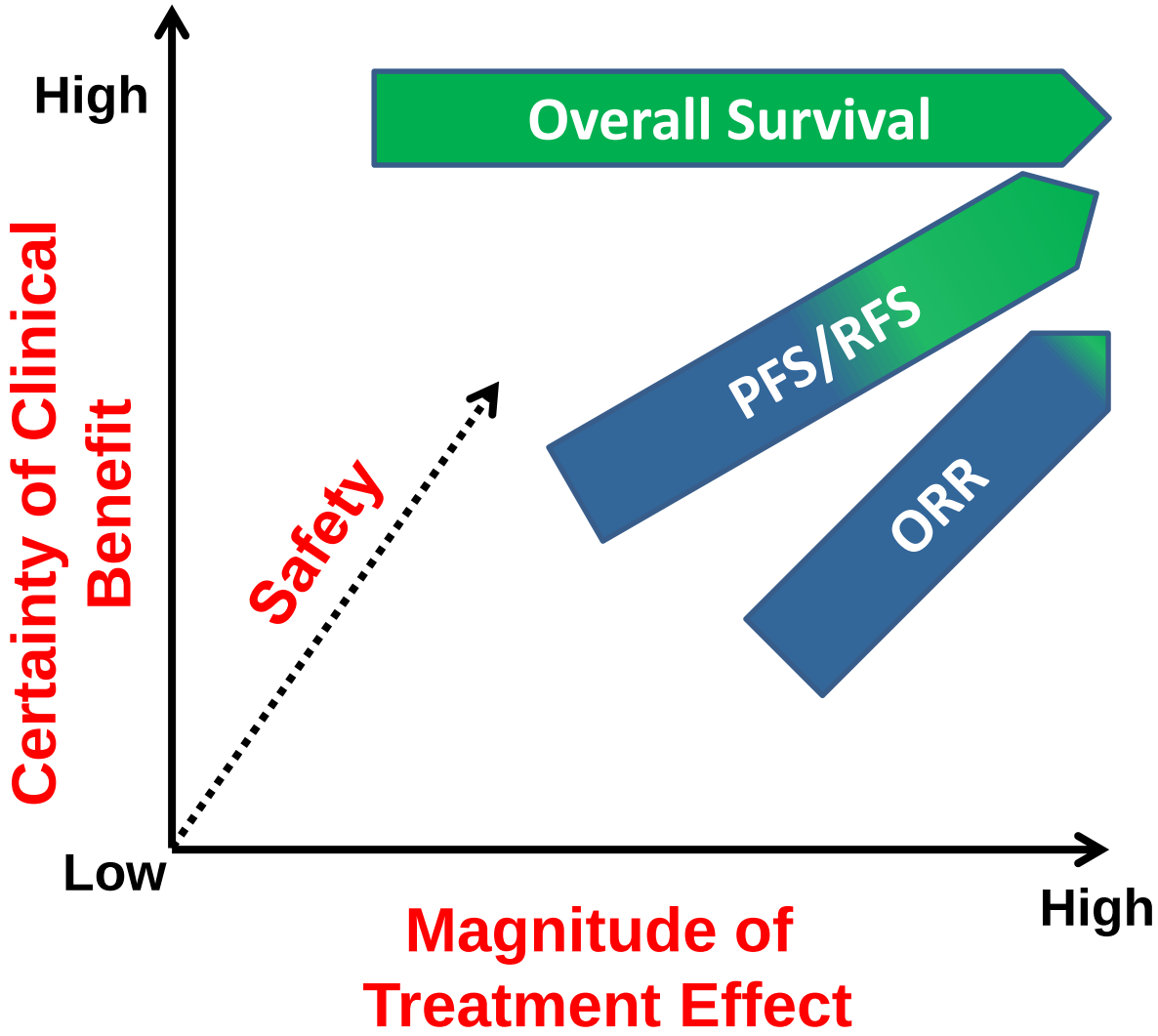
Radiographic Endpoints Strengths

- Earlier events than survival = smaller, shorter trial
- Radiographs can be captured and stored to verify the event
- Not confounded by cross over or subsequent therapies (Event occurs prior to crossover)

Radiographic Endpoints Limitations

- Uncertainty regarding Clinical Benefit: Will a given change in an radiographic finding predict true clinical benefit?
- Missing, incomplete, infrequent or uneven assessments
- Difficult to measure disease (ill-defined lesions), Bone metastases, peritoneal carcinomatosis

Efficacy Endpoints and Approval: Magnitude of Treatment Effect



Approval Pathway:

Accelerated

Regular

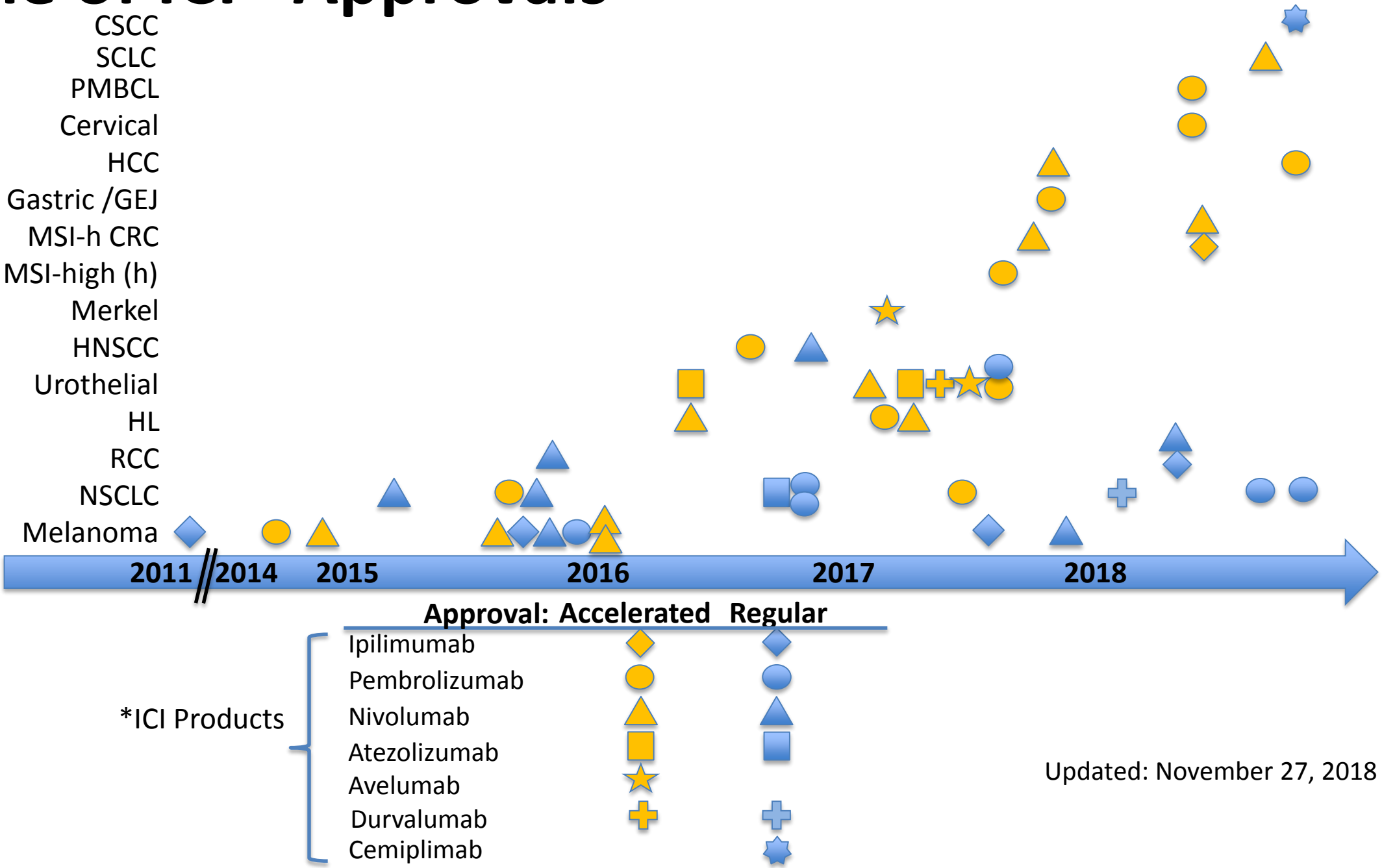
FDA Expedited Programs for Serious Conditions - Drugs

- **Accelerated Approval**
- **Priority Review Designation**
- **Breakthrough Therapy Designation**
- **Fast Track Designation**

All consider the available therapies to treat the serious condition for the disease context to determine whether there is an unmet medical need, or if the new therapy appears to provide an improvement or advantage over available therapies.

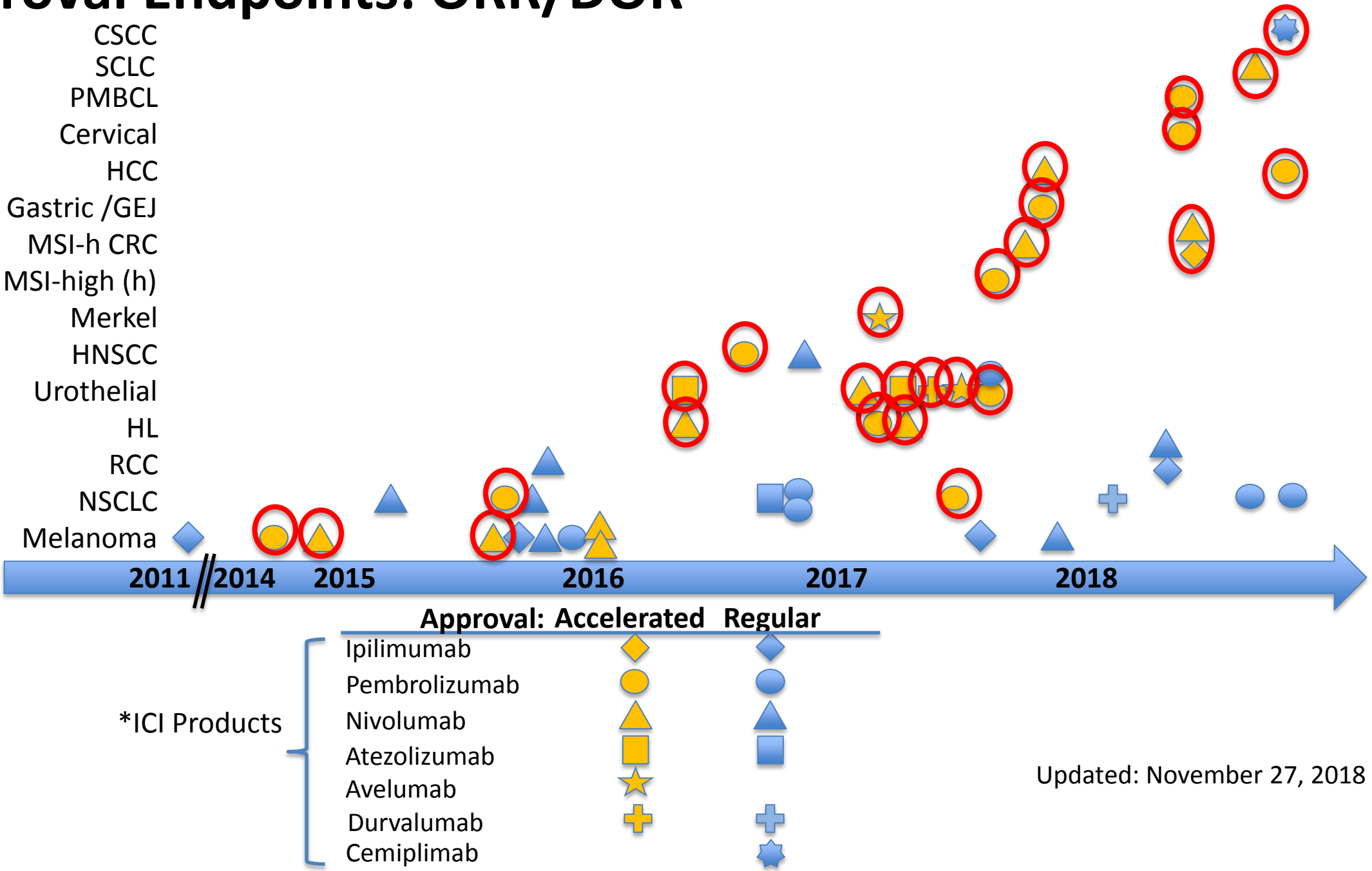
FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

Timeline of ICI* Approvals



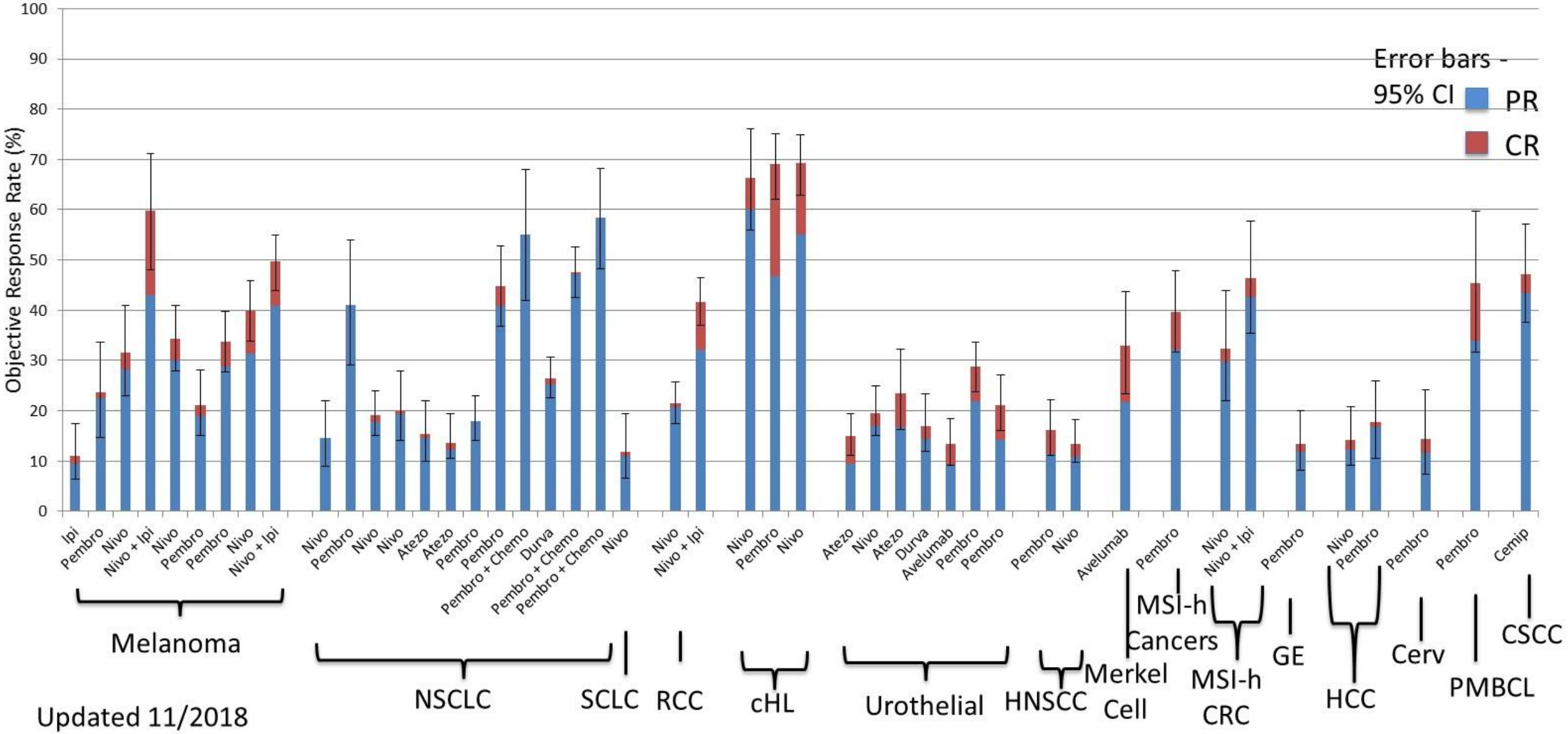
Updated: November 27, 2018

ICI* Approval Endpoints: ORR/DOR



Updated: November 27, 2018

ORR by Tumor Type – ICI Approvals



Striking the Balance

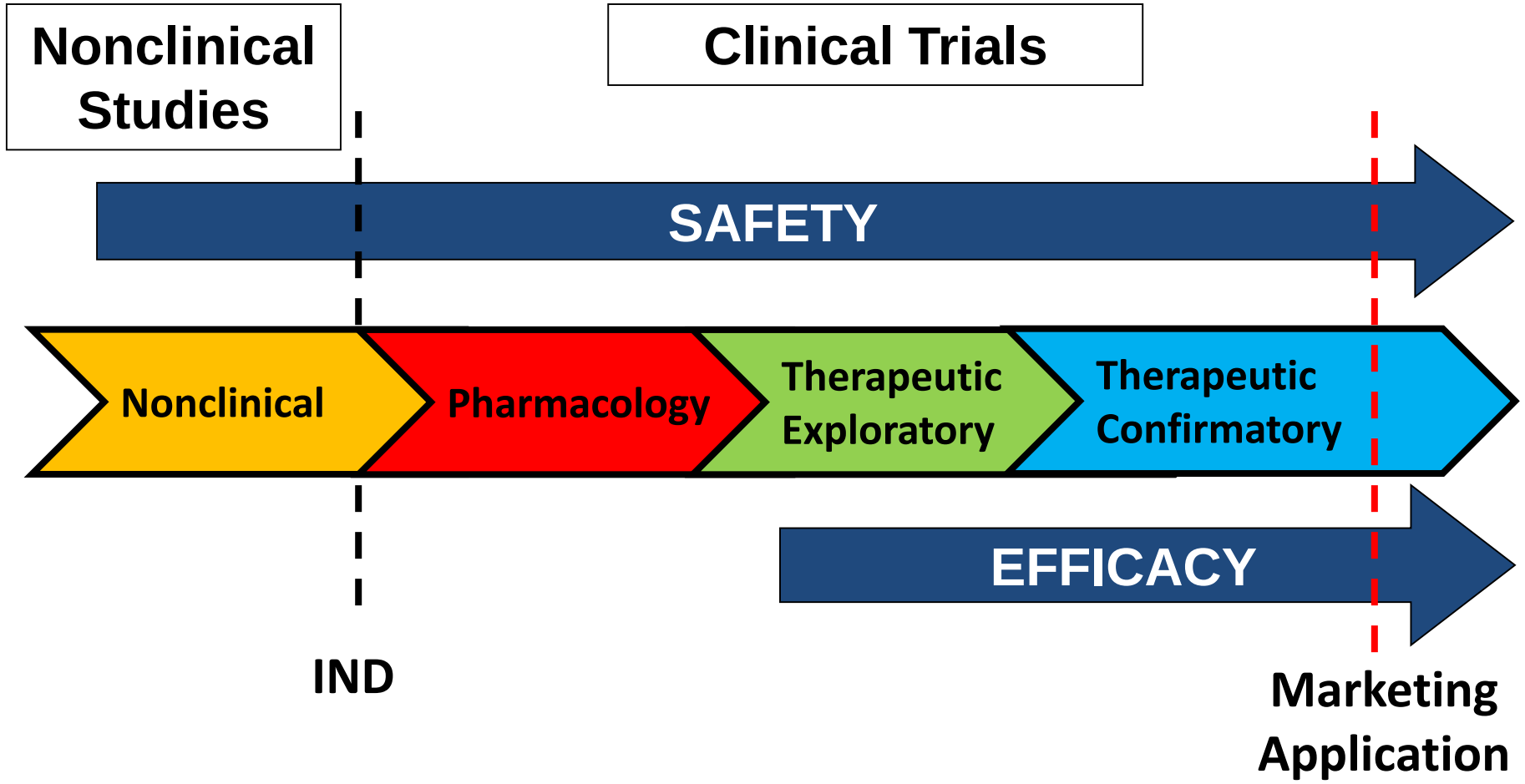
Flexible, Efficient, Interactive

Consistent, Thorough, Independent

Outline

- Background
  - FDA Oncology
  - Expedited Programs
  - Endpoints
- Evolving Drug Development Paradigm in Oncology
  - Expansion Cohorts – FIH Trials
  - Master Protocols
  - Tissue Agnostic Indications

Phased Drug Development Paradigm



www.fda.gov

Phases of Investigation - 21 CFR 312.21

- Phase 1 (20-80 patients)
  - Metabolism and pharmacologic actions in humans
  - Side effects with increasing doses
- Phase 2 (relatively small #, ≤ several hundred)
  - Includes controlled studies to evaluate effectiveness of the drug for a particular indication(s) in patients with disease or condition under study
  - Short term side effects and risks associated with drug
- Phase 3 (several hundred to thousands)
  - Performed after preliminary evidence suggests effectiveness
  - Gather additional information about effectiveness and safety to evaluate the overall benefit-risk relationship of the drug – adequate basis for physician labeling

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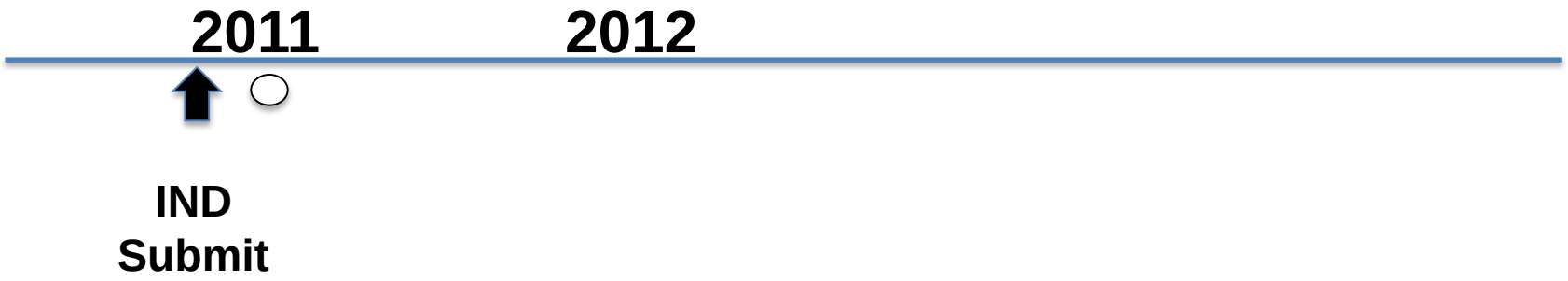
Evolving Drug Development Paradigm: Expansion Cohorts

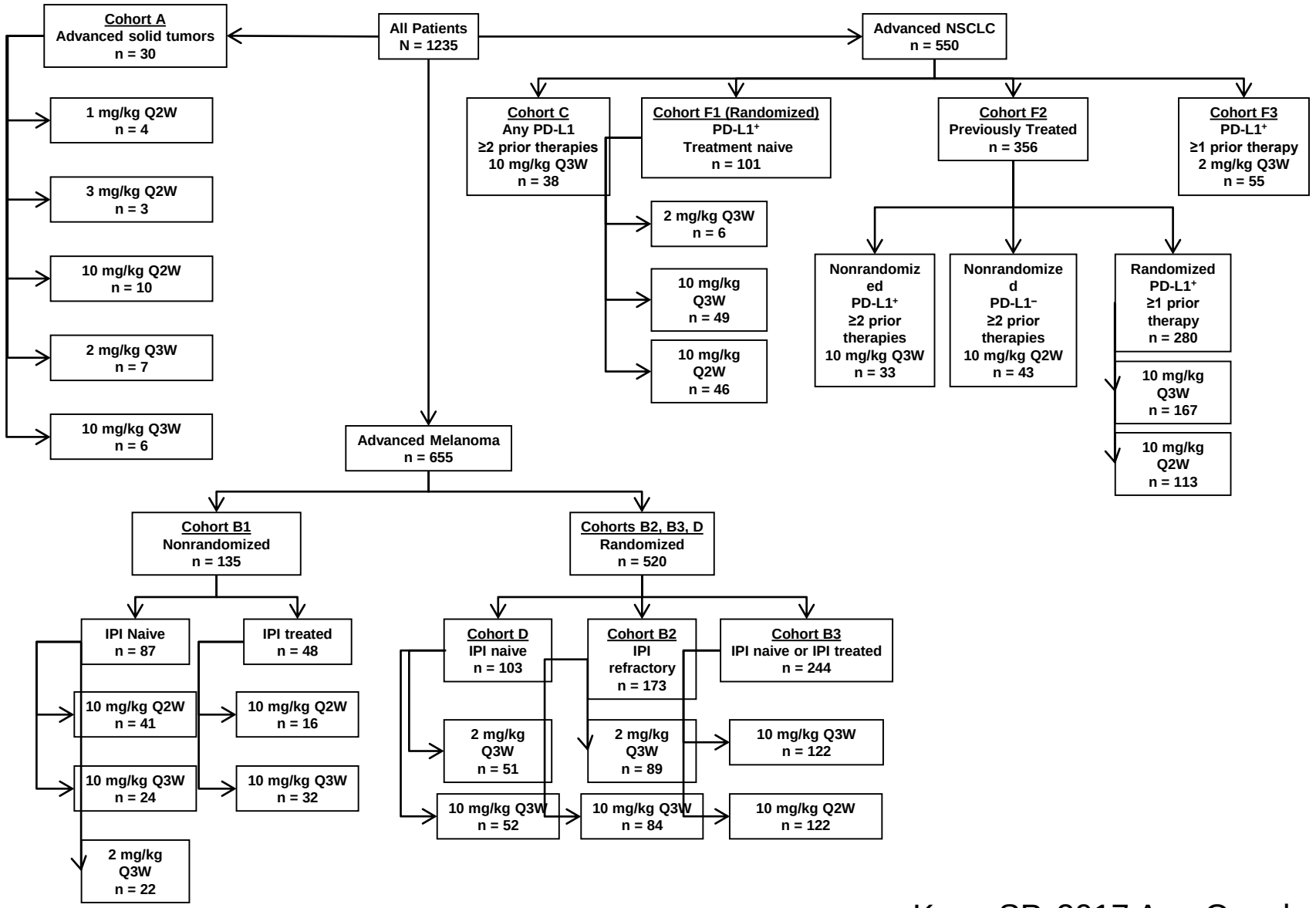
FIH Expansion Cohorts

- Single protocol with an **initial dose-escalation phase** that also contains 3 or more additional cohorts with cohort specific objectives
  - Anti-tumor activity in specific cancer types
  - Assessment of pediatric or elderly or pts with organ impairment, impact of food, DDI
  - Evaluation of alternative doses or schedules
  - Establishment of dose/schedule in combination with another drug
  - Evaluation of predictive value of potential biomarker
  - Evaluate CMC product changes

MK-3475: PN001 Trial

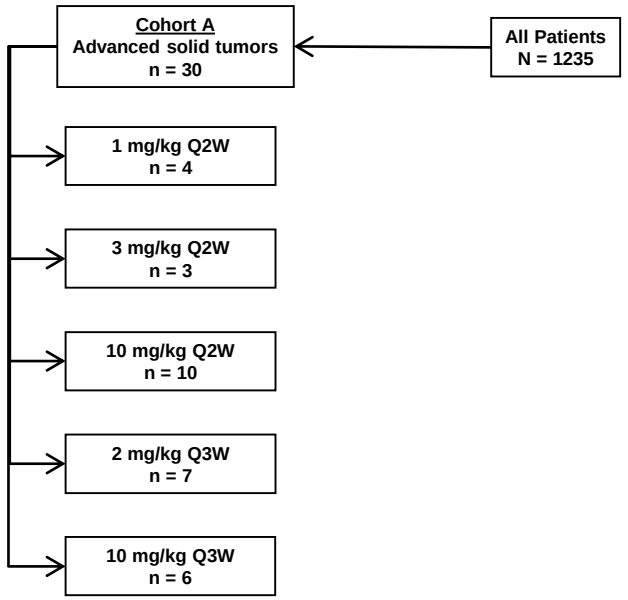


PN-001 Treatment Cohorts



Kang SP, 2017 Ann Oncol

PN001 Trial: Treatment Cohorts



MK-3475: PN001 Trial

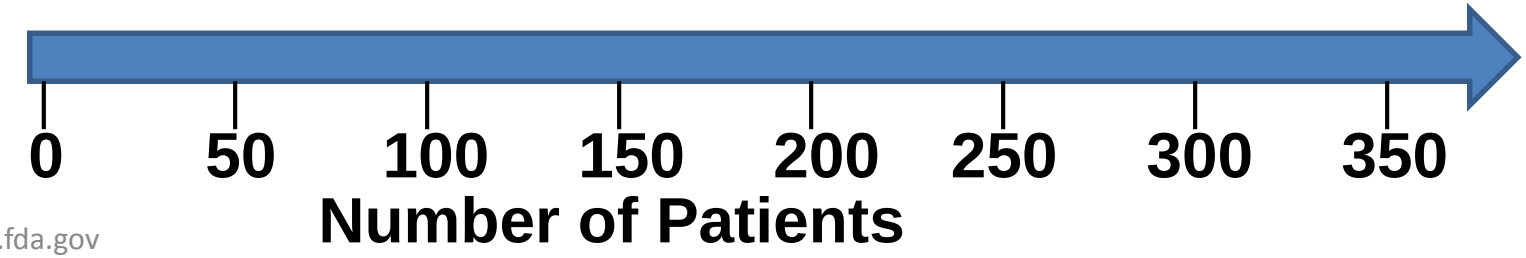
Amendment

1

Part A

Part B

32



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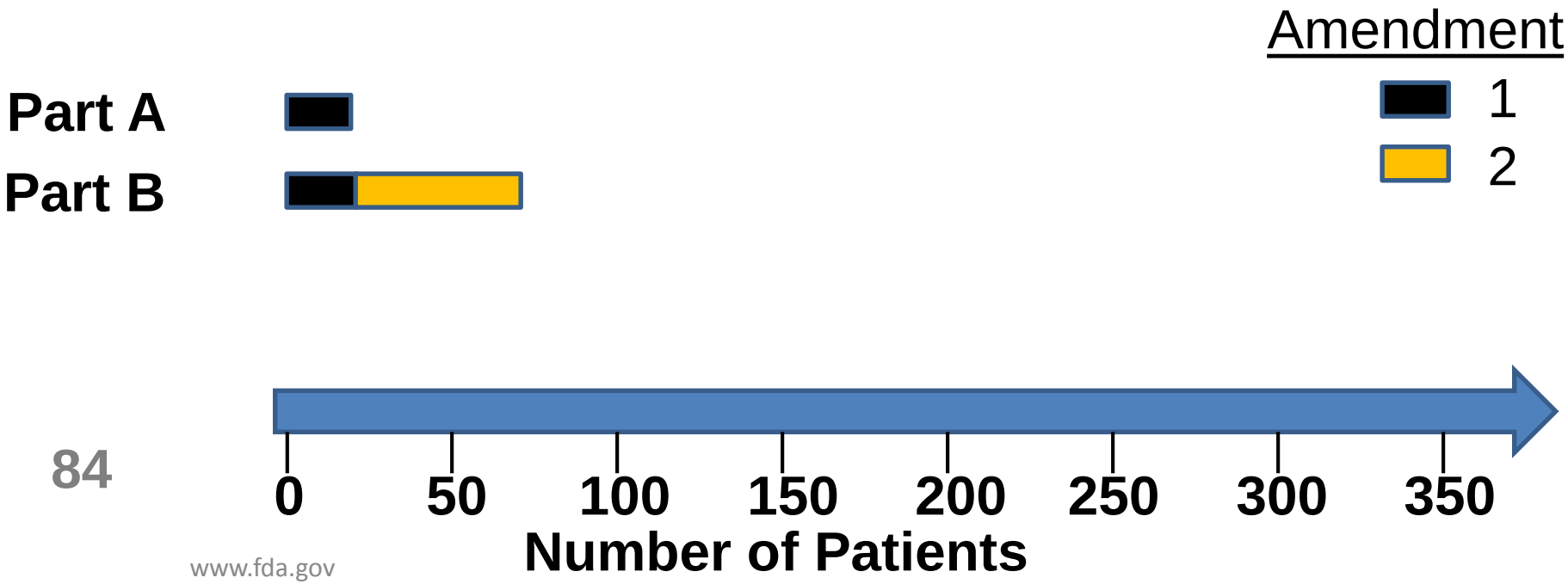

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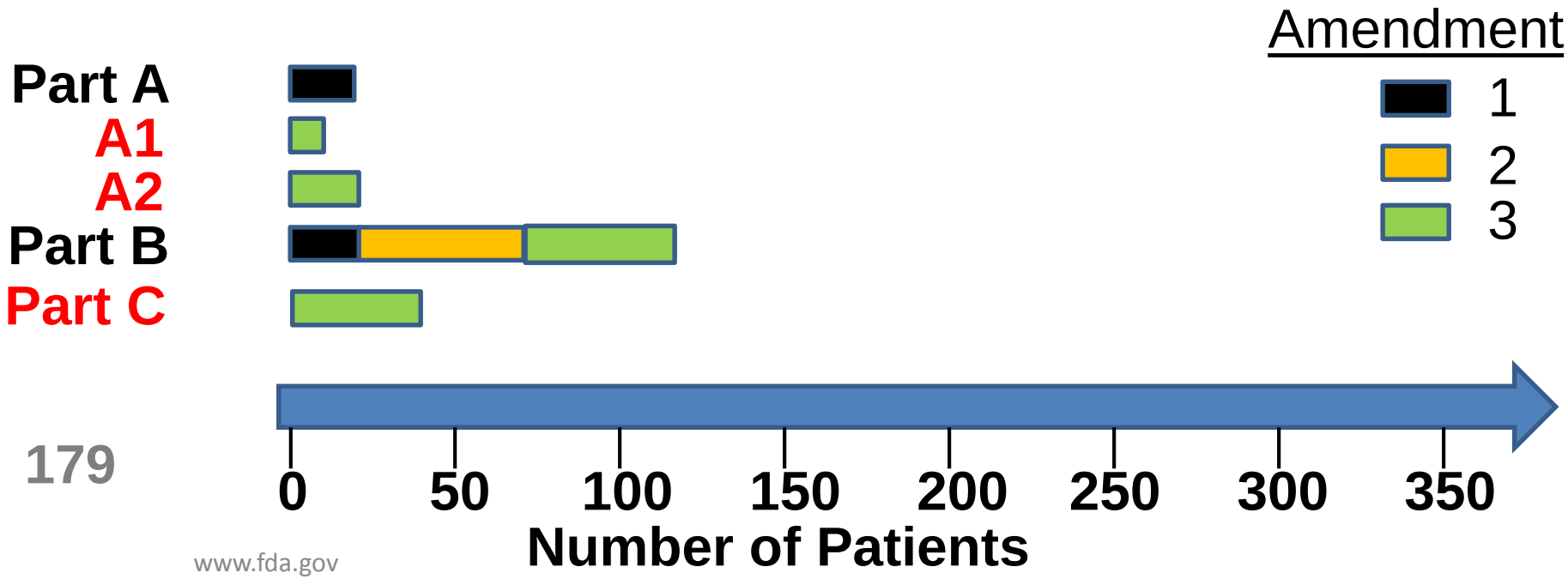

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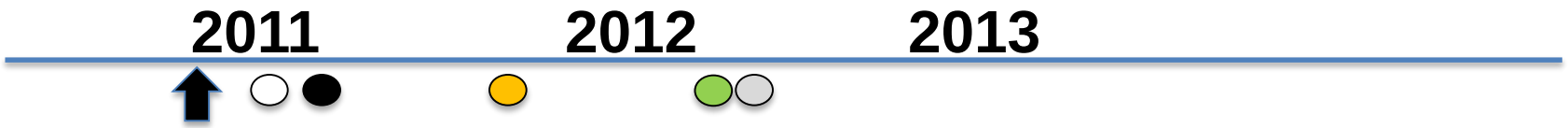

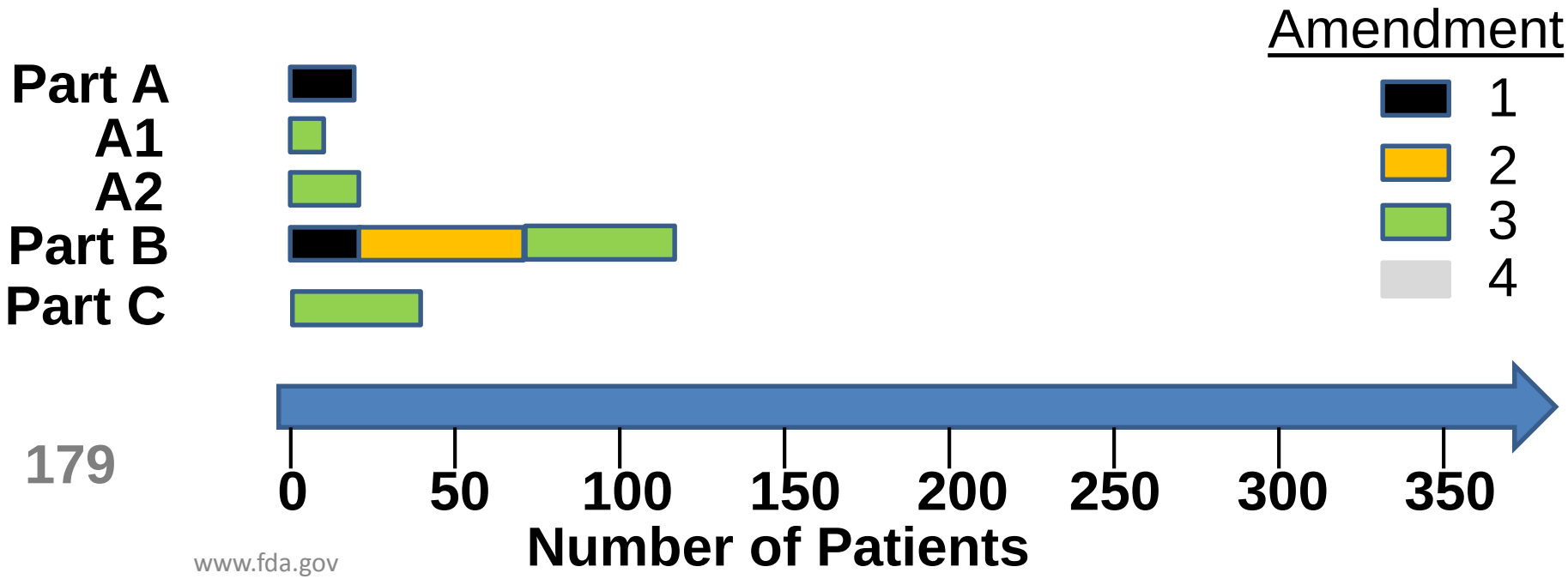

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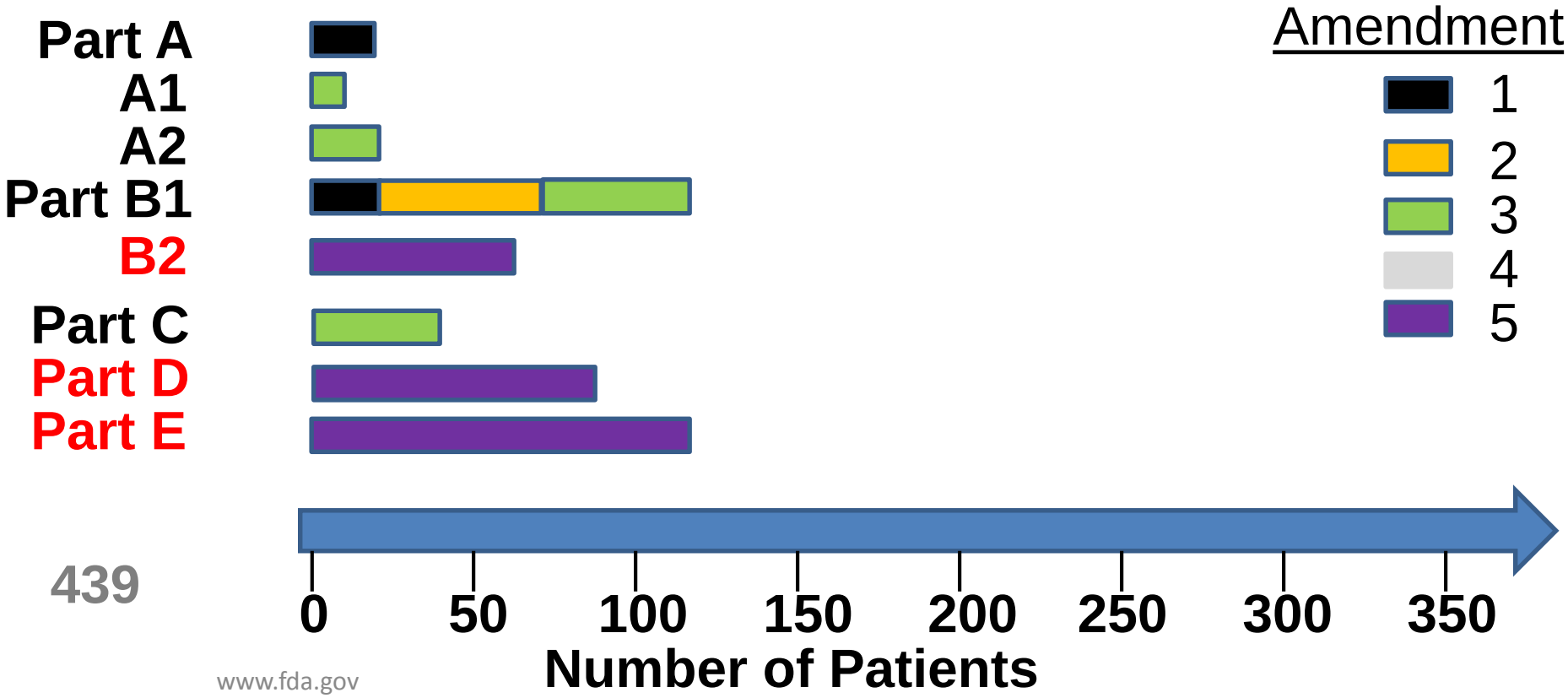

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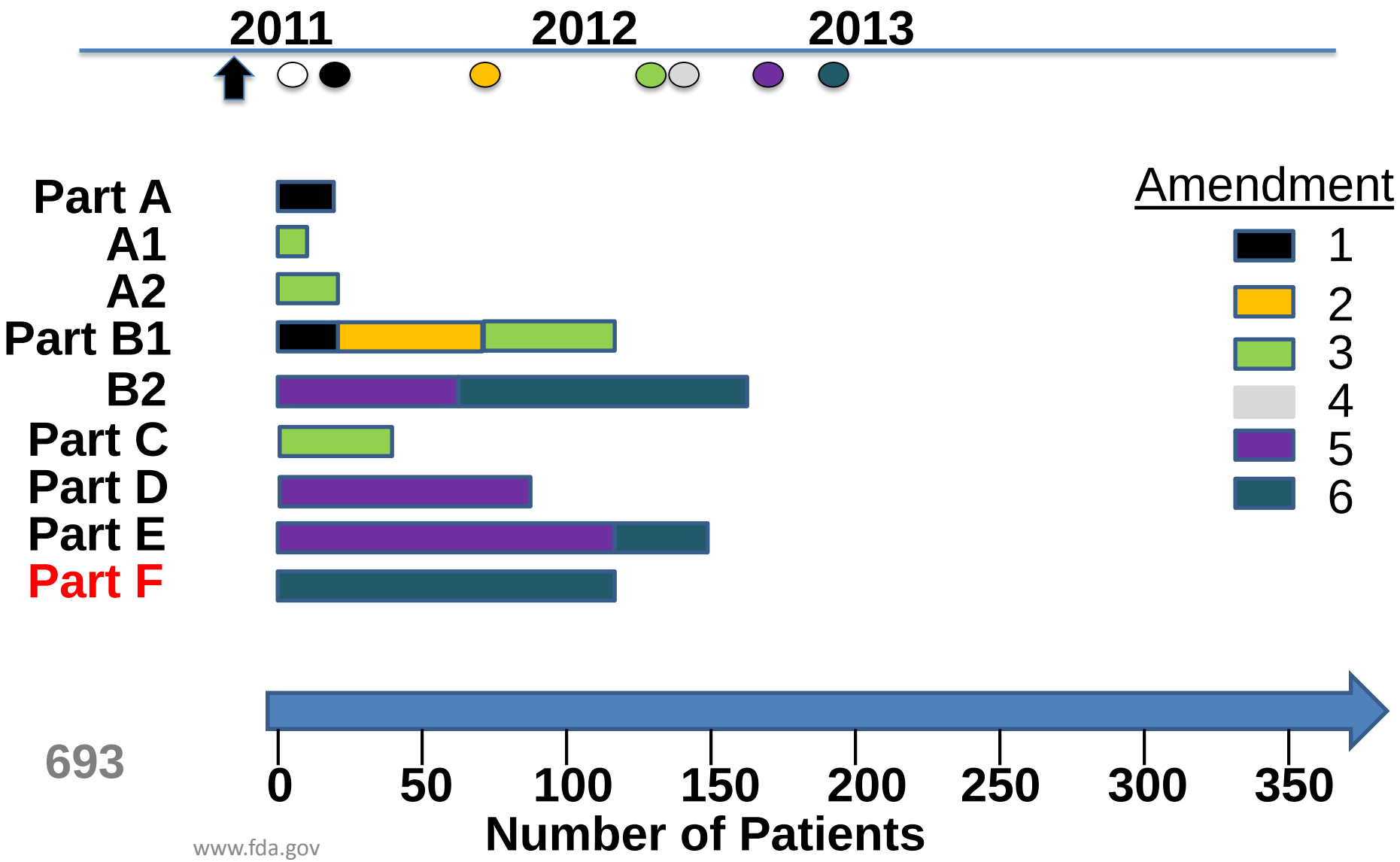

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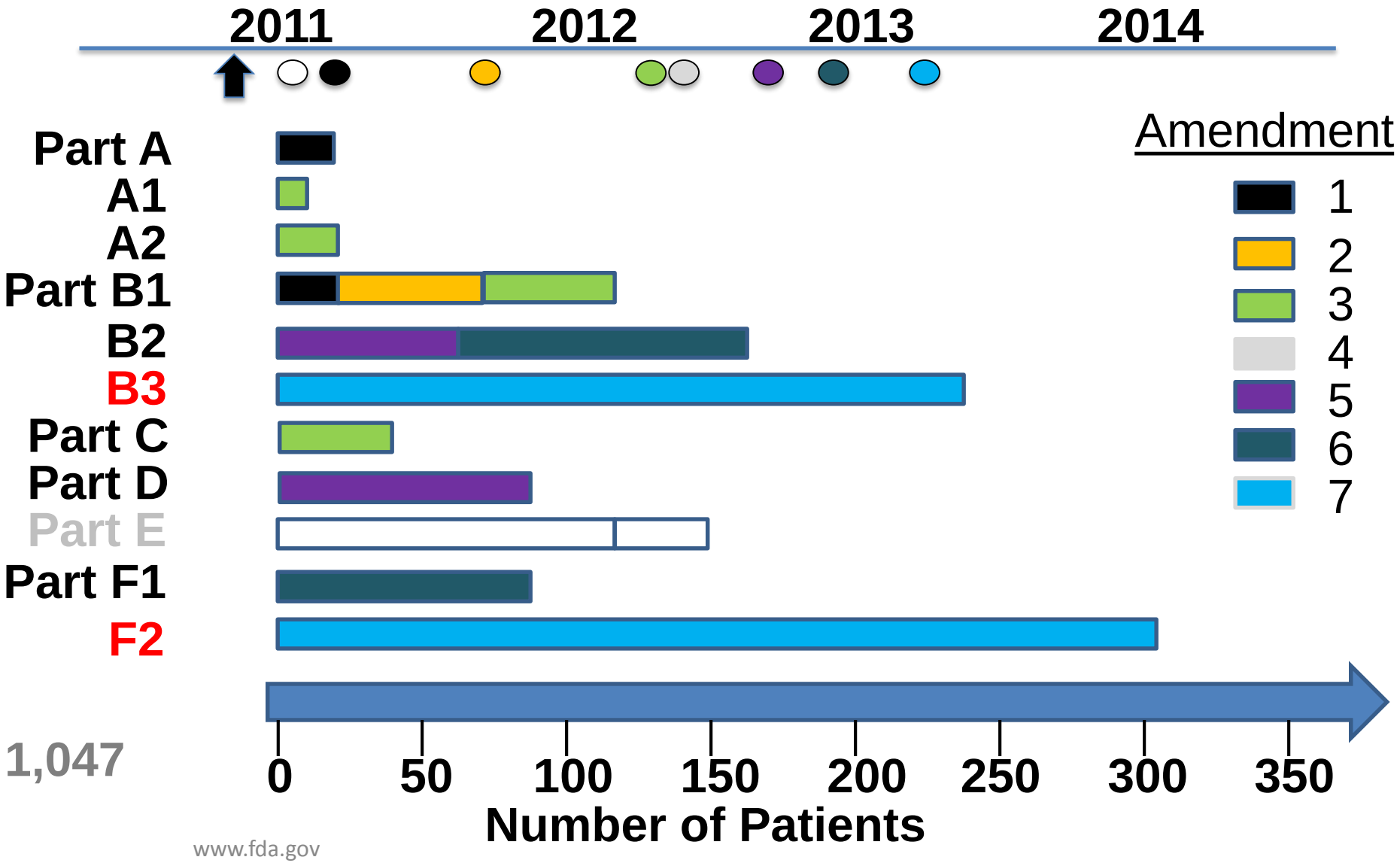

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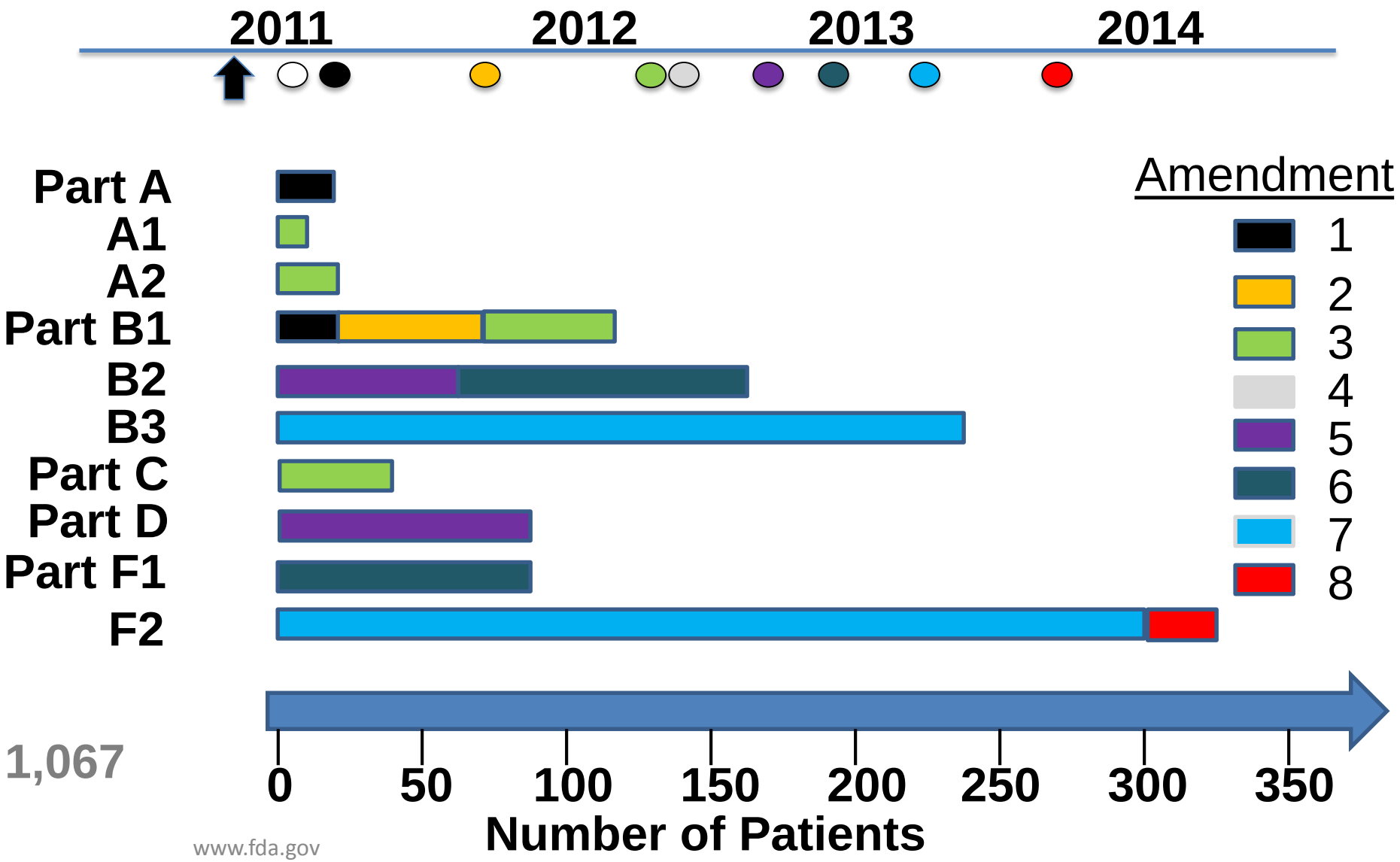

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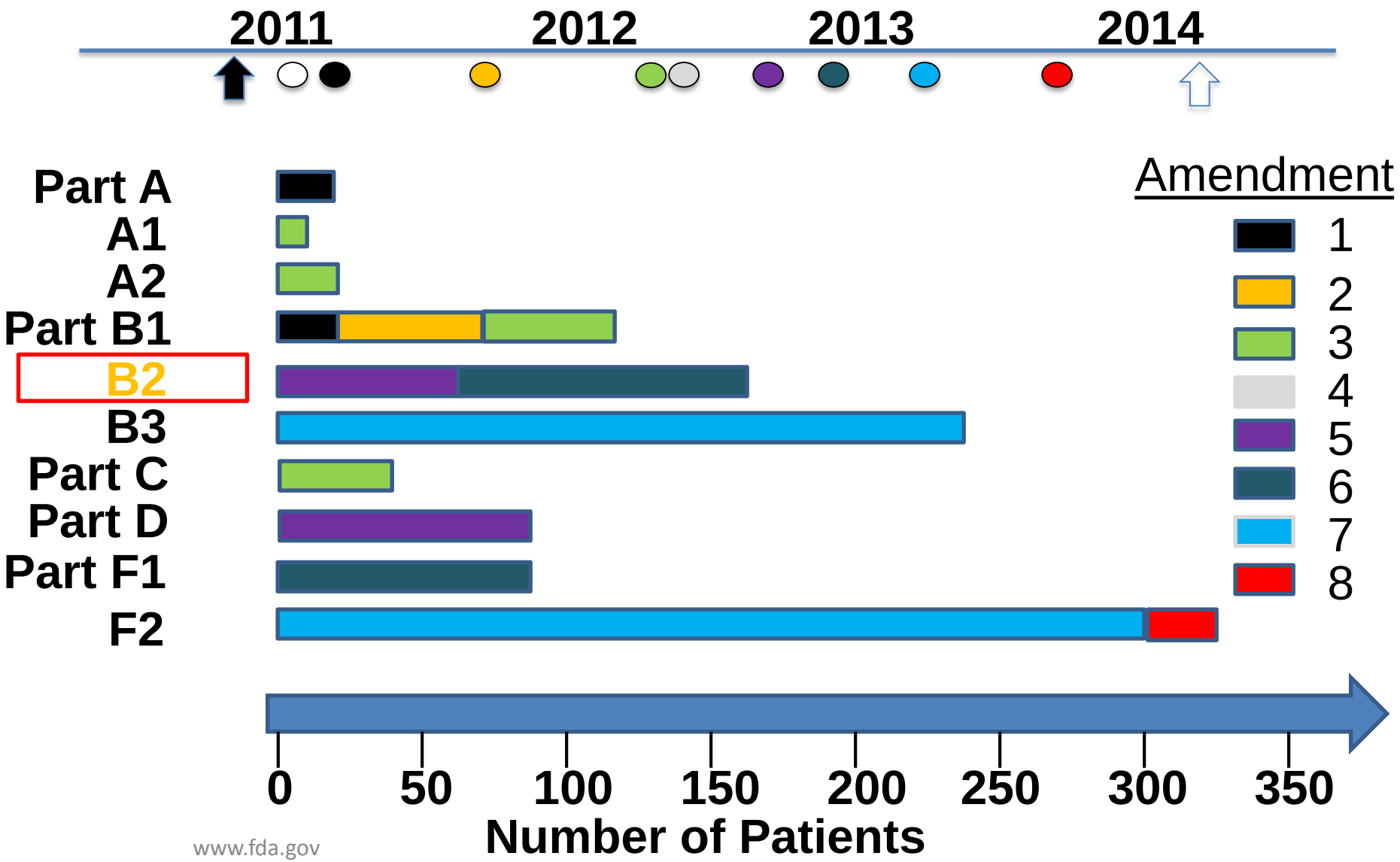

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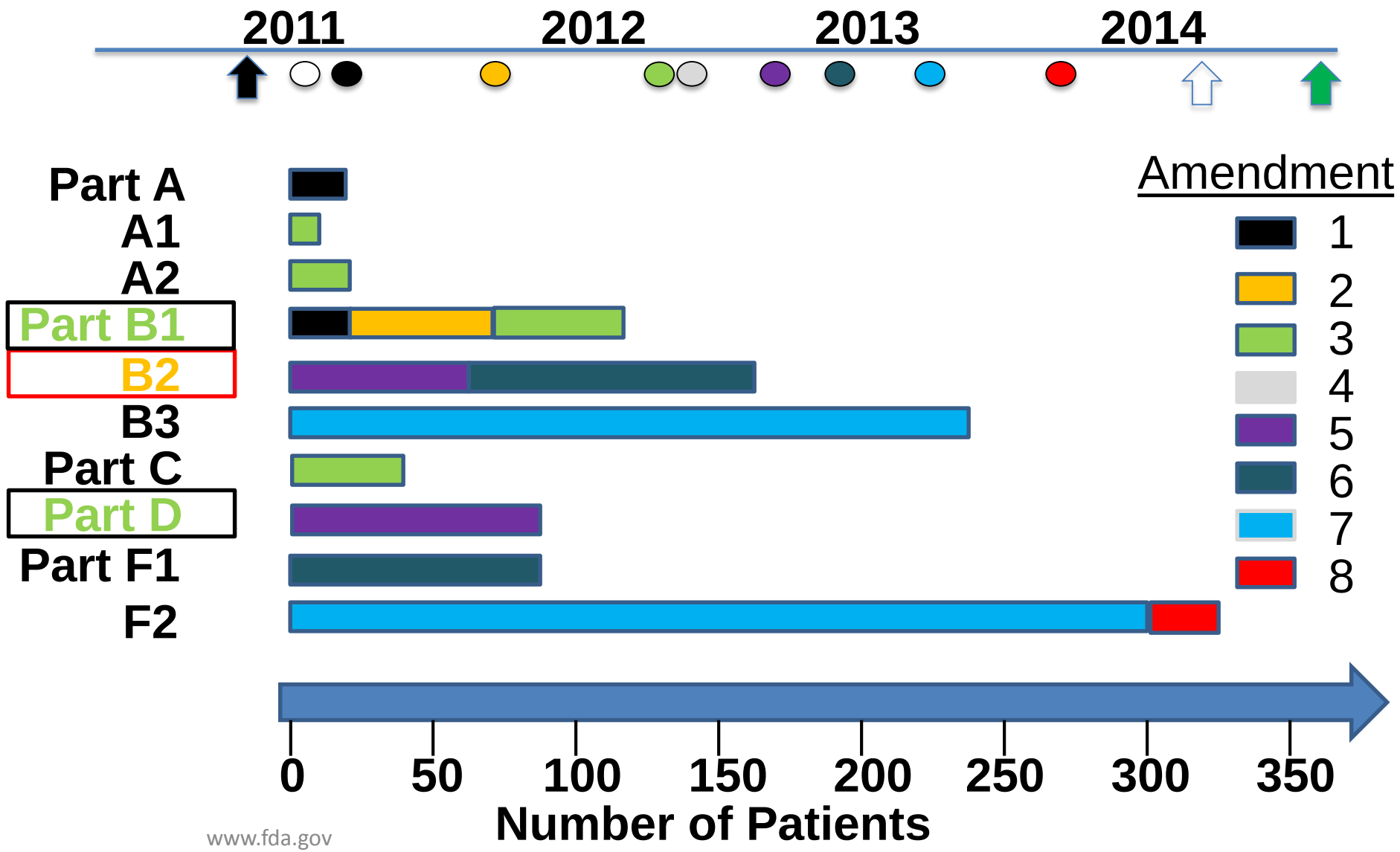

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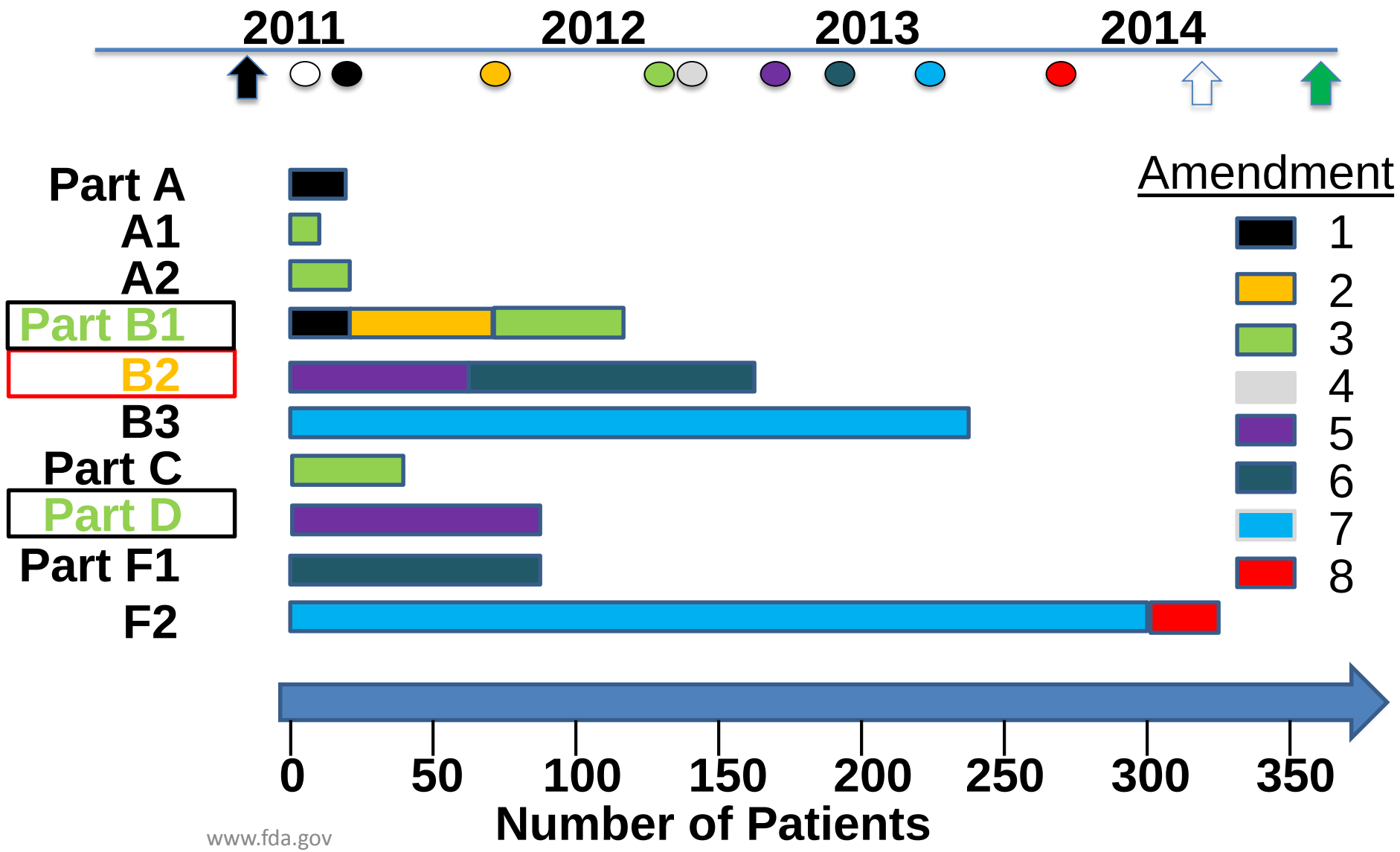
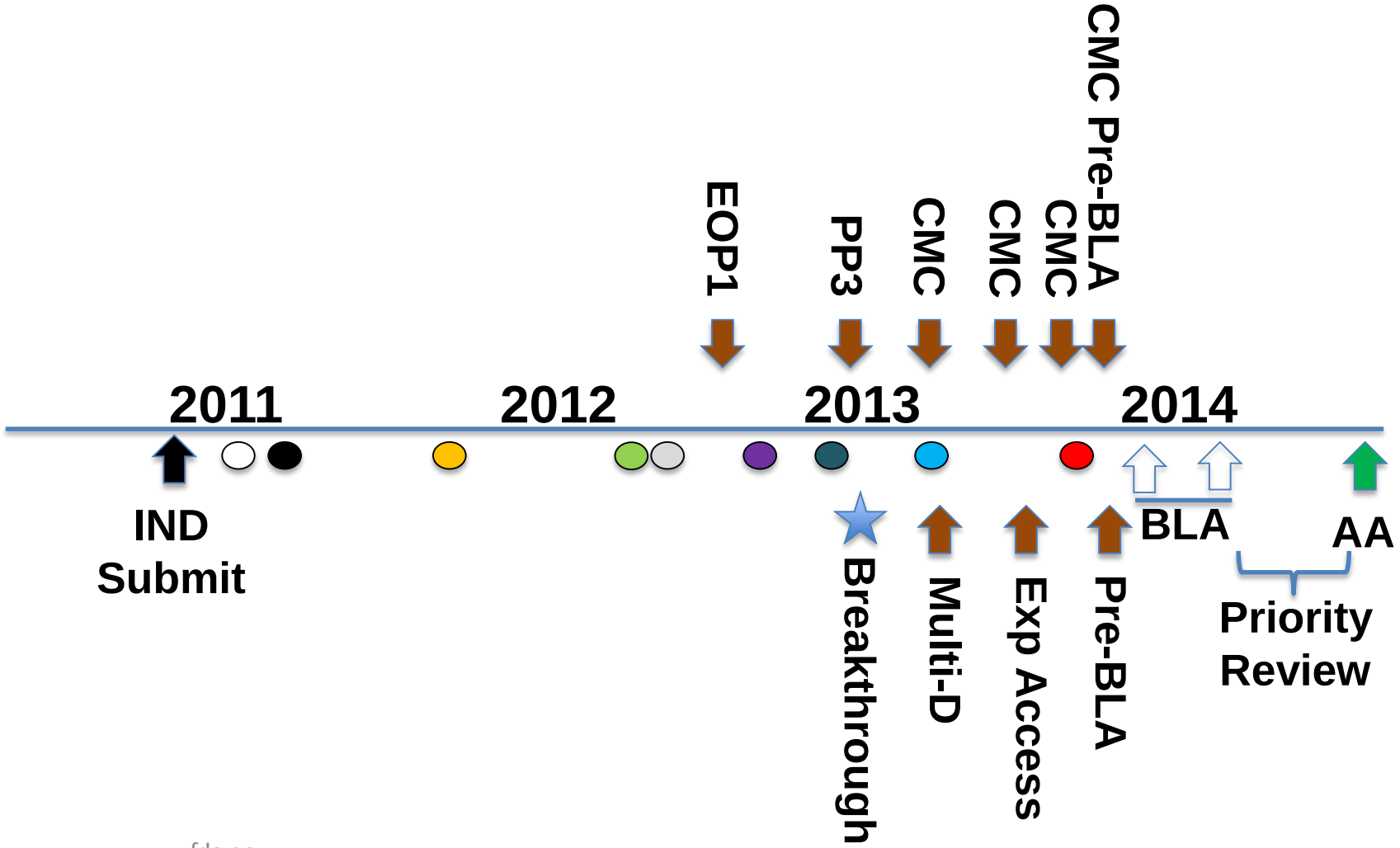
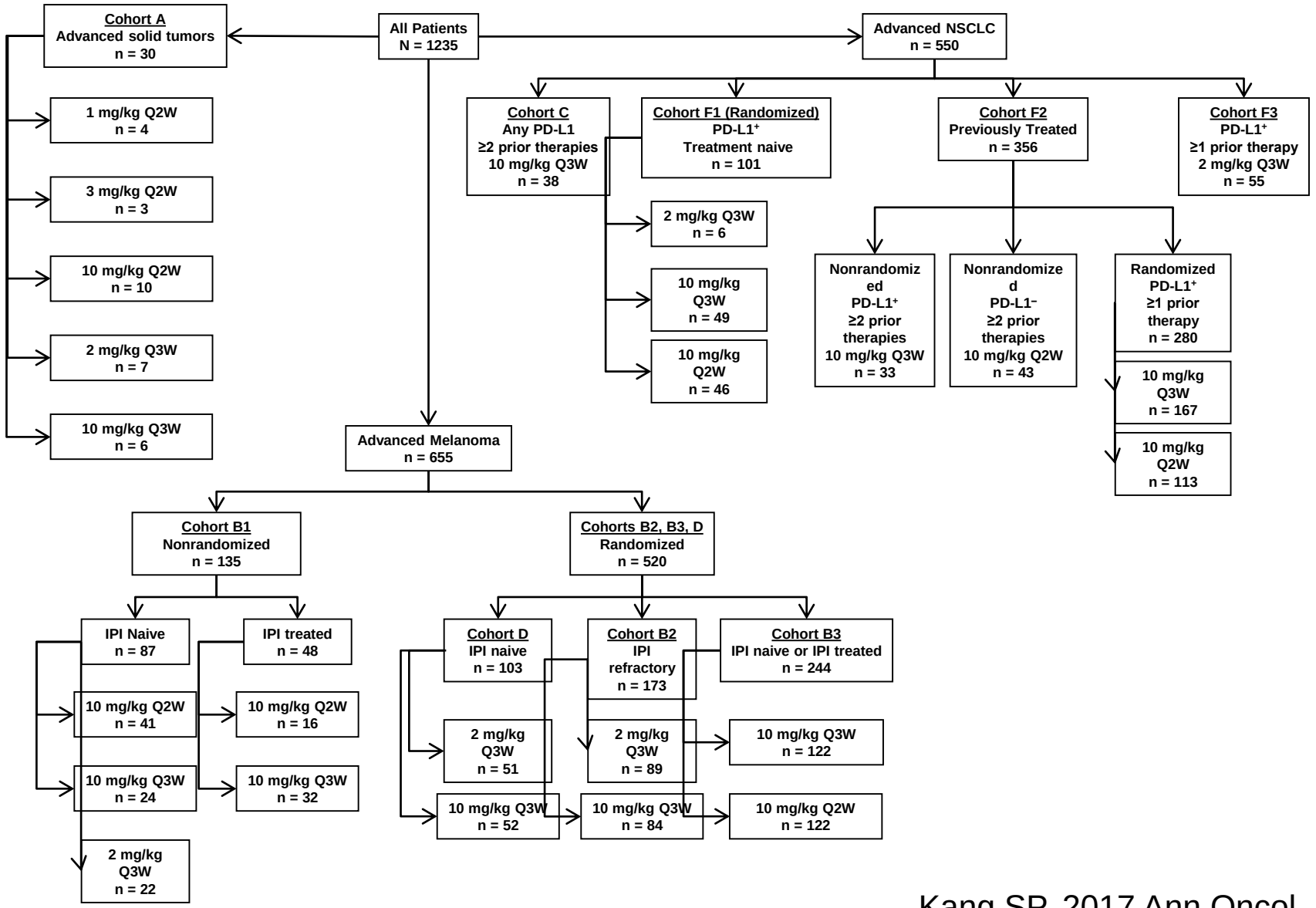


MK-3475: PN001 Trial and Selected Melanoma Development Milestones



KN-001 Treatment Cohorts



Kang SP, 2017 Ann Oncol

Approvals based on Expansion Cohorts from FIH

- Pembrolizumab (Keynote – 001)
  - Ipi refractory melanoma- Accelerated Approval
  - mNSCLC Accelerated Approval PD-L1 $\geq$50%
- Crizotinib (Study A8081001)
  - ALK+ mNSCLC expansion cohort- Accelerated Approval
  - ROS1+ mNSCLC expansion cohort- Regular Approval
- Ceritinib (Ascend1)
  - ALK+ mNSCLC expansion cohort- Accelerated Approval
- Avelumab (JAVELIN Solid Tumor)
  - Urothelial Carcinoma- Accelerated Approval

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Evolving Drug Development Paradigm:

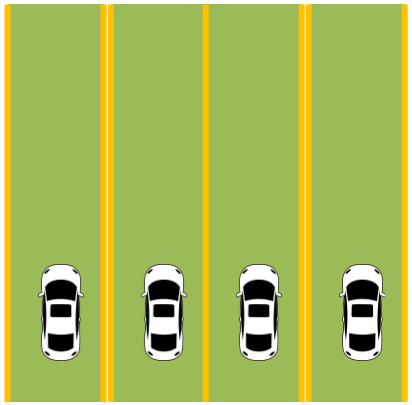
Master Protocols

Master Protocols

- Overarching protocol with multiple objectives that involve coordinated efforts to evaluate one or more investigational products in one or more patient populations within the overall trial structure. In general, the **RP2D** has been established for investigational agent(s)

Efficiencies with Master Protocols

OLD
1 Question = 1
Study = 1 Result



Build 1 Highway (Trial)
Drive 1 Car (Recruit)
Get to 1 Result
Dismantle the Highway

50% of study
costs to build trial
9-12 mos to start

Build Multi-Lanes (in one trial)
Drive Multiple (combos)
Get Multiple Results
Keep highways OPEN

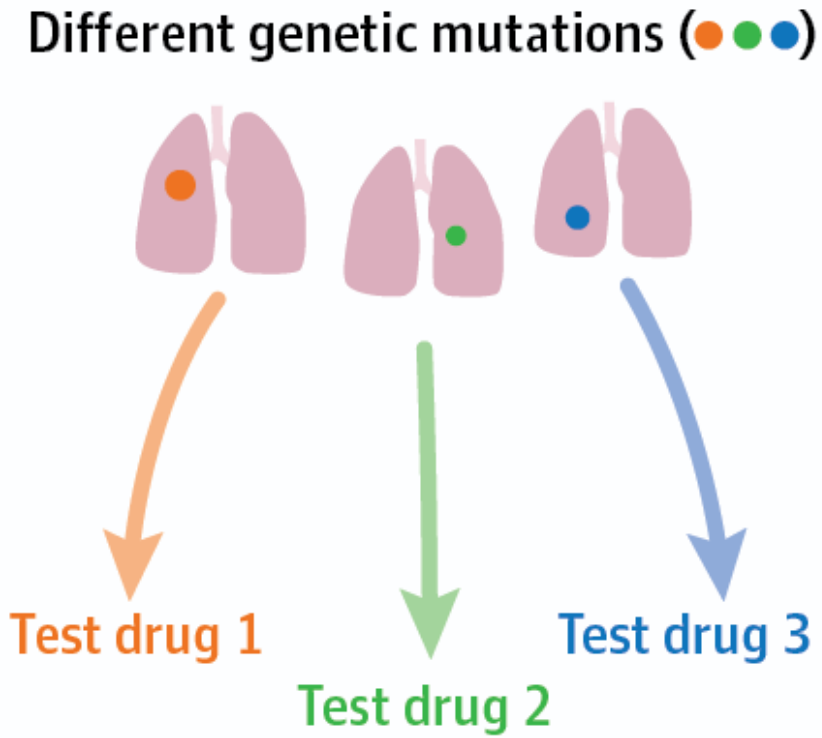
Aiman Shalabi, JPM 2018

Master Protocols: Umbrella Trials

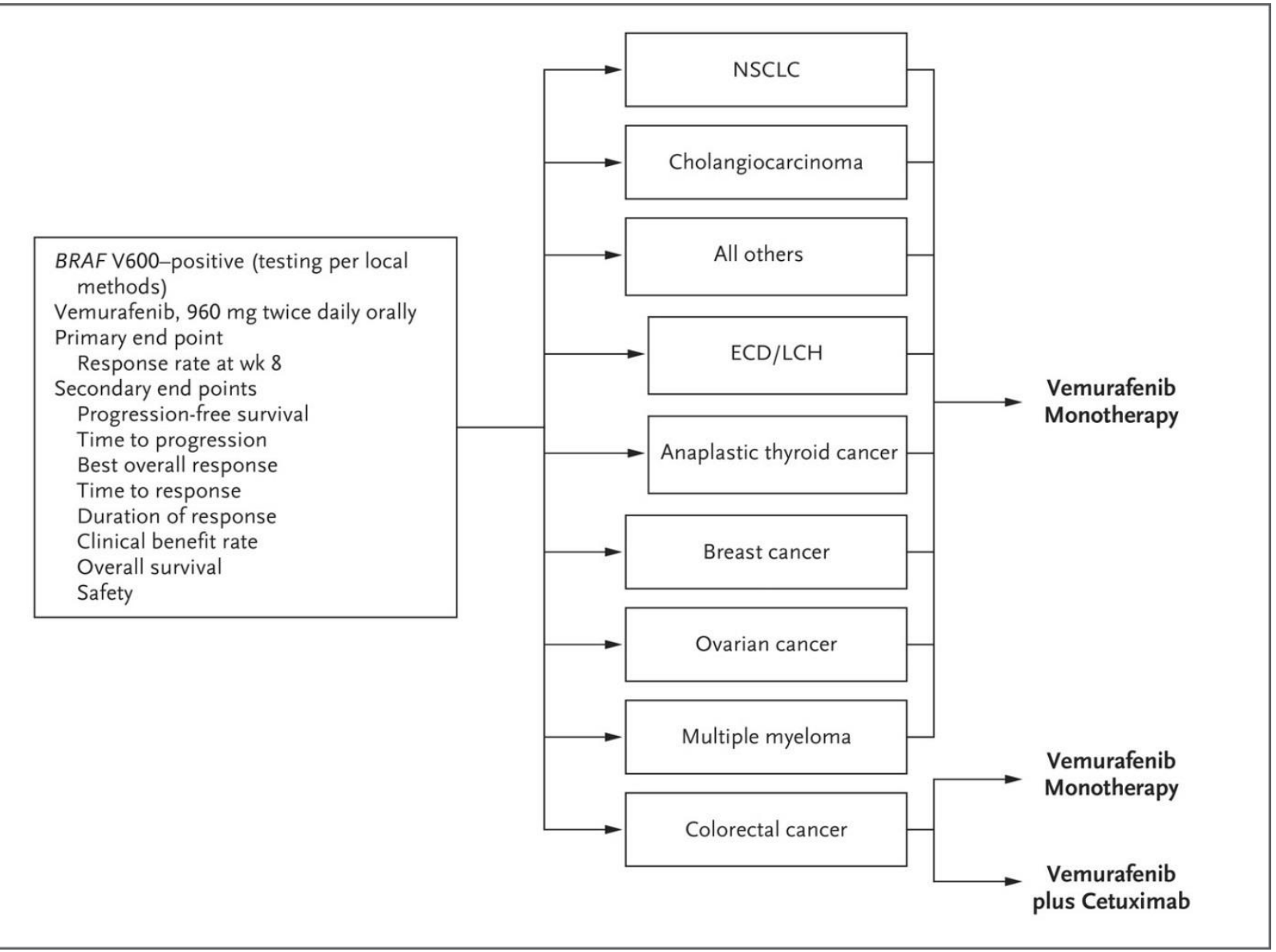
- **<u>One type of cancer</u>** with multiple drugs and predictive biomarkers

- Patients are matched based on biomarker analysis

- Examples
  - LUNG-MAP
  - BATTLE
  - I-SPY2



Master Protocols: Basket Trials

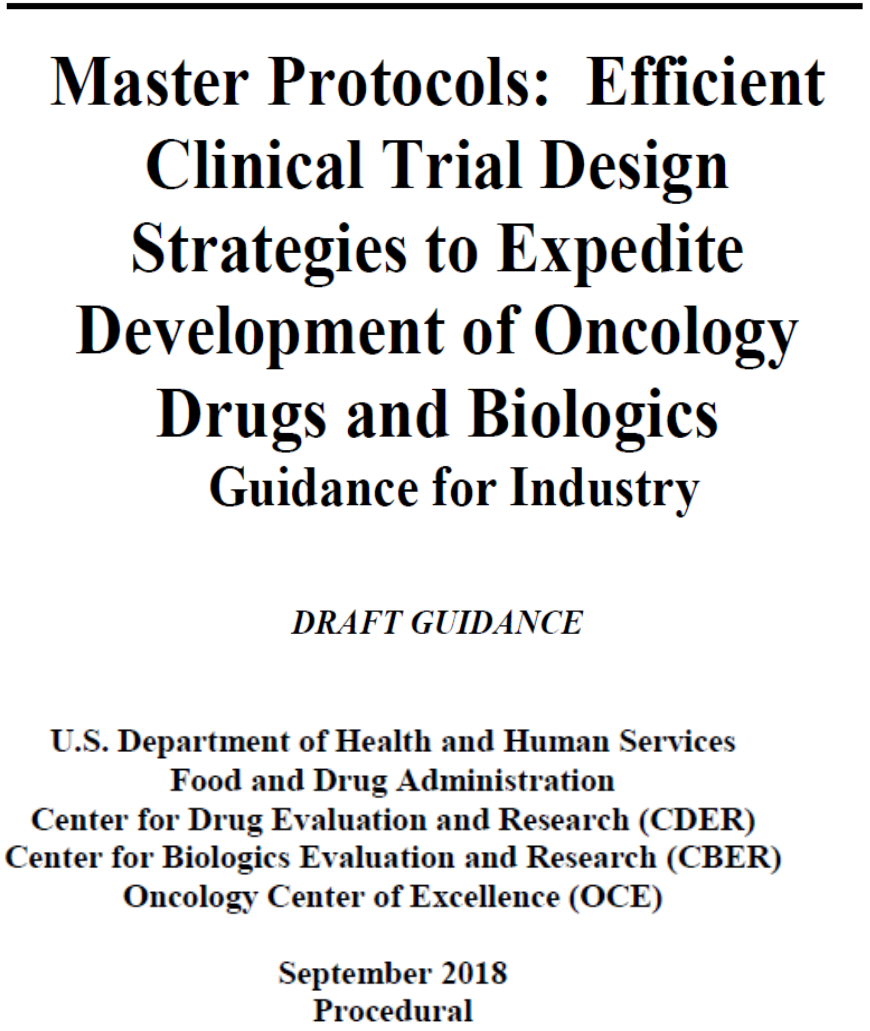


- **<u>Biomarker-driven approach</u>**: enroll patients across many different tumor types into discreet, biomarker defined baskets

  Examples:
  - VE-Match
  - NCI MATCH
  - ASCO TAPUR

Hyman DM et al, 2015, N Engl J Med

Draft Guidances on Master Protocols and Expansion Cohorts



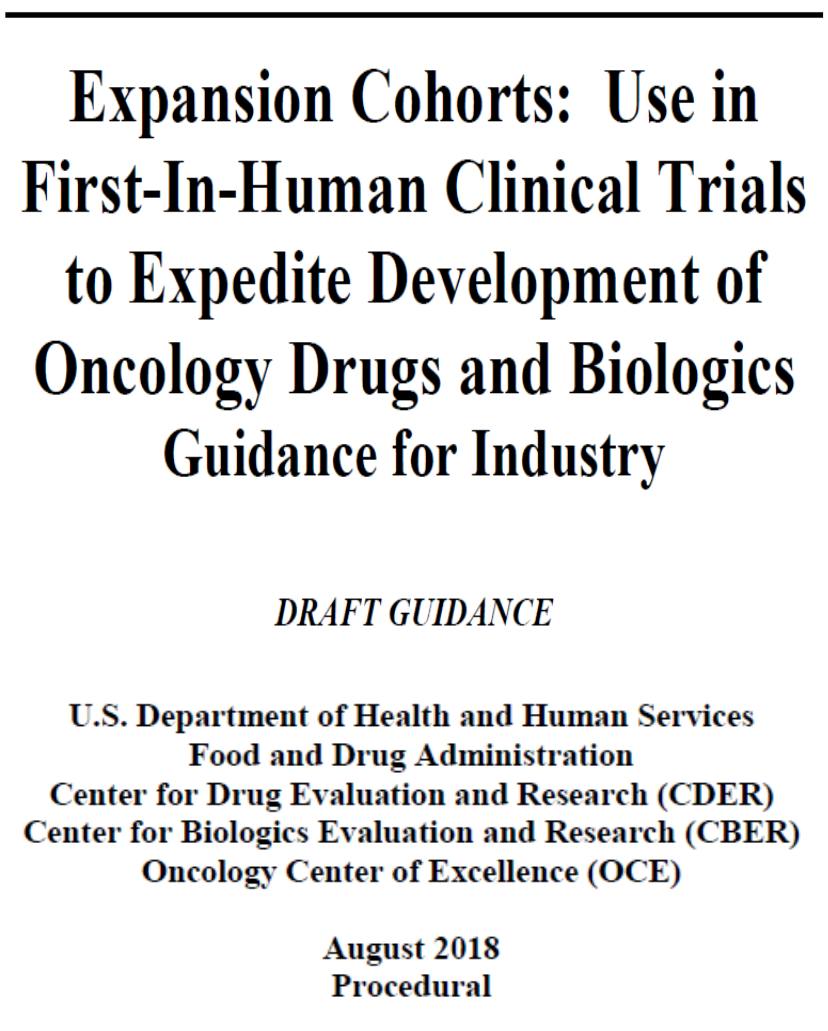
Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics

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)
Oncology Center of Excellence (OCE)

September 2018
Procedural



Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics

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)
Oncology Center of Excellence (OCE)

August 2018
Procedural

Approvals based on Master Protocols (Basket Studies)

- Imatinib (B2225)
  - Aggressive systemic mastocytosis (cKit D816V), MDS/MPD (PDGFR+), hypereosiniphilic syndrome and/or chronic eosinophilic leukemia (FIP1L1-PDFRa fusion kinase), dermatofibrosarcoma protuberans- Regular Approval
- Vemurafenib (VE-Basket)
  - Erdheim Chester- Regular Approval
- Dabrafenib + Trametinib (BRF117019)
  - Anaplastic Thyroid Cancer – Regular Approval
- Pembrolizumab (KN-016, KN-012, KN-158)
  - MSI-H or Mismatch Repair Deficient solid tumors- Accelerated Approval

Potential Challenges with Master Protocols and FIH Expansion Cohorts

- Dissemination of new safety info to investigators, IRBs, regulators in a timely manner→ failure to provide adequate informed consent
- Exposing large number pts across multiple, simultaneously accruing cohorts to potentially suboptimal or toxic doses investigational drug(s)
- Exposing more patients than necessary to achieve the objectives
- Inadequate drug development based on “over-interpretation” of study findings
  - E.g. selection of dosage regimens or biomarker populations based on ad hoc between-cohort comparisons

Safety Considerations

Safety monitoring and reporting

- Include a plan for submission of cumulative summary of safety on a periodic basis more frequently than annually
- Reference cumulative safety report in protocol amendments
- Select medical monitors with experience in treatment of cancer

Independent Data Monitoring Committee (IDMC) or Independent Safety Assessment Committee (ISAC)

- Should be instituted for all master protocols and FIH multiple expansion cohort protocols
- Real time review of serious adverse events
- Changing eligibility, altering dose/schedule, informing study participants of new risks

Institutional Review Board

- Recommend a central IRB

Informed Consent Document - update frequently

Statistical Considerations

- **Non-Randomized, activity-estimating design**
  - Primary endpoint is ORR: Limit exposure of large number of patients to ineffective drug (e.g. Simon 2 stage)
  - If results warrant seeking approval: SAP ensure that data collected is adequate quality to support approval
- **Randomized activity estimating protocols**
  - Umbrella design: use of common control arm Type-I error rate only for the comparison between one experimental drug vs. control
  - Avoid formal comparison between experimental drugs

Statistical Considerations

- **Protocols employing adaptive/Bayesian design strategies**
  - SAP should include details on implementation of Bayesian methods: details futility analysis and the criteria for when and how to modify the sample size. Justification for the control of type-I error rate.
  - Provide data from historical controls or rationale supporting the choice

- **Protocols with biomarker defined sub-groups**
  - When patient assignment to treatment arm is based on specific biomarker, pre-specify how patients with multiple markers will be assigned in to one of the substudies

Regulatory Considerations

- Request a pre-IND meeting
- Submit as a new IND (master protocols)
- Notify RPM 48 hrs prior to submission of protocol amendment that substantially affects safety/scope
- Encourage submission of substantial amendments at least 30 days prior to planned activation to allow for safety review
  - Certain amendments necessary to ensure safety (e.g. closure of cohort for unacceptable toxicity) should be implemented immediately
- The master protocol should be the only study that is conducted under the IND.
- Submitted to the review division responsible for reviewing the primary indication(s)
- Where indication(s) cross review divisions, sponsors should contact the appropriate clinical review division.

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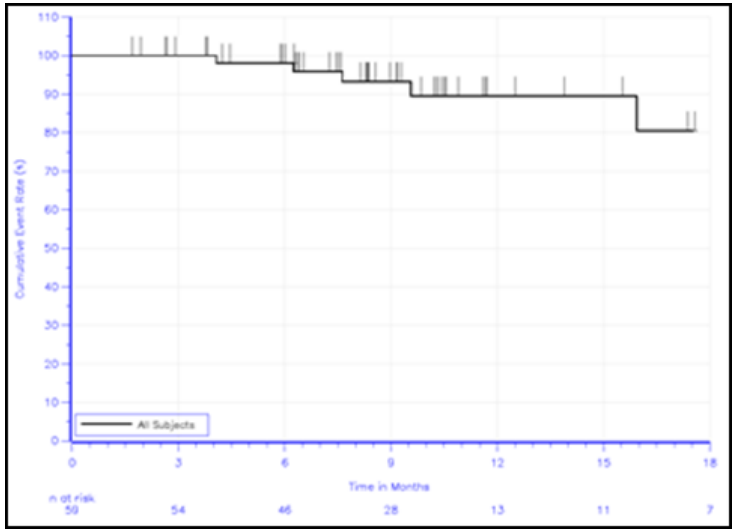
Evolving Drug Development Paradigm: Tissue Agnostic Indication

“Indications” in Oncology

- **Indications and Usage Section [21 CFR 201, CFR 201.57(c)(2)]**
  - **“must state that a drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.”**
- **Traditionally Treatment of Tumor Types based on Single Anatomic/Organ-Specific Sites**
- **Subtypes of Organ-specific Cancers Defined on Basis of Molecular Markers – Prognostic and/or Predictive**
- **Regulations do not Require That Disease be Defined Solely as a Specific Tumor Type**

Data supporting pembrolizumab MSI-H/dMMR approval

	N	ORR N (%)	95% CI
CRC	**90**	**32 (36%)**	**(26, 46)**
Non-CRC	**59**	**27 (46%)**	**(33, 59)**
Endometrial	14	5 (36%)	(13, 65)
Biliary	11	3 (27%)	(6, 61)
Gastric/GEJ	9	5 (56%)	(21, 86)
Pancreatic	6	5 (83%)	(36, 100)
Small Int.	8	3 (38%)	(9, 76)
Breast	2	PR, PR	
Prostate	2	PR, SD	
Bladder	1	NE	
Esophageal	1	PR	
Sarcoma	1	PD	
Thyroid	1	NE	
Retroperitoneal	1	PR	
SCLC	1	CR	
RCC	1	PD	



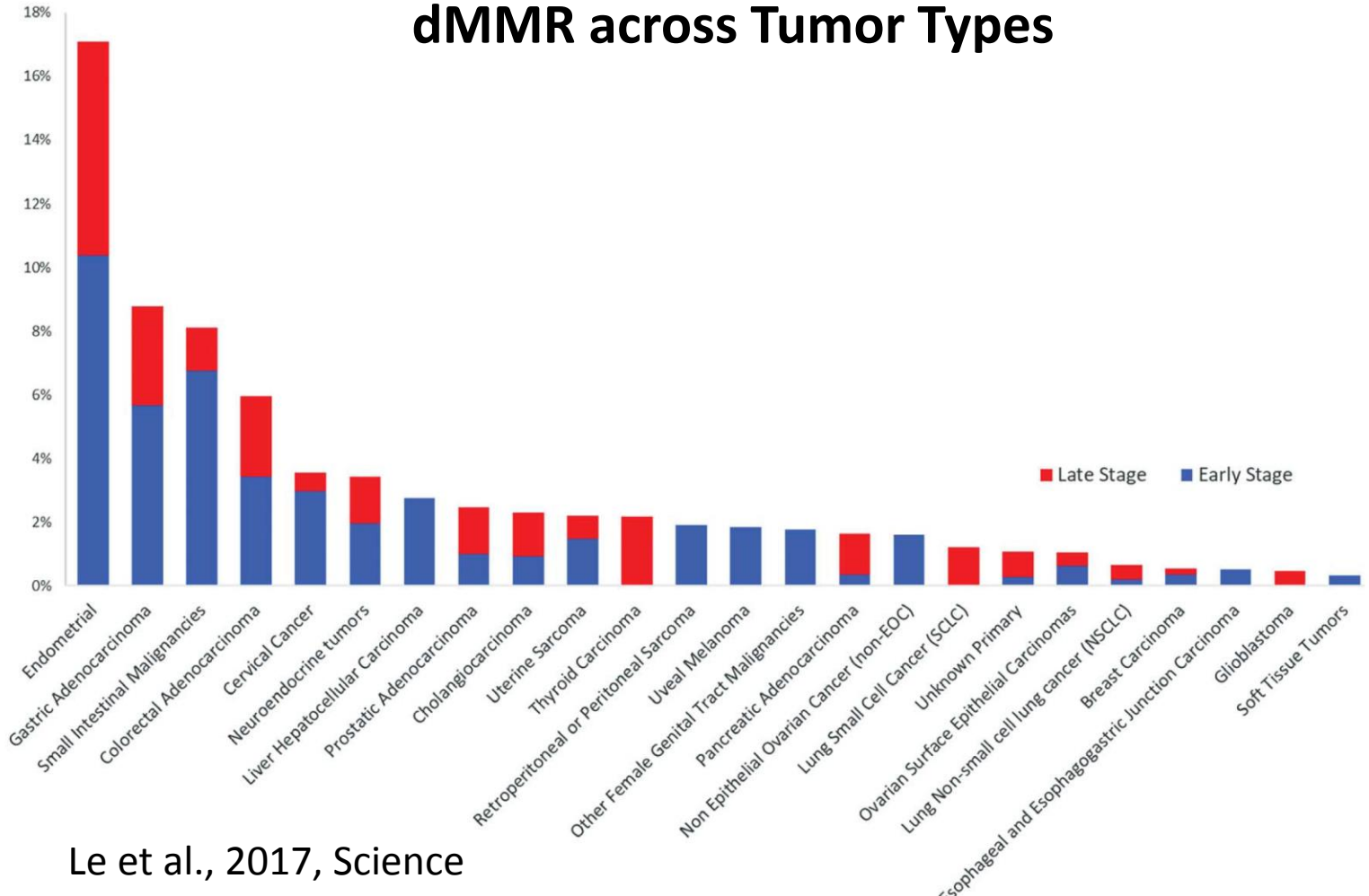
KM-DOR in 59 responding patients

At time of approval, responses observed in *at least* 14 MSI-H/dMMR tumor types; many ongoing (complete responses also observed)

Source: Keytruda labeling, BLA submission, FDA review documents

Pembrolizumab MSI-H approval considerations

- Biology
- Clinical data
- Approved for patients without available therapies (unmet need)
- Post-approval requirements

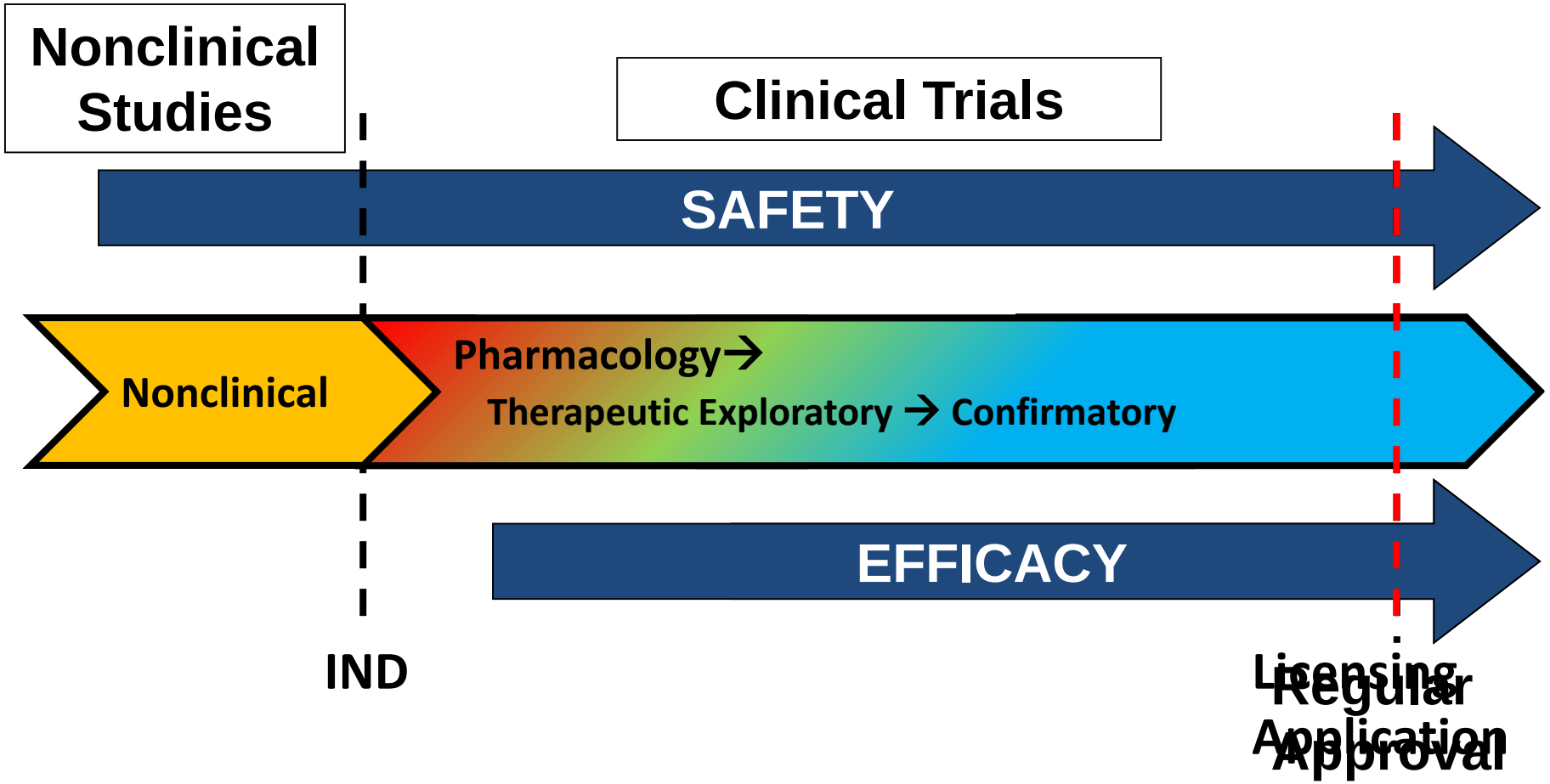


Le et al., 2017, Science

Future considerations: Tissue Agnostic

- How many tumor types necessary?
- Orphan drug designation?
- Pediatrics?
- In vitro diagnostics?

"Shaped" Oncology Drug Development Paradigm



Theoret et. al., 2015, Clinical Cancer Research, 2015

Thank you

- Richard Pazdur
- Paul Kluetz
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- Steven Lemery
- Kirsten Goldberg