U.S. FOOD & DRUG ADMINISTRATION

Oncology Drug Development: An OCE Perspective

Harpreet Singh, MD
Director, Division of Oncology 2
Office of Oncologic Diseases (OOD), CDER, FDA

California Cancer Consortium Conference
October 30th – November 1st, 2020

I have no disclosures.

FDA Mission

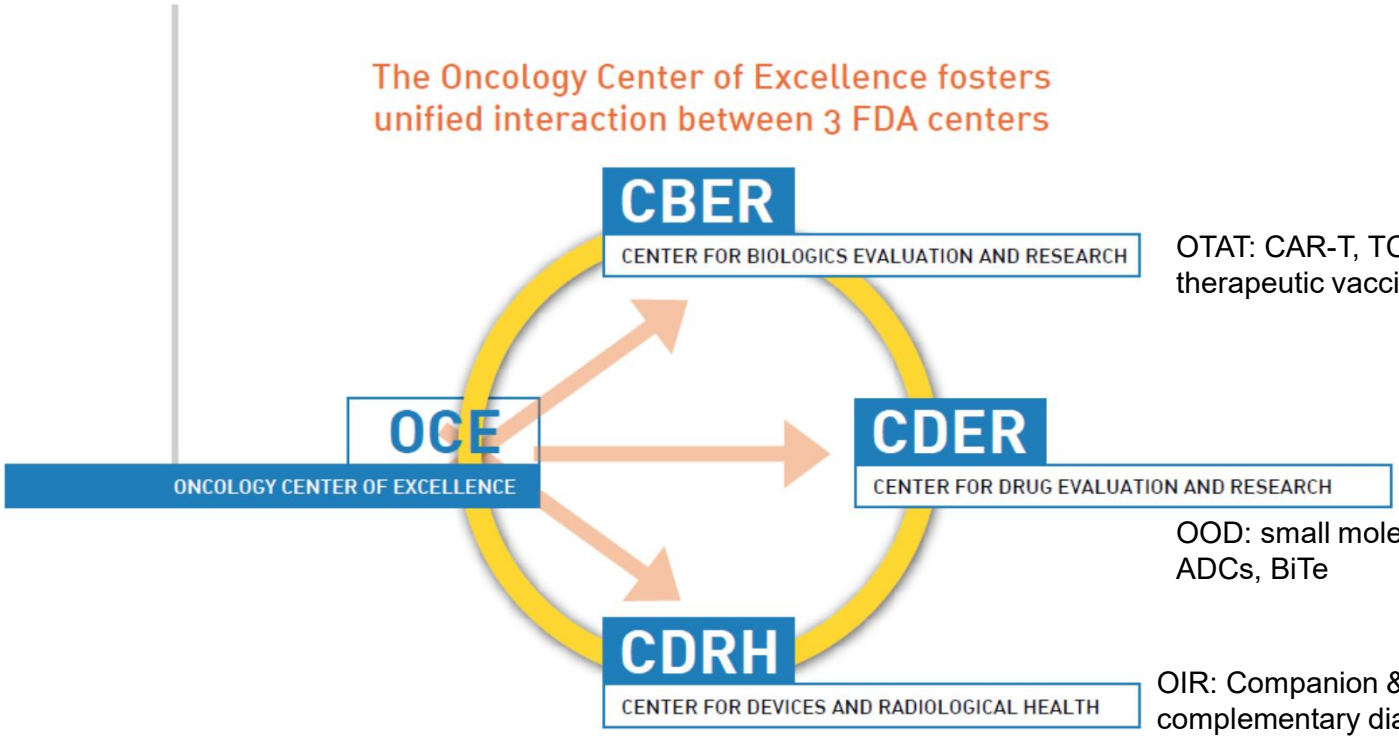
The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

New drugs and certain biologics must be proven safe and effective to FDA's satisfaction before companies can market them in interstate commerce.

FDA **does not** take into account cost or payment issues

FDA **does not** regulate "practice of medicine"

Oncology Center of Excellence



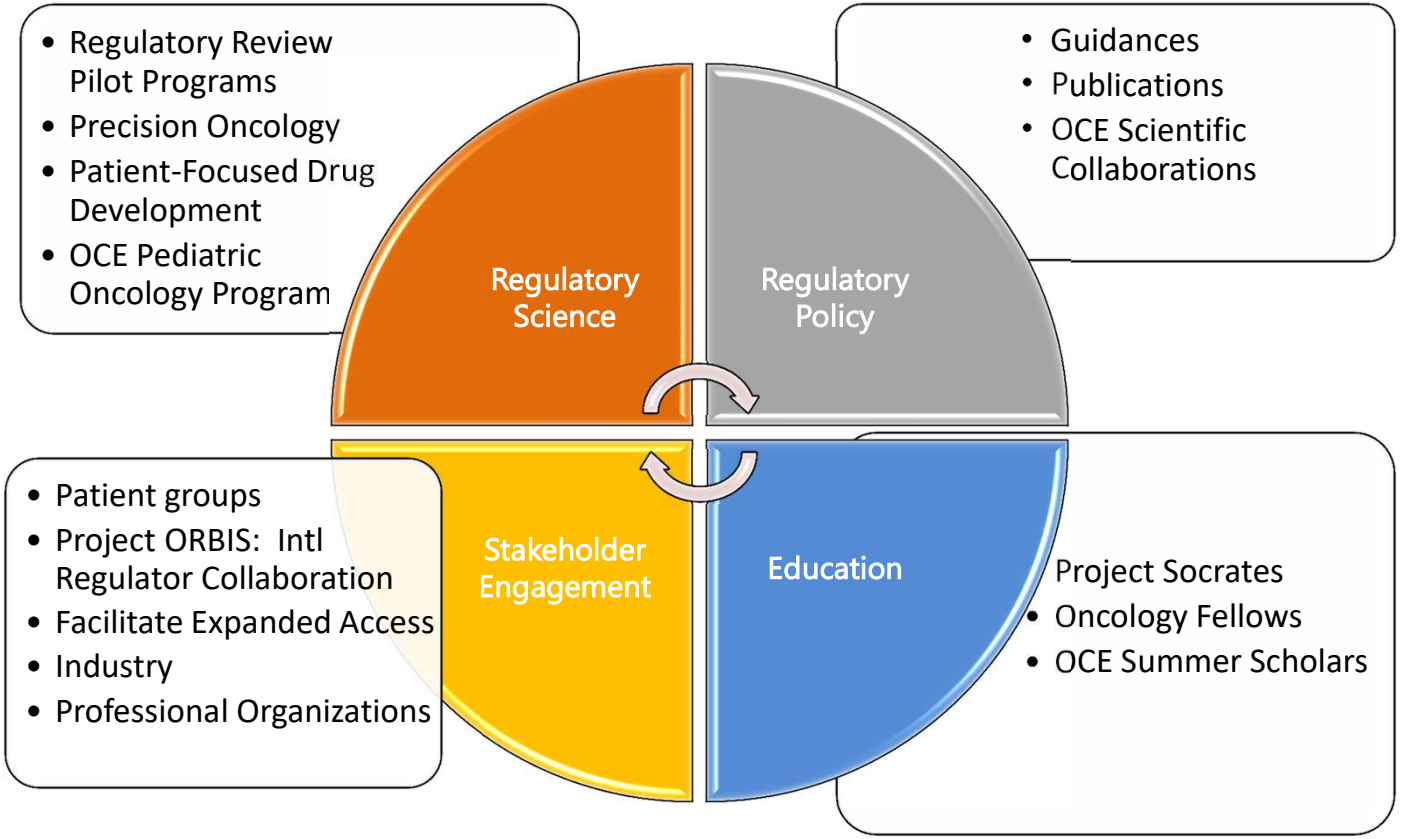
OTAT: CAR-T, TCR, therapeutic vaccines

OOD: small molecules, mABs, ADCs, BiTe

OIR: Companion & complementary diagnostics, Therapeutic devices

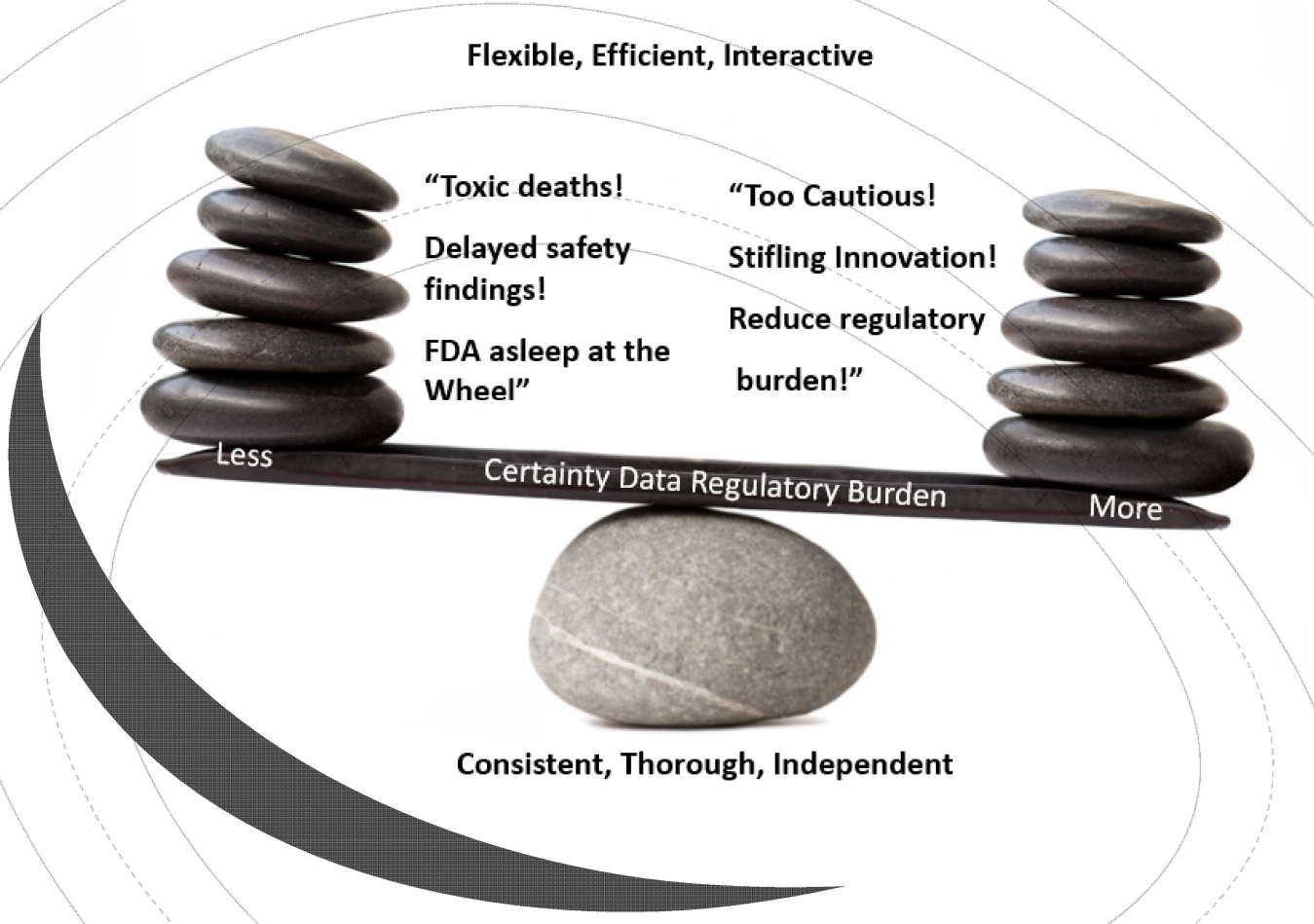
- Established January 20, 2017
- Created in response to National Cancer Moonshot Initiative
- Authorized by **21st Century Cures Act:** 1st FDA Inter-Center Institute

Oncology Center of Excellence



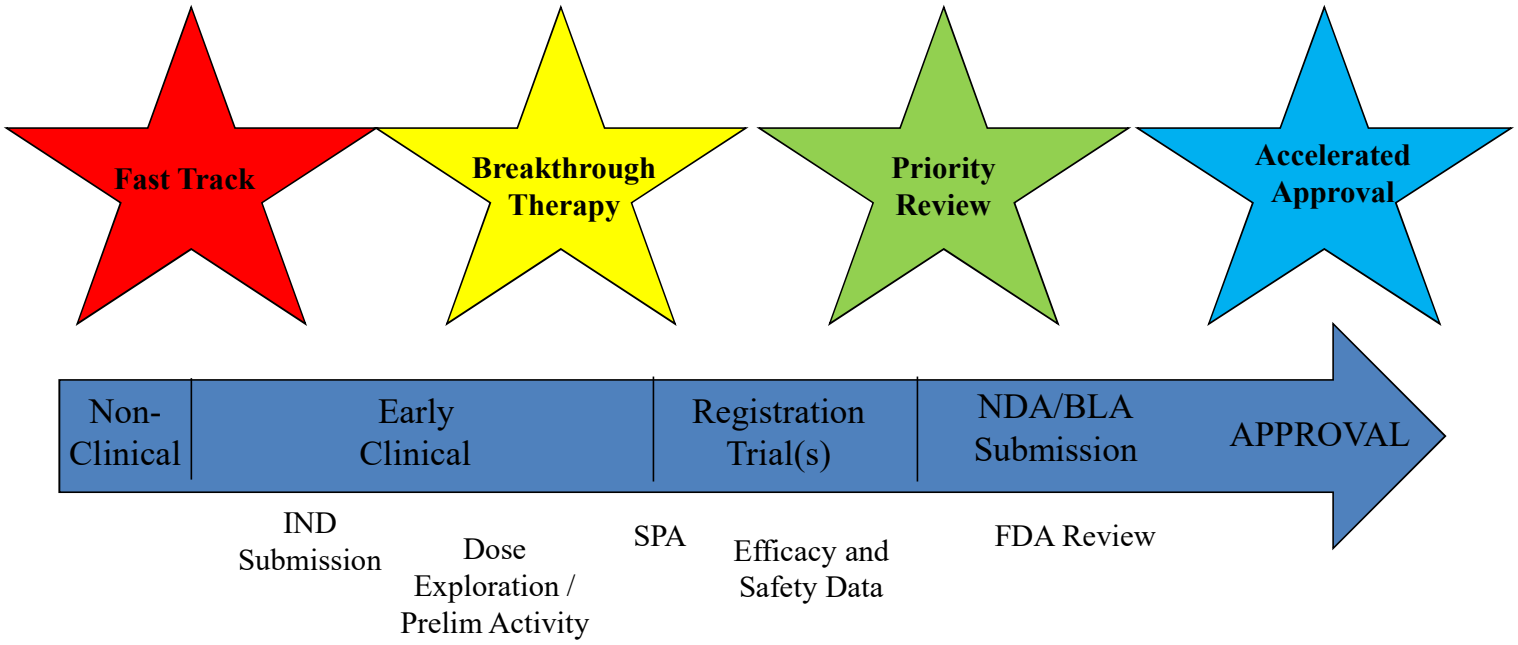
https://www.fda.gov/about-fda/fda-organization/oncology-center-excellence

Striking the Balance



SH1

FDA Expedited Programs

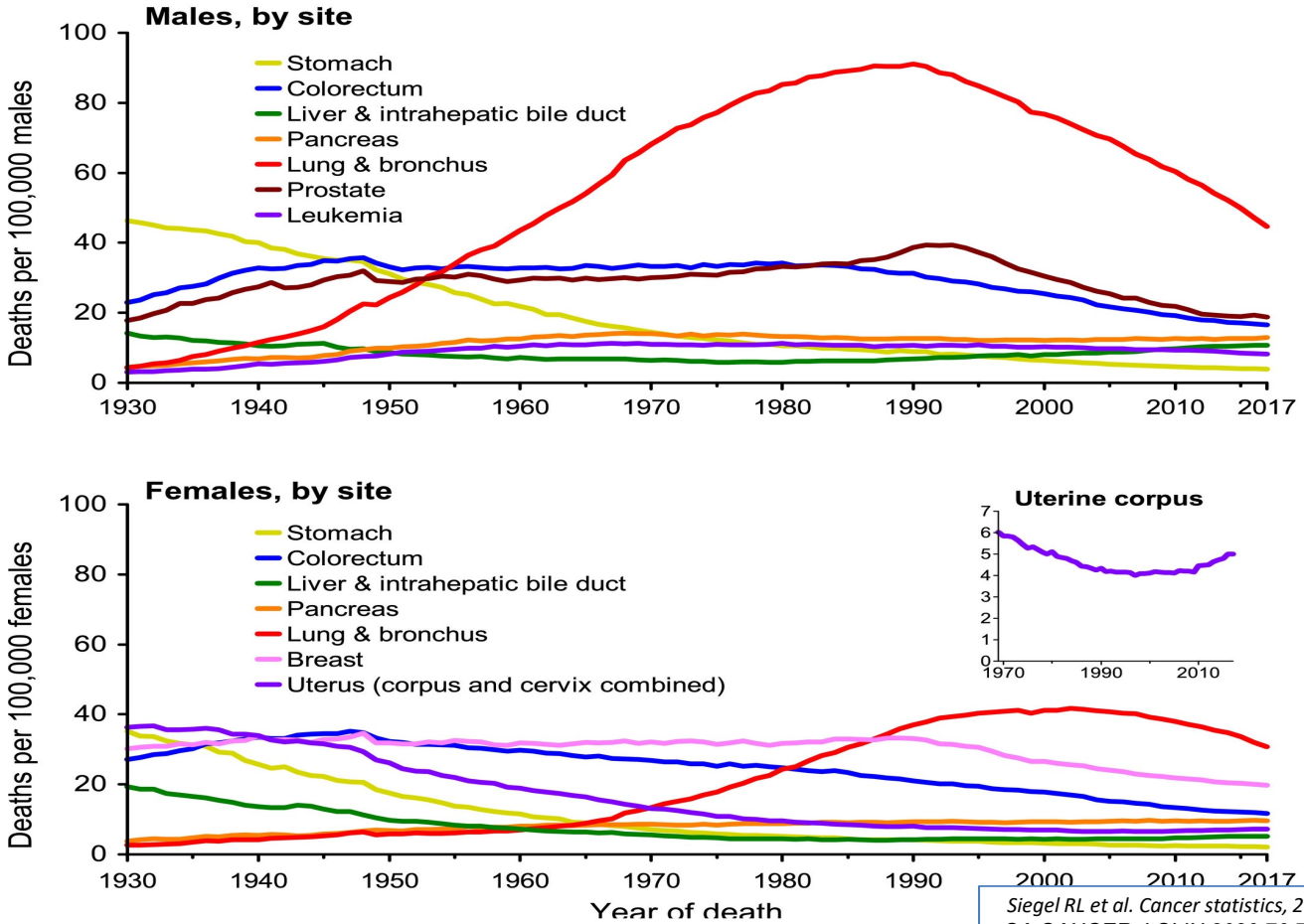


Other programs: Regenerative Medicine Advanced Therapeutics (RMAT); Breakthrough Device
OCE pilots: Real-Time Oncology Review (RTOR), Assessment Aid (AAid)

Slide 7

SH1 would note here that the majority of BTD are granted in Oncology
Singh, Harpreet, 10/25/2020

ACS Report 2020: Cancer Death Rate in US



Siegel RL et al. Cancer statistics, 2020
CA CANCER J CLIN 2020;70:7–30

Cancer death (US) decline by 29% (1991-2017) 2.2% drop in one year (2016-2017) Largest sin-

Lung Cancer Mortality Decreasing Faster than Lung Cancer Incidence

		Average annual percent change
Males	**Incidence** (2011-15)	**-2.6**
	Mortality (2012-16)	**-4.3**
Females	**Incidence** (2011-15)	**-1.2**
	Mortality (2012-16)	**-3.1**

Incidence: age standardized, delay-adjusted rate
Mortality: age-standardized rate

NIH NATIONAL CANCER INSTITUTE

Annual Report to the Nation on the Status of Cancer. J Natl Cancer (2019) 111(12). 5

Advances in Lung Cancer Research & Treatment: 2000-2020

AA = Accelerated Approval

2000

Second round of chemotherapy boosts survival in advanced NSCLC

2001-2002

2003

Gefitinib
First targeted drug approved for non-small cell lung cancer

2004

Erlotinib
metastatic NSCLC
Adjuvant therapy
proven effective in lung cancer

2005

2006

Bevacizumab
NSCLC

2007-2008

2009

Large trial shows **maintenance therapy** improves survival for advanced non-small cell lung cancer

2010

New lung cancer staging guidance
AJCC + UICC
NLST Results

2011

Crizotinib AA
ALK+ NSCLC

2012

2013

Crizotinib
ALK+ mNSCLC
Erlotinib
EGFRm mNSCLC
Afatinib
EGFRm mNSCLC

2014

Ceritinib AA
ALK+ NSCLC
Ramucirumab+ chemo mNSCLC 2L

2015

Pembro AA
PDL1+ (≥50%) mNSCLC 2L
Nivo
mNSCLC 2L
Gefitinib
EGFRm NSCLC
Osimertinib AA
EGFR T790M mNSCLC
Alectinib AA
ALK+ NSCLC 2L
Necitumumab+ chemo
mSqNSCLC 1L

2016

Pembro *PDL1*+ (>1%) NSCLC
Atezo mNSCLC 2L
Crizotinib *ROS1*+ NSCLC
Pembro *PDL1*+ (≥50%) NSCLC

2017

Dabrafenib + Trametinib
BRAF mNSCLC
Osimertinib
EGFR T790M NSCLC 2L
Alectinib *ALK*+ NSCLC 1L 2L
Ceritinib *ALK*+ NSCLC 1L
Brigatinib AA
ALK+ mNSCLC 2L
Pembro+chemo AA
mNSCLC 1L

2018

Larotrectinib AA
NTRK+ solid tumors
Osimertinib *EGFRm* NSCLC 1L
Lorlatinib AA
ALK+ NSCLC 3L
Dacomitinib
EGFRm NSCLC 1L
Afatinib
EGFR mNSCLC 1L
Pembro+chemo
Sq mNSCLC 1L
Pembro+chemo
NsqNSCLC

2019

Atezo+chemo w/bevaciz
Nsq mNSCLC 1L
Durva
Stg III unresectable NSCLC 1L
Entrectinib
ROS1 NSCLC
Atezo+chemo
Nsq mNSCLC w/o *EGFR, ALK alteration* 1L
Pembro
mNSCLC PDL1+ non- *EGFR ALK alt* 1L
Pembro+chemo
mNSCLC, 1L

2020

Capmatinib
MET exon 14 skipping
Selpercatinib
RET fusion NSCLC
Atezolizumab
PDL1 high NSCLC
Nivolumab/Ipilimumab
PD-L1 high NSCLC
Brigatinib
ALK mNSCLC
Ramucirumab + Erlotinib
EGFRm NSCLC
Nivo/Ipi/chemo
mNSCLC
Pralsetinib
RET fusion NSCLC

https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications

Immunotherapy Approvals in NSCLC

SH2

Drug	Indication	Accelerated Approval Endpoint (Year)	Regular Approval Endpoint (Year)
Nivolumab	2L mNSCLC (squamous and non-squamous)		**OS (2015)**
Pembrolizumab	2L mNSCLC (TPS≥1%) 1L mNSCLC (TPS≥50%)	ORR (2015)	**OS (2016)**
Atezolizumab	2L mNSCLC		**OS (2016)**
Pembrolizumab	1L mNSCLC (with pemetrexed and carboplatin)	PFS (2017)	**OS (2018)**
Durvalumab	Maintenance after chemoradiation		**PFS (2018)**
Pembrolizumab	1L sqNSCLC (paclitaxel and carboplatin)		**OS (2018)**
Atezolizumab	1L mNSCLC (with paclitaxel/carboplatin/bevacizumab)		**PFS/OS (2018)**
Pembrolizumab	1L mNSCLC (TPS≥1%)		**OS (2019)**
Atezolizumab	1L mNSCLC (with paclitaxel protein-bound and carboplatin)		**OS and PFS (2019)**

Slide 11

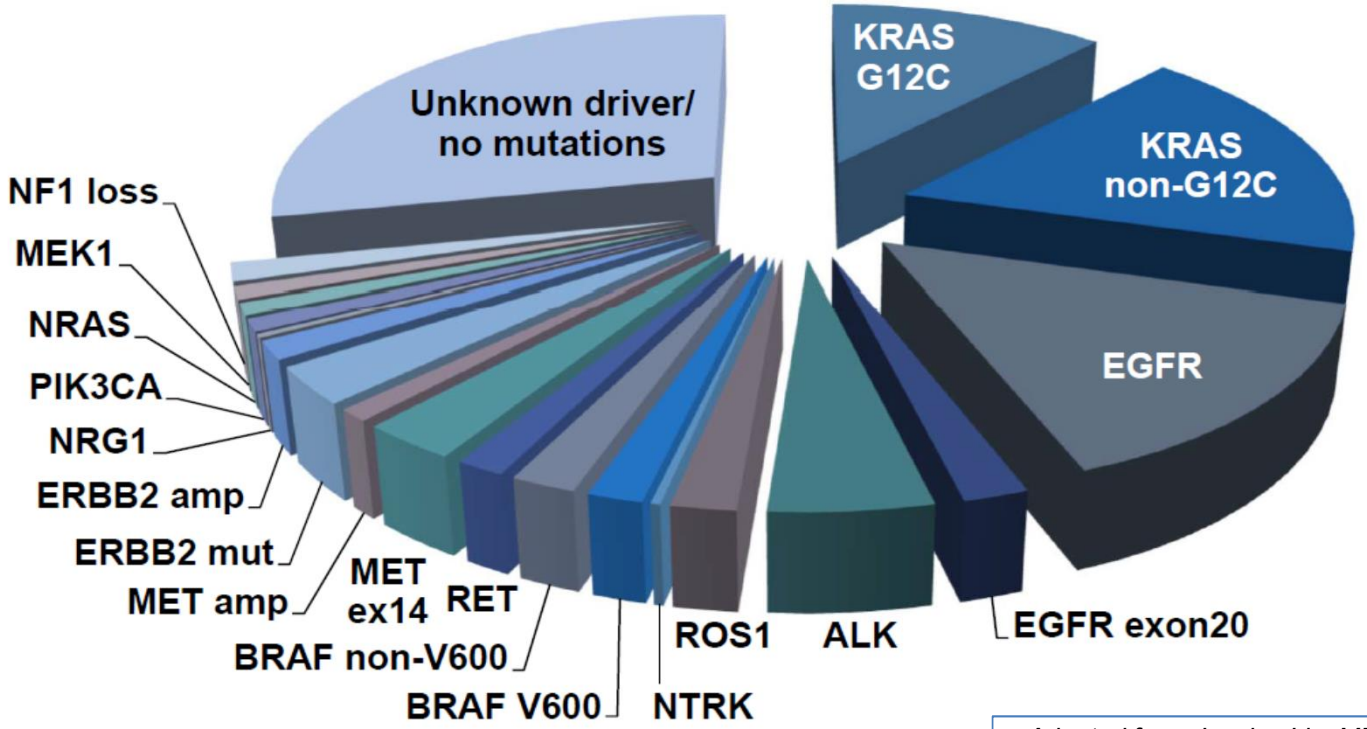
SH2 I will rework this slide to include 2020 approvals but wanted to show endpoints mostly OS
Singh, Harpreet, 10/25/2020

Re-evaluating OS as an endpoint

- Unprecedented response rates in diseases with few therapeutic options → loss of equipoise in randomized trial
- Cancers with long natural histories
- Rarity of cancers due to reclassification based on genomic factors

These features may limit use of Overall Survival as an endpoint and require evaluation of other endpoints.

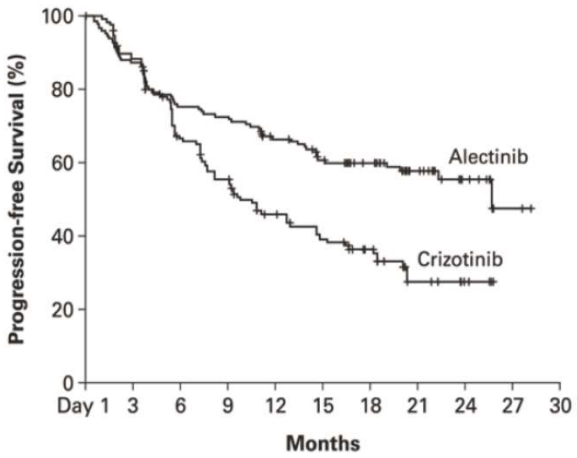
Oncogenic Driver Alterations in NSCLC



Adapted from Jessica Lin, MD
DC Lung Conference 2019

Alectinib: ALK+ mNCLC

Median PFS: 25.7 (19.9, NE) vs 10.4 (7.7, 14.6)
HR 0.53 (0.38, 0.73)



No. at Risk

Crizotinib	151	128	92	74	57	46	33	12	4	
Alectinib	152	132	112	108	95	83	69	35	15	2

Table 8: IRC-Assessed CNS Responses in Patients with Measurable CNS Lesions at Baseline in ALEX

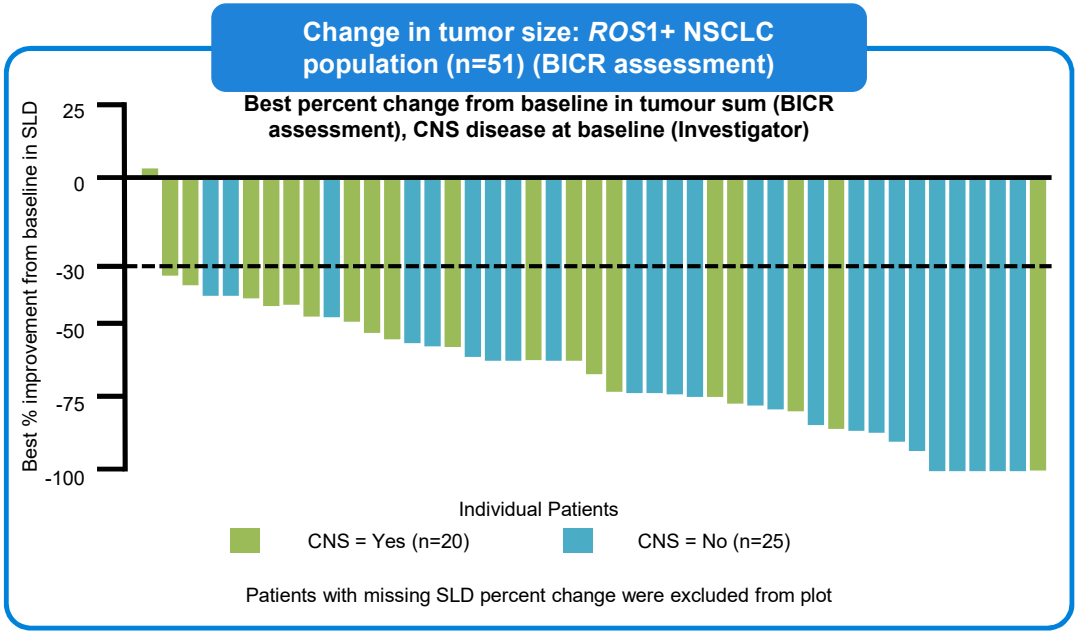
	ALECENSA	Crizotinib
CNS Tumor Response Assessment	N = 21	N = 22
CNS Objective Response Rate, % (95% CI[a])	81% (58, 95)	50% (28,72)
Complete Response	38%	5%
Duration of CNS Response		
Number of responders	17	11
CNS response duration ≥ 12 months	59%	36%

[a] Clopper and Pearson exact binomial 95% confidence interval
IRC: Independent Review Committee; CI: Confidence Interval; NE: Not Estimable

- Approval based on PFS
- Crossover at time of progression
- Enrolled patients with untreated CNS metastases (including leptomeningeal)

Entrectinib in *ROS*+ NSCLC

- Regular approval based on pooled subgroup analysis on ROS+ met NSCLC patients from 3 single-arm trials: ALKA, STARTRK-1 and 2
- 78% ORR (95% CI, 65-89), with 55% of responding patients having continued response for a year.



NSCLC: FDA Approved Targeted Therapy

Targetable Oncogene	FDA-approved drugs
EGFR	Erlotinib, gefitinib, afatinib, dacomitinib, osimertinib
ALK	Crizotinib, ceritinib, alectinib, **brigatinib**, lorlatinib
ROS1	Crizotinib, entrectinib
BRAF V600E	Dabrafenib + trametinib
TRK	Larotrectinib, entrectinib (tissue agnostic)
***MET*ex14 skipping**	**Capmatinib**: accelerated approval May 6, 2020 for metastatic NSCLC with *MET* exon 14 skipping alterations
RET	**Selpercatinib**: accelerated approval May 8, 2020 for • *RET* fusion-positive NSCLC • *RET* mutant medullary thyroid cancer • *RET* fusion-positive thyroid cancer **Pralsetinib**: accelerated approval September 4, 2020 for *RET* fusion-positive NSCLC

2020 Approvals for Thoracic Oncology

Drug(s)	Indication	Approval Endpoint
NSCLC Approvals		
Brigatinib	*ALK*+ mNSCLC	PFS
Capmatinib	*MET*ex14 mNSCLC	ORR (AA)
Selpercatinib	*RET* fusion-positive mNSCLC	ORR (AA)
Pralsetinib	*RET* fusion-positive mNSCLC	ORR (AA)
Ramucirumab/Erlotinib	1L *EGFR*-mutated mNSCLC	PFS
Nivolumab/Ipilimumab/Chemo	1L mNSCLC	OS
Nivolumab/Ipilimumab	1L mNSCLC (PD-L1 ≥1%)	OS
Atezolizumab	1L mNSCLC (PD-L1 TC ≥50% or IC ≥10%)	OS
SCLC Approvals		
Durvalumab/Chemo	1L ES-SCLC	OS
Lurbinectidin	2L mSCLC	ORR (AA)
Malignant Pleural Mesothelioma Approval		
Nivolumab/Ipilimumab	1L unresectable MPM	OS

AA = Accelerated Approval

Regulatory Endpoints in NSCLC 2010-2020

Regulatory Endpoint Supporting Initial Approval	Drug Name
Objective Response Rate	Crizotinib[1,3], Ceritinib[1], Gefitinib, Pembrolizumab[2], Osimertinib[1], Alectinib[1], Brigatinib[1], Dabrafenib+Trametinib[3], Lorlatinib, Entrectenib[3], Capmatinib, Selpercatinib, Pralsetinib
Progression-Free Survival	Erlotinib, Afatinib, Dacomitinib, Ramucirumab (with erlotinib)
Overall Survival	Ramucirumab (with docetaxel), Nivolumab/Ipilimumab, Necitumumab, Atezolizumab, Pembrolizumab

1. Subsequent confirmatory trial demonstrated PFS benefit
2. Subsequent confirmatory trial demonstrated OS benefit
3. Granted regular approval based on RR

NSCLC: Future Directions & Challenges

- Combination strategies
  - Rational and safe
- Effective therapies in earlier stages of disease
  - (Neo)adjuvant trials ongoing
- Liquid biopsies
  - FDA is open to discussing evidence generation for efficacy response
  - FDA welcomes proposals to incorporate liquid biopsy into early stage protocols

Paradigm Shift

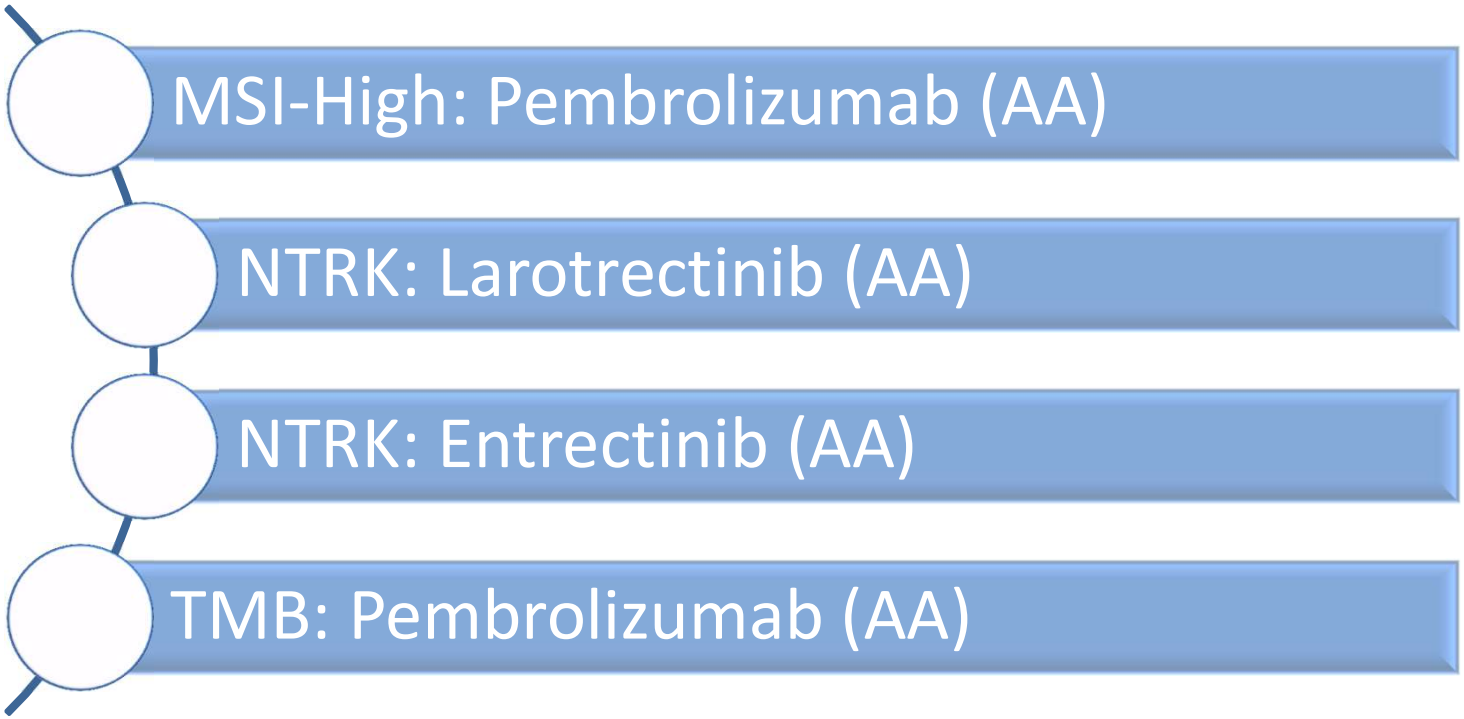
Location,
Location,
Location

Biomarker,
Biomarker,
Biomarker*

Prerequisite: detailed biologic understanding + clinical data showing large magnitude and consistency of effect

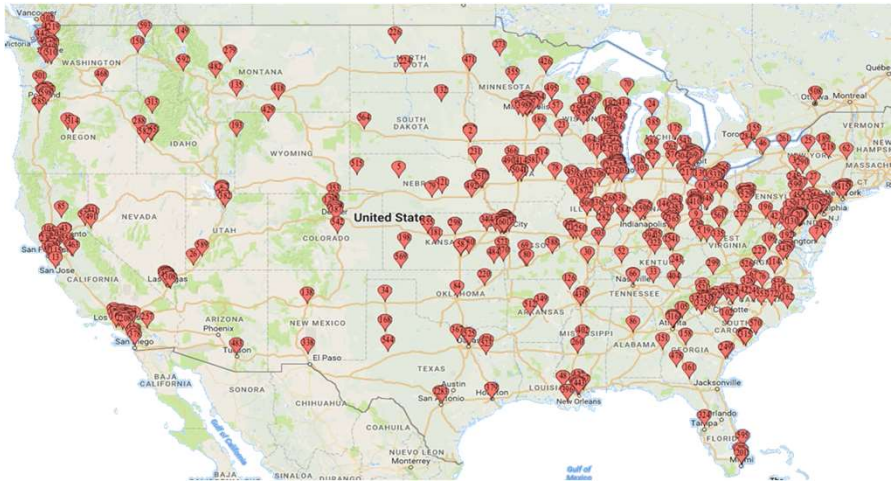
* At least- some of the time

Tissue Agnostic Approvals



Lung-MAP Master Protocol

As of 06/29/2020	Total	S1400	LUNGMAP
Screening Registrations	**3199**	**1864**	**1335**
Screened at PD	1679	1127	552
Pre-screened*	1520	737	783
Sub-study Assignments	**2840**	**1404**	**666**
Among Screened at PD	1437	996	441
Among Pre-screened	617	408	209
Additional Assignments after PD on a Sub-study	83	67	16
Sub-study Registrations	**876**	**687****	**188**



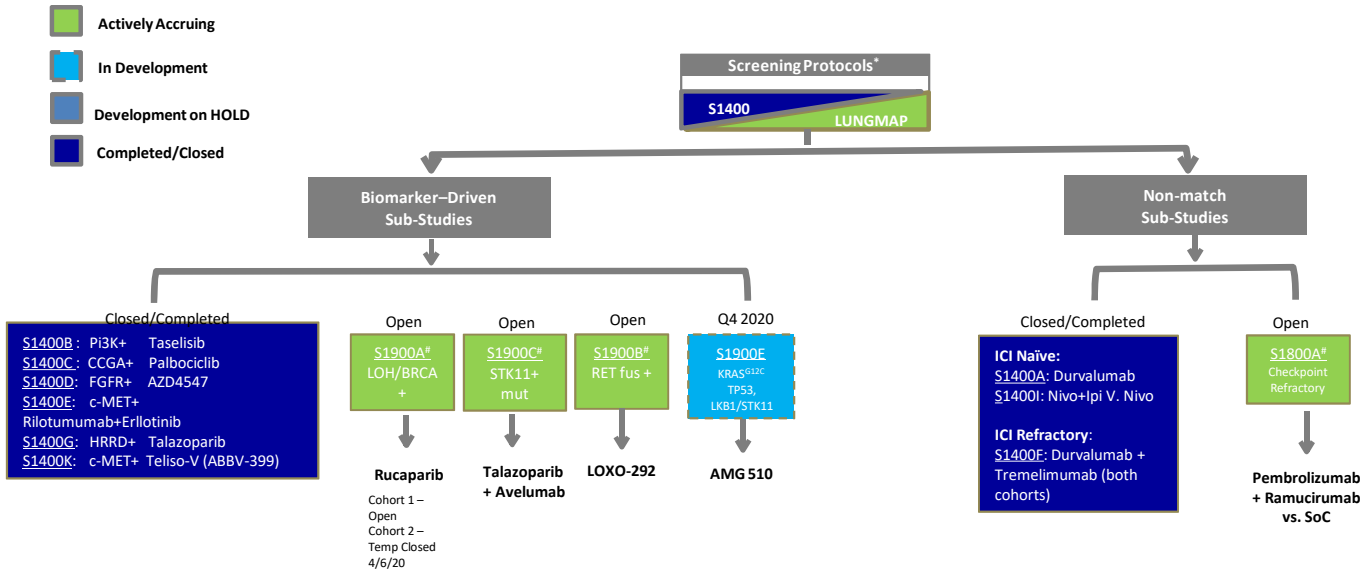
* pre-screening was added in May 2015 (11 months after activation)

** includes 21 pts registered to a LUNGMAP sub-study

LUNG-MAP

Current Lung-MAP Schema

Update on Existing & New Sub-Studies



*LUNGMAP screening protocol (activated 1/28/19) allows all histologic types of NSCLC. S1400, the original screening/umbrella protocol included only squamous lung cancer. S1400 accrued patients between 6/16/2014 and 1/28/2019. While S1400 is closed to accrual, patients enrolled to S1400 may participate in sub-studies they are eligible for.

LUNG-MAP

OCE PROJECTS

FDA takes first action under new international collaboration

with Australia and Canada designed to provide a framework for concurrent review of cancer therapies

- Global collaboration
- Launched Oct 2004
- September 17, 2019: first action under Project Orbis with TGA (Australia) and HC (Canada)
- Utilization of RTOR and AAid programs

Project Community

Project Silver

Improving the evidence base for treating older adults with cancer

- Regulatory policy
- Advocacy and outreach
- Global engagement
- Research and publications

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/seminoncol

FDA analyses of survival in older adults with metastatic non–small cell lung cancer in controlled trials of PD-1/PD-L1 blocking antibodies

Shanthi Marur[1], Harpreet Singh[1,*], Pallavi Mishra-Kalyani[1], Erin Larkins, Patricia Keegan, Rajeshwari Sridhara, Gideon M. Blumenthal, Richard Pazdur

U.S. Food and Drug Administration, White Oak, MD, USA

original reports

Outcomes of Older Women With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor–Negative Metastatic Breast Cancer Treated With a CDK4/6 Inhibitor and an Aromatase Inhibitor: An FDA Pooled Analysis

Lynn J. Howie, MD[1]; Harpreet Singh, MD[1]; Erik Bloomquist, PhD[1]; Suparna Wedam, MD[1]; Laleh Amiri-Kordestani, MD[1]; Shenghui Tang, PhD[1]; Rajeshwari Sridhara, PhD[1]; Jacqueline Sanchez, MA[1]; Tatiana M. Prowell, MD[1]; Paul G. Kluetz, MD[1]; Belinda L. King-Kallimanis, PhD[1]; Jennifer J. Gao, MD[1]; Amna Ibrahim, MD[1]; Kirsten B. Goldberg, MA[1]; Marc Theoret, MD[1]; Richard Pazdur, MD[1]; and Julia A. Beaver, MD[1]

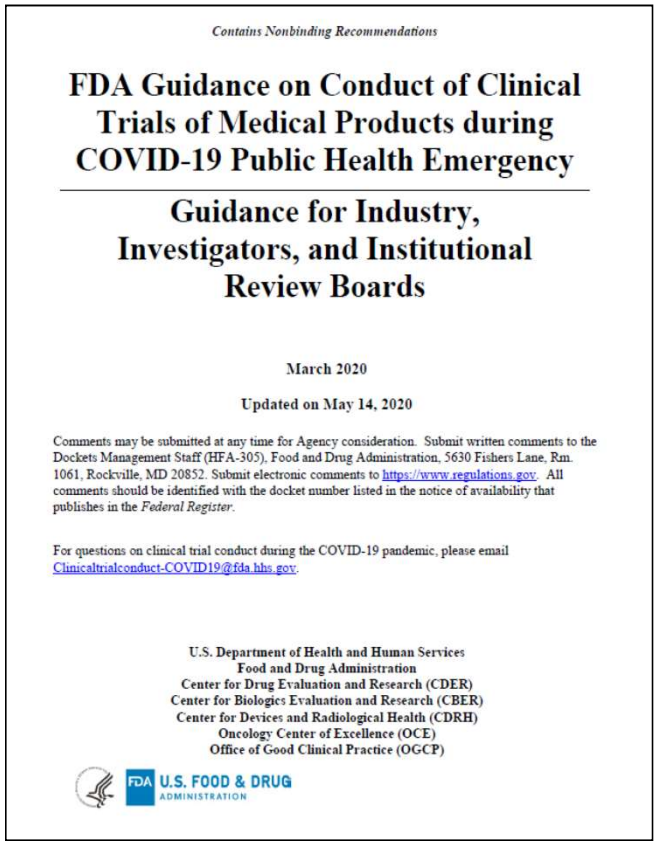
Perspectives

Enrollment of older adults on oncology trials: An FDA perspective☆

Harpreet Singh *, Julia A. Beaver, Geoffrey Kim, Richard Pazdur

Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, United States

COVID Guidances- Rapid Dissemination of Information



Contains Nonbinding Recommendations

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on May 14, 2020

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on clinical trial conduct during the COVID-19 pandemic, please email Clinicaltrialconduct-COVID19@fda.hhs.gov.

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)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic

- Initial release date: March 19, 2020
- Multiple updates:
  - Most Recent September 21, 2020

COVID-19 Guidances are **Expedited**

- Released without Public Comment

Potential Lessons "Silver Linings" from COVID-19

- Calls to make clinical trials more patient centered pre-dated COVID-19 → FDA's efforts and support longstanding
  - "Decentralize" Clinical Trials
    - Bring trial assessments to where patients live
    - Take Advantage of Digital Health Technology
  - Learn from "Real-World" Data → **COVID-19 Evidence Accelerator**

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

FRIENDS of CANCER RESEARCH

FDA U.S. FOOD & DRUG ADMINISTRATION

ONCOLOGY CENTER OF EXCELLENCE

PROJECT FACILITATE

Assisting healthcare providers with requests for access to investigational oncology products

DO YOU NEED HELP SUBMITTING A SINGLE PATIENT IND EXPANDED ACCESS (EA) REQUEST (ALSO KNOWN AS COMPASSIONATE USE) FOR A PATIENT WITH CANCER?

...FDA's Oncology Center of Excellence (OCE) can help:

- Locate IRB resources
- Find an EA contact for a drug/biotech company
- Complete Form FDA 3926

Phone: (240) 402-0004

Email: OncProjectFacilitate@fda.hhs.gov

www.fda.gov/oce

Patients: Talk to your healthcare provider to discuss whether expanded access is an appropriate option.

One Pill.

One Life.

One Career.

One pill can transform a life.

One life can transform many.

One career can transform that pill,

that life, that many.

Transformative Careers. FDA Oncology.

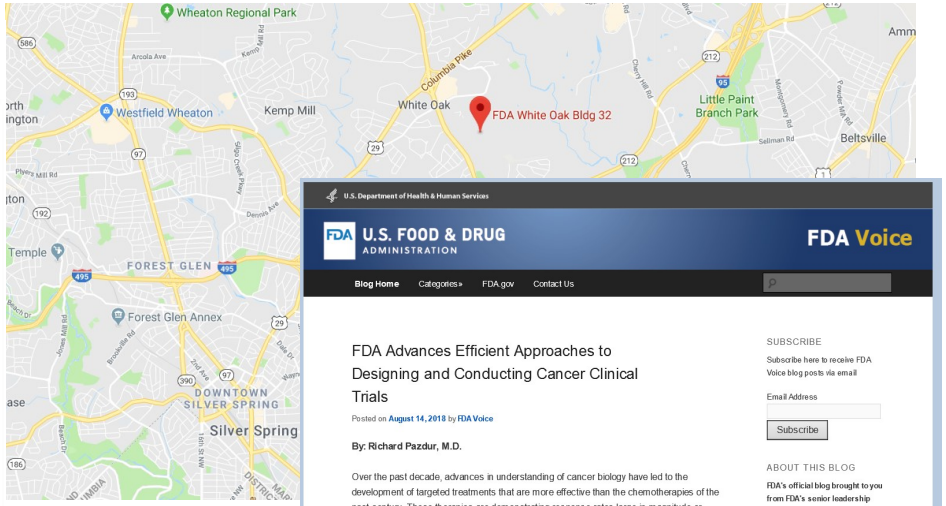
Further information regarding careers at FDA Oncology:
futureofhemeonc@fda.hhs.gov

About the FDA

Follow us on Twitter: @FDAOncology

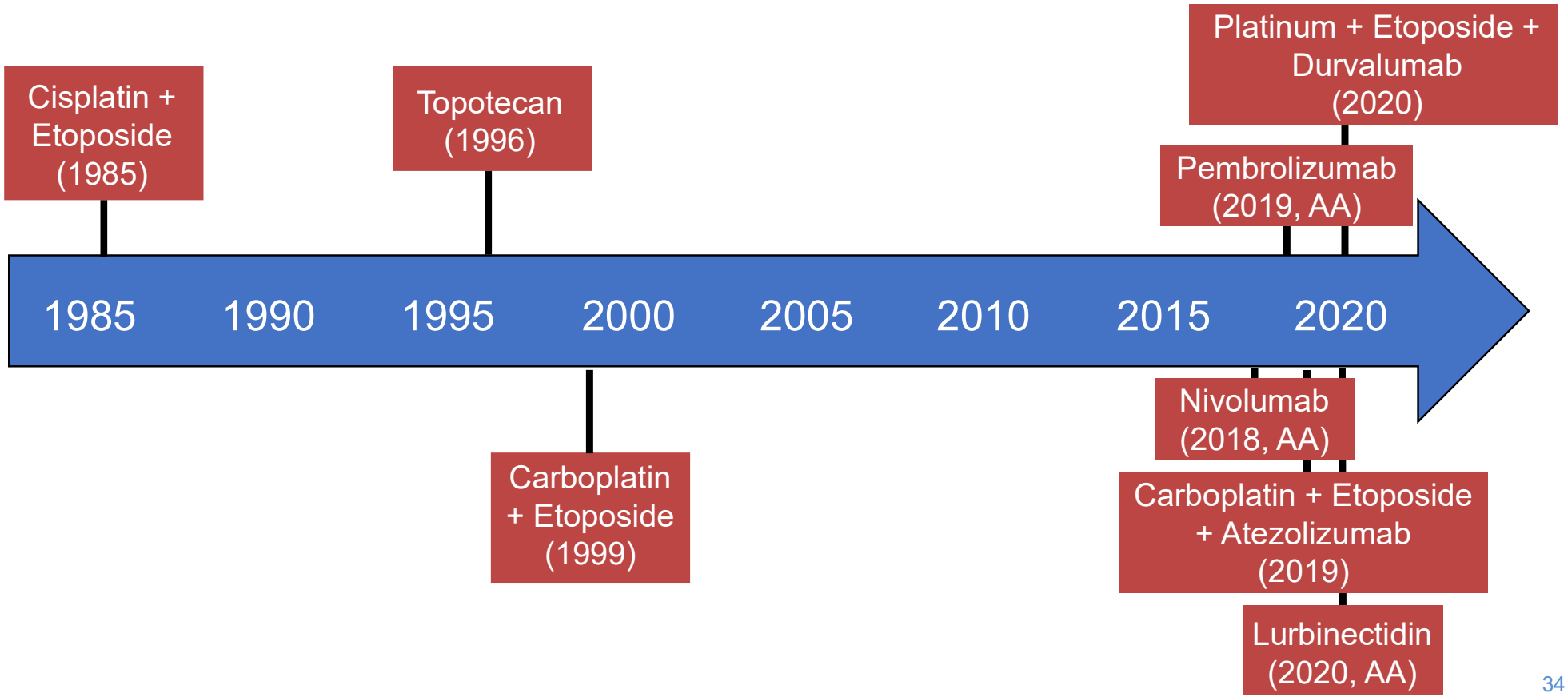
Almost 100 medical oncologists, radiation oncologists, physicians

Where is the FDA located?



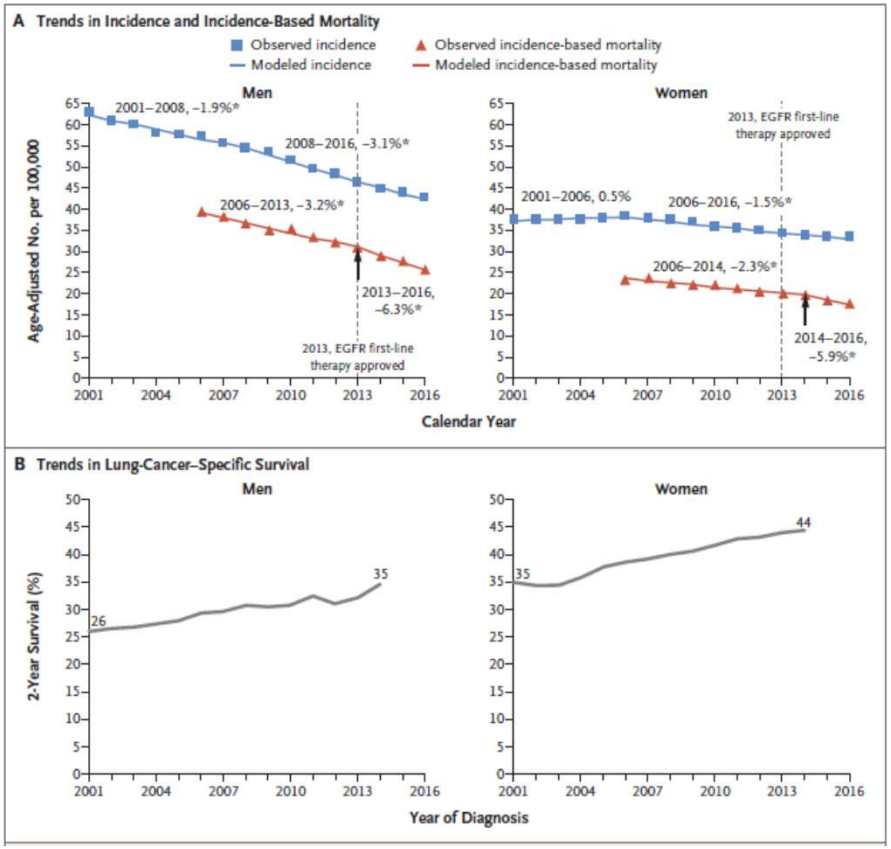

FDA
U.S. FOOD & DRUG
ADMINISTRATION

Challenges: Small Cell Lung Cancer

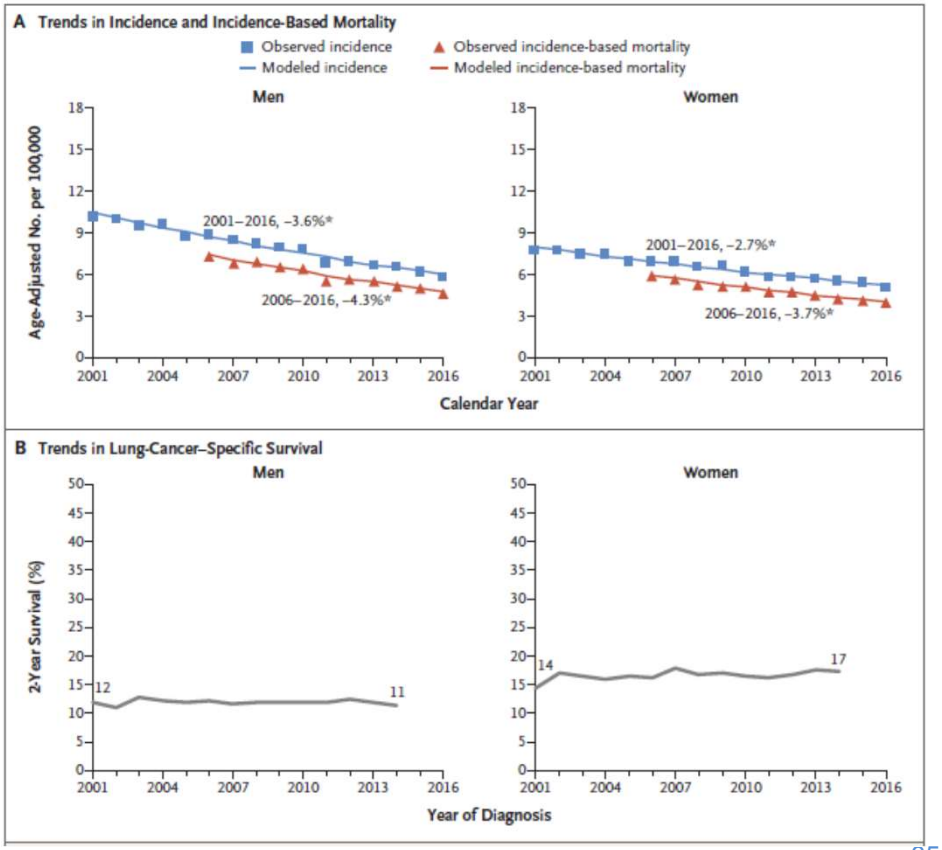


Treatment advances associated with improved survival for NSCLC but not SCLC

NSCLC



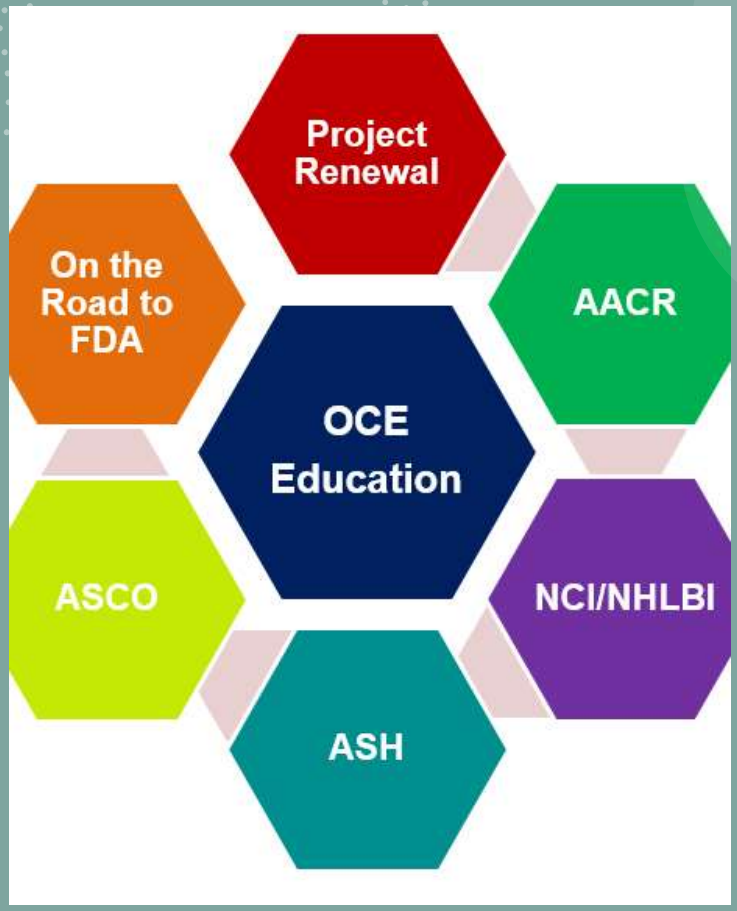
SCLC



Howlader N, N Eng J Med, 2020

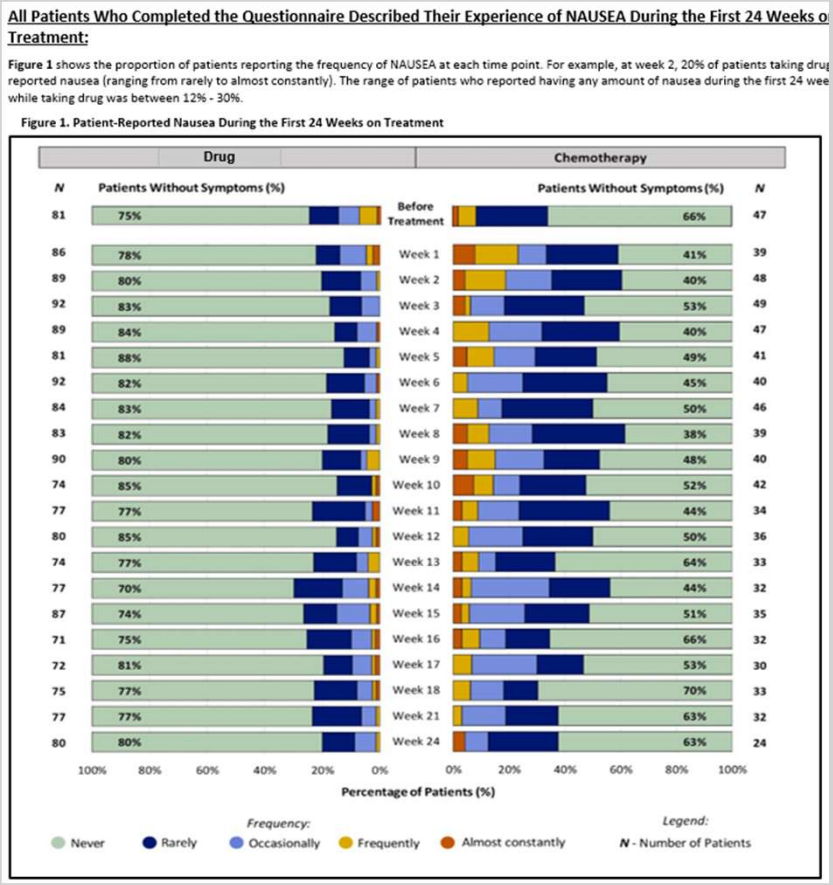
FDA-AACR Oncology Educational Fellowship

- Jointly developed by OCE and AACR
- Educational topics: IND, NDA/BLA, expedited pathways, animal studies, clinical pharmacology, statistics, clinical trial design, companion diagnostics, biomarkers, precision oncology
- Eligibility:
  - Current hematology/oncology fellows or early career faculty (within 5 yrs)
  - 10-15 Fellows per year
  - MD, PhD, MD/PhD, DO



Project Patient Voice

- Pilot
- Publicly available website
- Describes patient reported, longitudinal, symptomatic adverse events
- Data collected from cancer clinical trials for approved drugs
- Sponsors voluntarily provide existing PRO data (I.e. submitted with NDA/BLA) for consideration



All Patients Who Completed the Questionnaire Described Their Experience of NAUSEA During the First 24 Weeks o Treatment:

Figure 1 shows the proportion of patients reporting the frequency of NAUSEA at each time point. For example, at week 2, 20% of patients taking drug reported nausea (ranging from rarely to almost constantly). The range of patients who reported having any amount of nausea during the first 24 wee while taking drug was between 12% - 30%.

Figure 1. Patient-Reported Nausea During the First 24 Weeks on Treatment