FDA U.S. FOOD & DRUG ADMINISTRATION

Oncology Center of Excellence: fostering development of drugs and diagnostics to advance precision oncology

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PROJECT ORBIS

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Project Orbis: Collaborative Review

- Identify any regulatory divergence across review teams
- Drug labels exchanged to learn about differences
- OCE pilot programs may be used:
  - **Real-Time Oncology Review**: sponsor submits data prior to formal application
  - **Assessment Aid**: single document for sponsor-provided text/data and FDA review/analysis

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First Project Orbis Approval

Pembrolizumab + lenvatinib for advanced endometrial carcinoma not MSI-H or dMMR, with progression following systemic therapy and not candidate for curative surgery or radiation

Table 14: Efficacy Results per IRC in Endometrial Carcinoma that is not MSI-H or dMMR (Study 111)

	LENVIMA with pembrolizumab N=94*
Objective Response Rate (ORR)	
ORR (95% CI)	38.3% (29%, 49%)
Complete response, n (%)	10 (10.6%)
Partial response, n (%)	26 (27.7%)
Duration of Response	
Median in months (range)	NR (1.2+, 33.1+)†
Duration of response ≥6 months, n (%)	25 (69%)

Tumor assessments were based on RECIST 1.1 per independent radiologic review committee (IRC). All responses were confirmed.
*Median follow-up time of 18.7 months
† Based on patients (n=36) with a response by independent review
+ Censored at data cutoff
CI = confidence interval; NR= Not reached.

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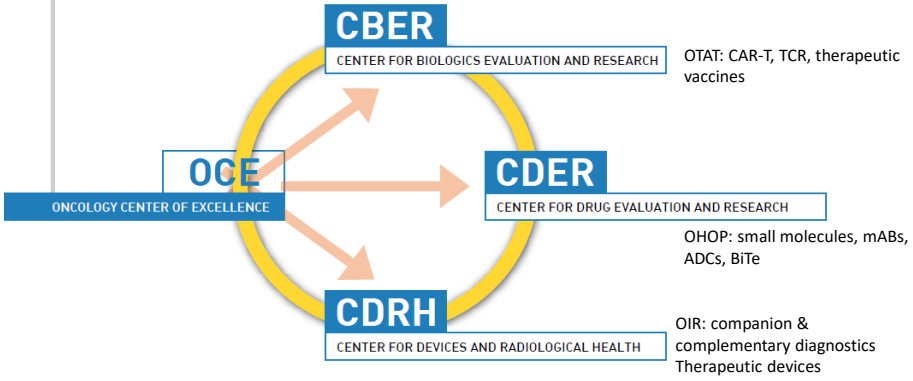
Oncology Center of Excellence (OCE)

The Oncology Center of Excellence fosters unified interaction between 3 FDA centers



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

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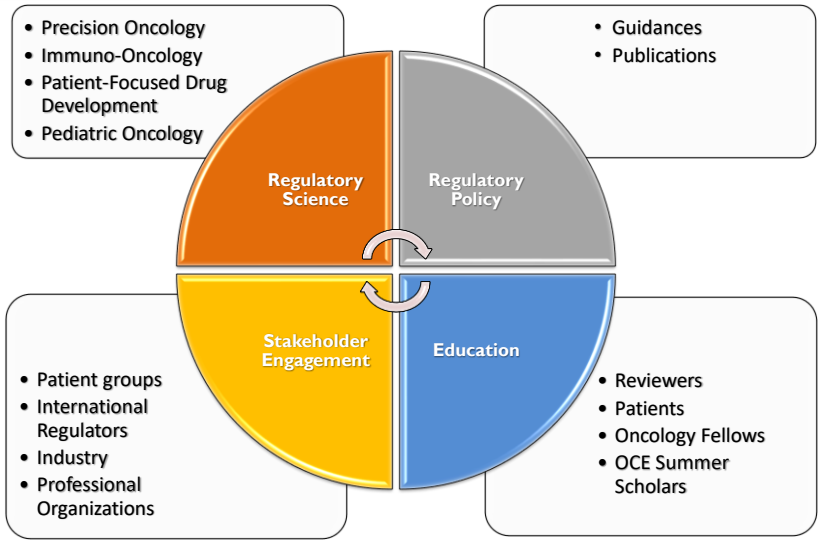
Oncology Center of Excellence



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OCE activities 2018-2019 (and beyond)

Notable Guidance

- Master Protocols
- Clinical Trial Endpoints
- Minimal Residual Disease
- Inclusion of Adolescent Patients

Programs

- Patient-focused drug development, immunotherapy, big data/real world evidence (INFORMED), precision oncology, pediatrics, education

Notable Workshops

- Tissue Agnostic
- Non-proportional hazards
- Neoadjuvant Lung Cancer
- Drug-Radiotherapy Combinations
- Partners in Progress- cancer patient advocates

Notable Pilots

- Project Renewal
- Project Facilitate
- Real Time Oncology Review (RTOR)
- Assessment Aid

https://www.fda.gov/about-fda/oncology-center-excellence/oce-annual-report

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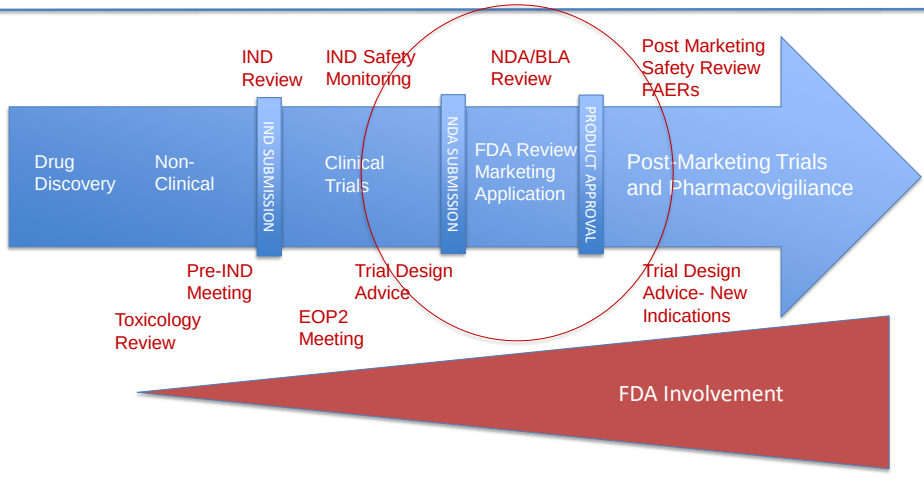
The Drug Development Lifecycle



IND: Investigational New Drug Application, **NDA**: New Drug Application, **BLA**: Biologic Licensing Application, **FAERs**: FDA Adverse Event Reporting System

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	Fast Track	Breakthrough Therapy	Priority Review	Accelerated Approval
Program	Designation	Designation	Designation	Approval Pathway
Qualifying Criteria (all require condition to be serious)	• Nonclinical or clinical data demonstrate potential to address unmet need	• Preliminary clinical evidence demonstrates substantial improvement over available therapies	• If approved would result in significant improvement in safety or efficacy	• Demonstrates effect on endpoint reasonably likely to predict clinical benefit over available therapies
When to Submit	IND or after	Ideally no later than EOP2	With (s)BLA, (s)NDA	Discuss during development
Features	• Expedite development and review • Rolling review	• Intensive development guidance • Organizational commitment • Rolling review	• 6 month vs. 10 month review clock for regulatory action after filing	• Approval based on effect on endpoint that is reasonably likely to predict clinical benefit

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Strength of Efficacy Endpoint Results

- **What** is being Measured**? (Endpoint Selection)**
  - Direct Benefit (Feels/Functions/Survives) considered more meaningful
- **How** accurately is it being measured**? (Measurement Characteristics)**
  - Accuracy of the measure
  - Susceptibility to Bias
  - Accuracy of the Timing of the Event
- **How Much** effect on the endpoint is observed? **(Magnitude of Effect)**

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No Free Lunch:
Strengths and Limitations of Endpoints

	Clinical Outcome	Low Risk of Bias	Feasibility
Overall Survival	✚	✚	▬
Tumor Endpoints	✚ / ▬	✚	✚
Clinical Outcome-PRO	✚	✚ / ▬	✚
Clinical Outcome-Reduction in Healthcare Utilization (e.g. Steroid Use, morbid procedure)	✚	▬	✚

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Benefit/Risk is More Than Efficacy

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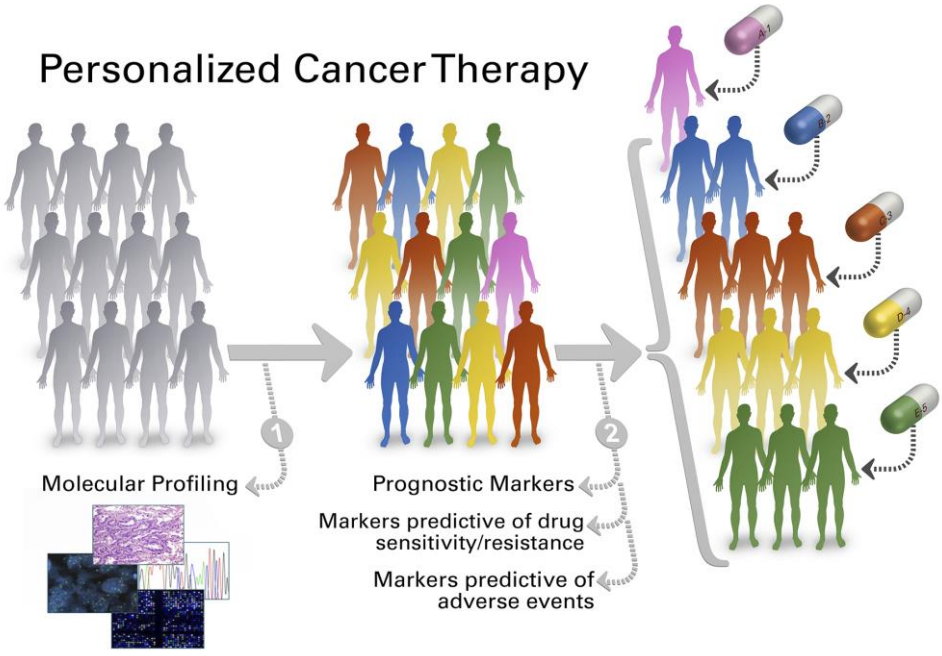

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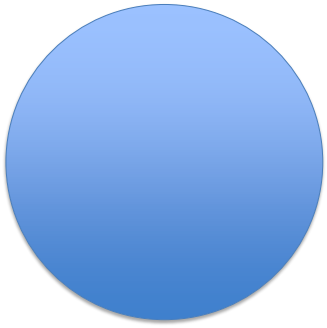
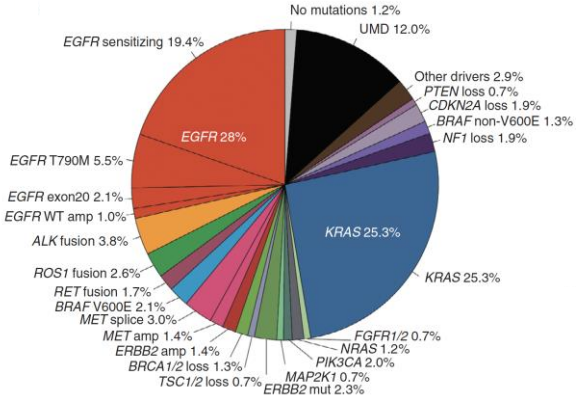
Oncogenic drivers in lung adenocarcinoma

Pie Chart 20 years ago



Pie Chart Today



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Jordan et al., Cancer Discov 7: 596-609, 2017

Precision Oncology success stories

- Broader, faster genomic sequencing
  - Approval/Clearance of multiplex NGS assays
    - FoundationCDx (parallel review with CMS)
    - MSKImpact
    - ThermoFisher Oncomine
    - Illumina RAS
  - Liquid Biopsy Assays
    - Cobas EGFR ctDNA NSCLC
    - Adaptive MRD assay Multiple Myeloma and ALL
    - BCR/ABL for monitoring CML
- "**On-label" genomic, proteomic targets**: EGFRm, ALK, ROS1, KRAS, NRAS, HER2, ER, PR, BRAF, PD-L1, PDGFR, KIT, ABL, FLT3, BRCA1, BRCA2, IDH1, IDH2, CD19, CD20, CD22, CD30, CD33, MSI-H, dMMR, HRD, FGFR

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Paradigm Shift?

Location,
Location,
Location

Biomarker,
Biomarker,
Biomarker*

Prerequisite: detailed **biologic understanding** + clinical data showing **large magnitude and consistency of effect** in patients with **rare & refractory cancers**, **limited therapeutic options**, **unmet need**

* At least- some of the time

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Pembrolizumab & Larotrectinib Accelerated Approvals

Pembrolizumab (supplement)	Larotrectinib (new molecular entity)
Pooled data from **149** pts with MSI-H or dMMR **advanced refractory** solid cancers across 5 trials	Pooled data from **55** pediatric and adult patients with **advanced refractory** solid tumors with NTRK gene fusions across 3 trials
PCR or IHC (local labs)	NGS/FISH (local labs)
ORR: 40% (95% CI 32, 48)	ORR: 75% (95% CI: 61, 85)
DoR > 6 months: 78%	DoR > 6 months: 73%
Responses in 12 of 15 tumor types	Responses in 8 of 12 tumor types (across multiple fusion partners)
Postmarketing study: patients with CRC, non-CRC, including prostate, thyroid, SCLC, ovarian, & children. Characterize response and duration for at least 12 months	Postmarketing study: Further characterize response/ durability: CRC, NSCLC, CNS, melanoma, breast, GIST, cholangio, biliary)

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Tissue agnostic approvals: pembrolizumab and larotrectinib

- Facilitated access to effective therapies for patients with unmet need and limited therapeutic options
- Most efficient approach to generate reliable evidence
  - Randomized trials likely infeasible and lacking equipoise
- Granted without every tumor type studied
  - Including children
  - Post-marketing data forthcoming
- Granted without companion in vitro diagnostic devices
  - Post-marketing commitments

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Summary

- OCE first inter-center institute under Cures Act
  - To create a unified and collaborative approach to patients with cancer
- Expedited programs such as breakthrough designation and accelerated approvals used extensively in oncology
- No "one size fits all" approach to trial design, endpoints

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Thank You

- Gideon Blumenthal
- Paul Kluetz
- Ke Liu
- Reena Philip
- Marc Theoret
- Tamy Kim
- Julia Beaver
- Kirsten Goldberg
- + all multidisciplinary staff in Oncology

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