# Development of Crizotinib for the Treatment of ALK-positive NSCLC

## A Case Study in Genomics-Based Drug Development

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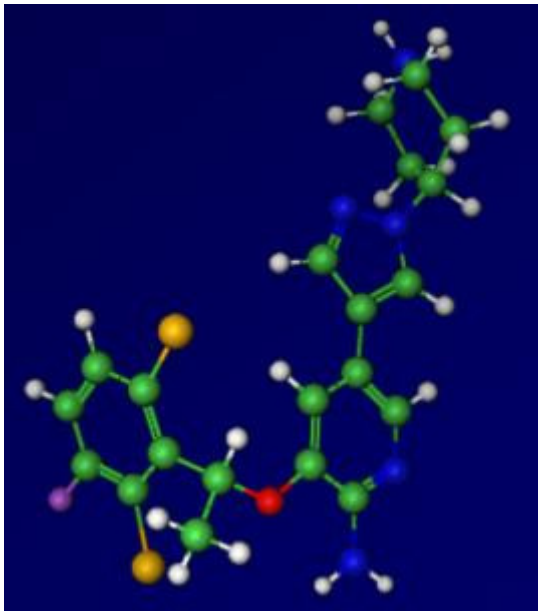
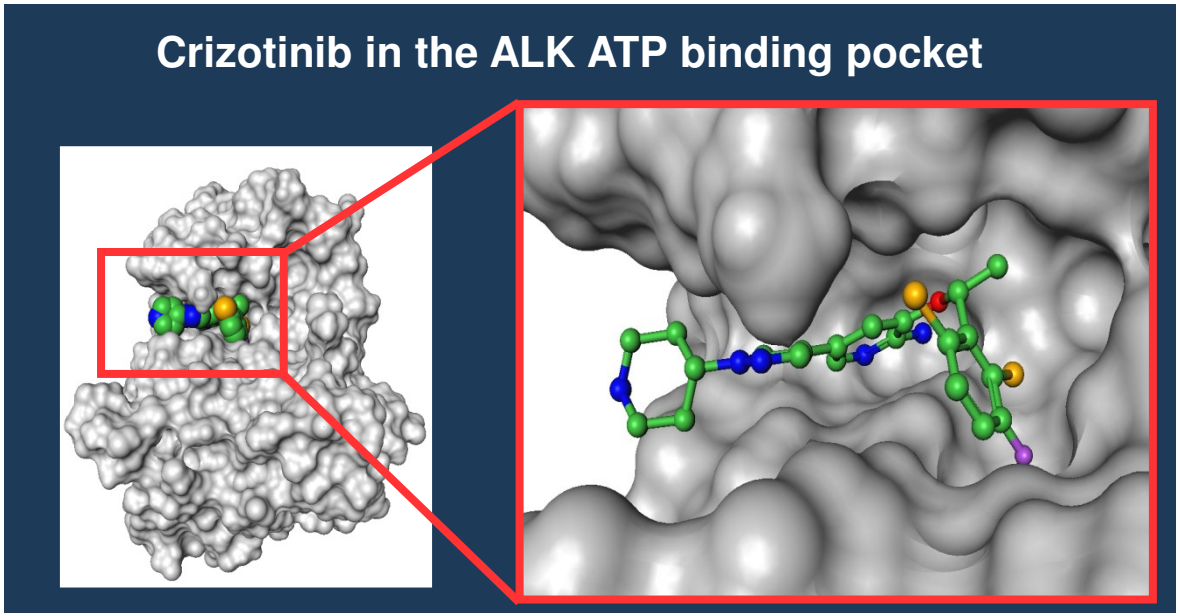
# Crizotinib: Overview

- Formulary name: PF-02341066
- Generic name: Crizotinib
- Trade name: XALKORI™
- Chemical formula: $C_{21}H_{22}Cl_2FN_5O$
- Mechanism of action: ATP competitive kinase inhibitor
- Main targets: c-Met, ALK, ROS
- Approved by US FDA August 26, 2011






**Pfizer, data on file**

# Contemporaneous Regulatory Approvals

**DRUG: Crizotinib - Indications and Usage[1]**

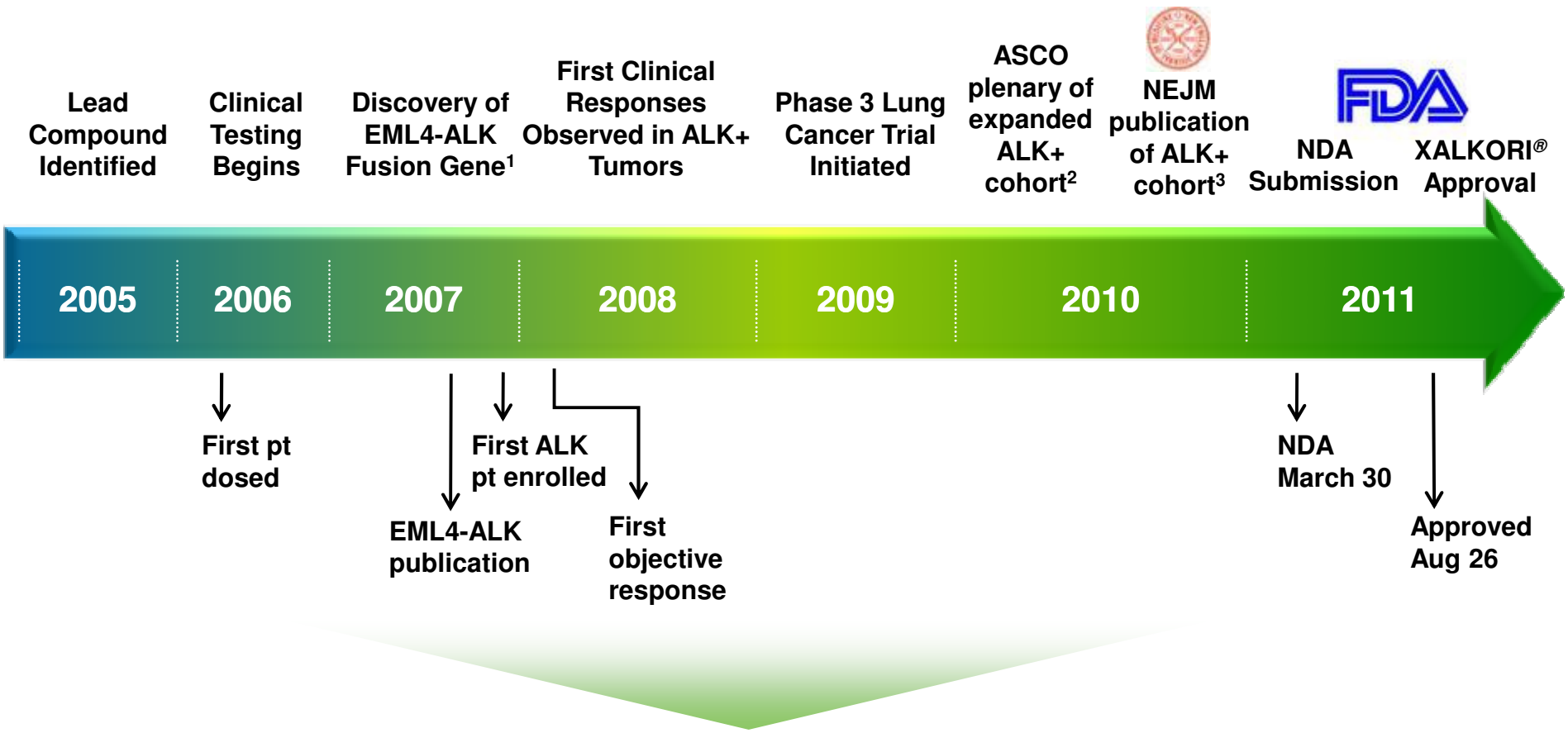
XALKORI® is a kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. (1) This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with XALKORI.

**DEVICE: Abbott Vysis® ALK Break Apart FISH Probe Kit - Intended Use[2]**

The Vysis ALK Break Apart FISH Probe Kit is a qualitative test to detect rearrangements involving the ALK gene via fluorescence in situ hybridization (FISH) in formalin-fixed paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue specimens to aid in identifying those patients eligible for treatment with XALKORI® (crizotinib). This test is for prescription use only.

1. XALKORI label; Reference FDA website
2. Vysis ALK BAP FISH Probe Kit Package Insert; http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110012c.pdf

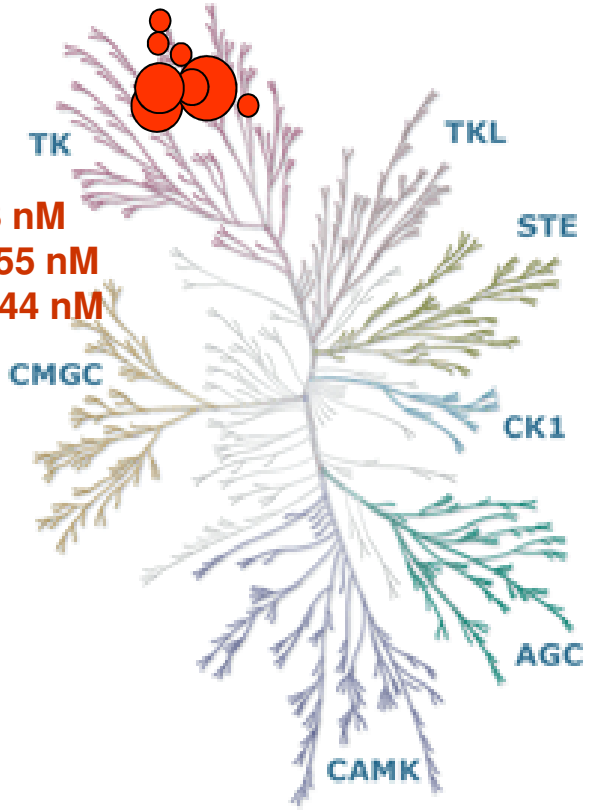
# Crizotinib Development: From Compound Identification to FDA Approval



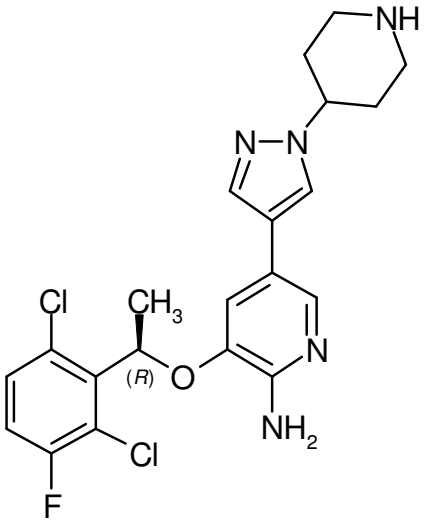

***Rapid Timeline from Compound Identification, Target Discovery and Clinical Results***


1. Soda et al. *Nature* 2007, 448: 561.
2. Bang JY *et al*. Oral presentation at ASCO, 2010
3. Kwak et al. *New Engl J Med*. 2010;363:1693–03

# Crizotinib Target Profile




Met = 8 nM
ALK = 55 nM
ROS = 44 nM



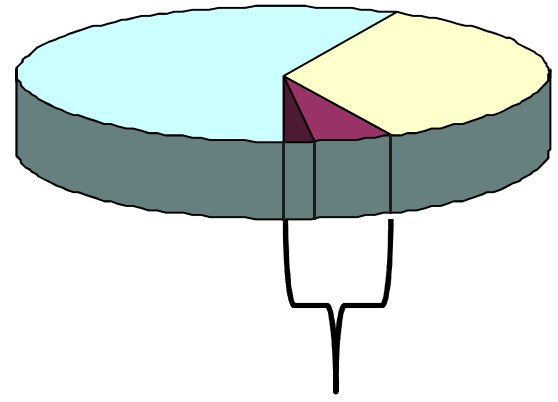

1-20 nM
20-60 nM
60-200 nM
200-1000 nM
>1000 nM
not depicted

- <u>High</u> probability of c-Met & ALK & ROS inhibition at clinically relevant doses
- <u>Moderate</u> probability of inhibiting RON kinase
- <u>Low</u> probability of inhibition of other kinases

ALK= anaplastic lymphoma kinase.

# Understanding Molecular Correlates with Response To Crizotinib

## Screening of >700 tumor cell lines for sensitivity to growth inhibition

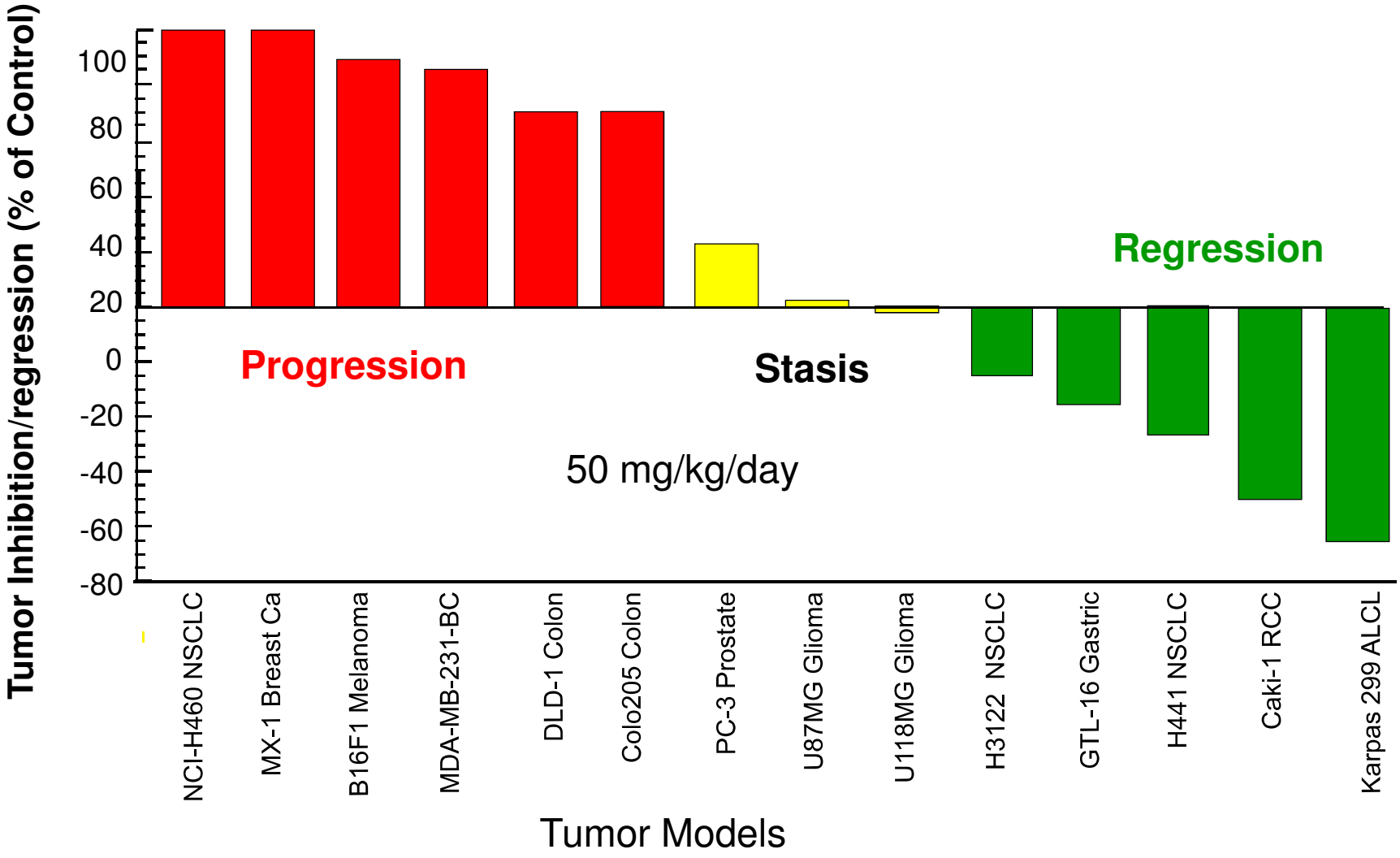



**Crizotinib sensitive cell lines included:**

- gastric, esophageal and NSCLC with MET amplification
- Neuroblastoma with ALK mutation or amplification
- anaplastic large cell lymphoma with NPM-ALK fusion
- NSCLC with EML4-ALK fusion
- NSCLC with ROS fusion

McDermott et al, 2007. PNAS 104: 19936–19941.

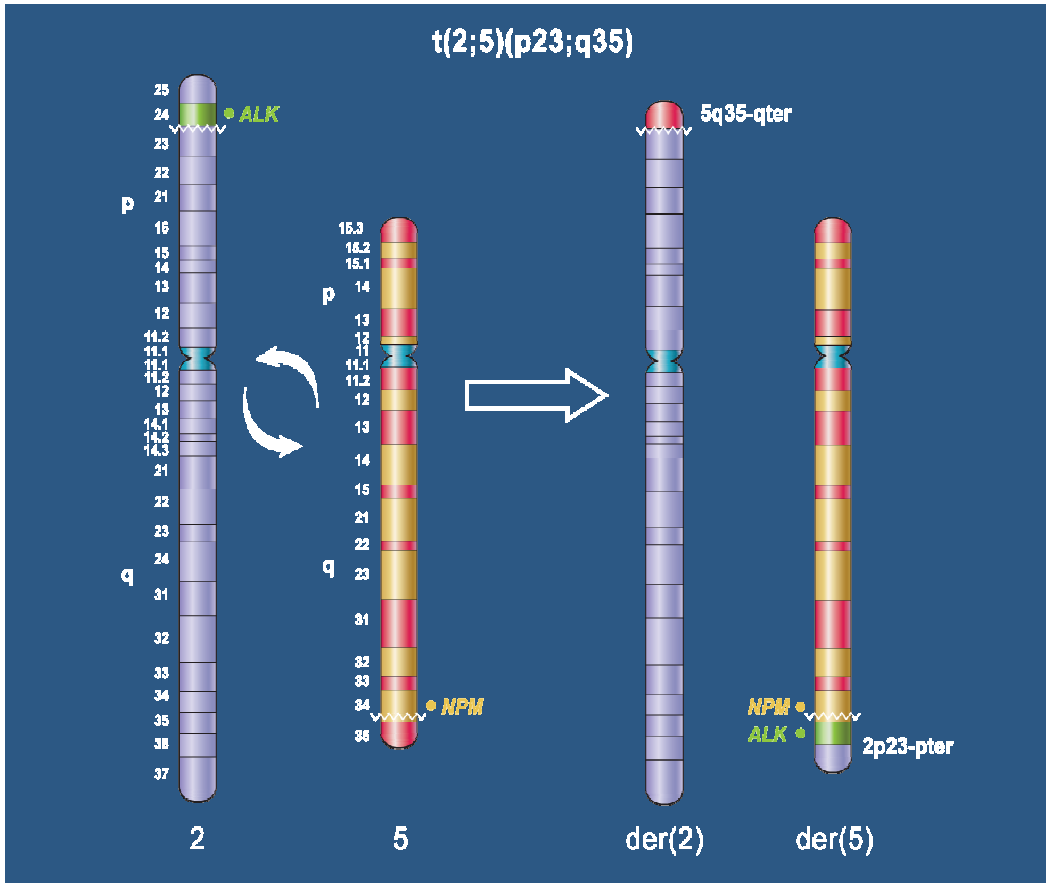
# Spectrum of Response to Crizotinib in Preclinical Tumor Models




**Models exhibiting dysregulation of MET or ALK are highly sensitive to crizotinib**

# Discovery of ALK in Lymphoma

- *ALK* first discovered in a subset of anaplastic large-cell lymphoma (ALCL), leading to the name *anaplastic lymphoma kinase*.
- ALK fused to the N-terminal portion of nucleophosmin (*NPM-ALK*), leading to constitutive activation of ALK activity.



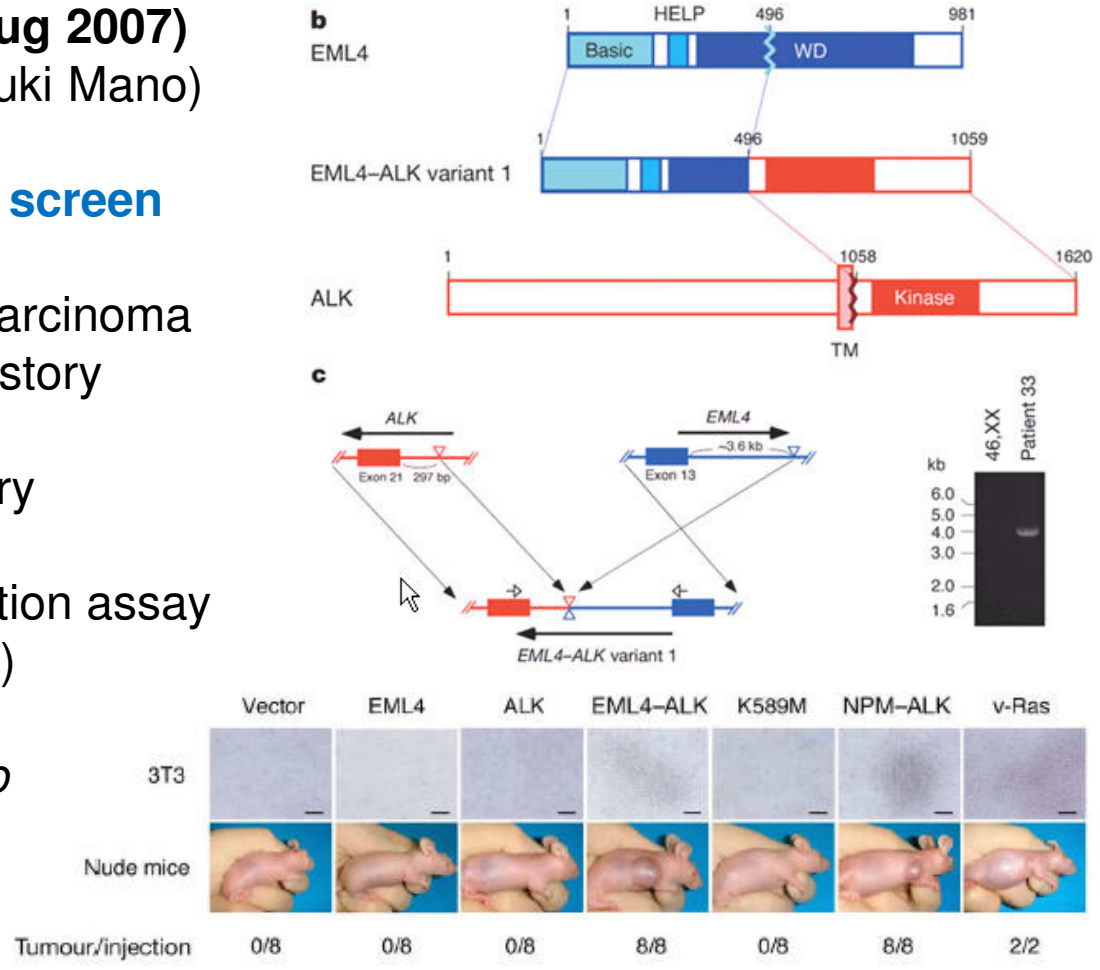

Morris et al., *Science* 1994; 263:1281-1284
Mathew et al. *Blood* 1997; 89:1678-1685

# Functional Genomic Screen Leading to ALK in NSCLC

**Soda et al. Nature 448, 561 (2 Aug 2007)**
(principal investigator: Prof. Hiroyuki Mano)

**"Classical" functional genomic screen**

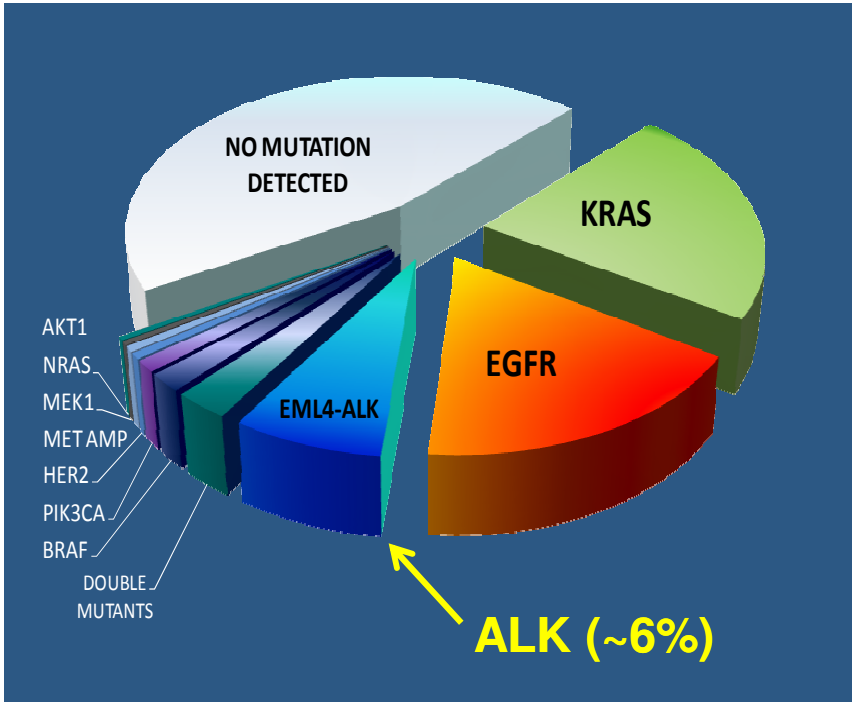
- surgically resected lung adenocarcinoma from 62 yo man with smoking history
- retroviral cDNA expression library
- screened in 3T3 cell transformation assay (anchorage independent growth)
- confirmed as tumorigenic *in vivo*
- *bonafide* oncogene




- also: Rikova et al. Cell v 131 (14 Dec 2007): Phosphoproteomic survey in NSCLC

# Challenges: low frequency population

## Lung Cancer Mutation Consortium (Adenocarcinomas)



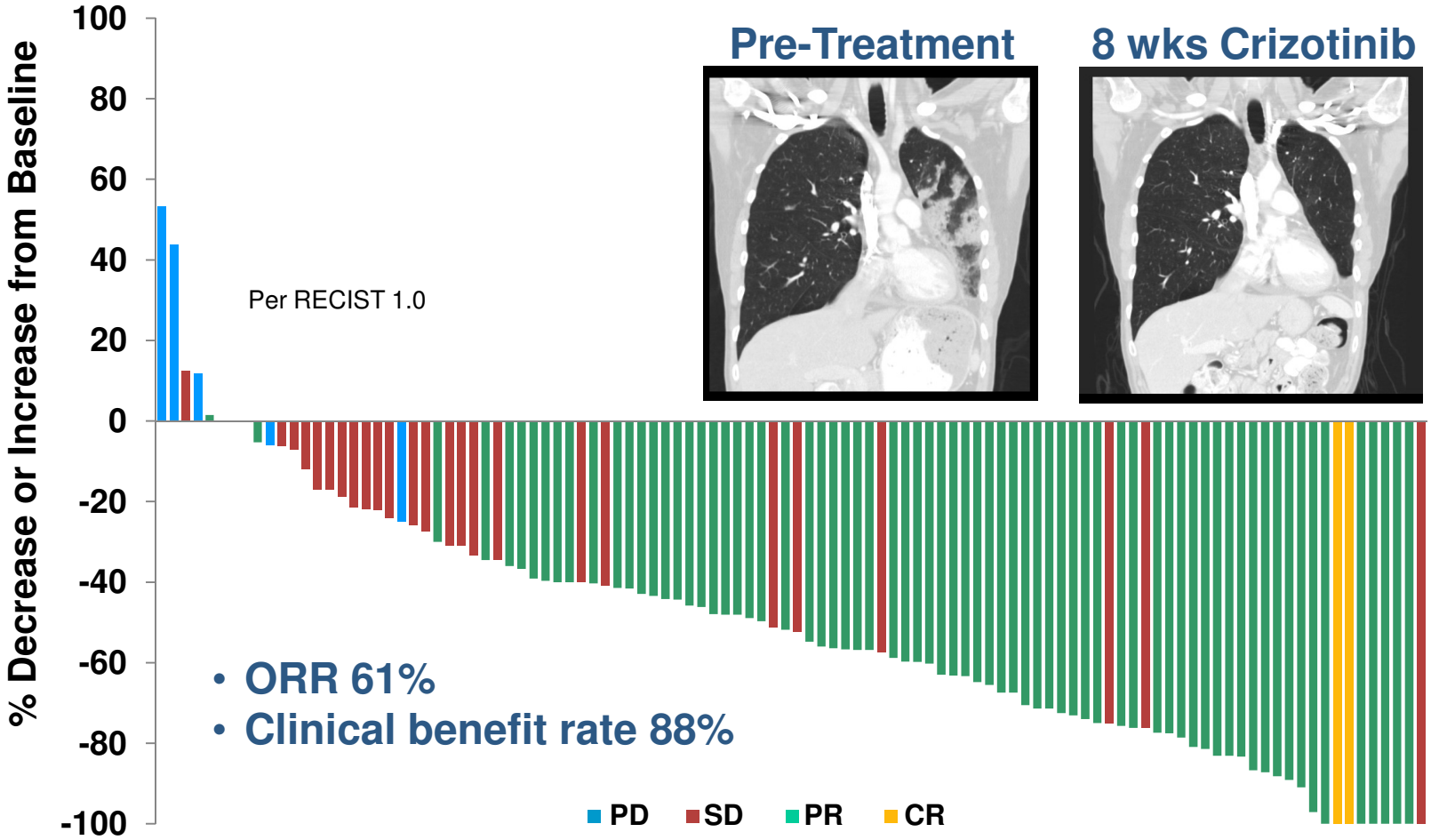

**ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; Her2 = human epidermal growth factor receptor 2; PIK3CA = phosphoinositide-3-kinase, catalytic, alpha chain**

- N=830 registered (varying numbers per test)
- Mutations identified in 60%
- Mutually exclusive in 95%
- ALK gene fusion identified by FISH analysis

Kris et al., ASCO 2011; Abs #7506

# ALK-Positive Non-Small Cell Lung Cancer
# Study A8081001: Tumor Responses to Crizotinib by Patient

## Best Percent Change in Tumor Size (N*=106)



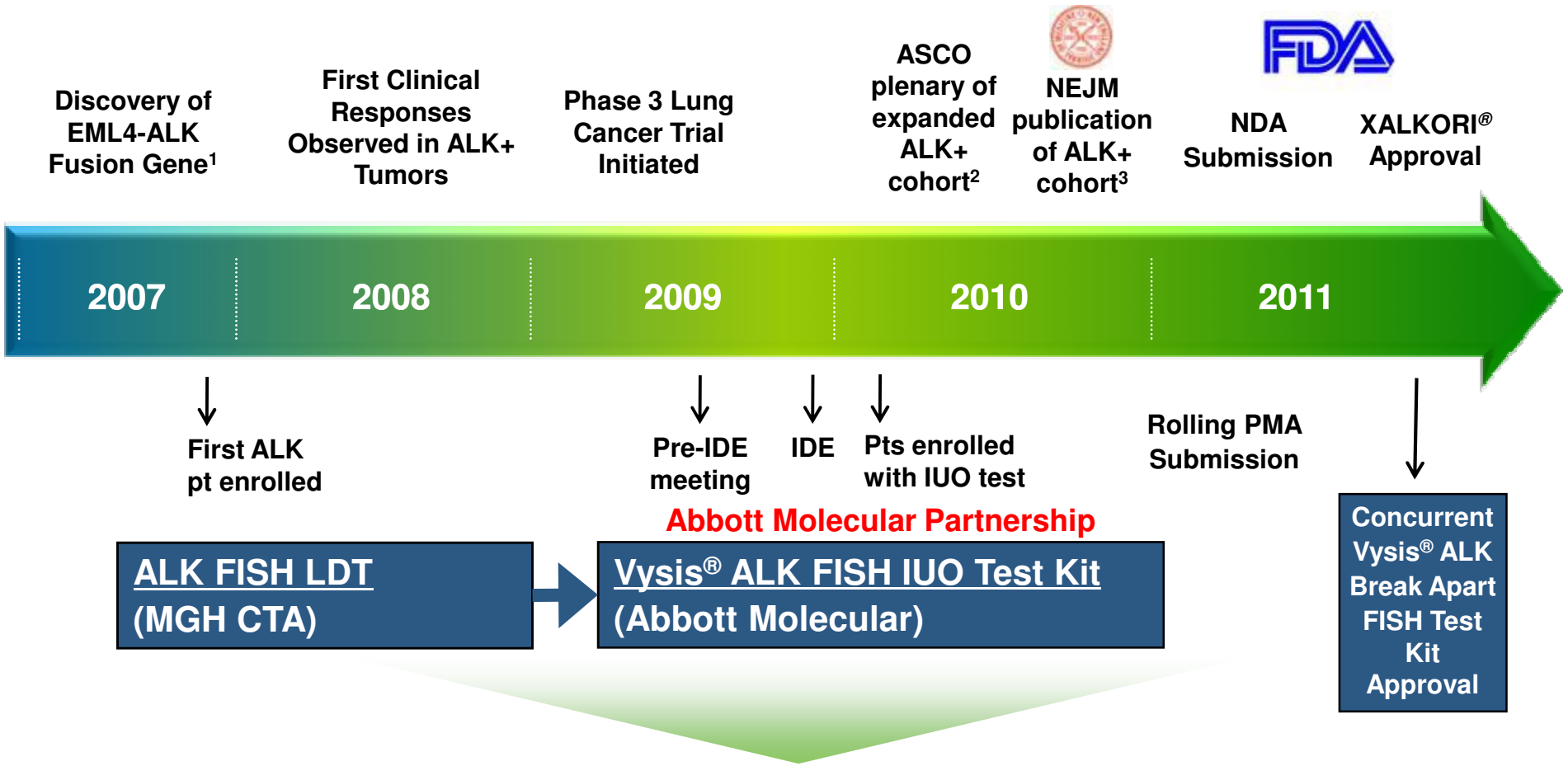

*N is based on the RE population that excludes patients with Early Death and Indeterminate

Camidge et al., ASCO 2011; Abs #2501
Kwak et al. 2011. New Engl J Med 364, 588

# Integration of genomics-based development

- Rationale for molecularly-defined target populations established pre-clinically based on target kinase profile and pre-clinical in vitro / in vivo efficacy
- Pivotal data supporting ALK gene fusion as a potential oncogenic driver in NSCLC rapidly established the key clinical predictive marker hypothesis
- Clinical efficacy supporting the ALK predictive marker hypothesis and clinical proof-of-concept early in development (Phase 1) resulted in the rapid integration of companion diagnostic test development into the clinical program
- The rapid clinical development timeline presented challenges to the co-development of a companion diagnostic test

# ALK CDx Development: From Phase 1 LDT to PMA approval



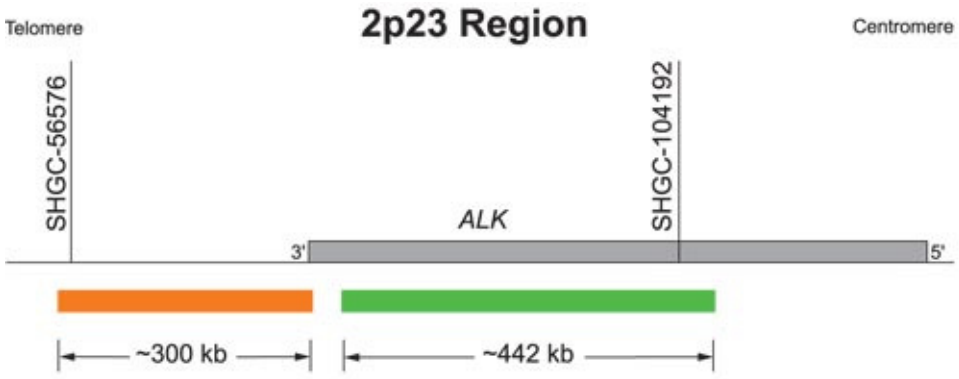

***Rapid Transition from LDT to IUO to PMA***


1. Soda et al. *Nature* 2007, 448: 561.
2. Bang JY *et al*. Oral presentation at ASCO, 2010
3. Kwak et al. *New Engl J Med*. 2010;363:1693–03

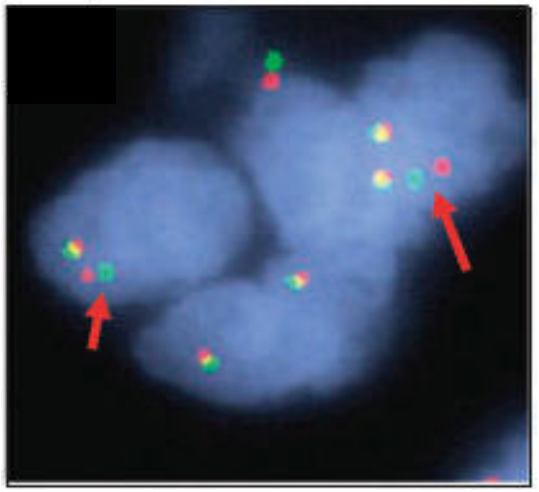
# Companion Diagnostic Test for ALK

## Platform Selection - FISH:

- clinically established platform
- break-apart assay for gene rearrangement independent of ALK fusion partner
- sample: utilizes FFPE tissue sections
- sensitive: interpretation can be made on a minimum of 50 tumor cells
- cut-off: positive defined as ≥ 15% of cells exhibiting ALK gene rearrangement
- considered lowest technical and regulatory risk




**LSI ALK Dual Color, Break Apart Rearrangement Probe**



# Clinical Development of Crizotinib in ALK-Positive Advanced NSCLC

| Protocol | Setting | Trial Design | Primary Endpoints |
|---|---|---|---|
| A8081001 | All Lines<br>Solid Tumors<br>ALK-Positive NSCLC | Single-Arm, Open-Label | Safety, PK, ORR |
| A8081005 | ≥2nd-Line | Single-Arm, Open-Label | ORR, Safety |
| A8081007<br>(confirmatory Phase 3) | 2nd-Line | Crizotinib vs. Pemetrexed or Docetaxel, Open-Label | PFS |
| A8081014<br>(confirmatory Phase 3) | 1st-Line | Crizotinib vs. Pem/Carbo or Pem/Cis, Open-Label | PFS |

**A8081001**
**LDT ALK FISH CTA**
**MGH**

→

**A8081005**
**ALK FISH IUO Test Kit**
**Abbott Molecular**

# Diagnostic Co-Development for Crizotinib

## Technical Issues

- Assay platform selection
- Specimen type(s) and analyte stability
- Selecting a cut-off value: clinical vs biologic rationale

## Operational Issues

- Tissue procurement
- CDx-focused Informed Consent Document
- Clinical data on biomarker negative population

## Partnership Coordination

- Integration of diagnostic testing into clinical trials
- Coordination of PMA submission with NDA submission

# Drug-Diagnostic Co-Development

- Advancing a candidate companion diagnostic test through early development and into PMA-enabling late development requires close integration with the clinical development plan

- Similar to the sequence of decisions committing increasing resources to advance a drug candidate through the pipeline (e.g. candidate nomination for FIH study, POM, POC), development of a candidate companion diagnostic test also a requires rigorous, data-driven evaluation:

    - Define quality predictive marker hypotheses that warrant clinical testing
    - Develop reliable clinical assays of sufficient quality to test hypothesis early in development (fit-for-purpose; technically rigorous; beware LDT)
    - Anticipate transition to IUO (plan for success)
    - Data-driven decision to initiate IUO development for use in pivotal studies

# Summary: Crizotinib as a Case Study for Drug Discovery and Development

- Quality science - pre-clinical and clinical disease biology
- Flexibility in clinical development
- Rigorous clinical IVD test development and validation
- Informed Dx development strategy anticipating IUO/PMA
- Productive collaboration with diagnostic company partner