Development of Crizotinib for the Treatment of ALK-positive NSCLC

Accelerated Approval August 26, 2011
Regular Approval November 20, 2013

YS CHO, M.D., Ph.D.

August 28, 2018

❖ *Crizotinib (Trade name: XALKORI™) Product Profile*

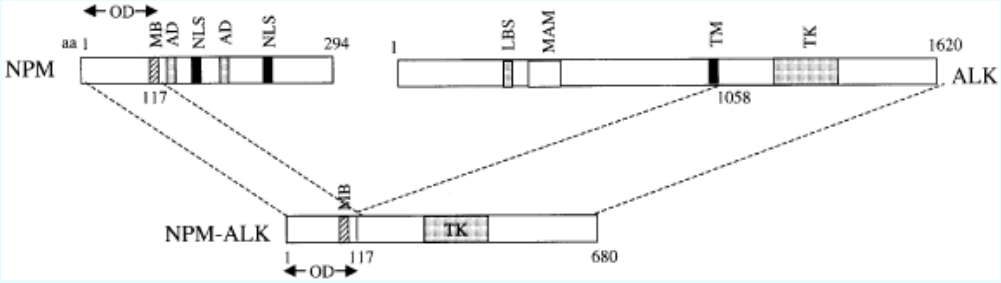
- **U.S. Sponsor: Pfizer, Inc.**
- **Indication:**
  - **metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test**
  - **metastatic NSCLC whose tumors are ROS1-positive.**
- **Capsules: 250 mg and 200 mg**
- **250 mg orally, twice daily**
- **NDA 252070**

❖ *Contents*

1. *Target ID & Discovery*
2. *Chemistry review*
3. *Pharmacology review*
4. *Medical & Clinical pharmacology review*
5. *Discussion*

❖ 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.

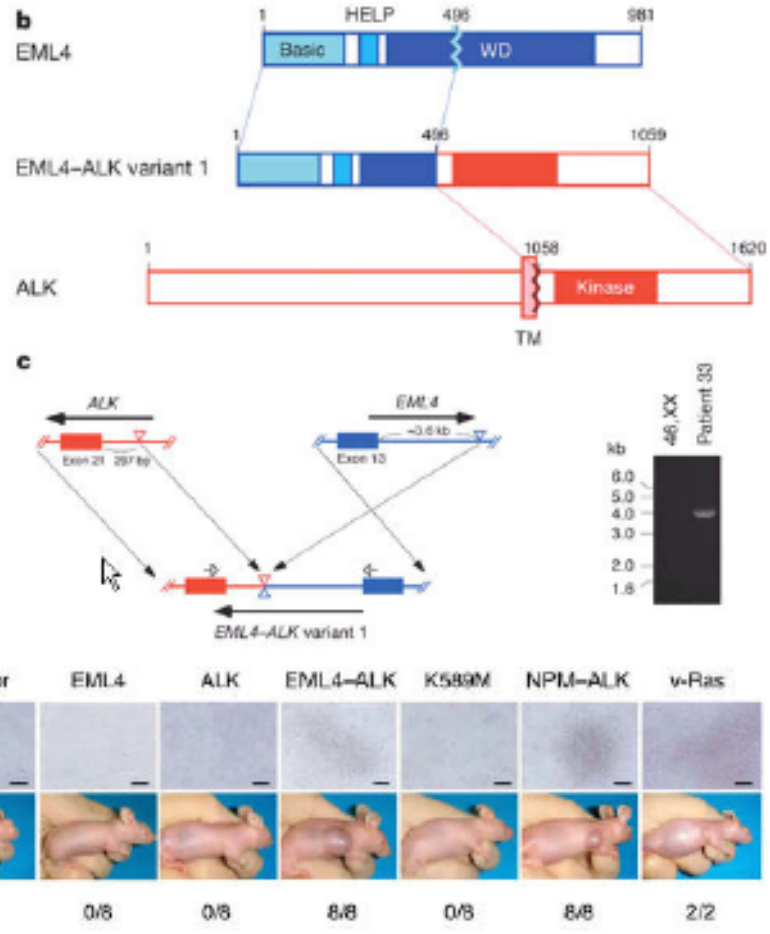


❖ Functional Genomic Screen Leading to ALK in NSCLC

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

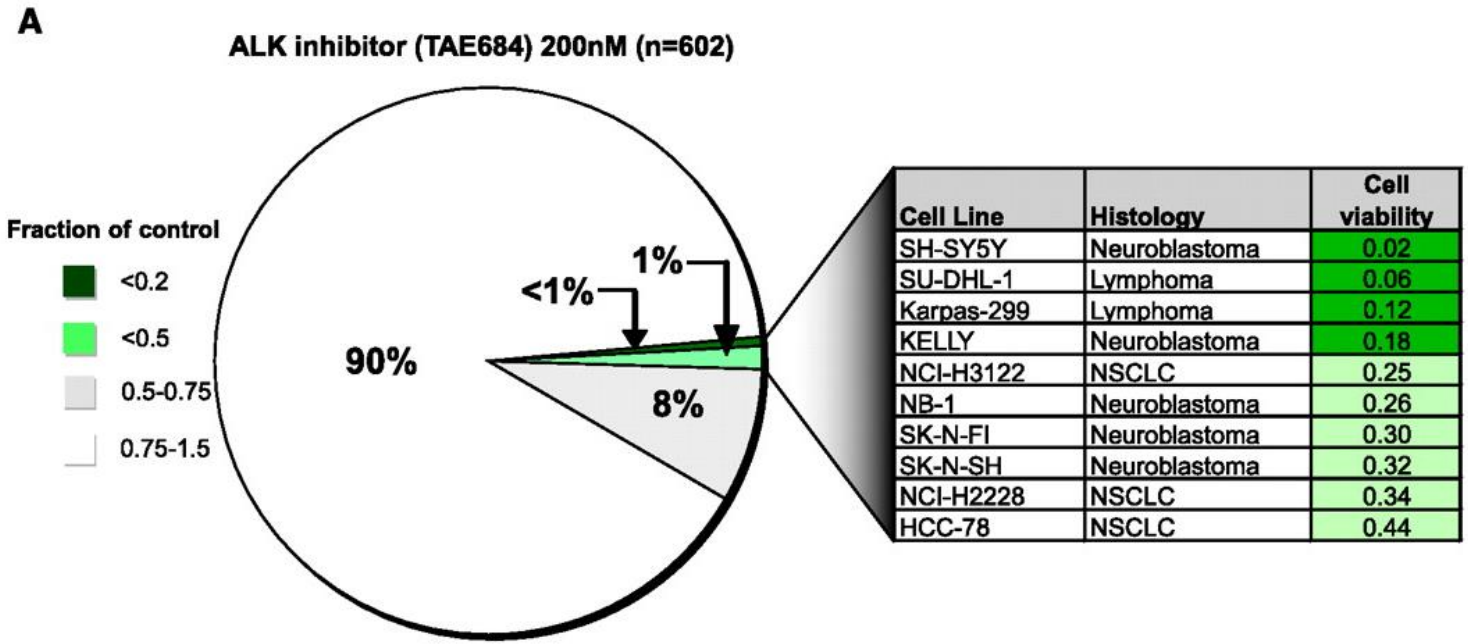
"Classical" functional genomic screen

- 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

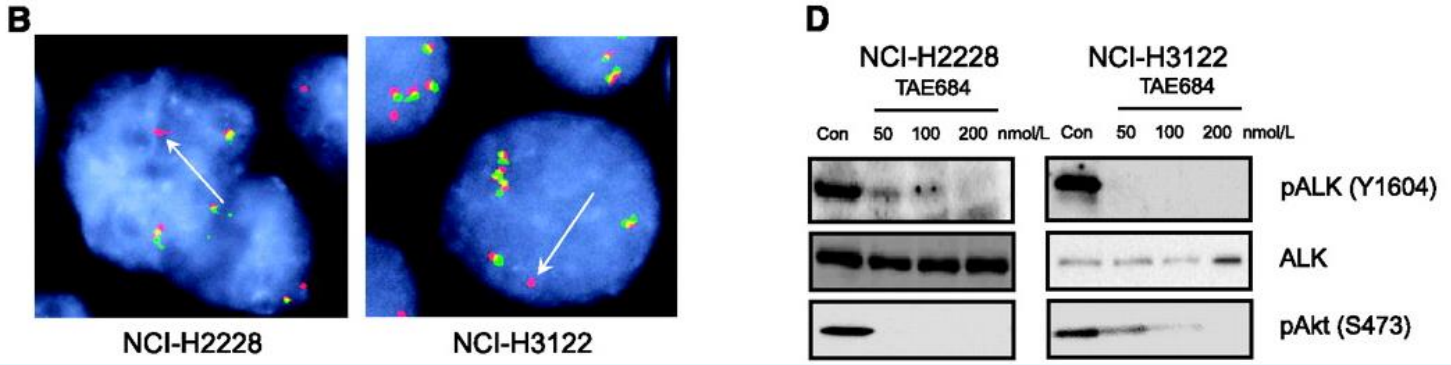


- also: Rikova et al. Cell v 131 (14 Dec 2007): Phosphoproteomic survey in NSCLC

❖ Functional Genomic Screen Leading to ALK in NSCLC



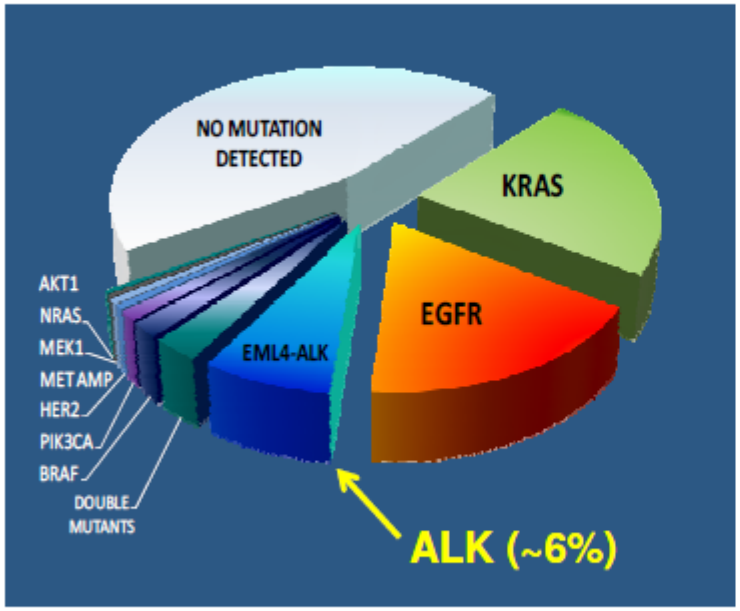
Cell Line	Histology	Cell viability
SH-SY5Y	Neuroblastoma	0.02
SU-DHL-1	Lymphoma	0.06
Karpas-299	Lymphoma	0.12
KELLY	Neuroblastoma	0.18
NCI-H3122	NSCLC	0.25
NB-1	Neuroblastoma	0.26
SK-N-FI	Neuroblastoma	0.30
SK-N-SH	Neuroblastoma	0.32
NCI-H2228	NSCLC	0.34
HCC-78	NSCLC	0.44



Cancer Res. 2008 May 1;68(9):3389-95

❖ Challenges: low frequency population

Lung Cancer Mutation Consortium (Adenocarcinomas)

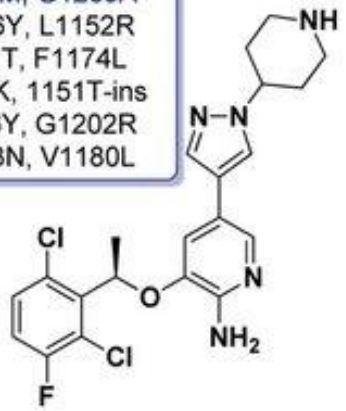


- N=830 registered (varying numbers per test)
- Mutations identified in 60%
- Mutually exclusive in 95%
- ALK gene fusion identified by FISH analysis

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

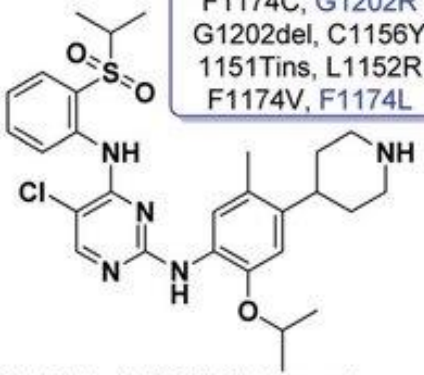
❖ ALK inhibitors

Crizotinib Resistance Mutations
L1196M, G1269A
C1156Y, L1152R
I1171T, F1174L
E1210K, 1151T-ins
S1206Y, G1202R
D1203N, V1180L



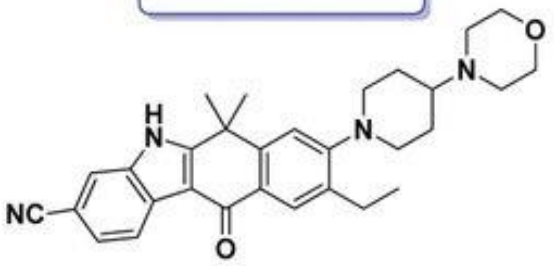
Crizotinib (PF-2341066), Pfizer
1st-generation ALK inhibitor
FDA approved in Aug, 2011 as ALK/c-Met inhibitor
FDA approved in Mar, 2016 as ROS1 inhibitor

Ceritinib Resistance Mutations
F1174C, G1202R
G1202del, C1156Y
1151Tins, L1152R
F1174V, F1174L

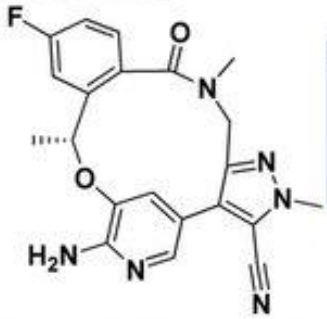


Ceritinib (LDK-378), Novartis
2nd-generation ALK inhibitor
Breakthrough therapy designation in March 2013
FDA approved in April, 2014 as ALK inhibitor
FDA approved in May, 2017 as first line therapy

Alectinib Resistance Mutations
I1171T/N/S, G1202R
V1180L

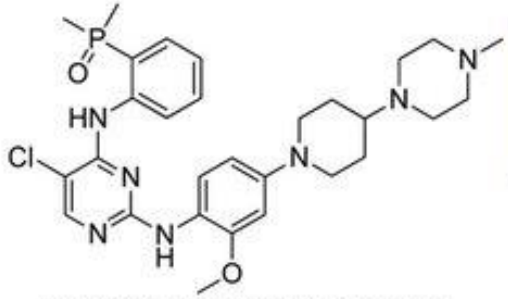


Alectinib (CH5424802), Chugai, Roche
2nd-generation ALK inhibitor
FDA approved in Dec, 2015 (Genentech Inc.)
ALK, GAK and LTK inhibitor



Lorlatinib Resistance Mutations
L1198F,
C1156Y/L1198F
C1156Y

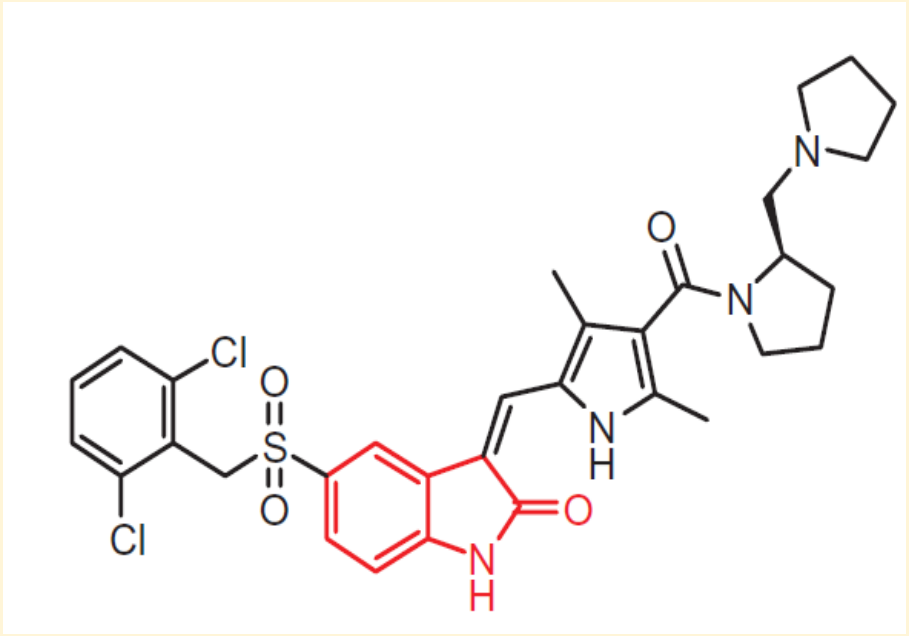
Lorlatinib (PF-06463922), Pfizer
3rd-generation ALK inhibitor
ALK/ROS1 inhibitor in Phase I/II trials
Breakthrough therapy designation in April 2017



Brigatinib Resistance Mutations
G1202R
E1210K + S1206C
E1210K + D1203N

Brigatinib (AP26113), Alunbrig
3rd-generation ALK inhibitor, Phase II
FDA approved in April, 2017 as ALK inhibitor

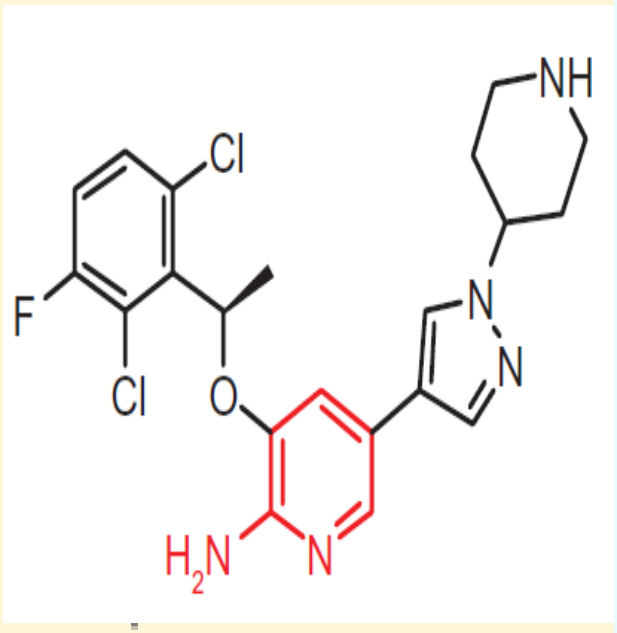
❖ Discovery: Structure Based Drug Design of Crizotinib



MW 641.61, LogD 3.20
c-Met cell IC_{50} 9 nM

SBDD

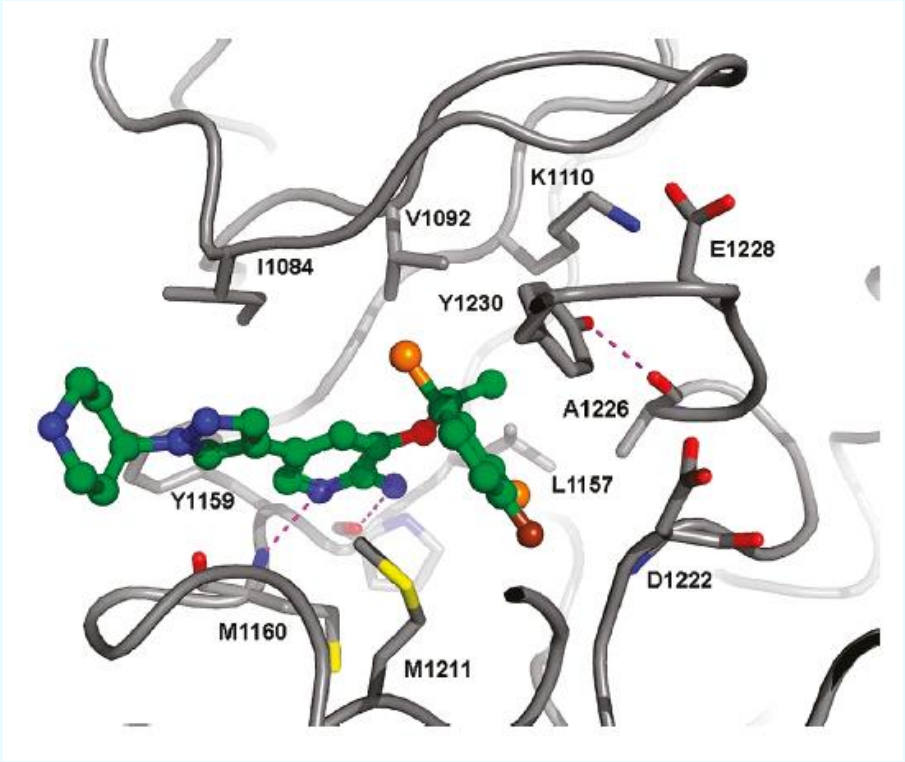
-1.24 LogD
-191 MW



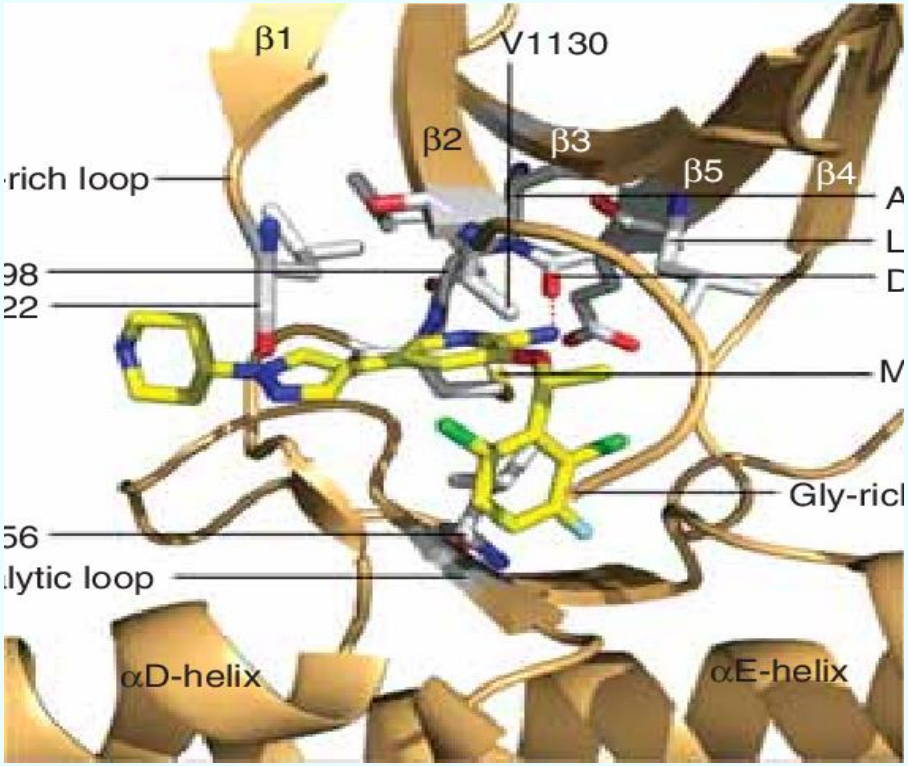
Crizotinib
MW 450.34, LogD 1.96
c-Met cell IC_{50} 8 nM
ALK cell IC_{50} 20 nM

J Med Chem. 2011 Sep 22;54(18):6342-63

❖ Mechanism of Action:
ATP competitive kinase inhibitor
Main targets: c-Met, ALK, ROS



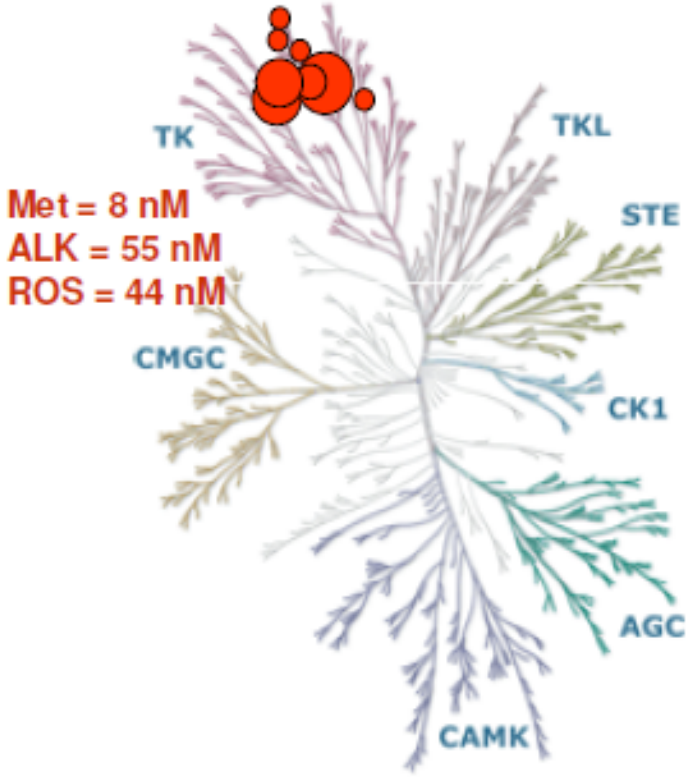
c-Met

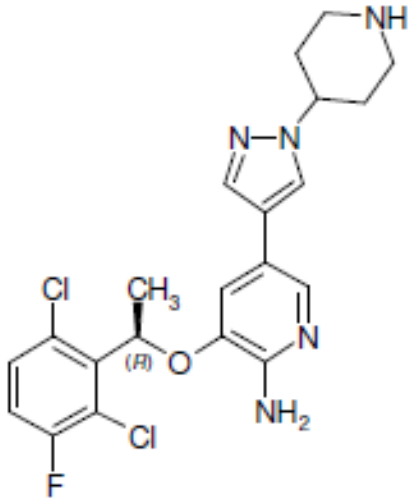


ALK

J Med Chem. 2011 Sep 22;54(18):6342-63

❖ Target Profile





1-20 nM

20-60 nM

60-200 nM

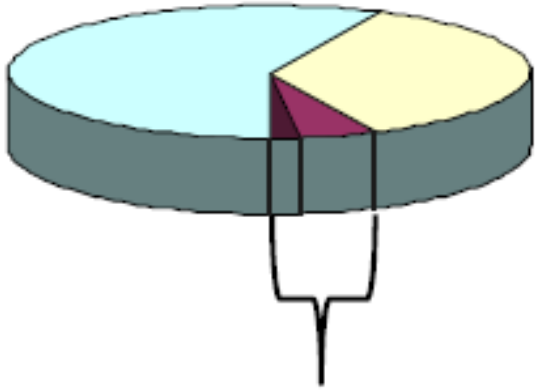
200-1000 nM

>1000 nM
not depicted

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

❖ Understanding Molecular Correlates with Response To Crizotinib

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



Crizotinib sensitive cell lines included:

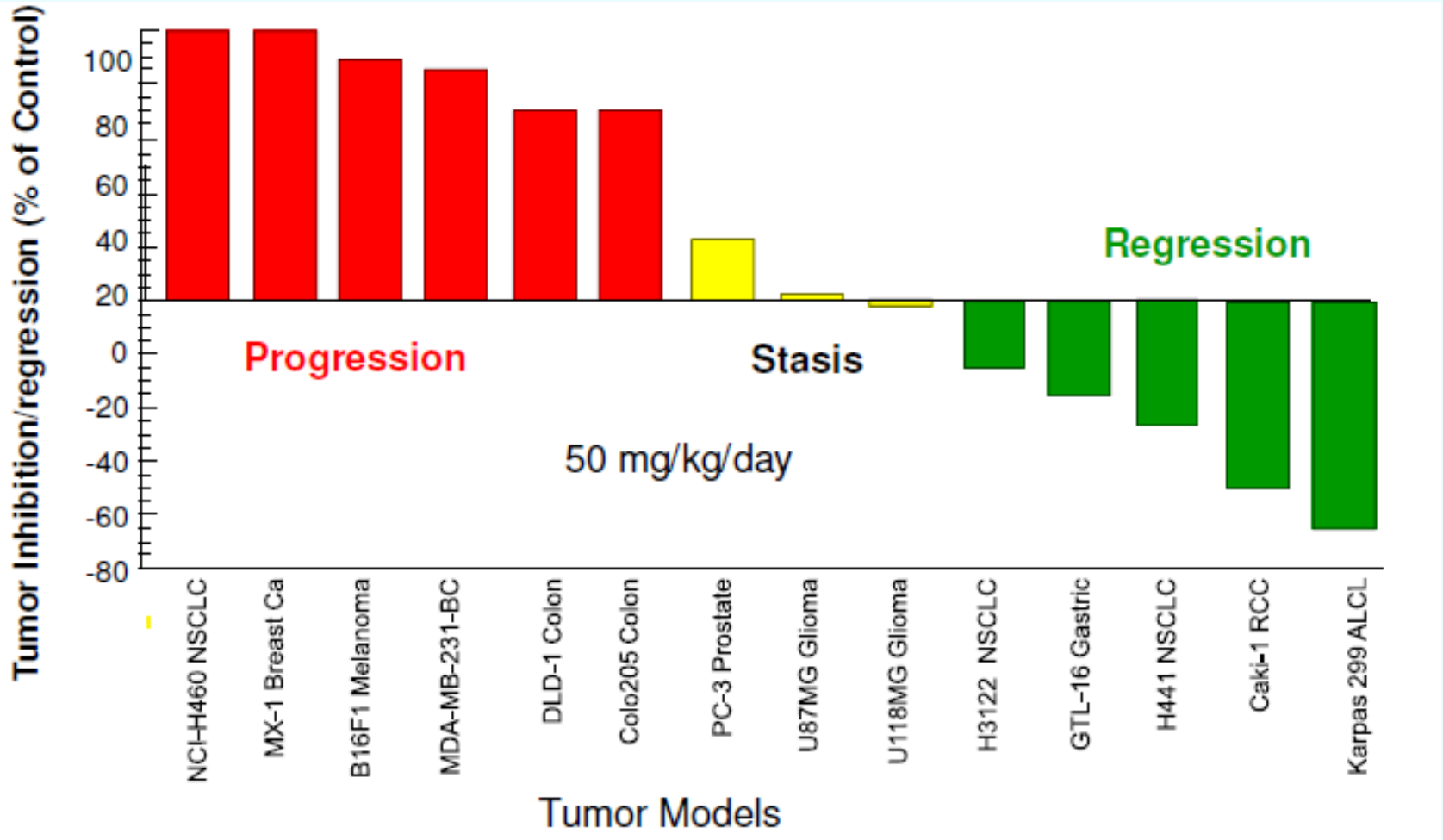
- gastric, esophageal and NSCLC with MET amplification
- Neuroblastoma with ALK mutation or amplification
- anaplastic large cell lymphoma with NPM-ALK fusion
- NSCLC with EML4-ALK fusion
- NSCLC with ROS fusion

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

❖ *CMC*

- **Drug Product**
  - **Three formulations : powder in capsule (PIC), immediate release tablet, and intravenous solution**
  - **Commercial : a hard gelatin capsule formulation**
  - **Stability test : 15 mon recommended expiry**
- **Drug Substance**
  - **New Molecular Entity (NME)**
  - **BCS class IV**

❖ Pharmacology-Spectrum of Response to Crizotinib in Preclinical Tumor Models



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

❖ Safety Pharmacology

- **Neurological : reduced locomotor activity**
- **Cardiovascular : inhibited the hERG channel at all concentrations tested with an IC_{50} of 1.1 µM**
- **Hemodynamic and electrophysiological :LVEDP increase**
- **Pulmonary : lower Minute Volume & RR, TV increase**

❖ General Toxicology

- **Repeated Dose Toxicity:**

Duration	Species	Route	Dose (mg/kg /day)	End Point	Target Organ
7 Day(s)	Rat	Oral	150	NOAEL	None identified
28 Day(s)	Mouse	Oral	200	NOAEL	None identified
1 Month(s)	Rat	Oral	10	NOAEL	Bone Marrow, Kidney, Male reproductive system
1 Month(s)	Dog	Oral	20	NOAEL	None identified
3 Month(s)	Rat	Oral	(M)100 / (F)250	LOAEL	Male reproductive system, Bone Marrow, Liver, Gastrointestinal system, Pituitary
3 Month(s)	Dog	Oral	25	NOAEL	Blood

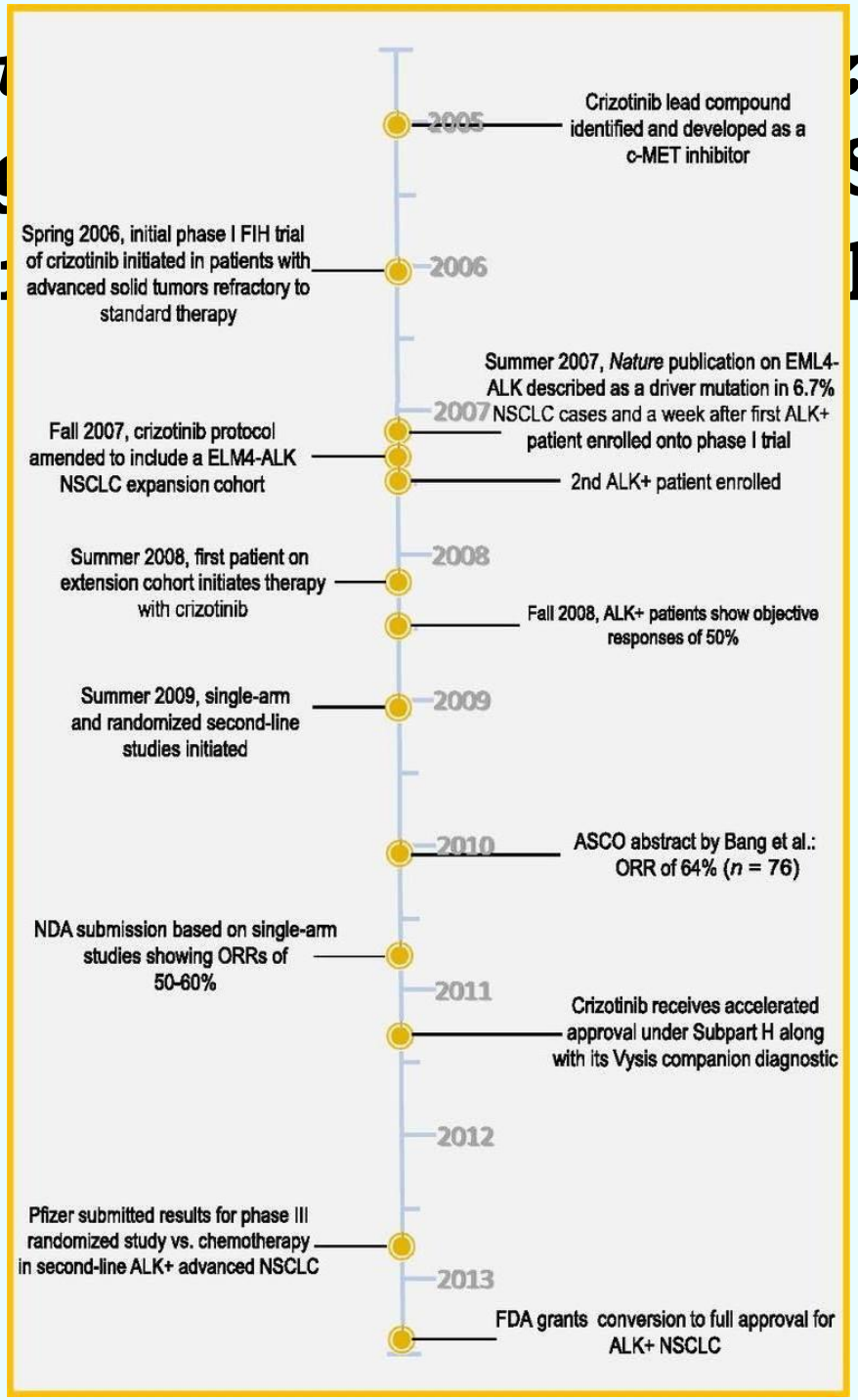
❖ Reproduction & Development Toxicity:

Duration	Species	Route	Dose (mg/kg /day)	End Point	Effects
Embryo / Fetal Devel.	Rat	Oral	200	LOAEL	Maternal toxicity, Developmental toxicity
--	Rabbit	Oral	60	NOAEL	Maternal Toxicity
--	Rabbit	Oral	60	LOAEL	Developmental toxicity

❖ Genetic Toxicity:

Study Type	Cell Type/Organism,	Result
Bacterial Mutagenicity (Ames)	*Salmonella* , *E. coli*	Negative
In Vitro Micronucleus	CHO cells	Positive without activation
In Vitro Chromosome Aberration	Human Lymphocytes	Positive
In Vivo Micronucleus	Rat Bone Marrow	Positive

- ***Cli… …otinib ag… …SCLC***
- **Timeli… …leopment**



❖ *Clinical Trials of Crizotinib against ELM4-ALK NSCLC*

2 Early Clinical Trials → Accelerated Approval

Subpart H--Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

(August 26, 2011)

- **1 Phase 1 Trials**
  (119 patients with ALK (+) NSCLC)
- **1 Phase 2 Trials**
  (136 patients with ALK (+) NSCLC)

❖ *Clinical Trials of Crizotinib against ELM4-ALK NSCLC*

Accelerated Approval

+ 2 Clinical Trials →

Full Approval

(November 20, 2013)

- **2 Phase 3 Trials**
- **Prospective comparison**

  1st line(343 patients with ALK (+) NSCLC)

  2nd line(347 patients with ALK (+) NSCLC)

❖ Phase 1 Clinical Trials

- **Multicenter, single arm**
- **1st Part**
- **Any solid tumor refractory to standard TX**
- **Dose-escalation study (MTD) :**

  50 ~ 2000mg, once or twice/day
- **2 patients with ALK (+) NSCLC**

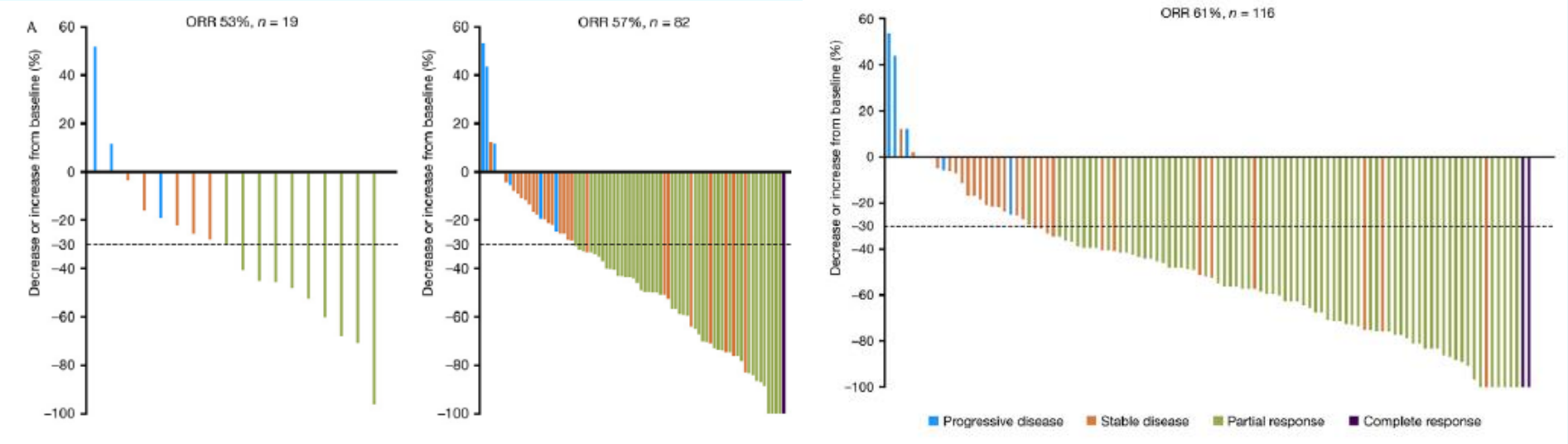
→ dramatic improvement in symptoms

→ large-scale prospective screening for ALK(+) NSCLC

→ enrollment into an expanded molecular cohort :2nd Part

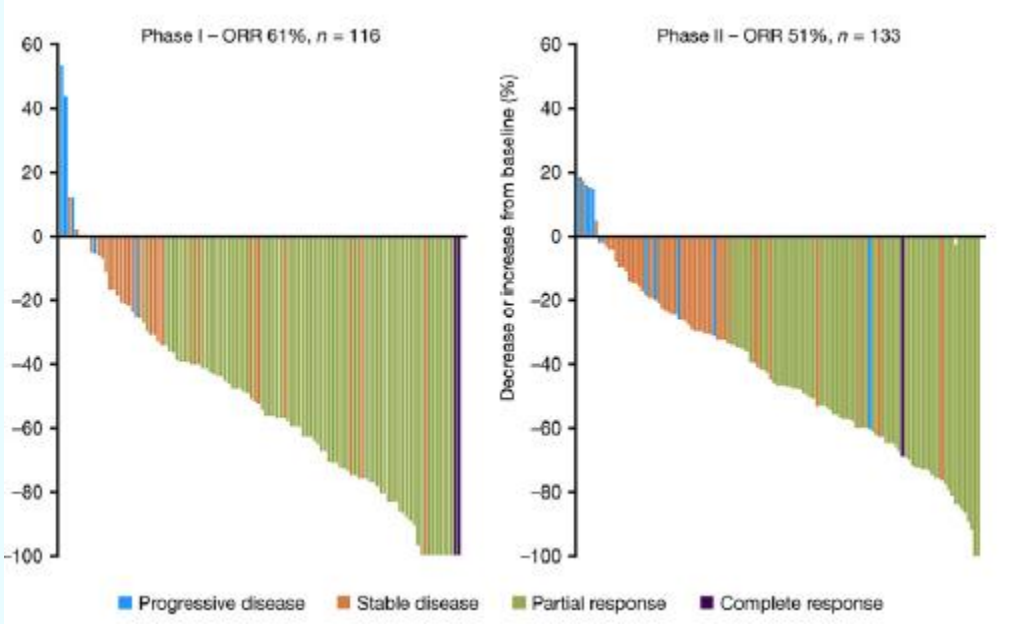
❖ Phase 1 Clinical Trials

- 2nd Part
  - Expanded molecular cohort :ALK (+) NSCLC
  - 250mg, twice/day
  - ORR: 61%
  - DOR: 48.1 weeks



❖ Phase 2 Clinical Trials

- **Advanced ALK (+) NSCLC after tumor progression on at least 1 line of chemotherapy, Multicenter, single arm**
- **250mg, twice/day**
- **ORR: 51%**
- **DOR: 41.9 weeks**



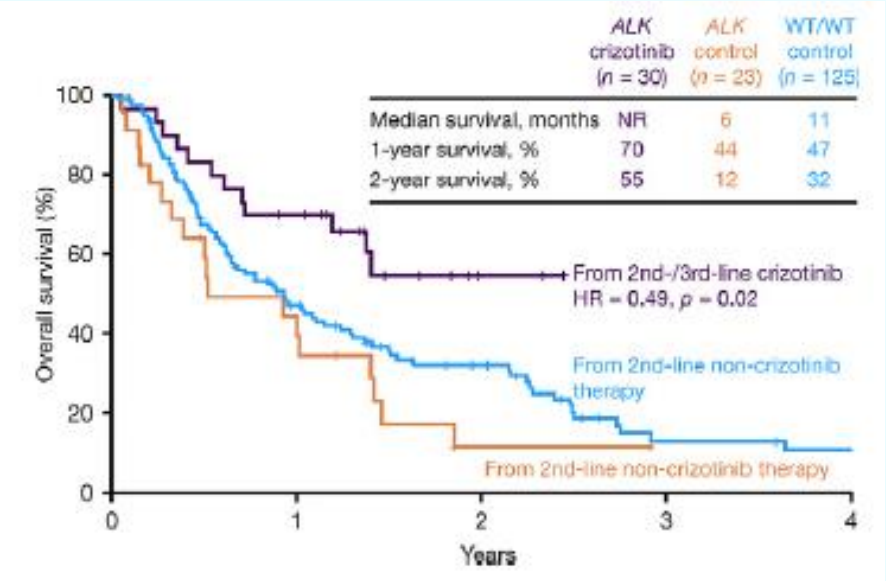
Crizotinib activity in the phase I and phase II trials.[a,b]

	Phase I (A8081001) $N = 119$[a]	Phase II (A8081005) $N = 136$[b]
ORR, %	61	50
Number of responders	71	68
Median (range) duration of response, weeks	48.1 (4.1+, 76.6+)	41.9 (6.1+, 42.1+)
Responses achieved during the first 8 weeks of treatment, %	55	79
Median duration of treatment, weeks	32	22

❖ Phase 1 & 2 Clinical Trials

- **Retrospective comparison of the duration of crizotinib TX with previous lines of TX:**
  - **lacking prospective comparative data**

•Historical case-match analysis of OS



❖ Phase 1 & 2 Clinical Trials

- **Adverse events (any causality) in >10% of patients**

Adverse event	Treatment-related	
	All grades n (%)	Grade 3–4 n (%)
Eye disorders*	159 (62%)	0
Gastrointestinal disorders		
Nausea	136 (53%)	0
Diarrhea	109 (43%)	0
Vomiting	101 (40%)	0
Constipation	69 (27%)	1 (<1%)
Esophageal disorder**	29 (11%)	0
General		
Edema	72 (28%)	0
Fatigue	51 (20%)	4 (2%)
Decreased appetite	49 (19%)	0
Nervous system disorder		
Dizziness	42 (16%)	0
Neuropathy	34 (13%)	1 (<1%)
Dysgeusia	30 (12%)	0
Liver disorders		
Alanine transaminase increase	34 (13%)	14 (5%)
Skin disorders		
Rash	25 (10%)	0

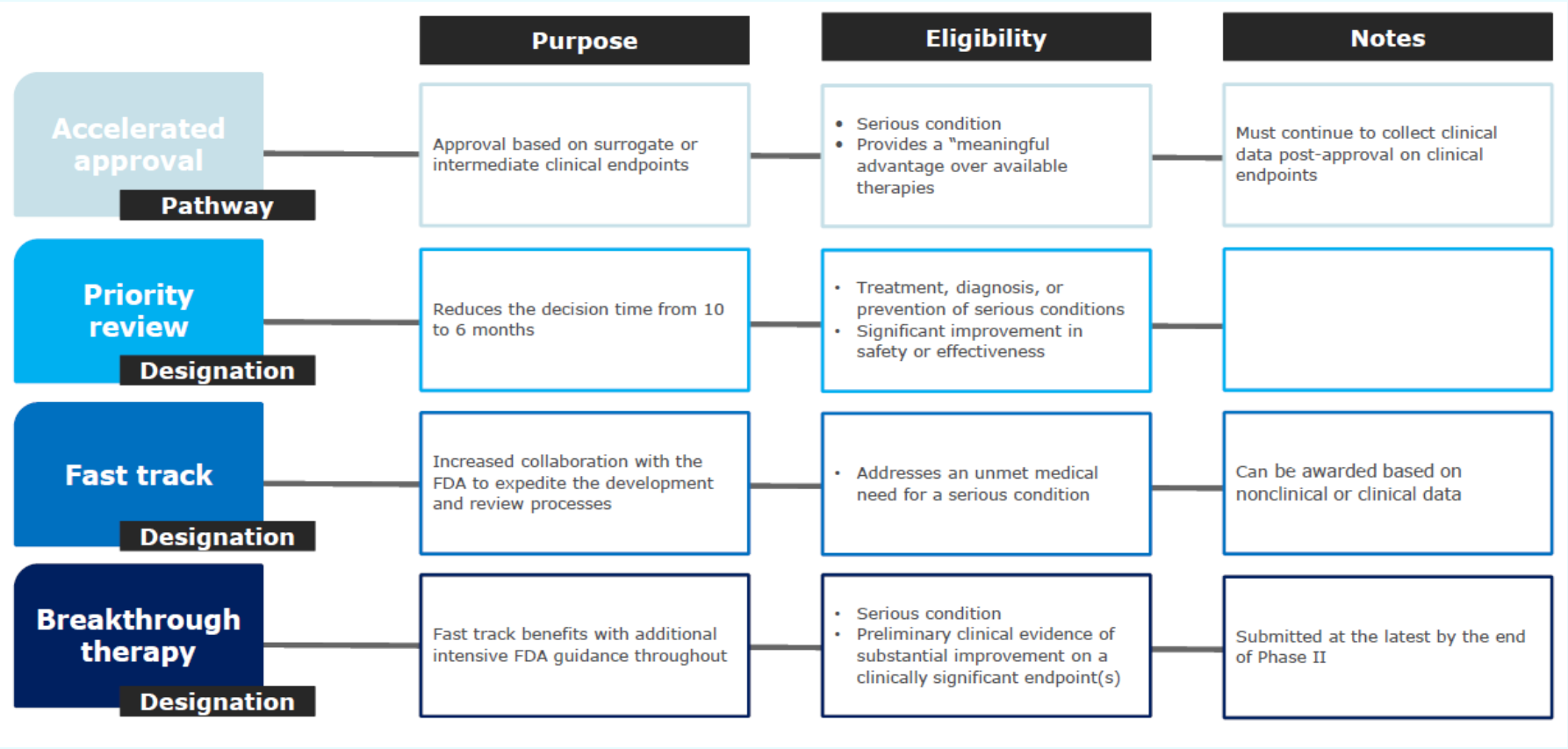
❖ Accelerated Approval (August 26, 2011)

21 CFR Part 314, Subpart H - Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

❖ **Requirements:**

- **a drug must address a serious or life-threatening condition**
- **The drug must demonstrate effect on an intermediate clinical endpoint (or surrogate endpoint)—a result that is reasonably likely to predict clinical long-term benefit and can be measured earlier than that benefit**
- **still need to conduct confirmatory trials**

❖ Accelerated Approval

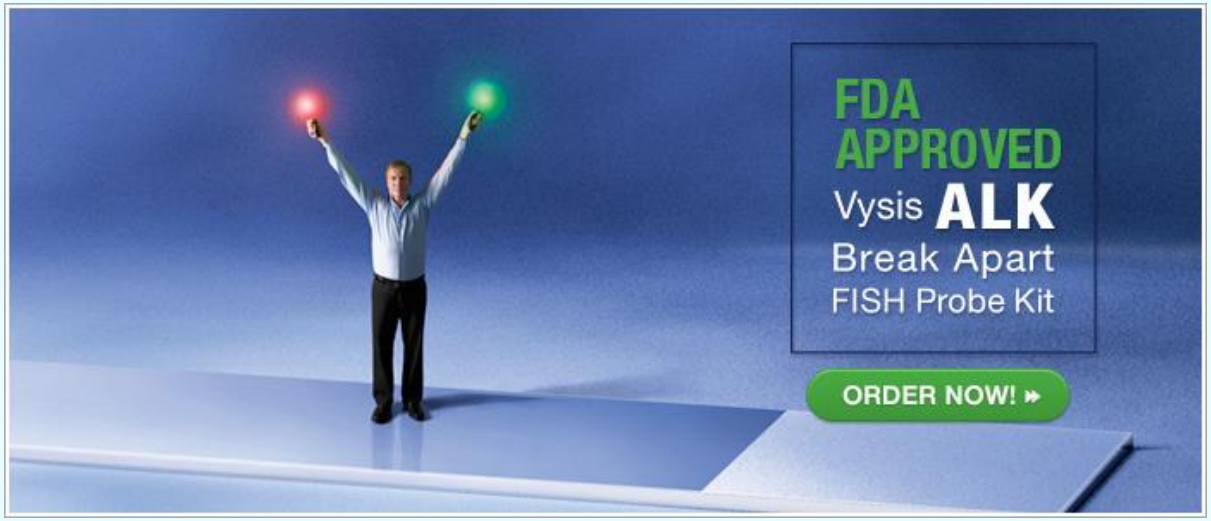


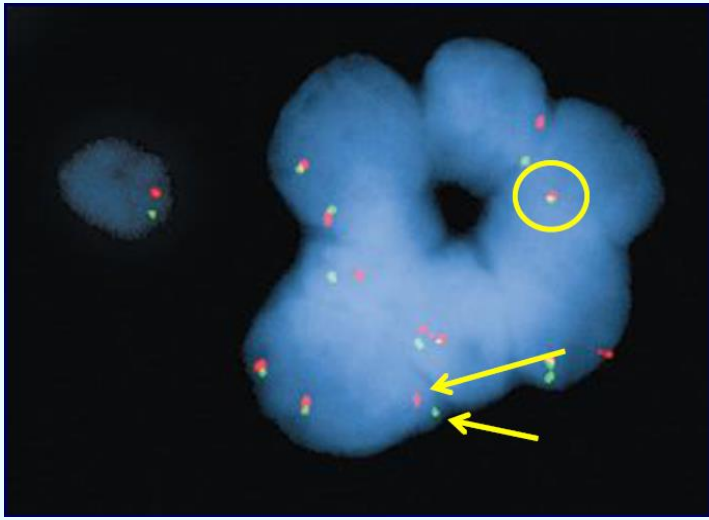
- **36 drugs were analysed, 19 of which were approved based on rate of response (RR), 17 based on progression-free or disease free survival (PFS or DFS)**
- **Based on a median follow-up of 4.4 years, only 5 drugs had demonstrated improvement in overall survival in randomized clinical trials**

Kim C, Prasad V. JAMA Intern Med. Online: October 19, 2015

❖ Accelerated Approval (August 26, 2011)

- **Vysis ALK Break-Apart FISH Probe Kit (Abbott Molecular, Inc.) was approved concurrently**





❖ Available methods for detecting ALK (+)

- **FISH**
- **IHC**
- **RT PCR**

	RT-PCR	FISH	IHC
Advantages	High sensitivity	High specificity	Easy reading
	Quick method	PETT is suitable for this technique	Quick method
		Possibility of detection of new promoters	Lower cost
		Gold standard technique for the clinical trials using ALK inhibitors	Possibility of detection of new variants
			Detection of all rearrangements, no specific promoter is required
			Widely available
			Commercialized antibodies
Disadvantages	High quality and enough RNA quantity is required	Lower sensitivity	The fusion gene is indirectly detected by the protein expression
	Difficult to obtain RNA from small biopsies	Expertise in interpreting the results	Risk of false negative results
	Potential degradation of RNA in PETT	Risk of false negative results	Results can vary according to type and dilution of the antibody and reading method
	No new promoters are detected	No widely available	Compared to other tumors, the protein expression can be weaker in lung cancer (risk of false negative)
	No widely available	More time consuming	Reading method has been adapted from EGFR and HER2 score systems
		Higher cost	

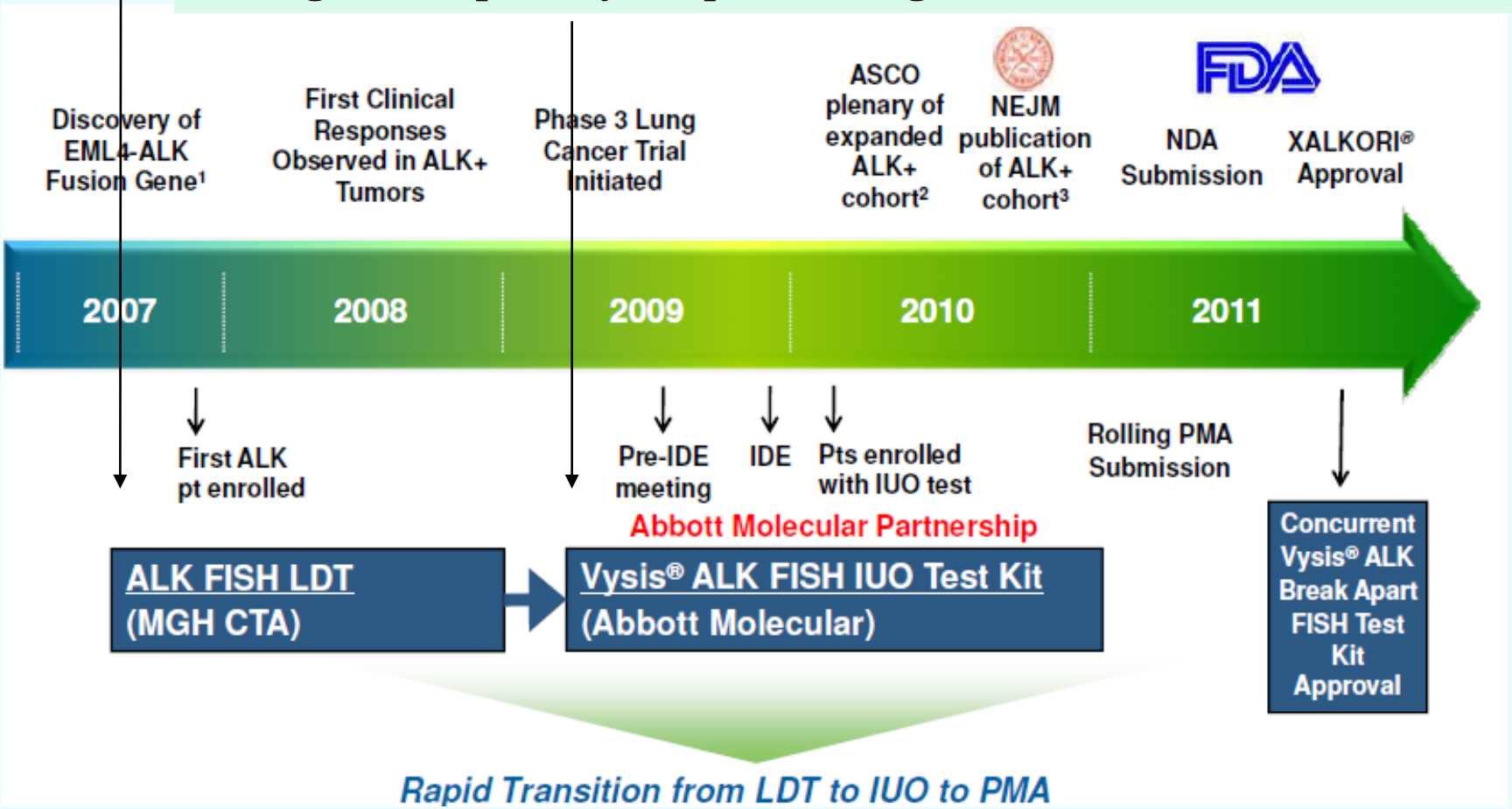
PETT, paraffin embedded tumor tissue

❖ ALK (+) CDx Development:

▪ From Phase I LDT to Approval

•cell lines harboring ALK rearrangement susceptible to crizotinib (Dr. Iafrate) - LDT

•Pfizer partnered with Abbott to devise this companion diagnostic for two reasons. First, Abbott made the fluorescent probes used in the LDT that Dr. Iafrate and his group devised. Second, "Abbott has a global capability for product registration,"



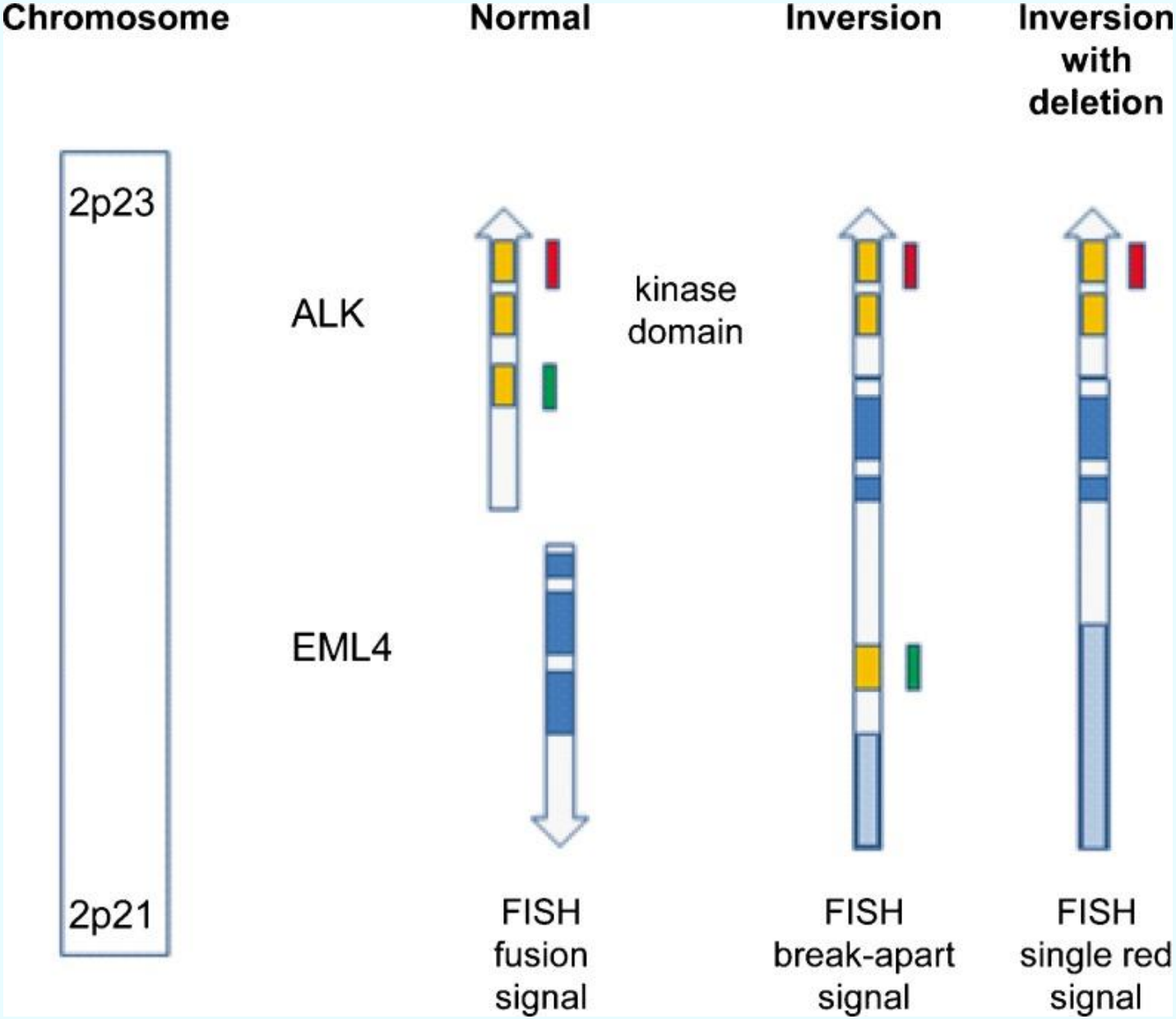
❖ PMA #: P110012

- **Preclinical Studies**
  - **Lab studies**
    - **Analytical performance for safety and effectiveness : 10 – 20 items**
- **Primary Clinical study**
  - **A8081005**
- **Criteria for FISH Break Apart ALK (+)**

Characteristics	Criteria for positivity
Number of cells counted	At least 50 cells
Percentage of positive signals	>15%
Distance between 5′ (green) and 3′ (red) *ALK* signals	Greater than two signal diameter separation
Presence of single 3′ *ALK* (red) signal only	Yes
Presence of single 5′ *ALK* (green) signal only	No

❖ Conclusion

- **Good reproducibility**
- **No significant difference btw readers, sites, and days**
- **Moderate-high CV%: not unexpected with FISH**
- **Safety : tissue section removal → safe**
- **Effectiveness : Response rate of 1005 study**


Chromosome
Normal
Inversion
Inversion with deletion
2p23
2p21
ALK
EML4
kinase domain
FISH fusion signal
FISH break-apart signal
FISH single red signal

❖ Phase 3 Clinical Trials

- **2nd line(347 patients with metastatic ALK (+) NSCLC): A8081007**
- **1st line(343 patients with metastatic ALK (+) NSCLC): A8081014**

❖ Phase 3 Clinical Trials

- **A8081007**
  - **Previously treated with 1 platinum-based chemoTX**
  - **Randomized, Multicenter, Open label, Active controlled (Pemetrexed or Docetaxel)**
  - **Primary efficacy endpoints: PFS**
  - **Option!!**

    At the time of progression, chemoTX → Crizotinib (1005)

❖ Phase 3 Clinical Trials

- **A8081007**

Table 8. Previously Treated ALK-Positive Metastatic NSCLC - Efficacy Results

	XALKORI (N=173)	Chemotherapy (N=174)
Progression-Free Survival (Based on IRR)		
Number of Events (%)	100 (58%)	127 (73%)
Progressive Disease	84 (49%)	119 (68%)
Death	16 (9%)	8 (5%)
Median, Months (95% CI)	7.7 (6.0, 8.8)	3.0[a] (2.6, 4.3)
HR (95% CI)[b]	0.49 (0.37, 0.64)	
p-value[c]	<0.001	
Overall Survival[d]		
Number of Events (%)	49 (28%)	47 (27%)
Median, Months (95% CI)	20.3 (18.1, NR)	22.8 (18.6, NR)
HR (95% CI)[b]	1.02 (0.68, 1.54)	
p-value[c]	0.92	
Tumor Responses (Based on IRR)		
Objective Response Rate % (95% CI)	65% (58, 72)	20% (14, 26)
CR, n (%)	1 (0.6%)	0
PR, n (%)	112 (65%)	34 (20%)
p-value[e]	<0.001	
Duration of Response		
Median, Months (95% CI)	7.4 (6.1, 9.7)	5.6 (3.4, 8.3)

HR=hazard ratio; CI=confidence interval; IRR=independent radiology review; NR=not reached; CR=complete response; PR=partial response.

[a] For pemetrexed, the median PFS was 4.2 months. For docetaxel, the median PFS was 2.6 months.

[b] Based on the Cox proportional hazards stratified analysis.

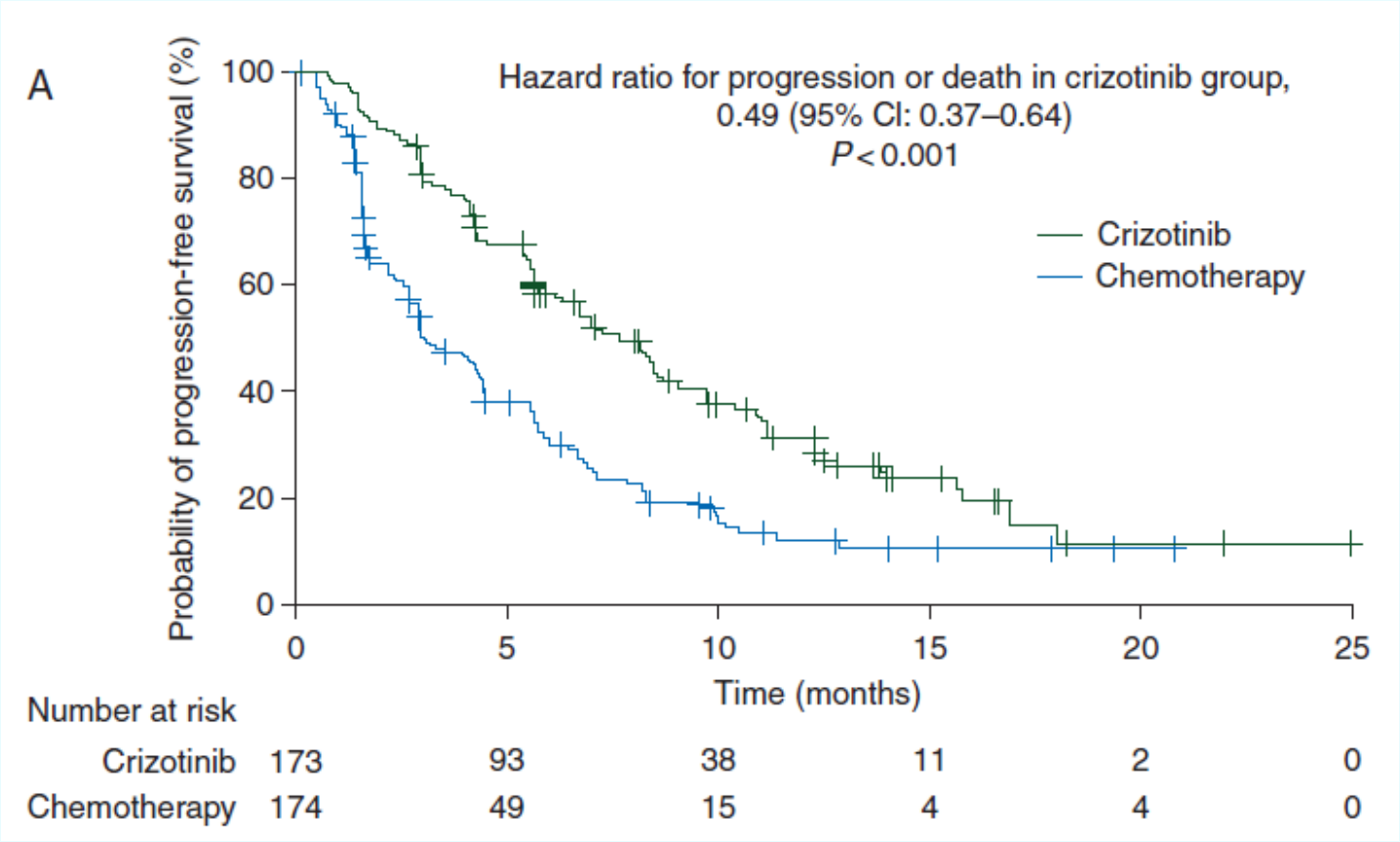
[c] Based on the stratified log-rank test.

[d] Interim OS analysis conducted at 40% of total events required for final analysis.

[e] Based on the stratified Cochran-Mantel-Haenszel test.

❖ Phase 3 Clinical Trials

- **A8081007**
  - **Statistically significant improvement in PFS**



❖ Phase 3 Clinical Trials

- **A8081014**
  - **not received previous systemic treatment for advanced disease**
  - **Randomized, Multicenter, Open label, Active controlled (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin)**
  - **Primary efficacy endpoints: PFS**
  - **Option!!**

    At the time of progression,

    chemoTX → Crizotinib

❖ Phase 3 Clinical Trials

- **A8081014**

Table 7. Previously Untreated ALK-Positive Metastatic NSCLC - Efficacy Results

	XALKORI (N=172)	Chemotherapy (N=171)
Progression-Free Survival (Based on IRR)		
Number of Events (%)	100 (58%)	137 (80%)
Progressive Disease	89 (52%)	132 (77%)
Death	11 (6%)	5 (3%)
Median, Months (95% CI)	10.9 (8.3, 13.9)	7.0 (6.8, 8.2)
HR (95% CI)[a]	0.45 (0.35, 0.60)	
p-value[b]	<0.001	
Overall Survival[c]		
Number of Events (%)	44 (26%)	46 (27%)
Median, Months (95% CI)	NR	NR
HR (95% CI)[a]	0.82 (0.54, 1.26)	
p-value[b]	0.36	
Tumor Responses (Based on IRR)		
Objective Response Rate % (95% CI)	74% (67, 81)	45% (37, 53)
CR, n (%)	3 (1.7%)	2 (1.2%)
PR, n (%)	125 (73%)	75 (44%)
p-value[d]	<0.001	
Duration of Response		
Median, Months[e] (95% CI)	11.3 (8.1, 13.8)	5.3 (4.1, 5.8)

HR=hazard ratio; CI=confidence interval; IRR=independent radiology review; NR=not reached; CR=complete response; PR=partial response.

[a] Based on the Cox proportional hazards stratified analysis.

[b] Based on the stratified log-rank test.

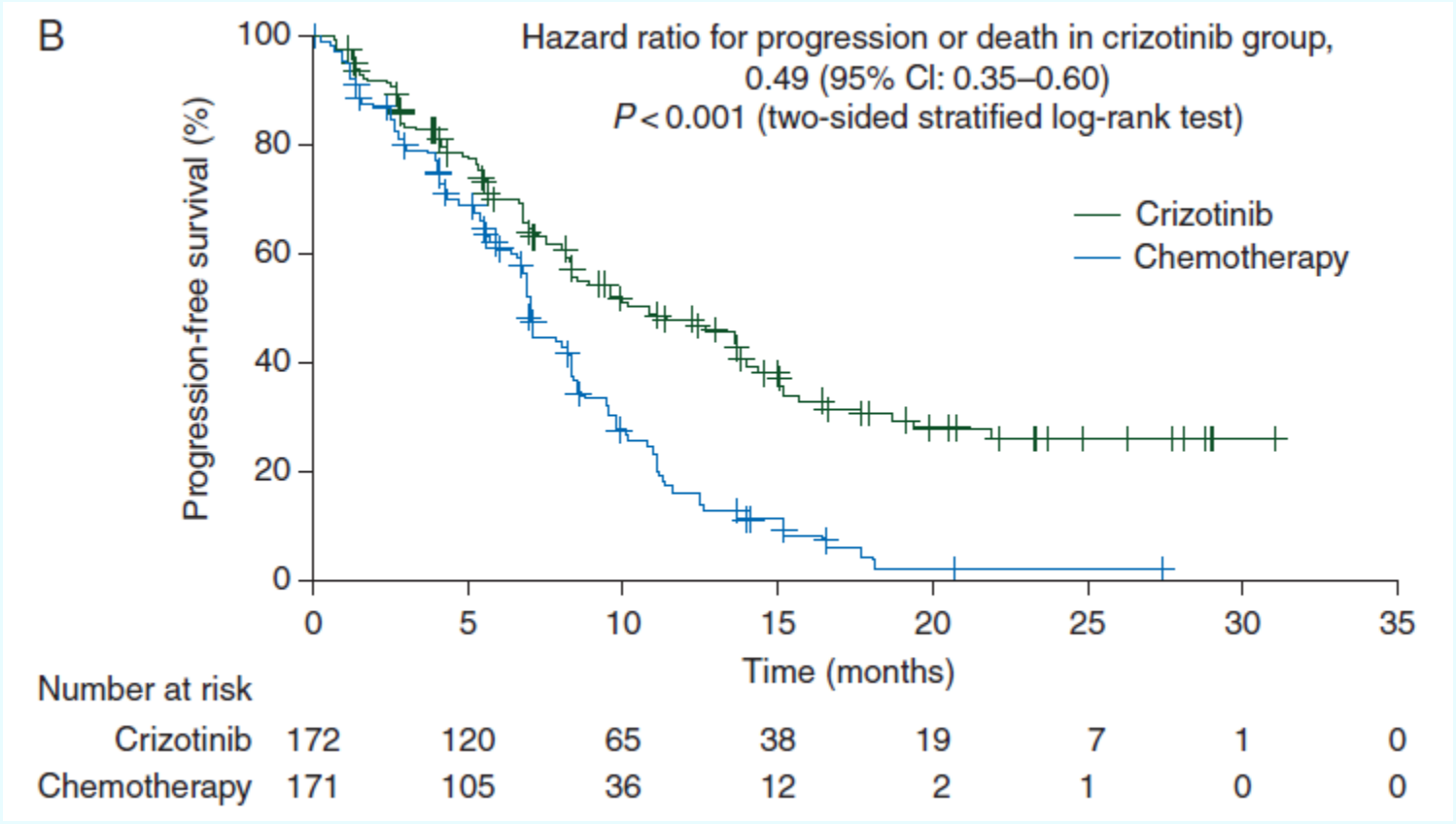
[c] OS analysis was not adjusted for the potentially confounding effects of cross over.

[d] Based on the stratified Cochran-Mantel-Haenszel test.

[e] Estimated using the Kaplan Meier method.

❖ Phase 3 Clinical Trials

- **A8081014**
  - **Statistically significant improvement in PFS**



❖ Phase 3 Clinical Trials

- **A8081007 & A8081014 Safety profile**

Response	Previously untreated patients (PROFILE 1014)		Previously treated patients (PROFILE 1007)	
	Crizotinib ($N = 171$)	Chemotherapy ($N = 169$)	Crizotinib ($N = 172$)	Chemotherapy ($N = 171$)
Adverse events that were ≥5% more frequent with crizotinib, *n* (%)				
Vision disorder	122 (71)	16 (9)	103 (60)	16 (9)
Diarrhoea	105 (61)	22 (13)	103 (60)	33 (19)
Oedema	83 (49)	21 (12)	54 (31)	27 (16)
Vomiting	78 (46)	60 (36)	80 (47)	30 (18)
Constipation	74 (43)	51 (30)	73 (42)	39 (23)
Elevated liver transaminases	61 (36)	22 (13)	66 (38)	25 (15)
Upper respiratory tract infection	55 (32)	21 (12)	44 (26)	22 (13)
Abdominal pain	45 (26)	20 (12)	NR	NR
Dysgeusia	45 (26)	9 (5)	44 (26)	16 (9)
Headache	37 (22)	25 (15)	NR	NR
Pyrexia	32 (19)	18 (11)	NR	NR
Dizziness	31 (18)	17 (10)	37 (22)	14 (8)
Pain in extremity	27 (16)	12 (7)	NR	NR
Nausea	NR	NR	94 (55)	64 (37)
Adverse events that were ≥5% more frequent with chemotherapy, *n* (%)				
Fatigue	49 (29)	65 (38)	46 (27)	57 (33)
Neutropenia	36 (21)	51 (30)	NR	NR
Stomatitis	24 (14)	34 (20)	NR	NR
Asthenia	22 (13)	41 (24)	NR	NR
Anaemia	15 (9)	54 (32)	NR	NR
Leucopenia	12 (7)	26 (15)	NR	NR
Thrombocytopenia	2 (1)	31 (18)	NR	NR
Dyspnoea	NR	NR	23 (13)	32 (19)
Rash	NR	NR	15 (19)	29 (17)
Alopecia	NR	NR	14 (8)	35 (20)

Cautious Safety items

- **Hepatotoxicity**
- **QT Interval Prolongation**
- **Bradycardia**
- **Interstitial Lung Disease (Pneumonitis)**

❖ Clinical Pharmacology

- **PK**
  - **Absorption**
    - **BA : 43%(32, 66)**
    - **Tmax : 4-6h**
    - **high-fat meal decreases the systemic exposure by an average of 15%**
  - **Distribution**
    - **Vss: 1772L**
    - **Protein binding: 91%**
    - **Blood/Plasma concentration ratio:1**

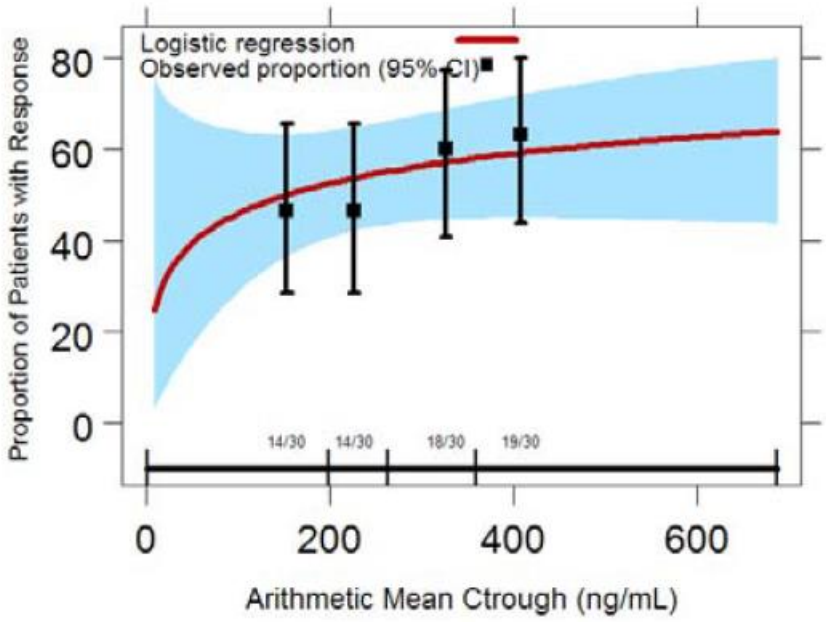
❖ Clinical Pharmacology

- **PK**
  - **Elimination**
    - **$t_{1/2}$: 42h**
    - **CL/F at steady state: 64.5 L/hr**
    - **Fraction of excreted unchanged drug in Urine or Feces: 2.3% 53%**
    - **Accumulation index : 4.8**
  - **Metabolism**
    - **Major metabolic CYP: CYP3A4/5**
  - **DDI**
    - **CYP3A inhibitor : auto-inhibition**

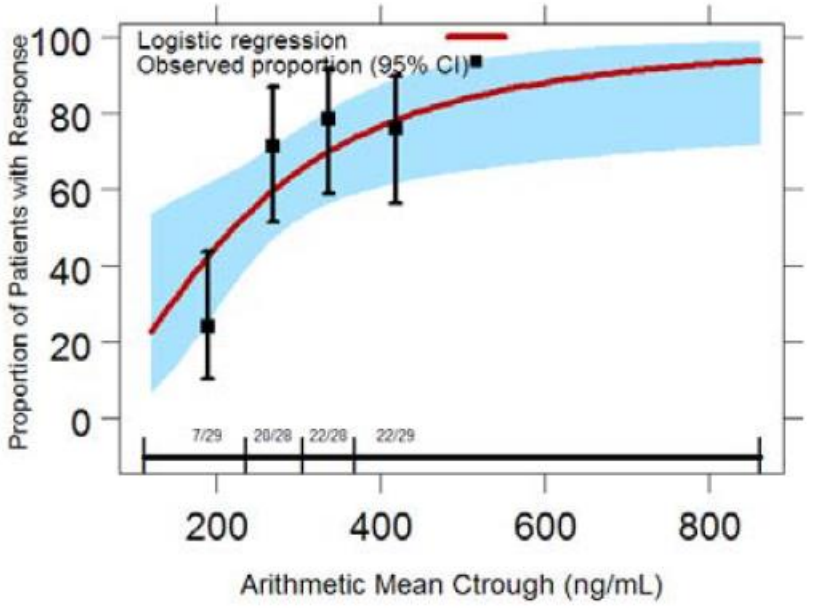
❖ Clinical Pharmacology

- **Exposure-response**
  - **exposure-response relationship for objective response rate (ORR)**

Trial 1005



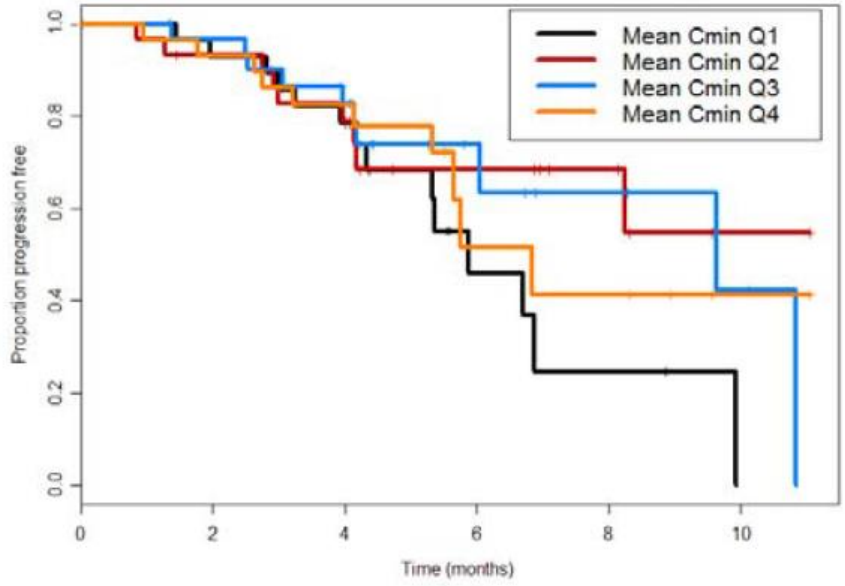
Trial 1001



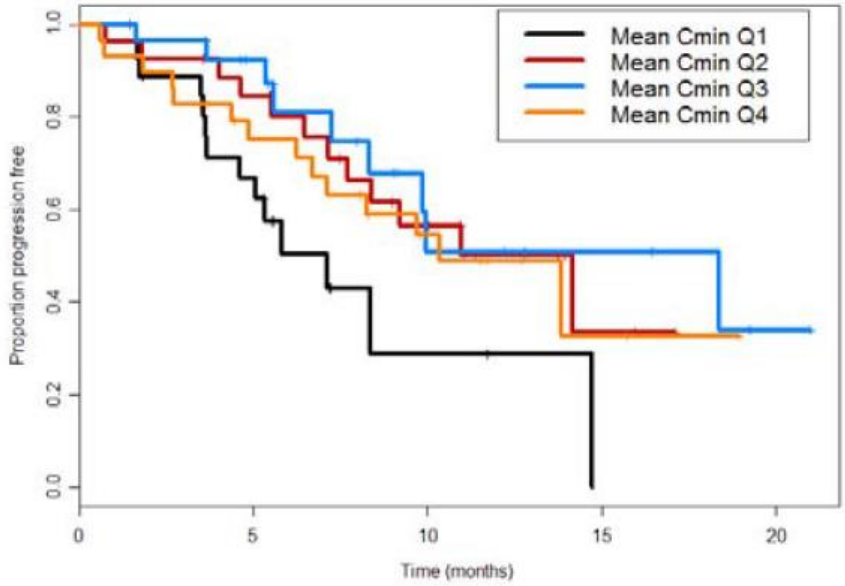
❖ Clinical Pharmacology

- **Exposure-response**
  - **exposure-response relationship for PFS**

Trial 1005

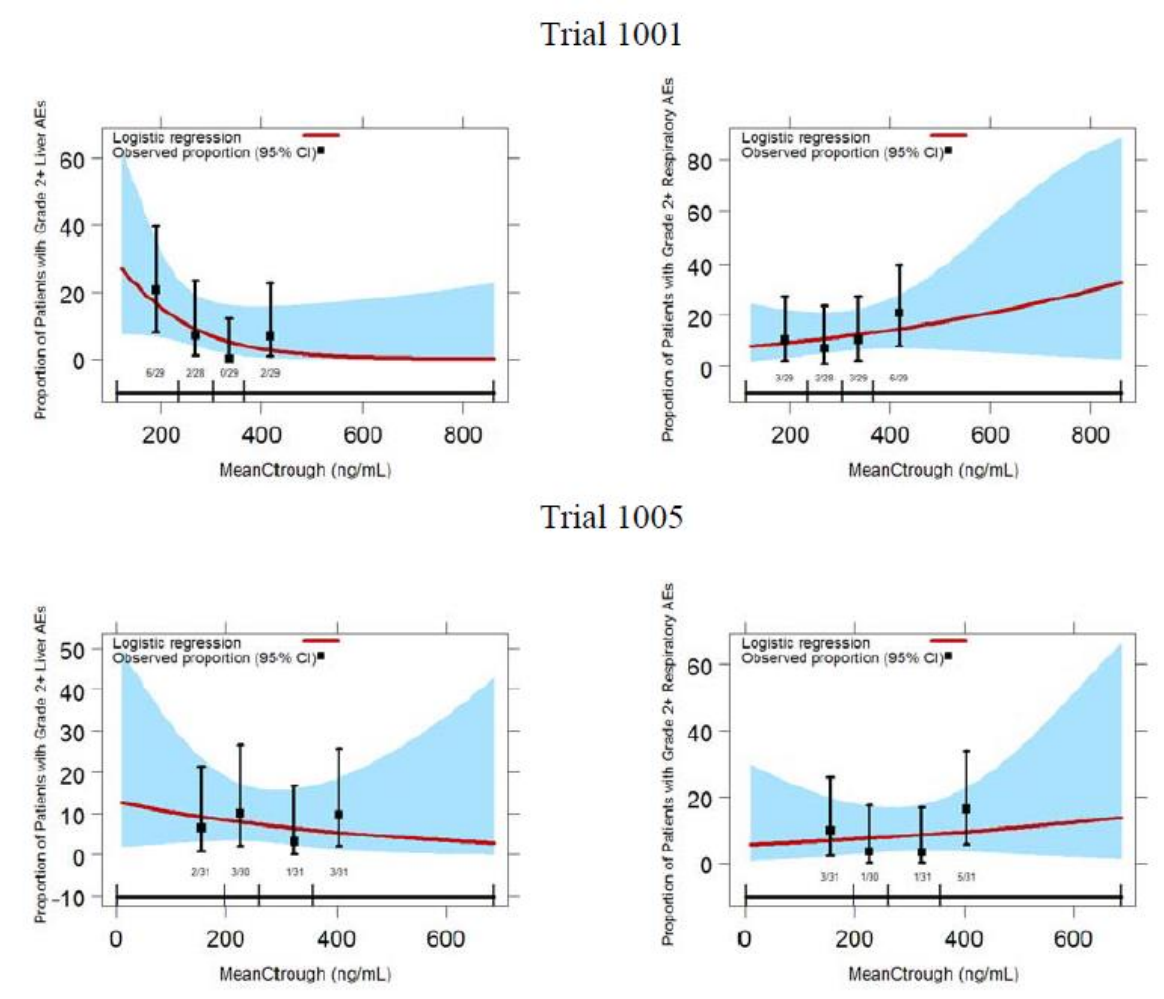


Trial 1001



❖ Clinical Pharmacology

- **Exposure-response**
  - **exposure-response relationship for safety**

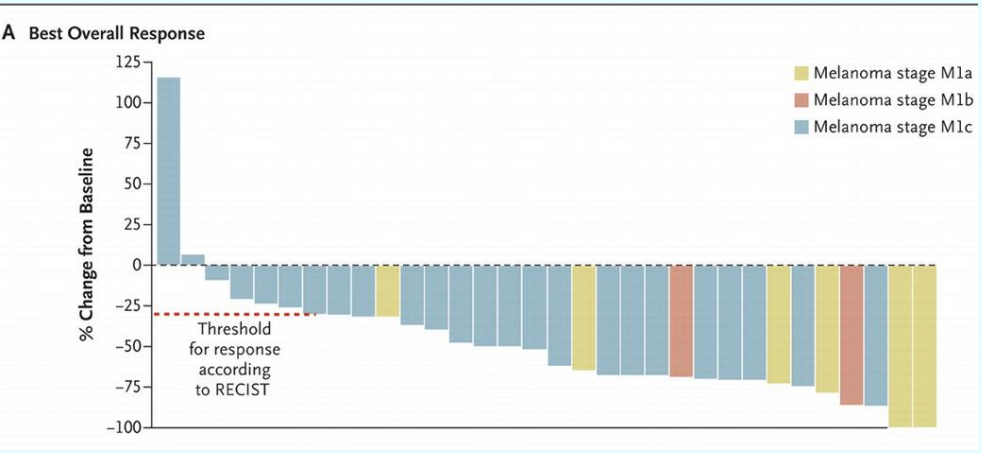


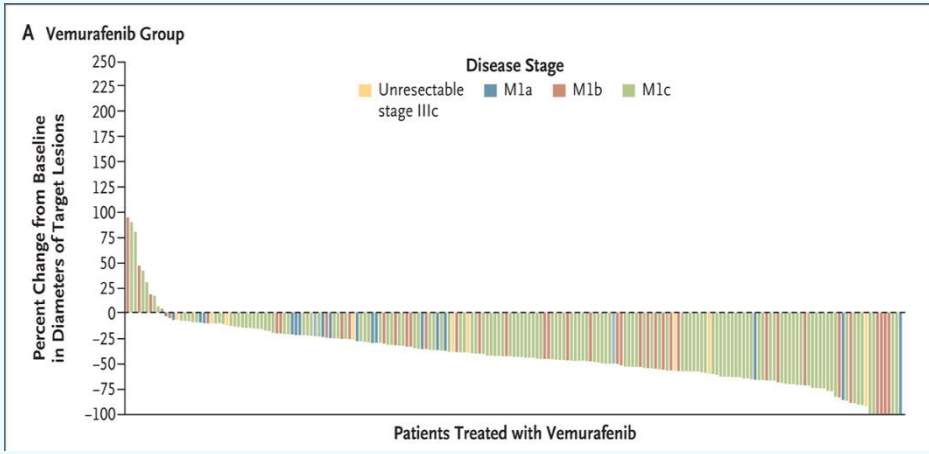
❖ Discussions

- **Key to the outstanding results for crizotinib**
  - **Drug target was a key oncogenic driver in the selected population**
  - **Molecular identification of patients with disease suitable for treatment → the effect of treatment was not diluted out by the inclusion of patients who were unlikely to respond**

❖ Discussions

- ♦ **Key to the outstanding results for crizotinib**
- ▪ **Clinical trials conducted in the molecularly selected populations will quite likely lead to similar results in other targeted agents**
- ▪ **ex) vemurafenib in patients with BRAF V600E-mutated melanoma**





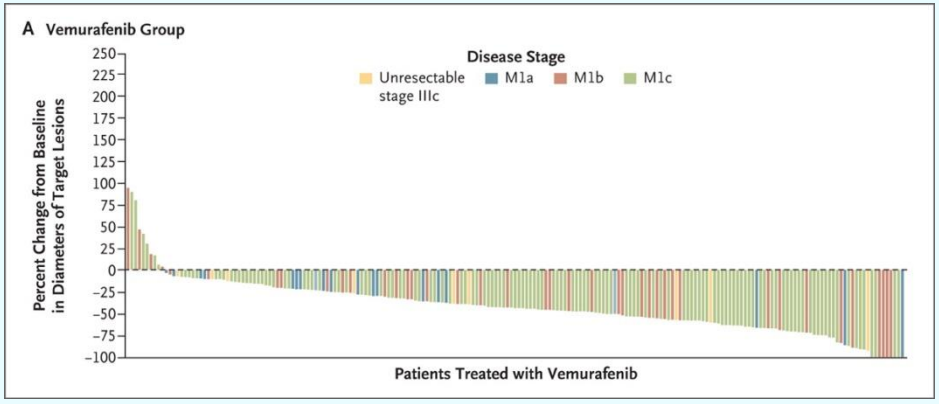
❖ Discussions

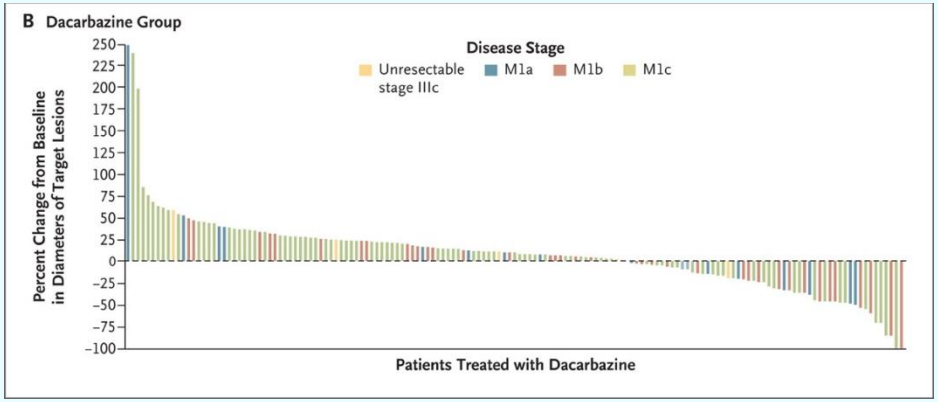
- **Supporting accelerated development of targeted agents demonstrating strong efficacy signals early in the development in molecularly selected patient populations**

❖ Discussions

♦ **Controversy over ethical aspects of employing a comparator arm (ex) chemoTX), widely acknowledged as suboptimal**

- **ex) vemurafenib phase III trial in melanoma**





❖ Discussions

- **Controversy over study design**
  - **Designing clinical trials to allow cross-over to investigational therapy following disease progression on the control arm, as is the case for the ongoing crizotinib phase III trials → impacts on the assessments of overall survival potentially confounding a key study endpoint**


THE END