Crizotinib in Patients with ROS1+ Non-Small Cell Lung Cancer: Rationale and Results

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EMA-ESMO Workshop on Single Arm Trials in Oncology
30 June 2016

Pfizer GLOBAL PRODUCT DEVELOPMENT

Identification of ROS1 and Relationship to NSCLC

- The ROS1 receptor tyrosine kinase (RTK) was first identified in 1986 as a cellular homologue of the *v-ros* sequence in an avian sarcoma virus
- No ligand for wild-type ROS1 identified and mice lacking wild-type ROS1 appeared healthy
- Cancer-related rearrangements in ROS1 first identified in a human glioblastoma cell line in 1987
- First oncogenic rearrangements of ROS1 in NSCLC identified in 2011
- Large scale screening of human NSCLC found ROS1 gene translocations in ~1.5% of tumors

How can a medicine be rigorously tested in such a rare circumstance?

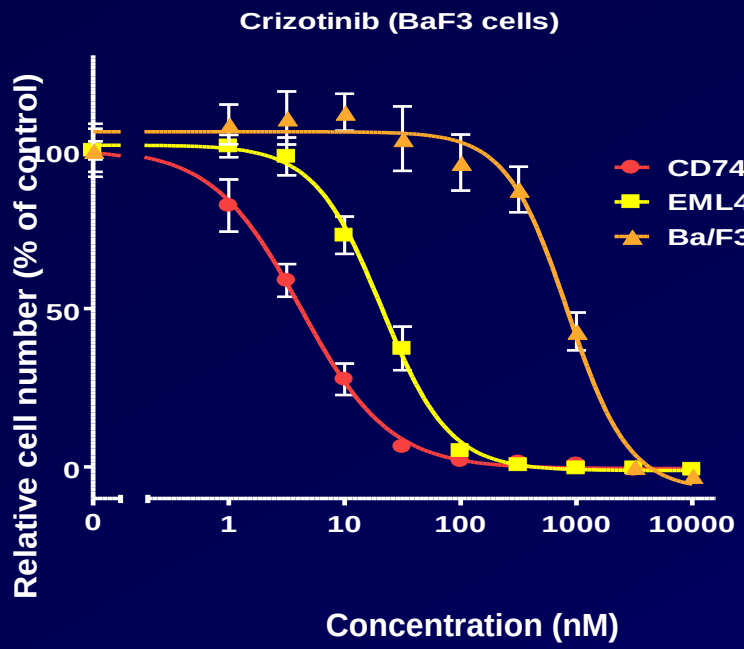
KD Davies et al: Clin Cancer Res 18:4570-4579, 2012
K Bergethon et al: J Clin Oncol 30:863-870, 2012

IC_{50} Concentrations for Crizotinib

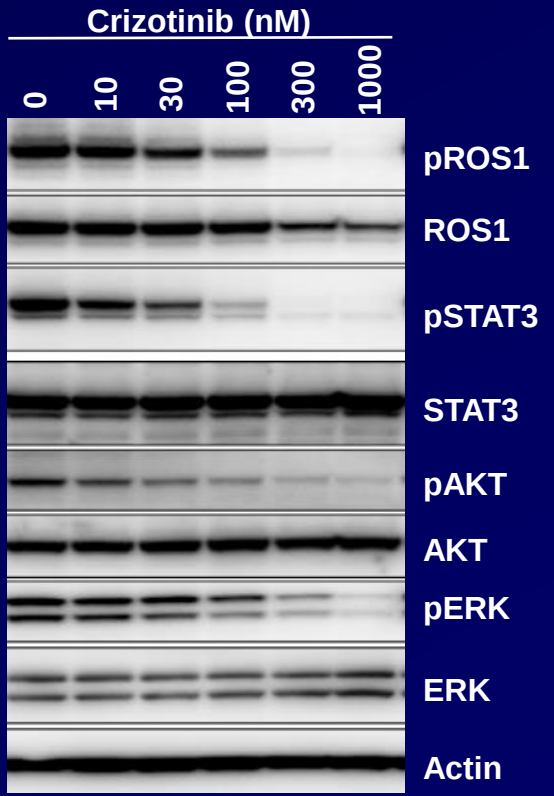
Kinase	IC_{50} (nM) mean	Selectivity ratio
c-MET	8	–
ALK	40-60	5–8X
ROS1	60	7X
RON	80	10X
Axl	294	34X
	322	37X
Tie-2	448	52X
Trk A	580	67X
Trk B	399	46X
Abl	1,159	166X
IRK	2,887	334X
Lck	2,741	283X
Sky	>10,000	>1,000X
VEGFR2	>10,000	>1,000X
PDGFRβ	>10,000	>1,000X

Cui et al. J Med Chem 2011;54: 6342-6363

Preclinical Activity of Crizotinib

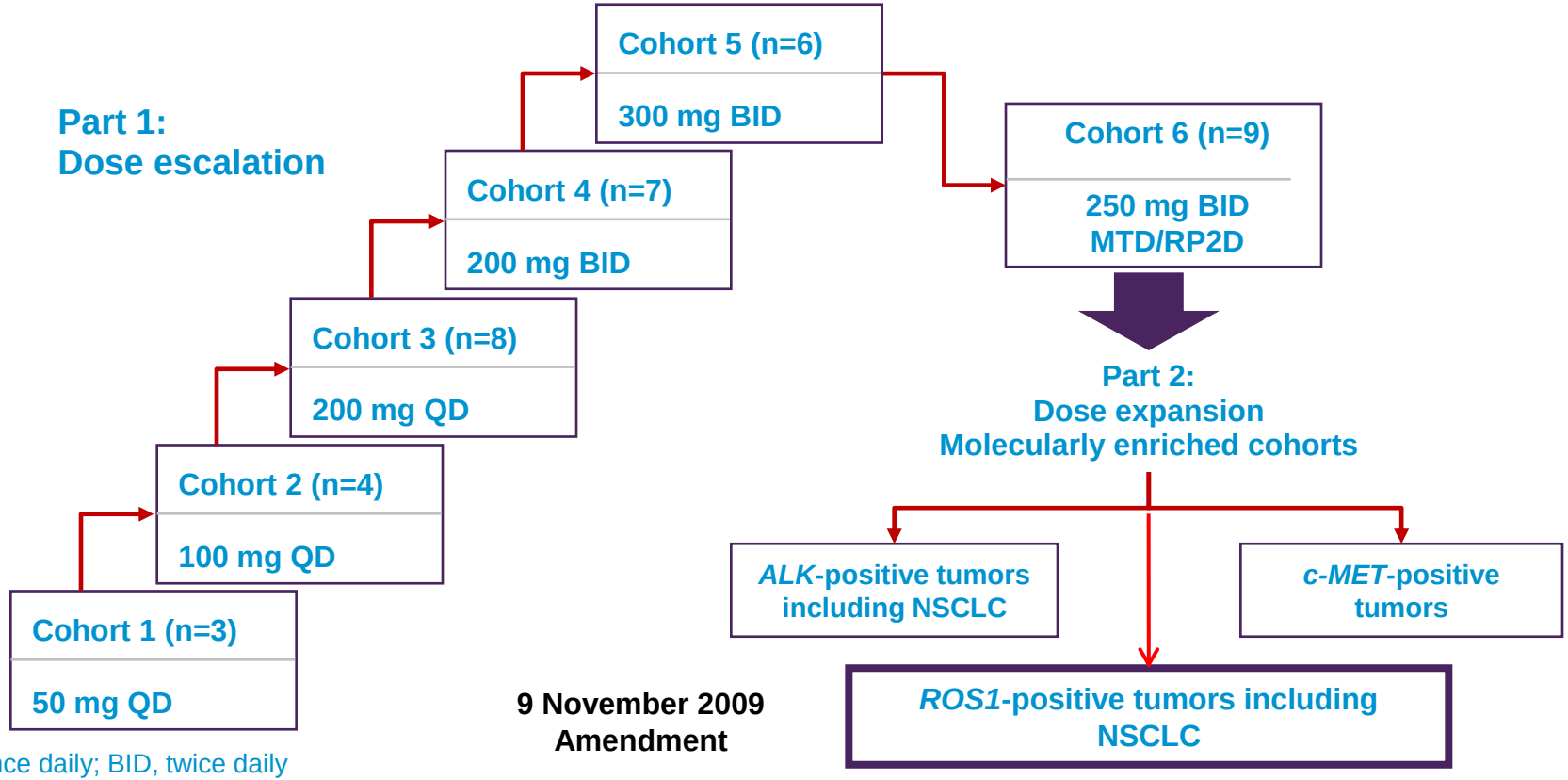


IC50 (nM)
4.2
20.8
839.3



Ryohei Katayama, unpublished

Phase I Study of Crizotinib (PROFILE 1001)



QD, once daily; BID, twice daily
MTD, maximum tolerated dose; RP2D, randomized phase 2 dose

ClinicalTrials.gov Identifier NCT00585195

PROFILE 1001: Activity of Crizotinib in ROS1+ NSCLC

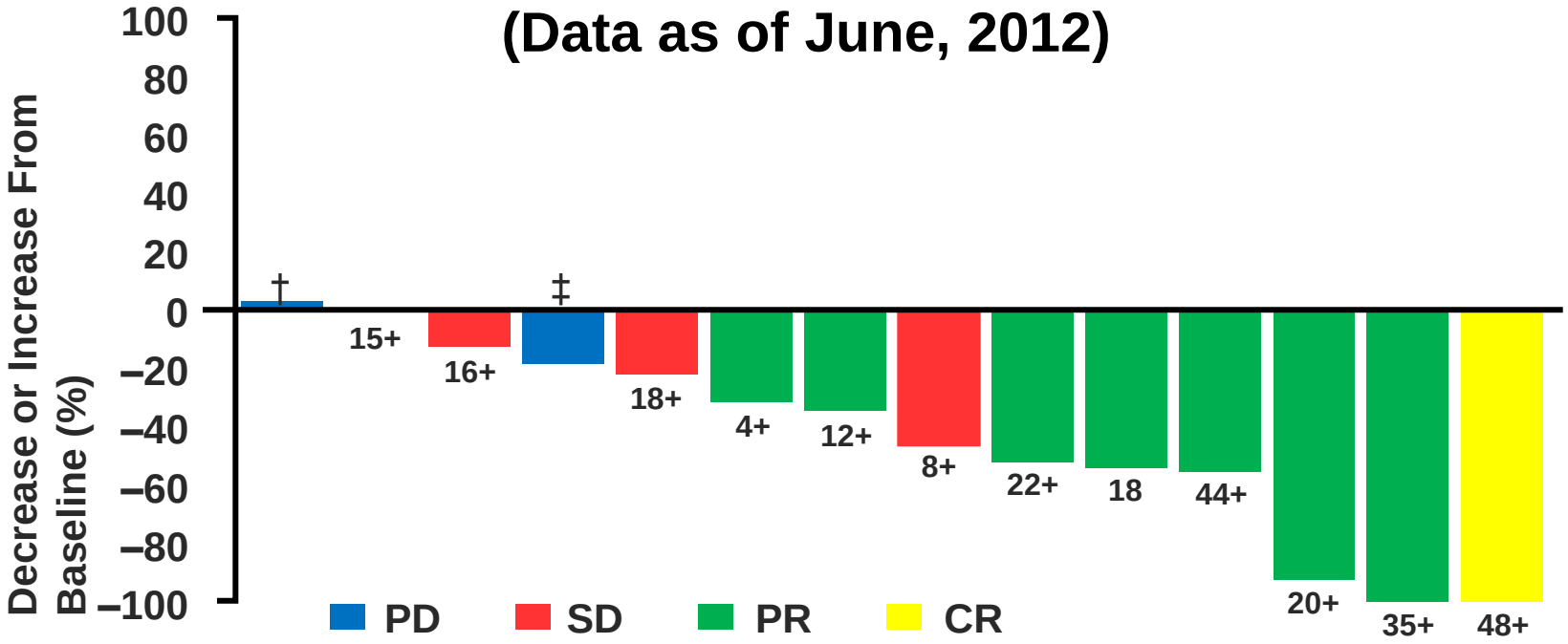
(Data as of June, 2012)

	ROS1-Positive (N=14)
Best response†	
Complete response	1
Partial response	7
Stable disease	4
Progressive disease	2
Other	0
ORR	**57.1%**
Median duration of treatment (weeks)	**25.7**
Disease control rate at 8 weeks	**79%**

RECIST 1.0; *Kwak et al., ASCO 2009

Shaw et al., ASCO 2012

PROFILE 1001: Waterfall Plot of ROS1+ Patients

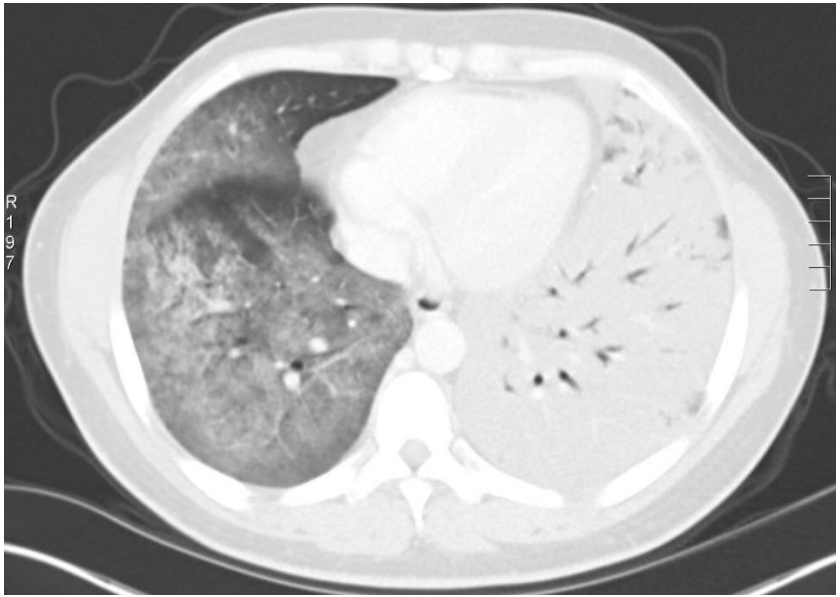


*Response-evaluable population. †Tumor ROS1 FISH-positive, but negative for ROS1 fusion gene expression ‡Crizotinib held for >6 wks prior to first scans which showed PD. +Treatment ongoing. For ongoing patients, duration of response/SD is the time from first documentation of tumor response/first dose to last available on treatment scan. For discontinued patients, duration is to the time of PD or death. Duration is in weeks.

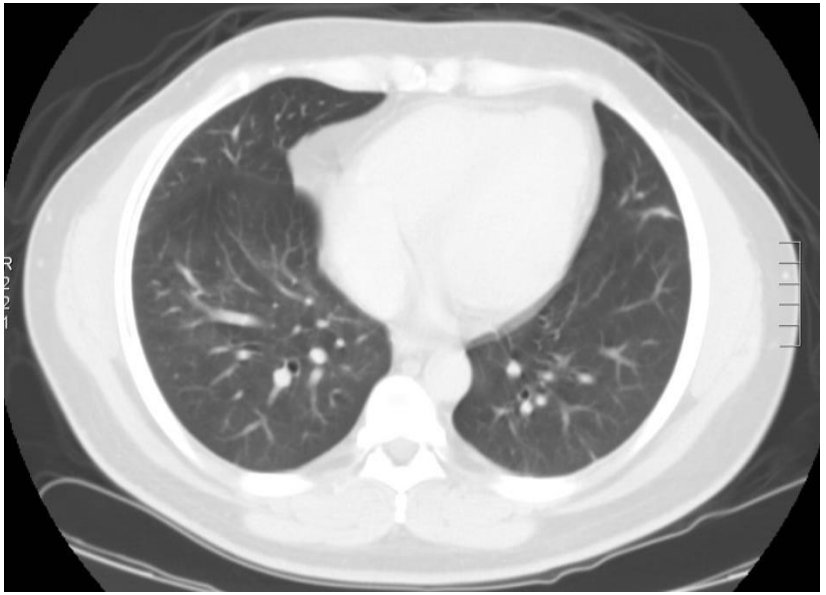
Shaw et al ASCO 2012

PROFILE 1001: Dramatic Response in ROS+ Patients

Pre-Treatment



8 Weeks of Crizotinib



Patient 10021119

PROFILE 1001: Activity of Crizotinib in ROS1+ NSCLC

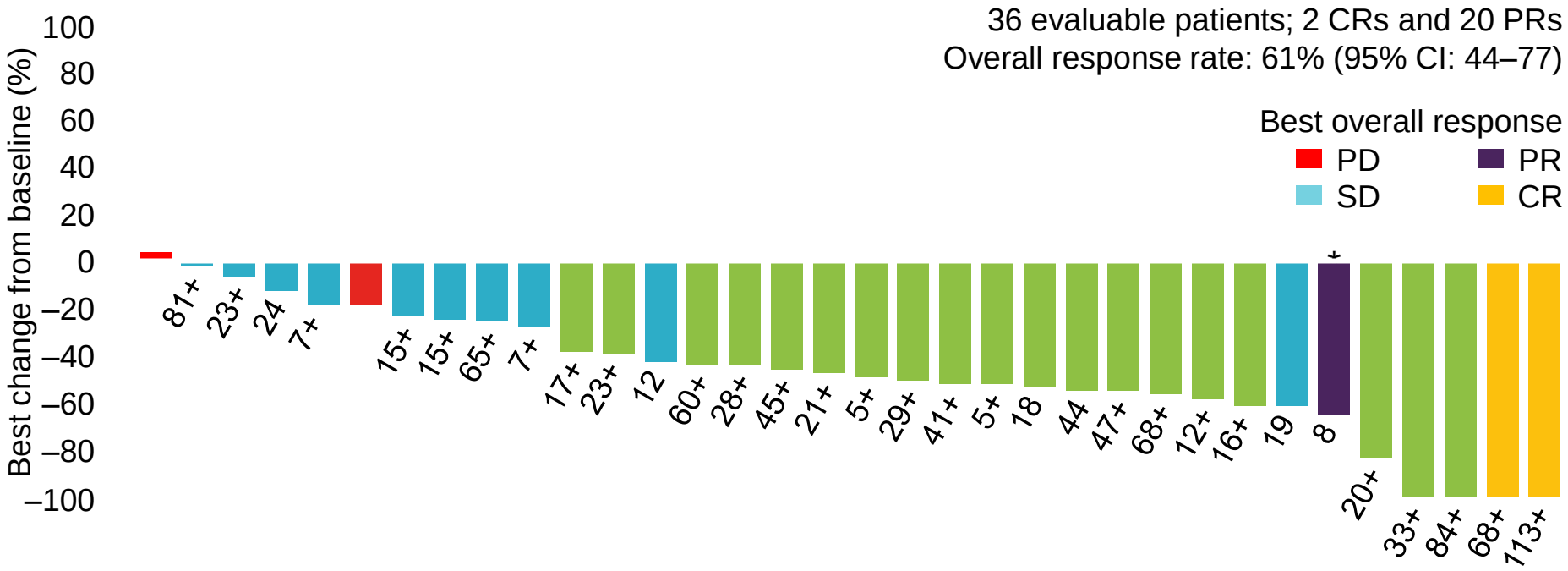
(Data as of April, 2013)

Response (RECIST v1.0)	Number & Per Cent of evaluable patients (n=36*)
Best response to therapy	
Complete response	2 (6%)
Partial response	20 (56%)
Stable disease	10 (28%)
Progressive disease	2 (6%)
Indeterminate response	0
Early death	2(6%)
ORR (%) (95% CI)	61% (44–77%)

* Two patients were subsequently confirmed negative for the *ROS1* rearrangment. One patient was ALK+ and had a Partial Response.

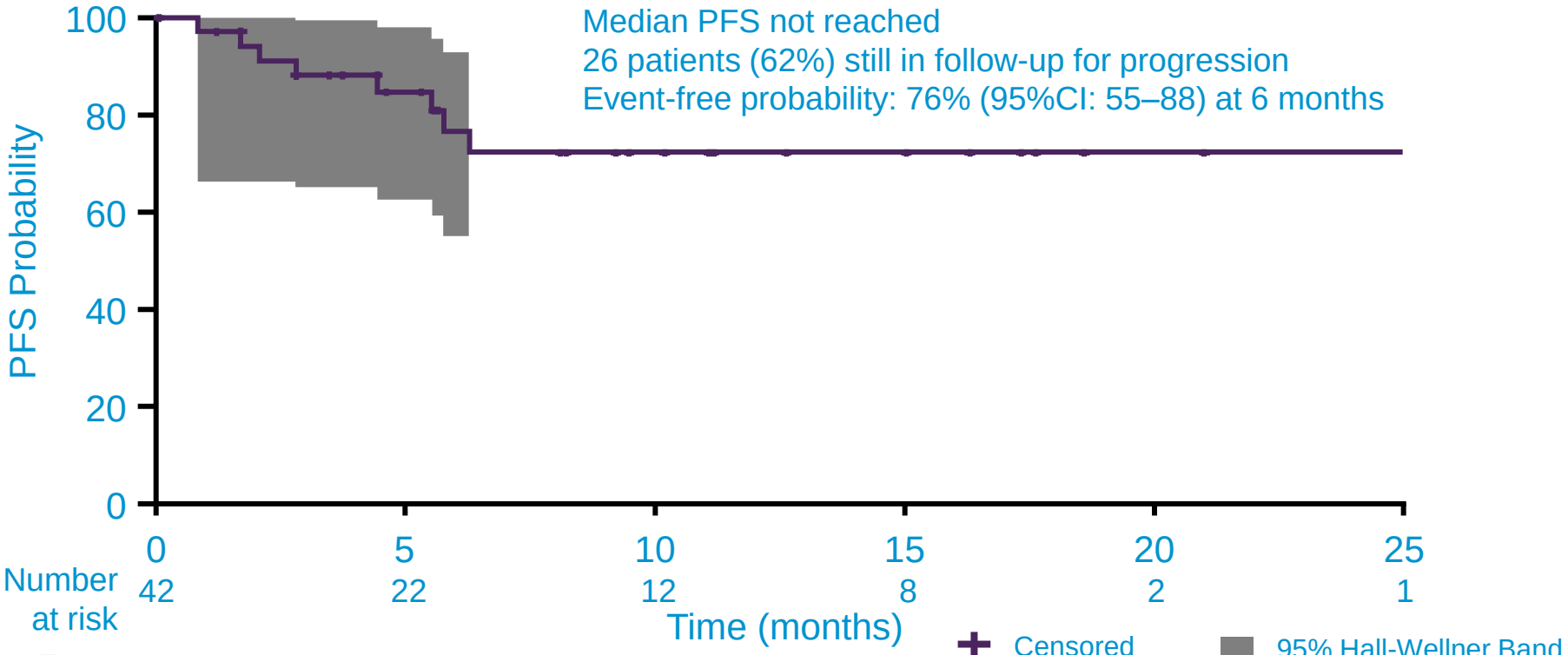
PROFILE 1001: Waterfall Plot of ROS1+ Patients

(Data as of April, 2013)



PROFILE 1001: PFS in ROS1+ NSCLC Patients

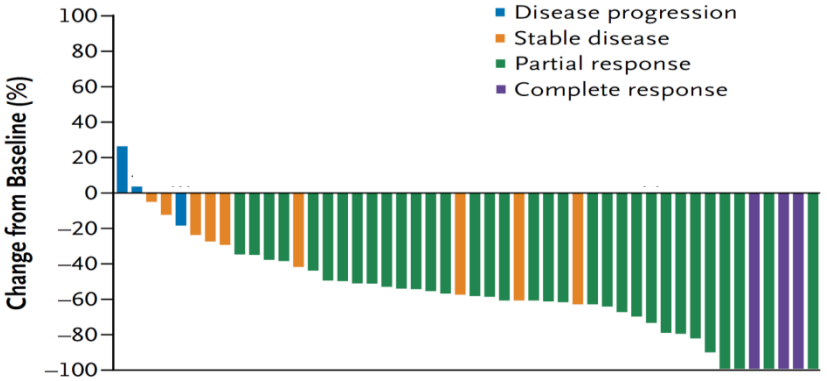
(Data as of April, 2013)



PROFILE 1001: Efficacy in ROS1+ Patients (n=50)

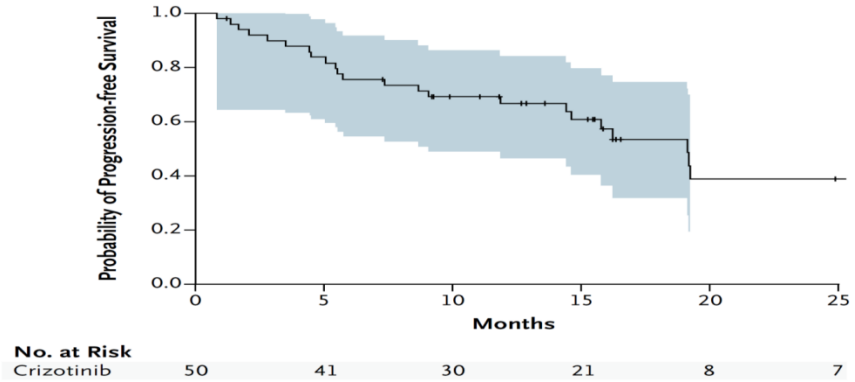
(Data as of May, 2014)

Best Response



- ORR = 72% (95% CI: 58%, 84%)
  - 3 patients (6%) achieved a CR
  - 33 patients (66%) achieved a PR
- Median duration of response: 17.6 months (95% CI: 15, NR)

Progression-Free Survival



- Median PFS: 19.2 months (95% CI: 14, not reached)
- 50% remain in follow-up for PFS

Shaw AT, *et al. N Engl J Med 2014*

ROS1+ NSCLC: Predictive or Prognostic?

Did ROS1+ simply identify a subset of NSCLC patients with a good prognosis or did it predict for sensitivity to a ROS1-targeted therapy?

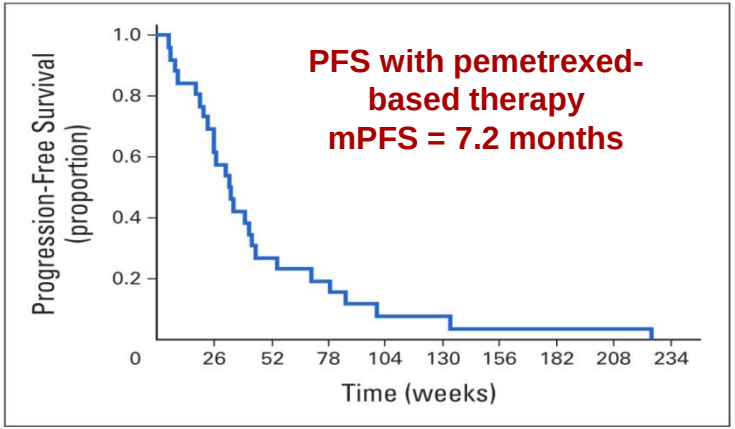


Fig 3. Progression-free survival on pemetrexed-based chemotherapy in patients with lung cancer and an *ROS1* rearrangement.

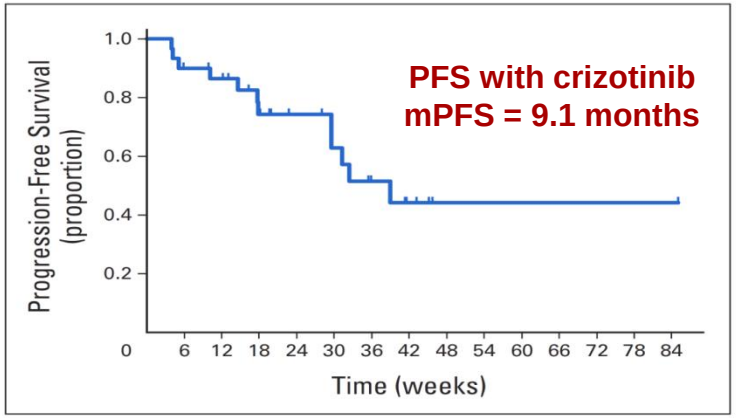


Fig 5. Progression-free survival on crizotinib in patients with lung cancer and an *ROS1* rearrangement.

J Mazieres et al: J Clin Oncol 33: 992-999, 2015

EUROS: Efficacy in ROS1+ Patients (n=30)

ORR = 80%

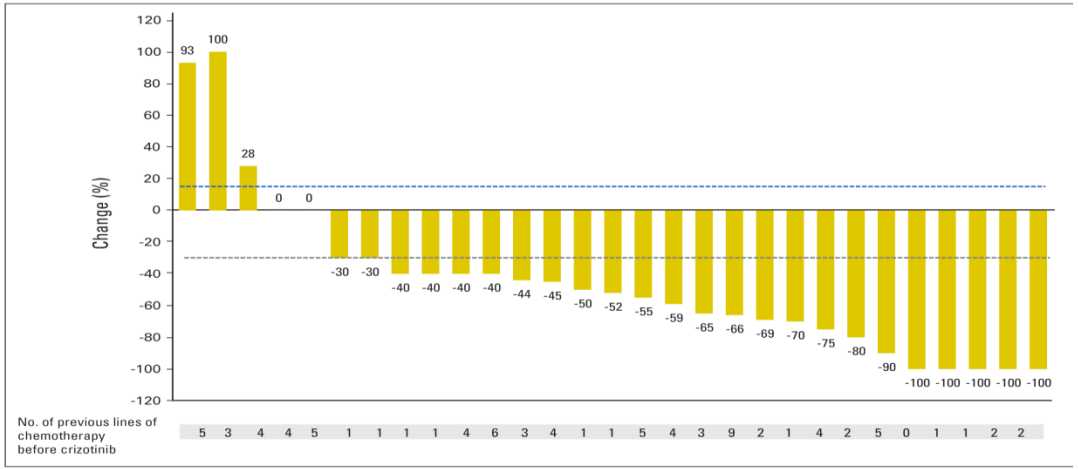
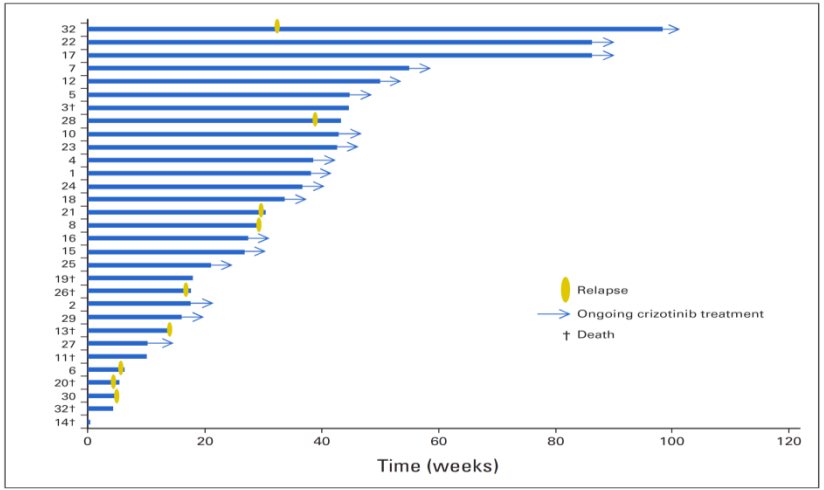


Fig 4. Waterfall plot of the best response to crizotinib in patients with lung cancer and an *ROS1* rearrangement.

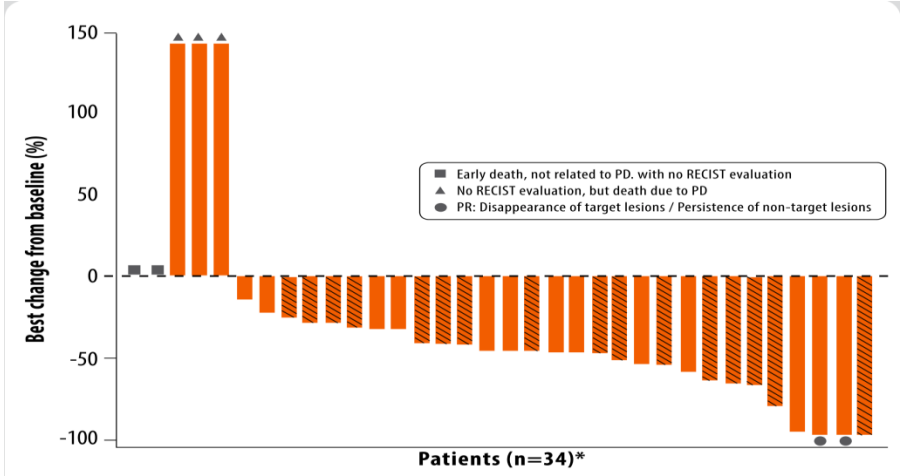
mPFS = 9.1 months



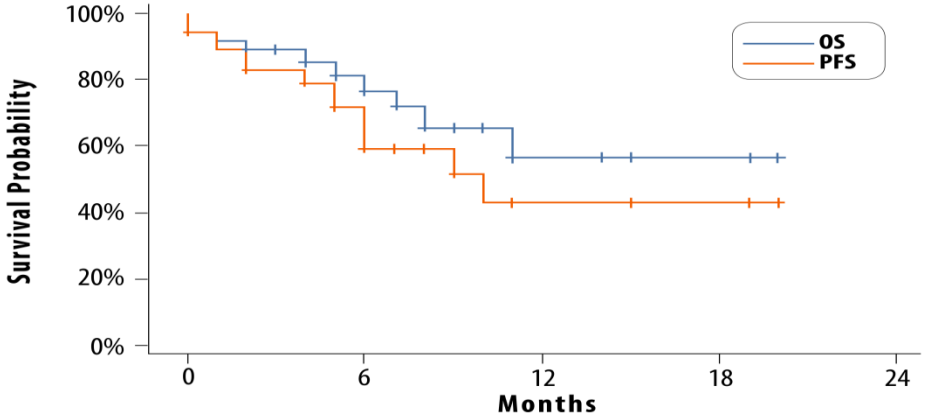
J Mazieres et al: J Clin Oncol 33: 992-999, 2015

AcSé: Efficacy in ROS1+ Patients (n=37)

ORR = 71%

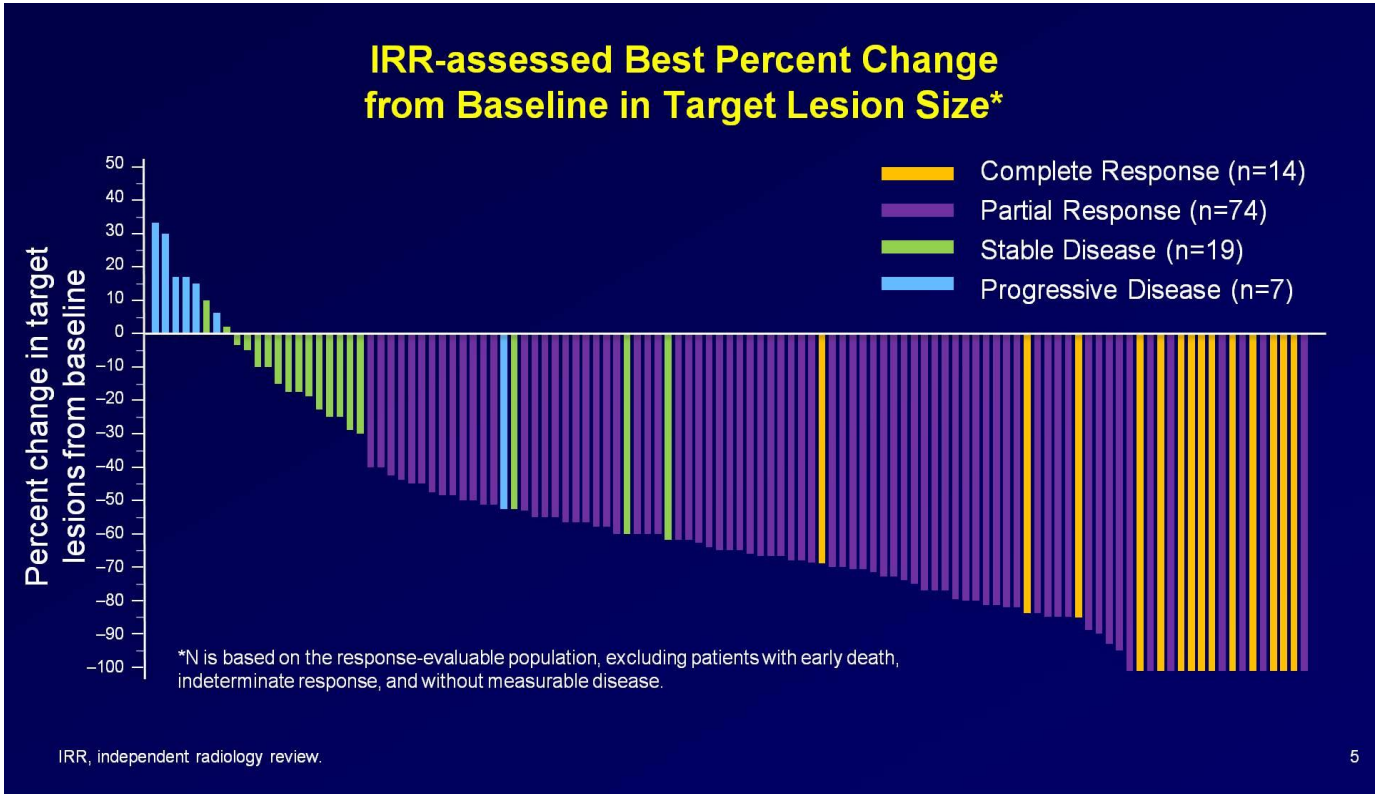


mPFS = 10 months
mOS=Not achieved



D Moro-Sibilot et al: ASCO 2015

OxOnc: Efficacy in ROS1+ Patients (n=127)



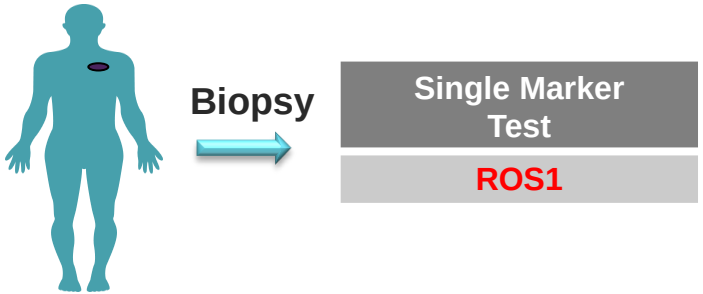
ORR = 88%

mPFS = 13.4 months
OS probability at 12 months: 84.4%

K Goto et al: ASCO 2016

OxOnc ROS1 Companion Diagnostic Testing

OO12-10 Patient Selection		
ROS1 Test	**Laboratory**	**Number (%) of patients enrolled**
PCR AmoyDx ROS1 Gene Fusion Detection Kit	**Central**	**110 (100)**
Total		**110 (100)**



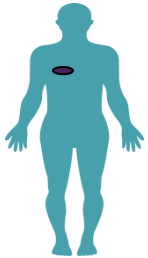
Commercially available as CE-IVD test

PROFILE 1001 ROS1 Companion Diagnostic Testing

OX ONC Patient Selection		
ROS1 LDT	**Laboratory**	**Number (%) of patients enrolled**
FISH	**All labs** **MGH** **Non-MGH**	**51 (96.2)** **26 (49.1)** **25 (47.2)**
PCR	**All labs** **MGH** **Non-MGH**	**2 (3.8)** **0 (0)** **2 (3.8)**
Total		**53 (100)**

Next Gen Sequencing (NGS)

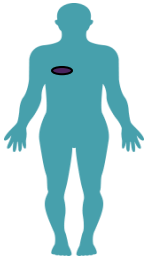
Oncomine Universal Dx Test
(ThermoFisher Ion PGM platform)



Biopsy

Single Marker Test
ROS1

- **Laboratory Developed Tests**
- **Limited commercial accessibility for CDx use in US (MGH FISH test available via MGH reference lab)**



Biopsy

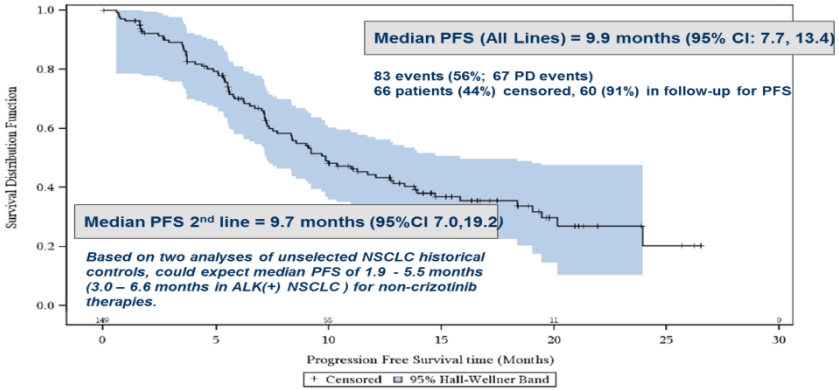
Multi-Marker (multiplex) Test
EGFR
ALK
BRAF
KRAS
ROS1
Others (analytical)

Oncomine Solid Tumor DNA panel and Solid Tumor Fusion Transcript kit available as CE-IVD tests

Similarities between ALK+ and ROS1+ NSCLC

Experience	Similar?	Different?
Disease: NSCLC	✓	
Activating Genomic Translocation	✓	
Predictive, not Prognostic	✓	
Defined by Companion Diagnostic	✓	
High ORR and Prolonged PFS	✓	

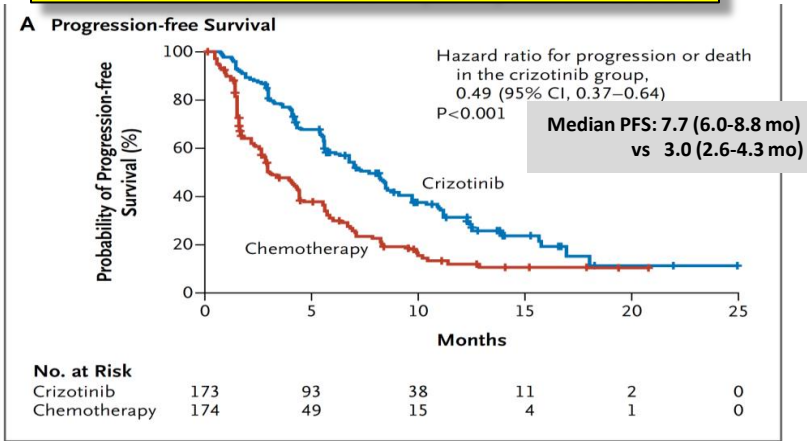
PROFILE 1005: Phase II (2011) ALK+ NSCLC



Study A8081005 med. PFS = 8.5 months (95% CI: 6.2, 9.9); 28% events

June 2011 data cutoff

PROFILE 1007: Phase III (2013) ALK+ NSCLC



AT Shaw et al: New Engl J Med 368:2385-2394, 2013

Crizotinib in ROS1+ NSCLC: US Regulatory Summary

	FDA
HA Consultations	• Registration strategy and data package agreed to by the FDA for regular approval • Two informational teleconferences held at the request of FDA + pre-sNDA meeting • Breakthrough Designation Granted: April 2015
Data Package	• Efficacy and safety data for 53 patients with ROS1 positive advanced NSCLC from single arm cohort in Study 1001 (pivotal study) • Locally developed test (Massachusetts General Hospital) as CDx initially with next generation sequencing post-marketing requirement
Submission	sNDA Submitted: 8 October 2015
Approval	sNDA Granted: 11 March 2016

Summary and Conclusion

- **Single arm clinical trial data suggest that crizotinib has promising activity against ROS1+ NSCLC**
- **The clinical activity of crizotinib in patients with ROS1+ NSCLC appears to be similar – as reflected by ORR, durability of response, and mPFS – to what is achieved in patients with ALK+ NSCLC**
- **Both the FDA and EMA granted accelerated/conditional marketing approval to crizotinib in ALK+ NSCLC based on the results of Phase II trials**
  - **Date of US approval: August, 2011 (Phase III results not available)**
  - **Date of EU approval: October, 2012 (Phase III results available)**
- **FDA granted regular approval (sNDA) to crizotinib in March, 2016 for patients with ROS1+ NSCLC based on Phase II data**

Where certain criteria are met, are data from single-arm trials sufficient to support marketing authorization in the EU?

Acknowledgements

- **Keith Wilner**
  - **Crizotinib Global Clinical Lead**
- **Silvia Chioato**
  - **Global Regulatory Portfolio Lead for Thoracic Malignancies**
- **Ramzi Dagher**
  - **Head, Worldwide Regulatory Strategy – Oncology**
- **Robin Wiltshire**
  - **Crizotinib Global Medical Affairs Lead**
- **Chuck Mebus**
  - **Crizotinib Asset Team Lead**
- **Leena Das-Young**
  - **Late Phase Strategy and Development Lead - Oncology**