International Association for the Study of Lung Cancer

IASLC

IASLC 15th World Conference on Lung Cancer
October 27 – October 30, 2013
Sydney, Australia
WCLC.IASLC.ORG

Abstract # 1354: First-In-Human Evaluation of CO-1686, an Irreversible, Highly Selective Tyrosine Kinase Inhibitor of Mutations of EGFR (Activating and T790M)

Jean-Charles Soria[1], Lecia V. Sequist[2], Shirish Gadgeel[3], Jonathan Goldman[4], Heather Wakelee[5], Andrea Varga[1], Panagiotis Fidias[2], Antoinette J. Wozniak[3], Joel W. Neal[5], Robert C. Doebele[6], Edward B. Garon[4], Sarah Jaw-Tsai[7], Lisa Caunt[7], Paramjit Kaur[7], Lindsey Rolfe[7], Andrew Allen[7], D. Ross Camidge[6];

[1]Institut Gustave Roussy, Villejuif, France, [2]Massachusetts General Hospital, Boston, USA, [3]Karmanos Cancer Institute, Detroit, USA, [4]UCLA, Santa Monica, California, USA, [5]Stanford University, Stanford, CA, USA, [6]University of Colorado, Denver, CO, USA, [7]Clovis Oncology, Boulder, Colorado, USA,

IASLC
15th World Conference on Lung Cancer
October 27 – October 30, 2013
Sydney, Australia
WCLC.IASLC.ORG

PRESENTATION NUMBER: PRESENTATION TITLE

DISCLOSURE INFORMATION

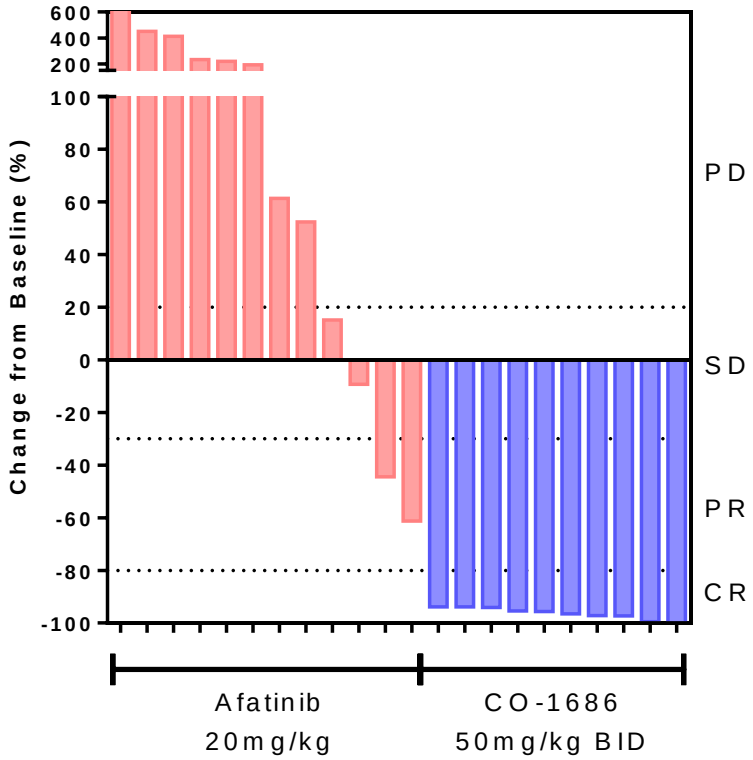
Presenting Author: Jean Charles Soria
Advisory board honoraria from Clovis Oncology

CO-1686 is a novel TKI specifically targeting mutated EGFR

- Novel, oral, selective covalent inhibitor of EGFR mutations in NSCLC
  - Inhibits key activating and T790M resistance mutations
  - Spares wild-type receptor signaling
- First-in-human study ongoing in EGFR-mutated patients with recurrent, advanced NSCLC
  - Started with free base capsule formulation
  - MTD not yet reached
- Hydrobromide salt form of CO-1686 recently introduced with improved drug availability and reduced variability
  - Dose escalation continuing
  - Currently dosing at 750mg BID

CO-1686 is potent against T790M mutation and spares wild-type EGFR

CO-1686 generates CRs in L858R/T790M transgenic model



CO-1686 shows limited activity in wild-type EGFR model

A431 xenograft model (EGFR WT-driven)		
Agent	**Dose**	**Tumor Growth Inhibition (% TGI)**
CO-1686	50 mg/kg BID	36
AZD9291	5 mg/kg QD	78*
Erlotinib	75 mg/kg QD	95
Afatinib	20 mg/kg QD	100

*Finlay et al. 2013 – AACR-NCI-EORTC meeting

Ascending dose study in patients with advanced EGFR+ NSCLC ongoing – MTD not reached

- Phase I dose escalation study in USA, France, Australia
  - Phase 2 dose not defined yet, dose escalation continues
  - Cohort expansions planned at RP2D
- Continuous oral CO-1686 in 21-day cycles
- Tumor biopsy at screening for central EGFR genotyping
  - Mutant EGFR required, T790M not mandated
- Treatment continued until disease progression
- Tumor assessment is by RECIST 1.1
- Free Base dosed to 900mg BID, MTD not reached
  - Cohort expansion at 900mg BID

Patient characteristics are consistent with other studies of EGFR mutated advanced NSCLC

Free base: 56 patients enrolled from 150mg QD to 900mg BID

Age (years)	
Median, (min-max)	60 (34,83)
Gender, N (%)	
Female	45 (80%)
Male	11 (20%)
Race (N%)	
Asian	10 (18%)
Black	1 (2%)
White	44 (79%)

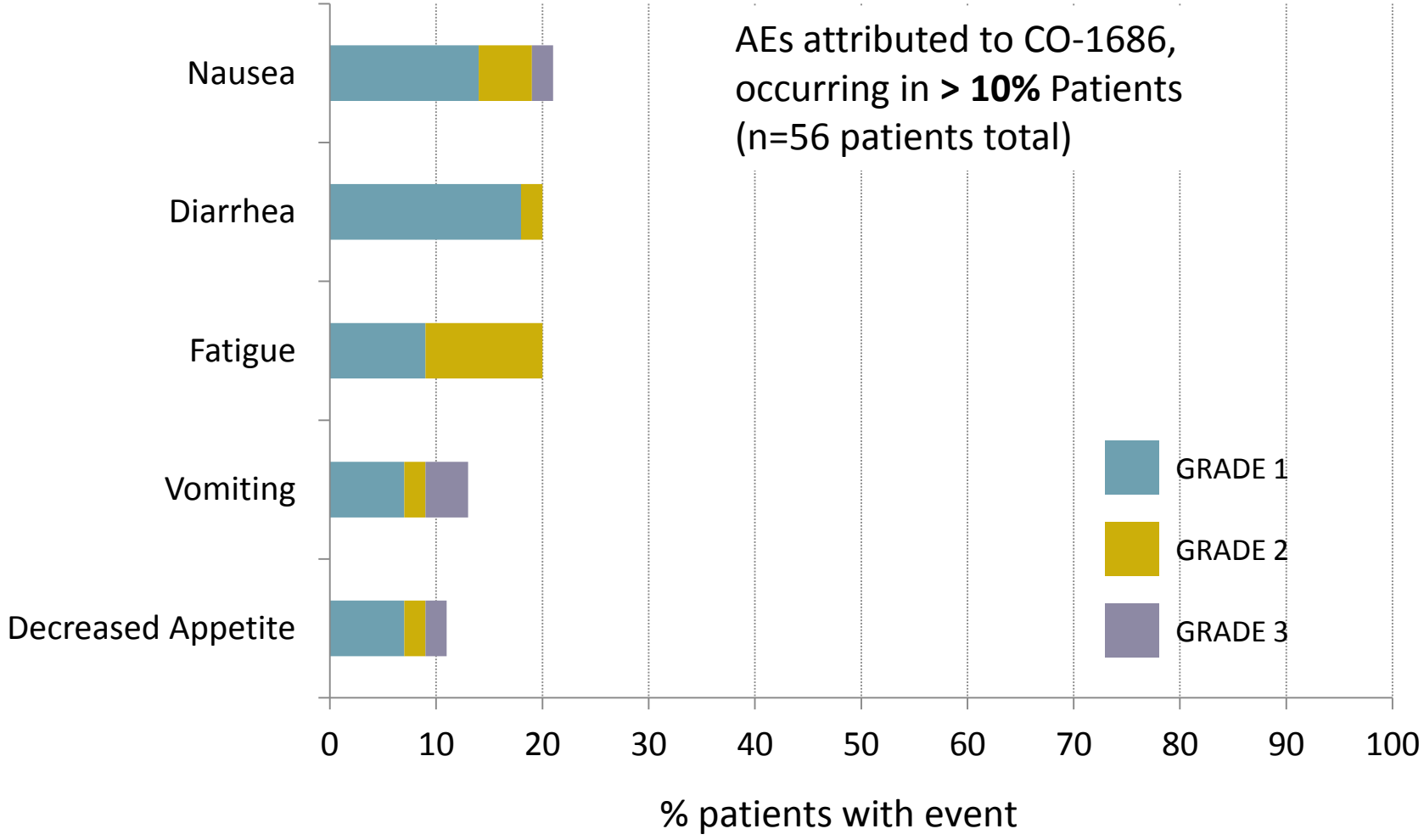
Activating Mutations	
Exon 19 Del	32 (57%)
L858R	20 (36%)
Other	4 (7%)
T790M Status	
Positive	39 (70%)
Negative	12 (21%)
Unknown	5 (9%)

Patients were heavily pretreated, many with ≥2 prior EGFR TKI

PREVIOUS THERAPY n= 56 patients	
Previous Anticancer Regimens	
Median (min-max)	3 (1,6)
≥ 5 prior regimens	10 (18%)
Number of previous TKI lines	
1	31 (55%)
≥ 2	25 (45%)
Previous EGFR TKIS	
erlotinib	53 (95%)
gefitinib	7 (13%)
afatinib	7 (13%)
dacomitinib	3 (5%)

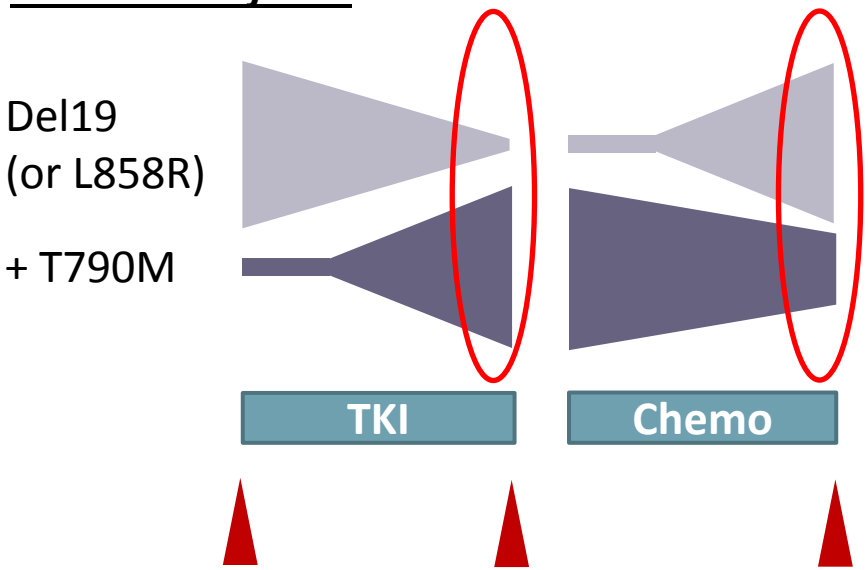
TIMING OF PREVIOUS EGFRi THERAPY n =56 patients				
	erlotinib	**gefitinib**	**afatinib**	**dacomitinib**
1st Line	22	4	1	
2nd Line	20	2	5	
3rd Line	17	2	1	1
4th Line	15			1
5th Line	3			1
6th Line	3			

CO-1686 has demonstrated limited and low-grade adverse events in patients to date



Immediate prior treatment matters: selection pressure is key

"Clonal Warfare"



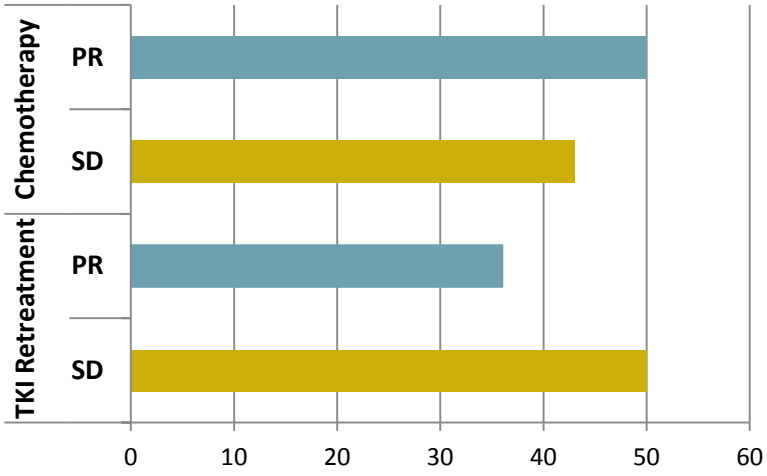
Diagnosis
Del19 dominates because clone is fitter

Progression #1
Driven by T790M in 60% because of TKI selection pressure

Progression #2
Heterogeneity of resistance:
- *Del19 fitter than T790M under chemo selection*

Clinical Evidence of Re-treatment Effect[1]

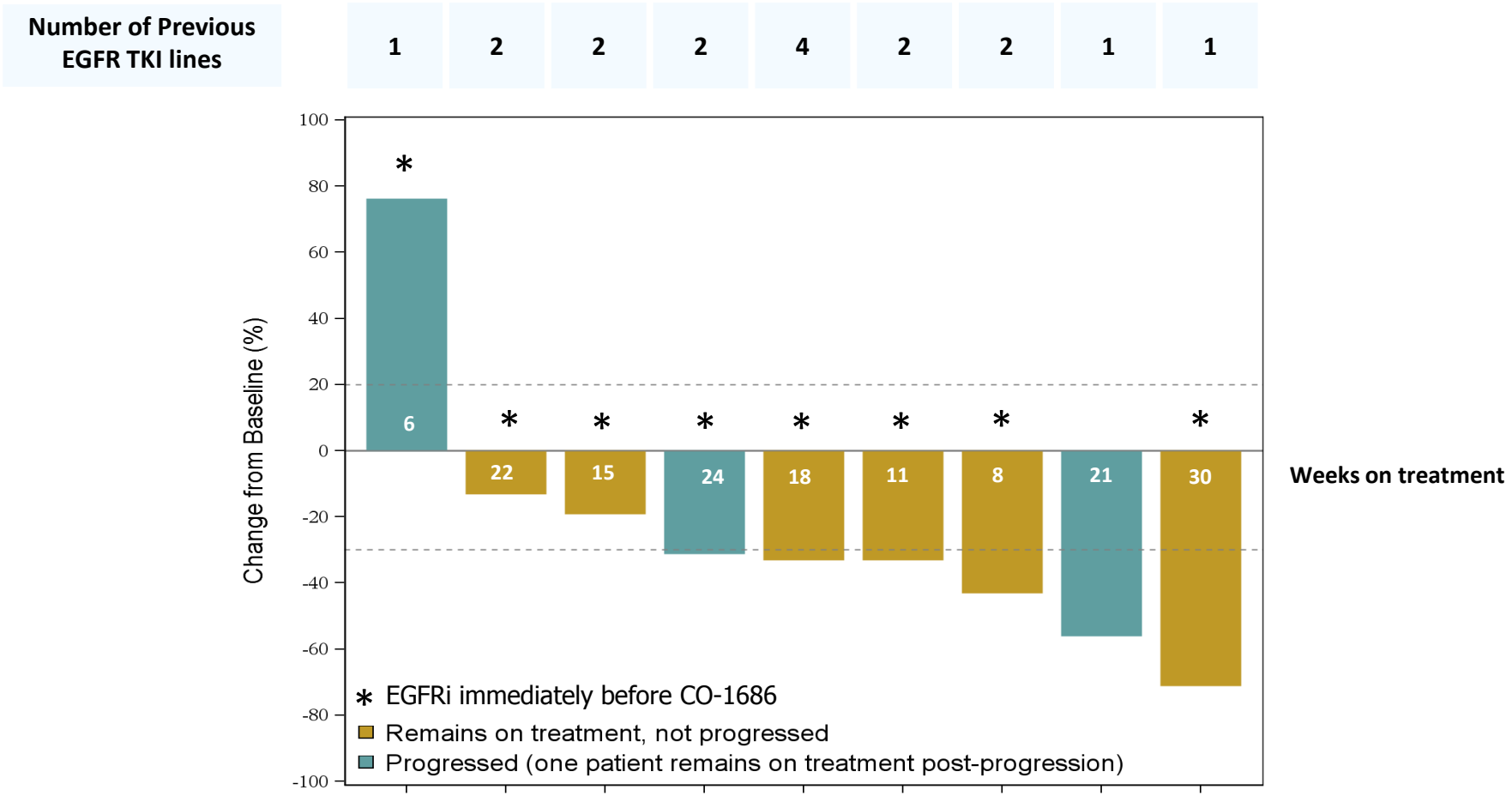
- Fourteen patients, EGFRmut NSCLC
- Treated with TKI, chemo, TKI
- Length of TKI 'holiday' 9.5 months
- 36% PR upon re-treatment with TKI



[1]Becker, et al, European Journal Cancer 2011

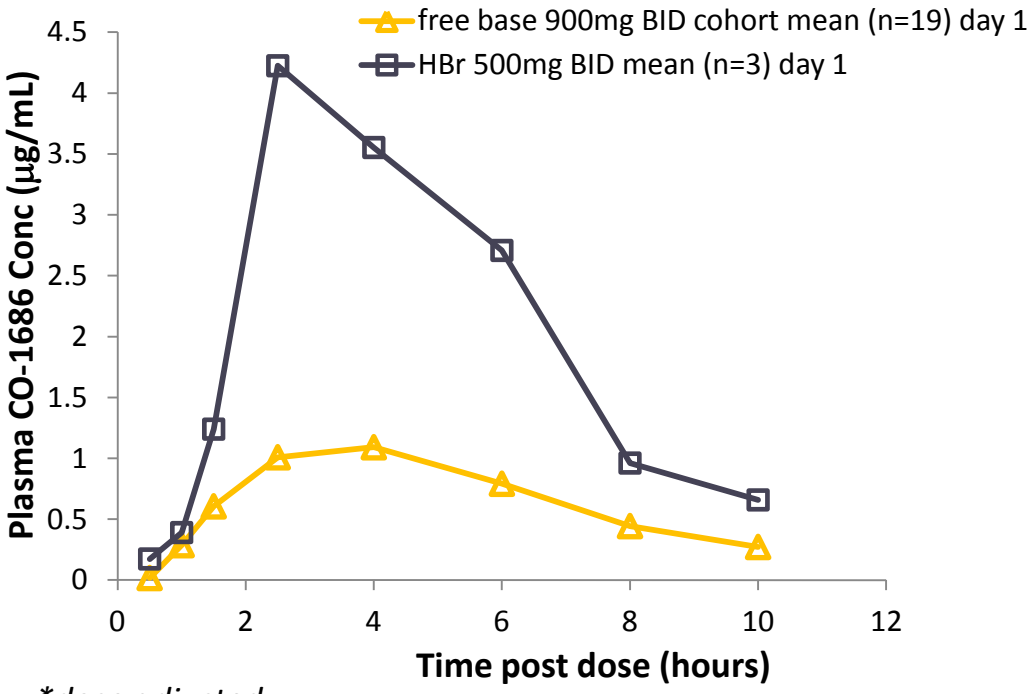
67% RECIST response rate in evaluable T790M+ patients treated at 900mg BID

8 of 9 patients progressed on TKI immediately prior to CO-1686



CO-1686 HBr increases exposure with reduced variability, compared with free base

HBr salt (500mg) delivers 8.5X mean exposure* compared with free base (900mg)



*dose adjusted

HBr salt is well tolerated

- 3 patients treated with CO-1686 HBr 500mg BID
- No cycle 1 DLTs
- **No rash or diarrhea**
- Patients continue on study with no dose reductions or delays
- Currently dosing at 750mg BID
- Reduced inter-subject variability, in patients and volunteers

Promising clinical activity observed with CO-1686 – no evidence of WT inhibition

- 67% RECIST response rate in evaluable T790M+ patients treated at 900mg BID (free base)
- CO-1686 is well tolerated with no acneiform rash, consistent with absence of wild-type EGFR inhibition
- A hydrobromide (HBr) formulation of CO-1686 with improved exposure and reduced PK variability has been introduced
- Dose escalation continues to establish RP2D
- Japanese phase 1 trial initiating early 2014