

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

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PRESENTATION NUMBER: PRESENTATION TITLE

DISCLOSURE INFORMATION

Presenting Author: Jean Charles Soria

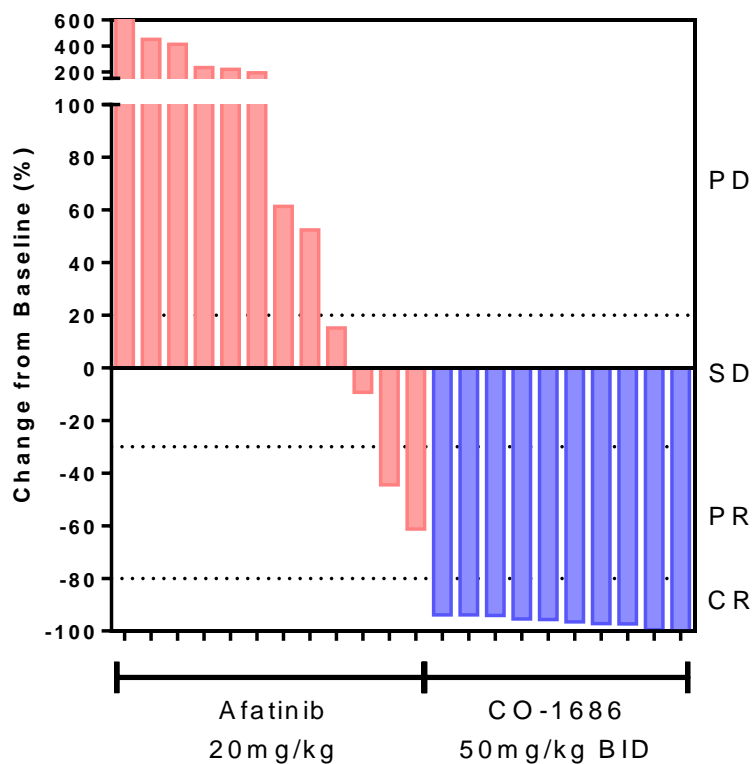
Advisory board honoraria from Clovis Oncology

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,	60
(min-max)	(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%)

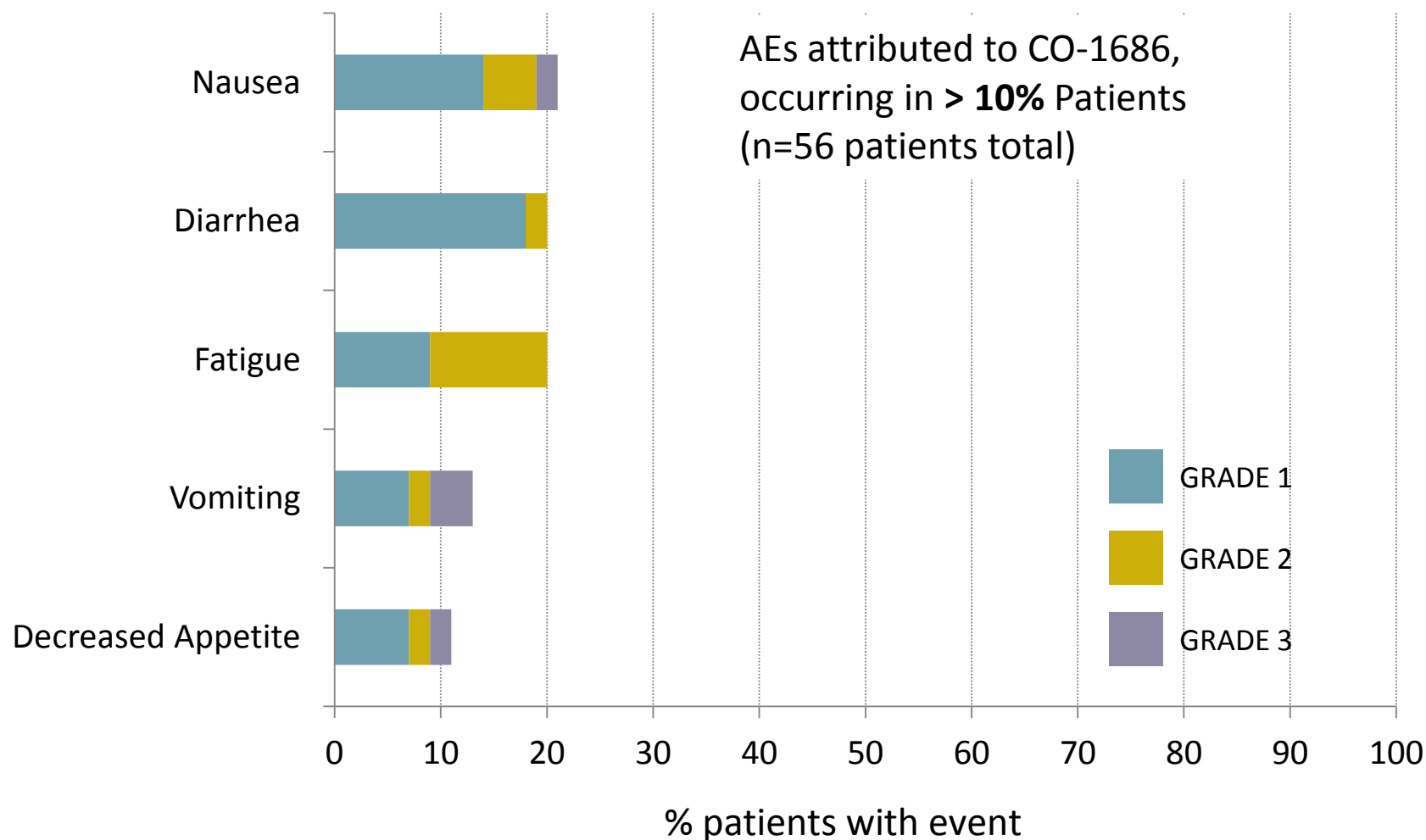
T790M Status

Positive	39 (70%)
Negative	12 (21%)
Unknown	5 (9%)

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

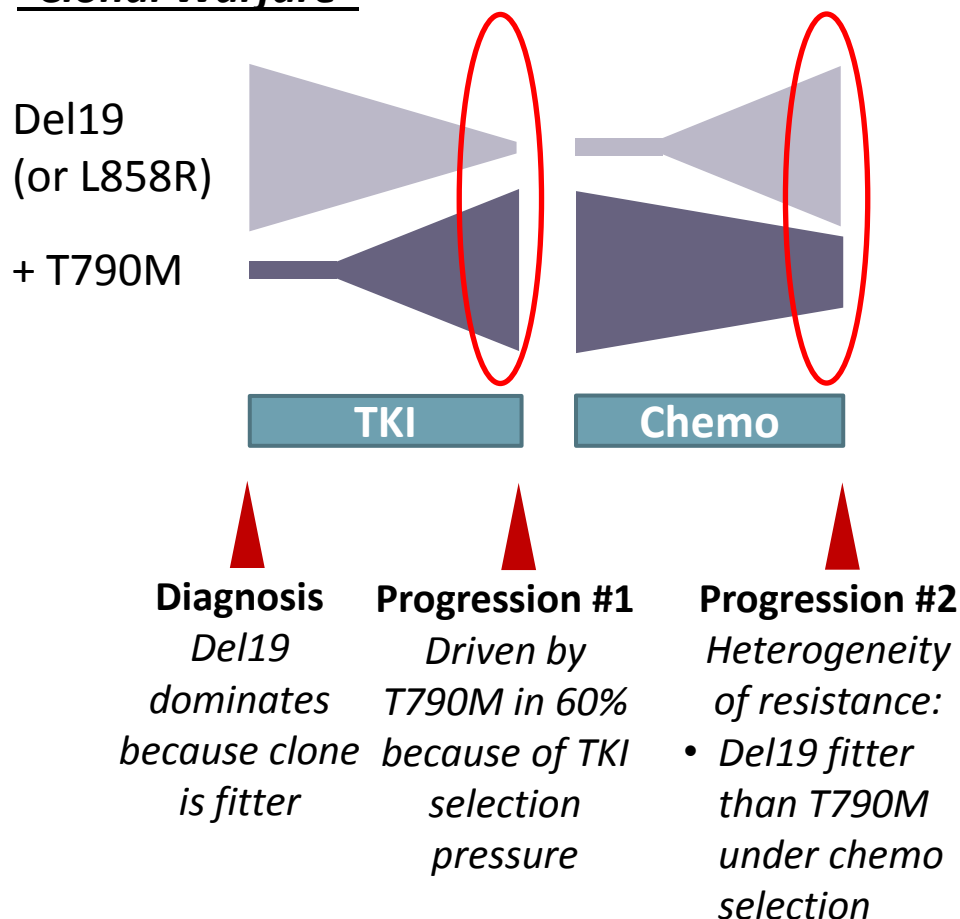
PREVIOUS THERAPY n= 56 patients		TIMING OF PREVIOUS EGFRi THERAPY n =56 patients				
Previous Anticancer Regimens			erlotinib	gefitinib	afatinib	dacomitinib
Median (min-max)	3 (1,6)					
≥ 5 prior regimens	10 (18%)	1 st Line	22	4	1	
Number of previous TKI lines		2 nd Line	20	2	5	
1	31 (55%)	3 rd Line	17	2	1	1
≥ 2	25 (45%)	4 th Line	15			1
Previous EGFR TKIS		5 th Line	3			1
erlotinib	53 (95%)	6 th Line	3			
gefitinib	7 (13%)					
afatinib	7 (13%)					
dacomitinib	3 (5%)					

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



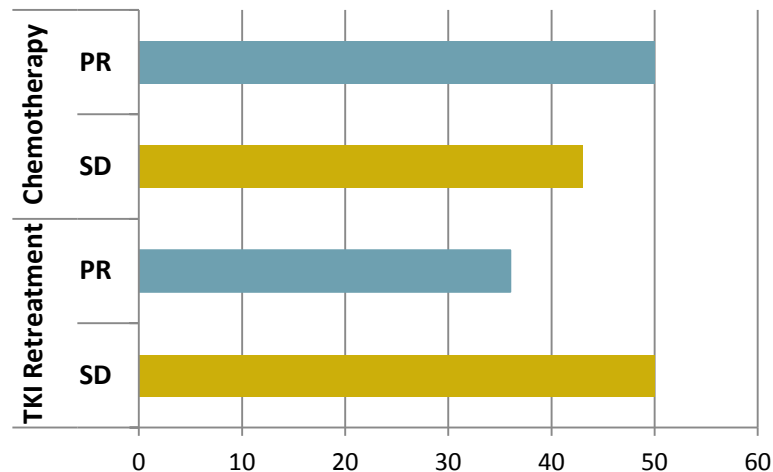
Immediate prior treatment matters: selection pressure is key

“Clonal Warfare”



Clinical Evidence of Re-treatment Effect¹

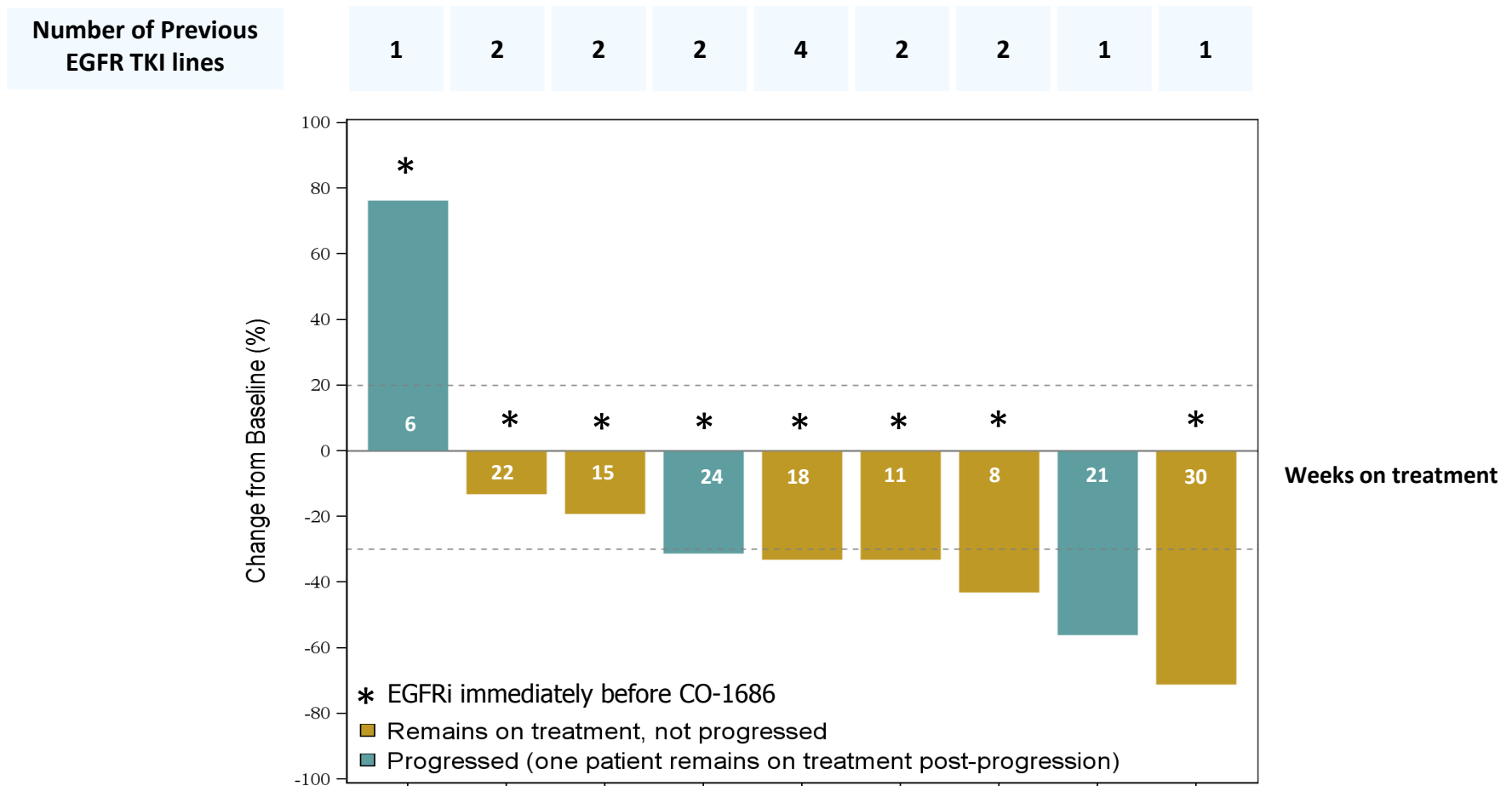
- Fourteen patients, EGFRmut NSCLC
- Treated with TKI, chemo, TKI
- Length of TKI 'holiday' 9.5 months
- 36% PR upon re-treatment with TKI



¹Becker, et al, European Journal Cancer 2011

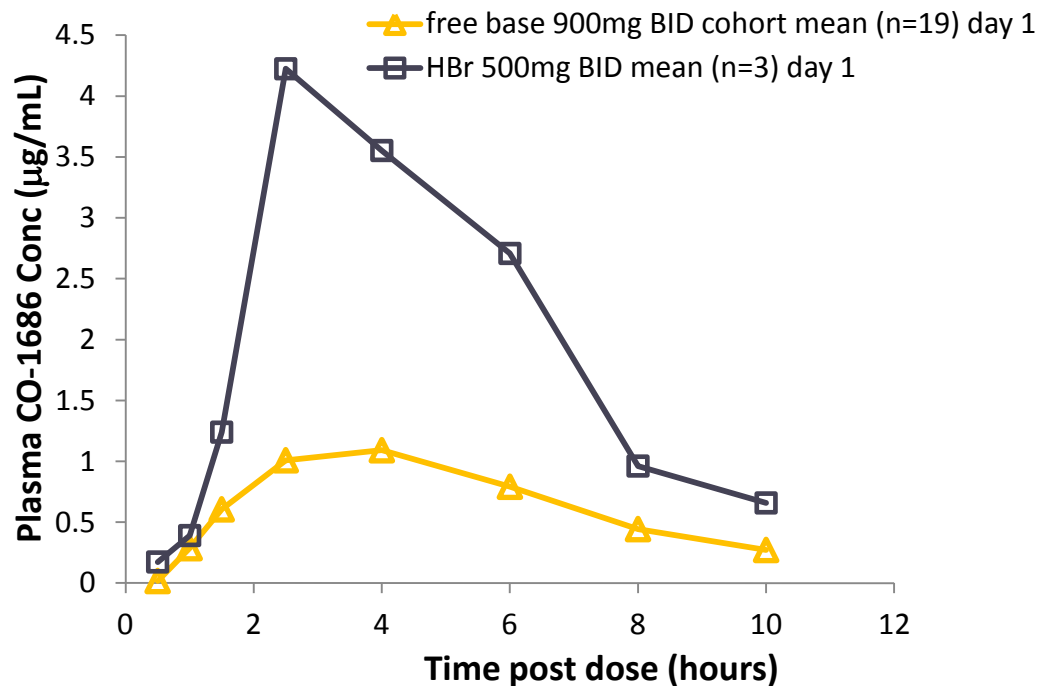
67% RECIST response rate in evaluable T790M+ patients treated at 900mg BID

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