FIRST-IN-HUMAN EVALUATION OF CO-1686, AN IRREVERSIBLE, SELECTIVE AND POTENT TYROSINE KINASE INHIBITOR OF EGFR T790M

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#2524

BACKGROUND

- CO-1686 is an oral potent, small molecule irreversible tyrosine kinase inhibitor (TKI) that selectively targets mutant forms of the EGFR, including T790M and the common initial activating mutations (L858R, del19), while sparing wild-type (WT) EGFR
- T790M is the dominant cause of acquired resistance to existing EGFR inhibitors (~60% of cases, Yu et al, Clin Cancer Res. 2013, 19 (8):2240-7)
- Utility of existing epidermal growth factor receptor (EGFR) inhibitors is limited by tolerability associated with wild type EGFR inhibition (acneiform rash, diarrhea)
- Animal models with cell lines demonstrate good efficacy of CO-1686 when plasma concentrations remain over 200 ng/mL for prolonged periods of time
- We report initial clinical data from an ongoing first-in-human study of CO-1686 in patients with EGFR mutated non small cell lung cancer (NCT01526928) – an MTD has not been reached and RP2D not yet defined
- Additionally PK data are presented from an ongoing healthy volunteer study of a hydrobromide salt form of CO-1686 which offers improved drug availability and reduced variability

STUDY DESIGN

- Phase I dose escalation study (standard 3+3 cohorts) at 6 sites in USA and France
- All patients must undergo tumor tissue biopsy within 28 days before study drug dosing for central EGFR genotyping during screening
- Oral CO-1686 is dosed every day in 21-day cycles and dose limiting toxicities (DLTs) were assessed over the first 21 day cycle
- Intra-patient dose escalation is allowed once a dose level is cleared for DLTs
- Treatment is continued until disease progression. Patients can stay on treatment following progression if overall benefit is seen
- Assessment is by RECIST 1.1
- Washout from prior EGFRI TKIs is 5 days (reversible) or 14 days (irreversible)

MAIN STUDY OBJECTIVES

Primary :

- To evaluate the toxicity profile of escalating doses of CO-1686 and to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D)
- To characterize the PK profile of CO-1686

Secondary:

- To characterize the PK profile of CO-1686 after a high-fat breakfast vs in the fasted state
- To identify signals of efficacy of CO-1686

KEY INCLUSION/EXCLUSION CRITERIA

Inclusion:

- Metastatic or unresectable locally advanced, recurrent NSCLC
- Documented evidence of any activating mutation in the EGFR (local laboratory)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
- Prior treatment with EGFR-directed TKI therapy (e.g. erlotinib, gefitinib, neratinib, afatinib, or dacomitinib). Prior chemotherapy, including intervening chemotherapy, is allowed

Note: Patients were not required to be T790M+ in the dose escalation phase of the study

Exclusion:

- History of interstitial lung disease related to prior EGFR inhibitor therapy
- Symptomatic brain metastases

PATIENT CHARACTERISTICS & DISPOSITION

DEMOGRAPHICS	
Variable	N=42
Age (years)	
Median, (min-max)	58 (34,83)
Gender, N (%)	
Female	35 (83%)
Male	7 (17%)
Race (N%)	
Asian	8 (19%)
Black	1 (2%)
White	33 (79%)

PREVIOUS THERAPY	
Variable	N=42
Previous Anticancer Regimens	
Median (min–max)	4 (1, 6)
≥5 prior regimens	14 (33%)
Previous EGFR TKIs	
Erlotinib	39 (93%)
Gefitinib	4 (10%)
Afatanib	4 (10%)
Dacomitinib	1 (2%)

PATIENT CHARACTERISTICS & DISPOSITION

42 patients (74% T790M+) have been treated with CO-1686 up to 1800mg/day

On-Study Biopsy Results	
	N=42
Activating Mutations	
Exon 19 Del	24 (57%)
L858R	16 (38%)
Other	2 (5%)
T790M Status	
Positive	31 (74%)
Negative	7 (17%)
Unknown	4 (9%)

Other: one G719X/L861Q and one very rare deletion in exon 19

- T790M status was determined by a central laboratory (Roche Molecular Systems, RMS)
- If RMS result was unavailable (pending/insufficient tissue), T790M status was determined based on local testing

SAFETY RESULTS

Once (QD), twice (BID), three times (TID) daily regimens evaluated. MTD not yet reached

Total Daily Dose (mg) and Administration Schedule					
Once Daily	N	Twice Daily	N	Three Times Daily	N
150	9				
200	3	200 (100 bid)	3		
300	3				
450	3				
600	3	600 (300 bid)	3		
900	3				
		1200 (600 bid)	3	1200 (400 tid)	3
		1800 (900 bid)	6		
Total	24	Total	15	Total	3

- 150mg once daily dose was taken fasted (N=6) and fed (N=3)
- 150mg, 200mg, 300mg once daily doses were taken fasted
- Other doses were taken fed

CO-1686 is well tolerated at doses up to 1800mg daily

Adverse Events (CTCAE Grades ≥ 3 and Attributed to Treatment) in any Patient					
Total Daily Dose Patients Treated	≤600mg N=27	900mg N=3	1200mg N=6	1800mg N=6	Total N=42
Number of Patients with at least one AE≥grade 3					
	2	0	0	2	4 (10%)
Event Term					
↑ AST	0	0	0	1	1 (2%)
↓ Appetite	0	0	0	1	1 (2%)
Hyperglycaemia	1	0	0	0	1 (2%)
Hypoglycaemia	1	0	0	0	1 (2%)
Thrombocytopenia	0	0	0	1	1 (2%)

- AEs were graded according to NCI CTCAE Version 4.0. Overall, 11 (26%) patients reported toxicities ≥ Grade 3 irrespective of association with treatment. No single toxicity ≥ Grade 3 was reported by more than 1 person
- The 4 patients with treatment related toxicities ≥ CTCAE grade 3 include:
  - *DLT (150mg QD) - grade 4 hypoglycemia occurred after 15 days in a diabetic patient who took oral hypoglycemics on a fasting PK day. Investigator noted that the patient's underlying diabetes, the overnight fast and use of glipizide and metformin significantly contributed to the event
  - Grade 3 hyperglycemia (100mg BID) occurred after 22 days of treatment. In a patient with a history of impaired glucose tolerance, and the event was judged by the investigator not to be clinically significant or dose-limiting
  - DLT (900 mg BID) - acute illness on day 3 with dehydration, transaminitis, diarrhea and abdominal cramps. Patient had grade 3 AST elevation and grade 3 anorexia. Treatment was stopped and patient recovered fully 2-4 days after onset
  - Grade 3 thrombocytopenia (900mg BID) for 1 day which rapidly improved to grade 1

Adverse Events (All Grades) in ≥10% of Patients and Attributed to Treatment					
Daily Dose Patients Treated	≤600mg N=27	900mg N=3	1200mg N=6	1800mg N=6	Total N=42
Number of Patients with at least one Treatment Related TE AE					
	15	3	4	4	26 (62%)
Event Term					
Fatigue	6	2	0	0	8 (19%)
Nausea	4	0	0	3	7 (17%)
Diarrhea	3	1	1	1	6 (14%)
Muscle spasms	3	0	0	1	4 (10%)
Anemia	2	1	0	1	4 (10%)

- *DLTs - AEs considered probably, possibly or definitively related to CO-1686 and which were:
  - Any nonhematological CTCAE Grade 3 or greater AE (except alopecia or nausea, vomiting, or diarrhea if well-controlled by systemic medication);
  - Absolute neutrophil count (ANC) <0.5 × 10^9/L >5 days duration or febrile neutropenia (i.e., fever >38.3°C with ANC <1.0 × 10^9/L);
  - Platelets <25 × 10^9/L or platelets <50 × 10^9/L with bleeding requiring a platelet transfusion; grade 4 anemia (life-threatening consequences, urgent intervention indicated)

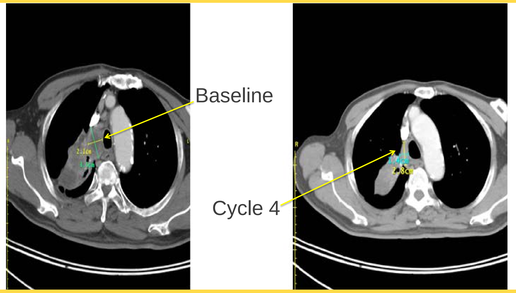
SAFETY RESULTS

CO-1686 shows no evidence of dose-related events related to wild type EGFR inhibition

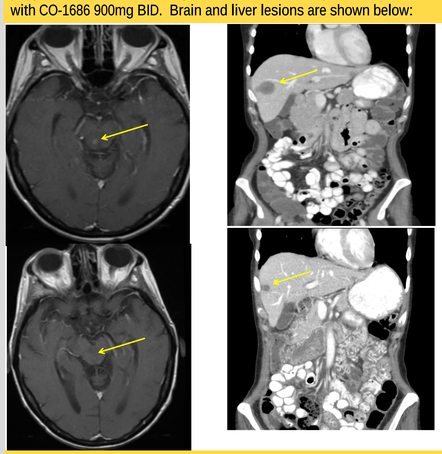
- Unselective EGFR inhibitors cause rash and diarrhea in most patients
- AE profile of CO-1686 is not typical of unselective EGFR inhibition
  - Unlike other EGFR inhibitors, rash and diarrhea were not commonly seen
  - With CO-1686, rash was rare (n=1) and was mild, transient and not related to dose
  - With CO-1686, diarrhea was rare (n=6; 5 mild,1 moderate), with rapid onset, was intermittent and was usually self limiting
- This AE profile is consistent with the expected lack of wild type EGFR inhibition with CO-1686

ACTIVITY OBSERVED IN DOSE ESCALATION COHORTS

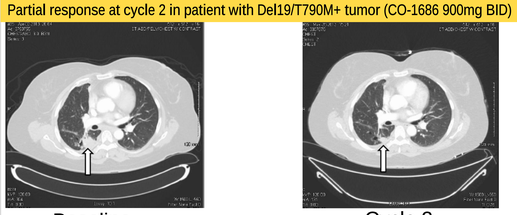
Confirmed partial response in patient with Del19/T790M+ tumor: patient had progressed on erlotinib immediately before CO-1686, and was dosed with CO-1686 300mg BID.



Partial response at cycle 4 in patient with L858R/T790M+ tumor: patient had previously had 6 lines of therapy, including two previous TKIs (dacomitinib and erlotinib) and had most recently progressed on erlotinib and gemcitabine immediately before CO-1686. The patient was dosed with CO-1686 900mg BID. Brain and liver lesions are shown below:



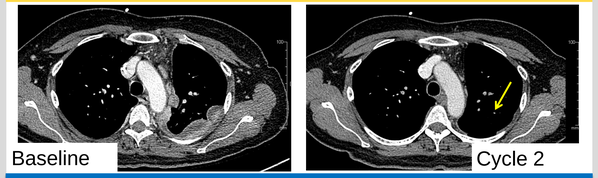
Partial response at cycle 2 in patient with Del19/T790M+ tumor (CO-1686 900mg BID)



2 additional T790M+ patients have achieved > 20% target lesion shrinkage - scans not shown

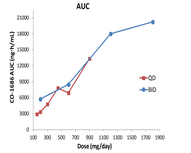
ACTIVITY OBSERVED IN DOSE ESCALATION COHORTS

Partial response at cycle 2 in patient with Del19/T790M+ tumor (CO-1686 900mg BID)



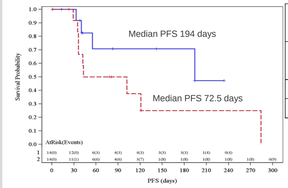
PHARMACOKINETICS

Plasma exposure of CO-1686 administered as free base capsules increases with dose



- T_{max} (1.5 to 4 h) and $T_{1/2}$ (3.5 to 5.5 h) were consistent across doses and there was no accumulation in CO-1686 at any dose
- A high-fat meal increased C_{24h} (+ 71% to + 300%) and AUC_{0-24} (+ 44% to > + 110%) with no change in $T_{1/2}$; a lower C_{max} and delayed T_{max} was also seen in a majority of patients
- Moderate intra-patient variation was observed

T790M+ patients (N=28): Time above Cmin **> 200ng/mL ≥ 16 hours is associated with improved** PFS and correlated with tumor shrinkage



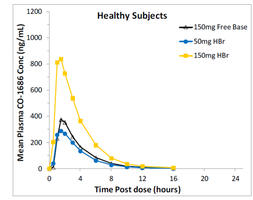
Time above C_{min} > 200 ng/mL and Tumor Shrinkage in T790M+ Patients			
	N	≤ 10% shrinkage	>10% shrinkage
<16hrs	12	11 (92%)	1 (8%)
≥16hrs	12	6 (50%)	6 (50%)

4 patients did not have measurable disease at baseline

+: censor
Blue line: T790M+ with Cmin > 200ng/mL ≥ 16 hours
Red line: T790M+ with Cmin > 200ng/mL < 16 hours

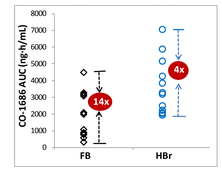
Data from most recently treated T790M+ patients (N=3; 900 mg bid) were not available for these assessments

The hydrobromide salt form of CO-1686 improved absorption (2 to 3-fold) and reduced variability (4-fold) relative to the free base in an ongoing phase 1 study in healthy volunteers



150mg HBr data was extrapolated from observed 125mg HBr data

Variability of 150mg Free Base (FB) vs salt (HBr)



- AUC and C_{max} of hydrobromide 2 to 3-fold higher relative to same dose of free base
- $T_{1/2}$ of hydrobromide and free base is comparable
- CO-1686 hydrobromide tablets will be available for continued dose escalation in Q3 2013

CONCLUSION

- CO-1686 is well tolerated with no evidence of dose related diarrhea or rash
- Encouraging activity has been observed (four PRs to date) in heavily pretreated T790M+ EGFR mutant patients resistant to erlotinib in the dose escalation portion of the study, especially in patients with higher drug exposures. Metastasis shrinkage has been observed at multiple organ sites, including in the CNS
- Activity appears to correlate to drug exposure. Three of four T790M+ patients on 900mg bid and evaluable for response achieved PRs to date
- A hydrobromide form of CO-1686 has improved exposure and reduced PK variability and will be introduced into the current phase 1/2 study during 2013, and into a phase 1 dose escalation study planned in Japan early in 2014
- The recommended phase 2 dose of CO-1686 is not yet defined
- CO-1686 has the potential to be effective in the treatment of EGFR mutant NSCLC including T790M+ patients, with better tolerability than existing agents

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