Rociletinib (CO-1686), an irreversible EGFR-mutant selective inhibitor

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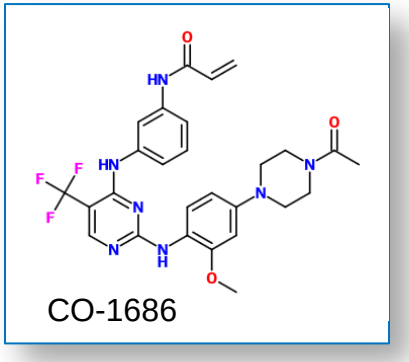
- I receive consultancy fees from Clovis, Roche and AstraZeneca

Rociletinib non-clinical summary

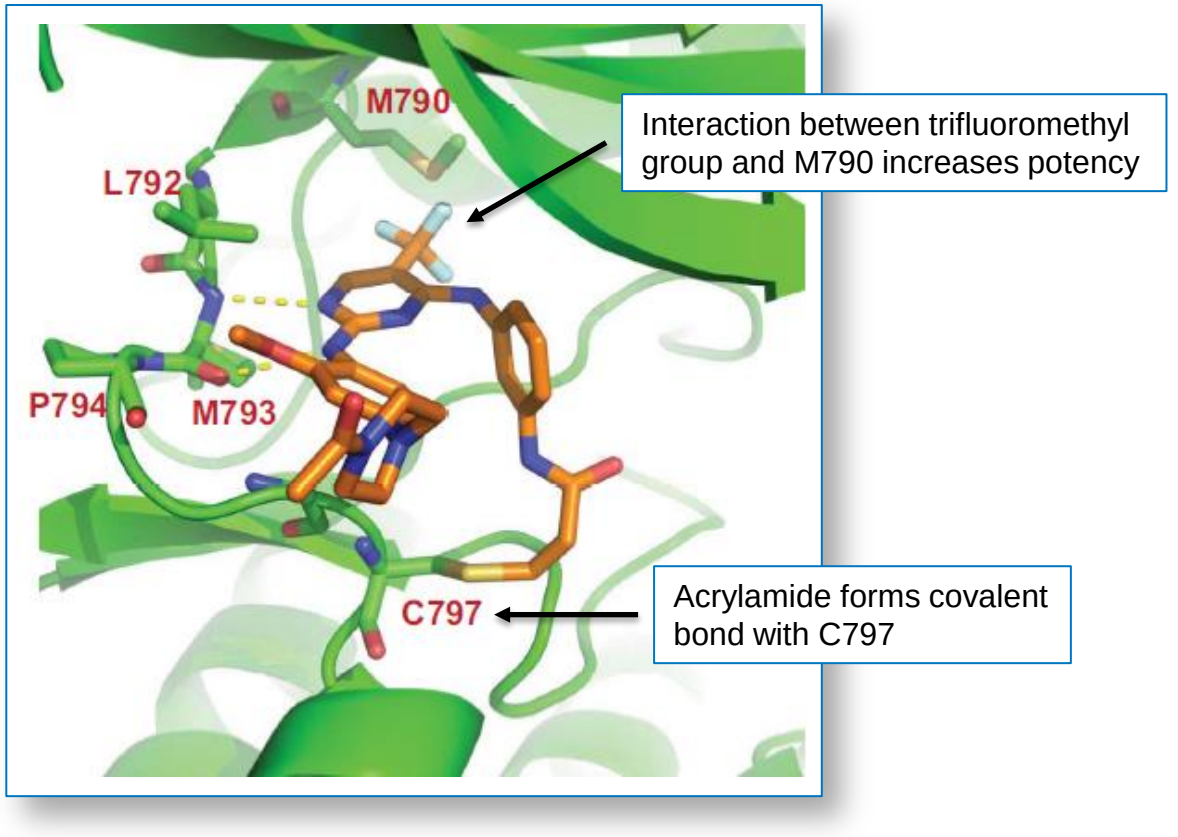
- Rociletinib
  - Irreversible (covalent) inhibitor
  - Inhibits EGFR activating mutations and T790M
  - Spares wild-type (WT) EGFR signaling
  - Highly selective across the entire kinome
- Rociletinib demonstrates potent activity and EGFR pathway blockade in cell lines with activating and T790M EGFR mutations
- As a single agent rociletinib causes tumor regressions in front-line and T790M xenograft models
  - Includes subcutaneous, PDX, and transgenic models



Walter et al., Cancer Discov. 2013

Rociletinib binds EGFR covalently

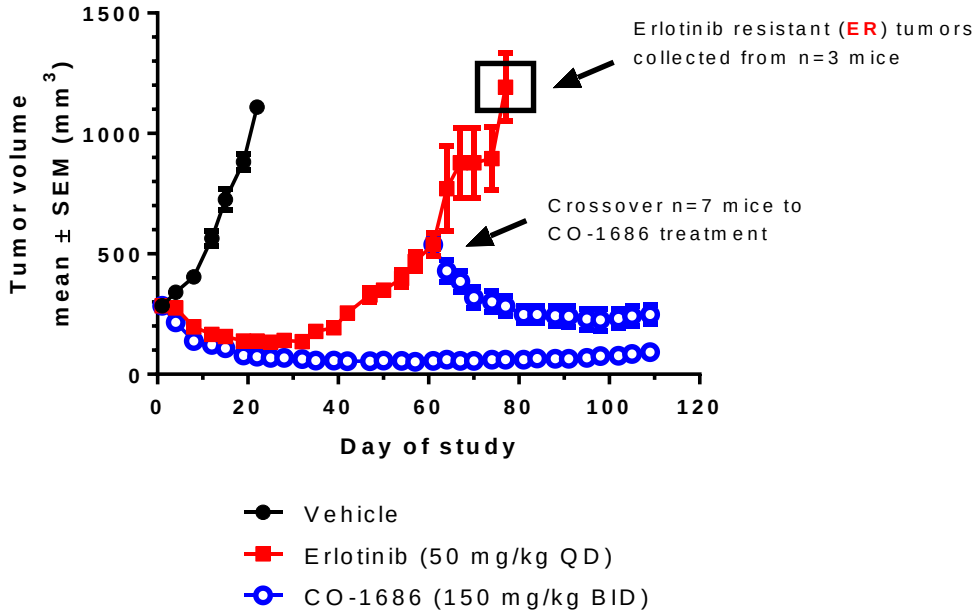
- Irreversible binding results in sustained EGFR pathway suppression

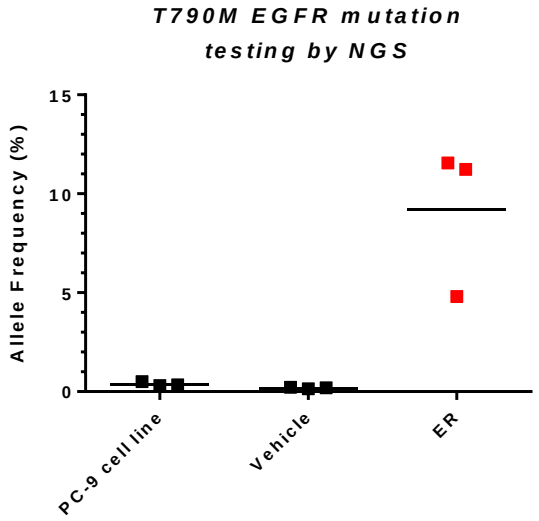


Walter et al., Cancer Discov. 2013

Long-term rociletinib activity superior to erlotinib in PC-9 (EGFRdel19) front line model

- Resistance emerges in erlotinib treated mice due to T790M
  - Impressive anti-tumor response in ~500 mm^3 tumors
- Rociletinib monotherapy delays the emergence of resistance





Clovis Oncology, data on file

Rociletinib clinical summary

- Promising activity seen across all doses used in Phase 1/2 trial
  - 67% ORR in T790M+ patients – durable responses
  - Current estimate of PFS exceeds 10 months
- US FDA breakthrough therapy designation granted May 2014
- Global phase 2/3 program underway

TIGER-X Phase 1

- TIGER-X, an international phase 1/2 study, examined 2 formulations and multiple doses/schedules of rociletinib
  - Therapeutic doses defined as 900 mg BID (original formulation) or ≥500 mg BID HBr salt tablet (PK optimized formulation)
- 625 mg BID of optimized oral formulation (fed state) was identified as the recommended dose and schedule
  - 500mg BID remains under study to provide comprehensive assessment of dose/response
  - Clinical dose group: patients treated with 625/500 mg BID (n=56)
- Early evidence of activity was observed with durable RECIST responses, particularly in T790M+ patients
- Wild-type EGFR sparing was confirmed by absence of cutaneous toxicity (rash, paronychia, stomatitis, etc)

HBr = hydrobromide; RECIST = Response Evaluation Criteria In Solid Tumors

TIGER-X expansion phase in T790M+

Key inclusion criteria:

- Advanced or metastatic EGFR mutation+ NSCLC
- At least 1 prior EGFR TKI therapy, with no other upper limit
- Asymptomatic brain metastases allowed
- Biopsy within 60 days of study entry – molecular analysis T790M+

Key exclusion criteria:

- Symptomatic CNS evolution
- Exon 20 insertion as activating EGFR mutation

- Patients with diabetes or cardiovascular disease were eligible
- Study sites in United States, Europe, and Australia

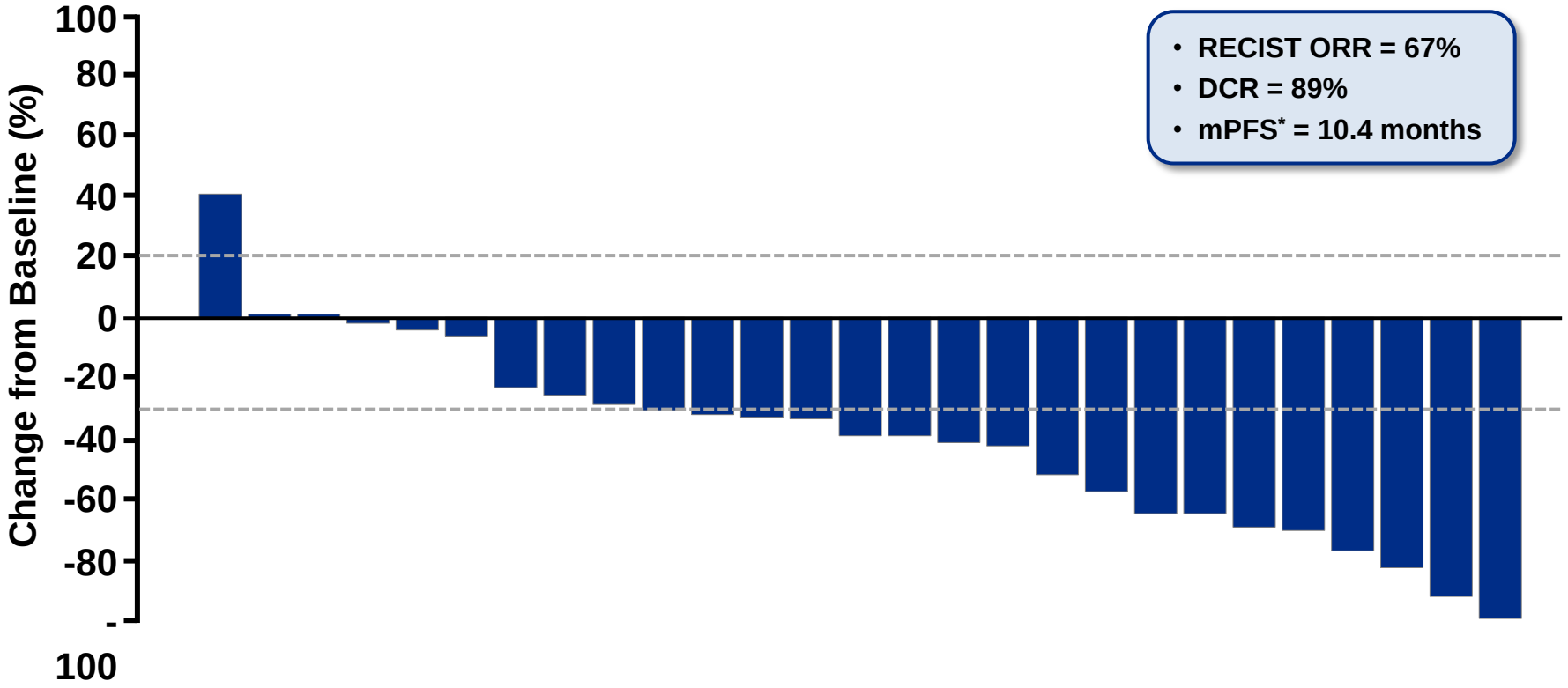
TIGER-X clinical dose group (T790M+) demographics

	625 mg BID	500 mg BID	Total
N	30	26	56
Median age, years	59	59	59
Female, %	63	77	70
Asian, %	7	15	11
ECOG PS grade 0, %	13	27	20
Median no. of prior Rx	3	3	3
No. of prior TKIs, %			
1	43	46	45
2	13	39	25
≥3	27	12	20
Immediate prior TKI, %	73	85	79
History of diabetes, %	3	12	7
History of cardiovascular disease, %	13	15	14

*7 patients started treatment with 900 mg BID free-base formulation and converted to 500 mg HBr salt tablet. The majority of their treatment was with HBr tablet and they are aggregated with the 500 mg BID HBr tablet group.
ECOG PS = Eastern Cooperative Oncology Group Performance Status.

TIGER-X clinical dose group responses

Best Response for Evaluable Centrally Confirmed T790M+ Patients



*Data as of 25 September 2014 reflecting 31% data maturity

TIGER-X clinical dose group: adverse events

Treatment-related adverse events (all grades) seen in >10% of patients

Adverse event	Frequency, %
Hyperglycemia	32
Diarrhea	25
Nausea	25
Reduced appetite	20
Fatigue	14
Muscle spasm	13
Vomiting	11

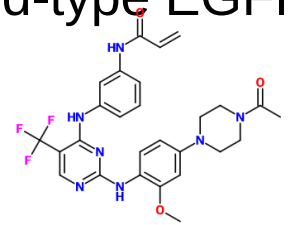
Grade 3/4 treatment-related adverse events seen in >5% of patients*

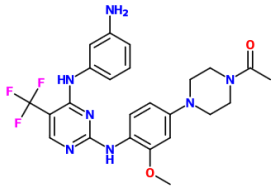
Adverse event	Frequency, %
Hyperglycemia	14

*21% of patients had a grade 3/4 treatment-related adverse event and only hyperglycemia was observed in ≥5% of patients

Observed hyperglycemia relates to metabolite of rociletinib

- Rociletinib metabolite M502 is a reversible inhibitor of IGF1R (and IR) that causes hyperglycemia in humans
  - No hyperglycemia observed in toxicology studies of rociletinib (cleared very rapidly in animals)
- Like rociletinib, M502 is wild-type EGFR sparing



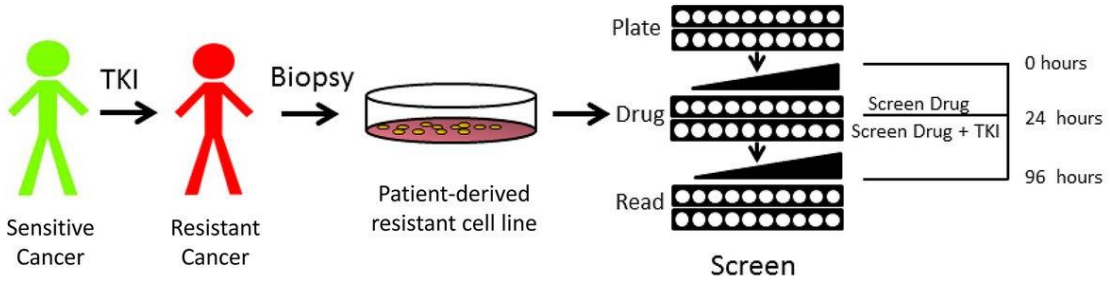


Assay	Rociletinib	M502
A431 (IC_{50}, nM) Cellular (wild-type EGFR)	903	907
NCI-H1975 (IC_{50}, nM) Cellular (T790M EGFR)	36	961
IGF1R (IC_{50}, nM) Kinase	477	57
IGF1R (IC_{50}, nM) Cellular	458	58

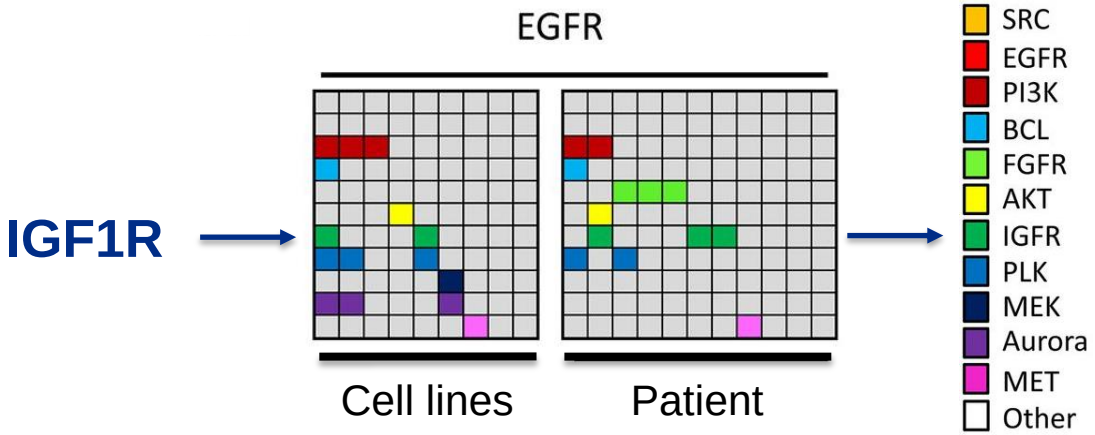
IC_{50} = half maximal inhibitory concentration
IGF1R = insulin-like growth factor 1 receptor

IGF1R inhibitors can overcome resistance in mutant EGFR patient derived cell lines

- Cell line models derived from biopsy specimens collected after the development of acquired resistance to EGFR inhibitors



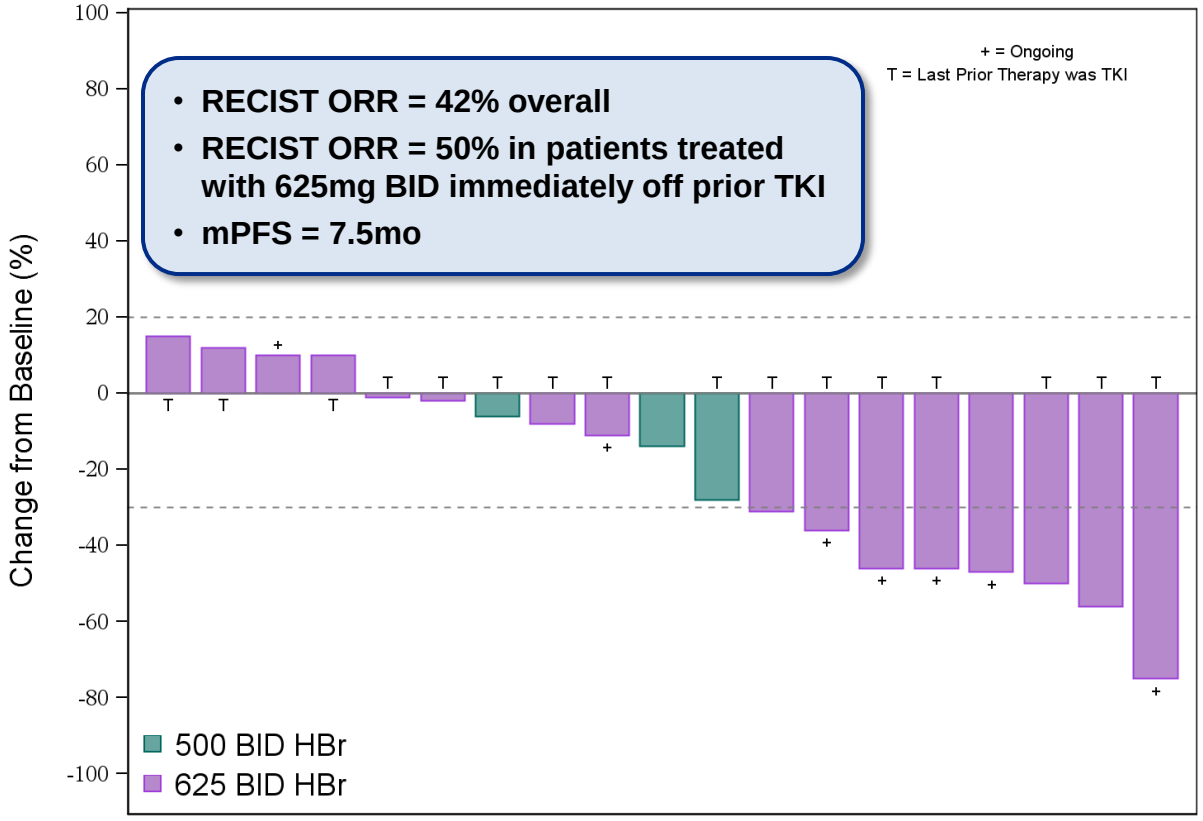
- IGF1R inhibitor combination restores activity in 3/11 patient cell lines



Crystal et al., Science 2014

Striking Activity in T790M-negative Patients

Best Response for Target Lesions
Centrally Confirmed T790M Negative 1686-008 Pts at 500 or 625mg BID (Clinical Dose Group)



Data as of 2 January 2015

Why Is a Targeted Therapy Active in an Off-Target Population?

- False negative
- Real tumor heterogeneity
- Specific mechanism of action of rociletinib
  - Extensive preclinical evidence that IGF1R is a driver of acquired resistance to EGFR TKIs
    - New data from patients show IGF1R pathway important in acquired EGFR TKI resistance (*Crystal et al., Science 2014*)
  - Rociletinib metabolite inhibits IGF1R and insulin receptor
  - Clovis now actively evaluating rociletinib in T790M-negative patients
    - T790M negative patients represent a significant unmet medical need
    - Rociletinib may possess a unique competitive advantage

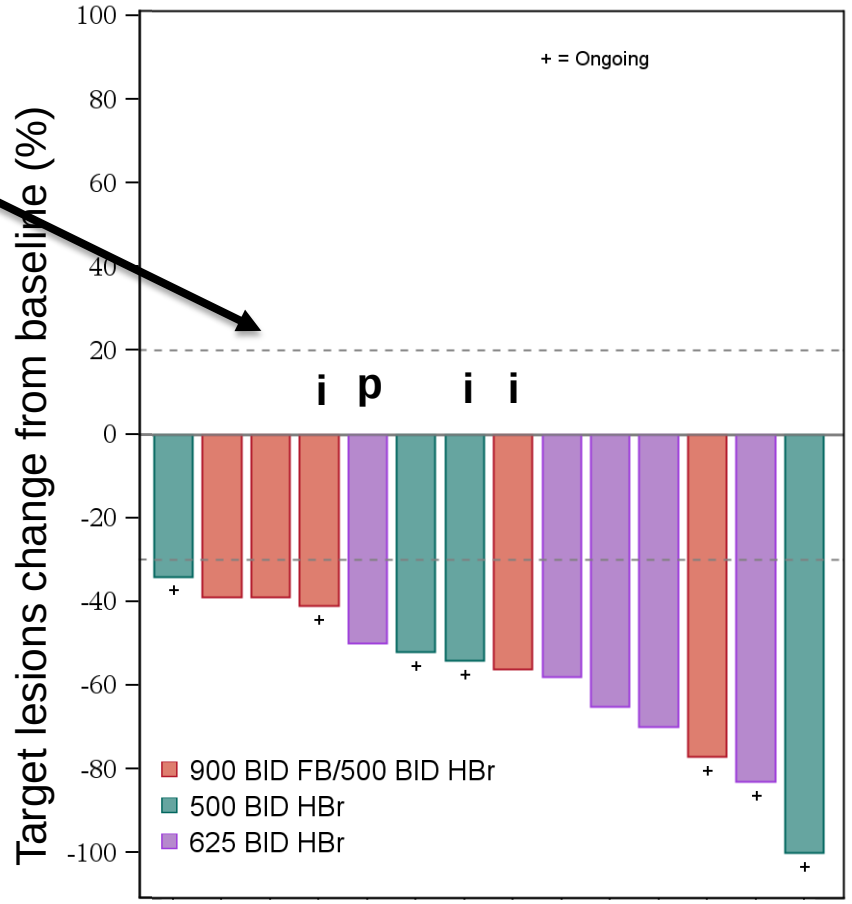
EGFR plasma testing can help address tumor heterogeneity

BEAMing plasma EGFR test identified 4 rociletinib responders missed by tissue test in Ph1

i = Plasma T790M-pos/tissue inadequate

p = Plasma T790M-pos/tissue neg

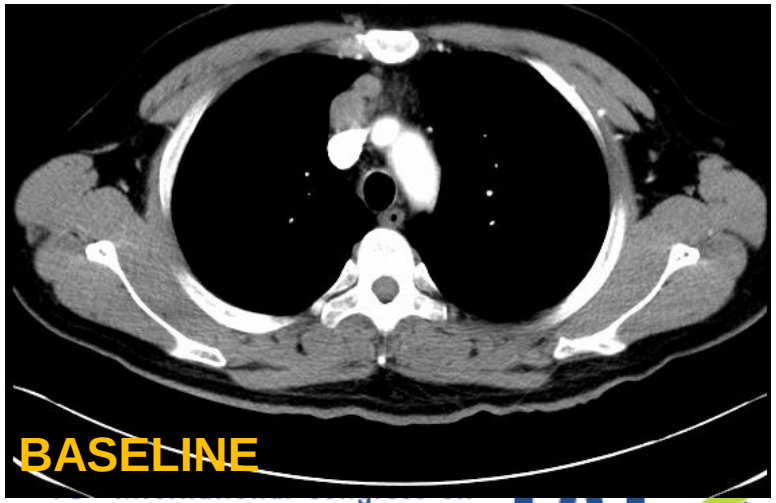
Responders identified by plasma

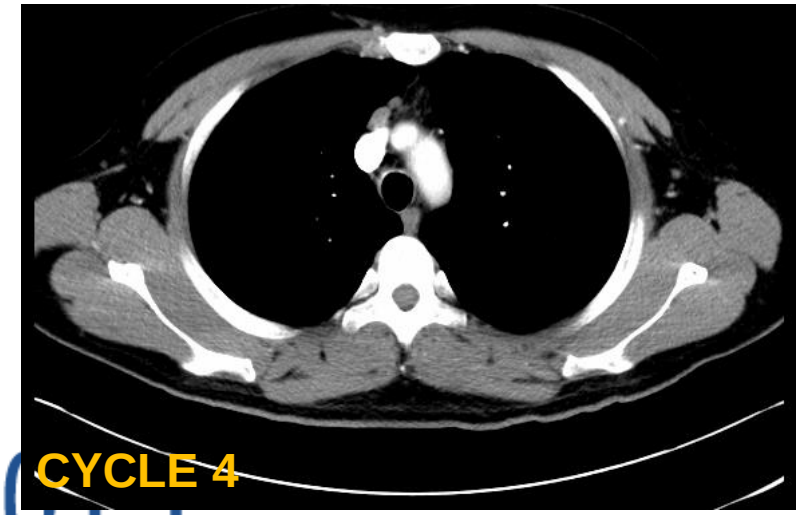


Plasma data from a subset of patients evaluated in Nov 2014

Tissue negative/plasma positive pt with excellent outcome

- 30 yr old male
- Progressed on front line gefitinib (15 months) immediately before rociletinib
  - Tumor in thorax, brain, supraclavicular nodes (readily accessible for bx)
- Negative T790M by local and central tissue testing
- Plasma T790M positive by BEAMing
- RECIST PR at cycle 2 (including biopsied node), maintained for 10 cycles





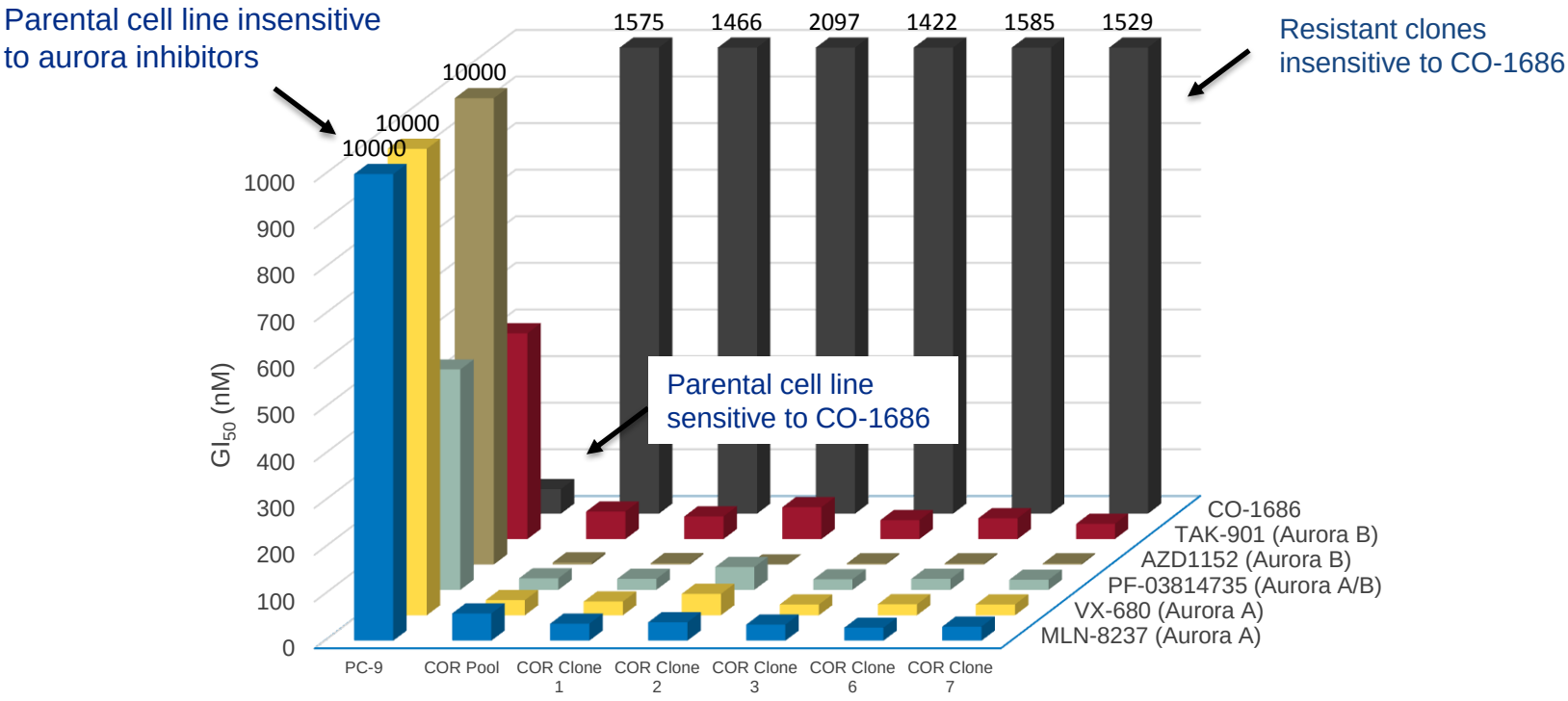
Combination studies to begin

- Rociletinib has a unique tolerability and efficacy profile
  - No evidence of WT EGFR inhibition observed in patients
  - Evidence of activity in T790M- patients
  - Moderately short plasma half-life allows for flexibility in dosing regimens and management of potential combination AEs
- Initial combinations with

Target	Drug
PDL1	mAb
PD1	Pembrolizumab (Merck)
MEK	Trametinib (GSK)
Aurora kinase	small molecule inhibitor

CO-1686 and Aurora kinase inhibitor combination potent in all PC-9 CO-1686 resistant clones

- PC-9 resistant lines generated by long term CO-1686 dosing
- Resistant cells maintained and tested in 1μM CO-1686



Comprehensive Monotherapy Development Program

TIGER-X (Ph 2)

- Single arm – expansion cohorts
- ≥2nd-line mutant EGFR NSCLC, T790M+

TIGER-1 (Ph 2/3)

- Randomized rociletinib vs erlotinib
- 1st-line, treatment-naïve

TIGER-2 (Ph 2)

- Single-arm
- 2nd-line mutant EGFR NSCLC, T790M+
- Patients progressing on 1st-line EGFR TKI
- Now adding T790M– cohort

TIGER-3 (Ph 3)

- Randomized rociletinib vs chemotherapy
- >2nd-line mutant EGFR NSCLC, T790M+ and T790M– (sequential analysis)

Conclusions

- Rociletinib is an oral, potent, irreversible inhibitor of activating EGFR mutations and T790M
- Compelling and durable activity was demonstrated with clinical doses in T790M+ patients
  - 67% objective response rate
  - Median (immature) PFS estimated at 10.4 months
- Wild-type sparing was confirmed, with no cutaneous toxicity
- The only grade 3/4 adverse event observed in >5% of patients was hyperglycemia, readily managed with oral Rx
- Encouraging activity was observed in T790M– patients
- Comprehensive pivotal trial program is advancing rapidly
- NDA and MAA filings planned for mid 2015