Serial monitoring of *EGFR* mutations in plasma and evaluation of *EGFR* mutation status in matched tissue and plasma from NSCLC patients treated with CO-1686

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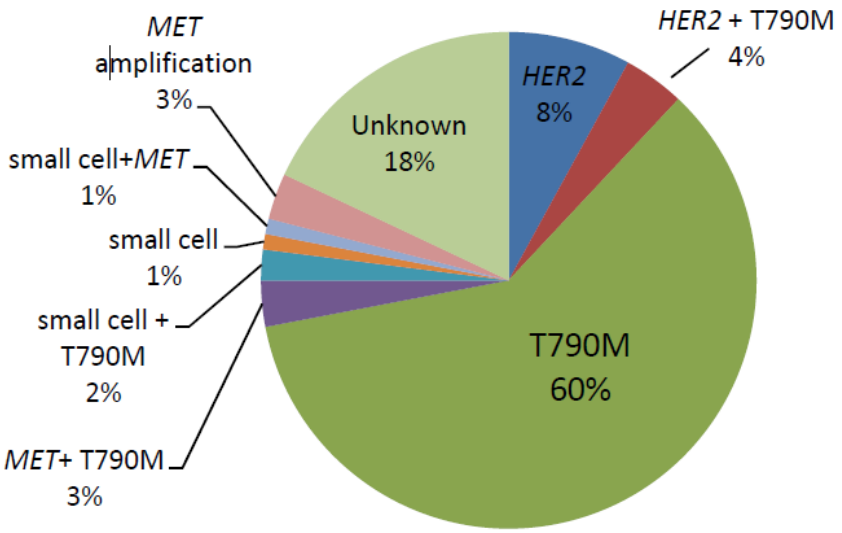
CNAPS VIII

CO-1686 Overview

T790M is dominant cause of acquired resistance to initial TKI therapy in EGFR^{mut} NSCLC



- CO-1686 is a novel, oral, selective covalent inhibitor of *EGFR* mutations in NSCLC
  - Inhibits key activating and T790M resistance mutations
  - Spares wild-type receptor signaling
  - Promising activity in an ongoing Ph 1/2 clinical trial

Source: Yu et al CCR (2013)

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An *EGFR* blood test would be advantageous but needs high sensitivity/specificity for use in clinical practice

- Why blood?
  - May capture tumor heterogeneity
  - Is non-invasive
  - Enables serial monitoring of circulating tumor DNA (ctDNA) kinetics and emergence of resistance
  - Biopsies often provide inadequate/insufficient material for molecular analysis

- ***Key questions to be addressed***
  - Are current EGFR testing platforms sensitive and specific enough to inform NSCLC patient management?
  - What clinical characteristics impact the sensitivity of *EGFR* mutation detection in plasma?

Methodology: Matched tissue and plasma were evaluated using the cobas EGFR test

- Matched tumor and plasma was obtained from NSCLC patients in ongoing Ph 1/2 trial of CO-1686 and an observational study
  - 97 evaluable Stage IIIB/IV patients; most received prior EGFR TKI
  - 10 Ph 1/2 patients not evaluable because of low/no tumor content
  - Plasma and tissue collections matched in time
  - Biopsies included CNB, FNA, bronchoscopic biopsies, and PE

- Baseline plasma and tissue evaluated with cobas EGFR mutation test
  - Qualitative test that uses allele-specific PCR (Taqman chemistry)
  - Input is ctDNA
  - Detects 41 mutations including T790M, L858R, ex19 deletions

- Baseline plasma from 30 patients was additionally tested by BEAMing for comparison with cobas results

cobas test results in matched tissue and plasma displayed good sensitivity and very good specificity for plasma test

		Tissue		Tissue	
		Activating Mutations		T790M	
		positive	negative	positive	negative
Plasma	positive	57	0	21	2
	negative	21	23	13	61
total		78*	23	34	63

	Activating	T790M
Plasma Sensitivity (tissue as reference)	**73%**	**62%**
Plasma Specificity (tissue as reference)	**100%**	**97%**

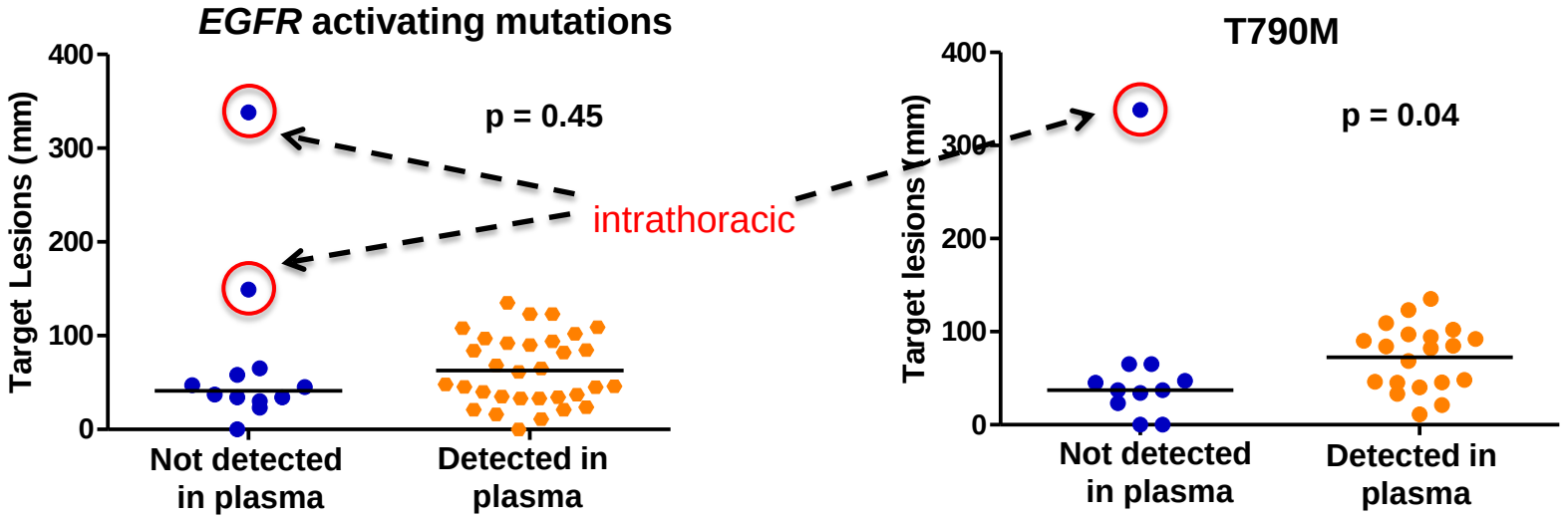
- Two T790M plasma+/tumor- patients were confirmed plasma-positive by BEAMing
  - May reflect tumor heterogeneity and highlights potential advantages of plasma
- Plasma-/tumor+ patients may be plasma-neg due to biology (low/no ctEGFRmut)

***4 patients had compound activating mutations in tissue (n = 97 patients)

Tumor burden is a weak predictor of ability to detect *EGFR* mutations in plasma of NSCLC patients

- Tumor burden has been found to be associated with ctDNA levels[1] but may not capture differences in tumor biology (e.g. vascularization, immune infiltration)

  - *While EGFR plasma test sensitivity was generally better in patients with higher tumor burden, there were notable exceptions*



[1] Bidard Sci Transl Med 2013

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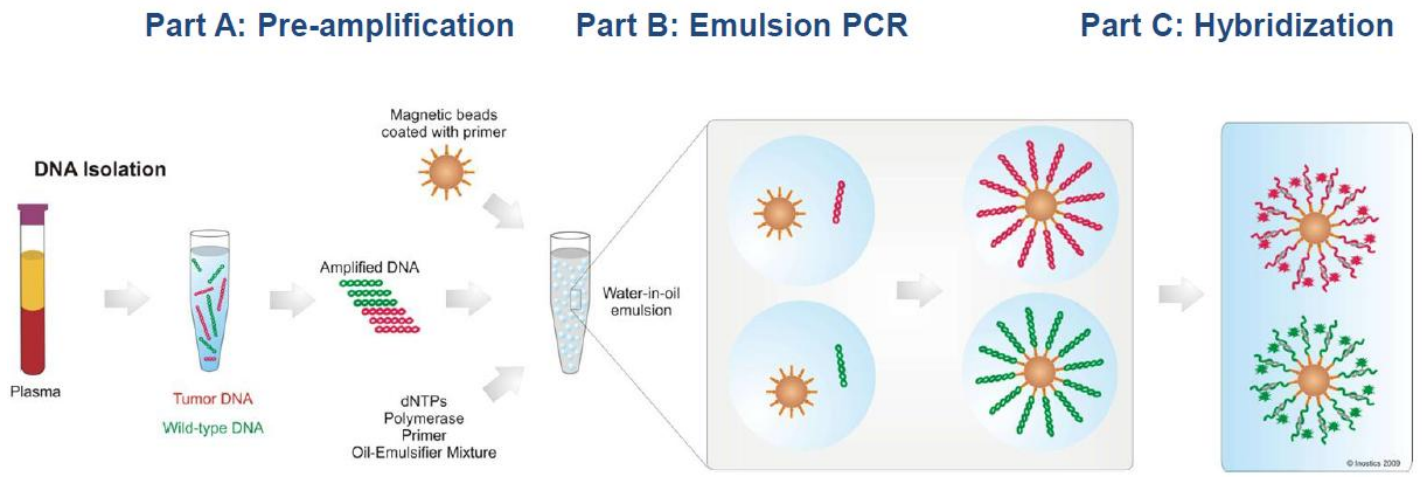
Mutations are more readily detected in plasma of patients with extrathoracic metastases (M1b) vs. intrathoracic (M1a/M0) disease

Mutation	Disease classification	Mutation detected in tissue	Subset with mutation in plasma	Percentage	P value
Activating Mutations	M1a/M0	24	12	50%	<0.001
	M1b	49	43	88%	
T790M	M1a/M0	13	2	15%	<0.001
	M1b	21	19	90%	

- M0/M1a/M1b status known for 73 patients

cobas EGFR plasma test results were compared to sensitive BEAMing test



Dressman *et al.* PNAS,2003
Diehl *et al.* PNAS, 2005

- Baseline plasma samples from subset of 30 patients were tested by BEAMing and compared with cobas results
  - Serial monitoring using BEAMing is also ongoing

- BEAMing is droplet digital PCR followed by flow cytometry
  - 0.02% sensitivity

Strong overall agreement observed between cobas and BEAMing *EGFR* plasma tests

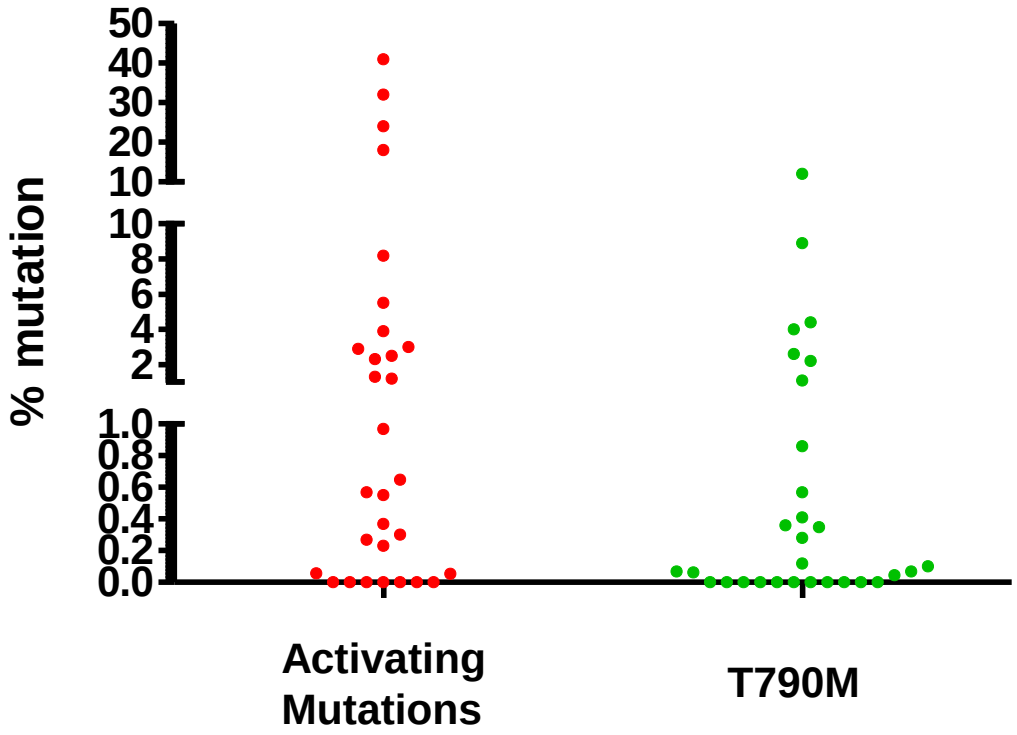
Plasma Results		BEAMing			
		Activating Mutations		T790M	
		positive	negative	positive	negative
cobas	positive	21	2	16	1
	negative	1	6	3	10

- Overall agreement between platforms (n = 30)
  - 87% for T790M
  - 90% for activating mutations
  - Discordance occurred only at very low allele frequencies (<0.3%)

- Cobas/BEAMing had similar plasma sensitivity wrt tissue (n = 27)

	Activating Mutations	T790M
cobas	**74%**	**70%**
BEAMing	**78%**	**70%**

Low median plasma *EGFR* allele fraction supports need for highly sensitive detection methods in this NSCLC patient population



***EGFR* allelic fraction in plasma by BEAMing**

T790M

median = 0.41%

range = 0.046 – 12%

Activating Mutations

median = 1.3%

range = 0.053 – 41%

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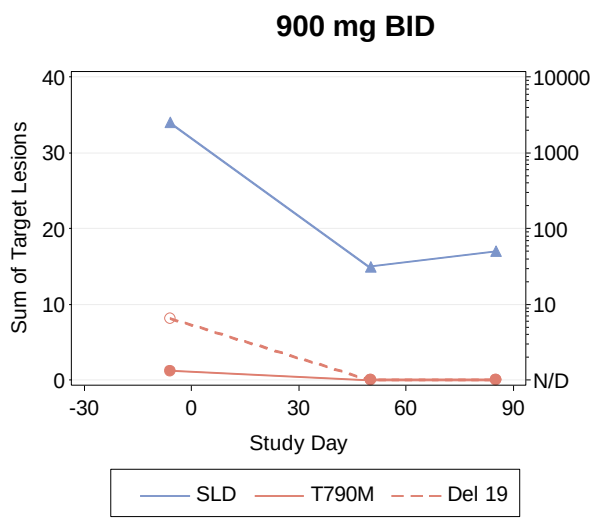
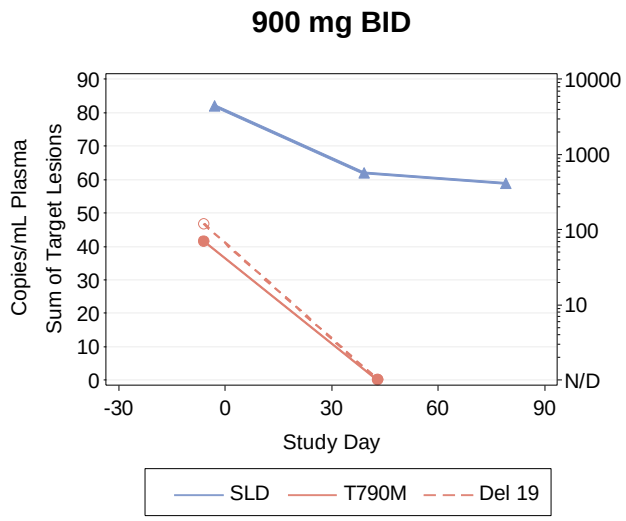
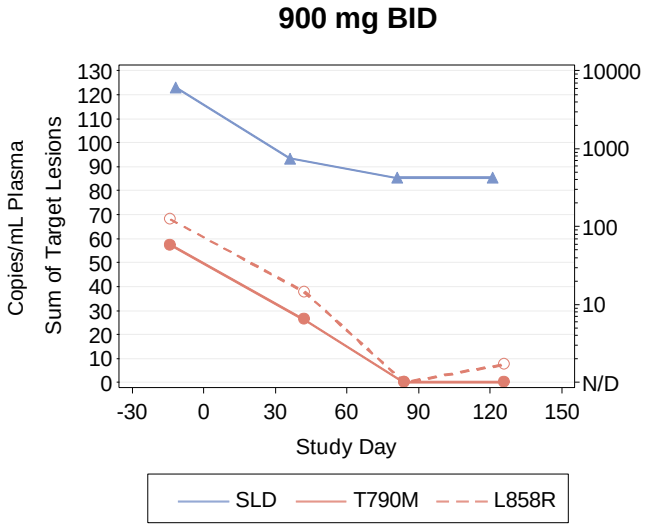
Serial Monitoring: Initial drop in plasma *EGFR* seen in patients where clinical activity observed

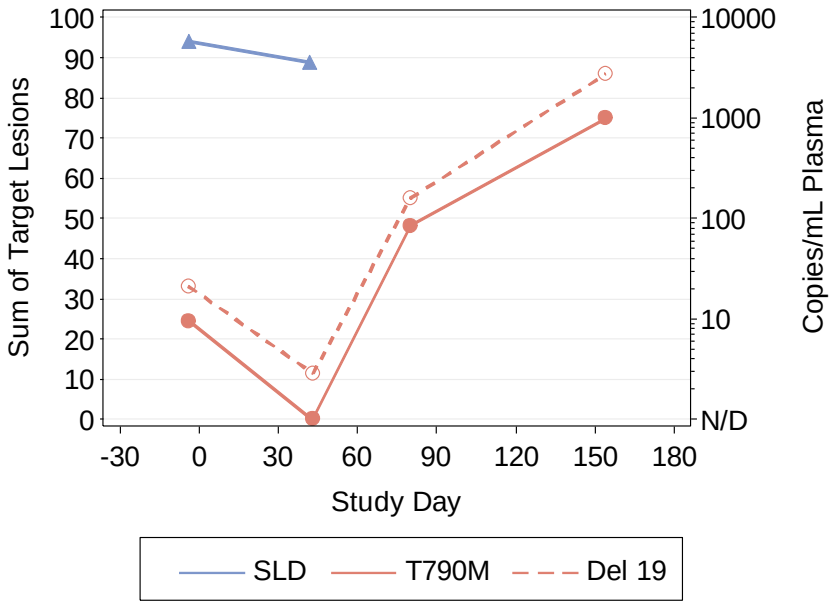






- Serial monitoring ongoing for Ph 1/2 patients; data not yet mature for most (n = 25)
- Initial drop in plasma *EGFR* seen in 13/14 patients with SD or PR as best response
- CO-1686 inhibits both activating and T790M mutations
- 6 patients have undetectable plasma *EGFR* at baseline & during serial monitoring

Serial monitoring will inform several key questions



Early cohort patient

- Does rate of initial decline in *EGFR* mutation levels correlate with response to CO-1686?
- When is re-emergence of mutant *EGFR* seen prior to clinical progression?
- Does the allele fraction of T790M relative to activating mutation correlate with response to CO-1686?

Summary

- A high proportion of *EGFR* mutations identified in tissue were also detected in plasma using the cobas EGFR mutation test
- Mutations were more readily detectable in the plasma of patients with M1b rather than M1a disease
- Strong overall agreement observed between BEAMing and cobas plasma *EGFR* results
- Baseline T790M levels of <1% in many patients support use of sensitive technologies such as digital PCR or allele-specific PCR for mutation detection
- Serial monitoring of plasma ct*EGFR* kinetics is ongoing in the Ph 1/2 trial of CO-1686