SUPPLEMENTALS

Supplemental Table 1. 54 gene panel (N = 40 patients): identifies potential tumor-related genomic alterations within 54 cancer-related genes including amplifications in *ERBB2, EGFR*, and *MET*. Only non-synonymous alterations were analyzed.

GENES WITH COMPLETE EXON COVERAGE					
ALK	*APC*	*AR*	*BRAF*	18 GENES **3 Copy Number Variations in BOLD**	
CDKN2A	***EGFR***	***ERBB2***	*FBXW7*		
KRAS	***MET***	*MYC*	*NOTCH1*		
NRAS	*PIK3CA*	*PTEN*	*PROC*		
RB1	*TP53*				
GENES WITH CRITICAL EXON COVERAGE			36 GENES		
ABL1	*AKT1*	*ATM*	*CDH1*	*CSF1R*	*CTNNB1*
ERBB4	*EZH2*	*FGFR1*	*FGFR2*	*FGFR3*	*FLT3*
GNA11	*GNAQ*	*GNAS*	*HNF1A*	*HRAS*	*IDH1*
IDH2	*JAK2*	*JAK3*	*KDR*	*KIT*	*MLH1*
MPL	*NPM1*	*PDGFRA*	*PTPN11*	*RET*	*SMAD4*
SMARCB1	***SMO***	***SRC***	***STK11***	***TERT***	***VHL***

Supplemental Table 2. 68 gene panel (N = 47 patients), comprising amplifications in 16 genes as well as some fusions and indels. Only non-synonymous alterations were analyzed.

POINT MUTATIONS (68 genes)				**AMPLIFI-CATIONS** (16 genes)	**FUSIONS** (4 genes)	**INDELS** (1 gene)
AKT1	*ALK*	***APC***	***AR***	*AR*	*ALK*	*EGFR* exon 19 deletions
AFAR	***ARID1A***	*ATM*	***BRAF***	*BRAF*	*RET*	*EGFR* exon 20 insertions
BRCA1	***BRCA2***	***CCDN1***	***CCDN2***	*CCNE1*	*ROS1*	
CCNE1	*CDH1*	***CDK4***	***CDK6***	*CDK4*	*NTRK1*	
CDKN2A	***CDKN2B***	*CTNNB1*	***EGFR***	*CDK6*		
ERBB2	*ESR1*	*EZH2*	*FBXW7*	*EGFR*		
FGFR1	***FGFR2***	*FGFR3*	*GATA3*	*ERBB2*		
GNA11	*GNAQ*	*GNAS*	*HNF1A*	*FGFR1*		
HRAS	*IDH1*	*IDH2*	*JAK2*	*FGFR2*		
JAK3	***KIT***	***KRAS***	*MAP2K1*	*KIT*		
MAP2K2	***MET***	*MLH1*	*MPL*	*KRAS*		
MYC	***NF1***	*NFE2L2*	*NOTCH1*	*MET*		
NPM1	***NRAS***	*NTRK1*	***PDGFRA***	*MYC*		
PIK3CA	***PTEN***	*PTPN11*	***RAF1***	*PDGFRA*		
RET	*RHEB*	*RHOA*	*RIT1*	*PIK3CA*		
ROS1	*SMAD4*	*SMO*	*SRC*	*RAF1*		
STK11	*TERT*	***TP53***	*VHL*	*Complete exon coverage for genes in **bold**		

Supplemental Table 3: 70 gene panel (N = 1 patient)

Only non-synonymous alterations were analyzed.

Complete Exon Sequencing									
Point Mutations (SNVs) (70 Genes)						**Amplifications (CNVs)** (18 Genes)		**Fusions** (6 Genes)	**Indels** (3 Genes)
AKT1	*ALK*	*APC*	*AR*	*ARAF*	*ARID1A*	*AR*	*BRAF*	*ALK*	*EGFR**
ATM	*BRAF*	*BRCA1*	*BRCA2*	*CCND1*	*CCND2*	*CCND1*	*CCND2*	*FGFR2*	*ERBB2**
CCNE1	*CDH1*	*CDK4*	*CDK6*	*CDKN2A*	*CDKN2B*	*CCNE1*	*CDK4*	*FGFR3*	*MET***
CTNNB1	*EGFR*	*ERBB2*	*ESR1*	*EZH2*	*FBXW7*	*CDK6*	*EGFR*	*NTRK1*	
FGFR1	*FGFR2*	*FGFR3*	*GATA3*	*GNA11*	*GNAQ*	*ERBB2*	*FGFR1*	*RET*	
GNAS	*HNF1A*	*HRAS*	*IDH1*	*IDH2*	*JAK2*	*FGFR2*	*KIT*	*ROS1*	
JAK3	*KIT*	*KRAS*	*MAP2K1*	*MAP2K2*	*MET*	*KRAS*	*MET*		
MLH1	*MPL*	*MYC*	*NF1*	*NFE2L2*	*NOTCH1*	*MYC*	*PDGFRA*		
NPM1	*NRAS*	*NTRK1*	*PDGFRA*	*PIK3CA*	*PTEN*	*PIK3CA*	*RAF1*		
PTPN11	*RAF1*	*RB1*	*RET*	*RHEB*	*RHOA*				**exons 19 & 20*
RIT1	*ROS1*	*SMAD4*	*SMO*	*SRC*	*STK11*				***exon 14 skipping*
TERT	*TP53*	*TSC1*	*VHL*						

Genes included on all three panel versions: point mutations (SNVs) in *AKT1, ALK, APC, AR, ATM, BRAF, CDH1, CDKN2A, CTNNB1, EGFR, ERBB2, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KIT, KRAS, MET, MLH1, MPL, MYC, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMO, SRC, STK11, TERT, TP53, and VHL;* gene amplifications in *EGFR, ERBB2 (HER2), and MET.* Fusions and indel mutations were assessed for only in the 48 patients evaluated by the 68-gene and 70-gene panel.

Supplemental Table 4. List of all alterations identified by the ctDNA test (and tissue NGS) and examples of potential actionability*

254	All Alterations (non-synonymous) (ctDNA variant allele fraction %)	Functionally Characterized Alterations Only (ctDNA variant allele fraction %)	Examples of Potentially actionable alterations: Cognate drugs**	Tissue NGS Results***
1	EGFR T790M (2.9%), TP53 E258K (2.4%), EGFR E746_A750Del (0.3%), MET R191W (0.1%)	EGFR T790M (2.9%), TP53 E258K (2.4%)	EGFR T790M: osimertinib	EGFR amplification – equivocal⌘, EGFR E746_A750del, EGFR T790M, AKT2 amplification – equivocal⌘, FGFR4 amplification, GNAS amplification – equivocal⌘, CCNE1 amplification, MCL1 amplification – equivocal⌘, TP53 E258K
2	EGFR T790M (29.28%), TP53 C2755 (8.61%), EGFR E746_A750Del (25.24%), EGFR Amplification, BRAF Amplification, CCNE Amplification	EGFR T790M (26.05%), TP53 C275S (8.03%), EGFR Exon 19 Del (25.26%), EGFR Amplification	EGFR T790M: osimertinib EGFR Amplification: erlotinib	EGFR amplification, EGFR E746_A750del, EGFR T790M, CCND3 amplification, CDKN2A/B loss, TP53 C275S
3	EGFR L861Q (1.3%), TP53 V157F (1.2%), EGFR G719S (1.1%), TP53 R248G (0.9%), EGFR T790M (0.8%)	EGFR L861Q (1.3%), TP53 V157F (1.2%), EGFR G719S (1.1%), TP53 R248G (0.9%), EGFR T790M (0.8%)	EGFR T790M: osimertinib	
4	EGFR T790M (0.5%), TP53 R273H (0.4%)	EGFR T790M (0.5%)	EGFR T790M: osimertinib	
5	EGFR L858R (0.4%), EGFR S768I (0.2%), NOTCH1 A1338V (0.2%)	EGFR L858R (0.4%), EGFR S768I (0.2%)	EGFR L858R: erlotinib	EGFR L858R, EGFR S768I, TP53 R273H, FLT3 splice 1304_1309+1delTAAGAAG, LRP1B L2478*
6	EGFR L858R (0.6%) TP53 C135Y (0.8%),	EGFR L858R (0.6%) TP53 C135Y (0.8%),	EGFR L858R; erlotinib	EGFR L858R, ERBB3 amplification, CDK4 amplification, GLI1 amplification, TP53 C135Y, NFKBIA amplification, NKX2-1 amplification, ZNF217 amplification
7	EGFR A743V (0.2%)	EGFR A743V (0.2%)	EGFR A743V: erlotinib	
8	EGFR L858R (19.5%), ERBB2 S310F (15.6%), TP53 Y205C (6.9%)	EGFR L858R (19.5%), ERBB2 S310F (15.6%), T P53 Y205C (6.9%)	EGFR L858R; erlotinib ERBB2 S310F: trastuzumab	EGFR L858R, ERBB2 S310F, CCND3 amplification, CDKN2A/B loss, TP53 Y205C

254	All Alterations (non-synonymous) (ctDNA variant allele fraction %)	Functionally Characterized Alterations Only (ctDNA variant allele fraction %)	Examples of Potentially actionable alterations: Cognate drugs**	Tissue NGS Results***
9	TP53 R306* (8.1%), EGFR T790M (4.3%), EGFR Amplification	TP53 R306* (8.1%), EGFR T790M (4.3%), EGFR Amplification (2.3%)	EGFR T790M: osimertinib	
10	EGFR T790M (1.8%), TP53 R273H (0.4%)	EGFR T790M (1.8%)	EGFR T790M: osimertinib	
11	EGFR E746_A750Del (2.5%), EGFR M881V (1.0%), EGFR Amplification, MET Amplification	EGFR Exon 19 Del (2.5%), EGFR Amplification, MET Amplification	EGFR Amplification: cetuximab	EGFR amplification, EGFR E746_A750del, NF1 splice site 3197+1G>A, AURKA amplification – equivocal, TP53 splice site 920-6_922delTCCTAGCAC, NKX2-1 amplification
12	EGFR L747_E749Del (0.4%)	EGFR L747_E749Del (0.4%)	EGFR L747_E749: erlotinib	EGFR A750P, EGFR amplification, EGFR L747_A750>S, CCND1 amplification, CDKN2A/B loss, TP53 R248L, RICTOR amplification, BCL2L2 amplification, NFKBIA amplification, FGF3 amplification, FGF4 amplification, FGF10 amplification, FGF19 amplification, NKX2-1 amplification
13	EGFR L858R (14.4%), TP53 H168R (8.4%)	EGFR L858R (14.4%), TP53 H168R (8.4%)	EGFR L858R: erlotinib	
14	EGFR Amplification MET Amplification,	EGFR Amplification MET Amplification,	MET Amplification: crizotinib EGFR Amplification: Cetuximab	
15	EGFR T790M (7.23%), BRAF Amplification, EGFR R932H (0.54%), EGFR Exon 19 Del (10.96%)	EGFR T790M (7.23%), BRAF Amplification, EGFR Exon 19 Del (10.96%)	EGFR T790M: osimertinib BRAF Amplification: vemurafenib	
16	EGFR S752F (0.51%), RAF1 R627Q (0.23%), EGFR Exon 19 Del (0.42%)	EGFR Exon 19 Del (0.42%)	EGFR Exon 19 Del: erlotinib	
17	SMAD4 D493N (8.30%), EGFR S768I (%)5.35, EGFR G719C (5.32%), ARID1A S744* (3.14%), CDKN2A S12L (0.84%), MYC Amplification	EGFR S768I (5.35%), EGFR G719C (5.32%), ARID1A S744* (3.14%), MYC Amplification	EGFR G719C: gefitinib	

254	All Alterations (non-synonymous) (ctDNA variant allele fraction %)	Functionally Characterized Alterations Only (ctDNA variant allele fraction %)	Examples of Potentially actionable alterations: Cognate drugs**	Tissue NGS Results***
18	PIK3CA E542K (17.1%), EGFR L861Q (10.9%), EGFR amplification, TP53 C238F (8.6%), TP53 F113V (0.1%), BRCA1 N1519S (2.1%), MET T1307I (0.4%)	PIK3CA E542K (17.1%), EGFR L861Q (10.9%), EGFR amplification, TP53 C238F (8.6%), TP53 F113V (0.1%)	EGFR amplification: cetuximab	
19	NF1 L1411F (2.8%), RIT1 F82C (1.6%), TP53 S241F (0.6%), KRAS Q22K (0.5%), KRAS G12D (0.3%), KRAS K5E (0.2%), MAP2K2 K61E (0.3%), MAP2K2 A62T (0.3%), NRAS T58I (0.3%), EGFR L747_P753 DelInsS (0.1%), EGFR amplification, FGFR1 amplification	TP53 S241F (0.6%), KRAS Q22K (0.5%), KRAS G12D (0.3%), NRAS T58I (0.3%), EGFR L747_P753 DelInsS (0.1%), EGFR amplification, FGFR1 amplification	EGFR L747_P753 Del: erlotinib FGFR1 amplification: lenvatinib	
20	EGFR L858R (16.3%), EGFR T790M (2.5%), EGFR amplification, SRC P488L (1.3%), APC L2401P (0.4%), MET amplification	EGFR L858R (16.3%), EGFR T790M (2.5%), EGFR amplification, MET amplification	EGFR L858R: erlotinib	
21	EGFR E746_A750 Del (4.9%), EGFR T790M (3.2%), TP53 L130P (1.8%)	EGFR E746_A750 Del (4.9%), EGFR T790M (3.2%), TP53 L130P (1.8%)	EGFR T790M: osimertinib	
22	EGFR P644L (1.0%), TP53 G266E (0.3%)	TP53 G266E (0.3 %)	TP53 G266E: WEE1 inhibitor AZD1775	BRCA2 deletion exons 11-16, TP53 G266E
23	EGFR C535R (0.13%), FGFR2 A315T (0.11%)	FGFR2 A315T (0.11%)	FGFR2 A315T: lenvatinib	
24	EGFR D612D (0.2%) NF1 F1261Y (0.6%),	None characterized		KRAS amplification, KRAS G12C, TP53 R65*
25	TP53 S241F (0.9%)	TP53 S241F (0.9%)	TP53 S241: WEE1 inhibitor AZ1775	RB1 S834*, MLL2 Q3623fs*52
26	VHL S80G (0.41%)	None characterized		EGFR G719A, :EGFR L861Q, MDM2 amplification, CDK4 amplification, GRIN2A R1022C
27	NOTCH1 V1599M (0.3%)	NOTCH1 V1599M (0.3%)	NOTCH1 V1599M LY3039478 (notch inhibitor)	
28	ALK S319C (0.2%), MET C95F (0.2%), SMAD4 D332N (0.1%)	None characterized		

254	All Alterations (non-synonymous) (ctDNA variant allele fraction %)	Functionally Characterized Alterations Only (ctDNA variant allele fraction %)	Examples of Potentially actionable alterations: Cognate drugs**	Tissue NGS Results***
29	TP53 V143M (1.3%)	TP53 V143M (1.3%)	TP53 V143M: WEE1 inhibitor AZD1775	RET CCDC6-RET fusion, TP53 V143M, CDKN2A/B loss, TNFAIP3 splice site 1907-2A>C
30	RB1 D878N (0.2%), MYC E431K (0.2%)	None characterized		
31	TP53 Y205C (0.1%)	TP53 Y205C (0.1%)	TP53 Y205C: WEE1 inhibitor AZD1775	EGFR L858R, ERBB3 amplification, MDM2 amplification, ARID1A Q1334_R1335insQ, E MSY amplification, NFKBIA amplification, NKX2-1 amplification
32	NOTCH1 L2368M (0.6%)	None characterized		EGFR E746_A750del, MYC amplification – equivocal⌘, TP53 D391fs*3+
33	PIK3CA N331K (2.49%)	None characterized		
34	KRAS G12C (11.5%), TP53 G154V (0.8%)	KRAS G12C (11.5%), TP53 G154V (0.8%)	KRAS G12C: Trametinib	
35	TP53 G145C (2.4%), ERBB4 D300N (0.7%), MET amplification	TP53 G145C (2.4%), MET amplification	MET amplification: crizotinib	
36	AR L393P (1.2%)	None characterized		
37	MLH1 Y379C (0.4%), TP53 R273L (0.3%), ALK EML4- ALK fusion (0.2%)	TP53 R273L (0.3%), ALK EML4- ALK fusion (0.2%)	EML4- ALK fusion: crizotinib	
38	KRAS G12C (40.9%), MET M1211L (4.2%), MET N1288H (3.9%)	KRAS G12C (40.9%)	KRAS G12C: trametinib	
39	KIT N828D (0.5%), MET N393S (0.4%)	None characterized		PIK3CA H1047R, IKBKE amplification - equivocal, ARID1A K1677*, MDM4 amplification - equivocal
40	MET C385Y (3.2%), TP53 V216L (0.3%), ALK N1583S (0.2%)	TP53 V216L (0.3%)	TP53 V216L: WEE1 inhibitor AZD177	
41	MYC F38L (0.3%), PIK3CA C901Y (0.2%)	None characterized		CCND3 P203S-subclonal, CDKN2A p16INK4a R58 and p14ARF P72L, TP53 loss exons 10-11, RET truncation intron 11
42	TP53 G245S (1.0 %)	TP53 G245S (1.0%)	TP53 G245S: WEE1 inhibitor AZD1775	

254	All Alterations (non-synonymous) (ctDNA variant allele fraction %)	Functionally Characterized Alterations Only (ctDNA variant allele fraction %)	Examples of Potentially actionable alterations: Cognate drugs**	Tissue NGS Results***
43	TP53 R248W (3.9%), NOTCH1 A1323S (0.6%), KRAS G12C (0.3%)	TP53 R248W (3.9%), KRAS G12C (0.3%)	KRAS G12C: trametinib	KRAS G12C, NF1 splice site 3198-1G>T, CDK4 amplification, NTRK3 D565H, TP53 G245V, GATA6 amplification-equivocal, LRP1B E1360
44	ERBB2 C504Y (0.2%)	None characterized		
45	TP53 C275F (9.9%), KRAS G12A (9.6%)	TP53 C275F (9.9%), KRAS G12A (9.6%)	KRAS G12A: trametinib	HGF amplification-equivocal, KRAS G12A, TP53 C275F, BCOL1 Y1692, EP300 splice site 3672-2insCTTA
46	TP53 C277Y (1.6%)	None characterized		
47	ALK A585T (8.7%)	None characterized		
48	TP53 P190R (0.5%), JAK2 V617F (0.4%), TP53 Y163C (0.1%)	TP53 P190R (0.5%), JAK2 V617F (0.4%), TP53 Y163C (0.1%)	JAK2 V617F: ruxolitinib	
49	TP53 E298* (8.0%), TP53 G245C (0.2%), TP53 R282W (0.1%), FGFR2 D602G (0.3%), BRAF amplification	TP53 E298* (8.0%), TP53 G245C (0.2%), TP53 R282W (0.1%), BRAF amplification	BRAF amplification: vemurafenib	STK11 A76fs*20, MAP2K1 C121S, TP53 E298*, FAM123B R199S
50	MAP2K1 K57N (3.01%), TP53 V203L (2.88%)	MAP2K1 K57N (3.01%), TP53 V203L (2.88%)	MAP2K1 K57N: trametinib	MAP2K1 K57N, MCL1 amplification – equivocal, TP53 V203L
51	TP53 E294* (23.89%), BRAF D594N (23.01%), TP53 R273H (18.36%), RHOA A44L (0.79%), RHOA A15D (0.62%), RHOA Y42C (0.28%), TP53 S33Y (0.25%), KRAS Amplification	TP53 E294* (23.89%), RHOA A44L (0.79%), T P53 S33Y (0.25%), KRAS Amplification	KRAS Amplification: trametinib	
52	KRAS G12V (10.57%), BRCA2 R329S (5.82%), PDGFRA E279D (3.36%), NF1 R2269C (0.34%)	KRAS G12V (10.57%), PDGFRA E279D (3.36%)	PDGFRA E279D: pazopanib	KRAS G12V
53	KRAS G12C (2.46%), PDGFRA L534P (2.17%), ROS1 E1763K (0.83%), NFE2L2 Q26H (0.79%), ERBB2 H495Y (0.50%),	KRAS G12C (2.46%), CTNNB1 S33C (0.43%)	KRAS G12C: trametinib	

254	All Alterations (non-synonymous) (ctDNA variant allele fraction %)	Functionally Characterized Alterations Only (ctDNA variant allele fraction %)	Examples of Potentially actionable alterations: Cognate drugs**	Tissue NGS Results***
	ARID1A S1791L (0.50%), CTNNB1 S33C (0.43%), MAP2K1 R96K (0.25%), NFE2L2 R34Q (0.25%), NF1 N390K (0.19%), RAF1 R627W (0.17%), MAP2K1 V117I (0.13%)			
54	TP53 Y163C (11.26%), MET Amplification	TP53 Y163C (11.26%), MET Amplification	MET Amplification: crizotinib	
55	SMAD4 R361C (1.44%), NF1 I1641T (0.65%)	None characterized		MAP3K1 R306H, SMAD4 R361C
56	TP53 E271K (26.62%), TP53 C277Y (6.63%), TP53 H179Q (0.34%), FGFR2 M735I (0.23%), KIT Amplification, PIK3CA Amplification, PDGFRA Amplification	TP53 E271K (26.62%), TP53 H179Q (0.34%), KIT Amplification, PIK3CA Amplification, PDGFRA Amplification	KIT Amplification: sorafenib PIK3CA amplification: everolimus PDGFRA amplification: pazopanib. olaratumab	
57	BRCA2 A1991T (0.23%), ERBB2 A390T (0.13%)	None characterized		
58	SMAD4 R496C (0.40%), TP53 V143M (0.32%), NOTCH1 H2092Y (0.21%)	TP53 V143M (0.32%)	TP53 V143M: WEE1 inhibitor AZD1775	
59	ARID1A Q708* (1.54%), KRAS G13D (0.91%), TP53 S94*(0.49%), RHOA R5W (0.28%), BRCA1 H1284Y (0.22%)	ARID1A Q708* (1.54%), KRAS G13D (0.91%), TP53 S94* (0.49%)	KRAS G13D: trametinib	KRAS G13D, TET2 S657*, MYC amplification, TP53 S94*, XPO1 Q916E, ARID1A Q708*
60	TP53 R273H (1.07%)	None characterized		
61	RET R693H (0.60%), SMAD4 G89R (0.24%), TP53 Y220C (0.11%), EML4 -ALK (4.74%)	TP53 Y220C (0.11%), EML4 -ALK (4.74%)	EML4 –ALK: crizotinib	
62	KRAS G12V (12.8%), BRAF amplification, CDK6 amplification	KRAS G12V (12.8%), BRAF amplification, CDK6 amplification	BRAF amplification: vemurafenib	KRAS G12V, PALB2 K862fs*22, NTRK1 amplification – equivocal⌘, EP300 Q884fs*73, LRP1B S4216*
63	KRAS G12C (1.1%), PIK3CA Q705H (0.8%)	KRAS G12C (1.1%)	KRAS G12C: trametinib	AKT3 amplification – equivocal⌘, CCND1 amplification – equivocal⌘, KRAS G12C, FGF19 amplification – equivocal⌘, FGF4 amplification – equivocal⌘,

254	All Alterations (non-synonymous) (ctDNA variant allele fraction %)	Functionally Characterized Alterations Only (ctDNA variant allele fraction %)	Examples of Potentially actionable alterations: Cognate drugs**	Tissue NGS Results***
				MCL1 amplification, MYC amplification, FGF3 amplification – equivocal⌘
64	ROS1 S1793* (0.2%)	None characterized		BRAF V600E, DNMT3A R882H, TP53 D281Y – subclonal⌘, TP53 Q331*
65	TP53 R158L (4.4%), KRAS G12C (3.0%), CDKN2A G35V (2.5%), PDGFRA V82M (1.1%)	TP53 R158L (4.4%), KRAS G12C (3.0%)	KRAS G12C: trametinib	
66	MET H61N (11.0%), MET amplification, TP53 Y126C (2.5%), TP53 R175H (1.0%), TP53 R283P (0.2%), TP53 P128R (0.1%), CCND1 Y226* (0.6%), NF1 G2001V (0.5%), ARID1A E2246* (0.5%), IDH2 R140Q (0.3%)	MET amplification, TP53 Y126C (2.5%), TP53 R175H (1.0%), TP53 R283P (0.2%), IDH2 R140Q (0.3%)	MET amplification: crizotinib	
67	AR A331T (0.3%), ALK S1427F (0.1%)	None characterized		
68	PTEN M134I (0.4%)	None characterized		
69	SMAD4 Q183* (7.7%), SMAD4 A451T (0.1%), BRCA2 S1855L (7.5%), BRCA2 D2242H (2.0%), BRCA2 E2355K (0.4%), MET S960L (6.7%), ROS1 CD74- ROS1 fusion (5.1%), TP53 Q331* (3.3%), TP53 Q192* (3.2%), TP53 S241C (1.3%), TP53 S215I (0.5%), TP53 E286K (0.2%), APC E40K (2.0%), APC R2560Q (0.4%), APC E1880K (0.4%), APC S2146L (0.2%), FGFR1 D674N (1.1%), FGFR1 V396I (0.5%), FGFR1 K542N (0.2%), ARID1A E1779D (0.3%), ATM L348F (0.2%)	ROS1 CD74- ROS1 fusion (5.1%), TP53 Q331* (3.3%), TP53 Q192* (3.2%), TP53 S241C (1.3%), TP53 S215I (0.5%), TP53 E286K (0.2%)	ROS1 CD74- ROS1 fusion: crizotinib	
70	TP53 L145P (0.5%), TP53 H179Y (0.4%), TP53 R282W (0.1%),	TP53 L145P (0.5%), TP53 H179Y (0.4%), TP53 R282W (0.1%)	TP53 L145P: WEE1 inhibitor AZ1775; anti-angiogenesis agents	

254	All Alterations (non-synonymous) (ctDNA variant allele fraction %)	Functionally Characterized Alterations Only (ctDNA variant allele fraction %)	Examples of Potentially actionable alterations: Cognate drugs**	Tissue NGS Results***
	AR E654K (0.1%)			
71	TP53 E62* (0.5%), TP53 R175H (0.3%)	TP53 E62* (0.5%), TP53 R175H (0.3%)	TP53 L145P: WEE1 inhibitor AZ1775; anti-angiogenesis agents	
72	CTNNB1 S45F (12.2%), MYC amplification, CCNE1 amplification	CTNNB1 S45F (12.2%), MYC amplification, CCNE1 amplification	MYC amplification: BET inhibitor GSK525762	

*Seventy-two of 88 patients had at least one alteration detected.

*** ***Examples of potentially actionable alterations are given. Additional alterations may also be theoretically actionable. (DGIdb - Mining the Druggable Genome: http://dgidb.genome.wustl.edu)

***Additional non-NGS genomic tests may have been done, but their results are not listed here.

Supplemental Table 5. *EGFR* alterations: Concordance between ctDNA and tissue testing

	Overall concordance**					Concordance for patients with tissue biopsy to blood draw time interval ≤ median[a,b]				Concordance for patients with tissue biopsy to blood draw time interval > median[a,b]				P-value* (≤ versus > median)
	(-)	(+)	Overall %	Kappa (SE)		(-)	(+)	Overall %	Kappa (SE)	(-)	(+)	Overall %	Kappa (SE)	
N=34 patients[a]	N=19	N=7	76.5%	0.471 (0.155)		N=13	N=2	88.2%	0.605 (0.241)	N=6	N=5	64.7%	0.301 (0.224)	0.22
N=26 patients[b]	N=14	N=7	80.8%	0.586 (0.165)		N=11	N=2	100%	1.0 (0.0)	N=3	N=5	61.5%	0.217 (0.269)	0.04

Negative concordance (-): alteration was not detected in both tests. Positive concordance (+): alteration was detected in both tests. Overall concordance percentages included negative and positive concordant cases, i.e. when both the tissue and the ctDNA were negative or positive. Kappa values range from $\kappa = 1$ (perfect agreement) to $\kappa = 0$ (no agreement other than would be expected by chance). We included patients with *EGFR* alterations that were common in both the ctDNA and tissue gene panels. SE=Standard Error.

aThirty-four patients had both ctDNA and a common tissue molecular test. For these N=34 patients, the median time interval between tissue biopsy to blood draw was 0.8 months.

bTwenty-six patients had both ctDNA and a common tissue molecular test, and had alterations in their ctDNA**. (**Patients with no alterations in their ctDNA were excluded). For these N=26 patients, the median time interval between tissue biopsy to blood draw was 1.0 month. (We performed this analysis excluding patients that had "no alterations detected" as it could be because no ctDNA was detected in the plasma).

*2-sided Chi-Square test, compares the % of overall concordance between patients with biopsy interval time ≤ or > median.

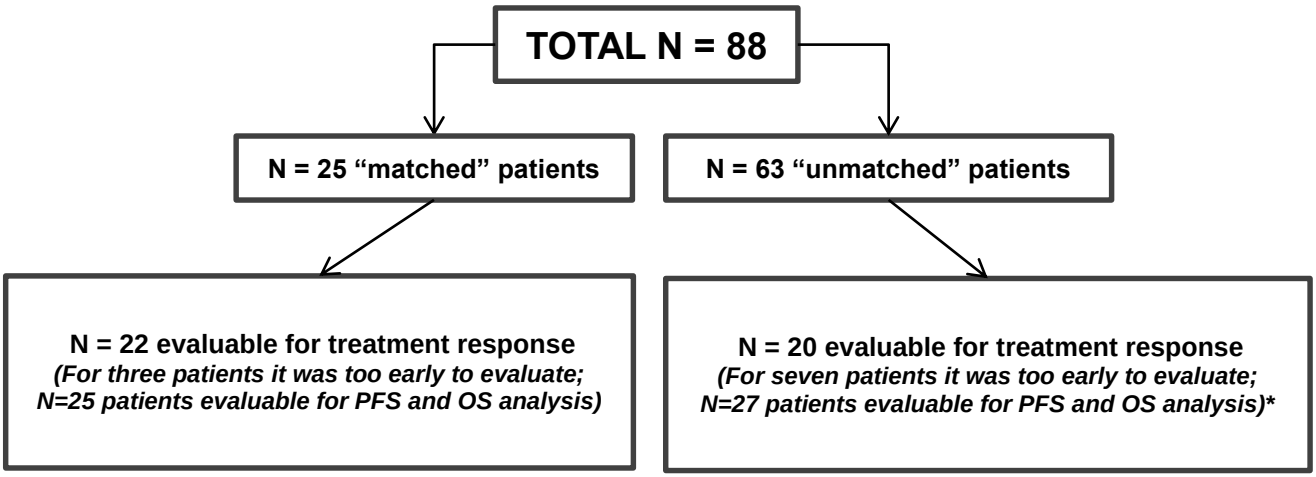
** All patients who were considered positively concordant had at least one identical EGFR mutation in the blood and tissue (see also **Supplemental Table 6**).

Supplemental Table 6: Patients with at least one concordant EGFR alteration on ctDNA and tissue NGS analysis*

#	Guardant ctDNA NGS Results	Foundation Medicine Tissue NGS
1	**EGFR T790M** 2.9%, TP53 E258K 2.4%, EGFR A750E 0.3%, MET R191W 0.1%	**EGFR T790M** ,EGFR amplification – equivocal⌘, EGFR E746_A750del, , AKT2 amplification – equivocal⌘, FGFR4 amplification, GNAS amplification – equivocal, CCNE1 amplification, MCL1 amplification – equivocal⌘, TP53 E258K
2	**EGFR T790M** 29.28%, TP53 C2755 8.61%, EGFR A750E 1.12%, EGFR Exon 19 Del 25.24%, EGFR Amplification, BRAF Amplification, CCNE Amplification	**EGFR T790M**, EGFR amplification, EGFR E746_A750del, CCND3 amplification, CDKN2A/B loss, TP53 C275S
5	**EGFR L858R 0.4%, EGFR S768I** 0.2%, NOTCH1 A1338V 0.2%	**EGFR L858R, EGFR S768I**, TP53 R273H, FLT3 splice 1304_1309+1delTAAGAAG, LRP1B L2478*
6	**EGFR L858R** 0.6%, TP53 C135Y 0.8%,	**EGFR L858R**, ERBB3 amplification, CDK4 amplification, GLI1 amplification, TP53 C135Y, NFKBIA amplification, NKX2-1 amplification, ZNF217 amplification
8	**EGFR L858R 19.5%,** ERBB2 S310F 15.6%, TP53 Y205C 6.9%	**EGFR L858R,** ERBB2 S310F**,** CCND3 amplification, CDKN2A/B loss, TP53 Y205C
11	**EGFR E746K** 2.5%, EGFR M881V 1.0%, EGFR Amplification 8.5, MET Amplification 2.3	**EGFR E746**_A750del, EGFR amplification, NF1 splice site 3197+1G>A, AURKA Amplification – equivocal, TP53 splice site 920-6_922delTCCTAGCAC, NKX2-1 amplification
12	**EGFR L747_E749Del** 0.4%	**EGFR L747_A750**>S , EGFR A750P, EGFR amplification, CCND1 amplification, CDKN2A/B loss, TP53 R248L, RICTOR amplification, BCL2L2 amplification, NFKBIA amplification, FGF3 amplification, FGF4 amplification, FGF10 amplification, FGF19 amplification, NKX2-1 amplification

*Additional non-NGS genomic tests may have been done in these or other patients, but their results are not listed here.

Supplemental Figure 1. Response evaluation and data availability



*The main reasons for the remaining unmatched patients not being evaluable were as follows: not treated yet, died, were too advanced to be treated or were loss to follow up prior to ctDNA results. Abbreviations: OS, Overall survival; PFS, Progression-free survival.