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SUPPLEMENTARY INFORMATION

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Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial

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Supplemental Table 1: Patient medical and demographic information by arm (Arm A: DNA; Arm B: RNA)

Variable		Arm A (N=69)	Arm B (N=38)	Total (N=107)
Center code	VHIO (Spain)	21 (30.4%)	23 (60.5%)	44 (41.1%)
	CSM (Israel)	21 (30.4%)	4 (10.5%)	25 (23.4%)
	IGR (France)	14 (20.3%)	9 (23.7%)	23 (21.5%)
	SCC (Canada)	13 (18.8%)	2 (5.3%)	15 (14.0%)
Sex	Men	36 (52.2%)	26 (68.4%)	62 (57.9%)
	Women	33 (47.8%)	12 (31.6%)	45 (42.1%)
Age dichotomized at age 60	<60 years	36 (52.2%)	21 (55.3%)	57 (53.3%)
	≥ 60 years	33 (47.8%)	17 (44.7%)	50 (46.7%)
Cancer Diagnosis	Colon	24 (34.8%)	10 (26.3%)	34 (31.8%)
	Head and neck	10 (14.5%)	11 (28.9%)	21 (19.6%)
	Lung	17 (24.6%)	4 (10.5%)	21 (19.6%)
	Other	18 (26.1%)	13 (34.2%)	31 (29.0%)
ECOG performance status at treatment start date	0	21 (30.4%)	15 (39.4%%)	36 (33.6%)
	1	48 (69.5%)	23 (60.5%)	71 (66.4%)
Number of Prior Therapies	1	6 (8.7%)	4 (10.5%)	10 (9.4%)
	2	17 (24.6%)	7(18.4%)	24 (22.4%)
	3	20 (29.0%)	9 (23.7%)	29 (27.1%)
	4	10 (14.5%)	6 (15.8%)	16 (15.0%)
	≥5	16 (23.2%)	12 (31.6%)	28 (26.2%)
Genomic Matching Score*	Low	19 (27.5%)	8 (21.1%)	27 (25.2%)
	High	50 (72.5%)	30 (78.9%)	80 (74.8%)
Median Age (Range)		59 (31-79)	59 (26-82)	59 (26-82)
Median Number of prior therapies (IQR)		3 (2-4)	3 (2-4)	3 (2-4)
Median time from biopsy to treatment in months (IQR)**		3.3 (2.4 to 5.2)	3.1 (2.5 to 6.2)	3.2 (2.4 to 5.5)

Abbreviations: CSM = the Chaim Sheba Medical Center (Tel Hashomer, Israel); IGR = Gustave Roussy (Villejuif, France); IQR = interquartile range; N = number; SCC = Segal Cancer Centre, Jewish General, QCROC-Quebec Cancer Consortium and Rossy Cancer Network, MCGill University (Montreal, Canada); SD = standard deviation; VHIO = Vall d'Hebron Institute of Oncology (Barcelona, Spain)

*: Cut-off for genomic Matching Score for Arm A (based on DNA matching) is <0.25 (low), >=0.25 (high); for Arm B (RNA matching) is <0.30 (low), >=0.30 (high). The cutoff points were determined by using the recursive partitioning function rpart() in R.

**To attenuate treatment delays, patients could be biopsied before failing current line of therapy (in anticipation of progression (they were not however started on WINTHER treatment until after imaging documentation of progression)); hence the time from biopsy to treatment might be lengthened in some cases without incurring a treatment delay.

Supplemental Table 2: Matched normal tissue biopsy

Tumor type	Tumor target lesion	Normal matched tissue	Type of intervention for biopsy
Lung	Metastasis	Bronchial mucosa	Interventional radiology for tumor tissue and fibroscopy for normal tissue
Colon	Metastasis	Rectal/colon mucosa	Interventional radiology for tumor tissue and colonoscopy for normal tissue
Breast	Metastasis	Normal breast tissue	Interventional radiology or echo
Hepatocellular cancer	Metastasis	Normal liver tissue	Interventional radiology or echo
Bladder	Metastasis	Normal urothelium tissue	Endoscopy
Rhabdomyosarcoma	Metastasis	Skeletal muscle	Interventional radiology or echo
Melanoma	Metastasis	Nevi	Dermatologic or by interventional radiology
Liposarcoma	Metastasis	Adipose tissue	Interventional radiology
Lymphoma	Metastasis	Lymph nodes	Interventional radiology
Head and Neck	Metastasis	Tongue, normal tissue depending on tumor type	Surgery and interventional radiology

Supplemental Table 3: Characteristics of WINTHER Treatments*

Characteristics of Drugs Administered	**Arm A**	**Arm B**	**Both Arms**
Total number of different drugs	46	31	77
Number of patients who received single agent treatment	36	27	63
Number of patients who received ≥2 drugs	33	11	44
Number of immunotherapy (checkpoint inhibitors) agents given	2	6	8
Number of gene-targeted agents given	90	35	125
Number of cytotoxic chemotherapies given	15	6	21
Number of hormonal modulator agents	1	4	5
On-label, off-label approved drugs and investigational drugs used**			
Number of investigational drugs	16	6	22
Number of approved off-label drugs	77	38	115
Number of approved on-label drugs	15	7	22
Drug targets (number of patients who received a drug that impacted designated target)***	**Arm A**	**Arm B**	**Both Arms**
BRAF	2	0	2
CDK4/6	3	0	3
HER pathway (EGFR/ERBB2/ERBB3/ERBB4)	11	6	17
FGFR	6	3	9
MEK	17	0	17
MET	1	10	11
PARP	1	0	1
Pan RAF	1	0	1
PI3K/AKT/mTOR	20	3	23
RET	3	1	4
VEGFR	14	18	32
WNT	5	0	5
HORMONAL RECEPTOR	0	2	2
IMMUNE	2	5	7
OTHER	11	11	22

*Overall, 22/159 drugs (13.8% of drugs) given were on label. Our analysis shows that 28 (26.2%) of 107 patients achieved stable disease of at least six months/PR/CR. Of these 28 patients, five received a therapy regimen that included an on-label drug.
**Whether a drug was approved on-label or off-label or was investigational was determined according to the indication approval status in the country in which the patient was treated. A drug may be approved in an indication but only if given with another specific drug or for a specific mutation: if the patient received that drug not in combination with the other drug for which it was approved, or if the patient did not have the mutation specified, then that drug was considered off-label. Finally, a drug may be approved in an indication but only in a particular sub-type histology. For example all lung patients recruited in the study were of non-small cell lung cancer histology. In France, authorization of carboplatin is only for small cell lung cancer. Sulindac (targeting APC mutation) was always counted OFF-label.
***Some drugs have more than one target

Supplemental Table 4. Detailed clinical and biological information for each patient

Study ID	Age	Sex	Cancer site	Date of WINTHER treatment start	Number of prior treatments	ECOG performance status at WINTHER treatment start	Arm	Response	Time_ PFS1	Event_ PFS1	Time_ PFS2	Event _PFS2	PFS_ Ratio	Date_Progression under WINTHER treatment	Date_Death	Date_Last Known Alive	Time_O S	Event_ OS	Drug_given***	DNA - List of molecular alterations (FM report)*	RNA - Relevant overexpressed genes** / *** (Overexpression presented as fold changes of expression in Tumor vs Normal matched tissues)	DNA_ matching score_ high	RNA_ matching score_ high	Raw matching score (see Supplemental explanations/ References and online Methods)****
1	52	F	Breast	01/07/2013	**2**	0	Arm A	4	57.2	1	1.7	1	**0.1**	23/08/2013		04/04/2017	45.7	0	PHASE 1 NCT01283945 LUCITANIB (E-3810) (FGFR and VEGFR inhibitor)	FGFR1amplification MYC amplification FGF3 amplification TP53 P177L mutation CCND1 amplification ZNF703 amplification FGF4 amplification FGF19 amplification GATA-3 splice		1		0.56
2	59	M	Head and Neck	13/08/2013	**2**	2	Arm A	4	2.8	1	1.4	1	**0.5**	27/09/2013	27/09/2013		1.5	1	PACLITAXEL + TRASTUZUMAB (ERBB2 targeting)	EGFR Amplification ERBB2 amplification CCND1 amplification CDKN2A/B loss FGF3 amplification TP53 G325fs*14 DNMT3A R882C LRP1B truncation, loss of LRP1Bx6 FGF19 amplification FGF4 amplification		0		0.1
4	59	M	Head and Neck	08/08/2013	**3**	1	Arm B	4	3.1	1	0.2	1	**0.1**	15/08/2013	15/08/2013		0.2	1	PHASE 1 NCT01391533 SAR125844 (MET inhibitor)	MDM2 amplification CDKN2A/B loss SOX2 amplification TP53 L206fs*41, exon 5 splice acceptor site deletion	MET (7.3 fold change↑) overexpression; ranked 1st in single interaction		1	1
5	52	M	Lung	18/07/2013	**4**	1	Arm A	2	22.8	1	10.4	1	**0.4**	27/05/2014	04/10/2016		39.1	1	PHASE 1 NCT01391533 SAR125844 (MET inhibitor)	EGFR amplification, truncation exon 20 MET amplification STK11 D2776*10 TP53 V976*26		1		0.25
6	64	F	Other: Carcinoma of Unknown Primary	01/07/2013	**1**	0	Arm A	3	6.7	1	8.1	1	**1.2**	04/03/2014	12/03/2014		8.4	1	EVEROLIMUS (mTor inhibitor)	TSC1 splice site 913+1G>T BRCA1 truncation, intron 11 CDKN2A/B loss DNMT3A R882H LRP1B loss		0		0
7	71	M	Lung	04/09/2013	**6**	1	Arm B	4	27.1	1	4.8	1	**0.2**	28/01/2014	01/09/2015		24.2	1	CAPECITABINE + TRASTUZUMAB (HER2 inhibitor)	KRAS G12D CDKN2A/B loss	**ERBB3 (7.4 fold change)** overexpression and **ERBB2 (1.8 Fold change)** overexpression; ranked 1st in single interaction; combined with a chemotherapy to potentiate the effect of the therapy. Overexpression score for capecitabine (see Comparative Toxicogenomic Database http://ctdbase.org/query.go?type=ixn). AGPAT2 (2.5 fold change), AGR2 (4.0 fold change), ERBB3 (7.4 fold change), IL17RB (5.1 fold change), LGALS4 (50.1 fold change), PTGS2 (12.9 fold change), S100P (9.1 fold change), TFF1 (56.9 fold change) and TRIM15 (53.7 fold change) overexpression; ranked 2nd in multiple interaction;		1	1
10	40	F	Lung	18/06/2013	**2**	1	Arm A	4	3.2	1	3.9	1	**1.2**	16/10/2013	29/10/2013		4.4	1	SORAFENIB (VEGFR and RET inhibitor)	RET KIF5B-RET fusion CDKN2A/B loss MYC amplification TP53 I251N, S241Y		1		0.5
23	57	M	Lung	05/09/2013	**1**	0	Arm A	4	7.0	1	5.5	1	**0.8**	19/02/2014		30/06/2017	46.4	0	PHASE 2 NCT01524978 Basket VEMURAFENIB (BRAF inhibitor)	BRAF V600E PIK3CA E545K SETD2 E348*, K2525fs*1		1		0.33
25	65	M	Head and Neck	15/10/2013	**2**	1	Arm B	2	5.1	1	5.3	1	**1.2**	26/03/2014	26/03/2014		5.4	1	AXITINIB (PDGFR and VEGFR) targeting)	TP53 I195F KDM6A L725fs*4 MSH6 K1358fs*2 NFE2L2 R18Q subclonal	**PDGFRA** (4.5 fold change)/**PDGFRB** (27.0 fold change), KDR (VEGFR2) (8.9 fold change)/FLT1(VEGFR1) (9.1 fold change) overexpression; ranked 4th in the multiple interaction; score.		0	0.25
30	66	F	Other:GI tract / Rectum	03/10/2013	**7**	0	Arm A	4	8.2	1	3.6	1	**0.4**	22/01/2014	20/04/2014		6.63	1	PHASE 1b NCT01449058 BYL719 + CMEK162 (PI3K + MEK inhibitors)	KRAS G12V PIK3CA D350G TP53 R175H BRCA2 K3326* APC E1286*, K534* ATRX L192F		1		0.33
42	65	M	Other: Kidney	16/10/2013	**3**	0	Arm B	2	11.5	1	2.5	1	**0.2**	01/01/2014	23/01/2014		3.3	1	CETUXIMAB + ERLOTINIB	VHL E55* PTEN splice site 164+1G>C SETD2 I1120fs*34	**EGFR** (8.8 fold change) overexpression; ranked 1st in single interaction;		1	1
59	54	M	Other: GI Tract / Gastric	28/01/2014	**5**	0	Arm B	4	1.6	1	1.2	1	**0.7**	07/03/2014	20/07/2014		5.7	1	PHASE 1 CL1-49076-001 S49076 (MET inhibitor)	CTNNB1 D32V	MET (2.2 fold change) overexpression; ranked 1st in single interaction HGF (MET ligand) (6.3 fold change) overexpression; ranked 1st in multiple interaction		1	1
69	32	F	Breast	31/01/2014	**6**	1	Arm A	4	1.8	1	0.8	1	**0.4**		25/02/2014		0.8	1	EVEROLIMUS	NF1 D724fs*2 PTEN G230* TP53 R306* MYC amplification BARD1 splice site 1569-2A>G		0		0
72	63	M	Colon	04/03/2015	**5**	1	Arm B	4	3.9	1	4.6	1	**1.1**	22/07/2015	12/11/2015		8.4	1	CABOZANTINIB (AXL/VEGFR/MET inhibitor)	KRAS G13D TP53 A76fs*55 APC R1450* FAM123B E627* MYST3 amplification - equivocal	AXL (3.5 fold change) overexpression, KDR/VEGFR2 (1.9 fold change) MET (2.9 fold change), HGF/MET Ligand (3.9 fold change) overexpression; ranked 2nd in multiple interaction		1	0.5
81	66	F	Other:GI Tract / Gastric	04/09/2015	**6**	0	Arm A	4	7.4	1	4.2	1	**0.5**		09/01/2016		4.2	1	CAPECITABINE + EVEROLIMUS	PIK3CA E542K ARID1A Q2976fs*65 SMAD4 Q455* KDM5C G1467fs*5		1		0.25
83	59	M	Head and Neck	04/06/2014	**4**		Arm B	3	5.4	1	8.8	1	**1.6**	27/02/2015	09/05/2016		23.5	1	AXITINIB (PDGFR and VEGFR inhibitor)	MTOR L2209V subclonal ETV6 truncation intron 5 CIC S3336fs*36 MLL2 G3698 fs*51	VEGFA (3.3 fold change) FLT1/VEGFR1 (3.8 fold change) , PDGFRB (3.0 fold change) and PDGFA (3.4 fold change); ranked 3rd in multiple interaction		1	0.33
84	35	F	Breast	29/01/2015	**5**	1	Arm A	4	8.9	1	1.2	1	**0.1**	06/03/2015	26/06/2015		4.9	1	PHASE 1 NCT01703481 JNJ-42756493 (Pan-FGFR Tyrosine Kinase Inhibitor)	FGFR1 amplification CDKN2B 156+23del1 MYC amplification-equivocal TP53 S303fs*17 MSH2 truncation exon 5 ZNF703 amplification		0		0.16
85	57	M	Lung	07/05/2014	**3**	1	Arm B	4	1.9	1	1.5	1	**0.8**	22/06/2014	22/06/2014		1.5	1	CAPECITABINE + BEVACIZUMAB (VEGF antibody)	KRAS G12C STK11 splice site 375-2A>G TP53 V1571, splice site 375 -1G>T PAX5 E263* SMAD2 R120* SMAD4 spllce site 1309-1G>T CIC R202W LRP1B G2125C	VEGFA (3.1 fold change) overexpression; ranked 1st in the single interaction; **combined with a chemotherapy ranked 11th in multiple interaction.** Overexpressed gene for capecitabine: see Comparative Toxicogenomic Database http://ctdbase.org/query.go?type=ixn).CDKN2A (3.6 fold change), IL17RB (10.1 fold change), LGALS4 (24.3 fold change), TFF1 (31.8 fold change), TRIM15 (85.8 fold change)		1	1
87	54	M	Bladder	07/08/2014	**2**	0	Arm A	4	8.6	1	1.9	1	**0.2**	05/10/2014	30/12/2015		17.0	1	VELIPARIB (PARP inhibitor) + CARBOPLATIN + PACLITAXEL	ATR pcolce2-atr fusion BRCA1 E236*17 CDKN2A/B loss		1		1
88	56	M	Lung	04/02/2015	**1**	0	Arm B	4	13.2	1	2.9	1	**0.2**	06/05/2015		30/06/2017	29.2	0	AXITINIB (PDGFR and VEGFR inhibitor)	DNMT3A R635P KRAS G12C TP53 Y220C MLL2 T1246M	FLT1/VEGFR1 (6.3 food change) VEGFA (7.4 fold change), PDGFRA (5.7 fold change), PDGFRB (11.1 fold change) overexpression, each ranked 1st in multiple interaction .		1	1
90	74	M	Head and Neck	10/12/2014	**2**	1	Arm A	4	5.3	1	1.3	1	**0.2**	18/01/2015	13/05/2015		5.1	1	EVEROLIMUS	PIK3CA Q546R EP300 D1154fs*30 NOTCH1 L1746fs*40		0		0
91	46	F	Rhabdomyosarcoma	30/06/2014	**4**	1	Arm B	4	1.3	1	1.8	1	**1.4**	25/08/2014	17/02/2016		19.9	1	PAZOPANIB (FGFR inhibitor)	CDK4 amplification	FGFR1 (6.1 fold change), FGFR2 (65.6 fold change), FGFR3 (34.4 fold change), FGFR4 (6.7 fold change) overexpression ; ranked 1st in the multiple interaction		1	1

97	40	F	Lung	05/11/2014	**2**	1	Arm A	3	7.9	1	13.1	1	**1.62**	06/12/2015	06/12/2015		13.2	1	PACLITAXEL + TEMSIROLIMUS followed by GEMCITABINE + EVEROLIMUS - Patient had an infusion reaction to temsirolimus	PIK3CA E542K SET2D L2512FS*7		1		0.5
98	70	M	Lung	30/07/2014	**6**		Arm B	4	0.8	1	3.9	1	**4.5**	26/11/2014	24/02/2015		6.9	1	NINTEDANIB (FGFR and VEGFR inhibitor) + DOCETAXEL	KRAS G12D TP53 Y220C	**FGFR1** (9.7 fold change), FLT1 (VEGFR1)(14.6 fold change), KDR (VEGFR2) (2.1 fold change), PDGFRA (44.8 fold change), PDGFRB (76.8 fold change) overexpression ranked 11th in the multiple interaction		0	0.1
99	43	F	Breast	01/09/2014	**4**	4	Arm A	4	1.8	1	0.4	1	**0.2**		15/09/2014		0.4	1	TEMSIROLIMUS + PACLITAXEL + BEVACIZUMAB	PTEN loss exon 1 CDKN2A/B loss TP53 H168R KDM6A loss exons 3-6 NOTCH1 deletion exons 3-27		1		0.4
100	43	M	Lung	26/06/2015	**2**	0	Arm A	2	9.1	1	6.6	1	**0.7**	13/01/2016	24/03/2016		9.0	1	TRAMETINIB (MEK inhibitor)	BRAF A598_T599insT IDH1 R132C		1		0.5
102	50	M	Head and Neck	22/01/2015	**4**	1	Arm A	4	4.6	1	1.6	1	**0.3**	12/03/2015	24/06/2015		5.1	1	PALBOCICLIB (targets CDK4/6 - deregulated by CCND1 and CDKN2A alterations)	CCND1 amplification CDKN2A p16INK4a E88* and p14ARF G102V TP53 R175H FGF19 amplification FGF3 amplification FGF4 amplification		1		0.33
103	56	F	Colon	24/10/2014	**4**	1	Arm A	4	1.8	1	1.5	1	**0.8**	09/12/2014	05/02/2015		3.4	1	TRAMETINIB (MEK inhibitor) + SULINDAC (inhibits beta catenin and WNT signals)	PTPN11 (G503V, G60C) MYC amplification APC Q757*		1		0.66
107	59	F	Colon	16/09/2014	**4**	1	Arm B	3	2.8	1	10.8	1	**3.8**		10/08/2015		10.9	1	CABOZANTINIB (MET inhibitor)	KRAS G12A MYC amplification equivocal TP53 M246V APC E1309*, L616fs*18 EPHA3 L642R SMAD4 P356L	MET (4.4 fold change) and HGF (MET ligand) (3.8 fold change) overexpression; 2nd in single interaction		1	0.5
108	65	M	Colon	26/09/2014	**2**	0	Arm A	2	5.2	1	9.8	1	**1.9**	21/07/2015	08/10/2015		12.56	1	CETUXIMAB (EGFR antibody) + IRINOTECAN followed by PANITUMUMAB (EGFR antibody)	EGFR amplification - equivocal TP53 R282W APC S1081fs*2		1		0.33
117	34	M	Head and Neck	14/11/2014	**2**	2	Arm A	4	8.1	1	1.9	1	**0.2**		12/01/2015		1.9	1	EVEROLIMUS	TSC2 S1431L TP53 G245S BCOR K3746*19 SMARCA4 R1135W		0		0
118	78	F	Lung	11/01/2015	**3**	2	Arm A	4	15.4	1	3.1	1	**0.2**	15/04/2015	30/06/2015		5.6	1	TRAMETINIB (MEK inhibitor)	KRAS G12C CDKN2A/B loss TP53 V157F, Y220 fs*27 MUTYH G382D		1		0.25
124	63	M	Head and Neck	27/02/2015	**2**	0	Arm A	3	16.1	1	7.8	1	**0.5**	23/10/2015		12/06/2017	27.8	0	EVEROLIMUS (mTor inhibitor) + BEVACIZUMAB (VEGF antibody)	PIK3R1 L370fs*8 ATM R250* TP53 SPLICE SITE 376-2_376-2delA		1		0.66
131	50	F	Lung	20/11/2014	**2**	4	Arm A	2	3.2	1	2.4	1	**0.7**	03/02/2015	10/04/2015		4.7	1	CRIZOTINIB (ALK inhibitor)	ALK rearrangement intron 19 TP53 R65* APC E1156*		1		0.33
132	59	M	Other: Kidney	10/11/2014	**2**	1	Arm B	4	1.5	1	1.9	1	**1.3**	08/01/2015	08/06/2015		7.0	1	ETOPOSIDE + TAMOXIFEN (ESR (estrogen) modulator)	TP53 K132N	PGR (1.4 fold change) overexpression ESRRA (2.8 fold change ESRRG (2.4 fold change); ranked 1st in the multiple interaction		1	1
136	79	M	Lung	23/12/2014	**3**	2	Arm A	4	5.1	1	0.4	1	**0.1**		05/01/2015		0.4	1	AFATINIB (pan-ERBB inhibitor)	ERBB3 amplification MET splice site 3028+1G>A STK11 Q100* ATM L2450fs*11, rearrangement exon 56 BRCA1 E23fs*17 CDK4 amplification CDKN2A/B loss MDM2 amplification APC I1307K KDM5C truncation MAP3K1 S1475*		0		0.09
137	66	F	Colon	18/02/2015	**3**	1	Arm A	4	2.1	1	3.5	1	**1.6**	04/06/2015	22/07/2015		5.1	1	TRAMETINIB (MEK inhibitor) + SULINDAC (Beta catenin/WNT inhibitor)	KRAS (G12V) TP53 R306* APC P9036*, E1135* SMAD4 (loss exons 1-2)		1		0.5
138	57	F	Colon	28/01/2015	**2**	1	Arm B	4	2.5	1	0.9	1	**0.3**	24/02/2015	02/04/2015		2.1	1	CABOZANTINIB (VEGFR and MET inhibitor)	KRAS G12S PIK3CA R88Q PTEN loss TP53 Q136E APC E1544*, R302*	**MET** (2.9 fold change) overexpression, VEGFA (2.9 fold change), ranked 1st and 2nd in the single interaction		1	1
140	67	M	Colon	11/12/2014	**3**	2	Arm A	4	2.9	1	2.4	1	**0.8**		22/02/2015		2.4	1	REGORAFENIB (VEGFR inhibitor; can inhibit WNT/Beta catenin pathway)	FGFR3 FGFR3-TACC3 fusion SRC amplification TOP1 amplification TP53 R282W APC R283*		1		0.4
146	74	F	Lymphoma	22/07/2015	**2**	1	Arm B	4	2.4	1	3.1	1	**1.2**	22/10/2015	02/10/2016		14.6	1	DASATINIB (multikinase inhibitor)	CARD11 L251P MLL2 K3583fs*8 TP53 M237I	See Comparative Toxicogenomic Database http://ctdbase.org/query.go?type=ixn). PLAU (3.8 fold change), ARHGAP11A (2.7 fc), CDK1 (5.2 fc), CENPA (7.1 fc), EXO1 (7.7 fc), FAM72D (8.2 fc), GINS1 (11.9 fc), HIST1H1 A (11.8 fc), MMP1 (47.3 fc), SKA1 (10.1 fc), STEAP1 (42.2 fc), TRIP13 (4.3 fc) overexpression; ranked 8th in multiple interaction		0	0.12
148	82	M	Other:Neuroendocrine	18/02/2015	**2**	0	Arm B	3	5.2	1	11.6	1	**2.2**	05/02/2016	03/04/2017		25.8	1	EVEROLIMUS (PI3K/Akt/mTor pathway inhibitor)	BCOR N1652fs*34 CDKN1B E126fs*1	**PIK3CA** (2.1 fold change) overexpression ranked 2nd in the single interaction		1	0.5
149	54	F	Other:GI Tract /	25/06/2015	**5**	0	Arm A	3	2.7	1	7.4	1	**2.7**		06/02/2016		7.5	1	TRAMETINIB (MEK inhibitor)	KRAS G12V ARID1A SPLICE SITE 2733-1G>A		1		0.5
153	71	M	Bladder	01/03/2015	**6**	1	Arm A	4	5.1	1	1.6	1	**0.3**	19/04/2015	13/07/2015		4.4	1	VEMURAFENIB (BRaf inhibitor)	BRAF V600E TET2 V218fs*32		1		0.5
156	71	F	Lung	12/01/2015	**2**	0	Arm A	1	17.7	1	14.3	1	**0.8**	24/03/2016	31/05/2017		29	1	AFATINIB (EGFR inhibitor) + CETUXIMAB (EGFR antibody)	EGFR E746_A750del, T790M CDKN2A/B loss CTNNB1 S33F MYC amplification SMAD4 P186fs*6 STAG2 splice site 1535-12_1630del108		1		0.33
159	48	F	Hepatocarcinoma	03/06/2015	**6**	2	Arm A	4	0.9	1	1.6	1	**1.7**	22/07/2015	26/07/2015		1.7	1	ETOPOSIDE + AXITINIB (KDR (VEGFR2) inhibitor)	KDR amplification KIT amplification EP300 N1126S		1		0.33
160	27	M	Other: Muscle / Leiomyosarcoma	18/02/2015	**6**	1	Arm B	4	2.01	1	1.5	1	**0.7**	07/04/2015	07/04/2015		1.6	1	ANASTROZOLE (estrogen and progesterone (PGR) inhibitor) + CRIZOTINIB (MET inhibitor)	RB1 loss exons 18-21 TP53 truncation intron 1	MKI67 (13.7 fold change), Progesterone receptor (5.3 fold change) overexpression; ranked 1st in multiple interaction;,HGF (MET ligand) (10.8 fold change) overexpression; ranked 3rd in multiple position; score.		1	1
162	60	F	Colon	03/02/2015	**4**	1	Arm A	4	3.1	1	2.3	1	**0.7**		14/04/2015		2.3	1	TRAMETINIB (MEK inhibitor) + EVEROLIMUS (PI3K/Akt/mTor pathway inhibitor)	KRAS G12D PIK3CA R108_E109>Q TP53 Y220C APC L1488fs*25 R499* CTCF T204fs*26 MAP2K4 loss exon 1		1		0.33
164	77	F	Colon	20/04/2015	**3**	1	Arm A	4	0.8	1	1.3	1	**1.5**	29/05/2015	25/06/2015		2.2	1	PHASE 1 NCT01351103 LGK974 (WNT inhibitor)	BRAF V600E TP53 R273H CREBBP loss RB1 loss exons 21-27 RNF43 R145* SLIT2 loss SMAD4 loss		0		0.14
165	69	M	Lung	15/04/2015	**3**	1	Arm A	4	5.1	1	1.8	1	**0.3**	11/06/2015	07/08/2015		3.8	1	CARBOPLATIN (targets BRCA) + EVEROLIMUS (Targets mTor pathway activated by NF2 and STK11)	BRCA1 V740fs*3 NF2 deletion exons 12-15, E270* STK11 K78* CDKN2A/B loss		1		0.75
179	57	F	Colon	14/04/2015	**3**	1	Arm A	4	6.63	1	5.7	1	**0.8**	06/10/2015	08/02/2016		10	1	BEVACIZUMAB (VEGF inhibitor) + TRAMETINIB (MEK inhibitor) + SULINDAC (WNT/Beta catenin inhibitor)	KRAS G12S ERBB4 E872G SUFU A256fs*23 TP53 R273C APC E4616fs*6, R1399fs*9 ARID1A Q1631*		1		0.5
181	75	M	Colon	13/05/2015	**3**	0	Arm B	4	2.5	1	0.9	1	**0.3**	11/06/2015	22/08/2015		3.3	1	CABOZANTINIB (MET and VEGFR inhibitor)	TP53 P151S APC Y935* FAM123B E507*	**VEGFA** (4.5 fold change) and **HGF** (4.5 fold change) overexpression; ranked 5th in the multiple interaction		0	0.2

183	66	M	Colon	04/03/2015	**2**	0	Arm A	2	9.4	1	25.5	0	**2.7**			19/04/2017	25.9	0	PEMBROLIZUMAB (anti PD-1)	ERBB3 V104M MAP2K1 E203K CDKN2A/B loss FBXW7 R465C PIK3CA E39K PIK3R1 R348*, R639* PTEN R233*, splice site 801+2T>G TP53 R158H, R273H APC R1450*, R499* ARID1A P1115fs*46, Q13066*17 ATRX Q2422* CDH1 D433N EP300 R2263* FAM123B R631* FAT1 A4305V FLCN H429fs*39 MSH6 L1330fs*12, S279fs*12		1		1
190	50	F	Lung	30/08/2015	**3**	0	Arm A	2	5.9	1	21.6	0	**3.6**			18/06/2017	21.93	0	OSIMERTINIB (EGFR inhibitor)	EGFR E746_A750del EGFR T790M AKT1 amplification-equivocal PDGFRA duplication exons 12-23 TP53 splice site 97-2A>C NKX2-1 amplification-equivocal		1		0.33
191	50	F	Other: Pleura	04/06/2015	**4**	1	Arm A	4	4.1	1	1.1	1	**0.2**	06/07/2015	13/07/2015		1.3	1	EVEROLIMUS (PI3K/Akt/mTor inhibitor) + BEVACIZUMAB (VEGF antibody)	NF2 M409fs17 CDKN2A/B loss TP53 H214R		1		0.66
192	55	F	Colon	20/05/2015	**4**	1	Arm A	4	2.	1	1.2	1	**0.5**	26/06/2015	04/08/2015		2.5	1	TRAMETINIB (MEK inhibitor) + CARBOPLATIN (targets FANCA)	KRAS G12D CTNNB1 S45F FANCA G972fs*17 TP53 C176Y-subcllonal, R273H MLL2 L3948fs*88 SOX9 R394*, T460fs*11		1		0.33
194	48	F	Head and Neck	22/05/2015	**5**	0	Arm B	4	1.8	1	1.2	1	**0.6**	29/06/2015	04/08/2015		2.4	1	IPILUMIMAB	CDKN2A/B loss	**CTLA4** 6.8 fold change) overexpression; ranked 4th in the single interaction		0	0.25
195	57	M	Head and Neck	30/04/2015	**3**	1	Arm B	4	0.8	1	1.2	1	**1.5**	05/06/2015	28/11/2015		7.1	1	IPILIMUMAB	CDKN2A/B loss	**CTLA4** (8.8 fold change) overexpression; ranked 2nd in the single interaction		1	0.5
200	76	F	Colon	28/05/2015	**4**	1	Arm A	4	2.5	1	2.0	1	**0.8**	28/07/2015	25/12/2015		7.0	1	AXITINIB (KDR (VEGFR2) and other VEGFR inhibitor) + TRAMETINIB (MEK inhibitor)	KDR K142R KRAS G12D TP53 S127P APC V1452fs*22		1		0.75
201	26	M	Other: GI Tract / Rectum	21/04/2015	**3**	0	Arm B	4	9.5	1	1.1	1	**0.1**	26/05/2015	28/09/2015		5.3	1	PHASE 1 NCT02912949 MCLA-128 (ERBB2 and ERBB3 inhibitor)	KRAS G12V MYC amplification TP53 C238Y APC V830fs*12	**AREG** (8.1 fold change) and EREG (22.6 fold change) overexpression ranked 3rd in multiple interaction		0	0.17
203	67	F	Other: GI Tract / Small Intestine neuroendocrine tumor	06/05/2015	**1**	1	Arm B	3	8.1	1	24.3	0	**2.9**			15/05/2017	24.6	0	EVEROLIMUS (PI3K/Akt/mTor inhibitor)	No mutation	**AKT2** (7.2 fold change)/**AKT3** (11.2 fold change) overexpression PIK3CA (1.8 fold change; Drugs targeting the mTOR pathway ranked 2nd in the multiple interaction		1	0.5
204	68	M	Colon	25/05/2015	**4**	1	Arm B	4	2.0	1	1.7	1	**0.8**	16/07/2015	13/09/2015		3.7	1	CABOZANTINIB (VEGFR/MET inhibitor)	KRAS Q61H PIK3CA Q546R TP53 G245S APC G309* SPTA1 R2016H	**VEGFA** (5.0 fold change) and **MET** (4.3 fold change) overexpression; ranked 1st and 2nd in the single interaction		1	1
205	69	M	Other: GI Tract / Rectum	20/05/2015	**3**	1	Arm A	4	1	1	1.2	1	**0.7**	25/06/2015	24/08/2015		3.2	1	PHASE 1b NCT02510001 MERCURIC PF-02341066 + PD-0325901 (MET and MEK inhibitors)	KRAS G12V FANCC rearrangement intron 12 TP53 S183* APC P1243fs*22 RUNX1T1 R149H SMAD4 D537E		1		0.33
210	72	M	Colon	01/04/2015	**2**	1	Arm A	4	3.7	1	1.6	1	**0.4**	19/05/2015	05/08/2015		4.2	1	PHASE 1 NCT01750918 MEK116833: TRAMETINIB + PANITUMAB (EGFR inhibitor)	BRAF V600E PTEN Q171E TP53 Q165* APC A2584fs*4, R499*, T1556fs*3 SMAD4 Q410*		1		0.6
211	74	M	Colon	11/05/2015	**5**	0	Arm B	4	0.1	1	1.9	1	**14.7**	09/07/2015	20/01/2017		20.6	1	ETOPOSIDE + BEVACIZUMAB (VEGF antibody)	MYC amplification equivocal TP53 S206fs*24 APC C995fs*10, L1488fs*19 BCL2L1 amplification – equivocal SMAD4 R97H	**VEGFA** (2.4 fold change) overexpression; ranked 4th in the single interaction;		0	0.25
212	55	M	Lung	08/05/2015	**3**	1	Arm A	4	1.5	1	1.11	1	**0.7**		11/06/2015		1.1	1	EVEROLIMUS (mTor inhibitor) + CARBOPLATIN	BRIP1 L914* STK11 E165* CCNE1 amplification TP53 splice site 376-2A>T SPTA1 Q17876*33		1		0.4
216	50	M	Head and Neck	06/05/2015	**3**	1	Arm B	4	3.3	1	0.75	1	**0.2**	29/05/2015	04/11/2015		6.1	1	IPILIMUMAB	PIK3CA C604R PTPN11 G503V TET2 T229fs*25 TP53 V147A AR F814V ARID1A G276fs*87, M1564fs*8 BCORL1 G1682fs*4 CDKN1B K81fs*44, N31fs*12 EPHA3 P239T FAS T219fs*4 MSH2 A230fs*16 MSH6 F1088fs*2 MUTYH G382D NOTCH1 V1229fs*2 SPEN T2496fs*2	**CTLA4** (4.9 fold change) overexpression; ranked 3rd in the single interaction		1	0.33
220	68	M	Lung	02/11/2015	**1**	0	Arm A	4	10.5	1	5.3	1	**0.5**	13/04/2016		02/07/2017	20.2	0	NINTEDANIB (RET inhibitor)	RET NCOA4-RET fusion		1		1
223	65	F	Head and Neck	22/09/2015	**3**	0	Arm B	3	6.7	1	7.1	1	**1.1**	26/04/2016		05/05/2017	19.7	0	AXITINIB (multikinase inhibitor including PDGFR and Kit)	CCND1 T286I	**PDGFRA** (6.1 fold change)/**PDGFRB** (3.5 fold change), KIT (5.2 fold change) overexpression; ranked 3rd in the multiple interaction		1	0.33
225	75	F	Colon	18/05/2015	**2**	1	Arm A	4	1.56	1	1.01	1	**0.66**	19/06/2015	04/08/2015		2.6	1	PHASE 2 NCT01953926 NERATINIB (pan-ERBB inhibitor)	BRAF amplification equivocal KRAS G13D ERBB3 T355A TP53 R342* APC D1636fs*5 CDK8 amplification KEL amplification equivocal MUTYH G382D MYST3 amplification SPTA1 R60*		0		0.1
226	76	M	Liposarcoma	15/06/2015	**3**	2	Arm A	4	2.1	1	1.8	1	**0.8**	10/08/2015	03/06/2016		11.8	1	CERITINIB (multikinase inhibitor; targets include IGFR)	AKT1 amplification CDK4 amplification IGF1R amplification MDM2 amplification ESR1 amplification		0		0.2
227	56	M	Liposarcoma	26/06/2015	**4**	1	Arm A	4	1.7	1	1.7	1	**0.9**	17/08/2015		18/01/2017	19.1	0	EVEROLIMUS	MTOR V2006F-SUBCLONAL STK11 F354L TERT promoter-124C>T		1		0.66
228	38	M	Colon	22/06/2015	**5**	1	Arm A	4	0.9	1	0.7	1	**0.8**	14/07/2015	22/08/2015		2.0	1	PHASE 1 NCT02052778 TAS-120 (FGFR inhibitor)	FGFR1 amplification equivocal TP53 C176F APC E1322*, R213* SMAD4 loss SOX9 V163fs*21		0		0.2
229	31	M	Colon	14/05/2015	**3**	1	Arm A	4	2.3	1	2.0	1	**0.8**	14/07/2015	30/08/2015		3.6	1	TRAMETINIB (MEK inhibitor) + CARBOPLATIN	KRAS G12W BRCA2 E532fs*3 BRIP1 T1152fs*15 ATM E1783* EZH2 P577Q FANCA splice site 1901-2A>G FBXW7 V671fs*23 GRM3 A575T subclonal PARK2 V330fs*17 SMARCB1 T118fs*52 SUFU A255fs*23 TP53 R273S subclonal, Y220C subclonal APC K2051fs*9, V2194fs*3 ARID1A G376fs*14 ARID2 E376* ATRX R1606fs*29 BCOR E1539* CHD2 V175fs*18 CHEK2 Y329fs*12 CIC P509fs*14, S326*, S961fs*190 CREBBP K1270fs*4, P1946fs*30 CTCF T204fs*26 HNF1A P291fs*51 KDM5C A1509fs*54 KEL L642fs*42 LRP1B I2387FS*2, SPLICE SITE 6024-1G>C MLL3 K2797FS*26 MSH6 F1088FS*5 NOTCH3 A1802FS*8 NUP93 P744fs*		0		0.18

232	51	M	Colon	17/02/2016	**6**	0	Arm B	4	8.8	1	1.6	1	**0.2**	05/04/2016	09/10/2016		7.8	1	PEMETREXED + BEVACIZUMAB (VEGF antibody)	TP53 R175H APC K670*, T1293fs*8	**VEGFA** (2.68 fold change) overexpression; ranked 1st in the single interaction		1	1
233	56	M	Head and Neck	05/06/2015	**3**	0	Arm A	4	1.9	1	1.8	1	**0.9**	29/07/2015	06/09/2015		3.1	1	PHASE 2 NCT01737450 BKM120 (PI3CA inhibitor)	PIK3CA E545K BAP1 R385* EP300 D1399N		0		0
235	60	F	Lung	16/07/2015	**1**	0	Arm A	3	7.0	1	11.3	1	**1.6**	26/06/2016		05/06/2017	23	0	AFATINIB (pan-ERBB inhibitor)	ERBB2 A775_G776insYVMA		1		1
236	58	M	Other: Neuroendocrine	13/07/2015	**3**	0	Arm B	4	18.9	1	2.3	1	**0.1**		22/09/2015		2.3	1	EVEROLIMUS (Akt inhibitor) + BUCALUTAMIDE + GOSERELIN (hormone modulators)	No mutation	**AKT2** (5.8 fold change), AKT3 (6.8 fold change), overexpression; each ranked 3rd in single interaction and ESR1 (1.8 fold change) ranked 1st single interaction		1	1
237	47	M	Head and Neck	18/11/2015	**6**	1	Arm A	3	3.9	1	19.3	0	**4.8**			28/06/2017	19.6	0	PHASE 1 NCT01004224 BGJ398 (FGFR inhibitor)	CCND1 amplification FGFR2 amplification equivocal CDKN2A/B loss FGF19 amplification FGF4 amplification BAP1 truncation exon 3 FGF3 amplification MAGI2 Q1077* PBRM1 E1155fs*17		1		0.44
238	68	F	Colon	02/10/2015	**5**	1	Arm A	4	5.7	1	3.5	1	**0.6**	16/01/2016	22/03/2016		5.7	1	BEVACIZUMAB (VEGF inhibitor) + EVEROLIMUS (mTor inhibitor)	TP53 G262V TSC2 loss exons 2-4 APC E1309fs*4		1		0.66
240	78	F	Lung	19/08/2015	**2**	2	Arm A	4	20.5	1	4.0	1	**0.2**	20/12/2015	12/02/2016		5.9	1	NINTEDANIB (RET and VEGFR inhibitor)	RET kif 5b-ret fusion CDKN2A/B loss TP53 loss exon 10-11 BCL2L1 amplifications RPTOR amplification		1		0.4
241	59	M	Lung	14/03/2016	**5**	1	Arm A	4	3.2	1	4.	1	**1.23**	15/07/2016	15/07/2016		4.1	1	EVEROLIMUS (PI3k/Akt/mTor pathway inhibitor) + CRIZOTINIB	NF2 (E167*) GRIN2A (A302T)		1		0.5
242	78	M	Other: Soft Tissue	29/10/2015	**1**	2	Arm A	4	6.2	1	1.2	1	**0.2**	06/12/2015	08/12/2015		1.3	1	PALBOCiCLIB (CDK4/6 inhibitor) + ETOPOSIDE	cdk4 amplification MDM2 amplification		1		0.5
246	51	F	Colon	07/12/2015	**3**	1	Arm A	2	3.3	1	6.2	1	**1.8**	09/06/2016	15/03/2017		15.4	1	TRASTUZUMAB + PERTUZUMAB (ERBB2 inhibitors) + PACLITAXEL (paclitaxel was added after start in supplement by investigator)	KRAS Q61L ERBB2 amplification FGFR1 amplification ARID1A Y2031* TOP2A amplification TP53 G266E TSC2 truncation intron 27 APC Q1429*, R876* MUTYH G382D MYST3 amplification PIK3CG V759I		0		0.09
247	67	M	Other: GI Tract / Esophagus	29/07/2015	**2**	1	Arm A	4	2.20	1	1.6	1	**0.7**	18/09/2015	16/11/2015		3.6	1	PHASE 1 NCT02052778 TAS-120 (FGFR inhibitor)	FGFR2 amplification - equivocal CDKN2A/B loss TP53 W91* ASXL1 splice site 472-2A>G		1		0.25
248	69	M	Colon	10/08/2015	**2**	2	Arm A	4	19.5	1	1.62	1	**0.1**	30/09/2015	16/11/2015		3.2	1	TRAMETINIB (MEK inhibitor) + EVEROLIMUS (PI3K/Akt/mTor pathway inhibitor)	KRAS (G13D) PTEN (A79T)		1		1
249	41	M	Colon	28/07/2015	**3**	2	Arm A	4	3.8	1	0.7	1	**0.12**	18/08/2015	21/09/2015		1.8	1	TRAMETINIB (MEK inhibitor) + SULINDAC (Wnt pathway inhibitor) + NILUTAMIDE	KRAS (G12V) APC (E1554*) RUNX1T1 (R395W) SMAD4 (loss)		1		0.5
251	61	F	Colon	16/10/2015	**3**	1	Arm A	4	29.6	1	1.9	1	**0.1**	13/12/2015	06/01/2016		2.7	1	PHASE 1 NCT02457351 Ronciclib (BAY 1000394) (CDK inhibitor)	KRAS (G12V) MYC amplification - equivocal TP53 (V122fs*26)		0		0
256	45	M	Head and Neck	27/08/2015	**1**	0	Arm A	4	8.2	1	4.5	1	**0.5**	13/01/2016		29/06/2017	22.4	0	PHASE 1 NCT01884285 AZD8186 (PI3K BETA inhibitor)	PTEN splice site 635-1G>C, splice site 801+1G>A TERT promoter -124C>T		1		0.5
257	67	F	Colon	09/09/2015	**5**	1	Arm B	4	2.9	1	2.1	1	**0.7**	11/11/2015		11/11/2015	2.1	0	BEVACIZUMAB (VEGF antibody) + TRASTUZUMAB	KRAS G12V ERBB2 R678Q IRS2 amplification TP53 C176G, splice site 919+1G>T APC K1437*, R283* FGF14 amplification	**VEGFA** (5.7 fold change) overexpression; ranked 1st in the single interaction		1	1
258	58	M	Head and Neck	01/03/2016	**4**	1	Arm B	4	7.0	1	0.2	1	**0.1**	08/03/2016	17/04/2016		1.5	1	SUNITINIB (multikinase PIEGFR and VEGFR inhibitor)	TP53 R205*	FLT1/VEGFR1 (1.4 fold change) , PDGFRB (1.4 fold change) overexpression; ranked 3rd in multiple interaction;		1	0.33
259	53	F	Head and Neck	06/01/2016	**4**	1	Arm B	3	10.9	1	6.2	1	**0.5**	12/07/2016		21/03/2017	14.6	0	AXITINIB (multikinase inhibitor including PDGFRA and KIT)	PDGFRA	PDGFRA (52.8 fold change),PDGFA (16.9 fold change), VEGFA (11.9 fold change) , PDGFB (3.4 fold change) and KIT (3.6 fold change) overexpression; ranked 2nd in the multiple interaction		1	0.5
263	29	F	Head and Neck	21/09/2015	**2**	0	Arm B	3	5.1	1	20.9	0	**4.01**			18/06/2017	21.2	0	PHASE 1 NCT02264418 ODM203 (VEGFR/FGFR inhibitor)	No mutation	**FLT4/VEGFR1** (1.2 fold change) VEGFA (2.3 fold change) and **FGFR1** (4.4 fold change) overexpression; ranked 1st and 2nd in the single interaction		1	1
267	39	M	Melanoma	09/09/2015	**4**	1	Arm B	4	4.6	1	2.8	1	**0.6**		03/12/2015		2.83	1	PHASE 1 NCT02912949 MCLA-128 (HER3 inhibitor)	CDKN2A/B loss ARID2 E186* TERT promoter -146C>T	**ERBB3** (1.7 fold change) overexpression; ranked 5th in the single interaction		0	0.2
268	51	F	Melanoma	18/11/2015	**5**	1	Arm A	4	1.8	1	3.9	1	**2.2**	18/03/2016	11/05/2017		18	1	EVEROLIMUS (PI3K/Akt/mTor inhibitor) + ETOPOSIDE	FGFR3 splice site 445+2delTAGG PTEN P95L MYC amplification		1		0.33
270	76	F	Colon	02/12/2015	**3**	1	Arm A	4	0.6	1	0.9	1	**1.5**	30/12/2015	03/04/2016		4.1	1	PHASE 1b NCT02350673 CERGUTUZUMAB (CEA-targeted IL-2 variant-based immunocytokine) + ATEZOLIZUMAB (anti PD1/PDL1)	FLT4 amplification FLT3 amplification equivocal BARD1 C536*5 MYC amplification PARK2 loss exons 3-5 TP53 R175H APC T1556fs*3 BCL2L1 amplification CDK8 amplification ETV6 rearrangement intron 5 FAM123B R497* GATA6 amplification equivocal KDM6A Y215* MUTYH Y165C NOTCH1 Q2123*		1		1
282	55	M	Head and Neck	12/08/2016	**3**	0	Arm A	4	3.5	1	1.5	1	**0.4**	28/09/2016		29/06/2017	10.7	0	PALBOCICLIB (CDK4/6 inhibitor) + CETUXIMAB	CCND1 amplification CDKN2A loss p16INK4a and loss p14ARF exons 2-3 FGF19 amplification FGF4 amplification TP53 R248L FGF3 amplification SMARCA4 G1266fs*3 SPTA1 R448W TERT promoter -146C>T		0		0.22
285	66	F	Lung	25/03/2016	**5**	1	Arm A	4	4.1	1	2.7	1	**0.6**	17/06/2016		18/04/2017	12.9	0	PHASE 1 NCT02014116 LY3009120 (pan-RAF inhibitor)	BRAF D594N PIK3CA E39K PIK3R1 Q572fs30 PTEN Y178fs1 ARID1A R1287fs8 MYC amplification MUTYH Y165C		0		0.14
286	52	M	Colon	11/01/2016	**3**	0	Arm A	2	7.8	1	10.4	1	**1.3**	22/11/2016	31/05/2017		16.8	1	PHASE 1 NCT01750918 PANITUMUMAB + TRAMETINIB (MEK inhibitor)	KRAS Q61H TP53 E271K TBX3 W113*		1		0.33
288	66	F	Colon	06/04/2016	**4**	1	Arm B	3	4.2	1	6.8	1	**1.6**	31/10/2016	13/02/2017		10.4	1	CABOZANTINIB (VEGFR/MET inhibitors)	KRAS G13C TP53 R196* APC E1451* DNMT3A Y735C subclonal	**MET** (7.2 fold change) and **VEGFA** (3.7 fold change) overexpression; ranket 1st and 2nd in the single interaction		1	1

292	76	M	Head and Neck	20/01/2016	**2**	2	Arm A	4	2.9	1	0.7	1	**0.2**	11/02/2016	18/03/2016		1.93	1	PAZOPANIB (FLT1 (VEGFR1) inhibitor)	FLT1 G401E HRAS G13D BARD1 W91* CDKN2A p16INK4a R80* and p14ARF P94L ARID2 E1247fs*1, R542* ASXL1 D1030fs*4 FAT1 G759*, P1646fs*3 NOTCH1 W1474* NOTCH2 Q807* RANBP2 L811R subclonal TERT promoter -146C>T TP53 Q375*, R213*		0		0.16
294	57	M	Head and Neck	03/10/2016	**1**	1	Arm B	4	19.0	1	1.7	1	**0.1**	24/11/2016	20/05/2017		7.6	1	NIVOLUMAB	BRCA2 K3408*	IL2RA (2.7 fold change), IL2RB (2.6 fold change), IL2RG (3.6 fold change) and CD52 (4.5 fold change) overexpression;reflects T-cell infiltrate. ranked 1st in the single interaction		1	1
295	61	F	Rhabdomyosarcoma	14/05/2016	**1**	0	Arm B	3	21.9	1	9.2	1	**0.4**	17/02/2017		20/06/2017	13.4	0	CERITINIB (multikinase inhibitor; targets include IGFR)	PIK3CA E542Q	**IGFR1** (5.3 fold change) overexpression; ranked 2nd in the single interaction report		1	0.5
296	63	M	Colon	15/02/2016	**6**	0	Arm B	4	1.1	1	3.3	1	**2.97**	26/05/2016	24/09/2016		7.4	1	CABOZANTINIB (VEGFR/MET inhibitor)	KRAS Q61H APC S1346* EP300 truncation exon 27 NOTCH2 A439fs*4 SMAD4 loss TP53 R196*	**MET** (5.2 fold change) and **VEGFA** (4.1 fold change) overexpression; ranked 1st and 2nd in the single interaction		1	1
297	67	M	Hepatocarcinoma	08/11/2016	**2**	0	Arm B	2	9.23	1	7.6	0	**0.8**			27/06/2017	7.7	0	PHASE 1 NCT01968109 NIVOLUMAB + ANTI-LAG3	PIK3CA K111E CTNNB1 N387K TERT promoter -124C>T	IL2RA (3.2 fold change), IL2RG (1.4 fold change) and CD52 (1.9 fold change) overexpression/suggests T-cell infiltrate; T cell targeting ranked 3rd in single interaction		1	0.33
298	59	M	Colon	23/05/2016	**5**	1	Arm A	4	2.3	1	1.7	1	**0.7**	15/07/2016	02/10/2016		4.4	1	PHASE 1b NCT02327169 MLN2480 (pan-RAF inhibitor) + alisertib (AURORA KINASE inhibitor)	NRAS Q61R AURKA amplification equivocal HGF P700T TP53 R175H		1		0.5
299	44	F	Colon	20/06/2016	**5**	0	Arm A	4	4.8	1	1.0	1	**0.2**	20/07/2016		15/06/2017	12	0	SORAFENIB (multikinase inhibitor including FLT3 and VEGFR)	FLT3 amplification equivocal IRS2 amplification equivocal APC S1100fs*26 CDK8 amplification equivocal FAT1 loss exons 2-24 LRP1B G1055R TP53 R175H		1		0.28
301	69	M	Colon	29/06/2016	**4**	0	Arm A	3	2.4	1	6.0	1	**2.5**	30/12/2016		02/03/2017	8.2	0	LENVATINIB (FGFR inhibitor)	NRAS G12D KRAS G12D FGFR2 K659E PIK3R1 splice site 1162_1299+174del312 APC E984*,R1450* CHD2 truncation exon 24 PPP2R1A R183W		0		0.14

*DNA - Molecular alterations: list of all molecular alterations given in the Foundation Medicine report.

**RNA - Relevant transcripts tumor versus normal that led to drug choice. Winther algorithm uses the Log in base 2 of the ratio of Tumor/Normal intensities ratio. For ease reading and interpretation, we present expression as fold change between expression in Tumors vs Normal matched tissue. Data is presented per interpretation at time of inital scoring.

***The selection of the drugs given was based on factors such as drug/clinical trial availability in the country/institute and patient co-morbidities; neither the selection of drugs or the scoring was locked down but was based on knowledge at the time. Drug selection was recommended by the CMC, but physicians could choose the drugs given; scoring was done post hoc, but by investigators and statistician blinded at the time to outcome; drugs in regimen that were unmatched were scored as zero.

****Scores over 1 were rounded to 1 herein; unmatched drugs were scored as zero; retrospectively, it was apparent that sometimes drugs matched both Arms A and B, in which case scoring was performed on the basis of the Arm that was considered matched at the time of the CMC teleconference; for multiple interaction scoring, the reciprocal of the rank for each drug constituted the score; for single interactions, the reciprocal of the rank of each distinct target impacted constituted the score (when targets were similar, eg ligand and receptor, they were scored as one).

Abbreviations and Definitions

Date_Death: Date of death	**OS:** Overal survival in month
Date_Last Known Alive: Date of last known alive	**PFS: P**rogression free survival in month
Date_Progression under WINTHER treatment: Date of progression	**PFS_ratio:** Time of PFS2/ time of PFS1
DNA_matching score_high: DNA matching score; 0=low, 1=high The Matching Score derived from the number of alterations matched to drug(s) received divided by the total number of alterations for any given	**Response:** Overall response of WINTHER treatment: 1=Complete response, 2=partial response; 3=stable disease for at least 6 months; 4=stable disease for less than 6 months or progressive disease
Drug_given: Drug(s) given in the WINTHER treatment	**RNA_matching score_high:** RNA matching score; 0=low, 1=high The Matching Score was assigned by adding the reciprocal of the ranks of each matched drug received by the patient based on the WINTHER algorithm (or simply the reciprocal of the rank if only one drug was
Event_OS: Censoring indicator of overall survival: 0=censored, 1=event	**Single interaction:** Drug with 1 known target gene
Event_PFS1: Censoring indicator of PFS1: 0=censored, 1=event	**Time_OS**: Time of overal survival in month
Event_PFS2: Censoring indicator of PFS2: 0=censored, 1=event	**Time_PFS1**: Time of PFS1 (before WINTHER) in month
One or Zero: One being high score; zero being low matching score	**Time_PFS2: T**ime of PFS2 (WINTHER trial) in month
Multiple interaction: Drug for which more than 1 gene was involved	**Zero or one:** Zero being low matching score; one being high score

Supplemental explanations and references for Supplemental Table 4

Below are references and considerations used for degree of matching evaluation (see also **Methods** and footnotes for **Supplemental Table 4**). Explanations are given for patients with complexity in scoring. For all patients, pertinent targets are given in brackets beside the drug name (**Supplemental Table 4**).

Patient ID6, ID69, ID90, ID117, ID233: Patients with multiple (≥ 2) alterations (and especially those with MEK pathway alterations) in addition to a PI3K/Akt/mTor alterations matched to a PI3K/Akt/mTor inhibitor as a single agent have low response rates and were considered unmatched; mTor inhibitors as part of a matched combination in this situation, however, have been reported to have higher response rates and were considered matched (14, 32, 36 and supplemental reference S1). mTor inhibitors as single agents matched by transcriptomics were considered matched.

Patient ID1, ID10, ID99, ID124, ID140, ID179, ID191, ID200, ID238, ID240, ID288: VEGFR/VEGF inhibitors were considered matched for *TP53* alterations. (Supplemental references S2, S3 and S4).

Patient ID87: *ATR* and *BRCA* alterations can be targeted by PARP inhibitors and platinum (Supplemental references S5, S6, S7 and S8).

Patient ID103: PTPN11 activates the MEK pathway (https://ghr.nlm.nih.gov/gene/PTPN11). APC activates Wnt/β--catenin signaling, which is inhibited by Sulindac (Supplemental reference S9).

Patient ID146: Dasatinib regulates many of the genes listed https://www.researchgate.net/publication/293865698_Additional_file_3 and supplemental reference S10.

Patient ID103, ID137, ID140, ID179, ID249: APC activates Wnt/β--catenin signaling, which is inhibited by Sulindac (Supplemental reference S9) and regorafenib (Supplemental reference S11).

Patient ID164: RNF43 regulates the WNT pathway (Supplemental reference S9).

Patient ID191, ID241: NF2 can activate the mTor pathway (Supplemental reference S12).

Patient ID201: AREG binds EGFR; EREG interacts with EGFR and ERBB4, both of which heterodimerize with ERBB2. The impact of an ERBB2/ERBB2 targeting antibody was hence unclear and was given half of the normal score (since relevant receptors formed a heterodimer). https://www.researchgate.net/figure/Binding-specificity-of-EGF-transforming-growth-factor-a-TGF-a-amphiregulin-AReG_fig1_283083537

Patient ID205, ID210, ID249: *SMAD4* alterations (as well as *KRAS* and *BRAF* alterations) activate the MEK pathway (Supplemental reference S13).

Patient ID210: EGFR inhibitors synergize with MEK/BRAF inhibitors in treating BRAF positive disease (Supplemental reference S14).

Patient ID212: STK11 activates mTor pathway (Supplemental reference S15). BRIP1 is BRCA1 interacting protein. BRCA1 alterations confer sensitivity to platinum and PARP inhibitors.

Patient ID220, ID240: Nintedanib is a multikinase inhibitor and RET and VEGFR are targets (supplemental reference S16).

Patient ID226, ID295: Ceritinib is a mutlikinase inhibitor whose targets at clinically relevant concentrations include IGFR (FDA package insert: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205755s009lbl.pdf)

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