ORANGE Report

CONFIGURED PRIMARY TUMOR	CUPPA CANCER TYPE	QC
skin melanoma (DOID 8923)	Melanoma (100%)	PASS

|	
Purity:	99% (97%-100%)
Ploidy:	3.1 (3.1-3.15)
Somatic variant drivers:	6 (BRAF, CDKN2A, TERT)
Germline variant drivers:	None
Copy number drivers:	1 (PTEN)
Disruption drivers:	None
Fusion drivers:	None
Viral presence:	None
Whole genome duplicated:	Yes
Microsatellite indels per Mb:	0.1 (Stable)
Tumor mutations per Mb:	13.7
Tumor mutational load:	186 (High)
HR deficiency score:	0 (Proficient)
DPYD status:	*1_HOM (Normal Function)
Number of SVs:	72 (Pan 22% | Skin 34%)
Max complex cluster size:	8
Telomeric SGLs:	0
Number of LINE insertions:	4
On-label treatments:	29 (A, B, C, D)
Off-label treatments:	61 (A, B, C, D)

Somatic Findings
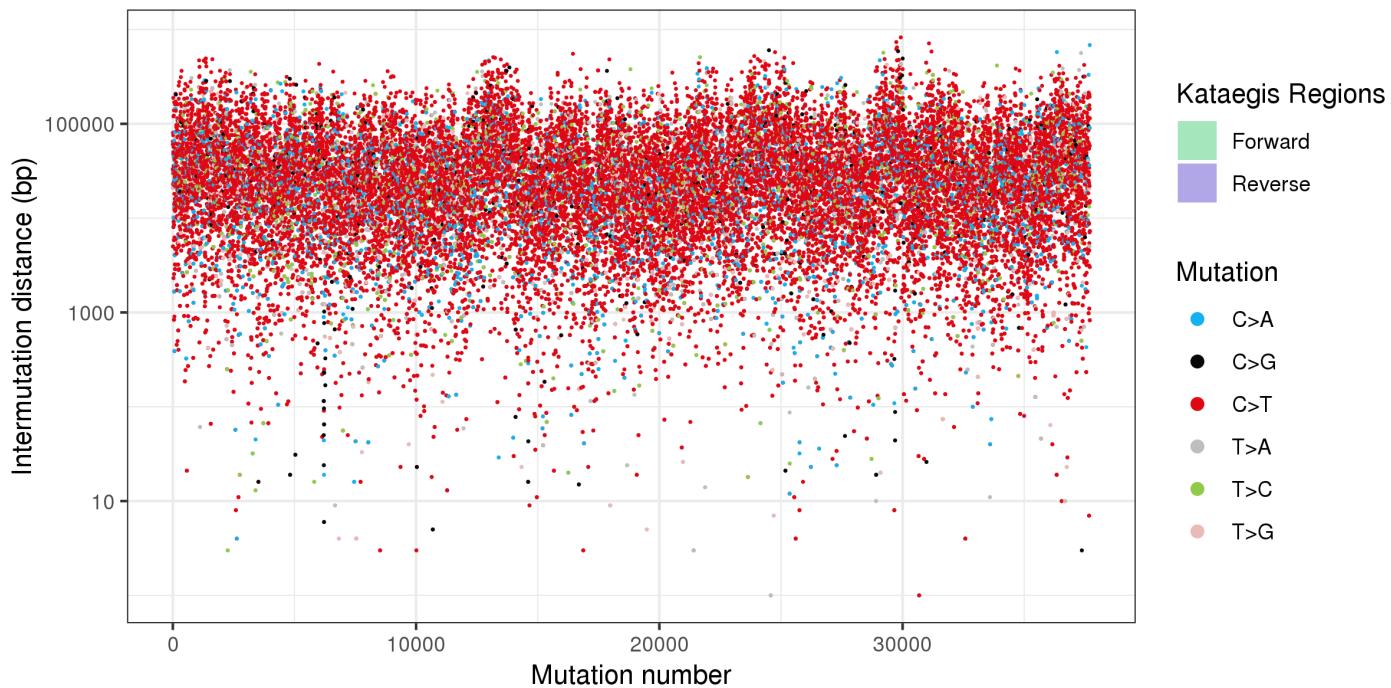
Driver variants (6)

VARIANT	VCN	CN	MACN	BIALLELIC	HOTSPOT	DL	CL	PHASE ID	RNA DEPTH
BRAF p.V600E	4.1	6.0	2.0	No	Yes	100%	100%		NA
CDKN2A p.A68fs	2.0	2.0	0.0	Yes	Near	100%	100%		NA
CDKN2A (alt) p.G83fs	2.0	2.0	0.0	Yes	Near	100%	100%		NA
TERT upstream	1.7	2.0	0.0	Yes	Yes	100%	100%	4410	NA
SF3B1 p.P718L	2.0	3.0	1.0	No	No	15%	100%		NA
TP63 p.M499I	1.7	4.0	2.0	No	No	0%	100%		NA

Other potentially relevant variants (3)

VARIANT	VCN	CN	MACN	BIALLELIC	HOTSPOT	DL	CL	PHASE ID	RNA DEPTH
ALB c.1059-53dupT	1.8	3.9	1.9	No	No		100%		NA
HDAC2 p.R409*	0.9	2.9	1.0	No	No		100%		NA
STK19 p.D89N	2.0	3.8	1.8	No	Yes		100%		NA

Kataegis plot

Kataegis Regions
- Forward
- Reverse

Mutation
- C>A
- C>G
- C>T
- T>A
- T>C
- T>G

Driver amps/dels (1)

CHR	REGION	GENE	TYPE	CN	TPM	PERC (TYPE)	FC (TYPE)	PERC (DB)	FC (DB)
10	q23.31	PTEN	partial loss	0	NA	NA	NA	NA	NA

Potentially interesting near-driver amps (0)

NONE

ORANGE Report

Other regions with amps (1)

CHR	REGION	GENE	TYPE	CN	TPM	PERC (TYPE)	FC (TYPE)	PERC (DB)	FC (DB)
3	p24.2	CFL1P7	full gain	12	NA	NA	NA	NA	NA

Regions with deletions in genes in other autosomal regions (1)

CHR	REGION	GENE	TYPE	CN	TPM	PERC (TYPE)	FC (TYPE)	PERC (DB)	FC (DB)
16	q21	CNOT1	partial loss	0	NA	NA	NA	NA	NA

Driver fusions (0)

NONE

Other potentially interesting fusions (0)

NONE

Driver viruses (0)

NONE

Other viral presence (0)

NONE

Homozygous disruptions (0)

NONE

Driver gene disruptions (1)

| LOCATION	GENE	RANGE	TYPE	CLUSTER ID	JUNCTION CN	UNDISRUPTED CN
10q23.31	PTEN	Intron 5 -> Intron 6	DEL	66	2.0	0.0

Other potentially interesting gene disruptions (0)

NONE

Potentially interesting LOH events in case of MSI or HRD (0)

NONE

Structural driver plots (3)

CHR 1 ... CHR 10 ...

CHR 10 ...

CHR 9 ...
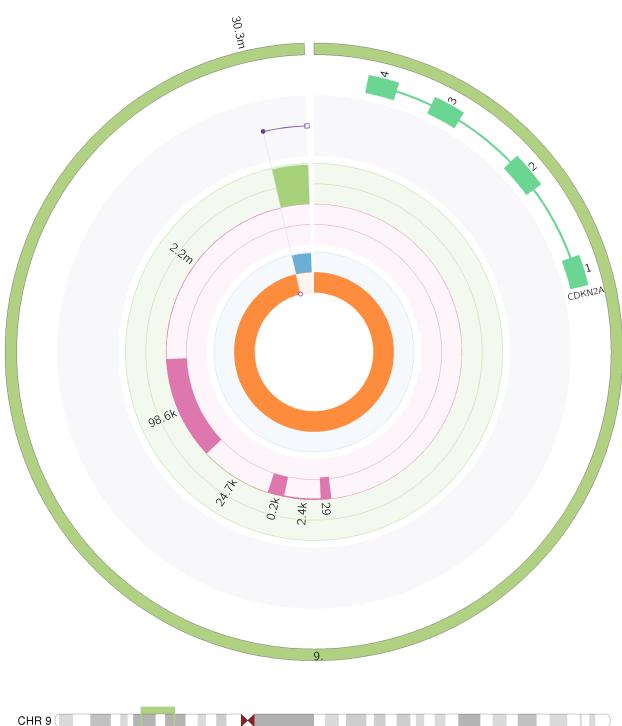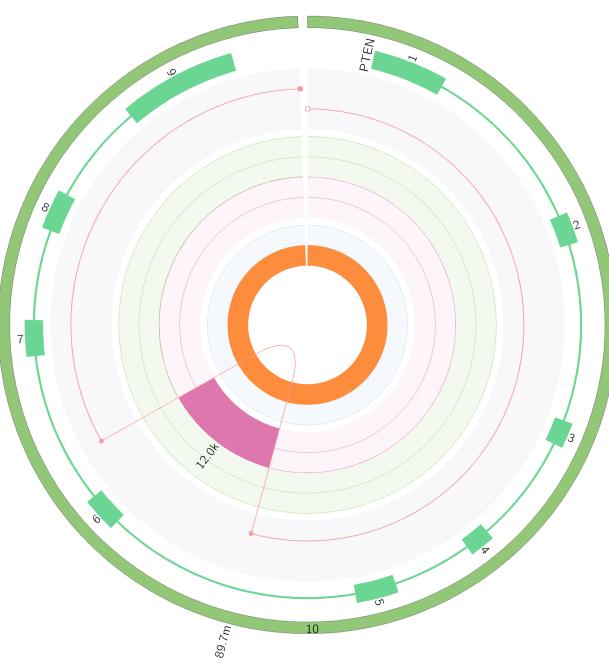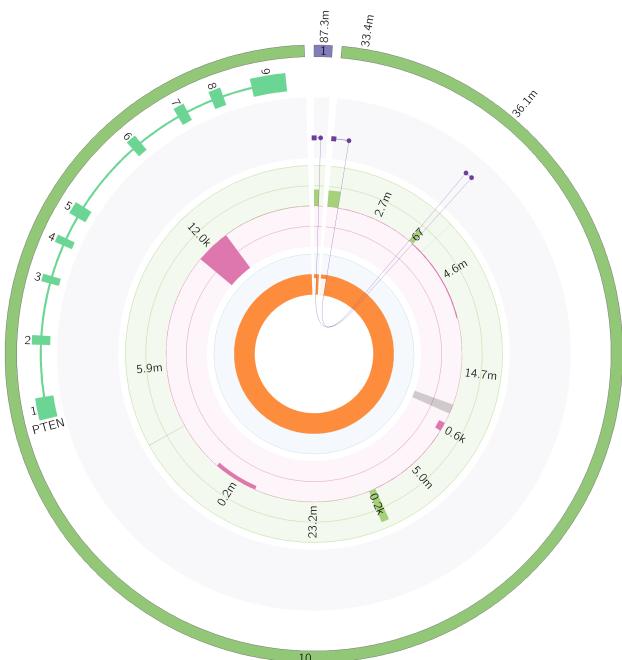
Germline Findings

Driver variants (0)

NONE

Other potentially relevant variants (3)

VARIANT	VCN	CN	MACN	RNA DEPTH	BIALLELIC	HOTSPOT	GENOTYPE
CYP2D6 p.?	1.8	4.0	2.0	NA	No	Yes	HET
CYP3A4 c.522-191C>T	2.5	4.0	2.0	NA	No	Yes	HET
CYP3A4 upstream	4.0	4.0	2.0	NA	Yes	Yes	HOM

Potentially pathogenic germline deletions (0)

NONE

Potentially pathogenic germline disruptions (0)

NONE

Genes with missed variant likelihood > 1% (0)
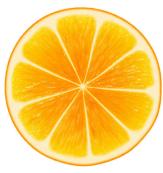
NONE

Germline CN aberrations (0)

NONE

Pharmacogenetics (1)

GENE	GENOTYPE	FUNCTION	LINKED DRUGS	SOURCE
DPYD	*1_HOM	Normal Function	5-Fluorouracil;Capecitabine;Tegafur	PHARMGKB

Immunology

HLA QC

QC Status: PASS

HLA Alleles (6)

ALLELE	REF FRAGS	TUMOR FRAGS	RNA FRAGS	TUMOR CN	SOMATIC #MUTATIONS
A*01:01	210	1602	NA	2	None
A*01:01	211	1602	NA	1.8	None
B*08:01	216	750	NA	1.8	None
B*40:02	196	721	NA	2	None
C*03:04	213	768	NA	2	None
C*07:01	225	767	NA	1.8	None

RNA Findings

QC	TOTAL FRAGMENTS	NON-DUPLICATE FRAGMENTS	DUPLICATE RATE
NA			

Genes with high expression (0)

NONE

Genes with low expression (0)

NONE

Known fusions detected in RNA and not in DNA (0)

NONE

Promiscuous fusions detected in RNA and not in DNA (0)

NONE

Potentially interesting novel splice junctions - Skipped exons (0)

NONE

Potentially interesting novel splice junctions - Novel exon/intron (0)

NONE

Cohort Comparison

	Acute myeloid leukemia	Anogenital	Bile duct/Gallbladder	Bone/Soft tissue: Other	Breast	Cartilaginous neoplasm	Chronic lymphocytic leukemia	Colorectum/Appendix/Smallintestine	Esophagus/Stomach	GIST	Glioma	Head and neck: other	Kidney	Leiomyosarcoma	Liposarcoma	Liver	Lung: NET	Lung: Non-small Cell	Lung: Small Cell	Lymphoid tissue	Medulloblastoma	Melanoma	Mesothelium	Myeloproliferative neoplasm	Osteosarcoma	Ovary/Fallopian tube	Pancreas	Pancreas: NET	Pilocytic astrocytoma	Prostate	Salivary gland/Adenoid cystic	Skin: Other	Small intestine/Colorectum: NET	Thyroid gland	Urothelial tract	Uterus: Endometrium
SNV 96 PAIRWISE SIMILARITY	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	0%	97%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%	0%	0%	0%	0%
GENOMIC POSITION SIMILARITY	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
FEATURE	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	96%	0%	0%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%
DNA COMBINED	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
SEX (MALE)	62%	16%	49%	53%	1%	78%	67%	56%	83%	65%	68%	76%	70%	29%	60%	76%	46%	44%	52%	57%	59%	61%	82%	46%	46%	0%	52%	60%	48%	100%	50%	67%	59%	76%	73%	0%

SNV SIGNATURES

	Acute myeloid leukemia	Anogenital	Bile duct/Gallbladder	Bone/Soft tissue: Other	Breast	Cartilaginous neoplasm	Chronic lymphocytic leukemia	Colorectum/Appendix/Smallintestine	Esophagus/Stomach	GIST	Glioma	Head and neck: other	Kidney	Leiomyosarcoma	Liposarcoma	Liver	Lung: NET	Lung: Non-small Cell	Lung: Small Cell	Lymphoid tissue	Medulloblastoma	Melanoma	Mesothelium	Myeloproliferative neoplasm	Osteosarcoma	Ovary/Fallopian tube	Pancreas	Pancreas: NET	Pilocytic astrocytoma	Prostate	Salivary gland/Adenoid cystic	Skin: Other	Small intestine/Colorectum: NET	Thyroid gland	Urothelial tract	Uterus: Endometrium
SIG 7 UV (24251)	34700%	1920%	4140%	98%	1260%	176000%	49600%	1670%	2560%	24700%	50000%	144%	2910%	9970%	14300%	5700%	11400%	791%	1600%	2350%	39800%	34%	7890%	4570000%	7990%	4330%	3580%	9450%	201000%	5660%	2930%	63%	10600%	27600%	747%	6130%
SIG 6 MMR (0)	50%	22%	36%	44%	38%	44%	44%	31%	40%	40%	49%	27%	42%	42%	50%	42%	38%	34%	46%	42%	44%	45%	38%	40%	44%	30%	43%	38%	42%	40%	43%	48%	32%	38%	39%	22%
SIG 4 SMOKING (2115)	664%	99%	107%	650%	120%	10000%	10000%	99%	189%	1450%	10000%	93%	124%	99%	10000%	96%	97%	41%	9%	10000%	5000%	99%	169%	10000%	227%	101%	168%	127%	49700%	152%	98%	99%	10000%	322%	92%	376%
SIG 2 13 AID APOBEC (3860)	20900%	67%	103%	98%	85%	41600%	10300%	100%	98%	805%	99%	88%	152%	518%	376%	456%	1980%	82%	125%	99%	4110%	34%	865%	16100%	99%	100%	165%	98%	35300%	225%	99%	52%	677%	96%	59%	105%
SIG 17 (1119)	1390%	97%	94%	97%	93%	22100%	208%	54%	24%	98%	10000%	97%	100%	285%	366%	100%	10000%	93%	97%	81%	10300%	97%	1560%	39300%	95%	99%	96%	99%	18000%	99%	93%	92%	701%	353%	90%	97%
SIG 11 (1328)	2410%	99%	100%	97%	100%	5370%	1870%	100%	100%	542%	93%	100%	336%	98%	352%	267%	386%	99%	123%	99%	923%	87%	431%	1360%	384%	100%	161%	98%	14600%	271%	231%	55%	556%	219%	96%	212%
SIG 10 POLE (0)	45%	24%	26%	37%	26%	50%	42%	15%	25%	32%	48%	16%	31%	41%	48%	37%	45%	38%	46%	30%	24%	48%	39%	42%	39%	44%	28%	42%	38%	35%	29%	40%	46%	22%	28%	41%
SIG 1 (0)	0%	-10000%	4%	3%	2%	-10000%	-10000%	3%	10%	2%	1%	4%	6%	2%	-10000%	22%	7%	24%	42%	8%	-10000%	41%	-10000%	-10000%	5%	2%	0%	4%	-10000%	0%	2%	22%	-10000%	8%	4%	6%

PERCENTILES

	Acute myeloid leukemia	Anogenital	Bile duct/Gallbladder	Bone/Soft tissue: Other	Breast	Cartilaginous neoplasm	Chronic lymphocytic leukemia	Colorectum/Appendix/Smallintestine	Esophagus/Stomach	GIST	Glioma	Head and neck: other	Kidney	Leiomyosarcoma	Liposarcoma	Liver	Lung: NET	Lung: Non-small Cell	Lung: Small Cell	Lymphoid tissue	Medulloblastoma	Melanoma	Mesothelium	Myeloproliferative neoplasm	Osteosarcoma	Ovary/Fallopian tube	Pancreas	Pancreas: NET	Pilocytic astrocytoma	Prostate	Salivary gland/Adenoid cystic	Skin: Other	Small intestine/Colorectum: NET	Thyroid gland	Urothelial tract	Uterus: Endometrium
SNV COUNT (37701)	1470%	91%	96%	97%	95%	2630%	860%	86%	83%	274%	92%	93%	99%	99%	327%	106%	384%	61%	40%	96%	1130%	38%	227%	2120%	211%	99%	99%	98%	5190%	97%	108%	56%	180%	111%	79%	87%
MS INDELS TMB (0.12)	634%	18%	48%	83%	62%	985%	134%	1%	16%	99%	48%	44%	88%	85%	94%	83%	99%	27%	12%	48%	99%	64%	94%	985%	98%	78%	40%	93%	2390%	37%	68%	36%	98%	91%	21%	31%
TELOMERIC SGL (0)	50%	32%	39%	26%	34%	50%	50%	38%	29%	43%	38%	40%	46%	2%	29%	42%	30%	25%	40%	46%	48%	28%	44%	50%	17%	38%	36%	34%	50%	42%	43%	39%	44%	35%	30%	44%
SIMPLE DUP 32B 200B (3)	96%	15%	26%	6%	19%	100%	100%	7%	28%	20%	4%	30%	12%	4%	6%	56%	17%	8%	8%	80%	94%	10%	20%	93%	53%	30%	55%	48%	98%	24%	5%	7%	12%	3%	14%	28%
MAX COMPLEX SIZE (8)	94%	22%	21%	38%	8%	76%	96%	28%	8%	51%	8%	36%	48%	9%	30%	50%	40%	10%	32%	63%	80%	25%	7%	100%	7%	24%	20%	77%	99%	8%	33%	37%	74%	70%	14%	53%
LINE (4)	133%	17%	52%	88%	48%	200%	200%	2%	10%	96%	98%	26%	91%	92%	77%	86%	81%	32%	52%	98%	100%	88%	95%	133%	75%	38%	52%	94%	100%	26%	41%	32%	94%	65%	6%	46%

FEATURES

	Acute myeloid leukemia	Anogenital	Bile duct/Gallbladder	Bone/Soft tissue: Other	Breast	Cartilaginous neoplasm	Chronic lymphocytic leukemia	Colorectum/Appendix/Smallintestine	Esophagus/Stomach	GIST	Glioma	Head and neck: other	Kidney	Leiomyosarcoma	Liposarcoma	Liver	Lung: NET	Lung: Non-small Cell	Lung: Small Cell	Lymphoid tissue	Medulloblastoma	Melanoma	Mesothelium	Myeloproliferative neoplasm	Osteosarcoma	Ovary/Fallopian tube	Pancreas	Pancreas: NET	Pilocytic astrocytoma	Prostate	Salivary gland/Adenoid cystic	Skin: Other	Small intestine/Colorectum: NET	Thyroid gland	Urothelial tract	Uterus: Endometrium
BRAF (1)	0%	1%	2%	1%	1%	0%	6%	13%	2%	2%	1%	1%	1%	0%	0%	1%	0%	7%	2%	2%	0%	52%	0%	0%	0%	2%	2%	0%	6%	2%	7%	0%	0%	10%	4%	1%
CDKN2A (1)	0%	15%	44%	23%	8%	0%	0%	4%	37%	39%	68%	48%	23%	4%	4%	8%	9%	41%	3%	10%	0%	52%	69%	0%	19%	10%	70%	12%	0%	2%	13%	24%	8%	24%	45%	7%
PTEN (1)	0%	8%	6%	2%	14%	0%	0%	10%	6%	5%	40%	4%	11%	12%	16%	3%	5%	6%	10%	4%	4%	23%	0%	0%	12%	5%	1%	4%	0%	42%	10%	16%	0%	0%	6%	47%
SF3B1 (0.15)	0%	1%	5%	0%	2%	0%	8%	0%	1%	0%	0%	0%	1%	0%	1%	1%	14%	1%	0%	0%	0%	2%	0%	0%	1%	0%	2%	1%	0%	1%	0%	0%	0%	0%	1%	0%
TERT (1)	0%	16%	8%	6%	1%	0%	1%	2%	0%	2%	70%	17%	12%	0%	28%	16%	0%	7%	0%	0%	8%	68%	5%	0%	2%	6%	1%	0%	0%	0%	13%	38%	0%	33%	70%	7%
TP63 (0.00)	0%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%	0%
INDEL_ALB (1)	0%	0%	6%	2%	1%	0%	0%	1%	1%	0%	0%	4%	1%	0%	0%	62%	0%	1%	2%	1%	0%	1%	0%	0%	0%	1%	1%	0%	0%	0%	3%	0%	0%	0%	0%	0%

Clinical Evidence

* Treatments are reported up to a maximum evidence level of B.

Applicable on-label evidence

EVENT	RESPONSIVE EVIDENCE	RESISTANCE EVIDENCE
BRAF p.V600E	Cobimetinib + Vemurafenib (A - CGI)	
	Dabrafenib (A - CGI)	
	Dabrafenib + Trametinib (A - CGI, CIViC)	
	Trametinib (A - CGI)	
	Vemurafenib (A - CGI, CIViC)	
	RO4987655 (B - CIViC)	
PTEN partial loss	Buparlisib + Carboplatin + Paclitaxel (B - CIViC)	

Applicable off-label evidence

EVENT	RESPONSIVE EVIDENCE	RESISTANCE EVIDENCE
BRAF p.V600E	CI-1040 (B - CIViC)	Bevacizumab (B - CIViC)
	Cetuximab + Irinotecan + Vemurafenib (B - CIViC)	Cetuximab (B - CGI, CIViC)
	Selumetinib (B - CIViC)	Fluorouracil (B - CIViC)
	Sorafenib (B - CIViC)	Irinotecan (B - CIViC)
		Oxaliplatin (B - CIViC)
		Panitumumab (B - CGI, CIViC)
PTEN partial loss		Anti-EGFR monoclonal antibody (B - CGI)
		Cetuximab (B - CIViC)
		Everolimus (B - CIViC)
		Lapatinib + Trastuzumab (B - CIViC)
		Trastuzumab (B - CIViC)

Applicable trials

NONE

Other potentially interesting on-label evidence

EVENT	RESPONSIVE EVIDENCE	RESISTANCE EVIDENCE
BRAF p.V600E	Cobimetinib + Vemurafenib (B - CIViC)	Bay (C - CIViC)
	Dabrafenib (B - CIViC)	Dasatinib (D - CIViC)
	Dabrafenib + Trametinib (B - CIViC)	
	Trametinib (B - CIViC)	
	Vemurafenib (B - CIViC)	
	Pictilisib (C - CIViC)	
	Raffinose (C - CGI)	
THE TABLE CONTINUES ON THE NEXT PAGE	Vemurafenib (C - CIViC)	
	0325901 (D - CIViC)	

Other potentially interesting on-label evidence

CONTINUED FROM THE PREVIOUS PAGE

EVENT	RESPONSIVE EVIDENCE	RESISTANCE EVIDENCE
	Vemurafenib (C - CIViC)	
	0325901 (D - CIViC)	
	Braf (D - CGI)	
	Braf + Cdk2 (D - CGI)	
	Braf + Hsp90 (D - CGI)	
	Cobimetinib (D - CIViC)	
	Dabrafenib (D - CIViC)	
	Dactolisib + Nvp + Selumetinib (D - CIViC)	
	Glu-arg-lys (D - CGI)	
	Gsk (D - CIViC)	
	Selumetinib (D - CIViC)	
	Sorafenib (D - CIViC)	
	Trametinib (D - CIViC)	
	Vemurafenib (D - CIViC)	

Other potentially interesting off-label evidence

EVENT	RESPONSIVE EVIDENCE	RESISTANCE EVIDENCE
BRAF p.V600E	Dabrafenib (A - CGI)	Cetuximab (C - CIViC)
	Dabrafenib + Trametinib (A - CGI, CIViC)	Dabrafenib (C - CIViC)
	Vemurafenib (A - CGI)	Egfr (C - CGI)
	Dabrafenib + Trametinib (B - CIViC)	Irinotecan (C - CIViC)
	Vemurafenib (B - CIViC)	Cetuximab (D - CIViC)
	2-butanone (C - CGI)	
	Braf (C - CGI)	
	Cetuximab + Irinotecan + Mab + Vemurafenib (C - CGI)	
	Dabrafenib (C - CGI)	
	Dabrafenib + Mab + Panitumumab (C - CGI)	
	Dabrafenib + Mab + Panitumumab + Trametinib (C - CGI)	
	Dabrafenib + Trametinib (C - CGI)	
	Dabrafenib + Trametinib + Vemurafenib (C - CIViC)	
	Glu-arg-lys (C - CGI)	
	Mab (C - CGI)	
	Panitumumab + Vemurafenib (C - CIViC)	
	Selumetinib (C - CGI)	
	Vemurafenib (C - CGI, CIViC)	
	0325901 (D - CIViC)	
	0879 + Dactolisib + Gdc + Nvp (D - CIViC)	
	119 (D - CIViC)	
	2-butanone (D - CGI)	

THE TABLE CONTINUES ON THE NEXT PAGE

Other potentially interesting off-label evidence

CONTINUED FROM THE PREVIOUS PAGE

EVENT	RESPONSIVE EVIDENCE	RESISTANCE EVIDENCE
	2-butanone (D - CGI)	
	957054-30-7 + Plx-4720 (D - CIViC)	
	Bevacizumab + Capecitabine + Vemurafenib (D - CIViC)	
	Braf (D - CGI)	
	Cetuximab + Gefitinib + Vemurafenib (D - CIViC)	
	Cetuximab + Sorafenib (D - CIViC)	
	Ci-1040 (D - CIViC)	
	Dasatinib (D - CIViC)	
	Nutlin + Plx-4720 (D - CIViC)	
	Panitumumab + Sorafenib (D - CIViC)	
	Plx-4720 (D - CGI)	
	Regorafenib (D - CIViC)	
	Selumetinib (D - CIViC)	
	Sorafenib (D - CIViC)	
	Vemurafenib (D - CIViC)	
PTEN partial loss	10-decarboxymethylaclacinomycin t (dcmat) (C - CGI)	Chemotherapy (B - CIViC)
	2206 (C - CIViC)	Byl-719 (C - CGI)
	Everolimus (C - CGI, CIViC)	Cetuximab + Mab (C - CGI)
	Parp inhibitors (C - CGI)	Mab + Panitumumab (C - CGI)
	Pik3cb (C - CGI)	Alpelisib (D - CIViC)
	154447-36-6 + Trastuzumab (D - CIViC)	Cisplatin (D - CIViC)
	2-butanone (D - CGI)	Gdc + Taselisib (D - CIViC)
	3'-azido-3'-deoxythymidine-5'-monophosphate (D - CGI)	Trastuzumab (D - CIViC)
	Alpelisib + Azd8186 + Enzalutamide (D - CIViC)	
	Azd5363 + Docetaxel (D - CIViC)	
	Azd8186 (D - CIViC)	
	Pi3k pathway inhibitor + ar antagonists (D - CGI)	
	Pi3k pathway inhibitors (D - CGI)	
	Temsirolimus (D - CIViC)	

Other potentially interesting trials

NONE

ORANGE Report
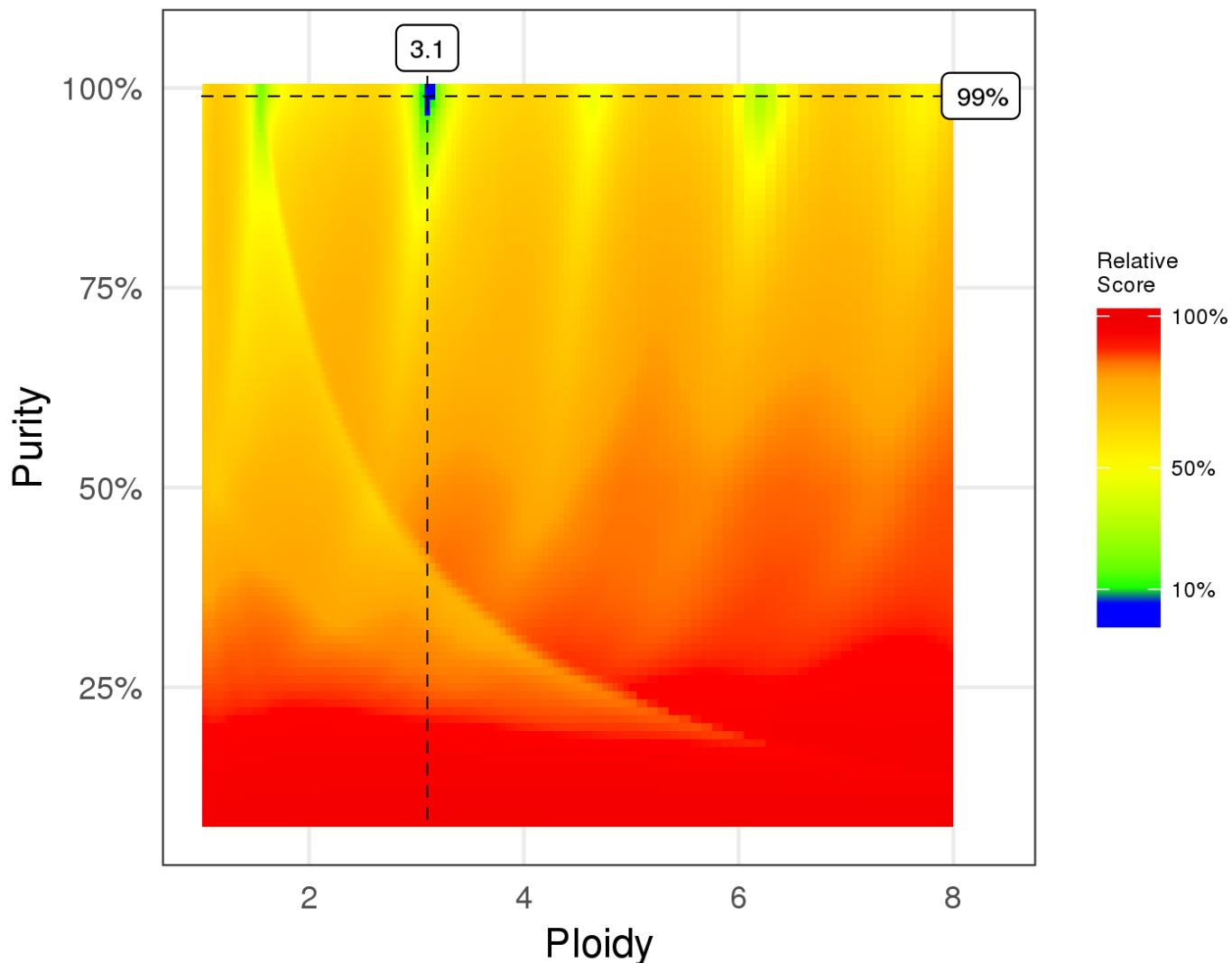
Quality Control

QC	REF GENOME	FIT METHOD	MEAN DEPTH	CONTAMINATION	UNS. SEGMENTS	DELETED GENES
PASS	V37	NORMAL	111	0%	0	4

Purity/Ploidy Scores

Flagstats

	UNIQUE RC	SECONDARY RC	SUPPLEMENTARY RC	MAPPED PROPORTION
Ref Sample	740406212	0	5742696	99%
Tumor Sample	2671674230	0	21477075	100%

ORANGE Report
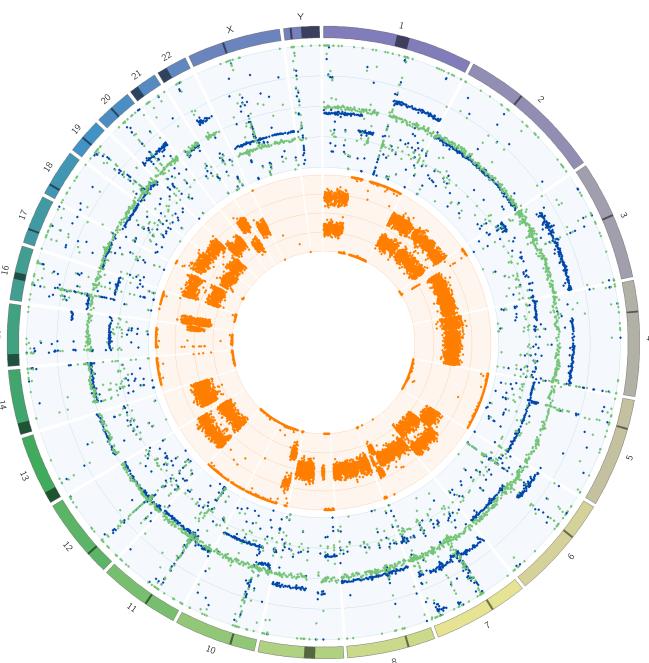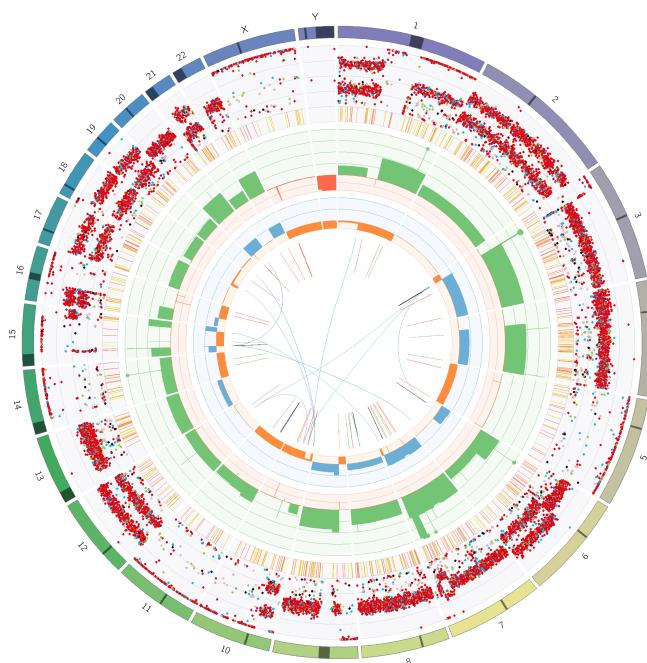
Coverage Stats

	MEAN COVERAGE	SD COVERAGE	MEDIAN COVERAGE	MAD COVERAGE
Ref Sample	31.4	10.1	32	5
Tumor Sample	108.1	35.0	109	24
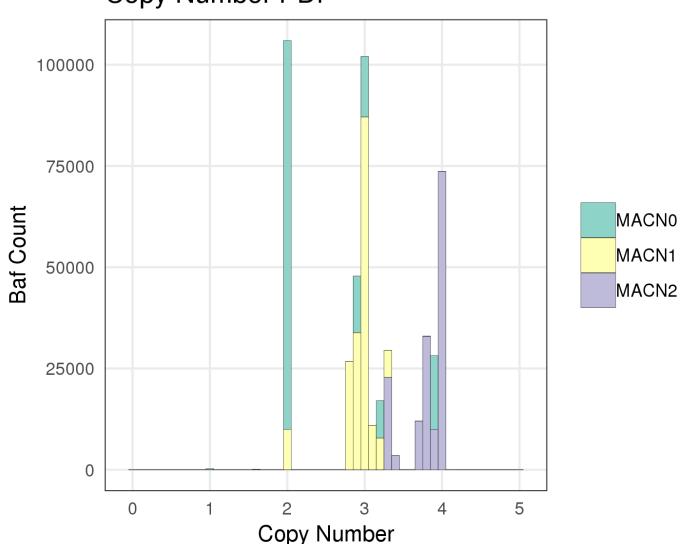
Excluded Percentages

	ADAPTER	BASEQ	CAPPED	DUPE	MAPQ	OVERLAP	UNPAIRED	TOTAL
Ref Sample	0%	0%	1%	11%	5%	1%	0%	18%
Tumor Sample	0%	0%	1%	15%	5%	1%	0%	22%
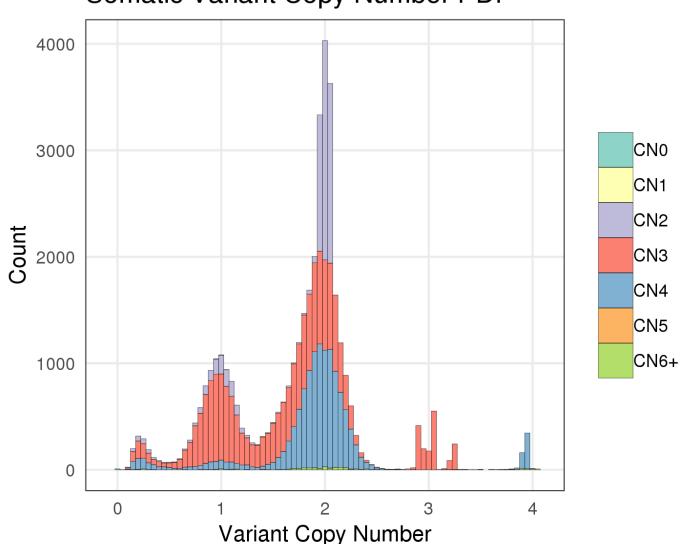
QC plots

Copy Number PDF

Somatic Variant Copy Number PDF

ORANGE Report
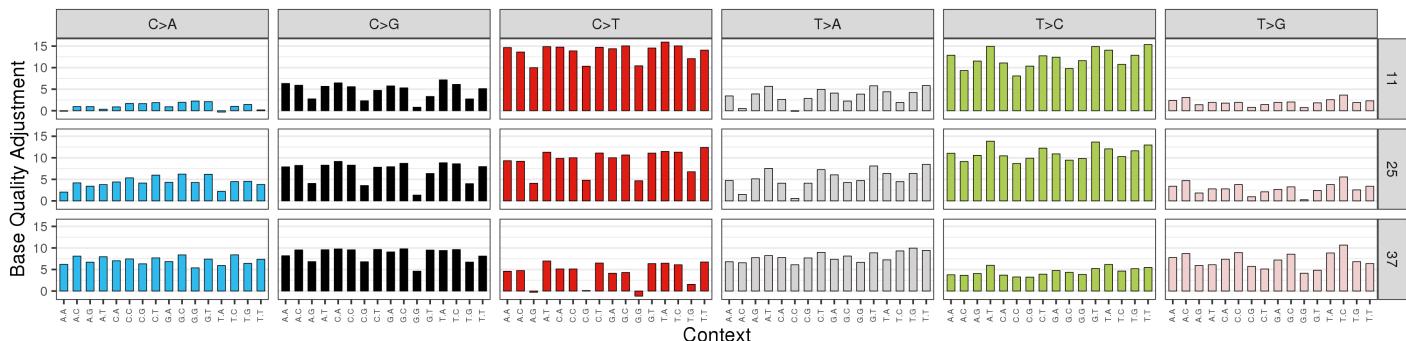
Reference Sample BQR plot

Tumor Sample BQR plot