

Supplement 1: Clinical characteristics- deleterious and likely deleterious mutations in TP53 gene

Genomic position	Protein change	DNA domain	Transcriptional activity in yeast (% of wild-type)	Relative fitness score (RFS)**	LFS/Chompret criteria	Index	Tumor subtype	Family history
c.375G>A	p.Thr125Thr	DNA binding domain	Unknown	$RFS \leq -1$	No	BC bilateral 39 yrs	HR pos, Her2 neg	none
c.542G>A	Arg181His	DNA binding domain	Medium reduction (50.3%)	$RFS \leq -1$	No	BC 46yrs	HR pos, Her2 neg	<u>mother</u> : BC 41 yrs <u>aunt (m)</u> : unknown cancer 40yrs
c.700T>C	Tyr234His	DNA binding domain	Very strong reduction (0.89%)	$RFS > -1$	Yes (Chompret criteria (1))	BC 33yrs and CRC 21yrs	HR neg HER2 pos	<u>brother</u> : glioblastoma 32yrs
c.717C>G	Asn239Lys	DNA binding domain	Moderate strong reduction (26.4%)	$RFS < -1$	Yes (classic LFS)	BC bilateral 32&34 yrs	32yrs: HR pos HER2 pos; 34yrs: TNBC	<u>brother</u> : lung cancer 36yrs <u>sister</u> : BC 26 yrs <u>sister</u> : BC 39 yrs; <u>corresponding son</u> : osteosarcoma 14 yrs and gastric cancer 35yrs <u>father</u> : brain tumor <50yrs
c.733G>A	Gly245Ser	DNA binding domain	Strong reduction (4.2%)	$RFS > -1$	Yes (Chompret criteria (1))	BC 49yrs	HR pos, Her2 neg	<u>sister</u> : bilateral BC 30&45 yrs and CRC 55yrs <u>brother</u> : ACC 56yrs, CRC 53yrs and prostate cancer 56 yrs; <u>father</u> : testicular cancer 32 yrs, prostate cancer 68yrs and lung cancer 71 yrs <u>uncle (p)</u> : brain tumor 48yrs <u>aunt (p)</u> : pancreas cancer 59 yrs
c.742C>T	Arg248Trp	DNA binding domain	Very strong reduction (0.09%)	$RFS > -1$	Yes (Chompret criteria (4))	BC 26 yrs	HR pos, Her2 pos	none
c.743G>A	p.Arg248Gln	DNA binding domain	Very strong reduction (0.21%)	$RFS > -1$	Yes (classic LFS)	BC 34yrs and osteosarcoma 16yrs	TNBC	<u>daughter</u> : neuroblastoma 2yrs
c.783-2A>G splice acceptor		DNA binding domain	Unknown	Unknown	Yes (Chompret criteria (4))	BC 35yrs	HR pos, Her2 neg	<u>sister</u> : BC 35yrs <u>mother</u> : BC: 28yrs <u>uncle (m)</u> : pharynx cancer 68yrs <u>grandmother (m)</u> : CRC 86 yrs
c.800G>C	p.Arg267 Pro	DNA binding domain	Very strong reduction (0.46%)	$RFS > -1$	Yes (Chompret criteria (4))	BC 22yrs	HR pos HER2 pos	none
c.817C>T	p.273Arg>Cys	DNA binding domain	Very strong reduction (0.76%)	$RFS > -1$	Yes (Chompret criteria (1))	BC 43 yrs	HR pos, Her2 pos	<u>daughter</u> : leukemia 4 yrs <u>brother</u> : rectum cancer 17yrs <u>mother</u> : BC 40 yrs and "abdominal cancer" 54 yrs <u>aunt (m)</u> : lung cancer 52 yrs

c.818G>A	Arg273His	DNA binding domain	Strong reduction (2.51%)	<i>RFS</i> > -1	Yes (Chompret criteria (4))	BC bilateral 28&32yrs	28yrs: TNBC; 32 yrs: HR pos, Her2 pos	<u>mother</u> : BC 28yrs
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Supplement 2: Clinical characteristics- variants of uncertain significance in *TP53* gene

Genomic position	Protein change	DNA domain	Transcriptional activity in yeast (% of wild-type)	Relative fitness score (RFS)**	LFS/Chompret criteria	Index	Tumor subtype	Family history
c.26G>A	p.Ser9Asn	Transactivation domain 1	(26.01%)	Unknown	No	DCIS 49 yrs	-	<u>father</u> : melanoma 70 yrs
c.29T>G	p.Val10Gly	Transactivation domain 1	(98.91%)	Unknown	Yes (Chompret criteria (4))	BC 28 yrs	HR pos HER2 pos	None
c.217G>A	p.Val73Met	Transactivation domain 2	(93.8%)	Unknown	No	DCIS 46 yrs	-	<u>mother</u> : BC 43 yrs <u>cousin (m)</u> : DCIS 45 yrs
c.255T>C	p.Pro85Pro	Transactivation domain 2	Unknown	Unknown	Yes (Chompret criteria (4))	BC 30 yrs	N.A.	none
c.266C>A	p.Pro89His	Transactivation domain 2	(5.96%)	Unknown	No	BC 45 yrs	HR pos HER2 neg	<u>father</u> : prostate cancer 62 yrs and pancreatic cancer 84 yrs
c.333G>T	p.Leu111Leu	DNA-binding domain	Unknown	<i>RFS</i> ≤-1	No	BC 39 yrs	HR pos HER2 neg	<u>mother</u> : BC bilateral 48 & 68 yrs <u>father</u> : CRC 51 yrs <u>grandmother (p)</u> : CRC 71 yrs
c.375+6T>C		DNA-binding domain	Unknown	Unknown	No	BC 45yrs	HR pos HER2 pos	<u>sister</u> : BC 41 yrs (negative for VUS TP53) <u>father</u> : CRC 65 yrs and pancreatic cancer 77 yrs
c.457C>T	p.Pro153Ser	DNA-binding domain	(83.55%)	<i>RFS</i> ≤-1	No	BC 39 yrs	HR pos HER2 neg	<u>sister</u> : BC 50yrs
c.470T>G	p.Val157Gly	DNA-binding domain	(9.2%)	<i>RFS</i> >-1	No	BC bilateral 33yrs	HR pos HER2 neg and HR neg HER2 pos	none
c.523C>T	p.Arg175 Cys	DNA binding domain	(84.36%)	<i>RFS</i> ≤-1	No	BC 48 yrs	HR pos Her2 neg	<u>mother</u> : BC 48yrs
c.529_546del	p.Pro177_Cys 182del	DNA binding domain	unknown	unknown	Yes (Chompret criteria (1))	BC bilateral 37&39yrs	37yrs: TNBC; 39yrs HR pos HER2 neg	<u>sister</u> : BC 32yrs <u>father</u> : choroidal melanoma 72yrs
c.572-574del	p.Pro191del	DNA-binding domain	Unknown	Unknown	Yes (Chompret criteria (1))	DCIS 45 yrs	-	<u>sister (twin)</u> : CRC 33 yrs <u>sister</u> : brain tumor 32 yrs <u>mother</u> : BC 53yrs and abdominal sarcoma 64yrs
c.663G>A	p.Glu221Glu	DNA-binding domain	Unknown	<i>RFS</i> ≤-1	No	BC 64 yrs	TNBC	<u>mother</u> : BC 67 yrs
c.847C>T	p.Arg283Cys	DNA-binding domain	(85.49%)	<i>RFS</i> ≤-1	No	BC 50 yrs	HR pos HER2 neg	<u>father</u> : plasmoytom 84yrs
c.927C>T	p.Pro309 Pro	Nuclear localization domain	Unknown	Unknown	No	BC bilateral 48&61yrs	BC 48yrs: HR pos HER2 neg; BC 61yrs: HR pos HER2 neg	<u>father</u> : gastric cancer 76 yrs <u>aunt (p)</u> : gastric cancer 75yrs
c.1014 C>T	p.Phe338Phe	tetramerization domain	Unknown	Unknown	No	DCIS 50 yrs	-	<u>sister</u> : BC bilateral 45 yrs <u>mother</u> : BC bilateral 81 & 85 yrs
c.1014 C>T	p.Phe338Phe	tetramerization domain	Unknown	Unknown	No	BC 34 yrs	HR pos HER 2	none

		n domain					neg	
c.1079G>C	p.Gly360Ala		(78.04%)	Unknown	No	BC bilateral 51&63 yrs	BC 51yrs: HR pos Her2 neg; BC 63 yrs: HR pos HER2 pos	<u>sister</u> : melanoma 50 yrs <u>brother</u> : prostate cancer <u>mother</u> : pleural carcinosis (unknown primaries) 75 yrs
c.1163A>C	p.Gln388Ala	regulatory domain	(112%)	Unknown	Yes (Chompret criteria (4))	BC 27 yrs	HR pos HER2 pos	Confirmed maternal inheritance, broader cancer diseases are missing
c.1171G>A	p.Asp391Asn	regulatory domain	(94.24%)	Unknown	No	BC 37 yrs	HR pos HER2 neg	None, parents healthy (mother s.a. bilateral Adnexectomy at the age of 30yrs)