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**Patient Name:** 홍길동2
**Gender:** F
**Sample ID:** 20250409-40100

**Primary Tumor Site:** Uterus
**Collection Date:** 2025-04-08

## Sample Cancer Type: Endometrial Carcinoma

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### Report Highlights

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## Relevant Endometrial Carcinoma Findings

| Gene | Finding |
|---|---|
| BRAF | ***BRAF p.(D594N) c.1780G>A*** |
| ERBB2 | None detected |
| NTRK1 | None detected |
| NTRK2 | None detected |
| NTRK3 | None detected |
| RET | ***RET p.(R912W) c.2734C>T*** |

| Genomic Alteration | Finding |
|---|---|
| Microsatellite Status | ***Microsatellite stable*** |
| Tumor Mutational Burden | ***232.48 Mut/Mb measured*** |

## Relevant Biomarkers

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IIC | *BRCA1 p.(R1443*) c.4327C>T*<br>BRCA1, DNA repair associated<br>Allele Frequency: 4.15%<br>Locus: chr17:41234451<br>Transcript: NM_007294.4 | None* | **abiraterone + niraparib** [1, 2 / II+]<br>**bevacizumab + olaparib** [1, 2 / II+]<br>**olaparib** [1, 2 / II+]<br>**rucaparib** [1 / II+]<br>**talazoparib + hormone therapy** [1 / II+]<br>bevacizumab + niraparib [II+]<br>niraparib [II+]<br>olaparib + hormone therapy [II+]<br>talazoparib [II+] | 13 |

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
**Line of therapy:** I: First-line therapy, II+: Other line of therapy
**Tier Reference:** Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

## Relevant Biomarkers (continued)

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IIC | *RET p.(R912W) c.2734C>T*<br>ret proto-oncogene<br>Allele Frequency: 25.95%<br>Locus: chr10:43617397<br>Transcript: NM_020975.6 | None* | **selpercatinib** [1]<br>**vandetanib** [2] | 2 |
| IIC | *ATM p.(R2849*) c.8545C>T, ATM p.(R457*) c.1369C>T, ATM p.(S131*) c.392C>A*<br>ATM serine/threonine kinase<br>Allele Frequency: 24.10%, 26.20%, 25.20% (3 variants)<br>Locus: chr11:108216596, chr11:108121561, chr11:108106457 (3 variants)<br>Transcript: NM_000051.4 | None* | **olaparib** [1 / II+]<br>**talazoparib + hormone therapy** [1 / II+] | 10 |
| IIC | *CDK12 p.(E519*) c.1555G>T*<br>cyclin dependent kinase 12<br>Allele Frequency: 25.39%<br>Locus: chr17:37627640<br>Transcript: NM_016507.4 | None* | **olaparib** [1 / II+]<br>**talazoparib + hormone therapy** [1 / II+] | 8 |
| IIC | *RAD54L p.(R609*) c.1825C>T*<br>RAD54 like (S. cerevisiae)<br>Allele Frequency: 28.18%<br>Locus: chr1:46740345<br>Transcript: NM_001142548.1 | None* | **olaparib** [1 / II+] | 5 |
| IIC | *ATR p.(R1951*) c.5851C>T*<br>ATR serine/threonine kinase<br>Allele Frequency: 23.99%<br>Locus: chr3:142215250<br>Transcript: NM_001184.4 | None* | **talazoparib + hormone therapy** [1 / II+] | 4 |
| IIC | *BRAF p.(D594N) c.1780G>A*<br>B-Raf proto-oncogene, serine/threonine kinase<br>Allele Frequency: 26.88%<br>Locus: chr7:140453155<br>Transcript: NM_004333.6 | None* | None* | 9 |
| IIC | *POLE p.(R1320*) c.3958C>T*<br>DNA polymerase epsilon, catalytic subunit<br>Allele Frequency: 10.18%<br>Locus: chr12:133225939<br>Transcript: NM_006231.4 | None* | None* | 3 |
| IIC | *MSH6 p.(R1076H) c.3227G>A*<br>mutS homolog 6<br>Allele Frequency: 16.16%<br>Locus: chr2:48030613<br>Transcript: NM_000179.3 | None* | None* | 2 |

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
**Line of therapy:** I: First-line therapy, II+: Other line of therapy
**Tier Reference:** Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

## Relevant Biomarkers (continued)

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IIC | *PDGFRA c.1559-1G>A*<br>platelet derived growth factor receptor alpha<br>Allele Frequency: 12.25%<br>Locus: chr4:55140697<br>Transcript: NM_006206.6 | None* | None* | 2 |
| IIC | *PTEN p.(G44D) c.131G>A, PTEN p.(R173H) c.518G>A*<br>phosphatase and tensin homolog<br>Allele Frequency: 18.17%, 24.25% (2 variants)<br>Locus: chr10:89653833, chr10:89711900 (2 variants)<br>Transcript: NM_000314.8 | None* | None* | 2 |
| IIC | *RAD52 p.(S346*) c.1037C>A*<br>RAD52 homolog, DNA repair protein<br>Allele Frequency: 53.33%<br>Locus: chr12:1023218<br>Transcript: NM_134424.4 | None* | None* | 2 |
| IIC | *TP53 p.(G244D) c.731G>A*<br>tumor protein p53<br>Allele Frequency: 24.99%<br>Locus: chr17:7577550<br>Transcript: NM_000546.6<br>**Prognostic significance:** ESMO: Poor | None* | None* | 2 |
| IIC | *XRCC2 p.(R215*) c.643C>T*<br>X-ray repair cross complementing 2<br>Allele Frequency: 26.90%<br>Locus: chr7:152345927<br>Transcript: NM_005431.2 | None* | None* | 2 |
| IIC | *FGFR2 p.(S252L) c.755C>T*<br>fibroblast growth factor receptor 2<br>Allele Frequency: 24.64%<br>Locus: chr10:123279677<br>Transcript: NM_000141.5 | None* | None* | 1 |
| IIC | *MAP2K4 p.(R134Q) c.401G>A*<br>mitogen-activated protein kinase kinase 4<br>Allele Frequency: 23.01%<br>Locus: chr17:11998899<br>Transcript: NM_003010.4 | None* | None* | 1 |
| IIC | *SMAD4 p.(R361H) c.1082G>A*<br>SMAD family member 4<br>Allele Frequency: 18.41%<br>Locus: chr18:48591919<br>Transcript: NM_005359.6 | None* | None* | 1 |

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
**Line of therapy:** I: First-line therapy, II+: Other line of therapy
**Tier Reference:** Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

## Relevant Biomarkers (continued)

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IIC | *SMARCA4 p.(R397*) c.1189C>T*<br>SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4<br>Allele Frequency: 28.11%<br>Locus: chr19:11100063<br>Transcript: NM_001128849.3 | None* | None* | 1 |
| IIC | *TSC2 c.1946+2T>C*<br>tuberous sclerosis 2<br>Allele Frequency: 25.66%<br>Locus: chr16:2121619<br>Transcript: NM_000548.5 | None* | None* | 1 |
| IIC | *VHL p.(*214W) c.642A>G*<br>von Hippel-Lindau tumor suppressor<br>Allele Frequency: 4.55%<br>Locus: chr3:10191649<br>Transcript: NM_000551.4 | None* | None* | 1 |

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
**Line of therapy:** I: First-line therapy, II+: Other line of therapy
**Tier Reference:** Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

### Prevalent cancer biomarkers without relevant evidence based on included data sources

*APC p.(R1858*) c.5572C>T, APC p.(R332*) c.994C>T, EIF1AX p.(R13C) c.37C>T, EZH2 c.2029+1G>A, Microsatellite stable, PIK3R1 p.(R348*) c.1042C>T, PPP2R1A p.(R183W) c.547C>T, TET2 p.(R1516*) c.4546C>T, ZRSR2 c.438+3A>G, CASP8 p.(R491*) c.1471C>T, UGT1A1 p.(G71R) c.211G>A, TGFBR2 p.(R485H) c.1454G>A, RASA2 p.(R526*) c.1576C>T, TRRAP p.(R816W) c.2446C>T, KMT2C p.(R110*) c.328C>T, CSMD3 p.(G1594*) c.4780G>T, CDH1 p.(K440N) c.1320G>T, ZFHX3 p.(E1888*) c.5662G>T, ARHGAP35 p.(R783*) c.2347C>T, Tumor Mutational Burden*

## Variant Details

### DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| RAD54L | p.(R609*) | c.1825C>T | . | chr1:46740345 | 28.18% | NM_001142548.1 | nonsense |
| MSH6 | p.(R1076H) | c.3227G>A | . | chr2:48030613 | 16.16% | NM_000179.3 | missense |
| CASP8 | p.(R491*) | c.1471C>T | . | chr2:202150030 | 2.35% | NM_001080125.2 | nonsense |
| UGT1A1 | p.(G71R) | c.211G>A | COSM4415616 | chr2:234669144 | 49.15% | NM_000463.3 | missense |
| VHL | p.(*214W) | c.642A>G | . | chr3:10191649 | 4.55% | NM_000551.4 | stoploss |
| TGFBR2 | p.(R485H) | c.1454G>A | . | chr3:30715721 | 23.35% | NM_001024847.2 | missense |
| RASA2 | p.(R526*) | c.1576C>T | . | chr3:141295934 | 14.85% | NM_006506.5 | nonsense |
| ATR | p.(R1951*) | c.5851C>T | . | chr3:142215250 | 23.99% | NM_001184.4 | nonsense |
| PDGFRA | p.(?) | c.1559-1G>A | . | chr4:55140697 | 12.25% | NM_006206.6 | unknown |
| TET2 | p.(R1516*) | c.4546C>T | COSM43420 | chr4:106196213 | 18.95% | NM_001127208.3 | nonsense |
| PIK3R1 | p.(R348*) | c.1042C>T | COSM85926 | chr5:67588951 | 24.22% | NM_181523.3 | nonsense |

# Variant Details (continued)

## DNA Sequence Variants (continued)

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| APC | p.(R332*) | c.994C>T | . | chr5:112154723 | 24.90% | NM_000038.6 | nonsense |
| APC | p.(R1858*) | c.5572C>T | . | chr5:112176863 | 28.25% | NM_000038.6 | nonsense |
| TRRAP | p.(R816W) | c.2446C>T | COSM248902 | chr7:98515126 | 23.11% | NM_001244580.1 | missense |
| BRAF | p.(D594N) | c.1780G>A | COSM27639 | chr7:140453155 | 26.88% | NM_004333.6 | missense |
| EZH2 | p.(?) | c.2029+1G>A | . | chr7:148507424 | 29.95% | NM_004456.5 | unknown |
| KMT2C | p.(R110*) | c.328C>T | . | chr7:152027747 | 3.30% | NM_170606.3 | nonsense |
| XRCC2 | p.(R215*) | c.643C>T | . | chr7:152345927 | 26.90% | NM_005431.2 | nonsense |
| CSMD3 | p.(G1594*) | c.4780G>T | . | chr8:113519035 | 27.53% | NM_198123.2 | nonsense |
| RET | p.(R912W) | c.2734C>T | COSM3415038 | chr10:43617397 | 25.95% | NM_020975.6 | missense |
| PTEN | p.(G44D) | c.131G>A | . | chr10:89653833 | 18.17% | NM_000314.8 | missense |
| PTEN | p.(R173H) | c.518G>A | COSM5039 | chr10:89711900 | 24.25% | NM_000314.8 | missense |
| FGFR2 | p.(S252L) | c.755C>T | . | chr10:123279677 | 24.64% | NM_000141.5 | missense |
| ATM | p.(S131*) | c.392C>A | . | chr11:108106457 | 25.20% | NM_000051.4 | nonsense |
| ATM | p.(R457*) | c.1369C>T | . | chr11:108121561 | 26.20% | NM_000051.4 | nonsense |
| ATM | p.(R2849*) | c.8545C>T | COSM922752 | chr11:108216596 | 24.10% | NM_000051.4 | nonsense |
| RAD52 | p.(S346*) | c.1037C>A | . | chr12:1023218 | 53.33% | NM_134424.4 | nonsense |
| POLE | p.(R1320*) | c.3958C>T | . | chr12:133225939 | 10.18% | NM_006231.4 | nonsense |
| TSC2 | p.(?) | c.1946+2T>C | . | chr16:2121619 | 25.66% | NM_000548.5 | unknown |
| CDH1 | p.(K440N) | c.1320G>T | . | chr16:68847398 | 26.34% | NM_004360.5 | missense |
| ZFHX3 | p.(E1888*) | c.5662G>T | . | chr16:72830919 | 30.55% | NM_006885.4 | nonsense |
| TP53 | p.(G244D) | c.731G>A | COSM10883 | chr17:7577550 | 24.99% | NM_000546.6 | missense |
| MAP2K4 | p.(R134Q) | c.401G>A | COSM98422 | chr17:11998899 | 23.01% | NM_003010.4 | missense |
| CDK12 | p.(E519*) | c.1555G>T | . | chr17:37627640 | 25.39% | NM_016507.4 | nonsense |
| BRCA1 | p.(R1443*) | c.4327C>T | . | chr17:41234451 | 4.15% | NM_007294.4 | nonsense |
| SMAD4 | p.(R361H) | c.1082G>A | COSM14122 | chr18:48591919 | 18.41% | NM_005359.6 | missense |
| SMARCA4 | p.(R397*) | c.1189C>T | . | chr19:11100063 | 28.11% | NM_001128849.3 | nonsense |
| ARHGAP35 | p.(R783*) | c.2347C>T | . | chr19:47424279 | 30.32% | NM_004491.5 | nonsense |
| PPP2R1A | p.(R183W) | c.547C>T | COSM51211 | chr19:52715982 | 24.05% | NM_014225.6 | missense |
| ZRSR2 | p.(?) | c.438+3A>G | . | chrX:15826397 | 16.40% | NM_005089.4 | unknown |
| EIF1AX | p.(R13C) | c.37C>T | COSM5899335 | chrX:20156720 | 19.40% | NM_001412.4 | missense |
| MIB2 | p.(G33E) | c.98G>A | . | chr1:1551982 | 23.35% | NM_080875.3 | missense |
| PGD | p.(S441N) | c.1322G>A | . | chr1:10479586 | 13.31% | NM_002631.4 | missense |
| SPEN | p.(Y559C) | c.1676A>G | . | chr1:16247405 | 27.06% | NM_015001.3 | missense |
| EPHA2 | p.(N744S) | c.2231A>G | . | chr1:16458653 | 12.77% | NM_004431.5 | missense |

# Variant Details (continued)

## DNA Sequence Variants (continued)

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| ARID1A | p.(L642I) | c.1924C>A | . | chr1:27087350 | 25.41% | NM_006015.6 | missense |
| MACF1 | p.(R269H) | c.806G>A | . | chr1:39748956 | 15.17% | NM_012090.5 | missense |
| MAGOH | p.(K61N) | c.183G>T | . | chr1:53699289 | 25.00% | NM_002370.4 | missense |
| C8A | p.(P454H) | c.1361C>A | . | chr1:57373767 | 15.70% | NM_000562.3 | missense |
| LRRC7 | p.(L296I) | c.886C>A | . | chr1:70452024 | 24.75% | NM_001370785.2 | missense |
| LRRC7 | p.(P1394H) | c.4181C>A | . | chr1:70518779 | 14.00% | NM_001370785.2 | missense |
| CDC7 | p.(S344P) | c.1030T>C | . | chr1:91980487 | 28.22% | NM_001134419.1 | missense |
| DPYD | p.(A784D) | c.2351C>A | . | chr1:97700499 | 24.34% | NM_000110.4 | missense |
| FNDC7 | p.(S219Y) | c.656C>A | . | chr1:109265014 | 26.78% | NM_001144937.3 | missense |
| PTGFRN | p.(S840P) | c.2518T>C | . | chr1:117529467 | 4.85% | NM_020440.4 | missense |
| NOTCH2 | p.(Q1732H) | c.5196G>T | . | chr1:120464876 | 23.71% | NM_024408.4 | missense |
| NOTCH2 | p.(N1642T) | c.4925A>C | . | chr1:120465336 | 26.10% | NM_024408.4 | missense |
| SDHC | p.(S19N) | c.56G>A | . | chr1:161293439 | 19.91% | NM_003001.5 | missense |
| DDR2 | p.(E795D) | c.2385A>C | . | chr1:162748471 | 5.21% | NM_006182.4 | missense |
| ABL2 | p.(T337A) | c.1009A>G | . | chr1:179087891 | 5.90% | NM_005158.5 | missense |
| BRINP3 | p.(A437T) | c.1309G>A | . | chr1:190068140 | 4.45% | NM_199051.3 | missense |
| CDC73 | p.(R513W) | c.1537C>T | . | chr1:193218979 | 21.65% | NM_024529.5 | missense |
| NSL1 | p.(R258I) | c.773G>T | . | chr1:212911823 | 26.48% | NM_015471.4 | missense |
| PARP1 | p.(P850S) | c.2548C>T | . | chr1:226552813 | 13.50% | NM_001618.4 | missense |
| OR6F1 | p.(T300I) | c.899C>T | . | chr1:247875159 | 22.66% | NM_001005286.1 | missense |
| OR6F1 | p.(C127*) | c.381C>A | . | chr1:247875677 | 2.60% | NM_001005286.1 | nonsense |
| OR2L13 | p.(L113I) | c.337C>A | . | chr1:248263014 | 28.96% | NM_175911.3 | missense |
| WDR35 | p.(Q984H) | c.2952G>T | . | chr2:20131075 | 28.31% | NM_001006657.2 | missense |
| ASXL2 | p.(D1338G) | c.4013A>G | . | chr2:25965193 | 19.92% | NM_018263.6 | missense |
| MSH6 | p.(K920N) | c.2760G>T | . | chr2:48027882 | 4.15% | NM_000179.3 | missense |
| MSH6 | p.(R976H) | c.2927G>A | . | chr2:48028049 | 50.73% | NM_000179.3 | missense |
| NRXN1 | p.(D1196N) | c.3586G>A | . | chr2:50318593 | 24.01% | NM_004801.5 | missense |
| LRRTM1 | p.(D317N) | c.949G>A | . | chr2:80529996 | 24.05% | NM_178839.5 | missense |
| REV1 | p.(G141C) | c.421G>T | . | chr2:100058861 | 2.25% | NM_016316.4 | missense |
| MARCO | p.(L236I) | c.706C>A | . | chr2:119735451 | 4.35% | NM_006770.4 | missense |
| ACVR2A | p.(D322G) | c.965A>G | . | chr2:148677801 | 29.76% | NM_001616.5 | missense |
| PPIG | p.(K702N) | c.2106G>T | . | chr2:170493874 | 5.06% | NM_004792.3 | missense |
| CASP8 | p.(G384D) | c.1151G>A | . | chr2:202149710 | 24.54% | NM_001080125.2 | missense |
| BMPR2 | p.(A35T) | c.103G>A | . | chr2:203329558 | 3.30% | NM_001204.7 | missense |

# Variant Details (continued)

## DNA Sequence Variants (continued)

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| BMPR2 | p.(A35V) | c.104C>T | . | chr2:203329559 | 19.79% | NM_001204.7 | missense |
| CUL3 | p.(A493T) | c.1477G>A | . | chr2:225367690 | 12.07% | NM_003590.5 | missense |
| CUL3 | p.(?) | c.378+1G>A | . | chr2:225400244 | 24.48% | NM_003590.5 | unknown |
| MTERF4 | p.(R190C) | c.568C>T | . | chr2:242036795 | 29.55% | NM_182501.4 | missense |
| CNTN6 | p.(S411F) | c.1232C>T | . | chr3:1371487 | 25.89% | NM_014461.4 | missense |
| FANCD2 | p.(A291T) | c.871G>A | . | chr3:10084330 | 3.46% | NM_033084.6 | missense |
| VHL | p.(E42D) | c.126G>T | . | chr3:10183657 | 20.08% | NM_000551.4 | missense |
| PP2D1 | p.([Y259=;A260T]) | c.777_778delCGinsTA | . | chr3:20042834 | 26.33% | NM_001252657.2 | synonymous, missense |
| CTNNB1 | p.(A360T) | c.1078G>A | . | chr3:41268840 | 4.05% | NM_001904.4 | missense |
| SETD2 | p.(N811H) | c.2431A>C | . | chr3:47163695 | 3.65% | NM_014159.7 | missense |
| PBRM1 | p.(P227H) | c.680C>A | . | chr3:52685792 | 21.97% | NM_018313.5 | missense |
| PBRM1 | p.(L143V) | c.427T>G | . | chr3:52696250 | 2.75% | NM_018313.5 | missense |
| CASR | p.(A12E) | c.35C>A | . | chr3:121973071 | 25.16% | NM_001178065.2 | missense |
| KALRN | p.(W299*) | c.897G>A | . | chr3:123988036 | 20.87% | NM_001024660.4 | nonsense |
| RASA2 | p.(Y762H) | c.2284T>C | . | chr3:141328320 | 30.91% | NM_006506.5 | missense |
| PIK3CA | p.(L339I) | c.1015C>A | . | chr3:178921533 | 24.81% | NM_006218.4 | missense |
| TP63 | p.(I482T) | c.1445T>C | . | chr3:189604278 | 14.47% | NM_003722.5 | missense |
| GAK | p.(D1179N) | c.3535G>A | . | chr4:844846 | 24.35% | NM_005255.4 | missense |
| KIT | p.(L706I) | c.2116C>A | . | chr4:55595626 | 26.96% | NM_000222.3 | missense |
| KDR | p.(K1110N) | c.3330G>T | . | chr4:55955615 | 18.21% | NM_002253.3 | missense |
| ADGRL3 | p.(G208V) | c.623G>T | . | chr4:62598700 | 25.41% | NM_015236.6 | missense |
| TET2 | p.(A251T) | c.751G>A | . | chr4:106155850 | 2.45% | NM_001127208.3 | missense |
| ALPK1 | p.(G733D) | c.2198G>A | . | chr4:113352901 | 4.50% | NM_001102406.2 | missense |
| MAML3 | p.(Q491Pfs*32) | c.1472_1506delAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsCAGCAGCAGCAGCAGCAGCAA | . | chr4:140811084 | 91.30% | NM_018717.5 | frameshift Block Substitution |
| MAML3 | p.(Q488_Q494delinsHDS) | c.1464_1506delGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsCGACAGCCAGCAGCAGCAGCAGCAGCAA | . | chr4:140811084 | 8.70% | NM_018717.5 | nonframeshift Block Substitution |
| INPP4B | p.(S324P) | c.970T>C | . | chr4:143129680 | 26.52% | NM_001101669.3 | missense |
| FBXW7 | p.(A305V) | c.914C>T | . | chr4:153253819 | 23.76% | NM_033632.3 | missense |
| FBXW7 | p.(S182Y) | c.545C>A | . | chr4:153271233 | 35.16% | NM_033632.3 | missense |

# Variant Details (continued)

## DNA Sequence Variants (continued)

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| FAT1 | p.(R3661C) | c.10981C>T | . | chr4:187524699 | 23.72% | NM_005245.4 | missense |
| FAT1 | p.(K390N) | c.1170G>T | . | chr4:187629812 | 27.76% | NM_005245.4 | missense |
| TERT | p.(S559A) | c.1675T>G | . | chr5:1282638 | 15.98% | NM_198253.3 | missense |
| MAP3K1 | p.(S416P) | c.1246T>C | . | chr5:56161749 | 4.95% | NM_005921.2 | missense |
| MAP3K1 | p.(S422P) | c.1264T>C | . | chr5:56161767 | 5.50% | NM_005921.2 | missense |
| MAP3K1 | p.(E567G) | c.1700A>G | . | chr5:56170872 | 3.70% | NM_005921.2 | missense |
| MAP3K1 | p.(S796P) | c.2386T>C | . | chr5:56177413 | 17.42% | NM_005921.2 | missense |
| PIK3R1 | p.(N406S) | c.1217A>G | . | chr5:67589229 | 3.60% | NM_181523.3 | missense |
| MSH3 | p.(A61_P63dup) | c.189_190insGCAGCGCCC | . | chr5:79950735 | 30.79% | NM_002439.5 | nonframeshift Insertion |
| SSBP2 | p.(P293T) | c.877C>A | . | chr5:80736452 | 25.01% | NM_001256732.2 | missense |
| RASA1 | p.(R245H) | c.734G>A | . | chr5:86628365 | 4.85% | NM_002890.3 | missense |
| ERAP1 | p.(E797D) | c.2391G>T | . | chr5:96117453 | 24.33% | NM_016442.4 | missense |
| WDR36 | p.(V205A) | c.614T>C | . | chr5:110439501 | 22.14% | NM_139281.3 | missense |
| APC | p.(P112H) | c.335C>A | . | chr5:112103000 | 25.71% | NM_000038.6 | missense |
| APC | p.(S996R) | c.2988T>G | . | chr5:112174279 | 3.25% | NM_000038.6 | missense |
| APC | p.(P2802S) | c.8404C>T | . | chr5:112179695 | 22.75% | NM_000038.6 | missense |
| APC | p.(S2842F) | c.8525C>T | . | chr5:112179816 | 24.20% | NM_000038.6 | missense |
| RAD50 | p.(N1063D) | c.3187A>G | . | chr5:131953784 | 28.18% | NM_005732.4 | missense |
| FAM71B | p.(T591A) | c.1771A>G | . | chr5:156589505 | 26.80% | NM_130899.3 | missense |
| SFXN1 | p.(A129V) | c.386C>T | . | chr5:174937162 | 12.91% | NM_022754.7 | missense |
| ADAMTS2 | p.(R424H) | c.1271G>A | . | chr5:178581161 | 23.05% | NM_014244.5 | missense |
| DDR1 | p.(R248L) | c.743G>T | . | chr6:30859856 | 4.00% | NM_001954.4 | missense |
| TCTE1 | p.(A9S) | c.25G>T | . | chr6:44255538 | 32.75% | NM_182539.4 | missense |
| PRDM1 | p.(S249N) | c.746G>A | . | chr6:106552781 | 2.85% | NM_001198.4 | missense |
| FYN | p.(D366G) | c.1097A>G | . | chr6:112015844 | 20.75% | NM_153047.4 | missense |
| HDAC2 | p.(R366C) | c.1096C>T | . | chr6:114265570 | 25.61% | NM_001527.4 | missense |
| ROS1 | p.(N2112K) | c.6336T>A | . | chr6:117631342 | 23.37% | NM_002944.3 | missense |
| ROS1 | p.(W119*) | c.357G>A | . | chr6:117725524 | 25.08% | NM_002944.3 | nonsense |
| TNFAIP3 | p.(A175T) | c.523G>A | . | chr6:138196861 | 25.46% | NM_001270507.2 | missense |
| TNFAIP3 | p.(D279Y) | c.835G>T | . | chr6:138198242 | 27.01% | NM_001270507.2 | missense |
| OPRM1 | p.([G39=;N40D]) | c.117_118delCAinsTG | . | chr6:154360796 | 31.65% | NM_001008505.2 | synonymous, missense |
| ARID1B | p.(L1730I) | c.5188C>A | . | chr6:157525044 | 27.13% | NM_001371656.1 | missense |

# Variant Details (continued)

## DNA Sequence Variants (continued)

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| ARID1B | p.(A2289V) | c.6866C>T | . | chr6:157528892 | 13.84% | NM_001371656.1 | missense |
| MAP3K4 | p.(K1315Q) | c.3943A>C | . | chr6:161527632 | 24.81% | NM_005922.4 | missense |
| MAP3K4 | p.(A1510T) | c.4528G>A | . | chr6:161533708 | 13.22% | NM_005922.4 | missense |
| CARD11 | p.(R576H) | c.1727G>A | . | chr7:2968259 | 15.72% | NM_032415.7 | missense |
| CARD11 | p.(R424W) | c.1270C>T | . | chr7:2976742 | 13.81% | NM_032415.7 | missense |
| HDAC9 | p.(T896I) | c.2687C>T | . | chr7:18914103 | 26.61% | NM_178425.3 | missense |
| PDE1C | p.(P553L) | c.1658C>T | . | chr7:31862791 | 24.34% | NM_001191058.4 | missense |
| PDE1C | p.(A320V) | c.959C>T | . | chr7:31890327 | 17.36% | NM_001191058.4 | missense |
| GALNT17 | p.(T463I) | c.1388C>T | . | chr7:71135078 | 23.35% | NM_022479.3 | missense |
| ABCB1 | p.(L754S) | c.2261T>C | . | chr7:87170731 | 19.15% | NM_000927.4 | missense |
| LMTK2 | p.(N675D) | c.2023A>G | . | chr7:97821800 | 4.01% | NM_014916.4 | missense |
| POT1 | p.(D563G) | c.1688A>G | . | chr7:124465410 | 6.08% | NM_015450.3 | missense |
| SMO | p.(W339*) | c.1017G>A | . | chr7:128846087 | 25.00% | NM_005631.5 | nonsense |
| BRAF | p.(P632S) | c.1894C>T | . | chr7:140449185 | 24.00% | NM_004333.6 | missense |
| KMT2C | p.(A4717V) | c.14150C>T | . | chr7:151842262 | 25.36% | NM_170606.3 | missense |
| KMT2C | p.(P4033T) | c.12097C>A | . | chr7:151851394 | 24.00% | NM_170606.3 | missense |
| KMT2C | p.(A3148D) | c.9443C>A | . | chr7:151868359 | 13.12% | NM_170606.3 | missense |
| KMT2C | p.(R1705H) | c.5114G>A | . | chr7:151880210 | 24.40% | NM_170606.3 | missense |
| KMT2C | p.(E1181A) | c.3542A>C | . | chr7:151917778 | 24.35% | NM_170606.3 | missense |
| KMT2C | p.(?) | c.2977-1G>T | . | chr7:151921702 | 23.40% | NM_170606.3 | unknown |
| FGFR1 | p.(D678G) | c.2033A>G | . | chr8:38272334 | 3.95% | NM_001174067.1 | missense |
| CA3 | p.(D41G) | c.122A>G | . | chr8:86352028 | 16.21% | NM_005181.4 | missense |
| DCAF4L2 | p.(R172H) | c.515G>A | . | chr8:88885685 | 24.05% | NM_152418.4 | missense |
| RUNX1T1 | p.(A512T) | c.1534G>A | . | chr8:92982924 | 27.76% | NM_001198634.2 | missense |
| CSMD3 | p.(D2726A) | c.8177A>C | . | chr8:113317039 | 4.11% | NM_198123.2 | missense |
| CSMD3 | p.(D779N) | c.2335G>A | . | chr8:113697782 | 23.03% | NM_198123.2 | missense |
| FAM135B | p.(L179*) | c.536T>A | . | chr8:139263090 | 6.47% | NM_015912.4 | nonsense |
| FAM135B | p.(S54N) | c.161G>A | . | chr8:139278082 | 26.40% | NM_015912.4 | missense |
| ZNF623 | p.([C125=;N126D]) | c.375_376delCAinsTG | . | chr8:144732417 | 17.77% | NM_014789.3 | synonymous, missense |
| JAK2 | p.(E274K) | c.820G>A | . | chr9:5054768 | 27.66% | NM_004972.4 | missense |
| FANCG | p.(R548Q) | c.1643G>A | . | chr9:35074485 | 23.54% | NM_004629.2 | missense |
| ANXA1 | p.(K128T) | c.383A>C | . | chr9:75775291 | 24.61% | NM_000700.3 | missense |
| FANCC | p.(V508A) | c.1523T>C | . | chr9:97869358 | 15.22% | NM_000136.3 | missense |

# Variant Details (continued)

## DNA Sequence Variants (continued)

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| PTCH1 | p.(A1157V) | c.3470C>T | . | chr9:98212202 | 17.08% | NM_000264.5 | missense |
| PTCH1 | p.(G1129D) | c.3386G>A | . | chr9:98215823 | 24.51% | NM_000264.5 | missense |
| PTCH1 | p.(D535G) | c.1604A>G | . | chr9:98238440 | 22.00% | NM_000264.5 | missense |
| ABL1 | p.(T389P) | c.1165A>C | . | chr9:133750334 | 20.39% | NM_005157.6 | missense |
| GLT6D1 | p.(G234D) | c.701G>A | . | chr9:138516073 | 4.40% | NM_182974.3 | missense |
| LARP4B | p.(A306T) | c.916G>A | . | chr10:875534 | 24.23% | NM_015155.3 | missense |
| BEND7 | p.(R156Q) | c.467G>A | . | chr10:13534825 | 41.49% | NM_152751.3 | missense |
| GPR158 | p.(C330Y) | c.989G>A | . | chr10:25510067 | 4.50% | NM_020752.3 | missense |
| GPR158 | p.(G497R) | c.1489G>A | . | chr10:25839989 | 26.29% | NM_020752.3 | missense |
| ARMC4 | p.(E206*) | c.616G>T | . | chr10:28273179 | 27.22% | NM_018076.5 | nonsense |
| ARMC4 | p.(E166G) | c.497A>G | . | chr10:28274026 | 17.90% | NM_018076.5 | missense |
| A1CF | p.(T512M) | c.1535C>T | . | chr10:52569752 | 24.94% | NM_138932.2 | missense |
| A1CF | p.(L478I) | c.1432C>A | . | chr10:52570852 | 15.66% | NM_138932.2 | missense |
| ARID5B | p.(E238K) | c.712G>A | . | chr10:63760059 | 28.18% | NM_032199.3 | missense |
| ARID5B | p.(D742G) | c.2225A>G | . | chr10:63851447 | 27.24% | NM_032199.3 | missense |
| ARID5B | p.(K1070T) | c.3209A>C | . | chr10:63852431 | 25.30% | NM_032199.3 | missense |
| WAPL | p.(S117I) | c.350G>T | . | chr10:88277477 | 14.90% | NM_015045.5 | missense |
| FAS | p.(D93N) | c.277G>A | . | chr10:90767537 | 24.20% | NM_000043.6 | missense |
| FAS | p.(R103K) | c.308G>A | . | chr10:90767568 | 23.44% | NM_000043.6 | missense |
| CYP2C9 | p.(E154D) | c.462G>T | . | chr10:96702079 | 16.00% | NM_000771.4 | missense |
| TCF7L2 | p.(A378T) | c.1132G>A | . | chr10:114911614 | 24.71% | NM_001146274.2 | missense |
| FGFR2 | p.(S788G) | c.2362A>G | . | chr10:123239475 | 3.21% | NM_000141.5 | missense |
| OR5L1 | p.(I49M) | c.147T>G | . | chr11:55579089 | 47.84% | NM_001004738.2 | missense |
| OR5L2 | p.(S233N) | c.698G>A | . | chr11:55595392 | 19.28% | NM_001004739.1 | missense |
| MEN1 | p.([D423=;G424D]) | c.1269_1271delCGGinsTGA | . | chr11:64572600 | 27.64% | NM_000244.3 | synonymous, missense |
| LRP5 | p.(E743K) | c.2227G>A | . | chr11:68177517 | 25.51% | NM_002335.4 | missense |
| FGF3 | p.(R192W) | c.574C>T | . | chr11:69625219 | 15.00% | NM_005247.4 | missense |
| EMSY | p.(P2S) | c.4C>T | . | chr11:76157986 | 22.56% | NM_020193.4 | missense |
| ATM | p.(I389M) | c.1167A>G | . | chr11:108119761 | 24.01% | NM_000051.4 | missense |
| ATM | p.(A1699V) | c.5096C>T | . | chr11:108170531 | 22.34% | NM_000051.4 | missense |
| ATM | p.(Y2437C) | c.7310A>G | . | chr11:108200943 | 24.41% | NM_000051.4 | missense |
| ATM | p.(P2793S) | c.8377C>T | . | chr11:108214057 | 14.90% | NM_000051.4 | missense |
| ATM | p.(L2952I) | c.8854C>A | . | chr11:108235812 | 25.31% | NM_000051.4 | missense |

# Variant Details (continued)

## DNA Sequence Variants (continued)

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| KMT2A | p.(R427W) | c.1279C>T | . | chr11:118343153 | 29.01% | NM_001197104.2 | missense |
| CHEK1 | p.(S467N) | c.1400G>A | . | chr11:125525184 | 20.41% | NM_001274.5 | missense |
| CAPRIN2 | p.(C534R) | c.1600T>C | . | chr12:30881764 | 3.55% | NM_001002259.2 | missense |
| ARID2 | p.(L316I) | c.946C>A | . | chr12:46230697 | 26.00% | NM_152641.4 | missense |
| ARID2 | p.(A496V) | c.1487C>T | . | chr12:46233268 | 4.50% | NM_152641.4 | missense |
| KMT2D | p.(R2847H) | c.8540G>A | . | chr12:49432599 | 4.45% | NM_003482.4 | missense |
| KMT2D | p.(P1439L) | c.4316C>T | . | chr12:49440494 | 24.31% | NM_003482.4 | missense |
| SP1 | p.(A506V) | c.1517C>T | . | chr12:53777248 | 5.46% | NM_138473.3 | missense |
| PPFIA2 | p.(R951H) | c.2852G>A | . | chr12:81688687 | 3.20% | NM_003625.5 | missense |
| ACACB | p.(G2069D) | c.6206G>A | . | chr12:109693984 | 5.30% | NM_001093.4 | missense |
| TBX3 | p.(A609T) | c.1825G>A | . | chr12:115110053 | 15.77% | NM_016569.4 | missense |
| TBX3 | p.(A470V) | c.1409C>T | . | chr12:115112331 | 2.40% | NM_016569.4 | missense |
| KSR2 | p.(S399P) | c.1195T>C | . | chr12:118020141 | 13.98% | NM_173598.6 | missense |
| HNF1A | p.(A269V) | c.806C>T | . | chr12:121432059 | 32.30% | NM_000545.8 | missense |
| POLE | p.(A1528D) | c.4583C>A | . | chr12:133219551 | 4.80% | NM_006231.4 | missense |
| POLE | p.(E978G) | c.2933A>G | . | chr12:133237682 | 27.11% | NM_006231.4 | missense |
| POLE | p.(T880M) | c.2639C>T | . | chr12:133240657 | 14.76% | NM_006231.4 | missense |
| LNX2 | p.(A215D) | c.644C>A | . | chr13:28143177 | 26.09% | NM_153371.4 | missense |
| FLT3 | p.(E708*) | c.2122G>T | . | chr13:28601310 | 22.87% | NM_004119.3 | nonsense |
| BRCA2 | p.(T751A) | c.2251A>G | . | chr13:32910743 | 23.86% | NM_000059.4 | missense |
| BRCA2 | p.(R898M) | c.2693G>T | . | chr13:32911185 | 23.96% | NM_000059.4 | missense |
| BRCA2 | p.(G934C) | c.2800G>T | . | chr13:32911292 | 27.10% | NM_000059.4 | missense |
| BRCA2 | p.(E2476D) | c.7428A>T | . | chr13:32929418 | 25.91% | NM_000059.4 | missense |
| FREM2 | p.(E1079*) | c.3235G>T | . | chr13:39264716 | 25.94% | NM_207361.6 | nonsense |
| TPP2 | p.(D34A) | c.101A>C | . | chr13:103249489 | 23.58% | NM_003291.4 | missense |
| CUL4A | p.(A301T) | c.901G>A | . | chr13:113891189 | 14.75% | NM_001008895.4 | missense |
| CUL4A | p.(V352I) | c.1054G>A | . | chr13:113897300 | 2.30% | NM_001008895.4 | missense |
| CDC16 | p.(E97D) | c.291G>T | . | chr13:115004875 | 26.68% | NM_001078645.3 | missense |
| FANCM | p.(D807G) | c.2420A>G | . | chr14:45644377 | 18.56% | NM_020937.4 | missense |
| SIX1 | p.(T165P) | c.493A>C | . | chr14:61115415 | 20.91% | NM_005982.4 | missense |
| MLH3 | p.(A410T) | c.1228G>A | . | chr14:75515131 | 26.91% | NM_001040108.2 | missense |
| MLH3 | p.(V207I) | c.619G>A | . | chr14:75515740 | 26.85% | NM_001040108.2 | missense |
| TTLL5 | p.(A1251T) | c.3751G>A | . | chr14:76368495 | 3.90% | NM_015072.5 | missense |
| DICER1 | p.(L1748M) | c.5242C>A | . | chr14:95560347 | 3.90% | NM_030621.4 | missense |

# Variant Details (continued)

## DNA Sequence Variants (continued)

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| DICER1 | p.(S3I) | c.8G>T | . | chr14:95599788 | 15.05% | NM_030621.4 | missense |
| OR4M2 | p.(C142Y) | c.425G>A | . | chr15:22369000 | 43.45% | NM_001004719.2 | missense |
| MGA | p.(I193V) | c.577A>G | . | chr15:41961669 | 15.65% | NM_001164273.1 | missense |
| MGA | p.(N435S) | c.1304A>G | . | chr15:41988512 | 27.36% | NM_001164273.1 | missense |
| MGA | p.(E563K) | c.1687G>A | . | chr15:41988895 | 26.14% | NM_001164273.1 | missense |
| MGA | p.(A1870D) | c.5609C>A | . | chr15:42041414 | 25.06% | NM_001164273.1 | missense |
| CD276 | p.(*535C) | c.1605A>C | . | chr15:74005297 | 3.55% | NM_001024736.2 | stoploss |
| CHRNA3 | p.(E48K) | c.142G>A | . | chr15:78911198 | 26.87% | NM_000743.5 | missense |
| FANCI | p.(D935E) | c.2805T>G | . | chr15:89843532 | 16.47% | NM_001113378.2 | missense |
| BLM | p.(S1025I) | c.3074G>T | . | chr15:91337451 | 25.68% | NM_000057.4 | missense |
| CREBBP | p.(A2336T) | c.7006G>A | . | chr16:3778042 | 22.91% | NM_004380.3 | missense |
| CREBBP | p.(R1866C) | c.5596C>T | . | chr16:3779452 | 15.94% | NM_004380.3 | missense |
| CREBBP | p.(R1810H) | c.5429G>A | . | chr16:3779619 | 22.16% | NM_004380.3 | missense |
| CREBBP | p.(K1141T) | c.3422A>C | . | chr16:3807997 | 20.03% | NM_004380.3 | missense |
| CREBBP | p.(S945L) | c.2834C>T | . | chr16:3820617 | 23.75% | NM_004380.3 | missense |
| CREBBP | p.(A487V) | c.1460C>T | . | chr16:3832798 | 26.00% | NM_004380.3 | missense |
| CBFB | p.(E162D) | c.486G>T | . | chr16:67116202 | 25.58% | NM_022845.3 | missense |
| CTCF | p.(G181E) | c.542G>A | . | chr16:67645277 | 5.67% | NM_006565.4 | missense |
| CDH1 | p.(P42S) | c.124C>T | . | chr16:68772275 | 17.46% | NM_004360.5 | missense |
| ZFHX3 | p.(A3537T) | c.10609G>A | . | chr16:72821566 | 4.15% | NM_006885.4 | missense |
| ZFHX3 | p.(C2713F) | c.8138G>T | . | chr16:72828443 | 18.93% | NM_006885.4 | missense |
| ZFHX3 | p.(A1576T) | c.4726G>A | . | chr16:72831855 | 21.63% | NM_006885.4 | missense |
| ZFHX3 | p.(G1080C) | c.3238G>T | . | chr16:72923840 | 25.05% | NM_006885.4 | missense |
| ZFHX3 | p.(N172S) | c.515A>G | . | chr16:72993530 | 2.66% | NM_006885.4 | missense |
| FANCA | p.(I1234S) | c.3701T>G | . | chr16:89809272 | 20.50% | NM_000135.4 | missense |
| RPA1 | p.(D328N) | c.982G>A | . | chr17:1782883 | 21.55% | NM_002945.5 | missense |
| TP53 | p.(*394W) | c.1182A>G | . | chr17:7572927 | 18.80% | NM_000546.6 | stoploss |
| MAP2K4 | p.(R287C) | c.859C>T | . | chr17:12028656 | 23.45% | NM_003010.4 | missense |
| NCOR1 | p.(E560K) | c.1678G>A | . | chr17:16024540 | 23.45% | NM_006311.4 | missense |
| NF1 | p.(A422T) | c.1264G>A | . | chr17:29533261 | 23.30% | NM_001042492.3 | missense |
| NF1 | p.(S1249F) | c.3746C>T | . | chr17:29562666 | 25.89% | NM_001042492.3 | missense |
| NF1 | p.(Y1948C) | c.5843A>G | . | chr17:29661886 | 25.83% | NM_001042492.3 | missense |
| RAD51D | p.(A132S) | c.394G>T | . | chr17:33430281 | 18.84% | NM_133629.3 | missense |
| BRCA1 | p.(Q1323H) | c.3969A>C | . | chr17:41243579 | 4.05% | NM_007294.4 | missense |

# Variant Details (continued)

## DNA Sequence Variants (continued)

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| BRCA1 | p.(R320I) | c.959G>T | . | chr17:41246589 | 25.68% | NM_007294.4 | missense |
| BRCA1 | p.(S104N) | c.311G>A | . | chr17:41256269 | 17.15% | NM_007294.4 | missense |
| RNF43 | p.(D521G) | c.1562A>G | . | chr17:56435575 | 3.25% | NM_017763.6 | missense |
| RAD51C | p.(E94D) | c.282G>T | . | chr17:56772428 | 15.56% | NM_058216.3 | missense |
| GNA13 | p.(S124L) | c.371C>T | . | chr17:63049759 | 22.55% | NM_006572.6 | missense |
| RPTOR | p.(V543I) | c.1627G>A | . | chr17:78857261 | 26.21% | NM_020761.3 | missense |
| DSC1 | p.(A214V) | c.641C>T | . | chr18:28728592 | 18.11% | NM_024421.2 | missense |
| SMAD4 | p.(G393C) | c.1177G>T | . | chr18:48593426 | 24.96% | NM_005359.6 | missense |
| SMAD4 | p.(R502M) | c.1505G>T | . | chr18:48604683 | 26.93% | NM_005359.6 | missense |
| MAP2K2 | p.(R231H) | c.692G>A | . | chr19:4101030 | 28.70% | NM_030662.4 | missense |
| SMARCA4 | p.(R466C) | c.1396C>T | . | chr19:11101976 | 25.00% | NM_001128849.3 | missense |
| NOTCH3 | p.(D852E) | c.2556C>A | . | chr19:15295116 | 24.52% | NM_000435.3 | missense |
| JAK3 | p.(R540H) | c.1619G>A | . | chr19:17948823 | 23.80% | NM_000215.4 | missense |
| KMT2B | p.(P566S) | c.1696C>T | . | chr19:36211945 | 32.03% | NM_014727.3 | missense |
| KMT2B | p.(A1634V) | c.4901C>T | . | chr19:36220181 | 19.36% | NM_014727.3 | missense |
| KMT2B | p.(F2631L) | c.7891T>C | . | chr19:36229201 | 16.15% | NM_014727.3 | missense |
| KMT2B | p.(R2709C) | c.8125C>T | . | chr19:36229435 | 26.05% | NM_014727.3 | missense |
| ERCC2 | p.(K133T) | c.398A>C | . | chr19:45868379 | 28.07% | NM_000400.4 | missense |
| ARHGAP35 | p.(R1147C) | c.3439C>T | . | chr19:47425371 | 22.51% | NM_004491.5 | missense |
| ARHGAP35 | p.(P1262S) | c.3784C>T | . | chr19:47440623 | 26.01% | NM_004491.5 | missense |
| BCL2L12 | p.(P70S) | c.208C>T | . | chr19:50170376 | 3.31% | NM_138639.2 | missense |
| ZIM3 | p.(V13A) | c.38T>C | . | chr19:57649944 | 5.30% | NM_052882.1 | missense |
| ZIM3 | p.(R7Kfs*103) | c.20_25delGAGTGAinsAAGATGG | . | chr19:57649957 | 12.14% | NM_052882.1 | frameshift Block Substitution |
| ASXL1 | p.(R323H) | c.968G>A | . | chr20:31019471 | 20.80% | NM_015338.6 | missense |
| ASXL1 | p.(G1058E) | c.3173G>A | . | chr20:31023688 | 26.10% | NM_015338.6 | missense |
| BPIFB4 | p.([D267G;I268V]) | c.800_802delACAinsGCG | . | chr20:31673844 | 22.01% | NM_182519.2 | missense, missense |
| PTPRT | p.(R1059W) | c.3175C>T | . | chr20:40739109 | 25.32% | NM_133170.4 | missense |
| MYBL2 | p.(G404D) | c.1211G>A | . | chr20:42331389 | 20.50% | NM_002466.4 | missense |
| GNAS | p.(R199H) | c.596G>A | . | chr20:57484415 | 4.80% | NM_000516.7 | missense |
| RUNX1 | p.(R232W) | c.694C>T | . | chr21:36206818 | 27.01% | NM_001754.5 | missense |
| NF2 | p.(A416V) | c.1247C>T | . | chr22:30069382 | 24.65% | NM_000268.4 | missense |
| EP300 | p.(R1478C) | c.4432C>T | . | chr22:41566555 | 24.46% | NM_001429.4 | missense |

# Variant Details (continued)

## DNA Sequence Variants (continued)

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| ZRSR2 | p.(T353A) | c.1057A>G | . | chrX:15840973 | 2.80% | NM_005089.4 | missense |
| BCOR | p.(A617V) | c.1850C>T | . | chrX:39932749 | 26.25% | NM_001123385.2 | missense |
| BCOR | p.(E481D) | c.1443G>T | . | chrX:39933156 | 23.55% | NM_001123385.2 | missense |
| DUSP21 | p.(R167C) | c.499C>T | . | chrX:44703877 | 26.55% | NM_022076.4 | missense |
| KDM6A | p.(R949C) | c.2845C>T | . | chrX:44937657 | 26.15% | NM_021140.3 | missense |
| KDM6A | p.(F1152L) | c.3456C>A | . | chrX:44945132 | 26.89% | NM_021140.3 | missense |
| RBM10 | p.(D365G) | c.1094A>G | . | chrX:47038892 | 2.40% | NM_001204468.1 | missense |
| RBM10 | p.(E494K) | c.1480G>A | . | chrX:47040650 | 26.34% | NM_001204468.1 | missense |
| RBM10 | p.(P497L) | c.1490C>T | . | chrX:47040660 | 27.25% | NM_001204468.1 | missense |
| KDM5C | p.(E466D) | c.1398G>T | . | chrX:53240682 | 25.40% | NM_004187.5 | missense |
| ZMYM3 | p.(R688H) | c.2063G>A | . | chrX:70467669 | 4.25% | NM_201599.3 | missense |
| ZMYM3 | p.(R478W) | c.1432C>T | . | chrX:70469349 | 24.14% | NM_201599.3 | missense |
| ATRX | p.(N2392T) | c.7175A>C | . | chrX:76776291 | 31.08% | NM_000489.6 | missense |
| ATRX | p.(R1803H) | c.5408G>A | . | chrX:76874314 | 23.69% | NM_000489.6 | missense |
| ATRX | p.(A1790V) | c.5369C>T | . | chrX:76874353 | 23.46% | NM_000489.6 | missense |
| ATRX | p.(G1290E) | c.3869G>A | . | chrX:76920208 | 10.87% | NM_000489.6 | missense |
| STAG2 | p.(K317Q) | c.949A>C | . | chrX:123184091 | 2.95% | NM_001042749.2 | missense |
| STAG2 | p.(Y319H) | c.955T>C | . | chrX:123184097 | 30.40% | NM_001042749.2 | missense |

# Biomarker Descriptions

**CSMD3 p.(G1594*) c.4780G>T**

*CUB and Sushi multiple domains 3*

Background: CSMD3 encodes the CUB and Sushi multiple domains 3 protein, a member of the CSMD family, which includes CSMD1 and CSMD2[1,2]. Proteins containing CUB and Sushi domains are known to mediate protein-protein interactions between the transmembrane and extracellular proteins[2,3]. CSMD family proteins have 14 CUB and 26–28 Sushi domains, which are reported to regulate dendrite growth, neuronal migration, and synapse formation[2,3]. In cancer, mutation of CMSD3 has been associated with greater tumor mutational burden (TMB)[2,4].

Alterations and prevalence: Somatic mutations of CSMD3 are observed in 43% of lung squamous cell carcinoma, 40% of lung adenocarcinoma, 37% of skin cutaneous melanoma, 25% of stomach adenocarcinoma, 24% of uterine corpus endometrial carcinoma, 19% of esophageal adenocarcinoma and head and neck squamous cell carcinoma, 17% of colorectal adenocarcinoma, 14% of bladder urothelial carcinoma, 10% of diffuse large B-cell lymphoma, 8% of liver hepatocellular carcinoma and cervical squamous cell carcinoma, 7% of ovarian serous cystadenocarcinoma, 5% of uterine carcinosarcoma, and 4% of adrenocortical carcinoma, kidney renal clear cell carcinoma, breast invasive carcinoma, prostate adenocarcinoma and, uveal melanoma[5,6]. Amplification of CSMD3 is observed in 20% of ovarian serous cystadenocarcinoma, 12% of breast invasive carcinoma, 11% of uterine carcinosarcoma, 10% of liver hepatocellular carcinoma, and esophageal adenocarcinoma, 8% of prostate adenocarcinoma, 7% of pancreatic adenocarcinoma, 6% of uveal melanoma and head and neck squamous cell carcinoma, and 5% of bladder urothelial carcinoma and stomach adenocarcinoma[5,6]. Biallelic loss of CSMD3 is observed in 2% of mesothelioma and prostate adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for CSMD3 aberrations.

## Biomarker Descriptions (continued)

**EIF1AX p.(R13C) c.37C>T**

*eukaryotic translation initiation factor 1A, X-linked*

Background: The EIF1AX gene encodes the eukaryotic translation initiation factor 1A X-linked protein[1]. EIF1AX, also known as EIF1A, stimulates protein translation initiation by promoting the recruitment of the ternary complex (TC; tRNA-eIF2-GTP) to the 40S ribosomal subunit and facilitating the assembly of the 43S preinitiation complex (PIC)[7,8].

Alterations and prevalence: Somatic mutations in EIF1AX are observed in 13% of uveal melanoma, 3% of uterine corpus endometrial carcinoma, and 1% of thymoma and thyroid carcinoma[5,6]. Mutations, including X113_splice, have been observed to be recurrent in thyroid cancers and have been proposed to cooperate with RAS mutation to drive thyroid tumorigenesis[5,6,8,9,10] Amplification of EIF1AX is observed in 2% of sarcoma, and 1% of cervical squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, and bladder urothelial carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for EIF1AX aberrations. EIF1AX mutations are considered a marker of low risk of distant metastasis of uveal melanoma[11].

**TGFBR2 p.(R485H) c.1454G>A**

*transforming growth factor beta receptor 2*

Background: TGFBR2 encodes transforming growth factor beta receptor 2[1]. Along with TGFBR1 and TGFBR3, TGFBR2 is a member of the TGF-beta receptor family[12]. Both TGFBR1 and TGFBR2 function as serine/threonine and tyrosine kinases, whereas TGFBR3 does not possess any kinase activity[12]. TGFBR1 heterodimerizes with TGFBR2 and activates ligand binding of TGF-beta cytokines namely TGFB1, TGFB2, and TGFB3[12]. Heterodimerization with TGFBR2 enables TGFBR1 to phosphorylate downstream SMAD2/3, which leads to activation of SMAD4[13]. This process regulates various signaling pathways implicated in cancer initiation and progression, including epithelial to mesenchymal transition (EMT) and apoptosis[14,15,16].

Alterations and prevalence: Somatic mutations in TGFBR2 are observed in 5% of esophageal adenocarcinoma, and head and neck squamous cell carcinoma, 4% of pancreatic adenocarcinoma, stomach adenocarcinoma, uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and cholangiocarcinoma[5,6]. Biallelic deletion of TGFRB2 is observed in 3% of kidney renal clear cell carcinoma and 2% of stomach adenocarcinoma and head and neck squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for TGFBR2 aberrations.

**VHL p.(*214W) c.642A>G**

*von Hippel-Lindau tumor suppressor*

Background: The VHL gene encodes the von Hippel-Lindau tumor suppressor protein[1]. VHL possesses ubiquitin ligase activity and forms a ternary complex with transcription elongation factors C and B to make up the VCB complex, which is critical for VHL function[1,17]. VHL is involved in hypoxia-inducible-factor (HIF) regulation through ubiquitination, thereby targeting HIFs, including HIF1α, for proteasomal degradation[17]. Mutations in VHL lead to a destabilized VCB complex that is rapidly degraded by the proteasome, resulting in defective HIF regulation and tumorigenesis[17]. Germline mutations in VHL cause the Von Hippel-Lindau hereditary cancer syndrome, which confers predisposition to several cancer types including clear cell renal carcinoma, central nervous system, and retinal hemangioblastomas, pheochromocytoma, and pancreatic neuroendocrine tumors[17]. Belzutifan is considered for the treatment of progressive pancreatic neuroendocrine tumor harboring VHL germline aberrations[18].

Alterations and prevalence: Somatic mutations in VHL are predominantly truncating followed by missense mutations and are collectively observed in 41% of kidney renal clear cell carcinoma, and 2% of pheochromocytoma and paraganglioma, thymoma and kidney chromophobe[5,6]. Biallelic deletions are observed in 3% of kidney renal clear cell carcinoma and 2% of prostate adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for VHL aberrations.

**BRCA1 p.(R1443*) c.4327C>T**

*BRCA1, DNA repair associated*

Background: The breast cancer early onset gene 1 (BRCA1) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA[19,20]. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable

## Biomarker Descriptions (continued)

and compromise genome integrity[19,20]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer[21,22,23]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%[21,24].

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer[25,26,27,28,29,30,31,32]. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme[5,6].

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[33]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[34,35]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[36] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[36] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[37] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[38] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[38] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib[39] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate[40] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[41]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[42]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[43], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. In 2024, the FDA granted fast track designation to TNG-348[44], a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

**TET2 p.(R1516*) c.4546C>T**

*tet methylcytosine dioxygenase 2*

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to a family of ten-eleven translocation (TET) proteins that also includes TET1 and TET3[45]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[46,47]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[48]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[45,46,47]

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40%-60% chronic myelomonocytic leukemia (CMML)[49]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[46,50]. TET2 mutations are also observed in 9% of uterine, 8% of melanoma and acute myeloid leukemia (AML), as well as 6% of diffuse large B-cell lymphoma (DLBCL).

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[51]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[51,52]

**EZH2 c.2029+1G>A**

*enhancer of zeste 2 polycomb repressive complex 2 subunit*

Background: The EZH2 gene encodes the enhancer of zeste homolog 2 protein, a histone methyltransferase that functions as both a transcriptional suppressor and co-activator[53]. EZH2 mediates methylation of histone H3 at Lys 27 (H3K27me3) and promotes tumor growth and metastasis through regulation of the cell cycle[53,54]. Since EZH2 loss-of-function is associated with the development of

## Biomarker Descriptions (continued)

cancer, it is considered a tumor suppressor. EZH2 is overexpressed in various cancer types, consequently, it can also function as an oncogene[53].

Alterations and prevalence: Diverse EZH2 alterations including missense, nonsense, frameshift mutations, and inactivating deletions are observed in 18-25% of T-cell acute lymphocytic leukemia (T-ALL), 3-13% of myeloproliferative neoplasms (MPN), 8-12% of myelodysplastic/myeloproliferative neoplasms overlap disorders (MDS/MPN), and 6% of diverse MDS[54,55]. Heterozygous gain-of-function mutations at tyrosine 641 (Y641) are observed in 22% of germinal center B-cell (GBC) and diffuse large B-cell lymphoma (DLBCL), and 7-17% of follicular lymphoma (FL)[54,56]. In solid tumors, EZH2 mutations are observed in up to 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 3% of cholangiocarcinoma[5,6]. Amplifications are observed in up to 7% of ovarian carcinoma[5,6]. Increased EZH2 copy number corresponds with enhanced protein expression and is observed in over 50% of hormone-refractory prostate cancers[57].

Potential relevance: The methyltransferase inhibitor tazemetostat[58] was FDA approved (2020) for EZH2 mutated relapsed or refractory follicular lymphoma after at least 2 prior systemic therapies. Tazemetostat was also granted FDA fast track designation in 2016 for DLBCL harboring EZH2 activating mutations[59]. Somatic mutation in EZH2 is one of the possible molecular abnormality requirements for the diagnosis of myelodysplasia-related AML (AML-MR)[60]. EZH2 nonsense or frameshift mutations are independently associated with poor prognosis in MDS and MDS/MPN[49]. EZH2 mutations also confer poor prognosis in essential thrombocythemia (ET), primary myelofibrosis (PMF), and AML[51,61,62]. EZH2 overexpression correlates with malignancy, poor prognosis, and poor survival, and has been detected in MDS and acute myeloid leukemia (AML)[53,63]. Several studies have shown that EZH2 overexpression enhances chemoresistance in solid tumor types[64,65].

**UGT1A1 p.(G71R) c.211G>A**

*UDP glucuronosyltransferase family 1 member A1*

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[1,66]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[66,67]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[68]. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[68,69,70,71]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[72].

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for UGT1A1 aberrations.

**RASA2 p.(R526*) c.1576C>T**

*RAS p21 protein activator 2*

Background: The RASA2 gene encodes the RAS p21 protein activator 2[73]. RASA2 is a member of the RasGAP family, which includes RASA1[74,75]. RASA2 functions as a GTPase activating protein (GAP) by enhancing RAS GTPase activity and promoting the inactive GDP-bound form[73,74]. In melanoma, loss of RASA2 function was found to increase RAS activation, cell growth, and migration[73].

Alterations and prevalence: Somatic mutations in RASA2 are observed in 7% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, and 3% of colorectal adenocarcinoma[5,6]. RASA2 and NF1 mutations strongly co-occur in melanoma[73].

Potential relevance: Currently, no therapies are approved for RASA2 aberrations.

**XRCC2 p.(R215*) c.643C>T**

*X-ray repair cross complementing 2*

Background: The XRCC2 gene encodes the X-ray repair cross complementing 2 protein, also known as FANCU, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC3 paralogs[1,76,77]. XRCC2 forms the BCDX2 complex with other RAD51 paralogs, RAD51B, RAD51C, and RAD51D[76,77]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[78]. XRCC2 regulates the assembly of RAD51 filaments to assist in strand-exchange activity during homologous recombination

## Biomarker Descriptions (continued)

repair (HRR)[76,77]. XRCC2 germline biallelic mutations result in Fanconi Anemia (FA) complementation group U, an atypical form of FA associated with defects in HRR[79].

Alterations and prevalence: Somatic mutations in XRCC2 are observed in 3% of uterine corpus endometrial carcinoma and 2% of diffuse large B-cell lymphoma (DLBCL), uterine carcinosarcoma, and colorectal adenocarcinoma[5,6]. Biallelic deletions in XRCC2 are observed in 2% of acute myeloid leukemia (AML), sarcoma, and esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for XRCC2 aberrations. Pre-clinical evidence suggests that XRCC2 biallelic mutations may demonstrate sensitivity to the PARP inhibitor olaparib[80].

**MSH6 p.(R1076H) c.3227G>A**

*mutS homolog 6*

Background: The MSH6 gene encodes the mutS homolog 6 protein[1]. MSH6 is a tumor suppressor gene that heterodimerizes with MSH2 to form the MutSα complex[81]. The MutSα complex functions in the DNA damage recognition of base-base mismatches or insertion/deletion (indels) of 1-2 nucleotides[81]. DNA damage recognition initiates the mismatch repair (MMR) process that repairs mismatch errors which typically occur during DNA replication. Mutations in MSH2 result in the degradation of MSH6[82]. MSH6, along with MLH1, MSH2, and PMS2 form the core components of the MMR pathway[81]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[83,84,85]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[83,86]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[84,86,87,88]. Specifically, MSH6 mutations are associated with increased risk of ovarian and pancreatic cancer[89,90,91,92].

Alterations and prevalence: Somatic mutations in MSH6 are observed in 11% of uterine corpus endometrial carcinoma, 4% colorectal adenocarcinoma, and 3% skin cutaneous melanoma[5,6].

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies[93]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[94,95].

**ATM p.(R2849*) c.8545C>T, ATM p.(R457*) c.1369C>T, ATM p.(S131*) c.392C>A**

*ATM serine/threonine kinase*

Background: The ATM gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATR and PRKDC (also known as DNA-PKc)[96]. ATM and ATR act as master regulators of DNA damage response. Specifically, ATM is involved in double-stranded break (DSB) repair while ATR is involved in single-stranded DNA (ssDNA) repair[97]. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB[97,98]. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins[99]. ATM is a tumor suppressor gene and loss of function mutations in ATM are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR), mimicking BRCA1 or BRCA2 loss[100,101]. Germline mutations in ATM often result in Ataxia-telangiectasia, a hereditary disease also referred to as DNA damage response syndrome that is characterized by chromosomal instability[102].

Alterations and prevalence: Recurrent somatic mutations in ATM are observed in 17% of endometrial carcinoma, 15% of undifferentiated stomach adenocarcinoma, 13% of bladder urothelial carcinoma, 12% of colorectal adenocarcinoma, 9% of melanoma as well as esophagogastric adenocarcinoma and 8% of non-small cell lung cancer[5,6].

Potential relevance: The PARP inhibitor, olaparib[36] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes ATM. Additionally, talazoparib[38] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATM. Consistent with other genes associated with the BRCAness phenotype, ATM mutations may aid in selecting patients likely to respond to PARP inhibitors[100,103,104]. Specifically, in a phase II trial of metastatic, castration-resistant prostate cancer, four of six patients with germline or somatic ATM mutations demonstrated clinical responses to olaparib[105]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[43], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

## Biomarker Descriptions (continued)

**MAP2K4 p.(R134Q) c.401G>A**

*mitogen-activated protein kinase kinase 4*

Background: The MAP2K4 gene encodes the mitogen-activated protein kinase kinase 4, also known as MEK4. MAP2K4 is a member of the mitogen-activated protein kinase 2 (MAP2K) subfamily which also includes MAP2K1, MAP2K2, MAP2K3, MAP2K5, and MAP2K6[106]. Activation of MAPK proteins occurs through a kinase signaling cascade[106,107,108]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[106,107,108]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[106,107,108]. Mutations observed in MAP2K4 were have been observed to impair kinase activity and promote tumorigenesis in vitro, supporting a possible tumor suppressor role for MAP2K4[109].

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[5,6]. Biallelic deletions have been observed in 3% of stomach cancer, and 2% of breast invasive carcinoma, diffuse large B-cell lymphoma (DLBCL), colorectal, pancreatic, and ovarian cancer[5,6]. Nonsense, frameshift, and missense mutations in MAP2K4 generally inactivate the kinase activity, and lost expression has been identified in prostate, ovarian, brain, and pancreatic cancer models[110,111].

Potential relevance: Currently, no therapies are approved for MA2PK4 aberrations.

**RAD54L p.(R609*) c.1825C>T**

*RAD54 like (S. cerevisiae)*

Background: The RAD54L gene encodes the RAD54-like protein and is a member of the Snf2 family of Superfamily 2 (SF2) helicase-like proteins, which also includes its homolog RAD54B[112]. The Snf2 family are a group of DNA translocases that use ATP-hydrolysis to remodel chromatin structure and therefore regulate genome integrity by controlling transcriptional regulation, chromosome stability, and DNA repair[112,113,114]. Structurally, these proteins contain a common Snf2 domain that consists of two RecA-like folds with seven conserved sequence motifs for identifying helicases[112,115]. RAD54L specifically appears to stabilize the association of RAD51 DNA strand exchange activity and binds Holliday junctions to promote branch migration during homologous recombination[116]. RAD54L is a tumor suppressor gene and loss of function mutations in RAD54L are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR) mimicking BRCA1 or BRCA2 loss[100].

Alterations and prevalence: Somatic mutations in RAD54L are observed in up to 5% of uterine cancer[5,6].

Potential relevance: The PARP inhibitor, olaparib[36] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD54L. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[43], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**ZFHX3 p.(E1888*) c.5662G>T**

*zinc finger homeobox 3*

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[1,117,118]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[118,119]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[120,121,122,123,124]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[120,123,125,126].

Alterations and prevalence: Somatic mutations in ZFHX3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6% of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid leukemia[5,6]. Biallelic loss of ZFHX3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3% of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for ZFHX3 aberrations.

## Biomarker Descriptions (continued)

**BRAF p.(D594N) c.1780G>A**

*B-Raf proto-oncogene, serine/threonine kinase*

Background: The BRAF gene encodes the B-Raf proto-oncogene serine/threonine kinase, a member of the RAF family of serine/threonine protein kinases which also includes ARAF and RAF1 (CRAF). BRAF is among the most commonly mutated kinases in cancer. Activation of the MAPK pathway occurs through BRAF mutations and leads to an increase in cell division, dedifferentiation, and survival[127,128]. BRAF mutations are categorized into three distinct functional classes namely, class 1, 2, and 3, and are defined by the dependency on the RAS pathway. Class 1 and 2 BRAF mutants are RAS-independent in that they signal as active monomers (Class 1) or dimers (Class 2) and become uncoupled from RAS GTPase signaling, resulting in constitutive activation of BRAF[129]. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead[129,130,131].

Alterations and prevalence: Recurrent somatic mutations in BRAF are observed in 40-60% of melanoma and thyroid cancer, approximately 10% of colorectal cancer, and about 2% of non-small cell lung cancer (NSCLC)[5,6,132,133,134]. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types[130,135]. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R/, G464V/E/, and BRAF fusions[130]. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I[130]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancer, and prevalent in histiocytic neoplasms[136,137,138]. Other recurrent BRAF somatic mutations cluster in the glycine-rich phosphate-binding loop at codons 464-469 in exon 11 as well as additional codons flanking V600 in the activation loop[135]. In primary cancers, BRAF amplification is observed in 8% of ovarian cancer and about 1% of breast cancer[5,6]. BRAF fusions are mutually exclusive to BRAF V600 mutations and have been described in melanoma, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types[139,140,141,142,143]. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain leading to constitutive kinase activation[131,139,141].

Potential relevance: Vemurafenib[144] (2011) was the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation. BRAF class 1 mutations, including V600E, are sensitive to vemurafenib, whereas class 2 and 3 mutations are insensitive[130]. BRAF kinase inhibitors including dabrafenib[145] (2013) and encorafenib[146] (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib[146] is approved in combination with cetuximab[147] (2020) for the treatment of BRAF V600E mutated colorectal cancer. Due to the tight coupling of RAF and MEK signaling, several MEK inhibitors have been approved for patients harboring BRAF alterations[130]. Trametinib[148] (2013) and binimetinib[149] (2018) were approved for the treatment of metastatic melanoma with BRAF V600E/K mutations. Combination therapies of BRAF plus MEK inhibitors have been approved in melanoma and NSCLC. The combinations of dabrafenib/trametinib (2015) and vemurafenib/cobimetinib[150] (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E/K mutation. Subsequently, the combination of dabrafenib and trametinib was approved for metastatic NSCLC (2017) with a BRAF V600E mutation. The PD-L1 antibody, atezolizumab[151], has also been approved in combination with cobimetinib and vemurafenib for BRAF V600 mutation-positive unresectable or metastatic melanoma. The FDA has granted fast track designation (2023) to ABM-1310[152] for BRAF V600E-mutated glioblastoma (GBM) patients. In 2018, binimetinib[153] was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The ERK inhibitor ulixertinib[154] was granted fast track designation in 2020 for the treatment of patients with non-colorectal solid tumors harboring BRAF mutations G469A/V, L485W, or L597Q. The FDA granted fast track designation (2022) to the pan-RAF inhibitor, KIN-2787[155], for the treatment of BRAF class II or III alteration-positive malignant or unresectable melanoma. The FDA also granted fast track designation (2023) to the BRAF inhibitor, plixorafenib (PLX-8394)[156], for BRAF Class I (V600) and Class II (including fusions) altered cancer patients who have already undergone previous treatments. BRAF fusion is a suggested mechanism of resistance to BRAF targeted therapy in melanoma[157]. Additional mechanisms of resistance to BRAF targeted therapy include BRAF amplification and alternative splice transcripts as well as activation of PI3K signaling and activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2)[158,159,160,161,162,163,164]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[143].

**Microsatellite stable**

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[165]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[84,86]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[85]. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250[166]. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)[166]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[87,167,168,169,170]. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes[86].

## Biomarker Descriptions (continued)

LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[84,86,87,88].

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma[84,86,171,172]. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers[171,172].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[93] (2014) and nivolumab[94] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[93] is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication[93]. Dostarlimab[173] (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer[168,174]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[95] (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location[168,175,176]. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients[176]. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors[177,178]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[177,178].

**APC p.(R1858*) c.5572C>T, APC p.(R332*) c.994C>T**

*APC, WNT signaling pathway regulator*

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β-catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation[179]. APC is an antagonist of WNT signaling as it targets β-catenin for proteasomal degradation[180,181]. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine[179,182]. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer[183].

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma[5,6,184]. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation[185,186].

Potential relevance: Currently, no therapies are approved for APC aberrations.

**PDGFRA c.1559-1G>A**

*platelet derived growth factor receptor alpha*

Background: The PDGFRA gene encodes the platelet derived growth factor receptor alpha, a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRB, CSF1R, FLT1, FLT3, FLT4, KDR, and KIT[187,188]. PDGFRA is a receptor for platelet derived growth factors, which are mitogens for cells of mesenchymal origin[189]. PDGFRA may function as a homodimer or heterodimer with PDGFRB depending on the ligand[190]. The PDGFRA gene is physically adjacent to KIT and KDR on chromosome 4q12. Ligand binding to PDGFRA results in kinase activation and stimulation of downstream pathways including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways promoting cell proliferation and survival.

Alterations and prevalence: Recurrent somatic PDGFRA alterations are observed in both solid and hematological cancers and include activating mutations, gene amplification, and translocations generating PDGFRA gene fusions. Recurrent PDGFRA activating mutations, including D842V, V561D, N659K, and in-frame deletions in exon 18, are common in 30-40% of KIT negative gastrointestinal stromal tumors (GISTs) and approximately 7% overall[191,192,193,194]. PDGFRA recurrent mutations are also described in adult and pediatric glioblastoma and high-grade gliomas[194,195]. In these cases, PDGFRA amplification is common (about 10% of cases) and recurrent mutations frequently co-occur with gene amplification[5,6]. PDGFRA fusions are observed in gliomas and glioblastomas as well as eosinophilic leukemias, of which the FIP1L1::PDGFRA fusion defines approximately half of patients with hypereosinophilic syndrome[196,197,198].

Potential relevance: The FDA has granted fast track designation to crenolanib[199] (2017) for GISTs harboring PDGFRA D842V mutation. Avapritinib[200] is a tyrosine kinase inhibitor (TKI) that is approved (2020) by the FDA for metastatic or unresectable GIST harboring PDGFRA exon 18 mutations including PDGFRA D842V mutation. Another TKI, imatinib[201], is approved (2001) for patients diagnosed

## Biomarker Descriptions (continued)

with chronic eosinophilic leukemia harboring FIP1L1::PDGFRA fusion. Additionally, imatinib is recommended for the treatment of GISTs harboring PDGFRA exon 18 mutations with the exception of D842V[202]. The TKI, dasatinib, is recommended as a second-line therapy for the treatment of GISTs harboring a PDGFRA exon 18 mutation that is insensitive to imatinib, including the D842V mutation[202].

**TRRAP p.(R816W) c.2446C>T**

*transformation/transcription domain associated protein*

Background: TRRAP encodes transformation/transcription domain associated protein and belongs to the phosphoinositide 3 kinase-related kinases (PIKK) family[1,203,204]. While TRRAP lacks the kinase activity of PIKK kinases, TRRAP functions as an adaptor protein in several histone acetylase complexes, thereby facilitating histone acetylation, chromatin remodeling, and gene expression, including genes involved in embryonic development[203,204]. Deregulation of TRRAP expression has been observed several cancer types and may contribute to oncogenesis in gliomas, breast and ovarian cancers[1,203,205,206].

Alterations and prevalence: Somatic mutations in TRRAP are observed in 19% of skin cutaneous melanoma, 16% of uterine corpus endometrial carcinoma, 11% of stomach adenocarcinoma, 9% of bladder urothelial carcinoma and colorectal adenocarcinoma, 7% of lung adenocarcinoma esophageal adenocarcinoma and lung squamous cell carcinoma, 5% of cervical squamous cell carcinoma, 4% of head and neck squamous cell carcinoma and uterine carcinosarcoma, 3% of cholangiocarcinoma, glioblastoma multiforme, and sarcoma, and 2% of ovarian serous cystadenocarcinoma, kidney chromophobe, and breast invasive carcinoma[5,6]. Amplification of TRRAP is observed in 11% of esophageal adenocarcinoma, 7% of stomach adenocarcinoma, 4% of lung squamous cell carcinoma, head and neck squamous cell carcinoma, pancreatic adenocarcinoma, and diffuse large B-cell lymphoma, 3% of ovarian serous cystadenocarcinoma and cholangiocarcinoma, and 2% of liver hepatocellular carcinoma, adrenocortical carcinoma, lung adenocarcinoma, prostate adenocarcinoma, and uterine carcinosarcoma[5,6].

Potential relevance: Currently, no therapies are approved for TRRAP aberrations.

**PTEN p.(G44D) c.131G>A, PTEN p.(R173H) c.518G>A**

*phosphatase and tensin homolog*

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities[207]. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT[208,209]. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency[210]. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation[211]. PTEN germline mutations are also associated with inherited cancer risk in several cancer types[212].

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are frequently observed in 50%-60% of uterine cancer[5,6]. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN[209,213,214,215,216]. PTEN gene deletion is observed in 15% of prostate cancer, 9% of squamous lung cancer, 9% of glioblastoma, and 1-5% of melanoma, sarcoma, and ovarian cancer[5,6].

Potential relevance: Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors[217,218]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[43], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib[219] in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

**RAD52 p.(S346*) c.1037C>A**

*RAD52 homolog, DNA repair protein*

Background: The RAD52 gene encodes the RAD52 homolog, DNA repair protein[1]. RAD52 binds to single- and double-stranded DNA and enables strand exchange for double-strand break (DSB) repair by binding to RAD51[220]. RAD52 also promotes DSB repair through homologous recombination repair (HRR) by recruiting BRCA1 to sites of DSBs, which leads to the removal of TP53BP1 and prevents DSB repair by non-homologous end joining (NHEJ)[221].

Alterations and prevalence: Somatic mutations in RAD52 are observed in 2% of uterine corpus endometrial carcinoma, uterine carcinosarcoma, and skin cutaneous melanoma[5,6].

## Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for RAD52 aberrations.

**CASP8 p.(R491*) c.1471C>T**

*caspase 8*

Background: CASP8 encodes caspase 8, a member of the cysteine-aspartic acid protease (caspase) family consisting of inflammatory caspases and apoptotic caspases. Apoptotic caspases consist of initiator and effector caspases[1,222,223]. CASP8 functions as an initiator caspase and following external stimulation of death receptors, undergoes processing and activation leading to CASP8 mediated cleavage of downstream targets[224]. CASP8 propagates the extrinsic apoptotic pathway by direct cleavage of effector caspases such as CASP3 and activates the intrinsic apoptotic pathway by cleaving BID, a pro-apoptotic proximal substrate of CASP8, resulting in an amplification of the death-inducing signal[224,225]. Certain cancer types have decreased expression or inactivation of CASP8, which results in poor prognosis and metastasis[226,227].

Alterations and prevalence: Somatic mutations in CASP8 are observed in 11% head and neck squamous cell carcinoma, 10% uterine corpus endometrial carcinoma, 5% stomach adenocarcinoma, 4% cervical squamous cell carcinoma, colorectal adenocarcinoma, and bladder urothelial carcinoma, 3% skin cutaneous melanoma, and 2% diffuse large B-cell lymphoma, lung squamous cell carcinoma, uterine carcinosarcoma, and breast invasive carcinoma[5,6]. Biallelic loss of CASP8 is observed in 2% bladder urothelial carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for CASP8 aberrations.

**ZRSR2 c.438+3A>G**

*zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2*

Background: The ZRSR2 gene encodes the zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2 protein, a component of the spliceosome. Specifically, ZRSR2 encodes a splicing factor that is involved in the recognition of the 3' intron splice site[228]. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer[228,229]. Mutations in ZRSR2 can lead to deregulated global and alternative mRNA splicing, nuclear-cytoplasm export, and unspliced mRNA degradation while concurrently altering the expression of multiple genes[228,230].

Alterations and prevalence: ZRSR2 alterations including nonsense and frameshift mutations are observed in 5-10% of myelodysplastic syndromes (MDS) and 4% of uterine cancer. ZRSR2 deletions are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of head and neck and esophageal cancers[6,49].

Potential relevance: Mutation of ZRSR2 is associated with poor prognosis in myelodysplastic syndromes as well as poor/adverse risk in acute myeloid leukemia (AML)[49,61,62].

**ATR p.(R1951*) c.5851C>T**

*ATR serine/threonine kinase*

Background: The ATR gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATM and PRKDC (also known as DNA-PKc)[96]. ATR and ATM act as master regulators of DNA damage response. Specifically, ATR and it's interacting protein ATRIP are involved in single-stranded DNA (ssDNA) repair while ATM is involved in double-stranded break (DSB) repair[97]. ATR is characterized as a tumor suppressor that plays a key role in maintaining genomic stability[231]. Upon activation, ATR phosphorylates downstream cell cycle and DNA damage signaling proteins such as CHK1, RAD17, RAD9, and BRCA1[232,233]. Germline mutations in ATR confer susceptibility to various cancers[234,235].

Alterations and prevalence: Somatic mutations of ATR are observed in 12% of melanoma, 11% of endometrial carcinoma, 8% of undifferentiated stomach adenocarcinoma and bladder urothelial carcinoma cases[5,6].

Potential relevance: The PARP inhibitor, talazoparib[38] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATR.

**ARHGAP35 p.(R783*) c.2347C>T**

*Rho GTPase activating protein 35*

Background: ARHGAP35 encodes Rho GTPase activating protein 35, human glucocorticoid receptor DNA binding factor. ARHGAP35 functions as a repressor of glucocorticoid receptor transcription[1]. Rho GTPases regulate various cellular processes such as cell adhesion, cell migration and play a critical role in metastasis through the negative regulation of RhoA which is localized to the cell

## Biomarker Descriptions (continued)

membrane[236,237]. Aberrations in ARHGAP35, including mutations, have been observed to result in both loss and gain of function thereby promoting tumor growth and metastasis[238,239].

Alterations and prevalence: Somatic mutations of AHGAP35 are observed in 20% of uterine corpus endometrial carcinoma, 11% of uterine carcinosarcoma, 6% of skin cutaneous melanoma, bladder urothelial carcinoma, and lung squamous cell carcinoma, 5% of colorectal adenocarcinoma, and 4% of stomach adenocarcinoma and lung adenocarcinoma[5,6]. In endometrial cancer, R997* has been observed to be recurrent and has been observed to confer loss of RhoGAP activity due to protein truncation and loss of its RhoGAP domain[240]. Amplification of AHGAP35 is observed in 4% of uterine carcinosarcoma, 2% of adrenocortical carcinoma, and diffuse large B-cell lymphoma[5,6]. Biallelic loss of AHGAP35 has been observed in 2% of sarcoma[5,6].

Potential relevance: Currently, no therapies are approved for ARHGAP35 aberrations.

**TSC2 c.1946+2T>C**

*tuberous sclerosis 2*

Background: The TSC2 gene encodes the tuberin protein. TSC2 and TSC1 (also known as hamartin) form a complex through their respective coiled-coil domains[241]. The TSC1-TSC2 complex is a negative regulator of the mTOR signaling pathway that regulates cell growth, cell proliferation, and protein and lipid synthesis[242]. Specifically, the TSC1-TSC2 complex acts as a GTPase activating (GAP) protein that inhibits the G-protein RHEB and keeps it in an inactivated state (RHEB-GDP). GTP bound RHEB (RHEB-GTP) is required to activate the mTOR complex 1 (mTORC1). TSC1 and TSC2 are tumor suppressor genes. Loss of function mutations in TSC1 and TSC2 lead to dysregulation of the mTOR pathway[241,243]. Inactivating germline mutations in TSC1 and TSC2 are associated with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous and progressive disorder that presents with multiple benign tumors in different organs[241].

Alterations and prevalence: Somatic mutations are observed in up to 8% of skin cutaneous melanoma, 7% of uterine corpus endometrial carcinoma, and 4% of cervical squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for TSC2 aberrations.

**SMARCA4 p.(R397*) c.1189C>T**

*SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4*

Background: The SMARCA4 gene encodes the SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4 protein[1]. SMARCA4, also known as BRG1, is a core member of ATP-dependent, multisubunit SWI/SNF chromatin-remodeling complex, along with SMARCB1/SNF5, SMARCC1/BAF155, SMARCC2/BAF170, and SMARCA2/BRM[244]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[244,245]. SMARCA4 and SMARCA2 are highly homologous and are mutually exclusive ATPase catalytic subunits for SWI/SNF chromatin remodeling complexes[244,245]. Germline loss of function mutations in SMARCA4 are associated with atypical teratoid/rhabdoid tumors (AT/RT), and a rare form of ovarian cancer called small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), which highlights the tumor suppressor function of SMARCA4.[246,247].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[245]. Recurrent somatic mutations in SMARCA4 are observed in 10% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, and 7% of esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for SMARCA4 aberrations. SMARCA4 mutations and deletions are considered a diagnostic marker for the SMARCA4-deficient uterine sarcoma (SDUS) subtype[248].

**KMT2C p.(R110*) c.328C>T**

*lysine methyltransferase 2C*

Background: The KMT2C gene encodes the lysine methyltransferase 2C protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1]. KMT2C belongs to the SET domain protein methyltransferase superfamily[249]. KMT2C is capable of di- and tri-methylation of histone 3 lysine 4 (H3K4) at select transcriptional enhancers depending on the cell type[250]. KMT2C is also found to interact with BAP1 to control ubiquitin-mediated gene silencing of H2A by Polycomb group (PcG) complexes[251,252]. Specifically, KMT2C interaction with BAP1 promotes KMT2C histone recruitment/methyltransferase activity and, along with BAP1 deubiquitination of H2A, facilitates transcription of target genes[251,252]. Mutations that occur within the SET domain of KMT2C are frequently observed in cancer and alter the methylation activity and target methylation states, thereby impacting gene regulation[250].

## Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in KMT2C are observed in 20% of bladder urothelial carcinoma and uterine corpus endometrial carcinoma, 19% of skin cutaneous melanoma and cervical squamous cell carcinoma, 15% of lung squamous cell carcinoma, 14% of stomach adenocarcinoma and lung adenocarcinoma, and 11% of cholangiocarcinoma[5,6]. Biallelic deletion of KMT2C is observed in 3% of sarcoma, stomach adenocarcinoma, 2% of esophageal adenocarcinoma, acute myeloid leukemia, uterine carcinosarcoma, and head and neck squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for KMT2C aberrations.

**CDK12 p.(E519*) c.1555G>T**

*cyclin dependent kinase 12*

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability[253,254,255]. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes[101,253,254,255,256]. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype[101,255]. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors[256]. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene[256].

Alterations and prevalence: Somatic alterations of CDK12 include mutations and amplification. Missense and truncating mutations in CDK12 are observed in 8% of undifferentiated stomach adenocarcinoma, 7% of bladder urothelial, and 6% endometrial carcinoma[1,5]. CDK12 is amplified in 9% of esophagogastric adenocarcinoma and invasive breast carcinoma, 8% of undifferentiated stomach adenocarcinoma, and 3% of bladder urothelial and endometrial carcinoma[1,5].

Potential relevance: The PARP inhibitor, olaparib[36] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CDK12. Additionally, talazoparib[38] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CDK12. Consistent with other genes associated with homologous recombination repair, CDK12 loss may aid in selecting patients likely to respond to PARP inhibitors[101,256]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[43], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**CDH1 p.(K440N) c.1320G>T**

*cadherin 1*

Background: The CDH1 gene encodes epithelial cadherin or E-cadherin, a member of the cadherin superfamily that includes the classical cadherins: neural cadherin (N-cadherin), retinal cadherin (R-cadherin), and placental cadherin (P-cadherin)[1,257]. E-cadherin proteins, composed of 5 extracellular cadherin repeats, a single transmembrane domain, and conserved cytoplasmic tail, are calcium-dependent transmembrane glycoproteins expressed in epithelial cells[1]. Extracellular E-cadherin monomers form homodimers with those on adjacent cells to form adherens junctions. Adherens junctions are reinforced by intracellular complexes formed between the cytoplasmic tail of E-cadherin and catenins, proteins which directly anchor cadherins to actin filaments[258]. E-cadherin is a critical tumor suppressor and when lost, results in epithelial-mesenchymal transition (EMT), anchorage-independent cell growth, loss of cell polarity, and tumor metastasis[259,260]. Germline mutations in CDH1 are enriched in a rare autosomal-dominant genetic malignancies such as hereditary diffuse gastric cancer, lobular breast cancer, and colorectal cancer[261].

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function[5,6,262,263]. In cancer, somatic mutation of CDH1 is observed in 12% of invasive breast carcinoma, 10% of stomach adenocarcinoma, 7% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma and skin cutaneous melanoma, 3% of bladder urothelial carcinomas, and 2% of lung squamous cell and liver hepatocelluar carcinomas[5,6]. Biallelic deletion of CDH1 is observed in 3% of prostate adenocarcinoma and ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for CDH1 aberrations.

**POLE p.(R1320*) c.3958C>T**

*DNA polymerase epsilon, catalytic subunit*

Background: The POLE gene encodes the DNA polymerase epsilon, catalytic subunit protein[1]. POLE is one of the four-subunits in the DNA polymerase epsilon complex that also includes POLE2, POLE3, and POLE4[264,265]. The DNA polymerase epsilon complex mediates DNA repair, chromosomal replication, and genomic stability[264,265]. Specifically, POLE is the largest subunit in the complex and contains the catalytic and proofreading exonuclease active sites proposed to function in leading strand synthesis during homologous recombination repair (HRR)[265,266]. Mutations in POLE lead to increased mutation rates and subsequent tumor formation thereby

## Biomarker Descriptions (continued)

impacting genomic stability[265,266]. Somatic POLE mutations are characterized by a hypermutated phenotype due to the increase in single-nucleotide substitutions[267]. Monoallelic POLE variants have also been associated with adenomatous polyposis and may confer an increased risk in colorectal cancer (CRC)[268,269,270,271,272]. Germline mutations in POLE exonuclease domains are associated with a predisposition to polymerase proofreading-associated polyposis[267].

Alterations and prevalence: Recurrent somatic mutations occur in 15% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 6% of colorectal adenocarcinoma, stomach adenocarcinoma, and bladder urothelial carcinoma, as well as 5% of lung squamous cell carcinoma and lung adenocarcinoma[5,6]. Specifically, mutations in the proofreading domain of POLE occur in 7-12% of endometrial cancer and 1-2% of colorectal cancer[265,267]. POLE mutations are associated with high tumor mutational burden (TMB)[265,267,273].

Potential relevance: Currently, no therapies are approved for POLE aberrations.

**PIK3R1 p.(R348*) c.1042C>T**

*phosphoinositide-3-kinase regulatory subunit 1*

Background: The PIK3R1 gene encodes the phosphoinositide-3-kinase regulatory subunit 1 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[1]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[274]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[274]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[274]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[275,276]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[275,276,277,278]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[279]. Loss of function mutations in PIK3R1 results in the inability of p85 to bind p110 or PTEN resulting in aberrant activation of the PI3K/AKT/MTOR pathway, a common driver event in several cancer types which supports a tumor suppressor role for PIK3R1[274].

Alterations and prevalence: Somatic mutations in PIK3R1 are predominantly truncating or missense and are observed in about 31% of uterine cancer, 10% of uterine carcinosarcoma and glioblastoma, 6% of colorectal cancer, and 3-4% of melanoma, low grade glioma (LGG), stomach, and cervical cancers[5]. Additionally, biallelic loss of PIK3R1 is observed in 3-4% of ovarian and prostate cancers[5].

Potential relevance: Currently, no therapies are approved for PIK3R1 aberrations.

**SMAD4 p.(R361H) c.1082G>A**

*SMAD family member 4*

Background: The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[280,281]. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF-β and BMP signaling pathways that are implicated in cancer initiation and progression[281,282,283]. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC[280,281]

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)[280]. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF-β signaling[6,283,284]. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers[5,6,184].

Potential relevance: Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers[281,283,285,286,287]. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy[288,289]. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)[289]. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors[290].

**TP53 p.(G244D) c.731G>A**

*tumor protein p53*

Background: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by

## Biomarker Descriptions (continued)

targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required for oncogenesis as they result in loss of protein function and gain of transforming potential[291]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[292,293].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[5,6,294,295,296,297]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R282[5,6]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[298,299,300,301].

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation[302]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[303] and breakthrough designation[304] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[305,306]. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)[49,51,61,62,307,308]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[309]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occuring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[310].

**FGFR2 p.(S252L) c.755C>T**

*fibroblast growth factor receptor 2*

Background: The FGFR2 gene encodes fibroblast growth receptor 2, a member of the fibroblast growth- factor receptor (FGFR) family that also includes FGFR1, 3, and 4. These proteins are single-transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[311,312,313].

Alterations and prevalence: Aberrations most common to the FGFR family are amplifications, followed by mutations and fusions. The majority of these aberrations result in gain of function[314]. Missense mutations are the most prevalent alterations in FGFR2 and are observed in up to 15% of uterine carcinomas[5,6,315]. These mutations are predominantly activating, most often involve substitutions at S252 and P253, and confer sensitivity to pan-FGFR2 inhibitors[315,316]. FGFR2 amplification occurs in up to 4% of gastric carcinoma, and is associated with poor prognosis as well as tumor invasion and metastasis[5,317,318,319]. FGFR2 fusions have also been reported in up to 14% of cholangiocarcinoma and confer sensitivity to select FGFR inhibitors[5,320,321].

Potential relevance: Several pan-FGFR inhibitors have been approved for FGFR2 aberrations in cancer. Futibatinib[322], is approved (2022) for FGFR2 rearrangement or fusion-positive locally advanced or metastatic intrahepatic cholangiocarcinoma. Infigratinib, was granted accelerated approval (2021) for previously treated, unresectable locally advanced or metastatic cholangiocarcinoma positive for FGFR2 fusion or other rearrangement[323]. Erdafitinib[324], received FDA approval (2019) for the treatment of locally advanced or metastatic urothelial cancer that is positive for FGFR2 fusions including, FGFR2::BICC1 and FGFR2::CASP7, FGFR3 fusions, or FGFR3 mutation. Pemigatinib[325], received FDA approval (2020), for previously treated, advanced or unresectable cholangiocarcinoma harboring FGFR2 fusions or other FGFR2 rearrangements. The FDA has granted Fast Track designation (2023) to the pan-FGFR inhibitor, KIN-3248, for unresectable, locally advanced or metastatic cholangiocarcinoma with FGFR2 fusions or other alterations after receiving at least one prior systemic therapy[326]. The FDA has granted Fast Track designation (2024) to the FGFR2 inhibitor, 3HP-2827, for the treatment of patients with cholangiocarcinoma harboring FGFR2 mutations[327]. The FDA also granted Fast Track designation (2018) to Debio 1347[328] for solid tumors harboring FGFR1, FGFR2, or FGFR3 aberrations. The FDA has granted Breakthrough Therapy Designation (2021) to Bemarituzumab in combination with modified FOLFOX6 (fluoropyrimidine, leucovorin, and oxaliplatin) for treating FGFR2b-overexpressing, HER2-negative metastatic and locally advanced gastric and gastroesophageal adenocarcinoma[329]. Additional FGFR inhibitors are under clinical evaluation for FGFR2 aberrations. In a phase II study of patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma, the pan-kinase inhibitor derazantinib, demonstrated an overall response rate (ORR) of 20.7% with progression-free survival (PFS) of 5.7 months[330]. Likewise, results of a phase II trial testing the pan-FGFR inhibitor, infigratinib (BGJ398) demonstrated an ORR of 14.8% (18.8% FGFR2 fusions only), disease control rate (DCR) of 75.4% (83.3% FGFR2 fusions only), and a median PFS of 5.8 months[331].

## Biomarker Descriptions (continued)

**PPP2R1A p.(R183W) c.547C>T**

*protein phosphatase 2 scaffold subunit Aalpha*

Background: The PPP2R1A gene encodes the protein phosphatase 2 regulatory subunit A alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family[1,332]. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (includes PPPP2CA and PPP2CB)[332,333]. Specifically, the A subunit is composed of 15 tandem HEAT repeats, consisting of approximately 40 amino acid residues organized into two anti-parallel alpha-helices which are responsible for binding both the regulatory B and catalytic C subunits[334]. Recurrent mutations in PPP2R1A have been observed to promote malignant growth in uterine cancer[335].

Alterations and prevalence: Somatic mutations in PPP2R1A are predominantly missense and are observed in 28% of uterine carcinosarcoma and 17% of uterine cancer[5]. Recurrent mutations are observed at codons P179, R183, and S256 within HEAT repeats 1-8 which are involved in interactions with the regulatory B subunit[5,335]. PPP2R1A mutations are also observed at lesser frequency in other cancer types including 2-3% of melanoma, uveal melanoma, lung adenocarcinoma, esophageal, squamous lung, stomach, cervical, and colorectal cancers[5]. PPP2R1A amplification is found to occur in about 4% of uterine cancer as well as 2% of diffuse large B-cell lymphoma (DLBCL), low grade glioma, adrenocortical carcinoma, and bladder cancer[5].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[336], in combination with camonsertib for the treatment of adult patients with PPP2R1A mutated endometrial cancer and platinum resistant ovarian cancer.

**RET p.(R912W) c.2734C>T**

*ret proto-oncogene*

Background: The RET gene encodes the RET receptor tyrosine kinase which is activated by a ligand family of glial cell line-derived neurotrophic factors (GDNF)[337]. RET is the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact RET tyrosine kinase domain combined with several fusion partner genes. RET fusion kinases are constitutively activated and drive oncogenic transformation which can lead to activation of PI3K/AKT, RAS/RAF/MEK/ERK, and PLCγ/PKC pathways resulting in cell survival and proliferation[338].

Alterations and prevalence: RET fusions occur in approximately 55% of papillary thyroid carcinomas (PTC) with even higher frequencies observed in PTC patients with radiation exposure[339,340,341]. RET rearrangement is also present in 1-2% of non-small cell lung cancer (NSCLC)[342]. Point mutations in RET are relatively common in sporadic medullary thyroid cancer (MTC), with 6% of patients found to contain germline mutations[343]. Somatic mutations (specifically at codon 918), which leads to increased kinase activity, have been observed in at least 25% of MTC cases[343].

Potential relevance: The FDA approved small-molecule tyrosine kinase inhibitor, cabozantinib (2012), is recommended for the treatment of NSCLC patients with RET rearrangements[344]. Cabozantinib has also demonstrated clinical benefit in RET mutated medullary thyroid cancer patients[345]. Selpercatinib[346] is approved (2020) for RET fusion-positive NSCLC, thyroid cancer, and metastatic solid tumors that have progressed following systemic treatment. Selpercatinib[346] is also approved for RET-mutation positive medullary thyroid cancer (MTC). Additionally, the RET inhibitor, pralsetinib[347], was approved (2020) for RET fusion-positive NSCLC and thyroid cancer as well as RET mutation-positive MTC. In 2024, the FDA granted fast track designation to the selective RET inhibitor, EP0031/A400[348], as a potential treatment option for RET-fusion positive NSCLC. Point mutations involving codons 804 and 806 have been shown to confer resistance to selective kinase inhibitors including vandetanib[349,350]. RET mutations at codon 918 are associated with high risk and adverse prognosis in patients diagnosed with MTC[351].

# Alerts Informed By Public Data Sources

## Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-01-22. For the most up-to-date information, search www.fda.gov.

## BRAF p.(D594N) c.1780G>A

### exarafenib

**Cancer type:** Melanoma

**Variant class:** BRAF Class III

**Supporting Statement:**

The FDA has granted Fast Track designation to the pan-RAF inhibitor, KIN-2787, for the treatment of BRAF Class II or III alteration-positive and/or NRAS mutation-positive stage IIb to IV malignant melanoma that is metastatic or unresectable.

**Reference:**

https://investors.kinnate.com/news-releases/news-release-details/kinnate-biopharma-inc-receives-fast-track-designation-us-food

# Genes Assayed

## Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

## Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

# Genes Assayed (continued)

## Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

## Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

# Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

## BRCA1 p.(R1443*) c.4327C>T

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| olaparib | ○ | ○ | ○ | ○ | ● (II) |
| bevacizumab + olaparib | ○ | ○ | ○ | ○ | ✖ |
| abiraterone + niraparib | ○ | ○ | ○ | ✖ | ✖ |
| rucaparib | ○ | ○ | ✖ | ○ | ✖ |
| talazoparib + enzalutamide | ○ | ○ | ✖ | ✖ | ✖ |
| niraparib | ✖ | ○ | ✖ | ○ | ● (II) |
| bevacizumab + niraparib | ✖ | ○ | ✖ | ✖ | ✖ |
| olaparib + abiraterone acetate | ✖ | ○ | ✖ | ✖ | ✖ |
| talazoparib | ✖ | ✖ | ✖ | ○ | ● (II) |
| niraparib, dostarlimab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| olaparib, talazoparib, atezolizumab + talazoparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| pamiparib, tislelizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| ZEN-3694, talazoparib | ✖ | ✖ | ✖ | ✖ | ● (II) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

## Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

### BRCA1 p.(R1443*) c.4327C>T (continued)

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| AMXI-5001 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| sacituzumab govitecan, berzosertib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| HS-10502 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| novobiocin | ✖ | ✖ | ✖ | ✖ | ● (I) |
| olaparib, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (I) |

### RET p.(R912W) c.2734C>T

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| selpercatinib | ○ | ○ | ✖ | ✖ | ✖ |
| vandetanib | ✖ | ✖ | ○ | ✖ | ✖ |
| cabozantinib, regorafenib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| sunitinib, regorafenib | ✖ | ✖ | ✖ | ✖ | ● (II) |

### ATM p.(R2849*) c.8545C>T, ATM p.(R457*) c.1369C>T, ATM p.(S131*) c.392C>A

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| olaparib | ○ | ○ | ✖ | ✖ | ● (II) |
| talazoparib + enzalutamide | ○ | ○ | ✖ | ✖ | ✖ |
| niraparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| niraparib, dostarlimab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| olaparib, ipilimumab + nivolumab, atezolizumab + talazoparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| pamiparib, tislelizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| talazoparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| sacituzumab govitecan, berzosertib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| HS-10502 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| novobiocin | ✖ | ✖ | ✖ | ✖ | ● (I) |
| olaparib, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (I) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

## Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

### CDK12 p.(E519*) c.1555G>T

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| olaparib | ○ | ○ | ✖ | ✖ | ✖ |
| talazoparib + enzalutamide | ○ | ○ | ✖ | ✖ | ✖ |
| atezolizumab + talazoparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| niraparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| niraparib, dostarlimab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| pamiparib, tislelizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| talazoparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| sacituzumab govitecan, berzosertib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| HS-10502 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| novobiocin | ✖ | ✖ | ✖ | ✖ | ● (I) |

### RAD54L p.(R609*) c.1825C>T

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| olaparib | ○ | ○ | ✖ | ✖ | ✖ |
| niraparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| niraparib, dostarlimab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| talazoparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| sacituzumab govitecan, berzosertib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| HS-10502 | ✖ | ✖ | ✖ | ✖ | ● (I) |

### ATR p.(R1951*) c.5851C>T

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| talazoparib + enzalutamide | ○ | ○ | ✖ | ✖ | ✖ |
| atezolizumab + talazoparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| niraparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| talazoparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| HS-10502 | ✖ | ✖ | ✖ | ✖ | ● (I) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

## Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

### BRAF p.(D594N) c.1780G>A

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| avutometinib, defactinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| regorafenib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| BGB-3245 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| ET0038 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| exarafenib, binimetinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| IK-595 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| JAB-3312 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| PF-07799544, PF-07799933 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| PF-07799933, cetuximab, binimetinib | ✖ | ✖ | ✖ | ✖ | ● (I) |

### POLE p.(R1320*) c.3958C>T

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| niraparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| pembrolizumab, ipilimumab + nivolumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| HS-10502 | ✖ | ✖ | ✖ | ✖ | ● (I) |

### MSH6 p.(R1076H) c.3227G>A

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| ipilimumab + nivolumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| niraparib | ✖ | ✖ | ✖ | ✖ | ● (II) |

### PDGFRA c.1559-1G>A

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| nilotinib, pazopanib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| sunitinib | ✖ | ✖ | ✖ | ✖ | ● (II) |

### PTEN p.(G44D) c.131G>A, PTEN p.(R173H) c.518G>A

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| niraparib | ✖ | ✖ | ✖ | ✖ | ● (II) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

## Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

### PTEN p.(G44D) c.131G>A, PTEN p.(R173H) c.518G>A (continued)

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| HS-10502 | ✖ | ✖ | ✖ | ✖ | ● (I) |

### RAD52 p.(S346*) c.1037C>A

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| niraparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| HS-10502 | ✖ | ✖ | ✖ | ✖ | ● (I) |

### TP53 p.(G244D) c.731G>A

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| niraparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| HS-10502 | ✖ | ✖ | ✖ | ✖ | ● (I) |

### XRCC2 p.(R215*) c.643C>T

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| niraparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| HS-10502 | ✖ | ✖ | ✖ | ✖ | ● (I) |

### FGFR2 p.(S252L) c.755C>T

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| sunitinib, futibatinib | ✖ | ✖ | ✖ | ✖ | ● (II) |

### MAP2K4 p.(R134Q) c.401G>A

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| ET0038 | ✖ | ✖ | ✖ | ✖ | ● (I) |

### SMAD4 p.(R361H) c.1082G>A

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| regorafenib | ✖ | ✖ | ✖ | ✖ | ● (II) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

## Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

### SMARCA4 p.(R397*) c.1189C>T

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| PRT-SCA2, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (I) |

### TSC2 c.1946+2T>C

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| temsirolimus | ✖ | ✖ | ✖ | ✖ | ● (II) |

### VHL p.(*214W) c.642A>G

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| sunitinib | ✖ | ✖ | ✖ | ✖ | ● (II) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

## HRR Details

| Gene/Genomic Alteration | Finding |
|---|---|
| LOH percentage | ***0.0%*** |
| BRCA1 | ***SNV, R320I, AF:0.26*** |
| BRCA1 | ***SNV, S104N, AF:0.17*** |
| BRCA2 | ***SNV, T751A, AF:0.24*** |
| BRCA2 | ***SNV, R898M, AF:0.24*** |
| BRCA2 | ***SNV, G934C, AF:0.27*** |
| BRCA2 | ***SNV, E2476D, AF:0.26*** |
| ATM | ***SNV, I389M, AF:0.24*** |
| ATM | ***SNV, A1699V, AF:0.22*** |
| ATM | ***SNV, Y2437C, AF:0.24*** |
| ATM | ***SNV, P2793S, AF:0.15*** |
| ATM | ***SNV, L2952I, AF:0.25*** |
| CHEK1 | ***SNV, S467N, AF:0.2*** |
| RAD51C | ***SNV, E94D, AF:0.16*** |

Homologous recombination repair (HRR) genes were defined from published evidence in relevant therapies, clinical guidelines, as well as clinical trials, and include - BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L.

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.0.2 data version 2025.02(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-01-22. NCCN information was sourced from www.nccn.org and is current as of 2025-01-02. EMA information was sourced from www.ema.europa.eu and is current as of 2025-01-22. ESMO information was sourced from www.esmo.org and is current as of 2025-01-02. Clinical Trials information is current as of 2025-01-02. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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