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Patient Name: 홍길동
Gender: F
Sample ID: 20250401-40701

Primary Tumor Site: Ovary
Collection Date: 2025-04-02

Sample Cancer Type: Ovarian Cancer

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Relevant Ovarian Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
BRCA1	None detected	NTRK2	None detected
BRCA2	None detected	NTRK3	None detected
ERBB2	None detected	RET	***RET amplification***

Genomic Alteration	Finding
Tumor Mutational Burden	***3.79 Mut/Mb measured***
Genomic Instability	***GIM 26 (High)***

HRD Status: ***HR Deficient (HRD+)***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*Genomic Instability* GIM 26 (High)	**bevacizumab + olaparib** [1, 2 / II+] bevacizumab [II+] bevacizumab + niraparib [II+] niraparib [II+]	None*	20
IIC	*TP53 p.(R213*) c.637C>T* tumor protein p53 Allele Frequency: 66.30% Locus: chr17:7578212 Transcript: NM_000546.6	None*	None*	6
IIC	*FGFR1 amplification* fibroblast growth factor receptor 1 Locus: chr8:38271452	None*	None*	5

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], 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 amplification* ret proto-oncogene Locus: chr10:43609070	None*	None*	2

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], 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.

Alerts informed by public data sources: ⊘ Contraindicated, Resistance, Breakthrough, Fast Track

Genomic Instability	**pidnarulex** [1]

Public data sources included in alerts: FDA[1], NCCN, **EMA**[2], ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources
MDM2 amplification, Microsatellite stable, IKBKB amplification, NQO1 p.(P187S) c.559C>T, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	50.90%	NM_000903.3	missense
TP53	p.(R213*)	c.637C>T	COSM10654	chr17:7578212	66.30%	NM_000546.6	nonsense
PP2D1	p.(M240*)	c.718delA	.	chr3:20042893	43.26%	NM_001252657.2	nonsense
HLA-B	p.(Y140L)	c.419_420delACinsTA	.	chr6:31324143	27.78%	NM_005514.8	missense
HLA-B	p.(C125S)	c.373T>A	.	chr6:31324190	62.50%	NM_005514.8	missense
FGFR2	p.(Y657*)	c.1971C>A	.	chr10:123247520	2.78%	NM_000141.5	nonsense
BRCA2	p.(E2918A)	c.8753A>C	.	chr13:32950927	66.84%	NM_000059.4	missense
MGA	p.(V3042M)	c.9124G>A	.	chr15:42059404	56.10%	NM_001164273.1	missense
ZFHX3	p.(Q1503H)	c.4509G>C	.	chr16:72832072	19.40%	NM_006885.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
FGFR1	chr8:38271452	9.69	3.57
IKBKB	chr8:42129602	5.67	2.23
RET	chr10:43609070	7.19	2.74
MDM2	chr12:69202958	8.79	3.28
BARD1	chr2:215593375	8	2.86
WT1	chr11:32410528	4.81	1.94
SMARCB1	chr22:24129273	5.54	2.19

Biomarker Descriptions

IKBKB amplification

inhibitor of nuclear factor kappa B kinase subunit beta

Background: The IKBKB gene encodes the nuclear factor kappa B kinase subunit beta, also known as IKK-B. IKBKB is a serine/threonine kinase, which acts as an enzyme protein subunit of the IKK complex[1]. IKBKB and IKBKA dimerize to form the regulatory subunit of the IKK complex. Along with modulator IKKγ/NEMO, the IKK complex acts as a master regulator of the family of NF-κB transcription factors.[1]. NF-κB signaling is critical in the inflammatory response and is also known to be implicated in other important physiological processes including cell proliferation[2]. In resting cells, NF-κB dimers are sequestered in the cytoplasm by IκB proteins[2]. Upon signal initiation, IκB proteins are phosphorylated by the IKK complex, leading to IκB protein degradation and liberation of NF-κB dimers[2]. Subsequently, released NF-κB dimers undergo nuclear translocation which leads to the expression of various proinflammatory and cell survival genes[3,4].

Alterations and prevalence: Somatic mutations in IKBKB are observed in 6% of uterine carcinoma, 5% of melanoma and diffuse large B-cell lymphoma (DLBCL)[5,6]. Amplifications are observed in 14% of uterine carcinosarcoma, 7% of breast invasive carcinoma and esophageal cancer[5,6]. IKBKB activating mutations are most commonly found at lysine 175 and are observed in 8% of splenic marginal B-cell lymphomas[1].

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

FGFR1 amplification

fibroblast growth factor receptor 1

Background: The FGFR1 gene encodes fibroblast growth receptor 1, a member of the fibroblast growth factor receptor (FGFR) family that also includes FGFR2, 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[7,8,9].

Alterations and prevalence: Recurrent somatic alterations common to the FGFR family include gene amplification, mutation, and chromosomal translocations leading to FGFR fusions[10]. Amplification of FGFR1 is observed in 15-20% of squamous lung cancer, 10-15% of breast cancer, 8% of bladder cancer, and 2-5% of uterine cancer cases[5,6,11,12,13]. The most common recurrent mutations, N546K and K656E, are relatively infrequent (<1%); they activate mutations in the kinase domain and are distributed in diverse cancer types[14]. FGFR1 translocations giving rise to expressed fusions are common in certain hematological cancers, but less common in solid tumors[15,16,17].

Potential relevance: The FGFR kinase inhibitor, pemigatinib[18] has been approved (2022) for the treatment of adults with relapsed/refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement. Additionally, the FDA granted fast-track designation (2018) to Debio 1347[19] for solid tumors harboring aberrations in FGFR1, FGFR2, or FGFR3. FDA has approved multi-kinase inhibitors, including regorafenib, ponatinib, lenvatinib, nintedanib, and pazopanib, that are known to inhibit FGFR family members. These inhibitors have demonstrated anti-tumor activity in select cancer types with FGFR alterations[20,21,22,23,24,25,26]. In a phase II clinical trial, dovitinib, a multi-tyrosine kinase inhibitor (TKI), exhibited an overall response rate (ORR) of 11.5% and a disease control rate (DCR) of 50% in patients with advanced squamous cell lung cancer possessing FGFR1 amplification. The patients had a median overall survival (OS) of 5 months and progression-free survival (PFS) of 2.9 months[27]. Likewise, in a phase Ib study testing the FGFR inhibitor AZD4547, the median OS was 4.9 months in patients with FGFR1-amplified advanced squamous cell lung cancer. One of 13 (8%) patients achieved a partial response, 4 (31%) exhibited stable disease, and 2 (13.3%) demonstrated PFS at 12 weeks[28].

TP53 p.(R213*) c.637C>T

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 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[29]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[30,31].

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%)[5,6,11,32,33,34]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense

Biomarker Descriptions (continued)

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[35,36,37,38].

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[39]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[40] and breakthrough designation[41] (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[42,43]. 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)[44,45,46,47,48,49]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[50]. 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[51].

MDM2 amplification

MDM2 proto-oncogene

Background: The MDM2 gene encodes the murine double minute 2 proto-oncogene. MDM2 is structurally related to murine double minute 4 (MDM4), with both proteins containing an N-terminal domain that binds p53, a zinc-finger domain, and a C-terminal RING domain[52]. MDM2 and MDM4 are oncogenes that function as negative regulators of the tumor suppressor TP53, and can homo- or heterodimerize with p53 through their RING domains[52]. Specifically, the MDM2 RING domain functions as an E3 ubiquitin ligase and is responsible for the polyubiquitination and degradation of the p53 protein when MDM2 is present at high levels[53]. Alternately, low levels of MDM2 activity promote mono-ubiquitination and nuclear export of p53[53]. MDM2 amplification and overexpression disrupt the p53 protein function, thereby contributing to tumorigenesis and supporting an oncogenic role for MDM2[53].

Alterations and prevalence: MDM2 is amplified in up to 13% of sarcoma, 8% of bladder urothelial carcinoma, glioblastoma, and 7% of adrenal cortical carcinoma[5,6]. MDM2 overexpression is observed in lung, breast, liver, esophagogastric, and colorectal cancers[54]. The most common co-occuring aberrations with MDM2 amplification or overexpression are CDK4 amplification and TP53 mutation[55,56].

Potential relevance: Currently, no therapies are approved for MDM2 aberrations. Amplification of region 12q13-15, which includes MDM2, is useful as an ancillary diagnostic marker of atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLS) and dedifferentiated liposarcoma[57].

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[58]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[59,60]. 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[61]. 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[62]. 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)[62]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[63,64,65,66,67]. 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[60]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[59,60,64,68].

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[59,60,69,70]. 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[69,70].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[71] (2014) and nivolumab[72] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[71] 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[71]. Dostarlimab[73] (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[65,74]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody,

Biomarker Descriptions (continued)

ipilimumab[75] (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[65,76,77]. 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[77]. 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[78,79]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[78,79].

Genomic Instability

Background: Homologous recombination repair (HRR) is a DNA repair mechanism that targets double stranded breaks (DSBs) and interstrand cross-links (ICL) in DNA[80]. Homologous recombination deficiency (HRD) is characterized by the cell's inability to repair these DSBs[80,81]. HRD is caused by genetic or epigenetic alterations in the HRR pathway genes, most notably BRCA1 and BRCA2 along with other genes such as ATM and PALB2[82,83,84,85]. A consequence of HRD due to the failure to repair DSBs is genomic instability[86,87]. Genomic instability is an increased tendency towards acquiring genomic alterations during cell division[88,89,90,91,92,93]. These alterations include small structural variations (i.e., single nucleotide variants (SNVs), insertions, and deletions) as well as significant structural variations (i.e., loss or gain of large chromosome fragments)[89,94,95]. Variations of genomic instability include chromosomal instability, intrachromosomal instability, microsatellite instability, and epigenetic instability[88]. Importantly, while the impact of frame-shift mutations in specific HRR genes can be mitigated by secondary mutations that restore the correct reading frame and thereby alleviate HRD, the effects of genomic instability are permanent and not reversible[96,97,98]. For this reason, the alterations characteristic of genomic instability are referred to as genomic scars[99,100]. Some of the genomic scar signatures that are characteristic of the HRD phenotype include loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transition (LST)[80,101]. Current methods for HRD detection are heterogeneous and the definition for HRD positive tumors varies depending on the cancer type[80]. Generally, these methods detect the causes of HRD (i.e., alterations in HRR genes) and/or the consequences (i.e., signatures of genomic instability/genomic scarring)[80,86,102,103].

Alterations and prevalence: In a pan-cancer analysis of HRR gene mutations and genomic scar signatures in 8847 tumors across 33 cancer types, 17.5% of tumors were HRD-positive and 4% of tumors were positive for the BRCA1/2 mutation[104]. Specifically, HRD-positive status was observed in over 50% of ovarian serous cystadenocarcinoma and lung squamous cell carcinoma, 35-45% of esophageal carcinoma, uterine carcinosarcoma, sarcoma, and lung adenocarcinoma, 20-30% of stomach adenocarcinoma, bladder urothelial carcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma, 5-15% of endometrial cancer, mesothelioma, cervical cancer, pancreatic adenocarcinoma, cutaneous melanoma, hepatocellular carcinoma, diffuse large B-cell lymphoma, and adrenocortical carcinoma, and 1-4% of rectum adenocarcinoma, prostate adenocarcinoma, colon adenocarcinoma, testicular germ cell tumors, kidney chromophobe, glioblastoma multiforme, low grade glioma, and renal clear cell carcinoma[104]. 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[105,106,107,108,109,110,111,112]. 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]. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme[5,6].

Potential relevance: HRD status is an important biomarker in advanced ovarian and prostate cancer because it predicts response to certain treatments including poly-ADP ribose polymerase (PARP) inhibitors and platinum chemotherapies[113,114,115]. Disruption of HRR or inhibition of PARP, are tolerated by cells through the utilization of complementary DNA repair pathways. However, presence of HRD and subsequent treatment with PARP inhibitors block DNA repair, causing accumulation of DNA damage and cell death through synthetic lethality[80,116,117,118]. Several PARP inhibitors are approved by the FDA for various cancers associated with markers of HRD. Olaparib[119] was the first PARP inhibitor originally approved in 2014 for ovarian cancer with germline mutations in BRCA1/2 (gBRCAm). The utility of olaparib has since expanded to include genomic instability markers and mutations in other HRR genes. Specifically, olaparib as monotherapy is now indicated for gBRCAm and somatic BRCA1/2 mutated (sBRCAm) ovarian cancer and in combination with bevacizumab for BRCA1/2 mutated or genomic instability positive ovarian cancer[119]. In addition, olaparib is approved in prostate cancer with germline or somatic mutations in HRR genes including ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L[83,119,120]. Olaparib is also approved for gBRCAm HER2 negative breast cancer and as maintenance therapies for gBRCAm pancreatic cancers[119]. Other PARP inhibitors that are FDA approved for BRCA mutated cancers include rucaparib[121] (2016) that is indicated for gBRCAm or sBRCAm ovarian and prostate cancers, niraparib[122] (2017) that is indicated for gBRCAm ovarian cancer, and talazoparib[123] (2018) that is indicated for gBRCAm HER2-negative metastatic breast cancer. Niraparib is also recommended for the treatment of HRD-positive ovarian cancer, defined by BRCA1/2 mutations and/or genomic instability[124]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA1/2 mutations. In 2022,

Biomarker Descriptions (continued)

the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[125], for BRCA1/2, PALB2, or other HRR gene mutations in breast and ovarian cancers. Like PARP inhibitors, pidnarulex[125] causes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. Despite tolerability and efficacy, acquired resistance to PARP inhibitors such as olaparib has been clinically reported[126]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[127]. Other potential mechanisms of resistance to PARP inhibitors include restoration of HRR activity, stabilization of the replication forks, inhibition of PARP trapping, increased drug efflux mediated by P-glycoprotein, and cell cycle control alterations[127,128,129,130].

RET amplification

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)[131]. 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[132].

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[133,134,135]. RET rearrangement is also present in 1-2% of non-small cell lung cancer (NSCLC)[136]. Point mutations in RET are relatively common in sporadic medullary thyroid cancer (MTC), with 6% of patients found to contain germline mutations[137]. Somatic mutations (specifically at codon 918), which leads to increased kinase activity, have been observed in at least 25% of MTC cases[137].

Potential relevance: The FDA approved small-molecule tyrosine kinase inhibitor, cabozantinib (2012), is recommended for the treatment of NSCLC patients with RET rearrangements[138]. Cabozantinib has also demonstrated clinical benefit in RET mutated medullary thyroid cancer patients[139]. Selpercatinib[140] is approved (2020) for RET fusion-positive NSCLC, thyroid cancer, and metastatic solid tumors that have progressed following systemic treatment. Selpercatinib[140] is also approved for RET-mutation positive medullary thyroid cancer (MTC). Additionally, the RET inhibitor, pralsetinib[141], 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[142], 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[143,144]. RET mutations at codon 918 are associated with high risk and adverse prognosis in patients diagnosed with MTC[145].

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.

Genomic Instability

pidnarulex

Cancer type: Breast Cancer, Ovarian Cancer

Variant class: HR Deficient

Supporting Statement:
The FDA has granted Fast Track designation to the small molecule inhibitor, pidnarulex, for BRCA1/2, PALB2, or other HRD mutations in breast and ovarian cancers.

Reference:

https://www.senhwabio.com//en/news/20220125

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

Genomic Instability

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + olaparib	●	●	●	●	✖
niraparib	✖	●	✖	●	● (II)
bevacizumab	✖	●	✖	✖	✖
bevacizumab + niraparib	✖	●	✖	✖	✖
olaparib	✖	✖	✖	✖	● (IV)
olaparib, bevacizumab	✖	✖	✖	✖	● (IV)
atezolizumab + talazoparib	✖	✖	✖	✖	● (II)
fluzoparib	✖	✖	✖	✖	● (II)
niraparib, chemotherapy	✖	✖	✖	✖	● (II)
tuvusertib, lartesertib, niraparib	✖	✖	✖	✖	● (II)
AMXI-5001	✖	✖	✖	✖	● (I/II)
niraparib, GSK-101	✖	✖	✖	✖	● (I/II)
sacituzumab govitecan, berzosertib	✖	✖	✖	✖	● (I/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

Genomic Instability (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
VIO-01	✖	✖	✖	✖	● (I/II)
CART-TAG72	✖	✖	✖	✖	● (I)
ceralasertib, olaparib, saruparib	✖	✖	✖	✖	● (I)
HS-10502	✖	✖	✖	✖	● (I)
MOMA-313, olaparib	✖	✖	✖	✖	● (I)
pidnarulex	✖	✖	✖	✖	● (I)
SIM-0501	✖	✖	✖	✖	● (I)
XL-309, olaparib	✖	✖	✖	✖	● (I)

TP53 p.(R213*) c.637C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
niraparib	✖	✖	✖	✖	● (II)
niraparib, GSK-101	✖	✖	✖	✖	● (I/II)
VIO-01	✖	✖	✖	✖	● (I/II)
HS-10502	✖	✖	✖	✖	● (I)
SIM-0501	✖	✖	✖	✖	● (I)
XL-309, olaparib	✖	✖	✖	✖	● (I)

FGFR1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pemigatinib	✖	✖	✖	✖	● (II)
regorafenib	✖	✖	✖	✖	● (II)
sunitinib	✖	✖	✖	✖	● (II)
BBI-355, futibatinib	✖	✖	✖	✖	● (I/II)
ABSK-121	✖	✖	✖	✖	● (I)

RET amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib, 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

RET amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
sunitinib, regorafenib	✖	✖	✖	✖	● (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	***31.14%***
BRCA1	***LOH, 17q21.31(41197602-41276231)x3***
BRCA2	***LOH, 13q13.1(32890491-32972932)x3***
BRCA2	***SNV, E2918A, AF:0.67***
BRIP1	***LOH, 17q23.2(59760627-59938976)x3***
CDK12	***LOH, 17q12(37618286-37687611)x3***
RAD51C	***LOH, 17q22(56769933-56811619)x3***
RAD51D	***LOH, 17q12(33427950-33446720)x3***

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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