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TEST REPORT

Ms. ABC

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Ms. ABC

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Patient Details

Name	:	Ms. ABC
Age	:	35 Years
Gender	:	Female
Address	:	---
Referring Doctor	:	Dr. XYZ

Specimen Details

Tumor Type	:	Invasive ductal carcinoma of breast
Specimen Type	:	Blood
Draw Date	:	26-Jan-2022 / 08.00 AM
Accession Date	:	28-Jan-2022 / 01.00 PM
Report Date	:	07-Feb-2022 / 11.00 AM

Specimen Analysis Summary

Blood

cf Total Nucleic acids	:	411 Genes (SNAs | Indels | CNAs | Fusion Transcripts)
RNA	:	20802 Genes
CTC- ICC	:	mTOR | VEGFR1 | VEGFR2 | VEGFA | EGFR
Pharmacogenetic analysis	:	25 Drugs
Chemosensitivity analysis	:	29 Drugs
Mismatch Repair (MMR)	:	MLH1, MSH2, MSH6, PMS1, PMS2

Targeted / Hormonal / Immunotherapy Drugs

(61 Clinical Trials Available : Refer to Page no. 32-45)

Report Highlights

Indications	USFDA Approved* / NCCN recommended* (Breast Cancer)	Off Label Therapy*
Germline BRCA2 p.C1975fs*29	☑ Olaparib ☑ Talazoparib	☑ Rucaparib ☑ Niraparib
ESR1 p.Y537S (MAF 21.84% at 28265X) p.Y537N (MAF 0.1% at 21500X) p.D538G (MAF 1% at 23503X) CYP2D6 normal metabolizer status (Tamoxifen)	☑ Fulvestrant ☑ Tamoxifen ☒ Letrozole ☒ Exemestane ☒ Anastrozole	⊟ None
PIK3CA p.H1047L (MAF 0.31% at 30792X)	☑ Alpelisib ☑ Everolimus	☑ Temsirolimus
VEGFA ICC Positive	☑ Bevacizumab	☑ Ziv-Aflibercept
KDR/VEGFR2 overexpression (+2.29 FC) **VEGFR1/FLT1** ICC Positive	⊟ None	☑ Axitinib ☑ Tivozanib ☑ Cabozantinib ☑ Lenvatinib ☑ Pazopanib ☑ Regorafenib ☑ Sorafenib ☑ Ponatinib ☑ Sunitinib
KDR/VEGFR2 overexpression (+2.29 FC)	⊟ None	☑ Vandetanib ☑ Ramucirumab

Biomarkers for Immune Checkpoint Inhibitors

Biomarker	Result
Blood based - tumor mutation burden (bTMB)	4 Mutations / Mb
MLH1, MSH2, MSH6, PMS1, PMS2 mutations	Negative

Longitudinal Monitoring Biomarkers

Biomarker	Result
Highest mutant allele frequency (HMAF)	32.1%
Number of CTCs detected	2 CTCs/ml

Germline Mutation

Germline BRCA2 p.C1975fs*29	Hereditary breast and ovarian cancer (HBOC) syndrome

☑ SOC Drugs with Benefit ☑ Off Label Drugs with Benefit* ☒ Drugs without Clinical Benefit / with Potential Resistance

SNA: Single Nucleotide Alteration; **CNA:** Copy Number Alteration; **INDELS:** Insertion / Deletion Polymorphism; **ICC:** Immunocytochemistry; **MAF:** Mutant Allele Frequency; **SOC:** Standard of Care; **CTC:** Circulating Tumor Cells; **FC:** Fold change; **MMR:** Mismatch Repair; **NCCN:** National Comprehensive Cancer Network.
*The USFDA approval or SOC recommendation may not be for the detected biomarker or alteration. The association of the detected biomarker or alteration and the drug may be based only on the literature evidence.

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Report Highlights

Cytotoxic Drugs

Chemosensitivity Analysis – % Cell Death (CD) ± Molecular biomarker

USFDA Approved / NCCN recommended (Breast Cancer)	
Drugs	**Result**
☑ Cyclophosphamide	84% CD
☑ Doxorubicin	84% CD
☑ 5FU/Capecitabine	47% CD
☒ Carboplatin	<25% CD
☒ Cisplatin	<25% CD
☒ Docetaxel	<25% CD
☒ Epirubicin	<25% CD
☒ Eribulin	<25% CD
☒ Gemcitabine	<25% CD
☒ Methotrexate	<25% CD
☒ Paclitaxel	<25% CD
☒ Vinorelbine	<25% CD

Off Label Therapy	
Drugs	**Result**
☑ Bleomycin	73% CD
☑ Etoposide	67% CD
☑ Mitoxantrone	47% CD
☑ Mitomycin	38% CD
☑ Dactinomycin	37% CD
☑ Pemetrexed	35% CD
☑ Cabazitaxel	32% CD
☑ Trabectedin	30% CD
☑ Vincristine	29% CD
☒ Dacarbazine	<25% CD
☒ Ifosfamide	<25% CD
☒ Irinotecan	<25% CD
☒ Melphalan	<25% CD
☒ Oxaliplatin	<25% CD
☒ Temozolomide	<25% CD
☒ Topotecan	<25% CD
☒ Vinblastine	<25% CD

Additional Report Highlights

Indications for Non-Oncology Drugs

Drug	Indication
☑ Atorvastatin	MAPK pathway activation - MAP4K4 (+2.27 FC) overexpression
☑ Celecoxib	MAPK pathway activation - MAP4K4 (+2.27 FC) overexpression
☑ Doxycycline	MMP9 (+5.08 FC), MMP12 (+9.89 FC), MMP25 (+3.34 FC) overexpression
☑ Berberine	MMP9 (+5.08 FC), MMP12 (+9.89 FC), MMP25 (+3.34 FC) overexpression

Disease Relevant Findings

Biomarker	Result
ERBB2/HER2	No alterations detected
NTRK1/3	No fusions detected

☑ SOC Drugs with Benefit ☑ Off Label Drugs with Benefit* ☒ Drugs without Clinical Benefit / with Potential Resistance

Pharmacogenetics : Drugs with Contraindications

Drug	Indication	Drug	Indication
⊟		⊟	

Pharmacogenetics : Drugs with Increased Risk of Toxicity

Drug	Indication	Drug	Indication
⚠ Belinostat	UGT1A1	⚠ Cisplatin	XPC, ERCC1
⚠ Erdafitinib	CYP2C9	⚠ Erlotinib	UGT1A1
⚠ Irinotecan	UGT1A1	⚠ Nilotinib	UGT1A1
⚠ Pazopanib	UGT1A1	⚠ Regorafenib	UGT1A1
⚠ Sacituzumab govitecan	UGT1A1		

Pharmacogenetics : Drugs with Labeled Risk of Toxicity

Drug	Indication	Drug	Indication
☑ 5-Fluorouracil	DPYD	☑ Capecitabine	DPYD
☑ Carboplatin	ERCC1, MTHFR	☑ Cyclophosphamide	GSTP1
☑ Dabrafenib	G6PD	☑ Epirubicin	GSTP1
☑ Gefitinib	CYP2D6	☑ Gemcitabine	NT5C2
☑ Mercaptopurine	TPMT, NUDT15	☑ Methotrexate	ABCB1, MTHFR
☑ Oxaliplatin	ERCC1	☑ Rasburicase	G6PD
☑ Tegafur	DPYD	☑ Thioguanine	TPMT, NUDT15
☑ Trametinib	G6PD	☑ Vincristine	CEP72

Summary of Other Genomic Alterations

Gene	Alteration Type (SNAs / Indels / CNAs/ Fusion)	Variant Classification	Therapeutic Significance
CYP2D6	p.R101C (MAF 32.1% at 4516X)	VUS	---
CTNNA1	p.A798V (MAF 1% at 4027X)	VUS	---
MYC	Gain	---	Refer to page no. 6
FANCD2, VHL, PPARG, RAF1, XPC	Gain (3 copies)	---	---
UBR5, CSMD3	Gain (3 copies)	---	---
MAP2K1, PML, NTRK3, IDH2, BLM, IGF1R	Gain (3 copies)	---	---
ETV4, ITGB3, COL1A1, HLF, FANCJ, CD79B, PRKAR1A, SEPT9, BIRC5, RNF213	Gain (3 copies)	---	---
BCL2L1, ASXL1, SRC, MAFB, TOP1, PLCG1, PTPRT, AURKA, GNAS	Gain (3 copies)	---	---

VUS: Variant of unknown / uncertain significance ⊟ Not Applicable ⚠ Drugs with Increased Risk of Toxicity ☑ Drugs with Labeled Risk of Toxicity

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Genomic Findings

Blood Based - Tumor Mutation Burden (bTMB)

Markers	Result
Blood based - Tumor Mutation Burden (bTMB)	**4 Mutations/Mb**
Interpretation	**Category**
Low bTMB	**Tier III**

Blood based - Tumor Mutation Burden (bTMB) is: 4 Mutations/Mb. bTMB was calculated based on the allelic fraction of the somatic mutations detected by Next Generation Sequencing analysis of 411 genes.

Tumor mutation burden (TMB), the total number of somatic coding mutations in a tumor, is a promising predictive biomarker for immunotherapy response in cancer patients[1, 2].The somatic mutations in tumor DNA can give rise to neoantigens, mutation-derived antigens that are recognized and targeted by the immune system, especially after treatment with agents that activate T cells. Therefore, more somatic mutations a tumor has, the more neoantigens it is likely to form, and TMB can represent a useful estimation of tumor neoantigenic load [1,2]. Tumor mutation burden (TMB) is, thus, an informative biomarker for predicting response to immune checkpoint inhibitors like Pembrolizumab, Nivolumab, Atezolizumab, Avelumab, Durvalumab and Ipilimumab.

Clinical studies have shown associations between elevated TMB and efficacy of immune checkpoint inhibitors, alone or in combination with other agents, in multiple solid tumors including, lung cancer, urothelial carcinoma, melanoma, colorectal cancer, head and neck squamous cell carcinoma and other cancer types [3-14].

Analysis of tumor mutation burden (TMB) across more than 100,000 multiple solid cancer specimens suggests that patients with TMB >20 mutations/Mb may derive benefit from immune checkpoint inhibitors [15].

In various malignancies TMB >10 mutations/Mb have shown benefit from immune checkpoint inhibitors [3,12,16-19].

Pembrolizumab has been USFDA approved for the treatment of patients with tumor mutation burden-high (TMB-H) [U10 mutations/megabase (mut/Mb)] solid tumors.

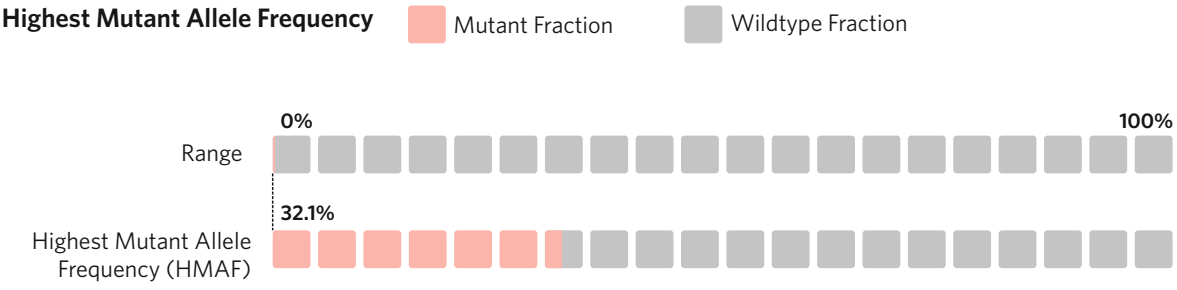
In a clinical trial of NSCLC patients with blood TMB (bTMB) of 6 or higher, anti-programmed cell death 1 (anti-PD-1) and antiprogrammed cell death ligand 1 (anti-PD-L1) therapy showed objective response rate of 39.3% [20]. Also, it is reported that, TMB measured from the blood is a predictive biomarker for PFS in patients receiving Atezolizumab monotherapy in NSCLC. Analyses of POPLAR and OAK trials demonstrate that, bTMB≥16 is a clinically meaningful and technically robust cutpoint to determine clinical benefit from immune checkpoint inhibitors [21].

The median tumor mutation burden (TMB) (n=4297) for breast invasive ductal carcinoma is reported to be 3.6 mutations/Mb, while the maximum TMB is 261.3 mutations/Mb (95% Confidence Interval, 1 - 1.7) [15].

High TMB (TMB-H) is indicative of potential benefit from immune checkpoint inhibitors. Blood based - Tumor mutation burden (bTMB) detected in the submitted sample is 4 mutations/Mb. **Therefore in this case, there is no indication of immune checkpoint inhibitor therapy based on TMB.**

Cell Free Nucleic Acids: Somatic Genome Alterations

Highest Mutant Allele Frequency



CYP2D6 p.R101C	**32.1%**
ESR1 p.Y537S	**21.84%**
ESR1 p.D538G	**1%**
CTNNA1 p.A798V	**1%**
PIK3CA p.H1047L	**0.31%**
ESR1 p.Y537N	**0.1%**

1. Highest mutant allele frequency of 32.1% was detected in the cell free nucleic acids isolated from patient's plasma.
2. Activating PIK3CA p.H1047L mutation, is suggestive of potential benefit from the PI3K inhibitor, Alpelisib as well as mTOR inhibitors, Everolimus, Temsirolimus.
3. The presence of activating ESR1 p.Y537S, p.D538G and p.Y537N mutations, in the cell free nucleic acids analysis, is suggestive of resistance to aromatase inhibitors Letrozole, Anastrozole and Exemestane. However, ESR1 activating mutations are suggestive of potential benefit from Fulvestrant and Tamoxifen, at higher standard doses.
4. The clinical significance of variants detected in CYP2D6 and CTNNA1 genes in breast cancer is not well evaluated, as per available literature.

Genomic Findings

Single Nucleotide Alterations / Indels / Copy Number Alterations / Fusion

Gene/s (Transcript ID)	Variant
PIK3CA (NM_006218.2)	**c.3140A>T, p.H1047L; [p.(His1047Leu)]**

Category : Tier I (Level A)

Interpretation

PIK3CA mutations are present in 30-40% of estrogen receptor positive (ER+), human epidermal growth factor receptor 2 - negative (HER2-) primary as well as metastatic breast cancer and result in the activation of PI3K/AKT pathway [22-25]. Therefore, activating mutations in PIK3CA gene, are suggestive of potential benefit from the PI3K inhibitor, Alpelisib as well as mTOR inhibitors, Everolimus, Temsirolimus [24-26].

Alpelisib is a kinase inhibitor indicated in combination with Fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer.

Everolimus is USFDA approved for treatment of multiple tumor types, including hormone receptor positive, HER2 negative breast cancer.

Alpelisib and Everolimus are also standard of care drugs for breast cancer as per NCCN guidelines [27].

Temsirolimus is USFDA approved for the treatment of patients with advanced renal cell carcinoma.

In a phase II study, Temsirolimus showed objective response rate of 9.2%, median time to progression of 12 weeks and tolerable safety profile in heavily pre-treated patients with locally advanced or metastatic breast cancer (n=109) [28].

In a phase II randomized 3-arm study, combination of Temsirolimus and Letrozole demonstrated a clinical benefit rate of 82% (Letrozole +10 mg daily Temsirolimus), 83% (Letrozole + 30 mg daily Temsirolimus for 5 days every 2 weeks) and 79% (Letrozole alone) in postmenopausal women with locally advanced or metastatic breast cancer (n=92). Progression free survival at one year was higher for the combination arms (69% and 62%), than for the Letrozole alone arm (48%) [29].

Mutations in PIK3CA gene are suggestive of acquired resistance to endocrine therapy in ER-positive breast cancer [30-34]. However, contradictory evidence exists for the same [35].

Various studies suggest simultaneous activating PIK3CA mutation leads to lower pathological complete response (pCR) to anti-HER2 therapies Trastuzumab, Lapatinib or their combination in HER2 positive breast cancer [36-42].

PIK3CA activating mutations are reported to be associated with potential lack of benefit from EGFR-targeted monoclonal antibodies, Cetuximab, Panitumumab and Necitumumab [43-45] as well as anti-EGFR tyrosine kinase inhibitors (TKIs) [46-50].

It is reported that PIK3CA mutated tumors are associated with worse survival in patients treated with immune checkpoint inhibitors [51,52]. However, contradictory evidence exists for the same [53,54].

PIK3CA p.H1047L is a hotspot mutation that lies within the PI3K/PI4K domain of the PIK3CA protein. This mutation results in increased phosphorylation of AKT and MEK1/2, growth factor-independent cell survival, and transformation in cell culture [55,56] It is reported in tumors of breast, lung, large intestine, endometrium and soft tissue.

The PIK3CA gene provides instructions for making the p110 alpha protein, which is a subunit of an enzyme called phosphatidylinositol 3-kinase (PI3K). The p110 alpha protein is called the catalytic subunit because it performs the action of PI3K, while the other subunit (produced by a different gene) regulates the enzyme's activity.

Gene/s (Transcript ID)	Variant
ESR1 (NM_001122740.1)	**c.1610A>C,p.Y537S; [p.(Tyr537Ser)]** **c.1613A>G,p.D538G; [p.(Asp538Gly)]** **c.1609T>A,p.Y537N; [p.(Tyr537Asn)]**

Category : Tier I (Level B)

Interpretation

ESR1 mutations are more frequently observed in metastatic tissue and circulating cell-free DNA of metastatic breast cancer patients pre-treated with endocrine therapy. ESR1 mutations within the ligand-binding domain (LBD) have been shown to result in resistance to aromatase inhibitors like Letrozole, Anastrozole and Exemestane as well as Tamoxifen and Fulvestrant [57-60]. Although some clinical as well as pre-clinical studies suggest that ligand binding domain (LBD) ESR1 mutants show resistance to Tamoxifen and Fulvestrant, higher standard doses of these agents might benefit patients with tumors harboring LBD-mutated ER [57,60-66].

Fulvestrant is USFDA approved for the treatment of hormone receptor positive (HR+) and HER2-negative advanced breast cancer or with Palbociclib in women with HR+ and HER2-negative advanced or metastatic cancer that got worse after treatment with hormone therapy.

Tamoxifen is USFDA approved for the treatment of hormone receptor positive early breast cancer and hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.

Fulvestrant and Tamoxifen are also standard of care drugs for the treatment of breast cancer, as per NCCN guidelines [27].

ESR1 p.Y537N, p.Y537S and p.D538G are activating mutations that lie in the ligand-binding domain (LBD) of ESR1. In vitro studies demonstrate that these mutations promote estrogen-independent activation of the receptor [57,60]. In silico analysis predicts these variants to be gain-of-function mutations. ESR1 p.Y537N is reported in tumors of breast and endometrium. ESR1

p.Y537S is reported in tumors of breast and ovary. ESR1 p.D538G are reported in tumors of breast.

ESR1 gene encodes an estrogen receptor, a ligand-activated transcription factor composed of several domains important for hormone binding, DNA binding, and activation of transcription. The protein localizes to the nucleus where it may form a homodimer or a heterodimer with estrogen receptor 2. Estrogen receptors are involved in multiple pathological processes including breast cancer.

Markers (Cytoband)	Result
MYC (8q24.21)	**Gain**

Category : Tier I (Level B)

Interpretation

MYC copy number gain is present in 30-50% of high-grade breast cancers. MYC, a proto-oncogene located at 8q24.21, plays a central role in proliferation and malignant transformation in breast cancer [67]. In breast cancer, amplification of MYC is consistently observed in aggressive forms of disease and correlates with an adverse prognosis and distant metastases in these patients [68,69].

Amplification of MYC gene is also reported to promote immune-suppression in triple negative breast cancer via inhibition of IFN signaling [70]. In a phase I clinical study, treatment with immune checkpoint inhibitor (ICI), Nivolumab resulted in hyperprogressive disease in a lung cancer patient harboring EGFR exon 20 insertion mutation with amplification of MYC gene. It is reported that EGFR aberrations and MYC amplification may act as potential mechanisms for hyperprogressive disease [71]. However, role of MYC gene copy number gain in hyperprogressive disease with immune checkpoint inhibitor therapy in breast cancer is not yet known.

BRCA1/2 Mutation Analysis

Sample is positive for germline pathogenic mutation, p.C1975fs*29 [c.5925delT, p.(Cys1975fsTer29)] in BRCA2 gene as evaluated by Next Generation Sequencing (NGS) and confirmed by Sanger sequencing.

No large genomic rearrangements (LGRs) (large deletions and duplications) detected in the BRCA1 /BRCA2 genes as evaluated by Multiplex Ligation-dependent Probe Amplification (MLPA).

Patient may derive potential benefit from poly ADP-ribose polymerase (PARP) inhibitors, Olaparib, Talazoparib, Rucaparib and Niraparib as well as platinum based chemotherapy drugs, Carboplatin, Cisplatin and Oxaliplatin.

Gene Transcript	Variant	Zygosity	Classification	Disease	Inheritance
BRCA2 (NM_000059.3)	c.5925delT, p.C1975fs*29; [p.(Cys1975fsTer29)] rs1555284465	Heterozygous	Pathogenic	Hereditary breast and ovarian cancer (HBOC) syndrome	Autosomal dominant

Interpretation

The germline c.5925delT, p.(Cys1975fsTer29) pathogenic variant in BRCA2 gene has been reported in patients with hereditary breast and ovarian cancer (HBOC) syndrome [72]. This variant is a single base pair deletion from exon 11 of the BRCA2 gene, results in frameshift after codon 1975 causing premature translational stop signal after 29 amino acid. This alteration is predicted to result in a truncated or absent protein and loss of function. Loss of function variants of the BRCA2 gene are an established mechanism of disease in hereditary breast and ovarian cancer. Loss-of-function variants in BRCA2 gene are known to be pathogenic [72,73]. The allele frequency of this variant in general population is not yet known [74]. In summary, we interpret c.5925delT, p.(Cys1975fsTer29) in BRCA2 gene as a pathogenic variant for hereditary breast and ovarian cancer (HBOC) syndrome.

Studies indicate that women with pathogenic mutations in BRCA2 have a risk of breast cancer of 69% by age of 80 years. Women with pathogenic BRCA2 mutations have a high risk of developing a new primary cancer in the contralateral breast in the years following a breast cancer diagnosis. Around 38-84% of women with BRCA2 mutation can develop breast cancer. The risk of developing second primary breast cancer is reported to be 10% within next 10 years in BRCA2 carriers. This risk increases to approximately 62% by age of 70 years. The risk of ovarian cancer is 16.5 to 27% in women with BRCA2 mutation. In male carriers, the risk of breast cancer is up to 8% and the risk of prostate cancer is up to 15% by age of 65 years with 20% lifetime risk. There may be an increase in risk of pancreatic cancer and melanoma in BRCA2 carriers. Due to the autosomal dominant inheritance, each first degree relative of this individual has a one-in two chance of having this mutation [75]. Family members can be tested for this specific mutation.

The presence of pathogenic BRCA2 mutation is suggestive of potential therapeutic benefit from PARP inhibitors Olaparib, Talazoparib, Rucaparib and Niraparib.

Olaparib is USFDA approved for treatment of multiple cancers, including germline BRCA-mutated breast cancer. Talazoparib is USFDA approved for treatment of germline BRCA-mutated breast cancer.

Olaparib and Talazoparib are also standard of care drugs for germline BRCA-mutated breast cancer as per NCCN guidelines [27].

Rucaparib is USFDA approved for prostate cancer and advanced ovarian epithelial, fallopian tube, or primary peritoneal cancer patients with germline BRCA mutations.

In a phase 2 multicentre trial, Rucaparib in germline BRCA mutated breast and ovarian cancer was well tolerated with an overall response rate of 15% (n=71) [76].

Niraparib is USFDA approved for ovarian epithelial, fallopian tube or primary peritoneal cancer with BRCA mutations. In an open-label trial, treatment of Niraparib with Pembrolizumab demonstrated promising antitumor activity (objective response rate of 21% and disease control rate of 49%) in patients with advanced or metastatic breast cancer (n=47), with numerically higher response rates (objective response rate of 47%, disease control rate of 80% and median progression free survival of 8.3 months) in tumors with BRCA mutations [77].

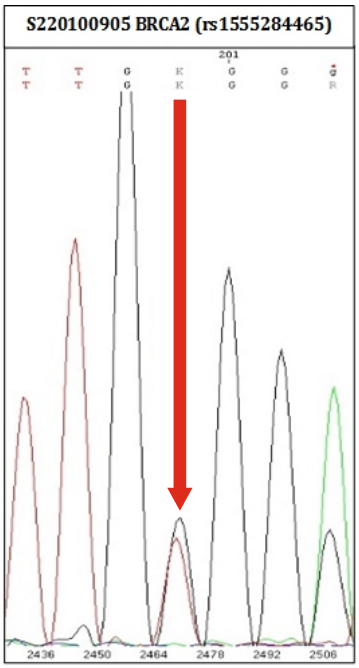
Studies also suggest that pathogenic BRCA2-positive patients demonstrate high pathological complete remission (pCR) after platinum-based neoadjuvant chemotherapy [78,79].

Carboplatin is USFDA approved for ovarian cancer.

Cisplatin is USFDA approved for bladder cancer, ovarian cancer and testicular cancer.

Carboplatin and Cisplatin are also standard of care drugs for breast cancer as per NCCN guidelines [27].

Oxaliplatin is USFDA approved for colorectal cancer and stage III colon cancer. In a clinical study, combination of Oxaliplatin and Capecitabine in anthracyclines and taxanes pretreated breast cancer patients (n=28) showed moderate activity (objective responses in 32%, median overall survival of 10 months) and was well tolerated [80].



Confirmation of BRCA2 c.5925delT, p.(Cys1975fsTer29) mutation on Sanger sequencing

Recommendation

- Consultation with a healthcare professional who has training and experience in cancer genetics is strongly recommended for this patient in order to discuss cancer risks and other disease risks associated with this genetic test result. The type and frequency of cancer surveillance, cancer prevention options and strategies and the impact of this result on the cancer risks for members of the patient's family are also recommended topics of discussion with a health care professional.
- Genetic testing for BRCA2 mutation of other family members like siblings (sisters as well as brothers) and children (daughters as well as sons) is recommended after counselling.

Mismatch Repair (MMR) Gene Mutations

Analysis of the mismatch repair (MMR) genes, MLH1, MSH2, MSH6, PMS1 and PMS2, did not detect any pathogenic or likely pathogenic germline mutations in the submitted sample.

It is reported that, immune checkpoint blockade therapy has a promising response in MMR- deficient (dMMR) cancers regardless of the tissue of origin [81,82]. Literature-based evidence suggests that loss of mismatch repair function via germline or somatic mutation confers the microsatellite instability (MSI) phenotype that is associated with high TMB and response to immune-checkpoint inhibitors [81-85]. An average of 1782 somatic mutations per tumor and 578 potential neoantigens are found in mismatch repair deficient (dMMR) tumors, compared with 73 mutations and 21 neoantigens in mismatch repair proficient (pMMR) tumors by exome sequencing (P = 0.007). Higher numbers of somatic mutations and neoantigens are correlated with better responses and longer progression free survival (PFS). Furthermore, dMMR tumors have a dense infiltration of CD8+ TILs, which induces a better and more durable response [86]. Subsequently, USFDA approved Pembrolizumab and Dostarlimab-gxly for all dMMR/MSI-H solid tumors [87-90].

No germline pathogenic and likely pathogenic mutations indicative of dMMR status are detected in the MMR genes. Therefore in this case, there is no indication of immune checkpoint inhibitor therapy based on germline analysis of MMR genes.

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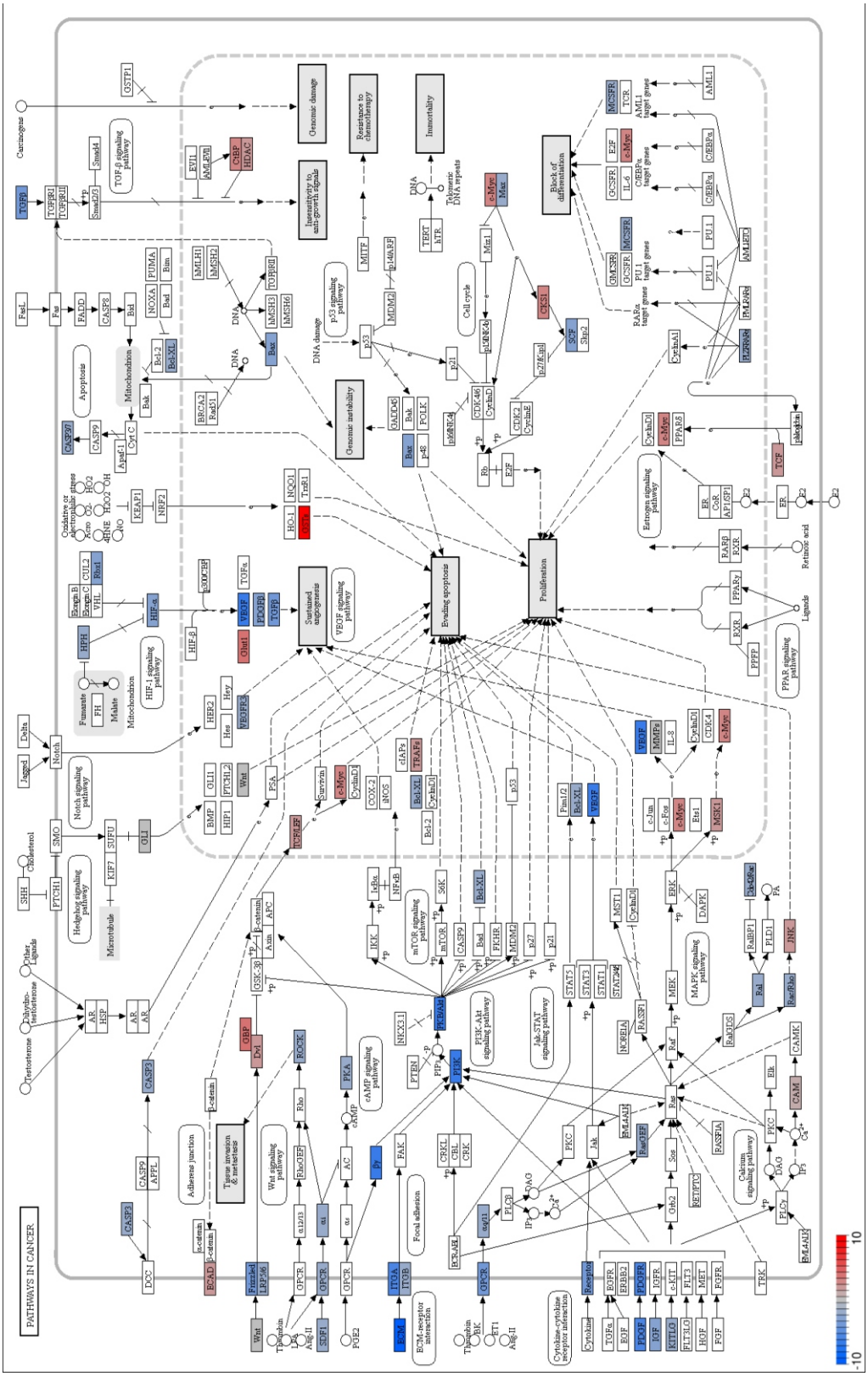
KEGG Pathway: 20802 Genes Analysis

KEGG Pathway

Comprehensive Pathway Perturbation in Primary Tumor



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Global Gene Expression Highlights

Gene Expression

Out of **20802** protein coding genes analyzed in the blood sample, **7879** genes were expressed in the analyzed blood sample. **1421** genes were found to be differentially regulated in the blood sample.

List of Oncology Drugs with Potential Benefit

Gene/s	Result (Fold Change)
KDR/VEGFR2	▲ **+2.29 FC**

Drugs With Benefit

- ☑ **Axitinib**
- ☑ **Cabozantinib**
- ☑ **Pazopanib**
- ☑ **Sorafenib**
- ☑ **Sunitinib**
- ☑ **Lenvatinib**
- ☑ **Vandetanib**
- ☑ **Ramucirumab**
- ☑ **Regorafenib**
- ☑ **Ponatinib**

Interpretation

Upregulation of VEGFR2/KDR gene is suggestive of potential benefit from Axitinib, Cabozantinib, Pazopanib, Sorafenib, Sunitinib, Regorafenib, Lenvatinib, Vandetanib, Ramucirumab and Ponatinib [91,92].

Axitinib is USFDA approved for the treatment of advanced renal cell carcinoma (RCC).

In a randomized double-blind phase II study, the combination of Axitinib (AG) and Docetaxel (DOC) demonstrated an acceptable safety profile and promising anti-tumor activity as compared to DOC plus placebo (PL) in metastatic breast cancer patients (n=168) (overall response rate of 40% for AG+DOC arm and 23% for DOC+PL arm) [93].

Cabozantinib is USFDA approved for the treatment of hepatocellular carcinoma, advanced renal cell carcinoma (RCC) and thyroid cancer.

In a phase II placebo-controlled randomized discontinuation study, Cabozantinib demonstrated clinical activity with objective response of 13.6% and disease control rate of 46.7% in heavily pretreated metastatic breast cancer patients (n=45) [94].

Pazopanib is USFDA approved for treatment of advanced renal cell carcinoma and soft tissue sarcoma.

In a phase II study, Pazopanib was well tolerated and showed partial response in 1, stable disease in 11 and clinical benefit rate of 26% in patients with recurrent or metastatic invasive breast carcinoma (n=19) [95].

Sorafenib is USFDA approved for the treatment of advanced renal cell, hepatocellular and thyroid carcinoma. Combination of Letrozole, metronomic Cyclophosphamide and Sorafenib was well tolerated and showed activity in estrogen receptor positive breast cancer patients (n=13). Complete clinical response in 6 patients and a significant reduction in tumor size between the baseline and 14 days of treatment was observed in all patients [96].

In a phase I/II study, the combination of Sorafenib and Letrozole used as first-line therapy in hormone-receptor positive metastatic breast cancer (MBC) patients (n=41) demonstrated activity (partial response: 39%, stable disease: 41%) with clinical benefit rate of 81% [97].

Sunitinib is USFDA approved for the treatment of advanced renal cell carcinoma, gastrointestinal stromal tumor and pancreatic neuroendocrine tumors.

Sunitinib in combination with Trastuzumab demonstrated antitumor activity with objective response rate of 37% and clinical benefit rate of 56% in a phase II study of advanced breast cancer patients (n=57). Among these, the patients who were treatment-naive or had only received prior adjuvant treatment showed an objective response rate of 44% and clinical benefit rate of 59% [98].

In an exploratory study, Sunitinib in combination with Docetaxel and Trastuzumab as first-line therapy for HER2-positive metastatic breast cancer patients (n=22) showed an acceptable toxicity profile and preliminary antitumor activity (objective response in 73%) [99].

In a phase II study, Sunitinib malate was found to be active (overall response rate of 11%; median time to progression and overall survival was 10 and 38 weeks, respectively) in patients with metastatic breast cancer (MBC) previously treated with an Anthracycline and a Taxane (n=64) [100].

Lenvatinib is USFDA approved for the treatment of endometrial, hepatocellular carcinoma, advanced renal cell carcinoma and thyroid cancer.

In a phase Ib/II trial, combination of Lenvatinib and Letrozole showed significant anti-tumor activity with overall disease control rate of 93.8% and stable disease rate of 43.8% in postmenopausal women with hormone receptor positive, locally advanced / metastatic breast cancer (n=16) [101].

Vandetanib is USFDA approved for the treatment of medullary thyroid cancer.

In a phase I study, the combination of Vandetanib and continuous oral metronomic Cyclophosphamide and Methotrexate in metastatic breast cancer patients (n=20) demonstrated modest clinical activity with partial response in 10%, stable disease in 65%, of which 15% showed a stable disease for ≥ 6 months [102].

Ramucirumab is USFDA approved for the treatment of non-small cell lung cancer, stomach adenocarcinoma or gastroesophageal junction adenocarcinoma and colorectal cancer.

In a multicenter phase Ib study, the combination of Ramucirumab and Docetaxel was tolerable in breast cancer patients (n=7) and showed partial response in 4 patients [103].

Regorafenib is USFDA approved for the treatment of colorectal, hepatocellular cancers and gastrointestinal stromal tumors (GIST).

In a pre-clinical study, Regorafenib reduced cell proliferation and enhanced radiosensitivity in breast cancer cells [104].

Ponatinib is USFDA approved for the treatment of Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia and/or acute lymphoblastic leukemia.

In a pre-clinical study, Ponatinib significantly inhibited the migration and mammosphere formation of breast cancer cells in vitro and blocked breast cancer lung metastasis in multiple in vivo models [105].

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List of Non-oncology Agents That May Provide Therapeutic Benefit

Gene Expression

Gene/s	Result (Fold Change)
MMP9	▲ +5.08 FC
MMP12	▲ +9.89 FC
MMP25	▲ +3.34 FC

Drugs With Benefit

☑ Doxycycline ☑ Berberine

Interpretation

The antibiotic agent, Doxycycline, non-selectively inhibits MMP activation and expression, and has been shown to suppress MMP activities in human cancer cells[106,107]

Numerous studies have shown that Berberine and its derivatives demonstrate important anti-tumor effects. Berberine appears to exert its anticancer properties by inducing ROS production and prevention of cell migration via inhibition of the gene expression of MMP in various cancers[108-111].

Gene/s	Result (Fold Change)
MAP4K4	▲ +2.27 FC

Drugs With Benefit

☑ Atorvastatin ☑ Celecoxib

Interpretation

Atorvastatin induces apoptosis in multiple cancers by inhibiting MAPK-Bcl-2 signaling pathway [112-117].

Several pre-clinical evidence demonstrate that Atorvastatin and Celecoxib and/or in combination, were more effective, than when given individually at higher doses. Inhibition of carcinogenesis by these agents is associated with the inhibition of cell proliferation and increase in apoptosis in tumor cells [112,114,118-122].

Pre-clinical studies have demonstrated that Mebendazole inhibits the growth of various cancer cells by targeting the MAPK pathway [123-128].

List of Oncology Drugs Without Therapeutic Benefit

⊟ Not Applicable

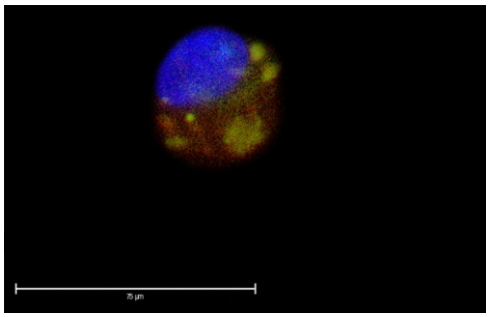
Circulating Tumor Cells Enumeration

CTCs

Circulating Tumor Cells (CTCs): **DETECTED**
Number of CTCs: **2 CTCs/ml peripheral blood**
CTCs are defined as EPCAM+ve, CK+ve, CD45-ve cells

Interpretation

2 CTCs/ml peripheral blood detected in the submitted sample.



Fluorescent microscopic image of CTC

Immunocytochemistry (ICC) Analysis on CTCs

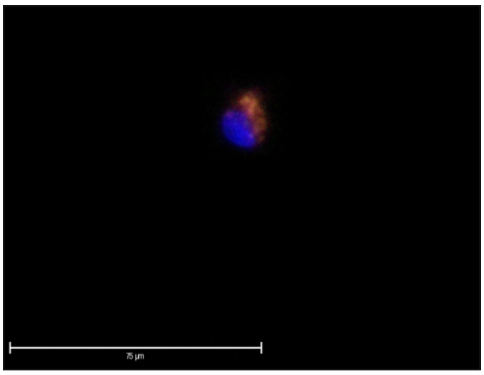
Markers	Result
VEGFR1/FLT1	**Positive**

Interpretation

Positive staining of VEGFR1/FLT1 is indicative of potential benefit from Axitinib, Cabozantinib, Pazopanib, Sorafenib, Sunitinib, Tivozanib, Lenvatinib, Regorafenib and Ponatinib[129-142].

Tivozanib is USFDA approved for the treatment of relapsed or refractory advanced renal cell carcinoma. In a phase I, dose-escalation study, Tivozanib with weekly Paclitaxel in metastatic breast cancer patients (n=13) showed partial response in 4 (30.8 %) and stable disease in 4 patients (30.8 %) of >6 months [143].

Kindly refer to USFDA labels of Axitinib, Cabozantinib, Pazopanib, Sorafenib, Sunitinib, Lenvatinib, Regorafenib and Ponatinib mentioned earlier.



VEGFR1/FLT1 **Positive**

Markers	Result
VEGFA	**Positive**

Interpretation

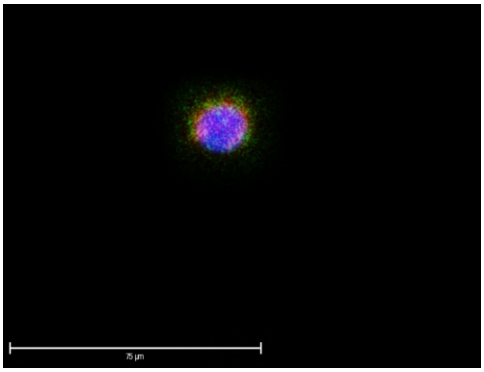
Positive staining of VEGFA is indicative of potential benefit from Bevacizumab and Ziv-Aflibercept [144,145].

Bevacizumab is USFDA approved for the treatment of renal cell carcinoma, hepatocellular, cervical, colorectal, lung cancers, ovarian epithelial, fallopian tube or primary peritoneal cancer and glioblastoma.

Combination of Paclitaxel and Bevacizumab is a standard of care therapy for breast cancer as per NCCN guidelines [27].

Ziv-Aflibercept is USFDA approved for the treatment of metastatic colorectal cancer.

In a phase I trial, treatment of Capecitabine with Aflibercept in patients with gastrointestinal and breast cancer showed manageable safety profile with objective response rate of 15.4% in arm A (continuous Capecitabine dosing) and 7.7% in arm B (intermittent Capecitabine dosing) among 26 assessable patients [146].



VEGFA ICC **Positive**

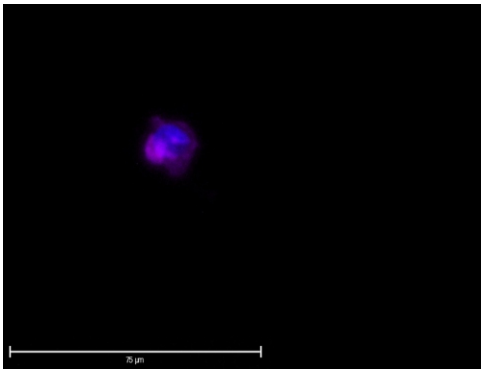
Markers	Result
mTOR	**Negative**

Interpretation

No staining of mTOR is indicative of potential lack of benefit from Everolimus and Temsirolimus [147-150].

Kindly refer to USFDA label for these drugs mentioned earlier.

However, simultaneous presence of activating PIK3CA mutation is indicative of potential benefit from these drugs.



mTOR ICC **Negative**

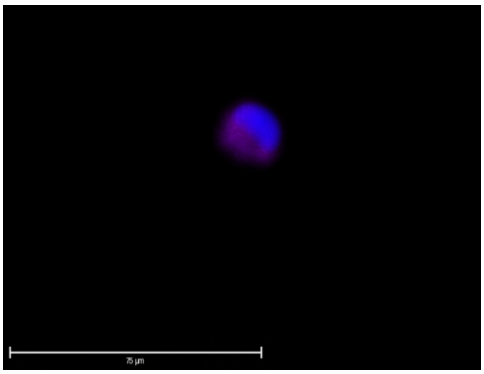
Markers	Result
VEGFR2/KDR	**Negative**

Interpretation

No staining of VEGFR2/KDR is indicative of potential lack of benefit from Axitinib, Cabozantinib, Pazopanib,Sorafenib, Sunitinib, Tivozanib, Lenvatinib, Vandetanib, Ramucirumab, Regorafenib and Ponatinib [129-142].

However, simultaneous overexpression of KDR/VEGFR2 is suggestive of potential benefit from these drugs.

Kindly refer to USFDA labels of these drugs mentioned earlier.



VEGFR2/KDR ICC **Negative**

Markers	Result
EGFR	**Negative**

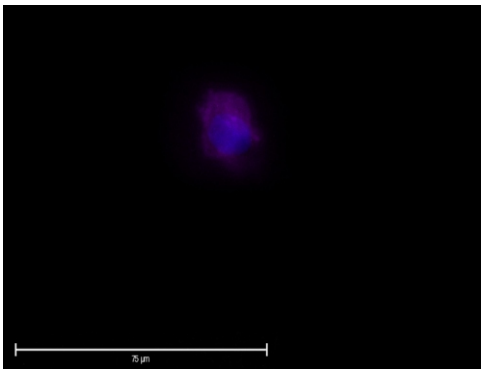
Interpretation

No staining of EGFR is indicative of potential lack of benefit from Cetuximab, Panitumumab and Necitumumab[151-154].

Cetuximab is USFDA approved for the treatment of head and neck and colorectal cancer.

Panitumumab is USFDA approved for treatment of colorectal cancer.

Necitumumab is USFDA approved for the treatment of squamous non-small cell lung cancer.



EGFR ICC **Negative**

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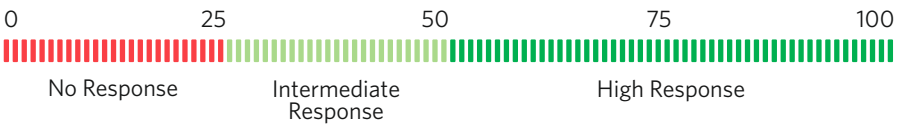
Chemosensitivity Analysis on CTCs

Chemosensitivity

Chemosensitivity assay performed on cultured circulating tumor and its associated cells indicates the effectiveness of chemotherapeutic drugs in descending order of in vitro response.

Drug Names	% Cell Death	Drug Response
Cyclophosphamide	84	
Doxorubicin	84	
Bleomycin	73	
Etoposide	67	
Mitoxantrone	47	
5-Fluorouracil/Capecitabine	47	
Mitomycin	38	
Dactinomycin	37	
Pemetrexed	35	
Cabazitaxel	32	
Trabectedin	30	
Vinblastine	29	
Carboplatin	< 25	
Cisplatin	< 25	
Dacarbazine	< 25	
Docetaxel	< 25	
Epirubicin	< 25	
Eribulin	< 25	
Gemcitabine	< 25	
Ifosfamide	< 25	
Irinotecan	< 25	
Melphalan	< 25	
Methotrexate	< 25	
Oxaliplatin	< 25	
Paclitaxel	< 25	
Temozolomide	< 25	
Topotecan	< 25	
Vincristine	< 25	
Vinorelbine	< 25	

CHEMO SCALE



Pharmacogenetic Analysis

Pharmacogenetics

Drug with Contraindication	Drug with Increased Risk of Toxicity	Drug with Labelled Toxicity
☒ None	! Belinostat	☑ 5-Fluorouracil
	! Cisplatin	☑ Capecitabine
	! Erdafitinib	☑ Carboplatin
	! Erlotinib	☑ Cyclophosphamide
	! Irinotecan	☑ Dabrafenib
	! Nilotinib	☑ Epirubicin
	! Pazopanib	☑ Gefitinib
	! Regorafenib	☑ Gemcitabine
	! Sacituzumab govitecan	☑ Mercaptopurine
		☑ Methotrexate
		☑ Oxaliplatin
		☑ Rasburicase
		☑ Tegafur
		☑ Thioguanine
		☑ Trametinib
		☑ Vincristine

Analysis of Pharmacogenetics Markers for Oncology Drugs

Drug	Gene Analysis
Belinostat	**UGT1A1; *28/*28**

Evidence level : Level 1A

Interpretation

The patient has a poor metabolizer status for UGT1A1 gene, leading to significantly reduced UGT1A1 activity.

Patients with such genotype may have decreased clearance of Belinostat. Reduce the starting dose of Belinostat to 750 mg/m2 to minimize dose limiting toxicities [155].

Drug	Gene Analysis
Cisplatin	**ERCC1; rs11615 GG** **XPC; rs2228001 GT**

Evidence level : Level 1B,2B

Interpretation

The patient has an unfavorable genotype in the analysed XPC gene variant.

Patients with such genotype may have an increased risk of hearing loss, neutropenia and decreased but not non-existent risk of nephrotoxicity when treated with Cisplatin [156-158].

Drug	Gene Analysis
Erdafitinib	**CYP2C9; *2/*2**

Evidence level : Level 1A

Interpretation

The patient has a poor metabolizer status for CYP2C9 leading to significantly reduced CYP2C9 activity.

Patients with such genotype may have an increased plasma concentration of Erdafitinib and increased drug toxicity. Monitor for increased adverse reactions. Consider alternative therapies that are not strong inhibitors of CYP2C9 [159].

Drug	Gene Analysis
Erlotinib	UGT1A1; *28/*28

Evidence level : Level 1A

Interpretation

The patient has a poor metabolizer status for UGT1A1.

Patients with this genotype who are treated with Erlotinib may have an increased risk of hyperbilirubinemia [160].

Drug	Gene Analysis
Irinotecan	UGT1A1; *28/*28

Evidence level : Level 1A

Interpretation

The patient has a poor metabolizer status for UGT1A1.

Patients with this genotype who are treated with Irinotecan based regimens may have an increased risk of neutropenia, diarrhea, or asthenia. When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of Irinotecan should be considered. If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count. Rigorous clinical surveillance is recommended [161].

Drug	Gene Analysis
Nilotinib	UGT1A1; *28/*28

Evidence level : Level 1A

Interpretation

The patient has a poor metabolizer status for UGT1A1.

Patients with this genotype who are treated with Nilotinib may have an increased risk of hyperbilirubinemia [162].

Drug	Gene Analysis
Pazopanib	UGT1A1; *28/*28

Evidence level : Level 1A

Interpretation

The patient has a poor metabolizer status for UGT1A1.

Patients with this genotype who are treated with Pazopanib may have an increased risk of hyperbilirubinemia [163].

Drug	Gene Analysis
Regorafenib	UGT1A1; *28/*28

Evidence level : Level 1A

Interpretation

The patient has a poor metabolizer status for UGT1A1.

Patients with this genotype who are treated with Regorafenib may have an increased risk of hyperbilirubinemia [164].

Drug	Gene Analysis
Sacituzumab govitecan	UGT1A1; *28/*28

Evidence level : Level 1A

Interpretation

The patient has a poor metabolizer status for UGT1A1 gene, leading to significantly reduced UGT1A1 activity. Patients with such genotype who are treated with Sacituzumab govitecan may have an increased risk of neutropenia and other adverse reactions. Closely monitor for severe neutropenia [165].

Drug	Gene Analysis
Trastuzumab	FCGR2A; rs1801274 AG FCGR3A; rs396991 AC

Evidence level : Level 1A

Interpretation

The patient has unfavorable genotypes in the investigated FCGR3A and FCGR2A gene variants.

Breast cancer patients with such genotypes may have reduced response to Trastuzumab and shorter progression-free survival in people with breast cancer [166,167].

Pharmacogenetics

Drug	Gene Analysis
5-Fluorouracil	**DPYD; *1/*1**

Evidence level : Level 2B

Interpretation

The patient has a normal metabolizer status for DPYD gene leading to normal DPYD activity.

Labelled risk for 5-Fluorouracil toxicity. Use as directed [168].

Drug	Gene Analysis
Capecitabine	**DPYD; *1/*1**

Evidence level : Level 1A

Interpretation

The patient has a normal metabolizer status for DPYD gene leading to normal DPYD activity.

Labelled risk for Capecitabine toxicity. Use as directed [169].

Drug	Gene Analysis
Carboplatin	**ERCC1; rs11615 GG** **MTHFR; rs1801133 AG**

Evidence level : Level 2A,2B

Interpretation

The patient has favorable genotypes in the analysed MTHFR and ERCC1 gene variants.

Patients with this genotype may have a decreased risk of drug toxicity including nephrotoxicity, when treated with Carboplatin [157, 158, 170].

Drug	Gene Analysis
Cyclophosphamide	**GSTP1; rs1695 AG**

Evidence level : Level 2A

Interpretation

The patient has a favorable genotype in the analysed variant of GSTP1 gene.

Breast cancer patients with such genotype may have an increased drug response and decreased severity of toxicity when treated with Cyclophosphamide [171].

Drug	Gene Analysis
Dabrafenib	**G6PD; wildtype/wildtype**

Evidence level : Level 1A

Interpretation

The patient is not a carrier of G6PD deficient genotype.

Patients with such genotype who are treated with Dabrafenib may have a reduced risk of hemolysis [172].

Drug	Gene Analysis
Epirubicin	**GSTP1; rs1695 AG**

Evidence level : Level 2A

Interpretation

The patient has a favorable genotype in the analysed variant of GSTP1 gene.

Breast cancer patients with such genotype may have an increased drug response and decreased severity of toxicity when treated with Epirubicin [171].

Drug	Gene Analysis
Gefitinib	**CYP2D6; *17/*41**

Evidence level : Level 1A

Interpretation

The patient has a normal metabolizer status for CYP2D6.

Patients with such genotype who are treated with Gefitinib may have normal metabolism of Gefitinib. Use as directed [173].

Drug	Gene Analysis
Gemcitabine	**NT5C2; rs11598702 CC**

Evidence level : Level 2B

Interpretation

The patient has a favorable genotype in the analysed variant of NT5C2 gene.

Patients with the such genotype may have an increased clearance of Gemcitabine and a decreased risk of toxicity [174].

Drug	Gene Analysis
Mercaptopurine	**NUDT15; *1/*1** **TPMT; *1/*1**

Evidence level : Level 1A

Interpretation

The patient is a normal metabolizer for TPMT and NUDT 15 genes.

Patients with such metabolizer status who are treated with Mercaptopurine may have an increased inactivation of Mercaptopurine and a decreased risk of developing severe, lifethreatening myelotoxicity. Use as directed. Start with normal starting dose and adjust doses of Mercaptopurine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment [175].

Drug	Gene Analysis
Methotrexate	**ABCB1; rs1045642 GG** **MTHFR; rs1801133 AG**

Evidence level : Level 2A

Interpretation

The patient has favorable genotypes in the analysed variants of ABCB1 and MTHFR genes.

Patients with such genotypes when treated with Methotrexate, may have a decreased risk of toxicity [176].

Drug	Gene Analysis
Oxaliplatin	**ERCC1; rs11615 GG**

Evidence level : Level 2B

Interpretation

The patient has a favorable genotype in analysed variant of ERCC1 gene.

Patients with this genotype when treated with Oxaliplatin may have decreased but not non-existent risk for nephrotoxicity [157,158].

Drug	Gene Analysis
Rasburicase	**G6PD; wildtype/wildtype**

Evidence level : Level 1A

Interpretation

The patient is not a carrier of G6PD deficient genotype.

Patients with such genotype who are treated with Rasburicase may have a reduced risk of hemolysis [177].

Drug	Gene Analysis
Tamoxifen	**CYP2D6; *17/*41**

Evidence level : Level 1A

Interpretation

The patient is a normal metabolizer for CYP2D6.

Breast cancer patients with this metabolizer status show optimal metabolism of Tamoxifen resulting in optimal endoxifen concentrations, decreased likelihood of recurrence and increased event-free and recurrence-free survival, when treated with Tamoxifen in an adjuvant setting. Use as directed [178].

Pharmacogenetics

Drug	Gene Analysis
Tegafur	**DPYD; *1/*1**

Evidence level : Level 1A

Interpretation

The patient has a normal metabolizer status for DPYD gene leading to normal DPYD activity.

Labelled risk for Tegafur toxicity. Use as directed [168].

Drug	Gene Analysis
Thioguanine	**NUDT15; *1/*1** **TPMT; *1/*1**

Evidence level : Level 1A

Interpretation

The patient is a normal metabolizer for TPMT and NUDT 15 genes.

Patients with such metabolizer status who are treated with Thioguanine may have an increased inactivation of Thioguanine and a decreased risk of developing severe, life-threatening myelotoxicity. Use as directed. Start with normal starting dose and adjust doses of Thioguanine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment [179].

Drug	Gene Analysis
Trametinib	**G6PD; wildtype/wildtype**

Evidence level : Level 1A

Interpretation

The patient is not a carrier of G6PD deficient genotype.

Patients with such genotype who are treated with Trametinib may have a reduced risk of hemolysis [180].

Drug	Gene Analysis
Vincristine	**CEP72; rs924607 CT**

Evidence level : Level 2B

Interpretation

The patient has a favorable genotype in the analysed variant of CEP72 gene.

Patients with such genotypes who are treated with Vincristine may have a decreased, but not absent, risk of peripheral nervous system diseases [181].

Variant Allele Fraction and Coverage

Variant (Transcript ID)	Genomic co-ordinates	Allele fraction	Coverage (X)
ESR1 (NM_001122740.1) c.1610A>C, p.Y537S	chr6: 152419923A>C	21.84	28265
ESR1 (NM_001122740.1) c.1609T>A, p.Y537N	chr6: 152419922T>A	0.1	21500
ESR1 (NM_001122740.1) c.1613A>G, p.D538G	chr6: 152419926A>G	1	23503
CTNNA1 (NM_001903.4) c.2393C>T, p.A798V	chr5: 138268361C>T	1	4027
CYP2D6 (NM_000106.5) c.301C>T, p.R101C	chr22: 42525791G>A	32.1	4516
PIK3CA (NM_006218.4) c.3140A>T, p.H1047L	chr3: 178952085A>T	0.31	30792

Due to minimum coverage or no sequence, the presence or absence of variants contained within certain target regions of the genes listed below could not be meaningfully assessed.

ABL1, ALK, AMER1, AR, BRAF, CTNNB1, EGFR, FLT3, GNAQ, GNAS, HRAS, IDH1, JAK2, KIT, KRAS, MAP2K2, MET, NF2, NRAS,PIK3CA, PTEN, SMAD4, SMO.

Analysis Criteria

Criteria for Classification of Somatic Variants

The criteria/guidance used in this report is in accordance with the guidelines provided by the American College of Medical Genetics and Genomics (ACMG) for the interpretation and reporting of sequence variants in cancer. Somatic sequence variations are categorized into four tiers based on their clinical significance[182].

Tier I: Variants/biomarkers with strong clinical significance (therapeutic, prognostic and/or diagnostic)

Level A evidence: FDA approved therapies or standard guidelines for a specific tumor type.

Level B evidence: Statistically significant studies with consensus for specific tumor type.

Tier II: Biomarkers with potential clinical significance (therapeutic, prognostic and/or diagnostic)

Level C evidence: FDA approved therapies or standard guidelines for a different tumor type (off-label use of the drug). An inclusion criteria for clinical trials.

Level D evidence: No consensus among different studies.

Tier III: Biomarker whose association with cancer is not evident from available literature and is not frequently present in general population.

Tier IV: Biomarker whose association with cancer has not been reported till date and is frequently present in general population. This category of variants is not included in this report as per guidelines.

Criteria of Classification for Pharmacogenetic Analysis

Each variant-drug combination can be graded based on the measure of co idence in the association and the strength of prescribing recommendation.

Level 1: Evidence based on pharmacogenetics guidelines or well-established association studies

Level 2: Evidence of moderate variant-drug association from studies.

Level 3: Evidence suggests no consensus among different studies.

Drug Metabolizer Status Categories

Based on the different combination of haplotypes an individual inherits in each drug metabolizing gene, a drug metabolizer status can be predicted. There are 4 different drug metabolizer status types:

Poor Metabolizers (also called "PM"), Poor metabolizers have two non-functional alleles and therefore have little to no enzyme activity.

Intermediate Metabolizers (also called "IM"), Intermediate metabolizers have one non-functional allele and one normally functioning allele, and therefore have decreased enzyme activity.

Normal Metabolizers (also called "NM") Normal metabolizers have 2 normally functioning alleles and therefore have normal enzyme activity.

Ultra-Rapid Metabolizers (also called "UM"). Ultra-rapid metabolizers have one or more alleles which result in increased enzyme activity compared to extensive metabolizers.

The impact of each metabolizer type on medication response depends on the role of the enzyme in the metabolism of the specific drug in question. For example, for a drug that is inactivated by the enzyme, an ultra-rapid metabolizer may need

a higher dose of the drug to reach a therapeutic range while for another drug, that is activated by the enzyme; ultra-rapid metabolizer status may be associated with increased exposure to the drug and therefore an increased risk of adverse drug reactions.

Criteria for Classification of Germline Variants

Analysis Criteria

The American College of Medical Genetics and Genomics (ACMG) developed guidance for the interpretation of sequence variants and recommended the use of following specific standard terminology to describe variants identified in genes that cause Mendelian disorders[183].

Pathogenic: Functional or expression evidence suggests deleterious effect on gene function.

Likely Pathogenic/Probably Deleterious: Limited or no functional evidence available, but overall biological expectations suggestive of deleterious effect.

Variants of unknown significance (VUS): Little or nothing has been reported on this variant or its effects.

Likely Benign: The variant has been seen in cases, but also in controls. Variant may be present in a high percentage of the population, and may be present in a non-conserved region.

Benign: Established in the literature as a variant that is not associated with Mendelian (single-gene inherited) disease, or known to have an allele frequency that is far too high to be compatible with the prevalence of disease, mode of inheritance and penetrance patterns known for that condition.

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Genes Analyzed

Gene List

SNA Genes

ABL1	ABL2	ACVR2A	ADAMTS20	AFF1	AFF3	AKAP9	AKT1	AKT2	AKT3
ALK	APC	AR	ARAF	ARID1A	ARID2	ARNT	ASXL1	ATF1	ATM
ATR	ATRX	AURKA	AURKB	AURKC	AXL	BAI3	BAP1	BCL10	BCL11A
BCL11B	BCL2	BCL2L1	BCL2L2	BCL3	BCL6	BCL9	BCR	BIRC2	BIRC3
BIRC5	BLM	BLNK	BMPR1A	BRAF	BRD3	BRIP1	BTK	BUB1B	CARD11
CASC5	CBL	CCND1	CCND2	CCND3	CCNE1	CD79A	CD79B	CDC73	CDH1
CDH11	CDH2	CDH20	CDH5	CDK12	CDK4	CDK6	CDK8	CDKN2A	CDKN2B
CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CKS1B	CMPK1	COL1A1	CRBN	CREB1
CREBBP	CRKL	CRTC1	CSF1R	CSMD3	CTNNA1	CTNNB1	CYLD	CYP2C19	CYP2D6
DAXX	DCC	DDB2	DDIT3	DDR2	DEK	DICER1	DNMT3A	DPYD	DST
EGFR	EML4	EP300	EP400	EPHA3	EPHA7	EPHB1	EPHB4	EPHB6	ERBB2
ERBB3	ERBB4	ERCC1	ERCC2	ERCC3	ERCC4	ERCC5	ERG	ESR1	ETS1
ETV1	ETV4	EXT1	EXT2	EZH2	FAM123B	FANCA	FANCC	FANCD2	FANCF
FANCG	FAS	FBXW7	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN	FLI1
FLT1	FLT3	FLT4	FN1	FOXL2	FOXO1	FOXO3	FOXP1	FOXP4	FZR1
G6PD	GATA1	GATA2	GATA3	GDNF	GNA11	GNAQ	GNAS	GPR124	GRM8
GUCY1A2	HCAR1	HIF1A	HLF	HNF1A	HOOK3	HRAS	HSP1915AA1	HSP90AB1	ICK
IDH1	IDH2	IGF1R	IGF2	IGF2R	IKBKB	IKBKE	IKZF1	IL2	IL21R
IL6ST	IL7R	ING4	IRF4	IRS2	ITGA10	ITGA9	ITGB2	ITGB3	JAK1
JAK2	JAK3	JUN	KAT6A	KAT6B	KDM5C	KDM6A	KDR	KEAP1	KIT
KLF6	KRAS	LAMP1	LCK	LIFR	LPHN3	LPP	LRP1B	LTF	LTK
MAF	MAFB	MAGEA1	MAGI1	MALT1	MAML2	MAP2K1	MAP2K2	MAP2K4	MAP3K7
MAPK1	MAPK8	MARK1	MARK4	MBD1	MCL1	MDM2	MDM4	MEN1	MET
MITF	MLH1	MLL	MLL2	MLL3	MLLT10	MMP2	MN1	MPL	MRE11A
MSH2	MSH6	MTOR	MTR	MTRR	MUC1	MUTYH	MYB	MYC	MYCL1
MYCN	MYD88	MYH11	MYH9	NBN	NCOA1	NCOA2	NCOA4	NF1	Nf2
NFE2L2	NFKB1	NFKB2	NIN	NKX2-1	NLRP1	NOTCH1	NOTCH2	NOTCH4	NPM1
NRAS	NSD1	NTRK1	NTRK3	NUMA1	NUP214	NUP98	PAK3	PALB2	PARP1
PAX3	PAX5	PAX7	PAX8	PBRM1	PBX1	PDE4DIP	PDGFB	PDGFRA	PDGFRB
PER1	PGAP3	PHOX2B	PIK3C2B	PIK3CA	PIK3CB	PIK3CD	PIK3CG	PIK3R1	PIK3R2
PIM1	PKHD1	PLAG1	PLCG1	PLEKHG5	PML	PMS1	PMS2	POT1	POU5F1
PPARG	PPP2R1A	PRDM1	PRKAR1A	PRKDC	PSIP1	PTCH1	PTEN	PTGS2	PTPN11
PTPRD	PTPRT	RAD50	RAF1	RALGDS	RARA	RB1	RECQL4	REL	RET
RHOH	RNASEL	RNF2	RNF213	ROS1	RPS6KA2	RRM1	RUNX1	RUNX1T1	SAMD9
SBDS	SDHA	SDHB	SDHC	SDHD	Sep-09	SETD2	SF3B1	SGK1	SH2D1A
SMAD2	SMAD4	SMARCA4	SMARCB1	SMO	SMUG1	SOCS1	SOX11	SOX2	SRC
SSX1	STK11	STK36	SUFU	SYK	SYNE1	TAF1	TAF1L	TAL1	TBX22
TCF12	TCF3	TCF7L1	TCF7L2	TCL1A	TET1	TET2	TFE3	TGFBR2	TGM7
THBS1	TIMP3	TLR4	TLX1	TNFAIP3	TNFRSF14	TNK2	TOP1	TP53	TPR
TRIM24	TRIM33	TRIP11	TRRAP	TSC1	TSC2	TSHR	UBR5	UGT1A1	USP9X
VHL	WAS	WHSC1	WRN	WT1	XPA	XPC			

CNA Genes

ABL1	ABL2	ACVR2A	ADAMTS20	AFF1	AFF3	AKAP9	AKT1	AKT2	AKT3
ALK	APC	AR	ARID1A	ARID2	ARNT	ASXL1	ATF1	ATM	ATR
ATRX	AURKA	AURKB	AURKC	AXL	BAI3	BAP1	BCL10	BCL11A	BCL11B
BCL2	BCL2L1	BCL2L2	BCL3	BCL6	BCL9	BCR	BIRC2	BIRC3	BIRC5
BLM	BLNK	BMPR1A	BRAF	BRD3	BRIP1	BTK	BUB1B	CARD11	CASC5
CBL	CCND1	CCND2	CCND3	CCNE1	CD79A	CD79B	CDC73	CDH1	CDH11
CDH2	CDH20	CDH5	CDK12	CDK4	CDK6	CDK8	CDKN2A	CDKN2B	CDKN2C
CEBPA	CHEK1	CHEK2	CIC	CKS1B	CMPK1	COL1A1	CRBN	CREB1	CREBBP

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Genes Analyzed

Gene List

CRKL	CRTC1	CSF1R	CSMD3	CTNNA1	CTNNB1	CYLD	CYP2C19	CYP2D6	DAXX
DCC	DDB2	DDIT3	DDR2	DEK	DICER1	DNMT3A	DPYD	DST	EGFR
EML4	EP300	EP400	EPHA3	EPHA7	EPHB1	EPHB4	EPHB6	ERBB2	ERBB3
ERBB4	ERCC1	ERCC2	ERCC3	ERCC4	ERCC5	ERG	ESR1	ETS1	ETV1
ETV4	EXT1	EXT2	EZH2	FAM123B	FANCA	FANCC	FANCD2	FANCF	FANCG
FAS	FBXW7	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN	FLI1	FLT1
FLT3	FLT4	FN1	FOXL2	FOXO1	FOXO3	FOXP1	FOXP4	FZR1	G6PD
GATA1	GATA2	GATA3	GDNF	GNA11	GNAQ	GNAS	GPR124	GRM8	GUCY1A2
HCAR1	HIF1A	HLF	HNF1A	HOOK3	HRAS	HSP90AA1	HSP90AB1	ICK	IDH1
IDH2	IGF1R	IGF2	IGF2R	IKBKB	IKBKE	IKZF1	IL2	IL21R	IL6ST
IL7R	ING4	IRF4	IRS2	ITGA10	ITGA9	ITGB2	ITGB3	JAK1	JAK2
JAK3	JUN	KAT6A	KAT6B	KDM5C	KDM6A	KDR	KEAP1	KIT	KLF6
KRAS	LAMP1	LCK	LIFR	LPHN3	LPP	LRP1B	LTF	LTK	MAF
MAFB	MAGEA1	MAGI1	MALT1	MAML2	MAP2K1	MAP2K2	MAP2K4	MAP3K7	MAPK1
MAPK8	MARK1	MARK4	MBD1	MCL1	MDM2	MDM4	MEN1	MET	MITF
MLH1	MLL	MLL2	MLL3	MLLT10	MMP2	MN1	MPL	MRE11A	MSH2
MSH6	MTOR	MTR	MTRR	MUC1	MUTYH	MYB	MYC	MYCL1	MYCN
MYD88	MYH11	MYH9	NBN	NCOA1	NCOA2	NCOA4	NF1	NF2	NFE2L2
NFKB1	NFKB2	NIN	NKX2-1	NLRP1	NOTCH1	NOTCH2	NOTCH4	NPM1	NRAS
NSD1	NTRK1	NTRK3	NUMA1	NUP214	NUP98	PAK3	PALB2	PARP1	PAX3
PAX5	PAX7	PAX8	PBRM1	PBX1	PDE4DIP	PDGFB	PDGFRA	PDGFRB	PER1
PGAP3	PHOX2B	PIK3C2B	PIK3CA	PIK3CB	PIK3CD	PIK3CG	PIK3R1	PIK3R2	PIM1
PKHD1	PLAG1	PLCG1	PLEKHG5	PML	PMS1	PMS2	POT1	POU5F1	PPARG
PPP2R1A	PRDM1	PRKAR1A	PRKDC	PSIP1	PTCH1	PTEN	PTGS2	PTPN11	PTPRD
PTPRT	RAD50	RAF1	RALGDS	RARA	RB1	RECQL4	REL	RET	RHOH
RNASEL	RNF2	RNF213	ROS1	RPS6KA2	RRM1	RUNX1	RUNX1T1	SAMD9	SBDS
SDHA	SDHB	SDHC	SDHD	Sep-09	SETD2	SF3B1	SGK1	SH2D1A	SMAD2
SMAD4	SMARCA4	SMARCB1	SMO	SMUG1	SOCS1	SOX11	SOX2	SRC	SSX1
STK11	STK36	SUFU	SYK	SYNE1	TAF1	TAF1L	TAL1	TBX22	TCF12
TCF3	TCF7L1	TCF7L2	TCL1A	TET1	TET2	TFE3	TGFBR2	TGM7	THBS1
TIMP3	TLR4	TLX1	TNFAIP3	TNFRSF14	TNK2	TOP1	TP53	TPR	TRIM24
TRIM33	TRIP11	TRRAP	TSC1	TSC2	TSHR	UBR5	UGT1A1	USP9X	VHL
WAS	WHSC1	WRN	WT1	XPA	XPC	XPO1	XRCC2	ZNF384	ZNF521

Fusion Genes:

ALK	BRAF	ERG	ETV1	FGFR1	FGFR2	FGFR3	MET	NTRK1	NTRK3
RET	ROS1								

Exosomal Gene Expression Analysis

Exosomal RNA 20802 mRNA

Biomarkers Analyzed for Mismatch Repair (MMR) Genes

MLH1, MSH2, MSH6, PMS1, PMS2

BRCA1/2 Mutation Analysis

BRCA1 and BRCA2 genes sequencing; deletion and duplication (MLPA)

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Genes Analyzed for Pharmacogenetics

Gene List

Genes	Variants Analyzed
ABCB1	c.3435T>C
CEP72	n.366+1469G>A
CYP2C9	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *18, *35
CYP2D6	*1, *2, *3, *4, *6, *7, *8, *9, *10, *11, *12, *15, *17, *19, *20, *29, *35, *38, *41, *42, *44, *56 and *5, XN
DPYD	*1, *10, *11, *12, *13, *2A, *3, *4, *5, *6, *7, *8, *9A, *9B, c.1024G>A, c.1057C>T, c.1314T>G, c.1896T>C, c.2279C>T, c.2639G>T, c.2846A>T, c.2872A>G, c.2933A>G, c.496A>G, c.557A>G, c.61C>T, c.62G>A, c.1129-5923C>G (HapB3), c.1236G>A (HapB3)
ERCC1	c.354T>C
FCGR2A	c.497A>G
FCGR3A	c.526T>G
G6PD	Gaohe; Sunderland; Orissa; Murcia Oristano; Ube Konan; Vancouver; Santa Maria; G6PD A- 680T_376G; Mt Sinai; Sierra Leone; G6PD A- 968C_376G; Ananindeua; Taipei Chinese-3; Malaga; Mediterranean Haplotype; Mediterranean_Dallas_Panama_Sassari_Cagliari_ Birmingham; Coimbra Shunde; Sibari; Cincinnati; Minnesota_Marion_Gastonia_LeJeune; Nanning; Chinese-5; Ierapetra; Serres; Iowa_Walter Reed_Springfield; Guadalajara; Riverside; Asahi; Ludhiana; Pawnee; Surabaya; Japan_Shinagawa; Puerto Limon; Alhambra; Nashville_Anaheim_Portici; Beverly Hills_Genova_Iwate_Niigata_Yamaguchi; Tomah; Montpellier; Loma Linda; Mira d'Aire; Chatham; Rehevot; Kalyan-Kerala_Jamnaga_Rohini; Viangchan_Jammu; Seattle_Lodi_Modena_Ferrara II_Athens-like; Aveiro; Nilgiri; Nankang; Ilesha; Crispim; Sao Borja; Lagosanto; Namouru; A-202A_376G; Hechi; Metaponto; Aures; Acrokorinthos; A; Vanua Lava; Mediterranean_Dallas_Panama_Sassari_Cagliari_Birmingham; wildtype; 202G>A_376A>G_1264C>G
GSTP1	c.313A>G
MTHFR	c.665C>T
NT5C2	c.175+1178A>G
NUDT15	*1, *2, *3, *4, *5, *6
TPMT	*1, *2, *3A, *3B, *3C, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *20, *21, *23, *24, *25, *26, *29, *31, *32, *33, *34, *37
UGT1A1	*1, *28
XPC	c.2815C>A

Drugs Tested in Chemosensitivity Analysis

Drug List

5-Fluorouracil/Capecitabine, Bleomycin, Cabazitaxel, Carboplatin, Cisplatin, Cyclophosphamide, Dacarbazine, Dactinomycin, Docetaxel, Doxorubicin, Epirubin, Eribulin, Etoposide, Gemcitabine, Ifosfamide, Irinotecan, Melphalan, Methotrexate, Mitomycin, Mitoxantrone, Oxaliplatin, Paclitaxel, Pemetrexed, Temozolomide, Topotecan, Trabectedin, Vinblastine, Vincristine, Vinorelbine.

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Antibody Details - Immunocytochemistry (ICC) Analysis

Antibody

Marker	Clone
EPCAM	REA831
CK	REA764
CD45	HI30
mTOR	Polyclonal

Marker	Clone
VEGFR1	REA569
VEGFR2	REA1116
VEGFA	JH121
EGFR	Ep22

Methods and Limitations

Methods

Cell free nucleic acids analysis

Cell free nucleic acids were analyzed for mutation and fusion detection using semiconductor based Next Generation Sequencing technology. Cell free nucleic acids extracted from the plasma of submitted specimen was subjected to target enrichment by multiplex PCR amplification using Ion AmpliSeq™ Comprehensive Cancer panel targeting 409 (see gene list in the 'Genes analyzed section') as well as Oncomine™ Pan-Cancer Cell-Free Assay 52 (see underlined genes in the 'Genes analyzed section'). Oncogenes and Tumor suppressor genes. Enriched DNA sequences were ligated with platform specific adaptor molecules and were sequenced using semiconductor chip. Sequenced data was aligned with the human genome (hg19), analyzed at 17000x minimum average depth for 52 gene panel and 1000x for 409 gene panel using a customized in-house pipeline DCGL NGS Bioinformatics Pipeline v7.10 and DCGL NGS Bioinformatics Pipeline v11.8, designed to accurately detect the rare somatic variants.

Paired analysis was performed to differentiate between somatic and germline mutations. Lower limit of detection of the mutations targeted is 0.1% for underlined genes in genes analyzed section and 1% for other genes and variants present below LOD may not be detectable with this assay, whereas analytical sensitivity is 94.6% and specificity is 96.37%.

A negative test result does not exclude the possibility of mutations being present in the test sample probably due to the reads representing minor allele fraction is below the detectable limit of the assay or other limiting technical/analytical factors. The scope of copy number variations analysis includes copy number gain/amplification of the detected gene(s).

The clinical sensitivity of most assays for detection of alterations in cell free nucleic acids is limited as compared with tumor tissue based testing. This may result from a high ratio of normal to tumor DNA or excess degradation of cell free nucleic acids or may simply reflect the biologic heterogeneity of solid tumors, some of which may shed abundant nucleic acid into the circulation and others that may not. Tumor type, size, disease stage, sites of metastasis, histologic grade, or other features may also affect levels, however, much remains to be elucidated.

Exosomal mRNA analysis

Blood was analyzed for mRNA expression analysis using semiconductor based Next Generation Sequencing method. High quality Exosomal RNA was extracted from the submitted specimen. It was subjected to mRNA library preparation using a targeted Ion AmpliSeq™ Transcriptome Human Gene Expression panel. RNA sequencing was performed to achieve at least 4 million mappable high-quality reads for the paired analysis. Sequence reads were aligned to the hg19 transcriptome reference sequence in Torrent Suite Software using the Ion Torrent Mapping Alignment Program. Differential Gene Expression analysis was performed using a customized in-house pipeline DCGL NGS Bioinformatics Pipeline v5.9 designed to detect the Significantly expressed genes.

MMR gene analysis

EDTA blood was analysed for mutation detection using semiconductor based Next Generation Sequencing technology. High quality genomic DNA was extracted from the submitted specimen and subjected to target enrichment by high multiplex PCR amplification using Ion AmpliSeq™ panel targeting mutation of genes mentioned above. Enriched DNA sequences were ligated with platform specific adaptor molecules and was sequenced on using semiconductor chip. Sequenced data was aligned with the human genome (hg19), analyzed at 500x minimum average depth using a customized in-house pipeline DCGL NGS Bioinformatics Pipeline v2.11, designed to accurately detect the germline variants.

Analytical Validation of this assay shown sensitivity of 100% and specificity 100%.

Pathogenic/likely pathogenic mutation if detected in the sample is confirmed by gold standard Sanger Sequencing method. Sanger sequencing data is analyzed using SeqScape® Software ver 3.0.

Methods

BRCA1/2 gene analysis

Genomic DNA was analyzed for mutation as well as deletion/duplication detection in BRCA1/2 genes using Ion Proton sequencer. High quality genomic DNA extracted from the submitted specimen was subjected to target enrichment by multiplex PCR amplification using panel targeting BRCA genes. Enriched DNA sequences were ligated with platform specific adaptor molecules and sequenced using semiconductor P1 chip. The minimum average depth was 1000x for gene panel analyzed. High quality sequencing data (proportion Q20 bases U75%) was analyzed using a customized in-house pipeline DCGL NGS Bioinformatics Pipeline v17 designed to accurately detect the rare somatic variants.

Multiplex Ligation-dependent Probe Amplification (MLPA) assay

The simultaneous analysis was performed by the Multiplex Ligation-dependent Probe Amplification (MLPA) for BRCA1 and BRCA2 to rule out deletions and duplications. Genomic DNA was isolated from sample submitted. Using MLPA reagents from MRC-Holland B.V. (Amsterdam, the Netherlands) and the MLPA procedure was performed as recommended by the manufacturer. Analytical Validation of this assay shown sensitivity of 100% and specificity 100%.

Pharmacogenetic Analysis

Blood was analyzed for genotyping using semiconductor based NGS technology. High quality genomic DNA was extracted from the submitted specimen and subjected to target enrichment by high multiplex PCR amplification using Ion AmpliSeq™ panel targeting variants of genes. Enriched DNA sequences were ligated with platform specific adaptor molecules and was sequenced on using semiconductor P1 chip. The minimum average depth was 500x for panel of genes analyzed. High quality sequencing data (proportion of Q20 bases U75%) was analyzed using DCGL NGS Bioinformatics Pipeline v14.5. This test does not detect polymorphisms other than those listed. Drug metabolism may be affected by non-genetic factors. DNA testing does not replace the need for clinical and therapeutic drug monitoring. Analytical Validation of this assay shown sensitivity of 100% and specificity 98.55%.

CTC Enumeration and CTC-ICC Analysis

Enriched CTCs from the submitted peripheral blood were labelled with EPCAM, Cytokeratin and CD45 antibodies and analyzed by high content imaging platform. Analytical Validation of this assay shown sensitivity of 99.9% and specificity 99.9%.

Circulating Tumor and associated cells from the submitted peripheral blood were analyzed through cell stabilization protocol using Cell Wizard™ System. Cells were labelled with mTOR, VEGFR1, VEGFR2, VEGF-A and EGFR antibodies and analyzed by Fluorescent microscopy for Immunocytochemistry (ICC).

Blood Based Chemosensitivity Analysis

Circulating tumor and its associated cells were isolated from the submitted peripheral blood sample. The live cancer cells were tested against multiple chemotherapy agents. The number of drugs selected for testing depend on the number of C-TACs isolated from the submitted sample.

A defined number of cells were incubated with different drugs with respective drug concentrations, mean peak plasma concentration and cell death events were measured. The extent of cell death was determined using Varioskan LUX platform. Percent cell death was calculated to evaluate the response level of the drug. Appropriate positive and negative controls were tested and evaluated in a similar manner simultaneously with the test sample. Analytical Validation of this assay shown sensitivity of 99.9% and specificity 99.9%.

Disclaimer

This report documents the genetic alterations detected in the submitted sample material. Information in this report is provided for information purpose only and should only be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment.

Decisions on patient care and treatment must be based on the independent medical judgment of the treating physicians, taking into consideration all applicable information concerning the patient's condition, such as personal and family history, physician's examination, information from other diagnostic test and patient references, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test or on the information contained in this report.

This information in this report does not constitute a treatment recommendation by Datar Cancer Genetics, either to use or not to use any specific therapeutic agent, and should not be interpreted as treatment advice. Decisions on patient care and treatment rest solely within the discretion of the patient's treating physician.

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****End of Report****

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Director - Application

Clinical Trials Relevant to Patient's Genomic Findings

Clinical Trials

MYC amplification

NCT number: NCT03568656
Phase: I/II
Treatment: CCS-1477
Cancer Type: Unspecified Solid Tumor

Study Title: An Open-label Phase I/IIa Study to Evaluate the Safety and Efficacy of CCS1477 as Monotherapy and in Combination, in Patients With Advanced Solid/Metastatic Tumours.
Variant Classification: MYC amplification
Locations: United Kingdom, United States
Contacts: Dr. Karen Clegg [746-454-7447; Karen.Clegg@cellcentric.com]

NCT number: NCT03838042
Phase: I /II
Treatment: Entinostat, Nivolumab
Cancer Type: Unspecified Solid Tumor

Study Title: INFORM2 Exploratory Multinational Phase I/II Combination Study of Nivolumab and Entinostat in Children and Adolescents with Refractory High-risk Malignancies
Variant Classification: MYC amplification
Locations: Australia, Austria, France, Germany, Netherlands, Sweden, Switzerland

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NCT number: NCT04718675
Phase: I/II
Treatment: KB-0742
Cancer Type: Unspecified Solid Tumor

Study Title: Phase I, First-in-human, Open-label Dose Escalation and Cohort Expansion Study of KB-0742 in Patients With Relapsed or Refractory Solid Tumors or Non-Hodgkin Lymphoma
Variant Classification: MYC amplification
Locations: United States
Contacts: Director of Clinical Operations [650-484-1583; clinicaltrials@kronosbio.com]

NCT number: NCT02635672
Phase: I
Treatment: BAY-1251152
Cancer Type: Unspecified Solid Tumor

Study Title: An Open-label, Multicenter Phase I Dose Escalation Study to Characterize Safety, Tolerability, Preliminary Anti-tumor Activity, Pharmacokinetics and Maximum Tolerated Dose of VIP152 (BAY 1251152) in Patients With Advanced Cancer.
Variant Classification: MYC amplification
Locations: United States
Contacts: Vincerx Clinical Trials Contact [650-800-6676; clinicaltrials@vincerx.com]

NCT number: NCT03936465
Phase: I
Treatment: BMS-986158
Cancer Type: Unspecified Solid Tumor

Study Title: An Open Label, Escalating Multiple Dose Study to Evaluate the Safety, Toxicity, and Pharmacokinetics of BTX A51 in Subjects With Advanced Solid Tumors and Non-Hodgkin Lymphoma
Variant Classification: MYC amplification
Locations: United States
Contacts: Dr. Dung "Zung" Thai [415-225-9338; zthai@biotheryx.com]

ESR1 p.(Y537N) c.1609T>A

Clinical Trials

NCT number:
NCT04256941

Phase: II

Treatment:
Ribociclib, Palbociclib, Abemaciclib, Hormone Therapy

Cancer Type:
Breast Cancer

Study Title:
INTERACT- Integrated Evaluation of Resistance and Actionability Using Circulating Tumor DNA in HR Positive Metastatic Breast Cancers

Variant Classification:
ESR1 Y537N mutation

Locations:
United States

Contacts:
Senthilkumar Damodaran [713-792-2817; sdamodaran@mdanderson.org]

NCT number:
NCT04964934

Phase: III

Treatment:
Hormone Therapy, Palbociclib, Abemaciclib

Cancer Type:
Breast Cancer

Study Title:
A Phase III, Double-blind, Randomised Study to Assess Switching to AZD9833 (a Next Generation, Oral SERD) + CDK4/6 Inhibitor (Palbociclib or Abemaciclib) vs Continuing Aromatase Inhibitor (Letrozole or Anastrozole)+ CDK4/6 Inhibitor in HR+/HER2-MBC Patients With Detectable ESR1Mutation Without Disease Progression During 1L Treatment With Aromatase Inhibitor+ CDK4/6 Inhibitor- A ctDNA Guided Early Switch Study

Variant Classification:
ESR1 mutation

Locations:
Bulgaria, Hungary, Italy, Japan, Poland, Republic of Korea, Russian Federation, Taiwan, Turkey, United Kingdom, United States

Contacts:
AstraZeneca Clinical Study Information Center [877-240-9479; information.center@astrazeneca.com]

NCT number:
NCT04256941

Phase: II

Treatment:
Ribociclib, Palbociclib, Abemaciclib, Hormone Therapy

Cancer Type:
Unspecified Solid Tumor

Study Title:
INTERACT- Integrated Evaluation of Resistance and Actionability Using Circulating Tumor DNA in HR Positive Metastatic Breast Cancers

Variant Classification:
ESR1 Y537S mutation

Locations:
United States

Contacts:
Senthilkumar Damodaran [713-792-2817; sdamodaran@mdanderson.org]

NCT number:
NCT04964934

Phase: III

Treatment:
Hormone Therapy, Palbociclib, Abemaciclib

Cancer Type:
Breast Cancer

Study Title:
A Phase III, Double-blind, Randomised Study to Assess Switching to AZD9833 (a Next Generation, Oral SERD) + CDK4/6 Inhibitor (Palbociclib or Abemaciclib) vs Continuing Aromatase Inhibitor (Letrozole or Anastrozole)+ CDK4/6 Inhibitor in HR+/HER2-MBC Patients With Detectable ESR1Mutation Without Disease Progression During 1L Treatment With Aromatase Inhibitor+ CDK4/6 Inhibitor- A ctDNA Guided Early Switch Study

Variant Classification:
ESR1 mutation

Locations:
Bulgaria, Hungary, Italy, Japan, Poland, Republic of Korea, Russian Federation, Taiwan, Turkey, United Kingdom, United States

Contacts:
AstraZeneca Clinical Study Information Center [877-240-9479; information.center@astrazeneca.com]

Clinical Trials

ESR1 p.(D538G) c.1613A>G

NCT number: NCT04256941
Phase: II
Treatment: Ribociclib, Palbociclib, Abemaciclib, Hormone Therapy
Cancer Type: Breast Cancer

Study Title: INTERACT- Integrated Evaluation of Resistance and Actionability Using Circulating Tumor DNA in HR Positive Metastatic Breast Cancers

Variant Classification: ESR1 D538G mutation

Locations: United States

Locations: Senthilkumar Damodaran [713-792-2817; sdamodaran@mdanderson.org]

NCT number: NCT04964934
Phase: III
Treatment: Hormone Therapy, Palbociclib, Abemaciclib
Cancer Type: Breast Cancer

Study Title: A Phase III, Double-blind, Randomised Study to Assess Switching to AZD9833 (a Next Generation, Oral SERD) + CDK4/6 Inhibitor (Palbociclib or Abemaciclib) vs Continuing Aromatase Inhibitor (Letrozole or Anastrozole)+ CDK4/6 Inhibitor in HR+/HER2-MBC Patients With Detectable ESR1Mutation Without Disease Progression During 1L Treatment With Aromatase Inhibitor+ CDK4/6 Inhibitor- A ctDNA Guided Early Switch Study

Variant Classification: ESR1 mutation

Locations: Bulgaria, Hungary, Italy, Japan, Poland, Republic of Korea, Russian Federation, Taiwan, Turkey, United Kingdom, United States

Locations: AstraZeneca Clinical Study Information Center [877-240-9479; information.center@astrazeneca.com]

PIK3CA p.(H1047L) c.3140A>T

NCT number: NCT04586335
Phase: I
Treatment: HH-CYH33, Olaparib
Cancer Type: Breast Cancer

Study Title: Open Label, Phase Ib Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Clinical Activity of CYH33, an Oral a-specific PI3K Inhibitor in Combination With Olaparib, an Oral PARP Inhibitor in Patients With Advanced Solid Tumors.

Variant Classification: PIK3CA H1047 mutation

Locations: Australia, United States

Locations: Dr. Jason Sudia [908-380-1329; jason.sudia@haihepharma.com]

NCT number: NCT05025735
Phase: II
Treatment: Alpelisib, Hormone Therapy, Dapagliflozin
Cancer Type: Breast Cancer

Study Title: Alpelisib, Fulvestrant and Dapagliflozin for the Treatment of HR+, HER2 -, PIK3CA Mutant Metastatic Breast Cancer

Variant Classification: PIK3CA activating mutation

Locations: United States

Locations: Kelley Aldrich [816-932-2677; slci1research@saint-lukes.org]

NCT number:
NCT04191499

Phase: II/III

Treatment:
Inavolisib, Palbociclib, Hormone Therapy

Cancer Type:
Breast Cancer

Study Title:
A Phase III, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of GDC-0077 Plus Palbociclib and Fulvestrant Versus Placebo Plus Palbociclib and Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer

Variant Classification:
PIK3CA mutation

Locations:
Australia, Belgium, Canada, China, Denmark, France, Germany, Greece, Hong Kong, Hungary, Italy, New Zealand, Poland, Portugal, Republic of Korea, Russian Federation, Singapore, Spain, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States

Contacts:
Reference Study ID Number: WO41554 [888-662-6728; global-roche-genentechtrials@gene.com]

NCT number:
No CTC ID

Phase: II

Treatment:
Alpelisib, Hormone Therapy

Cancer Type:
Breast Cancer

Other identifiers: ACTRN12619001117101, BCT 1901, BCT 1901 (CAPTURE), CAPTURE

Study Title:
BCT 1901 (CAPTURE): A Phase II Randomised Study To Evaluate Alpelisib Plus Fulvestrant Versus Capecitabine In Oestrogen Receptor Positive, HER2-Negative Advanced Breast Cancer Patients With PIK3CA Mutant Circulating DNA.

Variant Classification:
PIK3CA H1047L mutation

Locations:
Australia

NCT number:
NCT04524000

Phase: II

Treatment:
Alpelisib, Hormone Therapy

Cancer Type:
Breast Cancer

Study Title:
A Phase II Open-label, 2-Part, Multi-center Study of BYL719 (Alpelisib) in Combination With Fulvestrant for Men and Postmenopausal Women With PIK3CA Mutation Hormone Receptor (HR) Positive, HER2-negative, Advanced Breast Cancer Which Progressed on or After Aromatase Inhibitor (AI) Treatment in Japan

Variant Classification:
PIK3CA mutation

Locations:
Japan

ESR1 p.(D538G) c.1613A>G

NCT number:
NCT04256941

Phase: II

Treatment:
Ribociclib, Palbociclib, Abemaciclib, Hormone Therapy

Cancer Type:
Breast Cancer

Study Title:
INTERACT- Integrated Evaluation of Resistance and Actionability Using Circulating Tumor DNA in HR Positive Metastatic Breast Cancers

Variant Classification:
ESR1 D538G mutation

Locations:
United States

Locations:
Senthilkumar Damodaran [713-792-2817; sdamodaran@mdanderson.org]

NCT number: NCT04964934
Phase: III
Treatment: Hormone Therapy, Palbociclib, Abemaciclib
Cancer Type: Breast Cancer

Study Title: A Phase III, Double-blind, Randomised Study to Assess Switching to AZD9833 (a Next Generation, Oral SERD) + CDK4/6 Inhibitor (Palbociclib or Abemaciclib) vs Continuing Aromatase Inhibitor (Letrozole or Anastrozole)+ CDK4/6 Inhibitor in HR+/HER2-MBC Patients With Detectable ESR1Mutation Without Disease Progression During 1L Treatment With Aromatase Inhibitor+ CDK4/6 Inhibitor- A ctDNA Guided Early Switch Study
Variant Classification: ESR1 mutation
Locations: Japan, Republic of Korea, Russian Federation, Taiwan, Turkey

ESR1 p.(Y537N) c.1609T>A

NCT number: NCT04256941
Phase: II
Treatment: Ribociclib, Palbociclib, Abemaciclib, Hormone Therapy
Cancer Type: Breast Cancer

Study Title: INTERACT- Integrated Evaluation of Resistance and Actionability Using Circulating Tumor DNA in HR Positive Metastatic Breast Cancers
Variant Classification: ESR1 Y537N mutation
Locations: United States
Contacts: Senthilkumar Damodaran [713-792-2817; sdamodaran@mdanderson.org]

NCT number: NCT04053322
Phase: II
Treatment: Durvalumab, Olaparib, Hormone Therapy
Cancer Type: Breast Cancer

Study Title: An International Multicenter Phase II Trial of Durvalumab (MEDI4736) Plus OLAparib Plus Fulvestrant in Metastatic or Locally Advanced ER-positive, HER2- negative Breast Cancer Patients Selected Using Criteria That Predict Sensitivity to Olaparib
Variant Classification: ESR1 mutation
Locations: France

BRCA2 p.(C1975Wfs*29) c.5925delT

NCT number: NCT03025035
Phase: II
Treatment: Pembrolizumab, Olaparib
Cancer Type: Breast Cancer

Study Title: Open Label, Phase II Pilot Study of Immune Checkpoint Inhibition With Pembrolizumab in Combination With PARP Inhibition With Olaparib in Advanced BRCA-mutated or HDR-defect Breast Cancers
Variant Classification: BRCA mutation, HR Deficient
Locations: United States
Locations: Parisa Mirzadehgan [310-967-4387; Parisa.Mirzadehgan@cshs.org]

NCT number: NCT04053322
Phase: II
Treatment: Durvalumab, Olaparib, Hormone Therapy
Cancer Type: Breast Cancer

Study Title: An International Multicenter Phase II Trial of Durvalumab (MEDI4736) Plus OLAparib Plus Fulvestrant in Metastatic or Locally Advanced ER-positive, HER2-negative Breast Cancer Patients Selected Using Criteria That Predict Sensitivity to Olaparib
Variant Classification: BRCA2 mutation
Locations: France

NCT number: NCT03344965
Phase: II
Treatment: Olaparib
Cancer Type: Breast Cancer

Study Title:
A Phase II Study of Olaparib Monotherapy in Metastatic Breast Cancer Patients With Germline or Somatic Mutations in DNA Repair Genes (Olaparib Expanded)

Variant Classification:
BRCA2 mutation

Locations:
United States

Contacts:
Dr. Nadine Tung [617-667-1962; ntung@bidmc.harvard.edu]

NCT number: NCT03742895
Phase: II
Treatment: Olaparib
Cancer Type: Breast Cancer

Study Title:
A Phase II Study of Olaparib Monotherapy in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer

Variant Classification:
BRCA2 mutation

Locations:
Argentina, Australia, Canada, Colombia, Denmark, France, Guatemala, Ireland, Israel, Italy, Mexico, Peru, Republic of Korea, Romania, Russian Federation, Spain, Switzerland, Turkey, United Kingdom, United States

Contacts:
Toll Free Number [888-577-8839; Trialsites@merck.com]

NCT number: NCT02849496
Phase: II
Treatment: Olaparib, Atezolizumab
Cancer Type: Breast Cancer

Study Title:
A Phase II Open-Label, Randomized Study of PARP Inhibition (Olaparib) Either Alone or in Combination With Anti-PD-L1 Therapy (Atezolizumab; MPDL3280A) in Homologous DNA Repair (HDR) Deficient, Locally Advanced or Metastatic Non-HER2-Positive Breast Cancer.

Variant Classification:
BRCA2 mutation

Locations:
United States

Contacts:
Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

NCT number: NCT03990896
Phase: II
Treatment: Talazoparib
Cancer Type: Breast Cancer

Study Title:
Evaluation of Talazoparib, a PARP Inhibitor, in Patients With Somatic BRCA Mutant Metastatic Breast Cancer: Genotyping Based Clinical Trial

Variant Classification:
BRCA2 mutation

Locations:
United States

Contacts:
Dr. Neelima Vidula [617-724-4000; nvidula@mgh.harvard.edu]

NCT number: NCT04892693
Phase: II
Treatment: Talazoparib
Cancer Type: Breast Cancer

Study Title: Talazoparib in Advanced Breast Cancer Patients With Homologous Recombinant Deficiency: A Phase II Clinical and Exploratory Biomarker Study of Talazoparib
Variant Classification: BRCA2 mutation
Locations: Republic of Korea

NCT number: NCT03685331
Phase: I/II
Treatment: Olaparib, Palbociclib, Hormone Therapy
Cancer Type: Breast Cancer

Study Title: Harnessing Olaparib, Palbociclib and Endocrine Therapy: A Phase I/II Trial of Olaparib, Palbociclib and Fulvestrant in Patients With BRCA Mutation-associated, Hormone Receptor-positive, Human Epidermal Growth Factor Receptor 2 (HER2)- Negative Metastatic Breast Cancer (HOPE)
Variant Classification: BRCA2 mutation
Locations: United States
Contacts: Alexandra Torres [855-216-0098; PennCancerTrials@emergingmed.com]

NCT number: NCT03964532
Phase: I/II
Treatment: Talazoparib, Avelumab
Cancer Type: Breast Cancer

Study Title: TALAVE: A Pilot Trial of Induction Talazoparib Followed by Combination of Talazoparib and Avelumab in Advanced Breast Cancer
Variant Classification: BRCA2 mutation
Locations: United States
Contacts: Dr. Julie Collins [202-444-2223; Julie.Collins@gunet.georgetown.edu]

NCT number: NCT04586335
Phase: I
Treatment: HH-CYH33, Olaparib
Cancer Type: Breast Cancer

Study Title: Open Label, Phase Ib Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Clinical Activity of CYH33, an Oral a-specific PI3K Inhibitor in Combination With Olaparib, an Oral PARP Inhibitor in Patients With Advanced Solid Tumors.
Variant Classification: BRCA2 mutation
Locations: Australia, United States
Contacts: Dr. Jason Sudia [908-380-1329; jason.sudia@haihepharma.com]

NCT number: NCT04673448
Phase: I
Treatment: Niraparib, Dostarlimab
Cancer Type: Breast Cancer

Study Title: Phase IB Trial of Niraparib and TSR-042 in Patients With BRCA-Mutated Breast, Pancreas or Ovary Cancer
Variant Classification: BRCA2 mutation
Locations: United States
Contacts: Elizabeth M. Swisher [206-543-3669; swishere@uw.edu]

Clinical Trials

NCT number:
NCT04915755

Phase: III

Treatment:
Niraparib

Cancer Type:
Breast Cancer

Study Title:
A Randomized Phase III Double-Blinded Study Comparing the Efficacy and Safety of Niraparib to Placebo in Participants With Either HER2-Negative BRCA-Mutated or Triple-Negative Breast Cancer With Molecular Disease Based on Presence of Circulating Tumor DNA After Definitive Therapy (ZEST)

Variant Classification:
BRCA mutation

Locations:
Argentina, Brazil, Canada, Finland, France, Ireland, Italy, Japan, Netherlands, Norway, Poland, Russian Federation, South Africa, Spain, United Kingdom, United States

Contacts:
US GSK Clinical Trials Call Center [877-379-3718; GSKClinicalSupportHD@gsk.com]

NCT number:
NCT05085626

Phase: II

Treatment:
Fluzoparib, Tucidinostat, Camrelizumab

Cancer Type:
Breast Cancer

Study Title:
An Open, Single-center, Cohort Clinical Study of Fluzoparib in Combination With Chidamide or Camrelizumab for HRD Positive and HER2-negative Advanced Breast Cancer

Variant Classification:
BRCA mutation

Locations:
China

NCT number:
NCT02264678

Phase: I

Treatment:
Ceralasertib, Olaparib

Cancer Type:
Breast Cancer

Study Title:
A Modular Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ceralasertib in Combination With Cytotoxic Chemotherapy and/or DNA Damage Repair/Novel Anti-cancer Agents in Patients With Advanced Solid Malignancies

Variant Classification:
BRCA mutation

Locations:
France, Republic of Korea, United Kingdom, United States

Contacts:
AstraZeneca Clinical Study Information Center [877-240-9479; information.center@astrazeneca.com]

NCT number:
NCT04169841

Phase: II

Treatment:
Durvalumab, Tremelimumab, Olaparib

Cancer Type:
Breast Cancer

Study Title:
Precision Medicine Phase II Study Evaluating the Efficacy of a Double Immunotherapy by Durvalumab and Tremelimumab Combined With Olaparib in Patients With Solid Cancers and Carriers of Homologous Recombination Repair Genes Mutation in Response or Stable After Olaparib Treatment

Variant Classification:
HRR mutation

Locations:
France

Clinical Trials

NCT number:
NCT05002868

Phase: I

Treatment:
RP12146

Cancer Type:
Breast Cancer

Study Title:
A Multi-center, Open-label, Phase I/Ib Study to Assess the Safety, Pharmacokinetics and Anti-tumor Activity of RP12146, a Poly (ADP-ribose) Polymerase (PARP) Inhibitor, in Patients With Locally Advanced or Metastatic Solid Tumors

Variant Classification:
HRR mutation

Locations:
Czech Republic, Poland

NCT number:
NCT04095273

Phase: I

Treatment:
BAY-1895344, Pembrolizumab

Cancer Type:
Breast Cancer

Study Title:
A Multicenter, Non-randomized, Open-label Phase Ib Study to Determine the Maximum Tolerated and Recommended Phase II Dose of the ATR Inhibitor BAY1895344 in Combination With Pembrolizumab and to Characterize Its Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumor Activity in Patients With Advanced Solid Tumors

Variant Classification:
DNA repair mutation

Locations:
Germany, Spain, Switzerland, United States

Contacts:
Bayer Clinical Trials Contact [clinical-trials-contact@bayer.com]

NCT number:
NCT02810743

Phase: III

Treatment:
Chemotherapy, Olaparib

Cancer Type:
Breast Cancer

Study Title:
Substantially Improving the Cure Rate of High-risk BRCA1-like Breast Cancer Patients With Personalized Therapy (SUBITO) - an International Randomized Phase III Trial

Variant Classification:
HR Deficient

Locations:
France, Netherlands

NCT number:
NCT05085626

Phase: II

Treatment:
Fluzoparib, Tucidinostat, Camrelizumab

Cancer Type:
Breast Cancer

Study Title:
An Open, Single-center, Cohort Clinical Study of Fluzoparib in Combination With Chidamide or Camrelizumab for HRD Positive and HER2-negative Advanced Breast Cancer

Variant Classification:
HR Deficient

Locations:
China

NCT number:
NCT04240106

Phase: II

Treatment:
Niraparib, Hormone Therapy

Cancer Type:
Breast Cancer

Study Title:
Multicenter, Open-label, Phase II Clinical Trial to Evaluate the Efficacy and Safety of Niraparib Plus Aromatase Inhibitors for (HR)-Positive/ (HER2)-Negative Metastatic Breast Cancers With Either Germline BRCA-mutated or Germinal BRCAwild- type and Homologous Recombination Deficiency (HRD)

Variant Classification:
HR Deficient

Locations:
Spain

NCT number:
No NCT ID

Phase: II

Treatment:
Olaparib

Cancer Type:
Breast Cancer

Other identifiers: ACTRN12617000855325, CTC0160, EMBRACE study

Study Title:
Phase II Clinical Trial of the PARP Inhibitor, Olaparib, in HR-Deficient Metastatic Breast and Relapsed Ovarian Cancer in Patients Without Germline Mutations in BRCA1 and BRCA2: The EMBRACE study ACTRN12617000855325, CTC0160, EMBRACE study

Variant Classification:
HR Deficient

Locations:
Australia

NCT number:
NCT04826341

Phase: I/II

Treatment:
Berzosertib + Sacituzumab Govitecan

Cancer Type:
Unspecified Solid Tumor

Study Title:
A Phase I/II Study of Sacituzumab Govitecan Plus Berzosertib in Small Cell Lung Cancer and Homologous Recombination-Deficient Cancers Resistant to PARP Inhibitors

Variant Classification:
BRCA2 mutation, HR Deficient

Locations:
United States

Contacts:
Rasa Vilimas [240-858-3158; rasa.vilimas@nih.gov]

NCT number:
NCT02029001

Phase: II

Treatment:
Olaparib

Cancer Type:
Unspecified Solid Tumor

Study Title:
A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients with Progressive Locally-advanced or Metastatic Solid Tumors.

Variant Classification:
BRCA2 mutation

Locations:
France

NCT number:
NCT03967938

Phase: II

Treatment:
Olaparib

Cancer Type:
Unspecified Solid Tumor

Study Title:
Efficacy of Olaparib in Advanced Cancers Occurring in Patients With Germline Mutations or Somatic Tumor Mutations in Homologous Recombination Genes

Variant Classification:
BRCA2 mutation

Locations:
Belgium

NCT number:
NCT02693535

Phase: II

Treatment:
Olaparib, Talazoparib, Atezolizumab +Talazoparib

Cancer Type:
Unspecified Solid Tumor

Study Title:
Targeted Agent and Profiling Utilization Registry (TAPUR) Study.

Variant Classification:
BRCA2 mutation

Locations:
United States

Contacts:
Pam Mangat [pam.mangat@asco.org]

NCT number:
NCT04171700

Phase: II

Treatment:
Rucaparib

Cancer Type:
Unspecified Solid Tumor

Study Title:
A Phase II Multicenter, Open-label Study of Rucaparib as Treatment for Solid Tumors Associated With Deleterious Mutations in Homologous Recombination Repair Genes

Variant Classification:
BRCA2 mutation

Locations:
United States

Contacts:
Clovis Oncology For North America [844-258-7662; medinfo@clovisoncology.com]

NCT number:
NCT02286687

Phase: II

Treatment:
Talazoparib

Cancer Type:
Unspecified Cancer

Study Title:
Phase II Study of the PARP Inhibitor Talazoparib in Advanced Cancer Patients With Somatic Alterations in BRCA1/2, Mutations/Deletions in Other BRCA Pathway Genes and Germline Mutation in BRCA1/2 (Not Breast or Ovarian Cancer)

Variant Classification:
BRCA2 mutation

Locations:
United States

Contacts:
Dr. Sarina Piha-Paul [713-563-1930; spihapau@mdanderson.org]

NCT number:
NCT04550494

Phase: II

Treatment:
Talazoparib

Cancer Type:
Unspecified Solid Tumor

Study Title:
A Pharmacodynamics-Driven Trial of Talazoparib, an Oral PARP Inhibitor, in Patients With Advanced Solid Tumors and Aberrations in Genes Involved in DNA Damage Response

Variant Classification:
BRCA2 mutation

Locations:
United States

Contacts:
Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

NCT number:
NCT03842228

Phase: I

Treatment:
Copanlisib, Olaparib, Durvalumab

Cancer Type:
Unspecified Solid Tumor

Study Title:
A Phase Ib Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and Durvalumab (MEDI4736) in Patients With Advanced Solid Tumors

Variant Classification:
BRCA2 mutation

Locations:
United States

Contacts:
Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

NCT number:
NCT03415659

Phase: I

Treatment:
HWH-340

Cancer Type:
Unspecified Solid Tumor

Study Title:
A Phase I, Open-label, Single-center, Single/Multiple-dose, Dose-escalation/Doseexpansion Clinical Study on Tolerance and Pharmacokinetics of HWH340 Tablet in Patients With Advanced Solid Tumors

Variant Classification:
BRCA2 mutation

Locations:
China

NCT number: NCT03297606
Phase: II
Treatment: Olaparib
Cancer Type: Unspecified Solid Tumor

Study Title: Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial
Variant Classification: BRCA2 aberration
Locations: Canada

NCT number: NCT04497116
Phase: I/II
Treatment: RP-3500, Talazoparib
Cancer Type: Unspecified Solid Tumor

Study Title: Phase I/IIa Study of the Safety, Pharmacokinetics, Pharmacodynamics and Preliminary Clinical Activity of RP-3500 Alone or in Combination With Talazoparib in Advanced Solid Tumors With ATR Inhibitor Sensitizing Mutations (TRESR Study)
Variant Classification: BRCA2 aberration
Locations: Canada, Denmark, United Kingdom, United States
Contacts: Dr. Peter Manley [857-322-5553; pmanley@reparerx.com]

NCT number: NCT04174716
Phase: I/II
Treatment: Venadaparib
Cancer Type: Unspecified Solid Tumor

Study Title: An Open-label, Multi-center, Phase Ib/IIa Basket Trial of IDX-1197 in Patients With Homologous Recombination Repair Mutated Solid Tumors
Variant Classification: HRR mutation
Locations: Republic of Korea

NCT number: NCT03767075
Phase: II
Treatment: Atezolizumab
Cancer Type: Unspecified Solid Tumor

Study Title: Basket of Baskets: A Modular, Open-label, Phase II, Multicentre Study To Evaluate Targeted Agents in Molecularly Selected Populations With Advanced Solid Tumours
Variant Classification: DNA repair mutation
Locations: France, Germany, Netherlands, Spain, Sweden, United Kingdom

NCT number: NCT04905914
Phase: I/II
Treatment: ATRN-119
Cancer Type: Unspecified Solid Tumor

Study Title: A Phase I/IIa, Open-Label, Safety, Pharmacokinetic, And Preliminary Efficacy Study Of Oral ATRN-119 In Patients With Advanced Solid Tumors
Variant Classification: DNA repair mutation
Locations: United States
Contacts: Robert Hasson [619-540-6253; rhasson@pacificlinkconsulting.com]

Clinical Trials

NCT number: NCT04423185
Phase: II
Treatment: Niraparib
Cancer Type: Unspecified Solid Tumor

Study Title: Platform Study of Genotyping Guided Precision Medicine for Rare Tumors in China
Variant Classification: HR Deficient
Locations: China

NCT number: NCT03155620
Phase: II
Treatment: Olaparib
Cancer Type: Unspecified Solid Tumor

Study Title: NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol
Variant Classification: DNA repair pathway
Locations: Puerto Rico, United States
Contacts: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

NCT number: NCT03233204
Phase: II
Treatment: Olaparib
Cancer Type: Unspecified Solid Tumor

Study Title: NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase 2 Subprotocol of Olaparib in Patients With Tumors Harboring Defects in DNA Damage Repair Genes
Variant Classification: DNA repair pathway
Locations: Puerto Rico, United States
Contacts: Multiple contacts: See www.clinicaltrials.gov for complete list of contacts.

NCT number: NCT03297606
Phase: II
Treatment: Olaparib
Cancer Type: Unspecified Solid Tumor

Study Title: Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial
Variant Classification: HR Deficient
Locations: Canada

NCT number: NCT03742895
Phase: II
Treatment: Olaparib
Cancer Type: Unspecified Solid Tumor

Study Title: A Phase II Study of Olaparib Monotherapy in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer
Variant Classification: HR Deficient
Locations: Argentina, Australia, Canada, Colombia, Denmark, France, Guatemala, Ireland, Israel, Italy, Mexico, Peru, Republic of Korea, Romania, Russian Federation, Spain, Switzerland, Turkey, United Kingdom, United States
Contacts: Toll Free Number [888-577-8839; Trialsites@merck.com]

Clinical Trials

NCT number:
NCT04267939

Phase: I

Treatment:
BAY-1895344, Niraparib

Cancer Type:
Unspecified Solid Tumor

Study Title:
An Open-label Phase Ib Study to Determine the Maximum Tolerated and/or Recommended Phase II Dose of the ATR Inhibitor BAY 1895344 in Combination With PARP Inhibitor Niraparib, in Patients With Recurrent Advanced Solid Tumors and Ovarian Cancer

Variant Classification:
DNA repair pathway

Locations:
United States

Contacts:
Bayer Clinical Trials Contact [888-842-2937; clinical-trials-contact@bayer.com]

NCT number:
NCT04693468

Phase: I

Treatment:
Talazoparib, Palbociclib, Axitinib, Crizotinib

Cancer Type:
Unspecified Solid Tumor

Study Title:
Modular Phase IB Hypothesis-Testing, Biomarker-Driven, Talazoparib Combination Trial (TalaCom)

Variant Classification:
DNA repair pathway

Locations:
United States

Contacts:
Timothy A. Yap [713-563-1784; tyap@mdanderson.org]

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