Patient Information

Name:	Mrs. Nodira Ashurova
Age/Gender:	43 years/ Female
Referring Physician:	Dr. Chandragouda D
Referring Centre:	Walk in Delhi
Specimen Type:	FFPE Block (5520/23A)
Sample ID:	2300103790
Patient ID:	1002331062
Date received:	31.05.2023
Report Date:	10.07.2023

Oncoprecise™ CGP (Somatic) REPORT

Clinical History

Mrs. Nodira Ashurova is a case of Recurrent Metastatic High Grade Serous Carcinoma of Ovary.

Report Summary

Test was performed on Block No-5520/23A which showed presence of 50% tumor cells.

Alteration Description	Findings
Genomic Alteration	***PTEN (c.274G>T)***
	***TP53* (c.844C>T)**
Genomic Fusions	**Not detected**
Copy number variants (CNVs)	**Not detected**
Tumor mutation burden (TMB)	**Borderline Intermediate (10.46 mut/mb)***
Microsatellite instability (MSI)- Status	**MSS (Score:9.09)**
Loss of Heterozygosity (LOH)	**55.38 %****

*Note: This High TMB Score might be affected by higher deamination in this sample which is may be due to intrinsic nature of FFPE tissue.
**Note: Assessment of HRR/HRD using orthogonal methods is recommended.

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Therapeutic summary of actionable variations

Tier	Variant	VAF/CN	Therapy	Potential drug resistance
II	PTEN c.274G>T p.D92Y	83.40%	Copanlisib + With Fulvestrant# Afuresertib + Paclitaxel# Copanlisib + Nivolumab + Ipilimumab# AZD5363 + Olaparib + Durvalumab# Ipatasertib + Atezolizumab# TAS0612# Temsirolimus#	Chemotherapy*
II	TP53 c.844C>T p.R282W	74.63%	Arsenic Trioxide# Atorvastatin#	Chemotherapy*

Note 1:The therapies in bold have been approved by the FDA. Further information about these therapies can be found in the "Immunotherapy" and "Gene and Variant description" section of this report.
Note 2: The therapies labeled as # are being tested in registered clinical trials for which the patient may be eligible to enroll. Please see the "Clinical trials" section for more details.
Note 3: The *drug resistance associations mentioned in the above table may be observed in preclinical models. More details can be found in the "Drug resistance" section for each variation.
Note 4: Additional therapeutic information and the prognostic information can be found in the "variant details" and the "clinical trials" section of the report

Immunotherapy associated markers

Immunotherapy associated markers

1. PDL1 by IHC (22C3)-Negative (TPS<1%, No PD-L1 expression)
2. Tumor Mutation Burden- Borderline Intermediate (10.46 mut/mb)
3. Microsatellite Instability- MSS (Microsatellite Stable) (Score:9.09)
4. MMR (Mismatch repair) status- Loss-of-function mutation is not observed in any of the MMR genes MLH1, MSH2, MSH6 and PMS2

Approved Immunotherapy

There is no immunotherapy that is FDA-approved specifically for the ovarian carcinoma patients.

Following immunotherapy is FDA-approved for all the TMB-high solid tumors
Pembrolizumab

Pembrolizumab is approved for solid tumors that are tumor mutational burden-high (TMB-H >10) and have spread to other parts of the body or cannot be removed by surgery. Pembrolizumab is used in adults and children whose cancer got worse after treatment and who are not able to receive other therapies.

In-trial Immunotherapy

Multiple immunotherapies are being investigated in clinical trials for this patient's genomic profile and/or diagnosis (Please see "Clinical trials" section for more details).

Variant Details

Table-1: List of variants identified in this sample

Gene	Genomic alteration	Variant Allelic Frequency (VAF%)	Impact on protein Function	Clinical Significance	AMP^ Classification
PTEN **NM_000314.8**	**c.274G>T p.Asp92Tyr**	**83.40%**	**Loss-of-Function**	**Pathogenic**	**Tier IIC**
TP53 **NM_000546.6**	**c.844C>T p.Arg282Trp**	**74.63%**	**Loss-of-Function**	**Pathogenic**	**Tier IIC**

Refer to supplementary information for the classification criteria details. ^

Table-2: Significance of Variants reported in database

Variant	dbSNP rs ID	COSMIC	ClinVar [ID]	*In- silico* predictors			Population Database	
				SIFT	Polyphen	MT2	gnomAD	ExAc
PTEN (c.274G>T)	-	**COSM86049**	-	**D**	**D**	**D**	-	-
TP53 (c.844C>T)	**rs28934574**	**COSM10704**	**VCV000012364**	**P**	**P**	**P**	**0.0003978%**	**0.001659%**

P- Pathogenic, D- Damaging, B-Benign

Gene and Variant Description

PTEN
c.274G>T
p.Asp92Tyr

Gene Summary

This gene was identified as a tumor suppressor that is mutated in a large number of cancers at high frequency. The protein encoded by this gene is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase. It contains a tensin like domain as well as a catalytic domain similar to that of the dual specificity protein tyrosine phosphatases. Unlike most of the protein tyrosine phosphatases, this protein preferentially dephosphorylates phosphoinositide substrates. It negatively regulates intracellular levels of phosphatidylinositol-3,4,5-trisphosphate in cells and functions as a tumor suppressor by negatively regulating the AKT/PKB signaling pathway.

Altered variant

The p.Asp92Tyr variant (also known as c.274G>T), was detected in PTEN gene on chromosome 10 at position 89692790 with variant allele frequency of 83.40% (represented by 739 reads). This heterozygous mutation has a total depth of 886X. It is located at exon 5 of NM_000314.8 transcript and was found to change amino acid, Aspartic acid to Tyrosine at codon 92. It leads to Loss-of-Function. It is a hotspot variant. It is represented by COSM86049 in the Cosmic database. It is predicted as deleterious by SIFT, polyphen2, FATHMM and MutationTaster2 which are an in-silico DNA variant effect prediction tool.
This variant was not found in the population frequency database like gnomAD, ExAC and 1000G database.

The PTEN D92Y mutation is located in the phosphatase domain of the protein. This mutation has been identified in endometrioid carcinoma and is a statistically significant hotspot (PMID: 28103826). In vivo studies with yeast expressing PTEN D92Y suggest that the mutation is likely inactivating as measured abrogated phosphatase activity compared to wildtype (PMID: 21828076).

Disease association

PTEN, phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN, is a tumor suppressor (PMID: 30562755) with roles in the cell cycle, growth, DNA repair, cell survival and regulation of the Akt-mTOR pathway (PMID: 24656806, PMID: 30145641). PTEN germline mutations are common in Cowden syndrome (PMID: 30562755) and PTEN somatic alterations resulting in loss of function have been found in many types of cancer including, but not limited to endometrial (PMID: 30142194), melanoma (PMID: 30148988), and prostate (PMID: 18767981, PMID: 30153654).

Somatic mutations of PTEN occur in multiple malignancies, including glioma, melanoma, prostate, endometrial, breast, ovarian, renal, and lung cancers. Germline mutations of PTEN lead to inherited hamartoma and Cowden syndrome (for reviews see PMID: 18767981 and PMID: 17827710).

PTEN is altered in 7.24% of all cancers with endometrial endometrioid adenocarcinoma, conventional glioblastoma multiforme, prostate adenocarcinoma, breast invasive ductal carcinoma, and colon adenocarcinoma having the greatest prevalence of alterations [My cancer genome].

Prognostic significance

Downregulation of cytoplasmic PTEN expression was most frequent in *ENOC (most frequently in younger patients;p value = 0.0001) and *CCOC and was associated with longer overall survival in *HGSOC (hazard ratio: 0.78, 95% CI: 0.65 -- 0.94, p value = 0.022). PTEN expression was associated with ER, PR and AR expression (p values: 0.0008, 0.062 and 0.0002, respectively) in HGSOC and with lower CD8 counts in CCOC (p value < 0.0001). Heterogeneous expression of PTEN was more prevalent in advanced HGSOC (p value = 0.019) and associated with higher CD8 counts (p value = 0.0016) (PMID: 32555365)

*ENOC:endometrioid ovarian carcinoma
*CCOC:Clear cell ovarian carcinoma
*HGSOC:High grade serous ovarian carcinoma

Prognostic significance of germline mutation

Pathogenic germline PTEN mutations are associated with The PTEN hamartoma tumor syndrome (PHTS). The PTEN hamartoma tumor syndrome (PHTS) shows autosomal dominant inheritance and includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and PTEN-related Proteus-like syndrome. CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, kidney, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules, and present by the late 20s. The lifetime risk of developing breast cancer is 85%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer (usually follicular, rarely papillary, but never medullary thyroid cancer) is approximately 35%. The lifetime risk for renal cell cancer (predominantly of papillary histology) is 34%. The risk for endometrial cancer may approach 28%. BRRS is a congenital disorder characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, and pigmented macules of the glans penis. PS is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses (MedGen).

***Note: Germline testing is recommended to determine if the identified pathogenic PTEN mutation is germline or somatic.**

Therapy

Approved therapy

There is no FDA-approved targeted therapy available for tumors with PTEN mutations.

In-trial therapy

Therapies are being investigated in the clinical trials for patients with Ovarian cancer or solid tumors with PTEN mutation. The patient may be eligible to enroll in these clinical trials. Please see the “Clinical trial” section for more details.

Drug resistance information

Chemotherapy

In a study with high-grade serous ovarian cancer (HGSC) patients, it is shown that PTEN alterations are associated with acquired resistance to chemotherapy (PMID: 26503049).

TP53
c.844C>T
p.Arg282Trp

Gene Summary

This gene encodes a tumor suppressor protein containing transcriptional activation, DNA binding, and oligomerization domains. The encoded protein responds to diverse cellular stresses to regulate expression of target genes, thereby inducing cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. Mutations in this gene are associated with a variety of human cancers, including hereditary cancers such as Li-Fraumeni syndrome. Alternative splicing of this gene and the use of alternate promoters result in multiple transcript variants and isoforms. Additional isoforms have also been shown to result from the use of alternate translation initiation codons from identical transcript variants (PMIDs: 12032546, 20937277).

Altered variant

The p.Arg282Trp variant (also known as c.844C>T), was detected in TP53 gene on chromosome 17 at position 7577094 with variant allele frequency of 74.63% (represented by 1492 reads). This heterozygous mutation has a total depth of 1999X. It is located at exon 8 of NM_000546.6 transcript and was found to change amino acid, Arginine to Tryptophan at 282 codon. It leads to Loss-of-Function. It is a hotspot variant. It is represented by rs28934574 in dbSNP and COSM10704 in the Cosmic database. It is interpreted as pathogenic by the ClinVar database [VCV000012364]. It is predicted as pathogenic by SIFT, Polyphen2, FATHMM and MutationTaster2 which is an in-silico DNA variant effect prediction tool. It was found in the population frequency database like gnomAD exome and ExAC at global minor allele frequency of 0.0003978% and 0.001659% respectively.

The TP53 R282W mutation occurs in the protein's DNA binding domain. Expression of this mutation in TP53-null cell lines resulted in aggregation of mutant proteins, likely leading to destabilization of TP53 and upregulation of heat shock proteins (PMID: 21445056).

Disease association

TP53, tumor protein p53, is a tumor suppressor (PMID: 30562755) and oncogene (PMID: 30577483) involved in cell cycle arrest and apoptosis, and is the most frequently mutated gene in cancer (PMID: 10065147, PMID: 22713868). TP53 germline mutations are common in Li-Fraumeni syndrome (PMID: 30239254) and somatic missense mutations are frequent in almost all cancer types (PMID: 30224644) and are also implicated in chemoresistance (PMID: 9927204, PMID: 24065105, PMID: 27066457).

TP53 is the most frequently mutated gene in cancer; it is mutated in about half of all cancers . TP53 is most frequently mutated in ovarian, colon, and esophageal cancers, although it is significantly mutated in many other cancer types (COSMIC).
TP53 is altered in 39.52% of all cancers with lung adenocarcinoma, colon adenocarcinoma, breast invasive ductal carcinoma, pancreatic adenocarcinoma, and high grade ovarian serous adenocarcinoma having the greatest prevalence of alterations [My cancer genome].

Prognostic significance

In cases of ovarian serous cystadenocarcinoma, the co-occurrence of TP53 and BRCA mutations resulted in longer survival and disease-free survival times than the presence of neither TP53 nor BRCA mutations (PMID: 30542790).

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TP53 mutations are the most common genetic events that occur at a single gene in sporadic human EOC. The majority of HGSOCs harbor inactive p53 molecules because of single genetic mutations. Therefore, p53 plays a critical role in preventing and inhibiting the development and progression of EOCs (PMID: 30613473). In the investigation of EOC, the general trend is that TP53 mutations are associated with poor survival, as well as with chemo-resistance. Many other studies also reported no significant relationship, and few showed opposite results (PMID: 30613473).

*EOC: Epithelial Ovarian Cancer
*HGSOC: High grade serous ovarian carcinoma

Prognostic significance of germline mutation

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated with high risks for a diverse spectrum of childhood- and adult-onset malignancies. The lifetime risk of cancer in individuals with LFS is =70% for men and =90% for women. Five cancer types account for the majority of LFS tumors: adrenocortical carcinomas, breast cancer, central nervous system tumors, osteosarcomas, and soft-tissue sarcomas. LFS is associated with an increased risk of several additional cancers including leukemia, lymphoma, gastrointestinal cancers, cancers of head and neck, kidney, larynx, lung, skin (e.g., melanoma), ovary, pancreas, prostate, testis, and thyroid. Individuals with LFS are at increased risk for cancer in childhood and young adulthood; survivors are at increased risk for multiple primary cancers.

***Note: Germline testing is recommended to determine if the identified pathogenic TP53 mutation is germline or somatic.**

Therapy

Approved therapy

No FDA-approved therapy is available for solid tumors with TP53 mutations.

In-trial therapy

Therapies are being investigated in the clinical trials for patients with solid tumors and TP53 mutation. The patient may be eligible to enroll in these clinical trials. Please see the "Clinical trial" section for more details.

Drug resistance information

Chemoresistance

The poor chemoresponse of a subset of HGSOC patients suggest p53 aggregation as a new biomarker for chemoresistance (PMID: 30613473). This patient's TP53 mutation, R282W, is known to cause aggregation of the protein (PMID: 21445056).

Ovarian cancer patients harboring different mutated TP53 show different chemotherapy resistances and survival outcomes. R248G confers chemoresistance and is not acetylated during epoB treatment, while R273H demonstrated high MDR1 expression and resistance to paclitaxel. Optimally cyto-reduced patients with codon R273, R248, or R175 HSMs, or any other TP53 mutation have different overall survivals for 84.1, 33.6, 62.1, and 44.5 months, respectively. The study from 153 patients with advanced EOC who received platinum-based chemotherapy, showed that TP53 K351N mutation is associated with induction of platinum resistance after NACT, and is an independent factor for shorter disease free survival in multivariate analysis (PMID: 30613473).

Homologous Recombination Repair genes

Homologous recombination repair (HRR) pathway genes play a vital role in maintaining genome stability and tumor suppression. Alterations in HRR genes can lead to genome instability which in turn may increase the risk of developing tumors. Thus knowing the alterations in HRR genes can act as potential biomarkers to decide the personalized therapy to be undertaken.

Note: This patient shows 55.38 % of LOH within the HRR gene panel that includes BRCA1/2. To further confirm the HRR/HRD status, assessment of HRR/HRD using orthogonal methods is recommended.

Gene/Genomic Alteration	Finding
LOH Percentage	**55.38%**
BRCA1	***LOH, 17q21.31(41197602-41244291)x2***
BRCA1	***CNV, CN:0.0***
BRCA1	***LOH, 17q21.31(41244280-41256159)x0***
BRCA1	***SNV, P982Q, AF:0.24***
BRCA1	***CNV(BigDel), CN:0.19***
BRCA2	***CNV(BigDup), CN:4.47***
BRCA2	***CNV(BigDup), CN:4.58***
BRCA2	***CNV(BigDup), CN:3.78***
BLM	***LOH, 15q26.1(91290599-91358551)x4***
BRIP1	***LOH, 17q23.2(59760627-59938976)x4***
CDK12	***LOH, 17q12(37618286-37687611)x2***
CHEK2	***LOH, 22q12.1(29083868-29130729)x2***
POLE	***LOH, 12q24.33(133201214-133257891)x2***
PTEN	***LOH, 10q23.31(89623659-89725309)x2***
PTEN	***SNV, D92Y, AF:0.83***
RAD51B	***LOH, 14q24.1(68290164-69061406)x4***
RAD51C	***LOH, 17q22(56769933-56811619)x4***
RAD51D	***LOH, 17q12(33427950-33446720)x2***

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*Note: From the total of 46 HRR genes (including BRCA1 and BRCA2) covered in Oncomine Comprehensive Assay Plus, these alterations are Identified. Confirmation with other orthogonal methods is recommended.

*Note: Homologous recombination repair (HRR) genes were defined from published evidence in relevant therapies, clinical guidelines, as well as clinical trials, and include - BRCA1, BRCA2, ATM, BARD1, BLM, BRIP1, CDK12, CHEK1, CHEK2, FANCL, NBN, PALB2, POLD1, POLE, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L.

Therapy (This patient is not a confirmed case of HRD)

Clinical Trials

Following ongoing clinical trials are relevant for the patient's diagnosis and genomic profile (Additional trials that are investigating immunotherapies relevant for the patient's diagnosis or relevant trials that are recruiting patients in India are also listed below)

Relevant Variant/ Parameter	Clinical trial	Intervention	Phase	Trial identifier	Recruiting location
PTEN mutation in ER/PR positive ovarian cancer	Phase 2 Study of PI3K Inhibitor Copanlisib in Combination With Fulvestrant in Selected ER+ and/or PR+ Cancers With PI3K (PIK3CA, PIK3R1) and/or PTEN Alterations	Copanlisib + With Fulvestrant	Phase 2	NCT05082025	USA
Platinum resistant high grade serous OC with PTEN mutation	An Open Label Randomized Active Controlled Phase II Clinical Study to Assess the Efficacy and Safety of Afuresertib Plus Paclitaxel Versus Paclitaxel in Patients With Platinum-Resistant Ovarian Cancer	Afuresertib + Paclitaxel	Phase 2	NCT04374630	USA, China
Metastatic solid tumors with PTEN mutation	A Phase I/II Biomarker Driven Combination Trial of Copanlisib and Immune Checkpoint Inhibitors in Patients With Advanced Solid Tumors	Copanlisib + Nivolumab + Ipilimumab	Phase 1, Phase 2	NCT04317105	USA, Canada

Metastatic solid tumors with PTEN mutation	An Investigator Sponsored Phase I Study of the Safety, Tolerability and Pharmacodynamics of Escalating Doses of Combination Treatment of AZD5363 + Olaparib + Durvalumab (MEDI4736) in Patients With Advanced or Metastatic Solid Tumor Malignancies.	AZD5363 + Olaparib + Durvalumab	Phase 1	NCT03772561	Singapore
Metastatic solid tumors with PTEN mutation	Ice-CAP: A Phase I Trial of Ipatasertib in Combination With Atezolizumab in Patients With Advanced Solid Tumors With PI3K Pathway Hyperactivation	Ipatasertib + Atezolizumab	Phase 1, Phase 2	NCT03673787	UK
Metastatic solid tumors with PTEN mutation	A Phase 1 Study of TAS0612 in Patients With Locally Advanced or Metastatic Solid Tumors	TAS0612	Phase 1	NCT04586270	USA, France
Metastatic solid tumors with PTEN mutation	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	Temsirolimus	Phase 2	NCT03297606	Canada
Solid tumor with mutant TP53	Arsenic Trioxide in Refractory Solid Tumors With Rescuable p53 Mutation	Arsenic Trioxide**	Phase 2	NCT04869475	China
Solid tumor with mutant TP53	A Pilot Trial of Atorvastatin in p53-Mutant and p53 Wild-Type Malignancies	Atorvastatin*	Phase 1	NCT03560882	USA
Metastatic ovarian carcinoma, TMB-high tumors	A Phase 1/2 Open Label, Dose Escalation and Expansion Study of MDNA11, IL-2 Superkine, Administered Alone or in Combination With Immune Checkpoint Inhibitor in Patients	MDNA11 (IL-2 Superkine)	Phase 1, Phase 2	NCT05086692	USA, Australia, Canada

	With Advanced Solid Tumors				
Metastatic, platinum-resistant epithelial ovarian cancer, high-TMB tumors	A Phase 1/2a, Multicenter, Open-Label, Dose-Escalation and Expansion Study of Intravenously Administered 23ME-00610 in Patients With Advanced Solid Malignancies	23ME-00610	Phase 1, Phase 2	NCT05199272	USA, Canada
Metastatic high grade serous ovarian carcinoma progressed on prior PARP inhibitor therapy	A Phase 1b/2 Basket Study To Assess The Safety And Efficacy Of AsiDNA™ In Combination With Olaparib In Participants With Recurrent Solid Tumors	*AsiDNA™ + Olaparib	Phase 1, Phase 2	NCT05700669	
Immunotherapy for metastatic ovarian cancer patients	T-cell Therapy in Combination With Nivolumab, Relatlimab and Ipilimumab for Patients With Advanced Ovarian-, Fallopian Tube- and Primary Peritoneal Cancer	Tumor Infiltrating Lymphocytes infusion + Nivolumab + Relatlimab +Ipilimumab	Phase 1, Phase 2	NCT04611126	Denmark
Immunotherapy for metastatic ovarian cancer patients	A Phase II Study Using Short-Term Cultured, Autologous Tumor-Infiltrating Lymphocytes Following a Lymphodepleting Regimen in Metastatic Cancers Plus the Administration of Pembrolizumab	Cyclophosphamide + Fludarabine + young unselected TIL + Aldesleukin + Pembrolizumab	Phase 2	NCT01174121	USA
Immunotherapy for Platinum sensitive, metastatic, recurrent, serous adenocarcinoma of ovary	Phase 1b/2, Single Arm Clinical Trial to Evaluate the Safety and Activity of Oregovomab and Bevacizumab, Paclitaxel Carboplatin as a Combinatorial Strategy in Subjects With BRCA-wild Type Platinum Sensitive	Oregovomab + Bevacizumab + Paclitaxel +Carboplatin	Phase 1, Phase 2	NCT04938583	Korea

	Recurrent Ovarian Cancer				
Immunotherapy for stage IV ovarian cancer	Phase I Study of Tumor Treating Fields (TTF) in Combination With Cabozantinib, or With Atezolizumab and Nab-Paclitaxel in Patients With Advanced Solid Tumors Involving the Abdomen or Thorax	Tumor Treating Fields (TTF) +Cabozantinib Or Tumor Treating Fields (TTF) + Atezolizumab + Nab-Paclitaxe	Phase 1	NCT05092373	USA
Immunotherapy for Metastatic, recurrent, serous ovarian cancer	An Open-label, Multicentre, Dose-escalation, First-in-human Phase I Study to Evaluate Safety, Tolerability and Antineoplastic Activity of OATD-02 in Patients With Selected Advanced and/or Metastatic Solid Tumours (Colorectal Cancer, Ovarian Cancer, Pancreatic Cancer or Renal Cell Carcinoma)	OATD-02 (ARG1 and ARG2 dual inhibitor)	Phase 1	NCT05759923	Poland
Immunotherapy for Metastatic, recurrent, ovarian cancer	The Efficacy of T-regulatory Cell Depletion With E7777 Combined With Immune Checkpoint Inhibitor, Pembrolizumab, in Recurrent or Metastatic Solid Tumors: Phase I/II Study	Pembrolizumab + E7777	Phase 1, Phase 2	NCT05200559	USA
Immunotherapy for Metastatic, ovarian cancer	A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of NC762 in Subjects With Advanced or Metastatic Solid Tumors	NC762	Phase 1, Phase 2	NCT04875806	USA
Immunotherapy for metastatic ovarian cancer	A Phase II Study Using the Administration of Autologous T-Cells Genetically Engineered to Express T-Cell	Cyclophosphamide and Fludarabine + Individual Patient TCR-	Phase 2	NCT03412877	USA

	Receptors Reactive Against Neoantigens in Patients With Metastatic Cancer	Transduced PBL + high- or low-dose Aldesleukin			
Clinical trial recruiting ovarian cancer patients in India	Evaluation of cell-based vaccine therapy – dendritic cell-based immunotherapy for epithelial ovarian cancer patients who have failed two systemic therapies	Dendritic cell-based immunotherapy	Phase 2	CTRI/2020/11/029436	India
Clinical trial recruiting ovarian cancer patients in India	"A phase III randomised trial of metronomic maintenance with oral methotrexate and propranolol versus observation after chemotherapy in relapsed platinum sensitive high grade epithelial ovarian cancer".	Oral methotrexate and propranolol	Phase 3	CTRI/2019/11/021924	India
Clinical trial recruiting ovarian cancer patients in India	A Randomized, Open-Label, Multicenter, Two Treatment, Two Period, Two Sequence, Single Dose, Crossover Bioequivalence Study Of Doxorubicin Hydrochloride Liposome Injection 2mg/mL (50 mg/m2 dose) Of Alembic Pharmaceuticals Limited, India And PrTaro-DOXOrubicin Liposomal 2mg/mL (Pegylated Liposomal Doxorubicin Hydrochloride for Injection) (50 mg/m2 dose) Of Taro Pharmaceuticals Inc, 130 East Drive, Brampton, Ontario, Canada, L6T 1C1, Administered in Patient With Advanced Ovarian Cancer Under Standard	Doxorubicin	Phase 1	CTRI/2021/12/038914	India

	diet (non-high-fat) Conditions.				
Clinical trial recruiting ovarian cancer patients in India	A randomized, open-label, balanced, multi-center, two-treatment, two-period, two-sequence, two-way crossover, single-dose, bioequivalence study of Doxorubicin Hydrochloride Liposome Injection 20 mg/10 mL (2 mg/mL) manufactured by Alembic Pharmaceuticals Limited, India with Doxorubicin Hydrochloride Liposome Injection 20 mg/10 mL (2 mg/mL) manufactured by Sun Pharmaceutical Ind. Ltd., India administered through intravenous infusion in ovarian cancer subjects whose disease has progressed or recurred after platinum-based chemotherapy under standard diet (non-high-fat) conditions.	Doxorubicin	N/A	CTRI/2022/12/048463	India

Note 1: Confirmation of somatic/germline status is necessary for certain variants to determine the patient's eligibility for the trial.
Note 2: Patient's known treatment history, as per the discharge summary is also taken into consideration while matching the trials.
Note 3: To further determine the patient's eligibility for the trial, careful matching of the inclusion criteria based upon the patient's condition and other clinical parameters is necessary. Certain comorbidities may make the patient ineligible for the trial.
Note 4: **Arsenic Trioxide: Structural p53 mutation R282W was rescued potently by ATO in transactivation in this study (PMID: 33357454)
Note 5: *Atorvastatin. By conducting a chemical library screen to identify compounds that can degrade mutant p53, Parrales and colleagues recently discovered statins (lovastatin, atorvastatin and mevastatin) as biologically active compounds that preferentially induce degradation of p53 with conformational or misfolded mutation changes (V157F, R172H, R175H, Y220C, R248W, R273H, and R280K) (PMID: 28643165).
Note 6: *AsiDNA™ is a short double-stranded DNA fragment (oligonucleotide) that acts as a decoy, mimicking double-strand breaks in the DNA of the tumor cell. AsiDNA molecules trigger false DNA break signals to activate and attract DNA repair proteins, which prevents their recruitment to the site of actual DNA damage. As a result, damages to tumor cells' DNA remain unrepaired.
Note 7: *NCT04884360 (Olaparib), NCT01932125 (Bevacizumab) are the clinical trials currently recruiting high grade serous ovarian cancer patients in India but these trials exclude the patients who are already treated with Olaparib and Bevacizumab respectively.

Dr. Madhavi Pusalkar, Ph.D.
GM-Genomics Operations

Supplementary Information

Test Description

Comprehensive genomic profiling (CGP) is advancing precision oncology research through the analysis of multiple relevant biomarkers in a single next-generation sequencing (NGS) test. The test can detect all types of single-gene variants, such as single-nucleotide variants (SNVs), insertions and deletions (indels), novel and known fusions, splice variants, and copy number variants (CNVs), including both copy number gains and losses.A study potential responses to immunotherapies with measurement of tumor mutational burden (TMB) and predisposition to genetic hypermutability by comparing microsatellite instability (MSI) regions, and analyse mutational signatures for insights into etiological factors in tumorigenesis. It can detect both gene-level and sample-level loss of heterozygosity (LOH) to assess genomic instability and mutations in 46 key genes in the homologous recombination repair (HRR) pathway.

Quality Control Statics

Mean depth coverage	2,319
Target Base coverage at 500X	90.50 %

Genes Analyzed

Genes Assayed for the Detection of DNA Sequence Variants: *ABL1, ABL2, ACVR1, ACVR2A, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARID1A, ARID1B, ARID2, ASXL1, ASXL2, ATM, ATP1A1, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BCL2, BCL2L12, BCL6, BCOR, BCR, BLM, BMP5, BRAF, BRCA1, BRCA2, BRIP1, BTK, CACNA1D, CALR, CARD11, CASP8, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDC73, CDH1, CDK4, CDK6, CDKN2A, CDKN2C, CHD4, CHEK2, CIC, CREBBP, CSF1R, CTCF, CTNNB1, CUL1, CUL3, CYP2D6, CYSLTR2, DDR2, DDX3X, DGCR8, DICER1, DNMT3A, DPYD, DROSHA, E2F1, EGFR, EIF1AX, EP300, EPAS1, EPHA2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC5, ERRFI1, ESR1, EZH2, FAM135B, FANCM, FBXW7, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, FUBP1, GATA2, GATA3, GLI1, GNA11, GNA13, GNAQ, GNAS, GPS2, H2BC5, H3-3A, H3-3B, H3C2, HIF1A, HNF1A, HRAS, ID3, IDH1, IDH2,*

IKBKB, IL6ST, IL7R, IRF4, IRS4, JAK1, JAK2, JAK3, KDM6A, KDR, KEAP1, KIT, KLF4, KLF5, KMT2B, KMT2D, KNSTRN, KRAS, LARP4B, LATS1, MAGOH, MAP2K1, MAP2K2, MAP2K4, MAP2K7, MAP3K4, MAPK1, MAPK8, MAX, MDM4, MECOM, MED12, MEF2B, MEN1, MET, MGA, MITF, MLH3, MPL, MSH3, MSH6, MTOR, MYC, MYCN, MYD88, MYOD1, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PARP1, PAX5, PBRM1, PCBP1, PDGFRA, PDGFRB, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R2, PIM1, PLCG1, PMS2, POLE, PPM1D, PPP2R1A, PPP6C, PRKACA, PTCH1, PTEN, PTPN11, PTPRD, PXDNL, RAC1, RAD50, RAD51, RAF1, RARA, RB1, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, RNF43, ROS1, RPL10, RPL5, RUNX1, RUNX1T1, SDHD, SETBP1, SETD2, SF3B1, SIX1, SIX2, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SNCAIP, SOCS1, SOS1, SOX2, SPOP, SRC, SRSF2, STAG2, STAT3, STAT5B, STAT6, STK11, TAF1, TCF7L2, TERT, TET2, TGFBR1, TGFBR2, TNFAIP3, TOP1, TP53, TPMT, TRRAP, TSC2, TSHR, U2AF1, UGT1A1, USP8, VHL, WAS, WT1, XPO1, XRCC2, ZFHX3, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations: *ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, H3-3A, H3-3B, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2*

Genes Assayed for the Detection of Fusions: *AKT1, AKT2, AKT3, ALK, AR, BRAF, BRCA1, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, MAP3K8, MET, MTAP, MYB, MYBL1, NOTCH1, NOTCH2, NOTCH3, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PIK3CA, PIK3CB, PPARG, PRKACA, PRKACB, RAF1, RARA, RELA, RET, ROS1, RSPO2, RSPO3, STAT6, TERT, TFE3, TFEB, YAP1*

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

Methodology

Nucleic acid (DNA/RNA) was extracted from FFPE tissue sample, using standard Qiagen nucleic acid isolation kits. The DNA/RNA was quantified using Qubit and 20-30ng of DNA/RNA was amplified using Oncomine Comprehensive assay plus as per the instruction manual. The QC of library prepeared is checked by Agilent Bioanalyser. The 150-200bp library size samples are sequenced on Ion S5 platform as per manufacture protocol.

Data Analysis

The sequence data is processed using the analaysis pipeline Ion reporter software 5.18.2.0 as suggested by the vendor. This software can detects and annotates low frequency somatic variants (SNPs, InDels, CNVs) from targeted Ion AmpliSeq™ DNA manual or Ion Chef™ automated libraries, computes automatic tumor cellularity, Loss-of-Heterozygosity, TMB and microsatellite instability (MSI), as well as gene fusions from targeted Ion AmpliSeq™ RNA manual or Ion Chef™ automated libraries, from Oncomine™ Comprehensive Assay Plus run on the Ion 540™ Chip. TMB uses the TMB (Non-Germline Mutations) filter chain with TMB algorithm v4.0. MSI status is computed using a baseline with MSI algorithm v4.0.3. Released with: Ion Reporter™ Software 5.18.4. Workflow Version: 2.4. Samples are classifies as TMB-High or TMB-low using a cutoff vcalue of 10mut/mb.

Interpretation of Variants

The interpretation of the report is based on the clinical information provided. The annotation for variants was derived using various diseases databases like dbSNP, ClinVar. The population frequency information from 1000 genomes, ExAC, GnomAD was used for the elimination of common variants/polymorphism. For prediction of the possible impact of coding non-synonymous SNVs on the structure and function of protein, PolyPhen-2, MT2 and SIFT score was used. Further Oncomine Reporter software was used for annotating variants with a curated list of relevant labels, guidelines, and global clinical trials. Oncomine Comprehensive genomic profiling assay will analyze across >500 genes(SNVs,Indels,CNVs,Fusions), plus key immuno-oncology research biomarkers like tumor mutational burden (TMB), microsatellite instability (MSI), and Homologous Recombination Repair genes (HRR).

The variant is reported as per the Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer- A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.

Variant Classification	
Tier I: Variants of Strong clinical significance	
Level A	FDA-approved therapy included in professional guidelines
Level B	Well-powered studies with consensus from experts in the field
Tier II: Variants of Potential Clinical Significance	
Level C	FDA- approved therapies for different tumor types or investigational therapies

	Multiple small published studies with some consensus
Level D	Preclinical trials or a few case reports without consensus
Tier III: Variants of Unknown Clinical Significance	
Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases. No convincing published evidence of cancer association	
Tier IV: Benign or Likely Benign Variants	
Observed at significant allele frequency in the general or specific subpopulation databases. No existing published of cancer association	

The transcript used for clinical reporting generally represents the canonical transcript (according to the Ensembl release 37 gene model), which is usually the longest coding transcript with strong/multiple supporting evidence. However, clinically relevant variants annotated in alternate complete coding transcripts could also be reported**.**
The in silico predictions are based on Variant Effect Predictor, Ensembl release 91 (SIFT version - 5.2.2; PolyPhen - 2.2.2); 2019 release from dbNSFPv4.0 and MutationTaster2 based on build NCBI/ Ensembl 66.

Disclaimer

- This report is based on the sample received in the Lilac Insights laboratory; the analysis is based on the assumption that samples received are representative of the patient demographics mentioned on the test requisition form and the sample tube.
- Despite all the necessary precautions and stringency adopted whilst performing DNA tests, the currently available data indicates that the technical error rate associated with all types of DNA analysis, is approximately 2%.
- As with all diagnostic tests, the laboratory report must be interpreted in conjunction with the presenting clinical profile of the individual tested and evaluation of all reports. Interpretation of variants is performed based on the current knowledge standards and reporting guidelines. In cases of presence of a VUS, we recommend periodic review of these variants to determine any change in classification based on new published research.
- The classification and interpretation of all the variants is carried out based on the current state of scientific knowledge and medical understanding. The results should be correlated clinically.
- This report cannot be used for medicolegal purpose.

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End of Report