MI PROFILE
MOLECULAR INTELLIGENCE TUMOR REPORT

CARIS LIFE SCIENCES

PATIENT	SPECIMEN INFORMATION	ORDERED BY
[redacted]	**Primary Tumor Site:** Breast, NOS **Specimen Site:** Breast, NOS **Specimen Collected:** Sep 29, 2014 **Specimen Received:** Nov 11, 2014 **Initiation of Testing:** Nov 11, 2014 **Completion of Testing:** Nov 18, 2014	[redacted]

Clinical History: Per the submitted documents, the patient is a 41 year-old female with breast cancer.
Pathologic Diagnosis: Right breast lump: Grade 3 infiltrating ductal carcinoma.

Caris Molecular Intelligence™ – Final Report

MI-2014-11-16.0

Agents Associated with Potential BENEFIT

anastrozole, exemestane, fulvestrant, goserelin, letrozole, leuprolide, megestrol acetate, tamoxifen, toremifene

capecitabine, fluorouracil, pemetrexed

docetaxel, paclitaxel

everolimus, temsirolimus

gemcitabine

irinotecan

nab-paclitaxel

Current Agents in CLINICAL TRIALS Associated by Biomarker Results

Chemotherapies (6)

Targeted Therapies (1)

For a detailed list of clinical trial opportunities, please see the Clinical Trials Connector™ results page or visit MI Portal.

Agents Associated With Potential LACK OF BENEFIT

ado-trastuzumab emtansine (T-DM1), lapatinib, pertuzumab

dabrafenib, vemurafenib

dacarbazine, temozolomide

doxorubicin, epirubicin, liposomal-doxorubicin

trastuzumab

Agents With Indeterminate Benefit (Biomarker Results Do Not Impact Potential Benefit or Lack of Potential Benefit)

carboplatin	cisplatin	imatinib	oxaliplatin
vandetanib			

Agents associated with potential benefit or lack of benefit, as indicated above, are based on biomarker results provided in this report and are based on published medical evidence. This evidence may have been obtained from studies performed in the cancer type present in the tested patient's sample or derived from another tumor type. The selection of any, all, or none of the matched agents resides solely with the discretion of the treating physician. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all available information in addition to this report concerning the patient's condition in accordance with the applicable standard of care.

[redacted]

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SUMMARY OF BIOMARKER RESULTS (see appendix for full results)

Biomarkers With Notable Results

Biomarker	Method	Result
Androgen Receptor	IHC	Positive
ER	IHC	Positive
PR	IHC	Positive
RRM1	IHC	Negative
SPARC Monoclonal	IHC	Positive

Biomarker	Method	Result
TLE3	IHC	Positive
TOPO1	IHC	Positive
TP53	NGS	Mutated | R249W
TS	IHC	Negative

Biomarkers Without Notable Results

Biomarker	Method	Result
ABL1	NGS	Wild Type
AKT1	NGS	Wild Type
ALK	NGS	Wild Type
APC	NGS	Wild Type
ATM	NGS	Wild Type
BRAF	NGS	Wild Type
BRCA1	NGS	Wild Type
BRCA2	NGS	Wild Type
CDH1	NGS	Wild Type
c-KIT	NGS	Wild Type
cMET	NGS	Wild Type
cMET	IHC	Negative
cMET	CISH	Not Amplified
CSF1R	NGS	Wild Type
CTNNB1	NGS	Wild Type
EGFR	NGS	Wild Type
EGFR	IHC	Negative
ERBB4	NGS	Wild Type
FBXW7	NGS	Wild Type
FGFR1	NGS	Wild Type
FGFR2	NGS	Wild Type
FLT3	NGS	Wild Type
GNA11	NGS	Wild Type
GNAQ	NGS	Wild Type
GNAS	NGS	Wild Type
Her2/Neu	IHC	Negative
Her2/Neu	CISH	Not Amplified
Her2/Neu (ERBB2)	NGS	Wild Type
HNF1A	NGS	Wild Type

Biomarker	Method	Result
HRAS	NGS	Wild Type
IDH1	NGS	Wild Type
JAK2	NGS	Wild Type
JAK3	NGS	Wild Type
KDR (VEGFR2)	NGS	Wild Type
KRAS	NGS	Wild Type
MGMT	IHC	Positive
MPL	NGS	Wild Type
NOTCH1	NGS	Wild Type
NPM1	NGS	Wild Type
NRAS	NGS	Wild Type
PD-1 IHC	IHC	Negative
PDGFRA	NGS	Wild Type
PD-L1 IHC	IHC	Negative
PGP	IHC	Negative
PIK3CA	NGS	Wild Type
PTEN	NGS	Wild Type
PTEN	IHC	Positive
PTPN11	NGS	Wild Type
RB1	NGS	Wild Type
RET	NGS	Wild Type
SMAD4	NGS	Wild Type
SMARCB1	NGS	Wild Type
SMO	NGS	Wild Type
SPARC Polyclonal	IHC	Negative
STK11	NGS	Wild Type
TOP2A	CISH	Not Amplified
TUBB3	IHC	Positive
VHL	NGS	Wild Type

IHC: Immunohistochemistry

CISH: Chromogenic in situ hybridization

NGS: Next-Generation Sequencing

See the Appendix section for a detailed overview of the biomarker test results for each technology.

Agents Associated with Potential BENEFIT

Agents	Test	Method	Result	Value†	Clinical Association			Literature Assessment	
					Potential Benefit	Decreased Potential Benefit	Lack of Potential Benefit	Highest Level of Evidence*	Reference
anastrozole, exemestane, fulvestrant, goserelin, letrozole, leuprolide, megestrol acetate, tamoxifen, toremifene	ER	IHC	Positive	2+ 60%	✔			I / Good	10, 13, 14, 15, 16, 17, 18, 19, 20
	PR	IHC	Positive	2+ 40%	✔			I / Good	10, 11, 12, 13, 14, 15, 16, 17, 18
capecitabine, fluorouracil, pemetrexed	TS	IHC	Negative	1+ 2%	✔			II-1 / Good	21, 22, 23
docetaxel, paclitaxel	PGP	IHC	Negative	0+ 100%	✔			II-3 / Fair	35, 36
	TLE3	IHC	Positive	2+ 80%	✔			II-2 / Good	34
everolimus, temsirolimus	ER	IHC	Positive	2+ 60%	✔			I / Good	42, 43, 44
	PIK3CA	Next Gen SEQ	Wild Type			✔		II-2 / Good	45, 46, 47
gemcitabine	RRM1	IHC	Negative	2+ 20%	✔			I / Good	48
irinotecan	TOPO1	IHC	Positive	2+ 70%	✔			II-1 / Good	54, 55, 56
nab-paclitaxel	SPARC Monoclonal	IHC	Positive	2+ 30%	✔			II-2 / Good	57, 58
	SPARC Polyclonal	IHC	Negative	1+ 90%		✔		II-2 / Good	57, 58

*The level of evidence for all references is assigned according to the Literature Level of Evidence Framework consistent with the US Preventive Services Task Force described further in the Appendix of this report. The level of evidence reported is the highest level of evidence based on the body of evidence, overall clinical utility, competing biomarker interactions and tumor type from which the evidence was gathered.

† Refer to Appendix for detailed Result and Value information for each biomarker, including appropriate cutoffs, unit of measure, etc.

Agents Associated with Potential LACK OF BENEFIT

Agents	Test	Method	Result	Value†	Clinical Association			Literature Assessment	
					Potential Benefit	Decreased Potential Benefit	Lack of Potential Benefit	Highest Level of Evidence*	Reference
ado-trastuzumab emtansine (T-DM1), lapatinib, pertuzumab	Her2/Neu	CISH	Not Amplified	1.03			✔	I / Good	1, 2, 3, 4, 5, 6, 7, 8, 9
	Her2/Neu	IHC	Negative	0+ 100%			✔	I / Good	1, 2, 3, 4, 5, 6, 7, 9
dabrafenib, vemurafenib	BRAF	Next Gen SEQ	Wild Type				✔	I / Good	28, 29, 30, 31
dacarbazine, temozolomide	MGMT	IHC	Positive	2+ 55%			✔	II-2 / Good	32, 33
doxorubicin, epirubicin, liposomal-doxorubicin	Her2/Neu	CISH	Not Amplified	1.03			✔	I / Good	2, 8, 37, 38
	TOP2A	CISH	Not Amplified	1.34			✔	I / Good	38, 39, 40, 41
trastuzumab	Her2/Neu	CISH	Not Amplified	1.03			✔	I / Good	2, 5, 8, 61, 62
	Her2/Neu	IHC	Negative	0+ 100%			✔	I / Good	2, 5, 61, 62
	PIK3CA	Next Gen SEQ	Wild Type					II-3 / Good	59, 60
	PTEN	IHC	Positive	1+ 70%				II-3 / Good	59, 60

*The level of evidence for all references is assigned according to the Literature Level of Evidence Framework consistent with the US Preventive Services Task Force described further in the Appendix of this report. The level of evidence reported is the highest level of evidence based on the body of evidence, overall clinical utility, competing biomarker interactions and tumor type from which the evidence was gathered.

† Refer to Appendix for detailed Result and Value information for each biomarker, including appropriate cutoffs, unit of measure, etc.

Agents with Indeterminate Benefit (Biomarker Results Do Not Impact Potential Benefit or Lack of Potential Benefit)

Agents	Test	Method	Result	Value†	Clinical Association			Literature Assessment	
					Potential Benefit	Decreased Potential Benefit	Lack of Potential Benefit	Highest Level of Evidence*	Reference
carboplatin, cisplatin, oxaliplatin	BRCA1	Next Gen SEQ	Mutation Not Detected				✔	II-2 / Good	24, 25, 26, 27
	BRCA2	Next Gen SEQ	Mutation Not Detected				✔	II-2 / Good	24, 26, 27
imatinib	c-KIT	Next Gen SEQ	Wild Type				✔	II-2 / Good	49, 50
	PDGFRA	Next Gen SEQ	Wild Type				✔	II-3 / Good	51, 52, 53
vandetanib	RET	Next Gen SEQ	Wild Type					I / Good	63

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† Refer to Appendix for detailed Result and Value information for each biomarker, including appropriate cutoffs, unit of measure, etc.

Clinical Trials Connector™ Results Summary

For a complete list of open, enrolling clinical trials visit MI Portal to access the Clinical Trials Connector. This highly personalized, real-time web-based service provides additional clinical trial information and enhanced searching capabilities, including, but not limited to:

- Location: filter by geographic area
- Biomarker(s): identify specific biomarkers associated with open clinical trials to choose from
- Drug(s): search for specific therapies
- Trial Sponsor: locate trials based on the organization supporting the trial(s)

Visit www.CarisMolecularIntelligence.com to view all matched trials.

Chemotherapies			
Drug Class	Biomarker	Method	Investigational Agent(s)
Anti-hormonal therapy	Androgen Receptor ER PR	IHC IHC IHC	ARN-810, TAK-700, abiraterone, anastrozole, degarelix, enzalutamide, exemestane, fulvestrant, goserelin, letrozole, leuprolide, tamoxifen, toremifene, triptorelin
Nucleoside analog	RRM1	IHC	gemcitabine
Nanoparticle-bound agents	SPARC Monoclonal	IHC	nab-paclitaxel
Taxanes	TLE3	IHC	cabazitaxel, docetaxel, paclitaxel
Antifolates	TS	IHC	methotrexate, pemetrexed
Pyrimidine analog	TS	IHC	capecitabine, fluorouracil

Targeted Therapies			
Drug Class	Biomarker	Method	Investigational Agent(s)
Cell cycle inhibitors	TP53	Next Gen SEQ	LY2606368, MK-1775

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Mutational Analysis by Next Generation Sequencing

Genes Tested With Alterations

Gene	Alteration	Frequency (%)	Exon	Result
TP53	R249W	49	7	Mutated, Pathogenic

Interpretation: A mutation was detected in TP53. This mutation has been determined to cause loss of TP53 activity and to have a possible dominant negative effect (inhibition of wild-type TP53 activity) (Dearth et al Carcinogenesis Feb 2007).

TP53, or p53, plays a central role in modulating response to cellular stress through transcriptional regulation of genes involved in cell-cycle arrest, DNA repair, apoptosis, and senescence. Inactivation of the p53 pathway is essential for the formation of the majority of human tumors. Mutation in p53 (TP53) remains one of the most commonly described genetic events in human neoplasia, estimated to occur in 30-50% of all cancers. Generally, presence of a disruptive p53 mutation is associated with a poor prognosis in all types of cancers, and diminished sensitivity to radiation and chemotherapy. In addition, various clinical trials (on www.clinicaltrials.gov) investigating agents which target p53's downstream or upstream effectors may have clinical utility depending on the p53 status. Germline p53 mutations are associated with the Li-Fraumeni syndrome (LFS) which may lead to early-onset of several forms of cancer currently known to occur in the syndrome, including sarcomas of the bone and soft tissues, carcinomas of the breast and adrenal cortex (hereditary adrenocortical carcinoma), brain tumors and acute leukemias.

Genes Tested Without Alterations

ABL1	AKT1	ALK	APC	ATM	BRAF
c-KIT	CDH1	cMET	CSF1R	CTNNB1	EGFR
ERBB2	ERBB4	FBXW7	FGFR1	FGFR2	FLT3
GNA11	GNAQ	GNAS	HNF1A	HRAS	IDH1
JAK2	JAK3	KDR	KRAS	MPL	NOTCH1
NPM1	NRAS	PDGFRA	PIK3CA	PTEN	PTPN11
RB1	RET	SMAD4	SMARCB1	SMO	STK11
VHL					

Comments on Next Gen Profile Analysis

Molecular testing of this specimen was performed after harvesting of targeted tissues with an approved manual microdissection technique.
Candidate slides were examined under a microscope and areas containing tumor cells (and separately normal cells, when necessary for testing) were circled.
A laboratory technician harvested targeted tissues for extraction from the marked areas using a dissection microscope.
The areas marked and extracted were microscopically reexamined on post-microdissected slides and adequacy of microdissection was verified by a board certified Pathologist.

[redacted]

P[redacted]

Mutational Analysis by Next Generation Sequencing

Genes Tested Without Alterations

BRCA1 BRCA2

[redacted]