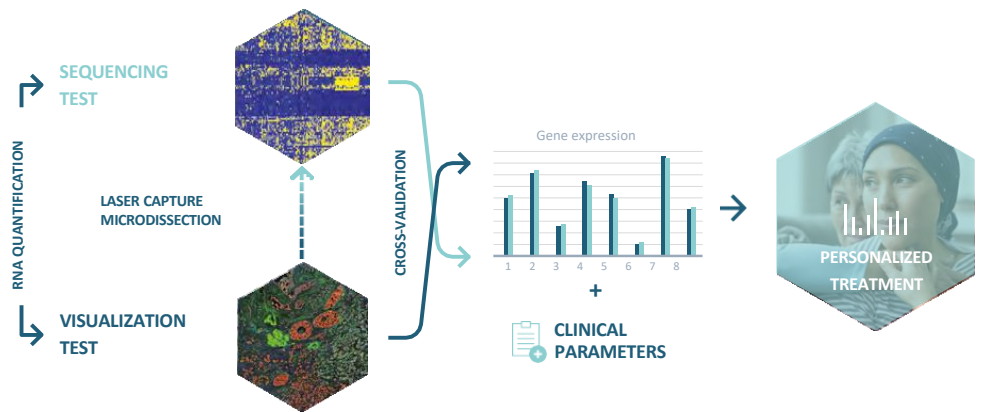


| PATIENT      |                   | SAMPLE              |            | ORDERING PHYSICIAN |  |
|--------------|-------------------|---------------------|------------|--------------------|--|
| Name:        |                   | Specimen ID:        | MDX-PT-19  | Name:              |  |
| ID:          |                   | Date of collection: |            | Address:           |  |
| Report date: | 12 September 2023 | Type:               | Metastatic | Contact:           |  |

## TEST DESCRIPTION

The **Multiplex8+** breast cancer test assesses RNA-based biomarkers by conducting a **VISUALIZATION TEST** that uses RNA fluorescent in situ hybridization (RNA-FISH) to visualize a panel of biomarkers. Based on the expression of these biomarkers and the tissue histology, laser capture microdissection is used to dissect out regions of interest. With these tumor-enriched samples, a **SEQUENCING TEST** that utilizes total RNA next generation sequencing to survey gene expression in a spatially resolved manner, is further carried out. Analytical validation of **Multiplex8+** was conducted on a large retrospective cohort of 1 080 breast tumors.



THE TEST PROVIDES INFORMATION ABOUT:

- RECEPTOR STATUS:** for RNA expression of the estrogen receptor, progesterone receptor, Her2 receptor, and Ki67 measured and cross-validated by the two tests.
- MOLECULAR SUBTYPE:** based on RNA gene expression tumor biology.
- GENE SIGNATURES:** personalized for patients' tumor biology and clinical status.

A SUMMARY IS PROVIDED BELOW AND ADDITIONAL DETAILS ARE PROVIDED IN THE FOLLOWING PAGES

## RESULTS SUMMARY

### RECEPTOR STATUS

| Sample | ESR1 | PGR | ERBB2    | MKI67 |
|--------|------|-----|----------|-------|
| A      | +    | -   | +        | +     |
| B      | +    | -   | -<br>low | +     |

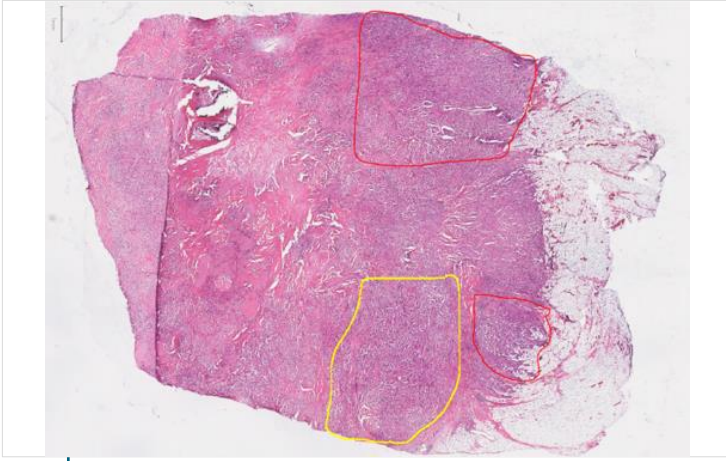
### MOLECULAR SUBTYPE

| Intrinsic subtype | TNBC subtype |
|-------------------|--------------|
| Luminal B         | -            |
| Luminal B         | -            |

### RELEVANT TREATMENT

| THERAPY                         | KEY FINDINGS   | CLINICAL BENEFIT  |
|---------------------------------|--|-------------------|
| Anti-Her2                       | Gene expression, gene expression signature, molecular subtype, clinical parameters | Predicted benefit |
| Endocrine therapy               | Gene expression, gene expression signature, molecular subtype, clinical parameters | Predicted benefit |
| Sacituzumab govitecan (Trodely) | Gene expression  | Predicted benefit |

## LASER CAPTURE MICRODISSECTION



Based on histological assessment and RNA-FISH biomarker expression, two samples were laser capture microdissected for further analysis.

**Sample A** (red outline)

**Sample B** (yellow outline)

## MOLECULAR SUBTYPE

| Intrinsic subtype | TNBC subtype <sup>2-4</sup> |
|-------------------|-----------------------------|
| Luminal B         | -                           |
| Luminal B         | -                           |

## INTERPRETATION

- The biology of the Luminal B tumor type is consistent with the immunohistochemical and clinical designation.
- Luminal B tumors are generally ER+, but may have variable ER/PR expression, and they can be either Her2+ or Her2-. Relative to Luminal A tumors, they may have higher grade, proliferative activity, poorer outcomes, and consequently may require chemotherapy in addition to endocrine therapy.

## GENE SIGNATURE

- Based on the assigned molecular subtype, and TNBC subtype (if applicable), we evaluated several individual genes and gene signatures that demonstrate prognostic and predictive potential in early and advanced/metastatic settings.

| Treatment type/ Pathway | Gene signature                 | Description   | Sample A Percentile | Sample B Percentile |
|-------------------------|--------------------------------|---|---------------------|---------------------|
| <b>Prognosis</b>        | Consensus prognostic signature | The prognostic signature is derived from a consensus of three research-based prognostic signatures, including the 21-gene signature GENE21 <sup>5</sup> , the 70-gene GENE70 signature <sup>6</sup> , and the 50-gene risk of relapse based on subtype alone (ROR-S) signature <sup>7</sup> . The prognostic signatures are intended for early-stage breast cancer patients with ER+/Her2- IHC, lymph node-negative, or 1-3 positive lymph nodes. The score is reported as high, intermediate, or low. Patients with high signature scores are at a greater risk of relapse and may benefit from adjuvant chemotherapy, while patients with low scores have lower risk of relapse and may not benefit from adjuvant chemotherapy. | <b>N/A</b>          | <b>N/A</b>          |

## RECEPTOR STATUS

| Sample   | ESR1     | PGR      | ERBB2        | MKI67    |
|----------|----------|----------|--------------|----------|
| <b>A</b> | <b>+</b> | <b>-</b> | <b>+</b>     | <b>+</b> |
| <b>B</b> | <b>+</b> | <b>-</b> | <b>- low</b> | <b>+</b> |

Receptor status was determined using both the **VISUALIZATION TEST** and **SEQUENCING TEST**: the table shows results after cross-validation.

## INTERPRETATION

- The results from both RNA-FISH and RNA-SEQ are concordant with the IHC findings.

Based on the **SEQUENCING TEST**, we used a consensus subtyping approach consisting of our proprietary 293 gene molecular subtyping signature, a research-based PAM50 test and the AIMS method to classify the intrinsic molecular subtype<sup>1</sup>. TNBC subtype, if applicable, was classified according to Lehmann<sup>2-4</sup>.

## GENE SIGNATURE

| Treatment type/ Pathway | Gene signature         | Description  | Sample A Percentile | Sample B Percentile |
|-------------------------|------------------------|--|---------------------|---------------------|
| Luminal signatures      | ESR1                   | The ESR1 and PGR genes encode for the estrogen (ER) and progesterone (PR) hormone receptors, respectively, which are involved in growth, metabolism, and reproductive functions. High ER/PR is predictive of endocrine therapies and low or negative ER/PR is associated with poor prognosis <sup>8</sup> .  | High (97%)          | High (97%)          |
|                         | PGR                    |  | Medium (36%)        | Low (33%)           |
|                         | ESR1_PGR average       | The average gene expression of ESR1 and PGR. Higher levels of hormone receptors are predictive markers for endocrine therapies.  | High (95%)          | High (95%)          |
|                         | E2F4_score             | This gene signature assesses activity of the E2F4 transcription factor and its targets. A high E2F4 signature is associated with endocrine resistance to aromatase inhibitors and may predict sensitivity to CDK4/6 inhibitors <sup>9</sup> .  | High (69%)          | Medium (41%)        |
| Her2                    | ERBB2                  | The ERBB2 gene is translated into Her2, a receptor tyrosine kinase involved in cell growth/proliferation and is both a prognostic marker and predictive of response to Her2 targeted therapies <sup>8</sup> .  | High (89%)          | High (73%)          |
|                         | MUC4                   | Mucin 4 (MUC4) is a glycoprotein that is implicated in resistance to trastuzumab through interactions with the Her2 receptor. High MUC4 is associated with reduced sensitivity to trastuzumab <sup>10</sup> .  | Low (10%)           | Low (5%)            |
|                         | NRG1                   | NRG1 codes for neuregulin 1, a ligand of the Her3 receptor. In the phase II NeoSphere trial, high NRG1 gene expression was associated with reduced response to neoadjuvant trastuzumab, but not combination trastuzumab-pertuzumab <sup>11</sup> .   | High (82%)          | High (85%)          |
|                         | pSTAT3-GS              | A signature that predicts phosphorylation of STAT3 and was found to be predictive of trastuzumab resistance in the FinHer study <sup>12</sup> .  | Low (10%)           | Low (24%)           |
|                         | Her2 amplicon_MDX      | Proprietary MDX 43-gene signature used to assess Her2 status.  | High (91%)          | High (75%)          |
|                         | Module7_ERBB2          | Her2-signaling signature predictive of response to multiple anti-Her2 treatments in the I-SPY2 trial <sup>13</sup> .   | High (86%)          | Medium (65%)        |
| Proliferation           | AURKA                  | Aurora Kinase A (AURKA) is a protein coding gene involved in cell proliferation and is an independent prognostic marker in breast cancer.  | Medium (59%)        | Medium (49%)        |
|                         | MKI67                  | MKI67 codes for the marker of proliferation Ki67 protein, a marker of poor prognosis in ER+/Her2- tumors, but not Her2+ or TNBC tumors. Ki67 levels are also predictive of sensitivity to neoadjuvant endocrine and chemotherapies <sup>8</sup> .  | High (73%)          | Medium (64%)        |
|                         | Module11_proliferation | Proliferation index used in I-SPY2 trial broadly predictive of pathological complete response in hormone receptor positive patients <sup>4</sup> .   | High (86%)          | High (73%)          |
|                         | Proliferation_MDX      | Proprietary MDX 7-gene signature used to assess cellular proliferation and cross-validate MKI67 expression levels.   | High (77%)          | Medium (55%)        |
| CDK4/6 inhibitors       | CDK4                   | Cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) are important proteins that regulate cell cycle progression from G1 to S phases. They are the main targets of CDK4/6 inhibitors such as palbociclib (Ibrance), ribociclib (Kisqali), and abemaciclib (Verzenio); however, it is unclear whether their expression level predicts CDK4/6 inhibitor sensitivity. | High (91%)          | High (71%)          |
|                         | CDK6                   |  | Medium (55%)        | Medium (56%)        |
|                         | CCNE1                  | Elevated expression of the G1/S cell cycle regulators, CCNE1, CCND3, and CDKN2D, was associated with resistance to palbociclib (Ibrance) in the single-arm phase II neoadjuvant trial (NeoPalAna) <sup>14</sup> .  | High (67%)          | Medium (58%)        |
|                         | CCND3                  |  | Medium (65%)        | Medium (36%)        |
|                         | CDKN2D                 |  | Medium (61%)        | Medium (35%)        |
| PIK3CA mutations        | PIK3CA-GS              | A gene signature that is predictive of mutations in the PIK3CA gene and consequently the PI3K inhibitor alpelisib (Piqray). A high PIK3CA-GS score is also associated with activation of the PI3K/AKT pathway and loss of mTORC1 signaling, which may be relevant for response to mTOR inhibitors (e.g., everolimus) <sup>15</sup> .                           | Medium (46%)        | High (100%)         |

GENE SIGNATURE

| Treatment type/<br>Pathway | Gene signature                       | Description   | Sample A<br>Percentile | Sample B<br>Percentile |
|----------------------------|--------------------------------------|---|------------------------|------------------------|
| Chemotherapy               | TOP1                                 | The gene encoding DNA topoisomerase I, an enzyme critical for DNA transcription, is a target for anticancer drugs.  | High<br>(98%)          | High<br>(99%)          |
|                            | TOP2A                                | The gene encoding DNA topoisomerase IIa, an enzyme critical for DNA transcription, is a target for anticancer drugs.  | Medium<br>(59%)        | Low<br>(17%)           |
|                            | RAD51                                | The DNA repair protein RAD51 homolog 1 (RAD51) is involved in the repair of damaged DNA and is associated with resistance to chemotherapy.  | Medium<br>(47%)        | Medium<br>(53%)        |
|                            | ERCC1                                | The DNA excision repair protein ERCC-1 (ERCC1) is involved in the repair of DNA damage and is associated with resistance to chemotherapy.   | High<br>(85%)          | Medium<br>(61%)        |
|                            | TYMS                                 | The Thymidylate Synthetase (TYMS) gene encodes a protein involved in DNA biosynthesis and is the target of the antimetabolite chemotherapy, 5-Fluorouracil <sup>16</sup> .                          | Medium<br>(59%)        | Medium<br>(51%)        |
|                            | SLC29A1                              | SLC29A1 codes for the equilibrative nucleoside transporter 1 (ENT1) protein, which is a nucleoside transporter that is involved in transporting gemcitabine and capecitabine <sup>17</sup> .        | High<br>(89%)          | High<br>(80%)          |
|                            | DHFR                                 | Dihydrofolate reductase is an enzyme coded by the DHFR gene and is involved in folate metabolism and cell growth. It is the target of the antimetabolite chemotherapy, methotrexate <sup>18</sup> . | High<br>(83%)          | High<br>(74%)          |
|                            | SLC19A1                              | SLC19A1 codes for the reduced folate carrier 1 (RFC1) protein, which transports methotrexate into the cell <sup>18</sup> .  | High<br>(77%)          | High<br>(69%)          |
|                            | CDK12                                | The protein product of the Cyclin Dependent Kinase 12 (CDK12) gene regulates transcription, DNA repair pathways, and cell cycle <sup>19</sup> .   | High<br>(84%)          | Medium<br>(62%)        |
|                            | MAPs_Mitotic_kinases_neoadj_chemo118 | A 118-gene signature predicting response to neoadjuvant taxane chemotherapy <sup>20</sup> .   | High<br>(78%)          | High<br>(70%)          |
|                            | MAPs_Mitotic_kinases_neoadj_chemo17  | A 17-gene signature predicting response to neoadjuvant taxane chemotherapy <sup>20</sup> .  | Medium<br>(49%)        | Low<br>(22%)           |
|                            | Early_Relapse_ER.Neg                 | Chemoresistance gene signature predicting early relapse in ER-negative (ER-) patients after taxane-anthracycline chemotherapy <sup>21</sup> .   | High<br>(85%)          | Medium<br>(55%)        |
|                            | Residual_disease_ER.Neg              | Chemoresistance gene signature predicting residual disease in ER-negative (ER-) patients after taxane-anthracycline chemotherapy <sup>21</sup> .  | High<br>(73%)          | Medium<br>(56%)        |
|                            | Pathologic_response_ER.Neg           | Chemosensitivity gene signature predicting pathological complete response in ER-negative (ER-) patients after taxane-anthracycline chemotherapy <sup>21</sup> .                                     | High<br>(97%)          | High<br>(87%)          |
|                            | Early_Relapse_ER.Pos                 | Chemoresistance gene signature predicting early relapse in ER-positive (ER+) patients after taxane-anthracycline chemotherapy <sup>21</sup> .   | High<br>(76%)          | High<br>(69%)          |
|                            | Residual_disease_ER.Pos              | Chemoresistance gene signature predicting residual disease in ER-positive (ER+) patients after taxane-anthracycline chemotherapy <sup>21</sup> .  | High<br>(91%)          | High<br>(91%)          |
|                            | Pathologic_response_ER.Pos           | Chemosensitivity gene signature predicting pathological complete response in ER-positive (ER+) patients after taxane-anthracycline chemotherapy <sup>21</sup> .                                     | High<br>(76%)          | High<br>(82%)          |

**GENE SIGNATURE**

| Treatment type/<br>Pathway                   | Gene signature                                      | Description   | Sample A<br>Percentile | Sample B<br>Percentile |
|--|---|---|------------------------|------------------------|
| Immune system                                | PDCD1   | PDCD1 codes for the immune checkpoint marker PD-1. PD-1 is the target of pembrolizumab (Keytruda), an immunotherapy approved for the first-line treatment of metastatic TNBC.   | Low<br>(33%)           | Low<br>(19%)           |
|  | CD274   | CD274 codes for the immune checkpoint marker PD-L1. PD-L1 is the target of atezolizumab (Tecentriq), an immunotherapy approved for approved for the first-line treatment of metastatic TNBC.  | Medium<br>(37%)        | Medium<br>(54%)        |
|  | CTLA4   | Cytotoxic T lymphocyte-associated antigen 4 (CTLA4) is an immune checkpoint marker and the target of several immunotherapies such as durvalumab (Imfinzi).  | Medium<br>(44%)        | Low<br>(23%)           |
|  | Module5_<br>TcellBcell                              | Immune signatures predictive of response to pembrolizumab in TNBC patients enrolled in (I-SPY2 trial) <sup>14</sup> . All signatures, with the exception of Mast_cells, were associated with increased probability of achieving pathological complete response. | Medium<br>(52%)        | Medium<br>(44%)        |
|  | Chemokine12   |   | Medium<br>(50%)        | Low<br>(28%)           |
|  | STAT1   |   | Medium<br>(59%)        | Medium<br>(54%)        |
|  | Dendritic_cells                                     |   | Medium<br>(44%)        | Medium<br>(47%)        |
| Mast_cells                                   | High<br>(84%)                                       |   | High<br>(93%)          |                        |
| DNA damage and repair                        | VCpred_TN   | DNA damage repair / immune signature predictive of response to veliparib (PARP inhibitor) and carboplatin (I-SPY2 trial) <sup>14</sup> .  | Low<br>(33%)           | High<br>(72%)          |
| Angiogenesis/<br>hypoxia                     | VEGFA   | A gene coding for vascular endothelial growth factor, a protein involved in angiogenesis, vasodilation, and endothelial cell growth. VEGF is the target of the drug bevacizumab (Avastin).  | Medium<br>(50%)        | Medium<br>(37%)        |
|  | Hypoxia /<br>Angiogenesis /<br>Inflammatory_<br>MDX | Proprietary MDX 7-gene signature used to assess hypoxia, angiogenesis, and inflammation. Signature includes genes known to be predictive of response to bevacizumab (Avastin) in the neoadjuvant GeparQuinto trial <sup>22</sup> .                              | Medium<br>(60%)        | Medium<br>(54%)        |
| ADC (antibody-<br>drug conjugate)<br>targets | ERBB2   | ERBB2 codes for the protein receptor Her2, which is a target for classical anti-Her2 treatments. Low and ultralow levels of Her2 can be eligible for treatment with the antibody-drug conjugate, trastuzumab deruxtecan (Enhertu) <sup>23</sup> .               | High<br>(89%)          | High<br>(73%)          |
|  | TACSTD2   | TACSTD2 codes for Tumor-associated calcium signal transducer 2, also called Trop-2, which is the target of sacituzumab govitecan (Trodelvy), an antibody-drug conjugate approved for metastatic TNBC <sup>24</sup> .  | High<br>(76%)          | High<br>(98%)          |
|  | NECTIN4   | Nectin Cell Adhesion Molecule 4 (NECTIN4) is a cell adhesion molecule that is a target for antibody-drug conjugates in clinical trials for breast cancer.   | High<br>(83%)          | Medium<br>(64%)        |
|  | ERBB3   | ERBB3 codes for a member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases. It is under investigation in clinical trials for the antibody-drug conjugate patritumab deruxtecan.  | High<br>(88%)          | High<br>(82%)          |
|  | FOLR1   | FOLR1 encodes the protein Folate Receptor Alpha, which is an antibody-drug conjugate target under investigation for the treatment of metastatic TNBC in several phase 1 and 2 clinical trials.  | Medium<br>(57%)        | Low<br>(14%)           |
|  | F3  | F3 codes for tissue factor, coagulation factor III a target of several antibody-drug conjugates in phase 1 clinical trials.   | High<br>(75%)          | Medium<br>(56%)        |
|  | SLC39A6   | The SLC39A6 genes encodes for the zinc transporter LIV-1, which is highly expressed in luminal breast cancers and is under investigation in several phase 1 and 2 clinical trials.  | Medium<br>(64%)        | High<br>(90%)          |
|  | TPBG  | The trophoblast glycoprotein (TPBG) is overexpressed in many breast cancers and is the target of at least two antibody-drug conjugates undergoing phase 1 clinical trials.  | Medium<br>(39%)        | Low<br>(25%)           |



| Treatment type/<br>Pathway | Gene signature | Description   | Sample A<br>Percentile | Sample B<br>Percentile |
|----------------------------|----------------|---|------------------------|------------------------|
|                            | ROR2           | A gene that encodes the Receptor Tyrosine Kinase Like Orphan Receptor 2 protein, a target of the antibody-drug conjugate (Ozuriftamab Vedotin (BA3021/CAB-ROR2-ADC) that is under investigation in a phase clinical trial for advanced solid cancers, including TNBC.                 | High<br>(96%)          | High<br>(95%)          |
|                            | CD276          | This gene codes for an immune checkpoint marker called CD276 (also known as B7-H3). It is the target of the antibody-drug conjugate (Mirzotamab clezutoclax (ABBV-155) that is in a phase 1 and 2 clinical trial for advanced solid cancers, including breast cancer.                 | High<br>(92%)          | High<br>(90%)          |
|                            | VTCN1          | V-Set Domain Containing T Cell Activation Inhibitor 1 (VTCN1 also called B7-H4) is an immune checkpoint marker and the target of the antibody-drug conjugate, SGN-B7H4V, which is under investigation in a phase1 clinical trial for advanced solid cancers, including breast cancer. | Medium<br>(38%)        | Low<br>(21%)           |
|                            | CEACAM5        | A gene that encodes CEA Cell Adhesion Molecule 5 protein, a target of the antibody-drug conjugate Tusamitamab ravtansine (SAR408701) that is under investigation in a phase 2 clinical trial for advanced solid cancers, including breast cancer.                                     | High<br>(91%)          | Medium<br>(55%)        |

### INTERPRETATION AND RECOMMENDATIONS

- Increased levels of ERBB2 and its related Her2 amplicon signature, together with low expression of resistance markers (MUC4 and pSTAT3-GS), indicate that Her2-related therapies such as trastuzumab, pertuzumab, trastuzumab emtansine, and tucatinib may be beneficial. The high expression of ERBB2 and TOP1, which is the target of the cytotoxic payload for the ADC trastuzumab deruxtecan, suggests that these treatments may also be beneficial. However, it is important to note the high expression of resistance marker NRG1.
- High ER expression moderate PR expression, subtype classification as Luminal B and clinical parameters (IHC) indicate treatment with endocrine therapy.
- Both A and B samples had high expression of TACSTD2 (76<sup>th</sup> and 98<sup>th</sup> percentile). TACSTD2 is the drug target of sacituzumab govitecan, an ADC approved for the treatment of metastatic TNBC. The cytotoxic payload of this ADC, SN-38, targets TOP1 (98<sup>th</sup> and 99<sup>th</sup> percentiles). The high levels of both antibodies and cytotoxic component targets suggest that sacituzumab govitecan may be effective in advanced/metastatic setting.
- High expression of ERBB3 suggests possible treatment using antibody-drug conjugate patritumab deruxtecan, currently under investigation in clinical trials for the antibody-drug conjugate.
- The tumor contains several markers indicating response to chemotherapy, such as gemcitabine and capecitabine (high expression of SLC29A1) and methotrexate (high expression of DHFR and SLC19A1).
- PIK3CA mutations are reported to be present in approximately 25% of breast cancer cases. A high PIK3CA-GS (Sample B) may signify the presence of mutations in the PIK3CA gene. Patients with PIK3CA mutations are eligible for treatment with the PI3K inhibitor, alpelisib, administered with fulvestrant. To confirm the presence of PIK3CA mutations, an approved companion diagnostic test is recommended.
- A high PIK3CA-GS (Sample B) is also associated with reduced activity of the mTOR and may predict sensitivity to mTOR pathway inhibitors like everolimus, which is given in combination with exemestane or fulvestrant in the second line setting of advanced hormone receptor positive breast cancer.
- The high expression of ROR2 (96<sup>th</sup> and 95<sup>th</sup> percentile) and CD276 (92<sup>nd</sup> and 90<sup>th</sup> percentile) suggests potential benefits from several other antibody-drug conjugates currently in clinical trials.

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