ONCOMPASS™ Medicine

Precision Oncology Report

ID	[redacted]
NAME	[redacted]
PRINTED AT	[redacted]

PATIENT INFORMATION

Patient ID: [redacted]
Name: [redacted]
Year of birth: 1984

Primary Tumor Site: breast
Histology Type: invasive carcinoma
Metastatic sites: Unknown

MEDICAL TEAM

Molecular Pharmacologist: István Peták, MD PhD
Genetic Counselor: Júlia Déri, MSc
Molecular Biologist: Edit Várkondi, PhD
Consulting Physician: Gábor Pajkos, MD CSc
Info-bionics Engineer: Dóra Tihanyi, MSc
Molecular Biologist: Barbara Vodicska, PhD

PATHOLOGICAL AND MOLECULAR DIAGNOSTIC TESTS

Sample ID: [redacted]
Sample source: Primary Tumor
Sampling type: Surgery
Tumor type: breast invasive ductal carcinoma

Sample ID: [redacted]
Sample source: Primary Tumor
Tumor cell rate: 30%
Sampling type: Surgery
Tumor type: breast invasive ductal carcinoma

Tests performed:
NGS - 591 genes - ([redacted])
MSI test (NGS-based) - MSS (microsatellite stable) - ([redacted])
TMB - LOW (2,03 Muts/Mb) - ([redacted])

Previously performed molecular test:
IHC - PD-L1 (Overexpression)
MSI test (NGS-based) - MSS (microsatellite stable) - ([redacted])
NGS - FoundationOne - ([redacted])
TMB - LOW - 4 mutations/Mb - ([redacted])

PREVIOUS THERAPIES

Line: adjuvant - CYCLOPHOSPHAMIDE + DOCETAXEL - (from 08/07/2021)

SUMMARY

Oncompass Report of your patient, [redacted] diagnosed with a T1N0M0 triple-negative breast cancer, has been completed for digital drug assignment and therapy planning purposes using Realtime Oncology Treatment Calculator. Molecular profiling, based on FoundationOneDx, was carried out from a primary tumor surgical sample ([redacted]) with a tumor cell ratio of 20%.

NGS-591 was carried out from the same primary surgical sample (different block, [redacted]) with a tumor cell ratio of 30%.

SUMMARY

Relevant differences between FMI and OCM results:
ABRAXAS1-R361Q present in OCM (ABRAXAS1 gene is not part of FMI panel)
KIT/PDGFRA/KDR co-amplification present in FMI vs only KIT cnv (x5) in OCM

Previous cancer history: DLBCL in 2004, s/p CHOP and external beam radiation, in remission since 2008.

Tumor-agnostic biomarkers: none
The tumor is considered to be TMB-Low and MSS.
NTRK fusions were not detected.

Tumor-specific on-label biomarkers:
Tumor-infiltrating immune cell (IC) result: positive, IC score:15%
ATEZOLIZUMAB (PD-L1 inhibitor) is EMA approved in combination with nab-paclitaxel for adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1.
PEMBROLIZUMAB (PD-1 inhibitor) is approved by the FDA in combination with chemotherapy for advanced TNBC patients whose tumors express PD-L1 (10%). PEMBROLIZUMAB (PD-1 inhibitor) is also approved by the FDA for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery.

According to several studies, PTEN loss or mutations are associated with reduced T cell infiltration, altered tumor microenvironment, and resistance to anti-PD-1 therapy. Treatment with a selective PI3Kbeta inhibitor (GSK2636771) improved the efficacy of both anti-PD-1 and anti-CTLA-4 antibodies in murine models.
A phase Ib study evaluated the combination of ipatasertib, atezolizumab, and chemotherapy as a first-line treatment option for patients with advanced TNBC. According to initial results, the regimen demonstrated a confirmed ORR of 73%, irrespective of tumor biomarker status.
Though PTEN loss may negatively influence the effect of immunotherapy, the detected ABRAXAS1 mutation could be a favorable biomarker for using ICI.

PARP inhibitors, Olaparib or Talazoparib, are approved in germline deleterious, likely deleterious BRCA mutant locally advanced/metastatic breast cancer. **No BRCA pathogenic mutations were detected**.
PTEN loss of function (PTEN-C83*), however, is in positive association with ATM and PARP inhibitors.

Histology-based on-label treatment options: Bevacizumab (VEGFR inhibitor) is registered in breast cancer indication, which is also supported by the KDR amplification found in the molecular profile.
According to the scientific literature 25-35% of triple-negative breast cancers (TNBCs) overexpress androgen receptor (AR), in which case AR inhibitors may be effective (AR status is unknown).
The FDA approved SACITUZUMAB GOVITECAN, a TROP2-directed antibody and topoisomerase inhibitor drug conjugate, for patients with metastatic TNBC after two or more prior lines of therapy. TROP2 (trophoblast cell-surface antigen-2) is highly expressed in many epithelial tumors, including TNBC.

Based on the NGS results, the following additional results could be relevant for off-label treatment options:
(new finding) ABRAXAS1-R361Q mutation is listed in COSMIC with low frequency (n<5) and according to ClinVar, it has uncertain significance. This gene is a tumor suppressor and this mutation leads to reduced protein levels as well as nuclear localization of BRCA1. This causes disturbances in basal BRCA1-A complex localization, which is reflected by restraint in error-prone DNA double-strand break (DSB) repair pathway usage. Abraxas R361Q demonstrated exclusive association with cancer, segregation with the disease within families, and loss of biological function in the DNA damage response. PARP inhibitor, as an indirect target, is in positive association with the molecular profile. HR mutations correlated with improved prognosis in certain cancers when treated with ICI.
PTEN - C83* stop mutation likely results in loss of function. PTEN is a negative regulator of the PI3K-AKT-mTOR signaling pathway by dephosphorylating phosphoinositides and thereby acting as a tumor suppressor. PI3K, AKT, mTOR, PARP, and ATM inhibitors are in positive association with PTEN loss-of-function mutations. However, the scientific literature is contradictory regarding the relevance of mTOR inhibition.

SUMMARY

Loss of PTEN function is a frequent molecular alteration in triple-negative breast cancer (TNBC) cases. In the phase II LOTUS trial, ipatasertib (AKT inhibitor) combined with paclitaxel resulted in improved median PFS (6.2 vs 4.9 months) and OS (25.8 vs 6.9 months) compared with placebo and paclitaxel as first-line therapy for TNBC patients (n=124). In the phase II PAKT study, the efficacy of the addition of capivasertib (AKT inhibitor) to paclitaxel therapy was examined among TNBC patients. In the PIK3CA/AKT1/PTEN mutant subgroup, the ORR was 35.3% (6/17) vs 18.2% (2/11), the median PFS was 9.3 vs 3.7 months, the median OS was not reached and was 10.4 months in the capivasertib + paclitaxel (CP) and in the placebo + paclitaxel (PP) treated groups, respectively.
In addition to immunotherapy, PTEN loss-of-function might cause resistance to PI3Kalpha inhibition, including the PI3Kalpha inhibitor alpelisib and also to EGFR or HER2 inhibition.
FBXW7-Q127* This mutation has not been listed in the known oncodriver databases, and it has not been functionally evaluated. Due to the premature STOP codon (nonsense mutation) in the FBXW7 gene, a variant encoding a substantially shorter protein version is generated, thus loss of function is highly likely. According to preclinical evidence, FBXW7 mutations sensitize cells to mTOR inhibitors, which were also studied in a clinical trial (3, 4). Moreover, mTOR inhibition protected FBXW7-deficient mice from radiation-induced tumor development. Registered mTOR inhibitors include EVEROLIMUS, TEMSIROLIMUS, SIROLIMUS, and METFORMIN.
TP53-375+1G>A (11,5% AF) is a splice site mutation causing loss of function.. In the presence of loss of function TP53 alterations CHEK1), ATR, PLK1, WEE1 and CDK inhibitors can be mentioned in positive association with the molecular profile. The CDK inhibitors PALBOCICLIB, RIBOCICLIB, and ABEMACICLIB are approved in breast cancer indication.
Co-amplification of the three tyrosine kinase receptor genes in the 4q12 chromosomal region, **PDGFRA, KIT, and KDR** (VEGFR2), is common, mainly in glioblastoma and other tumors of the nervous system, but has also been detected in a significant proportion of lung tumors (adenocarcinoma: 3-7 %, squamous cell carcinoma: 8–10%). Approved inhibitors targeting all three kinases are PAZOPANIB, REGORAFENIB, SORAFENIB, SUNITINIB, RIPRETINIB, AXITINIB, LENVATINIB, and MIDOSTAURIN. IMATINIB resulted in 3 years of stable disease in PDGFRA/KIT /KDR amplificated head and neck cancer patients. AXITINIB treatment in two adenoid cystic carcinoma patients carrying PDGFRA/KIT/KDR amplification resulted in more than 6 months of stable disease in a phase II trial, and one of them had a significant reduction in tumor size and the longest 21.8-month PFS observed in the study (progression-free survival). In a preclinical study, cells carrying PDGFRA/KIT/KDR amplification showed increased sensitivity to LENVATINIB in vitro

Based on the histology, current stage and therapy, and available molecular profile, and the AI-based Digital Drug Assignment (DDA) technology the patient would likely benefit from the following treatment options:

On-label-based treatment options:
Atezolizumab (AEL: 2812) + nap-paclitaxel plus off label metformin (AEL: 39.78)
Bevacizumab (AEL: 61.05) plus off label Olaparib (AEL: 131)+metformin (AEL: 39.78)
Olaparib became more relevant going from AEL: 53 to AEL: 131

Off-label options:
Olaparib (AEL 131)
Everolimus (AEL:92.17)
(Imatinib(AEL: 323.27), or Lenvatinib(AEL: 240.49) + Pembrozilumab (AEL: 6533)) less significant

Clinical trial options:
An Open-label, Randomized, Phase 2/3 Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab After Induction of Clinical Benefit With First-line Chemotherapy Plus Pembrolizumab in Participants With Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer (TNBC) (KEYLYNK-009) NCT04191135 (EU, USA)
A Study of the Efficacy and Safety of Atezolizumab Plus Chemotherapy for Patients With Early Relapsing Recurrent Triple-Negative Breast Cancer NCT03371017
A Study of the Safety, Efficacy, and Pharmacokinetics of Tiragolumab in Combination With Atezolizumab and Chemotherapy in Participants With Triple-Negative Breast Cancer NCT04584112
Efficacy and Safety of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) in Previously Treated Participants With Select Solid Tumors (MK-7902-005/E7080-G000-224/LEAP-005) NCT03997123
Study Assessing the Efficacy and Safety of Alpelisib + Nab-paclitaxel in Subjects With Advanced TNBC Who Carry Either a PIK3CA Mutation or Have PTEN Loss NCT04251533 (please note, that PTEN may cause resistance to Alpelisib and thus this may not be beneficial to the patient)

MOLECULAR TARGET ANALYSIS

MOLECULAR ALTERATIONS

PD-L1 protein overexpression driver (AEL: 624.04, AF/TR: NA/NA),
TP53-375+1G>A driver (AEL: 46.10, AF/TR: 12%/30%, 11.5%/NA),
ABRAXAS1-R361Q driver (AEL: 38.36, AF/TR: 56.09%/30%),
KIT amplification presence driver (AEL: 28.59, AF/TR: NA/NA),
PTEN-C83* driver (AEL: 24.38, AF/TR: 12.79%/30%, 12.1%/NA),
KDR amplification presence driver (AEL: 21.21, AF/TR: NA/NA),
PDGFRA amplification presence driver (AEL: 12.56, AF/TR: NA/NA),
NOTCH1-R879Q VUS in a driver gene (AEL: 4.85, AF/TR: NA/NA),
FBXW7-Q127* VUS in a driver gene (AEL: 4.61, AF/TR: 22.86%/30%, 19.2%/NA),
GNAS-S113R VUS in a driver gene (AEL: 0.85, AF/TR: NA/NA),
MUC16-G1727E VUS in a driver gene (AEL: 0.49, AF/TR: 55.35%/30%),
MUC16-T1454I VUS in a driver gene (AEL: 0.49, AF/TR: 54.79%/30%),
MUC16-V2472I VUS in a driver gene (AEL: 0.49, AF/TR: 34.89%/30%),
RICTOR-D1182G VUS in a driver gene (AEL: 0.30, AF/TR: 47.5%/30%, NA/NA),
CHEK1-G361D VUS in a driver gene (AEL: 0.09, AF/TR: 4.55%/30%, NA/NA),
CSMD3-R1228Q VUS in a driver gene (AEL: 0.03, AF/TR: 41.45%/30%),
SLC45A3-V470I conflicting driver (AEL: 0.00, AF/TR: 43.81%/30%),
ZNF226-T582A conflicting driver (AEL: 0.00, AF/TR: 48.17%/30%),
CYP2D6-R296C variant of unknown significance (AEL: 0.00, AF/TR: 34.67%/30%),
CYP2D6-R380H variant of unknown significance (AEL: 0.00, AF/TR: 13.6%/30%),
RPTOR-A496fs*15 variant of unknown significance (AEL: 0.00, AF/TR: 3.95%/30%),
USP16-T19I variant of unknown significance (AEL: 0.00, AF/TR: 53.91%/30%),
CYP2D6-R329C variant of unknown significance (AEL: 0.00, AF/TR: 47.41%/30%),
CYP2A6-S467* variant of unknown significance (AEL: 0.00, AF/TR: 22.44%/30%),
CYP2D6-S486T variant of unknown significance (AEL: 0.00, AF/TR: 47.62%/30%),
FLT1-S733del variant of unknown significance (AEL: 0.00, AF/TR: NA/NA),
TSC1-G560S non-driver (AEL: -5.00, AF/TR: NA/NA),
EP300-P925T non-driver (AEL: -10.00, AF/TR: 37.77%/30%),
MYC-N26S non-driver (AEL: -68.74, AF/TR: 44.5%/30%)

TARGET GENES

CD274 wild-type (AEL: 901.17),
- MUC16-G1727E VUS in a driver (AEL: 0.49) ;
- MUC16-V2472I VUS in a driver (AEL: 0.49) ;
- MUC16-T1454I VUS in a driver (AEL: 0.49) ;
- PD-L1 protein overexpression driver (AEL: 624.04)

PDCD1 wild-type (AEL: 612.36),
- MUC16-G1727E VUS in a driver (AEL: 0.49) ;
- MUC16-T1454I VUS in a driver (AEL: 0.49) ;
- PTEN-C83* driver (AEL: -24.38) ;
- PD-L1 protein overexpression driver (AEL: 624.04) ;
- MUC16-V2472I VUS in a driver (AEL: 0.49)

NOTCH1 wild-type (AEL: 75.03),
- FBXW7-Q127* VUS in a driver (AEL: 4.61) ;
- NOTCH1-R879Q VUS in a driver (AEL: 4.85)

PARP1 wild-type (AEL: 66.51),
- PTEN-C83* driver (AEL: 24.38) ;
- ABRAXAS1-R361Q driver (AEL: 38.36) ;
- CHEK1-G361D VUS in a driver (AEL: 0.08)

KIT wild-type (AEL: 58.19),
- KIT amplification presence driver (AEL: 28.59)

KDR wild-type (AEL: 53.92),
- KDR amplification presence driver (AEL: 21.21)

WEE1 wild-type (AEL: 49.90),
- TP53-375+1G>A driver (AEL: 46.10)

CHEK1 wild-type (AEL: 47.88),
- TP53-375+1G>A driver (AEL: 46.10)

ATR wild-type (AEL: 47.44),
- TP53-375+1G>A driver (AEL: 46.10)

CDK4 wild-type (AEL: 47.08),
- TP53-375+1G>A driver (AEL: 46.10)

RARG wild-type (AEL: 46.99),
- TP53-375+1G>A driver (AEL: 46.10)

PLK1 wild-type (AEL: 46.58),
- TP53-375+1G>A driver (AEL: 46.10)

PRKDC wild-type (AEL: 46.50),
- TP53-375+1G>A driver (AEL: 46.10)

CDK1 wild-type (AEL: 46.43),
- TP53-375+1G>A driver (AEL: 46.10)

CDK2 wild-type (AEL: 46.43),
- TP53-375+1G>A driver (AEL: 46.10)

CDK9 wild-type (AEL: 46.43),
- TP53-375+1G>A driver (AEL: 46.10)

AURKB wild-type (AEL: 46.38),
- TP53-375+1G>A driver (AEL: 46.10)

PDGFRA wild-type (AEL: 42.16),
- PDGFRA amplification presence driver (AEL: 12.56)

MTOR wild-type (AEL: 40.09),
- FBXW7-Q127* VUS in a driver (AEL: 4.61) ;
- PTEN-C83* driver (AEL: 24.38)

PIK3CB wild-type (AEL: 28.15),
- PTEN-C83* driver (AEL: 24.38)

ATM wild-type (AEL: 25.23),
- PTEN-C83* driver (AEL: 24.38)

AKT1 wild-type (AEL: 24.88),
- PTEN-C83* driver (AEL: 24.38)

	RICTOR wild-type (AEL: 14.80), • RICTOR-D1182G VUS in a driver (AEL: 0.30) MCL1 wild-type (AEL: 5.06), • FBXW7-Q127* VUS in a driver (AEL: 4.61) CTLA4 wild-type (AEL: 2.38), • MUC16-V2472I VUS in a driver (AEL: 0.49) ; • MUC16-G1727E VUS in a driver (AEL: 0.49) ; • MUC16-T1454I VUS in a driver (AEL: 0.49) PRKACA wild-type (AEL: 1.35) • GNAS-S113R VUS in a driver (AEL: 0.85)

DRUGS WITH THE HIGHEST AEL SCORES

DRUGS IN CLINICAL USE

PEMBROLIZUMAB (skin - Merkel cell carcinoma (MCC) [FDA]; all - mediastinal B-cell lymphoma [FDA]; breast - all [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; skin - squamous cell carcinoma [FDA]; all - Hodgkin lymphoma [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]; all - malignant melanoma [FDA+EMA]; bile duct - all [EMA]; lung - adenocarcinoma [FDA+EMA]; cervix - all [FDA+EMA]; rectum - all [FDA+EMA]; gastroesophageal junction - adenocarcinoma [FDA+EMA]; all - endometrioid carcinoma [FDA+EMA]; head-neck - squamous cell carcinoma [FDA+EMA]; esophagus - carcinoma [FDA+EMA]; gastric - adenocarcinoma [FDA+EMA]; colon - all [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]; biliary tract - all [EMA]; all - endometroid carcinoma [FDA+EMA]; all - cholangiocarcinoma [EMA]; esophagus - squamous cell carcinoma [FDA+EMA]; gastric - all [EMA]; all - urothelial carcinoma [FDA+EMA]; liver - hepatocellular carcinoma [FDA]; endometrium - all [FDA+EMA]; small intestine - all [EMA]) (AEL: 6791.74)
- PTEN-C83* driver (AEL: -24.38) ;
- PDCD1 wild-type target (AEL: 612.36) ;
- PD-L1 protein overexpression driver (AEL: 624.04)

ATEZOLIZUMAB (all - malignant melanoma [FDA]; breast - all [EMA]; soft tissue - alveolar soft part sarcoma (ASPS) [FDA]; lung - non-small cell carcinoma [FDA+EMA]; liver - hepatocellular carcinoma [FDA+EMA]; lung - small cell carcinoma [FDA+EMA]; all - urothelial carcinoma [EMA]) (AEL: 3380.54)
- PD-L1 protein overexpression driver (AEL: 624.04) ;
- CD274 wild-type target (AEL: 901.17)

NIVOLUMAB (all - urothelial carcinoma [FDA+EMA]; head-neck - squamous cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; esophagus - squamous cell carcinoma [FDA+EMA]; bone marrow - Hodgkin lymphoma [FDA+EMA]; rectum - all [FDA+EMA]; liver - hepatocellular carcinoma [FDA]; kidney - renal cell carcinoma [FDA+EMA]; gastroesophageal junction - adenocarcinoma [FDA+EMA]; esophagus - adenocarcinoma [FDA+EMA]; gastric - adenocarcinoma [FDA+EMA]; all - malignant melanoma [FDA+EMA]; colon - all [FDA+EMA]; pleura - mesothelioma [FDA+EMA]) (AEL: 2680.97)
- PD-L1 protein overexpression driver (AEL: 624.04) ;
- PDCD1 wild-type target (AEL: 612.36) ;
- PTEN-C83* driver (AEL: -24.38)

AVELUMAB (kidney - renal cell carcinoma [FDA+EMA]; bladder - urothelial carcinoma [FDA+EMA]; ureter - all [FDA+EMA]; bladder - all [FDA+EMA]; skin - Merkel cell carcinoma (MCC) [FDA+EMA]) (AEL: 1777.91)
- PD-L1 protein overexpression driver (AEL: 624.04) ;
- CD274 wild-type target (AEL: 901.17)

DURVALUMAB (biliary tract - all [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; lung - small cell carcinoma [FDA+EMA]; liver - hepatocellular carcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; all - cholangiocarcinoma [FDA]) (AEL: 1594.16)
- PD-L1 protein overexpression driver (AEL: 624.04) ;
- CD274 wild-type target (AEL: 901.17)

CEMIPLIMAB (lung - squamous cell carcinoma [FDA+EMA]; cervix - all [EMA]; lung - non-small cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; skin - squamous cell carcinoma [FDA+EMA]; skin - basal cell carcinoma [FDA+EMA]) (AEL: 612.56)
- PDCD1 wild-type target (AEL: 612.36)

IMATINIB (all - chronic lymphocytic leukemia (CLL) [FDA+EMA]; all - gastrointestinal stromal tumor (GIST) [FDA+EMA]; skin - dermatofibrosarcoma [FDA+EMA]; all - myeloplastic/myeloproliferative neoplasms [FDA+EMA]; all - chronic myeloid leukemia [FDA+EMA]; all - acute lymphoblastic leukemia [FDA+EMA]; all - myelodysplastic syndromes [FDA+EMA]; all - chronic eosinophilic leukemia (CEL) [FDA+EMA]) (AEL: 323.27)
- KIT amplification presence driver (AEL: 28.59) ;
- KDR amplification presence driver (AEL: 21.21) ;
- PDGFRA amplification presence driver (AEL: 12.56) ;
- KIT wild-type target (AEL: 58.19) ;
- PDGFRA wild-type target (AEL: 42.16)

AXITINIB (kidney - renal cell carcinoma [FDA+EMA]) (AEL: 255.04)
- PDGFRA wild-type target (AEL: 42.16) ;
- KIT amplification presence driver (AEL: 28.59) ;

DRUGS WITH THE LOWEST AEL SCORES

DRUGS IN CLINICAL USE

R-CHOP group (lymph node - diffuse large B-cell lymphoma [FDA+EMA]) (AEL: -128.39)
- TP53-375+1G>A driver (AEL: -46.10) ;
- NOTCH1-R879Q VUS in a driver (AEL: -4.85)

CETUXIMAB (head-neck - squamous cell carcinoma [FDA+EMA]; colon - all [FDA+EMA]; rectum - all [FDA+EMA]) (AEL: -103.68)
- FBXW7-Q127* VUS in a driver (AEL: -4.61) ;
- EGFR wild-type target (AEL: -41.80) ;
- PTEN-C83* driver (AEL: -24.38)

ALPELISIB (breast - all [FDA+EMA]) (AEL: -101.78)
- PTEN-C83* driver (AEL: -24.38) ;
- PIK3CA wild-type target (AEL: -33.37)

PANITUMUMAB (rectum - all [FDA+EMA]; colon - all [FDA+EMA]) (AEL: -100.75)
- FBXW7-Q127* VUS in a driver (AEL: -4.61) ;
- EGFR wild-type target (AEL: -41.80) ;
- PTEN-C83* driver (AEL: -24.38)

VANDETANIB (thyroid - medullary carcinoma [FDA+EMA]) (AEL: -72.69)
- KDR amplification presence driver (AEL: -21.21) ;
- KDR wild-type target (AEL: 53.92) ;
- EGFR wild-type target (AEL: -41.80)

TAMOXIFEN (breast - all [FDA]) (AEL: -68.65)
- ESR1 wild-type target (AEL: -29.39) ;
- PTEN-C83* driver (AEL: -24.38)

CHOP (AEL: -63.11)
- TP53-375+1G>A driver (AEL: -46.10)

CISPLATIN (AEL: -60.21)
- TP53-375+1G>A driver (AEL: -46.10)

CRIZOTINIB (all - inflammatory myofibroblastic tumor (IMT) [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; all - anaplastic large cell lymphoma [FDA+EMA]) (AEL: -54.24)
- TP53-375+1G>A driver (AEL: -46.10)

DOXORUBICIN (breast - carcinoma [FDA]; bone marrow - multiple myeloma [FDA]; blood vessel - kaposi sarcoma [FDA]; ovary - carcinoma [FDA]) (AEL: -46.70)
- TP53-375+1G>A driver (AEL: -46.10)

DRUGS WITH THE HIGHEST AEL SCORES

- KIT wild-type target (AEL: 58.19) ;
- KDR wild-type target (AEL: 53.92) ;
- KDR amplification presence driver (AEL: 21.21) ;
- PDGFRA amplification presence driver (AEL: 12.56)

LENVATINIB (liver - hepatocellular carcinoma [FDA+EMA]; all - endometrioid adenocarcinoma [FDA+EMA]; all - renal cell carcinoma [FDA+EMA]; thyroid - all [FDA+EMA]; all - endometrioid carcinoma [FDA+EMA]; endometrium - all [FDA+EMA]) (AEL: 240.49)

- KDR wild-type target (AEL: 53.92) ;
- KIT wild-type target (AEL: 58.19) ;
- KDR amplification presence driver (AEL: 21.21) ;
- KIT amplification presence driver (AEL: 28.59) ;
- PDGFRA wild-type target (AEL: 42.16) ;
- PDGFRA amplification presence driver (AEL: 12.56)

OLAPARIB (ovary - all [FDA+EMA]; peritoneum - all [FDA+EMA]; breast - all [FDA+EMA]; prostate - all [FDA+EMA]; pancreas - all [FDA+EMA]; fallopian tube - all [FDA+EMA]) (AEL: 132.68)

- ABRAXAS1-R361Q driver (AEL: 38.36) ;
- PARP1 wild-type target (AEL: 66.51) ;
- PTEN-C83* driver (AEL: 24.38)

DRUGS WITH THE LOWEST AEL SCORES

DRUGS IN CLINICAL DEVELOPMENT

TORIPALIMAB (AEL: 1376.39)

- PDCD1 wild-type target (AEL: 612.36) ;
- PD-L1 protein overexpression driver (AEL: 624.04)

SINTILIMAB (AEL: 1276.39)

- PDCD1 wild-type target (AEL: 612.36) ;
- PD-L1 protein overexpression driver (AEL: 624.04)

SUGEMALIMAB (AEL: 901.42)

- CD274 wild-type target (AEL: 901.17)

BINTRAFUSP ALFA (AEL: 901.17)

- CD274 wild-type target (AEL: 901.17)

PACMILIMAB (AEL: 901.17)

- CD274 wild-type target (AEL: 901.17)

TIRAGOLUMAB (AEL: 644.04)

- PD-L1 protein overexpression driver (AEL: 624.04)

TISLELIZUMAB (AEL: 613.50)

- PDCD1 wild-type target (AEL: 612.36)

RIVICICLIB (AEL: 186.37)

- CDK1 wild-type target (AEL: 46.43) ;
- CDK2 wild-type target (AEL: 46.43) ;
- CDK9 wild-type target (AEL: 46.43) ;
- CDK4 wild-type target (AEL: 47.08)

RGB-286638 (AEL: 186.37)

- CDK4 wild-type target (AEL: 47.08) ;
- CDK2 wild-type target (AEL: 46.43) ;
- CDK9 wild-type target (AEL: 46.43) ;
- CDK1 wild-type target (AEL: 46.43)

RONICICLIB (AEL: 186.37)

- CDK1 wild-type target (AEL: 46.43) ;
- CDK4 wild-type target (AEL: 47.08) ;
- CDK9 wild-type target (AEL: 46.43) ;
- CDK2 wild-type target (AEL: 46.43)

DRUGS IN CLINICAL DEVELOPMENT

ALLITINIB (AEL: -68.20)

- ERBB2 wild-type target (AEL: -26.40) ;
- EGFR wild-type target (AEL: -41.80)

AV-412 (AEL: -68.20)

- EGFR wild-type target (AEL: -41.80) ;
- ERBB2 wild-type target (AEL: -26.40)

CUDC-101 (AEL: -68.20)

- ERBB2 wild-type target (AEL: -26.40) ;
- EGFR wild-type target (AEL: -41.80)

FLUDARABINE (AEL: -46.22)

- TP53-375+1G>A driver (AEL: -46.10)

PATUPILONE (AEL: -46.17)

- TP53-375+1G>A driver (AEL: -46.10)

GSK1059615 (AEL: -33.37)

- PIK3CA wild-type target (AEL: -33.37)

MLN1117 (AEL: -33.37)

- PIK3CA wild-type target (AEL: -33.37)

TASELISIB (AEL: -33.37)

- PIK3CA wild-type target (AEL: -33.37)

AZD9496 (AEL: -29.39)

- ESR1 wild-type target (AEL: -29.39)

SRN-927 (AEL: -29.39)

- ESR1 wild-type target (AEL: -29.39)

Compound scores displayed represent aggregated evidence levels (AEL). AEL represents the number, scientific impact and clinical relevance of evidence relations in the system, connecting tumor types, molecular alterations, targets and compounds. Individual evidence relation scores are normalized and weighted according to the degree of similarity of the parameters to the parameters of the given patient case. Compound AELs are obtained by aggregating all relevant associations (and AELs) between the specific compound, tumor type, drivers and targets. Compounds are listed in descending order of their AELs.
(Abbreviations: AEL - aggregated evidence level, AF - allele frequency, TR: tumor ratio)

AVAILABLE CLINICAL TRIALS

IDENTIFIER	DESCRIPTION
NCT04644068	Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies (PETRA)

Active recruiting

Line	Phase	Compounds
Neoadjuvant-10	1-2	AZD5305, AZD5305, AZD5305, AZD5305, CARBOPLATIN, PACLITAXEL, TRASTUZUMAB DERUXTECAN

Countries	Allocation	Masking
	Non Randomized	Single Group Assignment

NCT04191135 — An Open-label, Randomized, Phase 2/3 Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab After Induction of Clinical Benefit With First-line Chemotherapy Plus Pembrolizumab in Participants With Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer (TNBC) (KEYLYNK-009)

Active recruiting

Line	Phase	Compounds
1-10	3	CARBOPLATIN, GEMCITABINE, OLAPARIB, PEMBROLIZUMAB, PEMBROLIZUMAB

Countries	Allocation	Masking
Germany, Taiwan, Province of China, Japan, Korea, Republic of, Chile, Ukraine, France, Colombia, Hungary, Spain, United Kingdom, Ireland, Poland, Canada, United States	Randomized	Open Label

Exclusive Biomarkers

ERBB2 protein overexpression, ESR1 protein overexpression, PGR protein overexpression

Active recruiting

Line	Phase	Compounds
1-10	2	CARBOPLATIN, GEMCITABINE, OLAPARIB, PEMBROLIZUMAB, PEMBROLIZUMAB

Countries	Allocation	Masking
Germany, Taiwan, Province of China, Japan, Korea, Republic of, Chile, Ukraine, France, Colombia, Hungary, Spain, United Kingdom, Ireland, Poland, Canada, United States	Randomized	Open Label

Exclusive Biomarkers

ERBB2 protein overexpression, ESR1 protein overexpression, PGR protein overexpression

This list of clinical trials has been generated by Genomate™ by matching the clinical and molecular profile of the patient with inclusion and exclusion criteria of trials recorded in the system. Search criteria have been manually set to filter matching clinical trials but do not necessarily cover all screening parameters. Genomate Health Inc. does not take responsibility for the validity of the recorded clinical trial data concerning inclusion and exclusion criteria and status and cannot guarantee that the patient is going to be enrolled in any of the trials included in the list provided.

ANALYZED MOLECULAR PROFILE

MUTANT GENES

ABRAXAS1-R361Q, CHEK1-G361D, CSMD3-R1228Q, CYP2A6-S467*, CYP2D6-R296C, CYP2D6-R329C, CYP2D6-R380H, CYP2D6-S486T, EP300-P925T, FBXW7-Q127*, FLT1-S733DEL, GNAS-S113R, MUC16-G1727E, MUC16-T1454I, MUC16-V2472I, MYC-N26S, NOTCH1-R879Q, PTEN-C83*, RICTOR-D1182G, RPTOR-A496FS*15, SLC45A3-V470I, TP53-375+1G>A, TSC1-G560S, USP16-T19I, ZNF226-T582A

WILD TYPE GENES

ABCB1, ABCC2, ABL1, ABL2, ACVR1B, ACVRL1, ADGRB3, AGTRAP, AIP, AKAP9, AKT1, AKT2, AKT3, ALK, ALOX12B, AMER1, AMPH, APC, APEX1, AR, ARAF, ARFRP1, ARID1A, ARID1B, ARID2, ASXL1, ATM, ATP11B, ATP4A, ATP6V0D2, ATR, ATRX, AURKA, AURKB, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BAX, BAZ2B, BCL2, BCL2L1, BCL2L11, BCL2L2, BCL6, BCL9, BCOR, BCORL1, BCR, BIRC2, BIRC3, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRD4, BRIP1, BTG1, BTG2, BTK, BUB1B, CALR, CARD11, CASP8, CASR, CBFB, CBL, CBLB, CBLC, CCDC178, CCDC6, CCN6, CCND1, CCND2, CCND3, CCNE1, CD22, CD274, CD70, CD74, CD79A, CD79B, CDA, CDC27, CDC73, CDH1, CDK12, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CDKN2C, CEBPA, CEP57, CHD1, CHD2, CHD4, CHD7, CHEK2, CHIC2, CIC, CIT, CREBBP, CRKL, CRLF2, CSF1R, CSF3R, CSNK2A1, CTCF, CTNNA1, CTNNB1, CUBN, CUL3, CUL4A, CXCR4, CYLD, CYP17A1, CYP19A1, CYP2B6, CYP2C19, CYP2C9, DAXX, DCC, DCUN1D1, DDB2, DDR1, DDR2, DDX11, DDX3X, DICER1, DIS3, DIS3L2, DMD, DNMT3A, DOT1L, DPYD, DSE, ECT2L, EED, EGFR, ELMO1, EML4, EMSY, EP300, EPCAM, EPHA2, EPHA3, EPHA5, EPHA7, EPHB1, EPHB4, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERG, ERRFI1, ESR1, ESR2, ESRP1, ETV6, EXOC2, EXT1, EXT2, EZH2, EZR, FAM46C, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF,

ANALYZED MOLECULAR PROFILE

FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FAT3, FBXO11, FBXO32, FGF10, FGF12, FGF14, FGF19, FGF23, FGF3, FGF4, FGF5, FGF6, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLT1, FLT3, FLT4, FN1, FOXA1, FOXL2, FOXO1, FOXP1, FRS2, FSTL5, FUBP1, FZD3, G6PD, GABRA6, GALNT17, GAS6, GATA1, GATA2, GATA3, GATA4, GATA6, GEN1, GID4, GLI1, GNA11, GNA13, GNAI2, GNAQ, GNAS, GNAT2, GOPC, GPC3, GPR78, GREM1, GRIN2A, GRM3, GRM8, GSK3B, GSTP1, GXYLT1, H3F3A, HDAC1, HGF, HIST1H3B, HNF1A, HOXB13, HRAS, HSD3B1, HSP90AA1, HSPH1, ID3, IDH1, IDH2, IFITM1, IFITM3, IGF1R, IGF2, IGF2R, IGSF10, IKBKE, IKZF1, IKZF4, IL2RA, IL2RB, IL2RG, IL6, IL6ST, IL7R, INHBA, INPP4B, IRAK4, IRF2, IRF4, IRS2, ITCH, JAK1, JAK2, JAK3, JUN, KAT6A, KDM4B, KDM5A, KDM5C, KDM6A, KDR, KEAP1, KEL, KIAA1549, KIF5B, KIT, KLF6, KLHL6, KMT2A, KMT2C, KMT2D, KNSTRN, KRAS, KREMEN1, LAMA2, LCK, LMO1, LPAR2, LRP1B, LRRK2, LTK, LYN, LZTR1, MAF, MAGI2, MAGI3, MAGOH, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP3K13, MAP3K4, MAP4K3, MAP7, MAPK1, MAPK3, MAS1L, MAX, MCL1, MDM2, MDM4, MED12, MED13, MEF2B, MEN1, MERTK, MET, MIER3, MITF, MKNK1, MLH1, MLLT3, MPL, MRE11, MSH2, MSH3, MSH6, MST1R, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, MYO18A, MYO1B, NBN, NCOA2, NCOR1, NEK2, NELL2, NF1, NF2, NFE2L2, NFKBIA, NIPA2, NKX2-1, NKX2-8, NKX3-1, NOTCH1, NOTCH2, NOTCH3, NPM1, NRAS, NRCAM, NRG1, NSD1, NSD3, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, OR5L1, OTOP1, P2RY8, PAK3, PALB2, PARK2, PARP1, PARP2, PARP3, PAX3, PAX5, PAX7, PBRM1, PCBP1, PCGF2, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDK1, PDZRN3, PHF6, PHOX2B, PIK3C2B, PIK3C2G, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R2, PIM1, PLCG2, PMS1, PMS2, PNP, POLD1, POLE, POT1, PPARG, PPM1L, PPP2R1A, PPP2R2A, PRDM1, PREX2, PRF1, PRKAR1A, PRKCI, PRKDC, PRKN, PRPF40B, PRSS8, PSMB1, PSMB2, PSMB5, PSMD1, PSMD2, PTCH1, PTGFR, PTPN11, PTPN12, PTPRD, PTPRO, QKI, RAC1, RAC2, RAD21, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RANBP2, RARA, RARB, RARG, RB1, RBM10, RECQL4, RECQL5, REL, RET, RHBDF2, RHEB, RHOA, RIT1, RNF43, ROS1, RPS6KB1, RPTOR, RUNX1, RUNX1T1, RXRA, RXRB, RXRG, S1PR2, SAMD9L, SBDS, SCN11A, SDC4, SDHA, SDHAF2, SDHB, SDHC, SDHD, SEC16A, SEPT9, SETBP1, SETD2, SF1, SF3A1, SF3B1, SGK1, SH2B3, SHH, SHOC2, SLC22A1, SLC22A2, SLC31A1, SLC34A2, SLC7A8, SLC9A9, SLCO1B1, SLIT2, SLX4, SMAD2, SMAD3, SMAD4, SMARCA4, SMARCB1, SMARCE1, SMC1A, SMC3, SMO, SNCAIP, SOCS1, SOS1, SOX10, SOX2, SOX9, SPEG, SPEN, SPOP, SPRED1, SPTA1, SRC, SRSF2, SSTR1, STAG2, STAT3, STAT4, STK11, SUFU, SUZ12, SYK, SYNE3, TACC3, TAF1, TAS2R38, TBX20, TBX3, TCERG1, TCF7L2, TEK, TENT5C, TERC, TERT, TET2, TFG, TGFBR2, THSD7B, TIAF1, TIPARP, TMEM127, TMPRSS2, TNFAIP3, TNFRSF14, TOP1, TOP2A, TP53BP1, TP63, TPM3, TPM4, TPMT, TRAF5, TRIO, TRRAP, TSC1, TSC2, TSHR, TYK2, TYRO3, U2AF1, U2AF2, UBR3, UGT1A1, USP25, VCL, VEGFA, VHL, WDCP, WEE1, WHSC1, WNK2, WRN, WT1, WWP1, XPA, XPC, XPO1, XRCC2, YAP1, YES1, ZBED4, ZBTB2, ZFHX3, ZIC3, ZMYM3, ZNF2, ZNF217, ZNF473, ZNF595, ZNF703, ZRSR2

FISH/CNA/IHC POSITIVE GENES

KDR AMPLIFICATION PRESENCE, KIT AMPLIFICATION PRESENCE, PD-L1 PROTEIN OVEREXPRESSION, PDGFRA AMPLIFICATION PRESENCE

FISH/CNA/IHC NEGATIVE GENES

ABL1 TRANSLOCATION ABSENCE, ALK TRANSLOCATION ABSENCE, BCL2 TRANSLOCATION ABSENCE, BCR TRANSLOCATION ABSENCE, BRAF TRANSLOCATION ABSENCE, BRCA1 TRANSLOCATION ABSENCE, BRCA2 TRANSLOCATION ABSENCE, BRD4 TRANSLOCATION ABSENCE, CD74 TRANSLOCATION ABSENCE, EGFR TRANSLOCATION ABSENCE, ETV4 TRANSLOCATION ABSENCE, ETV5 TRANSLOCATION ABSENCE, ETV6 TRANSLOCATION ABSENCE, EWSR1 TRANSLOCATION ABSENCE, EZR TRANSLOCATION ABSENCE, FGFR1 TRANSLOCATION ABSENCE, FGFR2 TRANSLOCATION ABSENCE, FGFR3 TRANSLOCATION ABSENCE, KIF5B TRANSLOCATION ABSENCE, KIT TRANSLOCATION ABSENCE, KMT2A TRANSLOCATION ABSENCE, MET TRANSLOCATION ABSENCE, MSH2 TRANSLOCATION ABSENCE, MYB TRANSLOCATION ABSENCE, MYC TRANSLOCATION ABSENCE, NOTCH2 TRANSLOCATION ABSENCE, NRG1 TRANSLOCATION ABSENCE, NTRK1 TRANSLOCATION ABSENCE, NTRK2 TRANSLOCATION ABSENCE, NTRK3 TRANSLOCATION ABSENCE, NUTM1 TRANSLOCATION ABSENCE, PDGFRA TRANSLOCATION ABSENCE, RAF1 TRANSLOCATION ABSENCE, RARA TRANSLOCATION ABSENCE, RET TRANSLOCATION ABSENCE, ROS1 TRANSLOCATION ABSENCE, RSPO2 TRANSLOCATION ABSENCE, SDC4 TRANSLOCATION ABSENCE, SLC34A2 TRANSLOCATION ABSENCE, TACC1 TRANSLOCATION ABSENCE, TACC3 TRANSLOCATION ABSENCE, TERC TRANSLOCATION ABSENCE, TERT TRANSLOCATION ABSENCE, TMPRSS2 TRANSLOCATION ABSENCE

MICROSATELLITE INSTABILITY

MSS

BIOMEDICAL INTERPRETATION

Functional interpretation of the detected alterations:

The detected genetic alterations were classified into the following categories by the Molecular Treatment Calculator (MTC), based on their functional consequences and their contribution to tumor formation (gains selective growth advantage compared to healthy cells): driver, variant of unknown significance in a driver gene (VUS, driver gene), non-confirmed driver, biomarker, variant of unknown significance (VUS), non-driver.

The algorithm calculates with positive score, in case of scientific evidence describing that a mutation or a gene contributes to cancer formation. It calculates with negative score, in case of scientific evidence describing that a mutation or a gene does not contribute to cancer formation.
The classification of a given variant is based on evidence describing the given alteration, the mutant gene or other specific mutations of the same gene as driver alterations. The algorithm summarizes and biases the related evidence and calculates the aggregated evidence level (AEL).

Driver: The algorithm classifies variants as drivers if there is available matching evidence in the database (describing the detected alteration) and it has a positive AEL.

BIOMEDICAL INTERPRETATION

Variant of unknown significance in a driver gene (VUS in a driver gene): In case of these variants there is no available matching evidence. The classification is based on evidence describing the mutant gene or other specific mutations of the same gene as drivers.

VUS (variant of unknown significance): There is no available evidence regarding the given alteration, the mutant gene or other specific mutations of the same gene.

Biomarker: These alterations are associated with the efficacy of a targeted drug based on matching scientific evidence (describing the detected alteration), but it does not fulfill the criteria to be a driver.

Conflicting driver: In case of these variants the number and level of the available matching evidence describing the detected alteration as a driver is limited.

Non-driver: The AEL values of these variants are negative.

PD-L1 overexpression in triple negative breast cancer

There is correlation in several tumor-types between PD-L1 overexpression and the efficacy of PD-1 and PD-L1 inhibitory immunotherapies (1, 2).
According to a study 19% (20/105) of triple negative breast cancer (TNBC) patients show >5% PD-L1 expression (3). Immunotherapies are extensively investigated in TNBC (4).
In TNBC indication, approved immunotherapies are ATEZOLIZUMAB and PEMBROLIZUMAB (FDA only).

ATEZOLIZUMAB (PD-L1 inhibitor) is approved in combination with nab-paclitaxel (nanoparticle albumin-bound paclitaxel) for adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1.
According to the results of the IMpassion130 trial involving 902 patients with TNBC, in patients with PD-L1 expressing tumors, the combination of atezolizumab and nab-paclitaxel (A+nP) resulted in more favorable outcomes than treatment with placebo and nab-paclitaxel (P+nP), for patients without PD-L1 expressing tumors no significant difference was observable. The median progression-free survival (PFS) values were 7.4 vs 3.9 months and 9.3 vs 6.1 months, and the median overall survival (OS) values were 22.6 vs 15.0 months and 28.9 vs 20.8 months for patients with low (IC 1% and <5%, n=243) and high (IC 5%, n=125) PD-L1 expression for A+nP vs P+nP treatment, respectively. In the intention-to-treat population, the objective response rate (ORR) was 56% and 45.9% in the A+nP vs P+nP arms, respectively (5, 6). BRCA1/2 mutations (detected in 14.5% patients) were not associated with PD-L1 IC status, and PD-L1 IC+ patients benefited from A+nP regardless of BRCA1/2 mutation status (6).
According to the primary analysis of the IMpassion031 phase III trial, atezolizumab combined with nab-paclitaxel followed by doxorubicin+cyclophosphamide chemotherapy (A-chemo) resulted in improved pathological complete responses compared with placebo combined with nab-paclitaxel followed by chemotherapy (P-chemo) among untreated early-stage TNBC patients, regardless of PD-L1 status as a neoadjuvant therapy (7). However, the EMA has not granted approval to this extension of indication yet based on the results of this study.
Primary analysis of the IMpassions131 phase III trial revealed that atezolizumab and paclitaxel did not improve PFS or OS significantly as a first-line treatment for TNBC patients compared with placebo+paclitaxel (8).
In a phase I study (NCT01375842), patients with metastatic TNBC (n=112) were treated with atezolizumab. The one-year OS rate was 45% for patients with high PD-L1 expression of tumor-infiltrating immune cells versus 37% for those with low to no PD-L1 expression. The response rate was 13% and 5%, respectively (9).
A phase Ib study evaluated the combination of ipatasertib, atezolizumab and chemotherapy as a first-line treatment option for patients with advanced TNBC. According to initial results, the regimen demonstrated a confirmed ORR of 73%, irrespective of tumor biomarker status (10).

In a phase Ib solid tumor trial (JAVELIN, NCT01772004), efficacy of avelumab (PD-L1 inhibitor) was examined in heavily pretreated metastatic breast cancer patients (n=168), unselected for PD-L1 status. The ORR was 3.0% overall, and 5.2% in the subgroup of patients with TNBC (n=58). A trend toward higher ORR was observed in TNBC patients with PD-L1 positive versus negative status (22.2% vs 2.6%) of tumor-associated immune cells (11).

PEMBROLIZUMAB (PD-1 inhibitor) is approved by the FDA in combination with chemotherapy for advanced TNBC patients whose tumors express PD-L1 (10%). Approval was based on the phase III KEYNOTE-355 study, comparing pembrolizumab versus placebo in combination with chemotherapy. In the subgroup of TNBC patients with higher than 10% PD-L1 expression, median PFS was 9.7 months in the pembrolizumab arm (n=220) and 5.6 months in the placebo arm (n=103). In patients irrespective of PD-L1 status, median PFS was 7.5 months in the pembrolizumab arm (n=566) and 5.6 months in the placebo arm (n=281) (12).
In a phase II study (KEYNOTE-086, NCT02447003) the efficacy/safety of pembrolizumab was examined in previously treated mTNBC (cohort A). The ORR was 5% regardless of PD-L1 expression. Median PFS and OS were 2.0 months and 9 months, with 6-months rates of 14.9% and 69.1%, respectively (13).

BIOMEDICAL INTERPRETATION

PEMBROLIZUMAB (PD-1 inhibitor) is also approved by the FDA for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

In the GeparNUEVO phase II study, the addition of DURVALUMAB (anti-PD-L1 inhibitor) to neoadjuvant chemotherapy in TNBC (n=174) significantly improved long-term outcome despite a small pathological CR increase (53.4% vs 44.2%) and no continuation after surgery. The 3-year invasive DFS rate was 84.9% vs 76.9%, the 3-year OS rate was 95.1% vs 83.1% in the durvalumab and placebo arms, respectively (14).

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Molecular alterations and mechanisms associated with resistance / reduced efficacy in case of immunotherapies

Based on preclinical and clinical evidence, genetic alterations that may result in decreased efficacy or resistance to immunotherapies are loss of function mutations in the B2M (1), CBLB (2), JAK1/2 (3-6), NSD1 (7), PTEN (8, 9) and STK11 (10-12) genes as well as deletion of TET2 (13), and the activation of the WNT/beta-catenin signalling pathway (14). IDO expression (15) and IFNGR1 gene loss (6) may induce resistance to CTLA-4 targeting immunotherapies. Furthermore, immunotherapies were shown to be ineffective in case of non-small cell lung cancer (NSCLC) tumors harboring EGFR (16, 17), HER2 (18), or RB1 mutations (19), ROS1 translocations (18) and MET exon 14 skipping mutations (20). Immunotherapies were also ineffective in case of medullary thyroid carcinoma (MTC) and NSCLC tumors with RET fusions, and mutations (21, 22). Poor clinical outcome and hyperprogression have been reported in patients with MDM2, MDM4 or MYC amplifications after receiving immunotherapy (17, 23, 24).

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Foundation results:

TP53 c.375+1G>A

This mutation induces aberrant splicing, and it has been shown to cause loss of p53 function (1, 2). It is reported as a pathogenic/likely pathogenic variant in the ClinVar database.

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TP53 loss-of-function mutation - targets

The p53 tumor suppressor encoded by the TP53 gene functions to block the cell cycle or to initiate apoptosis in response to cellular stress (e.g. genomic damage).
In the presence of loss of function TP53 alterations CHEK1 (1-3), ATR (4), PLK1 (5), WEE1 (6) and CDK (7, 8) inhibitors can be mentioned in positive association with the molecular profile. The CDK inhibitors PALBOCICLIB, RIBOCICLIB, and ABEMACICLIB are approved in breast cancer indication.
In addition, in the presence of non-functional p53 protein, the small molecule eprenetapopt (APR-246) can also be mentioned as a potential therapeutic agent with anti-tumor activity (9). The MQ (methylene quinuclidinone) prodrug APR-246 is a methylated structural analog of PRIMA-1 (p53 reactivation and induction of massive apoptosis). By binding to the cysteine residues of the mutant p53 protein, MQ induces its destabilization, thereby reconstituting endogenous p53 activity. In addition, APR-246 also might have chemoradiotherapy sensitizing effect in tumor cells, through restoring p53 activity and induction of oxidative stress (9, 10). APR-246 is currently tested in phase I/II trials in hematologic and solid malignancies. The FDA granted fast track designation to eprenetapopt in TP53-mutant acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) indications.

According to preclinical data, certain TP53 mutations (e.g. R175H, R248G, R273H, and C135F), may cause resistance to the chemotherapeutic drugs cisplatin, doxorubicin, paclitaxel, etoposide, and carboplatin.
In a study, the combination of ramucirumab plus paclitaxel achieved better overall survival in gastric cancer patients with loss of function TP53 mutations, compared with chemotherapy (11).
In patients with different types of TP53 mutant advanced cancer median PFS on standard systemic therapy was significantly longer with bevacizumab-containing regimens as compared to non-bevacizumab containing regimen (11.0 vs. 4.0 months), whereas no difference was seen in TP53 wild-type cases (12).
In a study, TP53 mutations were associated with improved PFS and OS in endometrial cancer patients who received chemotherapy combined with bevacizumab as compared to chemotherapy plus temsirolimus (PFS: HR 0.48; OS: HR 0.61) (13).

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TP53 mutant breast cancer

In a study, TP53 mutations were uncommon in breast cancer patients but associated with poor prognosis, with an increased recurrence risk compared to patients with wild type TP53 (1).
In a study, TP53 mutations were found in 28.3% of breast tumors, conferring a worse overall and breast cancer-specific survival, and were also found to be an independent marker of poor prognosis in estrogen receptor-positive cases (2).
According to a study, TP53 mutations are present at a very high frequency in central nervous system metastases of breast tumors. Furthermore, complex mutations (non-sense, deletions, insertions) are over-represented in metastatic lesions in both triple-negative breast cancer and hormone receptor/HER2-positive cases (3).

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PDGFRA, KIT, KDR coamplifcation

Co-amplification of the three tyrosine kinase receptor genes in the 4q12 chromosomal region, PDGFRA, KIT and KDR (VEGFR2), is common, mainly in glioblastoma and other tumors of the nervous system (1-3), but has also been detected in a significant proportion of lung tumors (adenocarcinoma: 3-7 %, squamous cell carcinoma: 8–10%) (4).
Approved inhibitors targeting all three kinases are PAZOPANIB, REGORAFENIB, SORAFENIB, SUNITINIB, RIPRETINIB, AXITINIB, LENVATINIB and MIDOSTAURIN.
IMATINIB resulted in 3 years of stable disease in PDGFRA/KIT/KDR amplificated head and neck cancer patients (5).
AXITINIB treatment in two adenoid cystic carcinoma patients carrying PDGFRA/KIT/KDR amplification resulted in more than 6 months of stable disease in a phase II trial, and one of them had a significant reduction in tumor size and the longest 21.8-month PFS observed in the study (progression-free survival) (6).
In a preclinical study, cells carrying PDGFRA/KIT/KDR amplification showed increased sensitivity to LENVATINIB *in vitro* (7).

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PTEN-C83*

BIOMEDICAL INTERPRETATION

This variant is reported as a pathogenic variant in the ClinVar database. Due to the premature STOP codon (nonsense mutation) in the PTEN gene, a variant encoding a substantially shorter protein version is generated, thus loss of function is highly likely.

PTEN mutant gene - targets

PTEN (phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase) is a negative regulator of the PI3K-AKT-mTOR signaling pathway by dephosphorylating phosphoinositides and thereby acting as a tumor suppressor.
PI3K (1), AKT (2), mTOR (2-6), PARP (7) and ATM (8) inhibitors are in positive association with PTEN loss-of-function mutations. However, the scientific literature is contradictory regarding the relevance of mTOR inhibition. IDELALISIB and DUVELISIB are PIK3CD inhibitors in clinical use. PARP inhibitors in clinical use are OLAPARIB, RUCAPARIB, NIRAPARIB, and TALAZOPARIB. EVEROLIMUS, TEMSIROLIMUS, METFORMIN, and SIROLIMUS are mTOR inhibitors in clinical use.

PTEN loss-of-function alterations cause resistance to EGFR inhibitors (9, 10). MEK + mTOR combined inhibition was synergistic in PTEN loss preclinical models (11). PTEN loss-of-function might cause resistance to PI3Kalpha inhibition, including the PI3Kalpha inhibitor alpelisib (12, 13), and also to HER2 inhibition (14-16).
According to several studies, PTEN loss or mutations are associated with reduced T cell infiltration, altered tumor microenvironment and resistance to anti-PD-1 therapy (17, 18). Treatment with a selective PI3Kbeta inhibitor (GSK2636771) improved the efficacy of both anti-PD-1 and anti-CTLA-4 antibodies in murine models (18).

References:
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BIOMEDICAL INTERPRETATION

PTEN mutant triple negative breast cancer

Loss of PTEN function is a frequent molecular alteration in triple negative breast cancer (TNBC) cases.

In the phase II LOTUS clinical trial, TNBC patients were treated with paclitaxel or paclitaxel + ipatasertib (AKT inhibitor). In the PIK3CA/AKT1/PTEN mutant subgroup the PFS was 9.0 months by the combination treatment, while paclitaxel reached 4.9 months alone. These results were 6.2 and 4.9 months among the all recruited patients, respectively (1).

In the phase II PAKT study, the efficacy of the addition of capivasertib (AKT inhibitor) to paclitaxel therapy was examined among TNBC patients. In the PIK3CA/AKT1/PTEN mutant subgroup, the ORR was 35.3% (6/17) vs 18.2% (2/11), the median PFS was 9.3 vs 3.7 months, the median OS was not reached and was 10.4 months in the capivasertib + paclitaxel (CP) and in the placebo + paclitaxel (PP) treated groups, respectively. In the intention-to-treat population, the ORR was 34.8% (23/66) vs 28.8% (19/66), the median PFS was 5.9 vs 4.2 months, and the median OS was 19.1 vs 12.6 months in the CP and PP arms, respectively (2).

References:

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FBXW7-Q127*

This mutation has not been listed in the known oncodriver databases, and it has not been functionally evaluated. Due to the premature STOP codon (nonsense mutation) in the FBXW7 gene, a variant encoding a substantially shorter protein version is generated, thus loss of function is highly likely.

FBXW7 mutant gene - target genes

FBXW7 (F-box and WD repeat domain containing 7) protein is a known tumor suppressor, that degrades several proto-oncogenes (MYC, cyclin E, NOTCH and JUN) as a component of the SCF complex (1). Its mutation might impair substrate recognition and degradation, resulting in sustained NOTCH1 intracellular domain and MYC expression (2).

According to preclinical evidence, FBXW7 mutations sensitize cells to mTOR inhibitors, which was also studied in a clinical trial (3, 4). Moreover, mTOR inhibition protected FBXW7-deficient mice from radiation-induced tumor development (5). Registered mTOR inhibitors include EVEROLIMUS, TEMSIROLIMUS, SIROLIMUS, and METFORMIN.

In case study of a patient with lung adenocarcinoma harboring an FBXW7 mutation, temsirolimus therapy showed antitumor activity (6).

Some studies suggest that the loss of p53-dependent tumor surveillance mechanisms is likely to be a necessary step in the transformation of FBXW7 mutant tumor-initiating cells (7).

Wild type FBXW7 inhibits NOTCH signaling. Upon FBXW7 inactivation, NOTCH activity increases (8). Therefore, NOTCH inhibition might be a potential therapeutic strategy (9). NOTCH inhibitors are available in clinical trials only.

FBXW7-deficient cells show increased sensitivity to sorafenib (10). This is explained by the fact that sorafenib is an inhibitor of receptor tyrosine kinases (PDGF, VEGF, RAF) involved in tumor growth and angiogenesis. The RAF kinase enzyme can activate the MAPK signaling pathway. Sorafenib reduces MCL-1 levels by inactivating MAPK kinase. It has also been shown to have an inhibitory effect on MCL-1. In FBXW7 - / - cells, increased levels of MCL-1 play a critical role in avoiding the apoptotic pathway. Thus, FBXW7-deficient cells are much more sensitive to sorafenib than FBXW7 wild-type cells, and the MCL-1 gene could be considered as a target gene (11).

FBXW7 mutations might induce resistance to taxane- and vincristine-based chemotherapy (11), and also to EGFR inhibitors (12).

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Additional results of the Oncompass test:

Result of the tumor mutational burden (TMB) analysis (TMB low)

The tumor mutational burden (TMB) value is 2,03 mutations/megabase. The calculation is based on the NGS analysis. Based on our database of calculated TMB values (n=830), 49% of our cases had lower TMB values.

Please note, that this calculation is not yet validated, therefore the result is not listed in the molecular profile and is not included in the calculation of the Molecular Treatment Calculator.

Immunotherapy-treated patients (n=151) with various tumor types (n=17) were analyzed in a study. High TMB was defined as 20 mutations/mb. The RR (response rate) for patients with high vs. low/intermediate TMB was 22/38 (58%) vs. 23/113 (20%). Results were similar when anti-PD-1/PD-L1 monotherapy was analyzed (n=102 patients), with a positive correlation between higher TMB and more favorable outcome (1). Similar benefit was obtained upon analyzing microsatellite stable (MSS), high versus low/intermediate TMB samples from 60 patients (14 different histologies) treated with anti-PD-1/PD-L1 monotherapy, the median progression-free survival was 26.8 and 4.3 months (2).

Survival data of 1662 immunotherapy treated cancer patients was analysed in a study. The top 20% of the TMB values was considered high in every histology group. Overall survival was significantly higher in the TMB-high group. Survival benefit was shown to be increasing with the level of TMB (3).

References:

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The result of MSI analysis (MSS - NGS-based)

The tumor is microsatellite stable (MSS), microsatellite instability indicating mismatch-repair (MMR) deficiency was not detected. The result was determined by an NGS-based MSI detection method, that classifies MSI status based on the calculated MSI score.

The MSI score is determined by the ratio of unstable loci detected among total microsatellite loci analyzed (MSI score = N(unstable loci) / N(total loci)). Loci with insufficient coverage for instability calling are excluded from total loci. MSI status of the tumor is interpreted based on using a stability cutoff value of 0.2 for the MSI score. An MSI score lower than the cutoff value (MSI score < 0.2) is classified as MSS, while an MSI score greater than or equal to the cutoff (MSI score >= 0.2) is classified as MSI-HIGH.

In this analysis, 11 loci were determined as unstable of the 136 total loci, so the obtained MSI score is 0.0809, classified as MSS.

According to the scientific literature in the case of microsatellite unstable tumors, the efficacy of immunotherapies is higher compared to microsatellite stable tumors (1, 2).

References:

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BIOMEDICAL INTERPRETATION

Result of the copy number variation (CNV) analysis

CNV analysis was performed within the NGS test. Copy number variation means, that the detected copy number is different from the normal copy number (n=2). With NGS based technology it is possible to estimate the copy number variations.

Based on the NGS test, copy number gain was detected in KLF6 (n=5), KIT (n=5), CD79A (n=5), MCL1 (n=5), PRDM1 (n=5), PCBP1 (n=5), NFKBIA (n=5) genes.

We recommend the validation of clinically relevant NGS-derived CNV results by FISH analysis. CNV results obtained solely by NGS analysis are not included in the molecular profile during digital therapy planning.

MCL1 amplification

MCL1 is an anti-apoptotic protein frequently amplified in tumor cells. High MCL1 expression is associated with worse prognosis in triple negative breast cancer (1). In preclinical studies, MCL1 inhibition had anti-tumor effect in breast cancer xenograft models (1). MC-1 inhibition sensitized breast cancer cells to dasatinib treatment (2). MCL-1 amplification has been reported to be associated with chemoresistance (3).

References:

(1) Campbell KJ et al., MCL-1 is a prognostic indicator and drug target in breast cancer. Cell Death Dis. 2018 Jan 16;9(2):19. PMID: 29339815

(2) Young AI et al., MCL-1 inhibition provides a new way to suppress breast cancer metastasis and increase sensitivity to dasatinib. Breast Cancer Res. 2016 Dec 8;18(1):125. PMID: 27931239

(3) Beroukhim R et al., The landscape of somatic copy-number alteration across human cancers. Nature. 2010 Feb 18;463(7283):899-905. PMID: 20164920

Results of the next generation sequencing (NGS)

The NGS sequencing of 591 genes resulted in 4841 genetic alterations. The 21 variants listed in the molecular profile were selected via bioinformatic and functional filtering.

These variants have been uploaded into the Realtime Oncology Calculator for further biomedical functional interpretation and medical decision support.

The following filters of the QIAGEN Clinical Insight Interpret software were used:

- CONFIDENCE: Filtering is based on variant call quality (QUAL), read depth (DP), allele fraction (computed from AD), upstream filter (PASS) and genotype quality (GQ). If the presence of a variant was uncertain based on the sequencing quality scores, the alteration was filtered out.
- COMMON VARIANTS: The filter is used to exclude variants that are commonly observed in the healthy population. If the frequency of a certain variant is at least 10% in the population according to the 1000 Genomes Project, the ExAC or the NHLBI ESP exomes database, it was excluded from further analysis.
- PREDICTED DELETERIOUS: The filter was used to identify variants in a dataset that have either predicted or observed evidence suggesting they could disrupt gene function or expression. The alterations, which are "benign" or "likely benign" according to the ACMG guideline were filtered out.
- CANCER DRIVER VARIANTS: The filter can be used to identify variants within a dataset that have predicted or established association with driving tumorigenesis or metastasis. Variants, which are related to cancer pathways, cell cycle regulation or cellular processes according to the scientific literature were selected. Alterations, which have been mentioned in the scientific literature related to cancer indication were also selected.

Other filtering methods used besides the Variant Analysis:
- Non-exonic alterations were excluded
- Further bioinformatic filtering was used considering other sequencing quality scores

The filtered variants are listed in the molecular profile of the patient.

Databases used for the interpretation of the detected alterations:

COSMIC (Catalogue Of Somatic Mutations In Cancer): This database is designed to store and display somatic mutations detected in various neoplasms.

BIOMEDICAL INTERPRETATION

NCBI dbSNP (National Center for Biotechnology Information, Single Nucleotide Polymorphism database): Database dbSNP serves as a central repository for both single base nucleotide substitutions and short deletion and insertion polymorphisms detected as germline variants in either healthy population or in patients with various diseases (including, but not only cancer patients).
NCBI ClinVar: It is a publicly available archive of relations between human variations and phenotypes (clinical significance), with supporting evidence. It is not restricted to cancer diseases.
SNPEffect: This database contains the clinical relevance of single nucleotide mutations/polymorphisms based on OMIM and other databases and in silico predictions.
IARC (International Agency for Research on Cancer) TP53 Database: The IARC TP53 Database compiles various types of data and information on human TP53 gene variations related to cancer. Data is compiled from peer-reviewed literature and generalized databases. Functional classification of the mutations based on the overall transcriptional activity on 8 different promoters can also be found in the database.
BRCA Exchange: BRCA Exchange contains functional information about and classification of BRCA1 and BRCA2 mutations.
UniProt: UniProt is a knowledgebase of protein sequences and their function.

Mutational Signature (no mutational signature was obtained)
Mutational signature analysis (1-3) has been performed on the filtered variants of the NGS results. The analysis did not reveal significant contribution values fitting any identified single-base substitution signatures. The variant count was 182.

References:
(1) Alexandrov LB et al., Signatures of mutational processes in human cancer. Nature. 2013 Aug 22;500(7463):415-21. doi: 10.1038/nature12477. Epub 2013 Aug 14. PMID: 23945592
(2) Alexandrov LB et al., The repertoire of mutational signatures in human cancer. Nature. 2020 Feb;578(7793):94-101. doi: 10.1038/s41586-020-1943-3. Epub 2020 Feb 5. PMID: 32025018; PMCID: PMC7054213.
(3) cancer.sanger.ac.uk/cosmic/signatures

ABRAXAS1-R361Q
This mutation is listed in COSMIC with low frequency (n<5) and according to ClinVar, it has uncertain significance. But this gene is a tumor suppressor and this mutation leads to reduced protein levels as well as nuclear localization of BRCA1. This causes disturbances in basal BRCA1-A complex localization, which is reflected by restraint in error-prone DNA double-strand break (DSB) repair pathway usage (1). Abraxas R361Q demonstrated exclusive association with cancer, segregation with the disease within families, and loss of biological function in the DNA damage response (2).

References:
(1) Bose M, Sachsenweger J, Laurila N, Parplys AC, Willmann J, Jungwirth J, Groth M, Rapakko K, Nieminen P, Friedl TWP, Heiserich L, Meyer F, Tuppurainen H, Peltoketo H, Nevanlinna H, Pylkäs K, Borgmann K, Wiesmüller L, Winqvist R, Pospiech H. BRCA1 mislocalization leads to aberrant DNA damage response in heterozygous ABRAXAS1 mutation carrier cells. Hum Mol Genet. 2019 Dec 15;28(24):4148-4160. doi: 10.1093/hmg/ddz252. PMID: 31630195.
(2) Solyom S, Aressy B, Pylkäs K, Patterson-Fortin J, Hartikainen JM, Kallioniemi A, Kauppila S, Nikkilä J, Kosma VM, Mannermaa A, Greenberg RA, Winqvist R. Breast cancer-associated Abraxas mutation disrupts nuclear localization and DNA damage response functions. Sci Transl Med. 2012 Feb 22;4(122):122ra23. doi: 10.1126/scitranslmed.3003223. PMID: 22357538; PMCID: PMC3869525.

ABRAXAS1 mutant gene
ABRAXAS1 is a tumor suppressor gene required for DNA damage resistance, DNA repair, and cell cycle checkpoint control. It is a homologous recombination repair gene, so PARP inhibitors (1), platinum-based therapies (2), or immunotherapies (3) can also be efficient in ABRAXAS1 mutant cancers.

References:
(1) Castillo A, et al. The BRCA1-interacting protein Abraxas is required for genomic stability and tumor suppression. Cell Rep. 2014 Aug 7;8(3):807-17. doi: 10.1016/j.celrep.2014.06.050. Epub 2014 Jul 24. PMID: 25066119; PMCID: PMC4149256.
(2) Pennington KP, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res. 2014 Feb 1;20(3):764-75. doi: 10.1158/1078-0432.CCR-13-2287. Epub 2013 Nov 15. PMID: 24240112.
(3) LIU, Zaoqu, et al. Somatic mutations in homologous recombination pathway predict favorable prognosis after immunotherapy across multiple cancer types. 2021.

BIOMEDICAL INTERPRETATION

RPTOR-A496fs*15

This variant is not listed in the relevant databases, its functional effect is not discussed in the scientific literature. Due to the frameshift mutation in the RPTOR gene, a variant encoding a substantially shorter protein version is generated, thus loss of function is highly likely. RPTOR is a proto-oncogene. Its loss of function presumably does not contribute to tumorigenesis.

MUC16-V2472I

This variant is listed in the COSMIC database with low frequency (n<5). Functional effect of this mutation is not discussed in the scientific literature.

MUC16-G1727E

This variant is listed in the COSMIC database with low frequency (n<5). Functional effect of this mutation is not discussed in the scientific literature.

CSMD3-R1228Q

This variant is listed in the COSMIC database with low frequency (n=5). Functional effect of this mutation is not discussed in the scientific literature.

MYC-N26S

The variant did not show association with increased risk of tumor formation in different cancer types (1-3). It is listed in the COSMIC database (n<50).

References:

(1) Kiemeney LA et al., Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. Nat Genet. 2008 Nov;40(11):1307-12. doi: 10.1038/ng.229. Epub 2008 Sep 14. PubMed PMID: 18794855; PubMed Central PMCID: PMC4539560.

(2) Salinas CA, Kwon E, Carlson CS, Koopmeiners JS, Feng Z, Karyadi DM, Ostrander EA, Stanford JL. Multiple independent genetic variants in the 8q24 region are associated with prostate cancer risk. Cancer Epidemiol Biomarkers Prev. 2008 May;17(5):1203-13. doi: 10.1158/1055-9965. EPI-07-2811. PubMed PMID: 18483343.

(3) Fernberg P, Chang ET, Duvefelt K, Hjalgrim H, Eloranta S, Sørensen KM, Porwit A, Humphreys K, Melbye M, Ekström Smedby K. Genetic variation in chromosomal translocation breakpoint and immune function genes and risk of non-Hodgkin lymphoma. Cancer Causes Control. 2010 May;21(5):759-69. doi: 10.1007/s10552-010-9504-y. Epub 2010 Jan 20. PubMed PMID: 20087644.

Triple negative breast cancer - targeted drugs regardless of molecular profile

According to the scientific literature 25-35% of triple negative breast cancers (TNBCs) overexpress androgen receptor (AR), in which case AR inhibitors may be effective (1).

50-70% of triple negative breast cancers have increased EGFR expression (2, 3). In a randomized phase II study adding cetuximab to cisplatin doubled the objective response rate (ORR) and appeared to prolong progression-free survival (PFS) and overall survival (OS) in a molecularly not selected group of TNBC patients. Cisplatin plus cetuximab resulted in longer median PFS compared with cisplatin alone (3.7 v 1.5 months) (4).

In the phase II LOTUS trial, ipatasertib (AKT inhibitor) combined with paclitaxel resulted in improved median PFS (6.2 vs 4.9 months) and OS (25.8 vs 6.9 months) compared with placebo and paclitaxel as first-line therapy for TNBC patients (n=124) (5).

The FDA approved SACITUZUMAB GOVITECAN, a TROP2-directed antibody and topoisomerase inhibitor drug conjugate, for patients with metastatic TNBC after two or more prior lines of therapy. TROP2 (trophoblast cell-surface antigen-2) is highly expressed in many epithelial tumors, including TNBC.

The approval was based on a phase II trial enrolling previously treated (a median of 3 previous therapies) metastatic TNBC patients (n=108). Sacituzumab govitecan monotherapy resulted in an ORR of 33% (36/108), and a median duration of response of 7.7 months. The median PFS was 5.5 months, and the median OS was 13.0 months (6).

In the phase III ASCENT trial, sacituzumab govitecan (SG) treatment resulted in improved outcomes compared with single-agent TPC (capecitabine, eribulin, vinorelbine, or gemcitabine) among metastatic TNBC patients (n=468 without brain metastases) after at least 2 prior lines of therapy. The median PFS was 5.6 vs 1.7 months, median OS was 12.1 vs 6.7 months, and the ORR was 35% vs 5% in the SG and TPC groups, respectively (7). In the biomarker analysis, patients with known TROP2 expression and BRCA1/2 status were included. SG outperformed TPC across all TROP2 expression subgroups, and higher TROP2 levels were associated with better outcomes. Stratification by BRCA1/2 status, SG was showed superiority over TPC (8).

BIOMEDICAL INTERPRETATION

In a phase I clinical trial, trastuzumab duocarmazine, a HER2-directed antibody-drug conjugate (ADC), treatment resulted in a 40% overall response rate in patients with triple-negative breast cancer with low HER2 expression (9). In a phase Ib trial, trastuzumab deruxtecan demonstrated an objective response rate of 37% (20/54) and a disease control rate of 87% among patients with HER2-low–expressing (IHC 1+ or 2+ with negative FISH) advanced breast cancer. The median duration of response was 10.4 months, the median progression-free survival (PFS) was 11.1 months, and the median overall survival was 29.4 months (10).
In phase IIb trial, the HER2-derived vaccine nelipepimut-S (NPS) was investigated among breast cancer patients. Subset analysis identified improvement in 36-month disease-free survival (DFS) between NPS (n=55) and placebo (n=44) in TNBC and those who express HLA-A24. The TNBC cohort demonstrated improved 36-month DFS in those with HER2 1+ expression (HR 0.17, p=0.01) (11).

Ladiratuzumab vedotin (LV) is an anti-LIV-1 and MMAE (monomethyl auristatin E) antibody-drug conjugate. LIV-1 (SLC39A6) is highly expressed in metastatic triple negative and ER positive breast cancers (12). In phase I/II trials, LV showed promising activity in TNBC patients, either as a monotherapy in heavily pretreated patients (13) or in combination with pembrolizumab as a first-line therapy (14).

References:

(1) Shah PD et al., The role of the androgen receptor in triple-negative breast cancer. Womens Health (Lond Engl). 2013 Jul;9(4):351-60. Review. PMID: 23826776
(2) Zhang L et al., Androgen receptor, EGFR, and BRCA1 as biomarkers in triple-negative breast cancer: a meta-analysis. Biomed Res Int. 2015; 2015:357485. Review. PMID: 25695063
(3) Nechushtan H et al., A phase 1/2 of a combination of Cetuximab and Taxane for "triple negative" breast cancer patients. Breast. 2014 Aug;23 (4):435-8. Epub 2014 May 14. PMID: 24836394
(4) Baselga J et al., Randomized phase II study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic triple-negative breast cancer. J Clin Oncol. 2013 Jul 10;31(20):2586-92. Epub 2013 Jun 3. PMID: 23733761
(5) Dent R et al., Final results of the double-blind placebo (PBO)-controlled randomised phase II LOTUS trial of first-line ipatasertib (IPAT) + paclitaxel (PAC) for inoperable locally advanced/metastatic triple-negative breast cancer (mTNBC). Annals of Oncology. 2020;31(suppl_2):S62-S82. doi: 10.1016/annonc/annonc122.
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(8) Hurvitz SA et al., Abstract GS3-06: Biomarker evaluation in the phase 3 ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer. Cancer Res. February 15 2021;81(4 Supplement)GS3-06; doi: 10.1158/1538-7445.SABCS20-GS3-06.
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(11) Chick RC et al., Subgroup analysis of nelipepimut-S plus GM-CSF combined with trastuzumab versus trastuzumab alone to prevent recurrences in patients with high-risk, HER2 low-expressing breast cancer. Clin Immunol. 2021 Apr;225:108679. Epub 2021 Jan 22. PMID: 33485895
(12) Sussman D et al., SGN-LIV1A: a novel antibody-drug conjugate targeting LIV-1 for the treatment of metastatic breast cancer. Mol Cancer Ther. 2014 Dec;13(12):2991-3000. Epub 2014 Sep 24. PMID: 25253783
(13) Modi S et al., Abstract PD3-14: Phase 1 study of the antibody-drug conjugate SGN-LIV1A in patients with heavily pretreated triple-negative metastatic breast cancer. Cancer Res. Feb 15 2018;78(4 Supplement):PD3-14. doi: 10.1158/1538-7445.SABCS17-PD3-14.
(14) Hyo HH et al., Abstract PD1-06: Open label phase 1b/2 study of ladiratuzumab vedotin in combination with pembrolizumab for first-line treatment of patients with unresectable locally-advanced or metastatic triple-negative breast cancer. Cancer Res. Feb 15 2020;80(4 Supplement):PD1-06. doi: 10.1158/1538-7445.SABCS19-PD1-06.

Targeted therapies registered in breast cancer indication regardless of the molecular profile

Bevacizumab (VEGFR inhibitor) is registered in breast cancer indication.
In an open-label, randomized, phase III trial, 722 patients were enrolled. Paclitaxel plus bevacizumab significantly prolonged median progression-free survival (PFS) compared to paclitaxel alone (11.8 vs. 5.9 months) and it increased the objective response rate (36.9% vs. 21.2%) (1).

BIOMEDICAL INTERPRETATION

Another phase III study compared the efficacy and safety of bevacizumab when combined with several standard chemotherapy regimens versus those regimens alone. Median PFS was longer for each bevacizumab combination. In case of bevacizumab added to paclitaxel, the average PFS was 11.4 months, compared with 5.8 months in those receiving paclitaxel alone. When bevacizumab was added to capecitabine, the average PFS was 8.6 months, compared to 5.7 months in those receiving capecitabine with placebo (2).

References:

(1) Miller K et al., Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007 Dec 27;357(26):2666-76. PubMed PMID: 18160686

(2) Robert NJ et al., RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol. 2011 Apr 1; 29(10):1252-60. Epub 2011 Mar 7. PubMed PMID: 21383283