ONCOMPASS™ Medicine

Precision Oncology Report

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

PATIENT INFORMATION

Patient ID: [redacted]
Name: [redacted]
Year of birth: 1958

Primary Tumor Site: rectum
Histology Type: adenocarcinoma
Metastatic sites: lung

MEDICAL TEAM

Treating Physician: [redacted]
Molecular Pharmacologist: István Peták, MD PhD
Genetic Counselor: Júlia Déri, MSc
Molecular Biologist: Edit Várkondi, PhD
Consulting Physician: Gábor Pajkos, MD CSc
Case Manager: Julia Deri
Case Coordinator: Réka Czető
Molecular Biologist: Helga Barti-Juhász, PhD
Molecular Biologist: Róbert Dóczi, PhD

PATHOLOGICAL AND MOLECULAR DIAGNOSTIC TESTS

Sample ID: [redacted]
Sample source: Primary Tumor
Tumor cell rate: 60%
Specimen Type: FFPE tissue/cell block
Tumor type: rectum adenocarcinoma

Tests performed by Oncompass Medicine (www.oncompassmedicine.com)
Oncompass Oncodriver Panel:
NGS - 591 genes - [redacted]
Total variants identified: 5540
Variant count after filtering: 27
TMB - LOW: 2.37 muts/Mb - [redacted])
MSI test (NGS-based) - MSS (microsatellite stable) - [redacted])

MSI test (PCR-based) - MSS (microsatellite stable) - [redacted])

PREVIOUS THERAPIES

Line: 1 - Bevacizumab + FOLFOX - 6 cycles - (04/10/2021 - 29/12/2021)
Line: 2 - CAPECITABINE - (02/2022 - 08/2022)

SUMMARY

Oncompass Report of [redacted] 1958, diagnosed with **rectum adenocarcinoma** has been completed for digital drug assignment and treatment planning purposes using the Realtime Oncology Treatment Calculator.

The following molecular tests were used for our analysis:
ONCOMPASS ONCODRIVER assay (NGS-591) was carried out from the primary tumor (sample ID: [redacted]) with a tumor cell ratio of 60%.

Tumor-agnostic biomarkers/Immunotherapy-related biomarkers:
The tumor is **MSS** and **TMB-Low** (2,37 muts/Mb).
Based on these biomarkers, immunotherapy is not supported as a monotherapy.

SUMMARY

Previous studies revealed that immune checkpoint inhibitors are ineffective in MSS colorectal cancer (CRC) patients, however, a subset (~10%) of MSS CRC patients were found to respond to PD-1/PD-L1 inhibitors. According to a phase Ib study, the combination of REGORAFENIB and NIVOLUMAB (AEL: 1559.77) had a manageable safety profile and encouraging anti-tumor activity in previously treated MSS CRC patients. Objective tumor response was observed in 33.3% of MSS CRC (8/24) patients with a median progression-free survival of 7.9 months in the group of 24 MSS and 1 MSI patient. In phase II clinical trial with previously treated non-MSI-H/pMMR CRC patients, PEMBROLIZUMAB (AEL: 1445.78) + LENVATINIB treatment resulted in an ORR of 22%, mPFS of 2.3 months, and OS of 7.5 months.
Frameshift mutations located in an NMD-resistant position were not detected.
NTRK fusions were not detected in the tested sample.
BRAF-V600E mutation was not detected in the molecular test.
There were no alterations detected which could demonstrably cause resistance to immunotherapies.

Tumor-specific on-label biomarkers:
In the investigated tumor sample **KRAS, PIK3CA, NRAS,** and **SMAD4** mutations were detected which may cause resistance to EGFR inhibitors as monotherapy. **CETUXIMAB and PANITUMUMAB are negatively associated with the molecular profile of the tumor.**
ENCORAFENIB + CETUXIMAB combination therapy is approved in BRAF-V600E mutant, previously treated, metastatic colorectal cancer. No BRAF mutation was detected in the tumor.

Histology-based on-label treatments independent of the molecular profile:
Registered targeted drugs in the patient's tumor type are the VEGF inhibitor BEVACIZUMAB (AEL: 1830.81), RAMUCIRUMAB (AEL: 15.45) and AFLIBERCEPT (AEL: 2.51), and the multikinase inhibitor REGORAFENIB. The FDA granted fast-track status to the multi-VEGFR inhibitor FRUQUINTINIB. TAS-102 (Lonsurf, trifluridine / tipiracil; AEL: 12.96) is approved to treat metastatic colorectal cancer (CRC) patients after other therapies have failed. The patient has already received bevacizumab therapy.

Based on the NGS results, the following additional results could be relevant as off-label treatments:
KRAS-G12V driver (AEL: 1549.68, AF/TR: 41.7%/60%): In the scientific literature, it is described as an activating, driver mutation. In the case of oncogenic KRAS mutations, inhibitors of **MEK (TRAMETINIB**, COBIMETINIB, BINIMETINIB and SELUMETINIB) and **CDK** (PALBOCICLIB, RIBOCICLIB and **ABEMACICLIB**) may be positively associated with the molecular profile of the patient based on preclinical evidence. Based on cell line experiments, the combined targeting of MEK and EGFR, or MEK and both EGFR+HER2, MEK and CDK, MEK and CRAF or MEK and mTOR could be more effective than MEK or CDK inhibitor monotherapy. The combination of MEK and PARP inhibition had a synergistic effect in several KRAS mutant cell lines, independently of BRCA status. Preclinical data suggest that mTOR inhibitors combined with chemotherapy might be effective in KRAS mutant cancer**.** Administration of **METFORMIN** (AEL: 4427.19) was beneficial in activating KRAS mutated mCRC with prolonged in OS compared to EVEROLIMUS. **Resistance to or decreased efficacy of BEVACIZUMAB might emerge due to KRAS-G12V mutations.**

PIK3CA-E545K driver (AEL: 1161.61, AF/TR: 29.32%/60%) it is a known activating, driver mutation. Because of this driver mutation in the PIK3CA oncogene, the tumor is associated with response to PI3K/AKT/mTOR signaling pathway inhibitors. Among patients with PIK3CA mutant colorectal cancers (CRCs), regular use of acetylsalicylic acid (Aspirin) after diagnosis was associated with higher colorectal cancer-specific survival (hazard ratio (HR): 0.18) and overall survival (OS) (HR: 0.54). PIK3CA mutations might also confer resistance to first-line chemotherapy in CRC.
Concurrent mutations in KRAS and PIK3CA: KRAS and PIK3CA mutations may cause resistance to each other's targeted inhibition, but combined targeted inhibition has been shown to be effective in cells harboring both KRAS and PIK3CA mutations.

NRAS-Q61L driver (AEL: 196.52, AF/TR: 30.16%/60%) It is described in the scientific literature as a driver mutation. **MEK**, PLK1, ERK1/2, and mTOR inhibitors are in positive association with the NRAS-Q61L. According to preclinical data, the combination of MEK + CDK, MEK + mTOR, or MEK + EGFR inhibitors might also be effective. According to preclinical experiments, MEK (NRAS indirect target) inhibitors AS703026 and selumetinib (AZD6244) inhibit the growth of cetuximab-resistant CRC cell lines and tumor xenografts. In a phase II study, MEK-inhibitor CI-1040 was well tolerated but did not show any antitumor effect, however, the efficacy of selumetinib (MEK1/2 inhibitor) proved to have similar effects to capecitabine in patients with CRC.

SMAD4-R361C driver (AEL: 78.02, AF/TR: 43.37%/60%) According to the ClinVar, LOVD databases, and the scientific literature, it is a pathogenic variant associated with cancer, resulting in an unstable protein *in vivo*. Based on the scientific literature, SMAD4 loss can cause resistance to 5-FU based chemotherapy regimens by activating the Akt pathway, therefore inhibitors of Akt signaling pathway may be sensitizing to 5-FU therapy. Mutations of SMAD4 gene has been associated with resistance to EGFR inhibitors

SUMMARY

CNV analysis and Mutational signature analysis were performed within the NGS test, but no clinically relevant results were obtained.

Several other alterations were identified and classified as non-driver or variants of unknown significance. The role and significance of these alterations are not clear, however, their contribution to tumorgenesis cannot be ruled out.

According to the VMTB, based on the histology, molecular profile, and DDA, the following treatments could be considered:

On-label options 2/3L: Lonsurf plus metformin (AEL: 4427.19))

Regorafenib is expected to be less effective based on the detected biomarkers

EGFR inhibitor is not recommended due to the NRAS, KRAS, and SMAD4 mutations.

Off-label options: Trametinib (AEL: 3594.03)**+metformin +/-abemaciclib** (AEL: 3107.69)

Other off-label options or clinical trial participation: MEK inhibitor, e.g Trametinib, and PIK3CA inhibitor e.g. Alpelisib could be considered.

MOLECULAR TARGET ANALYSIS

MOLECULAR ALTERATIONS

KRAS-G12V driver (AEL: 1549.68, AF/TR: 41.7%/60%),
PIK3CA-E545K driver (AEL: 1161.61, AF/TR: 29.32%/60%),
NRAS-Q61L driver (AEL: 196.52, AF/TR: 30.16%/60%),
BRCA2-F892L VUS in a driver gene (AEL: 84.51, AF/TR: 51.22%/60%),
SMAD4-R361C driver (AEL: 78.02, AF/TR: 43.37%/60%),
SMAD4-I179V VUS in a driver gene (AEL: 5.65, AF/TR: 27.21%/60%),
KMT2D-S5366N VUS in a driver gene (AEL: 4.47, AF/TR: 5.56%/60%),
KMT2C-E4189G VUS in a driver gene (AEL: 2.00, AF/TR: 52.21%/60%),
ROS1-I1549T VUS in a driver gene (AEL: 1.43, AF/TR: 31.64%/60%),
AR-D154E VUS in a driver gene (AEL: 1.36, AF/TR: 76.42%/60%),
MUC16-G1727E VUS in a driver gene (AEL: 0.76, AF/TR: 50.89%/60%),
ADGRB3-V34L VUS in a driver gene (AEL: 0.04, AF/TR: 28.62%/60%),
NELL2-A74D VUS in a driver gene (AEL: 0.02, AF/TR: 11.09%/60%),
VCL-S434Y variant of unknown significance (AEL: 0.00, AF/TR: 50.97% /60%),
EZR-V457* variant of unknown significance
KDM5A-H808L variant of unknown significance (AEL: 0.00, AF/TR: 60.42%/60%),
SPEG-P2285L variant of unknown significance (AEL: 0.00, AF/TR: 70.34%/60%),
PAX7-R269C variant of unknown significance (AEL: 0.00, AF/TR: 24.51%/60%),
MYO18A-D789N variant of unknown significance (AEL: 0.00, AF/TR: 23.08%/60%),
ZNF595-N468S variant of unknown significance (AEL: 0.00, AF/TR: 48.39%/60%),
SPEG-R910C variant of unknown significance (AEL: 0.00, AF/TR: 21.92% /60%),
GRIN2A-T1212M variant of unknown significance (AEL: 0.00, AF/TR: 29.72%/60%),
IGSF10-R61C variant of unknown significance (AEL: 0.00, AF/TR: 51.58% /60%),
SYNE3-R313C variant of unknown significance (AEL: 0.00, AF/TR: 51.29%/60%),
MYCL-H78Y variant of unknown significance (AEL: 0.00, AF/TR: 33.33% /60%),
XPC-K481N non-driver (AEL: -10.00, AF/TR: 48.48%/60%),
KMT2C-D1319H non-driver (AEL: -15.00, AF/TR: 46.47%/60%)

TARGET GENES

RAF1 wild-type (AEL: 1752.56),
- KRAS-G12V driver (AEL: 1549.68) ;
- NRAS-Q61L driver (AEL: 196.52)

PLK1 wild-type (AEL: 1750.44),
- KRAS-G12V driver (AEL: 1549.68) ;
- NRAS-Q61L driver (AEL: 196.52)

MAPK1 wild-type (AEL: 1749.10),
- KRAS-G12V driver (AEL: 1549.68) ;
- NRAS-Q61L driver (AEL: 196.52)

MAPK3 wild-type (AEL: 1749.10),
- KRAS-G12V driver (AEL: 1549.68) ;
- NRAS-Q61L driver (AEL: 196.52)

PIK3CA wild-type (AEL: 1624.05),
- PIK3CA-E545K driver (AEL: 1161.61)

CDK4 wild-type (AEL: 1557.03),
- KRAS-G12V driver (AEL: 1549.68)

XPO1 wild-type (AEL: 1555.38),
- KRAS-G12V driver (AEL: 1549.68)

TBK1 wild-type (AEL: 1552.82),
- KRAS-G12V driver (AEL: 1549.68)

CDC7 wild-type (AEL: 1550.85),
- KRAS-G12V driver (AEL: 1549.68)

CDK9 wild-type (AEL: 1550.53),
- KRAS-G12V driver (AEL: 1549.68)

CNKSR1 wild-type (AEL: 1550.53),
- KRAS-G12V driver (AEL: 1549.68)

PTPN11 wild-type (AEL: 1550.48),
- KRAS-G12V driver (AEL: 1549.68)

HSP90AA1 wild-type (AEL: 1550.44),
- KRAS-G12V driver (AEL: 1549.68)

FAK wild-type (AEL: 1550.18),
- KRAS-G12V driver (AEL: 1549.68)

CDK1 wild-type (AEL: 1549.98),
- KRAS-G12V driver (AEL: 1549.68)

MTOR wild-type (AEL: 1377.60),
- PIK3CA-E545K driver (AEL: 1161.61) ;
- NRAS-Q61L driver (AEL: 196.52)

SOS1 wild-type (AEL: 1359.35),
- NRAS-Q61L driver (AEL: -196.52) ;
- KRAS-G12V driver (AEL: 1549.68)

	AKT1 wild-type (AEL: 1184.42), • PIK3CA-E545K driver (AEL: 1161.61) CTNNB1 wild-type (AEL: 1162.05), • PIK3CA-E545K driver (AEL: 1161.61) MAP2K1 wild-type (AEL: 619.40), • KRAS-G12V driver (AEL: 1549.68) ; • PIK3CA-E545K driver (AEL: -1161.61) ; • NRAS-Q61L driver (AEL: 196.52) CSNK2A1 wild-type (AEL: 197.18), • NRAS-Q61L driver (AEL: 196.52) CD274 wild-type (AEL: 86.76), • MUC16-G1727E VUS in a driver (AEL: 0.76) ; • BRCA2-F892L VUS in a driver (AEL: 84.51) TGFB1 wild-type (AEL: 86.26), • SMAD4-I179V VUS in a driver (AEL: 5.65) ; • SMAD4-R361C driver (AEL: 78.02) TGFBR1 wild-type (AEL: 86.26), • SMAD4-I179V VUS in a driver (AEL: 5.65) ; • SMAD4-R361C driver (AEL: 78.02) ROS1 wild-type (AEL: 30.39), • ROS1-I1549T VUS in a driver (AEL: 1.43) BRD4 wild-type (AEL: 4.14), • KMT2C-E4189G VUS in a driver (AEL: 2.00) CTLA4 wild-type (AEL: 1.67), • MUC16-G1727E VUS in a driver (AEL: 0.76) DNMT1 wild-type (AEL: 0.84)

DRUGS WITH THE HIGHEST AEL SCORES

DRUGS IN CLINICAL USE

METFORMIN (AEL: 4427.19)
- KRAS-G12V driver (AEL: 1549.68) ;
- PIK3CA-E545K driver (AEL: 1161.61) ;
- SMAD4-I179V VUS in a driver (AEL: 5.65) ;
- MTOR wild-type target (AEL: 1377.60) ;
- TGFB1 wild-type target (AEL: 86.26) ;
- SMAD4-R361C driver (AEL: 78.02)

TRAMETINIB (all - malignant melanoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; all - all [FDA]) (AEL: 3594.03)
- KRAS-G12V driver (AEL: 1549.68) ;
- MAP2K1 wild-type target (AEL: 619.40) ;
- PIK3CA-E545K driver (AEL: 1161.61) ;
- NRAS-Q61L driver (AEL: 196.52)

SELINEXOR (all - diffuse large B-cell lymphoma [FDA]; all - multiple myeloma [FDA+EMA]) (AEL: 3129.61)
- XPO1 wild-type target (AEL: 1555.38) ;
- KRAS-G12V driver (AEL: 1549.68)

ABEMACICLIB (breast - all [FDA+EMA]) (AEL: 3107.69)
- CDK4 wild-type target (AEL: 1557.03) ;
- KRAS-G12V driver (AEL: 1549.68)

ALPELISIB (breast - all [FDA+EMA]) (AEL: 2814.81)
- PIK3CA-E545K driver (AEL: 1161.61) ;
- PIK3CA wild-type target (AEL: 1624.05)

COPANLISIB (lymph node - follicular non-Hodgkin lymphoma [FDA]) (AEL: 2792.00)
- PIK3CA-E545K driver (AEL: 1161.61) ;
- PIK3CA wild-type target (AEL: 1624.05)

SIROLIMUS (AEL: 2548.13)
- MTOR wild-type target (AEL: 1377.60) ;
- PIK3CA-E545K driver (AEL: 1161.61)

SELUMETINIB (all - plexiform neurofibroma [FDA+EMA]; all - neurofibroma [FDA+EMA]) (AEL: 2431.76)
- MAP2K1 wild-type target (AEL: 619.40) ;
- KRAS-G12V driver (AEL: 1549.68) ;
- NRAS-Q61L driver (AEL: 196.52)

BINIMETINIB (skin - malignant melanoma [FDA+EMA]) (AEL: 2401.67)
- MAP2K1 wild-type target (AEL: 619.40) ;
- NRAS-Q61L driver (AEL: 196.52) ;
- KRAS-G12V driver (AEL: 1549.68)

PALBOCICLIB (breast - all [FDA+EMA]) (AEL: 1953.14)
- PIK3CA-E545K driver (AEL: -1161.61) ;
- CDK4 wild-type target (AEL: 1557.03) ;
- KRAS-G12V driver (AEL: 1549.68)

BEVACIZUMAB (cervix - all [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; liver - hepatocellular carcinoma [FDA]; peritoneum - all [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]; fallopian tube - all [FDA+EMA]; colon - all [FDA+EMA]; rectum - all [FDA+EMA]; breast - all [FDA+EMA]; brain - glioblastoma multiforme [FDA]; ovary - epithelial carcinoma [FDA+EMA]) (AEL: 1830.81)
- NRAS-Q61L driver (AEL: 196.52) ;
- KRAS-G12V driver (AEL: 1549.68)

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: 1559.77)
- PD-1 wild-type target (AEL: -110.93) ;
- KRAS-G12V driver (AEL: 1549.68) ;
- BRCA2-F892L VUS in a driver (AEL: 84.51)

DRUGS WITH THE LOWEST AEL SCORES

DRUGS IN CLINICAL USE

PANITUMUMAB (rectum - all [FDA+EMA]; colon - all [FDA+EMA]) (AEL: -6866.51)
- NRAS-Q61L driver (AEL: -196.52) ;
- PIK3CA-E545K driver (AEL: -1161.61) ;
- KRAS-G12V driver (AEL: -1549.68) ;
- EGFR wild-type target (AEL: -3370.09)

ERLOTINIB (pancreas - all [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]) (AEL: -6433.22)
- PIK3CA-E545K driver (AEL: -1161.61) ;
- KRAS-G12V driver (AEL: -1549.68) ;
- NRAS-Q61L driver (AEL: -196.52) ;
- EGFR wild-type target (AEL: -3370.09)

DACOMITINIB (lung - adenocarcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]) (AEL: -6089.75)
- EGFR wild-type target (AEL: -3370.09) ;
- ERBB2 wild-type target (AEL: -2719.74)

CRIZOTINIB (all - inflammatory myofibroblastic tumor (IMT) [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; all - anaplastic large cell lymphoma [FDA+EMA]) (AEL: -5673.97)
- ALK wild-type target (AEL: -1552.89) ;
- ROS1 wild-type target (AEL: 30.39) ;
- PIK3CA-E545K driver (AEL: -1161.61) ;
- NRAS-Q61L driver (AEL: -196.52) ;
- MET wild-type target (AEL: -1162.09) ;
- ROS1-I1549T VUS in a driver (AEL: -1.43) ;
- KRAS-G12V driver (AEL: -1549.68)

TRASTUZUMAB (breast - all [FDA+EMA]; gastric - adenocarcinoma [FDA+EMA]; gastroesophageal junction - adenocarcinoma [FDA+EMA]) (AEL: -5447.96)
- ERBB2 wild-type target (AEL: -2719.74) ;
- PIK3CA-E545K driver (AEL: -1161.61) ;
- KRAS-G12V driver (AEL: -1549.68)

CETUXIMAB (head-neck - squamous cell carcinoma [FDA+EMA]; colon - all [FDA+EMA]; rectum - all [FDA+EMA]) (AEL: -5420.29)
- NRAS-Q61L driver (AEL: -196.52) ;
- KRAS-G12V driver (AEL: -1549.68) ;
- SMAD4-I179V VUS in a driver (AEL: 0.00) ;
- SMAD4-R361C driver (AEL: 0.00) ;
- PIK3CA-E545K driver (AEL: 0.00) ;
- EGFR wild-type target (AEL: -3370.09)

VEMURAFENIB (all - malignant melanoma [FDA+EMA]) (AEL: -4721.92)
- KRAS-G12V driver (AEL: -1549.68) ;
- BRAF wild-type target (AEL: -1756.18) ;
- PIK3CA-E545K driver (AEL: -1161.61) ;
- NRAS-Q61L driver (AEL: -196.52)

DABRAFENIB (all - all [FDA]; lung - adenocarcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; skin - malignant melanoma [FDA+EMA]) (AEL: -4669.79)
- BRAF wild-type target (AEL: -1756.18) ;
- NRAS-Q61L driver (AEL: -196.52) ;
- KRAS-G12V driver (AEL: -1549.68) ;
- PIK3CA-E545K driver (AEL: -1161.61)

ALECTINIB (lung - non-small cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]) (AEL: -2717.11)
- PIK3CA-E545K driver (AEL: -1161.61) ;
- ALK wild-type target (AEL: -1552.89)

DRUGS WITH THE HIGHEST AEL SCORES

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: 1445.78)

- KRAS-G12V driver (AEL: 1549.68) ;
- PD-1 wild-type target (AEL: -110.93)

EVEROLIMUS (rectum - neuroendocrine carcinoma [FDA+EMA]; colon - neuroendocrine carcinoma [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]; breast - all [FDA+EMA]; pancreas - all [FDA]; brain - subependymal giant cell astrocytoma (SEGA) [FDA+EMA]; lung - neuroendocrine carcinoma [FDA+EMA]; pancreas - neuroendocrine carcinoma [FDA+EMA]; all - neuroendocrine carcinoma [FDA]) (AEL: 1205.32)

- KRAS-G12V driver (AEL: -1549.68) ;
- PIK3CA-E545K driver (AEL: 1161.61) ;
- MTOR wild-type target (AEL: 1377.60) ;
- NRAS-Q61L driver (AEL: 196.52)

OXALIPLATIN (rectum - all [FDA]; colon - all [FDA]) (AEL: 88.03)

- BRCA2-F892L VUS in a driver (AEL: 84.51)

RAMUCIRUMAB (gastroesophageal junction - adenocarcinoma [FDA+EMA]; liver - hepatocellular carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; rectum - all [FDA+EMA]; gastric - adenocarcinoma [FDA+EMA]; colon - all [FDA+EMA]) (AEL: 15.45)

TAS-102 (gastroesophageal junction - adenocarcinoma [FDA+EMA]; colon - all [FDA+EMA]; rectum - all [FDA+EMA]; gastric - adenocarcinoma [FDA+EMA]) (AEL: 12.96)

IPILIMUMAB (pleura - mesothelioma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; liver - hepatocellular carcinoma [FDA]; esophagus - squamous cell carcinoma [FDA+EMA]; rectum - all [FDA+EMA]; colon - all [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]; skin - malignant melanoma [FDA+EMA]) (AEL: 6.88)

- CTLA4 wild-type target (AEL: 1.67)

ZIV-AFLIBERCEPT (rectum - all [FDA]; colon - all [FDA]) (AEL: 2.51)

CAPECITABINE (breast - all [FDA]; colon - all [FDA]; rectum - all [FDA]) (AEL: 0.42)

DRUGS WITH THE LOWEST AEL SCORES

REGORAFENIB (gastroesophageal junction - gastrointestinal stromal tumor (GIST) [FDA+EMA]; gastric - gastrointestinal stromal tumor (GIST) [FDA+EMA]; rectum - all [FDA+EMA]; liver - hepatocellular carcinoma [FDA+EMA]; esophagus - gastrointestinal stromal tumor (GIST) [FDA+EMA]; colon - all [FDA+EMA]) (AEL: -1938.26)

- BRAF wild-type target (AEL: -1756.18) ;
- NRAS-Q61L driver (AEL: -196.52) ;
- KRAS-G12V driver (AEL: -1549.68) ;
- RAF1 wild-type target (AEL: 1752.56) ;
- RET wild-type target (AEL: -197.04)

BORTEZOMIB (all - mantle cell lymphoma [FDA+EMA]; all - multiple myeloma [FDA+EMA]) (AEL: -1758.75)

- NRAS-Q61L driver (AEL: -196.52) ;
- KRAS-G12V driver (AEL: -1549.68)

ENCORAFENIB (rectum - all [FDA+EMA]; colon - all [FDA+EMA]; skin - malignant melanoma [FDA+EMA]) (AEL: -1756.18)

- BRAF wild-type target (AEL: -1756.18)

5-FLUOROURACIL (pancreas - all [FDA]; rectum - all [FDA]; colon - all [FDA]; gastric - all [FDA]; breast - all [FDA]) (AEL: -1269.47)

- SMAD4-R361C driver (AEL: -78.02) ;
- PIK3CA-E545K driver (AEL: -1161.61) ;
- SMAD4-I179V VUS in a driver (AEL: -5.65)

DRUGS WITH THE HIGHEST AEL SCORES

DRUGS IN CLINICAL DEVELOPMENT

RIVICICLIB (AEL: 4657.54)
- CDK4 wild-type target (AEL: 1557.03) ;
- CDK1 wild-type target (AEL: 1549.98) ;
- CDK9 wild-type target (AEL: 1550.53)

RGB-286638 (AEL: 4657.54)
- CDK9 wild-type target (AEL: 1550.53) ;
- CDK4 wild-type target (AEL: 1557.03) ;
- CDK1 wild-type target (AEL: 1549.98)

RONICICLIB (AEL: 4657.54)
- CDK4 wild-type target (AEL: 1557.03) ;
- CDK1 wild-type target (AEL: 1549.98) ;
- CDK9 wild-type target (AEL: 1550.53)

RIGOSERTIB (AEL: 4364.66)
- PIK3CA wild-type target (AEL: 1624.05) ;
- KRAS-G12V driver (AEL: 1549.68) ;
- PIK3CA-E545K driver (AEL: 1161.61)

DACTOLISIB (AEL: 4193.76)
- PIK3CA-E545K driver (AEL: 1161.61) ;
- PIK3CA wild-type target (AEL: 1624.05) ;
- MTOR wild-type target (AEL: 1377.60)

GEDATOLISIB (AEL: 4191.42)
- MTOR wild-type target (AEL: 1377.60) ;
- PIK3CA-E545K driver (AEL: 1161.61) ;
- PIK3CA wild-type target (AEL: 1624.05)

ONVANSERTIB (AEL: 3309.00)
- KRAS-G12V driver (AEL: 1549.68) ;
- PLK1 wild-type target (AEL: 1750.44)

Simurosertib (AEL: 3105.19)
- KRAS-G12V driver (AEL: 1549.68) ;
- CDC7 wild-type target (AEL: 1550.85)

GANETESPIB (AEL: 3102.16)
- KRAS-G12V driver (AEL: 1549.68) ;
- HSP90AA1 wild-type target (AEL: 1550.44)

SHP099 (AEL: 3100.96)
- PTPN11 wild-type target (AEL: 1550.48) ;
- KRAS-G12V driver (AEL: 1549.68)

DRUGS WITH THE LOWEST AEL SCORES

DRUGS IN CLINICAL DEVELOPMENT

ALLITINIB (AEL: -6089.83)
- EGFR wild-type target (AEL: -3370.09) ;
- ERBB2 wild-type target (AEL: -2719.74)

AV-412 (AEL: -6089.83)
- ERBB2 wild-type target (AEL: -2719.74) ;
- EGFR wild-type target (AEL: -3370.09)

CANERTINIB (AEL: -6089.83)
- ERBB2 wild-type target (AEL: -2719.74) ;
- EGFR wild-type target (AEL: -3370.09)

SITRAVATINIB (AEL: -2714.75)
- MET wild-type target (AEL: -1162.09) ;
- ALK wild-type target (AEL: -1552.89)

AZD1480 (AEL: -1749.93)
- RET wild-type target (AEL: -197.04) ;
- ALK wild-type target (AEL: -1552.89)

TAE684 (AEL: -1559.27)
- ROS1-I1549T VUS in a driver (AEL: -1.43) ;
- ALK wild-type target (AEL: -1552.89)

SALIRASIB (AEL: -1553.63)
- KRAS-G12V driver (AEL: -1549.68)

ABT767 (AEL: -1372.46)
- PARP1 wild-type target (AEL: -1372.46)

INIPARIB (AEL: -1372.46)
- PARP1 wild-type target (AEL: -1372.46)

CEP-9722 (AEL: -1372.46)
- PARP1 wild-type target (AEL: -1372.46)

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)

ANALYZED MOLECULAR PROFILE

MUTANT GENES

ADGRB3-V34L, AR-D154E, BRCA2-F892L, EZR-V457*, GRIN2A-T1212M, IGSF10-R61C, KDM5A-H808L, KMT2C-D1319H, KMT2C-E4189G, KMT2D-S5366N, KRAS-G12V, MUC16-G1727E, MYCL-H78Y, MYO18A-D789N, NELL2-A74D, NRAS-Q61L, PAX7-R269C, PIK3CA-E545K, ROS1-I1549T, SMAD4-I179V, SMAD4-R361C, SPEG-P2285L, SPEG-R910C, SYNE3-R313C, VCL-S434Y, XPC-K481N, ZNF595-N468S

WILD TYPE GENES

ABCB1, ABCC2, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVRL1, AGTRAP, AIP, AKAP9, AKT1, AKT2, AKT3, ALK, AMER1, AMPH, APC, APEX1, 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, BRD4, BRIP1, BTG1, BTK, BUB1B, CARD11, CASP8, CASR, CBFB, CBL, CBLB, CBLC, CCDC178, CCDC6, CCN6, CCND1, CCND2, CCND3, CCNE1, CD274, CD74, CD79A, CD79B, CDA, CDC27, CDC73, CDH1, CDK12, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CDKN2C, CEBPA, CEP57, CHD1, CHD2, CHD4, CHD7, CHEK1, CHEK2, CHIC2, CIC, CIT, CREBBP, CRKL, CRLF2, CSF1R, CSMD3, CSNK2A1, CTCF, CTNNA1, CTNNB1, CUBN, CUL3, CYLD, CYP19A1, CYP2A6, CYP2B6, CYP2C19, CYP2C9, CYP2D6, DAXX, DCC, DCUN1D1, DDB2, DDR1, DDR2, DDX11, DDX3X, DICER1, DIS3L2, DMD, DNMT3A, DOT1L, DPYD, DSE, ECT2L, EED, EGFR, ELMO1, EML4, EMSY, EP300, EPCAM, EPHA2, EPHA3, EPHA5, EPHA7, EPHB1, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERG, ERRFI1, ESR1, ESR2, ESRP1, ETV6, EXOC2, EXT1, EXT2, EZH2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FAT3, FBXO11, FBXO32, FBXW7, FGF10, 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, GRM3, GRM8, GSK3B, GSTP1, GXYLT1, H3F3A, HGF, HIST1H3B, HNF1A, HOXB13, HRAS, HSD3B1, HSP90AA1, HSPH1, IDH1, IDH2, IFITM1, IFITM3, IGF1R, IGF2, IGF2R, IKBKE, IKZF1, IKZF4, IL2RA, IL2RB, IL2RG, IL6, IL6ST, IL7R, INHBA, INPP4B, IRAK4, IRF2, IRF4, IRS2, ITCH, JAK1, JAK2, JAK3, JUN, KAT6A, KDM4B, KDM5C, KDM6A, KDR, KEAP1, KEL, KIAA1549, KIF5B, KIT, KLF6, KLHL6, KMT2A, KNSTRN, KREMEN1, LAMA2, LCK, LMO1, LPAR2, LRP1B, LRRK2, LTK, LYN, LZTR1, MAGI2, MAGI3, MAGOH, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP3K4, MAP4K3, MAP7, MAPK1, MAPK3, MAS1L, MAX, MCL1, MDM2, MDM4, MED12, MED13, MEF2B, MEN1, MET, MIER3, MITF, MLH1, MLLT3, MPL, MRE11, MSH2, MSH3, MSH6, MST1R, MTOR, MUTYH, MYC, MYCN, MYD88, MYO1B, NBN, NCOA2, NCOR1, NEK2, NF1, NF2, NFE2L2, NFKBIA, NIPA2, NKX2-1, NKX2-8, NKX3-1, NOTCH1, NOTCH2, NOTCH3, NPM1, NRCAM, NRG1, NSD1, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, OR5L1, OTOP1, PAK3, PALB2, PAX3, PAX5, PBRM1, PCBP1, PCGF2, PDCD1LG2, PDGFRA, PDGFRB, PDK1, PDZRN3, PHF6, PHOX2B, PIK3C2B, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R2, 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, PTEN, PTGFR, PTPN11, PTPN12, PTPRD, QKI, RAC1, RAC2, RAD21, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, RAF1, RANBP2, RARA, RARB, RARG, RB1, RBM10, RECQL4, RECQL5, RET, RHBDF2, RHEB, RHOA, RICTOR, RIT1, RNF43, RPS6KB1, RPTOR, RUNX1, RUNX1T1, RXRA, RXRB, RXRG, S1PR2, SAMD9L, SBDS, SCN11A, SDC4, SDHA, SDHAF2, SDHB, SDHC, SDHD, SEC16A, SEPT9, SETBP1, SETD2, SF1, SF3A1, SF3B1, SH2B3, SHH, SHOC2, SLC22A1, SLC22A2, SLC31A1, SLC34A2, SLC45A3, SLC7A8, SLC9A9, SLCO1B1, SLIT2, SLX4, SMAD2, SMAD3, SMARCA4, SMARCB1, SMARCE1, SMC1A, SMC3, SMO, SNCAIP, SOCS1, SOS1, SOX10, SOX2, SOX9, SPEN, SPOP, SPRED1, SPTA1, SRC, SRSF2, SSTR1, STAG2, STAT3, STAT4, STK11, SUFU, SUZ12, SYK, TACC3, TAF1, TAS2R38, TBX20, TBX3, TCERG1, TCF7L2, TENT5C, TERC, TERT, TET2, TFG, TGFBR2, THSD7B, TIAF1, TMEM127, TMPRSS2, TNFAIP3, TNFRSF14, TOP1, TOP2A, TP53, TP53BP1, TP63, TPM3, TPM4, TPMT, TRAF5, TRIO, TRRAP, TSC1, TSC2, TSHR, TYK2, U2AF1, U2AF2, UBR3, UGT1A1, USP16, USP25, VEGFA, VHL, WDCP, WEE1, WNK2, WRN, WT1, WWP1, XPA, XPO1, XRCC2, YAP1, YES1, ZBED4, ZBTB2, ZFHX3, ZIC3, ZMYM3, ZNF2, ZNF217, ZNF226, ZNF473, ZNF703, ZRSR2

FISH/CNA/IHC POSITIVE GENES

FISH/CNA/IHC NEGATIVE GENES

ABL1 TRANSLOCATION ABSENCE, ALK TRANSLOCATION ABSENCE, BCR TRANSLOCATION ABSENCE, BRAF TRANSLOCATION ABSENCE, BRD4 TRANSLOCATION ABSENCE, CD74 TRANSLOCATION ABSENCE, EGFR TRANSLOCATION ABSENCE, FGFR1 TRANSLOCATION ABSENCE, FGFR2 TRANSLOCATION ABSENCE, FGFR3 TRANSLOCATION ABSENCE, KIF5B TRANSLOCATION ABSENCE, MET TRANSLOCATION ABSENCE, NRG1 TRANSLOCATION ABSENCE, NTRK1 TRANSLOCATION ABSENCE, NTRK2 TRANSLOCATION ABSENCE, NTRK3 TRANSLOCATION ABSENCE, RAF1 TRANSLOCATION ABSENCE, RARA TRANSLOCATION ABSENCE, RET TRANSLOCATION ABSENCE, ROS1 TRANSLOCATION ABSENCE, TACC1 TRANSLOCATION ABSENCE, TACC3 TRANSLOCATION ABSENCE

MICROSATELLITE INSTABILITY

MSS

BIOMEDICAL INTERPRETATION

Result of the tumor mutational burden (TMB) analysis

The tumor mutational burden (TMB) value is 2.37 mutations/megabase. The calculation is based on the NGS analysis. Based on our database of calculated TMB values (n=1261), 55% of our cases had lower TMB values.

PEMBROLIZUMAB is approved by the FDA for the treatment of adult and pediatric patients with unresectable or metastatic TMB-high solid tumors.

BIOMEDICAL INTERPRETATION

The approval was based on the prospectively-planned retrospective analysis of the KEYNOTE-158 phase II trial (NCT02628067). According to study results, tissue TMB-high status (defined as 10 mutations/mb) was associated with improved outcomes with pembrolizumab monotherapy in previously treated, advanced solid tumor patients (n=790, 10 tumor types). The objective response rate was 29% (30/102) in the TMB-high group, 28% (23/81) in the TMB-high group excluding patients with high or unknown MSI status, and 6% in (43/688) in the TMB-low group. As of data cutoff with a median follow-up of 37.1 months, the median duration of response had not been reached in the TMB-high group and was 33.1 months in the TMB-low group. In this study, 13% of the tested patient were classified to be TMB-high and 87% to be TMB-low [1]. In this study, 13% of the tested patients were classified as TMB-high and 87% as TMB-low [1]. Because the numerical value of TMB is dependent on the applied NGS panel, we defined TMB-high status as TMB values higher than 87% of all samples previously tested.

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 [2]. A 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 [3].
Survival data of 1662 immunotherapy treated cancer patients were analyzed in a study. The top 20% of the TMB values were 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 [4].

Result of the 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, the MSI score is below 0.2, so the sample is 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 [5,6].

Immunotherapy in microsatellite stable (MSS) colorectal cancer
Previous studies revealed that immune checkpoint inhibitors are ineffective in MSS colorectal cancer (CRC) patients, however a subset (~10%) of MSS CRC patients were found to respond to PD-1/PD-L1 inhibitors [6-8].
According to a phase Ib study, the combination of REGORAFENIB and NIVOLUMAB had a manageable safety profile and encouraging anti-tumor activity in previously treated MSS CRC patients. Objective tumor response was observed in 33.3% of MSS CRC (8/24) patients with a median progression-free survival of 7.9 months in the group of 24 MSS and 1 MSI patient [9].
In a phase II clinical trial with previously treated non-MSI-H/pMMR CRC patients, PEMBROLIZUMAB + LENVATINIB treatment resulted in an ORR of 22%, mPFS of 2.3 months, and OS of 7.5 months [10].
In a phase I/II study, MSS CRC patients were given pembrolizumab + regorafenib. The trial didn't meet its primary endpoint, though the median OS was high (10.9 months) [11].
In a retrospective study, unselected Chinese patients having metastatic MSS CRC received a combination of regorafenib + anti-PD-1 antibodies. No objective response was observed, but the PFS and disease control rate might have a modest benefit from this treatment [12].
In a phase II clinical trial patients with KRAS/NRAS/BRAF wild-type, MSS, metastatic CRC received panitumumab in combination with ipilimumab and nivolumab. The 12-week response rate was 35% and the median PFS proved to be 5.7 months [13].
In a phase II clinical trial patients with metastatic CRC received nivolumab and mFOLFOX6 + bevacizumab (standard-of-care, SOC) or SOC as first-line treatment. The median PFS was 11.9 months in both arms, however PFS rates after 12 months were higher with nivolumab + SOC vs SOC (18-month PFS rate: 28% (nivolumab + SOC) and 9% (SOC)). ORR was 60% (nivolumab + SOC) and 46% (SOC) and median DOR was 12.9 months (nivolumab + SOC) and 9.3 months (SOC) [14].
In a phase II trial patients with MSS and MGMT-silenced metastatic CRC received temozolomide followed by the combination of low-dose ipilimumab and nivolumab. After a median follow-up of 23.1 months, 8-month PFS rate was 36%. Median PFS and OS were 7.0 and 18.4 months, respectively, and overall response rate was 45% [15].
In a phase I/II trial patients with MSS, BRAF-V600E mutant metastatic CRC were treated with encorafenib plus cetuximab plus nivolumab. ORR was 45%, and disease control rate (DCR) was 95%. Median PFS was 7.3 months, and median OS proved to be 11.4 months [16].

BIOMEDICAL INTERPRETATION

The FDA has granted fast track designation to GCC19CART (autologous CAR T therapy), for the treatment of patients with relapsed and refractory metastatic colorectal cancer.
In a phase II clinical trial, patients with locally advanced rectal adenocarcinoma received neoadjuvant short-course radiation followed by mFOLFOX-6 plus avelumab. 15/40 patients (37.5%) achieved pathologic complete response (pCR). In addition, 12/40 (30%) had a near complete response. In total, 27/40 patients (67.5%) had a major pathologic response [17].
In a phase II study patients with locally advanced rectal cancer were treated with preoperative chemoradiotherapy plus avelumab. Out of 96 patients, 22 (23%) patients achieved a pCR and 59 (61.5%) patients a major pathological response [18].
In a phase II clinical trial patients with metastatic CRC received atezolizumab plus bevacizumab plus FOLFOXIRI or bevacizumab plus FOLFOXIRI. Median progression-free survival was 13.1 months in the atezolizumab group and 11.5 months in the control group [19].

Molecular alterations and mechanisms associated with resistance / reduced efficacy 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 [20], CBLB [21], JAK1/2 [22-25], NSD1 [26], PTEN [27,28], CDKN2A [29] and STK11 [30-32] genes as well as deletion of TET2 [33], and the activation of the WNT/beta-catenin signalling pathway [34]. IDO expression [35] and IFNGR1 gene loss [25] 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 [36,37], or HER2 mutations [38], ROS1 translocations [38] and MET exon 14 skipping mutations [39]. Immunotherapies were also ineffective in case of medullary thyroid carcinoma (MTC) and NSCLC tumors with RET fusions, and mutations [40,41]. Mutations in RB1 have also been associated with resistance to immunotherapies [42,43], but further studies are needed to confirm this observation. Poor clinical outcome and hyperprogression have been reported in patients with MDM2, MDM4 or MYC amplifications after receiving immunotherapy [37,44,45]. NTRK1 overexpression may also contribute to the development of resistance to immune checkpoint inhibitors [46].
Epigenetic processes can also contribute to immunotherapy resistance. Epidrugs can restore sensitivity to immunotherapies [47]. In a murine melanoma model the combination of panobinostat, a HDAC inhibitor and an anti-PD-1 agent B16-F10 yielded better response rates than those obtained with either drug alone [48]. Combination of HDAC inhibitors and anti-PD-1 drugs proved to be safe in phase I and II clinical trials [49-51]. There are several ongoing clinical trials using this combination (vorinostat + pembrolizumab: NCT02638090, NCT02538510, NCT02909452, NCT02437136, NCT04357873, entinostat + pembrolizumab: NCT02453620, vorinostat + (pembrolizumab or nivolumab): NCT01928576, NCT02437136, belinostat + nivolumab: NCT04315155, mocatnostat + pembrolizumab: NCT03220477, NCT02954991, mocetinostat + durvalumab: NCT02805660, NCT02993991, panobinostat + spartalizumab: NCT02890069, citarinostat + nivolumab: NCT02635061, NCT02718066). Preliminary results from a randomized phase II trial comparing the combination of vorinostat with pembrolizumab versus pembrolizumab alone in metastatic non-small cell lung cancer patients having PD-L1 expression > 1% showed a higher ORR in the combination arm (48% versus 25%, $P = 0.026$) [50]. The ENCORE 601 phase II study evaluated the combination of entinostat and pembrolizumab in melanoma patients pretreated with anti PD-1 drugs. The ORR was 19% with a median duration of response of 12.5 months [52].

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 only approximation of copy number variations is feasible.
There weren't any relevant copy number changes in the examined genes.

Mutational Signature Analysis

Mutational signature analysis [53-55] has been performed on the filtered variants of the NGS results. The analysis did not reveal significant contribution values fitting any identified clinically relevant single-base substitution signatures. The variant count was 152.

Results of the next generation sequencing (NGS)

The 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.

BIOMEDICAL INTERPRETATION

- 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:

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.

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.

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.

BIOMEDICAL INTERPRETATION

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

KRAS-G12V

It is classified as pathogenic in the ClinVar database. In the scientific literature, it is described as an activating, driver mutation [56-59].

The KRAS-G12V variant is associated with worse prognosis and shorter survival compared to other KRAS mutations or KRAS wild-type in colorectal tumors [58,59].

KRAS-G12V is an activating driver mutation that is commonly seen in low-grade ovarian cancers [60,61]. In a study, patients harboring the G12V mutation and with ovarian serous borderline tumors and ovarian low-grade serous carcinomas (LGSOC) had shorter survival times than patients with the wild type or rare KRAS variants [62]. According to a case report, a patient with recurrent LGSOC and with the KRAS-G12V mutation received selumetinib treatment for more than 7 years without tumor progression [63].

KRAS-G12V targeting drugs are in development, but clinical results are not available yet [64].

There is an ongoing Phase I clinical trial (NCT03948763) targeting this mutation in advanced or Metastatic Non-Small Cell Lung Cancer with an mRNA vaccine and there is a pilot study of Mature Dendritic Cell Vaccination is ongoing (NCT0359288) in ResectablePancreatic Cancer [65].

For patients with metastatic colorectal cancer harboring G12V mutation and treated with bevacizumab, the median PFS and OS was 6.6 and 19.2 months, compared to 11.6 and 26.3 months for patients with tumors harboring other KRAS mutation type (G12C/D/S or G13D), while the survival of patients with tumors harboring these other KRAS mutation types was comparable to those harboring wild-type KRAS gene [58].

Chinese patients having gastric cancer with the KRAS-G12V mutant have shorter OS than other mutation carriers or wild type.(18 months vs not reached) [66].

In a study, the effectiveness of osimertinib treatment is attenuated in the presence of this mutation in advanced NSCLC [67].

KRAS mutant gene - targets

In the case of oncogenic KRAS mutations, inhibitors of MEK (MAP2K1) [68], CDK [69,70], HSP90 [71], PLK1 [72], CRAF (RAF1) [73,74], ERK1/2 (MAPK3, MAPK1) [75] DNMT1 [76] and CNK1 [77] may be positively associated with the molecular profile of the patient based on preclinical evidence. In KRAS mutant tumors BRAF inhibition may enhance tumorigenesis [78], so BRAF is marked as a negative target. Based on cell line experiments, the combined targeting of MEK and EGFR [68], or MEK and both EGFR+HER2 [79], MEK and CDK [80,81], MEK and CRAF [82,83] or MEK and mTOR [84,85] could be more effective than MEK or CDK inhibitor monotherapy. TRAMETINIB, COBIMETINIB, BINIMETINIB (MEK inhibitors) and PALBOCICLIB, RIBOCICLIB, ABEMACICLIB (CDK inhibitors) are registered in melanoma and breast cancer indications, respectively. The MEK inhibitor SELUMETINIB is approved in neurofibromatosis type I indication. SORAFENIB and REGORAFENIB are multi-targeted kinase inhibitors in clinical use able to inhibit CRAF. DECITABINE is a DNMT1 inhibitor in clinical use. CNK1 inhibitors are not yet available in clinical development.

A number of recent preclinical studies have revealed cross-talk between KRAS-activated signaling and DNA damage response, which has important therapeutic implications. The combination of MEK and PARP inhibition had synergistic effect in several KRAS mutant cell lines, independently of BRCA status [86]. The authors concluded that PARPi and MEKi each block adaptive responses induced by the other drug and thus induce a synthetic lethal interaction. According to these experiments, activating KRAS mutation can result in resistance to PARPi monotherapy. However, in other model systems, this result wasn't confirmed [87].

Another publication demonstrated a synergistic interaction between CHK1 and MK2 inhibitors in KRAS-mutant cancer [88]. Similarly, pharmacological inhibition targeting HRR signaling combined with PARP inhibition selectivity killed KRAS-mutant cells [89]. Synergistic effect was also observed in radiosensitization of KRAS mutant non small cell lung cancer (NSCLC) lines by the combination of adavosertib (a WEE1 inhibitor) and olaparib [90].

The effectiveness of the MEK inhibitor trametinib is limited in KRAS mutant tumors due to a feedback activation that causes resistance to the treatment. Latest preclinical evidence suggests that addition of zoledronic acid to trametinib overcomes trametinib resistance and augments antitumor activity in KRAS mutant tumors both in vitro and in vivo. Zoledronic acid (a registered drug in non-tumor indication) disrupts the biological activity of RAS by inhibiting its isoprenylation [91]. Using this combination in a patient with KRAS-mutant colorectal cancer led to a significant response: Target and non-target lesions displayed a strong partial response and remained stable for 11 months [92].

The BI 1701963 inhibitor binds the SOS1 protein, thereby inhibiting the interaction and activation of the KRAS. It is currently being investigated in a phase I trial as a monotherapy and in combination with the MEK inhibitor trametinib, in patients with KRAS mutation-positive solid tumors (NCT04111458).

In an ongoing phase I trial (NCT03948763), testing mRNA-5671, an mRNA-based cancer vaccine targeting G12C, G12D, G12V, G13D KRAS mutations, is tested alone and with pembrolizumab in patients with KRAS-mutated or metastatic NSCLC, CRC or pancreatic adenocarcinoma. The first part of the study will take all HLA comers, and a second part of the study will restrict treatment to specific HLA types [93].

Driver alterations in the KRAS gene can cause resistance to EGFR inhibitors [94], therefore these drugs are listed in negative association with the KRAS mutant status.

BIOMEDICAL INTERPRETATION

The OS of KRAS-mutant mCRC patients with METFORMIN use was 37.8 months longer than those treated with other hypoglycemic drugs, and the median PFS was also 8.1 months longer. However, metformin use could not improve OS and PFS in KRAS wild-type patients.The effect of metformin in case of the former mutations has also been confirmed by preclinical experiments [95]. In another study, the proliferation of KRAS mutant cells was also effectively inhibited by metformin, compared to cells with wild-type KRAS [96].
EVEROLIMUS treatment was ineffective according to a phase II study, it resulted in shorter OS and DCR in mCRC patients with mutant KRAS, compared to those with wild-type (WT) KRAS [97]. This result is supported by another preclinical study and analysis, everolimus showed no inhibitory effect on KRAS mutant cells, and11 of the 12 patients with KRAS mutant tumors had disease progression, while only 16 of 31 of WT cases did not benefit from treatment [98].
In a case study, a patient with lung adenocarcinoma harbouring low-level MET amplification was treated with crizotinib, which resulted in durable response. At time of progression a KRAS mutation and loss of MET amplification was found in a new lesion as a potential mechanism of acquired resistance [99]. Patients with lung cancer harboring MET exon 14 alterations were treated with MET-inhibitors. The presence of a concurrent KRAS alteration was associated either with a short period of disease control or primary progressive disease [100]. In a preclinical study, the presence of KRAS mutations resulted in resistance to MET inhibitors, however this effect was reversed when MET inhibition was combined with MEK inhibitors [101].
In a phase III study, in case of patients with medullary thyroid cancer, treatment with cabozantinib resulted in enhanced ORR in RAS-mutant patients than in patients without RET/RAS mutation (31% vs 21%) [102].

KRAS mutant colorectal cancer
KRAS mutant tumors are usually resistant to EGFR inhibitors, including CETUXIMAB and PANITUMUMAB, which are registered in colorectal cancer (CRC) [103-105].

According to preclinical experiments MEK inhibitors AS703026 and selumetinib (AZD6244) inhibit the growth of cetuximab-resistant CRC cell lines and tumor xenografts [106]. In a phase II study MEK-inhibitor CI-1040 was well tolerated, but did not show any antitumor effect [107], however the efficacy of selumetinib (MEK1/2 inhibitor) proved to be similar to capecitabine in patients with CRC [108].

In a phase II study 15 CRC patients harboring KRAS mutation were treated with palbociclib. No tumor response was observed but 5 patients had stable disease [109].

In a phase I/II study recruiting metastatic, KRAS mutant CRC patients second- or third-line SORAFENIB (a multi-tyrosine kinase inhibitor, which is not yet approved in CRC) therapy combined with irinotecan resulted in the median progression-free survival (PFS) to be 3.7 months and the OS 8.0 months [110].

The clinical efficacy and safety of REGORAFENIB have been evaluated in a randomized, double-blind, placebo-controlled phase III study in patients with metastatic CRC who have progressed after failure of standard therapy. The median OS was 6.4 months in the REGORAFENIB arm compared to 5.0 months in the placebo arm. The median PFS was 1.9 versus 1.7 months, respectively. Subgroup analysis based on KRAS mutational status showed a therapeutic benefit in OS in favor of REGORAFENIB over placebo for patients with KRAS wild-type tumors whereas a lower efficacy was reported in patients with KRAS mutant tumors. The benefit in PFS favoring REGORAFENIB over placebo was observed regardless of KRAS mutational status [111].

According to preliminary results of a phase Ib/II trial (NCT03829410), onvansertib (PLK1 inhibitor) in combination with BEVACIZUMAB and FOLFIRI showed promising efficacy as a second line treatment for KRAS mutant metastatic CRC. The ORR was 36% (5/14), and DCR was 86% (12 /14), 76% of patients had durable responses (longer than 6 months), median PFS has not been reached [112]. FDA granted fast track designation to onvansertib for the second-line treatment of KRAS-mutated CRC.
In a clinical trial, patients with RAS (KRAS and NRAS) mutant colorectal cancer with unresectable liver metastases received mFOLFOX6 plus bevacizumab (arm A) or mFOLFOX6 alone (arm B) as first-line treatment. Patients in arm A had significantly better objective response rates (54.5% vs. 36.7%), median progression-free survival (9.5 vs. 5.6 months) and median overall survival (25.7 vs. 20.5 months) compared with those in arm B [113].

In diabetic colorectal cancer patients, metformin use was associated with improved outcome in the KRAS mutant subgroup, but not in the KRAS wild-type subgroup [95].

In a phase II clinical trial, adavosertib (WEE1 inhibitor) significantly improved PFS compared with active monitoring (median 3.61 vs. 1.87 months) in patients with TP53- and RAS-mutant metastatic colorectal cancer [114].

BIOMEDICAL INTERPRETATION

In a phase I/II clinical trial patients with metastatic CRC received selinexor and pembrolizumab as second line therapy. Among patients with RAS mutations (n=9), 6 had stable disease, while 3 patients had disease progression. In patients with RAS wild-type tumors, stable disease was observed in 1 case, and 8 patients had progressive disease. Median PFS was 120 days for patients with RAS mutant CRC and 41 days for those with RAS wild-type CRC [115].

mTOR inhibitor resistance in KRAS mutant tumors

According to preclinical and clinical data, KRAS mutant tumors are resistant to everolimus or temsirolimus mTOR inhibitors [116,98]. However, preclinical data suggest that mTOR inhibitors combined with chemotherapy might be effective in KRAS mutant cancer [117]. MEK inhibitioin combined with mTOR inhibition has been shown to be effective in KRAS mutant preclinical models with PI3K pathway activation [118].

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

Based on preclinical and clinical evidence, decreased efficacy of or resistance to MEK inhibitors may arise due to various genetic alterations and mechanisms.

STAT3 [119], or AKT activation, activating PIK3CA mutation [120,121], amplification or overexpression of BRAF/KRAS harboring activating mutations [122], FBXO42 loss with NRAS mutation [123] can be mentioned in a negative association with the efficacy of MEK inhibitors.

Further alterations may also cause resistance to the following compounds or reduce their efficacy.

Resistance to or decreased efficacy of SELUMETINIB might emerge due to MED12 loss of function [124]; TGFB/TGFBR2 [124], PDGFRB [125], ERBB3 [79], DDX43 [122] overexpression, or coordinated overexpression of genes in the Wnt signaling pathway [126].

YAP1 [127,128] overexpression or activation may cause decreased efficacy or resistance to TRAMETINIB treatment. Concomitant PTEN and NF1 loss-of-function may also confer resistance to trametinib treatment or combined MEK + EGFR inhibition [129].

The efficacy of MIRDAMETINIB may be reduced by NF1 mutation [130].

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

Resistance to CDK4/6 inhibitors (palbociclib, abemaciclib, ribociclib, lerociclib) may arise through diverse direct or indirect molecular mechanisms [131,132].

Various cell cycle-specific mechanisms were reported to promote resistance to CDK4/6 inhibitors by the deregulation of the cyclin D-CDK4/6–INK4–RB pathway, the key regulator of G1-S transition. These alterations include loss of RB function due to mutations or regulatory suppression, amplification of CDKN2A (p16) alone or with the concurrent loss of RB, amplification or overexpression of CDK2/4/6/7, CCNE1 (cyclin E) and E2F. Other cell cycle related alterations that also might contribute to resistance are the overexpression of MDM2 and WEE1, and HDAC activation [131-133].

Cell cycle-nonspecific mechanisms have also been identified to be involved in resistance to CDK4/6 inhibitors in breast cancer models, such as the activation of the FGFR or PI3K/AKT/mTOR pathways, or the loss of ER or PR expression [131].

According to preclinical evidences, resistance mechanisms can be categorized into irreversible (e.g. mutations of RB), and reversible (gain of cyclin E, overexpression of CDK2/4/6) types. Reversible resistance mechanisms were shown to be amenable to a drug holiday, leading to re-sensitisation to CDK4/6 inhibitors in vitro and in vivo [133,134].

Combinations of CDK4/6 inhibitors with other targeted compounds were suggested to enhance the durability of response or may overcome resistance [135].

In urothelial and pancreatic cancer cell lines, combinations of CDK4/6 inhibitors with inhibitors targeting PI3K-AKT and RAS/MAPK exhibited synergism [136-138], and could reverse acquired resistance [137]. In another study, MAPK induction was identified in preclinical models with acquired resistance to palbociclib, that sensitized cells to MEK inhibition [139]. In KRAS-mutant colorectal and non-small cell lung cancer models, the combination of MEK and CDK4/6 inhibitors synergistically inhibited cancer cell growth in vitro and caused tumor regression in vivo [81,140]. The combination of CDK4/6 and MEK inhibitors are currently tested in several clinical trials.

PIK3CA-E545K

This variation is mentioned in the ClinVar database as a pathogenic/likely pathogenic alteration, and in the LOVD database as a dominant pathogenic alteration. In the scientific literature it is described as a driver mutation [141-143]. The mutant protein has increased kinase activity, it is oncogenic [144].

In a study, PET/CT scans of 52 cervical cancer patients (46 PIK3CA wild-type, 6 PIK3CA E542K and E545K mutant) were analyzed. The level of glucose metabolism in patients with mutant PIK3CA was dramatically higher than that of patients with wild-type PIK3CA. Enhanced proliferation and glucose metabolism was further confirmed in cervical cancer cells and xenograft models with mutant PIK3CA [145].

BIOMEDICAL INTERPRETATION

In a preclinical study, alpelisib inhibited cell proliferation, migration, and invasion of lung squamous cell carcinoma cells harboring the PIK3CA-E545K mutation [146].

PIK3CA mutant gene - targets

PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) as part of the PI3K-Akt signaling pathway, plays an important role in cell proliferation and cell survival, also during tumorigenesis.

Because of the driver mutation detected in the PIK3CA oncogene, the tumor is associated with response to PI3K/AKT/mTOR signaling pathway inhibitors [147-149].

ALPELISIB (FDA and EMA) and COPANLISIB (FDA) are PIK3CA inhibitors in clinical use. EVEROLIMUS is an approved mTOR inhibitor to treat ER+, HER2- advanced breast carcinoma patients. Other mTOR inhibitors in clinical use are TEMSIROLIMUS, METFORMIN and SIROLIMUS.

TASELISIB, an experimental PIK3CA inhibitor, resulted in 36% response rate among PIK3CA mutant solid tumor patients in a phase I study, while patients without PIK3CA mutation had no tumor response [150]. In a larger phase I study among heavily pretreated PIK3CA mutant solid tumor patients, taselisib reached 8,9% response rate [151]. ALPELISIB reached 6% response rate and 58.2% disease control rate among heavily pretreated PIK3CA mutant or amplified solid tumor patients in a phase I study [152].

According to a preclinical study, oral squamous cell carcinoma cell lines harboring PIK3CA mutant gene showed resistance to PALBOCICLIB alone, but demonstrated increased sensitivity to it when combined with a PI3K inhibitor, PF-04691502, and the combination treatment inhibited proliferation in the cell culture [153].

PIK3CA mutant colorectal cancer

Among patients with PIK3CA mutant colorectal cancers (CRCs), regular use of acetylsalicylic acid (Aspirin) after diagnosis was associated with higher colorectal cancer-specific survival (hazard ratio (HR): 0.18) and overall survival (OS) (HR: 0.54). Regular use of acetylsalicylic acid after diagnosis was associated with longer survival among patients with PIK3CA mutated colorectal cancer, but not among patients with wild-type PIK3CA. These findings suggest that the PIK3CA mutation in CRC may serve as a predictive molecular biomarker for adjuvant acetylsalicylic acid therapy [154]. Preclinical experiments also confirm that aspirin induces greater loss of cell viability in PIK3CA mutant cells than in PIK3CA wild-type cells [155].

Multiple publications found that EGFR inhibitors cetuximab, and panitumumab had lower efficacy in PIK3CA mutant CRC patients and cell lines compared to the PIK3CA wild-type groups [156-159]. According to preclinical data, cetuximab combined with AKT or mTOR inhibitors is effective in PIK3CA mutant CRC models [160].

35 CRC patients participated in the phase I study testing alpelisib, a PIK3CA inhibitor, among PIK3CA mutant of amplified solid cancer patients. 2 patients has tumor response and 10 had stable disease (response rate: 5.7%, disease control rate: 34.3%) [152].

PIK3CA mutations might confer resistance to first-line chemotherapy in CRC [161].

Concurrent mutations in KRAS and PIK3CA

KRAS and PIK3CA mutations may cause resistance to each other's targeted inhibition. According to preclinical results, PIK3CA mutant cells were sensitive to the mTOR inhibitor everolimus, however, cells harboring both KRAS and PIK3CA mutations did not respond to the same treatment. Consistently, in a cohort of metastatic cancer patients, the presence of KRAS mutations was associated with lack of benefit after everolimus therapy [98].

Conversely, activating mutations of PIK3CA reduced the sensitivity to MEK inhibition in KRAS mutant cells. Combined targeted inhibition was required to induce an apoptotic response in cells harboring both KRAS and PIK3CA mutations [118]. In another study, PI3K/MEK co-targeted inhibition was synergistic in double mutant NSCLC cell lines [162].

However, in a phase Ib clinical trial, trametinib + everolimus combination therapy resulted in frequent treatment-related adverse events. The study was unable to identify a recommended phase II dose and schedule of trametinib in combination with everolimus that provided an acceptable tolerability and adequate drug exposure [163].

NRAS-Q61L

According to the ClinVar database, this mutation is listed as a pathogenic/likely pathogenic. It is described in the scientific literature as a driver mutation [164,165].

A preclinical study using lung cancer cells showed that the NRAS mutant status, and also the NRAS-Q61L mutation detected in a patient sample were sensitive to MEK inhibitors, including trametinib and selumetinib, while resistant to EGFR inhibition [166]. According to an other preclinical study the NRAS-Q61L mutation causes constitutive activation of the PI3K/AKT and MAPK pathway that is independent of RET signaling, therefore the mutation causes resistance againts RET inhibition [167]

In a phosphoproteomic preclinical study, NRAS-Q61L expressing cells showed pronounced MAPK signaling, and CK2alpha levels, and were more sensitive to CK2alpha inhibition with silmitasertib than NRAS-G12V variant bearing cells [168].

BIOMEDICAL INTERPRETATION

NRAS mutant gene - targets

MEK (MAP2K1) [169,170], PLK1 [171], ERK1/2 (MAPK3, MAPK1) [75], and mTOR [172] inhibitors are in positive association with NRAS driver mutations. According to preclinical data, the combination of MEK + CDK [173], MEK + mTOR [85,172,174], or MEK + EGFR [175] inhibitors might also be effective. In the NCI-MATCH trial, single-agent binimetinib (MEK inhibitor) did not demonstrate promising efficacy in NRAS-mutated solid tumors excluding melanoma [176].

MEK inhibitors in clinical use are TRAMETINIB, COBIMETINIB and BINIMETINIB, registered in BRAF-V600 mutant melanoma indication. SELUMETINIB (MEK inhibitor) is approved in neurofibromatosis type I indication. EVEROLIMUS, TEMSIROLIMUS, METFORMIN, and SIROLIMUS are mTOR inhibitors in clinical use.

A number of recent preclinical studies have revealed cross-talk between NRAS-activated signaling and DNA damage response, which has important therapeutic implications. The combination of MEK and PARP inhibition had synergistic effect in several NRAS mutant cell lines [86]. The authors concluded that PARPi and MEKi each block adaptive responses induced by the other drug and thus induce a synthetic lethal interaction. According to these experiments, activating NRAS mutation can result in resistance to PARPi monotherapy. However, in other model systems with KRAS mutation, this result was not confirmed [87]. According to a study NRAS mutant melanoma patients had lower response rates to anti-PD-1 monotherapy compared to patients bearing wild type NRAS [177].

NRAS mutant colorectal cancer

NRAS mutant tumors are usually resistant to EGFR inhibitors, included CETUXIMAB and PANITUMUMAB, which are registered in colorectal cancer (CRC) [178,179].

According to preclinical experiments MEK (NRAS indirect target) inhibitors AS703026 and selumetinib (AZD6244) inhibit the growth of cetuximab-resistant CRC cell lines and tumor xenografts [106]. In a phase II study MEK-inhibitor CI-1040 was well tolerated, but did not show any antitumor effect [107], however, the efficacy of selumetinib (MEK1/2 inhibitor) proved to have similar effects to capecitabine in patients with CRC [108].

Three members of the RAS family - HRAS, KRAS and NRAS - are found to be activated by mutation in human tumors. These three genes have 85% amino acid sequence identity and they function in very similar ways [180].

In a phase II study 15 colorectal cancer patients harboring KRAS mutation were treated with palbociclib. No tumor response was observed, but 5 patients had stable disease [181].

In a phase I/II study recruiting metastatic, KRAS mutant CRC patients second or third line SORAFENIB (a multi-tyrosine kinase inhibitor, which is not yet approved in CRC) therapy combined with irinotecan resulted in the median progression-free survival (PFS) to be 3.7 months and the overall survival (OS) 8.0 months [110].

The clinical efficacy and safety of REGORAFENIB have been evaluated in a randomized, double-blind, placebo-controlled phase III study in patients with metastatic CRC who have progressed after failure of standard therapy. The median OS was 6.4 months in the REGORAFENIB arm compared to 5.0 months in the placebo arm. The median PFS was 1.9 versus 1.7 months, respectively. Subgroup analysis based on KRAS mutational status showed a therapeutic benefit in OS in favor of REGORAFENIB over placebo for patients with KRAS wild-type tumors whereas a lower efficacy was reported in patients with KRAS mutant tumors. The benefit in PFS favoring REGORAFENIB over placebo was observed regardless of KRAS mutational status [182].

In a clinical trial, patients with RAS (KRAS and NRAS) mutant colorectal cancer with unresectable liver metastases received mFOLFOX6 plus bevacizumab (arm A) or mFOLFOX6 alone (arm B) as first-line treatment. Patients in arm A had significantly better objective response rates (54.5% vs. 36.7%), median progression-free survival (9.5 vs. 5.6 months) and median overall survival (25.7 vs. 20.5 months) compared with those in arm B [113].

SMAD4-R361C

According to the ClinVar, LOVD databases, and the scientific literature, it is a pathogenic variant associated with cancer [183], resulting in an unstable protein *in vivo* [184]. SMAD4 is a tumor suppressor gene that regulates the TGF-beta signaling pathway [185], therefore its loss-of-function mutations can be considered as drivers.

SMAD4 mutant gene - targets

SMAD4 is a tumor suppressor gene [183-185].

According to a preclinical evidence, loss of SMAD4 might underlie the functional shift of TGF-beta from a tumor suppressor to a tumor promoter in colorectal cancer cells, by activation of SMAD-independent oncogenic pathways. Inhibitors of TGF-beta signaling are therefore in positive association with SMAD4 loss [186].

Based on the scientific literature, SMAD4 loss can cause resistance to 5-FU based chemotherapy regimens by activating the Akt pathway, therefore inhibitors of Akt signaling pathway may be sensitizing to 5-FU therapy [187,188].

BIOMEDICAL INTERPRETATION

Mutations of SMAD4 gene has been associated with resistance to EGFR inhibitors [189]. In an APC and SMAD4-deficient CRC model, simultaneous inhibition of mTOR and EGFR/MEK showed marked antitumor activity [190].
Metformin treatment significantly improved clinical outcomes and survival in patients with SMAD4-deficient PDAC (pancreatic ductal adenocarcinoma) but not in patients with SMAD4-normal PDAC, which results was also supported by *in vitro* and *in vivo* experiments [191].

EZR-V457*
This variant is not listed in the ClinVar database. Due to the premature STOP codon (nonsense mutation) in the EZR gene, a variant encoding a substantially shorter protein version is generated, thus loss of function is highly likely.

Targeted therapies registered in colorectal cancer indication regardless of the molecular profile
Registered targeted drugs in the patient's tumor type are the VEGF inhibitor BEVACIZUMAB, RAMUCIRUMAB and AFLIBERCEPT, and the multi-kinase inhibitor REGORAFENIB. The FDA granted fast track status to the multi-VEGFR inhibitor FRUQUINTINIB.
In a randomized, double-blind study of RAMUCIRUMAB in colorectal cancer (CRC) patients overall survival (OS) was statistically significantly improved in patients receiving RAMUCIRUMAB + FOLFIRI compared with those receiving placebo + FOLFIRI. There was an increase in median survival of 1.6 months in favor of the RAMUCIRUMAB + FOLFIRI arm: 13.3 months in the RAMUCIRUMAB + FOLFIRI arm and 11.7 months in the placebo + FOLFIRI arm. There was an increase in median progression-free survival (PFS) of 1.2 months in favor of the RAMUCIRUMAB + FOLFIRI arm: 5.7 months in the RAMUCIRUMAB + FOLFIRI arm and 4.5 months in the placebo + FOLFIRI arm [192].
AFLIBERCEPT was examined in a randomized, double-blind, placebo-controlled study in patients with metastatic CRC. The median OS was 12.06 versus 13.5 months, while the median PFS was 4.67 versus 6.9 months in the placebo + FOLFIRI versus AFLIBERCEPT + FOLFIRI arms, respectively [193].
The clinical efficacy and safety of REGORAFENIB have been evaluated in a randomized, double-blind, placebo-controlled phase III study in patients with metastatic CRC who have progressed after failure of standard therapy. The median OS was 6.4 months in the REGORAFENIB arm compared to 5.0 months in the placebo arm. The median PFS was 1.9 versus 1.7 months, respectively. Subgroup analysis based on KRAS mutational status showed a therapeutic benefit in OS in favor of REGORAFENIB over placebo for patients with KRAS wild-type tumors whereas a lower efficacy was reported in patients with KRAS mutant tumors. The benefit in PFS favoring REGORAFENIB over placebo was observed regardless of KRAS mutational status [194]. In another phase III clinical trial previously treated patients with metastatic CRC also received regorafenib monotherapy or placebo. After a median follow-up of 7.4 months, OS was significantly better with regorafenib (8.8 months) than it was with placebo (6.3 months) [195].
In a phase III clinical trial fruquintinib (VEGFR1/2/3) treatment significantly improved PFS and OS compared to placebo (3.7 vs 1.8 months; 9.3 vs 6.6 months, respectively) in metastatic CRC patients [196].
Molecular alterations and mechanisms associated with resistance / reduced efficacy in case of angiogenesis inhibitors
Based on preclinical and clinical evidence, decreased efficacy of or resistance to angiogenesis inhibitors may arise due to various genetic alterations and mechanisms.
Amplification or overexpression of angiogenic and lymphangiogenic mediators such as FGF1/2, VEGF, PDGF, PIGF, EFNA1/2, IL8, ANGPT1/2, EGF, G-CSF, HGF, IGF1, SDF-1, TGF can be mentioned in a negative association with the efficacy of angiogenesis inhibitors [197,198].

Molecular alterations in general that may also cause resistance to each antiangiogenic compound or reduce their efficacy include the following growth factor receptors, such as VEGFR, FGFR, EGFR, PDGFR, IGF1R, MET, and alterations that activate their downstream signaling pathways, such as PI3K/AKT/mTOR, RAS/RAF/MEK/ERK, JAK/STAT, as well as activation of the following genes or signaling pathways: AXL, EPHA2, HIF-1a /2a, JNK, SRC, NF-kB, NOTCH1, TGF-a/b, BCLAF1, CCR2, CCR7, FOXF1, MDM2, NRF2, PIN1, POLR1D, PSMD10, RIT1, TBX5, XPO1, YAP, YB1, and PD-1/PD-L1 overexpression. Furthermore, PTEN inactivation and DUSP6, FBXW7, KEAP1, MED12, IFNG, IFNG, IFNGR, PTPRD, PTPRT loss-of-function, as well as certain polymorphisms in the ABCB1, CYP3A5, IL8, PXR genes, or also ABCB1, CYP3A4, MDR1 overexpression may reduce the efficacy of certain angiogenesis inhibitors [199,200]. In the report, alterations associated with reduced efficacy are calculated with a negative score in the aggregated evidence level (AEL) of each antiangiogenic compound.

According to a preclinical study, loss of TP53 function may result in reduced efficacy of VEGFR2 inhibition [201]. However, conflicting results were obtained in several clinical trials, in which TP53 mutant status (vs. wild type) associated with longer survival in case of bevacizumab- or pazopanib-containing treatments [202-204]. In two other trials no significant association was found between bevacizumab- or ramucirumab-containing therapies and TP53 expression or mutant status [205,206].

TAS-102 in colorectal cancer

BIOMEDICAL INTERPRETATION

TAS-102 (Lonsurf, trifluridine / tipiracil) is approved to treat metastatic colorectal cancer (CRC) patients after other therapies have failed. In randomized studies TAS-102 reached 7.1 months median overall survival (OS). The median OS was 5.3 months in the placebo arm. Survival benefit was observed both in KRAS mutant and KRAS wild-type subgroups [207].

In a phase III trial patients with previously treated metastatic CRC were treated with TAS-102 monotherapy or placebo. Median OS proved to be significantly longer in the TAS-102 than in the placebo arm (7.8 months vs. 7.1 months, respectively) [208].

In a phase II study the median OS was 9.0 months in the TAS-102 arm and 6.6 months in the placebo arm [209].

In a phase I/II study, TAS-102 plus bevacizumab prolonged progression-free survival (PFS) and helped achieve higher 16-week PFS rate compared with TAS-102 monotherapy (median PFS: 3.7 months vs. 2.2 months, PFS rate at 16 weeks: 46.6% vs. 33.9%) in patients with heavily pretreated metastatic CRC with manageable toxicities [210]. According to a retrospective analysis, treatment with BEVACIZUMAB in combination with TAS-102 is significantly associated with longer median OS (median OS: 14.4 months with bevacizumab + TAS-102 vs. 4.5 months with TAS-102) in patients with metastatic CRC refractory to standard therapies [211].

According to a meta-analysis TAS-102 plus bevacizumab provides benefits over TAS-102 in patients with refractory mCRC. The DCR was 64% in the TAS-102 plus bevacizumab group and 43% in the TAS102 group. Median PFS and median OS were also improved in patients receiving TAS-102 plus bevacizumab (median PFS: 4.2 months, median OS: 9.8 months) compared to TAS-102 alone (median PFS: 2.6 months, median OS: 8.1 months) [212].

Statins in colorectal cancer

Statins are cholesterol-lowering agents, inhibiting 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMGCR), the rate-limiting enzyme of the mevalonate pathway. Besides the lipid-lowering effects, statins have been reported to have suppressive effects on tumor development and progression. However, the molecular mechanism behind their antitumor activity has not yet been revealed. According to retrospective analyses, statin uses are associated with reduced mortality for colorectal cancer patients [213,214]. According to a meta-analysis, statin use was associated with a 20% lower risk of colorectal cancer in non-IBD patients [215].

PDE5 inhibitors in colorectal cancer

In a study, the use of PDE5 inhibitors was associated with a decreased risk of colorectal cancer specific mortality as well as a decreased risk of metastasis [216].

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with the patients tumors molecular profile, rendering an automatically calculated score, the Aggregated Evidence Level (AEL). The AEL of a particular molecularly targeted agent is influenced by the aggregated AEL of drivers and targets a treatment is associated with, as well as the AEL of the associations between the treatment and these drivers and targets. The AEL of treatments may change if used in combinations, due to possible synergism at molecular level. The 2022 version of the system uses evidence-based 32,000+ driver-target-compound interactions in its computational model.

This report can be used and clinically interpreted only by physicians or other qualified healthcare professionals. It provides information about the AEL scores of drivers, targets and treatment options associated with the tumor type and molecular profile provided as an input for this analysis. The output scores depend on the type of molecular diagnostic assay used for the analysis. The physician may consider or disregard the information to choose between treatment options provided by this report. The drugs indicated in this report may or may not be registered and/or reimbursed in the specific tumor type in the country in which this report is used. The scores indicated in this report do not guarantee efficacy or lack of efficacy of any treatment. Genomate Health Inc. does not take responsibility for the content of referenced pieces of evidence, nor for any decision made by physicians.

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