FOUNDATIONONE® LIQUID CDx

Beispielbericht

Lungenkrebs

Das aktuelle Bestellformular zum Herunterladen finden Sie auf der Website des Universitätsspitals Zürich unter der Rubrik «Informationen zur Bestellung FoundationOne®».

https://go.roche.com/USZ-molekulares-tumorprofiling

USZ Universitäts Spital Zürich

FOUNDATION MEDICINE®

Roche

FOUNDATIONONE®LIQUID CDx

PATIENT XXXX

TUMOR TYPE Lung adenocarcinoma

COUNTRY CODE CH

REPORT DATE XXXX

ORDERED TEST # XXXX

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

PATIENT

DISEASE Lung adenocarcinoma
NAME XXXX
DATE OF BIRTH XXX
SEX Male
MEDICAL RECORD # XXXX

PHYSICIAN

ORDERING PHYSICIAN Zoche, Martin
MEDICAL FACILITY Universitätsspital Zürich Institut für Pathologie und Molekularpathologie
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID XXXX
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN ID XXXX
SPECIMEN TYPE Blood
DATE OF COLLECTION XXXX
SPECIMEN RECEIVED XXXX

Biomarker Findings

Blood Tumor Mutational Burden - 14 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

ERBB2 L755F
KRAS G12C
ARID1A G324fs*34
DNMT3A W440*
TP53 P72fs*76, K382fs*40

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Atezolizumab** (p. 12), **Cemiplimab** (p. 13), **Durvalumab** (p. 14), **Nivolumab** (p. 15), **Pembrolizumab** (p. 16), **Ado-trastuzumab emtansine** (p. 18), **Fam-trastuzumab deruxtecan** (p. 19), **Sotorasib** (p. 17)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 21)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***KRAS*** **G12C** (p. 7)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***DNMT3A*** W440* (p. 9)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Blood Tumor Mutational Burden - 14 Muts/Mb	Atezolizumab	1	Avelumab
	Cemiplimab	1	
	Durvalumab	1	
	Nivolumab	1	
	Pembrolizumab	1	
	Dostarlimab		
10 Trials see p. 21			
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**		
Tumor Fraction - Elevated Tumor Fraction Not Detected	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).**		

GENOMIC FINDINGS	VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
ERBB2 - L755F	0.24%	Afatinib Dacomitinib	Ado-trastuzumab emtansine 2A Fam-trastuzumab deruxtecan 2A Neratinib Trastuzumab Trastuzumab + Pertuzumab
10 Trials see p. 25			
KRAS - G12C	4.2%	Sotorasib 2A	None
10 Trials see p. 27			
ARID1A - G324fs*34	1.6%	None	None
7 Trials see p. 23			

2A *NCCN category*

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

DNMT3A - W440* ..... p. 9

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

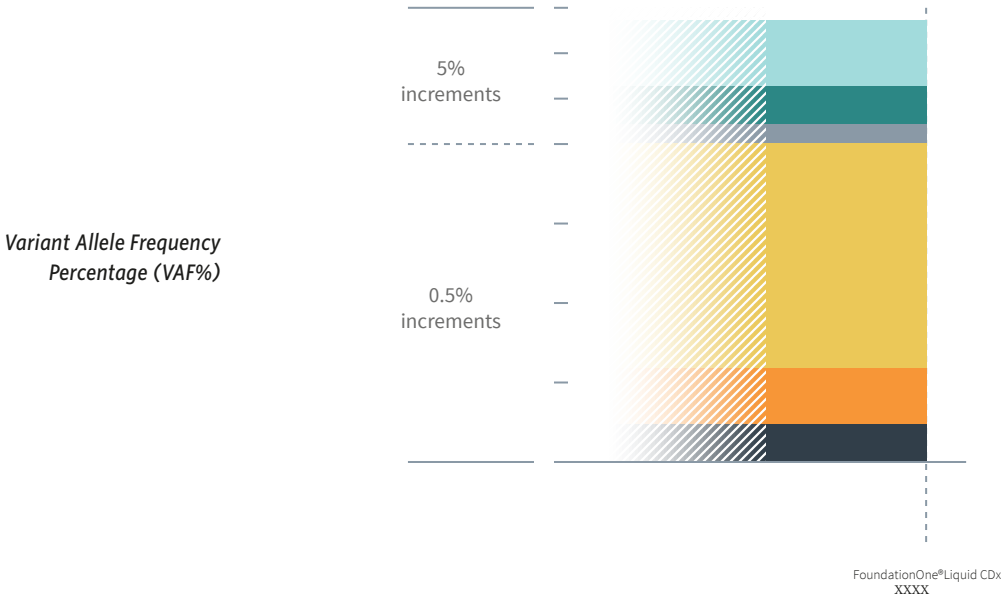
For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

DNMT3A - W440* ..... p. 9

TP53 - P72fs*76, K382fs*40 ..... p. 10

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and/or exhaustive. Neither the therapies nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies. Therapies contained in this report may have been approved by the US FDA or other national authorities; however, they might not have been approved in your respective country. In the appropriate clinical context, germline testing of *APC*, *ATM*, *BAP1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FH*, *FLCN*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF1*, *NF2*, *PALB2*, *PMS2*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.



HISTORIC PATIENT FINDINGS		ORD-1267677-01 VAF%
Blood Tumor Mutational Burden		14 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Elevated Tumor Fraction Not Detected
ERBB2	● L755F	0.24%
KRAS	● G12C	4.2%
ARID1A	● G324fs*34	1.6%
DNMT3A	● W440*	7.2%
TP53	● P72fs*76	2.0%
	● K382fs*40	0.35%

NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx, FoundationOne®Liquid, FoundationOne®, or FoundationOne®CDx tests. Up to five previous tests may be shown.

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

As new scientific information becomes available, alterations that had previously been listed as Variants of Unknown Significance (VUS) may become reportable.

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

BIOMARKER

Blood Tumor Mutational Burden

RESULT

14 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb[1]. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[4].

FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb (range 1.9-52.5 Muts/Mb)[3]. Retrospective analysis of the Phase 3 OAK and Phase 2 POPLAR trials for patients with advanced or metastatic non-small cell lung cancer (NSCLC) reported that bTMB ≥7 Muts/Mb was associated with shorter PFS (2.8 vs. 4.2 months) and OS (7.4 vs. 11.9 months) compared with bTMB <7 Muts/Mb for patients treated with docetaxel[5]. In one study of advanced NSCLC in China, bTMB ≥6 Muts/Mb was associated with decreased PFS (10 vs. 18 months) and OS (11 vs. 25 months) compared with bTMB <6 Muts/Mb for patients treated with platinum-based chemotherapy[6]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[7]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[8]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[8-9].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[10-11] and cigarette smoke in lung cancer[12-13], treatment with temozolomide-based chemotherapy in glioma[14-15], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[16-20], and microsatellite instability (MSI)[16,19-20]. This sample harbors a bTMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-3].

BIOMARKER

Tumor Fraction

RESULT

Elevated Tumor Fraction Not Detected

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. However, if elevated tumor fraction is not detected, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[21-26].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[27]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[28], Ewing sarcoma and osteosarcoma[29], prostate cancer[24], breast cancer[30], leiomyosarcoma[31], esophageal cancer[32], colorectal cancer[33], and gastrointestinal cancer[34].

FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[35], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[36-37].

GENE

ERBB2

ALTERATION
L755F

TRANSCRIPT ID
NM_004448

CODING SEQUENCE EFFECT
2265G>C

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[38-43], pertuzumab in combination with trastuzumab[40,44-46], and zanidatamab (ZW25)[47], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[48] and fam-trastuzumab deruxtecan[49], HER2 kinase inhibitors such as tucatinib[50-53], and dual EGFR/HER2 kinase inhibitors such as lapatinib[54-62], afatinib[43,63-72], neratinib[73-76], dacomitinib[77], and pyrotinib[78-79] . Early clinical studies aimed at preventing or overcoming resistance to anti-HER2 therapies are underway, including agents targeting the PI3K-AKT pathway or HSP90[80-81]. A Phase 1 basket trial of pyrotinib demonstrated an ORR of 17.4% (4/23) for ERBB2-altered solid tumors, with PRs for 1 patient each with HER2-positive salivary, biliary, ovarian, or endometrial cancers[82]. Clinical data in solid tumors other than NSCLC and extra-mammary Pagets disease of the skin are limited; a Phase 2 study of afatinib for patients with solid tumors and ERBB2 activating mutations reported an ORR of 2.7% and a 6-month progression-free survival rate of 11%, missing its primary endpoint[83]. Two Phase 2 trials of the EGFR/HER2 inhibitor pyrotinib for patients with previously treated NSCLC and ERBB2 exon 20 mutations reported ORRs of 32–53% and median PFS of 6–7 months, with responses observed across a variety of exon 20 insertions and point mutations, including L755P, G776C, and V777L[84].

— Potential Resistance —

On the basis of clinical and preclinical support, the ERBB2 L755S mutation may predict resistance to trastuzumab[85-88]; limited clinical[89] and extensive preclinical evidence suggests that this mutation may also confer resistance to lapatinib[86-87,90-94]. Combination treatment with lapatinib and trastuzumab did not lead to a pathologic CR in a patient with breast cancer with the ERBB2 L755S mutation[95]. However, it is unclear if ERBB2 L755S confers reduced sensitivity to trastuzumab in combination with other therapies, such as tucatinib, lapatinib, and pertuzumab. Other ERBB2 L755 mutations are less characterized, but limited preclinical data demonstrate that L755P also confers reduced sensitivity to lapatinib[91,96].

FREQUENCY & PROGNOSIS

ERBB2 mutations have been reported in 2.2–4.2% of lung adenocarcinomas and lung squamous cell carcinomas across several genomic studies[97-102]. HER2 overexpression has been documented in 11-32% of NSCLC cases, and is generally reported more frequently in non-squamous histologies[103-104]. Expression of HER2 has generally been associated with poor prognosis in NSCLC in several studies[105-109].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. Missense mutations of the ERBB2 kinase domain at L755, as seen here, are predicted to be activating based on the functional characterization of L755S and L755P[88,90-91]. Clinical[85-86] and preclinical[86-88] evidence suggests that L755S predicts resistance to trastuzumab. ERBB2 L755S may also confer resistance to lapatinib, on the basis of limited clinical[89] and extensive preclinical[86-87,90-94] evidence. Preclinical studies suggest that L755S mutations are sensitive to irreversible EGFR/HER2 inhibitors such as afatinib[87-88,94] and neratinib[86-88,92-94]. Patients with breast cancer and ERBB2 L755S treated with neratinib achieved 1 CR, 3 PRs, and 1 SD[73-74]; however, 4 PDs were also reported[74].

GENE
KRAS

ALTERATION
G12C

TRANSCRIPT ID
NM_004985

CODING SEQUENCE EFFECT
34G>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

In a Phase 1 study evaluating the MEK-pan-RAF dual inhibitor CH5126766, 6 patients harboring KRAS mutations experienced PRs, including 3 with non-small cell lung cancer (NCSLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma[110]. Another Phase 1 study of CH5126766 combined with the FAK inhibitor defactinib reported 4 PRs in KRAS-mutated LGSOC[111]. KRAS G12C may predict sensitivity to G12C-targeted inhibitors such as sotorasib[112-114] and adagrasib[115]. The Phase 1 CodeBreaK 100 trial of sotorasib in G12C-mutated solid tumors observed clinical benefit for patients with non-small cell lung cancer (NSCLC) and colorectal cancer (CRC), with additional responses observed in several other tumor types[114]; patients with CRC achieved a relatively low ORR (7.1% [3/42]) but demonstrated a high DCR of 74% (31/42) with mPFS of 4 months[114]. In the Phase 1/2 KRYSTAL-1 trial, treatment with single-agent adagrasib elicited a 45% (23/51) ORR and a 96% (49/51) DCR for patients with G12C-mutated NSCLC[116]. Responses to single-agent adagrasib were also reported for patients with other types of G12C-mutated tumors, including CRC with an ORR of 17% (3/18) and individual responses reported for patients with endometrial cancer, pancreatic cancer, ovarian cancer, and cholangiocarcinoma[117]. Preclinical data suggests that sotorasib in combination with the EGFR inhibitor cetuximab may lead to more effective suppression of KRAS G12C-mutated CRC tumors[118]. Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[119-120]. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations[121]. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer[122]. Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[123-128]. Multiple clinical studies have reported either low response rates or response rates similar to those of chemotherapy in patients with KRAS-mutated NSCLC receiving MEK inhibitors as a monotherapy[129-131]. In a Phase 3 study, the addition of selumetinib to docetaxel did not significantly improve the PFS or OS of patients with KRAS-mutant NSCLC relative to docetaxel alone[132]. In a Phase 1/1b study evaluating trametinib with either docetaxel or pemetrexed, responses were independent of KRAS mutation status[133]. Combinatorial approaches involving MEK inhibitors and other targeted therapies, including PI3K or EGFR inhibitors, have generally had limited clinical efficacy in patients with NSCLC and have been associated with high toxicity[134-136] despite preclinical evidence supporting the effectiveness of combinatorial strategies involving inhibitors of PI3K[137-138], RAF[139], pan-ERBB[140], or BCL2[141-142]. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors[143-144]. Phase 1 studies of the SOS1 inhibitor BI 1701963 alone or in combination with MEK inhibitors, KRAS G12C inhibitors, or irinotecan are recruiting for patients with solid tumors harboring KRAS mutations[145-146] . However, a Phase 1 combination trial of the MEK inhibitor PD-0325901 with the CDK4/6 inhibitor palbociclib that included 17 patients with KRAS-mutant NSCLC reported 1 PR, >50% SD, and 5 patients with PFS >6 months; clinical benefit was seen among patients with tumors harboring KRAS mutation alone or together with inactivation of TP53 or CDKN2A/B, but not among patients with tumors harboring KRAS mutation and STK11 inactivation[147]. The CDK4/6 inhibitor abemaciclib demonstrated increased activity in KRAS-mutated NSCLC compared to KRAS-wildtype NSCLC (median PFS of 2.8 vs. 1.9 months) in a Phase 1 trial[148] but did not prolong median OS compared to erlotinib (7.4 vs. 7.8 months, HR=0.97), in spite of improved PFS (3.6 vs. 1.9 months, HR=0.58) and ORR (8.9% vs. 2.7%) relative to erlotinib, in a Phase 3 study for patients with platinum-refractory KRAS-mutated advanced NSCLC[149]. Although some studies have suggested that KRAS mutation status may predict a lack of response to the EGFR inhibitors erlotinib and gefitinib in patients with lung cancer, a retrospective study suggests that there is no statistically significant difference in response to EGFR tyrosine kinase inhibitors among KRAS-wildtype and KRAS-mutated patients[150-153]. A study assessing the immune checkpoint inhibitor nivolumab for pretreated patients with KRAS-mutated (n=206) or KRAS-wildtype (n=324) advanced NSCLC observed a similar ORR (20% vs. 17%), median PFS (4 vs. 3 months) and OS (11.2 vs. 10 months) in both cohorts, although the 3-month PFS rate was significantly longer in KRAS-positive than KRAS-negative patients (53% vs. 42%)[154]. Co-occurring KRAS and STK11 alterations are associated with poorer response to immune checkpoint inhibitors for patients with NSCLC. Following anti-PD-1-based regimens, retrospective analyses have reported shorter OS for patients with KRAS- and STK11-mutated tumors than for those whose KRAS-mutated tumors were STK11-wildtype (6.4 vs. 16.1 months, HR=1.99), as well as markedly fewer objective responses for patients with KRAS-/STK11-mutated versus KRAS-/TP53-mutated tumors in the CheckMate-057 (0% [0/6] vs. 57% [4/7])[155] and GEMINI (0% [0/6], vs. 53% [9/17])[156]. Another study observed that patients with NSCLC and KRAS-mutated tumors without STK11 alteration who were treated with second-line immunotherapy experienced similar median PFS (2.8 vs. 2.2 months, HR = 1.64) and numerically longer median OS (7.7 vs. 3.5 months, HR = 2.3; p=0.09) compared to patients harboring mutations in both KRAS and STK11[157]. A Phase 1 study on the combination of the RAF-MEK inhibitor CH5126766 and the FAK inhibitor defactinib in KRAS-mutated non-small cell lung cancer (NSCLC) reported a PR rate of 12% (2/17), including 100% (2/2) of patients with KRAS G12V mutations, and an SD rate of 59% (10/17)[158]. Additional clinical responses for patients with low-grade serous ovarian cancer (PR rate 50% [4/8]) and NSCLC (PR rate 10% [1/10]) with KRAS mutations have been reported[111].

FREQUENCY & PROGNOSIS

KRAS G12C mutations have been identified in 14% of non-small cell lung cancers[159]. Studies have reported KRAS mutations in 10-38% of non-small cell lung cancers (NSCLC), including 27-37% of lung adenocarcinomas[99-100,160-169], 10.5-33% of lung adenosquamous carcinomas[170-172], 22% of lung large cell carcinoma without neuroendocrine features, and 6% of lung large cell neuroendocrine carcinomas[173]. KRAS mutation in lung adenocarcinoma has been correlated with disease progression, poorly differentiated tumors, and

aggressive tumor behavior (NCCN NSCLC Guidelines, v4.2021)[163,169,174]. However, the prognostic value of KRAS mutation in lung adenocarcinoma may differ among ethnic groups and may depend upon the specific allelic variant present[175]. KRAS mutation was associated with shorter PFS (7.0 vs. 8.6 months, p=0.026) and OS (14.2 vs. 21.6 months, p=0.019) with first-line treatment with bevacizumab plus chemotherapy in a retrospective study[176] and a lower major pathological response rate (0% [0/10] vs. 35.5% [11/31]) after neoadjuvant bevacizumab plus chemotherapy followed by adjuvant bevacizumab in a Phase 2 trial[177], relative to those patients lacking KRAS mutation. However, addition of atezolizumab to first-line bevacizumab and chemotherapy improved PFS regardless of KRAS status in the Phase 3 IMpower150 study (HR=0.50 for KRAS mutant vs. 0.47 for KRAS wild-type vs. 0.67 for KRAS unknown)[178]. In one study of 55 patients with lung adenocarcinoma, KRAS mutations, especially in combination with TP53 alterations, correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab, likely as a consequence of association with some immunogenic features such as tumor mutation burden[179].

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[124,180]. Clinical benefit has been reported for patients with KRAS G12C-mutated solid tumors following treatment with G12C inhibitors such as sotorasib[112-114] or adagrasib[115]. However, clinical and preclinical resistance to G12C inhibitors, either by emergence of additional alterations in KRAS or other genes in the RTK/MAPK/PI3K pathway, have also been observed[181-184]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, R68S, and K117N have been characterized as activating and oncogenic[124,185-207].

GENE

ARID1A

ALTERATION
G324fs*34

TRANSCRIPT ID
NM_006015

CODING SEQUENCE EFFECT
969_984delGGGCGCCGGCAAGGGC

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620 and ceralasertib[208]. In a Phase 2 study of ceralasertib in solid tumors, 2 patients with endometrial carcinoma in the cohort with loss of ARID1A expression achieved CRs on ceralasertib monotherapy; at least 1 of these 2 patients carried an inactivating ARID1A mutation. In contrast, no responses were observed for patients with normal ARID1A expression treated with ceralasertib combined with olaparib[209]. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[210]. In a Phase 1 trial, a patient with metastatic colorectal cancer harboring both an ARID1A mutation and ATM loss treated with single-agent M6620 achieved a CR that was ongoing at 29 months[211]. On the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to EZH2 inhibitors[212-213], which are under investigation in clinical trials. Other studies have reported that the loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[214-216]. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy[217]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma[218-219] and to 5-fluorouracil in colorectal cancer cell lines[220].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma, and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, Jan 2022)[221-229]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[217,230-233], CRC[217,234-236], and gastric cancer[217,237-241]. ARID1A protein loss is associated with tumors of poor histological grade for many tumor types, including colorectal cancer (CRC)[234-236], cervical cancer[242-243], gastric cancer[237-241], urothelial carcinoma[244-246], ovarian and endometrial cancers[219,230-233,247-251], breast carcinoma[252-254], and clear cell renal cell carcinoma[255]; ARID1A mutation has been associated with poor outcomes for patients with cholangiocarcinoma[256-259]. However, prognostic data regarding patient survival are often mixed and conflicting.

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[225,240,253,260-265]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[225,238,261-262,266], whereas ARID1A missense mutations are mostly uncharacterized.

GENE

DNMT3A

ALTERATION
W440*

TRANSCRIPT ID
NM_022552

CODING SEQUENCE EFFECT
1320G>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in DNMT3A in solid tumors.

FREQUENCY & PROGNOSIS

DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2021)[222-223]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2021).

FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[267-268]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[269-274]. Alterations such as seen here may disrupt DNMT3A function or expression[275-278].

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[279-284]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[279-280]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[285]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[283,286-287]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE

TP53

ALTERATION
P72fs*76, K382fs*40

TRANSCRIPT ID
NM_000546, NM_000546

CODING SEQUENCE EFFECT
215_216delCC, 1146delA

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[288-291], or p53 gene therapy and immunotherapeutics such as SGT-53[292-296] and ALT-801[297]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[298]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[299]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[300]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[301]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[302]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[303]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[296]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[304]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[305-306]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[307-308]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[99,102,309-314], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)[99-100,102,315]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)[222-223]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[179]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[316].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[317]. Alterations such as seen here may disrupt TP53 function or expression[318-322].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[323-325], including sarcomas[326-327]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[328] to 1:20,000[327]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[329]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[279-284]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[279-280]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[285]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[283,286-287]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Afatinib

Assay findings association

ERBB2
L755F

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) and nonresistant EGFR mutations and for the treatment of patients with metastatic, squamous NSCLC after progression on platinum-based chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Clinical and preclinical data support sensitivity of multiple activating mutations in ERBB2, including A775_G776insYVMA and P780_Y781insGSP, to afatinib[68-72,330-333] . Studies have reported DCRs of 54-70% for patients with ERBB2-mutated NSCLC treated with afatinib, most of whom harbored exon 20 insertions[68-72] .

SUPPORTING DATA

Extensive clinical data have demonstrated that afatinib is effective for patients with EGFR-mutated advanced NSCLC, including exon 19 deletions and L858 mutations, as well as uncommon sensitizing mutations in exons 18 or 20[334-340] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[43,65-69,71-72,330,341-343] . The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma (SCC) reported significantly longer median OS (7.9 vs. 6.8 months, HR=0.81), significantly longer median PFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[339]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[344].

Atezolizumab

Assay findings association

Blood Tumor Mutational Burden
14 Muts/Mb

AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) and urothelial carcinoma, depending on treatment setting. Atezolizumab is also approved in combination with other therapies to treat patients with non-squamous NSCLC lacking EGFR or ALK alterations, small cell lung cancer, hepatocellular carcinoma, and BRAF V600-positive melanoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,345] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

The Phase 2 B-F1RST study prospectively evaluated blood tumor mutational burden (bTMB) as a biomarker of response to first-line atezolizumab in non-small cell lung cancer (NSCLC), reporting improved ORR (29% vs. 4.4%) and a trend toward improved median PFS (mPFS; 5.0 vs. 3.5 months, HR=0.80) and median OS (mOS; 23.9 vs. 13.4 months, HR=0.66) for patients with bTMB ≥16 Muts/Mb compared with bTMB <16 Muts/Mb; improved PFS and OS were seen with increasing bTMB cutoffs[346]. Retrospective analysis of the Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic NSCLC reported improved mOS (11.2 vs. 10.3 months, HR=0.87) and mPFS (5.5 vs. 4.3 months, HR=0.74) compared with chemotherapy for patients with bTMB levels ≥10 Muts/Mb (approximate equivalency ≥9 Muts/Mb as measured by this assay), with greater efficacy observed at higher bTMB cutoffs[347]. Retrospective analysis of the Phase 3 OAK and Phase 2 POPLAR trials for patients with advanced or metastatic NSCLC reported atezolizumab significantly improved OS across bTMB levels compared with docetaxel (p=0.0001); patients with bTMB levels ≥10 Muts/Mb (approximate equivalency ≥9 Muts/Mb as measured by this assay) achieved greater clinical benefit with atezolizumab than those with bTMB <10 Muts/Mb, with greater efficacy observed at higher bTMB cutoffs[1,348] ; patients with two or more mutations in DNA damage response and repair pathway genes (DDR) had an increased bTMB (20 vs. 7 muts/Mb), and reported a superior durable clinical benefit compared with patients without DDR mutations (57% vs. 31%, p=0.003)[349]. In the first-line setting, the Phase 3 IMpower130, IMpower150, and IMpower132 studies have shown that the addition of atezolizumab to chemotherapy-based regimens significantly improves survival for patients with non-squamous NSCLC without EGFR or ALK alterations[178,350-351] . In IMpower130, median PFS (7.0 vs. 5.5 months, HR=0.64) and median OS (18.6 vs. 13.9 months, HR=0.79) were significantly improved with atezolizumab plus nab-paclitaxel and carboplatin relative to chemotherapy alone; benefit was observed irrespective of PD-L1 status[350]. Similarly, IMpower150 reported improved median PFS (8.3 vs. 6.8 months, HR=0.62) and median OS (19.2 vs. 14.7 months, HR=0.78) with the addition of atezolizumab to bevacizumab, paclitaxel, and carboplatin; longer PFS was observed irrespective of PD-L1 status or KRAS mutation[178]. In IMpower132, the addition of atezolizumab to first-line carboplatin or cisplatin with pemetrexed in non-squamous NSCLC increased median PFS (7.6 vs. 5.2 months, HR=0.60) relative to chemotherapy alone[351]. The Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic non-small cell lung cancer (NSCLC) reported improved median OS (mOS; 20.2 vs. 13.1 months, HR=0.59), median PFS (8.1 vs. 5.0 months), and ORR (38% vs. 29%) compared with chemotherapy for patients whose tumors had high PD-L1 expression and no genomic alterations in EGFR or ALK[347]. The Phase 3 OAK trial comparing atezolizumab with docetaxel for patients with previously treated NSCLC reported a significant increase in mOS (13.8 vs. 9.6 months) and duration of response (16.3 vs. 6.2 months)[352], confirming previous Phase 2 trial data[353-354] . In the OAK trial, improved OS was observed for patients, regardless of histology (HR=0.73 for squamous and non-squamous) or PD-L1 status, although greater benefit was reported for patients with high PD-L1 tumor cell (>50%) or tumor-infiltrating immune cell (>10%) expression (HR=0.41) compared with those possessing <1% expression on either cell type (HR=0.75)[352]. Retrospective analyses of the OAK trial also identified clinical benefit for patients receiving atezolizumab and metformin compared with atezolizumab alone (ORR of 25% vs. 13%)[355], and for patients with 2 or more mutations in DNA damage response and repair pathway genes compared with those without (durable clinical benefit rate of 57% vs. 31%, p=0.003)[349]. The Phase 3 IMpower010 study of adjuvant atezolizumab treatment following adjuvant chemotherapy for patients with resected Stage II-IIIA NSCLC reported improved median disease-free survival compared with best supportive care (42.3 vs. 35.3 months, HR=0.79), with the greatest benefit observed for patients with PD-L1 tumor cell expression of ≥1% (not reached vs. 35.3 months, HR=0.66)[356]. In the randomized Phase 2 CITYSCAPE study of treatment-naive advanced NSCLC, the addition of tiragolumab to atezolizumab showed clinically meaningful improvement in ORR (37% [25/67] vs. 21% [14/68]) and PFS (5.6 vs. 3.9 months, HR=0.58), with greater ORR (66% [19/29] vs. 24% [7/29]) and PFS (not reached vs. 4.1 months, HR=0.30) observed for patients with PD-L1 tumor proportion scores (TPS) ≥50%[357].

Cemiplimab

Assay findings association

Blood Tumor Mutational Burden
14 Muts/Mb

AREAS OF THERAPEUTIC USE

Cemiplimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved to treat patients with NSCLC with high PD-L1 expression (TPS ≥ 50%), cutaneous squamous cell carcinoma (CSCC), or basal cell carcinoma (BCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,345] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

The Phase 3 EMPOWER-Lung 1 trial for treatment-naive advanced non-small cell lung cancer (NSCLC) reported that cemiplimab improved median PFS (mPFS, 8.2 vs. 5.7 months, hazard ratio [HR]=0.54), median OS (mOS, not reached vs. 14.2 months, HR=0.57), and ORR (39% vs. 20%) compared with chemotherapy in patients with high PD-L1 expression (TPS ≥ 50%); improved mPFS (6.2 vs. 5.6 months, HR=0.59), mOS (22.1 vs. 14.3 months, HR=0.68), and ORR (37% vs. 21%) were also reported for cemiplimab over chemotherapy in the intention-to-treat population[358]. In a Phase 2 trial of cemiplimab-containing regimens as second-line therapy for NSCLC, cemiplimab combined with ipilimumab elicited a numerically higher ORR (46% [5/11]) compared with high-dose (11% [1/9]) and standard-dose cemiplimab monotherapy (0% [0/8])[359].

Dacomitinib

Assay findings association

ERBB2
L755F

AREAS OF THERAPEUTIC USE

Dacomitinib is a second generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Prospective early-phase single-arm clinical trials report anti-tumor activity of dacomitinib in advanced solid tumors with ERBB2 activating mutations[77,360] , ERBB2 amplification[361-362] , or HER2 overexpression[363].

SUPPORTING DATA

In a Phase 2 study, 3/26 (12%) of patients with ERBB2 exon 20 mutations experienced PRs to dacomitinib treatment; the median PFS was 3 months and median OS was 9 months in this cohort[77]. In ERBB2-amplified NSCLC, response rates of 0/4 (0%)[77] to 1/3 (33%)[362] have been reported, with disease control (PR or SD) achieved in 4/9 (44%) patients total[77,360,362] . A Phase 1 trial of combination dacomitinib and a MEK1/2 inhibitor for patients with KRAS-mutated CRC, NSCLC, or pancreatic cancer reported 20/36 SDs and 16 PDs, however toxicity from this combination prevented long-term treatment in this patient population[364]. A Phase 2 study of dacomitinib in patients with NSCLC who had been previously treated with chemotherapy or erlotinib and were not selected for EGFR mutations reported an ORR of 4.5% (3/66)[362]. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC[365].

Dostarlimab

Assay findings association

Blood Tumor Mutational Burden
14 Muts/Mb

AREAS OF THERAPEUTIC USE

Dostarlimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor response. It is FDA approved to treat patients with mismatch repair deficient recurrent or advanced endometrial cancer or solid tumors. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,345] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In the Phase 1 GARNET trial of dostarlimab, patients with non-small cell lung cancer (NSCLC) experienced an immune-related ORR (irORR) of 27% with 2 CRs[366]. Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[367-369] . In the Phase 1 GARNET trial, single-agent dostarlimab elicited an ORR of 39% (41/106) and an immune-related ORR of 46% (50/110) for patients with non-endometrial dMMR solid tumors[367,370] .

Durvalumab

Assay findings association

Blood Tumor Mutational Burden
14 Muts/Mb

AREAS OF THERAPEUTIC USE

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,345] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

The MYSTIC trial for patients with treatment-naïve, EGFR/ALK-negative metastatic NSCLC reported that a bTMB score ≥20 Muts/Mb (approximately 10 Muts/Mb as measured by this assay) associated with improved survival following either a combination treatment of durvalumab with the CTLA-4 inhibitor tremelimumab, regardless of tumor PD-L1 expression, or following durvalumab monotherapy for patients with tumor cell PD-L1 expression <1%[345]. In the Phase 3 PACIFIC trial for patients with Stage 3 unresectable non-small cell lung cancer (NSCLC) who did not have progression on chemoradiotherapy, durvalumab monotherapy improved PFS versus placebo across PD-L1 expression subgroups; median PFS (mPFS) was 23.9 versus 5.6 months (HR=0.49) for patients with PD-L1 expression ≥1% and 10.7 versus 5.6 months (HR=0.79) for patients with PD-L1 expression <1%. Median OS (mOS) benefit was observed for patients with PD-L1 expression ≥1% (57.4 vs. 29.6 months, HR=0.60), but not for those with PD-L1 expression <1% (33.9 vs. 43.0 months, HR=1.05)[371-372] . In the Phase 3 ARCTIC study for patients with metastatic NSCLC who had progressed on 2 or fewer prior therapies, single-agent durvalumab improved OS (11.7 vs. 6.8 months, HR=0.63) and PFS (3.8 vs. 2.2 months, HR=0.71) versus the investigator's choice of standard of care (SOC) for patients in cohort A (PD-L1 ≥25%)[373]. However, durvalumab plus tremelimumab did not significantly improve OS (11.5 vs. 8.7 months, HR=0.80) or PFS (3.5 vs. 3.5 months, HR=0.77) compared with SOC for patients in cohort B (PD-L1 <25%)[373]. In the Phase 3 MYSTIC trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC and PD-L1 expression ≥25%, neither durvalumab monotherapy nor durvalumab plus tremelimumab improved OS versus chemotherapy (HR=0.76 vs. HR=0.85); however, patients with blood tumor mutational burden (bTMB) ≥20 Muts/Mb showed improved OS for durvalumab plus tremelimumab versus chemotherapy (21.9 vs. 10.0 months, HR=0.49)[374]. In the Phase 3 POSEIDON trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC, the addition of durvalumab and tremelimumab to chemotherapy improved mOS (14.0 vs. 11.7 months, HR=0.77) and mPFS (6.2 vs 4.8 months, HR=0.72) versus chemotherapy[375]. In Phase 2 trials for patients with advanced or relapsed NSCLC, improved ORR[376-377] and OS[376] for durvalumab monotherapy corresponded with increased tumor cell PD-L1 positivity; patients with very high PD-L1 expression (≥90%) had an ORR of 31% (21/68) compared with ORRs of 16% (24/146) for patients with ≥25% and 7.5% (7/93) for patients with <25% PD-L1 positivity[377]. Re-treatment with durvalumab for patients with PD-L1-positive (≥25%) EGFR-negative or ALK-negative advanced NSCLC who had progressed following previous disease control resulted in a PR or SD for 25% (10/40) of patients[378].

Nivolumab

Assay findings association

Blood Tumor Mutational Burden
14 Muts/Mb

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor immune response. It is FDA approved as monotherapy in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, classical Hodgkin lymphoma (cHL), gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma or squamous cell carcinoma (ESCC). Furthermore, nivolumab is approved to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). It is also approved in combination with cabozantinib to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,345] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

For patients with platinum-refractory non-squamous non-small cell lung cancer (NSCLC), nivolumab improved median OS (mOS; 12.2 vs. 9.4 months) and ORR (19% vs. 12%) compared with docetaxel in the Phase 3 CheckMate 057 study; PD-L1 expression was associated with OS benefit from nivolumab in this study (HR=0.40-0.59)[379]. In advanced squamous NSCLC, second-line nivolumab resulted in longer mOS (9.2 vs. 6.0 months) and higher ORR (20% vs. 9%) than docetaxel in the Phase 3 CheckMate 017 study; PD-L1 expression was neither prognostic nor predictive of nivolumab efficacy[380-381] . Pooled analysis of CheckMate 057 and CheckMate 017 showed improved long-term OS and PFS benefit for nivolumab over docetaxel, with 5-year OS rates of 13% versus 2.6% (HR=0.68) and PFS rates of 8.0% versus 0% (HR=0.79)[382]. In the CheckMate 227 study, the combination of nivolumab and platinum-based doublet chemotherapy did not improve OS over chemotherapy alone (18.3 vs. 14.7 months, HR=0.81)[383], despite Phase 1 results in the same setting suggesting improved ORR and OS[384]. In the Phase 3 CheckMate 816 study, the combination of nivolumab and platinum-based doublet chemotherapy did show benefit as a neoadjuvant treatment for patients with resectable NSCLC, reporting a pathological CR (pCR) rate of 24% versus 2.2% for chemotherapy alone, and the benefit was consistent across subgroups stratified by PD-L1 expression, stage of disease, or tumor mutational burden (TMB)[385]. A Phase 1 study of nivolumab combined with the immunostimulatory therapy bempegaldesleukin for immunotherapy-naive patients with NSCLC reported an ORR of 60% (3/5; 2 CRs) and mPFS of 18.0 months[386].

Pembrolizumab

Assay findings association

Blood Tumor Mutational Burden
14 Muts/Mb

AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved for patients with tumor mutational burden (TMB)-high (≥10 Muts/Mb), microsatellite instability-high (MSI-H), or mismatch repair-deficient (dMMR) solid tumors; as monotherapy for PD-L1-positive non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), cervical cancer, or gastric, esophageal, or gastroesophageal junction (GEJ) cancer; and in combination with chemotherapy for PD-L1-positive triple-negative breast cancer (TNBC) or cervical cancer. It is also approved in various treatment settings as monotherapy for patients with melanoma, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, classical Hodgkin lymphoma, or primary mediastinal large B-cell lymphoma, and in combination with chemotherapy or targeted therapy for NSCLC, HNSCC, esophageal or GEJ cancer, renal cell carcinoma, TNBC, or endometrial carcinoma that is not MSI-H or dMMR. Please see the drug label for full prescribing information. A voluntary withdrawal of the accelerated approval of pembrolizumab for the treatment of patients with recurrent advanced PD-L1-positive gastric or GEJ adenocarcinoma with disease progression on or after two or more prior lines of therapy has been initiated by the manufacturer.

GENE ASSOCIATION

On the basis of clinical data[1-3,345] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

A pilot study for first-line pembrolizumab alone or in combination with chemotherapy, for patients with newly diagnosed metastatic NSCLC, reported significantly improved median PFS in patients with bTMB levels ≥16 Muts/Mb (approximately 8 Muts/Mb as measured by this assay) compared with those with bTMB <16 Muts/Mb (14.1 vs. 4.7 months, HR=0.30); median OS was not reached in the bTMB ≥16 Muts/Mb cohort, compared with 8.8 months for those with bTMB <16 (HR=0.48)[3]. The superiority of pembrolizumab over platinum chemotherapy as first-line treatment for patients with PD-L1-positive non-small cell lung cancer (NSCLC) lacking EGFR or ALK alterations was demonstrated in the Phase 3 KEYNOTE-042 and -024 studies, which reported improved median OS (mOS) for PD-L1 tumor proportion scores (TPS) ≥1% (16.7 vs. 12.1 months, HR=0.81)[387] and ≥50% (26.3 vs. 13.4 months, HR=0.62-0.69)[388], with estimated 5-year OS rates of 32% versus 16% in the KEYNOTE-024 study[388]. In the Phase 1b KEYNOTE-100 study of pembrolizumab, mOS was numerically higher for patients with NSCLC and PD-L1 TPS ≥50% relative to those with lower levels of PD-L1 expression in both the first-line (35.4 vs. 19.5 months) and previously treated (15.4 vs. 8.5 months) settings[389]. A retrospective study showed that among patients with NSCLC and high PD-L1 expression treated with first-line pembrolizumab, mOS was improved for patients with TPS of 90-100% relative to those with TPS of 50-89% (not reached vs. 15.9 months, HR=0.39)[390]. Phase 3 studies showed that the addition of pembrolizumab to chemotherapy is superior to chemotherapy alone in the first-line setting for patients with either non-squamous (KEYNOTE-189)[391] or squamous (KEYNOTE-407)[392-393] NSCLC, regardless of PD-L1 or tumor mutational burden (TMB) status[394]. An exploratory analysis of KEYNOTE-189 demonstrated the superiority of the pembrolizumab combination therapy, regardless of blood TMB (bTMB) status[395]. For the first-line treatment of patients with NSCLC and high PD-L1 expression (TPS ≥50%), a meta-analysis of KEYNOTE-024 and -189 reported the combination of pembrolizumab and chemotherapy to be non-superior to pembrolizumab alone in terms of survival benefit; however, the combination did increase ORR (+22%, p=0.011)[396]. In the Phase 2/3 KEYNOTE-010 study, pembrolizumab extended mOS relative to docetaxel (10.4-12.7 vs. 8.2 months) for patients with previously treated PD-L1-positive NSCLC[397]. Multiple clinical trials have demonstrated the efficacy of pembrolizumab, both as a single agent and in combination with chemotherapy, to treat patients with NSCLC and brain metastases[398-400] . Clinical activity has also been achieved with pembrolizumab in combination with the AXL inhibitor bemcentinib[401], the anti-CTLA-4 antibody ipilimumab[402], the anti-TIGIT antibody vibostolimab[403], the HDAC inhibitor vorinostat[404], the multikinase inhibitor lenvatinib[405], and the PARP inhibitor niraparib[406].

Sotorasib

Assay findings association

KRAS
G12C

AREAS OF THERAPEUTIC USE

Sotorasib is a KRAS G12C inhibitor that is FDA approved for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sotorasib has been reported to confer clinical benefit for patients with KRAS G12C-mutated non-small cell lung cancer (NSCLC)[114,407] ; limited clinical data suggest

SUPPORTING DATA

The Phase 1/2 CodeBreaK 100 trial of sotorasib for patients with previously treated locally advanced or metastatic G12C-mutated solid tumors observed significant benefit for patients with non-small cell lung cancer (NSCLC), achieving an ORR of 37%, a DCR of 81%, median PFS (mPFS) of 6.8 months, and median OS of 12.5 months[114,407] . In the same study, patients with colorectal cancer (CRC) achieved a lower ORR of 7% (3/42) but had a high DCR of 74% (31/42) and mPFS of 4.0 months, and

Ado-trastuzumab emtansine

Assay findings association

ERBB2
L755F

AREAS OF THERAPEUTIC USE

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, which inhibits HER2 signaling; it also releases the cytotoxic therapy DM1 into cells, leading to cell death. T-DM1 is FDA approved to treat patients with HER2-positive (HER2+) metastatic breast cancer and disease progression on prior therapy as well as patients with HER2+ early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1[48,409-424] .

SUPPORTING DATA

In a Phase 2 basket trial of T-DM1, patients with ERBB2-mutated and/or -amplified non-small cell lung cancer (NSCLC) achieved an ORR of 51% (25/49) and a median PFS of 5 months. The ERBB2-amplified cohort had an ORR of 55% (6/11), while the ERBB2-mutated cohort had an ORR of 50% (5/10). A subset of patients with tumors harboring both an ERBB2 mutation and amplification had an ORR of 50% (5/10)[411]. Another Phase 2 trial of T-DM1 in chemotherapy-refractory ERBB2-positive NSCLC reported an ORR of 6.7% and a median PFS of 2.0 months; patients with ERBB2 expression experienced an ORR of 0% (0/8) and a DCR of 38% (3/8), whereas patients with ERBB2 exon 20 insertion mutations experienced an ORR of 14% (1/7) and DCR of 71% (5/7)[412]. A patient with ERBB2-amplified and A775_G776insYVMA-mutated NSCLC experienced disease progression on 2 prior lines of chemotherapy but experienced a rapid and durable response to T-DM1[342,425] .

Avelumab

Assay findings association

Blood Tumor Mutational Burden
14 Muts/Mb

AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 in order to enhance antitumor immune responses. It is FDA approved to treat patients 12 years and older with Merkel cell carcinoma, or for urothelial carcinoma in various treatment settings. The combination of avelumab and axitinib is FDA approved for patients with renal cell carcinoma (RCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data[1-3,345] , patients with NSCLC whose tumors harbor a bTMB of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In the Phase 3 JAVELIN Lung 200 study for patients with advanced non-small cell lung cancer (NSCLC) previously treated with platinum therapy, avelumab did not improve median OS (mOS) when compared with docetaxel (11.4 vs. 10.6 months; HR=0.87) for patients with PD-L1 expression in ≥1% of tumor cells; a prespecified exploratory analysis at higher PD-L1 expression cutoffs showed improved mOS for PD-L1 ≥50% (13.6 vs. 9.2 months; HR=0.67) and ≥80% (17.1 vs. 9.3 months; HR=0.59)[426], and improved 2-year OS rates of 30% versus 21% (≥1% PD-L1), 36% versus 18% (≥50% PD-L1), and 40% versus 20% (≥80% PD-L1)[427]. A post-hoc analysis of this study suggested that a relatively high proportion of patients in the docetaxel arm received subsequent immune checkpoint inhibitor treatment, which may have confounded the outcomes of this study[428]. A Phase 1 study evaluating single-agent avelumab to treat patients with advanced NSCLC reported an ORR of 20%, median PFS (mPFS) of 4.0 months, and mOS of 14.1 months in the first-line setting[429]. A Phase 2 study of avelumab with axitinib to treat advanced NSCLC reported an ORR of 32% (13/41) and mPFS of 5.5 months; tumor reduction was observed for PD-L1-negative and -positive (≥1% PD-L1) samples[430]. A Phase 1b/2 study of avelumab combined with the anti-semaphorin 4D antibody pepinemab to treat advanced NSCLC reported an ORR of 24% (5/21) and DCR of 81% for immunotherapy-naive patients, and ORR of 6.9% (2/29) and DCR of 59% for patients who had disease progression on prior immunotherapy treatment[431]. A study of neoadjuvant avelumab plus chemotherapy to treat early-stage resectable NSCLC reported an ORR of 27% (4/15), which was not considered an enhancement over chemotherapy alone[432].

Fam-trastuzumab deruxtecan

Assay findings association

ERBB2
L755F

AREAS OF THERAPEUTIC USE

Fam-trastuzumab deruxtecan is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface and delivers the cytotoxic payload DXd, which inhibits DNA topoisomerase I to induce DNA damage. Fam-trastuzumab deruxtecan is FDA approved to treat patients with HER2-positive breast cancer and gastric or gastroesophageal junction adenocarcinoma who have received prior HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer (NSCLC)[433-434] , ERBB2 mutation may predict sensitivity to fam-trastuzumab deruxtecan.

SUPPORTING DATA

The multi-cohort Phase 2 DESTINY-Lung01 study of single-agent fam-trastuzumab deruxtecan for patients with ERBB2-altered non-small cell lung cancer (NSCLC) reported clinical benefit for both the ERBB2-mutated[434] and ERBB2-overexpressing cohorts[435]. In the ERBB2-mutated cohort, predominantly comprised of patients with NSCLC harboring exon 20 insertions, the ORR was 55% (50/91) with a median duration of response of 9.3 months and the median PFS (mPFS) and OS were 8.2 and 17.8 months, respectively[434]. In the ERBB2-overexpressing cohort, the ORR and DCR were 25% (12/49) and 69% (34/49), respectively[435]. A Phase 1 basket study evaluating fam-trastuzumab deruxtecan for patients with ERBB2-expressing or -mutated NSCLC elicited an ORR of 56% (10/18) and a DCR of 83% (15/18), with an mPFS of 11 months[433]. In this study, the ORR was 73% (8/11) for patients with ERBB2-mutated NSCLC, with 6 responses reported for patients with ERBB2 exon 20 insertions[433]. A patient with lung cancer harboring both ERBB2 amplification and the S310F mutation who had progressed on ado-trastuzumab emtansine after 4 months was treated with fam-trastuzumab deruxtecan and exhibited a PR that lasted for 1 year[411].

Neratinib

Assay findings association

ERBB2
L755F

AREAS OF THERAPEUTIC USE

Neratinib is an irreversible tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the extended adjuvant treatment of early-stage HER2-positive (HER2+) breast cancer following adjuvant trastuzumab. Neratinib is also approved in combination with capecitabine to treat patients with advanced or metastatic HER2+ breast cancer who have been previously treated with 2 or more anti-HER2 regimens. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[73-76,436-438] and preclinical[88,92,439-441] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib.

SUPPORTING DATA

In the Phase 2 SUMMIT trial of neratinib in patients with ERBB2 or ERBB3 mutations, the ORR was 3.8% (1/26) and the median PFS was 5.5 months for patients with NSCLC, most of whom harbored ERBB2 exon 20 insertions; PR was observed in one patient with L755S mutation[75]. A Phase 2 study in ERBB2-mutated NSCLC reported objective response and clinical benefit in 19% (8/43) and 51% (22/43) of patients treated with neratinib plus the mTOR inhibitor temsirolimus, compared with 0% (0/17) and 35% (6/17) for patients treated with single-agent neratinib; exon 20 insertions were the most common ERBB2 mutation[442-443] .

Trastuzumab

Assay findings association

ERBB2
L755F

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets the protein ERBB2/HER2. It is FDA approved as monotherapy and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal adenocarcinoma. Trastuzumab biosimilars are also FDA approved for these indications. Please see the drug label(s) for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification, overexpression, or activating mutations may confer sensitivity to trastuzumab[38-39,43,58,444-448] .

SUPPORTING DATA

In a Phase 2a basket trial (MyPathway), trastuzumab plus pertuzumab treatment in non-small cell lung cancer (NSCLC) elicited PRs in 2/16 patients with ERBB2 amplification or overexpression and in 3/14 patients with HER2 mutation[446]. A Phase 2 trial of docetaxel with trastuzumab for the treatment of NSCLC reported PRs for 8% of patients, although the response did not correlate with HER2 status as assessed by immunohistochemistry[449]. Another Phase 2 study of 169 patients with NSCLC reported an ORR of 23% (7/30) with combination therapy of docetaxel and trastuzumab and 32% (11/34) with paclitaxel and trastuzumab; HER2 expression did not impact the results of this study[450]. A patient with lung adenocarcinoma that was HER-positive by FISH and harbored an ERBB2 G776L mutation experienced a PR on trastuzumab and paclitaxel[41]. In a retrospective analysis of patients with NSCLC harboring ERBB2 exon 20 insertion mutations, disease control was reported in 93% of patients (13/14) treated with trastuzumab in combination with chemotherapy[43].

Trastuzumab + Pertuzumab

Assay findings association

ERBB2
L755F

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets ERBB2/HER2, and pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. These therapies are FDA approved in combination for the treatment of patients with HER2-positive (HER2+) metastatic breast cancer who have not received prior chemotherapy or HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification or activating mutations may predict sensitivity to trastuzumab in combination with pertuzumab[45,446,451-455] .

SUPPORTING DATA

In the Phase 2a MyPathway basket trial, trastuzumab plus pertuzumab treatment in patients with ERBB2-positive (amplification or overexpression) non-small cell lung cancer (NSCLC) achieved an ORR of 26% (7/27)[446,456] . The combination of trastuzumab, pertuzumab, and docetaxel was evaluated in patients with ERBB2-mutated NSCLC lacking mutations in known driver genes and reported a 29% (13/45) ORR, 6.8-month median PFS, and 17.6-month median OS[457].

NOTE Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies listed in this report may have varied evidence in the patient's tumor type. The listed therapies are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. The therapies listed in this report may not be complete and/or exhaustive. Furthermore, the listed therapies are limited to US FDA approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be US FDA approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by the US FDA or other national authorities. There may also be other treatment modalities available than pharmaceutical drug products.

IMPORTANT Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. However, clinicaltrials.gov does not list all clinical trials that might be available.

BIOMARKER

Blood Tumor Mutational Burden

RESULT

14 Muts/Mb

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 (alone or in combination with anti-CTLA-4) or anti-PD-L1 immune checkpoint inhibitors.

NCT04385368

PHASE 3

Phase III Study to Determine the Efficacy of Durvalumab in Combination With Chemotherapy in Completely Resected Stage II-III Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-L1

LOCATIONS: Zürich (Switzerland), Strasbourg Cedex (France), Lausanne (Switzerland), Monza (Italy), Orbassano (Italy), Maastricht (Netherlands), Hasselt (Belgium), Leuven (Belgium), Villejuif Cedex (France), Bruxelles (Belgium)

NCT03924869

PHASE 3

Efficacy and Safety Study of Stereotactic Body Radiotherapy (SBRT) With or Without Pembrolizumab (MK-3475) in Adults With Medically Inoperable Stage I or IIA Non-Small Cell Lung Cancer (NSCLC) (MK-3475-867/KEYNOTE-867)

TARGETS
PD-1

LOCATIONS: Zuerich (Switzerland), Innsbruck (Austria), Heidelberg (Germany), Geneva (Switzerland), Modena (Italy), Linz (Austria), Firenze (Italy), Essen (Germany), Hamm (Germany), Paris (France)

NCT04026412

PHASE 3

A Study of Nivolumab and Ipilimumab in Untreated Patients With Stage 3 NSCLC That is Unable or Not Planned to be Removed by Surgery

TARGETS
PD-1, PD-L1, CTLA-4

LOCATIONS: Zuerich (Switzerland), St.Gallen (Switzerland), Basel (Switzerland), Kempten (Germany), Stuttgart (Germany), Lausanne (Switzerland), Loewenstein (Germany), Monza (Italy), Milano (Italy), Heidelberg (Germany)

NCT03906071

PHASE 3

Phase 3 Study of Sitravatinib Plus Nivolumab vs Docetaxel in Patients With Advanced Non-Squamous NSCLC

TARGETS
PD-1, AXL, KIT, DDR2, VEGFRs, PDGFRA, TRKA, MET, FLT3, RET, TRKB

LOCATIONS: Winterthur (Switzerland), Bern (Switzerland), Immenstadt (Germany), Strasbourg (France), Lausanne (Switzerland), Monza (Italy), Heilbronn (Germany), Genève (Switzerland), Gauting (Germany), Milano (Italy)

NCT04294810

PHASE 3

A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer

TARGETS
PD-L1, TIGIT

LOCATIONS: St. Gallen (Switzerland), Basel (Switzerland), Bern (Switzerland), Stuttgart (Germany), Lausanne (Switzerland), Loewenstein (Germany), Monza (Italy), Milano (Italy), Rozzano (Italy), Orbassano (Italy)

NCT03110107

PHASE 1/2

First-In-Human Study of Monoclonal Antibody BMS-986218 by Itself and in Combination With Nivolumab in Patients With Advanced Solid Tumors

TARGETS
CTLA-4, PD-1

LOCATIONS: Zurich (Switzerland), Lausanne (Switzerland), Rozzano (Italy), Essen (Germany), Siena (Italy), Gent (Belgium), Dresden (Germany), Amsterdam (Netherlands), Barcelona (Spain), Napoli (Italy)

NCT03965468

PHASE 2

Immunotherapy, Chemotherapy, Radiotherapy and Surgery for Synchronous Oligo-metastatic NSCLC

TARGETS
PD-L1

LOCATIONS: Zurich (Switzerland), Bern (Switzerland), Lausanne (Switzerland), Geneva (Switzerland), Maastricht (Netherlands), Rotterdam (Netherlands), Barcelona (Spain), Valencia (Spain), Madrid (Spain), Granada (Spain)

NCT01968109

PHASE 1/2

Safety Study of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors

TARGETS
PD-1, LAG-3

LOCATIONS: Zurich (Switzerland), Lausanne (Switzerland), Heilbronn (Germany), Milano (Italy), Wuerzburg (Germany), Pierre Benite Cedex (France), Padova (Italy), Essen (Germany), Villejuif (France), Marseille Cedex 5 (France)

NCT03516981

PHASE 2

A Study of Biomarker-Directed, Pembrolizumab (MK-3475) Based Combination Therapy for Advanced Non-Small Cell Lung Cancer (MK-3475-495/KEYNOTE-495)

TARGETS
CTLA-4, LAG-3, PD-1, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Zuerich (Switzerland), St. Gallen (Switzerland), Basel (Switzerland), Chur (Switzerland), Rozzano (Italy), Orbassano (Italy), Legnago (Italy), Meldola (Italy), Siena (Italy), Roma (Italy)

NCT04245514

PHASE 2

Multimodality Treatment in Stage III Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-L1

LOCATIONS: Zurich (Switzerland), Zürich (Switzerland), Baden (Switzerland), Aarau (Switzerland), St. Gallen (Switzerland), Basel (Switzerland), Chur (Switzerland), Bern (Switzerland), Thun (Switzerland), Bellinzona (Switzerland)

GENE
ARID1A

RATIONALE
ARID1A loss or inactivation may predict sensitivity to ATR inhibitors.

ALTERATION
G324fs*34

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Villejuif (France), Saint Herblain (France), Sutton (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Withington (United Kingdom), Massachusetts, New York, Seoul (Korea, Republic of), Seongnam-si (Korea, Republic of)

NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
ATR

LOCATIONS: Cambridge (United Kingdom)

NCT03641547

PHASE 1

M6620 Plus Standard Treatment in Oesophageal and Other Cancer

TARGETS
ATR

LOCATIONS: Oxford (United Kingdom), Cardiff (United Kingdom), Manchester (United Kingdom), Glasgow (United Kingdom)

NCT04266912

PHASE 1/2

Avelumab and M6620 for the Treatment of DDR Deficient Metastatic or Unresectable Solid Tumors

TARGETS
ATR, PD-L1

LOCATIONS: Texas

NCT04514497

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to Usual Chemotherapy for Advanced Stage Solid Tumors, With a Specific Focus on Patients With Small Cell Lung Cancer, Poorly Differentiated Neuroendocrine Cancer, and Pancreatic Cancer

TARGETS
ATR, TOP1

LOCATIONS: Connecticut, Tennessee, Missouri, Oklahoma, Arizona

NCT02595931

PHASE 1

ATR Kinase Inhibitor VX-970 and Irinotecan Hydrochloride in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
ATR

LOCATIONS: Massachusetts, Connecticut, Pennsylvania, Tennessee, Missouri, Florida, California

NCT02630199

PHASE 1

Study of AZD6738, DNA Damage Repair/Novel Anti-cancer Agent, in Combination With Paclitaxel, in Refractory Cancer

TARGETS
ATR

LOCATIONS: Seoul (Korea, Republic of)

GENE
ERBB2

ALTERATION
L755F

RATIONALE
ERBB2 amplification or activating mutation may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of HSP90 inhibitors. Although L755S and L755P are associated with reduced sensitivity to lapatinib and/or trastuzumab, the sensitivity of other alterations at L755 to these therapies is unclear.

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha

LOCATIONS: Heilbronn (Germany), Milano (Italy), Brescia (Italy), Firenze (Italy), Charleroi (Belgium), Leuven (Belgium), Bruxelles (Belgium), Siena (Italy), Edegem (Belgium), Barcelona (Spain)

NCT01953926

PHASE 2

An Open-label, Phase 2 Study of Neratinib in Patients With Solid Tumors With Somatic Human Epidermal Growth Factor Receptor (EGFR, HER2, HER3) Mutations or EGFR Gene Amplification

TARGETS
ERBB2, EGFR, ERBB4, ER

LOCATIONS: Milano (Italy), Cremona (Italy), Lyon (France), Leuven (Belgium), Villejuif (France), Saint-Cloud (France), Roma (Italy), Bordeaux (France), Barcelona (Spain), Napoli (Italy)

NCT03810872

PHASE 2

An Explorative Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation

TARGETS
EGFR, ERBB4, ERBB2

LOCATIONS: Liège (Belgium), Brussels (Belgium), Gent (Belgium)

NCT04579380

PHASE 2

Basket Study of Tucatinib and Trastuzumab in Solid Tumors With HER2 Alterations

TARGETS
ERBB2, ER

LOCATIONS: Charleroi (Belgium), Massachusetts, Connecticut, New York, Virginia, Pennsylvania, Ohio, North Carolina, Wisconsin, Minnesota

NCT02183883

PHASE 2

Deciphering Afatinib Response and Resistance With INtratumour Heterogeneity

TARGETS
EGFR, ERBB4, ERBB2

LOCATIONS: London (United Kingdom), London Borough Of Barnet (United Kingdom), Birmingham (United Kingdom), Manchester (United Kingdom), Glasgow (United Kingdom), Aberdeen (United Kingdom)

NCT02768337

PHASE 1/2

Cambridge Brain Mets Trial 1

TARGETS
EGFR, ERBB4, ERBB2

LOCATIONS: Cambridge (United Kingdom), Oxford (United Kingdom), Birmingham (United Kingdom), Manchester (United Kingdom), Liverpool (United Kingdom), Glasgow (United Kingdom)

NCT04042701

PHASE 1

DS8201a and Pembrolizumab in Participants With Locally Advanced/Metastatic Breast or Non-Small Cell Lung Cancer

TARGETS
PD-1, ERBB2

LOCATIONS: Villejuif (France), Marseille (France), Toulouse (France), Bordeaux (France), Sutton (United Kingdom), London (United Kingdom), Barcelona (Spain), Zaragoza (Spain), Madrid (Spain), Massachusetts

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, ROS1, AXL, TRKA, MET, TRKC, CDK4, CDK6, FLT3, CSF1R, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Maine

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, ROS1, AXL, TRKA, MET, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, FLT3, CSF1R, RET, mTOR, ERBB2, ERBB3, MEK, BRAF, SMO

LOCATIONS: Montreal (Canada), Ottawa (Canada), Kingston (Canada), Toronto (Canada), London (Canada), Saskatoon (Canada), Regina (Canada), Edmonton (Canada), Vancouver (Canada)

NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, PD-L1, ERBB2, ERBB3, PI3K-alpha, RET, AKTs

LOCATIONS: Connecticut, New York, New Jersey, Michigan, Ohio

GENE
KRAS

ALTERATION
G12C

RATIONALE
Clinical evidence suggests that patients with the KRAS G12C mutation may be sensitive to G12C-targeted inhibitors such as sotorasib and adagrasib. KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. Limited clinical and preclinical studies indicate KRAS mutations may predict sensitivity to MEK-pan-RAF dual inhibitors. KRAS alterations are not predictive biomarkers for MEK inhibitor monotherapy in NSCLC and combinatorial approaches may yield improved efficacy. Clinical evidence suggests that patients with KRAS-mutant NSCLC may be sensitive to the CDK4/6 inhibitor abemaciclib.

NCT03600883

PHASE 1/2

A Phase 1/2, Study Evaluating the Safety, Tolerability, PK, and Efficacy of AMG 510 in Subjects With Solid Tumors With a Specific KRAS Mutation.

TARGETS
KRAS, PD-1, PD-L1

LOCATIONS: Zurich (Switzerland), Basel (Switzerland), Innsbruck (Austria), Geneve (Switzerland), München (Germany), Köln (Germany), Essen (Germany), Créteil (France), Leuven (Belgium), Villejuif (France)

NCT03337698

PHASE 1/2

A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)

TARGETS
PD-L1, MEK, CEA, CXCR4, EZH2, MDM2, ADORA2A

LOCATIONS: Dijon (France), Marseille (France), Montpellier (France), Toulouse (France), Saint Herblain (France), Sutton (United Kingdom), London (United Kingdom), Barcelona (Spain), Pamplona (Spain), Newcastle upon Tyne (United Kingdom)

NCT03099174

PHASE 1

This Study in Patients With Different Types of Cancer (Solid Tumours) Aims to Find a Safe Dose of Xentuzumab in Combination With Abemaciclib With or Without Hormonal Therapies. The Study Also Tests How Effective These Medicines Are in Patients With Lung and Breast Cancer.

TARGETS
CDK4, CDK6, IGF-1, IGF-2, Aromatase, ER

LOCATIONS: Besançon (France), Paris (France), Marseille (France), Barcelona (Spain), L'Hospitalet de Llobregat (Spain), Plerin Sur Mer (France), København Ø (Denmark), Herlev (Denmark), Madrid (Spain), Pozuelo de Alarcón (Spain)

NCT02974725

PHASE 1

Study of LXH254 and LTT462 in NSCLC

TARGETS
CDK6, CDK4, ERK1, ERK2, ARAF, BRAF, MEK

LOCATIONS: Milano (Italy), Heidelberg (Germany), Rozzano (Italy), Verona (Italy), Frankfurt (Germany), Lyon Cedex (France), Aviano (Italy), Koeln (Germany), Essen (Germany), Paris Cedex 10 (France)

NCT04111458

PHASE 1

A Study to Test Different Doses of BI 1701963 Alone and Combined With Trametinib in Patients With Different Types of Advanced Cancer (Solid Tumours With KRAS Mutation)

TARGETS
KRAS, SOS1, MEK

LOCATIONS: Frankfurt am Main (Germany), Köln (Germany), Utrecht (Netherlands), Rotterdam (Netherlands), Massachusetts, North Carolina, Tennessee, Texas

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, ROS1, AXL, TRKA, MET, TRKC, MEK, AKTs, EGFR, PD-L1, KIT, DDR2, VEGFRs, PDGFRA, FLT3, RET, TRKB

LOCATIONS: Maidstone (United Kingdom), Colchester (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Southampton (United Kingdom), Oxford (United Kingdom), Leicester (United Kingdom), Bristol (United Kingdom), Birmingham (United Kingdom), Exeter (United Kingdom)

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: Sutton (United Kingdom), London (United Kingdom)

NCT03875820

PHASE 1

Phase I Trial of VS-6063 and RO5126766.

TARGETS
RAFs, MEK, FAK

LOCATIONS: Sutton (United Kingdom), Manchester (United Kingdom)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT03785249

PHASE 1/2

MRTX849 in Patients With Cancer Having a KRAS G12C Mutation

TARGETS
KRAS, PD-1, EGFR, ERBB4, ERBB2

LOCATIONS: Maine, Massachusetts, Connecticut, New York, Pennsylvania, Delaware, Maryland, Virginia

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

BRCA1
E1000Q

HGF
splice site 1405+2T>C

KMT2A (MLL)
A492T

MERTK
R421Q

MET
H792P

NOTCH3
R2207W

PBRM1
R760L

POLE
splice site 910-1G>C

RET
R475L

SDHD
P24A

SETD2
D122H

SMO
G765V

TBX3
S4Y and T551N

APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *); 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*C11orf30* (EMSY)	*C17orf39* (GID4)	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*
CD274 **(PD-L1)**	*CDC73*	***CDH1***	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*
CDKN2A	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***
CSF1R	*CSF3R*	*CTCF*	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*
DAXX	*DDR1*	***DDR2*** **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15**, 24-27**	*EP300*
EPHA3	*EPHB1*	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***
ESR1 **Exons 4-8**	*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FAM46C*	*FANCA*
FANCC	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*
FLCN	*FLT1*	***FLT3*** **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*
GNA11 **Exons 4, 5**	*GNA13*	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3F3A*	*HDAC1*	*HGF*
HNF1A	***HRAS*** **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*
INPP4B	*IRF2*	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*
KDM5C	*KDM6A*	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)

APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *); 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

KRAS	*LTK*	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*
MAPK1	*MCL1*	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***
MITF	*MKNK1*	*MLH1*	***MPL*** **Exon 10**	*MRE11A*	*MSH2* Intron 5	*MSH3*	*MSH6*	*MST1R*
MTAP	***MTOR*** **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	*MYB** Intron 14	***MYC*** **Intron 1**	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**	*NBN*
NF1	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2* Intron 26	*NOTCH3*	***NPM1*** **Exons 4-6, 8, 10**
NRAS **Exons 2, 3**	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11**
PDGFRB **Exons 12-21, 23**	*PDK1*	*PIK3C2B*	*PIK3C2G*	***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)**	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	***PTPN11***	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	***RAF1*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8	*RARA* Intron 2	***RB1***	*RBM10*	*REL*	***RET*** Introns 7, 8, **Exons 11, 13-16, Introns 9-11**
RICTOR	*RNF43*	***ROS1*** **Exons 31, 36-38, 40, Introns 31-35**	*RPTOR*	*RSPO2** Intron 1	*SDC4** Intron 2	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SLC34A2** Intron 4	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*
SMO	*SNCAIP*	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*
STAT3	***STK11***	*SUFU*	*SYK*	*TBX3*	*TEK*	*TERC** ncRNA	***TERT**** **Promoter**	*TET2*
TGFBR2	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*	*TYRO3*
U2AF1	***VEGFA***	*VHL*	*WHSC1*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

FoundationOne Liquid CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

FoundationOne Liquid CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details.

INTENDED USE

FoundationOne Liquid CDx is a next generation sequencing based *in vitro* diagnostic device that analyzes 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects the genomic signatures blood tumor mutational burden (bTMB), microsatellite instability (MSI), and tumor fraction. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labeling. Additionally, FoundationOne Liquid CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with malignant neoplasms.

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also reports tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. *Note:* A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls.

RANKING OF THERAPIES AND CLINICAL TRIALS

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from the observed level of aneuploidy in the sample. Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected and is significantly distinct from that typically found in non-tumor samples.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited

to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

11. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >30%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, ATM, CBL, CHEK2, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne Liquid CDx.

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this test or the information contained in this report.

Certain sample of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
Muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

MR Suite Version 5.2.0

1. Gandara DR, et al. Nat. Med. (2018) pmid: 30082870
2. Wang Z, et al. JAMA Oncol (2019) pmid: 30816954
3. Aggarwal C, et al. Clin. Cancer Res. (2020) pmid: 32102950
4. Li et al., 2020; ASCO Abstract 6511
5. Nie W, et al. J Natl Compr Canc Netw (2020) pmid: 32380463
6. Ma Y, et al. Front Oncol (2021) pmid: 34055609
7. Xiao D, et al. Oncotarget (2016) pmid: 27009843
8. Chen Y, et al. J. Exp. Clin. Cancer Res. (2019) pmid: 31088500
9. Yu H, et al. J Thorac Oncol (2019) pmid: 30253973
10. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
11. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
12. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
13. Rizvi NA, et al. Science (2015) pmid: 25765070
14. Johnson BE, et al. Science (2014) pmid: 24336570
15. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
16. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
17. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
18. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
19. Nature (2012) pmid: 22810696
20. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
21. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
22. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
23. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
24. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
25. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
26. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
27. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
28. Lapin M, et al. J Transl Med (2018) pmid: 30400802
29. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
30. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
31. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
32. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
33. Fan G, et al. PLoS ONE (2017) pmid: 28187169
34. Vu et al., 2020; DOI: 10.1200/PO.19.00204
35. Li G, et al. J Gastrointest Oncol (2019) pmid: 31602320
36. Zhang EW, et al. Cancer (2020) pmid: 32757294
37. Butler TM, et al. Cold Spring Harb Mol Case Stud (2019) pmid: 30833418
38. Slamon DJ, et al. N. Engl. J. Med. (2001) pmid: 11248153
39. Bang YJ, et al. Lancet (2010) pmid: 20728210
40. Chumsri S, et al. J Natl Compr Canc Netw (2015) pmid: 26358791
41. Cappuzzo F, et al. N. Engl. J. Med. (2006) pmid: 16775247
42. Falchook GS, et al. J Thorac Oncol (2013) pmid: 23328556
43. Mazières J, et al. J. Clin. Oncol. (2013) pmid: 23610105
44. Baselga J, et al. N. Engl. J. Med. (2012) pmid: 22149875
45. Swain SM, et al. N. Engl. J. Med. (2015) pmid: 25693012
46. Meric-Bernstam F, et al. Lancet Oncol. (2019) pmid: 30857956
47. Meric-Bernstam et al., 2019; ESMO Abstract 453PD
48. Verma S, et al. N. Engl. J. Med. (2012) pmid: 23020162
49. Modi S, et al. N. Engl. J. Med. (2019) pmid: 31825192
50. Murthy RK, et al. N. Engl. J. Med. (2020) pmid: 31825569
51. Borges VF, et al. JAMA Oncol (2018) pmid: 29955792
52. Murthy R, et al. Lancet Oncol. (2018) pmid: 29804905
53. Moulder SL, et al. Clin. Cancer Res. (2017) pmid: 28053022
54. Fan Y, et al. Mol Oncol (2020) pmid: 32478891
55. Cameron D, et al. Oncologist (2010) pmid: 20736298
56. Geyer CE, et al. N. Engl. J. Med. (2006) pmid: 17192538
57. Serra V, et al. Cancer Discov (2013) pmid: 23950206
58. Ali SM, et al. J. Clin. Oncol. (2014) pmid: 24516025
59. Grellety T, et al. Ann. Oncol. (2016) pmid: 26487584
60. Vornicova O, et al. Oncologist (2014) pmid: 25085898
61. Ronellenfitsch MW, et al. J Clin Invest (2020) pmid: 32017710
62. Hou JY, et al. Gynecol Oncol Rep (2020) pmid: 32405522
63. Lin NU, et al. Breast Cancer Res. Treat. (2012) pmid: 22418700
64. Schwab CL, et al. Br. J. Cancer (2014) pmid: 25268372
65. De Grève J, et al. Lung Cancer (2015) pmid: 25682316
66. De Grève J, et al. Lung Cancer (2012) pmid: 22325357
67. Li BT, et al. Lung Cancer (2015) pmid: 26559459
68. Dziadziuszko R, et al. J Thorac Oncol (2019) pmid: 30825613
69. Lai WV, et al. Eur. J. Cancer (2019) pmid: 30685684
70. Liu Z, et al. Onco Targets Ther (2018) pmid: 30425522
71. Fang W, et al. Oncologist (2019) pmid: 31748336
72. Yuan B, et al. Front Oncol (2020) pmid: 32477948
73. Ben-Baruch NE, et al. J Natl Compr Canc Netw (2015) pmid: 26358790
74. Ma CX, et al. Clin. Cancer Res. (2017) pmid: 28679771
75. Hyman DM, et al. Nature (2018) pmid: 29420467
76. Smyth LM, et al. Cancer Discov (2019) pmid: 31806627
77. Kris MG, et al. Ann. Oncol. (2015) pmid: 25899785
78. Jiang et al., 2019; ASCO Abstract 1001
79. Xu et al., 2020; ASCO Abstract 1003
80. Jones KL, et al. Lancet Oncol. (2009) pmid: 19959074
81. Zagouri F, et al. Breast (2013) pmid: 23870456
82. Li et al., 2020; ASCO Abstract 3510
83. Bedard et al., 2019; AACR Abstract CT139
84. Wang Y, et al. Ann. Oncol. (2019) pmid: 30596880
85. Aung KL, et al. Cold Spring Harb Mol Case Stud (2016) pmid: 27626067
86. Zuo WJ, et al. Clin. Cancer Res. (2016) pmid: 27697991
87. Kloth M, et al. Gut (2016) pmid: 26001389
88. Kavuri SM, et al. Cancer Discov (2015) pmid: 26243863
89. Hoadley et al., 2015; AACR Abstract S3-06
90. Trowe T, et al. Clin. Cancer Res. (2008) pmid: 18413839
91. Kancha RK, et al. PLoS ONE (2011) pmid: 22046346
92. Bose R, et al. Cancer Discov (2013) pmid: 23220880
93. Cocco E, et al. Sci Signal (2018) pmid: 30301790
94. Xu X, et al. Clin. Cancer Res. (2017) pmid: 28487443
95. Xu et al., 2014; AACR Abstract P5-05-03
96. Yang B, et al. J Mol Model (2015) pmid: 25620423
97. Campbell JD, et al. Nat. Genet. (2016) pmid: 27158780
98. Rizvi H, et al. J. Clin. Oncol. (2018) pmid: 29337640
99. Nature (2014) pmid: 25079552
100. Imielinski M, et al. Cell (2012) pmid: 22980975
101. Jordan EJ, et al. Cancer Discov (2017) pmid: 28336552
102. Nature (2012) pmid: 22960745
103. Swanton C, et al. Clin. Cancer Res. (2006) pmid: 16857814
104. Nakamura H, et al. Cancer (2005) pmid: 15770690
105. Xia Q, et al. Tumour Biol. (2012) pmid: 22736332
106. Takenaka M, et al. Anticancer Res. (2011) pmid: 22199341
107. Gómez AM, et al. Tumour Biol. (2014) pmid: 24443268
108. Tan D, et al. Diagn. Mol. Pathol. (2003) pmid: 14639106
109. Selvaggi G, et al. Cancer (2002) pmid: 12173335
110. Norton ML, et al. Leg Med (1986) pmid: 3312887
111. Shinde et al., 2020; AACR Abstract CT143
112. Canon J, et al. Nature (2019) pmid: 31666701
113. Lanman BA, et al. J. Med. Chem. (2020) pmid: 31820981
114. Hong DS, et al. (2020) pmid: 32955176
115. Hallin J, et al. Cancer Discov (2019) pmid: 31658955
116. Janne et al., 2020; EORTC-NCI-AACR Abstract 3LBA
117. Johnson et al., 2020; EORTC-NCI-AACR Abstract 4LBA
118. Amodio V, et al. Cancer Discov (2020) pmid: 32430388
119. Lu H, et al. Mol Cancer Ther (2019) pmid: 31068384
120. Mainardi S, et al. Nat Med (2018) pmid: 29808006
121. Koczywas et al., 2021; AACR Abstract LB001
122. Bendell et al., 2020; EORTC-NCI-AACR Abstract 5
123. Nakano H, et al. Proc. Natl. Acad. Sci. U.S.A. (1984) pmid: 6320174
124. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
125. Yamaguchi T, et al. Int. J. Oncol. (2011) pmid: 21523318
126. Watanabe M, et al. Cancer Sci. (2013) pmid: 23438367
127. Gilmartin AG, et al. Clin. Cancer Res. (2011) pmid: 21245089
128. Yeh JJ, et al. Mol. Cancer Ther. (2009) pmid: 19372556
129. Blumenschein GR, et al. Ann. Oncol. (2015) pmid: 25722381
130. Leijen S, et al. Clin. Cancer Res. (2012) pmid: 22767668
131. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
132. Jänne PA, et al. JAMA (2017) pmid: 28492898
133. Gandara DR, et al. J Thorac Oncol (2017) pmid: 27876675
134. Carter CA, et al. Ann. Oncol. (2016) pmid: 26802155
135. Bedard PL, et al. Clin. Cancer Res. (2015) pmid: 25500057
136. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
137. Castellano E, et al. Cancer Cell (2013) pmid: 24229709
138. Ku BM, et al. Invest New Drugs (2015) pmid: 25342139
139. Lamba S, et al. Cell Rep (2014) pmid: 25199829
140. Sun C, et al. Cell Rep (2014) pmid: 24685132
141. Hata AN, et al. Cancer Res. (2014) pmid: 24675361
142. Tan N, et al. Mol. Cancer Ther. (2013) pmid: 23475955
143. Hillig RC, et al. Proc Natl Acad Sci U S A (2019) pmid: 30683722
144. Hofmann MH, et al. Cancer Discov (2021) pmid: 32816843
145. Hofmann et al., 2021; AACR Abstract CT210
146. Gort et al., 2020; ASCO Abstract TPS3651
147. Shapiro et al., 2017; AACR Abstract CT046
148. Patnaik A, et al. Cancer Discov (2016) pmid: 27217383
149. Goldman et al., 2018; ASCO Abstract 9025
150. Mao C, et al. Lung Cancer (2010) pmid: 20022659
151. Sun JM, et al. PLoS ONE (2013) pmid: 23724098
152. Pao W, et al. PLoS Med. (2005) pmid: 15696205
153. Ludovini V, et al. J Thorac Oncol (2011) pmid: 21258250
154. Passiglia F, et al. Br. J. Cancer (2019) pmid: 30377342
155. Skoulidis F, et al. Cancer Discov (2018) pmid: 29773717
156. Skoulidis et al., 2017; IASLC 17th World Congress on Lung Cancer Abstract MA04.07
157. Marmarelis et al., 2018, IASLC WCLC Abstract P1.01-64
158. Krebs et al., 2021; AACR Abstract CT019
159. Nassar AH, et al. N Engl J Med (2021) pmid: 33497555
160. Ding L, et al. Nature (2008) pmid: 18948947
161. Aviel-Ronen S, et al. Clin Lung Cancer (2006) pmid: 16870043
162. Villaruz LC, et al. Cancer (2013) pmid: 23526491

163. Rekhtman N, et al. Mod. Pathol. (2013) pmid: 23619604
164. Ragusa M, et al. Am. J. Clin. Oncol. (2014) pmid: 23357969
165. Kim ST, et al. Med. Oncol. (2013) pmid: 23307237
166. Russell PA, et al. J Thorac Oncol (2013) pmid: 23486266
167. Stella GM, et al. J. Cancer Res. Clin. Oncol. (2013) pmid: 23644698
168. Cai G, et al. Cancer Cytopathol (2013) pmid: 23495083
169. Yip PY, et al. J Thorac Oncol (2013) pmid: 23392229
170. Tochigi N, et al. Am. J. Clin. Pathol. (2011) pmid: 21502435
171. Shu C, et al. Mod. Pathol. (2013) pmid: 22996376
172. Wang R, et al. J Thorac Oncol (2014) pmid: 24481316
173. Karlsson A, et al. Oncotarget (2015) pmid: 26124082
174. Scoccianti C, et al. Eur. Respir. J. (2012) pmid: 22267755
175. Curr Opin Oncol (2014) pmid: 24463346
176. Ghimessy AK, et al. Cancers (Basel) (2019) pmid: 31600989
177. Chaft JE, et al. J Thorac Oncol (2013) pmid: 23857398
178. Socinski MA, et al. N. Engl. J. Med. (2018) pmid: 29863955
179. Dong ZY, et al. Clin. Cancer Res. (2017) pmid: 28039262
180. Kahn S, et al. Anticancer Res. () pmid: 3310850
181. Awad MM, et al. N Engl J Med (2021) pmid: 34161704
182. Tanaka N, et al. Cancer Discov (2021) pmid: 33824136
183. Ryan MB, et al. Clin Cancer Res (2020) pmid: 31776128
184. Dunnett-Kane V, et al. Cancers (Basel) (2021) pmid: 33466360
185. Akagi K, et al. Biochem. Biophys. Res. Commun. (2007) pmid: 17150185
186. Bollag G, et al. J. Biol. Chem. (1996) pmid: 8955068
187. Buhrman G, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20194776
188. Sci. STKE (2004) pmid: 15367757
189. Edkins S, et al. Cancer Biol. Ther. (2006) pmid: 16969076
190. Feig LA, et al. Mol. Cell. Biol. (1988) pmid: 3043178
191. Gremer L, et al. Hum. Mutat. (2011) pmid: 20949621
192. Janakiraman M, et al. Cancer Res. (2010) pmid: 20570890
193. Kim E, et al. Cancer Discov (2016) pmid: 27147599
194. Lukman S, et al. PLoS Comput. Biol. (2010) pmid: 20838576
195. Naguib A, et al. J Mol Signal (2011) pmid: 21371307
196. Prior IA, et al. Cancer Res. (2012) pmid: 22589270
197. Privé GG, et al. Proc. Natl. Acad. Sci. U.S.A. (1992) pmid: 1565661
198. Scheffzek K, et al. Science (1997) pmid: 9219684
199. Scholl C, et al. Cell (2009) pmid: 19490892
200. Smith G, et al. Br. J. Cancer (2010) pmid: 20147967
201. Tyner JW, et al. Blood (2009) pmid: 19075190
202. Valencia A, et al. Biochemistry (1991) pmid: 2029511
203. White Y, et al. Nat Commun (2016) pmid: 26854029
204. Wiest JS, et al. Oncogene (1994) pmid: 8058307
205. Angeles AKJ, et al. Oncol Lett (2019) pmid: 31289513
206. Tong JH, et al. Cancer Biol. Ther. (2014) pmid: 24642870
207. Loree JM, et al. Clin Cancer Res (2021) pmid: 34117033
208. Williamson CT, et al. Nat Commun (2016) pmid: 27958275
209. Aggarwal et al., 2021; ESMO Abstract 5120
210. Thomas A, et al. J. Clin. Oncol. (2018) pmid: 29252124
211. Yap TA, et al. J Clin Oncol (2020) pmid: 32568634
212. Bitler BG, et al. Nat. Med. (2015) pmid: 25686104
213. Kim KH, et al. Nat. Med. (2015) pmid: 26552009
214. Wiegand KC, et al. BMC Cancer (2014) pmid: 24559118
215. Huang HN, et al. Mod. Pathol. (2014) pmid: 24336158
216. Samartzis EP, et al. Oncotarget (2014) pmid: 24979463
217. Okamura R, et al. J Immunother Cancer (2020) pmid: 32111729
218. Yokoyama Y, et al. J Gynecol Oncol (2014) pmid: 24459582
219. Katagiri A, et al. Mod. Pathol. (2012) pmid: 22101352
220. Xie C, et al. Tumour Biol. (2014) pmid: 24833095
221. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
222. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
223. Gao J, et al. Sci Signal (2013) pmid: 23550210
224. Wu RC, et al. Cancer Biol. Ther. (2014) pmid: 24618703
225. Jones S, et al. Hum. Mutat. (2012) pmid: 22009941
226. Dulak AM, et al. Nat. Genet. (2013) pmid: 23525077
227. Streppel MM, et al. Oncogene (2014) pmid: 23318448
228. Jiao Y, et al. J. Pathol. (2014) pmid: 24293293
229. Ross JS, et al. Oncologist (2014) pmid: 24563076
230. Huang HN, et al. Histopathology (2015) pmid: 25195947
231. Hussein YR, et al. Mod. Pathol. (2015) pmid: 25394778
232. Bosse T, et al. Mod. Pathol. (2013) pmid: 23702729
233. Allo G, et al. Mod. Pathol. (2014) pmid: 23887303
234. Chou A, et al. Hum. Pathol. (2014) pmid: 24925223
235. Ye J, et al. Hum. Pathol. (2014) pmid: 25311944
236. Wei XL, et al. World J. Gastroenterol. (2014) pmid: 25561809
237. Chen K, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25583476
238. Wang K, et al. Nat. Genet. (2011) pmid: 22037554
239. Abe H, et al. Virchows Arch. (2012) pmid: 22915242
240. Wang DD, et al. PLoS ONE (2012) pmid: 22808142
241. Wiegand KC, et al. Hum. Pathol. (2014) pmid: 24767857
242. Katagiri A, et al. Int. J. Gynecol. Cancer (2012) pmid: 22274316
243. Cho H, et al. Hum. Pathol. (2013) pmid: 23427874
244. Gui Y, et al. Nat. Genet. (2011) pmid: 21822268
245. Balbás-Martínez C, et al. PLoS ONE (2013) pmid: 23650517
246. Faraj SF, et al. Hum. Pathol. (2014) pmid: 25175170
247. Rahman M, et al. Hum. Pathol. (2013) pmid: 22939958
248. Maeda D, et al. Int J Mol Sci (2010) pmid: 21614196
249. Lowery WJ, et al. Int. J. Gynecol. Cancer (2012) pmid: 22193641
250. Fadare O, et al. Mod. Pathol. (2013) pmid: 23524907
251. Mao TL, et al. Am. J. Surg. Pathol. (2013) pmid: 24076775
252. Zhang X, et al. Cancer Epidemiol (2012) pmid: 21889920
253. Mamo A, et al. Oncogene (2012) pmid: 21892209
254. Zhao J, et al. Tumour Biol. (2014) pmid: 24430365
255. Lichner Z, et al. Am. J. Pathol. (2013) pmid: 23416164
256. Feng F, et al. Int J Clin Oncol (2021) pmid: 33387086
257. Conci S, et al. Updates Surg (2020) pmid: 32020551
258. Simbolo M, et al. Sci Rep (2018) pmid: 29740198
259. Ruzzenente A, et al. Ann. Surg. Oncol. (2016) pmid: 26717940
260. Guan B, et al. Cancer Res. (2011) pmid: 21900401
261. Wiegand KC, et al. N. Engl. J. Med. (2010) pmid: 20942669
262. Jones S, et al. Science (2010) pmid: 20826764
263. Yan HB, et al. Carcinogenesis (2014) pmid: 24293408
264. Huang J, et al. Nat. Genet. (2012) pmid: 22922871
265. Chan-On W, et al. Nat. Genet. (2013) pmid: 24185513
266. Zang ZJ, et al. Nat. Genet. (2012) pmid: 22484628
267. Trowbridge JJ, et al. Nat. Genet. (2011) pmid: 22200773
268. Prog Mol Biol Transl Sci (2011) pmid: 21507354
269. Yang J, et al. Mol Med Rep () pmid: 21887466
270. Vallböhmer D, et al. Clin Lung Cancer (2006) pmid: 16870044
271. Daskalos A, et al. Cancer (2011) pmid: 21351083
272. Fabbri M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17890317
273. Gao Q, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 22011581
274. Kim MS, et al. APMIS (2013) pmid: 23031157
275. Chen ZX, et al. J. Cell. Biochem. (2005) pmid: 15861382
276. Guo X, et al. Nature (2015) pmid: 25383530
277. Sandoval JE, et al. J. Biol. Chem. (2019) pmid: 30705090
278. Zhang ZM, et al. Nature (2018) pmid: 29414941
279. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
280. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
281. Xie M, et al. Nat. Med. (2014) pmid: 25326804
282. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
283. Severson EA, et al. Blood (2018) pmid: 29678827
284. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
285. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
286. Chabon JJ, et al. Nature (2020) pmid: 32269342
287. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
288. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
289. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
290. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
291. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
292. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
293. Xu L, et al. Mol. Med. (2001) pmid: 11713371
294. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
295. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
296. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
297. Hajdenberg et al., 2012; ASCO Abstract e15010
298. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
299. Moore et al., 2019; ASCO Abstract 5513
300. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
301. Oza et al., 2015; ASCO Abstract 5506
302. Lee J, et al. Cancer Discov (2019) pmid: 31315834
303. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
304. Ma CX, et al. J. Clin. Invest. (2012) pmid: 22446188
305. Kwok M, et al. Blood (2016) pmid: 26563132
306. Boudny M, et al. Haematologica (2019) pmid: 30975914
307. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
308. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
309. Mogi A, et al. J. Biomed. Biotechnol. (2011) pmid: 21331359
310. Tekpli X, et al. Int. J. Cancer (2013) pmid: 23011884
311. Vignot S, et al. J. Clin. Oncol. (2013) pmid: 23630207
312. Maeng CH, et al. Anticancer Res. (2013) pmid: 24222160
313. Cortot AB, et al. Clin Lung Cancer (2014) pmid: 24169260
314. Itakura M, et al. Br. J. Cancer (2013) pmid: 23922113
315. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
316. Seo JS, et al. Genome Res. (2012) pmid: 22975805
317. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
318. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
319. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
320. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130

321. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
322. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
323. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
324. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
325. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
326. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
327. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
328. Lalloo F, et al. Lancet (2003) pmid: 12672316
329. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
330. Greulich H, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22908275
331. Robichaux JP, et al. Cancer Cell (2019) pmid: 31588020
332. Jang J, et al. Angew. Chem. Int. Ed. Engl. (2018) pmid: 29978938
333. Koga T, et al. Lung Cancer (2018) pmid: 30527195
334. Januszewski et al., 2018; IASLC WCLC Abstract P1.13-17
335. Chang et al., 2018; IASLC WCLC Abstract P1.01-11
336. Sequist LV, et al. J. Clin. Oncol. (2013) pmid: 23816960
337. Wu YL, et al. Lancet Oncol. (2014) pmid: 24439929
338. Yang JC, et al. Lancet Oncol. (2015) pmid: 25589191
339. Soria JC, et al. Lancet Oncol. (2015) pmid: 26156651
340. Paz-Ares L, et al. Ann. Oncol. (2017) pmid: 28426106
341. Gow CH, et al. J Thorac Oncol (2015) pmid: 26134234
342. Mazières J, et al. Ann. Oncol. (2016) pmid: 26598547
343. Costa DB, et al. J Thorac Oncol (2016) pmid: 26964772
344. Schuler M, et al. Ann. Oncol. (2016) pmid: 26646759
345. Rizvi et al., 2019; ASCO Abstract 9016
346. Socinski et al., 2019; ESMO Abstract LBA83
347. Herbst RS, et al. N Engl J Med (2020) pmid: 32997907
348. Chen YT, et al. Front Oncol (2019) pmid: 31921683
349. Nie et al., 2020; WCLC Abstract OA07.03
350. West H, et al. Lancet Oncol. (2019) pmid: 31122901
351. Barlesi et al., 2018; ESMO Abstract LBA54
352. Rittmeyer A, et al. Lancet (2017) pmid: 27979383
353. Smith et al., 2016; ASCO Abstract 9028
354. Fehrenbacher L, et al. Lancet (2016) pmid: 26970723
355. Pietras et al., 2018; WCLC Abstract P1.04-3
356. Felip E, et al. Lancet (2021) pmid: 34555333
357. Rodriguez-Abreu et al., 2020; ASCO Abstract 9503
358. Sezer A, et al. Lancet (2021) pmid: 33581821
359. Shim et al., 2020; ESMO Abstract 1269P
360. Jänne PA, et al. Clin. Cancer Res. (2011) pmid: 21220471
361. Kim HS, et al. Clin. Cancer Res. (2015) pmid: 25424851
362. Reckamp KL, et al. Cancer (2014) pmid: 24501009
363. Oh DY, et al. Gastric Cancer (2016) pmid: 26581547
364. van Geel RMJM, et al. Br. J. Cancer (2020) pmid: 32147669
365. Jänne PA, et al. J Thorac Oncol (2016) pmid: 26899759
366. Subramanian et al., 2020; ESMO Abstract 1399P
367. Andre et al., 2021; ASCO GI Abstract 9
368. Oaknin A, et al. JAMA Oncol (2020) pmid: 33001143
369. Berton et al., 2021; ASCO Abstract 2564
370. Andre et al., 2021; ESMO GI Abstract SO-9
371. Paz-Ares L, et al. Ann. Oncol. (2020) pmid: 32209338
372. Faivre-Finn C, et al. J Thorac Oncol (2021) pmid: 33476803
373. Planchard D, et al. Ann. Oncol. (2020) pmid: 32201234
374. Rizvi NA, et al. JAMA Oncol (2020) pmid: 32271377
375. Johnson et al., 2021; WCLC Abstract PL02.01
376. Antonia SJ, et al. J Thorac Oncol (2019) pmid: 31228626
377. Garassino MC, et al. Lancet Oncol. (2018) pmid: 29545095
378. Garassino et al., 2018; WCLC Abstract P1.01-21
379. Borghaei H, et al. N. Engl. J. Med. (2015) pmid: 26412456
380. Brahmer J, et al. N. Engl. J. Med. (2015) pmid: 26028407
381. Rizvi NA, et al. Lancet Oncol. (2015) pmid: 25704439
382. Lind et al., 2020; BTOG Abstract 113
383. Paz-Ares et al., 2019; ESMO Immuno-Oncology Congress Abstract LBA3
384. Rizvi NA, et al. J. Clin. Oncol. (2016) pmid: 27354481
385. Forde et al., 2021; AACR Abstract CT003
386. Diab A, et al. Cancer Discov (2020) pmid: 32439653
387. Mok TSK, et al. Lancet (2019) pmid: 30955977
388. Brahmer et al., 2020; ESMO LBA51
389. Garon EB, et al. J. Clin. Oncol. (2019) pmid: 31154919
390. Aguilar EJ, et al. Ann. Oncol. (2019) pmid: 31435660
391. Gadgeel S, et al. J. Clin. Oncol. (2020) pmid: 32150489
392. Paz-Ares L, et al. N. Engl. J. Med. (2018) pmid: 30280635
393. Paz-Ares L, et al. J Thorac Oncol (2020) pmid: 32599071
394. Paz-Ares et al., 2019; ESMO Abstract LBA80
395. Garassino et al., 2020; ASCO Abstract 9521
396. Doherty et al., 2018; WCLC Abstract P1.01-16
397. Herbst RS, et al. Lancet (2016) pmid: 26712084
398. Powell et al., 2019; ESMO Abstract 1483PD
399. Mansfield et al., 2019; ESMO Abstract 1482O
400. Goldberg SB, et al. Lancet Oncol. (2016) pmid: 27267608
401. Spicer et al., 2020; SITC Abstract 362
402. Gubens MA, et al. Lung Cancer (2019) pmid: 30885353
403. Niu et al., 2020; ESMO Abstract 1410P
404. Gray JE, et al. Clin. Cancer Res. (2019) pmid: 31409616
405. Brose et al., 2019; DOI: 10.1200/JCO.2019.37.8_suppl.16
406. Ramalingam SS, et al. Cancer (2021) pmid: 34478166
407. Skoulidis F, et al. N Engl J Med (2021) pmid: 34096690
408. Strickler et al., 2020; ESMO Asia Abstract 83MO
409. Jhaveri KL, et al. Ann. Oncol. (2019) pmid: 31504139
410. Li et al., 2018; ASCO Abstract 2502
411. Li BT, et al. Cancer Discov (2020) pmid: 32213539
412. Hotta K, et al. J Thorac Oncol (2018) pmid: 29313813
413. Krop IE, et al. Lancet Oncol. (2014) pmid: 24793816
414. Welslau M, et al. Cancer (2014) pmid: 24222194
415. Krop IE, et al. J. Clin. Oncol. (2012) pmid: 22649126
416. Burris HA, et al. J. Clin. Oncol. (2011) pmid: 21172893
417. Jhaveri et al., 2018; ASCO Abstract 100
418. Baselga J, et al. Clin. Cancer Res. (2016) pmid: 26920887
419. Perez EA, et al. J. Clin. Oncol. (2017) pmid: 28056202
420. Hurvitz SA, et al. J. Clin. Oncol. (2013) pmid: 23382472
421. von Minckwitz G, et al. N. Engl. J. Med. (2019) pmid: 30516102
422. Hurvitz SA, et al. J. Clin. Oncol. (2019) pmid: 31157583
423. Martin M, et al. Ann. Oncol. (2016) pmid: 27052654
424. Mondaca S, et al. JCO Precis Oncol (2019) pmid: 32923849
425. Weiler D, et al. J Thorac Oncol (2015) pmid: 25789838
426. Barlesi F, et al. Lancet Oncol (2018) pmid: 30262187
427. Park K, et al. J Thorac Oncol (2021) pmid: 33845211
428. Park K, et al. Lung Cancer (2021) pmid: 33636453
429. Verschraegen CF, et al. J Immunother Cancer (2020) pmid: 32907924
430. Galffy et al., 2020; SITC Abstract 281
431. Shafique M, et al. Clin Cancer Res (2021) pmid: 33820783
432. Tfayli A, et al. Cancer Med (2020) pmid: 32991781
433. Tsurutani J, et al. Cancer Discov (2020) pmid: 32213540
434. Li BT, et al. N Engl J Med (2021) pmid: 34534430
435. Nakagawa et al., 2021; WCLC Abstract OA04.05
436. Li et al., 2020; WCLC Abstract FP14.15
437. Chan A, et al. Lancet Oncol. (2016) pmid: 26874901
438. Park JW, et al. N. Engl. J. Med. (2016) pmid: 27406346
439. Schwab CL, et al. Gynecol. Oncol. (2015) pmid: 26260909
440. Menderes G, et al. Med. Oncol. (2017) pmid: 28397106
441. Hu Z, et al. Oncotarget (2015) pmid: 26375550
442. Gandhi et al. 2017; WCLC Abstract MA04.02
443. Gandhi L, et al. J. Clin. Oncol. (2014) pmid: 24323026
444. Gianni L, et al. Lancet Oncol. (2014) pmid: 24657003
445. Morris PG, et al. Cancer (2013) pmid: 24037735
446. Hainsworth JD, et al. J. Clin. Oncol. (2018) pmid: 29320312
447. Wang K, et al. Clin. Cancer Res. (2016) pmid: 27334835
448. Nishikawa K, et al. Int. J. Cancer (2017) pmid: 27521503
449. Lara PN, et al. Clin Lung Cancer (2004) pmid: 14967075
450. Krug LM, et al. Cancer (2005) pmid: 16208701
451. Hurvitz SA, et al. Lancet Oncol. (2018) pmid: 29175149
452. von Minckwitz G, et al. N. Engl. J. Med. (2017) pmid: 28581356
453. Swain SM, et al. Ann Oncol (2018) pmid: 29253081
454. Gianni L, et al. Lancet Oncol. (2016) pmid: 27179402
455. Shao Z, et al. JAMA Oncol (2020) pmid: 31647503
456. Meric-Bernstam et al., 2021; ASCO Abstract 3004
457. Mazieres et al., 2021; ASCO Abstract 9015

03/2022 M-CH-00001908

USZ Universitäts Spital Zürich

FOUNDATION MEDICINE®

Roche

Roche Pharma (Schweiz) AG, 4052 Basel