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PATIENT

DISEASE Bladder urothelial (transitional cell) carcinoma
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Biomarker Findings

Tumor Mutational Burden - TMB-High (23 Muts/Mb)
Microsatellite Status - MS-Stable

Genomic Findings

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

CCND1 amplification
ERBB3 amplification
RAF1 amplification
BCL2L1 amplification
CDKN2A p16INK4a D84N and p14ARF R98Q
FGF19 amplification
FGF3 amplification
FGF4 amplification
LYN amplification
TERT promoter -146C>T
TP53 E285K

18 Therapies with Clinical Benefit
0 Therapies with Lack of Response
26 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - TMB-High (23 Muts/Mb)	Atezolizumab Avelumab Durvalumab Nivolumab Pembrolizumab	none
10 Trials *see p. 17*		
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
CCND1 - amplification	none	Abemaciclib Palbociclib Ribociclib
6 Trials *see p. 20*		
ERBB3 - amplification	none	Ado-trastuzumab emtansine Afatinib Lapatinib Pertuzumab Trastuzumab Trastuzumab-dkst
3 Trials *see p. 21*		

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
RAF1 **-** amplification	none	Cobimetinib
		Regorafenib
		Sorafenib
9 Trials *see p. 22*		Trametinib

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 Alterations section.

BCL2L1 amplification ..... p. 5
CDKN2A p16INK4a D84N and p14ARF R98Q ..... p. 5
FGF19 amplification ..... p. 6
FGF3 amplification ..... p. 6
FGF4 amplification ..... p. 7
LYN amplification ..... p. 7
TERT promoter -146C>T ..... p. 8
TP53 E285K ..... p. 8

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents 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.

BIOMARKER

Tumor Mutational Burden

CATEGORY

TMB-High (23 Muts/Mb)

POTENTIAL TREATMENT STRATEGIES

On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-4[1], anti-PD-L1[2-4], and anti-PD-1 therapies[5-7]; FDA-approved agents include ipilimumab, atezolizumab, avelumab, durvalumab, pembrolizumab, and nivolumab. In multiple solid tumor types, higher mutational burden has corresponded with response and improved prognosis. Pembrolizumab improved progression-free survival (14.5 vs. 3.4-3.7 months) in patients with non-small cell lung cancer (NSCLC) and higher mutational load (greater than 200 nonsynonymous mutations; hazard ratio = 0.19)[5]. In studies of patients with either NSCLC or colorectal cancer (CRC), patients whose tumors harbor elevated mutational burden reported higher overall response rates to pembrolizumab[5-7]. Anti-PD-1 therapies have achieved clinical benefit for certain patients with high mutational burden, including 3 patients with endometrial adenocarcinoma who reported sustained partial responses following treatment with pembrolizumab[8] or nivolumab[9], a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab[10], and two pediatric patients with biallelic mismatch repair deficiency (bMMRD)-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab[11]. In patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab[1,12] and anti-PD-1/anti-PD-L1 treatments[4]. For patients with metastatic urothelial carcinoma, those who responded to atezolizumab treatment had a significantly increased mutational load [12.4 mutations (mut) per megabase (Mb)] compared to nonresponders (6.4 mut/Mb)[2], and mutational load of 16 mut/Mb or higher was associated with significantly longer overall survival[3].

FREQUENCY & PROGNOSIS

In the Bladder Urothelial Carcinoma TCGA dataset, the median somatic mutation burden was 5.5 mutations per megabase (mut/MB)[13]. One study found somatic mutation number to positively correlate with increased tumor stage and grade of bladder cancers[14]. For patients with metastatic urothelial carcinoma receiving atezolizumab, however, higher median mutation load has been reported to be significantly associated with improved progression-free and overall survival[3,15].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[16-17] and cigarette smoke in lung cancer[5,18], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[19-23], and microsatellite instability (MSI)[19,22-23]. The tumor seen here harbors a high TMB. This type of mutation load has been shown to be associated with sensitivity to immune checkpoint inhibitors, including anti-CTLA-4 therapy in melanoma[1], anti-PD-L1 therapy in urothelial carcinoma[2], and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer[5-6], potentially due to expression of immune-reactive neoantigens in these tumors[5].

BIOMARKER

Microsatellite status

CATEGORY

MS-Stable

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[24-26], including approved therapies nivolumab and pembrolizumab[6,27]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[28]. Pembrolizumab therapy resulted in a significantly lower objective response rate (ORR) in MSS colorectal cancer (CRC) compared with MSI-H CRC (0% vs. 40%)[6]. Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with MSI-H tumors than those without[27].

FREQUENCY & PROGNOSIS

MSI has been detected in 26-49% of urothelial carcinomas[29-30]; MSI-high (MSI-H) has also been reported in multiple case studies of upper urinary tract urothelial carcinoma[31]. MSI, as determined through loss of MSH2 or MSH6 protein expression, correlated with non-invasive, well-differentiated tumors and favorable overall survival[29].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[32]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[32-34]. The tumor seen here is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[35-37]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[32,34,36-37].

Electronically signed by Julia Elvin, M.D., Ph.D. | Jeffrey Ross, M.D., Medical Director | 25 May 2018 | Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531

GENE
CCND1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
Amplification of CCND1 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[38-39 40-44]. Clinical benefit has been reported for patients with solid tumors harboring CCND1 amplification or expression in response to treatment with palbociclib[45] and ribociclib[38-39 40,43].

FREQUENCY & PROGNOSIS
CCND1 amplification has been reported in 12-15% of bladder urothelial carcinomas[13,46-47]. In patients with surgically treated lymph node-positive bladder urothelial carcinoma, CCND1 amplification correlated with shorter survival, although high nuclear cyclin D1 in metastases predicted a favorable response to adjuvant chemotherapy[48]. One study of non-muscle-invasive bladder cancer correlated high cyclin D1 expression with increased progression-free survival[49-52].

FINDING SUMMARY
CCND1 encodes cyclin D1, which interacts with the cyclin-dependent kinases CDK4 and CDK6, resulting in the phosphorylation and inactivation of Rb and the progression of the cell cycle. Amplification of CCND1 and/or overexpression of cyclin D1 may therefore lead to excessive proliferation[53-54]. CCND1 amplification has been positively correlated with overexpression of cyclin D1[55].

GENE
ERBB3

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
ERBB3/HER3 possesses a low-activity kinase domain and requires other ERBB family members for efficient signaling[56-58]. Therefore, ERBB3 amplification or activating mutation may predict sensitivity to therapies targeting ERBB2, such as pertuzumab, trastuzumab, ado-trastuzumab, lapatinib, and afatinib. In a study of afatinib monotherapy for patients with metastatic urothelial carcinoma, patients with ERBB3 mutation or ERBB2 amplification had significantly improved overall survival compared to patients without alterations (6.6 months vs. 1.4 months)[59]. A patient with HER2-negative breast cancer harboring an activating ERBB3 mutation had a partial response to the combination of trastuzumab and lapatinib[60]. In preclinical studies, cells with ERBB3 activating mutations were reported to be sensitive to anti-ERBB2 inhibition[57]. Antibodies targeting ERBB3 are also being studied in clinical trials.

FREQUENCY & PROGNOSIS
Amplification of ERBB3 has been reported in 2.3% of bladder urothelial carcinoma samples[13]. Expression of ERBB3 has been reported in urothelial carcinoma of the bladder in multiple studies, although the data surrounding the association between HER3 expression and invasion and metastasis is conflicting[61-66].

FINDING SUMMARY
ERBB3 (also known as HER3) encodes a member of the epidermal growth factor receptor (EGFR) family[67]. Focal amplification of ERBB3 is relatively rare, observed in a limited number of cancer types, although signaling through ERBB3 has been shown to have important roles in oncogenic signaling in several cancer types[56]. ERBB3 has been reported to be amplified in cancer[68] and may be biologically relevant in this context[69-70]. One study has demonstrated a weak but significant association between ERBB3 gene amplification and protein expression in breast cancer tissue[71].

GENE
RAF1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
Alterations that activate RAF1 may predict sensitivity to inhibitors that target RAF1 such as sorafenib and regorafenib. Activation of RAF1 kinase leads to the downstream activation of MEK; activating alterations may also confer sensitivity to MEK inhibitors such as cobimetinib and trametinib. The addition of sorafenib to chemotherapy improved progression-free survival for patients with melanoma and RAF1 copy number gains (HR=0.372, p=0.025)[72]. A patient with RAF1-rearranged pancreatic cancer achieved a partial response to sorafenib combination therapy[73].

FREQUENCY & PROGNOSIS
In the Bladder Urothelial Carcinoma TCGA dataset, RAF1 amplification is reported in 13% of cases[13]. One study reports RAF1 amplification in 2% (1/50 samples) of urothelial cancers analyzed[74]. Amplification and overexpression of RAF1 have been reported to be associated with high tumor grade, advanced tumor stage, and poor patient survival in urothelial carcinoma, and may be involved in tumor progression[75-76].

FINDING SUMMARY
RAF1, also known as CRAF, is a member of the RAF family of signaling kinases[77]. These kinases are downstream of RAS proteins and activate the MEK-ERK signaling pathway that promotes cell proliferation and survival[78]. RAF1 has been reported to be amplified in cancer[68], and may be biologically relevant in this context[69-70].

GENE
BCL2L1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies that target BCL2L1 amplification in cancer. Multiple investigational drugs that target BCL-2 family members including ABT-737, oblimersen sodium, AT-101, ABT-263 (navitoclax), and GX15-070 (obatoclax) are being studied in clinical trials[79]. Preclinical studies have shown activity of BCL-XL inhibitors in NSCLC cell lines and a xenograft mouse model[80-81]. Elevated BCL-XL levels protect cancer cells against apoptosis in multiple cancer types and may contribute to chemotherapy resistance[82-85].

FREQUENCY & PROGNOSIS

Gain of the 20q region where BCL2L1 is located has been reported in 34% of lung adenocarcinoma samples and in 75% of lung adenocarcinomas with EGFR mutations[86-87]. Expression of BCL-XL protein has been associated with poor prognosis in ovarian cancer and has been reported to be associated with taxane resistance in colorectal cancer[88-92].

FINDING SUMMARY

BCL2L1 encodes BCL-XL, an anti-apoptotic member of the BCL-2 protein family that is frequently overexpressed in cancer[93]. In colorectal cancer, 20q gain has been associated with BCL-XL protein overexpression[94-96].

GENE
CDKN2A

ALTERATION
p16INK4a D84N and p14ARF R98Q

POTENTIAL TREATMENT STRATEGIES

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[97-100]. However, multiple clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[42,101-103], and it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[104-105], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

CDKN2A loss or mutation has been found in 36% and 5.5% of bladder urothelial carcinomas, respectively[13]. CDKN2A loss of heterozygosity has been reported in 33% of bladder tumors (n=28)[106]. Studies have reported loss of p16INK4a expression in 13-59% of patients with bladder urothelial carcinoma[107-110]. Assessment of p16INK4a immunoreactivity in urine cytology has been proposed as a diagnostic tool for low-grade urothelial carcinomas[111]. Loss of expression of p16INK4a has not consistently been associated with histological stage or grade, nor with prognosis in patients with bladder urothelial carcinoma[108,112-115].

FINDING SUMMARY

CDKN2A encodes two distinct tumor suppressor proteins, p16INK4a and p14ARF[116-117]. p16INK4a inhibits CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; inactivation of p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and cell cycle control[118-119]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via MDM2 inhibition[120-121]. This alteration is predicted to result in p16INK4a[122-142] and p14ARF[126,143-145] loss of function.

GENE
FGF19

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies that directly address genomic alterations in FGF19. However, amplification of FGF19 predicts sensitivity to inhibitors of FGFR4 in liver cancer cell lines[146]; in one preclinical study, selective inhibition of FGFR4 reduced tumor burden in an FGF19-amplified HCC xenograft model[147]. A Phase 1 study of the FGFR4 inhibitor BLU-554 for previously treated HCC (11/14 sorafenib) reported 1 partial response and 1 stable disease (SD) in patients with FGF19-positive HCC[148]. Preliminary results from the dose escalation part of a Phase 1/2 study evaluating another FGFR4 inhibitor, FGF401, showed an overall response rate of 8% (4/53), 53% (28/53) SDs, and a median time to progression of 4.1 months; responses were observed in both FGF19-positive and -negative cases[149]. In one clinical study, a trend toward response to sorafenib treatment and FGF19 copy number gain was observed in patients with HCC, and 2 patients harboring FGF19 copy number gain experienced a complete response[150]. Multiple therapies targeting FGF19 or FGFR4 signaling are in preclinical development[151], and clinical trials evaluating inhibitors of FGFR4 are under way for patients with solid tumors.

FREQUENCY & PROGNOSIS

In the TCGA datasets, FGF19 amplification has been reported with highest incidence in esophageal carcinoma (35%), head and neck squamous cell carcinoma (28%), breast carcinoma (16%), lung squamous cell carcinoma (12%), bladder urothelial carcinoma (12%), and cholangiocarcinoma (11%) (cBioPortal, 2017). In HCC, FGF19 is an important driver gene[147,152–153], and FGF19 protein expression correlates with tumor progression and poorer prognosis[154]. Exogenous FGF19 has been shown to promote prostate cancer tumorigenesis in a preclinical study[155], and the presence of FGF19-positive tissues is an independent factor for worse prognosis following radical prostatectomy[156].

FINDING SUMMARY

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver[147,157]. FGF19 lies in a region of chromosome 11q13 frequently amplified in a diverse range of malignancies that also contains FGF3, FGF4, and CCND1[158]. Correlation between FGF19 amplification and protein expression has been demonstrated in hepatocellular carcinoma (HCC)[159] but was not observed in several other tumor types[152].

GENE
FGF3

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies that directly address genomic alterations in FGF3. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers.

FREQUENCY & PROGNOSIS

FGF3 lies in a region of chromosome 11q13 that also contains FGF19, FGF4, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[53].

FINDING SUMMARY

FGF3 encodes fibroblast growth factor 3, a growth factor that plays a central role in development of the inner ear. Germline mutations in FGF3 give rise to an autosomal recessive syndrome characterized by microdontia, deafness, and complete lack of inner ear structures[160].

GENE
FGF4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
FGF4 amplification and overexpression was associated with cell sensitivity to the multikinase inhibitor sorafenib in preclinical studies[161-162] and amplification of FGF4/FGF3 in HCC significantly correlated with patient response to sorafenib (p=0.006)[161]. Therefore, FGF4 amplification may confer sensitivity to sorafenib, which is FDA approved to treat HCC, renal cell carcinoma, and differentiated thyroid carcinoma. Sorafenib is under investigation in clinical trials in multiple tumor types.

FREQUENCY & PROGNOSIS
This chromosomal region is frequently amplified in a diverse range of malignancies[53] including esophageal carcinoma (35%), head and neck squamous cell carcinoma (HNSCC; 28%), breast invasive carcinoma (16%), lung squamous cell carcinoma (12%), bladder urothelial carcinoma (12%), ovarian serous cystadenocarcinoma (8%), stomach adenocarcinoma (7%), skin melanoma (6%), and hepatocellular carcinoma (HCC; 5%) (cBioPortal, 2017).

FINDING SUMMARY
FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth[163] and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development[164]. FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. Amplification of FGF4, along with that of FGF3, FGF19, and CCND1, has been reported in a variety of cancers[47,53,161,165-167] and may confer sensitivity to the multi-kinase inhibitor sorafenib[161].

GENE
LYN

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
Dasatinib is a kinase inhibitor that targets the BCR-ABL fusion protein, SRC family kinases including LYN specifically at nanomolar concentration[168-169], and other kinases, and has been approved for the treatment of chronic myelocytic leukemia (CML) and acute lymphoblastic leukemia (ALL). Dasatinib and other kinase inhibitors that target LYN are under investigation in clinical trials in solid tumors. In preclinical studies, dasatinib has been reported to inhibit cell migration and invasion in LYN-expressing solid tumor cells[168-170]. However, amplification or other genomic alterations in LYN in solid tumors, and their potential predictive value for sensitivity of these tumors to dasatinib and other kinase inhibitors, remain poorly understood. LYN is known to play oncogenic roles in hematopoietic malignancies such as CML, acute myeloid leukemia (AML), and chronic lymphocytic leukemia (CLL)[171], and a clinical trial examining LYN inhibition in patients with CLL is recruiting participants.

FREQUENCY & PROGNOSIS
LYN mutations have been documented infrequently in various cancers (COSMIC, cBioPortal, 2017), but LYN amplification has been reported at high frequencies in endometrial carcinosarcoma (19%), breast carcinoma (7%), and prostate adenocarcinoma (4%) and at lower frequencies in other tumor types (cBioPortal, 2017). LYN expression and activation have also been reported in several types of solid tumors, including glioblastoma[172], prostate cancer[173], head and neck squamous cell carcinoma (HNSCC)[174], and Ewing sarcoma[175]. LYN has also been reported to be overexpressed in 14.2% of breast cancer specimens (in particular in 47% of triple-negative breast cancers vs. 4% of others) and LYN overexpression was an independent poor prognostic variable (p=0.02) in that study[170]. LYN activation and overexpression has also been implicated in chemoresistance of colorectal cancer cells[176]. In preclinical studies, inhibition of LYN decreased the proliferation and tumorigenicity of multiple cancer cell lines in vitro and/or in xenografted mice[173,175] and cell invasion and migration of other cell lines[168,170,174].

FINDING SUMMARY
LYN encodes a SRC family intracellular membrane-associated tyrosine protein kinase. LYN is expressed predominantly in hematopoietic cells and conveys signals from the B-cell receptor (BCR) and other receptors to activate the PI3K, STAT, and other signaling pathways[171,177].

GENE
TERT

ALTERATION
promoter -146C>T

POTENTIAL TREATMENT STRATEGIES

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches are under development, including immunotherapies utilizing TERT as a tumor-associated antigen, antisense oligonucleotide- or peptide-based therapies, and TERT promoter-directed cytotoxic molecules.

FREQUENCY & PROGNOSIS

TERT promoter mutations have been observed in melanoma, glioma, and thyroid and bladder cancers[178-186]. One study reported TERT promoter mutations in 67% (14/21) of high-grade and 56% (34/61) of low-grade bladder carcinomas[179], while another study demonstrated that 85% (44/52) of all bladder cancer samples and 88% (7/8) of bladder cancer cell lines exhibited TERT promoter alteration[185]. TERT promoter mutations correlated with increased TERT mRNA expression in urothelial cancer cells[187]. In patients with bladder urothelial carcinoma, both TERT promoter mutations and increased TERT expression associate with poor prognosis, although carrying an additional germline alteration at -245 (rs2853669) may confer a better prognosis[181,187-188].

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[189]. TERT activation is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[190-192]. Mutations within the TERT promoter region that confer enhanced promoter activity have been reported in two hot spots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[178-179,193], as well as tandem mutations at positions -124/-125 bp and -138/-139 bp[193].

GENE
TP53

ALTERATION
E285K

POTENTIAL TREATMENT STRATEGIES

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 AZD1775[194-197], therapies that reactivate mutant p53 such as APR-246[198-201], or p53 gene therapy and immunotherapeutics such as SGT-53[202-206] and ALT-801[207]. In a Phase 1 study, AZD1775 in combination with gemcitabine, cisplatin, or carboplatin elicited partial response in 10% (17/176) and stable disease in 53% (94/176) of patients with solid tumors; the response rate was 21% (4/19) in patients with TP53 mutations versus 12% (4/33) in patients who were TP53-wild-type[208]. Combination of AZD1775 with paclitaxel and carboplatin achieved significantly longer progression-free survival than paclitaxel and carboplatin alone in patients with TP53-mutant ovarian cancer[209]. Furthermore, AZD1775 in combination with carboplatin achieved a 27% (6/22) response rate and 41% (9/22) stable disease rate in patients with TP53-mutant ovarian cancer refractory or resistant to carboplatin plus paclitaxel[210]. In a Phase 1b trial in patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% disease control rate[198]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including two confirmed and one unconfirmed partial responses and two instances of stable disease with significant tumor shrinkage[206]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53 mutant, but not TP53 wild-type, breast cancer xenotransplant mouse model[211]. Kevetrin has also been reported to activate p53 in preclinical studies and might be relevant in the context of mutant p53[212]. Clinical trials of these agents are under way for some tumor types for patients with a TP53 mutation.

FREQUENCY & PROGNOSIS

Mutations in TP53 have been reported in 48% of bladder urothelial carcinoma samples analyzed in the TCGA dataset[13]. A study of Stage 4 urothelial carcinomas that had undergone relapse or progression after surgery and chemotherapy reported genomic alterations in TP53 in 54% (19/35) of cases[46].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[213]. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis[214-216]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[217-222]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[223] to 1:20,000[222], and in the appropriate clinical context, germline testing of TP53 is recommended.

Atezolizumab

Assay findings association

Tumor Mutational Burden
TMB-High (23 Muts/Mb)

APPROVED INDICATIONS

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 advanced urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy or who progress during or following platinum-based chemotherapy and to treat patients with metastatic non-small cell lung cancer (NSCLC) and disease progression on prior treatments.

GENE ASSOCIATION

On the basis of emerging clinical data in patients with urothelial carcinoma[2-3], non-small cell lung cancer (NSCLC)[224-225], or melanoma[4], high tumor mutation burden (TMB) may predict sensitivity to anti-PD-L1 therapies such as atezolizumab.

SUPPORTING DATA

Patients with metastatic urothelial carcinoma who were treated with atezolizumab as first-line therapy experienced an overall response rate (ORR) of 23%, a complete response (CR) rate of 9%, and a clinical benefit rate of 30%[3]. Increased tumor mutational burden (TMB) was associated with response to atezolizumab, and patients with the highest TMB [at least 16 mutations per megabase (muts/Mb)] lived significantly longer than patients with lower TMB[3]. As second-line therapy for advanced urothelial carcinoma, atezolizumab compared with chemotherapy did not significantly improve median overall survival [OS; 11.1 vs. 10.6 months, hazard ratio (HR) of 0.87] for patients with PD-L1 expression on 5% or more of tumor-infiltrating immune cells. ORRs (23% vs. 22%) and median progression-free survival (PFS, HR of 1.01) were similar between the treatment arms, but atezolizumab was associated with a numerically longer median duration of response (15.9 vs. 8.3 months) and a favorable adverse event profile[226]. Median OS with atezolizumab was numerically longer in the PD-L1-unselected overall study population (8.6 vs. 8.0 months, HR of 0.85) as well as for patients with high TMB (above 9.7 muts/Mb) compared with those with lower TMB (11.3 vs. 8.3 months)[226]. An earlier Phase 2 trial reported an ORR of 15%, with 80% (37/46) of the responses ongoing at the median follow-up of 14.4 months; the median PFS was 2.1 months, and the 12-month OS rate was 37%[2,227]. A significantly higher median TMB (12.4 muts/Mb) was observed in patients who responded to atezolizumab compared with that in nonresponders (6.4 muts/Mb)[2]. Long-term follow-up of a Phase 1 expansion cohort reported a 3-year OS rate of 27% on second-line atezolizumab[228]. In an expanded access study, the benefit/risk profile of atezolizumab for a broader range of previously treated patients was comparable with the one observed in Phase 1-3 trials[229].

Avelumab

Assay findings association

Tumor Mutational Burden
TMB-High (23 Muts/Mb)

APPROVED INDICATIONS

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 metastatic Merkel cell carcinoma and patients with advanced urothelial carcinoma who have progressed on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy.

GENE ASSOCIATION

On the basis of emerging clinical data in patients with urothelial carcinoma[2], non-small cell lung cancer[224-225], or melanoma[4], high tumor mutation burden (TMB) may predict sensitivity to immune checkpoint inhibitors targeting PD-1/PD-L1 signaling such as avelumab.

SUPPORTING DATA

In a Phase 1b trial evaluating single-agent avelumab, patients with metastatic urothelial carcinoma achieved a median progression-free survival (PFS) of 6.4 weeks, a median overall survival (OS) of 7 months, and an objective response rate (ORR) of 17.6% (27/153), which included 9 complete responses; the median PFS, median OS, and ORR were similar regardless of PD-L1 status[230].

Durvalumab

Assay findings association

Tumor Mutational Burden
TMB-High (23 Muts/Mb)

APPROVED INDICATIONS

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 advanced urothelial carcinoma that has progressed on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy. Durvalumab is also approved to treat patients with unresectable, Stage 3 non-small cell lung cancer that has not progressed following concurrent platinum-based chemotherapy and radiation.

GENE ASSOCIATION

On the basis of emerging clinical data in patients with urothelial carcinoma[2], non-small cell lung cancer[224-225], or melanoma[4], high tumor mutational burden (TMB) may predict sensitivity to immune checkpoint inhibitors targeting PD-1/PD-L1 signaling such as durvalumab.

SUPPORTING DATA

In a Phase 1/2 study of single-agent durvalumab, patients with locally advanced or metastatic urothelial carcinoma experienced an objective response rate (ORR) of 20.4% (21/103), including 4 complete responses (CRs) and 17 partial responses; the ORR was higher in patients with PD-L1 positivity on ≥ 25% of tumor cells or tumor-infiltrating immune cells (31.1%, 19/61) than in PD-L1-negative patients (5.1%, 2/39), although CRs were reported in both groups[231-232]. Durvalumab is being evaluated in the DANUBE Phase 3 study (NCT02516241) in combination with the CTLA4-targeting antibody tremelimumab in the first-line setting for urothelial carcinoma (May 2017).

Nivolumab

Assay findings association

Tumor Mutational Burden
TMB-High (23 Muts/Mb)

APPROVED INDICATIONS

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby reducing inhibition of the antitumor immune response. It is FDA approved as adjuvant treatment for completely resected advanced melanoma and as treatment for unresectable or metastatic melanoma as both a single agent and in combination with the immunotherapy ipilimumab. Nivolumab is also approved in combination with ipilimumab to treat intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC) and as monotherapy to treat advanced RCC after prior antiangiogenic therapy. Nivolumab is also approved to treat metastatic non-small cell lung cancer (NSCLC) following disease progression on prior treatments, recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) following disease progression on or after platinum-based therapy, advanced urothelial carcinoma that has progressed on or after platinum chemotherapy or within 12 months of neoadjuvant or adjuvant platinum chemotherapy, hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib, and classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and posttransplantation brentuximab vedotin. Furthermore, nivolumab is approved to treat patients 12 years and older with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan.

GENE ASSOCIATION

On the basis of emerging clinical data in patients with non-small cell lung cancer[5,225], colorectal cancer[6], or melanoma[233] and case reports in endometrial cancer[8-9] and glioblastoma[11], high tumor mutation burden (TMB) may predict sensitivity to anti-PD-1 therapies such as nivolumab.

SUPPORTING DATA

In a Phase 2 study evaluating nivolumab in patients with platinum-refractory metastatic urothelial carcinoma, the objective response rate (ORR) was 19.6%, with 2% and 17% of patients achieving a complete response (CR) or a partial response (PR), respectively; median progression-free survival (PFS) was 2.0 months and median overall survival (OS) was 8.7 months[234]. In a Phase 1/2 study for patients with metastatic urothelial carcinoma who progressed on platinum-based therapy, nivolumab treatment resulted in an ORR of 24.4%, with a median PFS of 2.8 months and a median OS of 9.7 months[235]. In a retrospective study of patients with non-melanoma cancer types (of which 13% were urothelial carcinomas) who were treated with nivolumab or pembrolizumab, 19% of patients achieved a PR, and 25% had stable disease (SD)[236]. Another retrospective study of 27 patients with solid tumors, including 4 patients with urothelial bladder cancer, who received nivolumab or pembrolizumab, reported 1 CR, 4 PRs, and 11 SDs, with median PFS of 169 days[237].

Pembrolizumab

Assay findings association

Tumor Mutational Burden
TMB-High (23 Muts/Mb)

APPROVED INDICATIONS

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 as second-line treatment for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors or with MSI-H or dMMR colorectal cancer that has progressed on a fluoropyrimidine, oxaliplatin, and irinotecan. Pembrolizumab is also approved in unresectable or metastatic melanoma; recurrent or metastatic head and neck squamous cell carcinoma that has progressed on or after platinum chemotherapy; adult or pediatric classical Hodgkin lymphoma that is refractory or following relapse after three or more prior lines of therapy; advanced urothelial carcinoma that is not eligible for cisplatin-containing chemotherapy, has progressed on or after platinum chemotherapy, or has progressed within 12 months of neoadjuvant or adjuvant platinum chemotherapy; and PD-L1-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma that has progressed on two or more lines of therapy. Pembrolizumab is approved in PD-L1-positive metastatic non-small cell lung cancer (NSCLC) following progression on prior therapy, as first-line treatment for metastatic NSCLC with high PD-L1 expression and without EGFR or ALK genomic alterations, and as first-line treatment in combination with pemetrexed and carboplatin for metastatic nonsquamous NSCLC.

GENE ASSOCIATION

On the basis of emerging clinical data in patients with non-small cell lung cancer[5,225], colorectal cancer[6], or melanoma[233] and case reports in endometrial cancer[8-9] and glioblastoma[11], high tumor mutation burden (TMB) may predict sensitivity to anti-PD-1 therapies such as pembrolizumab.

SUPPORTING DATA

As second-line therapy for patients with advanced urothelial carcinoma and disease progression on or after platinum-containing chemotherapy, the Phase 3 KEYNOTE-45 trial found pembrolizumab superior to chemotherapy of choice in terms of overall survival [OS; 10.3 months vs. 7.4 months, hazard ratio (HR)=0.74, P=0.002] and overall response rate (ORR; 21.1% vs. 11.4%)[238]. Improved efficacy of pembrolizumab compared to chemotherapy was observed for all subgroups examined, including the subgroup positive for PD-L1 in 10% of cells or more (8.0 months vs. 5.2 months, HR=0.57), PD-L1 score of 1% or less, or for patients with liver metastases. Progression-free survival (PFS) was not significantly different between pembrolizumab and chemotherapy groups (2.1 months vs. 3.3 months on chemotherapy, HR=0.98, with no significant difference based on PD-L1 expression over 10%)[238]. Antitumor activity for pembrolizumab in urothelial carcinoma was also observed in the Phase 1b KEYNOTE-12 study, which reported 3/27 complete responses, 4/27 partial responses, median PFS of 2 months, and median OS of 13 months[239]. For cisplatin-ineligible patients with advanced urothelial carcinoma, the Phase 2 KEYNOTE-52 trial found first-line therapy with pembrolizumab achieved an ORR of 24%; 39% of patients with PD-L1-high status (at least 10%) responded[240]. Notably, pembrolizumab has been reported to benefit patients with both high and low tumor cell PD-L1 expression[238-239].

Abemaciclib

Assay findings association

CCND1
amplification

APPROVED INDICATIONS

Abemaciclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved to treat hormone receptor-positive (HR+), HER2-negative (HER2–) advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women, in combination with fulvestrant for women who have progressed on endocrine therapy, or as monotherapy for adults who have progressed on endocrine therapy and chemotherapy in the metastatic setting.

GENE ASSOCIATION

On the basis of clinical data in breast cancer and mantle cell lymphoma[44,241], CCND1 amplification or activation may be associated with response to abemaciclib. In a Phase 1 study, 4/10 patients with CCND1-amplified breast cancer responded to single-agent abemaciclib, with all of the responders having HR+ tumors[44].

SUPPORTING DATA

Abemaciclib has been investigated primarily in the context of breast cancer[44,242-243]. A Phase 1 study evaluating abemaciclib as monotherapy for patients with various solid tumors reported 11 partial responses (PRs)(31%, 11/36) and 18 stable diseases (SDs)(50%, 18/36) in HR+ breast cancer, 1 PR in patients with melanoma (4%, 1/26), and SDs in patients with colorectal carcinoma (13%, 2/15), melanoma (23%, 6/26), and glioblastoma (18%, 3/17)[44].

Ado-trastuzumab emtansine

Assay findings association

ERBB3
amplification

APPROVED INDICATIONS

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein HER2 on the cell surface, inhibiting HER2 signaling[244-245]; it also releases the cytotoxic therapy DM1 into cells, leading to cell death[245-246]. T-DM1 is FDA approved for the treatment of HER2-positive (HER2+) metastatic breast cancer.

GENE ASSOCIATION

ERBB3/HER3 possesses a low-activity kinase domain and requires other ERBB-family members for efficient signaling, HER2/neu in particular[56-58,247]. Tumors with activating mutations in or amplification of ERBB3 may be susceptible to therapies such as T-DM1.

SUPPORTING DATA

The vast majority of data investigating the therapeutic use of T-DM1 has been in the context of breast cancer. A Phase 3 trial with 602 HER2+ breast cancer patients reported that those who received T-DM1 showed an improved progression-free survival (PFS) and a lower rate of adverse events than patients who received the physician's choice of therapy[248]. A second Phase 3 trial with 991 HER2+ breast cancer patients reported that T-DM1 brought about significantly longer overall survival (OS) and PFS, as compared with lapatinib plus capecitabine, in patients previously treated with trastuzumab plus a taxane[249-250]. Two separate Phase 2 trials reported robust activity for single-agent T-DM1 as a treatment for HER2+ metastatic breast cancer in patients previously treated with standard HER2-directed therapies or HER2-directed therapies plus chemotherapy, with objective response rates of 34.5% and 25.9%, respectively, and PFS of 6.9 months and 4.9 months, respectively.[251-252].

Afatinib

Assay findings association

ERBB3
amplification

APPROVED INDICATIONS

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the treatment of metastatic non-small cell lung cancer (NSCLC) in patients with EGFR exon 19 deletions or exon 21 (L858R) missense mutations.

GENE ASSOCIATION

ERBB3/HER3 possesses a low-activity kinase domain and requires other ERBB family members for efficient signaling, ERBB2/HER2 in particular[56-58,247]; therefore, ERBB3 amplification or activating mutations may indicate sensitivity to therapies such as afatinib. Partial response (PR) or stable disease (SD) was elicited in 5/7 patients with urothelial carcinoma harboring ERBB3 mutations (V104M, R103G, or G284R) and/or HER2 copy number gain treated with afatinib[59].

SUPPORTING DATA

A Phase 2 study of afatinib in platinum-refractory urothelial carcinoma reported a response (1 PR and 4 SD) in 5/23 patients; response was observed in 5/7 patients with alterations in ERBB2 and/or ERBB3, and in 0/16 patients without alterations in these genes[59]. A Phase 2 trial of afatinib in patients with either EGFR or ERBB2 amplification and esophagogastric, biliary tract, urothelial tract, or gynecologic cancer reported a 5% (1/20) objective response, with complete response achieved in one patient and stable disease achieved in 8 patients; the authors concluded that afatinib activity as a single agent was encouraging[253]. A Phase 1 trial of afatinib in advanced cancer reported disease stabilization in 14/31 patients[254]. A Phase 1 study of afatinib combined with pemetrexed in patients with advanced solid tumors reported confirmed partial response in 3% (1/30) of patients and stable disease in 33% (10/30) of patients[255]. A Phase 1 trial of volasertib and afatinib in patients with advanced solid tumors reported partial response in 7% (2/29) of patients[256]. Outcomes of partial response and/or stable disease have been reported in various clinical trials involving multiple cancer types, including HER2-positive breast cancer, NSCLC, colorectal cancer, and esophageal cancer[257-261].

Electronically signed by Julia Elvin, M.D., Ph.D. | Jeffrey Ross, M.D., Medical Director | 25 May 2018 | Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531

Cobimetinib

Assay findings association

RAF1
amplification

APPROVED INDICATIONS

Cobimetinib is a MEK inhibitor that is FDA approved in combination with vemurafenib for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations.

GENE ASSOCIATION

RAF1 amplification or activating mutations may lead to activation of the MAPK pathway and may predict sensitivity to cobimetinib.

SUPPORTING DATA

Cobimetinib has been investigated primarily in the context of BRAF V600-mutant melanoma. A Phase 3 study with 495 patients treated either with the BRAF inhibitor vemurafenib plus cobimetinib or vemurafenib alone reported a 68-70% overall response rate, 9.9-12.3 months progression-free survival, and a lower rate of cutaneous squamous cell carcinoma in the combination group; benefit of cobimetinib was observed regardless of prognostic factors, and disease progression did not correlate with concurrent alterations in the RAS pathway[262-263 264]. In a Phase 1b study, vemurafenib combined with cobimetinib achieved an objective response rate of 87%, including 19% complete response rate, for patients with BRAF V600-mutant melanoma who had not previously received a BRAF inhibitor; median OS of this patient cohort was >2.5 years[265-266]. One study reported near-complete response to vemurafenib in a patient with BRAF V600K-mutant melanoma who subsequently developed chronic myelomonocytic leukemia (CMML) with NRAS G12R mutation, and concurrent cobimetinib treatment led to suppression of CMML[267]. A Phase 1b study evaluated cobimetinib in combination with the anti-PD-L1 immune checkpoint inhibitor atezolizumab for advanced solid tumors and enrolled 23 patients with colorectal cancer, who were mostly (22/23) KRAS-mutant; 17% (4/23) of these patients achieved objective partial responses, 22% (5/23) of patients experienced stable disease, and no dose-limiting toxicities were encountered[268]. In a Phase 1b study, out of 47 patients treated with cobimetinib and the AKT inhibitor ipatasertib, 3 patients with KRAS-mutant ovarian, mesonephric cervical, or endometrial carcinoma had a partial response, with prolonged stable disease lasting for >6 months[269].

Lapatinib

Assay findings association

ERBB3
amplification

APPROVED INDICATIONS

Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine or letrozole for the treatment of HER2-overexpressing (HER2+) metastatic breast cancer.

GENE ASSOCIATION

ERBB3 requires other ERBB-family members for efficient signaling, ERBB2 in particular[56-58,247], and may predict sensitivity to HER2 inhibitors such as trastuzumab. A patient with ERBB3-mutated breast cancer achieved a response to a lapatinib and trastuzumab combination therapy[60].

SUPPORTING DATA

Lapatinib has shown limited clinical benefit for the treatment of urothelial carcinoma. A Phase 3 study of lapatinib or placebo in patients with EGFR or ERBB2-positive metastatic urothelial bladder cancer who progressed on first-line chemotherapy reported no significant difference in progression-free survival (PFS) or overall survival (OS)[270]. A Phase 2 study of single-agent lapatinib in patients with urothelial carcinoma did not meet its primary endpoint of objective response rate, but clinical benefit was observed, particularly in patients with EGFR or ERBB2 amplification[271]. A small study of six patients with metastatic transitional cell carcinoma treated with paclitaxel and lapatinib reported negative side effects; most patients discontinued therapy[272]. A trial of lapatinib, gemcitabine, and cisplatin as a neoadjuvant regimen for patients intending to undergo radical cystectomy reported substantial treatment-related toxicity and the study was terminated early[273].

Palbociclib

Assay findings association

CCND1
amplification

APPROVED INDICATIONS

Palbociclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved to treat hormone receptor (HR)-positive/HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as first-line therapy for postmenopausal women or in combination with fulvestrant following progression on endocrine therapy.

GENE ASSOCIATION

Clinical studies in liposarcoma and mantle cell lymphoma as well as responses in patients with breast cancer or melanoma indicate that activation of cyclin D-CDK4/6 may predict sensitivity to therapies such as palbociclib[39,45,274].

SUPPORTING DATA

Palbociclib has been studied primarily for the treatment of ER+ breast cancer[42,102,275]. Single-agent palbociclib has shown limited activity against solid tumors, with a Phase 1 study reporting no partial responses (PR) and a 16% (6/37) stable disease (SD) rate (>9 months)[41]. Phase 2 trials of palbociclib in patients with KRAS-mutant colorectal cancer or p16INK4a-deficient non-small cell lung cancer (NSCLC) also reported no responses, although SD was seen in 33% (5/15) and 50% (8/16) of patients, respectively[101,276]. A Phase 2 study of palbociclib for the treatment of advanced Rb-positive hepatocellular carcinoma reported disease control (responses or stable disease) for 9/21 (43%) patients, including one patient with a PR; the trial has met its primary endpoint[277]. For various tumor types, preclinical studies suggest that palbociclib may be useful in combination with other therapies targeting oncogenic drivers such as MEK, BRAF, PI3K, or IGF1R[278-282].

Pertuzumab

Assay findings association

ERBB3
amplification

APPROVED INDICATIONS

Pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. It is FDA approved in combination with trastuzumab and docetaxel to treat a subset of patients with HER2-positive (HER2+) breast cancer[283].

GENE ASSOCIATION

ERBB3 amplification or activating mutations may predict sensitivity to pertuzumab.

SUPPORTING DATA

Of 9 patients with HER2-activated advanced bladder cancer treated with trastuzumab plus pertuzumab, 5 patients achieved clinical benefit, including 1 complete and 2 partial responses[284]. Pertuzumab has been studied primarily for the treatment of HER2+ breast cancer, and addition of pertuzumab to trastuzumab and docetaxel significantly improved median progression-free survival and overall survival as first-line treatment for patients with HER2+ metastatic breast cancer[283,285-286].

Regorafenib

Assay findings association

RAF1
amplification

APPROVED INDICATIONS

Regorafenib is a small-molecule inhibitor of multiple kinases, including RET, VEGFRs, PDGFRs, KIT, and RAF family proteins[287]. It is FDA approved to treat hepatocellular carcinoma that has been previously treated with sorafenib[288], metastatic colorectal cancer (CRC), or advanced gastrointestinal stromal tumors (GISTs)[289-291].

GENE ASSOCIATION

RAF1 amplification or activating mutations may lead to increased RAF1 activity, and may therefore indicate sensitivity to RAF inhibitors such as regorafenib.

SUPPORTING DATA

Published clinical studies have not evaluated regorafenib specifically for the treatment of bladder carcinoma (PubMed, Aug 2017). Regorafenib has primarily been studied as a treatment for CRC and GIST, and data are limited for other tumor types. Regorafenib improved overall survival in patients with CRC and progression-free survival in patients with imatinib/sunitinib-refractory GIST as compared with placebo[289-290]. A Phase 1 trial of regorafenib in 47 patients with solid tumors reported 3 (6%) partial responses in patients with CRC, renal cell carcinoma, or osteosarcoma[292].

Ribociclib

Assay findings association

CCND1
amplification

APPROVED INDICATIONS

Ribociclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved in combination with aromatase inhibitor as first-line therapy to treat postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

GENE ASSOCIATION

On the basis of clinical responses for 3 patients with bladder cancer, BRAF/NRAS-wild-type melanoma, or ER-positive breast cancer[39,43], CCND1 amplification may predict sensitivity to CDK4/6 inhibitors such as ribociclib. In a prospective trial, 1 out of 12 patients with CCND1-amplified solid tumors responded to ribociclib[39].

SUPPORTING DATA

The Phase 1 Signature study of ribociclib for the treatment of patients with CDK4/6 pathway activated tumors reported clinical benefit for 18.4% (19/103) of cases, 58% (11/19) of whom had p16INK4a mutation or loss; antitumor activity was observed in 3 patients[39]. Phase 1 studies of ribociclib for the treatment of patients with Rb+ advanced solid tumors reported 2.4% partial responses and 23.5-34.4% stable diseases (SD)[43,293]; the 3 responders had alterations in the CDK4/6 pathway[43]. Another Phase 1 study of ribociclib monotherapy reported some efficacy in pediatric patients with neuroblastoma (4 SD - including two for >280 days and four progressive disease [PD]) and CNS rhabdoid tumors, including ATRT (1 SD [ongoing after 444 days] and 9 PD), although RB1 status was not determined in any of the patients; of the patients with CDK4-amplified tumors (all neuroblastoma) 1 achieved SD (for >280 days) and 2 exhibited PD[294].

Sorafenib

Assay findings association

RAF1
amplification

APPROVED INDICATIONS

Sorafenib is a kinase inhibitor that targets the RAF kinases, KIT, FLT3, RET, VEGFRs, and PDGFRs. It is FDA approved for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and recurrent or metastatic differentiated thyroid carcinoma.

GENE ASSOCIATION

RAF1 amplification or activating mutations may lead to increased RAF1 activity, and may therefore indicate sensitivity to RAF inhibitors such as sorafenib. Addition of sorafenib to chemotherapy improved progression-free survival in patients with melanoma harboring RAF1 copy number gains (HR=0.372, P=0.025)[72].

SUPPORTING DATA

Two Phase 2 trials showed minimal activity of sorafenib as a single agent in metastatic urothelial cancer[295]. A Phase 2 clinical trial comparing sorafenib with gemcitabine and cisplatin therapy to gemcitabine/cisplatin alone in locally advanced or metastatic urothelial cancer was terminated due to the lack of clear benefit from sorafenib addition[296]. Sorafenib has been shown to enhance proliferation of bladder cancer cell lines[297].

Trametinib

Assay findings association

RAF1
amplification

APPROVED INDICATIONS

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy and in combination with dabrafenib to treat patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as well as in combination with dabrafenib as adjuvant treatment for completely resected advanced BRAF V600E- or V600K-positive melanoma. It is also approved in combination with dabrafenib to treat patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation and to treat patients with BRAF V600E-positive anaplastic thyroid cancer (ATC) who lack satisfactory locoregional treatment options.

GENE ASSOCIATION

Amplification or activating mutation of RAF1 may lead to the downstream activation of MEK and may predict sensitivity to trametinib.

SUPPORTING DATA

Clinical data on the efficacy of trametinib specifically for the treatment of bladder cancer are limited (PubMed, Feb 2017). A Phase 1 trial of trametinib in 206 patients with solid tumors reported 21 (10%) objective responses[298]. Phase 1 monotherapy trials of RO4987655, another MEK inhibitor, have shown significant response rates in patients with melanoma, including those with BRAF and NRAS mutations, but very low response rates in patients with other solid tumors, including those with KRAS mutations[299-300]. A Phase 1b trial of trametinib in combination with gemcitabine in patients with solid tumors showed a complete response in a patient with breast cancer, as well as partial responses in pancreatic and salivary gland cancer[301]. A Phase 1b trial of combination treatment with the MEK inhibitor MEK162 and the PI3K-alpha inhibitor BYL719 reported disease control (partial responses or stable disease) in 47% (21/45) of patients, including partial responses in 2 of 3 patients with KRAS-mutant ovarian cancer and 1 of 3 patients with NRAS-mutant melanoma; a 43% rate of stable disease was observed in patients with KRAS-mutant colorectal cancer, with responses independent of PIK3CA mutation status[302]. However, a Phase 1b trial of a combination of trametinib and the mTOR inhibitor everolimus in patients with solid tumors reported frequent adverse events and was unable to identify a recommended Phase 2 dose and schedule for the combination[303].

Trastuzumab

Assay findings association

ERBB3
amplification

APPROVED INDICATIONS

Trastuzumab is a monoclonal antibody that targets the protein HER2/neu (encoded by ERBB2). It is FDA approved for the treatment of HER2-overexpressing breast and metastatic gastric or gastroesophageal adenocarcinomas.

GENE ASSOCIATION

ERBB3 requires other ERBB-family members for efficient signaling, ERBB2 in particular[56-58,247], and may predict sensitivity to HER2 inhibitors such as trastuzumab. A patient with ERBB3-mutated breast cancer achieved a response to a lapatinib and trastuzumab combination therapy[60].

SUPPORTING DATA

A multi-center, randomized Phase 2 study comparing trastuzumab in combination with gemcitabine and platinum chemotherapy to chemotherapy alone for the treatment of patients with urothelial carcinoma reported no significant difference in progression-free survival (PFS), objective response rate, or median overall survival between the two treatment arms; however, the authors noted that only 13% (75/563) patients in this study were HER2-positive[304]. In a Phase 2a umbrella basket trial, out of 9 patients with bladder cancer and HER2 alteration, 1 patient had a complete response, 2 patients had a partial response, and 2 patients had stable disease[284]. Trastuzumab has been reported to show activity in combination with chemotherapy in patients with HER2-positive urothelial carcinoma, but the relative benefit is difficult to ascertain without Phase 3 data[305-306]. Trastuzumab was approved for breast cancer on the basis of a Phase 3 randomized clinical trial comparing treatment with trastuzumab and chemotherapy to treatment with chemotherapy alone. The addition of trastuzumab was associated with significant improvements in time to progression, objective response rate, response duration, and overall survival[307].

Trastuzumab-dkst

Assay findings association

ERBB3
amplification

APPROVED INDICATIONS

Trastuzumab-dkst is FDA approved as a biosimilar therapy to trastuzumab. Trastuzumab-dkst is a monoclonal antibody that targets the protein ERBB2/HER2, and is FDA approved as monotherapy and in combination with chemotherapy for HER2-positive (HER2+) metastatic and early breast carcinoma and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal junction adenocarcinoma.

GENE ASSOCIATION

ERBB3 possesses a low-activity kinase domain and requires other ERBB family members for efficient signaling, HER2 in particular[56-58,247]; therefore, ERBB3 amplification or activating mutations may indicate sensitivity to anti-HER2 therapies such as trastuzumab-dkst[57]. A patient with HER2-negative breast cancer harboring an activating ERBB3 mutation had a partial response to the combination of trastuzumab and lapatinib[60].

SUPPORTING DATA

The Phase 3 Heritage study demonstrated comparable 24-week objective response rates (69.6% vs. 64.0%) and progression-free survival for patients with treatment-naïve HER2+ metastatic breast cancer treated with either trastuzumab-dkst or trastuzumab in combination with taxane[308]. In both patients with HER2+ breast cancer and in healthy adults, trastuzumab-dkst demonstrated comparable pharmacokinetic, safety, and immunomodulation profiles to trastuzumab[308-309 310].

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs, however the agents listed in this report may have little or no evidence in the patient's tumor type.

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. 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 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. Or, visit https://www.foundationmedicine.com/genomic-testing#support-services.

BIOMARKER

Tumor Mutational Burden

CATEGORY

TMB-High (23 Muts/Mb)

RATIONALE

High tumor mutational burden may predict response to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "PD-L1", "B7-H1", "PD-1", "pembrolizumab", "nivolumab", "atezolizumab", "MPDL3280A", "durvalumab", "MEDI4736", "avelumab", "MSB0010718C", "BMS-936559", "CT-011", "bladder carcinoma", "urothelial carcinoma", "solid tumor", and/or "advanced cancer".

NCT02450331

PHASE 3

A Phase III, Open-Label, Multicenter, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) Versus Observation as Adjuvant Therapy in Patients With High-Risk Muscle-Invasive Urothelial Carcinoma After Surgical Resection

TARGETS

PD-L1

LOCATIONS: Wroclaw (Poland), Villejuif (France), Helsinki (Finland), Lyon (France), Meldola (Italy), London (Canada), Nanjing (China), Iwate (Japan), Bochum (Germany), Terni (Italy), Nizhny Novgorod (Russian Federation), Edmonton (Canada), Beijing (China), Melbourne (Australia), Hiroshima (Japan), Rhode Island, Gent (Belgium), Oshawa (Canada), Izmir (Turkey), Florida, Ramat Gan (Israel), Berlin (Germany), Arizona, Angers (France), Istanbul (Turkey), Tokyo (Japan), Dresden (Germany), Ekaterinburg (Russian Federation), Hokkaido (Japan), Edirne (Turkey), Bristol (United Kingdom), Ulm (Germany), Gyeonggi-do (Korea, Republic of), Aachen (Germany), Herne (Germany), East Bentleigh (Australia), Tampere (Finland), Pardubice (Czechia), Shizuoka (Japan), Quebec (Canada), Osaka (Japan), München (Germany), Bruxelles (Belgium), Arezzo (Italy), San Sebastian (Spain), Kyoto (Japan), Macquarie University (Australia), California, Preston (United Kingdom), Ufa (Russian Federation), Taichung (Taiwan), Utrecht (Netherlands), Taipei (Taiwan), Athens (Greece), Adana (Turkey), Moscow (Russian Federation), Hamburg (Germany), Warszawa (Poland), Düsseldorf (Germany), Stuttgart (Germany), Hafia (Israel), Barcelona (Spain), Taoyuan (Taiwan), Ohio, Oxford (United Kingdom), Kharkiv (Ukraine), Illinois, Bordeaux (France), Barrie (Canada), Saitama (Japan), Montreal (Canada), Sabadell (Spain), London (United Kingdom), Tübingen (Germany), Nancy (France), Bologna (Italy), Changchun (China), Caen (France), Valencia (Spain), Orbassano (Italy), Groningen (Netherlands), Novi Sad (Serbia), Madrid (Spain), Shanghai City (China), Rostock (Germany), North Carolina, Roma (Italy), Kiev (Ukraine), Amsterdam (Netherlands), Maryland, Michigan, Leuven (Belgium), Mannheim (Germany), Kentucky, Matsuyama-shi (Japan), Kfar-Saba (Israel), Saint Herblain (France), Massachusetts, Tel Aviv (Israel), Guangzhou City (China), Nebraska, Rotterdam (Netherlands), Maine, Aichi (Japan), Birmingham (United Kingdom), Niigata (Japan), Zerifin (Israel), Milano (Italy), Connecticut, Okayama (Japan), Petach Tikva (Israel), New York, Colorado, Ottawa (Canada), Praha 5 (Czechia), Ibaraki (Japan), Nice (France), Karşıyaka (Turkey), Jerusalem (Israel), Pennsylvania, Clermont Ferrand (France), Vancouver (Canada), Middlesborough (United Kingdom), Halifax (Canada), New Jersey, Lublin (Poland), Seoul (Korea, Republic of), Texas, Poznan (Poland), Dnipropetrovsk (Ukraine), Patras (Greece), Iowa, Brno (Czechia), Ivanovo (Russian Federation), Herston (Australia), Napoli (Italy), Turku (Finland), Paris (France), Avignon (France), Virginia, Olomouc (Czechia), Southampton (United Kingdom), Toruń (Poland), Washington, Zürich (Switzerland), Toronto (Canada), Shanghai (China), Belgrade (Serbia), Aomori (Japan)

NCT02853305

PHASE 3

A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab With or Without Platinum-Based Combination Chemotherapy Versus Chemotherapy in Subjects With Advanced or Metastatic Urothelial Carcinoma

TARGETS

PD-1

LOCATIONS: Dublin (Ireland), Louisiana, South Carolina, Istanbul (Turkey), Haarlem (Netherlands), Oregon, Utah, Madrid (Spain), Midrand (South Africa), Buenos Aires (Argentina), Haar (Germany), Illinois, Tennessee, California, Connecticut, Hoddesdon (United Kingdom), Santiago (Chile), North Carolina, Missouri, Florida, Montana, Maryland, Maine, New York, Kirkland (Canada), Budapest (Hungary), Bangkok (Thailand), Oklahoma, Sao Paulo (Brazil), Texas, Chiyoda-Ku, Tokyo (Japan), Colorado, Vermont, Nebraska, Virginia, Taipei (Taiwan), Michigan, Washington, Brussels (Belgium), Pennsylvania, District of Columbia, Moscow (Russian Federation), Hod Hasharon (Israel), Seoul (Korea, Republic of), Paris (France), Arizona

NCT02632409 — **PHASE 3**

A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab Versus Placebo in Subjects With High Risk Invasive Urothelial Carcinoma (CheckMate 274: CHECKpoint Pathway and nivoluMAb Clinical Trial Evaluation 274)

TARGETS
PD-1

LOCATIONS: Hirosaki-shi (Japan), Tennessee, Athens (Greece), Stuttgart (Germany), Osaka-Sayama-Shi (Japan), Perth (Australia), Seoul (Korea, Republic of), Florida, Niigata-shi (Japan), Viedma (Argentina), Ciudad de Buenos Aires (Argentina), Villejuif (France), Sapporo-shi (Japan), Jena (Germany), Regensburg (Germany), Michigan, Oregon, London (United Kingdom), Tsukuba-shi (Japan), Liege (Belgium), Edmonton (Canada), Mexico City (Mexico), Guadalajara (Mexico), Greifswald (Germany), Akita-shi (Japan), Seongnam-si (Korea, Republic of), Paris (France), Strasbourg (France), Df (Mexico), Sheffield (United Kingdom), Lodz (Poland), Ciudad Autonoma De Buenos Aire (Argentina), Ramat Gan (Israel), Nijmegen (Netherlands), Chemnitz (Germany), Hasselt (Belgium), Sevilla (Spain), San Miguel De Tucuman (Argentina), Roma (Italy), Santiago (Chile), Maastrict (Netherlands), Haifa (Israel), Nebraska, Suresnes (France), Vina Del Mar (Chile), Aalborg (Denmark), São Paulo (Brazil), Liverpool (Australia), Lund (Sweden), Basel (Switzerland), St. Leonards (Australia), Zerifin (Israel), Dublin (Ireland), Bunkyo-ku (Japan), Floridablanca (Colombia), Muenster (Germany), Barretos (Brazil), Lima (Peru), Nevada, Okayama-shi (Japan), Taipei (Taiwan), Pisa (Italy), Vienna (Austria), Porto Alegre (Brazil), Bogota (Colombia), Munich (Germany), Shinjuku-Ku (Japan), Marseille Cedex 9 (France), Colorado, Sutton (United Kingdom), Monterrey (Mexico), Elizabeth Vale (Australia), Amsterdam (Netherlands), Chiba-shi (Japan), Madrid (Spain), Copenhagen (Denmark), Medellin (Colombia), Badalona-barcelona (Spain), Berazategui (Argentina), Aarhus C (Denmark), Alaska, Minnesota, Sherbrooke (Canada), Pennsylvania, Louisiana, Higashinari-ku (Japan), Hamburg (Germany), South Carolina, Hamamatsu-shi (Japan), Milano (Italy), Edinburgh (United Kingdom), Shinjuku-ku (Japan), Wilton (Ireland), Bucuresti (Romania), Craiova (Romania), Wien (Austria), California, Heidelberg (Germany), Arezzo (Italy), Siena (Italy), Mexico (Mexico), Indiana, Nagasaki-shi (Japan), Ijui (Brazil), Jerusalem (Israel), Fukuoka-shi (Japan), Zuerich (Switzerland), Timisoara, Timis (Romania), Moscow (Russian Federation), Waratah (Australia), SB B o Paulo (Brazil), Floresti (Romania), Temuco (Chile), Arizona, Kaohsiung (Taiwan), Barcelona (Spain), New York, Manchester (United Kingdom), Illinois, Capital Federal (Argentina), Sao Paulo (Brazil), Taichung (Taiwan), North Carolina, Linz (Austria), Saint-Petersburg (Russian Federation), Montreal (Canada), Thessaloniki (Greece), Wroclaw (Poland), Gdansk (Poland), La Roche sur Yon (France), Essen (Germany)

NCT02834013 — **PHASE 2**

DART: Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors

TARGETS
CTLA-4, PD-1

LOCATIONS: Nevada, Florida, Kentucky, North Carolina, Kansas, Idaho, Wisconsin, Washington, Colorado, Iowa, Mississippi, Alaska, Missouri, Delaware, North Dakota, Montana, Ohio, Tennessee, South Dakota, District of Columbia, New York, Louisiana, New Hampshire, Oklahoma, Wyoming, Hawaii, Massachusetts, Utah, Maryland, South Carolina, Vermont, California, Oregon, Michigan, Indiana, Alabama, West Virginia, Nebraska, Illinois, Minnesota, Georgia, Connecticut, Texas, Pennsylvania, New Mexico, Arkansas

NCT02500121 — **PHASE 2**

A Randomized, Double-blinded, Phase II Study of Maintenance Pembrolizumab Versus Placebo After First-Line Chemotherapy in Patients With Metastatic Urothelial Cancer: Hoosier Cancer Research Network GU14-182

TARGETS
PD-1

LOCATIONS: Maryland, California, Utah, South Carolina, Pennsylvania, Indiana, Minnesota, Virginia, Missouri, New Mexico, Ohio, Arizona, Nebraska, Florida, North Carolina, District of Columbia, New York, New Jersey

NCT02693535 — **PHASE 2**

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

TARGETS
ABL, CDK4, PARP, EGFR, DDR2, PDGFRs, VEGFRs, ROS1, CSF1R, ERBB2, PD-1, ERBB3, MEK, RAF1, KIT, AXL, SMO, TRKC, mTOR, TRKA, MET, ALK, BRAF, RET, SRC, FLT3, CDK6

LOCATIONS: North Dakota, Pennsylvania, Washington, Illinois, Georgia, Arizona, Utah, North Carolina, Oklahoma, South Dakota, Michigan, Oregon, Nebraska

CLINICAL TRIALS

NCT02178722	PHASE 1 / PHASE 2
A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of Pembrolizumab (MK-3475) in Combination With Epacadostat (INCB024360) in Subjects With Selected Cancers (KEYNOTE-037/ ECHO-202)	**TARGETS** IDO1, PD-1

LOCATIONS: Illinois, Tennessee, Texas, Florida, Kansas, New Jersey, California, Colorado, Georgia, Ohio, Maryland, Pennsylvania, Minnesota, Connecticut, Michigan, South Carolina, Virginia

NCT02118337	PHASE 1 / PHASE 2
A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) in Combination With MEDI4736 and MEDI0680 Monotherapy in Subjects With Select Advanced Malignancies	**TARGETS** PD-L1, PD-1

LOCATIONS: California, New Jersey, Oregon, Kansas, Kentucky, Florida, New York, South Carolina, New Hampshire, West Virginia, Ohio, Minnesota, Oklahoma, Washington, Pennsylvania

NCT02475213	PHASE 1
A Phase 1, Open-Label, Dose Escalation Study of MGA271 in Combination With Pembrolizumab in Patients With B7-H3-Expressing Melanoma, Squamous Cell Cancer of the Head and Neck, Non-Small Cell Lung Cancer and Other B7H3 Expressing Cancers	**TARGETS** B7-H3, PD-1

LOCATIONS: Nebraska, Florida, Nevada, Texas, Pennsylvania, Maryland, Michigan, New York, Massachusetts

NCT02655822	PHASE 1
A Phase 1/1b, Open-Label, Multicenter, Repeat-Dose, Dose-Selection Study of CPI-444 as Single Agent and in Combination With Atezolizumab in Patients With Selected Incurable Cancers	**TARGETS** ADORA2A, PD-L1

LOCATIONS: Illinois, Hamilton (Canada), Camperdown (Australia), Missouri, Wisconsin, Brisbane (Australia), Maryland, Clayton (Australia), Georgia, Massachusetts, Colorado, Vancouver (Canada), New York, Michigan, North Carolina, Edmonton (Canada), Nebraska, Ohio, Melbourne (Australia), Arizona, Pennsylvania, Washington, Indiana, Ottawa (Canada), California, District of Columbia, Connecticut, Texas, Malvern (Australia)

GENE
CCND1

ALTERATION
amplification

RATIONALE
Amplification of CCND1 may predict sensitivity to CDK4/6 inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "CDK4", "LEE011", "LY2835219", "PD0332991", "palbociclib", "ribociclib", "bladder carcinoma", "urothelial carcinoma", "solid tumor", and/or "advanced cancer".

NCT02703571 — **PHASE 1/PHASE 2**

A Phase I/II Study of Safety and Efficacy of Ribociclib (LEE011) in Combination With Trametinib (TMT212) in Patients With Metastatic or Advanced Solid Tumors

TARGETS
CDK4, CDK6, MEK

LOCATIONS: Arkansas, California, Connecticut, Florida, Massachusetts, Texas, Alberta (Canada), Amsterdam (Netherlands), British Columbia (Canada), Catalunya (Spain), Koeln (Germany), Leuven (Belgium), Ulm (Germany), Utrecht (Netherlands), Victoria (Australia)

NCT03099174 — **PHASE 1**

An Open Label, Phase Ib Dose-escalation Study Evaluating the Safety and Tolerability of BI 836845 and Abemaciclib in Patients With Locally Advanced or Metastatic Solid Tumors and in Combination With Endocrine Therapy in Patients With Locally Advanced or Metastatic Hormone Receptor-positive Breast Cancer, Followed by Expansion Cohorts

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

LOCATIONS: Connecticut, Paris (France), Barcelona (Spain), Minnesota

NCT02934568 — **PHASE 2**

An Open-label, Multi-center Rollover Protocol for Patients Who Have Participated in a Novartis-sponsored Ribociclib (LEE011) Study and Are Continuing to Benefit From Ribociclib as Single Agent or in Combination With Other Investigational Treatments

TARGETS
CDK4, CDK6

LOCATIONS: Singapore (Singapore), Madrid (Spain), Villejuif Cedex (France), Michigan, Tennessee, Massachusetts

NCT02897375 — **PHASE 1**

A Phase 1 Study of Palbociclib in Combination With Cisplatin or Carboplatin in Advanced Solid Malignancies

TARGETS
CDK4, CDK6

LOCATIONS: Georgia

NCT01037790 — **PHASE 2**

Phase II Trial of the Cyclin-Dependent Kinase Inhibitor PD 0332991 in Patients With Cancer

TARGETS
CDK4, CDK6

LOCATIONS: Pennsylvania

NCT03065062 — **PHASE 1**

Phase I Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
CDK4, mTORC1, PI3K-gamma, mTORC2, PI3K-alpha, CDK6

LOCATIONS: Massachusetts

GENE
ERBB3

ALTERATION
amplification

RATIONALE
Activating mutations or amplification of ERBB3 may be associated with response to therapies targeting this kinase. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "ERBB3", "MM-121", "U3-1287", "AV-203", "afatinib", "pertuzumab", "lapatinib", "trastuzumab", "ado-trastuzumab emtansine", "bladder carcinoma", "urothelial carcinoma", "solid tumor", and/or "advanced cancer".

NCT02506517 — **PHASE 2**

Molecular Basket Trial In Multiple Malignancies With Common Target Pathway Aberrancies

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Toronto (Canada)

NCT02451553 — **PHASE 1**

Phase I/IB Multi-center Study of Irreversible EGFR/HER2 Tyrosine Kinase Inhibitor Afatinib (BIBW 2992) in Combination With Capecitabine for Advanced Solid Tumors and Pancretico-Biliary Cancers

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Indiana, Washington

NCT02152943 — **PHASE 1**

Combination Treatment With Everolimus, Letrozole and Trastuzumab in Hormone Receptor and HER2/Neu-positive Patients With Advanced Metastatic Breast Cancer and Other Solid Tumors: Evaluating Synergy and Overcoming Resistance

TARGETS
Aromatase, ERBB2, mTOR

LOCATIONS: Texas

GENE
RAF1

ALTERATION
amplification

RATIONALE
RAF1 amplification or activating mutation may lead to increased RAF1 activity and subsequent activation of the MEK pathway; therefore, tumors with RAF1 alterations may be sensitive to RAF inhibitors and/or MEK inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "RAF", "MEK", "sorafenib", "regorafenib", "trametinib", "cobimetinib", "bladder carcinoma", "urothelial carcinoma", "solid tumor", and/or "advanced cancer".

NCT02693535 — **PHASE 2**

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

TARGETS
ABL, CDK4, PARP, EGFR, DDR2, PDGFRs, VEGFRs, ROS1, CSF1R, ERBB2, PD-1, ERBB3, MEK, RAF1, KIT, AXL, SMO, TRKC, mTOR, TRKA, MET, ALK, BRAF, RET, SRC, FLT3, CDK6

LOCATIONS: North Dakota, Pennsylvania, Washington, Illinois, Georgia, Arizona, Utah, North Carolina, Oklahoma, South Dakota, Michigan, Oregon, Nebraska

NCT02795156 — **PHASE 2**

Phase II Study to Evaluate the Activity of Commercially Available Molecularly Matched Targeted Therapies in Selected Tumor Types Based on Genomic Alterations

TARGETS
EGFR, BRAF, RET, ERBB2, RAF1, KIT, PDGFRs, VEGFRs, ERBB4

LOCATIONS: Tennessee, Colorado, Florida, Missouri

NCT02703571 — **PHASE 1/PHASE 2**

A Phase I/II Study of Safety and Efficacy of Ribociclib (LEE011) in Combination With Trametinib (TMT212) in Patients With Metastatic or Advanced Solid Tumors

TARGETS
CDK4, CDK6, MEK

LOCATIONS: Arkansas, California, Connecticut, Florida, Massachusetts, Texas, Alberta (Canada), Amsterdam (Netherlands), British Columbia (Canada), Catalunya (Spain), Koeln (Germany), Leuven (Belgium), Ulm (Germany), Utrecht (Netherlands), Victoria (Australia)

NCT02143401 — **PHASE 1**

A Phase I Trial of ABT-263 (Navitoclax), a Bcl-2 Inhibitor, and Sorafenib (Nexavar) in Patients With Relapsed or Refractory Solid Organ Tumors

TARGETS
BCL2, RAFs, RET, BCL-XL, FLT3, KIT, PDGFRs, VEGFRs, BCL-W

LOCATIONS: Maryland, Arizona, Minnesota, Iowa, New York

NCT02070549 — **PHASE 1**

A Phase I Trial of Single Agent Trametinib (GSK1120212) in Advanced Cancer Patients With Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Ohio, Pennsylvania, California, Missouri, Toronto (Canada), Texas, Massachusetts, Vancouver (Canada)

NCT03162627 — **PHASE 1**

Evaluation of the Combination of Selumetinib and Olaparib in Endometrial, Ovarian and Other Solid Tumors With Ras Pathway Alterations, and Ovarian Tumors With PARP Resistance

TARGETS
PARP, MEK

LOCATIONS: Texas

NCT02466802	PHASE 1
Phase I Study of Regorafenib and Sildenafil for Advanced Solid Tumors	TARGETS BRAF, RET, RAF1, KIT, PDGFRs, VEGFRs
LOCATIONS: Virginia	

NCT02583542	PHASE 1 / PHASE 2
A Phase Ib/IIa Study of AZD2014 in Combination With Selumetinib in Patients With Advanced Cancers	TARGETS mTORC1, MEK, mTORC2
LOCATIONS: London (United Kingdom)	

NCT02510001	PHASE 1
A Sequential Phase I Study of MEK1/2 Inhibitors PD-0325901 or Binimetinib Combined With cMET Inhibitor PF-02341066 in Patients With RAS Mutant and RAS Wild Type (With Aberrant c-MET) Colorectal Cancer	TARGETS MET, ALK, ROS1, MEK, AXL, TRKC, TRKA
LOCATIONS: Oxford (United Kingdom)	

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.

ATRX Q2330E	***AURKB*** S313L	***BRAF*** R384T	***ERBB2*** amplification†
GATA3 amplification	***GRM3*** R277H	***MET*** M849L	***MLL*** A53V
NOTCH2 Q1343H, S1804L, and V1667I	***NRAS*** P140A	***P2RY8*** A159V	***POLE*** R1580Q
PPARG amplification	***RPTOR*** D1042N	***SGK1*** E6K and Q30H	***STK11*** F354L
U2AF1 E225K	***WHSC1L1*** rearrangement		

† *An* ERBB2 *amplification of copy number 4 was detected. While this result is considered a variant of unknown significance across tumor types, in a clinical concordance study of breast cancer samples with an FDA-approved FISH test, 70% (7 out of 10 samples) with copy number 4 were positive with an average ratio of 2.3, and 30% (3 out of 10) samples were negative by the FISH test.*

INTENDED USE

FoundationOne CDx™ (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx 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 solid malignant neoplasms. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

INDICATION	GENOMIC FINDINGS	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), or Tarceva® (Erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (Osimertinib)
	ALK rearrangements	Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E or V600K	Mekinist® (Trametinib) or Cotellic® (Cobimetinib), in combination with Zelboraf® (Vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (Cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (Panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Rubraca® (Rucaparib)

TABLE 1

The median exon coverage for this sample is 888x

TEST PRINCIPLE

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using the Illumina® HiSeq 4000 platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including microsatellite instability (MS) and tumor mutational burden (TMB) will be reported.

PERFORMANCE CHARACTERISTICS

Please refer to product label:
foundationmedicine.com/f1cdx

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. Genomic findings other than those listed in Table 1 of the intended use are not prescriptive or conclusive for labeled use of any specific therapeutic product.
4. A negative result does not rule out the presence of a mutation below the limits of detection of the assay.
5. Samples with <25% tumor may have decreased sensitivity for the detection of CNAs including *ERBB2*.
6. Clinical performance of Tagrisso® (osimertinib) in patients with an *EGFR* exon 20 T790M mutation detected with an allele fraction <5% is ongoing and has not been established.
7. Concordance with other validated methods for CNA (with the exception of *ERBB2*) and gene rearrangement (with the exception of *ALK*) detection has not been demonstrated and will be provided in the post-market setting. Confirmatory testing using a clinically validated assay should be performed for all CNAs and rearrangements not associated with CDx claims noted in Table 1 of the Intended Use, but used for clinical decision making.
8. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. Refer to the Summary of Safety of Effectiveness Data (SSED) for additional details on methodology. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established.
9. TMB by F1CDx is defined based on counting the total number of all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit rounded to the nearest integer. The clinical validity of TMB defined by this panel has not been established.
10. 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.
11. The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.

FoundationOne CDx™ is designed to include all genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 28 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*	*PARK2*
PARP1	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*	*PDGFRB*
PDK1	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*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*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*	*RICTOR*
RNF43	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*	*SF3B1*
SGK1	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*	*SOX2*
SOX9	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*	*SYK*
TBX3	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*
TSC2	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WHSC1L1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC IS A NCRNA
**THE PROMOTER REGION OF TERT INTERROGATED

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite Status (MS)
Tumor Mutational Burden (TMB)

QUALIFIED ALTERATION CALLS (EQUIVOCAL AND SUBCLONAL)

An alteration denoted as "amplification –equivocal" implies that the FoundationOne CDx™ assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx™ for identifying a copy number amplification is four (4) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx™ assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx™ analytical methodology has identified as being present in <10% of the assayed tumor DNA.

PROFESSIONAL SERVICES FINDINGS

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.

RANKING OF ALTERATIONS AND DRUGS

Biomarker Findings

Appear at the top of the report, but are not ranked higher than Genomic Findings.

Genomic Findings

Therapies with Clinical Benefit In Patient's Tumor Type → Therapies with Clinical Benefit in Other Tumor Type → Clinical Trial Options → No Known Options (if multiple findings exist within any of these categories, the results are listed alphabetically by gene name).

Therapies

Sensitizing therapies → Resistant therapies (if multiple therapies exist within any of these categories, they are listed in no particular order).

Clinical Trials

Pediatric trial qualification → Geographical Proximity → Later trial phase.

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

Foundation Medicine makes no promises or guarantees that a particular drug will be effective in the treatment of disease of 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 CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced 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 with the 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.

TUMOR MUTATIONAL BURDEN

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations occurring in sequenced genes on the FoundationOne CDx test and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne CDx samples and may be reported in Professional Services as "TMB-High", "TMB-Intermediate", "TMB-Low", or "Cannot Be Determined". TMB results, which are rounded to the nearest integer, are determined as follows: TMB-High corresponds to greater than or equal to 20 mutations per megabase (muts/Mb); TMB-Intermediate corresponds to 6-19 muts/Mb; TMB-Low corresponds to fewer than or equal to 5 muts/Mb. Tumor Mutational Burden is reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

Genomic Findings with Evidence of Clinical Significance

Genomic findings listed at Level 2 are associated with clinical significance. Clinical significance may be indicated by evidence of therapeutic sensitivity or resistance and/or diagnostic, prognostic or other clinically relevant implications. Included in this category will be findings associated with clinical validity as supported by professional guidelines and/or peer-reviewed publications.

Genomic Findings with Potential Clinical Significance

Genomic findings listed at Level 3 are cancer-related mutations and biomarkers with potential clinical significance. These include findings in genes known to be associated with cancer and are supported by evidence from publicly available databases, and/or peer-reviewed publications.

A Fluid Approach to Reporting Levels

As additional information becomes available, as recognized by the clinical community (professional guidelines and/or peer-reviewed publications), findings may move between Levels 2 and 3 in accordance with the above descriptions.

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

1 Snyder A, Makarov V, Merghoub T, et al. (2014) Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 371(23):2189-99

2 Rosenberg JE, Hoffman-Censits J, Powles T, et al. (2016) Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 387(10031):1909-20

3 Balar AV, Galsky MD, Rosenberg JE, et al. (2017) Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 389(10064):67-76

4 Johnson DB, Frampton GM, Rioth MJ, et al. (2016) Targeted next generation sequencing identifies markers of response to PD-1 blockade. Cancer Immunol Res ePub Sep 2016

5 Rizvi NA, Hellmann MD, Snyder A, et al. (2015) Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 348(6230):124-8

6 Le DT, Uram JN, Wang H, et al. (2015) PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med ePub May 2015

7 Dong ZY, Zhong WZ, Zhang XC, et al. (2016) Potential Predictive Value of TP53 and KRAS Mutation Status for Response to PD-1 Blockade Immunotherapy in Lung Adenocarcinoma. Clin Cancer Res

8 Mehnert JM, Panda A, Zhong H, et al. (2016) Immune activation and response to pembrolizumab in POLE-mutant endometrial cancer. J Clin Invest 126(6):2334-40

9 Santin AD, Bellone S, Buza N, et al. (2016) Regression of chemotherapy-resistant Polymerase epsilon (POLE) ultra-mutated and MSH6 hyper-mutated endometrial tumors with nivolumab. Clin Cancer Res ePub Aug 2016

10 Johanns TM, Miller CA, Dorward IG, et al. (2016) Immunogenomics of Hypermutated Glioblastoma: a Patient with Germline POLE Deficiency Treated with Checkpoint Blockade Immunotherapy. Cancer Discov ePub Sep 2016

11 Bouffet E, Larouche V, Campbell BB, et al. (2016) Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency. J Clin Oncol ePub Mar 2016

12 Van Allen EM, Miao D, Schilling B, et al. (2015) Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science 350(6257):207-11

13 The Cancer Genome Atlas Research Network (2014) Comprehensive molecular characterization of urothelial bladder carcinoma. Nature ePub Jan 2014

14 Cazier JB, Rao SR, McLean CM, et al. (2014) Whole-genome sequencing of bladder cancers reveals somatic CDKN1A mutations and clinicopathological associations with mutation burden. Nat Commun 5:3756

15 Rosenberg et al., 2016; ASCO Abstract 104

16 Pfeifer GP, You YH, Besaratinia A (2005) Mutations induced by ultraviolet light. Mutat Res 571(1-2):19-31

17 Hill VK, Gartner JJ, Samuels Y, et al. (2013) The genetics of melanoma: recent advances. Annu Rev Genomics Hum Genet 14:257-79

18 Pfeifer GP, Denissenko MF, Olivier M, et al. (2002) Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. Oncogene 21(48):7435-51

19 Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. (2013) Integrated genomic characterization of endometrial carcinoma. Nature 497(7447):67-73

20 Briggs S, Tomlinson I (2013) Germline and somatic polymerase ε and δ mutations define a new class of hypermutated colorectal and endometrial cancers. J Pathol 230(2):148-53

21 Heitzer E, Tomlinson I (2014) Replicative DNA polymerase mutations in cancer. Curr Opin Genet Dev 24:107-13

22 Cancer Genome Atlas Network (2012) Comprehensive molecular characterization of human colon and rectal cancer. Nature 487(7407):330-7

23 Roberts SA, Gordenin DA (2014) Hypermutation in human cancer genomes: footprints and mechanisms. Nat Rev Cancer 14(12):786-800

24 Gatalica Z, Snyder C, Maney T, et al. (2014) Programmed cell death 1 (PD-1) and its ligand (PD-L1) in common cancers and their correlation with molecular cancer type. Cancer Epidemiol Biomarkers Prev 23(12):2965-70

25 Kroemer G, Galluzzi L, Zitvogel L, et al. (2015) Colorectal cancer: the first neoplasia found to be under immunosurveillance and the last one to respond to immunotherapy? Oncoimmunology 4(7):e1058597

26 Lal N, Beggs AD, Willcox BE, et al. (2015) An immunogenomic stratification of colorectal cancer: Implications for development of targeted immunotherapy. Oncoimmunology 4(3):e976052

27 Overman et al., 2016; ASCO Abstract 3501

28 ASCO-SITC 2016; Abstract P60

29 Mylona E, Zarogiannos A, Nomikos A, et al. (2008) Prognostic value of microsatellite instability determined by immunohistochemical staining of hMSH2 and hMSH6 in urothelial carcinoma of the bladder. APMIS 116(1):59-65

30 Amira N, Rivet J, Soliman H, et al. (2003) Microsatellite instability in urothelial carcinoma of the upper urinary tract. J Urol 170(4 Pt 1):1151-4

31 Bai S, Nunez AL, Wei S, et al. (2013) Microsatellite instability and TARBP2 mutation study in upper urinary tract urothelial carcinoma. Am J Clin Pathol 139(6):765-70

32 Kocarnik JM, Shiovitz S, Phipps AI (2015) Molecular phenotypes of colorectal cancer and potential clinical applications. Gastroenterol Rep (Oxf) 3(4):269-76

33 You JF, Buhard O, Ligtenberg MJ, et al. (2010) Tumours with loss of MSH6 expression are MSI-H when screened with a pentaplex of five mononucleotide repeats. Br J Cancer 103(12):1840-5

34 Bairwa NK, Saha A, Gochhait S, et al. (2014) Microsatellite instability: an indirect assay to detect defects in the cellular mismatch repair machinery. Methods Mol Biol 1105:497-509

35 Boland CR, Thibodeau SN, Hamilton SR, et al. (1998) A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res 58(22):5248-57

36 Pawlik TM, Raut CP, Rodriguez-Bigas MA (2004) Colorectal carcinogenesis: MSI-H versus MSI-L. Dis Markers 20(4-5):199-206

37 Boland CR, Goel A (2010) Microsatellite instability in colorectal cancer. Gastroenterology 138(6):2073-2087.e3

38 Juric et al., 2016; ASCO Abstract 568

39 Peguero et al., 2016; ASCO Abstract 2528

40 Tolaney et al., 2016; SABCS P4-22-12

41 Flaherty KT, Lorusso PM, Demichele A, et al. (2012) Phase I, dose-escalation trial of the oral cyclin-dependent kinase 4/6 inhibitor PD 0332991, administered using a 21-day schedule in patients with advanced cancer. Clin Cancer Res 18(2):568-76

42 Finn RS, Crown JP, Lang I, et al. (2014) The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol ePub Dec 2014

43 Infante JR, Cassier PA, Gerecitano JF, et al. (2016) A Phase I Study of the Cyclin-Dependent Kinase 4/6 Inhibitor Ribociclib (LEE011) in Patients with Advanced Solid Tumors and Lymphomas. Clin Cancer Res 22(23):5696-5705

44 Patnaik A, Rosen LS, Tolaney SM, et al. (2016) Efficacy and Safety of Abemaciclib, an Inhibitor of CDK4 and CDK6, for Patients with Breast Cancer, Non-Small Cell Lung Cancer, and Other Solid Tumors. Cancer Discov 6(7):740-53

45 Leonard JP, LaCasce AS, Smith MR, et al. (2012) Selective CDK4/6 inhibition with tumor responses by PD0332991 in patients with mantle cell lymphoma. Blood 119(20):4597-607

46 Ross JS, Wang K, Al-Rohil RN, et al. (2014) Advanced urothelial carcinoma: next-generation sequencing reveals diverse genomic alterations and targets of therapy. Mod Pathol 27(2):271-80

47 Zaharieva BM, Simon R, Diener PA, et al. (2003) High-throughput tissue microarray analysis of 11q13 gene amplification (CCND1, FGF3, FGF4, EMS1) in urinary bladder cancer. J Pathol 201(4):603-8

48 Seiler R, Thalmann GN, Rotzer D, et al. (2014) CCND1/CyclinD1 status in metastasizing bladder cancer: a prognosticator and predictor of chemotherapeutic response. Mod Pathol 27(1):87-95

49 Fristrup N, Birkenkamp-Demtröder K, Reinert T, et al. (2013) Multicenter validation of cyclin D1, MCM7, TRIM29, and UBE2C as prognostic protein markers in non-muscle-invasive bladder cancer. Am J Pathol 182(2):339-49

50 Olsson H, Hultman P, Monsef N, et al. (2012) Immunohistochemical evaluation of cell cycle regulators: impact on predicting prognosis in stage t1 urinary bladder cancer. ISRN Urol 2012:379081

51 Takagi Y, Takashi M, Koshikawa T, et al. (2000) Immunohistochemical demonstration of cyclin D1 in bladder cancers as an inverse indicator of invasiveness but not an independent prognostic factor. Int J Urol 7(10):366-72

52 Tut VM, Braithwaite KL, Angus B, et al. (2001) Cyclin D1 expression in transitional cell carcinoma of the bladder: correlation with p53, waf1, pRb and Ki67. Br J Cancer 84(2):270-5

53 Fu M, Wang C, Li Z, et al. (2004) Minireview: Cyclin D1: normal and abnormal functions. Endocrinology 145(12):5439-47

54 Takahashi-Yanaga F, Sasaguri T (2008) GSK-3beta regulates cyclin D1 expression: a new target for chemotherapy. Cell Signal 20(4):581-9

55 Elsheikh S, Green AR, Aleskandarany MA, et al. (2008) CCND1 amplification and cyclin D1 expression in breast cancer and their relation with proteomic subgroups and patient outcome. Breast Cancer Res Treat 109(2):325-35

56 Baselga J, Swain SM (2009) Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer 9(7):463-75

57 Jaiswal BS, Kljavin NM, Stawiski EW, et al. (2013) Oncogenic ERBB3 mutations in human cancers. Cancer Cell 23(5):603-17

58 Jura N, Shan Y, Cao X, et al. (2009) Structural analysis of the catalytically inactive kinase domain of the human EGF receptor 3. Proc Natl Acad Sci USA 106(51):21608-13

59 Choudhury NJ, Campanile A, Antic T, et al. (2016) Afatinib Activity in Platinum-Refractory Metastatic Urothelial Carcinoma in Patients With ERBB Alterations. J Clin Oncol ePub Apr 2016

60 Bidard FC, Ng CK, Cottu P, et al. (2015) Response to dual HER2 blockade in a patient with HER3-mutant metastatic breast cancer. Ann Oncol ePub May 2015

61 Rajkumar T, Stamp GW, Pandha HS, et al. (1996) Expression of the type 1 tyrosine kinase growth factor receptors EGF receptor, c-erbB2 and c-erbB3 in bladder cancer. J Pathol 179(4):381-5

62 Junttila TT, Laato M, Vahlberg T, et al. (2003) Identification of patients with transitional cell carcinoma of the bladder overexpressing ErbB2, ErbB3, or specific ErbB4 isoforms: real-time reverse transcription-PCR analysis in estimation of ErbB receptor status from cancer patients. Clin Cancer Res 9(14):5346-57

63 Røtterud R, Nesland JM, Berner A, et al. (2005) Expression of the epidermal growth factor receptor family in normal and malignant urothelium. BJU Int 95(9):1344-50

64 Tsai YS, Tzai TS, Chow NH, et al. (2005) Frequency and clinicopathologic correlates of ErbB1, ErbB2, and ErbB3 immunoreactivity in urothelial tumors of upper urinary tract. Urology 66(6):1197-202

65 Chow NH, Liu HS, Yang HB, et al. (1997) Expression patterns of erbB receptor family in normal urothelium and transitional cell carcinoma. An immunohistochemical study. Virchows Arch 430(6):461-6

66 Chow NH, Chan SH, Tzai TS, et al. (2001) Expression profiles of ErbB family receptors and prognosis in primary transitional cell carcinoma of the urinary bladder. Clin Cancer Res 7(7):1957-62

67 Sheng Q, Liu J (2011) The therapeutic potential of targeting the EGFR family in epithelial ovarian cancer. Br J Cancer 104(8):1241-5

68 Gao J, Aksoy BA, Dogrusoz U, et al. (2013) Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 6(269):pl1

69 Zack TI, Schumacher SE, Carter SL, et al. (2013) Pan-cancer patterns of somatic copy number alteration. Nat Genet 45(10):1134-1140

70 Beroukhim R, Mermel CH, Porter D, et al. (2010) The landscape of somatic copy-number alteration across human cancers. Nature 463(7283):899-905

71 Sassen A, Rochon J, Wild P, et al. (2008) Cytogenetic analysis of HER1/EGFR, HER2, HER3 and HER4 in 278 breast cancer patients. Breast Cancer Res 10(1):R2

72 Wilson MA, Zhao F, Khare S, et al. (2015) Copy number changes are associated with response to treatment with carboplatin, paclitaxel, and sorafenib in melanoma. Clin Cancer Res ePub Aug 2015

73 Mehnert et al., 2016; EORTC-NCI-AACR Abstract 435

74 Habuchi T, Kinoshita H, Yamada H, et al. (1994) Oncogene amplification in urothelial cancers with p53 gene mutation or MDM2 amplification. J Natl Cancer Inst 86(17):1331-5

75 Simon R, Richter J, Wagner U, et al. (2001) High-throughput tissue microarray analysis of 3p25 (RAF1) and 8p12 (FGFR1) copy number alterations in urinary bladder cancer. Cancer Res 61(11):4514-9

76 Mhawech-Fauceglia P, Fischer G, Beck A, et al. (2006) Raf1, Aurora-A/STK15 and E-cadherin biomarkers expression in patients with pTa/pT1 urothelial bladder carcinoma; a retrospective TMA study of 246 patients with long-term follow-up. Eur J Surg Oncol 32(4):439-44

77 Gollob JA, Wilhelm S, Carter C, et al. (2006) Role of Raf kinase in cancer: therapeutic potential of targeting the Raf/MEK/ERK signal transduction pathway. Semin Oncol 33(4):392-406

78 Maurer G, Tarkowski B, Baccarini M (2011) Raf kinases in cancer-roles and therapeutic opportunities. Oncogene 30(32):3477-88

79 Kang MH, Reynolds CP (2009) Bcl-2 inhibitors: targeting mitochondrial apoptotic pathways in cancer therapy. Clin Cancer Res 15(4):1126-32

80 Zhou H, Aguilar A, Chen J, et al. (2012) Structure-based design of potent Bcl-2/Bcl-xL inhibitors with strong in vivo antitumor activity. J Med Chem 55(13):6149-61

81 Zhou H, Chen J, Meagher JL, et al. (2012) Design of Bcl-2 and Bcl-xL inhibitors with subnanomolar binding affinities based upon a new scaffold. J Med Chem 55(10):4664-82

82 Zhang YL, Pang LQ, Wu Y, et al. (2008) Significance of Bcl-xL in human colon carcinoma. World J Gastroenterol 14(19):3069-73

83 Ni Chonghaile T, Sarosiek KA, Vo TT, et al. (2011) Pretreatment mitochondrial priming correlates with clinical response to cytotoxic chemotherapy. Science 334(6059):1129-33

84 Lei X, Huang Z, Zhong M, et al. (2007) Bcl-XL small interfering RNA sensitizes cisplatin-resistant human lung adenocarcinoma cells. Acta Biochim Biophys Sin (Shanghai) 39(5):344-50

85 Qian J, Zou Y, Rahman JS, et al. (2009) Synergy between phosphatidylinositol 3-kinase/Akt pathway and Bcl-xL in the control of apoptosis in adenocarcinoma cells of the lung. Mol Cancer Ther 8(1):101-9

86 Shen H, Gao W, Wu YJ, et al. (2009) Multicolor fluorescence in situ hybridization and comparative genomic hybridization reveal molecular events in lung adenocarcinomas and squamous cell lung carcinomas. Biomed Pharmacother 63(6):396-403

87 Reinmuth N, Jauch A, Xu EC, et al. (2008) Correlation of EGFR mutations with chromosomal alterations and expression of EGFR, ErbB3 and VEGF in tumor samples of lung adenocarcinoma patients. Lung Cancer 62(2):193-201

88 Elstrand MB, Kleinberg L, Kohn EC, et al. (2009) Expression and clinical role of antiapoptotic proteins of the bag, heat shock, and Bcl-2 families in effusions, primary tumors, and solid metastases in ovarian carcinoma. Int J Gynecol Pathol 28(3):211-21

89 Postma C, Terwischa S, Hermsen MA, et al. (2007) Gain of chromosome 20q is an indicator of poor prognosis in colorectal cancer. Cell Oncol 29(1):73-5

90 Biroccio A, Benassi B, D'Agnano I, et al. (2001) c-Myb and Bcl-x overexpression predicts poor prognosis in colorectal cancer: clinical and experimental findings. Am J Pathol 158(4):1289-99

91 Williams J, Lucas PC, Griffith KA, et al. (2005) Expression of Bcl-xL in ovarian carcinoma is associated with chemoresistance and recurrent disease. Gynecol Oncol 96(2):287-95

92 Wong M, Tan N, Zha J, et al. (2012) Navitoclax (ABT-263) reduces Bcl-x(L)-mediated chemoresistance in ovarian cancer models. Mol Cancer Ther 11(4):1026-35

93 Hockenbery 2010; 20213841

94 Annunziata CM, Kleinberg L, Davidson B, et al. (2007) BAG-4/SODD and associated antiapoptotic proteins are linked to aggressiveness of epithelial ovarian cancer. Clin Cancer Res 13(22 Pt 1):6585-92

95 Kar R, Sen S, Singh A, et al. (2007) Role of apoptotic regulators in human epithelial ovarian cancer. Cancer Biol Ther 6(7):1101-5

96 Sillars-Hardebol AH, Carvalho B, Beliën JA, et al. (2012) BCL2L1 has a functional role in colorectal cancer and its protein expression is associated with chromosome 20q gain. J Pathol 226(3):442-50

97 Konecny GE, Winterhoff B, Kolarova T, et al. (2011) Expression of p16 and retinoblastoma determines response to CDK4/6 inhibition in ovarian cancer. Clin Cancer Res 17(6):1591-602

98 Katsumi Y, Iehara T, Miyachi M, et al. (2011) Sensitivity of malignant rhabdoid tumor cell lines to PD 0332991 is inversely correlated with p16 expression. Biochem Biophys Res Commun 413(1):62-8

99 Cen L, Carlson BL, Schroeder MA, et al. (2012) p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells. Neuro-oncology 14(7):870-81

100 Logan JE, Mostofizadeh N, Desai AJ, et al. (2013) PD-0332991, a potent and selective inhibitor of cyclin-dependent kinase 4/6, demonstrates inhibition of proliferation in renal cell carcinoma at nanomolar concentrations and molecular markers predict for sensitivity. Anticancer Res 33(8):2997-3004

101 Gopalan et al., 2014; ASCO Abstract 8077

102 DeMichele A, Clark A, Tan KS, et al. (2014) CDK 4/6 Inhibitor Palbociclib (PD0332991) in Rb+ Advanced Breast Cancer: Phase II Activity, Safety and Predictive Biomarker Assessment. Clin Cancer Res ePub Dec 2014

103 Johnson DB, Dahlman KH, Knol J, et al. (2014) Enabling a genetically informed approach to cancer medicine: a retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel. Oncologist 19(6):616-22

104 Van Maerken T, Rihani A, Dreidax D, et al. (2011) Functional analysis of the p53 pathway in neuroblastoma cells using the small-molecule MDM2 antagonist nutlin-3. Mol Cancer Ther 10(6):983-93

105 Gamble LD, Kees UR, Tweddle DA, et al. (2012) MYCN sensitizes neuroblastoma to the MDM2-p53 antagonists Nutlin-3 and MI-63. Oncogene 31(6):752-63

106 Packenham JP, Taylor JA, Anna CH, et al. (1995) Homozygous deletions but no sequence mutations in coding regions of p15 or p16 in human primary bladder tumors. Mol Carcinog 14(3):147-51

107 Korkolopoulou P, Christodoulou P, Lazaris A, et al. (2001) Prognostic implications of aberrations in p16/pRb pathway in urothelial bladder carcinomas: a multivariate analysis including p53 expression and proliferation markers. Eur Urol 39(2):167-77

108 Bartoletti R, Cai T, Nesi G, et al. (2007) Loss of P16 expression and chromosome 9p21 LOH in predicting outcome of patients affected by superficial bladder cancer. J Surg Res 143(2):422-7

109 Piaton E, Advenier AS, Carré C, et al. (2013) p16(INK4a) /Ki-67 dual labelling as a marker for the presence of high-grade cancer cells or disease progression in urinary cytopathology. Cytopathology 24(5):327-34

110 Piaton E, Carré C, Advenier AS, et al. (2013) p16(INK4a) overexpression and p16/Ki-67 dual labeling versus conventional urinary cytology in the evaluation of urothelial carcinoma. Cancer Cytopathol ePub Dec 2013

111 Alameda F, Juanpere N, Pijuan L, et al. (2012) Value of p16(INK4a) in the diagnosis of low-grade urothelial carcinoma of the urinary bladder in urinary cytology. Cancer Cytopathol 120(4):276-82

112 Pollard C, Smith SC, Theodorescu D (2010) Molecular genesis of non-muscle-invasive urothelial carcinoma (NMIUC). Expert Rev Mol Med 12:e10

113 Lee K, Jung ES, Choi YJ, et al. (2010) Expression of pRb, p53, p16 and cyclin D1 and their clinical implications in urothelial carcinoma. J Korean Med Sci 25(10):1449-55

114 Yin M, Bastacky S, Parwani AV, et al. (2008) p16ink4 immunoreactivity is a reliable marker for urothelial carcinoma in situ. Hum Pathol 39(4):527-35

115 Rebouissou S, Hérault A, Letouzé E, et al. (2012) CDKN2A homozygous deletion is associated with muscle invasion in FGFR3-mutated urothelial bladder carcinoma. J Pathol 227(3):315-24

116 Quelle DE, Zindy F, Ashmun RA, et al. (1995) Alternative reading frames of the INK4a tumor suppressor gene encode two unrelated proteins capable of inducing cell cycle arrest. Cell 83(6):993-1000

117 Sharpless NE (2005) INK4a/ARF: a multifunctional tumor suppressor locus. Mutat Res 576(1-2):22-38

118 Gazzeri S, Gouyer V, Vour'ch C, et al. (1998) Mechanisms of p16INK4A inactivation in non small-cell lung cancers. Oncogene 16(4):497-504

119 Roussel MF (1999) The INK4 family of cell cycle inhibitors in cancer. Oncogene 18(38):5311-7

120 Sherr CJ, Bertwistle D, DEN Besten W, et al. (2005) p53-Dependent and -independent functions of the Arf tumor suppressor. Cold Spring Harb Symp Quant Biol 70:129-37

121 Ozenne P, Eymin B, Brambilla E, et al. (2010) The ARF tumor suppressor: structure, functions and status in cancer. Int J Cancer 127(10):2239-47

122 Ruas M, Brookes S, McDonald NQ, et al. (1999) Functional evaluation of tumour-specific variants of p16INK4a/CDKN2A: correlation with protein structure information. Oncogene 18(39):5423-34

123 Jones R, Ruas M, Gregory F, et al. (2007) A CDKN2A mutation in familial melanoma that abrogates binding of p16INK4a to CDK4 but not CDK6. Cancer Res 67(19):9134-41

124 Haferkamp S, Becker TM, Scurr LL, et al. (2008) p16INK4a-induced senescence is disabled by melanoma-associated mutations. Aging Cell 7(5):733-45

125 Huot TJ, Rowe J, Harland M, et al. (2002) Biallelic mutations in p16(INK4a) confer resistance to Ras- and Ets-induced senescence in human diploid fibroblasts. Mol Cell Biol 22(23):8135-43

126 Rizos H, Darmanian AP, Holland EA, et al. (2001) Mutations in the INK4a/ARF melanoma susceptibility locus functionally impair p14ARF. J Biol Chem 276(44):41424-34

127 Gombart AF, Yang R, Campbell MJ, et al. (1997) Inhibition of growth of human leukemia cell lines by retrovirally expressed wild-type p16INK4A. Leukemia 11(10):1673-80

128 Yang R, Gombart AF, Serrano M, et al. (1995) Mutational effects on the p16INK4a tumor suppressor protein. Cancer Res 55(12):2503-6

129 Parry D, Peters G (1996) Temperature-sensitive mutants of p16CDKN2 associated with familial melanoma. Mol Cell Biol 16(7):3844-52

130 Greenblatt MS, Beaudet JG, Gump JR, et al. (2003) Detailed computational study of p53 and p16: using evolutionary sequence analysis and disease-associated mutations to predict the functional consequences of allelic variants. Oncogene 22(8):1150-63

131 Yarbrough WG, Buckmire RA, Bessho M, et al. (1999) Biologic and biochemical analyses of p16(INK4a) mutations from primary tumors. J Natl Cancer Inst 91(18):1569-74

132 Poi MJ, Yen T, Li J, et al. (2001) Somatic INK4a-ARF locus mutations: a significant mechanism of gene inactivation in squamous cell carcinomas of the head and neck. Mol Carcinog 30(1):26-36

133 Byeon IJ, Li J, Ericson K, et al. (1998) Tumor suppressor p16INK4A: determination of solution structure and analyses of its interaction with cyclin-dependent kinase 4. Mol Cell 1(3):421-31

134 Kannengiesser C, Brookes S, del Arroyo AG, et al. (2009) Functional, structural, and genetic evaluation of 20 CDKN2A germ line mutations identified in melanoma-prone families or patients. Hum Mutat 30(4):564-74

135 Lal G, Liu L, Hogg D, et al. (2000) Patients with both pancreatic adenocarcinoma and melanoma may harbor germline CDKN2A mutations. Genes Chromosomes Cancer 27(4):358-61

136 Koh J, Enders GH, Dynlacht BD, et al. (1995) Tumour-derived p16 alleles encoding proteins defective in cell-cycle inhibition. Nature 375(6531):506-10

137 McKenzie HA, Fung C, Becker TM, et al. (2010) Predicting functional significance of cancer-associated p16(INK4a) mutations in CDKN2A. Hum Mutat 31(6):692-701

138 Miller PJ, Duraisamy S, Newell JA, et al. (2011) Classifying variants of CDKN2A using computational and laboratory studies. Hum Mutat 32(8):900-11

139 Kutscher CL, Wright WA (1977) Unconditioned taste aversion to quinine induced by injections of NaCl and LiCl: dissociation of aversion from cellular dehydration. Physiol Behav 18(1):87-94

140 Scaini MC, Minervini G, Elefanti L, et al. (2014) CDKN2A unclassified variants in familial malignant melanoma: combining functional and computational approaches for their assessment. Hum Mutat 35(7):828-40

141 Jenkins NC, Jung J, Liu T, et al. (2013) Familial melanoma-associated mutations in p16 uncouple its tumor-suppressor functions. J Invest Dermatol 133(4):1043-51

142 Walker GJ, Gabrielli BG, Castellano M, et al. (1999) Functional reassessment of P16 variants using a transfection-based assay. Int J Cancer 82(2):305-12

143 Itahana K, Zhang Y (2008) Mitochondrial p32 is a critical mediator of ARF-induced apoptosis. Cancer Cell 13(6):542-53

144 Zhang Y, Xiong Y (1999) Mutations in human ARF exon 2 disrupt its nucleolar localization and impair its ability to block nuclear export of MDM2 and p53. Mol Cell 3(5):579-91

145 Zhang Y, Xiong Y, Yarbrough WG (1998) ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways. Cell 92(6):725-34

146 Guagnano V, Kauffmann A, Wöhrle S, et al. (2012) FGFR genetic alterations predict for sensitivity to NVP-BGJ398,a selective pan-FGFR inhibitor. Cancer Discov ePub Sep 2012

147 Hagel M, Miduturu C, Sheets M, et al. (2015) First Selective Small Molecule Inhibitor of FGFR4 for the Treatment of Hepatocellular Carcinomas with an Activated FGFR4 Signaling Pathway. Cancer Discov 5(4):424-37

148 Kim et al., 2016; EORTC-NCI-AACR Symposium Abstract 105A

149 Chan et al., 2017; AACR Abstract CT106/24

150 Kaibori M, Sakai K, Ishizaki M, et al. (2016) Increased FGF19 copy number is frequently detected in hepatocellular carcinoma with a complete response after sorafenib treatment. Oncotarget ePub Jun 2016

151 Packer LM, Pollock PM (2015) Paralog-Specific Kinase Inhibition of FGFR4: Adding to the Arsenal of Anti-FGFR Agents. Cancer Discov 5(4):355-7

152 Sawey ET, Chanrion M, Cai C, et al. (2011) Identification of a therapeutic strategy targeting amplified FGF19 in liver cancer by Oncogenomic screening. Cancer Cell 19(3):347-58

153 Desnoyers LR, Pai R, Ferrando RE, et al. (2008) Targeting FGF19 inhibits tumor growth in colon cancer xenograft and FGF19 transgenic hepatocellular carcinoma models. Oncogene 27(1):85-97

154 Miura S, Mitsuhashi N, Shimizu H, et al. (2012) Fibroblast growth factor 19 expression correlates with tumor progression and poorer prognosis of hepatocellular carcinoma. BMC Cancer 12:56

155 Feng S, Dakhova O, Creighton CJ, et al. (2013) Endocrine fibroblast growth factor FGF19 promotes prostate cancer progression. Cancer Res 73(8):2551-62

156 Nagamatsu H, Teishima J, Goto K, et al. (2015) FGF19 promotes progression of prostate cancer. Prostate ePub Apr 2015

157 Xie MH, Holcomb I, Deuel B, et al. (1999) FGF-19, a novel fibroblast growth factor with unique specificity for FGFR4. Cytokine 11(10):729-35

158 Katoh M (2002) WNT and FGF gene clusters (review). Int J Oncol 21(6):1269-73

159 Kan Z, Zheng H, Liu X, et al. (2013) Whole-genome sequencing identifies recurrent mutations in hepatocellular carcinoma. Genome Res 23(9):1422-33

160 Tekin M, Hişmi BO, Fitoz S, et al. (2007) Homozygous mutations in fibroblast growth factor 3 are associated with a new form of syndromic deafness characterized by inner ear agenesis, microtia, and microdontia. Am J Hum Genet 80(2):338-44

161 Arao T, Ueshima K, Matsumoto K, et al. (2013) FGF3/FGF4 amplification and multiple lung metastases in responders to sorafenib in hepatocellular carcinoma. Hepatology 57(4):1407-15

162 Yamada T, Abei M, Danjoh I, et al. (2015) Identification of a unique hepatocellular carcinoma line, Li-7, with CD13(+) cancer stem cells hierarchy and population change upon its differentiation during culture and effects of sorafenib. BMC Cancer 15:260

163 Kratochwil K, Galceran J, Tontsch S, et al. (2002) FGF4, a direct target of LEF1 and Wnt signaling, can rescue the arrest of tooth organogenesis in Lef1(-/-) mice. Genes Dev 16(24):3173-85

164 Scherz PJ, Harfe BD, McMahon AP, et al. (2004) The limb bud Shh-Fgf feedback loop is terminated by expansion of former ZPA cells. Science 305(5682):396-9

165 Arai H, Ueno T, Tangoku A, et al. (2003) Detection of amplified oncogenes by genome DNA microarrays in human primary esophageal squamous cell carcinoma: comparison with conventional comparative genomic hybridization analysis. Cancer Genet Cytogenet 146(1):16-21

166 Ribeiro IP, Marques F, Caramelo F, et al. (2014) Genetic imbalances detected by multiplex ligation-dependent probe amplification in a cohort of patients with oral squamous cell carcinoma-the first step towards clinical personalized medicine. Tumour Biol 35(5):4687-95

167 Schulze K, Imbeaud S, Letouzé E, et al. (2015) Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. Nat Genet 47(5):505-11

168 Williams NK, Lucet IS, Klinken SP, et al. (2009) Crystal structures of the Lyn protein tyrosine kinase domain in its Apo- and inhibitor-bound state. J Biol Chem 284(1):284-91

169 Nam S, Kim D, Cheng JQ, et al. (2005) Action of the Src family kinase inhibitor, dasatinib (BMS-354825), on human prostate cancer cells. Cancer Res 65(20):9185-9

170 Choi YL, Bocanegra M, Kwon MJ, et al. (2010) LYN is a mediator of epithelial-mesenchymal transition and a target of dasatinib in breast cancer. Cancer Res 70(6):2296-306

171 Ingley E (2012) Functions of the Lyn tyrosine kinase in health and disease. Cell Commun Signal 10(1):21

172 Stettner MR, Wang W, Nabors LB, et al. (2005) Lyn kinase activity is the predominant cellular SRC kinase activity in glioblastoma tumor cells. Cancer Res 65(13):5535-43

173 Goldenberg-Furmanov M, Stein I, Pikarsky E, et al. (2004) Lyn is a target gene for prostate cancer: sequence-based inhibition induces regression of human tumor xenografts. Cancer Res 64(3):1058-66

174 Wheeler SE, Morariu EM, Bednash JS, et al. (2012) Lyn kinase mediates cell motility and tumor growth in EGFRvIII-expressing head and neck cancer. Clin Cancer Res 18(10):2850-60

175 Guan H, Zhou Z, Gallick GE, et al. (2008) Targeting Lyn inhibits tumor growth and metastasis in Ewing's sarcoma. Mol Cancer Ther 7(7):1807-16

176 Bates RC, Edwards NS, Burns GF, et al. (2001) A CD44 survival pathway triggers chemoresistance via lyn kinase and phosphoinositide 3-kinase/Akt in colon carcinoma cells. Cancer Res 61(13):5275-83

177 Xu Y, Harder KW, Huntington ND, et al. (2005) Lyn tyrosine kinase: accentuating the positive and the negative. Immunity 22(1):9-18

178 Huang FW, Hodis E, Xu MJ, et al. (2013) Highly recurrent TERT promoter mutations in human melanoma. Science 339(6122):957-9

179 Vinagre J, Almeida A, Pópulo H, et al. (2013) Frequency of TERT promoter mutations in human cancers. Nat Commun 4:2185

180 Pinyol R, Tovar V, Llovet JM (2014) TERT promoter mutations: Gatekeeper and driver of hepatocellular carcinoma. J Hepatol 61(3):685-7

181 Rachakonda PS, Hosen I, de Verdier PJ, et al. (2013) TERT promoter mutations in bladder cancer affect patient survival and disease recurrence through modification by a common polymorphism. Proc Natl Acad Sci USA 110(43):17426-31

182 Liu X, Bishop J, Shan Y, et al. (2013) Highly prevalent TERT promoter mutations in aggressive thyroid cancers. Endocr Relat Cancer 20(4):603-10

183 Landa I, Ganly I, Chan TA, et al. (2013) Frequent somatic TERT promoter mutations in thyroid cancer: higher prevalence in advanced forms of the disease. J Clin Endocrinol Metab 98(9):E1562-6

184 Nonoguchi N, Ohta T, Oh JE, et al. (2013) TERT promoter mutations in primary and secondary glioblastomas. Acta Neuropathol 126(6):931-7

185 Liu X, Wu G, Shan Y, et al. (2013) Highly prevalent TERT promoter mutations in bladder cancer and glioblastoma. Cell Cycle 12(10):1637-8

186 Killela PJ, Reitman ZJ, Jiao Y, et al. (2013) TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. Proc Natl Acad Sci USA 110(15):6021-6

187 Borah S, Xi L, Zaug AJ, et al. (2015) Cancer. TERT promoter mutations and telomerase reactivation in urothelial cancer. Science 347(6225):1006-10

188 Kinde I, Munari E, Faraj SF, et al. (2013) TERT promoter mutations occur early in urothelial neoplasia and are biomarkers of early disease and disease recurrence in urine. Cancer Res 73(24):7162-7

189 Shay JW, Wright WE (2011) Role of telomeres and telomerase in cancer. Semin Cancer Biol 21(6):349-53

190 Shay JW, Bacchetti S (1997) A survey of telomerase activity in human cancer. Eur J Cancer 33(5):787-91

191 Kim NW, Piatyszek MA, Prowse KR, et al. (1994) Specific association of human telomerase activity with immortal cells and cancer. Science 266(5193):2011-5

192 Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100(1):57-70

193 Horn S, Figl A, Rachakonda PS, et al. (2013) TERT promoter mutations in familial and sporadic melanoma. Science 339(6122):959-61

194 Hirai H, Arai T, Okada M, et al. (2010) MK-1775, a small molecule Wee1 inhibitor, enhances anti-tumor efficacy of various DNA-damaging agents, including 5-fluorouracil. Cancer Biol Ther 9(7):514-22

195 Bridges KA, Hirai H, Buser CA, et al. (2011) MK-1775, a novel Wee1 kinase inhibitor, radiosensitizes p53-defective human tumor cells. Clin Cancer Res 17(17):5638-48

196 Rajeshkumar NV, De Oliveira E, Ottenhof N, et al. (2011) MK-1775, a potent Wee1 inhibitor, synergizes with gemcitabine to achieve tumor regressions, selectively in p53-deficient pancreatic cancer xenografts. Clin Cancer Res 17(9):2799-806

197 Osman AA, Monroe MM, Ortega Alves MV, et al. (2015) Wee-1 kinase inhibition overcomes cisplatin resistance associated with high-risk TP53 mutations in head and neck cancer through mitotic arrest followed by senescence. Mol Cancer Ther 14(2):608-19

198 Gourley et al., 2016; ASCO Abstract 5571

199 Lehmann S, Bykov VJ, Ali D, et al. (2012) Targeting p53 in vivo: a first-in-human study with p53-targeting compound APR-246 in refractory hematologic malignancies and prostate cancer. J Clin Oncol 30(29):3633-9

200 Mohell N, Alfredsson J, Fransson Å, et al. (2015) APR-246 overcomes resistance to cisplatin and doxorubicin in ovarian cancer cells. Cell Death Dis 6:e1794

201 Fransson Å, Glaessgen D, Alfredsson J, et al. (2016) Strong synergy with APR-246 and DNA-damaging drugs in primary cancer cells from patients with TP53 mutant High-Grade Serous ovarian cancer. J Ovarian Res 9(1):27

202 Xu L, Huang CC, Huang W, et al. (2002) Systemic tumor-targeted gene delivery by anti-transferrin receptor scFv-immunoliposomes. Mol Cancer Ther 1(5):337-46

203 Xu L, Tang WH, Huang CC, et al. (2001) Systemic p53 gene therapy of cancer with immunolipoplexes targeted by anti-transferrin receptor scFv. Mol Med 7(10):723-34

204 Camp ER, Wang C, Little EC, et al. (2013) Transferrin receptor targeting nanomedicine delivering wild-type p53 gene sensitizes pancreatic cancer to gemcitabine therapy. Cancer Gene Ther 20(4):222-8

205 Kim SS, Rait A, Kim E, et al. (2015) A tumor-targeting p53 nanodelivery system limits chemoresistance to temozolomide prolonging survival in a mouse model of glioblastoma multiforme. Nanomedicine 11(2):301-11

206 Pirollo KF, Nemunaitis J, Leung PK, et al. (2016) Safety and Efficacy in Advanced Solid Tumors of a Targeted Nanocomplex Carrying the p53 Gene Used in Combination with Docetaxel: A Phase 1b Study. Mol Ther 24(9):1697-706

207 Hajdenberg et al., 2012; ASCO Abstract e15010

208 Leijen S, van Geel RM, Pavlick AC, et al. (2016) Phase I Study Evaluating WEE1 Inhibitor AZD1775 As Monotherapy and in Combination With Gemcitabine, Cisplatin, or Carboplatin in Patients With Advanced Solid Tumors. J Clin Oncol ePub Sep 2016

209 Oza et al., 2015; ASCO Abstract 5506

210 Leijen et al., 2015; ASCO Abstract 2507

211 Ma CX, Cai S, Li S, et al. (2012) Targeting Chk1 in p53-deficient triple-negative breast cancer is therapeutically beneficial in human-in-mouse tumor models. J Clin Invest 122(4):1541-52

212 Kumar et al., 2012; AACR Abstract 2874

213 Brown CJ, Lain S, Verma CS, et al. (2009) Awakening guardian angels: drugging the p53 pathway. Nat Rev Cancer 9(12):862-73

214 Joerger AC, Fersht AR (2008) Structural biology of the tumor suppressor p53. Annu Rev Biochem 77:557-82

215 Kato S, Han SY, Liu W, et al. (2003) Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis. Proc Natl Acad Sci USA 100(14):8424-9

216 Kamada R, Nomura T, Anderson CW, et al. (2011) Cancer-associated p53 tetramerization domain mutants: quantitative analysis reveals a low threshold for tumor suppressor inactivation. J Biol Chem 286(1):252-8

217 Bougeard G, Renaux-Petel M, Flaman JM, et al. (2015) Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. J Clin Oncol 33(21):2345-52

218 Sorrell AD, Espenschied CR, Culver JO, et al. (2013) Tumor protein p53 (TP53) testing and Li-Fraumeni syndrome : current status of clinical applications and future directions. Mol Diagn Ther 17(1):31-47

219 Nichols KE, Malkin D, Garber JE, et al. (2001) Germline p53 mutations predispose to a wide spectrum of early-onset cancers. Cancer Epidemiol Biomarkers Prev 10(2):83-7

220 Taubert H, Meye A, Würl P (1998) Soft tissue sarcomas and p53 mutations. Mol Med 4(6):365-72

221 Kleihues P, Schäuble B, zur Hausen A, et al. (1997) Tumors associated with p53 germline mutations: a synopsis of 91 families. Am J Pathol 150(1):1-13

222 Gonzalez KD, Noltner KA, Buzin CH, et al. (2009) Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. J Clin Oncol 27(8):1250-6

223 Lalloo F, Varley J, Ellis D, et al. (2003) Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. Lancet 361(9363):1101-2

224 Kowanetz et al., 2016; ESMO Abstract 77P

225 Spigel et al., 2016; ASCO Abstract 9017

226 Powles T, Durán I, van der Heijden MS, et al. (2018) Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 391(10122):748-757

227 Dreicer et al., 2016; ASCO Abstract 4515

228 Petrylak DP, Powles T, Bellmunt J, et al. (2018) Atezolizumab (MPDL3280A) Monotherapy for Patients With Metastatic Urothelial Cancer: Long-term Outcomes From a Phase 1 Study. JAMA Oncol ePub Feb 2018

229 Pal SK, Hoffman-Censits J, Zheng H, et al. (2018) Atezolizumab in Platinum-treated Locally Advanced or Metastatic Urothelial Carcinoma: Clinical Experience from an Expanded Access Study in the United States. Eur Urol ePub Feb 2018

230 Patel et al., 2016; ESMO Abstract 777PD

231 Powles et al., 2017; ASCO Genitourinary Abstract 286

232 Massard C, Gordon MS, Sharma S, et al. (2016) Safety and Efficacy of Durvalumab (MEDI4736), an Anti-Programmed Cell Death Ligand-1 Immune Checkpoint Inhibitor, in Patients With Advanced Urothelial Bladder Cancer. J Clin Oncol 34(26):3119-25

233 Johnson et al., 2016; ASCO Abstract 105

234 Sharma P, Retz M, Siefker-Radtke A, et al. (2017) Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol ePub Jan 2017

235 Sharma P, Callahan MK, Bono P, et al. (2016) Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol 17(11):1590-1598

236 Zibelman et al., 2016; ASCO abstract e14510

237 Kanz BA, Pollack MH, Johnpulle R, et al. (2016) Safety and efficacy of anti-PD-1 in patients with baseline cardiac, renal, or hepatic dysfunction. J Immunother Cancer 4:60

238 Bellmunt J, de Wit R, Vaughn DJ, et al. (2017) Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med ePub Feb 2017

239 Plimack ER, Bellmunt J, Gupta S, et al. (2017) Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study. Lancet Oncol 18(2):212-220

240 Balar et al., 2017; ASCO GU Abstract 284

241 Morschhauser et al., 2014; ASH Abstract 3067

242 Sledge GW, Toi M, Neven P, et al. (2017) MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol 35(25):2875-2884

243 Dickler MN, Tolaney SM, Rugo HS, et al. (2017) MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(-) Metastatic Breast Cancer. Clin Cancer Res 23(17):5218-5224

244 Junttila TT, Li G, Parsons K, et al. (2011) Trastuzumab-DM1 (T-DM1) retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib insensitive breast cancer. Breast Cancer Res Treat 128(2):347-56

245 Lewis Phillips GD, Li G, Dugger DL, et al. (2008) Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res 68(22):9280-90

246 Erickson HK, Park PU, Widdison WC, et al. (2006) Antibody-maytansinoid conjugates are activated in targeted cancer cells by lysosomal degradation and linker-dependent intracellular processing. Cancer Res 66(8):4426-33

247 Li M, Zhang Z, Li X, et al. (2014) Whole-exome and targeted gene sequencing of gallbladder carcinoma identifies recurrent mutations in the ErbB pathway. Nat Genet 46(8):872-6

248 Krop IE, Kim SB, González-Martín A, et al. (2014) Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol 15(7):689-99

249 Verma S, Miles D, Gianni L, et al. (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 367(19):1783-91

250 Welslau M, Diéras V, Sohn JH, et al. (2014) Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer. Cancer 120(5):642-51

251 Krop IE, LoRusso P, Miller KD, et al. (2012) A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. J Clin Oncol 30(26):3234-41

252 Burris HA, Rugo HS, Vukelja SJ, et al. (2011) Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. J Clin Oncol 29(4):398-405

253 Kwak EL, Shapiro GI, Cohen SM, et al. (2013) Phase 2 trial of afatinib, an ErbB family blocker, in solid tumors genetically screened for target activation. Cancer 119(16):3043-51

254 Marshall J, Shapiro GI, Uttenreuther-Fischer M, et al. (2013) Phase I dose-escalation study of afatinib, an ErbB family blocker, plus docetaxel in patients with advanced cancer. Future Oncol 9(2):271-81

255 Chu et al., 2013; ASCO Abstract 2523

256 Peeters et al., 2013; ASCO Abstract 2521

257 Sequist LV, Yang JC, Yamamoto N, et al. (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 31(27):3327-34

258 De Grève J, Teugels E, Geers C, et al. (2012) Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. Lung Cancer 76(1):123-7

259 Katakami N, Atagi S, Goto K, et al. (2013) LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J Clin Oncol 31(27):3335-41

260 Yap TA, Vidal L, Adam J, et al. (2010) Phase I trial of the irreversible EGFR and HER2 kinase inhibitor BIBW 2992 in patients with advanced solid tumors. J Clin Oncol 28(25):3965-72

261 Eskens FA, Mom CH, Planting AS, et al. (2008) A phase I dose escalation study of BIBW 2992, an irreversible dual inhibitor of epidermal growth factor receptor 1 (EGFR) and 2 (HER2) tyrosine kinase in a 2-week on, 2-week off schedule in patients with advanced solid tumours. Br J Cancer 98(1):80-5

262 Larkin J, Ascierto PA, Dréno B, et al. (2014) Combined Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma. N Engl J Med ePub Sep 2014

263 Larkin et al., 2015; ASCO Abstract 9006

264 McArthur et al., 2016; ASCO Abstract 9530

265 Daud et al., 2016; ASCO Abstract 9510

266 Ribas A, Gonzalez R, Pavlick A, et al. (2014) Combination of vemurafenib and cobimetinib in patients with advanced BRAF(V600)-mutated melanoma: a phase 1b study. Lancet Oncol 15(9):954-65

267 Abdel-Wahab O, Klimek VM, Gaskell AA, et al. (2014) Efficacy of intermittent combined RAF and MEK inhibition in a patient with concurrent BRAF- and NRAS-mutant malignancies. Cancer Discov 4(5):538-45

268 Bendell et al., 2016; ASCO Abstract 3502

269 Bendell et al., 2014; AACR Abstract CT328

270 Powles T, Huddart RA, Elliott T, et al. (2017) Phase III, Double-Blind, Randomized Trial That Compared Maintenance Lapatinib Versus Placebo After First-Line Chemotherapy in Patients With Human Epidermal Growth Factor Receptor 1/2-Positive Metastatic Bladder Cancer. J Clin Oncol 35(1):48-55

271 Wülfing C, Machiels JP, Richel DJ, et al. (2009) A single-arm, multicenter, open-label phase 2 study of lapatinib as the second-line treatment of patients with locally advanced or metastatic transitional cell carcinoma. Cancer 115(13):2881-90

272 Culine S, Sellam Z, Bouaita L, et al. (2012) Combining paclitaxel and lapatinib as second-line treatment for patients with metastatic transitional cell carcinoma: a case series. Anticancer Res 32(9):3949-52

273 Narayan V, Mamtani R, Keefe S, et al. (2015) Cisplatin, Gemcitabine, and Lapatinib as Neoadjuvant Therapy for Muscle-Invasive Bladder Cancer. Cancer Res Treat ePub Dec 2015

274 Dickson MA, Tap WD, Keohan ML, et al. (2013) Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. J Clin Oncol 31(16):2024-8

275 Turner NC, Ro J, André F, et al. (2015) Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med ePub Jun 2015

276 O'Hara et al., 2015; ASCO GI Abstract 626

277 Littman et al., 2015; ASCO GI Abstract 277

278 Kwong LN, Costello JC, Liu H, et al. (2012) Oncogenic NRAS signaling differentially regulates survival and proliferation in melanoma. Nat Med 18(10):1503-10

279 Huillard E, Hashizume R, Phillips JJ, et al. (2012) Cooperative interactions of BRAFV600E kinase and CDKN2A locus deficiency in pediatric malignant astrocytoma as a basis for rational therapy. Proc Natl Acad Sci USA 109(22):8710-5

280 Vora SR, Juric D, Kim N, et al. (2014) CDK 4/6 Inhibitors Sensitize PIK3CA Mutant Breast Cancer to PI3K Inhibitors. Cancer Cell 26(1):136-49

281 Miller ML, Molinelli EJ, Nair JS, et al. (2013) Drug synergy screen and network modeling in dedifferentiated liposarcoma identifies CDK4 and IGF1R as synergistic drug targets. Sci Signal 6(294):ra85

282 Heilmann AM, Perera RM, Ecker V, et al. (2014) CDK4/6 and IGF1 Receptor Inhibitors Synergize to Suppress the Growth of p16INK4A-Deficient Pancreatic Cancers. Cancer Res 74(14):3947-58

283 Baselga J, Cortés J, Kim SB, et al. (2012) Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 366(2):109-19

284 Hainsworth et al., 2016; ASCO Abstract LBA11511

285 Swain SM, Kim SB, Cortés J, et al. (2013) Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 14(6):461-71

286 Swain SM, Baselga J, Kim SB, et al. (2015) Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 372(8):724-34

287 Wilhelm SM, Dumas J, Adnane L, et al. (2011) Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer 129(1):245-55

288 Bruix J, Qin S, Merle P, et al. (2017) Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 389(10064):56-66

289 Grothey A, Van Cutsem E, Sobrero A, et al. (2013) Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381(9863):303-12

290 Demetri GD, Reichardt P, Kang YK, et al. (2013) Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381(9863):295-302

291 Aprile G, Macerelli M, Giuliani F (2013) Regorafenib for gastrointestinal malignancies : from preclinical data to clinical results of a novel multi-target inhibitor. BioDrugs 27(3):213-24

292 Mross K, Frost A, Steinbild S, et al. (2012) A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res 18(9):2658-67

293 Yamada et al., 2015; AACR-NCI-EORTC Abstract B31

294 Geoerger B, Bourdeaut F, DuBois SG, et al. (2017) A Phase I Study of the CDK4/6 Inhibitor Ribociclib (LEE011) in Pediatric Patients with Malignant Rhabdoid Tumors, Neuroblastoma, and Other Solid Tumors. Clin Cancer Res

295 Dreicer R, Li H, Stein M, et al. (2009) Phase 2 trial of sorafenib in patients with advanced urothelial cancer: a trial of the Eastern Cooperative Oncology Group. Cancer 115(18):4090-5

296 Krege S, Rexer H, vom Dorp F, et al. (2014) Prospective randomized double-blind multicentre phase II study comparing gemcitabine and cisplatin plus sorafenib chemotherapy with gemcitabine and cisplatin plus placebo in locally advanced and/or metastasized urothelial cancer: SUSE (AUO-AB 31/05). BJU Int 113(3):429-36

297 Rose A, Grandoch M, vom Dorp F, et al. (2010) Stimulatory effects of the multi-kinase inhibitor sorafenib on human bladder cancer cells. Br J Pharmacol 160(7):1690-8

298 Infante JR, Fecher LA, Falchook GS, et al. (2012) Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. Lancet Oncol 13(8):773-81

299 Leijen S, Middleton MR, Tresca P, et al. (2012) Phase I dose-escalation study of the safety, pharmacokinetics, and pharmacodynamics of the MEK inhibitor RO4987655 (CH4987655) in patients with advanced solid tumors. Clin Cancer Res 18(17):4794-805

300 Zimmer L, Barlesi F, Martinez-Garcia M, et al. (2014) Phase I Expansion and Pharmacodynamic Study of the Oral MEK Inhibitor RO4987655 (CH4987655) in Selected Patients with Advanced Cancer with RAS-RAF Mutations. Clin Cancer Res 20(16):4251-61

301 Infante JR, Papadopoulos KP, Bendell JC, et al. (2013) A phase 1b study of trametinib, an oral Mitogen-activated protein kinase kinase (MEK) inhibitor, in combination with gemcitabine in advanced solid tumours. Eur J Cancer 49(9):2077-85

302 Juric et al., 2014; ASCO Abstract 9051

303 Tolcher AW, Bendell JC, Papadopoulos KP, et al. (2014) A Phase IB Trial of the Oral MEK Inhibitor Trametinib (GSK1120212) in Combination With Everolimus in Patients With Advanced Solid Tumors. Ann Oncol ePub Oct 2014

304 Oudard S, Culine S, Vano Y, et al. (2015) Multicentre randomised phase II trial of gemcitabine+platinum, with or without trastuzumab, in advanced or metastatic urothelial carcinoma overexpressing Her2. Eur J Cancer 51(1):45-54

305 Hussain MH, MacVicar GR, Petrylak DP, et al. (2007) Trastuzumab, paclitaxel, carboplatin, and gemcitabine in advanced human epidermal growth factor receptor-2/neu-positive urothelial carcinoma: results of a multicenter phase II National Cancer Institute trial. J Clin Oncol 25(16):2218-24

306 Marín AP, Arranz EE, Sánchez AR, et al. (2010) Role of anti-Her-2 therapy in bladder carcinoma. J Cancer Res Clin Oncol 136(12):1915-20

307 Slamon DJ, Leyland-Jones B, Shak S, et al. (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344(11):783-92

308 Rugo et al., 2016; ASCO Abstract LBA503

309 Waller et al., 2016; ASCO Abstract 583

310 Audran et al., 2017; ASCO-SITC Clinical Immuno-Oncology Symposium Abstract 10