FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Bladder urothelial (transitional cell) carcinoma

REPORT DATE

COUNTRY CODE
IT

PRF#

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

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 Bladder
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Genomic Signatures

Tumor Mutational Burden - 29 Muts/Mb
Microsatellite status - MS-Stable

Gene Alterations

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

BRCA2 Q3321*
CDK4 amplification
ERBB2 S310Y, amplification
ARID1A S2264* - subclonal, Q1212* - subclonal†
FGFR1 amplification
CCNE1 amplification
CDKN2A/B p16INK4a D74N and p14ARF R88Q
NBN Q460* - subclonal†
NSD3 (WHSC1L1) amplification
TERT promoter -124C>T
TP53 Q192*
ZNF703 amplification

† See About the Test in appendix for details.

19 Therapies approved in the EU
0 Therapies with Lack of Response
52 Clinical Trials

GENOMIC SIGNATURES

Tumor Mutational Burden - 29 Muts/Mb

10 Trials *see p. 20*

Microsatellite status - MS-Stable

THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)		THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)	
Pembrolizumab	1	Avelumab	2A
Atezolizumab	2A	Durvalumab	2A
Nivolumab	2A	Cemiplimab	

No therapies or clinical trials. see Genomic Signatures section

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Sample Analysis: FMI Germany GmbH, Nonnenwald 2, 82377 Penzberg, Germany

GENE ALTERATIONS	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
BRCA2 - Q3321*	none	Niraparib
		Olaparib
		Rucaparib
		Talazoparib
10 Trials *see p. 24*		
CDK4 - amplification	none	Palbociclib
		Ribociclib
10 Trials *see p. 26*		
ERBB2 - S310Y, amplification	none	Afatinib
		Dacomitinib
		Lapatinib
		Neratinib
		Pertuzumab
		Trastuzumab
		Trastuzumab emtansine
10 Trials *see p. 28*		
ARID1A - S2264* - subclonal, Q1212* - subclonal	none	none
7 Trials *see p. 23*		
FGFR1 - amplification	none	none
10 Trials *see p. 30*		

☐ *NCCN category (resistance may not be reflected in NCCN category)*

GENE ALTERATIONS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. 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. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

Therapies contained in this report may have been approved through a centralized EU procedure or a national procedure in an EU Member State. Therapies, including but not limited to the following, have been approved nationally and may not be available in all EU Member States: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, Triptorelin.

GENOMIC SIGNATURE

Tumor Mutational Burden

RESULT
29 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3] and anti-PD-1 therapies[1-4]. In multiple studies of immune checkpoint inhibitors in urothelial carcinoma, higher TMB has corresponded with clinical benefit from treatment with anti-PD-L1[1,5-9] and anti-PD-1 immunotherapeutic agents[10-11] . For patients with metastatic urothelial carcinoma, those who responded to treatment with the PD-L1 inhibitor atezolizumab had a significantly increased mutational load (12.4 Muts/Mb) compared with nonresponders (6.4 Muts/Mb)[5]. Similarly, in a study of pembrolizumab in muscle invasive bladder cancer, the median TMB in responders was 12.3 Muts/Mb, versus 7.0 Muts/Mb in nonresponding patients[11]. Increased TMB has also been associated with longer OS with atezolizumab treatment in metastatic urothelial carcinoma, with studies reporting increased benefit for patients with a mutational load above 9.7 Muts/Mb[7], 16 Muts/Mb[6], or 22.9 Mut/Mb[1] compared with those with lower TMB. The PD-1 inhibitor nivolumab led to increased ORR, PFS, and OS for patients with a TMB of 9 Muts/Mb or higher compared with those harboring lower TMB in a study of metastatic urothelial cancer (Galsky et al., 2017 ESMO Abstract 848PD).

FREQUENCY & PROGNOSIS

In the Bladder Urothelial Carcinoma TCGA dataset, the median somatic mutation burden was 5.5 mutations per megabase (muts/Mb)[12]. One study reported that the number of somatic mutations positively correlates with increased tumor stage and grade of bladder cancers[13]. 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[5-6,14].

FINDING SUMMARY

Tumor mutational 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[15-16] and cigarette smoke in lung cancer[17-18], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[19-23], and microsatellite instability (MSI)[19,22-23]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in urothelial carcinoma[1,5-9].

GENOMIC SIGNATURE

Microsatellite status

RESULT
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[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].

FREQUENCY & PROGNOSIS

MSI has been detected in 26-49% of urothelial carcinomas[29-30]; 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 bladder 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]. This sample 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].

GENE
BRCA2

ALTERATION
Q3321*

TRANSCRIPT NUMBER
NM_000059

CODING SEQUENCE EFFECT
9961C>T

POTENTIAL TREATMENT STRATEGIES

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[38-54]. Clinical response to PARP inhibitors has been reported for patients with either germline or somatic BRCA2 mutations[39,44,47,54] and for patients who were platinum-resistant or refractory[38,43,50,53]. Inactivation of BRCA2 may also predict sensitivity to DNA-damaging drugs such as the platinum chemotherapies cisplatin and carboplatin[55-57]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

BRCA2 mutation has been reported in 0-8% of bladder urothelial carcinoma samples[12,58-60]. An analysis of 104 patients with metastatic urothelial carcinoma reported that expression of BRCA1 or BRCA2 was not associated with overall survival[61].

FINDING SUMMARY

The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage[62]. Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis[63]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance. Germline mutations in BRCA1 or BRCA2 are associated with breast-ovarian cancer familial susceptibility (BROVCA), also known as hereditary breast-ovarian cancer (HBOC)[64-65]. The lifetime risk of breast and ovarian cancer in BRCA1/2 mutation carriers has been estimated to be as high as 87% and 44%, respectively[66], and elevated risk of other cancers, including gastric, pancreatic, prostate, and colorectal tumors, has been identified at frequencies of 20-60%[67-74]. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population[66,68,75-79]. In the appropriate clinical context, germline testing of BRCA2 is recommended.

GENE
CDK4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

CDK4 amplification or activation may predict sensitivity to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib[80-83]. Clinical benefit has been reported for patients with CDK4-amplified solid tumors in response to treatment with palbociclib[80,84] and ribociclib[85].

FREQUENCY & PROGNOSIS

In the Bladder Urothelial Carcinoma TCGA dataset, CDK4 amplification has been observed in 1.5% of cases (cBioPortal, Jan 2019). CDK4 amplification was detected in 1.1% of bladder cancer cases, including urothelial carcinomas, in one study[86]. CDK4 amplification has been correlated with shortened disease-specific survival in bladder cancer, including bladder urothelial carcinoma[86].

FINDING SUMMARY

CDK4 encodes the cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis[87]. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[88-89]. Amplification of the chromosomal region that includes CDK4 has been reported in multiple cancer types, including lung cancer, glioblastoma, and liposarcoma, and has been associated with overexpression of CDK4 protein[80,90-96].

GENE
ERBB2

ALTERATION
S310Y, amplification

TRANSCRIPT NUMBER
NM_004448

CODING SEQUENCE EFFECT
929C>A

POTENTIAL TREATMENT STRATEGIES

On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[97-102], pertuzumab in combination with trastuzumab[99,103-105], margetuximab[106], and ZW25[107] as well as antibody-directed conjugates such as ado-trastuzumab emtansine[108] and fam-trastuzumab deruxtecan[109], HER2 kinase inhibitors such as tucatinib[110-112], and dual EGFR/HER2 kinase inhibitors such as lapatinib[113-117], afatinib[102,118-123], neratinib[124-125], dacomitinib[126], and pyrotinib[127]. In a Phase 1 trial of margetuximab for HER2-overexpressing solid tumors, 12% (7/60) of patients, including 4 with breast, 2 with gastroesophageal, and 1 with lacrimal gland cancers, experienced PRs, and a further 52% (31/60) of the cohort experienced SD[106]. Early clinical studies aimed at preventing or overcoming resistance to anti-HER2 therapies are underway, including agents targeting the PI3K-AKT pathway or HSP90[128-129]. A patient with breast cancer and ERBB2 S310F had 12 months of clinical benefit from the combination of trastuzumab, pertuzumab, and fulvestrant[99], and a patient with inflammatory breast cancer and ERBB2 V777L and S310F activating mutations experienced tumor shrinkage in response to combined treatment with lapatinib and trastuzumab[116].

FREQUENCY & PROGNOSIS

ERBB2 mutations and amplification have been found in 9-10% and 5-9% of bladder urothelial carcinoma samples[12,58], and amplifications have been reported at a higher frequency in lymph node metastases[130-131]. One study reported enrichment for ERBB2 mutations in micropapillary urothelial carcinoma (MPUC; 40% of samples), as compared with non-MPUC urothelial carcinomas (9% of samples)[132]. HER2 overexpression has been identified in 19% of bladder urothelial cancers with enrichment in Grade 3 and muscle-invasive tumors[133-134]. Studies have generally reported inconsistent results with respect to the prognostic value of HER2 expression in patients with bladder urothelial carcinoma[135].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. Amplification or overexpression of ERBB2 can lead to excessive proliferation and tumor formation[136]. S310 is located in the HER2 extracellular domain and mutations at this position, including S310F and S310Y, have been reported to be activating[137-138]. In clinical studies, patients with the ERBB2 S310F mutation have benefited from ERBB2-targeted therapies including trastuzumab, pertuzumab, and lapatinib[99,116]; a patient with concurrent EGFR L858R and ERBB2 S310F mutations also reported a complete and durable response to the dual EGFR/ERBB2 inhibitor afatinib[139].

GENE
ARID1A

ALTERATION
S2264* - subclonal, Q1212* - subclonal

TRANSCRIPT NUMBER
NM_006015

CODING SEQUENCE EFFECT
- 6791C>G
- 3634C>T

POTENTIAL TREATMENT STRATEGIES

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620; 1 patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[140-141]. On the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to inhibitors of EZH2[142-143], which are under investigation in clinical trials. Other studies have reported that loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[144-146]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy in patients with ovarian clear cell carcinoma[147-148] and to 5-fluorouracil (5-FU) in CRC cell lines[149]. Limited clinical evidence indicates that ARID1A-altered urothelial cancer may be sensitive to pan-HDAC inhibitors; a retrospective analysis reported a CR to belinostat and a PR to panobinostat in patients with ARID1A alterations[150].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma (CRC), and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2019)[151-156]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[157-160], CRC[161-163], and gastric cancer[164-168]. In the context of urothelial carcinomas, one study reported no association between ARID1A mutation and tumor grade[169], whereas others have reported contradictory associations between ARID1A protein loss and prognosis[170-171].

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[152,167,172-178]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[152,165,173-174,179], whereas ARID1A missense mutations are mostly uncharacterized.

GENE
FGFR1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

Tumors with alterations that activate FGFR1 may be sensitive to FGFR family inhibitors[180]. In addition to the pan-FGFR inhibitor erdafitinib[181-182], other FGFR inhibitors such as infigratinib, AZD4547, Debio 1347, TAS-120 and the multikinase inhibitors lenvatinib and lucitanib, are under clinical investigation. Two case studies reported PRs in patients with FGFR1-amplified breast cancer treated with pazopanib[183]. In addition to preclinical evidence supporting the activity of ponatinib for FGFR1 alterations[184-188], limited activity of ponatinib has been demonstrated in patients with FGFR1-rearranged hematological malignancies, including leukemia[189-190] and myeloproliferative neoplasms[191], and SD was reported in 2 of 4 cases of FGFR1-positive lung squamous cell carcinoma[192]. In a Phase 1/2a study of patients with breast carcinoma harboring an amplification of FGFR1, FGF3, FGF4, or FGF19, lucitanib resulted in a disease control rate (DCR) of 100%; 50% (6/12) of patients achieved PR and 50% (6/12) of patients had SD[193]. A Phase 1 study of infigratinib reported a DCR of 50% (18/36), including 4 PRs and 14 SDs, for patients with FGFR1-amplified squamous non-small cell lung carcinoma (NSCLC); although no responses were reported for patients with other tumor types harboring FGFR1 alterations, 32% (10/31) of patients with FGFR1- or FGFR2-amplified breast cancer experienced SD[194]. Preclinical studies suggest that overexpression of FGFR1 may be a mechanism of acquired resistance to gefitinib; addition of an FGFR inhibitor restored gefitinib sensitivity in lung cancer cell lines[195-196].

FREQUENCY & PROGNOSIS

FGFR1 amplification and mutation have been reported in 3-9% and 2-3% of bladder urothelial carcinomas, respectively[12,197-198]. In another study, FGFR1 alterations (mutations, amplifications, or fusions) were reported in 14% (5/35) of cases of bladder urothelial carcinoma[199]. FGFR1 is frequently overexpressed in urothelial carcinoma, and has been associated with MAPK pathway activation and the epithelial-mesenchymal transition (EMT)[200-202]. FGFR1 expression was reported to be higher in more invasive stages of bladder cancer[203].

FINDING SUMMARY

FGFR1 encodes the protein fibroblast growth factor receptor 1, which plays key roles in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and AKT signaling pathways[204]. Amplification of FGFR1 has been correlated with protein expression[205-206] and may predict pathway activation and sensitivity to therapies targeting this pathway[180,207].

GENE
CCNE1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies that directly target CCNE1 alterations. Because amplification or overexpression of CCNE1 leads to increased genomic instability though the ATR-CHK1 pathway[208] and cyclin E1 promotes cell cycle progression in a complex with CDK2[209], clinical and preclinical studies have investigated inhibitors of CHK1, ATR, and CDK2 as potential therapeutic approaches for tumors with CCNE1 activation. Clinical benefit has been reported for patients with recurrent high-grade ovarian carcinoma with CCNE1 amplification or expression in response to treatment with the CHK1 inhibitor prexasertib[210]. Preclinical studies have demonstrated that cell lines with CCNE1 amplification or overexpression were sensitive to inhibitors of ATR[211-212] or CDK2[213]. However, other studies have shown that sensitivity of various cell lines to CDK2 inhibitors, including SNS-032, dinaciclib, and seliciclib, at clinically achievable doses, is largely independent of CCNE1 copy number or expression[214-217]. One study has reported a reduction in tumor CCNE1 levels in 4/6 lung and esophageal cancer cases following treatment with the HDAC inhibitor vorinostat[218].

FREQUENCY & PROGNOSIS

In the Bladder Urothelial Carcinoma TCGA dataset, CCNE1 amplification has been reported in 15% of cases[12]. Amplification of 19q13, which includes the CCNE1 gene, has been reported in 3-6% of urothelial carcinoma tumors[219-220]. Cyclin E1, as well as p21, p27, p53, and Rb, have been reported to be biomarkers of bladder cancer[221]. Low cyclin E1 expression has been found in 55% of advanced urothelial carcinomas[222]. Although amplification of 19q13 in urothelial carcinoma has been correlated with metastasis and lymph vessel involvement in several studies, low expression of cyclin E1 correlated with advanced tumor stage, lymphovascular invasion, lymph node metastasis, and disease-specific mortality in another study[222-224].

FINDING SUMMARY

CCNE1 encodes the protein cyclin E1, which plays a role in the regulated transition from the G1 to S phase by binding to and activating cyclin-dependent protein kinase 2 (CDK2). It also has a direct role in initiation of replication and the maintenance of genomic stability[209]. Amplification of chromosomal region 19q12-q13 has been demonstrated in many types of cancer, and CCNE1 is a well-studied gene within this amplicon[225-226]. Increased copy number of CCNE1 is highly associated with overexpression of the cyclin E1 protein[227-228]. Cyclin E1 overexpression can lead to cell transformation as a result of an increase in cyclin E1 activity[209,229].

GENE
CDKN2A/B

ALTERATION
p16INK4a D74N and p14ARF R88Q

TRANSCRIPT NUMBER
NM_000077

CODING SEQUENCE EFFECT
220G>A

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[230-233]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[234-235], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[83,85,236-240]; 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[241-242], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS
In the Bladder Urothelial Carcinoma TCGA dataset, concurrent homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of cases, and CDKN2A mutation has been found in 5.5% of cases[12]. Loss of CDKN2A/B or loss of p14ARF, p16INK4a, or p15INK4b protein expression occurs frequently in bladder urothelial carcinoma, with reports of frequency ranging from 18% to 77%[199,243-250]. Several studies have associated loss of CDKN2A/B or loss of p16INK4a and p15INK4b expression with disease progression, decreased recurrence-free disease, and poor prognosis in patients with urothelial cell carcinoma, although results have been inconsistent[60,243-244,246,248,251-253].

FINDING SUMMARY
CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[254-255]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[256-257]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[258-259]. This alteration is predicted to result in p16INK4a[260-281] loss of function. The effect of this alteration on p14ARF function is unclear. This alteration does not affect the function of p15INK4b.

GENE
NBN

ALTERATION
Q460* - subclonal

TRANSCRIPT NUMBER
NM_002485

CODING SEQUENCE EFFECT
1378C>T

POTENTIAL TREATMENT STRATEGIES
There are no approved therapies to target NBN mutation. NBN inactivation has been associated with sensitivity to PARP inhibitors in preclinical studies, although the clinical relevance of this has not been investigated[282-285]. Case studies of NBS patients with malignancies have reported hypersensitivity and adverse effects from radiation therapy and chemotherapy[286-289].

FREQUENCY & PROGNOSIS
Somatic NBN mutations occur infrequently in solid tumors and hematologic malignancies, reported in 0-2% of samples (COSMIC, 2019). A high rate of malignancy, particularly B- and T-cell lymphomas, has been observed in NBS patients with biallelic NBN disruption[290-291]. Several studies have described heterozygous NBN mutation as a mild to moderate risk allele for certain cancers, such as breast cancer[292-294], prostate cancer[295], medulloblastoma[296], acute lymphoblastic leukemia[297], and non-Hodgkin lymphoma[298-299], although other studies found no such risk associations[300-302]; it is unclear if alterations other than the 657del5/K219fs*16 founder mutation are also putative risk alleles[303].

FINDING SUMMARY
NBN (also known as NBS1, p95) encodes nibrin, a component of a DNA double-strand break repair complex containing MRE11A and RAD50[304]. Germline NBN mutations, most frequently the K219fs*16 (657del5) founder mutation, are associated with Nijmegen breakage syndrome (NBS), a chromosomal instability syndrome with similarity to ataxia-telangiectasia, characterized by microcephaly, intrauterine growth restriction, immunodeficiency, and predisposition to certain cancers[304-305]. Limited data suggest that NBN overexpression may also be associated with cell transformation[306].

GENE
NSD3 (WHSC1L1)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in NSD3.

FREQUENCY & PROGNOSIS
In TCGA datasets, NSD3 amplification has been most frequently observed in lung squamous cell carcinoma (17%)[307], breast invasive carcinoma (13%)[308], bladder urothelial carcinoma (9%)[12], and head and neck squamous cell carcinoma (9%)[309] samples. NSD3-NUP98 fusion has been detected in a patient with acute myeloid leukemia (AML)[310], and NUP98 and NSD3 rearrangements have been identified in a patient with radiation-associated myelodysplastic syndrome (MDS)[311]. NSD3-NUT fusion has been reported as a recurrent fusion in midline carcinoma[312-315].

FINDING SUMMARY
NSD3, also known as WHSC1L1, encodes an enzyme that mediates histone methylation[316]. NSD3 has been shown to be amplified in various cancers[317-319].

GENE
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT NUMBER
NM_198253

CODING SEQUENCE EFFECT
-124C>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 a variety of solid tumors, including bladder cancer[320-328]. One study reported TERT promoter mutations in 67% (14/21) of high-grade and 56% (34/61) of low-grade bladder carcinomas[320], 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[327]. TERT promoter mutations correlated with increased TERT mRNA expression in urothelial cancer cells[329]. 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[323,329-330].

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[331]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[332-334]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[320-321,335], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[335].

GENE
TP53

ALTERATION
Q192*

TRANSCRIPT NUMBER
NM_000546

CODING SEQUENCE EFFECT
574C>T

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 adavosertib[336-339], or p53 gene therapy and immunotherapeutics such as SGT-53[340-344] and ALT-801[345]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 10% (17/176) and SDs 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[346]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR in patients with platinum refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[347]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[348]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[349]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate in patients with TP53 alterations[350]. 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 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[344]. 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[351].

FREQUENCY & PROGNOSIS

TP53 mutation has been reported in 49–54% of bladder urothelial carcinoma (UC)[12,199], 33% of renal pelvis UC[352], and 25% (22/71) of ureter UC samples[353]. Expression of p53 has been correlated with TP53 mutation, and reported in 52–84% of bladder cancers[60,354-358], 48% (24/50) bladder SCCs[359], 36–53% of upper urinary tract UCs (UTUC)[360-362], and in 4/4 urethral clear cell carcinomas[363]. TP53 mutations in both bladder and renal pelvis UC are more common in invasive tumors[60,219,352,364], and have been associated with inferior survival in patients with renal pelvis UC[352] or UTUC[365]. Alterations to the p53 pathway are correlated with aggressive disease and poor prognosis in bladder cancer[366-368], and p53 overexpression has been linked to poor progression-free survival in UTUC[365,369], disease progression in UC of the renal pelvis and ureter[370], and higher tumor grade in bladder squamous cell carcinoma[371-373].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[374]. 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[375-377]. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers[378-380], including sarcomas[381-383]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[384] to 1:20,000[383]. In the appropriate clinical context, germline testing of TP53 is recommended.

GENE
ZNF703

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
There are no available targeted therapies to directly address ZNF703 alterations in cancer. One preclinical study suggested that ZNF703 expression in breast cancer cell lines is associated with reduced sensitivity to tamoxifen through AKT-mTOR activation[385], although these findings have not been verified in the clinical setting.

FREQUENCY & PROGNOSIS
Amplification and high expression of ZNF703 has been observed in luminal B breast tumors, a subtype associated with aggressive disease progression and poor patient outcomes[386-388]. ZNF703 expression has also been linked with aggressive tumor characteristics in patients with gastric and colorectal cancers[389-390]. Putative high-level amplification of ZNF703 has been reported with the highest frequency in breast carcinoma, bladder urothelial carcinoma, uterine carcinosarcoma, lung squamous cell carcinoma (SCC), esophageal carcinoma and head and neck SCC (5-13% of samples)(cBioPortal, 2019).

FINDING SUMMARY
ZNF703 encodes a transcriptional repressor that plays roles in stem cell proliferation, cell cycle progression, and other key cellular functions[387,391]. Amplification of ZNF703 has been correlated with protein expression[386-387]. ZNF703 was established as a breast cancer oncoprotein by studies showing that ZNF703 expression resulted in transformation and increased proliferation of cultured cells[386-387,392], as well as increased lung metastases in a breast cancer xenograft model[392].

Atezolizumab

Assay findings association

Tumor Mutational Burden
29 Muts/Mb

AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is available in the EU to treat patients with advanced or metastatic urothelial carcinoma following platinum-based chemotherapy or patients who are not eligible for cisplatin-containing chemotherapy and whose tumors have PD-L1 expression ≥ 5%. It is also available as a first-line treatment in combination with bevacizumab, paclitaxel, and carboplatin or in combination with nab-paclitaxel and carboplatin for patients with metastatic non-squamous NSCLC without EGFR or ALK alterations and as monotherapy to treat patients with metastatic NSCLC following chemotherapy. Patients whose tumors harbor EGFR or ALK alterations should also have received targeted therapy for these alterations. It is additionally available in combination with carboplatin and etoposide as first-line treatment for patients with extensive-stage small cell lung cancer. Atezolizumab is also available in combination with nab-paclitaxel to treat patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

GENE ASSOCIATION

On the basis of clinical data[1,5-11,393] , patients with urothelial carcinoma whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

Patients with metastatic urothelial carcinoma who were treated with atezolizumab as first-line therapy experienced an ORR of 23%, a CR rate of 9%, and a clinical benefit rate of 30%[6]. 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[6]. As second-line therapy for advanced urothelial carcinoma, atezolizumab compared with chemotherapy did not significantly improve median OS (11.1 vs. 10.6 months, 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 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[7]. 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)[7]. 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%[5,394] . 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)[5]. Long-term follow-up of a Phase 1 expansion cohort reported a 3-year OS rate of 27% on second-line atezolizumab[395]. 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[396].

Nivolumab

Assay findings association

Tumor Mutational Burden
29 Muts/Mb

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby reducing inhibition of the antitumor immune response. It is available in the EU as adjuvant treatment for patients with completely resected advanced melanoma and as monotherapy or in combination with the immunotherapy ipilimumab to treat patients with unresectable or metastatic melanoma. Nivolumab is also available 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 therapy. Nivolumab is available as a monotherapy to treat patients with chemotherapy-refractory advanced non-small cell lung cancer (NSCLC), classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (ASCT) and brentuximab vedotin treatment, head and neck squamous cell carcinoma (HNSCC) following disease progression on or after platinum-based therapy, and advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy.

GENE ASSOCIATION

On the basis of clinical data[1,5-11,393] , patients with urothelial carcinoma whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

The Phase 2 CheckMate 275 and Phase 1/2 CheckMate 032 studies evaluating nivolumab for patients with platinum-refractory metastatic urothelial carcinoma (UC) reported ORRs of 20.4% (6.3% CR) and 25.6% (10.3% CR), PFS of 1.9 and 2.8 months, and OS of 8.6 and 9.9 months, respectively[397-399] . CheckMate 032 additionally reported a 38% ORR, a 4.9 month median PFS, and a 15.3 month median OS for patients treated with nivolumab and ipilumumab; a 58% ORR was observed for patients with ≥1% tumor PD-L1 expression[397]. In a Phase 3 trial of neoadjuvant nivolumab and ipilimumab for patients with high-risk, advanced UC, 60.0% (9/15) of patients with a combined positive PD-L1 score ≥10 experienced a pathologic CR compared to 22.2% (2/9) of patients with lower PD-L1 expression[400]. A Phase 2 study of ipilimumab and nivolumab for patients with platinum-refractory metastatic UC who progressed on nivolumab monotherapy observed PRs for 22.7% (5/22) of patients[401]. Combining the multikinase inhibitor cabozantinib with nivolumab or with nivolumab plus ipilimumab demonstrated activity for immunotherapy-naive patients with chemotherapy-refractory metastatic UC (ORR of 50.0% [6/12] and 22.2% [2/9], respectively; median PFS of 24 months and 10 months, respectively); cabozantinib combined with nivolumab also benefited immunotherapy-refractory patients (ORR of 28.6% [2/7])[402] and responses to these combination treatments were observed for patients with bladder squamous cell carcinoma or bladder adenocarcinoma[403]. Addition of the IDO1 inhibitor BMS986205 to nivolumab in previously-treated advanced UC elicited ORRs for 37.0% (3/27 CRs, 7/27 PRs) of immunotherapy-naive patients but no responses for 3 patients who had prior immunotherapy[404]. As first-line therapy for advanced UC, nivolumab combined with the immunostimulatory therapy bempegaldesleukin achieved an ORR of 48.1% (13/27, 5/27 CRs), with 50.0% (6/12) of PD-L1-positive and 45.5% (5/11) of PD-L1-negative patients responding[405].

Pembrolizumab

Assay findings association

Tumor Mutational Burden
29 Muts/Mb

AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is available in the EU to treat patients with unresectable or metastatic melanoma; as adjuvant treatment for completely resected advanced melanoma with lymph node involvement; classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) treatment or after BV if transplant ineligible; and for patients with locally advanced or metastatic urothelial carcinoma who have received prior platinum chemotherapy or who are not eligible for cisplatin-containing chemotherapy and whose tumors are PD-L1-positive (combined positive score of at least 10). It is also available as first-line treatment for metastatic non-small cell lung cancer (NSCLC) with high PD-L1 expression (at least 50% tumor proportion score) and without EGFR or ALK genomic alterations; as first-line treatment in combination with pemetrexed and carboplatin for metastatic nonsquamous NSCLC without EGFR or ALK genomic alterations; as first-line treatment in combination with carboplatin and paclitaxel or nab-paclitaxel for metastatic squamous NSCLC; and as monotherapy for PD-L1-positive (at least 1% tumor proportion score) advanced NSCLC following prior therapy. Pembrolizumab is also available to treat patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) whose tumors express high PD-L1 and have progressed on or after platinum chemotherapy. Pembrolizumab is also available in combination with axitinib as first-line treatment for patients with advanced renal cell carcinoma (RCC).

GENE ASSOCIATION

On the basis of clinical data[1,5-11,393] , patients with urothelial carcinoma whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

The Phase 3 KEYNOTE-045 trial for patients with advanced urothelial carcinoma found second-line pembrolizumab superior to chemotherapy in terms of median OS (10.1 months vs. 7.3 months, HR=0.740, P<0.001) and ORR (21.1% vs. 11.0%) but not PFS (2.1 months vs. 3.3 months, HR=0.96)[406]; a 2-year follow-up revealed PFS rates were higher in patients who received pembrolizumab (12.4% vs 3.0%)[407]. First-line pembrolizumab therapy for patients with advanced urothelial carcinoma achieved a confirmed ORR of 29.0%, median DOR of 30.1 months, and median OS of 11.3 months in the KEYNOTE-052 trial; improved median OS (18.5 months) and ORR (47.0%) were observed in the subset of patients with a PD-L1 confirmed positive score (CPS) ≥ 10[408]. The PURE-01 Phase 2 study investigated neoadjuvant pembrolizumab followed by radical cystectomy in muscle-invasive urothelial bladder carcinoma and reported pathologic CRs in 39.5% (17/43) of patients; there was a significant association between CR rate and PBRM1 mutation (P=0.0024) and non-significant trends towards association with increased PD-L1 expression (by combined positive score, P=0.0549) and increased median TMB (P=0.0773)[409]. For patients with high-risk non-muscle invasive bladder cancer unresponsive to the Bacillus Calmette-Guerin vaccine, follow-up analysis from the Phase 2 KEYNOTE-057 trial reported a 3-month CR rate of 40.2% (41/102) for patients treated with pembrolizumab, 75.0% and 53.0% of whom experienced a CR duration of at least 6 months and 12 months, respectively[410]. In a Phase 1b/2 trial, treatment of patients with advanced urothelial cancer with combination pembrolizumab and lenvatinib elicited an ORR of 25.0% (5/20; 1 CR, 4PR) at 24 weeks[411].

Afatinib

Assay findings association

ERBB2
S310Y, amplification

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is available in the EU to treat patients with advanced non-small cell lung cancer (NSCLC) and activating EGFR mutations and for the treatment of patients with advanced squamous NSCLC after progression on platinum-based chemotherapy.

GENE ASSOCIATION

Clinical and preclinical data support sensitivity of multiple activating mutations in ERBB2, including A775_G776insYVMA and P780_Y781insGSP, to afatinib[137,412-418] . Studies have reported DCRs of 54 to 70% for patients with ERBB2-mutated NSCLC treated with afatinib, most of whom harbored exon 20 insertions[412-415] . A patient with refractory lung adenocarcinoma and both EGFR L858R and ERBB2 S310F mutations reported a complete and durable response subsequent to afatinib treatment[139].

SUPPORTING DATA

A Phase 2 study of afatinib in platinum-refractory urothelial carcinoma reported a DCR of 22%, with 2 PRs and 3 SDs in 23 patients; benefit was seen in 5 of 6 patients with ERBB2 amplification and/or ERBB3 activating mutation and in 0 of 15 patients without these alterations[419]. A Phase 2 trial of afatinib for patients with either EGFR or ERBB2 amplification and esophagogastric, biliary tract, urothelial tract, or gynecologic cancer reported an ORR of 5% (1/20, 1 CR), with SD achieved in 8 patients[420].

Avelumab

Assay findings association

Tumor Mutational Burden
29 Muts/Mb

AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is available in the EU to treat patients with metastatic Merkel cell carcinoma (MCC). It is also available in combination with axitinib as first-line treatment for patients with advanced renal cell carcinoma (RCC).

GENE ASSOCIATION

On the basis of clinical data[1,5-11,393] , patients with urothelial carcinoma whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In a Phase 1b trial evaluating single-agent avelumab, patients with metastatic urothelial carcinoma achieved a median PFS of 6.3 weeks, a median OS of 6.5 months, an ORR of 17% (27/161) which included 9 CRs and a DCR of 40%; the median PFS, median OS, and ORR were similar regardless of PD-L1 status[421].

Cemiplimab

Assay findings association

Tumor Mutational Burden
29 Muts/Mb

AREAS OF THERAPEUTIC USE

Cemiplimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is available in the EU to treat patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC) that is not amenable to surgery or radiation therapy.

GENE ASSOCIATION

On the basis of clinical data[1,5-11,393] , patients with urothelial carcinoma whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

Clinical data on the efficacy of cemiplimab for the treatment of urothelial carcinoma are limited (PubMed, May 2019). Cemiplimab has been studied primarily in advanced CSCC, where it elicited a combined ORR of 48% (41/85) in Phase 1 and 2 studies[422]. Clinical responses have also been reported in non-small cell lung cancer (40% ORR, 1 CR and 7 PRs) and basal cell carcinoma (1 PR)[423-424] .

Dacomitinib

Assay findings association

ERBB2
S310Y, amplification

AREAS OF THERAPEUTIC USE

Dacomitinib is a second-generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is available in the EU for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) with EGFR activating mutations.

GENE ASSOCIATION

On the basis of strong clinical[126,425-428] and preclinical[429-432] data, ERBB2 amplification or activating mutation may indicate sensitivity to dacomitinib.

SUPPORTING DATA

Clinical data on the efficacy of dacomitinib for the treatment of urothelial carcinoma are limited (PubMed, Sep 2019). Investigations into the efficacy of dacomitinib have primarily been in the context of non-small cell lung cancer (NSCLC). Patients with EGFR-mutant NSCLC treated with dacomitinib exhibited significant improvement in OS compared with gefitinib treatment (median OS, 34.1 vs. 26.8 months)[433-434] . A Phase 2 study of dacomitinib in patients with advanced penile squamous cell carcinoma (SCC) reported an ORR of 32% (1 CR, 8 PR), including a 100% DCR (1 CR, 1 PR, 2 SD) in four patients with EGFR amplification[435-436]. A Phase 2 study of dacomitinib in patients with recurrent or metastatic head and neck SCC reported clinical benefit (defined as PFS>4 months) in 13/31 (42%) of patients[427]. Studies of dacomitinib in esophageal[437] and cutaneous[438] SCC reported RRs of 12.5% (6/48) and 28.6% (12/42), respectively, but high DCRs of 73% and 86%, respectively. In contrast, trials of dacomitinib in heavily pretreated patients with HER2+ gastric cancer[428] and patients with EGFR-amplified glioblastoma[439] found RRs of fewer than 10% and DCRs of fewer than 50%: 11/27 (41%) DCR in HER2+ gastric cancer[428] and 15/49 (31%) in EGFR-amplified glioblastoma[439].

Durvalumab

Assay findings association

Tumor Mutational Burden
29 Muts/Mb

AREAS OF THERAPEUTIC USE

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is available in the EU to treat patients with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose tumors express PD-L1 on ≥ 1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy.

GENE ASSOCIATION

On the basis of clinical data[1,5-11,393] , patients with urothelial carcinoma whose tumors harbor a tumor mutational burden (TMB) of 10 Muts/Mb or higher may experience greater benefit from treatment with immune checkpoint inhibitors targeting PD-1 or PD-L1.

SUPPORTING DATA

In a Phase 1/2 study of single-agent durvalumab, patients with locally advanced or metastatic urothelial carcinoma experienced an ORR of 20% (21/103), including 4 CRs and 17 PRs; the ORR was higher in patients with PD-L1 positivity on ≥25% of tumor cells or tumor-infiltrating immune cells (31%, 19/61) than in PD-L1-negative patients (5%, 2/39), although CRs were reported in both groups[440-441] . In a Phase 1 study of durvalumab with tremelimumab in a cohort of patients with platinum-refractory metastatic urothelial cancer, an ORR of 21% (35/168), including 4 CRs, and a median PFS and OS of 1.9 and 9.5 months, respectively, were reported[442].

Lapatinib

Assay findings association

ERBB2
S310Y, amplification

AREAS OF THERAPEUTIC USE

Lapatinib inhibits the tyrosine kinases EGFR and ERBB2 (HER2). It is available in the EU to treat patients with HER2-positive advanced breast cancer in combination with capecitabine following prior therapy and in combination with trastuzumab for HER2-positive, hormone receptor (HR)-negative metastatic breast cancer following progression on trastuzumab combined with chemotherapy. It is also available in combination with an aromatase inhibitor to treat postmenopausal women with HER2- and HR-positive metastatic breast cancer.

GENE ASSOCIATION

Activation or amplification of ERBB2 may predict sensitivity to lapatinib. In one study, a patient with inflammatory breast cancer and ERBB2 V777L and S310F activating mutations, but without ERBB2 amplification or protein overexpression, experienced tumor shrinkage in response to combined treatment with lapatinib and trastuzumab[116].

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 PFS or OS[443]. 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[444]. A small study of six patients with metastatic transitional cell carcinoma treated with paclitaxel and lapatinib reported negative side effects; most patients discontinued therapy[445]. 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[446].

Neratinib

Assay findings association

ERBB2
S310Y, amplification

AREAS OF THERAPEUTIC USE

Neratinib is an irreversible tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and ERBB4. It is available in the EU for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer who are less than 1 year from the completion of prior adjuvant trastuzumab treatment.

GENE ASSOCIATION

On the basis of extensive clinical[125,447-450] and preclinical[451-455] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib.

SUPPORTING DATA

The Phase 2 SUMMIT study reported no responses (0/16) in patients with ERBB2-mutated bladder cancer treated with neratinib[456]. Neratinib has been primarily evaluated in the context of breast cancer and there are limited data in other tumor types. In a Phase 3 study of patients with HER2-positive, early stage breast cancer previously treated with trastuzumab, neratinib significantly improved the two-year invasive disease-free survival compared to placebo (HR=0.67, p=0.0091)[449]. In Phase 2 trials of patients with ERBB2-mutated, non-amplified, metastatic breast cancer, a clinical benefit rate of 31-42% and median PFS of 3.5-4 months were achieved with neratinib[447-448]. For patients with advanced HER2-positive breast cancer, neratinib treatment resulted in PFS of 22.3 weeks for patients with prior trastuzumab treatment and of 39.6 weeks for those with no prior trastuzumab treatment[457]. In patients with breast cancer and HER2-positive brain metastases treated with neratinib, the CNS ORR was 8% (3/40)[458]. In the context of breast cancer, neratinib in combination with various other agents has also shown significant clinical activity[447,450,459-463] . A Phase 2 study of neratinib in ERBB2-mutated NSCLC reported ORR and CBR of 0% (0/17) and 35% (6/17) for neratinib and 19% (8/43) and 51% (22/43) for neratinib plus the mTOR inhibitor temsirolimus[124,464].

Niraparib

Assay findings association

BRCA2
Q3321*

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is available in the EU for the maintenance treatment of patients with relapsed high grade serous epithelial ovarian, Fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.

GENE ASSOCIATION

On the basis of clinical evidence in ovarian and breast cancers[42-43,465] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Clinical data on the efficacy of niraparib for the treatment of urothelial carcinomas are limited (PubMed, Jul 2019). Niraparib has been primarily evaluated in the context of ovarian cancer. In a Phase 3 study of patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS, as compared to placebo, in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months) as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)[42]. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer achieved SD[43]. A Phase 1 study of the combination of niraparib and bevacizumab in patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)[466].

Olaparib

Assay findings association

BRCA2
Q3321*

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is available in the EU as maintenance therapy for patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, Fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy, or as first-line maintenance for patients with these cancers who have a germline or somatic BRCA mutation and are in CR or PR after platinum-based chemotherapy. Olaparib is also approved to treat patients with HER2-negative advanced breast cancer and germline BRCA mutations who have been previously treated with chemotherapy; patients with hormone receptor-positive breast cancer should have been previously treated with, or considered not appropriate for, endocrine therapy.

GENE ASSOCIATION

Based on extensive clinical evidence in ovarian cancer[48-52] as well as strong clinical evidence in multiple other cancer types[38-40,48,51,467] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A case study reported that a previously treated patient with muscle-invasive urothelial bladder carcinoma harboring homozygous BRCA2 loss experienced a partial metabolic response and clinical benefit from olaparib[468]. Olaparib has been studied primarily for the treatment of ovarian cancer, and numerous studies have demonstrated significant clinical activity for patients with ovarian cancer harboring BRCA1/2 mutations, with response rates often significantly higher for patients with mutations than for those without[48,51] . For patients previously treated with chemotherapy, DCRs of 40-80% have been reported with olaparib, with response rates of up to 50%[48-53,469] . Two of three studies have shown significant correlation of platinum sensitivity and response to olaparib[50,53,467] . Olaparib significantly extended PFS when used as maintenance therapy either in the first-line[54] or relapsed[46] settings in Phase 3 trials for patients with advanced ovarian, fallopian tube, or primary peritoneal cancers that were BRCA-mutated and platinum-sensitive. Combining olaparib with chemotherapy resulted in response rates up to 61%[467] and significantly longer PFS compared to chemotherapy alone[470] for patients with BRCA1/2-mutated ovarian cancer. Combining olaparib with the VEGFR inhibitor cediranib also increased the response rate and lengthened relapse-free survival for patients with platinum-sensitive ovarian cancer, compared to treatment with olaparib alone[471]. Clinical[472-473] and preclinical[474-475] studies have reported BRCA2 reversion mutations as a mechanism of olaparib resistance in ovarian cancer; similar resistance mechanisms have also been identified in prostate[476] and breast[477] cancers. Olaparib treatment has also demonstrated clinical activity for patients with breast, prostate, pancreatic cancer, and intrahepatic cholangiocarcinoma and BRCA1/2 mutations[38,40,48,51,467,478-480] , with 1 study reporting a response rate of 41% for patients with BRCA1/2-mutant breast cancer[40].

Palbociclib

Assay findings association

CDK4
amplification

AREAS OF THERAPEUTIC USE

Palbociclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is available in the EU to treat hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor or in combination with fulvestrant following 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[80,84-85,481] .

SUPPORTING DATA

A Phase 2 trial of palbociclib in metastatic platinum-refractory urothelial carcinoma that enrolled 12 patients with p16INK4a-negative and Rb-positive tumors did not observe any responses and reported a median PFS of 1.9 months and median OS of 6.3 months, thereby suggesting a lack of single-agent palbociclib activity in this setting[482]. Palbociclib combined with the antifolate pralatrexate has been compared with gemcitabine/cisplatin in a retrospective analysis of bladder cancer outcomes[483].

Pertuzumab

Assay findings association

ERBB2
S310Y, amplification

AREAS OF THERAPEUTIC USE

Pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. It is available in the EU in combination with trastuzumab and docetaxel to treat patients with HER2-positive (HER2+) metastatic or unresectable breast cancer who have not received prior chemotherapy or HER2-targeted therapy. It is also available in combination with trastuzumab and chemotherapy as neoadjuvant treatment for HER2+; locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence; and as adjuvant treatment for patients with HER2+ early breast cancer at high risk of recurrence.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification or activating mutations may predict sensitivity to pertuzumab[103-104,484-487].

SUPPORTING DATA

Of 9 patients with HER2-activated advanced bladder cancer treated with trastuzumab plus pertuzumab, 5 patients achieved clinical benefit, including 1 CR and 2 PRs[488].

Ribociclib

Assay findings association

CDK4
amplification

AREAS OF THERAPEUTIC USE

Ribociclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6). It is available in the EU to treat hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

GENE ASSOCIATION

On the basis of clinical responses in sarcomas[80,84-85], CDK4 amplification may predict sensitivity to CDK4/6 inhibitors such as ribociclib.

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[85]. 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)[83,489]; the 3 responders had alterations in the CDK4/6 pathway[83].

Rucaparib

Assay findings association

BRCA2
Q3321*

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is available in the EU to treat patients with platinum-sensitive relapsed or progressive BRCA mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 2 or more prior lines of platinum-based chemotherapy and who are unable to tolerate further platinum-based chemotherapy. Rucaparib is also available for the maintenance treatment of patients with platinum sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.

GENE ASSOCIATION

On the basis of strong clinical evidence in ovarian cancer[44-45,347] , as well as clinical data in other cancer types[45,490-491] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of urothelial carcinomas are limited (PubMed, Jul 2019). Rucaparib has primarily been evaluated in the context of ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median PFS was significantly longer in patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared to patients with low LOH (5.2 months).

Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and for 10% (7/10) with low LOH[44]. In heavily pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment[347]. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported in breast cancer patients (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved SD lasting 12 weeks or more[45]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations[490]. A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 CR, 2/19 PR (one unconfirmed) and 4/19 SD. Of the 19 patients treated in the study, 15 (79%) had a BRCA2 mutation[491]. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 8/46 patients achieved a PR and 8/46 had SD[492]; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma[493]. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of advanced solid tumors reported a disease control rate of 68.8% (53/77), including 1 CR and 9 PRs[494].

Talazoparib

Assay findings association

BRCA2
Q3321*

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is available in the EU as monotherapy to treat patients with HER2-negative locally advanced or metastatic breast cancer with germline BRCA mutations, who have been previously treated with, or are not considered candidates for, available therapies.

GENE ASSOCIATION

On the basis of strong clinical data in breast cancer[495-497] and additional clinical evidence in ovarian, pancreatic, and prostate cancer[498-500] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A Phase 2 study of talazoparib monotherapy in advanced solid tumors reported a PR in a patient with bladder cancer harboring a PALB2 mutation[501]. A patient with bladder cancer harboring a BRCA2 germline mutation achieved a PR to a combination of talazoparib and carboplatin as a part of a Phase 1 study[502].

Trastuzumab

Assay findings association

ERBB2
S310Y, amplification

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets the protein ERBB2/HER2. It is available in the EU as monotherapy and in combination with other therapies for HER2-positive (HER2+) metastatic and early breast carcinoma and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal adenocarcinoma. Trastuzumab biosimilars are also available in the EU for these indications.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification, overexpression, or activating mutations may confer sensitivity to trastuzumab[97-98,102,116,486,503-506] .

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[507]. 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[488]. 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[508-509] .

Trastuzumab emtansine

Assay findings association

ERBB2
S310Y, amplification

AREAS OF THERAPEUTIC USE

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, inhibiting HER2 signaling; it also releases the cytotoxic therapy DM1 into cells, leading to cell death. T-DM1 is available in the EU to treat patients with HER2-positive (HER2+) advanced breast carcinoma and disease progression on prior therapy.

GENE ASSOCIATION

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1.

SUPPORTING DATA

Clinical data on the efficacy of ado-trastuzumab emtansine for the treatment of urothelial carcinoma are limited (PubMed, Aug 2019). The vast majority of data on the therapeutic use of T-DM1 have been collected in the context of breast cancer, although clinical trials investigating T-DM1 are underway in several tumor types, primarily in HER2+ cancers. Phase 2 basket trials for HER2-amplified cancers have reported ORR of 8-28% with T-DM1, including responses in salivary gland, lung, endometrial, biliary tract, and ovarian cancers[510-511]. A Phase 3 trial in 602 patients with HER2+ breast cancer 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[512]. A second Phase 3 trial in 991 patients with HER2+ breast cancer 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[108,513] . 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[514-515] .

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies listed in this report may not be complete and exhaustive and the therapeutic agents are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type.

IMPORTANT Clinical trials are ordered by gene and prioritized in the following descending order: Pediatric trial qualification → Geographical proximity → Trial phase → Trial verification within last 2 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. The clinical trials listed in this report may not be complete and exhaustive or may include trials for which the patient does not meet the clinical trial enrollment criteria. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov or local registries in your region.

GENOMIC SIGNATURE

Tumor Mutational Burden

RESULT

29 Muts/Mb

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 or anti-PD-L1 immune checkpoint inhibitors.

NCT03898180

PHASE 3

Study of First-line Pembrolizumab (MK-3475) With Lenvatinib (MK-7902/E7080) in Urothelial Carcinoma Cisplatin-ineligible Participants Whose Tumors Express Programmed Cell Death-Ligand 1 and in Participants Ineligible for Platinum-containing Chemotherapy (MK-7902-011/E7080-G000-317/LEAP-011)

TARGETS
PD-1, FGFRs, KIT, PDGFRA, RET, VEGFRs

LOCATIONS: Hirosaki (Japan), Arizona, Badalona (Spain), California, Kashiwa (Japan), Daejeon (Korea, Republic of), Toon (Japan), Romford (United Kingdom), Stevenage (United Kingdom), Sapporo (Japan), Tsukuba (Japan), Illinois, Sagamihara (Japan), Canterbury (United Kingdom), Venlo (Netherlands), Maine, Missouri, Kashihara (Japan), Nevada, North Ryde (Australia), Nottingham (United Kingdom), Hamilton (Canada), Oshawa (Canada), Toronto (Canada), Aviano (Italy), Pennsylvania, Sherbrooke (Canada), Viedma (Argentina), Hidaka (Japan), Rosario (Argentina), South Carolina, Clayton (Australia), Heidelberg (Australia), Virginia, Washington, Ube (Japan), Buenos Aires (Argentina), Cordoba (Argentina), Quebec (Canada), Aarhus N (Denmark), Copenhagen (Denmark), Herlev (Denmark), Odense (Denmark), Angers (France), Bayonne (France), Bordeaux (France), La Roche sur Yon (France), Marseille (France), Montpellier (France), Nancy (France), Paris (France), Poitiers (France), Quimper (France), Saint Herblain (France), Strasbourg (France), Villejuif (France), Gottingen (Germany), Hamburg (Germany), Tuebingen (Germany), Budapest (Hungary), Kaposvar (Hungary), Kecskemet (Hungary), Miskolc (Hungary), Szolnok (Hungary), Szombathely (Hungary), Haifa (Israel), Jerusalem (Israel), Kfar Saba (Israel), Petach-Tikwa (Israel), Ramat Gan (Israel), Zerifin (Israel), Bari (Italy), Bologna (Italy), Catania (Italy), Milano (Italy), Terni (Italy), Akita (Japan), Chiba (Japan), Nagasaki (Japan), Osaka (Japan), Tokushima (Japan), Tokyo (Japan), Goyang-si (Korea, Republic of), Hwasun Gun (Korea, Republic of), Seoul (Korea, Republic of), Breda (Netherlands), Den Haag (Netherlands), Maastricht (Netherlands), Rotterdam (Netherlands), Utrecht (Netherlands), Bielsko-Biala (Poland), Otwock (Poland), Siedlce (Poland), Tarnow (Poland), Warszawa (Poland), Wroclaw (Poland), Moscow (Russian Federation), Murmansk (Russian Federation), Nizhny Novgorod (Russian Federation), Omsk (Russian Federation), Saint-Petersburg (Russian Federation), Yaroslavl (Russian Federation), A Coruna (Spain), Badajoz (Spain), Barcelona (Spain), Madrid (Spain), Manresa (Spain), Kaohsiung (Taiwan), Kaoshiung (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Adana (Turkey), Ankara (Turkey), Antalya (Turkey), Istanbul (Turkey), Konya (Turkey), Sakarya (Turkey), İzmir (Turkey), London (United Kingdom), Plymouth (United Kingdom), Preston (United Kingdom), Sheffield (United Kingdom), Stoke-on-Trent (United Kingdom)

NCT03523572

PHASE 1/2

Trastuzumab Deruxtecan (DS-8201a) With Nivolumab in Advanced Breast and Urothelial Cancer

TARGETS
PD-1, ERBB2

LOCATIONS: California, Connecticut, London (United Kingdom), Florida, Kentucky, New York, North Carolina, Ohio, Tennessee, Utah, Washington, Brussels (Belgium), Wilrijk (Belgium), Milano (Italy), Siena (Italy), Madrid (Spain), London Borough of Sutton (United Kingdom)

NCT03668119

PHASE 2

A Study of Nivolumab Combined With Ipilimumab and Nivolumab Alone in Patients With Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H)

TARGETS
PD-1, CTLA-4

LOCATIONS: Edmonton (Canada), Ciudad Autonoma Beunos Aires (Argentina), Ciudad Autonoma de Buenos Aires (Argentina), California, Colorado, London (United Kingdom), Warszawa (Poland), Santiago (Chile), Santiago de Chile (Chile), Minnesota, Darlinghurst (Australia), St Leonards (Australia), New York, North Carolina, Hamilton (Canada), Oregon, Montreal (Canada), Woolloongabba (Australia), Texas, Caba (Argentina), Cordoba (Argentina), Brussels (Belgium), Bruxelles (Belgium), Leuven (Belgium), Copenhagen (Denmark), Herlev (Denmark), Lyon Cedex 08 (France), Marseille Cedex 9 (France), Paris Cedex 5 (France), Toulouse (France), Villejuif (France), Berlin (Germany), Bonn (Germany), Dresden (Germany), Essen (Germany), Wuerzburg (Germany), Genova (Italy), Milano (Italy), Napoli (Italy), Siena (Italy), Amsterdam (Netherlands), Rotterdam (Netherlands), Gdansk (Poland), San Juan (Puerto Rico), Singapore (Singapore), Barcelona (Spain), Madrid (Spain), Pamplona (Spain), Preston (United Kingdom)

NCT03170960

PHASE 1/2

Study of Cabozantinib in Combination With Atezolizumab to Subjects With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-L1, MET, RET, ROS1, VEGFRs

LOCATIONS: Arizona, California, Villejuif (France), Colorado, Connecticut, District of Columbia, Florida, Nijmegen (Netherlands), Illinois, Kansas, Kentucky, Louisiana, Massachusetts, Michigan, Rozzano (Italy), Minnesota, Missouri, Nebraska, New Jersey, New York, Düsseldorf (Germany), Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Utah, Virginia, Gent (Belgium), Leuven (Belgium), Paris (France), Tübingen (Germany), Milano (Italy), Barcelona (Spain), Madrid (Spain), London (United Kingdom)

NCT02983045

PHASE 1/2

A Dose Escalation and Cohort Expansion Study of CD122-Biased Cytokine (NKTR-214) in Combination With Anti-PD-1 Antibody (Nivolumab) in Patients With Select Advanced or Metastatic Solid Tumors

TARGETS
PD-1, CD122, CTLA-4

LOCATIONS: Marseille (France), California, Colorado, Connecticut, Florida, Georgia, Illinois, Indiana, Kansas, Saint-Herblain (France), Massachusetts, Michigan, Missouri, New York, Toronto (Canada), Oregon, Texas, Virginia, Washington, Edegem (Belgium), Lyon (France), Marseille Cedex 20 (France), Villejuif (France), Milano (Italy), Roma (Italy), Siena (Italy), Turin (Italy), Barcelona (Spain), Madrid (Spain), Pamplona (Spain), Sevilla (Spain), London (United Kingdom), Northwood (United Kingdom), Withington (United Kingdom)

NCT02671435

PHASE 1/2

A Study of Durvalumab (MEDI4736) and Monalizumab in Solid Tumors

TARGETS
PD-L1, NKG2A

LOCATIONS: Arizona, Vancouver (Canada), California, Colorado, Florida, Illinois, Maryland, Massachusetts, Michigan, New Jersey, New York, Toronto (Canada), Pennsylvania, Rhode Island, Tennessee, Texas, Utah, Blacktown (Australia), Clayton (Australia), Waratah (Australia), Bruxelles (Belgium), Edegem (Belgium), Gent (Belgium), Leuven (Belgium), Quebec (Canada), Marseille CEDEX 5 (France), Nantes CEDEX 1 (France), Debrecen (Hungary), Milano (Italy), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Grafton (New Zealand), Barcelona (Spain), Madrid (Spain), Málaga (Spain), Pamplona (Spain), Sevilla (Spain), London (United Kingdom), Sutton (United Kingdom)

NCT02658890

PHASE 1/2

An Investigational Immuno-therapy Study of BMS-986205 Given in Combination With Nivolumab and in Combination With Both Nivolumab and Ipilimumab in Cancers That Are Advanced or Have Spread.

TARGETS
CTLA-4, PD-1, IDO1

LOCATIONS: Edmonton (Canada), Vancouver (Canada), Warszawa (Poland), Darlinghurst (Australia), North Sydney (Australia), Westmead (Australia), Toronto (Canada), Greenfield Park (Canada), Montreal (Canada), Brisbane (Australia), Clayton (Australia), Melbourne (Australia), Nedlands (Australia), Helsinki (Finland), Essen (Germany), Heilbronn (Germany), Milano (Italy), Rozzano MI (Italy), Oslo (Norway), Barcelona (Spain), Madrid (Spain), Solna (Sweden)

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

LOCATIONS: Melbourne (Australia), Randwick (Australia), Meldola (Italy), Milano (Italy), Napoli (Italy), Ravenna (Italy), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), A Coruna (Spain), Barcelona (Spain), Majadahonda (Spain), Pamplona (Spain), Tainan (Taiwan), Taipei (Taiwan)

NCT03207867

PHASE 2

A Phase 2 Study of NIR178 in Combination With PDR001 in Patients With Solid Tumors and Non-Hodgkin Lymphoma

TARGETS
PD-1, ADORA2A

LOCATIONS: California, Barcelona (Spain), Brno (Czechia), Florida, Milano (Italy), Maryland, Ohio, Texas, Koto ku (Japan), Wisconsin, Salzburg (Austria), Liege (Belgium), Marseille (France), Essen (Germany), Koeln (Germany), Napoli (Italy), Rotterdam (Netherlands), Singapore (Singapore), St. Gallen (Switzerland), Taipei (Taiwan)

NCT03260322

PHASE 1

A Multiple-dose Study of ASP8374, an Immune Checkpoint Inhibitor, as a Single Agent and in Combination With Pembrolizumab in Subjects With Advanced Solid Tumors

TARGETS
TIGIT, PD-1

LOCATIONS: Edmonton (Canada), Arizona, California, Florida, Goyang-si (Korea, Republic of), Seongnam-Si (Korea, Republic of), Iowa, Kansas, Michigan, New York, North Carolina, Ohio, Toronto (Canada), Pennsylvania, Montreal (Canada), Tennessee, Texas, Utah, Virginia, Wisconsin, Ancona (Italy), Meldola (Italy), Milano (Italy), Modena (Italy), Negrar (Italy), Pisa (Italy), Siena (Italy), Chuo-ku (Japan), Seoul (Korea, Republic of), Lisboa (Portugal), Porto (Portugal), Barcelona (Spain), Madrid (Spain), Valencia (Spain), Taichung (Taiwan), Tainan (Taiwan), Taipei City (Taiwan), Leeds (United Kingdom), London (United Kingdom), Newcastle upon Tyne (United Kingdom), Sutton Surry (United Kingdom)

GENE
ARID1A

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

ALTERATION
S2264* - subclonal, Q1212* - subclonal

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT02278250

PHASE 1

An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of VX-803/M4344 as a Single Agent and in Combination With Cytotoxic Chemotherapy in Participants With Advanced Solid Tumors

TARGETS
ATR

LOCATIONS: California, Massachusetts, Michigan, Missouri, New Jersey, Tennessee, Wisconsin, Rotterdam (Netherlands), Barcelona (Spain), London (United Kingdom), Sutton (United Kingdom)

NCT03641547

PHASE 1

M6620 Plus Standard Treatment in Oesophageal and Other Cancer

TARGETS
ATR

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

NCT02723864

PHASE 1

Veliparib (ABT-888), an Oral PARP Inhibitor, and VX-970, an ATR Inhibitor, in Combination With Cisplatin in People With Refractory Solid Tumors

TARGETS
PARP, ATR

LOCATIONS: Maryland, Massachusetts, Texas

NCT02595931

PHASE 1

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

TARGETS
ATR

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

NCT02487095

PHASE 1/2

Trial of Topotecan With VX-970, an ATR Kinase Inhibitor, in Small Cell Cancers

TARGETS
ATR

LOCATIONS: Maryland

NCT02619253

PHASE 1

Phase I/Ib Study of Pembrolizumab With Vorinostat for Patients With Advanced Renal or Urothelial Cell Carcinoma

TARGETS
PD-1, HDAC

LOCATIONS: California, Indiana, Maryland

GENE
BRCA2

ALTERATION
Q3321*

RATIONALE
BRCA2 loss or inactivating alterations may predict sensitivity to PARP inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT03565991

PHASE 2

Javelin BRCA/ATM: Avelumab Plus Talazoparib in Patients With BRCA or ATM Mutant Solid Tumors

TARGETS
PD-L1, PARP

LOCATIONS: Torette Di Ancona (Italy), California, Kashiwa (Japan), Meldola (Italy), Georgia, Louisiana, Monza (Italy), Milano (Italy), Massachusetts, Missouri, Pamplona (Spain), New Jersey, New York, Amsterdam (Netherlands), Ohio, Oklahoma, Pennsylvania, Tennessee, Texas, Chuo-ku (Japan), Rotterdam (Netherlands), Brussel (Belgium), Brussels (Belgium), Edegem (Belgium), Copenhagen (Denmark), Odense C (Denmark), Clermont Ferrand (France), La Rochelle (France), Montpellier Cedex 5 (France), Napoli (Italy), Roma (Italy), Barcelona (Spain), Madrid (Spain), Sevilla (Spain), London (United Kingdom)

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Nagoya (Japan), Medellin (Colombia), Arizona, Oradea (Romania), Berazategui (Argentina), Ciudad de Buenos Aires (Argentina), California, Chelyabinsk (Russian Federation), Kashiwa (Japan), Comuna Floresti (Romania), Bogota (Colombia), Craiova (Romania), Georgia, Seongnam-si (Korea, Republic of), Guadalajara (Mexico), Istanbul (Turkey), Kentucky, Trujillo (Peru), Pozuelo de Alarcon (Spain), Maryland, Massachusetts, Michigan, Nebraska, New Jersey, Port Macquarie (Australia), New York, Monterrey (Mexico), Oklahoma, Suita (Japan), Pennsylvania, Montreal (Canada), South Dakota, Darlinghurst (Australia), Madero (Mexico), Utah, Washington, Nedlands (Australia), Buenos Aires (Argentina), Quebec (Canada), Barranquilla (Colombia), Cali (Colombia), Monteria (Colombia), Valledupar (Colombia), Copenhagen (Denmark), Herlev (Denmark), Odense (Denmark), Bordeaux (France), Dijon (France), Nice (France), Poitiers (France), Strasbourg (France), Villejuif (France), Guatemala (Guatemala), Quetzaltenango (Guatemala), Cork (Ireland), Dublin (Ireland), Haifa (Israel), Jerusalem (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Napoli (Italy), Rozzano (Italy), Siena (Italy), Kyoto (Japan), Tokyo (Japan), Seoul (Korea, Republic of), Chihuahua (Mexico), Mexico City (Mexico), Oaxaca (Mexico), Santiago De Queṭaro (Mexico), Lima (Peru), Brasov (Romania), Bucuresti (Romania), Cluj Napoca (Romania), Arkhangelsk (Russian Federation), Kazan (Russian Federation), Moscow (Russian Federation), Ryazan (Russian Federation), Saint Petersburg (Russian Federation), Saint-Petersburg (Russian Federation), Samara (Russian Federation), St.Petersburg (Russian Federation), Barcelona (Spain), Bellinzona (Switzerland), Geneva (Switzerland), Zuerich (Switzerland), Adana (Turkey), Ankara (Turkey), Antalya (Turkey), Edirne (Turkey), Izmir (Turkey), Konya (Turkey), Manchester (United Kingdom), Newcastle-upon-Tyne (United Kingdom), Oxford (United Kingdom), Sheffield (United Kingdom)

NCT03869190

PHASE 1/2

A Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-based Treatment Combinations in Patients With Locally Advanced or Metastatic Urothelial Carcinoma After Failure With Platinum-Containing Chemotherapy

TARGETS
CD38, PARP, CD47, PD-L1, Nectin-4, IL-6R

LOCATIONS: L'Hospitalet de Llobregat (Spain), California, Kentucky, Pamplona (Spain), Caen (France), Lyon (France), Montpellier (France), Toulouse (France), Seoul (Korea, Republic of), Barcelona (Spain), Madrid (Spain), London (United Kingdom), Sutton (United Kingdom)

NCT02921919

PHASE 2

Open-Label Extension and Safety Study of Talazoparib

TARGETS
PARP

LOCATIONS: California, Florida, Indiana, Massachusetts, Michigan, Hamilton (Canada), Montreal (Canada), Sutton (United Kingdom), Texas, Marseille cedex 09 (France), Erlangen (Germany), Budapest (Hungary), Warszawa (Poland), Moscow (Russian Federation), Saint-Petersburg (Russian Federation)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT03330405

PHASE 2

Javelin Parp Medley: Avelumab Plus Talazoparib In Locally Advanced Or Metastatic Solid Tumors

TARGETS
PD-L1, PARP

LOCATIONS: Edmonton (Canada), Arkansas, California, District of Columbia, Obninsk (Russian Federation), Massachusetts, Minnesota, Sydney (Australia), New York, Ohio, Toronto (Canada), Brisbane (Australia), Texas, Murdoch (Australia), Brussels (Belgium), Bruxelles (Belgium), Charleroi (Belgium), Copenhagen (Denmark), Herlev (Denmark), Budapest (Hungary), Miskolc (Hungary), Pecs (Hungary), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Chelyabinsk (Russian Federation), Moscow (Russian Federation), Omsk (Russian Federation), Yaroslavl (Russian Federation), Leicester (United Kingdom), London (United Kingdom), Newcastle Upon Tyne (United Kingdom)

NCT02029001

PHASE 2

Adapting Treatment to the Tumor Molecular Alterations for Patients With Advanced Solid Tumors: My Own Specific Treatment

TARGETS
mTOR, FLT3, KIT, PDGFRs, RAFs, RET, VEGFRs, ERBB2, EGFR, FGFR1, FGFR2, FGFR3, PARP, PD-L1, CTLA-4

LOCATIONS: Bordeaux (France), Lyon (France), Marseille (France), Paris (France), Pierre-Bénite (France), Toulouse (France)

NCT03127215

PHASE 2

Study of Olaparib/Trabectedin vs. Doctor's Choice in Solid Tumors

TARGETS
FUS-DDIT3, PARP

LOCATIONS: Heidelberg (Germany)

NCT03967938

PHASE 2

Efficacy of Olaparib in Advanced Cancers Occurring in Patients With Germline Mutations or Somatic Tumor Mutations in Homologous Recombination Genes

TARGETS
PARP

LOCATIONS: Brussels (Belgium)

NCT03534492

PHASE 2

Durvalumab Plus Olaparib Administered Prior to Surgery of Resectable Urothelial Bladder Cancer (NEODURVARIB)

TARGETS
PARP, PD-L1

LOCATIONS: Oviedo (Spain), Badalona (Spain), Bilbao (Spain), Cáceres (Spain), Lugo (Spain), Madrid (Spain), Sevilla (Spain)

GENE
CDK4

RATIONALE
CDK4 amplification may predict sensitivity to CDK4/6 inhibitors.

ALTERATION
amplification

NCT03099174

PHASE 1

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

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

LOCATIONS: California, Connecticut, Florida, Minnesota, Nevada, North Carolina, Herlev (Denmark), København Ø (Denmark), Helsinki (Finland), Tampere (Finland), Turku (Finland), Besançon (France), Caen (France), Marseille (France), Paris (France), Plerin Sur Mer (France), Strasbourg (France), Aichi, Nagoya (Japan), Chiba, Kashiwa (Japan), Kanagawa, Isehara (Japan), Tokyo, Chuo-ku (Japan), Barcelona (Spain), L'Hospitalet de Llobregat (Spain), Madrid (Spain), Malaga (Spain), Pozuelo de Alarcón (Spain)

NCT03339843

PHASE 2

Multiorgan Metabolic Imaging Response Assessment of Abemaciclib

TARGETS
CDK4, CDK6

LOCATIONS: Bruxelles (Belgium), Kortrijk (Belgium), Liège (Belgium), Mons (Belgium), Namur (Belgium)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Alaska, Arkansas, California, Colorado, Georgia, Idaho, Illinois, Iowa, Kentucky, Louisiana, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Utah, Vermont, Virginia, Washington, Wisconsin, Wyoming

NCT03310879

PHASE 2

Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT02693535

PHASE 2

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

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, RAF1, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Alabama, Arizona, California, Florida, Georgia, Hawaii, Illinois, Indiana, Massachusetts, Michigan, Nebraska, North Carolina, North Dakota, Oklahoma, Oregon, Pennsylvania, South Dakota, Texas, Utah, Virginia, Washington

NCT03965845

PHASE 1/2

A Study of Telaglenastat (CB-839) in Combination With Palbociclib in Patients With Solid Tumors

TARGETS
CDK4, CDK6, GLS

LOCATIONS: Georgia, Texas

NCT01037790

PHASE 2

PHASE II TRIAL OF THE CYCLIN-DEPEDENT KINASE INHIBITOR PD 0332991 IN PATIENTS WITH CANCER

TARGETS
CDK4, CDK6

LOCATIONS: Pennsylvania

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB2, ERBB4, PARP, mTOR, MET, RET, ROS1, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT03065062

PHASE 1

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

LOCATIONS: Massachusetts

GENE
ERBB2

ALTERATION
S310Y, amplification

RATIONALE
ERBB2 amplification or activating mutation may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of HSP90 inhibitors.

NCT03523572

PHASE 1/2

Trastuzumab Deruxtecan (DS-8201a) With Nivolumab in Advanced Breast and Urothelial Cancer

TARGETS
PD-1, ERBB2

LOCATIONS: California, Connecticut, London (United Kingdom), Florida, Kentucky, New York, North Carolina, Ohio, Tennessee, Utah, Washington, Brussels (Belgium), Wilrijk (Belgium), Milano (Italy), Siena (Italy), Madrid (Spain), London Borough of Sutton (United Kingdom)

NCT01953926

PHASE 2

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

TARGETS
EGFR, ERBB2, ERBB4, ER

LOCATIONS: Alabama, Arizona, Vancouver (Canada), California, Wilton (Ireland), Delaware, Florida, Georgia, Saint-Cloud (France), Illinois, Dublin (Ireland), Louisiana, Massachusetts, Minnesota, Missouri, New York, Ohio, Villejuif (France), Pennsylvania, Seodaemun-Gu (Korea, Republic of), South Carolina, Tennessee, Texas, East Melbourne (Australia), Wisconsin, Leuven (Belgium), Kopenhagen (Denmark), Lyon (France), Jerusalem (Israel), Petah Tikva (Israel), Rehovot (Israel), Tel Aviv (Israel), Cremona (Italy), Barcelona (Spain), Madrid (Spain), Valencia (Spain), London (United Kingdom)

NCT03810872

PHASE 2

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

TARGETS
EGFR, ERBB2, ERBB4

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

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT02693535

PHASE 2

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

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, PDGFRs, RET, mTOR, EGFR, ERBB3, ERBB2, BRAF, MEK, SMO, DDR2, RAF1, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Alabama, Arizona, California, Florida, Georgia, Hawaii, Illinois, Indiana, Massachusetts, Michigan, Nebraska, North Carolina, North Dakota, Oklahoma, Oregon, Pennsylvania, South Dakota, Texas, Utah, Virginia, Washington

CLINICAL TRIALS

NCT02091141

PHASE 2

A Study Evaluating Herceptin/Perjeta, Tarceva, Zelboraf/Cotellic, and Erivedge Treatment Targeted Against Certain Mutations in Cancer Patients

TARGETS
ERBB3, ERBB2, EGFR, BRAF, MEK, SMO, ALK, RET, PD-L1

LOCATIONS: Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Maryland, Minnesota, Missouri, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, South Dakota, Tennessee, Texas, Washington, Wisconsin

NCT02892123

PHASE 1

Trial of ZW25 in Patients With Advanced HER2-expressing Cancers

TARGETS
ERBB2

LOCATIONS: Alabama, California, Colorado, Seongnam-si (Korea, Republic of), Illinois, Ottawa (Canada), Toronto (Canada), Montréal (Canada), Tennessee, Texas, Washington, Seoul (Korea, Republic of)

NCT03013218

PHASE 1

A Study of ALX148 in Patients With Advanced Solid Tumors and Lymphoma

TARGETS
PD-1, CD47, ERBB2, CD20

LOCATIONS: Colorado, Connecticut, Massachusetts, Michigan, Washington, Seongnam (Korea, Republic of), Seoul (Korea, Republic of)

NCT02795156

PHASE 2

Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations

TARGETS
BRAF, KIT, PDGFRs, RAF1, RET, VEGFRs, EGFR, ERBB2, ERBB4, MET, ROS1

LOCATIONS: Colorado, Florida, Missouri, Tennessee, Wisconsin

NCT03809013

PHASE 2

A Open-label, Single-arm, Multicenter, Phase II Study of RC48-ADC to Evaluate the Efficacy and Safety of Subjects With HER2 Overexpressing Locally Advanced or Metastatic Urothelial Cancer

TARGETS
ERBB2

LOCATIONS: Hefei (China), Beijing (China), Guangzhou (China), Changsha (China), Jinan (China), Chendu (China)

GENE
FGFR1

ALTERATION
amplification

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR1.

NCT03390504

PHASE 3

A Study of Erdafitinib Compared With Vinflunine or Docetaxel or Pembrolizumab in Participants With Advanced Urothelial Cancer and Selected Fibroblast Growth Factor Receptor (FGFR) Gene Aberrations

TARGETS
PD-1, FGFRs

LOCATIONS: Alaska, Kelowna (Canada), Vancouver (Canada), California, District of Columbia, Florida, Illinois, Kentucky, Winnipeg (Canada), Nevada, New Hampshire, New York, North Carolina, Thunder Bay (Canada), Toronto (Canada), Regina (Canada), Texas, Virginia, Washington, Camperdown (Australia), Frankston (Australia), Kogarah (Australia), Melbourne (Australia), Murdoch (Australia), Graz (Austria), Linz (Austria), Salzburg (Austria), Vienna (Austria), Aalst (Belgium), Antwerpen (Belgium), Brussel (Belgium), Charleroi (Belgium), Gent (Belgium), Liège (Belgium), Wilrijk (Belgium), Yvoir (Belgium), Barretos (Brazil), Belo Horizonte (Brazil), Curitiba (Brazil), Itajai (Brazil), Porto Alegre (Brazil), Rio de Janeiro (Brazil), Sao Paulo (Brazil), São José do Rio Preto (Brazil), São Paulo (Brazil), BeiJing (China), Beijing (China), Chengdu (China), Chongqing (China), Guangzhou (China), Hangzhou (China), Nanchang (China), Nanjing (China), ShangHai (China), Shanghai (China), Shenyang (China), Xi'an (China), Angers (France), Besancon Cedex (France), Bordeaux (France), Clermont Ferrand (France), Dijon (France), Lille (France), Marseille (France), Montpellier (France), Nice (France), Nîmes (France), Paris (France), Pierre-Bénite (France), Poitiers Cedex (France), Quimper (France), Rennes Cedex (France), Saint-Priest-en-Jarez (France), Strasbourg CEDEX (France), Toulouse (France), Valenciennes (France), Villejuif (France), Berlin (Germany), Braunschweig (Germany), Dresden (Germany), Duesseldorf (Germany), Freiburg (Germany), Göttingen (Germany), Hamburg (Germany), Hannover (Germany), Lubeck (Germany), Muenster (Germany), Nuertingen (Germany), Rostock (Germany), Velbert (Germany), Weiden (Germany), Achaïa (Greece), Athens (Greece), Athina (Greece), Larisa (Greece), Thessaloniki (Greece), Budapest (Hungary), Nyíregyháza (Hungary), Pécs (Hungary), Haifa (Israel), Jerusalem (Israel), Kfar Saba (Israel), Petach Tikvah (Israel), Tel Hashomer (Israel), Zerifin (Israel), Arezzo (Italy), Aviano (Italy), Bergamo (Italy), Brescia (Italy), Cremona (Italy), Macerata (Italy), Meldola (Italy), Milano (Italy), Napoli (Italy), Novara (Italy), Orbassano (Italy), Padova (Italy), Parma (Italy), Pavia (Italy), Poggibonsi (SI) (Italy), Roma (Italy), Torino (Italy), Torrette Di Ancona (Italy), Chiba (Japan), Hirosaki (Japan), Kashiwa (Japan), Kita-Gun (Japan), Kobe (Japan), Koshigaya (Japan), Matsuyama (Japan), Miyazaki (Japan), Nagano (Japan), Nagoya-shi (Japan), Osaka (Japan), Osaka-Sayama (Japan), Osaka-shi (Japan), Sagamihara (Japan), Sakura (Japan), Sapporo (Japan), Shinjuku-ku (Japan), Tsukuba (Japan), Ube (Japan), Yokohama (Japan), Busan (Korea, Republic of), Daejeon (Korea, Republic of), Goyangsi (Korea, Republic of), Incheon (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Wonju-si (Korea, Republic of), Aguascalientes (Mexico), Chihuahua (Mexico), Nieuwegein (Netherlands), Lisboa (Portugal), Lisbon (Portugal), Barnaul (Russian Federation), Chelyabinsk (Russian Federation), Ivanovo (Russian Federation), Moscow (Russian Federation), Nizhni Novgorod (Russian Federation), Omsk (Russian Federation), Pyatigorsk (Russian Federation), Saint Petersburg (Russian Federation), Saint-Petersburg (Russian Federation), Saransk (Russian Federation), Saratov (Russian Federation), Sochi (Russian Federation), St. Petersburg (Russian Federation), Tyumen (Russian Federation), Ufa (Russian Federation), Vologda (Russian Federation), Badajoz (Spain), Badalona (Spain), Barcelona (Spain), Córdoba (Spain), Granada (Spain), Jaén (Spain), Lugo (Spain), Madrid (Spain), Majadahonda (Spain), Manresa (Spain), Pamplona (Spain), Sevilla (Spain), Valencia (Spain), Zaragoza (Spain), Kaohsiung (Taiwan), Liou Ying Township (Taiwan), Niao-Sung Hsiang (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Taipei City (Taiwan), Taoyuan (Taiwan), Adana (Turkey), Ankara (Turkey), Istanbul (Turkey), Izmir (Turkey), Kocaeli (Turkey), Malatya (Turkey), Dnipro (Ukraine), Dnipropetrovsk (Ukraine), Ivano-Frankivsk (Ukraine), Kharkov (Ukraine), Kyiv (Ukraine), Uzhgorod (Ukraine), Vinnytsia (Ukraine), Bristol (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Plymouth (United Kingdom), Southampton (United Kingdom), Sutton (United Kingdom)

NCT03898180

PHASE 3

Study of First-line Pembrolizumab (MK-3475) With Lenvatinib (MK-7902/E7080) in Urothelial Carcinoma Cisplatin-ineligible Participants Whose Tumors Express Programmed Cell Death-Ligand 1 and in Participants Ineligible for Platinum-containing Chemotherapy (MK-7902-011/E7080-G000-317/LEAP-011)

TARGETS
PD-1, FGFRs, KIT, PDGFRA, RET, VEGFRs

LOCATIONS: Hirosaki (Japan), Arizona, Badalona (Spain), California, Kashiwa (Japan), Daejeon (Korea, Republic of), Toon (Japan), Romford (United Kingdom), Stevenage (United Kingdom), Sapporo (Japan), Tsukuba (Japan), Illinois, Sagamihara (Japan), Canterbury (United Kingdom), Venlo (Netherlands), Maine, Missouri, Kashihara (Japan), Nevada, North Ryde (Australia), Nottingham (United Kingdom), Hamilton (Canada), Oshawa (Canada), Toronto (Canada), Aviano (Italy), Pennsylvania, Sherbrooke (Canada), Viedma (Argentina), Hidaka (Japan), Rosario (Argentina), South Carolina, Clayton (Australia), Heidelberg (Australia), Virginia, Washington, Ube (Japan), Buenos Aires (Argentina), Cordoba (Argentina), Quebec (Canada), Aarhus N (Denmark), Copenhagen (Denmark), Herlev (Denmark), Odense (Denmark), Angers (France), Bayonne (France), Bordeaux (France), La Roche sur Yon (France), Marseille (France), Montpellier (France), Nancy (France), Paris (France), Poitiers (France), Quimper (France), Saint Herblain (France), Strasbourg (France), Villejuif (France), Gottingen (Germany), Hamburg (Germany), Tuebingen (Germany), Budapest (Hungary), Kaposvar (Hungary), Kecskemet (Hungary), Miskolc (Hungary), Szolnok (Hungary), Szombathely (Hungary), Haifa (Israel), Jerusalem (Israel), Kfar Saba (Israel), Petach-Tikwa (Israel), Ramat Gan (Israel), Zerifin (Israel), Bari (Italy), Bologna (Italy), Catania (Italy), Milano (Italy), Terni (Italy), Akita (Japan), Chiba (Japan), Nagasaki (Japan), Osaka (Japan), Tokushima (Japan), Tokyo (Japan), Goyang-si (Korea, Republic of), Hwasun Gun (Korea, Republic of), Seoul (Korea, Republic of), Breda (Netherlands), Den Haag (Netherlands), Maastricht (Netherlands), Rotterdam (Netherlands), Utrecht (Netherlands), Bielsko-Biala (Poland), Otwock (Poland), Siedlce (Poland), Tarnow (Poland), Warszawa (Poland), Wroclaw (Poland), Moscow (Russian Federation), Murmansk (Russian Federation), Nizhny Novgorod (Russian Federation), Omsk (Russian Federation), Saint-Petersburg (Russian Federation), Yaroslavl (Russian Federation), A Coruna (Spain), Badajoz (Spain), Barcelona (Spain), Madrid (Spain), Manresa (Spain), Kaohsiung (Taiwan), Kaoshiung (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Adana (Turkey), Ankara (Turkey), Antalya (Turkey), Istanbul (Turkey), Konya (Turkey), Sakarya (Turkey), İzmir (Turkey), London (United Kingdom), Plymouth (United Kingdom), Preston (United Kingdom), Sheffield (United Kingdom), Stoke-on-Trent (United Kingdom)

NCT03473756

PHASE 1/2

Phase 1b/2 Study of Rogaratinib (BAY1163877) in Combination With Atezolizumab in Urothelial Carcinoma

TARGETS
FGFR1, FGFR2, FGFR3, FGFR4, PD-L1

LOCATIONS: Arizona, Kashiwa (Japan), Matsuyama (Japan), Modena (Italy), Tsukuba (Japan), Illinois, Milano (Italy), Michigan, New York, Essen (Germany), Köln (Germany), Linz (Austria), Mainz (Germany), Koto-ku (Japan), Padova (Italy), Verona (Italy), Salzburg (Austria), Wien (Austria), Bordeaux Cedex (France), Lille Cedex (France), Nantes (France), Seoul (Korea, Republic of), Barcelona (Spain), Madrid (Spain), Valencia (Spain)

NCT03473743

PHASE 1/2

A Study to Evaluate Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Erdafitinib Plus JNJ-63723283, an Anti-PD-1 Monoclonal Antibody, in Participants With Metastatic or Surgically Unresectable Urothelial Cancer With Selected FGFR Gene Alterations

TARGETS
PD-1, FGFRs

LOCATIONS: Colorado, Kentucky, Maryland, New Jersey, New York, North Carolina, Ohio, Texas, Virginia, Gomel (Belarus), Grodno (Belarus), Lesnoy (Belarus), Mogilev (Belarus), Bruxelles (Belgium), Haine-Saint-Paul, La Louviere (Belgium), Kortrijk (Belgium), Liege (Belgium), Sint-Niklaas (Belgium), Wilrijk (Belgium), Angers Cedex 02 (France), Bordeaux (France), Caen (France), La Rochelle Cedex 1 (France), Marseille (France), Paris (France), Tours (France), Vandoeuvre lès Nancy (France), Villejuif (France), Milano (Italy), Gwangju (Korea, Republic of), Seoul (Korea, Republic of), Yangsan (Korea, Republic of), Barnaul (Russian Federation), Ivanovo (Russian Federation), Kislino Village, Ryshkovsky Ru (Russian Federation), Kuzmolovsky (Russian Federation), Moscow (Russian Federation), Nizhny Novgorod (Russian Federation), Omsk (Russian Federation), Pyatigorsk (Russian Federation), Saint Petersburg (Russian Federation), Saint-Petersburg (Russian Federation), Tambov (Russian Federation), Tyumen (Russian Federation), Barcelona (Spain), Madrid (Spain), Málaga (Spain), Ourense (Spain), Pontevedra (Spain), Pozuelo de Alarcon (Spain), Sabadell (Spain), Santander (Spain), Santiago de Compostela (Spain), Sevilla (Spain), Valencia (Spain), Lancaster (United Kingdom), Nottingham (United Kingdom)

NCT02872714

PHASE 2

A Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Urothelial Carcinoma

TARGETS
FGFR1, FGFR2, FGFR3

LOCATIONS: Arizona, California, Colorado, Besancon Cedex (France), Florida, Georgia, Bordeaux cedex (France), London (United Kingdom), Toulouse cedex 09 (France), Saint Herblain (France), Angers Cedex 9 (France), Maryland, Massachusetts, Minnesota, Pamplona (Spain), Nebraska, Nevada, New York, North Carolina, Nottingham (United Kingdom), Ohio, Oregon, Paris Cedex 10 (France), Pennsylvania, Lyon Cedex 8 (France), Strasbourg (France), South Carolina, Glasgow (United Kingdom), Tennessee, Texas, Utah, Virginia, Washington, Birmingham (United Kingdom), Wisconsin, Edegem (Belgium), Gent (Belgium), Kortrijk (Belgium), Roeselare (Belgium), Copenhagen (Denmark), Paris (France), Villejuif (France), Berlin (Germany), Dresden (Germany), Hamburg (Germany), Koeln (Germany), Mainz (Germany), Muenster (Germany), Nürtingen (Germany), Tuebingen (Germany), Be'er Sheva (Israel), Be'er Ya'aqov (Israel), Kfar-Saba (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Bologna (Italy), Candiolo (Italy), Milano (Italy), Napoli (Italy), Rimini (Italy), Rome (Italy), San Giovanni Rotondo (Italy), Siena (Italy), Fukuoka-shi (Japan), Hidaka-shi (Japan), Hirosaki-shi (Japan), Itabashi-ku (Japan), Kashihara-shi (Japan), Kitaadachi-gun (Japan), Osaka-shi (Japan), Suita-shi (Japan), Tochigi-ken (Japan), Amsterdam (Netherlands), Den Haag (Netherlands), Terneuzen (Netherlands), Venlo (Netherlands), Barcelona (Spain), Girona (Spain), Madrid (Spain)

NCT03517956

PHASE 1

Phase 1 Study of the Combination of Rogaratinib With Copanlisib in Patients With Fibroblast Growth Factor Receptor (FGFR)-Positive, Locally Advanced or Metastatic Solid Tumors

TARGETS
FGFR1, FGFR2, FGFR3, FGFR4, PI3K

LOCATIONS: California, Frankfurt (Germany), Illinois, Maryland, Massachusetts, Michigan, New York, Köln (Germany), Texas, Bruxelles - Brussel (Belgium), Edegem (Belgium), Liege (Belgium), Würzburg (Germany), Seoul (Korea, Republic of), Singapore (Singapore), Barcelona (Spain), Valencia (Spain)

NCT01948297

PHASE 1

Debio 1347-101 Phase I Trial in Advanced Solid Tumours With Fibroblast Growth Factor Receptor (FGFR) Alterations

TARGETS
FGFR1, FGFR2, FGFR3

LOCATIONS: Massachusetts, New York, Texas, Seoul (Korea, Republic of), Singapore (Singapore), Barcelona (Spain), Taipei (Taiwan)

CLINICAL TRIALS

NCT02393248

PHASE 1/2

Open-Label, Dose-Escalation Study of INCB054828 in Subjects With Advanced Malignancies

TARGETS
PD-1, FGFR1, FGFR2, FGFR3

LOCATIONS: Alabama, Florida, Michigan, Missouri, New Jersey, North Carolina, Ohio, South Carolina, Texas, Copenhagen (Denmark)

NCT02699606

PHASE 2

A Study to Evaluate the Clinical Efficacy of JNJ-42756493 (Erdafitinib), A Pan-Fibroblast Growth Factor Receptor (FGFR) Tyrosine Kinase Inhibitor, In Asian Participants With Advanced Non-Small-Cell Lung Cancer, Urothelial Cancer, Esophageal Cancer Or Cholangiocarcinoma

TARGETS
FGFRs

LOCATIONS: Beijing (China), Harbin (China), Nanjing (China), Seoul (Korea, Republic of), Kaohsiung (Taiwan), Tainan (Taiwan)

NCT04045613

PHASE 1/2

Derazantinib and Atezolizumab in Patients With Urothelial Cancer

TARGETS
FGFRs, PD-L1

LOCATIONS: Texas, Washington

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.

AKT1
A58V

ALK
E1568K and K1524N

ARID1A
S265del

ASXL1
L424V

AXIN1
rearrangement

BRCA2
D1769H, E1550Q and E1581Q

BRIP1
D153N

CDK12
G710A

CIC
E258K

CUL4A
A37S

EP300
I1226R

KIT
G93S

MED12
E1494K

MET
R384K

MTOR
E73Q

NSD3 (WHSC1L1)
G1276A

PALB2
D1052V

PBRM1
G176E

RAD51D
L97F

SMARCA4
I1597M and R1591W

TBX3
S235G

TET2
E772K

Electronically signed by Douglas Lin, M.D. | Julia Elvin, M.D., Ph.D., Laboratory Director | Foundation Medicine, Inc. | Roche Customer Care: +49 7624 14 2098 or europe.foundationmedicine@roche.com

Sample Preparation: FMI Germany GmbH, Nonnenwald 2, 82377 Penzberg, Germany
Sample Analysis: FMI Germany GmbH, Nonnenwald 2, 82377 Penzberg, Germany

FoundationOne CDx is designed to include 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 36 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*	*NSD3 (WHSC1L1)*	*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*	*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 an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER GENOMIC SIGNATURES

Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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

ABOUT FOUNDATIONONE CDX

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

Please refer to technical information for performance specification details: www.rochefoundationmedicine.com/f1cdxtech.

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), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, 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 therapies in accordance with 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.

TEST PRINCIPLES

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 an Illumina® HiSeq 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 loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: The association of a therapy with a genomic alteration or signature does not necessarily indicate pharmacologic effectiveness (or lack thereof); no association of a therapy with a genomic alteration or signature does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness).

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

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.

Ranking of Alterations and Therapies

Genomic Signatures and Gene Alterations

Therapies are ranked based on the following criteria: Therapies approved in the EU in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies approved in the EU in another tumor type (ranked alphabetically within each NCCN category).

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NCCN Categorization

Genomic signatures and gene alterations detected may be associated with certain National Comprehensive Cancer Network (NCCN) Compendium drugs or biologics (www.nccn.org). The NCCN categories indicated reflect the highest possible category for a given therapy in association with each genomic signature or gene alteration. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories please refer to the NCCN Compendium.

Limitations

1. 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. 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. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is defined based on counting the total number of all synonymous and nonsynonymous 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.
3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH.

Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

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The median exon coverage for this sample is 1,042x

1. Samstein RM, Lee CH, Shoushtari AN, et al. ePub 02 2019 (2019) PMID: 30643254
2. Goodman AM, Kato S, Bazhenova L, et al. ePub 11 2017 (2017) PMID: 28835386
3. Goodman AM, Sokol ES, Frampton GM, et al. ePub Oct 2019 (2019) PMID: 31405947
4. Cristescu R, Mogg R, Ayers M, et al. ePub 10 2018 (2018) PMID: 30309915
5. Rosenberg JE, Hoffman-Censits J, Powles T, et al. ePub May 2016 (2016) PMID: 26952546
6. Balar AV, Galsky MD, Rosenberg JE, et al. ePub 01 2017 (2017) PMID: 27939400
7. Powles T, Durán I, van der Heijden MS, et al. ePub Feb 2018 (2018) PMID: 29268948
8. Mariathasan S, Turley SJ, Nickles D, et al. ePub 02 2018 (2018) PMID: 29443960
9. Miao D, Margolis CA, Vokes NI, et al. ePub Sep 2018 (2018) PMID: 30150660
10. Galsky et al., 2017; ESMO Abstract 848PD
11. Necchi et al., 2018; AACR Abstract CT003
12. null ePub Mar 2014 (2014) PMID: 24476821
13. Cazier JB, Rao SR, McLean CM, et al. ePub Apr 2014 (2014) PMID: 24777035
14. Rosenberg et al., 2016; ASCO Abstract 104
15. Pfeifer GP, You YH, Besaratinia A 571 (1-2):19-31 (2005) PMID: 15748635
16. Hill VK, Gartner JJ, Samuels Y, et al. ePub 2013 (2013) PMID: 23875803
17. Pfeifer GP, Denissenko MF, Olivier M, et al. 21 (48):7435-51 (2002) PMID: 12379884
18. Rizvi NA, Hellmann MD, Snyder A, et al. ePub Apr 2015 (2015) PMID: 25765070
19. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. ePub May 2013 (2013) PMID: 23636398
20. Briggs S, Tomlinson I ePub Jun 2013 (2013) PMID: 23447401
21. Heitzer E, Tomlinson I ePub Feb 2014 (2014) PMID: 24583393
22. null ePub Jul 2012 (2012) PMID: 22810696
23. Roberts SA, Gordenin DA ePub 12 2014 (2014) PMID: 25568919
24. Gatalica Z, Snyder C, Maney T, et al. ePub Dec 2014 (2014) PMID: 25392179
25. Kroemer G, Galluzzi L, Zitvogel L, et al. 4 (7):e1058597 (2015) PMID: 26140250
26. Lal N, Beggs AD, Willcox BE, et al. 4 (3):e976052 (2015) PMID: 25949894
27. Le DT, Uram JN, Wang H, et al. ePub Jun 2015 (2015) PMID: 26028255
28. Ayers et al., 2016; ASCO-SITC Abstract P60
29. Mylona E, Zarogiannos A, Nomikos A, et al. 116 (1):59-65 (2008) PMID: 18254781
30. Amira N, Rivet J, Soliman H, et al. 170 (4 Pt 1):1151-4 (2003) PMID: 14501713
31. Bai S, Nunez AL, Wei S, et al. ePub Jun 2013 (2013) PMID: 23690119
32. Kocarnik JM, Shiovitz S, Phipps AI 3 (4):269-76 (2015) PMID: 26337942
33. You JF, Buhard O, Ligtenberg MJ, et al. ePub Dec 2010 (2010) PMID: 21081928
34. Bairwa NK, Saha A, Gochhait S, et al. ePub 2014 (2014) PMID: 24623249
35. Boland CR, Thibodeau SN, Hamilton SR, et al. 58 (22):5248-57 (1998) PMID: 9823339
36. Pawlik TM, Raut CP, Rodriguez-Bigas MA 20 (4-5):199-206 (2004) PMID: 15528785
37. Boland CR, Goel A ePub Jun 2010 (2010) PMID: 20420947
38. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. ePub Jan 2015 (2015) PMID: 25366685
39. Mateo J, Carreira S, Sandhu S, et al. ePub Oct 2015 (2015) PMID: 26510020
40. Tutt A, Robson M, Garber JE, et al. ePub Jul 2010 (2010) PMID: 20609467
41. Robson M, Im SA, Senkus E, et al. ePub 08 2017 (2017) PMID: 28578601
42. Mirza MR, Monk BJ, Herrstedt J, et al. ePub 12 2016 (2016) PMID: 27717299
43. Sandhu SK, Schelman WR, Wilding G, et al. ePub Aug 2013 (2013) PMID: 23810788
44. Swisher EM, Lin KK, Oza AM, et al. ePub Jan 2017 (2017) PMID: 27908594
45. Drew Y, Ledermann J, Hall G, et al. ePub Mar 2016 (2016) PMID: 27002934
46. Pujade-Lauraine E, Ledermann JA, Selle F, et al. ePub Sep 2017 (2017) PMID: 28754483
47. Ledermann JA, Harter P, Gourley C, et al. ePub Nov 2016 (2016) PMID: 27617661
48. Fong PC, Boss DS, Yap TA, et al. ePub Jul 2009 (2009) PMID: 19553641
49. Audeh MW, Carmichael J, Penson RT, et al. ePub Jul 2010 (2010) PMID: 20609468
50. Fong PC, Yap TA, Boss DS, et al. ePub May 2010 (2010) PMID: 20406929
51. Gelmon KA, Tischkowitz M, Mackay H, et al. ePub Sep 2011 (2011) PMID: 21862407
52. Kaye SB, Lubinski J, Matulonis U, et al. ePub Feb 2012 (2012) PMID: 22203755
53. Domchek SM, Aghajanian C, Shapira-Frommer R, et al. ePub Feb 2016 (2016) PMID: 26723501
54. Moore K, Colombo N, Scambia G, et al. ePub Oct 2018 (2018) PMID: 30345884
55. Isakoff SJ, Mayer EL, He L, et al. ePub Jun 2015 (2015) PMID: 25847936
56. Dann RB, DeLoia JA, Timms KM, et al. ePub Jun 2012 (2012) PMID: 22406760
57. Evers B, Drost R, Schut E, et al. 14 (12):3916-25 (2008) PMID: 18559613
58. Guo G, Sun X, Chen C, et al. ePub Dec 2013 (2013) PMID: 24121792
59. Iyer G, Al-Ahmadie H, Schultz N, et al. ePub Sep 2013 (2013) PMID: 23897969
60. Kim PH, Cha EK, Sfakianos JP, et al. ePub Feb 2015 (2015) PMID: 25092538
61. Mullane SA, Werner L, Guancial EA, et al. ePub 08 2016 (2016) PMID: 26778300
62. Yang H, Jeffrey PD, Miller J, et al. ePub Sep 2002 (2002) PMID: 12228710
63. null ePub Jul 2011 (2011) PMID: 21731065
64. Miki Y, Swensen J, Shattuck-Eidens D, et al. 266 (5182):66-71 (1994) PMID: 7545954
65. Wooster R, Bignell G, Lancaster J, et al. 378 (6559):789-92 (null) PMID: 8524414
66. Ford D, Easton DF, Bishop DT, et al. 343 (8899):692-5 (1994) PMID: 7907678
67. null ePub Jun 2005 (2005) PMID: 16369438
68. Struewing JP, Hartge P, Wacholder S, et al. 336 (20):1401-8 (1997) PMID: 9145676
69. Bougie O, Weberpals JI ePub 2011 (2011) PMID: 22312502
70. null 91 (15):1310-6 (1999) PMID: 10433620
71. Hahn SA, Greenhalf B, Ellis I, et al. 95 (3):214-21 (2003) PMID: 12569143
72. Monnerat C, Chompret A, Kannengiesser C, et al. 6 (4):453-61 (2007) PMID: 17624602
73. Casula M, Muggiano A, Cossu A, et al. ePub Oct 2009 (2009) PMID: 19799798
74. Moran A, O'Hara C, Khan S, et al. ePub Jun 2012 (2012) PMID: 22187320
75. Whittemore AS, Gong G, Itnyre J 60 (3):496-504 (1997) PMID: 9042908
76. Claus EB, Schildkraut JM, Thompson WD, et al. 77 (11):2318-24 (1996) PMID: 8635102
77. Oddoux C, Struewing JP, Clayton CM, et al. 14 (2):188-90 (1996) PMID: 8841192
78. King MC, Marks JH, Mandell JB, et al. ePub Oct 2003 (2003) PMID: 14576434
79. Hall MJ, Reid JE, Burbidge LA, et al. 115 (10):2222-33 (2009) PMID: 19241424
80. Dickson MA, Tap WD, Keohan ML, et al. ePub Jun 2013 (2013) PMID: 23569312
81. Flaherty KT, Lorusso PM, Demichele A, et al. 18 (2):568-76 (2012) PMID: 22090362
82. Patnaik A, Rosen LS, Tolaney SM, et al. ePub 07 2016 (2016) PMID: 27217383
83. Infante JR, Cassier PA, Gerecitano JF, et al. 22 (23):5696-5705 (2016) PMID: 27542767
84. Dickson MA, Schwartz GK, Keohan ML, et al. ePub Jul 2016 (2016) PMID: 27124835
85. Peguero et al., 2016; ASCO Abstract 2528
86. Simon R, Struckmann K, Schraml P, et al. 21 (16):2476-83 (2002) PMID: 11971182
87. Choi YJ, Anders L ePub Apr 2014 (2014) PMID: 23644662
88. null 81 (3):323-30 (1995) PMID: 7736585
89. Musgrove EA, Caldon CE, Barraclough J, et al. ePub Jul 2011 (2011) PMID: 21734724
90. Wikman H, Nymark P, Väyrynen A, et al. 42 (2):193-9 (2005) PMID: 15543620
91. Rao SK, Edwards J, Joshi AD, et al. ePub Jan 2010 (2010) PMID: 19609742
92. Chung L, Lau SK, Jiang Z, et al. ePub Nov 2009 (2009) PMID: 19574885
93. Ragazzini P, Gamberi G, Pazzaglia L, et al. 19 (2):401-11 (2004) PMID: 15024701
94. Dujardin F, Binh MB, Bouvier C, et al. ePub May 2011 (2011) PMID: 21336260
95. Zhang K, Chu K, Wu X, et al. ePub Feb 2013 (2013) PMID: 23393200
96. Horvai AE, DeVries S, Roy R, et al. ePub Nov 2009 (2009) PMID: 19734852
97. Slamon DJ, Leyland-Jones B, Shak S, et al. 344 (11):783-92 (2001) PMID: 11248153
98. Bang YJ, Van Cutsem E, Feyereislova A, et al. ePub Aug 2010 (2010) PMID: 20728210
99. Chumsri S, Weidler J, Ali S, et al. ePub Sep 2015 (2015) PMID: 26358791
100. Cappuzzo F, Bemis L, Varella-Garcia M ePub Jun 2006 (2006) PMID: 16775247
101. Falchook GS, Janku F, Tsao AS, et al. ePub Feb 2013 (2013) PMID: 23328556
102. Mazières J, Peters S, Lepage B, et al. ePub Jun 2013 (2013) PMID: 23610105
103. Baselga J, Cortés J, Kim SB, et al. ePub Jan 2012 (2012) PMID: 22149875

104. Swain SM, Baselga J, Kim SB, et al. ePub Feb 2015 (2015) PMID: 25693012

105. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. ePub Apr 2019 (2019) PMID: 30857956

106. Bang YJ, Giaccone G, Im SA, et al. ePub 04 2017 (2017) PMID: 28119295

107. Meric-Bernstam et al., 2019; ESMO Abstract 453PD

108. Verma S, Miles D, Gianni L, et al. ePub Nov 2012 (2012) PMID: 23020162

109. Modi S, Saura C, Yamashita T, et al. ePub Dec 2019 (2019) PMID: 31825192

110. Borges VF, Ferrario C, Aucoin N, et al. ePub Sep 2018 (2018) PMID: 29955792

111. Murthy R, Borges VF, Conlin A, et al. ePub 07 2018 (2018) PMID: 29804905

112. Moulder SL, Borges VF, Baetz T, et al. 23 (14):3529-3536 (2017) PMID: 28053022

113. Cameron D, Casey M, Oliva C, et al. ePub 2010 (2010) PMID: 20736298

114. Geyer CE, Forster J, Lindquist D, et al. ePub Dec 2006 (2006) PMID: 17192538

115. Serra V, Vivancos A, Puente XS, et al. ePub Nov 2013 (2013) PMID: 23950206

116. Ali SM, Alpaugh RK, Downing SR, et al. ePub Sep 2014 (2014) PMID: 24516025

117. Grellety T, Soubeyran I, Robert J, et al. ePub Jan 2016 (2016) PMID: 26487584

118. Bedard et al., 2019; AACR Abstract CT139/5

119. Lin NU, Winer EP, Wheatley D, et al. ePub Jun 2012 (2012) PMID: 22418700

120. Schwab CL, Bellone S, English DP, et al. ePub Oct 2014 (2014) PMID: 25268372

121. De Grève J, Teugels E, Geers C, et al. ePub Apr 2012 (2012) PMID: 22325357

122. De Grève J, Moran T, Graas MP, et al. ePub Apr 2015 (2015) PMID: 25682316

123. Li BT, Lee A, O'Toole S, et al. ePub Dec 2015 (2015) PMID: 26559459

124. Gandhi L, Bahleda R, Tolaney SM, et al. ePub Jan 2014 (2014) PMID: 24323026

125. Ben-Baruch NE, Bose R, Kavuri SM, et al. ePub Sep 2015 (2015) PMID: 26358790

126. Kris MG, Camidge DR, Giaccone G, et al. ePub Jul 2015 (2015) PMID: 25899785

127. Jiang et al., 2019; ASCO Abstract 1001

128. Jones KL, Buzdar AU ePub Dec 2009 (2009) PMID: 19959074

129. Zagouri F, Sergentanis TN, Chrysikos D, et al. ePub Oct 2013 (2013) PMID: 23870456

130. Laé M, Couturier J, Oudard S, et al. ePub Apr 2010 (2010) PMID: 19889613

131. Fleischmann A, Rotzer D, Seiler R, et al. ePub Aug 2011 (2011) PMID: 21640482

132. Ross JS, Wang K, Gay LM, et al. 20 (1):68-75 (2014) PMID: 24192927

133. Gardiner RA, Samaratunga ML, Walsh MD, et al. 20 (2):117-20 (1992) PMID: 1348155

134. Gandour-Edwards R, Lara PN, Folkins AK, et al. 95 (5):1009-15 (2002) PMID: 12209684

135. Tsai YS, Cheng HL, Tzai TS, et al. ePub 2012 (2012) PMID: 22991510

136. Higgins MJ, Baselga J ePub Oct 2011 (2011) PMID: 21965336

137. Greulich H, Kaplan B, Mertins P, et al. ePub Sep 2012 (2012) PMID: 22908275

138. Lee JC, Vivanco I, Beroukhim R, et al. ePub Dec 2006 (2006) PMID: 17177598

139. Jia Y, Ali SM, Saad S, et al. ePub Aug 2014 (2014) PMID: 24835218

140. Thomas A, Redon CE, Sciuto L, et al. ePub Jun 2018 (2018) PMID: 29252124

141. Williamson CT, Miller R, Pemberton HN, et al. ePub 12 2016 (2016) PMID: 27958275

142. Bitler BG, Aird KM, Garipov A, et al. ePub Mar 2015 (2015) PMID: 25686104

143. Kim KH, Kim W, Howard TP, et al. ePub Dec 2015 (2015) PMID: 26552009

144. Wiegand KC, Hennessy BT, Leung S, et al. ePub Feb 2014 (2014) PMID: 24559118

145. Huang HN, Lin MC, Huang WC, et al. ePub Jul 2014 (2014) PMID: 24336158

146. Samartzis EP, Gutsche K, Dedes KJ, et al. ePub Jul 2014 (2014) PMID: 24979463

147. Yokoyama Y, Matsushita Y, Shigeto T, et al. 25 (1):58-63 (2014) PMID: 24459582

148. Katagiri A, Nakayama K, Rahman MT, et al. ePub Feb 2012 (2012) PMID: 22101352

149. Xie C, Fu L, Han Y, et al. ePub Aug 2014 (2014) PMID: 24833095

150. Gupta S, Albertson DJ, Parnell TJ, et al. ePub 01 2019 (2019) PMID: 30301863

151. Wu RC, Wang TL, Shih IeM ePub Jun 2014 (2014) PMID: 24618703

152. Jones S, Li M, Parsons DW, et al. ePub Jan 2012 (2012) PMID: 22009941

153. Dulak AM, Stojanov P, Peng S, et al. ePub May 2013 (2013) PMID: 23525077

154. Streppel MM, Lata S, DelaBastide M, et al. ePub Jan 2014 (2014) PMID: 23318448

155. Jiao Y, Yonescu R, Offerhaus GJ, et al. ePub Mar 2014 (2014) PMID: 24293293

156. Ross JS, Wang K, Gay L, et al. ePub Mar 2014 (2014) PMID: 24563076

157. Huang HN, Lin MC, Tseng LH, et al. ePub Mar 2015 (2015) PMID: 25195947

158. Hussein YR, Weigelt B, Levine DA, et al. ePub Apr 2015 (2015) PMID: 25394778

159. Bosse T, ter Haar NT, Seeber LM, et al. ePub Nov 2013 (2013) PMID: 23702729

160. Allo G, Bernardini MQ, Wu RC, et al. ePub Feb 2014 (2014) PMID: 23887303

161. Chou A, Toon CW, Clarkson A, et al. ePub Aug 2014 (2014) PMID: 24925223

162. Ye J, Zhou Y, Weiser MR, et al. ePub Dec 2014 (2014) PMID: 25311944

163. Wei XL, Wang DS, Xi SY, et al. ePub Dec 2014 (2014) PMID: 25561809

164. Chen K, Yang D, Li X, et al. ePub Jan 2015 (2015) PMID: 25583476

165. Wang K, Kan J, Yuen ST, et al. ePub Oct 2011 (2011) PMID: 22037554

166. Abe H, Maeda D, Hino R, et al. ePub Oct 2012 (2012) PMID: 22915242

167. Wang DD, Chen YB, Pan K, et al. ePub 2012 (2012) PMID: 22808142

168. Wiegand KC, Sy K, Kalloger SE, et al. ePub Jun 2014 (2014) PMID: 24767857

169. Gui Y, Guo G, Huang Y, et al. ePub Aug 2011 (2011) PMID: 21822268

170. Balbás-Martínez C, Rodríguez-Pinilla M, Casanova A, et al. ePub 2013 (2013) PMID: 23650517

171. Faraj SF, Chaux A, Gonzalez-Roibon N, et al. ePub Nov 2014 (2014) PMID: 25175170

172. Guan B, Wang TL, Shih IeM ePub Nov 2011 (2011) PMID: 21900401

173. Wiegand KC, Shah SP, Al-Agha OM, et al. ePub Oct 2010 (2010) PMID: 20942669

174. Jones S, Wang TL, Shih IeM, et al. ePub Oct 2010 (2010) PMID: 20826764

175. Yan HB, Wang XF, Zhang Q, et al. ePub Apr 2014 (2014) PMID: 24293408

176. Huang J, Deng Q, Wang Q, et al. ePub Oct 2012 (2012) PMID: 22922871

177. Chan-On W, Nairismägi ML, Ong CK, et al. ePub Dec 2013 (2013) PMID: 24185513

178. Mamo A, Cavallone L, Tuzmen S, et al. ePub Apr 2012 (2012) PMID: 21892209

179. Zang ZJ, Cutcutache I, Poon SL, et al. ePub May 2012 (2012) PMID: 22484628

180. Dienstmann R, Rodon J, Prat A, et al. ePub Mar 2014 (2014) PMID: 24265351

181. Formisano L, Lu Y, Servetto A, et al. ePub 03 2019 (2019) PMID: 30914635

182. Perera TPS, Jovcheva E, Mevellec L, et al. ePub 06 2017 (2017) PMID: 28341788

183. Cheng FT, Ou-Yang F, Lapke N, et al. ePub 12 2017 (2017) PMID: 29223982

184. Gozgit JM, Wong MJ, Moran L, et al. ePub Mar 2012 (2012) PMID: 22238366

185. Ren M, Hong M, Liu G, et al. ePub Jun 2013 (2013) PMID: 23563700

186. Wynes MW, Hinz TK, Gao D, et al. 20 (12):3299-309 (2014) PMID: 24771645

187. Zhang J, Zhang L, Su X, et al. 18 (24):6658-67 (2012) PMID: 23082000

188. Chase A, Bryant C, Score J, et al. ePub Jan 2013 (2013) PMID: 22875613

189. Khodadoust MS, Luo B, Medeiros BC, et al. ePub Apr 2016 (2016) PMID: 26055304

190. Tanasi I, Ba I, Sirvent N, et al. ePub Aug 2019 (2019) PMID: 31434701

191. Strati P, Tang G, Duose DY, et al. ePub 07 2018 (2018) PMID: 29119847

192. Ng TL, Yu H, Smith DE, et al. ePub 01 2019 (2019) PMID: 30297175

193. Soria JC, DeBraud F, Bahleda R, et al. ePub Nov 2014 (2014) PMID: 25193991

194. Nogova L, Sequist LV, Perez Garcia JM, et al. ePub Jan 2017 (2017) PMID: 27870574

195. Ware KE, Hinz TK, Kleczko E, et al. 2 :e39 (2013) PMID: 23552882

196. Terai H, Soejima K, Yasuda H, et al. ePub Jul 2013 (2013) PMID: 23536707

197. Mayr D, Hirschmann A, Löhrs U, et al. 103 (3):883-7 (2006) PMID: 16806438

198. Mayer A, Takimoto M, Fritz E, et al. 71 (8):2454-60 (1993) PMID: 8095852

199. Ross JS, Wang K, Al-Rohil RN, et al. ePub Feb 2014 (2014) PMID: 23887298

200. Tomlinson DC, Lamont FR, Shnyder SD, et al. ePub Jun 2009 (2009) PMID: 19458078

201. Tomlinson DC, Baxter EW, Loadman PM, et al. ePub 2012 (2012) PMID: 22701738

202. di Martino E, Tomlinson DC, Knowles MA ePub 2012 (2012) PMID: 22899908

203. Abdul-Maksoud RS, Shalaby SM, Elsayed WS, et al. ePub Oct 2016 (2016) PMID: 27259667

204. Turner N, Grose R ePub Feb 2010 (2010) PMID: 20094046

205. Kohler LH, Mireskandari M, Knösel T, et al. ePub Jul 2012 (2012) PMID: 22648708

206. Kim HR, Kim DJ, Kang DR, et al. ePub Feb 2013 (2013) PMID: 23182986

207. André F, Bachelot T, Commo F, et al. ePub Mar 2014 (2014) PMID: 24508104

208. Lin AB, McNeely SC, Beckmann RP 23 (13):3232-3240 (2017) PMID: 28331049

209. Möröy T, Geisen C 36 (8):1424-39 (2004) PMID: 15147722

210. Lee JM, Nair J, Zimmer A, et al. ePub Feb 2018 (2018) PMID: 29361470

211. Toledo LI, Murga M, Zur R, et al. ePub Jun 2011 (2011) PMID: 21552262

212. Buisson R, Boisvert JL, Benes CH, et al. ePub Sep 2015 (2015) PMID: 26365377

213. Yang L, Fang D, Chen H, et al. ePub Aug 2015 (2015) PMID: 26204491

214. Taylor-Harding B, Aspuria PJ, Agadjanian H, et al. ePub Jan 2015 (2015) PMID: 25557169

215. Etemadmoghadam D, Au-Yeung G, Wall M, et al. 19 (21):5960-71 (2013) PMID: 24004674

216. Scaltriti M, Eichhorn PJ, Cortés J, et al. ePub Mar 2011 (2011) PMID: 21321214

217. Nanos-Webb A, Jabbour NA, Multani AS, et al. ePub Apr 2012 (2012) PMID: 21695458

218. Ma T, Galimberti F, Erkmen CP, et al. ePub Aug 2013 (2013) PMID: 23686769

219. Lindgren D, Sjödahl G, Lauss M, et al. ePub 2012 (2012) PMID: 22685613

220. Veltman JA, Fridlyand J, Pejavar S, et al. 63 (11):2872-80 (2003) PMID: 12782593

221. Shariat SF, Karakiewicz PI, Ashfaq R, et al. 112 (2):315-25 (2008) PMID: 18008359

222. Shariat SF, Ashfaq R, Sagalowsky AI, et al. 37 (12):1568-76 (2006) PMID: 16949911

223. Hurst CD, Platt FM, Taylor CF, et al. 18 (21):5865-5877 (2012) PMID: 22932667

224. Nishiyama N, Arai E, Nagashio R, et al. ePub Apr 2011 (2011) PMID: 21177765

225. Leung SY, Ho C, Tu IP, et al. 19 (6):854-63 (2006) PMID: 16575401

226. Lin L, Prescott MS, Zhu Z, et al. 60 (24):7021-7 (2000) PMID: 11156406

227. Mayr D, Kanitz V, Anderegg B, et al. 126 (1):101-9 (2006) PMID: 16753589

228. Nakayama N, Nakayama K, Shamima Y, et al. 116 (11):2621-34 (2010) PMID: 20336784

229. Stamatakos M, Palla V, Karaiskos I, et al. ePub Dec 2010 (2010) PMID: 21176227

230. Konecny GE, Winterhoff B, Kolarova T, et al. 17 (6):1591-602 (2011) PMID: 21278246

231. Katsumi Y, Iehara T, Miyachi M, et al. ePub Sep 2011 (2011) PMID: 21871868

232. Cen L, Carlson BL, Schroeder MA, et al. ePub Jul 2012 (2012) PMID: 22711607

233. Logan JE, Mostofizadeh N, Desai AJ, et al. ePub Aug 2013 (2013) PMID: 23898052

234. Elvin JA, Gay LM, Ort R, et al. ePub 04 2017 (2017) PMID: 28283584

235. Gao J, Adams RP, Swain SM 22 (6):e498-501 (2015) PMID: 26715889

236. Gopalan et al., 2014; ASCO Abstract 8077

237. Konecny et al., 2016; ASCO Abstract 5557

238. DeMichele A, Clark AS, Tan KS, et al. 21 (5):995-1001 (2015) PMID: 25501126

239. Finn RS, Crown JP, Lang I, et al. ePub Jan 2015 (2015) PMID: 25524798

240. Johnson DB, Dahlman KH, Knol J, et al. ePub Jun 2014 (2014) PMID: 24797823

241. Van Maerken T, Rihani A, Dreidax D, et al. ePub Jun 2011 (2011) PMID: 21460101

242. Gamble LD, Kees UR, Tweddle DA, et al. ePub Feb 2012 (2012) PMID: 21725357

243. Lee K, Jung ES, Choi YJ, et al. ePub Oct 2010 (2010) PMID: 20890425

244. Bartoletti R, Cai T, Nesi G, et al. 143 (2):422-7 (2007) PMID: 17612565

245. Eissa S, Ahmed MI, Said H, et al. 56 (9):557-64 (2004) PMID: 15590562

246. Korkolopoulou P, Christodoulou P, Lazaris A, et al. 39 (2):167-77 (2001) PMID: 11223676

247. Le Frère-Belda MA, Cappellen D, Daher A, et al. 85 (10):1515-21 (2001) PMID: 11720438

248. Yurakh AO, Ramos D, Calabuig-Fariñas S, et al. 50 (3):506-15; discussion 515 (2006) PMID: 16624482

249. Le Frère-Belda MA, Gil Diez de Medina S, Daher A, et al. 35 (7):817-24 (2004) PMID: 15257544

250. Orlow I, Lacombe L, Hannon GJ, et al. 87 (20):1524-9 (1995) PMID: 7563186

251. Pollard C, Smith SC, Theodorescu D ePub Mar 2010 (2010) PMID: 20334706

252. Yin M, Bastacky S, Parwani AV, et al. 39 (4):527-35 (2008) PMID: 18234280

253. Rebouissou S, Hérault A, Letouzé E, et al. ePub Jul 2012 (2012) PMID: 22422578

254. Quelle DE, Zindy F, Ashmun RA, et al. 83 (6):993-1000 (1995) PMID: 8521522

255. null 576 (1-2):22-38 (2005) PMID: 15878778

256. Gazzeri S, Gouyer V, Vour'ch C, et al. 16 (4):497-504 (1998) PMID: 9484839

257. null 18 (38):5311-7 (1999) PMID: 10498883

258. Sherr CJ, Bertwistle D, DEN Besten W, et al. 70 :129-37 (2005) PMID: 16869746

259. Ozenne P, Eymin B, Brambilla E, et al. ePub Nov 2010 (2010) PMID: 20549699

260. Ruas M, Brookes S, McDonald NQ, et al. 18 (39):5423-34 (1999) PMID: 10498896

261. Jones R, Ruas M, Gregory F, et al. 67 (19):9134-41 (2007) PMID: 17909018

262. Haferkamp S, Becker TM, Scurr LL, et al. ePub Oct 2008 (2008) PMID: 18843795

263. Huot TJ, Rowe J, Harland M, et al. 22 (23):8135-43 (2002) PMID: 12417717

264. Rizos H, Darmanian AP, Holland EA, et al. 276 (44):41424-34 (2001) PMID: 11518711

265. Gombart AF, Yang R, Campbell MJ, et al. 11 (10):1673-80 (1997) PMID: 9324288

266. Yang R, Gombart AF, Serrano M, et al. 55 (12):2503-6 (1995) PMID: 7780957

267. Parry D, Peters G 16 (7):3844-52 (1996) PMID: 8668202

268. Greenblatt MS, Beaudet JG, Gump JR, et al. 22 (8):1150-63 (2003) PMID: 12606942

269. Yarbrough WG, Buckmire RA, Bessho M, et al. 91 (18):1569-74 (1999) PMID: 10491434

270. Poi MJ, Yen T, Li J, et al. 30 (1):26-36 (2001) PMID: 11255261

271. Byeon IJ, Li J, Ericson K, et al. 1 (3):421-31 (1998) PMID: 9660926

272. Kannengiesser C, Brookes S, del Arroyo AG, et al. ePub Apr 2009 (2009) PMID: 19260062

273. Lal G, Liu L, Hogg D, et al. 27 (4):358-61 (2000) PMID: 10719365

274. Koh J, Enders GH, Dynlacht BD, et al. 375 (6531):506-10 (1995) PMID: 7777061

275. McKenzie HA, Fung C, Becker TM, et al. ePub Jun 2010 (2010) PMID: 20340136

276. Miller PJ, Duraisamy S, Newell JA, et al. ePub Aug 2011 (2011) PMID: 21462282

277. Kutscher CL, Wright WA 18 (1):87-94 (1977) PMID: 905385

278. Scaini MC, Minervini G, Elefanti L, et al. ePub Jul 2014 (2014) PMID: 24659262

279. Jenkins NC, Jung J, Liu T, et al. ePub Apr 2013 (2013) PMID: 23190892

280. Walker GJ, Gabrielli BG, Castellano M, et al. 82 (2):305-12 (1999) PMID: 10389768

281. Rutter JL, Goldstein AM, Dávila MR, et al. 22 (28):4444-8 (2003) PMID: 12853981

282. Oplustilova L, Wolanin K, Mistrik M, et al. ePub Oct 2012 (2012) PMID: 22983061

283. Yamamoto Y, Miyamoto M, Tatsuda D, et al. ePub Jul 2014 (2014) PMID: 24830725

284. McCabe N, Turner NC, Lord CJ, et al. ePub Aug 2006 (2006) PMID: 16912188

285. Krenzlin H, Demuth I, Salewsky B, et al. ePub 2012 (2012) PMID: 22396666

286. Bakhshi S, Cerosaletti KM, Concannon P, et al. 25 (3):248-51 (2003) PMID: 12621246

287. Distel L, Neubauer S, Varon R, et al. 41 (1):44-8 (2003) PMID: 12764742

288. Meyer S, Kingston H, Taylor AM, et al. 154 (2):169-74 (2004) PMID: 15474156

289. Pastorczak A, Szczepanski T, Mlynarski W, et al. ePub Mar 2016 (2016) PMID: 26826318

290. Gładkowska-Dura M, Dzierzanowska-Fangrat K, Dura WT, et al. ePub Nov 2008 (2008) PMID: 18788073

291. Wolska-Kuśnierz B, Gregorek H, Chrzanowska K, et al. ePub Aug 2015 (2015) PMID: 26271390

292. Zhang B, Beeghly-Fadiel A, Long J, et al. ePub May 2011 (2011) PMID: 21514219

293. Bogdanova N, Feshchenko S, Schürmann P, et al. ePub Feb 2008 (2008) PMID: 17957789

294. Damiola F, Pertesi M, Oliver J, et al. ePub Jun 2014 (2014) PMID: 24894818

295. Cybulski C, Wokołorczyk D, Kluźniak W, et al. ePub Feb 2013 (2013) PMID: 23149842

296. Ciara E, Piekutowska-Abramczuk D, Popowska E, et al. ePub Mar 2010 (2010) PMID: 19908051

297. Mosor M, Ziółkowska I, Pernak-Schwarz M, et al. 20 (8):1454-6 (2006) PMID: 16810201

298. Chrzanowska KH, Piekutowska-Abramczuk D, Popowska E, et al. 118 (5):1269-74 (2006) PMID: 16152606

299. Varon R, Reis A, Henze G, et al. 61 (9):3570-2 (2001) PMID: 11325820

300. Li J, Meeks H, Feng BJ, et al. ePub Jan 2016 (2016) PMID: 26534844

301. Couch FJ, Shimelis H, Hu C, et al. ePub Sep 2017 (2017) PMID: 28418444

302. Taylor GM, O'Brien HP, Greaves MF, et al. 63 (19):6563-4; author reply 6565 (2003) PMID: 14559852

303. Seemanová E, Jarolim P, Seeman P, et al. ePub Dec 2007 (2007) PMID: 18073374

304. Carney JP, Maser RS, Olivares H, et al. 93 (3):477-86 (1998) PMID: 9590181

305. Varon R, Vissinga C, Platzer M, et al. 93 (3):467-76 (1998) PMID: 9590180

306. Chen YC, Su YN, Chou PC, et al. 280 (37):32505-11 (2005) PMID: 16036916

307. null ePub Sep 2012 (2012) PMID: 22960745

308. Ciriello G, Gatza ML, Beck AH, et al. ePub Oct 2015 (2015) PMID: 26451490

309. null ePub Jan 2015 (2015) PMID: 25631445

310. Rosati R, La Starza R, Veronese A, et al. 99 (10):3857-60 (2002) PMID: 11986249

311. Taketani T, Taki T, Nakamura H, et al. ePub Apr 2009 (2009) PMID: 19380029

312. Harms A, Herpel E, Pfarr N, et al. ePub Dec 2015 (2015) PMID: 26490121

313. Kuroda S, Suzuki S, Kurita A, et al. 2015 :572951 (2015) PMID: 25685583

314. Suzuki S, Kurabe N, Ohnishi I, et al. ePub May 2015 (2015) PMID: 25466466

315. French CA, Rahman S, Walsh EM, et al. ePub Aug 2014 (2014) PMID: 24875858

316. Kim SM, Kee HJ, Eom GH, et al. 345 (1):318-23 (2006) PMID: 16682010

317. Kang D, Cho HS, Toyokawa G, et al. ePub Feb 2013 (2013) PMID: 23011637

318. Chen Y, McGee J, Chen X, et al. ePub 2014 (2014) PMID: 24874471

319. Morishita M, di Luccio E 1816 (2):158-63 (2011) PMID: 21664949

320. Vinagre J, Almeida A, Pópulo H, et al. ePub 2013 (2013) PMID: 23887589

321. Huang FW, Hodis E, Xu MJ, et al. ePub Feb 2013 (2013) PMID: 23348506

322. Pinyol R, Tovar V, Llovet JM ePub Sep 2014 (2014) PMID: 24859456

323. Rachakonda PS, Hosen I, de Verdier PJ, et al. ePub Oct 2013 (2013) PMID: 24101484

324. Liu X, Bishop J, Shan Y, et al. ePub Aug 2013 (2013) PMID: 23766237

325. Landa I, Ganly I, Chan TA, et al. ePub Sep 2013 (2013) PMID: 23833040

326. Nonoguchi N, Ohta T, Oh JE, et al. ePub Dec 2013 (2013) PMID: 23955565

327. Liu X, Wu G, Shan Y, et al. ePub May 2013 (2013) PMID: 23603989

328. Killela PJ, Reitman ZJ, Jiao Y, et al. ePub Apr 2013 (2013) PMID: 23530248

329. Borah S, Xi L, Zaug AJ, et al. ePub Feb 2015 (2015) PMID: 25722414

330. Kinde I, Munari E, Faraj SF, et al. ePub Dec 2013 (2013) PMID: 24121487

331. Shay JW, Wright WE ePub Dec 2011 (2011) PMID: 22015685

332. Shay JW, Bacchetti S 33 (5):787-91 (1997) PMID: 9282118

333. Kim NW, Piatyszek MA, Prowse KR, et al. 266 (5193):2011-5 (1994) PMID: 7605428

334. Hanahan D, Weinberg RA 100 (1):57-70 (2000) PMID: 10647931

335. Horn S, Figl A, Rachakonda PS, et al. ePub Feb 2013 (2013) PMID: 23348503

336. Hirai H, Arai T, Okada M, et al. ePub Apr 2010 (2010) PMID: 20107315

337. Bridges KA, Hirai H, Buser CA, et al. 17 (17):5638-48 (2011) PMID: 21799033

338. Rajeshkumar NV, De Oliveira E, Ottenhof N, et al. 17 (9):2799-806 (2011) PMID: 21389100

339. Osman AA, Monroe MM, Ortega Alves MV, et al. ePub Feb 2015 (2015) PMID: 25504633

340. Xu L, Huang CC, Huang W, et al. 1 (5):337-46 (2002) PMID: 12489850

341. Xu L, Tang WH, Huang CC, et al. 7 (10):723-34 (2001) PMID: 11713371

342. Camp ER, Wang C, Little EC, et al. ePub Apr 2013 (2013) PMID: 23470564

343. Kim SS, Rait A, Kim E, et al. ePub Feb 2015 (2015) PMID: 25240597

344. Pirollo KF, Nemunaitis J, Leung PK, et al. ePub Sep 2016 (2016) PMID: 27357628

345. Hajdenberg et al., 2012; ASCO Abstract e15010

346. Leijen S, van Geel RM, Pavlick AC, et al. ePub Dec 2016 (2016) PMID: 27601554

347. Moore et al., 2019; ASCO Abstract 5513

348. Leijen S, van Geel RM, Sonke GS, et al. ePub 12 2016 (2016) PMID: 27998224

349. Oza et al., 2015; ASCO Abstract 5506

350. Méndez E, Rodriguez CP, Kao MC, et al. 24 (12):2740-2748 (2018) PMID: 29535125

351. Ma CX, Cai S, Li S, et al. ePub Apr 2012 (2012) PMID: 22446188

352. Bringuier PP, McCredie M, Sauter G, et al. 79 (5):531-6 (1998) PMID: 9761125

353. Furihata M, Shuin T, Takeuchi T, et al. 16 (3):491-6 (2000) PMID: 10675480

354. Esrig D, Spruck CH, Nichols PW, et al. 143 (5):1389-97 (1993) PMID: 7901994

355. Cordon-Cardo C, Dalbagni G, Saez GT, et al. 56 (3):347-53 (1994) PMID: 7906253

356. Diaz-Cano SJ, Blanes A, Rubio J, et al. 80 (3):279-89 (2000) PMID: 10744064

357. Kapur P, Lotan Y, King E, et al. ePub Jun 2011 (2011) PMID: 21571954

358. Lotan Y, Bagrodia A, Passoni N, et al. ePub Sep 2013 (2013) PMID: 23571005

359. El-Kenawy Ael-M, El-Kott AF, Khalil AM 18 (4):284-9 (null) PMID: 14756544

360. Joung JY, Yang SO, Jeong IG, et al. ePub 2008 (2008) PMID: 18931548

361. Jinza S, Takano Y, Iki M, et al. 60 (3):147-51 (1998) PMID: 9644783

362. Kamijima S, Tobe T, Suyama T, et al. 12 (11):941-7 (2005) PMID: 16351648

363. Alexiev BA, Tavora F ePub Feb 2013 (2013) PMID: 23307189

364. Goebell PJ, Knowles MA ePub (null) PMID: 20610279

365. Feng C, Wang L, Ding G, et al. ePub Feb 2014 (2014) PMID: 24500328

366. Eissa S, Zohny SF, Zekri AR, et al. ePub Dec 2010 (2010) PMID: 20012564

367. Mitra AP, Birkhahn M, Cote RJ 25 (6):563-71 (2007) PMID: 17710407

368. Lambrou GI, Adamaki M, Delakas D, et al. ePub May 2013 (2013) PMID: 23624844

369. Lee YC, Wu WJ, Li WM, et al. ePub Mar 2013 (2013) PMID: 23482786

370. Hashimoto H, Sue Y, Saga Y, et al. 7 (12):457-63 (2000) PMID: 11168685

371. Osman I, Scher HI, Zhang ZF, et al. 3 (4):531-6 (1997) PMID: 9815716

372. Helal Tel A, Fadel MT, El-Sayed NK 12 (3):173-8 (2006) PMID: 16998598

373. Jalali MM, Heidarzadeh A, Zavarei MJ, et al. ePub 2011 (2011) PMID: 22126554

374. Brown CJ, Lain S, Verma CS, et al. ePub Dec 2009 (2009) PMID: 19935675

375. Joerger AC, Fersht AR 77 :557-82 (2008) PMID: 18410249

376. Kato S, Han SY, Liu W, et al. 100 (14):8424-9 (2003) PMID: 12826609

377. Kamada R, Nomura T, Anderson CW, et al. ePub Jan 2011 (2011) PMID: 20978130

378. Bougeard G, Renaux-Petel M, Flaman JM, et al. ePub Jul 2015 (2015) PMID: 26014290

379. Sorrell AD, Espenschied CR, Culver JO, et al. ePub Feb 2013 (2013) PMID: 23355100

380. Nichols KE, Malkin D, Garber JE, et al. 10 (2):83-7 (2001) PMID: 11219776

381. Taubert H, Meye A, Würl P 4 (6):365-72 (1998) PMID: 10780879

382. Kleihues P, Schäuble B, zur Hausen A, et al. 150 (1):1-13 (1997) PMID: 9006316

383. Gonzalez KD, Noltner KA, Buzin CH, et al. ePub Mar 2009 (2009) PMID: 19204208

384. Lalloo F, Varley J, Ellis D, et al. 361 (9363):1101-2 (2003) PMID: 12672316

385. Zhang X, Mu X, Huang O, et al. ePub 2013 (2013) PMID: 23991038

386. Holland DG, Burleigh A, Git A, et al. ePub Mar 2011 (2011) PMID: 21337521

387. Sircoulomb F, Nicolas N, Ferrari A, et al. ePub Mar 2011 (2011) PMID: 21328542

388. Reynisdottir I, Arason A, Einarsdottir BO, et al. ePub Aug 2013 (2013) PMID: 24156016

389. Yang G, Ma F, Zhong M, et al. ePub Apr 2014 (2014) PMID: 24481460

390. Ma F, Bi L, Yang G, et al. ePub Sep 2014 (2014) PMID: 25017610

391. Bazarov AV, Yaswen P ePub May 2011 (2011) PMID: 21635707

392. Slorach EM, Chou J, Werb Z ePub Mar 2011 (2011) PMID: 21317240

393. Sarid et al., 2019; ESMO Abstract 938

394. Dreicer et al., 2016; ASCO Abstract 4515

395. Petrylak DP, Powles T, Bellmunt J, et al. ePub Apr 2018 (2018) PMID: 29423515

396. Pal SK, Hoffman-Censits J, Zheng H, et al. ePub May 2018 (2018) PMID: 29478735

397. Sharma P, Siefker-Radtke A, de Braud F, et al. ePub Jul 2019 (2019) PMID: 31100038

398. Sharma P, Retz M, Siefker-Radtke A, et al. ePub 03 2017 (2017) PMID: 28131785

399. Sharma et al., 2018; AACR Abstract CT178

400. van der Heijden et al., 2019; ESMO Abstract 904PD

401. Keegan et al., 2019; ASCO GU Abstract 481

402. Nadal et al., 2018; ASCO Abstract 4528

403. Nadal et al., 2018; ASCO GU Abstract 515

404. Luke et al., 2019; ASCO GU Abstract 358

405. Siefker-Radtke et al., 2019; ASCO GU Abstract 388

406. Bellmunt J, de Wit R, Vaughn DJ, et al. ePub 03 2017 (2017) PMID: 28212060

407. Fradet Y, Bellmunt J, Vaughn DJ, et al. ePub May 2019 (2019) PMID: 31050707

408. O'Donnell et al., 2019; ASCO Abstract 4546

409. Necchi et al., 2018; ASCO Abstract 4507

410. De Wit et al., 2019; ASCO Abstract 4530

411. Vogelzang et al., 2019; DOI: 10.1200/JCO.2019.37.8_suppl.11

412. Dziadziuszko R, Smit EF, Dafni U, et al. ePub Jun 2019 (2019) PMID: 30825613

413. Lai WV, Lebas L, Barnes TA, et al. ePub Mar 2019 (2019) PMID: 30685684

414. Liu Z, Wu L, Cao J, et al. 11 :7323-7331 (2018) PMID: 30425522

415. Fang W, Zhao S, Liang Y, et al. ePub Nov 2019 (2019) PMID: 31748336

416. Robichaux JP, Elamin YY, Vijayan RSK, et al. ePub Oct 2019 (2019) PMID: 31588020

417. Jang J, Son J, Park E, et al. ePub 09 2018 (2018) PMID: 29978938

418. Koga T, Kobayashi Y, Tomizawa K, et al. ePub 12 2018 (2018) PMID: 30527195

419. Choudhury NJ, Campanile A, Antic T, et al. ePub Jun 2016 (2016) PMID: 27044931

420. Kwak EL, Shapiro GI, Cohen SM, et al. ePub Aug 2013 (2013) PMID: 23775486

421. Patel MR, Ellerton J, Infante JR, et al. ePub Jan 2018 (2018) PMID: 29217288

422. Migden MR, Rischin D, Schmults CD, et al. ePub 07 2018 (2018) PMID: 29863979

423. Moreno et al., 2018; WCLC Abstract MA04.01

424. Falchook GS, Leidner R, Stankevich E, et al. ePub 2016 (2016) PMID: 27879972

425. Jänne PA, Boss DS, Camidge DR, et al. 17 (5):1131-9 (2011) PMID: 21220471

426. Reckamp KL, Giaccone G, Camidge DR, et al. ePub Apr 2014 (2014) PMID: 24501009

427. Kim HS, Kwon HJ, Jung I, et al. 21 (3):544-52 (2015) PMID: 25424851

428. Oh DY, Lee KW, Cho JY, et al. ePub Oct 2016 (2016) PMID: 26581547

429. Kalous O, Conklin D, Desai AJ, et al. ePub Sep 2012 (2012) PMID: 22761403

430. Zhu L, Lopez S, Bellone S, et al. ePub Jul 2015 (2015) PMID: 25669172

431. Tilio M, Gambini V, Wang J, et al. ePub 10 2016 (2016) PMID: 27475932

432. Kosaka T, Tanizaki J, Paranal RM, et al. ePub 05 2017 (2017) PMID: 28363995

433. Opsomer RJ, Wese FX, Van Gangh PJ 53 (1):89-95 (1985) PMID: 2986437

434. Wu YL, Cheng Y, Zhou X, et al. ePub Nov 2017 (2017) PMID: 28958502

435. Necchi et al., 2018; ASCO Abstract 399

436. Necchi A, Lo Vullo S, Perrone F, et al. ePub 03 2018 (2018) PMID: 28921872

437. Kim HS, Kim SM, Kim H, et al. ePub Dec 2015 (2015) PMID: 26462025

438. Cavalieri S, Perrone F, Miceli R, et al. ePub Jul 2018 (2018) PMID: 29734047

439. Sepúlveda-Sánchez JM, Vaz MÁ, Balañá C, et al. ePub Oct 2017 (2017) PMID: 28575464

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

441. Massard C, Gordon MS, Sharma S, et al. ePub Sep 2016 (2016) PMID: 27269937

442. Balar et al., 2018; AACR abstract CT112

443. Powles T, Huddart RA, Elliott T, et al. ePub Jan 2017 (2017) PMID: 28034079

444. Wülfing C, Machiels JP, Richel DJ, et al. 115 (13):2881-90 (2009) PMID: 19399906

445. Culine S, Sellam Z, Bouaita L, et al. ePub Sep 2012 (2012) PMID: 22993342

446. Narayan V, Mamtani R, Keefe S, et al. ePub Jul 2016 (2016) PMID: 26639198

447. Hyman et al., 2016; San Antonio Breast Cancer Symposium Abstract PD2-08

448. Ma CX, Bose R, Gao F, et al. 23 (19):5687-5695 (2017) PMID: 28679771

449. Chan A, Delaloge S, Holmes FA, et al. ePub Mar 2016 (2016) PMID: 26874901

450. Park JW, Liu MC, Yee D, et al. ePub Jul 2016 (2016) PMID: 27406346

451. Schwab CL, English DP, Black J, et al. ePub Oct 2015 (2015) PMID: 26260909

452. Menderes G, Bonazzoli E, Bellone S, et al. ePub May 2017 (2017) PMID: 28397106

453. Hu Z, Hu Y, Liu X, et al. ePub Oct 2015 (2015) PMID: 26375550

454. Kavuri SM, Jain N, Galimi F, et al. ePub Aug 2015 (2015) PMID: 26243863

455. Bose R, Kavuri SM, Searleman AC, et al. ePub Feb 2013 (2013) PMID: 23220880

456. Hyman DM, Piha-Paul SA, Won H, et al. ePub 02 2018 (2018) PMID: 29420467

457. Burstein HJ, Sun Y, Dirix LY, et al. ePub Mar 2010 (2010) PMID: 20142587

458. Freedman RA, Gelman RS, Wefel JS, et al. ePub Mar 2016 (2016) PMID: 26834058

459. Saura C, Garcia-Saenz JA, Xu B, et al. ePub Nov 2014 (2014) PMID: 25287822

460. Awada A, Dirix L, Manso Sanchez L, et al. ePub Jan 2013 (2013) PMID: 22967996

461. Martin M, Bonneterre J, Geyer CE, et al. ePub Dec 2013 (2013) PMID: 23953056

462. Chow LW, Xu B, Gupta S, et al. ePub May 2013 (2013) PMID: 23632474

463. Awada A, Colomer R, Inoue K, et al. ePub Dec 2016 (2016) PMID: 27078022

464. Gandhi et al. 2017; WCLC Abstract MA04.02

465. Konstantinopolous et al., 2018; ASCO Abstract 106

466. Mirza et al., 2016; ASCO Abstract 5555

467. Del Conte G, Sessa C, von Moos R, et al. ePub Aug 2014 (2014) PMID: 25025963

468. Necchi A, Raggi D, Giannatempo P, et al. ePub Jun 2018 (2018) PMID: 29680362

469. Matulonis UA, Penson RT, Domchek SM, et al. ePub 06 2016 (2016) PMID: 26961146

470. Oza AM, Cibula D, Benzaquen AO, et al. ePub Jan 2015 (2015) PMID: 25481791

471. Liu JF, Barry WT, Birrer M, et al. ePub Oct 2014 (2014) PMID: 25218906

472. Barber LJ, Sandhu S, Chen L, et al. ePub Feb 2013 (2013) PMID: 23165508

473. Norquist B, Wurz KA, Pennil CC, et al. ePub Aug 2011 (2011) PMID: 21709188

474. Sakai W, Swisher EM, Jacquemont C, et al. ePub Aug 2009 (2009) PMID: 19654294

475. Rytelewski M, Maleki Vareki S, Mangala LS, et al. ePub Apr 2016 (2016) PMID: 26959114

476. Quigley D, Alumkal JJ, Wyatt AW, et al. ePub 09 2017 (2017) PMID: 28450426

477. Gornstein EL, Sandefur S, Chung JH, et al. ePub 04 2018 (2018) PMID: 29325860

478. Li M, Mou Y, Hou S, et al. ePub Nov 2018 (2018) PMID: 30407325

479. Ma Y, He L, Huang Q, et al. ePub Oct 2018 (2018) PMID: 30333000

480. Cheng Y, Zhang J, Qin SK, et al. 11 :5957-5962 (2018) PMID: 30271179

481. Leonard JP, LaCasce AS, Smith MR, et al. ePub May 2012 (2012) PMID: 22383795

482. Rose TL, Chism DD, Alva AS, et al. ePub Oct 2018 (2018) PMID: 30293995

483. Wang X, Wang H, Song Y 17 (1):201-208 (2019) PMID: 30655756

484. Hurvitz SA, Martin M, Symmans WF, et al. ePub Jan 2018 (2018) PMID: 29175149

485. von Minckwitz G, Procter M, de Azambuja E, et al. ePub 07 2017 (2017) PMID: 28581356

486. Hainsworth JD, Meric-Bernstam F, Swanton C, et al. ePub Feb 2018 (2018) PMID: 29320312

487. Swain SM, Kim SB, Cortés J, et al. ePub May 2013 (2013) PMID: 23602601

488. Hainsworth et al., 2016; ASCO Abstract LBA11511

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

490. Kristeleit et al., 2014; ASCO Abstract 2573

491. Domcheck et al., 2016; ASCO Abstract 4110

492. Plummer R, Lorigan P, Steven N, et al. ePub May 2013 (2013) PMID: 23423489

493. Plummer R, Jones C, Middleton M, et al. 14 (23):7917-23 (2008) PMID: 19047122

494. Wilson RH, Evans TJ, Middleton MR, et al. ePub Mar 2017 (2017) PMID: 28222073

495. Turner et al., 2017; ASCO Abstract 1007

496. Litton JK, Rugo HS, Ettl J, et al. ePub Aug 2018 (2018) PMID: 30110579

497. Ettl J, Quek RGW, Lee KH, et al. ePub Sep 2018 (2018) PMID: 30124753

498. Meehan et al., 2017; AACR Abstract 4687

499. de Bono J, Ramanathan RK, Mina L, et al. ePub 06 2017 (2017) PMID: 28242752

500. Lu E, Thomas GV, Chen Y, et al. ePub 08 2018 (2018) PMID: 30099369

501. Piha-Paul et al., 2017; AACR-NCI-EORTC Abstract A096

502. Dhawan MS, Bartelink IH, Aggarwal RR, et al. 23 (21):6400-6410 (2017) PMID: 28790114

503. Gianni L, Eiermann W, Semiglazov V, et al. ePub May 2014 (2014) PMID: 24657003

504. Morris PG, Iyengar NM, Patil S, et al. ePub Nov 2013 (2013) PMID: 24037735

505. Wang K, Russell JS, McDermott JD, et al. 22 (24):6061-6068 (2016) PMID: 27334835

506. Nishikawa K, Takahashi T, Takaishi H, et al. ePub Jan 2017 (2017) PMID: 27521503

507. Oudard S, Culine S, Vano Y, et al. ePub Jan 2015 (2015) PMID: 25459391

508. Hussain MH, MacVicar GR, Petrylak DP, et al. ePub Jun 2007 (2007) PMID: 17538166

509. Marín AP, Arranz EE, Sánchez AR, et al. ePub Dec 2010 (2010) PMID: 20213094

510. Li et al., 2018; ASCO Abstract 2502

511. Jhaveri et al., 2018; ASCO Abstract 100

512. Krop IE, Kim SB, González-Martín A, et al. ePub Jun 2014 (2014) PMID: 24793816

513. Welslau M, Diéras V, Sohn JH, et al. ePub Mar 2014 (2014) PMID: 24222194

514. Krop IE, LoRusso P, Miller KD, et al. ePub Sep 2012 (2012) PMID: 22649126

515. Burris HA, Rugo HS, Vukelja SJ, et al. ePub Feb 2011 (2011) PMID: 21172893