CellMax LBx 癌可明™
Liquid Biopsy 液態切片

Test Report 檢驗報告

CellMax Life

Elite FUNCTIONAL 功能營養醫學門診 Medical Center
菁英診所

CellMax Life

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Liquid Biopsy 液態切片

OncoLBx Test Report

Patient ID:	Example 123	**Report ID:**	POC1
Gender:	male	**Client ID:**	
Physician:	Dr. Sample	**Specimen Site:**	peripheral blood
Test Ordered:	Dec 9, 2016	**Disease:**	Adenocarcinoma of sigmoid colon (disorder)
Report Date:	Jan 10th, 2017	**Disease SNOMED ID:**	301756000

I. Adenocarcinoma of sigmoid colon

Test Report / 檢測報告

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Liquid Biopsy 液態切片

Order Information / 客戶資訊

Requisition Number / 申請者編號	Example123
Patient Name /受檢者姓名	Mr. Great Example
Taiwan ID /身分證字號	
Date of Birth / 生日	
Gender / 性別	Male
Patient Phone Number / 受檢者連絡電話	
Patient E-mail / 電子信箱	
Name of Lab / 實驗室名稱	
Lab Phone Number / 實驗室連絡電話	
Name of Physician / 醫師姓名	Dr. Sample
Date of Collection / 收檢日期	2016/12/09
Date of Report / 報告日期	2017/01/10

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Patient Test Result / 評估結果

SUMMARY RESULT: POSITIVE

Clinically Relevant Genomic Alterations Detected

Marker	Biological Association	Test	Result	Therapies approved in Sigmoid colon adenocarcinoma	Therapies approved in other indications	May indicate resistance to therapies	Trials
EGFR	ErbB family	- MUTN (seq) - MUTN (seq)	- p.Ser492Arg (S492R) - amplification	Cetuximab, Panitumumab	Erlotinib, Afatinib, Gefitinib	Cetuximab	Yes
APC	APC	MUTN (seq)	p.Glu1209Ter (E1209*)	None	Celecoxib	No	Yes
TP53	p53	MUTN (seq)	p.Met237Ile (M237I)	None	None	No	Yes

Comments / 備註

Electronic Signatures / 電子簽名

Laboratory Manager / 實驗室經理

陳律吾 Leon Chen

Date / 日期

Pathologist / 病理學家

Manana Kvezereli-Javey, MD, PhD

Date / 日期

CellMax Life

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Test Report / 檢測報告

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Report Details

Patient ID: Example 123
Gender: male
Physician: Dr. Sample
Test Ordered: Dec 9, 2016
Report Date: Jan 10th, 2017

Report ID: POC1
Client ID:
Specimen Site: peripheral blood
Disease: Adenocarcinoma of sigmoid colon (disorder)
Disease SNOMED ID: 301756000

1. Summary

1.1. POSITIVE BIOMARKERS

Marker	Biological Association	Test	Result	Therapies approved in Sigmoid colon adenocarcinoma	Therapies approved in other indications	May indicate resistance to therapies	Trials
EGFR	ErbB family	- MUTN (seq) - MUTN (seq)	- p.Ser492Arg (S492R) - amplification	Cetuximab, Panitumumab	Erlotinib, Afatinib, Gefitinib	Cetuximab	Yes
APC	APC	MUTN (seq)	p.Glu1209Ter (E1209*)	None	Celecoxib	No	Yes
TP53	p53	MUTN (seq)	p.Met237Ile (M237I)	None	None	No	Yes

1.2. VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE

Marker	Biological Association	Test	Result
EGFR	ErbB family	MUTN (seq)	p.Val441Gly (V441G)

The functional or therapeutic consequences of VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE are unknown.

1.3. VARIANTS NOT CURATED BY CellMaxLife

Marker	Biological Association	Test	Result
PDGFRA	Tyrosine kinase	MUTN (seq)	p.Thr192Thr (T192T)
MTOR	PI3K/Akt/mTOR	MUTN (seq)	p.Phe2202Leu (F2202L)
BRCA2	BRCA1/2	MUTN (seq)	p.Ser2012Ser (S2012S)

1.4. LABORATORY TECHNICAL DATA

Variant	Map Location	Variant Allele Frequency	Coding Sequence Change	Transcript ID
EGFR-S492R	chr7:55228007	0.6%	c.1474A>C	NM_005228
EGFR-amplification	chr7:55086725-552750	NA (amplification)	amplification	NM_005228
APC-E1209*	chr5:112174916	3.8%	c.3625G>T	NM_000038
TP53-M237I	chr17:7577570	2.9%	c.711G>A	NM_000546
EGFR-V441G	chr7:55227855	0.1%	c.1322T>G	NM_005228
PDGFRA-T192T	chr4:55130042	15.4%	c.576C>T	NM_006206
MTOR-F2202L	chr1:11184611	0.2%	c.6606N>G	NM_004958
BRCA2-S2012S	chr13:32914528	3.1%	c.6036C>G	NM_000059

The data in this table was generated by the laboratory in the course of molecular testing. It has not been altered in any way by CellMaxLife.

2. Guidelines - None Applicable

3. Actionable Biomarkers/Pathways

3.1. EGFR-S492R (p.Ser492Arg)

3.1.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
EGFR	- MUTN (seq): p.Ser492Arg (S492R)	EGFR-S492R exhibits altered function compared to wild type. EGFR activating mutations or amplification may predict sensitivity to Egfr-targeted therapies, including inhibitors of multiple ErbB family members, and several have received FDA approval in some tumor types (Mok et al., 2009; 19692680, Rosell et al., 2009; 19692684, Tsao et al., 2005; 16014883). Egfr activation or overexpression may also lead to activation of the PI3K and MAPK pathway and may confer sensitivity to PI3K and MAPK pathway inhibitors (Bancroft et al., 2002; 11992543). EGFR S492R has been reported to prevent the binding of cetuximab to the Egfr protein and result in cetuximab resistance; however, sensitivity to panitumumab has been reported in the context of the EGFR S492R mutation (Arena et al., 2015; 25623215, Montagut et al., 2012; 22270724).

3.1.2 BIOLOGICAL RELEVANCE of EGFR-S492R (p.Ser492Arg)

EGFR alterations in Sigmoid colon adenocarcinoma	
Molecular function	EGFR S492R is a missense alteration that occurs in the extracellular domain of the Egfr protein (UniProt). EGFR S492R has been reported to emerge in colorectal carcinoma cells that develop resistance to cetuximab. Studies indicate that this alteration prevents the binding of cetuximab to Egfr and the ability of cetuximab to inhibit ligand-mediated Egfr activation. However, panitumumab was able to inhibit Egfr activation in cells harboring EGFR S492R (Montagut et al., 2012; 22270724, Arena et al., 2015; 25623215). Furthermore, studies have reported EGFR S492R as an acquired resistance mutation in some colorectal cancer patients upon cetuximab treatment; although this alteration was associated with cetuximab resistance in patients, one cancer patient harboring this mutation was reported to respond to panitumumab treatment (Montagut et al., 2012; 22270724, Newhall et al., 2014; ESMO World GI 2014, Abstract O-0011, Price et al., 2015; ASCO 2015, Abstract 740, Arena et al., 2015; 25623215). Yet, the specific effect of EGFR S492R on the function of Egfr has not been characterized (PubMed, Nov 2015), and is therefore unknown.
Incidence in disease	Sigmoid colon adenocarcinoma samples have not been analyzed in COSMIC for mutations in EGFR. EGFR mutations have been reported in 2.5% (108/4372) of Colorectal adenocarcinoma samples analyzed in COSMIC (Sep 2016). EGFR hotspot mutations have been reported in 0-11% of CRC samples (Barber et al., 2004; 15625347, Tsuchihashi et al., 2005; 16014894, Dallol et al., 2016; 27146902, Malapelle et al., 2016; 26797410, Phua et al., 2015; 26622882).

3.1.3 CLINICAL RELEVANCE of EGFR-S492R (p.Ser492Arg)

EGFR alterations in Sigmoid colon adenocarcinoma	
Role in disease	The presence of an EGFR abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Egfr protein, which can lead to excessive proliferation (Ciardiello and Tortora, 2008; 18337605). Egfr expression has been significantly associated with tumor grade, tumor stage, lymph node metastasis, increased tumor size, poor differentiation, and TNM stage in CRC cases (Mokhtari et al., 2012; 23798940, Garouniatis et al., 2013; 22733437, Ding et al., 2016; 27729020, Larsson et al., 2016; 27160084). Egfr expression has been associated with increased tumor growth and macrophage-induced growth in a colon cancer mouse model (Zhang et al., 2016; 27683110).
Effect on drug sensitivity	The presence of a sensitizing EGFR mutation in a tumor is the strongest biological predictor of sensitivity to an Egfr tyrosine kinase inhibitor (TKI). Compared with conventional chemotherapy, Egfr TKIs have been shown to improve progression-free survival in non-small cell lung cancer patients whose tumors harbor EGFR mutations (Mok et al., 2009; 19692680, Rosell et al., 2009; 19692684, Tsao et al., 2005; 16014883, Rosell et al., 2012; 22285168). The Egfr TKIs erlotinib and afatinib have been approved by the FDA for the treatment of EGFR mutant non-small cell lung cancer; gefitinib has been approved in Europe and Asia for this indication (Shepherd et al., 2005; 16014882, Rosell et al., 2012; 22285168, Sequist et al., 2013; 23816960). Erlotinib, in combination with gemcitabine, has also been approved by the FDA for the treatment of locally advanced, unresectable, or metastatic pancreatic cancer (Moore et al., 2007; 17452677, Senderowicz et al., 2007; 18247017). Anti-Egfr monoclonal antibodies are also approved in some indications, including cetuximab, which is an approved therapy for HNSCC and colorectal cancer, panitumumab, which is approved in colorectal cancer, and necitumumab, which has received approval for the treatment of advanced squamous NSCLC (Cunningham et al., 2004; 15269313, Vermorken et al., 2008; 18784101, Van Cutsem et al., 2007; 17470858, Thatcher et al., 2015; 26045340). However, EGFR S492R has been reported to prevent the binding of cetuximab to the Egfr protein and result in cetuximab resistance; yet, sensitivity to panitumumab has been reported in the context of the EGFR S492R mutation (Arena et al., 2015; 25623215, Montagut et al., 2012; 22270724). According to the NCCN guidelines for colon cancer (v2.2015, Oct 2014), there is not enough evidence to support Egfr as a predictive biomarker of response for anti-Egfr monoclonal antibodies and no patient should be included or excluded from such therapy based on Egfr test results. The guidelines suggest the use of anti-Egfr therapeutics in combination with chemotherapy for KRAS/NRAS wild type metastatic CRC (v2.2015, Oct 2014).
Effect on drug resistance	Preclinical studies have suggested that Egfr activity may contribute to resistance to BRAF inhibitors in BRAF-mutant melanoma cells and colorectal cancer cells (Mao et al., 2013; 23251002, Girotti et al., 2013; 23242808, Liu et al., 2014; 24200969, Corcoran et al., 2012; 22448344, Sun et al., 2014; 24670642, Wang et al., 2015; 25243790). EGFR S492R has been reported as an acquired cetuximab resistance mutation in colorectal cancer cells and patients upon cetuximab treatment. Studies indicate that this alteration prevents the binding of cetuximab to Egfr and the ability of cetuximab to inhibit ligand-mediated Egfr activation (Montagut et al., 2012; 22270724, Newhall et al., 2014; ESMO World GI 2014, Abstract O-0011, Price et al., 2015; ASCO 2015, Abstract 740, Arena et al., 2015; 25623215). KRAS mutations (exon 2 or non-exon 2) and NRAS mutations have been associated with resistance to Egfr inhibitors in colorectal carcinoma; therefore patients with these mutations should not be treated with cetuximab or panitumumab according to the NCCN guidelines for colon cancer (v2.2015, Oct 2014) (Lièvre et al., 2006; 16618717, De Roock et al., 2011; 21163703, Sorich et al., 2015; 25115304). MET gene amplification has been associated with resistance to Egfr inhibitors; in one study, MET amplification could be identified in circulating tumor DNA prior to clinical symptoms and relapse (Bardelli et al., 2013; 23729478). Preclinical studies have suggested that Egfr activity may contribute to resistance to BRAF inhibitors in BRAF-mutant melanoma cells and colorectal cancer cells (Mao et al., 2013; 23251002, Girotti et al., 2013; 23242808, Liu et al., 2014; 24200969, Corcoran et al., 2012; 22448344, Sun et al., 2014; 24670642, Wang et al., 2015; 25243790).

3.1.4 CLINICAL EVIDENCE in Sigmoid colon adenocarcinoma

EGFR alterations in Sigmoid colon adenocarcinoma	
FDA Approved	Panitumumab.
Phase III Data	Three Phase 3 trials compared maintenance treatment with bevacizumab plus erlotinib to bevacizumab alone in 249 and 452 patients with metastatic colorectal cancer and in 71 patients with KRAS wild-type metastatic colorectal cancer who did not progress after treatment with chemotherapy and/or bevacizumab. These studies reported no significant differences in median progression-free survival (PFS) or in PFS rate at three months between groups who received maintenance therapy of bevacizumab alone and bevacizumab plus erlotinib; toxicities were reported to be greater in the groups receiving erlotinib (Johnsson et al., 2013; 23788755, Tournigand et al., 2015; 26474518, Hagman et al., 2016; 26483047).
Phase II Data	A Phase 2 trial of afatinib treatment alternating with administration of the angiokinase inhibitor BIBF 1120 in 46 patients with advanced colorectal cancer has reported no objective responses. Stable disease was observed in 43.5% (20/46) of patients, seven of whom remained stable for 16 weeks or more (Bouche et al., 2011; 21737652). A Phase 2 clinical trial of erlotinib in 31 patients with metastatic colorectal cancer has reported stable disease for at least eight weeks in 39% of patients; in eight matched tumor pair samples, Egfr activity was significantly lower eight days after treatment initiation than before treatment (Townsley et al., 2006; 16570047). A Phase 2 study has reported 35% (15/43) of colorectal cancer patients showed a partial response to the combination of gefitinib and FOLFOX treatment. Median PFS was 7.8 months. Overexpression of Egfr in colorectal cancer cases was not reported to significantly impact patient response in this study (Cascinu et al., 2008; 18059397). In a single arm Phase 2 study of stage 4 colorectal carcinoma patients, where gefitinib was given in combination with FOLFOX, an overall response rate of 72% (31/43) and a median overall survival of 20.5 months were reported; grades 3 and 4 toxicities were reported at a higher rate than with FOLFOX alone (Fisher et al., 2008; 18981005).
Phase I Data	Analysis from a Phase 1 trial of two circulating tumor DNA samples from colorectal cancer patients with acquired resistance mutations to cetuximab and panitumumab reported a decrease in EGFR-mutant allelic fraction following MM-151 treatment; a reduction in tumor volume and prolonged stable disease were correlated with the decrease in allelic frequency (Arena et al., 2016; 26843189). A Phase 1 study of 60 patients with solid tumors treated with neratinib reported partial responses in 32% (8/25) of breast cancer cases, and stable disease of 24 weeks or greater in 43% (6/14) of non-small cell lung cancer patients and 4% (1/25) of breast cancer patients (Wong et al., 2009; 19318484). A Phase 1 clinical trial of the pan-ErbB inhibitor dacomitinib in advanced, solid tumor patients reported that 1/13 evaluable patients had a partial response (a lung adenocarcinoma patient) and 9/13 had stable disease for at least six weeks (Takahashi et al., 2012; 22249430). A Phase 1 trial of dacomitinib with the anti-IGF-1R antibody figitumumab in patients with advanced solid tumors reported partial responses in 4.9% (3/61) of patients (one of each with ovarian, salivary gland, and adenoid cystic carcinoma), and stable disease in 42.6% (22/61) of cases (Calvo et al., 2016; 27733479).
Preclinical	N/A: Preclinical data are not presented when higher level data are available.

3.1.5 SAMPLE RELEVANT THERAPIES

Therapies targeting EGFR

Drug	Trade Name	Target/Rationale	Current Status
Erlotinib	Tarceva	Egfr tyrosine kinase inhibitor.	Phase 3 (Colorectal carcinoma (CRC)) FDA Approved (Pancreatic carcinoma, Lung large cell neuroendocrine carcinoma, EGFR-mutant NSCLC)
Gefitinib	Iressa	Egfr tyrosine kinase inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) FDA Approved (EGFR-mutant NSCLC)
Afatinib	Gilotrif	Irreversible pan-ErbB kinase inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) FDA Approved (Lung squamous cell carcinoma, EGFR-mutant NSCLC)
Dacomitinib		Pan-ErbB family tyrosine kinase inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) Phase 3 (Non-small cell lung carcinoma (NSCLC))
Neratinib		Egfr/Her2/ErbB4 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) Phase 3 (Breast carcinoma)
ASP8273		EGFR mutant-specific inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Non-small cell lung carcinoma (NSCLC))
Icotinib	Conmana	EGFR inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC))
TH4000		Hypoxia-activated Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC), Head and neck squamous cell carcinoma (HNSCC))
Varlitinib		EGFR/Her-2 inhibitor.	Phase 2 (Gastric carcinoma, Pancreatic carcinoma)
MM-151		Anti-Egfr monoclonal antibody.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Pancreatic carcinoma, Non-small cell lung carcinoma (NSCLC), Endometrial carcinoma, Ovarian carcinoma, Breast carcinoma)
KBP-5209		ErbB family inhibitor.	Phase 1 (Solid Tumor)

3.1.6 BIOMARKER-MATCHED CLINICAL TRIALS

Trials Prioritized By Clinical Specificity*

	Markers	Trial ID	Title	Phase	Targe	Locations/contacts
1	EGFR	NCT02785068	Evaluation of MM-151 + Nal-IRI + 5-FU + Leucovorin in RAS/RAF Wild-type Metastatic Colorectal Cancer	Phase 1/Phase 2	EGFR	• Overall contact: Sharon Chen, schen@merrimack.com, (774) 776-1446 • AZ (1), FL (1), IN (1), NH (1), TN (1), UT (1), WA (1)
2	EGFR	NCT02538627	Phase 1 Combination Study of MM-151 and MM-121	Phase 1	EGFR, ERBB3	• University of Colorado: Colorado, USA, Christopher Lieu, MD, CHRISTOPHER.LIEU@UCDENVER.EDU, (CO) • Northside Hospital: Georgia, USA, Rodolfo Bordoni, MD, (GA) • Northwestern: Illinois, USA, Benedito A Carneiro, MD, benedito.carneiro@northwestern.edu, (IL) • Vanderbilt: Tennessee, USA, Jordan Berlin, MD, jordan.berlin@vanderbilt.edu, (TN)
3	EGFR	NCT02925234	The Drug Rediscovery Protocol (DRUP Trial)	Phase 2	EGFR, PARP, BRAF, ABL1, PDGFR, KIT, PDGFRA, MEK, ERBB2, ERBB3, SMO, VEGFR2, FGFR1, VEGFR3, Raf, FGFR2, PDGFRB, RET, PDCD1	• Overall contact: E.E. Voest, prof., • DRUP@nki.nl, 0031205129111 Amersfoort (1), Amsterdam (2), Breda (1), Eindhoven (1), Geleen (1), Groningen (1), Leiden (1), Maastricht (1), NIjmegen (1), Rotterdam (2), Tilburg (1), Utrecht (1)

4	EGFR, MTOR	NCT02029001	Adapting Treatment to the Tumor Molecular Alterations for Patients With Advanced Solid Tumors: My Own Specific Treatment	Phase 2	MTOR, ABL1, PDGFR, KIT, PDGFRA, RAF1, VEGFR2, VEGFR3, CSF1R, VEGFR1, FLT4, BRAF, PDGFRB, FLT3, RET, ERBB2, EGFR, FGFR3, FGFR1, FGFR2	•Overall contact: Jean-Yves BLAY, MD, jean-yves.blay@lyon.unicancer.fr, +33478785126 •Bordeaux (1), Clermont-Ferrand (1), Grenoble (1), Lyon (2), Marseille (1), Paris (1), Pierre-Bénite (1), Saint-Priest-en-Jarez (1), Toulouse (1)
5	EGFR	NCT02442414	A Phase 1 Study of KBP-5209 in Patients With Advanced Solid Tumors	Phase 1	EGFR	•Overall contact: Matthew S Hunt, BA, Matthew.hunt2@covance.com, 608 332 8641 •Indiana University Melvin and Bren Simon Cancer Center: Indiana, USA, Bert O'Neil, (IN) •University of Texas MD Anderson Cancer Center: Texas, USA, Sarina Piha-Paul, (TX) University of Utah •Huntsman Cancer Institute: Utah, USA, Sunil Sharma, (UT)

**Note The trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.*

Trials Prioritized By Region*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	EGFR	NCT02785068	Evaluation of MM-151 + Nal-IRI + 5-FU + Leucovorin in RAS/RAF Wild-type Metastatic Colorectal Cancer	Phase 1/Phase 2	EGFR	•Overall contact: Sharon Chen, schen@merrimack.com, (774) 776-1446 •AZ (1), FL (1), IN (1), NH (1), TN (1), UT (1), WA (1)
2	EGFR	NCT02538627	Phase 1 Combination Study of MM-151 and MM-121	Phase 1	EGFR, ERBB3	•University of Colorado: Colorado, USA, Christopher Lieu, MD, CHRISTOPHER.LIEU@UCDENVER.EDU, (CO) •Northside Hospital: Georgia, USA, Rodolfo Bordoni, MD, (GA) •Northwestern: Illinois, USA, Benedito A Carneiro, MD, benedito.carneiro@northwestern.edu, (IL) •Vanderbilt: Tennessee, USA, Jordan Berlin, MD, jordan.berlin@vanderbilt.edu, (TN)
3	EGFR	NCT02442414	A Phase 1 Study of KBP-5209 in Patients With Advanced Solid Tumors	Phase 1	EGFR	•Overall contact: Matthew S Hunt, BA, Matthew.hunt2@covance.com, 608 332 8641 •Indiana University Melvin and Bren Simon Cancer Center: Indiana, USA, Bert O'Neil, (IN) •University of Texas MD Anderson Cancer Center: Texas, USA, Sarina Piha-Paul, (TX) •University of Utah Huntsman Cancer Institute: Utah, USA, Sunil Sharma, (UT)
4	EGFR	NCT02451553	Afatinib Dimaleate and Capecitabine in Treating Patients With Advanced Refractory Solid Tumors, Pancreatic Cancer or Biliary Cancer	Phase 1	ERBB2, ERBB4, EGFR, ERBB3	•Indiana University - Melvin and Bren Simon Cancer Center LAPS: Indiana, USA, Safi Shahda, shahdas@iu.edu, (IN) •Fred Hutch/University of Washington Cancer Consortium: Washington, USA, Elena G. Chiorean, gchiorea@uw.edu, (WA)
5	EGFR	NCT02648425	Safety and Tolerability of ASLAN001 in Combination With Cisplatin and 5-FU or Cisplatin With Capecitabine	Phase 1	Her2/neu, EGFR	•Overall contact: ASLAN Pharma, contact@aslanpharma.com, +65 6222 4235 •National Taiwan University Hospital: Taipei, Taiwan •Taipei Veterans General Hospital: Taipei, Taiwan

**Note The trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.*

3.2. EGFR-amplification

3.2.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
EGFR	- MUTN (seq): amplification	EGFR-amplification is an activating alteration. EGFR activating mutations or amplification may predict sensitivity to Egfr-targeted therapies, including inhibitors of multiple ErbB family members, and several have received FDA approval in some tumor types (Mok et al., 2009; 19692680, Rosell et al., 2009; 19692684, Tsao et al., 2005; 16014883). Egfr activation or overexpression may also lead to activation of the PI3K and MAPK pathway and may confer sensitivity to PI3K and MAPK pathway inhibitors (Bancroft et al., 2002; 11992543).

3.2.2 BIOLOGICAL RELEVANCE of EGFR-amplification

EGFR alterations in Sigmoid colon adenocarcinoma	
Molecular function	High-level EGFR gene amplification has been correlated with elevated Egfr protein expression, as measured by immunohistochemistry, although this correlation is not consistent for low-level gene amplification (Hemmings et al., 2009; 19404848, Liang et al., 2010; 20637128, Yang et al., 2012; 22490401, Bhargava et al., 2005; 15920544, Miyai et al., 2010; 20608935).
Incidence in disease	Putative high-level amplification of EGFR has been reported in less than 1% of Colorectal carcinoma (CRC) cases (cBioPortal for Cancer Genomics, Sep 2016). In the literature, EGFR gene amplification has been reported in approximately 4-30% of colorectal cancer specimens analyzed, with some differences depending upon study methodology (Frattini et al., 2007; 17940504, Laurent-Puig et al., 2009; 19884556, Shia et al., 2005; 15832190, Ålgars et al., 2011; 21694725). Egfr expression has been reported in 32-85% of colorectal cancer (CRC) samples analyzed in scientific studies (Rokita et al., 2013; 23926437, Shia et al., 2005; 15832190, Kim et al., 2015; 25589885, Fan et al., 2015; 26731987, Choi et al., 2016; 26632406). One study has reported low and high Egfr expression in 80% (880/1102) and 20% (222/1102) of CRC samples, respectively (Larsson et al., 2016; 27160084).

3.2.3 CLINICAL RELEVANCE of EGFR-amplification

EGFR alterations in Sigmoid colon adenocarcinoma	
Role in disease	The presence of an EGFR abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Egfr protein, which can lead to excessive proliferation (Ciardiello and Tortora, 2008; 18337605). Egfr expression has been significantly associated with tumor grade, tumor stage, lymph node metastasis, increased tumor size, poor differentiation, and TNM stage in CRC cases (Mokhtari et al., 2012; 23798940, Garouniatis et al., 2013; 22733437, Ding et al., 2016; 27729020, Larsson et al., 2016; 27160084). Egfr expression has been associated with increased tumor growth and macrophage-induced growth in a colon cancer mouse model (Zhang et al., 2016; 27683110).
Effect on drug sensitivity	EGFR amplification or increased copy number have been reported to be associated with increased sensitivity to Egfr targeted therapies in studies of lung cancer, whereas studies in colorectal cancer (CRC) patients have been mixed; efficacy in patients with CRC is dependent on the absence of KRAS and NRAS mutations (Tsao et al., 2005; 16014883, Bell et al., 2005; 16204011, Hirsch et al., 2005; 15998906, Ålgars et al., 2011; 21694725, Sartore-Bianchi et al., 2007; 17664472, Yang et al., 2012; 22897982). The Egfr TKIs erlotinib, afatinib, and gefitinib have been approved by the FDA for the treatment of EGFR mutant non-small cell lung cancer (NSCLC) (Shepherd et al., 2005; 16014882, Rosell et al., 2012; 22285168, Sequist et al., 2013; 23816960, Douillard et al., 2014; 24263064, Mok et al., 2009; 19692680). Erlotinib, in combination with gemcitabine, has also been approved by the FDA for the treatment of locally advanced, unresectable, or metastatic pancreatic cancer (Moore et al., 2007; 17452677, Senderowicz et al., 2007; 18247017). Anti-Egfr monoclonal antibodies are also approved in some indications, including cetuximab, which is an approved therapy for HNSCC and colorectal cancer, panitumumab, which is approved in colorectal cancer, and necitumumab, which has received approval for the treatment of advanced squamous NSCLC (Cunningham et al., 2004; 15269313, Vermorken et al., 2008; 18784101, Van Cutsem et al., 2007; 17470858, Thatcher et al., 2015; 26045340). Studies have reported varied results as to whether EGFR amplification or high Egfr expression in colorectal cancer is predictive of response to treatment with Egfr antibodies, such as cetuximab and panitumumab (Grothey, 2010; 20921457, Tol et al., 2010; 20413299, Frattini et al., 2007; 17940504, Cappuzzo et al., 2008; 17974556, Moroni et al., 2005; 15863375, Park et al., 2011; 21340604, Ålgars et al., 2011; 21694725, Lièvre et al., 2006; 16618717). For colorectal carcinoma patients with metastatic disease and tumors harboring a KRAS or NRAS mutation, the NCCN guidelines (v.1.2016) recommend against the use of cetuximab and panitumumab.
Effect on drug resistance	Preclinical studies have suggested that Egfr activity may contribute to resistance to Braf inhibitors in BRAF-mutant melanoma cells and colorectal cancer cells (Mao et al., 2013; 23251002, Girotti et al., 2013; 23242808, Liu et al., 2014; 24200969, Corcoran et al., 2012; 22448344, Sun et al., 2014; 24670642, Wang et al., 2015; 25243790).

3.2.4 CLINICAL EVIDENCE in Sigmoid colon adenocarcinoma

EGFR alterations in Sigmoid colon adenocarcinoma	
FDA Approved	Panitumumab. Cetuximab.
Phase III Data	Large, randomized Phase 3 trials have found that panitumumab, when combined with chemotherapy, results in prolonged progression-free survival compared to chemotherapy alone in patients with wild-type, but not mutant, KRAS colorectal cancer (Douillard et al., 2010; 20921465, Peeters et al., 2010; 20921462, Douillard et al., 2014; 24718886, Peeters et al., 2014; 24356622, Peeters et al., 2015; 26341920). A randomized Phase 3 trial of panitumumab in patients with metastatic colorectal cancer reported an objective response rate of 15% (11/72) in patients with wild-type KRAS or NRAS, as compared with 1% (1/95) in patients with mutant KRAS or NRAS (Patterson et al., 2013; ASCO 2013, Abstract 3617). A Phase 3 trial of panitumumab versus cetuximab in 999 patients with chemotherapy-refractory wild-type KRAS metastatic colorectal cancer (ASPECCT) reported that these agents provide a similar overall survival benefit in this population; median overall survival was 10.4 months with panitumumab and 10.0 months with cetuximab (Price et al., 2014; 24739896). A Phase 3 trial (CALGB/SWOG 80405) of 1420 patients with wild-type KRAS (codons 12 and 13) metastatic adenocarcinoma of the colon or rectum who were randomized to treatment with cetuximab or bevacizumab, in combination with irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6), reported no significant difference in overall survival between the cetuximab combined with chemotherapy arm and the bevacizumab combined with chemotherapy arm, with both arms showing an overall survival of approximately 29 months (29.9 month vs. 29.0 months, respectively), and a similar progression-free survival of 10.5 months vs. 10.8 months, respectively; the initial study included the combination arm of cetuximab and bevacizumab, which was discontinued (Venook et al., 2014; ASCO 2014, Abstract LBA3). A Phase 3 trial (FIRE-3) reported significantly better overall survival (28.8 mo vs 25.0 mo) in KRAS (exon 2) wild-type metastatic CRC patients treated with FOLFIRI in combination with cetuximab compared to FOLFIRI with bevacizumab (Heinemann et al., 2013; ASCO 2013, Abstract LBA3506). A retrospective analysis of 649 chemotherapy-refractory colorectal cancer patients treated with cetuximab plus chemotherapy reported a response rate of 38.1% (110/289) in wild-type NRAS patients as compared with 7.7% (1/13) in those harboring NRAS mutations (De Roock et al., 2010; 20619739). Three Phase 3 trials compared maintenance treatment with bevacizumab plus erlotinib to bevacizumab alone in 249 and 452 patients with metastatic colorectal cancer and in 71 patients with KRAS wild-type metastatic colorectal cancer who did not progress after treatment with chemotherapy and/or bevacizumab. These studies reported no significant differences in median progression-free survival (PFS) or in PFS rate at three months between groups who received maintenance therapy of bevacizumab alone and bevacizumab plus erlotinib; toxicities were reported to be greater in the groups receiving erlotinib (Johnsson et al., 2013; 23788755, Tournigand et al., 2015; 26474518, Hagman et al., 2016; 26483047).
Phase II Data	A Phase 2 study of 21 rectal cancer patients receiving nimotuzumab, capecitabine, and radiotherapy has reported a pathologic complete response in 19% (4/21) of patients and at least moderate tumor regression in 71% of patients. This therapeutic combination was well tolerated with approximately 5-10% of patients having a grade 3 adverse event (Jin et al., 2015; 25564344). A Phase 2 trial of afatinib treatment alternating with administration of the angiokinase inhibitor BIBF 1120 in 46 patients with advanced colorectal cancer has reported no objective responses. Stable disease was observed in 43.5% (20/46) of patients, seven of whom remained stable for 16 weeks or more (Bouche et al., 2011; 21737652). A Phase 2 clinical trial of erlotinib in 31 patients with metastatic colorectal cancer has reported stable disease for at least eight weeks in 39% of patients; in eight matched tumor pair samples, Egfr activity was significantly lower eight days after treatment initiation than before treatment (Townsley et al., 2006; 16570047). A Phase 2 study has reported 35% (15/43) of colorectal cancer patients showed a partial response to the combination of gefitinib and FOLFOX treatment. Median PFS was 7.8 months. Overexpression of Egfr in colorectal cancer cases was not reported to significantly impact patient response in this study (Cascinu et al., 2008; 18059397). In a single arm Phase 2 study of stage 4 colorectal carcinoma patients, where gefitinib was given in combination with FOLFOX, an overall response rate of 72% (31/43) and a median overall survival of 20.5 months were reported; grades 3 and 4 toxicities were reported at a higher rate than with FOLFOX alone (Fisher et al., 2008; 18981005).

EGFR alterations in Sigmoid colon adenocarcinoma	
Phase I Data	A retrospective study of cetuximab combined with chemotherapy (n=51) or chemotherapy alone (n=107) in metastatic CRC patients with wild-type KRAS reported that the median overall survival was longer in patients treated with the combination. In addition, the median overall survival in patients treated with the combination was longer in patients with high versus low Egfr tumor expression, 25.0 and 19.0 months, respectively, and in patients with normal PTEN versus loss of PTEN, 24.0 versus 19.0 months, respectively, which were reported to be statistically significant differences (Chen et al., 2015; 26448020). A Phase 1 study of 60 patients with solid tumors treated with neratinib reported partial responses in 32% (8/25) of breast cancer cases, and stable disease of 24 weeks or greater in 43% (6/14) of non-small cell lung cancer patients and 4% (1/25) of breast cancer patients (Wong et al., 2009; 19318484). A Phase 1 clinical trial of the pan-ErbB inhibitor dacomitinib in advanced, solid tumor patients reported that 1/13 evaluable patients had a partial response (a lung adenocarcinoma patient) and 9/13 had stable disease for at least six weeks (Takahashi et al., 2012; 22249430). A Phase 1 trial of dacomitinib with the anti-IGF-1R antibody figitumumab in patients with advanced solid tumors reported partial responses in 4.9% (3/61) of patients (one of each with ovarian, salivary gland, and adenoid cystic carcinoma), and stable disease in 42.6% (22/61) of cases (Calvo et al., 2016; 27733479).
Preclinical	N/A: Preclinical data are not presented when higher level data are available.

3.2.5 SAMPLE RELEVANT THERAPIES

Therapies targeting EGFR

Drug	Trade Name	Target/Rationale	Current Status
Cetuximab	Erbitux	Anti-Egfr monoclonal antibody.	FDA Approved (Colorectal carcinoma (CRC)) FDA Approved (Head and neck squamous cell carcinoma (HNSCC))
Panitumumab	Vectibix	Anti-Egfr monoclonal antibody.	FDA Approved (Colorectal carcinoma (CRC)) Phase 3 (Gastric carcinoma, Head and neck carcinoma, Gastroesophageal junction carcinoma, Urothelial carcinoma, Esophageal carcinoma)
Erlotinib	Tarceva	Egfr tyrosine kinase inhibitor.	Phase 3 (Colorectal carcinoma (CRC)) FDA Approved (Pancreatic carcinoma, Lung large cell neuroendocrine carcinoma, EGFR-mutant NSCLC)
Afatinib	Gilotrif	Irreversible pan-ErbB kinase inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) FDA Approved (Lung squamous cell carcinoma, EGFR-mutant NSCLC)
Gefitinib	Iressa	Egfr tyrosine kinase inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) FDA Approved (EGFR-mutant NSCLC)
Necitumumab	Portrazza	Anti-Egfr monoclonal antibody.	Phase 2 (Solid Tumor) FDA Approved (Lung squamous cell carcinoma)
Dacomitinib		Pan-ErbB family tyrosine kinase inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) Phase 3 (Non-small cell lung carcinoma (NSCLC))
Neratinib		Egfr/Her2/ErbB4 inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) Phase 3 (Breast carcinoma)
Nimotuzumab	Theraloc	Egfr inhibitory antibody.	Phase 2 (Colorectal carcinoma (CRC)) Phase 3 (Gastric carcinoma, Glioblastoma, Glioma, Pancreatic carcinoma, Non-small cell lung carcinoma (NSCLC), Head and neck carcinoma, and various other cancers)
ASP8273		EGFR mutant-specific inhibitor.	Phase 1 (Solid Tumor) Phase 3 (Non-small cell lung carcinoma (NSCLC))
Icotinib	Conmana	EGFR inhibitor.	Phase 3 (Non-small cell lung carcinoma (NSCLC))
TH4000		Hypoxia-activated Egfr tyrosine kinase inhibitor.	Phase 2 (Non-small cell lung carcinoma (NSCLC), Head and neck squamous cell carcinoma (HNSCC))
Varlitinib		EGFR/Her-2 inhibitor.	Phase 2 (Gastric carcinoma, Pancreatic carcinoma)
SYN004		Anti-Egfr monoclonal antibody.	Phase 1 (Colorectal carcinoma (CRC)) Phase 1 (Solid Tumor, Lung squamous cell carcinoma)
KBP-5209		ErbB family inhibitor.	Phase 1 (Solid Tumor)

3.2.6 BIOMARKER-MATCHED CLINICAL TRIALS

Trials Prioritized By Clinical Specificity*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	EGFR	NCT02885753	Systemic Oxaliplatin or Intra-arterial Chemotherapy Combined With LV5FU2 and an Target Therapy in First Line Treatment of Metastatic Colorectal Cancer Restricted to the Liver	Phase 3	EGFR, VEGFA	•Overall contact: Marie MOREAU, marie.moreau@u-bourgogne.fr, +33 (0)380393404 •Polyclinique Bordeaux Nord: Bordeaux, France, Cedric LECAILLE •HEGP: Paris, France, Simon PERNOT •Saint Gregoire - Chp: Saint Gregoire, France, Laurent MIGLIANICO •Saint- Etienne Chu: Saint- Etienne, France, Jean Marc PHELIP
2	EGFR	NCT01312857	Study of Hepatic Arterial Infusion With Intravenous Irinotecan, 5FU and Leucovorin With or Without Panitumumab, in Patients With Wild Type RAS Who Have Resected Hepatic Metastases From Colorectal Cancer	Phase 2	EGFR	•Overall contact: Nancy Kemeny, MD, 646-888-4180 •Memorial Sloan Kettering Basking Ridge: New Jersey, USA, Nancy Kemeny, MD, (NJ) •Memorial Sloan Kettering Commack: New York, USA, Nancy Kemeny, MD, PhD, (NY) •Memorial Sloan Kettering Cancer Center: New York, USA, Nancy Kemeny, MD, (NY) •Memorial Sloan Kettering Rockville Centre: New York, USA, Nancy Kemeny, MD, (NY) •Memorial Sloan Kettering Westchester: New York, USA, Nancy Kemeny, MD, (NY)
3	EGFR	NCT02508077	FOLFIRI and Panitumumab in Treating Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer	Phase 2	TOP1, EGFR	•City of Hope Medical Center: California, USA, Marwan G. Fakih, mfakih@coh.org, (CA) •City of Hope Antelope Valley: California, USA, Nimit Sudan, MD, (CA) •City of Hope Rancho Cucamonga: California, USA, Valerie Estala, vestal@coh.org, (CA) •South Pasadena Cancer Center: California, USA, Stephen Koehler, MD, (CA)
4	EGFR	NCT01814501	Panitumumab and Chemotherapy in Patients With Advanced Colorectal Cancer After Prior Therapy With Bevacizumab	Phase 2	EGFR, TOP1	•Overall contact: Ohio State University Comprehensive Cancer Center, Jamesline@osumc.edu, 1- •800-293-5066 Arthur G. James Cancer Hospital and Solove Research Institute at Ohio State University Medical Center: Ohio, USA, Kristen •Ciombor, MD, Kristin.Ciombor@osumc.edu, (OH) Vanderbilt-Ingram Cancer Center: Tennessee, USA, Emily Chan, MD, Emily.Chan@vanderbilt.edu, (TN)

5	EGFR	NCT02391727	Safety, Immunogenicity and Pharmacokinetics of SYN004 in Patients With Solid Tumors	Phase 1	EGFR	•Overall contact: Jason Critchlow, 1-919-972-2294 •Ochsner Medical Center: Louisiana, USA, (LA) •Washington University Medical Center: Missouri, USA, (MO)

**Note The trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.*

Trials Prioritized By Region*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	EGFR	NCT02791334	A Study of Anti-PD-L1 Checkpoint Antibody (LY3300054) Alone and in Combination in Participants With Advanced Refractory Solid Tumors	Phase 1	VEGFR2, EGFR, CDK4, CDK6, AXL, ROS1, MET, FLT3	•Overall contact: There may be multiple sites in this clinical trial. 1-877-CTLILLY (1-877-285-4559) or, 1-317-615-4559 •TN (1), TX (2), Amsterdam (1), Barcelona (1), Bordeaux (1), Brussels (1), Calgary (1), Edegem (1), Guadalajara (1), Haifa (1), Jongno-gu (1), Madrid (1), Monterrey (1), Ramat Gan (1), Rotterdam (1), Seodaemun-gu (1), Tainan (1), Taipei (1), Toronto (1), Villejuif (1)
2	EGFR	NCT01312857	Study of Hepatic Arterial Infusion With Intravenous Irinotecan, 5FU and Leucovorin With or Without Panitumumab, in Patients With Wild Type RAS Who Have Resected Hepatic Metastases From Colorectal Cancer	Phase 2	EGFR	•Overall contact: Nancy Kemeny, MD, 646-888-4180 •Memorial Sloan Kettering Basking Ridge: New Jersey, USA, Nancy Kemeny, MD, (NJ) •Memorial Sloan Kettering Commack: New York, USA, Nancy Kemeny, MD, PhD, (NY) •Memorial Sloan Kettering Cancer Center: New York, USA, Nancy Kemeny, MD, (NY) •Memorial Sloan Kettering Rockville Centre: New York, USA, Nancy Kemeny, MD, (NY) •Memorial Sloan Kettering Westchester: New York, USA, Nancy Kemeny, MD, (NY)
3	EGFR	NCT02508077	FOLFIRI and Panitumumab in Treating Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer	Phase 2	TOP1, EGFR	•City of Hope Medical Center: California, USA, Marwan G. Fakih, mfakih@coh.org, (CA) •City of Hope Antelope Valley: California, USA, Nimit Sudan, MD, (CA) •City of Hope Rancho Cucamonga: California, USA, Valerie Estala, vestal@coh.org, (CA) •South Pasadena Cancer Center: California, USA, Stephen Koehler, MD, (CA)
4	EGFR	NCT01814501	Panitumumab and Chemotherapy in Patients With Advanced Colorectal Cancer After Prior Therapy With Bevacizumab	Phase 2	EGFR, TOP1	•Overall contact: Ohio State University Comprehensive Cancer Center, Jamesline@osumc.edu, 1-800-293-5066 •Arthur G. James Cancer Hospital and Solove Research Institute at Ohio State University Medical Center: Ohio, USA, Kristen Ciombor, MD, Kristin.Ciombor@osumc.edu, (OH) •Vanderbilt-Ingram Cancer Center: Tennessee, USA, Emily Chan, MD, Emily.Chan@vanderbilt.edu, (TN)

5	EGFR	NCT02391727	Safety, Immunogenicity and Pharmacokinetics of SYN004 in Patients With Solid Tumors	Phase 1	EGFR	•Overall contact: Jason Critchlow, 1-919-972-2294 •Ochsner Medical Center: Louisiana, USA, (LA) •Washington University Medical Center: Missouri, USA, (MO)

**Note The trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.*

3.3. APC-E1209* (p.Glu1209Ter)

3.3.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
APC	- MUTN (seq): p.Glu1209Ter (E1209*)	APC-E1209* is an inactivating mutation. Inactivation of Apc results in the deregulation of Wnt signaling through beta-catenin (Fu et al., 2011; 21455986). There are currently no approved drugs targeted to APC defects or Wnt upregulation in solid tumors; however, several potential approaches, including Wnt pathway inhibitors, Cox-2 inhibitors, and TRAIL agonists, are in clinical trials (Zhang et al., 2010; 20348907, Tuynman et al., 2008; 18281498, Lu et al., 2009; 19026633).

3.3.2 BIOLOGICAL RELEVANCE of APC-E1209* (p.Glu1209Ter)

APC alterations in Sigmoid colon adenocarcinoma	
Molecular function	The alteration reported here is expected to truncate the Apc protein within the beta-catenin binding domain, and is therefore likely to result in a disruption of the ability of the Apc protein to bind to beta-catenin, which in turn may upregulate Wnt signaling (Dikovskaya et al., 2010; 20144988, Eklof et al., 2001; 11707392, Liu et al., 2006; 16753179).
Incidence in disease	Sigmoid colon adenocarcinoma samples have not been analyzed in COSMIC for mutations in APC. APC mutations have been reported in 45% (2199/4909) of Colorectal adenocarcinoma samples analyzed in COSMIC (Sep 2016). Scientific studies have reported somatic mutations in the APC gene in 17-56% of colorectal cancer samples, and one study reported germline mutations in APC in 37% (586/1591) of cases of familial adenomatous polyposis (Chen et al., 2013; 23773491, Yu et al., 2015; 24951259, Su et al., 2014; 25025473, Stachler et al., 2015; 25683705, Kerr et al., 2013; 23159591).

3.3.3 CLINICAL RELEVANCE of APC-E1209* (p.Glu1209Ter)

APC alterations in Sigmoid colon adenocarcinoma	
Role in disease	APC is a tumor suppressor gene that was originally characterized based on the prominent role that inactivation of Apc plays in colorectal carcinogenesis; however, APC mutation and Wnt/beta-catenin pathway activation have subsequently been implicated in other tumor types as well (Fu et al., 2011; 21455986, Giles et al., 2003; 12781368, Prosperi and Goss, 2010; 20545611). In the absence of functional Apc, beta-catenin accumulates and is translocated to the nucleus, where it promotes the transcription of genes promoting cellular proliferation (Hisamuddin and Yang, 2006; 19079560). In addition, Apc has been reported to play a role in microtubule spindle formation and chromosomal segregation (Kaplan et al., 2001; 11283619, Green and Kaplan, 2003; 14662741, Fodde et al., 2001; 11283620). A preclinical study in a mouse model of mucinous colorectal adenocarcinoma reported that allelic loss of APC in combination with a dominant active PI3K resulted in increased tumor number and size, as well as more aggressive and less differentiated tumors as compared with mice expressing an activated PI3K alone (Deming et al., 2014; 23708654). Loss of APC in combination with activation of K-Ras or loss of p53 function has been reported to lead to the development of colorectal tubular adenoma or intramucosal adenocarcinoma tumors; expression of Apc in these models resulted in increased cellular differentiation and tumor regression (Dow et al., 2015; 26091037).
Effect on drug sensitivity	There are currently no approved therapies that target Apc deficiency in cancer; however, several potential therapies, including Wnt pathway inhibitors, are in clinical trials. Cox-2 inhibitors, such as celecoxib, may reduce Wnt signaling (Tuynman et al., 2008; 18281498, Lu et al., 2009; 19026633). In addition, preclinical studies have reported that Apc inactivation or beta-catenin activation confer synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated (Zhang et al., 2010; 20348907). TRAIL agonists are currently in clinical trials in some cancer types.

3.3.4 CLINICAL EVIDENCE in Sigmoid colon adenocarcinoma

APC alterations in Sigmoid colon adenocarcinoma	
FDA Approved	None.
Phase III Data	None.
Phase II Data	A Phase 2 clinical trial of celecoxib with irinotecan and capecitabine in colorectal carcinoma patients reported objective response in 41% (21/51) of patients; the addition of celecoxib did not significantly improve the response rate compared with chemotherapy alone (El-Rayes et al., 2008; 17429629). A meta-analysis of clinical trials evaluating the effectiveness of celecoxib in cancer patients has reported finding a significant overall response rate in colorectal cancer patients; celecoxib therapy was significantly associated with an increase of cardiovascular effects (Chen et al., 2014; 25016505).
Phase I Data	A Phase 1 trial of PRI-724 in 18 patients with advanced solid tumors reported acceptable toxicity, and three patients with colon cancer reported stable disease for eight, ten, and 12 weeks (El-Khoueiry et al., 2013; ASCO 2013, Abstract 2501). Early results from a Phase 1 study of the Wnt pathway inhibitor OMP-54F28 (FZD8-Fc) in solid tumors has reported that OMP-54F28 was well tolerated through 10 mg/kg, and stable disease was achieved in 18% (3/17) of patients for 2-3 months (Smith et al., 2013; AACR 2013, Abstract B79).
Preclinical	N/A: Preclinical data are not presented when higher level data are available.

3.3.5 SAMPLE RELEVANT THERAPIES

Therapies targeting COX-2

Drug	Trade Name	Target/Rationale	Current Status
Aspirin	Ecotrin	Cox-1,2 inhibitor, nonsteroidal anti-inflammatory.	Phase 3 (Colorectal carcinoma (CRC)) FDA Approved (Pain)
Celecoxib	Celebrex	Cox-2 inhibitor, nonsteroidal anti-inflammatory.	Phase 3 (Colorectal carcinoma (CRC)) FDA Approved (Rheumatoid arthritis, Osteoarthritis)
Etoricoxib	Arcoxia	Cox-2 inhibitor, nonsteroidal anti-inflammatory.	Phase 2 (Melanoma, Prostate carcinoma)
Apricoxib		Cox-2 inhibitor, nonsteroidal anti-inflammatory.	Phase 2 (Pancreatic carcinoma, Non-small cell lung carcinoma (NSCLC), Breast carcinoma)

Therapies targeting Wnt pathway

Drug	Trade Name	Target/Rationale	Current Status
OTSA101		Anti-FZD10 monoclonal antibody, Wnt antagonist.	Phase 1 (Solid Tumor)
OMP-54F28		Fzd8 fusion protein, Wnt antagonist.	Phase 1 (Solid Tumor)

Therapies targeting Porcupine

Drug	Trade Name	Target/Rationale	Current Status
LGK974		Porcupine inhibitor, inhibits Wnt signaling.	Phase 1 (Colorectal carcinoma (CRC)) Phase 2 (Head and neck squamous cell carcinoma (HNSCC))

Therapies targeting beta-catenin

Drug	Trade Name	Target/Rationale	Current Status
PRI-724		CBP/beta-catenin inhibitor.	Phase 2 (Colorectal carcinoma (CRC)) Phase 2 (Acute myelocytic leukemia (AML), Chronic myelocytic leukemia (CML))

3.3.6 BIOMARKER-MATCHED CLINICAL TRIALS

Trials Prioritized By Clinical Specificity*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	APC	NCT01545141	Chemokine-Modulatory Regimen for Recurrent Resectable Colorectal Cancer	Phase 1/Phase 2	COX-2, TLR3	•Overall contact: Amer H Zureikat, MD, zureikatah@upmc.edu, 412-623-7931 •UPMC Hillman Cancer Center: Pennsylvania, USA, (PA)
2	APC	NCT00565708	Aspirin for Dukes C and High Risk Dukes B Colorectal Cancers	Phase 3	COX-2	•Overall contact: John Chia, MBBS, MRCP, nmocwk@nccs.com.sg, 65-96536990 •Australia (26), China (8), India (7), Indonesia (2), Korea, Republic of (1), Malaysia (3), New Zealand (2), Saudi Arabia (1), Singapore (1), Sri Lanka (1), Taiwan (4)
3	APC	NCT02804815	Add-Aspirin: A Trial Assessing the Effects of Aspirin on Disease Recurrence and Survival After Primary Therapy in Common Non Metastatic Solid Tumours	Phase 3	COX-2	•Overall contact: Marta Campos, mrcctu@add-aspirin.ac.uk, 02076704892 •United Kingdom (67)
4	APC	NCT02301286	A Trial of Aspirin on Recurrence and Survival in Colon Cancer Patients	Phase 3	COX-2	•Overall contact: M.A. Frouws, MD, m.a.frouws@lumc.nl, 0031715265890 •Netherlands (25)
5	APC	NCT02280694	Low Dose Metronomic Poly-chemotherapy for Metastatic CRC	Phase 2	COX-2	•Overall contact: David Loven, MD, loven_da@clalit.org.il, 972-4-6495540 •Gastrointestinal Oncology Unit, Institute of Oncology, Davidoff Center, Rabin Medical Center, Belinson Campus,: Petach Tiqva, Israel

**Note The trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.*

Trials Prioritized By Region*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	APC	NCT01545141	Chemokine-Modulatory Regimen for Recurrent Resectable Colorectal Cancer	Phase 1/Phase 2	COX-2, TLR3	•Overall contact: Amer H Zureikat, MD, zureikatah@upmc.edu, 412-623-7931 •UPMC Hillman Cancer Center: Pennsylvania, USA, (PA)
2	APC	NCT02521844	A Study to Evaluate the Safety and Tolerability of ETC-1922159 in Advanced Solid Tumours	Phase 1	Porcupine	•Overall contact: Veronica Diermayr, PhD, vdiermayr@d3.a-star.edu.sg, 6598171664 •University of Colorado Anschutz Cancer Pavilion: Colorado, USA, (CO) •MD Anderson Cancer Center: Texas, USA, (TX) •National University Hospital: Singapore, Singapore •National Cancer Centre Singapore: Singapore, Singapore
3	APC	NCT00565708	Aspirin for Dukes C and High Risk Dukes B Colorectal Cancers	Phase 3	COX-2	•Overall contact: John Chia, MBBS, MRCP, nmocwk@nccs.com.sg, 65-96536990 •Australia (26), China (8), India (7), Indonesia (2), Korea, Republic of (1), Malaysia (3), New Zealand (2), Saudi Arabia (1), Singapore (1), Sri Lanka (1), Taiwan (4)
4	APC	NCT02804815	Add-Aspirin: A Trial Assessing the Effects of Aspirin on Disease Recurrence and Survival After Primary Therapy in Common Non Metastatic Solid Tumours	Phase 3	COX-2	•Overall contact: Marta Campos, mrcctu@add-aspirin.ac.uk, 02076704892 •United Kingdom (67)
5	APC	NCT02301286	A Trial of Aspirin on Recurrence and Survival in Colon Cancer Patients	Phase 3	COX-2	•Overall contact: M.A. Frouws, MD, m.a.frouws@lumc.nl, 0031715265890 •Netherlands (25)

**Note The trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.*

3.4. TP53-M237I (p.Met237Ile)

3.4.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
TP53	- MUTN (seq): p.Met237Ile (M237I)	TP53-M237I is an inactivating mutation. TP53 is a tumor suppressor that encodes the p53 protein; alterations in TP53 may result in a loss of p53 function, yet an increase in the expression and stability of the mutant p53 protein in the nucleus, sometimes leading to oncogenic effects, including genomic instability and excessive cell proliferation (Levine, 1997; 9039259, Wang et al., 2005; 15625370, Koga et al., 2001; 11400116, Kato et al., 2003; 12826609, Houben et al., 2011; 21760960, Olivier et al., 2009; 18802452). At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines (Schuler et al., 2014; 24583792, Vermeij et al., 2011; 21541192, Saito et al., 2014; 24982341). Tumors with TP53 mutations may be sensitive to the Wee1 inhibitor MK-1775, and clinical trials are currently underway for patients with solid tumors and hematologic malignancies (Hirai et al., 2010; 20107315, Bridges et al., 2011; 21799033). Aurora kinase A inhibitors are another therapeutic approach under investigation for TP53-mutated cancers (Vilgelm et al., 2015; 25398437, Li et al., 2015; 25512615, Katayama and Sen, 2011; 21761334, Tentler et al., 2015; 25758253, Kalous et al., 2013; 24091768).

3.4.2 BIOLOGICAL RELEVANCE of TP53-M237I (p.Met237Ile)

TP53 alterations in Sigmoid colon adenocarcinoma	
Molecular function	TP53 M237I is a missense alteration located within the DNA-binding domain (DBD) of the p53 protein (Joerger and Fersht, 2008; 18410249). DBD mutations are thought to result in loss of function via the loss of transactivation of p53-dependent genes (Kato et al., 2003; 12826609). In vitro characterization of the M237I alteration suggests that the mutant protein exhibits a reduced level of DNA-binding and transactivation activity, as compared with normal p53 (IARC TP53 Database, release R18) (Jordan et al., 2010; 20407015, Bullock et al., 2000; 10713666, Kato et al., 2003; 12826609, Petitjean et al., 2007; 17311302). Therefore, the mutation is predicted to be inactivating.
Incidence in disease	Sigmoid colon adenocarcinoma samples have not been analyzed in COSMIC for mutations in TP53. TP53 mutations have been reported in 43% (4964/11557) of Colorectal adenocarcinoma samples analyzed in COSMIC (Sep 2016). Literature studies have reported TP53 mutations in 21-44% of CRC samples (Mouradov et al., 2013; 24042191, Chang et al., 2016; 26471487, Malapelle et al., 2016; 26797410, Stachler et al., 2015; 25683705).

3.4.3 CLINICAL RELEVANCE of TP53-M237I (p.Met237Ile)

TP53 alterations in Sigmoid colon adenocarcinoma	
Role in disease	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers (Brown et al., 2009; 19935675). Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias (Malkin et al., 1990; 1978757, Srivastava et al., 1991; 2259385, Santibáñez-Koref et al., 1991; 1683921). Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects (Wang et al., 2005; 15625370, Koga et al., 2001; 11400116, Kato et al., 2003; 12826609, Houben et al., 2011; 21760960, Olivier et al., 2009; 18802452). Studies have reported that TP53 mutations are more frequent in colorectal cancer patients of less than approximately 56 years old than in older age groups (Berg et al., 2010; 21103049, Russo et al., 2014; 24500602). Expression of p53 has been significantly correlated with high Ki67 expression in one analysis of 1653 colorectal carcinoma samples (Melling et al., 2016; 26281861).
Effect on drug sensitivity	At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines (Schuler et al., 2014; 24583792, Vermeij et al., 2011; 21541192, Saito et al., 2014; 24982341). Inhibition of components of the DNA damage checkpoint, including Checkpoint Kinase 1 (Chk1) and Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical cancer models with deficiency of p53 function (Ma et al., 2011; 21087899, Hirai et al., 2010; 20107315, Bridges et al., 2011; 21799033). Clinical trials of the Wee1 inhibitor MK-1775 are currently underway for patients with solid tumors and hematologic malignancies. Studies have reported Aurora kinase A to be activated in cells harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in cellular assays; thus, tumors retaining a wild-type TP53 allele may benefit from Aurora kinase inhibitors (Vilgelm et al., 2015; 25398437, Li et al., 2015; 25512615, Katayama and Sen, 2011; 21761334, Tentler et al., 2015; 25758253, Gully et al., 2012; 22611192, Marxer et al., 2014; 23955083).
Effect on drug resistance	Mutations in TP53 may increase resistance to ionizing radiation therapy (El-Deiry, 2003; 14576853, Miyasaka et al., 2015; 25913131). One study of 68 metastatic colon cancer patients with known TP53 status reported no differences in response to oxaliplatin- or irinotecan-based chemotherapy between patients harboring a TP53-mutation and patients with wild-type TP53 (Netter et al., 2015; 25609485).

3.4.4 CLINICAL EVIDENCE in Sigmoid colon adenocarcinoma

TP53 alterations in Sigmoid colon adenocarcinoma	
FDA Approved	None.
Phase III Data	None.
Phase II Data	None.
Phase I Data	A Phase 1 study of ENMD-2076 in patients with advanced cancer reported stable disease of 12 weeks or longer in 26% (5/19) of colorectal cancer patients. Therapy was well-tolerated overall, with hypertension, nausea/vomiting, and fatigue being the most common adverse events (Diamond et al., 2011; 21131552). A Phase 1 trial of MK-1775 in 21 evaluable patients with refractory solid tumors, including seven patients with documented BRCA1/2 mutations, reported confirmed partial responses in one head and neck cancer and one ovarian cancer patient, both harboring BRCA1 mutations; however, no responses were seen in any of five patients with confirmed TP53 mutations (Do et al., 2015; 25964244). A Phase 1 study of alisertib, an Aurora A kinase inhibitor, in patients with solid tumors noted a durable response for longer than one year in one patient and stable disease for at least three months in 23% (20/87) of patients (Dees et al., 2012; 22767670). A Phase 1 study of alisertib in combination with docetaxel in 41 adults with advanced solid tumors has reported partial response in 29% (8/28) of efficacy-evaluable patients, including one complete response in a bladder cancer patient, one partial response in an angiosarcoma patient, and six partial responses in castration-resistant prostate cancer patients (Graff et al., 2016; 27192055). A Phase 1 trial of SGT-53 in 11 patients with refractory cancer reported that the gene therapy complex was well tolerated with stable disease achieved in seven patients at six weeks and a median survival of 340 days; in addition, one tumor which was previously classified as inoperable was able to be resected (Senzer et al., 2013; 23609015). A Phase 1 trial of SGT-53 in combination with docetaxel in 14 patients with advanced cancer has reported three partial responses and two stable diseases per RECIST; this combination was well tolerated (Pirollo et al., 2016; 27357628).
Preclinical	In preclinical experiments, the Wee1 tyrosine kinase inhibitor MK-1775 appeared to sensitize p53-deficient tumor cells to chemotherapeutic agents and to radiation; in particular, in several p53-deficient human colon cancer cell lines, MK-1775 has been reported to enhance the cell growth inhibition of 5-fluorouracil or capecitabine (Bridges et al., 2011; 21799033, Hirai et al., 2010; 20107315, Rajeshkumar et al., 2011; 21389100). Alisertib has been reported to inhibit proliferation of colorectal carcinoma cell lines and inhibit tumor growth in 33% (7/21) of colorectal patient-derived xenograft models utilized in one study (Pitts et al., 2016; 27385211).

3.4.5 SAMPLE RELEVANT THERAPIES

Therapies targeting TP53

Drug	Trade Name	Target/Rationale	Current Status
SGT-53		TP53 gene therapy delivered via transferrin-targeted nanoparticles.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma, Glioma, Pancreatic carcinoma)

Therapies targeting Aurora kinase A

Drug	Trade Name	Target/Rationale	Current Status
Alisertib		AuroraA small molecule kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 3 (T-cell Lymphoma)
AT9283		AuroraA, B, Jak2, Jak3, Bcr-Abl kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Myeloproliferative neoplasm (MPN), Acute myelocytic leukemia (AML), Multiple myeloma (MM), Chronic myelocytic leukemia (CML), Acute lymphocytic leukemia (ALL), Myelodysplastic Syndrome (MDS))
ENMD-2076		AuroraA small molecule kinase inhibitor.	Phase 1 (Colorectal carcinoma (CRC)) Phase 2 (Fibrolamellar hepatocellular carcinoma, Ovarian carcinoma, Breast carcinoma (triple negative), Fallopian tube adenocarcinoma, Soft tissue sarcoma)
AMG 900		AuroraA, B, C small molecule kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myelocytic leukemia (AML))
SNS-314		AuroraA, B small molecule kinase inhibitor.	Phase 1 (Solid Tumor)
TAS-119		Selective AuroraA kinase inhibitor.	Phase 1 (Solid Tumor)

Therapies targeting p53

Drug	Trade Name	Target/Rationale	Current Status
ALT-801		p53-targeted T-cell receptor-IL2 fusion.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Urothelial carcinoma, Bladder carcinoma, Urethral carcinoma, Multiple myeloma (MM))
Kevetrin		Blocks Mdm2-p53 interaction, restoring transcriptional activity of p53.	Phase 1 (Solid Tumor)

Therapies targeting Wee1

Drug	Trade Name	Target/Rationale	Current Status
MK-1775		Wee1 tyrosine kinase inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Small cell lung carcinoma (SCLC), Ovarian carcinosarcoma, MDS/MPN, unclassifiable, Peritoneal papillary serous carcinoma, Myelodysplastic Syndrome (MDS))

3.4.6 BIOMARKER-MATCHED CLINICAL TRIALS

Trials Prioritized By Clinical Specificity*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	TP53	NCT02319018	Alisertib and Combination Chemotherapy in Treating Patients With Gastrointestinal Tumors	Phase 1	Aurora kinase A	•Smilow Cancer Center/Yale-New Haven Hospital: Connecticut, USA, Stacey M. Stein, (CT) •Yale University: Connecticut, USA, Stacey M. Stein, (CT) •Johns Hopkins University/Sidney Kimmel Cancer Center: Maryland, USA, Nilofer S. Azad, jhcccro@jhmi.edu, (MD) •Wayne State University/Karmanos Cancer Institute: Michigan, USA, Ulka N. Vaishampayan, (MI) •Vanderbilt University/Ingram Cancer Center: Tennessee, USA, Laura W. Goff, (TN)
2	BRCA2, MTOR, TP53	NCT01827384	Molecular Profiling-Based Targeted Therapy in Treating Patients With Advanced Solid Tumors	N/A	MTOR, PARP, Wee1, MEK	•Overall contact: Nancy Moore, R.N., nancy.moore@nih.gov, (301) 402-5640 •University of Colorado Cancer Center - Anschutz Cancer Pavilion: Colorado, USA, Stephen Leong, (CO) •National Cancer Institute Developmental Therapeutics Clinic: Maryland, USA, A P. Chen, chenali@mail.nih.gov, (MD) •Washington University School of Medicine: Missouri, USA, Albert C. Lockhart, info@siteman.wustl.edu, (MO)
3	BRCA2, MTOR, TP53	NCT02576444	OLAParib COmbinations	Phase 2	PARP, AKT, Wee1, MTOR, mTORC1, mTORC2	•Overall contact: Alexandra Minnella, alexandra.minnella@yale.edu •Yale Cancer Center: Connecticut, USA, Clinical Trials Office - Yale Cancer Center, (CT) •Dana-Farber Cancer Institute: Massachusetts, USA, (MA)
4	BRCA2, TP53	NCT02511795	AZD1775 Combined With Olaparib in Patients With Refractory Solid Tumors	Phase 1	Wee1, PARP	•Overall contact: AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479 •CA (1), CO (1), FL (1), NY (1), TN (1), TX (1)
5	MTOR, TP53	NCT02719691	Phase I Study of MLN0128 and MLN8237 in Patients With Advanced Solid Tumors and Metastatic Triple-negative Breast Cancer	Phase 1	Aurora kinase A, MTOR, mTORC1, mTORC2	•Overall contact: Matthew Lee, matthew.lee@ucdenver.edu, 303-848-0630 •University of Colorado Cancer Center: Colorado, USA, Matthew Lee, matthew.lee@ucdenver.edu, (CO)

**Note The trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.*

Trials Prioritized By Region*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	TP53	NCT02319018	Alisertib and Combination Chemotherapy in Treating Patients With Gastrointestinal Tumors	Phase 1	Aurora kinase A	•Smilow Cancer Center/Yale-New Haven Hospital: Connecticut, USA, Stacey M. Stein, (CT) •Yale University: Connecticut, USA, Stacey M. Stein, (CT) •Johns Hopkins University/Sidney Kimmel Cancer Center: Maryland, USA, Nilofer S. Azad, jhcccro@jhmi.edu, (MD) •Wayne State University/Karmanos Cancer Institute: Michigan, USA, Ulka N. Vaishampayan, (MI) •Vanderbilt University/Ingram Cancer Center: Tennessee, USA, Laura W. Goff, (TN)
2	BRCA2, MTOR, TP53	NCT01827384	Molecular Profiling-Based Targeted Therapy in Treating Patients With Advanced Solid Tumors	N/A	MTOR, PARP, Wee1, MEK	•Overall contact: Nancy Moore, R.N., nancy.moore@nih.gov, (301) 402-5640 •University of Colorado Cancer Center - Anschutz Cancer Pavilion: Colorado, USA, Stephen Leong, (CO) •National Cancer Institute Developmental Therapeutics Clinic: Maryland, USA, A P. Chen, chenali@mail.nih.gov, (MD) •Washington University School of Medicine: Missouri, USA, Albert C. Lockhart, info@siteman.wustl.edu, (MO)
3	BRCA2, MTOR, TP53	NCT02576444	OLAParib COmbinations	Phase 2	PARP, AKT, Wee1, MTOR, mTORC1, mTORC2	•Overall contact: Alexandra Minnella, alexandra.minnella@yale.edu •Yale Cancer Center: Connecticut, USA, Clinical Trials Office - Yale Cancer Center, (CT) •Dana-Farber Cancer Institute: Massachusetts, USA, (MA)
4	BRCA2, TP53	NCT02511795	AZD1775 Combined With Olaparib in Patients With Refractory Solid Tumors	Phase 1	Wee1, PARP	•Overall contact: AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479 •CA (1), CO (1), FL (1), NY (1), TN (1), TX (1)
5	MTOR, TP53	NCT02719691	Phase I Study of MLN0128 and MLN8237 in Patients With Advanced Solid Tumors and Metastatic Triple-negative Breast Cancer	Phase 1	Aurora kinase A, MTOR, mTORC1, mTORC2	•Overall contact: Matthew Lee, matthew.lee@ucdenver.edu, 303-848-0630 •University of Colorado Cancer Center: Colorado, USA, Matthew Lee, matthew.lee@ucdenver.edu, (CO)

**Note The trials listed above were matched to the biomarkers identified in this tumor; the list may not be comprehensive.*

3.5. EGFR-V441G (p.Val441Gly)

3.5.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
EGFR	- MUTN (seq): p.Val441Gly (V441G)	The functional consequences of EGFR-V441G are unknown. EGFR activating mutations or amplification may predict sensitivity to Egfr-targeted therapies, including inhibitors of multiple ErbB family members, and several have received FDA approval in some tumor types (Mok et al., 2009; 19692680, Rosell et al., 2009; 19692684, Tsao et al., 2005; 16014883). Egfr activation or overexpression may also lead to activation of the PI3K and MAPK pathway and may confer sensitivity to PI3K and MAPK pathway inhibitors (Bancroft et al., 2002; 11992543). However, as this mutation has not been functionally characterized, the relevance of therapeutic approaches is unknown.

3.5.2 BIOLOGICAL RELEVANCE of EGFR-V441G (p.Val441Gly)

EGFR alterations in Sigmoid colon adenocarcinoma	
Molecular function	EGFR V441G is a missense alteration that lies in the extracellular domain of the Egfr protein (UniProt). This alteration has not been reported (COSMIC, Dec 2016) or functionally characterized (PubMed, Dec 2016), and its effect on protein function is therefore unknown.
Incidence in disease	Sigmoid colon adenocarcinoma samples have not been analyzed in COSMIC for mutations in EGFR. EGFR mutations have been reported in 2.5% (108/4372) of Colorectal adenocarcinoma samples analyzed in COSMIC (Sep 2016). EGFR hotspot mutations have been reported in 0-11% of CRC samples (Barber et al., 2004; 15625347, Tsuchihashi et al., 2005; 16014894, Dallol et al., 2016; 27146902, Malapelle et al., 2016; 26797410, Phua et al., 2015; 26622882).

3.5.3 CLINICAL RELEVANCE of EGFR-V441G (p.Val441Gly)

EGFR alterations in Sigmoid colon adenocarcinoma	
Role in disease	The presence of an EGFR abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Egfr protein, which can lead to excessive proliferation (Ciardiello and Tortora, 2008; 18337605). Egfr expression has been significantly associated with tumor grade, tumor stage, lymph node metastasis, increased tumor size, poor differentiation, and TNM stage in CRC cases (Mokhtari et al., 2012; 23798940, Garouniatis et al., 2013; 22733437, Ding et al., 2016; 27729020, Larsson et al., 2016; 27160084). Egfr expression has been associated with increased tumor growth and macrophage-induced growth in a colon cancer mouse model (Zhang et al., 2016; 27683110).
Effect on drug sensitivity	The presence of a sensitizing EGFR mutation in a tumor is the strongest biological predictor of sensitivity to an Egfr tyrosine kinase inhibitor (TKI). Compared with conventional chemotherapy, Egfr TKIs have been shown to improve progression-free survival in non-small cell lung cancer patients whose tumors harbor EGFR mutations (Mok et al., 2009; 19692680, Rosell et al., 2009; 19692684, Tsao et al., 2005; 16014883, Rosell et al., 2012; 22285168). The Egfr TKIs erlotinib, afatinib, and gefitinib have been approved by the FDA for the treatment of EGFR mutant non-small cell lung cancer (NSCLC) (Shepherd et al., 2005; 16014882, Rosell et al., 2012; 22285168, Sequist et al., 2013; 23816960, Douillard et al., 2014; 24263064, Mok et al., 2009; 19692680). Erlotinib, in combination with gemcitabine, has also been approved by the FDA for the treatment of locally advanced, unresectable, or metastatic pancreatic cancer (Moore et al., 2007; 17452677, Senderowicz et al., 2007; 18247017). For colorectal carcinoma patients with metastatic disease and tumors harboring a KRAS or NRAS mutation, the NCCN guidelines (v.1.2016) recommend against the use of cetuximab and panitumumab. In the case of this uncharacterized variant, the relevance of any available therapeutic approaches is unknown.
Effect on drug resistance	Preclinical studies have suggested that Egfr activity may contribute to resistance to Braf inhibitors in BRAF-mutant melanoma cells and colorectal cancer cells (Mao et al., 2013; 23251002, Girotti et al., 2013; 23242808, Liu et al., 2014; 24200969, Corcoran et al., 2012; 22448344, Sun et al., 2014; 24670642, Wang et al., 2015; 25243790).

3.5.4 CLINICAL EVIDENCE in Sigmoid colon adenocarcinoma

EGFR alterations in Sigmoid colon adenocarcinoma	
FDA Approved	None.
Phase III Data	Three Phase 3 trials compared maintenance treatment with bevacizumab plus erlotinib to bevacizumab alone in 249 and 452 patients with metastatic colorectal cancer and in 71 patients with KRAS wild-type metastatic colorectal cancer who did not progress after treatment with chemotherapy and/or bevacizumab. These studies reported no significant differences in median progression-free survival (PFS) or in PFS rate at three months between groups who received maintenance therapy of bevacizumab alone and bevacizumab plus erlotinib; toxicities were reported to be greater in the groups receiving erlotinib (Johnsson et al., 2013; 23788755, Tournigand et al., 2015; 26474518, Hagman et al., 2016; 26483047).
Phase II Data	A Phase 2 trial of afatinib treatment alternating with administration of the angiokinase inhibitor BIBF 1120 in 46 patients with advanced colorectal cancer has reported no objective responses. Stable disease was observed in 43.5% (20/46) of patients, seven of whom remained stable for 16 weeks or more (Bouche et al., 2011; 21737652). A Phase 2 clinical trial of erlotinib in 31 patients with metastatic colorectal cancer has reported stable disease for at least eight weeks in 39% of patients; in eight matched tumor pair samples, Egfr activity was significantly lower eight days after treatment initiation than before treatment (Townsley et al., 2006; 16570047). A Phase 2 study has reported 35% (15/43) of colorectal cancer patients showed a partial response to the combination of gefitinib and FOLFOX treatment. Median PFS was 7.8 months. Overexpression of Egfr in colorectal cancer cases was not reported to significantly impact patient response in this study (Cascinu et al., 2008; 18059397). In a single arm Phase 2 study of stage 4 colorectal carcinoma patients, where gefitinib was given in combination with FOLFOX, an overall response rate of 72% (31/43) and a median overall survival of 20.5 months were reported; grades 3 and 4 toxicities were reported at a higher rate than with FOLFOX alone (Fisher et al., 2008; 18981005).
Phase I Data	A Phase 1 study of 60 patients with solid tumors treated with neratinib reported partial responses in 32% (8/25) of breast cancer cases, and stable disease of 24 weeks or greater in 43% (6/14) of non-small cell lung cancer patients and 4% (1/25) of breast cancer patients (Wong et al., 2009; 19318484). A Phase 1 clinical trial of the pan-ErbB inhibitor dacomitinib in advanced, solid tumor patients reported that 1/13 evaluable patients had a partial response (a lung adenocarcinoma patient) and 9/13 had stable disease for at least six weeks (Takahashi et al., 2012; 22249430). A Phase 1 trial of dacomitinib with the anti-IGF-1R antibody figitumumab in patients with advanced solid tumors reported partial responses in 4.9% (3/61) of patients (one of each with ovarian, salivary gland, and adenoid cystic carcinoma), and stable disease in 42.6% (22/61) of cases (Calvo et al., 2016; 27733479).
Preclinical	N/A: Preclinical data are not presented when higher level data are available.

3.5.5 SAMPLE RELEVANT THERAPIES

+ The functional consequences of EGFR-V441G are unknown. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain.

3.6. PDGFRA-T192T (p.Thr192Thr)

3.6.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
PDGFRA	- MUTN (seq): p.Thr192Thr (T192T)	The effect of PDGFRA-T192T has not been determined by CellMax. PDGFRA encodes the tyrosine kinase receptor human platelet-derived growth factor receptor alpha, also known as Pdgfr-alpha (UniProt) (Kawagishi et al., 1995; 8586421). PDGFRA amplification, overexpression, or activating mutation may predict sensitivity to small molecule tyrosine kinase inhibitors that target Pdgfrs as well as other kinases. Several kinase inhibitors have been approved by the FDA in certain indications; others are under investigation in clinical trials (Andrae et al., 2008; 18483217, Keir et al., 2012; 22190407, Dai et al., 2013; 24132921). However, as the alteration reported here has not been functionally characterized, the relevance of any available therapeutic approaches is unknown. However, PDGFRA-T192T has not been analyzed by CellMax, and therefore the relevance of any therapeutic approaches is uncertain.

3.6.2 BIOLOGICAL RELEVANCE of PDGFRA-T192T (p.Thr192Thr)

PDGFRA alterations in Sigmoid colon adenocarcinoma	
Molecular function	PDGFRA-T192T has not been analyzed by CellMax; therefore its effect on protein function cannot be described.
Incidence in disease	Sigmoid colon adenocarcinoma samples have not been analyzed in COSMIC for mutations in PDGFRA. PDGFRA mutations have been reported in 2.4% (39/1618) of Colorectal adenocarcinoma samples analyzed in COSMIC (Sep 2016). PDGFRA mutations have been identified in 1% (3/332) of colorectal carcinoma samples in one study (Li et al., 2016; 27050078).

3.6.3 CLINICAL RELEVANCE of PDGFRA-T192T (p.Thr192Thr)

PDGFRA alterations in Sigmoid colon adenocarcinoma	
Role in disease	PDGFR aberrations, including point mutations, translocations, amplification, and/or overexpression, have been associated with various malignancies, leading authors to consider the Pdgfrs as oncoproteins (Fletcher, 2004; 15175998). Both autocrine and paracrine activation of PDGF signaling have been implicated in numerous tumor types (Andrae et al., 2008; 18483217). One study reported that Pdgfr-alpha expression correlated with tumor stage and lymph node metastasis in colorectal cancer cases (Wehler et al., 2008; 18288404).
Effect on drug sensitivity	Several tyrosine kinase inhibitors that target the Pdgfrs, as well as other kinases, have received FDA approval in various indications. These agents, including imatinib, sunitinib, sorafenib, dasatinib, nilotinib, ponatinib, regorafenib, pazopanib, and lenvatinib, are currently in clinical trials for patients with multiple solid tumor types (Dai et al., 2013; 24132921). In addition, olaratumab, a monoclonal antibody targeting Pdgfra-alpha, has been demonstrated to have anti-tumor effects in mouse xenografts derived from multiple cancer types, and has been FDA-approved for certain indications (Loizos et al., 2005; 15767546, Tap et al., 2016; 27291997). Pdgfr-alpha activation leads to activation of the PI3K/Akt and mTOR pathways (Andrae et al., 2008; 18483217). Therefore, PI3K and mTOR pathway inhibitors may be relevant in a tumor with PDGFRA amplification, overexpression, or activating mutation. The mTOR inhibitors everolimus and temsirolimus have been approved by the FDA in some indications and remain under investigation in various tumor types. However, the functional consequences of PDGFRA-T192T have not been analyzed by CellMax. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain. In the case of this uncharacterized variant, the relevance of any available therapeutic approaches is unknown.
Effect on drug resistance	Secondary resistance to imatinib occurs in most tumors eventually, and can be attributed, for the most part, to the gain of a second KIT or PDGFRA mutation in the same allele as the primary mutation (Wardelmann et al., 2005; 15811621, Lee et al., 2013; 24369323, Lopes and Bacchi, 2010; 19968734).

3.6.4 CLINICAL EVIDENCE in Sigmoid colon adenocarcinoma

PDGFRA alterations in Sigmoid colon adenocarcinoma	
FDA Approved	Regorafenib.
Phase III Data	A Phase 3 clinical trial of 768 metastatic colorectal cancer patients treated with fluorouracil, leucovorin, and irinotecan (FOLFIRI), in combination with sunitinib, did not show significant clinical benefit; sunitinib in combination with FOLFIRI also showed a poor safety profile (Carrato et al., 2013; 23358972). Regorafenib has been approved to treat patients with metastatic colorectal cancer based on the results of a trial (Study 14387) of 760 previously treated metastatic colorectal cancer patients; the study reported a significant increase in overall survival (6.4 months versus 5.0 months) and progression-free survival (1.9 months versus 1.7 months) in patients treated with regorafenib as compared with placebo (Grothey et al., 2013; 23177514). A Phase 3 study of regorafenib versus placebo in 204 previously treated metastatic colorectal cancer patients of Asian origin reported a median overall survival of 8.8 months in the regorafenib arm (n=136) and 6.3 months in the placebo arm (n=68); adverse events were more frequently reported in the regorafenib arm compared to the placebo arm (97% vs. 46%) (Li et al., 2015; 25981818).
Phase II Data	A Phase 2 study of oxaliplatin, leucovorin, and fluorouracil in combination with sorafenib or placebo in metastatic colorectal cancer reported no benefit in terms of progression-free survival with the addition of sorafenib (Tabernero et al., 2013; 23532888). A Phase 2 trial of dasatinib in 19 previously treated metastatic colorectal cancer patients was terminated due to lack of efficacy, with no objective responses, stable disease for 7.3 months in one patient, a progression-free survival (PFS) rate at four months of 5.3%, and a median PFS and overall survival of 1.6 and 5.1 months, respectively (Sharma et al., 2012; 21552992). A Phase 2 trial of everolimus in heavily pretreated colorectal cancer patients reported no significant efficacy; however, patients were not selected according to mutational or activity status of any PI3K/Akt/mTOR pathway members (Ng et al., 2013; 23743569). A Phase 1/2 study examining imatinib in combination with capecitabine, oxaliplatin, and bevacizumab in 49 patients with CRC reported that 76% of patients were progression-free for at least six months (Hoehler et al., 2013; 23963139).
Phase I Data	A Phase 1 study of pazopanib plus gemcitabine in 22 patients with advanced solid tumors reported that the combination was well tolerated; in this study, a partial response was observed in a melanoma patient and stable disease for at least 12 treatment cycles was observed in three patients (one each with cholangiocarcinoma, melanoma, and colorectal cancer) (Plummer et al., 2013; 23064954). A Phase 1 study of colorectal cancer patients treated with pazopanib in combination with either FOLFOX6 (20 patients) or CapeOx (21 patients) reported an overall response rate of 40% and 38% with these therapy combinations, respectively (Brady et al., 2013; 23456563). Several Phase 1 trials of temsirolimus in combination with other therapies in patients with solid tumors have reported clinical benefit in terms of complete and partial responses in 2.5-11% of patients and stable disease in 4.8-56% of patients (Ganesan et al., 2013; 23982248, Wang-Gillam et al., 2014; 24916546, Kyriakopoulos et al., 2015; ASCO 2015, Abstract 2554, Chiu et al., 2016; 26686201, Khawaja et al., 2016; 27014780). A Phase 1 study of olaratumab in patients with advanced solid tumors reported stable disease (per radiographical review) in 43.8% (7/16) of cases; treatment was described as well-tolerated overall (Doi et al., 2014; 24816152). A Phase 1 study of olaratumab in patients with advanced solid tumors reported stable disease (SD, per RECIST) in 63.2% (12/19) of cases, with median SD duration of 3.9 months; drug-related grade 3 alkaline phosphatase events were noted in one patient, and grade 3 deep vein thromboses were reported in 10.5% (2/19) cases as well (Chiorean et al., 2014; 24452395). A Phase 1 trial of the tyrosine kinase inhibitor lenvatinib (E7080) in 82 patients with advanced solid tumors established a maximum tolerated dose of 25mg and reported partial responses in seven patients (9%) and stable disease in 38 patients (46%) (Boss et al., 2012; 22516948). A Phase 1 study of lenvatinib in 77 patients with advanced solid tumors reported partial responses in 15.6% (12/77) of patients and stable disease lasting greater than 23 weeks in 24.7% (19/77) of patients; treatment was well-tolerated (Hong et al., 2015; 26169970). Several Phase 1 studies have examined imatinib in combination with chemotherapy in colorectal cancer, and have reported efficacy; one study reported that 76% of patients (n=49) were progression-free for at least six months (Michael et al., 2013; 23108698, Hoehler et al., 2013; 23963139, Kelley et al., 2013; 24022191).

PDGFRA alterations in Sigmoid colon adenocarcinoma	
Preclinical	A preclinical study in a mouse xenograft model of colon cancer reported that nilotinib treatment led to decreased stromal reaction in the colon; a synergistic anti-tumor response was seen at the primary and metastatic tumor sites upon co-treatment with everolimus (Yuge et al., 2015; 25478811). Ponatinib has shown efficacy in preclinical models of endometrial, bladder, gastric, breast, lung, colon, and medullary thyroid carcinoma, and is under clinical investigation in various tumor types (Gozgit et al., 2012; 22238366, Gozgit et al., 2013; 23468082).

3.6.5 SAMPLE RELEVANT THERAPIES

The functional consequences of PDGFRA-T192T have not been analyzed by CellMax. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain.

3.6.6 BIOMARKER-MATCHED CLINICAL TRIALS

The functional consequences of PDGFRA-T192T have not been analyzed by CellMax. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain.

3.7. MTOR-F2202L (p.Phe2202Leu)

3.7.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
MTOR	- MUTN (seq): p.Phe2202Leu (F2202L)	The effect of MTOR-F2202L has not been determined by CellMax. Activation of the mTOR signaling pathway may lead to deregulated cell growth, proliferation, and transcription, which can subsequently lead to tumor formation (Zoncu et al., 2011; 21157483, Laplante and Sabatini, 2012; 22500797). The mTOR inhibitors everolimus and temsirolimus have been FDA approved for various indications (Zaytseva et al., 2012; 22261336). Inhibitors of mTORC1 and mTORC2, and dual inhibitors of PI3K and mTOR, have also shown activity in tumors displaying mTOR activity; these and other agents are being tested in clinical trials (Laplante and Sabatini, 2012; 22500797, Zoncu et al., 2011; 21157483, Fan et al., 2006; 16697955, Vilar et al., 2011; 21216931). However, MTOR-F2202L has not been analyzed by CellMax, and therefore the relevance of any therapeutic approaches is uncertain.

3.7.2 BIOLOGICAL RELEVANCE of MTOR-F2202L (p.Phe2202Leu)

MTOR alterations in Sigmoid colon adenocarcinoma	
Molecular function	MTOR-F2202L has not been analyzed by CellMax; therefore its effect on protein function cannot be described.
Incidence in disease	Sigmoid colon adenocarcinoma samples have not been analyzed in COSMIC for mutations in MTOR. MTOR mutations have been reported in 6.0% (79/1309) of Colorectal adenocarcinoma samples analyzed in COSMIC (Sep 2016).

3.7.3 CLINICAL RELEVANCE of MTOR-F2202L (p.Phe2202Leu)

MTOR alterations in Sigmoid colon adenocarcinoma	
Role in disease	mTOR acts downstream of multiple pathways, including the PI3K/Akt pathway, and has been implicated in many cellular functions, including cell growth, proliferation, and survival (Zoncu et al., 2011; 21157483). Increased expression of MTOR mRNA or p-mTOR-positivity has been associated with presence of lymph node metastasis, advanced tumor stage, and poorly differentiated disease in colorectal carcinoma (CRC) samples (Alqurashi et al., 2013; 23773481, Wang et al., 2011; 22320958, Lu et al., 2015; 26171014).
Effect on drug sensitivity	Activation of mTOR may predict sensitivity to inhibitors of mTOR signaling, as well as to inhibitors of upstream signaling, including PI3K and Akt (Wagle et al., 2014; 24625776, Li et al., 2014; 25086744, Laplante and Sabatini, 2012; 22500797, Feng et al., 2005; 15928081). The mTOR inhibitors everolimus and temsirolimus are FDA-approved for certain indications and are in clinical trials in multiple tumor types (Zaytseva et al., 2012; 22261336). Other agents which target mTOR, including dual mTORC1/mTORC2 inhibitors and dual PI3K/mTOR inhibitors, are currently in preclinical and clinical development (Dienstmann et al., 2014; 24748656, Fumarola et al., 2014; 24863259, Kolev et al., 2015; 25432176). These and other agents, alone and in combination therapy, are currently in under investigation in multiple tumor types. However, the functional consequences of MTOR-F2202L have not been analyzed by CellMax. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain.

3.7.4 CLINICAL EVIDENCE in Sigmoid colon adenocarcinoma

MTOR alterations in Sigmoid colon adenocarcinoma	
FDA Approved	None.
Phase III Data	None.
Phase II Data	A Phase 2 trial of everolimus in heavily pretreated colorectal cancer patients reported no significant efficacy; however, patients were not selected according to mutational or activity status of any PI3K/Akt/mTOR pathway members (Ng et al., 2013; 23743569).
Phase I Data	A Phase 1 clinical trial of ridaforolimus in advanced solid tumors reported that the drug was generally well tolerated, with stable disease in 11/11 evaluable patients (including four colon and two rectal cancer patients) over a mean treatment duration of 9.6 weeks. The most common drug-related adverse events, occurring in more than 40% of patients, included stomatitis, proteinuria, leukopenia, hyperglycemia, and pyrexia (Liu et al., 2013; 23829943). Several Phase 1 trials of temsirolimus in combination with other therapies in patients with solid tumors have reported clinical benefit in terms of complete and partial responses in 2.5-11% of patients and stable disease in 4.8-56% of patients (Ganesan et al., 2013; 23982248, Wang-Gillam et al., 2014; 24916546, Kyriakopoulos et al., 2015; ASCO 2015, Abstract 2554, Chiu et al., 2016; 26686201, Khawaja et al., 2016; 27014780). A Phase 1b study of apitolisib in combination with capecitabine (arm A, n=19) or in combination with mFOLFOX6 plus bevacizumab (arm B, n=22) in 41 patients with solid tumors, including an expansion cohort of 11 colorectal cancer patients in arm B, reported two confirmed partial responses in arm A and three partial responses (two confirmed) in the escalation stage in arm B. In the colorectal cancer expansion cohort, three confirmed partial responses (two confirmed) and one disease control sustained for 462 days were reported. Treatment was found to be well-tolerated (Rosen et al., 2014; EORTC 2014. Abstract 382). A Phase 1 dose escalation trial of CC-223 in 28 patients with solid tumors and multiple myeloma reported one partial response of 220 days in a breast cancer patient, stable disease in eight patients (lasting 36-168 days), and progressive disease in 12 patients (Bendell et al., 2015; 26177599). A Phase 1 clinical trial of INK128 in 115 advanced, solid tumor patients reported partial response in 2/10 renal cancer patients assessed, and stable disease for greater than or equal to six cycles in five study patients (Infante et al., 2013; AACR 2013, Abstract C252). An ongoing Phase 1 clinical trial of INK128 in combination with bevacizumab in 36 patients with recurrent glioblastoma or other advanced solid tumors has reported one complete response in a glioblastoma patient, partial responses in three glioblastoma and three ovarian carcinoma patients, and stable disease in six glioblastoma, eight ovarian, and two endometrial carcinoma patients (Nayak et al., 2016; ASCO 2016, Abstract 2013). A Phase 1 clinical trial of AZD2014 with paclitaxel reported RECIST partial response in 3/12 patients evaluated, including 2 patients with taxane-pretreated ovarian cancer and one with docetaxel-pretreated squamous non-small cell lung cancer (Roda et al., 2014; ASCO 2014, Abstract 2607). A Phase 1 study in advanced solid tumor patients reported that PF-05212384 treatment resulted in stable disease in 35% (27/77) of patients, including eight patients that experienced stable disease lasting longer than six months. Partial response (PR) was observed in 3% (2/77) of cases (with a third unconfirmed PR); treatment was well tolerated, with no grade 4/5 adverse events noted at any treatment dose (Shapiro et al., 2015; 25652454).
Preclinical	One preclinical study reported that INK128 reduced tumor growth and delayed formation of tumors in colorectal cancer samples transplantable in animal models (Shibuya et al., 2015; 25591719). Another preclinical study reported that INK128 inhibited cell survival and migration of colorectal cancer cell lines, and inhibited the survival of primary cultured colon cancer cells; co-administration of low-dose INK128 with 5-fluorouracil reduced cell survival and tumor growth in a colorectal cancer cell line and xenograft mouse model, respectively, compared to either single agent (Li et al., 2015; 25692620). A preclinical study reported that the dual mTORC1-mTORC2 inhibitor AZD2014 was able to suppress cellular growth and inhibit the activation of both mTORC1 and mTORC2 in colorectal cancer cell lines. Moreover, AZD2014 was able to suppress tumor growth and improve survival in a colorectal cancer xenograft model (Huo et al., 2014; 24309100). A preclinical study reported that PF-05212384 (PKI-587) inhibited the growth of the HCT116 colorectal cancer cell line, which harbors KRAS and PIK3CA mutations, but had no effect on tumor growth in a HCT116 xenograft mouse model; combination therapy with PF-05212384 and irinotecan significantly inhibited tumor growth compared to treatment with either single agent (Mallon et al., 2011; 21325073).

3.7.5 SAMPLE RELEVANT THERAPIES

The functional consequences of MTOR-F2202L have not been analyzed by CellMax. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain.

3.7.6 BIOMARKER-MATCHED CLINICAL TRIALS

The functional consequences of MTOR-F2202L have not been analyzed by CellMax. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain.

3.8. BRCA2-S2012S (p.Ser2012Ser)

3.8.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
BRCA2	- MUTN (seq): p.Ser2012Ser (S2012S)	The effect of BRCA2-S2012S has not been determined by CellMax. Alterations in BRCA2 frequently result in the loss of the tumor suppressor function of the Brca2 protein, disrupting DNA repair processes and leading to an accumulation of DNA damage (Yang et al., 2002; 12228710). There are no approved targeted therapies to address BRCA2 alterations at this time. BRCA2 alterations may predict sensitivity to DNA-damaging drugs, such as cisplatin and carboplatin, and to poly(ADP-ribose) polymerase (PARP) inhibitors (Banerjee and Kaye, 2011; 21913063, Rios and Puhalla, 2011; 22106552). The PARP inhibitor olaparib has been approved by the FDA for use in advanced ovarian cancer patients with germline BRCA1 or BRCA2 mutations (Ledermann et al., 2014; 24882434, Kaufman et al., 2015; 25366685, Oza et al., 2015; 25481791). However, BRCA2-S2012S has not been analyzed by CellMax, and therefore the relevance of any therapeutic approaches is uncertain.

3.8.2 BIOLOGICAL RELEVANCE of BRCA2-S2012S (p.Ser2012Ser)

BRCA2 alterations in Sigmoid colon adenocarcinoma	
Molecular function	BRCA2-S2012S has not been analyzed by CellMax; therefore its effect on protein function cannot be described.
Incidence in disease	Sigmoid colon adenocarcinoma samples have not been analyzed in COSMIC for mutations in BRCA2. BRCA2 mutations have been reported in 5.3% (59/1112) of Colorectal adenocarcinoma samples analyzed in COSMIC (Sep 2016).

3.8.3 CLINICAL RELEVANCE of BRCA2-S2012S (p.Ser2012Ser)

BRCA2 alterations in Sigmoid colon adenocarcinoma	
Role in disease	Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis (Holloman, 2011; 21731065). BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers (Bougie and Weberpals, 2011; 22312502, Nathanson and Domchek, 2011; 21034216, Breast Cancer Linkage Consortium 1999; 10433620, Hahn et al., 2003; 12569143, Monnerat et al., 2007; 17624602, Zhang et al., 2009; 19070627, Casula et al., 2009; 19799798, Moran et al., 2012; 22187320, Cruz et al., 2011; 22025144). Two large-scale studies have reported that BRCA1 germline mutation was associated with increased risk of colorectal carcinoma, but that BRCA2 germline mutation was not associated with increased risk (Kadouri et al., 2007; 17307836, Phelan et al., 2014; 24292448, Sopik et al., 2015; 25195694).
Effect on drug sensitivity	There are no approved targeted therapies that directly target BRCA2 alterations at this time. BRCA2 alterations may predict sensitivity to DNA-damaging drugs, such as cisplatin and carboplatin, and to poly(ADP-ribose) polymerase (PARP) inhibitors (Banerjee and Kaye, 2011; 21913063, Rios and Puhalla, 2011; 22106552, Burgess and Puhalla, 2014; 24579064). PARP inhibitors are currently under investigation in both preclinical and clinical studies (Steffen et al., 2013; 24392349). The PARP inhibitor olaparib has been approved by the FDA for use in advanced ovarian cancer patients with germline BRCA1 or BRCA2 mutations (Kaufman et al., 2015; 25366685, Kim et al., 2015; 26187614). There is some evidence to suggest that both somatic and germline BRCA1 or BRCA2 mutations may predict sensitivity to PARP inhibitors (Ledermann et al., 2014; 24882434, Burgess and Puhalla, 2014; 24579064, Hennessy et al., 2010; 20606085). However, the functional consequences of BRCA2-S2012S have not been analyzed by CellMax. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain.

3.8.4 CLINICAL EVIDENCE in Sigmoid colon adenocarcinoma

BRCA2 alterations in Sigmoid colon adenocarcinoma	
FDA Approved	None.
Phase III Data	None.
Phase II Data	A Phase 2 trial of olaparib in 20 patients with microsatellite stable (MSS) colorectal cancer (CRC) and 13 with CRC with high-level microsatellite instability (MSI) has reported no complete or partial responses, with a median progression-free survival for all patients of 1.84 months; similar median progression-free and overall survival times were noted regardless of MSS or MSI status (Leichman et al., 2016; 26786262).
Phase I Data	A Phase 1 study of olaparib in 60 patients with advanced solid tumors (22 with BRCA1 or BRCA2 germline mutation) noted few adverse effects and some anti-tumor activity was observed, but only in those patients with BRCA1 or BRCA2 germline mutations (Fong et al., 2009; 19553641). A Phase 1 clinical trial of olaparib in combination with irinotecan in 25 patients with advanced CRC has reported a lack of anti-tumor efficacy, with stable disease as the best response in 36% (9/25) of patients; continuous olaparib administration was not tolerable (Chen et al., 2016; 27075016). A Phase 1 trial of niraparib in patients with advanced solid tumors has reported partial responses in 50% (2/4) of breast cancer patients with germline BRCA1/2 mutations and in 40% (8/20) of ovarian cancer patients with BRCA1/2 mutations, as well as anti-tumor activity in sporadic high-grade serous ovarian cancer, non-small-cell lung cancer, and prostate cancer (Sandhu et al., 2013; 23810788). A Phase 1 trial of talazoparib (BMN-673) enrolled 39 patients, including subjects with ovarian/primary peritoneal, breast, pancreatic, colon and prostate cancer, of which 25 harbored BRCA1 (17) or BRCA2 (8) mutations. Talazoparib was reported to be well tolerated and responses were reported in 65% (11/17) of BRCA1/2 mutation carrying ovarian/peritoneal cancer patients as well as in 33% (2/6) of breast cancer subjects with a BRCA1/2-mutation (De Bono et al., 2013; ASCO 2013, Abstract 2580). In a Phase 1 study of veliparib and cyclophosphamide in patients with refractory solid tumors and lymphomas, 20% (7/35) of patients exhibited partial responses and 17.1% (6/35) of patients exhibited stable disease for at least six treatment cycles; in patients with BRCA mutations, 46.2% (6/13) of patients exhibited partial responses and 23.1% (3/13) of patients exhibited prolonged stable disease (Kummar et al., 2012; 22307137). A Phase 1b study of veliparib (V) in combination with bendamustine (B) in patients with solid tumors, B-cell lymphoma, or myeloma reported a median progression free survival (PFS) of 6.9 months, an overall response rate (ORR) of 71% (5/7), and a complete response rate (CRR) of 57% (4/7) in seven evaluable lymphoma patients. An expansion cohort in seven additional patients with CD20+ B-cell lymphoma treated with VB + rituximab (VBR) reported an ORR and CRR of 86% (6/7) and 71% (5/7), respectively. A median PFS had not been established after 12.4 months, at time of abstract publication. The most common grade 3 and higher toxicities reported overall in the study included lymphopenia, anemia, and neutropenia (Soumerai et al., 2015; ASH 2015, Abstract 2691). A Phase 1 trial has reported that the combination treatment of rucaparib and temozolomide was well tolerated; the combination showed inhibition of PARP activity and increased single strand DNA breaks in solid tumors. Preliminary activity was also demonstrated, with a complete and a partial response in melanoma patients, and one partial response in a patient with a desmoid tumor. Stable disease lasting at least six months was also noted in the single leiomyosarcoma patient (Plummer et al., 2008; 19047122).
Preclinical	A preclinical study has reported that niraparib treatment of microsatellite stable and instable colorectal cancer cell lines inhibits proliferation and enhances the anti-proliferative effects of SN-38 in vitro, as well as further delays tumor regrowth when combined with irinotecan in vivo, compared with irinotecan treatment alone (Genther et al., 2015; 25685067). A preclinical study reported that veliparib increased the sensitivity of colorectal cancer cells and xenograft tumors to radiation and chemotherapeutics (Shelton et al., 2013; 23540347).

3.8.5 SAMPLE RELEVANT THERAPIES

The functional consequences of BRCA2-S2012S have not been analyzed by CellMax. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain.

3.8.6 BIOMARKER-MATCHED CLINICAL TRIALS

The functional consequences of BRCA2-S2012S have not been analyzed by CellMax. Therefore, the relevance of any available therapies and clinical trials targeting this alteration is uncertain.

4. Variants of Unknown Significance - No CellMaxLife Analysis Provided

Gene	Protein Sequence Change	Coding Sequence Change	Map Location
MET	p.Ala1339Ala	c.4017G>A	chr7:116436022
MET	p.Pro1364Pro	c.4092G>A	chr7:116436097
BRCA2	p.Asn289His	c.865A>C	chr13:32906480
BRCA2	p.Ser455Ser	c.1365A>G	chr13:32906980
BRCA2	p.His743His	c.2229T>C	chr13:32910721
BRCA2	p.Asn991Asp	c.2971A>G	chr13:32911463
BRCA2	p.Lys1132Lys	c.3396A>G	chr13:32911888
BRCA2	p.Ser2414Ser	c.7242A>G	chr13:32929232
TP53	p.Pro72Arg	c.215C>G	chr17:7579472
KEAP1	p.Leu471Leu	c.1413C>G	chr19:10600442
APC	p.Val1414Ter	c.4239delG	chr5:112175529

The variants in this table were identified by the laboratory as variants of unknown significance. CellMax analysis was not requested for these variants.

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6. APPENDIX: Glossary of Biomarkers

Marker	Gene Name	Description
APC	APC	APC (adenomatous polyposis coli) encodes the protein Apc, a tumor suppressor with critical roles in regulating cell division and adhesion. Apc interacts with beta-catenin and controls signaling in the Wnt pathway, which helps regulate embryonic development and cell differentiation.
BRCA2	BRCA2	The BRCA2 gene encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51.
EGFR	EGFR	EGFR encodes the Epidermal growth factor receptor (Egfr), a receptor tyrosine kinase that passes biochemical messages to the cell that stimulate it to grow and divide. Amplification, mutation, and overexpression of EGFR may cause excessive proliferation and tumor formation.
MTOR	MTOR	MTOR encodes the mechanistic target of rapamycin protein (mTOR, formerly known as mammalian target of rapamycin). mTOR is an intracellular serine/threonine protein kinase and a member of the phosphatidylinositol 3-kinase-(PI3K) related kinase family, and regulates several cellular processes by integrating signals from multiple upstream pathways, including the PI3K/Akt pathway. Constitutive activation of mTOR has been reported in multiple cancer types and may occur via mutations in upstream pathways, such as the PI3K pathway. In addition, loss of p53 has been reported to lead to oncogenic activation of mTOR.
PDGFRA	PDGFRA	PDGFRA encodes the tyrosine kinase receptor human platelet-derived growth factor receptor alpha (Pdgfr-alpha), one of three Pdgf receptors, which is structurally similar to c-Kit. Binding of cognate ligands (PDGFA or PDGFB) activates several signaling pathways, including PI3K and MAPK.
TP53	TP53	The TP53 gene encodes the tumor suppressor p53. p53 is involved in the DNA-damage cell cycle checkpoint; it causes a cell-cycle arrest when it senses DNA damage. p53 can also activate DNA repair genes, or induce apoptosis in the presence of DNA damage. It has been called the "cellular gatekeeper".

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