IBM **Watson for Genomics**

Version 38.155

SAMPLE REPORT

IBM PROPRIETARY

REPORT FOR: **IBM Watson Demo**

ANALYZED ON: **May 23 15:46:46 CDT 2018**

CASE: **NSCLC**

AGE: **60**

GENDER: **Male**

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IBM Watson Demo

SUMMARY

DIAGNOSIS: **Non-Small Cell Lung Carcinoma** AGE: **60** GENDER: **Male**

The L858R mutation in gene EGFR is a strong predictive marker of response to treatment with afatinib, erlotinib, gefitinib and osimertinib. In addition, mutations in CDKN2A resulting in activation of the CDK signaling pathway and mutations in RICTOR resulting in activation of the MTOR/PI3K signaling pathway have been detected. Treatment strategies with drugs targeting one or both of these pathways may be therapeutic options for this patient.

The L858R mutation in gene EGFR is a predictor of good prognosis in Non-Small Cell Lung Carcinoma.

5 Actionable Alterations	4 FDA Approved for Non-Small Cell Lung Carcinoma	30 Therapies with Clinical Trial(s)	0 FDA Approved for Other Indication(s)
EGFR *L858R*	1 Afatinib Erlotinib Gefitinib Osimertinib	Phase 3 Trial 4 Icotinib Hydr... Phase 2 Trial 4 AP32788 CK-101 EGF816 Sym013 Phase 1 Trial 3A Dacomitinib Vandetanib 4 HLX07 JNJ-61186372	-
CDKN2A *Loss*	-	Phase 2 Trial 3A Abemaciclib 3B Palbociclib Ribociclib Phase 1 Trial 4 CDKI AT7519	-

RICTOR	*Amplification*	-	Phase 2 Trial 3A Sapanisertib 4 Sirolimus Temsirolimus Phase 1 Trial 3A PQR309 4 Everolimus Gedatolisib LY3023414	-
ATR	*Loss*	-	Phase 2 Trial 3B Olaparib 4 BGB-290 Talazoparib Veliparib	-
DNMT3A	*Loss*	-	Phase 2 Trial 4 Mocetinostat Phase 1 Trial 3B Panobinostat 4 ACY-241 Belinostat KA2507 Romidepsin	-

For the complete molecular diagram see last page.

ACTIONABLE ALTERATIONS WITH THERAPIES

EGFR	*L858R*	4	FDA Approved for Non-Small Cell Lung Carcinoma	9	Therapies with Clinical Trial(s)	0	FDA Approved for Other Indication(s)

Gene Summary: EGFR is a widely expressed transmembrane receptor tyrosine kinase of the ERBB family. EGFR signaling is initiated by ligand binding to the extracellular ligand-binding domain. This initiates receptor homo-/hetero-dimerization and autophosphorylation by the intracellular kinase domain, resulting in receptor activation and the initiation of downstream signaling cascades that regulate growth, survival, proliferation, and differentiation. (PubMed: 16729045). EGFR is involved by increased expression, amplification and/or expression of an aberrant protein in a high proportion of GBM, NSCLC, HNSCC, bladder and GI cancers. Numerous mutants of the gene have been identified and investigated for their role in cancerogenesis, role in sensitivity/resistance to targeted therapy.

L858R Px **:** L858R is the predominant single-point mutation in exon 21, which encodes part of the tyrosine kinase domain, and it has the highest prevalence of any missense activating mutation accounting for more than 40% of all EGFR tyrosine kinase activating mutations (PubMed: 19922469). This mutation confers sensitivity of EGFR inhibitors like Erlotinib and gefitinib and related agents. Compared to patients without EGFR mutation, those with EGFR-mutated tumors display a longer progression-free survival on EGFR TKI therapy than those who receive chemotherapy. (PubMed: 19692680, 20573926, 21670455). In NSCLC grades I to III, patients with EGFR L858R mutation have better OS (HR 0.51, p<0.001) than patients with EGFR wildtype lung cancers when treated with regimens that include EGFR-targeting therapies like Erlotinib, Afatinib and Gefitinib (PubMed: 22810899, 23154553) (NCCN guidelines, 2017).
Database Reference: rs121434568

Afatinib 1

TARGET: **EGFR**

FDA Approved for Non-Small Cell Lung Carcinoma

FDA Label: For the first-line treatment of patients with metastatic NSCLC, whose tumors have non-resistant EGFR mutations as detected by an FDA-approved test.
The approval of Afatinib was based on demonstration of durable responses in a subset of 32 afatinib-treated patients with metastatic NSCLC harboring non-resistant EGFR mutations (S768I, L861Q, and/or G719X) other than exon 19 deletions or exon 21 L858R substitutions enrolled in either the LUX-Lung 2, LUX-Lung 3, or LUX-Lung 6 clinical trial. Non-resistant EGFR mutations were identified using either Sanger sequencing or by the therascreen EGFR RGQ PCR Kit. EGFR mutations included in the non-resistant subgroup demonstrated inhibition of cellular proliferation in EGFR-mutant dependent cell lines at clinically relevant concentrations of afatinib. All patients in the subgroup received afatinib 40 mg or 50 mg orally once daily. The confirmed ORR, as assessed by independent radiology review, was 66%. Among the 21 responders, the proportion of patients with response duration of ≥12 months was 52% and the proportion with response durations of ≥18 months was 33%. The most common adverse reactions reported for afatinib (≥20%) across clinical trials are diarrhea, rash/acneiform dermatitis, stomatitis, paronychia, dry skin, decreased appetite, nausea, vomiting, and pruritus.

Erlotinib 1

TARGET: **EGFR**

FDA Approved for Non-Small Cell Lung Carcinoma

FDA Label: For the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.
FDA approval of Erlotinib was based on the results of double-blind, placebo-controlled clinical studies enrolling 731 patients with confirmed locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients were randomized to receive Erlotinib or placebo orally once daily. With Median OS in the Erlotinib arm was 6.7 months vs 4.7 months in the placebo groups. One-year survival rates for Erlotinib were 31.2% vs 21.5%. In the EGFR-positive subset, Erlotinib produced a median survival duration of 10.7 months versus 3.8 months, while no survival effect in the Erlotinib group was observed in the EGFR-negative subset (PubMed: 16079312). The significance of EGFR activating mutations for efficacy of the drug was demonstrated by the result of the IUNO trial, a randomized, double-blind trial of erlotinib as maintenance therapy in 643 patients with advanced NSCLC who had not experienced disease progression or unacceptable toxicity during four cycles of platinum-based first-line chemotherapy. Patients whose tumors harbored activating EGFR mutations (exon 19 deletions or exon 21 L858R mutations) were excluded from this trial. Patients were randomized to receive erlotinib or placebo orally once daily. Following progression on initial therapy, patients were eligible to enter an open-label phase. 50% of patients randomized to erlotinib entered the open-label phase and received chemotherapy, while 77% of patients randomized to placebo entered the open-label phase and received erlotinib. The primary endpoint was OS. Survival following treatment with erlotinib was not better than placebo administered as maintenance in patients with metastatic NSCLC tumors not harboring EGFR-activating mutations. No difference in PFS between the erlotinib arm and the placebo arm was observed.

Gefitinib 1

TARGET: **EGFR**

FDA Approved for Non-Small Cell Lung Carcinoma

FDA Label: For the first-line treatment of patients with or metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.
The FDA approved gefitinib for the treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutation as detected by an FDA-approved test. The approval was based on the results of a multicenter, single-arm, open-label clinical study of 106 treatment-naïve patients with metastatic EGFR mutation-positive NSCLC who received gefitinib, 250 mg daily, until disease progression or intolerable toxicity. ORR was 50% [95% confidence interval (CI), 41-59] with a median duration of response of 6.0 months. These efficacy results were supported by a retrospective analysis of a randomized, open-label trial on 1,217 patients with metastatic NSCLC. 186 (15%) of patients were retrospectively determined to be EGFR positive and evaluable for assessment. PFS for gefitinib-treated patients was 10.9 months and 7.4 months for the carboplatin/paclitaxel-treated patients. In addition, ORR was 67% (95% CI: 56, 77) with a DoR of 9.6 months for gefitinib-treated patients versus a DoR of 5.5 months for carboplatin/paclitaxel-treated patients (PubMed: 26980062).

Osimertinib 1

TARGET: **EGFR**

FDA Approved for Non-Small Cell Lung Carcinoma

FDA Label: For the first-line treatment of patients with metastatic NSCLC, whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations.
The approval of osimertinib was based on a randomized, double-blind trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received systemic treatment for advanced disease. Patients were randomized (1:1) to receive osimertinib (80 mg/d) or SOC treatment consisting of either gefitinib 250 mg ,or erlotinib 150 mg, orally once daily. Of those randomized to SOC, 20% received osimertinib as the next line of therapy. The estimated median PFS was 18.9 months (95% CI: 15.2, 21.4) in the osimertinib arm and 10.2 months (95% CI: 9.6, 11.1) in the SOC arm (hazard ratio 0.46 (95% CI: 0.37, 0.57), p<0.0001). The confirmed ORR was 77% for the osimertinib arm and 69% for the SOC arm. The estimated median response durations were 17.6 and 9.6 months, respectively. At the time of the primary PFS analysis, there were too few deaths to estimate or compare survival outcomes. Adverse events of grade 3 or higher were less frequent with osimertinib than with standard EGFR-TKIs (34% vs. 45%). The most common adverse reactions (>20% of patients treated with osimertinib) were diarrhea, rash, dry skin, nail toxicity, stomatitis, and decreased appetite. The most common serious adverse reactions (≥1%) were pneumonia (2.9%), ILD/pneumonitis (2.1%), and pulmonary embolism (1.8%) (PubMed: 29151359).

Icotinib Hydrochloride 4

TARGET: **EGFR**

Therapy with Clinical Trial(s)

Mechanism of Action: An orally available quinazoline-based inhibitor of epidermal growth factor receptor (EGFR), with potential antineoplastic activity. Icotinib selectively inhibits the wild-type and several mutated forms of EGFR tyrosine kinase. This may lead to an inhibition of EGFR-mediated signal transduction and may inhibit cancer cell proliferation. EGFR, a receptor tyrosine kinase, has been upregulated in a variety of cancer cell types.

NCT #	Clinical Trials	Phase
NCT03008109	Short-term Injection of Recombinant Human Endostatin Plus EGFR-TKI as a Treatment of EGFR Mutation-positive Advanced Non-small Cell Lung Cancer	3 Not yet recruiting
NCT03153358	Icotinib Combined With Stereotactic Body Radiation Therapy (SBRT) for Patients With Metastatic Non-squamous Non-small Cell Lung Cancer With EGFR Sensitive Mutation	2 Not yet recruiting
NCT02788058	A Phase II Trial of Hypofractionated Radiotherapy for Limited Metastatic NSCLC Harboring Sensitizing EGFR Mutations After First Line TKI Therapy	2 Not yet recruiting

AP32788 4

TARGET: **EGFR**

Therapy with Clinical Trial(s)

Mechanism of Action: An orally available inhibitor of specific mutant forms of both human epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2; ERBB2), with potential antineoplastic activity. Upon oral administration, EGFR/HER2 inhibitor AP32788 specifically and irreversibly binds to and inhibits certain mutant forms of EGFR and HER2. This prevents EGFR- and HER2-mediated signaling and leads to cell death in EGFR mutant- and HER2 mutant-expressing tumor cells. EGFR and HER2, receptor tyrosine kinases mutated in many tumor cell types, play key roles in tumor cell proliferation and tumor vascularization.

Rationale

Preclinical activity of AP32788 was assessed in vitro by measuring viability of cell lines engineered to express 20 mutant variants of EGFR (n = 14) or ERBB2 (n = 6): 4 EGFR variants containing a common activating mutation with or without a T790M resistance mutation, 8 EGFR/ERBB2 variants containing an exon 20 activating insertion (eg, EGFR ASV, HER2 YVMA), and 8 EGFR/ERBB2 variants containing uncommon activating mutations (eg, EGFR G719A, ERBB2 G776V). Inhibition of WT EGFR was assessed by measuring effects on EGFR phosphorylation in cells that over-express WT EGFR. AP32788 inhibited all 14 mutant variants of EGFR, and all 6 mutant variants of ERBB2 at nanomolar concentrations more potently than it inhibited WT EGFR including all 8 variants with exon 20 activating insertions. In vivo efficacy was tested by oral dosing of AP32788 and shown to induce regression of patient-derived xenograft tumors (PDX) containing an EGFR exon 20 activating insertion and of xenografts consisting of engineered cells containing an ERBB2 exon 20 activating insertion (Gonzalvez et al. AACR 2016; abstract #2644)

NCT #	Clinical Trials	Phase
NCT02716116	A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor AP32788 in Non-Small Cell Lung Cancer	1 or 2

CK-101 4

TARGET: **EGFR**

Therapy with Clinical Trial(s)

Mechanism of Action: An orally available third-generation and selective inhibitor of certain epidermal growth factor receptor (EGFR) activating mutations, including the resistance mutation T790M, and the L858R and del 19 mutations, with potential antineoplastic activity. Upon administration, the EGFR mutant-specific inhibitor CK-101 specifically and covalently binds to and inhibits selective EGFR mutations, with particularly high selectivity against the T790M mutation, which prevents EGFR mutant-mediated signaling and leads to cell death in EGFR mutant-expressing tumor cells. Compared to some other EGFR inhibitors, CK-101 may have therapeutic benefits in tumors with T790M-mediated Drug resistance. This agent shows minimal activity against wild-type EGFR (WT EGFR), and does not cause dose-limiting toxicities that occur during the use of non-selective EGFR inhibitors, which also inhibit WT EGFR. EGFR, a receptor tyrosine kinase mutated in many tumor cell types, plays a key role in tumor cell proliferation and tumor vascularization.

Rationale

Preclinical studies of CK-101 have demonstrated selective inhibition of cell lines expressing both activating and resistance mutations. Single agent CK-101 significantly inhibited tumor growth in EGFR-mutated NSCLC tumor xenograft models, with no activity in a WT EGFR tumor xenograft model (Qian et al. AACR 2017; abstract #2078)

NCT #	Clinical Trials	Phase
NCT02926768	A Phase I/II, Open-Label, Safety, Pharmacokinetic and Efficacy Study of Ascending Doses of Oral CK-101 in Patients With Advanced Solid Tumors	1 or 2

EGF816 4

TARGET: **EGFR**

Therapy with Clinical Trial(s)

Mechanism of Action: An orally available, irreversible, third-generation, mutant-selective epidermal growth factor receptor (EGFR) inhibitor, with potential antineoplastic activity. Upon oral administration, EGF816 covalently binds to and inhibits the activity of mutant forms of EGFR, including the T790M EGFR mutant, thereby preventing EGFR-mediated signaling. This may both induce cell death and inhibit tumor growth in EGFR-overexpressing tumor cells. EGFR, a receptor tyrosine kinase mutated in many tumor cell types, plays a key role in tumor cell proliferation and tumor vascularization. EGF816 preferentially inhibits mutated forms of EGFR including T790M, a secondarily acquired resistance mutation, and may have therapeutic benefits in tumors with T790M-mediated resistance when compared to other EGFR tyrosine kinase inhibitors. As this agent is selective towards mutant forms of EGFR, its toxicity profile may be reduced as compared to non-selective EGFR inhibitors which also inhibit wild-type EGFR.

NCT #	Clinical Trials	Phase
NCT03292133	A Phase 2 Study of EGF816 and Gefitinib in TKI-naïve EGFR-mutant Non-Small Cell Lung Cancer	2
NCT02335944	A Phase Ib/II, Multicenter, Open-label Study of EGF816 in Combination With INC280 in Adult Patients With EGFR Mutated Non-small Cell Lung Cancer.	1 or 2
NCT02900664	Phase Ib, Open-label, Multi-center Study to Characterize the Safety, Tolerability and Pharmacodynamics (PD) of PDR001 in Combination With CJM112, EGF816, Ilaris® (Canakinumab) or Mekinist® (Trametinib)	1

Sym013 4

TARGET: **EGFR**

Therapy with Clinical Trial(s)

Mechanism of Action: An antibody mixture composed of six humanized, immunoglobulin G1 (IgG1) monoclonal antibodies directed against three members of the human epidermal growth factor receptor (EGFR; HER) family: EGFR (HER1; ErbB1), HER2 (ErbB2) and HER3 (ErbB3), with potential antineoplastic activity. Upon administration of anti-EGFR/HER2/HER3 monoclonal antibody mixture Sym013, the six antibodies bind to non-overlapping epitopes on EGFR, HER2 and HER3, which prevents both ligand binding and receptor activation, and induce simultaneous down-modulation of EGFR, HER2 and HER3. This inhibits the activation of HER-dependent signaling pathways and HER-dependent tumor cell proliferation. Overexpression of the HER family plays a key role in many cancers; targeting multiple HER family members simultaneously may increase therapeutic efficacy.

Rationale

Preclinical studies have shown that Sym013 induces down-regulation of all ERBB family members in vitro and tit riggers a 30-60% reduction in cell growth in several cancer cell lines with EGFR, ERBB2, and/or ERBB3 expression (Francis et. Al.,AACR 2014; Abstract#4495).

NCT #	Clinical Trials	Phase
NCT02906670	An Open-label, Multicenter, Phase 1a/2a Trial Investigating the Safety, Tolerability and Antitumor Activity of Multiple Doses of Sym013, a mAb Mixture Targeting EGFR, HER2 and HER3, in Patients With Advanced Epithelial Malignancies	1 or 2

Dacomitinib 3A

TARGET: **EGFR**

Therapy with Clinical Trial(s)

Mechanism of Action: A highly selective, orally bioavailable small-molecule inhibitor of the HER family of tyrosine kinases with potential antineoplastic activity. Dacomitinib specifically and irreversibly binds to and inhibits human Her-1, Her-2, and Her-4, resulting in the proliferation inhibition and apoptosis of tumor cells that overexpress these receptors.

Rationale

Dacomitinib (PF00299804) is an irreversible pan-ERBB inhibitor that is characterized by irreversible binding to ATP pocket (PubMed: 18089823). In a Phase II study, 89 patients, including 45 patients with EGFR mutant, tyrosine kinase inhibitor-naive lung cancers, were treated with first-line Dacomitinib. The ORR was 95.5% (95% CI 83.2-98.9) in the patient population with EGFR activating mutations and 76.8% (95% CI 66.4-84.4) in the patient population as a whole (PubMed: 25456362). Other Phase II studies have determined that the 1-year PFS in EGFR-mutant patients is 77% (95% CI, 61-87%) (PubMed: 22753918, 25456362, 24501009). A Phase III study comparing Dacomitinib to Erlotinib in patients with NSCLC showed a hazard ratio of 0.707 for patients with exon 19 or exon 20 activating mutations, with a PFS of 14.6 months in the Dacomitinib group (95% CI, 7.4-NR) vs 9.6 months in the Erlotinib group (95% CI, 7.3-16.6) (PubMed: 26768165).

NCT #	Clinical Trials	Phase

NCT01920061	A Phase 1b Open-Label Three-Arm Multi-Center Study To Assess The Safety And Tolerability Of PF-05212384 ((PI3K/mTOR Inhibitor) In Combination With Other Anti-Tumor Agents	1

Vandetanib 3A

TARGET: **EGFR**

Therapy with Clinical Trial(s)

Mechanism of Action: An orally bioavailable 4-anilinoquinazoline. Vandetanib selectively inhibits the tyrosine kinase activity of vascular endothelial growth factor receptor 2 (VEGFR2), thereby blocking VEGF-stimulated endothelial cell proliferation and migration and reducing tumor vessel permeability. This agent also blocks the tyrosine kinase activity of epidermal growth factor receptor (EGFR), a receptor tyrosine kinase that mediates tumor cell proliferation and migration and angiogenesis.

Rationale

A randomized phase III study assessed the efficacy of Vandetanib plus docetaxel versus placebo plus docetaxel as second line treatment of advanced NSCLC. 14% of evaluable samples were EGFR mutation positive, 35% were EGFR FISH positive, and 88% were EGFR protein expression positive. Compared with the overall study population, in which PFS but not OS were significantly improved with Vandetanib, there was greater relative clinical benefit for patients with EGFR mutation or FISH-positive tumor samples who received Vandetanib (PubMed: 25057173).

NCT #	Clinical Trials	Phase
NCT01582191	A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer	1

HLX07 4

TARGET: **EGFR**

Therapy with Clinical Trial(s)

Mechanism of Action: Not available.

Rationale

HLX07 has shown strong affinity towards EGFR in biochemical and cellular studies where it causes cell death through the induction of antibody-dependent cell-mediated toxicity. In addition, xenogenic studies have demonstrated that HLX07 inhibits tumor cell growth as single agent, and in combination with gemcitabine or cisplatin, was more active than either agent alone (http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e14078).

NCT #	Clinical Trials	Phase

NCT02648490	A Prospective,Open-label, Dose Escalation Phase 1 Study to Investigate the Safety, and Tolerability and to Determine the Maximum Tolerated Dose and Recommended Phase 2 Dose of a HLX07, in Patients With Advanced Solid Cancers.	1

JNJ-61186372 4

TARGET: **EGFR**

Therapy with Clinical Trial(s)

Mechanism of Action: A human bispecific antibody targeting both epidermal growth factor receptor EGFR and hepatocyte growth factor receptor (HGFR; cMet), with potential antineoplastic activity. Upon administration, anti-EGFR/c-Met bispecific antibody JNJ-61186372 simultaneously targets and binds to wild-type or certain mutant forms of both EGFR and cMet expressed on cancer cells, thereby preventing receptor phosphorylation. This prevents the activation of both EGFR- and cMet-mediated signaling pathways. In addition, binding results in receptor degradation, which further inhibits EGFR- and cMet-mediated signaling. JNJ-61186372 also causes antibody-dependent cellular cytotoxicity (ADCC). Altogether, this results in the inhibition of tumor cell proliferation. EGFR and cMet, both upregulated or mutated in a variety of tumor cell types, play key roles in tumor cell proliferation.

NCT #	Clinical Trials	Phase
NCT02609776	A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects With Advanced Non-Small Cell Lung Cancer	1

CDKN2A	*Loss*	0	FDA Approved for Non-Small Cell Lung Carcinoma	4	Therapies with Clinical Trial(s)	0	FDA Approved for Other Indication(s)

Gene Summary: The CDKN2A gene encodes for two proteins, INK4A and ARF, which are generated through the use of shared coding regions and alternative reading frames. Both proteins act as tumor suppressors by regulating the cell cycle. INK4A inhibits cyclin dependent kinases 4 and 6 (CDK4 and CDK6) and thereby activates the retinoblastoma (RbB1) family of proteins, which block traversal from G1 to S-phase. Thus, it acts as a negative regulator of the proliferation of normal cells. ARF is an activator of the TP53 tumor suppressor protein. Mutations resulting in impaired or loss of function of CDKN2A are involved in the formation of tumors in a wide range of tissues and CDKN2A is an important tumor suppressor gene(PubMed: 7550353, 8153634, 8589035)

CNV Loss: CDKN2A codes for the protein p16, which has roles in inhibiting CDK4, CDK6 and Cyclin D type proteins. Loss or deletion of CDKN2A results in the inability to sequester the activity of CDK4 and CDK6, allowing for phosphorylation of the retinoblastoma protein (RB) which controls cell cycle progression beyond G1 phase and decreased expression of CDKN2A in various cell lines leads to dysregulated cell cycle progression and cellular proliferation (PubMed: 9516223).

Abemaciclib 3A

TARGETS: **CDK6, CDK4**

Therapy with Clinical Trial(s)

Mechanism of Action: An orally available cyclin-dependent kinase (CDK) inhibitor that targets the CDK4 (cyclin D1) and CDK6 (cyclin D3) cell cycle pathway, with potential antineoplastic activity. Abemaciclib specifically inhibits CDK4 and 6, thereby inhibiting Retinoblastoma (Rb) protein phosphorylation in early G1. Inhibition of Rb phosphorylation prevents CDK-mediated G1-S phase transition, thereby arresting the cell cycle in the G1 phase, suppressing DNA synthesis and inhibiting cancer cell growth. Overexpression of the serine/threonine kinases CDK4/6, as seen in certain types of cancer, causes cell cycle deregulation.

Rationale

In a trial, which tested the clinical activity of Abemaciclib in heavily pretreated patients with NSCLC (median 4, range 1-10 prior systemic therapies), partial response was achieved for one patient with KRAS-mutant NSCLC and for one patient with KRAS wild-type squamous NSCLC bearing copy-number loss of CDKN2A (PubMed: 27217383).

NCT #	Clinical Trials	Phase
NCT02308020	A Phase 2 Study of Abemaciclib in Patients With Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-small Cell Lung Cancer, or Melanoma	2
NCT01655225	A Phase 1 First-in-Human Dose Study of LY3023414 in Patients With Advanced Cancer	1
NCT02784795	A Phase 1b Study of LY3039478 in Combination With Other Anticancer Agents in Patients With Advanced or Metastatic Solid Tumors	1
NCT02791334	A Phase 1a/1b Study of a Novel Anti-PD-L1 Checkpoint Antibody (LY3300054) Administered Alone or in Combination With Other Agents in Advanced Refractory Solid Tumors (Phase 1a/1b Anti-PD-L1 Combinations in Tumors-PACT)	1
NCT02779751	A Phase 2 Study of Abemaciclib in Combination With Pembrolizumab for Patients With Stage IV Non-Small Cell Lung Cancer or Hormone Receptor Positive, HER2 Negative Breast Cancer	1
NCT02857270	A Phase 1 Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer	1

Palbociclib 3B

TARGETS: **CDK6, CDK4**

Therapy with Clinical Trial(s)

Mechanism of Action: An orally available cyclin-dependent kinase (CDK) inhibitor with potential antineoplastic activity. Palbociclib selectively inhibits cyclin-dependent kinase 4 (CDK4) and 6 (CDK6), thereby inhibiting Retinoblastoma (Rb) protein phosphorylation early in the G1 phase leading to cell cycle arrest. This suppresses DNA replication and decreases tumor cell proliferation. CDK4 and 6 are serine/threonine kinases that are upregulated in many tumor cell types and play a key role in the regulation of cell cycle progression.

Rationale

Clinical evidence for the activity of Palbociclib against tumors with loss of CDKN2A is provided by two cases reports. In the first report, a patient with HR+/ERBB2-negative metastatic breast cancer and CDKN2A loss was treated with Palbociclib as participant in an expanded-access program and started Palbociclib 125 mg daily for 21 days of a 28-day cycle and letrozole 2.5 mg daily. PR was noted on day 15 of the second treatment cycle (PubMed: 26715889). In the second report, a patient with metastatic carcinoma of the collecting duct and demonstrated loss of CDKN2A and CDKN2B, was treated with a single agent Palbociclib at a dose of 125 mg daily, 3 weeks on, 1 week off. After 3 months, a partial response in pulmonary metastases was noted. Moreover, the patient had substantial symptomatic relief, correlating with a decrease in the extent of bilateral pleural effusions. At the time of publication, at 6 months post start of treatment, this clinical response was maintained, with marked improvement in shortness of breath and improvement in functional status (Pal et al; JCO Precision Oncology 2017).

NCT #	Clinical Trials	Phase
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	2
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	2
NCT02349633	Phase 1/2 Open-Label Study Of PF-06747775 (Epidermal Growth Factor Receptor T790m Inhibitor) In Patients With Advanced Epidermal Growth Factor Receptor Mutant (Del 19 Or L858R ± T790M) Non-Small Cell Lung Cancer	2
NCT03065387	Phase I Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/Amplification or HER3/4 Mutation	1
NCT02897375	A Phase 1 Study of Palbociclib in Combination With Cisplatin or Carboplatin in Advanced Solid Malignancies	1

Ribociclib 3B

TARGETS: **CDK6, CDK4**

Therapy with Clinical Trial(s)

Mechanism of Action: An orally available cyclin-dependent kinase (CDK) inhibitor targets at cyclin D1/CDK4 and cyclin D3/CDK6 cell cycle pathway, with potential antineoplastic activity. Ribociclib specifically inhibits CDK4 and 6, thereby inhibiting Retinoblastoma (Rb) protein phosphorylation. Inhibition of Rb phosphorylation prevents CDK-mediated G1-S phase transition, thereby arresting the cell cycle in the G1 phase, suppressing DNA synthesis and inhibiting cancer cell growth. Overexpression of CDK4/6, as seen in certain types of cancer, causes cell cycle deregulation.

Rationale

The initial phase I study of single-agent Ribociclib enrolled 128 patients with RB1-wildtype advanced solid tumors and lymphomas (NCT01237236). Among 110 evaluable patients, three had confirmed PRs: one being a patient with head and neck acinar carcinoma and CDKN2A loss (PubMed: 27542767).

NCT #	Clinical Trials	Phase
NCT02703571	A Phase I/II Study of Safety and Efficacy of Ribociclib (LEE011) in Combination With Trametinib (TMT212) in Patients With Metastatic or Advanced Solid Tumors	1 or 2
NCT03237390	Phase I Study of CDK4/6 Inhibitor Ribociclib (LEE011) Combined With Gemcitabine in Patients With Advanced Solid Tumors	1

CDKI AT7519 4

TARGETS: **CDK6, CDK4**

Therapy with Clinical Trial(s)

Mechanism of Action: An orally bioavailable small molecule with potential antineoplastic activity. AT7519M selectively binds to and inhibits cyclin dependent kinases (CDKs), which may result in cell cycle arrest, induction of apoptosis, and inhibition of tumor cell proliferation. CDKs are serine/threonine kinases involved in regulation of the cell cycle and may be overexpressed in some types of cancer cells.

Rationale

The CDKN2A gene encodes for two proteins, INK4A and ARF, which are involved in regulation of the cell cycle. INK4A inhibits cyclin-dependent kinases 4 and 6 (CDK4 and CDK6)(PubMed: 23279822), and inactivation of CDKN2A may result in partial loss of CDK4/6 inhibition and sensitivity to CDK inhibitors (PubMed: 26715889, 28283584). The association of the Drug with CDKN2A inactivation has not been clinically verified and is by pathway only.

NCT #	Clinical Trials	Phase
NCT02503709	A Phase 1 Trial of the Combination of the Heat Shock Protein-90 (HSP90) Inhibitor Onalespib (AT13387) and the Cyclin-Dependent Kinase (CDK) Inhibitor AT7519M in Patients With Advanced Solid Tumors	1

RICTOR *Amplification* | **0** FDA Approved for Non-Small Cell Lung Carcinoma | **7** Therapies with Clinical Trial(s) | **0** FDA Approved for Other Indication(s)

Gene Summary: RICTOR is a regulatory binding partner of the kinase mTOR and part of a rapamycin-insensitive and raptor-independent pathway (mTORC2). It functions upstream of Rho GTPases to regulate the actin cytoskeleton. RICTOR interacts with Cullin1-Rbx1 to form an E3 ubiquitin ligase complex, and promotes ubiquitination and degradation of SGK1. It is degraded through an FBXW7-mediated ubiquitination/proteasome mechanism and inactivation of FBXW7 results in stabilization and increased RICTOR levels (PubMed: 25897075). Amplification of RICTOR has been detected in a wide variety of cancer types and oncogenic activities of mTORC2 in the regulation of cancer cell migration, invasion, and metastasis in gliomas and in breast, ovarian, prostate, and colorectal cancers have been described (PubMed: 19185849, 20978191, 19934294). The GBM-associated oncogenic EGFRvIII variant stimulates mTORC2 kinase activity, which renders cells resistant to chemotherapy independent of AKT (PubMed: 22145100). Recently, glucose-dependent acetylation of RICTOR has been shown to promote resistance of glioblastoma cells to AKT-, PI3K-, and EGFR-targeted therapies in vitro and in vivo (PubMed: 26170313).

CNV Amplification: The pathologic relevance of RICTOR amplification has been addressed by overexpression in hematopoietic cells resulting in growth factor-independent growth. Furthermore, in vitro and in vivo experiments demonstrated that knockdown of RICTOR has anti-tumor effects, with RNAi-mediated knockdown of RICTOR in cell lines resulting in decreased AKT phosphorylation and an overall decrease in cellular proliferation (PubMed: 26370156). This result is supported by xenograft experiments with RICTOR-knockdown cell lines, which demonstrated significantly decreased tumor growth (PubMed: 26370156).

Sapanisertib 3A

TARGET: **[MTORC1]**

Therapy with Clinical Trial(s)

Mechanism of Action: An orally bioavailable inhibitor of raptor-mTOR (TOR complex 1 or TORC1) and rictor-mTOR (TOR complex 2 or TORC2) with potential antineoplastic activity. Sapanisertib binds to and inhibits both TORC1 and TORC2 complexes of mTOR, which may result in tumor cell apoptosis and a decrease in tumor cell proliferation. TORC1 and 2 are upregulated in some tumors and play an important role in the PI3K/Akt/mTOR signaling pathway, which is frequently dysregulated in human cancers.

Rationale

Amplification of RICTOR was detected as the sole tumor-specific genomic mutation among the genes examined in a patient with advanced NSCLC. Further analysis of tumor tissue confirmed activation of MTOR pathway signaling. The patient was treated on a phase I clinical trial with a dual mTOR1/2 inhibitor and had stable disease for 12 months. After progression of disease and failure of a subsequent combination immunotherapy, he was started again with a dual mTOR1/2 inhibitor Sapanisertib in a phase I trial, and achieved lasting (> 6 months) stable disease on this regimen (PubMed: 26370156).

NCT #	Clinical Trials	Phase
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	2
NCT03430882	A Phase I Study of TAK-228 (MLN0128) in Combination With Carboplatin Plus Paclitaxel in Patients With Advanced Malignancies	1
NCT02142803	A Phase 1 Study of MLN0128 and Bevacizumab in Patients With Recurrent Glioblastoma and Other Solid Tumors	1
NCT03017833	Phase I Study of TAK-228 (MLN0128) in Combination With Metformin in Patients With Advanced Cancers	1
NCT02719691	A Phase Ib Study of the Combination of MLN0128 (Dual TORC1/2 Inhibitor) and MLN8237 (Aurora A Inhibitor, Alisertib) in Patients With Advanced Solid Tumors With an Expansion Cohort in Metastatic Triple-negative Breast Cancer (TNBC)	1
NCT02159989	Phase I Study of MLN0128 (NSC# 768435) in Combination With Ziv-Aflibercept (NSC# 724770) in Patients With Advanced Cancers	1

NCT02503722	A Phase 1 Trial of MLN0128 in Combination With AZD9291 in Advanced EGFR Mutation Positive Non-small Cell Lung Cancer (NSCLC) After Progression on a Previous EGFR Tyrosine Kinase Inhibitor	1
NCT03154294	A Phase 1 Evaluation of the Safety and Tolerability of TAK-228 in Combination With TAK-117 and Paclitaxel in Advanced Solid Tumors	1

Sirolimus 4

TARGET: **[MTORC1]**

Therapy with Clinical Trial(s)

Mechanism of Action: A natural macrocyclic lactone produced by the bacterium Streptomyces hygroscopicus, with immunosuppressant properties. In cells, Sirolimus binds to the immunophilin FK Binding Protein-12 (FKBP-12) to generate an immunosuppressive complex that binds to and inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This results in inhibition of T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (IL-2, IL-4, and IL-15) stimulation and inhibition of antibody production. (NCI04)

Rationale

Amplification of RICTOR was detected as the sole tumor-specific genomic mutation among the cancer-related genes examined in a patient with advanced NSCLC. Further analysis of tumor tissue confirmed activation of MTOR pathway signaling. The patient was treated on a phase I clinical trial with a dual mTOR1/2 inhibitor and had stable disease for 12 months. After progression of disease and failure of a subsequent combination immunotherapy, he was started again with a dual mTOR1/2 inhibitor Sapanisertib in a phase I trial, and achieved lasting (> 6 months) stable disease on this regimen (PubMed: 26370156). Sirolimus, which is an inhibitor of MTORC1, has not been clinically tested for the treatment of patients with RICTOR amplification. This association is by pathway only.

NCT #	Clinical Trials	Phase
NCT01737502	A Phase I-II Trial of Combined PKC and mTOR Inhibition for Patients With Advanced or Recurrent Lung Cancer (NSCLC and SCLC) Without Standard Treatment Options	1 or 2
NCT03217669	Phase I Study of Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy	1 Not yet recruiting

Temsirolimus 4

TARGET: **[MTORC1]**

Therapy with Clinical Trial(s)

Mechanism of Action: An ester analog of rapamycin. Temsirolimus binds to and inhibits the mammalian target of rapamycin (mTOR), resulting in decreased expression of mRNAs necessary for cell cycle progression and arresting cells in the G1 phase of the cell cycle. MTOR is a serine/threonine kinase which plays a role in the PI3K/AKT pathway that is upregulated in some tumors.

Rationale
Amplification of RICTOR was detected as the sole tumor-specific genomic mutation among the cancer-related genes examined in a patient with advanced NSCLC. Further analysis of tumor tissue confirmed activation of MTOR pathway signaling. The patient was treated on a phase I clinical trial with a dual mTOR1/2 inhibitor and had stable disease for 12 months. After progression of disease and failure of a subsequent combination immunotherapy, he was started again with a dual mTOR1/2 inhibitor Sapanisertib in a phase I trial, and achieved lasting (> 6 months) stable disease on this regimen (PubMed: 26370156). Temsirolimus, which is an inhibitor of MTORC1, has not been clinically tested for the treatment of patients with RICTOR amplification. This association is by pathway only.

NCT #	Clinical Trials	Phase
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	2

PQR309 3A

TARGET: **[MTORC1]**

Therapy with Clinical Trial(s)
Mechanism of Action: An orally bioavailable pan inhibitor of phosphoinositide-3-kinases (PI3K) and inhibitor of the mammalian target of rapamycin (mTOR), with potential antineoplastic activity. PI3K/mTOR kinase inhibitor PQR309 inhibits the PI3K kinase isoforms alpha, beta, gamma and delta and, to a lesser extent, mTOR kinase, which may result in tumor cell apoptosis and growth inhibition in cells overexpressing PI3K/mTOR. Activation of the PI3K/mTOR pathway promotes cell growth, survival, and resistance to both chemotherapy and radiotherapy. As mTOR, a serine/threonine kinase downstream of PI3K, may also be activated independent of PI3K, this agent may potentially be more potent than an agent that inhibits either PI3K kinase or mTOR kinase. By inhibiting mTOR to a lesser extent than PI3K, PQR309 does not interfere with the mTOR-mediated negative feedback loop on PI3K signaling. Blocking the negative feedback loop would potentially increase PI3K signaling and decrease therapeutic efficacy.

Rationale
Clinical efficacy of PQR309 for the treatment of tumors with activation of the PI3K/MTOR pathway has been demonstrated in a phase 1 clinical trial in patients with advanced cancers. Partial responses were reported in a patient with Thymic Carcinoma with RICTOR amplification, a patient with sinonasal carcinoma and the PIK3CA E545K mutation, and a patient with clear cell Bartholin's gland carcinoma (Kristeleit et al. ASCO 2015, Abstract# 25920. The biomarker association has been confirmed in another phase 1 trial, in which three patients experienced stable disease (Adjei et al. ASCO 2016; Abstract 2560).

NCT #	Clinical Trials	Phase
NCT02483858	Phase I Study of Oral PQR309 in Patients With Advanced Solid Tumors	1

Everolimus 4

TARGET: **[MTORC1]**

Therapy with Clinical Trial(s)

Mechanism of Action: A derivative of the natural macrocyclic lactone Sirolimus with immunosuppressant and anti-angiogenic properties. In cells, Everolimus binds to the immunophilin FK Binding Protein-12 (FKBP-12) to generate an immunosuppressive complex that binds to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), a key regulatory kinase. Inhibition of mTOR activation results in the inhibition of T lymphocyte activation and proliferation associated with antigen and cytokine (IL-2, IL-4, and IL-15) stimulation and the inhibition of antibody production. (NCI05)

Rationale

Amplification of RICTOR was detected as the sole tumor-specific genomic mutation among the cancer-related genes examined in a patient with advanced NSCLC. Further analysis of tumor tissue confirmed activation of MTOR pathway signaling. The patient was treated on a phase I clinical trial with a dual mTOR1/2 inhibitor and had stable disease for 12 months. After progression of disease and failure of a subsequent combination immunotherapy, he was started again with a dual mTOR1/2 inhibitor Sapanisertib in a phase I trial, and achieved lasting (> 6 months) stable disease on this regimen (PubMed: 26370156). Everolimus, which is an inhibitor of MTORC1, has not been clinically tested for the treatment of patients with RICTOR amplification. This association is by pathway only.

NCT #	Clinical Trials	Phase
NCT02890069	Phase Ib, Open-label, Multi-center Study to Characterize the Safety, Tolerability and Pharmacodynamics (PD) of PDR001 in Combination With LCL161, Everolimus (RAD001) or Panobinostat (LBH589)	1
NCT01582191	A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer	1
NCT03065387	Phase I Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/Amplification or HER3/4 Mutation	1
NCT02321501	A Phase I/Ib Dose Escalation and Biomarker Study of Ceritinib (LDK378) in Combination With Everolimus in Patients With Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression	1

Gedatolisib 4

TARGET: **[MTORC1]**

Therapy with Clinical Trial(s)

Mechanism of Action: An agent targeting the phosphatidylinositol 3 kinase (PI3K) and mammalian target of rapamycin (mTOR) in the PI3K/mTOR signaling pathway, with potential antineoplastic activity. Upon intravenous administration, Gedatolisib inhibits both PI3K and mTOR kinases, which may result in apoptosis and growth inhibition of cancer cells overexpressing PI3K/mTOR. Activation of the PI3K/mTOR pathway promotes cell growth, survival, and resistance to chemotherapy and radiotherapy; mTOR, a serine/threonine kinase downstream of PI3K, may also be activated independent of PI3K.

Rationale
Gedatolisib has been identified as a selective inhibitor for T-ALL cells dependent on the PI3K/mTOR pathway. Preclinical studies have shown that the Drug inhibited proliferation and colony formation of T-ALL cell lines. Additionally, it selectively abrogated PI3K/mTOR signaling without affecting MAPK signaling both in in vitro and in vivo. Inhibition of the PI3K/mTOR pathway using Gedatolisib delayed tumor progression, reduced tumor load and enhanced the survival rate in immune-deficient mouse xenograft models without inducing weight loss in the inhibitor treated mice (PubMed: 28159681).

NCT #	Clinical Trials	Phase
NCT01920061	A Phase 1b Open-Label Three-Arm Multi-Center Study To Assess The Safety And Tolerability Of PF-05212384 ((PI3K/mTOR Inhibitor) In Combination With Other Anti-Tumor Agents	1

LY3023414 4

TARGET: **[MTORC1]**

Therapy with Clinical Trial(s)
Mechanism of Action: An orally bioavailable, small molecule inhibitor of certain class I phosphoinositide 3-kinase (PI3K) isoforms and mammalian target of rapamycin kinase (mTOR) in the PI3K/mTOR signaling pathway, with potential antineoplastic activity. PI3K/mTOR inhibitor LY3023414 inhibits both certain PI3K isoforms and mTOR in an ATP-competitive manner which may inhibit both the PI3K/mTOR signaling pathway in and proliferation of tumor cells overexpressing PI3K and/or mTOR. The PI3K/mTOR pathway is upregulated in a variety of tumor cells and plays a key role in promoting cancer cell proliferation, and survival, motility and resistance to chemotherapy and radiotherapy. MTOR, a serine/threonine kinase downstream of PI3K, may also be activated in a PI3K-independent fashion; therefore, this agent may be more potent than an agent that inhibits either PI3K or mTOR alone. In addition, LY3023414 may inhibit DNA-dependent protein kinase (DNA-PK), thereby inhibiting the ability of tumor cells to repair damaged DNA. DNA-PK is activated upon DNA damage and plays a key role in repairing double-stranded DNA breaks.

NCT #	Clinical Trials	Phase
NCT01655225	A Phase 1 First-in-Human Dose Study of LY3023414 in Patients With Advanced Cancer	1
NCT02124148	A Phase 1b Trial of LY2606368 in Combination With Chemotherapy or Targeted Agents in Advanced and/or Metastatic Tumors	1
NCT02784795	A Phase 1b Study of LY3039478 in Combination With Other Anticancer Agents in Patients With Advanced or Metastatic Solid Tumors	1

ATR	*Loss*	0	FDA Approved for Non-Small Cell Lung Carcinoma	4	Therapies with Clinical Trial(s)	0	FDA Approved for Other Indication(s)

Gene Summary: ATR is a serine/threonine kinase most closely related to ATM. The protein activates checkpoint signaling upon genotoxic stresses such as IR, UV light, or DNA replication stalling, thereby acting as a DNA damage sensor. ATR phosphorylates BRCA1, CHEK1, and TP53, collectively inhibiting DNA replication and mitosis, while promoting DNA repair, recombination and apoptosis. The protein is critical for maintenance of fragile site stability and efficient regulation of centrosome duplication. ATR is frequently mutated in epithelial cancer types. The highest rate of amplification and mutation and an incidence of 18% has been reported in squamous cell carcinoma of the lung (PubMed: 22960745).

CNV Loss: Deletion of ATR is expected to be likely pathogenic.

Olaparib 3B

TARGET: **PARP1**

Therapy with Clinical Trial(s)

Mechanism of Action: A small molecule inhibitor of the nuclear enzyme poly(ADP-ribose) polymerase (PARP) with potential chemosensitizing, radiosensitizing, and antineoplastic activities. Olaparib selectively binds to and inhibits PARP, inhibiting PARP-mediated repair of single strand DNA breaks; PARP inhibition may enhance the cytotoxicity of DNA-damaging agents and may reverse tumor cell chemoresistance and radioresistance. PARP catalyzes post-translational ADP-ribosylation of nuclear proteins and can be activated by single-stranded DNA breaks.

NCT #	Clinical Trials	Phase
NCT02498613	A Phase 2 Study of Cediranib in Combination With Olaparib in Advanced Solid Tumors	2
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	2
NCT02264678	A Modular Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD6738 in Combination With Cytotoxic Chemotherapy and/or DNA Damage Repair/Novel Anti-cancer Agents in Patients With Advanced Solid Malignancies	1 or 2
NCT02484404	Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody (a PD-L1 Inhibitor) MEDI4736 in Combination With Olaparib or Cediranib for Advanced Solid Tumors and Recurrent Ovarian Cancer	1 or 2
NCT02419495	Phase IB Study to Evaluate the Safety of Selinexor (KPT-330) in Combination With Multiple Standard Chemotherapy Agents in Patients With Advanced Malignancies	1
NCT02588105	A Phase I, Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Ascending Doses of AZD0156 Monotherapy or in Combination With Either Cytotoxic Chemotherapies or Novel Anti-Cancer Agents in Patients With Advanced Malignancies	1

NCT03057145	Phase 1 Combination Study of Prexasertib (LY2606368), CHK1 Inhibitor, and Olaparib, PARP Inhibitor, in Patients With Advanced Solid Tumors	1

BGB-290 4

TARGET: **PARP1**

Therapy with Clinical Trial(s)
Mechanism of Action: An orally bioavailable inhibitor of the nuclear enzyme poly(ADP-ribose) polymerase (PARP), with potential antineoplastic activity. PARP inhibitor BGB-290 selectively binds to PARP and prevents PARP-mediated repair of single-strand DNA breaks via the base-excision repair (BER) pathway. This enhances the accumulation of DNA strand breaks, promotes genomic instability, and eventually leads to apoptosis. PARP is activated by single-strand DNA breaks and, subsequently, catalyzes post-translational ADP-ribosylation of nuclear proteins which then transduce signals to recruit other proteins to repair damaged DNA. BGB-290 may both potentiate the cytotoxicity of DNA-damaging agents and reverse tumor cell chemo- and radioresistance.

NCT #	Clinical Trials	Phase
NCT03150810	A Phase 1b Study to Assess the Safety, Tolerability and Clinical Activity of BGB-290 in Combination With Temozolomide (TMZ) in Subjects With Locally Advanced or Metastatic Solid Tumors	1 or 2

Talazoparib 4

TARGET: **PARP1**

Therapy with Clinical Trial(s)
Mechanism of Action: An orally bioavailable inhibitor of the nuclear enzyme poly(ADP-ribose) polymerase (PARP) with potential antineoplastic activity. Talazoparib selectively binds to PARP and prevents PARP-mediated DNA repair of single strand DNA breaks via the base-excision repair pathway. This enhances the accumulation of DNA strand breaks, promotes genomic instability and eventually leads to apoptosis. PARP catalyzes post-translational ADP-ribosylation of nuclear proteins that signal and recruit other proteins to repair damaged DNA and is activated by single-strand DNA breaks.

NCT #	Clinical Trials	Phase
NCT03330405	A Phase 1b/2 Study To Evaluate Safety And Anti Tumor Activity Of Avelumab In Combination With The Poly(Adenosine Diphosphate [Adp]-Ribose) Polymerase (Parp) Inhibitor Talazoparib In Patients With Locally Advanced Or Metastatic Solid Tumors	2
NCT02921919	A Single-Arm, Open-Label, Multicenter, Extended Treatment, Safety Study in Patients Treated With Talazoparib	2
NCT02997163	A Phase I, Open-Label, Pharmacokinetics and Safety Study of Talazoparib (MDV3800) in Patients With Advanced Solid Tumors and Normal or Varying Degrees of Renal Impairment	1

NCT02997176	A Phase I Open-Label Pharmacokinetics and Safety Study of Talazoparib (MDV3800) in Patients With Advanced Solid Tumors and Normal or Varying Degrees of Hepatic Impairment	1

Veliparib 4

TARGET: **PARP1**

Therapy with Clinical Trial(s)

Mechanism of Action: A poly(ADP-ribose) polymerase (PARP) -1 and -2 inhibitor with chemosensitizing and antitumor activities. With no antiproliferative effects as a single agent at therapeutic concentrations, ABT-888 inhibits PARPs, thereby inhibiting DNA repair and potentiating the cytotoxicity of DNA-damaging agents. PARP nuclear enzymes are activated by DNA single or double strand breaks, resulting in the poly(ADP-ribosyl)ation of other nuclear DNA binding proteins involved in DNA repair; poly(ADP-ribosyl)ation contributes to efficient DNA repair and to survival of proliferating cells exposed to mild genotoxic stresses as induced by as oxidants, alkylating agents or ionizing radiation.

NCT #	Clinical Trials	Phase
NCT02412371	A Phase 1 Dose Escalation and Phase 2 Randomized, Placebo-Controlled Study of the Efficacy and Tolerability of Veliparib in Combination With Paclitaxel/Carboplatin-Based Chemoradiotherapy Followed by Veliparib and Paclitaxel/Carboplatin Consolidation in Subjects With Stage III Non-Small Cell Lung Cancer (NSCLC)	1 or 2
NCT01012817	A Phase I/II Trial of ABT-888, an Inhibitor of Poly (ADP-ribose) Polymerase (PARP), and Topotecan (TPT) in Patients With Solid Tumors (Phase I) and Relapsed or Refractory Ovarian Cancer or Primary Peritoneal Cancer (Phase II) After Prior Platinum Containing First-Line Chemotherapy	1 or 2
NCT02944396	A Phase 1 Dose-Escalation and Phase 2 Randomized, Open-Label Study of Nivolumab and Veliparib in Combination With Platinum Doublet Chemotherapy in Subjects With Metastatic or Advanced Non-Small Cell Lung Cancer (NSCLC)	1 or 2
NCT01366144	An Early Phase 1 Study of ABT-888 in Combination With Carboplatin and Paclitaxel in Patients With Hepatic or Renal Dysfunction and Solid Tumors	1
NCT02723864	Phase I Study of Veliparib (ABT-888), an Oral PARP Inhibitor, and VX-970, an ATR Inhibitor, in Combination With Cisplatin in Patients With Refractory Solid Tumors	1
NCT03061188	Phase I/Ib Study of Nivolumab and Veliparib in Patients With Advanced Solid Tumors and Lymphoma With and Without Alterations in Selected DNA Repair Genes	1
NCT02631733	A Phase I Study of a Combination of MM-398 and Veliparib in Solid Tumors	1

NCT01434316	Phase 1 Trial of ABT-888 and SCH727965 in Patients With Advanced Solid Tumors	1

DNMT3A	*Loss*	0	FDA Approved for Non-Small Cell Lung Carcinoma	6	Therapies with Clinical Trial(s)	0	FDA Approved for Other Indication(s)

Gene Summary: DNMT3A is a methyltransferase that is required for genome-wide de novo methylation. It is essential for the establishment of DNA methylation patterns during development and it is involved in paternal and maternal imprinting. DNMT3 is strongly expressed in embryonic stem cells but to a lesser extent in adult somatic tissues. The protein has been shown to be critical for the epigenetic silencing of HSC regulatory genes and for HSC differentiation (PubMed: 22200773). Mutations in DNMT3A have been associated with hematological malignancies (PubMed: 22722925, 24283755).

CNV Loss: Deletion of DNMT3A is expected to be pathogenic.

Mocetinostat 4

TARGET: **HDAC**

Therapy with Clinical Trial(s)

Mechanism of Action: A rationally designed, orally available, Class 1-selective, small molecule, 2-aminobenzamide HDAC inhibitor with potential antineoplastic activity. Mocetinostat binds to and inhibits Class 1 isoforms of HDAC, specifically HDAC 1, 2 and 3, which may result in epigenetic changes in tumor cells and so tumor cell death; although the exact mechanism has yet to be defined, tumor cell death may occur through the induction of apoptosis, differentiation, cell cycle arrest, inhibition of DNA repair, upregulation of tumor suppressors, down regulation of growth factors, oxidative stress, and autophagy, among others. Overexpression of Class I HDACs 1, 2 and 3 has been found in many tumors and has been correlated with a poor prognosis.

NCT #	Clinical Trials	Phase
NCT02954991	A Parallel Phase 2 Study of Glesatinib, Sitravatinib or Mocetinostat in Combination With Nivolumab in Advanced or Metastatic Non-Small Cell Lung Cancer	2
NCT02805660	A Phase 1/2 Study of HDAC Inhibitor, Mocetinostat, in Combination With PD-L1 Inhibitor, Durvalumab, in Advanced or Metastatic Solid Tumors and Non-Small Cell Lung Cancer	1 or 2

Panobinostat 3B

TARGET: **HDAC**

Therapy with Clinical Trial(s)

Mechanism of Action: A cinnamic hydroxamic acid analogue with potential antineoplastic activity. Panobinostat selectively inhibits histone deacetylase (HDAC), inducing hyperacetylation of core histone proteins, which may result in modulation of cell cycle protein expression, cell cycle arrest in the G2/M phase and apoptosis. In addition, this agent appears to modulate the expression of angiogenesis-related genes, such as hypoxia-inducible factor-1alpha (HIF-1a) and vascular endothelial growth factor (VEGF), thus impairing endothelial cell chemotaxis and invasion. HDAC is an enzyme that deacetylates chromatin histone proteins.

NCT #	Clinical Trials	Phase
NCT02890069	Phase Ib, Open-label, Multi-center Study to Characterize the Safety, Tolerability and Pharmacodynamics (PD) of PDR001 in Combination With LCL161, Everolimus (RAD001) or Panobinostat (LBH589)	1

ACY-241 4

TARGET: **HDAC**

Therapy with Clinical Trial(s)

Mechanism of Action: An orally available histone deacetylase (HDAC) inhibitor, with potential antineoplastic activity. Upon oral administration, ACY-241 inhibits the activity of HDACs; this results in an accumulation of highly acetylated chromatin histones, the induction of chromatin remodeling and an altered pattern of gene expression. This leads to the inhibition of tumor oncogene transcription, and the selective transcription of tumor suppressor genes, which inhibit tumor cell division and induce tumor cell apoptosis. HDAC, an enzyme upregulated in many tumor types, deacetylates chromatin histone proteins.

NCT #	Clinical Trials	Phase
NCT02635061	A Phase 1b Study of the Selective HDAC6 Inhibitor ACY 241 in Combination With Nivolumab in Patients With Unresectable Non Small Cell Lung Cancer	1

Belinostat 4

TARGET: **HDAC**

Therapy with Clinical Trial(s)

Mechanism of Action: A novel hydroxamic acid-type histone deacetylase (HDAC) inhibitor with antineoplastic activity. Belinostat targets HDAC enzymes, thereby inhibiting tumor cell proliferation, inducing apoptosis, promoting cellular differentiation, and inhibiting angiogenesis. This agent may sensitize Drug-resistant tumor cells to other antineoplastic agents, possibly through a mechanism involving the down-regulation of thymidylate synthase.

Rationale

The DNA methyltransferase enzyme DNMT3A is recurrently mutated in T-ALL and T cell lymphoma patients and the gene is thought to act as a tumor suppressor of T-ALL (PubMed: 28321121, 22216861). Several HDAC inhibitors have been approved for the treatment of patients suffering from these diseases. However, DNMT3A mutations have not been investigated as biomarkers of response to these Drugs.

NCT #	Clinical Trials	Phase
NCT02679131	An Open-label, Nonrandomized, Phase 1 Study to Evaluate the Safety and Pharmacokinetics of Belinostat in Patients With Relapsed/Refractory Solid Tumors or Hematological Malignancies Who Have Mild, Moderate, and Severe Renal Impairment	1
NCT02680795	An Open-label, Nonrandomized, Phase 1 Study to Evaluate the Safety and Pharmacokinetics of Belinostat in Patients With Relapsed/Refractory Solid Tumors or Hematological Malignancies Who Have Wild-Type, Heterozygous, and Homozygous UGT1A1*28 Genotypes	1

KA2507 4

TARGET: **HDAC**

Therapy with Clinical Trial(s)
Mechanism of Action: KA2507 is an orally bioavailable inhibitor of histone deacetylase (HDAC) type 6 (HDAC6; HDAC-6), which is upregulated in many tumor cell types and deacetylates chromatin histone proteins. The Drug targets, binds to and inhibits the activity of HDAC6. This results in an accumulation of highly acetylated chromatin histones, the induction of chromatin remodeling and an altered pattern of gene expression. Specifically, inhibition of HDAC6 prevents STAT3 activity, which leads to a reduction in programmed death-1 (PD-1) expression. Eventually, this results in the selective transcription of tumor suppressor genes, tumor suppressor protein-mediated inhibition of tumor cell division and an induction of apoptosis in tumor cells that overexpress HDAC6.

NCT #	Clinical Trials	Phase
NCT03008018	An Open Label Ascending Dose Study Evaluating the Safety/Tolerability, Pharmacokinetic and Pharmacodynamic Effects of KA2507 in Patients With Solid Tumours	1

Romidepsin 4

TARGET: **HDAC**

Therapy with Clinical Trial(s)
Mechanism of Action: A bicyclic depsipeptide antibiotic isolated from the bacterium Chromobacterium violaceum with antineoplastic activity. After intracellular activation, Romidepsin binds to and inhibits histone deacetylase (HDAC), resulting in alterations in gene expression and the induction of cell differentiation, cell cycle arrest, and apoptosis. This agent also inhibits hypoxia-induced angiogenesis and depletes several heat shock protein 90 (Hsp90)-dependent oncoproteins.

Rationale
Preclinical analysis has shown that treatment with Romidepsin results in downregulation of DNMT3A in malignant T cells (PubMed: 26473529).

NCT #	Clinical Trials	Phase

NCT01638533	A Phase 1 and Pharmacokinetic Single Agent Study of Romidepsin in Patients With, Lymphomas, Chronic Lymphocytic Leukemia and Select Solid Tumors and Varying Degrees of Liver Dysfunction	1

ALTERATIONS WITHOUT THERAPIES

ARID1B *Loss*

Gene Summary: ARID1B is a component of the SWI/SNF chromatin remodeling complex and may play a role in cell-cycle activation. It is involved in transcriptional activation and repression of select genes by chromatin remodeling. the protein is expressed in the brain and in embryonic stem cells, and ARID1B-associated BAF complexes are important in the early stages of brain development and essential for the pluripotency of embryonic stem cells. Loss of function mutations have been observed in a wide variety of cancer types (PubMed: 23644491). A recent study showed that loss of ARID1A and ARID1B alleles cooperatively promotes cancer formation but also results in functional dependence (PubMed: 24562383). Loss of ARID1B in ARID1A-deficient backgrounds destabilizes SWI/SNF and impairs proliferation.

CNV Loss: Deletion of ARID1B is expected to be pathogenic.

PTCH1 *Loss*

Gene Summary: PTCH1 is a 12-pass transmembrane protein and the receptor for Sonic hedgehog, as well as the Desert and Indian hedgehog proteins. The receptor acts as a negative regulator of hedgehog signaling In the absence of Hedgehog proteins, PTCH suppresses the otherwise constitutively active signaling receptor Smoothened (Smo) so that the Hedgehog signaling pathway is in the off state. Low levels or absence of PTCH1 will result in increased HH signaling. PTCH1 is a tumor suppressor gene and low levels or absence of PTCH1 results in overstimulation of the Hh pathway that may result in the initiation and progression of cancer. Loss-of-function mutations have been associated with sporadic basal cell carcinoma as well as several other types of cancer.

CNV Loss: Deletion of PTCH1 is expected to be pathogenic.

PTPRD *Loss*

Gene Summary: PTPRD is a member of the protein tyrosine phosphatase (PTP) family. PTPs are signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. PTPRD is involved in the promotion of neurite growth and the regulation of neuron axon guidance. PTPRD is an inhibitor of STAT3. PTPRD is one of the most frequently inactivated genes in cancer. Loss of function, either by deletion or inactivation, results in hyperactivation of STAT3 signaling, a common observation in cancer. PTPRD undergoes both deletion and mutation, with copy number loss comprising the primary mode of inactivation in GBM (PubMed: 24843164) and loss-of-function mutations resulting in sensitivity to STAT3 inhibitors have been reported in HNSCC (PubMed: 26267899). In addition, PTPRD is also one of the most frequently inactivated genes in melanoma (PubMed: 19074898, 22842228).

CNV Loss: Knockdown of PTPRD in immortalized human astrocytes resulted in increased cell growth in vitro and enhanced tumor growth in vivo (PubMed: 19478061).

SMARCA4 *Loss*

Gene Summary: SMARCA4 is the central catalytic subunit of the chromatin remodeling complex SNF/SWI, which is required for transcriptional activation of genes normally repressed by chromatin. Although usually associated with transcriptional activation, SMARCA4 has also been found in complexes associated with transcriptional repression. SMARCA4 associates with STK11 and this interaction is necessary for SMARCA4-induced growth arrest (PubMed: 11445556). The association requires the N terminus of STK11 and the helicase domain of SMARCA4. Mutations in SMARCA4 have been reported with low frequency in a wide variety of cancer types. They have been more frequently associated with a subtype of medulloblastoma (PubMed: 22722829, 22832583, 22820256), and biallelic inactivating mutations have been identified as the cause of small cell carcinoma, hypercalcemic type, of the ovary. Mutations were identified in almost all cases (PubMed: 24658001, 24658004, 24658002) and included nonsense, frameshift and splice-site mutations as well as homozygous intragenic deletions, while no missense mutations were identified.

CNV Loss: Deletion of SMARCA4 is expected to be likely pathogenic.

APPENDIX A

VARIANTS OF UNKNOWN SIGNIFICANCE

Note: One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants have not been adequately characterized in the scientific literature and possible effects on protein function and pathological significance are unknown. We choose to include them in this report in the event that their clinical relevance is determined in the future.

(NONE FOUND)

APPENDIX B

POTENTIAL RESISTANCE IN THESE THERAPIES

(NONE FOUND)

APPENDIX C

CANCER GENE PANEL SPECIFIED FOR THE ANALYSIS OF THIS SAMPLE

(NONE FOUND)

APPENDIX D

LEVELS OF EVIDENCE

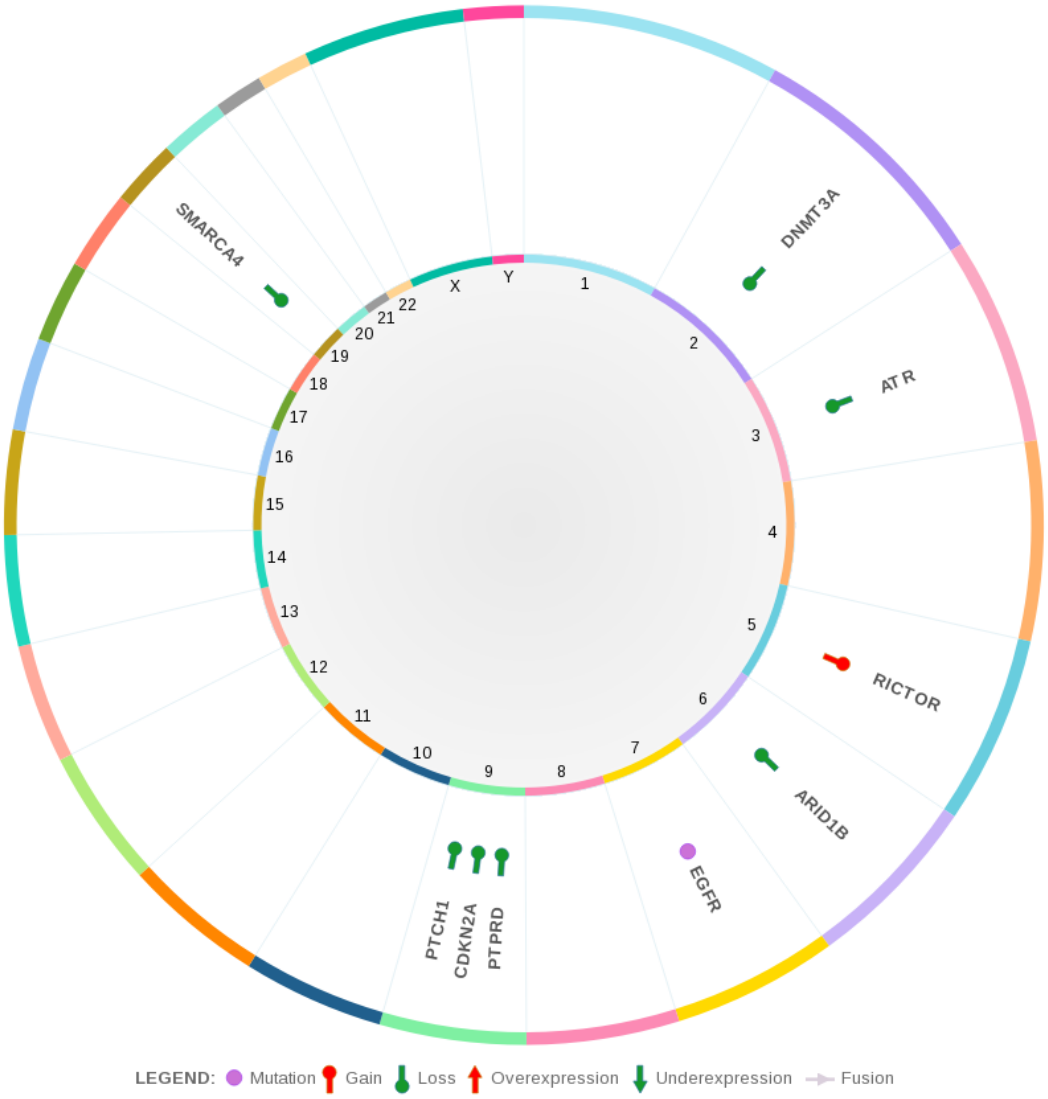
Level	Description
1	**1 -** Drug is FDA-approved and biomarker is standard of care (SOC) for this indication (excluding chemotherapeutic drugs and hormone therapies)
2A	**2A -** Drug is FDA-approved and the associated biomarker is predictive of response by NCCN for this indication
2B	**2B -** Drug is FDA-approved and the associated biomarker is predictive of response by NCCN for a different indication
3A	**3A -** Clinical evidence supports the biomarker as being predictive of response to a drug for this indication
3B	**3B -** Clinical evidence supports the biomarker as being predictive of response to a drug for a different indication
4	**4 -** Compelling preclinical evidence and/or case study reports support the biomarker as being predictive of response to this drug
R1	**R1 -** Standard of care biomarker predictive of resistance to an FDA-approved drug for this indication including biomarkers described by the NCCN
R2	**R2 -** Clinical evidence supports a biomarker not included in NCCN and not standard of care as of being predictive of resistance to an FDA-approved drug

APPENDIX E

Px Prognostic mutation: a genetic alteration predictive of the likely course of the disease

APPENDIX F

MOLECULAR PROFILE DIAGRAM



END OF REPORT