Research Prioritization Topic Brief: Comparative Effectiveness of Molecularly Directed Therapies

October 17, 2016

Topic X: Comparative effectiveness of Molecularly Directed Therapies

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2. **Glossary**

Molecularly directed cancer therapy is a complicated topic with many new concepts and terms – therefore we are providing this glossary.

Activating Mutation – A change in the DNA sequence of a gene resulting in an altered protein that has higher levels of activity (i.e., hypermorphic mutation) or new activity (i.e., neomorphic mutation). Activating mutations occurring in oncogenes contribute to the pathogenesis of cancer.

Anti-Angiogenic – Larger tumors require that new blood vessels be created to supply oxygen to tumor cells, a process known as angiogenesis. Anti-angiogenic drugs are a class of pharmaceuticals intended to interfere with the formation of new blood vessels.

Basket Trial – A clinical trial design that enrolls patients with cancers of different tissues of origin (e.g., bladder cancer, lung cancer) but sharing a common genetic change (i.e., activating mutation in a specific oncogene). These trials are based on the concept that the shared genetic make-up of these cancers may make them susceptible to treatment with the same molecularly directed therapy despite the cancers' different tissue of origin. These trials are intended to allow study of rare cancers that may not be amenable to study in enrichment trials because of the small number of patients.

Chromatin/Chromatin Regulation/Chromatin Regulatory Networks – Within cells, DNA is complexed with a set of proteins; this complex is known as chromatin. Chromatin is a dynamic structure that can be remodeled, increasing or decreasing the accessibility of the DNA in the remodeled area and altering expression of genes located in that area. Chromatin regulatory networks within the cell are responsible for establishing, modifying, and/or maintaining the state of chromatin.

Driver Mutation – A genetic mutation that has contributed to the development of the cancer and/or is contributing to the progression or survival of the cancer.

Enrichment Trial – In the context of molecularly targeted therapy, a clinical trial design that focuses on a single molecular target in a single cancer type. Typically, patients must test positive for the molecular target to be enrolled in the trial.

Germline Mutation – A change in the DNA sequence of a gene that is inherited from a parent and, therefore, is present in all cells of the body.

Molecularly directed therapy— a therapy that targets the activity of an aberrant or overexpressed protein encoded by a specific mutated gene in a cancer cell

Oncogene – A gene whose normal function is to promote cell growth and/or proliferation. When mutated, it can promote cancer formation. Oncogene mutations are usually activating mutations and only require that one of two copies of the gene be mutated.

Somatic Mutation – A change in the DNA sequence of a gene that occurs during the lifetime of the patient (typically in somatic tissues) and, therefore, is only present in a small subset of cells in the body.

Targeted therapy—a cancer therapy targeting a biomolecule or process thought to be important in sustaining the cancer (e.g., bevacizumab used to target angiogenesis).

Tumor Suppressor Gene – A gene whose normal function is to control cell growth or cell division; repair DNA damage; and/or promote cell death. When mutated, loss of tumor suppressor gene activity can promote cancer formation.

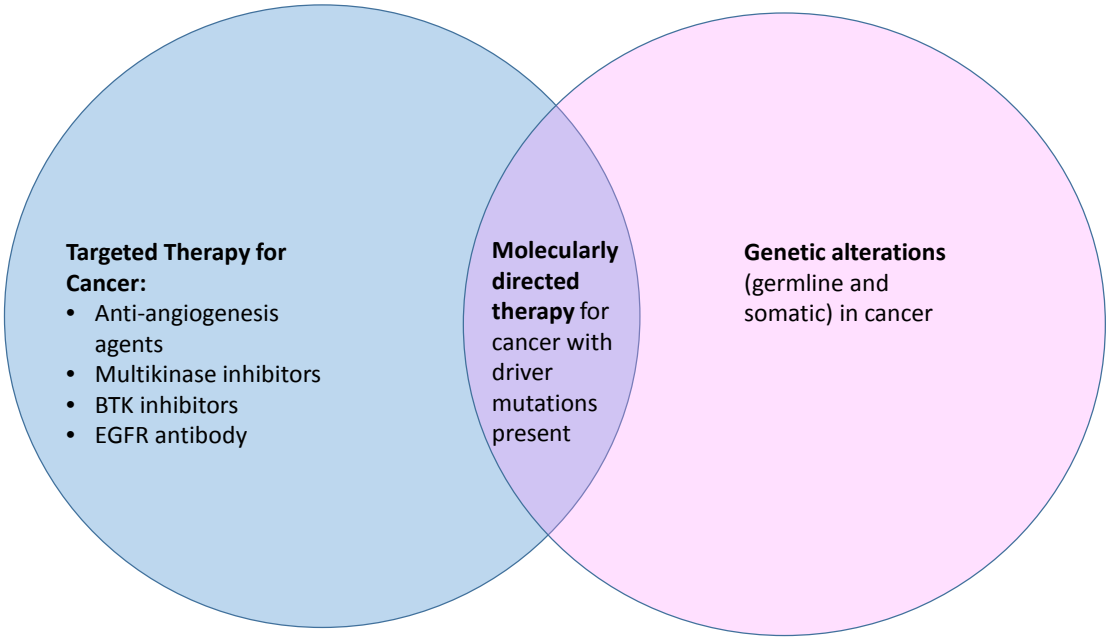
Umbrella Trial – A clinical trial design that enrolls patients with cancers of a single tissue of origin (e.g., bladder cancer) into a single trial testing multiple molecularly directed therapies (i.e., therapies targeting different genetic markers). These trials typically have a centralized screening procedure that is able to identify patients' eligibility for one of several sub-studies. Compared to enrichment trials, these trials are intended to increase the rate at which an appropriate molecularly directed therapy is identified.

3. Overview/Background/Definition of Topic

Recent years have seen substantial improvement in the understanding of the molecular bases of cancer.[1] These so-called "hallmarks of cancer" have provided a number of rational targets for the pharmacologic treatment of cancer and have contributed to the development of a substantial number of therapies that target specific biomolecules involved in these processes. A list compiled by the National Cancer Institute includes 82 targeted therapies that have been approved for treating one or more cancer types by the U.S. Food and Drug Administration (FDA).[2] Additionally, more than 800 medicines are reportedly in development for treating patients with cancer, a substantial fraction of which are targeted therapies.[3]

In parallel with this expansion in the set of therapeutics targeted at specific biomolecules, substantial progress has also been made in cancer genomics. Cancer can be thought of as a genetic disease in which both inherited (i.e., germline) and acquired (i.e., somatic) genetic variants lead to aberrant regulation of cellular pathways involved in cancer pathogenesis. Substantial reductions in the cost and time required to generate genetic sequence data has led to the accumulation of large amounts of genetic sequence data from a multitude of cancers.[4] These efforts have identified numerous genetic changes that recur within cancers; however, only a subset of the observed genetic changes are likely to promote the growth of cancers. Genetic changes that promote increased survival and/or proliferation of cancer cells are termed driver mutations, and the dependence of cancer cells upon the aberrant activity conferred by these mutations represents a logical therapeutic target.[5]

Figure 1. Molecularly directed therapy – a subset of targeted therapies used to treat cancers with specific genetic alterations



At the interface between these two research arms exists a subset of targeted therapies that are used in specific patient populations defined by the presence of a driver mutation. For the purposes of this report, we are referring to the use of targeted therapies in genetically defined patient populations as **molecularly directed therapy**. Molecularly directed therapy is intended to take advantage of the cancer cell's dependence on the activity of the aberrant or overexpressed protein encoded by the driver mutation. Prominent examples include the use of EGFR inhibitors (e.g., erlotinib, gefitinib) in EGFR mutation-positive non-small cell lung cancer (NSCLC)[6,7] and the use of BRAF inhibitors (e.g., dabrafenib, vemurafenib) in BRAF mutation-positive melanoma.[8,9] Cancer exhibits substantial genetic heterogeneity; the spectrum of genetic mutations present in tumors varies across individual instances of the disease. EGFR and BRAF inhibitors are only intended for use in the subset of NSCLCs and melanomas, respectively, verified to carry the corresponding driver mutation; approximately 10% to 15% of non-squamous NSCLCs harbor an activating mutation in *EGFR* and approximately 50% of melanomas harbor an activating mutation in *BRAF.*

These findings have led to widespread efforts to identify additional pairs of driver mutations and corresponding targeted therapies.[4] Basing treatment choice on a patient's genetic profile has been hypothesized to more accurately predict the activity of drugs in selected patients; however, it is clear that this approach will not be universally successful. For example, although BRAF inhibitors have been shown to be efficacious in patients with BRAF mutation-positive melanoma, and studies indicate that BRAF inhibitors also may have activity in BRAF mutation-positive NSCLC, they do not appear to have substantial activity in patients with BRAF mutation-positive colorectal cancer.[8,10,11] In addition, recently reported results from the SHIVA trial, which compared off-label targeted

therapies chosen on the basis of molecular profiling of the patients' cancers to standard-of-care therapies, failed to demonstrate a difference in progression-free survival (PFS) or rate of severe adverse events between the two groups.[12] These observations underscore the need for clinical trials to validate in each cancer type the efficacy of therapies hypothesized to have activity on the basis of molecular profiling.

Another obstacle to adoption of molecular profiling in all cancers is that, despite the increasing number of commercially available and experimental targeted therapies, not all driver mutations have a corresponding targeted therapy. Generally, pharmacologic approaches to molecularly directed therapy have been more successful in targeting oncogenes, which, when mutated, typically result in over-activity and are therefore frequently amenable to pharmacologic inhibition. Targeting of tumor suppressor genes, which, when mutated, typically result in the loss of function or reduced activity, has been less successful.[13]

In this report we aim to produce an evidence map regarding the state of research into molecularly directed therapy. Stakeholders nominated the specific topics of molecularly directed therapy for bladder cancer and pancreatic adenocarcinoma to PCORI. The authors of this report, in consultation with PCORI, suggested that molecularly directed therapies for metastatic non-small cell lung cancer (NSCLC) be added as an illustrative example of this approach to cancer therapy. In step 1, we used a literature review to identify likely driver mutations in the cancers of interest. In step 2, we used a literature review to identify whether a targeted therapy or therapies with the potential for activity in the molecular subtypes defined in step 1 exist. In step 3, we reviewed the literature, ongoing trials registered in clinicaltrials.gov, and oncology clinical practice guidelines to assess the state of the evidence for each identified molecular subtype-targeted therapy dyad. No external stakeholders were involved in preparing this report. One of our coauthors, Dr. Nathanson, is a geneticist whose research focuses on the genetics of human cancer. She also is Associate Director for Population Sciences and Chief Oncogenomics Physician for the Abramson Cancer Center within the University of Pennsylvania Health System. ECRI Institute provides information to hospitals and health plans on tests for genetic mutations.

4. Patient-Centeredness of This Topic

The identification of genetic mutations that render cancer amenable to treatment with corresponding targeted therapies is a central component of the promise of bringing a precision medicine approach to oncology. This approach holds the promise of tailoring treatments to more specific patient populations stratified by the patient's genetic makeup and the tumor's genetic profile. As such, this approach is fundamentally patient centered, with the goal of offering more informed treatment choices to patients based on their individual characteristics, with the hope of improving survival and/or quality of life.

5. Bladder Cancer

Impact/Burden of Bladder Cancer

The American Cancer Society (ACS) estimates that, in 2016, 76,960 people in the United States will receive a diagnosis of urinary bladder cancer and estimates that 16,390 people will die from the

disease.[14] The incidence of urinary bladder cancer is approximately 4 times higher in men than in women. For men, urinary bladder cancer represents the fourth most common cancer diagnosis and the eighth most common cause of cancer death. The vast majority of urinary bladder cancer is a type of cancer known as urothelial carcinoma (also known as transitional cell carcinoma), which arises from cells that line the inside of the bladder.[15]

Ongoing Evidence Gaps in Bladder Cancer

Molecularly directed therapy is at an early stage of development in bladder cancer. FDA has approved no molecularly directed therapies for treating patients with bladder cancer, and current treatment guidelines do not include any molecularly directed therapies as treatment options. Although no molecularly directed therapies have been validated for use in bladder cancer, genomic analyses have identified potential genetic targets in this disease. One such study indicated that 69% of bladder cancers analyzed harbored at least one potential therapeutic target.[16] Data are needed regarding the potential therapeutic utility of targeted therapies in these molecularly defined subsets of bladder cancer.

Current Guidelines for Bladder Cancer

The National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), and the European Association of Urology (EAU) have recently published guidelines regarding the treatment of bladder cancer.[17-19] These guidelines do not include any targeted therapies directed at molecularly defined subtypes among their recommended systemic therapies for metastatic bladder cancer. Although the NCCN guidelines include as a treatment option the anti-PD-L1 monoclonal antibody atezolizumab, this immunotherapy is not specifically indicated for use in a molecularly defined patient population.[17]

The ESMO guidelines include a section on personalized medicine for bladder cancer.[18] This section suggests that "personalised *[sic]* cancer therapies hold the promise to improve clinical outcomes, using readily obtainable biomarkers of response to predict their clinical benefits;" however, no specific personalized treatment options are recommended.

Ongoing Research in Bladder Cancer

Preliminary results are available from 6 trials of molecularly directed therapies in bladder cancer. These trials include 5 open-label, single arm studies and one randomized controlled trial (RCT). Genetic targets include EGFR, ERBB2, ERBB3, and ERBB4 (1 study), EGFR (HER1)/ERBB2 (HER2) (1 study), FGFR3 (2 studies) and genes that function in the PI3K/Akt/mTOR pathway (2 studies). Molecularly targeted therapies showing some potential benefit include afatinib in patients with platinum-refractory urothelial carcinoma with ERBB2 or ERBB3 alterations, and everolimus in patients with metastatic transitional cell carcinoma, between 1 and 4 prior systemic treatments for advanced or metastatic disease, with a loss-of-function mutation in TSC1, a negative regulator of the mTOR pathway. (See Appendix Table 1.)

Searches identified 17 ongoing trials registered in ClinicalTrials.gov examining the use of molecularly directed therapies in bladder cancer. (See Appendix Table 2.) Only one of the identified trials was an

RCT; the majority (11 of 17) were basket trials enrolling patients with cancers from multiple tissues of origin sharing a common genetic mutation. The majority of identified trials have a primary endpoint assessing tumor response to treatment (12 of 17). Targeted therapies under study in these trials included 17 unique compounds from 11 classes of targeted therapeutics. Among these 17 targeted therapies, none are FDA-approved for treating bladder cancer; however, 6 of the drugs are commercially available through approvals for other cancer types. Genetic targets under study in these trials included 13 unique genetic loci. Targeted genetic loci exhibited a wide range of prevalence among bladder cancers: PIK3CA (22%), EP300 (15%), FGFR3 (14%), CREBBP (12%), ERBB2 (12%), ERBB3 (11%), TSC1 (8%), CDKN2A (7%), HRAS (5%), BRAF (~1%), EGFR (~1%), NF1 (~1%), and TSC2 (~1%).[16,20]

Potential Research Areas and Comparative Effectiveness Research Questions in Bladder Cancer

The evidence base regarding the use of molecularly directed therapies in bladder cancer is very small; with two small trials demonstrating signs of anti-cancer activity in a handful of patients. Thus, it is likely that additional evidence supporting the efficacy of these therapies should be gathered before comparative effectiveness studies comparing molecularly directed therapies to conventional chemotherapy or immunotherapy (i.e., recently approved checkpoint inhibitors) would be warranted.

Potential areas for basic research may exist with regards to future molecularly directed therapy approaches for this disease. The most frequently mutated gene in bladder cancer is p53 (approximately 50% of bladder cancers harbor p53 mutations), a tumor suppressor gene frequently mutated in a wide variety of cancers.[20] Few approaches to targeting p53 are available and additional research into potential mechanisms of targeting p53 would be of potential benefit in a large number of cancer types, including bladder cancer. However, it should be noted that the lack of pharmaceutical approaches to p53-mutant cancer is a long standing problem.[13] Bladder cancer also exhibits unusually high rates of mutations in genes involved in chromatin regulation, which plays a role in the control of gene expression. Approximately 75% of bladder cancers harbor an inactivating mutation in at least one chromatin regulatory gene. Preclinical research into methods of targeting chromatin regulatory networks may be of future benefit to treatment of bladder cancer.[16]

6. Non-Small Cell Lung Cancer

Impact/Burden of NSCLC

ACS estimates that, in 2016, 224,390 people in the United States will receive a diagnosis of lung cancer and estimates that 158,080 people will die from the disease.[14] Approximately 85% of lung cancer is the NSCLC form of the disease, which can be further divided into adenocarcinomas (40% of all lung cancers), squamous cell carcinoma (25% to 30% of all lung cancers), and large cell carcinoma (10% to 15% of all lung cancers). Although death rates from lung cancer have been decreasing in recent years, lung cancer still represents the number one cause of cancer-related death for both men and women in the United States, accounting for approximately one quarter of all cancer-related deaths.

Ongoing Evidence Gaps in NSCLC

Molecularly targeted therapies for NSCLC can be categorized into two groups: (1) a small set of established targetable genetic alterations with corresponding molecularly directed therapies and (2) a larger set of emerging genetic alterations with the potential for targeting using molecularly directed therapies.

Established molecularly directed therapy approaches include the use of EGFR inhibitors in the 15% to 20% of patients with lung adenocarcinomas that harbor activating EGFR mutations and the use of ALK inhibitors in the 5% of patients with lung adenocarcinomas that harbor ALK rearrangements.[16,20] Data are available from multiple RCTs comparing these approaches to standard cytotoxic chemotherapy. A recent systematic review on the use of EGFR inhibitors in EGFR-mutated NSCLC identified the following implications for future research:[7]

- Further comparative trials with cytotoxic chemotherapy would seem unlikely to be of value in EGFR mutation-positive patients; the focus should instead be on identifying the predictive value of specific mutations to optimize survival and minimize toxicity from inappropriate therapy.
- Future trials of these agents should comprise participants with known EGFR mutations, and attempt to clarify the effectiveness of targeted therapies in the common mutant subtypes (codons 19, 20, and 21) as well as the small numbers with multiple and rare mutations.
- The role of combination of EGFR-targeted therapy and cytotoxic chemotherapy and the associated toxicity remains to be established, but the data from the BMSO99, FLEX, INTACT 1 and INTACT 2 trials do not favor this approach, either in terms of efficacy or toxicity. The FASTACT 2 trial demonstrated positive outcomes for the combination of erlotinib and cytotoxic chemotherapy given in an intercalated design [i.e., erlotinib administered between rounds of cytotoxic chemotherapy], however the number of EGFR [mutation-positive] participants in these trials was small.
- Cross-over designs with alternative targeted therapies should be initiated by academic groups, as these are unlikely to attract industry funding.
- The majority of studies in this review used a range of sequencing techniques from a primary tumor biopsy for stratification. Research is currently in progress to assess the utility of less invasive technologies such as cell-free DNA.
- Future trials should report in detail the degree and duration of symptom control as well as quality of life scores to improve patient selection.

In addition to the 20% to 25% of lung adenocarcinomas with available established molecularly directed therapies, genomic studies have estimated that an additional 50% of lung adenocarcinomas harbor mutations in genes affecting similar cellular processes that may be amenable to molecularly directed approaches.[16,20] For these less well established genetic alteration/targeted therapy pairs, current research consists primarily of single-arm studies designed to establish whether these molecularly directed therapies demonstrate sufficient efficacy and safety to warrant further study. Among the more advanced of the emerging targets is ROS1 rearrangements, which are present in approximately 1% to 2% of lung adenocarcinomas.[16,20] FDA has approved the multikinase inhibitor

crizotinib as a treatment for ROS1 rearrangement-positive NSCLC; however, no RCTs comparing crizotinib to cytotoxic chemotherapy have been completed nor are any such studies ongoing.

The majority of research on molecularly directed therapies in NSCLC has involved mutations that occur mainly in lung adenocarcinomas. The genetics of squamous cell carcinoma differs substantially from that of lung adenocarcinomas, and little data are available on the use of molecularly directed therapies in the squamous cell carcinoma subtype of NSCLC.[20] The genetics of large cell carcinoma is less well characterized.

Current Guidelines for NSCLC

NCCN, ESMO, and the American Society for Clinical Oncology (ASCO) have recently published guidelines regarding the treatment of metastatic NSCLC.[21,22] These guidelines include recommendations regarding multiple targeted therapies directed at molecularly defined NSCLC subtypes. All three guidelines recommend offering treatment with an EGFR inhibitor (e.g., afatinib, erlotinib, gefitinib) or an ALK inhibitor (e.g., alectinib, ceritinib, crizotinib) to patients whose disease harbors activating EGFR mutations or ALK rearrangements, respectively. Additionally, the ASCO and NCCN guidelines recommend offering treatment with a ROS1 inhibitor (i.e., crizotinib) to patients whose disease harbors rearrangements involving the ROS1 gene. The NCCN guidelines include ROS1 rearrangements in a set of "emerging targeted agents" for which there is generally only preliminary evidence of clinical efficacy consisting of case reports or single-arm clinical trials. Additional molecularly directed therapies in this list include:

- BRAF Mutations to be treated with BRAF inhibitor (dabrafenib, vemurafenib) or a combination of BRAF inhibitor and MEK inhibitor (dabrafenib plus trametinib)
- MET Amplification or Mutation to be treated with a MET inhibitor (crizotinib)
- RET rearrangements to be treated with a RET inhibitor (cabozantinib)
- ERBB2 mutations to be treated with an anti-HER2 monoclonal antibody (trastuzumab) or an EGFR family inhibitor (afatinib)

Ongoing Research in NSCLC

EGFR Mutations in NSCLC

Approximately 15% to 20% of lung adenocarcinomas harbor an activating mutation in EGFR.[23] For patients with advanced/metastatic NSCLC harboring an activating mutation in EGFR, treatment with EGFR inhibitors has become the standard of care. Several systematic reviews comparing treatment with EGFR inhibitor to treatment with cytotoxic chemotherapy have been published.[7,24-27] The most recently published meta-analysis included 17 RCTs in which 2,236 EGFR mutation-positive patients received treatment with an EGFR inhibitor (afatinib, erlotinib, or gefitinib) or cytotoxic chemotherapy.[7] Overall, EGFR inhibitors have been shown to significantly improve PFS compared to cytotoxic chemotherapy in EGFR mutation-positive patients; however, EGFR inhibitors do not lead to a statistically significant improvement in overall survival. Nonetheless, cytotoxic chemotherapy is associated with greater toxicity than EGFR inhibitors in this patient population.[7,24-27]

Questions remain regarding the relative effectiveness and toxicity of the three available EGFR inhibitors (afatinib, erlotinib, gefitinib) in EGFR mutation-positive NSCLC.[28] A recently presented RCT comparing erlotinib to gefitinib reported no statistically significant difference in PFS or overall survival.[29] A recently published RCT comparing afatinib to gefitinib reported a modest but statistically significant improvement in PFS and time to treatment failure (time during which some patients continue to receive targeted therapy after initial signs of disease progression) for afatinib.[30]

Cancers treated with EGFR inhibitors frequently develop resistance to therapy. Researchers have identified multiple molecular mechanisms underlying EGFR inhibitor resistance; however, the most common cause of resistance is a mutation in EGFR (T790M) that renders the encoded kinase insensitive to available inhibitors.[31] FDA recently approved an EGFR inhibitor with activity against EGFR T790M, osimertinib, which exhibited an overall response rate of 61% and a PFS of 9.6 months in a single-arm trial in patients with EGFR T790M-positive NSCLC previously treated with an EGFR inhibitor.[32] Randomized trials comparing osimertinib to cytotoxic chemotherapy in EGFR T790M mutation-positive NSCLC (NCT02151981 – estimated completion date of January 2018) and comparing osimertinib to erlotinib or gefitinib in EGFR mutation-positive NSCLC (NCT02296125 – estimated completion date of October 2018) are ongoing.[33]

ALK Mutations in NSCLC

Approximately 5% of lung adenocarcinomas harbor an ALK mutation (typically rearrangements resulting in gene fusions).[23] For patients with advanced/metastatic NSCLC harboring ALK rearrangements, treatment with multikinase inhibitors with activity against ALK (e.g., crizotinib) has become the standard of care. In two RCTs, crizotinib demonstrated a statistically significant improvement in PFS compared to cytotoxic chemotherapy in patients with ALK rearrangement-positive NSCLC.[34,35] Like EGFR-mutation positive NSCLC treated with EGFR inhibitors, ALK rearrangement-positive NSCLC treated with crizotinib frequently develops resistance to the inhibitor.[36] Two additional FDA-approved multikinase inhibitors with activity against ALK (i.e., alectinib and ceritinib) have been reported to have activity in non-randomized trials of ALK rearrangement-positive NSCLC that had progressed on treatment with crizotinib.[37-39] Randomized trials of these agents in the first-line setting compared to cytotoxic chemotherapy (NCT01828099 – estimated completion date of June 2018) or crizotinib (NCT02075840, NCT02838420 – estimated completion dates of December 2017 and December 2019, respectively) and in the third-line setting (previously treated with crizotinib and cytotoxic chemotherapy) compared to cytotoxic chemotherapy (NCT01828112, NCT02604342 – estimated completion dates of August 2018 and October 2018, respectively) are ongoing.[40] Our searches did not identify any ongoing RCTs comparing alectinib and ceritinib to each other.

Emerging Targets in NSCLC

Preliminary results are available from 24 trials of molecularly directed therapies targeting non-EGFR and non-ALK mutations in NSCLC. These trials include 19 open-label, non-randomized studies, 3 RCTs (2 open-label, 1 double-blind), and 2 retrospective cohort studies. Targeted mutations under study include BRAF (2 studies), DDR2 (1 study), ERBB2 (4 studies), FGFR1 (1 study), KRAS (8 studies), MET (1 study), RET (3 studies), and ROS1 (4 studies). Molecularly targeted therapies showing some

potential benefit in single-arm trials include BRAF inhibitors with or without MEK inhibitors in patients with BRAF mutant NSCLC; afatinib and trastuzumab in patients with ERBB2 (HER2) mutant NSCLC; crizotinib in patients with MET mutant NSCLC; cabozantinib or vandetanib with or without everolimus in patients with RET mutant NSCLC; and crizotinib in ROS1 mutant NSCLC. One RCT testing the addition of the MEK inhibitor selumetinib to cytotoxic chemotherapy with docetaxel in previously treated patients with KRAS mutation-positive NSCLC demonstrated a statistically significant improvement in overall survival; however, a larger confirmatory trial was recently reported to have failed to meet its primary endpoint of improving PFS in this patient population. See Appendix Table 3 for descriptions of the additional studies.

Searches identified 49 ongoing trials registered in ClinicalTrials.gov studying the use of a targeted therapy in a molecularly defined NSCLC subtype (excluding studies targeting EGFR-mutation positive NSCLC and ALK mutation-positive NSCLC). (See Appendix Table 4.) Only three of the identified trials were RCTs. Many of the gene-targeted therapy combinations were under study in 4 identified umbrella trials. These trials test multiple drugs in a single multi-arm trial with patients enrolled in the appropriate arm based on the genetic profile of their cancer. The majority of identified trials had a primary endpoint assessing tumor response to treatment (32 of 49). Targeted therapies under study in these trials included 38 unique compounds from 16 classes of targeted therapeutics. Among these 38 targeted therapies, only one is FDA-approved for use in the genetic subtype of cancer under study (crizotinib in ROS rearrangement-positive NSCLC); however, an additional 16 drugs are commercially available through approvals for other cancer types or for use in NSCLC unselected by genetic marker. Genetic targets under study in these trials included 23 unique genetic loci. Targeted genetic loci for which data were available exhibited a wide range of prevalence among NSCLCs. Additionally, the prevalence of molecular targets differed between the two major NSCLC subtypes (adenocarcinoma and squamous cell carcinoma) with the majority of molecular targets being specific to adenocarcinoma: KRAS mutations (25% to 30% of adenocarcinomas), FGFR1 amplifications (15% to 20% of squamous cell carcinomas), PIK3CA mutations (5% to 10% of both adenocarcinomas and squamous cell carcinomas), FGFR2/3/4 mutations or rearrangements (5% to 10% of squamous cell carcinomas, <1% of adenocarcinomas), DDR2 (4% of squamous cell carcinomas), MET mutations (2% to 4% of adenocarcinomas), ERBB2 (2% to 3% of adenocarcinomas), BRAF (1% to 3% of adenocarcinomas), MET amplification (1% to 2% of adenocarcinomas), RET rearrangements (1% to2% of adenocarcinomas), ROS1 rearrangements (1% to 2% of adenocarcinomas), NTRK1/2/3 rearrangements (<1% of adenocarcinomas), HRAS mutations (<0.5% of adenocarcinomas), NRAS mutations (<0.5% of adenocarcinomas).[23,41]

Potential Research Areas and Comparative Effectiveness Research Questions in NSCLC

EGFR (15% TO 20% of lung adenocarcinomas) or ALK (5% of lung adenocarcinomas)

- Comparative effectiveness trials comparing EGFR/ALK inhibitors to immunotherapy (i.e., checkpoint inhibitors) and/or the combination of EGFR/ALK Inhibitors and immunotherapy (several early phase trials ongoing NCT02584634, NCT02393625, NCT02511184, NCT01998126, NCT02364609).

- Comparative effectiveness trials comparing ALK inhibitor to combination therapy with ALK inhibitor and chemotherapy or combination therapy with ALK inhibitor and targeted therapy approved for non-molecularly defined NSCLC (e.g., anti-angiogenic monoclonal antibodies bevacizumab or ramucirumab). Some evidence exists for increased efficacy of erlotinib in combination with bevacizumab compared to erlotinib monotherapy in EGFR mutation positive NSCLC.[42] Two additional trials of erlotinib and bevacizumab are ongoing (NCT01562028 and NCT01532089 with completion dates of October 2016 and March 2018, respectively).
- A Cochrane review suggested that trials testing alternative targeted therapies be undertaken; however, our scans identified several ongoing trials comparing first-generation inhibitors of EGFR (i.e., erlotinib, gefitinib) or ALK (i.e., crizotinib) to second/third generation EGFR (i.e., afatinib, osimertinib) or ALK inhibitors (alectinib, ceritinib), respectively. (NCT02075840, NCT02838420, NCT02296125, NCT01466660)

ROS1 (1% TO 2% of lung adenocarcinomas)

- Comparative effectiveness trials comparing ROS1 inhibitors to cytotoxic chemotherapy in ROS1 rearrangement positive NSCLC

BRAF (1% TO 3% of lung adenocarcinomas)

- Comparative effectiveness trials comparing BRAF inhibitors, combination therapy with BRAF inhibitors and MEK inhibitors, and cytotoxic chemotherapy in BRAF mutation positive NSCLC

KRAS (25% to 30% of lung adenocarcinomas)

- No direct inhibitors of KRAS are available and recent approaches targeting downstream effectors of KRAS activity (e.g., treatment with MEK inhibitors) have not been successful. Basic science research into methods of targeting KRAS mutation positive NSCLC is needed. KRAS is frequently mutated in a large number of cancer types, and targeting of KRAS has been a long-standing difficulty in the field.

Additional molecularly directed therapies under study in adenocarcinoma and squamous cell carcinoma likely require that additional data be generated before comparative effectiveness studies are warranted. Many single-arm, basket, or umbrella trials involving these therapies are ongoing.

7. Pancreatic Ductal Adenocarcinoma

Impact/Burden of Pancreatic Ductal Adenocarcinoma

ACS estimates that, in 2016, 53,070 people in the United States will receive a diagnosis of pancreatic cancer (approximately 90% of which are pancreatic adenocarcinomas) and estimates that 41,780 people will die from the disease.[14,43] Although pancreatic cancer represents only approximately 3% of cancer diagnoses in the United States, it is responsible for approximately 7% of cancer deaths and represents the fourth leading cause of cancer death for both men and women. Additionally, ACS reports that the incidence of pancreatic cancer has increased by approximately 1% per year between 2000 and 2012.

Ongoing Evidence Gaps in Pancreatic Ductal Adenocarcinoma

Molecularly directed therapy is at an early stage of development in pancreatic ductal adenocarcinoma. FDA has approved no molecularly directed therapies for treating patients with pancreatic ductal adenocarcinoma, and current treatment guidelines do not include any molecularly directed therapies as treatment options. Although no molecularly directed therapies have been validated for use in pancreatic ductal adenocarcinoma, genomic analyses have identified potential genetic targets in this disease.[44,45] Data are needed regarding the potential therapeutic utility of directed therapies in these molecularly defined subsets of pancreatic cancer.

Current Guidelines for Pancreatic Ductal Adenocarcinoma

NCCN, ESMO, and ASCO have recently published guidelines regarding the treatment of pancreatic cancer.[46-48] These guidelines do not include any targeted therapies directed at molecularly defined subtypes among their recommended systemic therapies for metastatic pancreatic adenocarcinoma. While all three guidelines include as a treatment option combination therapy with gemcitabine and the EGFR inhibitor erlotinib, this regimen is not specifically indicated for use in a molecularly defined patient population (e.g., disease harboring activating EGFR mutations).

With respect to targeted/personalized therapy, the NCCN guidelines note that molecularly targeted therapies for pancreatic cancer are being developed and investigated and that "PARP inhibitors provide a promising avenue of treatment for cancers associated with BRCA 1/2 mutations."[46] Similarly, the ESMO guidelines state that "there is no role today for personalized medicine in this cancer" while noting that some potentially targetable mutations have been identified in pancreatic cancer (e.g., PARP inhibitors in tumors harboring mutations in BRCA 1/2 or PALB2; mTOR inhibitors in tumors harboring mutations in STK11, Hedgehog pathway inhibitors in tumors harboring PTCH mutations).[47] Lastly, the ASCO guidelines suggest that future directions in pancreatic cancer should include research into the genetics and biology of pancreatic cancer that could lead to the development of molecularly directed treatment strategies.[48]

Ongoing Research in Pancreatic Ductal Adenocarcinoma

Preliminary results are available from 4 trials of molecularly directed therapies in pancreatic ductal adenocarcinoma. These trials include 3 open-label, non-randomized studies and one open-label RCT. Targeted mutations include BRAF (1 study), BRCA1 or BRCA2 (2 studies), and EGFR (1 study). Molecularly targeted therapies showing some potential benefit include PARP inhibitors (olaparib or rucaparib) in pancreatic cancer in patients with germline BRCA mutations and EGFR inhibitors (erlotinib) in pancreatic cancer harboring EGFR mutations. See Appendix Table 5 for descriptions of these studies.

Searches identified 15 ongoing trials registered in ClinicalTrials.gov studying the use of a targeted therapy in a molecularly defined pancreatic ductal adenocarcinoma subtype. Only one of the identified trials was an RCT; the majority (10 of 15) were basket trials enrolling patients with cancers from multiple tissues of origin sharing a common genetic mutation. The majority of identified trials had a primary endpoint assessing tumor response to treatment (11 of 15). (See Appendix Table 6.) Targeted therapies under study in these trials included 14 unique compounds from 8 classes of

targeted therapeutics. Among these 14 targeted therapies, none are FDA-approved for treating pancreatic cancer; however, 8 of the drugs are commercially available through approvals for other cancer types. Genetic targets under study in these trials included 16 unique genetic loci. Targeted genetic loci for which data was available exhibited a wide range of prevalence among pancreatic cancers: KRAS (95%), CDKN2A (35%), germline BRCA2 (4%), ERBB2 (4%), germline PALB2 (3%), FGFR1 (2%), BRAF (~1%), CCND2 (~1%), FGFR2 (~1%), germline BRCA1 (~1%), MET (~1%), CCND1 (<1%), and CCND3 (<1%).[44,45]

In addition to these ongoing clinical trials, the Pancreatic Cancer Action Network recently announced that a pancreatic cancer-specific umbrella trial (Precision Promise), which will enroll patients in one of several sub-studies based on patients' molecular profiles, will be initiated in spring of 2017.[49]

Potential Research Areas and Comparative Effectiveness Research Questions in Pancreatic Cancer

The evidence base regarding molecularly directed therapy in pancreatic cancer is very small; our searches only identified publications or conference abstracts from 4 clinical trials. The most advanced molecularly directed therapy approach in pancreatic cancer is the use of PARP inhibitors in pancreatic cancers arising in patients with germline BRCA1 or BRCA2 mutations, which is currently under study in an RCT. Thus, it is likely that additional evidence supporting the efficacy of these therapies should be gathered before comparative effectiveness studies comparing molecularly directed therapies to conventional chemotherapy would be warranted.

Several of the most frequently mutated genes in pancreatic cancer do not have corresponding targeted therapies, including KRAS (95% of pancreatic cancers), p53 (74% of pancreatic cancers), and SMAD4 (31% of pancreatic cancers).[45] Although KRAS and p53 are frequently mutated in other cancers, SMAD4 mutations are relatively rare. Preclinical research into molecularly directed therapies targeting these mutations, in particular SMAD4, may be of future benefit to patients with pancreatic cancer.

8. Likelihood of Implementation in Practice and Feasibility of Carrying Out the Research

The oncology community has substantial interest in developing additional data on the use of molecularly directed therapies in genetically defined patient subpopulations. Based on the rapid adoption and incorporation into treatment guidelines of initial driver mutation-targeted therapy pairs (e.g., ALK inhibitors in ALK rearranged NSCLC and BRAF inhibitors in BRAF-mutant melanoma), it is likely that research findings in this area would influence treatment practice.

Although results of completed clinical trials are likely to inform future research or clinical practice, trials in certain patient populations may be hampered by the small percentage of patients who harbor alterations in a specific gene, which can be at or below 1% of the total number of patients. The need to screen large numbers of patients to identify the few patients eligible for a given targeted therapy may make difficult the recruitment of sufficient numbers of patients to achieve appropriate statistical power. Additionally, patients may be reluctant to enroll in RCTs comparing molecularly directed therapies to conventional chemotherapy because of the perception that molecularly directed therapies represent an improvement on non-targeted chemotherapy. In

particular, it may be difficult to enroll patients in randomized trials of molecularly directed therapies that are already commercially available and could be prescribed off-label.

9. Durability of Information

The evidence base for incorporation of genomic information into treatment decisions is developing rapidly. Within the three diseases scanned for this report (bladder cancer, NSCLC, and pancreatic ductal adenocarcinoma), 78 ongoing trials involving genetic markers hypothesized to be predictive of drug response were identified. The majority of these trials are early phase/non-randomized trials due to be completed in the next few years, which could substantially shift the landscape of potentially actionable genetic alterations in these diseases. Identification of additional putative driver mutations by ongoing sequencing efforts and the development of new investigational targeted therapies are also likely to increase the number of hypothesized actionable genetic alteration-targeted therapy combinations in coming years.

10. Conclusions

Bladder cancer, NSCLC, and pancreatic cancer account for approximately 36% of cancer-related deaths in the United States each year. For patients with advanced/metastatic disease, the use of cytotoxic chemotherapy has had limited impact on altering the course of disease and new approaches are being actively pursued. In particular, molecularly directed therapy based on genomic characterization of individual patient cancers is an active area of research. While this approach holds the promise of improving patient outcomes through the individualization of cancer therapy, there is limited evidence to date in support of this promise. For the three cancer types discussed in this report, only three classes of molecularly directed therapies have received FDA approval for use in genetically defined patient populations. All three are approved for use in molecularly defined subsets of NSCLC and collectively represent approximately 10% of all lung cancer cases. Additionally, only two of these FDA-approved approaches (EGFR inhibitors in EGFR-mutated NSCLC and ALK inhibitors in ALK rearrangement-positive NSCLC) have been studied in RCTs in the intended patient population. While the current evidence base for this approach is limited, this is a highly active area of research (particularly in NSCLC) with 49 disease-specific genetic alterations being tested in 78 ongoing clinical trials.

Given the paucity of data regarding the use of molecularly directed therapies in bladder cancer and pancreatic cancer, it appears premature to consider comparative effectiveness studies of molecularly directed therapies for these cancers at this time. Conversely, certain molecularly directed approaches in NSCLC have accumulated sufficient data to warrant consideration of comparative effectiveness research. However, for established approaches targeting EGFR mutations and ALK mutations a large number of comparative trials are ongoing, which could limit the durability of conclusions from comparative effectiveness research. Additionally, comparative effectiveness trials regarding emerging approaches that have accumulated preliminary data from non-comparative studies (e.g., targeting of BRAF mutations, targeting ROS1 mutations) could be limited by issues regarding feasibility (e.g., the small number of patients affected by these mutations and the potential unwillingness of patients to enroll in clinical trials of commercially available drugs).

List of Abbreviations:

ALK	Anaplastic Lymphoma Kinase
AXL	AXL receptor tyrosine kinase
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
CCND1	Cyclin D1
CCND2	Cyclin D2
CCND3	Cyclin D3
CDK 4/6	Cyclin Dependent Kinase 4/Cyclin Dependent Kinase 6
CDKN2A	Cyclin-Dependendent Kinase Inhibitor 2A
CHK1	Checkpoint Kinase 1
CREBBP	CREB Binding Protein
DDR2	Discoidin Domain Receptor Tyrosine Kinase 2
EGFR	Epidermal Growth Factor Receptor
EP300	E1A Binding Protein p300
ERBB2	Erb-B2 Receptor Tyrosine Kinase 2
ERBB3	Erb-B2 Receptor Tyrosine Kinase 3
ERBB4	Erb-B2 Receptor Tyrosine Kinase 4
FAK	Focal Adhesion Kinase
FGFR1/2/3/4	Fibroblast Growth Factor Receptor 1/2/3/4
HDAC	Histone Deacetylase
HER1	Human Epidermal Growth Factor Receptor 1 (also known as EGFR)
HER2	Human Epidermal Growth Factor Receptor 2 (also known as ERBB2)
HRAS	HRAS Proto-Oncogene, GTPase
JAK 1/2	Janus Kinase 1/Janus Kinase 2
KRAS	Kirsten Rat Sarcoma Proto-Oncogene, GTPase
MEK	Mitogen-Activated Protein Kinase Kinase
MET	MET Proto-Oncogene, Receptor Tyrosine Kinase
mTOR	Mammalian Target of Rapamycin
mTORC1	Mammalian Target of Rapamycin Complex 1
NSCLC	Non-Small Cell Lung Cancer

NRAS	Neuroblastoma RAS Viral Oncogene Homolog
NTRK1/2/3	Neurotrophic Receptor Tyrosine Kinase 1/2/3
PALB2	Partner and Localizer of BRCA2
PARP	Poly ADP Ribose Polymerase
PDGFRA	Pletelet Derived Growth Factor Receptor Alpha
PI3K	Phosphatidylinositol 3-Kinase
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PTCH	Patched (transmembrane protein receptor) coding gene
RET	RET Proto-Oncogene
ROS1	ROS Proto-Oncogene 1, Receptor Tyrosine Kinase
TSC1/2	Tuberous Sclerosis 1/2

Appendix Tables

Appendix Table 1. Recently Completed Trials/Ongoing Trials in Bladder Cancer with Preliminary Data

Genetic Target	Trial Name	Trial Type	Number of Patients and Patient/Disease Characteristics	Drug(s)	Primary Endpoint	Results
ERBB2 (HER2)/ERBB3	NCT02122172 Afatinib in Advanced Refractory Urothelial Cancer	Open-label, single arm	23 with Metastatic, platinum-refractory urothelial carcinoma	Afatinib	PFS	5/6 patients with ERBB2 and/or ERBB3 alterations achieved PFS of 3 mo vs. 0/15 patients without ERBB2 and/or ERBB3 alterations Investigators concluded that "afatinib demonstrated significant activity in patients with platinum-refractory urothelial carcinoma with ERBB2 or ERBB3 alterations" and that "afatinib deserves further investigation in molecularly selected urothelial carcinoma."[50]
EGFR (HER1)/ERBB2 (HER2)	NCT00949455 Double Blind Randomised Study of Lapatinib and Placebo in Metastatic TCC of the Urothelium (LaMB)	RCT (double blinded)	232 with Advanced or metastatic transitional cell positive for EGFR or HER2 expression by IHC who had achieved clinical benefit after completing first-line chemotherapy	Lapatinib or placebo	PFS	PFS 4.6 months (95% CI: 2.8 to 5.4) with lapatinib and 5.3 months (95% CI: 3.0 to 5.9) with placebo (HR=1.04 (95% CI: 0.79 to 1.39) Investigators concluded that "maintenance lapatinib does not improve outcomes in HER1 or HER2 positive individuals."[51]
FGFR3	NCT01004224 Dose Escalation Study in Adult Patients With Advanced Solid Malignancies	Open-label, single arm	33 with Metastatic urothelial carcinoma with FGFR3-alteration and prior systemic chemotherapy	Pan-FGFR inhibitor BGJ398	Dose for Phase II	RR: 36% (1 unconfirmed CR, 8 partial responses) in 25 evaluable patients Investigators concluded that this response rate "is notable given [the patients'] poor prognosis and limited therapeutic options."[52]
	NCT00790426 Phase II Study of TKI258 in Advanced Urothelial Carcinoma	Open-label, single arm	12 with Advanced urothelial carcinoma progressed after 1 to 3 rounds of systemic chemotherapy and FGFR3 mutation	Multikinase inhibitor dovitinib	Overall RR	"dovitinib has very limited single-agent activity in patients with previously treated advanced UC, regardless of FGFR3 mutation status."[53]
PI3K/Akt/mTOR	NCT01856101 Study of BEZ235 as Monotherapy in Patients With Transitional Cell Carcinoma After Failure of Platinum Based Chemotherapy (BEZ235)	Open-label, single arm	2 patients with PI3K/mTOR pathway mutations (loss of PTEN, PIK3CA mutation) of 22 with advanced or metastatic transitional cell carcinoma that had progressed after platinum-based chemotherapy	PI3K/mTORC1/2 inhibitor BEZ235	Overall RR	0/2 with PI3K/mTOR pathway mutations exhibited a response to treatment with BEZ235. Investigators concluded that "BEZ235 showed modest clinical activity and an unfavourable [sic] toxicity profile in patients with advanced and pretreated TCC." Development of this compound has been discontinued for all cancer indications.[54]

Appendix Table 1. Recently Completed Trials/Ongoing Trials in Bladder Cancer with Preliminary Data (continued)

Genetic Target	Trial Name	Trial Type	Number of Patients and Patient/Disease Characteristics	Drug(s)	Primary Endpoint	Results
PI3K/AKT/mTOR	NCT00805129 Everolimus (RAD001) in Metastatic Transitional Cell Carcinoma of the Urothelium	Open-label, single arm	46 with Metastatic transitional cell carcinoma and between 1 and 4 prior systemic treatments for advanced/metastatic disease	mTORC1 inhibitor everolimus	PFS at 2 months	1/46 CR >2 years. Whole-genome sequencing analysis of this patient revealed a loss-of-function mutation in TSC1, a negative regulator of the mTOR pathway. Genetic analysis of additional patients from this trial identified 4 additional patients with TSC1 mutations, 3 with PR.[55]

CI: confidence interval; CR Rate: complete response rate; HR: hazard ratio; MTD: maximum tolerated dose; ORR: objective response rate; PFS: progression-free survival; PR: partial response; RR: response rate

Appendix Table 2. Ongoing Trials of Targeted Therapies in Genetically Defined Bladder Cancer

Genetic Target	Drug(s)	Trial	Trial Type	Primary Endpoint	Completion Date
BRAF	Multikinase Inhibitor (Regorafenib)	NCT02795156	Basket	ORR	September 2018
CDKN2A	CDK 4/6 Inhibitor (Palbociclib)	NCT02334527	Non-Randomized	PFS	January 2025
CREBBP or EP300	HDAC Inhibitor (Mocetinostat [MGCD0103])	NCT02236195	Basket	ORR	December 2017
EGFR or ERBB2	EGFR Family Inhibitor (Afatinib)	NCT02795156	Basket	ORR	September 2018
EGFR or ERBB2 or ERBB3	EGFR Family Inhibitor (Neratinib [PB272])	NCT01953926	Basket	ORR	December 2018
ERBB2	Anti-HER2 Antibody Drug Conjugate (ado Trastuzumab Emtansine)	NCT02675829	Basket	ORR	February 2018
FGFR3	Anti-FGFR3 Antibody Drug Conjugate (LY3076226)	NCT02529553	Basket	MTD	September 2018
FGFR3	FGFR Inhibitor (BAY1163877)	NCT01976741	Basket	MTD, Pharmacokinetics	February 2018
FGFR3	FGFR Inhibitor (BGJ398)	NCT01004224	Basket	MTD	April 2017 (See preliminary results above)
FGFR3	FGFR Inhibitor (Dovitinib)	NCT01732107	Non-Randomized	CR Rate	January 2017
FGFR3	FGFR Inhibitor (JNJ-42756493)	NCT02365597	Non-Randomized	ORR	February 2018
FGFR3	FGFR Inhibitor (JNJ-42756493)	NCT02699606	Basket	ORR	October 2019
FGFR3	FGFR Inhibitor (Nintedanib)	NCT02278978	Non-Randomized	ORR	March 2016
HRAS	Farnesyl Transferase Inhibitor (Tipifarnib)	NCT02535650	Non-Randomized	ORR	March 2017
HRAS Wild-Type and KRAS Wild-Type	Anti-EGFR Antibody (Panitumumab)	NCT02818725	Randomized	PFS	September 2017
NF1 or PIK3CA or TSC1 or TSC2	mTORC1 Inhibitor (Albumin-Bound Rapamycin)	NCT02646319	Basket	CR Rate	May 2021
PIK3CA or TSC1 or TSC2	PI3K Inhibitor (Buparlisib [BKM120])	NCT01551030	Non-Randomized	ORR	March 2017
TSC1 or TSC2	mTORC1 Inhibitor (Everolimus)	NCT02201212	Basket	ORR	January 2022

CR Rate: complete response rate; MTD: maximum tolerated dose; ORR: objective response rate; PFS: progression-free survival

Appendix Table 3. Recently Completed Trials/Ongoing Trials in NSCLC with Preliminary Data

Genetic Target	Trial Name	Trial Type	Number of Patients with NSCLC	Number of Patients and Patient/Disease Characteristics	Drug(s)	Primary Endpoint	Results
BRAF	NCT01524978 Study of Zelboraf (Vemurafenib) in Patients With BRAF V600 Mutation-Positive Cancers	Open-Label, Basket	20	Patients with BRAF mutation-positive solid tumors, including patients with NSCLC	BRAF Inhibitor (Vemurafenib)	ORR	8 of 19 evaluable patients with NSCLC (42%) exhibited a partial response. Investigators concluded that "histologic context is an important determinant of response in BRAF V600-mutated cancers."[56]
BRAF	NCT01336634 Study of Selective BRAF Kinase Inhibitor Dabrafenib Monotherapy Twice Daily and in Combination With Dabrafenib Twice Daily and Trametinib Once Daily in Combination Therapy in Subjects With BRAF V600E Mutation Positive Metastatic (Stage IV) Non-Small Cell Lung Cancer	Open-Label, Single-Arm	174	Patients with a diagnosis of BRAF mutation-positive metastatic NSCLC who may or may not have received prior systemic therapy for metastatic disease	BRAF Inhibitor (Dabrafenib) or BRAF Inhibitor plus MEK Inhibitor (Dabrafenib plus Trametinib)	ORR	Among patients receiving dabrafenib monotherapy, the overall response rate was 33% (26 of 78) and 66% (4 of 6) in previously treated and treatment-naïve patients, respectively.[10] Among patients receiving combination therapy with dabarafenib and trametinib, the overall response rate was 63% (36 of 57; all patients had previously received therapy).[57] Investigators concluded that both dabrafenib monotherapy and dabrafenib/trametinib combination therapy represent potential treatment options for this patient population.[10,57]
DDR2	NCT01514864 Trial of Dasatinib in Patients With Advanced Cancers Harboring DDR2 Mutation or Inactivating B-RAF Mutation	Open-Label, Single-Arm	5	Patients with advanced NSCLC harboring a DDR2 mutation	Multikinase Inhibitor (Dasatinib)	ORR	The trial was terminated early due to slow accrual and lack of observed responses. Results posted on clinicaltrials.gov indicated that 0 of 5 patients harboring DDR2 mutations exhibited a response to dasatinib treatment.[58]
ERBB2 (HER2)	NCT00730925 Single-arm Trial of BIBW 2992 (Afatinib) in Demographically and Genotypically Selected NSCLC Patients	Open-Label, Single-Arm	7	Patients with advanced NSCLC harboring ERBB2 mutations	EGFR Family Inhibitor (Afatinib)	ORR	1 of 7 (14%) of patients harboring an ERBB2 mutation achieved an unconfirmed partial response to afatinib monotherapy with 5 of 7 patients (71%) exhibiting disease control (i.e., stable disease or objective response). Additionally, investigators reported that one patient receiving afatinib plus paclitaxel had a confirmed partial response lasting 41.9 weeks.[59]
ERBB2 (HER2)	NCT00818441 Dacomitinib (PF-00299804) As A Single Oral Agent In Selected Patients With Adenocarcinoma Of The Lung	Open-Label, Single-Arm	30	119 patients with advanced NSCLC, including 30 patients whose disease harbored a mutation in ERBB2	EGFR Family Inhibitor (Dacomitinib)	PFS at 4 Months	3 of 26 patients (12%) with mutations in exon 20 of ERBB2 had partial responses.[60]

Appendix Table 3. Recently Completed Trials/Ongoing Trials in NSCLC with Preliminary Data (continued)

Genetic Target	Trial Name	Trial Type	Number of Patients with NSCLC	Number of Patients and Patient/Disease Characteristics	Drug(s)	Primary Endpoint	Results
ERBB2 (HER2)	NCT00838539 Study Evaluating Neratinib In Combination With Temsirolimus In Subjects With Solid Tumors	Open-Label, Basket	6	63 patients with advanced cancer, including 6 patients with HER2-mutated NSCLC	EGFR Family Inhibitor plus mTORC1 inhibitor (Neratinib plus Temsirolimus)	MTD of Combination Therapy	Among patients with NSCLC harboring ERBB2 mutations, 2 of 6 (33%) exhibited a partial response.[61]
ERBB2 (HER2)	EUHER2 Retrospective Cohort Study	Retrospective Cohort	101	Patients with advanced HER2 mutation-positive NSCLC who had received at least one systemic therapy regimen that included chemotherapy and/or a HER2-targeted drug	Sixty-five patients received treatment with a HER2-targeted therapy including the anti-HER2 antibody trastuzumab, the EGFR family inhibitor neratinib, the EGFR family inhibitor afatinib, the EGFR family inhibitor lapatinib, and the anti-HER2 antibody drug conjugate ado-trastuzumab emtansine	N/A	Investigators reported an overall response rate of 50.9% for regimens including trastuzumab or ado-trastuzumab emtansine. The majority of treatments with trastuzumab included the addition of a cytotoxic agent (54 of 57 treatment regimens).[62]
FGFR1/FGFR2/ FGFR3/FGFR4	NCT01861197 Phase II Study of Dovitinib for FGFR1 Amplified Squamous Non-small Cell Lung Cancer	Open-Label, Single-Arm	26	Patients with advanced NSCLC previously treated with one or two lines of systemic chemotherapy and whose disease harbored an amplification of the FGFR1 gene	FGFR Family Inhibitor (Dovitinib)	ORR	Overall response rate was 11.5% (all partial responses) with a disease control rate of 50%.[63]

Appendix Table 3. Recently Completed Trials/Ongoing Trials in NSCLC with Preliminary Data (continued)

Genetic Target	Trial Name	Trial Type	Number of Patients with NSCLC	Number of Patients and Patient/Disease Characteristics	Drug(s)	Primary Endpoint	Results
KRAS	NCT01394016 Phase 1 Study of LY2835219 In Participants With Advanced Cancer	Open-Label, Single-Arm	49	Patients with advanced cancer including a cohort of patients with NSCLC who had received a median of 4 prior systemic treatments	CDK 4/6 Inhibitor (Abemaciclib)"	Number of participants with clinically significant effects (physical assessments and safety lab tests)	Disease-control rate for the entire NSCLC cohort was 51%. Among patients whose disease harbored mutations in KRAS, the disease control rate was 54% compared to 37% in patients with wild-type KRAS.[64]
KRAS	NCT01833143 Bortezomib in KRAS-Mutant Non-Small Cell Lung Cancer in Never Smokers or Those With KRAS G12D	Open-Label, Single-Arm	16	25 patients with advanced NSCLC including 16 patients whose disease harbored a mutation in KRAS	Proteasome Inhibitor (Bortezomib)	ORR	Overall response rate of 6% (one partial response) and a disease control rate of 44%. Investigators concluded that unless further study identifies an additional biomarker in this patient population that "no further study of bortezomib in KRAS-mutant lung cancers is warranted."[65]
KRAS	NCT01951690 Phase II Study of VS-6063 in Patients With KRAS Mutant Non-Small Cell Lung Cancer	Open-Label, Single-Arm	150	Patients with KRAS mutant NSCLC who had received at least one prior systemic therapy	FAK Inhibitor (VS-6063)	PFS at 12 Weeks	15 of the first 53 evaluable patients (28%) met the endpoint of progression-free survival at 12 weeks, including one patient with a partial response.[66]
KRAS	NCT01229150 Randomized Phase II Study of AZD6244 MEK-Inhibitor With Erlotinib in KRAS Wild Type and KRAS Mutant Advanced Non-Small Cell Lung Cancer	Open-Label, Randomized	79	41 KRAS mutant and 38 KRAS wild-type NSCLC patients whose disease had progressed following one or two prior systemic treatment regimens	Patients randomly assigned to MEK inhibitor (selumetinib) or MEK Inhibitor plus EGFR Inhibitor (selumetinib plus erlotinib)	ORR in KRAS-Mutant Patients	Overall response rate of 0% (95% CI: 0.0 to 33.6) for selumetinib monotherapy and 10% (95% CI: 2.1 to 26.3) for selumetinib plus erlotinib.[67]

Appendix Table 3. Recently Completed Trials/Ongoing Trials in NSCLC with Preliminary Data (continued)

Genetic Target	Trial Name	Trial Type	Number of Patients with NSCLC	Number of Patients and Patient/Disease Characteristics	Drug(s)	Primary Endpoint	Results
KRAS	NCT00890825 Comparison of AZD6244 in Combination With Docetaxel Versus Docetaxel Alone in KRAS Mutation Positive Non Small Cell Lung Cancer (NSCLC) Patients	Double-Blind, Randomized	87	Patients with KRAS-mutant NSCLC who had exhibited disease progression following first-line systemic treatment	Patients randomly assigned to treatment with MEK inhibitor plus cytotoxic chemotherapy (selumetinib plus docetaxel) or placebo plus cytotoxic chemotherapy (docetaxel)	OS	Median overall survival of 9.4 months (95% CI: 6.8 to 13.6 months) in the selumetinib arm compared to 5.2 months (95% CI: 3.8 to non-calculable) in the placebo arm. Investigators concluded that "these findings warrant further clinical investigation of selumetinib plus docetaxel in KRAS-mutant NSCLC."[68] A larger randomized control trial (SELECT-1, NCT01933932) was initiated in 2013; however, the trial sponsor recently reported that "the trial did not meet its primary endpoint of progression-free survival (PFS), and selumetinib did not have a significant effect on overall survival (OS)."[69] Full results await presentation and publication.
KRAS	NCT01192165 Safety and Tolerability Study of GSK1120212, a MEK Inhibitor, in Combination With Docetaxel, Erlotinib, Pemetrexed, Pemetrexed + Carboplatin, Pemetrexed + Cisplatin, or Nab-Paclitaxel	Open-Label, Non-Randomized	44	169 patients with advanced solid tumors.	MEK inhibitor (trametinib) in combination with one of several standard chemotherapy agents	Safety and Tolerability of Combination Regimens	Among 22 KRAS mutation-positive patients who received treatment with trametinib and docetaxel, investigators reported a response rate of 17% (all partial responses) and a disease control rate of 61%.[70] Among 20 KRAS mutation-positive patients who received treatment with trametinib and pemetrexed, investigators reported a response rate of 15% (all partial responses) and a disease control rate of 65%.[71]
KRAS	NCT01362296 Open-Label Study of GSK1120212 Compared With Docetaxel in Stage IV KRAS-mutant Non-small Cell Lung Cancer	Open-Label, Randomized	129	Patients with KRAS-mutant NSCLC previously treated with one platinum-based chemotherapy regimen	Patients randomly assigned in 2:1 ration to treatment with MEK inhibitor (Trametinib) or cytotoxic chemotherapy (docetaxel)	PFS	Median progression-free survival was 12 weeks in the trametinib arm compared with 11 weeks in the docetaxel arm.[72]
KRAS	NCT00531401 Study of Salirasib to Treat Non-Small Cell Lung Cancer	Open-Label, Single-Arm	30	Patients with treatment-naïve (n=7) or previously treated (n=23) KRAS mutation-positive NSCLC	RAS membrane delocalization agent (Salirasib)	Disease-Control Rate	No patient exhibited a radiographic response to salirasib. Investigators concluded that "salirasib at the current dose and schedule has insufficient activity in the treatment of KRAS mutant lung adenocarcinoma to warrant further evaluation"[73]

Appendix Table 3. Recently Completed Trials/Ongoing Trials in NSCLC with Preliminary Data (continued)

Genetic Target	Trial Name	Trial Type	Number of Patients with NSCLC	Number of Patients and Patient/Disease Characteristics	Drug(s)	Primary Endpoint	Results
MET	NCT00585195 Study Of Oral PF-02341066, A c-Met/Hepatocyte Growth Factor Tyrosine Kinase Inhibitor, In Patients With Advanced Cancer (PROFILE 1001)	Open-Label	28	Patients with various solid tumors, including patients with NSCLC harboring MET amplifications or MET exon 14 skipping mutations	Multikinase Inhibitor (Crizotinib)	Number of patients with Adverse Events, Pharmaco-kinetics, Maximum Tolerated Dose	The initial 13 NSCLC patients harboring MET amplifications exhibited an overall response rate of 33% (all partial responses) with a duration of response of 35 weeks.[74] The initial 15 NSCLC patients harboring MET exon 14 skipping mutations exhibited an overall response rate of 66% (all partial responses).[75]
RET	NCT01639508 Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity	Open-Label, Basket	3	Patients with advanced NSCLC harboring various genetic alterations, including RET rearrangements	Multikinase Inhibitor (Cabozantinib)	ORR	Among the first three RET mutation-positive patients enrolled in this trial, two patients exhibited a confirmed partial response while the third patient exhibited stable disease that was ongoing at 8 months of treatment.[76]
RET	NCT01823068 Vandetanib in Advanced NSCLC With RET Rearrangement	Open	18	Patients with advanced NSCLC harboring RET rearrangements that had received at least one prior systemic treatment for their disease	Multikinase Inhibitor (Vandetanib)	ORR	Overall response rate of 17% with another 44% of patients exhibiting stable disease.[77]
RET	NCT01582191 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	Open-Label, Non-Randomized	6	Patients with advanced cancers, including patients with NSCLC	Multikinase Inhibitor plus mTORC1 Inhibitor (Vandetanib plus Everolimus)	Maximum Tolerated Dose	Among 6 patients with RET rearrangement-positive NSCLC enrolled in the trial, 5 of 6 patients exhibited a partial response and the sixth patient exhibited stable disease.[78]

Appendix Table 3. Recently Completed Trials/Ongoing Trials in NSCLC with Preliminary Data (continued)

Genetic Target	Trial Name	Trial Type	Number of Patients with NSCLC	Number of Patients and Patient/Disease Characteristics	Drug(s)	Primary Endpoint	Results
ROS1	NCT00585195 Study Of Oral PF-02341066, A c-Met/Hepatocyte Growth Factor Tyrosine Kinase Inhibitor, In Patients With Advanced Cancer (PROFILE 1001)	Open-Label, Basket	50	Patients with various solid tumors, including patients with NSCLC harboring ROS1 rearrangements	Multikinase Inhibitor (Crizotinib)	Number of patients with Adverse Events, Pharmaco-kinetics, Maximum Tolerated Dose	Patients with NSCLC harboring a ROS1 rearrangement exhibited an objective response rate of 72% (3 complete responses and 33 partial responses) and a median progression-free survival of 19.2 months with 50% of patients still in follow-up for progression.[79]
ROS1	EUROS1 Retrospective Cohort Study	Retrospective Cohort	32	Patients with advanced ROS1 rearrangement-positive NSCLC	Multikinase Inhibitor (Crizotinib)	N/A	Among 29 patients evaluable for response, the overall response rate was 80% (5 complete responses, 19 partial responses) and the disease control rate was 86.7%. Progression-free survival for 30 evaluable patients was 9.1 months.[80]
ROS1	NCT02034981 Phase 2 Study Assessing Efficacy and Safety of Crizotinib in Patients Harboring an Alteration on ALK, MET or ROS1 (AcSé)	Open-Label, Umbrella	24	Approximately 488 patients with solid tumors harboring and ALK, MET, or ROS1 mutation, including patients with NSCLC	Multikinase Inhibitor (Crizotinib)	ORR at 8 Weeks	Among 24 evaluable patients, the overall response rate at 8 weeks was 63% (1 complete response, 14 partial responses). Among 15 patients evaluable at 6 months, the disease control rate was 53%.[81]
ROS1	NCT01945021 Phase II Safety and Efficacy Study of Crizotinib in East Asian Patients With ROS1 Positive, ALK Negative Advanced NSCLC	Open-Label, Single-Arm	129	Patients with ROS1-rearranged advanced NSCLC	Multikinase Inhibitor (Crizotinib)	ORR	Among 127 patients evaluable for response, the overall response rate was 69% and the median duration response had not yet been reached at an interim analysis 6 months after the last patient initiated treatment.[82]

CI: confidence interval; CR Rate: complete response rate; MTD: maximum tolerated dose; N/A: not applicable; NSCLC: nonsmall cell lung cancer; ORR: objective response rate; OS: overall survival; PFS: progression-free survival

Appendix Table 4. Ongoing Trials of Targeted Therapies in Genetically Defined NSCLC

Genetic Target	Drug(s)	Trial	Trial Type	Primary Endpoint	Completion Date
AKT	AKT Inhibitor (AZD5363)	NCT02664935	Umbrella	ORR, PFS	March 2018
AKT	AKT Inhibitor (AZD5363)	NCT02465060	Umbrella	ORR	June 2022
AXL	Multikinase Inhibitor (Cabozantinib)	NCT01639508	Non-Randomized	ORR	July 2017
AXL	Multikinase Inhibitor (MGCD265)	NCT00697632	Basket	Safety/Tolerability	March 2017
AXL	Multikinase Inhibitor (MGCD516)	NCT02219711	Basket	Dose Limiting Adverse Event, Pharmacokinetics	December 2018
BRAF	BRAF Inhibitor (Dabrafenib) or BRAF Inhibitor plus MEK Inhibitor (Dabrafenib plus Trametinib)	NCT01336634	Non-Randomized	ORR	August 2016 (See preliminary results above)
BRAF	BRAF Inhibitor (Vemurafenib)	NCT01524978	Basket	ORR	September 2016 (See preliminary results above)
BRAF	MEK Inhibitor (Selumetinib [AZD6244])	NCT01306045	Basket/Umbrella	ORR	December 2019
DDR2	Multikinase Inhibitor (Dasatinib)	NCT02465060	Umbrella	ORR	June 2022
DDR2	Multikinase Inhibitor (MGCD516)	NCT02219711	Basket	DLT, Pharmacokinetics	December 2018
ERBB2	Anti-HER2 Antibody Drug Conjugate (ado Trastuzumab Emtansine)	NCT02289833	Non-Randomized	ORR	June 2016
ERBB2	Anti-HER2 Antibody Drug Conjugate (ado Trastuzumab Emtansine)	NCT02465060	Umbrella	ORR	June 2022
ERBB2	Anti-HER2 Antibody Drug Conjugate (ado Trastuzumab Emtansine)	NCT02675829	Basket	ORR	February 2018
ERBB2	EGFR Family Inhibitor (Afatinib)	NCT02369484	Non-Randomized	Disease Control Rate	October 2018
ERBB2	EGFR Family Inhibitor (Afatinib)	NCT02465060	Umbrella	ORR	June 2022
ERBB2	EGFR Family Inhibitor (Afatinib)	NCT02597946	Non-Randomized	ORR	May 2018
ERBB2	EGFR Family Inhibitor (Lapatinib)	NCT01306045	Basket/Umbrella	ORR	December 2019
ERBB2	EGFR Family Inhibitor (Neratinib [PB272]) with or without mTORC1 Inhibitor (Temsirolimus)	NCT01827267	Non-Randomized (Patients are randomly assigned to one of two experimental arms)	Disease Control Rate	December 2016
FGFR1	FGFR1 Antagonist (GSK3052230)	NCT01868022	Basket	ORR, Safety, Pharmacokinetics	October 2016
FGFR1 or FGFR2 or FGFR3 or FGFR4	FGFR Inhibitor (AZD4547)	NCT02465060	Umbrella	ORR	June 2022
FGFR1 or FGFR2 or FGFR3 or FGFR4	FGFR Inhibitor (AZD4547)	NCT02664935	Umbrella	ORR, PFS	March 2018

Appendix Table 4. Ongoing Trials of Targeted Therapies in Genetically Defined NSCLC

Genetic Target	Drug(s)	Trial	Trial Type	Primary Endpoint	Completion Date
FGFR1 or FGFR2 or FGFR3 or FGFR4	FGFR Inhibitor (INCB054828)	NCT02393248	Basket	MTD	February 2018
FGFR1 or FGFR2 or FGFR3 or FGFR4	FGFR Inhibitor (JNJ-42756493)	NCT02699606	Basket	ORR	October 2019
FGFR1 or FGFR2 or FGFR3 or FGFR4	FGFR Inhibitor (Lucitanib [AL3810])	NCT02109016	Non-Randomized	ORR	October 2016
FGFR1 or FGFR2 or FGFR3 or FGFR4 or PDGFRA	Multikinase Inhibitor (Nintedanib)	NCT02299141	Non-Randomized	ORR	December 2017
HRAS	MEK Inhibitor (Selumetinib [AZD6244])	NCT01306045	Basket/Umbrella	ORR	December 2019
KRAS	CDK 4/6 Inhibitor (Abemaciclib [LY2835219])	NCT01394016	Basket	Safety/Tolerability	April 2017 (See preliminary results above)
KRAS	CDK 4/6 Inhibitor (Abemaciclib [LY2835219])	NCT02152631	Randomized	PFS, OS	August 2019
KRAS	CDK 4/6 Inhibitor (Palbociclib) plus MEK Inhibitor (PD0325901)	NCT02022982	Basket	MTD, Safety/Tolerability	December 2020
KRAS	CHK1 Inhibitor (Prexasertib [LY2606368]) with p38 MAPK Inhibitor (Ralimetinib [LY2228820])	NCT02860780	Non-Randomized	MTD	April 2020
KRAS	FAK Inhibitor (Defactinib [VS-6063])	NCT01951690	Non-Randomized	PFS	May 2016 (See preliminary results above)
KRAS	JAK 1/2 Inhibitor (Momelotinib [GS-0387]) plus MEK Inhibitor (Trametinib)	NCT02258607	Non-Randomized	Disease Control Rate	April 2017
KRAS	MEK Inhibitor (Selumetinib [AZD6244])	NCT00890825	Randomized	OS	December 2016 (See preliminary results above)
KRAS	MEK Inhibitor (Selumetinib [AZD6244])	NCT01306045	Basket/Umbrella	ORR	December 2019
KRAS	MEK Inhibitor (Selumetinib [AZD6244])	NCT01933932	Randomized	PFS	March 2017
KRAS	MEK Inhibitor (Binimetinib [MEK162]) plus EGFR Inhibitor (Erlotinib)	NCT01859026	Non-Randomized	MTD	March 2017

Appendix Table 4. Ongoing Trials of Targeted Therapies in Genetically Defined NSCLC

Genetic Target	Drug(s)	Trial	Trial Type	Primary Endpoint	Completion Date
KRAS	MEK Inhibitor (Selumetinib [AZD6244]) with or without EGFR Inhibitor (Erlotinib)	NCT01229150	Non-Randomized (Patients randomly assigned to one of two experimental arms)	PFS	September 2016 (See preliminary results above)
KRAS	Proteasome Inhibitor (Bortezomib)	NCT01833143	Non-Randomized	ORR	April 2017 (See preliminary results above)
KRAS or NRAS	MEK Inhibitor (Binimetinib [MEK162])	NCT02276027	Umbrella	ORR	April 2018
MET	MET Inhibitor (Capmatinib [INC280])	NCT01324479	Basket	Safety/Tolerability	February 2017
MET	MET Inhibitor (Capmatinib [INC280])	NCT01911507	Non-Randomized	MTD	December 2017
MET	MET Inhibitor (Capmatinib [INC280])	NCT02276027	Umbrella	ORR	April 2018
MET	MET Inhibitor (Capmatinib [INC280])	NCT02750215	Non-Randomized	ORR	December 2020
MET	MET Inhibitor (Tepotinib)	NCT02864992	Non-Randomized	ORR	September 2018
MET	Multikinase Inhibitor (Cabozantinib)	NCT01639508	Non-Randomized	ORR	July 2017
MET	Multikinase Inhibitor (Cabozantinib)	NCT02132598	Non-Randomized	ORR	June 2028
MET	Multikinase Inhibitor (Crizotinib)	NCT00585195	Non-Randomized	MTD, Safety/Tolerability, Pharmacokinetics	November 2019 (See preliminary results above)
MET	Multikinase Inhibitor (Crizotinib)	NCT02034981	Non-Randomized	ORR	July 2019
MET	Multikinase Inhibitor (Crizotinib)	NCT02465060	Umbrella	ORR	June 2022
MET	Multikinase Inhibitor (Crizotinib)	NCT02499614	Non-Randomized	ORR	January 2017
MET	Multikinase Inhibitor (Crizotinib)	NCT02664935	Umbrella	ORR, PFS	March 2018
MET	Multikinase Inhibitor (MGCD265)	NCT00697632	Basket	Safety/Tolerability	March 2017
MET	Multikinase Inhibitor (MGCD265)	NCT02544633	Non-Randomized	ORR	July 2018
MET	Multikinase Inhibitor (MGCD516)	NCT02219711	Basket	Dose Limiting Adverse Event, Pharmacokinetics	December 2018
NF1	MEK Inhibitor (Selumetinib [AZD6244])	NCT02664935	Umbrella	ORR, PFS	March 2018
NF1	MEK Inhibitor (Trametinib)	NCT02465060	Umbrella	ORR	June 2022
NRAS	MEK Inhibitor (Selumetinib [AZD6244])	NCT02664935	Umbrella	ORR, PFS	March 2018
NTRK1 or NTRK2 or NTRK3	Multikinase Inhibitor (Cabozantinib)	NCT01639508	Non-Randomized	ORR	July 2017
NTRK1 or NTRK2 or NTRK3	Multikinase Inhibitor (Entrectinib [RXDX-101])	NCT02097810	Basket	MTD, DLT	June 2017

Appendix Table 4. Ongoing Trials of Targeted Therapies in Genetically Defined NSCLC

Genetic Target	Drug(s)	Trial	Trial Type	Primary Endpoint	Completion Date
NTRK1 or NTRK2 or NTRK3	Multikinase Inhibitor (Entrectinib [RXDX-101])	NCT02568267	Basket	ORR	October 2018
NTRK1 or NTRK2 or NTRK3	Multikinase Inhibitor (MGCD516)	NCT02219711	Basket	Dose Limiting Adverse Event, Pharmacokinetics	December 2018
NTRK1 or NTRK2 or NTRK3	TRK Inhibitor (LOXO-101)	NCT02576431	Basket	ORR	April 2019
PIK3CA	AKT Inhibitor (AZD5363)	NCT02664935	Umbrella	ORR, PFS	March 2018
PIK3CA	AKT Inhibitor (MK2206)	NCT01306045	Basket/Umbrella	ORR	December 2019
PIK3CA	PI3K Inhibitor (Alpelisib [BYL719])	NCT02276027	Umbrella	ORR	April 2018
PIK3CA	PI3K Inhibitor (Taselisib [GDC-0032])	NCT02465060	Umbrella	ORR	June 2022
RET	Multikinase Inhibitor (Apatinib [YN968D1])	NCT02540824	Non-Randomized	ORR	December 2017
RET	Multikinase Inhibitor (Cabozantinib)	NCT01639508	Non-Randomized	ORR	July 2017 (See preliminary results above)
RET	Multikinase Inhibitor (Lenvatinib)	NCT01877083	Non-Randomized	ORR	September 2016
RET	Multikinase Inhibitor (MGCD516)	NCT02219711	Basket	Dose Limiting Adverse Event, Pharmacokinetics	December 2018
RET	Multikinase Inhibitor (Ponatinib)	NCT01813734	Non-Randomized	ORR	June 2018
RET	Multikinase Inhibitor (Vandetanib)	NCT01823068	Non-Randomized	ORR	July 2018 (See preliminary results above)
ROS1	Multikinase Inhibitor (Cabozantinib)	NCT01639508	Non-Randomized	ORR	July 2017
ROS1	Multikinase Inhibitor (Ceritinib)	NCT02186821	Non-Randomized	ORR	March 2018
ROS1	Multikinase Inhibitor (Ceritinib)	NCT02276027	Umbrella	ORR	April 2018
ROS1	Multikinase Inhibitor (Crizotinib)	NCT00585195	Non-Randomized	MTD, Safety/Tolerability, Pharmacokinetics	November 2019 (See preliminary results above)
ROS1	Multikinase Inhibitor (Crizotinib)	NCT02034981	Non-Randomized	ORR	July 2019 (See preliminary results above)
ROS1	Multikinase Inhibitor (Crizotinib)	NCT02183870	Non-Randomized	ORR	September 2017
ROS1	Multikinase Inhibitor (Crizotinib)	NCT02465060	Umbrella	ORR	June 2022
ROS1	Multikinase Inhibitor (Crizotinib)	NCT02499614	Non-Randomized	ORR	January 2017
ROS1	Multikinase Inhibitor (Crizotinib)	NCT02664935	Umbrella	ORR, PFS	March 2018
ROS1	Multikinase Inhibitor (Entrectinib [RXDX-101])	NCT02097810	Basket	MTD, DLT	June 2017
ROS1	Multikinase Inhibitor (Entrectinib [RXDX-101])	NCT02568267	Basket	ORR	October 2018
ROS1	Multikinase Inhibitor (PF-06463922)	NCT01970865	Non-Randomized	ORR	April 2018

DLT: dose-limiting toxicity; MTD: maximum tolerated dose; ORR: objective response rate; PFS: progression-free survival

Appendix Table 5. Recently Completed Trials/Ongoing Trials in Pancreatic Cancer with Preliminary Data

Genetic Target	Trial Name	Trial Type	Number of Patients with Pancreatic Cancer	Patient/Disease Characteristics	Drug(s)	Primary Endpoint	Results
BRAF	NCT01524978 Study of Zelboraf (Vemurafenib) in Patients With BRAF V600 Mutation-Positive Cancers	Open-Label, Basket	2	BRAF mutation-positive	Vemurafenib	Overall RR	1/2 experience minor response (<PR); Investigators concluded that "histologic context is an important determinant of response in BRAF V600-mutated cancers."[56]
BRCA1/BRCA2	NCT02042378 Study of Rucaparib in Patients With Pancreatic Cancer and a Known Deleterious BRCA Mutation	Open-Label, Single Arm	19	Metastatic pancreatic cancer with known deleterious germline BRCA1 or BRCA2 mutation, relapsed or progressive disease following 1 or 2 systemic chemotherapy-based regimens for metastatic disease	PARP inhibitor rucaparib	Overall RR	In 2016, Domchek and colleagues reported an overall response rate of 11% (1 complete response and 1 partial response).[83]
BRCA1/BRCA2	NCT01078662 Open Label Study to Assess Efficacy and Safety of Olaparib in Confirmed Genetic BRCA1 or BRCA2 Mutation Pats	Open-Label, Single Arm	23	Advanced pancreatic cancer with germline loss-of-function mutation in BRCA1 or BRCA2	PARP inhibitor olaparib	Overall RR	Investigators reported a response rate of 21.7% (95% CI: 7.5 to 43.7) among patients with pancreatic cancer.[84]
EGFR	NCT01608841 The Role of EGFR Mutations in Pancreatic Cancer Patients Receiving Gemcitabine With or Without Erlotinib	Open-Label, Randomized	88	Chemotherapy-naïve metastatic pancreatic cancer with or without a mutation in EGFR or KRAS	Gemcitabine or gemcitabine plus the EGFR inhibitor erlotinib	Disease control rate	In 2015, Wang and colleagues reported that the disease control rates in patients receiving gemcitabine plus erlotinib was 85% versus 33% (p=0.001) in patients with and without EGFR mutations, respectively. KRAS mutation status was not associated with treatment response.[85]

CI: confidence interval; CR Rate: complete response rate; MTD: maximum tolerated dose; ORR: objective response rate; PFS: progression-free survival

Appendix Table 6. Ongoing Trials of Targeted Therapies in Genetically Defined Pancreatic Ductal Adenocarcinoma

Genetic Target	Drug(s)	Trial	Trial Type	Primary Endpoint	Completion Date
BRAF	BRAF Inhibitor (Vemurafenib)	NCT01524978	Basket	ORR	September 2016 (See preliminary results above)
BRAF	BRAF Inhibitor + MEK Inhibitor (Dabrafenib + Trametinib)	NCT02465060	Umbrella	ORR	June 2022
BRCA 1 or BRCA 2	PARP Inhibitor (Olaparib)	NCT01078662	Basket	ORR	December 2016 (See preliminary results above)
BRCA 1 or BRCA 2	PARP Inhibitor (Olaparib)	NCT02184195	Randomized	PFS	August 2018
BRCA 1 or BRCA 2	PARP Inhibitor (Talazoparib [BMN-673])	NCT01286987	Basket	MTD	December 2016
BRCA 1 or BRCA 2	PARP Inhibitor (Veliparib [ABT-888])	NCT00892736	Basket	MTD, DLT	June 2016
BRCA 1 or BRCA 2 or Fanconi Anemia Gene or RAD 51	PARP Inhibitor (Olaparib)	NCT02511223	Non-Randomized	ORR	October 2017
BRCA 1 or BRCA 2 or Fanconi Anemia Gene or RAD 51	PARP Inhibitor (Olaparib)	NCT02677038	Non-Randomized	ORR	December 2019
BRCA 1 or BRCA 2 or PALB2	PARP Inhibitor (Veliparib [ABT-888])	NCT01585805	Non-Randomized	ORR	July 2017
CCND1 or CCND2 or CCND3	CDK 4/6 Inhibitor (Palbociclib)	NCT02465060	Umbrella	ORR	June 2022
CDKN2A	Aurora Kinase Inhibitor (Ilorasertib [ABT348])	NCT02478320	Basket	ORR	August 2022
CDKN2A	Aurora Kinase Inhibitor (Ilorasertib [ABT348])	NCT02540876	Basket	ORR	October 2017
CDKN2A or CCND1 or CCND2 or CCND3	CDK 4/6 Inhibitor (Palbociclib)	NCT02187783	Basket	ORR	April 2018
ERBB2	EGFR Family Inhibitor (Afatinib)	NCT02465060	Umbrella	ORR	June 2022
ERBB2	EGFR Family Inhibitor (Lapatinib)	NCT02342587	Basket	ORR	December 2016
FGFR1 or FGFR2	FGFR Inhibitor (AZD4547)	NCT02465060	Umbrella	ORR	June 2022
KRAS Mutant and PIK3CA Wild-Type	EGFR Family Inhibitor + MEK Inhibitor (Afatinib + Selumetinib)	NCT02450656	Basket	DLT, PFS	December 2019
KRAS Mutant and PIK3CA Wild-Type	EGFR Family Inhibitor + MEK Inhibitor (Lapatinib + Trametinib)	NCT02230553	Basket	DLT, ORR, PFS	December 2015
MET	MET Inhibitor (Crizotinib)	NCT02465060	Umbrella	ORR	June 2022
PIK3CA Mutant and RAS Wild-Type and PTEN Wild-Type	PI3K Inhibitor (Taselisib [GDC-0032])	NCT02465060	Umbrella	ORR	June 2022

DLT: dose-limiting toxicity; MTD: maximum tolerated dose; ORR: objective response rate; PFS: progression-free survival

Appendix – Searches

Methods

Literature Search:

In September 2016, we conducted a literature review to identify evidence-based research around the effectiveness of molecularly targeted therapies for specific solid tumors. We used PubMed, EMBASE, and Google Scholar to identify systematic reviews, meta-analyses and research reports, and the most current reviews, including those published by the Cochrane collaboration. We also searched the Websites for government agencies, such as the CDC, the NIH, and relevant professional associations (American Society of Clinical Oncology, National Comprehensive Cancer Network, European Society for Molecular Oncology), patient advocacy groups as likely to contain relevant material on the current prevalence and available treatment services as well as any references or sites suggested by our experts.

Clinical Trials and NIH Funding Announcements:

In September 2016, we conducted searches in ClinicalTrials.gov and NIH RePORTER for open clinical trials related to the topic. We used broad search terms for concepts like "molecularly guided therapy," "molecular targets," "personalized medicine," pharmacogenetics/pharmacogenomics, and "precision medicine." We used specific search terms for drugs and molecular subtypes, and combined those with specific search terms for bladder, lung, and pancreatic cancers. We also browsed PCORI's list of funded projects. The results are described above.

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