



**Pfizer Inc**

235 East 42nd Street  
New York, NY 10017

**Freda Lewis-Hall, M.D., DFAPA**  
Executive Vice President  
Chief Medical Officer

February 23, 2015

Tamara Syrek Jensen, J.D.  
Acting Director, Coverage and Analysis Group  
Centers for Medicare & Medicaid Services (CMS)  
7500 Security Boulevard  
Baltimore, MD 21244

Attn: Maria Ellis, Executive Secretary for MEDCAC  
Rita Redberg, MD, MSc, MEDCAC Committee Chair

Dear Ms. Syrek Jensen and MEDCAC Leadership:

On behalf of Pfizer, Inc., I am pleased to submit this comment letter focusing on molecular pathology testing to estimate prognosis in cancer, which provides insights that we hope will inform the discussion at the March 24, 2015 Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) meeting on the topic. Pfizer is a leading research-based biopharmaceutical company. As part of our mission, we seek to ensure that patients everywhere have access to high quality healthcare services and innovative medicines by working in partnership with stakeholders spanning the entire healthcare sector, including patients, providers, managed care organizations, government entities, and non-governmental organizations.

Over the last decade, Pfizer has dedicated time and resources towards enhancing the field of personalized medicine. As it relates to this MEDCAC meeting, Pfizer particularly is interested in the anaplastic lymphoma kinase (ALK) analyte for non-small cell lung cancer (NSCLC). Our focus on ALK stems from the fact that Pfizer developed and manufactures crizotinib, known by the trade name XALKORI<sup>®</sup>, which is indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by a Food and Drug Administration (FDA)-approved test.<sup>1</sup>

While we understand that this meeting is focused mainly on prognostic values of the listed biomarkers and clinical laboratory tests, we wish to reinforce the well-established predictive value of ALK to metastatic NSCLC patients in terms of determining eligibility for treatment with XALKORI. Further, the existing peer-reviewed literature and professional society guidelines support ALK testing of patients with

---

<sup>1</sup> XALKORI [package insert]. New York, NY: Pfizer Inc; 2014

a diagnosis of both metastatic (stage IV) and/or earlier stage (stages I, II, and III) NSCLC. Below are some more detailed comments on these points.

**ALK testing for metastatic (stage IV) NSCLC patients is well-established.** ALK predicts a potential response to XALKORI, which has demonstrated superior outcomes in terms of progression-free survival (PFS) when compared to standard chemotherapy. These findings were derived from two randomized, multicenter, open-label, phase 3 clinical trials, where XALKORI was compared directly to chemotherapy in either patients with previously treated<sup>12</sup> or patients with previously untreated<sup>3</sup> ALK-positive metastatic NSCLC. In both studies, patients with ALK-positive metastatic NSCLC were identified by the FDA-approved Vysis ALK fluorescence in situ hybridization (FISH) assay.

XALKORI was investigated as a first-line treatment compared to platinum doublet chemotherapy—either pemetrexed plus cisplatin or pemetrexed plus carboplatin. XALKORI demonstrated a significant improvement in PFS, with a hazard ratio of 0.45 vs. chemotherapy, with a p-value less than 0.001. Median PFS was 10.9 months in the XALKORI arm and 7.0 months in the chemotherapy arm. Secondary endpoints included objective response rate, duration of response, and overall survival (OS). With only 26% of all-cause deaths at data cutoff, median OS was not reached in either treatment arm.<sup>2</sup>

The most common adverse reactions of any cause occurring more frequently with XALKORI compared to chemotherapy in this study were vision disorder (71%), diarrhea (61%) and edema (49%). More serious potential adverse events previously reported with XALKORI were hepatotoxic and pulmonary toxic effects. Grade 3 or 4 elevations of aminotransferase levels occurred in 14% of the patients in the XALKORI group. Two patients discontinued XALKORI therapy because of interstitial lung disease, and one case of fatal pneumonitis was reported in a patient who had crossed over from chemotherapy to XALKORI.<sup>2</sup>

XALKORI also was investigated as a second-line treatment for ALK-positive metastatic NSCLC. For these patients, XALKORI demonstrated a significant improvement in PFS, achieving a hazard ratio of 0.49 when compared to chemotherapy and a p-value of less than 0.001, indicating statistical significance. Median PFS was 7.7 months in the XALKORI arm and 3.0 months in the chemotherapy arm. Secondary endpoints included objective response rate, duration of response, and OS.<sup>1</sup>

Median OS was 20.3 months in the XALKORI arm and 22.8 months in the chemotherapy arm according to a pre-specified interim analysis. The final median OS has not yet been reached, since only 40% of the total events required had occurred during analysis. Results could be confounded due to crossover: 64% of patients assigned to chemotherapy received XALKORI outside the study.<sup>1</sup>

In this study, serious adverse reactions were reported in 37% of patients treated with XALKORI and 23% of patients in the chemotherapy arm. Grade 3 or 4 laboratory abnormalities in 4% or more of XALKORI-treated patients included ALT elevation, Neutropenia, Lymphopenia, AST elevation, Hypokalemia, and Hypophosphatemia. Fatal adverse reactions in XALKORI-treated patients occurred in 9 patients or 5%.<sup>1</sup>

Together the results from these studies highlight the importance of not only testing NSCLC tissue specimens for the presence of ALK, but of the physician having those results in hand before determining

---

3 Solomon BJ, Mok T, et al. First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer. *N Eng J Med.* 2014; 371(23): 2167-77.

the most appropriate treatment option for each patient. The National Comprehensive Cancer Network (NCCN) has issued a clinical practice guideline that recommends ALK testing for all metastatic NSCLC that is non-squamous or not otherwise specified. This is a category 1 recommendation based upon high-level evidence<sup>4</sup>.

**ALK testing in earlier stage (stages I, II, III) NSCLC also is supported by medical specialty society guidelines.** Early ALK testing performed reflex to diagnosis is important to NSCLC patients because of the difficulty in obtaining adequate tissue samples or the lack of quality in using previous tissue samples for later testing. If ALK testing were limited solely to metastatic patients, care planning for early stage patients may be hindered, as there might not be adequate tissue available at that time or a patient's comorbidities may not allow for additional biopsies to obtain additional tissue. While patients may not always progress to metastatic cancer, early ALK testing, means that if the patient's cancer does metastasize or they experience a recurrence of disease, the timing to treatment initiation would not be impeded upon by turnaround time for obtaining ALK results. Additionally, early ALK testing may help determine eligibility for clinical trials in earlier stages of ALK-positive NSCLC.

In 2013, the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) issued a guideline titled, "Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors." The document included the following:

- A suggestion that ALK testing be ordered at time of diagnosis for patients diagnosed with advanced-stage disease (stage IV), including reflex testing where a separate order may not need to be placed;
- An expert consensus opinion that ALK testing at diagnosis from patients presenting with stage I, II, or III disease is encouraged, with a decision to perform this testing being made locally by the laboratory and oncology team; and
- A recommendation that tissue should be prioritized for ALK testing.<sup>5</sup>

These recommendations also were endorsed officially by the American Society of Clinical Oncology (ASCO) in 2014. Regarding the opinion on earlier stage ALK testing, the ASCO Clinical Practice Guidelines Committee issued a statement, which noted:

*"The advantage of this approach is that it enables rapid initiation of treatment in patients who experience a recurrence, because molecular information is immediately available to the oncologist. This benefit must be balanced against the extra cost incurred by molecular testing of patients with early-stage disease who do not experience a relapse."<sup>6</sup>*

In conclusion, we appreciate the opportunity to submit comments to the MEDCAC and reiterate the strong predictive value of ALK testing for NSCLC patients. We encourage CMS and other key healthcare stakeholders to continue providing adequate coverage for ALK testing for NSCLC patients at any stage of

---

<sup>4</sup> National Comprehensive Cancer Network, NCCN Guidelines, Non-Small Cell Lung Cancer, Version 4.2015. nccn.org

<sup>5</sup> Lindeman NI, Cagle PT, et al. Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors: Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. J Thorac Oncol. 2013;8:823–59.

<sup>6</sup> Leighl NB, Rekhtman N, et al. Molecular Testing for Selection of Patients With Lung Cancer for Epidermal Growth Factor Receptor and Anaplastic Lymphoma Kinase Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Society for the Study of Lung Cancer/Association of Molecular Pathologists Guideline. J Clin Oncol. 2014;32:3673-79.

diagnosis, with discretion regarding appropriateness granted to the patient's care team. We look forward to the discussion on March 24.

Sincerely,

A handwritten signature in cursive script that reads "Freda C. Lewis-Hall, M.D.".

Freda Lewis-Hall, M.D., DFAPA  
Executive Vice President and Chief Medical Officer

---

Bruce Quinn MD  
649 South Mansfield Avenue  
Los Angeles, CA 90036

February 22, 2015

To: MEDCAC Committee

Re: March 24, 2015 MedCAC (Molecular Pathology Testing to Estimate Prognosis in Cancer)

Comment Type: Comment Letter (No Auditorium Presentation)

## SUMMARY

*This letter raises concerns that this MedCAC may result in an unusual degree of confusion due to the oddly shaped topic, technology assessment, and Panel Questions.*

*The topic is “Molecular Pathology Testing to Estimate Prognosis in Cancer.” Several of the reviewed tests, such as Oncotype DX Breast, have exactly this indication and clinical usage, so a review of their data is appropriate. However, a substantial number of reviewed tests (ALK, KRAS, EGFR) have minimal prognostic value and are used for “prediction” of best chemotherapy choices based on the tumor’s characteristics.*

*The terms “predictive” and “prognostic” have developed very specific uses in oncology, at least since the late 1990s, and this is likely to be obscure to many panelists. By design, MedCAC are unlike FDA expert panels since MedCAC panels will sample a broad range of clinicians (a surgeon, an obstetrician, a rheumatologist, etc). The collision between the field-specific terminology, the odd selection of tests, and the question wording may cause confusion unless addressed by CMS and the Tech Assessment speaker in advance.*

## BACKGROUND & CONFLICT OF INTEREST

I am an MD PhD pathologist, and have worked in academic centers, for a global consulting company, for the Medicare as a regional medical director (2004-2008), and as a consulting federal health policy expert (2008-present). I have authored policy articles on diagnostic tests.<sup>1</sup> I have attended nearly every MedCAC held from 2008 to the present. I have written very detailed blogs about some MedCACs.<sup>2,3</sup> I could write a peer review policy article about the MedCAC process in the future. I became aware of the AHRQ technology assessment when a client brought it to my attention. However, this comment is my own.

---

<sup>1</sup> E.g. see: Frueh F & Quinn B (2014) Molecular diagnostics clinical utility strategy: A six part framework. Expert Rev Mol Diagn 14:777. (PMID 25109921). Quinn B (2010) Payers and the assessment of clinical utility for companion diagnostics. Clin Pharmacol Ther 88:751.

<sup>2</sup> <http://www.discoveriesinhealthpolicy.com/2015/01/cms-announces-medcac-on-molecular.html>

<sup>3</sup> <http://www.discoveriesinhealthpolicy.com/2014/05/lung-cancer-screening-cms-advisory.html>

## WHY THIS TECHNOLOGY ASSESSMENT IS UNUSUAL

Numerous sources since the 1990s have defined oncology tests as “**prognostic**” when they forecast the course of disease (e.g. low grade or high grade, short or long survival) and as “**predictive**” when they point to medication choices (e.g. estrogen-receptor positive breast cancer points to tamoxifen or other hormonal treatments.) Sometimes there is an overlap between prognostic and predictive features. For example, breast cancers that express estrogen receptors are (as a generalization) better differentiated with better prognosis than breast cancers that don’t, while at the same time, taking cases who all express estrogen receptors, randomized trials show that taxomifen therapy further improves the outlook for estrogen-positive cases.

Tests like **Oncotype DX Breast** are designed to correlate with breast cancer outcomes more accurately than existing clinical variables (such as tumor size alone). These are called “prognostic tests.”

The AHRQ technology assessment confusingly added a range of tests (**KRAS, EGFR, ALK**) that are **not used** primarily or routinely as “prognostic tests.” I cannot make this statement as a practicing oncologist, but for the past ten years, cancer diagnostics and therapies have been a major focus of my work, and I read widely and attend many conferences in this field. For example, the guidelines-basis Medscape summary for KRAS and EGFR testing in colon cancer discusses entirely their “predictive” use and not their prognostic use.<sup>4</sup> BCBS guidelines for use of KRAS and BRAF in cancers focus on their predictive uses for chemotherapy choices.<sup>5</sup> Such examples can be multiplied at length.

**The AHRQ review scrupulously avoided including any information about the actual uses of ALK/EGFR/KRAS genetic tests for predicting chemotherapy choices. However, this is mentioned only very briefly in the huge TA report. Any busy reader could easily overlook it. A clinical reader outside the field might not understand it.**

This is akin to studying aspirin, but excluding uses for fever and analgesia, and studying only aspirin’s effect on treating schizophrenia. The report would conclude there are no indications, no guidelines, no randomized controlled trials, etc, using aspirin to treat schizophrenia.

The wording of the MedCAC goals and questions has to be read very carefully. CMS writes, “Outcomes of interest to CMS include both beneficial and harmful outcomes experienced by patients from anti-tumor treatment decisions based on results of tests estimating cancer prognosis.” Not the benefits and harms of treatment decisions based on using KRAS, EGFR, ALK to as predictive tests to correctly select chemotherapy – their only main use.

## STUDY OF EGFR, KRAS, ALK FOR “PROGNOSTIC VALUE” WAS INCONSISTENT WITH MEDCAC GOALS

CMS has a public statement on when it refers to the MedCAC.<sup>6</sup> CMS will hold MedCACs “to address broad, significant issues relevant to coverage policy development....There is significant controversy among experts...the available research has not addressed policy questions...use of the

---

<sup>4</sup> <http://emedicine.medscape.com/article/1690010-overview#showall>

<sup>5</sup>

[https://www.bcbsnc.com/assets/services/public/pdfs/medicalpolicy/kras\\_and\\_braf\\_mutation\\_analysis\\_in\\_cancer.pdf](https://www.bcbsnc.com/assets/services/public/pdfs/medicalpolicy/kras_and_braf_mutation_analysis_in_cancer.pdf)

<sup>6</sup> <http://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=10>

technology is a subject of controversy among the public....” These statements today echo the NIH position on holding consensus conferences 40 years ago, “to hasten resolution of scientific issues...with important social dimensions...[to achieve] consensus on gaps in knowledge.”<sup>7</sup> While public concerns and evidentiary needs may be important for actual prognostic tests in cancer, there is no public demand or rich scientific debate about whether KRAS, ALK, or EGFR have pressing issues regarding their “prognostic” value. They have little, as the AHRQ authors found out, but this was well-known prior to the AHRQ report.

### **MEDCAC QUESTIONS ARE CONFUSING ENOUGH IN THE BEST OF TIMES**

I have attended most MedCACs since 2008, and panelists frequently debate the wording of the questions.

### **PAST “PEAK” FOR CONFUSING QUESTIONS**

The most misleading technical report (with resulting confusion) occurred in 2011. The title of the MedCAC was “**The Impact of ESA Use on Renal Transplant Graft Survival**” while the technical assessment was different, “**The Impact of Pre-Transplant Red Blood Cell Transfusions in Renal Allograft Rejection**” and the first question was, “**How confident are you that there is adequate evidence to determine whether or not current “panel reactive antibody (PRA) assays” predict renal transplant graft survival for individual patients** (in contrast to populations)?” This cascade of different topics is itself alarming. But one of the key issues for clinical commenters dealing with actual patients was that tech assessment asked only about the survival of kidney grafts after transplantation in donors with prior transfusions. Clinical experts were concerned, because the main transfusion issue is that patients on dialysis develop antibodies that PREVENT transplantation. This was “defined away” by the TA design. Studying only those carved-out patients who happened to not develop antibodies, and were transplanted, made no sense to dialysis clinicians.<sup>8</sup> Similarly, the pending MedCAC has “defined away” the clinical uses of ALK, EGFR, and KRAS, resulting in bizarre residual questions.

I attended the renal transplant MedCAC and the combination of title, tech assessment (and its evidence carveouts and rules) and the afternoon questions were very confusing, as can be witnessed in the 2011 transcript that is still online today.<sup>9</sup>

I am concerned this confusion may arise anew, in equal or greater fashion, for the EGFR, KRAS, and ALK tests component of the March 24, 2015 questions.

---

<sup>7</sup> Frederickson DS (1978) Seeking technical consensus on medical innovations. Clin Res 26:116. Cited in: Wortman PM et al. (1988) A process evaluation of the NIH consensus development program. J Health Politics, Policy, Law 13:469.

<sup>8</sup> “A patient who has been sensitized to HLA antigens prior to transplant will have antibodies directed against those antigens and, in general, will not be able to receive an organ transplant from a potential donor who has one or more of those HLA antigens. American Society of Nephrology, <https://www.asn-online.org/policy/webdocs/jan2011medcactestimonyharmon.pdf>

<sup>9</sup> <http://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/downloads/id57c.pdf> “You didn’t transplant patients that had a high risk of graft rejection if...they made these antibodies and were excluded.” The TA author noted the “dilemma,” “it’s not one of the key questions that we were given.” “Transplant outcomes include THREE things...graft survival, time on the wait list, whether you ever get a graft or not....The tech assessment [team] would [have been] able to do this if they had the questions addressed for them in that way.”



1414 Prince Street, Suite 204  
Alexandria, VA 22314  
703.548.1225 Fax 202.315.3871  
[www.FightColorectalCancer.org](http://www.FightColorectalCancer.org)

February 23, 2015

Maria Ellis, Executive Secretary for MEDCAC  
Centers for Medicare & Medicaid Services  
Center for Clinical Standards and Quality  
Coverage and Analysis Group  
7500 Security Boulevard  
Baltimore, MD

These comments are submitted on behalf of Fight Colorectal Cancer, a non-profit, nonpartisan advocacy organization that is committed to the fight against colon and rectal cancer. They address issues being discussed at the March 24, 2015 MEDCAC meeting.

Fight Colorectal Cancer (Fight CRC) is the leading colorectal cancer advocacy organization in Washington, DC, empowering survivors to raise their voices, training advocates around the country, and educating lawmakers and pushing them for better policies.

We offer support for patients, family members and caregivers, and we serve as a resource for colorectal cancer advocates, policymakers, medical professionals, and healthcare providers. Additionally, we do everything we can to both increase and improve research—at all stages of development and for all stages of cancer.

FightCRC believes in fully disclosing conflicts of interest. We have worked with and received unrestricted funding from many companies that have an interest in genetic testing around colorectal cancer, including Quest Diagnostics, Myriad, Bristol Myers Squibb, Amgen, Genomic Health and Foundation Health. None of these companies, nor any of our other corporate supporters has influenced our comments on this issue.

Being diagnosed with cancer is a life-changing experience. Suddenly patients are dropped into a world with a new language and multiple medical procedures. Frequently, they have a hard time understanding the implication of their diagnosis, especially patients with metastatic disease. When we look at the utility of these tests for patients, we do so from their unique vantage point:

- BRAF: Patients with metastatic BRAF-mutant tumors and low or stable micro-satellite instability status have a very poor prognosis. This information is important to patients because these patients frequently pass away relatively quickly after their diagnosis. Some patients want an understanding of their personal “timeline” so that they can put their affairs in order.
- KRAS: Patients with metastatic KRAS-mutant tumors do not respond to EGFR inhibitors such as cetuximab and panitumumab. Thus, the KRAS test is predictive of response, and is not

technically a prognostic test. KRAS testing is critical for patients to ensure that they are not exposed to treatment which will not benefit them.

- **Micro-satellite Instability (MSI):** MSI testing is the first step in determining whether a patient has Lynch Syndrome, a germline mutation which increases the risk of colorectal, uterine and many other cancers. It's related to good prognosis and predicts lack of benefit for adjuvant treatment, but it's most important use is diagnostic, because it helps patients and their families understand their risk so that they can be screened appropriately. Because of this, the National Comprehensive Cancer Network recommends routine MSI testing for all patients diagnosed under the age of 70.
- **MLH1 promoter methylation:** This is the second step in determining Lynch Syndrome, and the same comments apply.
- **Oncotype DX Colon:** This is a prognostic test which may help patients with Stage 2 colon cancer determine whether they should receive treatment or not. The "to treat or not to treat" decision for stage 2 patients and their physicians is very challenging, and we have heard mixed reviews on the utility of this test, because the difference between low risk of recurrence scores and high risk of recurrence scores is small. At the same time, we've also heard from patients who found the test useful. Our understanding is that there are other tests for patients in this situation, such as Coloprint, so we would appreciate understanding why this test was called out and others were not included.

The Oncotype test has been analytically validated. There are multiple versions of the other tests, some of which are FDA-cleared.

Our sense is that all of these tests have clinical utility, some more than others. The Stage 2 decision-making tests (including both Oncotype DX and Coloprint) have the least proof of clinical utility; however, in a community setting, tests such as these may help a general oncologist and patients make critical decisions.

In terms of the other questions being asked of the panel, please see our comments below:

*Please discuss whether each factor below might change the generalizability of evidence about prognostic molecular pathology tests in Medicare beneficiaries with cancer:*

- *Regulatory status of test (e.g., US Food & Drug Administration (FDA) approved/cleared vs. laboratory-developed test)?*
  - **COMMENT:** There isn't a black and white answer to this question. Presumably a cleared test is preferable to an LDT unless the LDT is performed in a high quality lab. At the same time, LDT panels may be able to perform multiple tests at once, which is much more efficient from the patient's perspective.



1414 Prince Street, Suite 204  
Alexandria, VA 22314  
703.548.1225 Fax 202.315.3871  
[www.FightColorectalCancer.org](http://www.FightColorectalCancer.org)

- *Type of performing laboratory (i.e., university medical center laboratories, independent commercial laboratories, or community hospital-based laboratories)?*
  - COMMENT: Again, there's not a black and white answer to this question because it depends on the test.
- *Subgroups in the Medicare beneficiary population (e.g., by age)?*
  - COMMENT: Lynch Syndrome screening is recommended for everyone diagnosed under the age of 70. The other tests have no real relationship to age.
- *Genomic variations within cancers (e.g., diversity of cancer genomes)?*
  - NO COMMENT

In conclusion, we hope that the panel discussion focuses on how these tests may help patients and physicians make critical decisions around treatment and the patients' lives as they live their journey with cancer.

Thank you for your consideration of our comments.

A handwritten signature in blue ink that reads "Anjelica Davis".

Anjelica Davis, MPPA  
President