Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer [ID1098]--Comments to the Appraisal consultation

We are The ROS1ders, a group of 259 patients and caregivers dealing with ROS1-positive (ROS1+) non-small cell lung cancer (NSCLC) in 32 countries. We network and collaborate with clinicians, researchers, cancer advocacy organizations and industry as part of the Global ROS1 Initiative. Our global group represents more than four times the number of ROS1 patients found in any ROS1 clinical trial cohort to date. With this letter, we are contributing our collective experience to the appraisal consultation.

Most of the patients in the ROS1ders have been treated with crizotinib. We believe crizotinib is an effective treatment for metastatic ROS1 non-small cell lung cancer (NSCLC), and gives us better quality of life than chemotherapy.

Crizotinib enables ROS1+ NSCLC patients to live normal lives instead of coping with a terminal disease

The majority of crizotinib-treated ROS1 patients are experiencing astonishing improvements in their state of health, which is unknown for chemotherapy. More than two-thirds of our members report a strong response to crizotinib and long progression-free periods with a very good quality of life. Many patients in our group started taking crizotinib in 2011 or 2012, and several of them continue to take the drug and enjoy no evidence of disease. These patients are dealing with lung cancer as a chronic illness rather than a terminal disease. We may have a chronic illness that will one day claim our lives, but we are NOT at “end of life.”

Crizotinib gives ROS1+ NSCLC patients a superior quality of life compared to chemo

Several of our members received one or more lines of chemotherapy prior to their treatment with crizotinib. Their quality of life was significantly worse while receiving chemo than while taking crizotinib. The QALY criteria for evaluating crizotinib does not capture the impact of crizotinib versus chemo on our daily lives. ROS1 patients are often younger than typical lung cancer patients; at the time of diagnosis, many of our members are employed and have children at home. When treated with crizotinib instead of chemo, most can continue living their usual lives with a minimum of side effects. When treated with chemo, many patients are too ill to participate in the aspects of life they most enjoyed, and most saw their cancer progress in less than a year.

The results of several clinical trials worldwide have led to consensus among ROS1+ NSCLC patients and their doctors that crizotinib is significantly superior to all chemotherapy regimens in ROS1 patients in terms of response rate, progression-free time, toxicity, quality of life and survival time. Our experience would indicate an improvement in overall survival as well. The patient-relevant parameters are quite similar to ALK-positive NSCLC patients (for whom NICE covers crizotinib). Fortunately, the progression-free time for ROS1 patients is significantly longer than for ALK patients.

Quality-adjusted Life Year (QALY) evaluation often does not capture all the relevant quality of life improvements experienced by patients on crizotinib. First, QALY analyses usually compare the state of health of NSCLC patients on crizotinib to that same patient’s state of health before taking crizotinib. A more honest evaluation would compare the health of a typical ROS1+ NSCLC patient on crizotinib (who survives for years with good quality of life) to the typical metastatic NSCLC patient on chemo (who usually dies within one year of diagnosis) or even on hospice. ROS1+ NSCLC patients on crizotinib are often able to continue working, caring for their families, and contributing to society, and are far less likely to be hospitalized with treatment complications compared to chemotherapy recipients. This places less emotional and financial burden on spouses, caregivers, and consumes fewer healthcare system resources.

Conducting a Randomized Controlled Trial (RCT) for ROS1 is not ethical nor reasonable

It is unethical to randomize patients to therapies known to be less effective. Several Phase 2 studies show crizotinib is effective in 70% to 80% of ROS1+ patients, whether those patients are untreated or heavily pretreated. Considerable scientific data shows chemotherapy is effective in about 20% of NSCLC patients in first line treatment, and effective in only 9% of NSCLC patients in second line treatment.

An RCT would also be complicated by the fact that ROS1+ NSCLC occurs in a very small population of patients, which means not enough patients would be available for a Phase 3 trial. To demonstrate:

- About 207,000 new NSCLC cases were predicted in the USA for 2017.
- Two recent journal articles found only 60% of NSCLC patients are getting tested for known driving oncogenes.
- ROS1 occurs in about 1% of tested NSCLC patients.
- Typically 3% of cancer patients enroll in clinical trials. The EUCROSS trial had to test 200 patients to find one ROS1 patient willing and able to enter a trial.

When all these factors are considered, about 37 new ROS1 patients were available to enroll in US ROS1 clinical trials during 2017—hardly enough to power a Phase 3 clinical trial. The UK has far fewer lung cancer patients than the USA. Therefore, creating a trial comparing crizotinib with chemotherapy in ROS1+ NSCLC patients would be an unnecessary waste of patients, time and money.

The scientific community strongly recommends testing NSCLC patients for ROS1 and treating them with crizotinib

Based on a comprehensive evaluation of ROS1 studies and clinical trials, the International Association for the Study of Lung Cancer (IASLC), the College of American Pathologists (CAP), and the Association for Molecular Pathology (AMP) strongly recommend testing for *ROS1* in the 2018 update to their lung cancer molecular testing guideline:

"ROS1 testing must be performed on all lung advanced stage adenocarcinoma patients, irrespective of clinical characteristics. … This recommendation is evidence based and supported by 9 studies. … All included studies were assessed for quality and none were found to have methodologic flaws that would raise concerns about the studies' findings … Although relatively rare, accounting for <2% of none small cell lung carcinomas and 2% to 3% of lung adenocarcinomas, structural rearrangements involving the ROS1 gene generate an oncogenic fusion that can be treated successfully with targeted inhibitors. A single phase I clinical trial of 50 NSCLC patients demonstrated that the presence of a ROS1 rearrangement by FISH or RT-PCR predicts response to targeted inhibition using crizotinib, with a response rate of 72% and median progression-free survival of 19.2 months. Based on this trial, the FDA approved the expanded use of crizotinib in patients with ROS1-rearranged NSCLC in 2016. A European multi-institutional retrospective study of 32 patients with ROS1-rearranged NSCLC treated with crizotinib demonstrated an 80% response rate and 9.1-month progression-free survival. Overall survival for patients with ROS1-rearranged tumors irrespective of use of targeted therapy appears longer than that for patients with other molecular alterations undergoing targeted therapy. As with ALK, ROS1 activation is driven by structural variants, with multiple different partners fusing to the C-terminal portion of ROS1 containing the cytoplasmic tyrosine kinase and driving downstream signaling through MAPK, JAK/STAT, and PI3K pathways."
Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors (Journal of Molecular Diagnostics), http://jmd.amjpathol.org/article/S1525-1578(17)30590-1/fulltext

Furthermore, the prospective European EUCROSS phase II trial evaluated crizotinib in ROS1+ lung adenocarcinoma and came to the conclusion: "Crizotinib is a highly effective and safe treatment in the subset of ROS1 rearranged NSCLC patients as determined by FISH and DNA-sequencing." In total, 34 patients were enrolled in this trial. Of these, the patients whose ROS1+

was identified by sequencing showed a response rate of 83%. Even after a long study period the median progression-free survival has yet to be determined.
EUCROSS: A European Phase II Trial of Crizotinib in Advanced Adenocarcinoma of the Lung Harboring ROS1 Rearrangements - Preliminary Results
http://www.jto.org/article/S1556-0864(16)31669-0/fulltext (Journal of Thoracic Oncology)

Conclusion: Crizotinib is superior to existing therapies for ROS1+ NSCLC, and a wise investment for NICE

For the first time ever, ROS1+ NSCLC patients have a truly effective therapy, with previously unattainable improvements in their quality of life and survival. There isn't a need to wait for an RCT comparing crizotinib to chemo when the improvement in outcomes is this dramatic. Allowing these patients to take crizotinib instead of other existing NSCLC therapies enables UK citizens to continue their lives instead of being "end of life" patients.

NICE, please provide crizotinib as a treatment option for ROS1+ NSCLC patients.

Sincerely,

The ROS1ders
ros1cancer.patient@gmail.com
http://ros1cancer.com

D. Ross Camidge, MD PhD
Professor of Medicine/Oncology, Joyce Zeff Chair in Lung Cancer Research
University of Colorado

Sai-Hong Ignatius Ou, MD, PhD
Health Science Clinical Professor of Medicine, Chao Family Comprehensive Cancer Center
Division of Hematology-Medical Oncology, Department of Internal Medicine
University of California Irvine School of Medicine

Alice T. Shaw, MD PhD
Director, Center for Thoracic Cancers, Massachusetts General Hospital
Professor of Medicine, Harvard Medical School

Professor Benjamin Solomon, MBBS, PhD, FRACP
Peter MacCallum Cancer Centre, Australia

Jürgen Wolf, MD, Professor
Cancer Center Cologne, Lung Cancer Group Cologne,
University Hospital of Cologne, Cologne/Germany