**Vemurafenib/Cobimetinib Combination Improves Outcomes in Advanced Melanoma**

**BACKGROUND:** Although the BRAF inhibitor vemurafenib (Zelboraf) improves progression-free survival (PFS) and overall survival (OS) in patients with advanced melanoma, 25% of patients using it as monotherapy end up with a second cancer. Combining BRAF and MEK inhibitors has been shown to prevent or delay the onset of resistance with BRAF inhibitors alone. A new study investigated the use of combining vemurafenib with the experimental MEK inhibitor cobimetinib.

**METHODS:** This international, multicenter, randomized, phase 3 trial included 495 patients with untreated, unresectable locally advanced or metastatic BRAF V600 mutation melanoma. Patients were randomized in a 1:1 ratio to vemurafenib (960 mg twice daily) together with placebo (control group) or to cobimetinib (combination group; 60 mg once daily for 21 days, followed by 7 days off). The median follow-up at the time of reporting was 7.3 months. The primary end point was investigator-assessed PFS. The secondary end points were rates of confirmed objective response and OS.

**RESULTS:** The median PFS was 9.9 months in the combination group compared with 6.2 months in the control group (hazard ratio for death or disease progression, 0.51; 95% confidence interval, 0.39-0.68; \( P < .001 \)). The combination group had a significantly higher complete or partial response compared with the control group—68% versus 45%, respectively (\( P < .001 \)); this included a complete response rate of 10% versus 4%, respectively. Interim OS analyses showed higher rates of survival at 9 months with the combination compared with control (81% vs 73%, respectively).

Adverse events were reported in ≥20% of the patients in either group (eg, arthralgia, alopecia, diarrhea, and rash); however, combining vemurafenib with cobimetinib decreased the number of secondary cutaneous cancers. No significant difference was observed in grade ≥3 adverse events. Drug discontinuations were similar (13% and 12%, respectively).

Approximately 50% of patients diagnosed with melanoma carry the BRAF mutation. Combination therapy with vemurafenib and cobimetinib demonstrated improvement in PFS and response rate, reduced second cancers, and early evidence of improved OS among patients with BRAF V600 mutation metastatic melanoma, at the cost of some increase in toxicity.


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**CONCERTDA MA**

The phase 3 study by Larkin and colleagues is an important advance in the concept of combination MEK and BRAF inhibition for the treatment of patients with malignant melanoma. The combination of vemurafenib and cobimetinib led to improved PFS/OS at 9 months, and tumor responses while minimizing the risk of second cancers associated with squamous-cell carcinoma, a worrisome problem when patients are treated with the BRAF inhibitor, vemurafenib, alone. Although the combination produced more grade 3 adverse effects (nausea, vomiting, and diarrhea), none were life-threatening and most were grade 1 or 2, which can be easily managed with supportive care medications. These results appear to be similar to those from another phase 3 trial evaluating the combination of other MEK and BRAF inhibitors, dabrafenib and trametinib.1

A New Drug Application has been filed by Genentech and was accepted by the US Food and Drug Administration, which announced an action date of August 11, 2015, to review the combination for the treatment of patients with advanced melanoma.

The landscape for treating patients with advanced melanoma has improved dramatically in the past few years with the discovery of new signaling pathways (BRAF, MEK, and MAP-kinase) that serve as therapeutic targets. Unfortunately, the monthly cost of a combination is likely to range between $16,000 and $20,000; vemurafenib alone has an average wholesale price of $11,200 per month.2

1. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and

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**COMMENTARY BY ROBERT J. IGNOFFO**

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Assessing the Economic Impact of Targeted Therapies in Advanced NSCLC

BACKGROUND: Improved understanding of the biology of non–small-cell lung cancer (NSCLC) has led to increasing stratification of treatment based on pathologic and molecular characteristics to obtain the greatest clinical benefit for patients while minimizing the adverse effects. However, these advances have come at a financial cost.

METHODS: In a review article, the researchers examined the economic impact of screening for molecular abnormalities and new targeted treatments for advanced NSCLC.

RESULTS: The researchers found that major determinants of cost are molecular testing and drug price. For a molecular targeted therapy, adequate tissue sampling and accuracy of testing method are important.

International guidelines recommend routine immunohistochemistry (IHC) staining for NSCLC diagnosis, the use of histologic subtype and molecular testing to detect EGFR mutation, and EML4-ALK fusion for patients with advanced NSCLC. The amount of tissue required and the labor intensiveness depends on the biomarker screening technique used (eg, IHC or fluorescence in situ hybridization [FISH]).

The researchers reviewed testing methods and cost across a range of studies. One study analyzed the cost-effectiveness of testing for using FISH and IHC. The data showed that FISH testing was assessed at $106,707 per quality-adjusted life-year (QALY) gained compared with $57,165 per QALY gained for IHC.

A Canadian study explored the cost-effectiveness of 2 treatment approaches for patients with EML4-ALK fusion–positive tumors. One approach consisted of molecular screening (initial IHC and, if positive, confirmatory testing with FISH) and targeted treatment with crizotinib (Xalkori). Molecular testing led to an increase of 0.11 QALYs and a $2725 (Canadian dollars) increase in cost per patient.

Fusion testing accounted for $60 of those costs. For patients who have confirmed EML4-ALK–positive tumors, first-line therapy with crizotinib resulted in an incremental cost-effectiveness ratio (ICER) of $250,632 per QALY gained, which is more than the frequently accepted cost-effectiveness thresholds.

Drug cost is an underlying concern for patients and payers regarding targeted therapies. Studies of EGFR tyrosine kinase inhibitors (TKIs) in patients with EGFR-mutated advanced NSCLC have demonstrated improved response rate, quality of life, and PFS compared with chemotherapy.

Given these clinical benefits, analyses have been performed to determine the cost-effectiveness of first-line EGFR TKI therapy. A British study that compared gefitinib (Iressa) with platinum-doublet chemotherapy calculated an estimated ICER of £59,216 to £70,390 per QALY for gefitinib; however, it was not considered cost-effective at standard willingness-to-pay thresholds.

In a separate study, from the perspective of the Chinese healthcare system, researchers compared the cost-effectiveness of erlotinib (Tarceva) monotherapy and platinum-doublet chemotherapy in patients with advanced EGFR mutation NSCLC. Treatment with erlotinib was deemed cost-effective, with an ICER of $85,927.41 per QALY gained.

The cost of lung cancer in the United States is predicted to be $15.19 billion by 2020, without accounting for changes in treatment and the FDA approval of novel agents. As technology advances, molecular testing costs may become lower. The advances in targeted therapies have dramatically changed the diagnosis and treatment of NSCLC for patients with a previously poor prognosis.

Collaboration among clinicians, payers, and manufacturers is needed to ensure that treatment cost does not limit patient accessibility to potentially beneficial treatments.

Source: Graham DM, Leighl NB. Economic impact of tissue testing and treatments of metastatic NSCLC in the era of personalized medicine. Front Oncol. 2014;4:258.

COMMENTARY BY ROBERT J. IGNOFFO

Strategies for the treatment of patients with metastatic lung cancer have been transformed substantially with the advancement of molecular testing and the development of personalized medications that target receptors responsible for the growth of NSCLC. Although the study by Graham and colleagues was performed in Canada, the results are relevant to the management of NSCLC in the United States.

Because the cost of molecular testing of tumors is likely to decrease as a result of increased future utilization, it appears that the cost of treating patient with advanced lung cancer will be associated primarily with the expensive targeted agents. If the cancer is curable, then cost is secondary. However, if the cancer is minimally curable, the cost to society will be at a great price, most notably for metastatic cancers involving malignant melanoma, renal-cell carcinoma, breast cancer, and colon cancer.

I agree with the authors that efforts must be made to work with payers and drug companies to ensure that our patients have access to newly targeted agents, but at a reasonable cost to society.
Government and Employer Trends

AGENDA
MAY 6, 2015

7:00 am – 8:00 am  Meet the Experts Breakfast
8:00 am – 8:15 am  Introduction and Opening Remarks
                     Jayson Slotnik, JD, MPH, Health Policy Strategies, Inc
                     F. Randy Vogenberg, PhD, RPh, Institute for Integrated Healthcare
8:15 am – 9:00 am  Session 1 - Oncology Bundled Payments
                    Speaker TBD
9:00 am – 9:45 am  Session 2 - Media Coverage Oncology Panel
                    Speaker TBD
9:45 am – 10:00 am Break
10:00 am – 10:45 am Session 3 - Actuary View and Future Market Landscape
                     Speaker TBD
10:45 am – 11:30 am Session 4 - Coverage Parameter Trends in Health Benefits Impacting Oncology
                     Speaker TBD
11:30 am – 12:15 pm Session 5 - Keynote Session – 21st-Century Cures
                     Speaker TBD

12:15 pm – 1:15 pm  Networking Lunch in Exhibit Hall or Sponsored Lunch Presentation
1:15 pm – 2:00 pm  Session 6 - Private Health Exchanges
                     Laurel Pickering, Northeast Business Group on Health
2:00 pm – 2:45 pm  Session 7 - Onsite and Retail Clinic Services Expansion
                     Larry Boress, Midwest Business Group on Health
2:45 pm – 3:30 pm  Session 8 - Group Health Benefits 2016 and Beyond
                     Brian Klepper, PhD, National Business Coalition on Health
3:30 pm – 4:15 pm  Session 9 - Panel Discussion: Patient Engagement
                     Patrick McKercher, PhD, Patient Assistance Network Foundation
4:15 pm – 4:30 pm  Closing Remarks

*Agenda subject to change.
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