

November 25, 2015

NCCN Guidelines® Panel: Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC)

Dear Panel Members,

On behalf of Eli Lilly and Company, we respectfully request the NCCN NSCLC Panel to review the enclosed data and consider inclusion of PORTRAZZA™ (necitumumab) in the NCCN Guidelines.

Specific Changes: We respectfully request that necitumumab be considered for inclusion in the NCCN Guidelines as a category 1 recommendation for the first-line treatment of metastatic squamous NSCLC in combination with gemcitabine and cisplatin.

FDA Clearance: On November 24, 2015, the FDA approved PORTRAZZA™, in combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous NSCLC.

See important safety information, including the Boxed Warning for cardiopulmonary arrest and hypomagnesemia, in the accompanying full prescribing information.

WARNING: CARDIOPULMONARY ARREST AND HYPOMAGNESEMIA

See full prescription information for complete boxed warning

- Cardiopulmonary arrest and/or sudden death occurred in 3.0% of patients treated with PORTRAZZA in combination with gemcitabine and cisplatin. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, with aggressive replacement when warranted during and after PORTRAZZA administration
- Hypomagnesemia occurred in 83% of patients receiving PORTRAZZA in combination with gemcitabine and cisplatin, and was severe in 20% of patients. Monitor patients for hypomagnesemia, hypocalcemia, and hypokalemia prior to each dose of PORTRAZZA during treatment and for at least 8 weeks following completion of PORTRAZZA. Withhold PORTRAZZA for grade 3 or 4 electrolyte abnormalities. Replete electrolytes as medically appropriate

Squamous NSCLC is a difficult-to-treat disease with little advancement in overall survival (OS) in the last two decades in the first-line setting. Several currently available treatments for NSCLC are not approved, or suitable, for patients with squamous NSCLC. Recent improvements in patient outcomes have largely been confined to patients with adenocarcinoma.¹⁻⁴ Median survival for patients with advanced squamous NSCLC receiving first-line therapy is approximately 30% shorter than in patients with other NSCLC subtypes.⁵⁻⁹ In 2015, there will be an estimated 50,000 cases of squamous NSCLC cases in the US with approximately one-third being initially diagnosed as stage IV disease.¹⁰⁻¹²

Necitumumab's approval is based on the results of SQUIRE, a global, open-label, randomized, phase III trial that compared necitumumab plus gemcitabine and cisplatin to gemcitabine and cisplatin alone in patients with previously untreated stage IV squamous NSCLC (N=1093). Necitumumab plus gemcitabine and cisplatin significantly improved OS (median OS, 11.5 months) compared to gemcitabine and cisplatin alone (median OS, 9.9 months) [HR (95% CI): 0.84 (0.74, 0.96; p=0.01)].¹³ Please see the enclosed Thatcher et al. publication for a full description of the study design and results.

Necitumumab was also studied in combination with pemetrexed and cisplatin in patients with nonsquamous NSCLC (INSPIRE trial), but did not reach its primary endpoint of OS. Study results indicated increased toxicity and increased mortality associated with necitumumab in combination with pemetrexed and cisplatin.¹⁴ Necitumumab is not indicated for treatment of nonsquamous NSCLC.

On July 9, 2015, the Oncologic Drugs Advisory Committee (ODAC) met to discuss the application of necitumumab for the first-line treatment of patients with metastatic squamous NSCLC. The majority of the ODAC committee agreed that the efficacy and safety results of SQUIRE support a positive benefit-risk assessment in combination with gemcitabine and cisplatin in squamous NSCLC. Most of the committee members noted that the 16% reduced risk of death and median 1.6 month survival benefit with necitumumab was modest yet significant and noteworthy. In addition, the majority of the committee agreed that the lack of efficacy in the INSPIRE trial in the nonsquamous NSCLC population did not appear to impact the robustness of the findings in the SQUIRE trial in the squamous population.¹⁵

Portrazza was granted Orphan Drug Status by the FDA for this indication on November 20, 2015. Orphan Drug Status is given in the U.S. by the FDA's Office of Orphan Products Development (OOPD) to medicines that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions.

The following resources are included for your review in support of this proposed inclusion/change.

1. FDA Approval letter
2. NECITUMUMAB Prescribing Information
3. Thatcher N, Hirsch F, Luft A, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 study [published online ahead of print June 2, 2015]. *Lancet Oncol*. doi: 10.1016/S1470-2045(15)00021-2.

We understand that NCCN has added affordability into the evidence blocks and that NSCLC will be unveiled later this year. We believe that necitumumab offers a valuable option to physicians and patients in a tumor and line of therapy that has seen limited advancements in recent decades. Should you desire any further information on affordability to the system as you make these determination, please let us know.

Thank you for your consideration and please do not hesitate to contact me for additional information.

Sincerely,

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References: 1. Am J Clin Oncol, published online July 24, 2013; 2. Clin Epidemiol 3:139–148, 2011. 3. J Thorac Oncol 3:1468–1481, 2008. 4. J Thorac Oncol 4:1524–1529, 2009. 5. J Clin Oncol 31:2895-2902, 2013. 6. N Engl J Med 355:2542-50, 2006. 7. J Clin Oncol 28:1835-1842, 2010. 8. J Clin Oncol 26:3543-3551, 2008. 9. J Clin Oncol 30:2055-2062, 2012. 10. ACS Cancer Facts & Figures, 2015. 11. SEER Cancer Statistics Review, 1975-2012, based on November 2014 SEER data submission, posted to the SEER web site, April 2015 (http://seer.cancer.gov/csr/1975_2012/). 12.. PLoS ONE 10(3): e0121323. doi:10.1371/journal.pone.0121323. 13. Lancet Oncol 16:763-774, 2015. 14. Lancet Oncol 16:328-337, 2015. 15. Link to FDA Minutes:
<http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/oncologicdrugsadvisorycommittee/ucm457542.pdf>