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Date of Request **November 20, 2017**
NCCN Guidelines Panel **Non-Small Cell Lung Cancer**

Dear Panel Members,

On behalf of Eli Lilly and Company, we respectfully request the NCCN Panel to consider listing CYRAMZA® (ramucirumab) plus docetaxel as a preferred second-line therapy for patients with non-small cell lung cancer (NSCLC) who are refractory to or have rapidly progressed on platinum-based chemotherapy in the first-line setting.

FDA STATUS

Ramucirumab, in combination with docetaxel, is indicated for the treatment of patients with metastatic NSCLC (mNSCLC) with disease progression on or after platinum-based chemotherapy based on the Phase 3 REVEL* Study.[1,2]

SPECIFIC CHANGE

Patients with refractory or rapidly-progressing mNSCLC have a poor prognosis and represent a challenging population to treat. Three separate recently disclosed subgroup analyses of patients with refractory or rapidly-progressing disease in the REVEL study demonstrated that efficacy results in this difficult-to-treat population were consistent with those observed in the REVEL intent-to-treat (ITT) population. Taken together, patients with platinum-refractory NSCLC represent an unmet need, and these results show that ramucirumab plus docetaxel is safe and efficacious in this difficult-to-treat patient population.[3,4,5]

Data in Patients with Rapidly Progressing Disease

Lilly first analyzed data from patients in REVEL by time to progression (TTP) on first-line therapy.[3] Results demonstrated that, for patients who had disease progression within 9 weeks (n=133), 12 weeks (n=209), or 18 weeks (n=354), median overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) were greater in patients who received ramucirumab and docetaxel compared with patients who received docetaxel and placebo.[3] These results are consistent with those observed in the overall REVEL ITT population.* Key efficacy results are summarized in Table 1. No new safety outcomes or detriment to quality of life were identified in this subgroup analysis.[3]

Table 1. Key Efficacy Results in REVEL Rapidly Progressing Subgroup[3]

Efficacy Outcomes	TTP ≤9 weeks		TTP ≤12 weeks		TTP ≤18 weeks	
	RAM + DOC n=71	PBO + DOC n=62	RAM + DOC n=111	PBO + DOC n=98	RAM + DOC n=182	PBO + DOC n=172
Median OS, mos	**8.3**	**4.8**	**9.1**	**5.8**	**8.5**	**6.0**
HR (95% CI)	0.69 (0.47-1.01)		0.74 (0.54-1.00)		0.80 (0.63-1.01)	
Median PFS, mos	**3.0**	**1.5**	**3.6**	**1.6**	**3.2**	**1.6**
HR (95% CI)	0.69 (0.48-0.98)		0.73 (0.55-0.97)		0.72 (0.58-0.89)	
ORR, %	**18**	**3**	**19**	**9**	**19**	**11**

Abbreviations: DOC = docetaxel; HR = hazard ratio; mos = months; ORR = objective response rate; OS = overall survival; PBO = placebo; PFS = progression-free survival; RAM = ramucirumab; TTP = time to progression

Data in Patients with Refractory Disease

A second subgroup analysis was performed to evaluate patients who were refractory to prior first-line chemotherapy.[4] This subgroup included 360 patients (20% of the REVEL ITT). In this refractory population, median OS, PFS, and

* REVEL intent to treat (ITT) patients demonstrated the following efficacy results:
- median OS with ramucirumab plus docetaxel was 10.5 months vs 9.1 months with placebo plus docetaxel (hazard ratio 0.86 [95% CI: 0.75, 0.98]; p=.024);
- median PFS with ramucirumab plus docetaxel was 4.5 months vs 3.0 months with placebo plus docetaxel (hazard ratio 0.76 [95% CI: 0.68, 0.86]; p<.001);
- ORR rate with ramucirumab plus docetaxel was 23% vs 14% with placebo plus docetaxel (p<.001).[1]

ORR were greater in patients who received ramucirumab and docetaxel compared with patients who received docetaxel and placebo. These results are consistent with the results from the REVEL ITT population and are summarized in Table 2.[4] No new safety outcomes or detriment to quality of life were observed in the primary refractory subgroup.[4]

Table 2. Key Efficacy Results in REVEL Primary Refractory Subgroup[4]

Efficacy Outcomes	RAM + DOC n=178	PBO + DOC n=182
Median OS, mos	**8.3**	**6.3**
HR (95% CI)	0.86 (0.68-1.08)	
Median PFS, mos	**4.0**	**2.5**
HR (95% CI);	0.71 (0.57-0.88)	
Median ORR, %	**23**	**13**

Abbreviations: DOC = docetaxel; HR = hazard ratio; mos = months; ORR = overall response rate; OS = overall survival; PBO = placebo; PFS = progression-free survival; RAM = ramucirumab

Data in Patients with High Symptom Burden

Lilly performed a third analysis to examine the association between baseline symptom burden, as measured by the Lung Cancer Symptom Scale (LCSS), and efficacy in patients in REVEL. The LCSS average symptom burden index was calculated and used at baseline to define symptom burden as low (≤ median) or high (> median). Patients experiencing low symptom burden (n=497) and high symptom burden (n=497) were analyzed across and by treatment arms for effects on efficacy. The preservation of improved PFS in the high symptom burden cohort suggests that ramucirumab and docetaxel treatment maintains an incremental efficacy over docetaxel and placebo, even in those patients with greater symptom burden at baseline.[5]

RESOURCES / REFERENCES

The following resources are submitted to assist the committee with their review:

1. CYRAMZA (ramucirumab)® Prescribing Information.
2. Garon EB, et al. Lancet. 2014;384(9944):665-673.
3. Reck M, et al. Effects of second-line ramucirumab after rapid time to progression on first-line therapy: subgroup analysis of REVEL in advanced non-small cell lung cancer. Oral Presentation at IASLC 18th World Conference on Lung Cancer: October 15-18, 2017. Yokohama, Japan.
4. Reck M, et al. Lung Cancer. 2017:112:181-187.
5. Winfree KB, et al. Association of baseline symptom burden with progression-free and overall survival: Exploratory analysis from the randomized phase III REVEL study in NSCLC. Poster Presentation at IASLC 2017 Chicago Multidisciplinary Symposium in Thoracic Oncology: September 14-16, 2017. Chicago, IL.

Conclusion

Patients with refractory or rapidly-progressing mNSCLC have a poor prognosis and represent a challenging population to treat. Three subgroup analyses from the REVEL trial demonstrated that ramucirumab plus docetaxel is safe and efficacious in patients with mNSCLC who are refractory to or who have rapidly progressed on initial platinum-based therapy.[4,5,6] These data support consideration of ramucirumab in combination with docetaxel as a preferred treatment option for this difficult-to-treat population.

Thank you for your consideration of this data. Please do not hesitate to contact us with any questions.

Sincerely,

William R. Schelman, MD, PhD
Senior Director, Medical
Eli Lilly and Company

Helen Ostojic, MD
Medical Fellow, Medical
Eli Lilly and Company