

Eli Lilly and Company, Indianapolis

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

Dear Panel Members,

Eli Lilly and Company respectfully submits this letter to address the recent classification of necitumumab in combination with gemcitabine-cisplatin for the first-line treatment of patients with metastatic squamous non-small cell lung cancer (SqNSCLC) as a category 3 recommendation in the NCCN guidelines.

- To our knowledge, this is the first time an NCCN committee has given a category 3 rating to an FDA-approved, on-label indication with overall survival (OS) improvement based on a large, global, randomized phase III trial against a standard of care.
- In this instance, the backbone, gemcitabine-cisplatin, has a category 1 recommendation.
- Given the unprecedented nature of this rating and the fact that the FDA Review Division, the FDA's Oncology Division Advisory Committee (ODAC) and the European Commission determined that the positive benefit:risk profile of necitumumab warranted approval, we are committed to providing the NCCN Lung Cancer Panel with evidence to ensure that the designation for necitumumab accurately reflects the strength of data available for the drug and recognizes necitumumab in combination with gemcitabine-cisplatin as the first FDA- approved biologic agent for the first-line treatment of patients with metastatic SqNSCLC.

Specific Changes: We respectfully request that NCCN review the enclosed additional context and evidence and re-evaluate the category recommendation for inclusion of necitumumab in the Lung Cancer Guidelines

1. Limited Therapeutic Advances in 1st Line Metastatic SqNSCLC. SqNSCLC is an aggressive cancer that is challenging to treat. Prognosis for SqNSCLC remains poor and is worse than for nonsquamous NSCLC due, in part, to differences in patient characteristics such as co-morbidities, clinical presentation, and molecular profile¹⁻³. Numerous targeted agents have been tested in combination with first-line chemotherapy for metastatic SqNSCLC, with the vast majority (e.g. sorafenib⁴, iniparib⁵, others⁶⁻⁸) falling short of demonstrating a survival benefit (Appendix 1). Most recently, the phase III study of ipilimumab, a CTLA-4 inhibitor, in combination with standard carboplatin-paclitaxel was negative⁹. Thus, there has been little to no advancement in terms of new therapies in first line treatment with significant survival advantages over the last 20 years (Table 1), and the standard of care has been doublet chemotherapy with median OS in the range of 8-10 months¹⁰. Recently, new treatment options have been approved in the second-line setting for patients with metastatic SqNSCLC, but only half of the patients that receive first-line chemotherapy are able to receive second-line therapy in the US¹¹. Therefore, maximizing the benefit that patients receive from first-line treatment is crucial.

Table 1. FDA-Approved Chemotherapy Regimens on 1st Line for Metastatic SqNSCLC prior to Necitumumab Approval (adapted from FDA ODAC Briefing Document¹²)

Treatment (Approval Year)	Study Design, Histologic Group, Primary Endpoint	Arms, Median Overall Survival, Months (p value)	mOS Difference (months)
Paclitaxel + cisplatin (1998)	Bonomi ¹³ : Phase III, open-label, 3-arm, 599 patients with <u>all histologies</u> Primary endpoint: OS	Pac+Cis vs Etop-Cis mOS: 10.0 vs 7.4 (p=0.08)	2.6
Gemcitabine + cisplatin (1998)	Sandler ¹⁴ : Phase III, 522 patients, <u>all histologies</u> Primary endpoint: OS	Gem+Cis vs Cis mOS: 9.0 vs 7.6 (p=0.008)	1.4
	Cardenal ¹⁵ : Phase III, 135 patients <u>all histologies</u> Primary endpoint: ORR	Gem+Cis vs Etop+Cis mOS: 8.7 vs 7.2 (p=0.19)	1.7
Vinorelbine + cisplatin (1994, 2001)	Wozniak ¹⁶ : Phase III, 432 patients, <u>all histologies</u> Primary endpoint: OS	Vin+Cis vs Cis mOS: 7.8 vs 6.2 (p=0.01)	1.6
	Le Chevalier ¹⁷ : Phase III 612 patients <u>all histologies</u> Primary endpoint: OS	Vin+Cis vs Vind+Cis or Vin mOS: 9.2 vs 7.4* or 7.2** (*p=0.09; **P=.05)	1.8, 2.0
Docetaxel + cisplatin (2002)	Fossella ¹⁸ : Phase III, 1218 patients <u>all histologies</u> Primary endpoint: OS	Doc+Cis vs Vin+Cis mOS: 10.9 vs 10.0 (p=0.122)	0.9
		Doc+Carbo vs Vin+Cis mOS: 9.1 vs 10.0 (p=ns)	-0.9
Nab-paclitaxel + carboplatin (2012)	Socinski ^{19,20} : Phase III, 1052 patients with <u>all histologies</u> (450 squamous patients) Primary endpoint: ORR	Nab-pac+Carbo vs Pac+Carbo Squamous ORR: 41% vs 24% (p <0.001) mOS: 10.7 vs 9.5 (p=0.310)	<i>Squamous</i> 1.2

Abbreviations: Cis: cisplatin, Carbo: carboplatin, Doc: docetaxel, Etop: etoposide, Gem: gemcitabine, Nab-pac: nab-paclitaxel, Pac: paclitaxel, ORR: objective response rate, mOS: median overall survival, Vin: vinorelbine, Vind: vindesine

2. Evaluation of Necitumumab plus Gemcitabine/Cisplatin in the Context of Other Treatment Regimens in the NCCN Guidelines. Current NCCN guideline recommendations for the first line treatment of metastatic SqNSCLC are based on studies evaluating broad NSCLC populations and/or subgroups not designed to detect differences in survival or specifically address patients with squamous histology. To our knowledge, the SQUIRE trial is the first and largest randomized phase III clinical trial specifically designed in metastatic squamous cell population in the first-line setting and the first to show statistical improvement in OS as primary endpoint when compared to a standard of care²¹. The use of OS as a primary endpoint ensures that the observed benefit is objectively and accurately measured, as well as relevant and meaningful to the individual patient, making it the gold standard for assessing efficacy in this population (FDA 2015). The significant OS results in SQUIRE were supported by consistent improvements across subgroups (sex, race, smoking status, geographic region, high burden disease), including patients with ECOG performance status (PS) 2 (often excluded from clinical trials), and an early and sustained separation of survival curves throughout the duration of the study. There was also a corresponding statistically significant improvement in progression-free survival (PFS) and disease control rate (DCR). There were no imbalances in baseline prognostic factors or post-discontinuation treatments that influenced the interpretation of efficacy in the SQUIRE study. In addition, the control arm was consistent with historical data for gemcitabine-cisplatin. In the context of a patient population lacking robust clinical evidence and new treatment options, a delta in median OS of 1.6 months and a hazard ratio (HR) of 0.84 (95% CI, 0.74, 0.96; p=0.012) are robust and clinically relevant.

Table 2 summarizes the most common platinum doublets used in the US for the treatment of this population with the corresponding NCCN categorization and evidence block information. Aside from necitumumab-gemcitabine-cisplatin (category 3), only one other regimen (gemcitabine and cisplatin,

category 1) showed a statistically significant HR for OS specifically for patients with squamous histology. Other regimens granted a NCCN category 1 rating either had survival data that are not specific to patients with squamous disease or survival data that did not meet statistical significance. In addition, in the recent released evidence blocks, the triplet necitumumab plus gemcitabine-cisplatin was evaluated on ‘efficacy of the regimen’ with 3 squares while other regimens lacking of statistical significant OS data were assessed as having higher efficacy.

Table 2. Most Commonly Used 1st Line Regimens in Metastatic SqNSCLC. Studies included Nonsquamous and Squamous Histologies.

Regimen	Author, Year	mOS (months) (HR: p value)	NCCN Rating Evidence Block
Neci-Gem-Cis vs. Cis-Gem	Thatcher ²¹ , et al. 2015	<i>Squamous</i> 11.5 vs. 9.9 (0.84: p=0.01)	3 
Cis-Gem vs. Cis-Pem	Scagliotti ²² , et al. 2008	<i>Squamous</i> 10.8 vs. 9.4 (1.23: p=0.05)	1 
Carbo-Nab-pac vs. Carbo-Pac	Socinski ¹⁹ , et al. 2012	<i>Squamous</i> 10.7 vs. 9.5 (0.89: p=0.28)	1 
Carbo-Pac (CP) vs. Cis-Irino (CI) Cis-Gem (CG) Cis-Vinor (CV)	Ohe ²³ , et al. 2007	<i>All histologies</i> CP vs. CI: 12.3 vs. 13.9 (1.1: p=0.46) CP vs. CG: 12.3 vs. 14 (0.94: p=0.9) CP vs. CV: 12.3 vs. 11.4 (1.1: p=0.24)	1 
Carbo-Gem vs. Mito-Ifo-Cis	Danson ²⁴ , et al. 2003	<i>All histologies</i> 8.2 vs 7.8 (HR: n/a: p=0.81)	1 

Abbreviations: Neci: necitumumab, Cis: cisplatin, Gem: gemcitabine, Carbo: carboplatin, Nab-pac: nab-paclitaxel, Pem: pemetrexed, Irino: irinotecan, Vinor: vinorelbine, Mito: mitoxantrone, Ifo: ifosfamide

Based on the objective scientific criteria used in the evaluation of new regimens, it would appear that necitumumab-gemcitabine-cisplatin would warrant a recommendation consistent with the backbone of gemcitabine-cisplatin in the NCCN guidelines. We also understand that the that guidelines and category ratings are intended to reflect the efficacy of treatment, utility of tests or evaluations, toxicity of the various interventions and level of evidence²⁵. To the extent that cost or economic impact played a role in this evaluation, NCCN has stated that these attributes will be evaluated exclusively in the context of the recently released NCCN evidence blocks for NSCLC²⁶.

3. Assessing Benefit-Risk with Necitumumab – Additional Context and Information. It is our understanding that the benefit:risk ratio of necitumumab plus cisplatin-gemcitabine was a primary consideration for the NCCN panel when assessing this regimen for the guidelines. NCCN highlighted the 10% higher incidence of grade ≥3 treatment-emergent adverse events (TEAEs) in the necitumumab arm compared to the control arm (72% vs 62%). It is important to note that this difference was driven primarily by two well-known class effects of anti-EGFR monoclonal antibody (mAb) therapies, hypomagnesemia (9% vs. 1%) and skin rash (4% vs. 1%), and that necitumumab did not exacerbate chemotherapy-associated toxicities, namely fatigue or myelosuppression²¹. With respect to skin toxicity associated with anti-EGFR mAbs, prophylactic treatment is currently recommended upon initiation of therapy. However, prophylactic skin care was not allowed during the first cycle of treatment in the

SQUIRE trial. By contrast, prophylactic treatment for skin toxicity was permitted in our phase II trial of necitumumab plus carboplatin-paclitaxel in patients with metastatic SqNSCLC (JFCL), and grade ≥ 3 skin rash was seen in only 2.8% of patients in the necitumumab arm²⁷. In regards to the incidence of grade ≥ 3 hypomagnesemia, prophylactic infusion of magnesium during cisplatin infusion is widely used in the US; however, it is not considered a standardized practice among oncologists outside of the US. The SQUIRE trial was mainly an international trial, and there are clearly differences in how patients are managed accordingly to regional standards. Further, the lung cancer scale symptom evaluation suggests that the addition of necitumumab to gemcitabine-cisplatin did not have a negative effect on health-related quality of life of patients, including PS and symptoms, and supportive care resource utilization was similar between study arms²⁸. Lastly, the SQUIRE trial showed a numerical and statistically-significant improvement in OS which, by definition, not only incorporates all the causes of death, but also accounts for efficacy and safety information. Notably, ODAC committee supported a favorable benefit:risk ratio prior to FDA approval. For additional data, please refer to:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm426351.htm>

In conclusion, necitumumab is the first biologic approved by the FDA that, in combination with cisplatin and gemcitabine, demonstrated a meaningful improvement in OS and PFS with a positive benefit:risk ratio for patients with metastatic SqNSCLC, a disease that has seen no substantial therapeutic advancements in the last two decades. We believe that every incremental innovation and improvement in survival results in a clinically meaningful impact for patients and that the evaluation of the SQUIRE data was inconsistent when compared to data observed with other category 1 regimens, namely cisplatin and gemcitabine. Moreover, the inconsistency between FDA approval and NCCN categorization has resulted in confusion amongst the oncology community and lack of access to a safe and effective regimen for some patients. We believe that physicians should be given the option of providing necitumumab in combination with gemcitabine-cisplatin for their appropriate patients and that all appropriate patients should have the opportunity to receive medications that could potentially extend their lives. On behalf of patients with SqNSCLC, their loved ones and their treating physicians, Eli Lilly respectfully requests that the NCCN lung panel committee to reconsider the category 3 recommendation for necitumumab plus gemcitabine-cisplatin based on the above data and rationale. We hope that with your reconsideration, physicians and patients will have access to treatment options that can optimize their care.

Sincerely,

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Appendix 1. Selected Phase 3 Trials of Novel Drugs in Combination with Standard Chemotherapy in Metastatic Squamous Non-Small Cell Lung Cancer (recent)

Reference	Drug	MOA	N Total Randomized (Squamous)	Study description	Endpoint (OS)
Scagliotti ⁴ , 2010	Sorafenib	RAF, VEGFR	926 (223)	Paclitaxel/carboplatin (HR detriment in squamous)	Negative
Sanofi ⁵ , 2013	Iniparib	PARP	780 (780)	Gemcitabine/carboplatin	Negative
Novello ⁶ , 2014	Motesanib	VEGFR, PDGFR	1450 (360)	Paclitaxel/carboplatin (unacceptable toxicity in squamous)	Negative
Laurie ⁷ , 2014	Cedinarib	VEGFR, PDGFR	306 (39)	Phase II/III with carboplatin/paclitaxel (halted for futility)	Negative
Langer ⁸ , 2014	Figitumumab	IGF1R	681 (584)	Carboplatin/paclitaxel	Negative
Lynch ⁹ , 2015	Ipilimumab	CTLA-4	867 (867)	Carboplatin/paclitaxel	Negative

Abbreviations: Raf: rapid accelerated fibrosarcoma; VEGFR: vascular-endothelial growth factor receptor; PARP: poly ADP ribose polymerase; PDGFR: platelet-derived growth factor receptor; IGF1R: insulin-like growth factor receptor 1; CTLA-4: cytotoxic T-lymphocyte-associated protein 4.

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