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FDA Approval Summary: Amivantamab for the Treatment of patients with non-small cell lung cancer with *EGFR* exon 20 insertion mutations

Katie Chon[1], **Erin Larkins**[1], **Somak Chatterjee**[1], **Pallavi S. Mishra-Kalyani**[1], **Stephanie Aungst**[1], **Emily Wearne**[1], **Sriram Subramaniam**[1], **Yangbing Li**[1], **Jiang Liu**[1], **Jielin Sun**[1], **Rosane Charlab**[1], **Hong Zhao**[1], **Banu Saritas-Yildirim**[2], **Rama Kamesh Bikkavilli**[2], **Soma Ghosh**[2], **Reena Philip**[2], **Julia A. Beaver**[1,3], **Harpreet Singh**[1,3]

[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration

[2]Center for Devices and Radiological Health, U.S. Food and Drug Administration

[3]Oncology Center of Excellence, U.S. Food and Drug Administration

Abstract

The FDA granted accelerated approval for amivantamab-vmjw (hereafter referred to as amivantamab), a bispecific antibody directed against epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) receptor, on May 21, 2021, for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with *EGFR* exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. Approval was based on results of an ongoing, multicenter, non-randomized, open-label, multi-cohort clinical trial (CHRYSALIS, NCT02609776), demonstrating a substantial overall response rate (ORR) and durable responses, with an ORR of 40% (95% CI: 29, 51) and a median response duration of 11.1 months (95% CI: 6.9, not evaluable). Guardant360® CDx was contemporaneously approved as a companion diagnostic for this indication to identify *EGFR* exon 20 insertion mutations in plasma specimens.

The most notable safety finding was the high incidence (66%) of infusion-related reactions (IRRs), which is addressed in both the Dosage and Administration and Warnings and Precautions sections of the product label. Other common adverse reactions (occurring in ≥20% of patients) were rash, paronychia, musculoskeletal pain, dyspnea, nausea and vomiting, fatigue, edema, stomatitis, cough, and constipation. The approval of amivantamab was the first approval of a targeted therapy for patients with advanced NSCLC harboring *EGFR* exon 20 insertion mutations.

Corresponding Author: Katie Chon, Office of Oncologic Diseases, CDER, U.S. Food and Drug Administration, WO22 Room 3235, 10903 New Hampshire Avenue, Silver Spring, MD 20993. Phone 240-402-6578. katie.chon@fda.hhs.gov .

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Introduction

Metastatic non-small cell lung cancer (NSCLC) is in most cases a fatal disease, with a 5-year survival rate of < 10% (1). Exon 20 insertion mutations in the epidermal growth factor receptor (*EGFR*) gene have been identified as oncogenic drivers in NSCLC and are reported to be present in approximately 2–3% of cases of advanced NSCLC (2). In comparison to many other *EGFR* oncogenic driver mutations, NSCLC with *EGFR* exon 20 insertion mutations does not respond well to treatment with currently approved EGFR tyrosine kinase inhibitors (3). Current treatment options for patients with NSCLC harboring *EGFR* exon 20 insertion mutations whose disease has progressed following platinum-based chemotherapy are the same therapies as those used for patients with NSCLC without a specific driver mutation (4). This includes ramucirumab plus docetaxel (ORR 23%) (5) or single agent chemotherapy (ORR 10–15%) (6), as well as treatment with anti-PD-(L)1 antibody as a single agent for patients who did not receive such treatment as part of first-line therapy (associated with ORR 14–19%) (7). While data regarding response to immunotherapy in this specific patient population is limited and conflicting, there is no clear indication that patients with NSCLC with *EGFR* exon 20 insertion mutations are less likely to respond to such therapy than patients with wild-type *EGFR* (8,9,10). Prior to the approval of amivantamab, there was no targeted therapy approved specifically for the treatment of patients with NSCLC with *EGFR* exon 20 insertion mutations. After amivantamab's approval, mobocertinib, an orally administered irreversible kinase inhibitor targeting EGFR and HER2 receptors, received accelerated approval in September 2021 for the treatment of patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy (11,12).

Regulatory History

Breakthrough Therapy Designation was granted to amivantamab on March 9, 2020, for the treatment of patients with metastatic NSCLC with *EGFR* exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy (11). The biologics license application (BLA) was submitted on November 24, 2020, and was granted priority review status; the applicant voluntarily used the Assessment Aid, which is designed to facilitate the FDA's assessment of marketing applications (12). This application was reviewed under FDA's Project ORBIS, in collaboration with the Brazilian Health Regulatory Agency (ANVISA) and United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA); the application reviews were ongoing at these other regulatory agencies at the time of FDA approval (13).

Mechanism of Action

Amivantamab is a low-fucose, fully human, IgG1-based bispecific antibody against the EGFR and mesenchymal-epithelial transition (MET) receptor with an established pharmacological class of bispecific EGF receptor-directed and MET receptor-directed antagonist (14,15). In binding studies, amivantamab bound to human EGFR and MET with K_D values of 1.43 and 0.04 nM, respectively. Amivantamab bound to the extracellular domains (ECD) of human and cynomolgus monkey EGFR and MET with similar EC_{50} values, but not to rat EGFR or rat MET. In addition, amivantamab bound to lung cancer

cell lines of various EGFR and MET status with IC_{50} values ranging from 0.9 to 12.1 nM. Amivantamab at concentrations of 0.1, 0.5, and 1 mg/mL dose-dependently inhibited proliferation of Ba/F3 cells expressing different exon 20 insertion mutations. Binding of amivantamab to EGFR and MET prevented binding of their ligands, epidermal growth factor (EGF) and hepatocyte growth factor (HGF), with IC_{50} values of 10 and 30 nM, respectively. Amivantamab inhibited ligand-induced receptor phosphorylation in NSCLC cell lines with both wild type (WT) and mutant *EGFR* (L858R, T790M) with WT MET with IC_{50} values ranging from 0.49 to 29 nM. In mice bearing patient derived tumors with exon 20 insertion mutations, amivantamab demonstrated anti-tumor activity and decreased protein expression and phosphorylation of EGFR and MET in the tumor tissue (15).

Clinical Pharmacology

The approved dosing regimen is based on baseline body weight and is 1050 mg for patients with body weight <80 kg and 1400 mg for patients with body weight ≥80 kg, administered intravenously (IV) weekly for 4 weeks and then every 2 weeks thereafter. In order to mitigate the risk of infusion-related reactions (IRRs), product labeling recommends slower initial infusion rates and splitting of doses in Week 1, with 350 mg on Day 1, and the remaining dose [700 mg for body weight <80kg, and 1050 mg for body weight ≥80 kg) on Day 2 (15, 16).

Amivantamab was investigated at doses up to 1750 mg with no maximum tolerated dose defined. Amivantamab systemic exposures increased proportionally over a dose range of 350 mg to 1750 mg, and increases in body weight increased the volume of distribution and clearance of amivantamab. Similar amivantamab exposures were achieved for patients with body weight <80 kg at dose of 1050 mg and patients with body weight ≥80 kg at dose of 1400 mg based on population pharmacokinetics (PK) analysis. The incidence of antibodies to amivantamab was 1% in the clinical trial of patients with locally advanced or metastatic NSCLC (16).

Clinical Trial Design

The efficacy of amivantamab in patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy was evaluated in a multicenter, non-randomized, open-label, dose escalation and multi-cohort dose expansion clinical trial (CHRYSALIS, NCT02609776). Patients with untreated brain metastases or with previously treated but symptomatic or clinically unstable brain metastases and patients with a history of interstitial lung disease (ILD) requiring treatment with prolonged steroids or other immunosuppressive agents within the last 2 years were not eligible for the study. The major efficacy outcome measure was overall response rate as assessed by blinded independent central review (BICR) according to RECIST v1.1, with duration of response (DOR) per BICR a secondary efficacy outcome measure (16).

As prophylaxis for IRR, the protocol required administration of an antihistamine and acetaminophen prior to each scheduled infusion and IV glucocorticoid prior to Week 1 dosing. Following treatment of approximately 30 patients, given the high incidence of IRR occurring during Cycle 1, the protocol was amended to administer the initial Cycle 1 dose

as a split infusion on Week 1 Days 1 and 2 and to require infusion of amivantamab via a peripheral vein for all Cycle 1 doses. Infusion via central line was allowed for subsequent dosing starting with the Cycle 2 Day 1 dose (16).

Disposition and Demographics, Disease Characteristics and Prior Treatment

The efficacy population from CHRYSALIS supporting this marketing application included 81 consecutively enrolled patients with *EGFR* exon 20 insertion mutation-positive NSCLC with measurable disease and a history of disease progression on or after platinum-based chemotherapy who received at least one dose of amivantamab at the dose(s) to be approved and started treatment on or before February 5, 2020 (Table 1). Among 81 patients with *EGFR* exon 20 insertion mutation-positive NSCLC previously treated with platinum-based chemotherapy, 46% had received PD-1/PD-L1 inhibitor and 22% of patients had received an EGFR tyrosine kinase inhibitor. The demographic and baseline disease characteristics of the efficacy population generally reflect the known profile of patients with this disease in the U.S. (Table 1), except for underrepresentation of Black or African American (2.5%). *EGFR* exon 20 insertion mutation status was identified by prospective local testing using tissue (94%) and/or plasma (6%) samples (16).

Efficacy Results

The confirmed ORR by BICR was 40% (95% CI: 29, 51) and the median DOR was 11.1 months (95% CI: 6.9, Not Evaluable) (Table 2). A total of 63% of responders had a DOR ≥ 6 months and 12% of responders had a DOR ≥ 12 months. At the data-cutoff, the response was ongoing for 41% responders. The ORRs observed in the subgroups of patients who received prior immunotherapy (n=37), those who did not receive prior immunotherapy (n=44), and those who received EGFR TKI therapy (n=18) were 46% (95% CI: 29, 63), 34% (95% CI: 21, 50), and 50% (26, 74), respectively (Supplementary Table 1). Overall, the results appear consistent across these subgroups with ORR confidence intervals overlapping but interpretation limited due to small sample size.

Safety Results

The safety review of amivantamab included data from 302 patients with NSCLC from CHRYSALIS who were treated with one dose of amivantamab at the dose(s) to be approved (1050 mg for patient BW <80 kg and 1400 mg for patient BW ≥80 kg), including 129 patients with NSCLC with *EGFR* exon 20 insertion mutations and disease progression following platinum-based chemotherapy (16).

Among the 302 patients, 36% were exposed to amivantamab for 6 months or longer and 12% were exposed for greater than one year. The most common treatment emergent adverse reactions and laboratory abnormalities occurring with amivantamab are presented in Tables 3 & 4.

Serious adverse reactions occurred in 30% of patients. Permanent discontinuation due to an adverse reaction occurred in 11% of patients; the most frequent (≥1%) adverse reactions leading to permanent discontinuation were pneumonia, IRR, pneumonitis/interstitial lung disease (ILD), dyspnea, pleural effusion, and rash. Fatal adverse reactions occurred in 3

patients (2.3%), with two fatal events of pneumonia and one event reported as sudden death. Dose interruptions due to an adverse reaction occurred in 78% of patients. IRR requiring infusion interruptions occurred in 59% of patients (16). Other than IRR, the most common reasons for dose interruptions due to an adverse reaction (≥5%) included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea. Adverse reactions requiring dosage reductions in ≥ 2% of patients included rash and paronychia.

Serious risks identified for inclusion in the Warnings and Precautions section of the USPI included IRR, ILD/pneumonitis, dermatologic adverse reactions, and ocular toxicity. IRR occurred in 66% of patients treated with amivantamab, with median time to onset 1 hour (range: 0.1 to 18 hours) after the start of the infusion. Over 90% of IRRs occurred on Day 1 or 2 of the Week 1 infusion (incidence 65% with Week 1 Day 1 infusion, 3.4% Week 1 Day 2, 0.4% Week 2, and 1.1% with subsequent infusions). Grade 3 and 4 IRR occurred in 2.2% and 0.4% of patients, respectively, and amivantamab was permanently discontinued due to IRR in 1.3% of patients (16).

ILD/pneumonitis occurred in 3.3% of patients (Grade 3 0.7%), and 1% of patients discontinued amivantamab due to ILD/pneumonitis. Rash (including dermatitis acneiform) occurred in 74% of patients (Grade 3 3.3%), and one patient (0.3%) had toxic epidermal necrolysis (TEN). Median time to onset of rash was 14 days (range: 1 to 276 days), and 0.7% of patients discontinued amivantamab due to rash. Ocular toxicity associated with amivantamab included keratitis (0.7%), dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis (0.3%) (15,16).

Regulatory Insights

Patients with *EGFR* exon 20 insertion mutations represent a distinct subset of patients with EGFR-mutated NSCLC (common or uncommon EGFR oncogenic driver mutations), and generally associated with limited response to EGFR tyrosine kinase inhibitors (5). The ORR per BICR of 40% (95% CI: 29, 51) with a median DOR of 11.1 months in the CHRYSALIS study is consistent with an improvement over available therapy for the intended patient population (15, 16). This was the first FDA approval for a targeted therapy specifically for the treatment of NSCLC harboring *EGFR* exon 20 insertion mutations and provides this patient population with a high unmet medical need an additional therapeutic option. After the amivantamab approval, mobocertinib, an oral, first-in class, irreversible kinase inhibitor targeting EGFR and HER2 receptors, received accelerated approval in September 2021 for the treatment of patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy (12).

Despite required premedication for amivantamab therapy, IRR occurred in the majority (approximately 65%) of patients treated with amivantamab. Over 90% of IRR occurred on Day 1 or 2 of the initial Week 1 infusion, and most IRR were Grades 1–2 in severity. To address this issue, product labeling includes clear instructions regarding premedication, slower initial infusion rates and splitting of doses in Week 1, with 350 mg on Day 1, and the remaining dose [700 mg for body weight <80kg, and 1050 mg for body weight ≥80 kg) on Day 2, administration via a peripheral line on Week 1 and Week 2, and management of IRR

with interruption of infusion and reduction in infusion rate or permanent discontinuation based on severity (15, 16).

Given the relatively limited duration of follow-up and the number of patients in the primary efficacy analysis population for this application, the submitted data were considered adequate to support accelerated approval rather than regular approval (11, 15). As a postmarketing requirement (PMR), Janssen agreed to complete a randomized clinical trial to verify and confirm the clinical benefit of amivantamab for the treatment of patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations (16). Results from the ongoing, randomized trial initiated on October 13, 2020, investigating amivantamab in combination with carboplatin and pemetrexed compared to carboplatin and pemetrexed alone as first-line treatment in patients with advanced NSCLC harboring *EGFR* exon 20 insertion mutations with a primary endpoint of progression-free survival may be used to verify the clinical benefit of amivantamab. At the time of accelerated approval, enrollment was underway, and the final report submission is expected in February 2023.

In addition, Janssen agreed to a post-marketing commitment (PMC) to collect and submit additional clinical trial data to further characterize the safety and efficacy of amivantamab in Black or African American patients with *EGFR* exon 20 insertion mutated NSCLC as real world data reported 9.4% of US patients with NSCLC with *EGFR* exon 20 insertion mutations were Black or African American and in the primary efficacy population of the global CHRYSALIS study, 2.3% of patients were Black or African American (16). This PMC was requested based on the relative underrepresentation of Black or African American patients in the primary efficacy population of CHRYSALIS relative to the proportion of Black or African American patients expected among the population of patients with *EGFR* exon 20 insertion mutated NSCLC in the US (16).

Finally, the FDA Center for Devices and Radiological Health (CDRH) contemporaneously approved the Guardant360 CDx (Guardant Health, Inc.) as a plasma-based companion diagnostic to select patients with *EGFR* exon 20 insertion mutations for the safe and effective use of amivantamab. Subsequently, the Oncomine™ Dx Target Test (ODxT Test, Life Technologies Corporation), a tissue-based CDx was also approved for the same indication for use (16). As a result of difference in sensitivities between plasma and tissue tests, a negative result from a plasma specimen may not provide assurance that the patient's tumor is negative for genomic findings. In such circumstances, tumor tissue testing is recommended, if feasible (15).

As part of the Agency-wide effort to assess the impact of the COVID-19 pandemic on clinical trials, FDA evaluated protocol changes and protocol deviations that occurred in CHRYSALIS due to the pandemic. Notable protocol modifications included permitting alternative sites for imaging and laboratory assessments and telehealth assessments for adverse events. In the primary efficacy population, 26 patients (32%) had protocol deviations related to the COVID-19 pandemic, including 15 patients (58%) missing data (e.g, labs, vitals, physical exam), 7 patients (27%) with missed visit or exceeded study visit window and 4 patients (15%) with assessments performed remotely. These study adaptations did not impact the assessment of overall efficacy or safety (16).

This application was reviewed under FDA's Project ORBIS (14), in collaboration with several international ORBIS partners including Brazil's National Health Surveillance Agency (ANVISA), Health Canada, Mexico's Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS), Singapore Health Sciences Authority (HAS), Swissmedic Switzerland, and the United Kingdom's Medicine and Healthcare Products Regulatory Agency (MHRA).

Amivantamab was granted approval by ANVISA in September 2021, conditional marketing authorization by MHRA in November 2021, and a Notice of Compliance with conditions by Health Canada in March 2022.

Conclusions

Amivantamab demonstrated substantial evidence of effectiveness and a favorable benefit-risk profile as a single agent for the treatment of patients with NSCLC with *EGFR* exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. The observed ORR, coupled with the durability of responses, is consistent with a meaningful advantage over available therapies. This indication was approved under accelerated approval, and a randomized clinical trial intended to verify the clinical benefit of amivantamab is currently ongoing with the final report submission due in February 2023.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Demographics and Disease Characteristics in the Efficacy and Safety Populations of CHRYSALIS

	Efficacy Population N=81	Safety Population N=302
Sex, n (%)		
Women	48 (59)	189 (63)
Men	33 (41)	113 (37)
Age at diagnosis (years), median [range]	62 [42, 84]	62 [32, 87]
≥65 years	33 (41)	119 (39)
Weight at study entry, n (%)		
<80 kg	60 (74)	255 (84)
≥80 kg	21 (26)	47 (16)
Race, n (%)		
Asian	40 (49)	180 (60)
White	30 (37)	94 (31)
Black or African American	2 (3)	9 (3)
Unknown	9 (11)	19 (6)
Ethnicity, n (%)		
Hispanic or Latino	3 (4)	8 (2.6)
Not Hispanic or Latino	68 (84)	278 (92)
Unknown	10 (12)	16 (5)
Region, n(%)		
Asia	37 (47)	154 (51)
Europe and Australia	27 (33)	59 (20)
North America	17 (21)	89 (29)
ECOG performance status at study entry, n (%)		
0	26 (32)	81 (27)
1	54 (67)	220 (73)
Disease Stage at study entry, n(%)		
Stage IV	81 (100)	302 (100)
Histopathology at study entry, n(%)		
Adenocarcinoma	77 (95)	291 (96)
Squamous cell carcinoma	3 (3.7)	7 (2.3)
Location of metastasis at study entry, n (%)[ǂ]		
Bone	34 (42)	130 (43)
Liver	7 (9)	52 (17)
Brain	18 (22)	77 (25)
Lymph Node	43 (53)	164 (54)
Adrenal Gland	3 (3.7)	22 (7)
Other	45 (56)	148 (49)

	Efficacy Population N=81	Safety Population N=302
Smoking History, n(%)		
Current/Former	38 (47)	119 (39)
Never	43 (53)	183 (61)
Number of Prior Lines of Therapy, median [range]	2 (1,7)	
1	31 (38)	
2	24 (30)	
≥3	26 (32)	
Type of Prior Therapy [*], n (%)		
Platinum-based chemotherapy	81 (100)	
Immunotherapy	37 (46)	
EGFR TKI	18 (22)	

[‡]Patient can be counted in more than one category

[*]Patients groups by type of prior therapy may overlap

Source: U.S. Food and Drug Administration. BLA Multi-disciplinary Review and Evaluation (16) and RYBREVANT USPI (15)

Table 2:

Efficacy Results in CHRYSALIS

	Exon 20ins mutation Previously Treated w/ Platinum Chemotherapy (N=81)
Overall Response Rate % (95% CI)	**40 (29, 51)**
Complete response, n (%)	**3 (3.7)**
Partial response, n (%)	**29 (35.8)**
Duration of Response	
Median in months (95% CI)	**11.1 (6.9, NE)**
% with ≥ 6 months	**62.5**

NE=Not Estimable

Source: U.S. Food and Drug Administration. BLA Multi-disciplinary Review and Evaluation (16) and RYBREVANT USPI (15)

Table 3:

Adverse Reactions (≥ 10%) in Patients with NSCLC with *EGFR* Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy and Received Amivantamab in CHRYSAL IS

Adverse Reactions	RYBREVANT (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Skin and subcutaneous tissue disorders		
Rash[a]	84	3.9
Pruritis	18	0
Dry skin	14	0
General disorders and administration site conditions		
Infusion related reaction	64	3.1
Fatigue[b]	33	2.3
Edema[c]	27	0.8
Pyrexia	13	0
Infections and infestations		
Paronychia	50	3.1
Pneumonia[d]	10	0.8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[e]	47	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea[f]	37	2.3
Cough[g]	25	0
Gastrointestinal disorders		
Nausea	36	0
Stomatitis[h]	26	0.8
Constipation	23	0
Vomiting	22	0
Diarrhea	16	3.1
Abdominal Pain[i]	11	0.8
Vascular disorders		
Hemorrhage[j]	19	0
Metabolism and nutrition disorders		
Decreased appetite	15	0
Nervous system disorders		
Peripheral neuropathy[k]	13	0
Dizziness	12	0.8
Headache[l]	10	0.8

[a] Rash: acne, dermatitis, dermatitis acneiform, eczema, eczema asteatotic, palmar-plantar erythrodysesthesia syndrome, perineal rash, rash, rash erythematous, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, toxic epidermal necrolysis

[b] Fatigue: asthenia, fatigue

[c] Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling

d Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, and pulmonary sepsis

[e] Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain

[f] Dyspnea: dyspnea, dyspnea exertional

[g] Cough: cough, productive cough, upper airway cough syndrome

[h] Stomatitis: aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis

[i] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort

[j] Hemorrhage: epistaxis, gingival bleeding, hematuria, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage

[k] Peripheral neuropathy: hypoesthesia, neuralgia, paresthesia, peripheral sensory neuropathy

[l] Headache: headache, migraine

Source: RYBREVANT USPI (15)

Table 4

Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYBREVANT in CHRYSALIS

Laboratory Abnormality	RYBREVANT+ (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Chemistry		
Decreased albumin	79	8
Increased glucose	56	4
Increased alkaline phosphatase	53	4.8
Increased creatinine	46	0
Increased alanine aminotransferase	38	1.6
Decreased phosphate	33	8
Increased aspartate aminotransferase	33	0
Decreased magnesium	27	0
Increased gamma-glutamyl transferase	27	4
Decreased sodium	27	4
Decreased potassium	26	6
Hematology		
Decreased lymphocytes	36	8

+The denominator used to calculate the rate was 126 based on the number of patients with a baseline value and at least one post-treatment value.

Source: RYBREVANT USPI (15)