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Running tittle: Afatinib plus vinorelbine for LSCC

Afatinib combined with oral metronomic vinorelbine as second-line treatment for advanced lung squamous cell carcinoma: a retrospective cohort study

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The aim of this study was to evaluate the efficacy and safety of afatinib combined with oral metronomic vinorelbine as a second-line treatment for patients with advanced lung squamous cell carcinoma (LSCC). A retrospective analysis was conducted on 38 patients with advanced LSCC who had failed first-line platinum-based doublet chemotherapy combined with immunotherapy between January 2022 and June 2024. All patients received afatinib (30 mg or 40 mg orally once daily) combined with oral metronomic vinorelbine (20 mg or 30 mg orally three times weekly on Monday, Wednesday, and Friday) until disease progression or unacceptable toxicity. The primary endpoints were objective response rate (ORR) and progression-free survival (PFS). Secondary endpoints included overall survival (OS), disease control rate (DCR), and treatment-related adverse events (TRAEs).

Based on the data, the ORR was 26.3%, and the DCR was 68.4%. The median PFS was 5.0 months (95% CI: 4.7-5.4), and the median OS was 9.0 months (95% CI: 8.6-10.0). Grade ≥3 TRAEs occurred in 23.7% (9/38) of patients, including diarrhea (5.3%), rash (5.3%), neutropenia (5.3%), stomatitis (2.6%), and fatigue (2.6%). No grade 4-5 TRAEs or treatment-related deaths occurred.

To conclude, the combination of afatinib and oral metronomic vinorelbine demonstrates promising antitumor activity and a manageable safety profile as a second-line treatment for advanced LSCC. This combo could represent an option as second-line after failure of chemo+IO.

Key words: afatinib; vinorelbine; metronomic chemotherapy; oral chemotherapy; lung squamous cell carcinoma; second-line treatment; EGFR inhibitor; efficacy; safety

Lung cancer remains one of the most prevalent and lethal malignancies globally, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases. Lung squamous cell carcinoma (LSCC), a major histological subtype of NSCLC, comprises about 25-30% of all NSCLC cases [1]. Compared to lung adenocarcinoma [2, 3], LSCC is more strongly associated with smoking and exhibits a complex landscape of driver gene mutations [4], with a very low prevalence of classic targetable driver genes such as EGFR, ALK, and ROS1[5]. This molecular profile limits the benefit LSCC patients derive from traditional targeted therapies, and treatment strategies have long relied on chemotherapy and, more recently, immunotherapy [6].

For first-line treatment of advanced LSCC, platinum-based doublet chemotherapy was the longstanding standard [7]. The advent of immune checkpoint inhibitors (ICIs), either as monotherapy or in combination with chemotherapy, has successfully improved first-line outcomes, significantly prolonging survival for some patients. However, a considerable proportion of patients do not benefit from immunotherapy due to low PD-L1 expression, an unfavorable tumor immune microenvironment, or contraindications to ICIs [8]. Furthermore, acquired resistance limits long-term benefit for those initially responsive. For patients who progress after first-line therapy, second-line treatment options are extremely limited [9]. Current guidelines recommend single-agent docetaxel, gemcitabine, or anti-angiogenic agents combined with chemotherapy; however, efficacy is generally poor, with objective response rates (ORRs) typically below 10% and median progression-free survival (PFS) of only 2-3 months. Moreover, intravenous chemotherapy is often associated with significant toxicity, severely impacting patients' quality of life (QoL). Therefore, there is an urgent need for effective and well-tolerated novel second-line regimens for LSCC [10].

Afatinib, a second-generation irreversible ErbB family inhibitor, potently and irreversibly blocks multiple receptors, including EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErbB4 [11, 12]. Although classical EGFR sensitizing mutations are rare in LSCC, EGFR protein overexpression or gene amplification is relatively common, and abnormal activation of other family members like HER2/HER3 occurs in some cases [13]. Preclinical studies have shown that afatinib inhibits the proliferation of EGFR wild-type tumor cells. The phase III LUX-Lung 8 trial demonstrated that afatinib was superior to erlotinib as second-line therapy for advanced LSCC, significantly improving both PFS and overall survival (OS), thereby establishing its role in LSCC treatment

[14-16].

Vinorelbine is a semi-synthetic vinca alkaloid that inhibits microtubule polymerization, arresting tumor cell mitosis, and is a conventional effective agent for NSCLC [17]. Metronomic chemotherapy involves the continuous administration of low-dose chemotherapy at frequent intervals. It exerts antitumor effects through multiple mechanisms, including anti-angiogenesis, immunomodulation, and direct inhibition of tumor cell proliferation, while significantly reducing the toxicity associated with conventional chemotherapy [18]. Oral vinorelbine administered in a metronomic schedule (e.g., three times weekly) has demonstrated favorable safety and promising antitumor activity in several studies [19], making it particularly suitable for patients requiring long-term maintenance therapy or those with poor tolerance to standard regimens [20, 21].

Based on this rationale, the combination of afatinib and oral metronomic vinorelbine may provide synergistic antitumor activity through complementary mechanisms: afatinib inhibits the EGFR family signaling pathway, while metronomic vinorelbine exerts both anti-microtubule and anti-angiogenic effects [22, 23]. Both agents are orally administered, allowing for an all-oral combination that may enhance patient adherence and QoL. Currently, clinical evidence for this combination in the second-line treatment of advanced LSCC is lacking. Therefore, this retrospective study aimed to preliminarily evaluate the efficacy and safety of afatinib combined with oral metronomic vinorelbine in this setting, providing a reference for clinical practice.

Patients and Methods

Study Population. This study retrospectively enrolled patients with advanced LSCC treated at our institution between January 2022 and June 2024. Inclusion criteria were: 1) Histologically or cytologically confirmed stage IIIB-IV LSCC; 2) Disease progression after first-line platinum-based doublet chemotherapy combined with immunotherapy or immunotherapy alone (depending on PD-L1 level), according to RECIST 1.1 criteria. Primary immune resistance was defined as disease progression during or within 3 months of completing ICI therapy, or stable disease (SD) as the best response without clinical benefit for at least 6 months of ICI therapy. Acquired resistance to immunotherapy was defined as disease progression during or after ICI therapy in patients who initially achieved an objective response (complete response [CR] or partial response [PR]) or SD with clinical benefit lasting at least 6 months [14, 15]; 3) Age 18-75 years; 4) ECOG performance

status (PS) 0-2; 5) At least one measurable target lesion; 6) No prior treatment with afatinib or vinorelbine; 7) Complete clinical and pathological data with accessible follow-up information. Exclusion criteria were: 1) Presence of known driver gene mutations (EGFR, ALK, ROS1, MET, etc.) with approved targeted therapies; 2) Active brain or leptomeningeal metastases; 3) Prior or concurrent other malignancies; 4) Contraindications to afatinib (e.g., history of interstitial lung disease, severe hepatic impairment); 5) Contraindications to vinorelbine (e.g., severe myelosuppression, severe infection); 6) Severe cardiac, hepatic, or renal insufficiency. 7) previous use of taxanes was not an exclusion criteria.

Treatment regimen. All patients received afatinib combined with oral metronomic vinorelbine. The specific regimen was: afatinib at 30 mg or 40 mg orally once daily, continuously; vinorelbine at 20 mg or 30 mg orally three times weekly (Monday, Wednesday, Friday), continuously. A treatment cycle was defined as 28 days. Treatment continued until disease progression, unacceptable toxicity, withdrawal of informed consent, or death. Dose adjustments or treatment delays were permitted based on adverse event (AE) profiles. Afatinib could be reduced to 30 mg (if starting at 40 mg) and further to 20 mg if intolerance persisted. Vinorelbine could be reduced to 20 mg (if starting at 30 mg) or temporarily withheld. Adjustments followed relevant guidelines and prescribing information.

Assessment and evaluation criteria. The primary endpoints were ORR and PFS. Secondary endpoints included DCR, OS, and safety. Tumor response was evaluated using RECIST version 1.1, categorized as CR, PR, SD, or progressive disease (PD). ORR was defined as the percentage of patients achieving CR or PR, and DCR as the percentage achieving CR, PR, or SD. Tumor assessments were performed every 2 cycles (approximately 8 weeks) until disease progression. PFS was defined as the time from treatment initiation to first documented PD or death from any cause. OS was defined as the time from treatment initiation to death from any cause. Safety was assessed according to the NCI-CTCAE version 5.0, recording all AEs occurring during treatment, with a focus on EGFR inhibitor-related AEs (e.g., diarrhea, rash, stomatitis) and vinorelbine-related AEs (e.g., myelosuppression, neurotoxicity, constipation). Data on age, sex, smoking history, PD-L1 expression level, prior treatment regimens, and responses were also collected for subgroup analyses.

Statistical analysis. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were compared using the t-test or Mann-Whitney U test, and categorical variables using the chi-square or Fisher's exact test. Survival curves were estimated

using the Kaplan-Meier method and compared using the log-rank test. Ninety-five percent confidence intervals (CIs) for median PFS and OS were calculated using the Brookmeyer-Crowley method. A two-sided p-value < 0.05 was considered statistically significant.

Ethics approval. The study adhered to the principles outlined in the Declaration of Helsinki (revised in 2013). Approval for this retrospective trial was obtained from the Ethics Committee of Hubei Cancer Hospital Affiliated with Tongji Medical College (Wuhan, China) (Approval No. LLHBCH2026YN-028). Informed consent was waived due to the retrospective nature of the study.

Results

Baseline characteristics. A total of 38 eligible patients with advanced LSCC were enrolled. Baseline characteristics are summarized in Table 1. The median age was 68 years (range 61-80), and 65.8% (25/38) were male. Most patients (76.3%, 29/38) had an ECOG PS of 0-1, while 23.7% (9/38) had a PS of 2. A history of smoking was present in 60.5% (23/38). PD-L1 expression levels were < 1% in 50.0% (19/38), 1-49% in 31.6% (12/38), and ≥ 50% in 18.4% (7/38). All patients had received prior first-line therapy including ICI (5.3% ICI monotherapy, 94.7% platinum-doublet chemotherapy plus ICI). The most common ICI agents were camrelizumab (34.2%), tislelizumab (28.9%), and sintilimab (18.4%). The best response to prior first-line therapy was CR/PR in 44.7% (17/38) and SD/PD in 52.6% (20/38). The interval from last prior treatment to study entry was ≥ 6 months in 57.9% (22/38), 3-6 months in 26.3% (10/38), and < 3 months in 15.8% (6/38). Common metastatic sites included bone (73.7%, 28/38), liver (18.4%, 7/38), and brain (18.4%, 7/38). The starting dose of afatinib was 40 mg in 68.4% (26/38) and 30 mg in 31.6% (12/38). The starting dose of vinorelbine was 30 mg in 57.9% (22/38) and 20 mg in 42.1% (16/38) (Table 1).

Efficacy. All 38 patients were evaluable for efficacy. The best overall responses were: PR in 10 patients (26.3%), SD in 16 (42.1%), and PD in 12 (31.6%). No CR was observed. The ORR was 26.3% (95% CI: 13.4-43.1%), and the DCR was 68.4% (95% CI: 51.3-82.5%) (Table 2). Subgroup analyses showed no significant difference in PFS or OS between patients with PD-L1 ≥ 1% and those with PD-L1 < 1%. Patients who achieved CR/PR as their best response to first-line therapy had significantly better outcomes than those with SD/PD (median PFS: 6.0 vs. 4.25 months, p=0.0041; median OS: 11.0 vs. 8.25 months, p=0.0112). Similarly, patients with an interval from last treatment of ≥ 6 months had significantly better outcomes compared to those with an interval <

6 months (median PFS: 5.5 vs. 4.0 months, p=0.0068; median OS: 9.5 vs. 7.75 months, p=0.0281) (Figure 1). At the data cutoff date (December 31, 2024), the median follow-up duration was 10.2 months (range 2.0-18.5 months). The median PFS for the entire cohort was 5.0 months (95% CI: 4.65-5.43), with 6-month and 12-month PFS rates of 36.5% and 12.8%, respectively. The median OS was 9.0 months (95% CI: 8.58-9.97), with 6-month and 12-month OS rates of 71.6% and 39.2%, respectively (Table 2).

Safety. All 38 patients were evaluable for safety. The incidence of any-grade treatment-related adverse events (TRAEs) was 100%. The most common TRAEs (incidence ≥ 20%) were rash (44.7%), nausea (36.8%), anorexia (36.8%), fatigue (34.2%), diarrhea (34.2%), stomatitis (23.7%), vomiting (21.1%), and peripheral neuropathy (23.7%). Grade ≥ 3 TRAEs occurred in 23.7% (9/38) of patients, including diarrhea (5.3%), rash (5.3%), neutropenia (5.3%), stomatitis (2.6%), and fatigue (2.6%). No grade 4-5 TRAEs or treatment-related deaths occurred.

The overall incidence of EGFR inhibitor-related AEs (e.g., diarrhea, rash, stomatitis, paronychia) was 81.6% (31/38), mostly grade 1-2, manageable with symptomatic support. The overall incidence of vinorelbine-related AEs (e.g., myelosuppression, neuropathy, constipation) was 55.3% (21/38). Myelosuppression was primarily grade 1-2; grade 3 neutropenia occurred in only 2 cases, with no febrile neutropenia (Table 3).

Dose reductions due to AEs were required for afatinib in 36.8% (14/38) of patients (10 from 40 mg to 30 mg, 4 from 30 mg to 20 mg) and for vinorelbine in 28.9% (11/38) (8 from 30 mg to 20 mg, 3 resumed after temporary withholding). Treatment was delayed in 23.7% (9/38) and discontinued in 5.3% (2/38) due to persistent grade 3 diarrhea or rash. Overall, the combination regimen demonstrated a manageable safety profile with no new safety signals, and the oral administration was well-accepted by patients.

Discussion

The scarcity of effective options after first-line failure for advanced LSCC remains a significant clinical challenge [24]. Although ICIs have reshaped first-line treatment (first-line platinum-based doublet chemotherapy combined with immunotherapy or immunotherapy alone, depending on PD-L1 level) [25], many patients with low PD-L1 expression, an unsuitable tumor immune microenvironment, or acquired resistance to immunotherapy face a lack of standard-of-care options

in the second-line setting [26, 27]. Conventional second-line chemotherapies, such as single-agent docetaxel, have limited efficacy (ORR < 10%, median PFS 2-3 months) and are associated with significant hematologic and other toxicities from intravenous administration, impairing QoL. Thus, exploring effective and well-tolerated novel regimens, particularly convenient all-oral strategies, is of high clinical value [28]. This study is the first to retrospectively evaluate the efficacy and safety of afatinib combined with oral metronomic vinorelbine as second-line therapy for advanced LSCC, offering a new therapeutic approach [10].

Our results show an ORR of 26.3%, DCR of 68.4%, median PFS of 5.0 months, and median OS of 9.0 months with this combination. These outcomes are notably superior to historical data for second-line single-agent chemotherapy and are comparable to results from recent studies of other targeted or combination regimens. For instance, the LUX-Lung 8 trial reported a median PFS of 2.6 months and median OS of 7.9 months for afatinib monotherapy in second-line LSCC. Historical data for docetaxel show median PFS of only 2-3 months [16]. The improved PFS and OS observed in our study suggest a potential synergistic effect between afatinib and metronomic vinorelbine. Potential mechanisms for this synergy include: 1) Afatinib, as a pan-ErbB inhibitor, suppresses proliferation of EGFR wild-type tumor cells beyond targeting sensitizing mutations. 2) Although EGFR mutations are rare in LSCC, EGFR protein overexpression or gene amplification is common, and afatinib is effective against such non-mutation-driven EGFR activation. 3) Metronomic vinorelbine not only inhibits tumor cell mitosis via anti-microtubule effects but also exerts indirect antitumor effects through anti-angiogenesis (inhibiting endothelial cell proliferation, inducing apoptosis) and immunomodulation (modulating Treg function) [29, 30]. 4) EGFR pathway inhibition by afatinib may enhance tumor cell sensitivity to chemotherapy. The all-oral nature of both agents facilitates a fully oral targeted-chemotherapy combination, potentially improving adherence [31, 32].

Subgroup analyses provide insights for selecting patients most likely to benefit. Patients with an interval from last prior therapy of ≥ 6 months and those who achieved CR/PR with first-line therapy had significantly longer PFS and OS. Although this association is attributable to several factors, such as the durable long- tail response to immunotherapy, the immune microenvironment of these patients, and the inherently less aggressive nature of their tumors [33, 34]. These parameters could serve as reference factors for identifying optimal candidates for this regimen. This also suggests that

the depth and duration of response to prior immunotherapy might predict long-term survival benefit and allow more time and opportunity for subsequent treatments, although the potential impact of the long-tail effect of immunotherapy on subsequent treatment efficacy cannot be excluded [35, 36]. In contrast, no significant difference in efficacy was observed between PD-L1 positive and negative patients. This may reflect the limitations of PD-L1 expression as a sole predictive biomarker, as well as the heterogeneity of tumors and complexity of the immune microenvironment [37]. Reliable prediction of efficacy and prognosis likely requires integrating multiple clinical observations or biomarkers. For patients with ECOG PS 2 or liver metastases [38], while some benefit was observed (ORR 12.5% and 14.3%, respectively), the degree of benefit was limited, suggesting these subgroups may require more intensive combination strategies or aggressive local therapy [39]. Although not statistically significant, a trend toward higher ORR was noted in patients with PD-L1 $\geq$ 50% (37.5%) [40], warranting further investigation in larger cohorts [41].

Regarding safety, the combination was generally well-tolerated, with a toxicity profile consistent with known AEs of each agent. This suggests that there was no overlapping toxicity between the two agents, such as afatinib- induced rash and vinorelbine- induced peripheral neuropathy [42]. The most common TRAEs were rash (44.7%), diarrhea (34.2%), nausea (36.8%), and fatigue (34.2%), aligning with the afatinib safety profile [43] but with slightly higher incidence, possibly due to the combination. The grade $\geq$ 3 AE rate (23.7%) was somewhat lower than rates reported for afatinib monotherapy in LUX-Lung 8 (~30-40%), potentially attributable to baseline dose selection (30 mg or 40 mg) and proactive AE management. Notably, metronomic vinorelbine administration resulted in a low incidence of grade $\geq$ 3 neutropenia (5.3%) and peripheral neuropathy (5.3%), significantly lower than that seen with conventional intravenous vinorelbine (typically 30-50%), demonstrating the "low toxicity" advantage of metronomic scheduling. EGFR inhibitor-related AEs (e.g., diarrhea, rash) were effectively managed with symptomatic support and dose adjustments [44]. The overall treatment discontinuation rate due to AEs was low (5.3%), indicating good clinical feasibility [45].

The all-oral administration is a key advantage of this regimen. For patients with advanced cancer receiving second-line therapy, QoL is a crucial consideration [46]. Oral administration avoids the inconvenience and discomfort of frequent intravenous infusions [47], reduces hospital visits and healthcare resource utilization, and may improve adherence and satisfaction. Most patients in this

study accepted the oral regimen well [48].

This study has limitations. Its single-center, retrospective design with a small sample size may introduce selection and information bias [49, 50]. A notable feature is the high proportion (40%) of non- smokers among the enrolled patients [51]. The lack of a randomized control arm prevents head-to-head comparison with current standard second-line therapies. The EGFR status was unknown for a considerable proportion of patients, precluding assessment of its impact on efficacy. Although national and international guidelines also recommend genetic testing for non- smoking lung squamous cell carcinoma [52]. Biomarker analyses (e.g., EGFR protein expression, copy number) were not performed, limiting investigation of predictive factors. Follow-up was relatively short, and long-term safety requires confirmation. QoL was not formally assessed using standardized questionnaires. The heterogeneity of the study population (different PD-L1 levels, prior therapies, EGFR status) suggests that larger, stratified, prospective studies are needed to validate these findings [53].

In conclusion, afatinib combined with oral metronomic vinorelbine demonstrates promising antitumor activity (ORR 26.3%, mPFS 5.0 months, mOS 9.0 months) and a manageable safety profile as a second-line treatment for advanced LSCC. The all-oral regimen offers high patient adherence. This study provides a new treatment option and clinical evidence for patients with advanced LSCC who have failed first-line therapy, particularly those with poor tolerance to intravenous chemotherapy or a preference for oral treatment [10]. Prospective, multicenter, randomized controlled trials are warranted to validate the clinical value of this regimen and explore predictive biomarkers for precision treatment [27, 54].

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Figure Legends

Figure 1. The median progression-free survival (PFS) and overall survival (OS) of afatinib combined with oral metronomic vinorelbine in second-line treatment of patients with advanced lung squamous cell carcinoma. A, B) Median PFS and OS for the general population, respectively; C, D) Comparisons of PFS and OS between patients with different prior immunotherapy response (CR/PR vs SD/PD); E, F) Comparisons of PFS and OS between patients with different interval since last immunotherapy (≥ 6 months vs. < 6 months). G, H) Comparisons of PFS and OS between patients with PD-L1 (+) and patients with PD-L1 (-) (PD-L1 (+) vs PD-L1 (-)); PD-L1 (+) is defined as a PD-L1 expression level ≥ 1%, and PD-L1 (-) is defined as a PD-L1 expression level < 1%. Abbreviations: mPFS-median progression-free survival; mOS-median overall survival

495 **Table 1.** Baseline clinical characteristics of the study cohort.

Characteristics	No. of patients (%)
Age	
Years	68
Range	61-80
Gender	
Male	25 (65.8%)
Female	13 (34.2%)
Smoking history	
never smoker	15 (39.5%)
former smoker	23 (60.5%)
ECOG score	
0-1	29 (76.3%)
≥ 2	9 (23.7%)
Previous radiotherapy	
Yes	11 (30.0%)
No	27 (70.0%)
Brain metastasis	
measurable	7 (18.4%)
unmeasurable	31 (81.6%)
Bone metastasis	
Yes	28 (73.7%)
No	10 (26.3%)
Liver metastasis	
Yes	7 (18.4%)
No	31 (81.6%)
Stage	
IVA	6 (15.8%)
IVB	15 (39.5%)
IVC	17 (44.7%)
PD-L1 expression	
< 1%	19 (50.00%)
1 << 49%	12 (31.6%)
>> 50%	7 (18.4%)
PD-1/L1 inhibitors	
pembrolizumab	5 (13.2%)
atezolizumab	2 (5.3%)
camrelizumab	13 (34.2%)
tislelizumab	11 (30.0%)
sintilimab	7 (18.4%)
IO treatment mode	
single PD-1/L1	2 (5.3%)
PD-1/L1 plus TP regimen	23 (60.5%)
PD-1/L1 plus GP regimen	13 (34.2%)
Best response to last anti–PD-(L)1–	

containing regimen, f No. (%)	
Responder (CR/PR)	17 (44.7%)
Nonresponder (SD/PD)	20 (52.6%)
Not available	1 (2.6%)
interval since last IO	
>> 6 m	22 (57.9%)
3 << 6 m	10 (26.3%)
< 3 m	6 (15.8%)
Comorbidities	
Yes	13 (34.2%)
No	25 (65.8%)

496

497 **Table 2.** The efficacy of afatinib combined with oral metronomic vinorelbine in second-line
498 treatment of patients with advanced lung squamous cell carcinoma.

	Patient No.	Ratio
Complete response	0	0
Partial response	10	26.3% (10/38)
Stable response	16	42.1% (16/38)
Progressive disease	12	31.6% (12/38)
Objective response		26.3%
Median PFS		5.0 m
Disease control Rate		68.4%
Median OS		9.0 m

499

500 **Table 3.** The safety of afatinib combined with oral metronomic vinorelbine in second-line treatment
501 of patients with advanced lung squamous cell carcinoma.

	afatinib plus NVB [n (%)]	
Adverse Event	Any Grade	Grade 3 or 4
Hematological		
Leukopenia	8 (21.1%)	2 (5.3%)
Neutropenia	7 (18.4%)	2 (5.3%)
Anemia	6 (15.8%)	2 (5.3%)
Thrombocytopenia	8 (21.1%)	2 (5.3%)
Nonhematologic		
Rash	17 (44.7%)	2 (5.3%)
nausea	14 (36.8%)	0.00%
Decreased appetite	14 (36.8%)	0.00%
Fatigue	13 (34.2%)	1 (2.6%)
Diarrhea	13 (34.2%)	2 (5.3%)
Stomatitis	9 (23.7%)	1 (2.6%)
peripheral neuropathy	9 (23.7%)	2 (5.3%)
Vomit	8 (21.1%)	0.00%
Constipation	7 (18.4%)	0.00%
Oral ulcer	7 (18.4%)	0.00%
paronychia	6 (15.8%)	0.00%
Elevated transaminase	6 (15.8%)	0.00%
Hyperbilirubinemia	4 (10.5%)	0.00%
Dysphagia	5 (13.2%)	0.00%
Dysphonia	4 (10.5%)	0.00%
Abdominal pain	4 (10.5%)	0.00%
Bleeding	4 (10.5%)	0.00%
ALP increased	3 (7.9%)	0.00%
Elevated GGT	3 (7.9%)	0.00%
Hypoproteinemia	2 (5.3%)	0.00%
Elevated LDH	1 (2.6%)	0.00%

502

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