

**Running title:** 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**

Chen Yin<sup>1,#</sup>, Binfeng Li<sup>2,#</sup>, Xi Lin<sup>3</sup>, Aoli Zhang<sup>3</sup>, Yi Peng<sup>4</sup>, Jing Tang<sup>5</sup>, Xiaobing Li<sup>3,\*</sup>

<sup>1</sup>Department of Oncology, Panyu Central Hospital, Cancer Institute of Panyu, Guangzhou, China;

<sup>2</sup>Department of Thoracic Surgery, Huber Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; <sup>3</sup>Department of Thoracic Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; <sup>4</sup>Department of Radiotherapy, Huber Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; <sup>5</sup>Department of Lymphoma, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

\*Correspondence: [lixiaobing0629@126.com](mailto:lixiaobing0629@126.com)

#Contributed equally to this work.

**Received May 6, 2026 / Accepted August 3, 2026**

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  $\geq 3$  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

46

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

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

68 Afatinib, a second-generation irreversible ErbB family inhibitor, potently and irreversibly blocks  
69 multiple receptors, including EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErbB4 [11, 12]. Although  
70 classical EGFR sensitizing mutations are rare in LSCC, EGFR protein overexpression or gene  
71 amplification is relatively common, and abnormal activation of other family members like  
72 HER2/HER3 occurs in some cases [13]. Preclinical studies have shown that afatinib inhibits the  
73 proliferation of EGFR wild-type tumor cells. The phase III LUX-Lung 8 trial demonstrated that  
74 afatinib was superior to erlotinib as second-line therapy for advanced LSCC, significantly  
75 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

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

114 **Treatment regimen.** All patients received afatinib combined with oral metronomic vinorelbine.  
115 The specific regimen was: afatinib at 30 mg or 40 mg orally once daily, continuously; vinorelbine at  
116 20 mg or 30 mg orally three times weekly (Monday, Wednesday, Friday), continuously. A treatment  
117 cycle was defined as 28 days. Treatment continued until disease progression, unacceptable toxicity,  
118 withdrawal of informed consent, or death. Dose adjustments or treatment delays were permitted  
119 based on adverse event (AE) profiles. Afatinib could be reduced to 30 mg (if starting at 40 mg) and  
120 further to 20 mg if intolerance persisted. Vinorelbine could be reduced to 20 mg (if starting at 30  
121 mg) or temporarily withheld. Adjustments followed relevant guidelines and prescribing information.

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

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

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

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

143

## 144 **Results**

145 **Baseline characteristics.** A total of 38 eligible patients with advanced LSCC were enrolled.  
146 Baseline characteristics are summarized in Table 1. The median age was 68 years (range 61-80),  
147 and 65.8% (25/38) were male. Most patients (76.3%, 29/38) had an ECOG PS of 0-1, while 23.7%  
148 (9/38) had a PS of 2. A history of smoking was present in 60.5% (23/38). PD-L1 expression levels  
149 were  $< 1\%$  in 50.0% (19/38), 1-49% in 31.6% (12/38), and  $\geq 50\%$  in 18.4% (7/38). All patients had  
150 received prior first-line therapy including ICI (5.3% ICI monotherapy, 94.7% platinum-doublet  
151 chemotherapy plus ICI). The most common ICI agents were camrelizumab (34.2%), tislelizumab  
152 (28.9%), and sintilimab (18.4%). The best response to prior first-line therapy was CR/PR in 44.7%  
153 (17/38) and SD/PD in 52.6% (20/38). The interval from last prior treatment to study entry was  $\geq 6$   
154 months in 57.9% (22/38), 3-6 months in 26.3% (10/38), and  $< 3$  months in 15.8% (6/38). Common  
155 metastatic sites included bone (73.7%, 28/38), liver (18.4%, 7/38), and brain (18.4%, 7/38). The  
156 starting dose of afatinib was 40 mg in 68.4% (26/38) and 30 mg in 31.6% (12/38). The starting dose  
157 of vinorelbine was 30 mg in 57.9% (22/38) and 20 mg in 42.1% (16/38) (Table 1).

158 **Efficacy.** All 38 patients were evaluable for efficacy. The best overall responses were: PR in 10  
159 patients (26.3%), SD in 16 (42.1%), and PD in 12 (31.6%). No CR was observed. The ORR was  
160 26.3% (95% CI: 13.4-43.1%), and the DCR was 68.4% (95% CI: 51.3-82.5%) (Table 2). Subgroup  
161 analyses showed no significant difference in PFS or OS between patients with PD-L1  $\geq 1\%$  and  
162 those with PD-L1  $< 1\%$ . Patients who achieved CR/PR as their best response to first-line therapy  
163 had significantly better outcomes than those with SD/PD (median PFS: 6.0 vs. 4.25 months,  
164  $p=0.0041$ ; median OS: 11.0 vs. 8.25 months,  $p=0.0112$ ). Similarly, patients with an interval from  
165 last treatment of  $\geq 6$  months had significantly better outcomes compared to those with an interval  $<$

166 6 months (median PFS: 5.5 vs. 4.0 months,  $p=0.0068$ ; median OS: 9.5 vs. 7.75 months,  $p=0.0281$ )  
167 (Figure 1). At the data cutoff date (December 31, 2024), the median follow-up duration was 10.2  
168 months (range 2.0-18.5 months). The median PFS for the entire cohort was 5.0 months (95% CI:  
169 4.65-5.43), with 6-month and 12-month PFS rates of 36.5% and 12.8%, respectively. The median  
170 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%,  
171 respectively (Table 2).

172 **Safety.** All 38 patients were evaluable for safety. The incidence of any-grade treatment-related  
173 adverse events (TRAEs) was 100%. The most common TRAEs (incidence  $\geq 20\%$ ) were rash  
174 (44.7%), nausea (36.8%), anorexia (36.8%), fatigue (34.2%), diarrhea (34.2%), stomatitis (23.7%),  
175 vomiting (21.1%), and peripheral neuropathy (23.7%). Grade  $\geq 3$  TRAEs occurred in 23.7% (9/38)  
176 of patients, including diarrhea (5.3%), rash (5.3%), neutropenia (5.3%), stomatitis (2.6%), and  
177 fatigue (2.6%). No grade 4-5 TRAEs or treatment-related deaths occurred.

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

183 Dose reductions due to AEs were required for afatinib in 36.8% (14/38) of patients (10 from 40 mg  
184 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  
185 resumed after temporary withholding). Treatment was delayed in 23.7% (9/38) and discontinued in  
186 5.3% (2/38) due to persistent grade 3 diarrhea or rash. Overall, the combination regimen  
187 demonstrated a manageable safety profile with no new safety signals, and the oral administration  
188 was well-accepted by patients.

189

## 190 **Discussion**

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

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

203 Our results show an ORR of 26.3%, DCR of 68.4%, median PFS of 5.0 months, and median OS of  
204 9.0 months with this combination. These outcomes are notably superior to historical data for  
205 second-line single-agent chemotherapy and are comparable to results from recent studies of other  
206 targeted or combination regimens. For instance, the LUX-Lung 8 trial reported a median PFS of 2.6  
207 months and median OS of 7.9 months for afatinib monotherapy in second-line LSCC. Historical  
208 data for docetaxel show median PFS of only 2-3 months [16]. The improved PFS and OS observed  
209 in our study suggest a potential synergistic effect between afatinib and metronomic vinorelbine.  
210 Potential mechanisms for this synergy include: 1) Afatinib, as a pan-ErbB inhibitor, suppresses  
211 proliferation of EGFR wild-type tumor cells beyond targeting sensitizing mutations. 2) Although  
212 EGFR mutations are rare in LSCC, EGFR protein overexpression or gene amplification is common,  
213 and afatinib is effective against such non-mutation-driven EGFR activation. 3) Metronomic  
214 vinorelbine not only inhibits tumor cell mitosis via anti-microtubule effects but also exerts indirect  
215 antitumor effects through anti-angiogenesis (inhibiting endothelial cell proliferation, inducing  
216 apoptosis) and immunomodulation (modulating Treg function) [29, 30]. 4) EGFR pathway  
217 inhibition by afatinib may enhance tumor cell sensitivity to chemotherapy. The all-oral nature of  
218 both agents facilitates a fully oral targeted-chemotherapy combination, potentially improving  
219 adherence [31, 32].

220 Subgroup analyses provide insights for selecting patients most likely to benefit. Patients with an  
221 interval from last prior therapy of  $\geq 6$  months and those who achieved CR/PR with first-line therapy  
222 had significantly longer PFS and OS. Although this association is attributable to several factors,  
223 such as the durable long- tail response to immunotherapy, the immune microenvironment of these  
224 patients, and the inherently less aggressive nature of their tumors [33, 34]. These parameters could  
225 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

256 study accepted the oral regimen well [48].

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

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

277

278 Acknowledgements: We would like to thank Xichen Wang (MSD China, Shanghai, China) for  
279 providing academic information consulting support.

280 The study was supported by The Beijing Integrative Medicine Association Research Project (No.  
281 ZHKY-2025-5193) and Chen Xiao-ping Foundation for the Development of Science and  
282 Technology of Hubei Province (No. CXPJJH126001-26008).

283

284

285 **References**

- 286 [1] SMOLARZ B, ŁUKASIEWICZ H, SAMULAK D, PIEKARSKA E, KOŁACIŃSKI R et al.  
287 Lung Cancer-Epidemiology, Pathogenesis, Treatment and Molecular Aspect (Review of  
288 Literature). *Int J Mol Sci* 2025; 26: 2049. <https://doi.org/10.3390/ijms26052049>
- 289 [2] BANERJEE A, VATHIOTIS I, HALDER D, SEN U, WANG X et al. Molecular Landscape  
290 and Therapeutic Strategies of Lung Cancer Lineage Plasticity. *J Thorac Oncol* 2025; 20:  
291 1582-1593. <https://doi.org/10.1016/j.jtho.2025.06.012>
- 292 [3] SHEN Y, CHEN JQ, LI XP. Differences between lung adenocarcinoma and lung squamous  
293 cell carcinoma: Driver genes, therapeutic targets, and clinical efficacy. *Genes Dis* 2024; 12:  
294 101374. <https://doi.org/10.1016/j.gendis.2024.101374>
- 295 [4] ALSATARI ES, SMITH KR, GALAPPATHTHI SPL, TURBAT-HERRERA EA,  
296 DASGUPTA S. The Current Roadmap of Lung Cancer Biology, Genomics and Racial  
297 Disparity. *Int J Mol Sci* 2025; 26: 3818. <https://doi.org/10.3390/ijms26083818>
- 298 [5] WANG C, YU Q, SONG T, WANG Z, SONG L et al. The heterogeneous immune landscape  
299 between lung adenocarcinoma and squamous carcinoma revealed by single-cell RNA  
300 sequencing. *Signal Transduct Target Ther* 2022; 7: 289.  
301 <https://doi.org/10.1038/s41392-022-01130-8>
- 302 [6] NIU Z, JIN R, ZHANG Y, LI H. Signaling pathways and targeted therapies in lung  
303 squamous cell carcinoma: mechanisms and clinical trials. *Signal Transduct Target Ther*  
304 2022; 7: 353. <https://doi.org/10.1038/s41392-022-01200-x>
- 305 [7] TRAVIS WD, BRAMBILLA E, NOGUCHI M, NICHOLSON AG, GEISINGER KR et al.  
306 International Association for the Study of Lung Cancer/American Thoracic  
307 Society/European Respiratory Society: international multidisciplinary classification of lung  
308 adenocarcinoma: executive summary. *Proc Am Thorac Soc* 2011; 8: 381-385.  
309 <https://doi.org/10.1513/pats.201107-042ST>
- 310 [8] SANTOS ES, RODRIGUEZ E. Treatment Considerations for Patients with Advanced  
311 Squamous Cell Carcinoma of the Lung. *Clin Lung Cancer* 2022; 23: 457-466.  
312 <https://doi.org/10.1016/j.clc.2022.06.002>
- 313 [9] BORGHAEI H, GETTINGER S, VOKES EE, CHOW LQM, BURGIO MA et al. Five-Year  
314 Outcomes from the Randomized, Phase III Trials CheckMate 017 and 057: Nivolumab  
315 Versus Docetaxel in Previously Treated Non-Small-Cell Lung Cancer. *J Clin Oncol* 2021;  
316 39: 723-733. <https://doi.org/10.1200/JCO.20.01605>
- 317 [10] WANG Y, ROSELL R, HIRSCH FR, LU S, GOVINDAN R et al. Emerging options and  
318 future strategies in immunotherapy for advanced lung squamous-cell carcinoma. *Ann Oncol*  
319 2026; 37: 289-313. <https://doi.org/10.1016/j.annonc.2025.11.008>
- 320 [11] LU S, LI W, ZHOU C, HU CP, QIN S et al. Afatinib vs erlotinib for second-line treatment of  
321 Chinese patients with advanced squamous cell carcinoma of the lung. *Onco Targets Ther*  
322 2018; 11: 8565-8573. <https://doi.org/10.2147/OTT.S161506>
- 323 [12] SANTOS ES, HART L. Advanced Squamous Cell Carcinoma of the Lung: Current  
324 Treatment Approaches and the Role of Afatinib. *Onco Targets Ther* 2020; 13: 9305-9321.  
325 <https://doi.org/10.2147/OTT.S250446>
- 326 [13] CHUANG JC, STEHR H, LIANG Y, DAS M, HUANG J et al. ERBB2-Mutated Metastatic  
327 Non-Small Cell Lung Cancer: Response and Resistance to Targeted Therapies. *J Thorac*  
328 *Oncol* 2017; 12: 833-842. <https://doi.org/10.1016/j.jtho.2017.01.023>
- 329 [14] CHEN YY, CHANG SC, CHANG CY, CHANG CF, LAI YC et al. Real-world effectiveness  
330 of second-line Afatinib versus chemotherapy for the treatment of advanced lung squamous

cell carcinoma in immunotherapy-naïve patients. *BMC Cancer* 2021; 21: 1225.  
<https://doi.org/10.1186/s12885-021-08920-3>

[15] SARTORI G, BELLUOMINI L, LOMBARDO F, AVANCINI A, TRESTINI I et al. Efficacy and safety of afatinib for non-small-cell lung cancer: state-of-the-art and future perspectives. *Expert Rev Anticancer Ther* 2020; 20: 531-542.  
<https://doi.org/10.1080/14737140.2020.1776119>

[16] SORIA JC, FELIP E, COBO M, LU S, SYRIGOS K et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2015; 16: 897-907. [https://doi.org/10.1016/S1470-2045\(15\)00006-6](https://doi.org/10.1016/S1470-2045(15)00006-6)

[17] CAMERINI A, MORABITO A, MONTANINO A, BERNABÉ R, GROSSI F et al. Metronomic oral vinorelbine in previously untreated advanced non-small-cell lung cancer patients unfit for platinum-based chemotherapy: results of the randomized phase II Tempo Lung trial. *ESMO Open* 2021; 6: 100051. <https://doi.org/10.1016/j.esmoop.2021.100051>

[18] BARBOLOSI D, CICCOLINI J, MEILLE C, ELHARRAR X, FAIVRE C et al. Metronomics chemotherapy: time for computational decision support. *Cancer Chemother Pharmacol* 2014; 74: 647-652. <https://doi.org/10.1007/s00280-014-2546-1>

[19] D'ASCANIO M, PEZZUTO A, FIORENTINO C, SPOSATO B, BRUNO P et al. Metronomic Chemotherapy with Vinorelbine Produces Clinical Benefit and Low Toxicity in Frail Elderly Patients Affected by Advanced Non-Small Cell Lung Cancer. *Biomed Res Int* 2018; 2018: 6278403. <https://doi.org/10.1155/2018/6278403>

[20] CHEN S, HE Z, LI M, WENG L, LIN J. Efficacy and safety of metronomic oral vinorelbine and its combination therapy as second- and later-line regimens for advanced non-small-cell lung cancer: a retrospective analysis. *Clin Transl Oncol* 2024; 26: 3202-3210. <https://doi.org/10.1007/s12094-024-03543-z>

[21] LI Y, LI W, LIU Y, PENG Y, TANG J et al. Efficacy and safety of anlotinib combined with vinorelbine as second- line treatment for elderly patients with advanced squamous cell lung carcinoma: A retrospective cohort. *Mol Clin Oncol* 2024; 22: 21. <https://doi.org/10.3892/mco.2024.2816>

[22] HUBER JM, AMANN A, KOECK S, LORENZ E, KELM JM et al. Evaluation of assays for drug efficacy in a three-dimensional model of the lung. *J Cancer Res Clin Oncol* 2016; 142: 1955-1966. <https://doi.org/10.1007/s00432-016-2198-0>

[23] LIU Z, FU Q, WANG Y, CUI L, ZHANG W et al. Synergy between vinorelbine and afatinib in the inhibition of non-small cell lung cancer progression by EGFR and p53 signaling pathways. *Biomed Pharmacother* 2021; 134: 111144. <https://doi.org/10.1016/j.biopha.2020.111144>

[24] HSU EC, WU KL, TSAI YM, LEE MH, TSAI MJ et al. Real-world treatment pattern and prognostic factors of stage IV lung squamous cell carcinoma patients. *Kaohsiung J Med Sci* 2022; 38: 1001-1011. <https://doi.org/10.1002/kjm2.12599>

[25] ZHOU C, HU Y, ARKANIAN E, KILICKAP S, YING K et al. A global phase 3 study of serplulimab plus chemotherapy as first-line treatment for advanced squamous non-small-cell lung cancer (ASTRUM-004). *Cancer Cell* 2024; 42: 198-208.e3. <https://doi.org/10.1016/j.ccell.2023.12.004>

[26] LIU N, ZHANG B, HE J, LI S. Efficacy and safety of immune checkpoint inhibitors for advanced squamous non-small cell lung cancer: a systematic review and network

- meta-analysis. *Front Immunol* 2025; 16: 1635757.  
<https://doi.org/10.3389/fimmu.2025.1635757>
- [27] WANG Y, SAFI M, HIRSCH FR, LU S, PETERS S et al. Immunotherapy for advanced-stage squamous cell lung cancer: the state of the art and outstanding questions. *Nat Rev Clin Oncol* 2025; 22: 200-214. <https://doi.org/10.1038/s41571-024-00979-8>
- [28] TONG Y, WANG Y, CHEN Y, FAN Y, LI H. Decoding the tumor immune microenvironment in lung squamous cell carcinoma: characteristics, regulatory mechanisms, and future directions in immunotherapy. *Transl Lung Cancer Res* 2025; 14: 4112-4130. <https://doi.org/10.21037/tlcr-2025-350>
- [29] GLORIEUX C, XIA X, YOU X, WANG Z, HAN Y et al. Cisplatin and gemcitabine exert opposite effects on immunotherapy with PD-1 antibody in K-ras-driven cancer. *J Adv Res* 2022; 40: 109-124. <https://doi.org/10.1016/j.jare.2021.12.005>
- [30] QIN RS, ZHANG ZH, ZHU NP, CHEN F, GUO Q et al. Enhanced antitumor and anti-angiogenic effects of metronomic Vinorelbine combined with Endostar on Lewis lung carcinoma. *BMC Cancer* 2018; 18: 967. <https://doi.org/10.1186/s12885-018-4738-2>
- [31] ROSSI D, LIPPE P, ROCCHI MBL, SARTI D, CATALANO V et al. Metronomic Oral Vinorelbine: An Alternative Schedule in Elderly and Patients PS2 With Local/Advanced and Metastatic NSCLC Not Oncogene-addicted. *In Vivo* 2020; 34: 2687-2691. <https://doi.org/10.21873/invivo.12088>
- [32] XU B, SUN T, WANG S, LIN Y. Metronomic therapy in advanced breast cancer and NSCLC: vinorelbine as a paradigm of recent progress. *Expert Rev Anticancer Ther* 2021; 21: 71-79. <https://doi.org/10.1080/14737140.2021.1835478>
- [33] LI X, PENG Y, WU D, TANG J, WU Y. Efficacy and safety of anlotinib as maintenance therapy in patients with advanced non-small cell lung cancer achieving SD post first-line chemotherapy combined with immunotherapy. *J Chemother* 2025; 37: 527-535. <https://doi.org/10.1080/1120009X.2024.2397924>
- [34] WU D, LIU K, PENG Y, LIU Y, TANG J et al. The Efficacy and Safety of Anlotinib Treatment for Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) Who Achieved Stable Disease (SD) After Two Cycles of First-Line Chemotherapy Combined with Immunotherapy: A Retrospective Cohort Study. *Cancer Manag Res* 2025; 17: 2795-2805. <https://doi.org/10.2147/CMAR.S539781>
- [35] CARBONE DP, CIULEANU TE, COBO M, SCHENKER M, ZURAWSKI B, et al. Nivolumab plus ipilimumab with chemotherapy as first-line treatment of patients with metastatic non-small-cell lung cancer: final, 6-year outcomes from CheckMate 9LA. *ESMO Open* 2025; 10: 105123. <https://doi.org/10.1016/j.esmoop.2025.105123>
- [36] PETERS S, PAZ-ARES LG, RECK M, CARBONE DP, BRAHMER JR et al. Long-Term Survival Outcomes with First-Line Nivolumab Plus Ipilimumab-Based Treatment in Patients with Metastatic NSCLC and Tumor Programmed Death-Ligand 1 Lower Than 1%: A Pooled Analysis. *J Thorac Oncol* 2025; 20: 94-108. <https://doi.org/10.1016/j.jtho.2024.09.1439>
- [37] ZHANG Z, LIN Y, CHEN S. Efficacy of neoadjuvant, adjuvant, and perioperative immunotherapy in non-small cell lung cancer across different PD-L1 expression levels: a systematic review and meta-analysis. *Front Immunol* 2025; 16: 1569864. <https://doi.org/10.3389/fimmu.2025.1569864>
- [38] TENG H, QIN N, LIU K, GONG C, TANG J et al. Efficacy and safety of albumin-bound paclitaxel combined with anlotinib and immunotherapy in advanced non-small cell lung

- cancer with liver metastases: a retrospective study. *BMC Cancer* 2026; 26: 653. <https://doi.org/10.1186/s12885-026-15996-2>
- [39] LIU K, LI B, XIANG Z, TANG J, LI X. Temozolomide and anlotinib as second-line therapy for non-small cell lung cancer patients with brain metastases: a retrospective cohort study. *Neoplasma* 2025; 72: 300-306. [https://doi.org/10.4149/neo\\_2025\\_250212N74](https://doi.org/10.4149/neo_2025_250212N74)
- [40] NOVELLO S, KOWALSKI DM, LUFT A, GÜMÜŞ M, VICENTE D et al. Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. *J Clin Oncol* 2023; 41: 1999-2006. <https://doi.org/10.1200/JCO.22.01990>
- [41] LIU J, CAI Y, LIU J, CHEN D, WU X. Immunotherapy Resistance and Therapeutic Strategies in PD-L1 High Expression Non-Small Cell Lung Cancer. *Onco Targets Ther* 2025; 18: 953-966. <https://doi.org/10.2147/OTT.S539978>
- [42] VERGNENEGRE A, MONNET I, RICORDEL C, BIZIEUX A, CURCIO H et al. Safety and efficacy of second-line metronomic oral vinorelbine-atezolizumab combination in stage IV non-small-cell lung cancer: An open-label phase II trial (VinMetAtezo). *Lung Cancer* 2023; 178: 191-197. <https://doi.org/10.1016/j.lungcan.2023.02.020>
- [43] KHRYSTOLUBOVA N, SHIEH M, PATEL AJ, BAILEY R. Pharmacist-led patient education and adverse event management in patients with non-small cell lung cancer receiving afatinib in a community-based, real-world clinical setting. *J Oncol Pharm Pract* 2020; 26: 13-22. <https://doi.org/10.1177/1078155219833441>
- [44] ZHOU S, KISHI N, ALERASOOL P, ROHS NC. Adverse Event Profile of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors for Non-small Cell Lung Cancer: An Updated Meta-Analysis. *Target Oncol* 2024; 19: 547-564. <https://doi.org/10.1007/s11523-024-01073-w>
- [45] XU K, LIU T, ZHANG J, ZHOU Y, YANG F et al. The efficacy and toxicity of metronomic oral vinorelbine monotherapy in patients with non-small cell lung cancer: a meta-analysis. *Int J Clin Oncol* 2020; 25: 1624-1634. <https://doi.org/10.1007/s10147-020-01707-9>
- [46] LIU T, HE J, WANG Y, YANG Y, ZHANG L et al. Health-related quality of life and symptoms in patients with previously untreated, locally advanced or metastatic non-squamous non-small cell lung cancer treated with sintilimab or placebo plus pemetrexed and platinum (ORIENT-11): A randomized, double-blind, phase 3 trial. *Lung Cancer* 2025; 200: 108108. <https://doi.org/10.1016/j.lungcan.2025.108108>
- [47] FELIP E, HIRSH V, POPAT S, COBO M, FÜLÖP A et al. Symptom and Quality of Life Improvement in LUX-Lung 8, an Open-Label Phase III Study of Second-Line Afatinib Versus Erlotinib in Patients with Advanced Squamous Cell Carcinoma of the Lung After First-Line Platinum-Based Chemotherapy. *Clin Lung Cancer* 2018; 19: 74-83.e11. <https://doi.org/10.1016/j.clc.2017.06.002>
- [48] ESTEVINHO F, GOMES R, HASMUCRAI D, BARATA F. Metronomic oral vinorelbine in a real-world population of advanced non-small cell lung cancer patients. *Pulmonology* 2022; 28: 368-375. <https://doi.org/10.1016/j.pulmoe.2020.09.003>
- [49] LI X, WU D, TANG J, WU Y. The Efficiency and Safety of Triple-Drug Combination of Albumin-Bound Paclitaxel, Anlotinib and PD-1/L1 Inhibitors in the 2(nd) or Above Line of Advanced NSCLC: A Retrospective Cohort Study. *Cancer Manag Res* 2024; 16: 1003-1012. <https://doi.org/10.2147/CMAR.S472196>

- 465 [50] TANG J, LI XY, LIANG JB, WU D, PENG L et al. Apatinib Plus Chemotherapy Shows  
466 Clinical Activity in Advanced NSCLC: Retrospective Study. *Oncol Res* 2019; 27: 635-641.  
467 <https://doi.org/10.3727/096504018X15288447760357>
- 468 [51] BALDASSARRI M, FALLERINI C, CETTA F, GHISALBERTI M, BELLAN C et al. Omic  
469 Approach in Non-smoker Female with Lung Squamous Cell Carcinoma Pinpoints to  
470 Germline Susceptibility and Personalized Medicine. *Cancer Res Treat* 2018; 50: 356-365.  
471 <https://doi.org/10.4143/crt.2017.125>
- 472 [52] MOSELE F, REMON J, MATEO J, WESTPHALEN CB, BARLESI F et al.  
473 Recommendations for the use of next-generation sequencing (NGS) for patients with  
474 metastatic cancers: a report from the ESMO Precision Medicine Working Group. *Ann Oncol*  
475 2020; 31: 1491-1505. <https://doi.org/10.1016/j.annonc.2020.07.014>
- 476 [53] LI X, WU D, TANG J, WU Y. The efficiency and safety of temozolomide and PD-1/L1  
477 inhibitors in pretreated NSCLC with brain metastasis: a retrospective cohort. *J Cancer Res*  
478 *Clin Oncol* 2024; 150: 271. <https://doi.org/10.1007/s00432-024-05808-0>
- 479 [54] DE ZUANI M, XUE H, PARK JS, DENTRO SC, SEFERBEKOVA Z et al. Single-cell and  
480 spatial transcriptomics analysis of non-small cell lung cancer. *Nat Commun* 2024; 15: 4388.  
481 <https://doi.org/10.1038/s41467-024-48700-8>
- 482

## 483 Figure Legends

484

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

494

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%)          |
| <b>Smoking history</b>                     |                     |
| never smoker                               | 15 (39.5%)          |
| former smoker                              | 23 (60.5%)          |
| ECOG score                                 |                     |
| 0-1                                        | 29 (76.3%)          |
| ≥ 2                                        | 9 (23.7%)           |
| <b>Previous radiotherapy</b>               |                     |
| Yes                                        | 11 (30.0%)          |
| No                                         | 27 (70.0%)          |
| <b>Brain metastasis</b>                    |                     |
| measurable                                 | 7 (18.4%)           |
| unmeasurable                               | 31 (81.6%)          |
| <b>Bone metastasis</b>                     |                     |
| Yes                                        | 28 (73.7%)          |
| No                                         | 10 (26.3%)          |
| <b>Liver metastasis</b>                    |                     |
| Yes                                        | 7 (18.4%)           |
| No                                         | 31 (81.6%)          |
| <b>Stage</b>                               |                     |
| IVA                                        | 6 (15.8%)           |
| IVB                                        | 15 (39.5%)          |
| IVC                                        | 17 (44.7%)          |
| <b>PD-L1 expression</b>                    |                     |
| < 1%                                       | 19 (50.00%)         |
| 1 << 49%                                   | 12 (31.6%)          |
| >> 50%                                     | 7 (18.4%)           |
| <b>PD-1/L1 inhibitors</b>                  |                     |
| pembrolizumab                              | 5 (13.2%)           |
| atezolizumab                               | 2 (5.3%)            |
| camrelizumab                               | 13 (34.2%)          |
| tislelizumab                               | 11 (30.0%)          |
| sintilimab                                 | 7 (18.4%)           |
| <b>IO treatment mode</b>                   |                     |
| 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%)          |
| <b>Best response to last anti-PD-(L)1-</b> |                     |

**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

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

| Adverse Event         | afatinib plus NVB [n (%)] |              |
|-----------------------|---------------------------|--------------|
|                       | 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%        |

Fig. 1 [Download full resolution image](#)

