Role of dasatinib in the management of lung cancer: A meta-analysis of clinical trials

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Abstract. Lung cancer, particularly non-small cell lung cancer (NSCLC), the leading cause of cancer-related deaths worldwide, has prompted extensive research into innovative treatments, including targeted therapies. The present meta-analysis aims to evaluate the efficacy of dasatinib, both as monotherapy and in combination with other therapies, for the treatment of lung cancer. Adhering to the PRISMA guidelines, a meticulous, thorough review of clinical trials was conducted across reputable databases, including Google Scholar, PubMed/MEDLINE, and EMBASE, focusing on studies published in English up to May 5th, 2024. Inclusion criteria were restricted to randomized clinical trials (RCTs) assessing the efficacy of dasatinib, either as a standalone therapy or in combination with other treatments. The search identified 55 studies, of which nine RCTs met the inclusion criteria: four phase II, three phase I, and two phase I/II. A total of 234 patients participated, with 107 receiving dasatinib alone and 127 undergoing combination therapy. Histological analyses revealed that 79.1% of patients had non-small cell lung cancer, with adenocarcinoma being the predominant subtype (63.8%), followed by squamous cell carcinoma (22.1%). Treatment responses varied, with 52.4% of the patients in the dasatinib alone group experiencing progressive disease, while 38.3% achieved stable disease; by contrast, 29.6% of patients in the combination therapy showed progressive disease. Adverse events, including anemia and fatigue, were more prevalent with combination therapies. Dasatinib treatment shows potential for improving overall survival with fewer adverse events compared with combination therapies in patients with lung cancer; however, large-scale clinical trials are essential to confirm its efficacy as a standalone treatment.

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Introduction

Lung cancer refers to tumors originating from the lung parenchyma (1). It is the most common cancer globally, both in terms of incidence and mortality. In total, ~2 million individuals are diagnosed with lung cancer annually, leading to ~1.8 million deaths (2). The mortality rate from lung cancer exceeds the combined deaths caused by prostate, breast, brain and colorectal cancers (3). Small-cell lung cancer (SCLC) accounts for 15% of all cases, while non-small cell lung cancer (NSCLC) comprises 85%, marking the two primary subtypes of the disease (4). NSCLC, in particular, is the most extensively studied form of cancer, with the highest number of publications recorded in 2022 (5). Epidemiological data indicate that the general population experiences a lung cancer incidence rate of 69 per 100,000 individuals, with this rate increasing substantially to 751 per 100,000 men over the age of 75. This increase is primarily attributed to both advanced age and the higher prevalence of lung cancer among males (6).

Effective management planning for lung cancer requires determining the tumor, lymph node and metastasis (TNM) staging, as treatment strategies are based on the cancer's stage and the extent of metastasis (7-9). Surgical intervention is an option for patients with resectable NSCLC in stages I, II and IIIA (10). In addition to surgery, the treatment of NSCLC includes radiotherapy, chemotherapy, immunotherapy and targeted molecular therapy. Targeted therapy, a relatively new treatment approach, continues to evolve as researchers identify new biological targets (7). Among the targeted therapies, dasatinib, an FDA-approved multi-kinase

inhibitor, is primarily utilized for the treatment of chronic myeloid leukemia. Additionally, it demonstrates significant antiproliferative effects on various solid tumors, particularly when used in combination with other therapeutic agents, including those for prostate, breast, lung and pancreatic cancers (11).

The present meta-analysis evaluates the efficacy of dasatinib, both as monotherapy and in combination with other therapies, in the management of lung cancer. All references have been checked to exclude any non-peer-reviewed data (12).

Materials and methods

Study design. The present study examines clinical trials evaluating the efficacy of dasatinib in treatment of lung cancer. The analysis includes investigations of dasatinib both as a monotherapy and in combination with other therapies. The combination groups are classified as follows: Group A (dasatinib with erlotinib), group B (dasatinib with Osimertinib), group C (dasatinib with afatinib) and group D (dasatinib with chemoradiation). The study strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Data sources and search strategy. A comprehensive search was conducted across several reputable databases, including Google Scholar (https://scholar.google.com/), PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/) and EMBASE (https://www.elsevier.com/en-gb/products/embase). The search strategy employed a well-defined set of keywords to identify relevant studies, specifically: (lung OR pulmonary OR bronchi OR bronchus OR chest OR pleural OR alveolus OR alveoli) AND (Dasatinib OR SPRYCEL OR Dasanix OR Dasanat). This approach ensured that all pertinent clinical trials related to dasatinib and lung cancer were identified for consideration.

Eligibility criteria. For the current meta-analysis, studies were required to meet specific inclusion and exclusion criteria. Eligible studies included randomized clinical trials (RCTs) that assessed the efficacy of dasatinib in the treatment of lung cancer, either as a monotherapy or in combination with other therapies. Studies were excluded if they were not RCTs, did not focus on dasatinib as a treatment for lung cancer, or lacked sufficient data on treatment efficacy or patient outcomes. These criteria were strictly followed to ensure that only relevant studies were included in the analysis.

Study selection process. The study selection process was conducted by two independent researchers who meticulously screened the titles and abstracts of identified studies. Each study was evaluated against the pre-established inclusion and exclusion criteria. In cases where there was a disagreement regarding the eligibility of a study, a third researcher was consulted to reach consensus.

Data items. Data extracted from the eligible studies included comprehensive details, including the first author's name, year of publication, median age of patients, sex distribution, smoking status, type of therapy, adverse events, histological characteristics of lung cancer, and various outcome measures.

Data analysis and synthesis. The extracted data were systematically organized using a Microsoft Excel (2019) workbook. Qualitative descriptive statistical analysis was performed utilizing the Statistical Package for Social Sciences version 26.0 (IBM Corp.). Results were presented in terms of frequencies, percentages, medians and ranges, providing a clear depiction of the findings across the included studies. For categorical variables, statistical comparisons were made using the Chi-square test and Fisher's exact test, as appropriate. For continuous variables, such as overall survival and progression-free survival (PFS), the Mann-Whitney U test was employed, a non-parametric method that accounts for differences in data distributions, ensuring that the heterogeneity within the data was appropriately addressed.

Results

Study selection process and eligibility criteria. The systematic search initially identified 55 studies related to dasatinib and lung cancer. After removing nine duplicates, two non-English publications, and 10 abstract-only studies, 34 studies remained for title and abstract screening. Following the initial assessment, one article was excluded due to irrelevance. Among the remaining 33 studies, 24 were excluded for not meeting the predefined inclusion criteria, resulting in a final total of nine eligible studies for analysis (13-21) (Fig. 1).

Characteristics of included RCTs. All the studies included were RCTs, consisting of four phase II trials, three phase I trials, and two studies that encompass both phase I and II designs. The raw data, along with key characteristics of each study, are summarized in Tables I-III. A meta-analysis of studies that utilized dasatinib alone for progressive disease, showing a pooled estimate of 0.54 [95% confidence interval (CI), 0.41-0.66] with moderate heterogeneity (I^2=39%, Tau^2=0.0826) (Fig. 2A). By contrast, studies that employed combination therapy, resulting in a lower pooled estimate of 0.18 [95% CI, 0.07-0.40] but with greater heterogeneity (I^2=57%, Tau^2=0.7982) (Fig. 2B). The increased heterogeneity in these studies may be attributed to the variability in treatment protocols across the included studies, a limitation that may impact the consistency of the findings.

Baseline characteristics and treatment group distribution in the included studies. A total of 234 patients were included across the eligible studies. These patients were categorized into two groups: 107 patients (45.7%) received dasatinib as a monotherapy, while 127 patients (54.3%) were treated with dasatinib in combination with other therapies. The median age of the patients in the dasatinib alone group and combination groups was 63 years, with an interquartile range of 6 for the dasatinib alone group and 6.75 for the combination group.

Patient demographics, histological subtypes and treatment response. Among the 234 patients, 121 (51.7%) patients were male. Smoking status was reported for only 50 patients

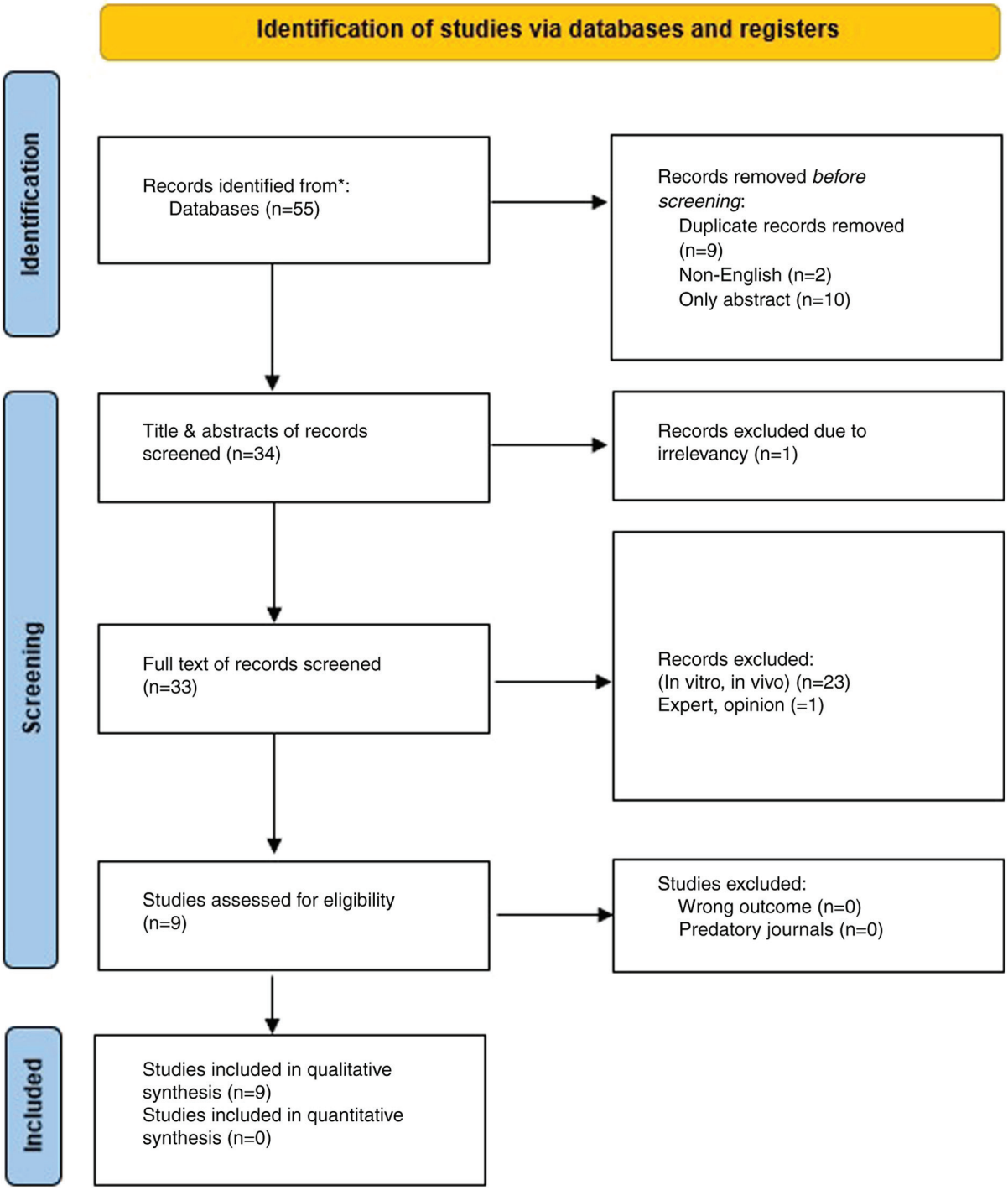

Figure 1. Study selection PRISMA flow chart.

(21.4%); of these, 39 (16.7%) were former smokers, three (1.3%) were active smokers, and 8 (3.4%) were never-smokers (<100 cigarettes in a lifetime). The smoking status of the remaining 184 (78.6%) patients was undocumented. Most patients had an Eastern Cooperative Oncology Group (ECOG) status of one [136 patients, (58.1%)], followed by scores of zero [68 patients, (29.1%)] and two [5 patients, (2.1%)]. Performance status was not reported for 25 patients (10.7%).

Histologically, 185 cases (79.1%) were diagnosed as NSCLC, while 44 cases (18.8%) were classified as SCLC. Within the NSCLC cohort, adenocarcinoma was the most prevalent subtype, identified in 118 patients (63.8%), followed by squamous cell carcinoma in 41 patients (22.1%).

The majority of the cohort presented with advanced disease, with 167 patients (71.4%) at stage IV, eight patients (3.4%) at stage IIIB, and six patients (2.6%) at stage IIIA. Disease stage was not documented for the remaining 53 patients (22.6%).

Regarding treatment, 127 patients (54.3%) received combination therapies, while 107 patients (45.7%) were treated with dasatinib alone. In the dasatinib alone group, 56 patients (52.4%) experienced progressive disease, 24 patients (22.4%) had stable disease, one patient (0.9%) demonstrated a partial

Table I. Baseline characteristics of patients enrolled in clinical trials evaluating dasatinib and combination therapies for lung cancer.

First author/s, year	Type of therapy	Phase of clinical trial	No. of patients	Sex		Median age	Smoking status				(Refs.)
				Male	Female		Former	Active	Never (<100 in lifetime)	N/A	
Johnson *et al*, 2010	Dasatinib	2	34	24	10	69	1	N/A	N/A	33	(13)
Haura *et al*, 2010	Dasatinib + Erlotinib	1 and 2	34	18	16	61	30	3	1	0	(14)
Gold *et al*, 2014	Dasatinib + Erlotinib	1 and 2	47	26	21	62	N/A	N/A	N/A	47	(15)
Kelly *et al*, 2016	Dasatinib	2	25	14	11	62	N/A	N/A	N/A	25	(16)
Kim *et al*, 2021	Dasatinib + Osimertinib	1	10	1	9	70.5	3	0	7	0	(17)
Creelan *et al*, 2019	Dasatinib + Afatinib	1	25	10	15	66	N/A	N/A	N/A	25	(18)
Miller *et al*, 2010	Dasatinib	2	43	17	26	64	N/A	0	0	43	(19)
Khurshid *et al*, 2012	Dasatinib + chemoradiation	1	11	8	3	63	N/A	N/A	N/A	11	(20)
Brunner *et al*, 2013	Dasatinib	2	5	3	2	59	5	N/A	N/A	0	(21)

Table II. Distribution of ECOG performance status and histological classification of lung cancers among study participants.

ECOG Status					Histology of lung cancers						
						NSCLC					
0	1	2	3	N/A	SCLC	Adenocarcinoma	Squamous cell carcinoma	Large cell carcinoma	NSCLC NOS[a]	Adenosquamous	Others
10	24	0	0	0	0	25	6	0	3	0	0
24	10	0	0	0	0	17	7	0	10	0	0
10	37	0	0	0	1	25	11	0	5	0	5
3	17	5	0	0	0	15	5	0	4	1	0
5	5	0	0	0	0	8	0	0	1	1	0
N/A	N/A	N/A	N/A	25	0	23	2	0	0	0	0
12	31	0	0	0	43	0	0	0	0	0	0
2	9	0	0	0	0	5	5	0	1	0	0
2	3	0	0	0	0	0	5	0	0	0	0

[a]This includes (Poorly differentiated NSCLC, NSCLC NOS, undifferentiated carcinoma, non-small cell undetermined and other types of NSCLC that cannot be exactly classified from the studies) all are referred to not specified NSCLC. ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; NOS, not otherwise specified.

response, and 26 patients (24.3%) had an undocumented response status. In group A, comprising patients treated with dasatinib and erlotinib, 31 patients (38.3%) achieved stable disease, 24 patients (29.6%) experienced progressive disease, seven patients (8.6%) had a partial response, and 19 patients (23.5%) had an undocumented response status. In group B, involving dasatinib and osimertinib, nine patients (90%) demonstrated a partial response, one patient (10%) achieved stable disease, and no patients (0%) expressed progressive disease (Table IV). The lack of data on certain factors (for

Table III. Treatment outcomes, prior therapies, and survival data for patients with lung cancer treated with dasatinib and combination therapies.

First author/s, year	No. of patients (evaluable for response)	Previous chemoradiation/ surgery for lung cancer		Type of therapy	Outcome				Median survival in months		(Refs.)
		Yes	No.		Partial response	Stable disease	Progressive disease	Not mentioned	Overall survival	Progression-free survival	
Johnson *et al*, 2010	34 (30)	13	21	Dasatinib alone	1	12	17	0	11.4	1.36	(13)
Haura *et al*, 2010	34 (29)	34 (Chemo)	0	Dasatinib + Erlotinib	2	16	11	0	5.6	2.7	(14)
Gold *et al*, 2014	47 (33)	N/A	N/A	Dasatinib + Erlotinib	5	15	13	0	13	3.3	(15)
Kelly *et al*, 2017	25 (16)	25 (chemo)	0	Dasatinib alone	0	5	11	9	3.7	N/A	(16)
Kim *et al*, 2021	10 (10)	N/A	N/A	Dasatinib + Osimertinib	9[a]	1	0	0	36.1	19.4	(17)
Creelan *et al*, 2018	25 (25)	25	0	Dasatinib + Afatinib	0	17	1	7	14.7	3.7	(18)
Miller *et al*, 2010	43 (35)	43 (Chemo) 34 (Radiation)	0	Dasatinib alone	0	7	28	0	3.9	1.4	(19)
Khurshid *et al*, 2012	11 (10)	0	11	Dasatinib + chemoradiation	2	N/A	N/A	8	18	N/A	(20)
Brunner *et al*, 2013	5 (0)	5	0	Dasatinib alone	N/A	N/A	N/A	5	N/A	N/A	(21)

Table IV. Patient demographics, lung cancer characteristics and treatment responses for various therapies.

Variables	Number of patients (234)
Sex	
Male	121 (51.7%)
Female	113 (48.3%)
Smoking status	
Former	39 (16.7%)
Active	3 (1.3%)
Never (<100 in a lifetime)	8 (3.4%)
Not mentioned	184 (78.6%)
ECOG status	Number of patients (234)
ECOG status (0)	68 (29.1%)
ECOG status (1)	136 (58.1%)
ECOG status (2)	5 (2.1%)
Not mentioned	25 (10.7%)
Histology of lung cancers	
Small cell lung cancer	44 (18.8%)
NSCLC	185 (79.1%)
Others	5 (2.1%)
Histology of NSCLC	Number of patients (185)
Squamous cell carcinoma	41 (22.1%)
Adenocarcinoma	118 (63.8%)
Adenosquamous	2 (1.1%)
NSCLC NOS	24 (13.0%)
Lung cancer stage	Number of patients (234)
Stage IIIA	6 (2.6%)
Stage IIIB	8 (3.4%)
Stage IV	167 (71.4%)
not mentioned	53 (22.6%)
Treatment group	Number of patients (234)
Dasatinib alone	107 (45.7%)
Combination group	127 (54.3%)
Response to dasatinib alone	Number of patients (107)
Partial response	1 (0.9%)
Stable disease	24 (22.4%)
Progressive disease	56 (52.4%)
Not mentioned	26 (24.3%)
Response to dasatinib combined with Erlotinib	Number of patients (81)
Partial response	7 (8.6%)
Stable disease	31 (38.3%)
Progressive disease	24 (29.6%)
Not mentioned	19 (23.5%)
Response to dasatinib combined with Osimertinb	Number of patients (10)
Partial response	9 (90%)
Stable disease	1 (10%)
Progressive disease	0 (0.0%)
Not mentioned	0 (0.0%)
Response to dasatinib combined with Afatinib	Number of patients (25)
Partial response	0 (0.0%)

Table IV. Continued.

Variables	Number of patients (234)
Stable disease	17 (68%)
Progressive disease	1 (4%)
Not mentioned	7 (28%)
Response to dasatinib combined with chemoradiation	Number of patients (11)
Partial response	2 (18.2%)
Stable disease	N/A
Progressive disease	N/A
Not mentioned	9 (81.8%)

example, smoking status and disease stage) limits a comprehensive understanding of outcomes across different subgroups.

Adverse events in different treatment groups. In terms of adverse events, anemia was the most frequent hematological adverse event, reported in 57 patients (42.2%). Specifically, the dasatinib monotherapy group reported in 4 cases (3.7%), while combination therapy groups reported 41 cases (50.6%) in group A, four cases (40.0%) in group B, six cases (24.0%) in group C, and two cases (18.3%) in group D.

Among gastrointestinal adverse events, diarrhea was the most common, affecting 86 patients (35.4%). This included three cases (2.8%) in the dasatinib monotherapy group, 59 cases (72.8%) in group A, eight cases (80.0%) in group C, and 15 cases (60.0%) in group C.

In dermatological adverse events, skin rash was frequently reported, affecting 80 patients (85.1%). Of these, three cases (2.8%) were in the dasatinib monotherapy group, 57 cases (70.4%) in group A, seven cases (70.0%) in group B, and 13 cases (52.0%) in group C. Additionally, fatigue was documented in 82 cases (28.8%), with 50 cases (61.7%) observed in group A, and 21 cases (19.6%) in the dasatinib monotherapy group (Table V).

Clinical outcomes revealed a significantly higher partial response in the combination therapy group (94.7%, 18/19) compared with the dasatinib alone group (5.3%, 1/19) with P<0.001. Stable disease was observed in 49 (67.1%) patients receiving combination therapy vs. 24 (32.9%) patients treated with dasatinib monotherapy. Conversely, progressive disease was more prevalent in the dasatinib monotherapy group (69.1%, 56/81) compared with the combination therapy group (30.9%, 25/81).

Survival outcomes favored combination therapy, with overall survival significantly longer (13.60±7.71 months) than dasatinib monotherapy (mean 6.35±3.59 months, P<0.001). Similarly, PFS was greater in the combination therapy group (4.60±4.58 months vs. 1.38±0.02 months, P<0.001).

Anemia was significantly more frequent in the combination therapy group 93.0% (53/57) than in the dasatinib-alone group 7.0% (4/57, P=0.033). Other gastrointestinal and dermatological adverse events, such as nausea, and vomiting, diarrhea, skin rash, alopecia showed no significant differences between groups. Fatigue was more common in combination therapy patients (74.4%, 61/82) compared with the dasatinib group (25.6%, 21/82). Additionally, pleural effusion was present in 67.6% (46/68) of the combination therapy group vs. 32.4% (22/68) in the dasatinib group (P<0.001) (Table VI).

Discussion

Cancer continues to pose a significant societal, public health, and economic challenge in the 21st century, accounting for nearly one in six deaths globally (16.8%) and one in four deaths (22.8%) attributed to non-communicable diseases (NCDs) (22). Traditionally viewed primarily as a genetic disease, this perspective fails to address complex clinical phenomena such as recurrence and drug resistance. Recent advancements suggest a more integrative framework, characterizing cancer as a 'multidimensional spatiotemporal unity of ecology and evolution', a dynamic pathological ecosystem which cancer cells interact with their microenvironment and undergo evolutionary changes over time. This paradigm offers critical insights into cancer progression, providing novel strategies to tackle clinical challenges such as therapeutic resistance and disease relapse (23). The disease accounts for 30.3% of premature deaths due to NCDs among individuals aged 30-69 years, ranking as one of the top three causes of death within this age group across 177 of 183 countries (22). For lung cancer specifically, exposure to cigarette smoke, radiation, asbestos, and metals such as nickel, chromium and arsenic significantly elevates risk (2). Smoking remains the primary cause, accounting for ~85% of all lung cancer cases (24). In the present study, 39 (16.7%) out of the 234 patients reported a history of smoking.

Lung cancer is broadly categorized into two primary types: SCLC and NSCLC (25). Within NSCLC, adenocarcinoma, squamous cell carcinoma and large cell carcinoma represent the major histological subtypes, with adenocarcinoma constituting 40%, squamous cell carcinoma 25-30% and large cell carcinoma 5-10% (5). The findings of the present study revealed that adenocarcinoma was present in 118 patients (63.8%), while squamous cell carcinoma was identified in 41 patients (22.1%). Sex distribution patterns also vary across studies. A study conducted by Ruano-Ravina *et al* indicated that among 13,950 participants, 25.6% were female, with female participants tending to be younger, while smoking prevalence was higher among males (26). By contrast, the current study found no significant sex disparity, with males comprising 51.7% and female 48.3% of the cohort.

Sehgal *et al* (27) conducted a study on patients with advanced-stage NSCLC undergoing treatment with pembrolizumab, demonstrating that those with an ECOG performance status of 2 or higher had significantly lower disease control rates, shorter median overall survival and reduced PFS. These findings underscore the critical importance of baseline ECOG status as a determinant of treatment effectiveness and patient outcomes. In the present study, the majority of patients had an ECOG status of one (58.1%), with fewer patients having a status of zero (29.1%) or two (2.1%).

Treatment strategies for lung cancer are according to the tumors' characteristics and stage of progression. Options include immunotherapy, chemotherapy, radiotherapy,

Table V. Adverse events in patients with lung cancer treated with dasatinib and combination therapies across treatment groups.

Adverse events	Total	Dasatinib (107)	Group A (81)	Group B (10)	Group C (25)	Group D (11)
Hematological						
Anemia	57 (42.2%)	4 (3.7%)	41(50.6%)	4 (40.0%)	6 (24.0%)	2 (18.3%)
Leukopenia	8 (5.9%)	1 (0.9%)	4 (4.9%)	3 (30.0%)	N/A	N/A
Neutropenia	14 (10.4%)	1 (0.9%)	4 (4.9%)	7 (70.0%)	N/A	2 (18.2%)
Lymphopenia	29 (21.5%)	7 (6.5%)	22 (27.2%)	N/A	N/A	N/A
Thrombocytopenia	27 (20.0%)	0 (0.0%)	18 (22.0%)	7 (70.0%)	2 (8.0%)	0 (0.0%)
Gastrointestinal						
Nausea	71 (29.2%)	7 (6.5%)	50 (61.7%)	4 (40.0%)	8 (32.0%)	2 (18.2%)
Vomiting	35 (14.4%)	4 (3.7%)	23 (28.4%)	N/A	7 (28.0%)	1 (9.1%)
Diarrhea	86 (35.4%)	3 (2.8%)	59 (72.8%)	8 (80.0%)	15 (60.0%)	1 (9.1%)
Anorexia	51 (20.9%)	5 (4.7%)	35 (43.2%)	4 (40.0%)	6 (24.0%)	1 (9.1%)
Dermatological						
Skin rash	80 (85.1%)	3 (2.8%)	57 (70.4%)	7 (70.0%)	13 (52.0%)	N/A
Alopecia	14 (14.9%)	N/A	12 (14.8%)	2 (20.0%)	N/A	N/A
Others						
Fatigue	82 (28.8%)	21 (19.6%)	50 (61.7%)	4 (40.0%)	5 (20.0%)	2 (18.2%)
Cough	9 (3.2%)	1 (0.9%)	3 (3.7%)	2 (20.0%)	3 (12.0%)	N/A
Dyspnea	54 (18.9%)	23 (21.5%)	24 (29.6%)	3 (30.0%)	3 (12.0%)	1 (9.1%)
Pain	39 (13.7%)	3 (2.8%)	28 (34.6%)	4 (40.0%)	3 (12.0%)	1 (9.1%)
Edema	13 (4.5%)	1 (0.9%)	5 (6.2%)	5 (50.0%)	2 (8.0%)	N/A
Pleural effusion	68 (23.9%)	22 (20.6%)	26 (32.1%)	10 (100%)	7 (28.0%)	3 (27.3%)
Pericardial effusion	6 (2.1%)	4 (3.7%)	1 (1.2%)	N/A	N/A	1 (9.1%)
Mucositis/stomatitis	14 (4.9%)	N/A	4 (17.3%)	3 (30.0%)	7 (28.0%)	N/A

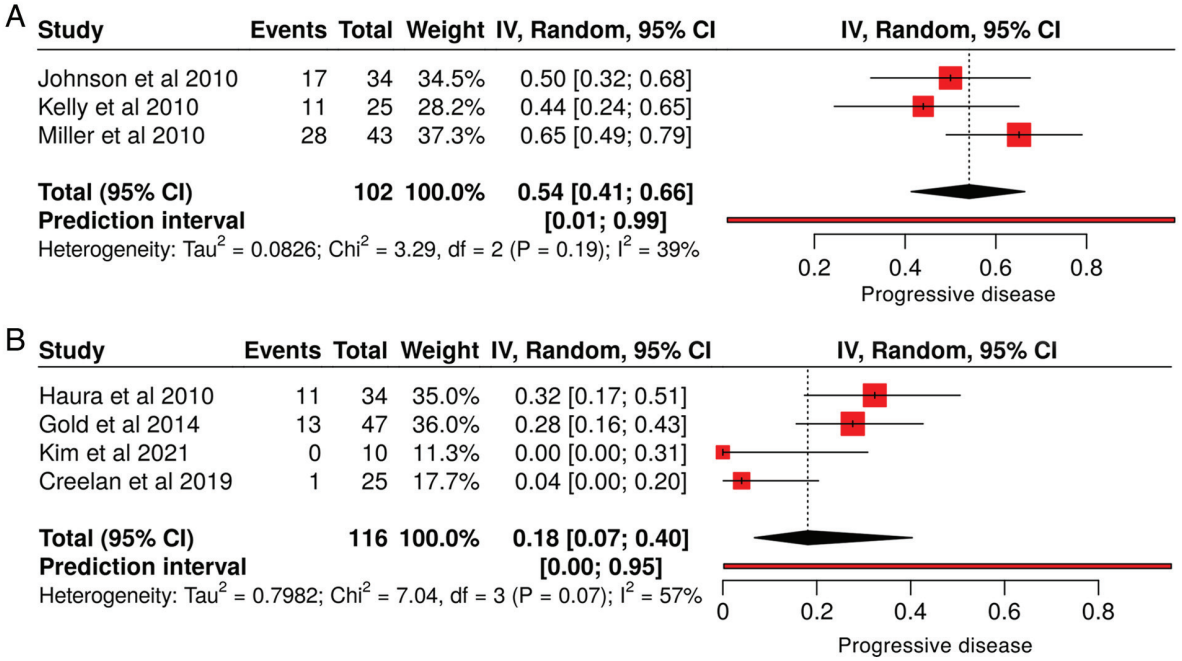

Figure 2. Forest plot of studies evaluating progressive disease rates with (A) dasatinib monotherapy vs. (B) combination therapy. CI, confidence interval.

molecular targeted therapy and surgical intervention. Surgical resection with curative intent is typically reserved for patients with early TNM stages (I or II) who are in sufficient overall health to endure the procedure (28,29). Despite transformative advancements in molecular targeted therapy and immuno-oncology, chemotherapy continues to serve as a

Table VI. Comparison of clinical outcomes and adverse events between dasatinib monotherapy and combination therapy.

Variables		Type of therapy		P-value
		Dasatinib alone	Combination therapy	
Outcome N (%)	Partial response	1 (5.3%)	18 (94.7%)	<0.001
	Stable disease	24 (32.9%)	49 (67.1%)	
	Progressive disease	56 (69.1%)	25 (30.9%)	
	Not mentioned	14 (48.3%)	15 (51.7%)	
Overall survival (Mean ± SD)		6.35±3.59	13.60±7.71	<0.001
Progression-free survival (Mean ± SD)		1.38±0.02	4.60±4.58	<0.001
Hematological adverse events, N (%)	Anemia	4 (7.0%)	53 (93.0%)	0.027
	Leukopenia	1 (12.5%)	7 (87.5%)	
	Neutropenia	1 (7.1%)	13 (92.9%)	
	Lymphopenia	7 (24.1%)	22 (75.9%)	
	Thrombocytopenia	0 (0.0%)	27 (100.0%)	
Gastrointestinal adverse events, N (%)	Nausea	7 (9.9%)	64 (90.1%)	0.247
	Vomiting	4 (11.4%)	31 (88.6%)	
	Diarrhea	3 (3.5%)	83 (96.5%)	
	Anorexia	5 (9.8)	46 (90.2%)	
Dermatological adverse events, N (%)	Skin rash	3 (3.7%)	77 (96.3%)	0.613
	Alopecia	0 (0.0%)	14 (100.0%)	
Others, N (%)	Fatigue	21 (25.6%)	61 (74.4%)	<0.001
	Cough	1 (11.1%)	8 (88.9%)	
	Dyspnea	23 (42.6%)	31 (57.4%)	
	Pain	3 (7.7%)	36 (92.3%)	
	Edema	1 (7.7%)	12 (92.3%)	
	Pleural effusion	22 (32.4%)	46 (67.6%)	
	Pericardial effusion	4 (66.7%)	2 (33.3%)	
	Mucositis/stomatitis	0 (0.0%)	14 (100.0%)	

cornerstone of lung cancer management. Studies consistently demonstrate its positive effect on both survival and quality of life, spanning early and advanced disease stages, whether administered as a monotherapy or in combination with other treatments. Moreover, emerging combination regimens and innovative drug delivery systems hold significant promise for enhancing treatment efficacy (30).

Radiotherapy plays a critical role in managing stage III NSCLC, though its effectiveness depends on the extent of the disease. For Pancoast tumors, a treatment regimen combining induction chemo-radiotherapy followed by surgery has demonstrated improved survival rates. However, in resectable N2-NSCLC, neoadjuvant chemoradiotherapy does not provide a survival benefit over chemotherapy alone. Postoperative radiotherapy does not generally improve outcomes in completely resected N2 disease, except in cases with positive margins. Concurrent chemoradiotherapy, often supplemented by durvalumab, remains the standard approach for unresectable N2 or N3 NSCLC. Advanced techniques such as intensity-modulated radiation therapy can mitigate the risk of severe pneumonitis; though their overall effectiveness varies. For patients at higher risk, radiotherapy alone may provide a modest survival benefit (31). Targeted therapy has emerged as a crucial strategy for treating NSCLC, based on the understanding that multiple oncogenic mutations drive lung cancer development. Identifying these specific genetic alterations enables the development of targeted therapies to directly combat these mutations (32). Beyond NSCLC, targeted therapies have also shown efficacy in treating other cancers, with pembrolizumab and durvalumab demonstrating effectiveness in mesothelioma (33,34).

Dasatinib inhibits cell proliferation and survival while inducing apoptosis in hematologic malignancies and solid tumors. At a concentration of 10 μM, it reduces viability and induces apoptosis in HSC-3 cells. Additionally, it significantly inhibits the proliferation and survival of YD-8, YD-10B, HSC-3 and YD-38 cells, with YD-38 cells being the most sensitive, underscoring its broad effectiveness across various cell lines (35). Johnson *et al* (13) conducted a phase II trial evaluating dasatinib in advanced NSCLC. Patients received dasatinib as first-line therapy, with response assessments performed via CT and PET imaging. Pre-treatment tissue samples were analyzed for EGFR and KRAS mutations as well as expression of phosphorylated Src family kinases (SFK). Among 34 patients, the disease control rate was 43%, with one partial response and a metabolic response rate of 32%. Notably, EGFR and KRAS mutations did not predict treatment response (13). In the aforementioned study, 56 patients

(52.4%) in the dasatinib-alone group exhibited progressive disease, 24 patients (22.4%) had stable disease, one patient (0.9%) had a partial response, and the response status of 26 patients (24.3%) was unknown. Several factors could account for these outcomes. One possibility is the inherent aggressiveness of the lung cancer in these patients, particularly in those with advanced stages of the disease. Dasatinib, though effective in some malignancies, may have limited efficacy as a monotherapy in specific lung cancer subtypes without actionable mutations (for example, EGFR or KRAS), which could partially explain the limited disease control observed. Another potential explanation is treatment-induced hyper-progression, where certain therapies, including tyrosine kinase inhibitors and immune checkpoint inhibitors, accelerate tumour growth in a subset of patients. While dasatinib has demonstrated efficacy in hematologic malignancies and certain solid tumors, it may induce hyper-progression in a minority of patients with lung cancer, leading to higher rates of progression (36). Further researches are needed to clarify the role of hyper-progression in dasatinib-treated patients with lung cancer, particularly concerning specific genetic profiles or pre-existing conditions.

Dasatinib has also been evaluated with other therapies such as osimertinib, afatinib and other targeted therapies. Haura *et al* (14) conducted a phase I trial involving group A combination therapy, where patients with advanced NSCLC received erlotinib for one week before dasatinib was introduced. Pharmacokinetics were assessed at weeks 1 and 2, across four dasatinib dosage cohorts. Adverse events included gastrointestinal issues, skin rash, cytopenia, pleural effusions and fatigue. The study reported two partial responses and one bone response, with a disease control rate of 63%. Additionally, plasma angiogenic markers decreased during treatment, correlating with disease control. This combination therapy was tolerable and demonstrated potential efficacy in NSCLC, warranting further exploration of personalized SFK-targeting strategies (14). In the present study, 127 patients (54.3%) underwent combination therapies, while 107 patients (45.7%) received dasatinib alone. In group A, 31 patients (38.3%) achieved stable disease, 24 patients (29.6%) experienced progression, and seven patients (8.6%) exhibited a partial response. The response status of the remaining 19 patients (23.5%) was unspecified.

The utilization of dasatinib in lung cancer treatment remains a topic of ongoing debate within the oncology community. While dasatinib is primarily approved for chronic myeloid leukemia and acute lymphoblastic leukemia with BCR-ABL positivity, its off-label use in various solid tumors, including lung cancer, raises important questions regarding efficacy and safety. Studies have indicated that dasatinib exhibits significant antiproliferative effects against a range of malignancies, particularly when used in conjunction with other therapeutic agents. These effects are largely attributed to its inhibition of SFKs, which induces cytotoxicity and apoptosis in tumor cells (11). Despite these promising findings, the lack of large-scale clinical trials specifically assessing effectiveness of dasatinib in lung cancer necessitates caution. Challenges such as the potential for drug resistance and the need for personalized treatment strategies highlight the complexities of its off-label use. As ongoing research continues to explore the therapeutic potential of dasatinib in various malignancies, a nuanced understanding of its role in lung cancer is essential to guide clinical decision-making and optimize patient outcomes.

Dasatinib is generally well tolerated, with adverse events that are typically manageable and often occur early in the course of treatment. These events are often mild to moderate, resolving either spontaneously, with supportive care, or through temporary treatment interruption or dose adjustments. Effective management of adverse events is crucial for ensuring treatment adherence and optimizing therapeutic outcomes. Adverse events are categorized using common terminology criteria, with the most frequent being cytopenia, fluid retention, pleural effusion, dyspnea, gastrointestinal problems, skin rash, headache and fatigue (34). In the current study, anemia was the most common hematological adverse event, affecting 57 patients (42.2%). The incidence of anemia was particularly higher in the combination therapy group, with 41 cases (50.6%) reported in group A, compared with only 4 cases (3.7%) in the dasatinib monotherapy group. Diarrhea was also a significant adverse event within the gastrointestinal group, affecting 86 patients (35.4%) overall. It was especially prevalent in the group A combination therapy cohort, where 59 patients (72.8%) experienced diarrhea, compared with only 3 cases (2.8%) in the dasatinib monotherapy group, 8 cases (80.0%) in group B, and 15 cases (60.0%) in the group C. Dermatological adverse events were also common, with skin rash reported in 80 cases (85.1%). Group A demonstrated the highest incidence, with 57 cases (70.4%), compared with 3 cases (2.8%) in the monotherapy group, 7 cases (70.0%) in group B, and 13 cases (52.0%) in group C.

In addition to the limitation of including only one published article on the role of dasatinib in lung cancer over the last five years, other limitations of the study include the small sample size, with only nine eligible studies included in the meta-analysis, which may reduce the generalizability of the findings. Additionally, significant heterogeneity across studies, particularly in the combination therapy group, complicates the interpretation of results and suggests variability in treatment protocols.

In conclusion, dasatinib treatment may improve overall survival and have fewer adverse events compared with combination therapies in patients with lung cancer. The present study holds significant practical implications by advancing the understanding and potential applications of targeted therapies such as dasatinib in lung cancer management. By systematically evaluating its efficacy and safety as a standalone treatment, current findings can inform clinical decision-making and optimize treatment strategies to improve patient outcomes. Furthermore, the present research highlights the need for large-scale trials to validate these findings, which could pave the way for more personalized and effective therapeutic approaches in oncology. If confirmed, the standalone use of dasatinib could offer a streamlined treatment option, reducing the complexity and adverse effects associated with combination therapies, thereby improving patient quality of life. The present study represents a critical step in expanding therapeutic options and guiding future research in this vital area of medicine.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DJHR, SOK, YMM and AGH were responsible for data collection and analysis, and final approval of the manuscript. FHK and FHF were major contributors to the conception of the study, as well as to the literature search for related studies. ReMA, HKA, RaMA, AMA and HAY were involved in the literature review, the design of the study, and the critical revision of the manuscript. FHK, SJH and BAA were involved in the literature review, the writing of the manuscript, and design of the study and data interpretation. BAA and FHK confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Siddiqui F, Vaqar S and Siddiqui AH: Lung Cancer. StatPearls Publishing, Treasure Island, FL, 2024.
2. Thandra KC, Barsouk A, Saginala K, Aluru JS and Barsouk A: Epidemiology of lung cancer. Contemp Oncol (Pozn) 25: 45-52, 2021.
3. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, Cercek A, Smith RA and Jemal A: Colorectal cancer statistics, 2020. CA Cancer J Clin 70: 145-164, 2020.
4. Sher T, Dy GK and Adjei AA: Small cell lung cancer. Mayo Clin Proc 83: 355-367, 2008.
5. Mingomataj E, Krasniqi M, Dedushi K, Sergeevich KA, Kust D and Qadir AA, Abdullah AS, Ahmed MK and Fatah GM: Cancer publications in one year (2023): A cross-sectional study. Barw Med J 2: 3-11, 2024.
6. Ali RM, Omar SS, Ahmed HK, Omar DA, Mahmood YM, Mustafa MQ, Abdullah AS, Hassan MN, Hussein DA, Kakamad SH, *et al*: Effect of sunitinib in the management of lung cancer: A systematic review of clinical trials. Barw Med J 2: 57-64, 2024.
7. Alduais Y, Zhang H, Fan F, Chen J and Chen B: Non-small cell lung cancer (NSCLC): A review of risk factors, diagnosis, and treatment. Medicine (Baltimore) 102: e32899, 2023.
8. Molina JR, Yang P, Cassivi SD, Schild SE and Adjei AA: Non-small cell lung cancer: Epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 83: 584-594, 2008.
9. Valk PE, Pounds TR, Hopkins DM, Haseman MK, Hofer GA, Greiss HB, Myers RW and Lutrin CL: Staging non-small cell lung cancer by whole-body positron emission tomographic imaging. Ann Thorac Surg 60: 1573-1581, discussion 1581-1582, 1995.
10. Zappa C and Mousa SA: Non-small cell lung cancer: Current treatment and future advances. Transl Lung Cancer Res 5: 288-300, 2016.
11. Ye Q, Gui C, Jin D, Zhang J, Zhang J, Ma N and Xu L: Synergistic effect of cannabidiol with dasatinib on lung cancer by SRC/PI3K/AKT signal pathway. Biomed Pharmacother 173: 116445, 2024.
12. Abdullah HO, Abdalla BA, Kakamad FH, Ahmed JO, Baba HO, Hassan MN, Bapir R, Rahim HM, Omar DA, Kakamad SH, *et al*: Predatory publishing lists: A review on the ongoing battle against fraudulent actions. Barw Med J 2: 26-30, 2024.
13. Johnson FM, Bekele BN, Feng L, Wistuba I, Tang XM, Tran HT, Erasmus JJ, Hwang LL, Takebe N, Blumenschein GR, *et al*: Phase II study of dasatinib in patients with advanced non-small-cell lung cancer. J Clin Oncol 28: 4609-4615, 2010.
14. Haura EB, Tanvetyanon T, Chiappori A, Williams C, Simon G, Antonia S, Gray J, Litschauer S, Tetteh L, Neuger A, *et al*: Phase I/II study of the Src inhibitor dasatinib in combination with erlotinib in advanced non-small-cell lung cancer. J Clin Oncol 28: 1387-1394, 2010.
15. Gold KA, Lee JJ, Harun N, Tang X, Price J, Kawedia JD, Tran HT, Erasmus JJ, Blumenschein GR, William WN, *et al*: A phase I/II study combining erlotinib and dasatinib for non-small cell lung cancer. Oncologist 19: 1040-1041, 2014.
16. Kelley MJ, Jha G, Shoemaker D, Herndon JE II, Gu L, Barry WT, Crawford J and Ready N: Phase II study of dasatinib in previously treated patients with advanced non-small cell lung cancer. Cancer Invest 35: 32-35, 2017.
17. Kim C, Liu SV, Crawford J, Torres T, Chen V, Thompson J, Tan M, Esposito G, Subramaniam DS and Giaccone G: A phase I trial of dasatinib and osimertinib in TKI naïve patients with advanced EGFR-mutant non-small-cell lung cancer. Front Oncol 11: 728155, 2021.
18. Creelan BC, Gray JE, Tanvetyanon T, Chiappori AA, Yoshida T, Schell MJ, Antonia SJ and Haura EB: Phase 1 trial of dasatinib combined with afatinib for epidermal growth factor receptor-(EGFR-) mutated lung cancer with acquired tyrosine kinase inhibitor (TKI) resistance. Br J Cancer 120: 791-796, 2019.
19. Miller AA, Pang H, Hodgson L, Ramnath N, Otterson GA, Kelley MJ, Kratzke RA and Vokes EE; Cancer and Leukemia Group B (CALGB): A phase II study of dasatinib in patients with chemosensitive relapsed small cell lung cancer (cancer and leukemia group B 30602). J Thorac Oncol 5: 380-384, 2010.
20. Khurshid H, Dipetrillo T, Ng T, Mantripragada K, Birnbaum A, Berz D, Radie-Keane K, Perez K, Constantinou M, Luppe D, *et al*: A phase I study of dasatinib with concurrent chemoradiation for stage III non-small cell lung cancer. Front Oncol 2: 56, 2012.
21. Brunner AM, Costa DB, Heist RS, Garcia E, Lindeman NI, Sholl LM, Oxnard GR, Johnson BE and Hammerman PS: Treatment-related toxicities in a phase II trial of dasatinib in patients with squamous cell carcinoma of the lung. J Thorac Oncol 8: 1434-1437, 2013.
22. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
23. Luo W: Nasopharyngeal carcinoma ecology theory: Cancer as multidimensional spatiotemporal 'unity of ecology and evolution' pathological ecosystem. Theranostics 13: 1607-1631, 2023.
24. World Health Organization: Lung cancer. https://www.who.int/news-room/fact-sheets/detail/lung-cancer. Accessed November 4, 2024.
25. Chen BT, Chen Z, Ye N, Mambetsariev I, Fricke J, Daniel E, Wang G, Wong CW, Rockne RC, Colen RR, *et al*: Differentiating peripherally-located small cell lung cancer from non-small cell lung cancer using a CT radiomic approach. Front Oncol 10: 593, 2020.
26. Ruano-Ravina A, Provencio M, Calvo de Juan V, Carcereny E, Estival A, Rodríguez-Abreu D, Benítez G, López-Castro R, Belver M, Guirado-Risueño M, *et al*: Are there differences by sex in lung cancer characteristics at diagnosis? -a nationwide study. Transl Lung Cancer Res 10: 3902-3911, 2021.

27. Sehgal K, Gill RR, Widick P, Bindal P, McDonald DC, Shea M, Rangachari D and Costa DB: Association of performance status with survival in patients with advanced non-small cell lung cancer treated with pembrolizumab monotherapy. JAMA Netw Open 4: e2037120, 2021.
28. Bitenc M, Cufer T, Kern I, Miklavcic M, Petrovic S, Groznik V and Sadikov A: Real-life long-term outcomes of upfront surgery in patients with resectable stage I-IIIA non-small cell lung cancer. Radiol Oncol 56: 346-354, 2022.
29. Lee SH: Chemotherapy for lung cancer in the era of personalized medicine. Tuberc Respir Dis (Seoul) 82: 179-189, 2019.
30. Petrella F, Rizzo S, Attili I, Passaro A, Zilli T, Martucci F, Bonomo L, Del Grande F, Casiraghi M, De Marinis F and Spaggiari L: Stage III non-small-cell lung cancer: An overview of treatment options. Curr Oncol 30: 3160-3175, 2023.
31. Guo Q, Liu L, Chen Z, Fan Y, Zhou Y, Yuan Z and Zhang W: Current treatments for non-small cell lung cancer. Front Oncol 12: 945102, 2022.
32. Omar SS, Ali RH, Abdullah SH, Hussein DM, Radha BMM, Latif AB, Ali SM, Hiwa DS, Ahmed HK, Hamasaeed AG, *et al*: Durvalumab (Anti-PD-1) in the management of mesothelioma: A systematic review of the current literature. Barw Med J 1: 32-39, 2023.
33. Ali RM, Kakamad FH, Abdullah HO, Abdulla SH, Ahmed SF, Amin BJH, Hassan MN, Hasan SJ, Hamasalih HM, Abdalla BA, *et al*: Pembrolizumab (Anti-PD-1) immunotherapy in malignant pleural mesothelioma: A systematic review of the current literature. Barw Med J 1: 6-13, 2023.
34. Park NS, Park YK, Yadav AK, Shin YM, Bishop-Bailey D, Choi JS, Park JW and Jang BC: Anti-growth and pro-apoptotic effects of dasatinib on human oral cancer cells through multi-targeted mechanisms. J Cell Mol Med 25: 8300-8311, 2021.
35. Conchon M, Freitas CM, Rego MA and Braga Junior JW: Dasatinib-clinical trials and management of adverse events in imatinib resistant/intolerant chronic myeloid leukemia. Rev Bras Hematol Hemoter 33: 131-139, 2011.
36. Shyam Sunder S, Sharma UC and Pokharel S: Adverse effects of tyrosine kinase inhibitors in cancer therapy: Pathophysiology, mechanisms and clinical management. Signal Transduct Target Ther 8: 262, 2023.