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NARRATIVE REVIEW

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Proteasome inhibitors in the treatment of nonsmall cell lung cancer: A systematic review of clinical evidence

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Abstract

Background and Aims: Nonsmall cell lung cancer accounts for over 85% of lung cancer incidences worldwide, and often has a poor prognosis. Proteasome inhibitors, such as bortezomib, have previously demonstrated evidence in preclinical and clinical models in the treatment of NSCLC both alone and as part of chemotherapeutic regimens.

Methods: Five databases were searched from inception to February 2023 to identify published clinical trial data and ongoing clinical trials on the use of proteasome inhibitors in treatment of NSCLC with a comprehensive search strategy.

Results: This review examines the clinical evidence from 21 completed and published phase I and II trials studying the use of bortezomib monotherapy and combination therapy in the treatment of NSCLC. Bortezomib/docetaxel combination resulted in longer median time-to-progression (TTP), median duration of response, median duration of disease control and median progression-free survival (PFS) than bortezomib monotherapy, with concurrent administration having greater 6-month PFS and median overall survival (OS) than sequential administration. Bortezomib/vorinostat with chemotherapy was well tolerated and effective. Bortezomib/gemcitabine/carboplatin, bortezomib/bevacizumab/carboplatin and bortezomib/paclitaxel/carboplatin combinations showed promising results and were of further investigational value.

Conclusion: Bortezomib showed some clinical promise in combination therapy but not monotherapy. It also demonstrated a manageable side effect profile. Combination regimens are of further investigation value in Phase II trials.

KEYWORDS

combination chemotherapy, lung cancer, monotherapy, nonsmall cell lung cancer, proteasome inhibitors

1 | INTRODUCTION

Lung cancer is a leading cause of cancer-related deaths, and second most common cancer in men and women globally.[1] Smoking, radon, asbestos exposure, and other occupational carcinogens have been identified as risk factors.[2] Amongst lung cancers, nonsmall cell lung cancer (NSCLC) accounts for over 85% of the lung cancer incidences worldwide.[3] Overall, lung cancer and its treatment, such as systemic chemotherapy and surgery, are also associated with significant morbidity,[4–8] highlighting the importance of advances in its treatment. Further histological subdivisions include adenocarcinoma, squamous cell carcinoma, mixed, and sarcomatoid carcinoma.[3] Common genetic mutations suspected of being responsible for tumor initiation include Epidermal Growth Factor Receptor (EGFR), Kirsten Rat Sarcoma (KRAS), and Anaplastic Lymphoma Kinase (ALK) mutation.[9]

1.1 | Current treatment modalities for NSCLC

The American Society of Clinical Oncology recommends for stage IV NSCLC, with a PS of 0 or 1, a regimen of a platinum (cisplatin or carboplatin) plus paclitaxel, gemcitabine, docetaxel, vinorelbine, irinotecan, or pemetrexed, in combination with resection surgery, radiation and targeted therapy. However, the recommended regimen is dependent on the biomarkers and driver mutations present, as specified by the National Comprehensive Cancer Network guidelines for Non-Small Cell Lung Carcinoma (Version 1.2023).[10]

The prognosis of patients with NSCLC remains poor, with 5-year survival rates as low as 15%.[9] This can potentially be attributed to the late diagnosis of most NSCLC patients due to the lack of prominent clinical symptoms and comprehensive screening programs. Advancements in molecular diagnosis techniques enable early diagnosis and treatment, improving the prognosis.[11]

1.2 | Mechanism of action of proteasome inhibitors

The ubiquitin-proteasome pathway is critical for cell survival and proliferation and is an attractive therapy target.[11,12] Proteasome functions as the final degradative enzyme in IkB/NF-kB, p53, p21, and p27 catabolic pathways.[13] Bortezomib (VELCADE®), is a 26S competitive proteasome inhibitor. 26S proteasome consists of the 20S core component and 19S regulatory component. Its activity is characterized by Chymotrypsin-like Activity, Trypsin-like Activity, PHGH-like activity, and Caspase-like activity.[14,15] Bortezomib's antineoplastic effect involves inhibition of cell growth and survival pathways, proapoptotic activity, gene inhibition of angiogenesis, adhesion, and migration related proteins.[16,17] Inhibition of the NF-kB pathway, whose dysregulation is often associated with increased antiapoptotic protein expression and contributes to standard therapy resistance in NSCLC as well as cyclin-dependent kinase inhibitors p21-p27 stabilization, are common modes of action.[13,15] Inhibition of the NF-kB pathway is achieved by preventing the degradation of IkB, in turn inhibiting the NF-kB pathway activation crucial for anti-apoptotic cell pathways.[18] Bortezomib causes a reduction in Bcl-2 levels, which overexpression is associated with poorer outcomes in NSCLC patients.[13] Bortezomib has also been touted to increase cancer cell sensitization to other drugs. Thus, several trials investigated the effect of bortezomib in combination with existing chemotherapeutic agents.

2 | METHODS

This systematic review on the use of proteasome inhibitors in the treatment of NSCLC was reported according to PRISMA guidelines.[19]

2.1 | Study selection

Comprehensive searches of multiple databases, MEDLINE via PubMed, EMBASE, and CENTRAL were searched for published data on clinical trials. Searches were performed using terms "proteasome inhibitors," "lung cancer," "non-small cell lung cancer," "bortezomib," "carfilzomib," "marizomib," "oprozomib," "ixazomib" and variations of the terms in combination from inception to February 2023. To identify unpublished evidence, clinical trials database ClinicalTrials.gov and preprint server medRxiv.org were searched with the same strategy. The search strategy for EMBASE is reported in Supporting Information: Table 1.

The following eligibility criteria was used to assess each full text report for inclusion in our review. We included any peer-reviewed publications of clinical trials involving the use of proteasome inhibitors in patients with NSCLC. Studies of any phase were included. Outcomes of interest included measures of efficacy such as overall response rate, overall survival, progression-free survival, and safety data including the incidence and severity of adverse events.

2.2 | Data extraction, organization, and analysis

Extraction was performed by two of four reviewers independently with quality checking performed at the end of the extraction phase. Subject matter information included the aims of study, country of study, number of patients in each arm and the demographics and characteristics of cancer patients, such as type and stage of cancer. Outcome-related information included the type of outcome, duration of follow-up or time period in which the outcome occurred, number of events and any analysis of the data reported by the included publications. We extracted and reported measures of effect such as absolute risk or risk ratios, confidence intervals, and p values of all outcomes of interest; overall response rate, overall survival, progression-free survival, and safety data. For studies that reported

adverse events, the method of assessing severity was extracted. All studies were analyzed using the synthesis without meta-analysis approach. Trials were grouped according to the chemotherapeutic regimen used, namely, proteasome inhibitor monotherapy or combination therapy. Results were further synthesized depending on the combination drugs and regimen used to elucidate regimens which may afford greater efficacy.

2.3 | Quality assessment and risk of bias

To assess methodological quality and the risk of bias of included studies, the Joanna Briggs Institute Critical appraisal checklists for randomized-controlled trials and quasi-experimental studies were used. These checklists evaluate domains related to the risk of bias including treatment allocation, blinding of participants, assessors, and the clinical trial team, comparability of characteristics in the intervention and control arms, reliability of outcome assessment, appropriateness of statistical analysis, and dropouts. This appraisal was performed by two reviewers independently, with discrepancies resolved by the independent verdict of a senior reviewer. All results are reported in Supporting Information: Tables 2 and 3.

2.4 | Ethical approval

No ethical approval was required for this study. No patients nor members of the public were involved in the design nor conduct of this study.

3 | RESULTS

From 3344 unique records, 25 reports of 21 studies meeting our inclusion criteria were analyzed in this review. The study selection process is detailed in the PRISMA flowchart (Figure 1).

3.1 | Bortezomib monotherapy

Key characteristics of trials examining bortezomib as monotherapy are outlined in Table 1.

3.1.1 | Investigation of bortezomib monotherapy in KRASG12D mutant NSCLC patients

NCT01833143:

This study investigated the usage of bortezomib in patients with KRASG12D mutant NSCLC. While the drug was mostly inactive, rapid clinical improvement, and substantial disease regression along with complete recovery was observed in patients with invasive mucinous adenocarcinoma. The overall response rate (ORR) was 6%, median PFS was 1.4 months, partial response was seen in one patient and stable disease in five others, and overall survival (OS) was 13.4 months.[20]

3.1.2 | Investigating bortezomib monotherapy as a frontline regime in advanced NSCLC

NCT00508625:

This study investigated bortezomib monotherapy in patients with advanced NSCLC. However, unsatisfactory efficacy results and significant toxicity levels led to premature trial closure. Out of the 17 assessable patients studied, the nonprogression rate after 6 weeks of bortezomib monotherapy was 59%. Ten patients experienced stable disease. No toxic deaths were recorded and no objective response was observed. The median OS rate and progression free survival (PFS) was 9.8 months and 2.4 months respectively.[21]

NCT00200382:

This study had similar objectives to NCT00508625, and had supporting results. With no objective clinical response recorded, the lack of efficacy prompted premature investigation closure.[22]

The rapid growth rate and division rate seemed to confer NSCLC resistance against bortezomib. Incomplete proteasome inhibition could also explain the limited efficacy. The clinical outcomes of this investigation were comparable to the effects of bortezomib monotherapy evaluated in other studies involving second-line NSCLC patients, with a median TTP of 1.3 months and 1.5 months, respectively.[22]

3.2 | Bortezomib dual therapies

Key characteristics of trials examining bortezomib as part of dual therapy are outlined in Tables 2 and 3.

3.2.1 | Comparison of docetaxel/bortezomib combination therapy with existing treatment regimens

NCT00118183:

Lilenbaum and colleagues compared docetaxel/cetuximab combination therapy against docetaxel/bortezomib therapy in patients with a PS of two. Docetaxel/cetuximab had a median PFS of 3.4 months, a 6-month PFS of 27.8%, and a median survival of 5.0 months. In comparison, the docetaxel/bortezomib arm had a median PFS of 1.9 months, a 6-month PFS of 13.8%, and a median survival of 3.9 months.[28]

Lara and colleagues:

This phase 1 clinical trial investigated the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of the docetaxel/bortezomib combination therapy in patients with NSCLC. The MTD was identified as 1.0/75 mg/m^2 of bortezomib/docetaxel.[15]

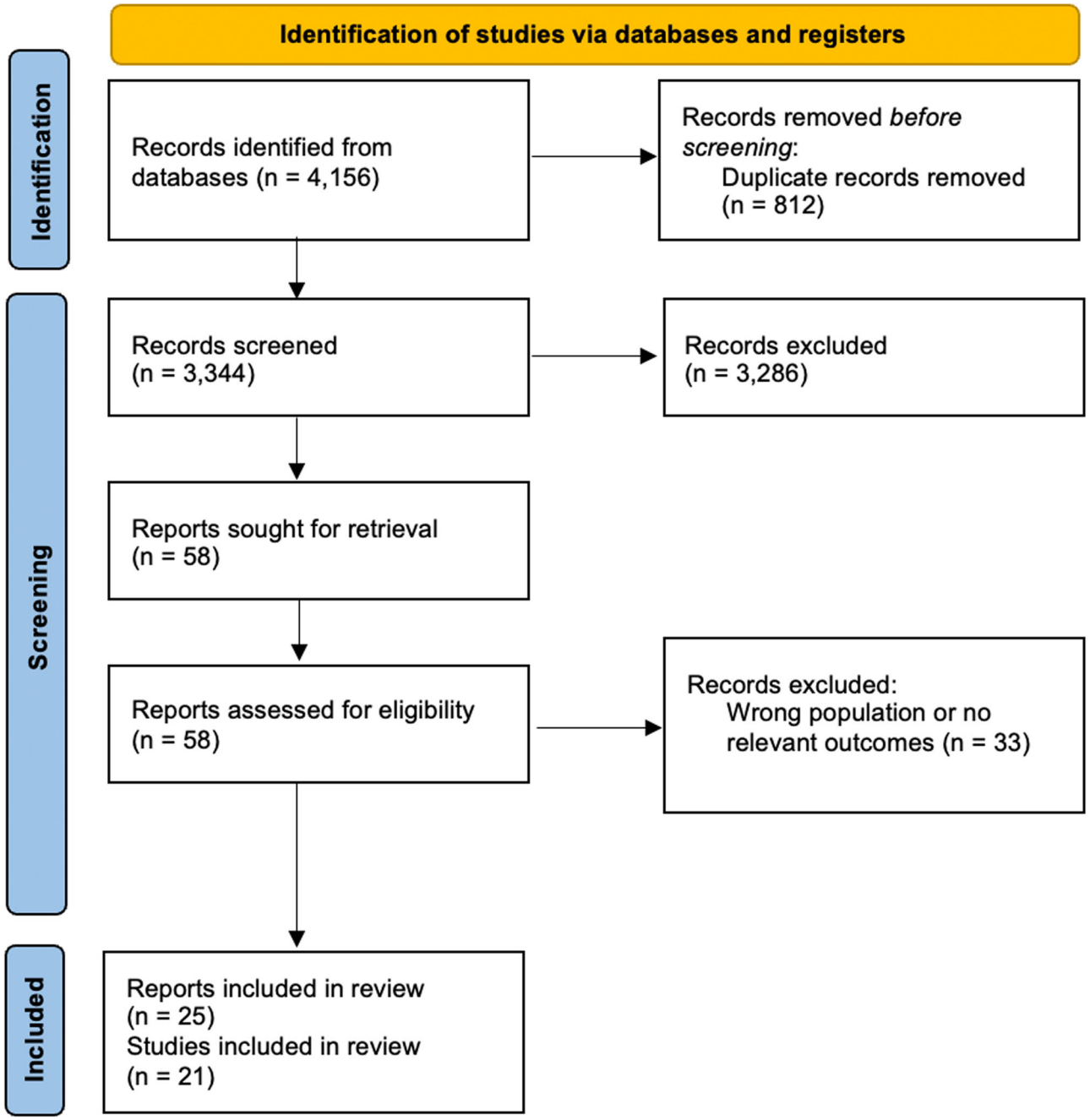

FIGURE 1 PRISMA flowchart.

3.3 | Comparison of sequential administration of docetaxel and bortezomib with concurrent administration in its use as a combination therapy

NCT00362882:

The study compared the effects of sequential administration of docetaxel followed by bortezomib against concurrent administration. The concurrent treatment arm reported a longer OS (13.3 months) compared to the sequential arm (7.8 months) and other previous studies. Several reasons for this higher OS were proposed, with random chance being the most likely. Other explanations include variations in biomolecular markers between the two groups and the fact that a greater percentage of patients had undergone EGFR inhibitor treatment in the concurrent treatment arm. p53 status was identified as a potential biomarker, with p53 null tumors having possibly gained increased resistance to docetaxel as a result of bortezomib action, improving OS. The PFS of the concurrent arm was also higher at 30% compared to 17% in the sequential arm.[29]

TABLE 1 Summary of other outcome factors reported in bortezomib monotherapy studies.[20–22]

Trial name	Regimen	*n* partial response/ total patients (PRR)	*n* stable disease/ total patients (SDR)	*n* disease control/ total patients (DCR)	Time to progression (months)[a]
Drilon et al.[20] NCT01833143	Bortezomib 1.3 mg/m^2 subcutaneous administration	1/16 (6)	7/16 (43)	5/16 (31)	1.4
Besse et al.[21] NCT00508625	Bortezomib 1.5 mg/m^2 IV bolus on days 1, 4, 8, and 11 every 21 days for a minimum of 6 weeks	NA	10/17 (59)	NA	1.3
Li et al.[22] NCT00200382	Patients were treated with bortezomib 1.3 mg/m^2/day as a 3–5 s bolus intravenous injection on days 1, 4, 8, and 11, followed by a 10 day rest period every 21 days, which was defined as one cycle	NA	3/14 (21.4)	NA	1.3

[a]Median (interquartile range) reported unless otherwise specified.

3.4 | Comparing the use of bortezomib monotherapy with bortezomib/docetaxel combination therapy

Fanucchi et al.[23]:

This study compared bortezomib/docetaxel combination therapy against bortezomib monotherapy as second-line therapy in relapsed NSCLC patients.

The bortezomib/docetaxel dual therapy reported higher values for median TTP (4.0 vs. 1.4 months), median duration of response (11.3 vs. 3.8 months), median duration of disease control (5.7 vs. 4.9 months), and median PFS values (3.1 vs. 1.5 months).[23]

The bortezomib treatment arm, despite the limited treatment cycles completed (median was two cycles), showed RRs, median OS and 1-year survival probability similar to other monotherapy agents such as docetaxel, pemetrexed, and erlotinib as demonstrated by the table below[23]:

However, study limitations meant that the significance of the results could not be established. The data also seemed to mimic the data for single agent docetaxel, making it unclear whether improvement in results was due to the combination of two agents.

The lack of substantial improvements has been attributed to several factors, including possible suboptimal dosing, scheduling and sequence of administration, negative drug interaction, low number of treatment cycles (median was two, previous single agent studies had higher medians), reduced dose density of bortezomib, and the prior administration of paclitaxel, which has been demonstrated by some studies to cause reduced RR.[23,26]

3.5 | Safety and efficacy of bortezomib in combination with pemetrexed in advanced NSCLC patients in comparison with bortezomib and pemetrexed monotherapy

NCT00389805:

This phase I study concluded that between the once weekly and twice weekly dosing of bortezomib in combination with pemetrexed, the once weekly dosing is more preferable due to reduced rate of neutropenia and more convenient dosing schedule without compromising efficacy.[30]

NCT00343720:

The study compared bortezomib and pemetrexed dual therapy against bortezomib monotherapy and pemetrexed monotherapy in NSCLC patients. For dual therapy, in squamous cell cancer, the RR was 5.3%, Disease control rate was 68.4%, median TTP was 2.9 months, 6-month TTP was 29.7% and median OS was 6.2 months. In NSCLC, the RR was 7.7%, disease control rate was 76.9%, median TTP was 4.1 months, 6 month TTP was 27.7% and median OS was 11.2 months. Pemetrexed monotherapy in the nonsquamous cancer type, performed better than dual therapy (RR was 3.8%, disease control rate was 73.1%, median TTP was 3.9 months, 6-month TTP was 35.6% and median OS was 13.6 months.)[18]

TABLE 2 Regimen and associated outcomes.

Trial name	Drug monotherapy and dosage	*n* response/total (response rates [%])	Median overall survival (months)	*n*/total (1 year survival probability [%])
Fanucchi et al.[23]	Bortezomib 1.5 mg/m^2	6/75 (8)	7.4	29/75 (38.7)
Fossella et al.[24]	Docetaxel 75 mg/m^2	8/125 (6.7)	5.7	40/125 (32)
Shepherd et al.[25]	Docetaxel 75 mg/m^2	3/55 (5.5)	7.5	20/55 (37)
Hanna et al.[26]	Docetaxel 75 mg/m^2	25/288 (8.8)	7.9	86/288 (29.7)
Hanna et al.[26]	Pemetrexed 500 mg/m^2	26/283 (9.1)	8.3	84/283 (29.7)
Sheperd et al.[27]	Erlotinib 150 mg	43/488 (8.9)	6.7	N.A.

3.6 | Comparison of erlotinib/bortezomib combination therapy against erlotinib monotherapy

Lynch and colleagues:

The study found that erlotinib monotherapy had a 16% RR, while the combination therapy yielded a RR of 9%. Median TTP and PFS were both 2.7 months for erlotinib monotherapy, and 1.5 months and 1.3 months respectively for the combination therapy. Median OS was 7.3 months for erlotinib monotherapy and 8.5 months for the combination therapy. Patients with EGFR mutations had a longer TTP and PFS than those with EGFR wild type, indicating EGFR mutation as being a potential biomarker for the use of bortezomib.[31]

3.7 | Safety and efficacy of vorinostat/bortezomib combination as third-line therapy in advanced NSCLC patients

Jones and colleagues:

In this phase I/II clinical trial, measurable tumor necrosis was histologically confirmed in 6/20 patients, suggesting potential benefits. The study was also powered to identify the genes regulation changes. Downregulated genes included Decorin, MMP1 and Zeb1, while upregulated genes include GAS5, CXCL2, and RBM6.[32]

Hoang and colleagues:

In this phase II trial there were no antitumor responses, stable disease in five patients, median PFS of 1.5 months, 3 month PFS rate of 11.1%, and median OS of 4.7 months. The unimpressive clinical efficacy led to premature trial closure. Lack of established biomarkers involved in bortezomib action makes it difficult to identify the patient groups most likely to benefit from bortezomib therapy.[33]

3.8 | Bortezomib triple therapy

Key characteristics of trials examining bortezomib as part of triple therapy are outlined in Table 4.

3.8.1 | Efficacy of bortezomib/gemcitabine/carboplatin triple therapy in NSCLC

NCT00075751:

The phase II trial investigated the bortezomib/gemcitabine/carboplatin triple therapy regime. The median OS was 11 months, and the 1-year survival rate was 47%, surpassing the results achieved in investigations of other drug combinations. However, the current paradigm shift is toward the paclitaxel/carboplatin/bevacizumab combination therapy which has a median OS of 12.3 months as frontline treatment and bortezomib/gemcitabine/carboplatin combination therapy has comparatively inferior results. The carboplatin/gemcitabine/bortezomib treatment line may still be more advantageous, having been studied in a wider patient sample compared to paclitaxel/carboplatin/bevacizumab combination therapy.[34]

The similarity of median PFS (5 months), ORR (23%), and disease control rate (68%) to other previous studies does seem to suggest that improvement in survivability might have been a result of increased usage of second line therapy such as docetaxel, pemetrexed, and erlotinib.[34]

Davies and colleagues:

This phase I clinical trial aimed to investigate the MTD and feasibility of including bortezomib in combination with gemcitabine and carboplatin for treatment of advanced NSCLC. Response rate recorded was 35%.[35]

3.8.2 | Safety and efficacy of bortezomib/carboplatin/bevacizumab as first line therapy in patients with NSCLC

Piperdi and colleagues:

The poor accrual rates of this combined phase I and phase II trial left the study underpowered in establishing response rates and PFS rates. Partial remission was observed in four out of nine patients, with a median PFS of 5.5 months and OS of 10.9 months respectively. Clinical activity was also observed in three patients with advanced NSCLC, but could not be proven through this study.[36]

TABLE 3 Summary of other outcome factors reported in bortezomib dual therapy studies.[15,18,23,28–33]

Trial name	Regimen	*n* Partial response/ total patients (PRR)	*n* stable disease/ total patients (SDR)	*n* disease control/ total patients (DCR)	Time to progression (months)
Lilenbaum et al.[28] NCT00118183	Docetaxel of 30 mg/m^2 on days 1, 8, and 15 every 28 days in combination with:				
	1) Cetuximab 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly	3/30 (10)	11/30 (37)	NA	NA
	2) Bortezomib 1.6 mg/m^2 on days 1, 8, and 15 every 28 days for up to four cycles	3/29 (10)	9/29 (31)		
Lara et al.[15]	Docetaxel 60 mg/m^2 Bortezomib 1.0 mg/m^2	0/4 (0)	3/4 (75)	NA	NA
	Docetaxel 65 mg/m^2 Bortezomib 1.0 mg/m^2	0/5 (0)	0/5 (0)		
	Docetaxel 70 mg/m^2 Bortezomib 1.0 mg/m^2	0/4 (0)	1/4 (25)		
	Docetaxel 75 mg/m^2 Bortezomib 1.0 mg/m^2	2/16 (13)	3/16 (19)		
	Docetaxel 75 mg/m^2 Bortezomib 1.3 mg/m^2	0/7 (0)	0/7 (0)		
Lara et al.[29] NCT00362882	Treatment cycles were 3 weeks in duration. Bortezomib 1.6 mg/m^2 was given I.V. as a bolus injection on Day 8 in both arms.				
	CON arm-Docetaxel 75 mg/m^2 I.V. over 60 min immediately followed by bortezomib 1.6 mg/m^2 I.V. as a bolus injection over 3–5 s on Day 1.	4/40 (10)	NA	20/40 (50)	NA
	SEQ Arm-Docetaxel 75 mg/m^2 I.V. on Day 1 followed 24 h later (Day 2) by bortezomib 1.6 mg/m^2 I.V. as a bolus injection over 3–5 s.	4/41 (10)	NA	20/41 (49)	NA
Fanucchi et al.[23]	Bortezomib 1.5 mg/m^2 on days 1, 4, 8, and 11 in a 21-day cycle	6/75 (8)	16/75 (21)	22/75 (29)	1.5
	Bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 in combination with docetaxel 75 mg/m^2 on Day 1 of a 21-day cycle	7/80 (9)	36/80 (45)	43/80 (54)	4.0

(Continues)

TABLE 3 (Continued)

Trial name	Regimen	*n* Partial response/ total patients (PRR)	*n* stable disease/ total patients (SDR)	*n* disease control/ total patients (DCR)	Time to progression (months)
Davies et al.[30] NCT00389805	Arm A: Pemetrexed IV (500–600 mg/m^2 on Day 1) + bortezomib twice weekly (0.7–1.3 mg/m^2 on days 1, 4, 8, and 11) of a 21-day cycle	2/16 (12.5)	4/15 (56.2)	68.8	NA
	Arm B: Pemetrexed IV (500–600 mg/m^2 on day 1) + bortezomib weekly (1.0–1.6 mg/m^2 on days 1 and 8) of a 21-day cycle		5/12 (42)		
Scagliotti et al.[18] NCT00343720	Arm A: Pemetrexed 500 mg/m^2 on day 1 + bortezomib 1.6 mg/m^2 on days 1 (60 min after pemetrexed) and 8	3/45 (7)	30/45 (67)	33/45 (73)	4.0 months (Squamous subgroup: 2.9 months, nonsquamous subgroup: 4.1 months)
	Arm B: Pemetrexed 500 mg/m^2 on Day 1	2/45 (4)	26/45 (58)	28/45 (62)	2.9 months (Squamous subgroup: 1.7 months, nonsquamous subgroup: 3.9 months)
	Arm C: Bortezomib 1.6 mg/m^2 on days 1 and 8	0/40 (0)	17/40 (43)	17/40 (43)	1.4 months (Squamous subgroup: 1.3 months, nonsquamous subgroup: 1.9 months)
Lynch et al.[31]	Arm A: Erlotinib 150 mg/d orally	3/25 (12)	9/25 (36)	13/25 (52)	2.7
	Arm B: Erlotinib 150 mg/d + bortezomib 1.6 mg/m^2	2/22 (9)	8/22 (36)	10/22 (45)	1.5
Jones et al.[32]	Bortezomib dose escalation starting at 1.0 mg/m^2 intravenously once a week for 3 weeks (on days 1, 8, and 15 of a 21-day cycle)	NA			
	Vorinostat dose escalation starting at 100 mg oral, once a Day, 3 days/week for 3 weeks (on days 1, 2, 3, 8, 9, 10, 15, 16, and 17 of a 21-day cycle)				
Hoang et al.[33]	Vorinostat 400 mg oral daily on days 1–14 + bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11, every 3 weeks	NA	5/18 (27.8)	NA	NA

TABLE 4 Summary of other outcome factors reported in bortezomib triple therapy studies.[13,34–38]

Trial name	Regimen	*n* partial response/ total patients (PRR)	*n* stable disease/ total patients (SDR)	*n* disease control/ total patients (DCR)	Time to progression (months)
Davies et al.[34] NCT000757	Gemcitabine 1000 mg/m^2 on days 1 and 8, carboplatin AUC 5.0 on Day 1, and bortezomib 1.0 mg/m^2 on days 1, 4, 8, and 11, in 21-day treatment cycles	2/114 (11)	52/114 (46)	78/114 (68)	NA
Davies et al.[35]	Level 1-bortezomib 1.0 mg/m^2, gemcitabine 800 mg/m^2, carboplatin AUC 5.0	1/3 (33.3)	1/3 (33.3)		
	Level 2-bortezomib 1.0 mg/m^2, gemcitabine 1000 mg/m^2, carboplatin AUC 5.0	6/16 (37.5)	5/16 (31.3)	NA	NA
	Level 3-bortezomib 1.3 mg/m^2, gemcitabine 1000 mg/m^2, carboplatin AUC 5.0	2/7 (28.6)	2/7 (28.6)		
Piperdi et al.[36]	Level 1-bortezomib 1.3 mg/m^2, carboplatin AUC 6.0, bevacizumab 15 mg/kg	0/3 (0)	2/3 (66.7)		
	Level 2-bortezomib 1.6 mg/m^2, carboplatin AUC 6.0, bevacizumab 15 mg/kg	2/4 (50)	2/4 (50)	NA	NA
	Level 3-bortezomib 1.8 mg/m^2, carboplatin AUC 6.0, bevacizumab 15 mg/kg	4/9 (44)	4/9 (44)	50% at fourth month	
Edelman et al.[13]	Bortezomib was administered on days 1, 4, 15, 18 during the 6-week induction chemoradiotherapy. Carboplatin AUC = 6 and paclitaxel 200 mg/m^2	NA			
Zhao et al.[37] NCT00093756	1.2 bortezomib (mg/m^2) + 175 paclitaxel (mg/m^2) + 6 carboplatin (AUC)	NA			
Kontopodis et al.[38] NCT01633645	Bortezomib 1 mg/m^2 on days 1 and 8, of a 21-day treatment cycle. Second cycle treatment: Gemcitabine 1000 mg/m^2 on days 1 and 8, cisplatin 70 mg/m^2 on day 1 and bortezomib 1 mg/m^2 on days 1 and 8, repeated every 21 days	9/43 (20.9)	13/43 (30.2)	NA	NA

3.8.3 | Safety and efficacy of bortezomib/paclitaxel/carboplatin triple therapy

Edelman and colleagues:

The phase I clinical trial aimed to establish MTD as well as safety of a trimodality approach comprising surgical resection, radiotherapy, and the triple drug regimen (bortezomib/paclitaxel/carboplatin).

The study was prematurely terminated before a MTD was established due to the unusually high incidence of deaths reported (25%). Reasons suggested for the increased treatment-related mortality included random chance as well as a proposed theory linking the deaths to the pulmonary toxicity caused by bortezomib treatment. Pathologic complete response was reported in 5 out of 12 patients on the treatment regimen.[13]

NCT00093756:

The study was a combined phase I and phase II clinical trial investigating the safety and efficacy of bortezomib/paclitaxel/carboplatin therapy combined with radiotherapy. While the study results cannot be validated as a result of early termination due to slow accrual, the early data from the investigation was in favor of the use of the triple therapy regime with radiation. The early data reported a 1-year survival rate of 73% and a median survival time of 25 months, which is higher than the investigation results yielded by investigations of other regimes.[37]

3.8.4 | Efficacy and survival rates of bortezomib/gemcitabine/cisplatin combination therapy

NCT01633645:

This study investigated the effect of adding bortezomib to the cisplatin/gemcitabine regimen. The ORR was 17%, the median duration of response was 6.6 months, and the median PFS was 2.5 months. The treatment mortality rate was 7.5%. Thus, the bortezomib/gemcitabine/cisplatin triple therapy had decreased efficacy and RR.[38]

Despite the decrease in ORR and PFS, there was no significant difference between the OS rate of the control (cisplatin/gemcitabine) and intervention (bortezomib/cisplatin/gemcitabine) groups. Possible explanations for the apparent reduction in efficacy include the lower than standard dosage of gemcitabine (1000 mg/m^2 instead of 1250 mg/m^2), higher of proportion of less treatment responsive adenocarcinoma type NSCLC in study, and possibly the high number of patient discontinuations at the beginning of the trial, who could not be evaluated.[38]

3.9 | Adverse effects of bortezomib monotherapy

The most common grade 3/4 adverse effect was fatigue. Others included haematological (neutropenia, and thrombocytopenia), infection without neutropenia, gastro-intestinal (anorexia, nausea, and mucositis), cardiovascular (atrial fibrillation, thrombosis, and atrioventricular block), sensory neuropathy, pain, abdominal pain, cachexia, dyspnea, and denutrition, vigilance trouble, visual trouble, and hyperglycemia.[21,22]

3.10 | Adverse effects of bortezomib combination therapies

Davies and colleagues and Lynch and colleagues reported trials in which bortezomib was added to another chemotherapeutic drug, pemetrexed and erlotinib respectively. In both trials, the addition of Bortezomib did not significantly increase the adverse events reported.

4 | DISCUSSION

As mentioned earlier, the paper aims to evaluate the clinical utility of proteasome inhibitors in NSCLC treatment. For the purposes of this paper, all the trials pertain to the use of the proteasome inhibitor bortezomib.

4.1 | Bortezomib/pemetrexed dual therapy versus bortezomib and pemetrexed monotherapy

Common grade 3/4 adverse effects of bortezomib/pemetrexed combination therapy included haematological (neutropenia, anaemia and thrombocytopenia), metabolic (increased transaminases), dyspnoea and fatigue.[18,30]

In the trial by Davies et al.[30] higher rates of grade 3/4 neutropenia, increased transaminases and fatigue were reported at the more frequent dosing of bortezomib (arm A).

In NCT00343720, more severe adverse effects (grade ≥3) were reported in bortezomib/pemetrexed combination (arm A) than pemetrexed (arm B) and bortezomib (arm C) monotherapy. Five treatment-related deaths were reported during the study. Three deaths occurred due to bronchopneumonia, circulatory collapse, and pancytopenia respectively. One death occurred due to appendiceal abscess, and one death occurred due to respiratory failure.[18]

4.2 | Bortezomib/erlotinib dual therapy versus erlotinib monotherapy

Both regimens were well tolerated, and adverse events were consistent with the known toxicological profiles of erlotinib and bortezomib. No additive toxicological effects were reported. Known bortezomib toxicities such as diarrhoea, peripheral neuropathy, and hypertension were less frequently reported as compared to other phase I trials, possibly due to the reduced dosage. The most commonly reported grade 3 adverse event was skin rash.[32]

When bortezomib was used in triple-agent chemotherapeutic regimens, the adverse events profile was largely tolerable.

4.3 | Bortezomib/gemcitabine/carboplatin triple therapy

Four deaths reported in NCT00075751 were possibly due to treatment. One death was due to dehydration and diarrhoea, one due to multiorgan failure, one sudden death in a patient with grade 4 thrombosis/embolism and thrombocytopenia, and one due to pneumonitis. No treatment-related deaths were reported in the trial by Davies and colleagues.[34,35]

4.4 | Bortezomib/bevacizumab/carboplatin triple therapy

The bortezomib/carboplatin/bevacizumab combination was generally well tolerated. At the recommended phase II dose level, elevated hematologic toxicities were reported (specifically neutropenia and thrombocytopenia) when continued for more than four cycles. Other grade 3/4 toxicities reported for all cycles included haematological (anaemia and lymphopenia), gastrointestinal (nausea, vomiting, and diarrhoea), infection, pulmonary (haemorrhage), and constitutional (fatigue, anorexia, pain, dehydration, hypertension, and thrombosis). Painful grade 2 sensory neuropathy and grade 3 peripheral neuropathy, both expected adverse events of bortezomib

administration, were not reported, possibly due to the weekly dosing and limiting to six cycles of administration.[36]

4.5 | Bortezomib/paclitaxel/carboplatin triple therapy

Bortezomib/paclitaxel/carboplatin triple therapy with radiation resulted in elevated haematological toxicity, possibly attributed to the overlapping toxicological profiles of the drugs. Common grade 3 toxicities reported in phase II of NCT00093756 included neutropenia, leukopenia, nausea and fatigue. Common grade 4 toxicities reported included haematological (neutropenia, thrombocytopenia, and leukopenia), nonhaematological (hyponatraemia, hypokalaemia, dyspnoea, hypoxia, myalgia, and depressed level of consciousness). One death reported due to pneumonitis was likely treatment-related.[37]

4.6 | Bortezomib/gemcitabine/cisplatin triple therapy

Similarly, Kontopodis and colleagues which utilized bortezomib-gemcitabine-cisplatin triple therapy observed few grade 3/4 adverse effects overall. These included haematological (thrombocytopenia, neutropenia, febrile neutropenia, and leukopenia), fatigue, diarrhoea, ototoxicity, AST/ALT elevation, and thromboembolism. Two treatment-related deaths were reported. One female patient died due to polyorganic failure and sepsis, while one male patient died due to pulmonary haemorrhage and type II respiratory failure after developing grade 2 anaemia, grade 3 neutropenia and grade 4 thrombocytopenia. Both patients experienced the adverse effects after the second cycle of treatment. Another death that occurred could not be ruled out to be study-related due to the lack of information.[38]

4.6.1 | Clinical significance of bortezomib monotherapy

The three papers investigating bortezomib monotherapy seem to indicate a lack of clinical efficacy in the treatment of Stage IIIB/IV NSCLC. This coupled with the short survival span and low survival rate of patients, is prohibitive usage of bortezomib monotherapy. There is limited evidence suggesting excellent clinical efficacy under certain conditions, and identifying the key biomarkers is of further investigational value.[21,22]

4.6.2 | Clinical significance of bortezomib combination therapies

Bortezomib/docetaxel dual therapy versus bortezomib monotherapy

Four trials investigating bortezomib/docetaxel combination therapy were included in this report, of which three aimed to establish the clinical efficacy against existing regimens or monotherapy, while a fourth investigated the effects of sequence of administration on clinical efficacy. For Fanucchi et al.[23] the bortezomib/docetaxel dual therapy reported longer median TTP, median duration of response, median duration of disease control and median PFS values, compared to bortezomib monotherapy. However, in NCT00118183,[28] the control arm of docetaxel/cetuximab reported statistically significant higher values for median PFS, median 6-month PFS and median survival compared to the bortezomib/docetaxel experimental arm. The effect of sequence of administration (concurrent vs. sequential) as investigated by NCT00362882,[29] appears to be of further investigational value, with the higher 6-month PFS and median OS rates seeming to indicate increased clinical survival for the concurrent administration of bortezomib and docetaxel compared to sequential administration.

Bortezomib/pemetrexed dual therapy versus bortezomib and pemetrexed monotherapy

The compiled data from the two studies do not indicate any clinical significance supporting the therapeutic usage of bortezomib/pemetrexed dual therapy. NCT00343720[18] reported inferior results for the pemetrexed/bortezomib dual therapy in the nonsquamous group compared to pemetrexed monotherapy, in terms of 6-month TTP, median OS and 1-year survival rate. In the squamous group, the 6-month TTP and TTP values reported were higher in the dual therapy regimen as compared to the pemetrexed monotherapy regimen, and is of potential investigational value. However, the median OS and 1-year survival rates were still higher in the pemetrexed monotherapy arm. No significant differences were reported when comparing different sequences of administration, thus indicating a lack of correlation between sequence of administration and clinical efficacy and is of no further investigational value.[30]

Bortezomib/erlotinib dual therapy versus erlotinib monotherapy

Bortezomib/erlotinib dual therapy showed inferior efficacy compared to erlotinib monotherapy and therefore does not seem to be of any further investigational value.[31]

Bortezomib/vorinostat dual therapy

While the single modality approach involving bortezomib/vorinostat dual therapy was ineffective, a dual modality approach involving surgical resection and the bortezomib/vorinostat chemotherapy regimen was well tolerated and effective, and is of further investigational value.[32,33]

Bortezomib/gemcitabine/carboplatin triple therapy

Bortezomib/gemcitabine/carboplatin triple therapy was investigated in NCT00075751.[34] Results obtained include a median OS of 11 months and a 1-year survival rate of 47%. However, while promising, this does not offer an improvement on some of the existing treatment lines such as paclitaxel/carboplatin/bevacizumab, which has a median OS 12.3 months. Regardless, the triple therapy regimen may still be of clinical relevance and of further investigation value,

especially the identification of clinical biomarkers indicated for the use of bortezomib/carboplatin/gemcitabine triple therapy.

Bortezomib/bevacizumab/carboplatin triple therapy

Bortezomib/bevacizumab/carboplatin triple therapy regimen as investigated by Piperdi et al.[36] seemed to be of further investigational value for the treatment of NSCLC. However the study results validity and accuracy were limited by the poor accrual rates and thus needs to be confirmed through further investigations.

Bortezomib/paclitaxel/carboplatin triple therapy

Bortezomib/paclitaxel/carboplatin triple therapy was investigated in a triple modality regimen, along with radiotherapy and surgical resection by Edelman et al.[13] and in a monomodality investigation by NCT00093756.[37] Results were unpromising, with the triple modality approach being potentially unfeasible due to the high mortality rate encountered,[13] and the results of the monomodality approach plagued by poor accrual rates in the study. However, the monomodality investigation did yield favorable results including 1-year survival rate of 73% and a median survival time of 25 months.[37] Thus, this triple therapy regimen may be of further investigational value. As indicated in previous studies, the use of bortezomib is best complemented by biomarkers identification.

Bortezomib/gemcitabine/cisplatin triple therapy

Gemcitabine/cisplatin dual therapy usually confers an ORR of 22%–44%, a median PFS of 5–7 months, and an OS of 8–11 months. However, the triple therapy yielded an ORR of 17%, median PFS of 2.5 months, and median duration of response of 6.6 months. Thus, the addition of bortezomib was reported to have caused a decrease in the clinical efficacy of gemcitabine/cisplatin dual therapy, and is not indicated for further clinical trials or clinical usage.[38]

4.7 | Upcoming trials

NCT00720785

This ongoing nonrandomized phase I clinical trial is being conducted by Richard W. Childs from the National Heart, Lung, and Blood Institute, on patients with chronic myeloid leukaemia, pancreatic cancer, colon/rectal cancer, multiple myeloma, and NSCLC. The trial aims to investigate the use of in vivo expanded NK cells with increased expression of TRAIL in treatment of cancers with increased TRAIL cytotoxicity due to bortezomib administration. The bortezomib dose is 1.3 mg/m^2. As the study is still in phase I, efforts are still ongoing to establish the MTD and safety of the proposed intervention and no preliminary results have been published at the time of writing.[39]

NCT00667082

This ongoing trial investigates the safety, efficacy, pharmacodynamics, and pharmacokinetics of marizomib (NPI-0052) (a proteasome inhibitor) in combination with vorinostat in the treatment of NSCLC, as well as other cancers such as pancreatic cancer, melanoma, lymphoma, and multiple myeloma. It is conducted by Steven D. Reich, and is an open label, single group assignment clinical trial. The trial intervention is as follows—intravenous marizomib at doses ranging from 0.15 to 0.7 mg/m^2 on days 1, 8, and 15 of each 28-day cycle, and oral vorinostat 300 mg administered with food on days 1 to 16 of each 28-day cycle. No preliminary study results have been published at time of writing.[40]

5 | CONCLUSION

The overall indication appears to be that both bortezomib monotherapy and combination therapy has limited clinical indication in the treatment of NSCLC. While it is well tolerated and presented with manageable side effects, bortezomib usage has been hampered by the lack of evidence regarding suitable biomarkers for bortezomib treatment. Bortezomib seemed to have performed well in phase I trials, but was ineffective in phase II studies.

Of the various combination therapies investigated, on bortezomib/gemcitabine/carboplatin, bortezomib/bevacizumab/carboplatin, and bortezomib/paclitaxel/carboplatin combinations showed promising results and were of further investigational value. Most investigations did not show any clinical benefit for bortezomib combination therapy.

Overall, the predicted synergistic effect of bortezomib was not conclusively identified in most of the investigations, and further investigations involving bortezomib will benefit greatly from identifying suitable biomarkers in which its use is indicated.

AUTHOR CONTRIBUTIONS

Alethea Dasha Wenning Chua: Data curation; investigation; methodology; resources; validation; visualization; writing—original draft; writing—review & editing. **Thirumeninathan Thaarun**: Data curation; investigation; methodology; resources; validation; visualization; writing—original draft; writing—review & editing. **Hui Yang**: Conceptualization; methodology; project administration; writing—review & editing. **Ainsley Ryan**: Conceptualization; investigation; methodology; project administration; resources; supervision; writing—review & editing. **Ainsley Ryan Yan Bin Lee**: Conceptualization; investigation; methodology; project administration; resources; supervision; writing—review & editing. All authors have read and approved the final version of the manuscript. Alethea Dasha Wenning Chua and Thirumeninathan Thaarun had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its Supporting Information.

TRANSPARENCY STATEMENT

The lead author Ainsley Ryan Yan Bin Lee affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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