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Research Article

Timing of Radiation Pneumonitis in Patients with Stage 3 Non-Small-Cell Lung Cancer Receiving Consolidation Durvalumab after Chemoradiation

Melinda Mushonga,[1,2,3] **Alexander Louie**,[1] **Susanna Cheng**,[1] **May N. Tsao**,[1] **Wee Loon Ong**,[1,4] **Patrick Cheung**,[1] **Ian Poon**,[1] **L. Zhang**,[1] **and Yee C. Ung**[1]

[1]*Sunnybrook Health Sciences, Odette Cancer Centre, University of Toronto, Department of Radiation Oncology, Toronto, Canada*
[2]*Kingston Health Sciences Centre, Queen's University, Kingston, Canada*
[3]*Department of Oncology, University of Zimbabwe, Harare, Zimbabwe*
[4]*Alfred Health Radiation Oncology, Monash University, School of Translational Medicine, Melbourne, Australia*

Correspondence should be addressed to Melinda Mushonga; melmush@yahoo.com

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Purpose. Consolidation with durvalumab is standard of care in the management of unresectable stage 3 non-small-cell lung cancer (NSCLC) postchemoradiation, and pneumonitis is an independent potential treatment complication of both treatment strategies. This study seeks to determine the timing of radiation pneumonitis (RP) by receipt of durvalumab. In addition, we reviewed the preventative strategies guided by pathophysiology of pneumonitis. *Methods*. We identified patients with unresectable Stage 3 NSCLC who developed grade ≥2 RP after chemoradiotherapy. Time-to-RP was defined from date of completion of radiotherapy to date of radiological diagnosis of RP and accompanying clinical symptoms. Early RP was defined as RP within 2 months of completion of radiotherapy. Differences in time-to-RP by receipt of durvalumab were evaluated using Wilcoxon rank-sum test. Differences in those who had early vs late RP by receipt of durvalumab was evaluated using Fisher's exact test. Logistic regression was used to evaluate patient and treatment factors associated with early RP. *Results*. Of the 144 patients with Stage 3 NSCLC who had definitive chemoradiotherapy, 31 (22%) developed grade ≥2 RP and were included in the study. There was one patient with grade 5 RP. The median age of the cohort was 67 years (range 41–87). The mean lung dose, V5Gy, and V20Gy were 15.8Gy (SD = 1.56), 60.14% (SD 2.73), and 29.96% (SD 1.82), respectively. Twelve (39%) patients received durvalumab. The median time-to-RP was 3.4 months (range: 1.7–7.2) and 2.3 months (range: 0.6–9.6) in patients who had durvalumab and no durvalumab, respectively ($P = 0.01$). 83% (10/12) of patients who had durvalumab and 58% (11/19) of patients who did not have durvalumab had late RP ($P = 0.14$). No other patient and treatment factors were associated with early RP. *Conclusion*. Patients on durvalumab may have late-onset RP; therefore, further studies with larger cohort of patients and development of new predictive models that incorporate evolving management are needed should preventative strategies of RP be considered in routine clinical practice.

1. Introduction

Clinical indications in the management of non-small-cell lung cancer (NSCLC) treated with both immunotherapy and radiation therapy (RT) due to the synergistic effect of the two treatment modalities is expanding. Adjuvant durvalumab is the standard of care in the management of unresectable Stage 3 NSCLC following definitive chemoradiation [1]. Several NSCLC clinical trials in early stage adjuvant and neoadjuvant settings are exploring or have explored sequential or concurrent use of immunotherapy with other treatment modalities with promising results [2–4]. Most recently, the phase II DOLPHIN study results have been published. The study evaluated the safety and efficacy of durvalumab and concurrent curative radiotherapy for programmed death ligand 1 (PD L1)-positive unresectable

locally advanced NSCLC without chemotherapy. The study met its primary end point, which showed a 12-month progression-free survival of 72.1%, after a median follow-up of 18.7 months with tolerable safety profile suggesting potential incorporation into clinical practice in the near future [5].

Pneumonitis is a recognized independent side effect of immunotherapy and radiotherapy [6, 7]. Severe pneumonitis secondary to immunotherapy results in treatment cessation to allow for medical management [8], potentially compromising clinical outcomes. Radiotherapy primes an immune response, which can potentiate the effects of immunotherapy [9, 10]. Pneumonitis is a dose-limiting factor in radiotherapy planning. Lung volume dosimetric parameters; lung volume receiving 20 Gy (V20Gy), lung volume receiving 5 Gy (V5Gy), and mean lung dose are used to predict the risk of radiation pneumonitis and therefore kept within criteria to reduce the risk of radiation pneumonitis (RP) for patients planned with curative intention [11]. Failure to meet radiotherapy dose metrics impedes ability to deliver standard of care management approaches for stage, therefore in turn compromising treatment outcomes.

Studies have been completed to explore strategies, which reduce the risk of RP guided by pathophysiology of the development of radiation-induced pneumonitis [12–14]. Most of these studies were however conducted pre-immunotherapy era. A higher risk of RP in patients receiving immunotherapy in addition to radiotherapy has been shown including in the practice changing Pacific trial where pneumonitis rate was 34% in the durvalumab arm vs 25% in the control arm, and overall median follow-up was 14.5 months (range: 0.2 to 29.9) [1]; similar findings are shown in other subsequent studies [15–19].

This study sought to determine the timing of RP in patients with unresectable Stage 3 NSCLC post-chemoradiation by receipt of durvalumab and review of preventative strategies. Findings will assist in designing clinical trials that seek to refine and integrate preventative strategies, which reduce the risk of RP in patients by receipt of immunotherapy guided by RP pathophysiology and timing of its development.

2. Methods

Patients with unresectable Stage 3 NSCLC from January 1, 2016, to December 31, 2019, treated with radical intent radiotherapy who developed grade ≥2 RP by radiological and clinical features were evaluated.

2.1. Radiation Planning Overview. All patients were simulated in the supine position with four-dimensional (4D) computed tomography (CT) planning (1.5 mm slice thickness). Patients were positioned on a wing board and neck rest, usually with arms up. Immobilization masks (with arms down) were used if nodal volumes extended to supraclavicular fields. Intravenous contrast for CT simulation was used at the discretion of the treating radiation oncologist. Staging positron emission tomography (PET) scans and CT data were used to identify gross tumor volumes (primary and nodal). Gross tumor volumes (GTV), primary and nodal, on inspiration, expiration, and maximum intensity projection CT planning images were contoured and combined to generate internal target volumes (ITV), primary and nodal. A uniform expansion of 7 mm was added to ITV to generate planning target volume (PTV) as per institutional protocol. Our center's specific contouring protocol does not include a clinical target volume (CTV). All patients were planned with intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) planning.

2.2. Diagnosis of Radiation Pneumonitis. After treatment, patients were followed up based on institutional guidelines, which recommend first review a month after treatment, then after every 3 months for the first 2 years, and then every 6 months for the subsequent 3 years to a total follow-up of 5 years. In the event, a patient was clinically unwell in the interval between scheduled visits, patients were seen earlier, and management was guided by presenting complaints. CT scans of the chest, abdomen, and pelvis were requested before each visit. Some patients would have an additional fluorodeoxyglucose (FDG) PET scan at the discretion of the treating radiation oncologist for the purpose of guiding next steps in the clinical decision-making process for suspected recurrent disease.

All images were reported by experienced thoracic radiologist. For this study, Grade 2 RP was based on documented diagnosis in their electronic chart on a background of respiratory symptoms (shortness of breath, dry cough, and low-grade fever) with accompanying imaging changes confined to treated radiation field and treatment with high-dose steroids, after receiving chest radiotherapy.

All patients had Stage III NSCLC according to the AJCC staging, 7th Edition. A retrospective review of electronic medical records was conducted, and information on patient characteristics, including age, gender, timing of RP diagnosis, radiation dosimetric parameters, and systemic therapy, was collated. In this study, time-to-RP was defined from date of completion of radiotherapy to date of the first CT imaging confirming RP in a patient with accompanying respiratory symptoms. This was selected for consistency as often patients did not know the specific timing when they developed symptoms. Early RP was defined as RP within 2 months of completion of radiotherapy. The time point was selected as guided by timelines of acute RP being as early as 1 month after completion of radiotherapy [20]. Severity of RP was graded based on the Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0 scoring system [21]. This retrospective study was completed under an institutional review board-approved protocol.

2.3. Statistical Analysis. Descriptive statistics were used to describe the characteristics of the cohort. Given the non-normal distribution of time-to-RP, the Wilcoxon rank-sum test was used to evaluate differences in time-to-RP between patients who had durvalumab vs no durvalumab. Fisher's exact test was used to evaluate differences in characteristics

for early vs late RP in patients who had durvalumab vs no durvalumab. Logistic regression was used to evaluate all other patient and treatment factors potentially associated with early RP. A P value of <0.05 was considered statistically significant.

3. Results

Of the 144 patients who had definitive chemoradiotherapy, 31 (22%) patients who developed grade ≥2 RP formed the final study cohort. There was one patient who had grade 5 toxicity (the patient died one day after hospital admission with respiratory symptoms), 33 days after completion of chemoradiotherapy, and they had not received durvalumab.

The median age was 67 years (range 41–87). Most patients received concurrent systemic chemotherapy (26/31; 84%), and the most common regimen received was cisplatin and etoposide in 11 patients. All patients received either 66Gy in 33 fractions (13/31; 42%) or 60 Gy in 30 fractions (18/31; 58%). The mean lung dose for the cohort was 15.8Gy (SD 1.56), and V5Gy and V20Gy were 60.14% (SD 2.73) and 29.96% (SD 1.82), respectively, Table 1 [16, 16]. Twelve patients (39%) of the 31 who developed RP had received durvalumab postchemoradiotherapy.

The median time-to-RP for the cohort was 2.4 months (range: 0.6–9.6 months), of which 10 (32%) had early RP (i.e., within 2 months of completion of radiotherapy). The median time-to-RP was 3.4 months (range: 1.7–7.2) in patients who had durvalumab, compared to 2.3 months (range: 0.6–9.6) in patients who did not have durvalumab ($P = 0.01$) (Table 2). 83% (10/12) and 58% (11/19) of patients who had durvalumab and did not have durvalumab had late RP, respectively.

There were no differences in characteristics of patients who developed early and late RP (Table 3).

Table 1: Patient and clinical characteristics.

Number of patients	$N = 31$
Age (years)	
Median (range)	67 (41, 87)
Gender	
Female	14 (45.2)
Male	17 (54.8)
EGFR (for adenocarcinoma or NOS histology)	
Negative	14 (45.2)
Positive	7 (22.6)
Unknown	10 (32.2)
ALK	
Negative	18 (58.1)
Positive	3 (9.7)
Unknown	10 (32.2)
PDL1	
<1%	0
1–49%	23 (74.2)
>50%	8 (25.8)
Stage	
Stage 3a	16 (51.6)
Stage 3b	14 (45.2)
Stage 3c	1 (3.2)
Durvalumab	
Yes	12 (39)
No	19 (61)
Concurrent chemotherapy	
No	5 (16)
Yes	26 (84)
Type of chemotherapy	
Cisplatin and etoposide	11 (35.5)
Cisplatin and pemetrexed	7 (22.6)
Carboplatin and paclitaxel	6 (19.4)
Carboplatin and pemetrexed	2 (6.5)
No chemo	5 (16)
Prescription dose	
66 Gy in 33	13 (41.9)
60 Gy in 30	18 (58.1)
Completed prescribed dose	
Yes	31 (100)
Mean lung dose Gy, mean (SD)	15.8 (1.56)
V5Gy, %, mean (SD)	60.14 (2.73)
V20Gy, %, mean (SD)	29.96 (1.82)

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; NOS, not otherwise specified; SD, standard deviation.

4. Discussion

Patients on durvalumab postchemoradiation had late-onset RP compared to patients who had chemoradiation alone. This is similar to study findings from an MD Anderson group, which suggested delayed onset of RP in patients treated with chemoradiation and durvalumab, mean time 3.4 months vs a mean time of 2.1 months in patients receiving chemoradiation alone [18]. In our study, the mean time to development of RP in patients receiving durvalumab postchemoradiation was 3.4 months vs 2.3 months in patients receiving chemoradiation alone.

4.1. Pathophysiology of Radiation Pneumonitis. RP is a complex process involving proinflammatory and profibrotic cytokines produced by damaged and activated cells of the lung parenchyma resulting from altered physiologic function in patients undergoing radiotherapy. The lung parenchyma consists of alveoli, which has an internal surface lined by a layer of cells in turn covered by endothelium. These cells include Type I (squamous) and Type II (cuboidal) pneumocytes, and ninety percent are Type I, which are involved in gaseous exchange, and Type II pneumocytes, which synthesize and secrete pulmonary surfactant.

The exact mechanism and chronology of how these cells and cytokines produced interact upon physiologic alteration on exposure to radiation has not been elucidated with precision. Nonetheless, the molecular events instigated by the interactions characterize RP. These changes can be divided into early, intermediate, and late stages, with resultant histopathologic, radiographic changes, and accompanying clinical symptoms [22].

4.1.1. Early Phase: 0–8 Weeks after Last Day of Radiotherapy. In our study, these phase-defined patients who had early-onset RP and Type I cells are affected within hours or days to

Table 2: Time-to-radiation pneumonitis between patients who had durvalumab vs no durvalumab.

	No durvalumab ($n = 19$)	Durvalumab ($n = 12$)	P value
Time-to-radiation pneumonitis, month median (range)	2.3 (0.6–9.6)	3.4 (1.7–7.2)	0.01
Early radiation pneumonitis	8 (42%)	2 (17%)	0.14
Late radiation pneumonitis	11 (58%)	10 (83%)	

Table 3: Characteristics of patients who had early (≤2 months) vs late (>2 months) radiation pneumonitis and the likelihood of having early RP.

	Early RP (≤2 months post-RT)	Late RP (>2 months post-RT)	OR (95% CI)	P value
	10 (32%)	21 (68%)		
Age, mean (SD)	64.7 (12.0)	66.7 (10.0)	0.98 (0.91–1.06)	0.6
Sex				
Male	4 (24%)	13 (76%)	Reference	
Female	6 (43%)	8 (57%)	0.41 (0.09–1.92)	0.3
Mean lung dose, Gy, median (range)	16.69 (11.9–17.44)	16.44 (12.86–18.27)	0.94 (0.58–1.52)	0.8
V5Gy, median (range)	57.93 (52.87–62.80)	58.79 (42.36–64.73)	1.01 (0.85–1.21)	0.9
<60	9 (35%)	17 (65%)	Reference	
≥60	1 (20%)	4 (80%)	2.11 (0.20–21.89)	0.5
V20Gy, median (range)	28.875 (17.9–35.52)	29.24 (21.04–33.53)	1.03 (0.85–1.27)	0.7
<30	6 (29%)	15 (71%)	Reference	
≥30	4 (40%)	6 (60%)	0.6 (0.12–2.91)	0.5
Stage				
3a	7 (44%)	9 (56%)	Reference	
3b/c	3 (20%)	12 (80%)	0.32 (0.06–1.60)	0.2
Durvalumab				
No	8 (42%)	11 (58%)	Reference	
Yes	2 (17%)	10 (83%)	0.28 (0.05–1.62)	0.1
Chemotherapy				
No	3 (60%)	2 (40%)	Reference	
Yes	7 (27%)	19 (73%)	0.25 (0.03–1.79)	0.1
Radiation dose				
60Gy	6 (33%)	12 (67%)	Reference	
66Gy	4 (31%)	9 (69%)	0.98 (0.76–1.27)	0.9

CI, confidence interval; OR, odds ratio.

radiation. They undergo apoptosis, leading to accelerated proliferation of Type II epithelial cells resulting in an increase in alveolar surfactant production and release of the surfactant ultimately exudates into the alveoli. This results in increased permeability evidenced by perivascular edema and congestion more pronounced the first 2–6 weeks after radiotherapy. In our study, most patients who developed RP in this early stage had not received durvalumab. The pathophysiology of this stage is due to the activation of macrophages, which results in enhanced production and release of cytokines, namely, transforming growth factor (TGF), platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), and tumor necrosis factor-alpha (TNF-alpha). TGF, regarded as the most significant, directly acts on endothelial cells altering production of three products (angiotensin-converting enzyme (ACE), prostacyclin, and plasminogen activator (PA)) by activating collagen-synthesizing genes. The resultant stimulation of collagens I/III/IV and fibronectin production persists until 8 weeks after radiation with the pronounced elevation of collagen IV [10, 23].

4.1.2. Intermediate Stage: 2 to 6 Months after Radiotherapy. The intermediate phase is characterized by a continuing inflammatory response.There is capillary obstruction by platelets, fibrin, and collagen; therefore, there is decreased lung perfusion and, in addition, increased expression of transforming growth factor stimulated by an increase in leukocytes, plasma cells, macrophages, fibroblasts, and collagen fibers [23]. In this phase, clinical RP is more common. In our study, the mean time to RP regardless of receipt of durvalumab was 3 months and median age of the cohort was 67. This is like findings from several trials, which have shown peak development of RP in the period ranging 2–12 months [6, 18]. Age greater than 65 years is a known predictive factor among other parameters based on the Thor model and a meta-analysis by Palma et al. [11, 16]. Most patients who did not receive durvalumab were over 65, possibly explaining why more patients who did not receive durvalumab had higher rates of pneumonitis compared to patients who received durvalumab. However, despite this increase in frequency, age was not predictive of early RP presentation. In the intermediate stage, mortality is not

uncommon with increasing severity [10]. One patient who presented with severe symptoms died a day after presentation, in keeping with these published findings [24].

4.1.3. Late Phase: Beyond 6 Months after Radiotherapy. Late radiation toxicity results in pulmonary fibrosis and these permanent changes take 6 to 24 months to evolve, remaining stable after 2 years in most cases. Patients may present with radiation fibrosis without exhibiting the characteristic RP clinical symptoms [22]. A sequela of repair initiated following tissue injury, confined to the area of irradiation, and stimulated by continued release of transforming growth factor-beta, fibronectin, and platelet-derived growth factor among other cytokines is characteristic of this phase [6, 10]. Radiology findings include architectural distortions characterized by diminished lung volume, consolidation, and bronchiectasis [25]. This component was beyond the scope of this review, therefore not explored in this study.

4.2. Durvalumab-Induced Pneumonitis. Immunotherapy agents harness the immune system to fight cancer cells utilizing several strategies. Durvalumab, an immune checkpoint blockade (ICB) PD L1 inhibitor, acts by promoting activation and proliferation of T lymphocytes against tumor cells. PD 1 found principally on T and B lymphocytes and macrophages binds to both PD L1 and PD L2 [26]. Cancer cells overexpress PD L1 and PD L2, of which PD L2 has a twofold to sixfold affinity to PD 1 compared to PD L1 [26]. Durvalumab competitively binds to PD L1, allowing continued activation and proliferation of cytotoxic T cells and proinflammatory cytokines. This enhancesantitumor immune responses hence positive outcomes in patients with stage 3 unresectable NSCLC.

Conversely, hyperactivation of immune responses can result in immune-related side effects, which can affect any organ and immunotherapy-induced pneumonitis, and the focus of this study is one of the most important, which can result in temporary or permanent cessation of treatment. Explicit pathophysiology outlining chronology to clinical symptom development and dominant components are poorly understood due to lack of preclinical models; however, PD L2 and IL6 have been suggested to be prominent in the pathophysiology [26]. Durvalumab, an anti-PD-1 agent, can potentially promote the interaction of PD L2 and repulsive guidance molecule b (RGMb) through competitive inhibition of PD L2 and PD 1 interaction, stimulating proliferation of T cells in lung parenchyma eventually leading to immune-mediated toxicity [27].

4.3. Understanding and Preventing Pneumonitis in Patients Receiving Radiotherapy and Immune Checkpoint Inhibitors. Findings from this study suggest timing to development of RP may occur later in patients initiated on durvalumab in comparison with patients not on durvalumab. This has implication in designing trials that seek to further investigate preventative strategies for RP in patients receiving immunotherapy and radiotherapy. Possibly, immunomodulatory components are stimulated to different magnitudes, causing competitive inhibition of pathways that would otherwise result in earlier presentation of RP. For instance, activation of macrophages resulting in secretion of proinflammatory cytokines, prominently TNF, is an established process in the early days following exposure to radiation. In the pathophysiology of immune-mediated pneumonitis, the pathway due to RGMb interaction with PD L2 stimulated by PD L1 inhibition may be more prominent. It can be argued that each independently increases the probability of pneumonitis, or perhaps a synergistic effect resulting in worse presentation.

On the contrary, these same immunogenic responses secondary to chemoradiation characterized by enhanced PD L1 expression may provide the most optimal benefit regarding disease control. This was the basis of the recommendation on the PACIFIC protocol to administer durvalumab as close as possible to last day of chemoradiation. In clinical practice, studies have indeed noted an increased risk of pneumonitis in patients receiving both modalities of care but no significant differences in severity as would be suggested [1, 17, 18]. This highlights the need for preclinical studies to better understand the pathophysiology of the development of immunotherapy-mediated pneumonitis independently. A better understanding of specific cells involved or immunomodulatory components allows refining preventative strategies to better suit the evolving treatment paradigm in NSCLC.

In this study, traditional dose volume metrics utilized for radiation planning were not predictive of pneumonitis by receipt of durvalumab. These metrics are incorporated in the QUANTEC, Appelt, and Thor models, which have been utilized to predict RP [11, 28, 29]. They were developed prior to incorporation of immunotherapy as standard of care. New models may therefore need to be developed aligned to evolving radiotherapy technology and expanding indications of immunotherapy in NSCLC management.

4.4. Preventative Strategies. Prevention of RP has been studied at different stages of evolvement [6]. Despite promising results, there is no standard of care adopted in current clinical practice.

Pentoxifylline and alpha tocopherol (vitamin E) have shown a reduction in lung fibrosis through immunomodulatory and anti-inflammatory properties mediated by the suppression of TNF-α and IL-1, prominent cytokines in radiotherapy-induced pneumonitis. ACE, a key component in the early phase in the pathogenesis of RP, has been studied with promising results as a potential target in preventing RP by using ACE inhibitors, which exhibit significant antifibrotic activity [12, 13, 22]. Amifostine, a radioprotector agent, scavenges free radicals, diminishing the concentration of TGF-β1 as noted in animal models; therefore, the benefit of amifostine at reducing the risk of RP has been evaluated and verified, with no negative effect on tumor response [30–32]. There could be an opportunity for improving delivery of some of the agents described by harnessing

microbubble and/or nanoparticle technology [33]; targeting cytokines stimulated by either radiotherapy or immunotherapy highly concentrated in high-risk region for RP by aiding precise delivery of radioprotector agents. Drugs, such as colchicine, penicillamine, statins, and interferon-gamma, can potentially modify the progression of fibrosis inhibiting excess collagen synthesis preventing RP (6). Efficacy of these medications is yet to be studied in patients receiving concurrent or sequential immune checkpoint inhibitors, with possibly a unique pathophysiology and hierarchal immunomodulatory mediation therefore warranting further studies.

4.5. Limitations. This study has limitations as it is a retrospective study. Missing data such as smoking history, chronic obstructive pulmonary disease, presence of interstitial lung disease, and unavailability of baseline pulmonary function test potentially confound the results. However, most patients with lung cancer are likely to have similar comormid conditions. The small cohort of patients precluded any meaningful analysis on the impact of systemic chemotherapy. Imaging was not reviewed by a specialized radiologist, and we relied on the report provided and reviewed by study team. The study also spanned a time when durvalumab was just becoming available, hence the ability to compare patients who received and those who did not receive durvalumab.

5. Conclusion

Patients on durvalumab had late-onset RP compared to patients who did not, and traditional dosimetric lung constraints were not predictive of development of grade 2 RP by receipt of durvalumab, suggesting development of new predictive models that incorporate evolving management is necessary. In addition, this study comprehensively discusses radiation-induced and immunotherapy-induced pneumonitis, highlighting potential areas of study that seek to explore prevention of treatment-induced pneumonitis in NSCLC management.

Data Availability

The data obtained from the institutional medical records used to support the findings of this study are included within the article.

Disclosure

This study abstract was presented at the 2022 America Society of Radiation Oncology (ASTRO) annual general meeting as a poster presentation.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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