



2026 World Conference on Lung Cancer

SEPTEMBER 12 – 15, 2026 | SEOUL, REPUBLIC OF KOREA

Addition of Chemotherapy to Targeted Therapy at Progression in RET- and ROS1- Rearranged NSCLC: Insights From a Case Series and Therapeutic Implications

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Introduction

In EGFR-mutant NSCLC, multiple studies have demonstrated the clinical benefit of combining chemotherapy with EGFR tyrosine kinase inhibitors (TKIs), leading to regulatory approval of these combinations. Similar approaches have been explored in ALK-rearranged NSCLC, with emerging case-based evidence supporting the feasibility of combining chemotherapy with ALK TKIs. In contrast, data supporting this strategy in other rare actionable genomic alterations remain scarce. Oncogene-driven non-small cell lung cancer (NSCLC), including RET- and ROS1-rearranged tumours, is characterised by high sensitivity to targeted therapies. However, clinical heterogeneity and resistance remain significant challenges, particularly in the context of smoking exposure and co-mutations. Mechanisms of resistance are incompletely understood, and optimal management at progression remains undefined in the absence of identifiable actionable resistance mechanisms. Here, we report three illustrative cases highlighting the potential role of adding chemotherapy to ongoing targeted therapy at progression in RET- and ROS1-rearranged NSCLC.

Case 1 – Clinical History

Figure 1



A 48-year-old never-smoker with RET fusion-positive NSCLC (KIF5B-RET), PD-L1 expression of 60%, and TP53 and PTEN co-mutations achieved prolonged disease control for approximately 3 years before developing mediastinal lymph node and pleural progression (Figure 1a–b), confirmed by pleural biopsy.

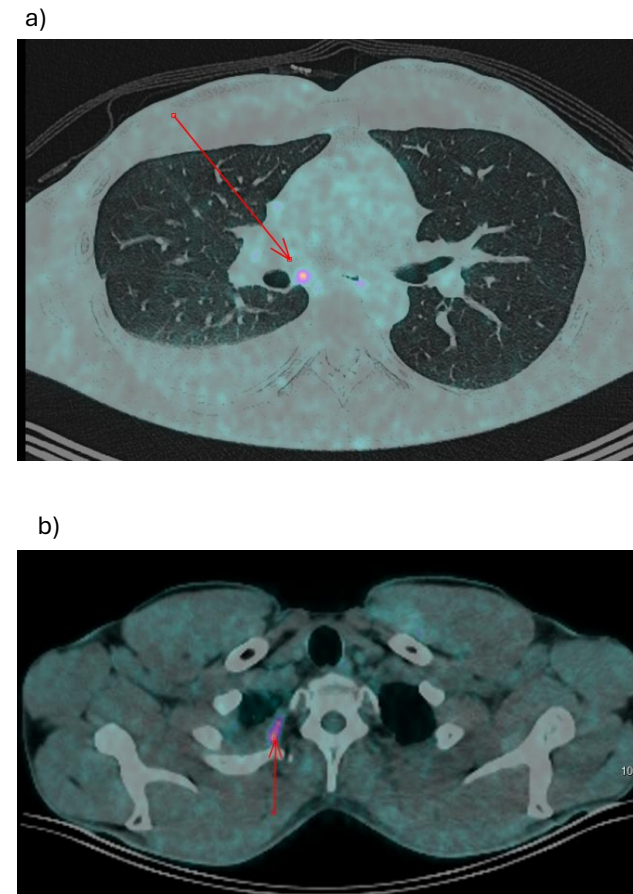
In the absence of actionable resistance alterations, platinum-based chemotherapy was initiated, along with pleurodesis for management of the pleural effusion..

Figure 1 ^{18}F -FDG PET/CT showing a new moderate right pleural effusion with several hypermetabolic right pleural foci, including the following target lesions: right posterior apical pleura, anterior to the posterior arch of the right 10th rib, and along the lateral aspect of the liver as well as in mediastinal lymph nodes.

Figure 2 a) Metabolic uptake in the right-sided mediastinal lymph node

Figure 2 b) Metabolic uptake in the right posterior apical pleura.

Figure 2

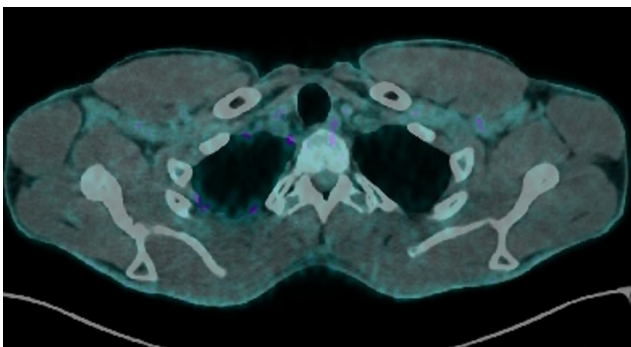


Case 1 – Clinical History

After three cycles of platinum-based chemotherapy, the patient achieved a complete response and remains in radiological remission 6 months after the addition of chemotherapy to targeted therapy. However, 8 months after initiation of the combination, the patient developed isolated sacral oligoprogression, which was treated with local radiotherapy, allowing continuation of the same systemic therapy.

Figure 3

a)



b)



Figure 3 a) Axial ^{18}F -FDG PET/CT showing no abnormal FDG uptake in the pleura
b) Axial ^{18}F -FDG PET/CT showing a large loculated right pleural effusion without FDG uptake in the adjacent pleura or mediastinal lymph nodes.

Figure 4



Figure 4 Follow-up ^{18}F -FDG PET/CT showing no evidence of metabolically active disease, with extensive right pleural FDG uptake related to prior pleurodesis.

Case 2 – Clinical History

Figure 1



A 46-year-old man, current smoker (45 pack-years), presented with stage IVB RET fusion-positive lung adenocarcinoma (KIF5B–RET), with bone, liver, and right adrenal metastases. The tumor showed PD-L1 expression of 100% with no identifiable co-mutations. First-line treatment with selpercatinib was initiated.

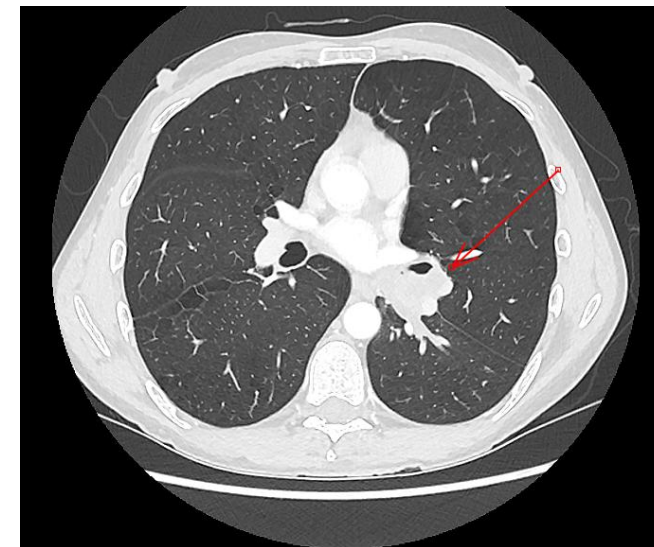
Figure 1 Baseline 18F-FDG PET/CT showing an intensely FDG-avid left hilar primary tumor with metastatic involvement of lymph nodes, liver, right adrenal gland, and bone.

He experienced rapid disease progression after 4 weeks of first-line selpercatinib (Figure 1 a) & b)). A repeat tumor biopsy did not identify any acquired resistance mechanism.

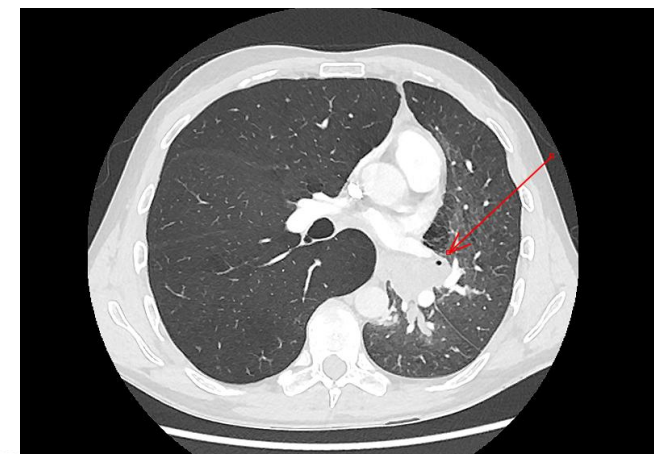
Figure 2.a) Baseline contrast-enhanced chest CT showing a left hilar/perihilar tumor (arrow) involving the left hilar bronchovascular structures 1. b) Follow-up chest CT after 4 weeks of selpercatinib showing rapid progression of the left hilar/perihilar tumor (arrow), with increased involvement of the adjacent bronchovascular structures

Figure 2

a)



b)



Platinum-based chemotherapy was added to the ongoing targeted therapy

Case 2 – Clinical History

After the addition of two cycles of platinum-based chemotherapy, the patient experienced marked regression of the primary left lower lobe lesion, complete regression of the metastatic lesions, and a slight decrease in the left hilar lesion (Figure 3 & 4).

Given the oligopersistent disease, consolidative radiotherapy was delivered to the residual left hilar lymph node.

Despite this response, multisite disease progression occurred 6 months after the addition of platinum-based chemotherapy to selpercatinib.

Figure 3.

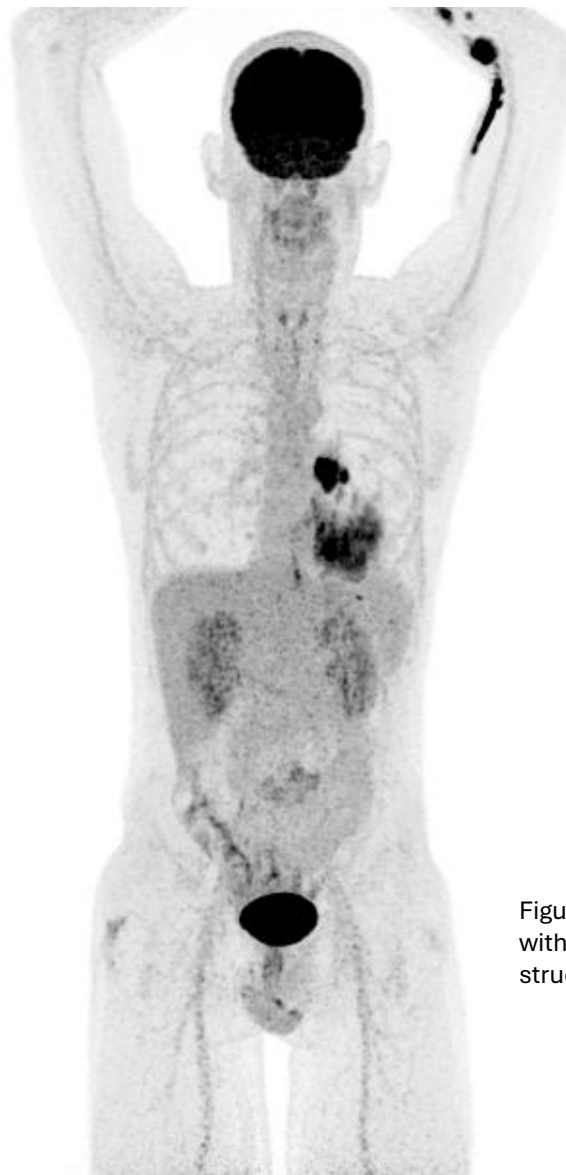


Figure 3. Marked metabolic response with near-complete regression of metastatic disease and persistent FDG-avid left hilar disease.

Figure 4.

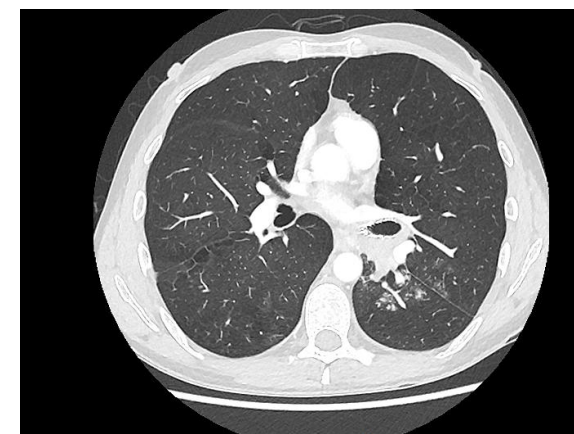


Figure 4. Follow-up chest CT showing marked regression of the left hilar tumor, with residual soft-tissue disease surrounding the left hilar bronchovascular structures.

Case 3 – Clinical History

Figure 1



A 60-year-old never-smoker presented with advanced ROS1 fusion-positive lung adenocarcinoma (PD-L1 5%) and had been heavily pretreated with multiple tyrosine kinase inhibitors, including entrectinib, repotrectinib following the emergence of the ROS1 G2032R (p.Gly2032Arg) resistance mutation in exon 38, and lorlatinib. Following multisite disease progression, the patient received a combination of lorlatinib and chemotherapy.

Figure 1 ^{18}F -FDG PET/CT showing morphometabolic progression of osseous disease, including non-healed pelvic fractures, with particularly marked progression of the L4 vertebral body lesion, associated with posterior wall destruction and findings suggestive of epidural involvement, as well as progression of the T12 vertebral body lesion, extending close to the posterior wall without cortical destruction. Progression of mediastinal and hilar lymph node disease, with new hypermetabolic left inguinal and external iliac lymph nodes.

Case 3 – Clinical History

Figure 2

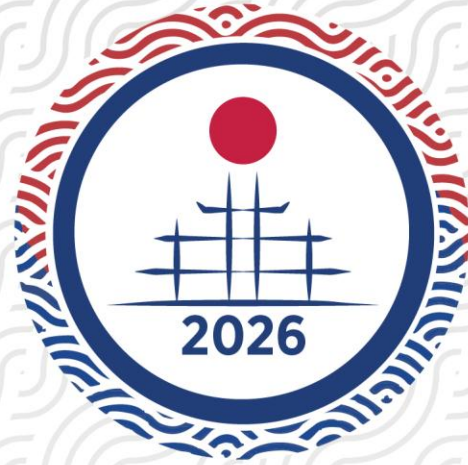


After 3 months of combined platinum-based chemotherapy and lorlatinib, the patient achieved a near-complete response, with oligopersistent disease confined to the left pelvic/iliac region. However, the patient experienced disease progression after electing to discontinue chemotherapy and died 3 months later.

Figure 2 PET/CT showing a good partial response of the osseous metastatic disease, although with morphometabolic progression of an osteolytic lesion involving the anterosuperior aspect of the left iliac wing. Marked metabolic regression of the pulmonary disease and mediastinal and hilar lymphadenopathy.

Conclusions

The addition of platinum-based chemotherapy to ongoing targeted therapy resulted in marked, albeit transient, responses in three patients with RET- or ROS1-rearranged NSCLC progressing on TKIs without actionable resistance mechanisms. Although all patients ultimately experienced disease progression, these cases suggest that maintaining oncogene inhibition while introducing chemotherapy may provide additional disease control in selected patients. Prospective evaluation is warranted to determine whether this strategy offers benefit over chemotherapy alone and to identify patients most likely to benefit.



Thank You.