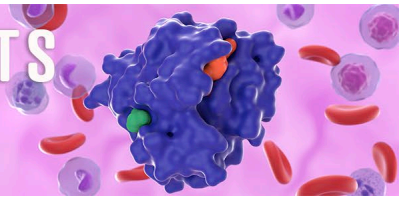
OPTIMIZING TREATMENT IN PATIENTS WITH ROS1 REARRANGED NSCLC



Editor's Note: This is a transcript of an online course released in September 2024. To obtain credit for participation, CLICK HERE.

Lung Cancer Overview and *ROS1* Rearrangement in Non-Small Cell Lung Cancer (NSCLC)

We'll begin with a lung cancer overview and an overview of *ROS1* rearrangement in NSCLC. As I think most are aware, lung cancer remains a significant public health burden in the United States, with over 234,000 new cases predicted for this year. That represents about 12% of all cancer diagnoses and 20% of cancer deaths. When you look at the 5-year survival by stage for lung cancer, if we catch the disease when it's localized, the survival is reasonable, with a 64% 5-year survival. But, as you see, it drops precipitously with regional and distant metastatic disease and, unfortunately, distant metastatic disease accounts for the majority of cases at presentation. The total number of deaths for lung cancer in the US in 2024 is predicted to be over 125,000 and that dwarfs those from breast cancer, pancreatic cancer and colorectal carcinoma.

NSCLC represents the most common type of lung cancer, approximately 80% to 85% of cases in the US, and the 5-year overall survival for the entire group, independent of stage, is approximately 25%, again primarily because so many patients present with advanced disease. Survival has clearly improved with our new targeted and immunotherapies, but significant treatment gaps remain.

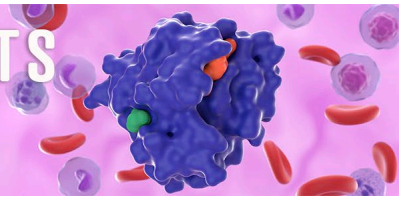
We have known for now over a decade that a significant portion of NSCLCs will have a molecular driver behind their malignant phenotype and that renders those tumors potentially susceptible to molecularly targeted therapy and, as shown in the pie graph, there are a number of molecular aberrations that have been identified that are significant in NSCLC. These, as I mentioned, may help us identify appropriate therapy, but certain alterations may also increase the risk for CNS metastases compared to non-small cell without mutation. The predominant mutations we see are KRAS and EGFR, but *ROS1* does represent about 2% to 3% of molecular aberrations that we see in NSCLC.

ROS1 rearrangements are rare, important genetic alterations in NSCLC. They occur in about 1% to 2% of patients with NSCLC. The *ROS1* oncogene encodes a tyrosine kinase that is related to ALK and that'll be important when we talk about some of the therapeutic options on subsequent slides. This rearrangement leads to a fusion of *ROS1* with various partner proteins and that drives cellular transformation and acts as a potent oncogenic driver for these tumors. There is a unique common presentation related to *ROS1* NSCLC. These patients tend to be younger, they tend to be female with adenocarcinoma, and they tend to be never-smokers. Now, these are not exclusive, but that's the most common phenotype we'll see with this presentation.

Regarding *ROS1*-targeted therapy in NSCLC, currently, for frontline treatment of metastatic disease, there are 4 agents to consider. Ceritinib and crizotinib are both *ROS1* and ALK-targeted multikinase inhibitors. It was discovered several years ago when they were in development for ALK treatment that they also had activity in *ROS1*, again going back to what I mentioned that the *ROS1* tyrosine kinase that results from the gene rearrangement is similar to ALK. More recently, both entrectinib and repotrectinib have been developed that have activity against both *ROS1* and NTRK and are both multikinase inhibitors. And you see the dosing there. The NCCN guidelines, I'll point out—and this is critical—recommend *ROS1*testing for *ROS1* gene rearrangements prior to first-line therapy in metastatic non-small cell. Obviously, if you're not testing, you're not going to find these rearrangements, and so testing is critical to identify these patients to allow them to receive these targeted therapy options.

When you look at the NCCN guidelines regarding *ROS1* rearrangement and the treatment algorithm, the preferred first-line options are either crizotinib, entrectinib or repotrectinib. Ceritinib is listed as an "other recommended" option, primarily due to toxicity with ceritinib. If the *ROS1* rearrangement is identified after first-line metastatic treatment has already begun, you really have 2 options, as shown in the panel at the bottom. You can complete your planned systemic therapy, including maintenance therapy, or interrupt that therapy and initiate one of the *ROS1*-targeted agents noted above.

When we look at subsequent therapy for metastatic *ROS1* NSCLC, the options and the algorithm are shown here. If you're progressing on first-line therapy, it's important to determine is this oligoprogression that's fairly asymptomatic or is this symptomatic multifocal progression? In the asymptomatic group, you could consider, if it's oligoprogression, definitive local therapy, such as surgery or stereotactic radiation and continuing your current therapy. However, if you were to switch agents, the agents of choice are repotrectinib or lorlatinib,



depending on what you've used previously if they had not received prior repotrectinib.

If the patient is symptomatic or has multifocal progression, then you're likely going to need to change therapies and, again, the options would be entrectinib, if crizotinib or ceritinib had been used previously, or repotrectinib, if not previously used, or lorlatinib. Similarly, that's if they have brain progression only. If they have symptoms, systemic progression with multiple lesions, then repotrectinib, if not used previously, or lorlatinib are options or you can consider other systemic therapy options, such as chemotherapy and immunotherapy. And, at this point, we really don't have comparative studies to clearly distinguish between these options.

I'm going to talk a little bit about *ROS1*-targeted therapy safety because there are some unique safety profiles for these agents. Regarding crizotinib, the common adverse events include vision disorders, which are typically mild, and GI toxicity, as shown, as well as edema. As far as serious and rare adverse events, there is occasional hepatotoxicity, rare interstitial lung disease, bradycardia which, in my experience, is usually mild but can occasionally be more serious, QT prolongation and, very rarely, severe vision loss. Monitoring visual symptoms is certainly important. You see the dose reduction strategies that can be employed there. The first dose reduction is to 200 mg twice daily and the second dose reduction to 250 mg once daily.

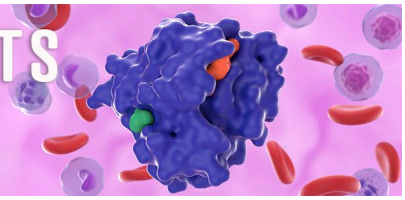
Regarding entrectinib, the common adverse events are shown here, again that are mostly low-grade. Fatigue, GI toxicity which includes nausea, vomiting, diarrhea or constipation, dysgeusia, edema, weight gain and vision disorders. There are some serious, rare adverse events to be aware of. Congestive heart failure, or CHF, CNS effects such as dizziness, cognitive impairment, mood disorders, sleep disturbances, skeletal fracture risk, hepatotoxicity, and QT prolongation. And the dose reductions are shown. Your first dose reduction is to 400 mg once daily and the second dose reduction is to 200 mg once daily. Again, it's recommended to discontinue permanently if the drug is not tolerated after a second dose reduction.

Lastly, regarding repotrectinib, the common adverse events are dizziness and dysgeusia, peripheral neuropathy, occasional GI toxicity, fatigue, some cognitive impairment and muscle weakness. Regarding serious and rare adverse events, similar to entrectinib, there are CNS effects, rare interstitial lung disease, hepatoxicity, skeletal fracture risk, hyperuricemia so it is recommended to monitor serum uric acid levels, as well as myalgia with CPK elevation. And again, it is recommended to monitor CPK initially on starting therapy. And you see the dose reductions there. The first dose reduction is 120 mg twice daily and the second dose reduction is 80 mg once daily. And it's recommended to discontinue permanently if not tolerated after the second dose reduction.

I want to make a few comments regarding sequencing of these agents when you're treating metastatic *ROS1* rearranged NSCLC. Repotrectinib, as noted, is a next generation *ROS1* TKI. It's able to overcome some of the known resistance mechanisms to prior agents and it also has excellent CNS penetration and activity. It is a good option for those patients with brain metastases or those who have failed prior *ROS1*-targeted therapy. Lorlatinib is a highly potent next generation *ROS1* TKI which also has good CNS penetration and efficacy. And so it can also be utilized as subsequent therapy in patients who've progressed on prior *ROS1* TKI therapy and, again, including those with CNS progression, given its good CNS penetration. It is not currently approved for first-line therapy. And some factors to consider for frontline and subsequent lines of therapy for *ROS1* rearranged NSCLC, certainly patient characteristics, patient preferences regarding some of the side effects and toxicity may be important, as well as shared decision-making is always a useful strategy to help the patient decide on which therapy they prefer. And certainly, disease features, as we noted, primarily those with brain disease ideally would get an agent with CNS protection.

To summarize, *ROS1* rearrangements are rare, but you will find them if you check for them and they are present in about 1% to 2% of patients with NSCLC. And all patients with metastatic disease should now be tested broadly for molecular aberrations, ideally with next generation sequencing, and that testing should include testing for *ROS1* rearrangements. Targeted therapy with tyrosine kinase inhibitors is standard first-line therapy for those with metastatic *ROS1* rearranged disease, however certainly these patients will eventually develop resistance and CNS progression is also a limitation of some of these agents and limits the impact of the first-generation *ROS1* targeted agents. Next generation *ROS1* targeted therapies, including repotrectinib, offer additional CNS activity and can overcome some of the resistance mechanisms in patients who've received prior *ROS1* targeted therapy. Therapy for *ROS1* rearrangements in patients with metastatic non-small cell should be optimized based on patient factors and shared decision-making, including monitoring and adverse event management.

OPTIMIZING TREATMENT IN PATIENTS WITH ROS1 REARRANGED NSCLC



ROS1 Rearranged Metastatic NSCLC – *ROS1* Overview/Patient Characteristics with *ROS1*

Which one of the following characteristics of patients with metastatic non-small cell lung cancer is associated with *ROS1 gene* rearrangement on genetic testing?

A. Age greater than 60 years
B. Squamous cell histologic phenotype
C. Female sex
D. Previous thoracic radiation

The correct answer is: C (Female sex)

Answer rationale:

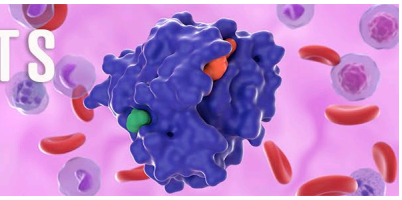
- *ROS1* gene rearrangements are a rare genetic abnormality in NSCLC, accounting for 1% to 2% of patients with advanced/metastatic NSCLC.
- *ROS1* gene rearrangements, however, are more common in women, younger patients, and patients without a history of smoking and typically occur in nonsquamous NSCLC (adenocarcinoma).
- This patient meets 3 of these common features: a younger female patient who is a never-smoker.
- Ethnicity and previous radiation therapy are not directly associated with increased occurrence in *ROS1* rearrangement lung cancer.

Dr. Dowell: This is getting at the typical patient that we see with *ROS1* rearranged NSCLC and of the characteristics listed, a patient who is female would be the most likely to have a *ROS1* rearrangement. I would add, though, that I would not restrict your molecular testing to patients who fit the phenotype. You will miss patients. There are males who have *ROS1* rearrangement. There are those even with non-adenocarcinoma or other features that are not typically associated with *ROS1* rearrangement that will have the rearrangement and so it's important that you're testing broadly, not based solely on patient features.

References:

1. Bergethon K, Shaw AT, Ou SH, et al. *ROS1* rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*. 2012;30(8):863-870. doi:10.1200/JCO.2011.35.6345
2. Bi H, Ren D, Ding X, et al. Clinical characteristics of patients with *ROS1* gene rearrangement in non-small cell lung cancer: a meta-analysis. *Transl Cancer Res*. 2020;9(7):4383-4392. doi:10.21037/tcr-20-1813
3. Dugay F, Llamas-Gutierrez F, Gournay M, et al. Clinicopathological characteristics of *ROS1*- and *RET*-rearranged NSCLC in caucasian patients: Data from a cohort of 713 non-squamous NSCLC lacking KRAS/EGFR/HER2/BRAF/PIK3CA/ALK alterations. *Oncotarget.* 2017;8(32):53336-53351. doi:10.18632/oncotarget.18408
4. Kim HR, Lim SM, Kim HJ, et al. The frequency and impact of *ROS1* rearrangement on clinical outcomes in never smokers with lung adenocarcinoma. *Ann Oncol*. 2013;24(9):2364-2370. doi:10.1093/annonc/mdt220
5. Marchetti A, Barberis M, Di Lorito A, et al. *ROS1* gene fusion in advanced lung cancer in women: A systematic analysis, review of the literature, and diagnostic algorithm. *JCO Precis Oncol*. 2017;1:1-9. doi:10.1200/PO.16.00010
6. Park S, Ahn BC, Lim SW, et al. Characteristics and outcome of *ROS1*-positive non-small cell lung cancer patients in routine clinical practice. *J Thorac Oncol*. 2018;13(9):1373-1382. doi:10.1016/j.jtho.2018.05.026
7. Takeuchi K, Soda M, Togashi Y, et al. RET, *ROS1* and ALK fusions in lung cancer. *Nat Med*. 2012;18(3):378-381. doi:10.1038/nm.2658

OPTIMIZING TREATMENT IN PATIENTS WITH ROS1 REARRANGED NSCLC



Case 1 - 40-year-old woman

Frontline treatment

A 40-year-old previously healthy woman is evaluated in the emergency department for a 1-month history of progressive shortness of breath and 6 months of worsening cough. She is married, has 3 children, and works as a per diem infusion nurse. The patient has never smoked, and her medical history includes depression and hypothyroidism. Her medications include sertraline and levothyroxine.

On physical examination, the patient is in some distress and has trouble speaking.
Vital signs:
Temperature: 37.6°C (99.7 °F)
Pulse: 104 beats/min
BP: 150/88 mm Hg
Respirations: 20/min
Oxygen saturation: 96% on room air

Chest X-ray: reveals large spiculated mass in the upper left lobe that is suspicious of lung cancer

PET/CT scan: positive for multiple liver lesions suspicious of metastases

Biopsy/Pathology: metastatic adenocarcinoma of the lung

Genetic testing: Foundation One testing shows *ROS1* rearrangement

Laboratory evaluation shows:

Leukocyte count	6,500/µL
Hemoglobin	13.0 g/dL
Platelet count	230,000/µL
Serum creatinine	0.9 mg/dL
Sodium	126 mEq/L
Potassium	4.6 mEq/L
Bilirubin	1.1 mg/dL
ALT	68 U/L
AST	45 U/L

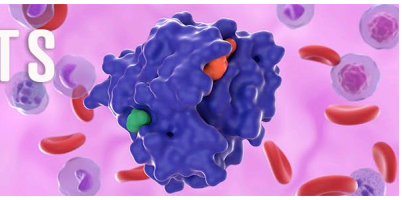
Which one of the following would be the most appropriate first-line treatment for this patient?

A. Ceritinib
B. Entrectinib
C. Lorlatinib
D. Pembrolizumab plus carboplatin plus pemetrexed

The correct answer is: B (Entrectinib)

Answer rationale:

- Based on NCCN guidelines and clinical data, the 3 preferred options for frontline treatment of *ROS1* rearranged NSCLC are
  - Crizotinib
  - Entrectinib
  - Repotrectinib
- Targeted therapy should be utilized in patients with genetic alterations and mutations, including *ROS1* rearrangements, due to better efficacy and safety.
- Crizotinib was studied in the phase 2 PROFILE 1001 study
  - Overall response rate (ORR)=72%, median duration of response (DOR)=17.6 months, median progression-free survival (PFS)=19.2 months. Based on these results, crizotinib is a preferred frontline treatment choice for patients with *ROS1* rearranged metastatic NSCLC
- Entrectinib was studied in multiple phase 2 trials including the ALKA-372-001, STARTRK-1, and STARTRK-2 trials. A comparative analysis of these 3 trials was evaluated for patients with *ROS1* metastatic NSCLC
  - ORR=77%, median DOR=25 months, median PFS=26 months
  - Based on this comparative analysis, entrectinib is a preferred recommended frontline option for patients with *ROS1* rearranged metastatic NSCLC
- Ceritinib is another *ROS1* targeted multikinase inhibitor that has shown efficacy and safety in patients with *ROS1* rearranged NSCLC
  - ORR = 62%, median PFS = 9.3 months, median overall survival (OS) = 24 months; median DOR = 21 months
  - However, ceritinib is only recommended as an "other recommended" therapy option in NCCN guidelines and is not a preferred treatment choice compared to crizotinib, entrectinib, or repotrectinib
- Lorlatinib has shown positive results in patients previously treated with *ROS1* targeted therapy with and without brain lesions, however, lorlatinib is not recommended or approved for patients with untreated *ROS1* rearranged metastatic NSCLC
  - Lorlatinib initially showed strong results in patients previously treated with crizotinib in a phase 1-2 clinical trial

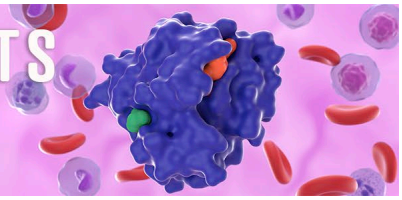


        - ORR = 35% and 50% intracranial response
    - In the recent LORLATU expanded access program in France, treatment sequencing was assessed with lorlatinib
        - Patients were on 1-3 previous *ROS1* TKIs before lorlatinib initiation (48% were on 1 TKI, 33% were on 2, and 25% were on 3 previously)
        - All patients had received crizotinib and 21% of patients had received a second generation *ROS1* TKI such as ceritinib, entrectinib, and repotrectinib)
        - 64% of patients evaluated had brain metastasis. The CNS objective response rate was 72% (n=46)
    - These study results highlight lorlatinib as a strong salvage therapy option for patients after failure on at least 1 prior *ROS1* TKI but not as a recommended frontline treatment option
- Patients with genetic alterations/mutations initiated on chemotherapy or immunotherapy (including chemoimmunotherapy combinations) prior to targeted therapy have negative outcomes and worse responses.
    - Pembrolizumab plus chemotherapy (carboplatin and pemetrexed) is a standard chemotherapy plus immunotherapy regimen for patients with metastatic NSCLC who do not have an actionable mutation
    - As this patient has an actional *ROS1* rearrangement, the patient should not be treated initially with immunotherapy plus chemotherapy due to risk of reduced efficacy and increased toxicity. Patient should be initiated on a preferred *ROS1* targeted agent.
- Repotrectinib is an additional frontline preferred option for patients with *ROS1* rearranged metastatic NSCLC.
    - Repotrectinib is a next generation *ROS1* targeted TKI agent with potential strong activity in the CNS
    - Efficacy and safety results are based on the phase 2 TRIDENT-1 study
        - ORR=79%, median DOR=34.1 months, median PFS=35.7 months
        - Based on TRIDENT-1, repotrectinib is a preferred recommended frontline option for patients with *ROS1* rearranged metastatic NSCLC

Dr. Dowell: This patient, again, does fit the typical profile of a patient who might have *ROS1* rearranged NSCLC, being a never-smoker and a young female. With her metastatic disease, there are really 3 options as preferred in this situation to consider for treatment. Entrectinib, repotrectinib or crizotinib. Of those options, my bias is that an agent with CNS penetration may be the best choice, but technically all 3 are approved in this setting. Specifically, entrectinib and repotrectinib have good CNS activity and good CNS penetration. They do, however, have some unique side effects that will be highlighted in the subsequent cases and so, for some patients, crizotinib may be the best option. Ceritinib is really an older drug with toxicity issues that have rendered it as an "other recommended" option and, I'll be honest, in my practice, I rarely use it in this setting, but it is an available drug for selected patients.

References:

1. Drilon A, Camidge DR, Lin JJ, et al. Repotrectinib in *ROS1* fusion-positive non-small-cell lung cancer. *N Engl J Med*. 2024;390(2):118-131. doi:10.1056/NEJMoa2302299
2. Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in *ROS1* fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet Oncol.* 2020;21(2):261-270. doi:10.1016/S1470-2045(19)30690-4
3. Girard N, Galland-Girodet S, Avrillon V, et al. Lorlatinib for advanced *ROS1*+ non-small-cell lung cancer: results of the IFCT-1803 LORLATU study. *ESMO Open*. 2022;7(2):100418. doi:10.1016/j.esmoop.2022.100418
4. Lim SM, Kim HR, Lee JS, et al. Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring *ROS1* rearrangement. *J Clin Oncol*. 2017;35(23):2613-2618. doi:10.1200/JCO.2016.71.3701
5. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer. V7.2024. Published June 26,2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf



6. Shaw AT, Riely GJ, Bang YJ, et al. Crizotinib in *ROS1*-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. *Ann Oncol*. 2019;30(7):1121-1126. doi:10.1093/annonc/mdz131
7. Shaw AT, Solomon BJ, Chiari R, et al. Lorlatinib in advanced *ROS1*-positive non-small-cell lung cancer: A multicentre, open-label, single-arm, phase 1-2 trial. *Lancet Oncol*. 2019;20(12):1691-1701. doi:10.1016/S1470-2045(19)30655-2

Safety Profile of *ROS1* TKI Therapy (Entrectinib)

The 40-year-old woman with newly diagnosed *ROS1* gene rearranged metastatic NSCLC begins therapy with oral entrectinib, 600 mg once daily. She is adherent to therapy and tolerates it well. After 1 month of therapy, her condition has improved, and evaluation shows a significant response to therapy and tumor shrinkage.

After 3 months of entrectinib therapy, the patient develops shortness of breath on mild exertion, mild chest pain, and edema. The patient is referred to cardiology service, and evaluation shows decreased ejection fraction. The patient is diagnosed with grade 2 entrectinib-induced congestive heart failure. Entrectinib therapy is discontinued, and after 3 weeks, the patient's heart failure symptoms have resolved. The patient would like to resume treatment for her lung cancer

Which one of the following would be the most appropriate treatment for this patient now?

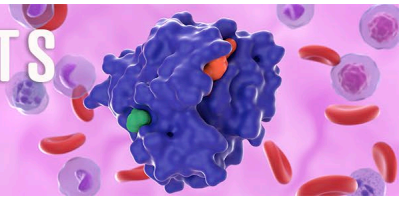
A. Discontinue entrectinib and initiate lorlatinib, 100 mg once daily
B. Discontinue entrectinib and initiate intravenous nivolumab plus ipilimumab therapy
C. Reduce entrectinib dosage to 400 mg once daily
D. Resume entrectinib at a dosage of 600 mg once daily

The correct answer is: C (Reduce Entrectinib dose to 400 mg once daily)

Answer rationale:

- The patient is unfortunately experiencing cardiac toxicities related to entrectinib.
- Congestive heart failure (CHF) occurred in 3.4% of patients including 2.3% grade 3 CHF.
- The median time to onset of CHF in clinical trials with entrectinib was 2 months (range 11 days to 12 months).
- Entrectinib was held in 50% of cases of CHF and discontinued in 17% of patients.
- The CHF toxicity resolved in 50% of patients following interruption/discontinuation.
- Monitoring should include baseline assessment of left ventricular ejection fraction (LVEF) prior to initiating entrectinib.
- Monitor patients for clinical signs of CHF including shortness of breath and edema. For patients with new or worsening CHF, hold entrectinib and institute appropriate cardiac medical management including referral to specialist team.
- For patients with grade 2 or 3 CHF toxicity, entrectinib can be resumed at a reduced dose once the patient recovers to a grade 1 CHF or less after holding therapy.
- The first dose reduction is 400 mg once daily if the patient is previously receiving 600 mg once daily.
    - The second dose reduction is 200 mg once daily. Patients who have a grade 4 CHF toxicity or cannot tolerate 200 mg once daily should be permanently discontinued from entrectinib
- Discuss importance of collaboration with specialist teams as needed and appropriate monitoring and follow-up with patients
- While CHF is a rare toxicity of entrectinib, other more common toxicities include fatigue, CNS effects (such as dizziness, mood disorders, cognitive impairment, and sleep disturbances) dysgeusia and dysesthesia, dyspnea, GI toxicities, vision abnormalities, and hepatotoxicity
- Other rare toxicities related to entrectinib include QT prolongation, hyperuricemia, and skeletal fractures (more common in pediatric patients)

Dr. Dowell: This patient unfortunately developed congestive heart failure with entrectinib. That can occur, but fortunately significant congestive failure is rare, and it tends to be reversible with interruption in treatment or, in many cases, it can be. But, if you see CHF that requires interruption of drug, when the drug is restarted, it has to be started at a dose reduction and the patient needs to be monitored closely for any signs or symptoms of recurrent CHF.



References:

1. Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in *ROS1* fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21(2):261-270. doi:10.1016/S1470-2045(19)30690-4
2. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Published Nov 27, 2017. Accessed Jul 13, 2024. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
3. Rozlytrek. Prescribing Information. Genentech, Inc 2024. Accessed Jul 20, 2024. https://www.gene.com/download/pdf/rozlytrek_prescribing.pdf

Subsequent Therapy Selection

The patient begins therapy with entrectinib, 400 mg once daily; the therapy is well tolerated and her disease continues to respond well to therapy. However, after 4 years of reduced dose entrectinib therapy, the patient again develops shortness of breath, along with pain in her back. On evaluation, the patient's disease is found to be progressing on entrectinib therapy, with increased and new lung lesions and multiple new metastatic lesions on her spine.

Evaluation of lung biopsy specimen shows new lesions are consistent with metastatic adenocarcinoma of the lung.

Repeat FoundationOne®CDx genetic test shows *ROS1* rearrangement is still present.

Immunohistochemistry reveals tissue is PD-L1 negative.

Entrectinib therapy is discontinued due to progression of disease.

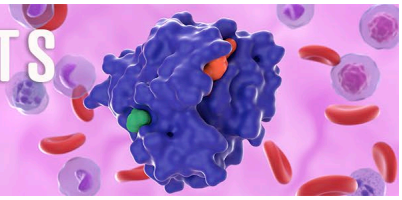
Which one of the following would be the most appropriate subsequent therapy for this patient?

A. Carboplatin plus pemetrexed
B. Crizotinib
C. Pembrolizumab
D. Repotrectinib

The correct answer is: D (Repotrectinib)

Answer rationale:

- Based on NCCN guidelines, patients with *ROS1* gene rearranged metastatic NSCLC who progress on *ROS1* targeted therapy and have multiple systemic lesions should be treated with subsequent therapy that involves additional targeted therapy against *ROS1*.
- As this patient has already progressed on entrectinib the patient would benefit from treatment with either repotrectinib (TRIDENT-1) or lorlatinib (LORLATU) in the second line setting.
- If the patient does not prefer oral targeted therapy, or is not appropriate for repotrectinib or lorlatinib, then the patient may be considered for systemic therapy for adenocarcinoma which would include combination immunochemotherapy.
- The case highlights that the patient's tumor is PD-L1 negative which eliminates single agent pembrolizumab as an appropriate choice for the patient and chemotherapy without a checkpoint inhibitor would not be the most effective option for the patient based on current guidelines and clinical trial data.
- Repotrectinib was evaluated in the phase 2, TRIDENT-1 trial which included treatment naive and *ROS1* TKI exposed patients with *ROS1* metastatic NSCLC.
    - Response rates were still strong in patients who had previously received a targeted *ROS1* agent, with ORR of 38% (n=56) in this group.
    - Of note, for the patients who previously received *ROS1* therapy, 82% received crizotinib, 16% received entrectinib, and 2% received ceritinib previously
    - The median duration of response was 14.8 months with a 9-month median progression-free survival in patients previously treated with a *ROS1* TKI.
- Tailor subsequent line therapy to the patient and have collaborative shared decision making with patient
- TRIDENT-1 included 4 cohorts in phase 2 portion of trial
    - Treatment naïve patients
    - Patients who had previously received one *ROS1* TKI and never received chemotherapy



- Patients who had previously received 1 *ROS1* TKI and platinum-based chemotherapy
- Patients who had previously received 2 *ROS1* TKIs and never received chemotherapy

Dr. Dowell: This patient has now developed progressive disease on entrectinib and has apparent multifocal progression in multiple sites and therefore the best option of those listed in the question would be repotrectinib. It has been shown to overcome some of the resistance mechanisms to first-line treatment and gets good CNS penetration and so it would be, of the available options, my preferred choice in this setting.

References:

1) Drilon A, Camidge DR, Lin JJ, et al. Repotrectinib in *ROS1* fusion-positive non-small-cell lung cancer. *N Engl J Med*. 2024;390(2):118-131. doi:10.1056/NEJMoa2302299
2) Girard N, Galland-Girodet S, Avrillon V, et al. Lorlatinib for advanced *ROS1*+ non-small-cell lung cancer: results of the IFCT-1803 LORLATU study. *ESMO Open*. 2022;7(2):100418. doi:10.1016/j.esmoop.2022.100418
3) National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer. V7.2024. Published Jun 26,2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
4) Shaw AT, Solomon BJ, Chiari R, et al. Lorlatinib in advanced *ROS1*-positive non-small-cell lung cancer: A multicentre, open-label, single-arm, phase 1-2 trial. *Lancet Oncol*. 2019;20(12):1691-1701. doi:10.1016/S1470-2045(19)30655-2

Case 2: - A 62-year-old man

Patient Specific Characteristics/Brain Metastasis

A 62-year-old man with a 2-month history of persistent dry cough, weight loss, fatigue, and headache is referred to oncology service for evaluation. The patient was evaluated 6 weeks ago by his primary care provider and was treated with levofloxacin for 7 days, along with a cough suppressant, for possible bronchitis without resolution. The weight loss and fatigue have intensified and have adversely affected his work as a college professor.

The patient's medical history includes hypertension, which is controlled with furosemide and metoprolol therapy. He reports being a nonsmoker and a social drinker (1-2 alcohol containing drinks per week). His ECOG performance status is 2.

On physical examination, the patient is overall well appearing with slight difficulty breathing.
Vital signs:
Temperature: 37.6°C (99.7 °F)
Pulse: 88 beats/min
BP: 145/80 mm Hg
Respirations: 20/min
Oxygen saturation: 94% on room air

Laboratory evaluation shows:

Leukocyte count	8,000/ µL
Hemoglobin	16.0 g/dL
Platelet count	300,000/µL
Serum creatinine	1.1 mg/dL
Sodium	128 mEq/L
Potassium	4.8 mEq/L
Bilirubin	0.9 mg/dL
Alanine aminotransferase	70 U/L
Aspartate aminotransferase	50 U/L

Chest radiography shows a large spiculated right lower lobe mass and multiple left lower and upper lobe masses.
CT scan of the abdomen and pelvis and bone scan are negative. MRI of the brain shows multiple lesions consistent with metastatic disease.

CT-guided evaluation of a lung biopsy specimen shows poorly differentiated non-small cell carcinoma, with adenocarcinoma phenotype.

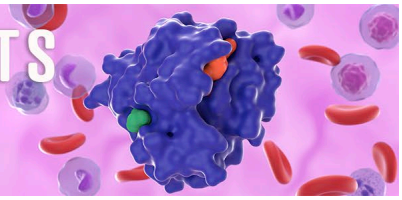
FoundationOne®CDx genetic test is positive for *ROS1* gene rearrangement and immunohistochemistry (IHC) shows tumor negative for PD-L1.
Patient is diagnosed with metastatic *ROS1* rearrangement positive non-small cell lung cancer (adenocarcinoma) with brain metastases.

What one of the following would be the most appropriate first-line therapy for this patient?

A. Ceritinib
B. Crizotinib
C. Nivolumab plus ipilimumab
D. Repotrectinib

The correct answer is: D (Repotrectinib)

OPTIMIZING TREATMENT IN PATIENTS WITH ROS1 REARRANGED NSCLC



Answer rationale:

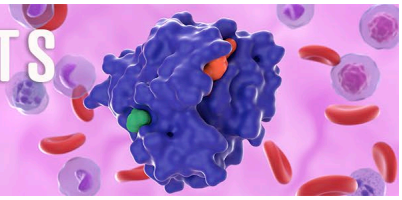
- The 3 preferred frontline treatment choices for *ROS1* rearranged metastatic NSCLC are crizotinib, entrectinib, and repotrectinib
- NCCN guidelines recommend repotrectinib or entrectinib for patients with brain metastasis because of better responses seen in clinical trials in this patient population
    - Crizotinib resulted in low concentration in cerebrospinal fluid and disease progression occurs in the CNS first in about 50% of patients treated with crizotinib
- Immunotherapy combination with nivolumab plus ipilimumab would not be appropriate choice for this patient due to PD-L1 negativity and *ROS1* gene rearrangement found. Also, at this time, the patient's performance status is likely making it a challenge for patient to tolerate ipilimumab combination therapy.
- Repotrectinib was designed to enhance intracranial activity and led to greater shrinkage of brain tumors and longer survival than entrectinib in patient-derived *ROS1* gene fusion-positive intracranial models
- In clinical trials, repotrectinib was studied in the TRIDENT-1 phase 1-2 trial where 24% of treatment naïve patients had brain metastasis at baseline
    - Treatment naïve intracranial ORR with repotrectinib was 89% (n=9)
    - Response was still seen in patients previously treated with *ROS1* targeted therapy with brain mets (ORR = 38%) highlighting activity in second-line setting as well
    - 83% of these patients had an intracranial response lasting at least 12 months
    - Intracranial progression-free survival (PFS) for patients with no brain metastases at baseline was 91% at 12 months
- Entrectinib intracranial data demonstrates an ORR of 55% and median duration of response of 12 months highlighting entrectinib as another treatment option for patients with brain metastasis at baseline
- As brain metastases are common in patients with *ROS1* gene rearrangement--positive NSCLC, appropriate therapy selection to maximize intracranial activity and response is paramount for optimizing patient care

Dr. Dowell: This patient has stage 4 *ROS1* rearranged NSCLC with brain metastases and, of the available choices, repotrectinib would be preferred. Again, very good CNS penetration and activity, generally well tolerated and highly effective in *ROS1* rearranged metastatic NSCLC.

References:

1. Drilon A, Camidge DR, Lin JJ, et al. Repotrectinib in *ROS1* fusion-positive non-small-cell lung cancer. *N Engl J Med*. 2024;390(2):118-131. doi:10.1056/NEJMoa2302299
2. Drilon A, Jenkins C, Iyer S, Schoenfeld A, Keddy C, Davare MA. *ROS1*-dependent cancers - biology, diagnostics and therapeutics. *Nat Rev Clin Oncol.* 2021;18(1):35-55. doi:10.1038/s41571-020-0408-9
3. Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in *ROS1* fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21(2):261-270. doi:10.1016/S1470-2045(19)30690-4
4. Lim SM, Kim HR, Lee JS, et al. Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring *ROS1* rearrangement. *J Clin Oncol.* 2017;35(23):2613-2618. doi:10.1200/JCO.2016.71.3701
5. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer. V7.2024. Published Jun 26,2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
6. Patil T, Smith DE, Bunn PA, et al. The incidence of brain metastases in stage IV *ROS1*-rearranged non-small cell lung cancer and rate of central nervous system progression on crizotinib. *J Thorac Oncol*. 2018;13(11):1717-1726. doi:10.1016/j.jtho.2018.07.001
7. Shaw AT, Riely GJ, Bang YJ, et al. Crizotinib in *ROS1*-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. *Ann Oncol.* 2019;30(7):1121-1126. doi:10.1093/annonc/mdz131

OPTIMIZING TREATMENT IN PATIENTS WITH ROS1 REARRANGED NSCLC



ROS1 Targeted Therapy Safety (Repotrectinib)

The 62-year-old man with newly diagnosed *ROS1* gene rearranged NSCLC with brain metastases begins therapy with oral repotrectinib, 160 mg once a day. After 2 weeks of therapy, which he has tolerated well, the dosage is increased to 160 mg twice daily. The patient tolerates this dosage well, and his disease responds well, including shrinkage of the brain lesions. His symptoms improve, and he resumes his teaching and research duties. After 6 months of therapy, the patient develops dizziness and vertigo. Evaluation does not show progression of disease, and therefore, a diagnosis of repotrectinib-induced grade 2 central nervous system toxicity is made.

Which one of the following would be the most appropriate management for this patient at this time?

A. Discontinue repotrectinib; when symptoms resolve start oral therapy with entrectinib, 600 mg once daily.
B. Discontinue repotrectinib; when symptoms resolve start intravenous therapy with pembrolizumab, carboplatin, pemetrexed combination.
C. Hold repotrectinib; when symptoms resolve restart oral repotrectinib therapy at 80 mg twice daily.
D. Hold repotrectinib; when symptoms resolve, resume oral repotrectinib therapy at previous dosage of 160 mg twice daily.

The correct answer is: D (Hold repotrectinib; when symptoms resolve, resume oral repotrectinib therapy at previous dosage of 160 mg twice daily.)

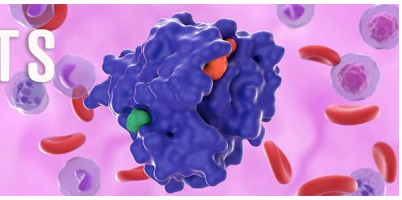
Answer rationale:

- A common toxicity of repotrectinib is broad spectrum CNS events including dizziness, ataxia, and cognitive disorders such as memory impairment
- These toxicities occurred in 77% of patients in the TRIDENT-1 study with grade 3 or 4 events occurring rarely in 4.5% of patients
- Dizziness, including vertigo, occurred in 65% of patients. The median time to onset was 7 days (range 1 day to 1.4 years).
- Dose interruptions were required in 9% of patients with 11% of patients requiring dose reduction due to dizziness
- This patient is experiencing a mild grade 2 CNS toxicity from repotrectinib with dizziness and vertigo.
    - The recommended management is to hold therapy until symptoms resolve
    - As the patient is maintaining a strong response the patient should remain on repotrectinib therapy and resume when symptoms return to baseline or less than or equal to a grade 1 toxicity level
    - The patient should resume therapy at the same original dose of 160 mg by mouth twice daily as this was a grade 2, mild event. A dose reduction could also be considered for the patient if desired, but the appropriate first level dose reduction would be 120 mg by mouth twice daily and not 80 mg by mouth twice daily (the second level for dose reduction).
- As the patient continues great response with repotrectinib and is experiencing a mild CNS toxicity, discontinuing repotrectinib and initiating an alternative therapy (chemoimmunotherapy or another *ROS1* targeted agent) would not be appropriate.

Dr. Dowell: CNS toxicity is fairly common with repotrectinib and, in my experience, generally mild, but it can include cognitive change, dizziness, ataxia. One clinical issue is to make sure that what you're seeing is not due to their brain disease, if they have metastatic disease to the brain. So it's always appropriate to consider CNS imaging to rule that out. Again, as with many of the toxicities with these agents, it often resolves with dose interruption and sometimes will require dose decrease. But in a setting like this, if it were to resolve quickly, since the drug appears to be very effective, based on the description in the question, the patient is responding well, I would try to resume at the prior dose to maintain that efficacy and, in many cases in my experience, the CNS toxicity does not recur.

References:

1. Drilon A, Camidge DR, Lin JJ, et al. Repotrectinib in *ROS1* fusion-positive non-small-cell lung cancer. *N Engl J Med*. 2024;390(2):118-131. doi:10.1056/NEJMoa2302299
2. Augtyro. Prescribing Information. Bristol-Myers Squibb. 2024. Accessed Jul 21, 2024. https://packageinserts.bms.com/pi/pi_augtyro.pdf



3. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Published Nov 27, 2017. Accessed Jul 13, 2024. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Background continued

The patient with *ROS1* gene rearranged NSCLC and brain metastases tolerated repotrectinib therapy well and had a significant CNS response. However, after 30 months of therapy, the patient developed confusion and agitation. MRI of the brain showed progression of metastases and the presence of new lesions. Repotrectinib therapy is discontinued. The patient wants to continue to treat his disease. His ECOG performance status is 1.

Which one of the following would be the most appropriate therapy for the patient?

A. Lorlatinib
B. Pembrolizumab, pemetrexed, and carboplatin
C. Ramucirumab plus docetaxel
D. Trastuzumab deruxtecan

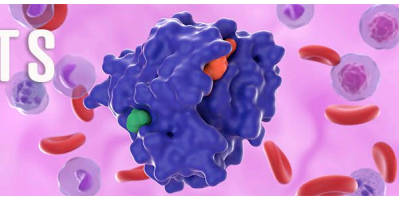
The correct answer is: A (Lorlatinib)

Answer rationale:

- This patient has lost response and progressed on *ROS1* targeted therapy repotrectinib with symptomatic brain lesion progression
- Based on NCCN guidelines and clinical data, lorlatinib is the most appropriate choice for this patient. The patient wishes to continue therapy.
- Chemotherapy combinations with immunotherapy pembrolizumab) or VEGF inhibitors (ramucirumab) would not be appropriate and likely have limited CNS activity/penetration
    - Trastuzumab deruxtecan is an antibody drug conjugate therapy that is utilized in later lines for NSCLC but only for patients with HER2 positive disease
- Lorlatinib has shown positive results in patients previously treated with *ROS1* targeted therapy with brain lesions
    - Intracranial response was 50% (n=24) in patients previously treated with crizotinib
    - In the more recent LORLATU expanded access program in France, treatment sequencing was assessed with lorlatinib
        - Patients were on 1-3 previous *ROS1* TKIs before lorlatinib initiation (48% were on 1 TKI, 33% were on 2, and 25% were on 3 previously)
        - All patients had received crizotinib and 21% of patients had received a second generation *ROS1* TKI such as ceritinib, entrectinib, and repotrectinib)
        - 64% of patients evaluated had brain metastasis. The CNS objective response rate was 72% (n=46)
    - These study results highlight lorlatinib as a strong salvage therapy option for patients after failure on at least 1 prior *ROS1* TKI
- Radiation therapy in consultation with a radiation oncologist is an option.
- Highlight continued need for clinical trial enrollment and advancements to address current treatment gaps
    - Novel mechanisms including Tumor Infiltrating Lymphocytes (TIL) are being evaluated in patients with *ROS1* rearrangement and other genetic mutations in NSCLC

Dr. Dowell: This patient now has progressive disease, unfortunately, on repotrectinib which eventually does happen for the majority of patients. In this setting, lorlatinib is a very reasonable option. Again, it has very good activity in this setting and very good CNS penetration in a patient with known brain metastases. It could also be reasonable in this setting to consider radiation for the brain. Depending on the size of the new brain lesions and their symptoms, I don't necessarily rely on the TKI to completely control the brain. You always want to engage your radiation oncology colleagues to see if additional radiation may be helpful.

OPTIMIZING TREATMENT IN PATIENTS WITH ROS1 REARRANGED NSCLC



References:

1) National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer. V7.2024. Published Jun 26,2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
2) Girard N, Galland-Girodet S, Avrillon V, et al. Lorlatinib for advanced *ROS1*+ non-small-cell lung cancer: results of the IFCT-1803 LORLATU study. *ESMO Open*. 2022;7(2):100418. doi:10.1016/j.esmoop.2022.100418
3) H. Lee Moffitt Cancer Center and Research Institute. Clinical trial of CD40L-augmented TIL for patients with EGFR, ALK, *ROS1*, or HER2-driven NSCLC. Last updated Mar 22, 2024. https://clinicaltrials.gov/study/NCT05681780
4) Shaw AT, Solomon BJ, Chiari R, et al. Lorlatinib in advanced *ROS1*-positive non-small-cell lung cancer: A multicentre, open-label, single-arm, phase 1-2 trial. *Lancet Oncol*. 2019;20(12):1691-1701. doi:10.1016/S1470-2045(19)30655-2

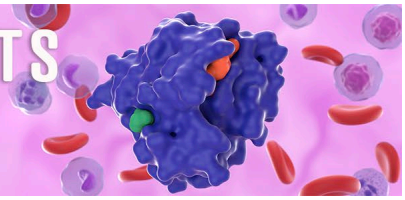
Which one of the following should be discussed with a 42-year-old female recently diagnosed with *ROS1* metastatic NSCLC before beginning tyrosine kinase inhibitor therapy with crizotinib, entrectinib, or repotrectinib?

A. Use of effective contraception because of the risk of embryo-fetal toxicity
B. Monitoring of thyroid function before and during treatment because of the risk of endocrine-related toxicity
C. Monitoring of urine output before and during treatment because of the risk of kidney toxicity
D. Testing for left ventricular ejection fraction before initiating therapy and throughout treatment because of the risk of congestive heart failure

The correct answer is: A (Use of effective contraception)

Answer rationale:
A key role of the interprofessional, multidisciplinary care team is to be sure the patient with *ROS1* gene rearranged metastatic NSCLC is adequately educated about the safety and tolerability of treatment.

- All 3 *ROS1* gene targeted agents (crizotinib, entrectinib, repotrectinib) have a warning and risk for embryo-fetal toxicity. These agents can cause fetal harm.
- All female patients of reproductive potential should be advised and counseled on the potential risk of taking these agents if pregnant. All such patients should use effective contraception methods while on therapy
    - Each agent has specific instructions for length to continue contraception for after treatment has been stopped
    - Crizotinib
        - Females: use effective contraception during treatment and for 45 days following last dose
        - Males with female partners of reproductive potential: use condoms during treatment and for 90 days after last dose
    - Entrectinib
        - Females: use effective contraception during treatment and for 5 weeks following last dose
        - Males with female partners of reproductive potential: use condoms during treatment and for 3 months after last dose
    - Repotrectinib
        - Females: use effective contraception during treatment and for 2 months following last dose
        - Males with female partners of reproductive potential: use condoms during treatment and for 4 months after last dose
- This is an especially important counseling point for patients as *ROS1* gene rearrangements often occur in female patients who are younger and may still be of child-bearing age
- The *ROS1* gene targeted therapies do not carry a risk of endocrine-related toxicities such as thyroid disorders and do not require monitoring of thyroid function. Endocrine-related toxicities are associated with immunotherapy treatment such as checkpoint inhibitors which are another key therapy in management of NSCLC.
- Crizotinib is the only therapy that may have a risk of renal toxicity and requires a dose reduction (250 mg once daily instead of twice daily) for patients with severe renal impairment (creatine clearance <30mL/min).
    - However, all 3 agents do have risk of hepatotoxicity and liver function tests should be monitored in all patients at baseline and periodically throughout treatment



- Cardiac monitoring is only required for entrectinib due to risk of potential congestive heart failure. Patients should have left ventricular ejection fraction (LVEF) assessed prior to initiating entrectinib.
    - However, crizotinib and repotrectinib do not have an associated risk with congestive heart failure and do not require monitoring for LVEF.

Dr. Dowell: With all of these agents, we have limited data, if any, on the safety of them in pregnancy. It is obviously important to counsel your patients who are of child-bearing age that they need to use effective contraception, as we would say with most, if not all, of our cancer therapies.

References:

5) Augtyro. Prescribing Information. Bristol-Myers Squibb. 2024. Accessed Jul 21, 2024. https://packageinserts.bms.com/pi/pi_augtyro.pdf
6) Drilon A, Camidge DR, Lin JJ, et al. Repotrectinib in *ROS1* fusion-positive non-small-cell lung cancer. *N Engl J Med*. 2024;390(2):118-131. doi:10.1056/NEJMoa2302299
7) Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in *ROS1* fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21(2):261-270. doi:10.1016/S1470-2045(19)30690-4
8) National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer. V7.2024. Published Jun 26,2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
9) Rozlytrek. Prescribing Information. Genentech, Inc.; Jan 2024. Accessed Jul 21, 2024. https://www.gene.com/download/pdf/rozlytrek_prescribing.pdf
10) Shaw AT, Riely GJ, Bang YJ, et al. Crizotinib in *ROS1*-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. *Ann Oncol.* 2019;30(7):1121-1126. doi:10.1093/annonc/mdz131
11) Xalkori. Prescribing information. Pfizer, Inc.; Sept 2023. Accessed Jul 21, 2024. https://labeling.pfizer.com/ShowLabeling.aspx?id=676

WRAP-UP

Though rare, *ROS1* gene rearrangements are seen in NSCLC in approximately 2% of patients, and it's critical that you identify and find those patients as we do have very effective therapeutic options that can lead to highly durable responses. My editorial comment would be to make sure that you're testing these patients with appropriate molecular testing and that the testing you're doing includes *ROS1*, whether that's ideally next generation sequencing—and my preference would be with a platform that includes both DNA and RNA because that increases the yield of finding some of these rare gene fusions and rearrangements—but if you're using a panel that isn't NGS, to make sure that that panel includes effective testing for *ROS1* because, obviously, if you're not testing, you're not going to find it.

Again, if you do find it, as I noted, there are several highly effective agents available to treat these patients, primarily entrectinib, repotrectinib and crizotinib in the first-line setting. And it is important to realize that all of these agents have unique side effect profiles and so to be cognizant of those as well as the management strategies for controlling those side effects. In my experience, for most patients, you can find an effective dose that leads to durable responses and is well tolerated, but it sometimes does require dose interruptions or dose adjustments along the way.