Roche's General Guidance on Alectinib + CYP3A4 Inhibitors

The **Alecensa (alectinib) U.S. Prescribing Information (PI)** and **EMA SmPC** provide clear recommendations regarding concomitant use with **CYP3A4 inhibitors**, including **strong inhibitors like ritonavir (a component of Paxlovid)**.

Key Points from Roche's Official Labeling:

1. **Avoid Strong CYP3A4 Inhibitors When Possible**
   - Alectinib is primarily metabolized by **CYP3A4**, and strong inhibitors (e.g., **ritonavir, clarithromycin, itraconazole, ketoconazole**) can significantly increase alectinib plasma concentrations, raising the risk of **toxicity (hepatotoxicity, QT prolongation, GI effects, etc.)**.
2. **If a Strong CYP3A4 Inhibitor Must Be Used:**
   - **Monitor closely for adverse reactions** (e.g., hepatotoxicity, bradycardia, myalgia, renal impairment).
   - **Consider reducing the alectinib dose** (though the PI does not specify an exact reduction; clinical judgment is needed).
   - After discontinuation of the CYP3A4 inhibitor, resume the original alectinib dose after **2-3 elimination half-lives** of the inhibitor (~3 days for ritonavir).
3. **No Specific Mention of Paxlovid (Nirmatrelvir/Ritonavir)**
   - Roche has **not issued Paxlovid-specific guidance**, but since ritonavir is a **strong CYP3A4 inhibitor**, the general recommendations apply.

Practical Management Strategies

- **Alternative COVID-19 Therapies:**
  - If feasible, consider **remdesivir** (no CYP3A4 interaction) or **molnupiravir** (minimal interaction risk).
- **If Paxlovid is Necessary:**
  - **Option 1:** Temporarily withhold alectinib during Paxlovid treatment (5 days) and resume 2-3 days after stopping ritonavir.

- o **Option 2:** Reduce alectinib dose (e.g., by **50%**) while on Paxlovid, with close monitoring.
- o **Monitor:** Liver function tests (ALT/AST), QT interval (if risk factors exist), and signs of toxicity (nausea, fatigue, myalgia).

Conclusion

While Roche has not published **Paxlovid-specific advice**, their **general guidance on strong CYP3A4 inhibitors** suggests **caution, dose adjustment, or temporary discontinuation** of alectinib when ritonavir is used.