Letter Format Consultation

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Robert Greene, MD
Community Oncology Partners
456 Medical Plaza Ave
Metropolis, CA 90209

RE: Banks, John (DOB: 09/07/1953; MRN: SYN085)
Consultation Regarding Acquired Resistance to Selpercatinib

Dear Dr. Greene,

Thank you for referring Mr. John Banks for consultation regarding further management options for his Stage IV RET Fusion-Positive Lung Adenocarcinoma. I had the pleasure of meeting him today. I have reviewed his comprehensive records and history, and concur with your assessment of acquired resistance to Selpercatinib.

Summary of Key Information:

- **Diagnosis:** Stage IV Lung Adenocarcinoma (Sept 24, 2020). Initial presentation RUQ pain.
- **Staging:** LUL primary, extensive hepatic metastases. Brain MRI negative.
- **Molecular Profile:** NGS identified **KIF5B-RET fusion**. PD-L1 negative (TPS 0%).
- **First-Line Therapy:** Selpercatinib (Retevmo) 160 mg PO BID initiated Oct 16, 2020.
- **Response:** Achieved excellent partial response (significant reduction in liver mets), durable for approximately **21 months**. Tolerated well (main side effects: Grade 1 dry mouth, Grade 1 LFT elevation – stable).
- **Progression:** Surveillance CT C/A/P July 28, 2022 demonstrated clear progression with enlargement of multiple known hepatic lesions and appearance of several new hepatic lesions compared to prior scan (Jan 2022). Patient remains largely asymptomatic but notes mild increase in fatigue. ECOG PS remains 1.

Assessment: Mr. Banks has developed acquired resistance to the RET inhibitor Selpercatinib after a commendable 21 months of disease control. He remains in good performance status and is motivated for further therapy.

Discussion of Options & Recommendations:
Acquired resistance to RET inhibitors is an evolving field. Potential mechanisms include on-target RET kinase domain mutations (e.g., solvent front G810 mutations) or activation of bypass signaling pathways. While next-generation RET inhibitors (e.g., Pralsetinib has overlapping but distinct profile; newer agents in trials) might be considered, and repeat

tissue/liquid biopsy could *potentially* identify a targetable resistance mechanism, this is often not feasible or fruitful outside of a clinical trial setting currently.

Therefore, the standard approach after progression on targeted therapy for RET-fusion positive NSCLC is **systemic chemotherapy.**

1. **Platinum-Doublet Chemotherapy:** Given his adenocarcinoma histology and lack of prior chemotherapy exposure, the preferred regimen is **Carboplatin (AUC 5) + Pemetrexed (500 mg/m2) IV every 3 weeks.** This offers a well-established balance of efficacy and tolerability. We discussed this regimen, including the need for B12/Folate supplementation and common side effects (myelosuppression, fatigue, nausea, renal monitoring).
2. **Clinical Trials:** We briefly discussed clinical trial options, particularly those investigating agents after RET TKI progression, but no suitable local trials are immediately available. He is not keen on traveling for trial participation at this time.
3. **Continuation of Selpercatinib + Chemo:** Data supporting this approach after clear progression on TKI alone is lacking and generally not recommended standardly.
4. **Single-Agent Chemotherapy:** Less effective than doublet chemotherapy in the first instance post-TKI.

Recommendation:
Based on current evidence and guidelines, I recommend proceeding with second-line **Carboplatin + Pemetrexed** chemotherapy. Mr. Banks understood the rationale and is agreeable to this plan. I have provided him with prescriptions to start Folic Acid 1mg daily immediately and counseling on the regimen.

I recommend initiating this therapy at your center at his earliest convenience. Please ensure pre-cycle labs (CBC, CMP), B12 injection administration, appropriate pre-medications, and GFR calculation for Carboplatin dosing. Monitoring with restaging CT scans after 2-4 cycles would be appropriate.

Thank you again for involving me in Mr. Banks' care. Please do not hesitate to contact me if you have any further questions or wish to discuss his case further.

Sincerely,

Vivian Wells, MD, FACP
Medical Oncology