Consulting Physician: Kevin Powell, MD

Thoracic Oncology Clinic

Date of Consultation: October 28, 2022

REASON FOR CONSULTATION: Disease progression on first-line targeted therapy (Selpercatinib) for RET-fusion positive NSCLC. Discussion of second-line options and resistance testing.

HISTORY OF PRESENT ILLNESS:
Mr. Smith is a 70-year-old gentleman diagnosed with metastatic NSCLC (adenocarcinoma, KIF5B-RET fusion positive, PD-L1 0%) in October 2020. His disease manifested primarily as multiple liver metastases. He was initiated on the selective RET inhibitor Selpercatinib 160 mg BID starting November 2, 2020.

He experienced an excellent and durable response for approximately 23 months. Treatment was generally well-tolerated, notable toxicities included Grade 1 dry mouth/edema, Grade 2 hypertension (requiring Amlodipine), and Grade 2 hypothyroidism (requiring Levothyroxine). His performance status remained ECOG 0-1.

Over the past two months, he developed increasing fatigue and decreased appetite. Labs two weeks ago revealed rising LFTs (AST 88, ALT 105) and CEA (15 ng/mL, up from <2). CT scan on 10/16/22 confirmed interval growth of multiple liver metastases and development of new small liver lesions, consistent with progressive disease (RECIST PD). No evidence of extrahepatic progression.

PAST MEDICAL HISTORY: Hypothyroidism (on Levo), Hypertension (on Amlodipine), Osteopenia, Appendectomy. Former light smoker (10 pack-years, quit >30 yrs).

MEDICATIONS: Levothyroxine 75mcg daily, Amlodipine 5mg daily, Calcium/Vit D. (Selpercatinib now held).

REVIEW OF SYSTEMS: Positive for fatigue (7/10), decreased appetite. Denies RUQ pain, jaundice, fever, cough, SOB, bone pain, neurological sx.

PHYSICAL EXAM:
VS: Stable. Wt stable.
Gen: NAD, appears stated age. ECOG 1.
HEENT: Mildly dry oral mucosa. No icterus.
Chest: Clear. CV: RRR.
Abd: Soft, NT/ND. No HSM.
Ext: Trace pedal edema. Skin: No rash.

ASSESSMENT:
Mr. Smith has clear disease progression after a prolonged 23-month response to first-line Selpercatinib for RET-fusion positive metastatic NSCLC. The progression appears confined to the liver. Acquired resistance is presumed. His performance status remains good (ECOG 1).

DISCUSSION & PLAN:
I met with Mr. Smith today to discuss these findings. We reviewed the imaging and labs confirming progression. I explained the concept of acquired resistance to targeted therapy and the importance of understanding the mechanism if possible.

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Options moving forward include:

1. **Resistance Testing:** Strongly recommended. Repeat biopsy of a progressing liver lesion for NGS (including RET resistance mutation panel) and/or liquid biopsy (ctDNA). This may identify specific RET mutations (e.g., solvent front G810 substitutions) that confer resistance to Selpercatinib and potentially cross-resistance to other RET inhibitors.
2. **Second-Line RET Inhibition (Pralsetinib):** Another potent selective RET inhibitor. Efficacy after Selpercatinib failure is variable and may depend on the resistance mechanism. If resistance testing is uninformative or shows no known cross-resistant mutations, a trial of Pralsetinib (400 mg PO daily) could be considered. Potential toxicities reviewed (pneumonitis, hypertension, LFTs, heme).
3. **Systemic Chemotherapy:** Standard platinum-doublet chemotherapy (e.g., Carboplatin/Pemetrexed given adenocarcinoma histology) remains a highly effective option in this setting. Would likely be recommended if resistance testing reveals mutations conferring resistance to both Selpercatinib and Pralsetinib, or if Pralsetinib is attempted and fails.
4. **Clinical Trials:** Options targeting RET resistance mechanisms could be explored depending on biopsy results.

Mr. Smith is motivated to understand the resistance mechanism and potentially try another targeted agent before chemotherapy. He agrees to proceed with resistance testing.

Action Plan:

1. Hold Selpercatinib permanently.
2. Schedule IR for CT-guided biopsy of progressing liver lesion ASAP. Request tissue NGS with focus on RET resistance mutations.
3. Send Guardant360 liquid biopsy today.
4. Obtain prior authorization for Pralsetinib 400 mg daily – will hold prescription until biopsy/ctDNA results are available and reviewed.
5. Continue Levothyroxine, Amlodipine, Calcium/Vit D. Monitor LFTs weekly while awaiting results/next steps.
6. Follow up in clinic in ~2 weeks (or sooner if results back) to review resistance testing and make definitive second-line treatment decision (Pralsetinib vs. Chemotherapy vs. Trial). Patient understands the plan and rationale.

Electronically Signed By:
Kevin Powell, MD
Thoracic Oncology
Date/Time: 10/28/2022 16:15

Patient: Smith, David **MRN:** SYN235 **Date of Birth:** 09/20/1952 (Age 70) **Gender:** Male