Comprehensive Cancer Institute – Thoracic Oncology
Consultation Note

REASON FOR CONSULTATION: Evaluation for management of Stage IV NTRK Fusion-Positive Lung Adenocarcinoma with acquired resistance after Entrectinib therapy. Requesting second opinion on further treatment options.

Patient: Plant, Robert Anthony (ID SYN055)
DOB: 02/07/1951
Date of Consultation: August 7, 2022
Consulting Physician: Dr. Vivian Wells, MD
Referring Physician: Dr. Stephen Jones (Community Oncology)

HISTORY OF PRESENT ILLNESS (Per records & patient):
Mr. Plant, a 72-year-old male, was diagnosed with Stage IV Lung Adenocarcinoma in December 2020 after presenting with persistent severe low back pain and sciatica. Staging PET/CT revealed a subtle LLL nodule (1cm) and extensive, intensely FDG-avid osseous metastases involving the lumbar spine (with L5 compression fracture), pelvis, sacrum, and proximal femora. Brain MRI negative. CT-guided biopsy of an L5 vertebral lesion confirmed metastatic adenocarcinoma.

- **Molecular Testing (NGS on bone biopsy):** Identified a **LMNA-NTRK1 fusion**. Other drivers negative. PD-L1 IHC (22C3): **TPS 0%, CPS <5, IC Score 0**.
- **First-Line Therapy:** Started Entrectinib (Rozlytrek) 600 mg PO Daily on January 4, 2021.
- **Response & Tolerability:** Experienced dramatic clinical improvement within weeks; back pain resolved completely, off opioids within 2 months. Radiographically achieved a significant partial response with sclerosis/decreased FDG avidity of bone lesions. Tolerated Entrectinib reasonably well, primary side effects included Grade 1 cognitive disturbance ("fogginess" - stable), Grade 1 weight gain (~10 lbs), Grade 1 dizziness (intermittent), and Grade 1 fatigue. Maintained excellent QOL and ECOG PS 0-1.
- **Acquired Resistance / Progression (July 2022):** Patient noted gradual return of low back pain over the preceding 6-8 weeks, initially mild but now requiring regular NSAIDs and occasional Tramadol. Surveillance PET/CT performed July 15, 2022, compared to Jan 2022 scan:
    - *Findings:* Clear evidence of disease progression. Increased FDG-avidity and apparent lytic changes within previously treated osseous metastases in the lumbar spine and pelvis. Development of several **new** FDG-avid osseous lesions in the thoracic spine (T7, T9) and right acetabulum. LLL pulmonary nodule remains stable/indolent. No new non-osseous metastases.
    - *Impression:* Disease progression in bone compartment

Patient referred by Dr. Jones to discuss next steps. He remains in good overall condition (ECOG 1) despite returning pain (now 4-5/10), and is motivated for further treatment.

PAST MEDICAL HISTORY: Hypertension (on Hydrochlorothiazide), Gout (on Allopurinol), Cataract surgery OU. Former Smoker (25 pack-years, quit 30+ yrs ago).

CURRENT MEDICATIONS:

- Entrectinib 600 mg PO Daily (*To be discontinued*)
- Hydrochlorothiazide 25 mg PO Daily
- Allopurinol 300 mg PO Daily
- Calcium/Vitamin D Supplement
- Naproxen 500 mg PO BID PRN pain
- Tramadol 50 mg PO Q6H PRN pain (using 1-2 doses/day recently)

REVIEW OF SYSTEMS: Positive for low back/R hip pain. Mild cognitive "fogginess". Mild fatigue. Negative for pulm/GI/neuro symptoms otherwise.

OBJECTIVE:

- Vitals: Stable. ECOG 1.
- Exam: Alert, pleasant male. Mild tenderness L-spine & R hip palpation. Neuro exam non-focal. Remainder normal.

ASSESSMENT:

1. **Stage IV NTRK Fusion-Positive Lung Adenocarcinoma:** Confirmed acquired resistance and disease progression (primarily bone) after effective first-line therapy with Entrectinib. Patient remains suitable for further systemic therapy (ECOG 1).
2. **Malignant Bone Pain:** Recurrent symptom requiring analgesics. May benefit from palliative radiation in addition to systemic therapy switch.
3. **Entrectinib Side Effects:** Mild cognitive effects, weight gain, fatigue likely attributable to drug, should improve upon discontinuation.

DISCUSSION & RECOMMENDATIONS:
Discussed the mechanism of acquired resistance to TRK inhibitors. While repeat biopsy/ctDNA could potentially identify specific resistance mutations (e.g., solvent front mutations) that might guide towards next-gen TRK inhibitors (like Selitrectinib/Repotrectinib, often in clinical trials), the standard approach and most readily available option after progression on a first-gen TRK inhibitor is typically chemotherapy.

Options Considered:

1. **Platinum-Doublet Chemotherapy:** Standard of care second-line treatment for most NSCLC after targeted therapy failure. Given no prior chemo exposure and good PS, **Carboplatin (AUC 5) + Pemetrexed (500 mg/m2) IV q3 weeks** is the preferred regimen for adenocarcinoma histology.
2. **Clinical Trial:** Enrollment in a trial investigating next-generation TRK inhibitors or other novel agents would be ideal if available and patient eligible/interested. (Quick search shows limited local options currently for post-TRK progression).

3. **Continue Entrectinib beyond progression:** Not generally recommended given clear radiographic and symptomatic progression.

Patient Preferences: After discussing rationale, schedule, potential benefits and side effects, Mr. Plant wishes to proceed with standard second-line chemotherapy (Carbo/Pem). He understands this is palliative in intent.

Recommendations to Dr. Jones / Plan:

1. **Discontinue Entrectinib.**
2. Initiate **Carboplatin (AUC 5) + Pemetrexed (500 mg/m2) IV q3 weeks**.
    - Start Folic Acid 1mg daily; B12 injection prior to C1D1.
    - Standard chemo pre-meds.
    - Monitor CBC, CMP prior to each cycle.
    - Restaging scans after 2-4 cycles.
3. **Pain Management:**
    - Continue current analgesics (Naproxen, Tramadol PRN). Reassess frequently after starting chemo.
    - **Radiation Oncology Consultation:** Strongly recommend consult for consideration of palliative radiation therapy to symptomatic lumbar spine / right acetabulum for better pain control. Referral placed from our center.
    - **Bone Health:** Initiate Denosumab 120 mg SC monthly after dental clearance (referral placed). Continue Ca/Vit D.
4. Expect improvement in cognitive fogginess/fatigue after stopping Entrectinib, though chemo will likely cause its own fatigue.
5. Happy to continue co-management or provide further input as needed. Thank you for the referral.

_____ M.D.
Vivian Wells, MD (Electronically Signed)
Medical Oncology