Metropolis Comprehensive Cancer Center – Thoracic Oncology Clinic

PATIENT: Richards, Leonard Michael
PATIENT ID: SYN181
DATE OF BIRTH: October 1, 1962

DATE OF ENCOUNTER: November 10, 2023
PROVIDER: Evelyn Reed, MD, PhD (Medical Oncology)

REASON FOR VISIT: Urgent follow-up to discuss recent surveillance imaging confirming disease progression on first-line Osimertinib therapy for Stage IV EGFR L858R-mutated Lung Adenocarcinoma. Evaluate symptoms, discuss potential resistance mechanisms, and establish plan for second-line treatment.

HISTORY OF PRESENT ILLNESS:
Mr. Richards is a 63-year-old gentleman diagnosed with Stage IV Lung Adenocarcinoma on May 27, 2022. His initial presentation was characterized by persistent, severe headaches and right hip pain. Staging workup revealed multiple enhancing brain metastases (largest 1.8 cm in L frontal lobe with significant edema), extensive osseous metastases involving the thoracic spine, pelvis, and proximal femora (most prominent R femur), and bilateral nodules on adrenal glands. A primary lung lesion (2.1 cm RUL nodule) was also identified.

- **Initial Pathology (CT-Guided R Femur Biopsy, 06/02/2022):** Metastatic Adenocarcinoma.
    - **Histology:** Moderately differentiated adenocarcinoma with a predominant **acinar growth pattern**, forming well-defined glands. Focal areas showed micropapillary features. Tumor cells exhibited moderate nuclear atypia and prominent nucleoli. Mitotic activity was noted. Minimal stromal desmoplasia.
    - **Immunohistochemistry (IHC):** Tumor cells strongly positive for TTF-1 and Napsin-A; Positive for Cytokeratin 7 (CK7); Negative for P40, CK5/6, GATA-3, confirming lung primary origin.
- **Molecular Profiling (NGS via FoundationOne CDx on bone biopsy tissue, report 06/10/2022):** Identified an **EGFR L858R point mutation** in exon 21. No co-occurring targetable alterations detected (ALK/ROS1/BRAF/MET/RET/NTRK negative). KRAS wild-type. TMB Low (4 mut/Mb).
- **PD-L1 IHC (22C3): TPS 0%, CPS <5, IC Score 0**.

Initial Treatment Course:

- **CNS Management:** Underwent Stereotactic Radiosurgery (SRS) to 5 targetable brain lesions (June 12-14, 2022). Started on Levetiracetam prophylaxis and Dexamethasone taper (completed July 2022).
- **Systemic Therapy:** Initiated first-line **Osimertinib 80 mg PO once daily starting June 18, 2022.**
- **Response & Tolerability:** Experienced excellent clinical response with resolution of headaches within days and significant improvement in hip pain over weeks (discontinued opioids). Radiographically achieved a deep partial response systemically (adrenals

resolved, primary shrank to <1cm, bone lesions stabilized/sclerotic) and complete response intracranially post-SRS on follow-up MRIs. Tolerated Osimertinib well overall, primary side effects being Grade 1 dry skin and Grade 1 diarrhea (managed PRN Loperamide). Maintained ECOG PS 0-1.

Disease Progression: Patient remained stable on Osimertinib until recent surveillance scans performed November 10, 2023 due to subtle increase in fatigue and return of mild R hip ache.

- **Recent Imaging (CT C/A/P + Bone Scan + Brain MRI, Nov 10, 2023):** Compared to July 2023 studies.
    - *CT C/A/P:* Subtle increase in size of residual RUL primary (now 1.1 cm vs 0.8 cm). Re-emergence of small bilateral adrenal nodules (<1 cm). Stable appearance of liver/other viscera.
    - *Bone Scan:* Increased tracer uptake in previously known R proximal femur lesion corresponding to patient's pain. New focal uptake in L 7th rib. Other lesions stable.
    - *Brain MRI:* Stable post-SRS changes. No new or recurrent intracranial metastases.
- **Impression:** Systemic disease progression, primarily involving bone and adrenals. CNS disease remains controlled.

SUBJECTIVE (Today): Patient reviewed scan results. Reports mild R hip ache (3/10), managed with occasional Acetaminophen. Notes mild persistent fatigue but otherwise feels well. No cough, SOB, headache, neuro sx. ECOG PS 1. Understands need to change therapy.

PAST MEDICAL HISTORY: Hypertension (on Losartan/HCTZ), Hyperlipidemia (on Rosuvastatin), Osteoarthritis (hands). Former Smoker (30 pack-years, quit 15 yrs ago).

CURRENT MEDICATIONS: Osimertinib 80mg daily (to be stopped), Losartan/HCTZ 100/25mg daily, Rosuvastatin 10mg daily, Levetiracetam 500mg BID, Calcium/Vit D, Acetaminophen PRN.

REVIEW OF SYSTEMS: Mild fatigue, mild R hip ache. Negative otherwise.

OBJECTIVE: Vitals stable. ECOG 1. Exam: Mild tenderness R greater trochanter. Neuro non-focal. Lungs clear. Labs (CBC, CMP, Mg) WNL.

ASSESSMENT:

1. **Stage IV EGFR L858R Lung Adenocarcinoma:** Confirmed systemic disease progression (bone, adrenals) consistent with acquired resistance to Osimertinib. CNS disease remains controlled. Patient maintains good PS (ECOG 1).
2. **Mild Symptom Burden:** R hip pain and mild fatigue related to progression.

PLAN:

1. **Discontinue Osimertinib:** Effective today.

2. **Acquired Resistance Assessment:** Sent **plasma ctDNA analysis (Guardant360)** today. Discussed potential resistance mechanisms (e.g., C797S mutation, MET amplification, transformation to SCLC – less common with L858R) and possibility ctDNA may be uninformative. Results typically take ~7-10 days.
3. **Second-Line Therapy:** Standard of care post-Osimertinib (without known targetable resistance) is platinum-doublet chemotherapy.
    - **Recommended Regimen: Carboplatin (AUC 5) + Pemetrexed (500 mg/m2) IV q3 weeks.** Rationale: Effective in EGFR+ post-TKI setting (IMpower150 subgroup, other data), adenocarcinoma histology preference, manageable toxicity profile in fit patient. Discussed addition of Bevacizumab (per Impower150) but decided against initially due to lack of specific indication (no major hemoptysis risk) and added toxicity/logistics. Patient agreeable to Carbo/Pem.
    - **Initiation:** Target C1D1 within 1-2 weeks, pending insurance authorization. Start **Folic Acid 1mg daily now.** Schedule B12 injection with C1D1. Provide anti-emetic Rxs (Ondansetron, Prochlorperazine). Schedule chemo education.
4. **Bone Metastasis Management:**
    - **Palliative RT:** Offer Rad Onc consult for palliative radiation to symptomatic R hip/femur if pain persists or worsens despite starting chemo. Patient wishes to defer RT consult for now, see if chemo helps pain first.
    - **Bone Modifying Agent:** Start **Denosumab 120 mg SC monthly** (preferred over zoledronic acid given CrCl borderline). Referral placed for mandatory dental clearance prior to first dose. Continue Ca/Vit D.
5. **Continue Levetiracetam:** Given history of brain mets, continue seizure prophylaxis for now, re-evaluate need with Neurology long-term.
6. **Monitoring:** Labs (CBC, CMP) prior to each chemo cycle. Restaging CT C/A/P after 2-4 cycles. Follow up on ctDNA results. Continue Brain MRI surveillance q3-4 months initially after starting chemo.
7. **Follow-up:** Return for chemo education and C1D1 infusion as scheduled. Call with ctDNA results.

_____ M.D., PhD.
Evelyn Reed, MD, PhD (Electronically Signed)