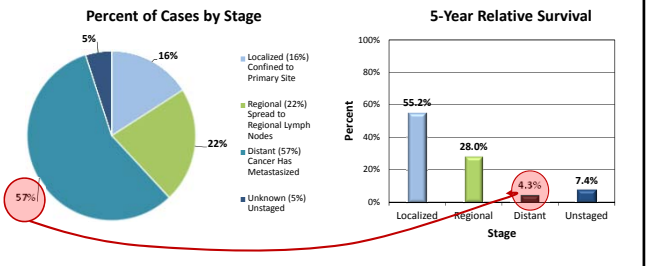
Update

- This activity was recorded on March 29, 2017 during the HOPA Annual Meeting.
- On September 28, 2017, the National Comprehensive Cancer Network updated its NSCLC Clinical Practice Guidelines to include the use of osimertinib as a 1st-line treatment option for patients with locally-advanced or metastatic *EGFR* mutation-positive NSCLC. Subsequently, on October 9, 2017, the FDA granted Breakthrough Therapy Designation for osimertinib in the 1st-line treatment of patients with *EGFR*-positive NSCLC.

Clinical Update on EGFR-Mutated NSCLC

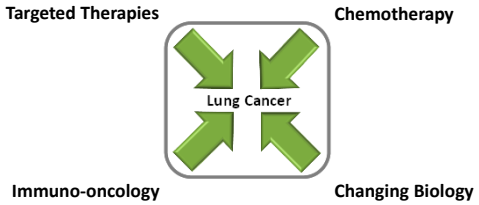
Val R. Adams, PharmD, FCCP, BCOP
Associate Professor of Pharmacy Practice and Science
Program Director, PGY2 Specialty Residency Hematology/Oncology
University of Kentucky College of Pharmacy
Lexington, KY

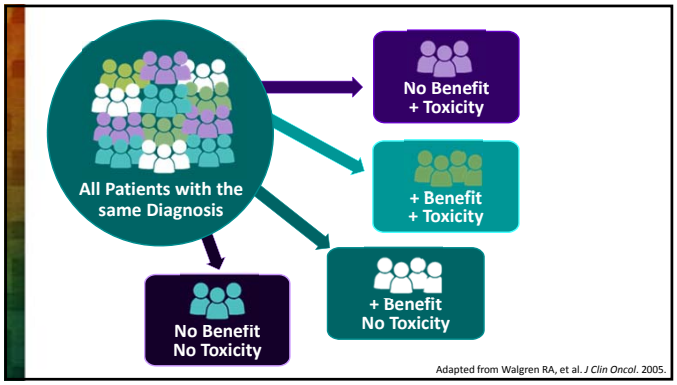
Lung Cancer

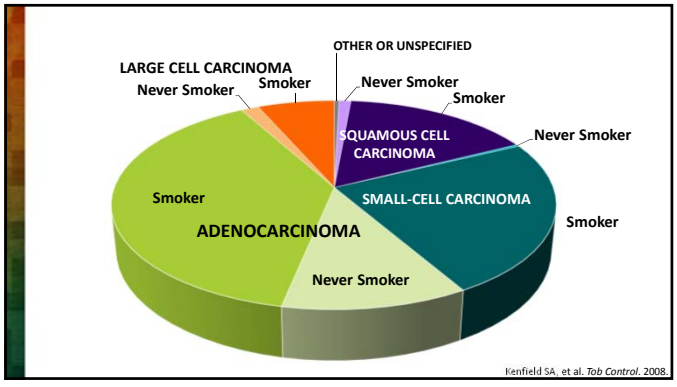


www.seer.cancer.gov/statfacts/html/lungb.html.

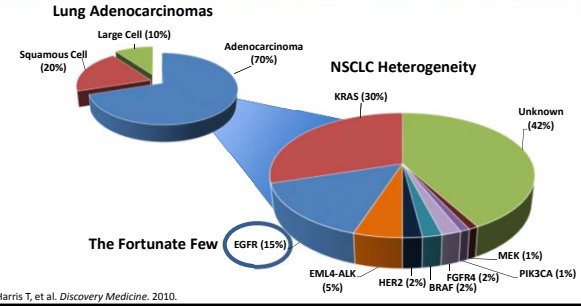
Merging Pieces







Targetable Mutations



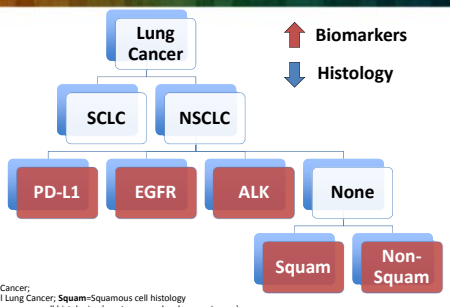
Harris T, et al. *Discovery Medicine*. 2010.

Evolving Biology

- Adenocarcinoma
- Percent of Lung Cancer from non-smokers
- Identified EGFR or ALK driven tumors
  - Adenocarcinoma
  - Non-smokers
- Treatments for EGFR and ALK

Meza R, et al. *PLoS One*. 2015; Köhler J. *Frontiers in Medicine*. 2017.

First-Line Treatment for Advanced Disease



SCLC=Small Cell Lung Cancer;
NSCLC=Non-Small Cell Lung Cancer; **Squam**=Squamous cell histology
Non-Squam=All non-squamous cell histologies (most commonly adenocarcinoma)

Patient Case

- SJ is a 61 yo WF who presents with NSCLC
- HPI: After failing antibiotics a CXR revealed a left lower lobe mass – FNA confirmed adenocarcinoma of the lung
- PMH: N/A
- FH/SH: Married w/ two sons 28 and 34 (none smoker)
- Drug History: NKDA
- PE: Findings consistent with lung cancer – otherwise WNL (PS 0-1)
- Labs: Hepatic, renal, and chemistry levels WNL
- Radiology: Multiple lesions in the liver – stage IV
- Genetics: KRAS – WT, EGFR exon 19 deletion, no ALK rearrangement

What treatment would you recommend?

A. None

B. Cisplatin – gemcitabine

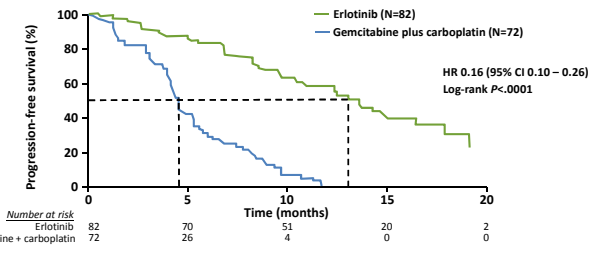
C. Carboplatin – paclitaxel – bevacizumab

D. Erlotinib

E. Crizotinib

OPTIMAL: First-Line Erlotinib is Associated with Longer PFS vs. G/C in EGFR Mutant NSCLC

OPTIMAL = Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive NSCLC



G/C = Gemcitabine/Carboplatin

Zhou C, et al. *Lancet Oncol.* 2011.

First-Line EGFR TKI

Study	Agents	N	Median PFS	Median OS
IPASS trial[1,2]	Gefitinib vs carbo-paclitaxel	261	9.5 mo vs 6.3 mo	21.6 mo vs 21.9 mo
EURTAC[3]	Erlotinib vs platinum doublet	173	9.7 mo vs 5.2 mo	19.3 mo vs 19.5 mo
LUX-Lung 3[4,5]	Afatinib vs cisplatin-pem	345	11.1 mo vs 6.9 mo	28.2 mo vs 28.2 mo

- Better than chemo first line based on PFS, OS roughly equivalent likely due to cross-over
- Survival curves do not plateau – Resistance develops during treatment

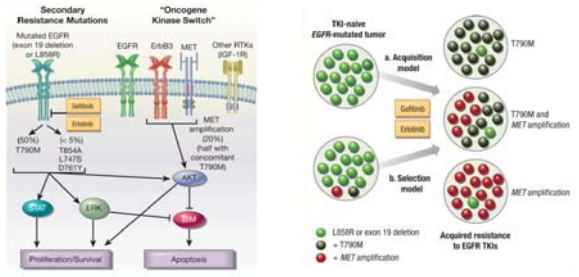
[1]Fukuorka M, et al. *J Clin Oncol*. 2011; [2]Wu YL, et al. *Lung Cancer*. 2017; [3]Rosell R, et al. *Lancet Oncol*. 2012; [4]Sequist LV, et al. *J Clin Oncol*. 2013; [5]Yang JC, et al. *Lancet Oncol*. 2015.

First-Line Gefitinib, Afatinib or Erlotinib?

	Afatinib	Erlotinib	Gefitinib
Improvement in PFS vs. chemo	4.2 months	4.5 months	3.5 months
Response rate	56%	58%	67%
Activity in T790 mutant clones	✓		
Common Grade 3 or 4 toxicity			
Rash	16%	13%	3%
Diarrhea	14%	5%	4%
Fatigue	1%	6%	< 1%
P-gp substrates	✓		
EGFR binding	Irreversible	Reversible	Reversible
Food effect (take on empty stomach)	Decrease AUC by 39%	Increase F from ~60% to ~100%	No change

AUC=Area under the curve; F=Bioavailability
FDA Prescribing Information; Sequist LV, et al. *J Clin Oncol*. 2013; Rossell R, et al. *Lancet Oncol*. 2012; Mok TS, et al. *N Engl J Med*. 2009.

Resistance to EGFR TKIs

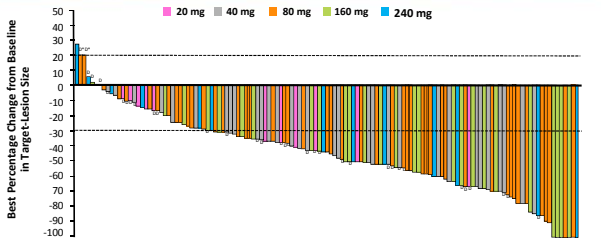


Nguyen KH, et al. *Clin Lung Cancer*. 2009.

SJ is our 62 yo WF who presents with recurrent metastatic adenocarcinoma of the lung after 12 months of erlotinib. PS=1, EGFR exon 19del and T790M, KRAS WT, PD-L1 -, CBC w/diff WNL, Chem 23 WNL except AST 78 and ALT 93. What treatment would you recommend?

A. Crizotinib
B. Gefitinib
C. Pembrolizumab
D. Osimertinib
E. Carboplatin – paclitaxel – bevacizumab

Osimertinib Efficacy



- EGFR T790M detected in 62% of patients, negative in 28%, unknown in 10%
- Overall Response Rate=51%; **Median PFS=9.6 months**

Jänne PA, et al. *N Engl J Med*. 2015.

Osimertinib

- FDA accelerated approval based on 2 single arm open label trials
- NSCLC patients with an EGFR mutation (T790M)
- EGFR testing was performed with the FDA approved companion diagnostic EGFR mutation test
- Dose determined to be 80 mg PO daily

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208065Orig1s000TOC.cfm.

Tissue for Genetic Testing

- Since this an acquired mutation – it requires repeat T790M analysis

EGFR Mutation Test	
Exon 19 deletion	
Sensitivity	82% (23/28)
Specificity	97% (30/31)
L858R	
Sensitivity	87% (20/23)
Specificity	97% (35/36)
T790M	
Sensitivity	73% (30/41)
Specificity	67% (16/24)

Plasma accuracy based on clinical trial samples (Tissue served as gold standard).
FDA approved EGFR mutation test v2 (CE-IVD) utilizes plasma to test for EGFR mutations.

http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120019S007c.pdf; Thress KS, et al. *Lung Cancer*. 2015.

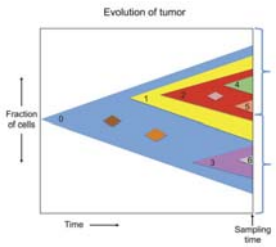
Sensitivity and Specificity

Tissue Biopsy

Plasma ctDNA	Mutation +	Mutation -
Mutation +	True Positive (TP)	False Positive (FP)
Mutation -	False Negative (FN)	True Negative (TN)

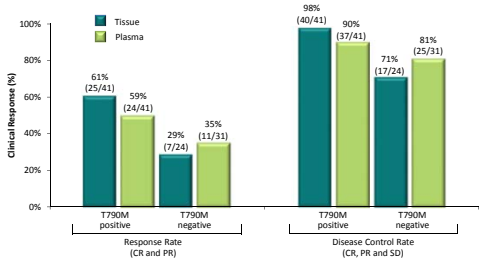
Sensitivity = TP/(TP + FN)

Specificity = TN/(TN + FP)



Mroz EA, Rocco JW. *Cancer*. 2017.

Clinical Response



CR=clinical response; PR=partial response; SD=stable disease

Thress KS, et al. *Lung Cancer*. 2015.

Comparison to Chemotherapy - AURA3

- Stratification variables
  - Asian vs. non-Asian

Eligibility:
- **Progression on 1st line EGFR TKI**
- **T790M mutation**
- **Stable CNS metastases w/o steroids**

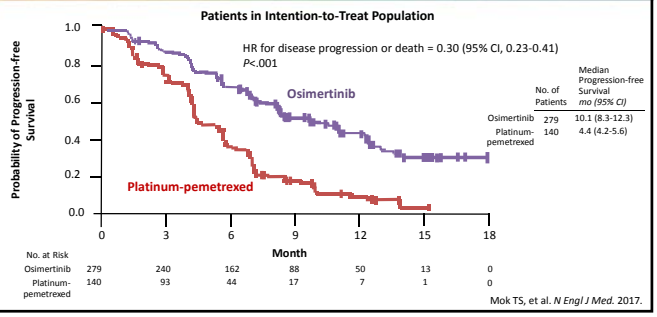
Osimertinib 80 mg PO daily N=279

Cisplatin or carboplatin +pemetrexed Repeat every 3 weeks up to 6 cycles (maintenance pemetrexed allowed) N=140

Primary Endpoint: PFS
Secondary Endpoints include: ORR, DoR, OS, Safety

Mok TS, et al. *N Engl J Med.* 2017.

Osimertinib vs. Chemotherapy – AURA3



Mok TS, et al. *N Engl J Med.* 2017.

Osimertinib and CNS Metastases Data – AURA3

CNS Efficacy by BICR in Patients with Measurable CNS Lesions at Baseline Brain Scan in AURA3

Efficacy Parameter	Osimertinib (N=30)	Chemotherapy (N=16)
CNS Objective Response Rate [a,b]		
CNS Objective Response Rate	57%	25%
95% CI	(37%, 75%)	(7%, 52%)
Complete Response	7%	0%
Partial Response	50%	25%
CNS Duration of Response[c]		
Median Duration of Response, Months (Range)	NR, (1.4, 12.5)	5.7 (1.4, 5.7)

BICR=Blinded Independent Central Review; NR=Not Reached
[a]According to RECIST v1.1; [b]Based on confirmed response; [c]Based on patients with response only; DoR defined as the time from the date of first documented response (complete response or partial response) until progression or death event

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208065s006lbl.pdf;
https://www.fda.gov/Drugs/InformationOnDrugs/%20ApprovedDrugs/ucm549683.htm.

First-Line Osimertinib?

- Pooled data from two Phase I expansion cohort studies with 80 or 160 mg PO daily look promising
- N=60
- Median PFS=19.3 mo (95% CI 13.7 – NC)
- Confirmed ORR=77% (95% CI 64 – 87)
- Disease control rate=97% (95% CI 88.5 – 99.6)
- Dose reduction 80 mg=10%; 160 mg=47%
- Most common toxicity=diarrhea, stomatitis, and paronychia (at 80 mg, no grade 3 or 4)

Ramalingam S, et al. European Lung Cancer Conference. Abstract LBA1_PR. 2016.

Adverse Event	Osimertinib (N=279)		Platinum-Pemetrexed (N=136)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	Number (percent)			
Diarrhea	113 (41)	3 (1)	15 (11)	2 (1)
Rash	94 (34)	2 (1)	8 (6)	0
Dry skin	65 (23)	0	6 (4)	0
Paronychia	61 (22)	0	2 (1)	0
Thrombocytopenia	28 (10)	1 (<1)	27 (20)	10 (7)
Nasopharyngitis	28 (10)	0	7 (5)	0
Headache	28 (10)	0	15 (11)	0
Dyspnea	24 (9)	3 (1)	18 (13)	0
Neutropenia	22 (8)	4 (1)	31 (23)	16 (12)
Leukopenia	22 (8)	0	20 (15)	5 (4)
Anemia	21 (8)	2 (1)	41 (30)	16 (12)
Asthenia	20 (7)	3 (1)	20 (15)	6 (4)
Pyrexia	18 (6)	0	14 (10)	0
ALT elevation	18 (6)	3 (1)	15 (11)	1 (1)

Mok TS, et al. *N Engl J Med.* 2017.

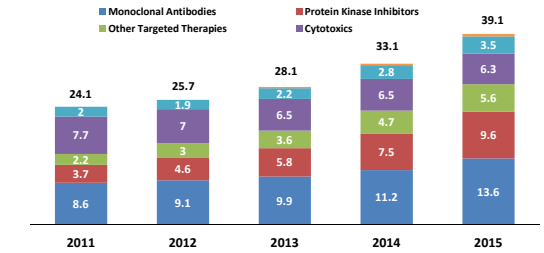
Individualized NSCLC Therapy Has Arrived, Now What?

Current Role and Future Opportunities for Oncology Pharmacy

Philip Schwieterman, PharmD, MHA
Pharmacy Director Oncology and Infusion Pharmacy
UK HealthCare and Markey Cancer Center
Lexington, KY

Cost and Utilization Trends

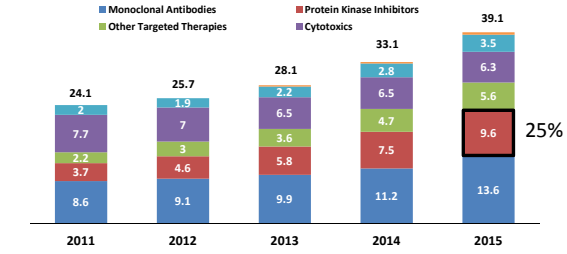
Spending on Oncology Medicines (US $ Bn)



www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/medicines-use-and-spending-in-the-us-a-review-of-2015-and-outlook-to-2020.

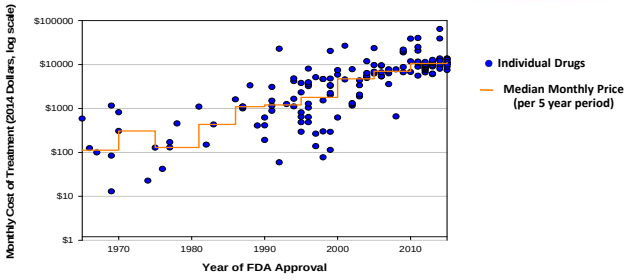
Cost and Utilization Trends

Spending on Oncology Medicines (US $ Bn)



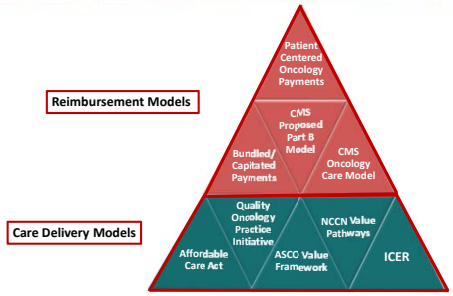
www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/medicines-use-and-spending-in-the-us-a-review-of-2015-and-outlook-to-2020.

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval (1965-2015)



Source: Peter B. Bach, MD, Memorial Sloan-Kettering Cancer Center.

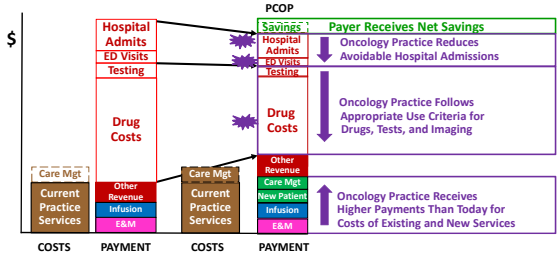
Aligning Cost and Care Delivery



http://www.asco.org/sites/www.asco.org/files/asco_patient-centered_oncology_payment_final_2.pdf

Costs and Savings in Oncology Care

Savings Offset Additional Payments Under Patient-Centered Oncology Payment (PCOP)



http://www.asco.org/sites/www.asco.org/files/asco_patient-centered_oncology_payment_final_2.pdf

The Cost of Poor Adherence

- Improve Care Coordination
- Enhance Patient Engagement and Education
- Utilize Counseling and Medication Management
- Expand Screening and Assessment
- Invest in HIT Infrastructure
- Employ Quality Measurement
- Establish Financial Incentives

http://www.nehi.net/bendthecurve/sup/documents/Medication_Adherence_Brief.pdf

A Factor of Poor Adherence

Chicago Tribune

Pharmacies miss half of dangerous drug combinations

Major pharmacy chains vow safety improvements

In response to the Tribune tests, some of the nation's largest pharmacy chains said they would take significant steps to improve patient safety.

http://www.chicagotribune.com/news/watchdog/druginteractions/ct-drug-interactions-pharmacy-met-20161214-story.html

Top 5 Health System Pharmacy Trends Outlined at ASHP

The Top Five Trends That Will Impact Health System Pharmacies in 2016

The Sleeping Giant: Health Systems Awaken to the Opportunities and Risks of Entering the Specialty Pharmacy Arena

Health Systems: Discovering Specialty Pharmacy

Jim Molz, RPh | October 12, 2015

Navigating financial assistance options for patients receiving specialty medications

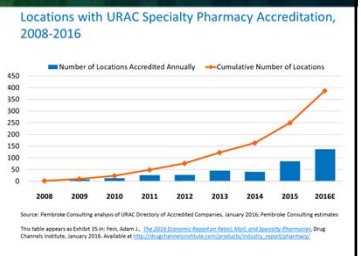
Health System Specialty Pharmacy

A briefing for health system executives

Executive Research Briefing | July 11, 2016

The Rise of Health System Specialty Pharmacy

- The Benefits
  - Integrates components of Accountable Care Organizations
  - Mitigates multiple redundancies
  - Shared health records
  - Support both Rx and Medical Coverage
  - Adherence rates higher*
  - Quicker access to therapy
  - Location, Location, Location



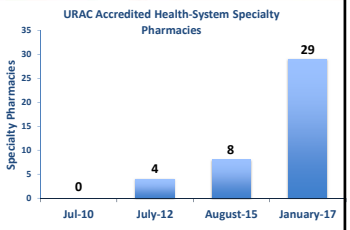
Source: Pembroke Consulting analysis of URAC Directory of Accredited Companies, January 2016; Pembroke Consulting estimates

This table appears as Exhibit 35 in: Fein, Adam J., *The 2016 Economic Report on Retail, Mail, and Specialty Pharmacies*, Drug Channels Institute, January 2016. Available at http://drugchannelsinstitute.com/products/industry_report/pharmacy/

*Hanson RL, et al. *Am J Health Syst Pharm.* 2014; https://accreditnet2.urac.org/UracPortal/directory/directorysearch; http://drugchannelsinstitute.com/products/industry_report/pharmacy/.

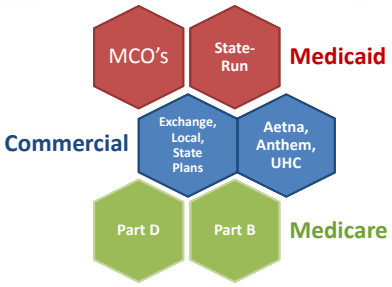
The Rise of Health System Specialty Pharmacy

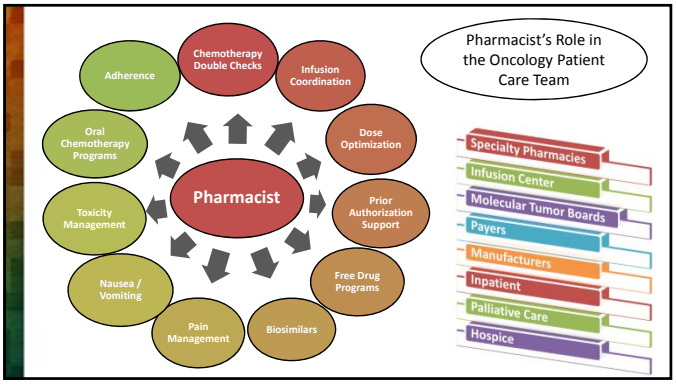
- The Benefits
  - Integrates components of Accountable Care Organizations
  - Mitigates multiple redundancies
  - Shared health records
  - Support both Rx and Medical Coverage
  - Adherence rates higher*
  - Quicker access to therapy
  - Location, Location, Location



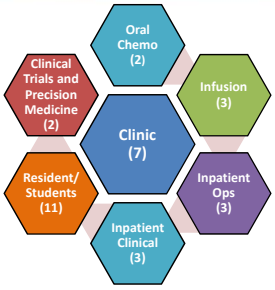
*Hanson RL, et al. *Am J Health Syst Pharm*. 2014; https://accreditnet2.urac.org/UracPortal/directory/directorysearch; http://drugchannelsinstitute.com/products/industry_report/pharmacy/.

Oral Chemotherapy Payers





Health System Daily Pharmacist Model



UK HealthCare
(Number of Pharmacists)

Aiming for Optimal Patient Outcomes

Case-based Treatment Strategies

Josiah D. Land, PharmD, BCOP
Clinical Pharmacy Specialist
Thoracic Medical Oncology Team
Memorial Sloan Kettering Cancer Center
New York, NY

Patient DD

- **May 2014**: 63 yo AAF with recent diagnosis of lung cancer presents to the thoracic oncology clinic for treatment options
- **HPI**:
  - **December 2013**: chest pain related to moving furniture—attributed to musculoskeletal in nature
  - **March 2014**: continued chest pain not relieved by prn naproxen→ further workup by PCP

Patient DD: Workup

- **CT chest**: 4.5 x 4.1 x 4.1 cm RUL mass encasing RUL bronchus and abutting distal trachea+ RUL/RML nodules
- **PET scan**: RUL hypermetabolic mass + multiple RUL satellite nodules + bony metastasis to sternum + pleural implant + FDG avid small pleural effusion
- **CT Head**: NED
- **RUL mass biopsy**
  - Primary lung adenocarcinoma: **CK7+/TTF-1+/Napsin A+/P63+/**CK20-
  - Molecular Pathology: **+EGFR exon 21 L858R substitution mutation**

Patient DD

- **PMH**: none
- **PSH**: lipoma removal
- **Allergies**: NKDA
- **SH**: never smoker, rare EtOH, married x 41 years, 2 adult children
- **FH**: father (alive) – prostate cancer; paternal grandmother (deceased) – head/neck cancer
- **Health Maintenance**
  - **2013**: GYN exam WNL
  - **2/2014**: mammogram WNL
- **Home Medications**
  - Naproxen 250 mg BID prn
  - Ibuprofen 400 mg PO Q4H prn

Patient DD

- **Diagnosis**: Stage IV EGFR mutant lung adenocarcinoma metastatic to bone and pleura
- **Treatment Decision(s)**

Treatment Decision: What would you do next?

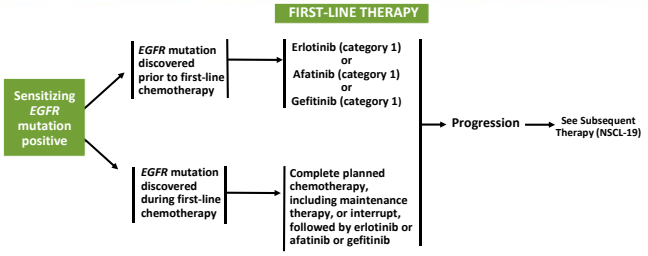
A. Platinum doublet + First line EGFR inhibitor

B. Platinum doublet alone

C. First line EGFR inhibitor alone

D. Platinum doublet until progression of disease followed by EGFR inhibitor

NCCN Guidelines Version 4.2017



Adapted from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

Patient DD: Treatment Course

- **6/12/14**: initiated **Erlotinib 150 mg PO daily**
- **7/28/14**: **partial response** in lung, pleura, bone
- **11/7/14**: **continued response** in lung, lymph nodes, pleura
- **2/2015 – 12/2016**: **stable disease**
- **12/2016**: CT CAP shows **POD** in RUL primary lesion, increased pleural disease, new osseous lytic mets in pelvis
- **Treatment Decision →**

Assess Adherence!

Treatment Decision: What would you do next?

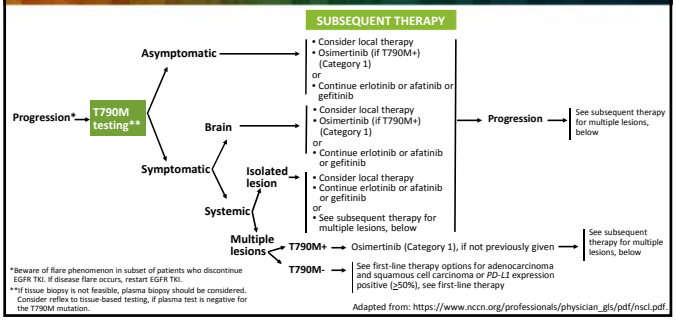
A. Platinum doublet (e.g. Carboplatin/Pemetrexed)

B. Cetuximab/Afatinib

C. Nivolumab monotherapy

D. Continue Erlotinib and send ctDNA testing for T790M resistance mutation

NCCN Guidelines Version 4.2017



Patient DD: Treatment Course

- **1/4/2017**: inpatient admission for sacral canal cord compression
  - Medically managed with supportive care/radiation oncology
  - ctDNA pending for T790M status prior to admission
- **1/14/2017**: ctDNA positive for EGFR T790M resistance mutation
- **Treatment Decision** → Osimertinib 80 mg once daily

What if the T790M by ctDNA was negative?

A. Continue erlotinib at the current dose

B. Consider tissue biopsy to confirm absence of T790M mutation

C. Initiate osimertinib regardless of T790M status

D. Plan for outpatient chemotherapy after discharge from hospital

Patient DD: Wrap Up

- **1/17/2017**: patient initiated Osimertinib 80 mg PO once daily
- **Patient counseling**:
  - Most common side effects: diarrhea, rash, nail changes, dry skin
  - Can be taken with or without food
  - Medication is restricted to a specialty pharmacy, patient and family must increase vigilance with regard to ongoing refills
  - Follow-up with thoracic medical oncology

Financial Toxicity?

Patient Perspective

Potential Financial Timeline

Date	Therapy(s)	Age	Insurance	Medication Therapy Out of Pocket Expenses
5/2014	Oncology referral and workup	63	Commercial Plan	Deductible, Premiums, Copays, Co-Insurance
6/2014	Erlotinib	63	Commercial Plan	Tier 4 ($250/mo)
3/2015	Erlotinib	64	Commercial Plan	Copay Card ($25/mo)
9/2015	Erlotinib	65	Medicare A, B, and D	Coverage Gap ($3,000) Catastrophic Coverage
1/2016	Erlotinib	66	Medicare A, B, and D	Foundation Support available ($4,000)
1/2017	Osimertinib	67	Medicare A, B, and D	New Plan Year Foundation Support?

https://www.medicare.gov/part-d/costs/coverage-gap/part-d-coverage-gap.html.