BCOP Clinical Sessions

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The BCOP Clinical Sessions are part of the professional development program for the recertification of board-certified oncology pharmacists, approved by the Board of Pharmacy Specialties and cosponsored by the American College of Clinical Pharmacy and the American Society of Health-System Pharmacists (ASHP).

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- Participants who pre-paid the post-test fee for the BCOP Clinical Sessions will have access to the posttest immediately following the session at www.accp.com/myaccount.
- Participants who paid the posttest fee in Las Vegas will receive access no later than December 20.

BCOP Clinical Sessions Posttest Cont.

- Reminders:
  - Post-tests must be submitted by March 1, 2017
  - Participants may only submit the posttest one time.

BCOP Clinical Sessions: Lung Cancer Therapy and Molecular Targets

Gary Jean, Pharm.D., BCOP
Assistant Professor
Texas Tech University Health Sciences Center School of Pharmacy
Clinical Coordinator, Hematology/Oncology
Clements University Hospital
UT Southwestern Medical Center
Dallas, Texas

Christine M. Walko, Pharm.D., BCOP, FCCP
Personalized Medicine Specialist
DeBartolo Family Personalized Medicine Institute
Moffitt Cancer Center,
Tampa, Florida

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Disclosures

- Christine M. Walko:
  - BMS- Honorarium for ICLIO Melanoma Subcommittee
  - Merck-Honorarium for ICLIO Melanoma Subcommittee

Objectives

- Review the common mutations present in Non-Small Cell Lung Cancer
- Review the history of targeted therapy in advanced Non-Small Cell Lung Cancer
- Discuss the common targeted treatment modalities in advanced Non-Small Cell Lung Cancer
- Identify the current barriers to targeted therapy in the management of advanced Non-Small Cell Lung Cancer

Objectives

- Discuss less common genetic alterations in NSCLC and their associated treatments and outcomes
- Explain the purpose and value of a molecular tumor board in terms of treatment recommendations
- Outline the support and process for obtaining off label genetic-guided therapy when clinical trials are not available
- Identify future challenges to the implementation of genetic-guided therapy into standard oncology clinical practice

Back to the Future: Advances in Lung Cancer Targeted Therapy

Gary Jean, Pharm.D., BCOP
Assistant Professor
Texas Tech University Health Sciences Center School of Pharmacy
Clinical Coordinator, Hematology/Oncology
Clements University Hospital
UT Southwestern Medical Center
Dallas, Texas

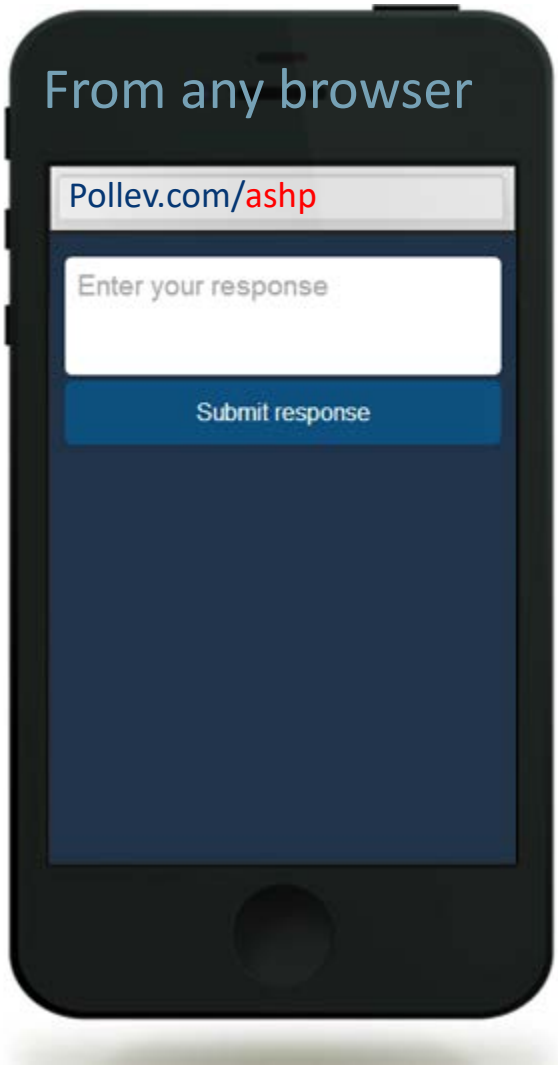
Patient Case

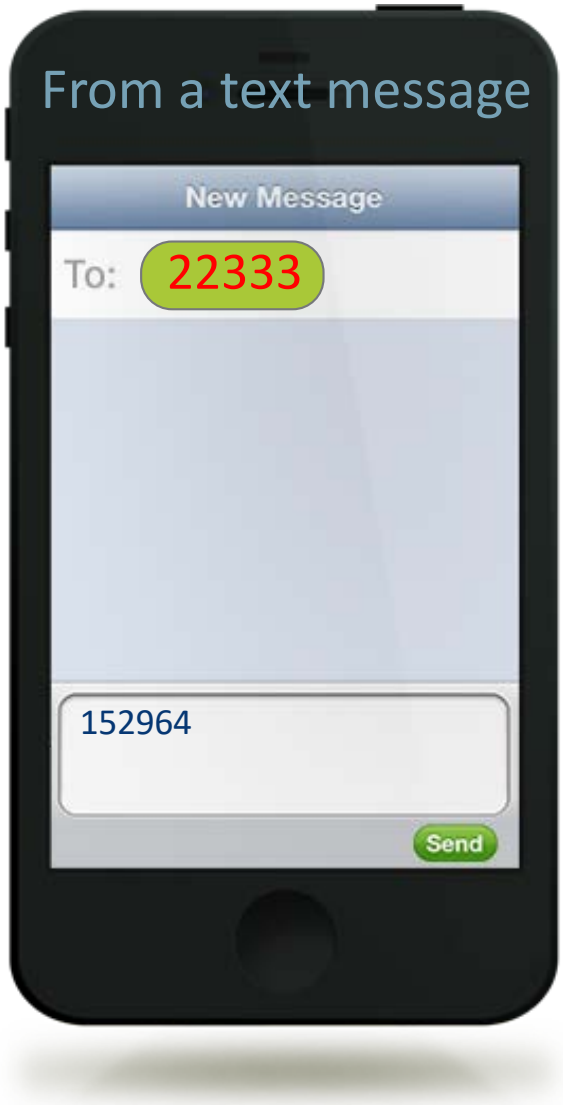
- JW is a 40 year old non smoking female recently diagnosed with metastatic adenocarcinoma non-small cell lung cancer.

- Her path is significant for an EGFR mutation with exon 19 deletion

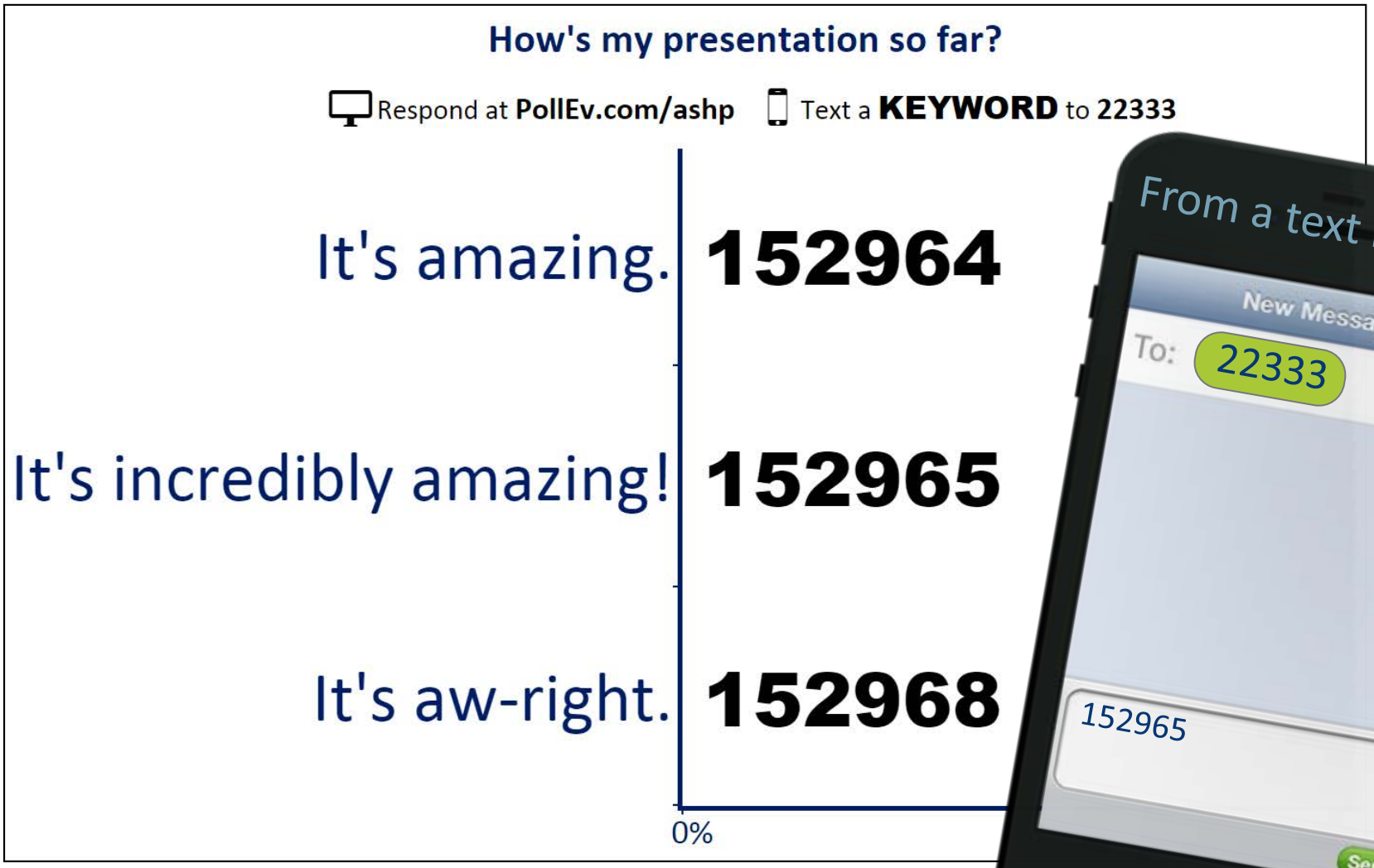
Time for a Poll

How to vote via the web or text messaging

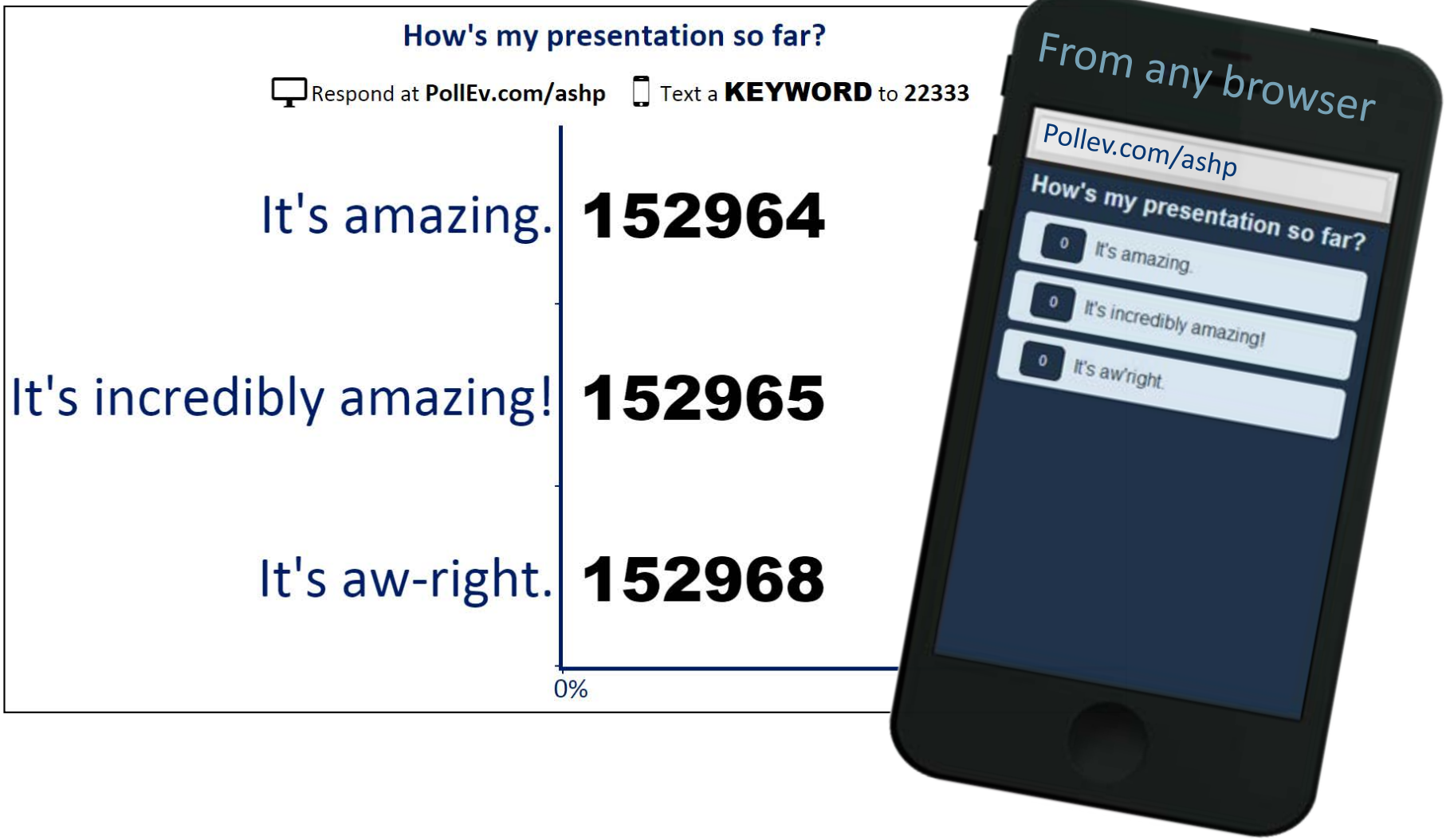




How to vote via text message



How to vote via the web



Patient Case: Question 1

- What is the most appropriate treatment for JW?
  - A Cisplatin + Pemetrexed
  - B Carboplatin + Paclitaxel + Bevacizumab
  - C Erolitnib
  - D Alectinib

Patient Case: Question 1

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1

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or

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Non-Small Cell Lung Cancer

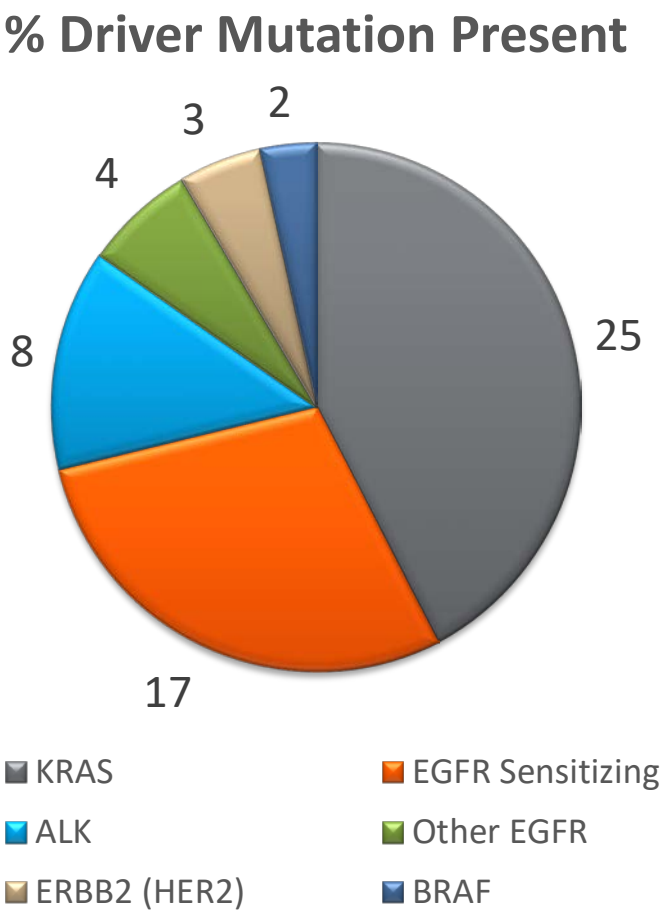
- New Cases: 224,390
  - 2nd most common among men and women
- Deaths: 158,080
  - Leading cause of cancer related death among men and women
- > 50% of patients present with metastatic disease
  - Treatment is histology driven
  - Starts with testing for driver mutations
    - Especially with adenocarcinoma

American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.4.2016 Accessed [July 22, 2016].

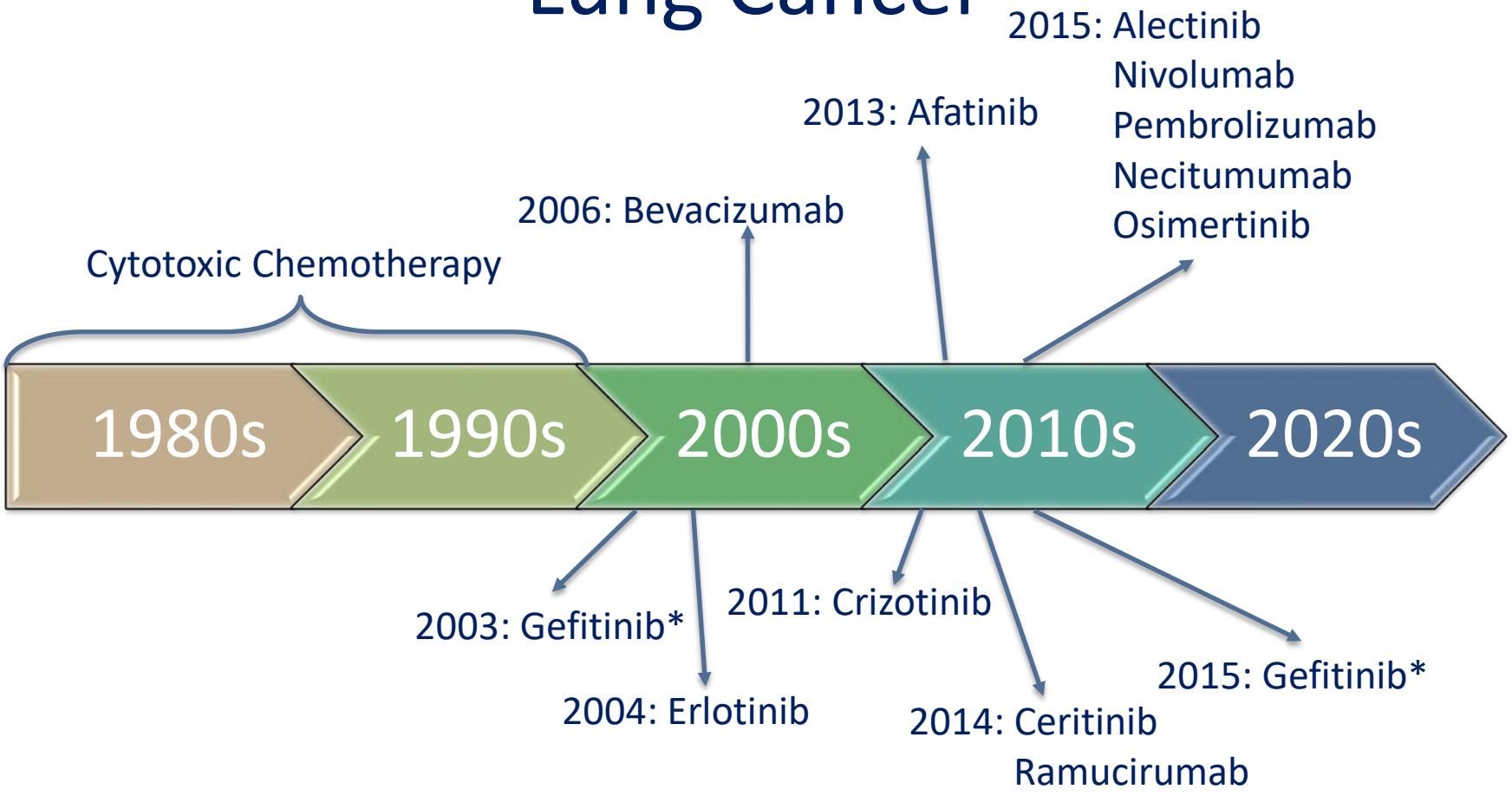
Driver Mutations

- 2009-2012 at 14 US sites
- 1007 metastatic adenocarcinoma lung cancer patients were tested for 10 oncogenic drivers
- An oncogenic driver was identified in 64% of patients
- Results were used to select a targeted therapy or clinical trial in 28%
  - Median survival was 3.5 years in patients with a mutation directed therapy compared to 2.4 years in those who didn't



Kris MG et al. JAMA. 2014;311:1998-2006.

Progression of Targeted Therapy in Lung Cancer



But First…

Where targeted therapy started

- Late 1990's-2000
  - Imatinib
    - —Originally approved in 2001
    - — Oral TKI that targets the fusion protein
    - —Game Changer → Replaced transplant based approach
      - Major Cytogenetic Response: 87.1%
      - Complete Cytogenetic Response: 76.2%
  - Trastuzumab
    - —Originally approved in 1998 in metastatic breast cancer

Afghani A, et al. Cancer J 2015;21:294-298
O'Brien SG, et al. N Engl J Med 2003;348:994-1004
Salmon DJ, et al. N Engl J Med 2001;344:783-92

2000's

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Gefitnib

- Originally approved in 2003
  - Accelerated approval on phase II data
  - 216 patients
    - 75% Adenocarcinoma
    - 2/3 Never smokers
    - 142 Evaluable patients
      - 15 partial responses ~ RR 10.6%
  - Marginal survival
- Limited Access in 2005
  - Based lack of efficacy demonstrated in follow up trials
- Fully approved for the first line treatment 2015
  - Median overall survival was 19.2 months in the Phase IV follow up

Cohen MH et al. Oncologist 2003;8:303-6
Fukuoka M, et al. J Clin Oncol 2003; 21:2237-46
Gefitinib. www.fda.gov Accessed July 25, 2016
Douillard JY, et al. Br J Cancer 2014;110:55-62

Erlotinb

- Got lucky…
  - Approved over best supportive care in 2004
    - —2 month survival benefit → No longer recommended
  - Added a switch maintenance indication in 2010
    - — 12.3 weeks vs 11.1 weeks → No longer recommended
  - Added First line treatment in EGFR mutation 2013 (exon 19 deletions, or exon 21 substitutions)
    - —PFS 13.1 vs 4.6 HR 0.16, 95% CI 0.10 – 0.26; p<0.0001

Erlotinib. www.fda.gov Accessed August 9, 2016.

Shepherd FA et al. *N Engl J Med.* 2005; 353:123-32.

Zhou C, et al. Lancet Oncol. 2011; 12:735-42

Non-Small Cell Lung Cancer. NCCN Guidelines V.4.2016. Accessed July 19, 2016

Bevacizumab

- A different target therapy
  - 2 month overall survival benefit when used as first line
  - Maintenance therapy
    - —Alone vs. combo (pemetrexed)

- Work horse

Sandler A et al. *N Engl J Med.* 2006; 355:2542-50.
Patel JD , et al. J Clin Oncol. 2013; 31:4349-57.
Barlesi F, et al. J Clin Oncol. 2013; 31:3004-11.

Then there's Cetuximab

- "Ground Breaking" – FLEX Trial
- Cetuximab plus Cisplatin/Vinorelbine
  - EGFR(+) – Expression… not mutation
  - Median OS: 11.3 vs. 10.1, HR 0.87 95% CI 0.762 – 0.996, p=0.044
  - PFS: 4.8 vs 4.4, HR 0.94 95% CI 0.825 – 1.077, p=0.39
- Targeting the receptor – Marginal benefit
  - Category 2B recommendation

Picker R, et al. Lancet 2009; 373: 1525-31

Non-Small Cell Lung Cancer. NCCN Guidelines V.4.2016. Accessed July 19, 2016

2010's

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Crizotinib/Ceritinib/Alectinib

- The ALK inhibitor boom
- Approved based on early clinical trials
  - Crizotinib RR in first line: ~ 60%
  - Ceritinib RR in crizotinib refractory patients: 56%
    - —20x more potent than Crizotinib
  - Alectinib RR in crizotinib refractory patients: 50%
- Limitation: Prevalence and Resistance
  - 5-10% of all NSCLC diagnoses
  - Duration of response ~12 months

Camidge DR, et al. Lancet Oncol. 2012;13:1011-9.
Shaw AT, et al. N Engl J Med. 2014;370:1189-97.
Ou SH, et al. J Clin Oncol. 2016;34:661-8.

Crizotinib

- Phase I data
- N=143(evaluable)
  - 60.8% Objective Response
    - —3 complete responses
    - —84 partial responses
  - Duration of Response: 49 weeks
  - PFS: 9.7 Months

Camidge DR, et al. Lancet Oncol. 2012;13:1011-9.

Ceritinib

- Phase I data → Second line
- N=130
  - 68% had received crizotinib in the past
- Overall Response Rate: 58%
  - 56% in crizotinib refractory
  - 62% in crizotinib naïve
- PFS: 7 months
  - 6.9 months in crizotinib refractory
  - 10.4 months in crizotinib naïve

Shaw AT, et al. N Engl J Med. 2014;370:1189-97.

Afatinib

- Another EGFR
- Afatinib vs. Cisplatin/Pemetrexed in EGFR Mut
  - 49.1% Exon 19 deletion; 39.6% Exon 21 substitution
  - PFS 11.9 vs 6.9 HR, 0.58; 95% CI, 0.43 to 0.78; p=.001

- Where do we go now?
  - Afatinib + Cetuximab?

Sequist LV, et al. J Clin Oncol. 2013; 31:3327-34

Non-Small Cell Lung Cancer. NCCN Guidelines V.4.2016. Accessed July 19, 2016

Ramucirumab

- REVEL
  - N=1253
  - Ramucirumab 10mg/kg and docetaxel 75 mg/m2 Q 21 days vs. placebo and docetaxel
  - Median OS: 10.5 vs 9.1 months (HR 0·86, 95% CI 0·75-0·98; p=0·023)
  - Median PFS: 4·5 months compared with 3·0 months for the control group (0·76, 0·68-0·86; p<0·0001).

- *Included patients with squamous cell histology

Garon EB, et al. *Lancet*. 2014;384:665-673

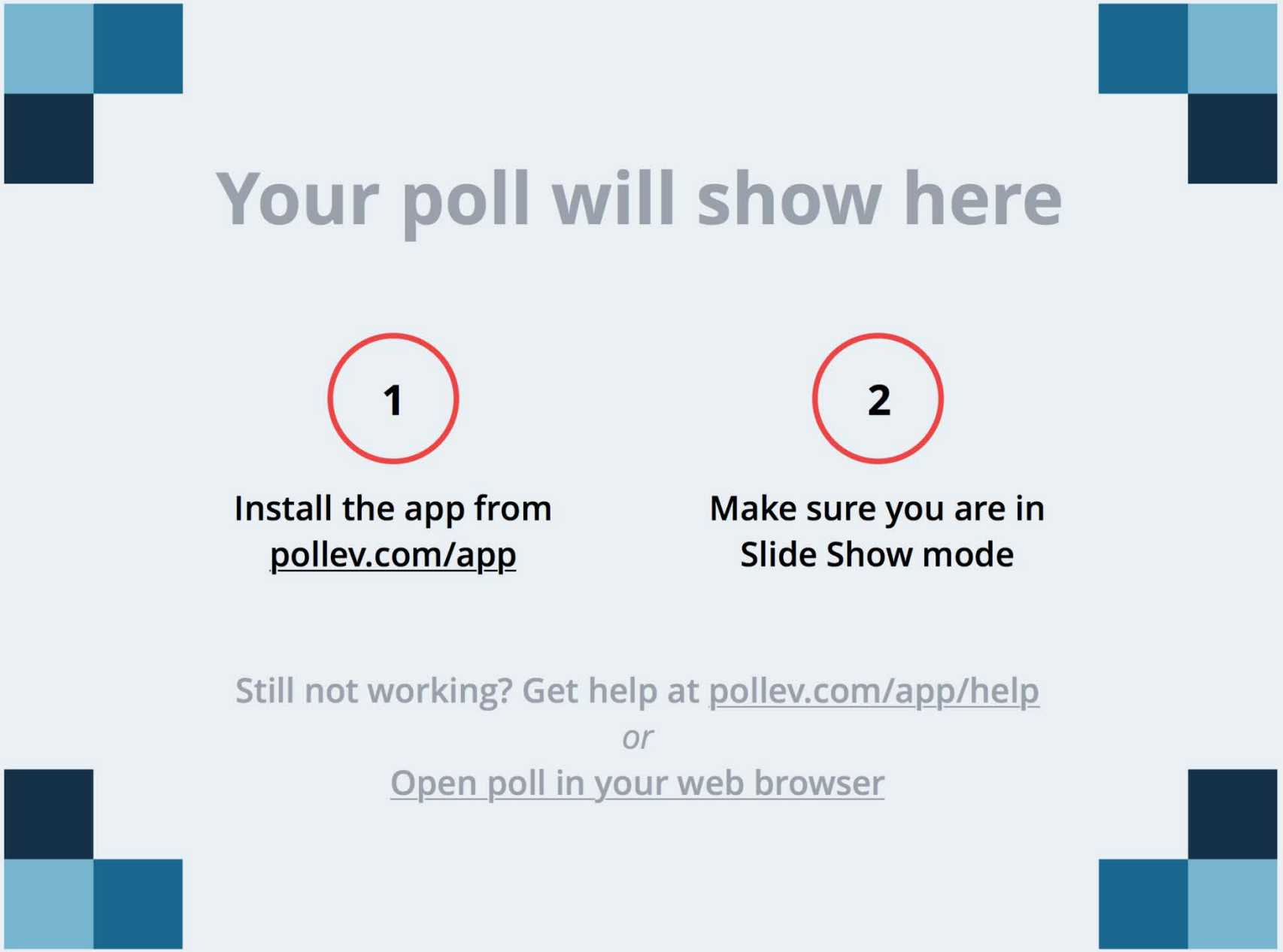
Patient Case

- JW presents to clinic for his 9 month follow
  - Staging scans reveal disease progression with new liver lesion and increased size in lung mass
  - Biopsy of new liver lesion reveals:
    - EGFR – T790M Mutation
- What is the next step in his treatment

Patient Case: Question 2

- What is the next step in JW treatment
  - A Cisplatin/Vinorelbine + Cetuximab
  - B Osimertinib
  - C Ceritnib
  - D Pembrolizumab

Patient Case: Question 2



T790M

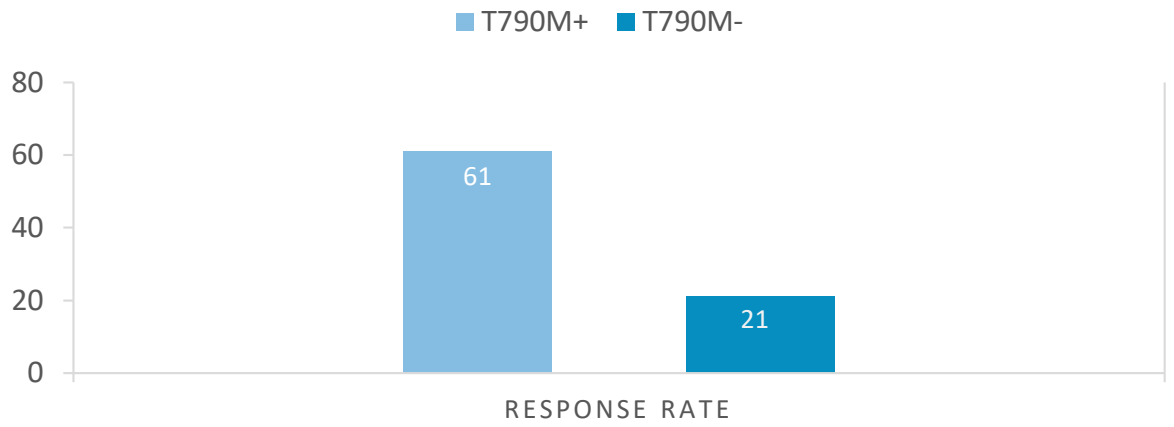
- Only present in 5% of all EGFR mutations
  - Increases the affinity of the kinase to ATP → Decreasing affinity to erlotinib/gefitinib
  - Most common resistance mechanism (50-60%)
    - —Can be present on diagnosis
    - —Or develop during treatment

- Was dreaded EGFR mutation until…

Inukai M, et al. Cancer Res. 2006;66:7854-8.
Black RC, et al. R I Med J. 2015;98:25-8.
Piotrowska Z, et al. Cancer J 2015;21: 371–377.

Osimertinib

- Rapid approval
- Potent irreversible inhibitor of EGFR TKI – T790M
  - N=253 patients → 138 confirmed T790M mutations



  - PFS 9.6months vs 2.8months

Janne PA, et al. N Engl J Med. 2015;372:1689-99.

Osimertinib

- Disease Control Rate: 84%
- 6 month response rate – 85%
  - Not fully mature at publication
- Lack of efficacy in non-T790M mutants

Janne PA, et al. N Engl J Med. 2015;372:1689-99.

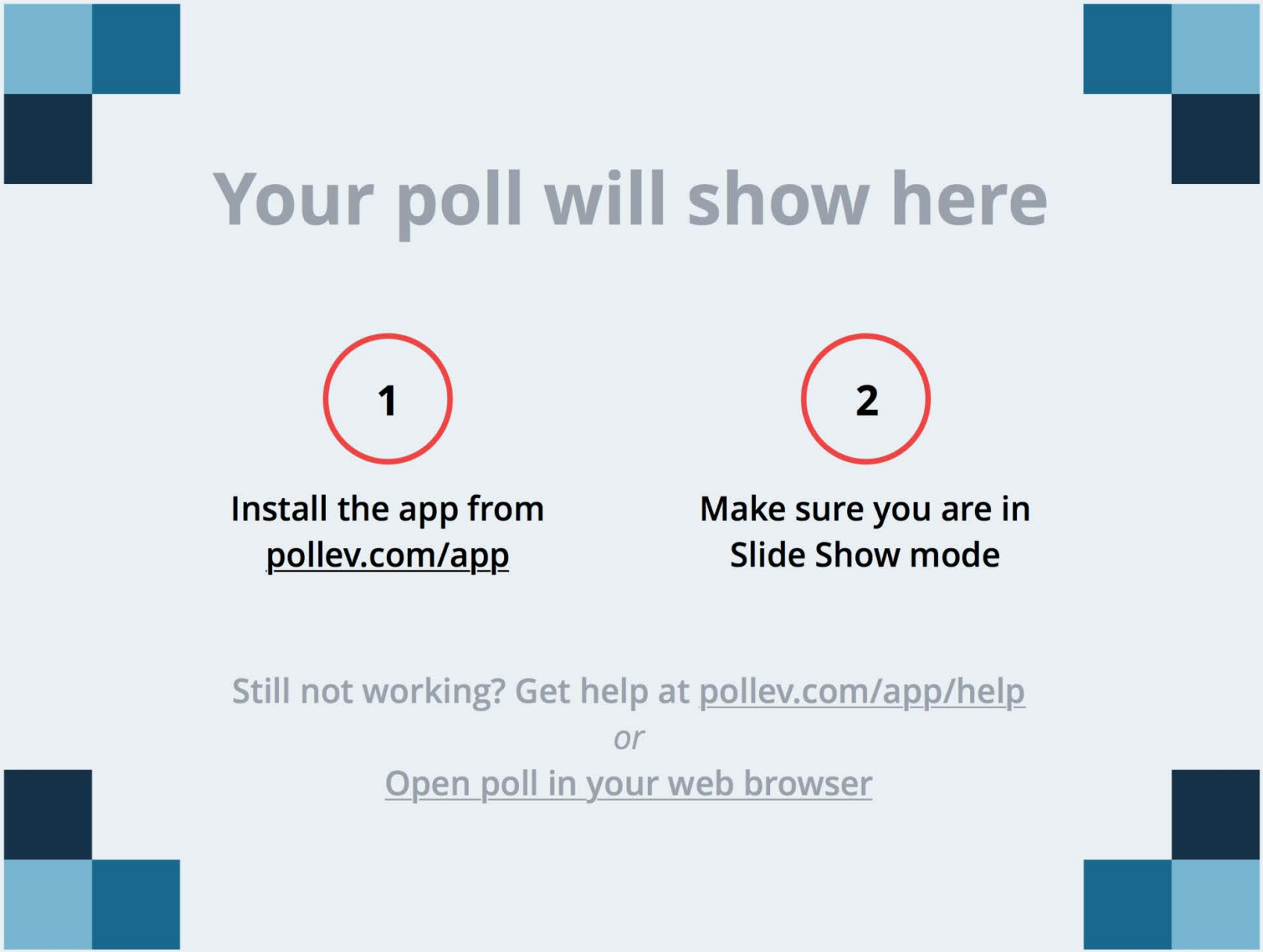
Patient Case

- JW presents to clinic for his 6 month follow up and staging scans reveal disease progression and new lesions on his liver.
- Path is sent of for further mutational analysis
- In the mean time JW want to pursue further treatment

Patient Case: Question 3

- Which of the following is the most appropriate treatment for JW
  - A Carboplatin+Paclitaxel
  - B Carboplatin+Pemetrexed+Bevacizumab
  - C Cisplatin+Vinorelbine+Cetuximab
  - D Nivolumab

Patient Case: Question 3



Nivolumab

- Rocky Start
  - Approved in March 2015 in squamous – only
  - Approved in October 2015 in non-squamous as well
- ~3 month *overall survival* benefit
  - No difference in PFS 2-4 months vs docetaxel
    - —1 year PFS rate was higher: 19% vs 8%
- ~20% response rate

Borghaei H. et al. N Engl J Med 2015;373:1627-39
Brahmer J. et al. N Engl J Med 2015;373:123-35

Nivolumab

- Only approved in as 2nd line
- Delayed response
- Toxicity management

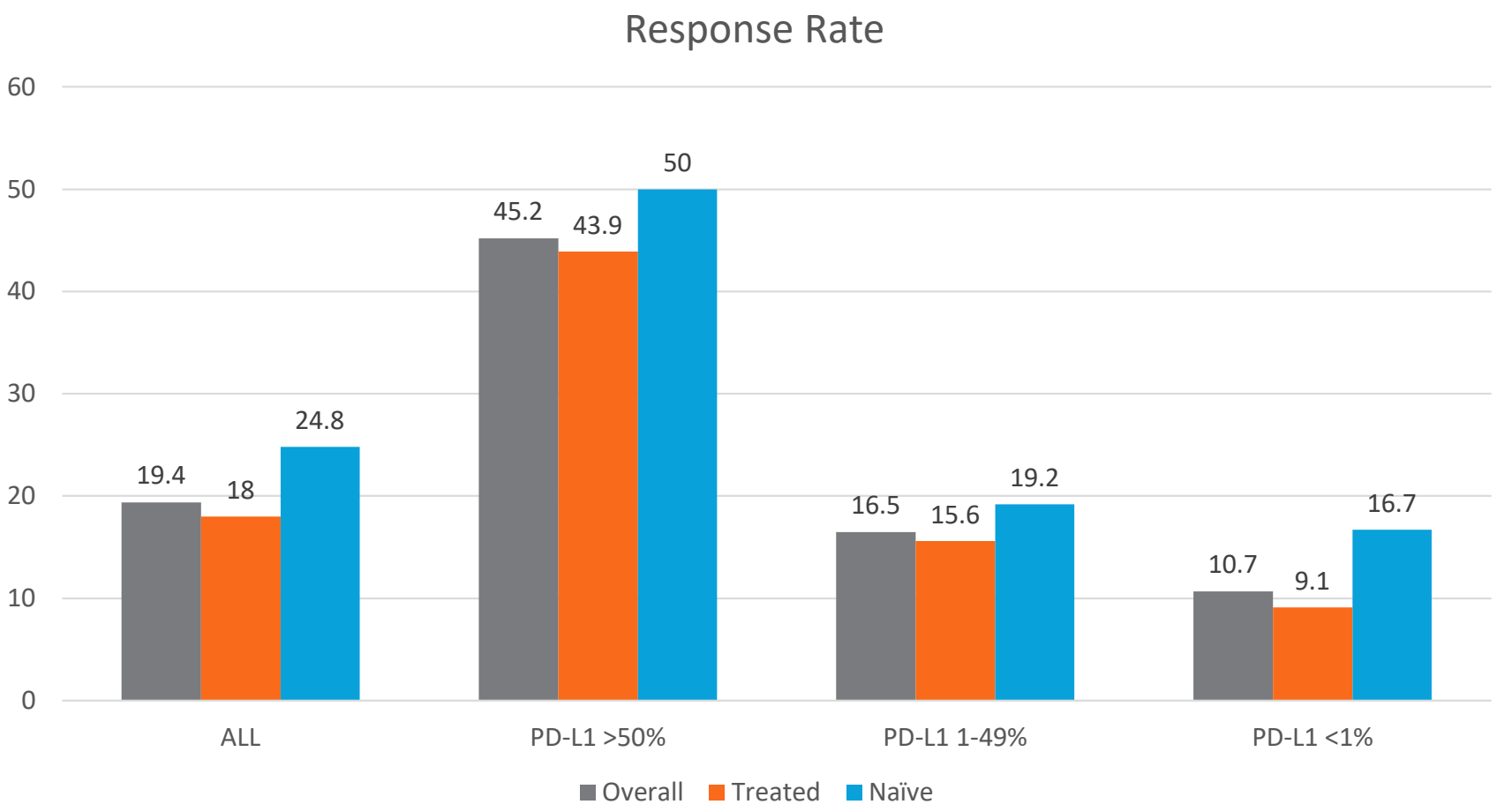
Borghaei H. et al. N Engl J Med 2015;373:1627-39
Brahmer J. et al. N Engl J Med 2015;373:123-35

Pembrolizumab

- Approved off of phase I data – KEYNOTE – 001
  - Must PD-L1 expression
  - Response Rate 19%
  - Overall Survival: 12 months
  - Progression Free: ~3.7 months

Garon EB, et al. *N Engl J Med*. 2015;372:2018-2028
Herbst RS, et al. Lancet. 2016;387:1540-50

Pembrolizumab



Garon EB, et al. N Engl J Med. 2015;372:2018-2028

Pembrolizumab

- PD-L1 Status
  - ≥ 1%
  - Catch 22?
- Dose?
  - 2mg vs 10mg
  - Q2week vs Q3Week
- Delayed Response
- Data Immature

Sul J, et al. Oncologist. 2016;21:643-50
Herbst RS, et al. Lancet. 2016;387:1540-50

Patient Case

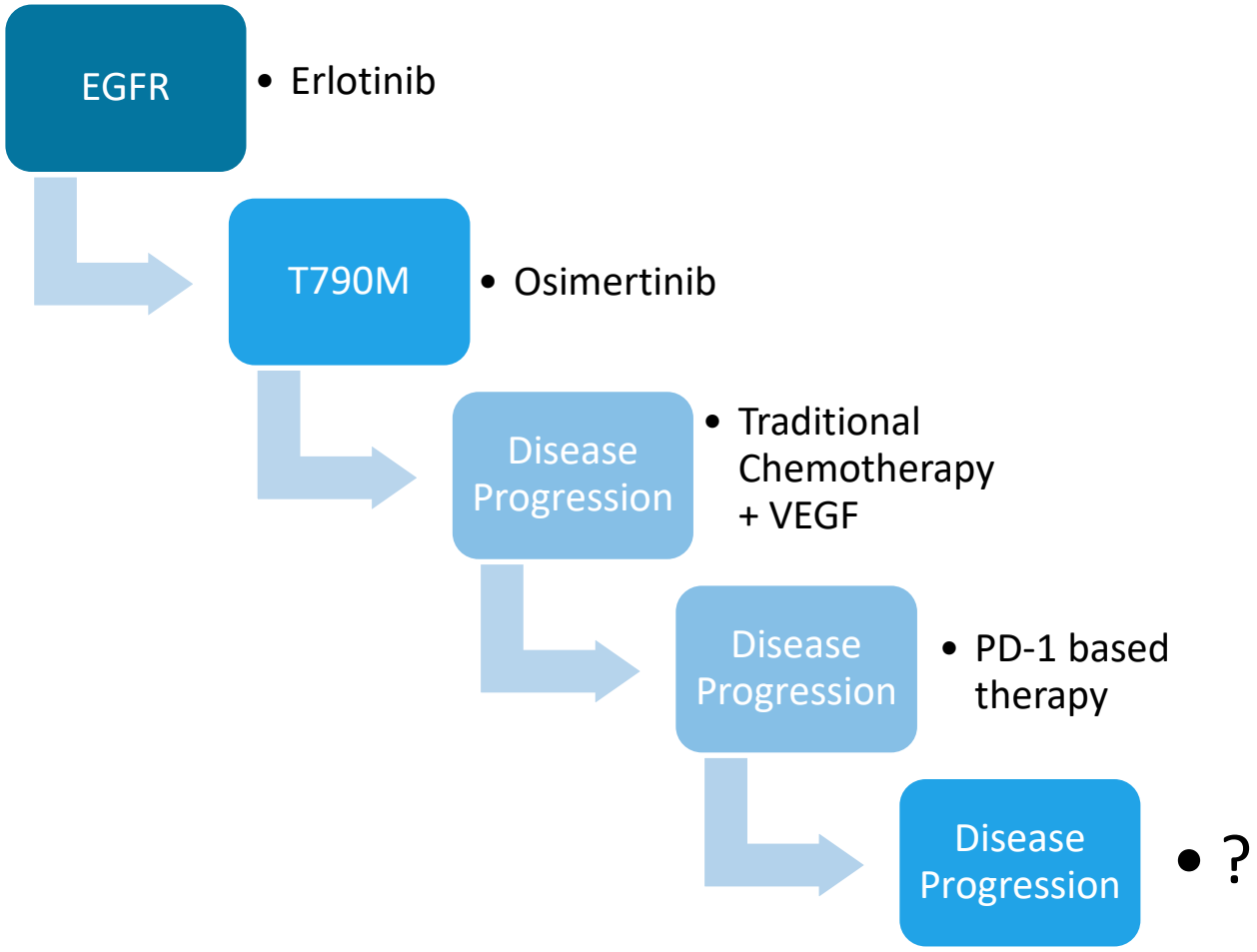
- Pathology Results
  - New C797S mutation

- What is the best course of treatment now?

What has the past shown us

- Strengths
  - Driver mutations provide a target for therapy
  - Profound Responses
  - Multiple new agents
- Weakness
  - Specific mutations not very prevalent
  - Responses are not very durable
  - Limited use
  - Re-biopsy
  - Duration of response
  - Onset of response (PD-1)

“Typical Patient”*



Patient Summary

Back to the Future

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Beyond the Standard of Care in Lung Cancer: Focus on Translation of Molecular Targets

Christine M. Walko, Pharm.D., BCOP, FCCP

Personalized Medicine Specialist

DeBartolo Family Personalized Medicine Institute

Moffitt Cancer Center

Tampa, Florida

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Guidelines are backward looking.

With cancer, things change too rapidly for doctors to be able to rely on yesterday's guidelines for long.

Vincent T. DeVita, Jr, MD

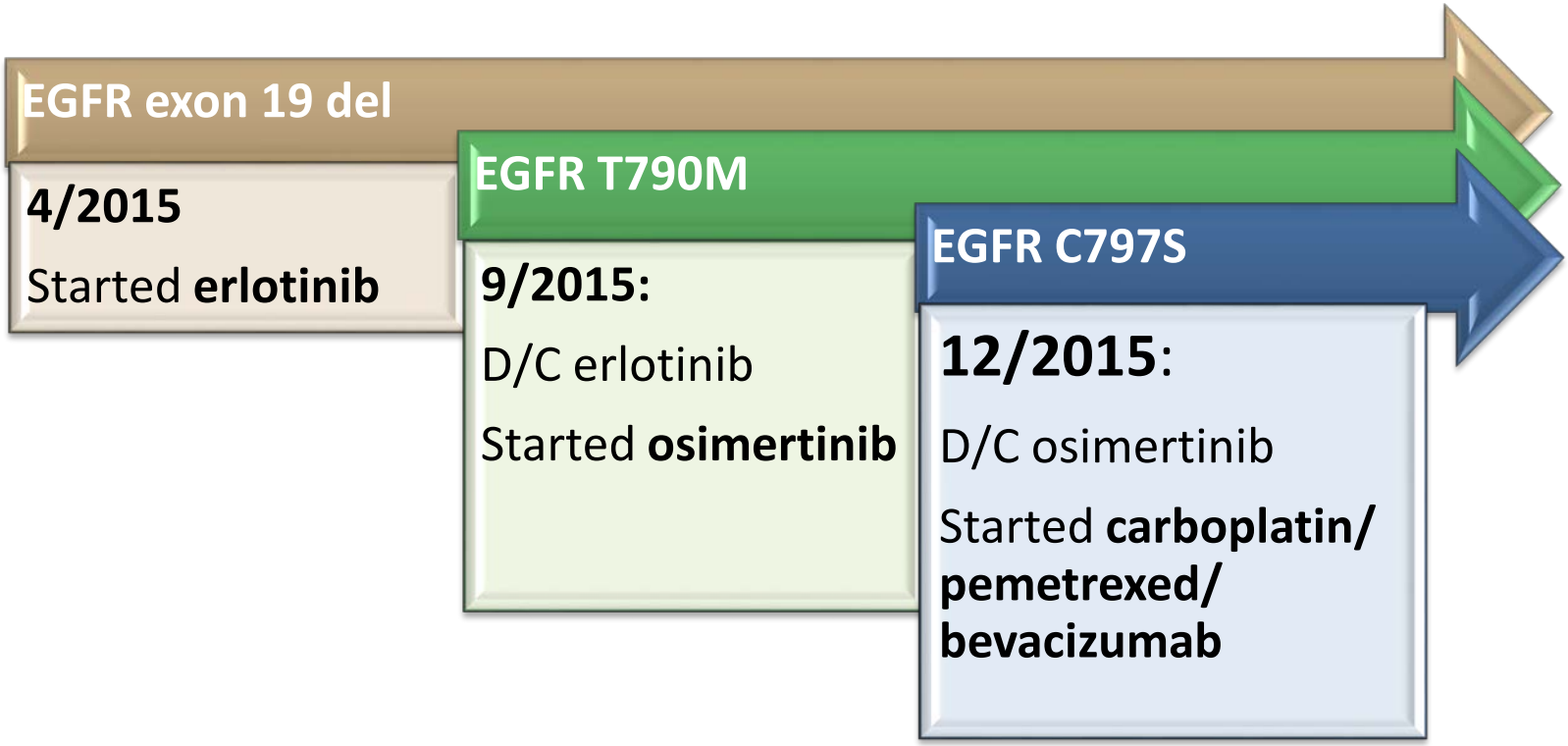
The Death of Cancer

Goal of Precision Medicine

- Determine the optimal treatment or **sequence** of treatments for a patient
  - Which therapy will yield the best response?
  - How do we optimize the response?
  - How do we minimize toxicity?

Mutation Landscape Changes over Time

- 40 yo non-smoking female diagnosed with Stage IV NSCLC, adenocarcinoma



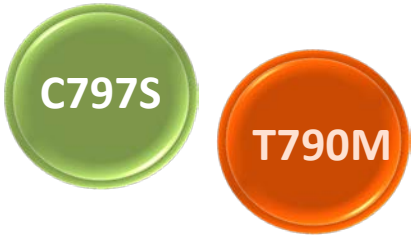
EGFR C797S and Resistance

- We are familiar with resistance mutations:
  - Erlotinib → T790M
  - Osimertinib → C797S → Retains activity to first generation agents
- EGFR C797S – acquired resistance mutation
  - Covalent binding site for 2nd and 3rd generation EGFR-inhibitors like afatinib and osimertinib

C797S mutation in **CIS** with **T790M**

Resistant to EGFR-inhibitors, use alternate therapy

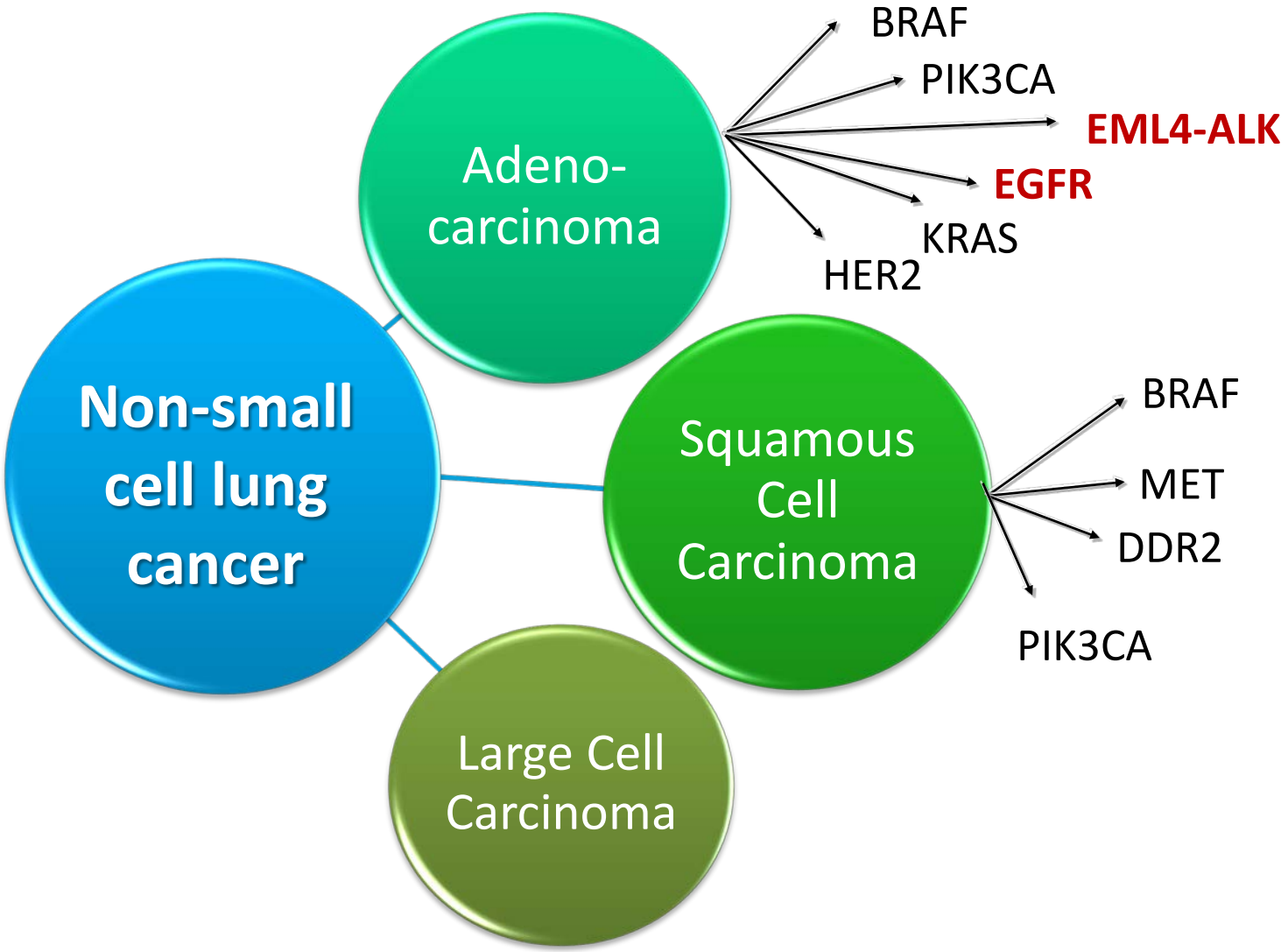
C797S mutation in **TRANS** with **T790M**



Combination of first- and third-line EGFR inhibitors

Clin Cancer Res. 2015;21:3924-33

Evolution of NSCLC Treatment



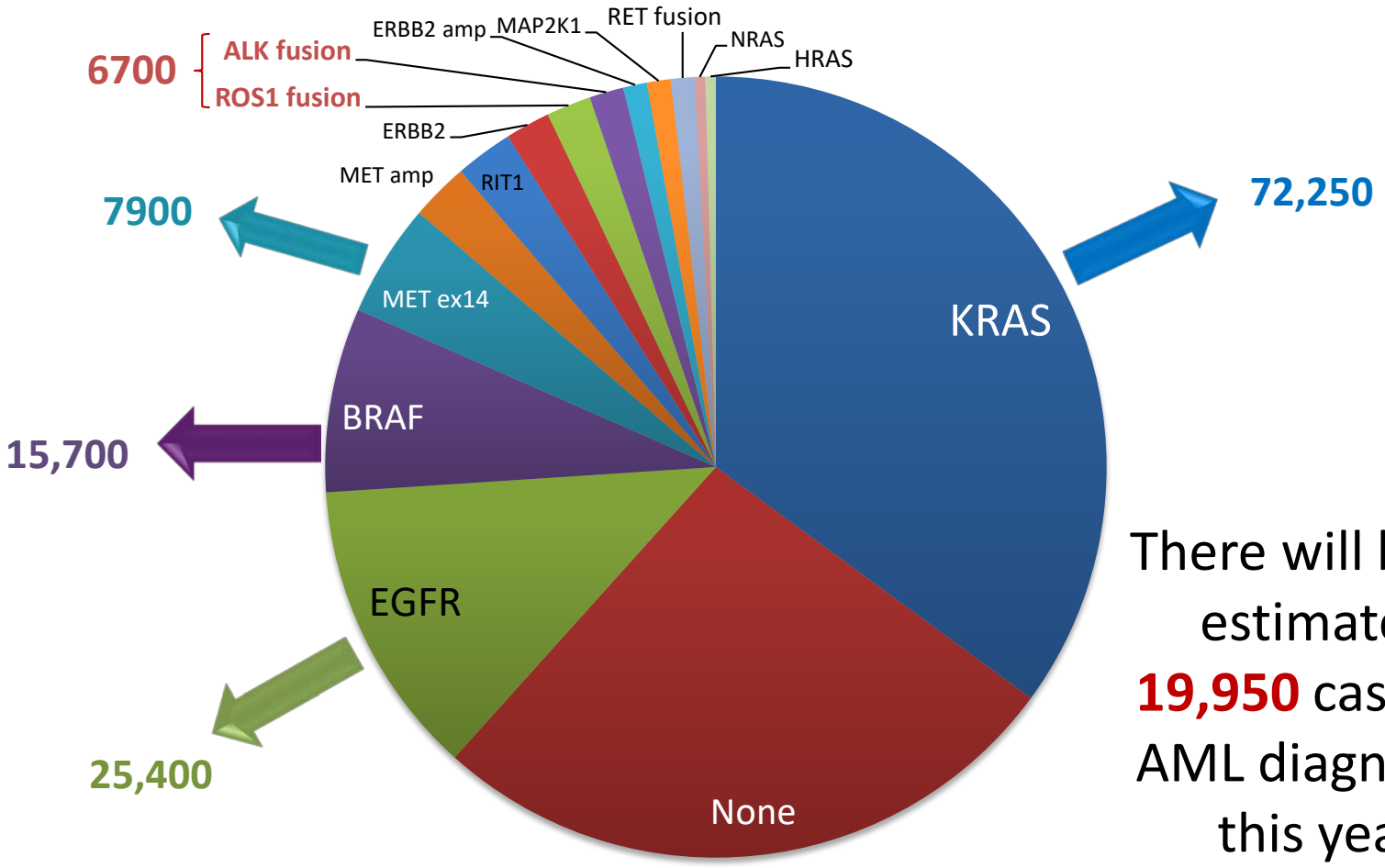
N Eng J Med. 2011;365:158-167

The Reality of Rare Mutations

224,390 new cases of lung cancer are expected in 2016

American Cancer Society.
Cancer Facts & Figures 2016
. Atlanta: American Cancer Society; 2016

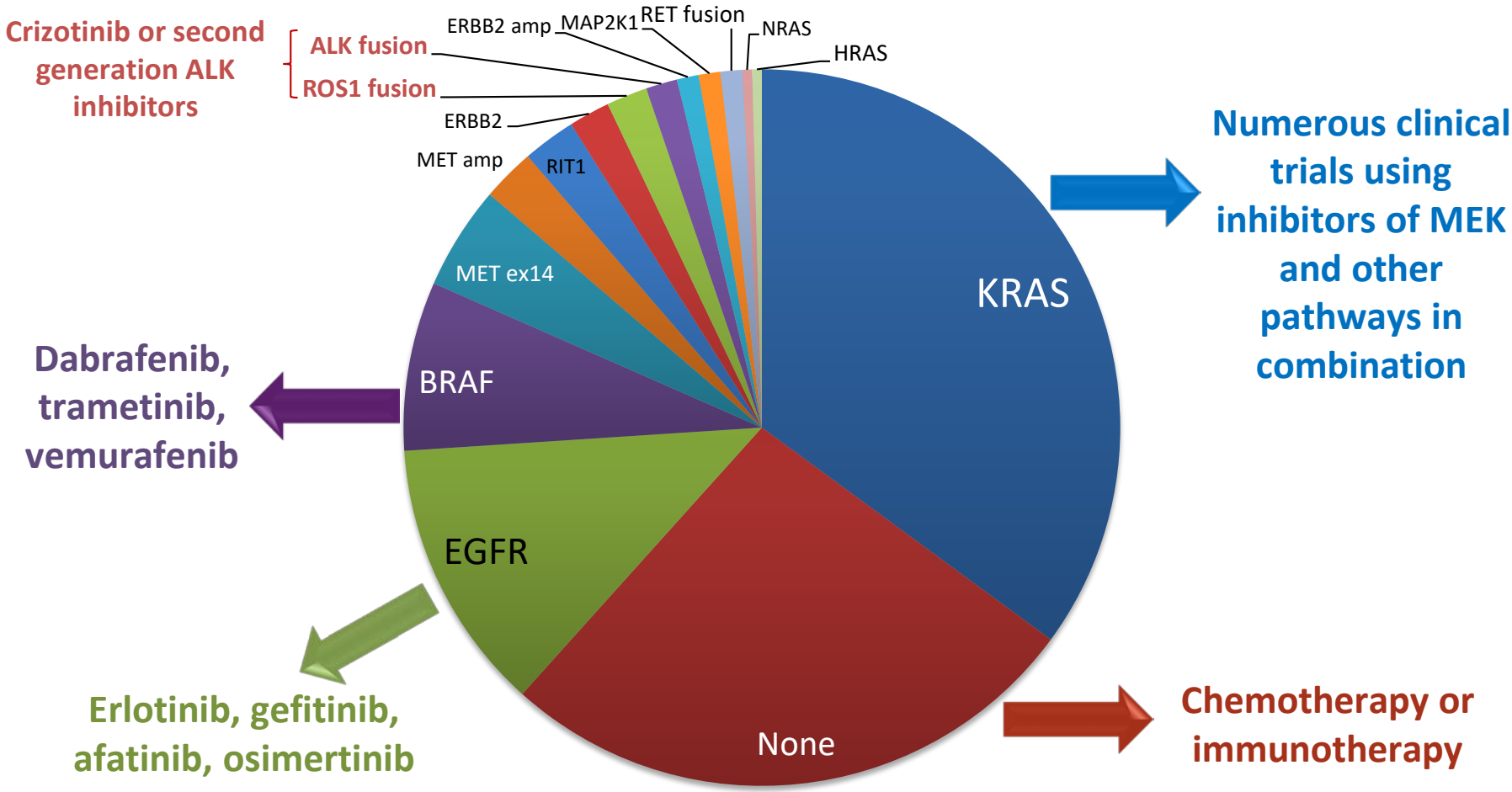
Number of Patients Per Mutation



There will be an estimated **19,950** cases of AML diagnosed this year

Nat Rev Clin Oncol. 2016;16:529

NSCLC Somatic Mutations



Nat. Rev. Clin Oncol. 2015;12:523

Targeting Therapy in Lung Cancer

BRAF

- Mutations seen in up to 7% of NSCLC with more than half being the V600E mutation which is associated with more aggressive disease
- **Dabrafenib** and **trametinib,** or **vemurafenib**

MET

- Exon 14 skipping seen in 3-4% of NSCLC
- Amplification in 2-4% untreated patients and 5-20% in EGFR-mutated tumors as acquired resistance
- **Crizotinib** or **Cabozantinib**

RET

- RET fusions seen in about 1% of NSCLC, but may be closer to 6-19% in select never-smokers
- **Cabozantinib, vandetinib, lenvatinib or ponatinib**

ERBB2

- Mutations seen in 2-4% of NSCLC with the majority being exon 20 insertion mutations
- **Trastuzumab**, **afatinib**, or investigational **neratinib**

Nat. Rev. Clin Oncol. 2015;12:523

Patient Case #1

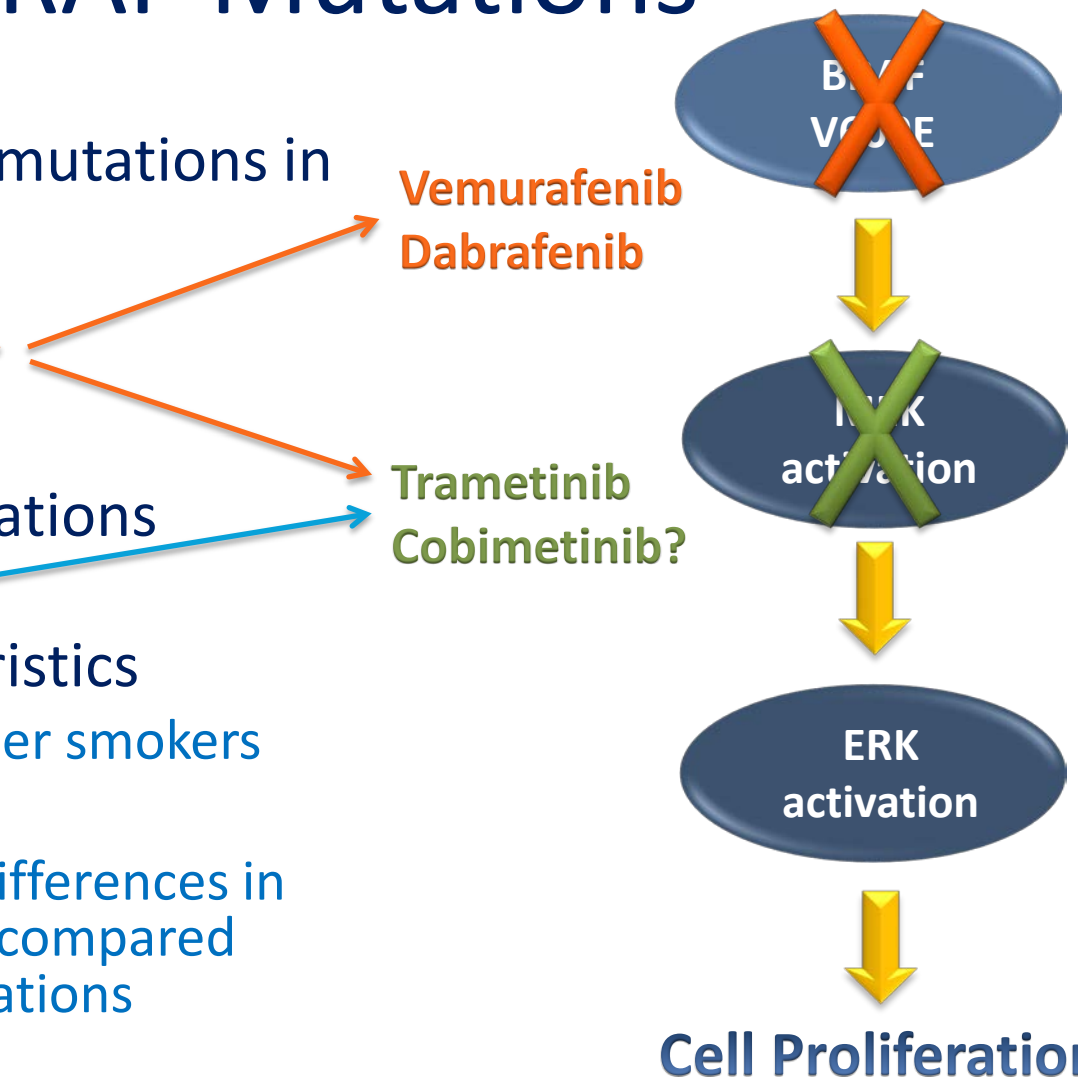
- CH is a 48 yo male, never smoker developed a chronic cough and shortness of breath, right pleural effusion found.
  - PET showed multiple avid areas in the lung
  - Thoracentesis was performed and cytology showed adenocarcinoma
  - An in house next generation sequencing (NGS) test was ordered on the subsequent lung biopsy

TEST PERFORMED	
TSiT	**TruSight Tumor Gene Set** Targeted next-generation sequencing was performed on this sample of adenocarcinoma,poorly differentiated. See under Test Details for more information.

RESULT SUMMARY		
Variants Detected	**FDA Approved Therapies, Prognostic Indication, or Other Course of Action (in patient's tumor type)**	**FDA Approved Therapies, Prognostic Indication, or Other Course of Action (in another tumor type)**
BRAF p.V600E	✓	✓

BRAF Mutations

- **Activating** BRAF mutations in NSCLC
  - V600E (50%)
  - G469A (39%)
  - D594G (11%)
- **Inactivating** mutations
  - G466V (7.5%)
- Patient characteristics
  - Current or former smokers
  - Female
  - No significant differences in overall survival compared with other mutations



Nat Rev Cancer. 2014;14:455-467, Trans Lung Cancer Res. 2013:2:244-250

BRAF V600E in Lung Cancer

Vemurafenib

- Histology independent, Phase 2 basket trial of BRAF V600E-mutation positive, non-melanoma cancers
  - 7 cohorts
- 20 patients with BRAF V600E positive NSCLC received vemurafenib 960 mg PO daily
  - Response rate = 42%
  - mPFS = 7.3 months

mPFS = median progression free survival

N Eng J Med. 2015;373;8:726-36

Dabrafenib + Trametinib

- Phase 2, non-randomized, open-label trial of BRAF V600E-mutation positive NSCLC patients
- 59 patients received dabrafenib 150 mg PO BID and trametinib 2 mg PO daily
  - Objective response = 63.2%
  - 2 patients had a complete response
  - 34 patients had a partial response
  - Median duration of response = 9.0 months
  - Survival data not yet mature

Lancet Oncol. 2016;17:984-93

Patient Case #1

- CH is a 48 yo male, never smoker developed a chronic cough and shortness of breath, right pleural effusion found.
  - PET showed multiple avid areas in the lung
  - Thoracentesis was performed and cytology showed adenocarcinoma
  - An in house next generation sequencing (NGS) test was ordered on the subsequent lung biopsy
  - She received first line therapy with carboplatin and pemetrexed and now has recurrent disease

TEST PERFORMED	
TSiT	**TruSight Tumor Gene Set** Targeted next-generation sequencing was performed on this sample of adenocarcinoma,poorly differentiated. See under Test Details for more information.

RESULT SUMMARY		
Variants Detected	**FDA Approved Therapies, Prognostic Indication, or Other Course of Action (in patient's tumor type)**	✓ **oved Therapies, Prognostic , or Other Course of Action (in another tumor type)**
BRAF p.V600E	✓	✗

Question 4:
Which of the following therapies would you recommend for this patient?

A Docetaxel and ramucirumab

B Vemurafenib and cobimetinib

C Dabrafenib and trametinib

D Nivolumab

Question 4:

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1

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or

Open poll in your web browser

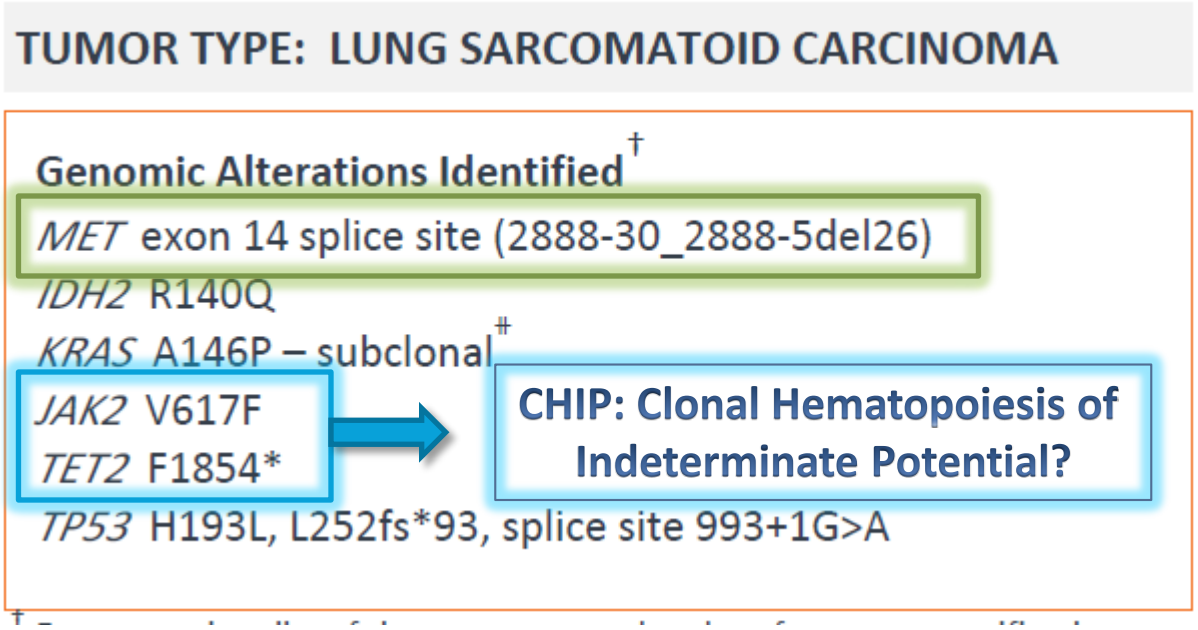
Off Label Drug Acquisition

- Let us all pause for a moment of thanks….

- The success of getting off label drug therapy depends heavily on the patient's insurance
- Appeal letters:
  - Explanation of the genetic mutation
  - Explanation of any human data with citations
  - Personalized Medicine Consult Notes or Genetic testing reports can be helpful

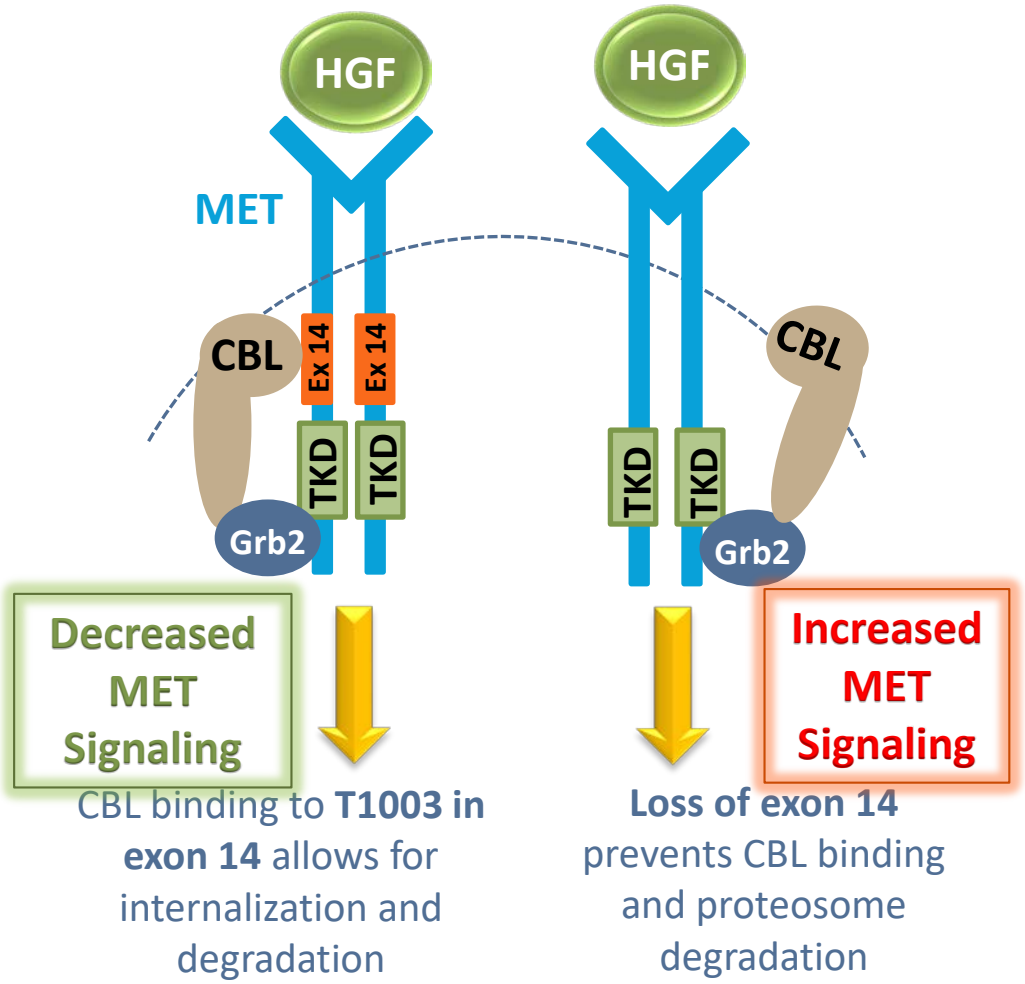
Patient Case #2

- PM is a 78 yo female, former smoker who was diagnosed with NSCLC on work up for pneumonia.
  - Biopsy showed pulmonary sarcomatoid carcinoma histology
  - Further scans showed involvement of the liver
  - A commercial next generation sequencing (NGS) test was ordered on the lung biopsy



MET Exon 14 Mutations

- Seen in 3-4% adenocarcinoma NSCLC
  - Enriched in pulmonary sarcomatoid carcinoma
  - Older patients (median about 72 years old)
  - Females
  - Former or current
- Most commonly result in skipping of MET exon 14 during pre-mRNA splicing
  - 47 amino acid deletion of the juxtamembrane domain
  - Loss of Y1003 CBL binding site



Ex 14 = Exon 14, TKD = Tyrosine Kinase Domain

J Clin Oncol. 2016;34:879-881, J Clin Oncol. 2016;34:721-730

MET inhibitors in NSCLC

- Phase I trial with Crizotinib 250 mg PO BID
  - 13 patients with MET amplification (not exon 14 skipping)
  - Partial response: 4 patients
  - Median duration of response: 35 weeks
- Case report series (MET exon 14 skipping)

Age (yr)	Sex	MET Therapy	Response	PFS (months)	OS (months)
80	Female	Cabozantinib (3rd line)	Stable disease	5.1 +	55.1 +
80	Female	Crizotinib (3rd line)	Partial response	3.6	22.2
80	Male	Crizotinib (3rd line)	Progressive disease	0	22.2
65	Male	Crizotinib (3rd line)	Partial response	4.6 +	17.9 +
90	Female	Crizotinib (3rd line)	Partial response	3.1 +	73.3 +

J Clin Oncol. 2014;32:abstr 8001, Cancer Discov. 2015;5:842-9

PFS: Progression free survival
OS: overall survival

Patient Case #2

- PM is a 78 yo female, former smoker who was diagnosed with NSCLC on work up for pneumonia.
  - Biopsy showed pulmonary sarcomatoid carcinoma histology
  - Further scans showed involvement of the liver
  - A commercial next generation sequencing (NGS) test was ordered on the lung biopsy
  - She has progressed on carboplatin and pemetrexed as well as single agent docetaxel but still desires therapy

TUMOR TYPE: LUNG SARCOMATOID CARCINOMA

Genomic Alterations Identified[†]

MET exon 14 splice site (2888-30_2888-5del26)

Question 5: Which of the following therapies would you recommend for this patient?

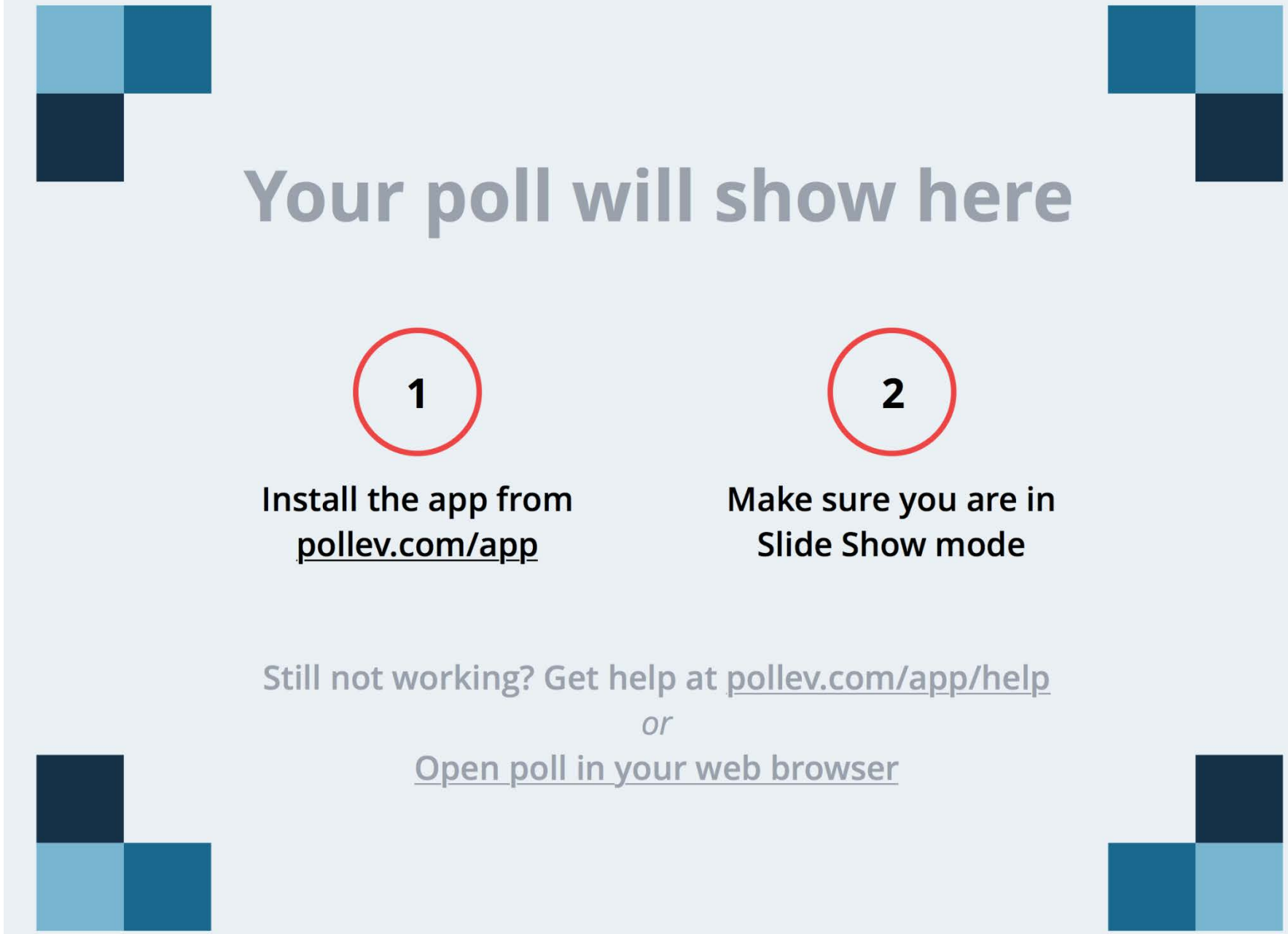
A Erlotinib

B Crizotinib

C Cabozantinib

D Nivolumab

Question 5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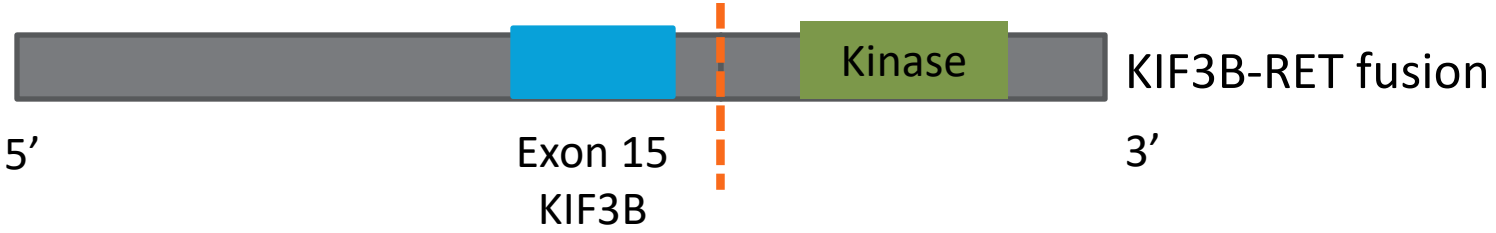
Patient Case #3

- LT is a 65 yo male, never smoker who was diagnosed who was found to have a right pleural effusion
  - Pleurocentesis analysis showed adenocarcinoma likely of lung origin
  - Further scans showed adrenal and bone involvement
  - A commercial cell free DNA (cfDNA) assay was ordered from blood sample given the difficulty of obtaining a biopsy

Alteration		% cfDNA	cfDNA Amplification	FDA Approved in Indication	Available for Use in Other Indications	Clinical Drug Trials
RET	*KIF5B-RET fusion*	0.1		None	Cabozantinib, Lenvatinib, Ponatinib, Regorafenib, Sorafenib, More drugs available	Trials Available
ARID1A	*G827G‡*	0.1	There is no change in the amino acid at this position and it is not likely to be a therapeutic target. Similar to other alterations in circulating cfDNA, the monitoring of this variant may be reflective of disease progression or treatment; clinical correlation is advised.			
EGFR	*D230D‡*	0.1	There is no change in the amino acid at this position and it is not likely to be a therapeutic target. Similar to other alterations in circulating cfDNA, the monitoring of this variant may be reflective of disease progression or treatment; clinical correlation is advised.			

RET Fusions in NSCLC



- Occur in 1-2% of NSCLC, most commonly in never-smokers with adenocarcinoma and no other molecular abnormalities
- Other fusion partners include CCDC6, NCOA4, and TRIM33

Drug	Tyrosine Kinase Targets	Anti-RET IC50
Cabozantinib	VEGFR 2, KIT, **RET**, MET, FLT-1/3/4, TIE-2 ,AXL	5-10 nM
Lenvatinib	VEGFR 1-3, FGFR 1-4, PDGFR, KIT, RET	1.5 nM
Ponatinib	BCR-ABL, VEGFR, PDGFR, FGFR, KIT, RET, TIE2 , FLT3	25.8 nM
Sorafenib	VEGFR 1/2, KIT, **RET**, CRAF, BRAF	6-47 nM
Sunitinib	VEGFR 2, KIT, **RET**, PDGFRα.	220-1300 nM
Vandetinib	VEGFR 2/3, EGFR, **RET**	100 nM

J Med Chem. 2015;58:3672-81

RET Inhibitors in NSCLC

- Cabozantinib has the most case report data in NSCLC
  - Of 3 patients with NSCLC adenocarcinoma:
    - 1 patient had a confirmed PR of 66% tumor decrease and remained progression free for at least 5 months,
    - 1 patient had a confirmed PR of 32% tumor decrease and remained progression free for at least 4 months
    - 1 patient had stable disease after 4 weeks and lasting at least 8 months
  - Second case series of 3 patients:
    - All 3 experienced a PR after 4 weeks of therapy
  - Dosing: 60 mg PO daily rather than FDA approved dosing of 140 mg PO daily
  - Numerous ongoing trials including with apatinib, cabozantinib, vandetinib, ponatinib, and lenvatinib

Cancer Discov. 2013;3:630-5, J Thorac Oncol. 2014;9:1714-9).

RET Inhibitors in NSCLC: ASCO 2016

- Global registry of RET-rearranged NSCLC
  - 132 patients, 62% never-smokers, 97% adenocarcinoma
  - 31% of the patients received therapy off protocol with a RET inhibitor, mostly 3rd line
- RET inhibitor results:
  - Cabozantinib (n=14): **1 CR, 3 PR**, 4 SD
  - Vandetinib (n=11): 2 PR, 3 SD
  - Sunitinib (n=10): 2 PR, 3 SD
  - Sorafenib (n=2): 2 SD

J Clin Oncol 34, 2016 (suppl; abstr 9014)

Patient Case #3

- LT is a 65 yo male, never smoker who was diagnosed who was found to have a right pleural effusion, determined to have Stage IV NSCLC with adenocarcinoma histology
  - A commercial cell free DNA (cfDNA) assay was ordered from blood sample given the difficulty of obtaining a biopsy
  - She received first line therapy with carboplatin and pemetrexed and then docetaxel and ramucirumab second line. She now has progressive disease

Alteration		% cfDNA	cfDNA Amplification	FDA Approved in Indication	Available for Use in Other Indications	Clinical Drug Trials
RET	*KIF5B-RET fusion*	0.1		None	Cabozantinib, Lenvatinib, Ponatinib, Regorafenib, Sorafenib, More drugs available	Trials Available
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Question 6:
Which of the following therapies would you recommend for this patient?

A Erlotinib

B Lenvatinib

C Nivolumab

D Cabozantinib

Question 6

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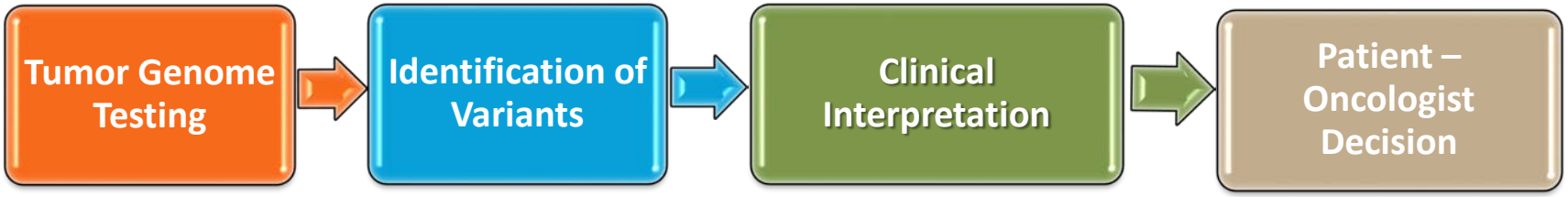
Turning tumor genetic sequencing into standard clinical practice

The value of the Molecular Tumor Board

accp American College of Clinical Pharmacy

ashp Certification Resources

Tumor Genome Analysis Workflow



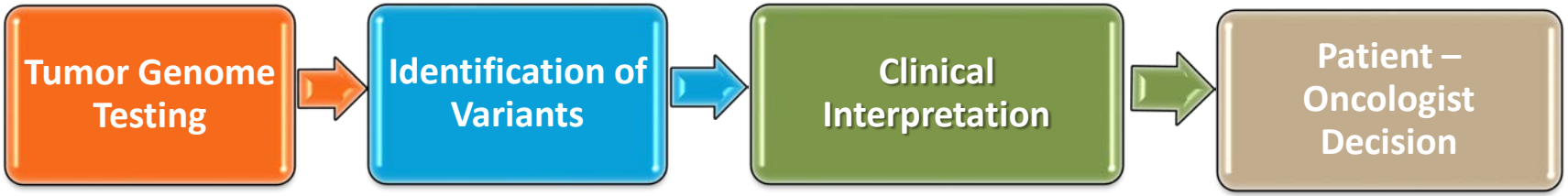
- What is the goal of the test?
- What test should be ordered?
- What tissue is available?

Cell Free DNA (cfDNA) Assays

- Tissue biopsies are not always feasible
- Enables serial monitoring over time to assess for resistance mutations and changes in frequency
- May better represent tumor heterogeneity
- Value of cell free DNA (cfDNA) and serial sampling
  - Plasma derived assays
    - Best concordance when higher number of metastatic sites, lower albumin, higher number of prior therapies
    - Site of disease also showed correlation
  - Cerebral Spinal Fluid (CSF)
    - Somatic alterations found in 63% of CNS metastases from solid tumors and 50% of primary brain tumors

J Clin Oncol. 2016;34:online 5/9/2016, Clin Cancer Res. 2016;22:2960-8

Tumor Genome Analysis Workflow



- What is the goal of the test?
- What test should be ordered?
- What tissue is available?

- What type of variants will be assessed?
- Lower limit of quantitation, number of reads, etc

- How is actionability determined?
- Priority given to multiple actionable variants?
- How to handle variants of unknown or almost known significance?
- Germline variants?

Clinical Actionability

- Genetic alteration predicts response to a particular therapy
  - Benefit or resistance to a particular therapy
  - FDA approved therapy in the patient's tumor or another type of tumor
  - Clinical trial for the particular alteration or reasonable based on molecular biology
- Genetic alteration provides diagnostic or prognostic information
- Clinically relevant germline alteration that informs disease risk or pharmacokinetic or pharmacodynamics

Actionability and Levels of Evidence

Clinical Actionability

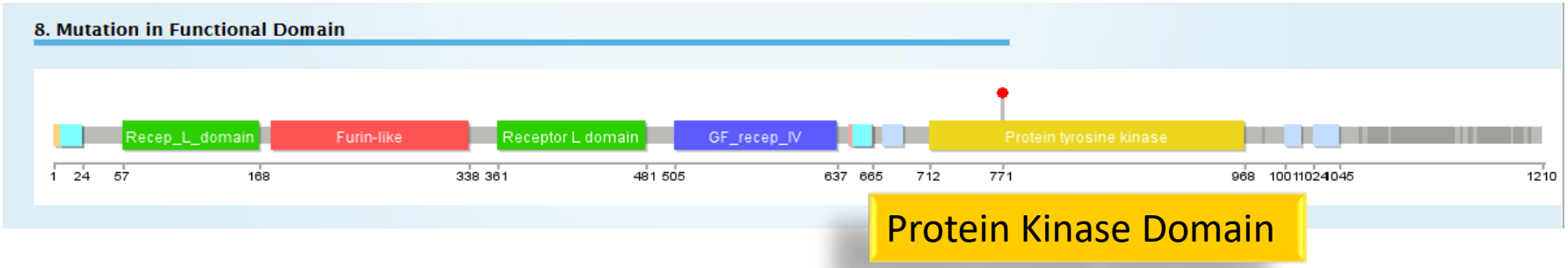
- FDA approved therapy in **patient's** tumor type
- FDA approved therapy in **different** tumor type
- Clinical trial based on specific mutation
- Clinical trial based on application of pathway biology
- Prognostic information
- Not clinically actionable at this time

Supporting Data

- Comparative trial with biomarker selection/stratification (patient's tumor type or different tumor type)
- Retrospective cohort or case-control trials
- Biomarker association with response less robust (secondary endpoint)
- Case study or case series
- Preclinical data only (in vitro or in vivo models)

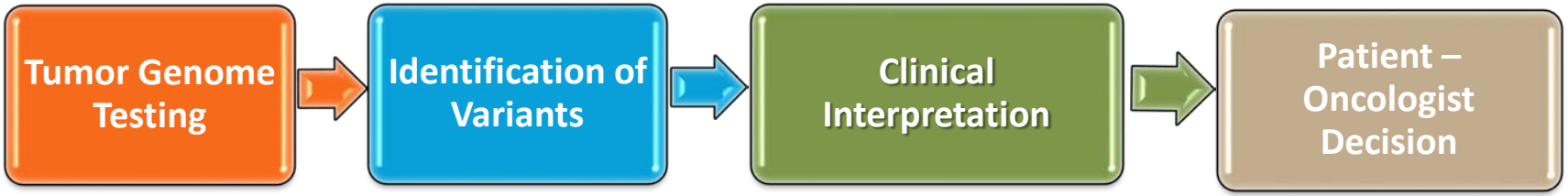
Variants of Almost Known Significance

- Variation found in clinically significant gene in area of known tyrosine kinase binding or other known relevant area
  - **Specific alteration itself is unknown**
  - Example**: EGFR N771Y**
    - Located in the EGFR tyrosine kinase domain in exon 20 but has not been previously reported in COSMIC or other sources



- Value of functional based assays
- Importance of data sharing, especially regarding relevant clinical outcomes

Tumor Genome Analysis Workflow



- What is the goal of the test?
- What test should be ordered?
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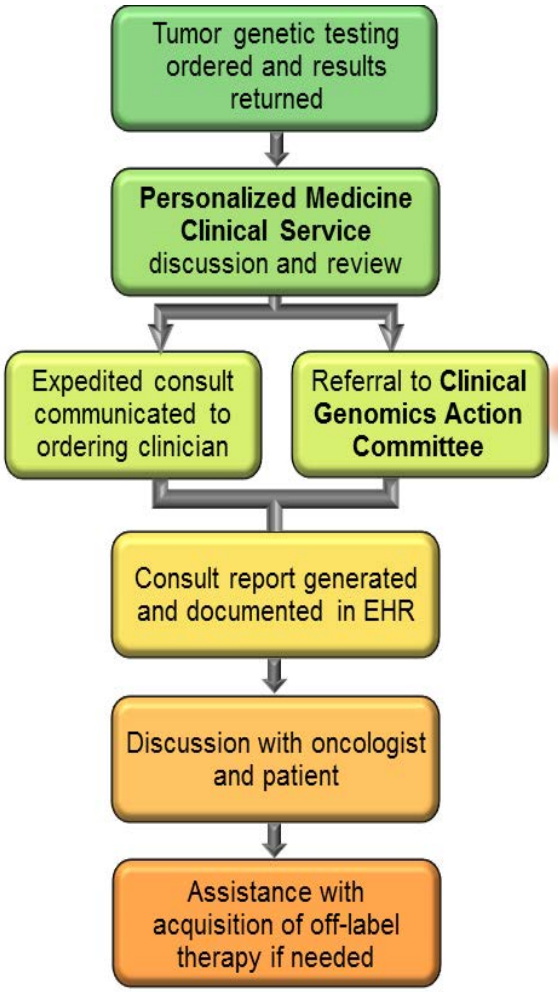
- How is actionability determined?
- Priority given to multiple actionable variants?
- How to handle variants of unknown or almost known significance?
- Germline variants?

- Ability to qualify and travel for a clinical trial?
- Ability to acquire off label therapy?
- Other patient factors to consider?

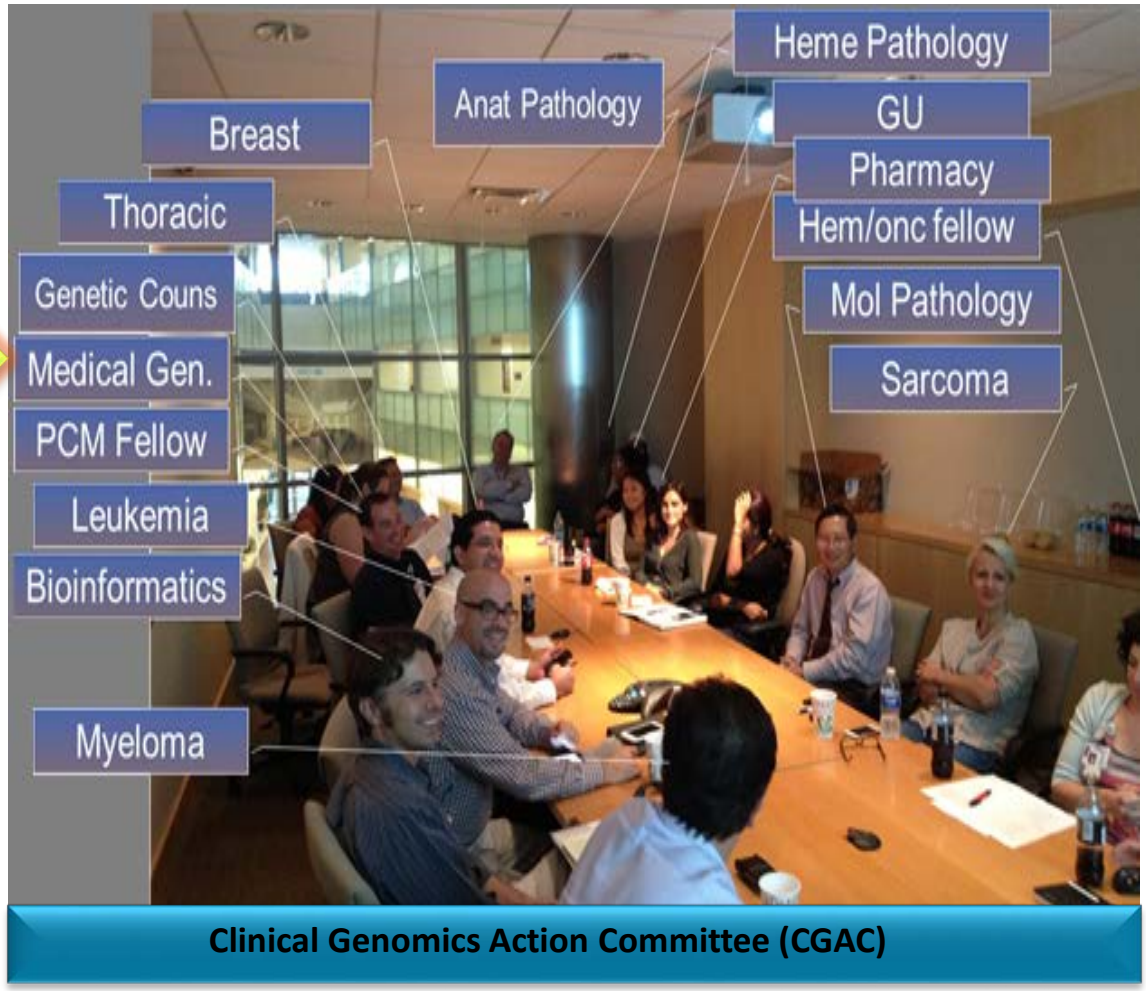
Translating Recommendations into Clinical Decision Making

- Researching and presenting available data to facilitate the decision making process
- Considering the interaction of all the mutations together
  - Cyclin D pathway alteration + RB1 loss
- Consideration of each patient's unique characteristics
  - Desire for a clinical trial and ability to travel
  - Availability and ability to qualify for a clinical trial
  - Sequencing of treatment options
  - Insurance coverage and ability to afford off label therapy
  - Patient preference on treatment options
  - Where patient is in his/her treatment course

Personalized Medicine Clinical Service (PMCS) and Clinical Genomics Action Committee (CGAC)



Tumor Genome Analysis Workflow



Clinical Genomics Action Committee (CGAC)

CGAC Clinical Database

Mutation Analysis

- Patient Summary
- Add Patient
- Patient List
- By Gene and Protein Change

Reports

- Report by Gene
- Report by Cancer Type
- Patient-Mutation Report

Review List

- Review List

Help

- Glossary

Other Tools by CIC

- MutationID
- ExpressionID
- GeneID

List of Findings for patient [redacted] **(FoundationOne Heme)**

Rows: 11 / 11 save to tsv

Gene	Location	Mutation	Significant	CNA	MAF	In EVS	Protein Domain	Actions
EP300	22q13.2	R695P	NO			No		Detail
TP53	17p13.1	R337C	YES			No	P53_tetramer	Detail
NUP93	16q13	A72V	NO			No		Detail
RB1	13q14.2	L331fs*1	YES			No		Detail
HDAC7	12q13.1	R166H	NO			Yes		Detail
LRRK2	12q12	Q923H	YES			Yes		Detail
KRAS	12p12.1	C180*	NO			Yes		Detail
CUX1	7q22.1	S1134C	NO			No		Detail
MAP3K1	5q11.2	A19S	NO			No		Detail
NOTCH2	1p13-p11	P6fs*27	YES			No	EGF	Detail
TMSL3		T23M	NO			No		Detail

Add Gene and Mutation

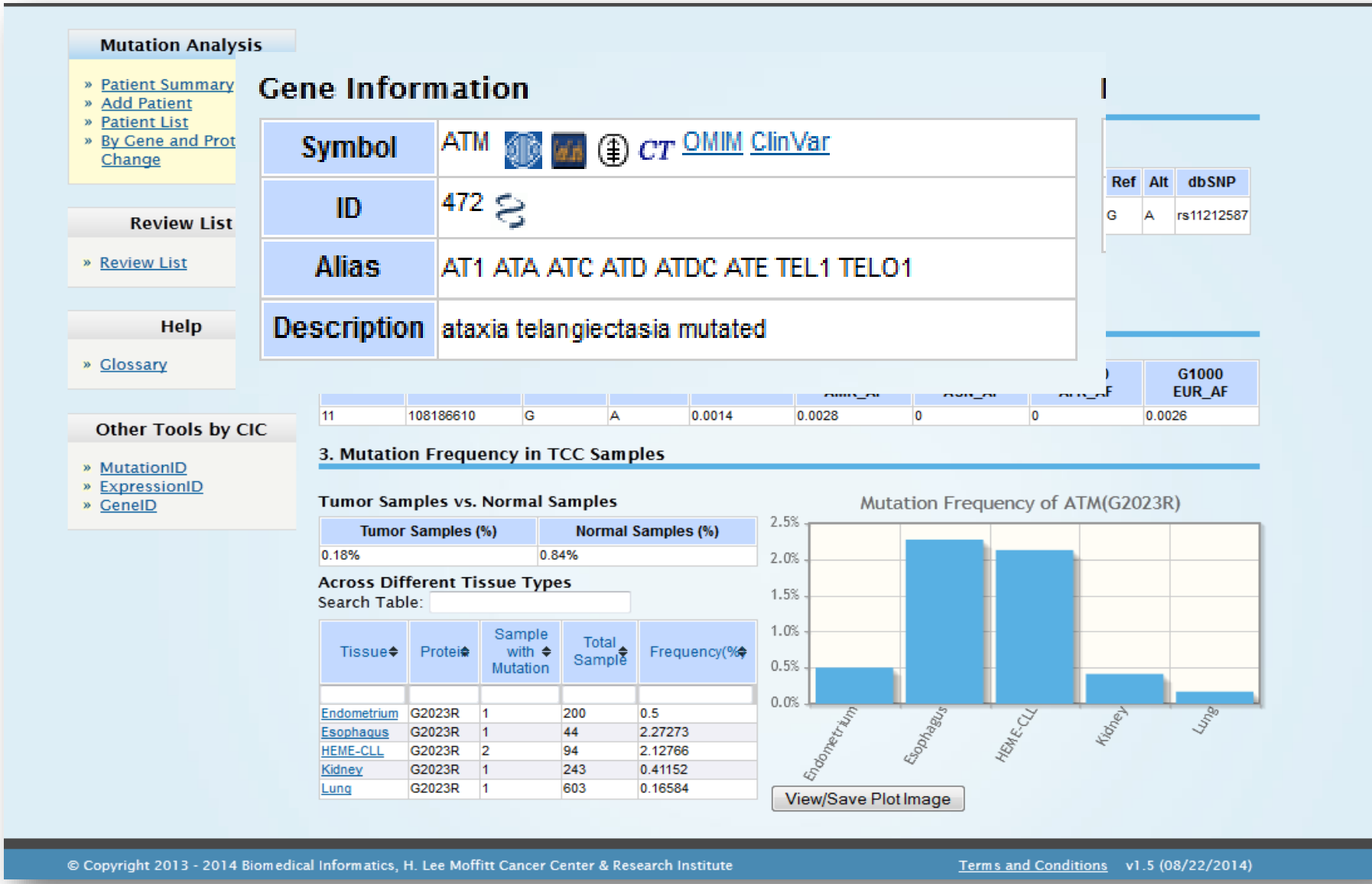
Gene:

Mutation (Change):

Significant: YES

CNA:

CGAC Database



Clinically Important Genetic Resources

Category	Resource	Utility
Variants of Unknown Significance	1000 Genomes Project (http://www.1000genomes.org/)	Provide a probability of the variant being germline
	Exome Variant Server (http://evs.gs.washington.edu/EVS/)	Provide a probability of the variant being germline
Inherited Cancer Risk	International Agency for Research on Cancer (IARC) (http://p53.iarc.fr/)	Frequency of a TP53 mutation in germline and tumor samples
	HCI Breast Cancer Gene Prior Probabilities (http://priors.hci.utah.edu/PRIORS)	Data on all possible single nucleotide substitutions in BRCA1/2
	ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/)	Association of a variant with an inherited disease
	American College for Clinical Genetics (ACMG)	Association of a variant with an inherited disease

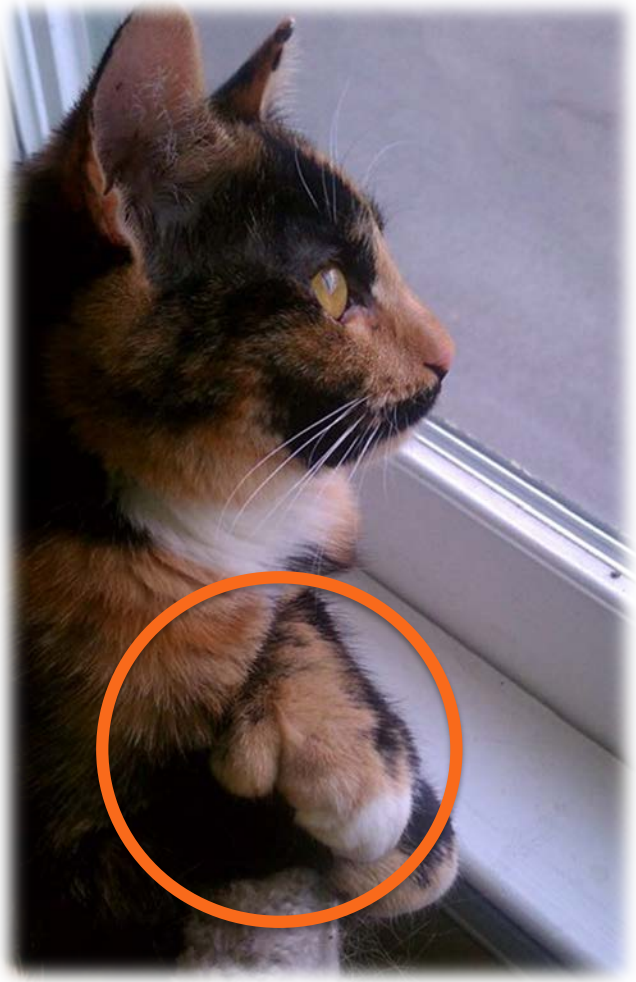
Knepper, T, et al. The Oncologist. 2016: in press

Clinically Important Genetic Resources

Category	Resource	Utility
Variants from across Cancer Types	cBioPortal (http://www.cbioportal.org/)	The frequency of a variant across cancer types and the location of the variant in the functional domains of the gene
	Catalogue of Somatic Mutations in Cancer (COSMIC) (http://cancer.sanger.ac.uk/cosmic)	The frequency of a variant across cancer types
Therapeutic Association	MyCancerGenome (http://www.mycancergenome.org/)	Association of mutation with tumorigenesis, related therapeutic implications and available clinical trials
	PharmGKB (https://www.pharmgkb.org/)	Interactive tool for researchers investigating how genetic variation effects drug response
	Personalized Cancer Therapy Knowledge Base for Precision Oncology (https://pct.mdanderson.org)	Knowledge base resource for the implementation of personalized cancer therapy and integrating information about tumor DNA, RNA, protein and metabolomics profiles with predicted therapy response

Knepper, T, et al. The Oncologist. 2016: in press

Germline Challenges



Patient Case #4

- PH is a 56 yo male former smoker who is diagnosed with squamous cell NSCLC.
- Work up and staging reveal several spinal metastases, but brain MRI is clear
- He is initially treated with carboplatin and gemcitabine x 4 cycles and has a near complete response for 5 months
- His most recent scan shows progressive disease with new adrenal involvement confirmed on biopsy
  - Tissue from the adrenal biopsy is sent for genetic analysis and reveals FGFR3 amplification and an FGFR3 S249C mutation

Question 7:

Which of the following would provide the best information regarding whether the **FGFR3 S249C** mutation has been previously reported in lung or another cancer?

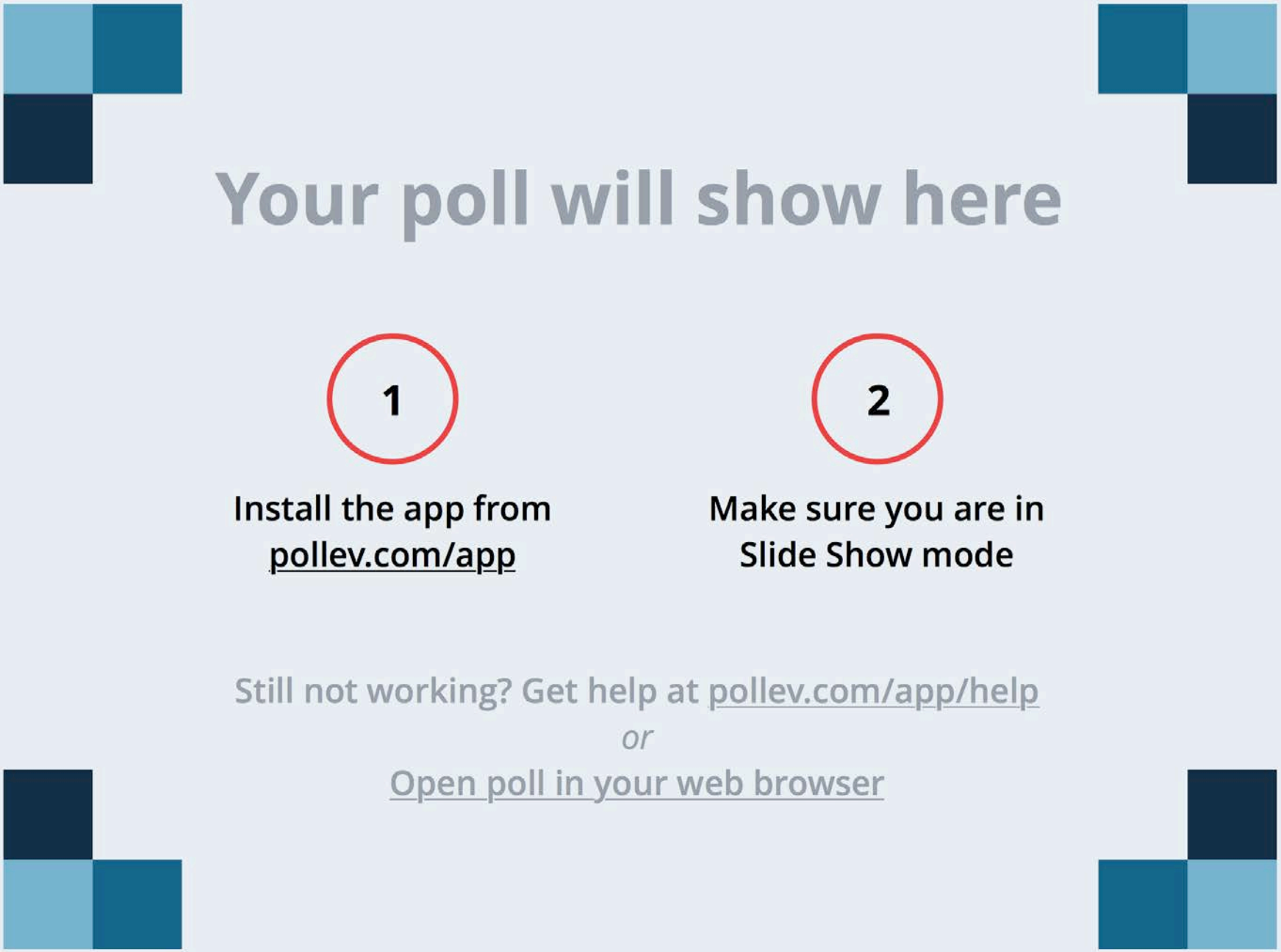
A 1000 Genomes Project

B MyCancerGenome

C ClinVar

D cBioPortal

Question 7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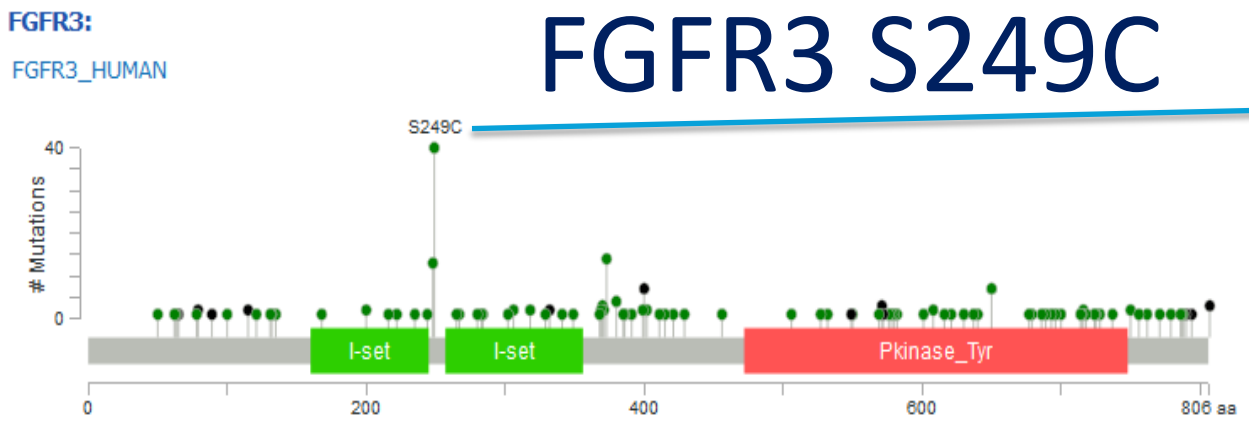
FGFR3 S249C



40 mutations
AA Change: S249C

Cancer Type	Count
Bladder Urothelial Carcinoma	36
Lung Squamous Cell Carcinoma	2
Head and Neck Squamous Cell Carcinoma	1
Papillary Renal Cell Carcinoma	1

- In vitro bladder cancer cell data supports this mutation induced phosphorylation of PLCg1, FRS2 and ERK1/2. Differences were seen between different FGFR3 mutations and different cell types
- Pazopanib was shown in vitro to inhibit FGFR3 activating mutations at an IC50 of 100nM-1uM and one SqCC head and neck cancer patient with an FGFR2 P253R mutation had a response to pazopanib
- 67 yo woman with metastatic papillary urothelial carcinoma s/p several chemotherapy agents found to have FGFR3 amp and **S249C** (58%), treated with **pazopanib** and had a PR > 6 months.
- **AZD4547** is part of the NCI-MATCH trial expanded arms
  - Subprotocol W (FGFR1-3 amplifications, mutations or translocations)

cBioPortal July 2016, Oncogene 2009;28:4306-16
European Urology. 2015;68:167-170

Mutation Load and Immunotherapy

- **Exciting therapy, but not everyone has a response**
  - Durable responses to anti-PD1 therapy were seen in:
    - 31-44% of melanoma
    - 19-20% of lung cancer
    - 22-25% of renal cell carcinoma
  - Potential biomarkers:
    - Density of CD8+ T cells in tumors
    - Expression of PDL1 on tumors
    - **Mutation burden and microsatellite instability:** now being reported by some molecular testing companies for individual patients

Example: MSI: Stable
Mutation Burden: **High**, 25 mutations per megabase

Nat Rev Cancer. 2016;16:275-287

Mutation Load and Immunotherapy

Number of Mutations

- Improved **overall survival** with CTLA4-inhibitors in melanoma patients with > 100 mutations (p=0.04)
  - 64 patients treated with ipiliumumab or tremelimumab
  - Neoantigen response signature developed
- Improved **mPFS** in lung cancer patients treated with pembrolizumab with high mutation burden
  - Patients with durable responses had a median of 302 mutations vs. 148 in those without a durable response (p=0.02)

N Eng J Med. 2014;371:2189-2199
Science. 2015;348:124-128

Microsatellite Instability

- 41 patients with MMR-deficient colorectal cancer, 9 patients with other MMR-deficient cancer and 21 MMR-intact colorectal cancer patients
  - All treated with pembrolizumab
- Whole exome sequencing mean number of somatic mutations per tumor
  - MMR-deficient: 1782 mutations
  - MMR-intact: 73 mutations
  - Higher somatic tumor burden = improved mPFS

N Eng J Med. 2015;372:2509-20

Future of Somatic Genomics

- What are the optimal mutational profiling approaches?
- How do we translate these findings into clinical practice for the average oncologist?
  - Defining “clinically actionable”
  - Handling “variants of unknown significance”
  - Facilitating patient discussions
  - Ethics on germline findings
- What clinical trials should we be doing?
  - Novel trial design like “Basket Studies”

J Clin Oncol. 2013;31:1806-1814.

Ongoing ~~Challenges~~ OPPORTUNITIES

- Identify, interrogate and validate the correct biomarkers for targeted and immunotherapies
- Utilize novel clinical trial designs to assess outcomes across tumor types and mutations
  - Basket trials
  - Genetic-guided Registry trials
    - **T**argeted **A**gent and **P**rofiling **U**tilization **R**egistry (TAPUR)
      - Goal: To learn from the real world practice of prescribing targeted therapies to patients with advanced cancer whose tumor harbors a genomic variant known to be a drug target or to predict sensitivity to a drug
      - Currently open at 4 sites with many more planned, 15 arms
      - NCT02693535

Optimizing Targeted Therapy

- Translate our understanding of cancer biology crosstalk and feedback signaling into rationale drug combinations
- Modify the immune environment to improve tumor identification and destruction
- Improve biomarker identification and validation to target the right genetic drivers

Nat Rev Drug Discov. 2014;13:140-156

Questions?