pshp ANNUAL ASSEMBLY

BRIDGING THE FUTURE OF PHARMACY 2022

PITTSBURGH, PA | NOVEMBER 2-5, 2022

PRECISION DIAGNOSTICS

HOW THE LABORATORY AND PHARMACY WORK TOGETHER TO OPTIMIZE PATIENT CARE

WHO ARE WE?

Allison Eck, MHA, HTL(ASCP)cm, QLS

- Director, Pathology and Laboratory Medicine
- Technical Supervisor – Next Generation Sequencing
- Histotechnologist – 20 years

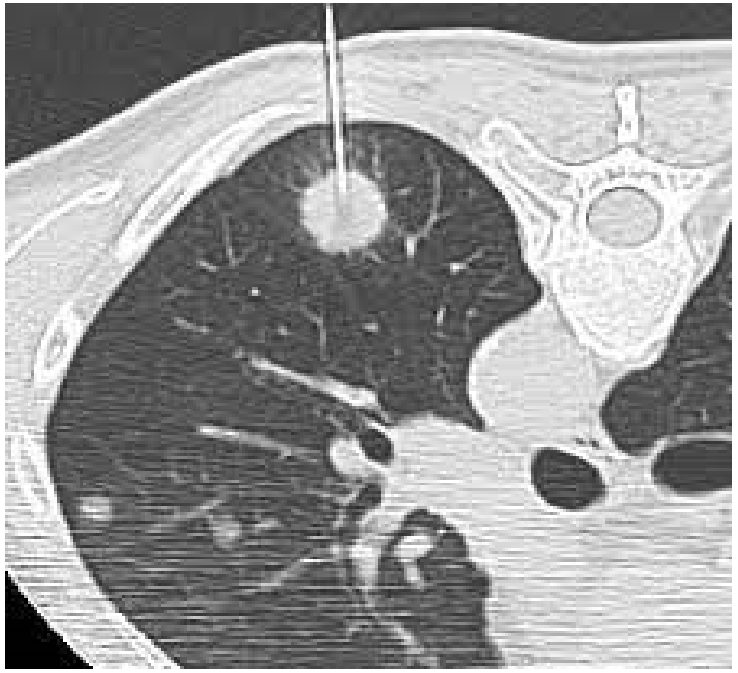
Christine Roussel, PharmD, BCOP, BCSCP

- Sr. Executive Director, Pharmacy, Laboratory & Medical Research
- Board certified oncology pharmacist

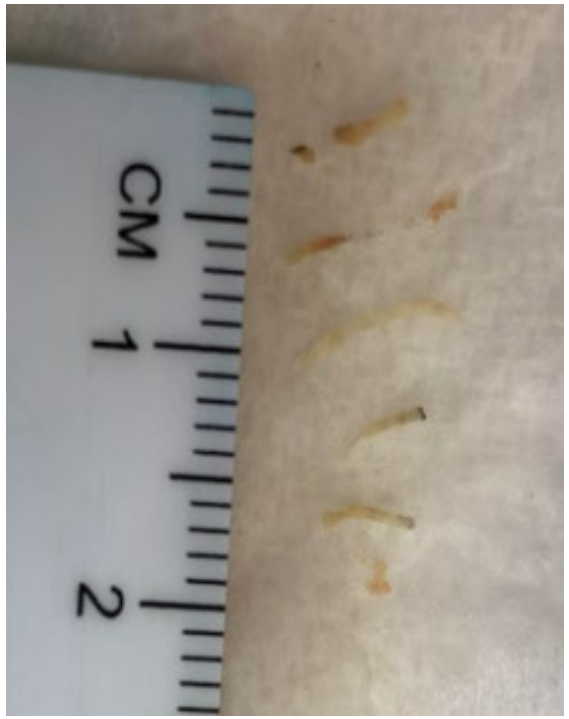
OBJECTIVES

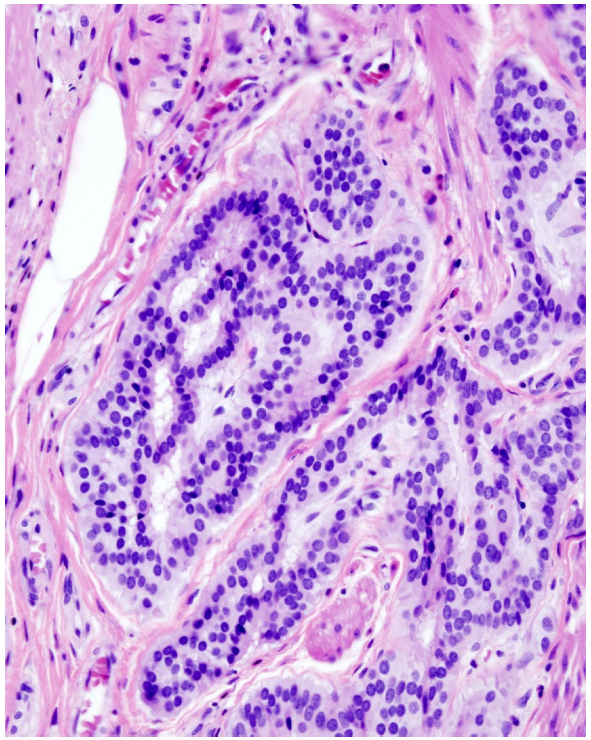
- Provide an introduction to precision diagnostics and how molecular pathology can allow for a personalized approach to treatment
- Investigate the partnership between pathology and pharmacy and how the partnership can optimize patient care
- Illustrate concepts of testing and matching tumors with pharmaceuticals to improve patient outcomes
- Follow a tumor's journey from identification to targeted destruction!

LET'S START AT THE BEGINNING



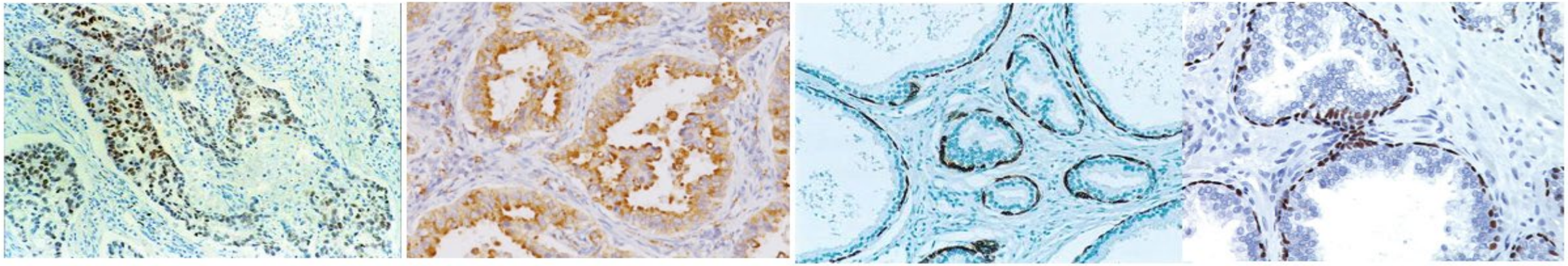
BIOPSY → HISTOLOGY

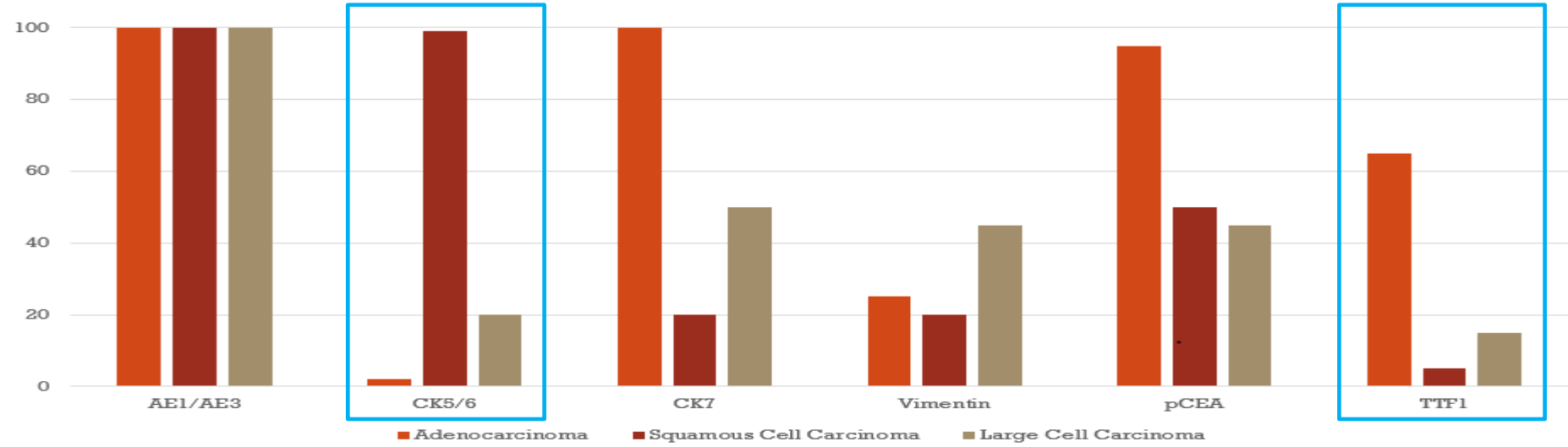




HISTOLOGY → IMMUNOHISTOCHEMISTRY

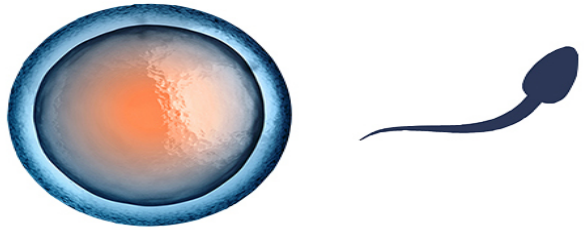
- TTF-1 Napsin A CK5/6 p63



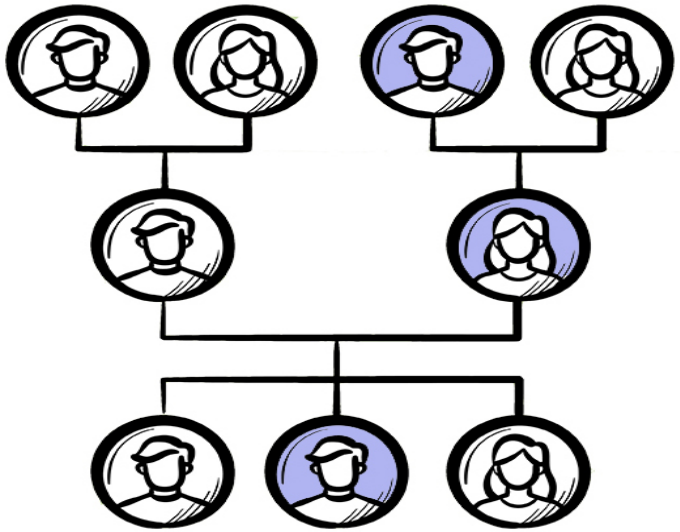


One test per lifetime

Germline Mutations



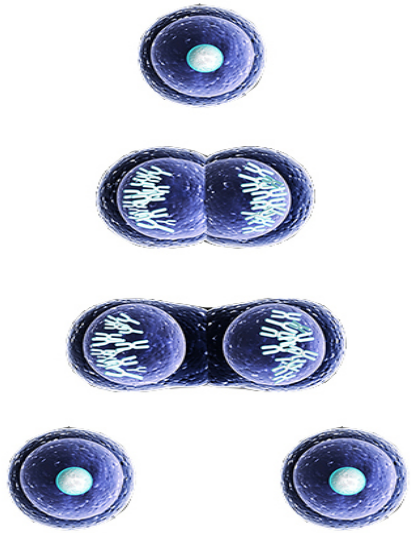
Hereditary mutations are referred to as germline mutations because they are found in the germ cells, also known as the egg and sperm.



Germline mutations can be passed down from generation to generation and can influence a person's risk for developing certain diseases. For instance, some BRCA1 and BRCA2 mutations increase the risk of developing cancer.

Somatic Mutations

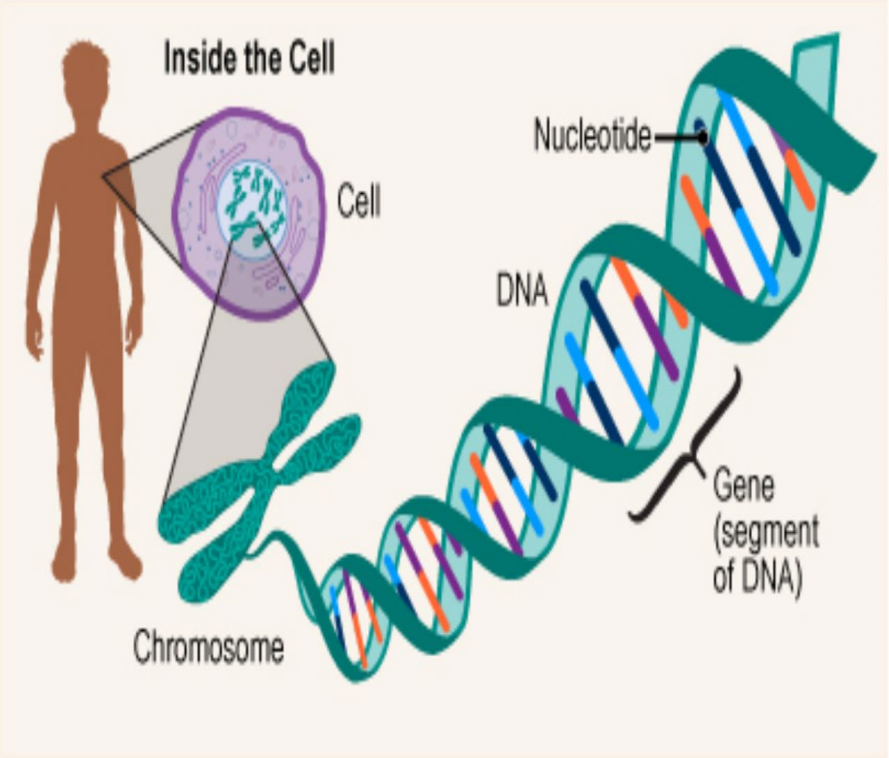
Somatic mutations occur in the nonreproductive cells in the body and cannot be passed down from parent to child. They are called somatic after the Greek work for body, soma.

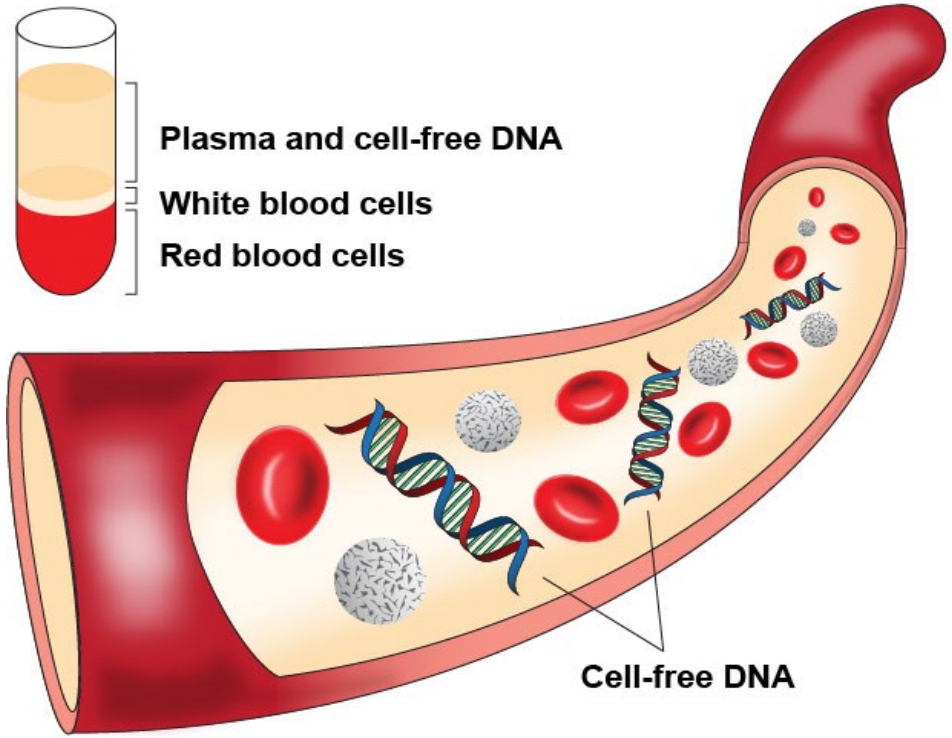


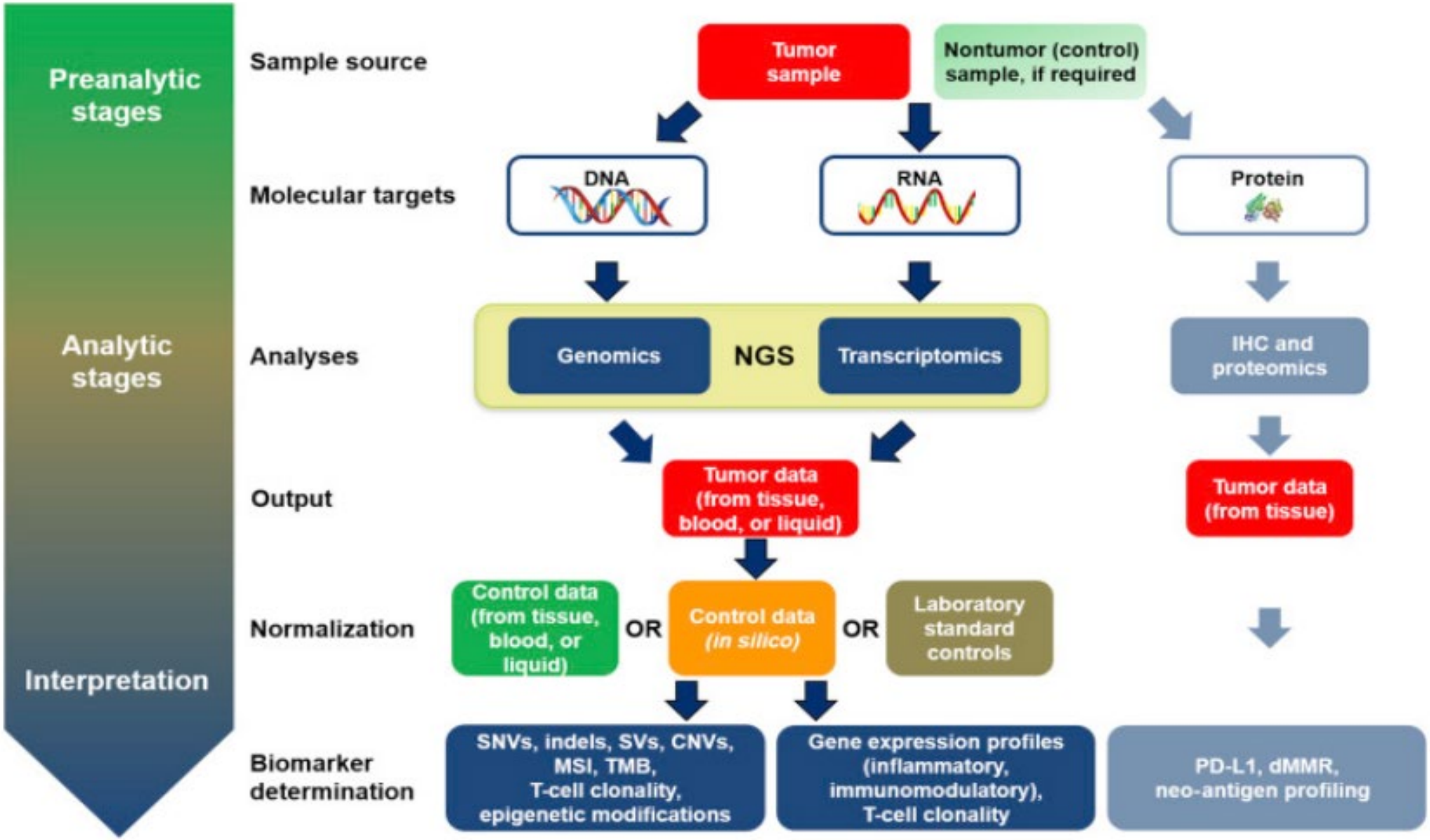
Cancer cells tend to accumulate somatic mutations. Some of these mutations help the cancer cells grow and divide and can be targeted with drugs, while others do not affect the fitness of the cancer cells.

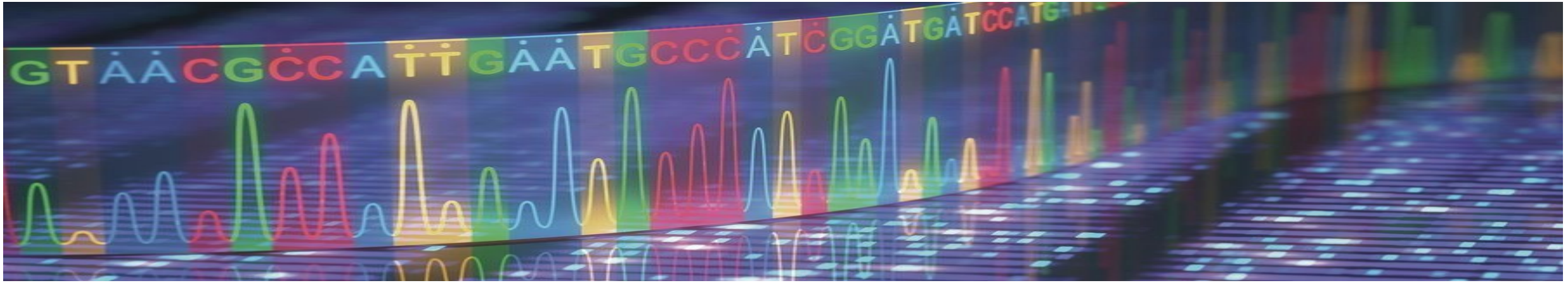
Serial Testing of tissue (ie. at initial diagnosis, during and after treatment for monitoring response

TISSUE DNA VS CELL FREE DNA

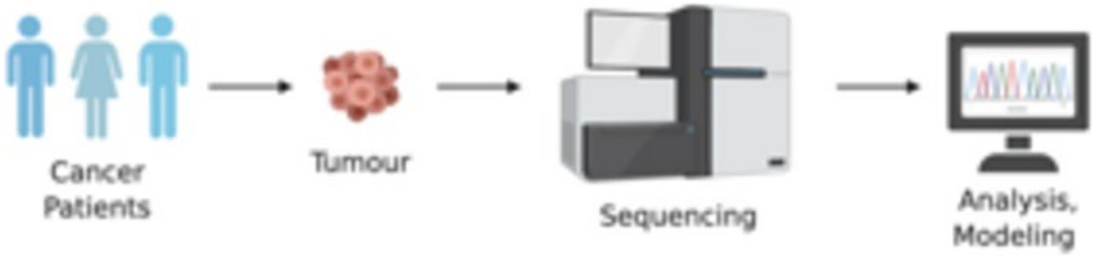


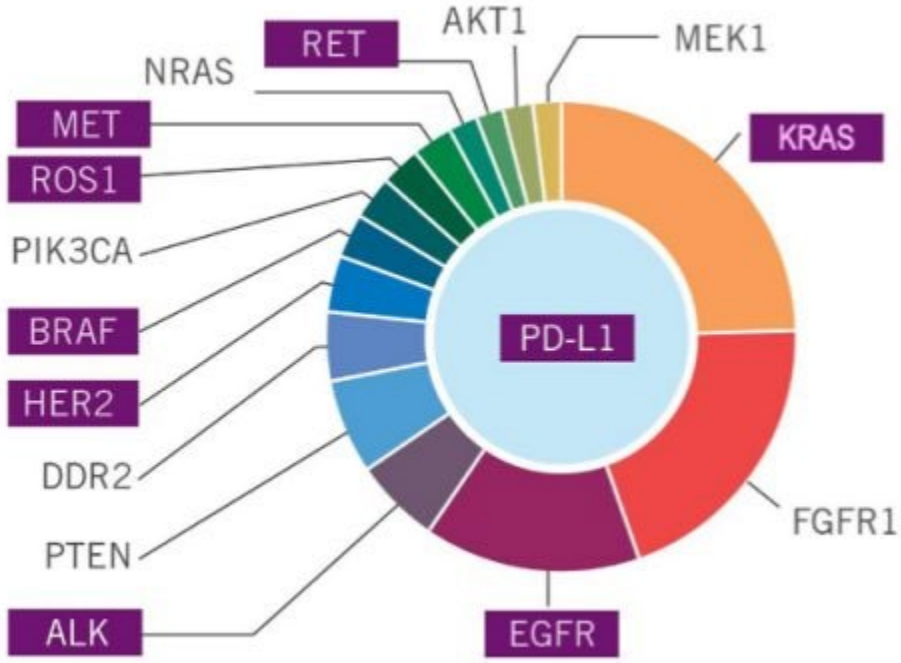



Preanalytic stages
Analytic stages
Interpretation
Sample source
Molecular targets
Analyses
Output
Normalization
Biomarker determination
Tumor sample
Nontumor (control) sample, if required
DNA
RNA
Protein
Genomics
NGS
Transcriptomics
IHC and proteomics
Tumor data (from tissue, blood, or liquid)
Tumor data (from tissue)
Control data (from tissue, blood, or liquid)
OR
Control data (in silico)
OR
Laboratory standard controls
SNVs, indels, SVs, CNVs, MSI, TMB, T-cell clonality, epigenetic modifications
Gene expression profiles (inflammatory, immunomodulatory), T-cell clonality
PD-L1, dMMR, neo-antigen profiling



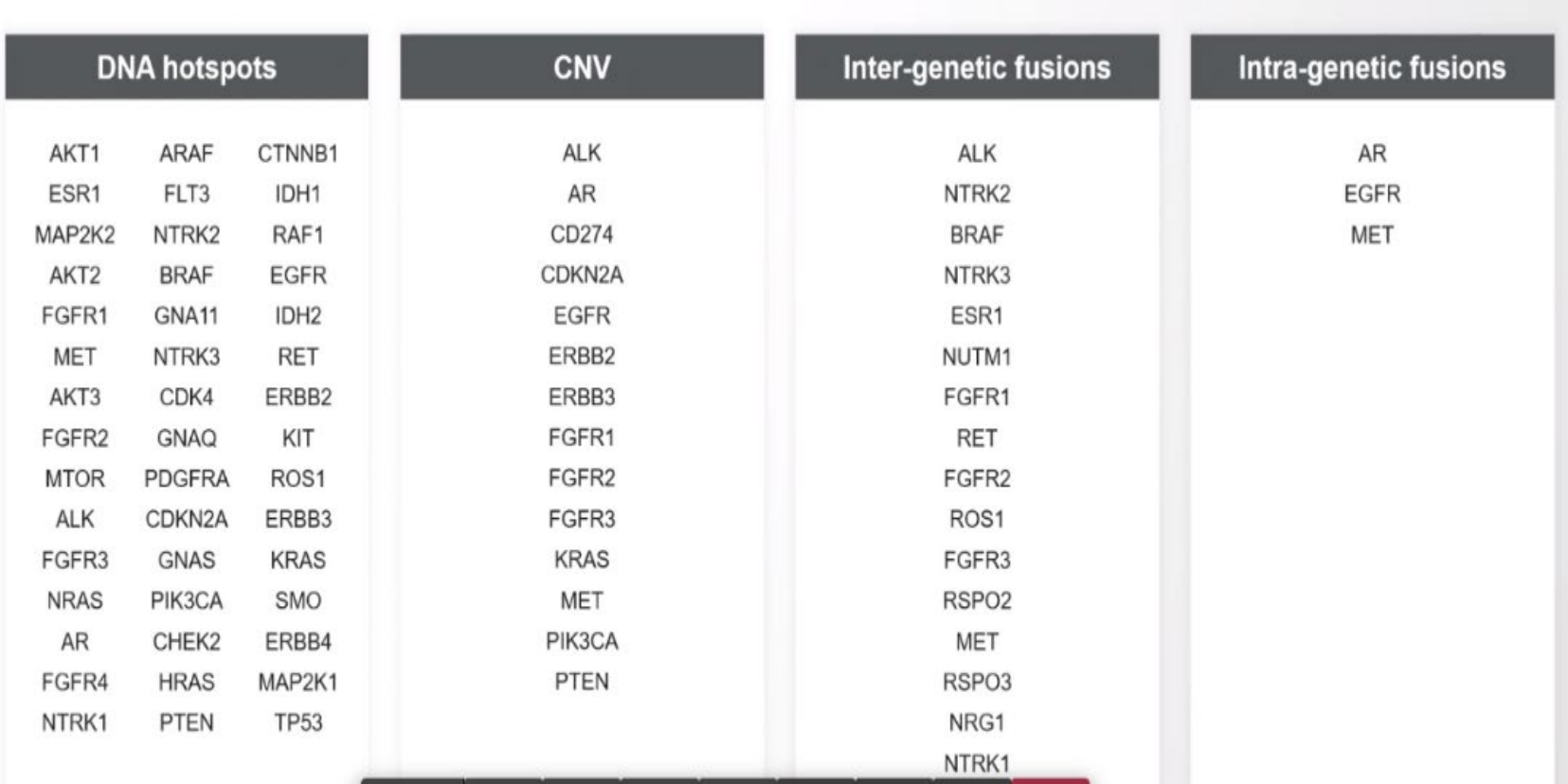
Technology for determining the sequence of DNA or RNA to study genetic variation associated with diseases or other biological phenomena





MOLECULAR PATHOLOGY

- "discipline that encompasses the development of molecular and genetic approaches to the diagnosis and classification of diseases and the design and validation of predictive biomarkers for treatment response and disease progression.
  - DNA hotspots
  - CNV
  - Inter-genetic fusions
  - Intra-genetic fusions

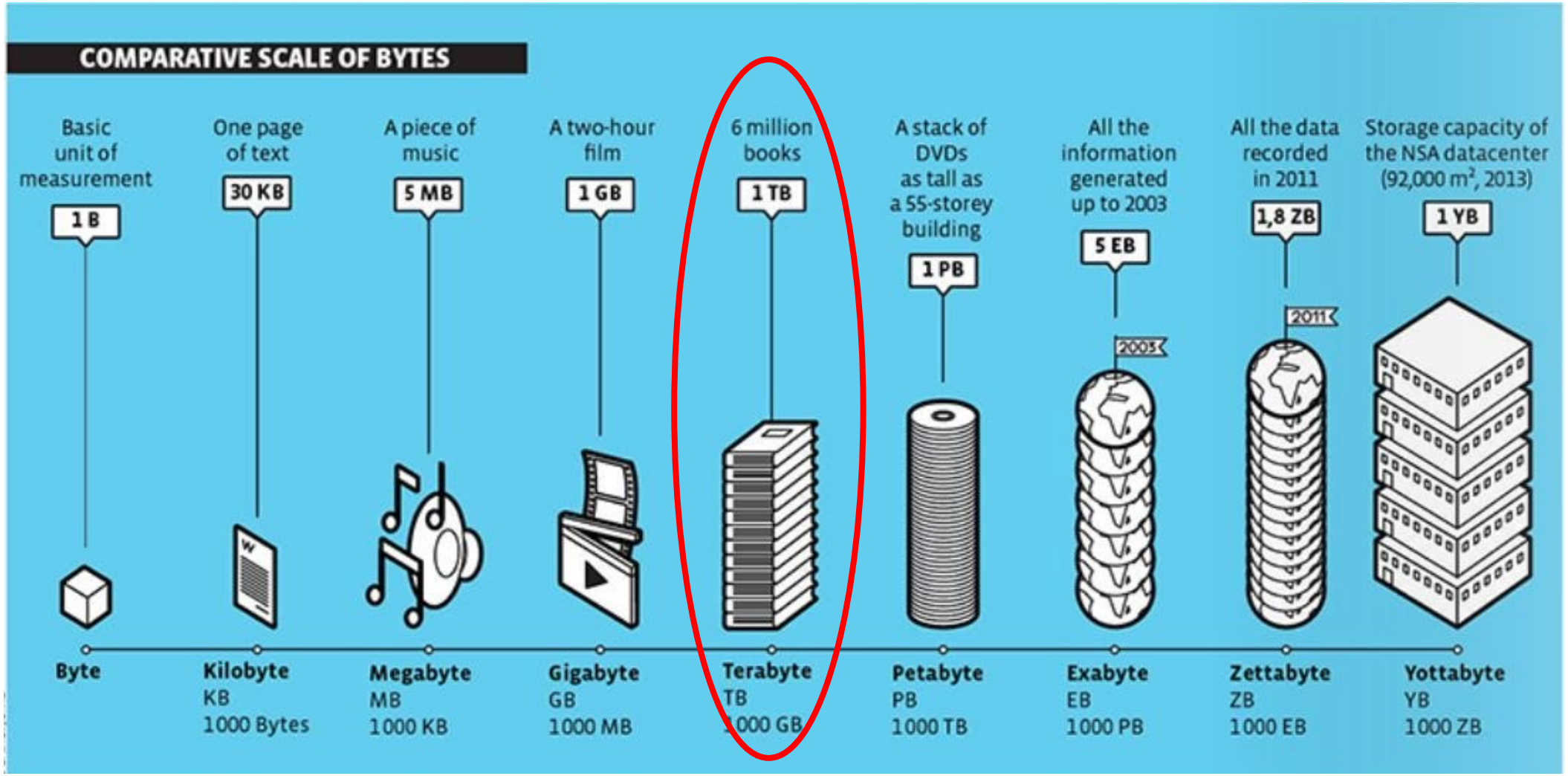


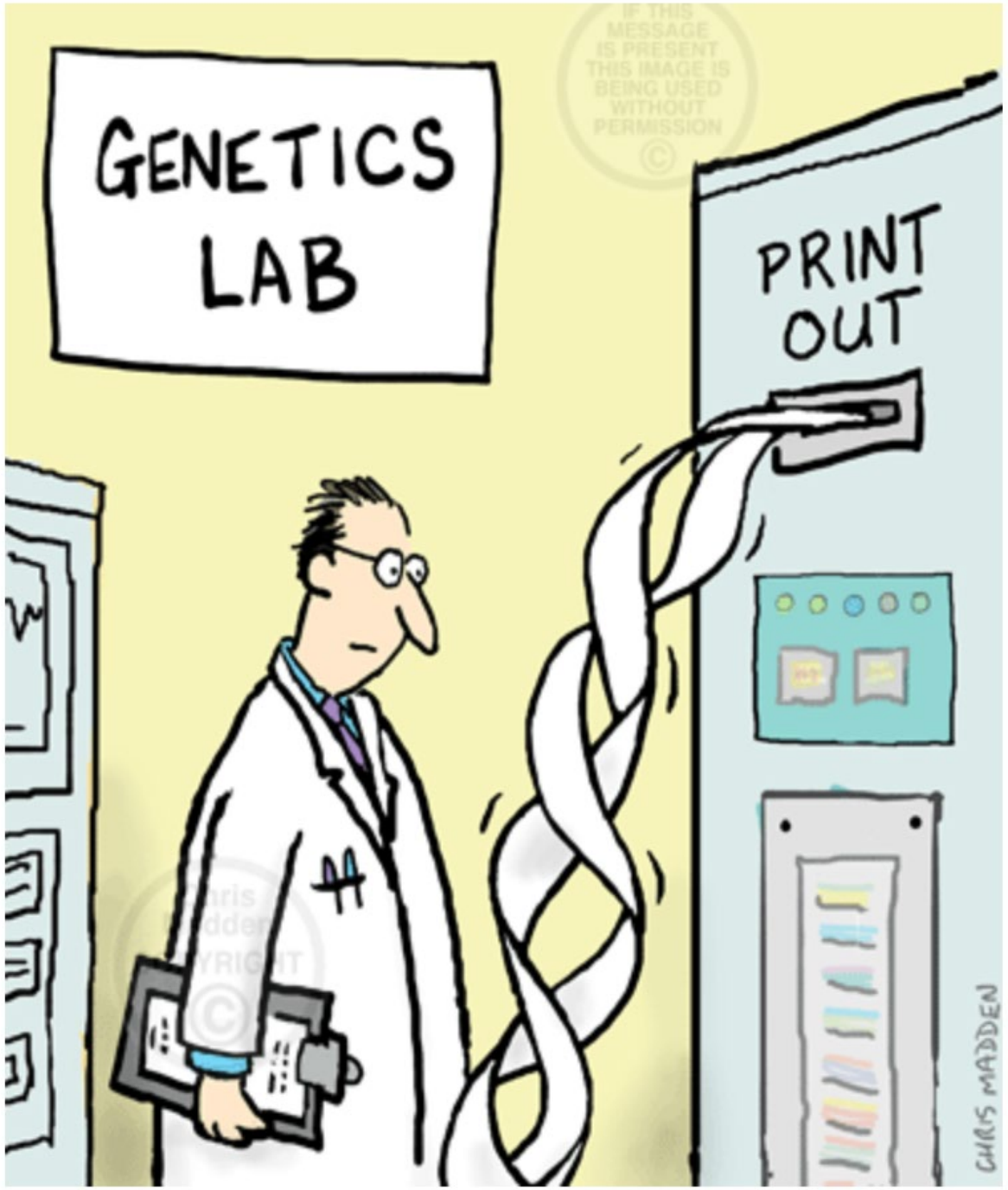

Genexus


1
2
3
4


GX5
DAHK00759

GENETICS = BIG DATA





https://www.chrismadden.co.uk/cartoon-gallery/genetics-cartoon-the-printer-in-a-genetics-laboratory-printing-out-with-the-paper-forming-a-double-helix-spiral/

How do we integrate millions of data points into patient care?

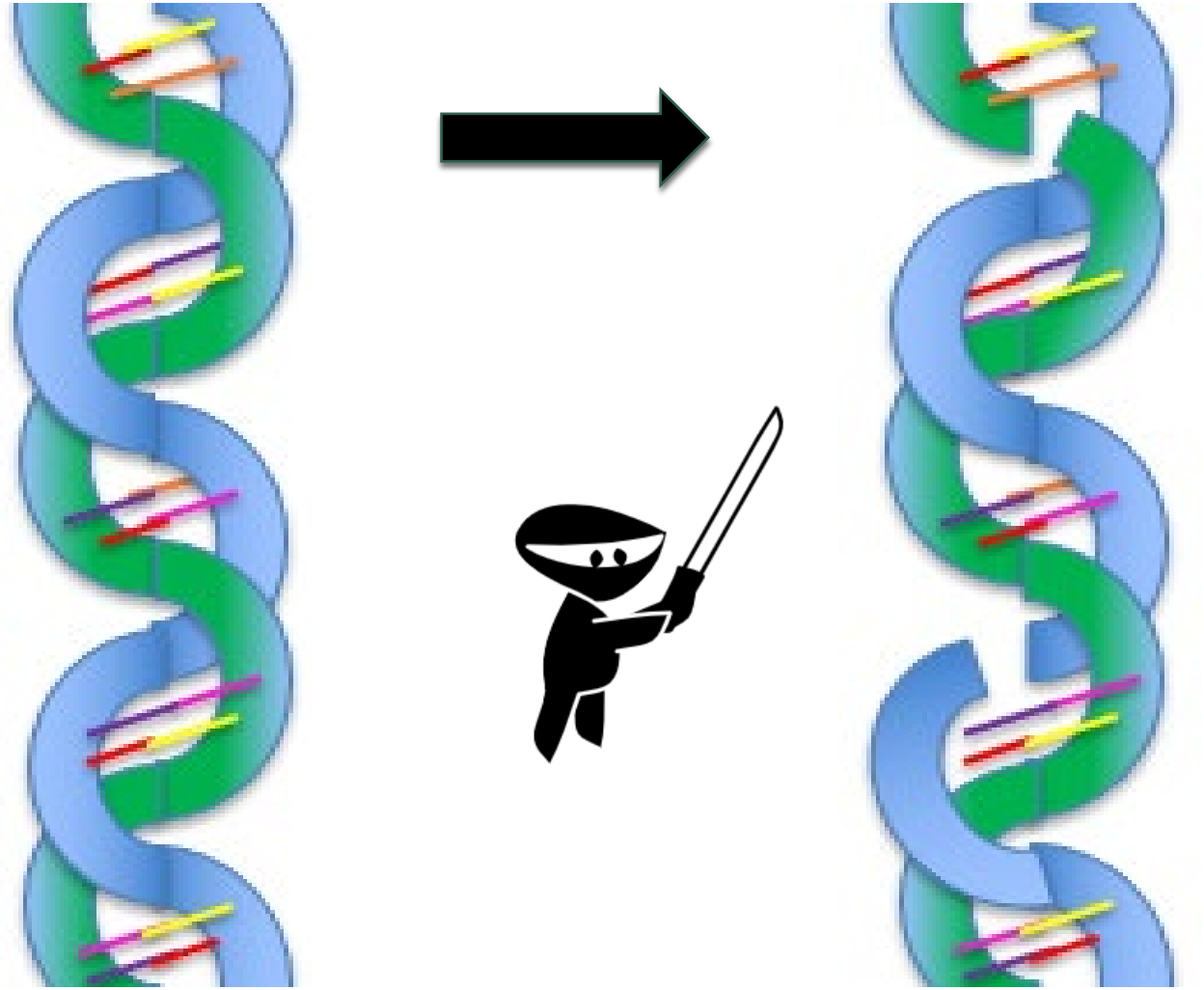
CONVERTING NGS DATA TO PATIENT OUTCOMES

CHEMOTHERAPY

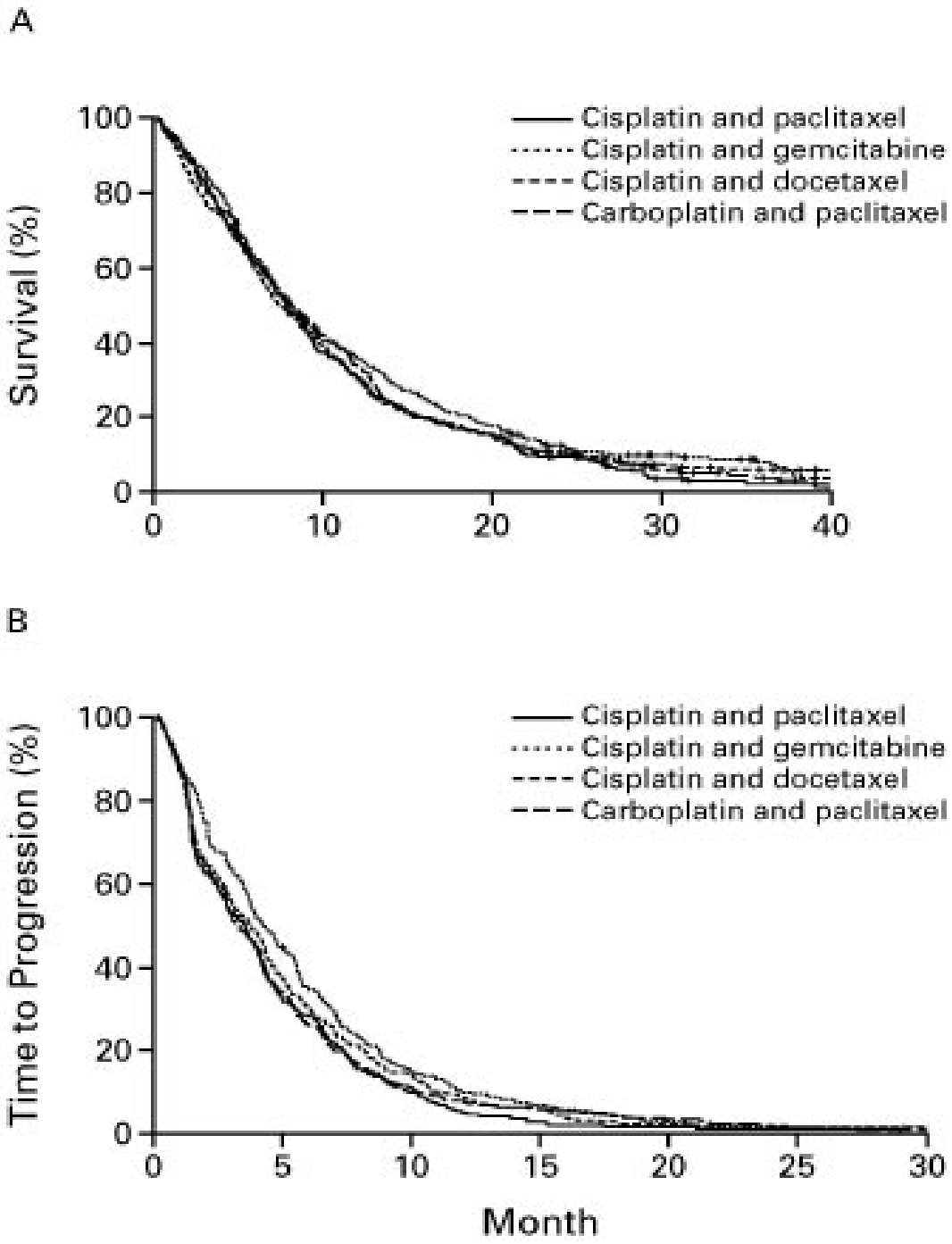
Interferes with Cell Replication

Indiscriminant Targeting of Dividing Cells

Significant Toxicity



NON-SMALL CELL LUNG CANCER TREATED WITH CHEMOTHERAPY (BEFORE GENOMICS …WHEN I STARTED IN ONC)



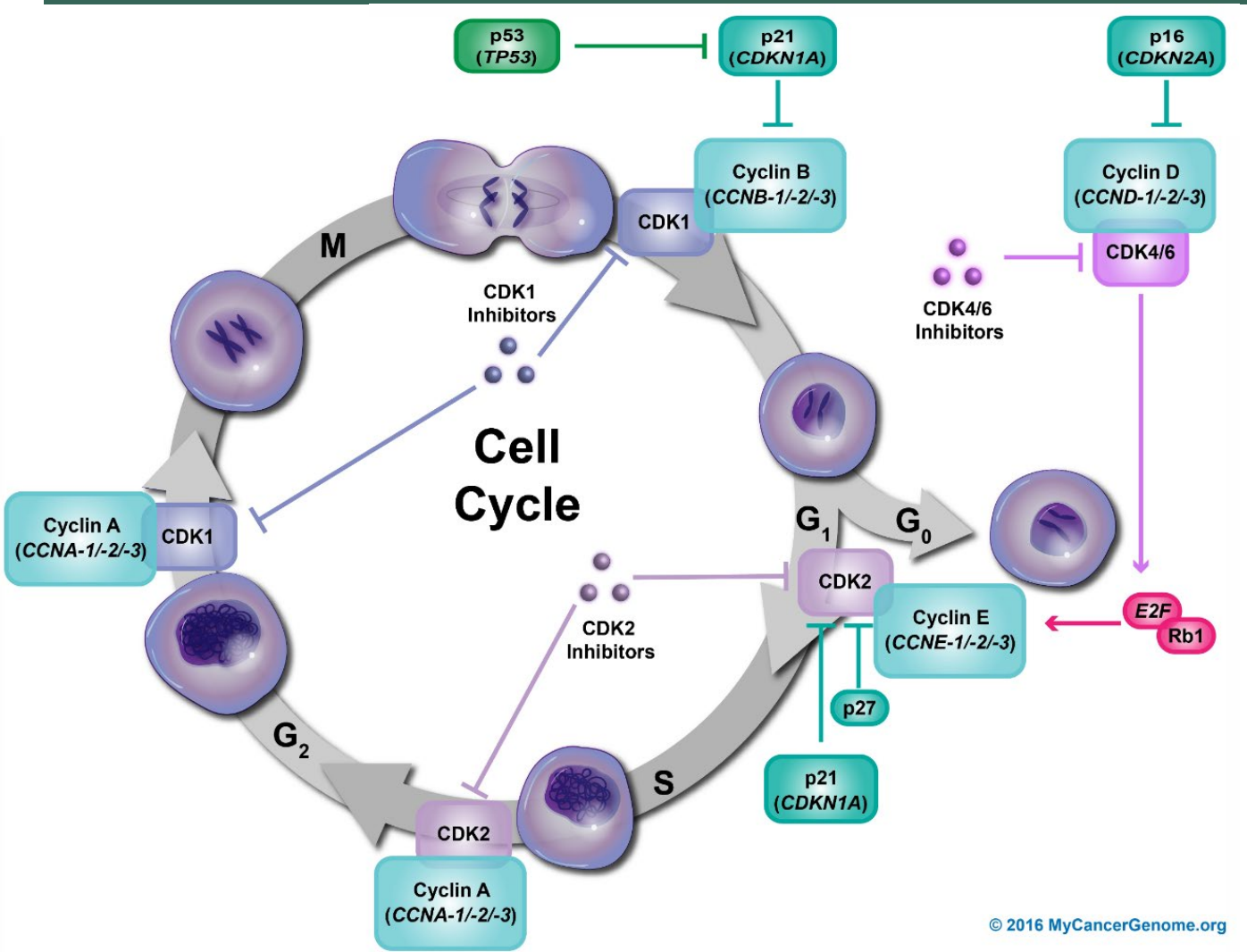
Median Survival = 8 months

Response Rate = 19%

Median Time to Tumor Progression = 3.7 months

Schiller JH. NEJM 2002; 346:92-98

CELL CYCLE AND MUTATIONS



https://www.mycancergenome.org/content/pathways/cell-cycle-control/

CELL CYCLE AND MUTATIONS

Proto-oncogenes:

- NORMAL genes
- Encodes for growth factors
- Signals

Oncogenes

- ABNORMAL
- Promote Cancer

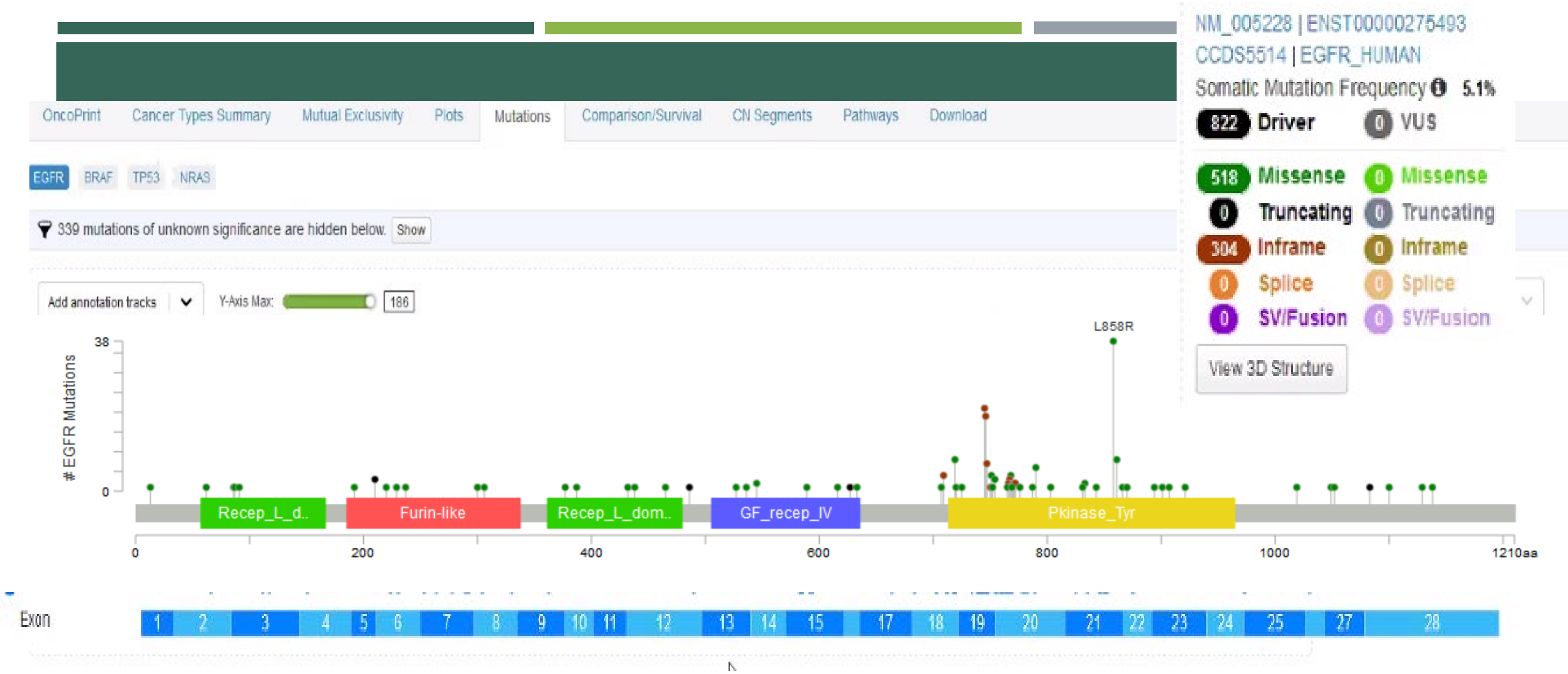
Mutation

Chromosomal Rearrangements

Gene Amplification

Gain of Function
More Gas!!

Loss of Function
No more Stop Sign


NM_005228 | ENST00000275493
CCDS5514 | EGFR_HUMAN
Somatic Mutation Frequency 5.1%
822 Driver
0 VUS
518 Missense
0 Missense
0 Truncating
0 Truncating
304 Inframe
0 Inframe
0 Splice
0 Splice
0 SV/Fusion
0 SV/Fusion
View 3D Structure
OncoPrint
Cancer Types Summary
Mutual Exclusivity
Plots
Mutations
Comparison/Survival
CN Segments
Pathways
Download
EGFR
BRAF
TP53
NRAS
339 mutations of unknown significance are hidden below.
Show
Add annotation tracks
Y-Axis Max:
186
EGFR Mutations
38
0
L858R
Recep_L_d..
Furin-like
Recep_L_dom..
GF_recep_IV
Pkinase_Tyr
0
200
400
600
800
1000
1210aa
Exon
1
2
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4
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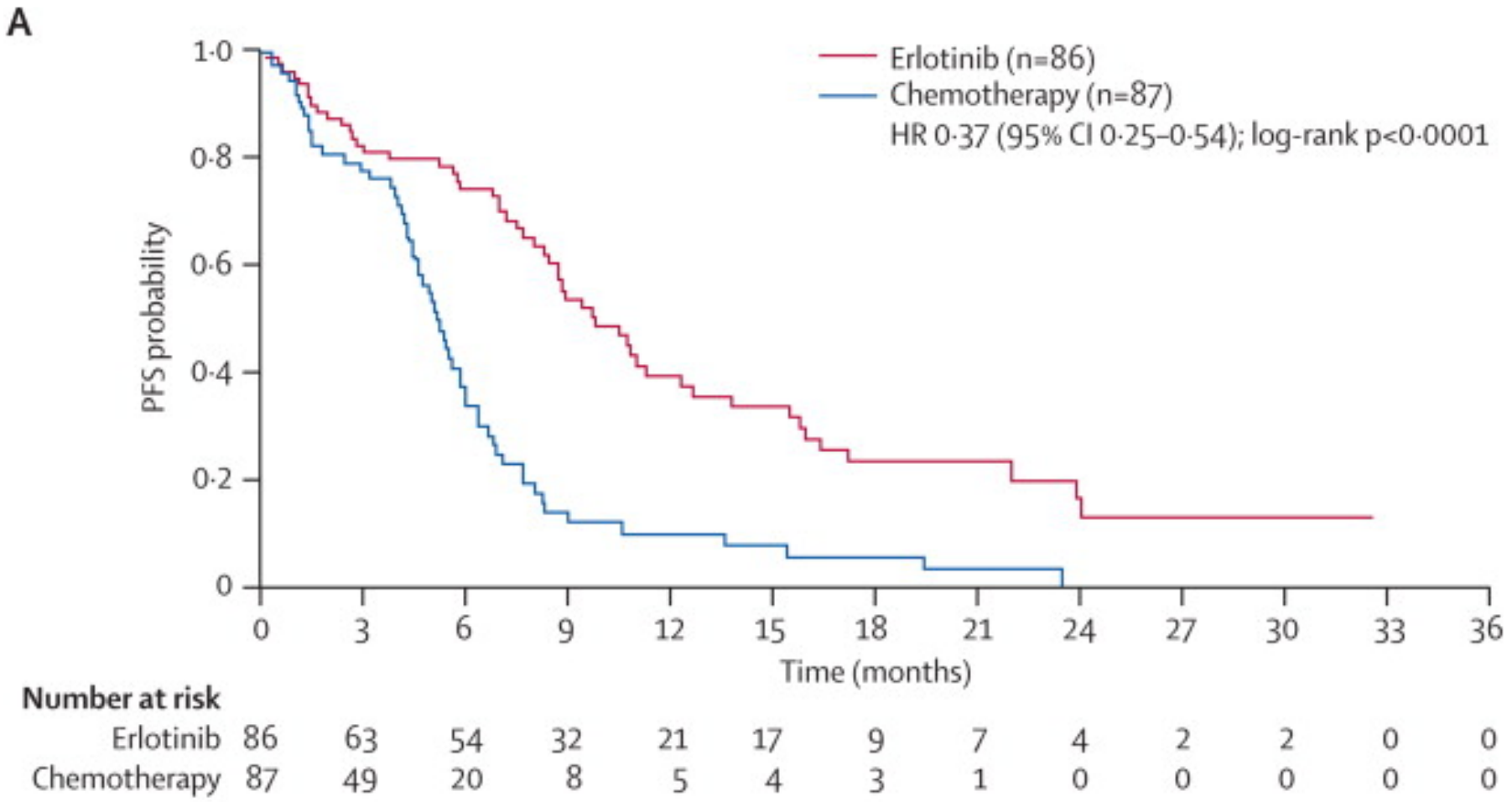
Erlotinib versus standard chemotherapy as first-line EGFR mutation-positive non-small-cell lung cancer



Erlotinib

median PFS = 9.7 months

6% severe treatment-related ADRs

.

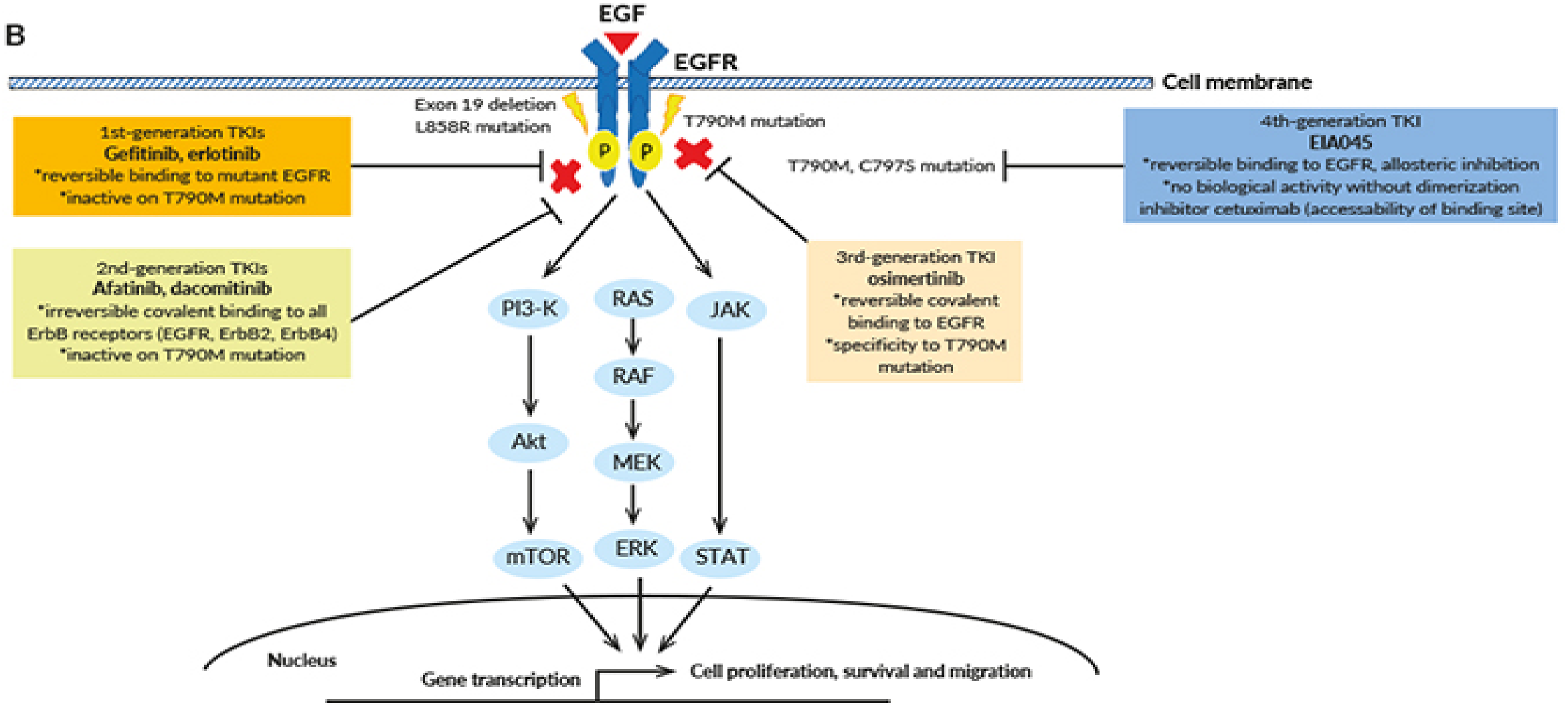
Chemotherapy

Median PFS = 5.2 months

20% severe treatment-related ADRs

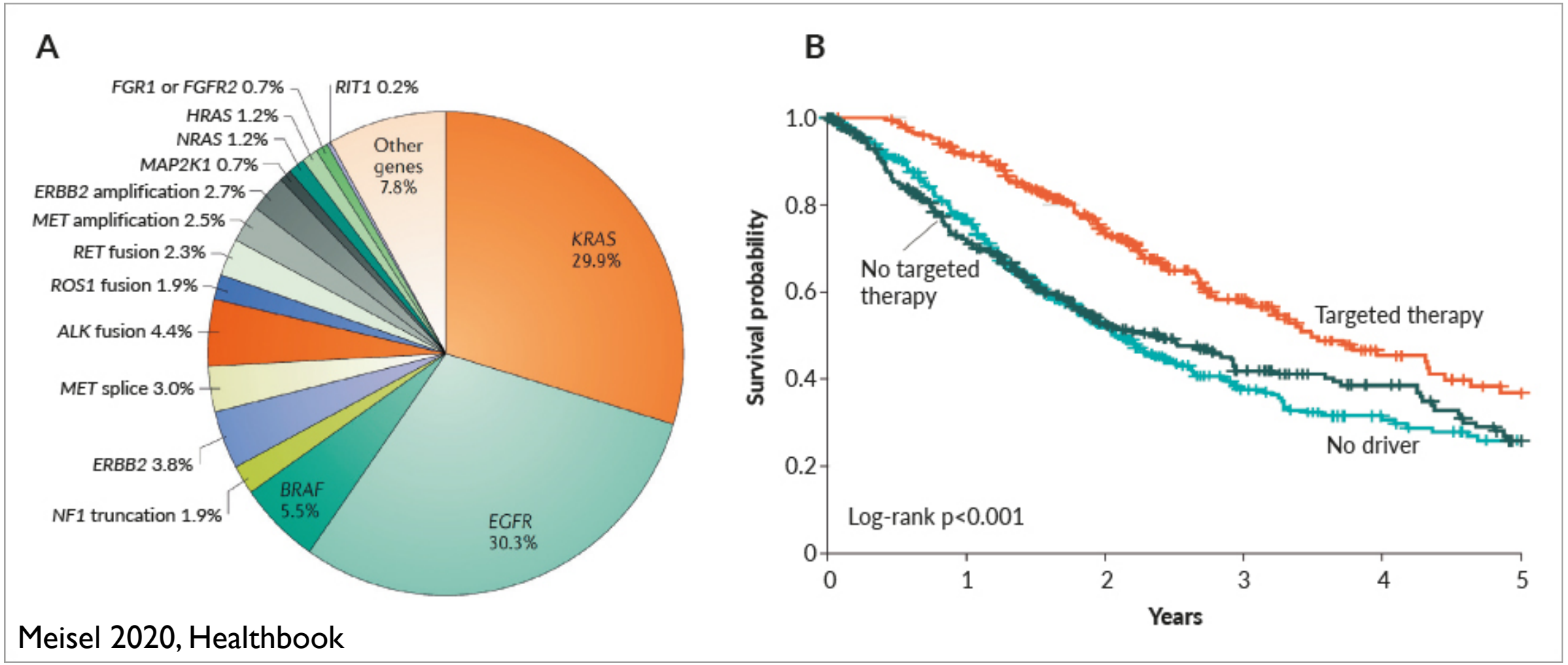
https://pubmed.ncbi.nlm.nih.gov/22285168/

BECOMING MORE TARGETED



Meisel 2020, Healthbook

Title



Meisel 2020, Healthbook

ASSOCIATION WITH DISEASE

Classification	
Pathogenic	**strong** non-conflicting evidence to **show** that the variant is associated with a **greatly increased (high) risk** of cancer.
Likely Pathogenic	non-conflicting evidence to **suggest** an **increased risk** of cancer, though there is not as much evidence to support their classification as with a pathogenic variant.
Variant of Uncertain Significance	not enough evidence, or the evidence is not clear enough, to classify the variant as pathogenic, likely pathogenic, likely benign, or benign.
Likely Benign	non-conflicting evidence **against** the variant being associated with **high risk** of cancer. However, likely benign variants **do not have quite as much evidence** to support their classification as benign variants.
Benign (Little Clinical Significance)	**substantial**, non-conflicting evidence **against** the variant being associated with a **greatly increased (high) risk** of cancer.

https://www.genome.gov/sites/default/files/media/files/2020-04/Guide_to_Interpreting_Genomic_Reports_Toolkit.pdf

VUS

There are several reasons why variants are classified as VUS, such as:

- The effect of the specific genetic alteration on gene function is not known.
- There are insufficient genetic data to definitively confirm that the variant is associated with risk of developing the disease.
- The patient is unaffected and has no symptoms, or different symptoms than those expected based on the variant found..”

PUBLIC DATABASES AND RESOURCES TO EVALUATE NGS RESULTS

Clinical Actionablity

cBioPortal

- https://www.cbioportal.org/

OncoKB

- https://www.oncokb.org/

JaxLab CKB

- https://ckb.jax.org/gene/show?geneId=5290

Genetic Databases

ClinVar

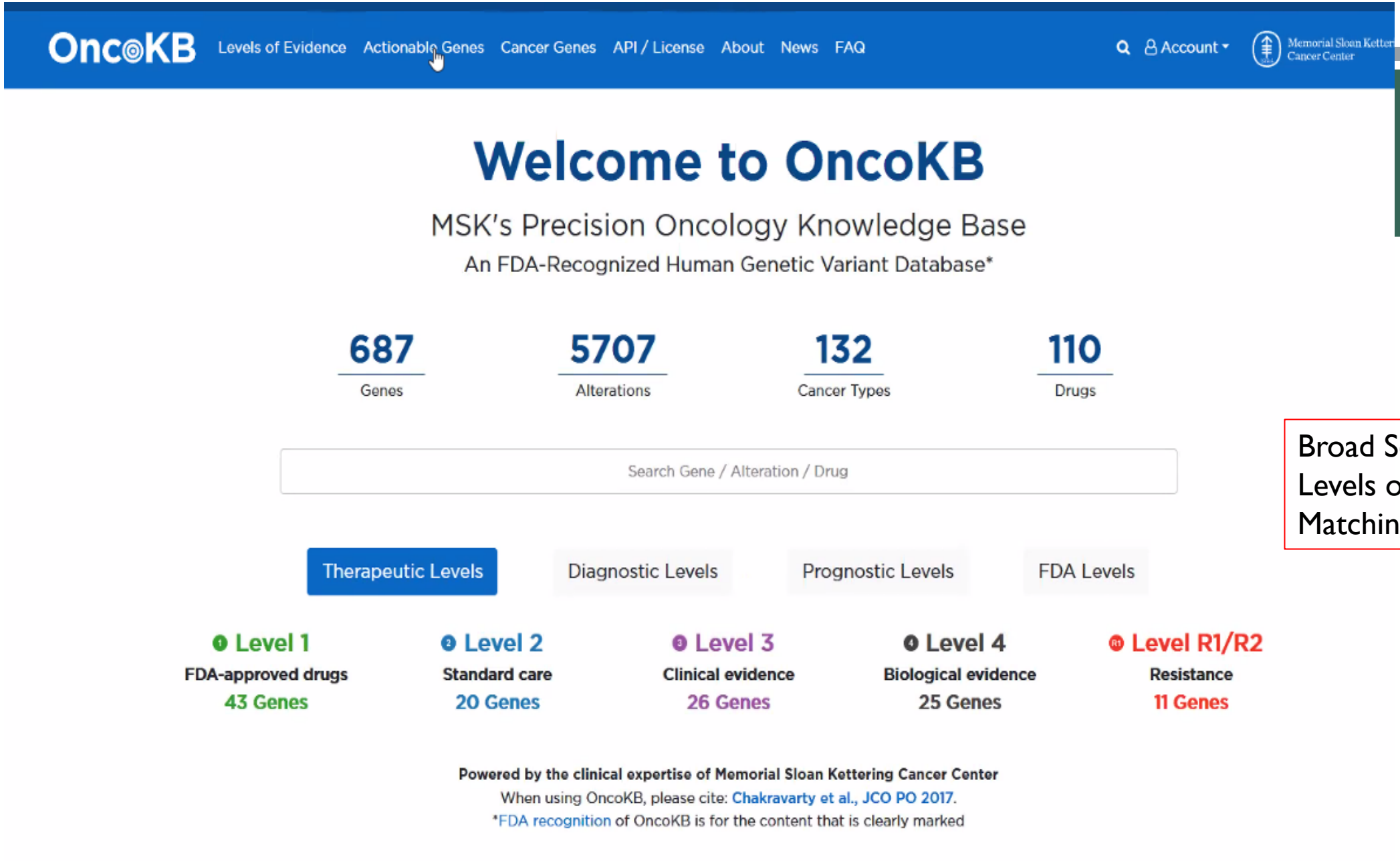
- https://www.ncbi.nlm.nih.gov/clinvar/

BRCA Exchange

- https://brcaexchange.org/
- Significant of specific

gnomAD (plus ExAC)

- https://gnomad.broadinstitute.org/
- Useful for determining if mutation is germline



Broad Search Ability
Levels of Evidence
Matching with Therapeutics

PIK3CA

Oncogene

Highest level of evidence: Level 1 · FDA Level 2

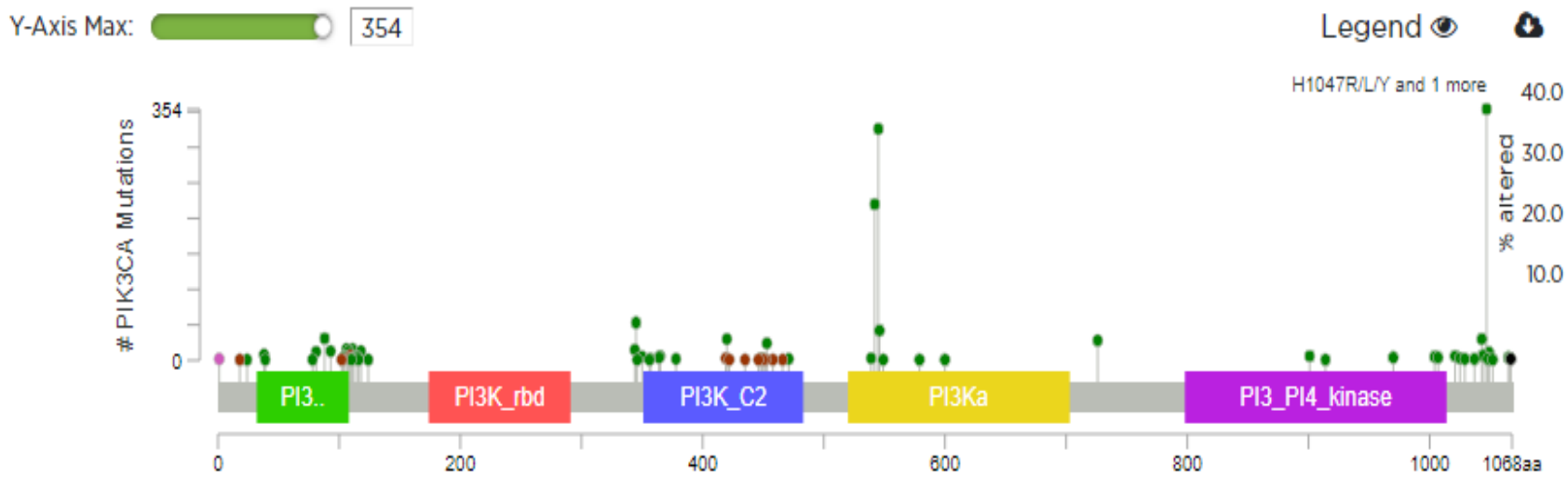
Also known as PI3K

PIK3CA, the catalytic subunit of PI3-kinase, is frequently mutated in a diverse range of cancers including breast, endometrial and cervical cancers.

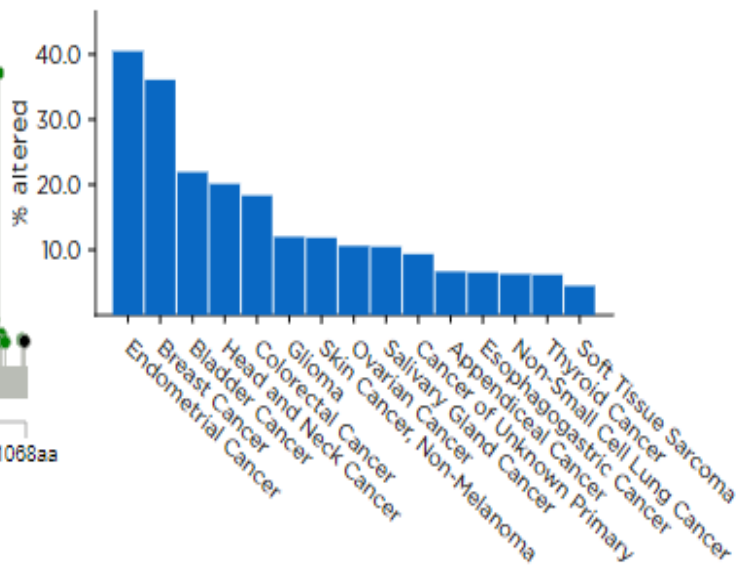
Show PIK3CA background

NCBI Gene	5290
Ensembl Gene	ENSG00000121879 (GRCh37/GRCh38)
Location	Chr3:178865902-178957881 (GRCh37) Chr3:179148114-179240093 (GRCh38)
Ensembl Transcript	ENST00000263967 (GRCh37/GRCh38)
RefSeq	NM_006218.2 (GRCh37/GRCh38)

Annotated Mutations in MSK-IMPACT Clinical Sequencing Cohort (Zehir et al., Nat Med 2017)



Cancer Types with PIK3CA Mutations



Annotated Alterations | Therapeutic | FDA-Recognized Content

A list of the oncogenic and mutation effects of **all OncoKB curated** PIK3CA alterations.

If you notice any mistakes or omissions, please reach out to us.

Search ...

Alteration	Oncogenic	Mutation Effect	Citations
Amplification	Likely Oncogenic	Likely Gain-of-function	16
M1V	Inconclusive	Inconclusive	2
W11L	Likely Neutral	Likely Neutral	1
C24Y	Likely Neutral	Likely Neutral	1
I31M	Likely Neutral	Likely Neutral	3
R38C	Likely Oncogenic	Likely Gain-of-function	1
R38H	Oncogenic	Gain-of-function	5
R38S	Inconclusive	Inconclusive	4
E39K	Likely Oncogenic	Likely Gain-of-function	2
Q60K	Likely Neutral	Likely Neutral	2
E78K	Oncogenic	Inconclusive	1
E81K	Inconclusive	Inconclusive	4
R88Q	Oncogenic	Gain-of-function	3

− Therapeutic

Level 1	Level 2	Level 3	Level 4	Level R1	Level R2
FDA-approved drugs	Standard care	Clinical evidence	Biological evidence	Standard care	Clinical evidence
43 Genes	20 Genes	26 Genes	25 Genes	8 Genes	6 Genes

+ Diagnostic (for hematologic malignancies only)

+ Prognostic (for hematologic malignancies only)

+ FDA-Recognized Content

43 actionable genes | Select a cancer type | 70 drugs

Showing 142 clinical implications (43 genes, 28 cancer types, 1 level of evidence) Associations Reset filters

Level	Gene	Alterations	Cancer Types	Drugs
1	ABL1	BCR-ABL1 Fusion	B-Lymphoblastic Leukemia/Lymphoma	Dasatinib
1	ABL1	BCR-ABL1 Fusion	B-Lymphoblastic Leukemia/Lymphoma	Imatinib
1	ABL1	BCR-ABL1 Fusion	B-Lymphoblastic Leukemia/Lymphoma	Ponatinib
1	ABL1	BCR-ABL1 Fusion	Chronic Myelogenous Leukemia	Asciminib
1	ABL1	BCR-ABL1 Fusion	Chronic Myelogenous Leukemia	Bosutinib
1	ABL1	BCR-ABL1 Fusion	Chronic Myelogenous Leukemia	Dasatinib
1	ABL1	BCR-ABL1 Fusion	Chronic Myelogenous Leukemia	Imatinib
1	ABL1	BCR-ABL1 Fusion	Chronic Myelogenous Leukemia	Nilotinib
1	ABL1	T315I	B-Lymphoblastic Leukemia/Lymphoma	Ponatinib
1	ABL1	T315I	Chronic Myelogenous Leukemia	Asciminib
1	ABL1	T315I	Chronic Myelogenous Leukemia	Ponatinib

INTERPRETING NGS REPORTS

- NGS is one component of the bigger picture
- Cancer Diagnosis
- Staging (ex. Locally advanced, metastatic)
- Prior Therapies
- Goal of Therapy (potentially curative, toxicity burden)
- Other medical conditions that affect therapeutic decision making

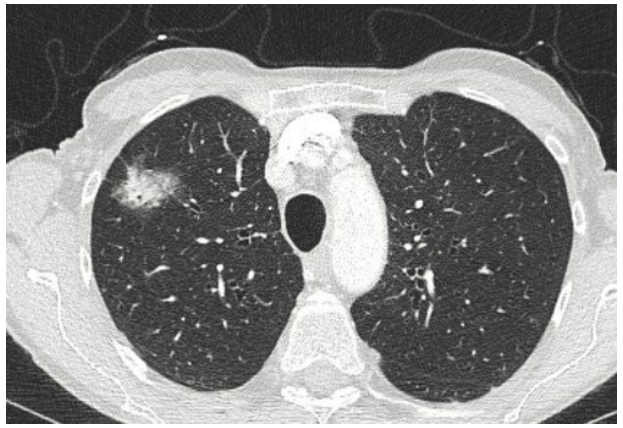
- The hope is that NGS will provide additional treatment options
- Treatment options must be prioritized based on level of evidence and individual patient factors
- While tumors can change, NGS can sometimes provide possible future options

MOLECULAR TUMOR BOARD

- Multidisciplinary team approach to discussing a patient's history, diagnosis, and treatment
  - Physicians
  - Surgeons
  - Oncologists
  - Pathologists
  - Radiologists / Radiation Oncologists
  - Genetics professionals
  - Pharmacists

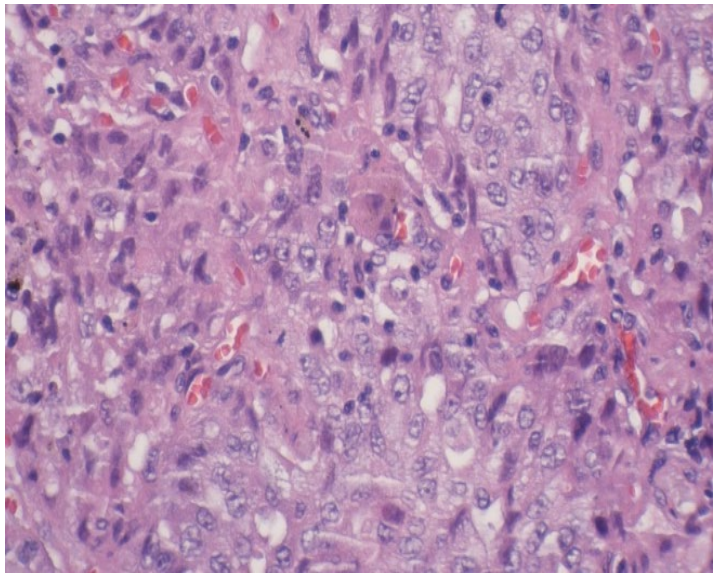
CASE STUDY - INITIAL VISIT 9/2/2015

- 64 year old women
- Presented to pulmonology with syncope and a complex left lower lobe lung mass w/ bilateral pulmonology nodules
- No symptoms of SOB, cough, hemoptysis, or weight loss
- No history of smoking
- Co-morbidities: hyperlipidemia, hypertension
- Labs: CBC, CMP – all within normal limits
- Sent for a CT guided needle biopsy of left lower lobe lung mass



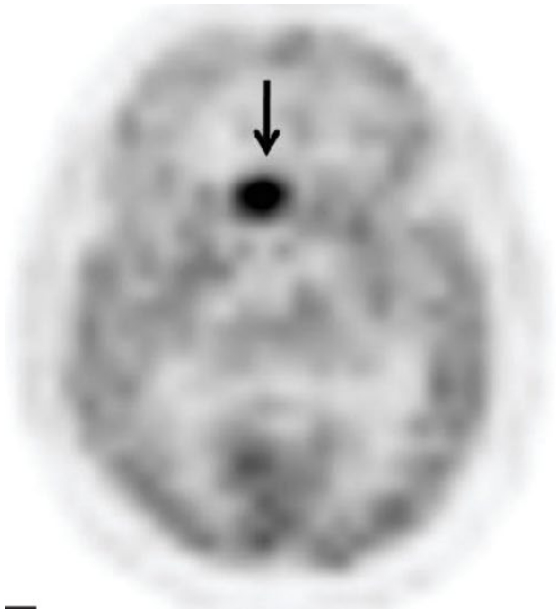
CASE STUDY

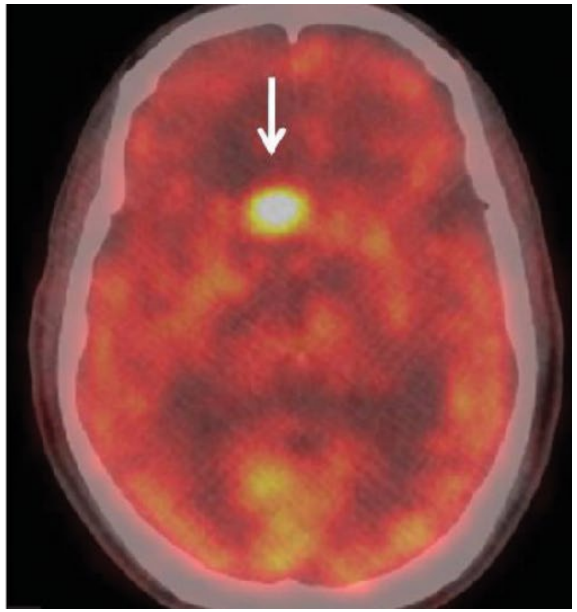
- CT guided needle biopsy performed:
  - Poorly differentiated adenocarcinoma
- Plan:
  - Stage with PET scan and MRI of brain
  - Molecular pathology studies of tumor to evaluate for actionable mutations



CASE STUDY – FOLLOW UP 9/16/2015

- Staging imaging confirms the presence of metastatic disease in the brain
- Surgical resection of primary tumor is contraindicated
- Surgical biopsy is too small to perform genetic analysis
- PLAN:
  - Repeat core biopsy of lung to perform molecular testing





CASE STUDY

- Biopsy was repeated and molecular testing was performed 10/14/15

Sex	Female	**Ordering Physician**	Zipin, Howard	**Specimen Site**	Lung
FMI Case #	TRF111685	**Additional Recipient**	Not Given	**Date of Collection**	22 September 2015
Medical Record #	79729	**Medical Facility ID #**	200481	**Specimen Type**	Block
Specimen ID	15-8512	**Pathologist**	Not Provided		

ABOUT THE TEST:
FoundationOne® is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

- 4 genomic alterations
- 8 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 12 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified†

EGFR A289V, L858R
PIK3R2 E691fs*64+
SUFU R393W

Additional Disease-relevant Genes with No Reportable Alterations Identified†

KRAS
MET
ERBB2
RET
ALK
BRAF

†For a complete list of the genes assayed and performance
‡See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
EGFR A289V, L858R	Afatinib Erlotinib Gefitinib	Cetuximab Lapatinib Panitumumab	Yes, see clinical trials section
PIK3R2 E691fs*64+	None	Everolimus Temsirolimus	Yes, see clinical trials section
SUFU R393W	None	None	Yes, see clinical trials section

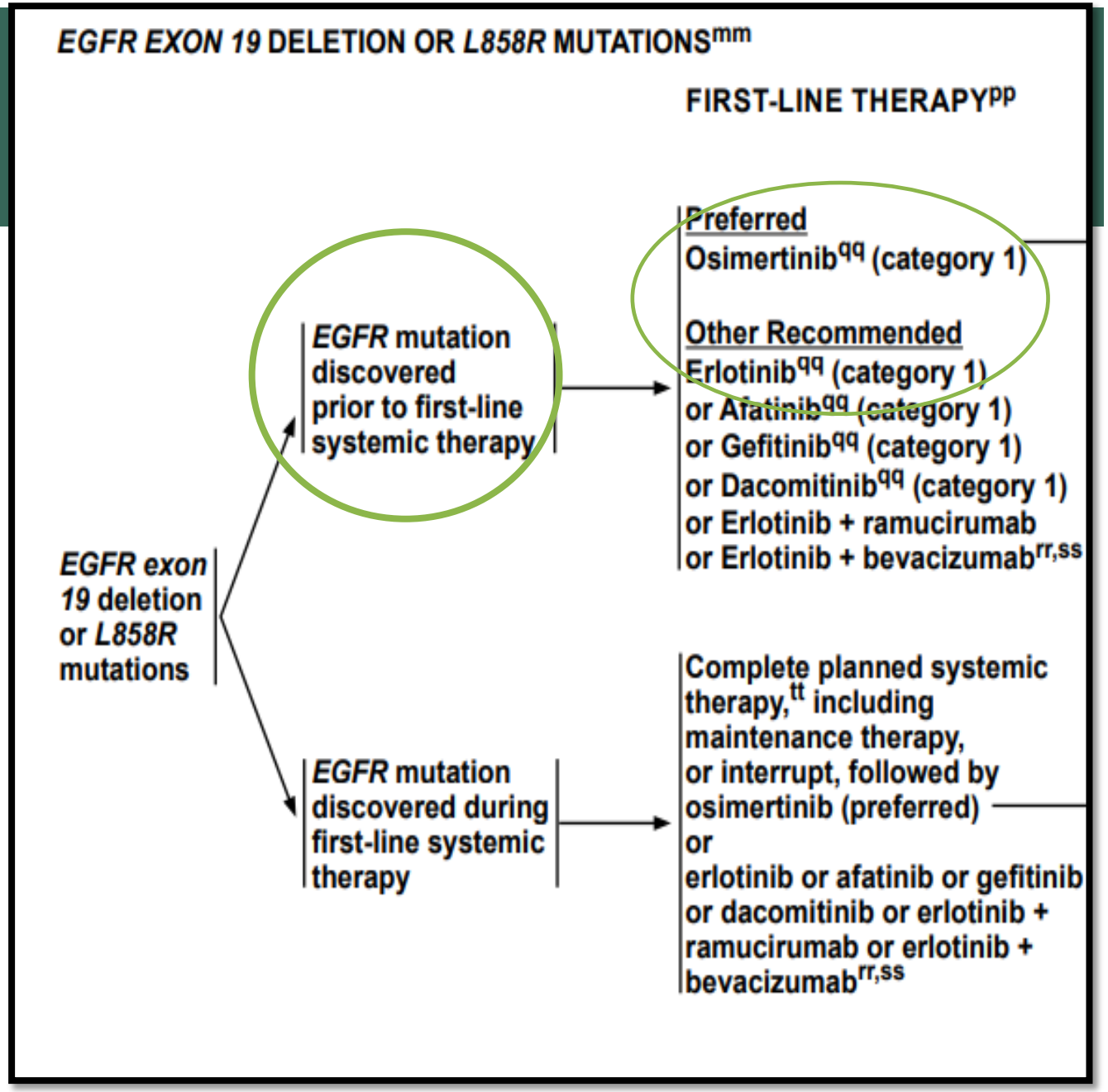
MOLECULAR TESTING 10/14/2015

Alteration	Function	Oncogenic	On Label	Clinical Trial (in PA)	Off Label Level of Evidence (OncoKb)
EGFR A289V	receptor tyrosine kinase	Oncogenic, GOF	None	None	Lapatanib in Glioma, Level 4
EGFR L858R	receptor tyrosine kinase	Oncogenic, GOF	Afatinib Dacomitinib Erlotinib Erlotinib + Ramucirumab Gefitinib Osimertinib	NCT04077463 NCT04487080	Patritumab Deruxtecan in NSCLC, Level 3A
PIK3R2 E691FS*64+	component of the pro-oncogenic PI3-kinase/AKT/mTOR signaling pathway	Tumor Suppressor, Likely LOF	None	None	Everolimus or Temsirolimus in RCC (Foundation One report)
SUFU R393W	encodes the protein suppressor of fused, which is a negative regulator of hedgehog signaling	Tumor Suppressor, Unknown	None	None	None

FOLLOW UP 10/08/2015

- **Diagnosis:** Stage IV EGFR L858R mutated left lower lobe lung adenocarcinoma

- **Plan:**
  - Initiate erlotonib
  - Repeat MRI of the brain in 6 weeks
  - Repeat PET scan in 3 months.



11/2015 TO 12/2016

- Continues on erlotinib
- Per patient "feeling excellent"
- Radiographically excellent response with almost complete remission in thorax and brain

FOLLOW UP 01/11/2017

- PET/CT scan for routine staging 12/27/16 reveals large pleural effusion
  - FDG inactive
  - Cytological positive for recurrent disease

- **Plan:**
  - Molecular testing: peripheral blood and cell block

MOLECULAR TESTING 02/2017

Peripheral Blood

Result	Value (Previous)	Units	Range	Lab
EGFR cobas(R) v2, NSCLC -*Final*	*Ordered by: H ZIPIN*			
Results:	NEGFP1			LabCorp-01

NEGATIVE

No EGFR mutation was detected in the provided plasma specimen.

(OPDIVO®) PD-L1 Immunohistochemical Analysis

RESULTS

PD-L1 IMMUNOHISTOCHEMICAL ANALYSIS: NEGATIVE

Percentage of Positive Tumor Cells: 0%

Cell Block from thoracentesis

RESULT SUMMARY: ABNORMAL

MARKERS IDENTIFIED IN SAMPLE:

EGFR p.Leu858Arg

EGFR p.Ala289Val

TUMOR TYPE: Adenocarcinoma

CLINICAL INFORMATION:

Left thorax pleural fluid thoracentesis showed adenocarcinoma consistent with secondary pulmonic adenocarcinoma (#17-NG-28).

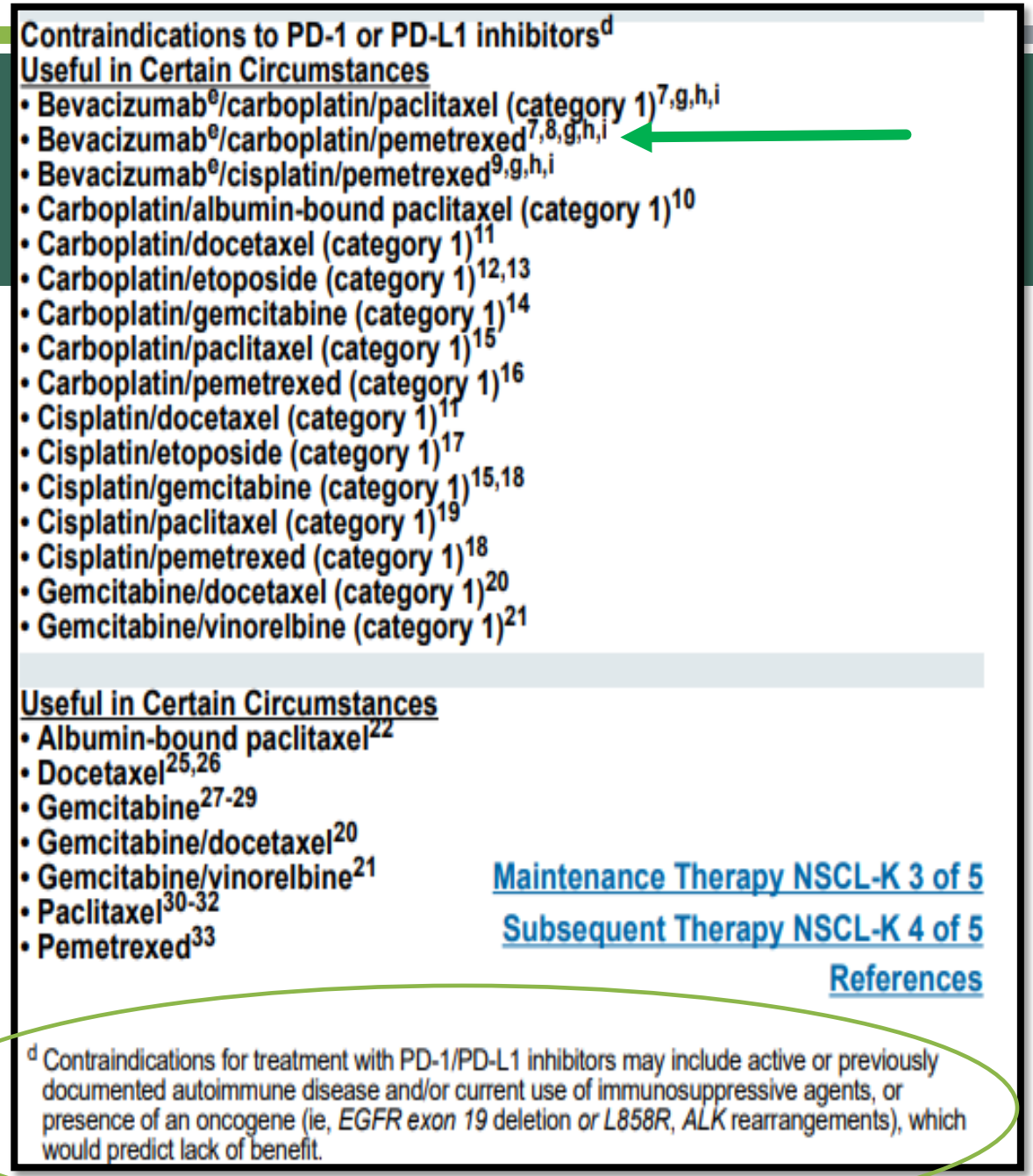
MOLECULAR TESTING 02/2017

Alteration		Function	Oncogenic	On Label	Clinical Trial (in PA)	Off Label Level of Evidence (OncoKb)
EGFR (peripheral blood)	**0%**					
EGFR A289V (lung)		receptor tyrosine kinase	Oncogenic, GOF	None	None	Lapatanib in Glioma, Level 4
EGFR L858R (Lung)		receptor tyrosine kinase	Oncogenic, GOF	Afatinib Dacomitinib Erlotinib Erlotinib + Ramucirumab Gefitinib Osimertinib	NCT04077463 NCT04487080	Patritumab Deruxtecan in NSCLC, Level 3A
PDL1 (IHC)	**0%**					

FOLLOW UP 03/2017

- Pleural effusion fluid positive for recurrent disease
- EGFR mutation was not identified in the peripheral blood sample
- EGFR L858 mutation identified in cell block (as previous)
- PDL1 IHC 0%

- Plan:
  - Pemetrexed/Carboplatin with Bevacizumab x 4 cycles (d/c due to fatigue and anemia)



Contraindications to PD-1 or PD-L1 inhibitors[d]

Useful in Certain Circumstances

- Bevacizumab[e]/carboplatin/paclitaxel (category 1)[7,g,h,i]
- Bevacizumab[e]/carboplatin/pemetrexed[7,8,g,h,i]
- Bevacizumab[e]/cisplatin/pemetrexed[9,g,h,i]
- Carboplatin/albumin-bound paclitaxel (category 1)[10]
- Carboplatin/docetaxel (category 1)[11]
- Carboplatin/etoposide (category 1)[12,13]
- Carboplatin/gemcitabine (category 1)[14]
- Carboplatin/paclitaxel (category 1)[15]
- Carboplatin/pemetrexed (category 1)[16]
- Cisplatin/docetaxel (category 1)[11]
- Cisplatin/etoposide (category 1)[17]
- Cisplatin/gemcitabine (category 1)[15,18]
- Cisplatin/paclitaxel (category 1)[19]
- Cisplatin/pemetrexed (category 1)[18]
- Gemcitabine/docetaxel (category 1)[20]
- Gemcitabine/vinorelbine (category 1)[21]

Useful in Certain Circumstances

- Albumin-bound paclitaxel[22]
- Docetaxel[25,26]
- Gemcitabine[27-29]
- Gemcitabine/docetaxel[20]
- Gemcitabine/vinorelbine[21]
- Paclitaxel[30-32]
- Pemetrexed[33]

Maintenance Therapy NSCL-K 3 of 5

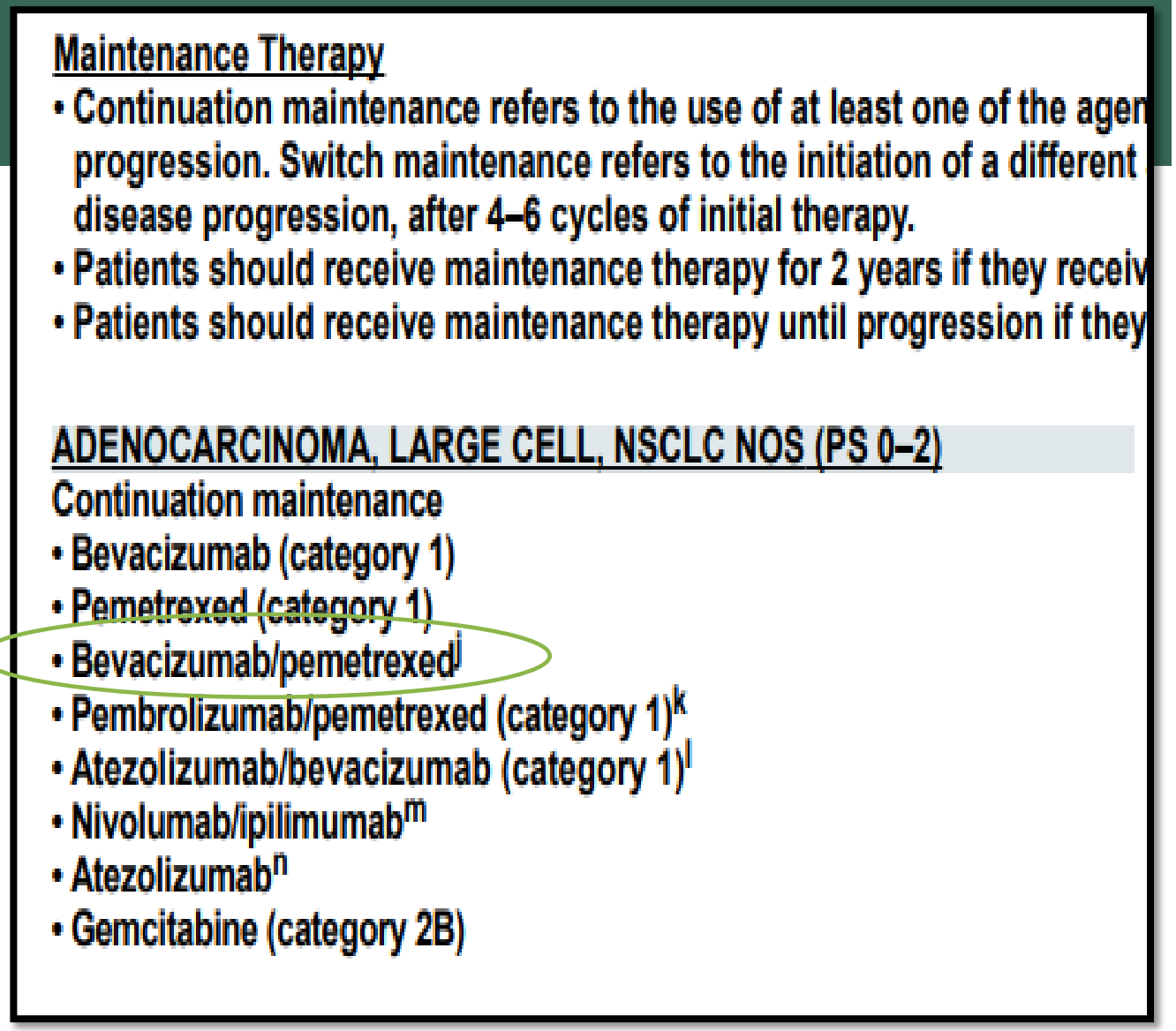
Subsequent Therapy NSCL-K 4 of 5

References

[d] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, or presence of an oncogene (ie, *EGFR exon 19* deletion *or L858R*, *ALK* rearrangements), which would predict lack of benefit.

06/2017 TO 10/2018

- Due to Fatigue and Anemia Patient Could not complete full course
- Pemetrexed / Carboplatin / Bevacizumab
- New Plan
  - Pemetrexed with Bevacizumab X 26 cycles



Maintenance Therapy

- Continuation maintenance refers to the use of at least one of the agen progression. Switch maintenance refers to the initiation of a different disease progression, after 4–6 cycles of initial therapy.
- Patients should receive maintenance therapy for 2 years if they receiv
- Patients should receive maintenance therapy until progression if they

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)

Continuation maintenance

- Bevacizumab (category 1)
- Pemetrexed (category 1)
- Bevacizumab/pemetrexed[j]
- Pembrolizumab/pemetrexed (category 1)[k]
- Atezolizumab/bevacizumab (category 1)[l]
- Nivolumab/ipilimumab[m]
- Atezolizumab[n]
- Gemcitabine (category 2B)

FOLLOW UP 10/03/2018

- Progressive disease: chest, bone
- D/C pemetrexed and bevacizumab

- **Plan:**
  - Start Nivolumab and bone modifier
  - Liquid biopsy for expanded molecular profile

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)

Preferred (no previous IO):

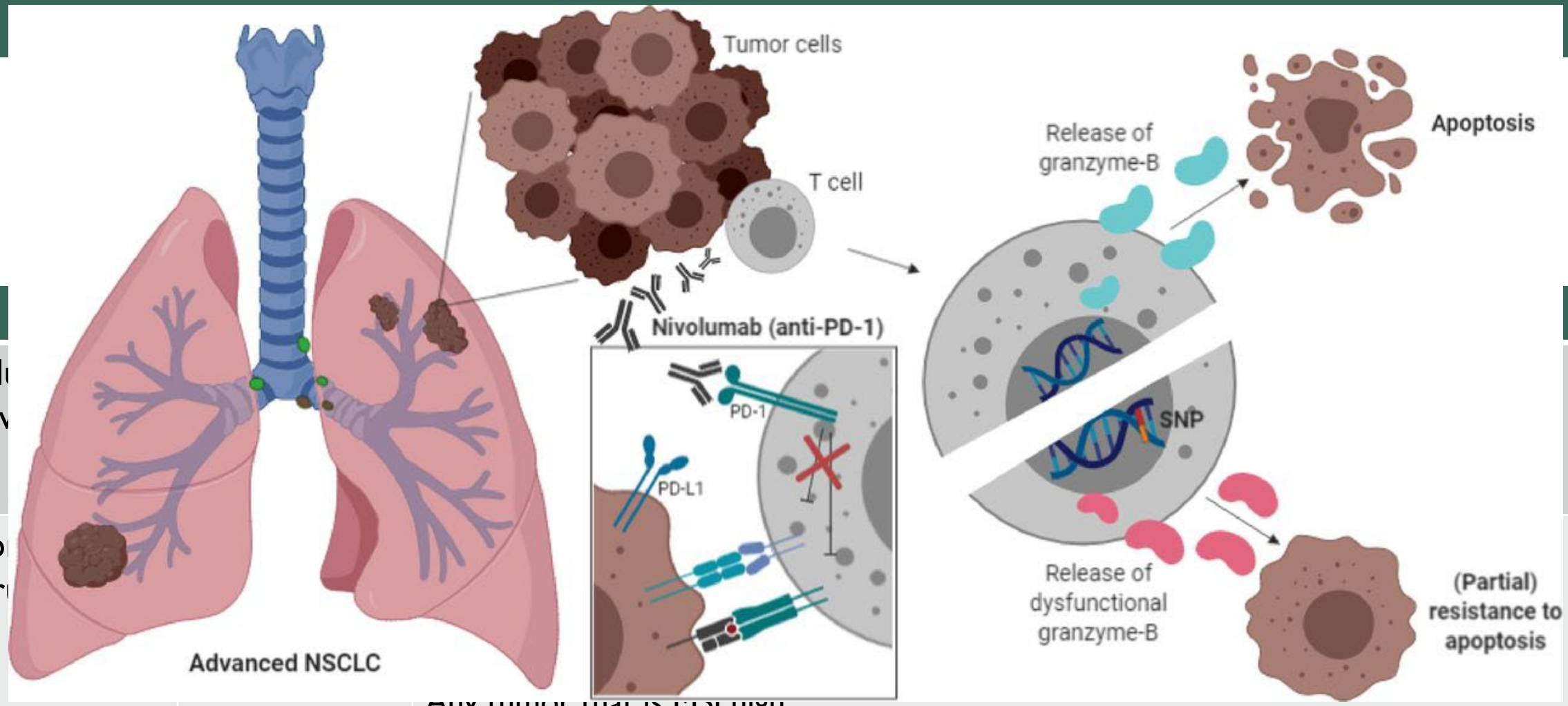
Systemic immune checkpoint inhibitors[e]

- Nivolumab (category 1)
- Pembrolizumab (category 1)[q]
- Atezolizumab (category 1)

Other Recommended (no previous IO or previous IO):[r]

- Docetaxel
- Pemetrexed
- Gemcitabine
- Ramucirumab/docetaxel
- Albumin-bound paclitaxel

PD-1 INHIBITORS (AKA IMMUNOTHERAPY)



Nivol
Opdiv

Pembr
Keytr

Any tumor that is MSI high
Any tumor MTB >10

MOLECULAR TESTING 11/21/2018

[redacted]
Patient MRN: [redacted] Gender: Female
Diagnosis: Small cell lung carcinoma | Test Number 1

GUARDANT360
Therapy Finder Page

REPORTING	
Report Date:	NOV-21-2018
Receipt Date:	NOV-15-2018
Collection Date:	NOV-14-2018
Specimen:	Blood
Status:	FINAL

PHYSICIAN
[redacted]
Additional Recipient: N/A

Complete Tumor Response Map on page 2

Summary of Somatic Alterations & Associated Treatment Options

KEY: Approved in indication | Approved in other indication | Lack of response

Alteration	% cfDNA or Amplification	Associated FDA-approved therapies	Clinical trial availability (see page 3)
EGFR T790M	3.1%	Osimertinib Afatinib, Dacomitinib, Erlotinib, Gefitinib, Neratinib	Yes
EGFR L858R	8.1%	Osimertinib	Yes
EGFR A289V	7.5%	Osimertinib	Yes
TP53 C238S	0.2%	None	Yes

Comments

Mircrosatellite status: MSI-High NOT DETECTED

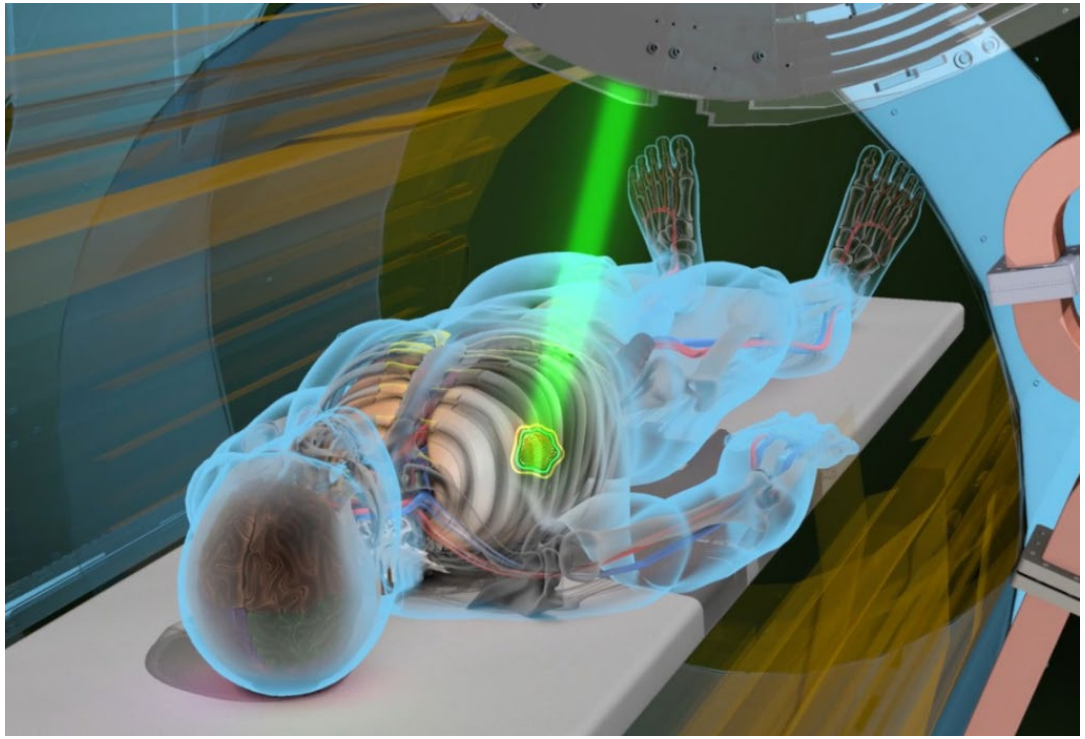
MOLECULAR TESTING 11/21/2018

Alteration		Function	Oncogenic	On Label	Clinical Trial (in PA)	Off Label Level of Evidence (OncoKb)
EGFR T790M (3.1%)		receptor tyrosine kinase	Oncogenic, GOF	Osimertinib	None	Predictor of resistance to Erlotinib, Gefitinib, Afatanib
EGFR L858R (8.1%)		receptor tyrosine kinase	Oncogenic, GOF	Afatinib Dacomitinib Erlotinib Erlotinib + Ramucirumab Gefitinib Osimertinib	NCT04077463 NCT04487080	Patritumab Deruxtecan in NSCLC, Level 3A
EGFR A289V (7.5%)		receptor tyrosine kinase	Oncogenic, GOF	None	None	Lapatanib in Glioma, Level 4
TP53 C238S (0.2%)		Tumor suppressor	Likely oncogenic, LOF	None	None	None
MSI-H	**No**					

FOLLOW UP 05/15/2019

- Progression of disease lungs, thoracic lymph nodes, brain
- Asymptomatic, functional status is well preserved

- Plan:
  - Discontinue Nivolumab
  - Whole Brain Radiation
  - Continue bone modifier
  - After completion WBRT, start Docetaxel/Ramucirumab



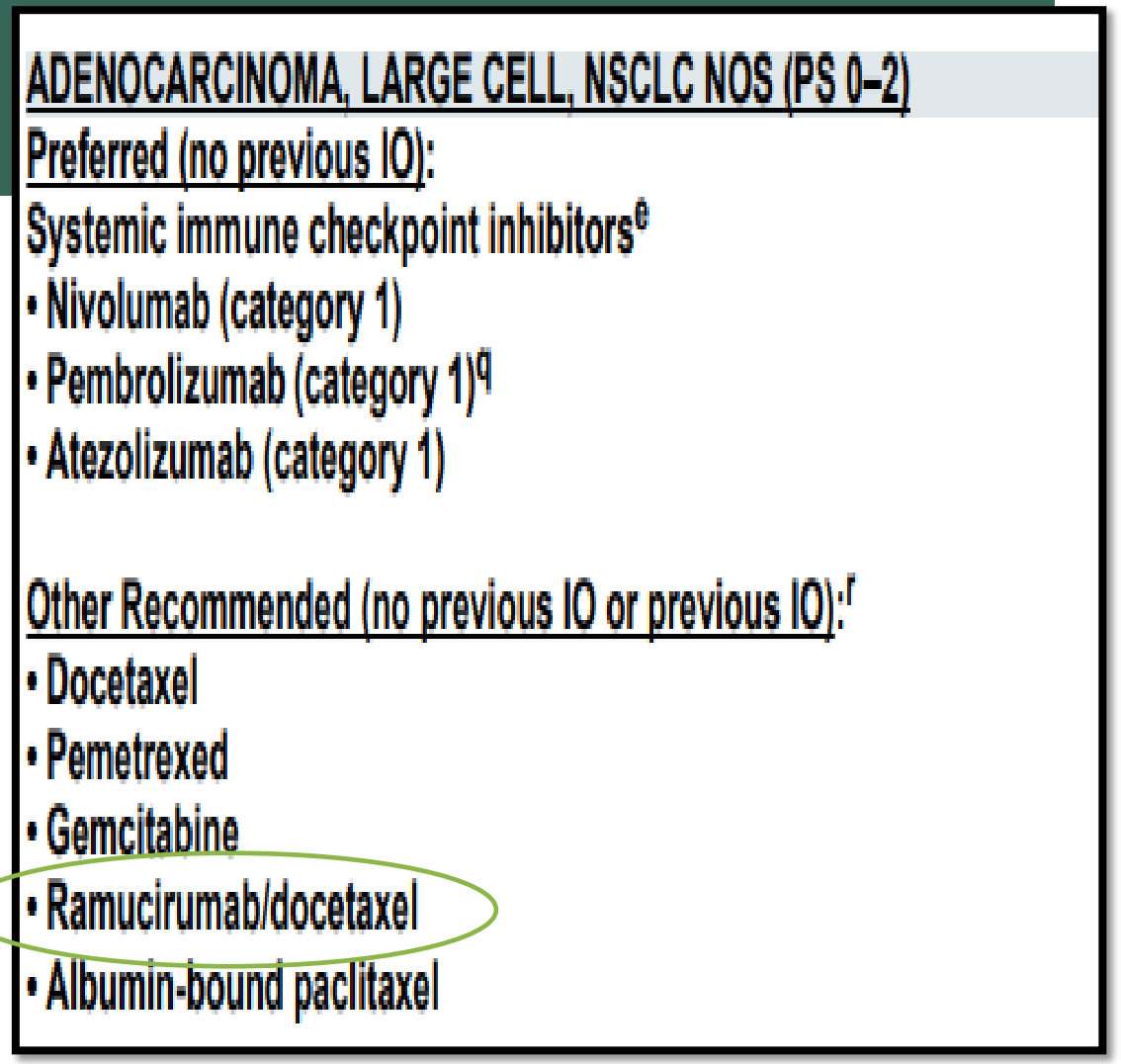
https://onlinelibrary.wiley.com/doi/full/10.1111/1759-7714.13429

Targeted therapies for NSCLC patients harboring driver oncogene alterations are generally recommended regardless of age; therefore, cytotoxic agents are still indicated in those with driver oncogene alterations after targeted therapy.

FOLLOW UP 09/04/2019

- Completed Docetaxel/Ramucirumab X 5 cycles with partial response
  - Brain MRI: progression of disease despite WBRT
  - CT scan of chest/abdomen/pelvis: shows a partial response

- **Plan:**
  - Repeat molecular testing
  - Change primary therapy for better CNS penetrati on



ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)

Preferred (no previous IO):

Systemic immune checkpoint inhibitors[e]

- Nivolumab (category 1)
- Pembrolizumab (category 1)[q]
- Atezolizumab (category 1)

Other Recommended (no previous IO or previous IO):[r]

- Docetaxel
- Pemetrexed
- Gemcitabine
- Ramucirumab/docetaxel
- Albumin-bound paclitaxel

PROGRESSION FREE SURVIVAL WITH EGFR INHIBITORS

B PFS achieved in trials of patients with *EGFR* mutation-positive non-small cell lung cancer treated with EGFR-TKIs in a first-line setting[a]

			Median PFS, mo (HR [95% CI])					
			Common Mutations		Del19		L858R	
EGFR TKI	Study	Comparator						
Erlotinib	ENSURE	Gemcitabine + cisplatin	n=110	11.0 (0.34 [0.22–0.51])[b]	n=57	11.1 (0.20 [0.11–0.37])[b]	n=52	8.3 (0.57 [0.31–1.05])[b]
	EURTAC	Platinum doublet	n=86	9.7 (0.37 [0.25–0.54])[b]	n=57	11.0 (0.30 [0.18–0.50])[b]	n=29	8.4 (0.55 [0.29–1.02])[b]
	OPTIMAL	Platinum doublet	n=82	13.1 (0.16 [0.10–0.26])[b]	n=43	15.3 (0.13 [0.07–0.25])[b]	n=39	12.5 (0.26 [0.14–0.49])[b]
Gefitinib	IPASS	Carboplatin + paclitaxel	n=132	NR	n=66	11.0 (0.38 [0.26–0.56])[b]	n=64	9.2 (0.55 [0.35–0.87])[b]
	NEJ002	Carboplatin + paclitaxel	n=114	10.8 (0.30 [0.22–0.41])[b]	n=58	11.5[b]	n=49	10.8[b]
	WJTOG3405	Cisplatin + docetaxel	n=86	9.2 (0.49 [0.34–0.71])[b]	n=50	NR (0.45 [0.27–0.77])[b]	n=36	NR (0.51 [0.29–0.90])[b]
Afatinib	LUX-Lung 3	Pemetrexed + cisplatin	n=204	13.6 (0.47 [0.34–0.65])	n=113	13.7 (0.28 [0.18–0.44])	n=91	10.8 (0.73 [0.46–1.17])
	LUX-Lung 6	Gemcitabine + cisplatin	n=216	11.0 (0.25 [0.18–0.35])	n=124	13.7 (0.20 [0.13–0.33])	n=92	9.6 (0.32 [0.19–0.52])
	LUX-Lung 7	Gefitinib	n=160	11.0 (0.73 [0.57–0.95])	n=93	12.7 (0.76 [0.55–1.06])	n=67	10.9 (0.71 [0.48–1.06])
Dacomitinib	ARCHER 1050	Gefitinib	n=227	14.7 (0.59 [0.47–0.74])	n=134	16.5 (0.55 [0.41–0.75])	n=93	12.3 (0.63 [0.44–0.88])[b]
Osimertinib	FLAURA	Gefitinib or erlotinib	n=279	17.7 (0.45 [0.36–0.57])	n=175	21.4 (0.43 [0.32–0.56])[b]	n=104	14.4 (0.51 [0.36–0.71])[b]

Meisel 2020, Healthbook

MOLECULAR TESTING 10/19/2019

[redacted] Gender: Female
Diagnosis: Lung adenocarcinoma | Test Number 1

GUARDANT360
Therapy Finder Page

REPORTING		PHYSICIAN
Report Date:	OCT-19-2019	[redacted]
Receipt Date:	OCT-15-2019	
Collection Date:	OCT-14-2019	
Specimen:	Blood	
Status:	FINAL	

Complete Tumor Response Map on page 2

Summary of Somatic Alterations & Associated Treatment Options

KEY ✓ Approved in indication ✓ Approved in other indication ✗ Lack of response

Alteration	% cfDNA or Amplification	Associated FDA-approved therapies	Clinical trial availability (see page 3)
EGFR T790M	0.2%	✓ Osimertinib ✗ Afatinib, Dacomitinib, Erlotinib, Gefitinib, Neratinib	Yes
EGFR L858R	0.4%	✓ Osimertinib	Yes
EGFR A289V	0.2%	✓ Osimertinib	Yes
TP53 C238S	0.2%	None	Yes

Comments

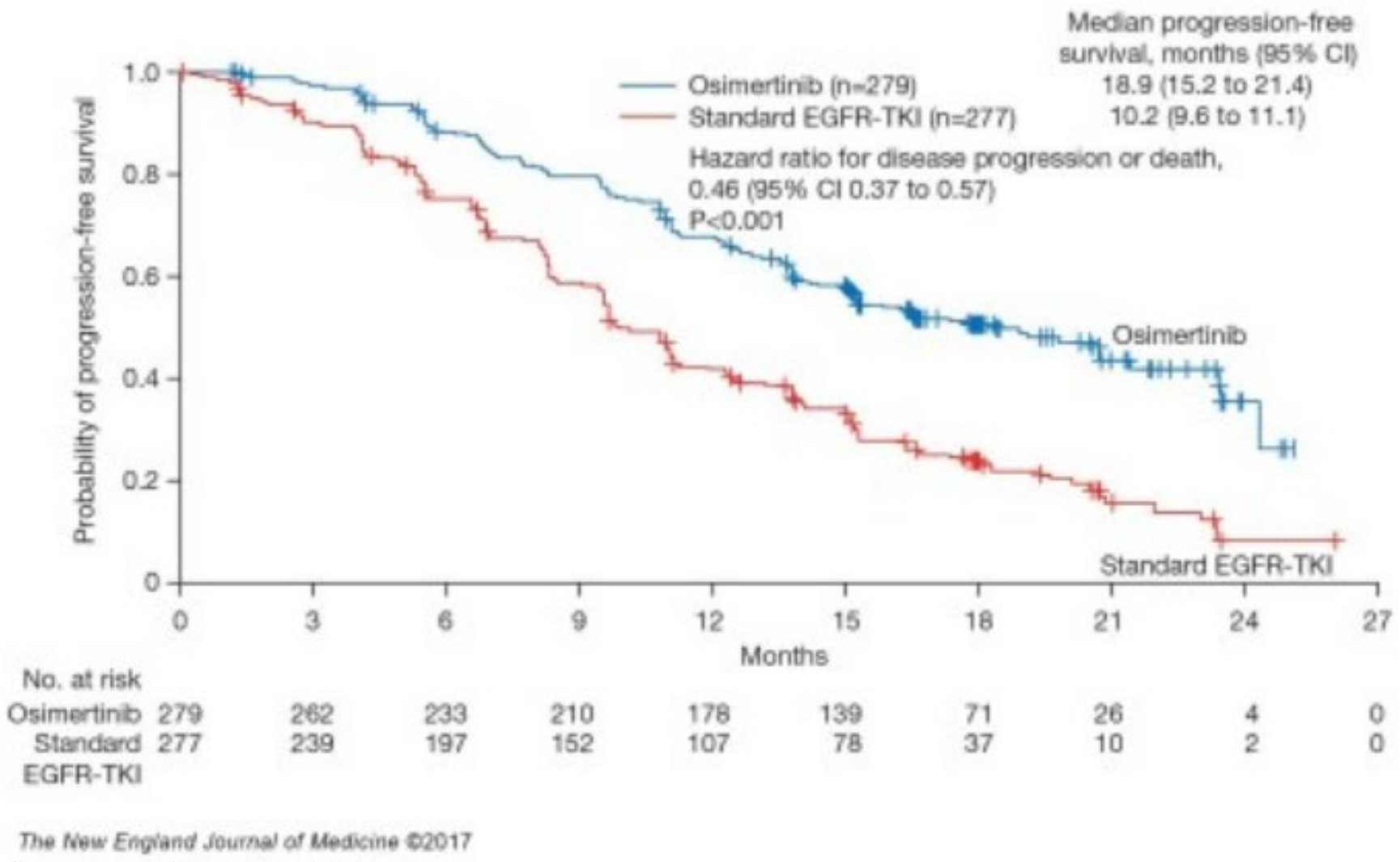
Microsatellite status: MSI-High NOT DETECTED

GenPath EGFR sequencing report | Bux-Mont MD Visit Note v8 [09/27/2 | Bux-Mont MD Visit Note v6 [04/26/2

MOLECULAR TESTING 10/19/2019

Alteration	Function	Oncogenic	On Label	Clinical Trial (in PA)	Off Label Level of Evidence (OncoKb)
EGFR T790M (0.2%)	receptor tyrosine kinase	Oncogenic, GOF	Osimertinib	None	Predictor of resistance to Erlotinib, Gefitinib, Afatanib
EGFR L858R (0.4%)	receptor tyrosine kinase	Oncogenic, GOF	Afatinib Dacomitinib Erlotinib Erlotinib + Ramucirumab Gefitinib Osimertinib	NCT04077463 NCT04487080	Patritumab Deruxtecan in NSCLC, Level 3A
EGFR A289V (0.2%)	receptor tyrosine kinase	Oncogenic, GOF	None	None	Lapatanib in Glioma, Level 4
TP53 C238S (0.2%)	tumor suppressor	Likely oncogenic, LOF	None	None	None
MSI-H **No**					

FIRST LINE TREATMENT OF EGFR-MUTATED NSCLC



Osimertinib

Median PFS = 18.9 months

Standard EGFR

median PFS = 10.2 months

https://www.newswire.co.kr/newsRead.php?no=860060

09/25/2019 TO PRESENT

- Osimertinib 80 mg po once daily
- Tolerating well with no toxicity.
- Repeat restaging CT scan 04/2022 reveals minimal residual stable
- MRI of the brain is NED

- **Plan:**
  - Continue Osimertinib 80 mg po once daily as well as bone modifying agent
  - Repeat CT scans every 4 months
  - Repeat peripheral blood testing