WVU Cancer Institute

MARY BABB RANDOLPH CANCER CENTER

Molecular Tumor Board – How Can We Learn Together?

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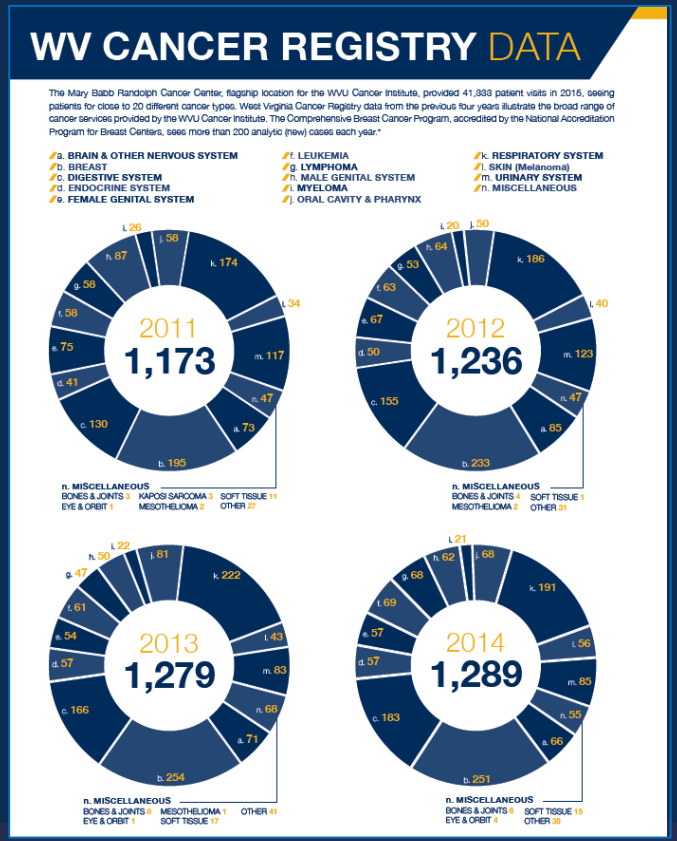
What is a Tumor Board?

Cancer.Net (ASCO)

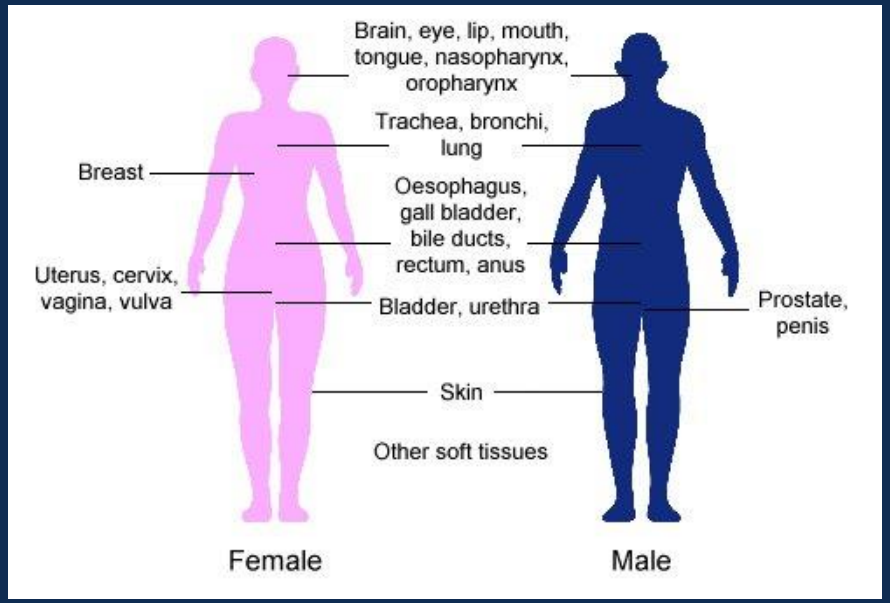
A “Tumor Board” is a group of doctors and other health care providers with different specialties that meets regularly at the hospital to discuss cancer cases and share knowledge. The board’s goal is to determine the best possible cancer treatment and care plan for an individual patient. Having fresh perspectives from other doctors makes it much easier to come up with that plan.

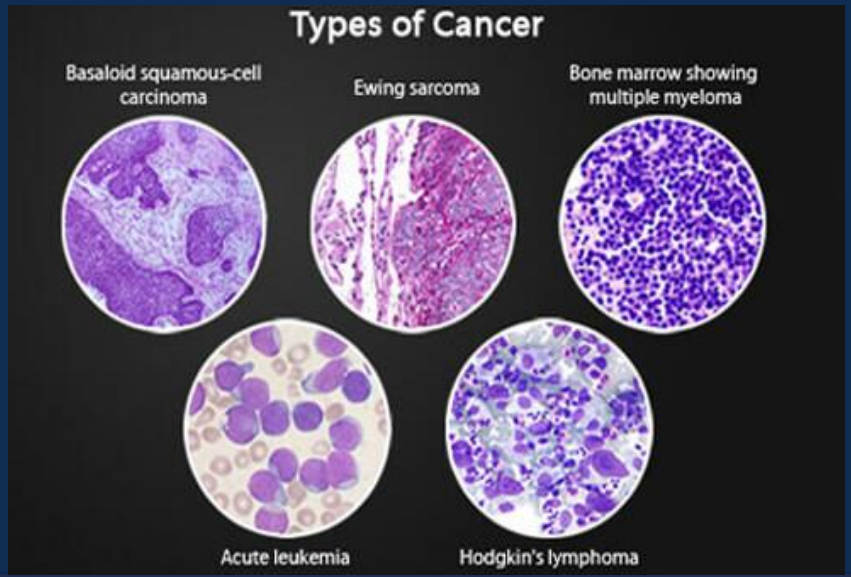
What is a Tumor Board?



The Signature – WVU Cancer Institute Annual Report 2015

What is a Tumor Board?



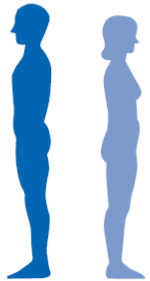


Cancer Sites – New Cases and Deaths

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2017 Estimates

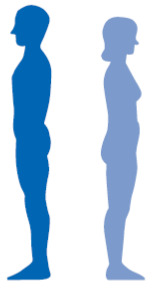
Estimated New Cases

Male			Female		
Prostate	161,360	19%	Breast	252,710	30%
Lung & bronchus	116,990	14%	Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%	Colon & rectum	64,010	8%
Urinary bladder	60,490	7%	Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%	Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%	Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%	Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%	Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%	Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%	Kidney & renal pelvis	23,380	3%
All sites	**836,150**	**100%**	**All sites**	**852,630**	**100%**



Estimated Deaths

Male			Female		
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%	Breast	40,610	14%
Prostate	26,730	8%	Colon & rectum	23,110	8%
Pancreas	22,300	7%	Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%	Ovary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All sites	**318,420**	**100%**	**All sites**	**282,500**	**100%**



Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

What is a Tumor Board?

The Cancer Genome Atlas

COMMENTARY

OPEN

The Cancer Genome Atlas Pan-Cancer analysis project

The Cancer Genome Atlas Research Network[1], John N Weinstein[2,3], Eric A Collisson[4], Gordon B Mills[3], Kenna R Mills Shaw[5,6], Brad A Ozenberger[7], Kyle Ellrott[8,9], Ilya Shmulevich[10], Chris Sander[11] & Joshua M Stuart[8,9]

The Cancer Genome Atlas (TCGA) Research Network has profiled and analyzed large numbers of human tumors to discover molecular aberrations at the DNA, RNA, protein and epigenetic levels. The resulting rich data provide a major opportunity to develop an integrated picture of commonalities, differences and emergent themes across tumor lineages. The Pan-Cancer initiative compares the first 12 tumor types profiled by TCGA. Analysis of the molecular aberrations and their functional roles across tumor types will teach us how to extend therapies effective in one cancer type to others with a similar genomic profile.

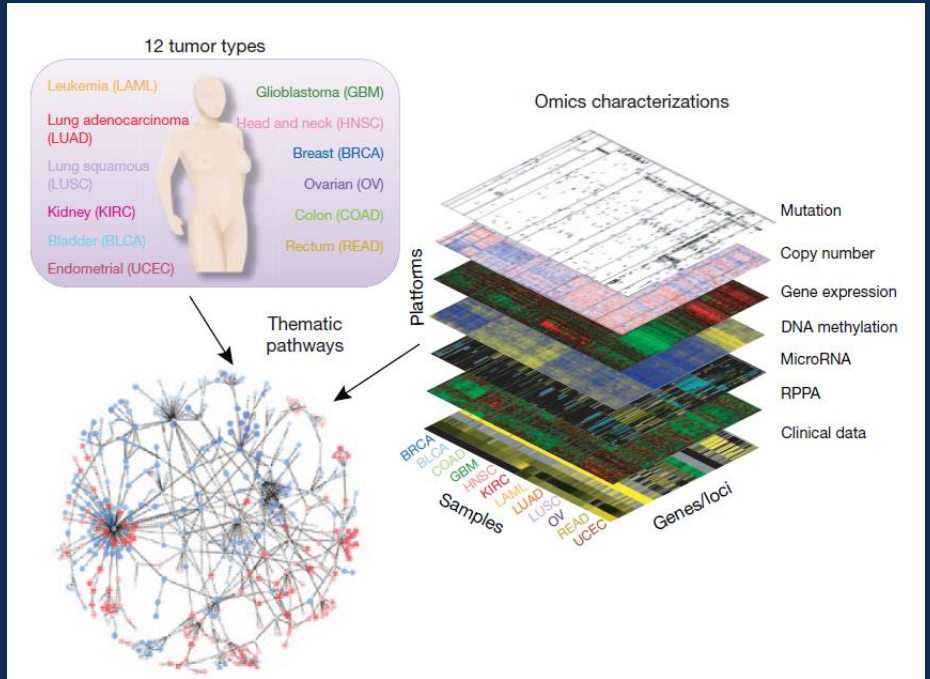


Figure 1 Integrated data set for comparing and contrasting multiple tumor types. The TCGA Pan-Cancer project assembled data from thousands of patients with primary tumors occurring in different sites of the body, covering 12 tumor types (top left) including glioblastoma multiformae (GBM), lymphoblastic acute myeloid leukemia (LAML), head and neck squamous carcinoma (HNSC), lung adenocarcinoma (LUAD), lung squamous carcinoma (LUSC), breast carcinoma (BRCA), kidney renal clear-cell carcinoma (KIRC), ovarian carcinoma (OV), bladder carcinoma (BLCA), colon adenocarcinoma (COAD), uterine cervical and endometrial carcinoma (UCEC) and rectal adenocarcinoma (READ).

Cancer Genome

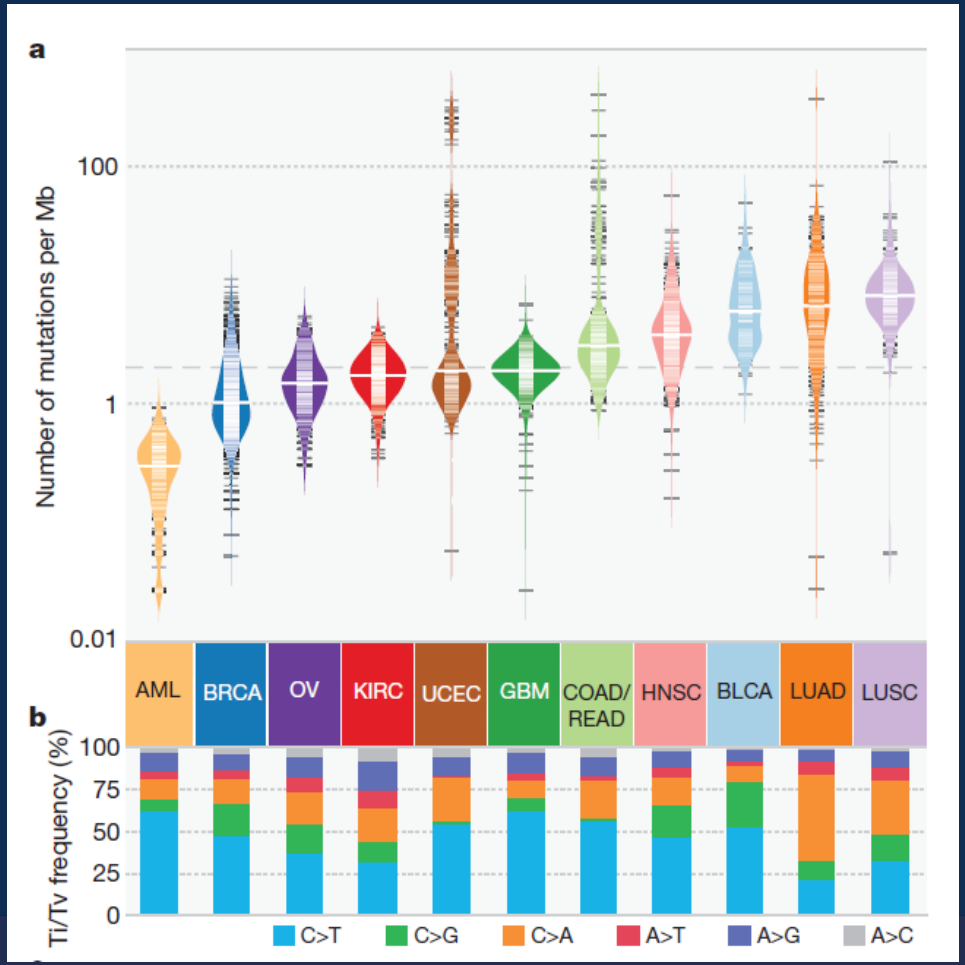
ARTICLE

OPEN

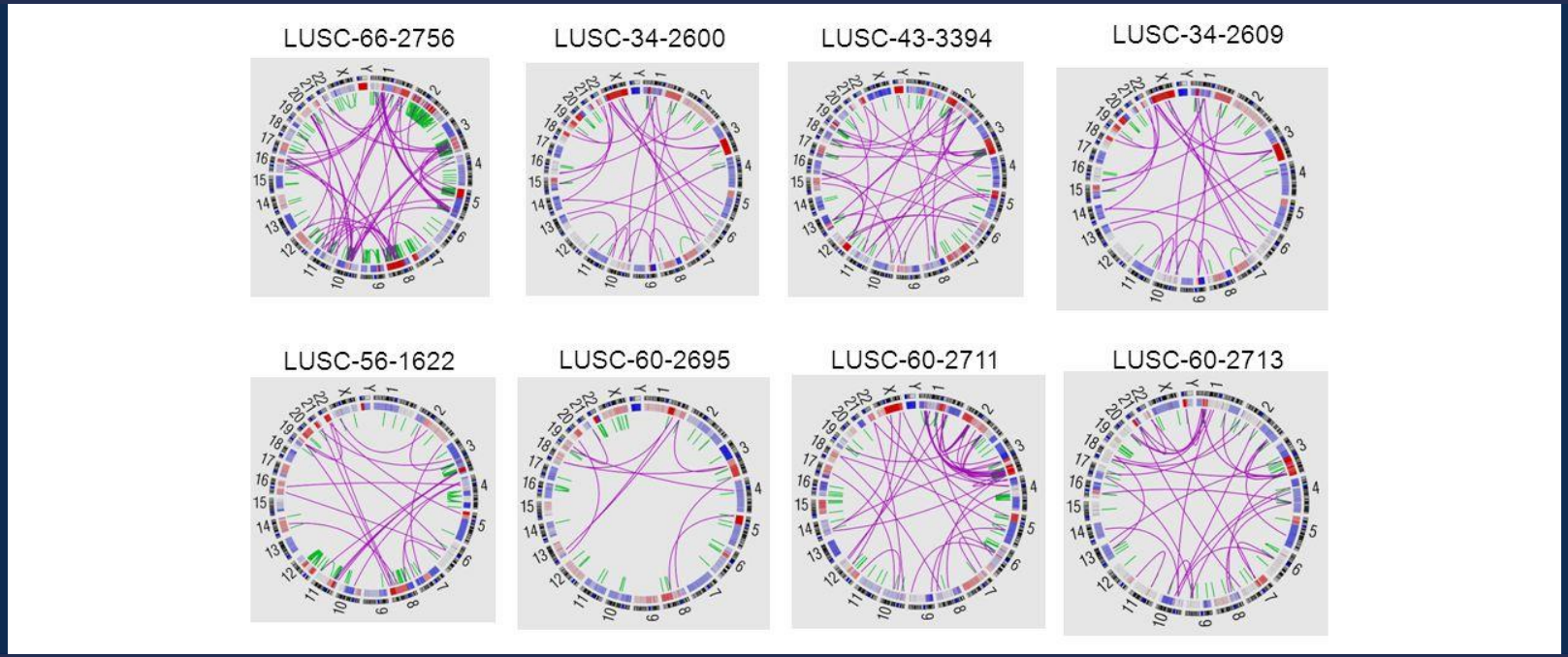
doi:10.1038/nature12634

Mutational landscape and significance across 12 major cancer types

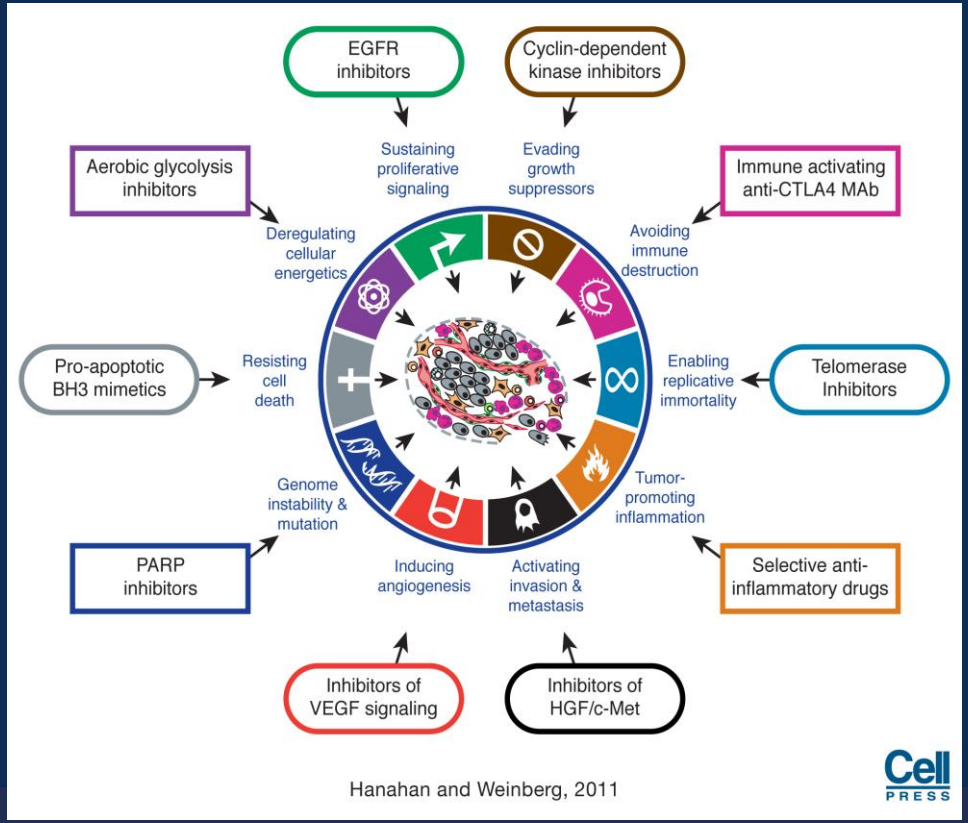
Cyriac Kandoth[1]*, Michael D. McLellan[1]*, Fabio Vandin[2], Kai Ye[1,3], Beifang Niu[1], Charles Lu[1], Mingchao Xie[1], Qunyuan Zhang[1,3], Joshua F. McMichael[1], Matthew A. Wyczalkowski[1], Mark D. M. Leiserson[2], Christopher A. Miller[1], John S. Welch[4,5], Matthew J. Walter[4,5], Michael C. Wendl[1,3,6], Timothy J. Ley[1,3,4,5], Richard K. Wilson[1,3,5], Benjamin J. Raphael[2] & Li Ding[1,3,4,5]



Cancer Genome Complexity and Heterogeneity

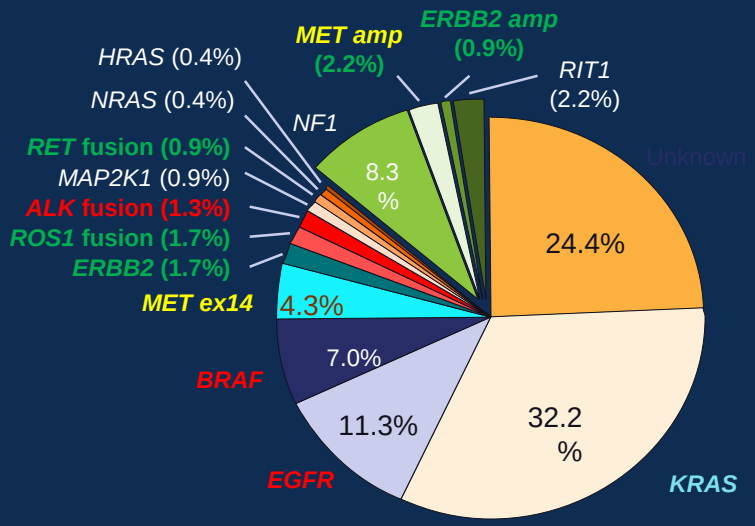


Hallmarks of Cancer - v.2.0



Lung Cancer Precision Therapy 2017

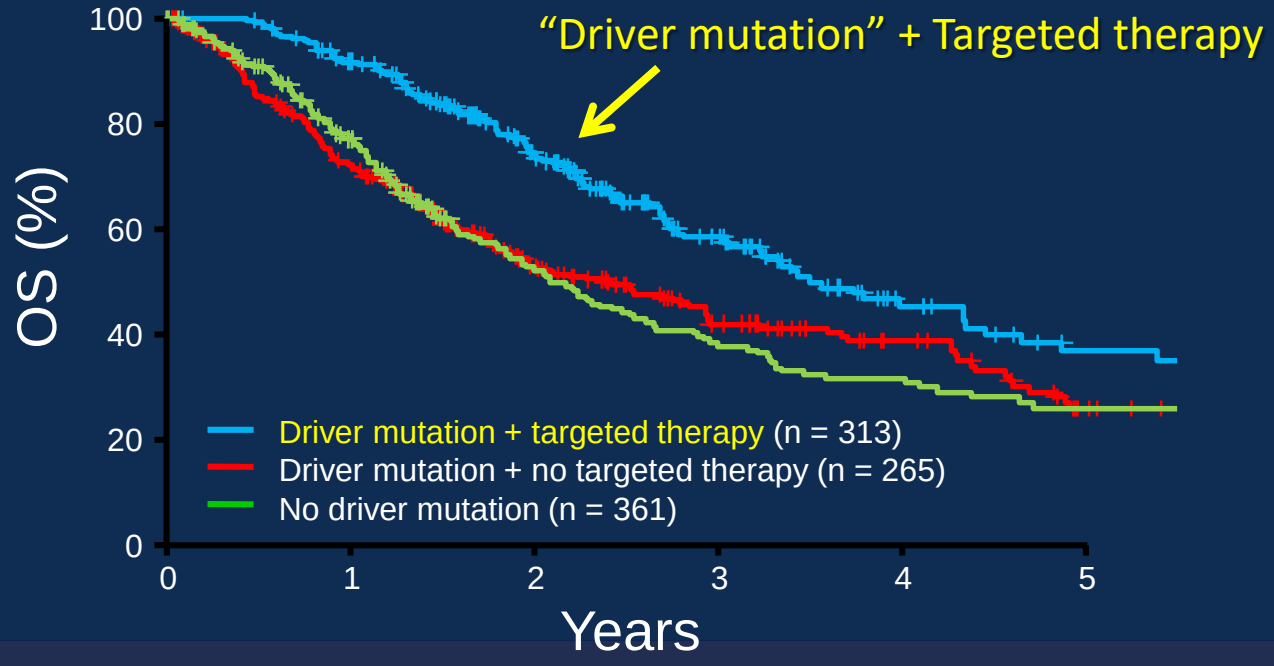
- Lung Cancer - composed of many distinct “driver” genomic mutations, often intrinsically actionable.



Genomic Classification - Lung Adenocarcinoma: “Actionable Mutations”

Lung Cancer Mutation Consortium

LCMC data supported the OS being the best when pts with “Driver mutations” were treated with matching “Targeted therapy”



Johnson B, et al. ASCO 2013. Abstract 8019.

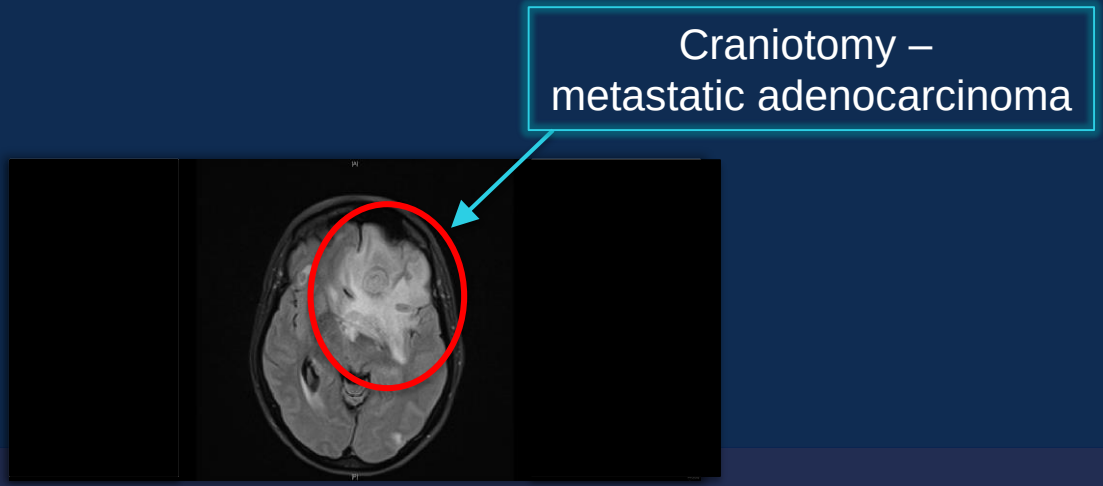
Molecular Tumor Board

WVU Cancer Institute – Molecular Tumor Board

- Launched September 2017
- Multidisciplinary Team Approach
- Objectives: Case Management and Educational
- Case review (clinical and molecular features) and literature review
- Attendee: Clinical – Surgical / Radiation / Medical Oncologists,
  Radiologist
  Pathology – Molecular Pathologist
  Basic Scientists (Ph.D.’s)
  Fellows, Graduate Students
  Nurses, Mid-Level Practitioners, Social Workers,
  Pharmacists, Cancer Prevention and Control

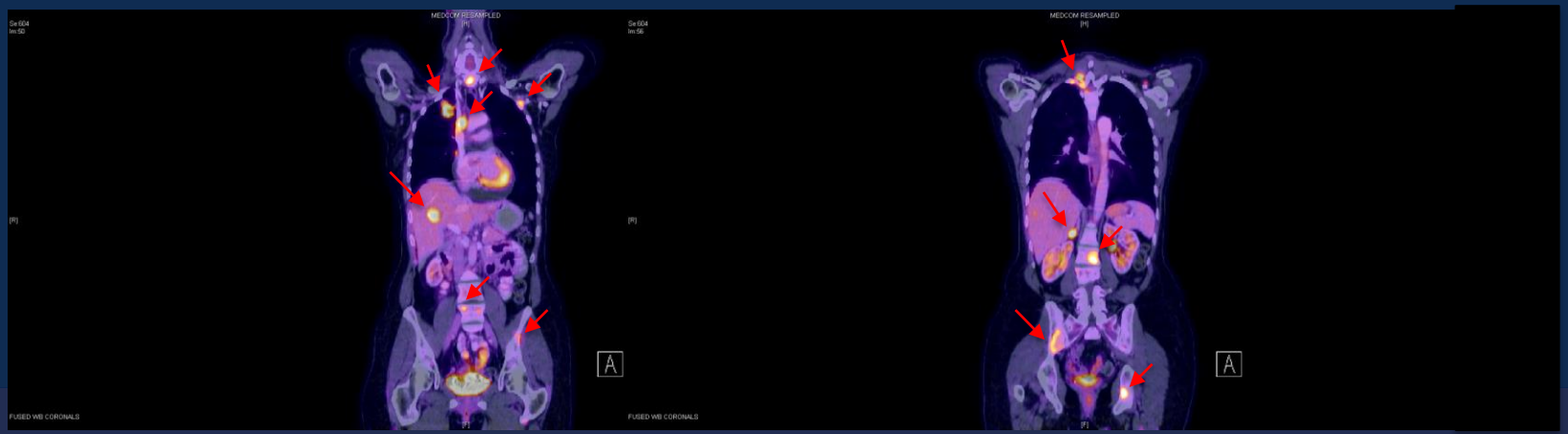
CASE 1:

- 46 y.o. Caucasian female, "*never-smoker*", otherwise healthy
  - Presents with progressive forgetfulness, then acute confusion
  - ED: brain MRI: At least 6 metastatic foci, with the largest identified within the inferior left frontal lobe (~1.5 cm) associated with extensive vasogenic edema and mass effect with subfalcine herniation.



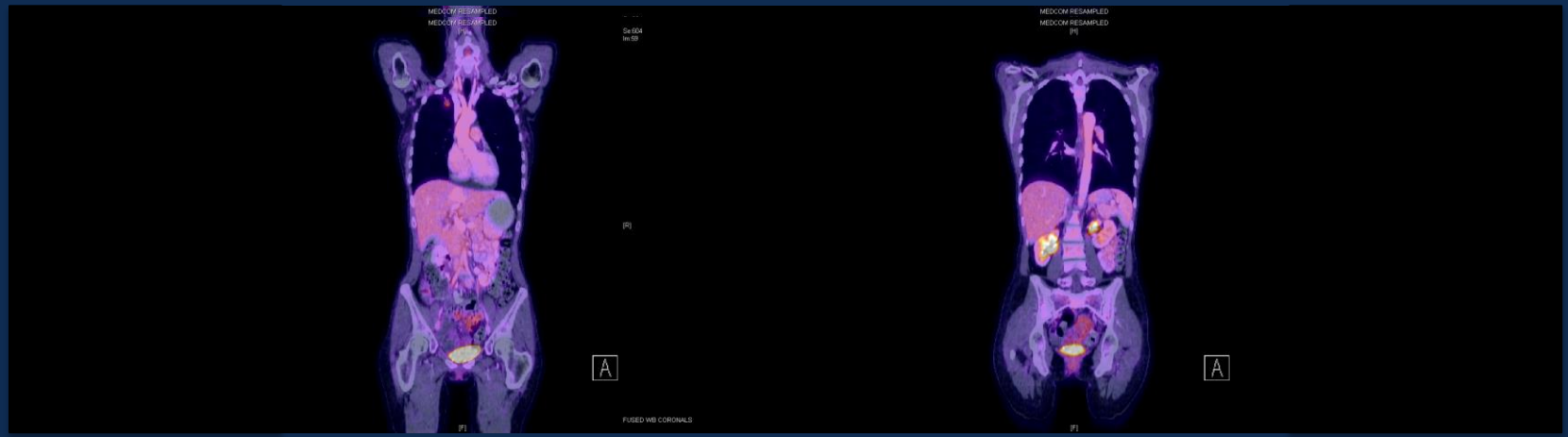
CASE 1: 46 y.o. never-smoker female

- **PET/CT scan:**
  - Hypermetabolic ***lung mass*** (RUL) (3.1 x 2.8 x 2 cm) with metastatic disease involving the ***brain***, ***skeletal system***, mediastinal ***lymph nodes***, right ***adrenal gland***, and ***liver***.
  - Small pericardial effusion.
  - Postoperative changes from resection of left frontal lobe metastatic brain lesion. Multiple known brain metastasis are partially demonstrated ……
  - Hypermetabolic enhancing lesion in the ***left infraspinatus muscle*** (2.1 x 1.5 cm) c/w necrotic metastatic lesion.

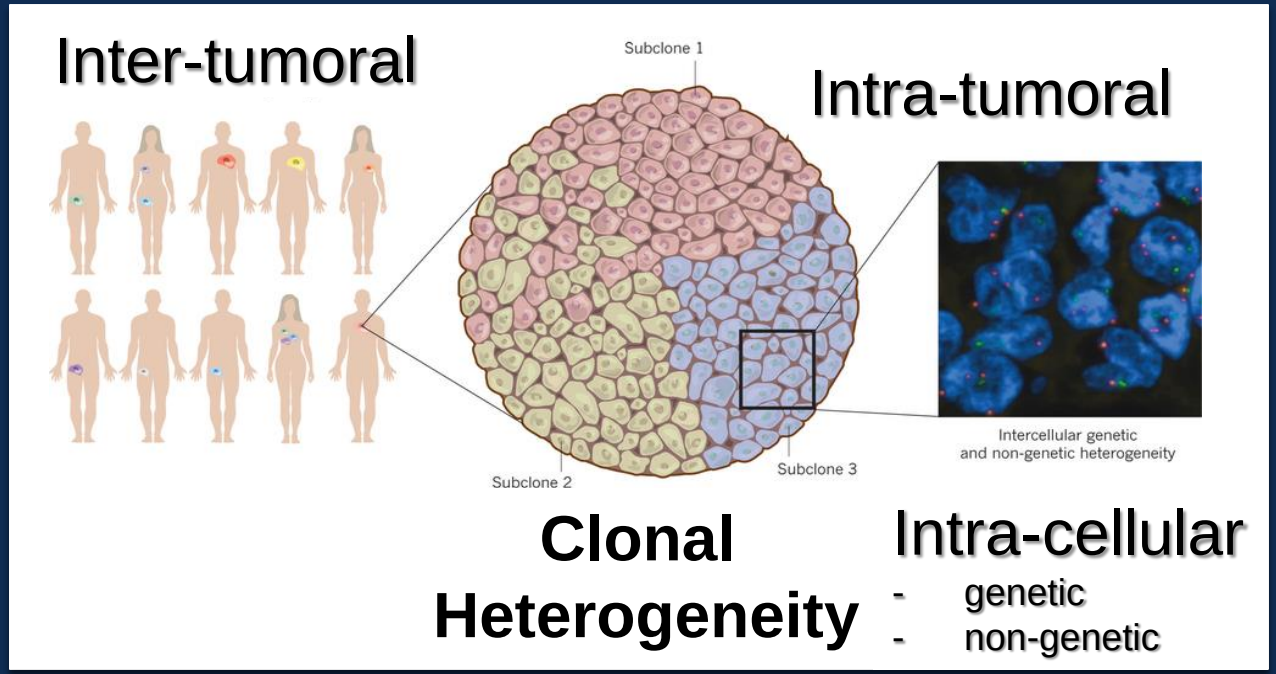


CASE 1: 46 y.o. never-smoker female

- Comprehensive Tumor Profiling (Caris CMI): *TP53* Exon 5 | C176F
- *EGFR* - Exon 19 | E746_A750del → Started on first-line Erlotinib (Tarceva) 150 mg once daily by mouth (9/2015)
- Essential complete response in 4 months



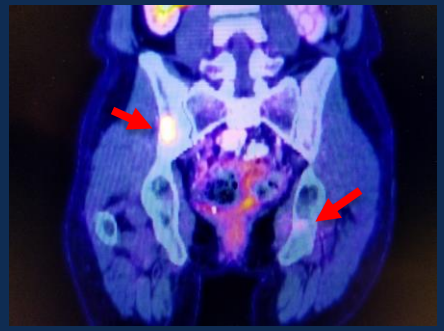
Tumor Heterogeneity



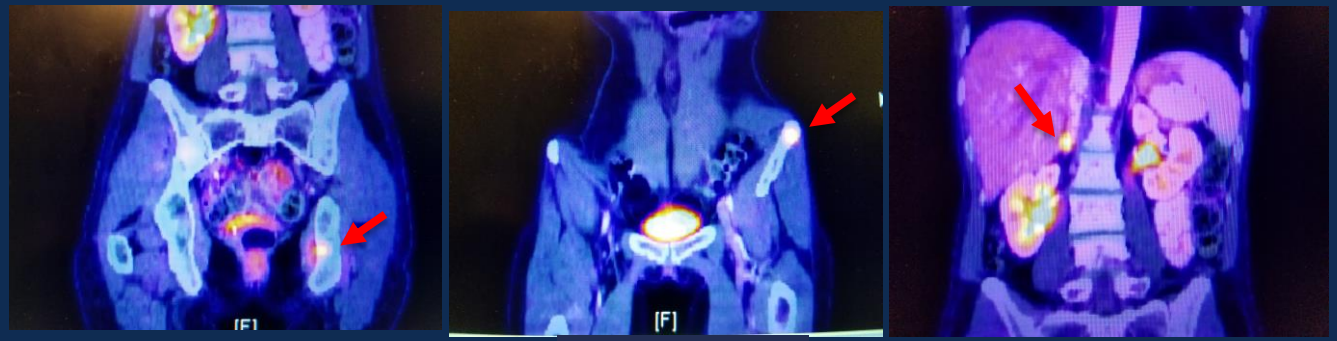
Burrell RA, McGranahan N, Bartek J, Swanton C. The causes and consequences of **genetic heterogeneity** in cancer evolution. *Nature*. 2013 Sep 19;501(7467):338-45. doi: 10.1038/nature12625. Review.

CASE 1: 46 y.o. never-smoker female

- Guardant360 Liquid Biopsy:
- 9/2016 (1-yr post-erlotinib: several bone mets progression):
  EGFR Exon 19 | E746_A750del



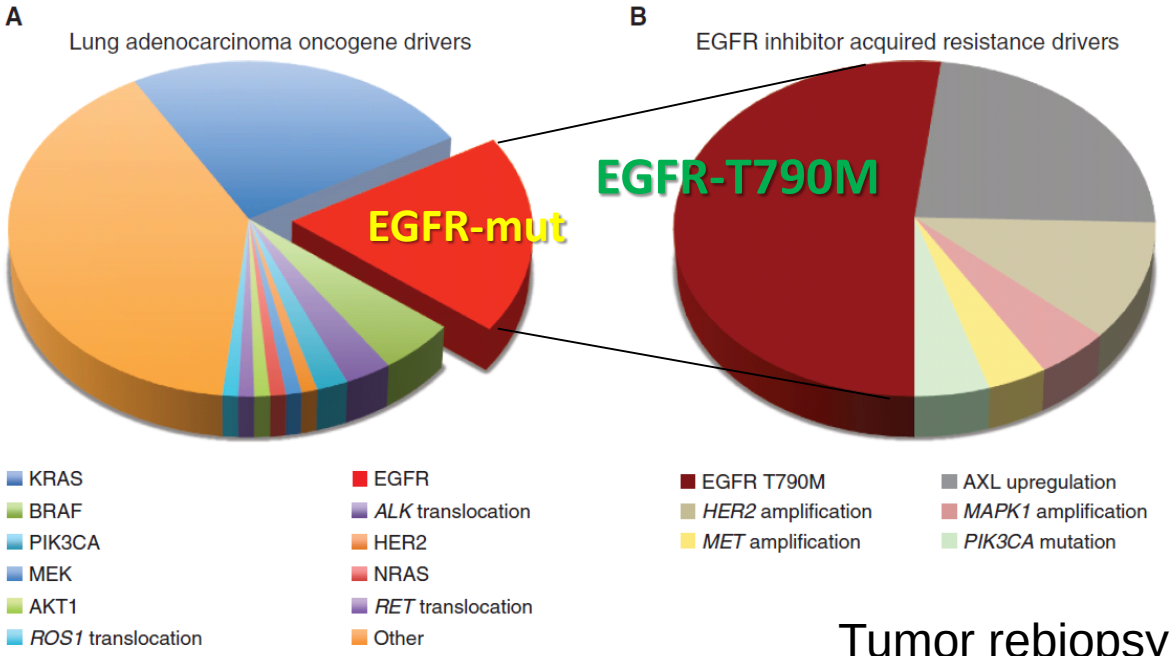
Sept 2016



Dec 2016

12/2016 (left ilium bone mets progression):
TP53 Exon 5 | C176F;
EGFR Exon 19 | E746_A750del
EGFR Exon 20 | T790M

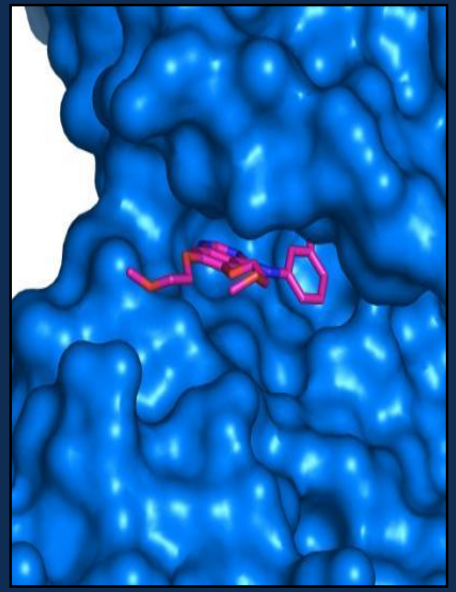
Targeting the New Achilles Heel in Drug Resistance

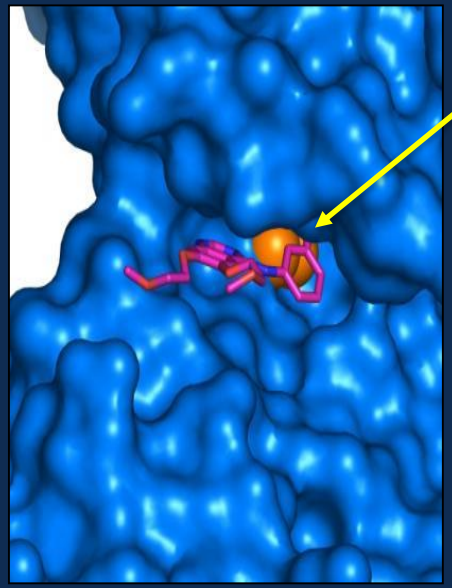


Tumor rebiopsy studies

Targeting the New Targets:

Overcoming Acquired Tumor Resistance to (EGFR) Targeted Therapy





Wild-type receptor: erlotinib (chemical structure) snugly fits into the ATP-binding pocket of EGFR blocking its function

T790M mutant receptor: methionine (M) 790 (orange) protrudes into the ATP-binding pocket, leads to steric hindrance disallowing erlotinib to bind

“Liquid Biopsy” in Cancer Diagnosis and Therapy (2017)

Multiple DNA abnormalities

RNA expression & fusion transcripts

Protein expression & phosphorylation

In vitro / in vivo Cell culture

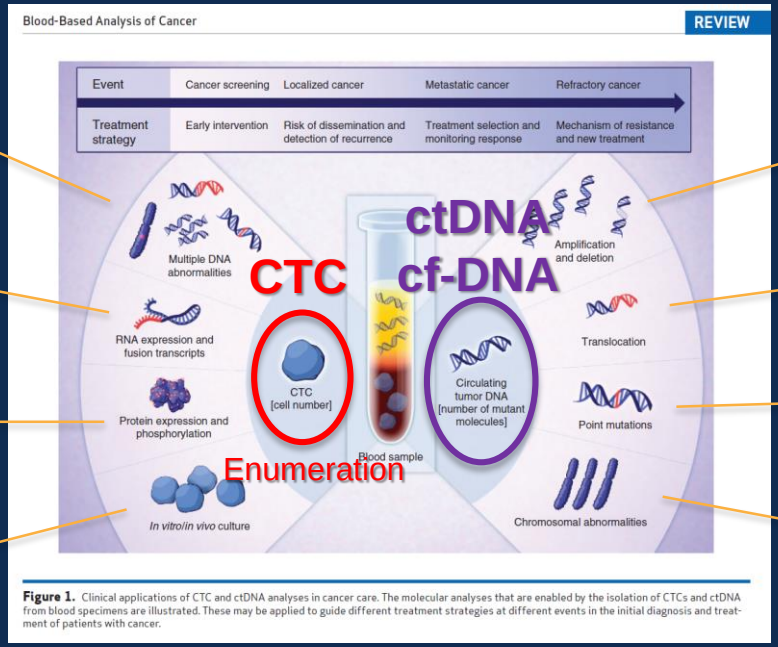


Figure 1. Clinical applications of CTC and ctDNA analyses in cancer care. The molecular analyses that are enabled by the isolation of CTCs and ctDNA from blood specimens are illustrated. These may be applied to guide different treatment strategies at different events in the initial diagnosis and treatment of patients with cancer.

Amplification & deletion

Translocation

Point mutations

Chromosomal abnormalities

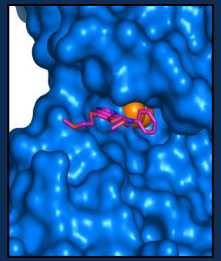
Cobas EGFR Mutation v2 Plasma Test – FDA Approved June 1st, 2016

Liquid Biopsy – Molecular Gneomic Profiling

Modified from: Haber DA and Velculescu VE, *Cancer Discovery* 2014;4:650-661.

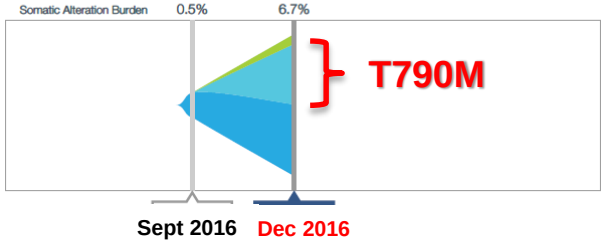
Targeting the New Targets:

Overcoming Acquired Tumor Resistance to (EGFR) Targeted Therapy



Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the mutant allele percentage (% cfDNA) of observed somatic variants at each sample submission time point. The "Somatic Alteration Burden" value below refers to the maximum % cfDNA detected at each time point. Amplifications are not plotted, and only the first and last four test dates are plotted. Please see the Physician Portal (https://portal.guardanthealth.com) for the Tumor Response Map with all test dates.



3 Total Somatic Alteration(s) Detected

2 with Associated Therapy
1 Associated with Lack of Response
Multiple Clinical Trials Available

Summary of Somatic Alterations & Associated Treatment Options

The percentage of altered cell-free DNA (% cfDNA) circulating in blood is related to the unique tumor biology of each patient. Factors that may affect the % cfDNA of detected somatic alterations include tumor growth, turn-over, size, heterogeneity, vascularization, disease progression, and treatment.

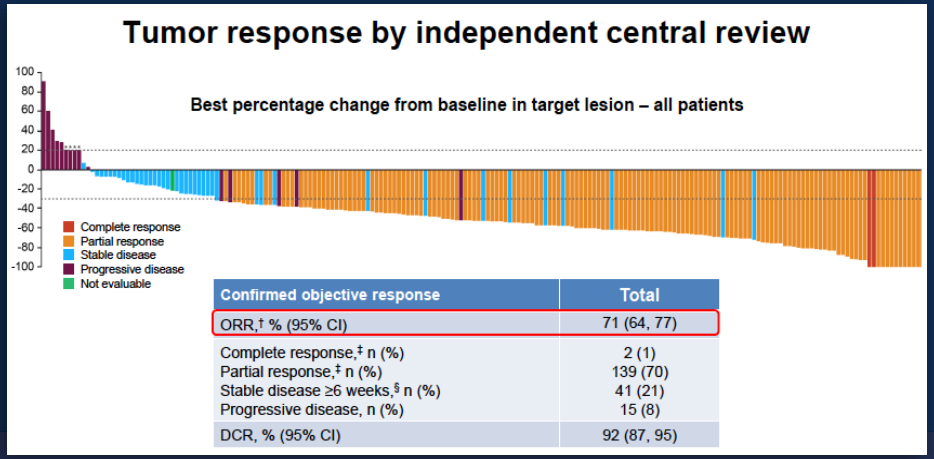
Alteration		Mutation Trend	% cfDNA or Amplification	FDA Approved in Indication *see page 3*	Available for Use in Other Indications *see page 3*	Clinical Drug Trials *see page 6*
Relevant for Therapy Selection						
EGFR	*Exon 19 Deletion*	100 / 50 / 5 / 0.5 / ND	6.7	Afatinib	None	Trials Available
EGFR	*T790M*	100 / 50 / 5 / 0.5 / ND	5.4	Osimertinib Lack of Response: Erlotinib, Gefitinib	Afatinib, Cetuximab	Trials Available
TP53	*C176F*	100 / 50 / 5 / 0.5 / ND	0.5	None	None	Trials Available

Third-Generation T790M-Targeting TKIs

- These novel and highly promising drugs largely spare EGFR WT signaling and preferentially block mutant/T790M signaling, leading to potentially wider therapeutic indices

- AZD9291 (osimertinib) – 56% response rate in T790M+ patients, well-tolerated, some rash, pneumonitis (3%), now FDA-approved

AURA-2: Osimertinib



Confirmed objective response	Total
ORR,† % (95% CI)	71 (64, 77)
Complete response,‡ n (%)	2 (1)
Partial response,‡ n (%)	139 (70)
Stable disease ≥6 weeks,§ n (%)	41 (21)
Progressive disease, n (%)	15 (8)
DCR, % (95% CI)	92 (87, 95)

Case 2

- 76 year old Caucasian male, never-smoker, PMHx: Diabetes, Hypothyroidism, Eczema, CAD, HTN, HLD seen as a referral from Cleveland Clinic Genomic Medicine Institute for Radioactive-Iodine Refractory Papillary Thyroid Cancer.
- Dec 2008 - Total thyroidectomy with pathology showing papillary thyroid carcinoma, 1/5 regional LN +. Radio-iodine study followed by RAI-ablation completed
- October 2015 - Recurrence of disease noted being RAI resistance, Lenvatinib was started.
- December 2015 - Significant proteinuria thought to be related to lenvatinib, initially dose reduced but eventually stopped Feb 2016.

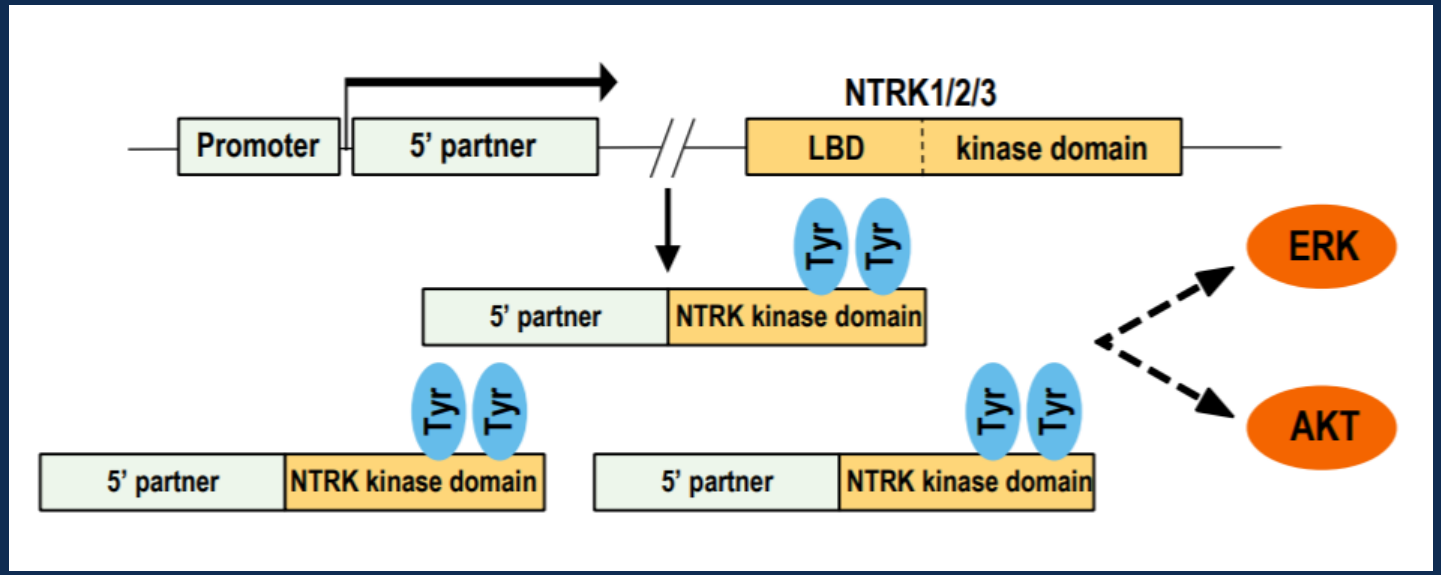
Case 2

- March 2016. Started on Sorafenib 200 mg daily, complicated by uncontrolled HTN and hence stopped after few months

- May 2016. All cancer directed therapies stopped. CT scan revealed B/L pulmonary nodules increased in size from 2015. Increased right hilar LN, small effusions

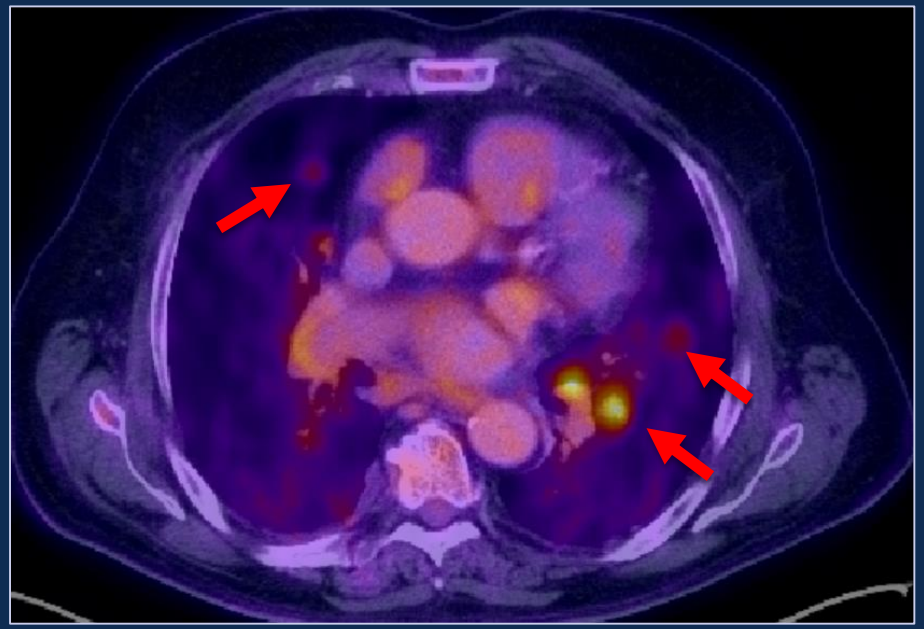
- September 2016. Molecular genomic tumor profiling reported presence of *ETV6-NTRK3* fusion and TERT promoter
- Enrolled in NTRK inhibitor clinical trial study

NTRK pathway



Case 2: Metastatic lung lesions

PET/CT



Case 2

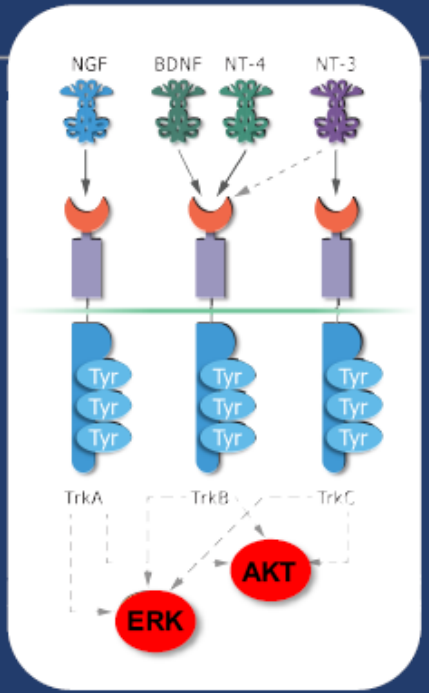
- April 4, 2017 - Completed 5 cycles of NTRK inhibitor. Restaging CT Chest showed Partial Response going in to stable disease
- June 2017 - Had an embolic stroke from atrial fibrillation, with resultant right-sided hemiparesis/hemiplegia, aphasia; undergoing rehab. Drug held for 2 weeks
- July 2017 - Restarted drug on trial protocol.
- Completed 12 cycles by September 2017.
- August 2017 - Restaging CT scan → ongoing partial response

TRK Fusions are Oncogenic and Signal Through Canonical Downstream Pathways

Normal TRK Proteins

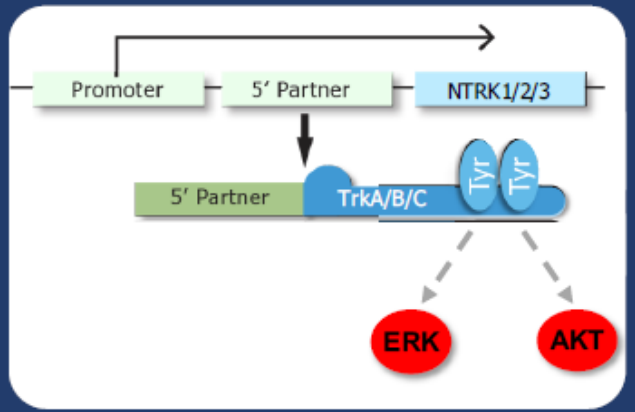
Family of neurotrophin receptors

- TrkA (*NTRK1*) → Pain, thermoregulation
- TrkB (*NTRK2*) → Movement, memory, mood, appetite, body weight
- TrkC (*NTRK3*) → Proprioception



TRK Fusions

- Ligand binding domain replaced by 5′ fusion partner; highly expressed by promoter of 5′ fusion gene
- Ligand-independent activation



TRK Fusions Found in Diverse Cancer Histologies

TRK FUSION FREQUENCY

<5%

CNS
- ✓ Astrocytoma
- ✓ Brain low-grade glioma
- ✓ Glioblastoma

GI
- ✓ Colorectal cancer
- ✓ Cholangiocarcinoma
- ✓ GIST
- ✓ Pancreatic cancer

Head and neck
- ✓ Squamous cell carcinoma

Lung
- ✓ Adenocarcinoma
- ✓ Large cell neuroendocrine

Other
- ✓ Acute myeloid leukemia
- ✓ Breast invasive carcinoma
- ✓ Melanoma
- ✓ Sarcoma

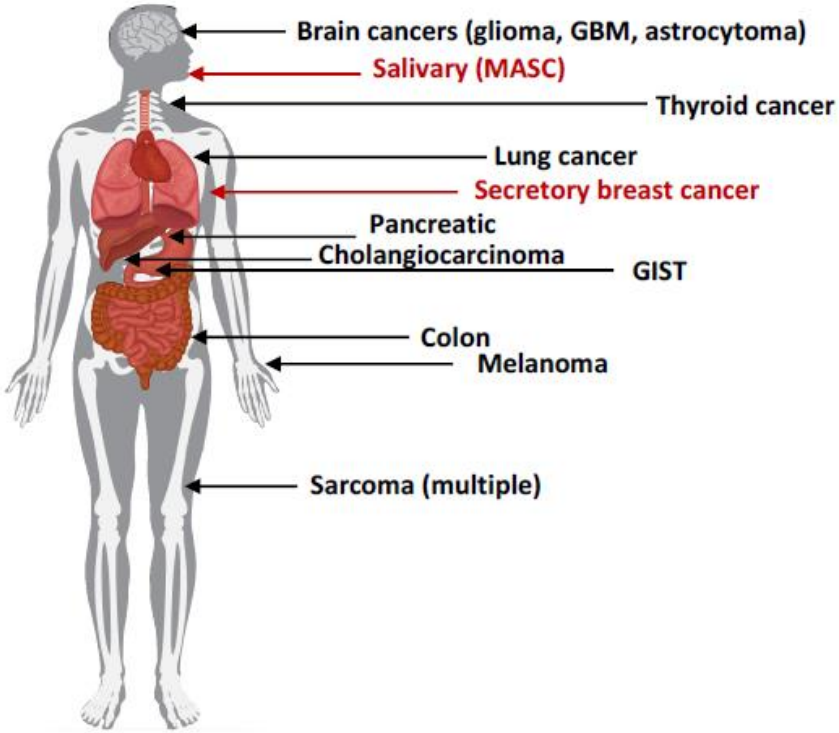
5–25%

- ✓ Congenital mesoblastic nephroma
- ✓ Papillary thyroid cancer
- ✓ Pontine glioma
- ✓ Spitz tumors

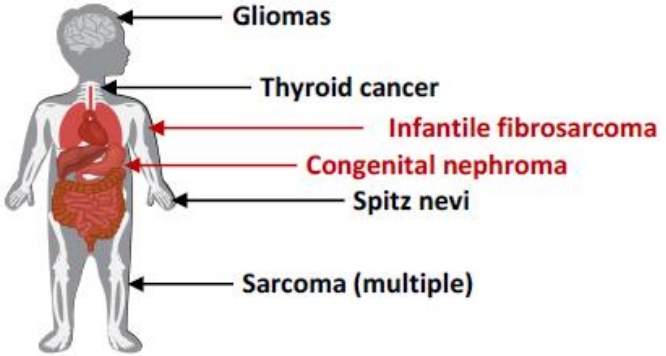
>75%

- ✓ Mammary analogue secretory carcinoma (MASC) of the salivary glands
- ✓ Secretory breast carcinoma
- ✓ Infantile fibrosarcoma

TRK fusions found in diverse cancer histologies

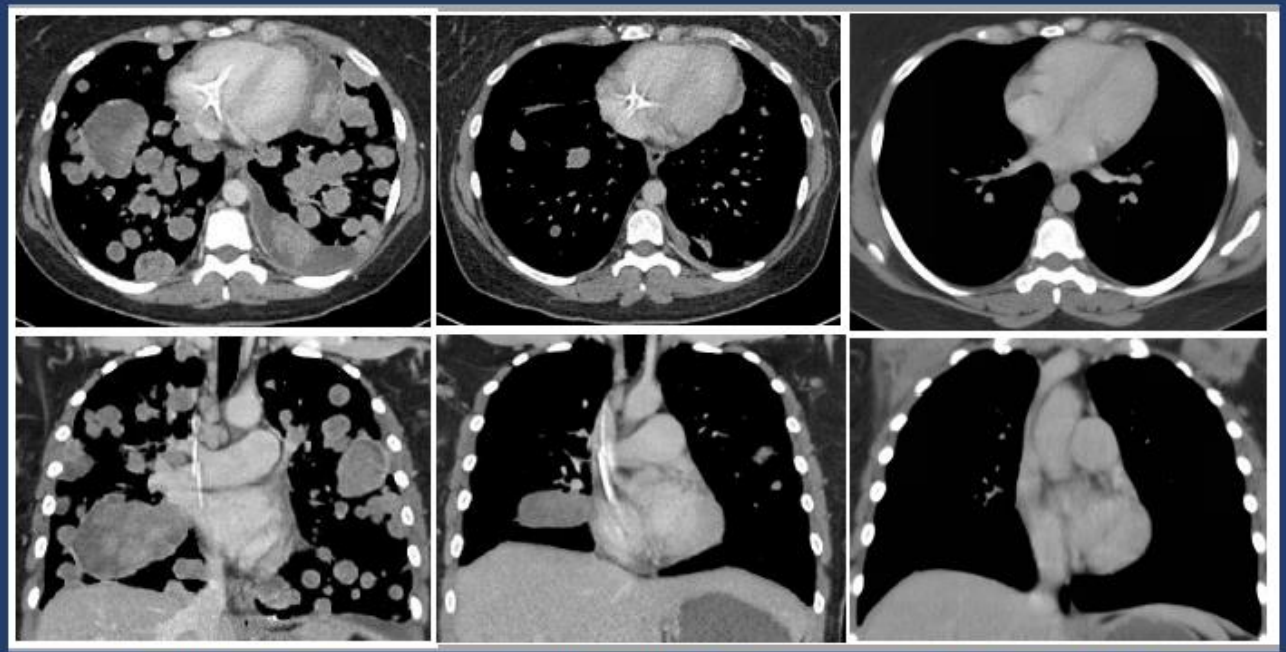


- Common cancer with low TRK fusion frequency
- Rare cancer with high TRK fusion frequency



Patient #1:
LMNA-NTRK1 fusion soft tissue sarcoma

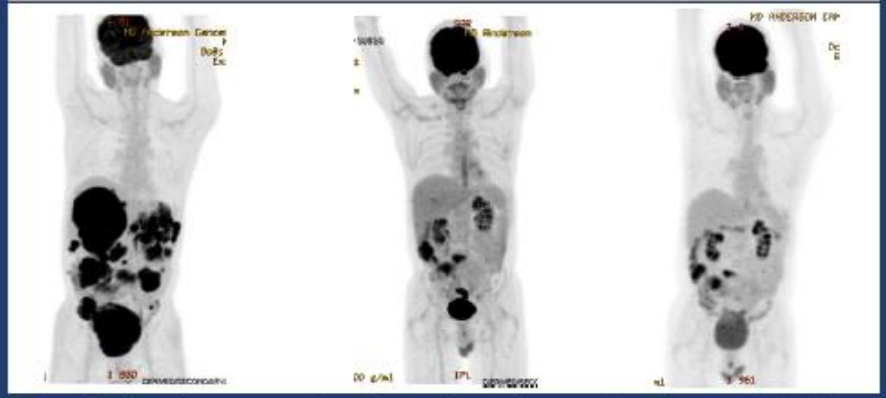
- 42 yo female with undifferentiated sarcoma progressed through epirubicin, ifosfamide, sorafenib, and doxorubicin
- 100mg BID
- Rapid resolution of dyspnea and hypoxemia
- Confirmed partial response
- Currently on study in cycle 14



Patient #2: ETV6-NTRK3 fusion GIST

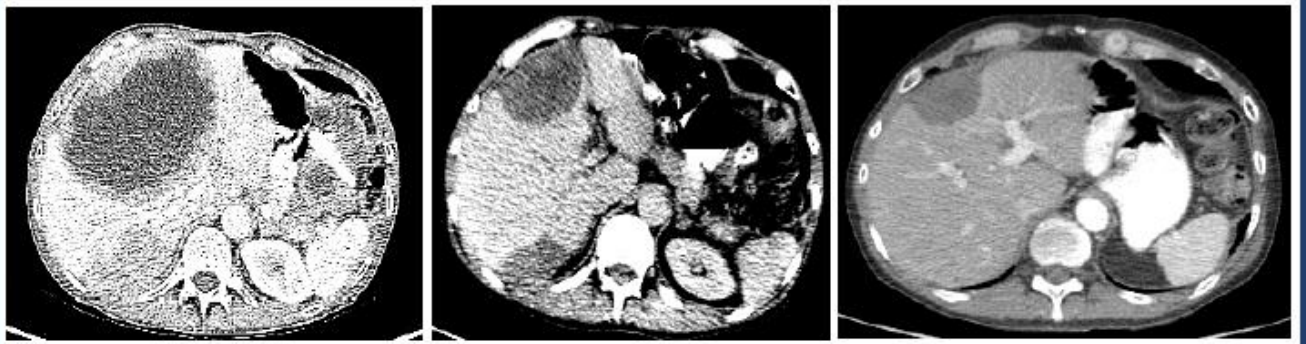
- 55 yo male with GIST progressed through imatinib, sunitinib, sorafenib, nilotinib, and regorafenib
- 150mg BID
- Confirmed partial response
- Currently on study in cycle 10

PET



Study baseline | Study cycle 3 day 1 | Study cycle 9 day 1

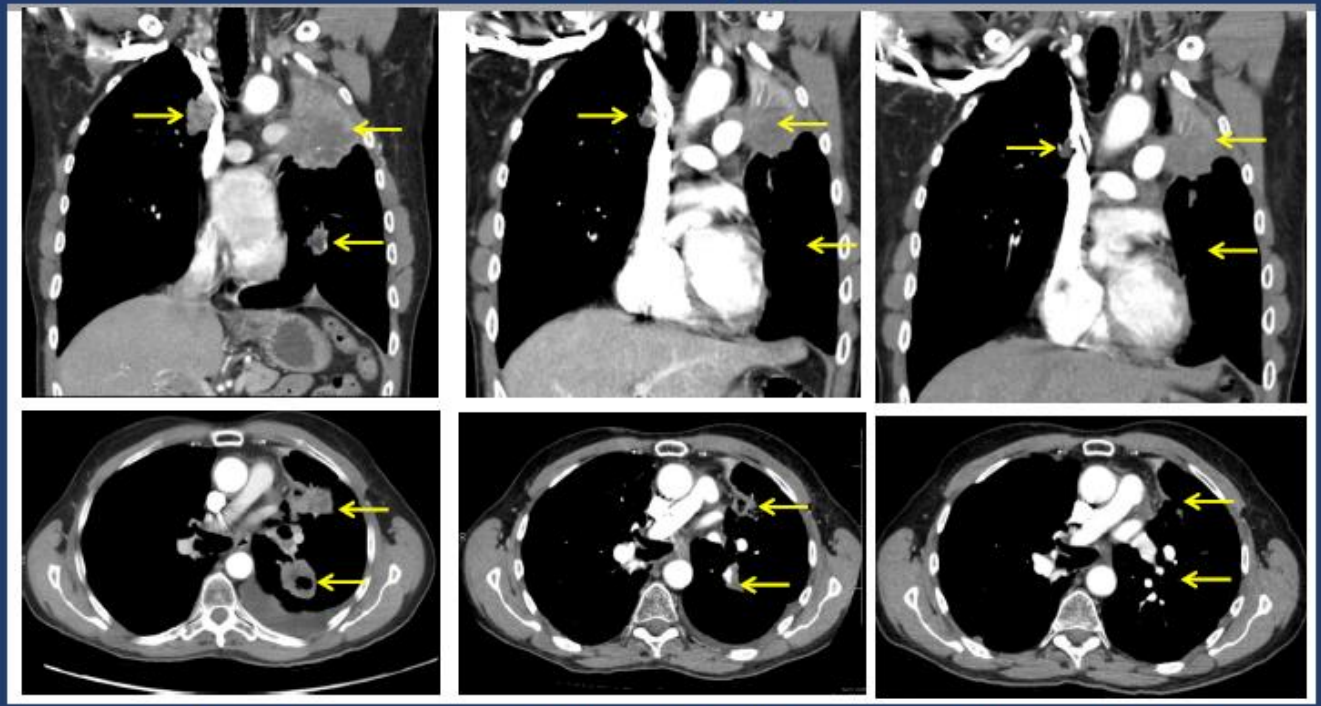
CT



Study baseline | Study cycle 5 day 1 | Study cycle 9 day 1

Patient #4: ETV6-NTRK3 fusion mammary analogue secretory carcinoma of the salivary gland (MASC)

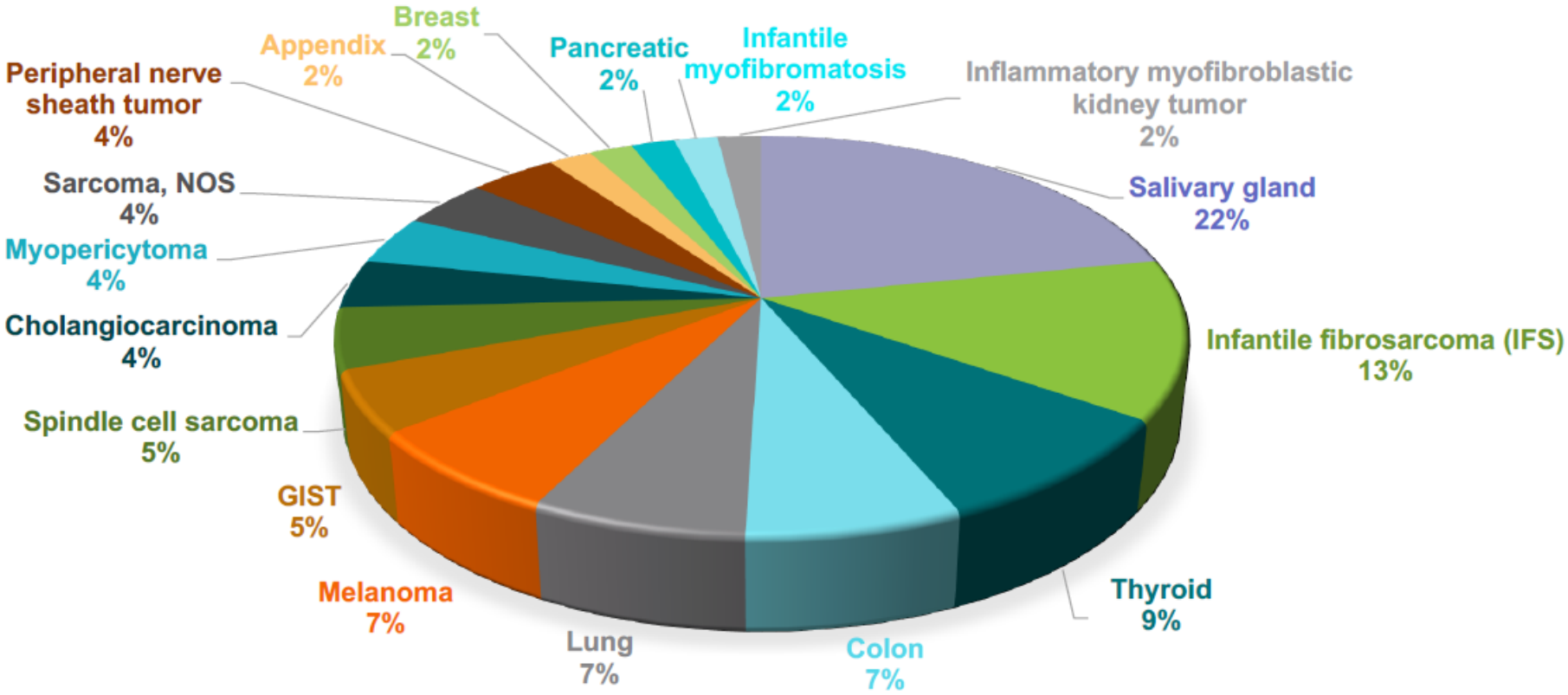
- 66 yo male progressed through radiotherapy, dasatinib, GDC-0941+ erlotinib, and ABBV-399
- 100mg QD*
- Confirmed partial response
- Currently on study in cycle 7



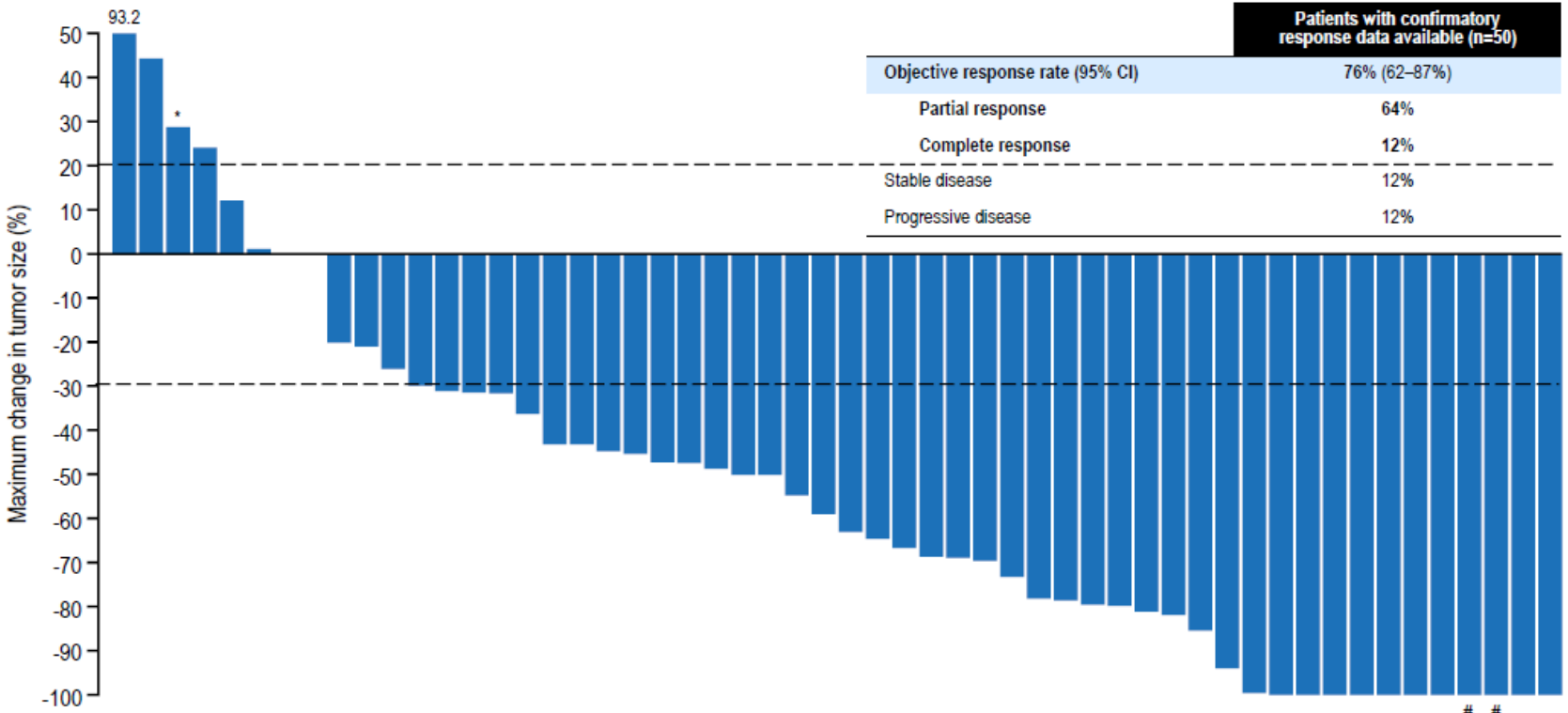
Study baseline | Study cycle 3 day 1 | Study cycle 7 day 1

* Patient enrolled at 100mg BID and dose reduced to 100mg QD on C1D2 due to transient dizziness possibly related to drug

Diversity of cancer types treated (n=17)



Efficacy of larotrectinib in TRK fusion cancers

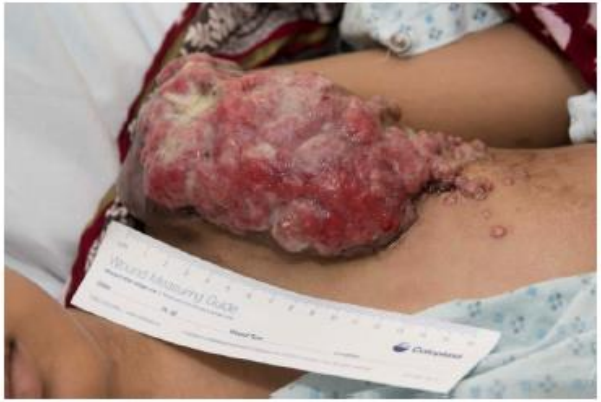


	Patients with confirmatory response data available (n=50)
Objective response rate (95% CI)	76% (62–87%)
Partial response	64%
Complete response	12%
Stable disease	12%
Progressive disease	12%

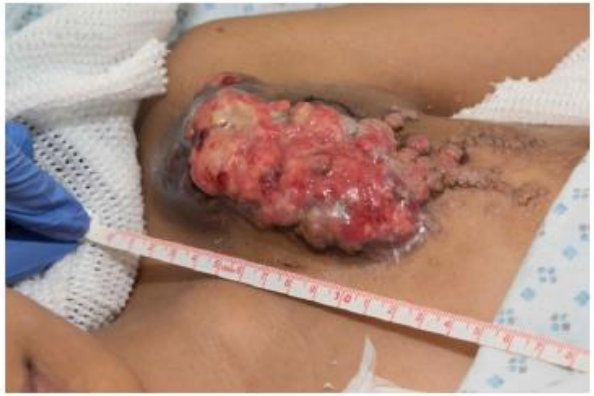
*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

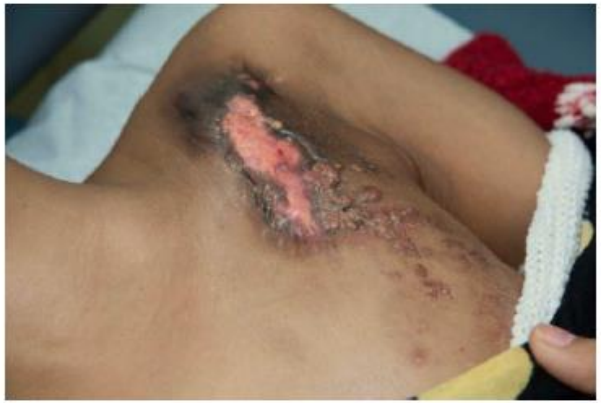
ETV6-NTRK3 secretory breast cancer patient



Baseline



Day 6



Day 20

14F, prior therapy: 4 lines of chemotherapy and repeated resections
Treated with larotrectinib under expanded access

Courtesy of N. Shukla, Memorial Sloan Kettering

Case 3

- 50-year-old Caucasian male with a 30 pack-year smoking history, who was healthy except hypertension, presented with a sore lump over the right lower chest wall.
- CT of the chest, abdomen, and pelvis in January 2015 confirmed an enlarging underlying soft tissue mass arising within the chest wall soft tissue/pleural tissue space, centered over the intercostal space, measuring 3.0 x 5.9 x 5.0 cm. An enlarged right mid-hilar lymph node (2.7 x 3.1 x 2.7 cm) was also seen.
- Ultrasound-guided needle biopsy on the chest wall mass → pathology review at the Mayo Clinic, revealed an extensively necrotic, poorly differentiated malignant neoplasm possibly representing a malignant SFTP (Solitary Fibrous Tumor of the Pleura)

Case 3

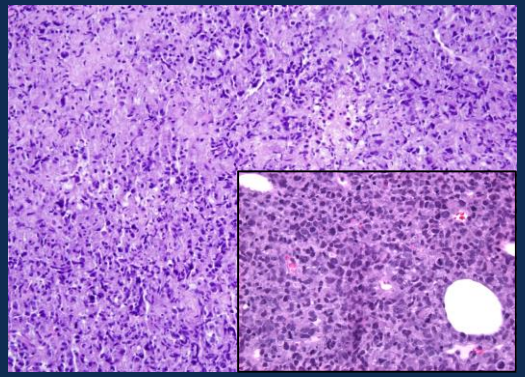
- Diffusely positive for CD34 and focally cytokeratin-positive. INI-1 expression was retained. WT-1, calretinin, ER, CD31, ERG protein, FLI-1 and high MW cytokeratin were negative.

- PET/CT imaging in February 2015 showed no evidence of metastatic lesions in the abdomen, pelvis, or bones, and a bone scan was also negative for any distant metastases.
- The right lower chest wall mass was found intensely hypermetabolic with SUV 23, with the right hilar mass having SUV 20.

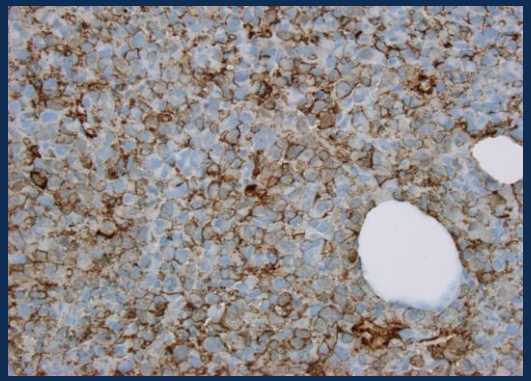
Case 3 - Pathology

H&E

A

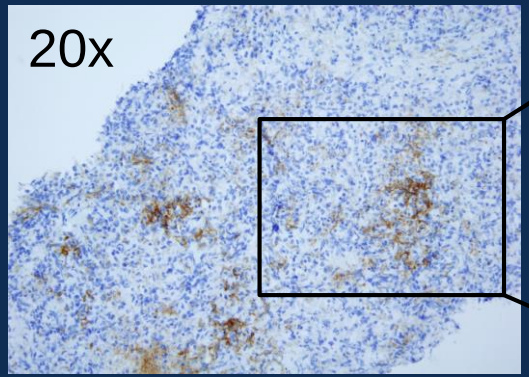


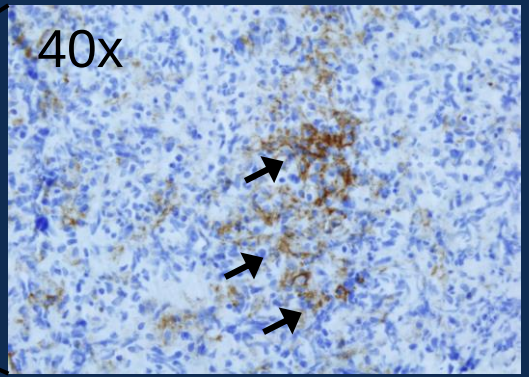
B



CD34

C

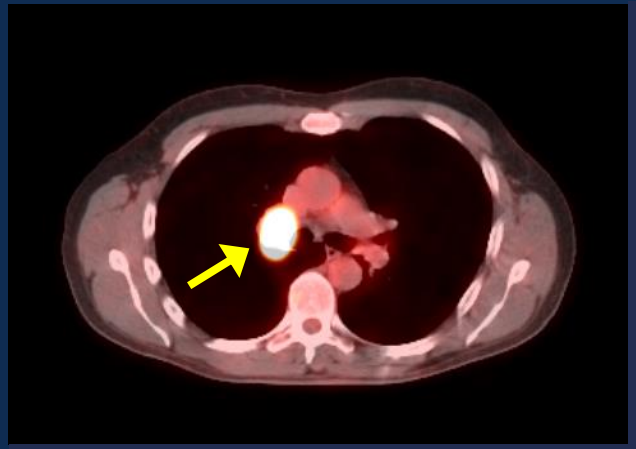




PD-L1

Case 3 - Radiology

A



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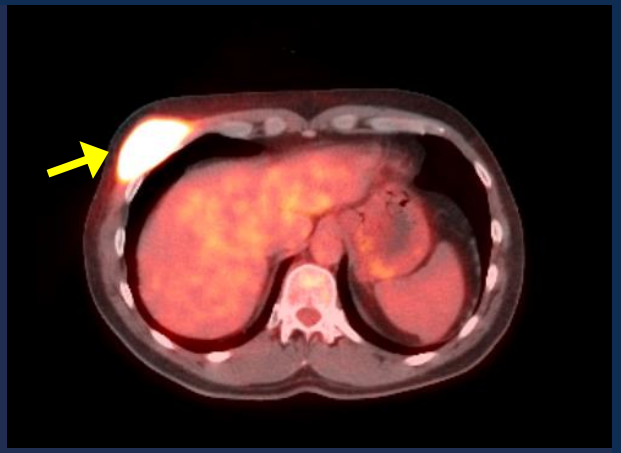

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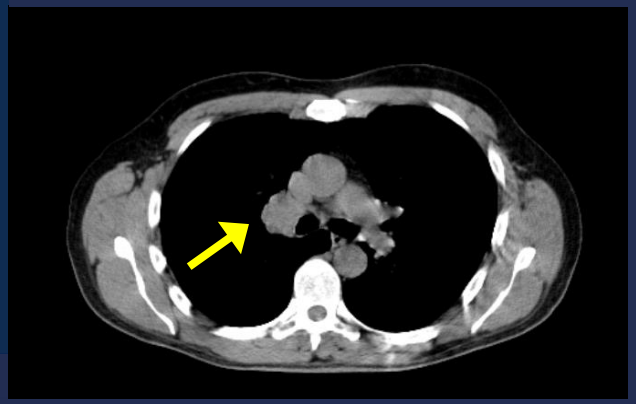
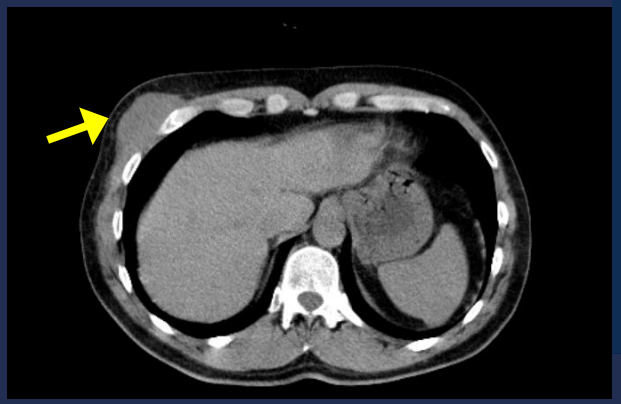


D



Case 3

- 1st line concurrent chemoRT: Restaging by PET/CT – shrinkage of the primary chest wall mass to 2.8 x 1.4 cm and persistence of the right hilar nodal mass.
- However, new PET-avid soft tissue foci seen in the deep subcutaneous tissue of the left posterior abdominal wall.
- Punch biopsy of the new subcutaneous mass revealed pathological characteristics similar to the previous biopsy, confirming metastatic dissemination.
- 2nd line - palliative gemcitabine/docetaxel → severe life-threatening treatment-related toxicities: neutropenic fever, pneumonia, severe fatigue, mouth sores, oral candidiasis, nausea/vomiting, decreased oral intake, and prerenal acute renal failure.

Case 3

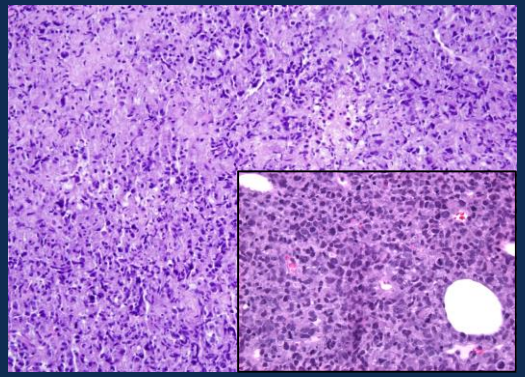
- MD Anderson Rx for malignant SFTP:

  Temozolomide and Bevacizumab (temozolomide 150 mg/m2 orally on days 1-7 and days 15-21, plus Bevacizumab 5 mg/kg IV on days 8 and 22, repeat every 28 days cycle) → further progression of the disease
- Comprehensive multi-platform molecular tumor profiling (CMI) while patient was undergoing temozolomide/ bevacizumab therapy. CMI-X tumor profiling confirmed positive PD-1 and PD-L1 (2+, 5%) in IHC.
- Temozolomide/bevacizumab tx was eventually found ineffective.
- Key genomic alterations: *TP53*-V157F (56%), *CDKN2A*-R112P (62%), and *MLH1*-E234Q (52%).

Case 3 - Pathology

H&E

A



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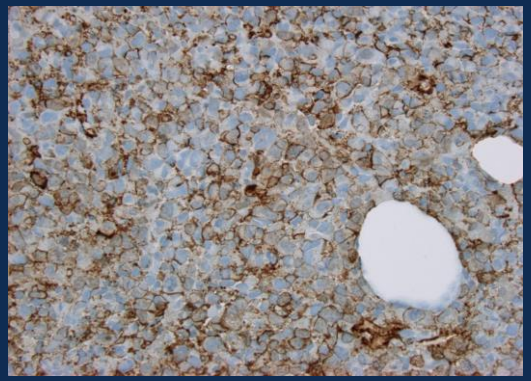
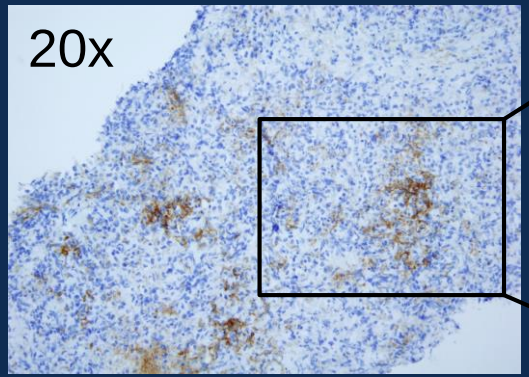
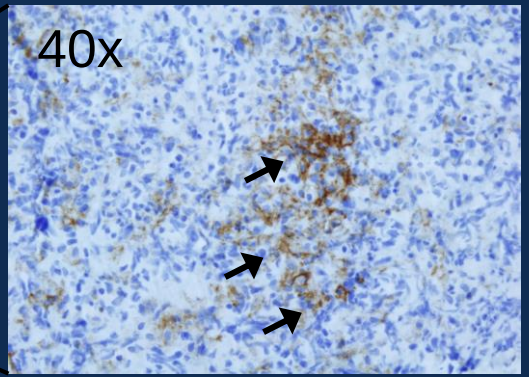


CD34

C





PD-L1

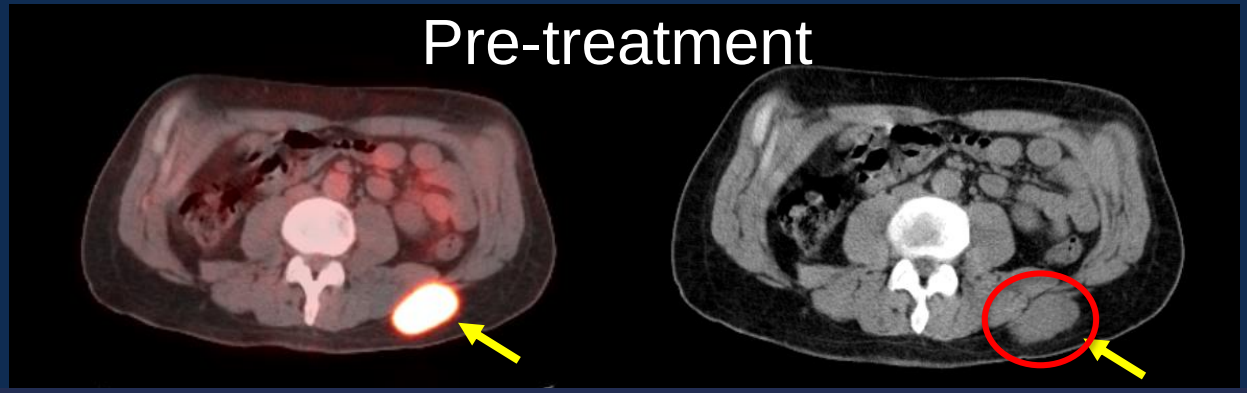
Case 3

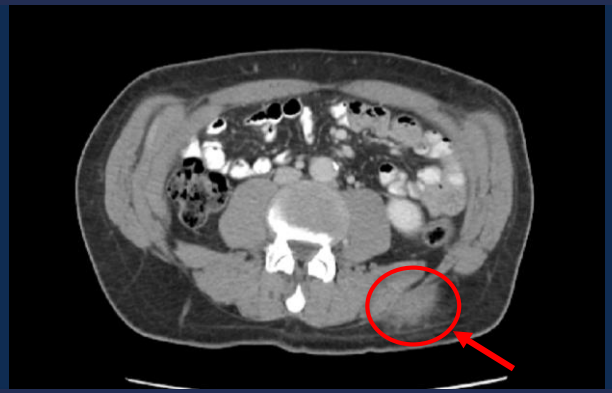
- initiated treatment with an anti-PD-1 immune checkpoint monoclonal antibody in October 2015; **Pembrolizumab** was selected for compassionate off-label use, using the FDA-approved dose regimen of 2 mg/kg i.v every 3 weeks.
- December 2015 after 2 cycles, excellent tolerance and remarkable prompt shrinkage response of the left abdominal wall mass, confirmed by CT scan.

- Restaging CT imaging s/p 5th cycle of pembrolizumab confirmed a near-CR in February 2016.
- Restaging via CT scan imaging in July 2016 confirmed an ongoing persistent near-complete response with no new disease recurrence.

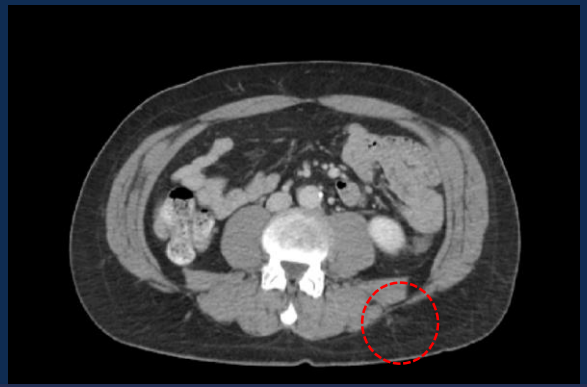
- Durable near-complete response after up to a total of 26 cycles of pembrolizumab infusions, and he remains well with excellent tolerance without significant adverse effects except for mild dry skin.

Case 3 - Radiology



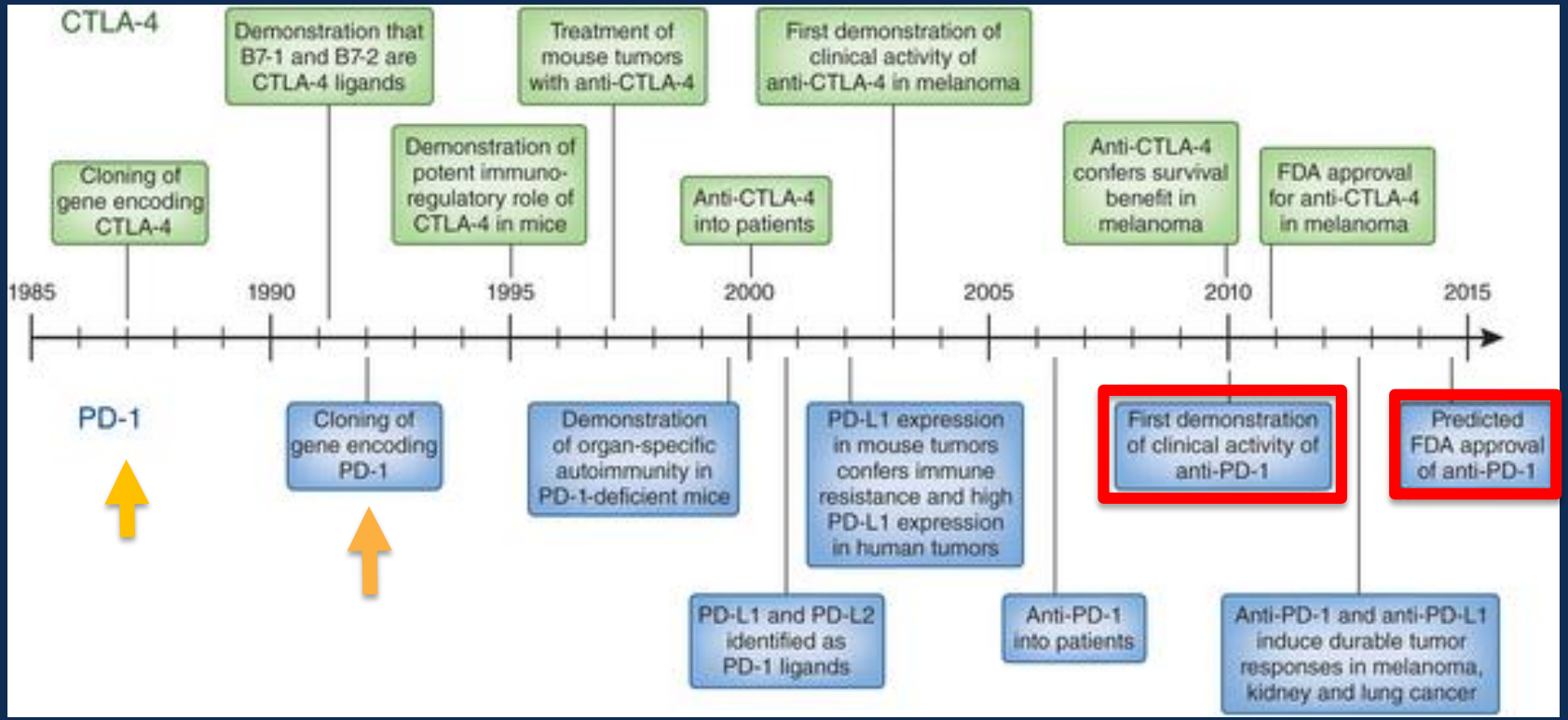


s/p C2

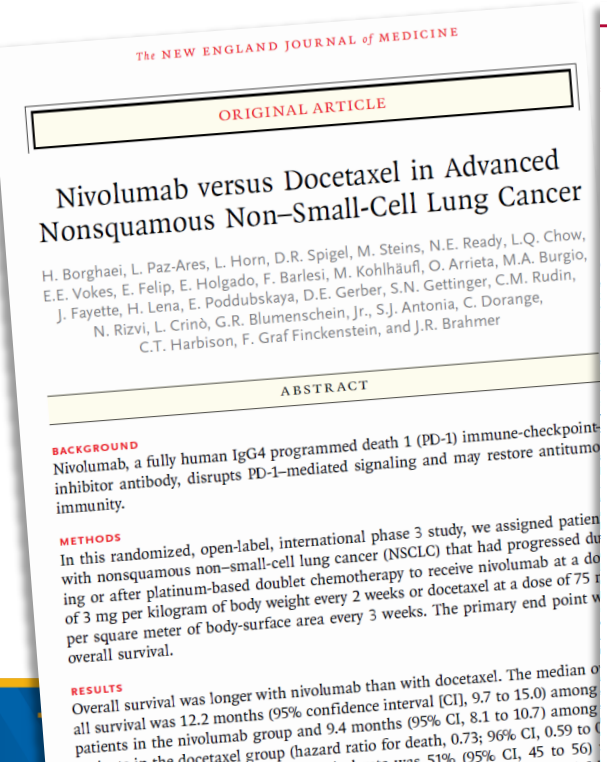


s/p C12 - Pembrolizumab

Progress of Immuno-Oncology



New Era - Cancer Immunotherapy: Targeting Immune Checkpoints



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

ABSTRACT

BACKGROUND

Nivolumab, a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint-inhibitor antibody, disrupts PD-1–mediated signaling and may restore antitumor immunity.

METHODS

In this randomized, open-label, international phase 3 study, we assigned patients with nonsquamous non–small-cell lung cancer (NSCLC) that had progressed during or after platinum-based doublet chemotherapy to receive nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks or docetaxel at a dose of 75 mg per square meter of body-surface area every 3 weeks. The primary end point was overall survival.

RESULTS

Overall survival was longer with nivolumab than with docetaxel. The median overall survival was 12.2 months (95% confidence interval [CI], 9.7 to 15.0) among patients in the nivolumab group and 9.4 months (95% CI, 8.1 to 10.7) among patients in the docetaxel group (hazard ratio for death, 0.73; 96% CI, 0.59 to 0

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubois, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon

Summary

Background Despite recent advances in the treatment of advanced non-small-cell lung cancer, there rem for effective treatments for progressive disease. We assessed the efficacy of pembrolizumab for p previously treated, PD-L1-positive, advanced non-small-cell lung cancer.

Methods We did this randomised, open-label, phase 2/3 study at 202 academic medical centres in 24 coun with previously treated non-small-cell lung cancer with PD-L1 expression on at least 1% of tumour cells w assigned (1:1:1) in blocks of six per stratum with an interactive voice-response system to receive pe 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m² every 3 weeks. The primary endpoints were and progression-free survival both in the total population and in patients with PD-L1 expression on tumour cells. We used a threshold for significance of p<0·00825 (one-sided) for the analysis of overal threshold of p<0·001 for progression-free survival. This trial is registered at ClinicalTrials.gov, number

Findings Between Aug 28, 2013, and Feb 27, 2015, we enrolled 1034 patients: 345 allocated to pembroli 346 allocated to pembrolizumab 10 mg/kg, and 343 allocated to docetaxel. By Sept 30, 2015, 521 patie the total population, median overall survival was 10·4 months with pembrolizumab 2 mg/kg, 12 pembrolizumab 10 mg/kg, and 8·5 months with docetaxel. Overall survival was significantly longer fo 2 mg/kg versus docetaxel (hazard ratio [HR] 0·71, 95% CI 0·58–0·88; p=0·0008) and for pembroli versus docetaxel (0·61, 0·49–0·75; p<0·0001). Median progression-free survival was 3·9 months wit 2 mg/kg, 4·0 months with pembrolizumab 10 mg/kg, and 4·0 months with docetaxel, with no sig for pembrolizumab 2 mg/kg versus docetaxel (0·88, 0·74–1·05; p=0·07) or for pembrolizumab docetaxel (HR 0·79, 95% CI 0·66–0·94; p=0·004). Among patients with at least 50% of tumo PD-L1, overall survival was significantly longer with pembrolizumab 2 mg/kg than with 14·9 months *vs* 8·2 months; HR 0·54, 95% CI 0·38–0·77; p=0·0002) and with pembrolizumab docetaxel (17·3 months *vs* 8·2 months; 0·50, 0·36–0·70; p<0·0001). Likewise, for this patient popu free survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (me 4·1 months; HR 0·59, 95% CI 0·44–0·78; p=0·0001) and with pembrolizumab 10 mg/kg (5·2 months *vs* 4·1 months; 0·59, 0·45–0·78; p<0·0001). Grade 3–5 treatment-related adve common with pembrolizumab than with docetaxel (43 [13%] of 339 patients given 2 mg/kg, 10 mg/kg, and 109 [35%] of 309 given docetaxel).

Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial

Achim Rittmeyer, Fabrice Barlesi, Daniel Waterkamp, Keunchil Park, Fortunato Ciardiello, Joachim von Pawel, Shirish M Gadgeel, Toyoaki Hida, Dariusz M Kowalski, Manuel Cobo Dols, Diego L Cortinovis, Joseph Leach, Jonathan Polikoff, Carlos Barrios, Fairooz Kabbinavar, Osvaldo Arén Frontera, Filippo De Marinis, Hande Turna, Jong-Seok Lee, Marcus Ballinger, Marcin Kowanetz, Pei He, Daniel S Chen, Alan Sandler, David R Gandara, for the OAK Study Group*

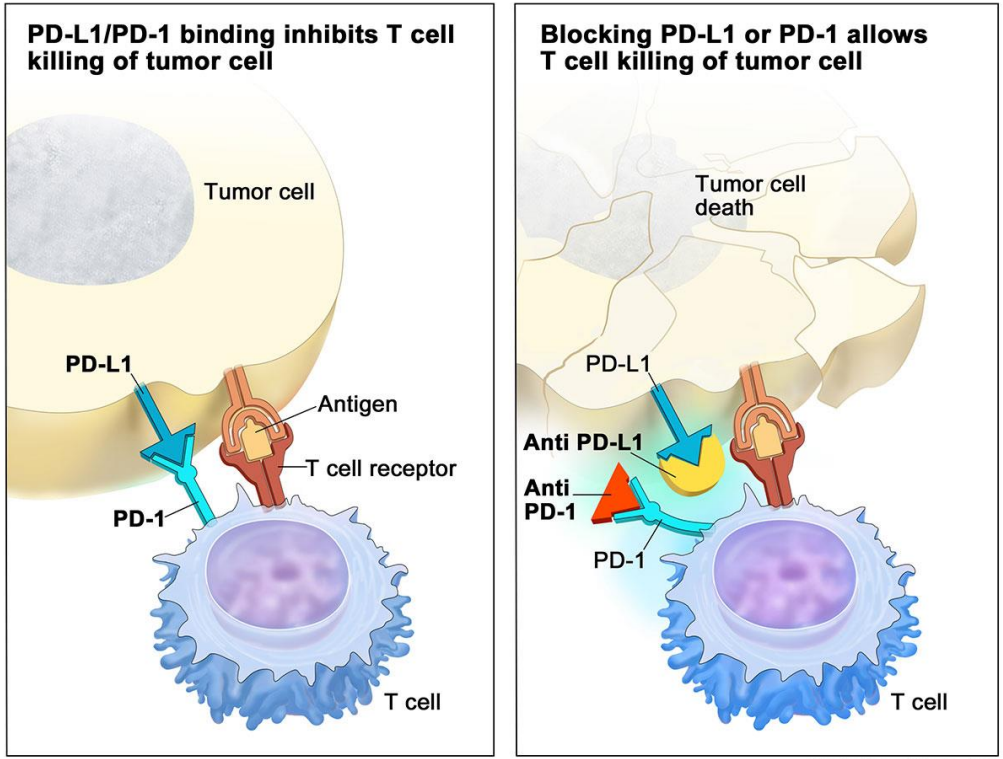
Summary

Background Atezolizumab is a humanised antiprogrammed death-ligand 1 (PD-L1) monoclonal antibody th inhibits PD-L1 and programmed death-1 (PD-1) and PD-L1 and B7-1 interactions, reinvigorating anticance immunity. We assessed its efficacy and safety versus docetaxel in previously treated patients with non-small-ce lung cancer.

Methods We did a randomised, open-label, phase 3 trial (OAK) in 194 academic or community oncology centres in 31 countries. We enrolled patients who had squamous or non-squamous non-small-cell lung cancer, were 18 years or older, had measurable disease per Response Evaluation Criteria in Solid Tumors, and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients had received one to two previous cytotoxic chemotherapy regimens (one or more platinum based combination therapies) for stage IIIB or IV non-small-cell lung cancer. Patients with a history of autoimmune disease and those who had received previous treatments with docetaxel, CD137 agonists, anti-CTLA4, or therapies targeting the PD-L1 and PD-1 pathway were excluded. Patients were randomly assigned (1:1) to intravenously receive either atezolizumab 1200 mg or docetaxel 75 mg/m² every 3 weeks by permuted block randomisation (block size of eight) via an interactive voice or web response system. Coprimary endpoints were overall survival in the intention-to-treat (ITT) and PD-L1-expression population TC1/2/3 or IC1/2/3 (≥1% PD-L1 on tumour cells or tumour-infiltrating immune cells). The primary efficacy analysis was done in the first 850 of 1225 enrolled patients. This study is registered with ClinicalTrials.gov, number NCT02008227.

Findings Between March 11, 2014, and April 29, 2015, 1225 patients were recruited. In the primary population, 425 patients were randomly assigned to receive atezolizumab and 425 patients were assigned to receive docetaxel. Overall survival was significantly longer with atezolizumab in the ITT and PD-L1-expression populations. In the ITT population, overall survival was improved with atezolizumab compared with docetaxel (median overall survival was 13·8 months [95% CI 11·8–15·7] *vs* 9·6 months [8·6–11·2]; hazard ratio [HR] 0·73 [95% CI 0·62–0·87], p=0·0003). Overall survival in the TC1/2/3 or IC1/2/3 population was improved with atezolizumab (median overall survival was 15·7 months [95% CI 12·6–18·0] with atezolizumab (n=241) compared with docetaxel (n=222; median overall survival was 8·4 months [8·8–12·0] with docetaxel; HR 0·74 [95% CI 0·58–0·93]; p=0·0102). Patients in the PD-L1 subgroup (TC0 and IC0) also had improved survival with atezolizumab *vs* 10·3 months; HR 0·75 [95% CI 0·59–0·96]; (HR 0·73 [95% CI 0·54–

Targeting Immune PD-L1/PD-1 Checkpoint Pathway



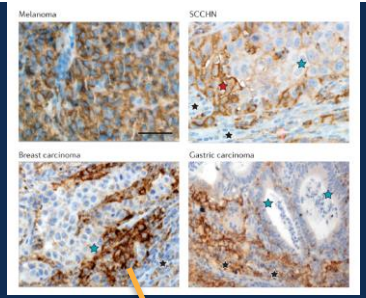
Targeting PD-L1/PD-1 Checkpoint Pathway

Nat Rev Cancer. 2016 May ; 16(5): 275–287. doi:10.1038/nrc.2016.36.

Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy

Suzanne L. Topalian[1], Janis M. Taube[2,3,4], Robert A. Anders[4], and Drew M. Pardoll[3]

PD-L1 expression



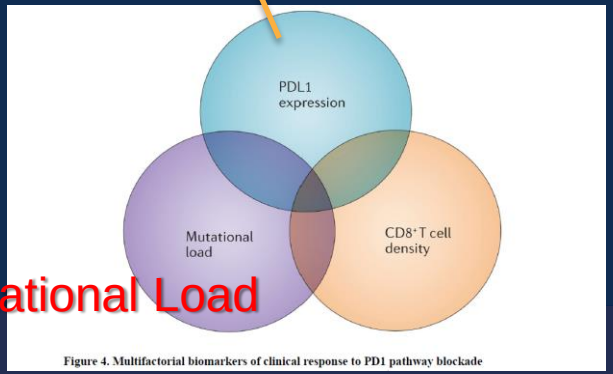


Figure 4. Multifactorial biomarkers of clinical response to PD1 pathway blockade

Total Mutational Load

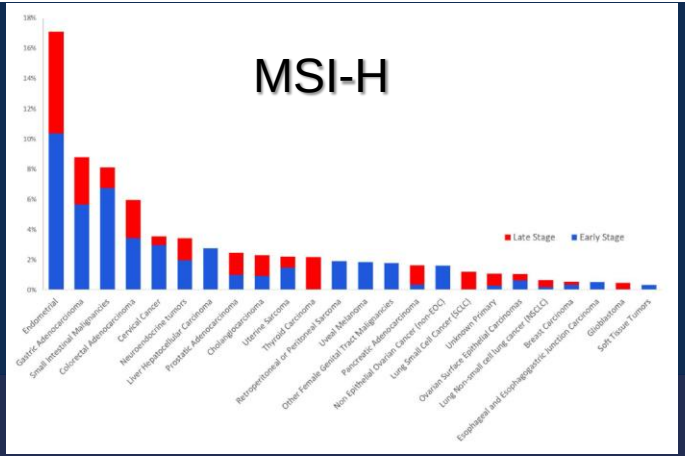
Science

REPORTS

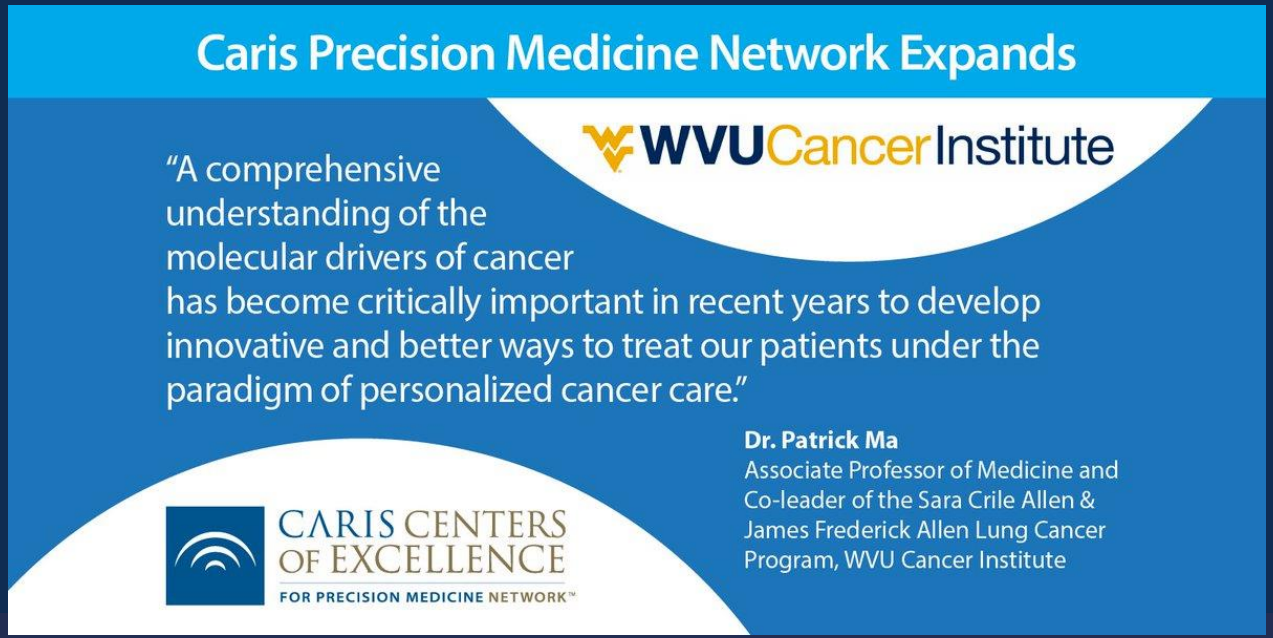
Cite as: D. T. Le *et al.*, *Science* 10.1126/science.aan6733 (2017).

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3*] Kellie N. Smith,[1,3*] Hao Wang,[3*] Bjarne R. Bartlett,[2,4*] Laveet K. Aulakh,[2,4] Steve Lu,[2,4] Holly Kemberling,[3] Cara Wilt,[3] Brandon S. Luber,[3] Fay Wong,[2,4] Nilofer S. Azad,[1,3] Agnieszka A. Rucki,[1,3] Dan Laheru,[3] Ross Donehower,[3] Atif Zaheer,[5] George A. Fisher,[6] Todd S. Crocenzi,[7] James J. Lee,[8] Tim F. Greten,[9] Austin G. Duffy,[9] Kristen K. Ciombor,[10] Aleksandra D. Eyring,[11] Bao H. Lam,[11] Andrew Joe,[11] S. Peter Kang,[11] Matthias Holdhoff,[3] Ludmila Danilova,[1,3] Leslie Cope,[1,3] Christian Meyer,[3] Shibin Zhou,[1,3,4] Richard M. Goldberg,[12] Deborah K. Armstrong,[3] Katherine M. Bever,[3] Amanda N. Fader,[13] Janis Taube,[1,3] Franck Housseau,[1,3] David Spetzler,[14] Nianqing Xiao,[14] Drew M. Pardoll,[1,3] Nickolas Papadopoulos,[3,4] Kenneth W. Kinzler,[3,4] James R. Eshleman,[15] Bert Vogelstein,[1,3,4] Robert A. Anders,[1,3,15] Luis A. Diaz Jr.[1,2,3†‡]



Caris Precision Oncology Alliance (POA) - WVU Cancer Institute

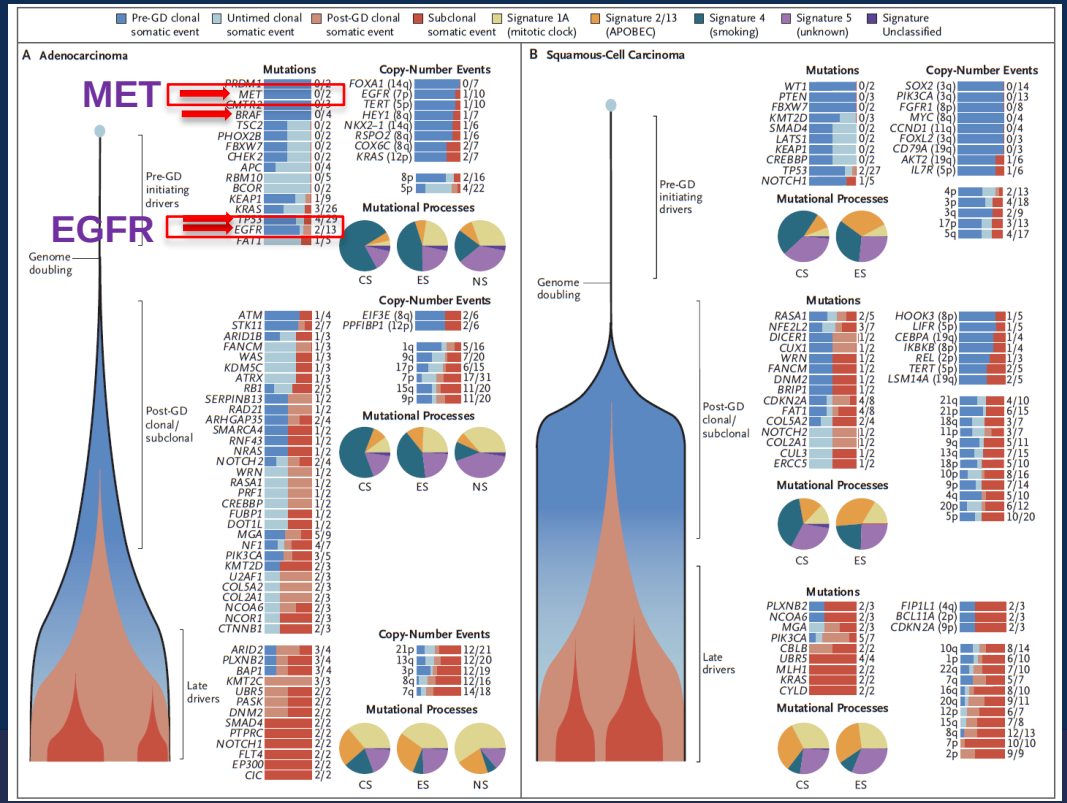


*TRA*cking NSCL*C* *E*volution through Therapy (TRACERx)

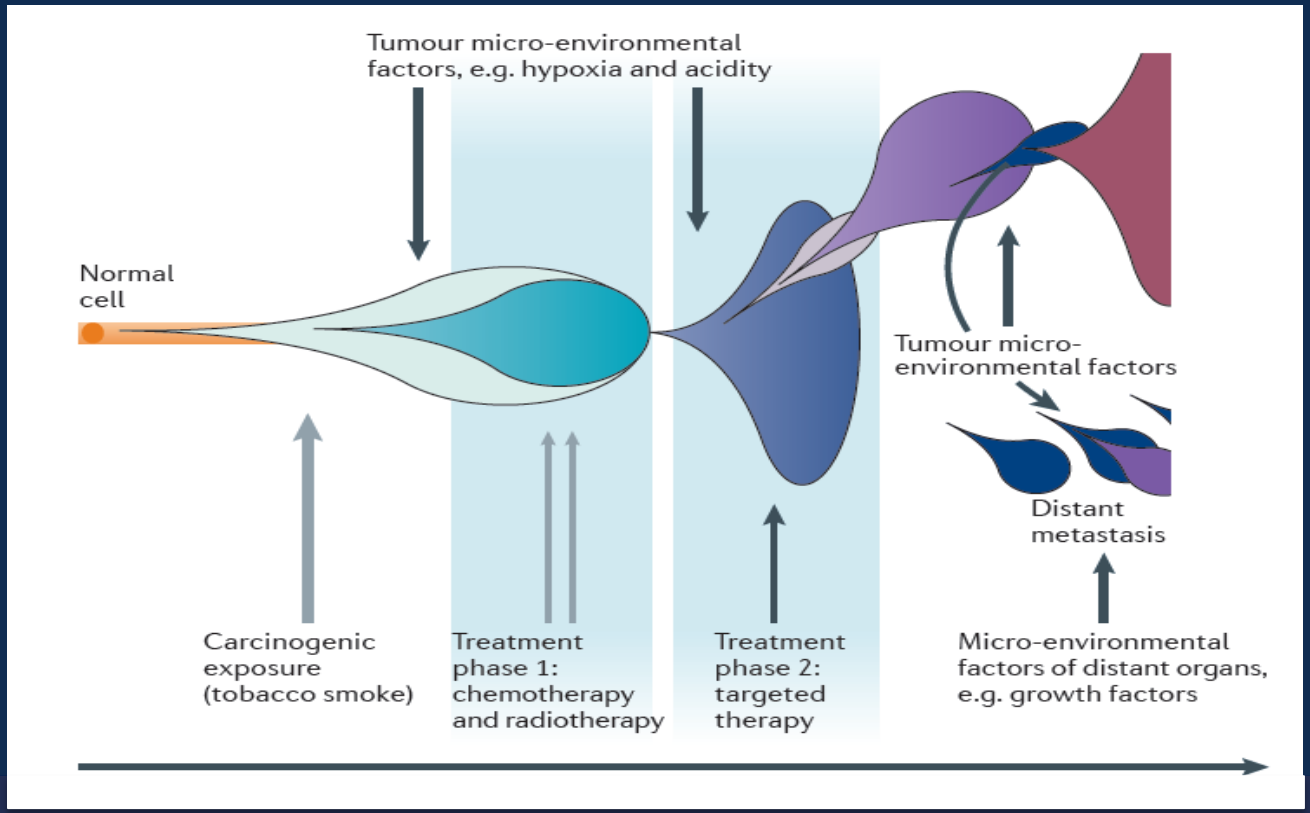
N Engl J Med 2017; 376:2109-2121, June 1, 2017

"**Intratumor Heterogeneity**" (CNV, mutations) is widespread and asso. with decreased disease-free survival and is caused by chromosomal instability.

Key driver mutations, and almost always clonal (TP53, BRAF, **EGFR, MET**)

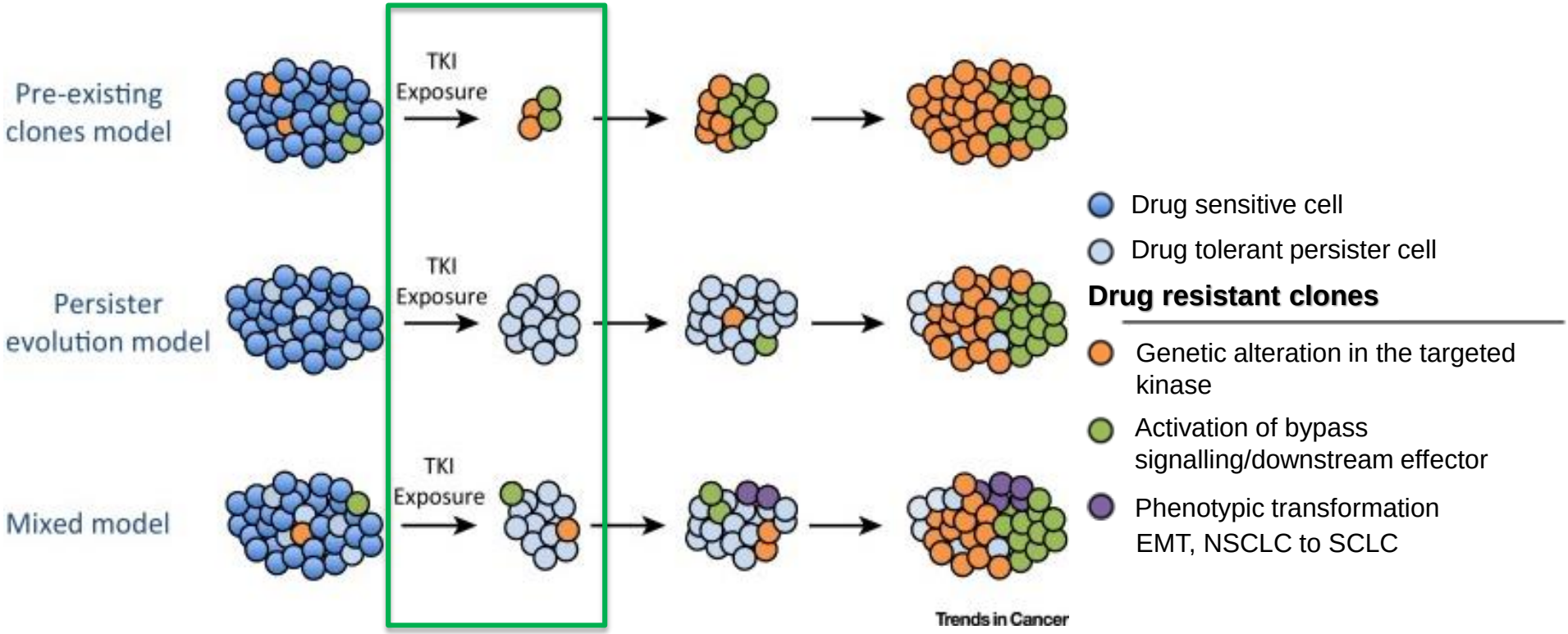


Combating Resistance: Cancer Genome Evolutionary Adaptation, Tumor Heterogeneity and Drug Resistance



Nature Rev Cancer, Nov 2012

Mechanisms of Targeted Therapy Drug Resistance



Lin JJ and Shaw AT. Resisting Resistance: Targeted Therapies in Lung Cancer. *Trends in Cancer* 2016; 2(7): 350–364.

Combating Resistance: Cancer Genome Evolutionary Adaptation, Tumor Heterogeneity and Drug Resistance

OnCore Protocol No.: WVU011117
IRB No.: 1704546158

Title: Serial ProspECtive bIopsy for Appalachian Lung Cancer Molecular Profiling (SPECIAL) Study

PI: Ma, Patrick
Protocol Status: OPEN TO ACCRUAL

Translational Research in Elucidating Molecular Mechanism of Tumor Resistance in Lung Cancer Therapies

WVU011117 - Serial ProspECtive bIopsy for Appalachian Lung Cancer Molecular Profiling **(**SPECIAL**)** Study

- Serial tumor biopsies-rebiopsies and blood collection on treatments
- Genomics sequencing and profiling
- Proteomics-Metabolomics profiling
- Predictive biomarkers discovery for treatment response-resistance
- Novel evolutionary treatment strategies and drug discovery