FMI has developed and analytically validated a highly specific and sensitive blood-based TMB (bTMB) assay

Average values across both bTMB cut-offs (established against an orthogonally validated TMB platform)[1]

95 % Positive predictive agreement

96 % Average precision

17 % Coefficient of variation

100 % Negative predictive agreement

Positive predictive value

Analytically validated for accuracy and precision with only

1 % of tumour content in ≥ 20 ng of cfDNA

The bTMB assay interrogates SNVs in 394 genes from cfDNA in plasma and reports a score based on the number of high-confidence SNVs identified[2]

bTMB: blood-based tumour mutational burden; cfDNA: cell-free DNA; CGP: comprehensive genomic profiling; MSAF: maximum somatic allele frequency; NSCLC: non-small cell lung cancer; SNV: single nucleotide variant.

1. Fabrizio, D.A., et al. (2017) *Ann Oncol* 28(suppl 5):v22-42;
2. Gandara, D.R., et al. (2017) *Ann Oncol* 28(suppl 5):v460-96.

Clinical validation of the FMI bTMB assay: Initial and ongoing studies

Initial trials: Plasma samples from two previous trials of atezolizumab▼, **OAK** and **POPLAR**, were analysed to correlate TMB with atezolizumab▼ clinical activity[1]

Ongoing trials: Aim to clinically **evaluate and prospectively validate** novel blood-based diagnostic assays for the **measurement of bTMB and somatic mutations** to determine the **efficacy and safety of first-line atezolizumab▼ or alectinib** in NSCLC patients[2]

B-F1RST (NCT02848651)[2-5]

- Phase 2, exploratory
- **Single-arm** study
- Evaluates safety and efficacy of **atezolizumab▼**
- Assesses association between bTMB (high: ≥ 16; low: < 16 muts / Mb) and efficacy in biomarker-unselected patients
- Blood samples collected prospectively and tested retrospectively

BFAST (NCT03178552)[2,4,6]

- Phase 3, confirmatory
- Screening and interventional randomised **umbrella** trial
- Patients selected based on bTMB (≥ 16 or ≥ 10 muts / Mb) or somatic mutations
- Pre-enrolment molecular screening to identify *ALK+*, *RET+* or bTMB+ patients*

* The RET / alectinib arm has been discontinued. bTMB: blood-based tumour mutational burden; muts / Mb: mutations / megabase; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; TMB: tumour mutational burden.

Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to Roche Registration GmbH.

1. Gandara., D.R., et al. (2017) *Ann Oncol* 28(suppl 5):v460-96;
2. Mok, T., et al. (2017) Ann Oncol 28(suppl 5):494-5; 3. Kim, E.S., et al. (2018) *Ann Oncol* 29 suppl 8:viii744; 4. Mok, T., et al. (2017) ESMO poster #1383TiP; 5. Clinicaltrials.gov identifier: NCT02848651. Available at https://clinicaltrials.gov/ct2/show/NCT02848651; 6. Clinicaltrials.gov identifier: NCT03178552. Available at https://clinicaltrials.gov/ct2/show/NCT03178552.

Blood First Assay Screening Trial (BFAST): Study concept and design

A global, open-label, multi-cohort phase II/III prospective study to evaluate blood-based biomarkers and their relationship with the clinical activity of targeted therapies, including atezolizumab▼, alectinib▼ and entrectinib in patients with NSCLC[1,2]

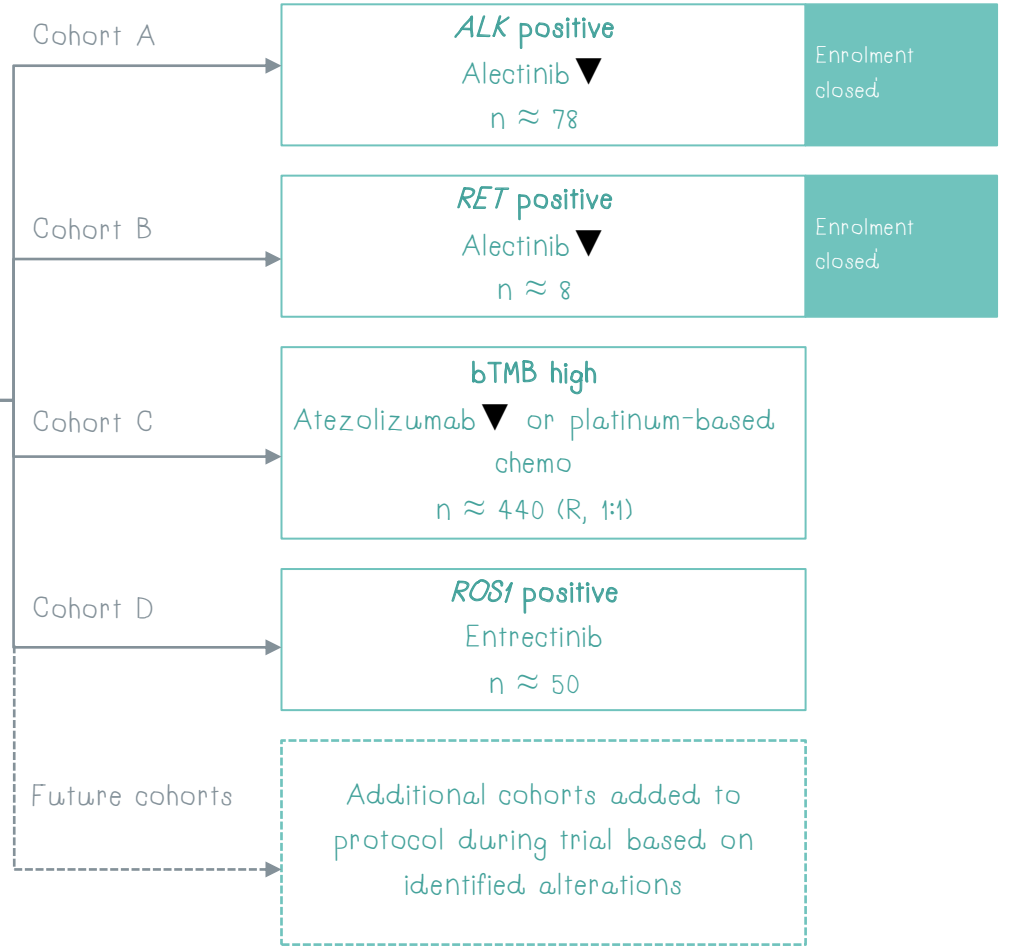
Patients with confirmed stage IIIB / IV advanced or metastatic NSCLC (any histology, n ≈ 3,500)[1-3]

Blood-based NGS ctDNA assays, including bTMB*

Key objectives[3]

Expand label indications and access for NSCLC patients through blood-based diagnostics

Demonstrate similar efficacy and safety to that from pivotal tissue-selected trial



bTMB: blood tumour mutational burden; ctDNA: circulating tumour DNA; NGS: next-generation sequencing; NSCLC: non-small cell lung cancer; R: randomised. * Consenting patients with key alteration profile of interest (e.g. *KRAS, HER2, BRAF* or *MEK* mutations) who are not enrolled in a treatment cohort will not receive study treatment and will enter natural history follow-up. Patients already enrolled will continue to undergo treatment and follow-up per protocol.

1. Mok, T., et al. (2017) *Ann Oncol* 28 (suppl. 5: v460-96: abstract 1383TIP and poster); 2. Clinicaltrials.gov NCT03178552;
3. Roche data on file, BFAST internal training deck. Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your respective local office.
Roche Registration GmbH: alectinib, atezolizumab.

BFAST *ALK*+ cohort

Goal

Demonstrate consistency of benefit with alectinib in a population selected by blood-based NGS as opposed to tissue-based assay, using ALEX alectinib data as reference

- **Unresectable, stage IIIB or IV NSCLC**
- ***ALK*+ by centralised blood screening only**
- **Treatment naïve**
- **ECOG PS 0–2**

→ **Alectinib 600mg BID** → **Until PD, toxicity, withdrawal or death**

Primary endpoint
Confirmed ORR by investigator

Exploratory endpoint
Confirmed ORR by investigator for patients with baseline CNS metastases

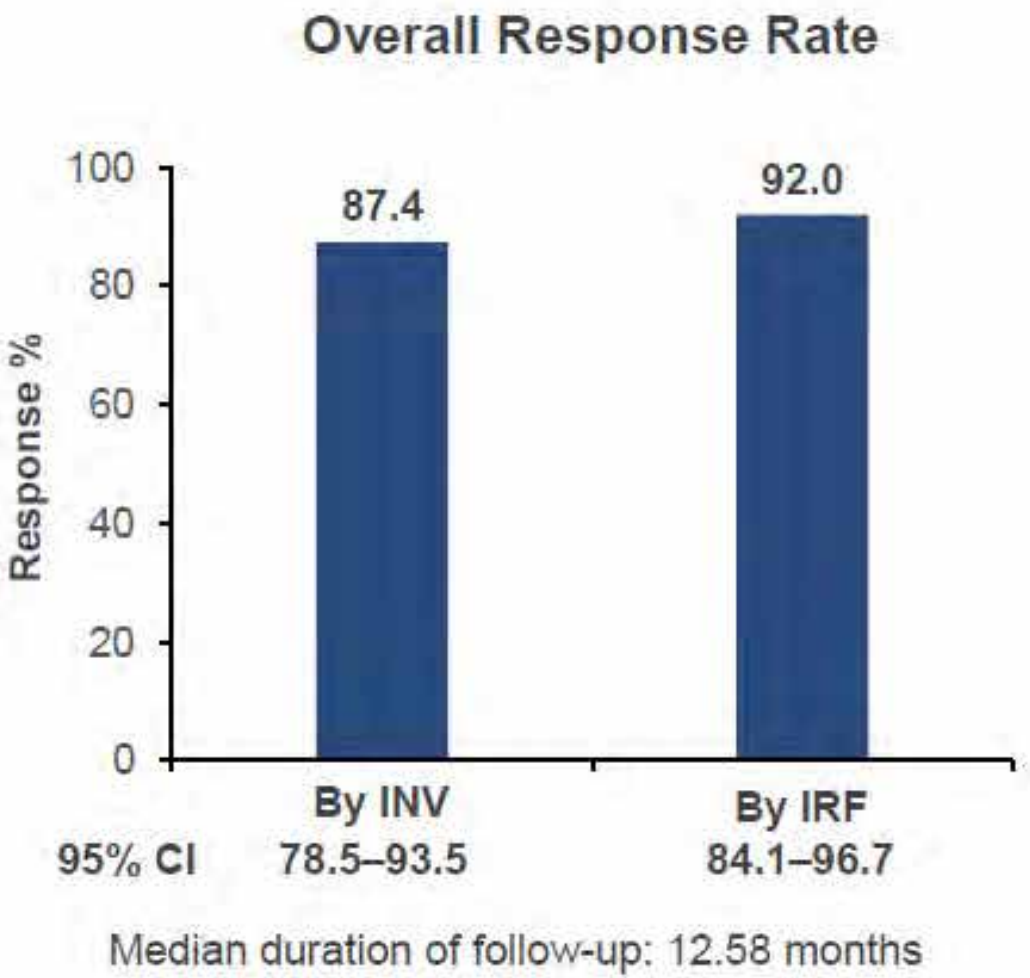
Secondary endpoints

By investigator	By independent review facility
DoR	ORR
PFS	DoR
	PFS

CNS = central nervous system; DoR = duration of response
ORR = overall response rate; PD = disease progression; PFS = progression-free survival
ECOG PS = Eastern Cooperative Oncology Group performance status; NGS = next generation sequencing

NCT03178552

Results: Confirmed response (INV vs IRF)



Median duration of follow-up: 12.58 months

These results demonstrate the clinical utility of blood-based NGS as a method to inform clinical decision-making in ALK+ NSCLC

	INV (N=87)	IRF (N=87)
Complete Response, n (%) 95% CI	0 (0.00–4.15)	11 (12.6) (6.48–21.50)
Partial Response, n (%) 95% CI	76 (87.4) (78.50–93.52)	69 (79.3) (69.29–87.25)
Progressive Disease, n (%) 95% CI	1 (1.1) (0.03–6.24)	1 (1.1) (0.03–6.24)

ALEX confirmed ORR = 71.7% (95% 63.8–78.7)[1]

INV = investigator-assessed; IRF = independent review facility-assessed

1. Mok, et al. ESMO 2019

Overall conclusions

Cancer disease have evolved to personalized treatment to achieve better outcome with targeted therapy

Comprehensive genomic profiling (CGP) offers broad vision of molecular targets across cancer-related genes that maybe missed by conventional testing

Standardization and validation are critical factors to ensure the precision of CGP panels.
FoundationONE CDx is the only commercialized CGP approved by US FDA.

NTRK fusions can be detected by FoundationONE CDx and FoundationONE HEME and are used for screening in several clinical trials and publications.

FoundationOne Liquid provides a less invasive and less biased method to identify genomic alterations, requiring only a single blood draw and not relying on sampling a single site

The interesting case discussion #1

Suebpong Tanasanvimon, M.D.
Medical Oncologist, King Chulalongkorn Memorial Hospital

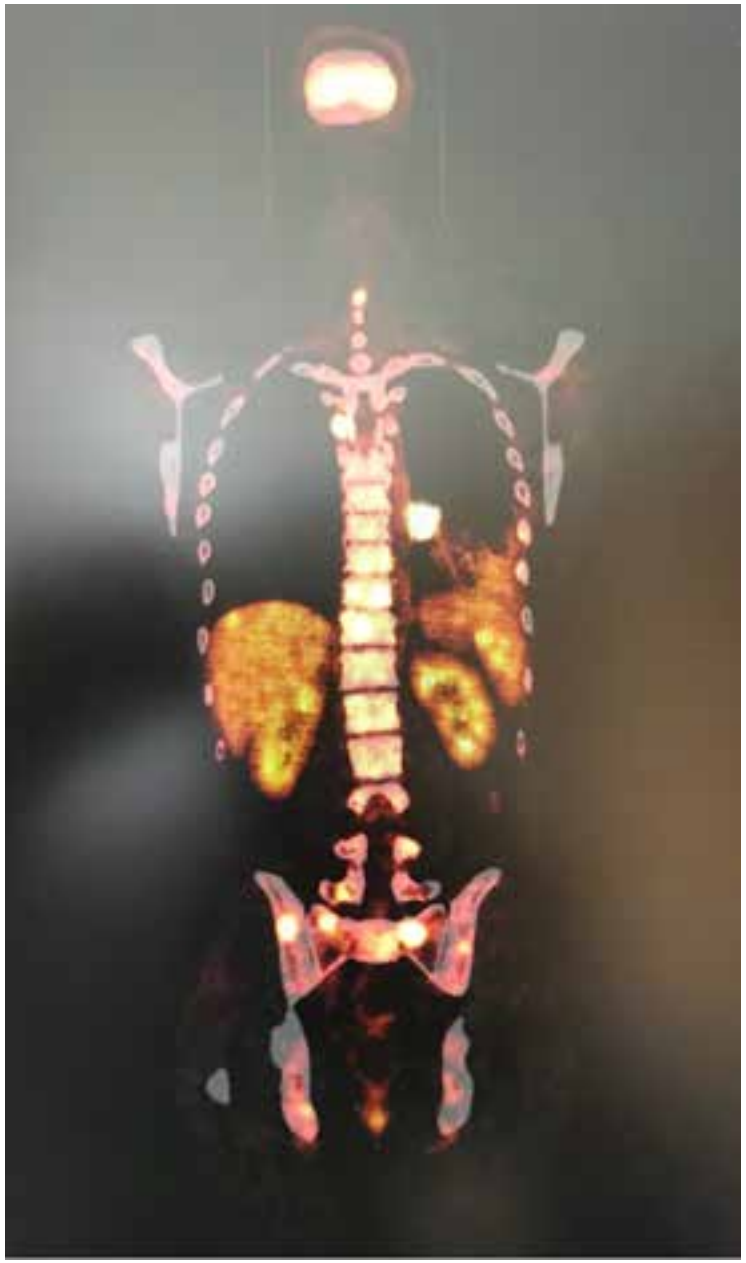
History of present illness

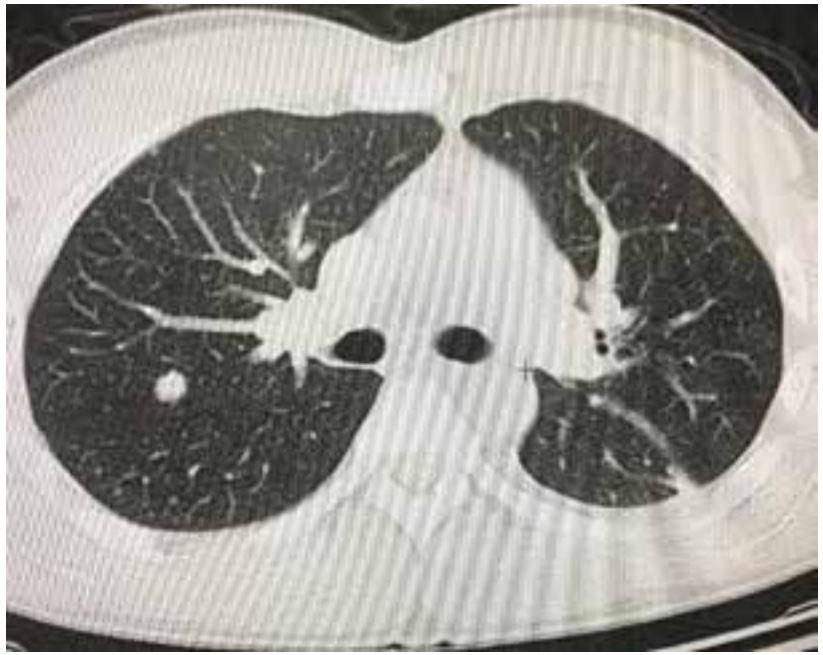
30 year-old non-smoker, male, previously healthy

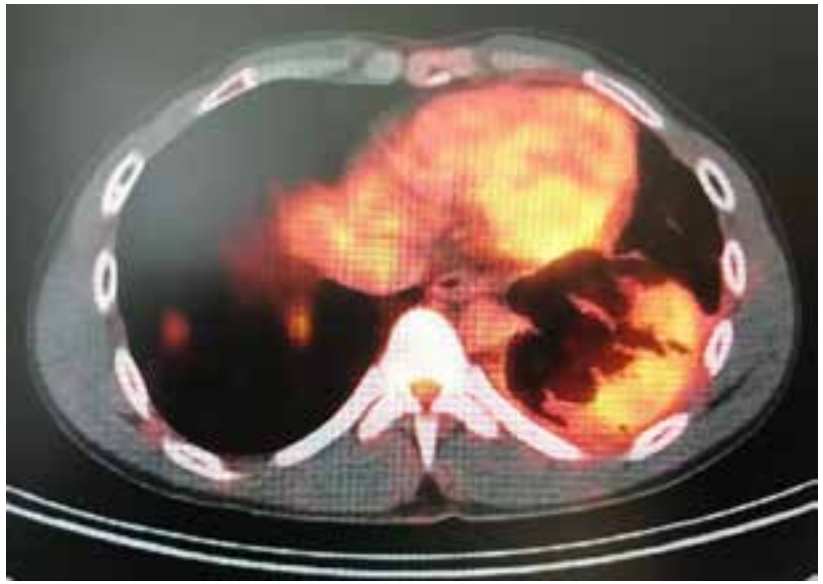
January 2018

- Dx aNSCLC
- Presented with LLL mass
- Transthoracic biopsy
  - Adenocarcinoma

PET/CT







History of present illness

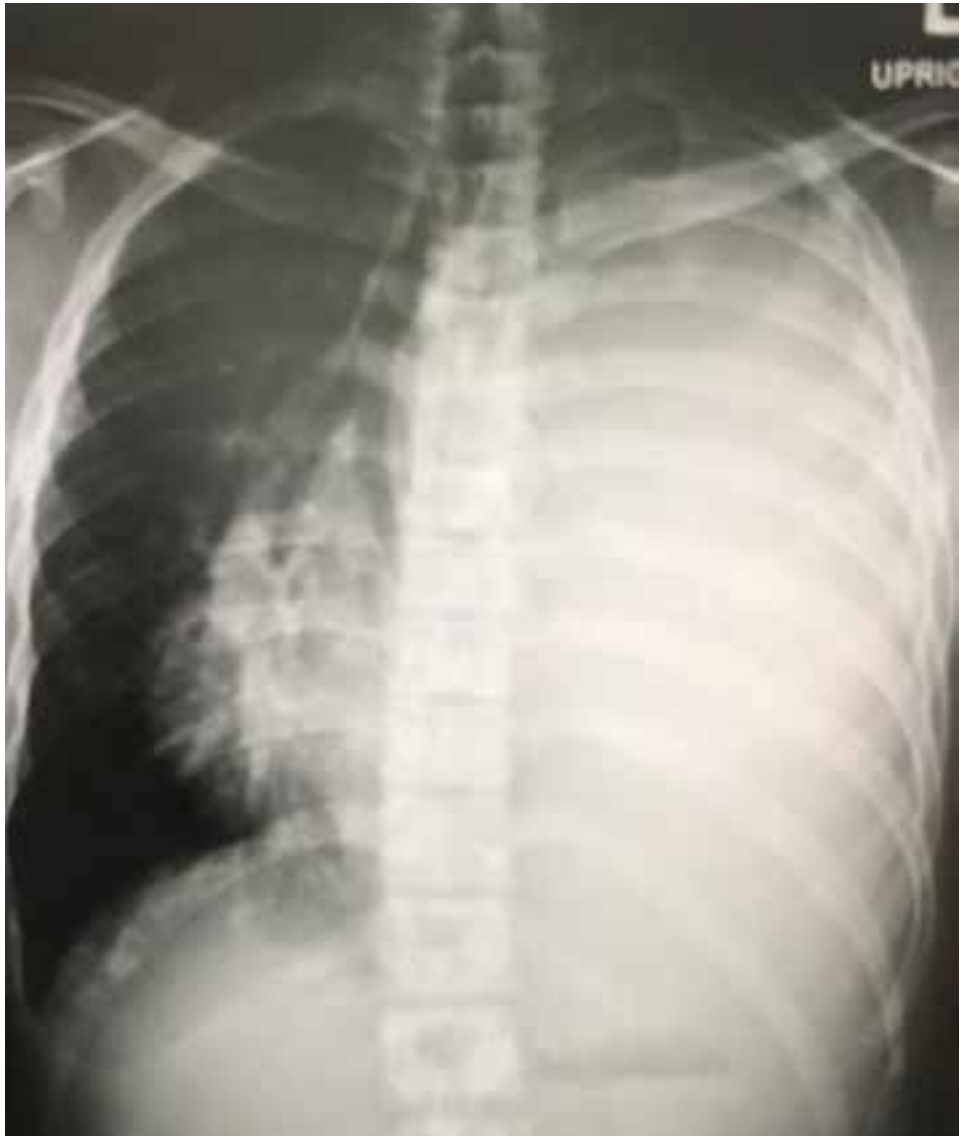
30 year-old male with aNSCLC

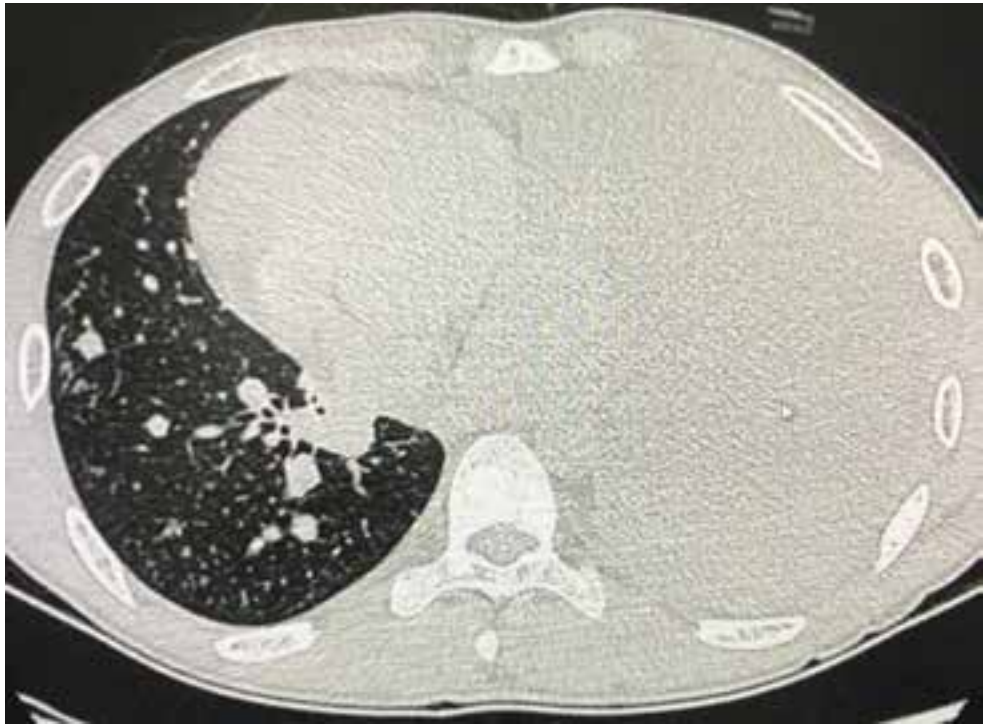
January 2018

- EGFR mutation negative
- ALK negative

Chemotherapy was offered
Opted to alternative therapy

10 months later...





Thoracentesis released pleural fluid
Cytology: adenocarcinoma

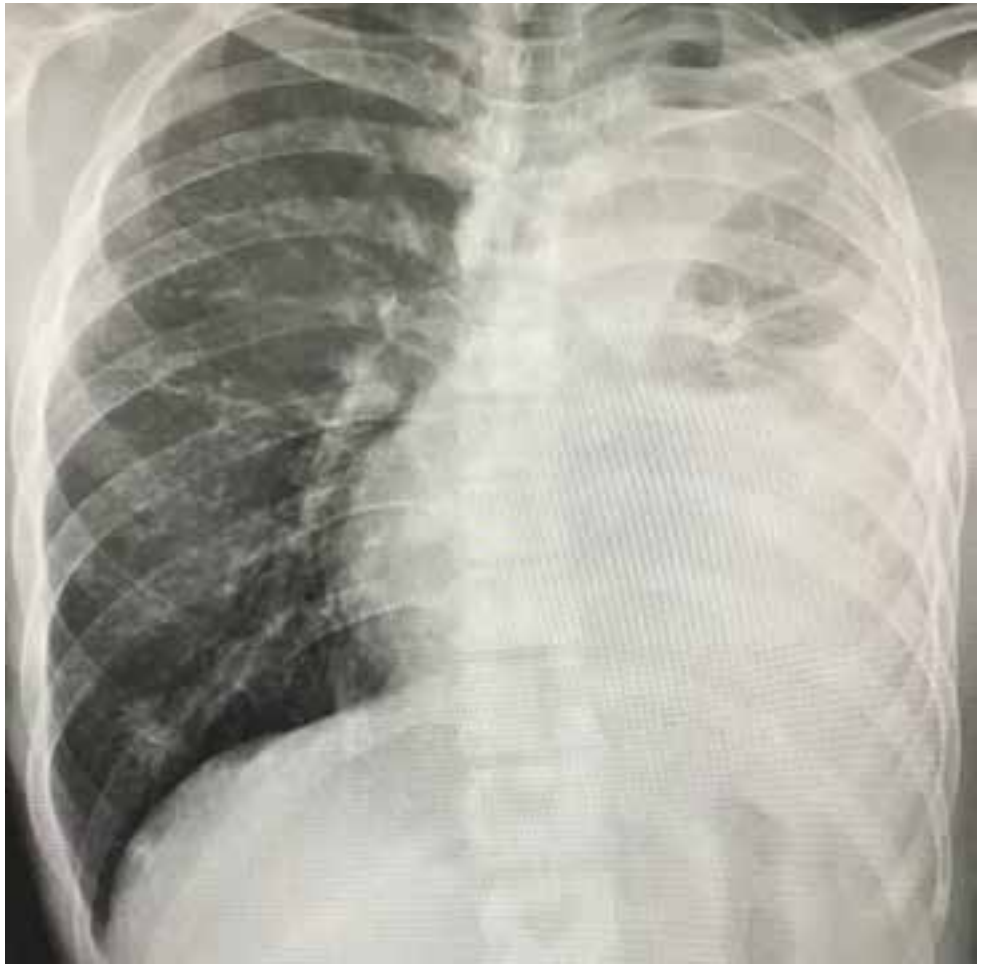
History of present illness

30 year-old male with EGFR-, ALK- aNSCLC

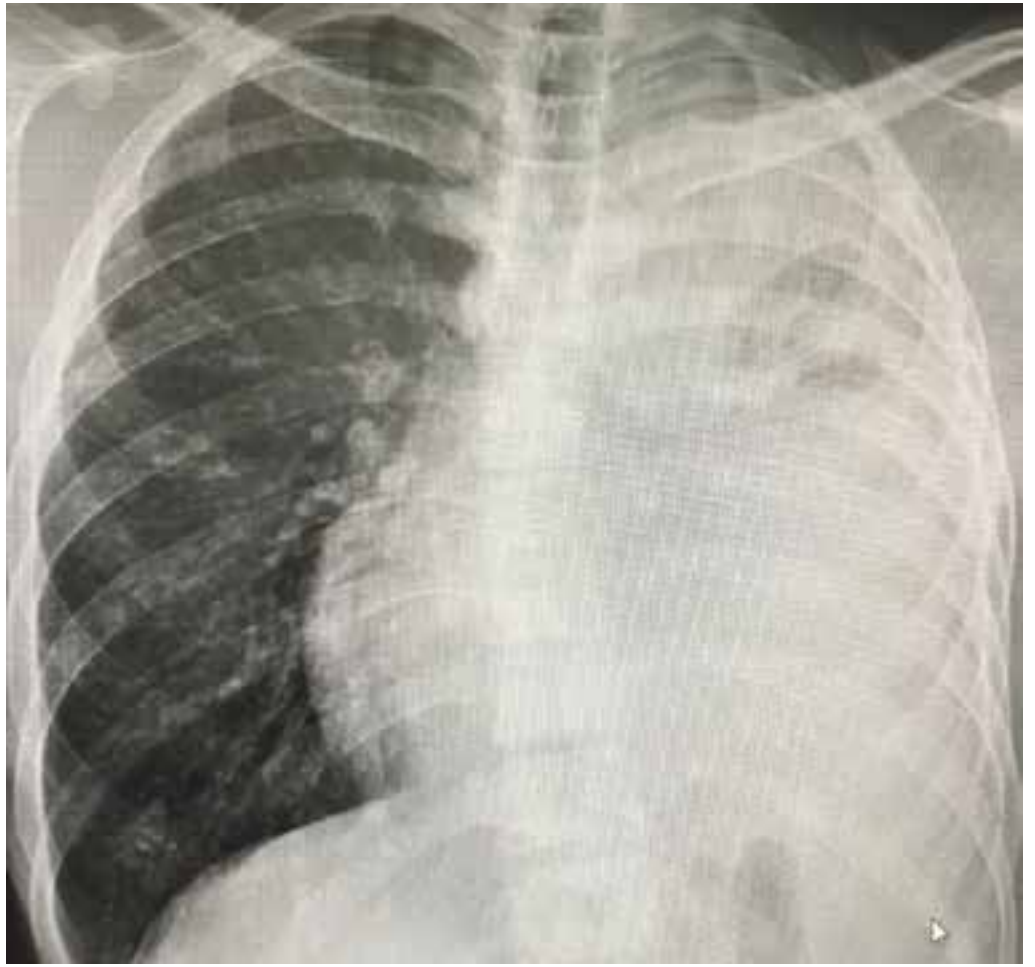
Bronchoscopic Bx

- Adenocarcinoma
- PD-L1 negative

Carboplatin and Paclitaxel for 4 cycles

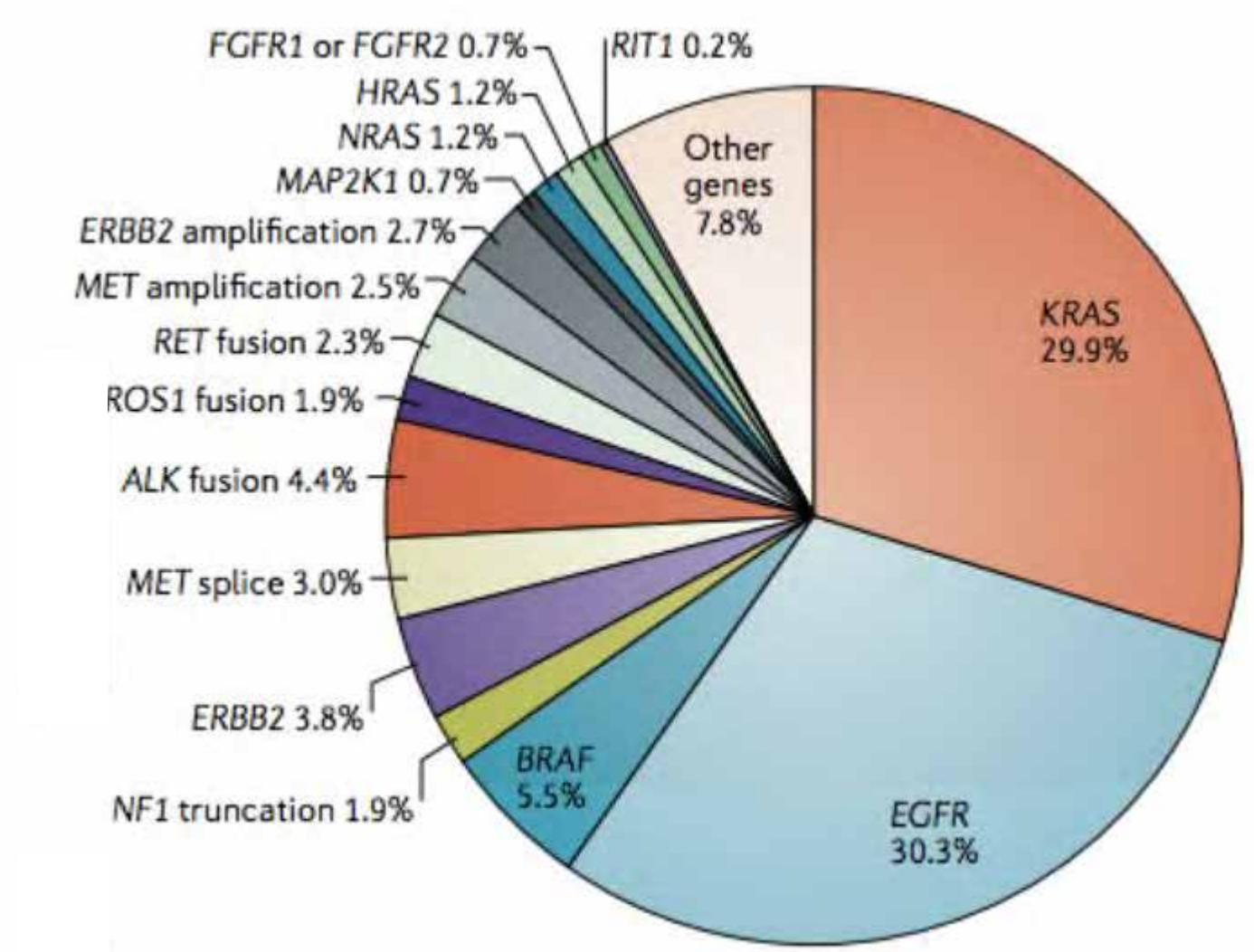


Before



After

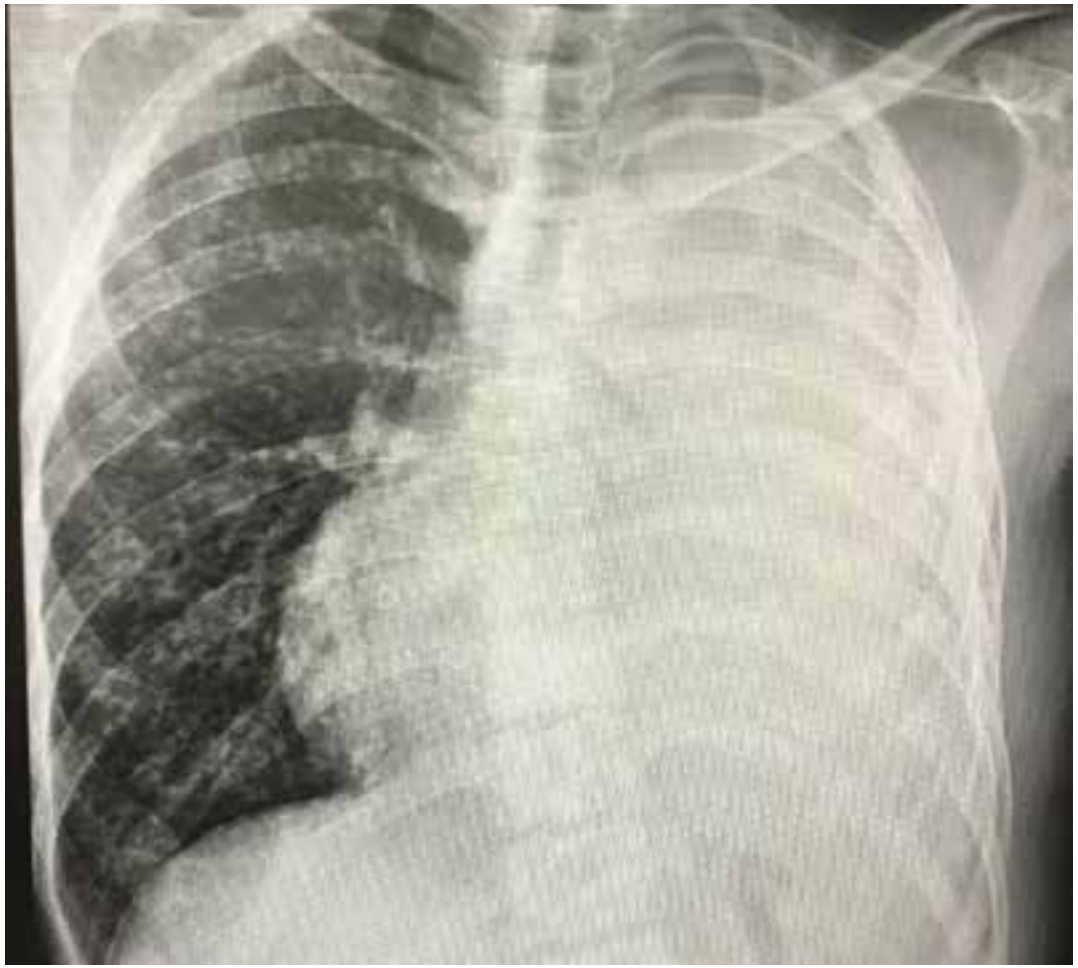
Molecular landscape in lung adenocarcinoma

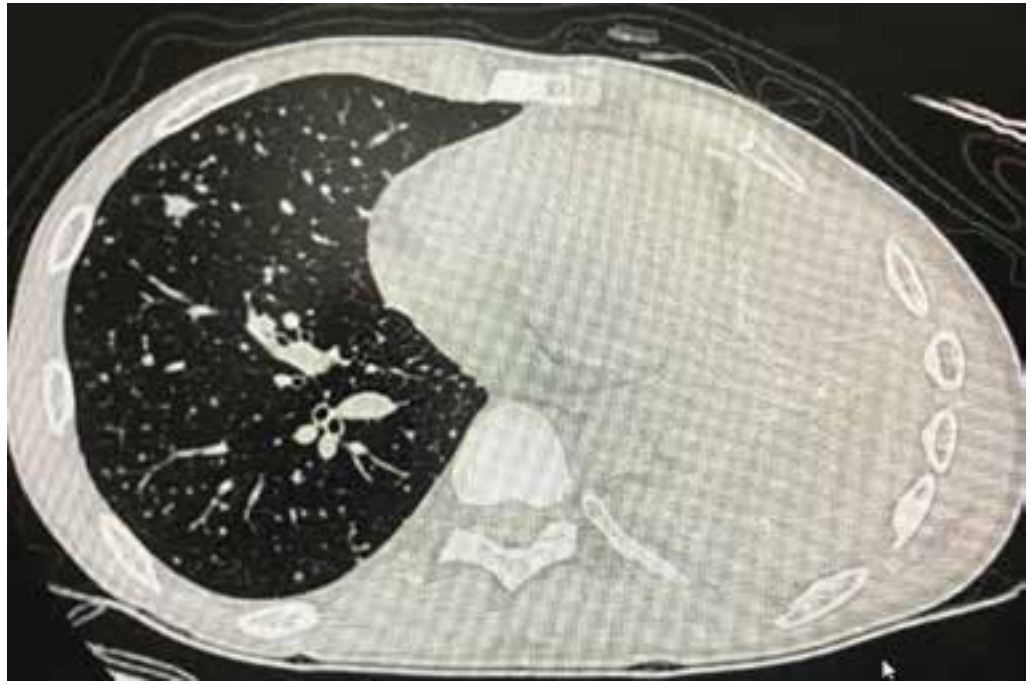


Data from MSK-IMPACT (Jordan et al.) and FoundationOne (Frampton et al.) panel (n = 5262)

Nat Rev Cancer 2019

2 months later...





FOUNDATIONONE® CDx

PATIENT

TUMOR TYPE
Lung adenocarcinoma

REPORT DATE

ORF#

Biomarker Findings

Tumor Mutational Burden - TMB-Intermediate (8 Muts/Mb)
Microsatellite status - MS-Stable

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

ROS1 CD74-ROS1 fusion
CDH1 Q23*
CDKN2A/B loss
MAP2K4 R304*

7 Disease relevant genes with no reportable alterations: *EGFR, KRAS, ALK, BRAF, MET, RET, ERBB2*

9 Therapies with Clinical Benefit
0 Therapies with Lack of Response
20 Clinical Trials

SPECIMEN

SPECIMEN SITE Pleura
SPECIMEN ID
SPECIMEN TYPE Block
DATE OF COLLECTION
SPECIMEN RECEIVED

APPENDIX Variants of Unknown Significance

AR Q72R and Q73R	***ARID1A*** A41V	***ATM*** N246T	***C11ORF30 (EMSY)*** K710_E711insGK
CD74 rearrangement	***GNAS*** E140K	***IKBKE*** R348P	***JAK1*** N226S
LTK R658Q	***MAP2K4*** T302I	***MST1R*** A973T	***RICTOR*** R910H
ZNF217 S593L			

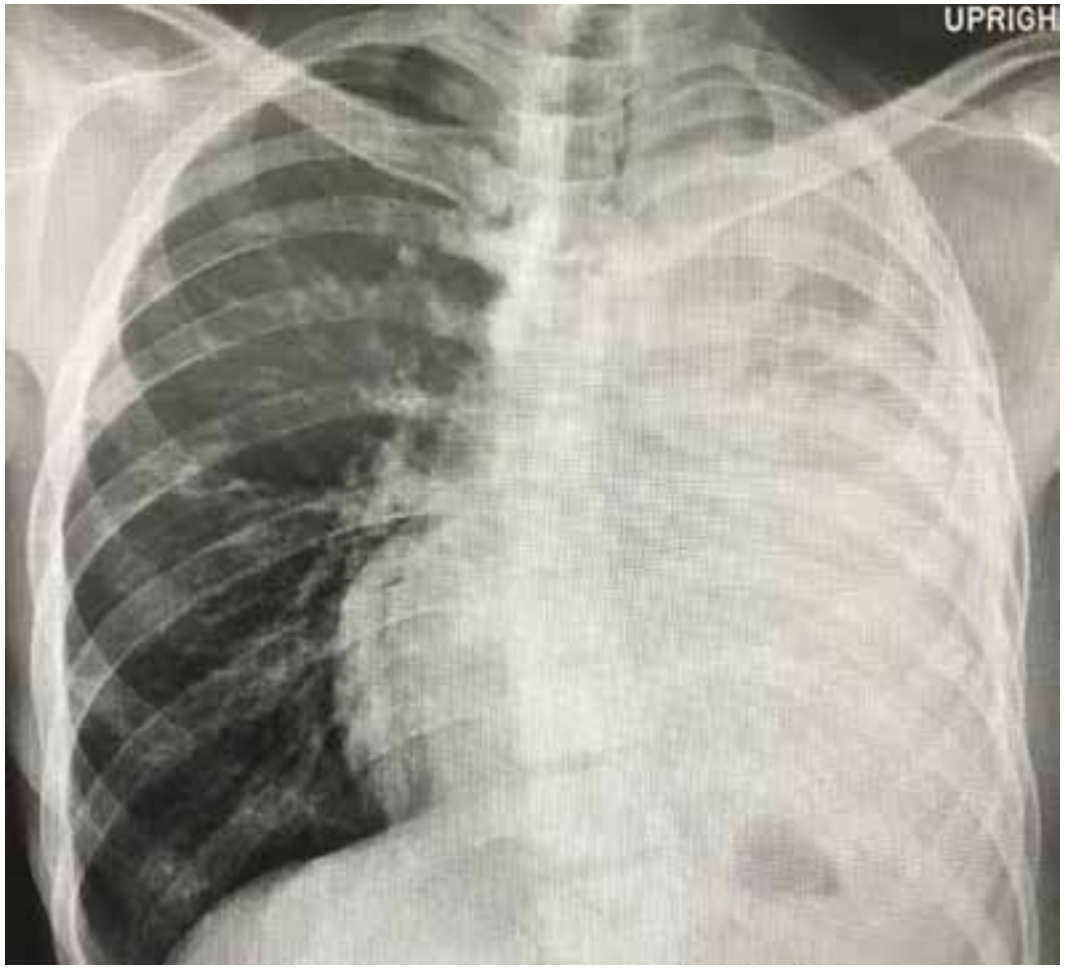
BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - TMB-Intermediate (8 Muts/Mb)	Atezolizumab	Avelumab
	Durvalumab	Cemiplimab-rwlc
	Nivolumab	
10 Trials *see p. 12*	Pembrolizumab	

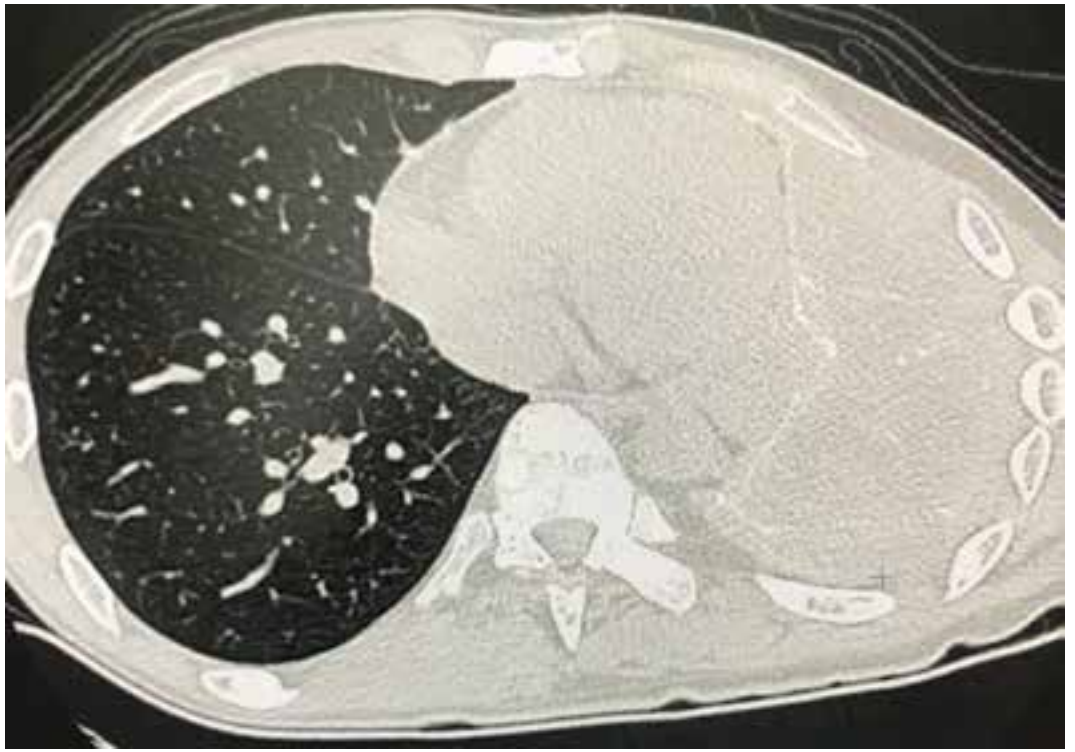
Microsatellite status - MS-Stable

No therapies or clinical trials. see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
ROS1 - CD74-ROS1 fusion	Ceritinib	none
	Crizotinib	
10 Trials *see p. 15*	Lorlatinib	

Ceritinib 450 mg PO





The interesting case discussion #2

Potjana Jitawatanarat, M.D.
Medical Oncologist, Bangkok Hospital

History of present illness

45 year-old man with history of 10 pack year smoking (1/2 PPD x 20 yrs) presented with 2 months history of intermittent brief black out.

13/3/19

Patient presented with near syncope so he was bring to SinPat hospital investigation MRI brain, CT chest/neck/whole abdomen

- MRI cervical spine revealed tiny acute infarction left temporal lobe, RUL/LLL, multiple lower neck lymphadenopathy.

21/3/19

Patient underwent supraclavicular LN biopsy:

- metastatic poorly differentiated adenocarcinoma, CK 7 positive, CK 20 negative, TTF1/napsin A negative.
- EGFR /ALK/ROS1-negative, PDL1 22C3 CPS score : 5%.

Patient come to wattanosoth hospital for evaluation and treatment.

History of present illness

PET/CT 8/4/19:
Large hypermetabolic nodules in right upper and left lower lung are likely malignant tumor with bilateral intrapulmonary metastases, progression from Mar 2019
Lymph node metastases in both sides of hilum, mediastinum and in supraclavicular spaces, no significant change in size. Suggest metastases in segment IVa, IVb and in segment VI, recently developed. Probable pneumonitis in right middle lung.

2 cycles carboplatin, paclitaxel, atezolizumab 29/4/19.
Patient presented 17/5/19 with abdominal pain and fever.

History of present illness

CT upper abdomen 18/5/19:

- Multiple peripheral enhancing lesions scatter in both hepatic lobes, correlate with clinical presenting fever, probably to be hepatic abscesses; DDx is mucin producing adenocarcinoma metastasis (DDx by radiologic picture)
- Two small cysts at right middle pole kidney and left lower pole kidney
- Multiple subcentrimeter paraaortic and paracaval lymph nodes

Liver biopsy 19/5/19:
adenocarcinoma, FoundationONE CDx sent

FOUNDATION MEDICINE

ABOUT THE TEST FoundationOne®CDx is the first and only FDA-Approved comprehensive companion diagnostic for all solid tumors

PATIENT

DISEASE Lung non-small cell lung carcinoma (NOS)
NAME Chalotthai, Pakpoom
DATE OF BIRTH 02 July 1973
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN Jitawatanarat, Potjana
MEDICAL FACILITY Bio-Molecular Laboratories
ADDITIONAL RECIPIENT Boonmalert, Rajatawatra
MEDICAL FACILITY ID 312370
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Liver
SPECIMEN ID HB19-3390 A
SPECIMEN TYPE Block
DATE OF COLLECTION 19 May 2019
SPECIMEN RECEIVED 29 May 2019

Biomarker Findings

Tumor Mutational Burden - TMB-Intermediate (14 Muts/Mb)
Microsatellite status - MS-Stable

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

ERBB2 **amplification - equivocal†**
BRCA1 **inversion exons 17-18**
CDKN2A/B **loss**
CREBBP **C1474fs*4**
MTAP **loss exons 2-8**
PARK2 **splice site 1083+1G>T**
SMARCA4 **splice site 3082-1G>T**
TP53 **P98fs*25**

7 Disease relevant genes with no reportable alterations: *EGFR, KRAS, ALK, BRAF, MET, RET, ROS1*

† See About the Test in appendix for details.

21 Therapies with Clinical Benefit

0 Therapies with Lack of Response

29 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - TMB-Intermediate (14 Muts/Mb)	Atezolizumab	Avelumab
	Durvalumab	Cemiplimab-rwlc
	Nivolumab	
10 Trials *see p. 22*	Pembrolizumab	
Microsatellite status - MS-Stable	No therapies or clinical trials. see Biomarker Findings section	

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
ERBB2 - amplification - equivocal	Afatinib	Ado-trastuzumab emtansine
	Dacomitinib	Lapatinib
		Neratinib
		Pertuzumab
		Trastuzumab
		Trastuzumab-dkst
		Trastuzumab-dttb
		Trastuzumab-pkrb
10 Trials see p. 27		Trastuzumab-qyyp
BRCA1 - inversion exons 17-18	none	Niraparib
		Olaparib
		Rucaparib
10 Trials see p. 25		Talazoparib

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

History of present illness

Patient has mixed response with atezolizumab, carboplatin, paclitaxel so we do give cycle 3 as atezolizumab, carboplatin, paclitaxel, avastin 23/5/19

06/19, Patient has abdominal pain, fever.

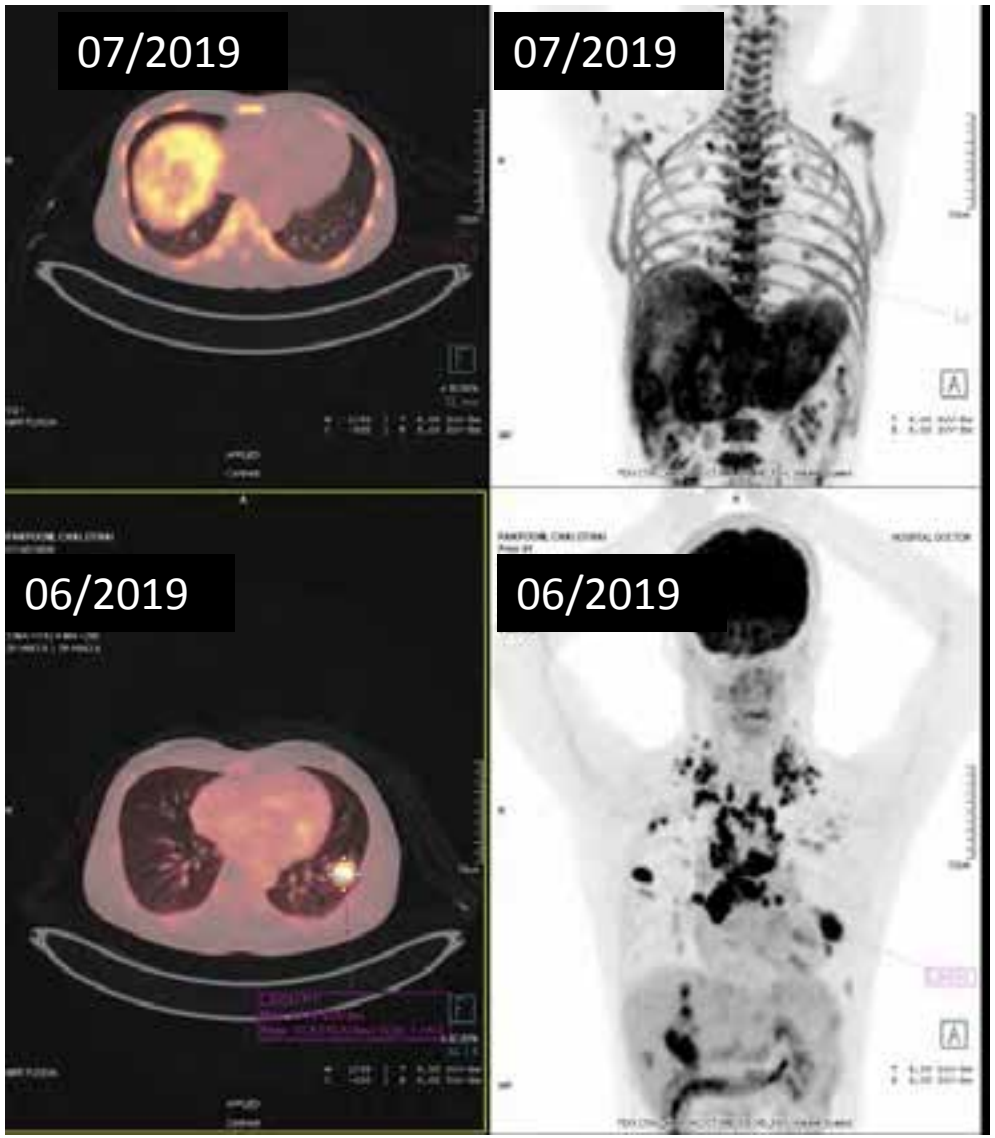
- CT chest/whole abdomen 11/6/19 revealed improved lung, liver lesion.
- Cycle 6 atezolizumab, carboplatin, paclitaxel, avastin given 24/7/19.

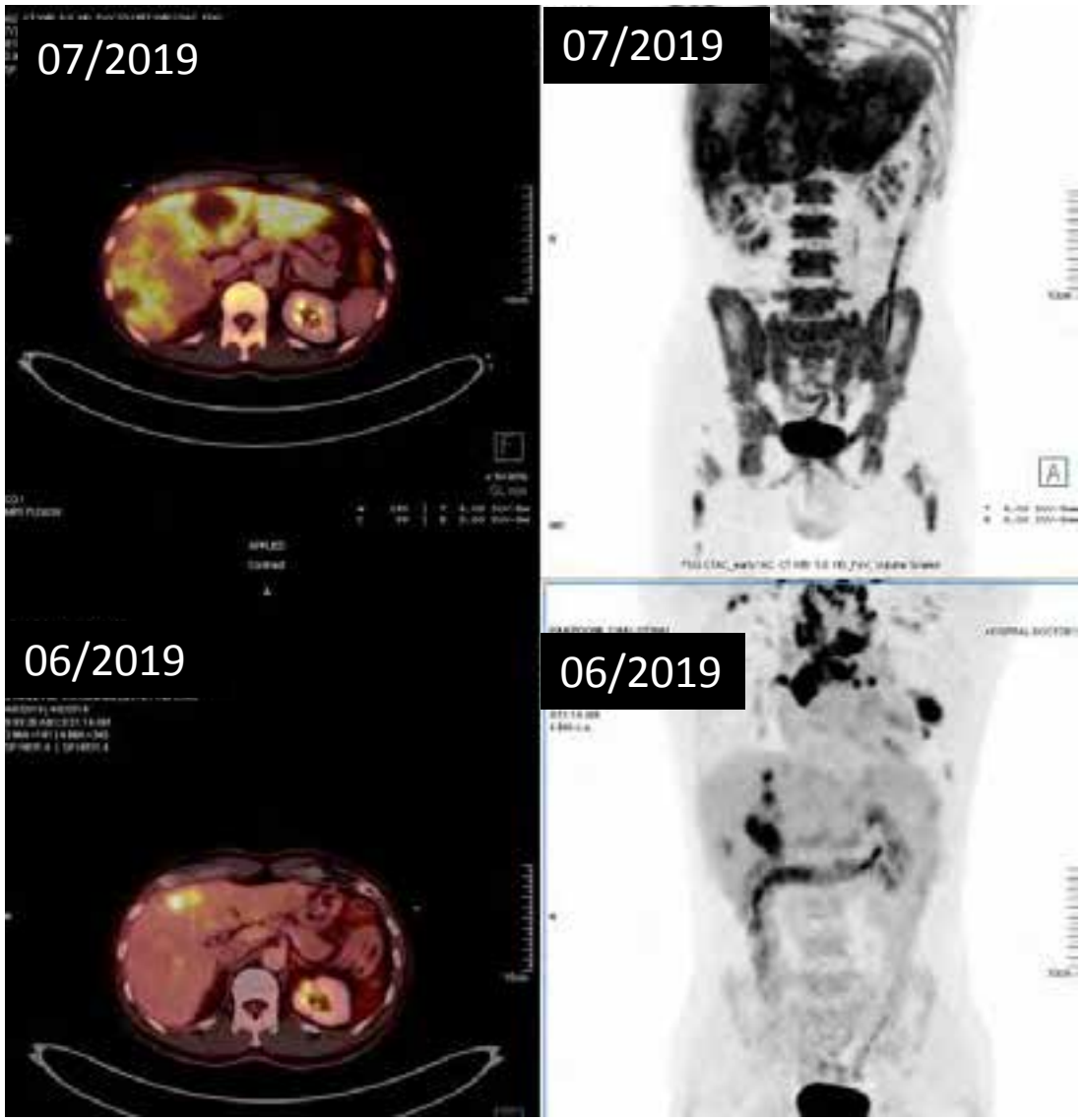
Patient was admitted 30/7/1 for not eat well, fatigue, epigastric pain, thrombocytopenia platelet 67,000 but no clinical bleeding

History of present illness

PET/CT 31/7/19:

- Compared to the previous PET-CT study on April 08, 2019, there is total regression of the hypermetabolic nodules in right upper and left lower lung and near total anatomic resolution of all lung nodules
- Almost total metabolic regression and decreased size of bilateral mediastinal node metastases with some residual metastatic nodes such as bilateral lower paratracheal nodes which show unchanged metabolic activity.
- New brain metastases in right cerebellum and both sides of cerebrum. Developed hypermetabolic activity in both lobes of liver, corresponding with segmental heterogeneous hypoenhancement on CT, with regression of the pre existing metastases. Progressed liver metastases and pseudoprogression are in the differential diagnosis.


07/2019
07/2019
06/2019
06/2019


07/2019
07/2019
06/2019
06/2019

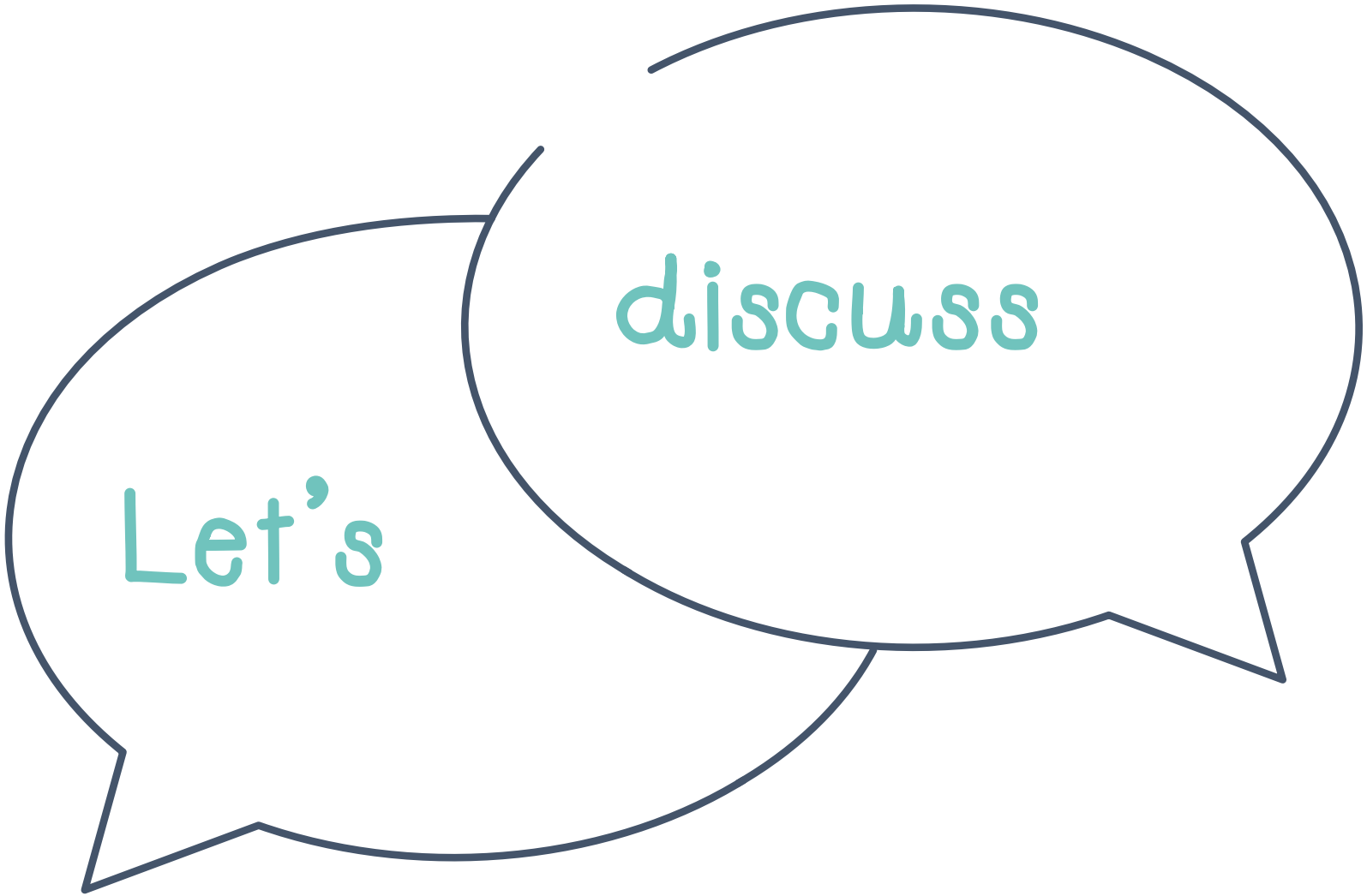
History of present illness

- WBRT 2800 cGy in 7 fractions finished 9/8/19

- Patient clinical improved able to eat, no dizziness or weakness
- Patient clinical fluctuate but platelet remain low around 20,000 – 40,000, no clinical bleeding

- After discussed with patient and family. Cycle 1 atezolizumab + olaparib 200 mg twice a day given 26/8/19, clinical worsening olaparib stop 30/8/19

- Patient passed away 6 September 2019


discuss
Let's

Post-Questionnaire

Please answer the questionnaire

Your feedback is important

Thank you for your participation!

Please let us know what you thought...

Doing now what patients need next