HER-2 In Lung Cancer

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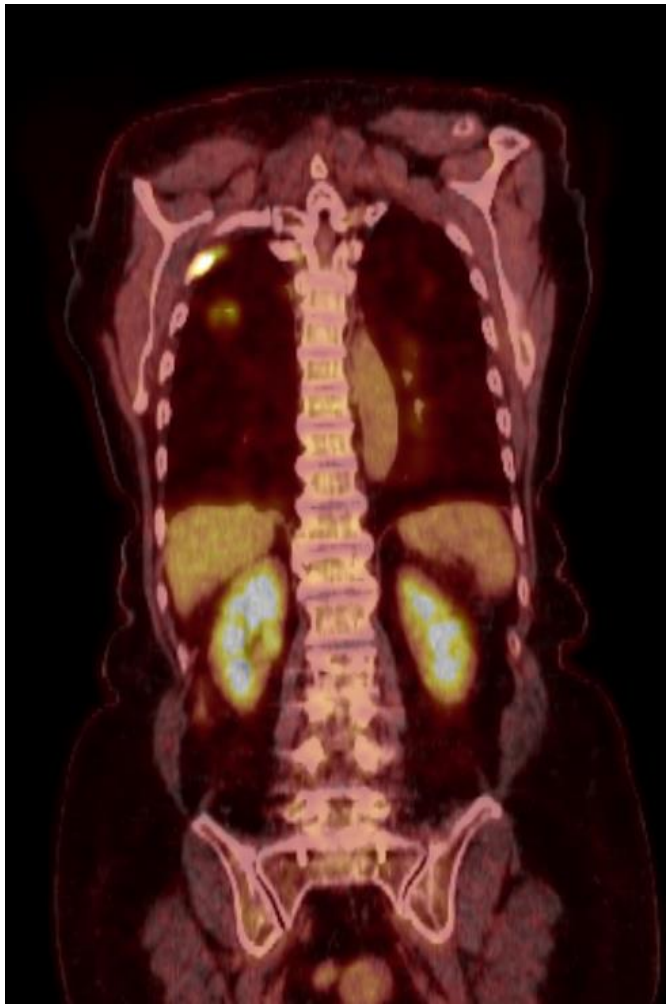
Case

78 year-old female with newly diagnosed adenocarcinoma of the right lung. The patient completed a CTA of the chest May 2021 which depicted a pulmonary embolism. Additionally, she was found to have a enlarging right upper lobe mass with accompanying right middle lobe mass and right hilar lymphadenopathy. In July 2021, she underwent a bronchoscopy with bronchoalveolar lavage with biopsy at N2 level (4R, 7, N1 and 11).

Pathology revealed rare cluster of poorly differentiated adenocarcinoma most compatible with a lung primary. IHC revealed that the tumor was CK7, TTF-1 and Napsin A positive, while negative for CK20, synaptophysin, PAX8, GATA3, CDX2 and p40. The patient had additional imaging completed including a brain MRI (negative) and PET scan which showed stage IV disease with FDG avid activity in the right rib.

TMP from lung biopsy: QNS, insufficient tissue. PD-L1 <1%

PET Scan



Tissue Biopsy 07/2021

PD-L1 EXPRESSION

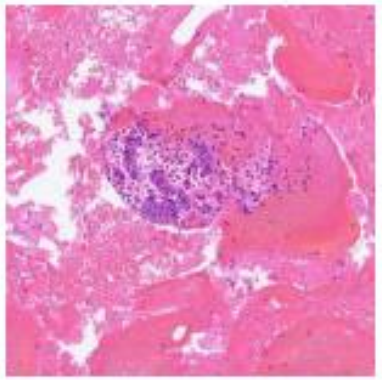
Negative

Tumor Proportion Score (TPS)

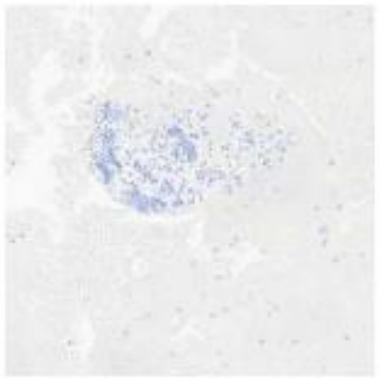
<1%

Combined Positive Score (CPS)

<1



H&E



PD-L1

Liquid Biopsy 07/2021

Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

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

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 3)	% cfDNA or Amplification
KRAS G12C	✓ Sotorasib ✓ Binimetinib	Yes	2.1%
ATM R3008C	✓ Niraparib, Olaparib, Rucaparib, Talazoparib	Yes	2.0%

Variants of Uncertain Significance
KIT P444T (0.7%), *MAP2K2* G153fs (0.3%)
The functional consequences and clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Synonymous Alterations
BRCA2 V1495V (1.9%)
This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Additional Biomarkers

Biomarker	Additional Details
Tumor Mutational Burden (TMB)	11.49 mut/MB
MSI-High	NOT DETECTED

Alterations or biomarkers that were "NOT DETECTED" have been excluded from the summary table above.

We evaluated this sample for 83 genes, including the following guideline-recommended genes for NSCLC

EGFR(T790M and others)	*ALK*	*ROS1*	*BRAF*	*MET*	*ERBB2*(HER2)	*RET*	*NTRK*

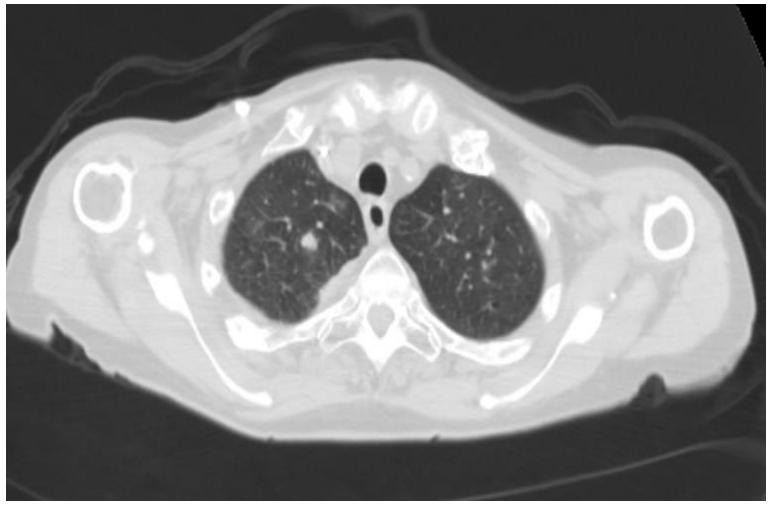
Treatment

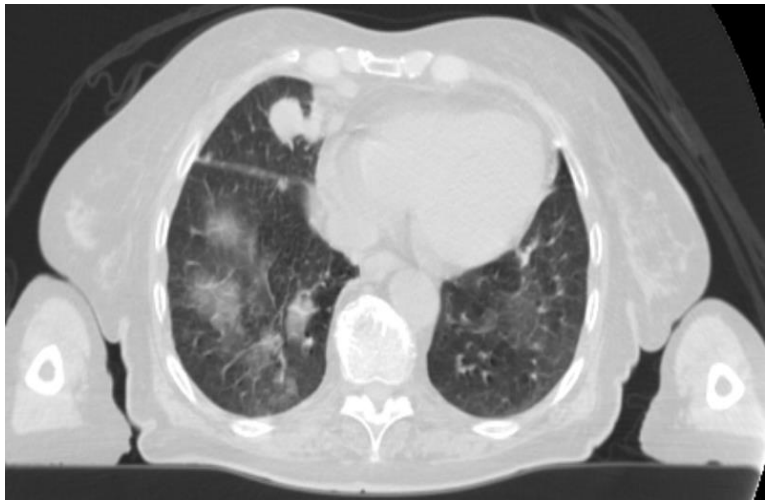
The patient was started on treatment with carboplatin, pemetrexed and pembrolizumab (4 cycles) followed by maintenance pemetrexed and pembrolizumab (6 cycles).

In January 2022, the patient underwent PET scan which showed progression of disease. A tissue biopsy was ordered but unable to be completed due to the patient not being able to stay stationary due to severe back pain. Subsequently, she underwent palliative radiation to L-4.

The patient was placed on sotorasib 960 mg/day based on prior liquid biopsy results.

Imaging January 2022 prior to treatment with sotorasib





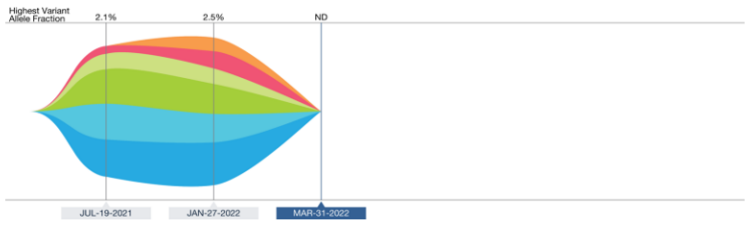
Clinical Course

The patient experienced adverse effects with sotorasib and it was dosage was decreased from 960 mg/day to 240 mg/day.

After 2 months of therapy, the patient's cfDNA was evaluated and showed a 100% decrease.

Response Interpretation	cfDNA Change
Decreasing†	100.0%

† Decreases in ctDNA of 50%-100% during the first 4-10 weeks of treatment are associated with clinical benefit in patients on anti-cancer therapies (Zhang, Q. et. al, 2020, Cancer Discovery; Paik, P.K. et al, 2020 N Engl J. Med; Thompson et al., 2021 JCO Precision Oncology). The clinical significance of ctDNA decreases of less than 50% is currently unknown.



Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	Alteration Trend
CHEK2 E239Q	ND	ND 0.6%
KRAS G12C	ND	2.1% 2.5% ND

Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	Alteration Trend
MAP2K2 G153fs	ND	0.3% 0.8%
KIT P444T	ND	0.7% 0.7% ND
ATM R3008C	ND	2% 1.5% ND
BRCA2 V1495V	ND	1.9% 1.6% ND

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.
§ See definitions section for more detail

Additional Biomarkers

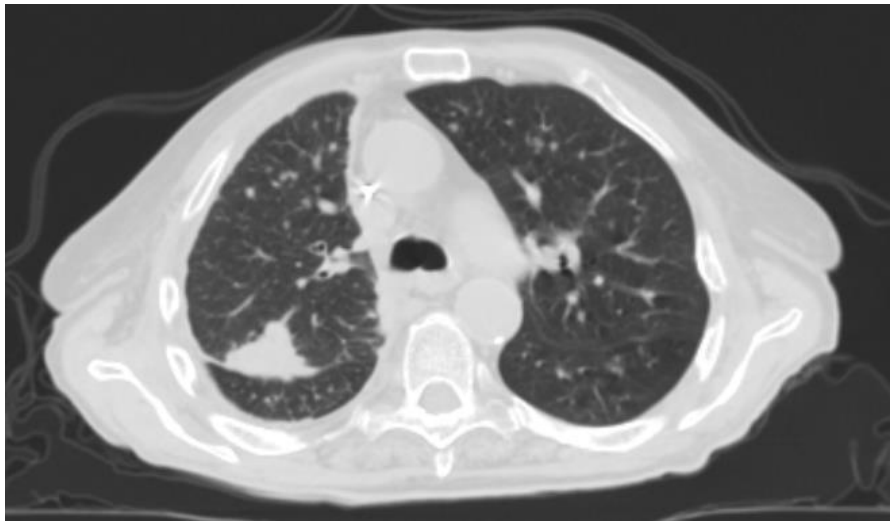
Biomarker	Additional Details
MSI-High	NOT DETECTED

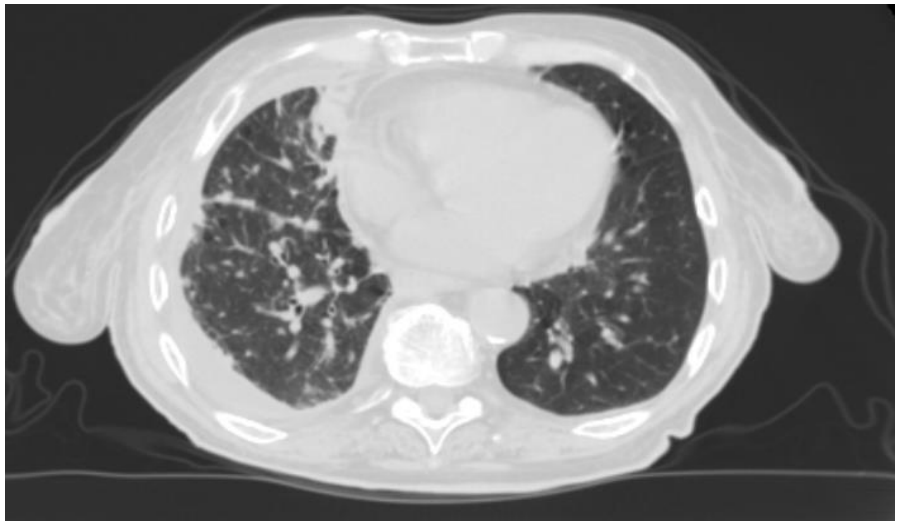
Clinical Course

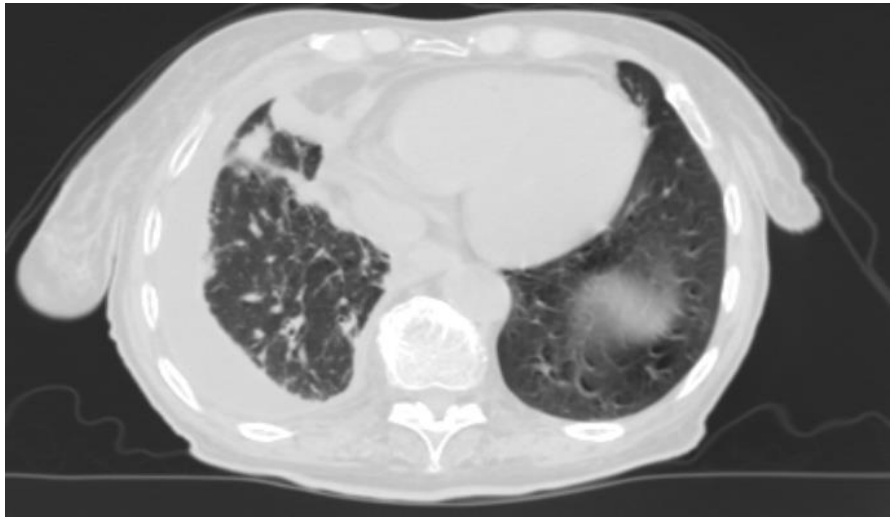
The patient remained on sotorasib 240 mg daily until mid June 2021 when she was found to have progression of disease on CT scan.

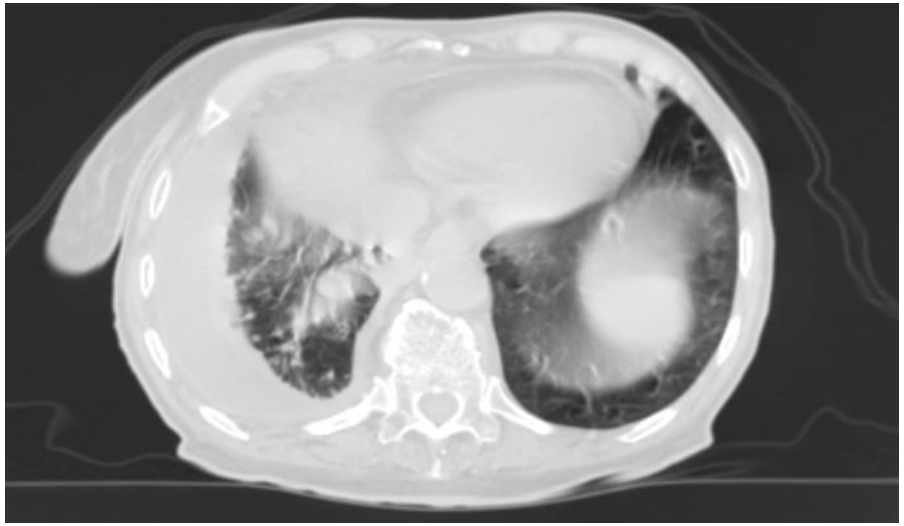
A repeat liquid biopsy and lung biopsy was ordered.

Imaging June 2022





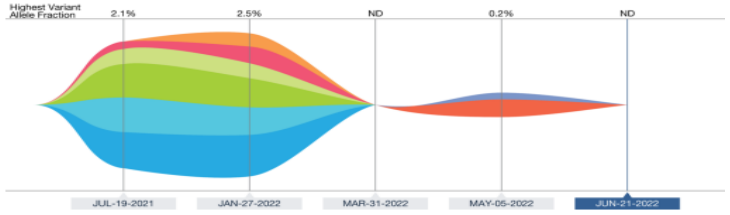




Liquid and Lung Biopsy Results

Lung Biopsy 06/28/2022 – core needle biopsy of the right lower lobe of the lung showed infiltrating moderately differentiated bronchogenic adenocarcinoma. The tumor cells were negative for CK20 and p63, but positive for CK7 and TTF-1.

Liquid biopsy 06/21/2022 (see below)



Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	Alteration Trend
AR A372A	ND	ND ND ND 0.2% ND
CHEK2 E239Q	ND	ND 0.6%
KRAS G12C	ND	2.1% 2.5% ND ND ND
MAP2K2 G153fs	ND	0.3% 0.8%
KIT P444T	ND	0.7% 0.7% ND ND ND
ATM R3008C	ND	2% 1.5% ND ND ND

Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	Alteration Trend
BRCA2 V1495V	ND	1.9% 1.6% ND ND ND
ERBB2 V777L	ND	ND ND ND 0.06% ND

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.
§ See definitions section for more detail

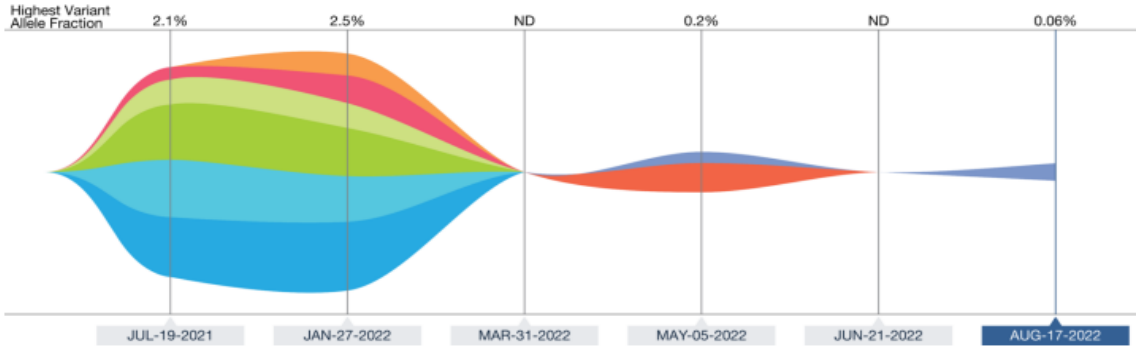
Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
ERBB2 (Her2/Neu)	Seq	DNA-Tumor	Pathogenic Variant Exon 20 | p.V777L	BENEFIT	ado-trastuzumab emtansine (T-DM1)	Level 3
ALK	IHC	Protein	Negative | 0	LACK OF BENEFIT	alectinib, ceritinib, crizotinib, lorlatinib	Level 1
					brigatinib	Level 2
	Seq	RNA-Tumor	Fusion Not Detected		alectinib, brigatinib, ceritinib, crizotinib, lorlatinib	Level 2
BRAF	Seq	DNA-Tumor	Mutation Not Detected	LACK OF BENEFIT	dabrafenib and trametinib combination therapy, vemurafenib	Level 2
EGFR	Seq	DNA-Tumor	Mutation Not Detected	LACK OF BENEFIT	erlotinib, gefitinib	Level 2
KRAS	Seq	DNA-Tumor	Mutation Not Detected	LACK OF BENEFIT	sotorasib	Level 2
RET	Seq	RNA-Tumor	Fusion Not Detected	LACK OF BENEFIT	pralsetinib, selpercatinib	Level 2
ROS1	Seq	RNA-Tumor	Fusion Not Detected	LACK OF BENEFIT	ceritinib, crizotinib, entrectinib, lorlatinib	Level 2
MET	CNA-Seq	DNA-Tumor	Amplification Not Detected	LACK OF BENEFIT	crizotinib	Level 3
	Seq	RNA-Tumor	Variant Transcript Not Detected			

* Biomarker reporting classification: Level 1 – Companion diagnostic (CDx); Level 2 – Strong evidence of clinical significance or is endorsed by standard clinical guidelines; Level 3 – Potential clinical significance. Bolded benefit therapies, if present, highlight the most clinically significant findings.

Clinical Course

A tumor mutational profile and liquid biopsy yielded the same genomic abnormality: ERBB2 V777L. The patient was started on fam-trastuzumab deruxtecan at 5.4 mg/kg August 2022.



Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	Alteration Trend
ERBB2 V777L	0.06%	ND ND ND 0.06% ND 0.06%
AR A372A	ND	ND ND ND 0.2% ND ND
CHEK2 E239Q	ND	ND 0.6%
KRAS G12C	ND	2.1% 2.5% ND ND ND ND

Images

The patient is doing well and is currently on treatment with fam-trastuzumab deruxtecan without any complications.