Lung Cancer Case Presentation

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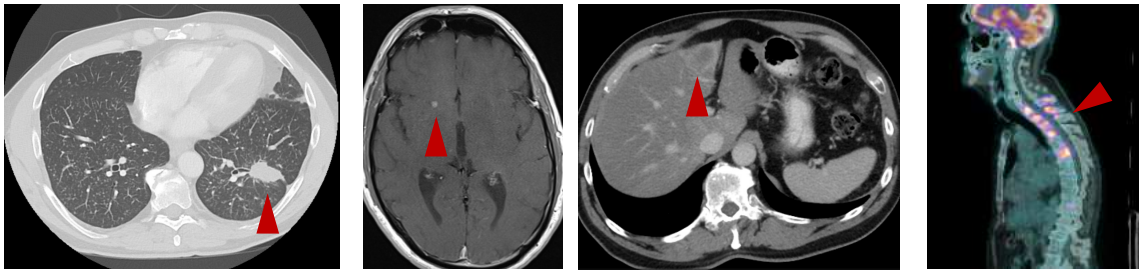
Case: Initial Diagnosis

- 62 yo M never smoker with stage IV lung cancer metastatic to bone, brain, liver, adrenals, lymph nodes



Diagnostic liver biopsy

- Rapid onsite evaluation (ROSE) confirmed presence of adenocarcinoma in fine needle aspiration specimen
- Core biopsies obtained

Plasma EGFR testing requested same day

- Resulted 24 hours later
- EGFR exon19del mutation detected

RESULT:

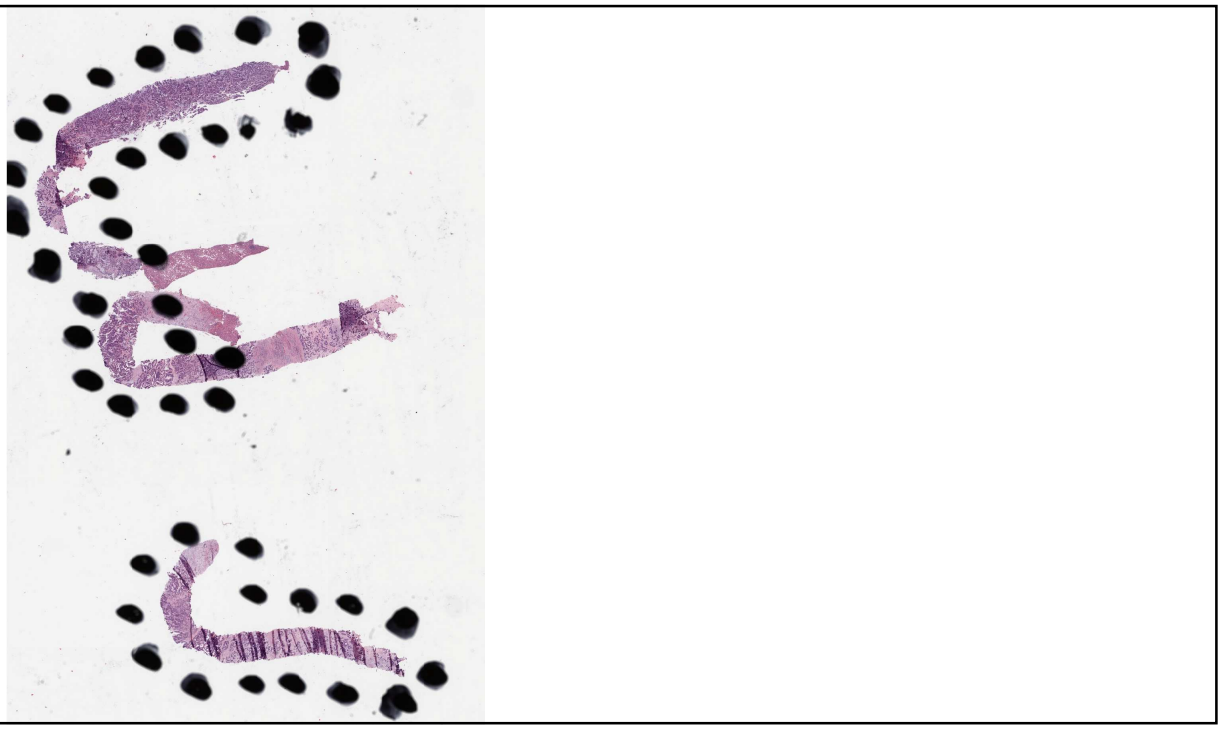
EGFR L858R	EGFR exon 19 deletion	EGFR T790M
NEGATIVE	POSITIVE	NEGATIVE

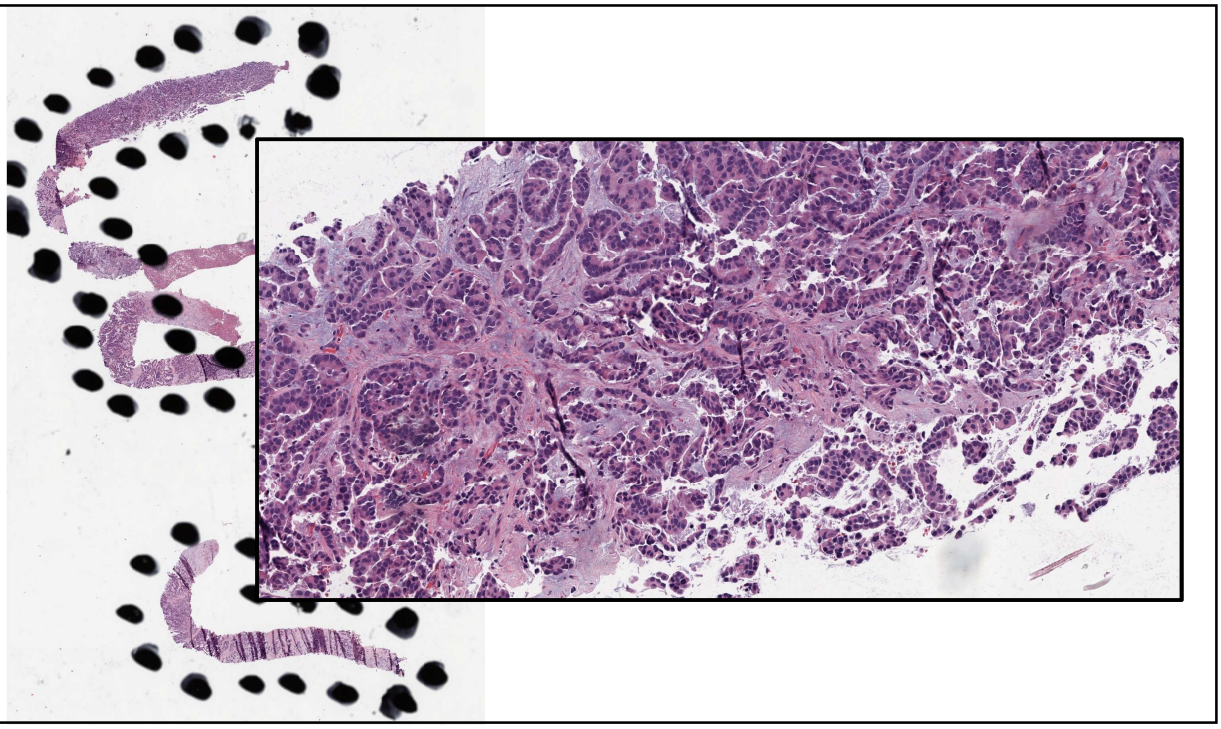
INTERPRETATION:

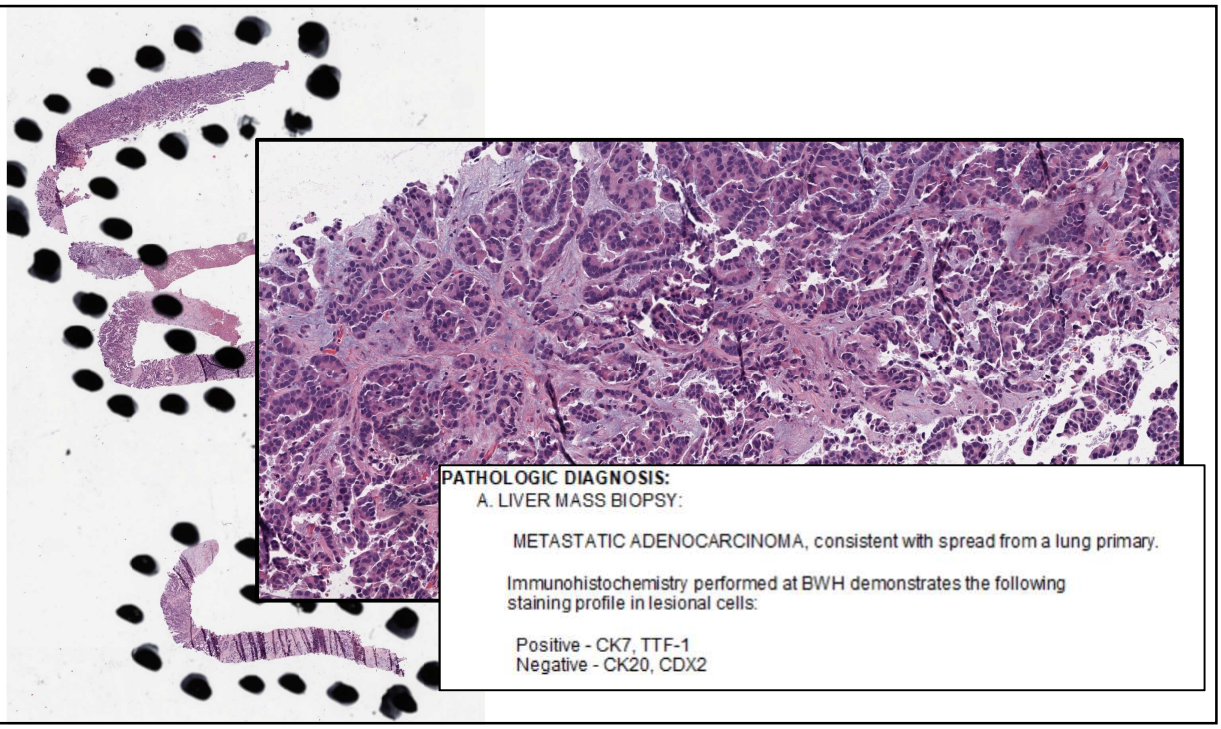
The results indicate that only wild type (normal) sequence is present at EGFR L858 in the tested sample.

The results indicate that only wild type (normal) sequence is present at EGFR T790 in the tested sample.

EGFR exon 19 deletion Positive: the assay detected exon 19 deletion in 4% of the alleles in this sample.







OncoPanel (Panel NGS) Results:

Tumor Mutational Burden/Megabase: 3.042

This is higher than 5% of all Non-Small Cell Lung Cancer cancers sequenced by this version of OncoPanel (n=994)
This is higher than 14% of all Profile cases sequenced by this version of OncoPanel (n=7303)

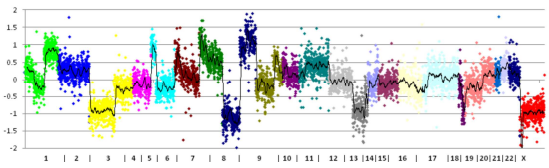
ACTIONABLE FINDINGS

Mismatch Repair Status: Proficient (MMR-P / MSS)

Mutations:
EGFR c.2236_2248delGAATTAAGAGAAGinsGAAC (p.L747_A750delinsP), exon 19 - in 21% of 436 reads

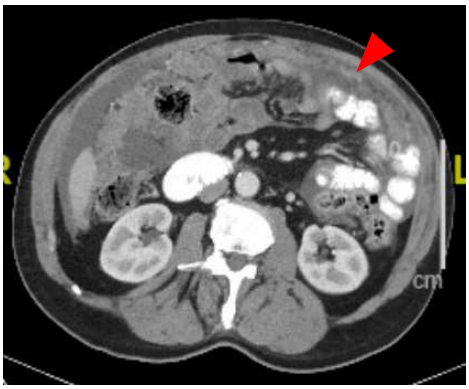
Investigational variants:

KMT2A c.10369C>T (p.Q3457*), exon 27 - in 21% of 591 reads**
SMAD4 c.1478A>G (p.D493G), exon 12 - in 68% of 116 reads**
TP53 c.742C>T (p.R248W), exon 7 - in 82% of 225 reads**

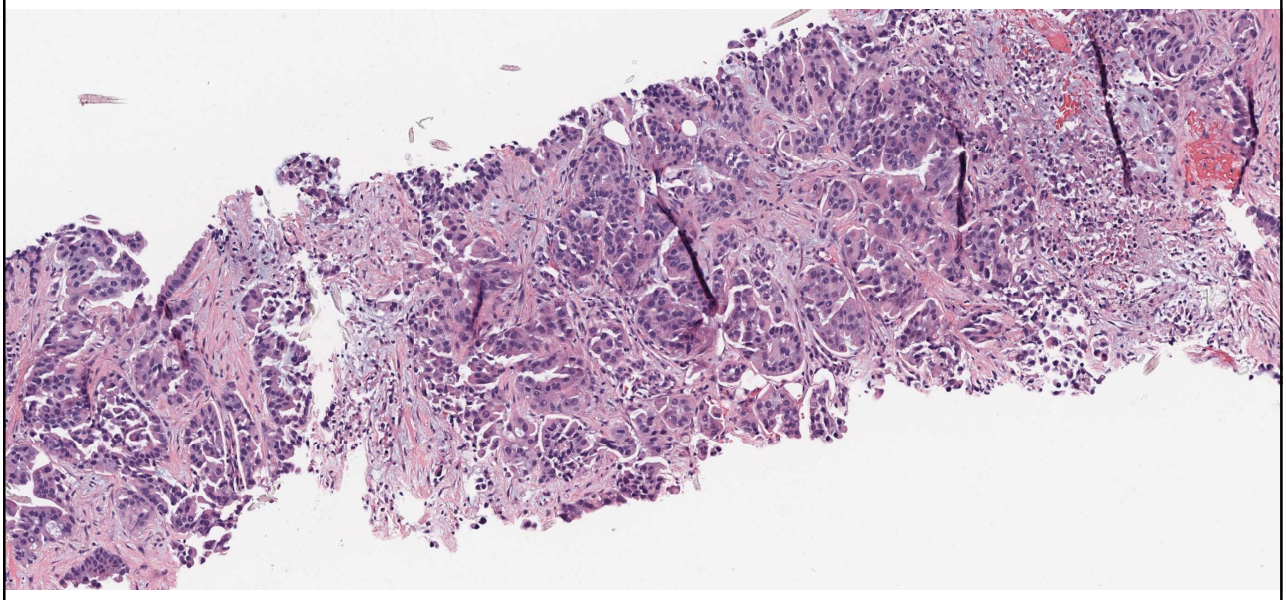


Case: Resistance to Osimertinib

- Received first-line treatment on clinical trial with an investigational combination of osimertinib (EGFRi) + selumetinib (MEKi)
- Progression after ~14 months with new omental metastases, ascites



Peritoneal mass biopsy:



Case: Resistance to Osimertinib

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Tier 1 variants:
EGFR c.2236_2248delGAATTAAGAGAAGinsGAAC
(p.L747_A750delinsP), exon 19 - in 17% of 499
reads

Tier 2 variants: None identified.

Structural Variants:

Tier 1 variants: None identified.

Tier 2 variants:
Rearrangement - CCDC6 intron 1 (chr10:61660746)
:: RET intron 11 (chr10:43610359)
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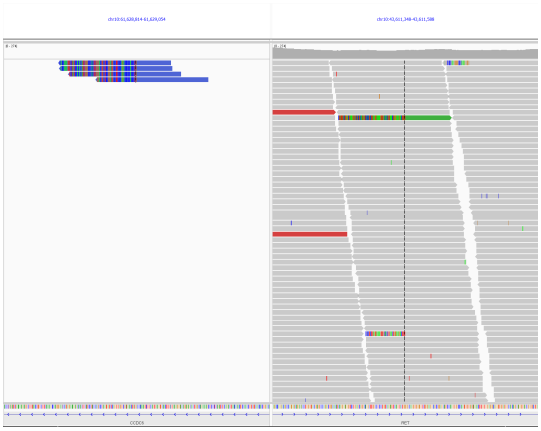
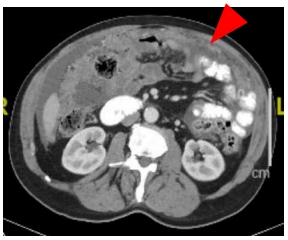


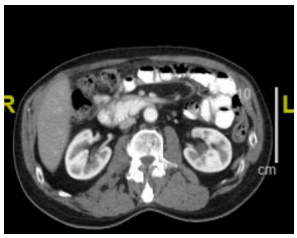
Case: Osimertinib + Selpercatinib (RETi)

- Enrolled to single patient protocol of LOXO-292 (selpercatinib, RETi) + osimertinib (EGFRi)
  - No dose reductions or dose holds needed
- Reduced disease burden after 2 months, progression after 10 months

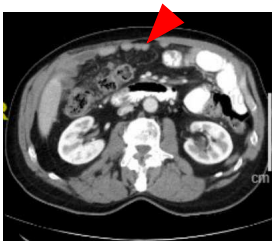
Pre-treatment

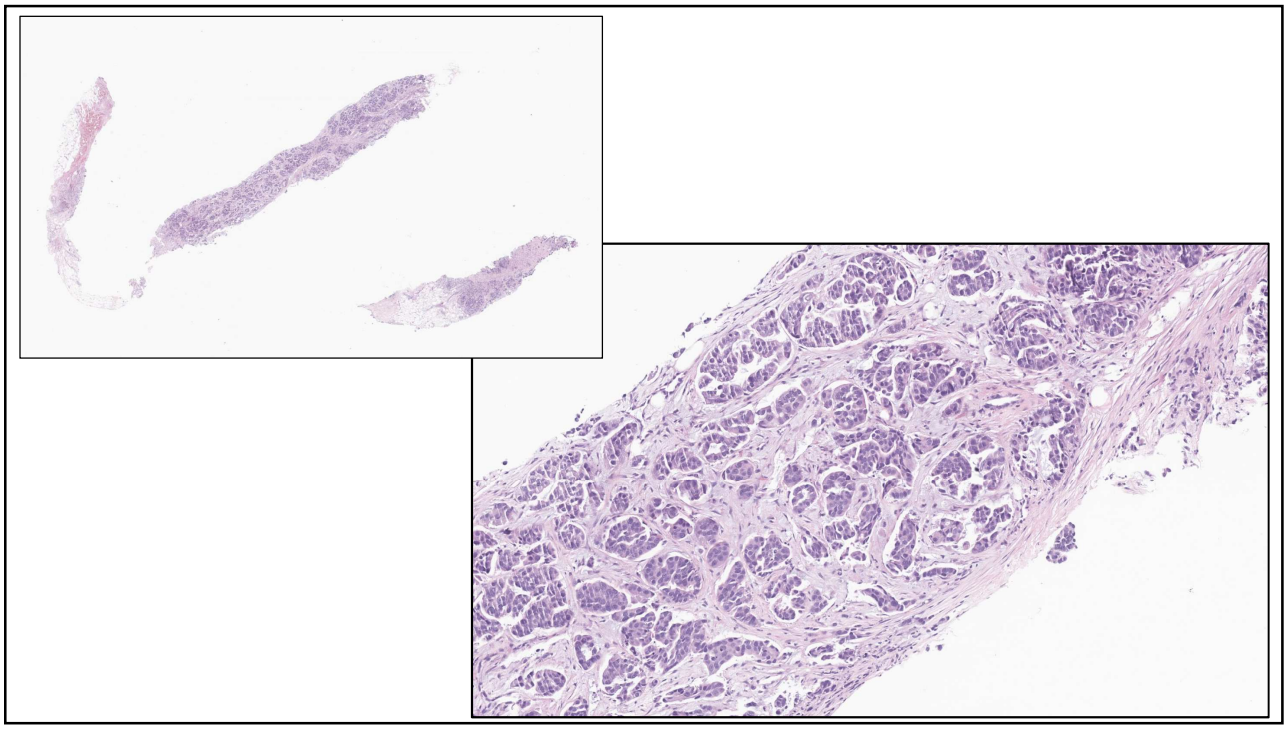


8 weeks



Progression





Tumor Mutational Burden/Megabase: 6.844 Up from 3.042 at diagnosis

ACTIONABLE FINDINGS

Mismatch Repair Status:Proficient (MMR-P / MSS)

Mutations:

Tier 1 variants:
EGFR c.2239_2248delinsC (p.L747_A750delinsP), exon 19 - in 18% of 437 reads
RET c.2428G>A (p.G810S), exon 14 - in 15% of 216 reads

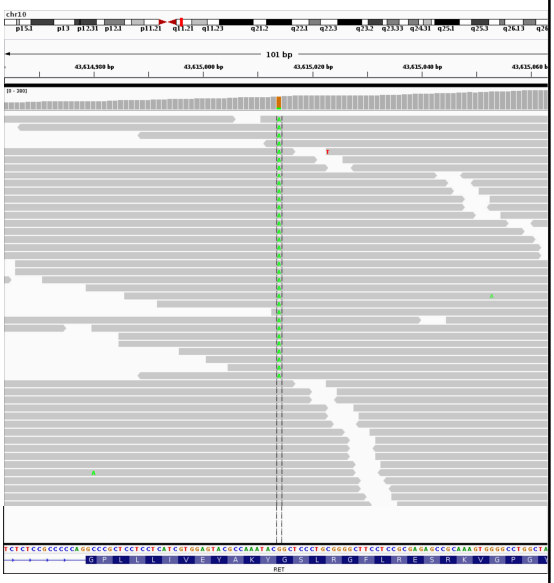
Structural Variants:

Tier 1 variants:
Rearrangement - CCDC6 intron 1 (chr10:61628934) :: RET intron 11 (chr10:43611468)

Investigational Variants

Tier 3 variants:
KMT2A c.10369C>T (p.Q3457*), exon 27 - in 24% of 687 reads
SMAD4 c.1478A>G (p.D493G), exon 12 - in 46% of 181 reads
TP53 c.742C>T (p.R248W), exon 7 - in 61% of 259 reads

Tier 4 variants:
CARD11 c.1864_1866del (p.S622del), exon 15 - in 3% of 300 reads
CIC c.1264C>T (p.R422*), exon 8 - in 8% of 437 reads
CTNNB1 c.100_106delinsA (p.G34_H36delinsN), exon 4 - in 17% of 375 reads
KMT2A c.2939C>G (p.A980G), exon 3 - in 4% of 555 reads
TSC2 c.1628C>T (p.P543L), exon 16 - in 28% of 294 reads



Summary of Somatic Alterations & Associated Tre

KEY Approved in indication Approved in other indication

Alteration	% cfDNA or Amplification
EGFR C797S	0.1%
EGFR L747_A750delinsP (Exon 19 deletion)	22.3%
EGFR Amplification	Medium (++)
CTNNB1 G34_H36delinsN	0.7%
CCDC6-RET Fusion	0.4%
CCNE1 Amplification	Low (+)
TP53 R248W	27.9%

Variants of Uncertain Significance

RET G810S (0.8%)

The functional consequences and clinical significance of alterations a

<u>ctDNA</u>

EGFR exon 19 deletion

EGFR C797S (osimertinib resistance mutation)

CCDC6-RET fusion

RET G810S (selpercatinib reistance mutation)

Case: Subsequent therapies

- Osimertinib + carboplatin/pemetrexed
- Clinical trial: HER3 antibody drug conjugate
- Clinical trial: EGFR-MET bispecific antibody
- Osimertinib + docetaxel

2/2018: Dx: stage IV lung adenocarcinoma	4/2019: Progressive disease	3/2020: Progressive disease	11/2020: Progressive disease	6/2021: Progressive disease
Liver met: EGFR p.L747_A750delinsP KMT2A p.Q3457* SMAD4 p.D493G TP53 p.R248W	**Peritoneal met:** EGFR p.L747_A750delinsP CCDC6-RET fusion KMT2A p.Q3457* SMAD4 p.D493G TP53 p.R248W	**ctDNA:** EGFR p.L747_A750delinsP EGFR p.C797S CCDC6-RET fusion RET p.G810S **"LUQ" Tissue:** EGFR p.L747_A750delinsP EGFR p.C797S KMT2A p.Q3457* SMAD4 p.D493G TP53 p.R248W BRIP1 c.2379+3768G>T IL7R p.V257F	**Inguinal LN:** EGFR p.L747_A750delinsP CCDC6-RET fusion RET p.G810S KMT2A p.Q3457* SMAD4 p.D493G TP53 p.R248W CTNNB1 p.G34_H36delinsN MTA1 p.R484C TSC2 p.P543L	**Inguinal LN:** EGFR p.L747_A750delinsP CCDC6-RET fusion RET p.G810S KMT2A p.Q3457* SMAD4 p.D493G TP53 p.R248W CTNNB1 p.G34_H36delinsN TSC2 p.P543L CARD11 p.S622del CIC p.R422*