Rare Lung Cancer with a Non-Functional NTRK Fusion: “A Cautionary Tale”

Abstract Category: Clinical solid tumor oncology

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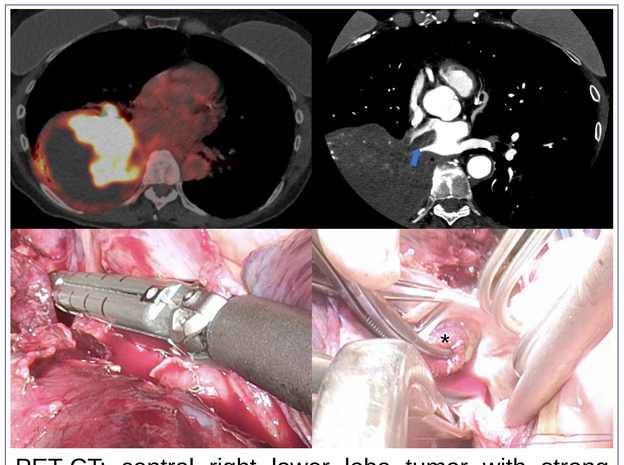
BACKGROUND

- *NTRK1-3* gene fusions are actionable oncogenic drivers across multiple tumor types.
- TRK inhibitors show high response rates in *functional NTRK1-3* fusion positive tumors.
- However, some detected *NTRK* fusions are **non-functional**, lacking biological and therapeutic relevance.
- Functional validation is therefore essential before initiating targeted therapy.

FIGURE 1



PET-CT: central right lower lobe tumor with strong FDG-uptake. Contrast-enhanced CT: tumor-associated thrombus (arrow) extending into the left atrium. Extended right pneumonectomy on cardiopulmonary bypass to allow extraction of the left atrial thrombus (*) and a direct suture of the left atrium.

METHODS / Case Presentation

Initial Course
Patient: 60-year-old female, smoker (30 py).
Presentation: CT with an 11 cm right lower-lobe lung mass and hilar lymphadenopathy.
Biopsy: Spindle-cell neoplasm (challenging morphology).
Initial molecular findings:
- *HP1BP3::NTRK1* fusion (RNA-based NGS)
- *TP53* p.E298Ter, *MYCN* amplification

Initial diagnosis: NTRK-rearranged spindle cell tumor of the lung (based on molecular findings)
Therapy: Larotrectinib
Outcome: Rapid progression under therapy, tumor enlargement, right atrial invasion, tumor thrombosis, Figure 1

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Due to unusual morphology and intrinsic resistance, re-evaluation of histology
Diagnosis: Sarcomatoid carcinoma of the lung (NSCLC)

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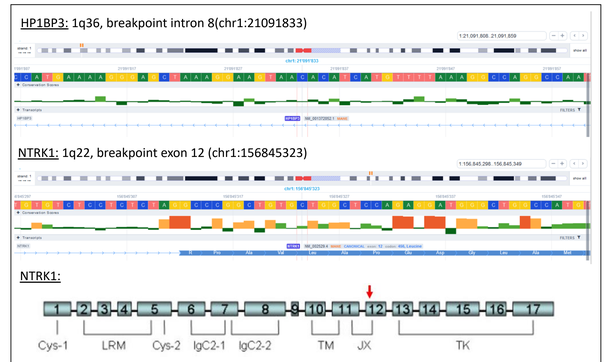
Treatment and Outcome
Therapy: Neoadjuvant carboplatin, docetaxel, durvalumab
followed by extended right pneumonectomy with partial atrial resection
Result: R0 resection
Residual tumor: 30% viable (non-responder)
Final diagnosis: pulmonary blastoma, with *DICER1* mutation (rare subtype of sarcomatoid carcinoma of the lung/ NSCLC)
TNM (8th edition): ypT4 ypN0 (0/10) cM0 R0

RESULTS

In depth analysis
Bioinformatics: Figure 2
Pan-TRK IHC (EPR17341): Negative
→ no TRK protein expression.
FISH: Polysomy, no break-apart signal.
CNV (methylation array): Deletion on chromosome 1q, no true fusion.
Histopathology (post-surgery): Biphasic morphology → pulmonary blastoma.
Additional molecular finding: *DICER1* mutation (driver event).

Interpretation:
Non-functional *NTRK1* fusion

FIGURE 2

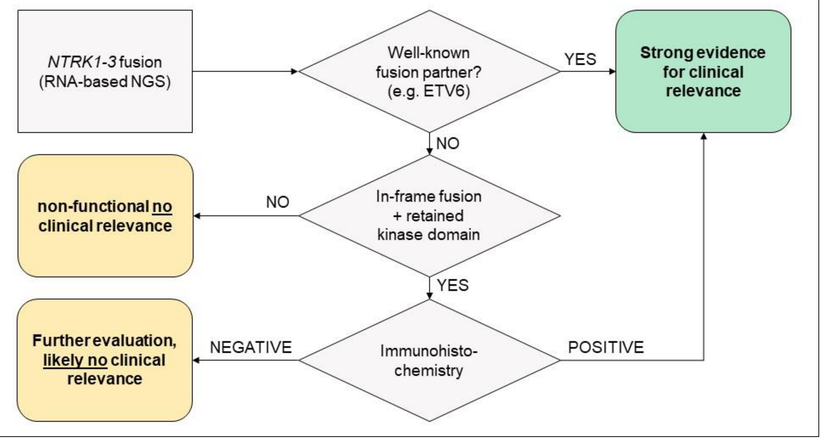


VarSome Genome Browser: *HP1BP3::NTRK1*
In-frame fusion, with retained kinase domain (TK) of *NTRK1* (exon 13-17), red arrow: breakpoint.

DISSCUSSION / CONCLUSION

- TRK inhibitor therapy should only be considered for confirmed functional *NTRK1-3* fusions.
- Histopathological diagnosis remains critical before targeted treatment.
- **Guideline-based multimodal therapy (ESMO) - including surgery - remains standard for resectable stage IIIA NSCLC**

Suggested algorithm:
Given the heterogeneity of fusion partners and break-point locations, compre-hensive functional charac-terization of *NTRK* fusions is essential to determine their oncogenic potential and therapeutic relevance.



RELEVANT REFERENCES

ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical. Marchiò, C. et al. Annals of Oncology, 2019
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