Updated efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase (TRK) fusion lung cancer. ASCO 2022

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Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions

- Oncogenic drivers in multiple tumor types
- Less than 1% of NSCLC (0.1-3.3%)
- Multiple fusion partners
- Mainly NTRK1 and 3
- Most common partner is TPM3
- Resistance in EGFR

- Diagnostic difficulty
- NGS is important
- RNA based NGS is preferred

- Larotrectinib and Entrectinib
- First Generation NTRK inhibitor
- Tumour agnostic approval
- Newer agents – Selitrectinib,repotrectinib,Taltrectinib

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Efficacy and Safety of Larotrectinib in Patients With Tropomyosin Receptor Kinase Fusion–Positive Lung Cancers

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- Patients from 2 registrational clinical trials
- A phase II basket trial and a phase 1 trial (NAVIGATE, NCT02576431 &(NCT02122913)
- Primary endpoint- ORR
- Secondary endpoint – PFS,OS,DoR
- 100 mg BD continuous 28 day cycles
- Response rate by IRC Recist v 1.1

9024 **Poster Discussion Session**

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- Data on the expanded cohort
- Till July 2021
- 26 patients
- 24 Patients had NSCLC
- 1- Atypical carcinoid
- 1-NEC
- 10 patients had CNS metastasis

- Median age 51.5 years (25-76)
- NTRK1(21,81%) > NTRK 3 (5,19%)
- Median prior lines-2
- At least 2 lines-19 (73%)

Evaluable patients n=23

Parameter	n
ORR	19 (83%) CI 61-95
CR	2(9%)
PR	17(74%)
SD	4
Median time to Response	1.8 months
ORR (CNS Metastasis)	80% (CR-2)
Median DoR	NR
Median PFS	NR
2 Year DoR/PFS	72%/67%
2 Y and 3 y OS	72% (Median FUP-12.9 mo)

CNS Metastasis
12 month
DoR – 26%
PFS-22%
OS- 78%

6 patients progressed at data cut off
All continuing for >/ 4 weeks

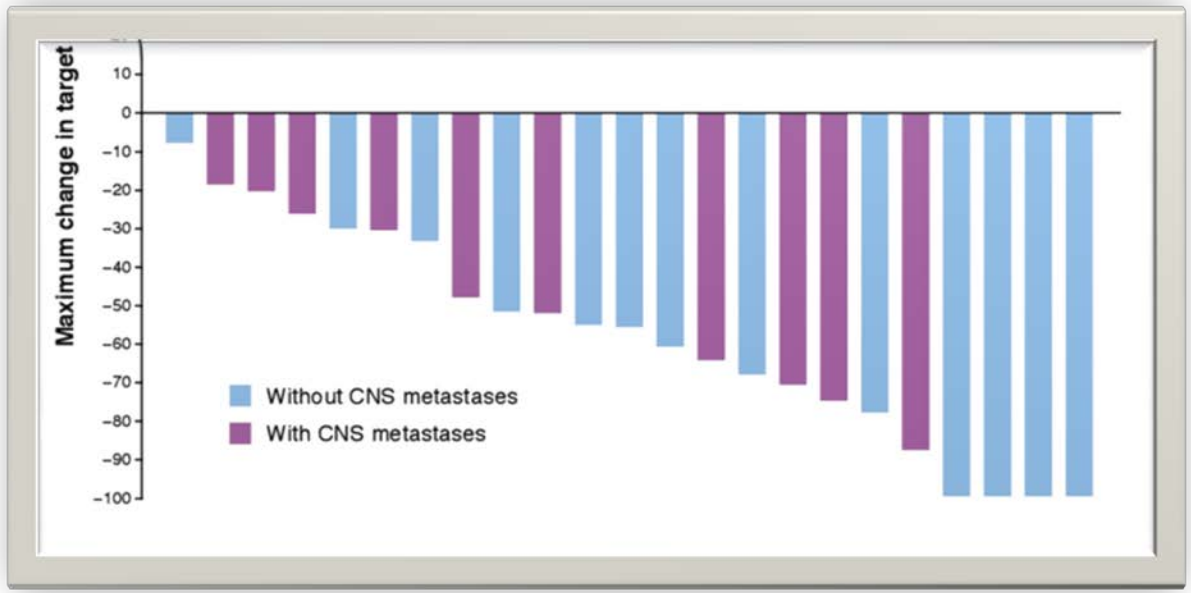
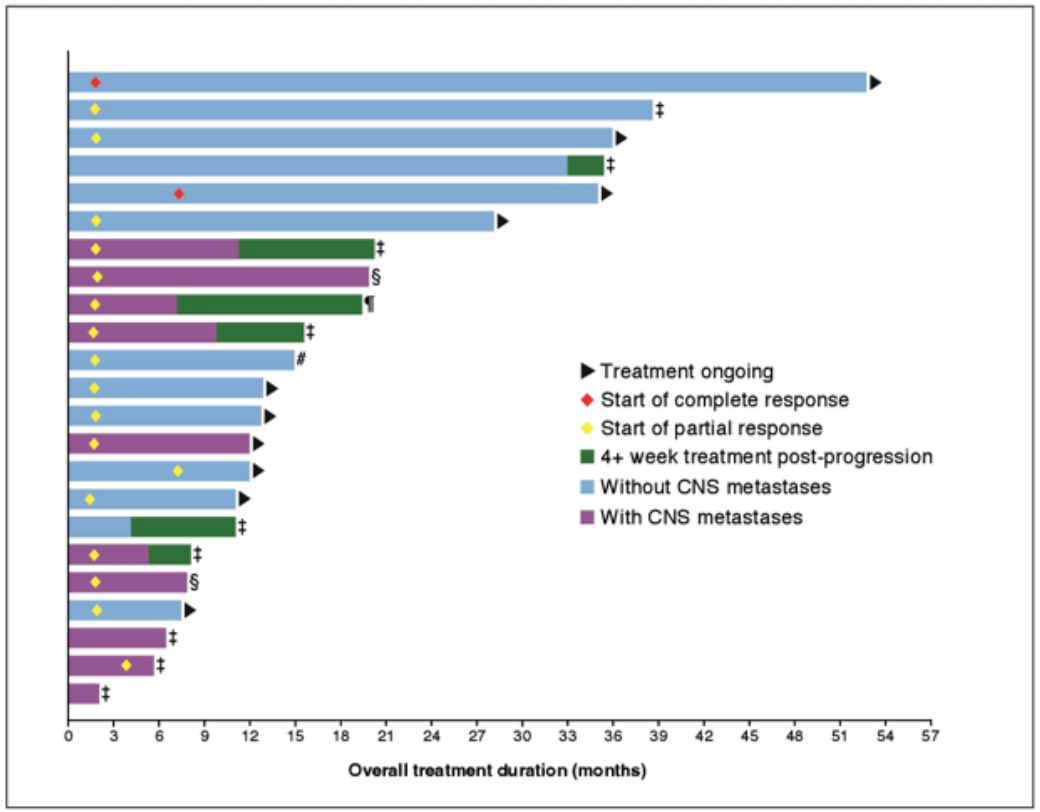
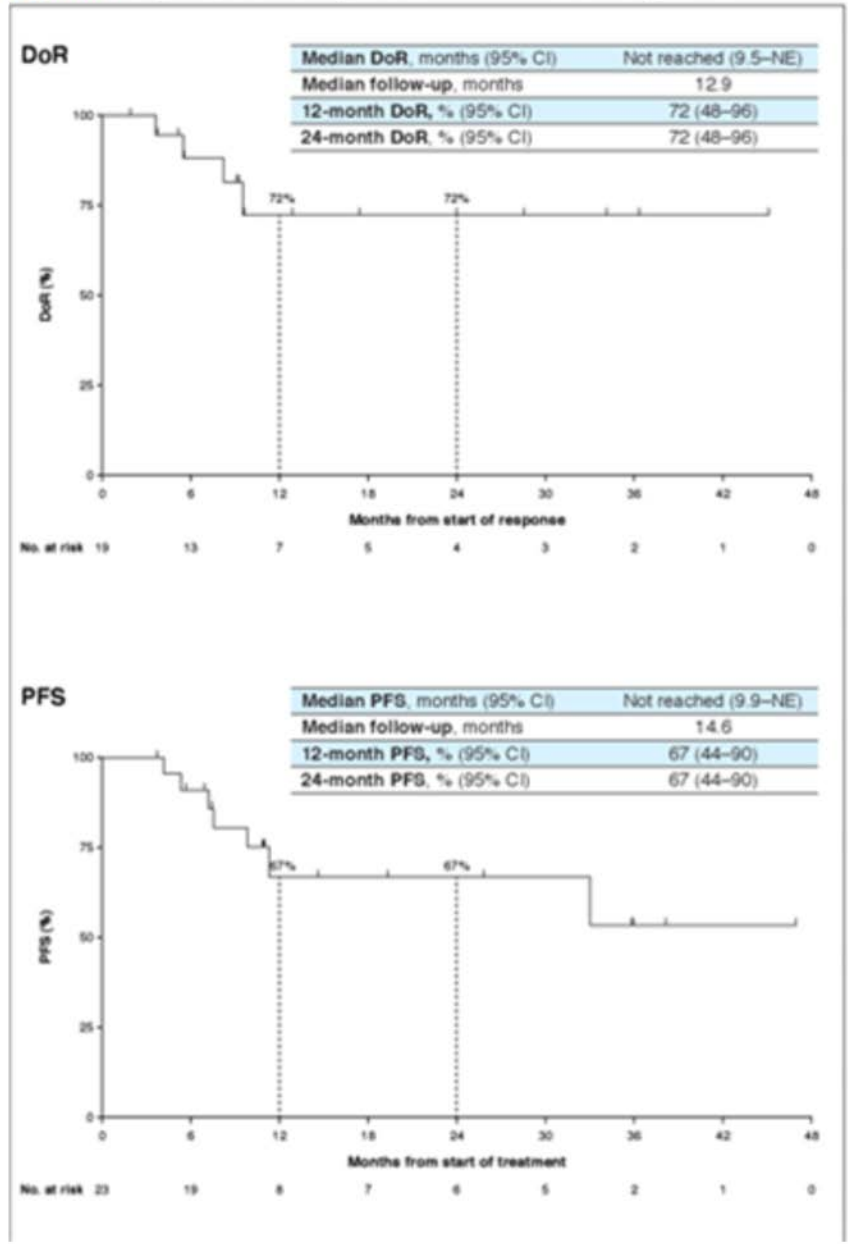


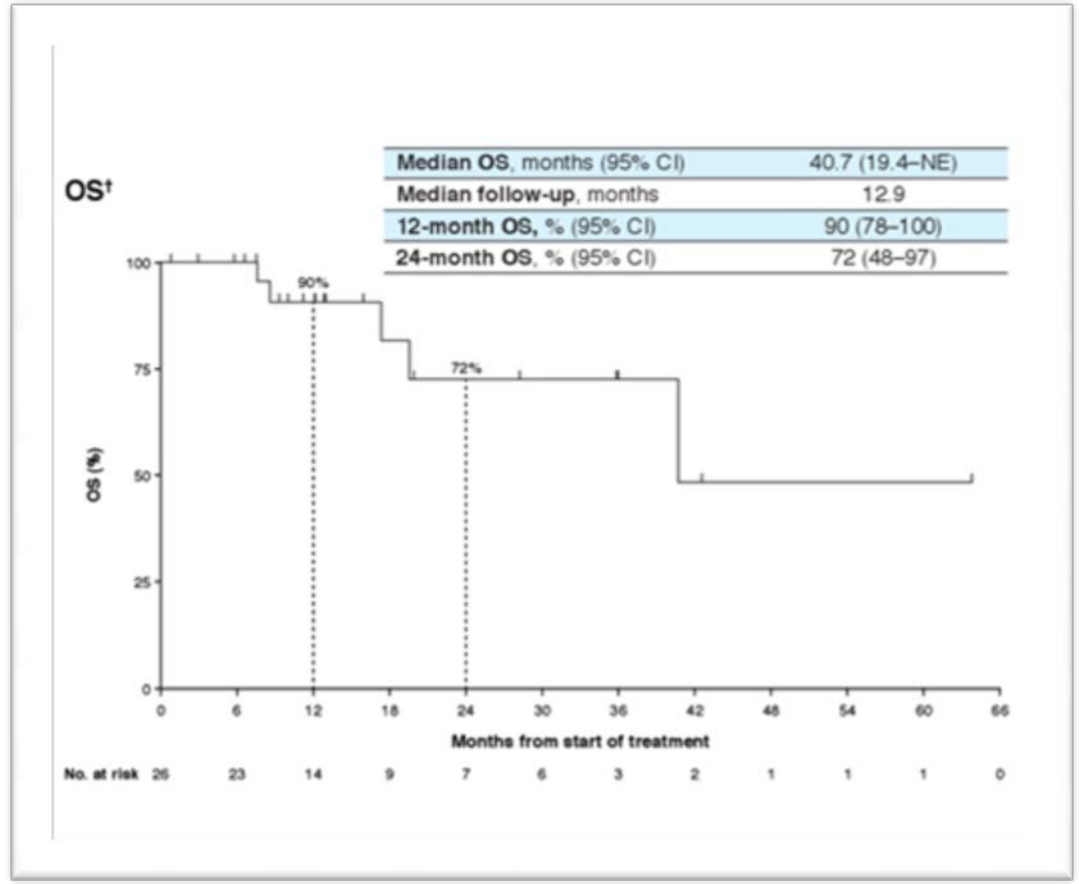
Figure 2. Treatment duration for all patients with TRK fusion lung cancer evaluable per IRC (n=23)



‡Discontinued due to disease progression. §Discontinued due to physician decision. ¶Discontinued due to death. #Discontinued due to protocol deviation.
CNS, central nervous system; IRC, independent review committee; TRK, tropomyosin receptor kinase.

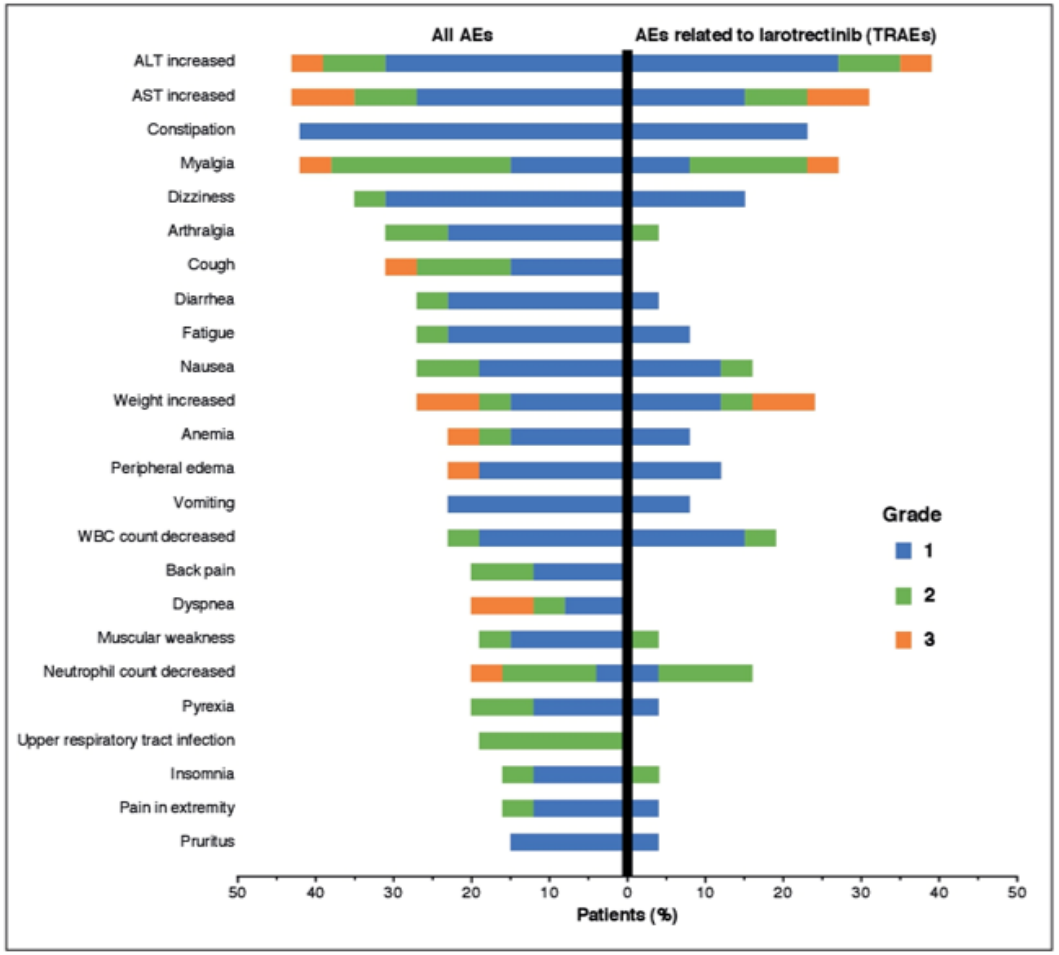
Figure 3. DoR, PFS, and OS in patients with TRK fusion lung cancer





- Treatment-related adverse events (TRAEs) were predominantly Grade 1–2.
- Grade 3–4 TRAEs were reported in five pts
- Increased alanine aminotransferases
- Increased aspartate aminotransferase
- Hypersensitivity, myalgia
- Increased weight
- There were no treatment discontinuations

Figure 4. AEs occurring in ≥15% of patients with TRK fusion lung cancer



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase;

Conclusions:

- In this larger dataset, larotrectinib demonstrated rapid and durable responses, extended survival, and a favorable long-term safety profile in pts with advanced lung cancer harboring NTRK gene fusions, including in pts with CNS metastases.
- These results support testing for NTRK gene fusions in pts with lung cancer.

- **Response comparable to other tumour types**
- **Lesser Nervous system side effects compared to Entrectinib**

- Limited CNS penetration
- On target and Off targe resistance

- **Very Rare mutation**
- **Diagnostic difficulty / Testing method**
- **Access to the drug ??**